Gastrointestinal Stromal Tumours

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Chair EORTC, Soft Tissue and Bone Sarcoma Group

Overview

- What is GIST
- How is it treated?
- What are the current developments?

Gastrointestinal Stromal Tumours (GISTs)

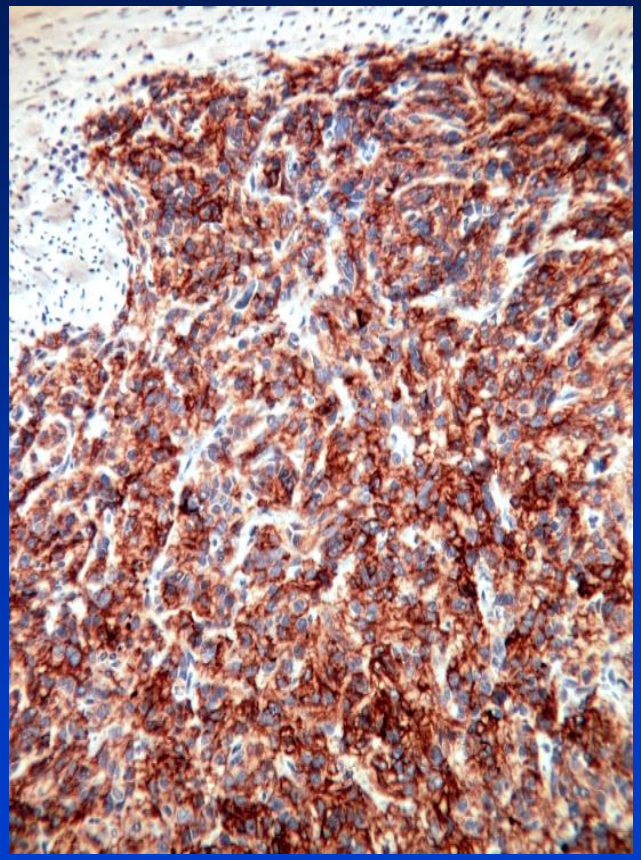
- Infrequent type of sarcoma, a tumour of mesenchymal (connective tissue) origin
  - 0.2% of gastrointestinal tumours
  - Incidence: 3000 to 5000 cases in Europe
- Similar male-to-female ratio
- Highest incidence in 5th to 7th decades of life
- Since 2000 recognized as a distinct clinical and histopathological entity

GISTs

- Originally classified as other tumours—leiomyoma, leiomyoblastoma, or leiomyosarcoma—because of their histological appearance
- Advances in modern molecular biology and immunohistochemistry have allowed GISTs to be distinguished reliably from these other histopathological subtypes of GI tumours

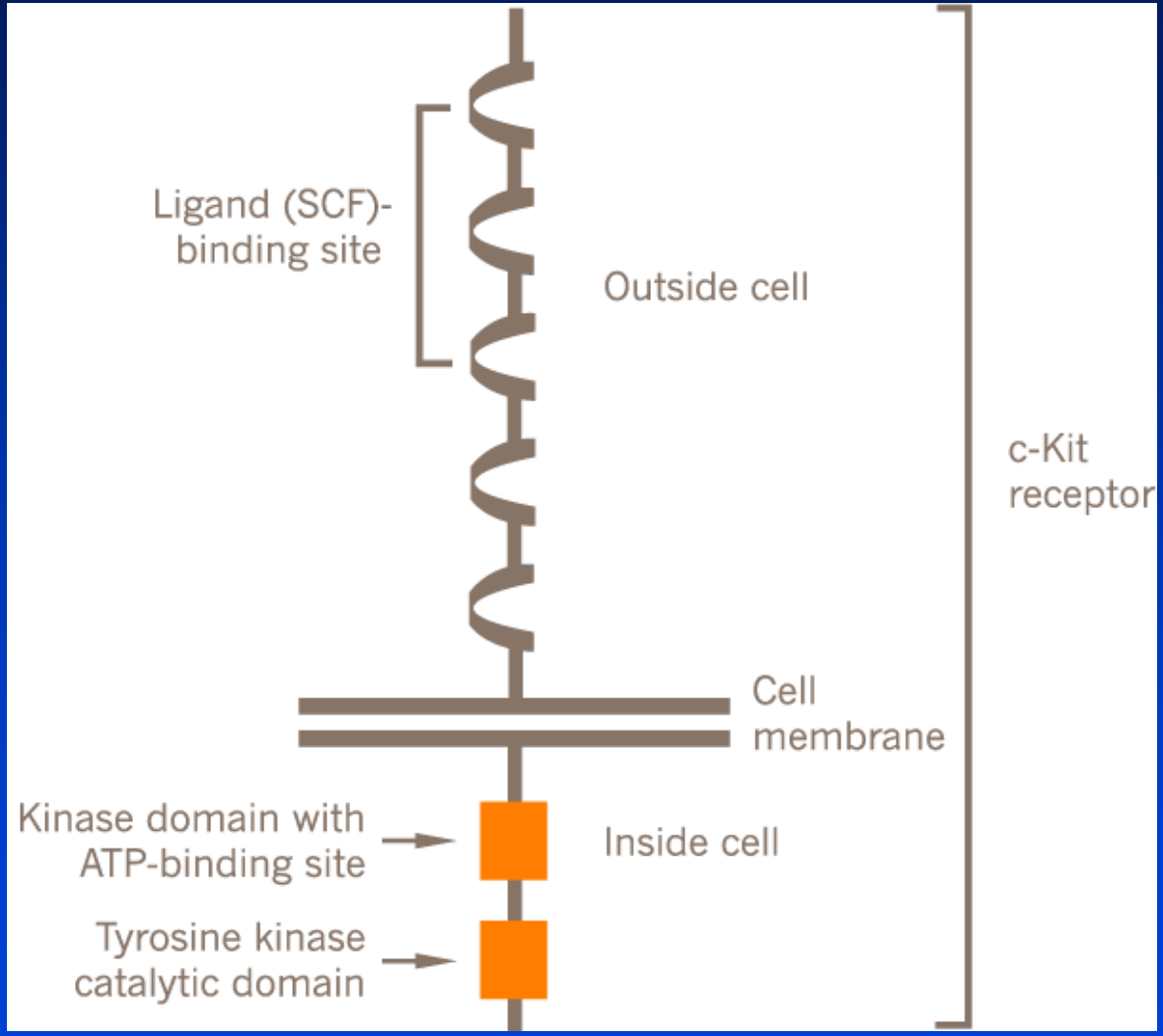
Histopathology of GIST: Biological Markers Used in Diagnosis of GIST

- GISTs positive for
  - CD117 (c-Kit receptor tyrosine kinase)
    - Positive in >95%
    - DOG-1 positive



CD117 (c-Kit)–positive staining GIST

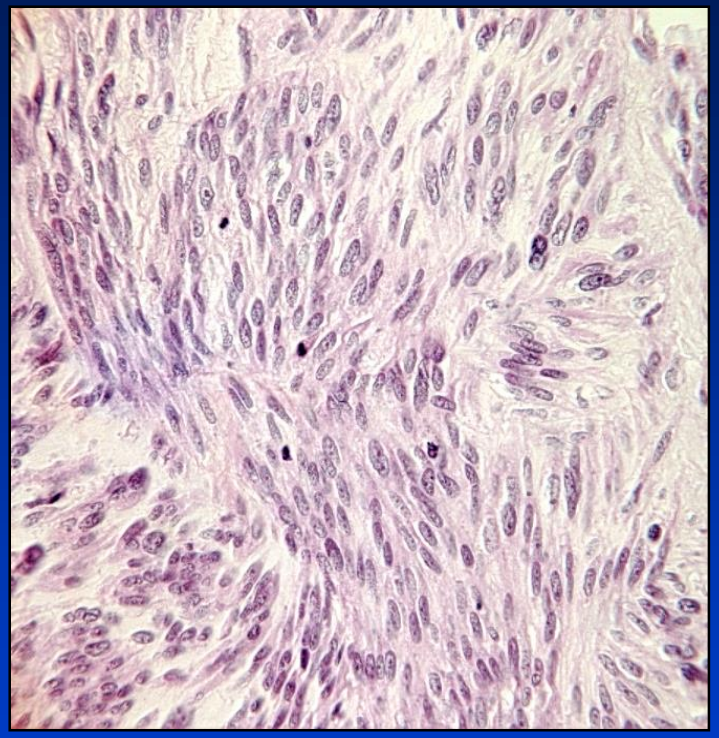
Structure of c-Kit Receptor



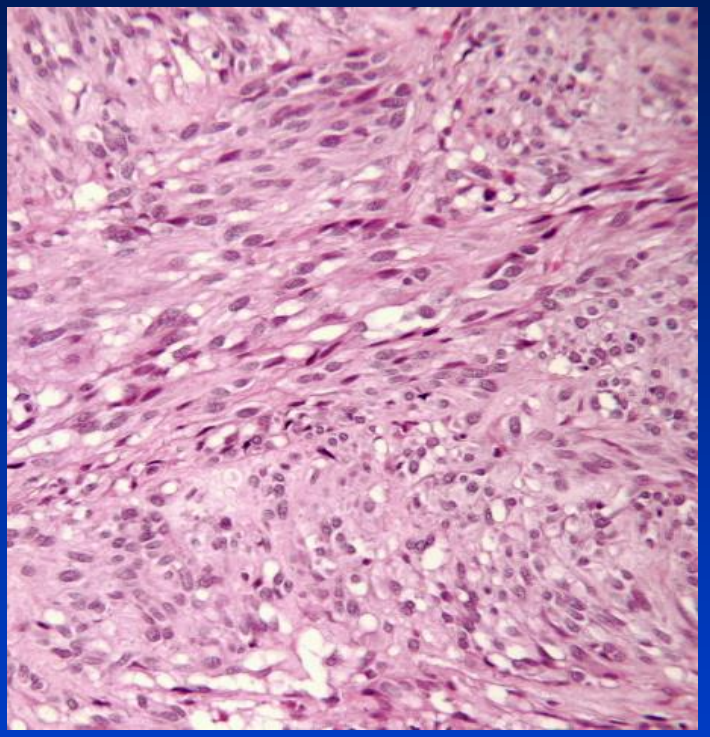
The Biology of c-Kit: Normal Functions

- c-Kit is found in many normal tissues and is essential for
  - Haematopoiesis
  - Melanogenesis
  - Gametogenesis
  - Interstitial cells of Cajal (ICCs) development
- Activation of c-Kit plays a critical role in different cell functions
  - Proliferation
  - Differentiation
  - Apoptosis/survival
  - Adhesion/chemotaxis

Histological Characterisation of GIST



Primary GIST with predominantly spindle-cell morphology



Aggressive (“high grade”) GIST with mixed morphology (spindle cell and epitheloid)

GIST: Involved Sites

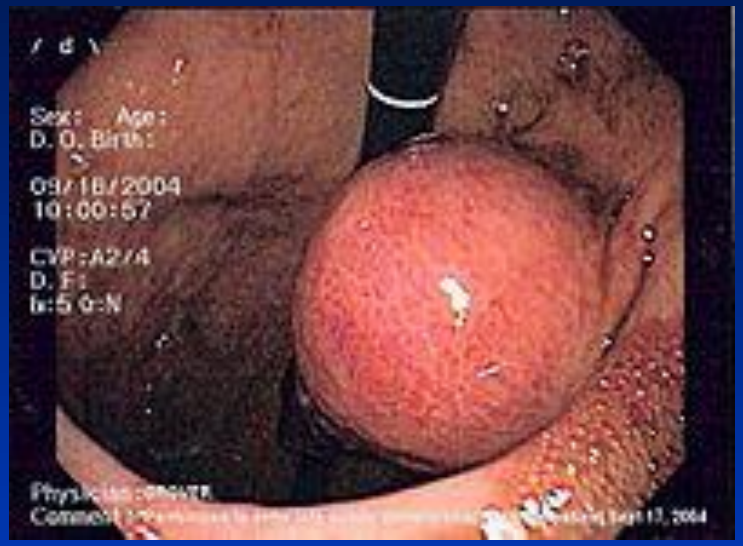
- Can occur anywhere in GI tract/abdomen

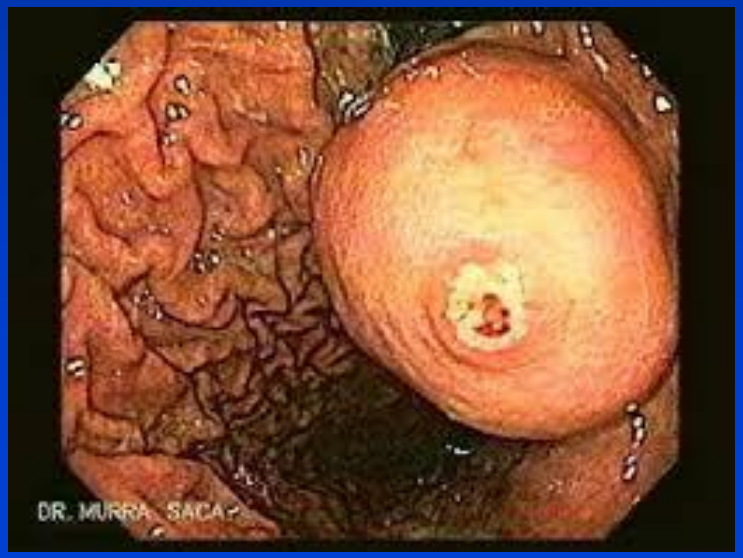
Site	Incidence
Gastric	60%–70%
Small Intestine	20%–30%
Colon	<5%
Other (omentum, mesentery, oesophagus)	<5%

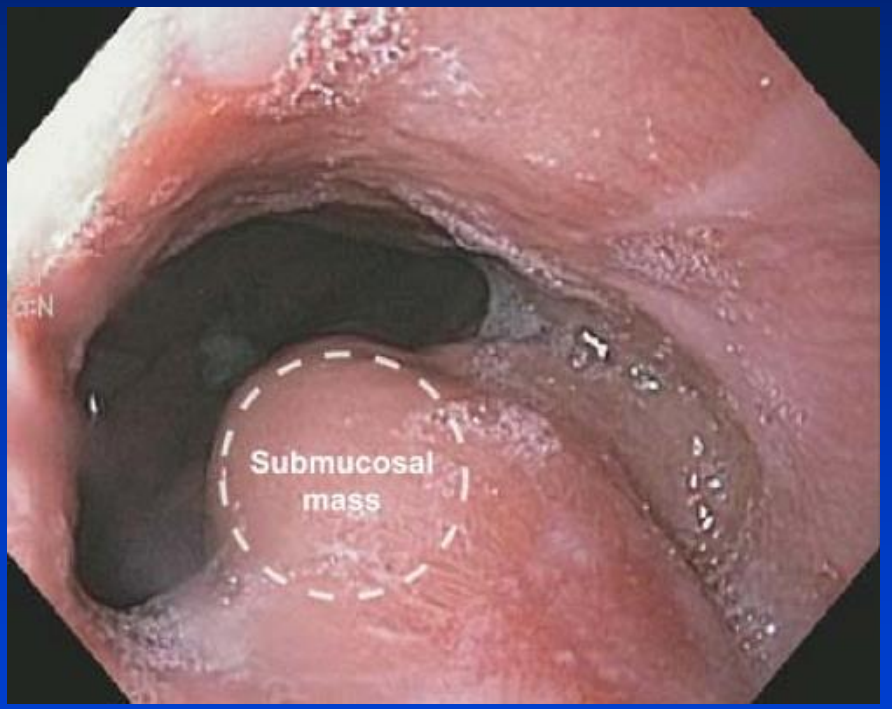
GIST Clinical Presentation

- Symptomatic: signs/symptoms related to location of tumour
  - Vague GI pain or discomfort
  - GI haemorrhage
  - Other symptoms include anorexia, weight loss, nausea, anaemia, and additional GI complaints
- Often asymptomatic, especially early in tumour development

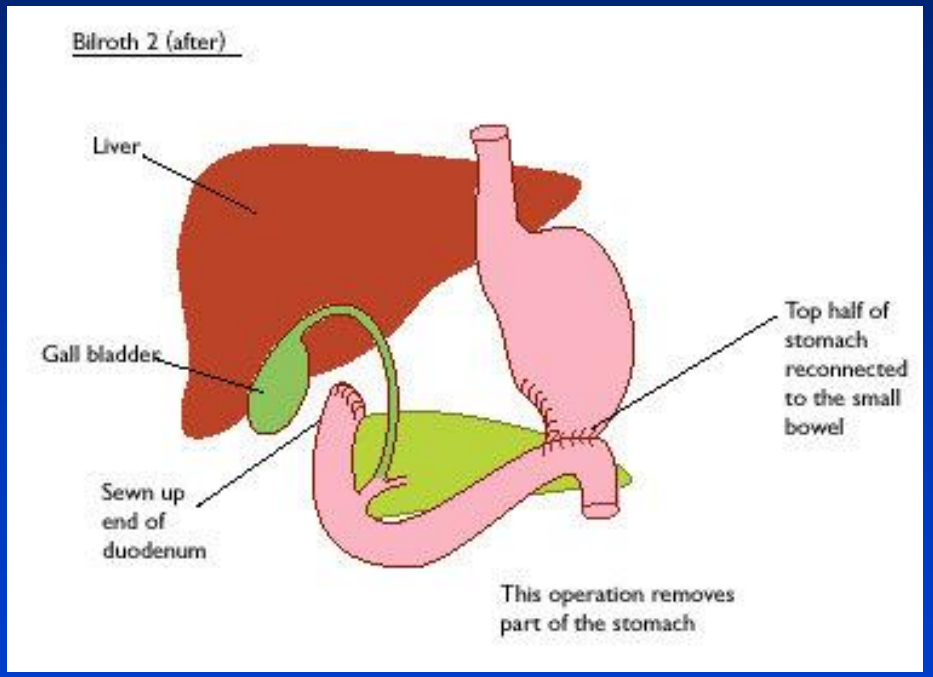
Endoscopy


Sex: Age:
D. O. Birth:
09/18/2004
10:00:57
CVP:A2/4
D. F:
h:5 v:N


DR. MURRA SACA


Submucosal
mass

Surgery: sometimes after neo-adjuvant therapy

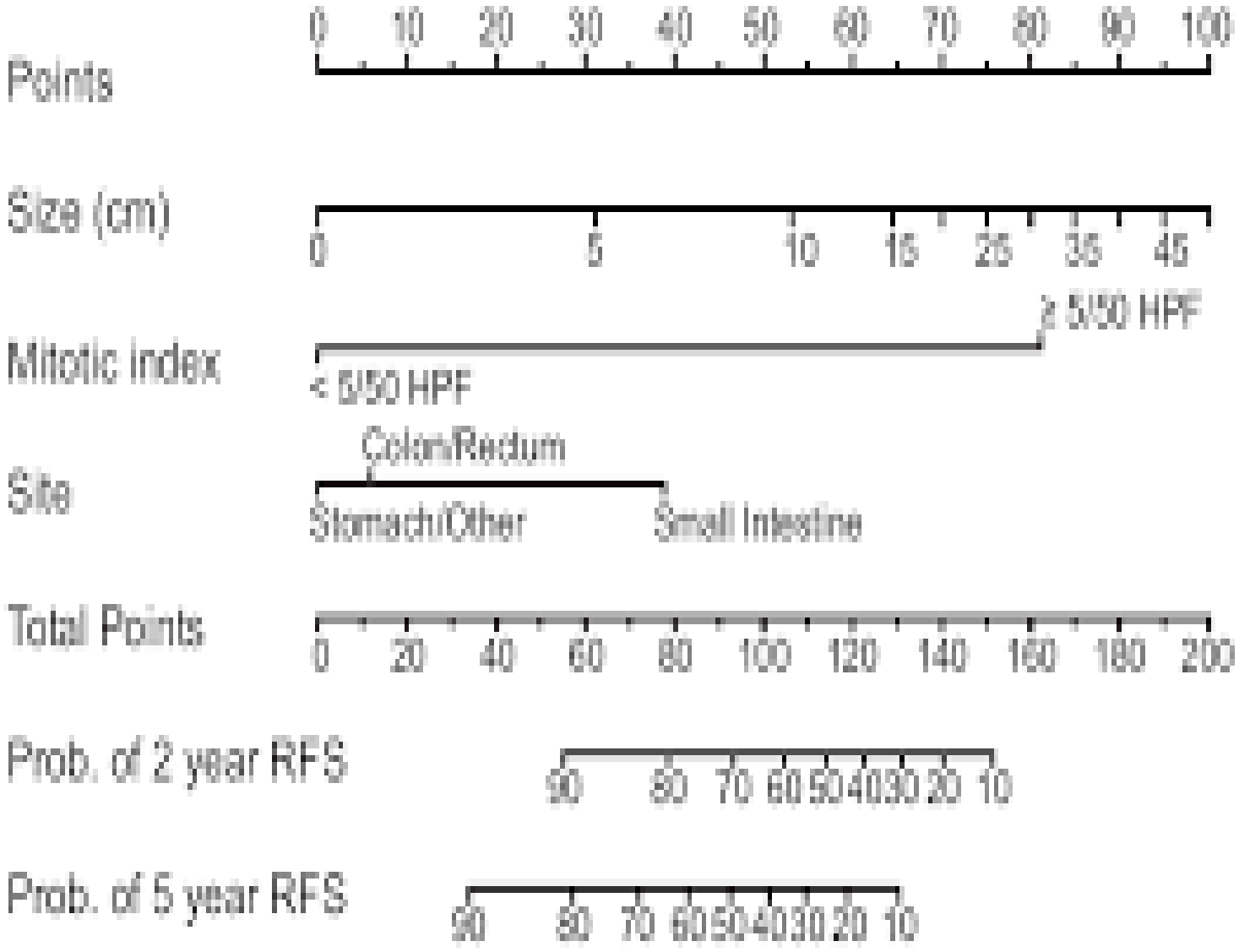


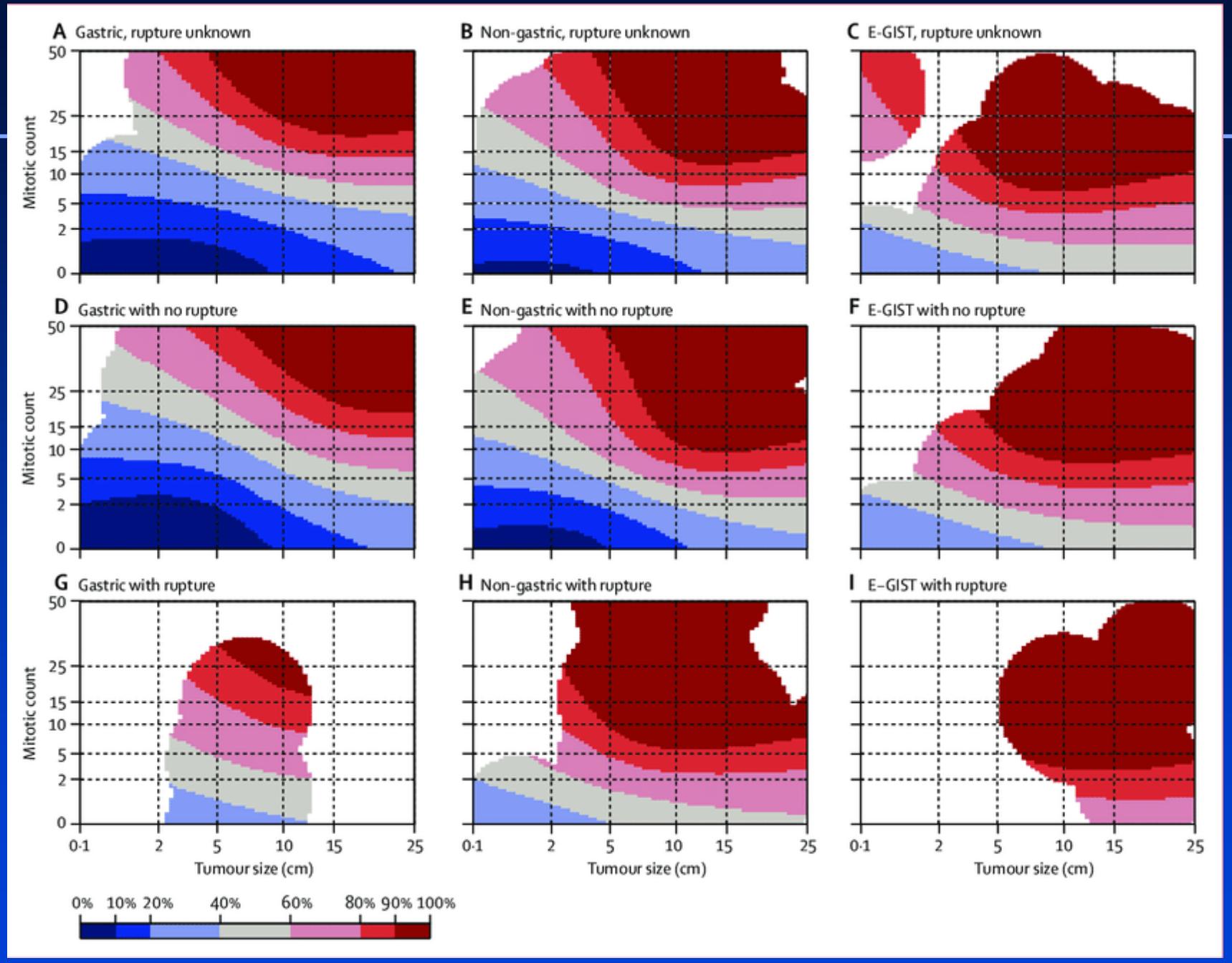
Malignant Potential of GISTs

- Pathological determinants:

Low Risk	High Risk
– Small tumours (2–5 cm)	– Larger
– Low mitotic count (<5 per 50 HPF)	– Mitotically active (>5 per 50 HPF)
– Stomach	– Other locations

HPF = high power fields


Points
0 10 20 30 40 50 60 70 80 90 100
Size (cm)
0 5 10 15 25 35 45
Mitotic Index
≥ 5/50 HPF
< 5/50 HPF
Site
Colon/Rectum
Stomach/Other
Small Intestine
Total Points
0 20 40 60 80 100 120 140 160 180 200
Prob. of 2 year RFS
90 80 70 60 50 40 30 20 10
Prob. of 5 year RFS
90 80 70 60 50 40 30 20 10


A Gastric, rupture unknown
B Non-gastric, rupture unknown
C E-GIST, rupture unknown
D Gastric with no rupture
E Non-gastric with no rupture
F E-GIST with no rupture
G Gastric with rupture
H Non-gastric with rupture
I E–GIST with rupture
Mitotic count
50
25
15
10
5
2
0
0·1
2
5
10
15
25
Tumour size (cm)
0% 10% 20% 40% 60% 80% 90% 100%

Traditional Treatment Options Pre-Imatinib Mesylate

- Surgery is primary treatment modality for GISTs
  - 5-year survival 50% to 65%
- If incomplete resection/metastatic at presentation
  - Median survival <1 year
  - 5-year survival <35%
- If disease unresectable
  - Median survival 9 to 12 months

Traditional Treatment Options Pre-Imatinib Mesylate

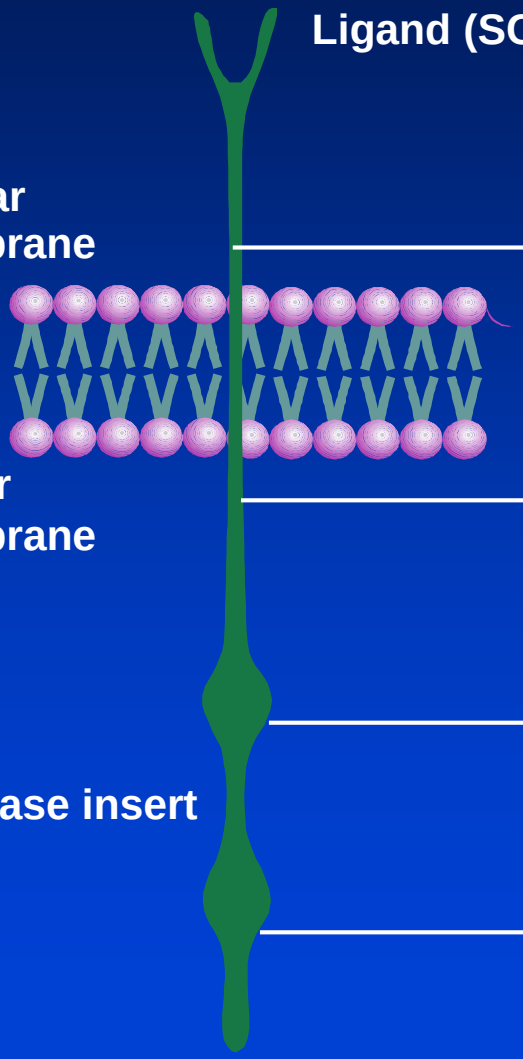
- Chemotherapy is not effective
  - Limited response rate: <10%
  - No survival advantage
- GISTs are not sensitive to radiotherapy
  - Limited response rate: <5%

Molecular Pathology of GISTs

- The majority of GISTs (~90%) express the product of a mutated c-*kit* gene
- c-*kit* oncogenic mutations:
  - Exon 11
  - Exon 9
  - Exon 13
  - Exons 17 and 2
  - PDGFR
  - NF
  - SDH
  - BRAF
  - Etc

c-*kit* Gene Mutations in GISTs

- Gene maps between 4q11 and 4q121
- 21 exons



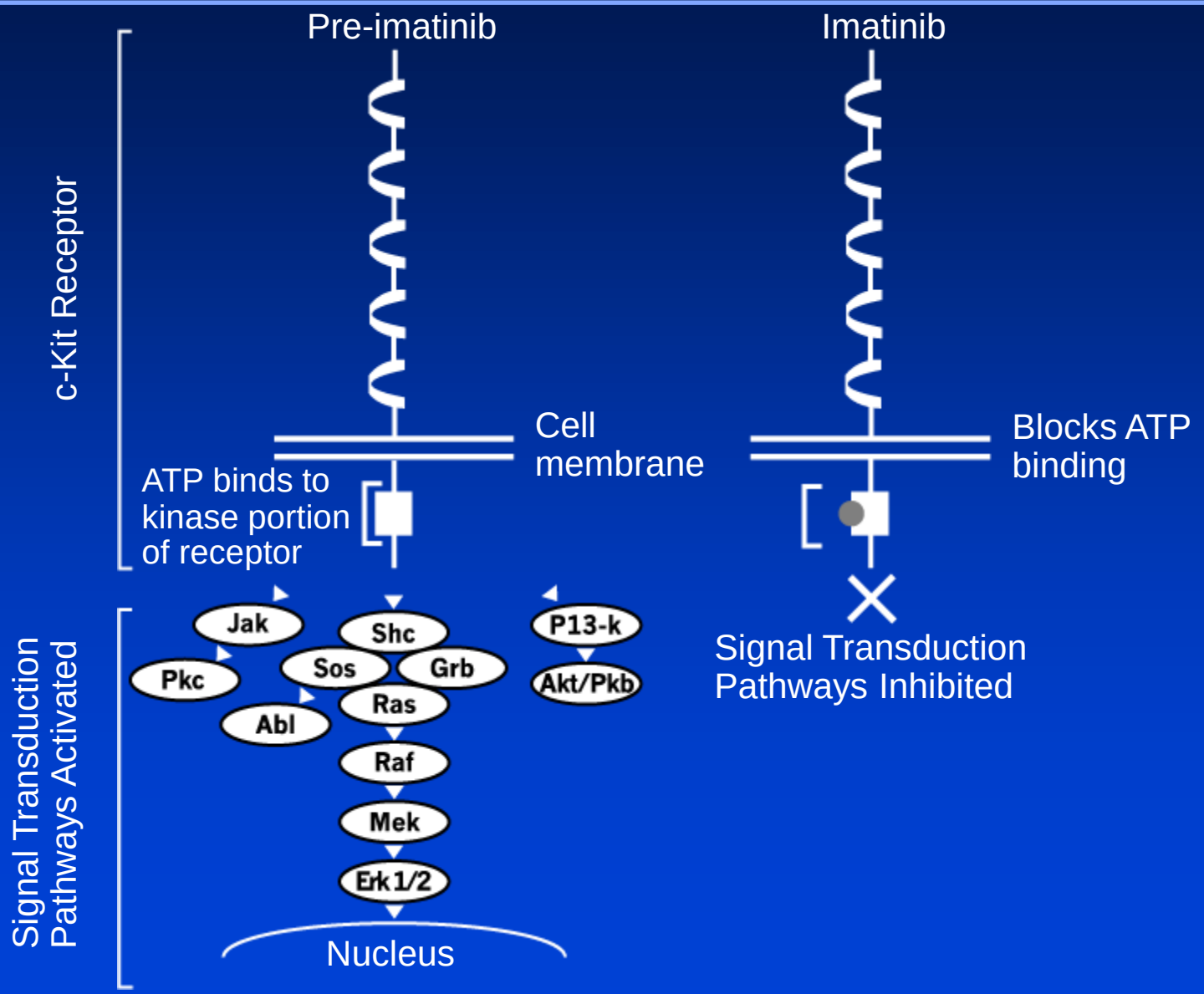
EXON 9 (~5%–10% of mutations)

EXON 11 (~70% of mutations)

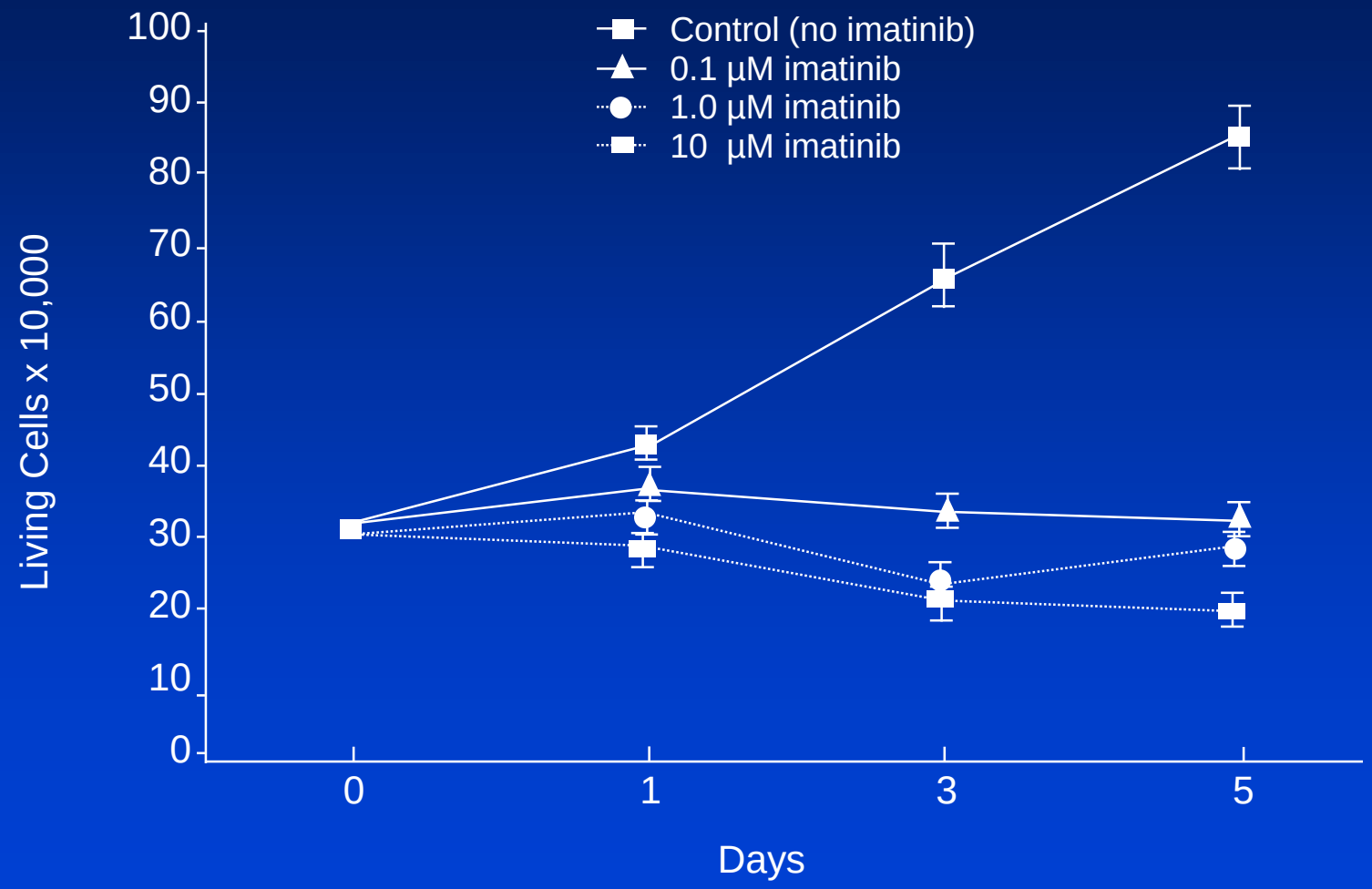
EXON 13 (~5% of mutations)

EXON 17 (~5 % of mutations)

Proposed Mechanism of Action of Imatinib



Imatinib Inhibits Proliferation of GIST Cells



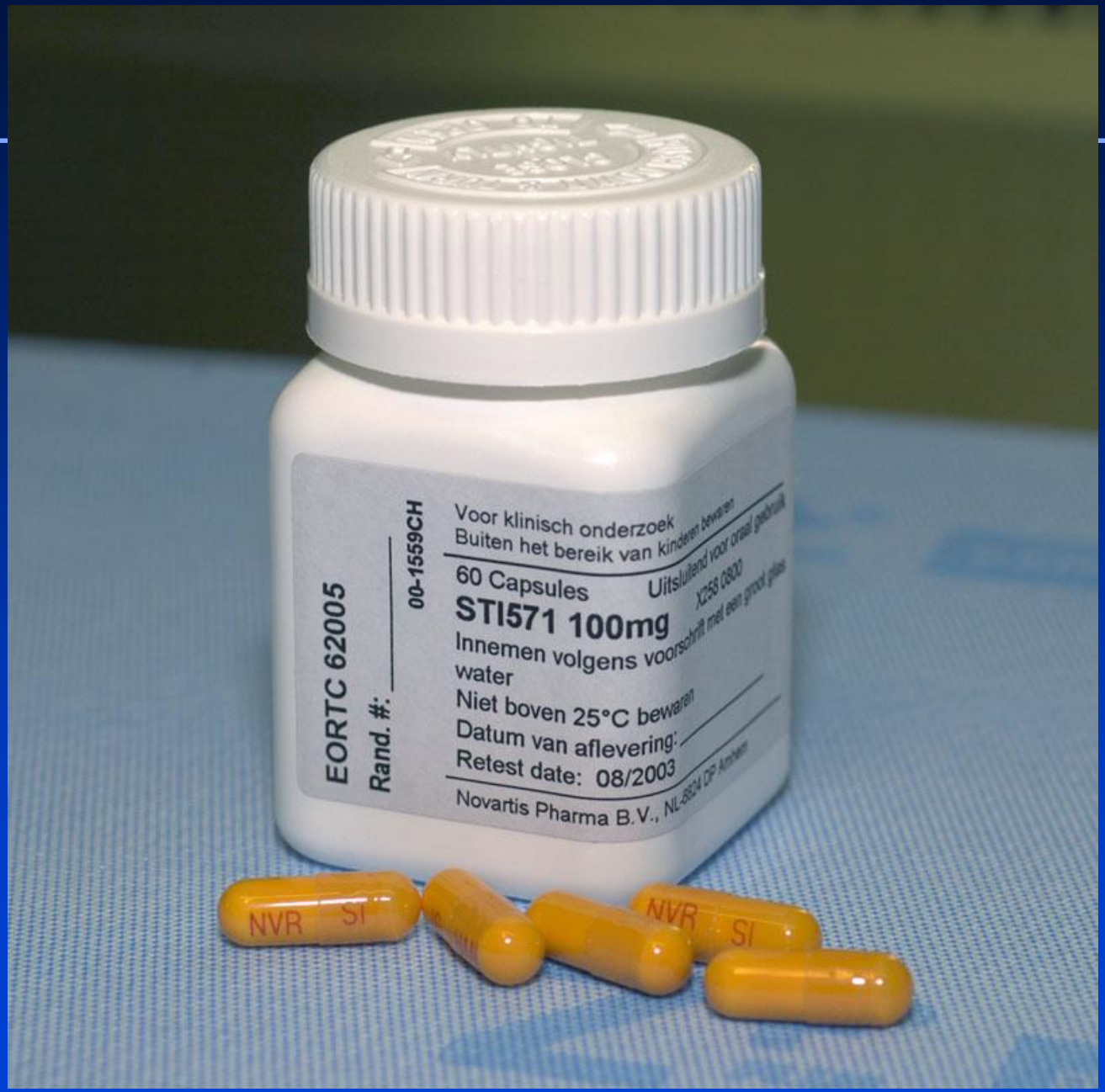
Tuveson et al. *Oncogene.* 2001;20:5054-5058.

Cellular Selectivity of Imatinib: IC_{50} μM

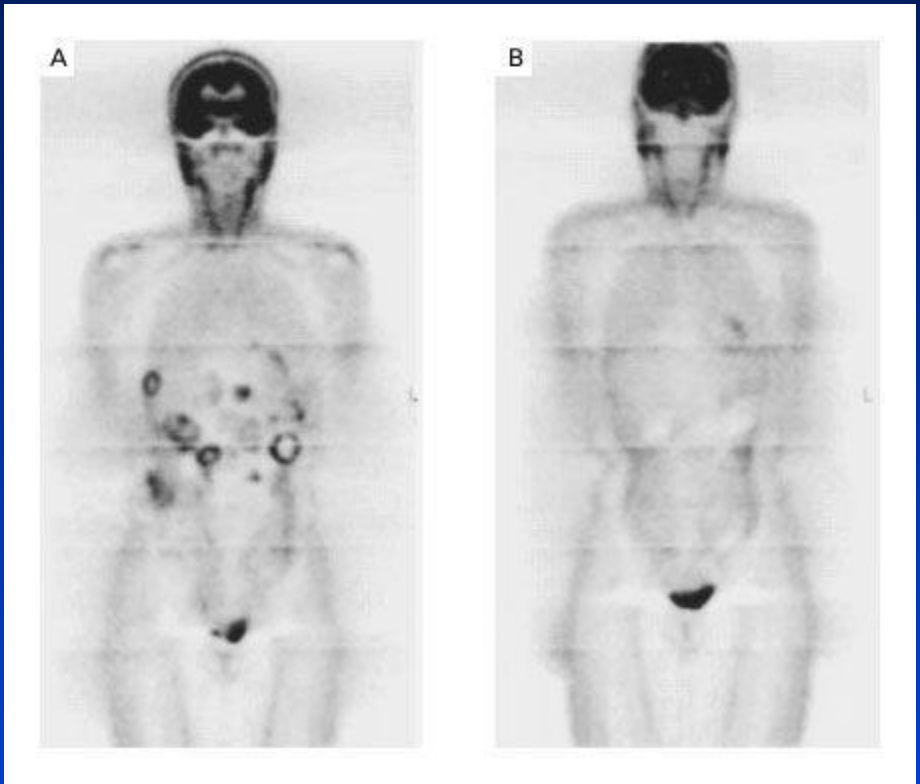
Kinases Inhibited		Kinases Not Inhibited	
v-Abl	0.1–0.3	Flt-3	>10
p210Bcr-Abl	0.25	c-Fms, v-Fms	>10
p185Bcr-Abl	0.25	EGF receptor	>100
TEL-Abl	0.35	c-erbB2	>100
PDGF-R	0.1	Insulin receptor	>100
TEL-PDGF-R	0.15	IGF-I receptor	>100
Kit	0.1	v-Src	>10
		JAK-2	>100

PDGF-R = platelet-derived growth factor receptor; EGF = epidermal growth factor; IGF-I = insulin-like growth factor I.

Druker BJ et al. *Nat Med.* 1996;2:561-566.


EORTC 62005
Rand. #:
00-1559CH
Voor klinisch onderzoek
Buiten het bereik van kinderen bewaren
60 Capsules
Uitsluitend voor oraal gebruik
X258 0820
STI571 100mg
Innemen volgens voorschrift met een groot glas water
Niet boven 25°C bewaren
Datum van aflevering:
Retest date: 08/2003
Novartis Pharma B.V., NL-6824 DP Arnhem
NVR SI
NVR SI

Imatinib and GIST: first patient



Multiple liver and upper abdominal ^{18}FDG-accumulating metastases

A marked decrease in ^{18}FDG uptake 4 weeks after starting imatinib

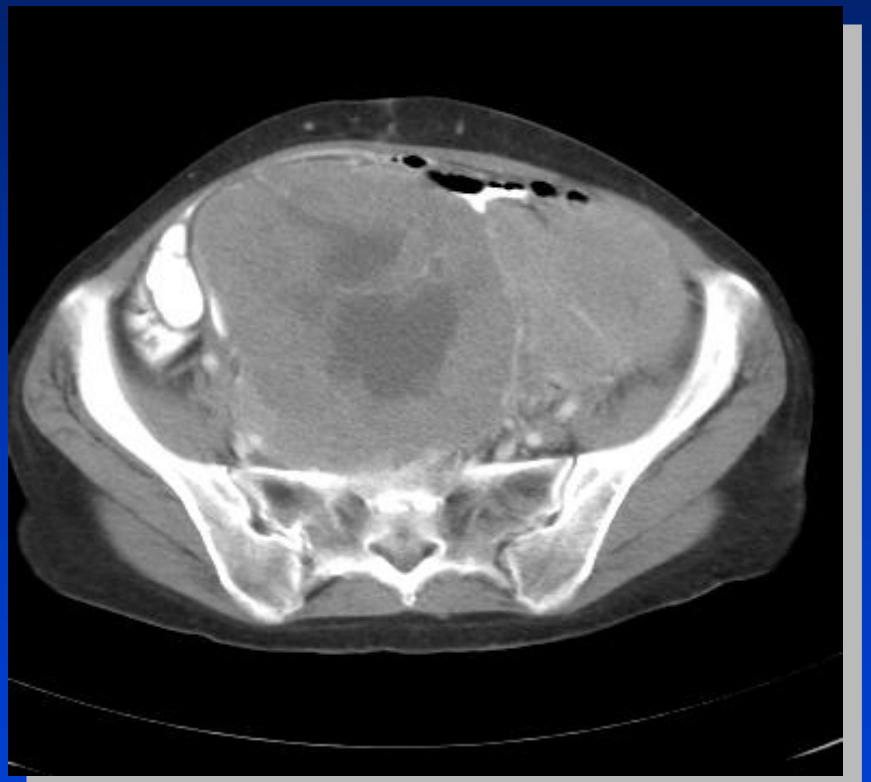
Joensuu et al. *N Engl J Med.* 2001;344:1052-1056.

EORTC GIST Phase I Study: Results

- GIST patients achieved:
  - Confirmed partial response: **52.7%**
  - Unconfirmed response: **16.7%**
- 24 of the 27 of patients experienced relief from symptoms
- A daily dose of 1000mg resulted in dose-limiting toxicities 5 of 8 patients
- A daily dose of 800mg (400mg twice daily) was well tolerated

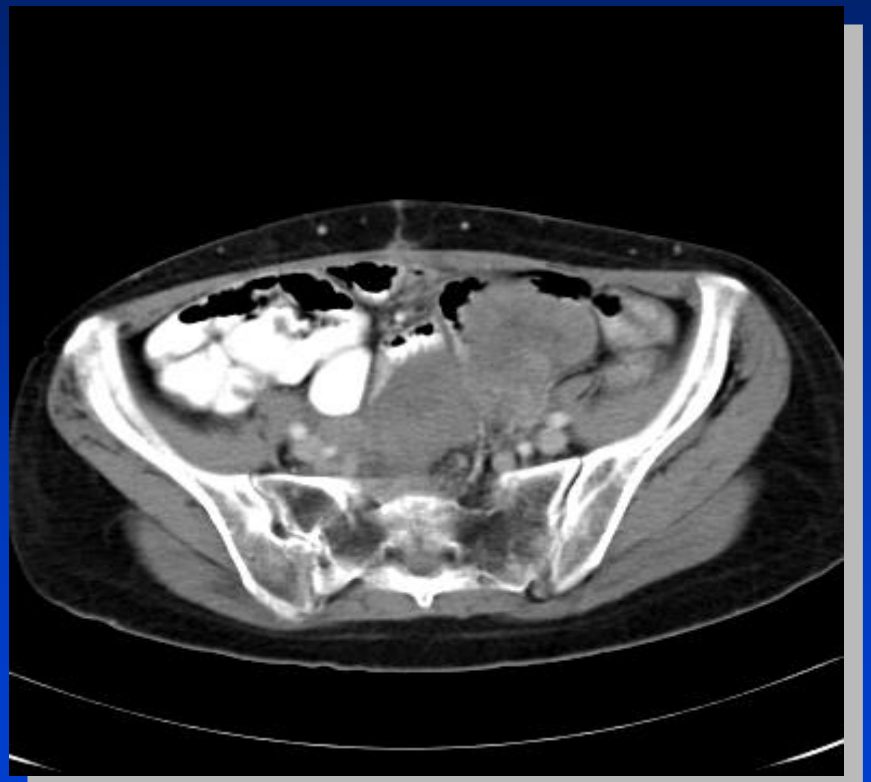
CT Scan Results: Decrease in Tumour Volume

June 27, 2000



Before imatinib

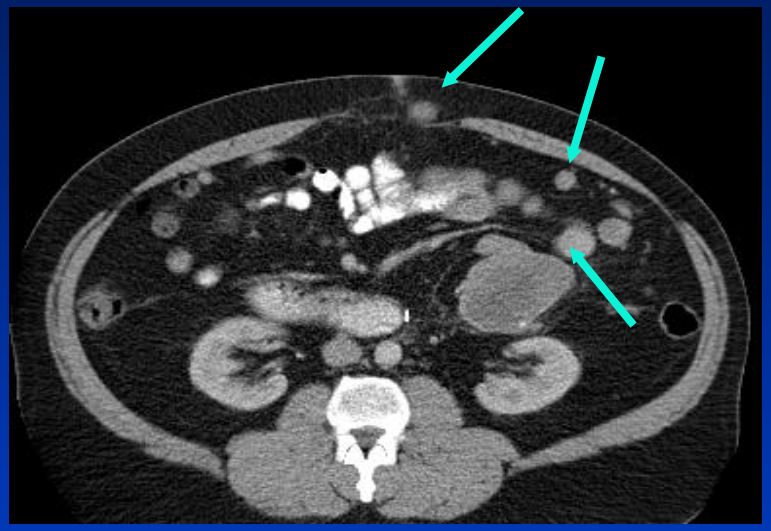
October 4, 2000

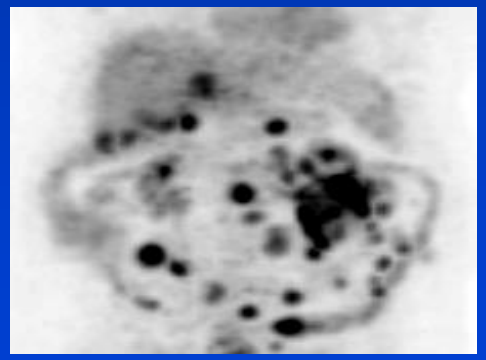


After imatinib

Comparison of CT and PET Scan Results

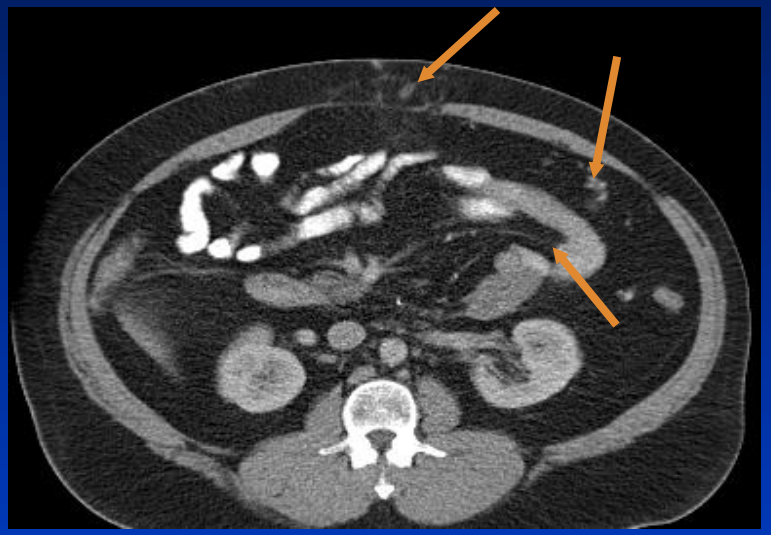
July 3, 2000

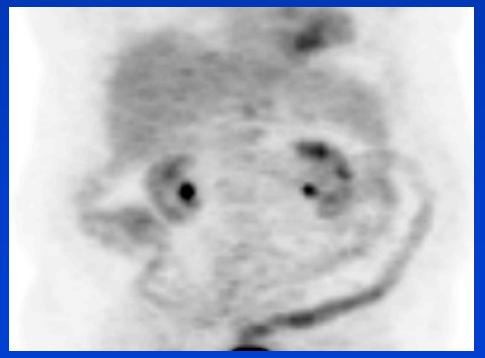




Before imatinib

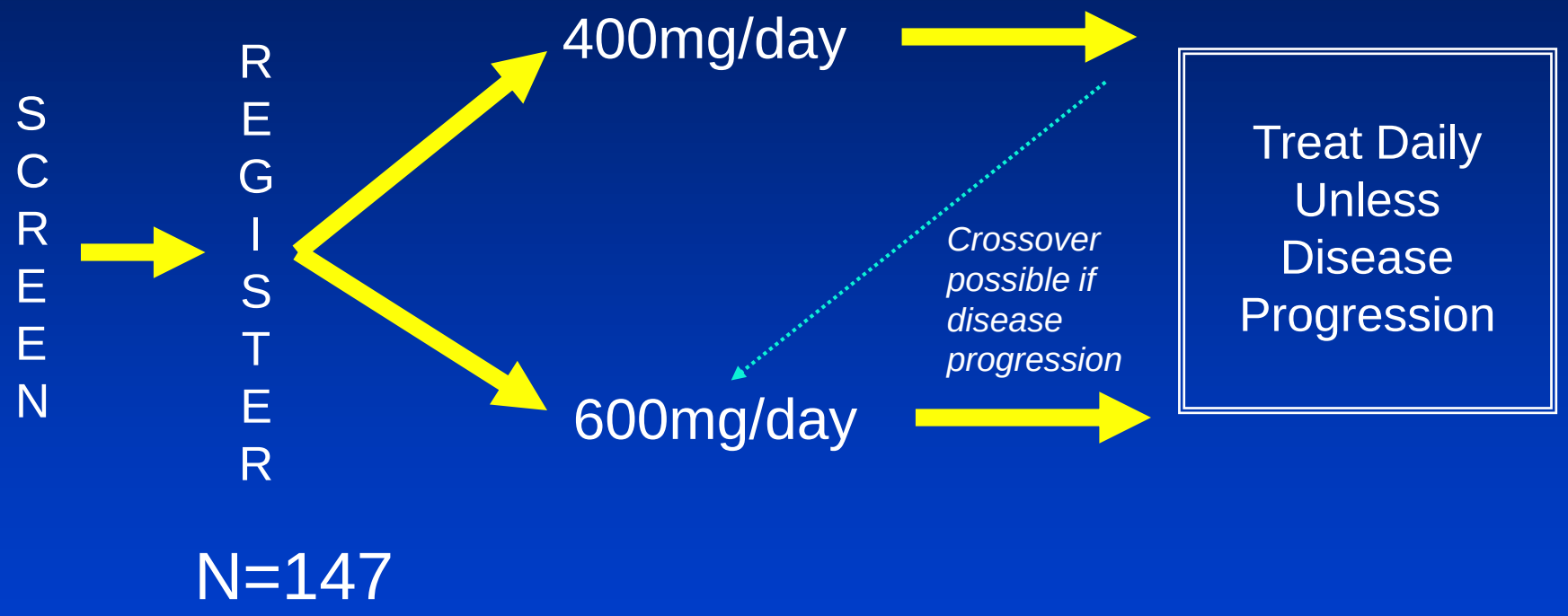
October 5, 2000





After imatinib

GIST Phase II Study



Functional imaging was performed with computed tomography (CT) scan or MRI. PET scan imaging was performed at the discretion of the investigator.

GIST Phase II Study: Summary of Efficacy

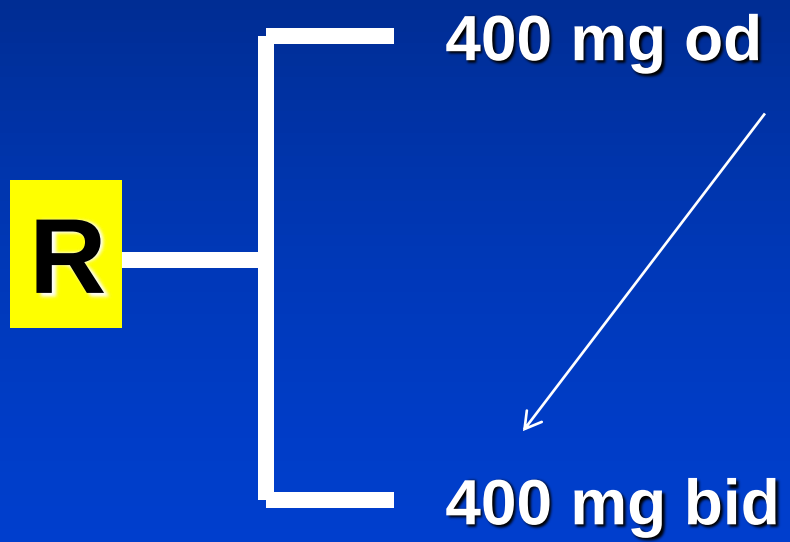
- Overall, more than 80% of patients benefited from imatinib
  - 54% PR
  - 28% SD
    - Durable responses
    - Additional follow-up will likely increase the response rate
- No significant differences in safety and efficacy between doses tested
- Only 14% of patients had initial progressive disease

GIST Phase II: Summary of Safety

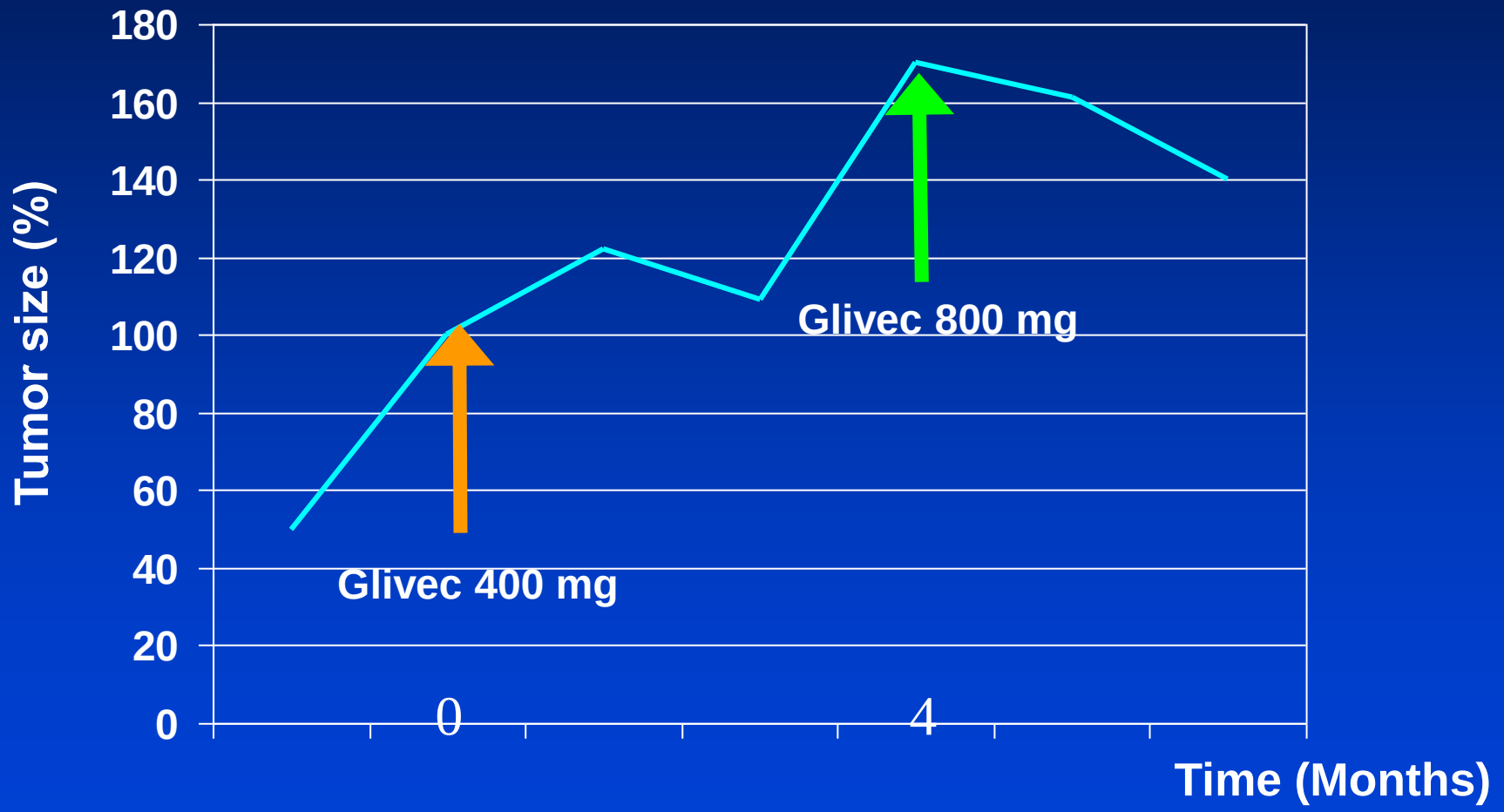
- Safe and well tolerated in patients with GIST
- Safety profile generally similar to CML
  - Oedema, nausea, diarrhoea
  - Most of the adverse events were mild to moderate in severity
- Less myelosuppression than CML

Glivec®: Randomized phase III study in GIST

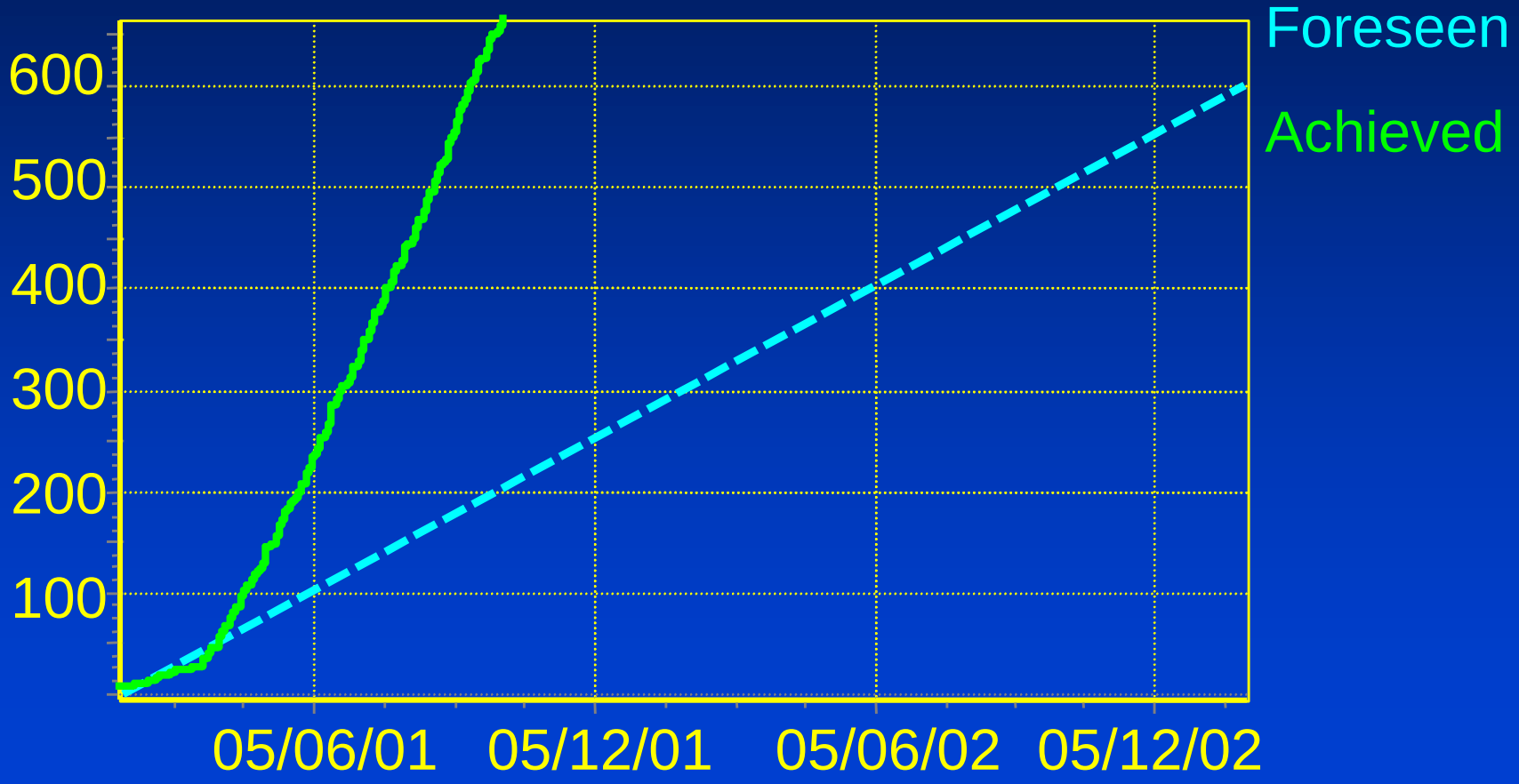
(Parallel by US intergroup and EORTC/SSG/ISG/AGITG)



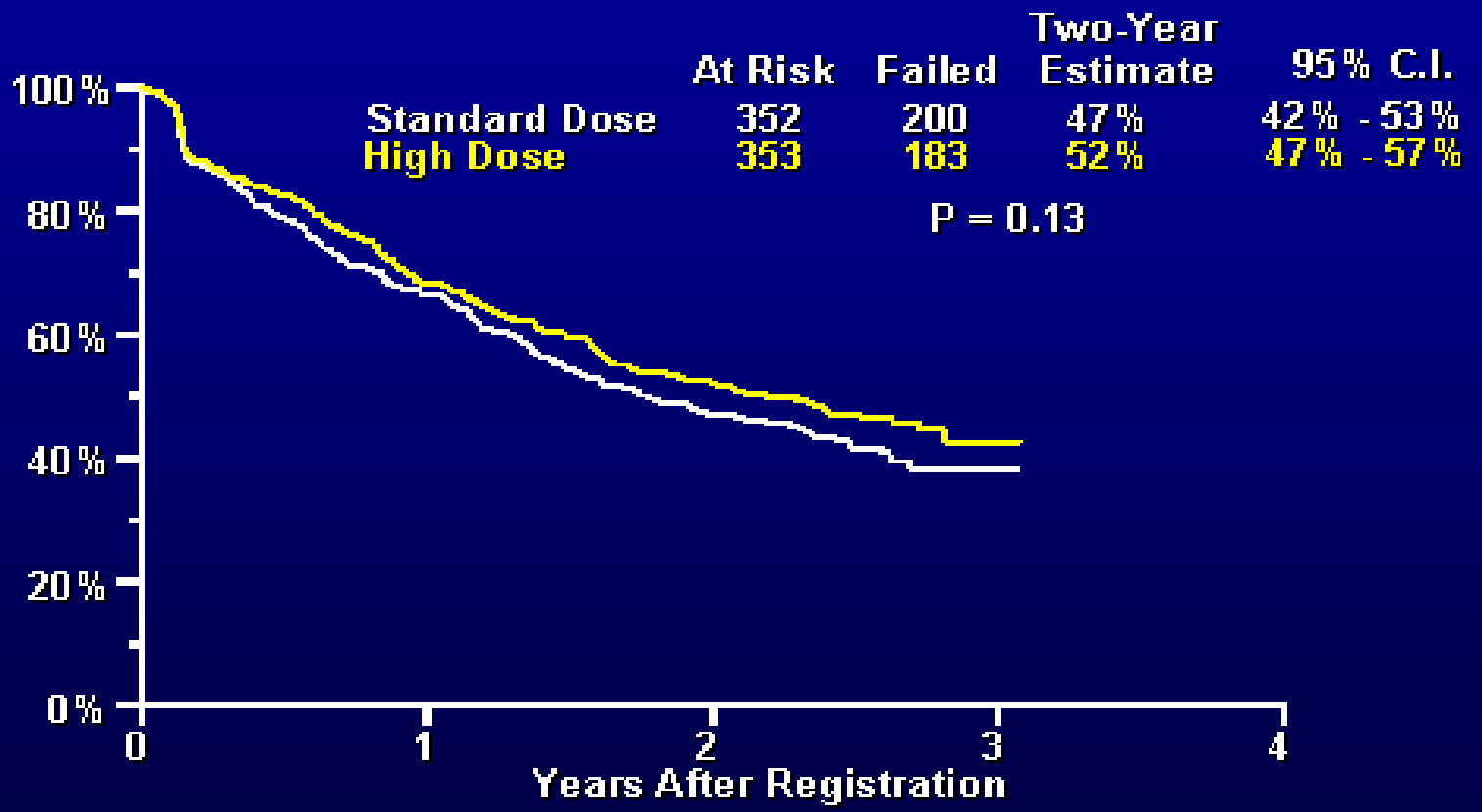
Glivec® in GIST: Is there a dose-response?



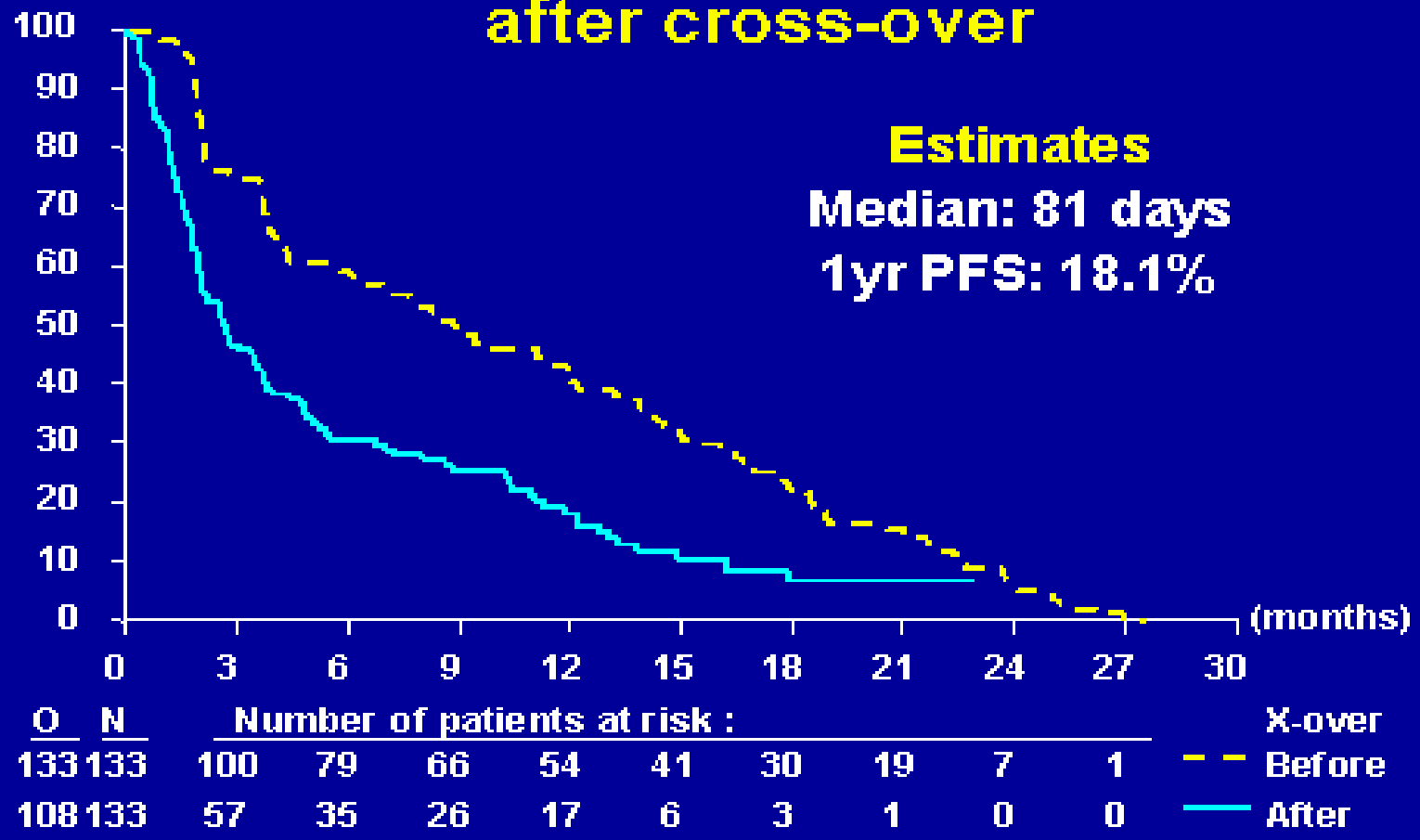
Accrual in EORTC trial 62005



Progression-Free Survival



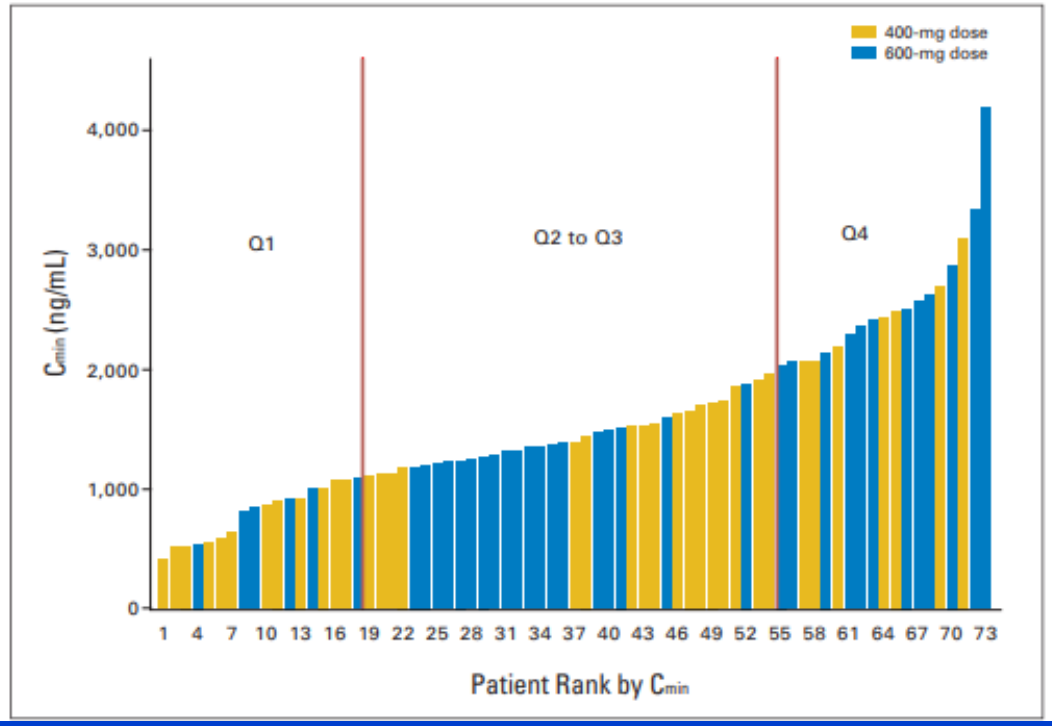
Progression free survival after cross-over



Mutational status and response (Heinrich JCO 2003)

- 88% KIT mutations
  - 76% exon 11: 84% PR
  - 21% exon 9: 48% PR
  - 1.6% exon 13: 100%PR
  - 1.6% exon 17: 50% PR
- 4.7% PDGFRA mutations: 0-67% PR
- Remainder no mutation:0% PR, 35% SD

Possible importance of imatinib blood levels



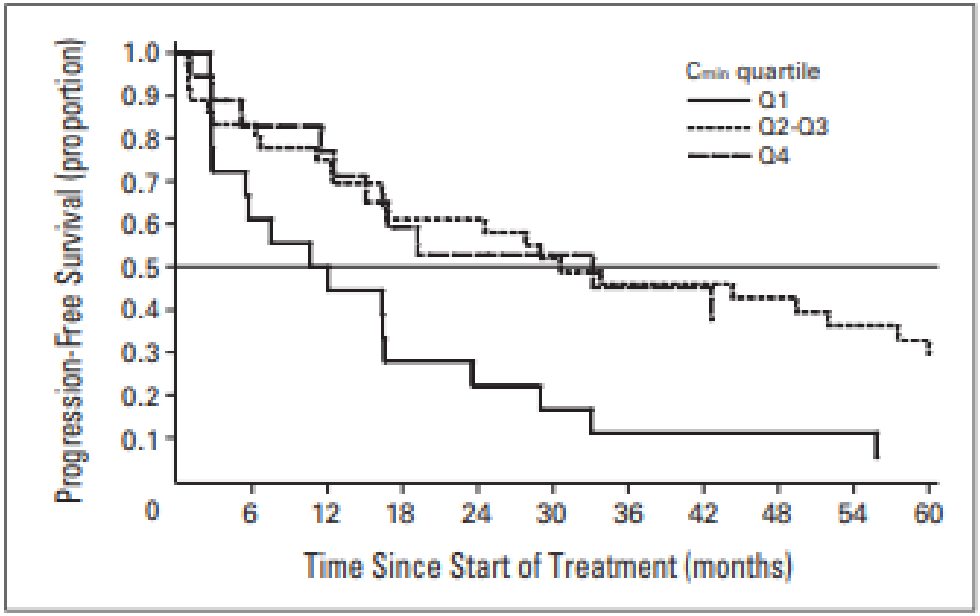
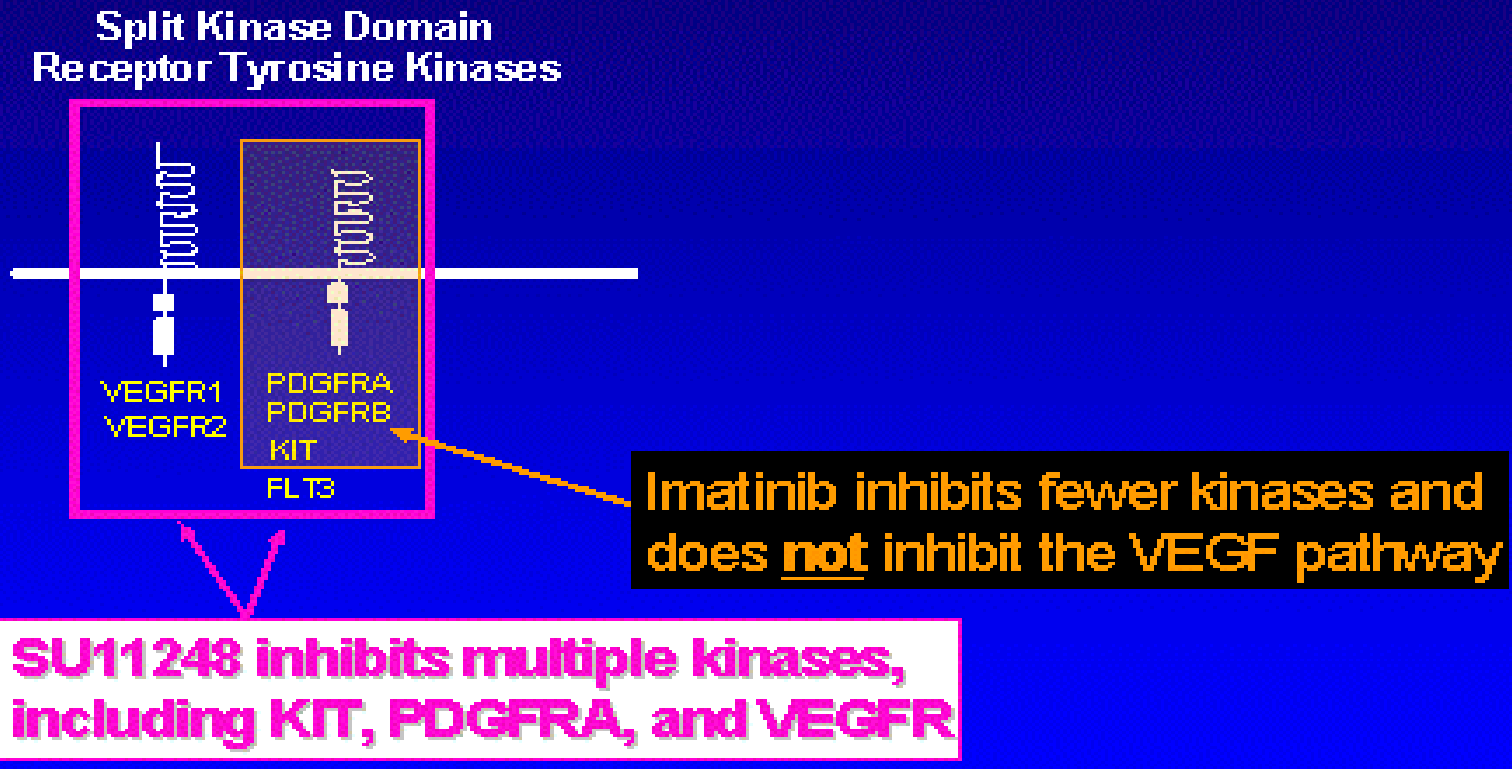
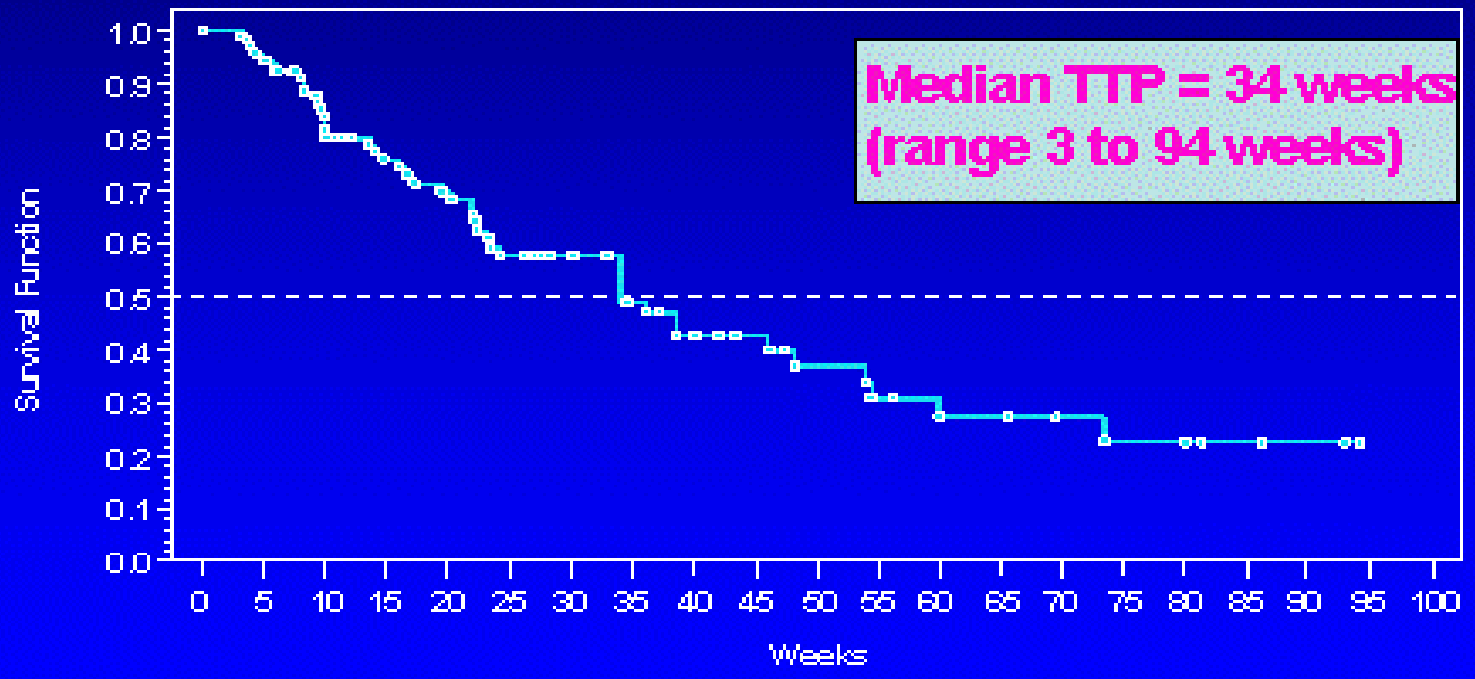


Fig 3. Time to progression by imatinib day 29 trough level (C_{min}) quartile (Q).

Different yet Overlapping Targets of SU11248 and Imatinib

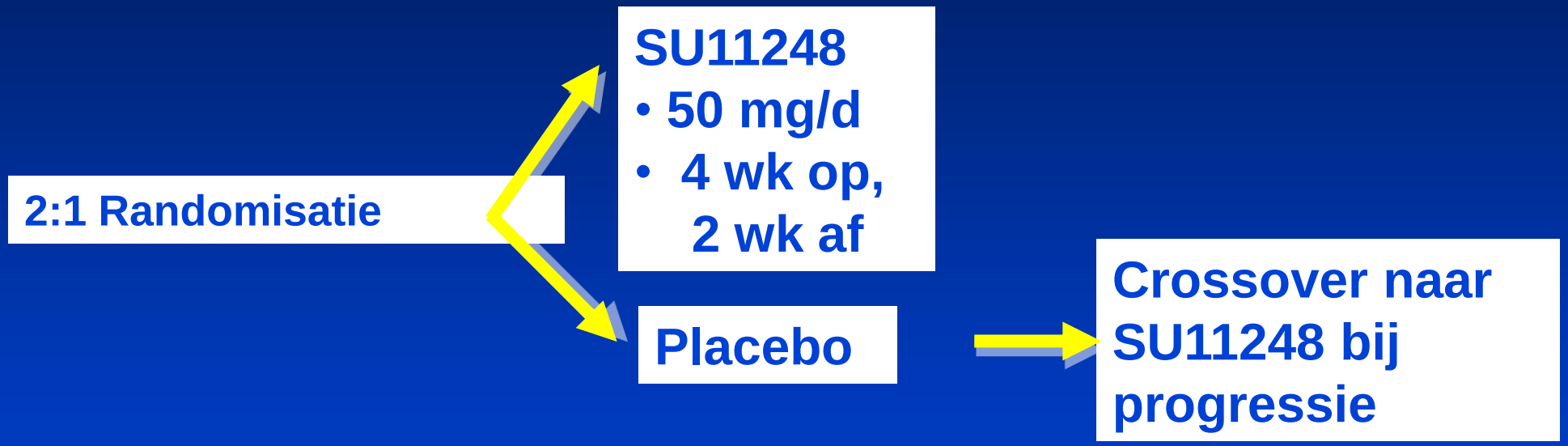


Time to Tumor Progression:
Imatinib-Resistant or Intolerant GIST Patients on SU11248 (n=92)



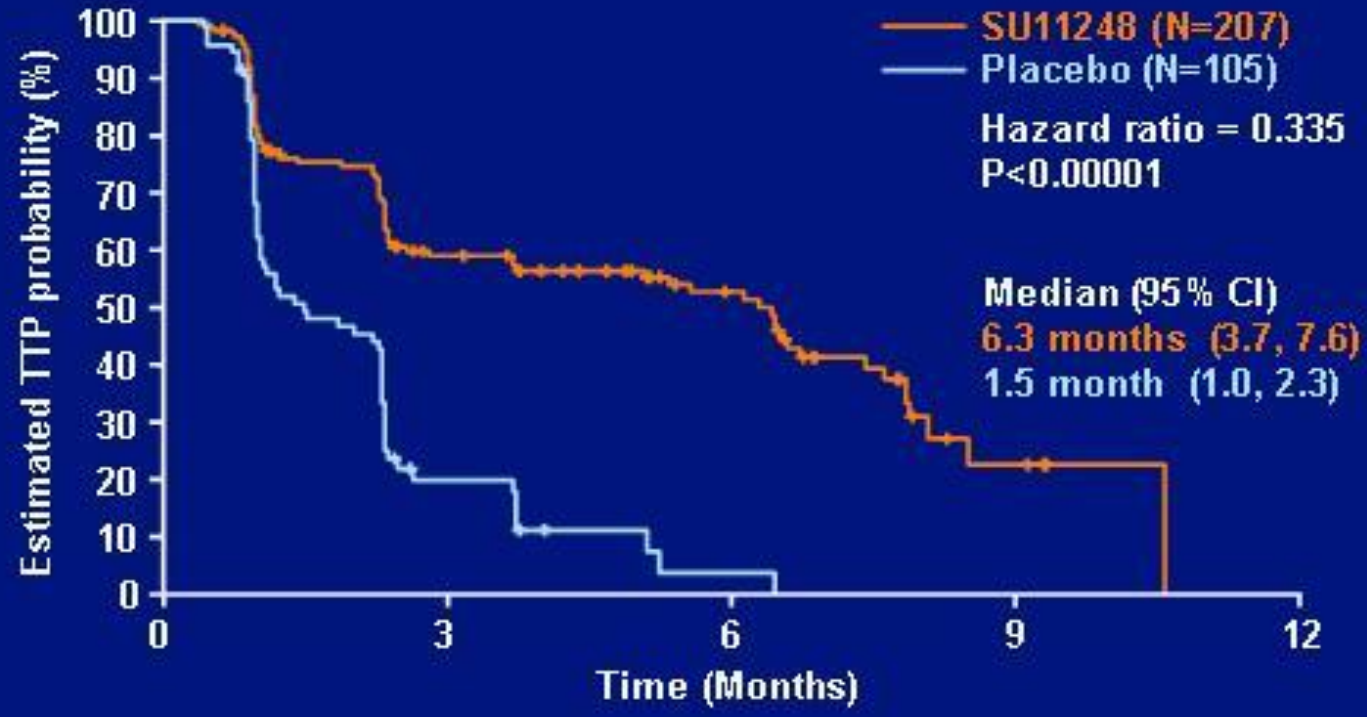
Database Cutoff as of April 28, 2004

SU11248 fase III studie bij Glivec-resistente GIST



doel: N = 357
Primair eindpunt: TTP

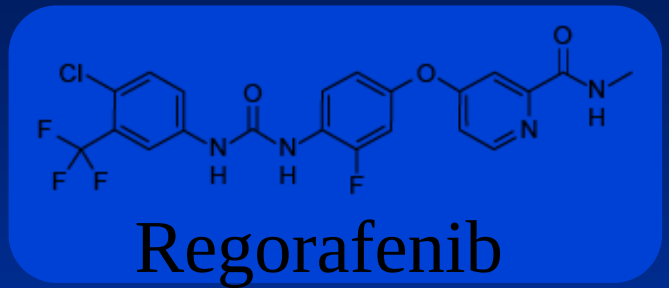
Time to Tumor Progression



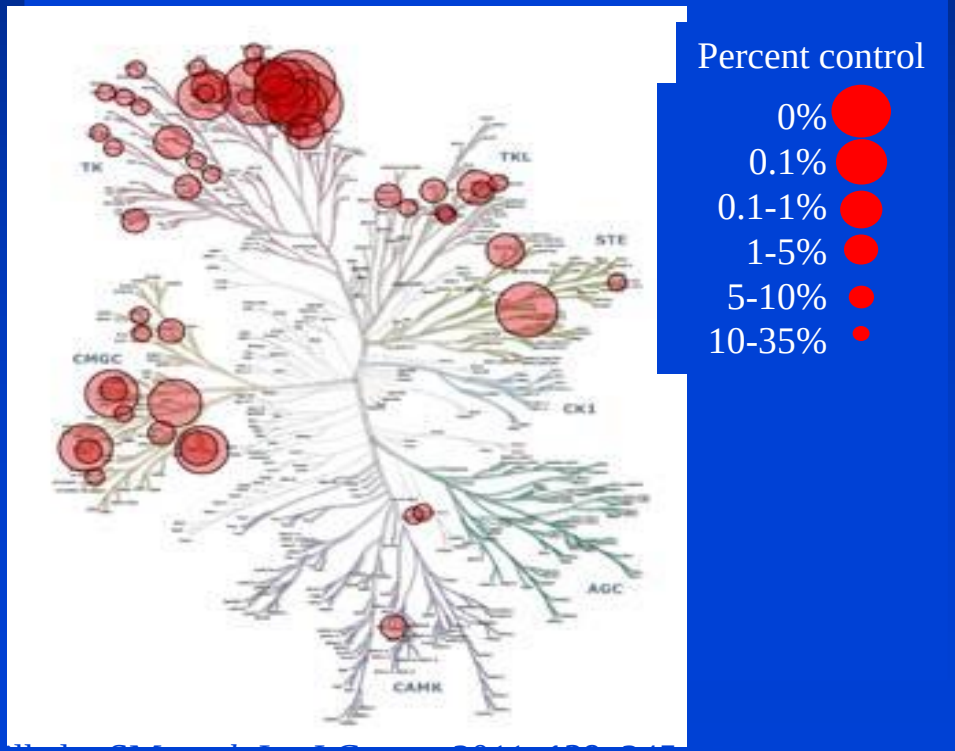
Objective disease response (%)

	SU11248 (N=207)	Placebo (N=105)
Partial response	8	0
Stable disease	58	50
Progressive disease	20	39
Not evaluable (too early or missing)	14	11

Regorafenib (Stivarga)



Regorafenib



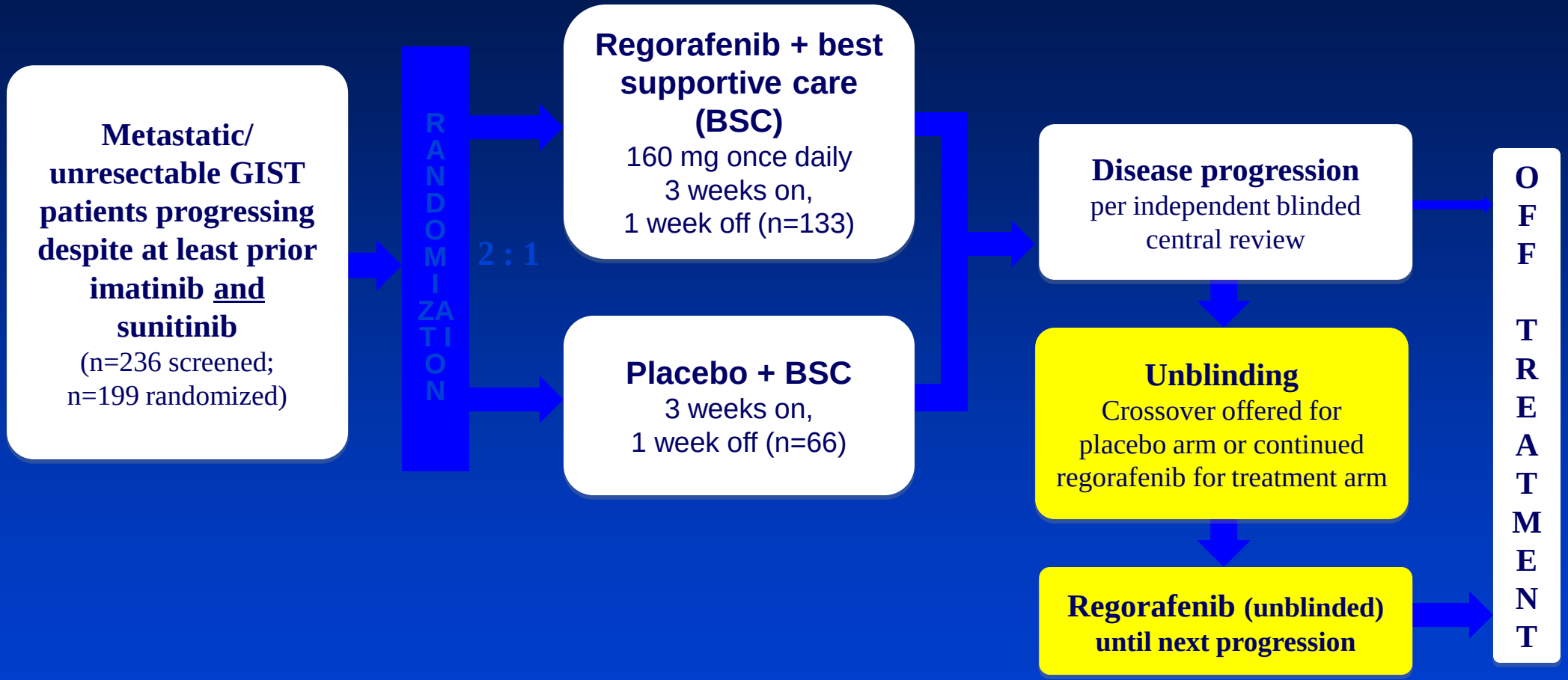
Percent control

0%
0.1%
0.1-1%
1-5%
5-10%
10-35%

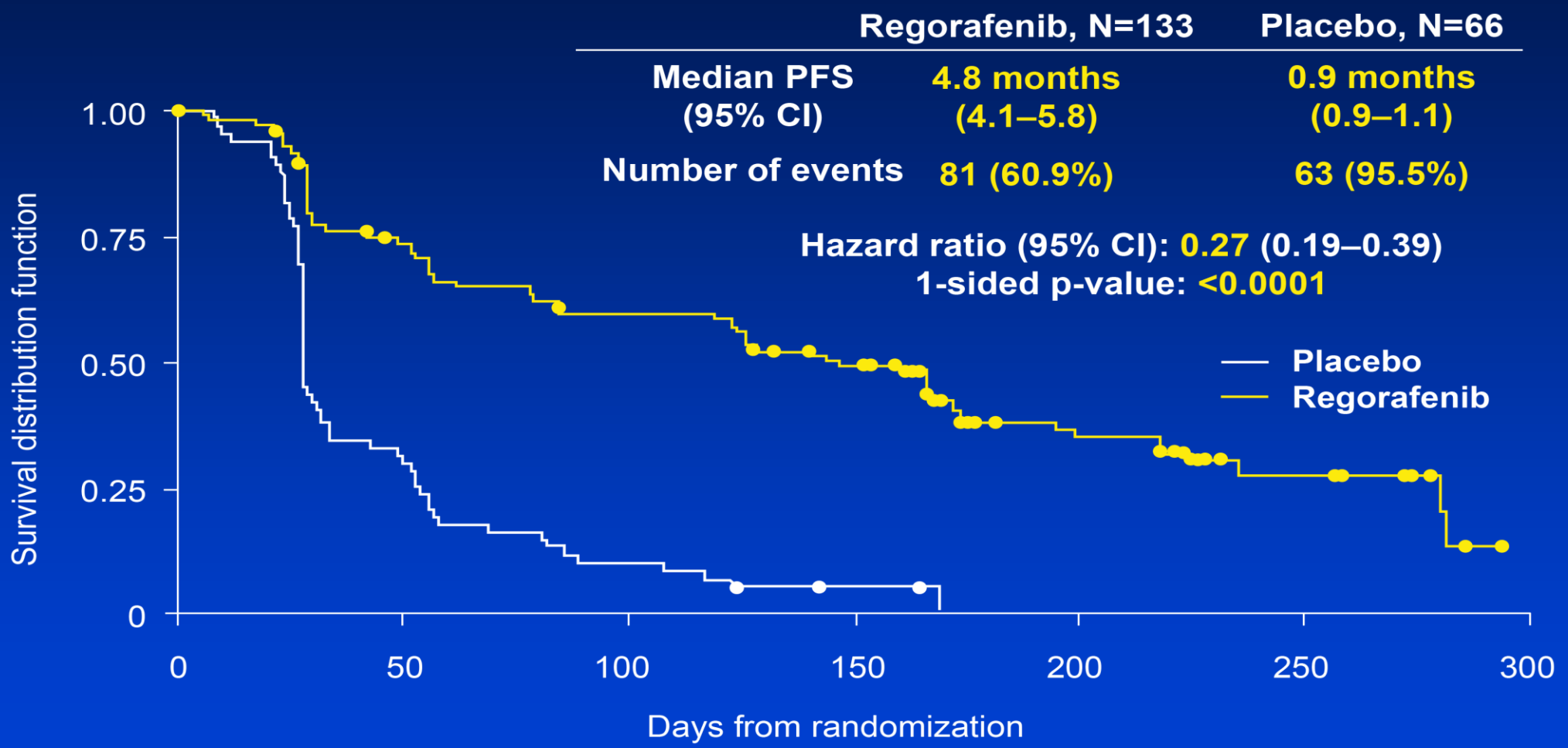
Biochemical activity

	IC_{50} (nmol/l)
KIT	7
VEGFR-1	13
Murine VEGFR-2	4
PDGFR-β	22
RET	1.5
B-RAF	28
FGFR1	202

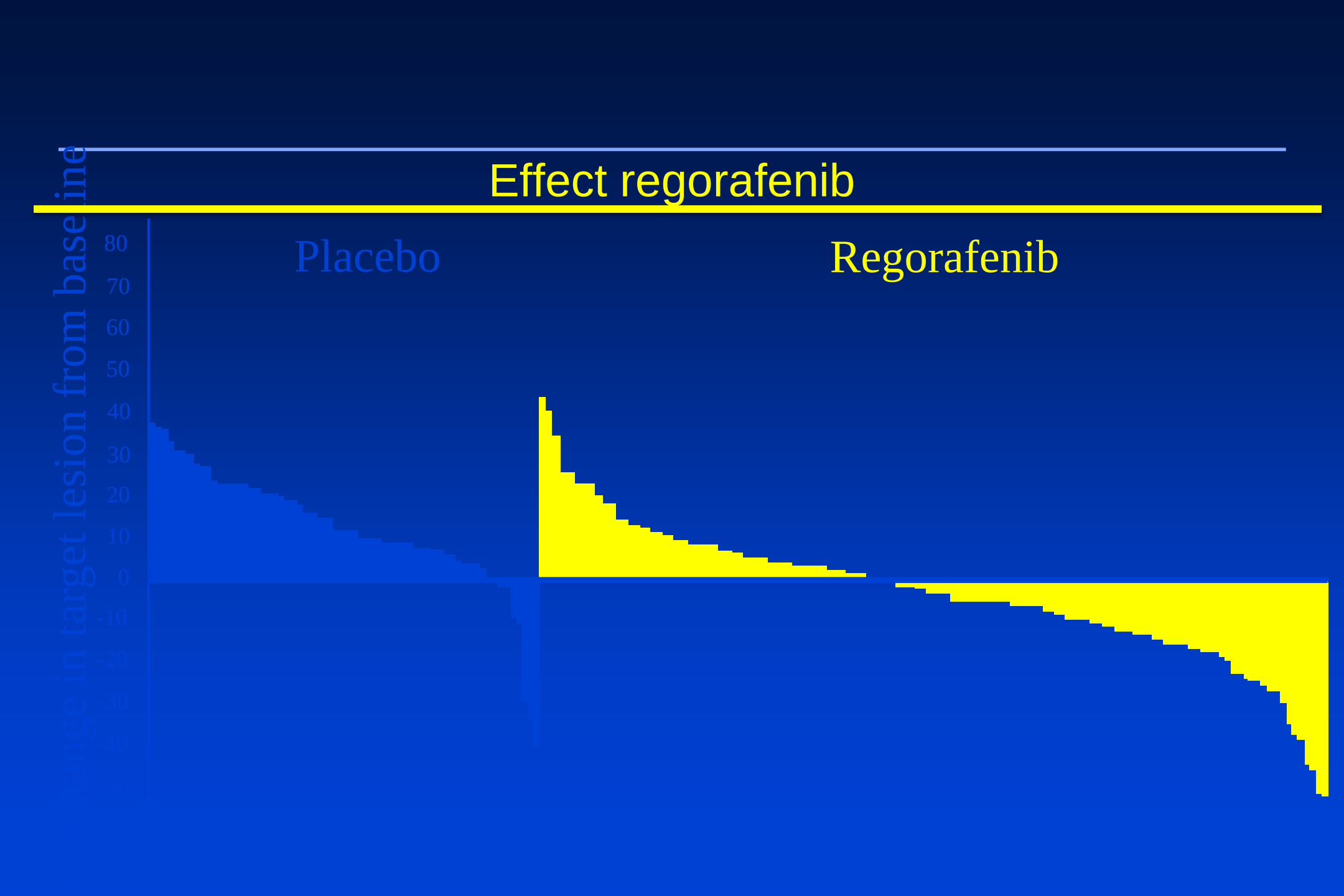
GIST – Regorafenib In Progressive Disease (GRID): study design



Progression-free survival (primary endpoint)

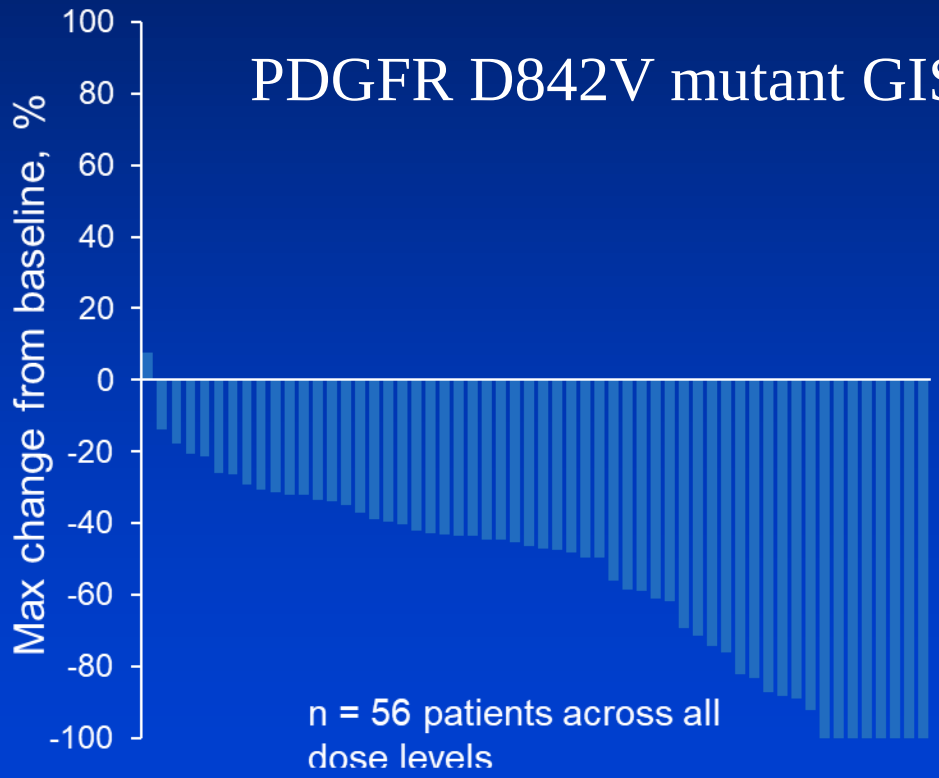


Effect regorafenib

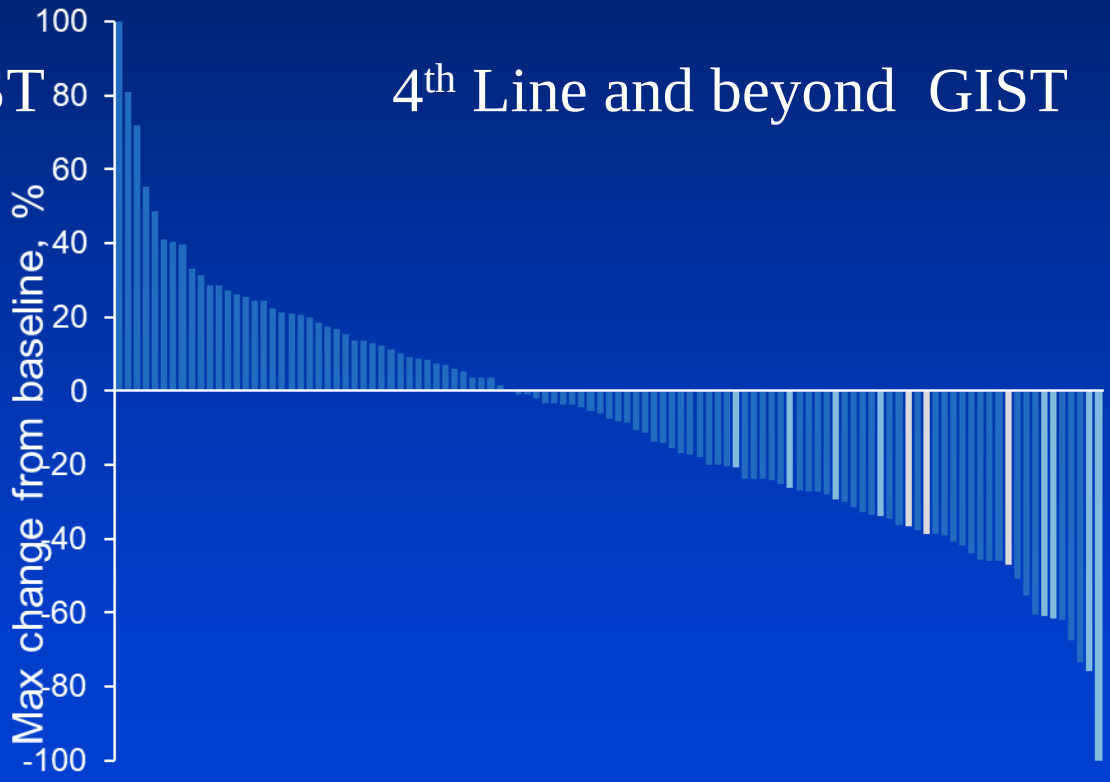


Avapritinib (BLU)

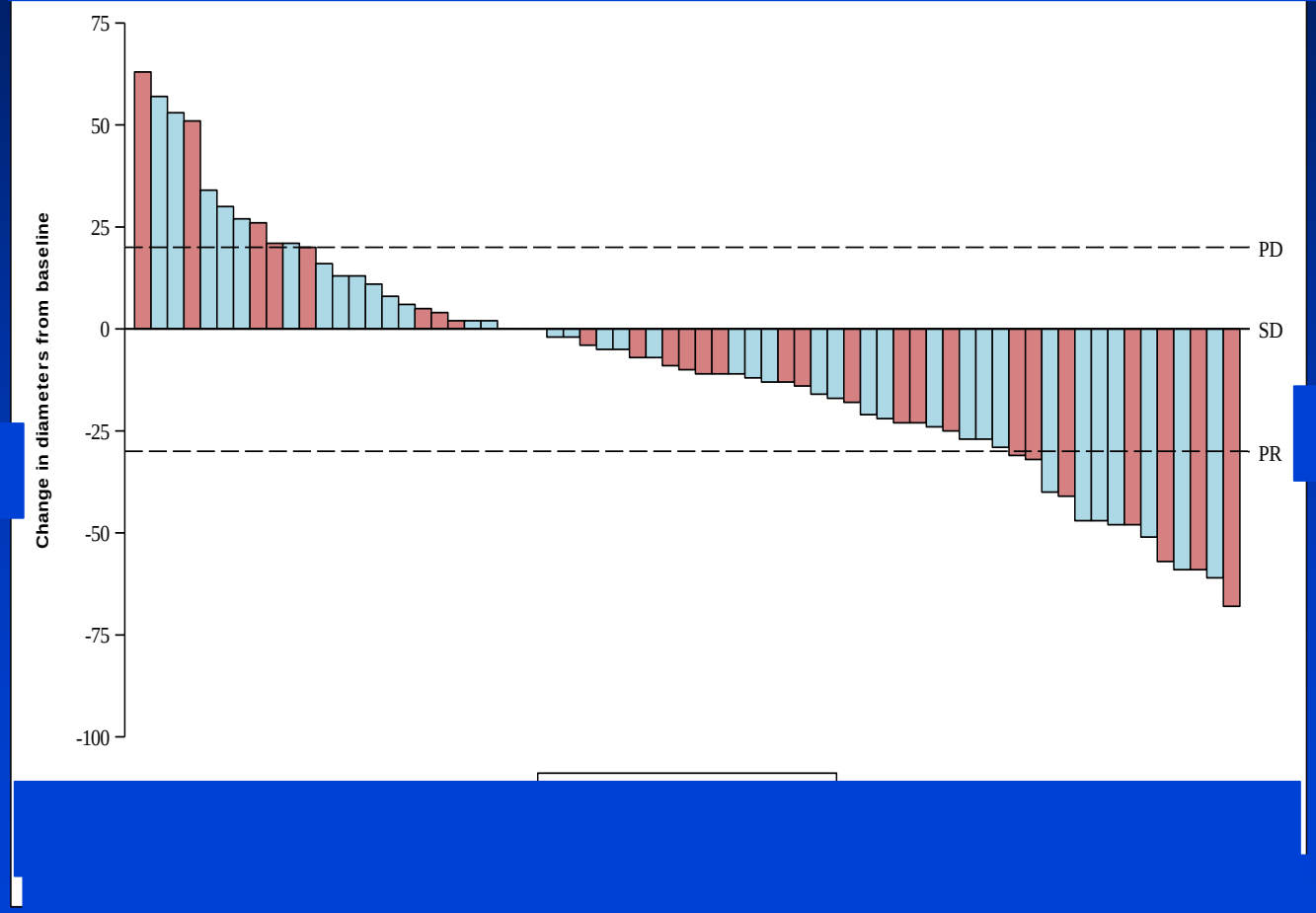
PDGFR D842V mutant GIST



4th Line and beyond GIST



Ripretinib



2nd Line (n=38)

- 7/38 PRs(1) (18%) as of data cut off

3rd line (n=29)

- 7/29 PRs(1) (24%) as of data cut off

2nd & 3rd line (n=67)

- 14/67 PRs (1) (21%) as of data cut off

Ripretinib registration

- INVICTUS Achieved Primary Endpoint, Ripretinib Significantly Improved Progression Free Survival (PFS) Versus Placebo in Patients with Fourth-line and Fourth-line Plus GIST
- Median PFS for Ripretinib of 6.3 Months Versus Placebo of 1.0 Month; Hazard Ratio of 0.15, $p<0.0001$
- Company Expects to Submit an NDA to the FDA in 1Q 2020 for the Treatment of Patients with Advanced GIST who have Received Prior Treatment with Imatinib, Sunitinib and Regorafenib

Conclusion

- GIST since 20 years well understood and much better treatments
- Avapritinib en ripretinib: new kids on the block
- Rare disease: treatment in reference centres