HELIOS Kliniken
Jeder Moment ist Medizin

The GIST model: Medical therapy

The clinical challenge of secondary resistance

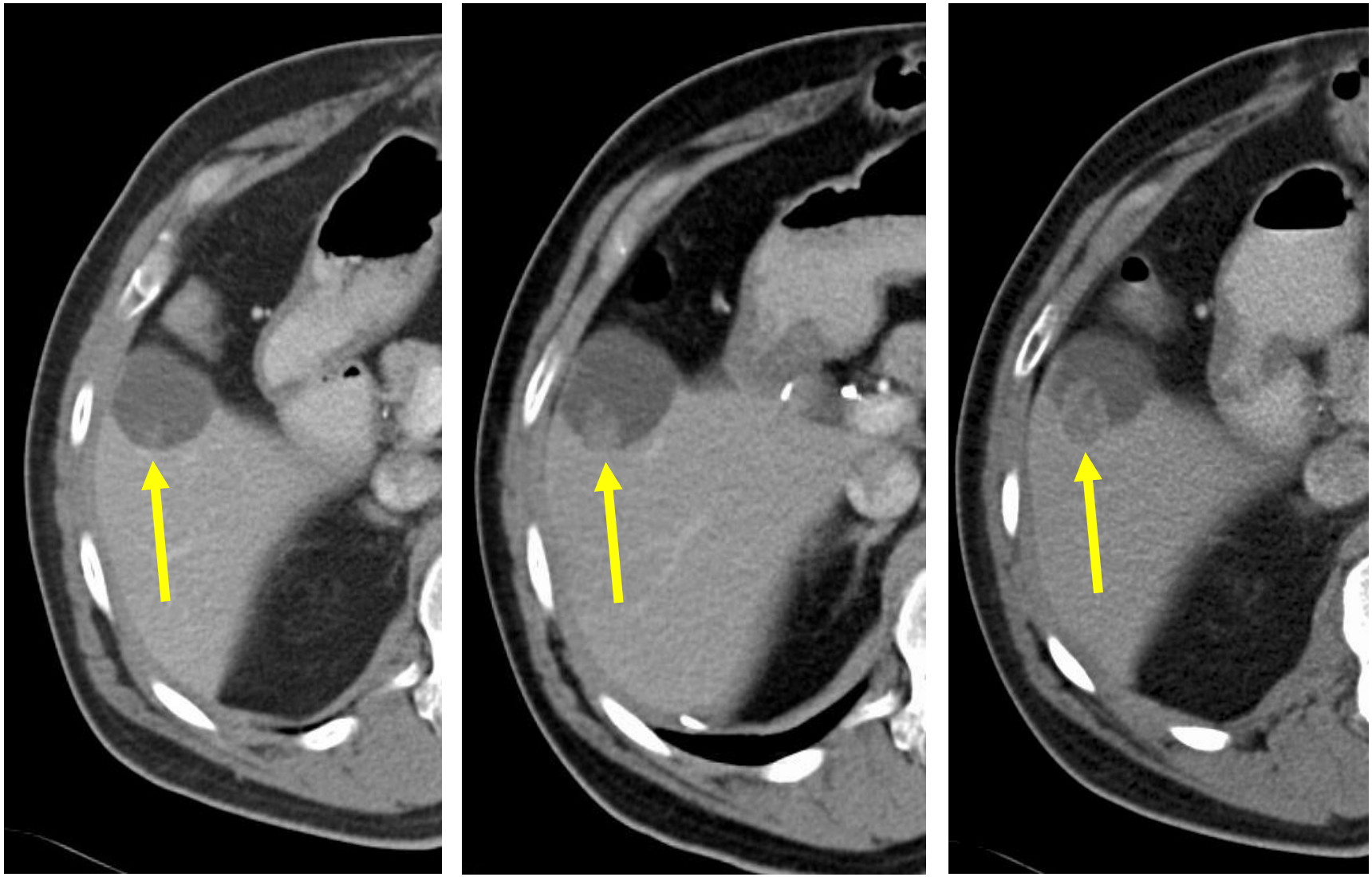
Peter Reichardt

HELIOS Klinikum Berlin-Buch / Department of Interdisciplinary Oncology /
Cancer Center Berlin-Buch / Sarcoma Center Berlin-Brandenburg

The challenge of secondary resistance

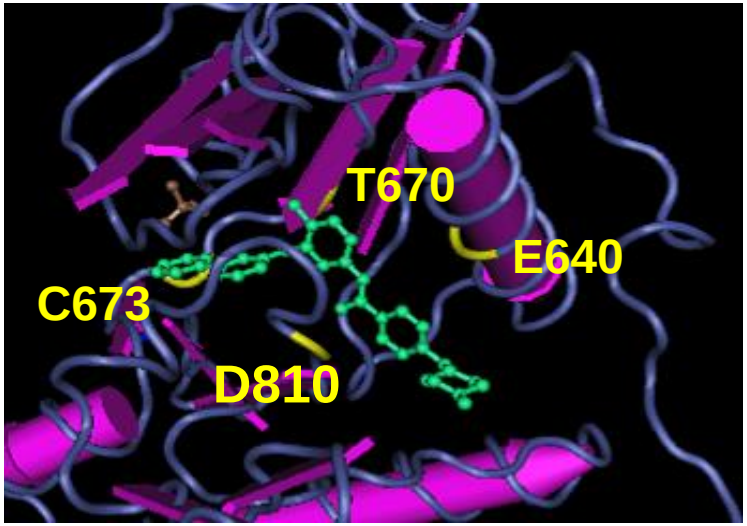
- Secondary resistance due to
  - Secondary resistance mutations
  - Insufficient drug levels
  - Target overexpression
  - Loss of target
  - Alternate pathway activation
  - Etc.

CT scan: focal progression

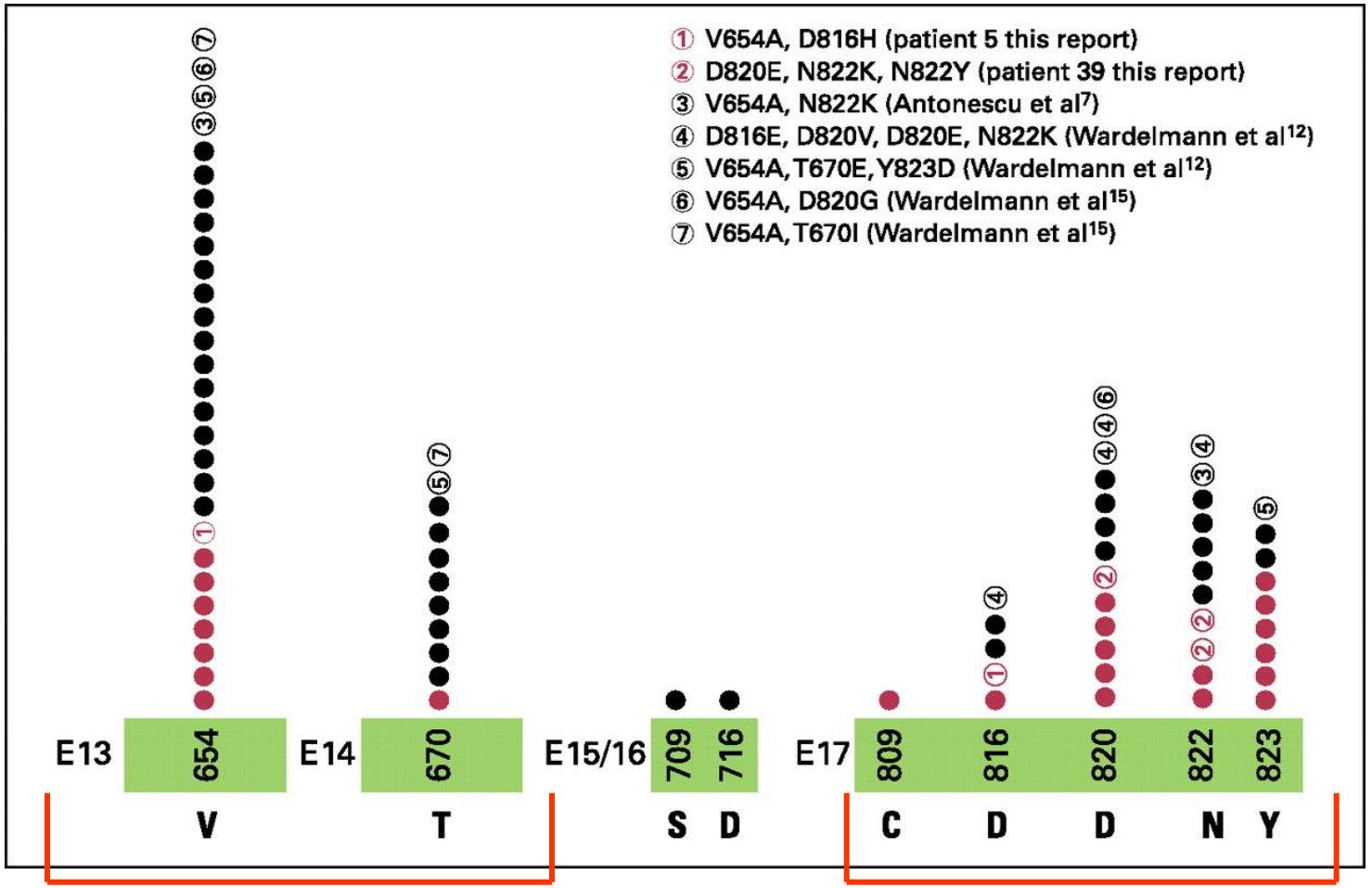


Secondary resistance in GIST

- Secondary mutations in target gene
  - Mutation of gatekeeper residue (ATP binding site)
  - Mutation in the p-loop and activation loop leading to stabilization of the activation loop in the active conformation



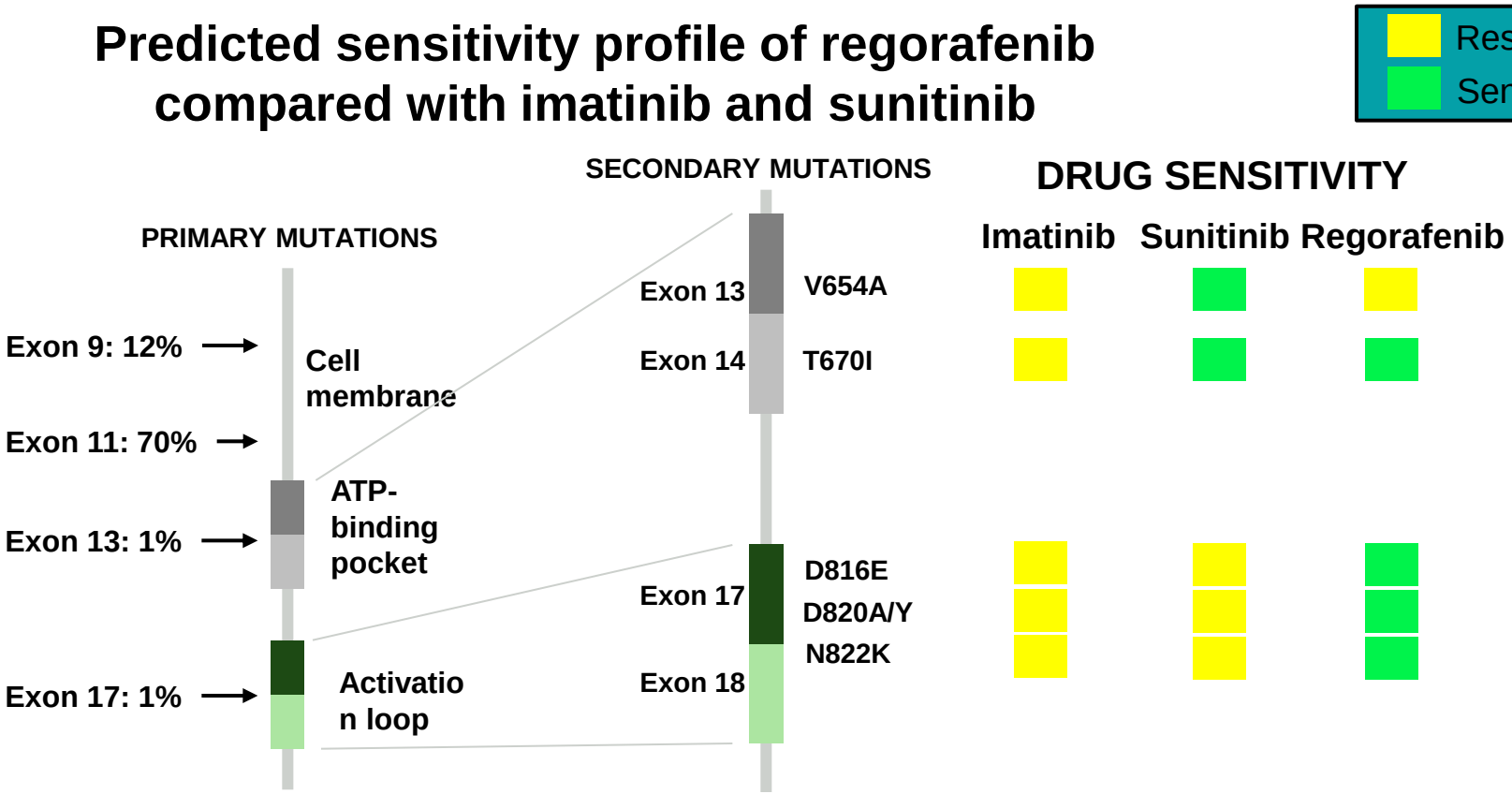
Secondary KIT mutations in imatinib-resistant GIST



Heinrich et al., J Clin Oncol 24:4764-4774, 2006

Drug Activity in Resistant GIST Cells

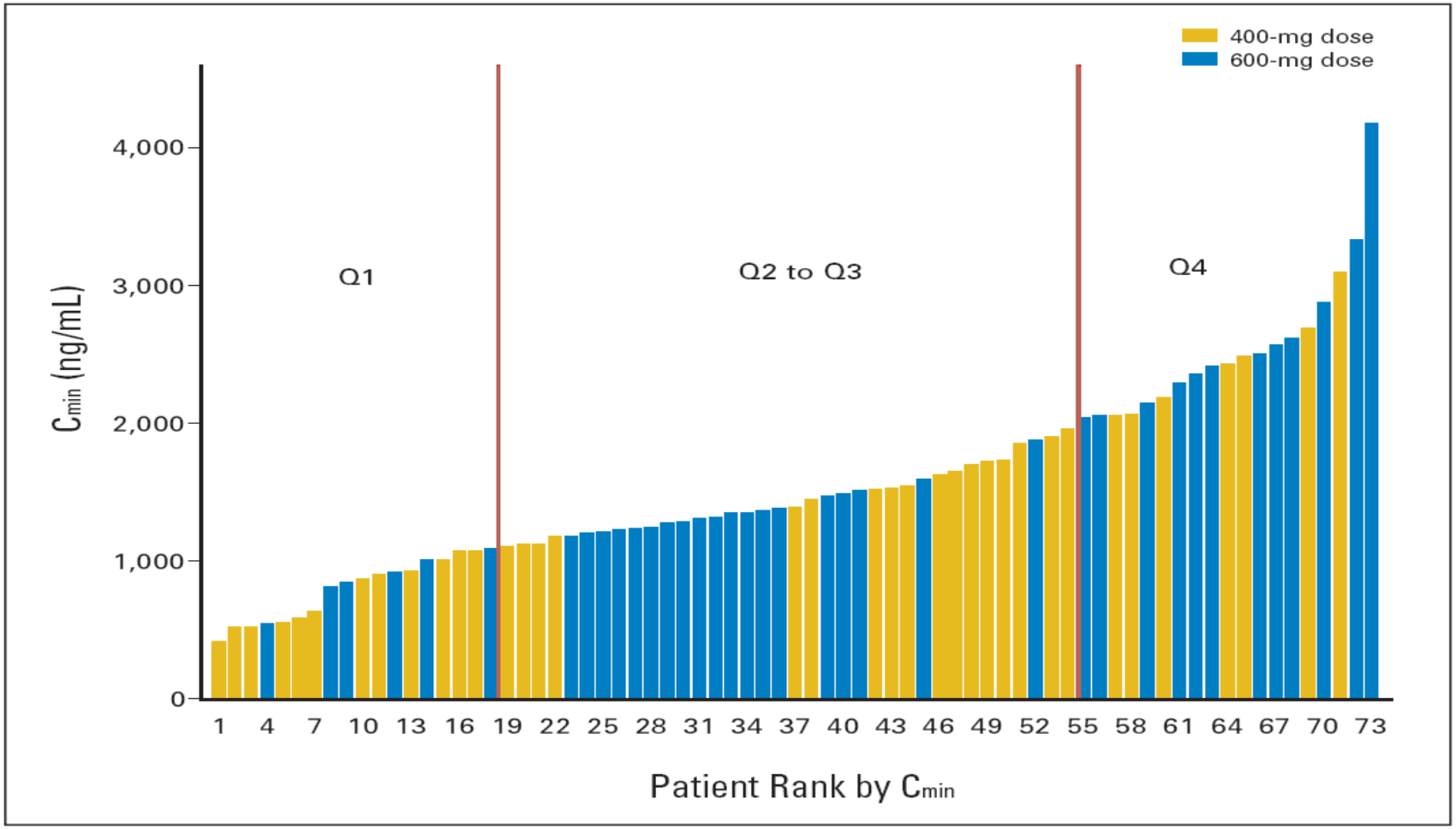
Predicted sensitivity profile of regorafenib compared with imatinib and sunitinib



Regorafenib has activity in GIST cells with KIT *primary* exon 11 mutations and secondary KIT exon 17 imatinib-resistant mutations,
but is less active against KIT exon 13 (V654A) mutations compared to sunitinib

Serrano-García C, et al. ASCO 2013. Abstract 10510.

Wide Distribution of Imatinib Exposure without Reliable Correlation with Dose



Demetri et al. J Clin Oncol. 2009 Jul 1;27(19):3141-7

GIST patients with lowest imatinib blood levels had higher risk for rapid disease progression

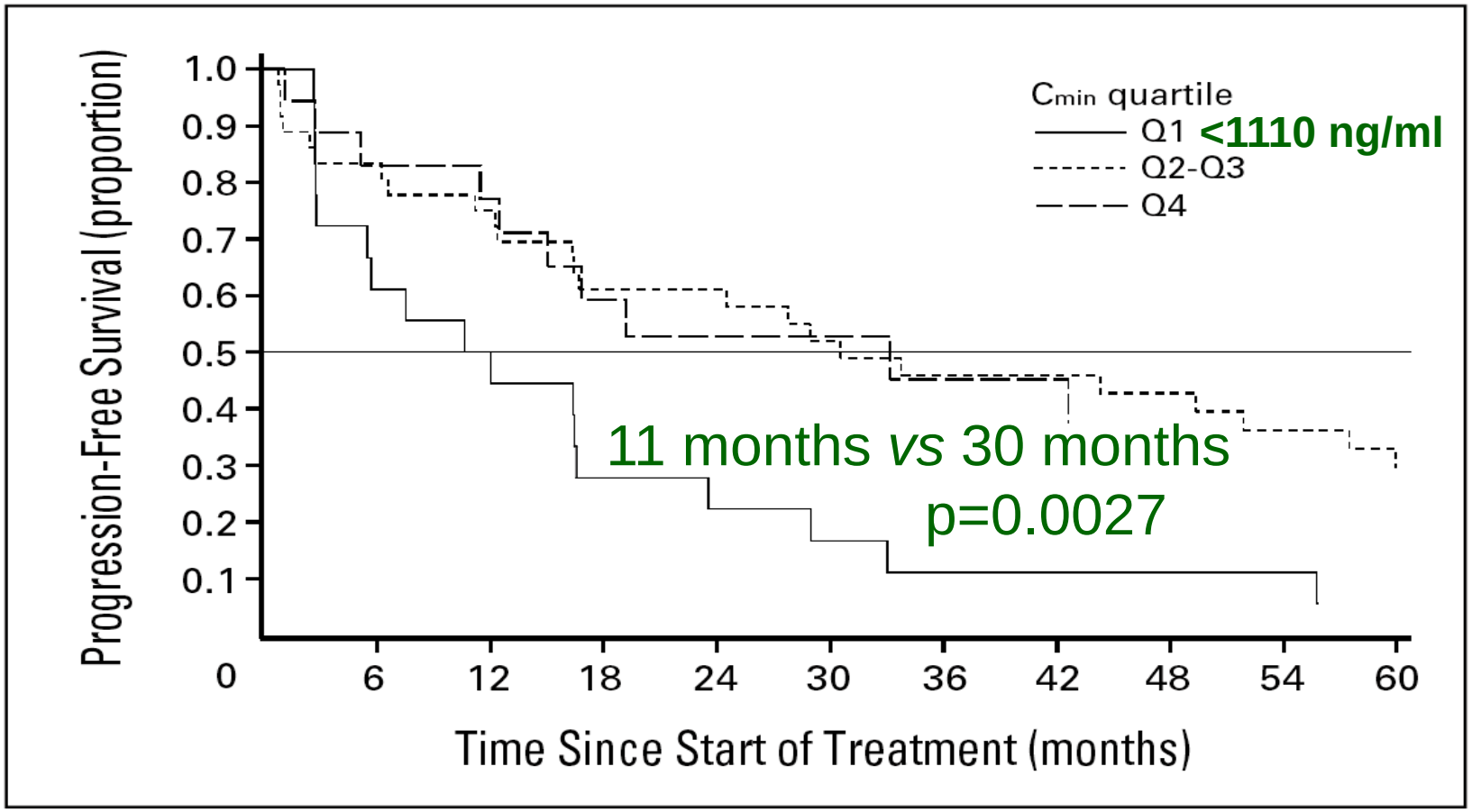


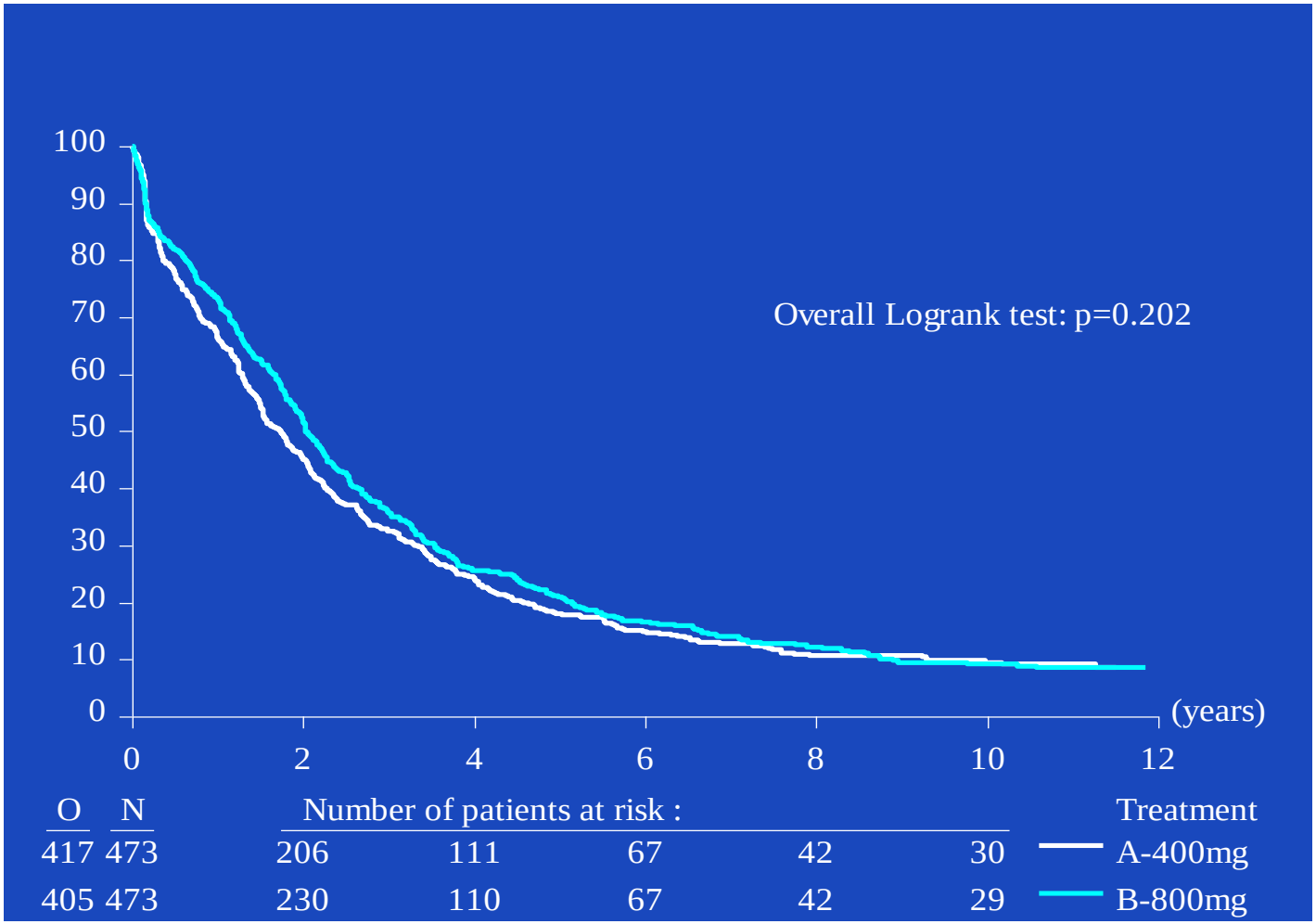
Fig 3. Time to progression by imatinib day 29 trough level (C_{min}) quartile (Q).

Demetri et al. J Clin Oncol. 2009 Jul 1;27(19):3141-7

The challenge of secondary resistance

- Secondary resistance due to
  - Secondary resistance mutations
  - Insufficient drug levels
  - Target overexpression
- Secondary resistance over time

EORTC 62005: PFS

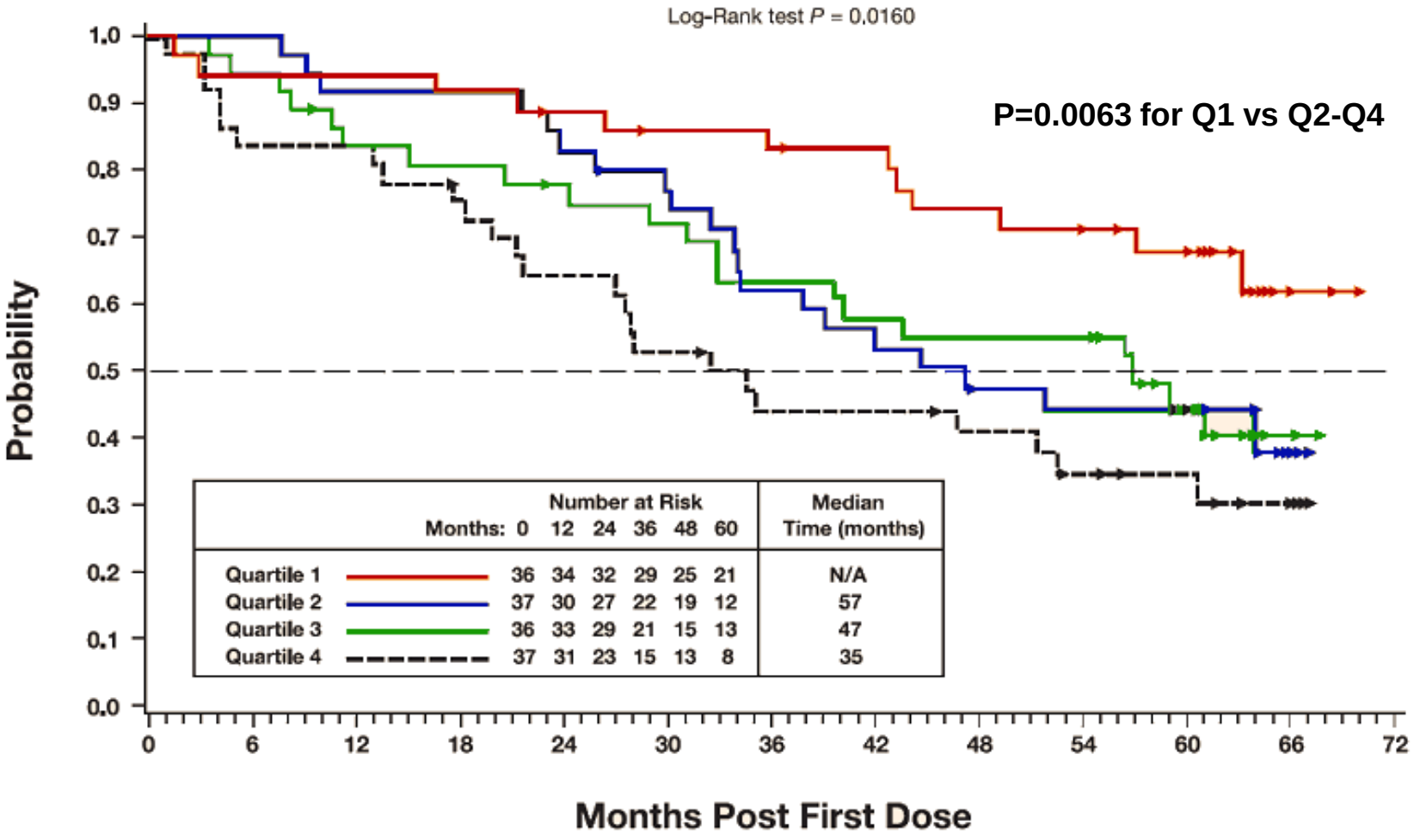


Casali PG et al., CTOS 2013

The challenge of secondary resistance

- Secondary resistance due to
  - Secondary resistance mutations
  - Insufficient drug levels
  - Target overexpression
- Secondary resistance over time
- Secondary resistance and tumor bulk

Overall Survival by Tumor Bulk Quartile – B2222



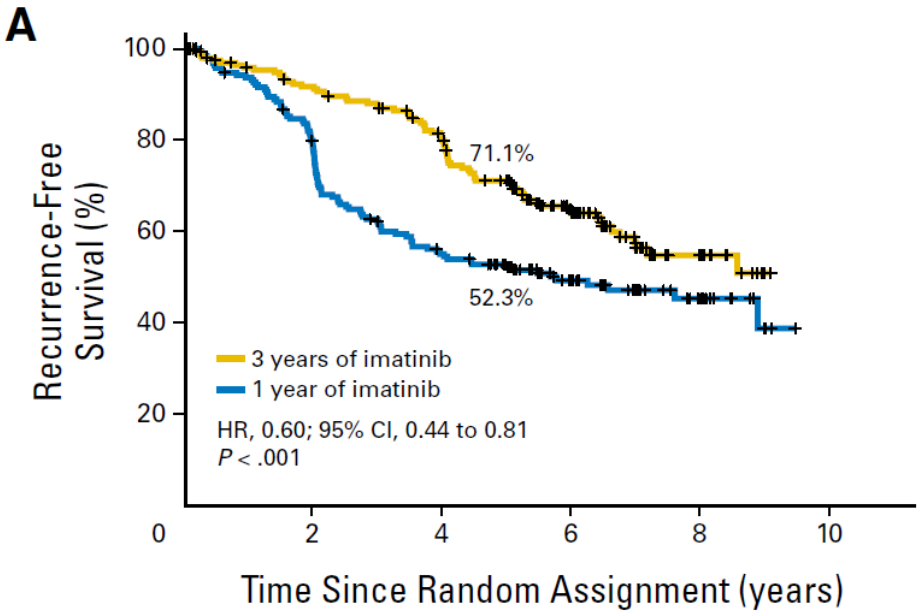
VOLUME 34 · NUMBER 3 · JANUARY 20, 2016

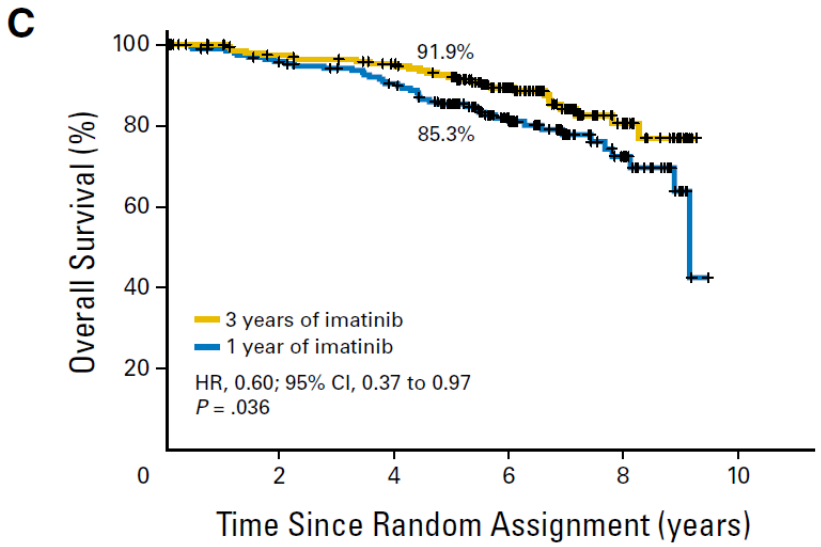
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Adjuvant Imatinib for High-Risk GI Stromal Tumor: Analysis of a Randomized Trial

Heikki Joensuu, Mikael Eriksson, Kirsten Sundby Hall, Annette Reichardt, Jörg T. Hartmann, Daniel Pink, Giuliano Ramadori, Peter Hohenberger, Salah-Eddin Al-Batran, Marcus Schlemmer, Sebastian Bauer, Eva Wardelmann, Bengt Nilsson, Harri Sihto, Petri Bono, Raija Kallio, Jouni Junnila, Thor Alvegård, and Peter Reichardt





The challenge of secondary resistance

- Secondary resistance due to
  - Secondary resistance mutations
  - Insufficient drug levels
  - Target overexpression
- Secondary resistance over time
- Secondary resistance and tumor bulk
- Heterogeneity of secondary resistance

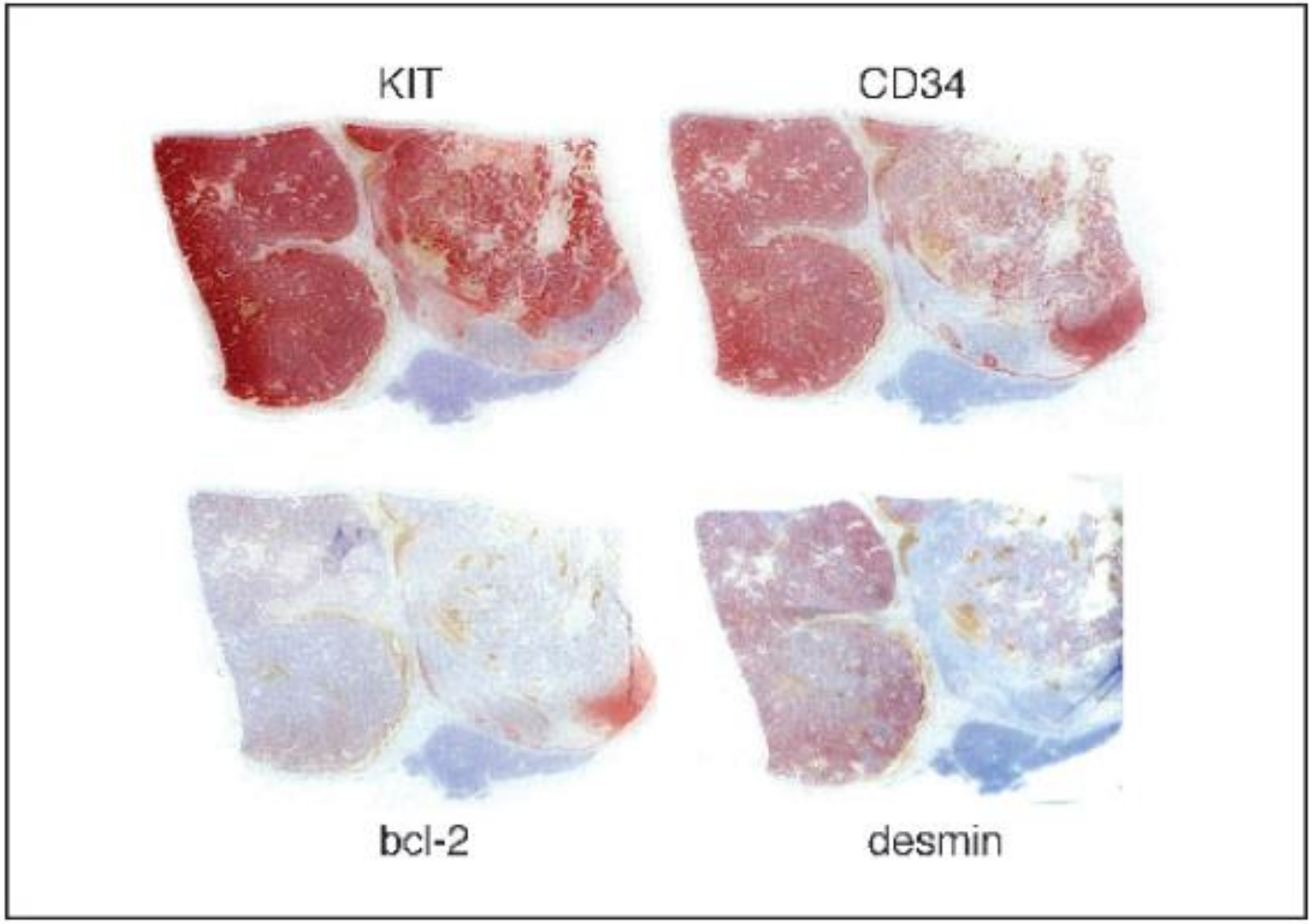


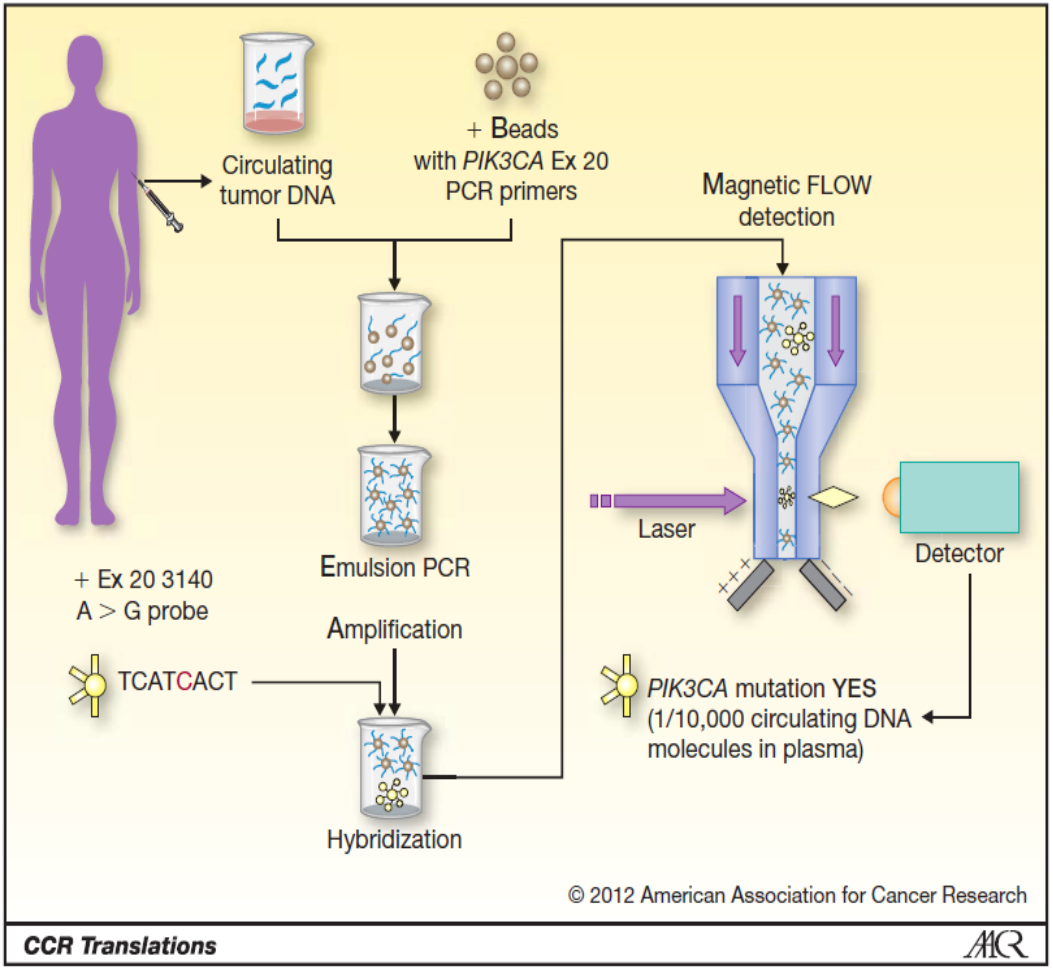
Fig. 1. Differential immunohistochemical expression patterns for KIT receptor, CD34, bcl-2, and desmin in a progressive peritoneal GIST lesion (case no. 27) with two different acquired KIT mutations in exon 13 (V654A) and exon 17 (Y823D). Different regions were microdissected and mutational analysis was done separately.

Wardelmann et al., Clin Cancer Res 2006

Limitations of Tumor Biopsies – and a Possible New Solution

- Tumor (“tissue”) biopsies may be problematic, because tumors are heterogeneous and only certain tumors (or even only certain parts of any given tumor) are sampled
- Tumor biopsies are invasive in patients with most solid tumors which are deep in internal organs
- Tumor cells are constantly dying and releasing DNA into the bloodstream
- A sophisticated assay of blood may be able to document a comprehensive picture of all the mutations in any given patient
- These “Liquid Biopsies” to assay mutations in circulating free DNA provide a potential alternative that may circumvent the limitations and risks of tumor-based DNA analysis from solid tissue biopsies

Mutational Analysis of Circulating DNA in Plasma via BEAMing Technology



- **B**eads, **E**mulsions, **A**mplification, **M**agnetics (done with *Inostics*):
  - *<u>laboratory steps</u>: pre-amplification, emulsion PCR, hybridization, flow cytometry*
  - *detection of tumor-associated mutations using circulating free DNA from **plasma***
  - *<u>Exquisitely sensitive detection</u>: 1 mutant allele in 10,000 normal alleles*
  - *Ideal concept to detect emergence of multiple gene mutations which can make GIST resistant to targeted therapies*

Richardson and Iglehart, Clinical Cancer Research, May 2012

BEAMing of GRID plasma DNA: results

- Data obtained from 163 (82%) GRID patients
- *KIT* mutations (primary and secondary) detected in 58% of samples
- Primary *KIT* mutations detected in exon 9 (15%) and exon 11 (12%)
- Secondary *KIT* mutations detected in 47% of samples and of these:
  - 25% were exon 13/14 mutations
  - 64% were exon 17/18 mutations
  - 12% were both
  - Most mutations (76%) in activation loop (imatinib/sunitinib resistance)
- 40% of samples with secondary *KIT* mutations had additional mutations
- Other mutations detected:
  - 1% of samples with *PDGFR* mutation; *KRAS* mutation in 1 of 2 samples tested; no *BRAF* mutations in any samples

The challenge of secondary resistance

- Secondary resistance due to
  - Secondary resistance mutations
  - Insufficient drug levels
  - Target overexpression
- Secondary resistance over time
- Secondary resistance and tumor bulk
- Heterogeneity of secondary resistance
- Prevention of secondary resistance

Response to Imatinib Correlates with Surgical Result

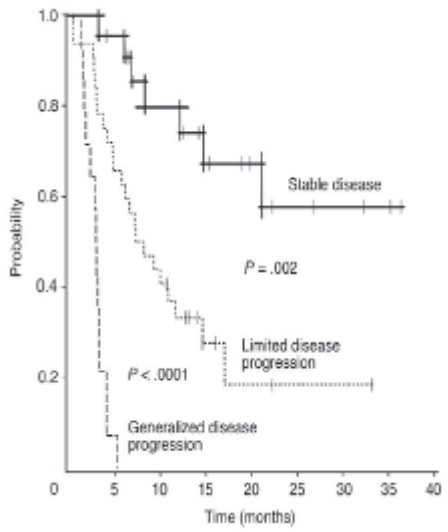
- Response to imatinib therapy at the time of surgery strongly correlated with surgical result (p<0.0001)

VOLUME 24 · NUMBER 15 · MAY 20 2006

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

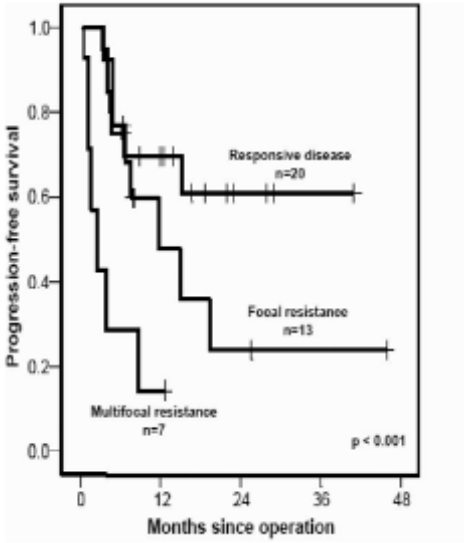
Surgical Management of Advanced Gastrointestinal Stromal Tumors After Treatment With Targeted Systemic Therapy Using Kinase Inhibitors

Chandrajit P. Raut, Matthew Posner, Jayesh Desai, Jeffrey A. Morgan, Suzanne George, David Zahrieh, Christopher D.M. Fletcher, George D. Demetri, and Monica M. Bertagnolli



Results of Tyrosine Kinase Inhibitor Therapy Followed by Surgical Resection for Metastatic Gastrointestinal Stromal Tumor

Ronald P. DeMatteo, MD, Robert G. Maki, MD, PhD,§ Samuel Si* (*Ann Surg* 2007;245: 347–352) *, † Murray F. Brennan, MD,* and Cristina R. Antonescu, MD‡*



The challenge of secondary resistance

- Use of alternating drugs

ClinicalTrials.gov

A service of the U.S. National Institutes of Health

Trial record **5 of 14** for: GIST regorafenib

Previous Study

A Randomised Trial of Imatinib Alternating Wi
Treatment of Advanced Gastrointestinal Stron

This study is currently recruiting participants. (see Cont

Verified December 2015 by Australasian Gastro-Intestinal Trials G

Sponsor:
Australasian Gastro-Intestinal Trials Group

Collaborators:
European Organisation for Research and Treatment of Canc
Scandinavian Sarcoma Group

Information provided by (Responsible Party):
Australasian Gastro-Intestinal Trials Group

ClinicalTrials.gov

A service of the U.S. National Institutes of Health

Trial record **4 of 14** for: GIST regorafenib

Previous Study | Return to List | Next Study

Phase Ib Study of SUnitinib Alternating With REgorafenib in Patients With Metastatic and/or Unresectable GIST (SURE)

This study is currently recruiting participants. (see Contacts and Locations)

Verified November 2015 by Dana-Farber Cancer Institute

Sponsor:
Dana-Farber Cancer Institute

Collaborators:
Bayer
Pfizer

Information provided by (Responsible Party):
Suzanne George, MD, Dana-Farber Cancer Institute

ClinicalTrials.gov Identifier:
NCT02164240

First received: June 12, 2014
Last updated: November 23, 2015
Last verified: November 2015
History of Changes