GISTS 2008….

GISTS 2009….

2018

2019

GASTROINTESTINAL STROMAL TUMOR (GIST)- 101

GIST SUMMIT 2025

Neeta Somaiah, M.D.

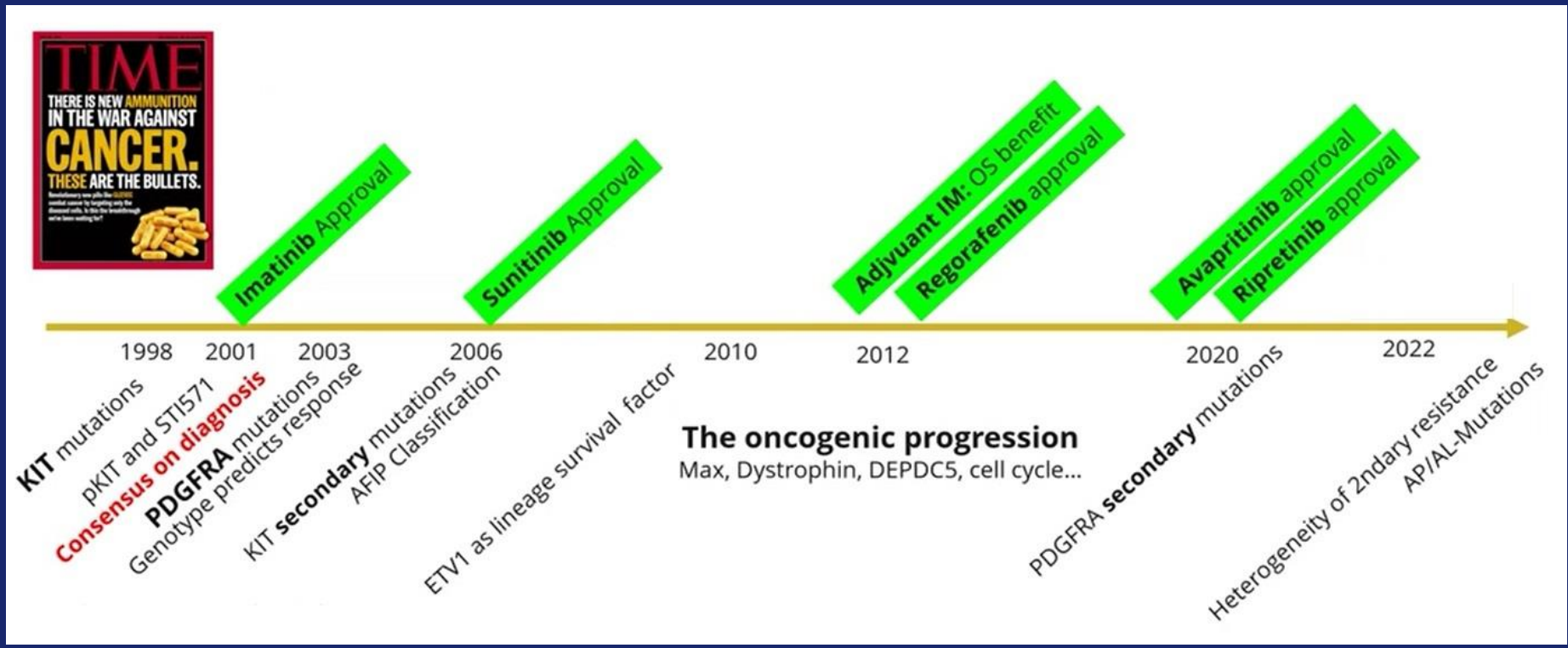
Professor & Chair

Sarcoma Medical Oncology

Milestones in GIST research and treatment 1998-present

Information from before 2000 is irrelevant.

To appreciate survival statistics –important to look back in time



(courtesy of Dr Sebastian Bauer)

BACKGROUND

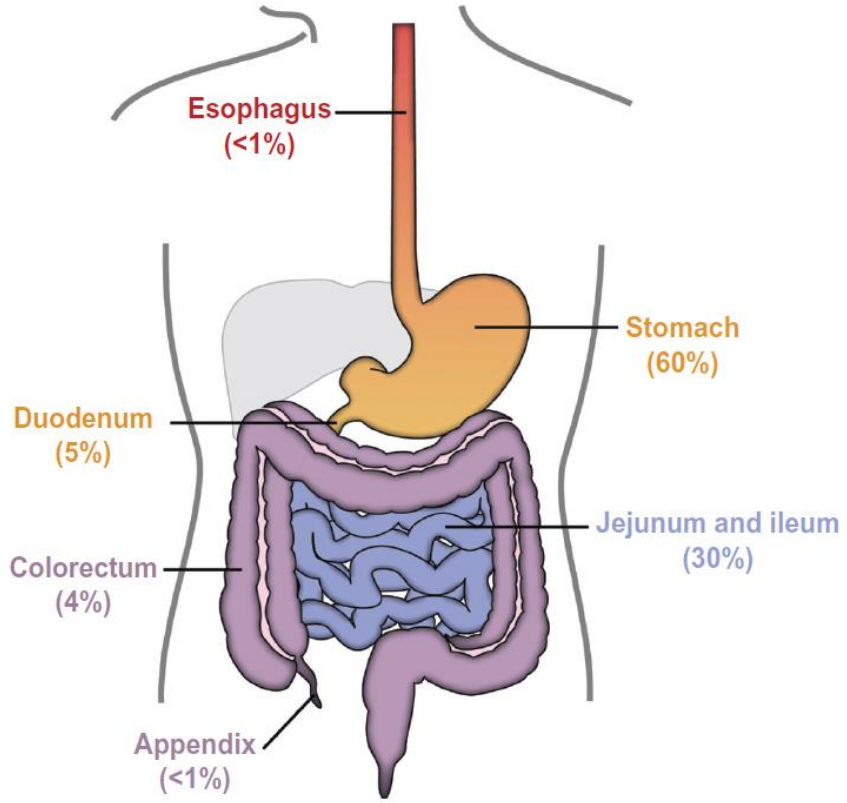
Carcinomas *vs.* sarcomas

Carcinomas are cancers that arise in epithelial tissues, such as the skin and the tissues that line the organs. Carcinomas are the most common cancers of the skin, breast, colon, prostate, lung, stomach, etc.

Sarcomas are cancers that arise in connective and supportive tissues. Examples: osteosarcoma (bone); liposarcoma (fat); angiosarcoma (blood vessels).

Sarcomas are rare (only about 1% of adult cancers).

GIST is a sarcoma of the gastrointestinal tract.

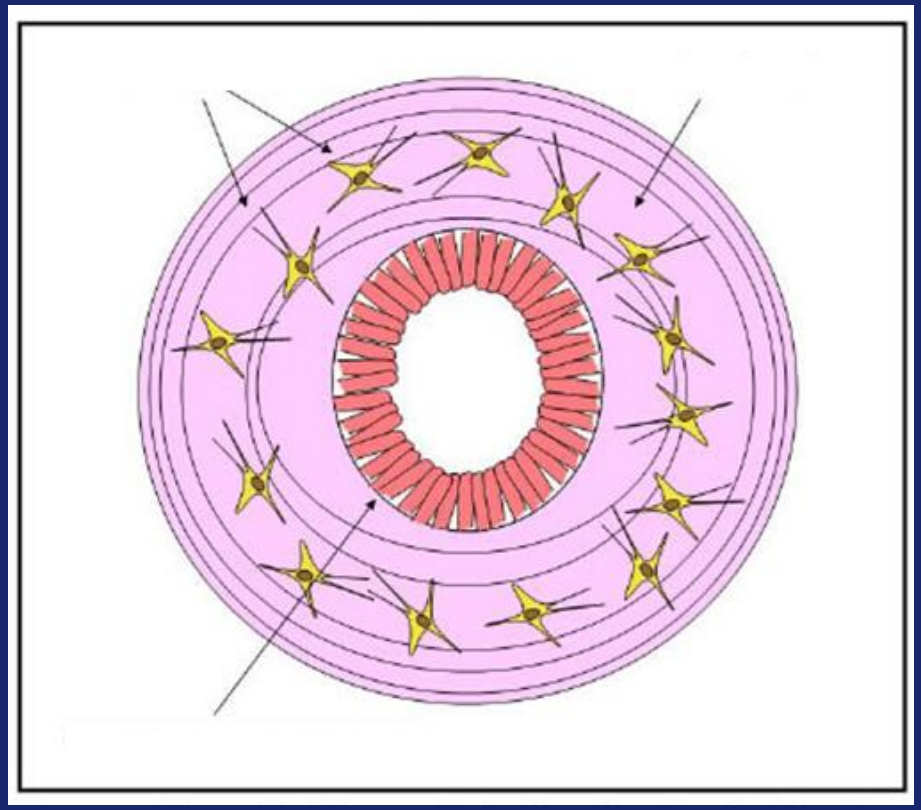


Primary GIST anatomic locations and relative frequencies.

- 0.2% of all GI tumors, but 80% of GI sarcomas
- Highest incidence in the 40-60 yr age group
- Similar male/female incidence
- About 5,000 newly diagnosed GIST patients/yr in the US
- Clinical presentation: pain, hemorrhage, anemia, anorexia, nausea, bleeding

Foo, Liegl-Atzwanger, and Lazar, *Clinical Medicine Insights: Pathology* 2012

Interstitial Cells of Cajal: the cells where GISTs start; the "pacemaker" cells that coordinate GI peristalsis.



Cajal (1852-1934)

Huizinga *et al.*, Interstitial cells of Cajal and human colon motility in health and disease, *Am. J. Physiol. Gastrointest. Liver Physiol.* (2021)

What causes GIST?

GISTs occur "sporadically", as a result of random mutations; majority GISTs are not inherited from one's parents and cannot be passed on to one's children*.

No environmental, occupational, dietary, lifestyle, ethnic, or geographical causes of GIST are known – and *if there were any substantial risk factors, they would have been identified by now.*

*There are very rare exceptions to this rule: germline (heritable) mutations in the genes *SDH*, *KIT*PDGFRA are known (Pantaleo *et al.*, *Front. Oncol.* 2022; *Burgoyne AM*, *Somaiah N*, *Sicklick JK*. Curr Opin Oncol. 2014; Yan *et al.*, *Oncologist* 2023)

Oncogenes

Oncogenes are human genes which, when mutated, can drive the development of a cancer.

Oncogenes encode proteins that act as cellular "gas pedals" or "master switches"- *when they receive an appropriate signal*, they "step on the gas" and instruct the cell to divide/ proliferate.

(Regulated cell division is a normal, essential process for growth and development, maintenance, wound repair, etc.)

Mutant oncogenes encode aberrant proteins that act like "gas pedals stuck to the floor", driving unregulated cell division.

The therapeutic concept: Disable the gas pedal!

GIST AND THE *KIT* GENE: THE 1998 BREAKTHROUGH THAT REVOLUTIONIZED GIST DIAGNOSIS AND TREATMENT.

- GIST cells almost always express a protein called "KIT" (very few other cells in the body do so)

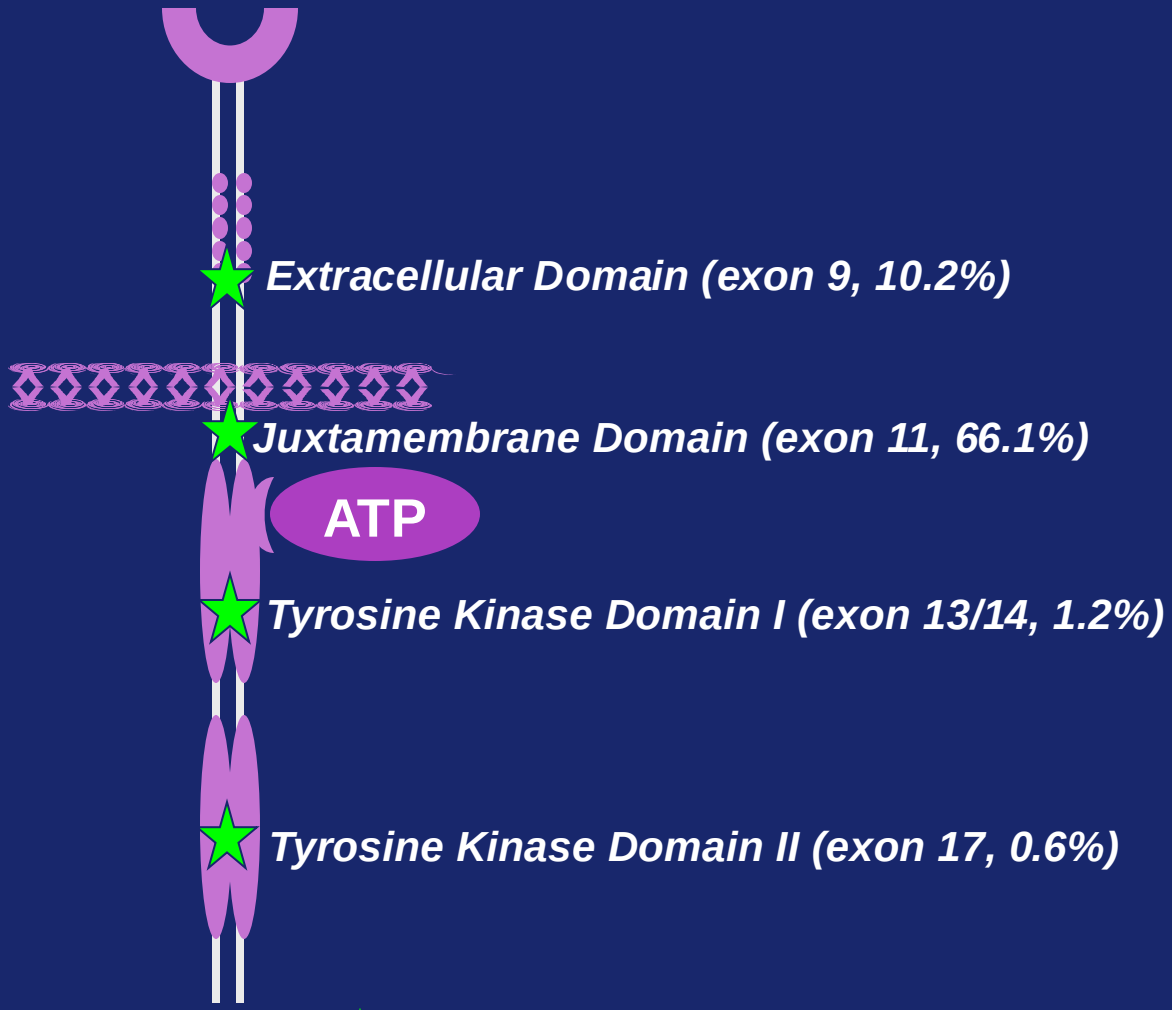
- In most GISTs, the *KIT* oncogene is mutated.

Yukihiko Kitamura, M.D. Seiichi Hirota, M.D.
Osaka University Medical School

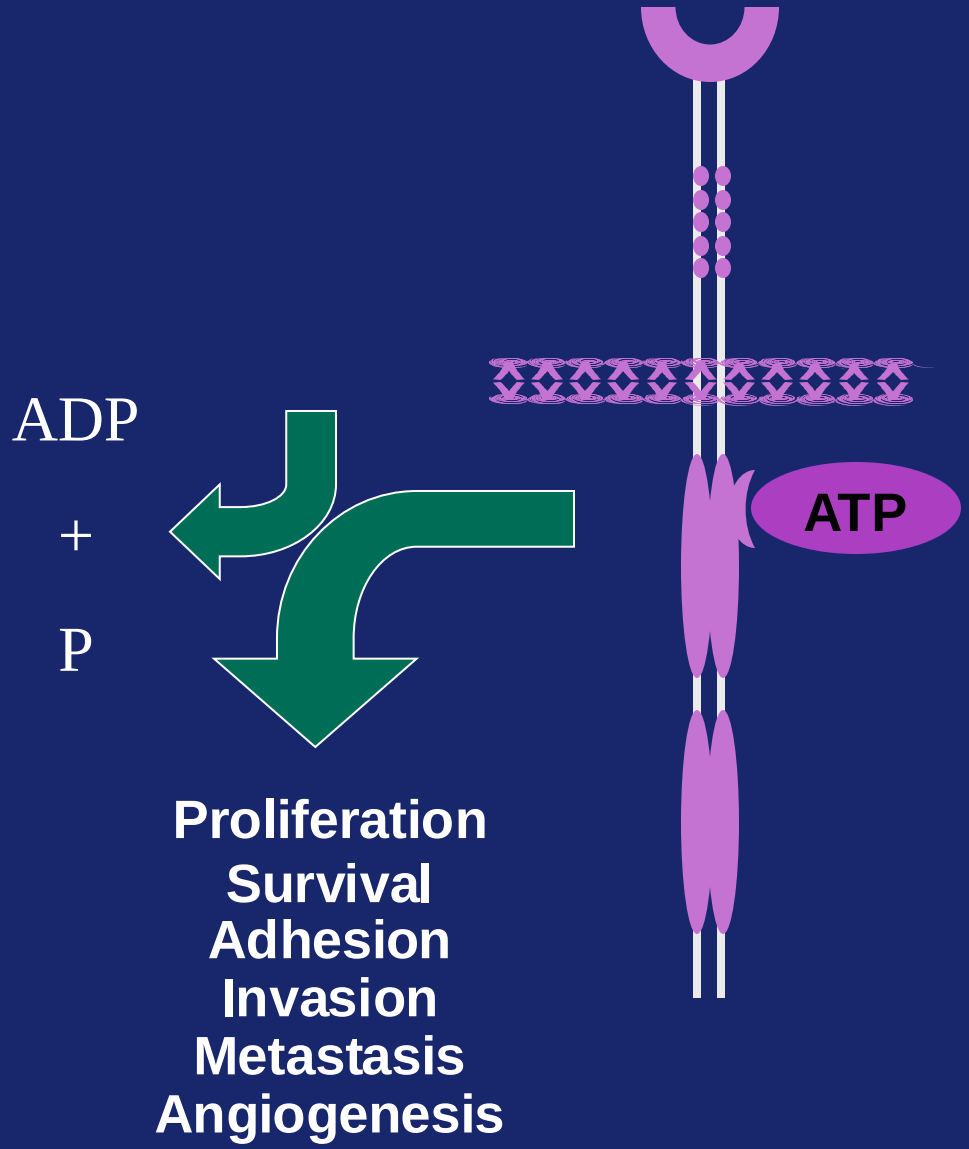
KIT (for "kitten"!)

The name "kit" refers to the fact that the gene was discovered as a gene from a virus that causes *sarcomas in cats*: HZ4 feline sarcoma virus.

Kit Receptor Structure

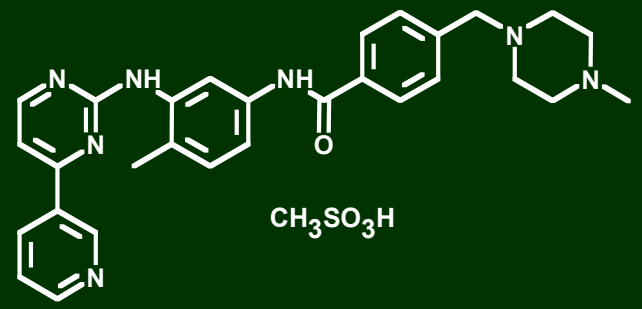


Kit Receptor Phenotype



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

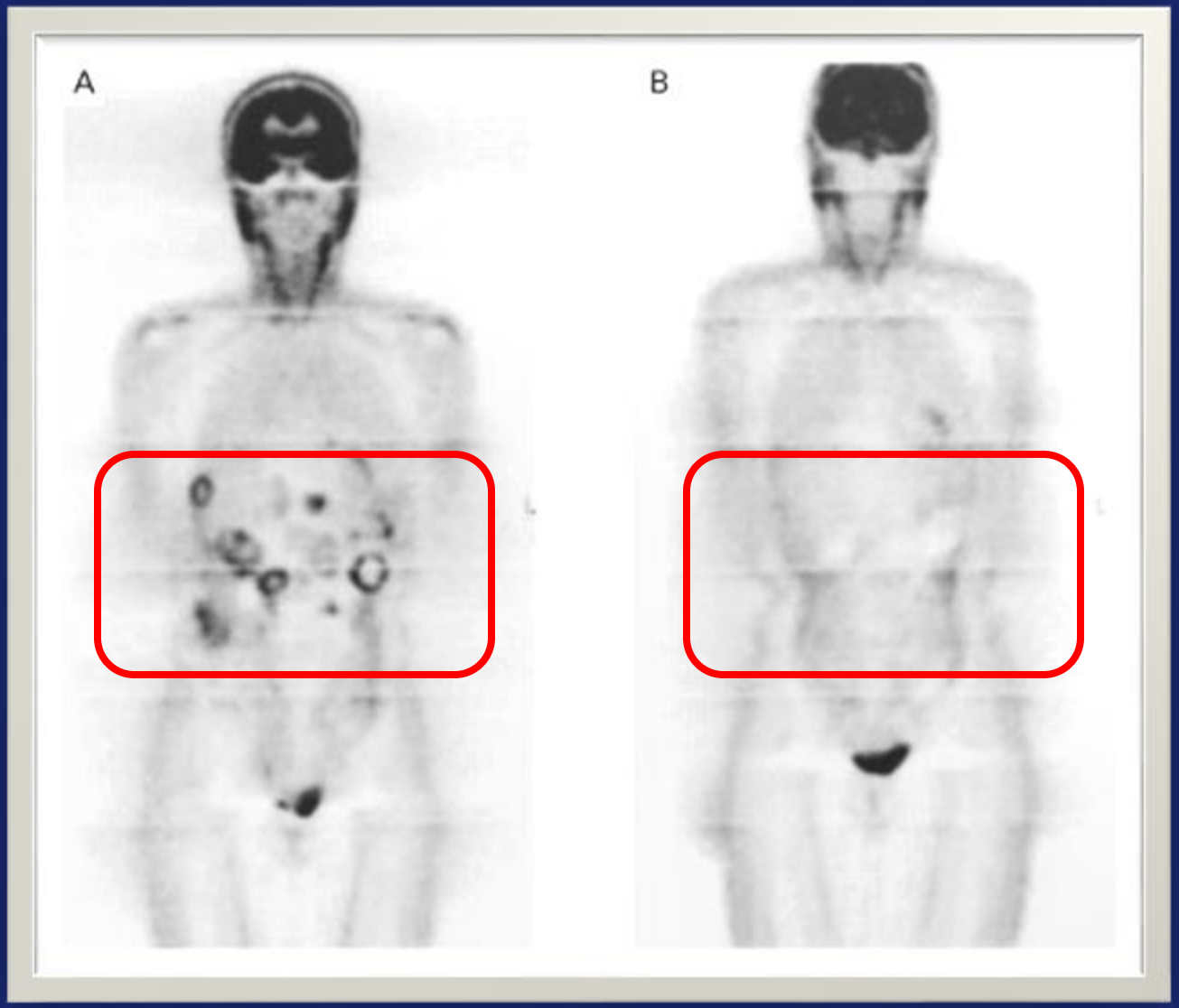
bcr-abl
PDGF-R
c-kit

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

1998: Imatinib used for the treatment of CML.

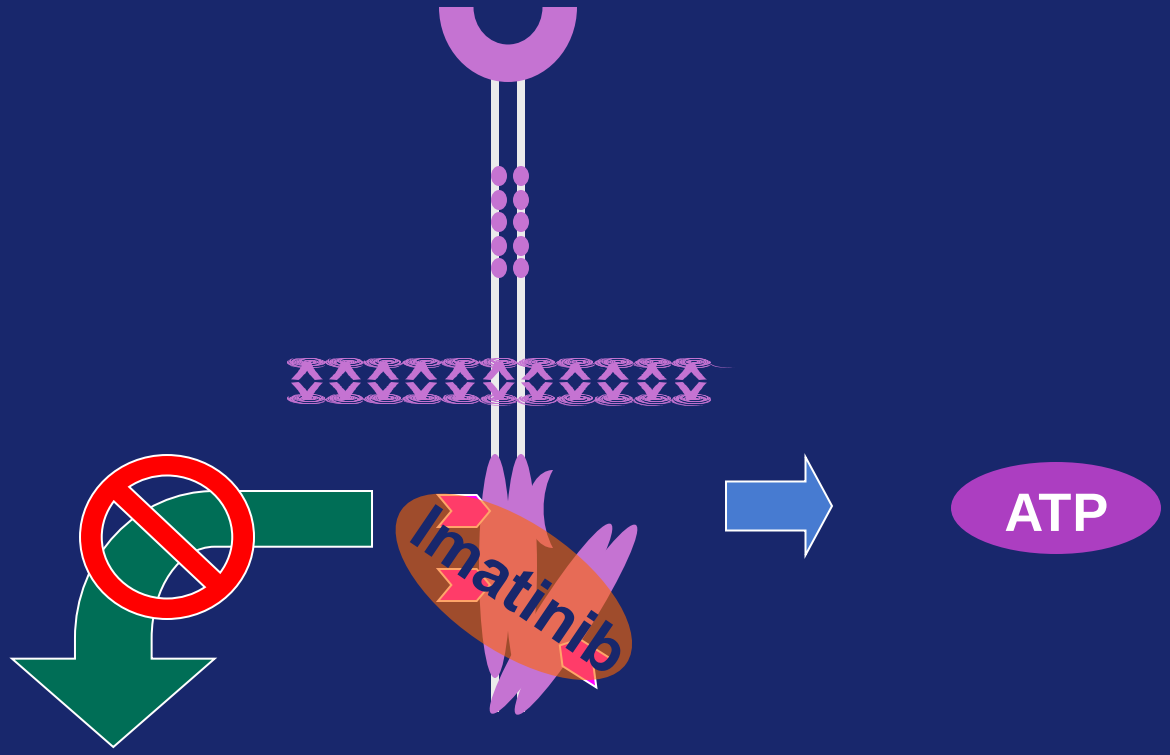
2000: Dr. Joensuu (Finland) and Dr. Demetri decided to treat a GIST patient with imatinib.

IMATINIB (Gleevec)



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

Kit Receptor Phenotype



Proliferation
Survival
Adhesion
Invasion
Metastasis
Angiogenesis

= imanitib contact point

Immunohistochemistry (IHC) *vs*. Mutational testing:
different tests, different questions, different answers

	Immunohistochemistry	Mutational testing
What it is:	**staining for the KIT protein**	**DNA sequencing of the *KIT* gene**
What it tells us:	**is the tumour GIST? (often, this simply confirms the diagnosis)**	**is the tumour a *KIT*-mutant GIST (and, if so, what is the *KIT* mutation?)***
What it requires:	**a tumour sample (tiny sample is enough)**	**a tumour sample (minimum core biopsy)**
Will the test be performed by the pathology lab?	***always***	***sometimes. If not done, the doctor will need to order it***

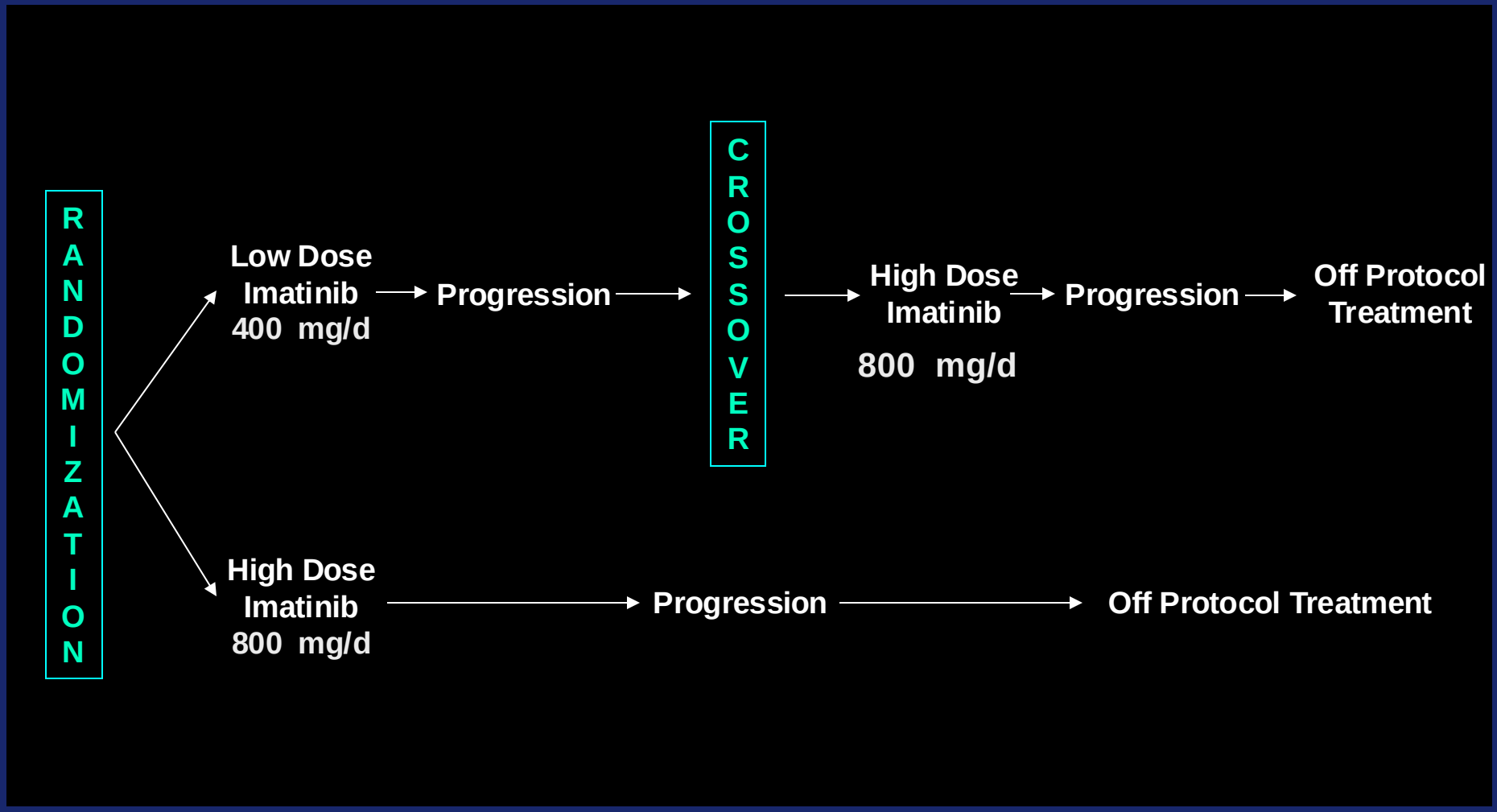
*If no mutation is found in the *KIT* gene, the lab will probably go on to examine other genes, *e.g. PDGFR*, *RAS*, *BRAF* …

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)

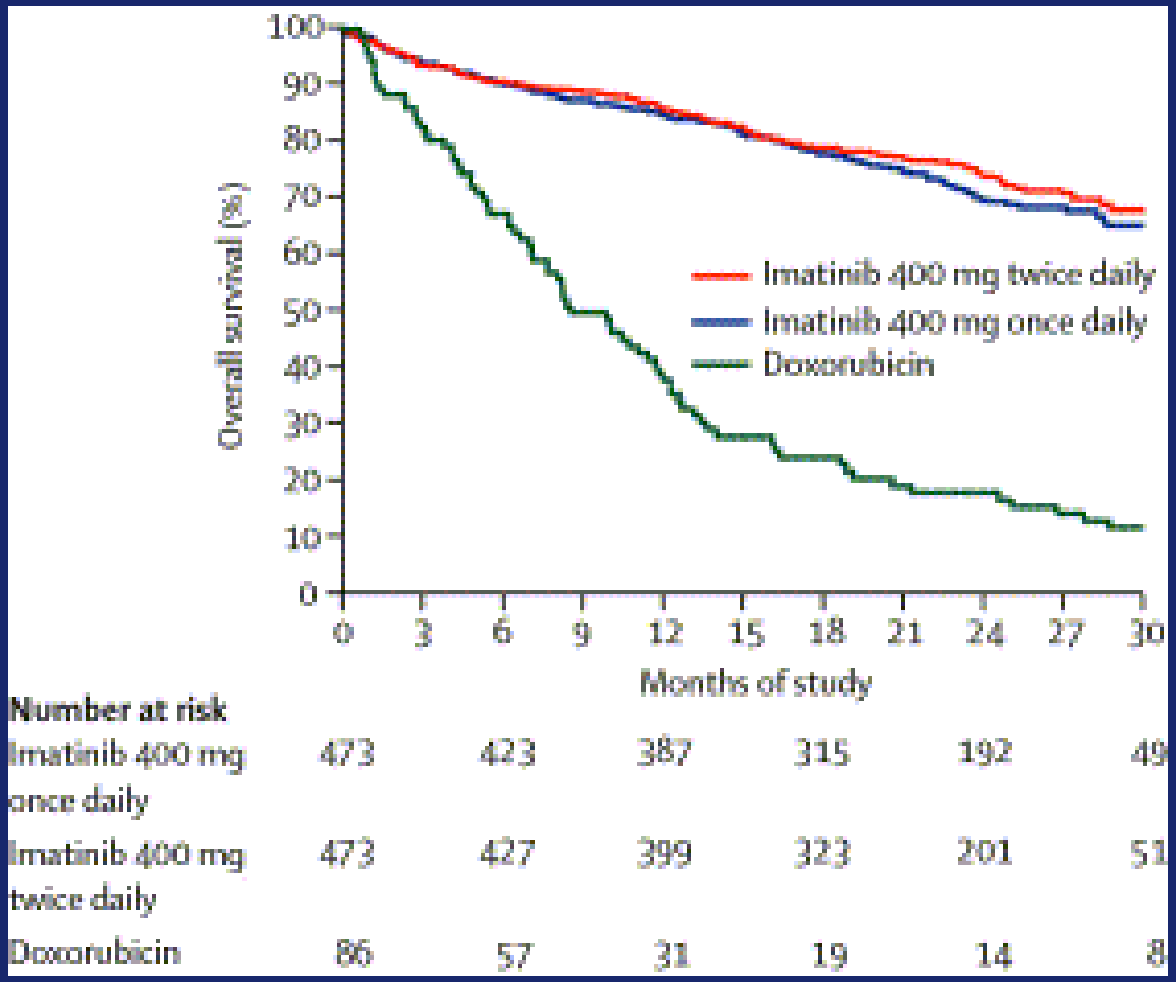
Courtesy Dejka Araujo, M.D.

North American Sarcoma Intergroup
Schema



EORTC PHASE III IMATINIB FOR ADVANCED GIST

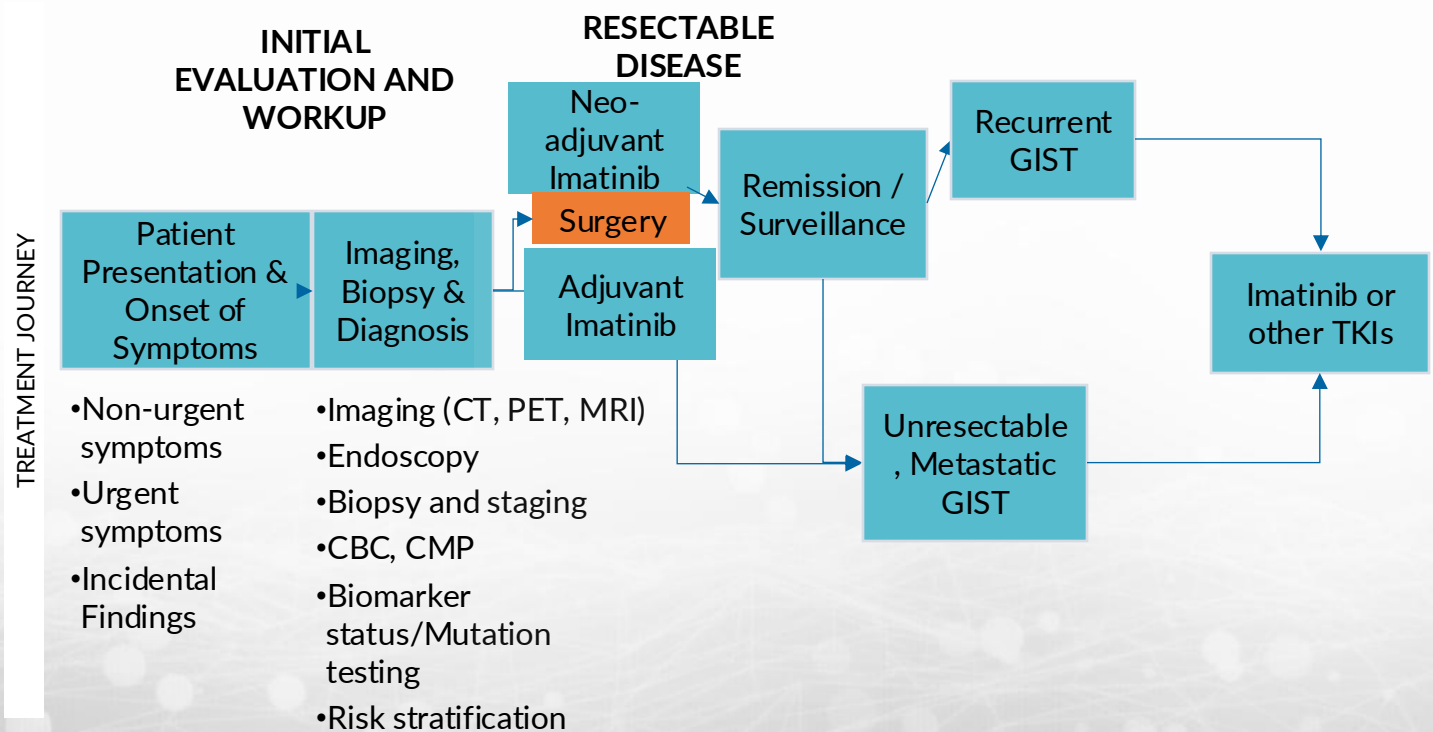
SURVIVAL BENEFIT



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

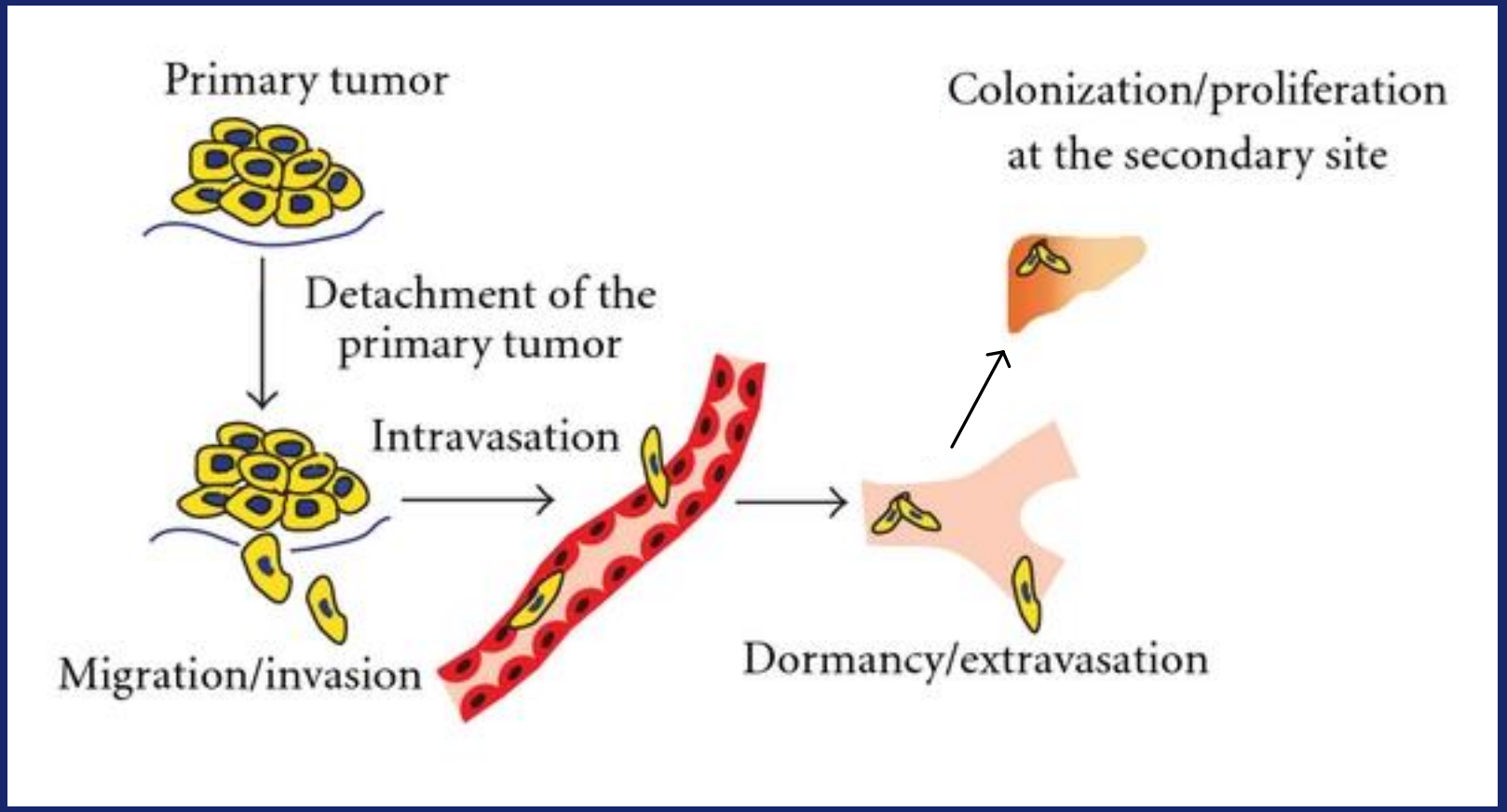
Verweij, et al 2004

INITIAL GIST WORK-UP AND TREATMENT



METASTASIS IN GIST

High recurrence rate after surgery (>50%)



GIST FOLLOW-UP 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
- Repeat Tumor mutation testing
- Liquid Biopsy

^{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

Kit exon 11

Kit exon 9

PDGFR D842V

SDH deficiency

Raf V600E

NF-1, Ras

PI3K

IGF-1R expressing

TRK fusion

PRIMARY MUTATIONS

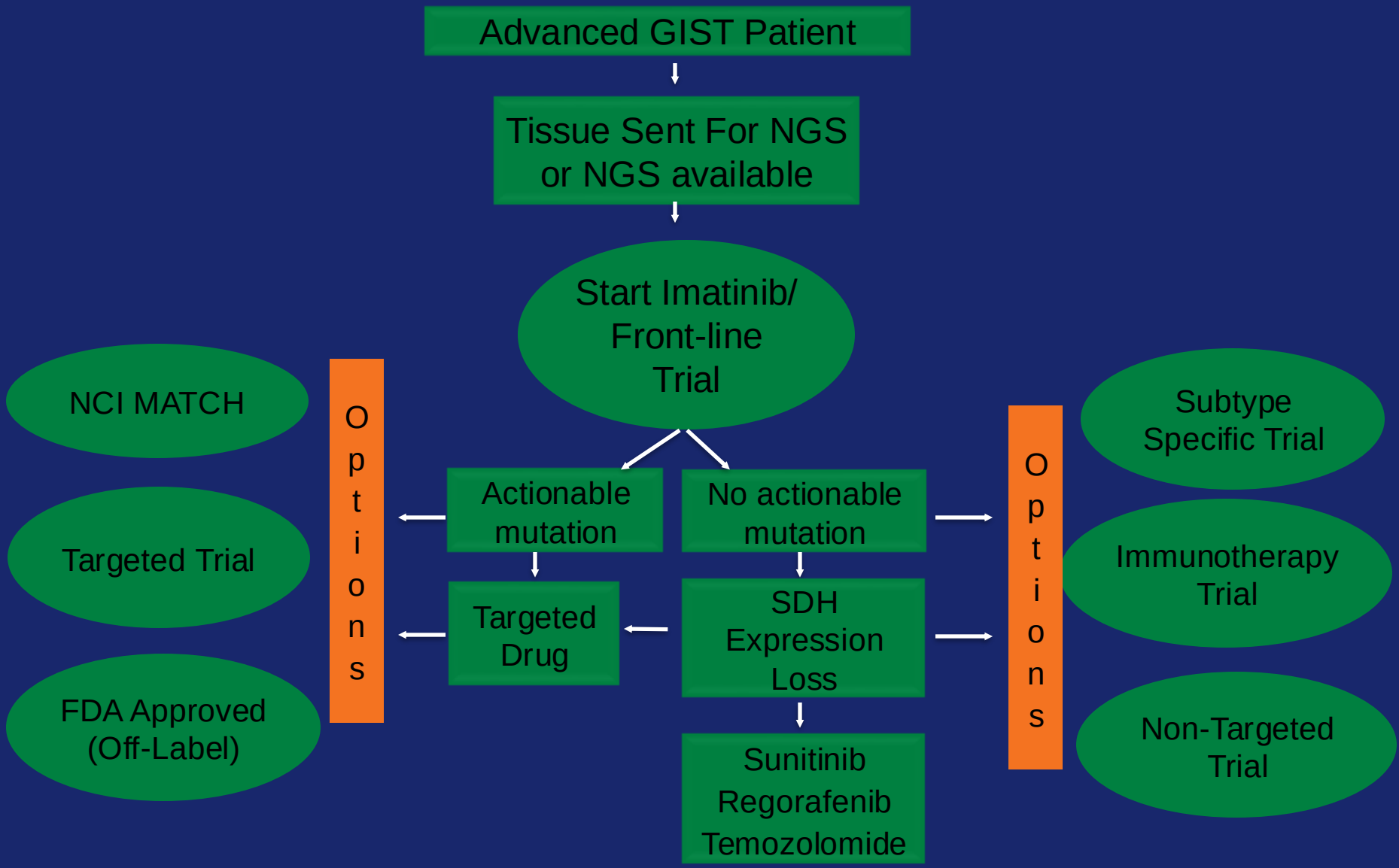
Personal Communication Jon Trent, MD, PhD (Sylvester Comprehensive Cancer Center)

GIST SUBTYPES AND TREATMENT

- Kit exon 11: Imatinib 400 mg
- Kit exon 9: Imatinib 800mg (or tolerated dose)
- PDGFR D842V: avapritinib
- SDH deficiency: Sunitinib or Regorafenib (TMZ trial, FGFR inhibitor trial)
- Raf V600E: Raf inhibitor
- NF-1, Ras: Raf or Mek inhibitor
- PI3K: mTOR inhibitor
- IGF-1R expressing – IGF-1R inhibitor trial
- TRK fusion – Larotrectenib NTRK inhibitor

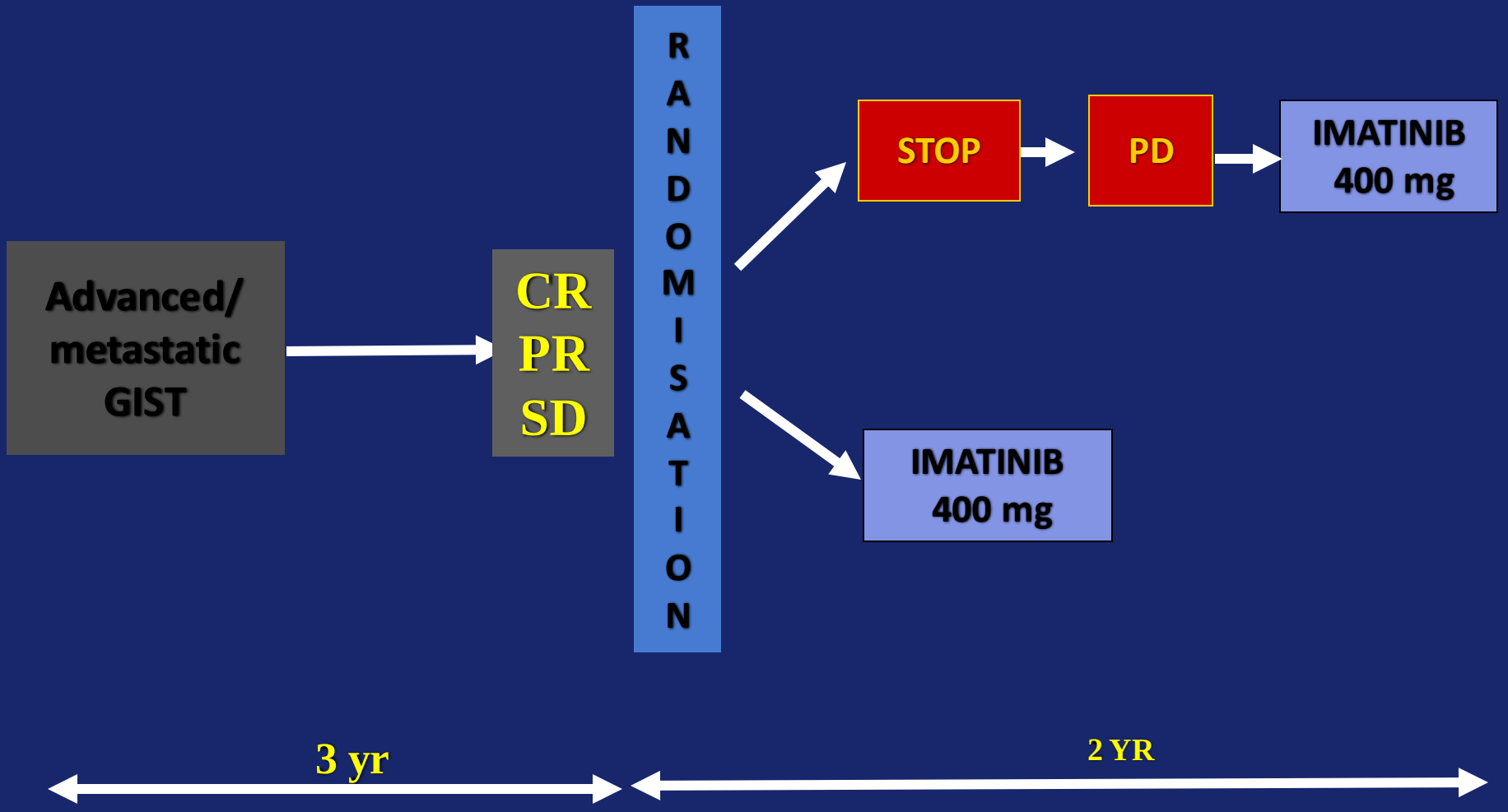
Personal Communication Jon Trent, MD, PhD (Sylvester Comprehensive Cancer Center)

GIST PRECISION MEDICINE

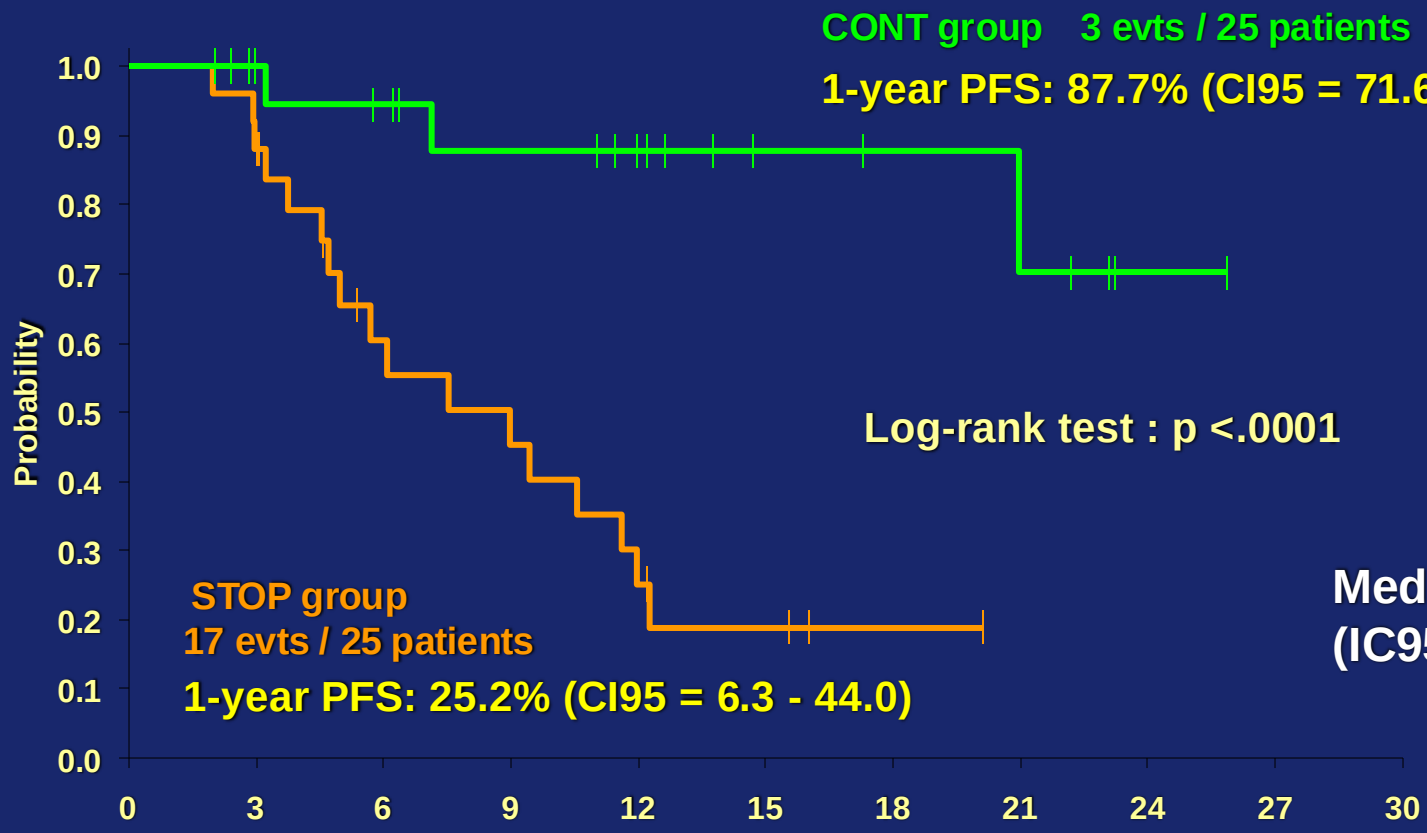


HOW LONG DO I TAKE IMATINIB OR OTHER KINASE INHIBITOR?

BFR14 3-YR RANDOMIZATION



BFR14 3-yr randomization
Progression Free Survival



Median f.u.: 11 m
(IC95: 4.8 – 13.8)

Rate of PD in STOP group

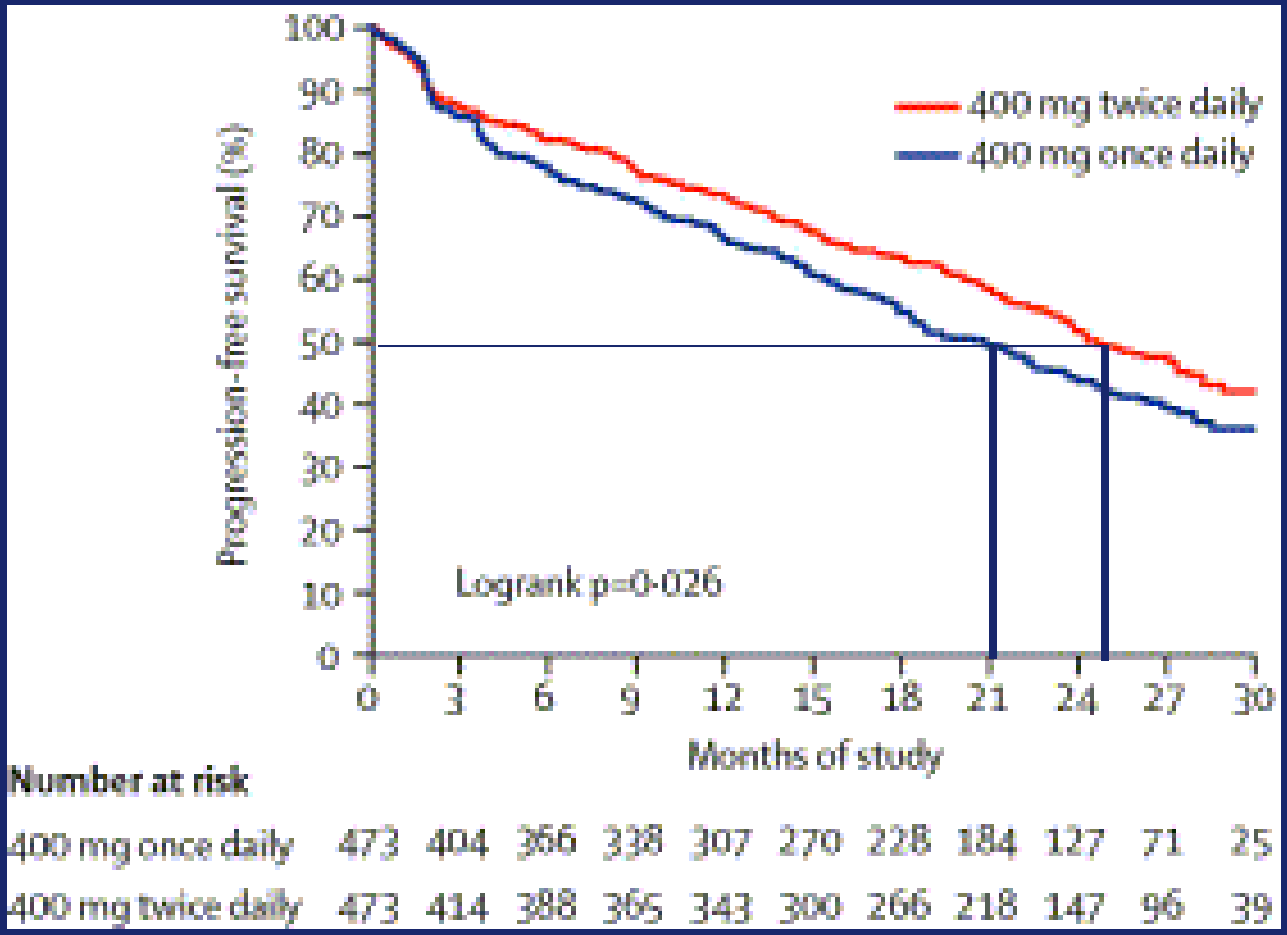
at 6 months: 40%
at 9 months: 55%
at 1 year: 75%

Updated sept 07, ECCO 14

WHAT DOSE OF IMATINIB DO I TAKE?

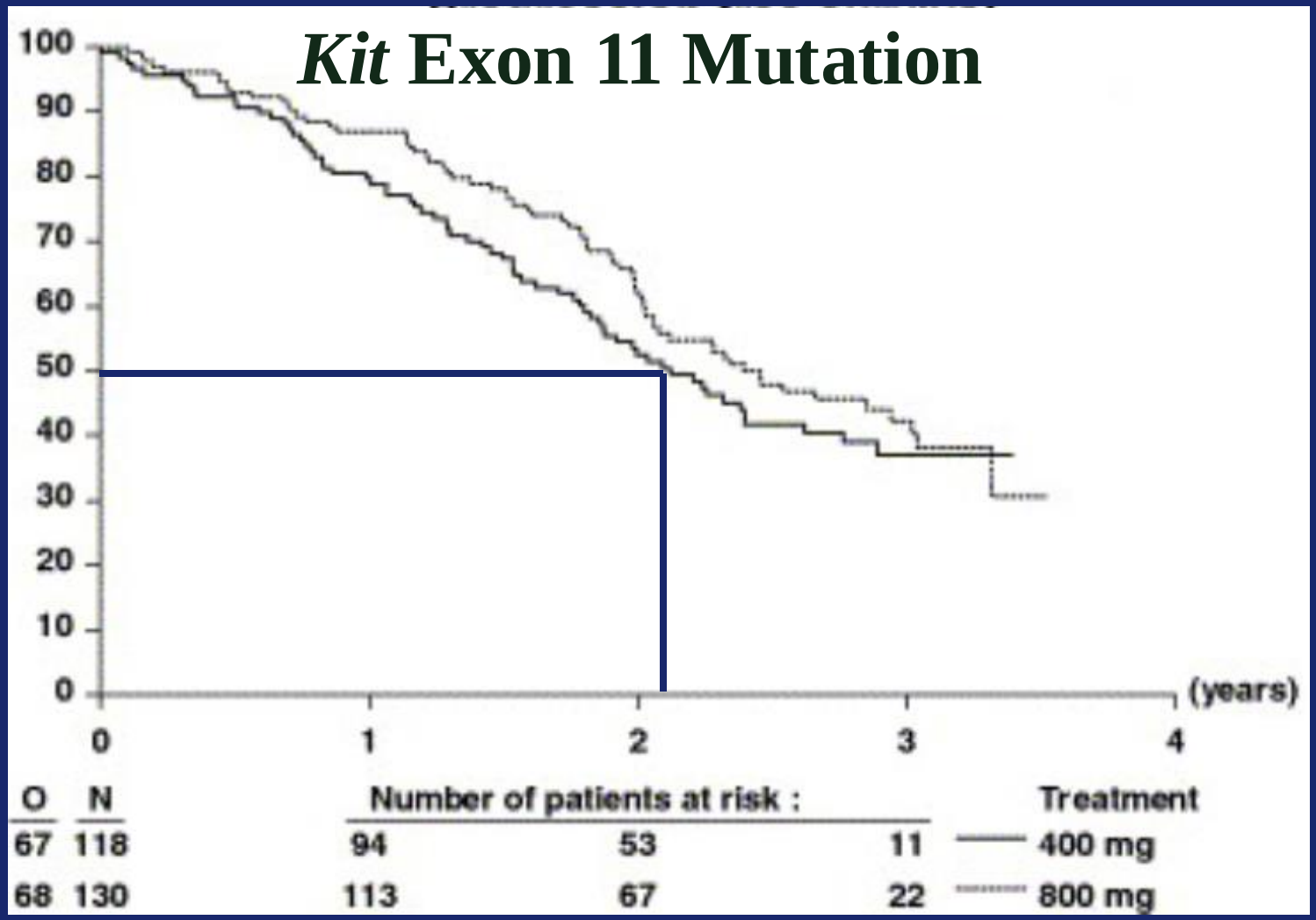
EORTC PHASE III IMATINIB FOR ADVANCED GIST

PROGRESSION-FREE SURVIVAL BENEFIT



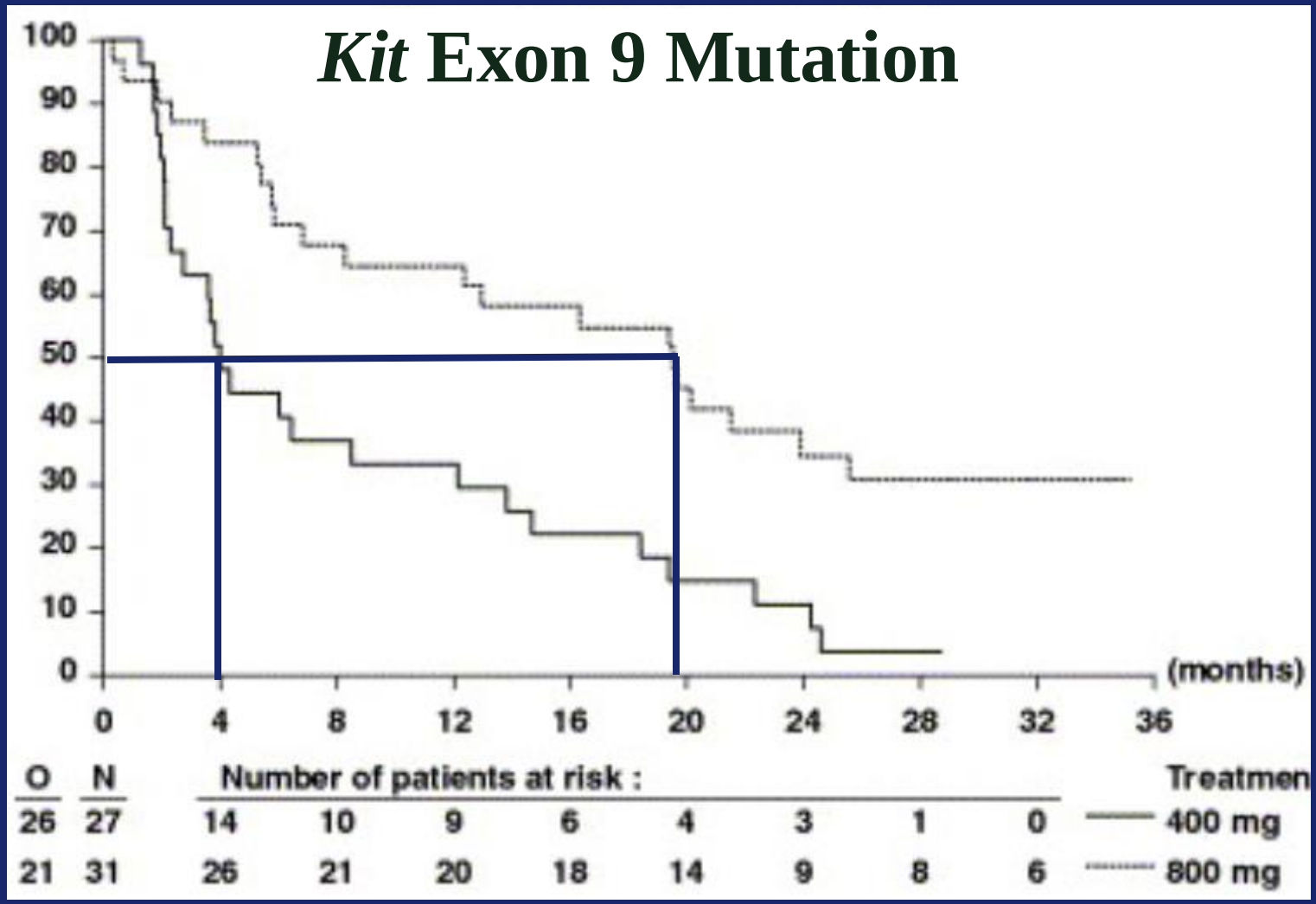
Verweij, et al 2004

PROGRESSION-FREE SURVIVAL BY IMATINIB DOSE



Debiec-Rhycter et al, 2007

PROGRESSION-FREE SURVIVAL BY IMATINIB DOSE



Debiec-Rhycter et al, 2007

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

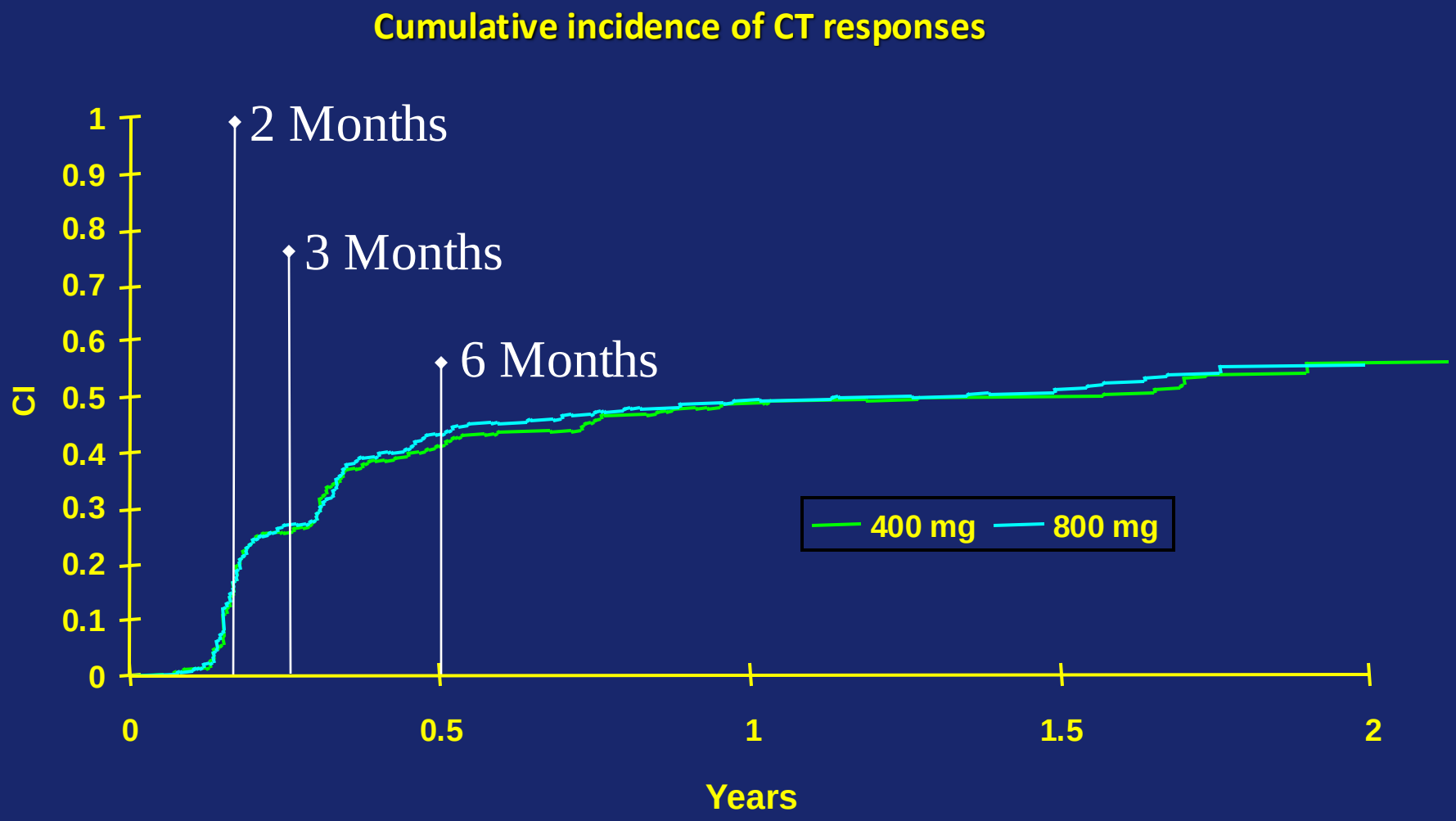
INTERRUPTIONS AND REDUCTIONS OF THERAPY

	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%

IS MY GIST "RESPONDING" TO THERAPY

RADIOGRAPHIC EFFICACY

Time to PR by "RECIST"

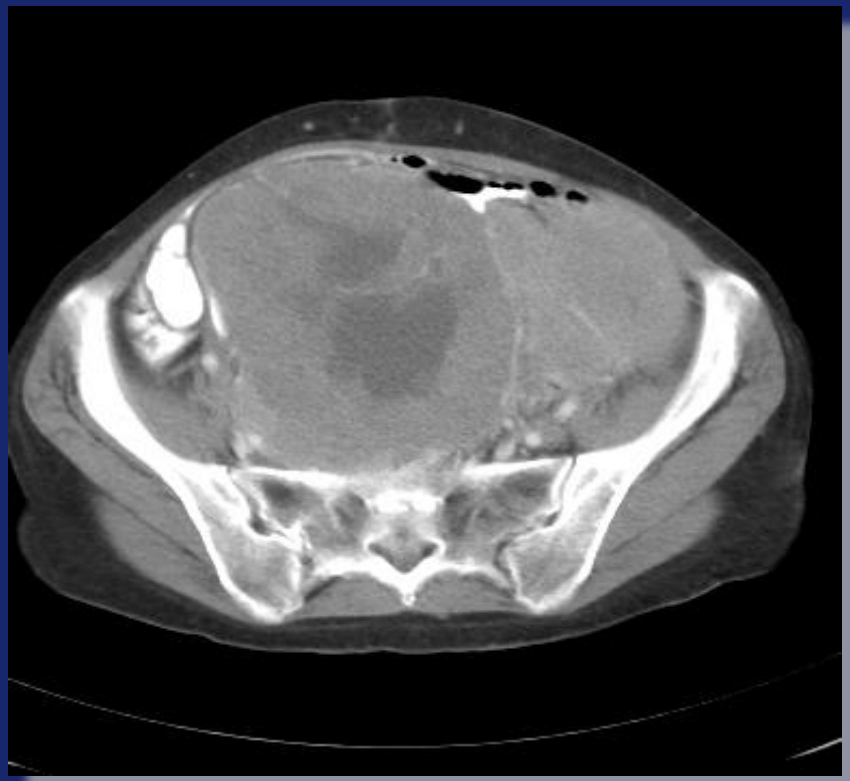


Verweij et al, ASCO 2003

Good "Response"

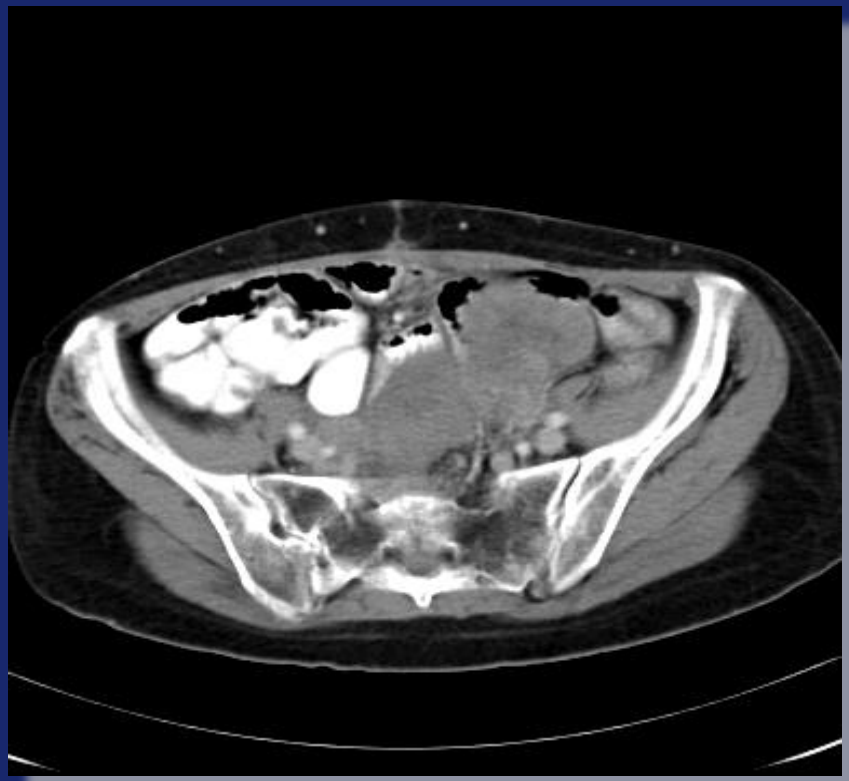
CT Scan Results

Jun 27, 2000



Before Imatinib

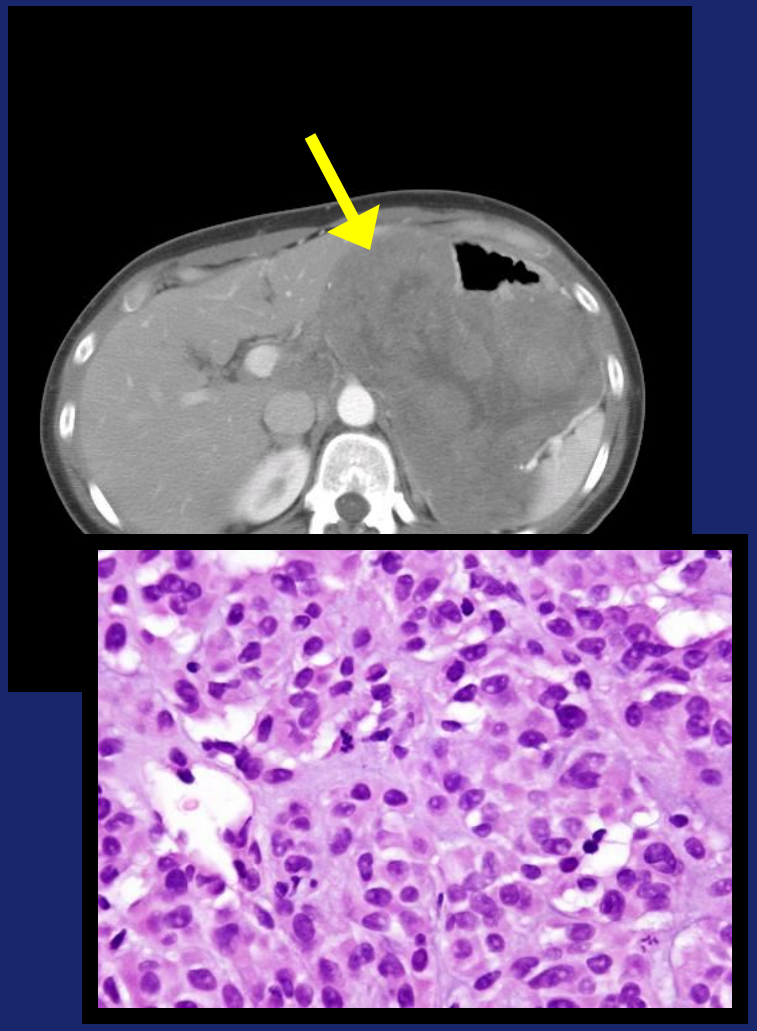
Oct 4, 2000



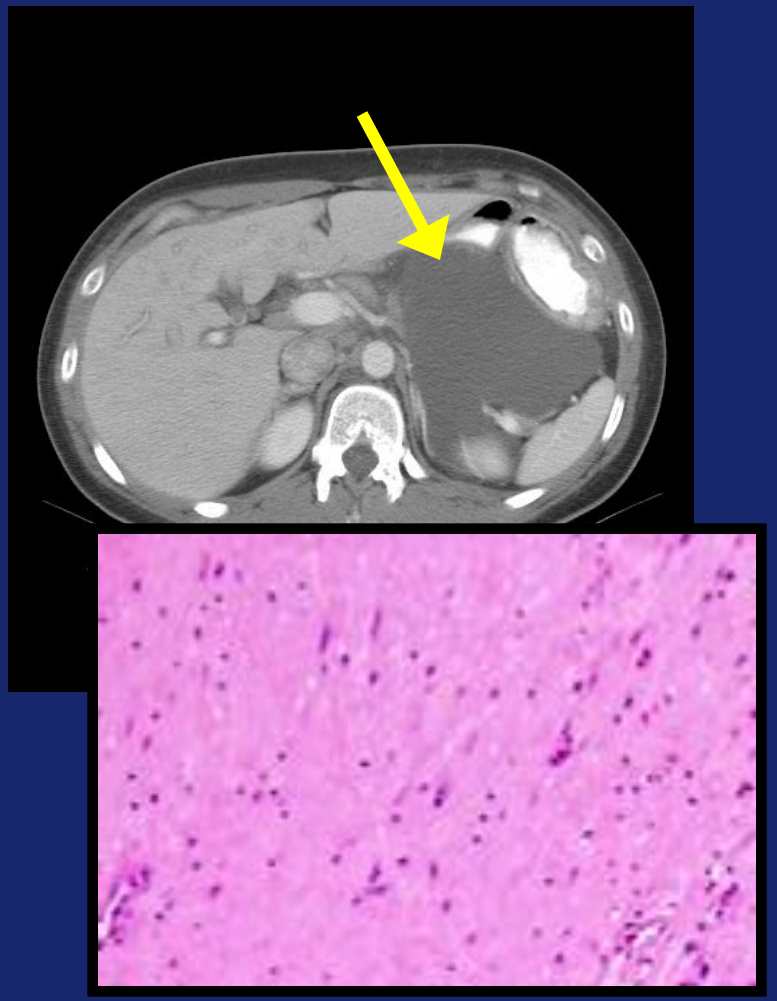
After Imatinib

Good "Response"

CT Scan Results



Pre-Imatinib



Post-Imatinib (8 weeks therapy)

Courtesy Jon Trent and Alex Lazar

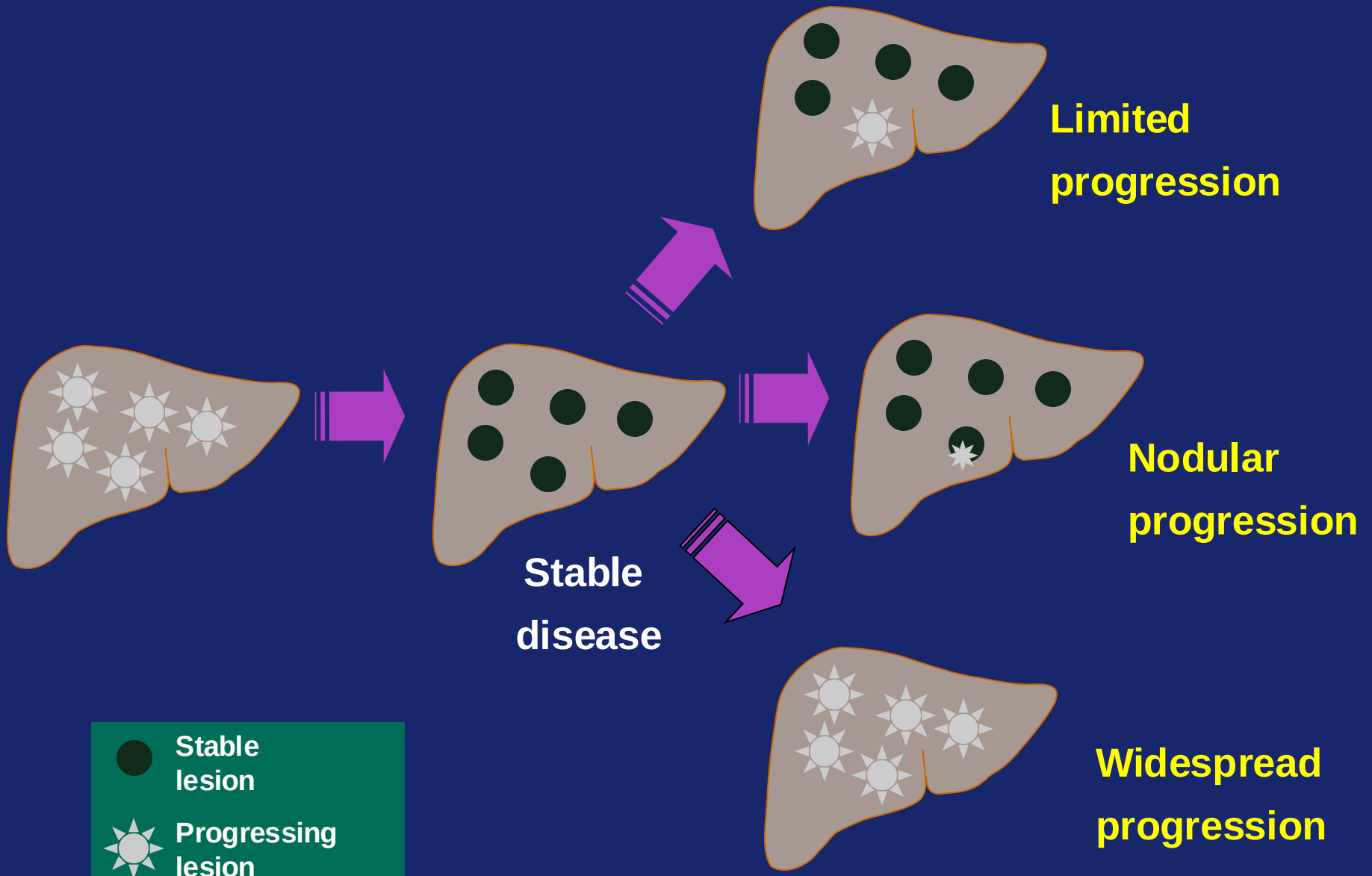
"When I am referred a GIST patient because he or she has progressed while on imatinib, I first stop and ask:

- Was it really progression
  (misinterpretation of radiology results??)

- Was the patient really taking the drug?
  (*non-compliance??*)"

WHAT DO I DO IF MY GIST IS RESISTANT?

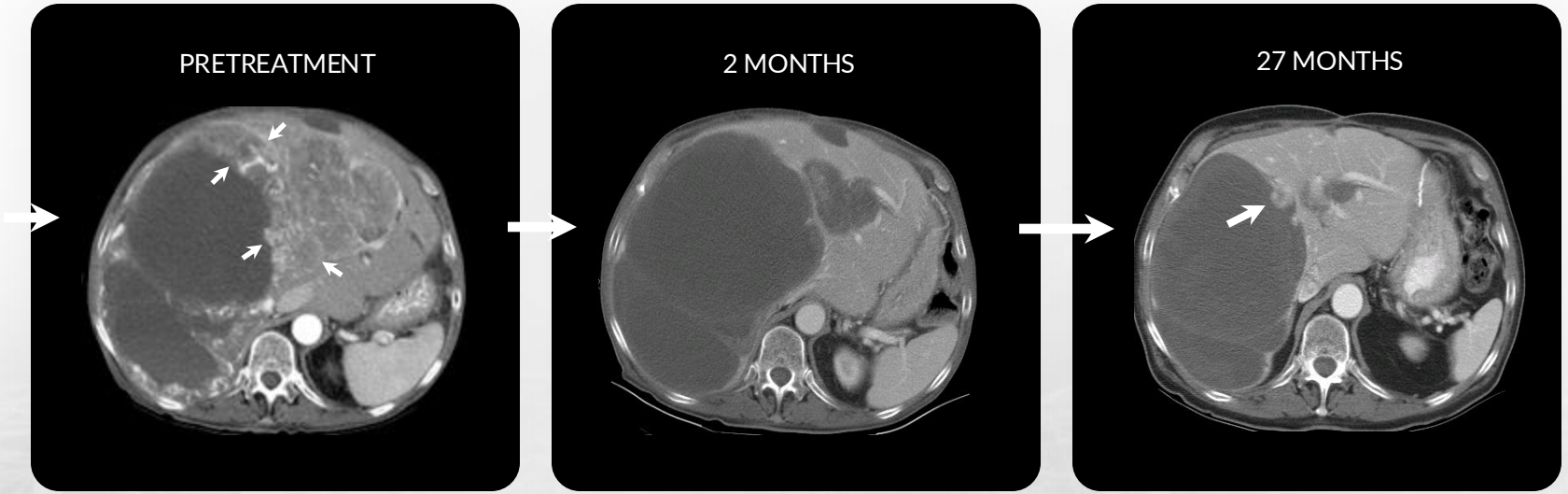
TYPE OF PROGRESSION



LIMITED PROGRESSION

IDENTIFYING RESPONSE

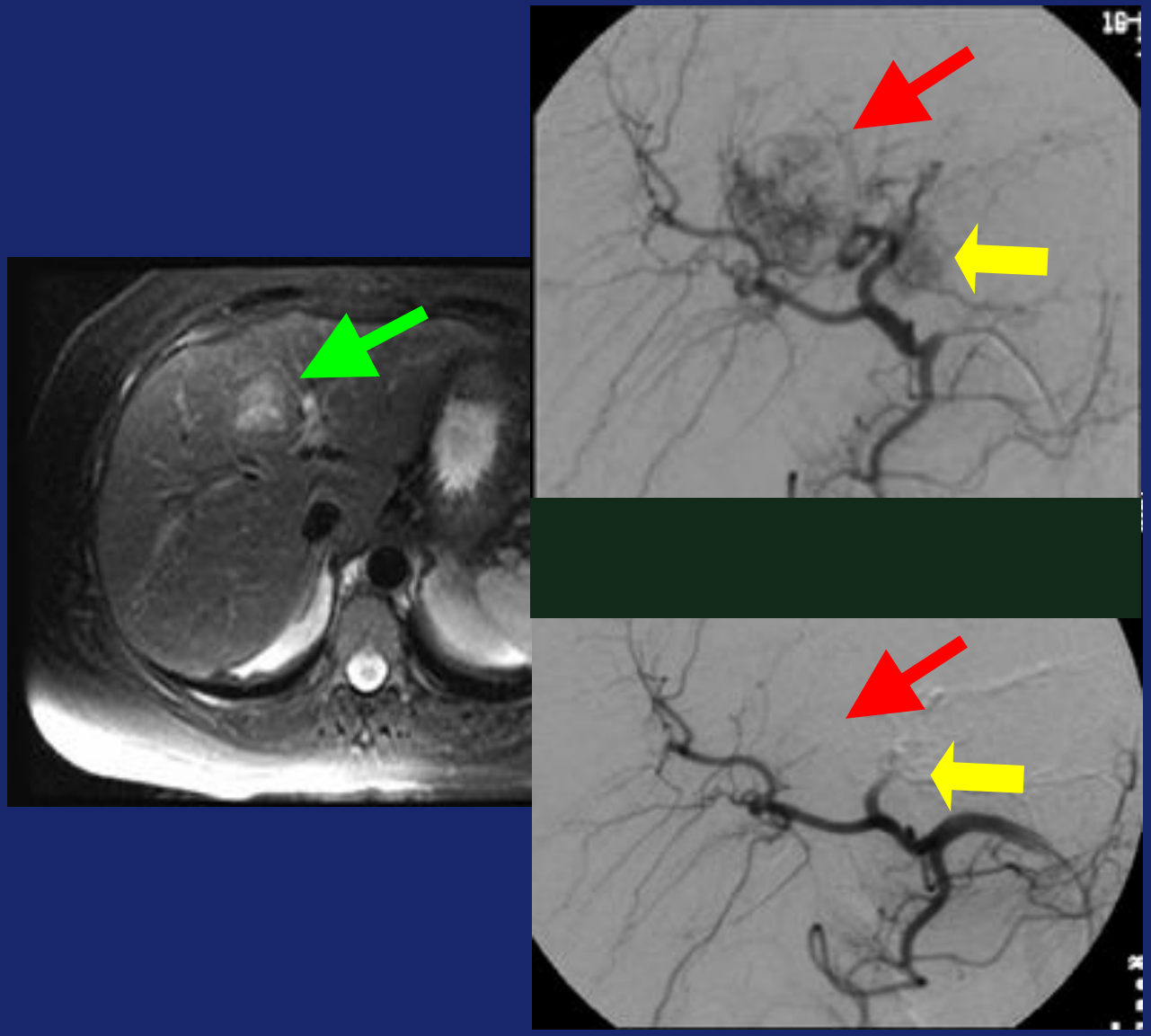
IDENTIFYING EARLY PROGRESSION-clonal evolution



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

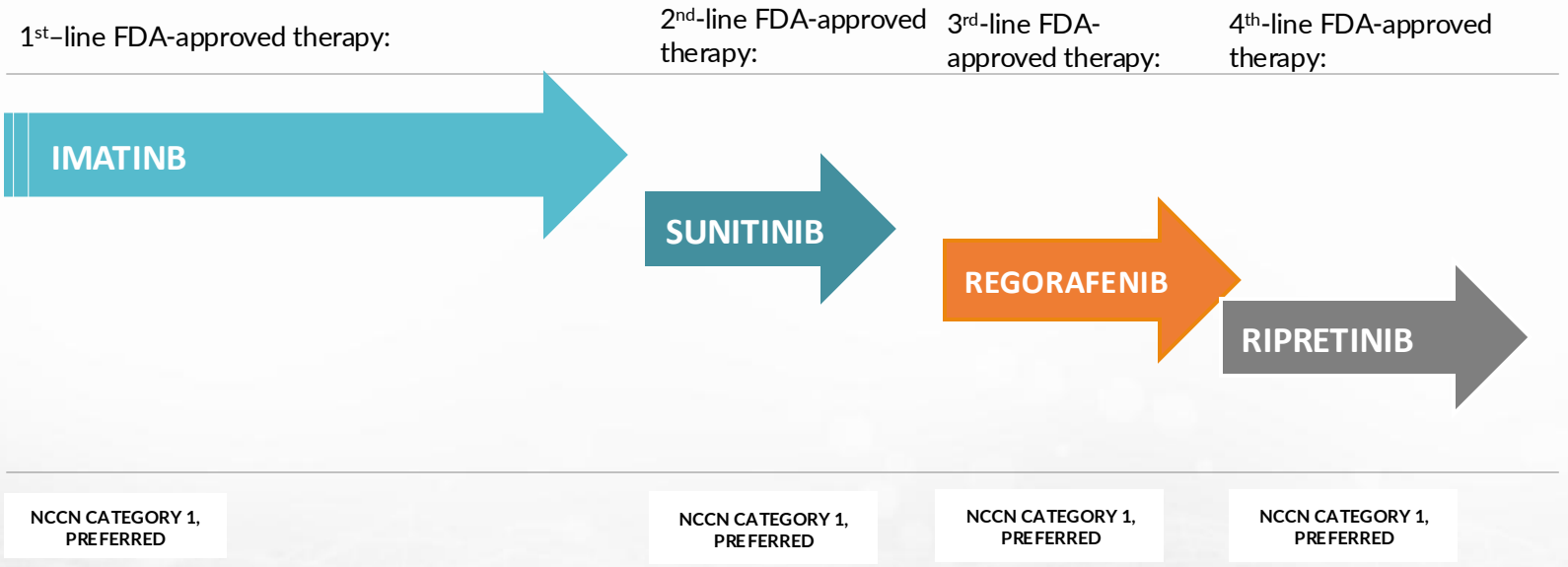


Pre-embolization

Post-embolization

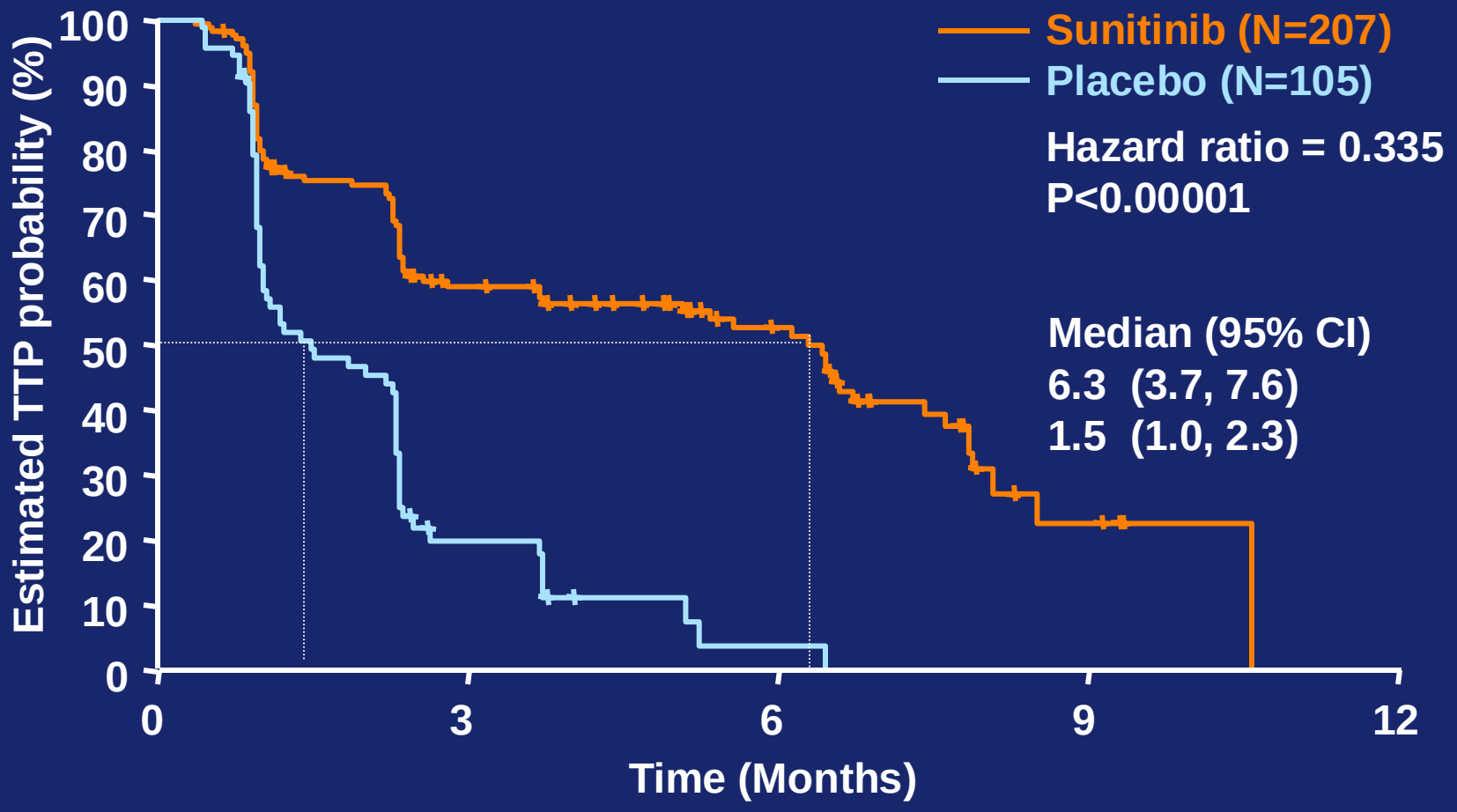
WHAT HAPPENS IF IMATINIB IS NO LONGER HELPING?

GIST TREATMENT PARADIGM- Post-Imatinib

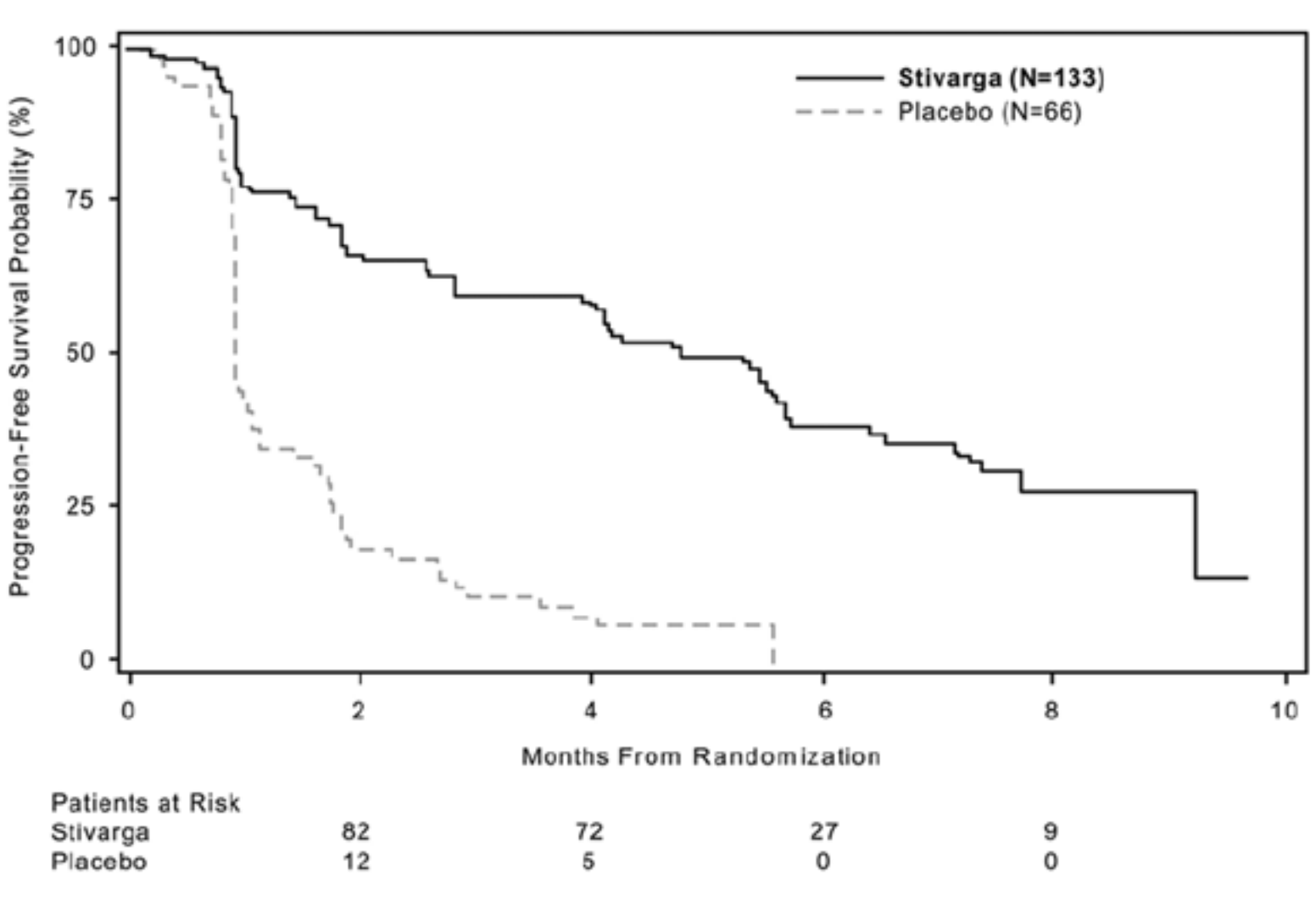


Avapritinib is approved for patients with unresectable or metastatic GIST harboring a **PDGFRA exon 18 mutation** (5%-6% of patients), irrespective of line of therapy.

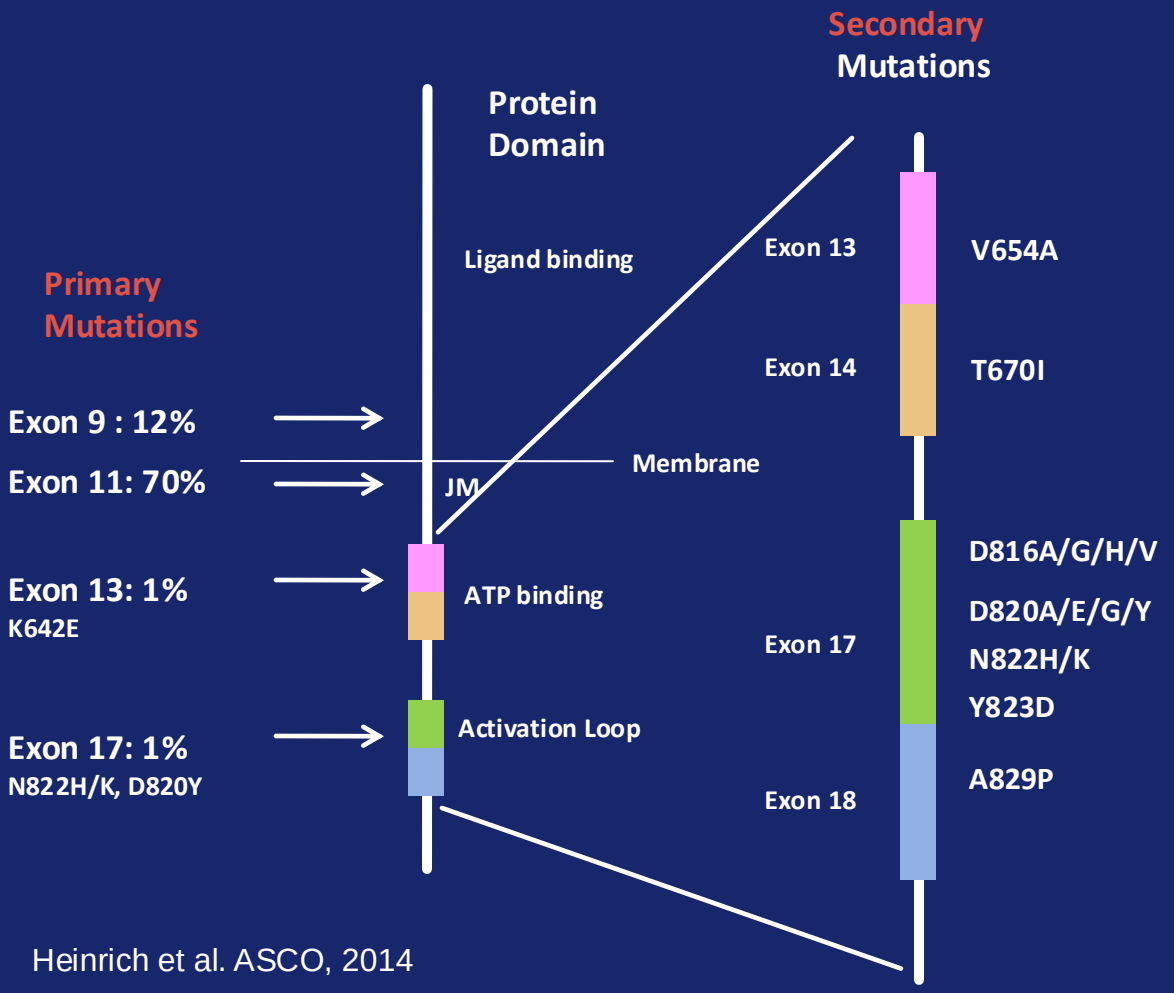
SUNITINIB VS PLACEBO
TIME TO TUMOR PROGRESSION



REGORAFENIB VS. PLACEBO

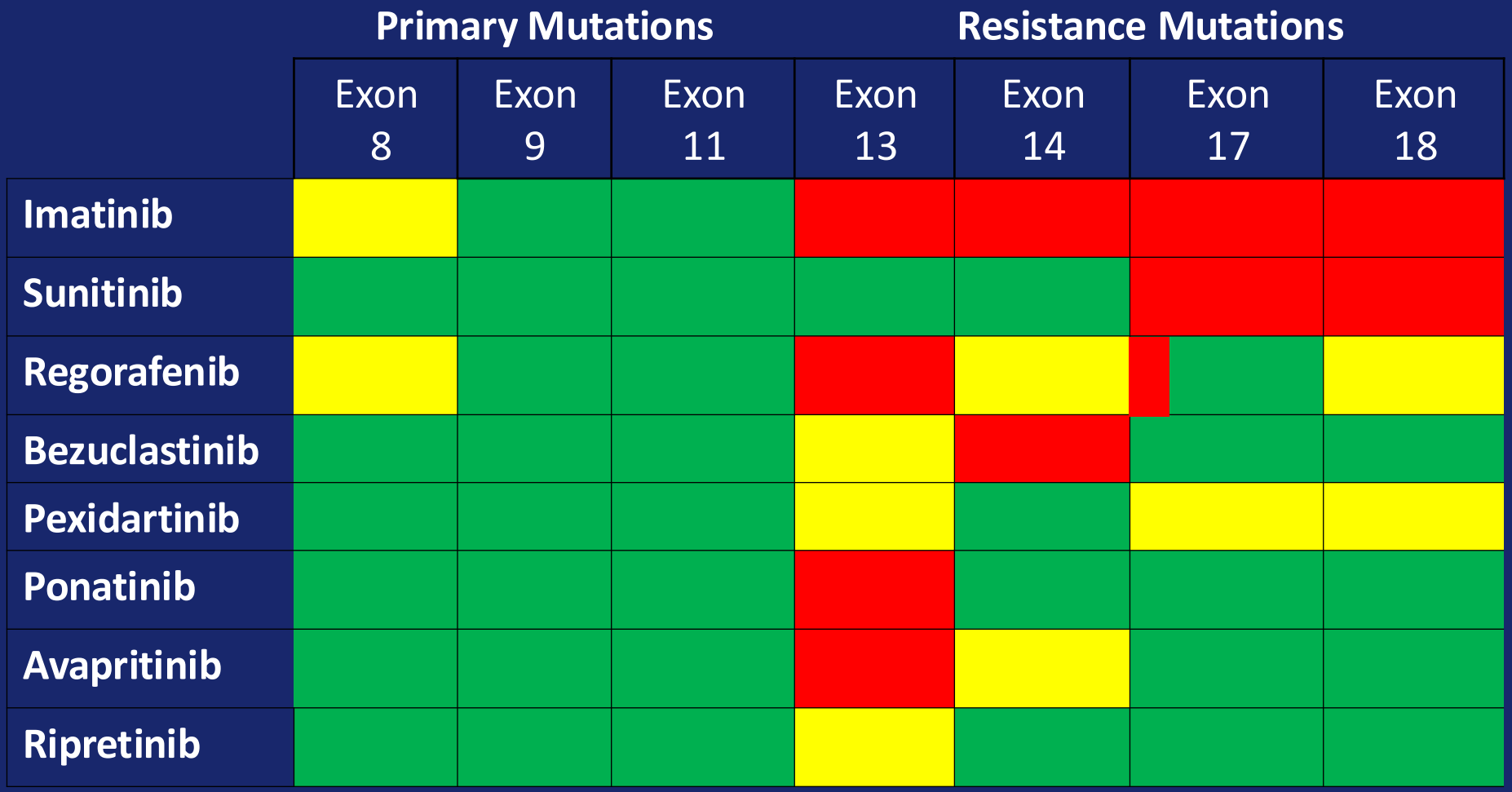


KIT SECONDARY MUTATION SITE AND DRUG SENSITIVITY



Heinrich et al. ASCO, 2014

DIFFERENTIAL SENSITIVITY TO TKI

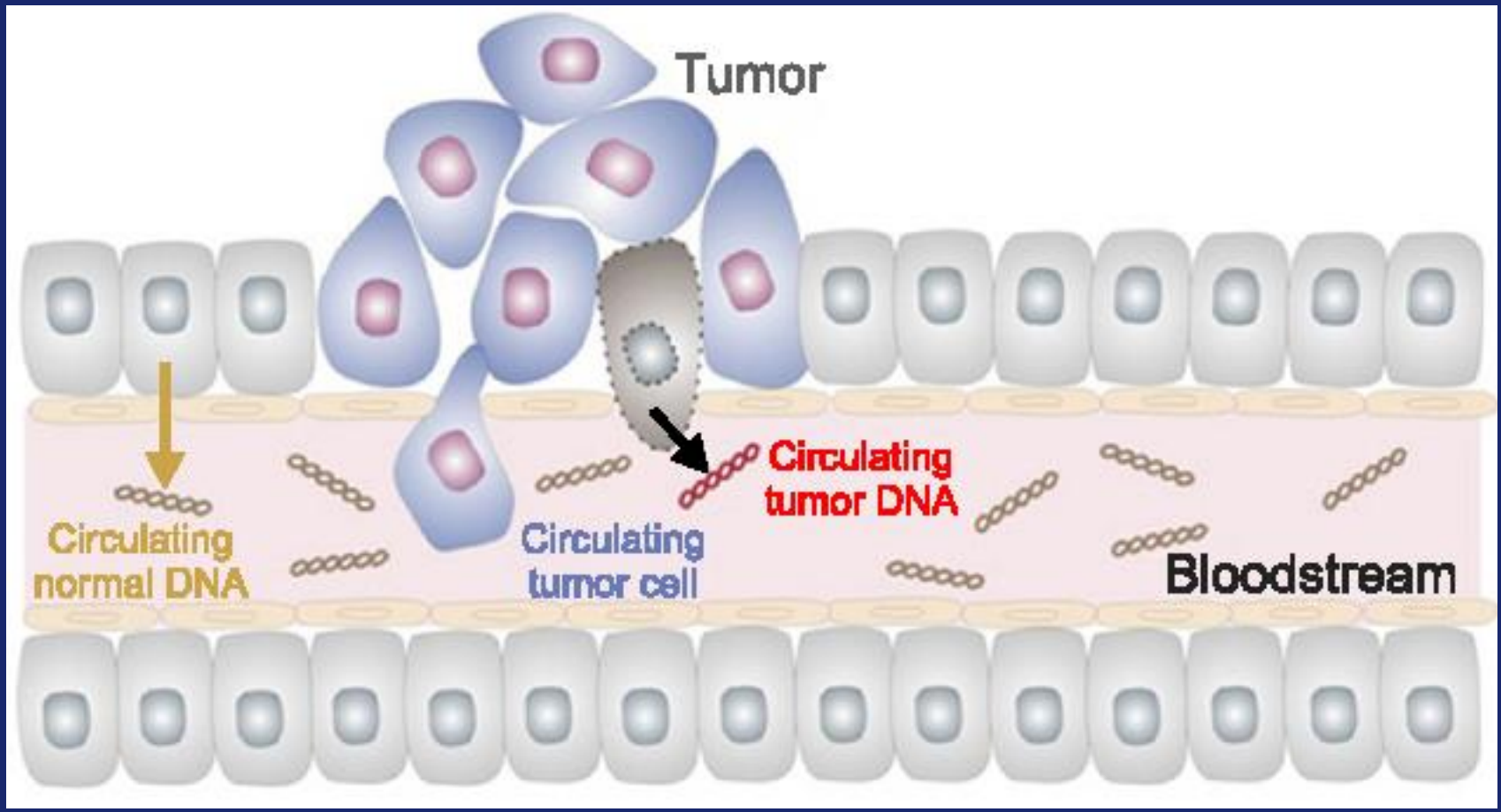


Trent, CTOS 2017; Serrano BJC 2018
Gramza et al, Clinical Cancer Research 15:7510, 2009
Heinrich et al, ASCO 2013 Poster/Abstract 10509

DETECTING SECONDARY MUTATIONS

NEW TUMOR BIOPSY

CIRCULATING TUMOR DNA: *MUTATION TESTING FROM BLOOD (LIQUID BIOPSY)*



Nurwidya et al, 2018

The fourth TKI approved for use in GIST:

4th-line: Ripretinib (Qinlock – Deciphera/Ono; 2020)

Ripretinib acts on KIT by a different mechanism – locking the protein in its inactive state ("switch-pocket" inhibitor).

The fifth TKI approved for use in GIST:

5th-line: Avapritinib (Ayvakit – Blueprint; 2020)

For PDGFRA exon 18 (D842V) GIST *only*.

CLINICAL TRIALS……

OFF-LABEL

FDA-APPROVED BUT NOT FOR GIST

Class	Agent
KIT Inhibitors (+/-VEGFR)	Sorafenib
	Dasatinib
	Nilotinib
	Pazopanib
	Ponatinib
	Axitinib
	Cediranib
	Cabozantinib
mTOR Inhibitors	Everolimus
	Temsirolimus

GIST "Top ten" list

1. GIST strikes randomly – getting GIST was not your fault.

2. Unlike the common GI tract cancers, GISTs are very treatable.

3. GISTs are rare! Find a GIST specialist.

4. Ask whether your GIST is 'localized' or has 'metastasized' (spread).

5. Ask for mutational testing of the tumor to be done.

6. For localized GIST: 'adjuvant' imatinib can reduce the risk of recurrence.

7. Four oral ('take-home') drugs are approved for GIST.

8. Side effects of GIST drugs can be managed successfully, in most cases.

9. Clinical Trials give access to promising drugs and can lead to new approvals

10. Join a support group: Gist Support International and/or Life Raft Group.

TEAM of EXPERTS

Thank you for your attention
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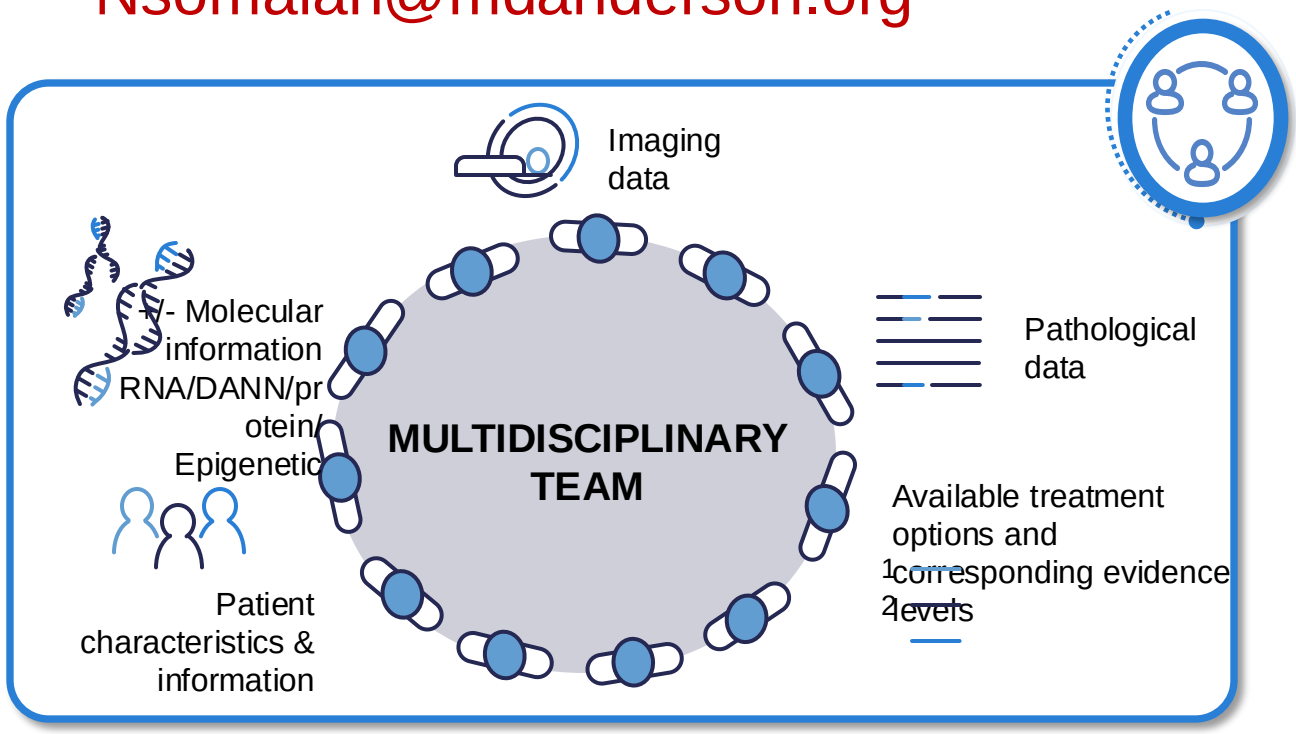

- Medical Oncology
- Surgical Oncology
- Pathology
- Radiology
- Interventional Radiology
- Advanced Practice Providers
- Research Team
- Nursing
- Social Work