# The emerging role of imatinib blood level testing in advanced GIST

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# Disclosures

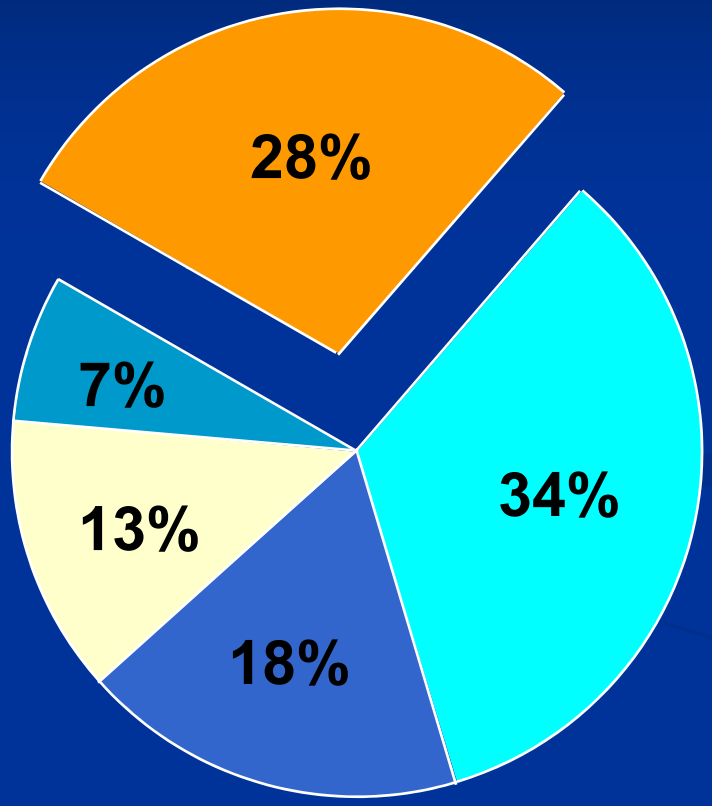
- Pfizer, Novartis – Advisory Board

# GIST

- We have learned a tremendous amount regarding GIST in the past decade
  - Importance of KIT signaling
  - Application of tyrosine kinase inhibition
  - Diverse mechanisms of TKI resistance
  - Ongoing efforts to develop novel therapeutic strategies, both medical and surgical, to combat resistance

# GIST: Historical Classification as Other Soft-Tissue Sarcomas

N=600




- A retrospective Swedish study determined that 72% of GI tumors now identified as GIST had been originally classified as other tumors

Kindblom et al. *Ann Oncol.* 2002;13:157. Abstract 577O.
Kindblom. At: www.peerviewpress.com/asco2003c.

# Finding the Critical Kinase Mutation in the Gastrointestinal Sarcoma: GIST

## Gain-of-Function Mutations of c-*kit* in Human Gastrointestinal Stromal Tumors

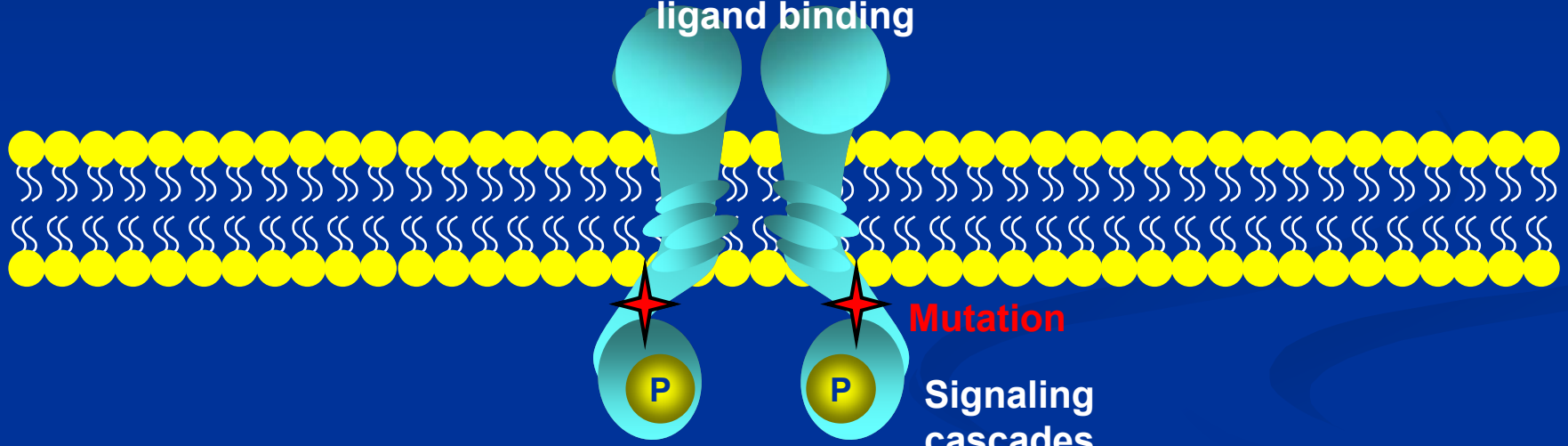
Seiichi Hirota,* Koji Isozaki,* Yasuhiro Moriyama, Koji Hashimoto, Toshirou Nishida, Shingo Ishiguro, Kiyoshi Kawano, Masato Hanada, Akihiko Kurata, Masashi Takeda, Ghulam Muhammad Tunio, Yuji Matsuzawa, Yuzuru Kanakura, Yasuhisa Shinomura, Yukihiko Kitamura†

Science 279:577-580

Sommer et al. *Proc Natl Acad Sci U S A*. 2003;100:6706.
Hirota et al. *Science*. 1998;279:577.

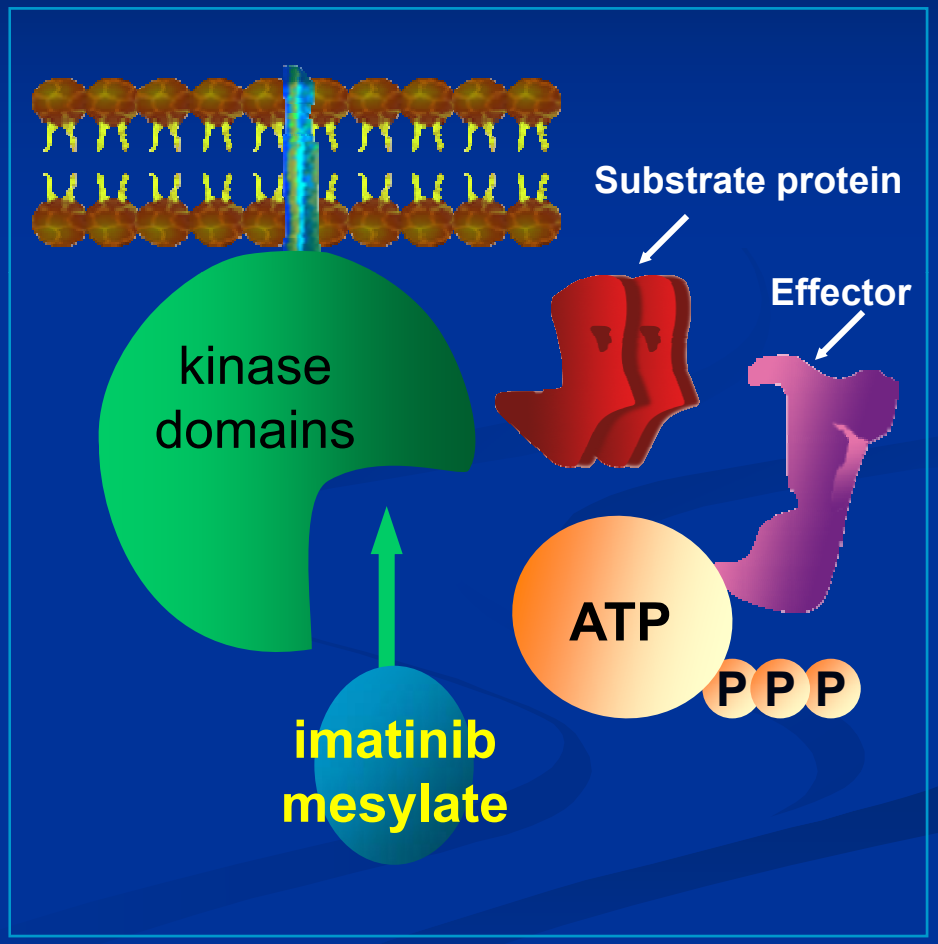
# Mutations Generate Uncontrolled Constant Activation of Receptor Tyrosine Kinases in GIST

RTK mutations in GIST allow for constitutive activation in the absence of ligand binding



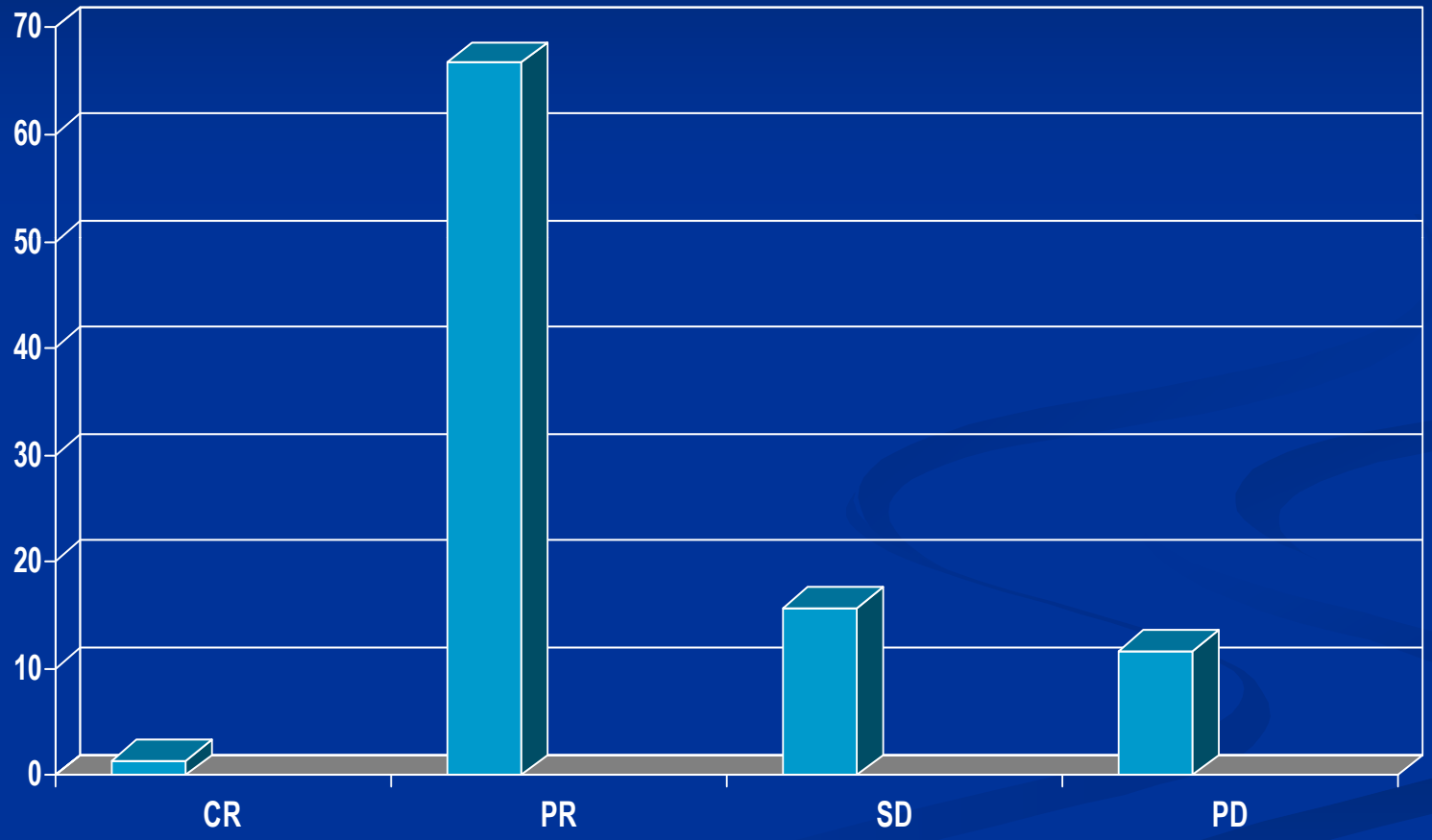
# Tyrosine Kinase Inhibition in GIST: Imatinib Mesylate

- Imatinib mesylate occupies ATP binding pocket of KIT kinase domain
  - Prevents substrate protein phosphorylation and signaling
  - Lack of signaling inhibits proliferation and survival




Adapted from Savage DG, Antman KH. *N Engl J Med*. 2002;346:683-93.

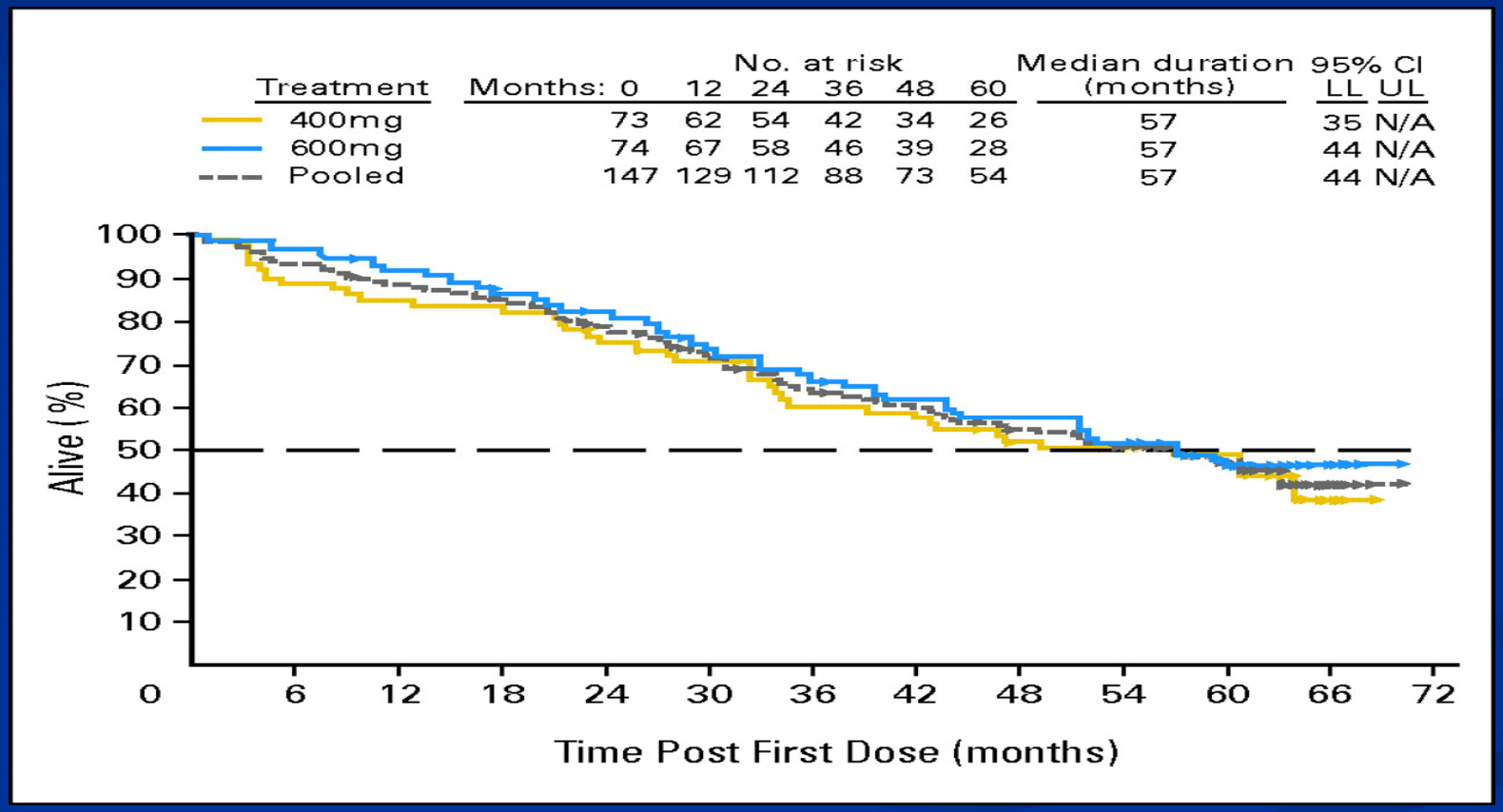
# Inhibiting TKI signaling with imatinib leads to dramatic disease control in GIST




Blanke et al, JCO 2008

Median followup 71months – B2222

# With a dramatic improvement in Overall Survival

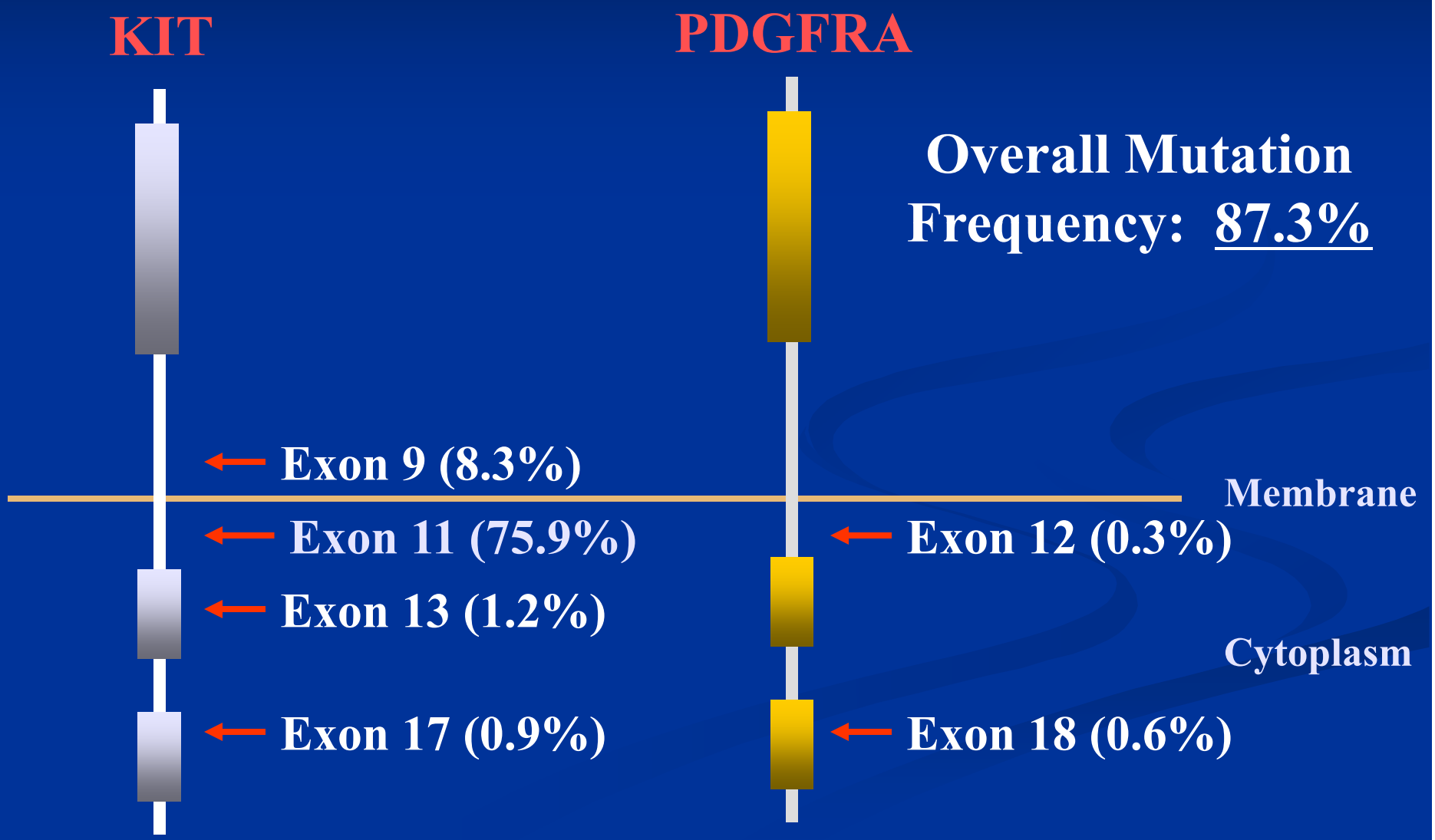





Blanke, C. D. et al. J Clin Oncol; 26:620-625 2008

JOURNAL OF CLINICAL ONCOLOGY

# Location of activating *KIT* and *PDGFRA* mutations in GISTs vary



# GIST

- **Heterogeneous Disease**
- Prognostic Factors
  - Primary Disease – risk of recurrence
    - Primary site of disease – gastric vs small bowel
    - Tumor size at presentation – small vs large
    - Number of mitoses/ 50Hpf – low vs high

# GIST Tumor Characteristics and Risk of Progression

| | Tumor Characteristics | | % of Patients with Progressive Disease During Follow-Up/Characterization of Malignant Potential | | | |
|---|---|---|---|---|---|---|
| Group | Size, cm | Mitotic rate per 50 HPFs | Gastric GISTs | | Small Intestinal GISTs | |
| | | | % of Pts | Malig Pot | % of Pts | Malig Pot |
| 1 | ≤ 2 | ≤ 5 | 0 | Very low if any | 0 | Very low if any |
| 2 | > 2, ≤ 5 | ≤ 5 | 1.9 | Low | 4.3 | Low |
| 3a | > 5, ≤ 10 | ≤ 5 | 3.6 | Low | 24 | Intermediate |
| **3b** | **> 10** | **≤ 5** | 12 | Intermediate | 52 | High |
| 4 | ≤ 2 | > 5 | 0 | Low* | 50 | High* |
| 5 | > 2, ≤ 5 | > 5 | 16 | Intermediate | 73 | High |
| 6a | > 5, ≤ 10 | > 5 | 55 | High | 85 | High |
| 6b | > 10 | > 5 | 86 | High | 90 | High |

*Denotes tumor categories with very small numbers of cases insufficient for prediction of malignant potential.
HFPs = High-power fields

Miettinen M, Lasota J. *Semin Diagn Pathol*. 2006;23:70-83.

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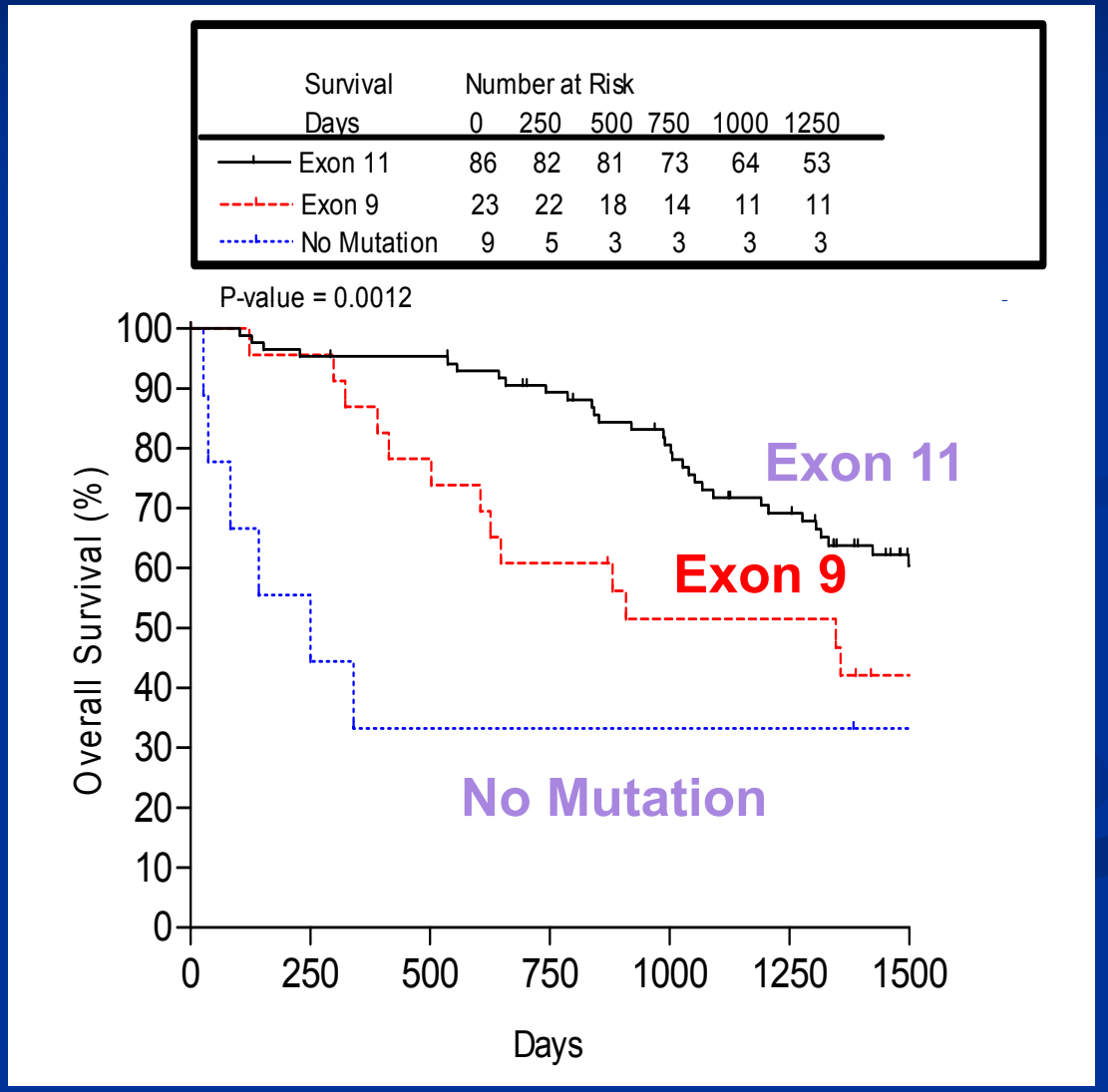
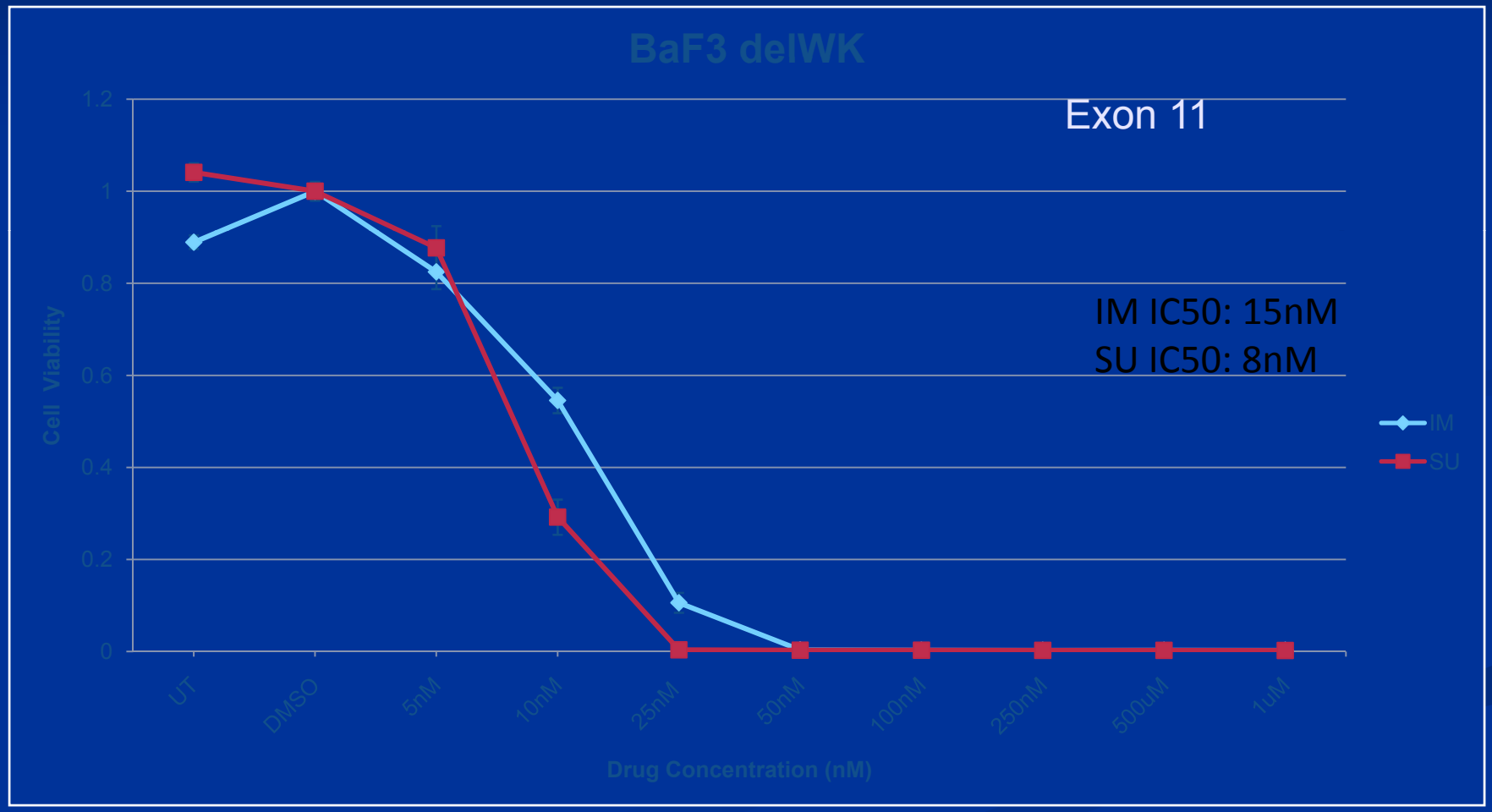
# GIST

- **Heterogeneous Disease**
- Predictive Factors
  - Response to Therapy
    - Presence of activating mutation – KIT, PDGFR
    - Location of activating mutation – KIT exon 11, exon 9, others

# Patients with metastatic GIST have different clinical outcomes based on tumor mutational status when treated with imatinib



# In the lab, there are different sensitivities to TKIs based on the location of the KIT mutation in GIST




Stephen Swank, Lab of Jonathan Fletcher, MD DFCI/BWH

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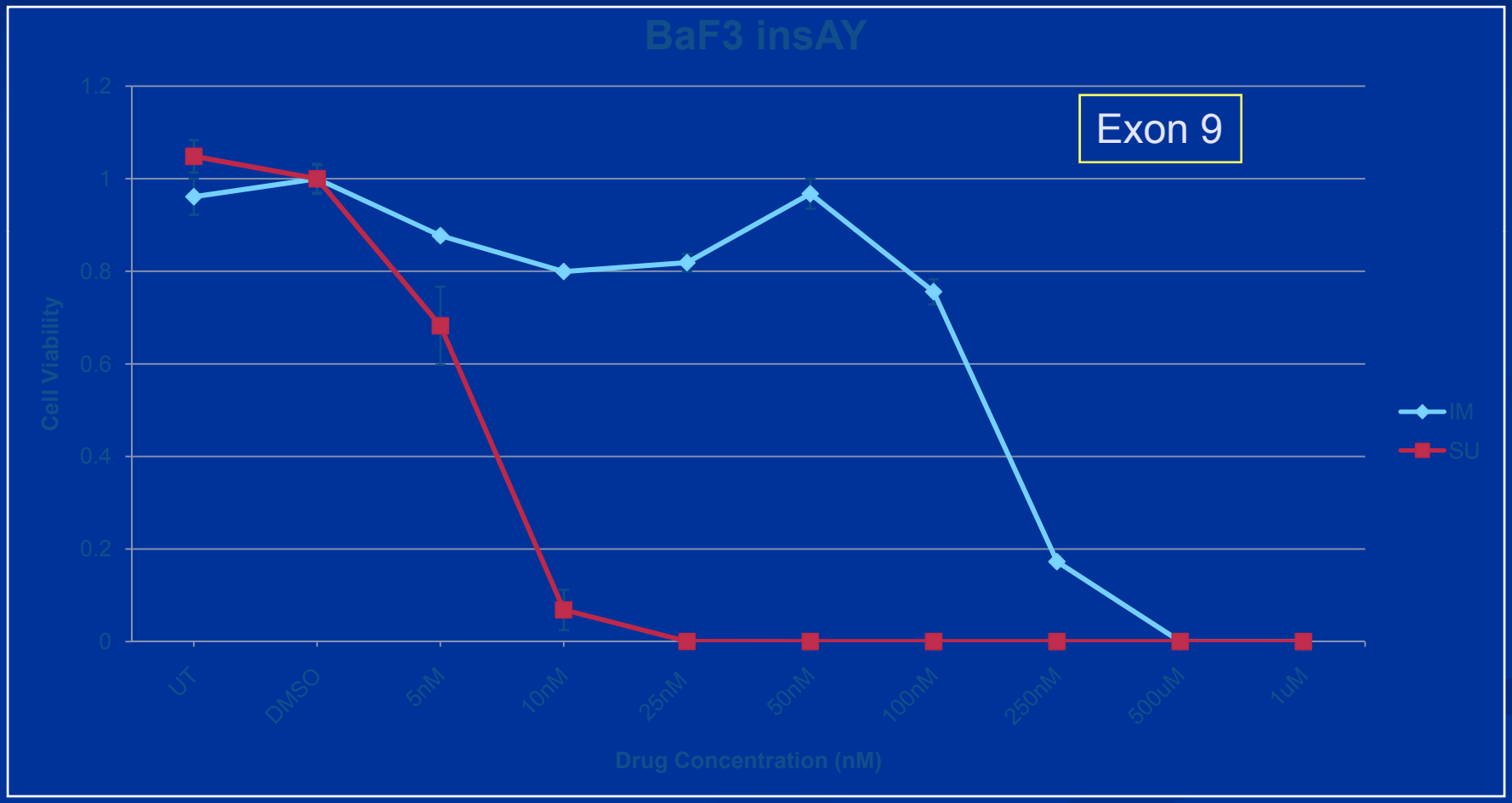


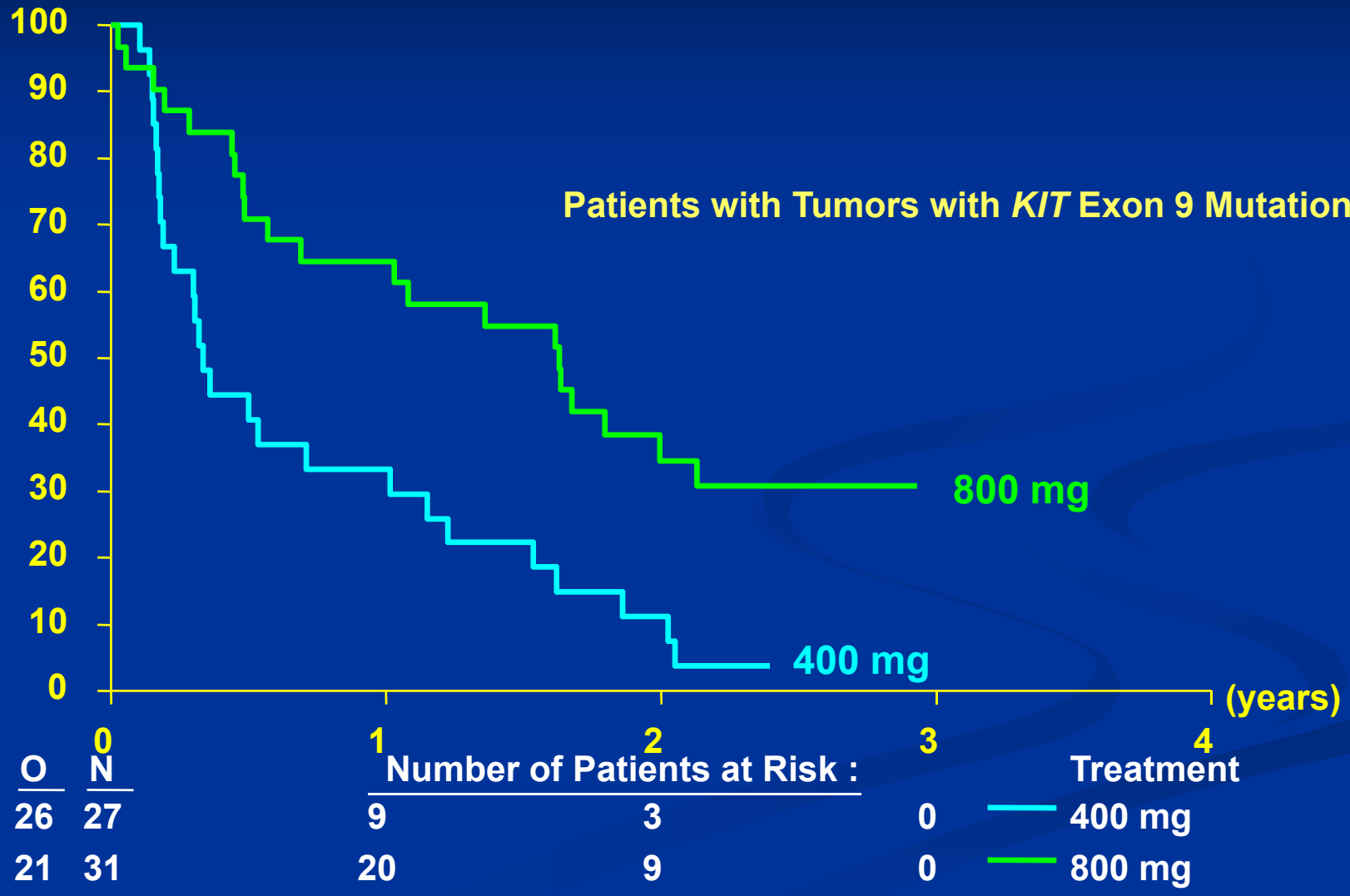

Stephen Swank, Lab of Jonathan Fletcher, MD DFCI/BWH

# Can dose overcome some of this difference in sensitivity?

- In the lab, perhaps higher exposure of IM is needed to control cells which harbor exon 9 mutations compared those which harbor to exon 11 mutations

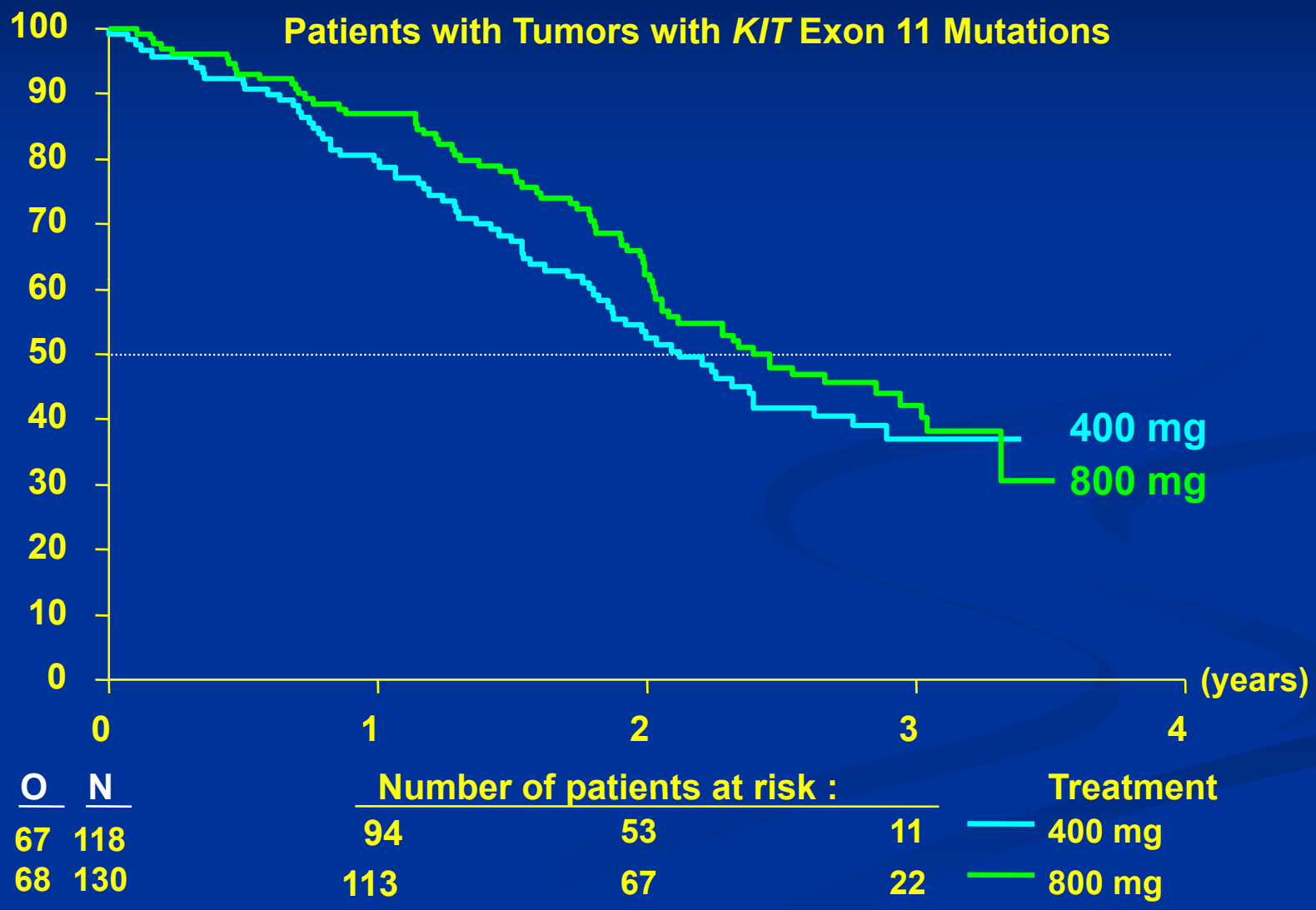
- Does this correlate clinically?

# Higher dose imatinib may provide benefit to specific molecular subtypes of GIST – exon 9




Debiec-Rychter M, et al. *Eur J Cancer*. 2006;42:1093-1103.

# But not to others……



# What does this have to do with imatinib blood levels?

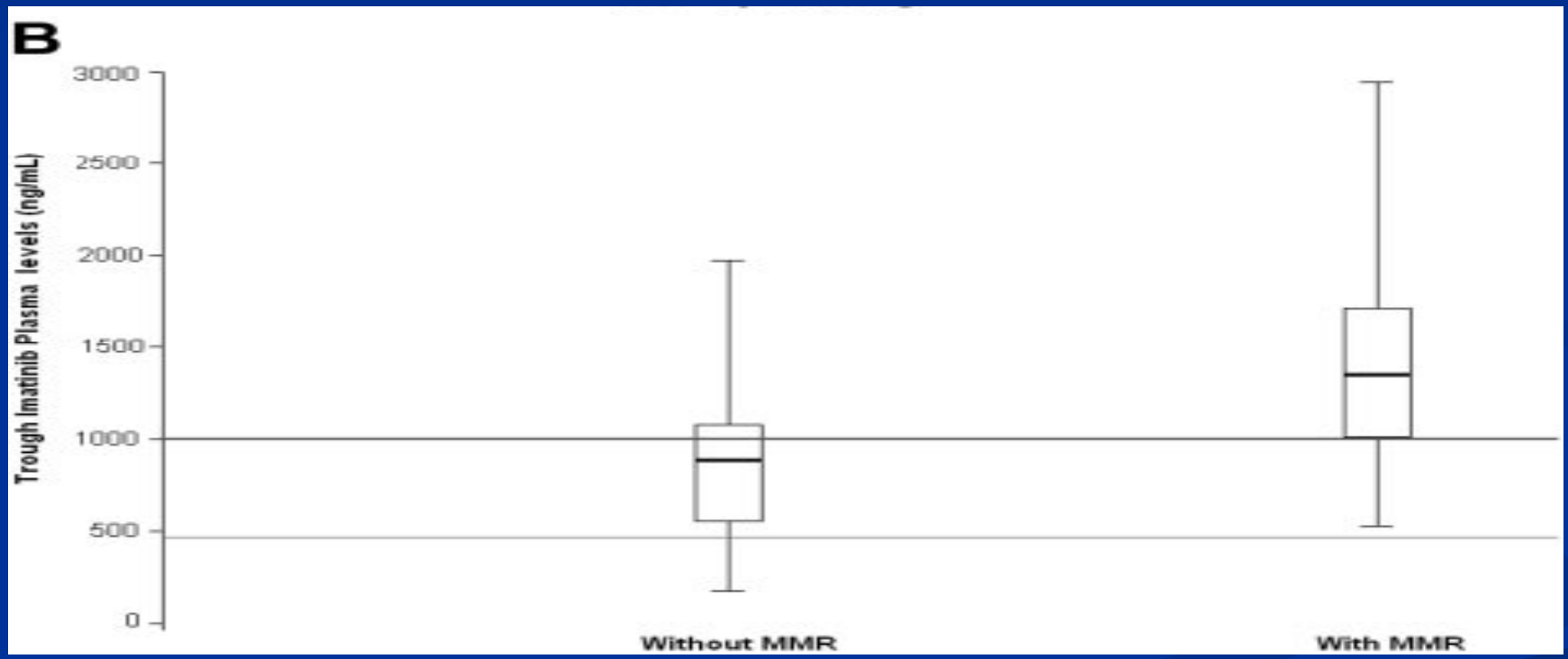
- There are may variables which may affect outcome
  - Patient characteristics: pediatric, adult
  - Tumor characterisitics: size, extent of disease, mutational status
  - Treatment characteristics: dose of IM
- In this wide array of factors how much does IM blood level play a role in the outcome of patients with GIST? Is the impact independent of dose?

# Imatinib Blood Levels

- Imatinib high oral bioavailability in humans
- Imatinib pK extensively studied in early Phase I/II in imatinib in both CML and GIST
- Excellent correlation between IM Cmin (trough level), Cmax (peak level) and AUC (exposure)

# What is the correlation of IM blood level to outcome in CML?

# Mean IM Trough Levels were higher for patients who achieved Major Molecular Response in CML- independent of dose (400mg vs 600mg)

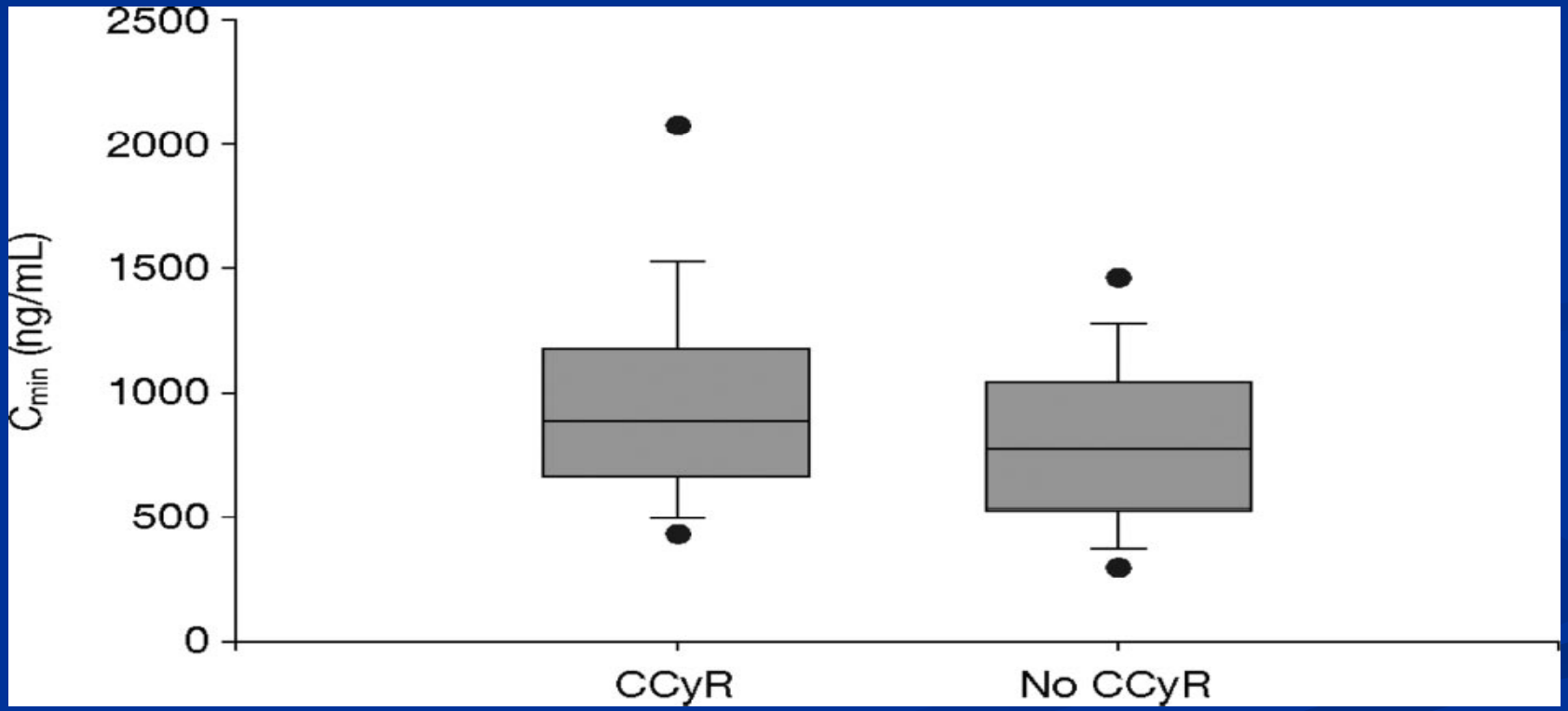



N=68

Comparison of mean IM C min p=0.03

Picard et al. Blood. 2007 109: 3496-3499

# Mean IM trough levels were higher for patients who responded to imatinib therapy – all patients treated at the same dose ( 400mg/day)



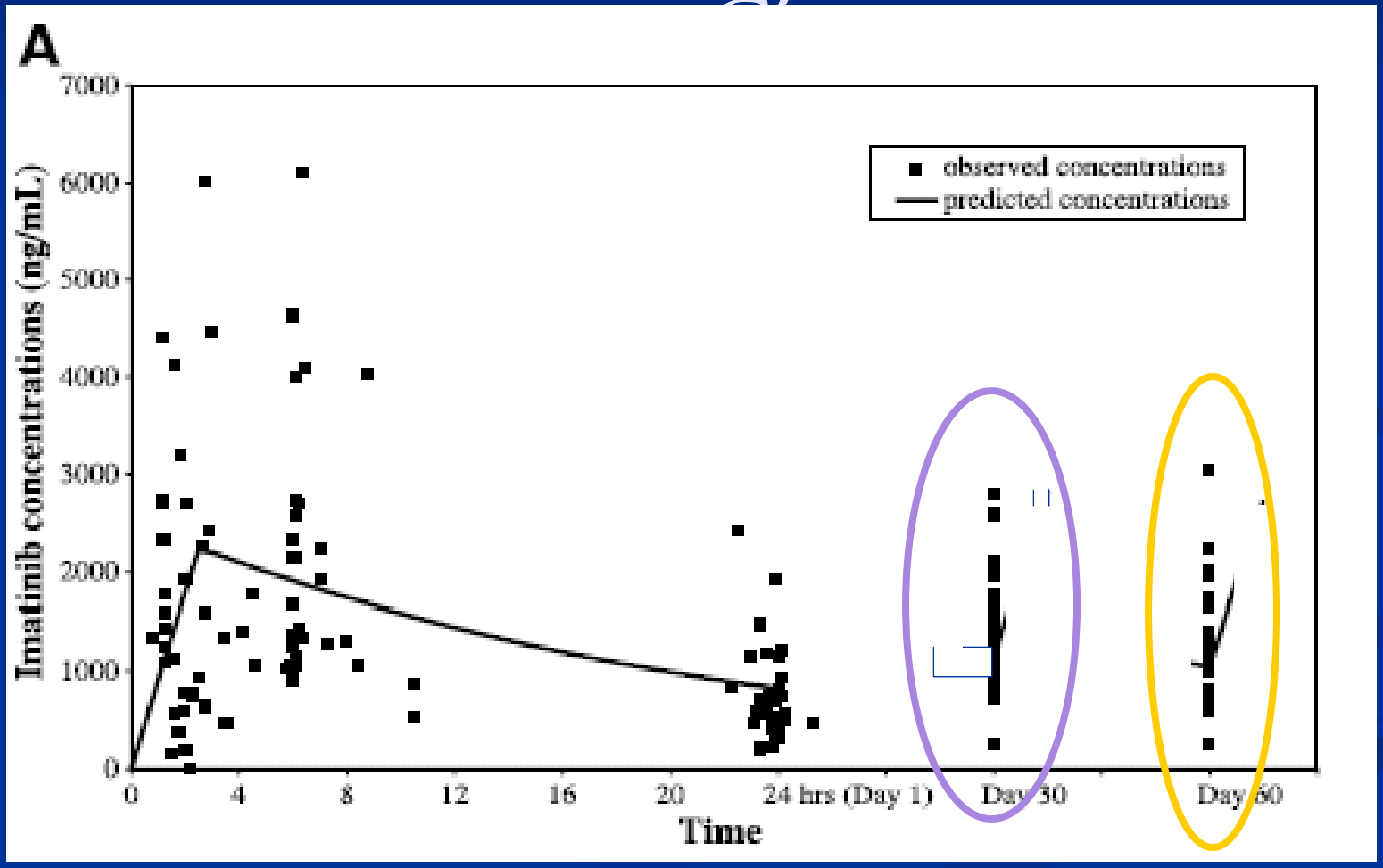

N=351
Imatinib 400mg per day

Comparison of mean IM C min p=0.01

Larson et al. Blood. 2008 111: 4022-4028

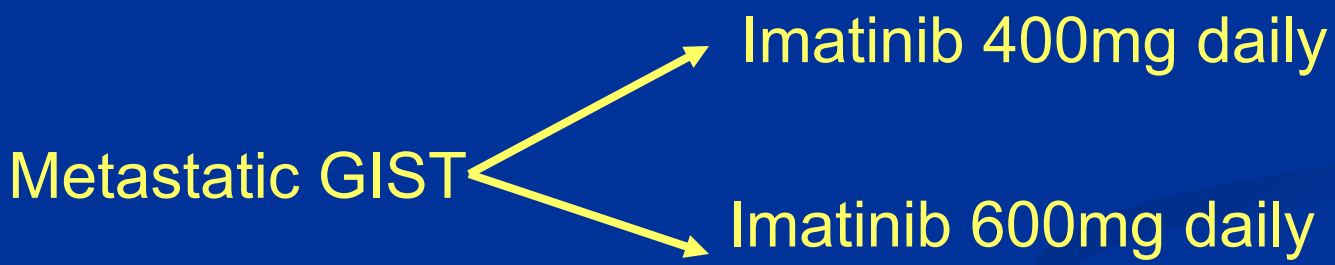
# What do we know about IM Blood Levels in GIST

# Significant inter-patient variability of IM levels in GIST patient at 400mg/d




Delbaldo C. et al. Clinical Cancer Research Vol. 12, 6073-6078, October 15, 2006.

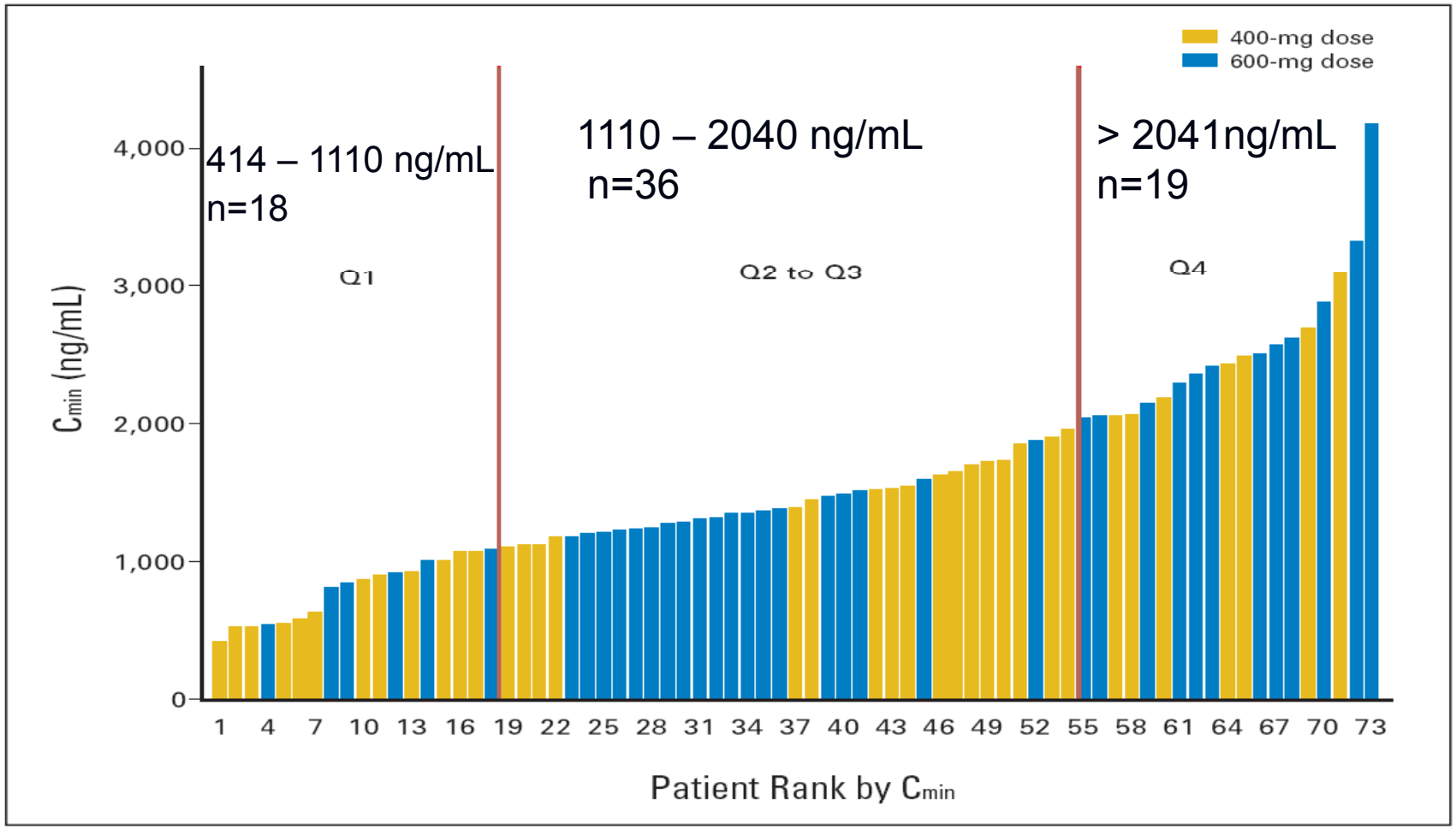
# D29 IM trough Levels were obtained in the Randomized Phase II trial in GIST – B2222




**Imatinib trough levels (Cmin) drawn at steady state (d29)**

**Patients followed for Response (WHO), PFS, OS**

# Wide Distribution of IM exposure without clear correlation with dose




Demetri et al. JCO 2009

# Median Imatinib trough level did not correlate with Clinical Benefit in GIST

57 pts (78%) achieved PR, CR or SD

| | Median Cmin ng/mL | Range | 25% - 75% |
|---|---|---|---|
| N=57<br>PR,CR or SD | 1446 | 414-3336 | 1204 -2062 |
| N=16<br>PD or na | 1155 | 545-4182 | 1041 - 1562 |

P=0.25

Demetri et al. JCO 2009

# GIST Patients whose IM exposure was in the lowest Quartile had a shorter PFS

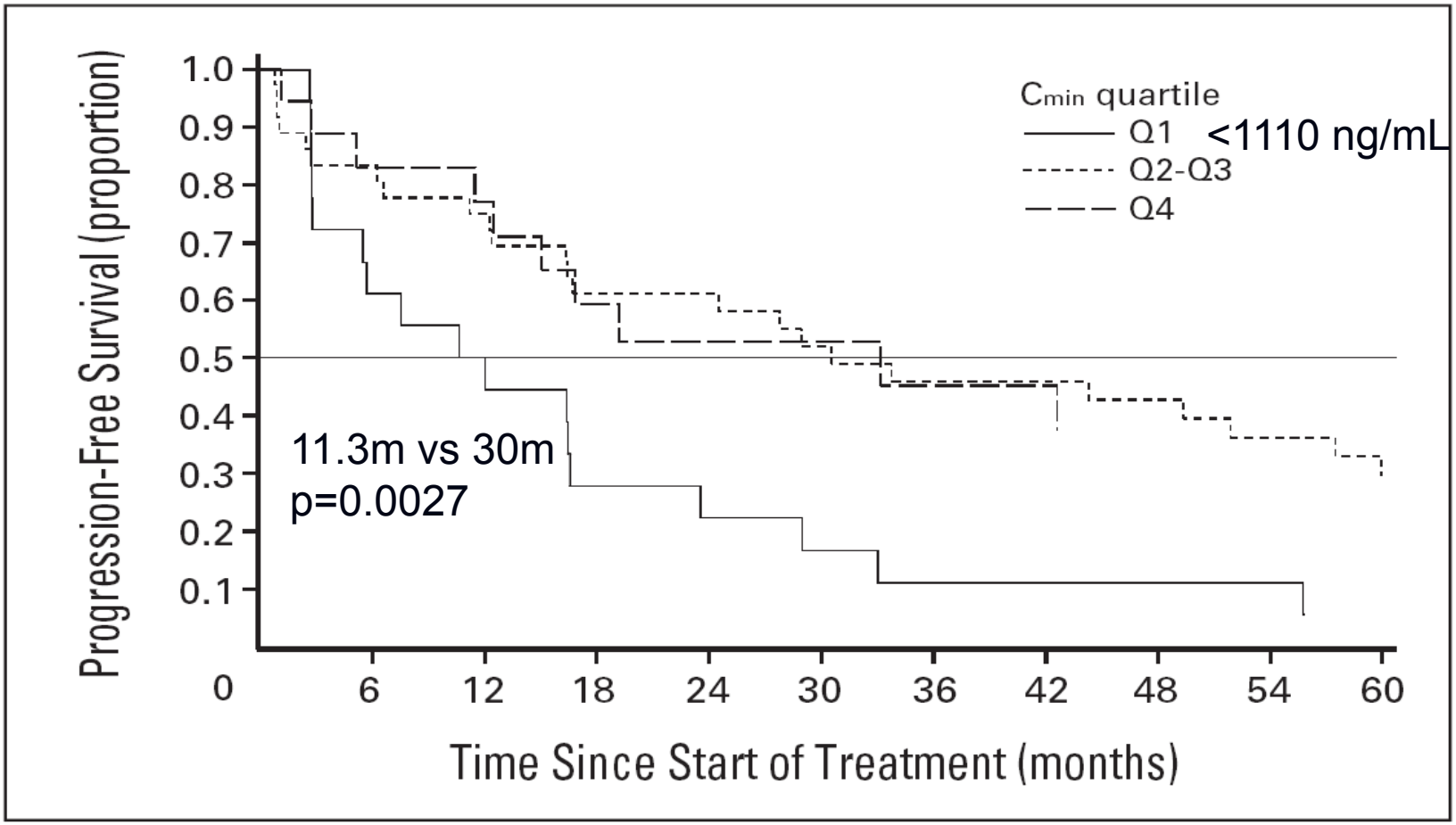



**Fig 3.** Time to progression by imatinib day 29 trough level ($C_{min}$) quartile (Q).

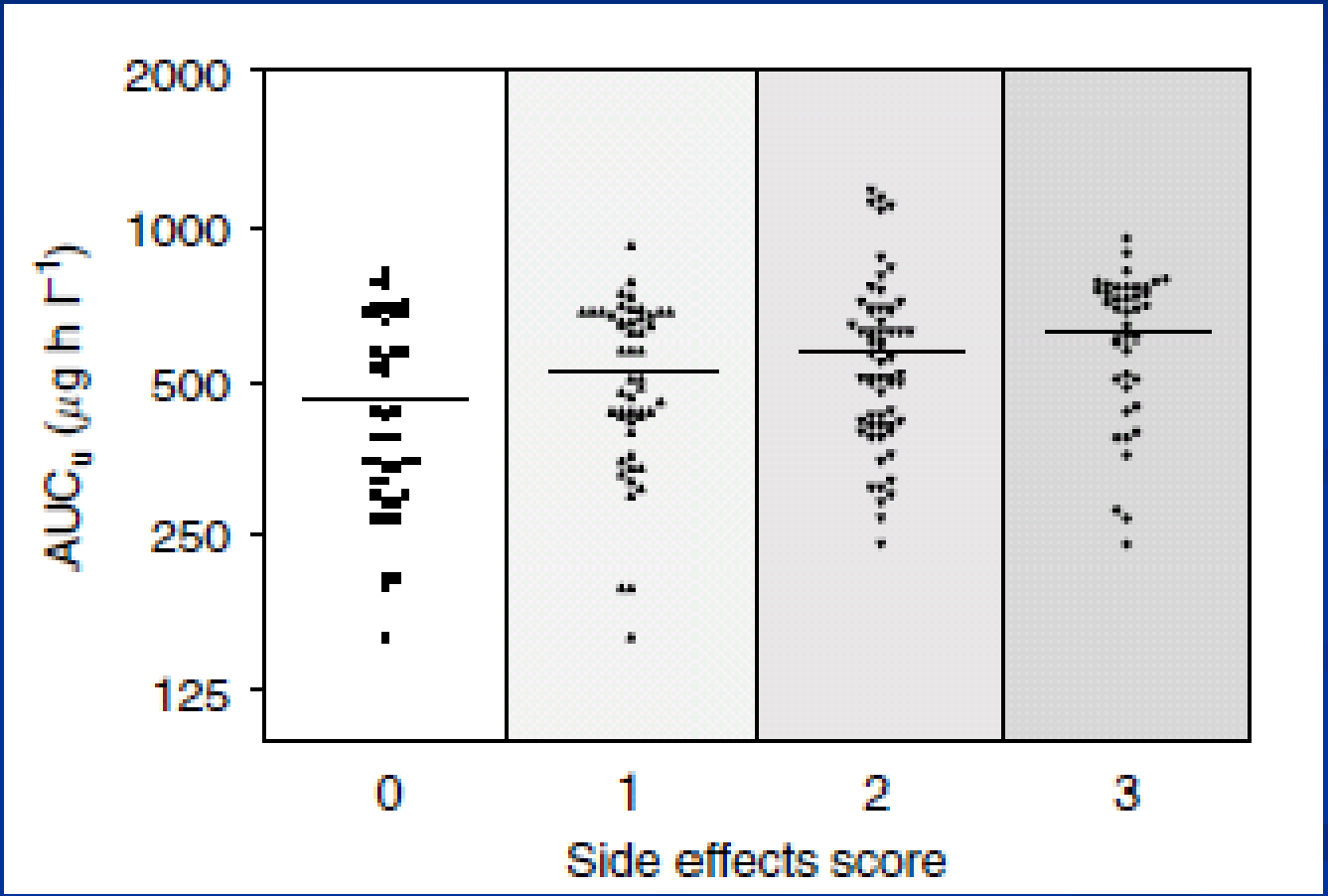
Demetri et al. JCO 2009

# Additional information…

- No apparent increase in reported grade 3/4 toxicity for patients in higher Quartiles
- Not enough data on molecular subtypes to draw definitive conclusions about relationship between genotype, drug level and response

Demetri et al. JCO 2009

# Higher exposure to imatinib may correlate with a greater number of side effects




Widmer et al. British Journal of Cancer (2008) 98, 1633 – 1640

# Conclusions

- Retrospective data suggests there may be a relationship between IM trough levels and progression free survival in patients with metastatic GIST
- IM trough level appears to be independent of dose (400mg vs 600mg) – however, not clear if also independent of dose for IM 800mg/d
- Other clinical and biologic variables also contribute to clinical outcome – the relative impact of IM trough levels is not yet known

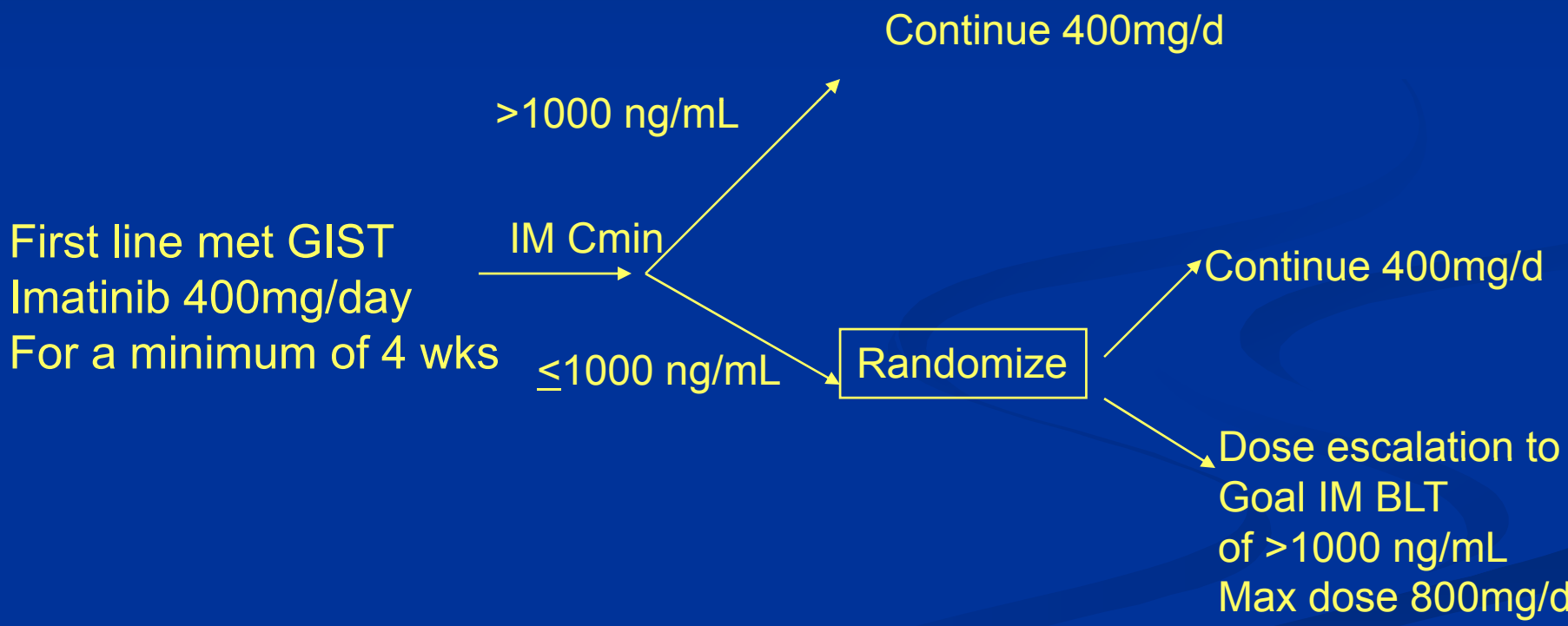
# Conclusions (con't.)

- "Optimal level" of drug exposure has yet to be prospectively confirmed for GIST
- Based on our understanding of GIST, there may be different "optimal levels" depending on the characteristics of the patient and the tumor
- Are drug blood levels relevant to outcomes for other TKIs??

# Conclusions

- Because of these ongoing questions prospective trials are needed to determine the optimal role of TKI blood level testing, if any, to improve the outcome of patients with GIST

# Simplified Tentative Schema



# Thank you