Gastrointestinal Stromal Tumor
Advanced Disease

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SYLVESTER
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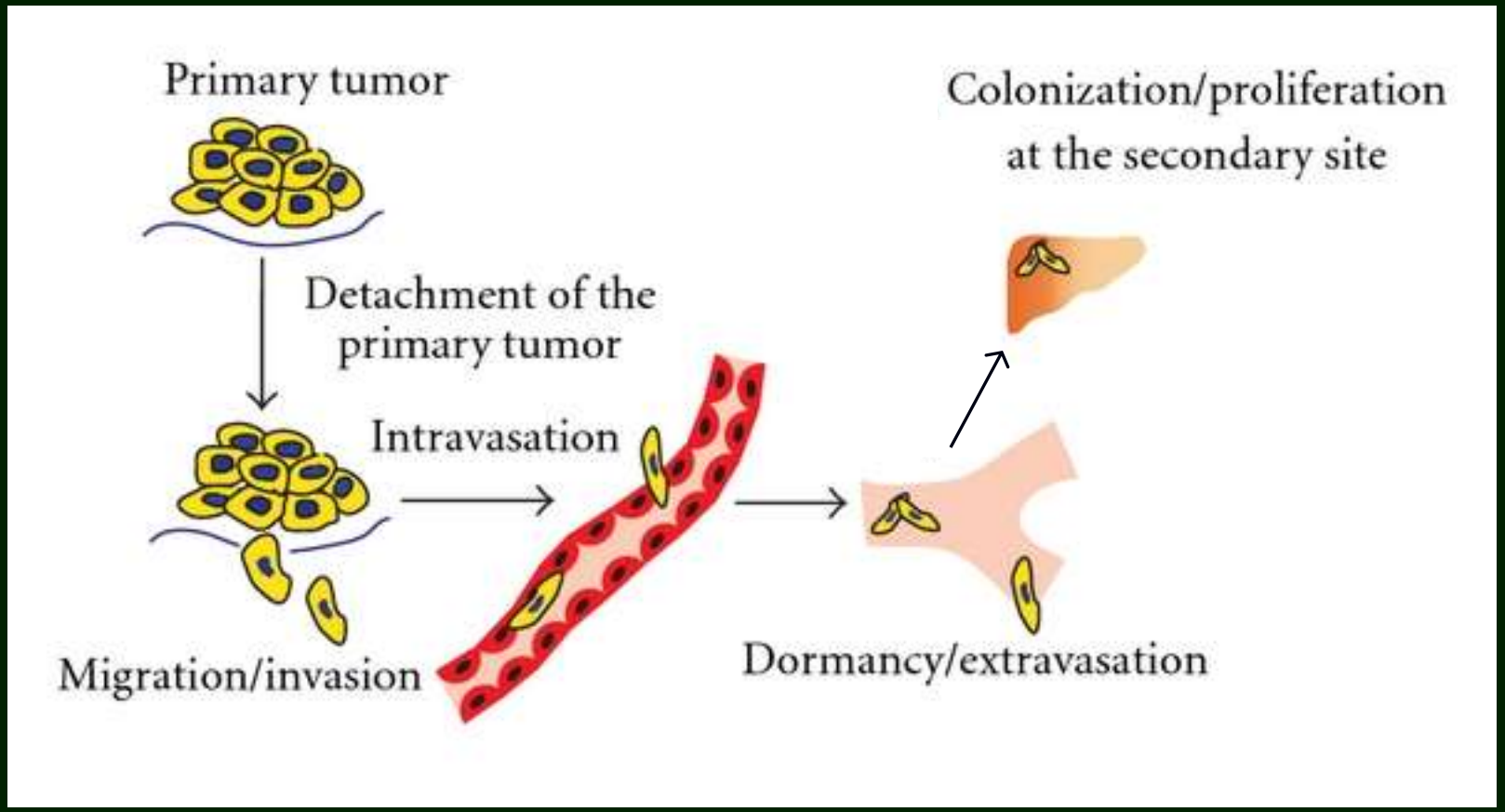
UNIVERSITY OF MIAMI HEALTH SYSTEM

Metastasis in GIST



Metastatic Sites

Liver

Peritoneum

Bone

Lymph nodes

Lung

Brain

Heart

Skin

GIST

Chemotherapy Trials

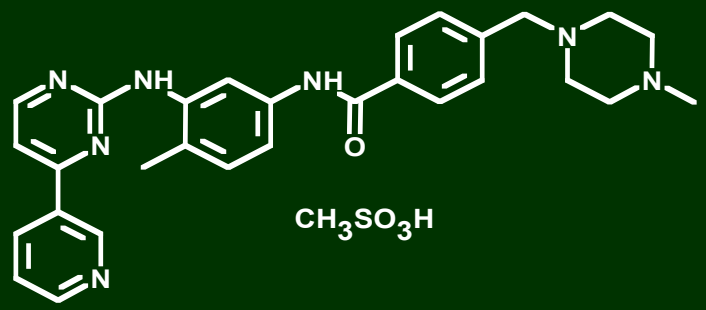
Regimen	Number of Patients	Partial Response n (%)
DOX + DTIC	43	3 (7%)
DOX + DTIC +/– IF	60	10 (15%)
IF + VP-16	10	0 (0%)
Paclitaxel	15	1 (7%)
Gemcitabine	17	0 (0%)
Liposomal DOX	15	0 (0%)
DOX	12	0 (0%)
DOX or docetaxel	9	0 (0%)
High-dose IF	26	0 (0%)
EPI + IF	13	0 (0%)
Various	40	4 (10%)
DTIC/MMC/DOX/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

EORTC 1st Line Chemotherapy: Active Single Agents or Combinations

Van Glabbeke, ASCO 2001

Median Overall Survival in Metastatic GIST

Imatinib Mesylate



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

MW: 589.7

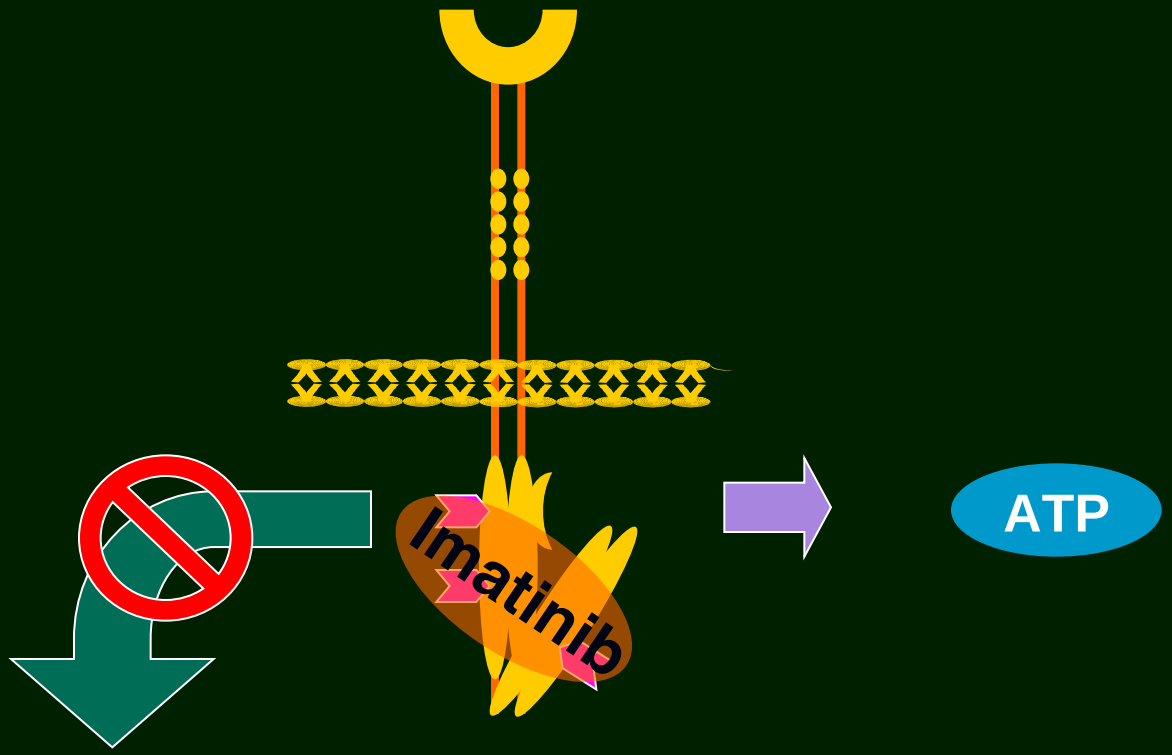
- Rational drug design
  - 2-phenylamino pyrimidine
  - Based on structure of ATP binding site
  - Highly water soluble
  - Oral bioavailability

Inhibitor of selective tyrosine kinases

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

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

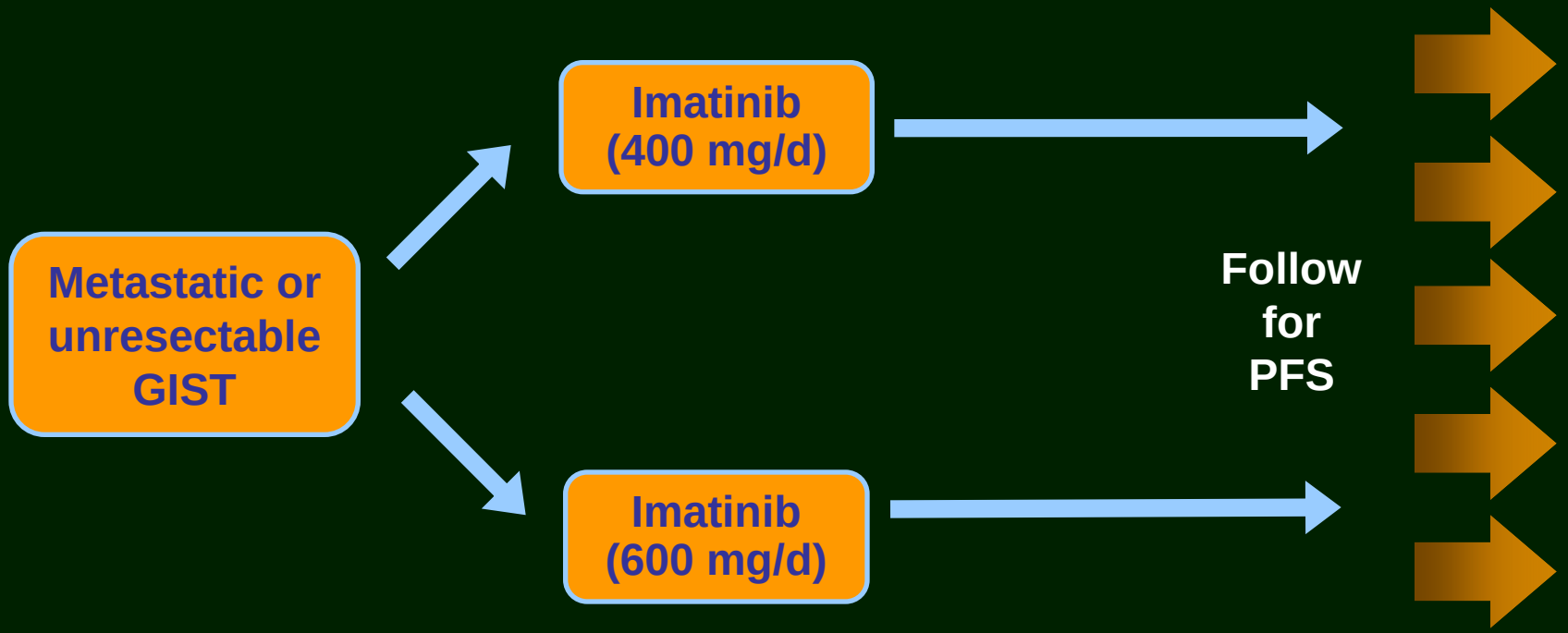
Kit Receptor Phenotype



Proliferation
Survival
Adhesion
Invasion
Metastasis
Angiogenesis

= imanitib contact point

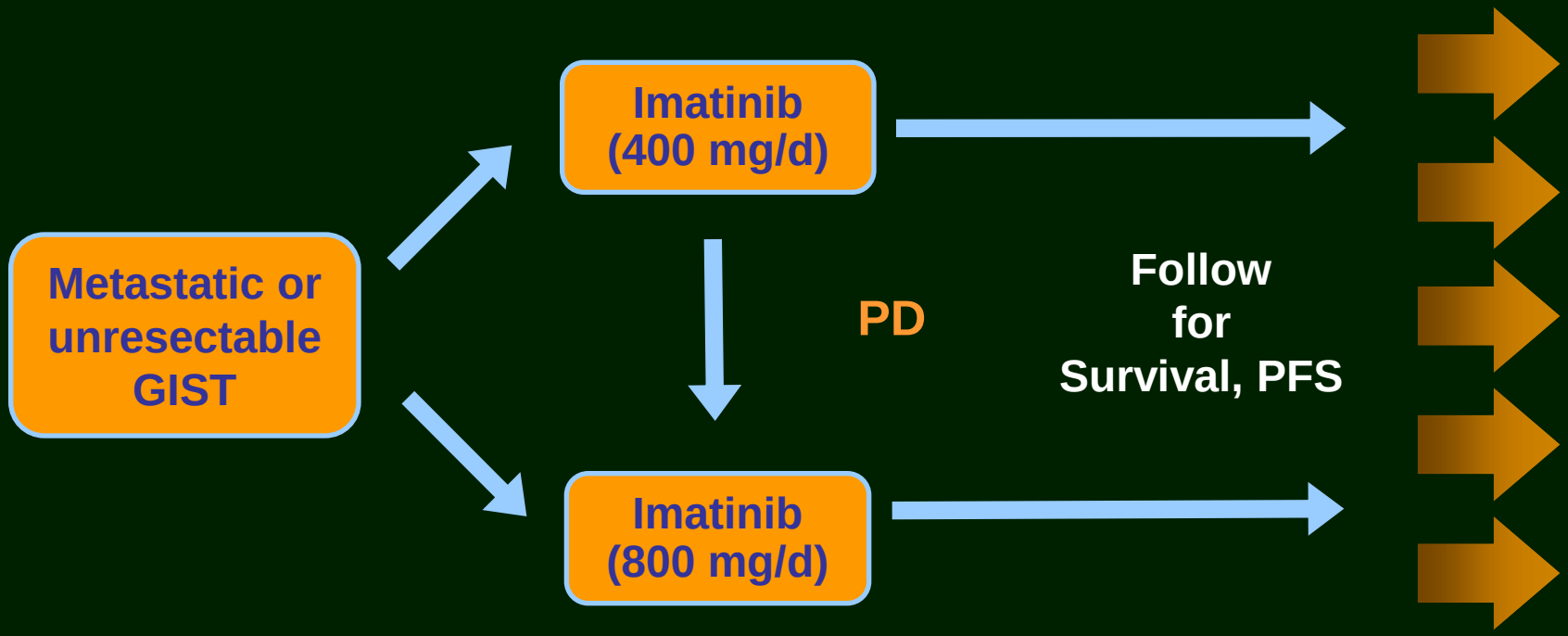
Ph II Trial: 400 mg/d vs 600 mg/d Imatinib in Advanced GIST



Demetri et al.

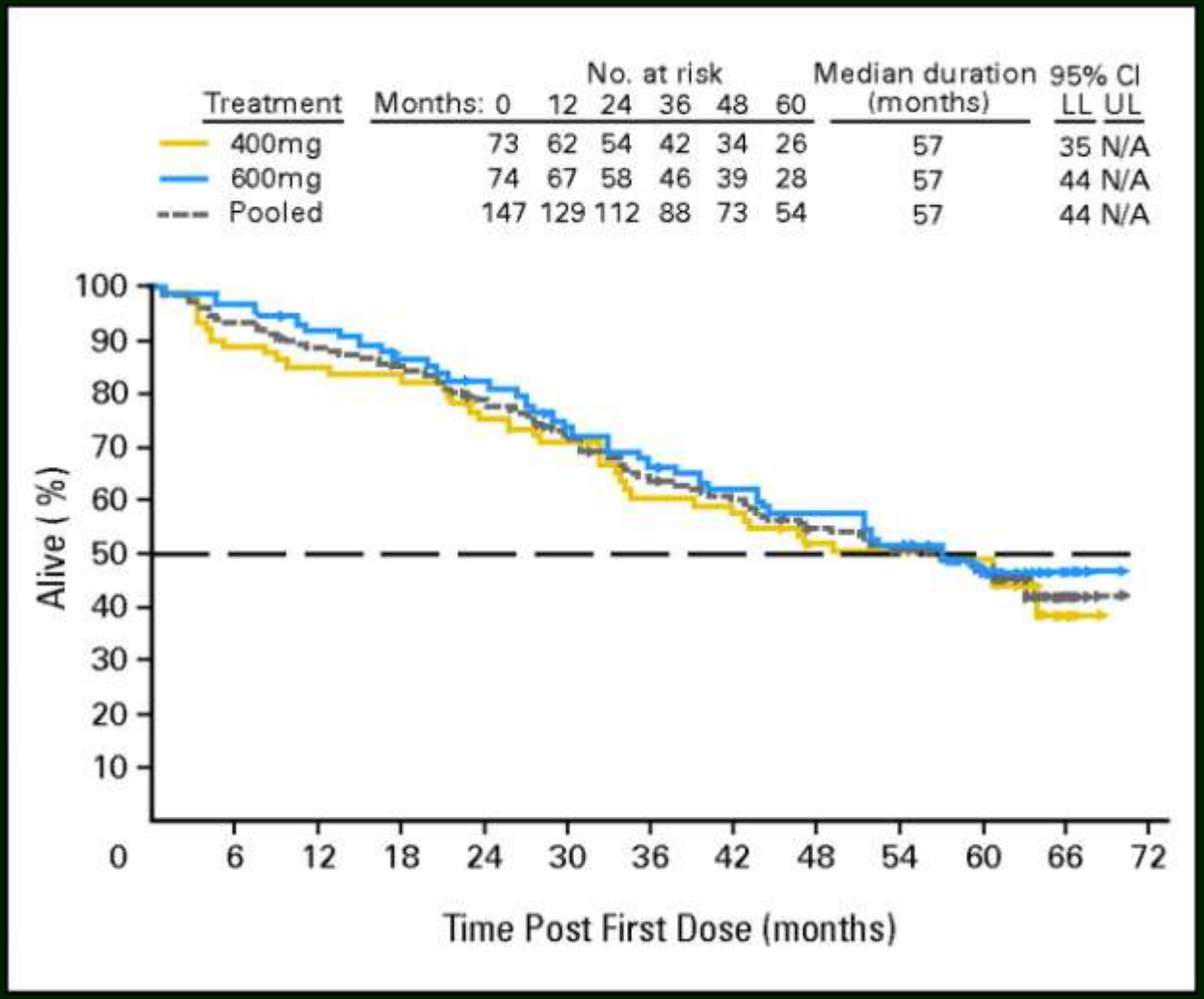
Ph III Trials: 400 mg/d vs 800 mg/d Imatinib in Advanced GIST

- US Intergroup SWOG S0033 Study
- EORTC 62005 Study



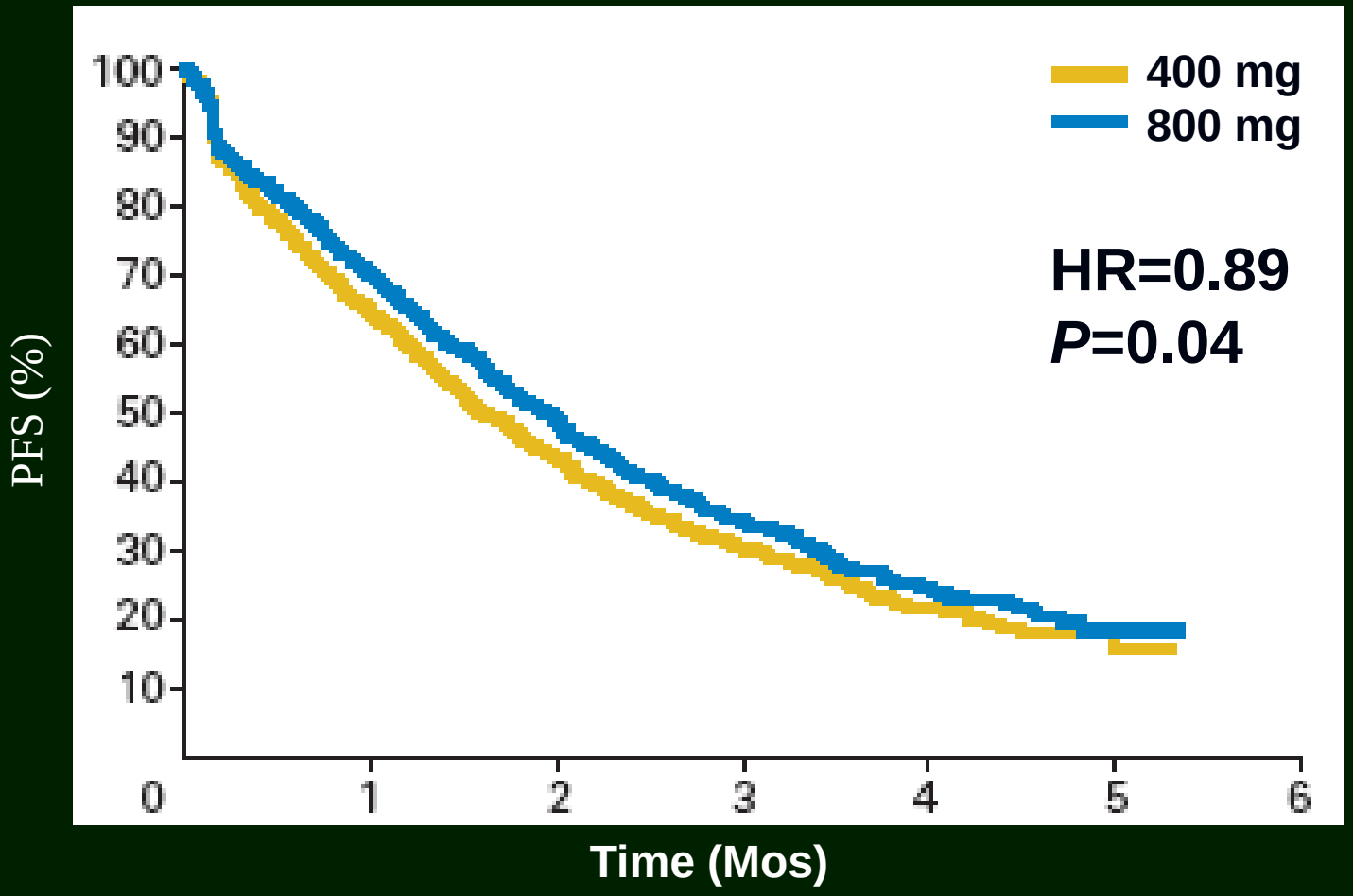
Benjamin RS et al. *Proc Am Soc Clin Oncol.* 2003;22:814. Abst. 3271.
Rankin C et al. *Proc Am Soc Clin Oncol.* 2004;23:815. Abst. 9005.
Verweij J et al. *Proc Am Soc Clin Oncol.* 2003;22:814. Abst. 3272.
Blanke C et al. *J Clin Oncol;* 2008;26:620

Overall Survival



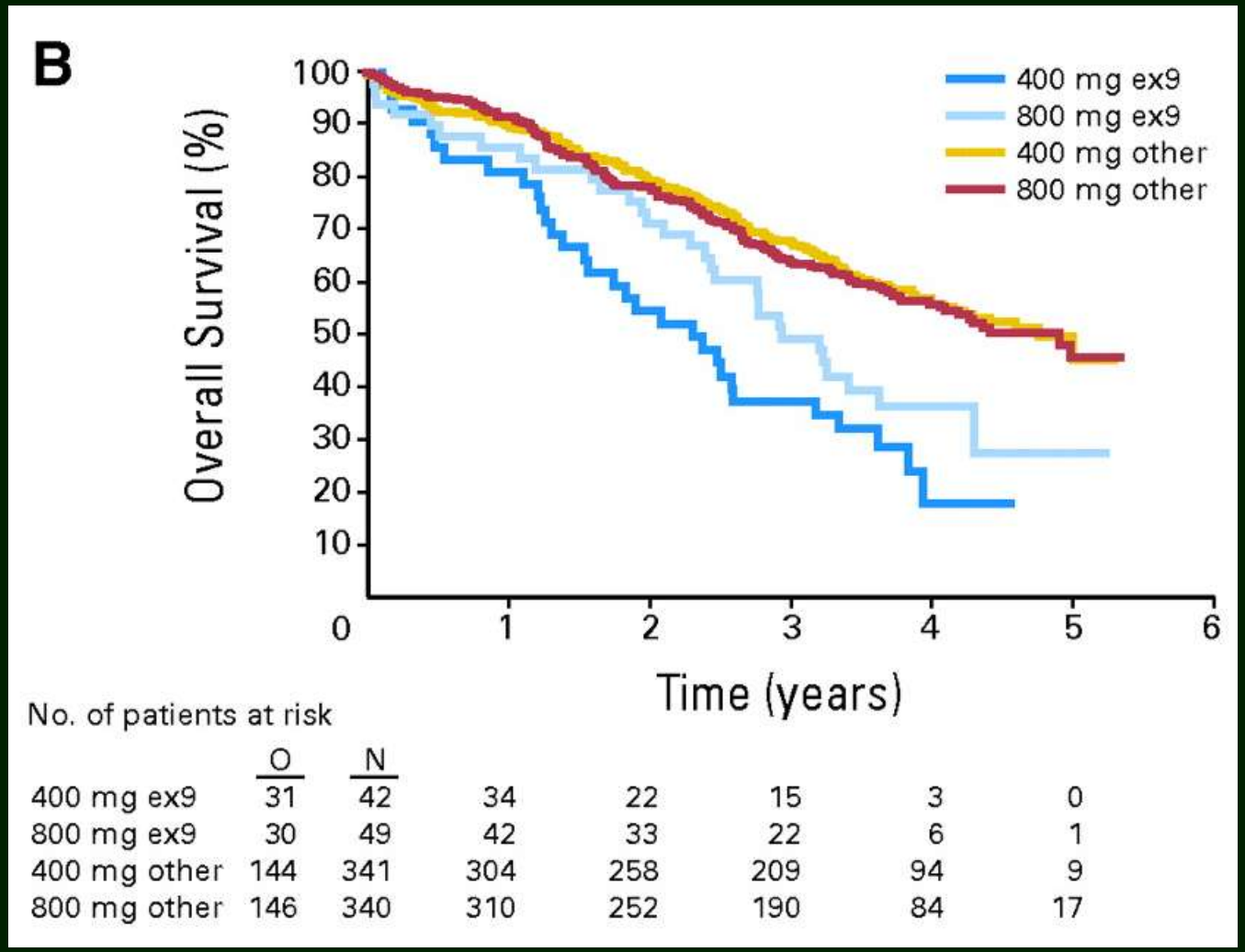
Blanke, C. D. et al. J Clin Oncol; 26:620-625 2008

MetaGIST: PFS



Reproduced with permission from Gastrointestinal Stromal Tumor Meta-Analysis Group (MetaGIST). *J Clin Oncol*. 2010;28:1247.

Tumor Genotype and Imatinib Dose Selection



No. of patients at risk

	O	N					
400 mg ex9	31	42	34	22	15	3	0
800 mg ex9	30	49	42	33	22	6	1
400 mg other	144	341	304	258	209	94	9
800 mg other	146	340	310	252	190	84	17

Reproduced with permission from Gastrointestinal Stromal Tumor Meta-Analysis Group (MetaGIST). *J Clin Oncol*. 2010;28:1247.

GIST Evaluation

- Every 2-4 months
- 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 2-4 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.

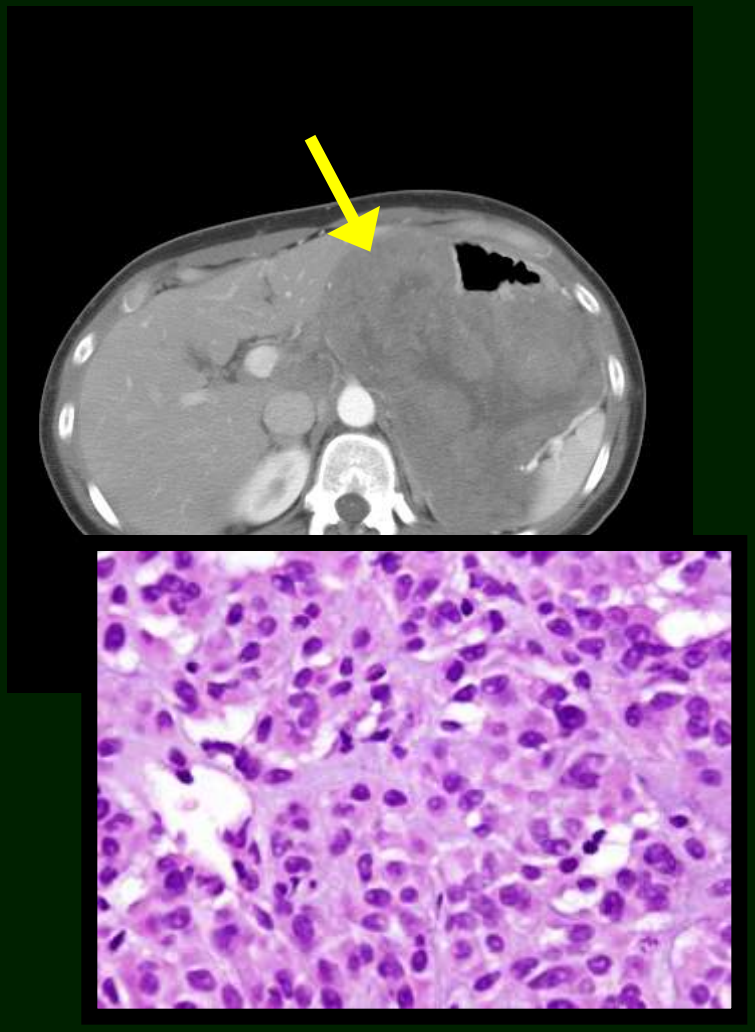
Side effects: 400 vs. 800 mg

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

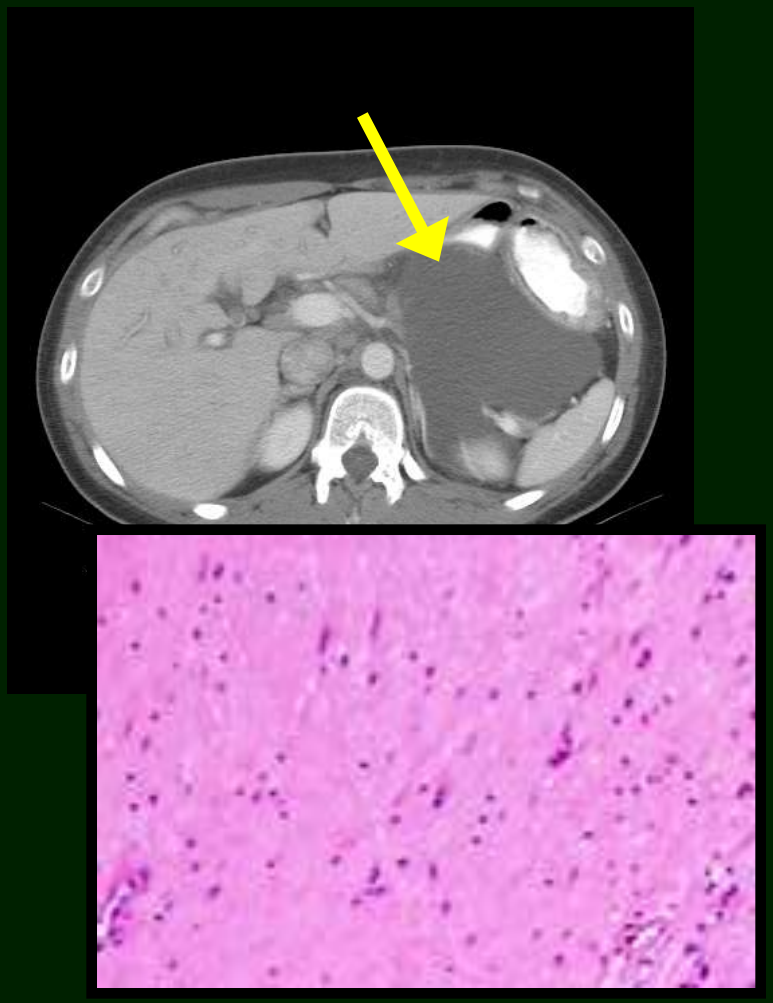
Verweij et al, 2004

Response to Therapy

GIST Response

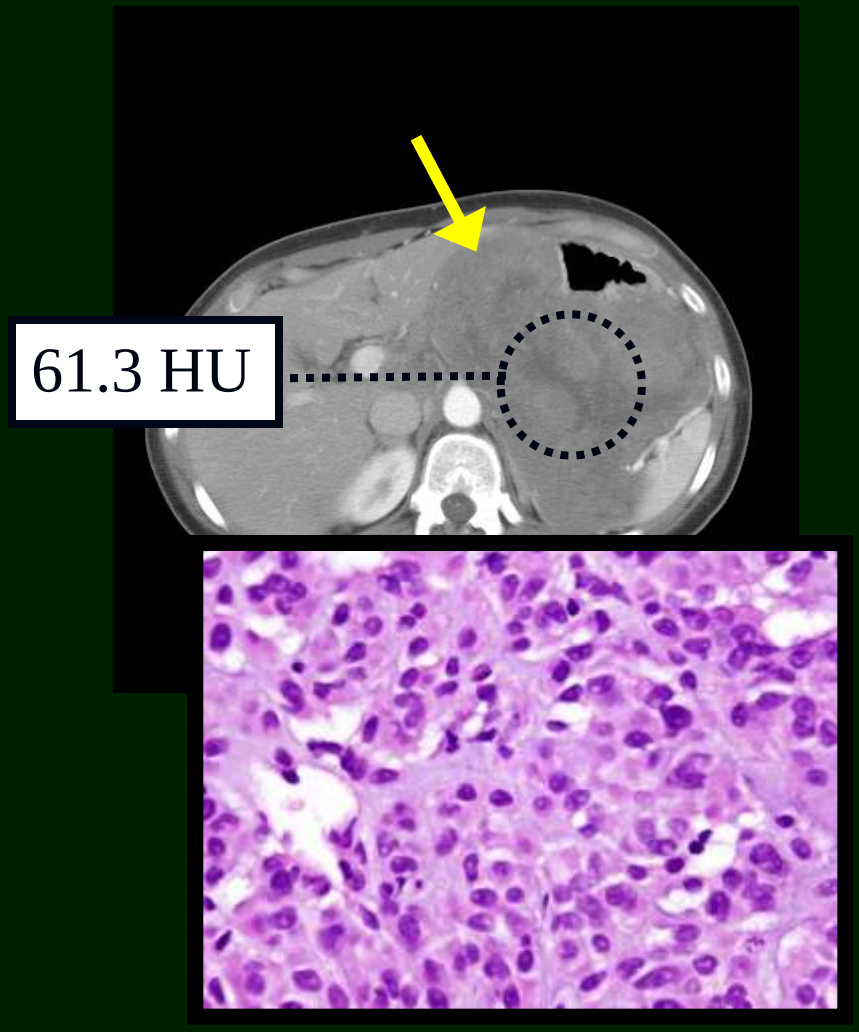


Pre-Imatinib

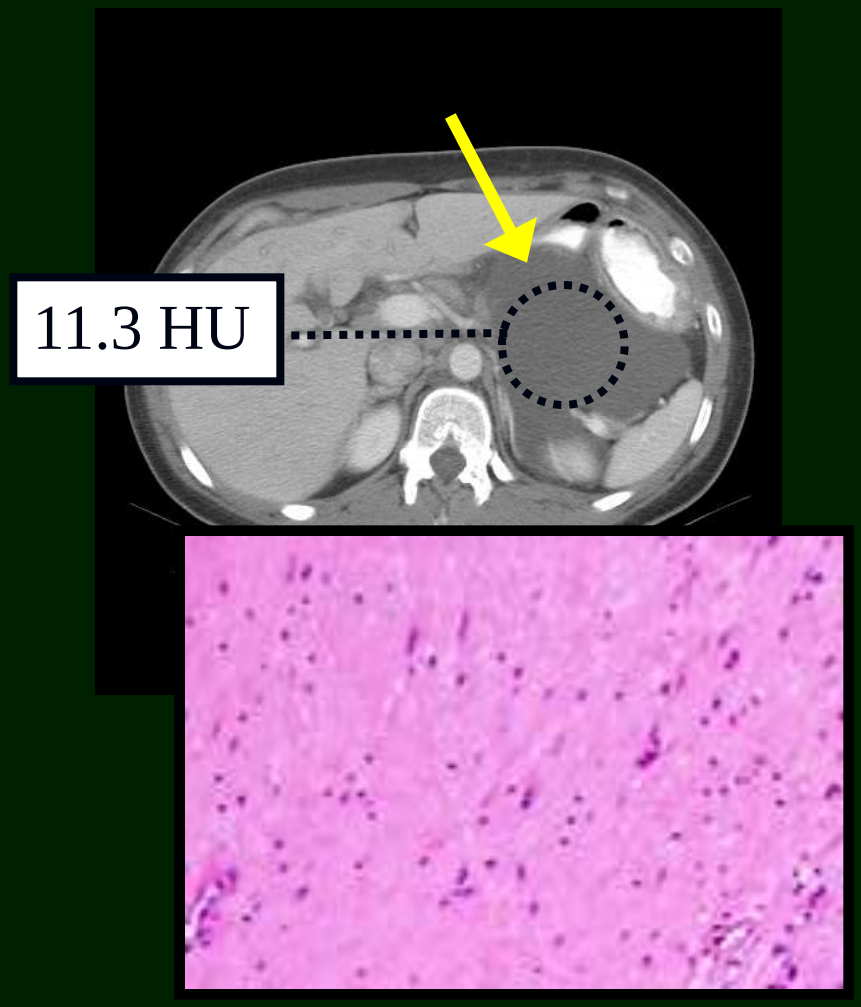


Post-Imatinib (8 weeks therapy)

GIST Response



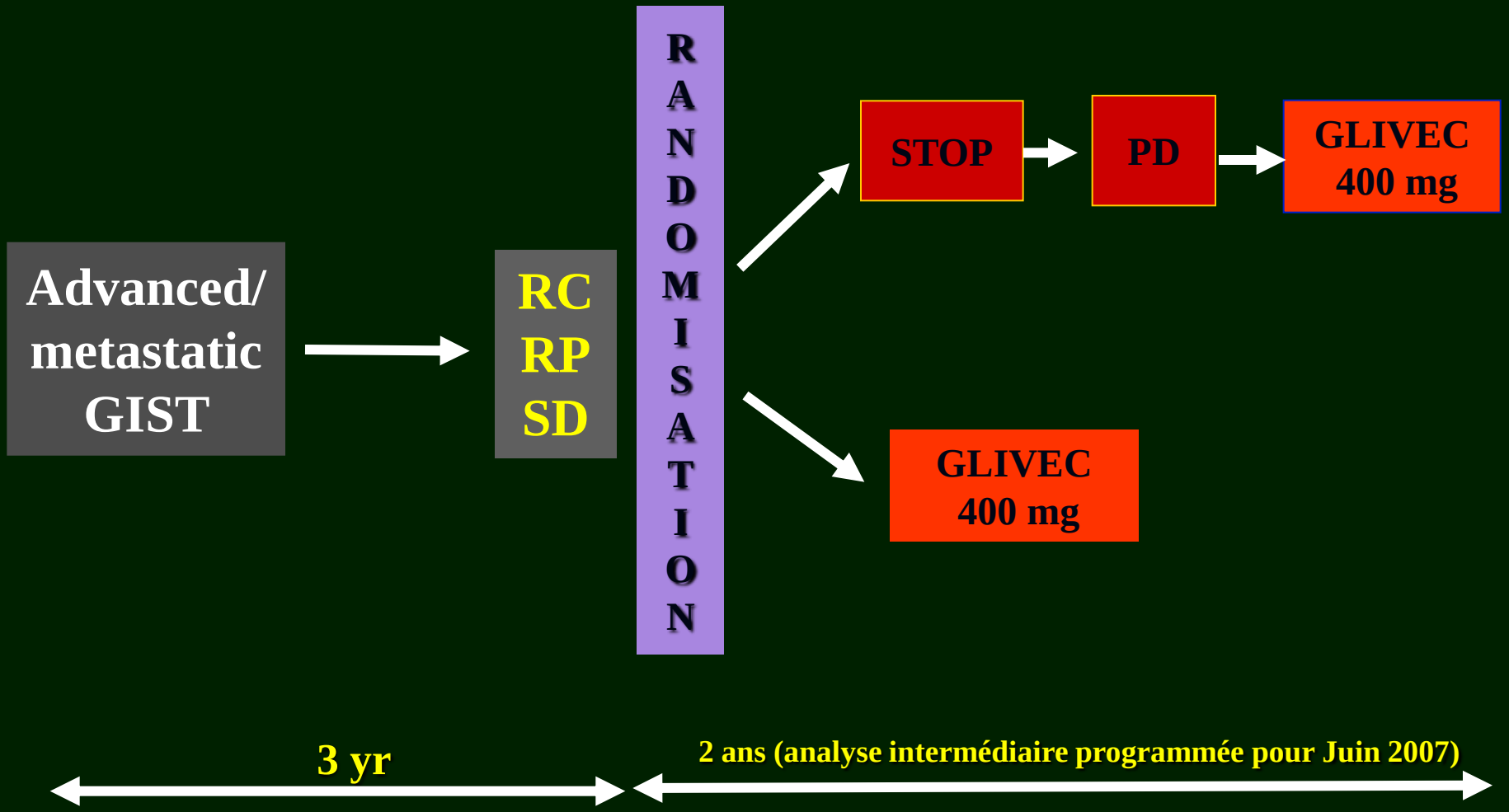
Pre-Imatinib



Post-Imatinib
(8 weeks therapy)

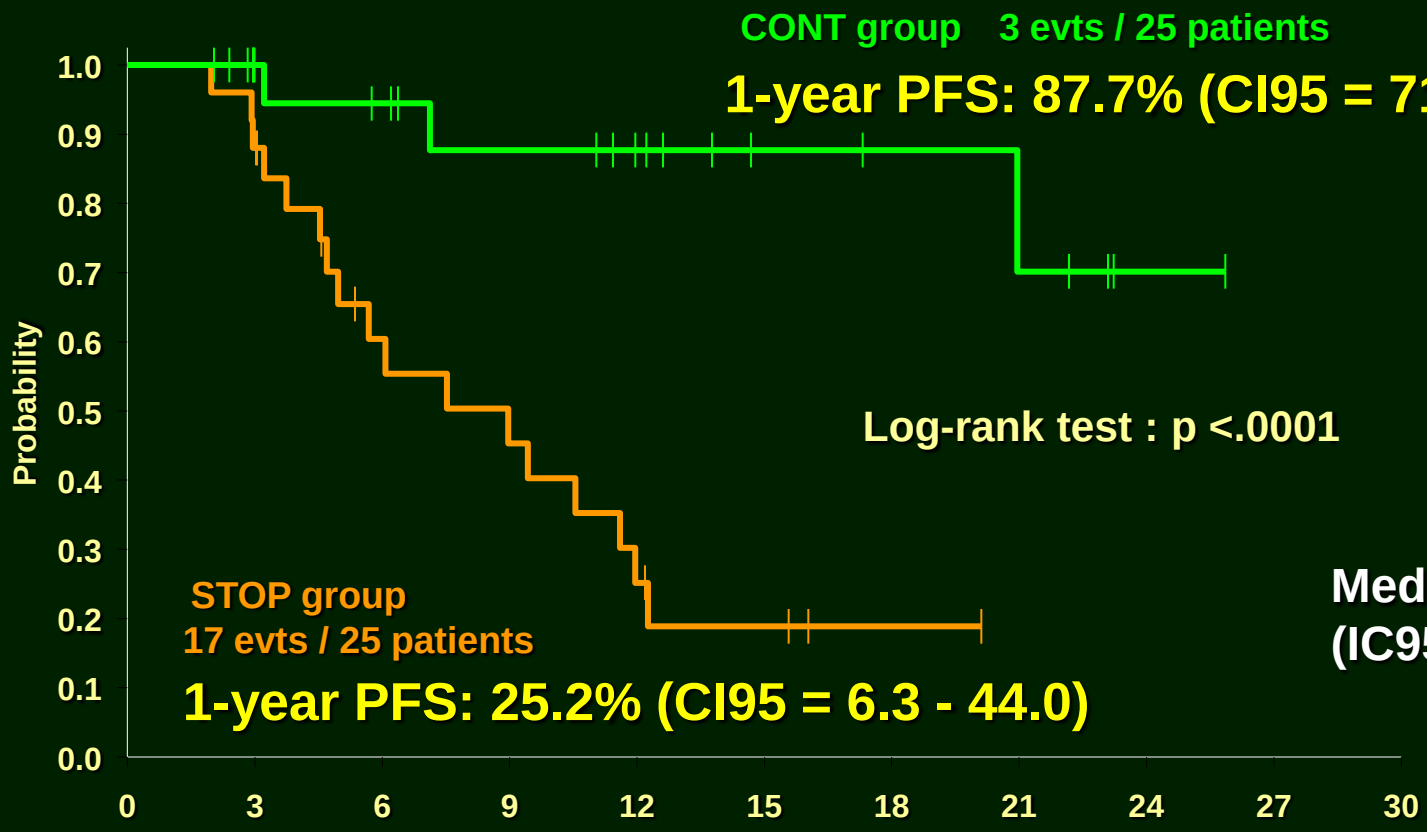
Continuous Target Inhibition

BFR14 3-yr randomization



BFR14 3-yr randomization

Progression Free Survival



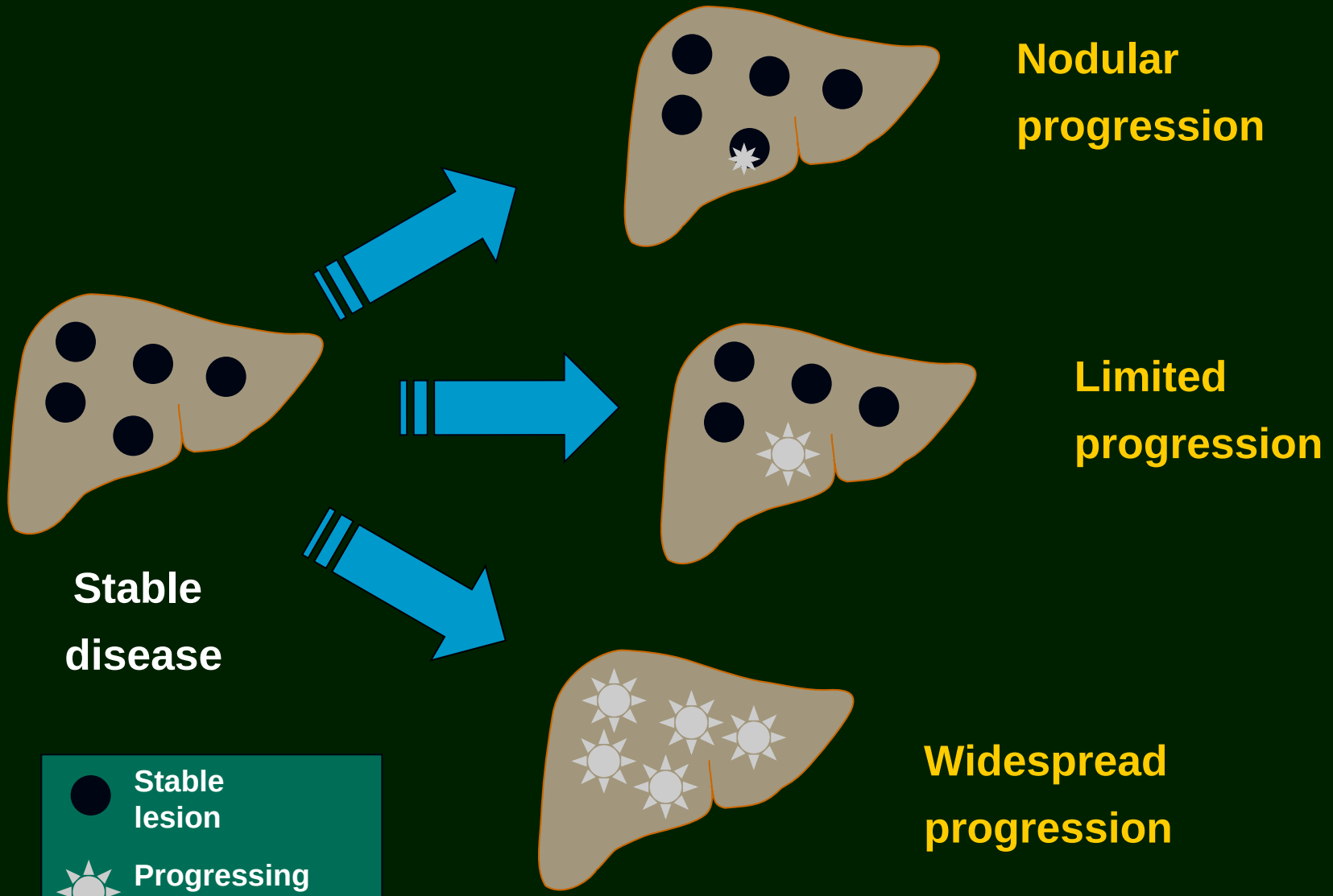
Median f.u.: 11 m
(IC95: 4.8 – 13.8)

Rate of PD in STOP group

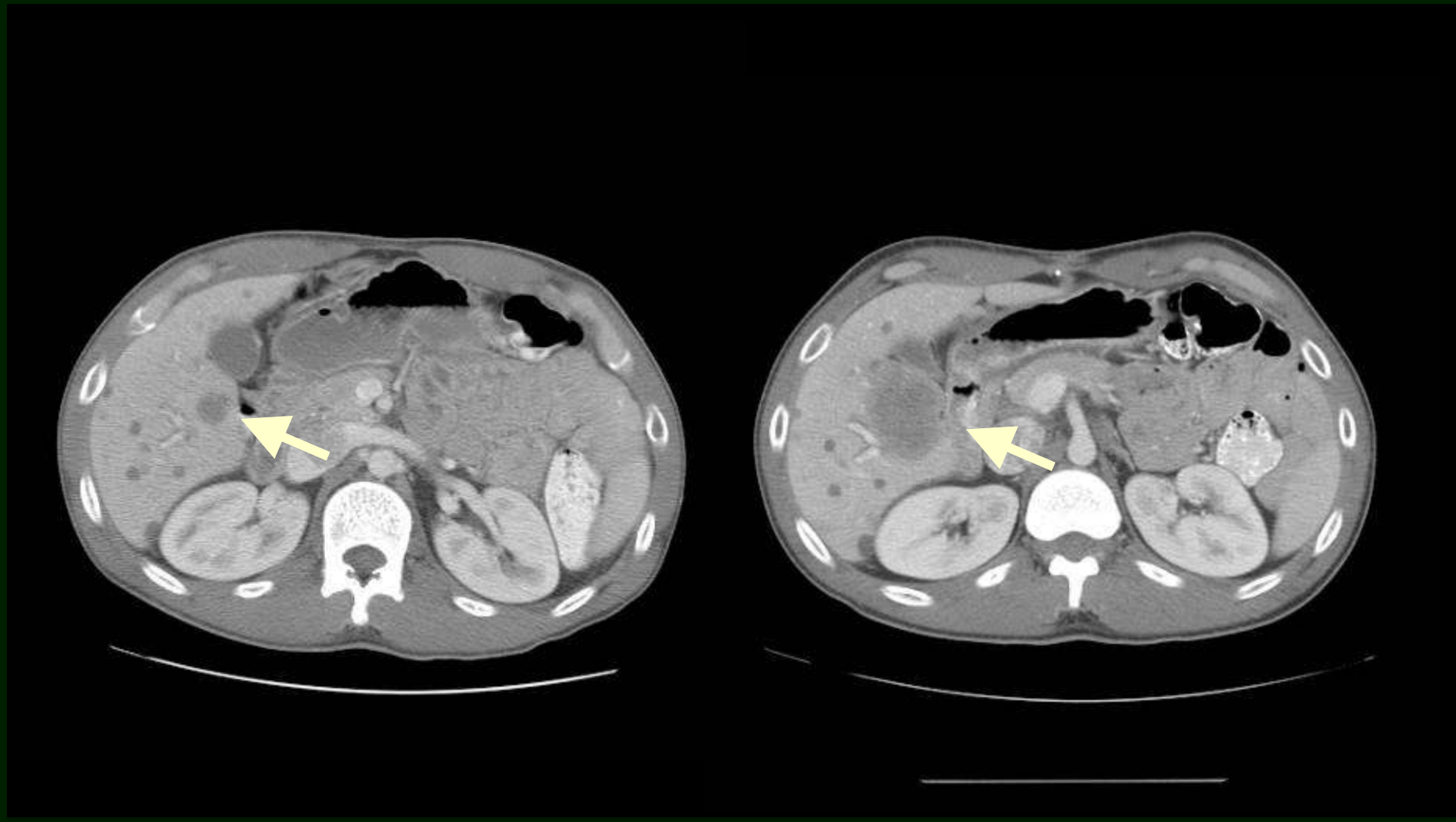
at 6 months: 40%
at 9 months: 55%
at 1 year: 75%

Progression of Disease

Type of Progression



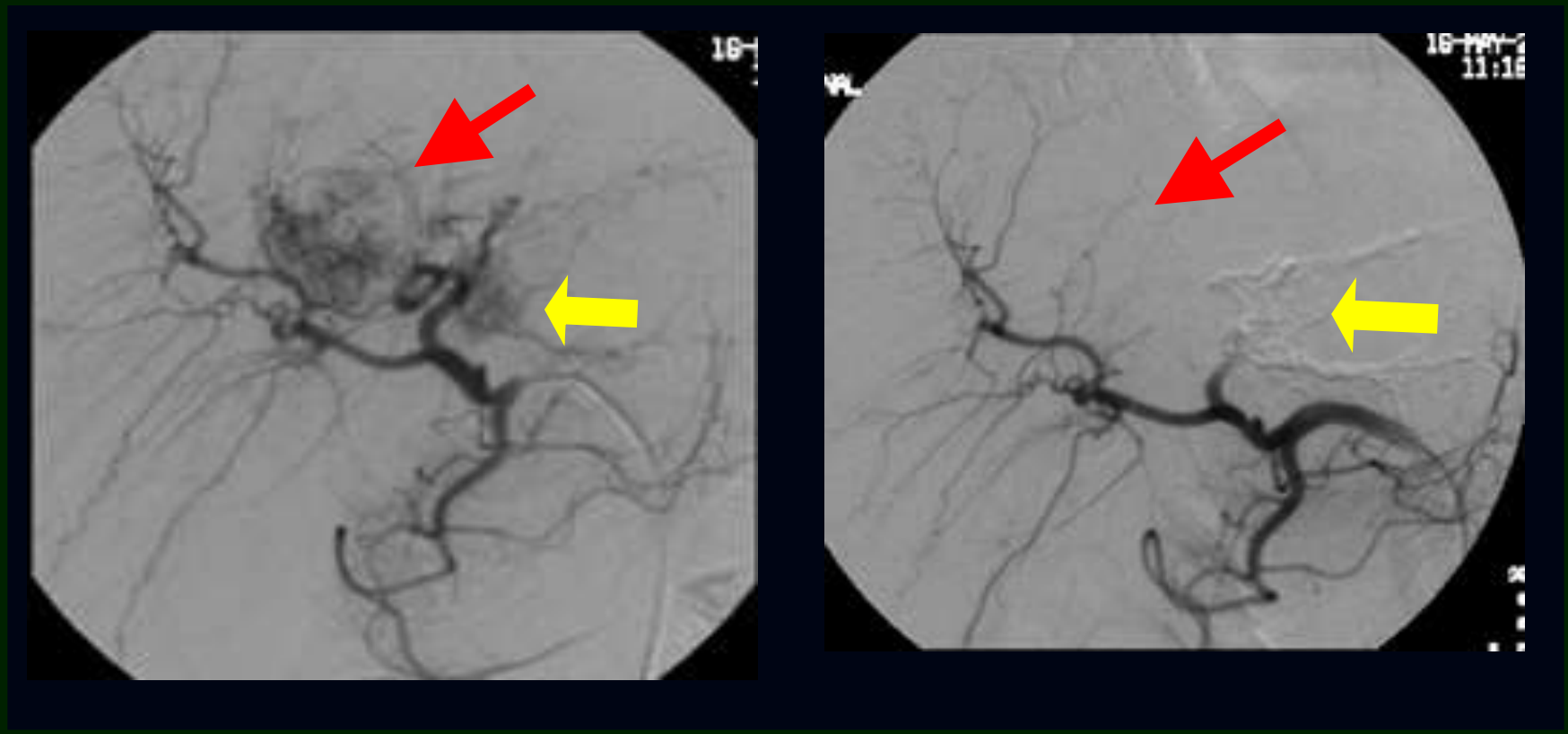
Limited Progression



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
  - Clinical Trial

Hepatic Artery Embolization



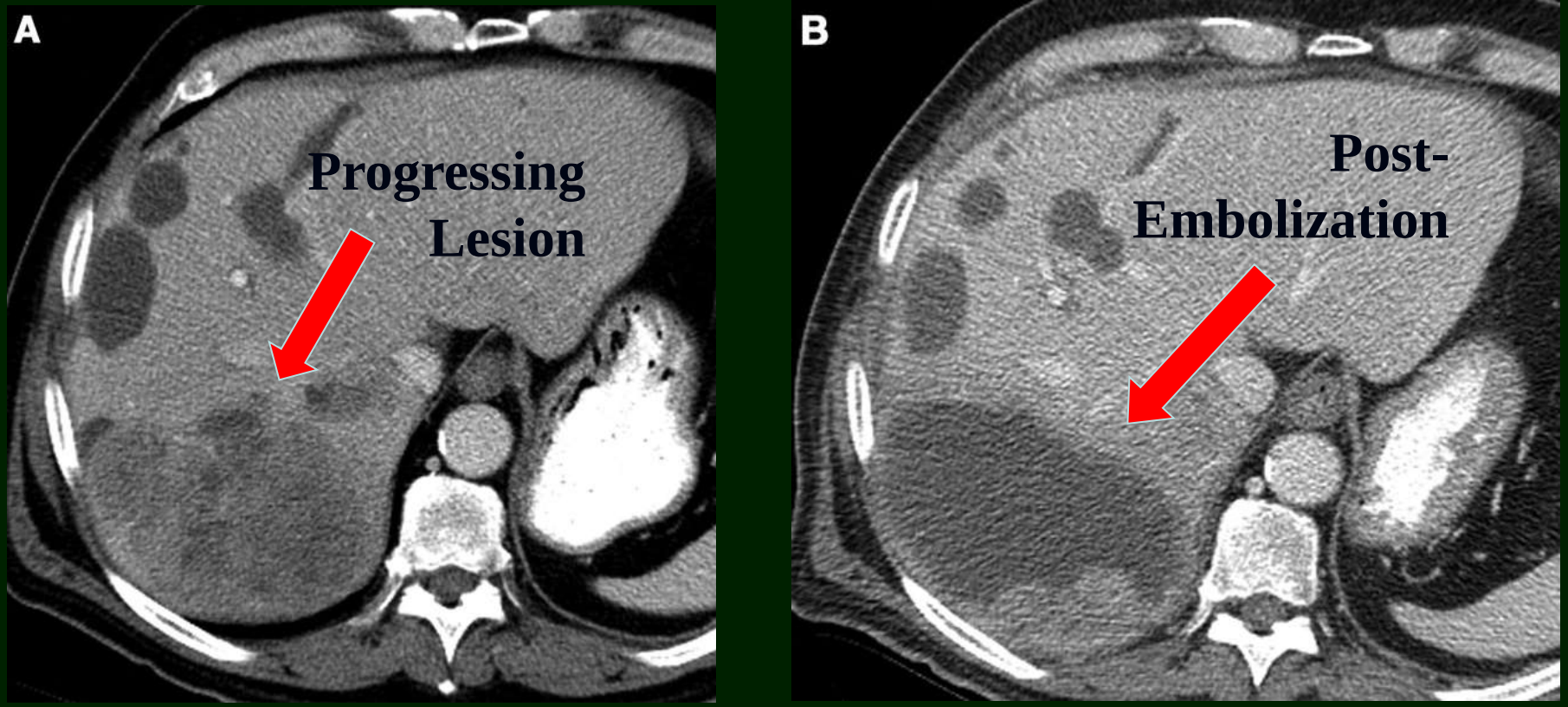
Pre-embolization

Post-embolization

Courtesy of Dr. R. DeMatteo.

Imatinib-Resistant Metastatic GIST

Limited Hepatic Progression



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

Hepatic Arterial Embolization

Radiographic Response Rates

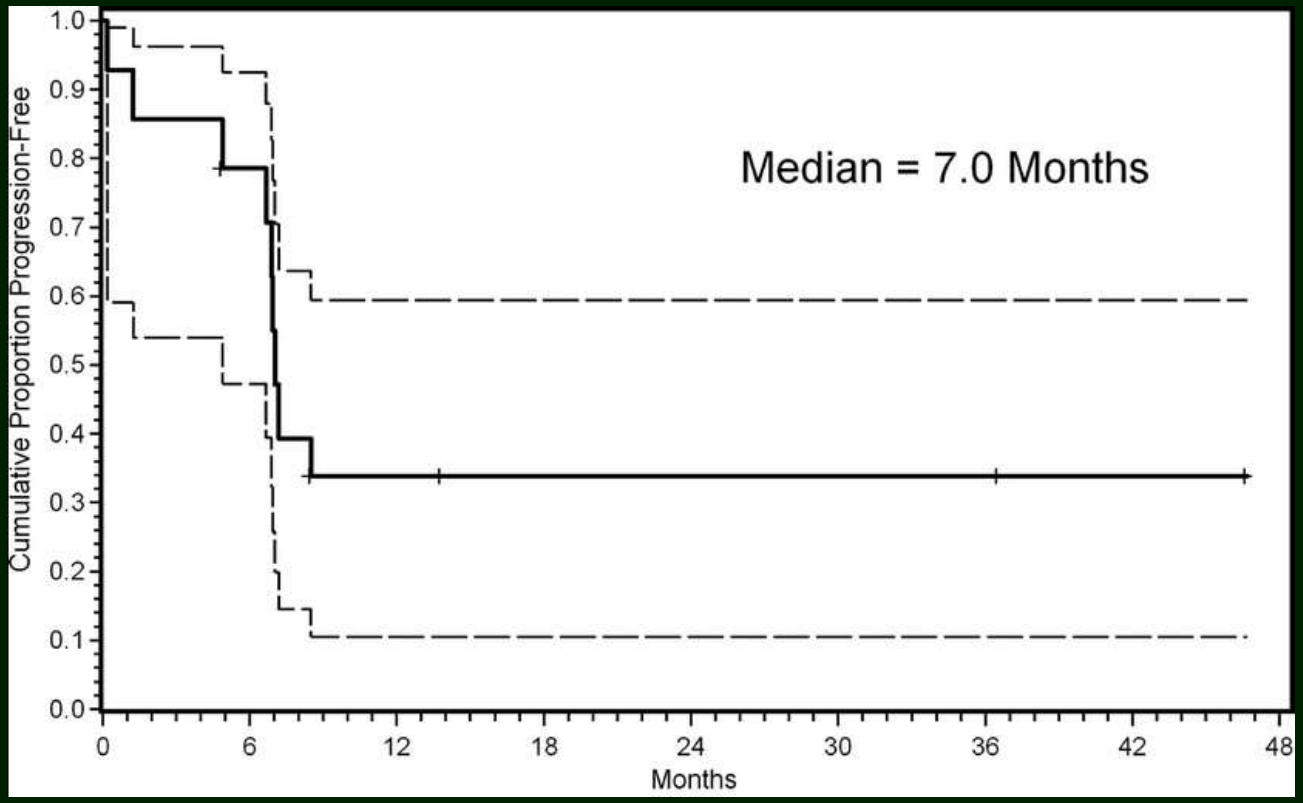
- 14 patients with imatinib-resistant GIST and progressive liver metastases
  - Treated with hepatic arterial embolization or chemoembolization
  - 13 patients evaluable for radiologic response

Response	Best Response (Choi Criteria)	Best Response (RECIST)
Overall	54%	8%
Complete	0%	0%
Partial	54%	8%
Stable	46%	92%
Progression	0%	0%

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

Hepatic Arterial Embolization

Progression-Free Survival



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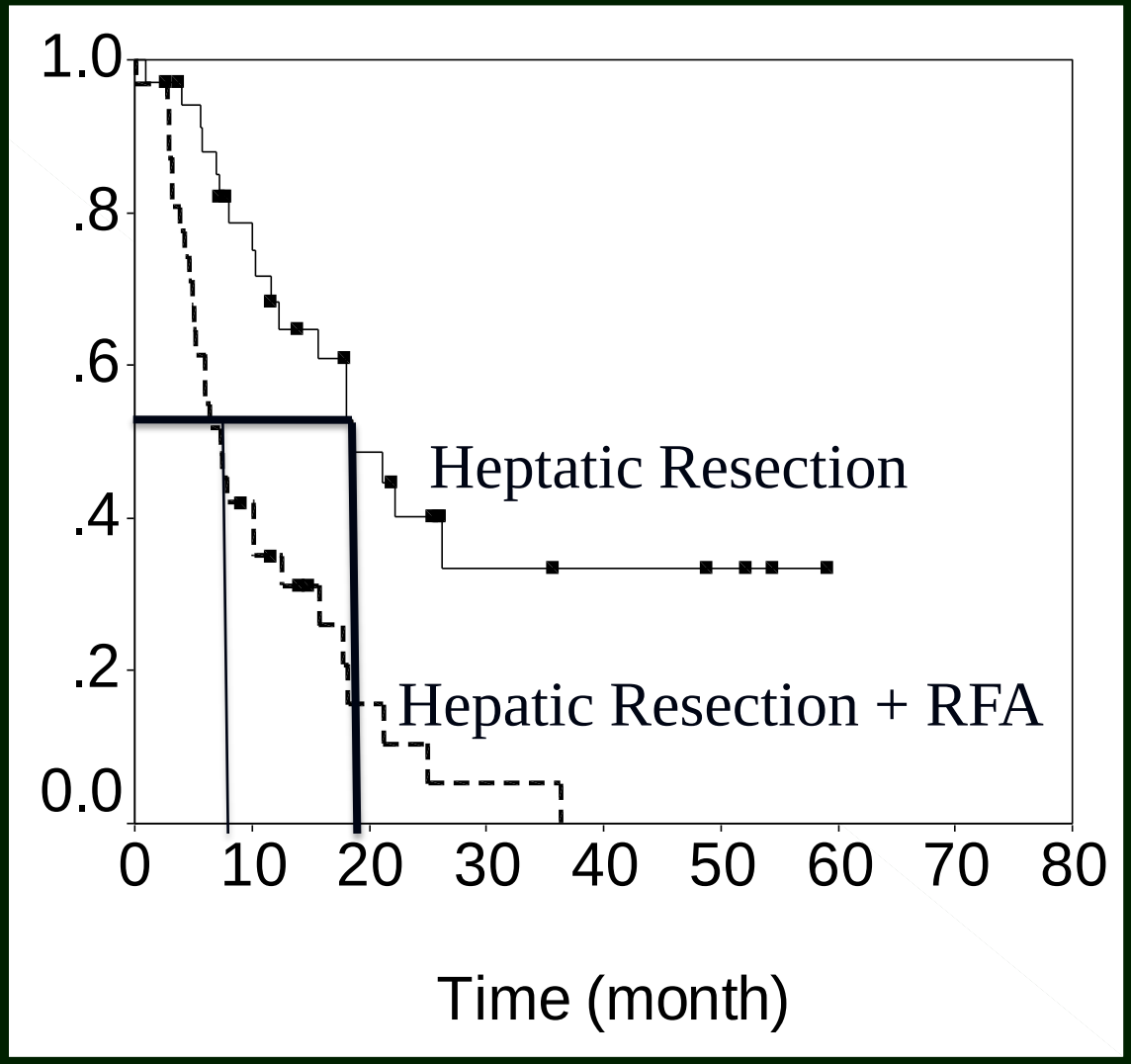
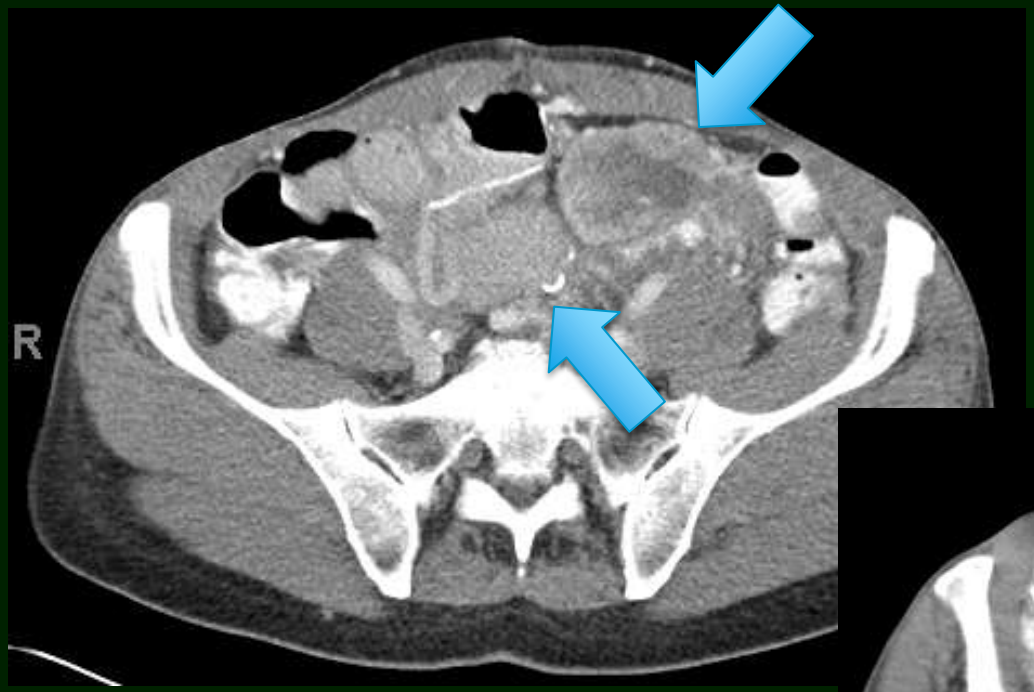
Imatinib-resistant GIST

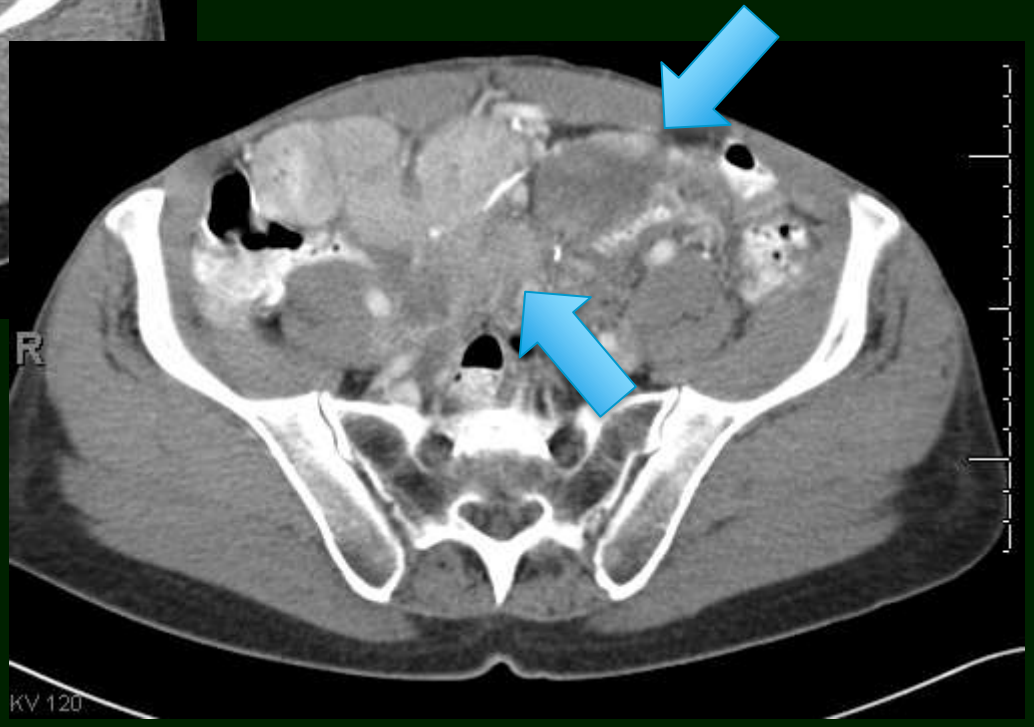
Disease-Free Survival



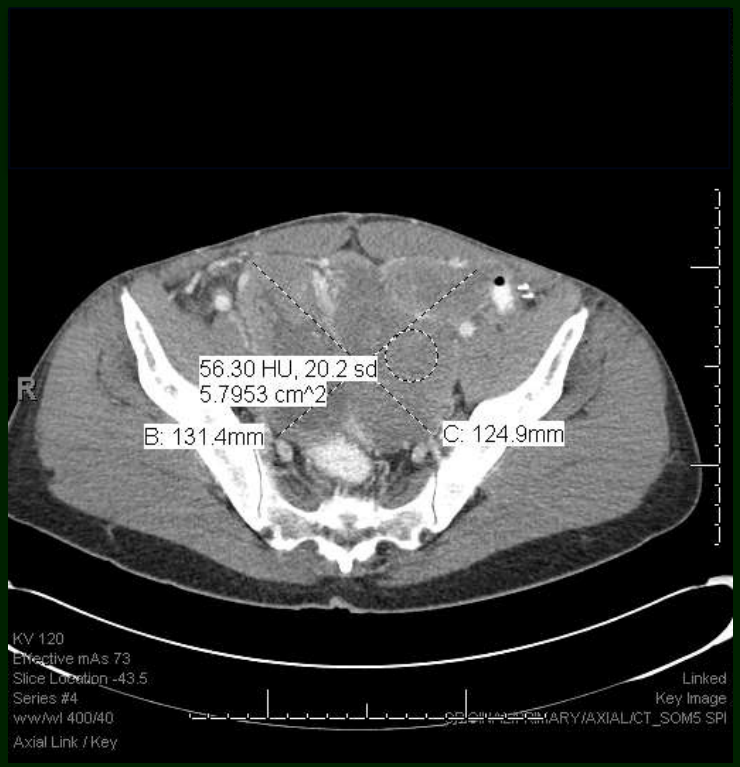
Arch Surg. 2006 Jun;141(6):537-43

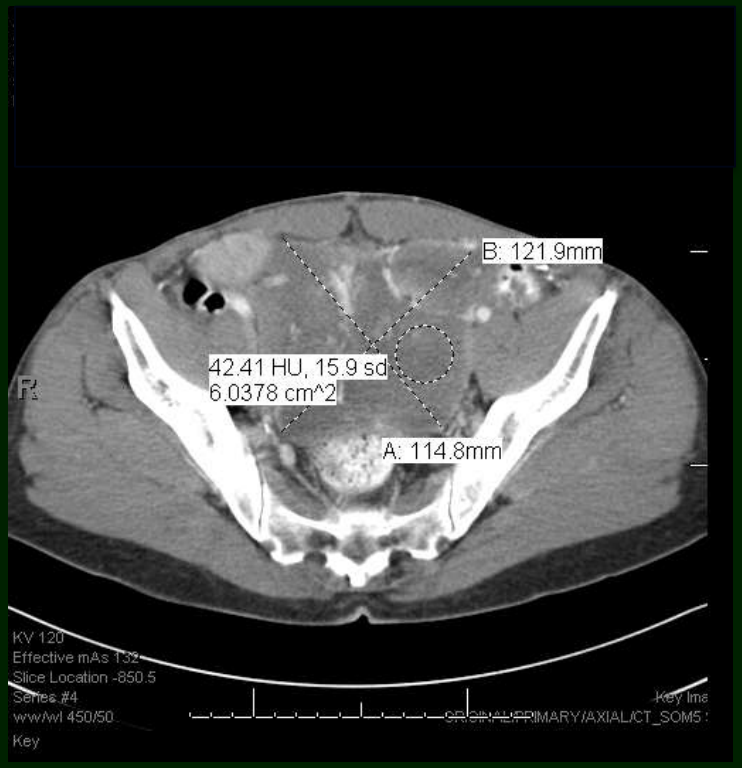
Radiotherapy for GIST





Radiotherapy for GIST





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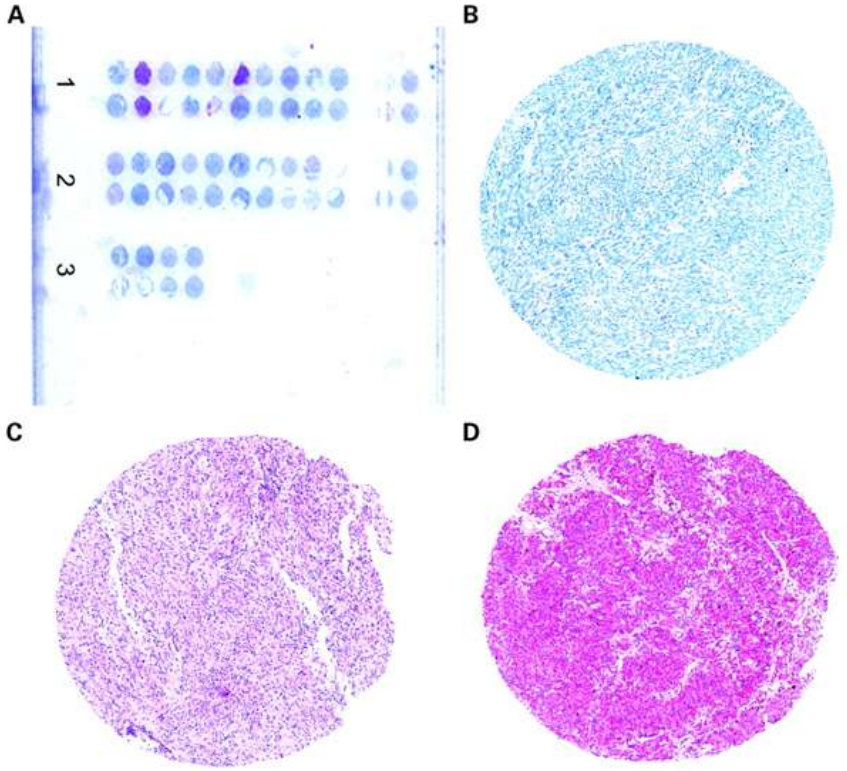
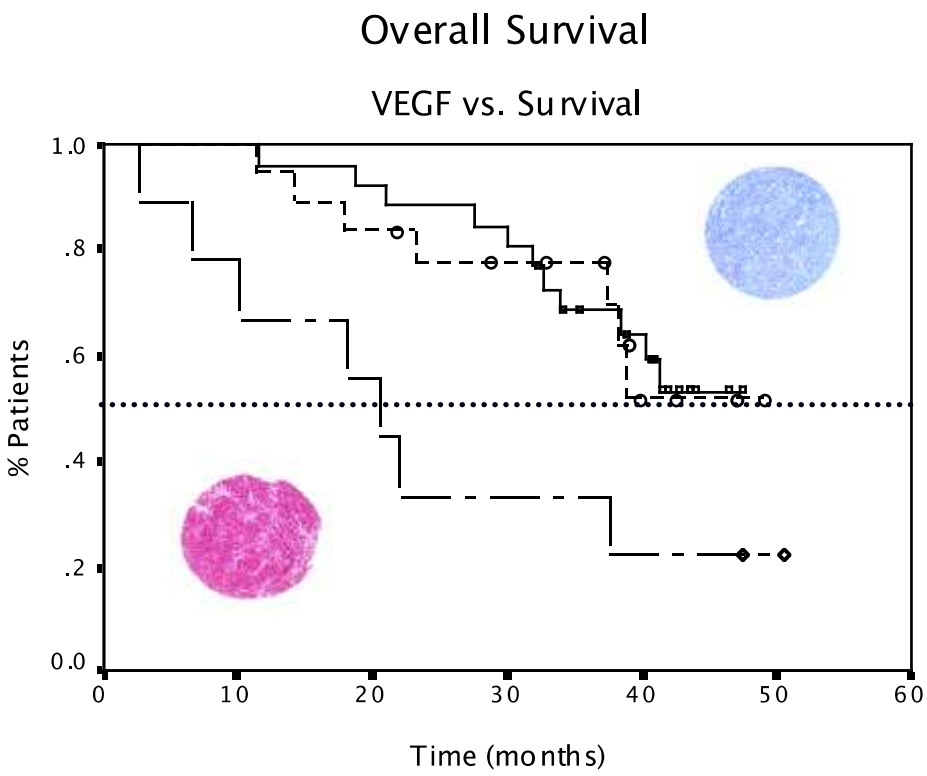
- Widespread progression
  - Increase Imatinib to 800 mg daily
  - Sunitinib
  - Clinical Trial

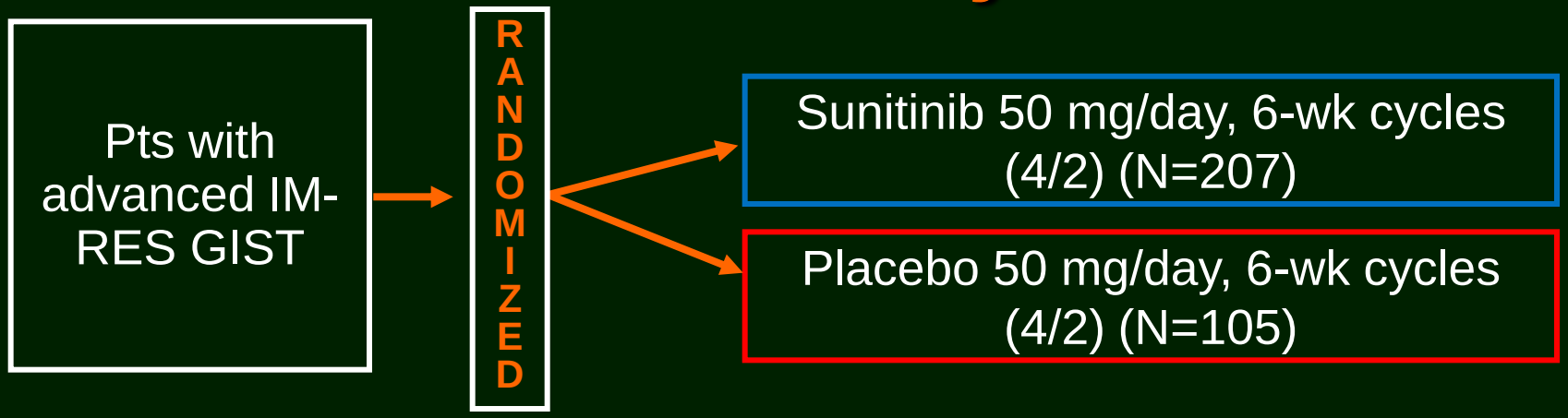
Association of Intratumoral Vascular Endothelial Growth Factor Expression and Clinical Outcome for Patients with Gastrointestinal Stromal Tumors Treated with Imatinib Mesylate

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]





Sunitinib Efficacy in Patients With Imatinib-Refractory GIST

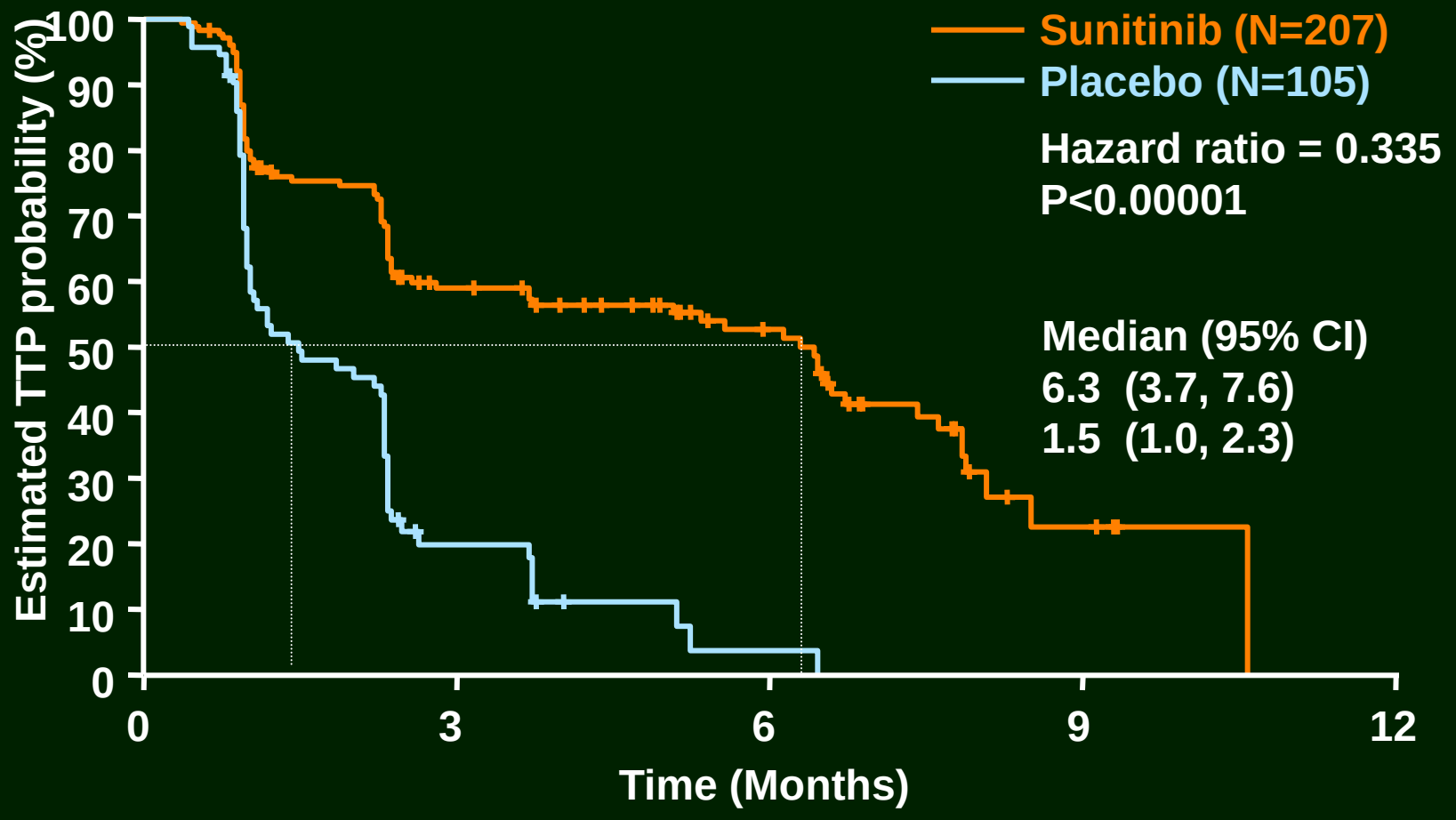


- Primary endpoint
  - TTP, as defined using RECIST
- Secondary endpoints
  - PFS, OS, ORR, TTR, DOR, and duration of PS maintenance
- At RECIST-defined disease progression, pts receiving placebo were eligible for crossover

IM=imatinib; ORR=overall response rate; RES=resistant; TTP=time to progression; TTR=time to tumor response.

Demetri. *Lancet*. 2006;368:1329.

Time to Tumor Progression



Other Agents for IM-RES 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	Ongoing
	Axitinib	ND	ND
Raf Inhibitors	Vemurafenib	I	ND
mTOR inhibitors	Everolimus	II/III	PR=2%, SD=43% PFS=3.5 months
	Temsirolimus	II	ND
HDAC inhibitors	SAHA	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.

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