Overview of GIST and its Medical Management (i.e. GIST 101)

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OVERVIEW

- What is GIST?
- How do we treat GIST?
- How do we use imatinib (Gleevec) in GIST?
- What are the options for imatinib-resistant GIST?
- How do we manage side effects of imatinib?

What is GIST?

- Gastrointestinal stromal tumor, the most common type of sarcoma
- A tumor of the interstitial cells of Cajal (ICC)
- Can occur at any point in the digestive organs, including stomach (most common), small intestine, large intestine, and rectum

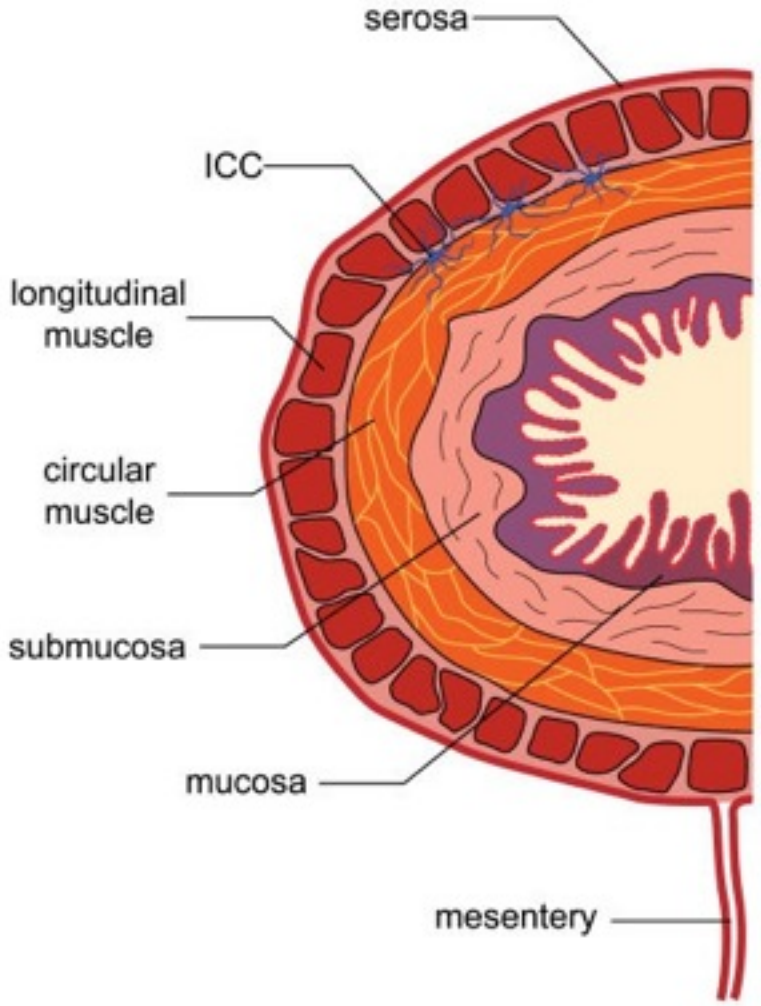
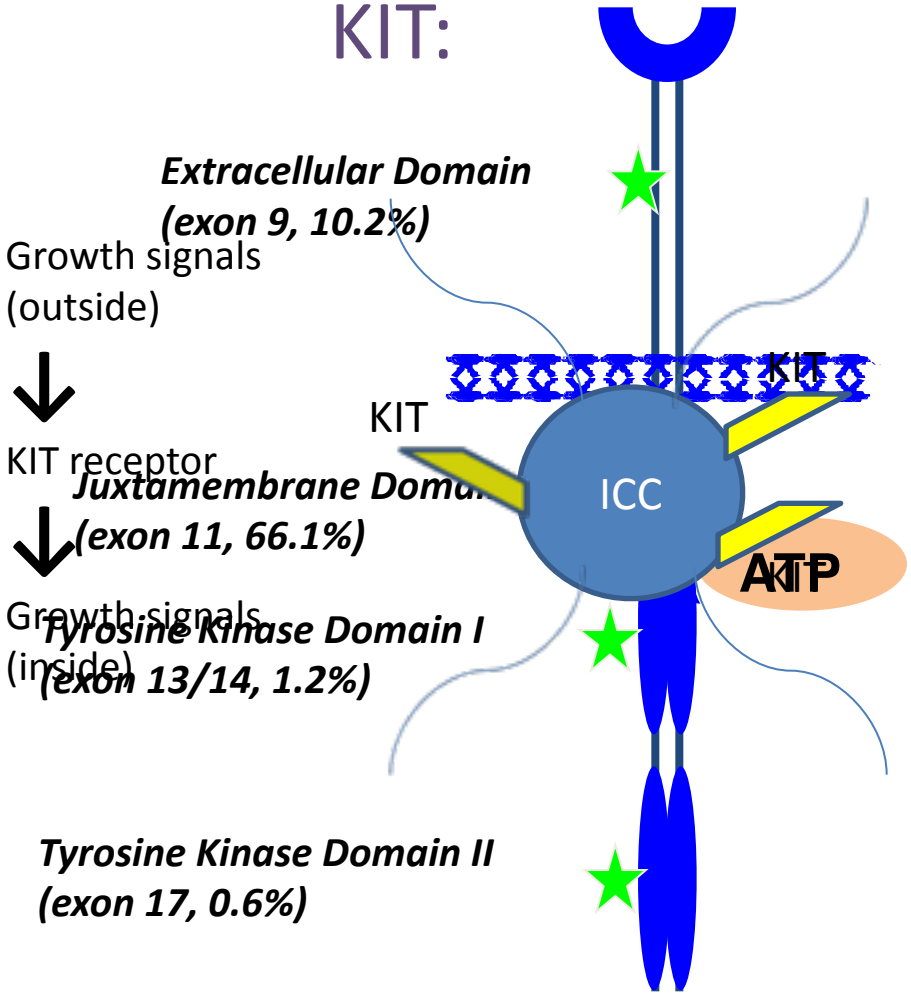


*Figure from Section VI, Gastrointestinal Physiology (Ginsburg, J.M. and Costoff, A. in **Essentials of Human Physiology** (edited by Nosek, T.M.),*

Why do GISTs grow?

- 80% of GISTs have a mistake (mutation) in the genetic code that results in a hyperactive KIT protein (light-switch ON)
- We recommend that patients have their tumor mapped (called sequencing) to determine which exon has the mutation
- Up to 20% of GISTs may have a mistake in a NON-KIT gene – important for treatment!!! (more later)



★= common mutation site

Who gets GIST?

- Overall, only about 5000 new GISTs per year
- Most common in 40-60 year old patients, similar rates in men and women
- Gastrointestinal symptoms of GIST include pain, nausea, lack of appetite, bleeding.
- Incidental findings in endoscopy
- Very rarely, a special type of GIST can be passed down in families or occur in children
- No known risk factors

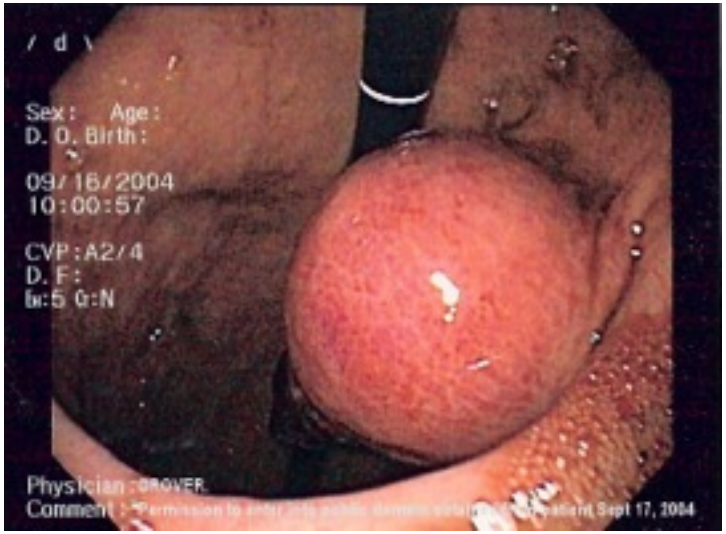


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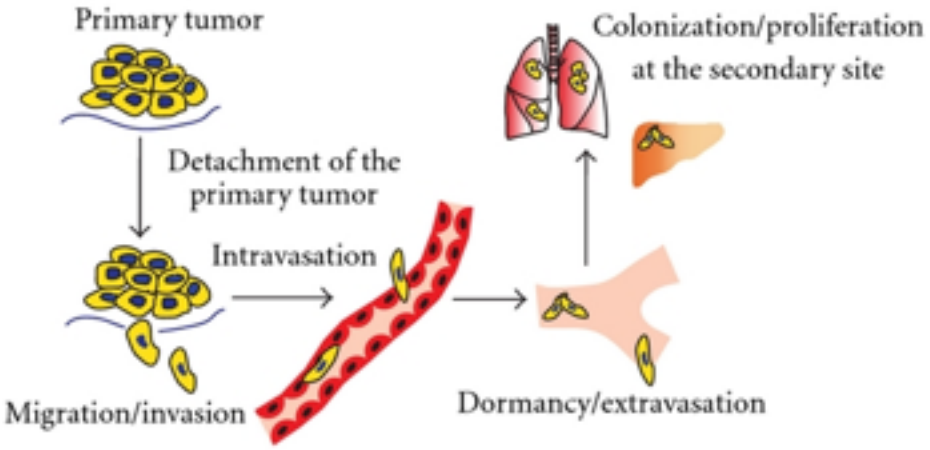
Photo from Wikipedia

How do we treat GIST?

- LOCAL vs. SYSTEMIC treatment
- Surgery is the goal! (Complete removal of the GIST)
- GISTs are relatively resistant to radiation



- Metastases – spread of the tumor cells to the liver, or inside the abdomen (peritoneal disease), less common to lung, bone, etc.
- Most recurrences happen within 2 years of the surgery

Risk determination in GIST

- **How likely is it that the GIST will come back after removal by surgery?**
- GISTs are classified into LOW risk, INTERMEDIATE risk, and HIGH risk based on:
  - Size (less than 5 cm, 5-10 cm, or greater than 10 cm)
  - Location (gastric vs other sites)
  - Mitoses (a measure of the speed of growth in the cells)

Estimated chance of recurrence/metastasis:

	GASTRIC (stomach)		OTHER (intestine, etc)	
	< 5 mitoses	> 5 mitoses	< 5 mitoses	> 5 mitoses
< 5 cm	< 5%	12-15%	< 5%	50-70%
5-10 cm	< 5%	49-86%	25%	70-90%
> 10 cm	12-15%	49-86%	30-60%	70-90%

Adapted from NCCN guidelines, from Miettinen M, Lasota J. Sem Diagn Pathol 2006.

Uses of systemic treatment in GIST

- To prevent the recurrence or metastasis after surgery in high-risk GIST patients
- To shrink a GIST tumor that cannot be removed completely by surgery at the time it is found. (it is in a bad spot…)
- To control GIST that has already spread to other organs or inside of the abdominal cavity (peritoneal disease)

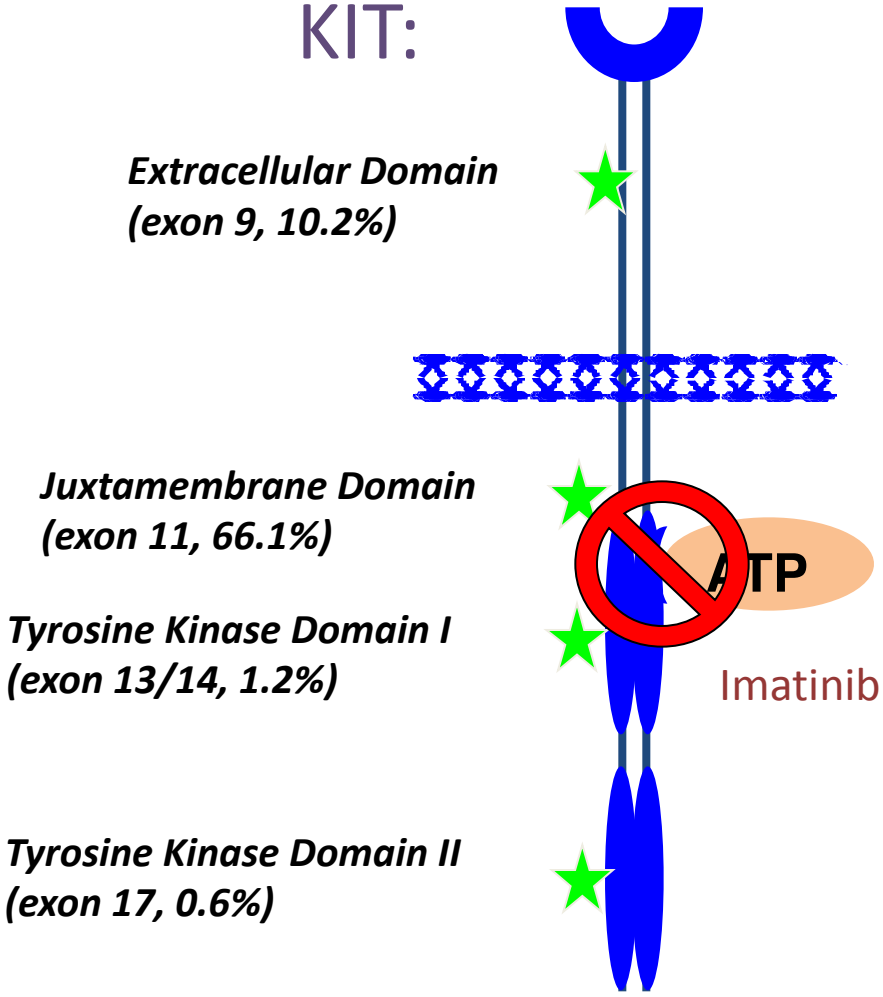
Systemic treatment in GIST

Old-school chemotherapy in advanced GIST

Regimen	# Patients	% Response
DOX + DTIC	43	7%
DOX + DTIC +/– IF	60	15%
IF + VP-16	10	0%
Paclitaxel	15	7%
Gemcitabine	17	0%
Liposomal DOX	15	0%
DOX	12	0%
DOX or docetaxel	9	0%
High-dose IF	26	0%
EPI + IF	13	0%
Various	40	10%
DTIC/MMC/DOX/ CDDP/GM–CSF	21	5%
Temozolamide	19	0%
TOTAL	**280**	**6.8%**

The role of imatinib in GIST

- Imatinib is an oral chemotherapy drug
- Binds to the ATP-binding site and blocks the downstream signaling to the cell from hyperactive KIT
- Works best in exon 11 mutated GIST, other mutation sites tend to be more resistant



★= common mutation site

GIST Subtypes

- Kit mutation ~80% of GISTs
  - Exon 11 (~70%): codon 557-558 (risky)
  - Exon 9 (~10%)
  - Exon 13/14 (~1%) resistant
  - Exon 17 (<1%) resistant
- PDGFR mutation ~10% of GISTs
  - Exon 12
  - Exon 18 D842V (resistant)
- SDH-B deficient
- Raf V600E
- NF-1
- Ras
- PI3K
- IGF-1R overexpressed
- TRK fusion
- "wild-type"

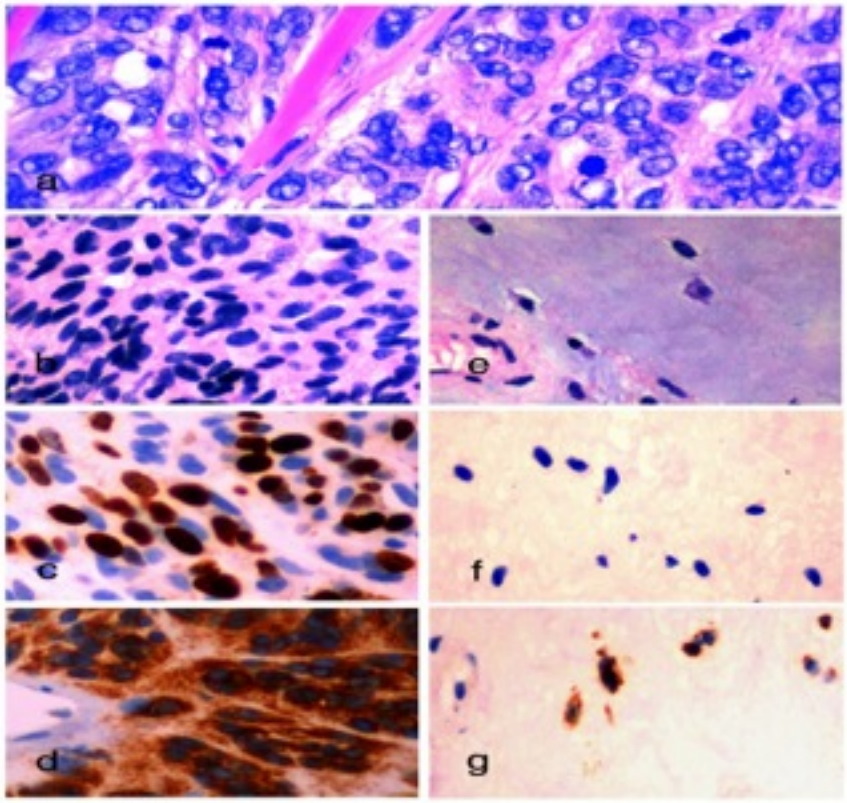
The First GIST Patient: Histology

H&E (at diagnosis)

H&E

Ki 67

CD117



Pretreatment

One month of therapy

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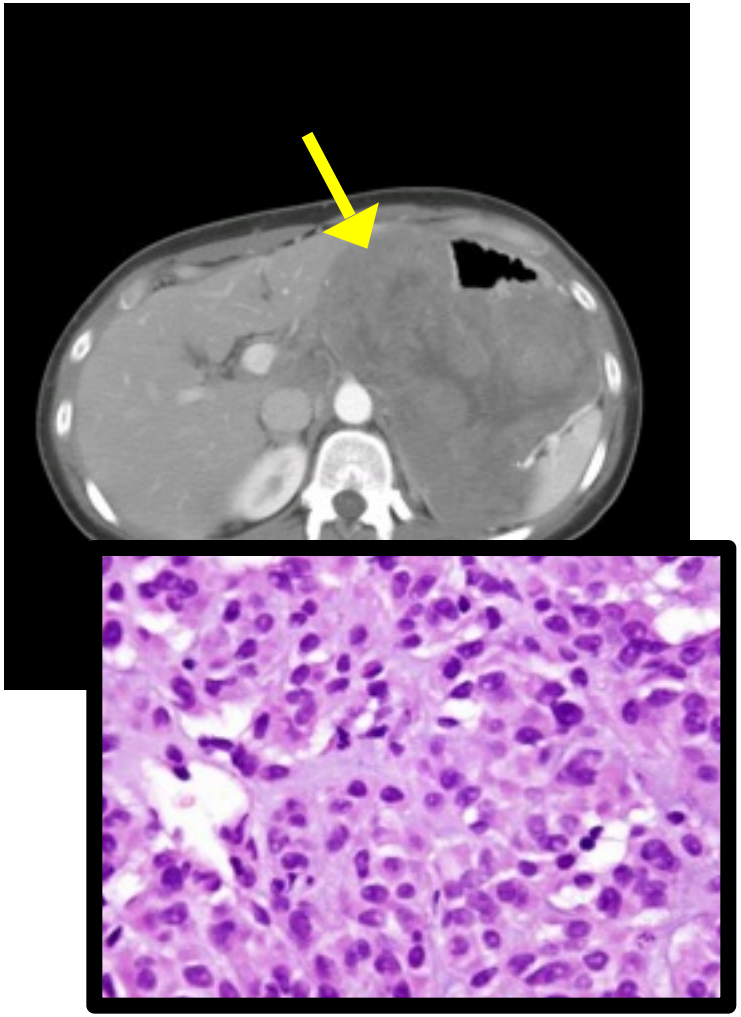
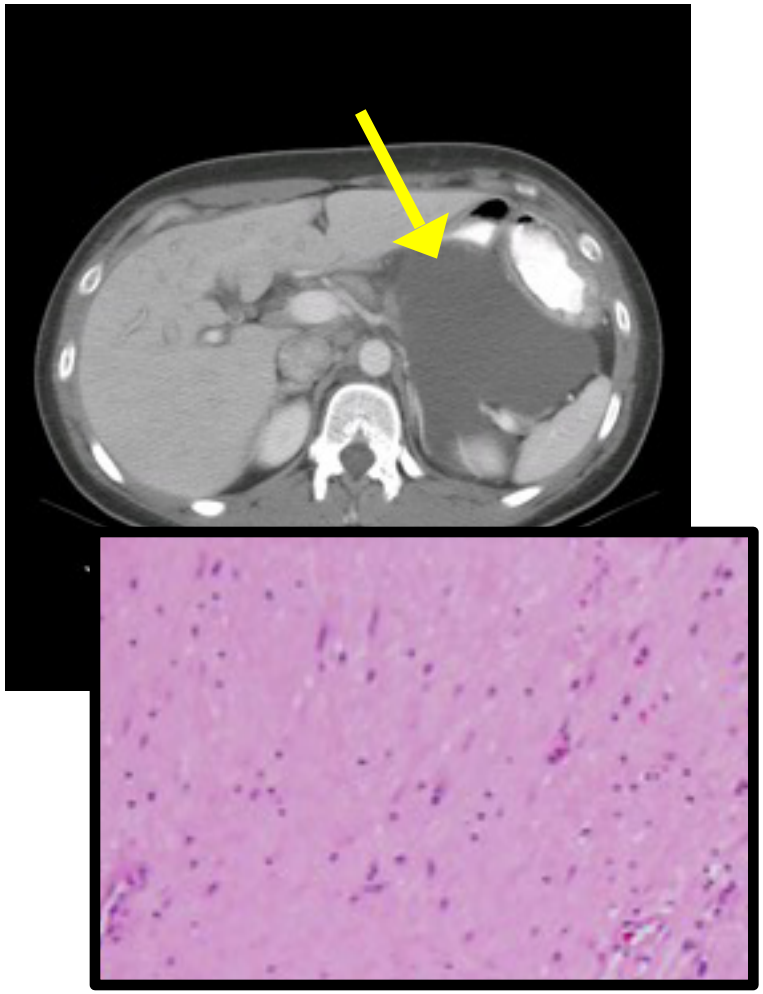
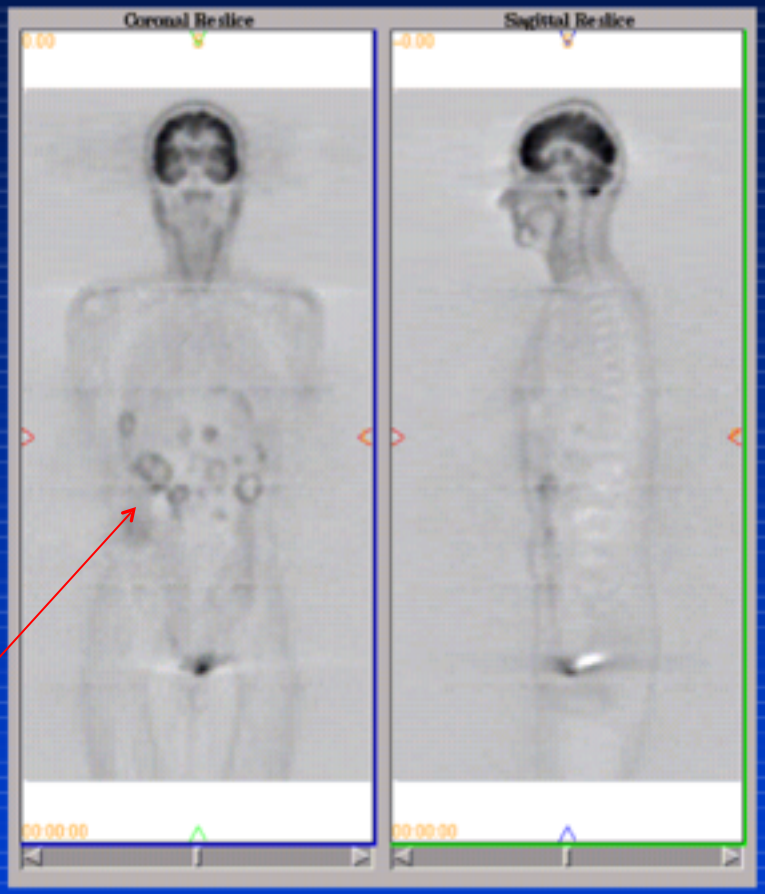
Joensuu H et al. N Engl J Med. 2001;344:1052-1056.

CT response in GIST

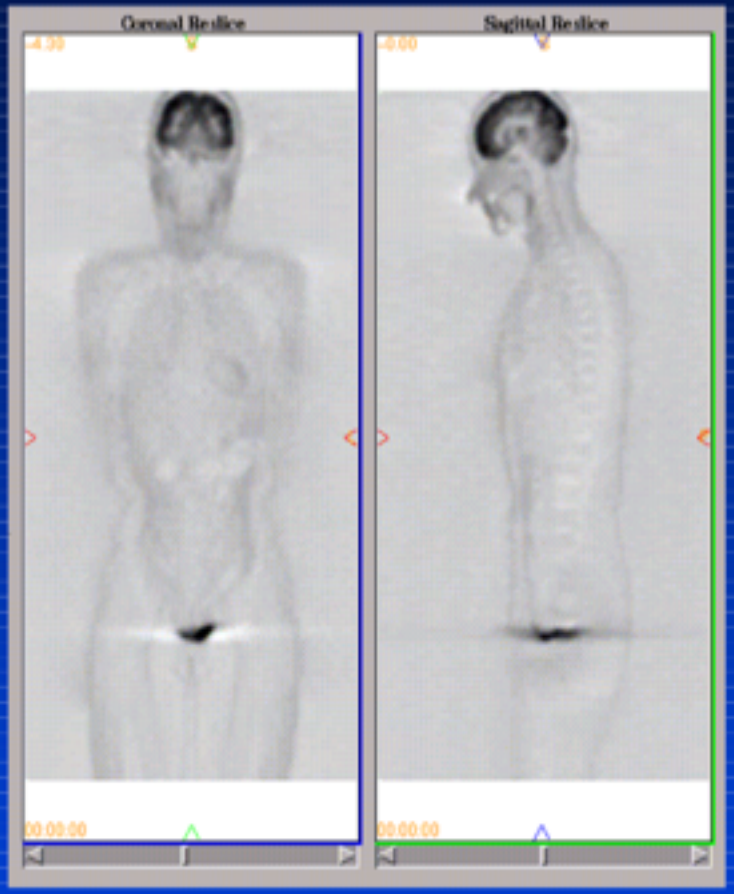




Marked Biologic Response Revealed by PET Scan



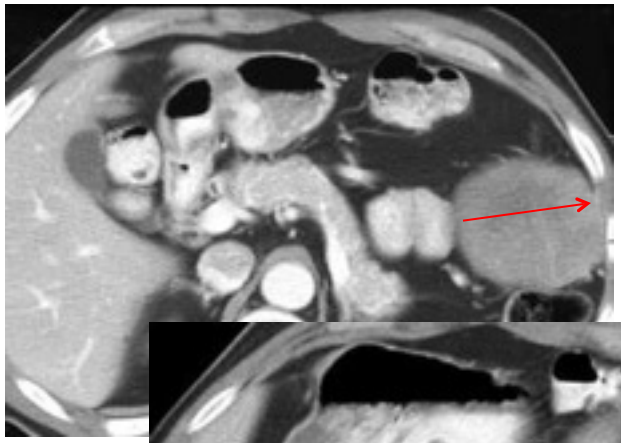
Multiple liver and upper abdominal ^{18}FDG-accumulating metastases



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.

“Pseudoprogression” in GIST



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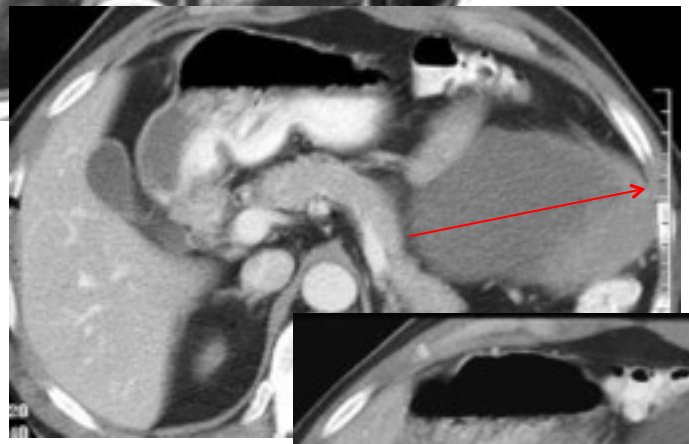

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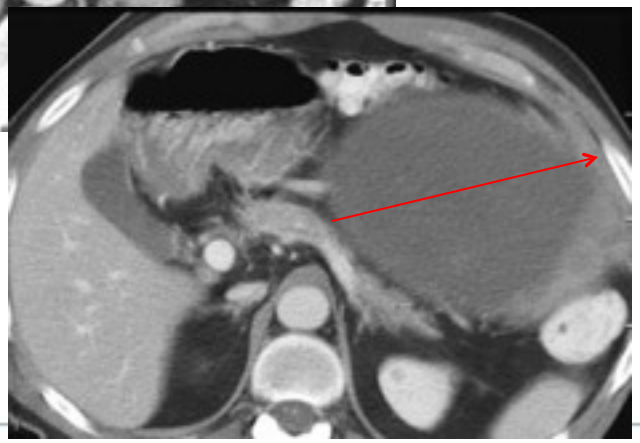

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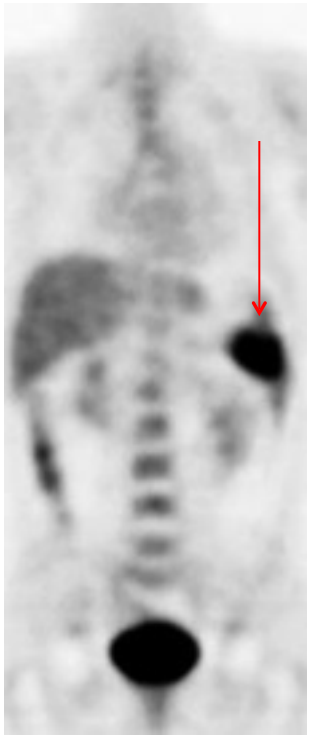

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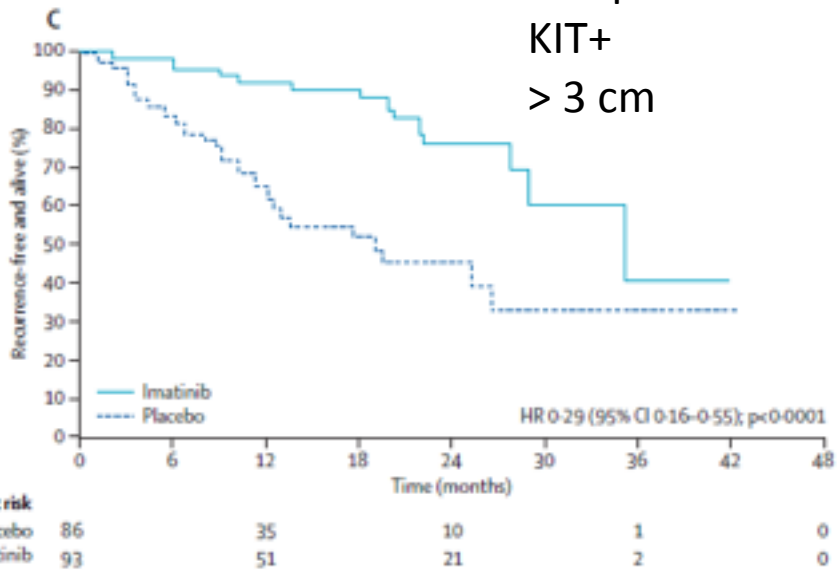
How do we treat GIST?

- Adjuvant therapy with imatinib
  - Use after surgery to prevent the GIST from coming back when there is NO visible evidence of remaining tumor.
  - Routinely recommended for high risk patients, and many intermediate risk patients
  - Optimal length of treatment still under investigation…

Adjuvant therapy

- 1-year RFS 98% - Imatinib 400 mg
- 1-year RFS 80% - Placebo
- Recurrence in imatinib arm increases at 18 months (6 months following discontinuation of therapy)

713 patients
KIT+
> 3 cm



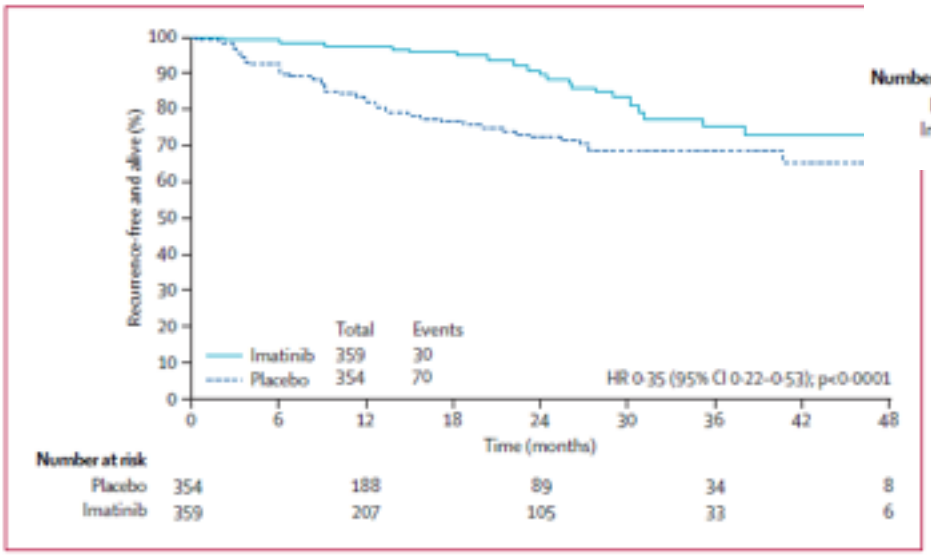


Figure 2: Recurrence-free survival

- RFS was significantly improved in Imatinib arm in each tumor size category but greatest for tumors > 10 cm

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(DeMatteo et al, 2009)

How long should we continue imatinib?

- Prospective, open-label, phase III trial
- 400 patients with operable primary GIST
  - >5cm, >5 mitoses/50 HPF
- Based on this study, standard duration is three years, but ongoing trial is investigating five year treatment (PERSIST5).
- At 3 year mark, only 4 / 91 patients have recurred (1 with resistant mutation, 3 after discontinuing imatinib.)
- Maybe longer…?

	36 months	12 months	
Imatinib (400mg/day)	N = 200	N = 200	
5-year RFS	Imatinib 66%	Imatinib 48%	P < 0.0001
5-year OS	Imatinib 92%	Imatinib 82%	P = 0.019

SSG XVIII, Joensuu H et al. ASCO 2011, ASCO 2015 abstract 10537, Raut et al.

How do we treat GIST?

Neo-adjuvant therapy with imatinib

- Shrink/liquefy GIST tumors so complete resection with surgery is possible
- Consider for
  - Unresectable/borderline resectable tumors
  - Tumors requiring extensive resection of involved organs
  - Potentially resectable metastatic GIST
- Controversial – multidisciplinary evaluation required

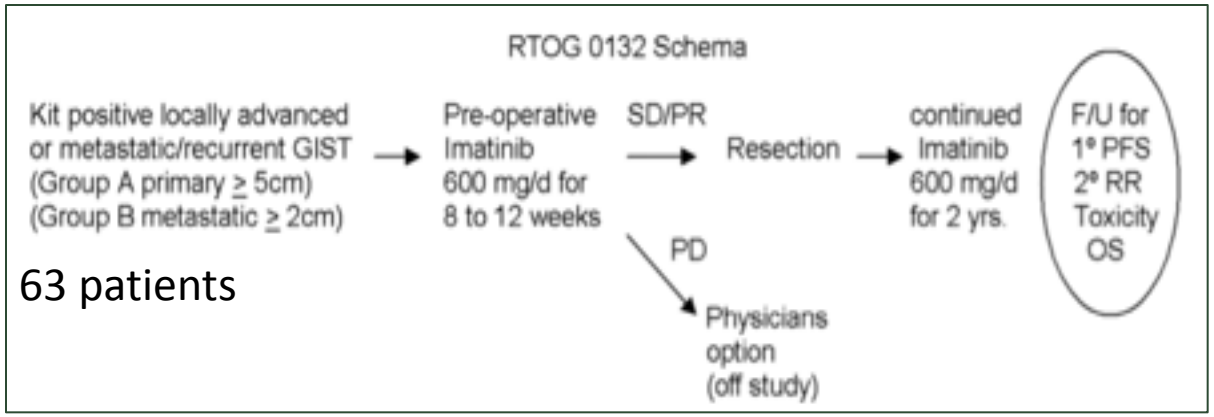
•Important steps –

- sequencing to determine mutation - Is it likely to respond to imatinib?
- Get accurate imaging at baseline, including a PET, as PET may show response to treatment even if size doesn't change.

RTOG = Radiation Therapy Oncology Group ; ACRIN = American College of Radiology Imaging Network
Van den Abbeele et al., *J Nucl Med 2012; 53:1–8.*; Eisenberg B et al. J of Surgical Oncology 2008.

Neoadjuvant imatinib

RTOG 0132-ACRIN 6665



63 patients

	Group A, localized (n=30)	Group B, metastatic (n=22)
Response	7% PR, 83% SD, 10% unk	4.5% PR, 91% SD, PD 4.5%
Estimated 2-year PFS	82.7%	77.3%
Estimated 5-year PFS	57%	30%
Estimated 2-year OS	93.3%	90.9%
Estimated 5-year OS	77%	68%
Type of Resection	**R0 77%** R1 15% R2 8%	**R0 58%** R1 5% R2 32% Unspecified 5%

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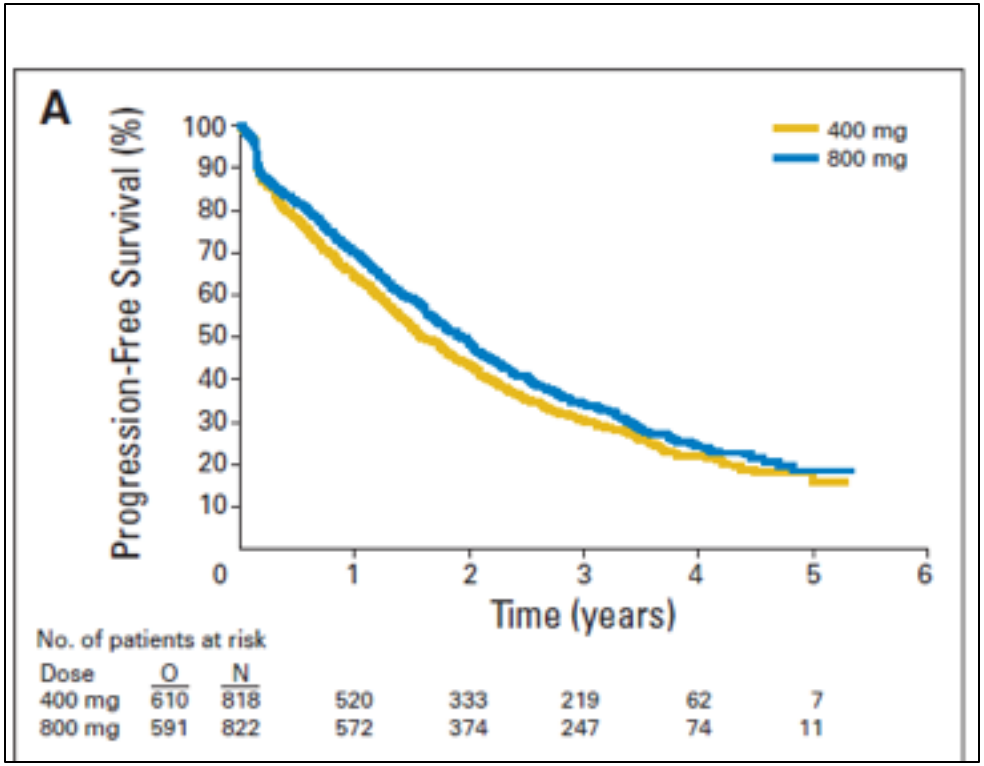
How do we treat GIST?

Treatment of metastatic disease with imatinib

- Goal is to neutralize the existing tumor and prolong the time to progression
- Progression on a treatment occurs when some of the cells in the tumor develop resistance to the drug, and begin growing (can be regrowth of a previous tumor, or the development of a new tumor)
- Most commonly, the resistant cells that remain have a different or additional mutation that makes them resistant to the imatinib
- Sometimes this can be overcome by increasing the imatinib dose

Imatinib for metastatic/unresectable GIST

- Combined data from two large trials (1640 patients) with metastatic or advanced GIST
- Treated with imatinib at either 400 mg or 800 mg
- Median time to progression 1.58 yrs on the 400 mg arm, 1.95 yrs on the 800 mg arm, 30-35% free from progression at 3 years
- Significant benefit to 800 mg only in exon 9 patients

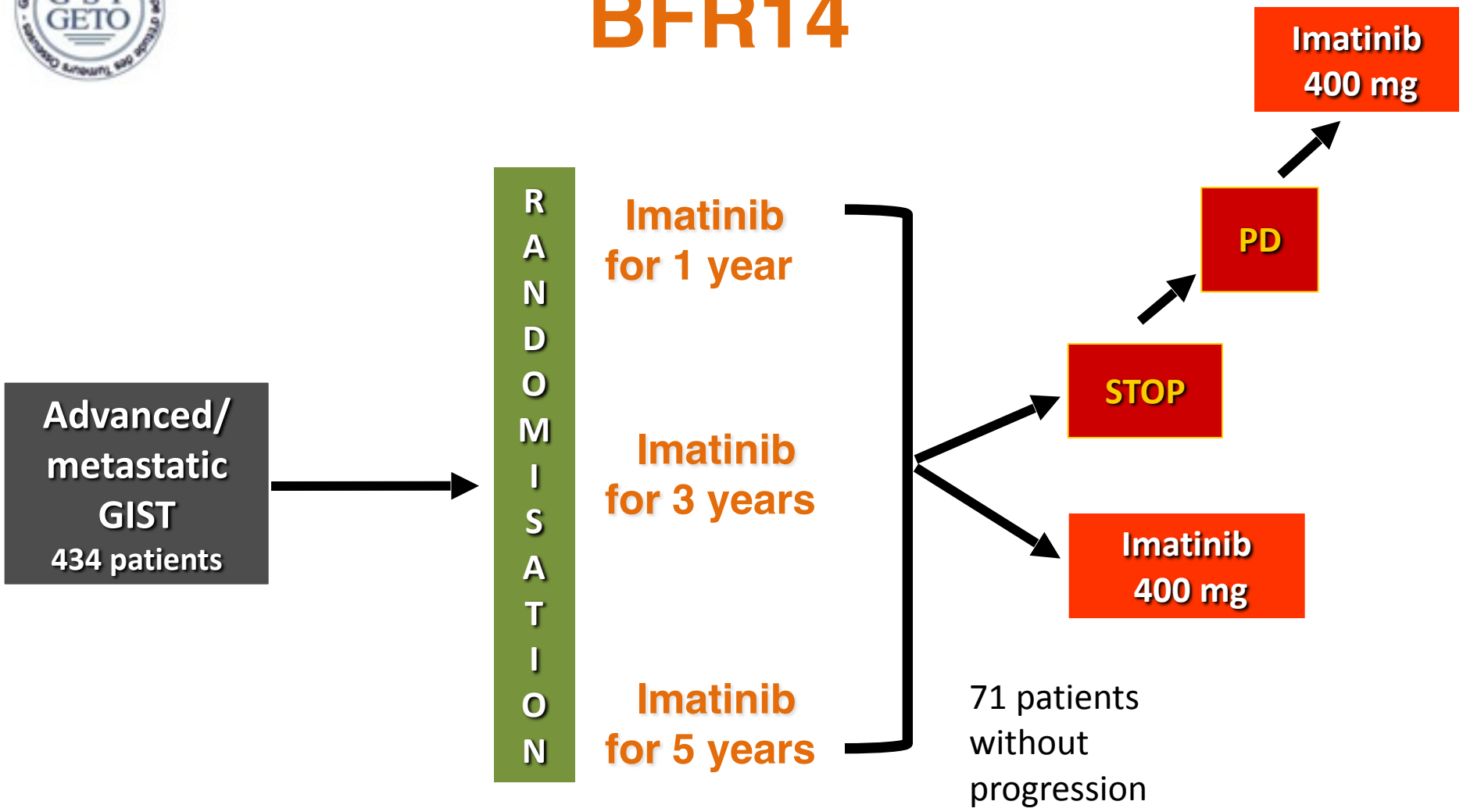


Gastrointestinal Stromal Tumor Meta-Analysis Group (MetaGIST). *J Clin Oncol*. 2010.

Length of treatment in metastatic GIST

- Ok, my GIST now has shrunk or stabilized – how long do I need to stay on imatinib?
- Can I take a break from imatinib or will my tumors start to grow again?
- Does staying on imatinib longer help prevent the GIST from developing resistance?

BFR14



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BFR14

- Patients who progressed were restarted on imatinib, and 94% of patients had tumors respond again to imatinib.
- BUT – in patients who got CR initially, only 41.7% achieved it again with rechallenge, and in patients with PR, only 56% were able to achieve it again. Development of resistance?
- Our practice – DON'T STOP!

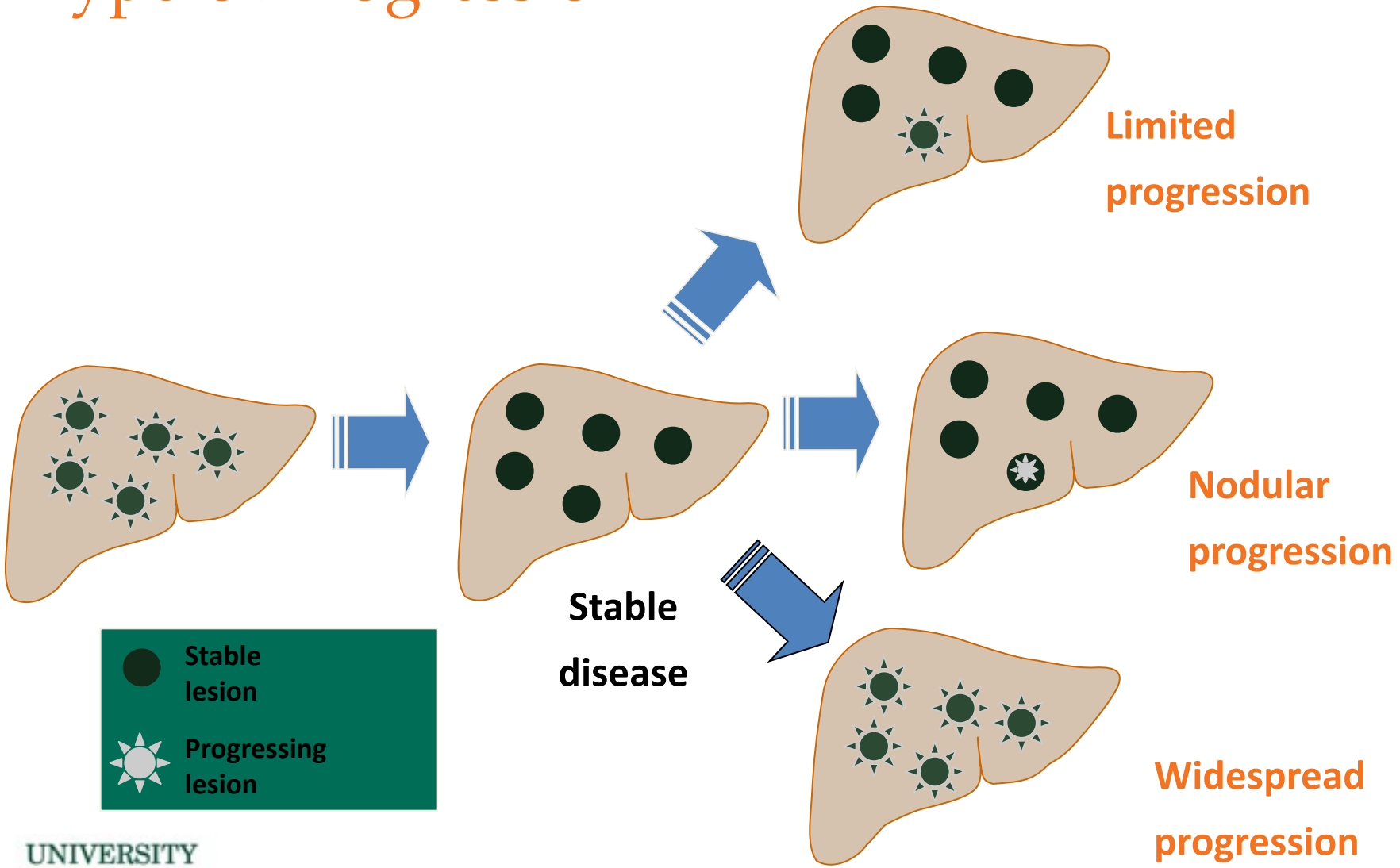
	Continued imatinib	Stopped imatinib
Imatinib 1 year	8/26 PD PFS 18 mos	26/32 PD PFS 6.1 mos
Imatinib 3 year	7/25 PD 1 yr PFS 92%	21/25 PD 1 yr PFS 32%
Imatinib 5 year	0/10 PD (at 1 year)	5/11 PD (at 1 year)

Blay JY et al, JCO 2007
Le Cesne A, et al, Lancet Oncol 2010
Ray-Coquard IL, ASCO 2010, abst 10032
Patrikidou et al, Annals Oncol 2012
Blay et al, Annals Oncol 2011

Putting it all together… so far?

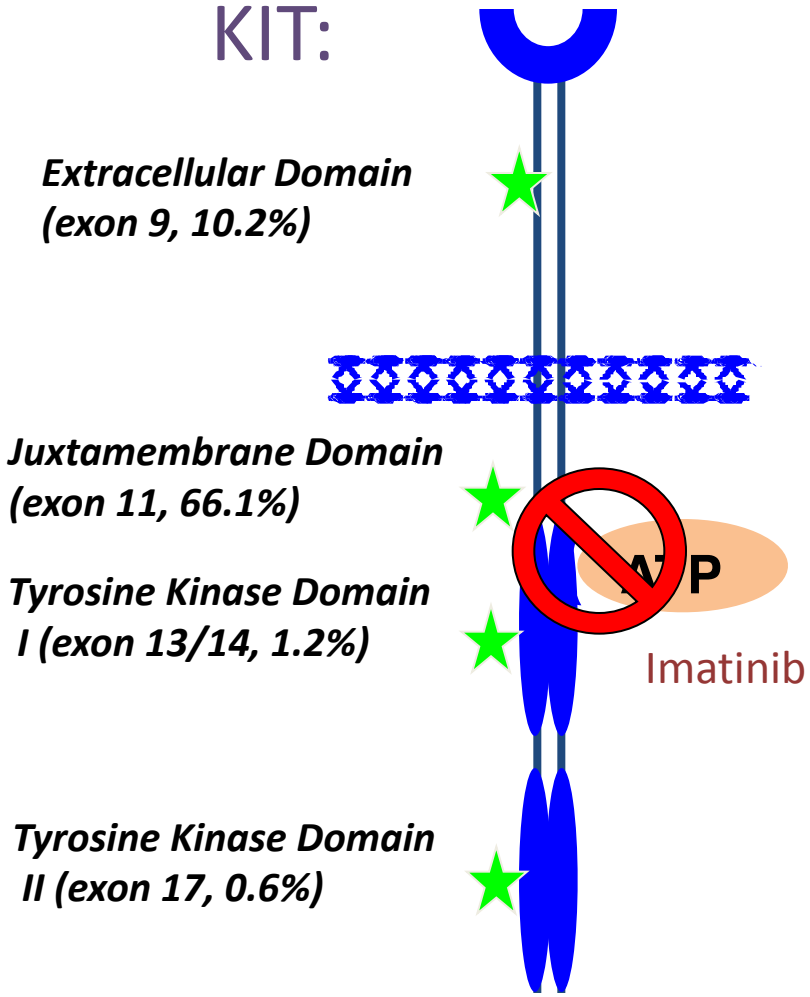
- Intermediate and high risk GISTs are likely to leak cells out into the abdomen which can lead to recurrence and metastasis, even if the initial tumor is completely removed
- The use of imatinib can result in rapid, dramatic tumor shrinkage, and is often underappreciated with traditional CT scans.
- If possible, surgical removal of tumors appears to improve the outcome, even if the GIST has already spread. Multidisciplinary evaluation with sarcoma surgeons is critical.
- Imatinib can control the growth of resistant cells for years, but when stopped, these cells often begin growing again.
- Unfortunately, most GIST tumors ultimately will progress despite imatinib therapy and we require new drugs that are effective against imatinib-resistant cells.
- Until we have new drugs that can KILL all of the GIST cells up front, the best defense is to use imatinib as a maintenance medication as long as possible for high-risk or metastatic tumors

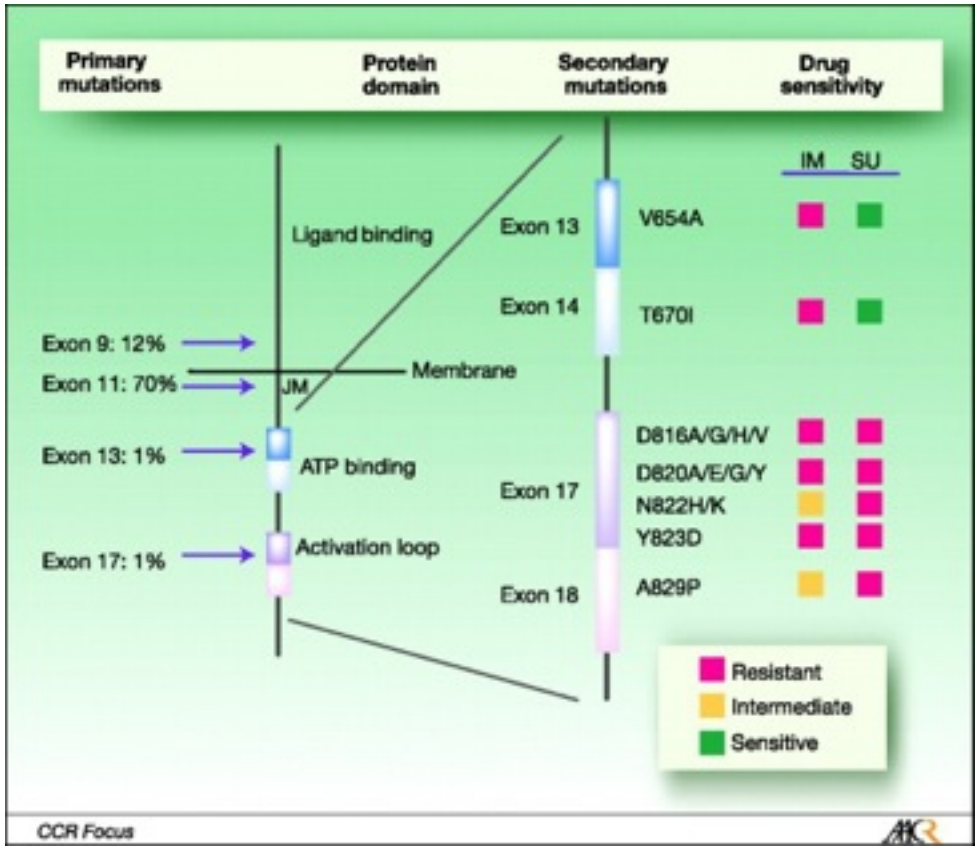
Type of Progression



Secondary mutations

KIT:





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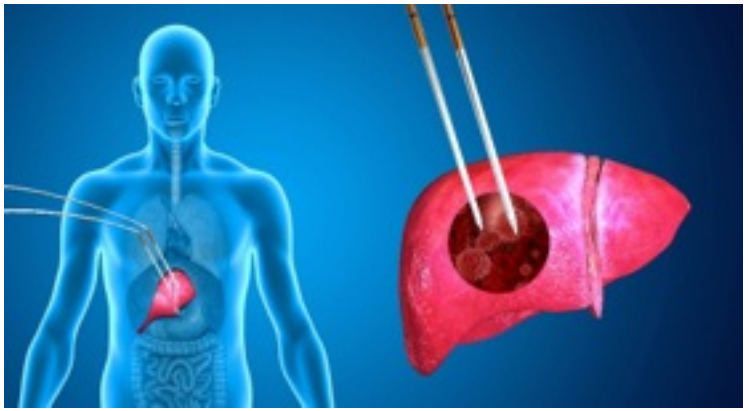
Gramza et al. Clin Cancer Res 2009;15:7510-7518

Options if imatinib-resistant

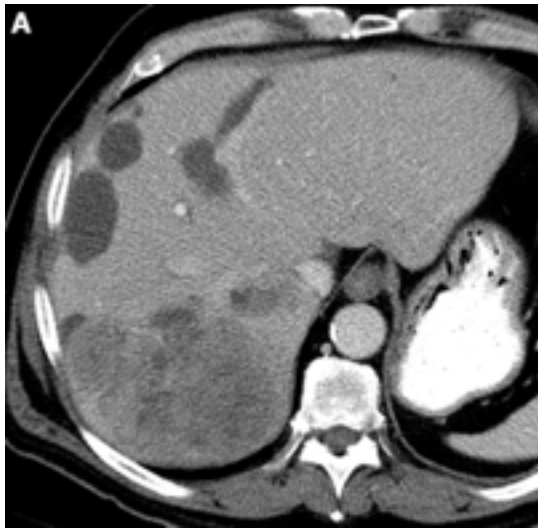
- Limited or Nodular Progression
  - Ablations (chemo, freeze, burn, electrocute…)
  - Surgical Resection
  - Radiation (including stereotactic - Cyberknife)



- Widespread progression
  - Consider sequencing or re-biopsy
  - Increase Imatinib to 800 mg daily
  - Sunitinib, Regorafenib
  - Clinical trial
  - Other tyrosine kinase inhibitors

Stable

Progressing lesion



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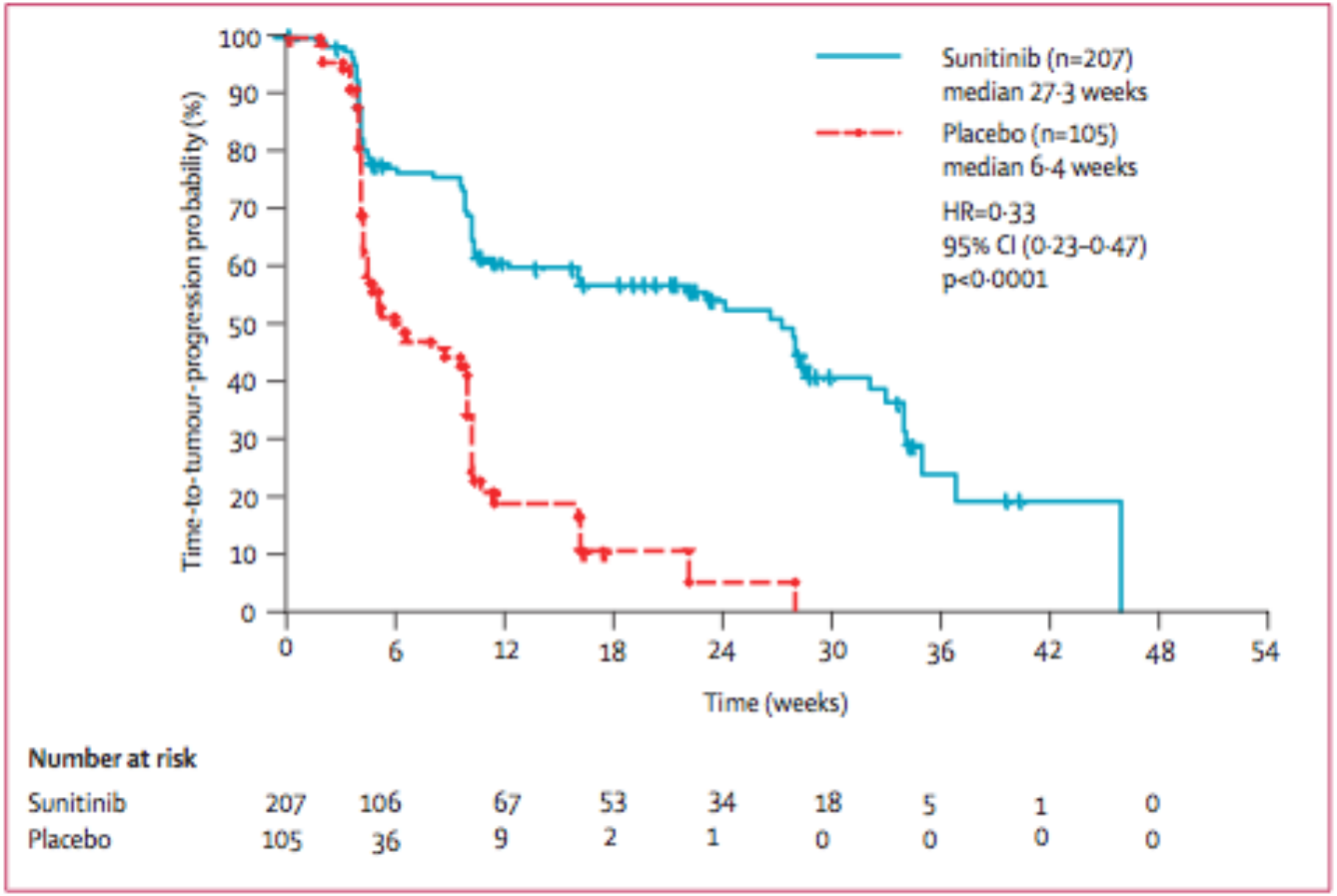
Kobayashi K, et al. Am J Clin Oncol. 2009;32:574-581.

Phase III Trial: US Intergroup S0033

TIME TO TUMOR PROGRESSION



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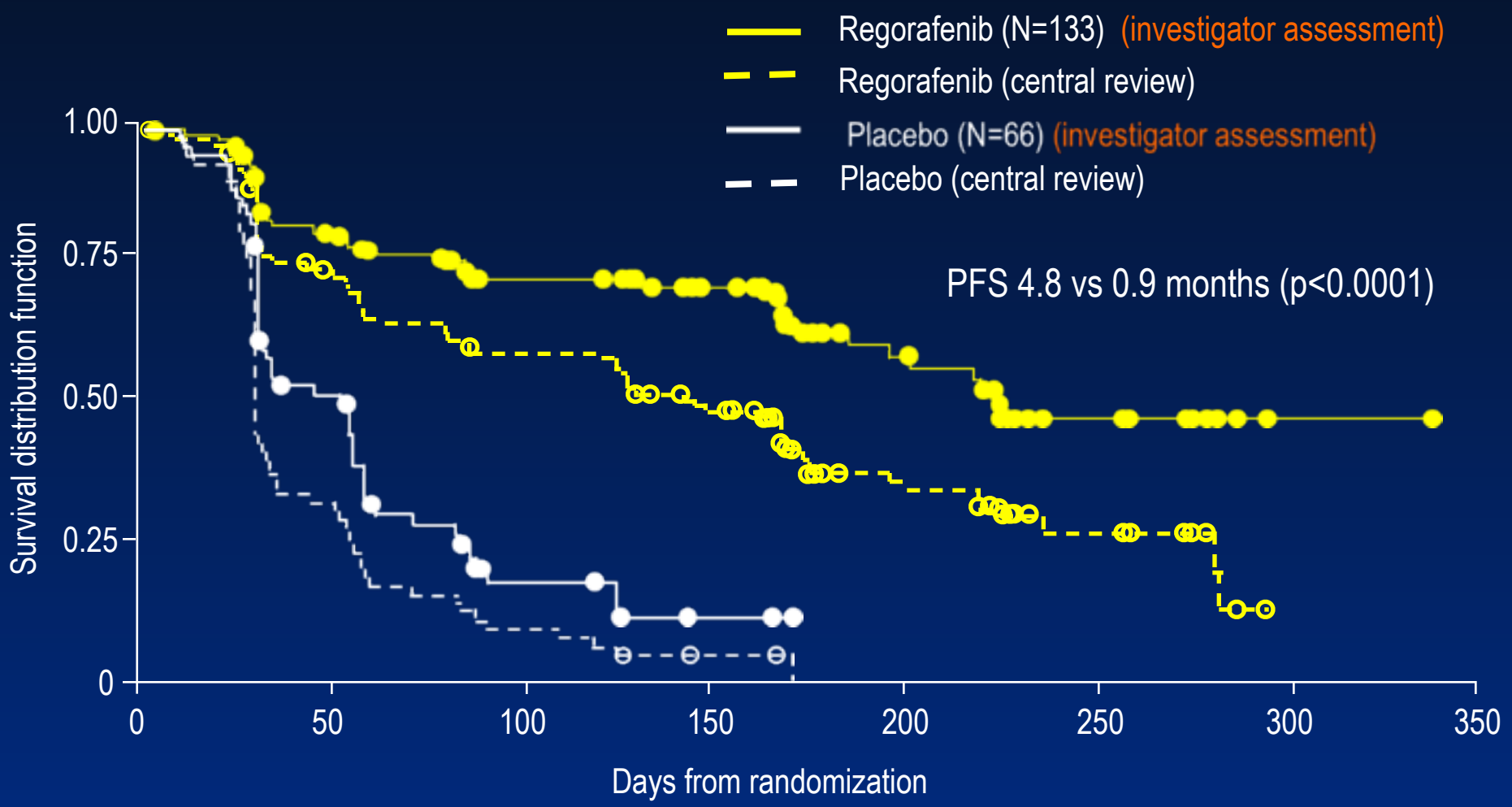
Demetri GD et al. *Lancet.* 2006;368:1329-1338.

Progression-free Survival

Comparison of Central Review vs Investigator Assessments



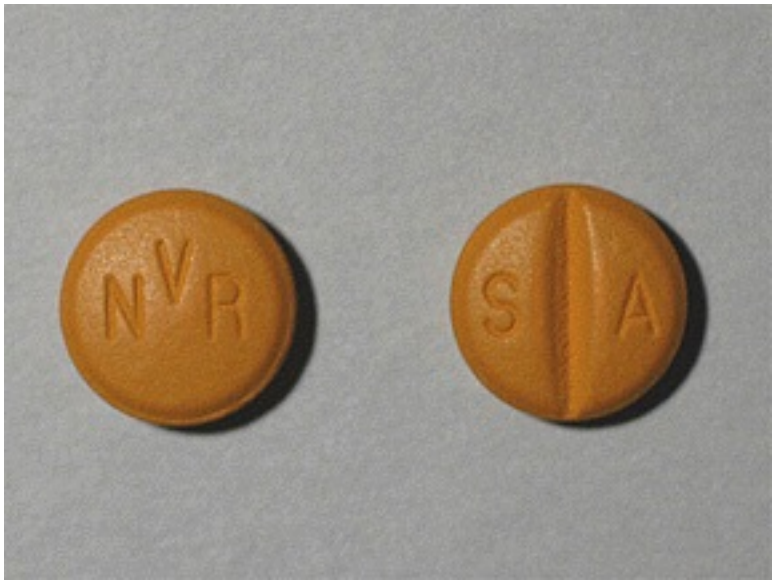
Casali PG, Reichardt P et al. Presented at: ESMO 2012; abstract 1478O.

Other Agents for Imatinib-Resistant 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	SD=48% PFS=1.9 months SDH-17 cycles
	Axitinib	ND	ND
PDGFR inhibitors (D842V)	Crenolanib, BLU-285	III, I	CBR 31%, 56% PFS>6 months
Raf Inhibitors	Vemurafenib	I	ND
mTOR Inhibitors	Everolimus	II/III	PR=2%, SD=43% PFS=3.5 months
PI3K Inhibitors	Buparlisib (BKM120)	I/II	Recruiting
HDAC inhibitors	Vorinostat	NA	ND
Placebo	Various	III	PR=0% PFS=1- 1.5 months

HDAC=histone deacetylase; IGF-1R=insulin-like growth factor–1 receptor; MKI=multitargeted kinase inhibitor; mTOR=mammalian target of rapamycin.

Life with imatinib



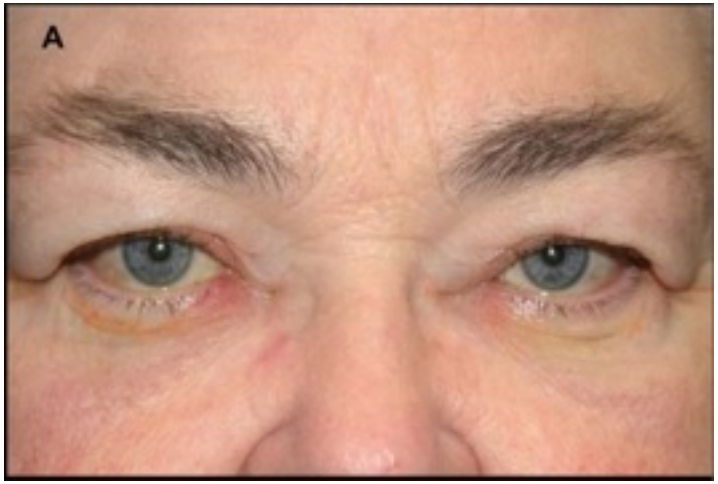
- Tyrosine kinase inhibitors
  - Block RECEPTORS on the surface of cells
  - Dirty drugs
  - The idea is that a particular receptor and its chain-of-command are MORE active in the cancer cell compared to a normal cell – but all cells have these receptors
  - Thus, while killing the cancer, non-cancer cells will also experience disruptions in their normal way of life = side effects (on-target effects)

Drug interactions

- Imatinib is meant to be taken with food and water – (taking on an empty stomach leads to LESS exposure to the active drug, or undertreatment!)
- Prohibited medications and juices/supplements (lead to increased levels of imatinib with worse side effects)
  - St. Johns Wort
  - Grapefruit juice
  - Star fruit, pomegranate juice
  - Coumadin
  - Can increase levels of cholesterol and blood pressure medications- check with your doctor
  - Tylenol, alcohol – stresses the liver
  - Iron supplements, changes absorption

Most common side effects

- Swelling/fluid retention, often around the eyes
- Nausea/vomiting/abdominal discomfort
- Loss of appetite
- Fatigue
- Muscle/bone/joint aches and pains
- Diarrhea
- Rashes and other skin issues
- Mild blood count abnormalities
- Mild electrolyte abnormalities

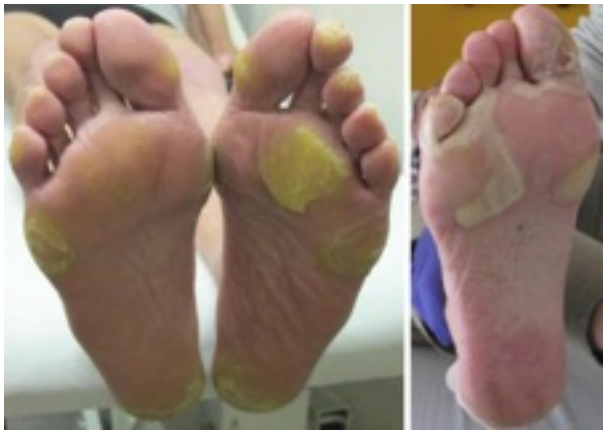


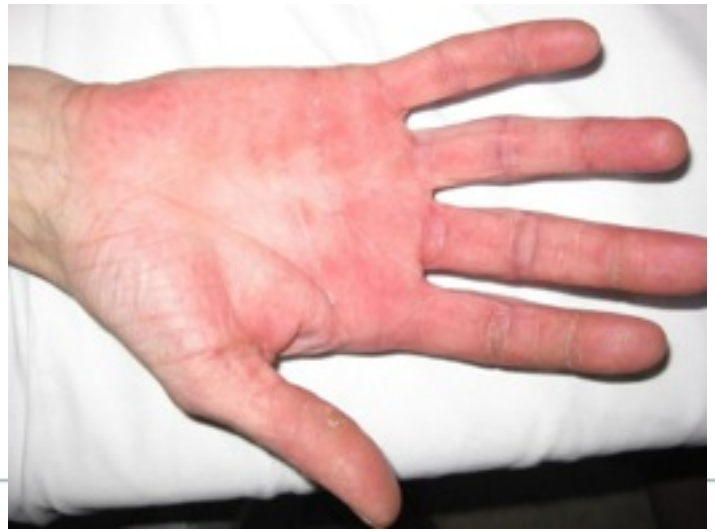
Dangerous side effects (call right away)

- New or sudden shortness of breath, especially at rest, or associated with new or worse swelling in the legs
- Chest pains
- Yellowing of the skin/eyes (liver abnormalities)
- Severe headache
- Foamy urine

Special side effects for Sunitinib (Sutent), regorafenib (Stivarga), and pazopanib (Votrient)

- High blood pressure – almost everyone
- Bleeding and clots
- Yellowish or pale skin, hair and nails
- Watch that thyroid and liver!
- Hand-foot syndrome





Management tricks

Side effect	Management
Fluid retention/ swelling	Daily weights – salt intake – diuretics – massage – support stockings
Nausea/vomiting/ abdominal pain	Anti-emetics – change time of day – take with food – small frequent meals - liver – small frequent meals – watch interacting meds -
Fatigue	Rule out contributing causes - Prioritize activities – water – sleep/ stress/exercise- meds
Aches and pains	Hydration – electrolytes – exercise – ivory soap – avoid OTC pain meds – Lidoderm patches/hot/cold
Diarrhea	Food diary – small frequent bland meals – yogurt – water - meds
Loss of appetite	Awareness – anti-emetics – high calories – grazing – supplements - meds
Rashes/skin issues	Variable types – sun – mouth sores – moisturizer/friction – antihistamines/steroids/antibiotic – drug holiday
Labs to watch	CBC - Liver – Kidneys - Thyroid (especially long term)

What about generic imatinib?

- Patent expired for CML, not GIST, but generics are now available
- Generic companies required to prove bioequivalence, but not therapeutic equivalence
- Usual concerns with different side effects based on fillers as with any generic
- Brand-name only assistance programs

Good source of info - https://liferaftgroup.org/generics/

Take-home recommendations

- Know about GIST
  - Foundation websites, Days of Learning, forums
- Know about your own GIST
  - Customize treatment based on the mutations and distribution of tumors (Dr. Trent's talk!)
- Know your options
  - Seek second opinions with GIST experts who are up-to-date on the newest drugs, clinical trials, science and research.

Thank you for coming today!

Questions???

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SYLVESTER COMPREHENSIVE CANCER CENTER

UNIVERSITY OF MIAMI HEALTH SYSTEM