

Gastrointestinal Stromal Tumor

GISTS 2010: After Standard of Care



Jon Trent, MD, PhD

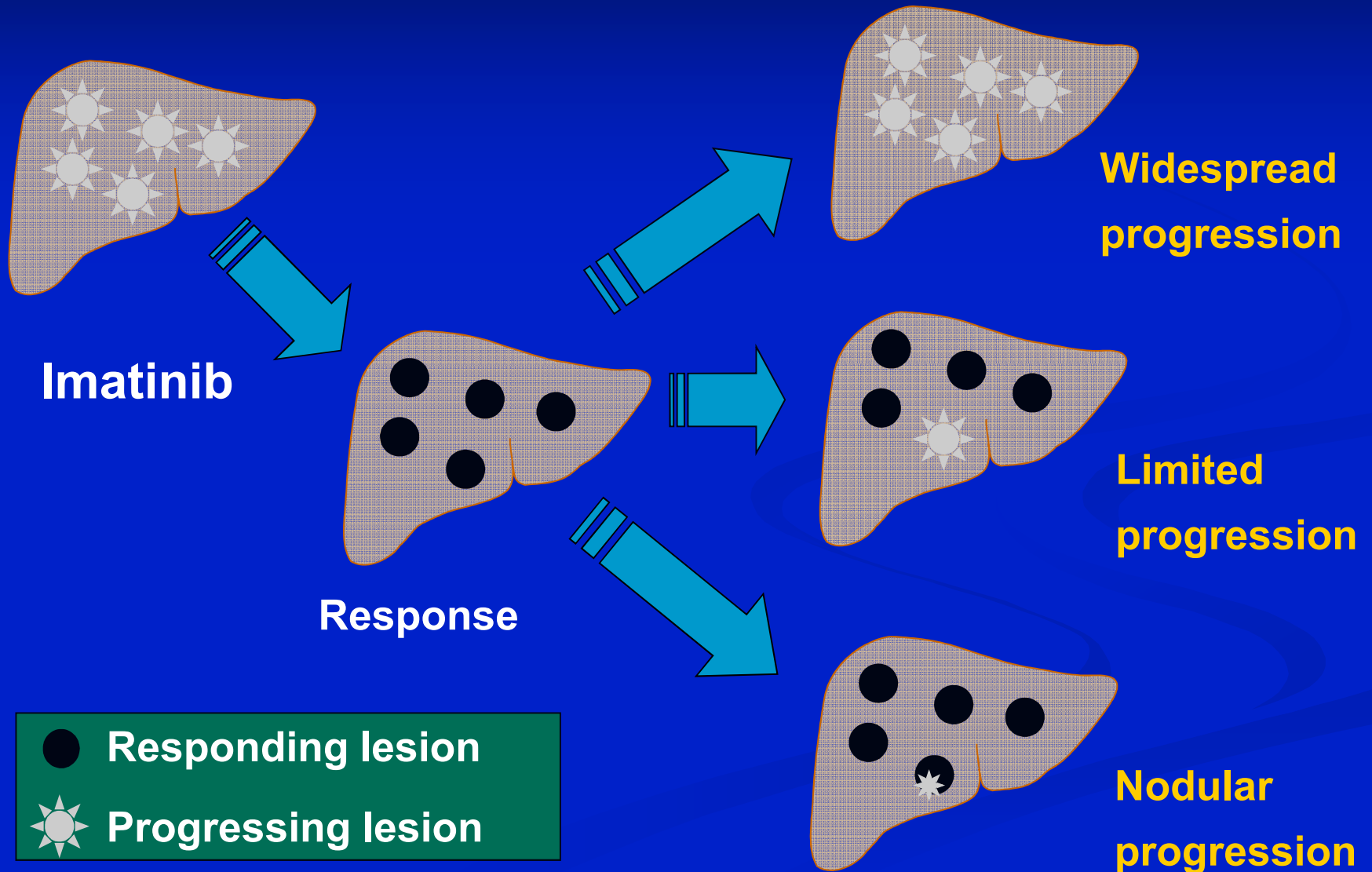
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**What do I do if my
GIST is resistant to
imatinib?**

Type of Progression



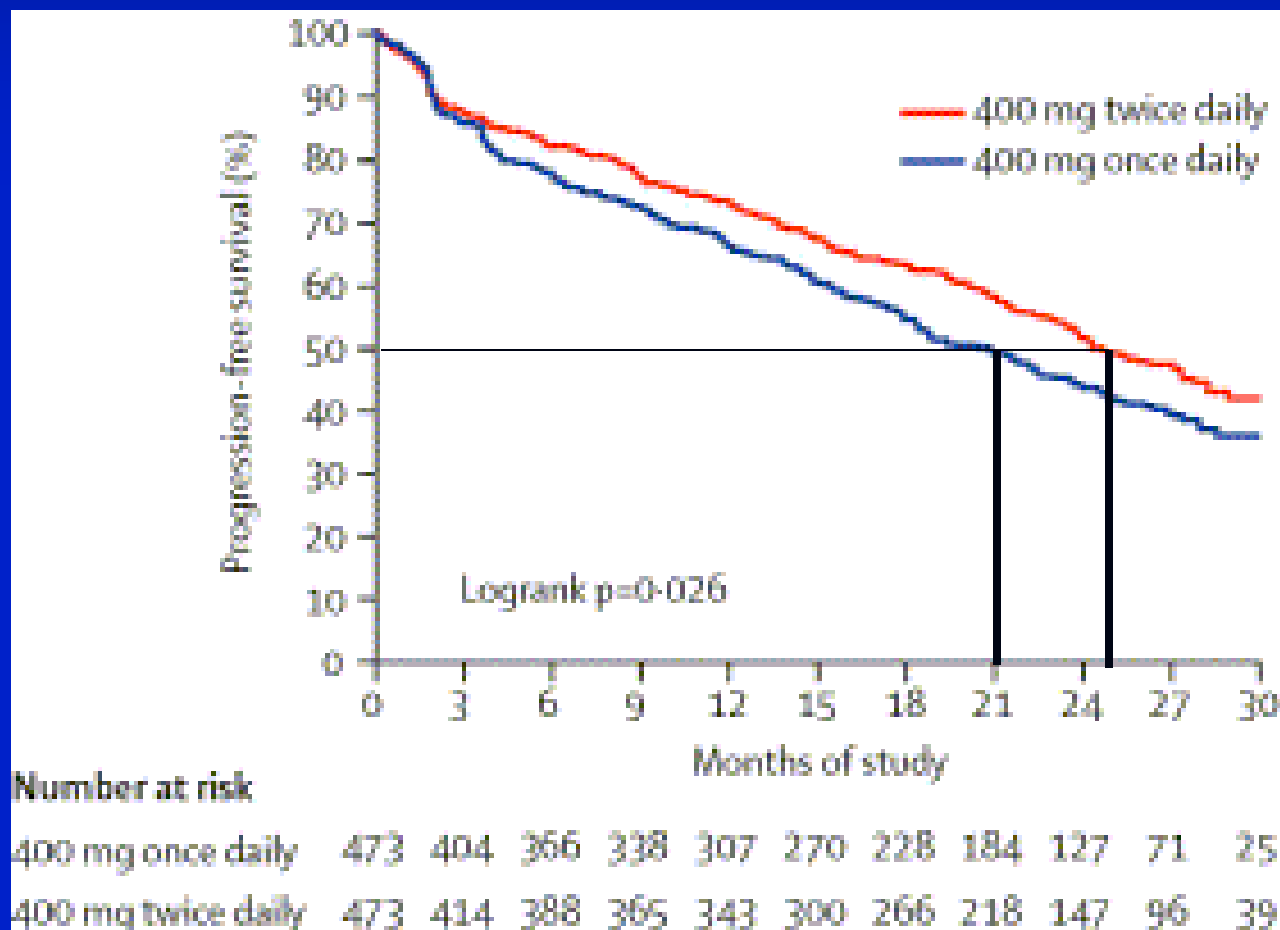
Advanced GIST

Widespread Progression

- Widespread progression
 - Increase Imatinib to 800 mg daily
 - Sunitinib
 - Nilotinib, Sorafenib, Dasatinib
 - Clinical Trial
 - Kit inhibitor
 - Kit inhibitor plus new agent

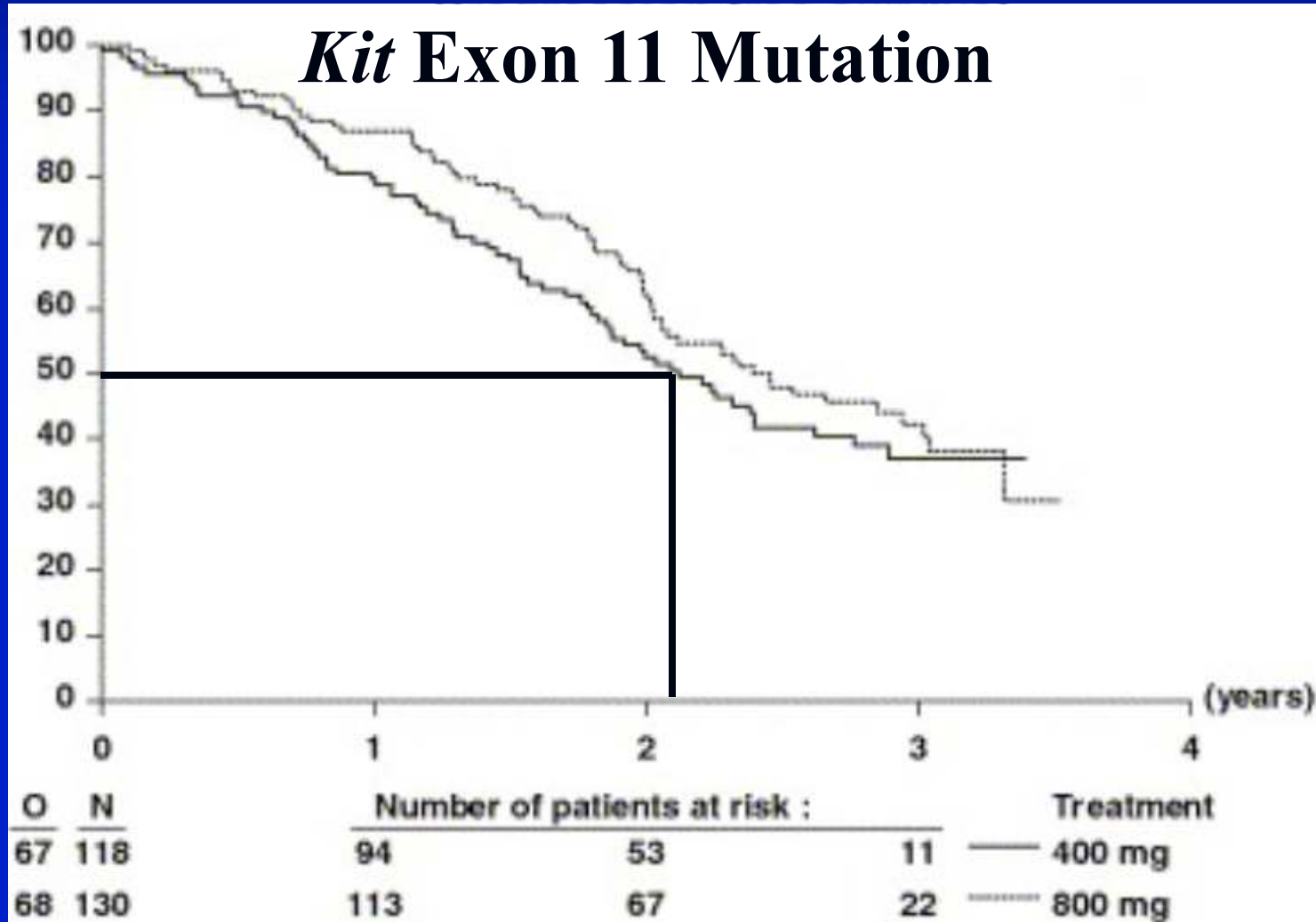
EORTC Phase III Imatinib for Advanced GIST

Progression-free Survival Benefit



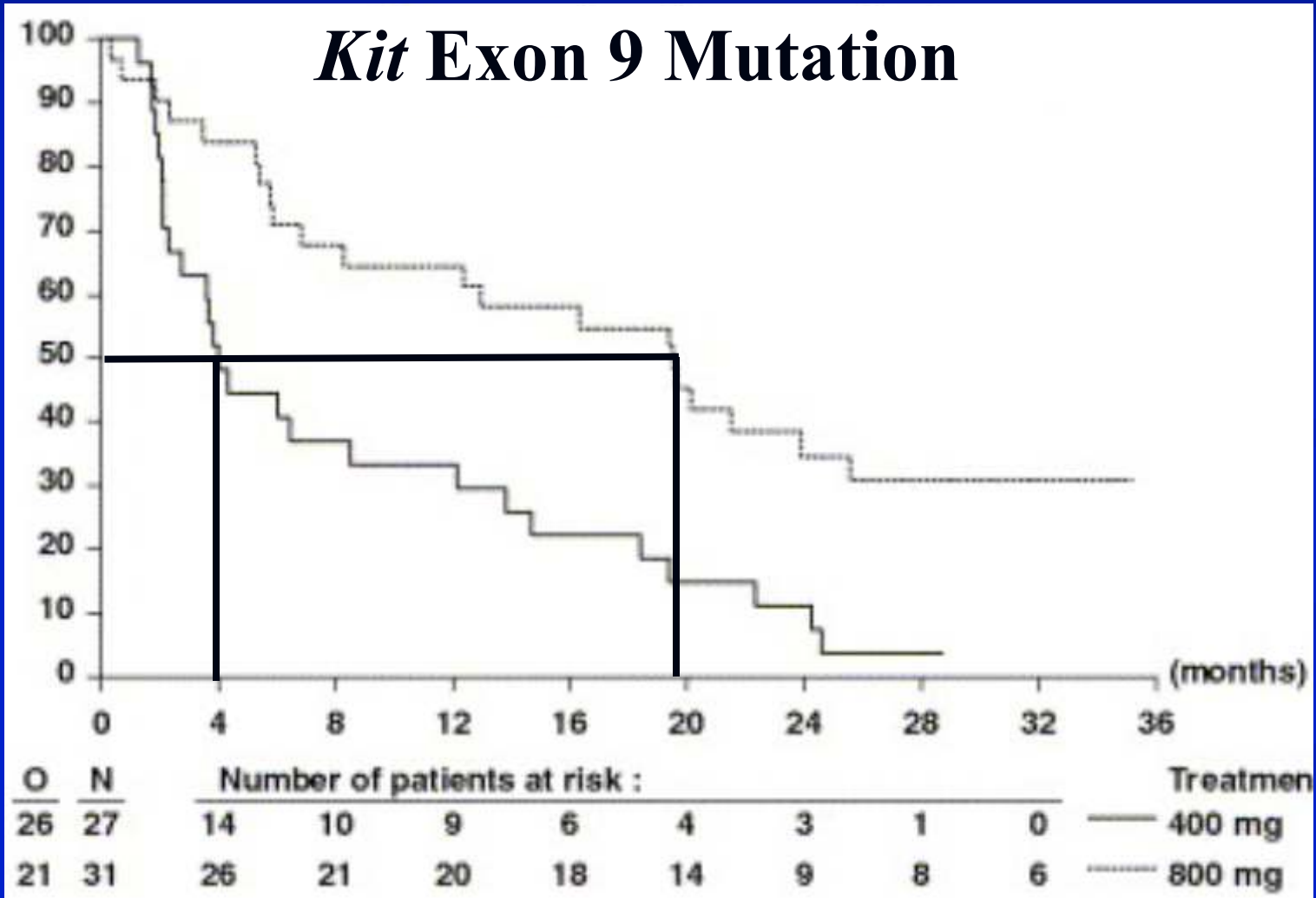
Verweij, et al 2004

Progression-free Survival By Imatinib Dose



Progression-free Survival By Imatinib Dose

Kit Exon 9 Mutation



Kit Mutation in GIST

Benefit from 800mg Imatinib

	Odds Ratio	P-value
Exon 11 (n=211)	1.0	0.96
Exon 9 (n=25)	8.0	0.03
Wild-type (n=33)	1.5	0.62

Heinrich et al, ASCO 2005

Advanced GIST

Imatinib Dose Escalation

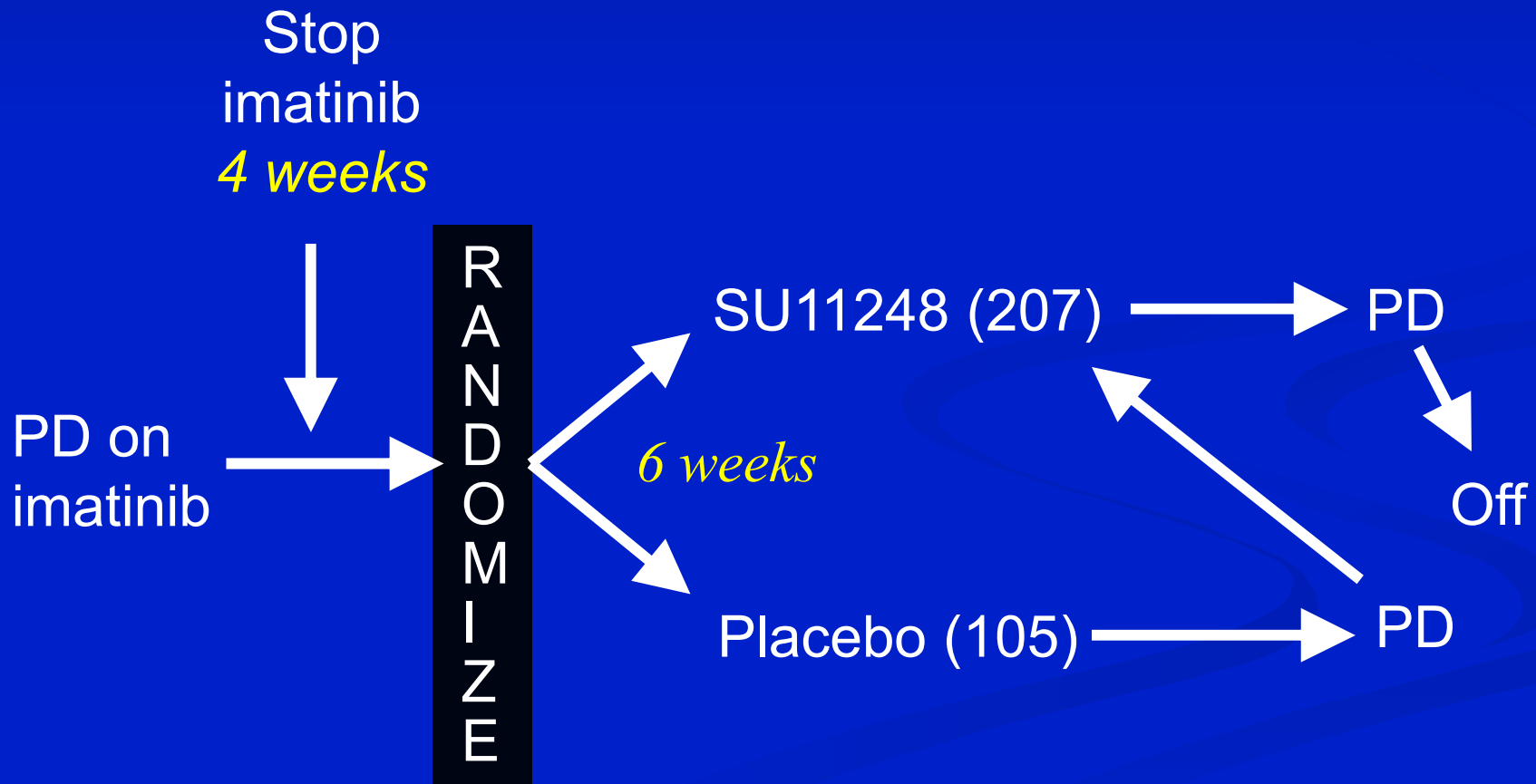
Best Response	Imatinib 800mg*
PR	3%
SD	28%
SD > 6 mo	ND
PD	48%
NE	13%

*Escalation of imatinib from 400 mg to 800 mg daily.

Second-line Therapy With Sunitinib

SU11248 in Advanced GIST

Sunitinib Malate, Sutent



Sunitinib in Advanced GIST

Objective Response Rates

	Sunitinib	Placebo
PR	7%	0%
SD	58%	50%
SD > 6 mo	19%	0%
PD	20%	39%
NE	14%	11%

*Escalation of imatinib from 400 mg to 800 mg daily.

Sunitinib in Imatinib-Resistant/Intolerant GIST

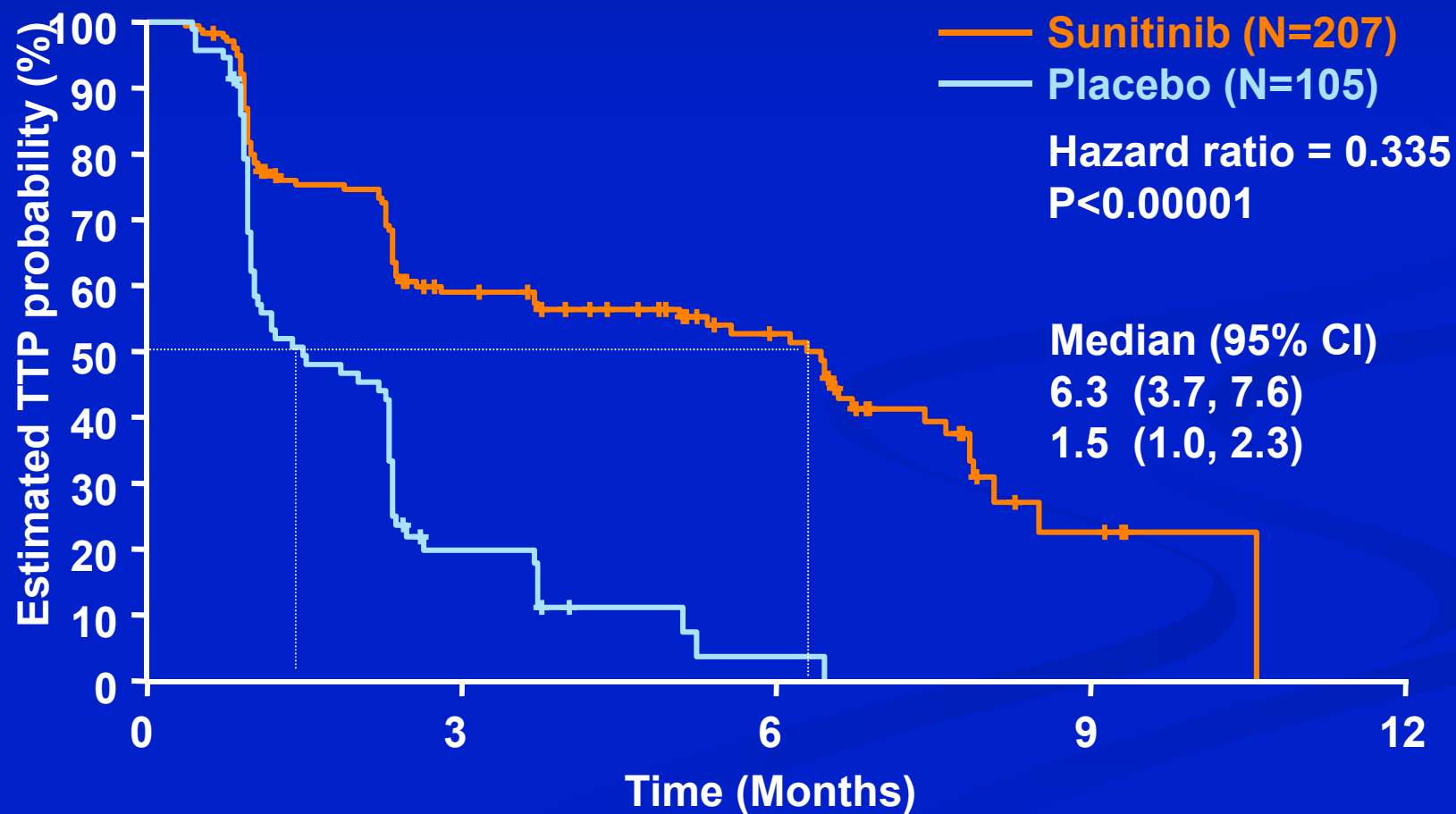
- Sunitinib a novel, broad spectrum TKI affecting FLT3, PDGFR, and VEGFR pathways, all relevant to GIST pathogenesis^[1]
 - Approved for imatinib-resistant, progressive GIST based on TTP results from randomized, phase III study (N = 312)^[2]

Outcome	Sunitinib (n = 207)	Placebo (n = 105)	P Value
Median TTP, weeks	27.3	6.4	< .0001
Most frequent grade 3/4 AEs,* %	(n = 202)	(n = 102)	
▪Neutropenia	10	0	-
▪Lymphopenia	9	3	-
Fatigue	5	2	-

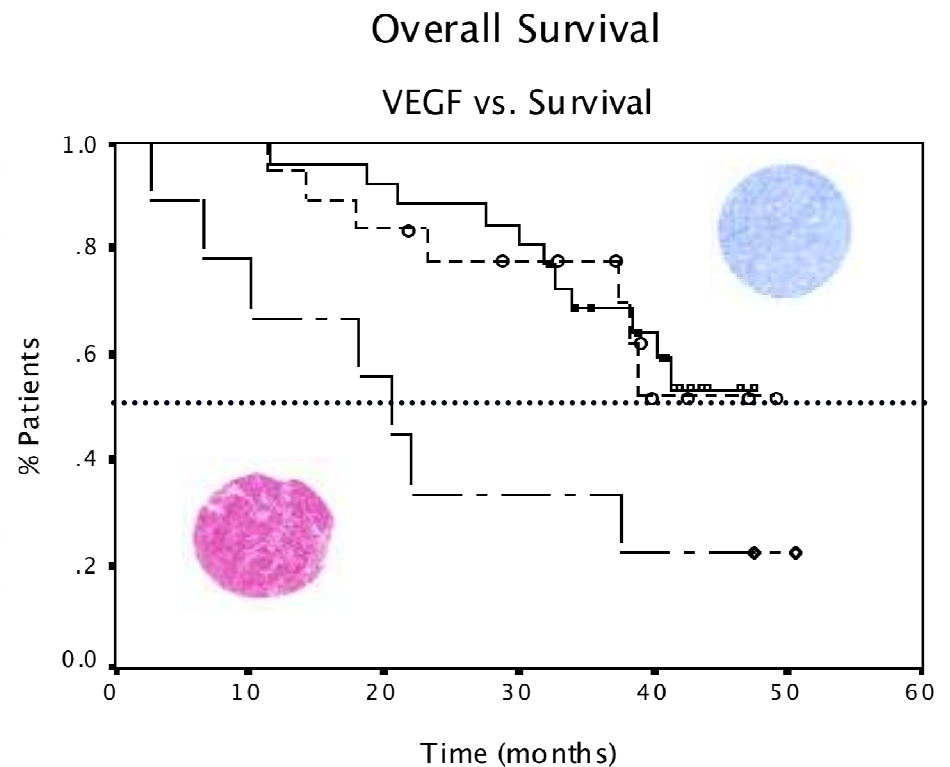
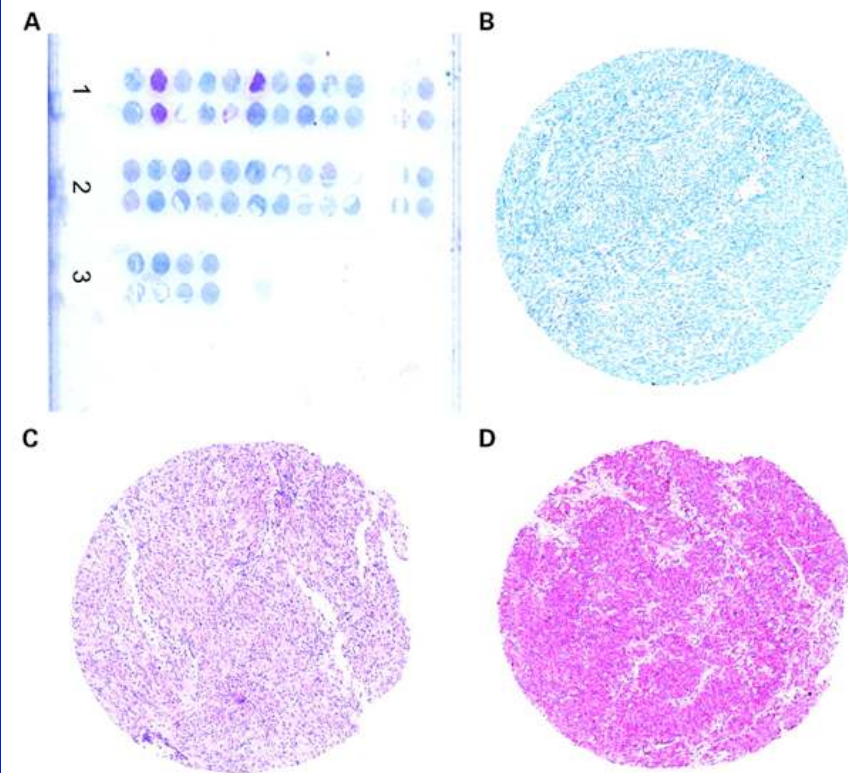
*Occurring in $\geq 5\%$ of patients in either treatment arm.

1. Hopkins TG, et al. Eur J Cancer Society. 2008;34:844-850.
2. Demetri GD, et al. Lancet. 2006;368:1329-1338.

Time to Tumor Progression



Which Patient Will Benefit From Sunitinib?

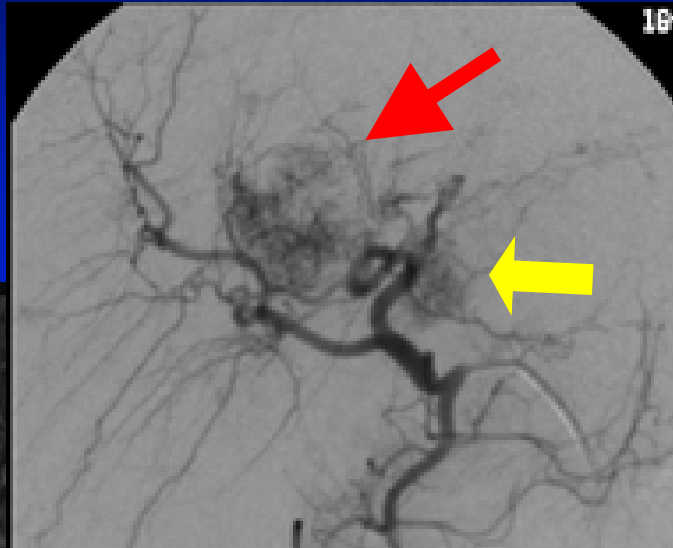
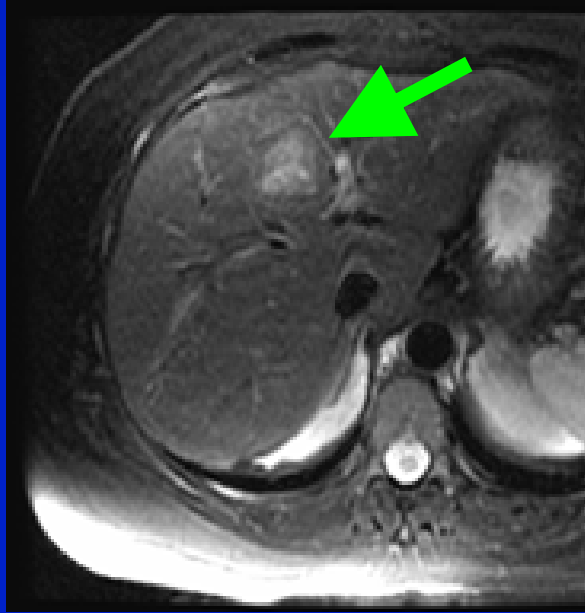


Advanced GIST

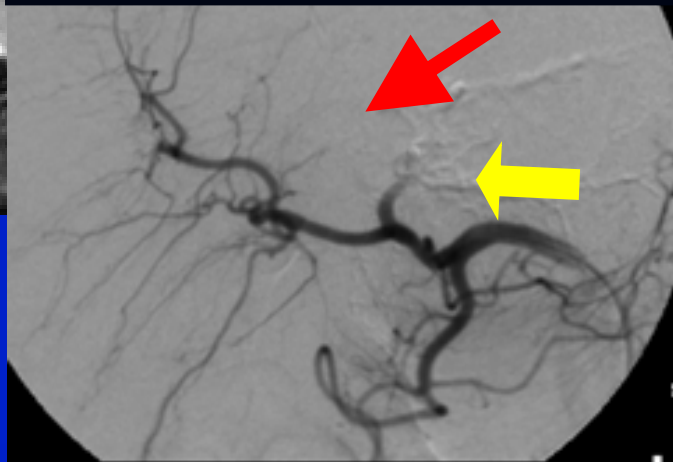
Therapy For Limited Progression

- Surgical Resection
- Hepatic Radio-frequency Catheter Ablation
- Hepatic Artery Embolization
- Hepatic Artery Chemoembolization
- Radiation Therapy (esophageal, rectal, bone lesions)

Hepatic Artery Embolization



Pre-embolization



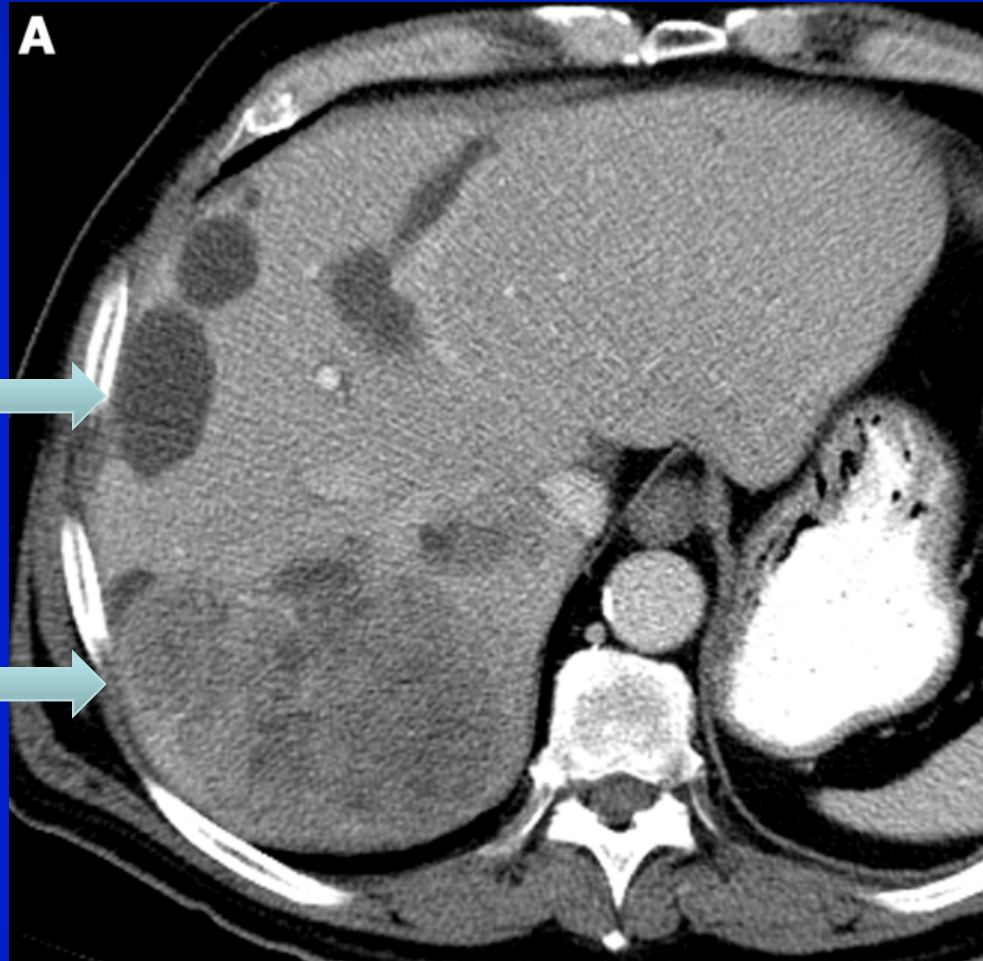
Post-embolization

Imatinib-Resistant Metastatic GIST

Limited Hepatic Progression

Stable,
Hypoattenuating
Lesions

Progressing
Lesion

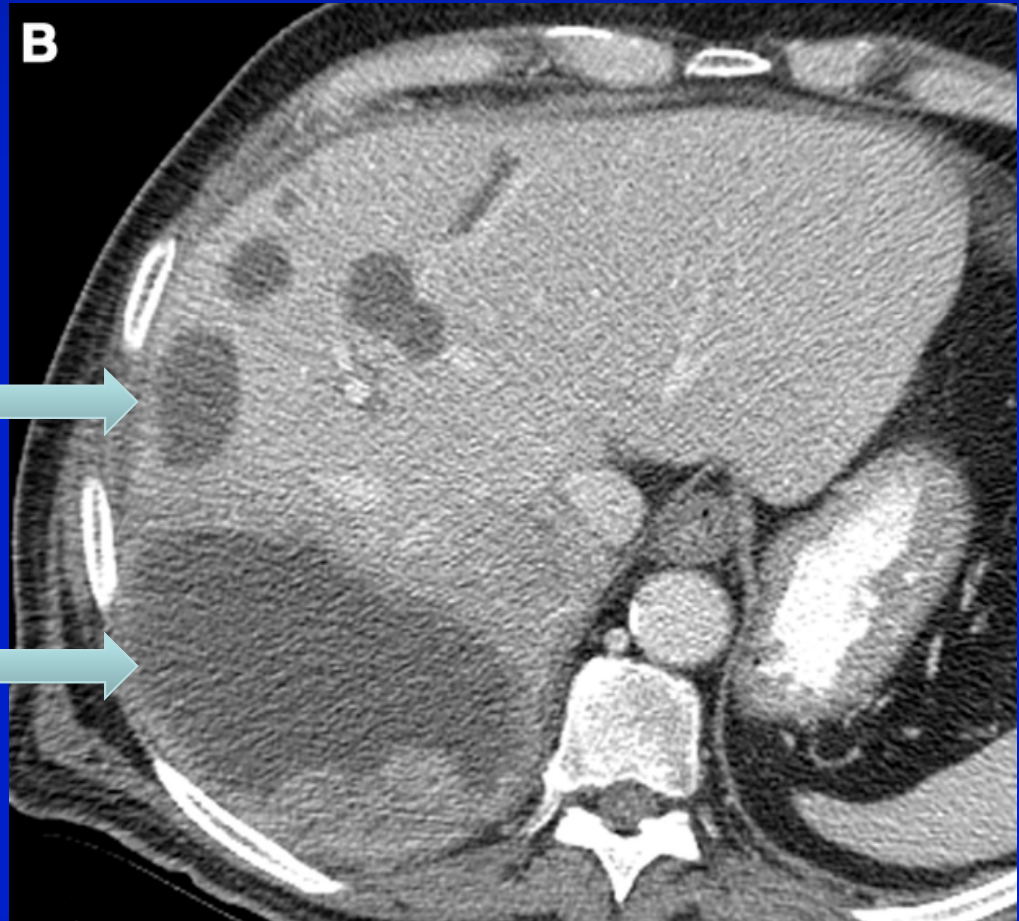


Hepatic Arterial Embolization

Post-embolization CT Imaging

Stable,
Hypoattenuating
Lesions

Embolized
Lesion



Hepatic Arterial Embolization

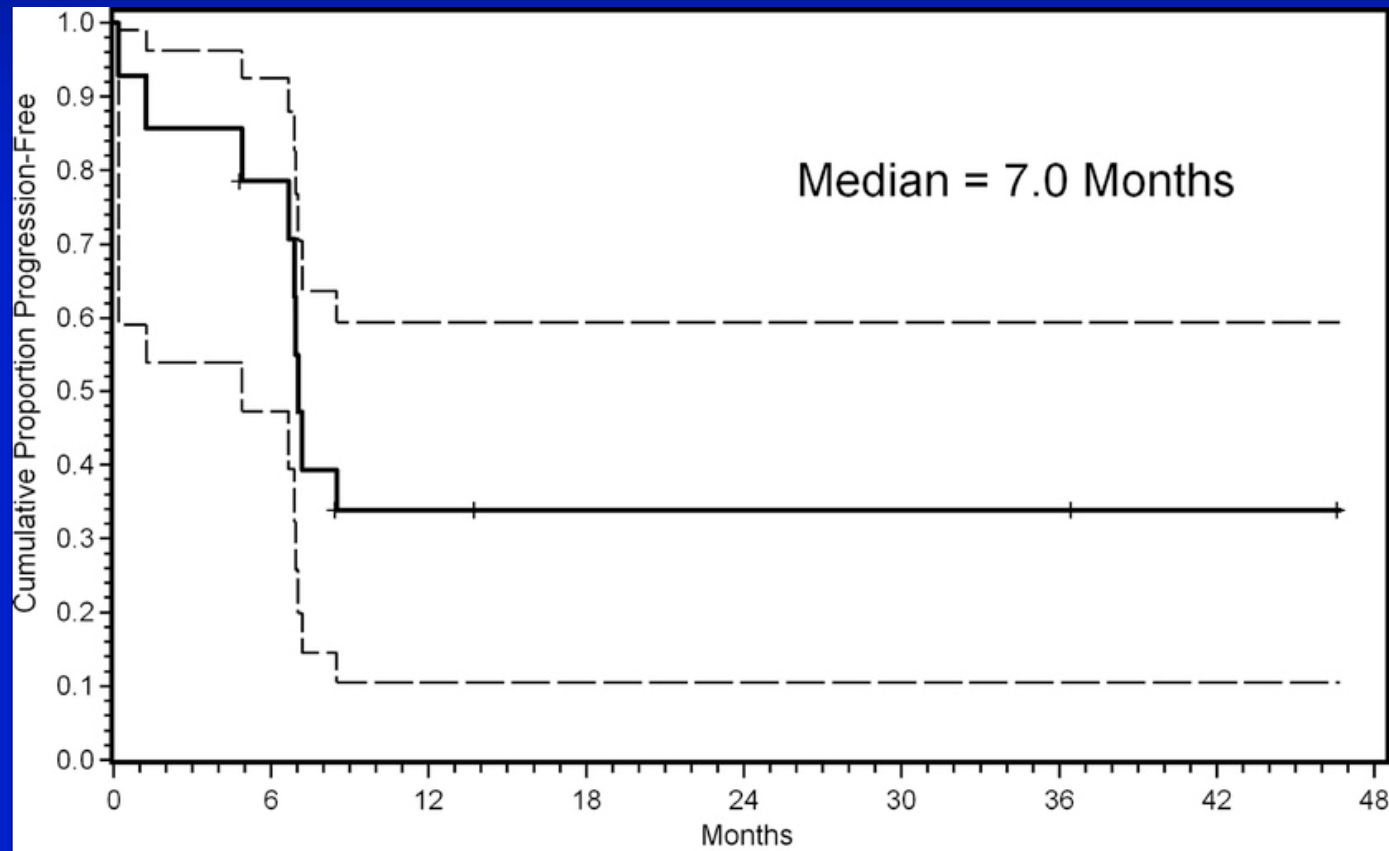
Radiographic Response Rates

- 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%

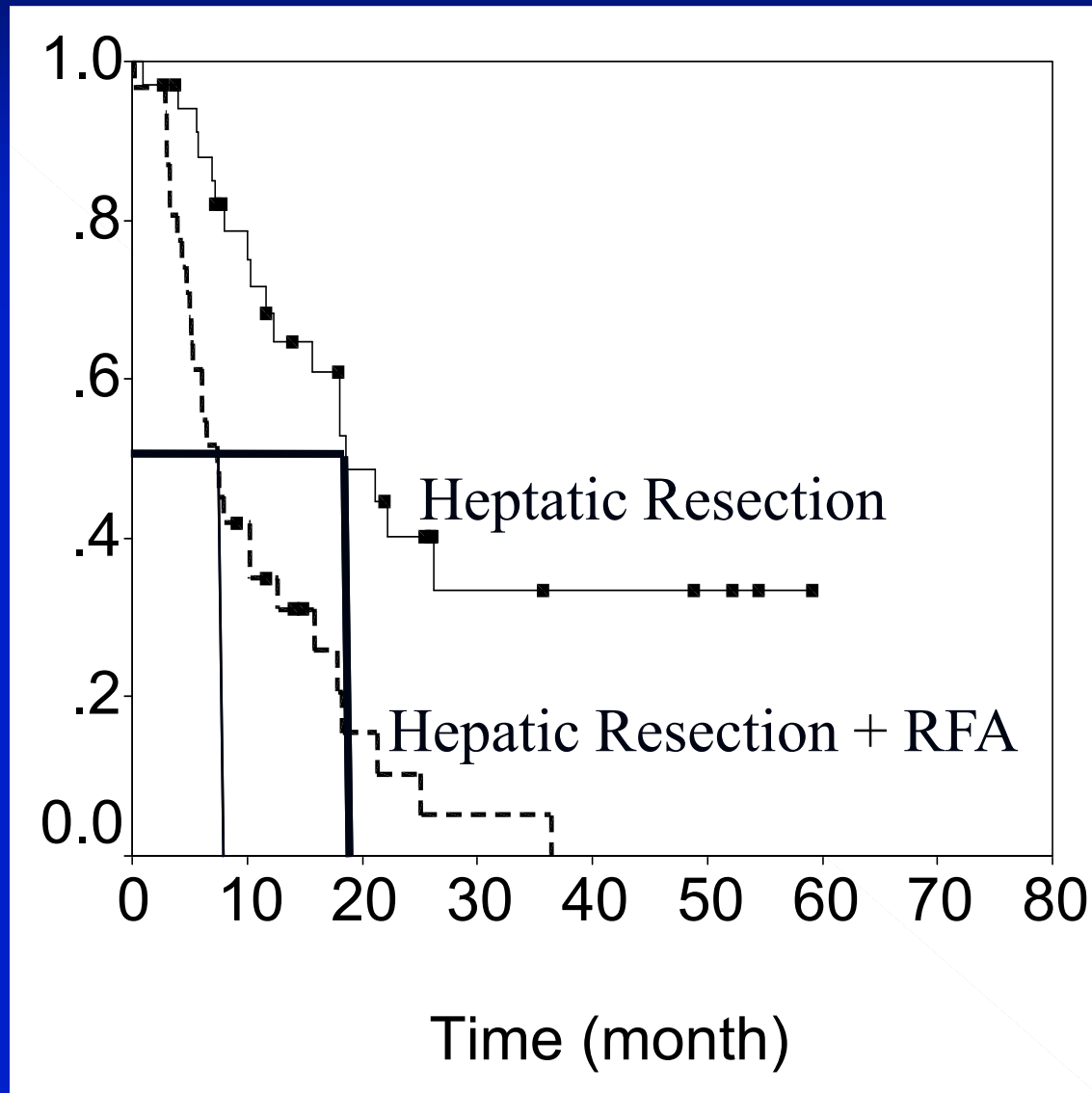
Hepatic Arterial Embolization

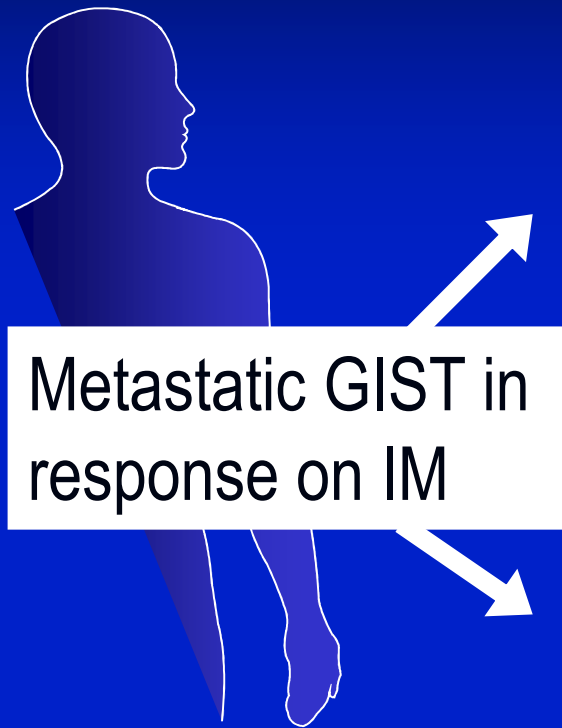
Progression-Free Survival



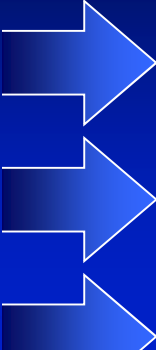
Imatinib-resistant GIST

Disease-Free Survival



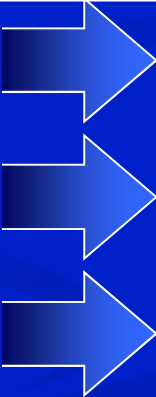


Imatinib



Follow for PFS & OS

Imatinib + surgery at best response (within 1 yr)



Courtesy Gronchi et al

Other Systemic Therapies

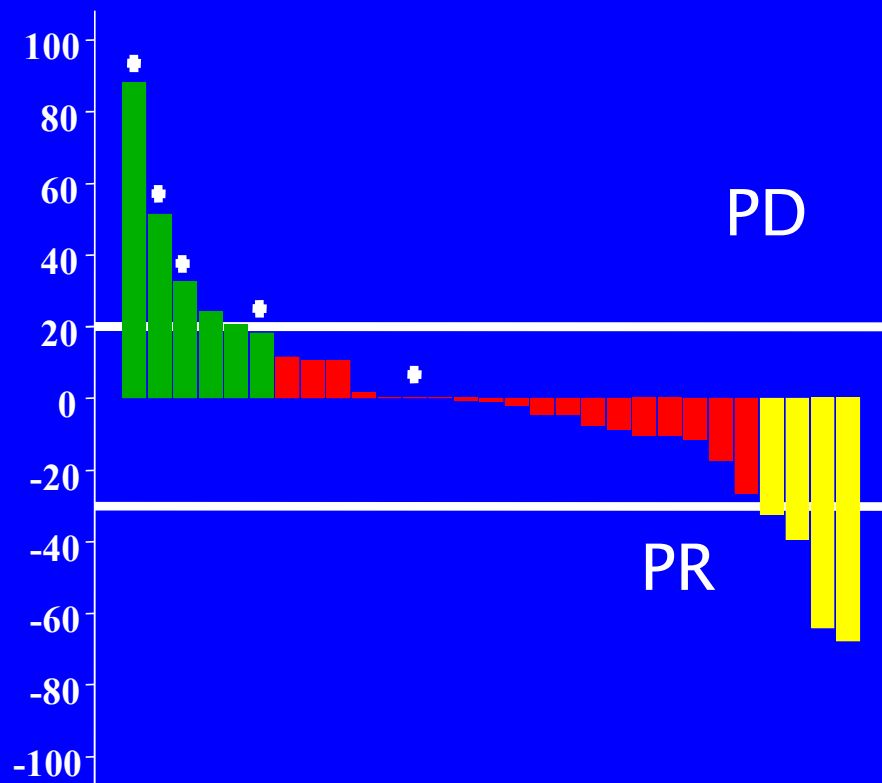
Investigational TKIs in GIST

Agent	Targets	Study Phase	Efficacy
Nilotinib	KIT , PDGFR, ABL	I (n = 18 monotherapy)	Single-agent: 78% \geq SD
		Retrospective (n = 52)	PR: 10% SD: 37%
Dasatinib	KIT, PDGFR, ABL	II (n = 37)	PR: 8% SD: 30%
Sorafenib	KIT, PDGFR, VEGFR, RAF	II (n = 29)	PR: 14% SD: 62%
Masatinib	KIT, PDGFR, FGFR3	Frontline II (n = 28)	PR: 21.5% SD: 75%
Vatalanib	KIT, PDGFR, VEGFR	II (n = 15 with GIST)	\geq SD for \geq 3 mos: 67%
Motesanib	KIT, PDGFR, VEGFR	II (n = 35)	\geq SD for \geq 24 mos: 23%

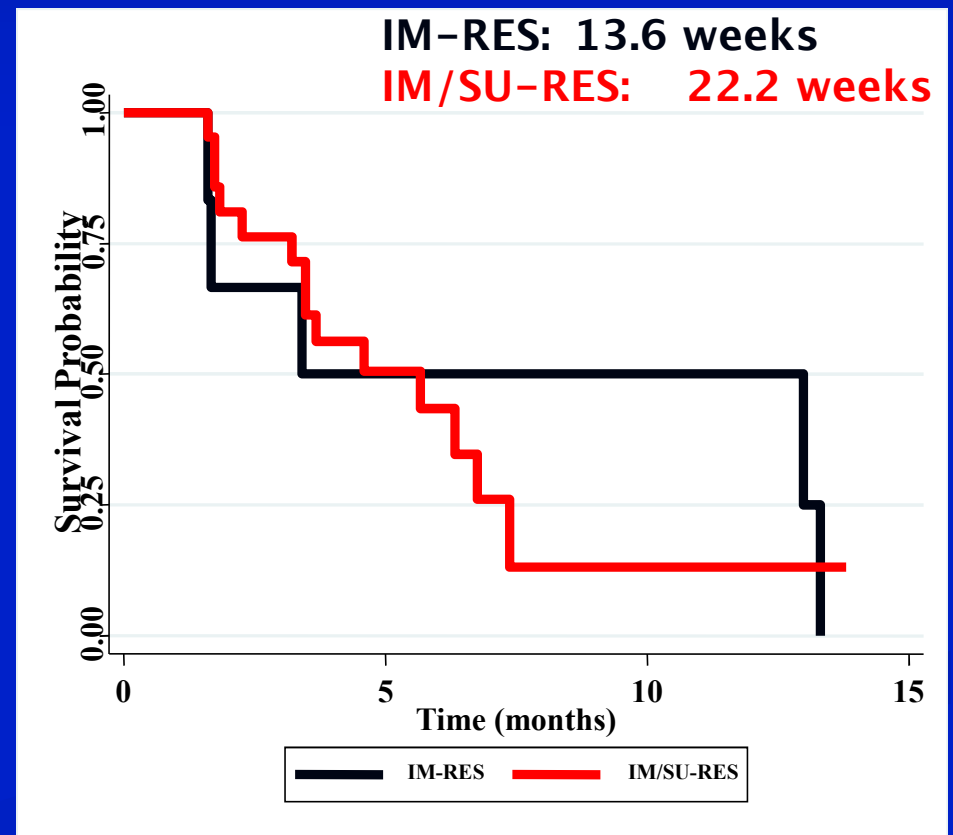
1. Blay JY, et al. ASCO 2008 Abstract 10553. 2. Montemurro M, et al. Eur J Cancer. 2009;45:2293-2297. 3. Le Cesne A, et al. ASCO 2009. Abstract 10507. 4. Joensuu H, et al. Ann Oncol. 2008;19:173-177. 5. Sawaki A, et al. Cancer Chmother Pharmacol. 2009;Aug 19:epub ahead of print.

Clinical Efficacy of Sorafenib

Radiographic Response



Progression Free Survival

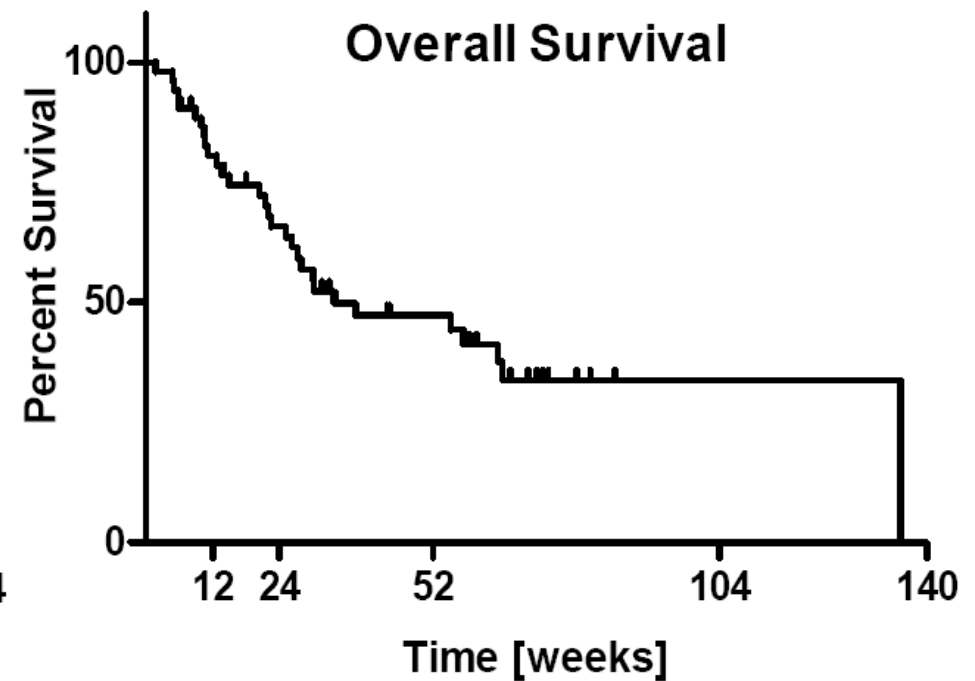
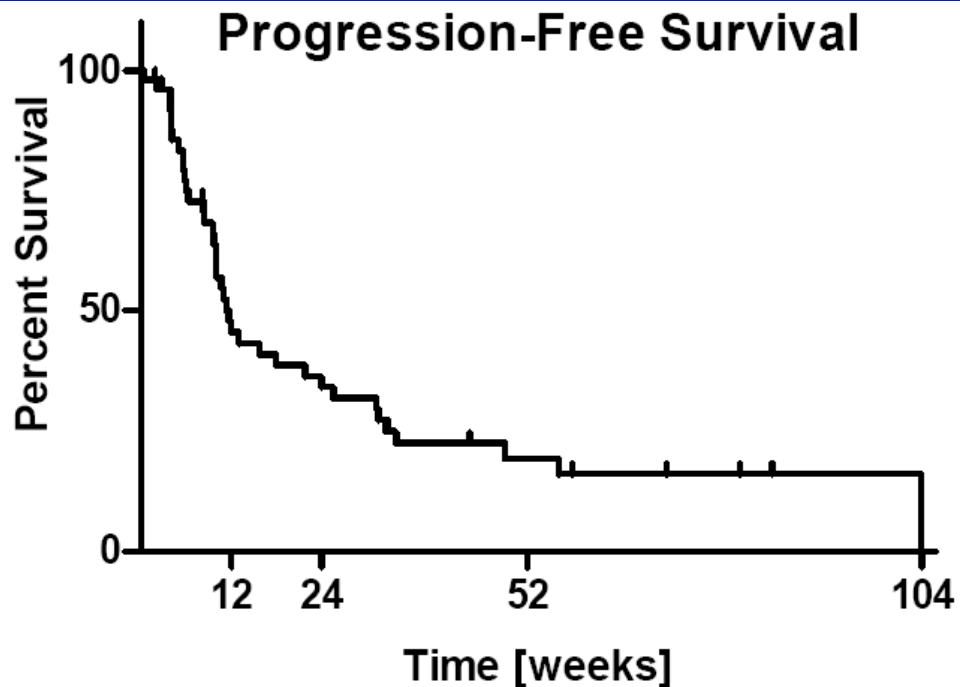


Wiebe et al, Proc Am Soc Clin Oncol, 2008; Abstract 10502

Nilotinib 3rd-line

- **47 % PR+SD**
- **40% > 3 months treatment**
- **mPFS 12 weeks**

OS 34 weeks



Third-line Nilotinib in GIST

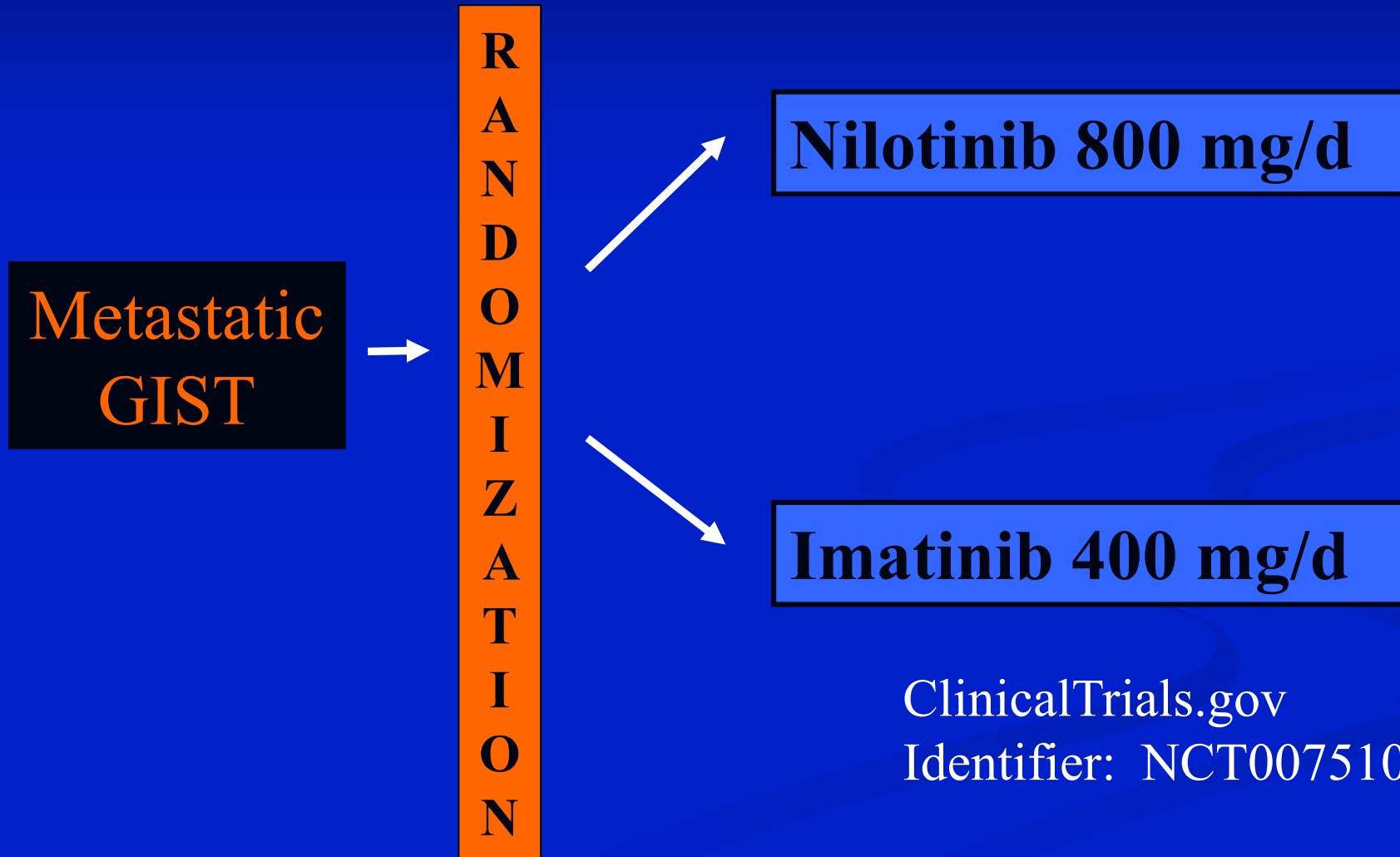
Progression-free Survival

	N 400 bid (N=9) N (%)	N 200 qd I 400 qd (N=4) N (%)	N 400 qd I 400 qd (N=3) N (%)	N 400 bid I 400 qd (N=4) N (%)	N 400 bid I 400 bid (N=13) N (%)
Observed PFS					
PFS at 4 months	6 (67)	2 (50)	1 (33)	1 (25)	1 (8)
PFS at 6 months	4 (44)	0	1 (33)	1 (25)	0
PFS - Kaplan Meyer estimates					
Median in days (min-max)	168 (1-393)	142.5 (56-223)	112 (22-336)	Not reached (1-322)	Not reached (27-180)

von Mehren M, et al. *Proc Am Soc Clin Oncol*, 2007. Abstract 10023.

Nilotinib For GIST

AMN 2201 – 1st Line



ClinicalTrials.gov
Identifier: NCT00751036

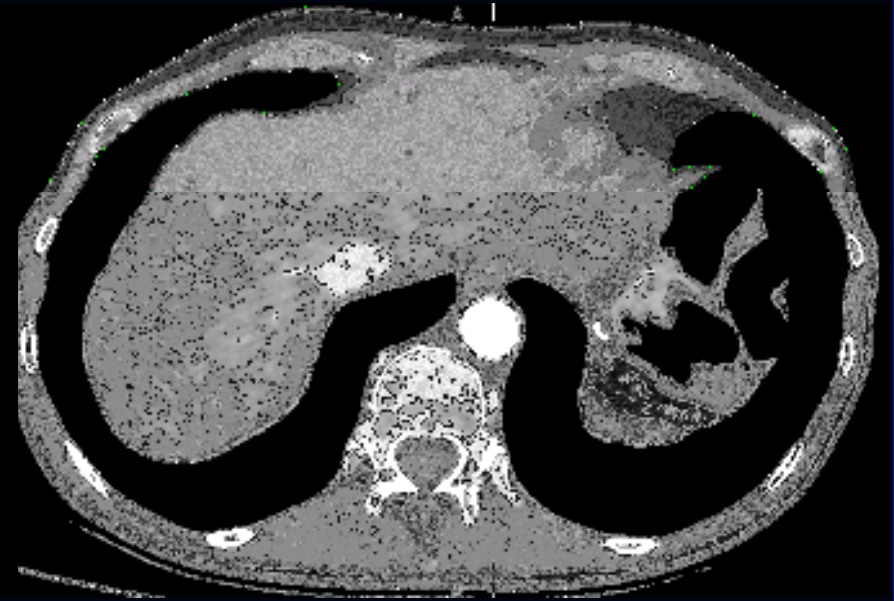
Courtesy Meg von Mehren

HSP90 Inhibitor (IPI-504)

Baseline



Cycle 3



- 1 yr on imatinib at 400 & 800 mg; 1 yr on sunitinib at 37.5 & 50 mg
- Partial Response (PR) to IPI-504 (70% reduction)

Wagner et al, ASCO 2009

Metastatic GIST Trials

- **Phase II studies** in advanced GIST
 - Nilotinib: Kit and Abl inhibitor
 - AMG 706: High affinity Kit inhibitor and VEGFR inhibitor
 - Dasatinib: High affinity Kit, Abl and Src inhibitor (+other targets)
 - Sorafinib: High affinity Kit inhibitor

 - Perifosine (AKT/MapK/p21 inhibitor)+Imatinib: inhibit PI3K activation of AKT
 - ABT (bcl-2 family inhibitor) + Imatinib : restore apoptosis
 - HDAC inhibitor +Imatinib

- **Phase I studies** in GISTs and other solid tumors
 - IGF-1R inhibitor
 - HSP-90 inhibitor

Gastrointestinal Stromal Tumor

Advanced Disease

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