GIST Day of Learning
March 10, 2018

Scottsdale, Arizona

Registration and Breakfast

9:00-9:30
Introductions and GIST 101
Laura Occhiuzzi – Life Raft Group
Mahesh Seetharam, MD - Mayo Clinic Hospital, Phoenix
Donald Northfelt, MD - Mayo Clinic Hospital, Phoenix

9:30-10:00
Surgical Management of GIST
Nabil Wasif, MD - Mayo Clinic Hospital, Phoenix

10:00-10:30
Pathologist Viewpoint: Discussion about Mutational Testing
Matt Zarka, MD - Mayo Clinic Hospital, Phoenix

10:30-10:45
Break

10:45-11:15
Role of Interventional Radiology in Treatment of Localized and Metastatic Disease
Scott Kriegshauser, MD - Mayo Clinic Hospital, Phoenix

11:15-11:45
Systemic Therapy in GIST Management: Discussion of Treatments, Promising Clinical Trials, and Immunotherapy
Mahesh Seetharam, MD - Mayo Clinic Hospital, Phoenix
Michael Gordon, MD - HonorHealth, Scottsdale

11:45 -12:15
Management of Drug Side Effects
Eric Yancey, Pharm.D - Mayo Clinic Hospital, Phoenix

12:15-1:00
Lunch and Patient Story

1:00-1:30
Panel Discussion

1:30-2:00
Q&A and Closing Remarks

March 10th, 2018

ABOUT GDOL

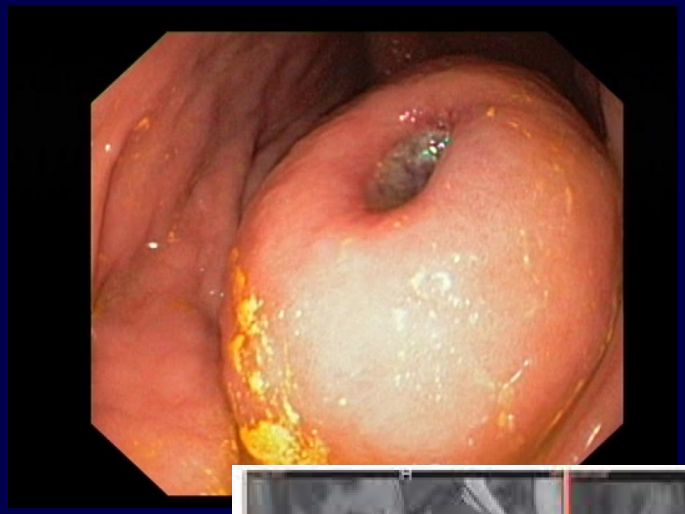
GDOL is a free one day event to help patients and caregivers learn more about this rare cancer, find support, and enhance their knowledge base to help them navigate their cancer journey.

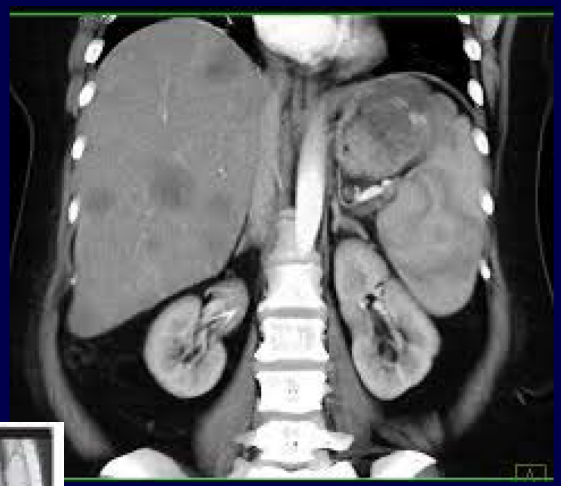
The Life Raft Group has a simple focus: to cure a form of cancer — GIST — and to help those living with it until then. To do this, the Life Raft Group focuses on three key areas: research, patient support & education, and advocacy, which lay the foundation of our mission to ensure the survival of GIST patients through a comprehensive approach connecting individual patients' needs, the worldwide community of GIST advocates and the global health and research environment.

LOCATION

Mayo Clinic
Taylor Auditorium
13400 E. Shea Blvd.
Scottsdale, AZ 85259

The many faces of gastrointestinal stromal tumor





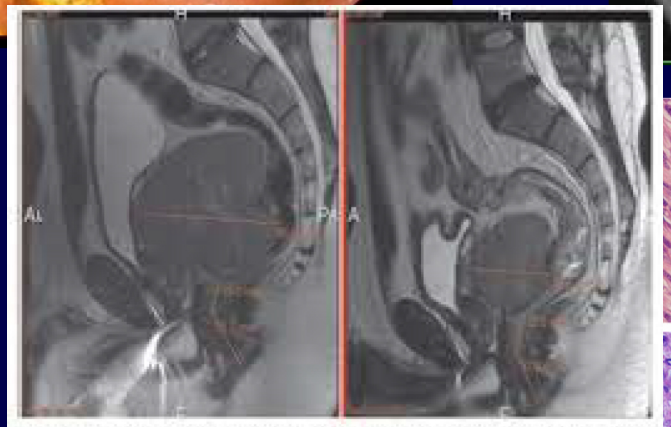
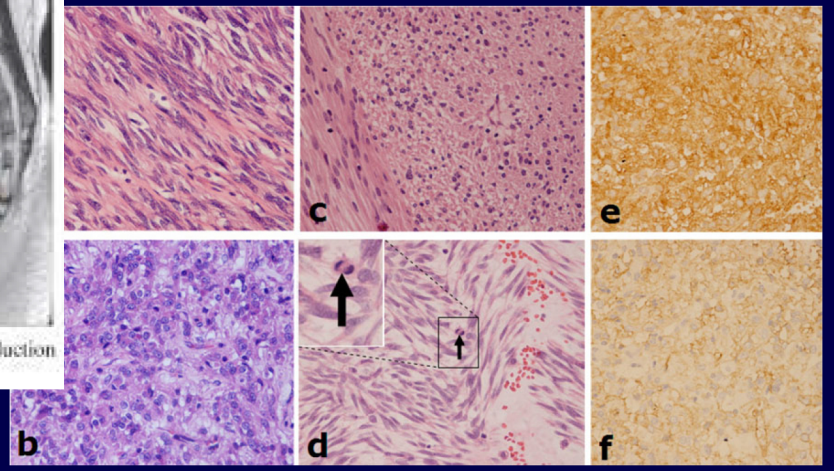


Figure1 - Pre- and post-treatment MRI (sagittal) illustrating the reduction in tumor size



Overview

- GIST background and molecular biology
- Symptomatology
- Diagnosis
- Treatment options
  - Localized disease
  - Metastatic disease
  - Recurrent disease

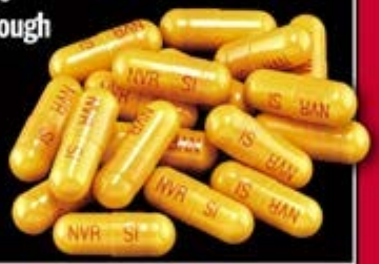
MAY 28, 2001

www.time.com AOL Keyword: TIME

TIME

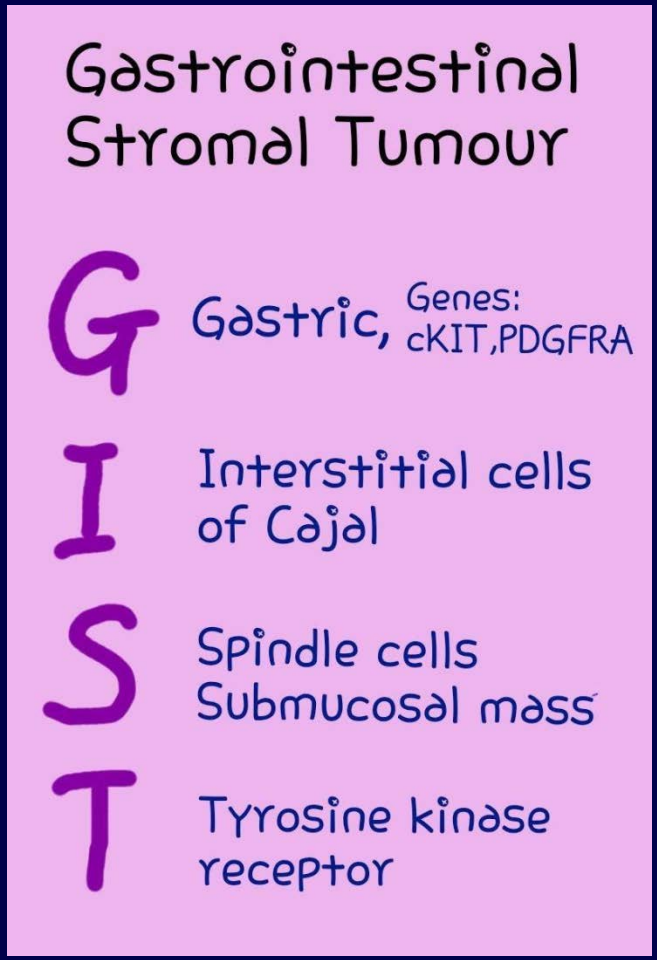
THERE IS NEW AMMUNITION IN THE WAR AGAINST CANCER. THESE ARE THE BULLETS.

Revolutionary new pills like GLEEVEC combat cancer by targeting only the diseased cells. Is this the breakthrough we've been waiting for?

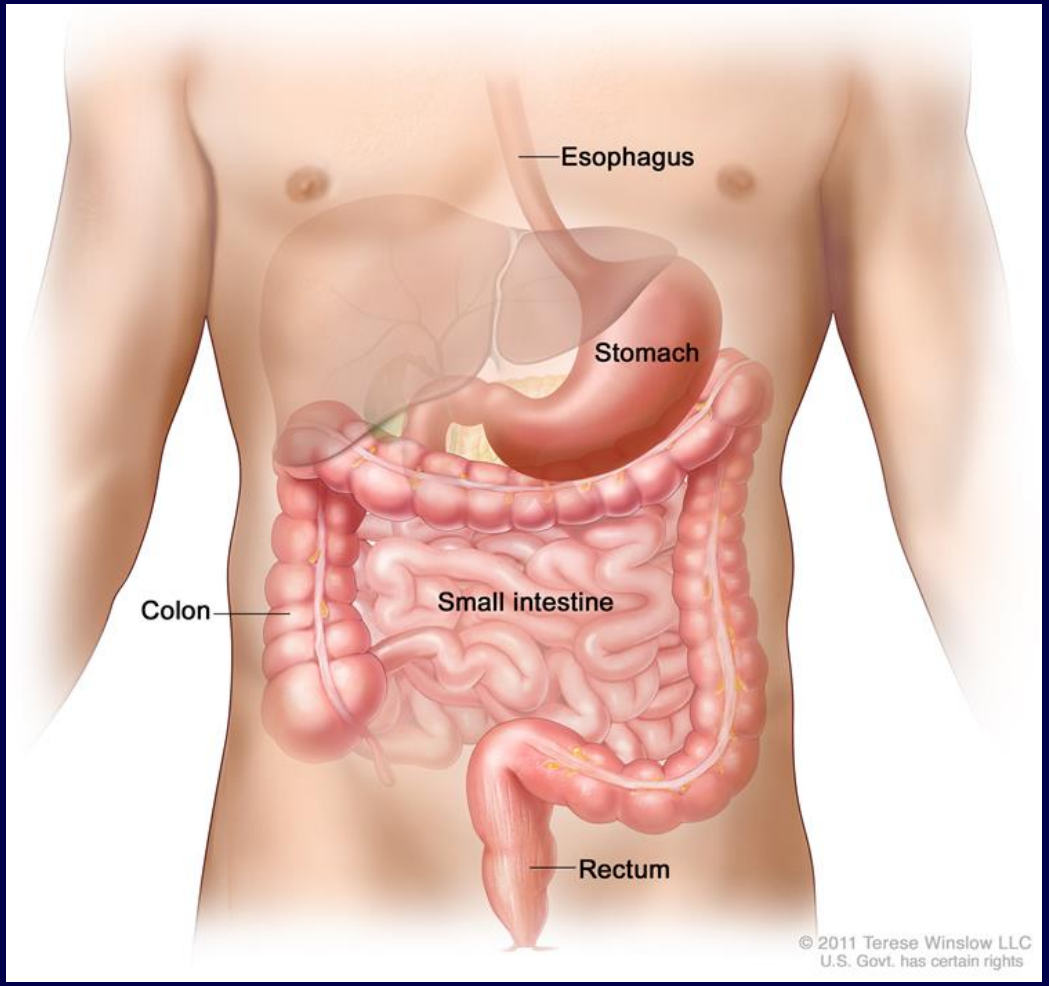


What are gastrointestinal stromal tumors?

- Sarcoma of digestive supportive tissue
- Birth year: 2000
- Rare: 10/million, 4K-6K/yr (US)
- Average age: 50 yrs, M>W
- Arise from pacemaker cells of the digestive tract (Interstitial cells of Cajal)
- CD117 (KIT) expression
- Genetic factors can increase risk of GIST (Neurofibromatosis-1, carney triad)



GISTs can happen anywhere in the digestive tract

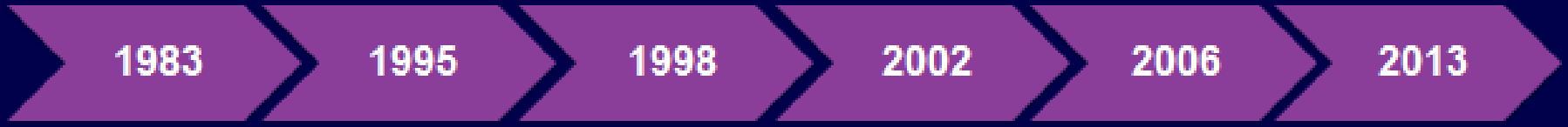


70%

20-25%

5-10%

GIST Timeline



1983

First described by Mazur and Clark[1]

1995

CD34 identified as relatively specific marker[2]; similarities between GIST cells and interstitial cells of Cajal

1998

2 major discoveries[3]:

- KIT staining 94% of GIST
- Activating mutations in *KIT* gene (5 out of 6)

2002

Accelerated FDA approval of imatinib[4]

2006

FDA approval of sunitinib as second-line therapy

2013

FDA approval of regorafenib as third-line therapy

1. Mazur MT, et al. Am J Surg Pathol. 1983;7:507-519. 2. Miettinen M, et al. Am J Surg Pathol. 1995;19:207-216. 3. Hirota S, et al. Science. 1998;279:577-580. 4. Dagher R, et al. Clin Cancer Res. 2002;8:3034-3038.

Slide credit: clinicaloptions.com

What symptoms could be expected?

- Abdominal pain/pressure
- Nausea
- Bleeding
- Anemia
- Fatigue
- Intestinal obstruction

How is it diagnosed?

- Blood test…anemia, iron deficiency , but no cancer marker
- CT scan (*choi criteria)
- MRI scan
- PET/CT scan
- Endoscopic ultrasound (EUS)
- Endoscopy (EGD, colonoscopy)
- Biopsy: KIT and DOG-1 staining, mutation testing for KIT/PDGFR, SDH

Can my cancer spread?

- 1 in 5 can have metastatic disease at diagnosis
- Sites: abdominal cavity, liver, peritoneum
- Spread to lung, bone or brain is RARE
- Lymph node spread is more common in pediatric GISTs, pediatric type GIST in young adults.

What determines outcome?

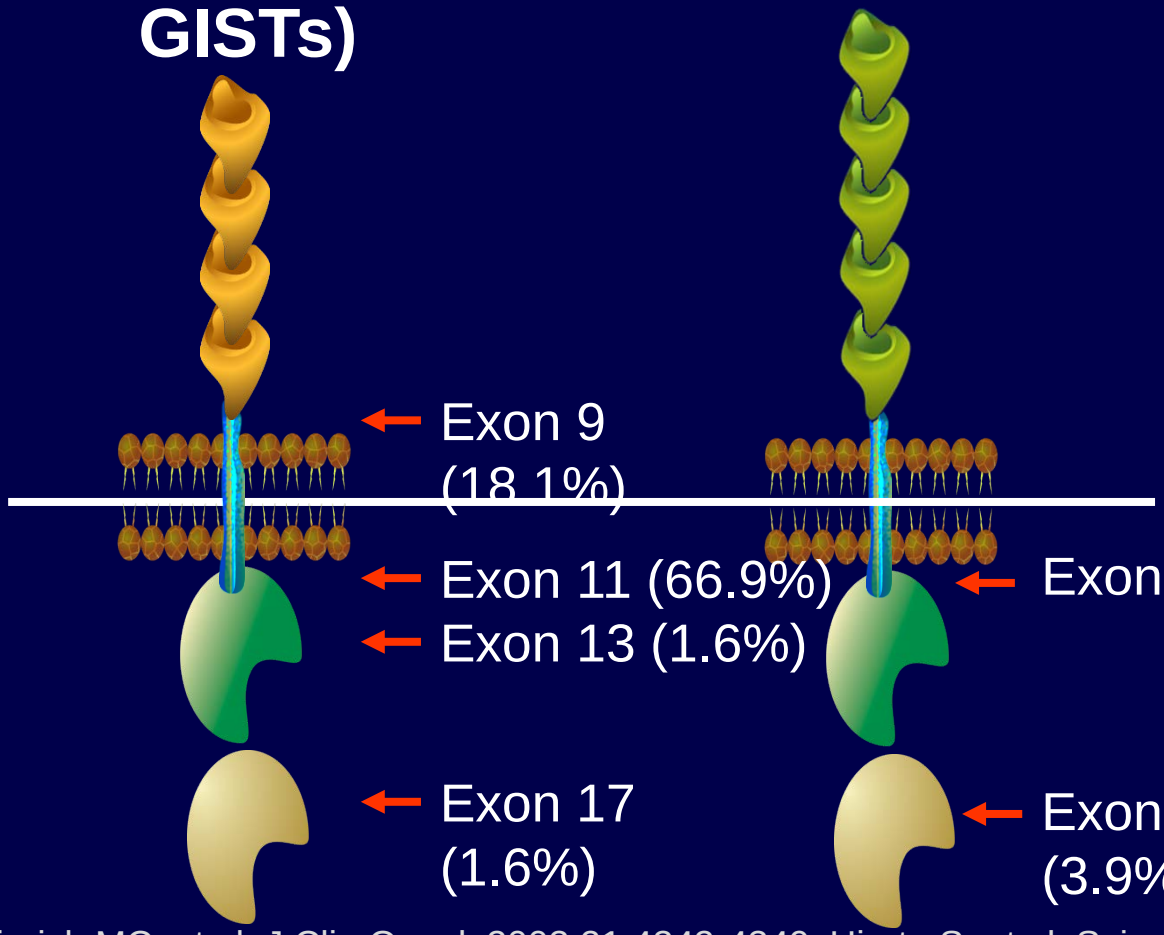
- Size of tumor
- Location (stomach vs. others
- Mitotic rate (high vs. low)
- **Molecular/Mutation status**
  - KIT vs. PDGFR
  - Wild type vs. SDH deficient

Figure 1 "You've got something unaffordable".
Note: Courtesy of Banx Cartoons/Financial Times, Thursday September 24, 2015, page 12, with permission.

Mutation, mutation, mutation

KIT (~ 85% GISTs)

PDGFRA (~ 5% to 7%)



Wild Type (10% to 15 %)

- BRAF mutation (V600E exon 15)
- IGF-1R
- Succinate Dehydrogenase
- Alternate mutations (AKT/PTEN/TRK)

Heinrich MC, et al. J Clin Oncol. 2003;21:4342-4349. Hirota S, et al. Science. 1998;279:577-580.

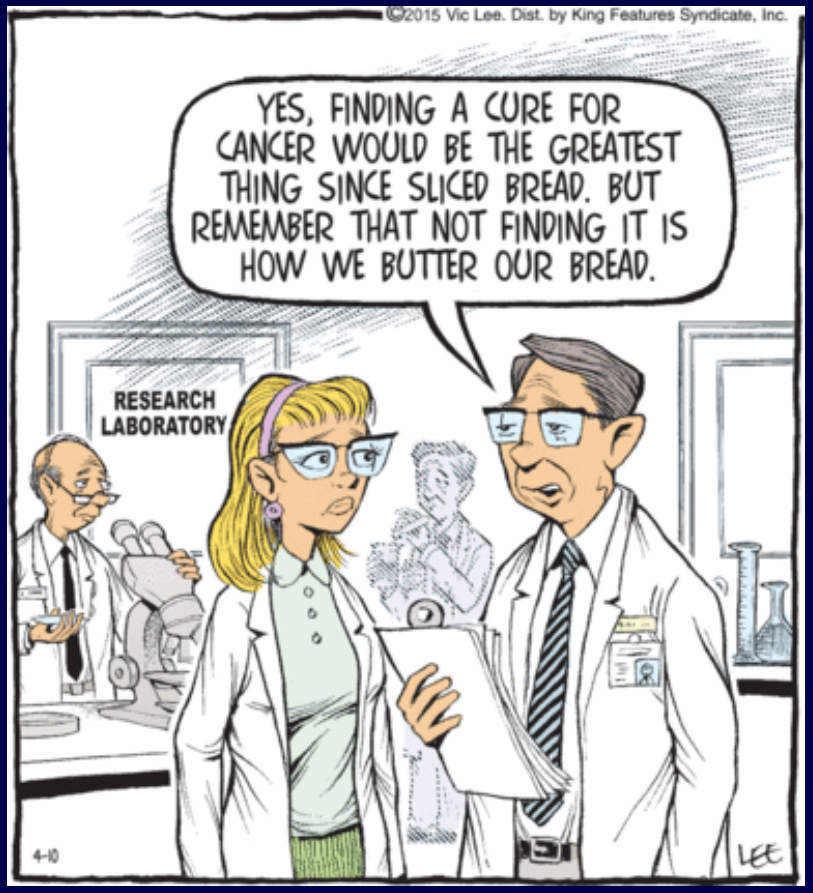
Slide credit: clinicaloptions.com

Why is mutation so important?

- Determine choice and dose of treatment
  - Neoadjuvant
  - Adjuvant
- Understand risk for family members
- Clinical trials

How long do I have to live?

- General survival rates (@ 5 yrs): NCI database
  - Localized disease: 91%
  - Locally advanced: 74%
  - Metastatic disease: 48%



Is my cancer treatable and curable?

- Depends on the stage, resectable vs. unresectable, risk category of disease
  - Operable: surgery (Dr. Wasif)

    Low risk: no additional therapy after surgery

    Intermediate or high risk: “adjuvant therapy” x 3 yrs after surgery
  - Locally advanced and not amenable to upfront surgery: medical treatment (such as Gleevec) before surgery

Primary GIST – Risk of Recurrence

	Size	Gastric (n=1055)	Jejunum/Ileum (n=629)	Duodenum (n=144)	Rectum (n=111)
Mitotic Index ≤5 per 5 mm^2	≤ 2 cm	0%	0%	0%	0%
	> 2 ≤ 5 cm	1.9%	4.3%	8.3%	8.5%
	> 5 ≤ 10 cm	3.6%	24%	Insuff. data	Insuff. data
	> 10 cm	10%	52%	34%	57%
Mitotic Index >5 per 5 mm^2	≤ 2 cm	(None)	(High)	Insuff. data	54%
	> 2 ≤ 5 cm	16%	73%	50%	52%
	> 5 ≤ 10 cm	55%	85%	Insuff. data	Insuff. data
	> 10 cm	86%	90%	86%	71%

Miettinen & Lasota, Semin Diagn Pathol, 23(2):70-83, 2006

Do I need chemotherapy?....NO

Chemotherapy Trials

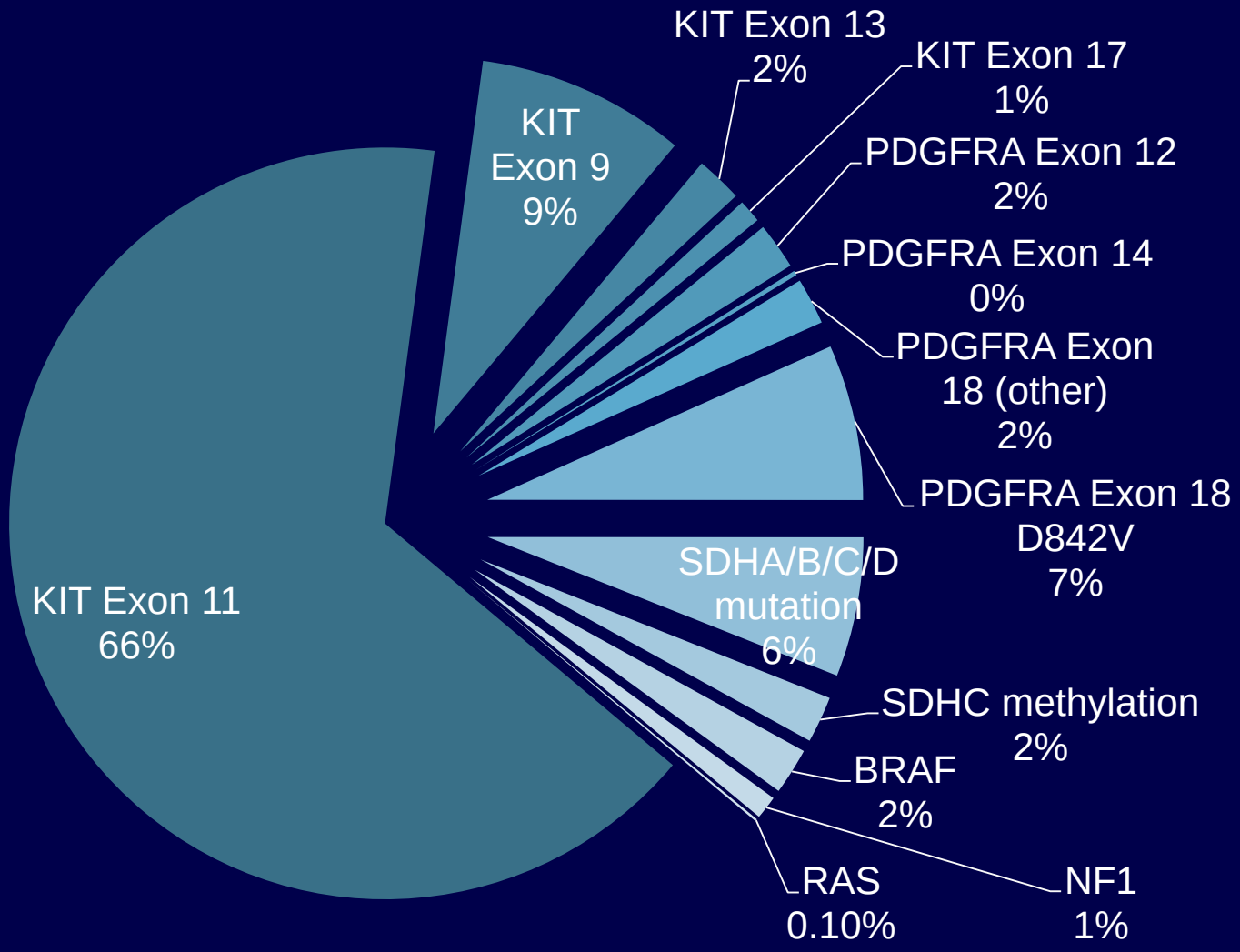
Advanced GIST

Regimen	Number of Patients	Partial Response n (%)
DOX + DTIC	43	3 (7%)
DOX + DTIC +/– IF	60	10 (15%)
IF + VP-16	10	0 (0%)
Paclitaxel	15	1 (7%)
Gemcitabine	17	0 (0%)
Liposomal DOX	15	0 (0%)
DOX	12	0 (0%)
DOX or docetaxel	9	0 (0%)
High-dose IF	26	0 (0%)
EPI + IF	13	0 (0%)
Various	40	4 (10%)
DTIC/MMC/DOX/ CDDP/GM–CSF	21	1 (5%)
Temozolamide	19	0 (0%)
TOTAL	**280**	**19 (6.8%)**

What are the approved treatment options?

- Imatinib (Gleevec)
- Sunitinib (Sutent)
- Regorafenib (Stivarga)

GIST molecular landscape has become very complicated



What are my chances of responding to treatment?

~ 20% of pts have unresectable/metastatic disease; > 40% of resected tumors recur and metastasize

- Pre-imatinib
  - Localized disease: 5-yr OS < 50%
  - Metastatic GIST median OS: 5-12 mos
- With targeted therapy (post-2001)
  - Localized disease 5-yr OS: > 80%
  - Metastatic GIST median OS: ≥ 60 mos (pre-sunitinib/regorafenib < 60 mos)
  - No difference between 400mg once vs. twice daily

What happens when imatinib stops working?

- Nearly one half of pts develop resistance to initial imatinib/targeted therapy within 2 yrs
- Primary resistance (within 6 mos, 10% to 15%)
  - KIT exon 17, PDGFR exon 18 mutations, BRAF, KRAS
- Secondary resistance
  - Acquired secondary mutations: usually in tumors with exon 11 primary mutation
  - Activation of alternate drivers/pathways: PI3K/AKT/mTOR, IGFR1

How effective are Sunitinib and Regorafenib?

Table 4 Key phase III randomized trials with tyrosine kinase inhibitors in patients with GIST

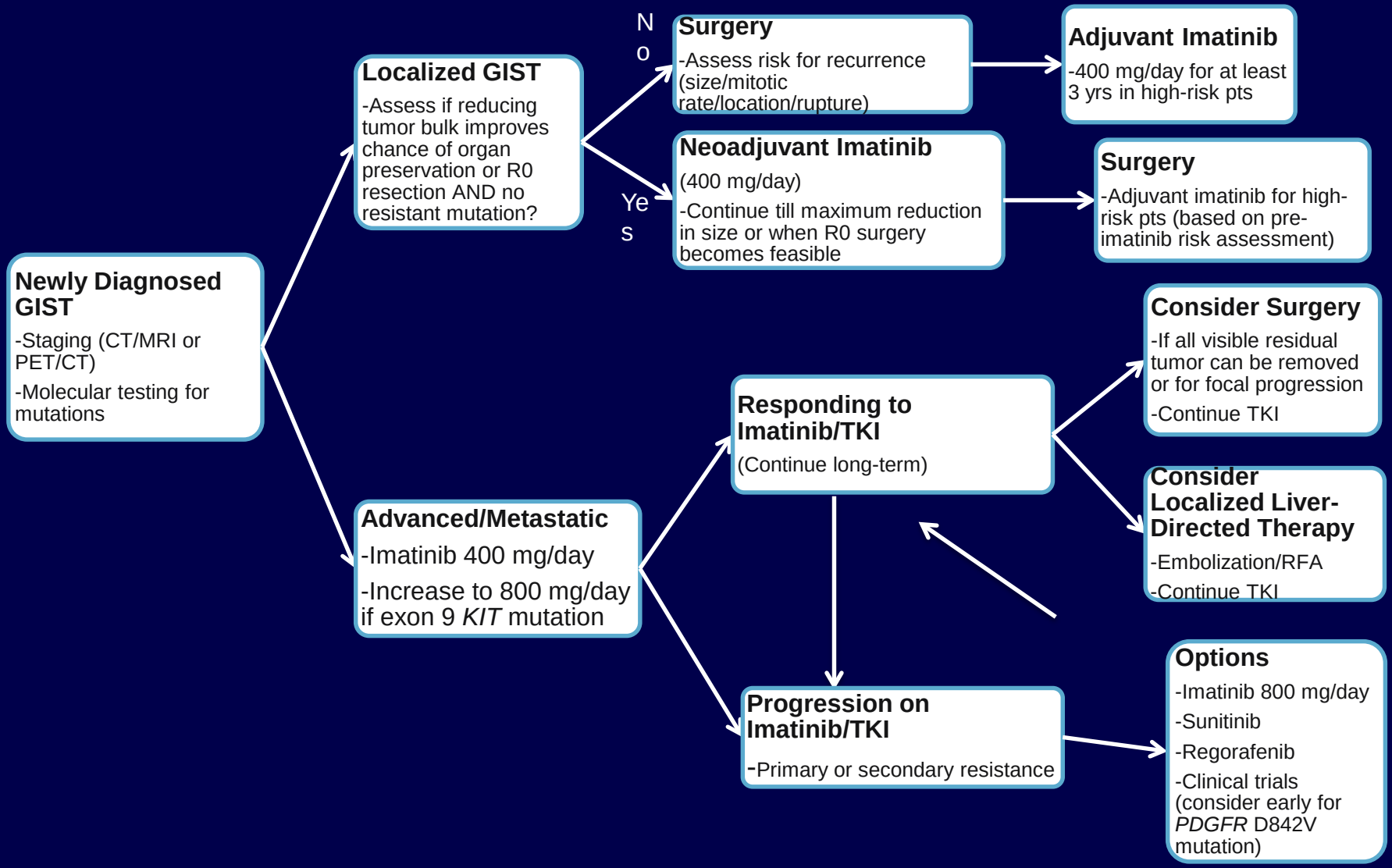
Name of study	Setting	N	Randomized arms	PFS/RFS	OS	Response rate
ACOSOG Z9001 (41)	Adjuvant	713	1-year imatinib *vs.* placebo	1-year RFS 98% *vs.* 83% (P<0.0001)	HR =0.816; P=0.438	Not available
SSG XVIII/AIO (29)	Adjuvant	400	1- *vs.* 3-year imatinib	5-year RFS 66% *vs.* 48% (P<0.0001)	5-year OS 92% *vs.* 82% (P=0.02)	Not available
EORTC (52)	1st line metastatic	946	400 *vs.* 800 mg imatinib	2-year PFS 56% *vs.* 50% (P=0.026)	2-year OS 69% *vs.* 74%	50% *vs.* 54%
North American Sarcoma Intergroup study (S0033) (53)	1st line metastatic	746	400 *vs.* 800 mg imatinib	2-year PFS 50% *vs.* 53%	2-year OS 73% *vs.* 78%	43% *vs.* 41%
Demetri *et al*. (63)	2nd line metastatic	243	Sunitinib *vs.* placebo	Median 27.3 *vs.* 6.4 weeks (P<0.0001)	Median 72.7 *vs.* 64.9 weeks (P=0.306)	Not available
GRID (72)	3rd line metastatic	199	Regorafenib *vs.* placebo	Median 4.8 *vs.* 0.9 months P<0.0001)	Same (HR =0.77; P=0.199)	76% *vs.* 35%

GIST, gastrointestinal stromal tumors; RFS, recurrence-free survival; OS, overall survival; HR, hazard ratio.

What is known about SDH deficient and Wild type GIST?

- Common in younger patients
- W>M
- Absent KIT/PDGFR mutation
- Gastric GISTs, multilobular, multiple
- Poor response to Imatinib
- Proven responses to Sunitinib, Regorafenib
- Novel therapies: targeting HIF, VEGF pathways
- Local therapies: surgery, RFA/Embolization

GIST Treatment Algorithm



Summary

- GISTs are very heterogenous
- Understand the molecular/mutational abnormality
- Adjuvant imatinib improves progression free and overall survival
- Resistance to tyrosine kinase inhibitors is a problem
- Newer drugs in clinical trials will likely improve outcomes
- Need better understanding and treatments for wild type and SDH deficient GIST

THANK YOU!