MUSCULOSCELETAL TUMOR UNIT
MedUni Wien | AKH Wien

COMPREHENSIVE CANCER CENTER VIENNA

GIST

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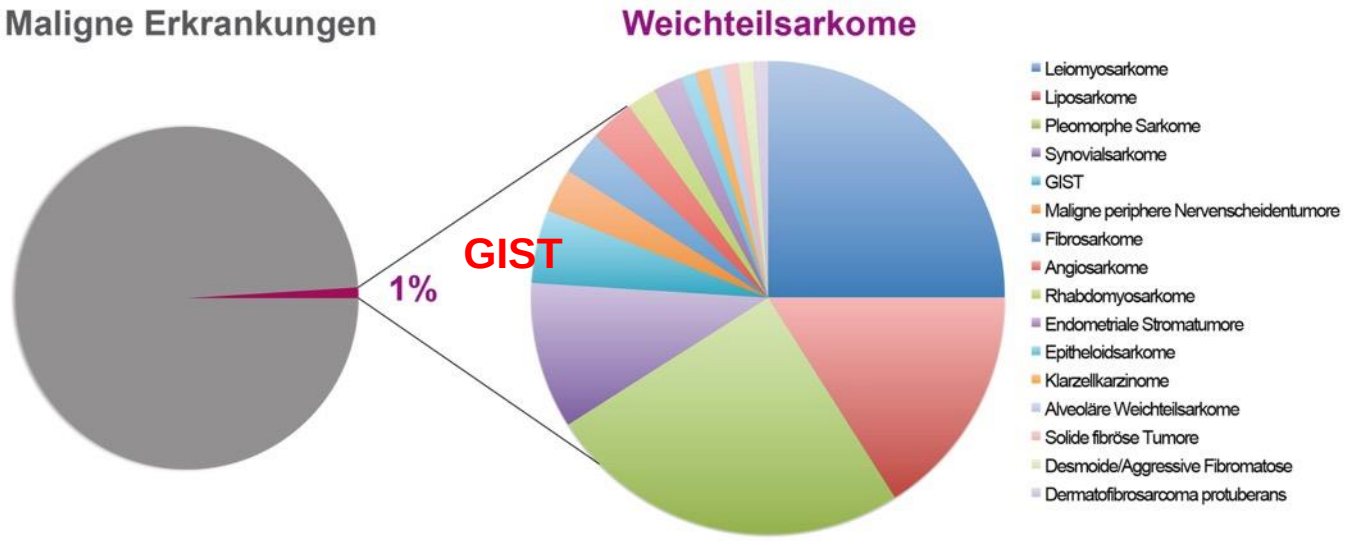
GastroIntestinal Stromal Tumor (GIST)

...a rare tumor!



15 per 1 million inh. (in Austria app. 120 newly diagnosed GIST pat. per year)
App. **10% M1 at initial diagnosis**

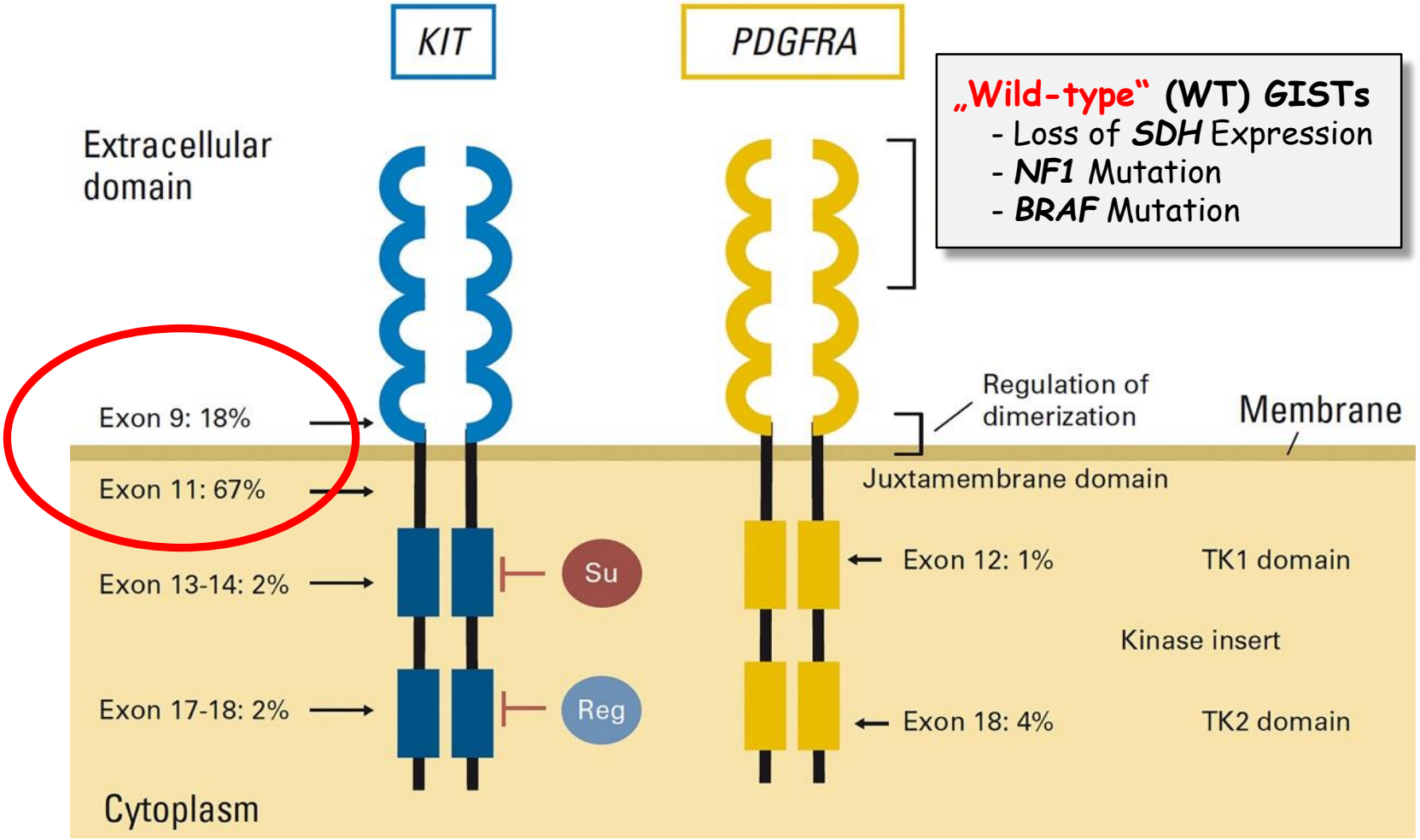
...with limited number of therapeutic options?

...until „1999“: **< 5% response to chemotherapy**
mOS 14 months

Identification of **„Driver-Mutations“** and **„Targeted Therapy“**

Oncogenic „Driver-Mutations“

85% of GISTs - activating mutations in ***KIT or PDGFRα***



Cioffi&Maki, JCO, 2015

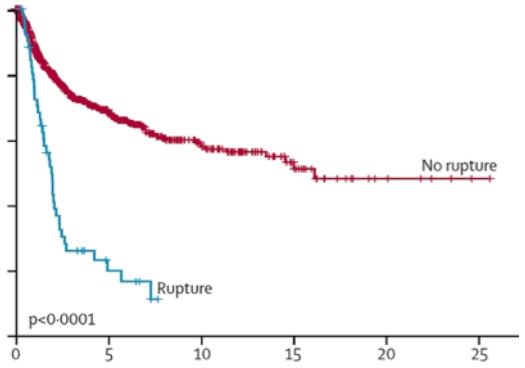
GIST – Risk Prediction

Post-operative relapse rate up 10 50% → adjuvant Therapy?

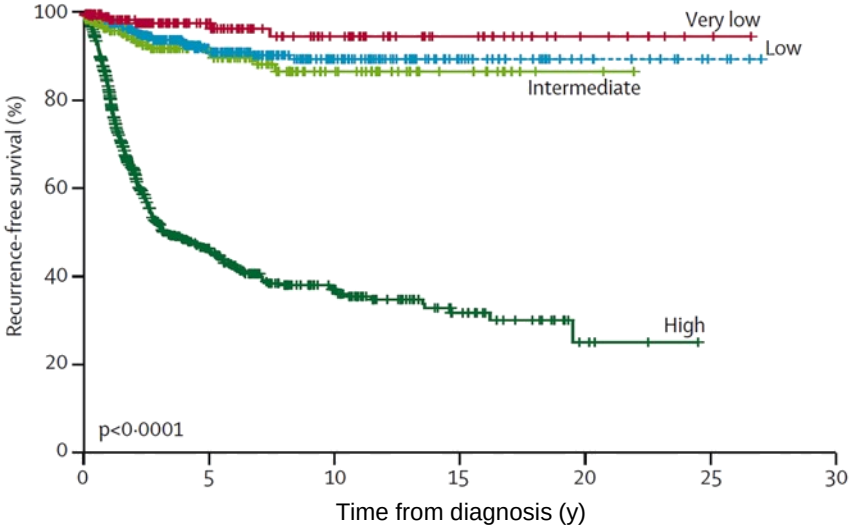
Risk factors:

- Mitotic Count
- Tu-Size
- Tu-Localisation
- Tumor Rupture

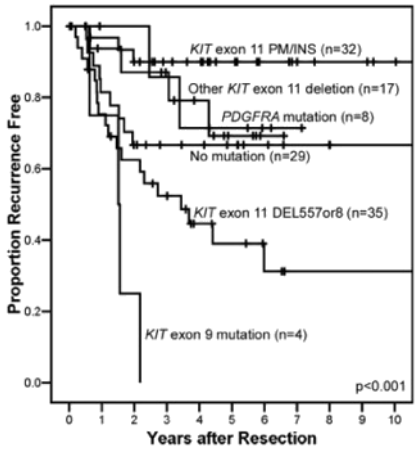
NIH /Fletcher Index
AFIP / Miettinen& Lasota



Joensuu *et al.*, Lancet Oncol., 2012



Joensuu *et al.*, Lancet Oncol., 2012



DeMatteo *et al.*, Cancer, 2008

RFS based on
Mutational Status

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Adjuvant Therapy
Therapy M1

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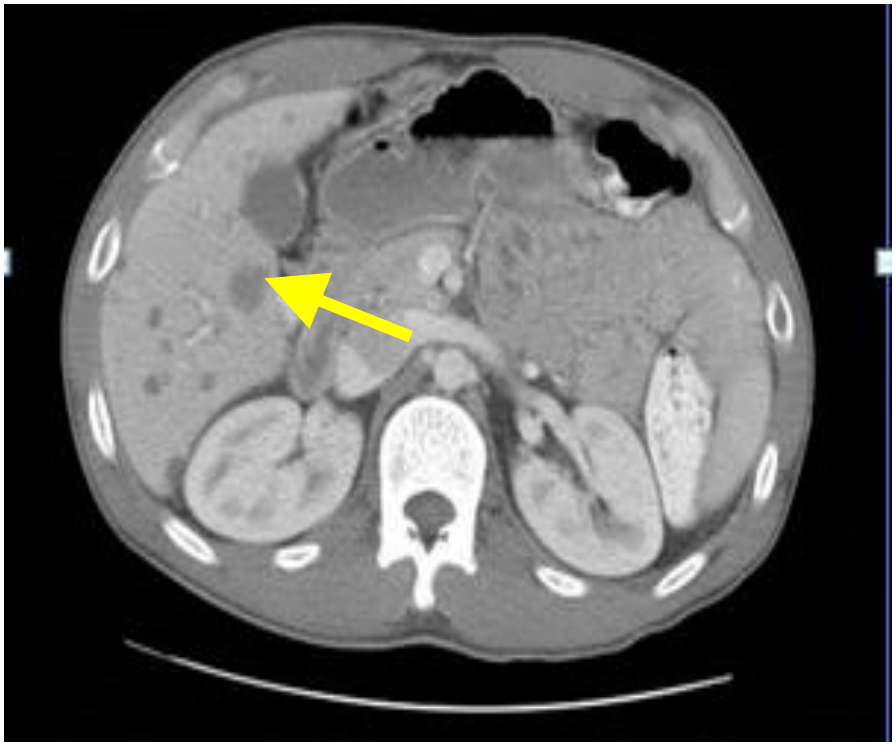
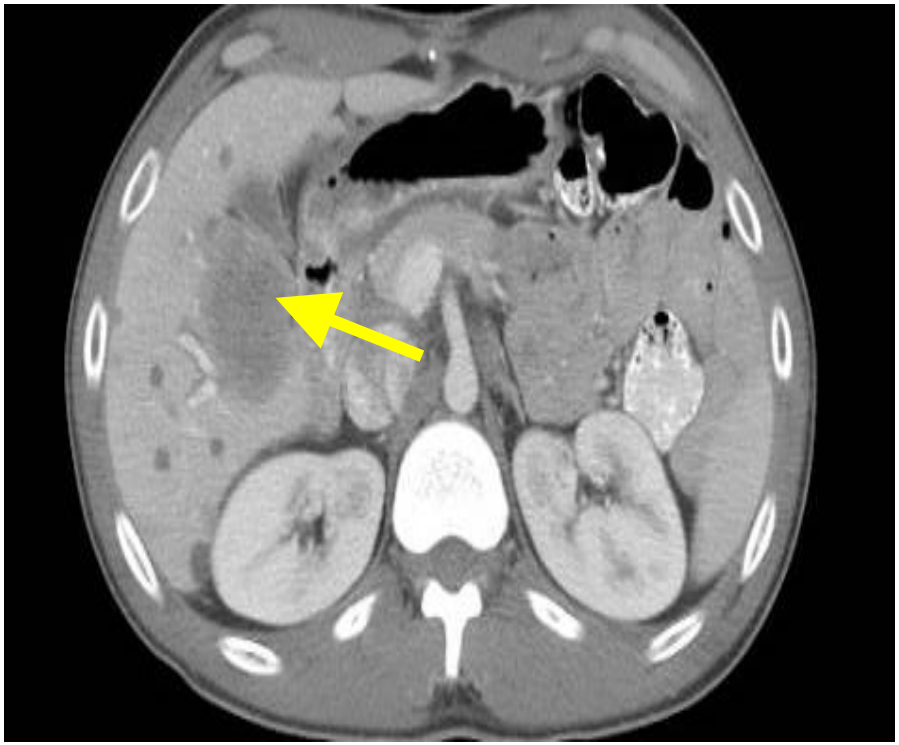
A 49yo woman with a history of erosive gastritis presents with a new onset of upper abdominal pain, fatigue, and a 5-kg weight loss over the past 2 months.

- Physical Exam: Liver edge palpable 4 cm below the right costal margin, no other abnormalities
- Laboratory: Hb 11.5 g/dL, AST and ALT 1.5 above upper limits of normal. Bilirubin level and renal function tests are normal
- Endoscopy: Results revealed a 5 x 4.5-cm gastric mass with mucosal erosion
- Biopsy: Spindle cell GIST, 15 mitoses/50 hpf, strongly positive for c-kit
  - Mutational analysis: An exon 11 mutation
- CT Chest/Abdomen/Pelvis: Several liver metastases (mets)
- ECOG PS: 0-1

Patient started imatinib 400 mg/d but had progression of one liver metastasis after 12 months of imatinib therapy.





What would you recommend now?

1. Biopsy of progressing lesion
2. Increase dose of imatinib to 800 mg/d
3. Switch patient to sunitinib
4. Local therapy (eg, arterial embolization, radiofrequency ablation, surgical resection) and continuation of imatinib 400 mg/d

Arterial embolization was performed for the progressing liver lesion that led to PR of the lesion and patient continued imatinib 400 mg/d for additional 5 months, when she developed widespread mets in the liver and peritoneum. Except for mild edema, she tolerated imatinib relatively well. PS is 1.

What would you recommend now?

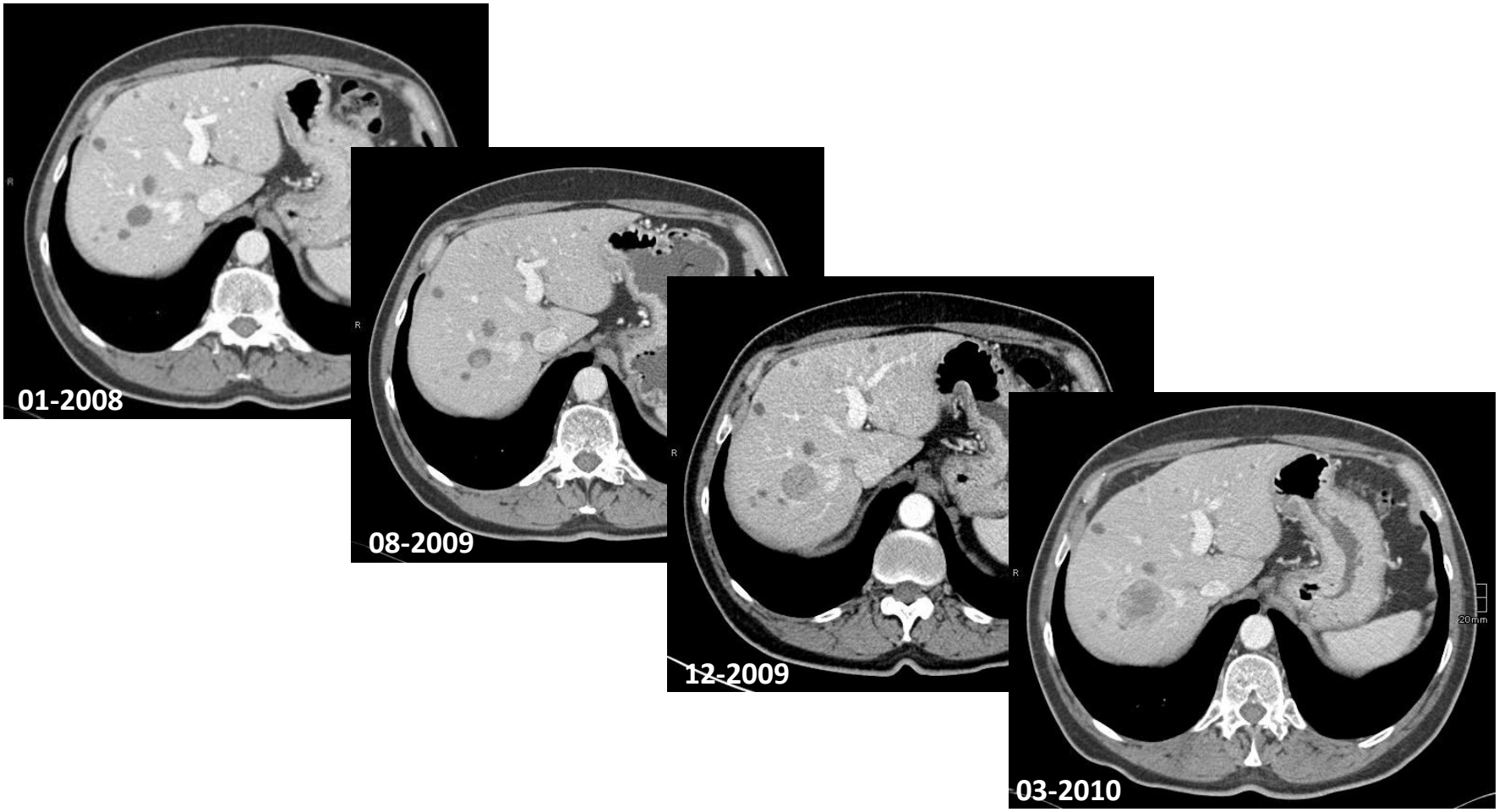
1. Increase dose of imatinib to 800 mg
2. Sunitinib
3. Regorafenib 160 mg
4. Clinical trial of other targeted agent

Patient received imatinib 800 mg and progressed, thus she was switched to continuous sunitinib 37.5 mg daily. After initial stabilization of disease, evaluation at 5 months confirmed PD of liver mets. PS is 1.

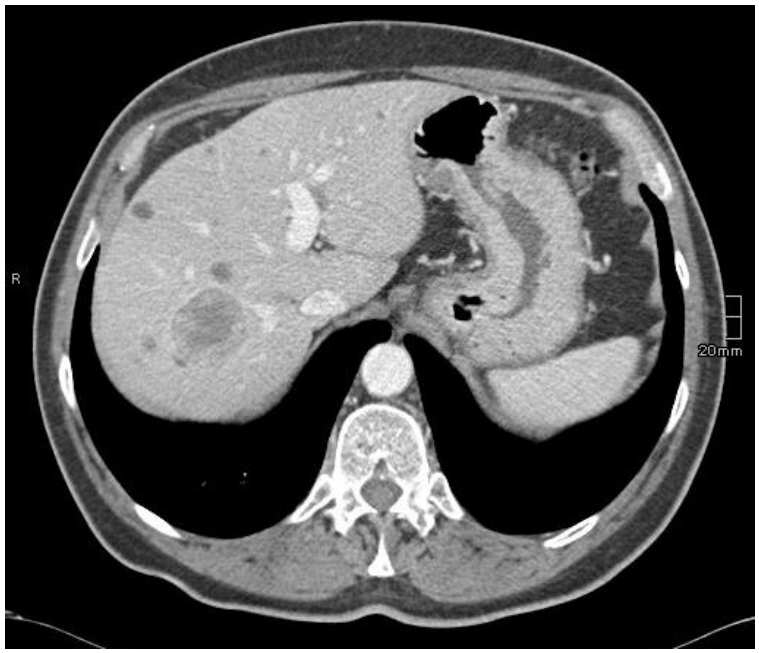
What would you recommend now?

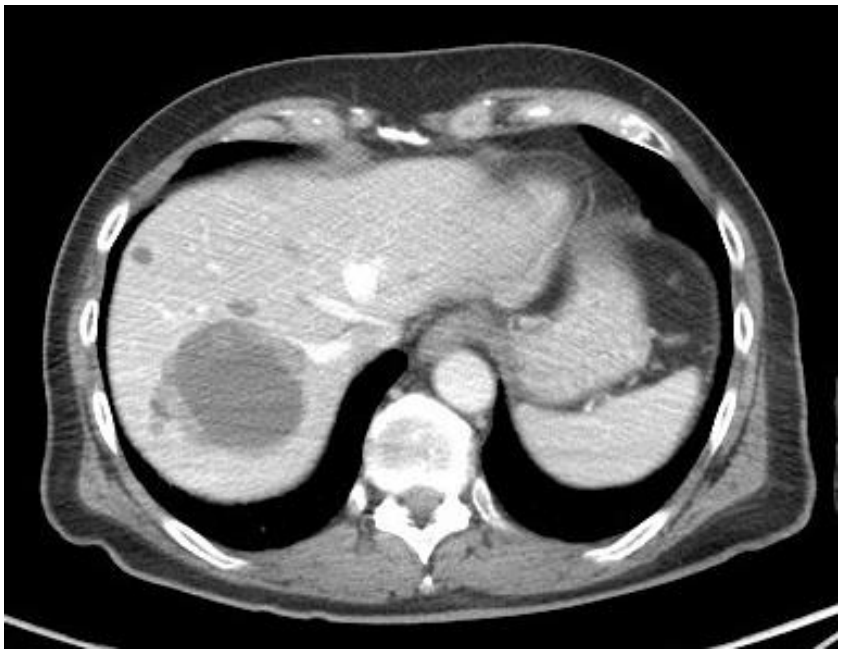
1. Regorafenib 160 mg/d
2. Clinical trial of other targeted agent
3. I would consider local therapy
4. Supportive care

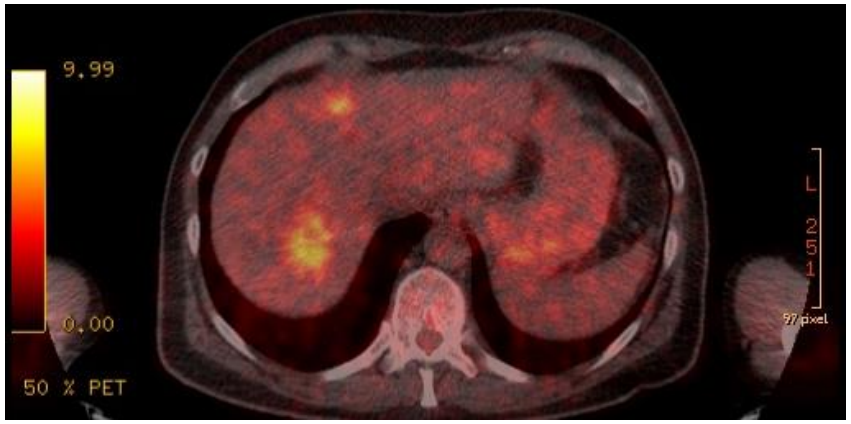
GIST—Progressive Disease Nodule in a Cyst

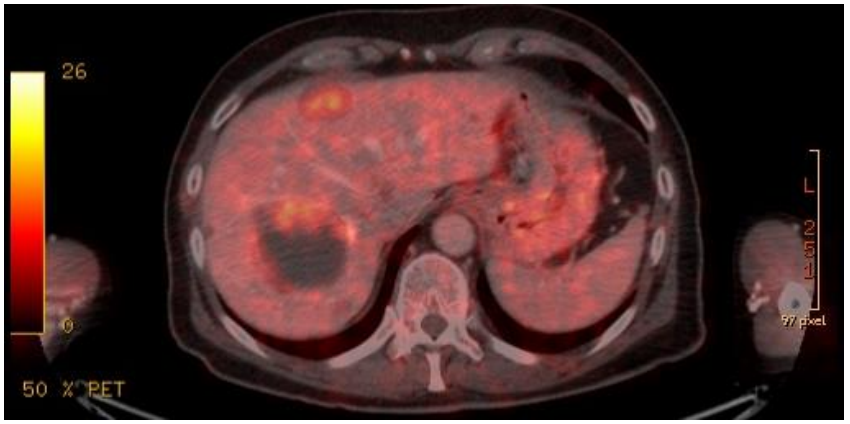


GIST—Pseudoprogression







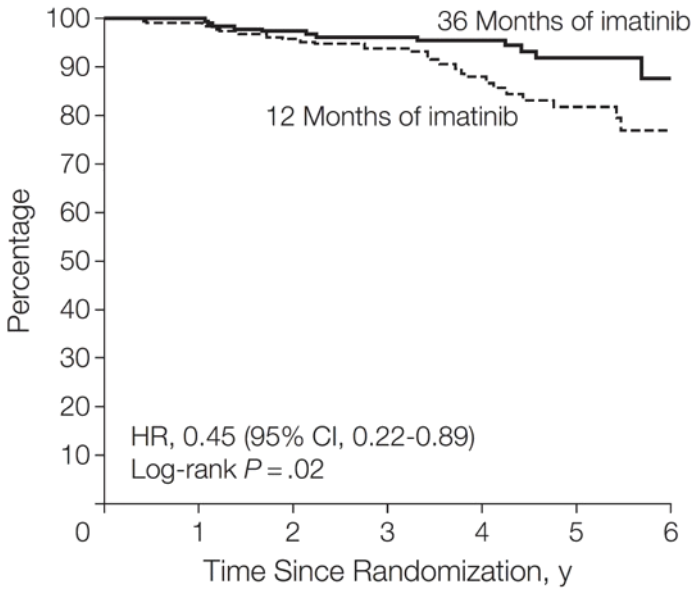


GIST – adjuvant therapy

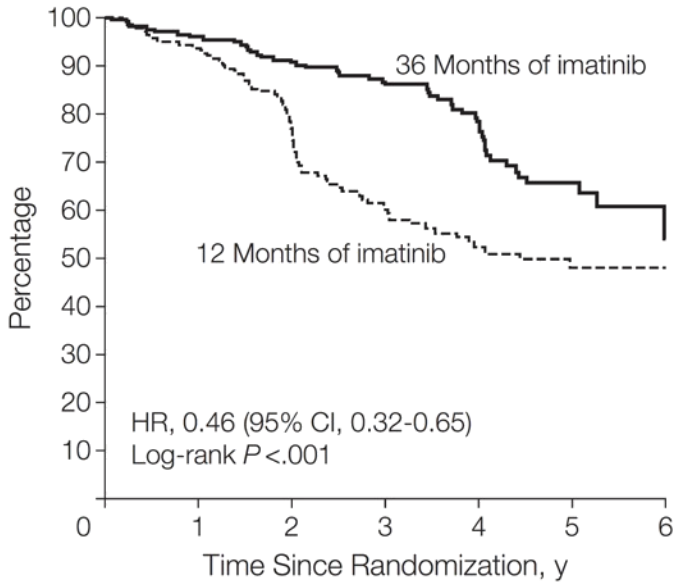
SSGX-VIII/AIO Studie

Imatinib 400mg/d
1 year vs. 3 years
high-risk GIST patients

Recurrence-free survival



Overall survival



→ **Imatinib 400mg/d** for **3 years** in **high-risk** GIST patients

Joensuu *et al.*, JAMA, 2012

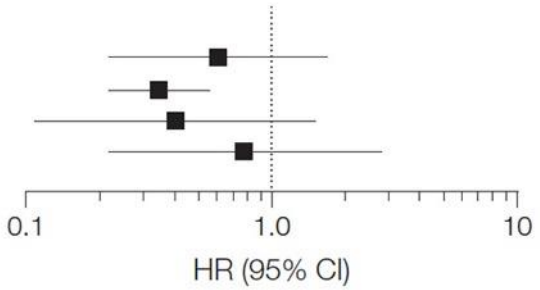
GIST – adjuvant therapy

SSGX-VIII/AIO Studie

Imatinib 400mg/d
1 year vs. 3 years
high-risk GIST Patients

Subgroup Analyses

Tumor mutation site						
KIT exon 9	12	14	8	8	0.61 (0.22-1.68)	.34
KIT exon 11	129	127	55	28	0.35 (0.22-0.56)	<.001
Wild type	19	14	9	3	0.41 (0.11-1.51)	.17
Other	28	23	6	4	0.78 (0.22-2.78)	.70



No adjuvant therapy in

- low-risk GIST
- WT-GIST
- *PDGFRα D842V* mutation

KIT exon 9 mutation

No consensus yet: **Imatinib 800mg/d?**

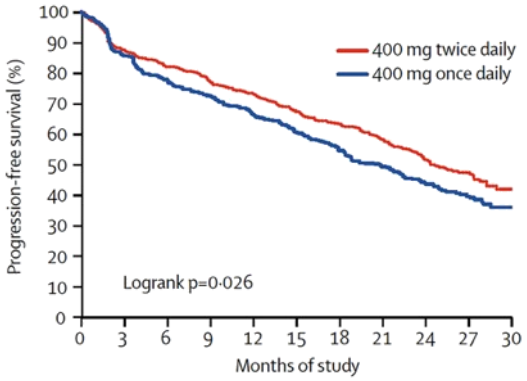
Joensuu *et al.*, JAMA, 2012

GIST – M1

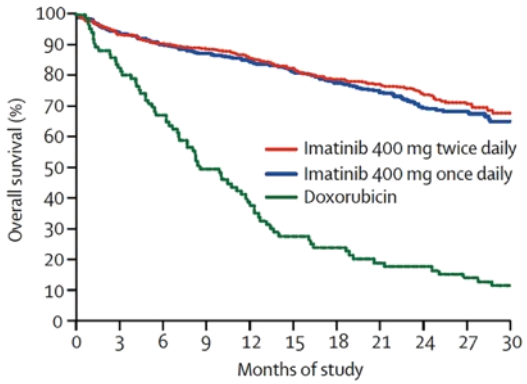
locally advanced / inoperable ± metastatic

EORTC-ISG-AGITG

Progression free survival



Overall survival



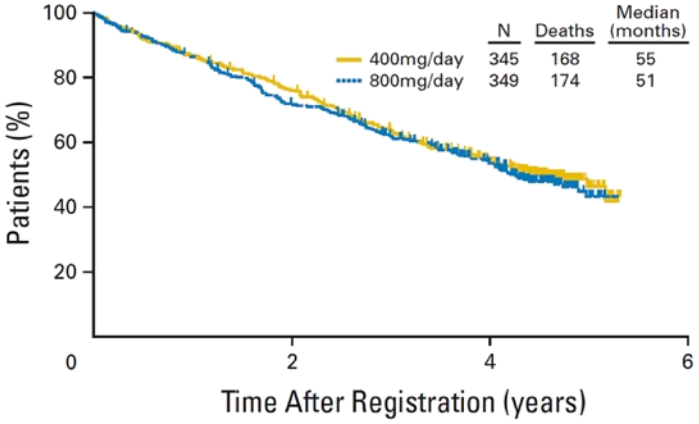
Verweij *et al.*, Lancet, 2004

Two Phase III Studies

Imatinib 400mg/d vs. **800mg/d**

NASG-S0033

Overall survival



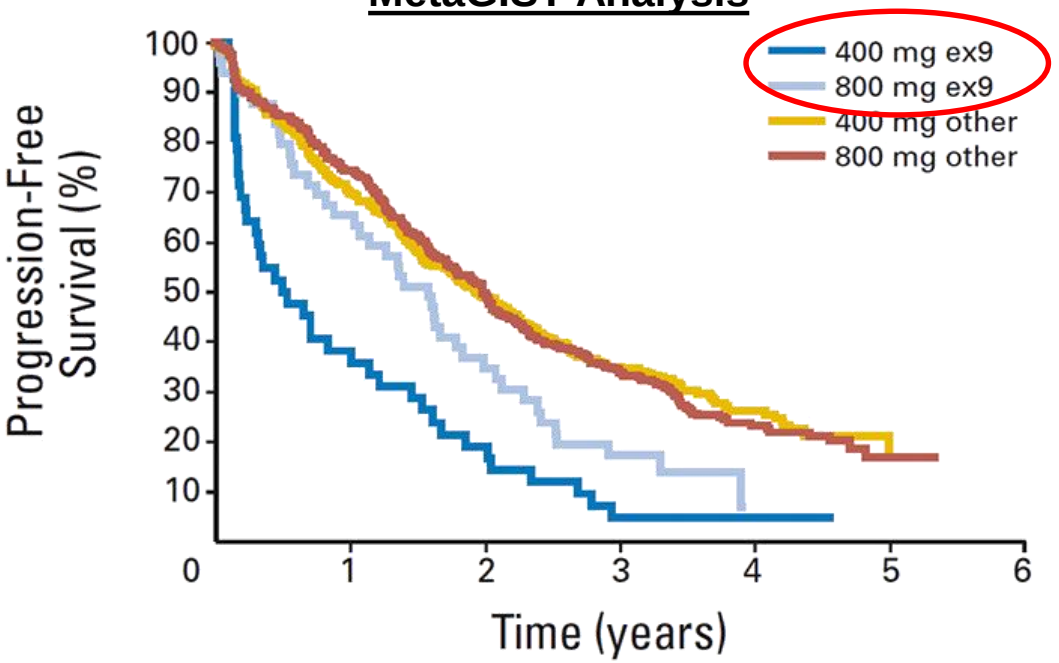
400mg equivalent to 800mg
in overall survival

Blanke *et al.*, JCO, 2008

GIST – M1

Therapy according to mutational status?

MetaGIST Analysis



KIT Exon9 mutation

significant **Benefit in PFS** (p=0,017) for **Imatinib 800mg/d**

no significant Benefit in OS

→ 1st-line Therapy: Imatinib 800mg/d

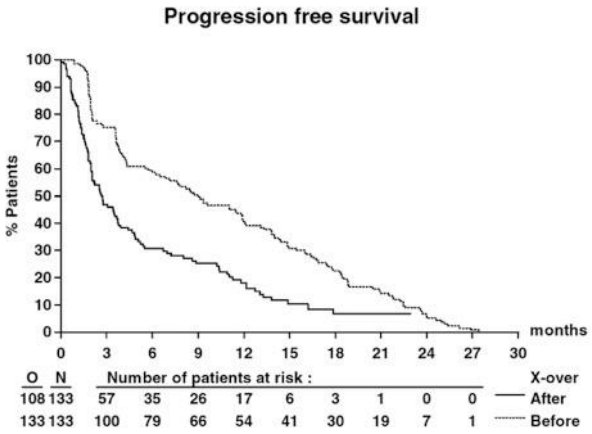
Van Glabbeke *et al.*, JCO, 2010

GIST – M1

Progressive Disease on Imatinib 400mg/d?

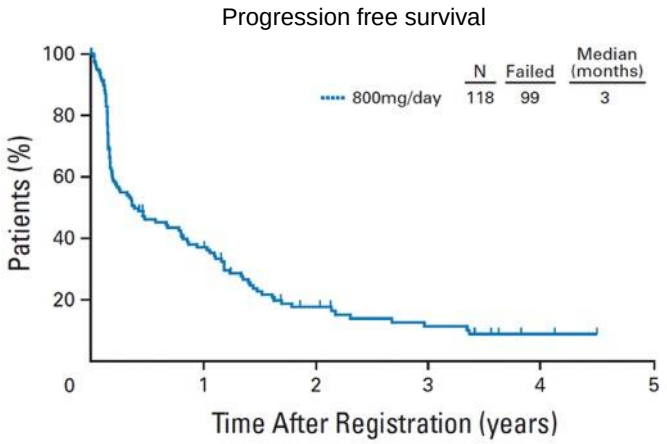
Analysis **cross-over 400mg to 800mg after PD** in two phase III studies

EORTCISG-AGITG study



Zalcberg *et al.*, EJC, 2005

American Intergroup study S0033



Blanke *et al.*, JCO, 2008

→ **Response** after **dose escalation** from 400mg/d to **800mg/d Imatinib**

mPFS: **3-4 months**

more side effects: v.a. **anemia & fatigue**

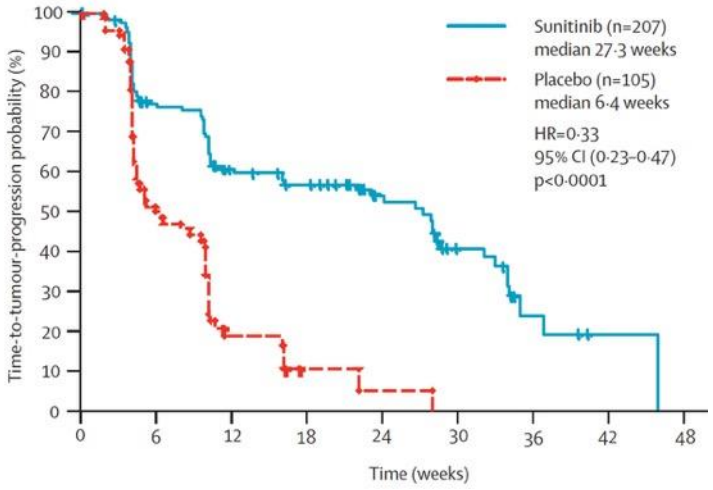
GIST – M1

2nd-line therapy after imatinib?

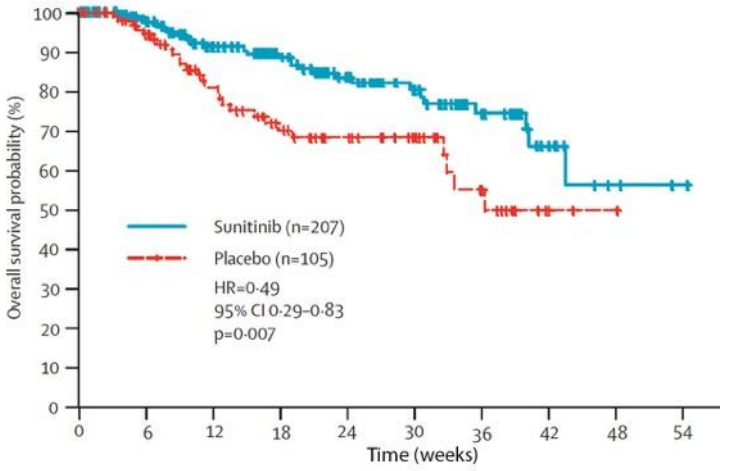
Phase III Study – **Sunitinib** vs. Placebo

Sunitinib 50mg/d; d1-28; q42

Progression free survival



Overall survival



→ significant **benefit** for **Sunitinib** in **PFS** (HR 0,33) and **OS** (HR 0,49)

Alternative dosing:

Sunitinib 37,5mg/d; continously

(George et al, EJC, 2009)

Demetri *et al.*, Lancet, 2006

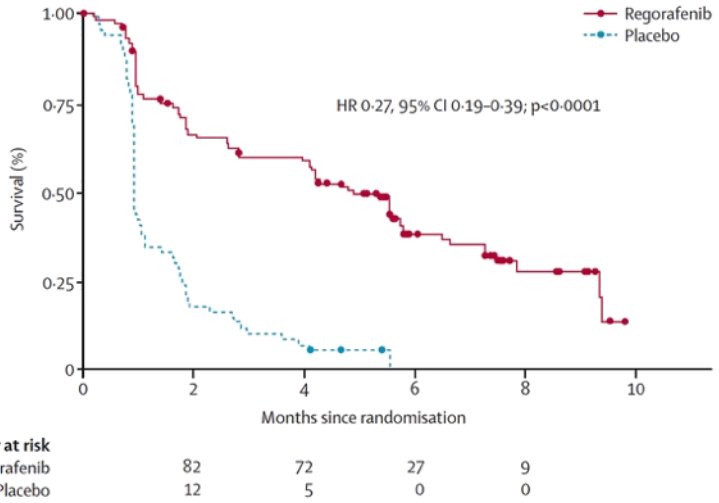
GIST – M1

3rd-line therapy – Progression after Imatinib & Sunitinib?

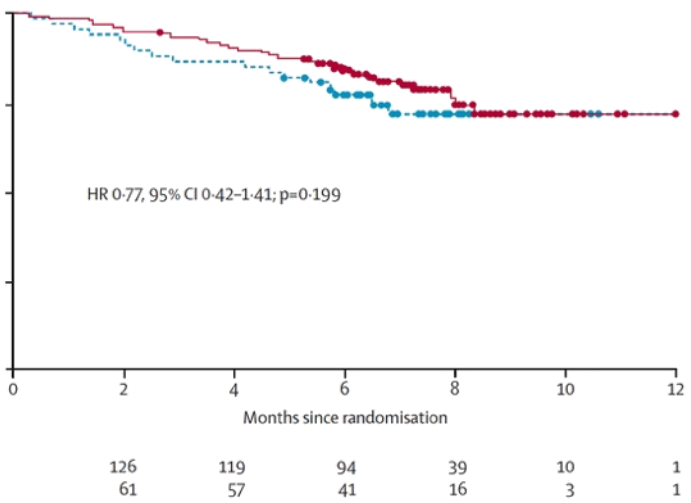
Phase III Study – **Regorafenib** vs. Placebo

Regorafenib 160mg/d; d1-21; q28

Progression free survival



Overall survival



→ significant **Benefit** for **Regorafenib** in **PFS** (HR 0,27)

mPFS 4,8 vs. 0,9 months

Demetri *et al.*, Lancet, 2013

Treatment Recommendations GIST

Neoadjuvante Therapy

Individualized decisions within **MDT**
Imatinib 400mg/d (*KIT exon9 Mut*: 800mg/d)

Adjuvant Therapy

Imatinib 400mg/d for 3 years in high-risk GIST patients
(**Not** in *PDGFRα D842V* and *WT*-GIST)

Therapy in Metastatic Disease

1st-line: **Imatinib 400mg/d**, continously; (*KIT exon9 Mut*: 800mg/d)
Dose Escalation (if **PD)** on 800mg/d

2nd-line: **Sunitnib** 50mg/d (d1-28; q42)
37,5mg/d (continously)

3rd-line: **Regorafenib** 160mg/d (d1-21; q28)

→ Mutational Analyses in any GIST

GIST: challenges

Distant relapse after adjuvant treatment with imatinib

Re-Induction of:
Imatinib 400mg/d (*KIT exon9 Mut*: 800mg/d)

D842V Mutation M1:

Clinical Stuy with Crenolanib not available „everywhere“. Has to be treated: with which drug?

Primary Exon 17/18 mutations in Metastatic Disease:

1st-line: **Imatinib** useful?

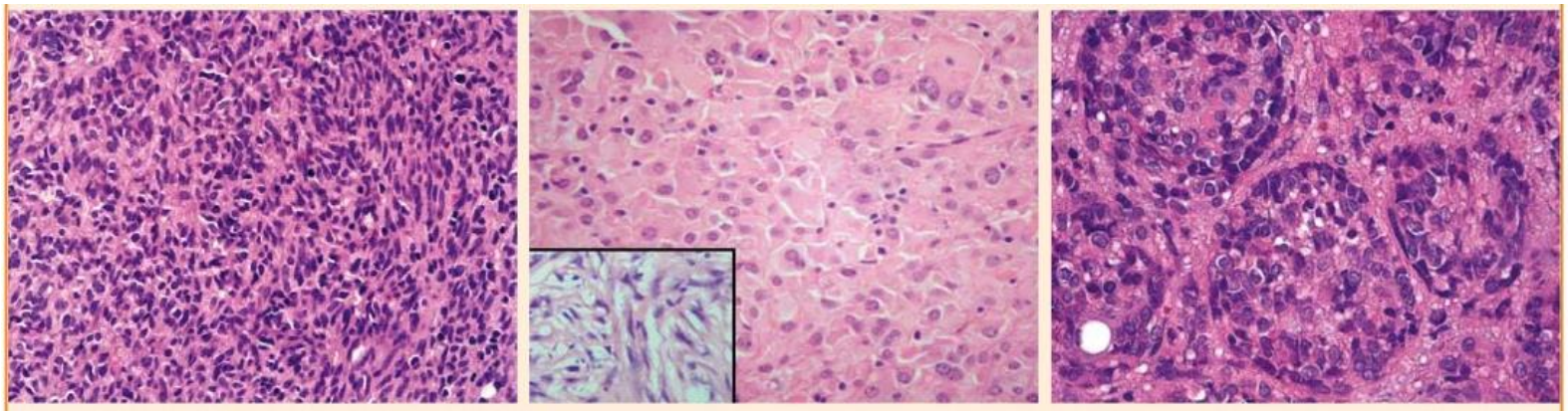
2nd-line: **Sunitnib** useful?

3rd-line: **Regorafenib** 160mg/d (d1-21; q28) as 1st-line?

RTK-WT: M1

any TKI useful?

Histopathology

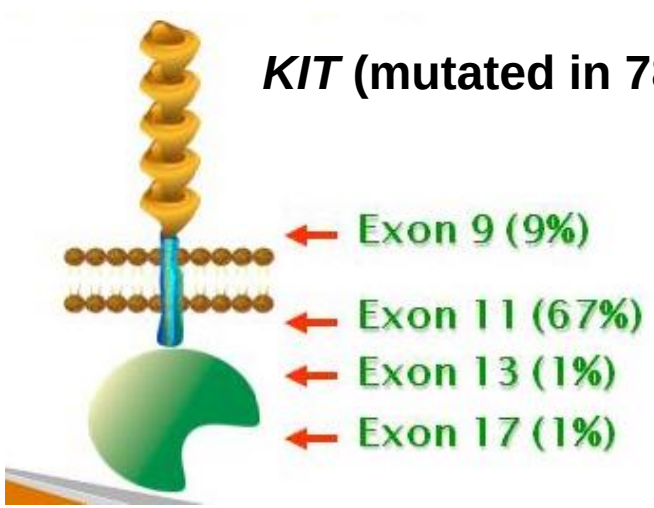


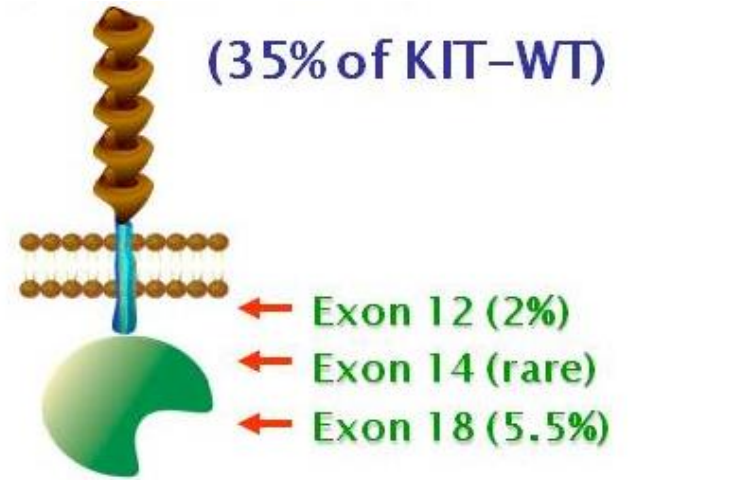
- GIST range in size from 1 cm to 40 cm (average ~5 cm)[2]
- GIST can be classified into 3 broad categories[1]
  - Spindle-cell type (70%)
  - Epithelioid-cell type (20%)
  - Mixed spindle-cell + epithelioid-cell type (10%)

1. Fletcher CD, et al. *Hum Pathol.* 2002;33(5):459-456. 2. Corless CL, et al. *Ann Rev Pathol.* 2008;3:557-586.

GIST Tumorigenesis and Immunohistochemistry

- >85% of GISTs are driven by activating mutations in either the *KIT* or *PDGFRA* genes
- Accurate diagnosis needs to involve IHC staining for KIT and GOD1
  - KIT protein (CD117): stains positive in 95% of cases
  - DOG1: positive in >95% of KIT-positive GIST and 35% of KIT-negative GIST
- Mutational analysis provides important information on prognosis and imatinib dosing

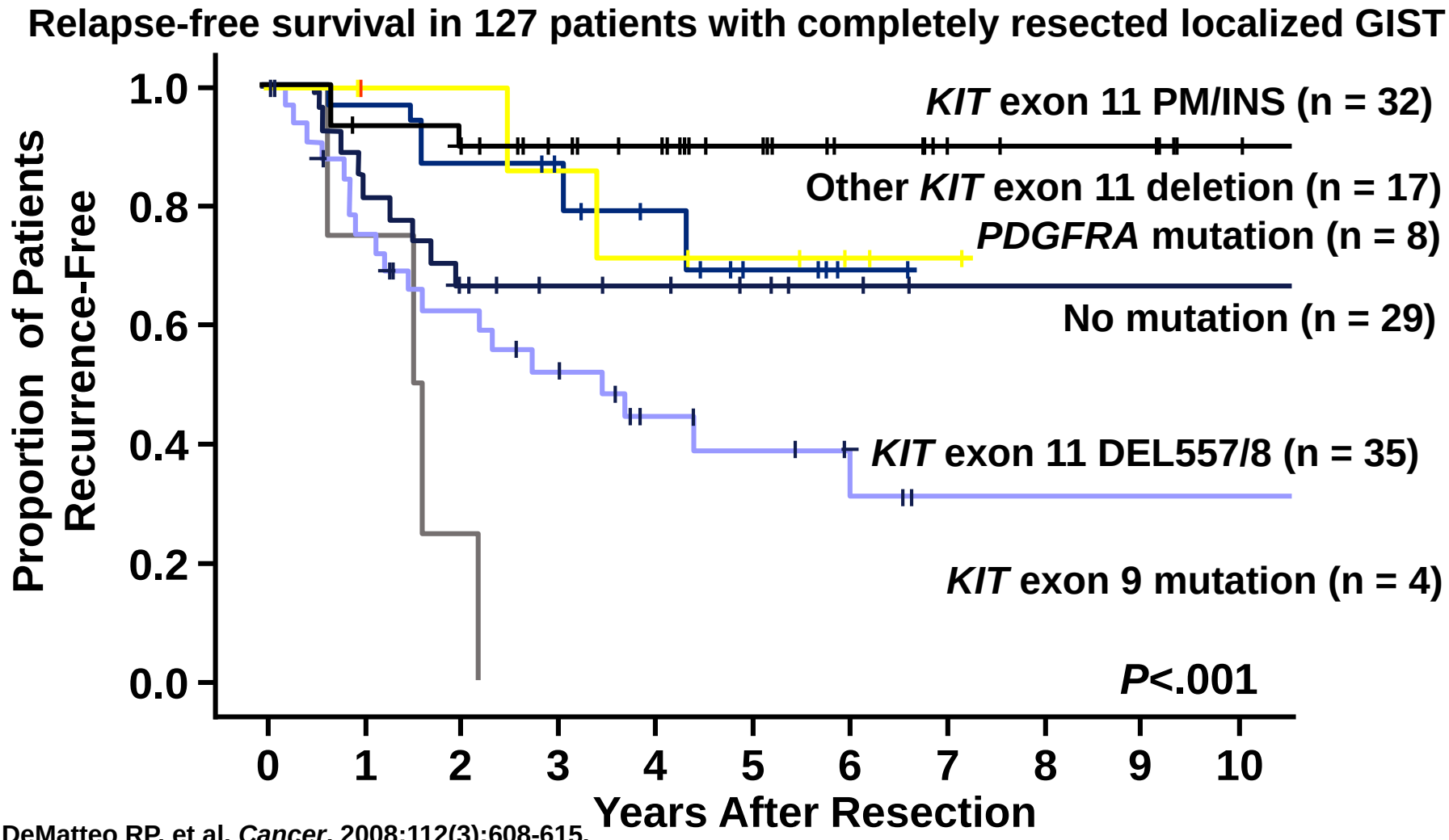




IHC, immunohistochemistry

Wardelmann E. et al. *J Mol Diagn.* 2004; 6(3): 197-204.

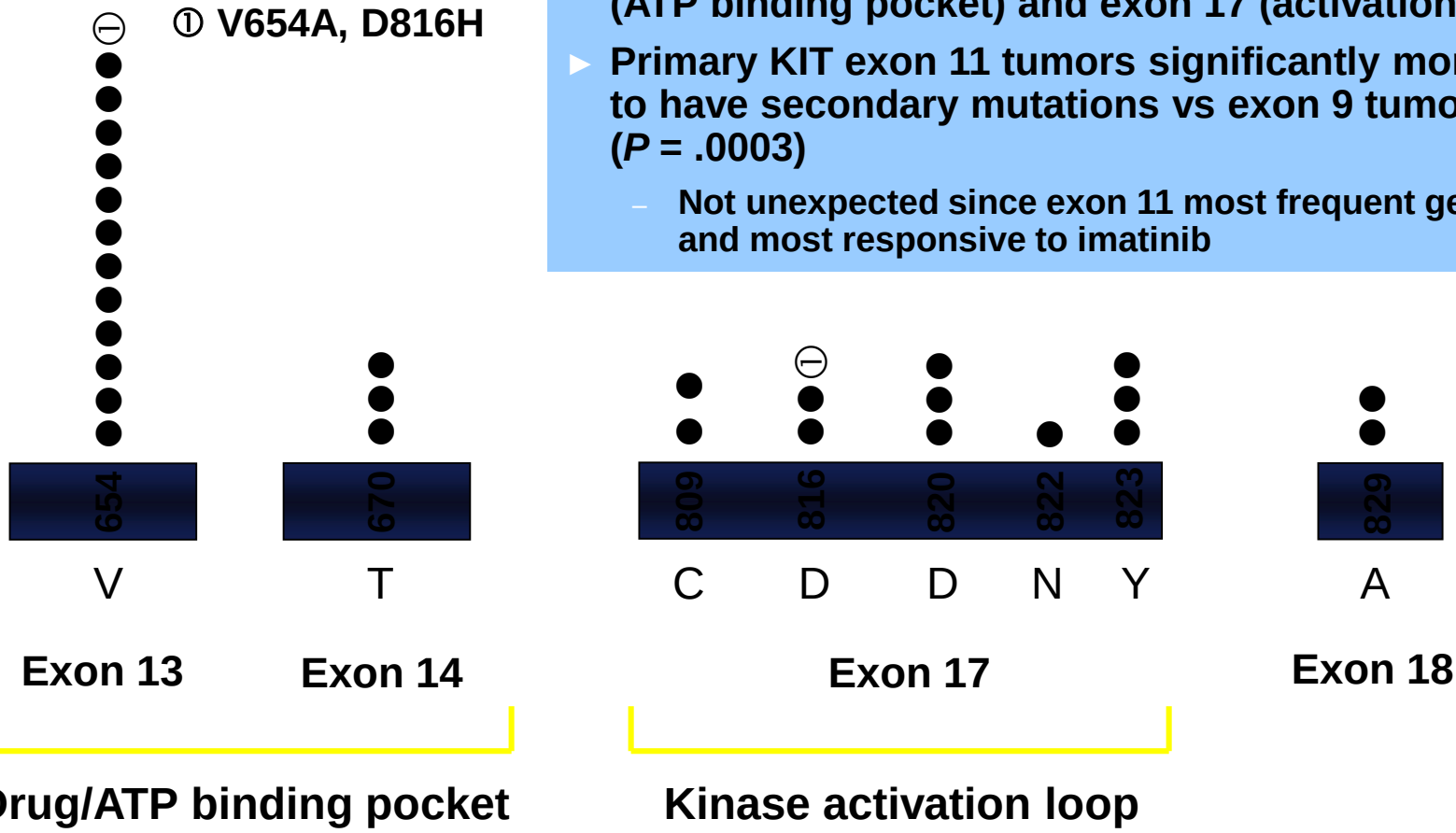
Mutational Subtype Has Prognostic Importance



DeMatteo RP, et al. *Cancer*. 2008;112(3):608-615.

Location and Frequency of Secondary *KIT* Mutations in the Phase I/II Study*

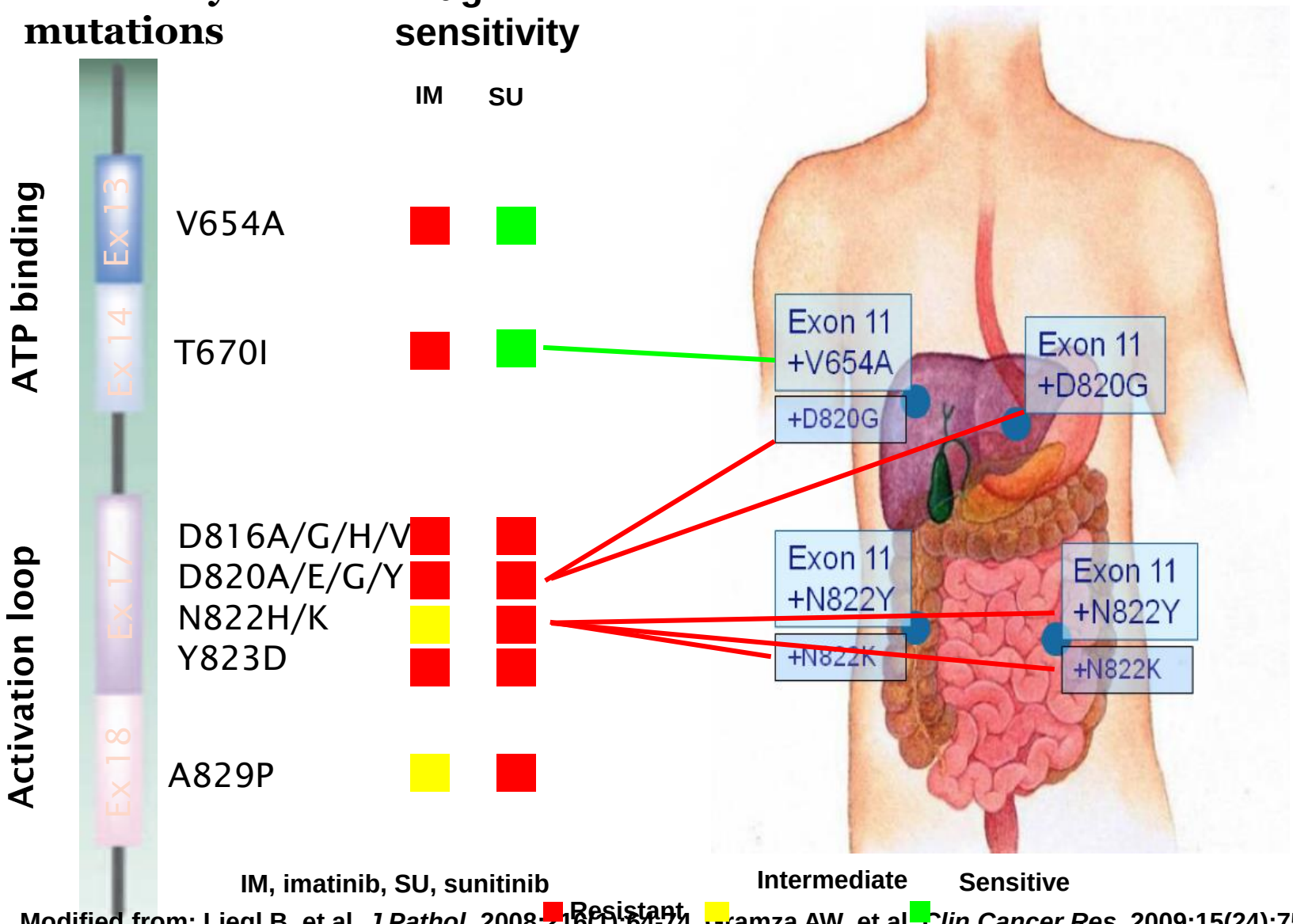
- Secondary mutations clustered around exons 13/14 (ATP binding pocket) and exon 17 (activation loop)
- Primary KIT exon 11 tumors significantly more likely to have secondary mutations vs exon 9 tumors (*P* = .0003)
  - Not unexpected since exon 11 most frequent genotype and most responsive to imatinib



*Analysis conducted on post-imatinib tissue specimens from 67 patients.

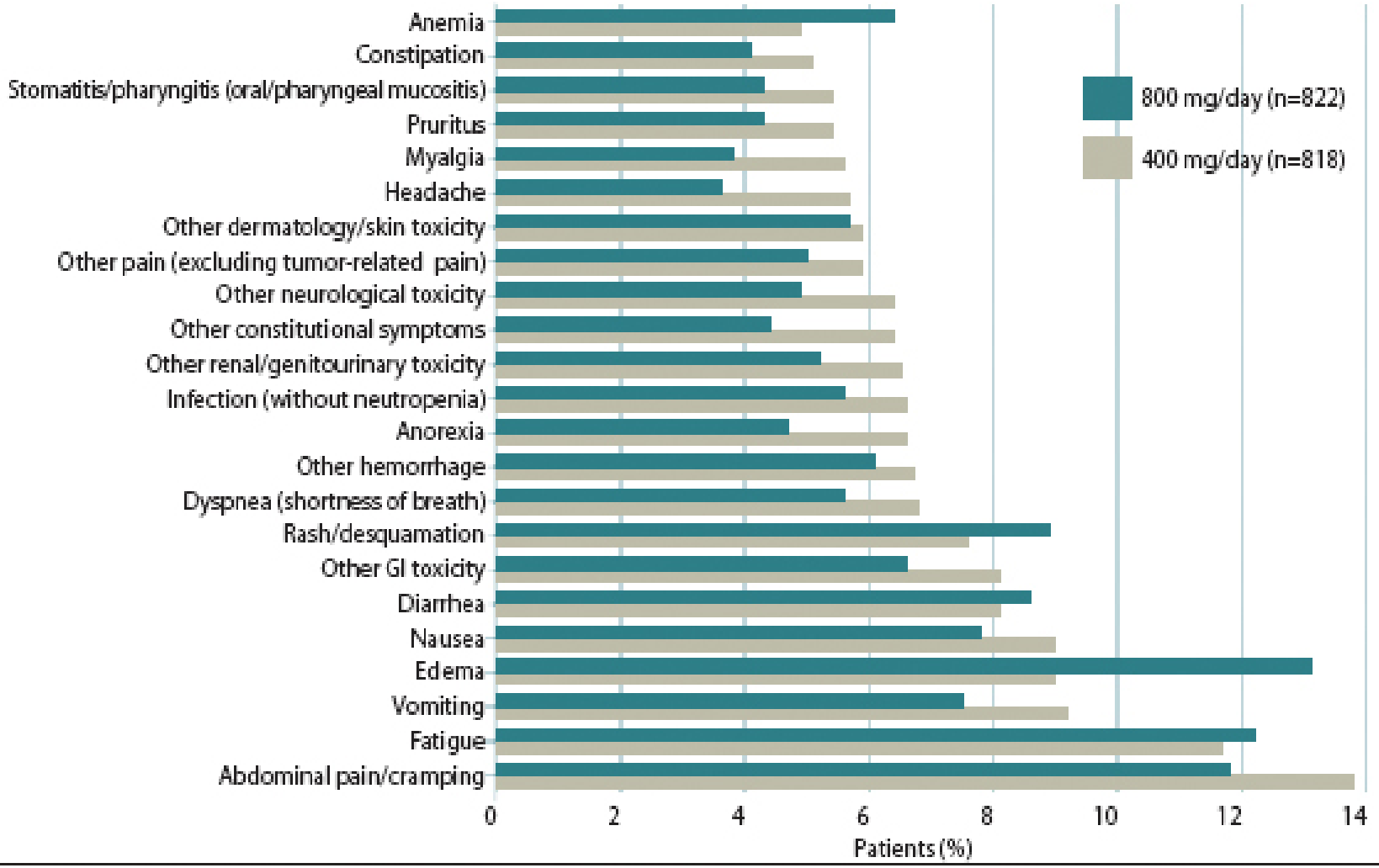
Heinrich MC, et al. *J Clin Oncol.* 2008;26(33):5352-5359.

Substantial Mutational Heterogeneity



Modified from: Liegl B, et al. *J Pathol.* 2008;216(1):64-74. Gramza AW, et al. *Clin Cancer Res*. 2009;15(24):7510-7518.

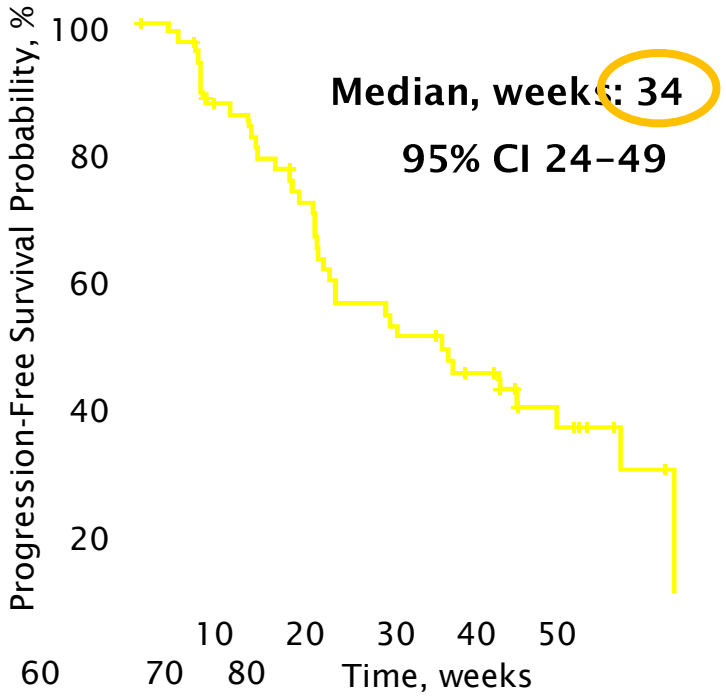
Incidence of ≥Grade 3 Adverse Effects to Imatinib in Patients With Advanced GIST



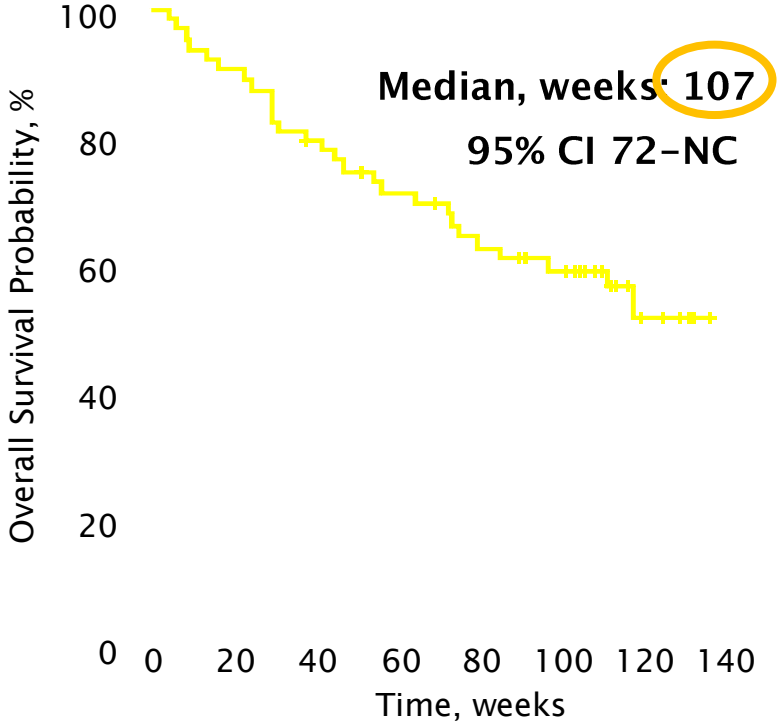
Demetri GD, et al. *J Natl Compr Canc Netw*. 2010;8 suppl 2:S1-S41.

PFS and OS With Continuous Dosing Schedule (CDD) of 37.5 mg of Sunitinib in Phase II Trial (N = 60)

Median PFS from CDD study[1]



Median OS from CDD Study[1]



	PFS of Phase III data[2]	OS of Phase III data[2]
Intermittent Sunitinib 50 mg (4/2)	Median, weeks: 22.9 (95% CI 10.9–28.00)	Median, weeks: 72.7 (95% CI 61.3–83.0)

1. George S, et al. *Eur J Cancer.* 2009;45(11):1959–1968. 2. Demetri GD, et al. *Clin Cancer Res.* 2012;18(11):3170-3179

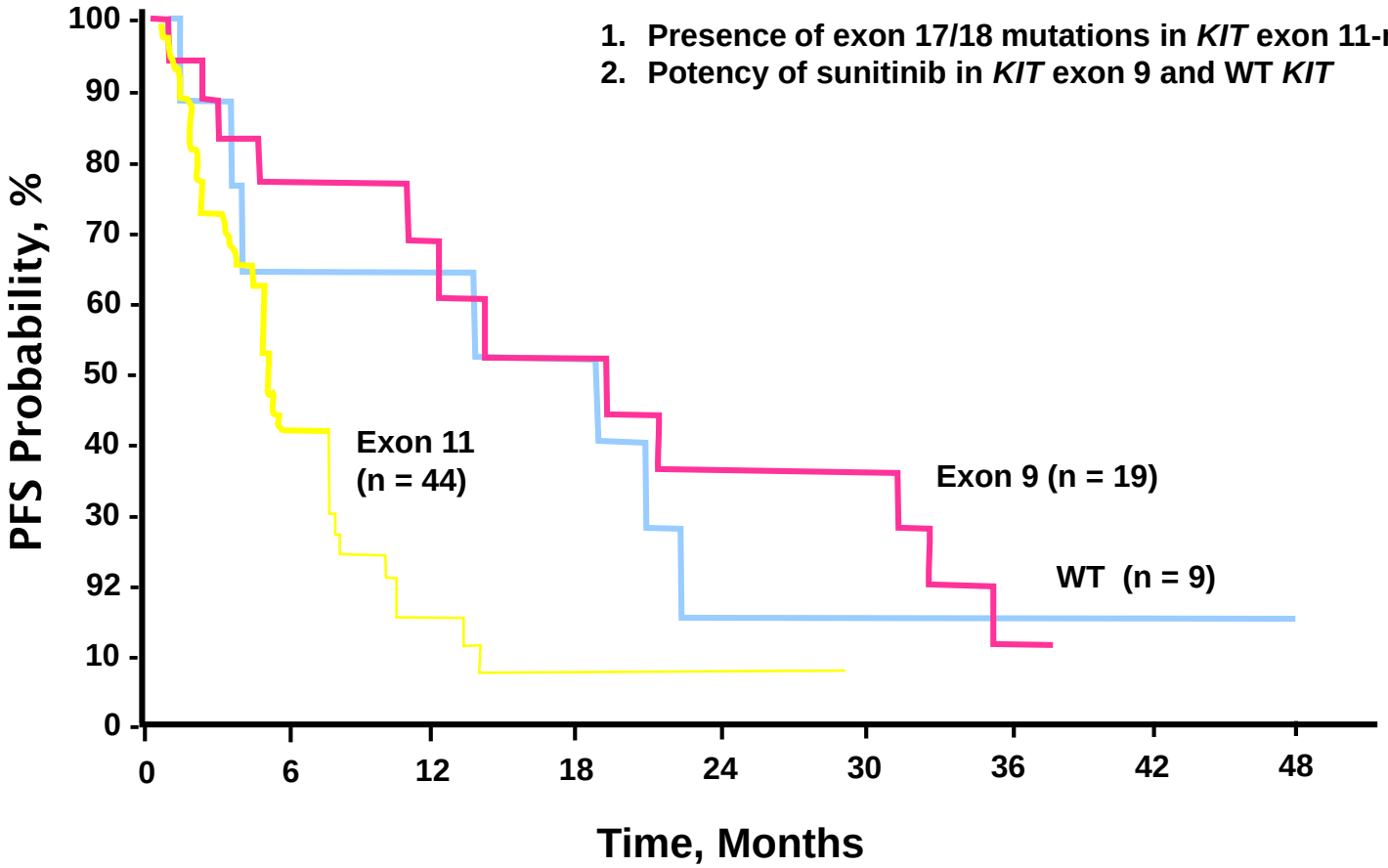
Most Common Treatment-Related AEs (≥20%) of Sunitinib in Patients Receiving Strict-Starting Dose Schedule (SSDS) vs Flexible Dose (FD): Incidence Overall and Adjusted for Duration of Treatment

	SSDS (n=602; total patient-years = 319)				FD (n=522; total patient-years = 725)			
	Any Grade*		Grade 3/4		Any Grade†		Grade 3/4	
AEs	N (%)	PPY	N (%)	PPY	N (%)	PPY	N (%)	PPY
Any treatment-related AE	519 (86)	163	199 (33)	62	513 (98)	71	383 (73)	53
Fatigue	176 (29)	55	19 (3)	6	303 (58)	42	78 (15)	11
Diarrhea	162 (27)	51	10 (2)	3	292 (56)	40	50 (10)	7
Hand–foot syndrome	123 (20)	39	16 (3)	5	239 (46)	33	105 (20)	14
Nausea	117 (19)	37	3 (<1)	1	209 (40)	29	20 (4)	3
Decreased appetite	113 (19)	35	7 (1)	2	189 (36)	26	18 (3)	2
Mucosal inflammation	99 (16)	31	6 (1)	2	157 (30)	22	16 (3)	2
Stomatitis	94 (16)	29	2 (<1)	1	164 (31)	23	20 (4)	3
Hypertension	91 (15)	29	17 (3)	5	196 (38)	27	57 (11)	8
Vomiting	90 (15)	28	7 (1)	2	157 (30)	22	21 (4)	3
Dysgeusia	76 (13)	24	0 (0)	0	104 (20)	14	0 (0)	0
Thrombocytopenia	79 (13)	25	20 (3)	6	143 (27)	20	42 (8)	6
Neutropenia	72 (12)	23	23 (4)	7	139 (27)	19	66 (13)	9
Anemia	66 (11)	21	29 (5)	9	116 (22)	16	32 (6)	4
Skin discoloration	66 (11)	21	0 (0)	0	108 (21)	15	1 (<1)	<1
Rash	57 (9)	18	3 (<1)	1	119 (23)	16	9 (2)	1
Hypothyroidism	28 (5)	9	4 (1)	1	116 (22)	16	8 (2)	1

PPY = patients per patient-year; *eleven grade 5 AEs deemed to be treatment-related occurred in the SSDS group
†Six grade 5 AEs deemed related to treatment occurred in the FD group

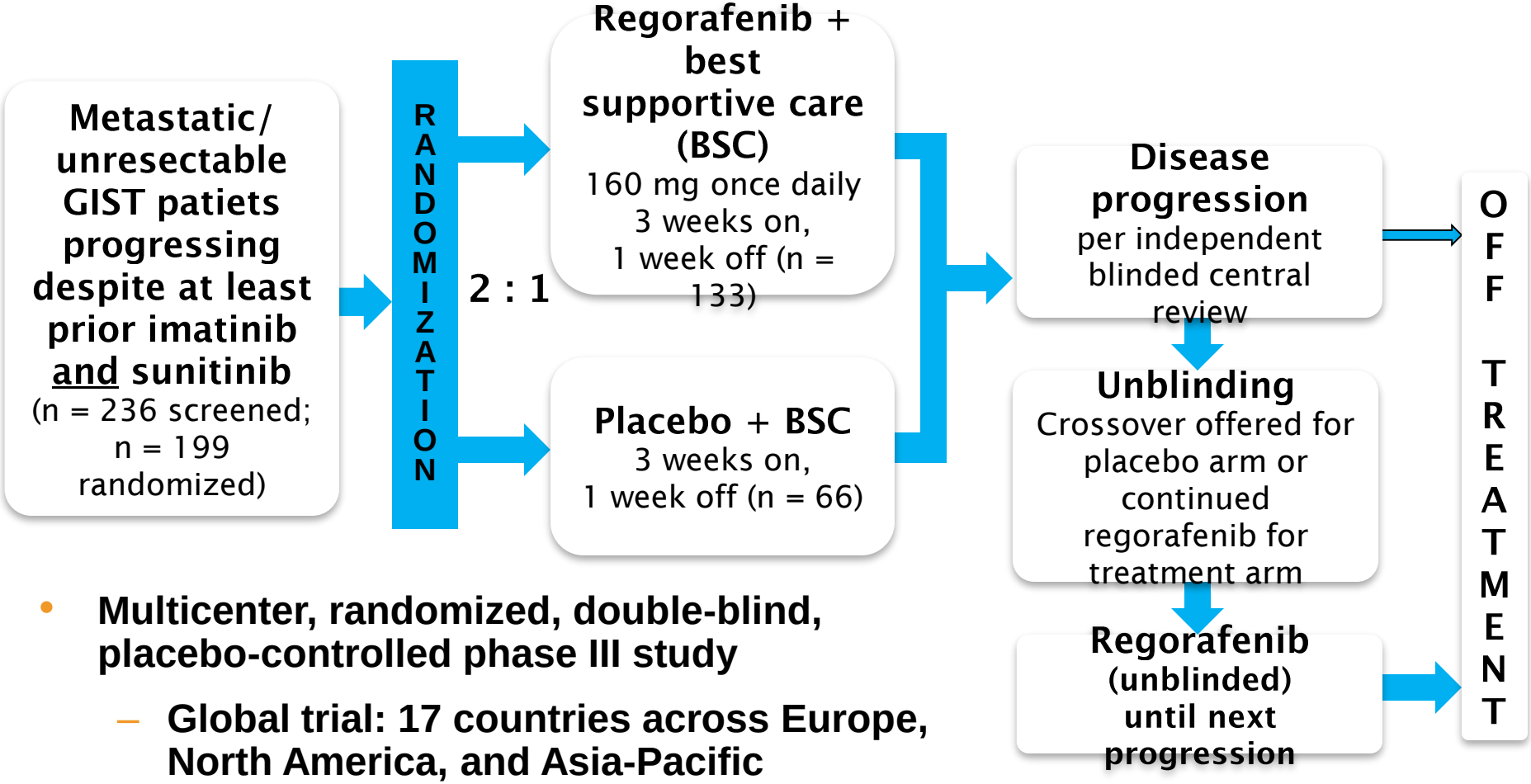
Reichardt P, et al. *Eur J Cancer.* 2011;47 (Suppl1): Abstract 9421.

Progression-Free Survival on Sunitinib in Imatinib-Resistant / Intolerant GIST



Heinreich MC, et al. *J Clin Oncol.* 2008;26(33):5352-5359.

GIST: Regorafenib In Progressive Disease (GRID)—Study Design



- **Multicenter, randomized, double-blind, placebo-controlled phase III study**
  - **Global trial: 17 countries across Europe, North America, and Asia-Pacific**
  - **Stratification: treatment line (2 *vs* >2 prior lines), geographical location (Asia *vs* "Rest of World")**

Demetri G, et al. *Lancet.* 2013;381(9863):295-302.

GRID—Adverse Events

	Regorafenib N = 132		Placebo N = 66	
	Grade 3	Grade 4	Grade 3	Grade 4
Any event	77 (58%)	2 (2%)	5 (8%)	1 (2%)
Hand-foot skin reaction	26 (20%)	0	0	0
Hypertension	30 (23%)	1 (1%)	2 (3%)	0
Diarrhea	7 (5%)	0	0	0
Fatigue	3 (2%)	0	0	0
Oral mucositis	2 (2%)	0	1 (2%)	0
Alopecia	2 (2%)	0	0	0
Hoarseness	0	0	0	0
Anorexia	0	0	0	0
Rash, maculopapular	3 (2%)	0	0	0
Nausea	1 (1%)	0	1 (2%)	0
Constipation	1 (1%)	0	0	0
Myalgia	1 (1%)	0	0	0
Voice alteration	0	0	0	0

Data are n (%). *Excluding one patient who did not receive study treatment.

Demetri G, et al. *Lancet.* 2013;381(9863):295-302.