

# Gastrointestinal Stromal Tumor GISTs 2018

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# Background

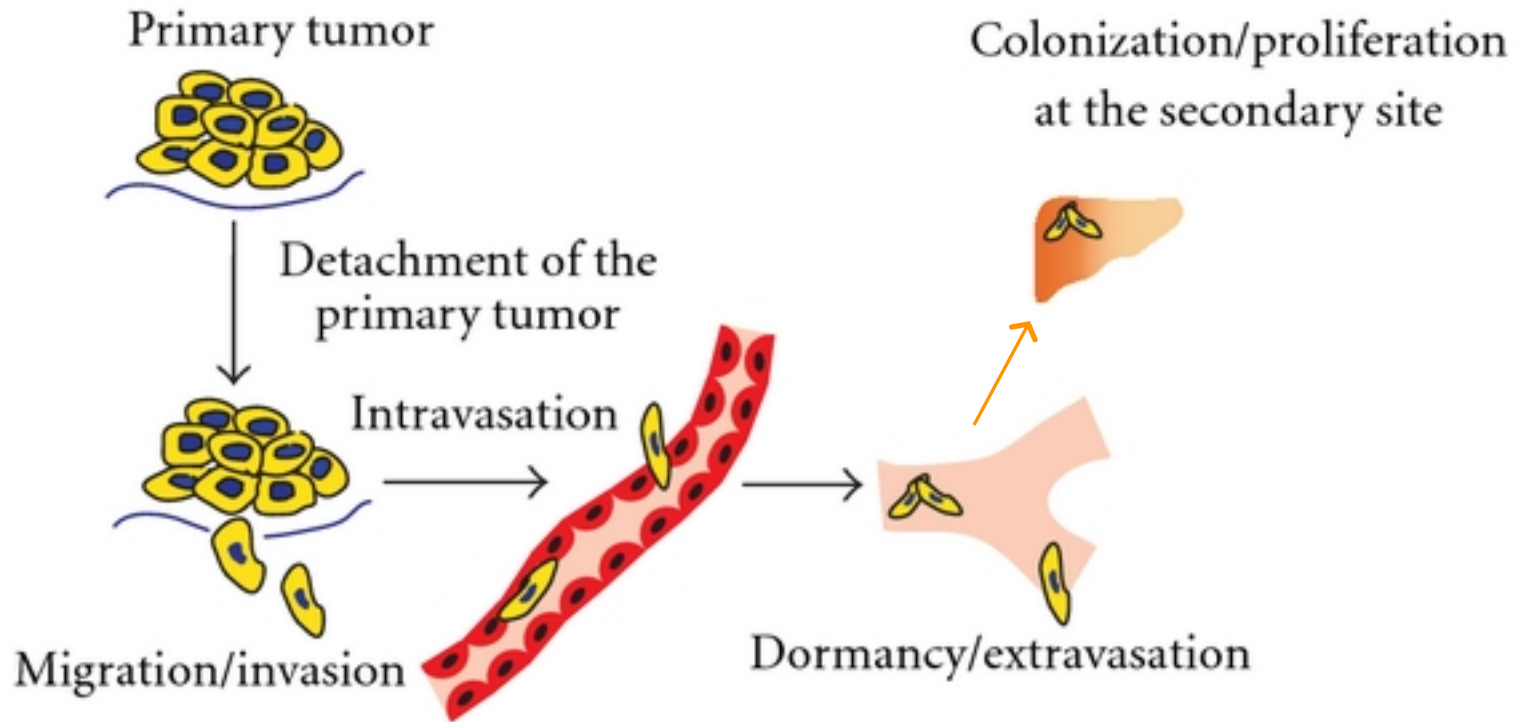


# GIST Overview

- Most common GI sarcoma
  - 0.2% of all GI tumors, but 80% of GI sarcomas
- Distinct clinical and histopathologic entity
  - Highest incidence in the 40-60 year age group
  - Similar male/female incidence
- About 5,000 newly diagnosed GIST patients per year in the US
- Clinical presentation is variable
  - pain, hemorrhage, anemia, anorexia, nausea, bleeding
- High recurrence rate after surgery (>50%)
- No effective chemotherapy

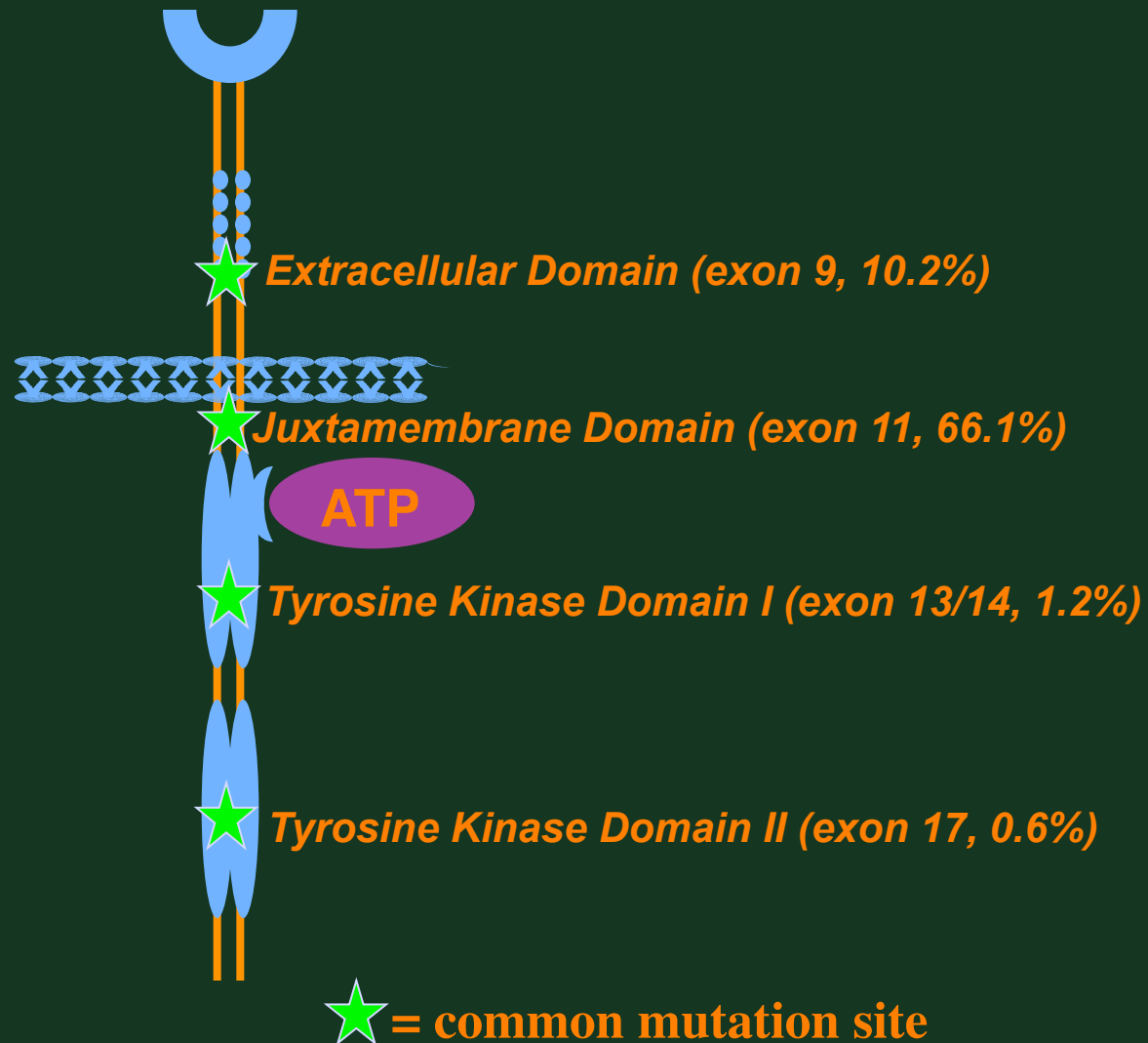


# Metastasis in GIST

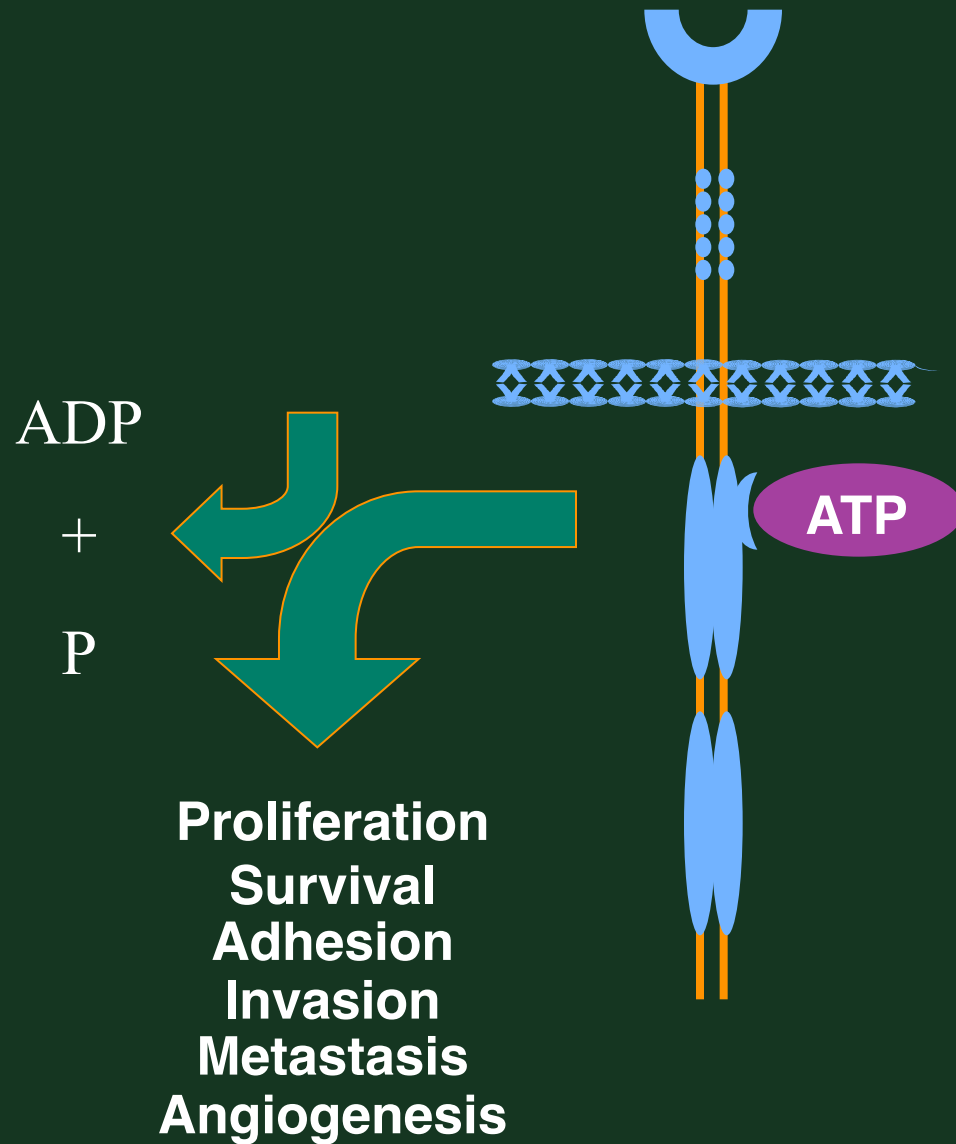




# Kit Receptor Structure

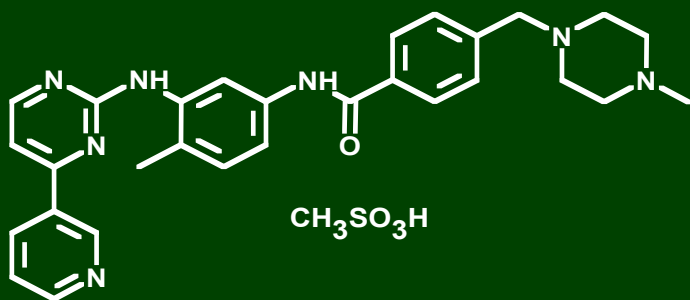


# Kit Receptor Phenotype



# Imatinib Mesylate

## *Kinase Inhibitor, TKI*



**Formula:**  $C_{30}H_{35}N_7SO_4$

**MW:** 589.7

- Rational drug design
  - 2-phenylamino pyrimidine
  - Based on structure of ATP binding site
  - Highly water soluble
  - Oral bioavailability

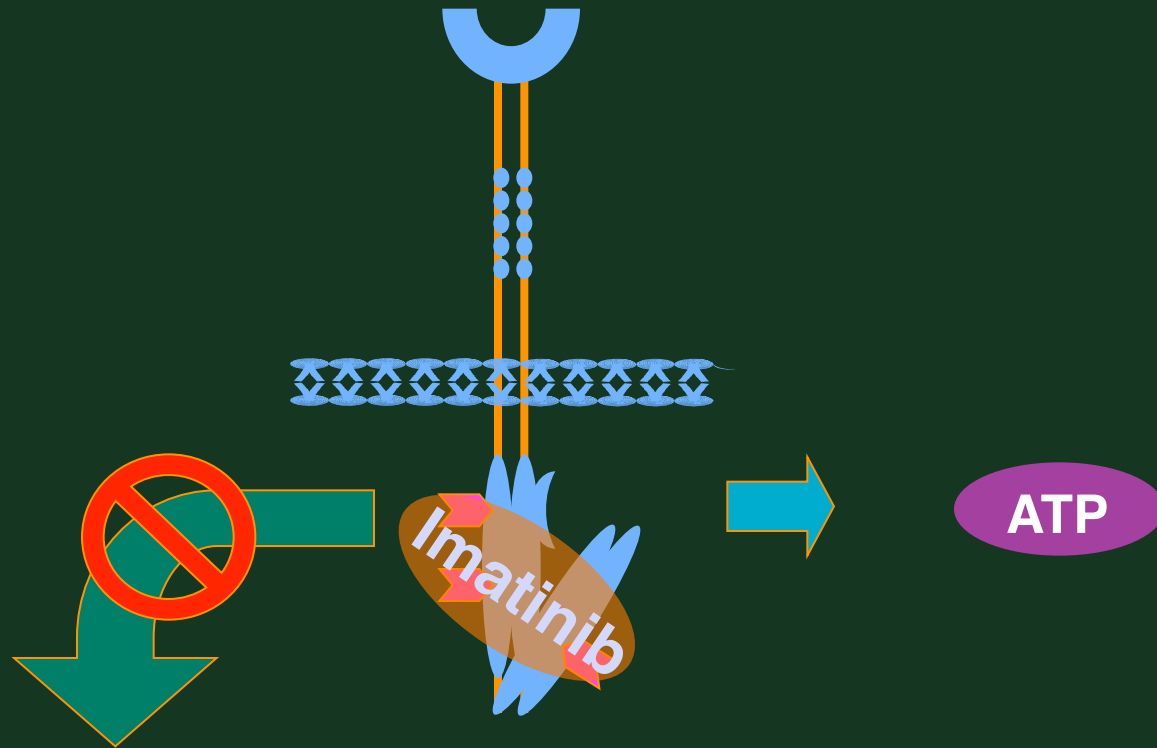
Inhibitor of selective tyrosine kinases

bcr-abl  
PDGF-R  
c-kit

Potent ( $IC_{50} \approx 0.1 \mu M$ )



# Kit Receptor Phenotype

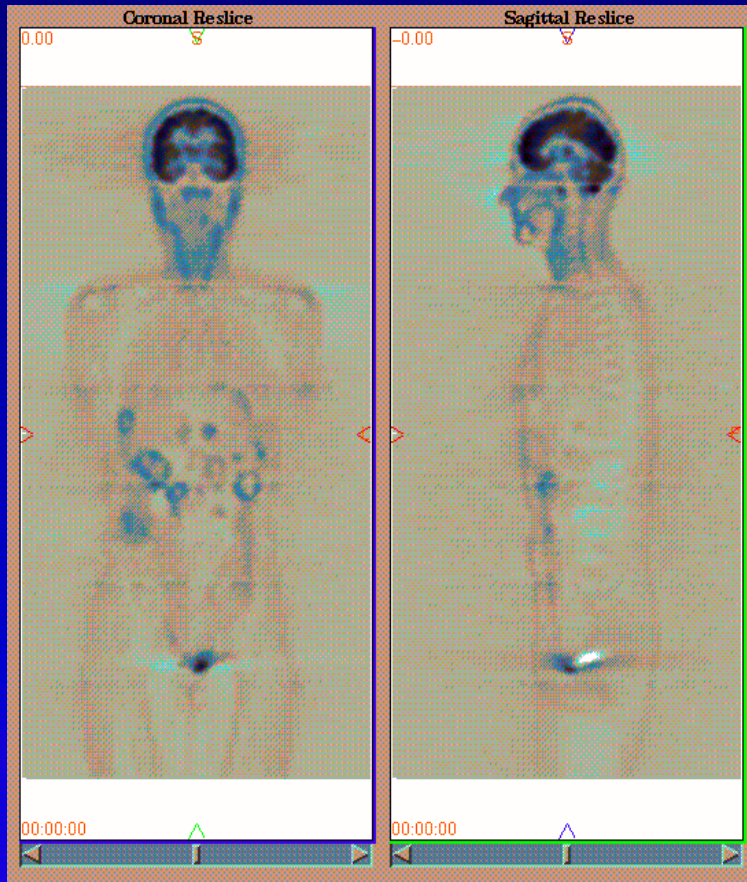


**Proliferation**  
**Survival**  
**Adhesion**  
**Invasion**  
**Metastasis**  
**Angiogenesis**

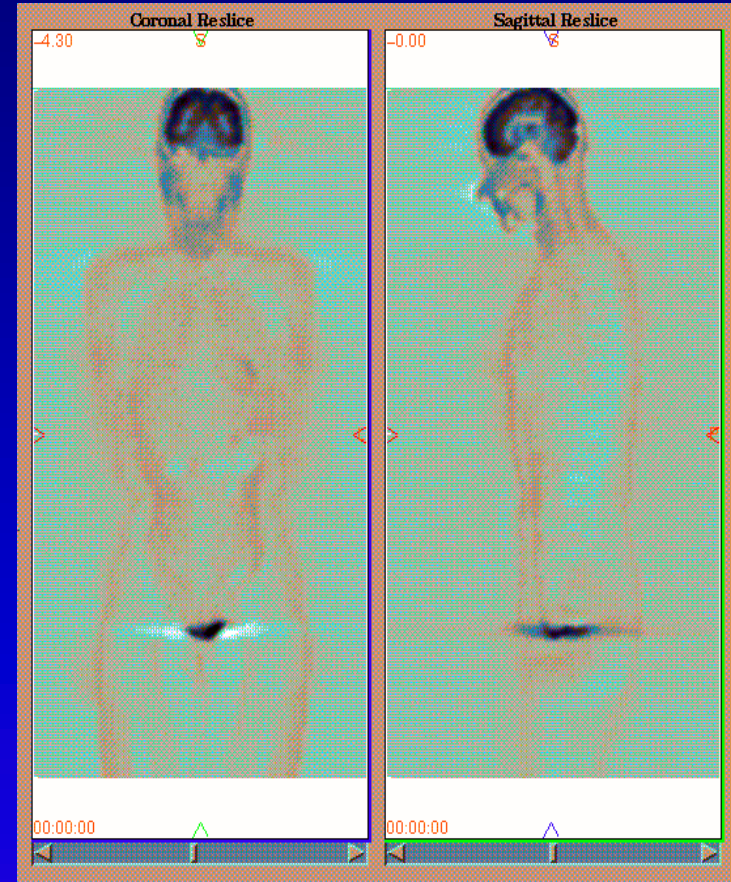
➤ = imanitib contact point



# Marked Biologic Response Revealed by PET Scan



Multiple liver and upper abdominal  
<sup>18</sup>F-FDG-accumulating metastases



A marked decrease in <sup>18</sup>F-FDG uptake  
4 weeks after starting imatinib mesylate

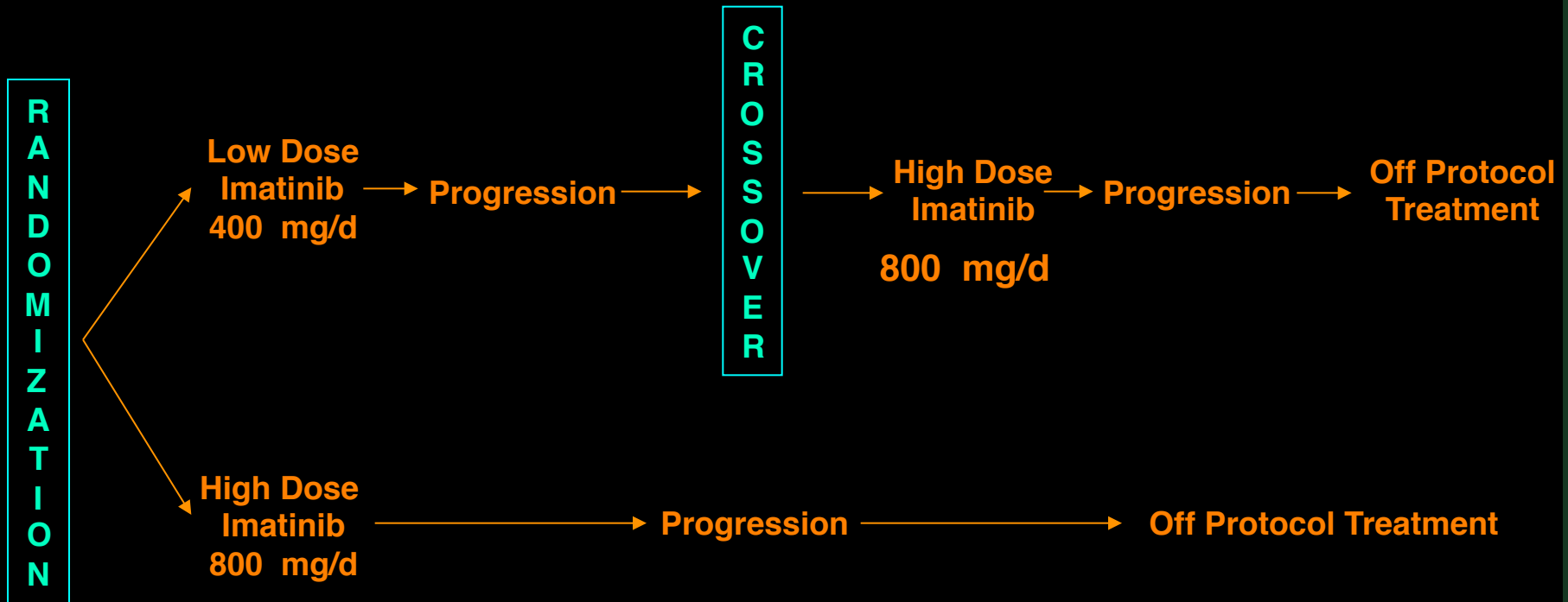
# Clinical Trials of Imatinib in GIST

Study	Phase	N	OR	CR	PR	SD	PD	OS (2 yr)	TTP (median)	PFS
van Oosterom, 2001	I	36	53%	0%	53%	36%	11%	-	-	-
von Mehren, 2002	II	147	63%	0%	63%	19%	12%	-	72 wks	-
Verweij, 2003	II	27	71%	4%	67%	18%	11%	-	-	73% (1 yr)
Rankin, 2004	III	746								
-400 mg daily			48%	3%	45%	-	-	78%	-	50% (2 yr)
-800 mg daily			48%	3%	45%	-	-	73%	-	53% (2 yr)
Verweij, 2004	III	946								
-400 mg daily			50%	5%	45%	32%	13%	69%	-	44% (2 yr)
-800 mg daily			54%	6%	48%	32%	9%	74%	-	52% (2 yr)

Courtesy Dejka Araujo, M.D.



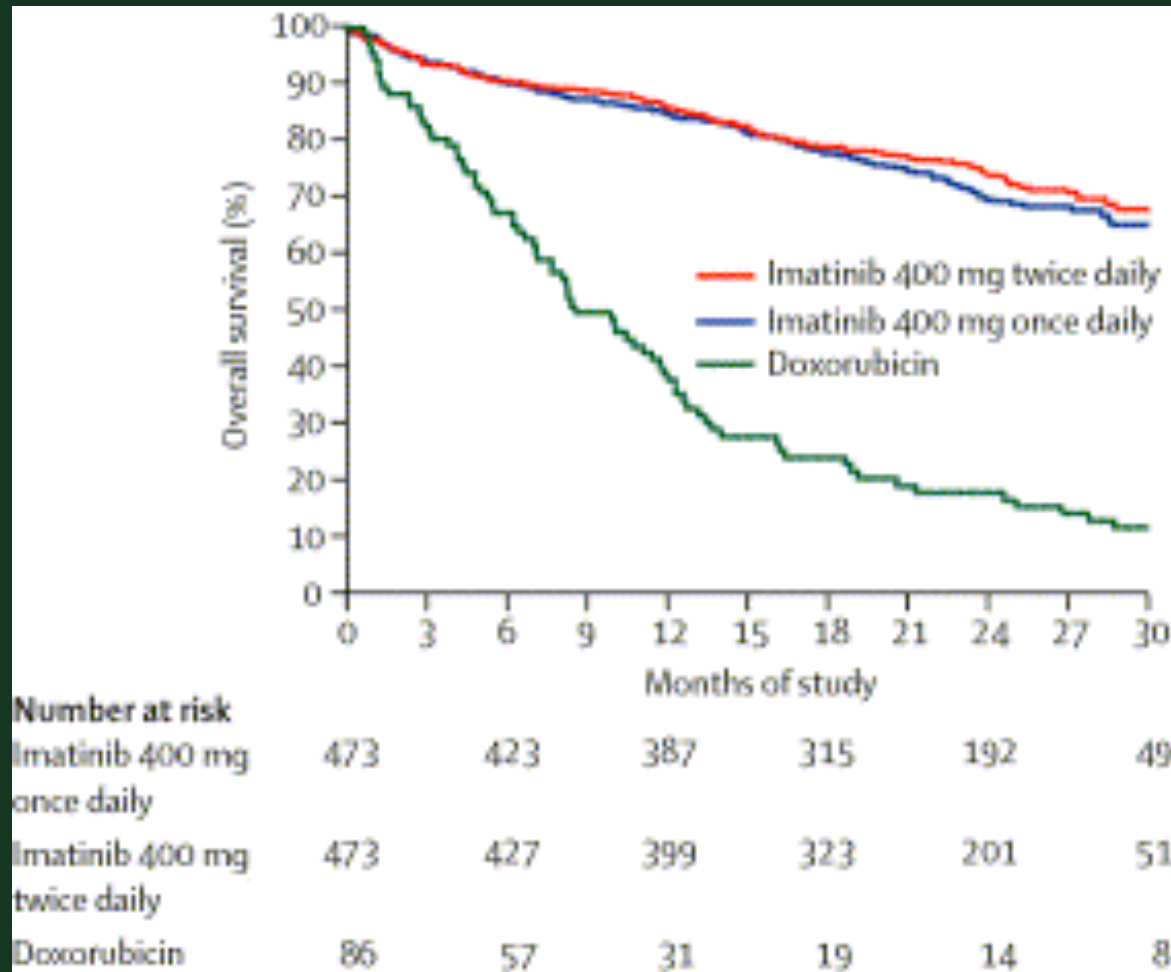
# North American Sarcoma Intergroup Schema





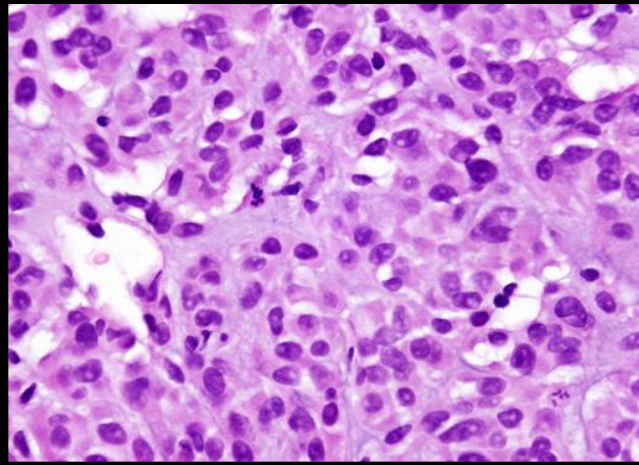
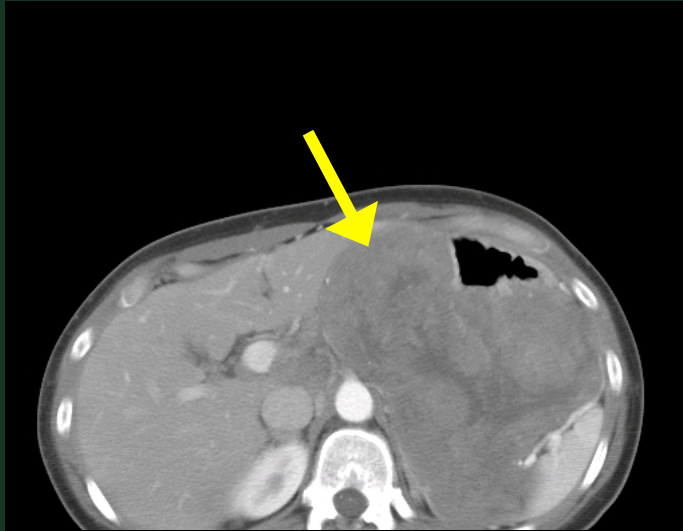
# EORTC Phase III Imatinib for Advanced GIST

## *Survival Benefit*

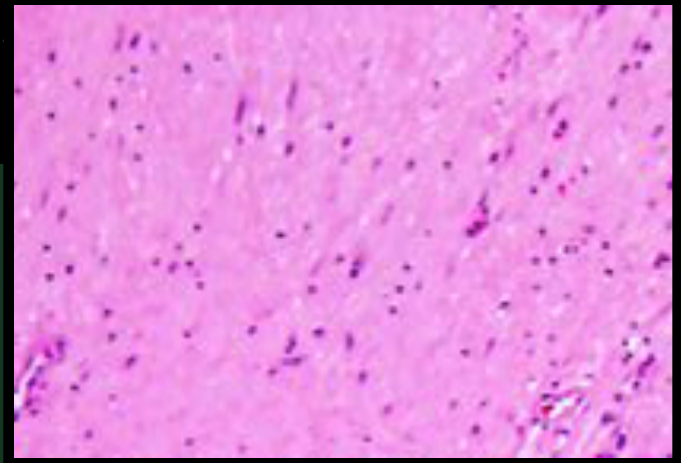
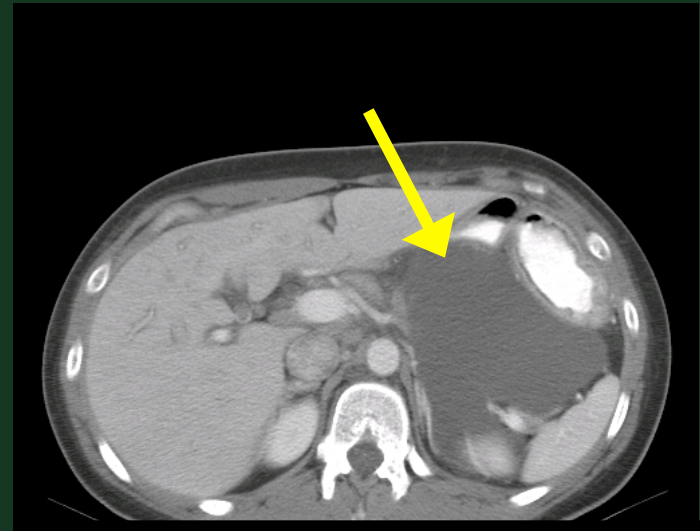




# GIST Response



Pre-Imatinib



Post-Imatinib (8 weeks therapy)

# GIST Evaluation

- Every 2-3 months (extend over time)
- History and Physical Examination
- Laboratory Testing
- Abdominal/pelvic CT with contrast
  - Recommended for diagnosis and staging
  - Also useful for assessing common sites of metastasis (eg, liver, peritoneum)
  - Every 2-6 months while on therapy
- Chest X-ray
- <sup>18</sup>F<sup>18</sup>FDG-PET
- MRI with gadolinium

<sup>18</sup>F<sup>18</sup>FDG-PET=fluorine-18-fluorodeoxyglucose positron emission tomography.

McAulliffe et al, *Annals of Surg Onc* 2009;16(4):910-9; Van den Abbeele. *Oncologist*. 2008;13:8.



**What if my GIST does not have a  
KIT mutation?**



# GIST Subtypes of GIST

- Kit exon 11
- Kit exon 9
- PDGFR D842V
- SDH deficiency
- Raf V600E
- NF-1, Ras
- PI3K
- IGF-1R expressing
- TRK fusion
- KIT resistance mutations
  - Exon 13 (ATP binding site)
  - Exon 17 (A-loop)

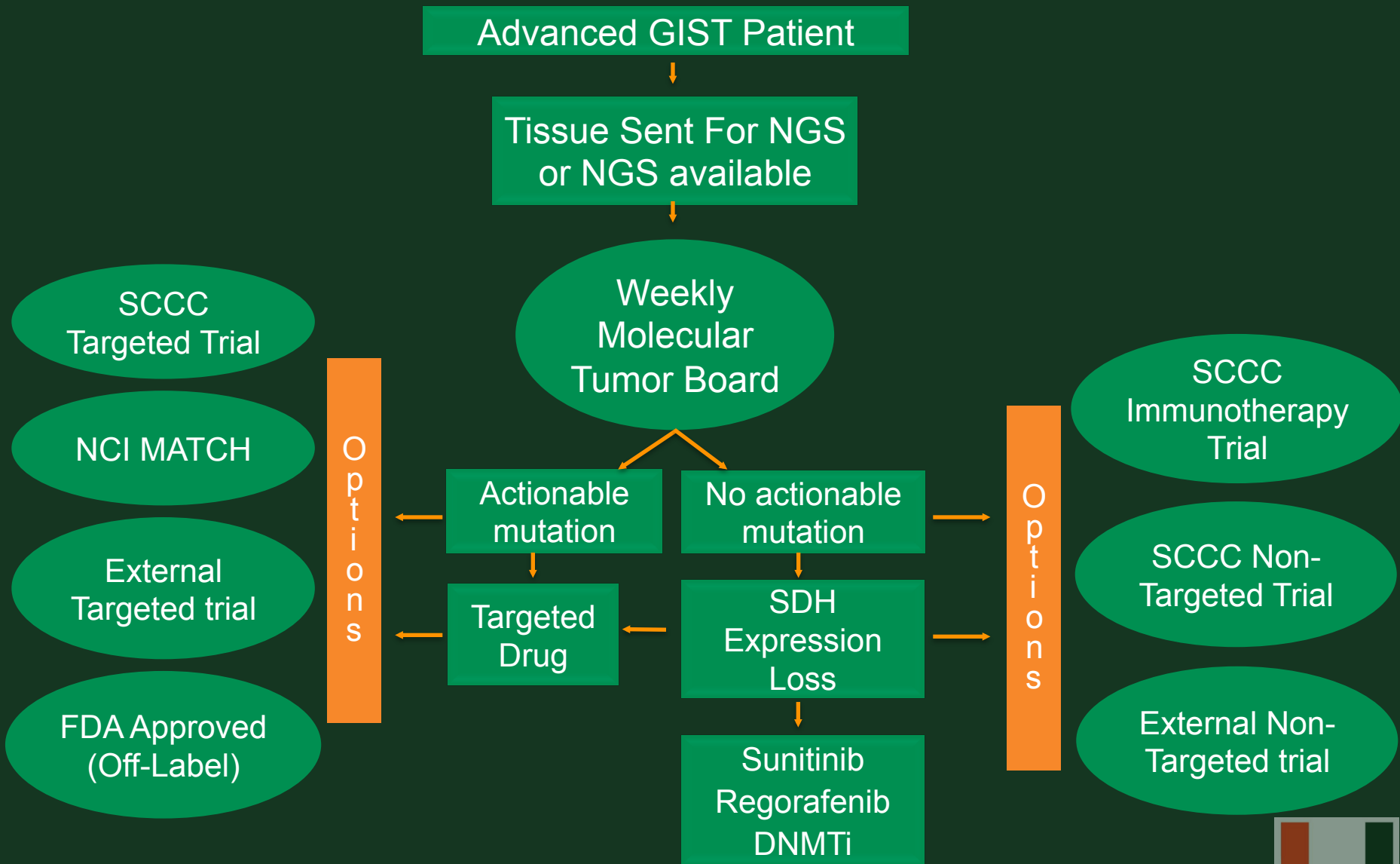


# GIST Subtypes and Treatment

- Kit exon 11: Imatinib 400 mg
- Kit exon 9: Imatinib 800mg (or tolerated dose)
- PDGFR D842V: anti-PDGFR trial (avapritinib, crenolanib)
- SDH deficiency: Sunitinib or Regorafenib
- Raf V600E: Raf inhibitor
- NF-1, Ras: Raf or Mek inhibitor
- PI3K: mTOR inhibitor
- IGF-1R expressing – IGF-1R inhibitor trial
- TRK fusion – LOXO-101 NTRK inhibitor trial
- KIT resistance mutations
  - Exon 13 (ATP binding site): Sunitinib 37.5 mg daily
  - Exon 17 (A-loop): Regorafenib 120 mg daily



# GIST Precision Medicine

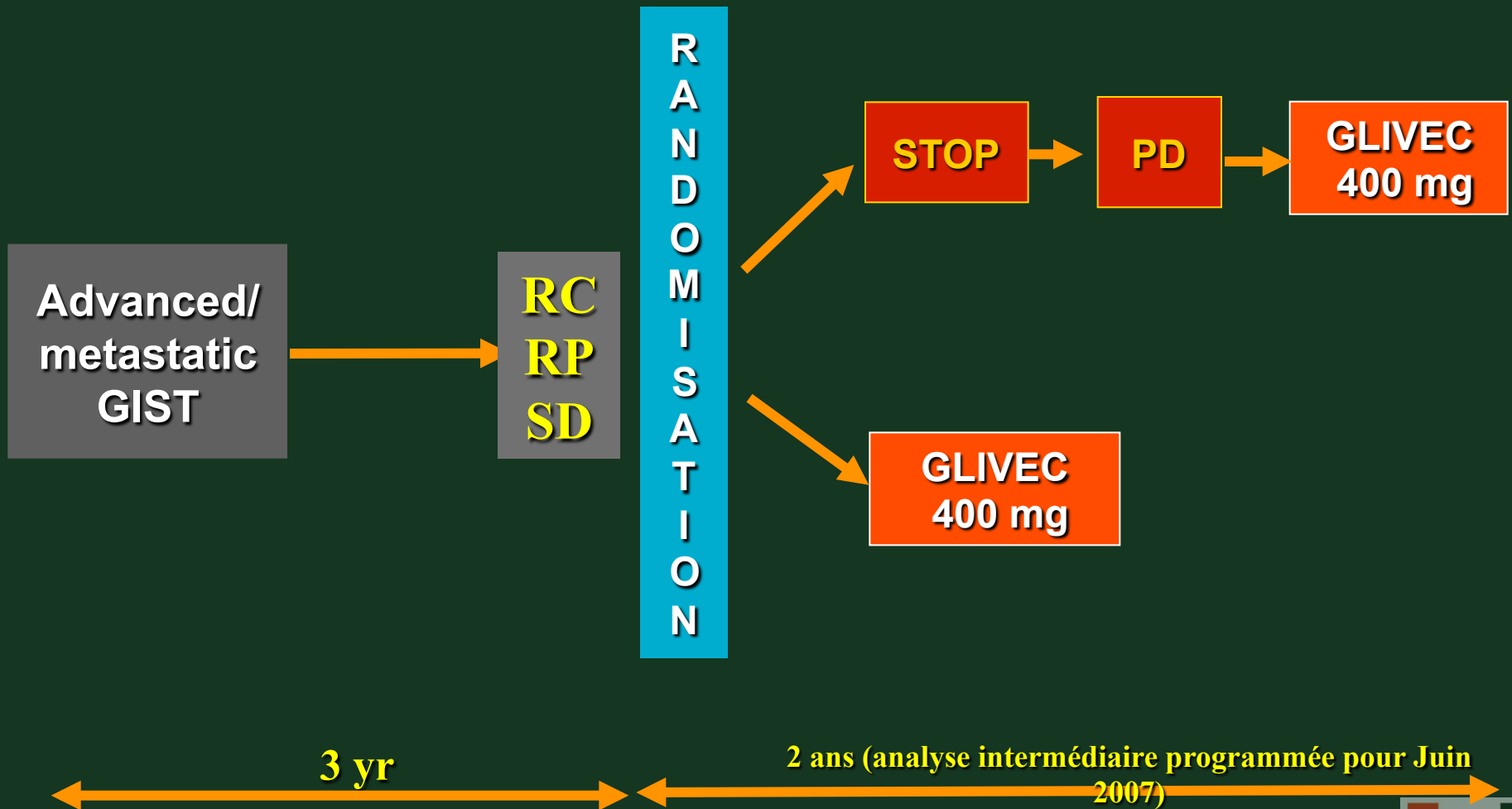


# How Long Do I take Imatinib or Other Kinase Inhibitor?



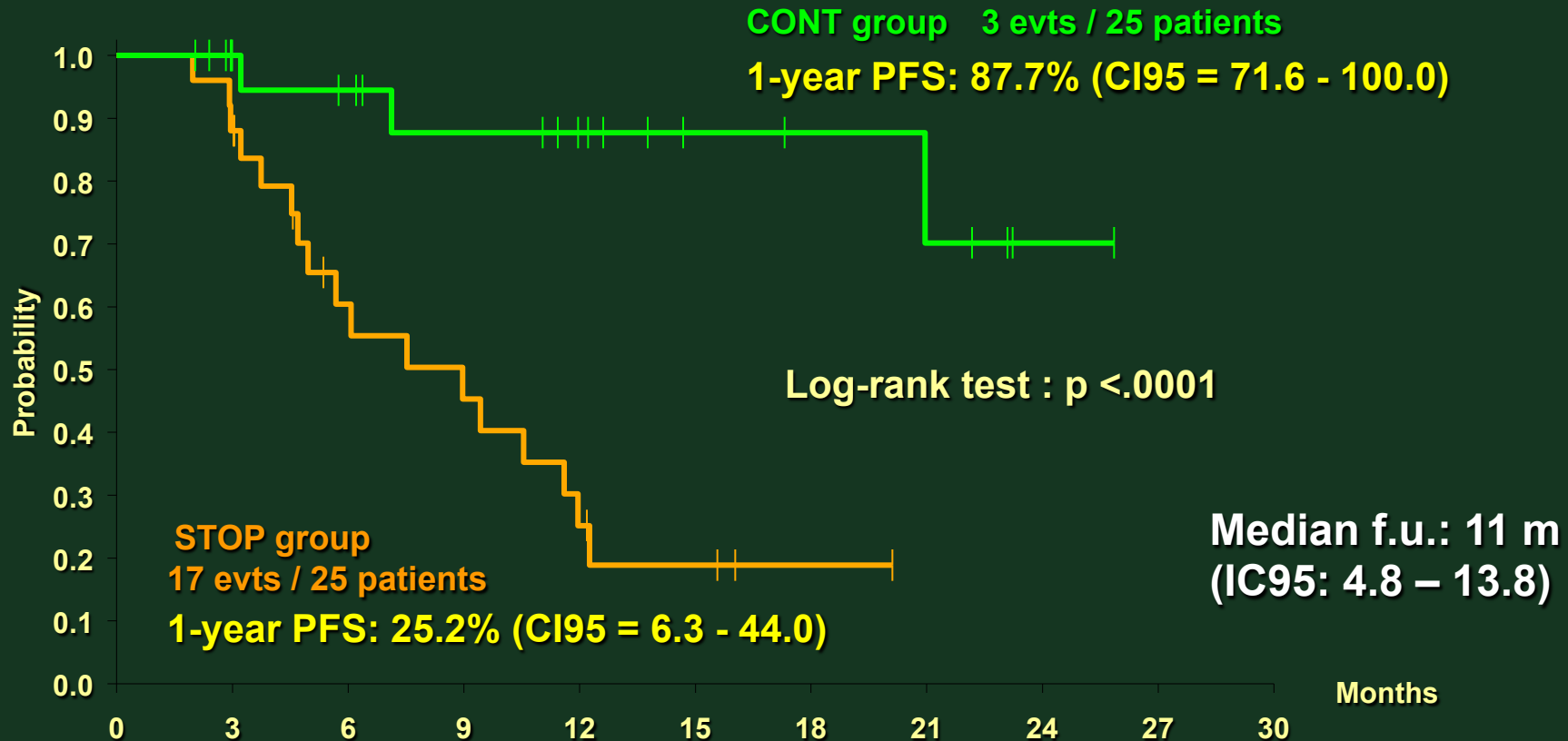


# BFR14 3-yr randomization





# BFR14 3-yr randomization Progression Free Survival



**Rate of PD  
in STOP group**

at 6 months: 40%  
at 9 months: 55%  
at 1 year: 75%

Updated sept 07, ECCO 14

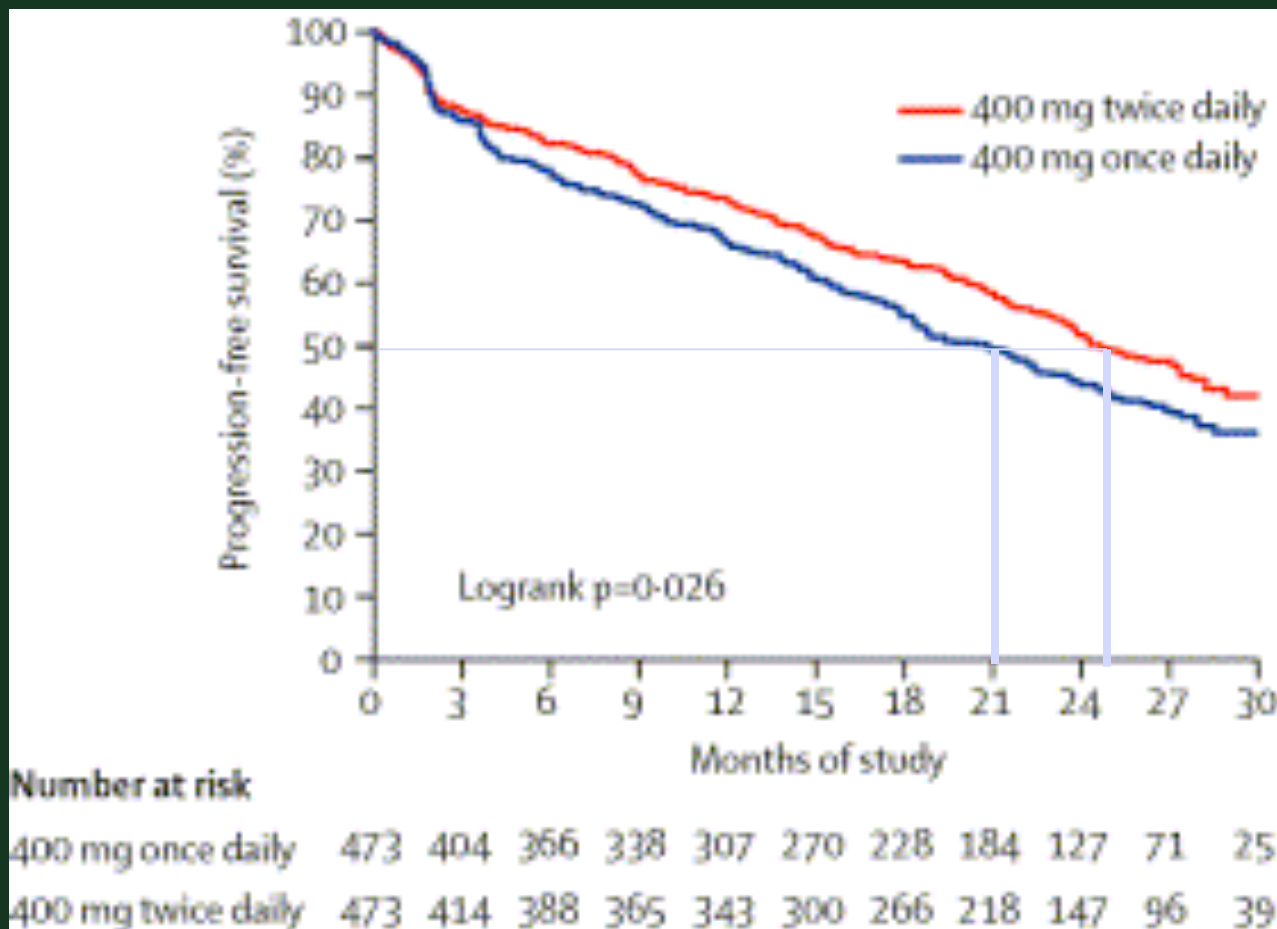


# What Dose of Imatinib Do I Take?

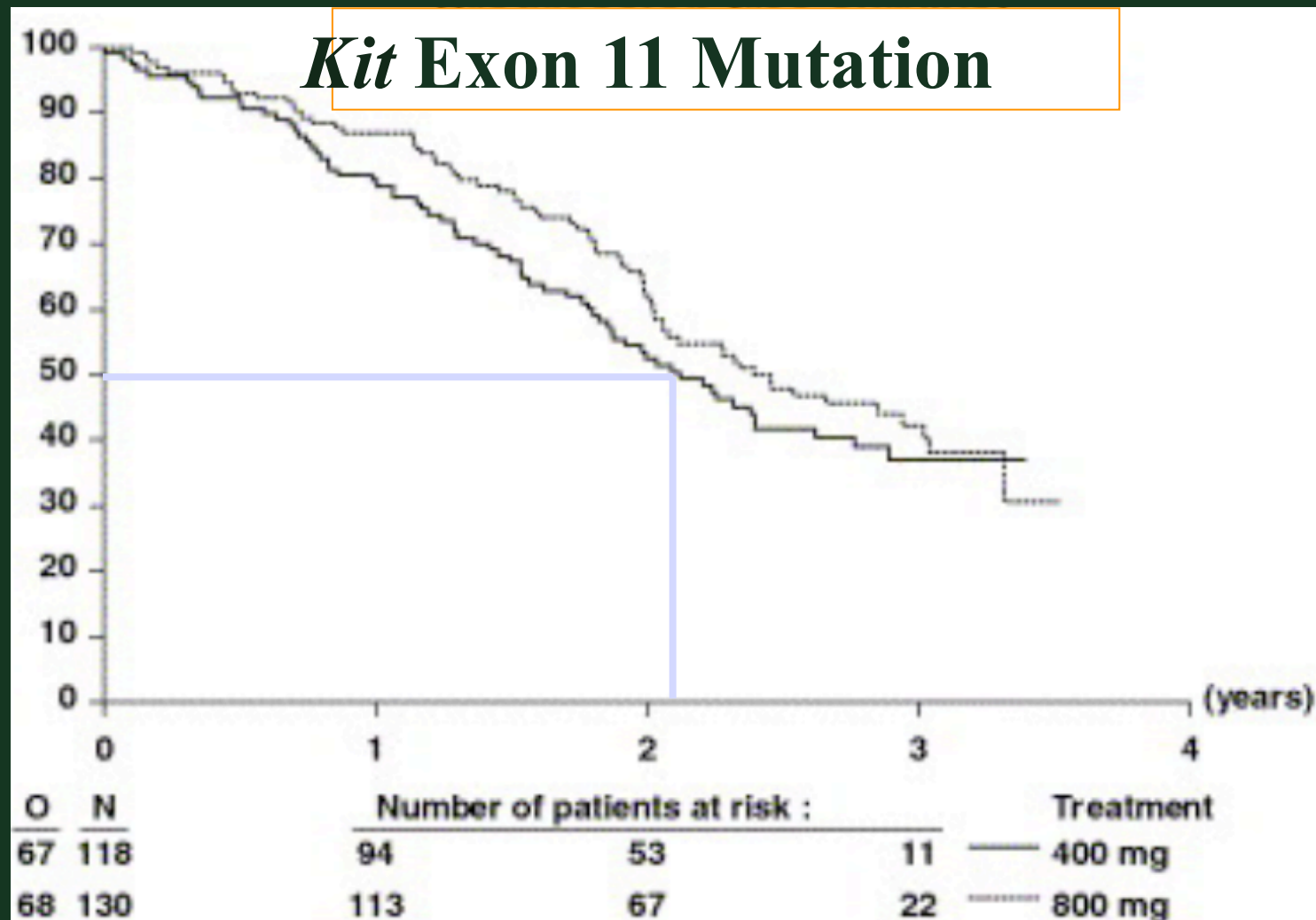


# EORTC Phase III Imatinib for Advanced GIST

## *Progression-free Survival Benefit*

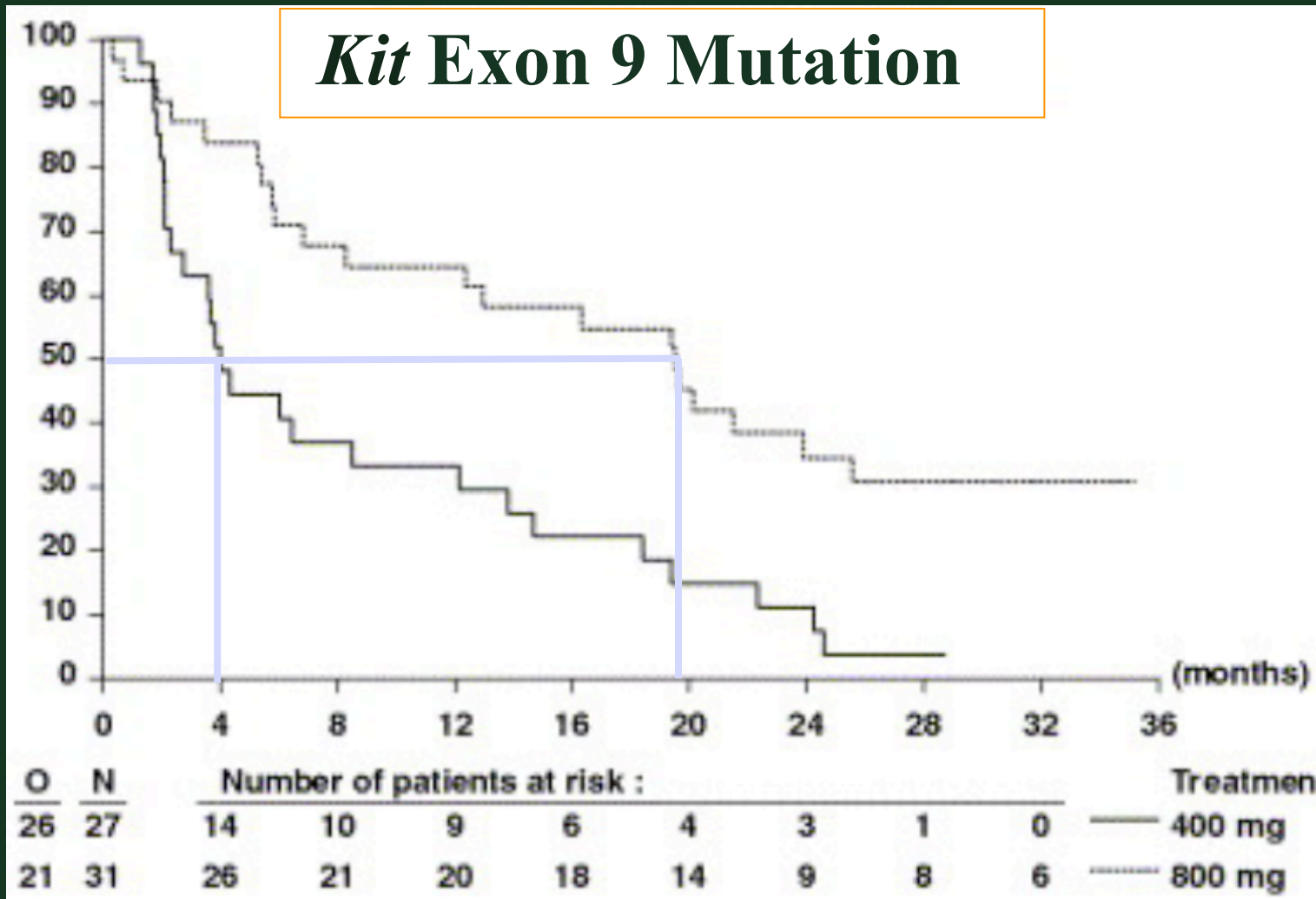


# Progression-free Survival By Imatinib Dose



# Progression-free Survival By Imatinib Dose

*Kit* Exon 9 Mutation



# Will I Have Side Effects?

How Do I Manage Them?



# Side effects: 400 vs. 800 mg

<b>Toxic Event</b>	<b>Adjusted <i>p</i>-Value</b>
Edema	<0.001
Anemia	<0.001
Rash	<0.001
Fatigue	<0.001
Nausea	<0.001
Hemorrhage	<0.001
Diarrhea	0.0026
Dyspnea	0.036
Pleuritic Pain	0.053



# Interruptions and Reductions of Therapy

	400 mg	800 mg
<b>Treatment Interruption</b>	40%	64%
-Hematologic	6%	7%
-Non-Heme	23%	43%
<b>Dose Reduction</b>	16%	60%
-Hematologic	2%	4%
-Non-heme	10%	42%





# North American Intergroup Phase III Study of Imatinib in Advanced GIST

<b>Dose Reduction</b>	<b>400 mg (376 pts)</b>	<b>800 mg (370 pts)</b>	<b>800 mg X-Over</b>
1	10%	44%	16%
2	7%	26%	5%
3	2%	11%	0%
4	1%	4%	0%



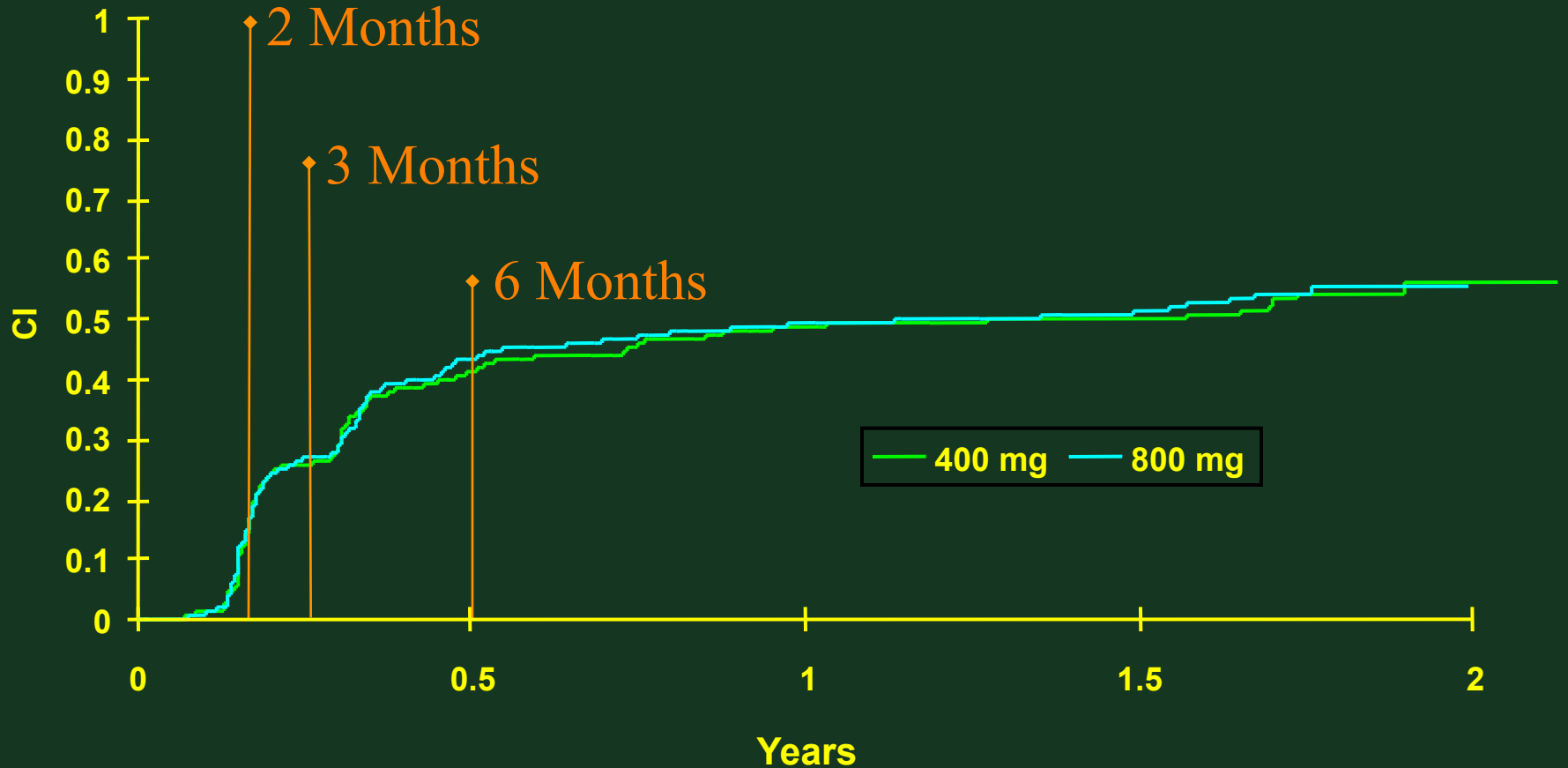
# Is My GIST “Responding” To Therapy

Radiographic Efficacy



# Time to PR by RECIST

Cumulative incidence of CT responses



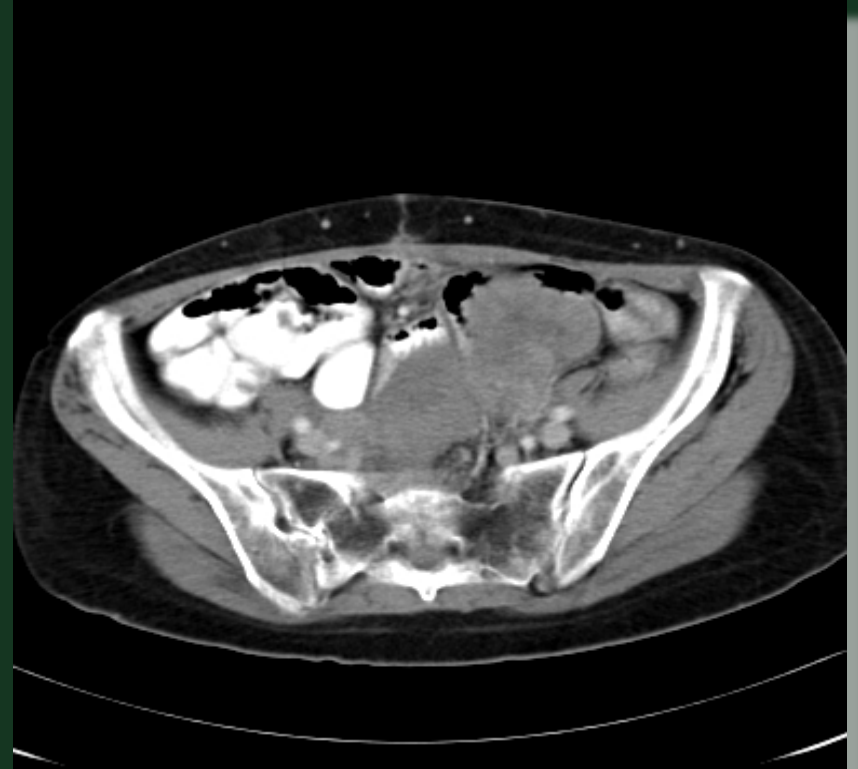
# Good “Response” CT Scan Results

*Jun 27, 2000*

*Oct 4, 2000*



**Before Imatinib**

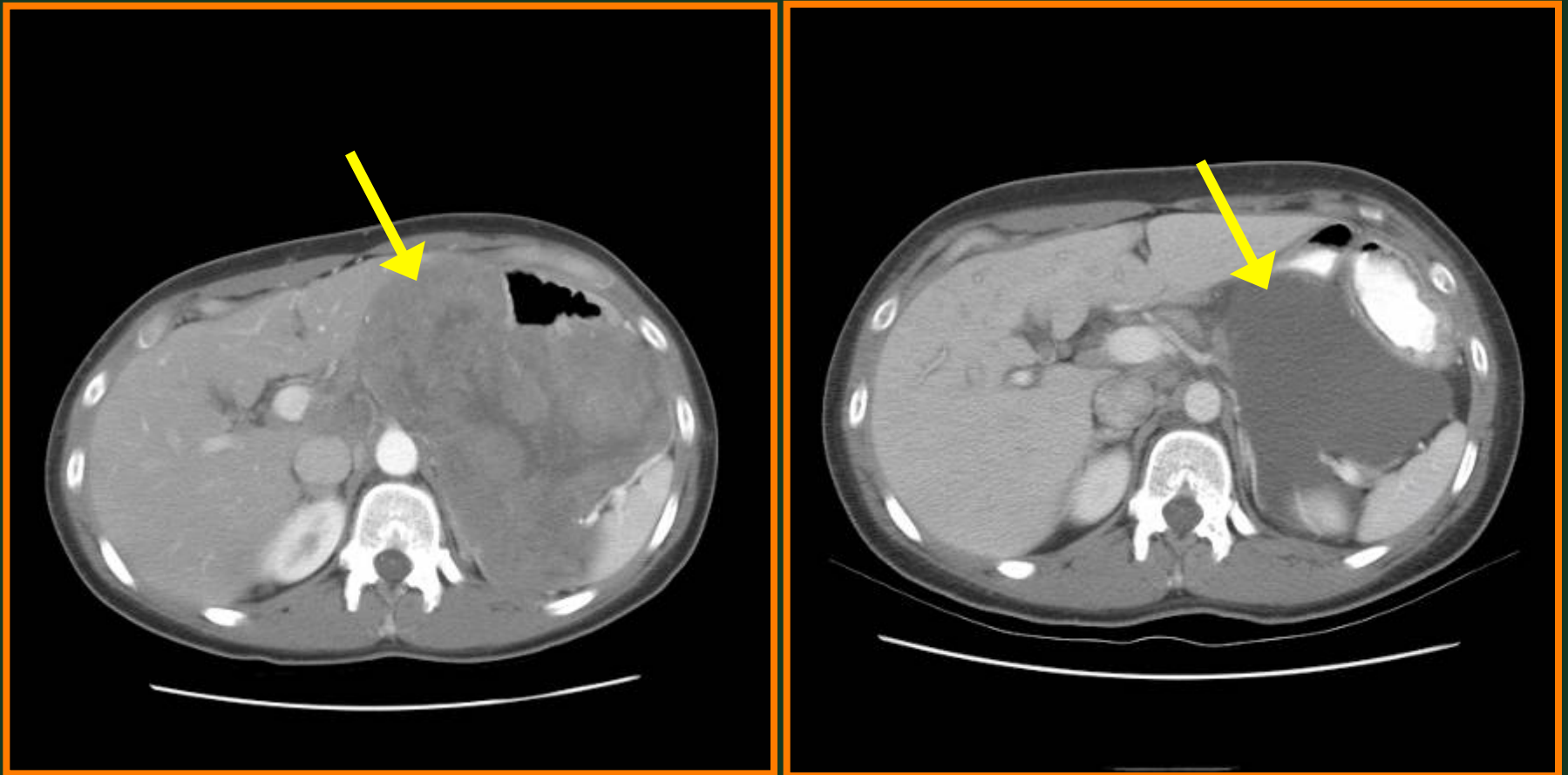


**After Imatinib**



# Good “Response”

## CT Scan Results



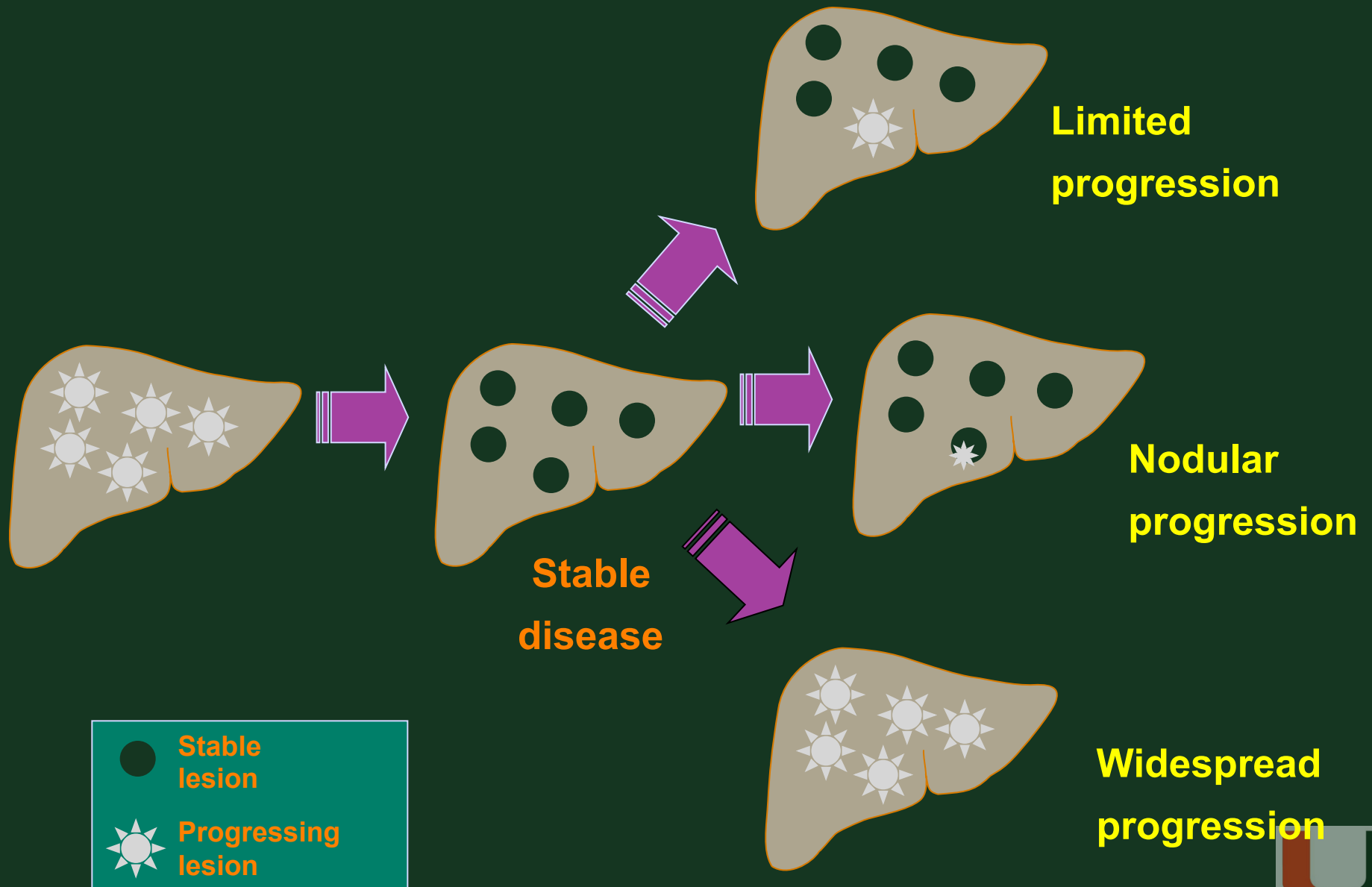
Decrease in GIST intravenous contrast uptake after patient is treated for 8 weeks with imatinib mesylate



**What do I do if my GIST is  
Resistant?**



# Type of Progression

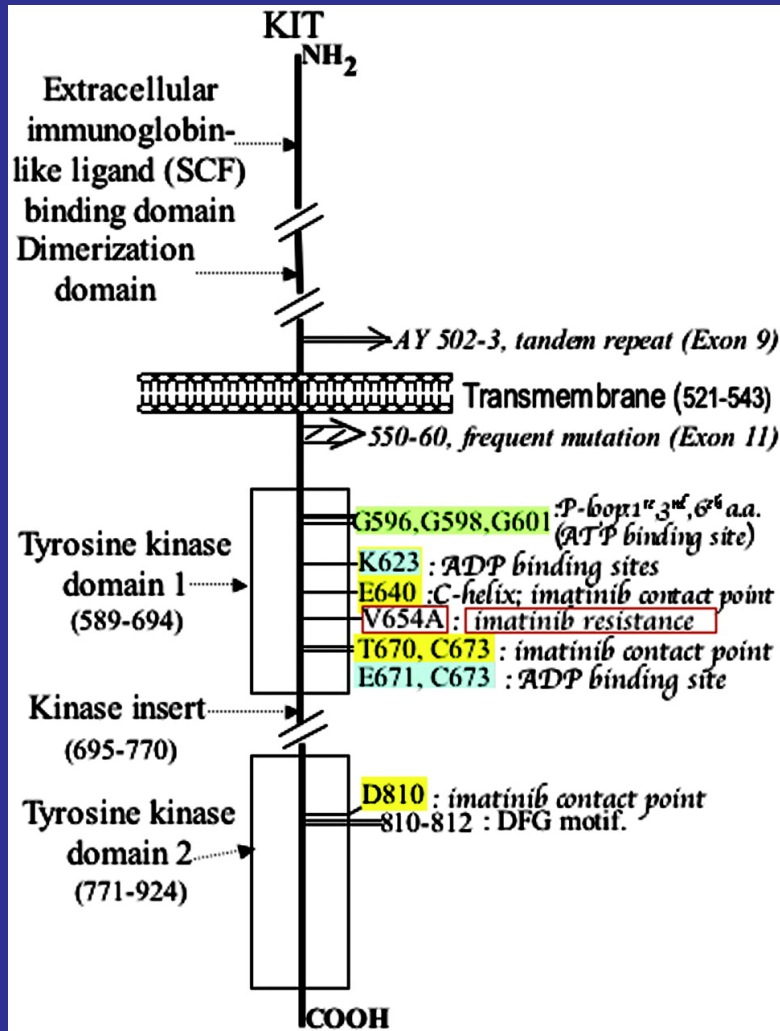


# Limited Progression





# Secondary Mutations in KIT



ATP/ADP Binding Site (V654)

Gate Keeper (T670)

Activation Loop (D820)

# Therapy by Type of Progression

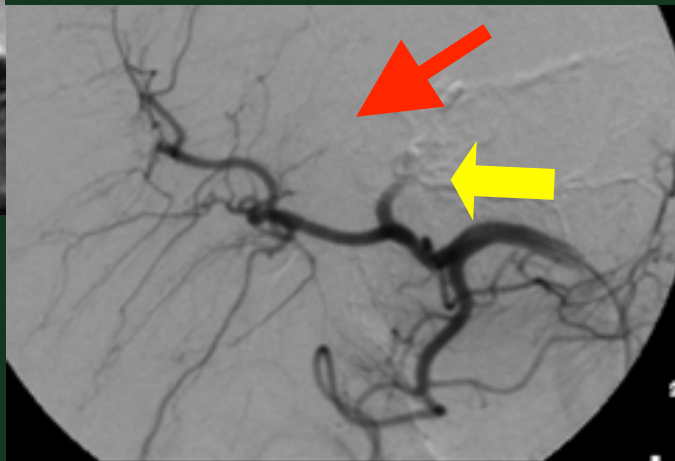
- **Limited or Nodular Progression**
  - Hepatic Artery Chemoembolization
  - Hepatic Radio-frequency Catheter Ablation
  - Surgical Resection
  - Radiation Therapy (esophageal or rectal)
- **Widespread progression**
  - Increase Imatinib to 800 mg daily
  - Sunitinib
  - Regorafenib
  - Clinical Trial



# Hepatic Artery Embolization



Pre-embolization



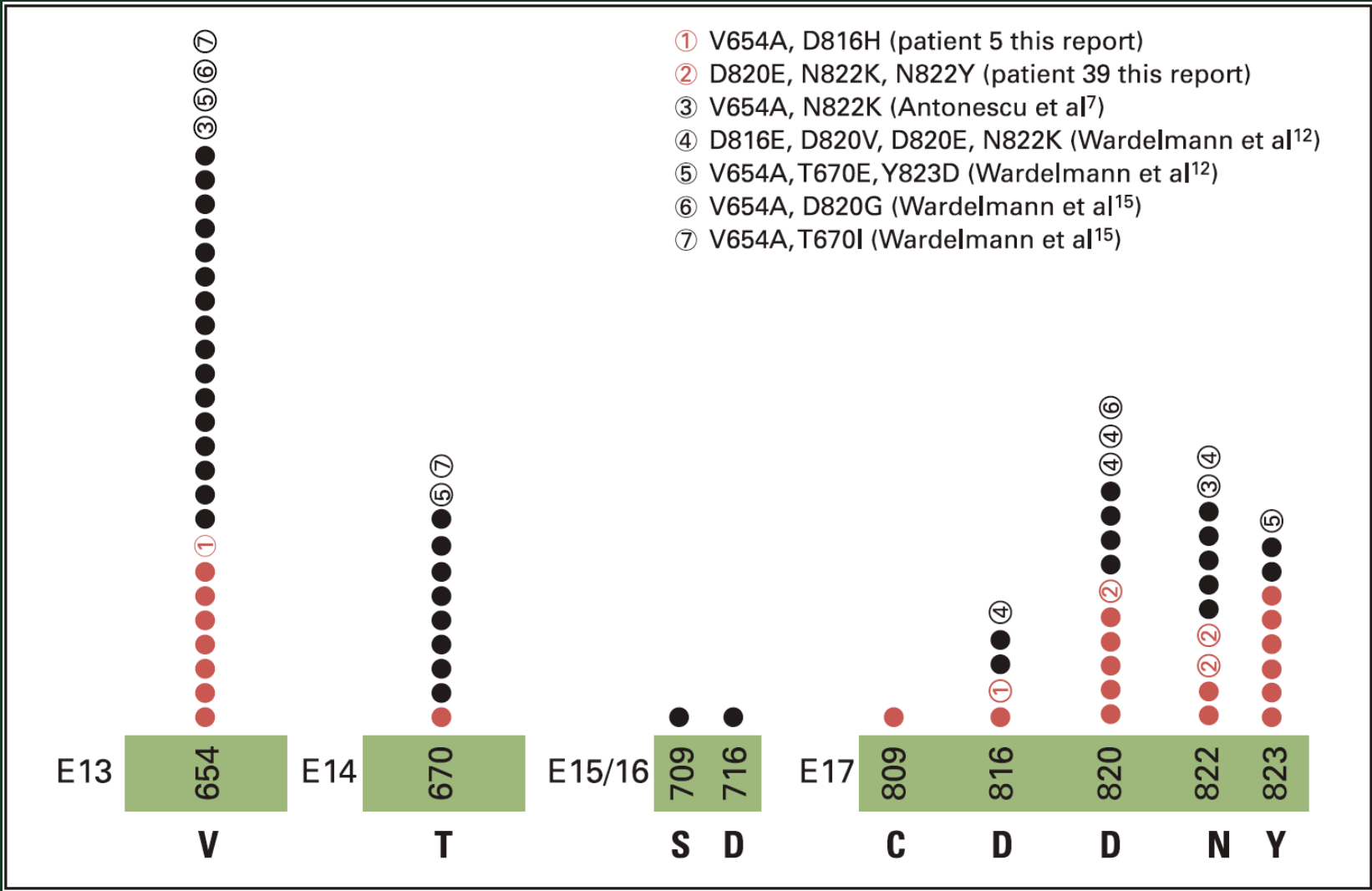
Post-embolization



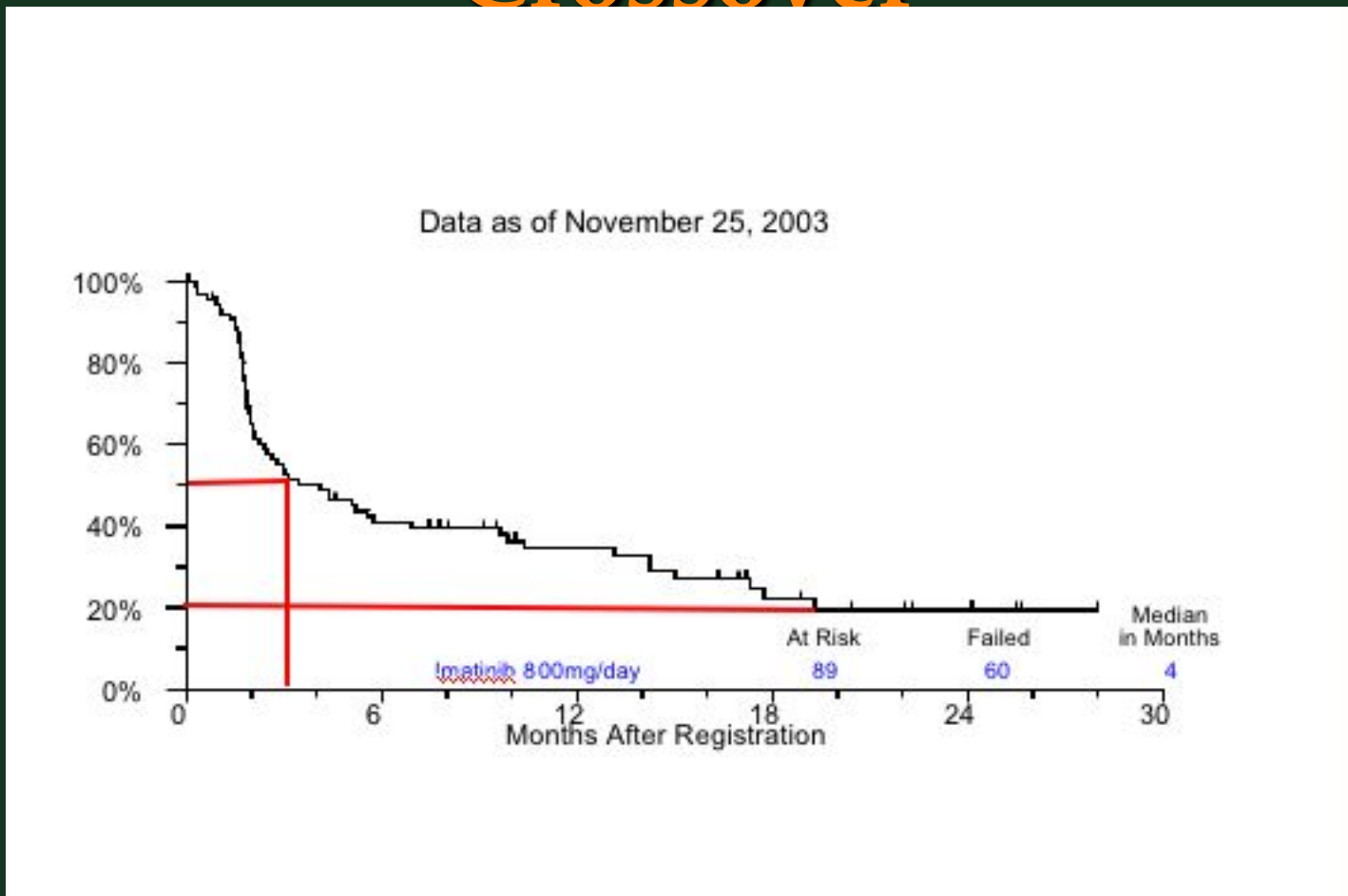
**What happens if imatinib is no longer helping?**



# Secondary Mutation

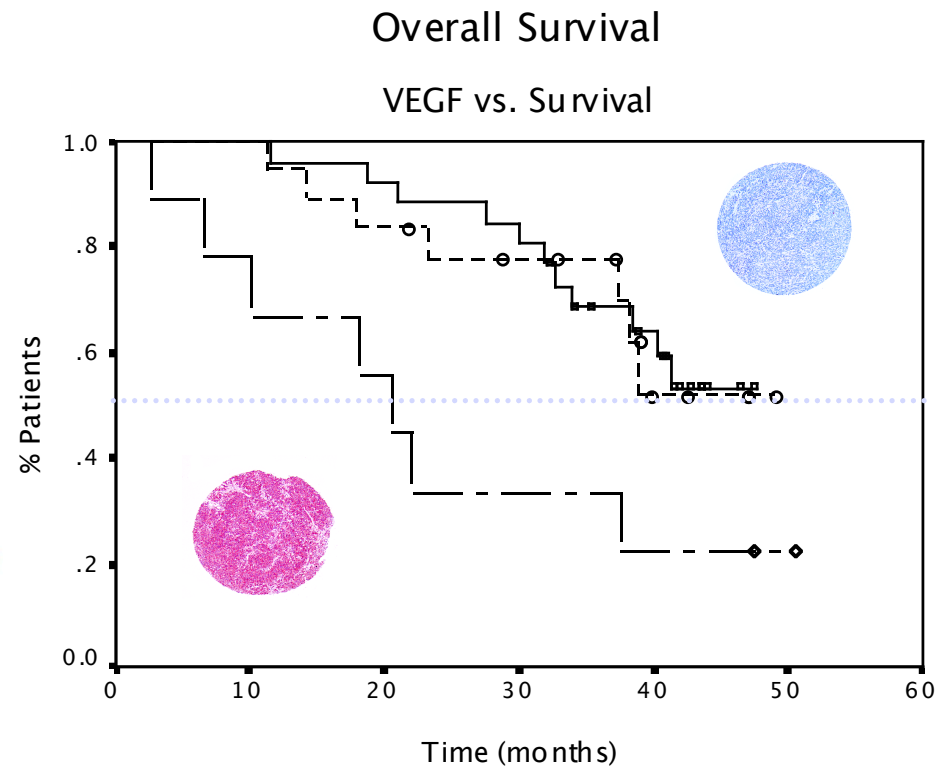
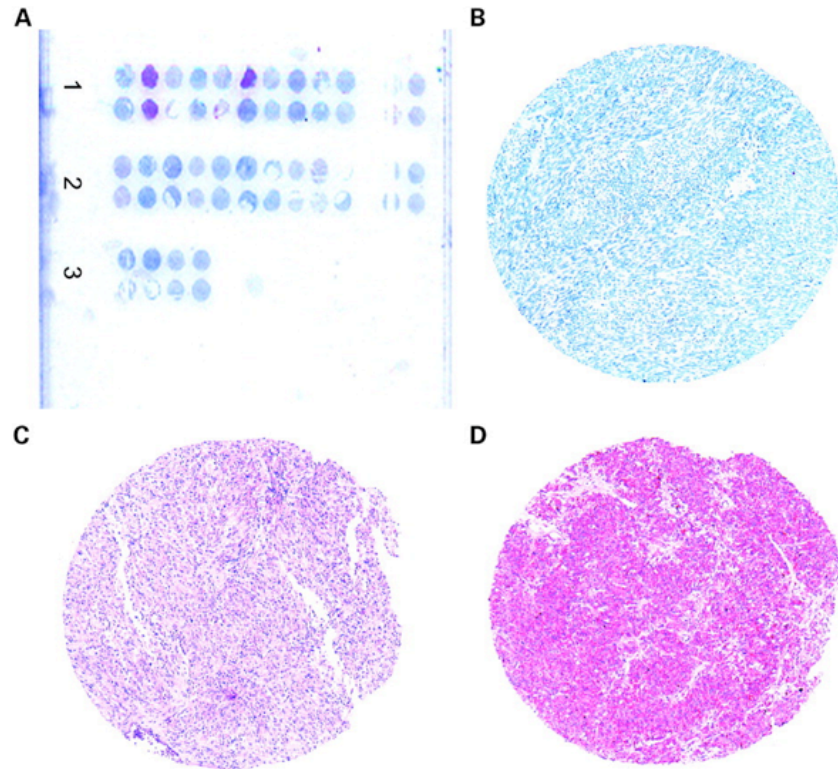


# Phase III Trial: US Intergroup S0033: Time to Progression on Crossover

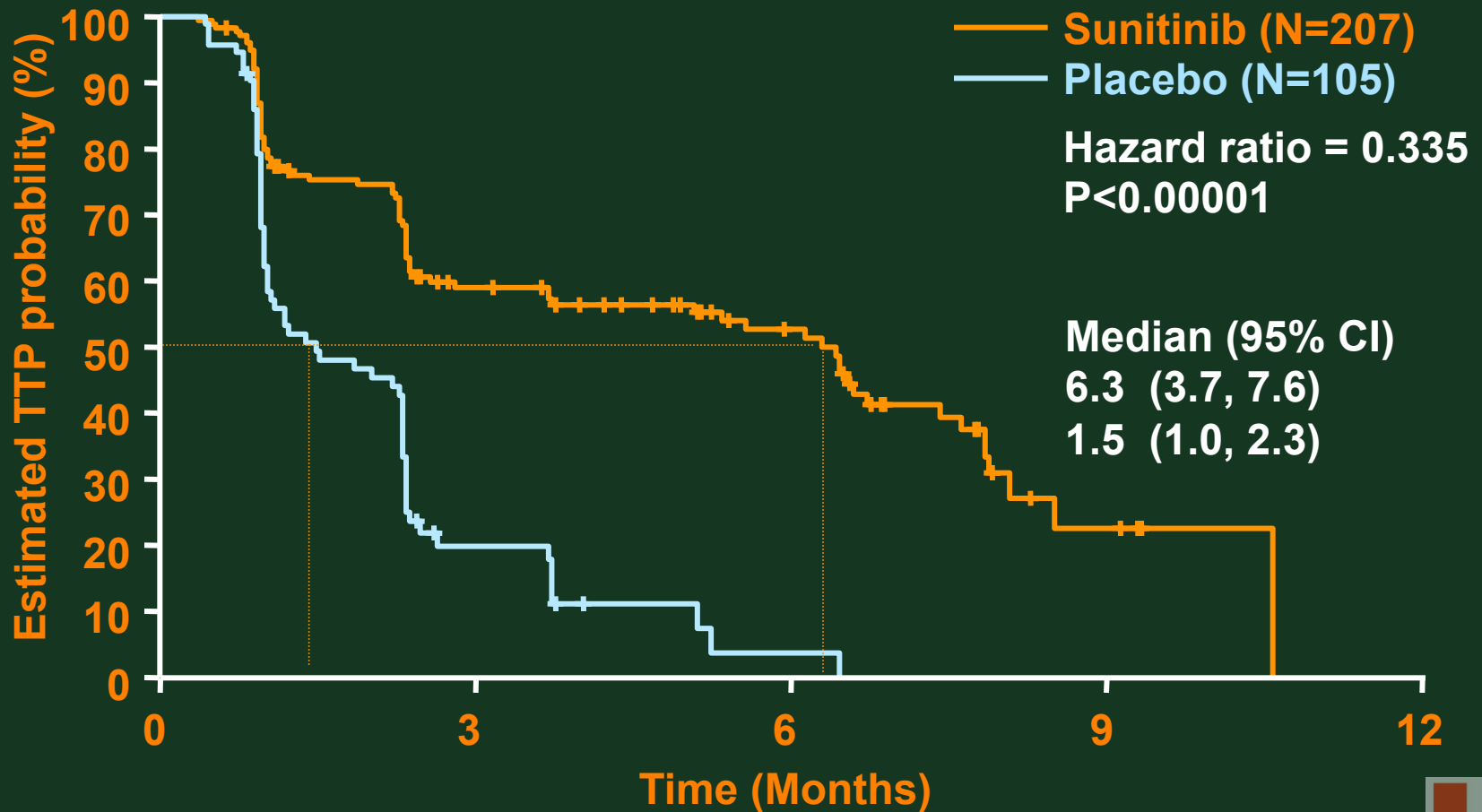


# Association of Intratumoral Vascular Endothelial Growth Factor Expression and Clinical Outcome for Patients with Gastrointestinal Stromal Tumors Treated with Imatinib Mesylate

John C. McAuliffe<sup>1</sup>, Alexander J.F. Lazar<sup>2</sup>, Dan Yang<sup>1</sup>, Dejka M. Steinert<sup>1</sup>, Wei Qiao<sup>3</sup>, Peter F. Thall<sup>3</sup>, A. Kevin Raymond<sup>2</sup>, Robert S. Benjamin<sup>1</sup> and Jonathan C. Trent<sup>1</sup>



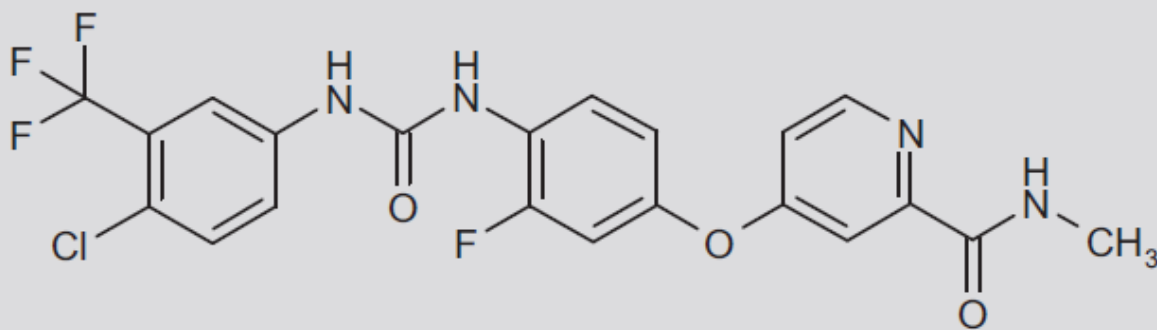
# Time to Tumor Progression



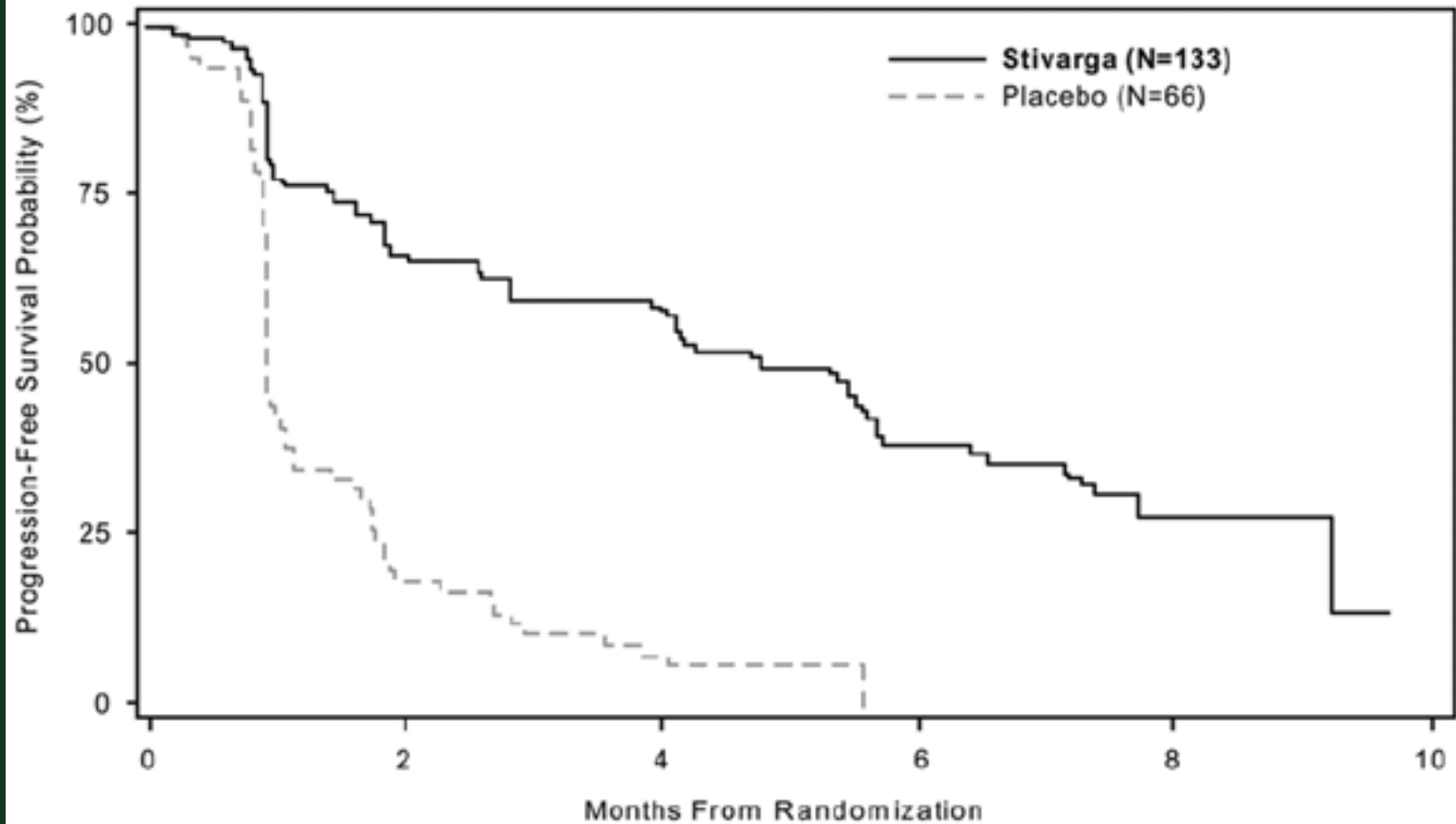


# Background - Regorafenib

- Regorafenib (BAY 73-4506) is a structurally distinct oral TKI with inhibitory activity against several kinases including KIT, PDGFRA, FGFR, VEGFR 2,3, TIE-2, and B-RAF.
- Regorafenib is physiologically processed into at least two bioactive metabolites, each with long half-lives (approximately 24 hrs), allowing target kinase inhibition with promising pharmacodynamics



# Regorafenib vs. Placebo



Patients at Risk

Stivarga

82

72

27

9

Placebo

12

5

0

0



# Clinical Trials.....



# Off-Label

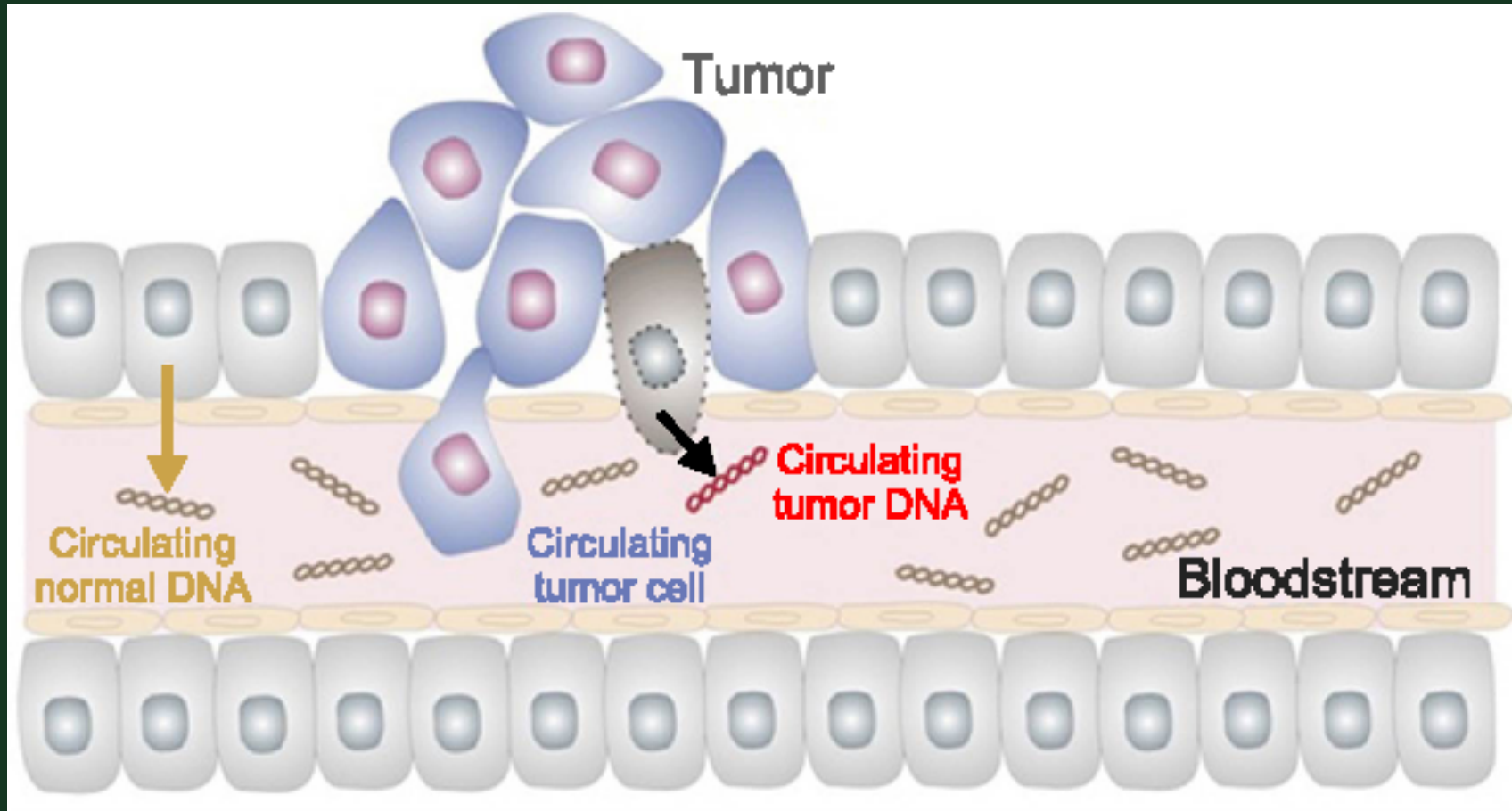
## FDA-approved but not for GIST

Class	Agent	Trial Phase	Results
KIT Inhibitors	Sorafenib	II	PR=13%, SD=58% PFS=5 months
	Dasatinib	II	PR=22%, SD=24% PFS= 2 months
	Nilotinib	I/II/III	PR=10%, SD=37% PFS=3 months
	Pazopanib	II	PazoGIST, PFS-1.9 months
	Ponatinib	II	Exon 11 CBR 37%, PFS 4.3 months
	Axitinib	ND	ND
RAF Inhibitors	Vemurafenib	ND	ND
	Dabrafenib	ND	ND
mTOR Inhibitors	Everolimus	II	PR=2%, SD=43% PFS=3.5 months
	Temsirolimus	ND	ND



# Circulating Tumor DNA

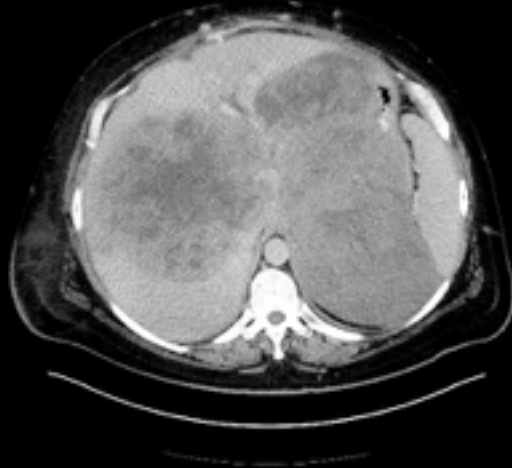
## *Mutation Testing From Blood (Liquid Biopsy)*



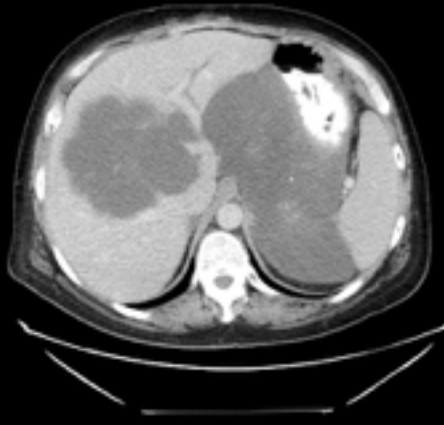
# Ponatinib

Case: *KIT Exon 11(W557-K558del), KIT Exon 17 (Y823D) ctDNA*

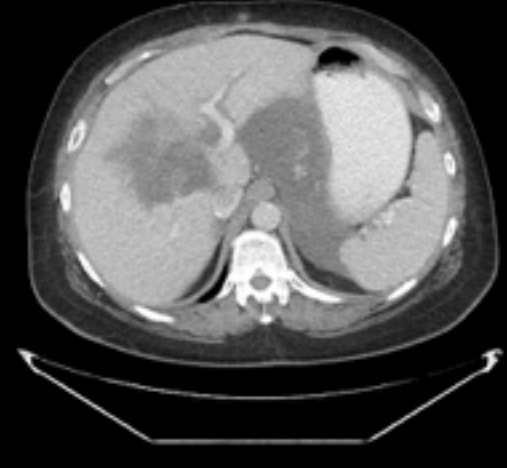
Baseline



6 months



12 months



# Sylvester Comprehensive Cancer Center

## *Sarcoma and GIST Team*

- **Medical Oncology**
  - Jon Trent
  - Breelyn Wilky
  - Matteo Trucco (Pediatric)
- **Pathology**
  - Andrew Rosenberg
  - Darcy Kerr
- **Radiology**
  - Ty Subhawong
  - Jean Jose
- **ARNP**
  - Morgan Smith
  - Ali Naveda
- **Nursing**
  - Eryka Lacayo
  - Yolanda Roper
- **Social Work**
  - Marlene Morales
- **Orthopedic Oncology**
  - Sheila Conway
  - Frank Eismont
  - Juan Pretell
  - Mo Al Maaieh
- **Surgical Oncology**
  - Nipun Merchant
  - Alan Livingstone
  - Danny Yakoub
- **Radiation Therapy**
  - Raphael Yechieli
  - Aaron Wolfson
- **Head & Neck Surgery**
  - Zoukaa Sargi
  - Frank Civantos
- **Thoracic Surgery**
  - Dao Nguyen
  - Nestor Villamizar
- **Interventional Radiology**
  - Shree Venkat
  - Ivan Chaitowitz
  - Evelyn Wempe
- **Gynecologic Oncology**
  - Brian Slomovitz
  - Marilyn Huang
- **Clinical Research**
  - Tamara Leon
  - Liz Bornote
  - Junet Alvarez
- **Lab Research**
  - Josie Eid
  - Joanna DeSalvo
  - Luyuan Li
  - Karina Galoian
  - Shuchao Zhang





# GISTs 2008....





# GISTS 2009.....



# Gastrointestinal Stromal Tumor GISTs 2018

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