Gastrointestinal Stromal Tumor
GISTs 2019

Jon Trent, MD, PhD
Professor of Medicine
Director, Bone and Soft-tissue Program
Associate Director, Clinical Research
Sylvester Comprehensive Cancer Center

jtrent@med.miami.edu

@JTrentMDPhD

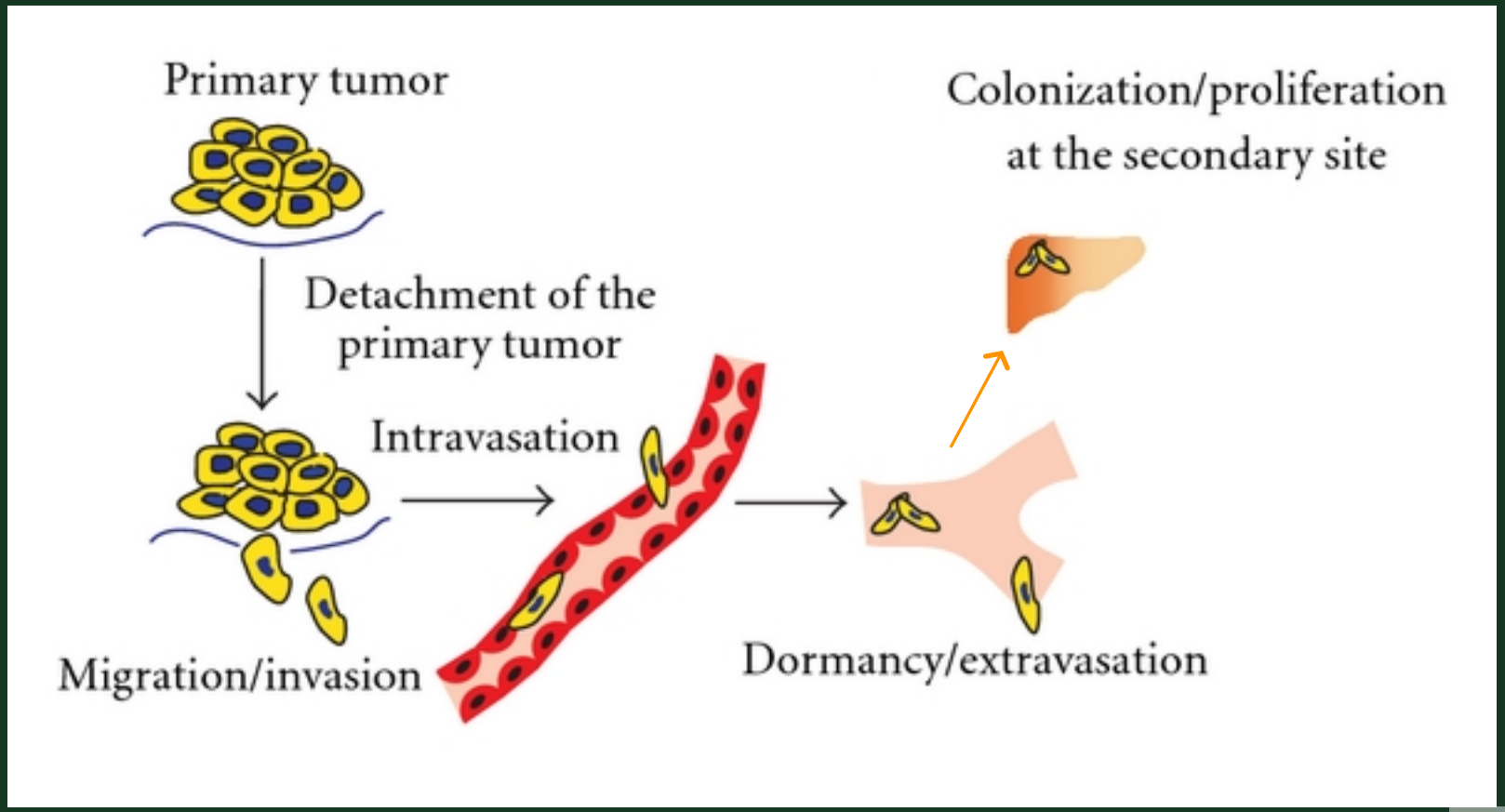
SYLVESTER
COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

Background

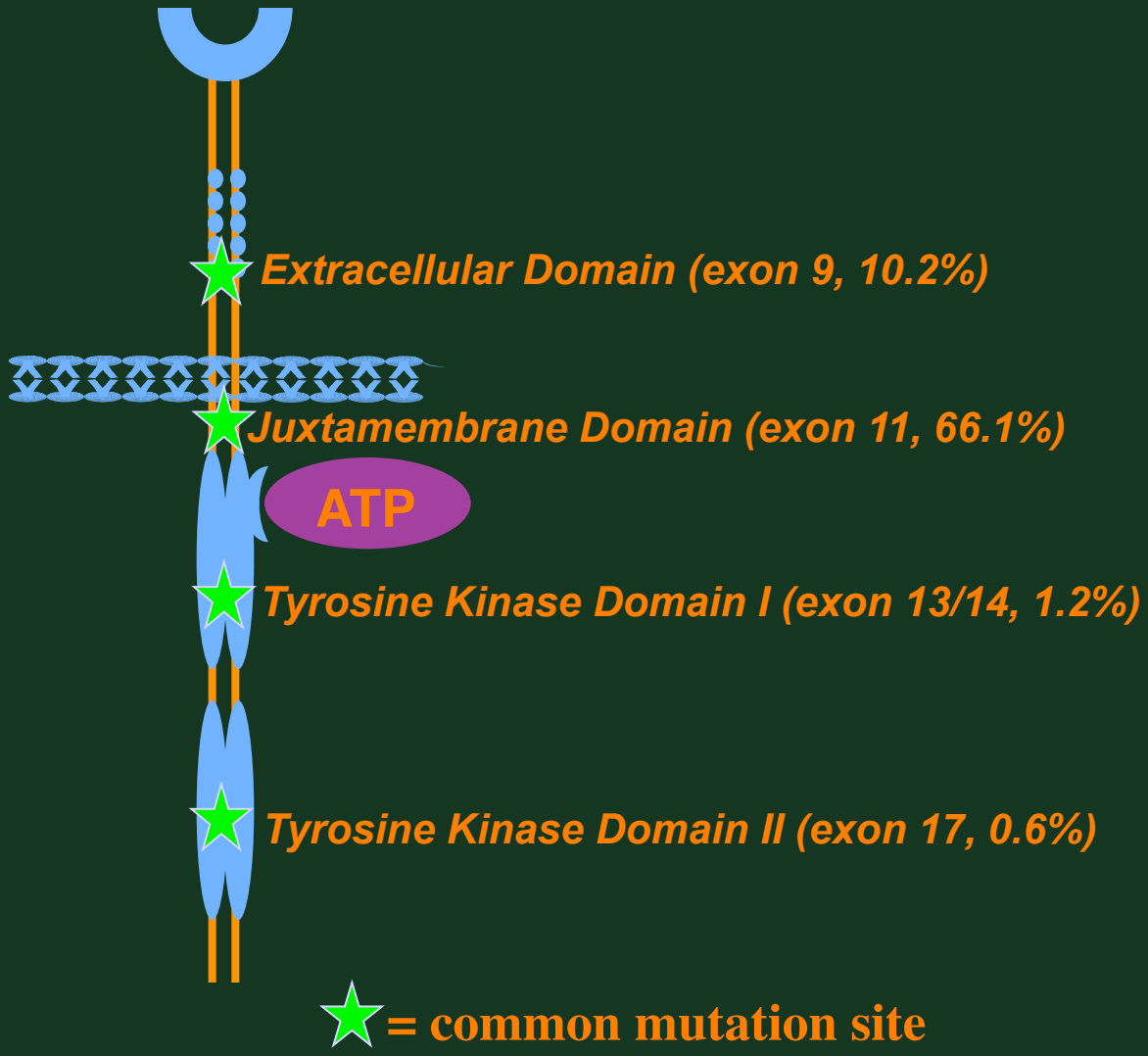
GIST Overview

- 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

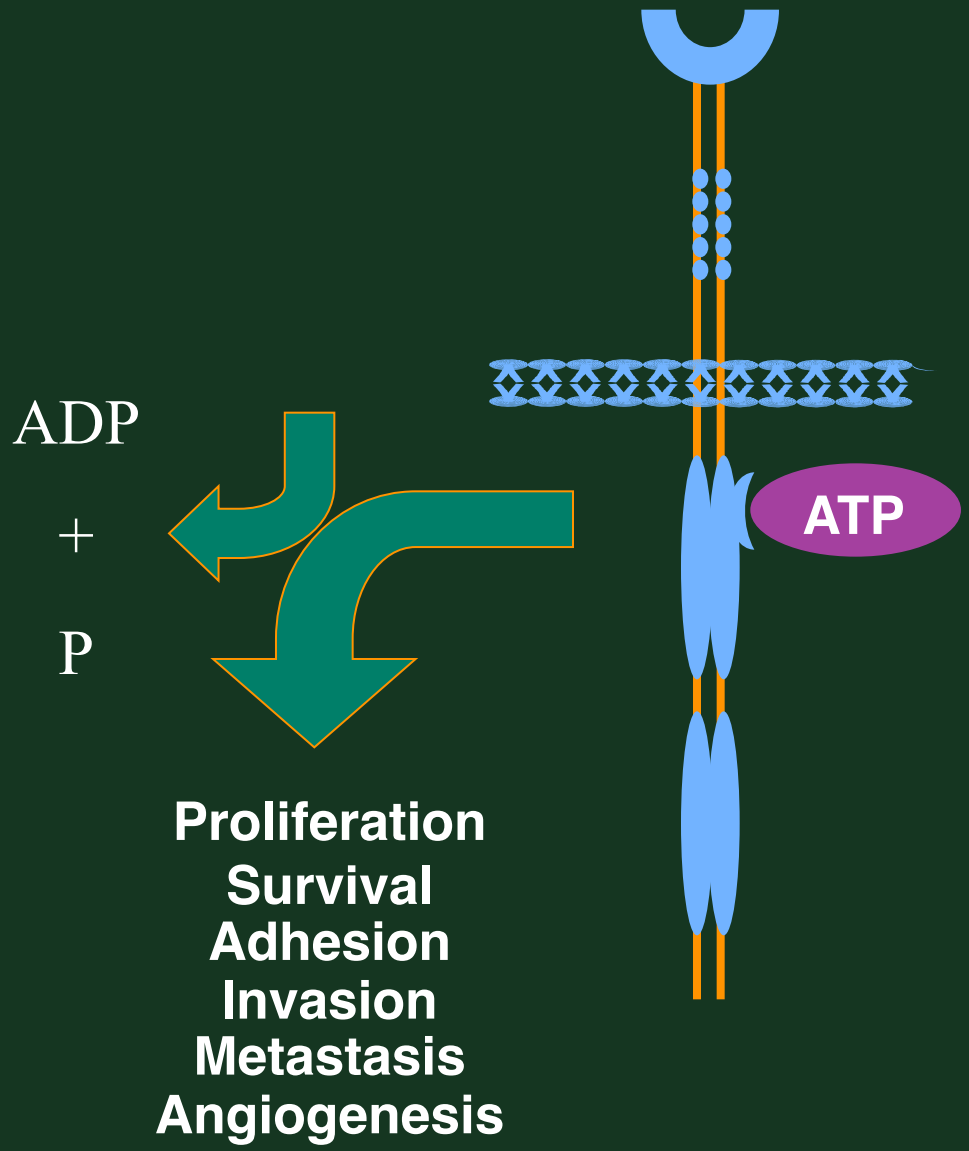
Metastasis in GIST



Kit Receptor Structure

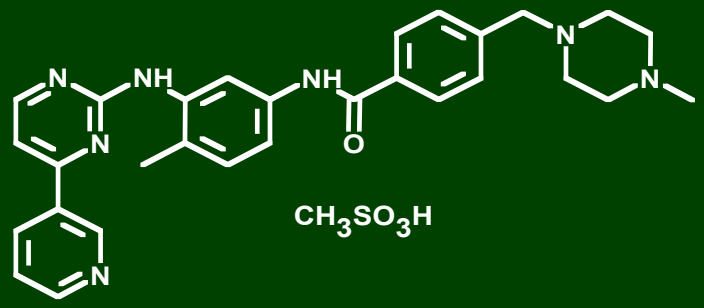


Kit Receptor Phenotype



Imatinib Mesylate

Kinase Inhibitor, TKI



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

MW: 589.7

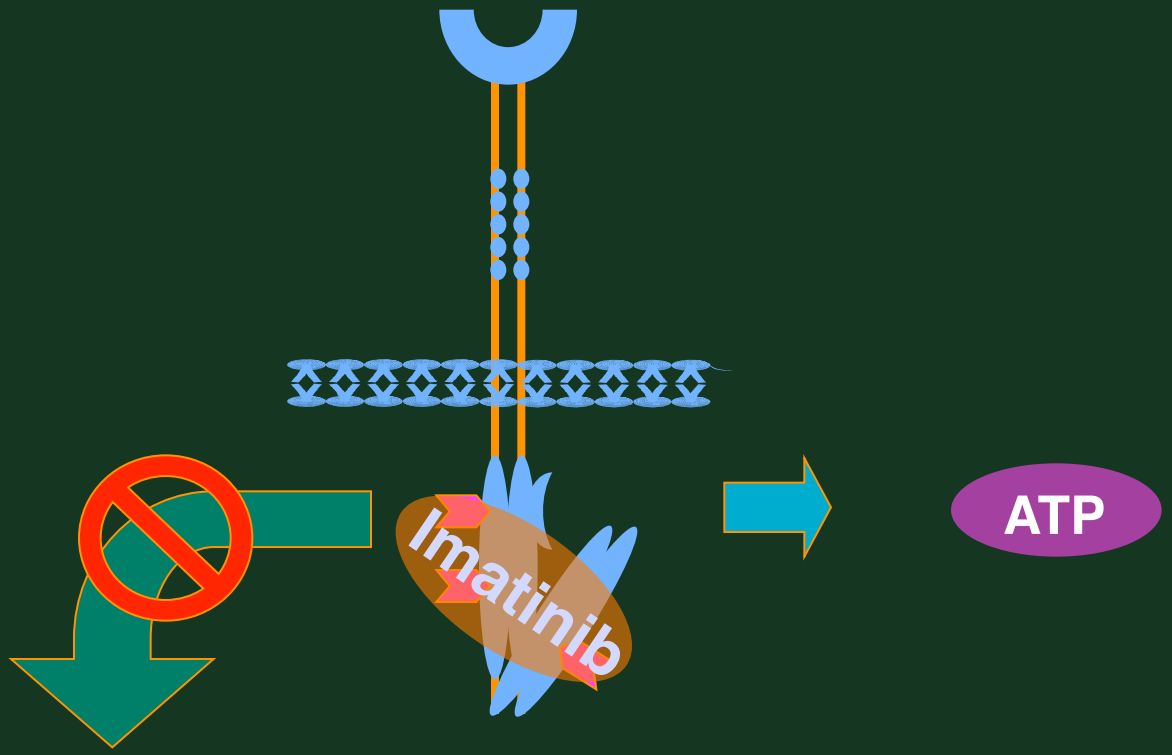
- Rational drug design
  - 2-phenylamino pyrimidine
  - Based on structure of ATP binding site
  - Highly water soluble
  - Oral bioavailability

Inhibitor of selective tyrosine kinases

- bcr-abl
- PDGF-R
- c-kit

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

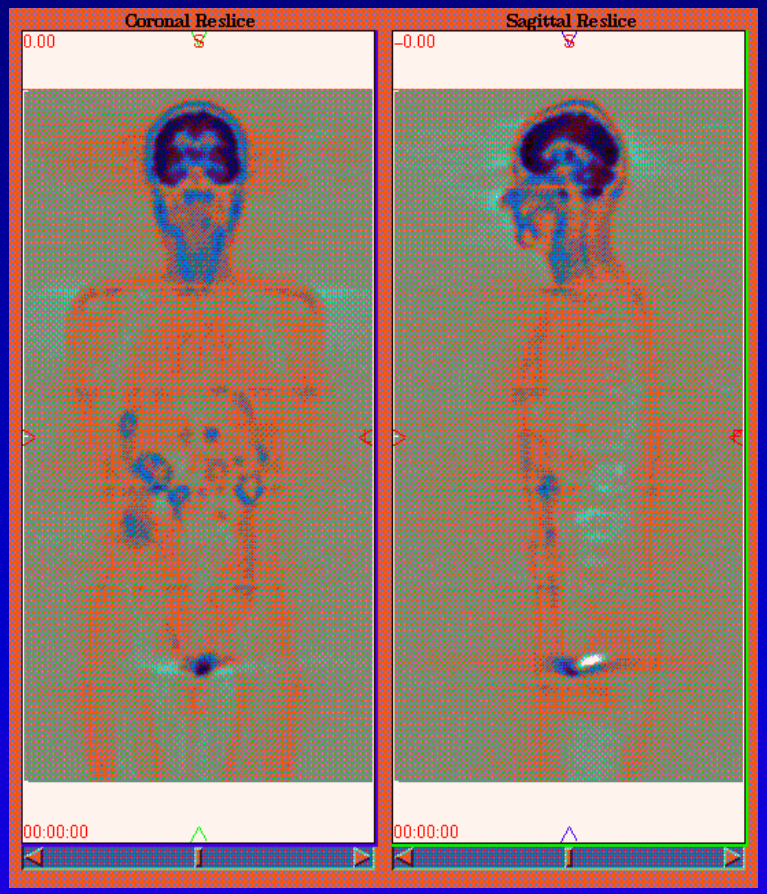
Kit Receptor Phenotype



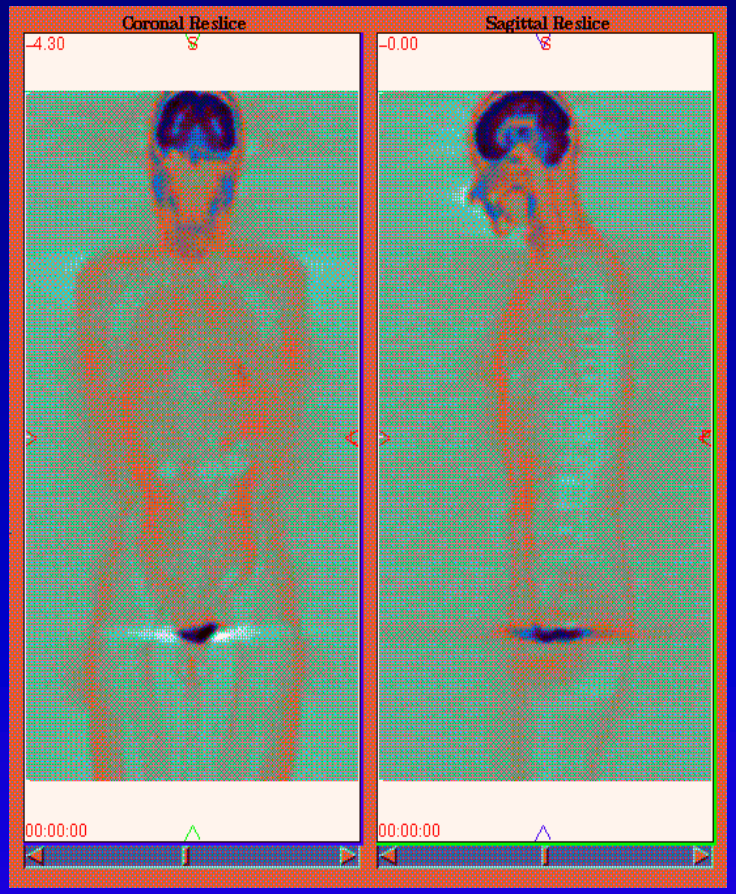
Proliferation
Survival
Adhesion
Invasion
Metastasis
Angiogenesis

= imanitib contact point

Marked Biologic Response Revealed by PET Scan



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



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

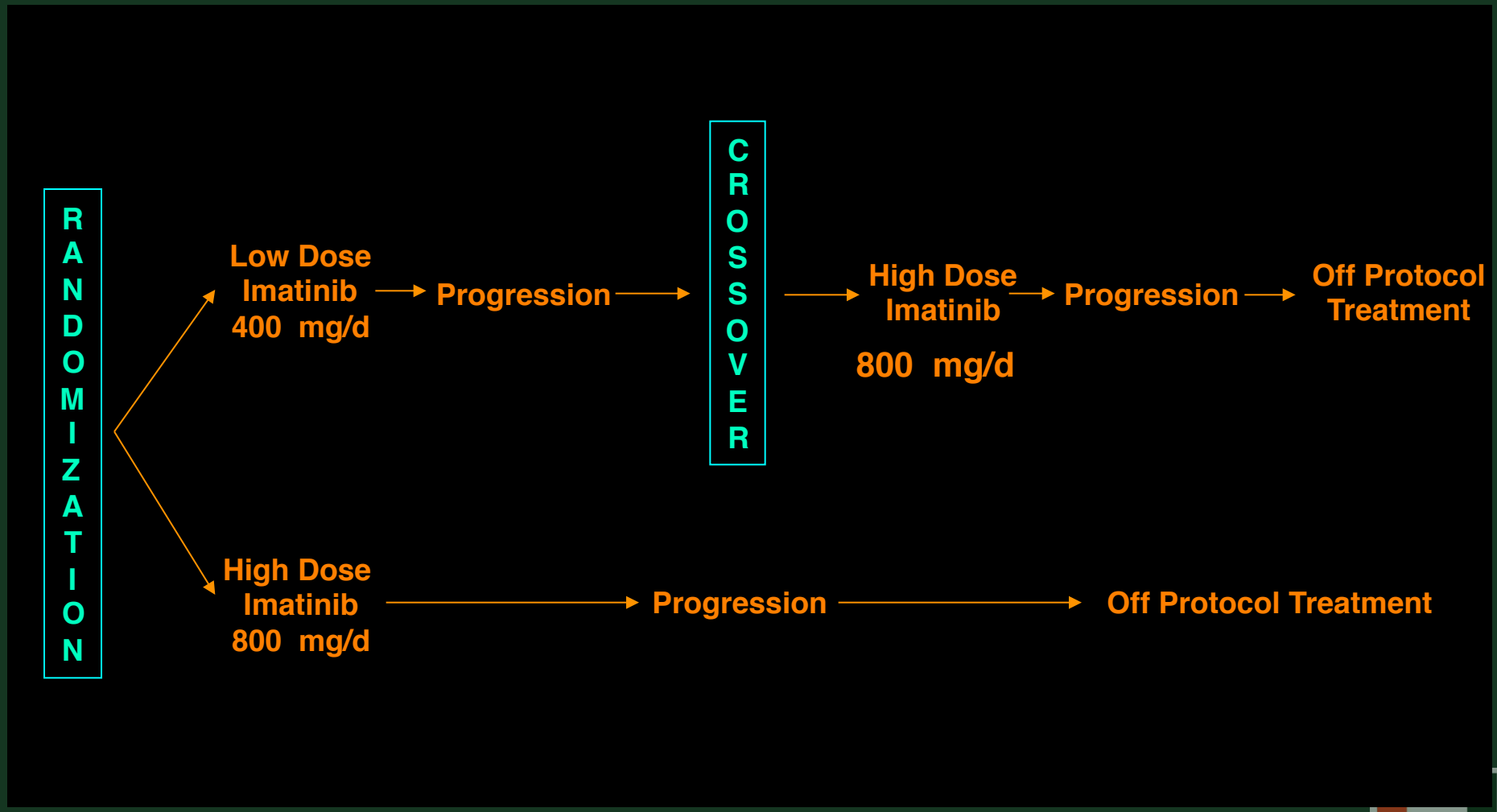
Joensuu H et al. *N Engl J Med.* 2001;344:1052-1056.

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)

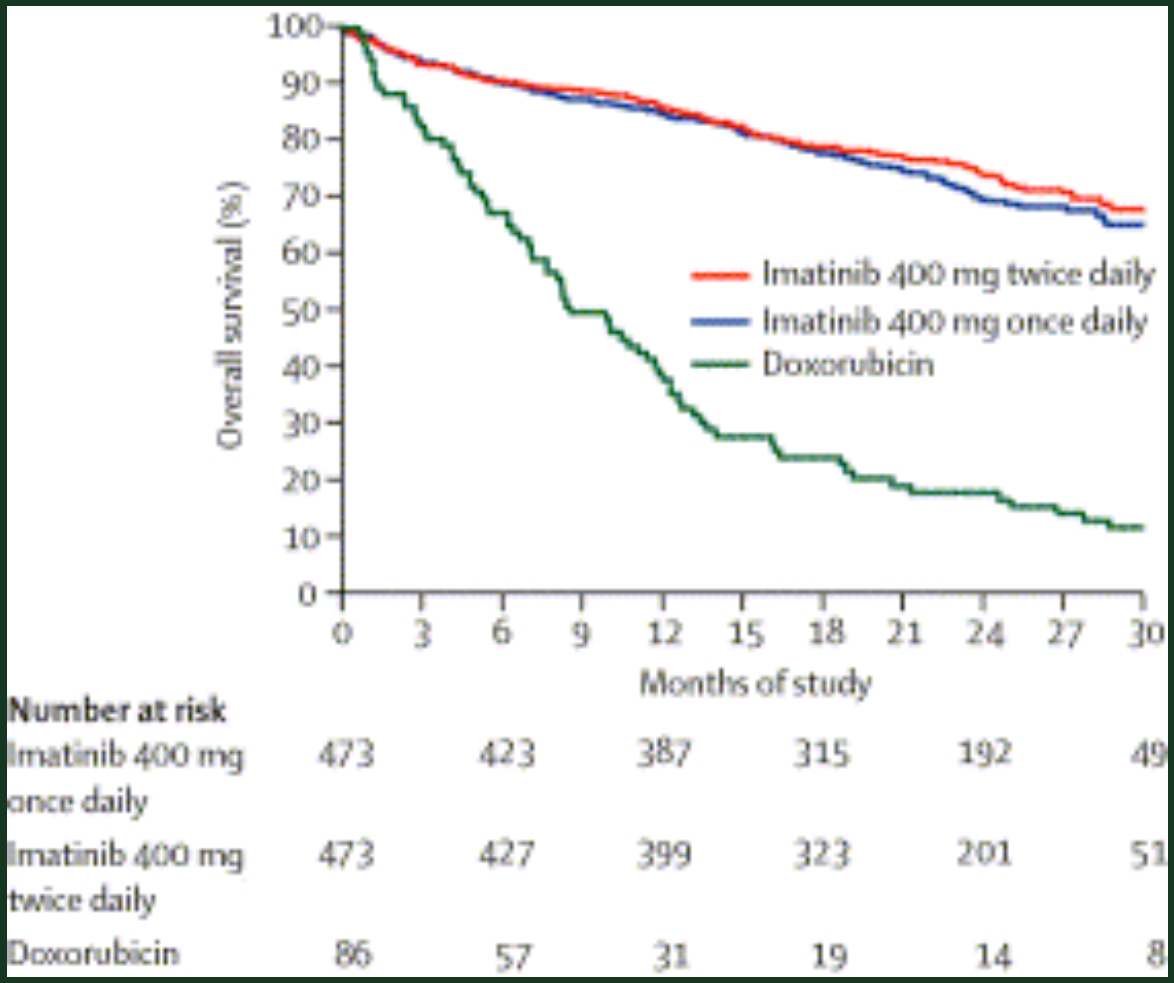
Courtesy Dejka Araujo, M.D.

North American Sarcoma Intergroup
Schema



EORTC Phase III Imatinib for Advanced GIST

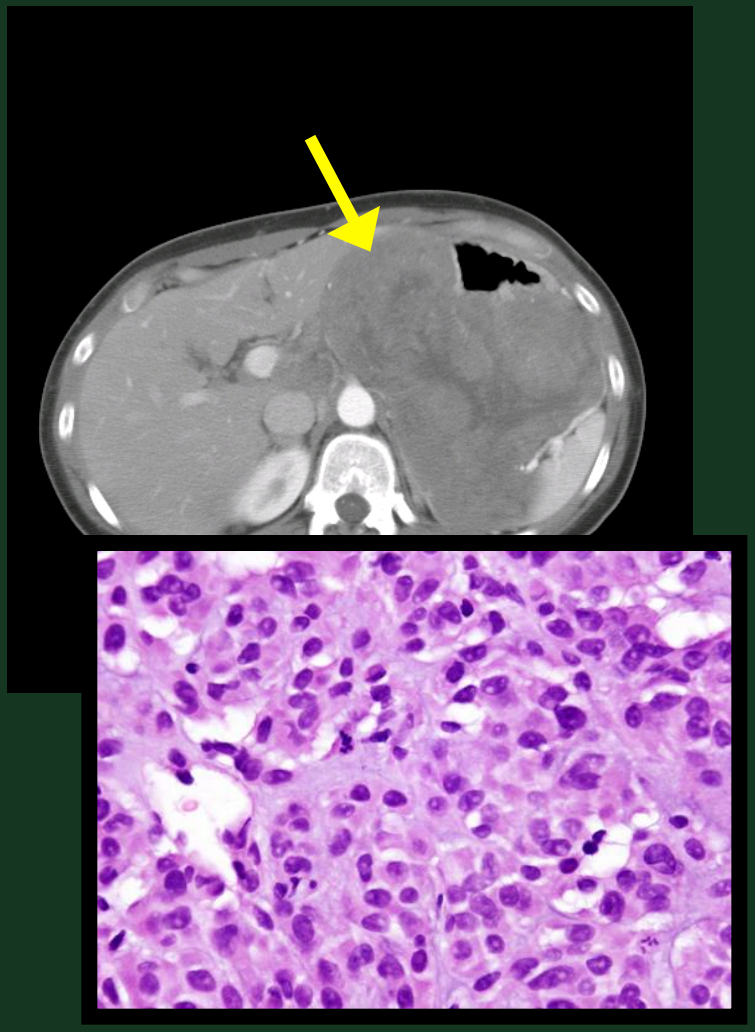
Survival Benefit



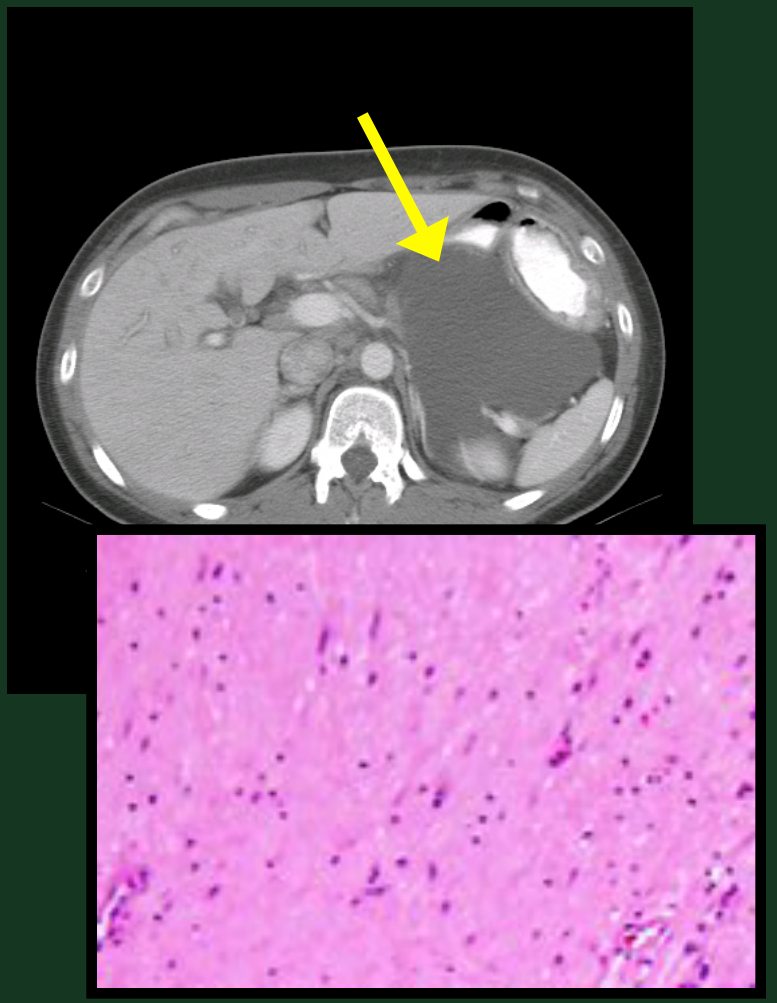
Number at risk						
Imatinib 400 mg once daily	473	423	387	315	192	49
Imatinib 400 mg twice daily	473	427	399	323	201	51
Doxorubicin	86	57	31	19	14	8

Verweij, et al 2004

GIST Response



Pre-Imatinib



Post-Imatinib (8 weeks therapy)

Courtesy Jon Trent and Alex Lazar

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
- ^{18}FDG-PET
- MRI with gadolinium

^{18}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)

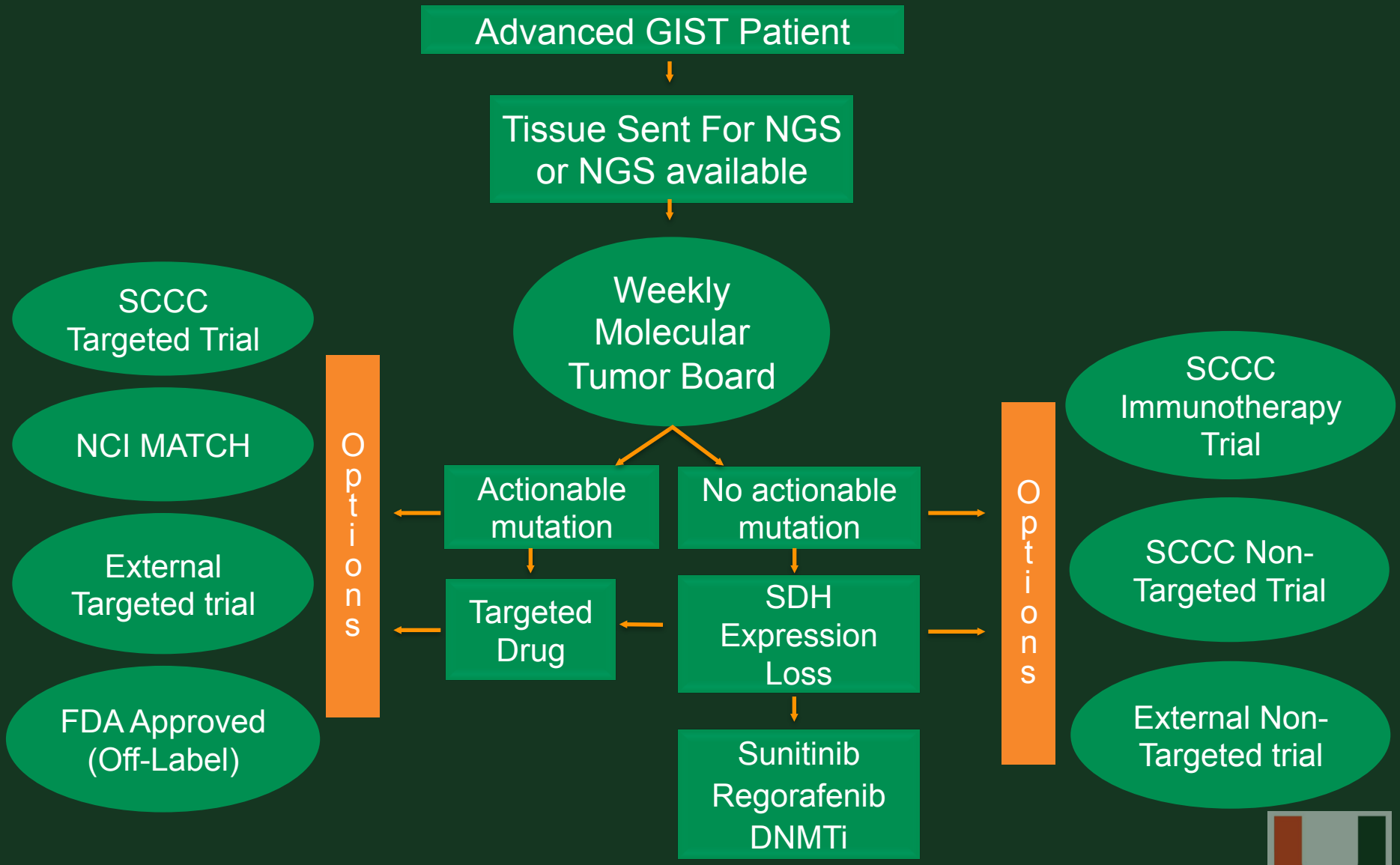
Personal Communication Jon Trent, MD, PhD (Sylvester Comprehensive Cancer Center)

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

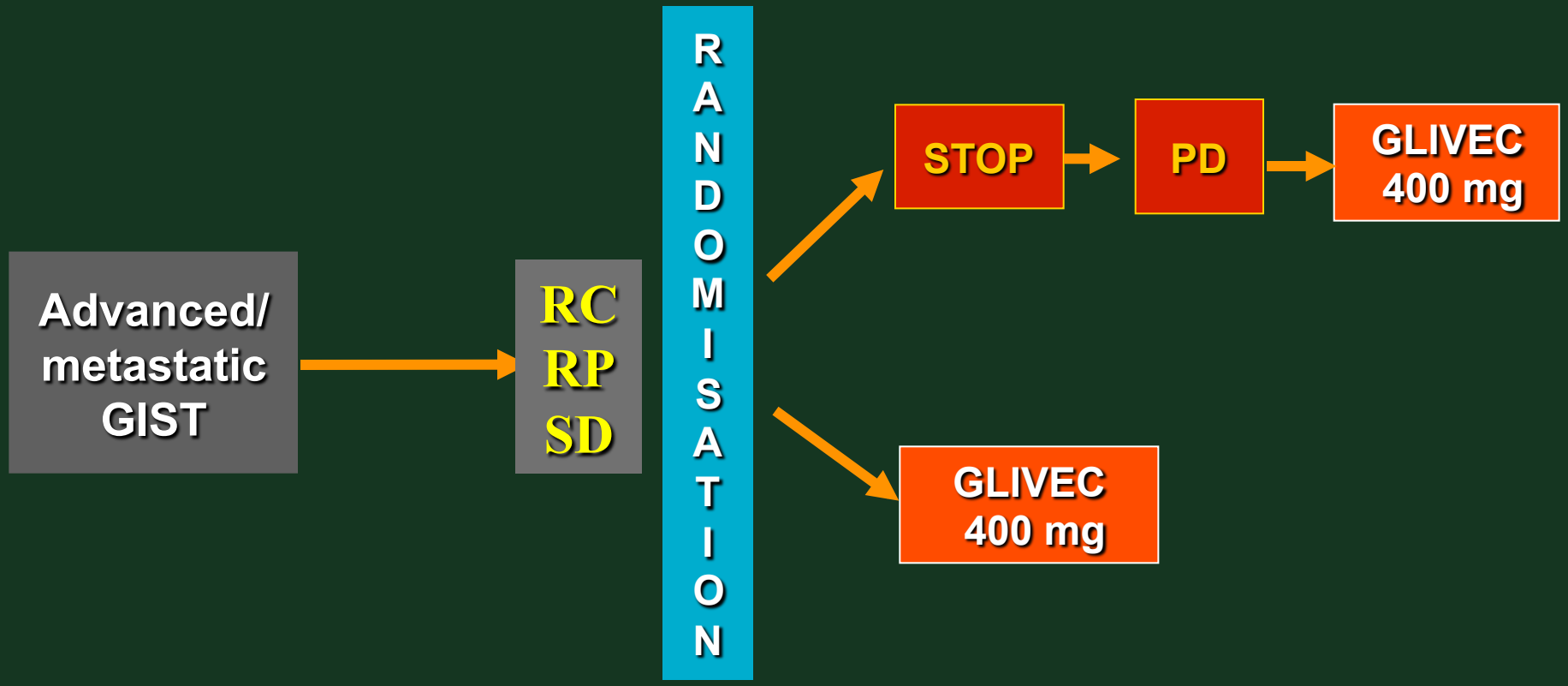
Personal Communication Jon Trent, MD, PhD (Sylvester Comprehensive Cancer Center)

GIST Precision Medicine

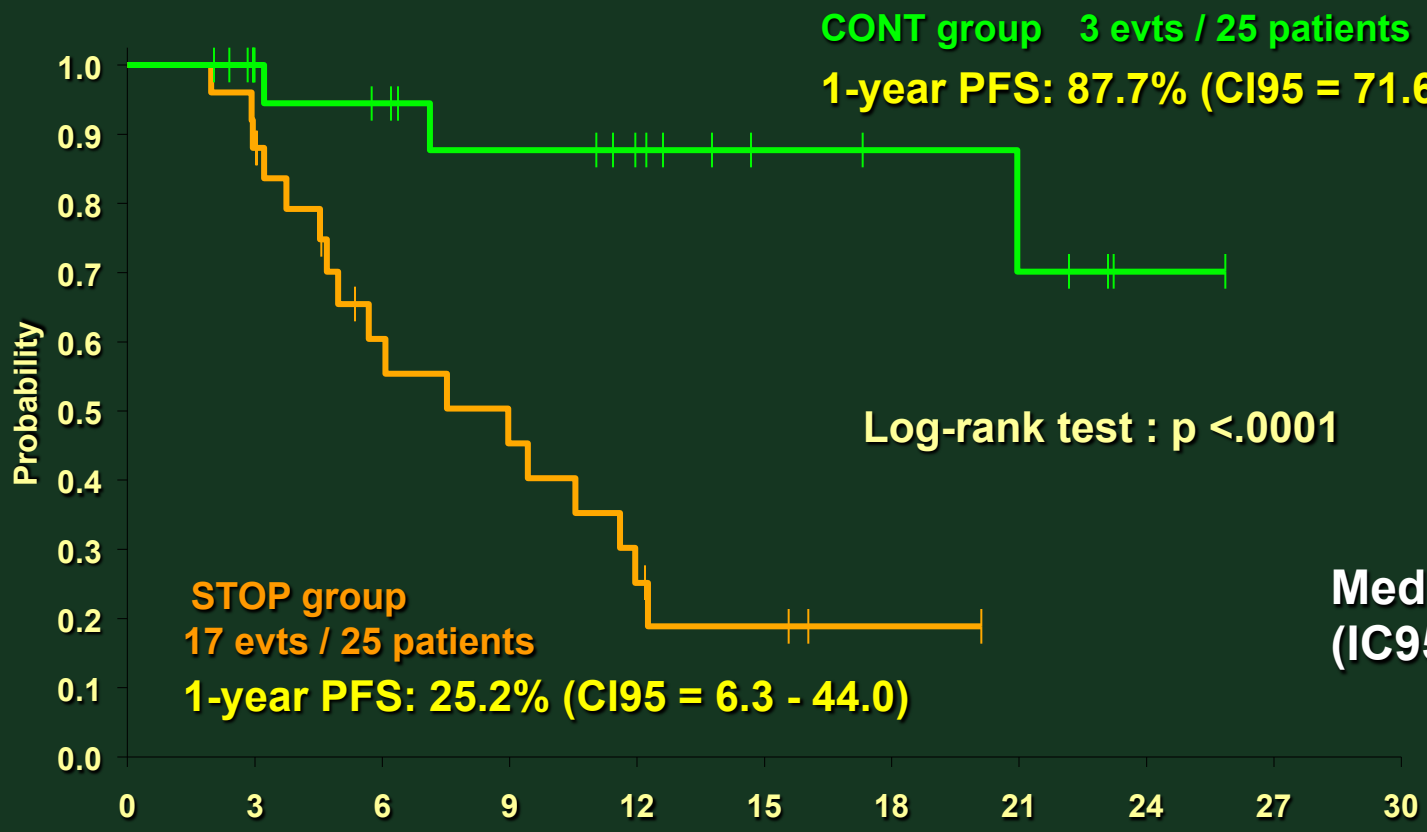


How Long Do I take Imatinib or Other Kinase Inhibitor?

BFR14 3-yr randomization



BFR14 3-yr randomization
Progression Free Survival



Rate of PD in STOP group

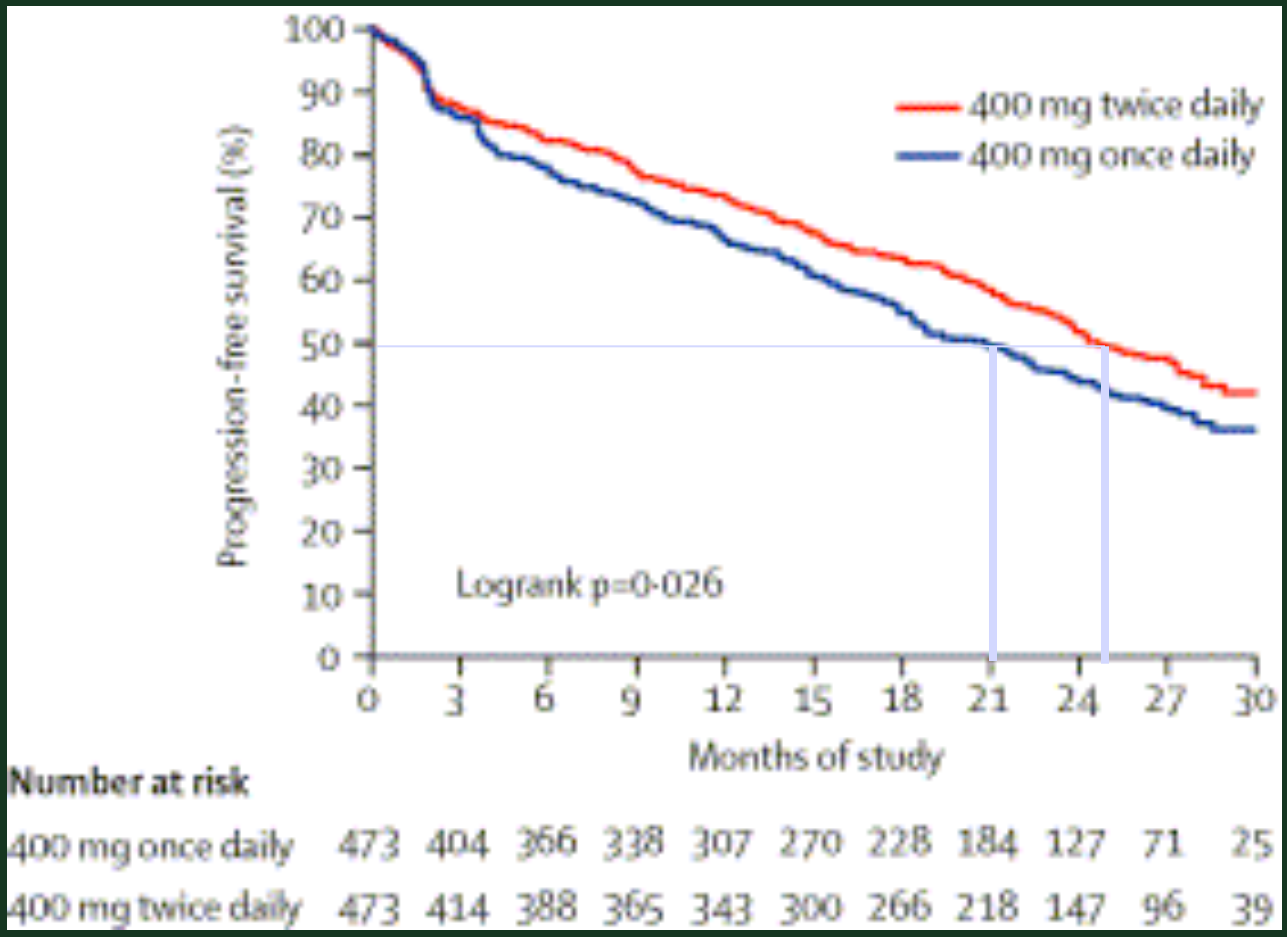
at 6 months: 40%
at 9 months: 55%
at 1 year: 75%

Updated sept 07, ECCO 14

What Dose of Imatinib Do I Take?

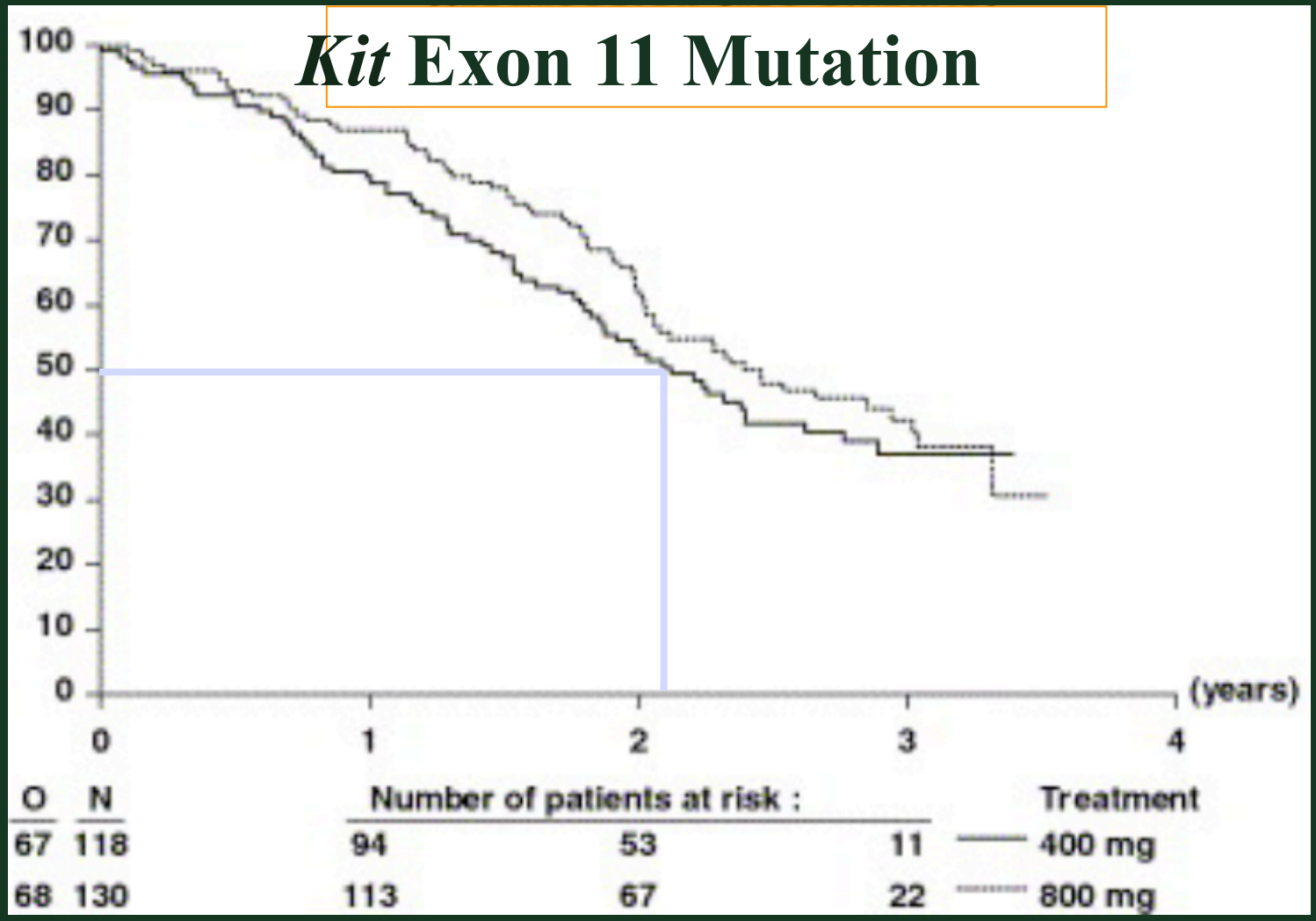
EORTC Phase III Imatinib for Advanced GIST

Progression-free Survival Benefit



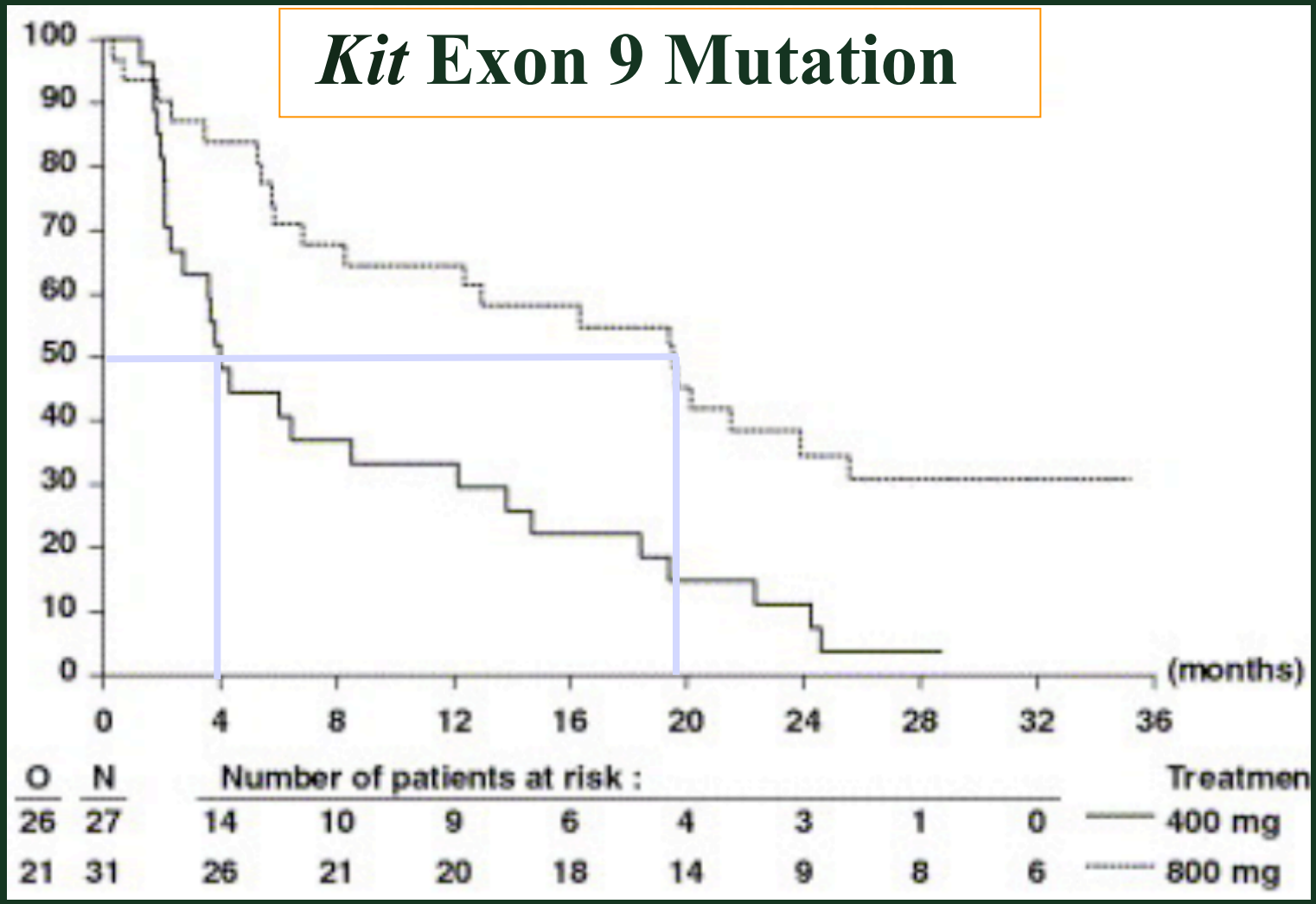
Verweij, et al 2004

Progression-free Survival By Imatinib Dose



Debiec-Rhycter et al, 200

Progression-free Survival By Imatinib Dose



Debiec-Rhycter et al, 200

Will I Have Side Effects?

How Do I Manage Them?

Side effects: 400 vs. 800 mg

Toxic Event	Adjusted *p*-Value
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

Verweij et al, 2004

Interruptions and Reductions of Therapy

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

North American Intergroup Phase III Study of Imatinib in Advanced GIST

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

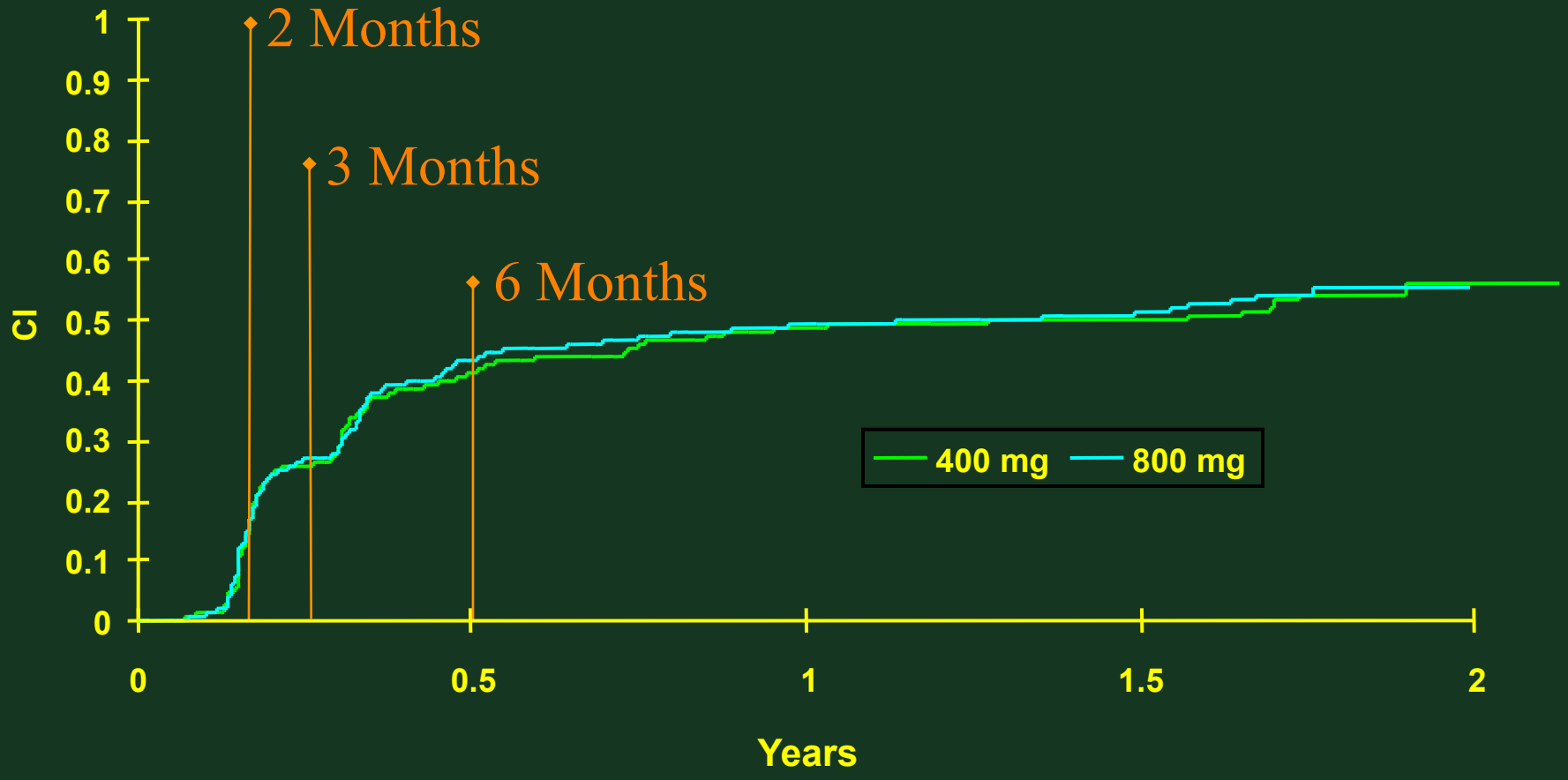
Dileo et al, ASCO 2005

Is My GIST "Responding" To Therapy

Radiographic Efficacy

Time to PR by RECIST

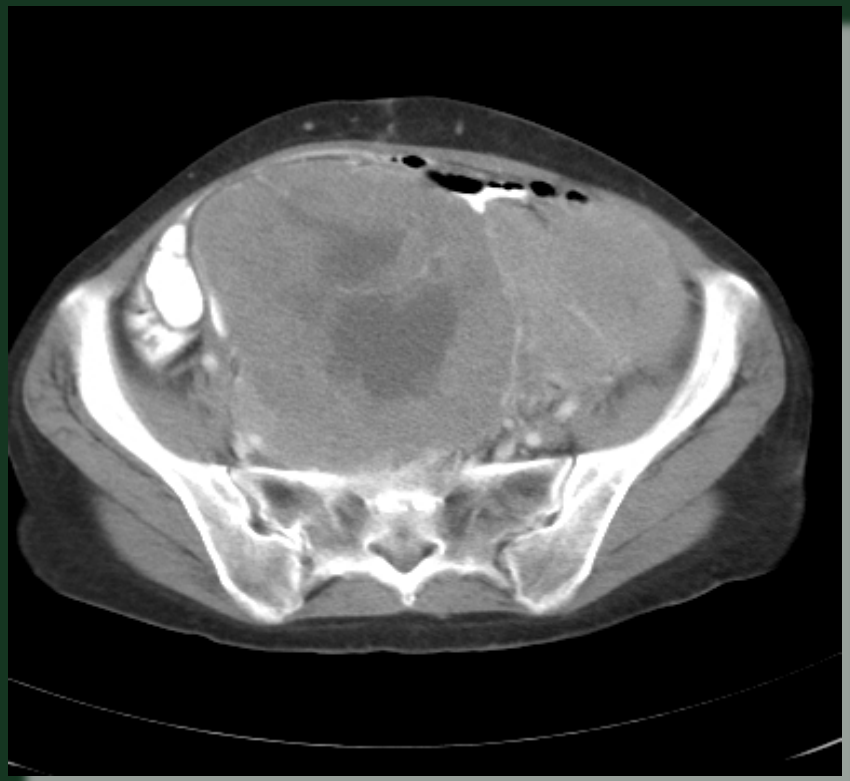
Cumulative incidence of CT responses



Verweij et al, ASCO 2003

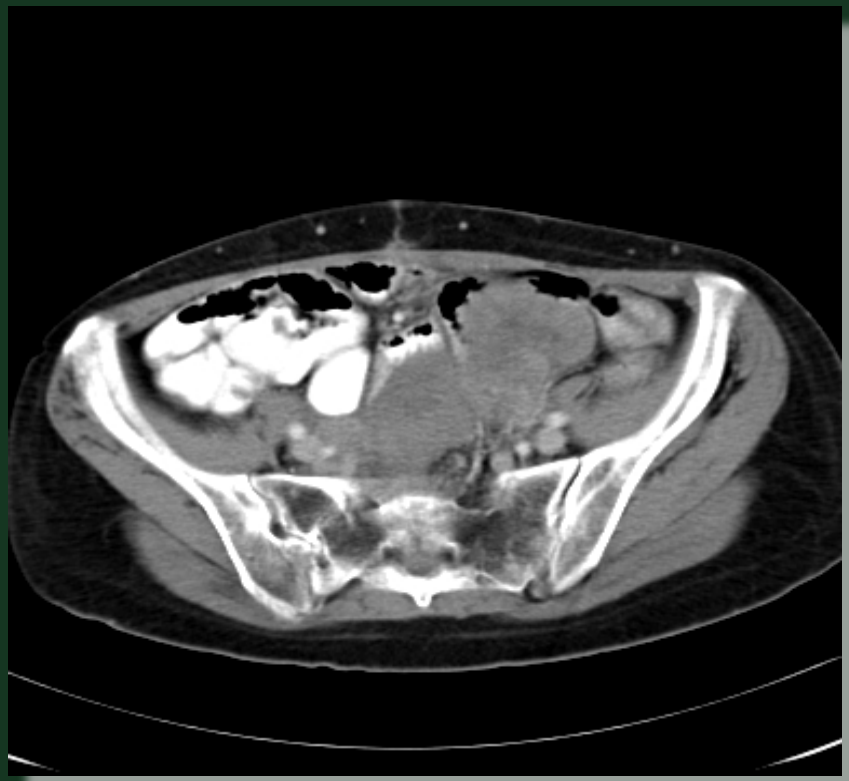
Good “Response”
CT Scan Results

Jun 27, 2000



Before Imatinib

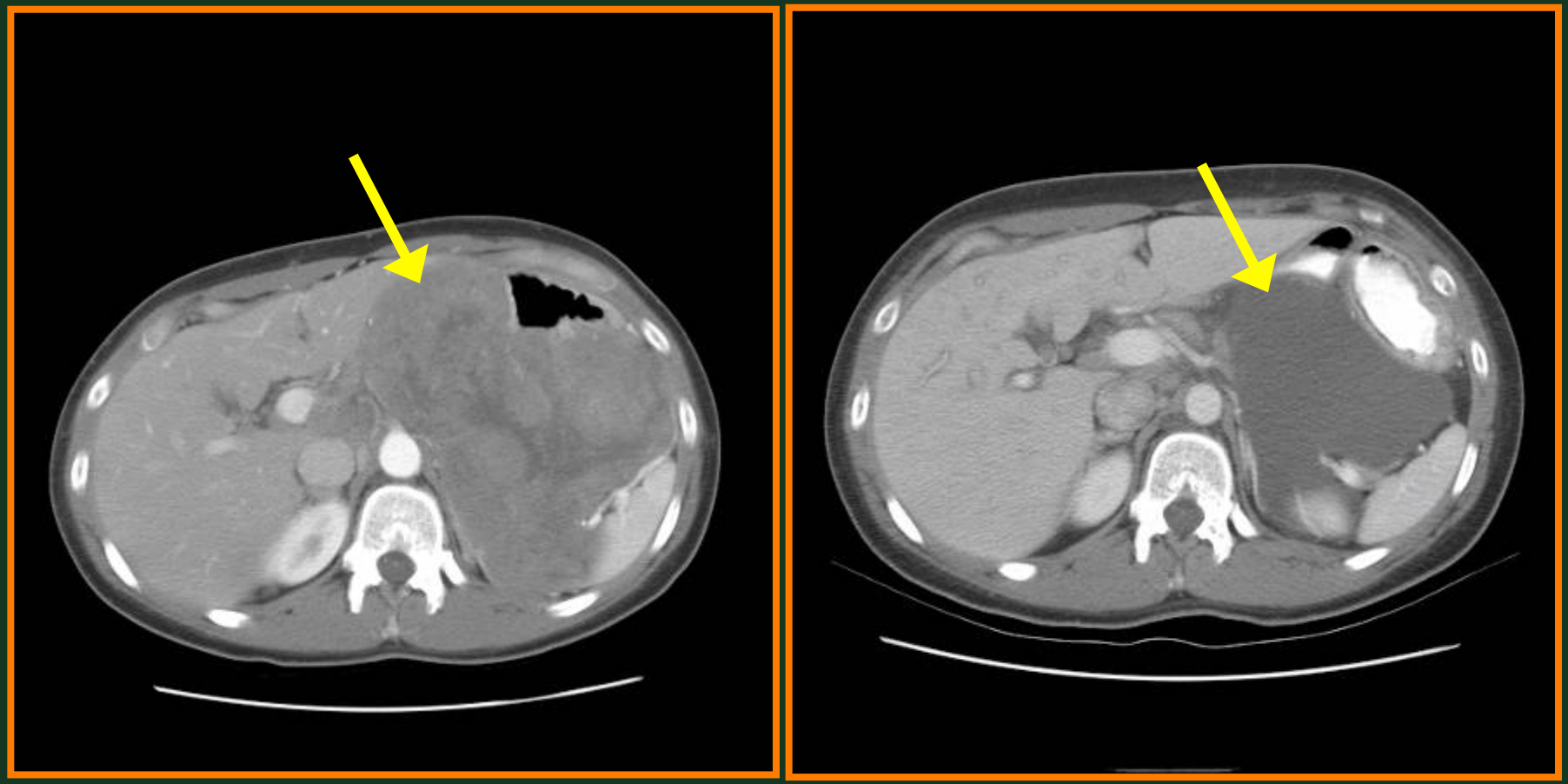
Oct 4, 2000



After Imatinib

Good "Response"

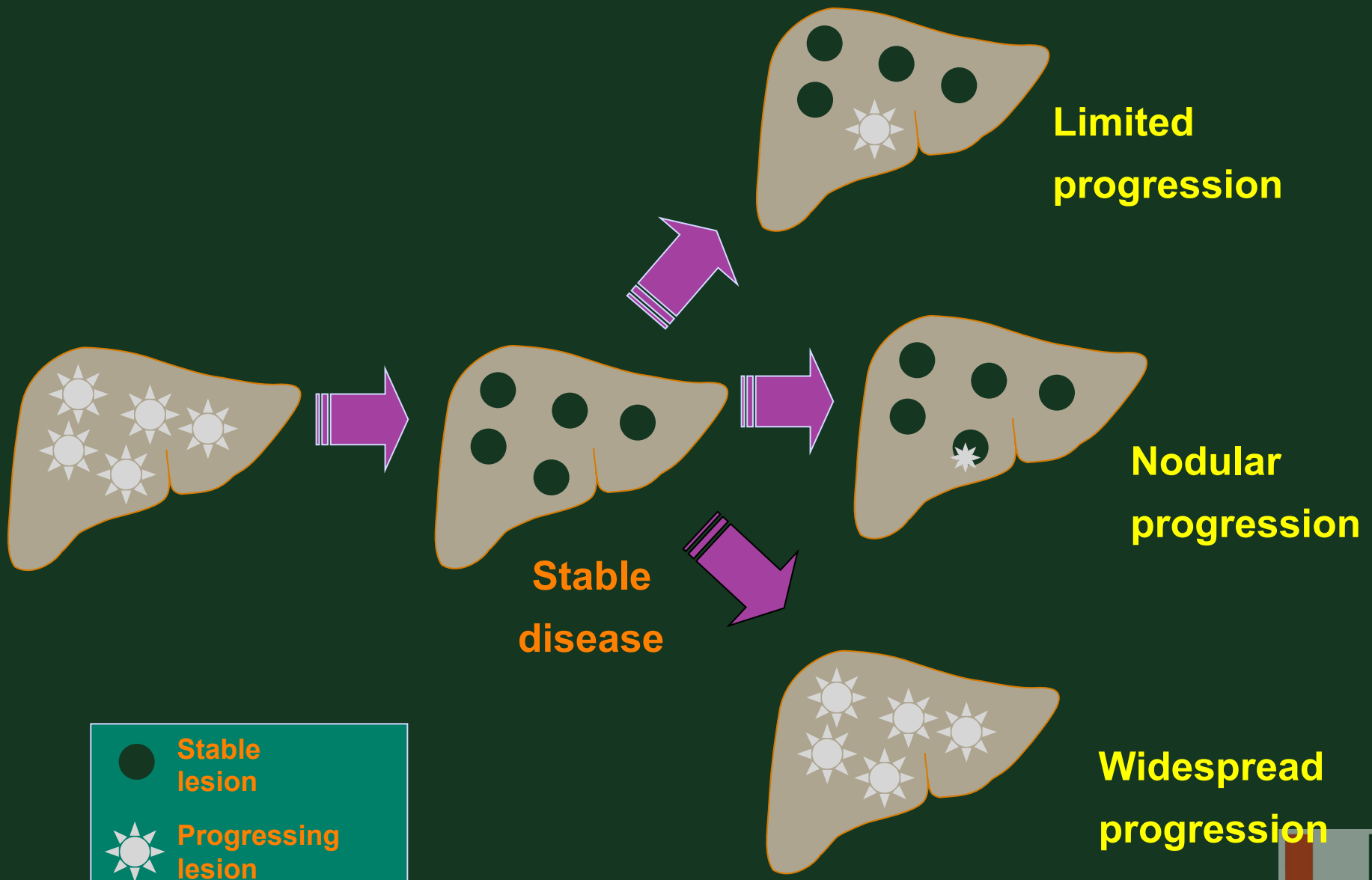
CT Scan Results



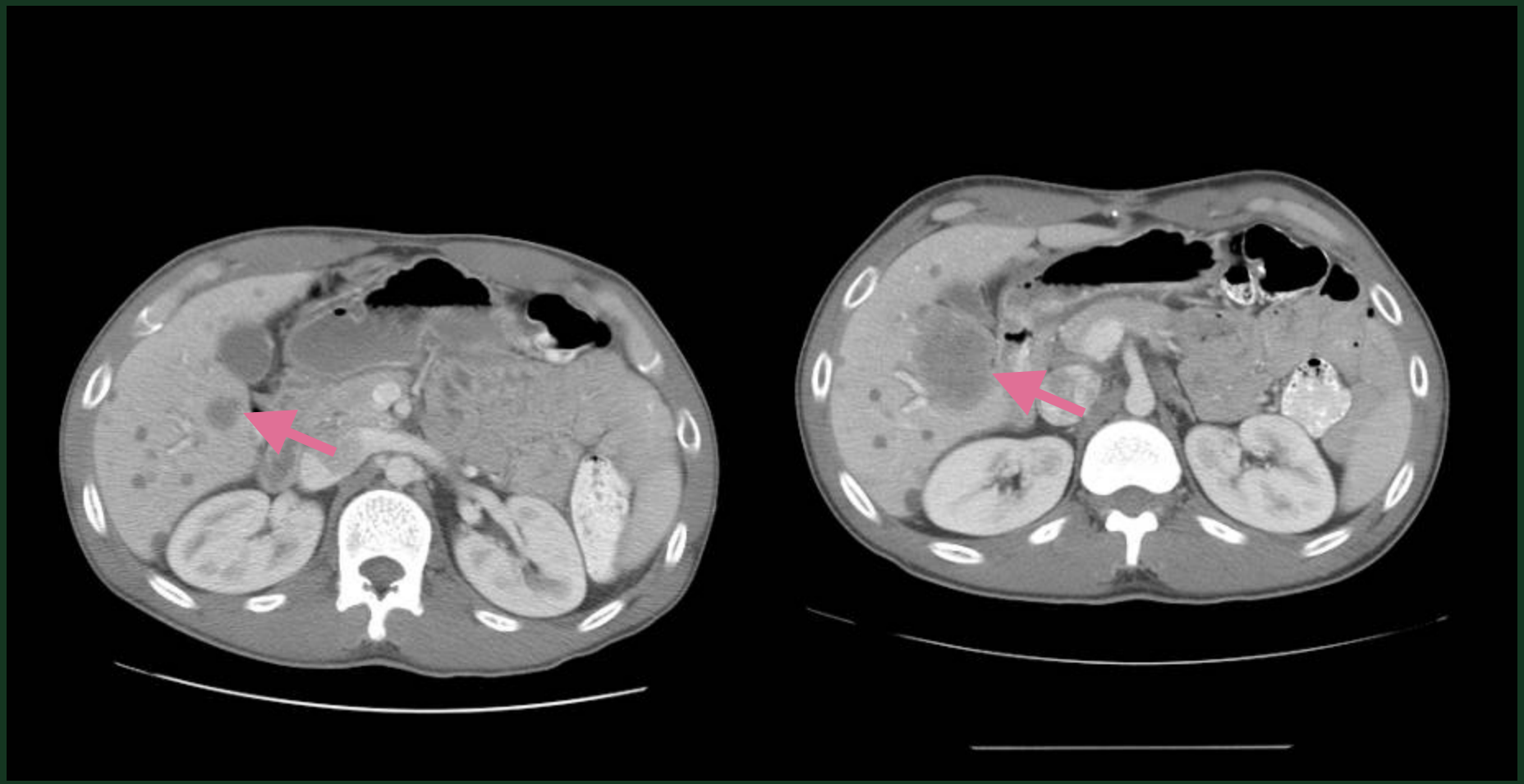
Decrease in GIST intravenous contrast uptake after patient is treated for 8 weeks with imatinib mesylate

What do I do if my GIST is Resistant?

Type of Progression

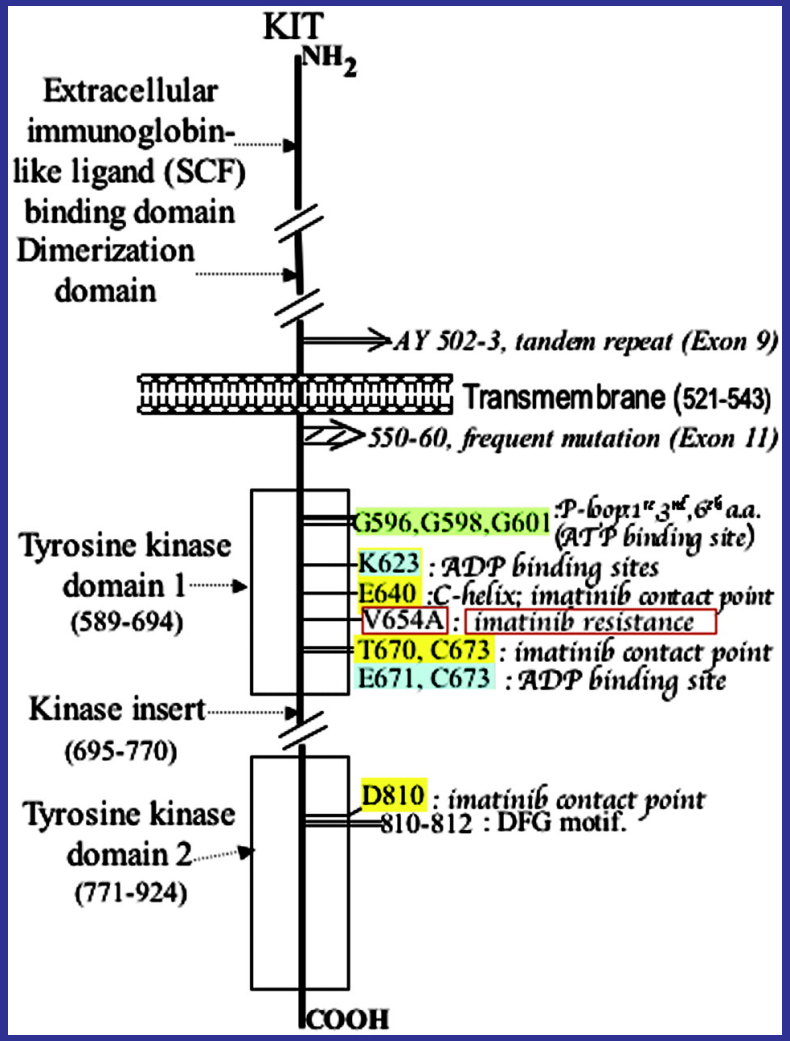


Limited Progression



Courtesy Jon Trent

Secondary Mutations in KIT



ATP/ADP Binding Site (V654)

Gate Keeper (T670)

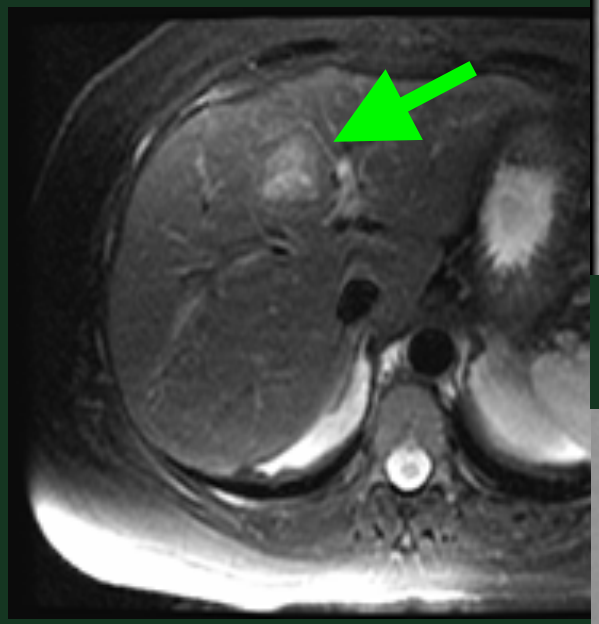
Activation Loop (D820)

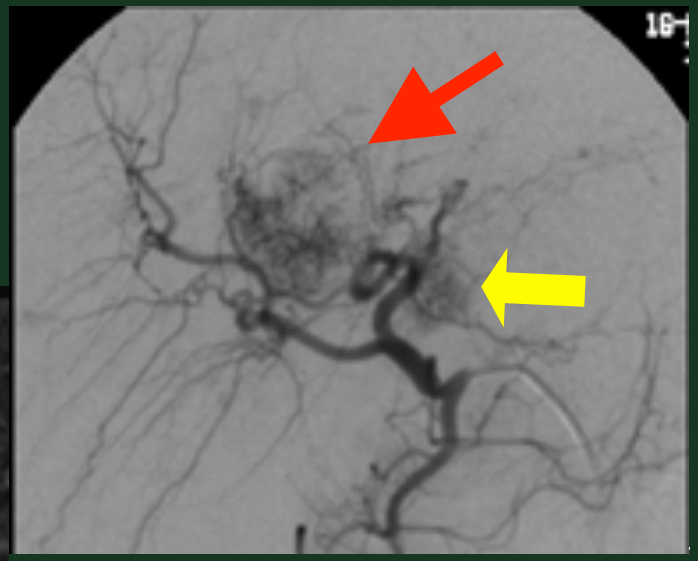
Chen, Trent, et al. Cancer Res 2004;64:5913-5919

Therapy by Type of Progression

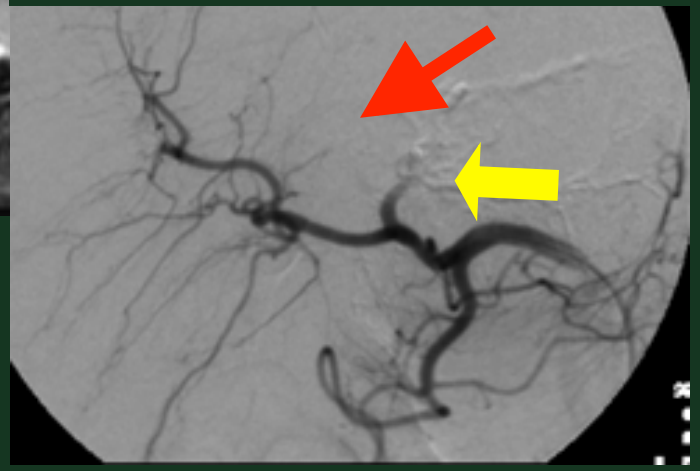
- Limited or Nodular Progression
  - Hepatic Artery Chemoembolization
  - Hepatic Radio-frequency Catheter Ablation
  - Surgical Resection
  - Radiation Therapy (esophageal or rectal)
- Widespread progression
  - Increase Imatinib to 800 mg daily
  - Sunitinib
  - Regorafenib
  - Clinical Trial

Hepatic Artery Embolization





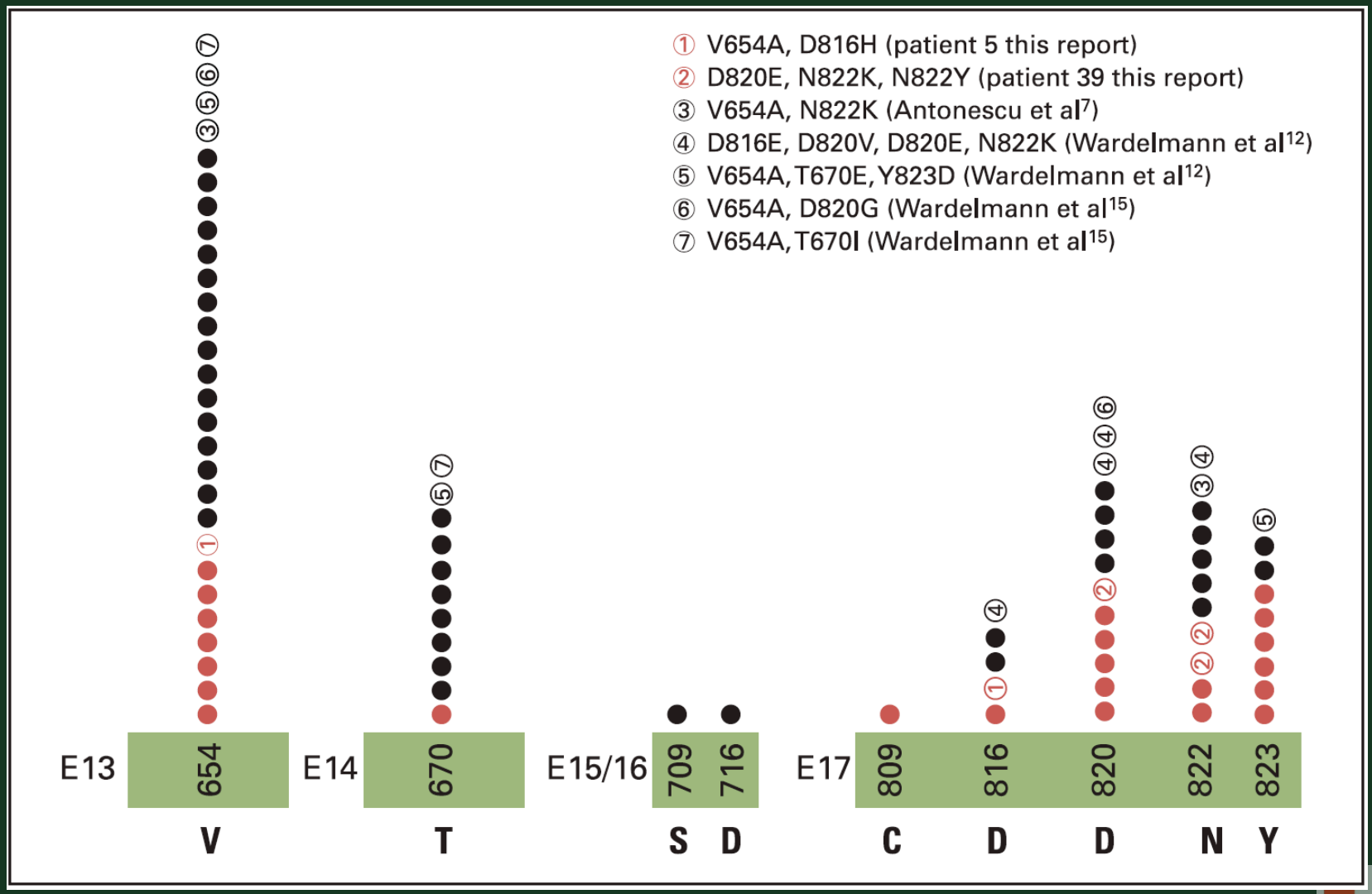
Pre-embolization



Post-embolization

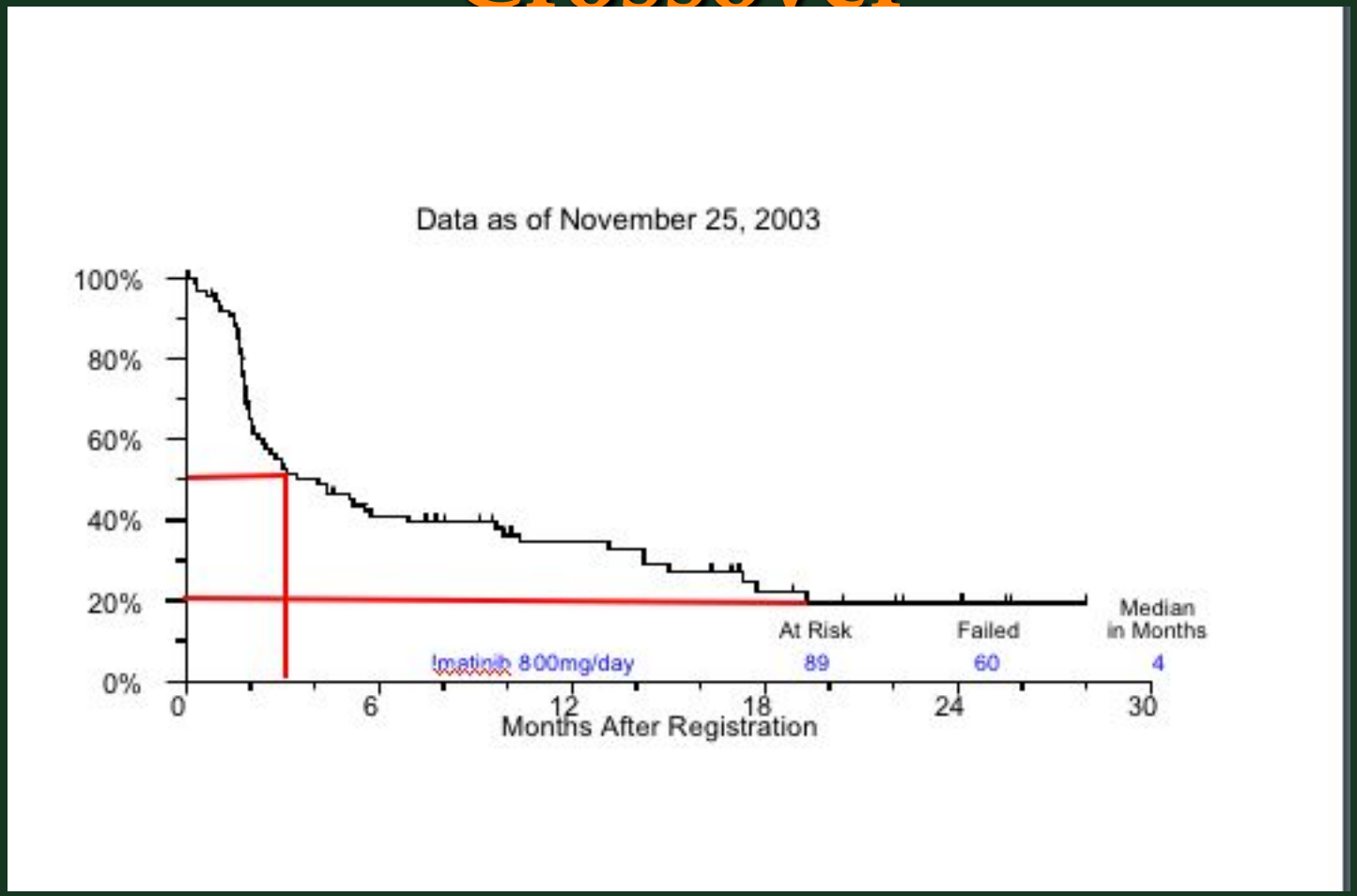
What happens if imatinib is no longer helping?

Secondary Mutation



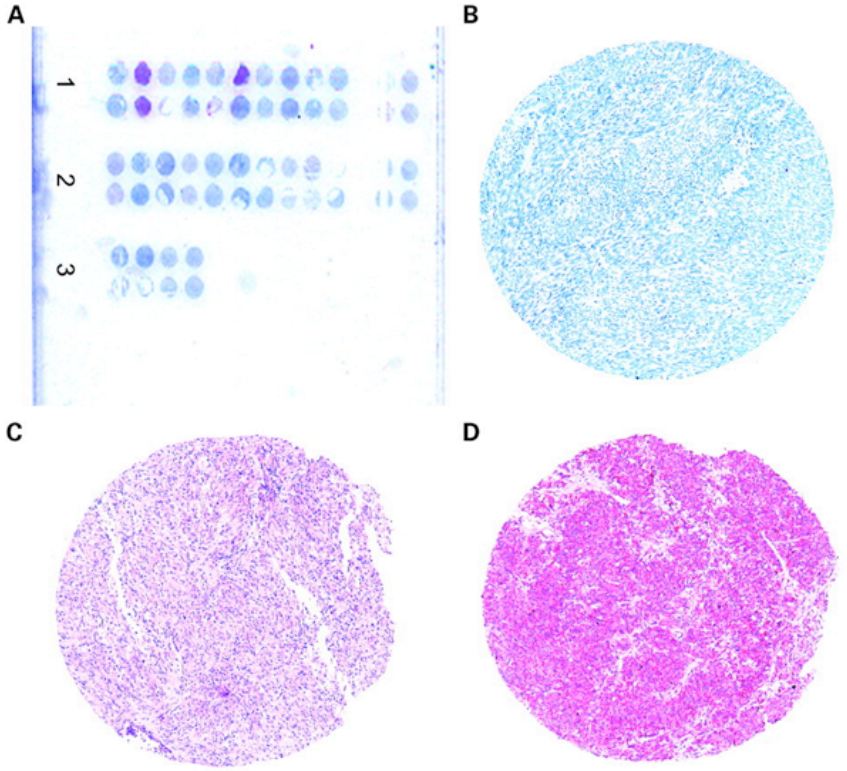
Heinrich et al, JCO 2006

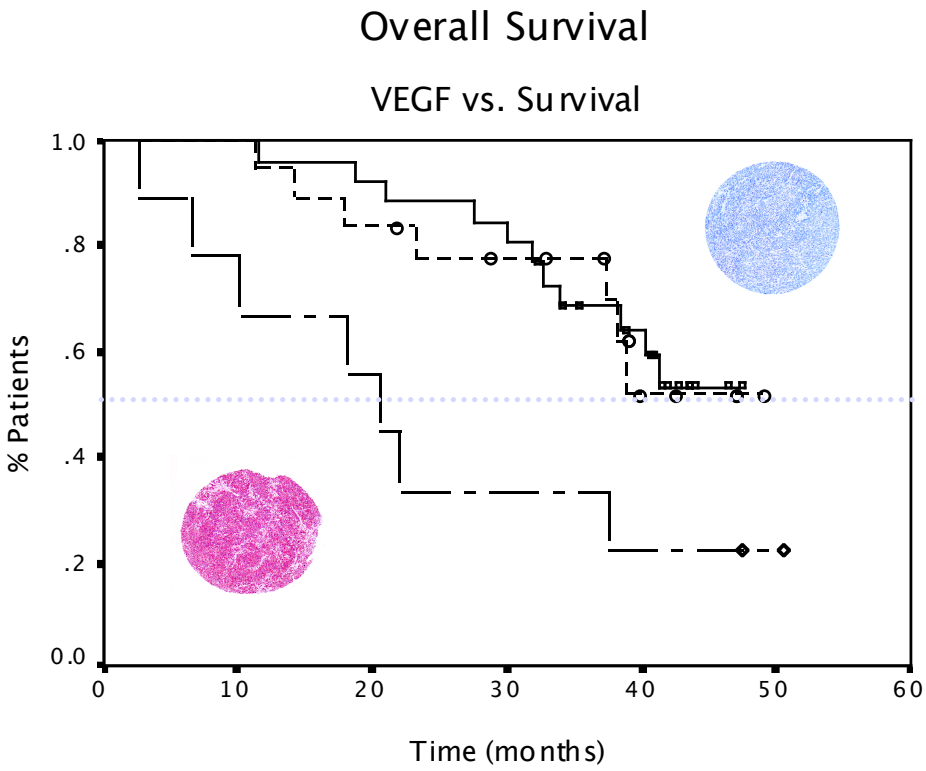
Phase III Trial: US Intergroup S0033: Time to Progression on Crossover



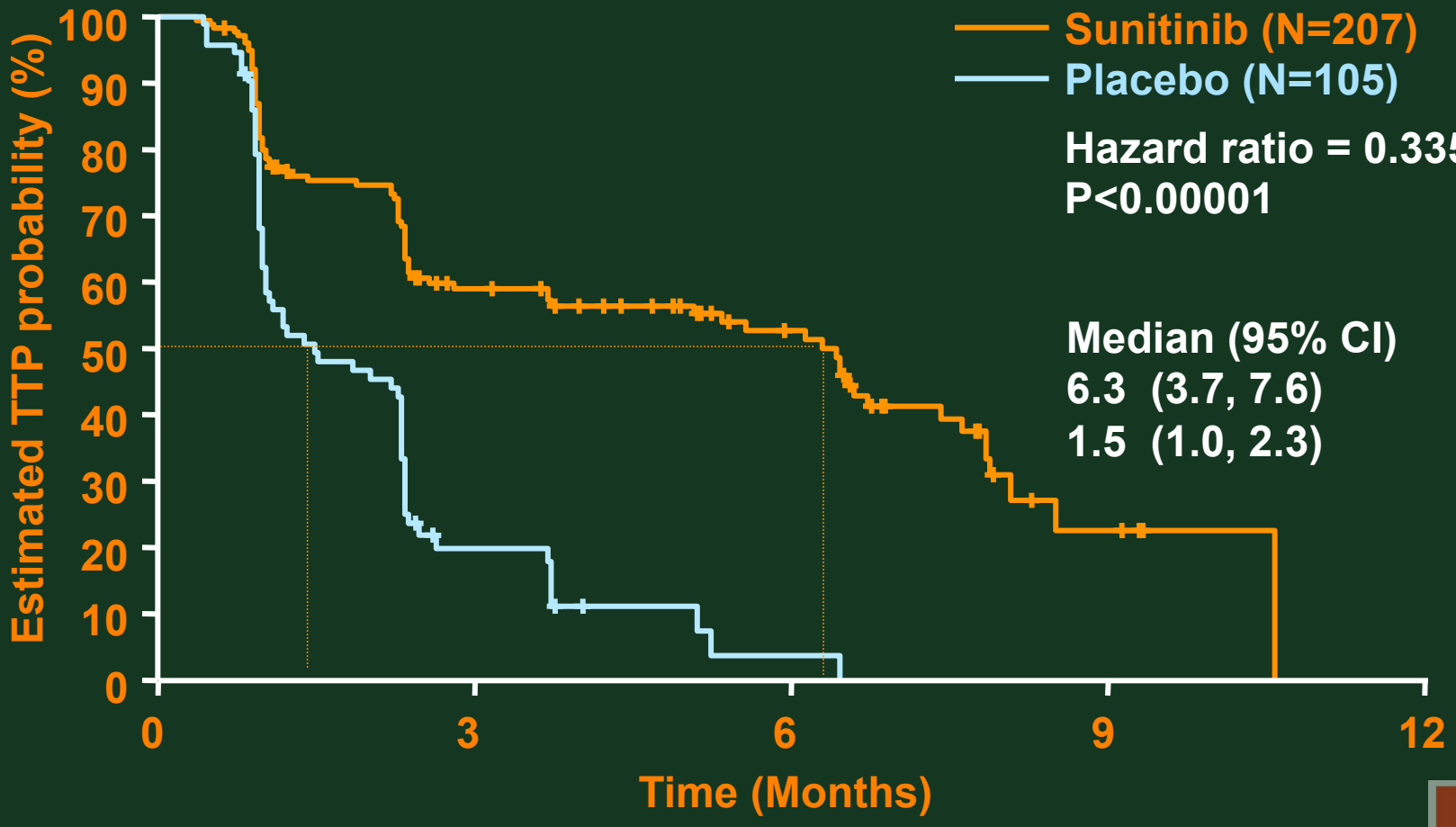
Association of Intratumoral Vascular Endothelial Growth Factor Expression and Clinical Outcome for Patients with Gastrointestinal Stromal Tumors Treated with Imatinib Mesylate

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



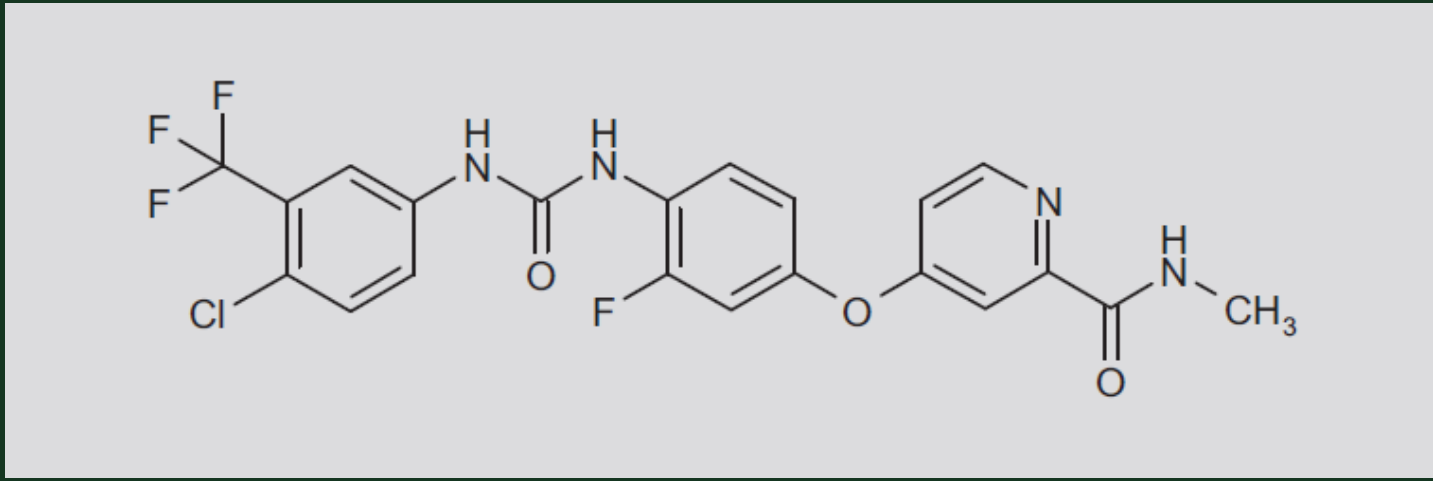


Time to Tumor Progression



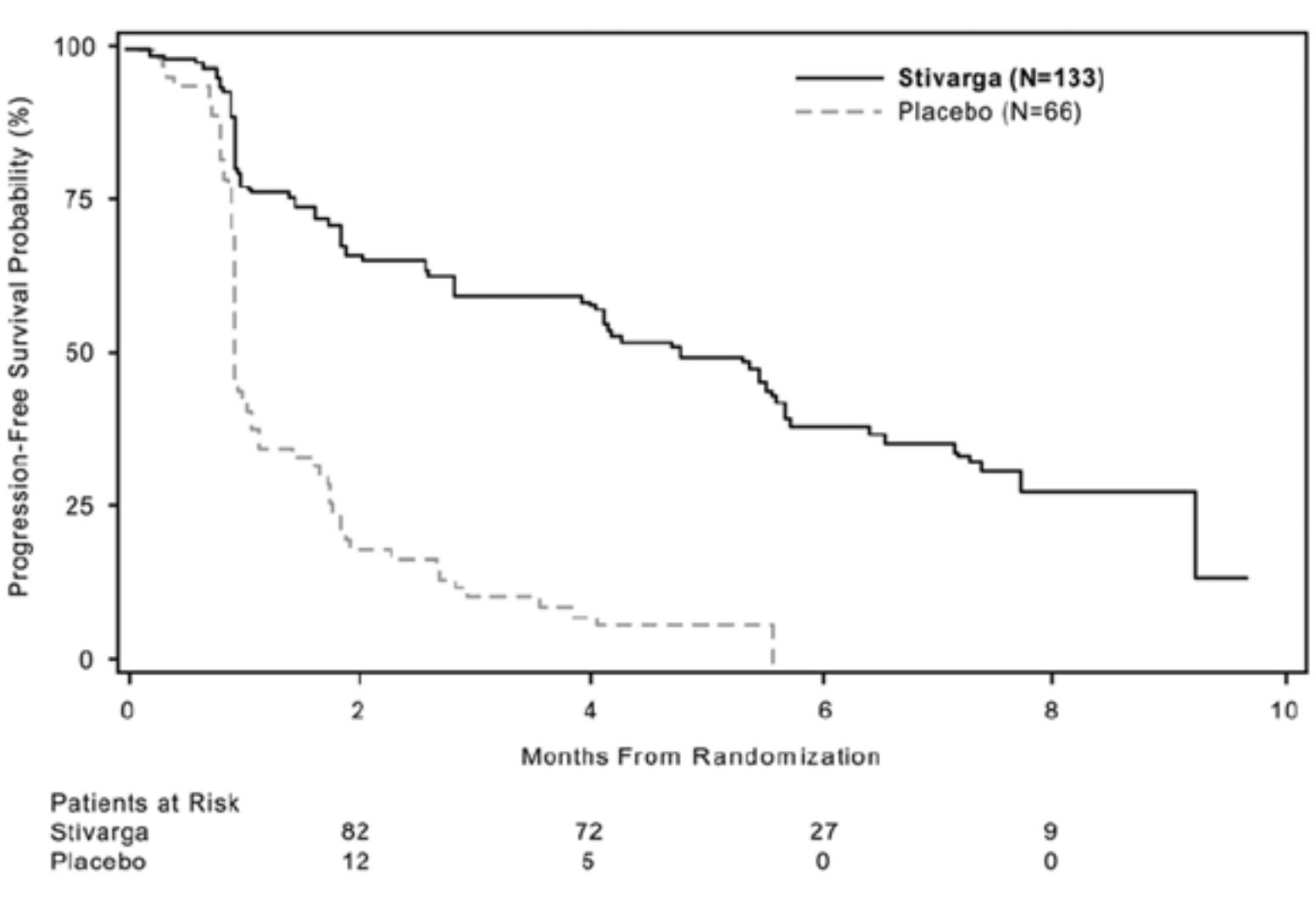
Background - Regorafenib

- 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



George et al ASCO 2103

Regorafenib vs. Placebo



Clinical Trials……

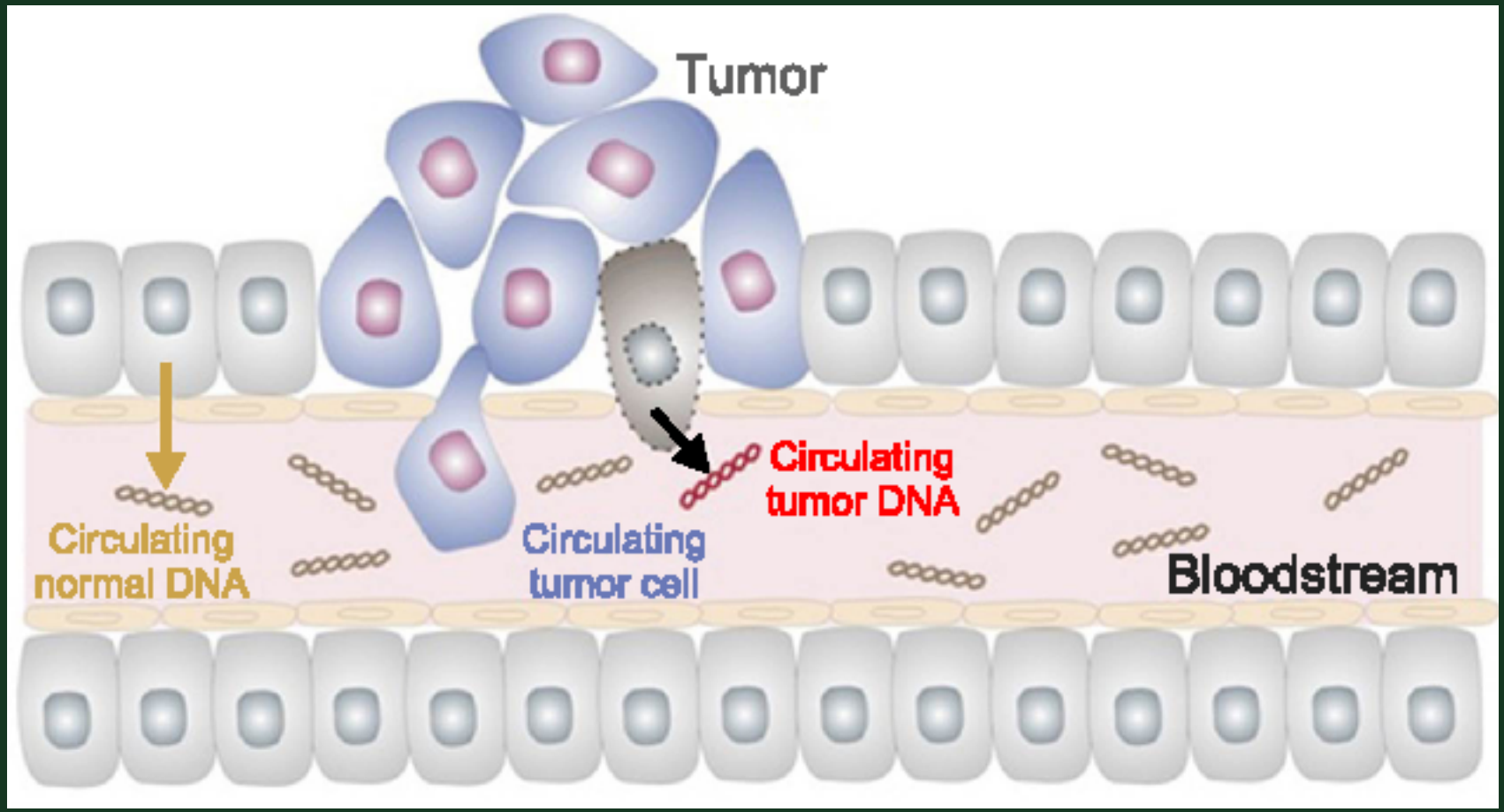
Jon Trent, MD, PhD

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)



Nurwidya et al, 2018

Ponatinib

Arshad ASCO 2018

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 2019

Jon Trent, MD, PhD
Professor of Medicine
Director, Bone and Soft-tissue Program
Associate Director, Clinical Research
Sylvester Comprehensive Cancer Center

jtrent@med.miami.edu

@JTrentMDPhD

SYLVESTER
COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM