Gastrointestinal Stromal Tumor (GIST) 101

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Background and Introduction

Epidemiology

4000 to 6000 new GIST are diagnosed in the United States each year

GIST is the most common tumor of mesenchymal origin in the gastrointestinal tract

- Approximately 60% to 70% of all identified gastrointestinal masses are determined to be GIST

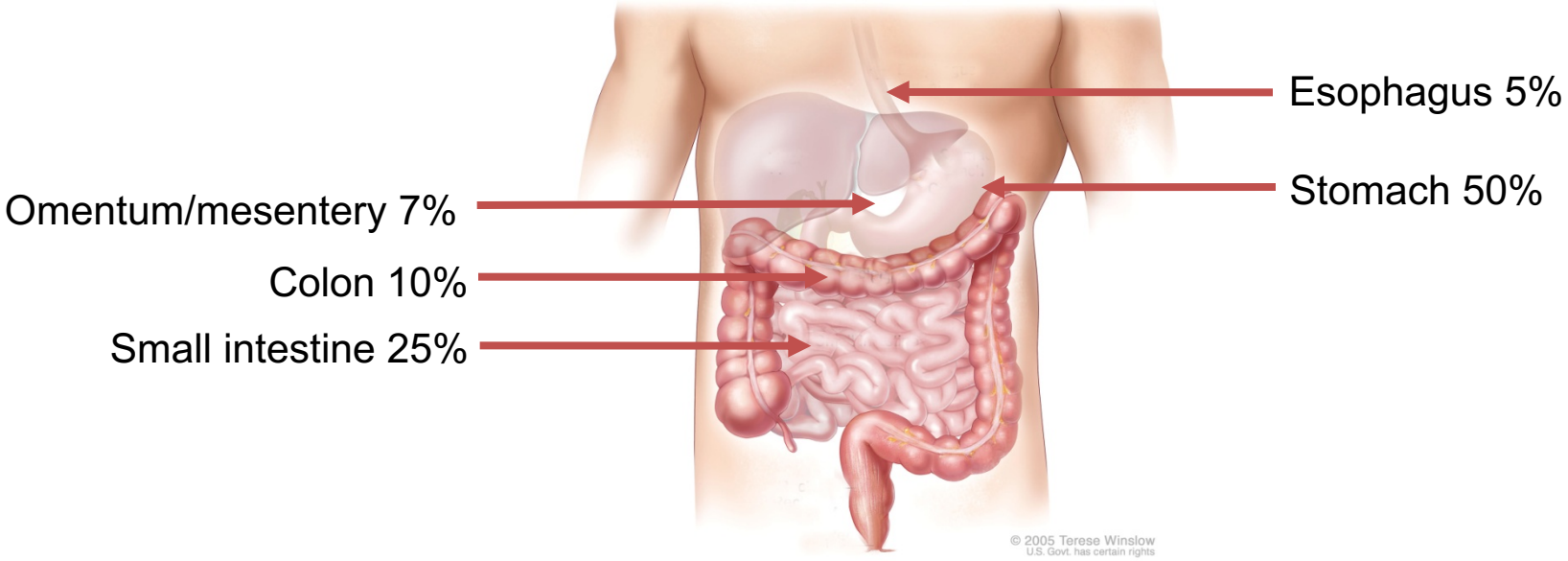


Image courtesy of Terese Winslow; Sepe. *Nat Rev Gastroenterol Hepatol.* 2009;6:363; Shah. *Dig Dis Sci.* 2009;54:1265; Tien. *Ann Surg Oncol.* 2010;17:109.

Initial Presentation

15% to 30% of GIST are discovered incidentally in asymptomatic pts

- Increased use of endoscopy to examine the upper gastrointestinal tract has led to an increased discovery of subepithelial lesions

GIST that are symptomatic at presentation:

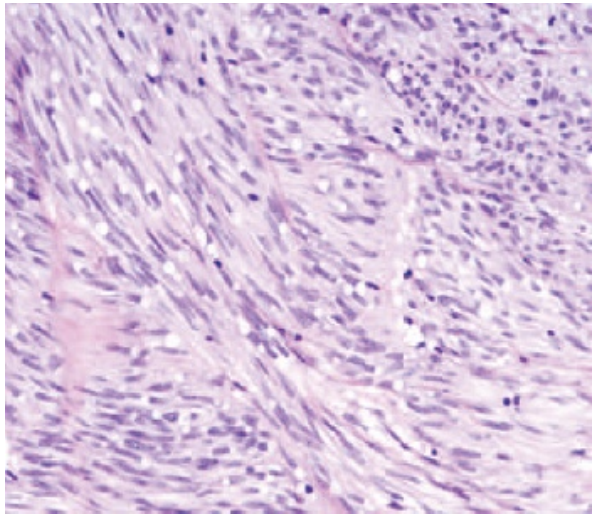
- Gastrointestinal bleeding (53%), overt gastrointestinal bleeding (34%), insidious bleeding that causes anemia (19%), abdominal pain or fullness (32%), and palpable mass (13%)

Sepe. *Gastrointest Endosc*. 2009;70:254; Nilsson. *Cancer*. 2005;103:821; Tryggvason. *Dig Dis Sci*. 2007;52:2249; Hedenbro. *Surg Endosc*. 1991;5:20; Demetri. *J Natl Compr Canc Netw*. 2010;8:S1.

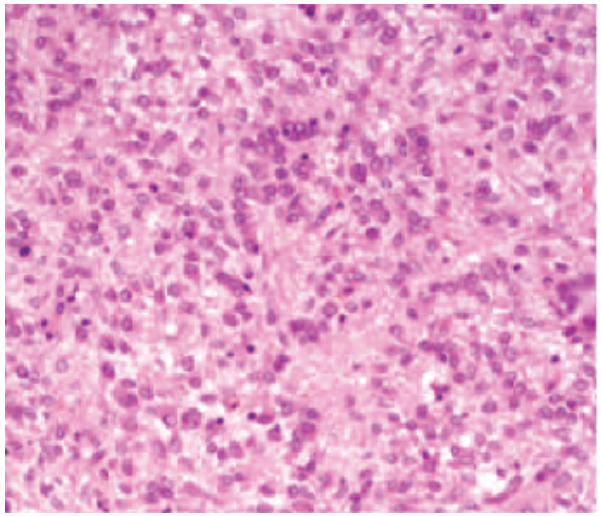
Pathology of GIST

Common histologic patterns

- Spindle cell (70%)
- Epithelioid cell type (20%)
- Spindle cell and epithelioid cell (mixed cell type)



Spindle Cell



Epithelioid Type

Reproduced with permission from Miettinen. *Arch Pathol Lab Med*. 2006;130:1466; Fletcher. *Hum Pathol*. 2002;33:459.

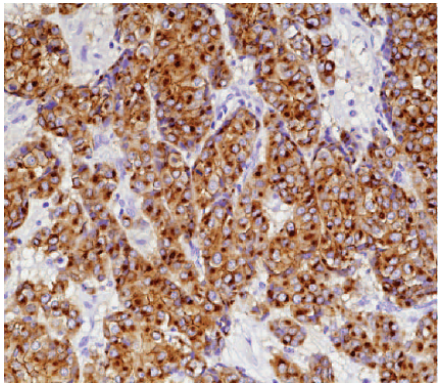
Diagnosis of GIST:

KIT (CD117) Staining

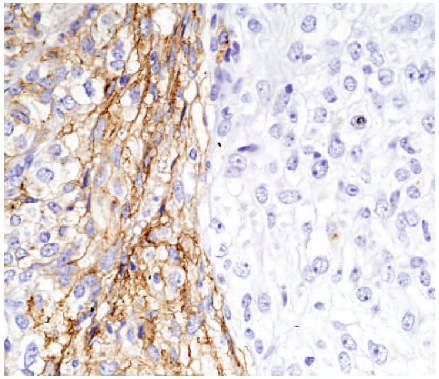
Staining in GIST is often strongly and diffusely positive but might not be uniform

Staining intensity does not predict therapeutic response

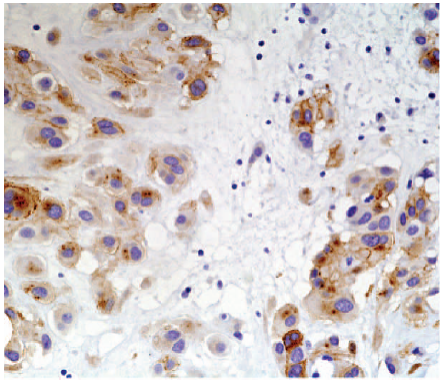
Other malignancies that express KIT: metastatic melanoma, angiosarcoma, neuroblastoma, extramedullary myeloid tumor, seminoma, and small cell lung carcinoma



Diffuse KIT Staining



Mixed KIT Staining



Dot-Like KIT Staining

Reproduced with permission from Miettinen. *Arch Pathol Lab Med.* 2006;130:1466; Demetri. *J Natl Compr Canc Netw.* 2010;8:S1; Fletcher. *Hum Pathol*. 2002;33:459.

Metastatic Potential of GIST

Miettinen Risk Score:

Size	Mitotic Index	Risk of Progressive Disease by Location (%)*			
		Gastric	Jejunal/Ileal	Duodenal	Rectal
≤2 cm	≤5/50 HPFs	None (0)	None (0)	None (0)	None (0)
>2 cm, ≤5 cm		Very low (1.9)	Low (4.3)	Low (8.3)	Low (8.5)
>5 cm, ≤10 cm		Low (3.6)	Moderate (24)	ID	ID
>10 cm		Moderate (12)	High (52)	High (34)	High (57)
≤2 cm	>5/50 HPFs	None (0)†	High (50)†	ID	High (54)
>2 cm, ≤5 cm		Moderate (16)	High (73)	High (50)	High (52)
>5 cm, ≤10 cm		High (55)	High (85)	ID	ID
>10 cm		High (86)	High (90)	High (86)	High (71)

*Metastasis and tumor-related deaths; †tumor categories with few pts.
HPF=microscopic high-power fields in tissue sections; ID=insufficient data.

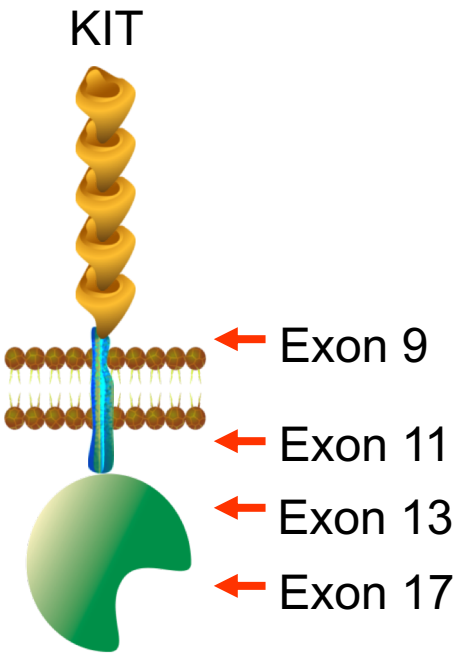
Miettinen. *Semin Diagn Pathol*. 2006;23:70; Sepe. *Gastrointest Endosc*. 2009;70:254.

GIST genomics

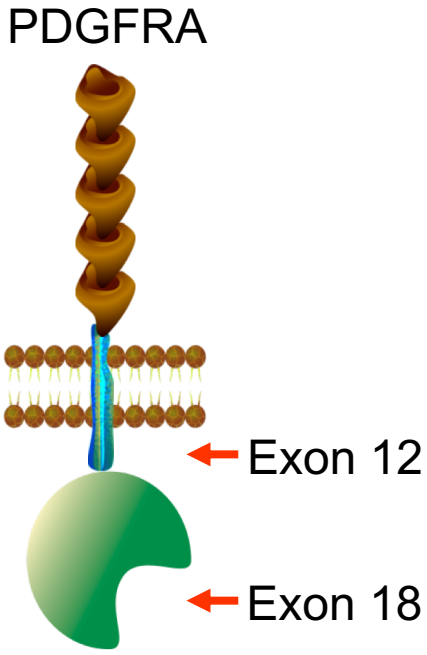
KIT and PDGFRA mutations

GIST genotyping can be useful for

- Confirmation of diagnosis
- Dosing decisions and therapeutic approaches
- Determination of prognosis

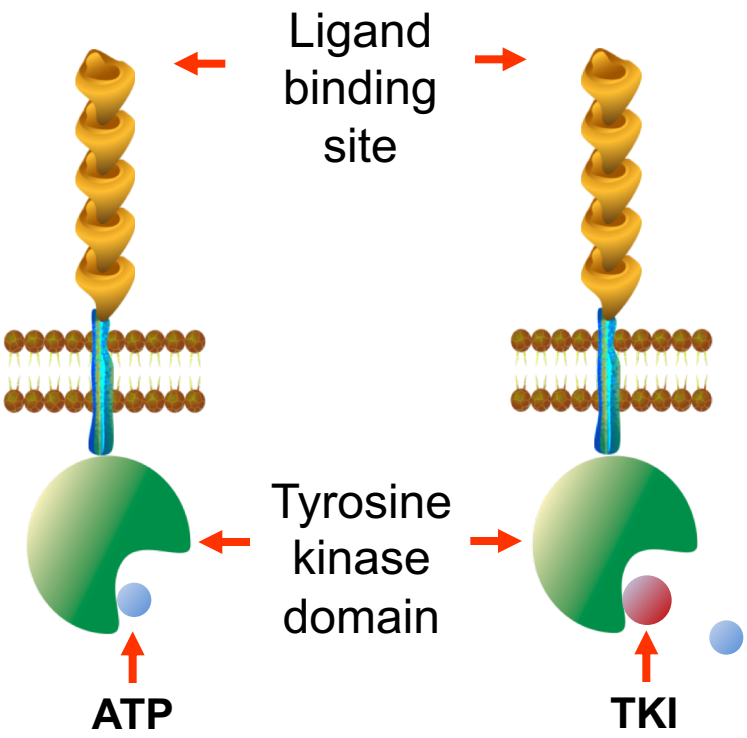


Gene	Exon	Prevalence
KIT	9	18%
	11	67%
	13	2%
	17	2%
PDGFRA	12	1%
	18	4%



Demetri. *J Natl Compr Canc Netw*. 2010;8:S1; Heinrich. *J Clin Oncol*. 2003;21:4342.

Inhibition of RTK Activity



TKIs inhibit RTKs, including KIT and PDGFRA

TKIs interact in the tyrosine kinase domain and block ATP binding and RTK function

ATP=adenosine triphosphate; FDA=US Food and Drug Administration; TKI=tyrosine kinase inhibitor.

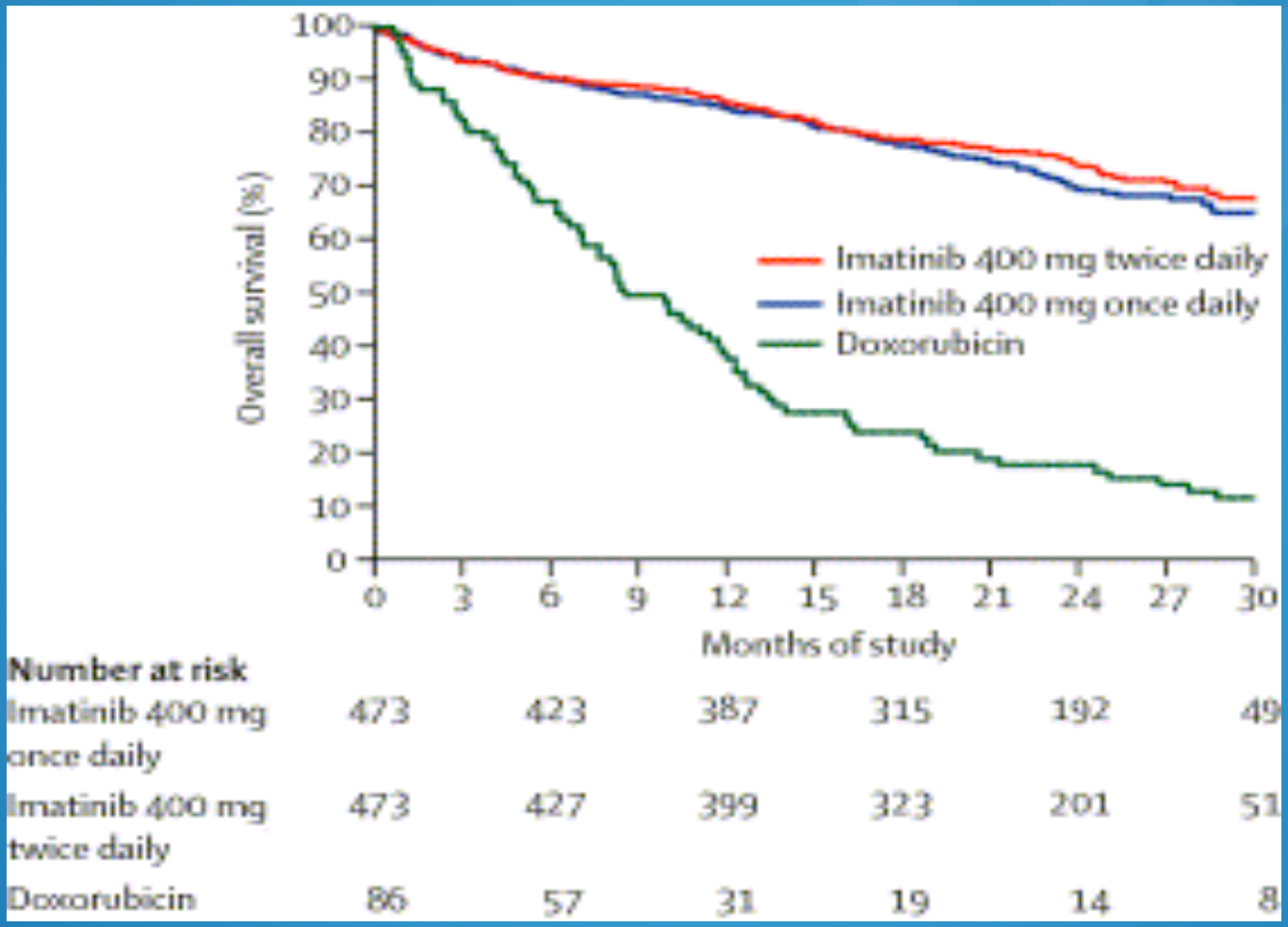
FDA-Approved GIST Therapies

Imatinib (Gleevec) - 2002

Sunitinib (Sutent) - 2006

Regorafenib (Stivarga) -2013

EORTC Phase III Imatinib for Advanced GIST



Number at risk						
Imatinib 400 mg once daily	473	423	387	315	192	49
Imatinib 400 mg twice daily	473	427	399	323	201	51
Doxorubicin	86	57	31	19	14	8

Verweij, et al 2004

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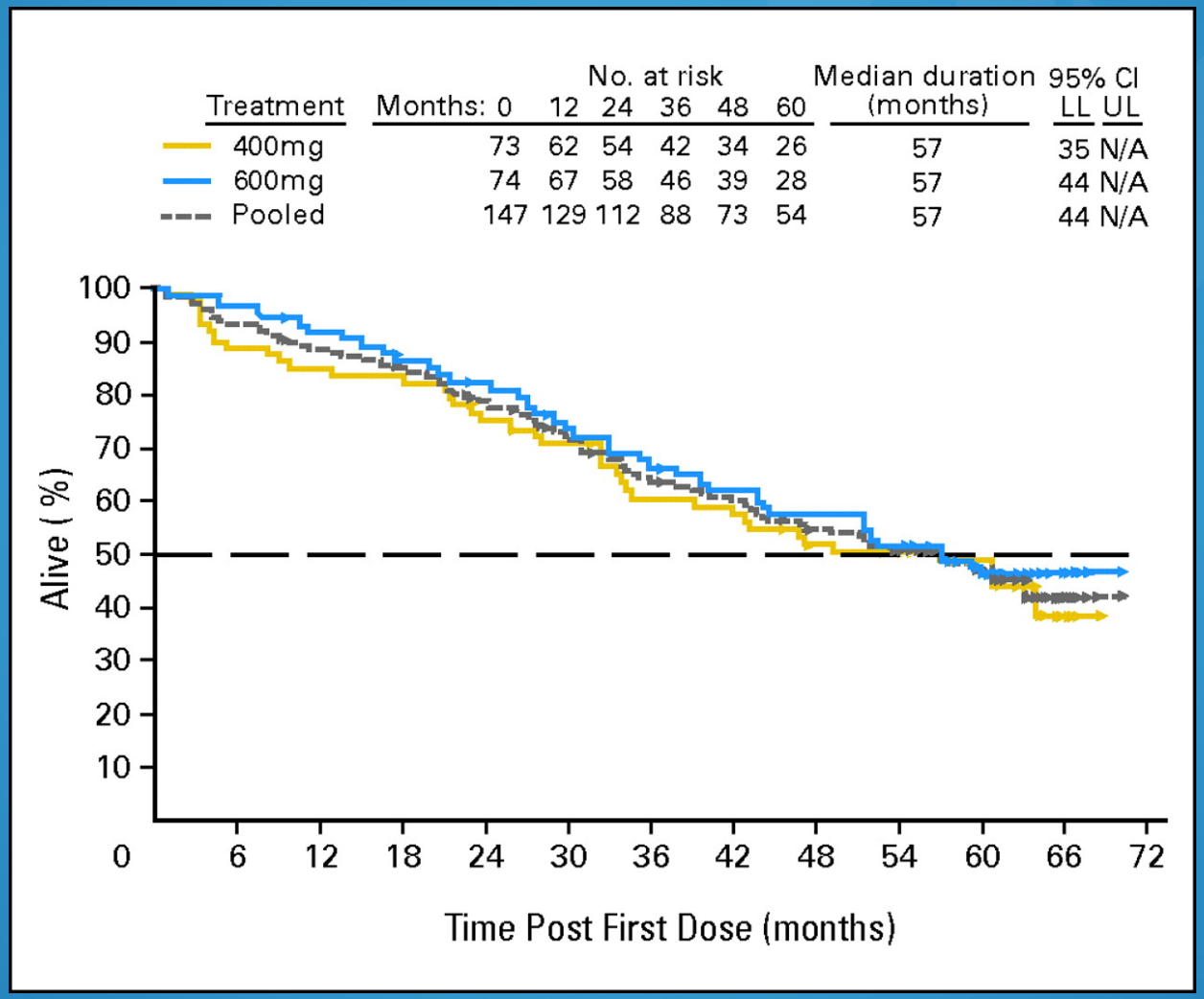
Overall Survival



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

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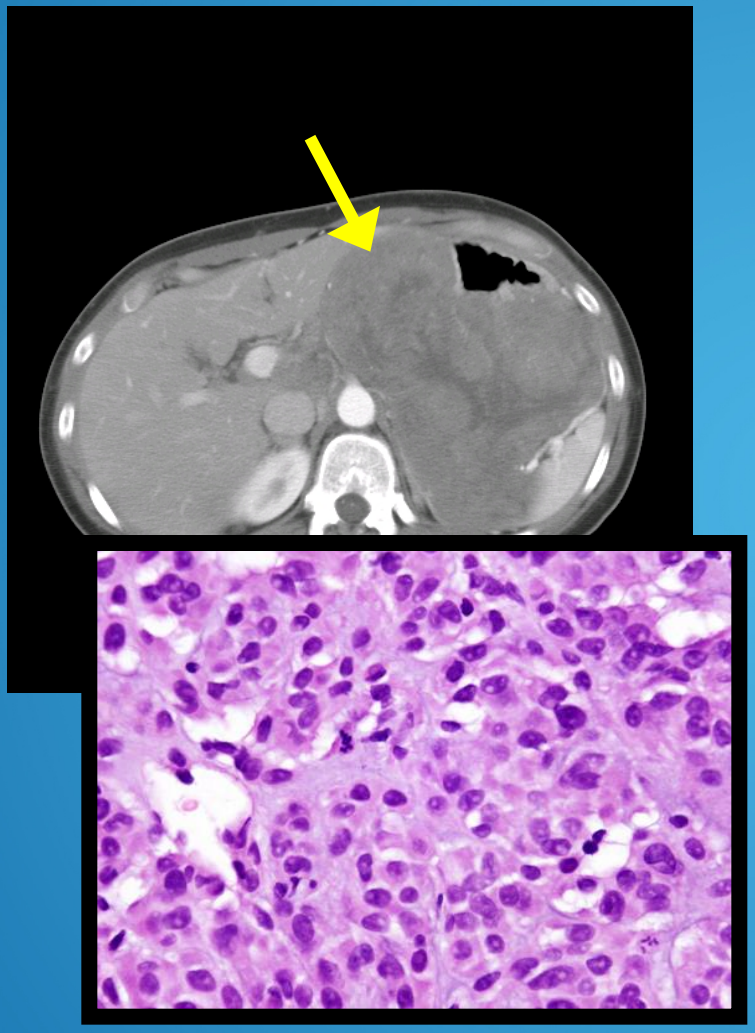
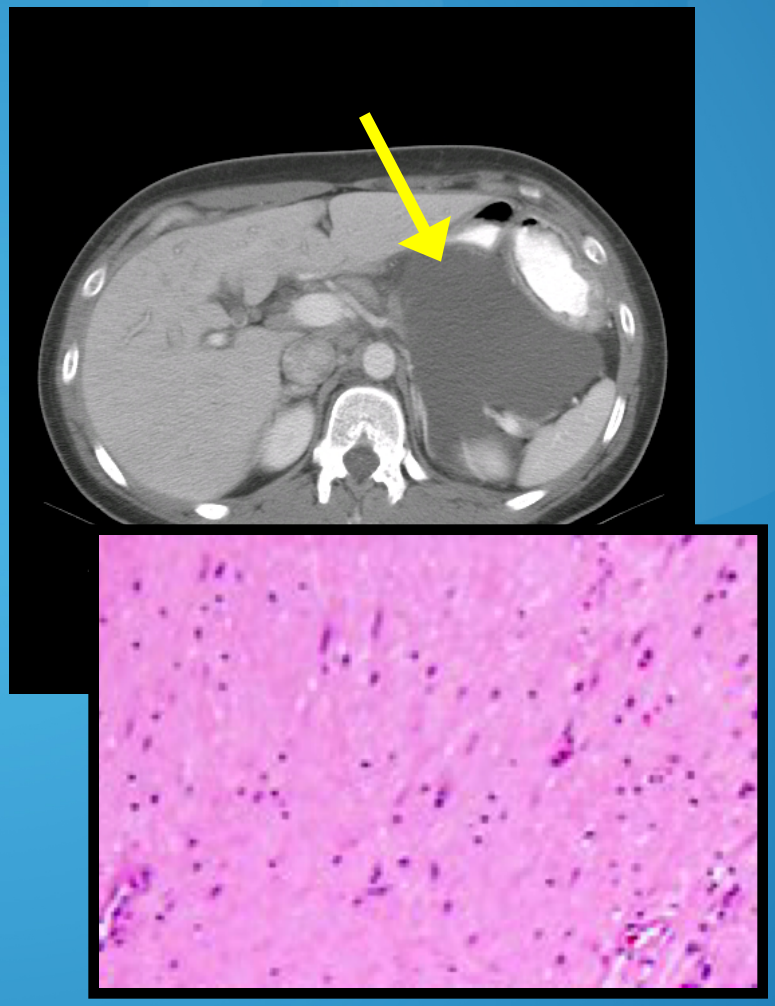
GIST Response



Pre-Imatinib



Post-Imatinib (8 weeks therapy)

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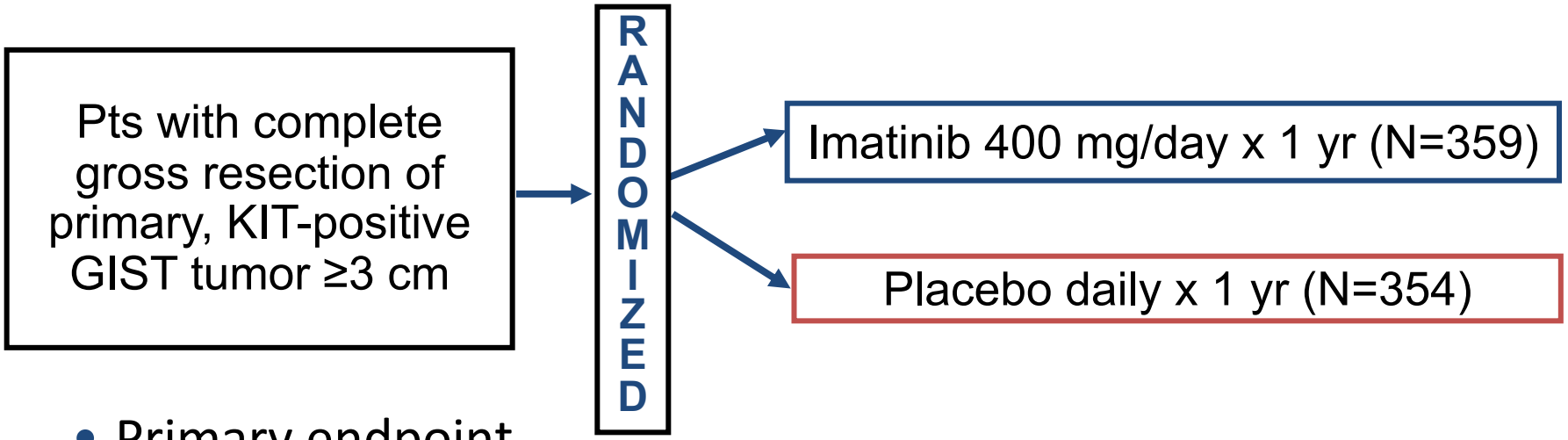
Phase III Postoperative Imatinib Trial

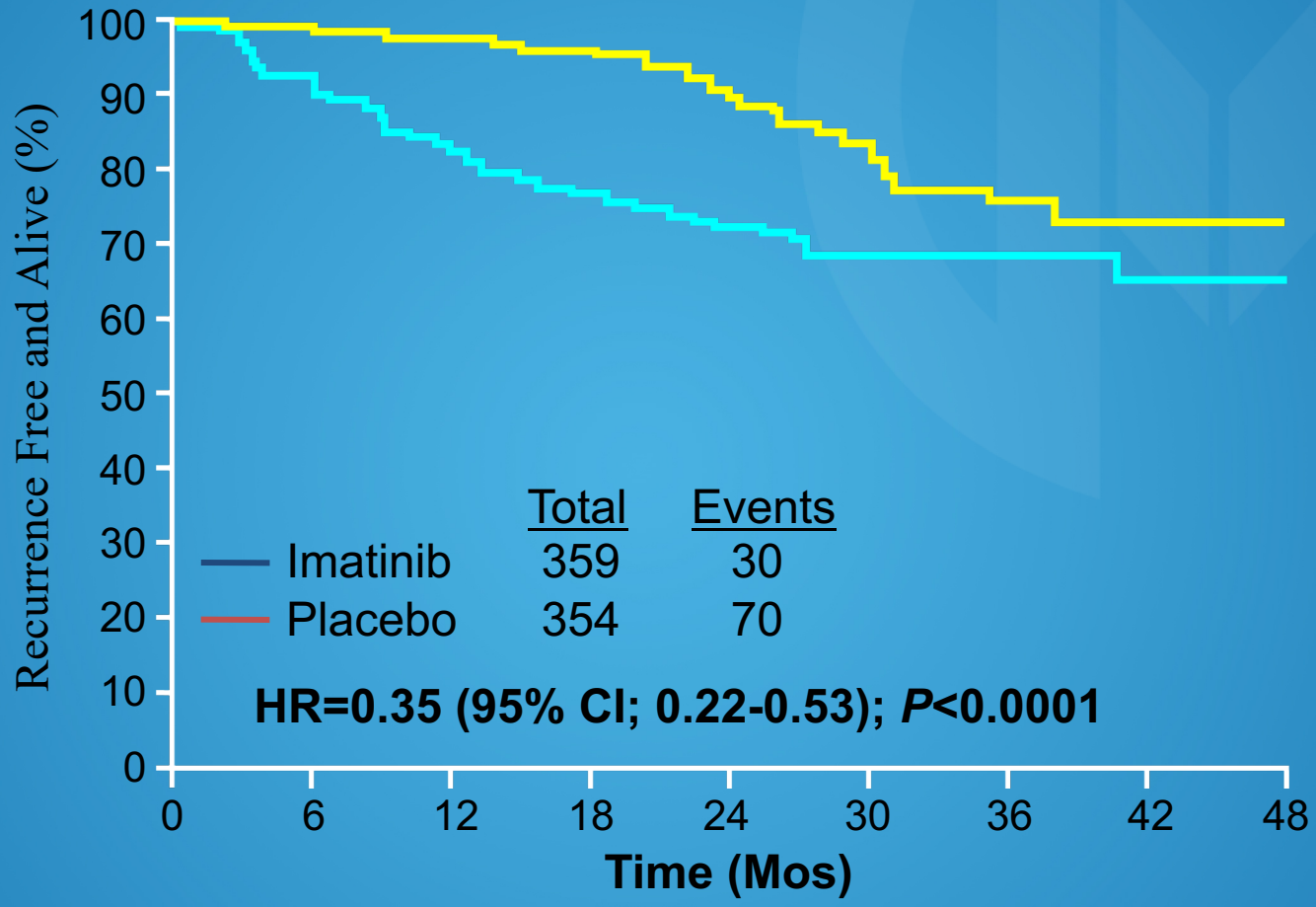
ACOSOG Z9001



- Primary endpoint
  - RFS
- Secondary endpoint
  - OS
- Pts assigned to placebo were eligible for crossover in the event of tumor recurrence

DeMatteo. *Lancet*. 2009;373:1097.

ACOSOG Z9001: RFS



Number at risk

Placebo	354	188	89	34	8
Imatinib	359	207	105	33	6

DeMatteo. *Lancet*. 2009;373:1097.

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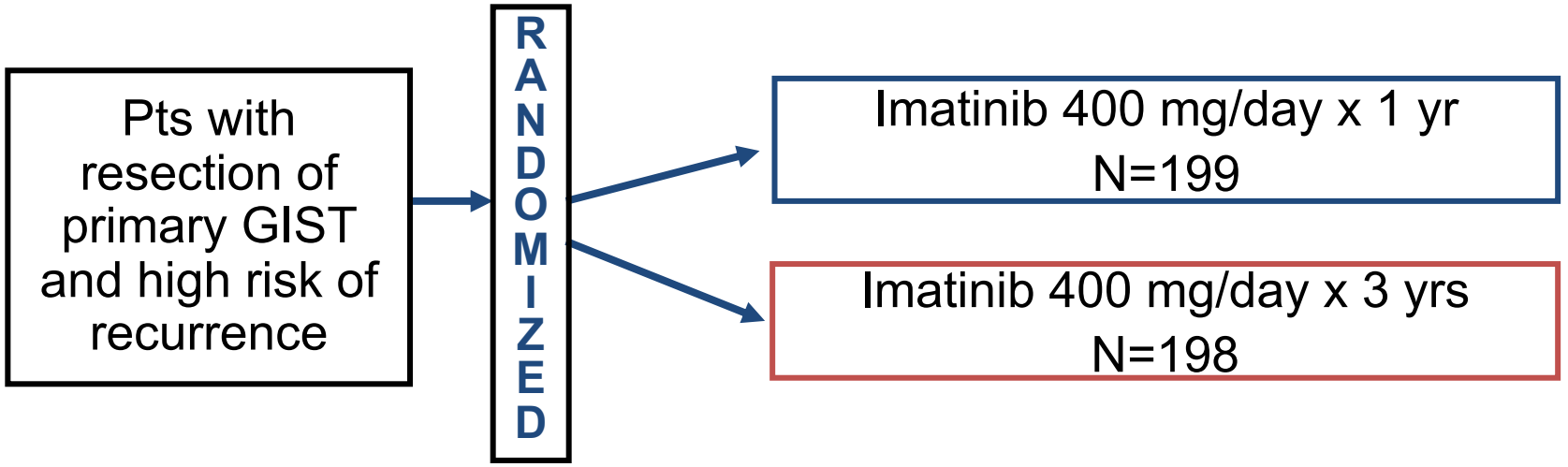
1 Yr vs 3 Yrs of Adjuvant Imatinib:

SSGXVIII

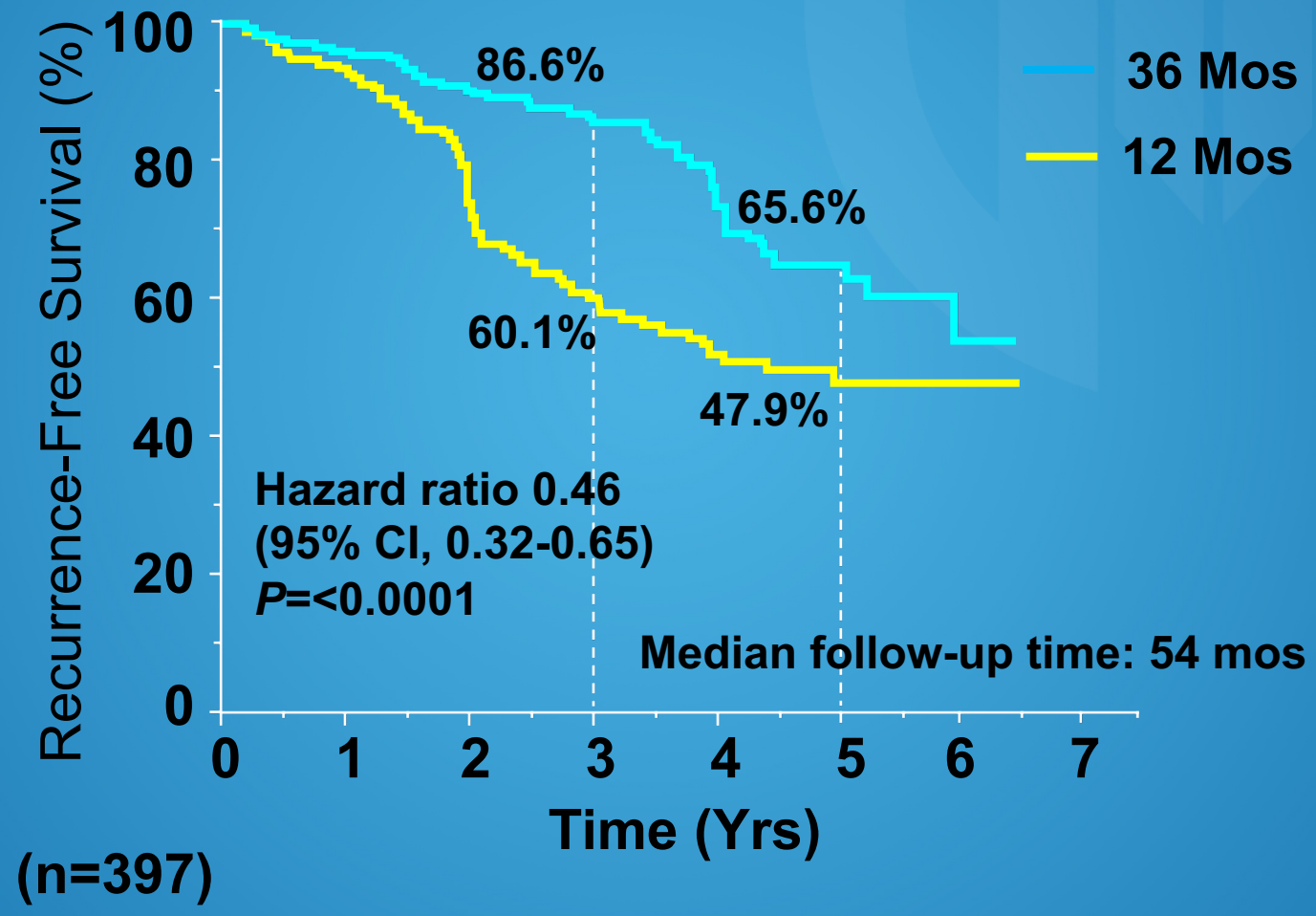


- Primary endpoint
  - RFS
- Secondary endpoints
  - AEs and OS

AE=adverse event.

Joensuu. *ASCO.* 2011 (abstr LBA 1).

SSGXVIII: rate of relapse



Joensuu. *ASCO.* 2011 (abstr LBA 1).

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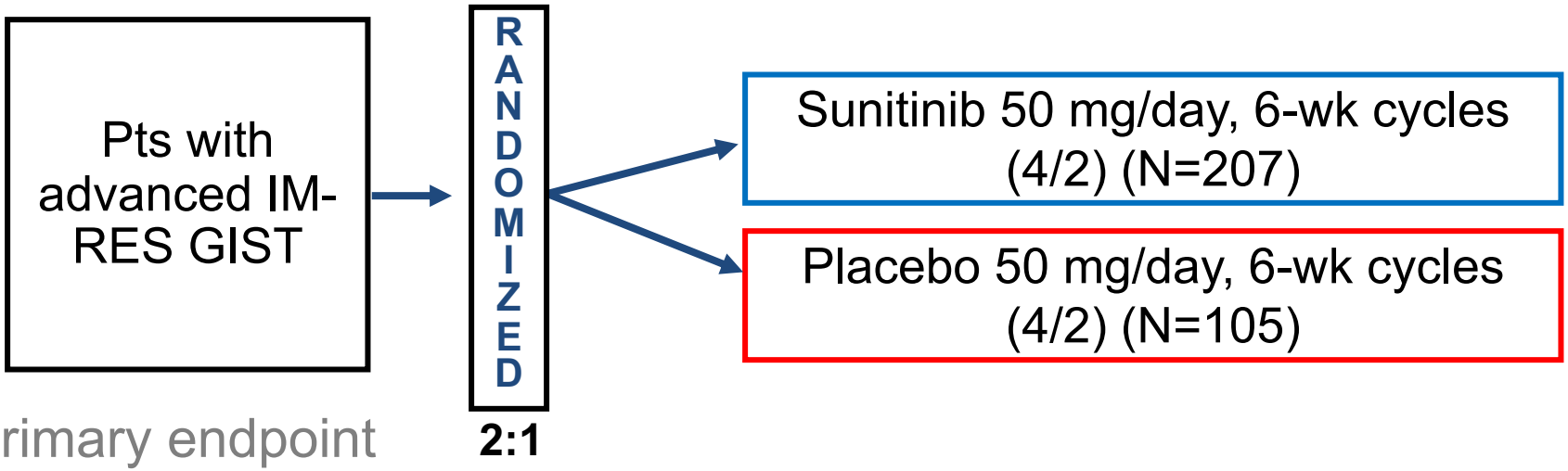
Sunitinib Efficacy in Patients With Imatinib-Refractory GIST



Primary endpoint

TTP, as defined using RECIST

Secondary endpoints

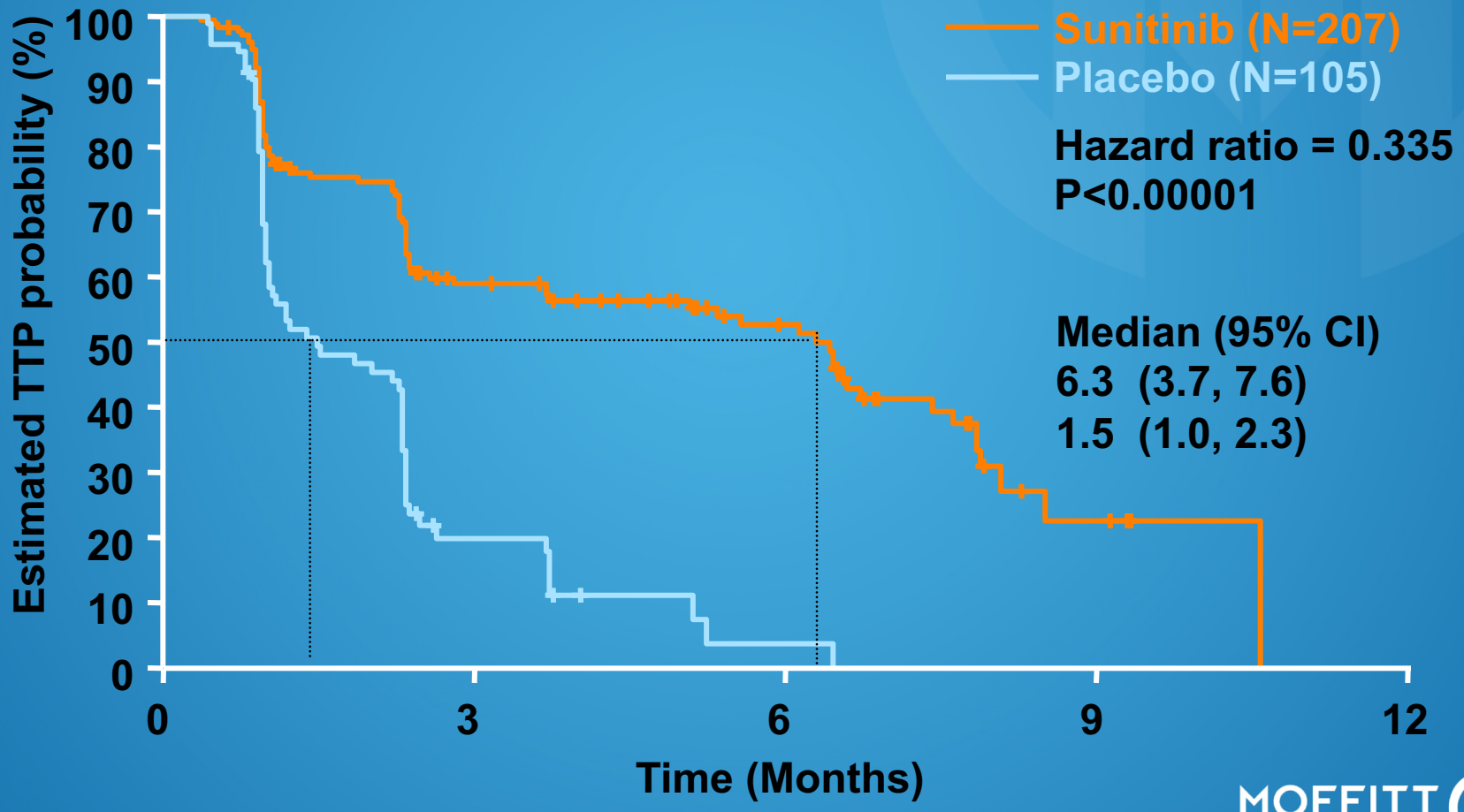
PFS, OS, ORR, TTR, DOR, and duration of PS maintenance

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



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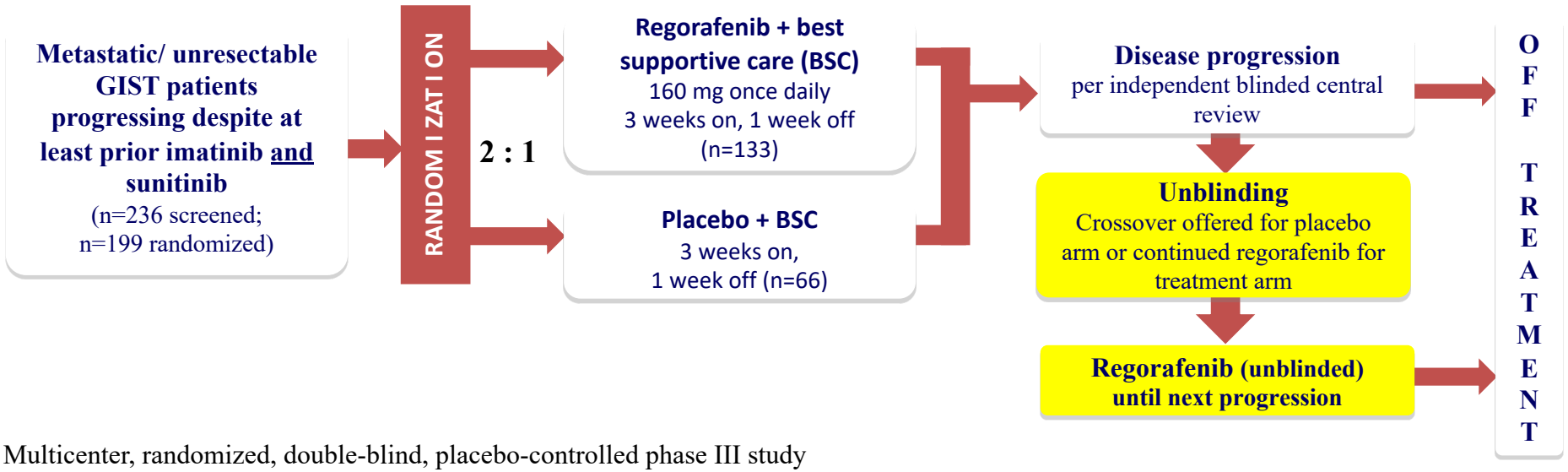
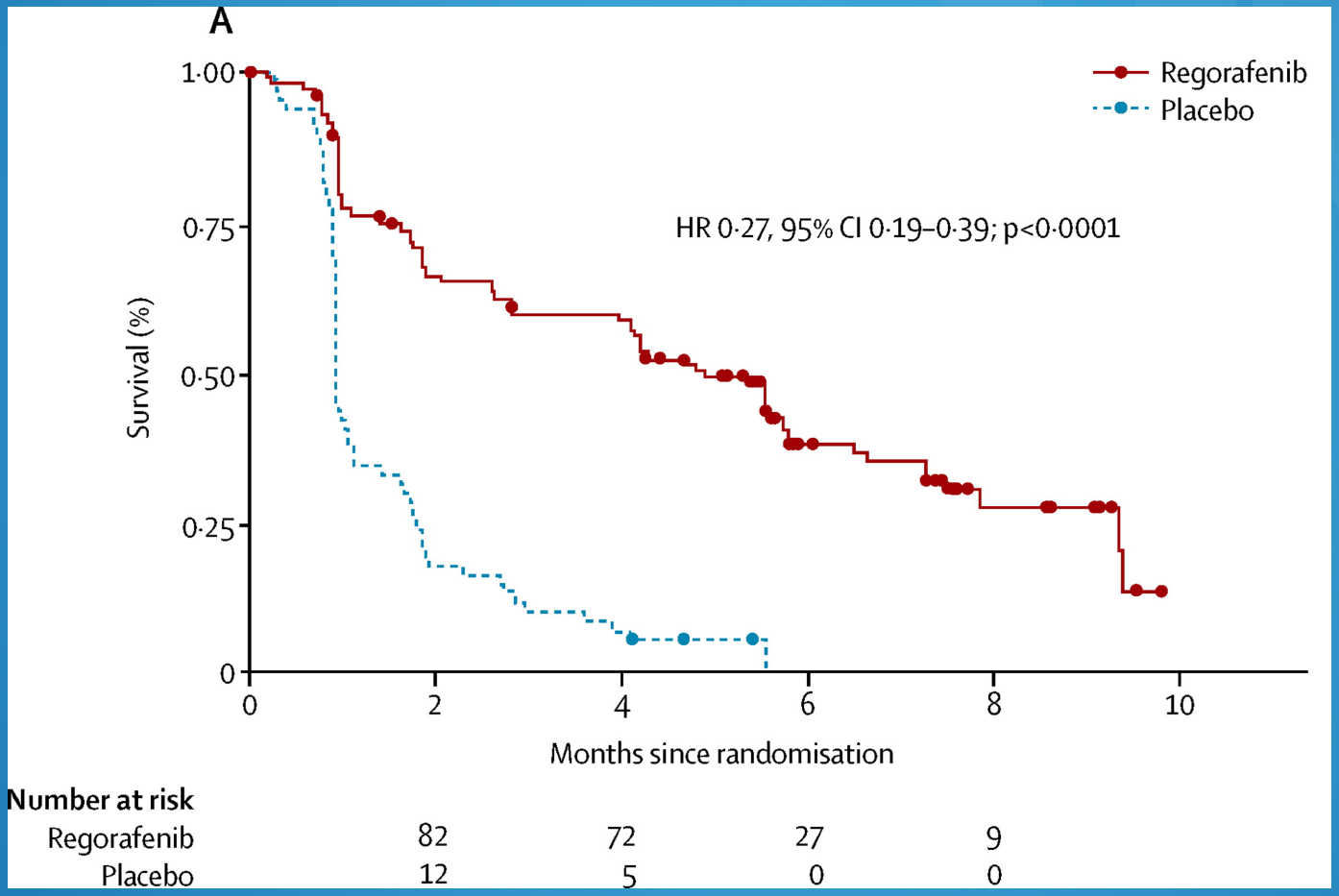
Regorafenib in imatinib and sunitinib resistant GIST

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")

Time to Tumor Progression



Other TKIs

FDA-approved but not for GIST

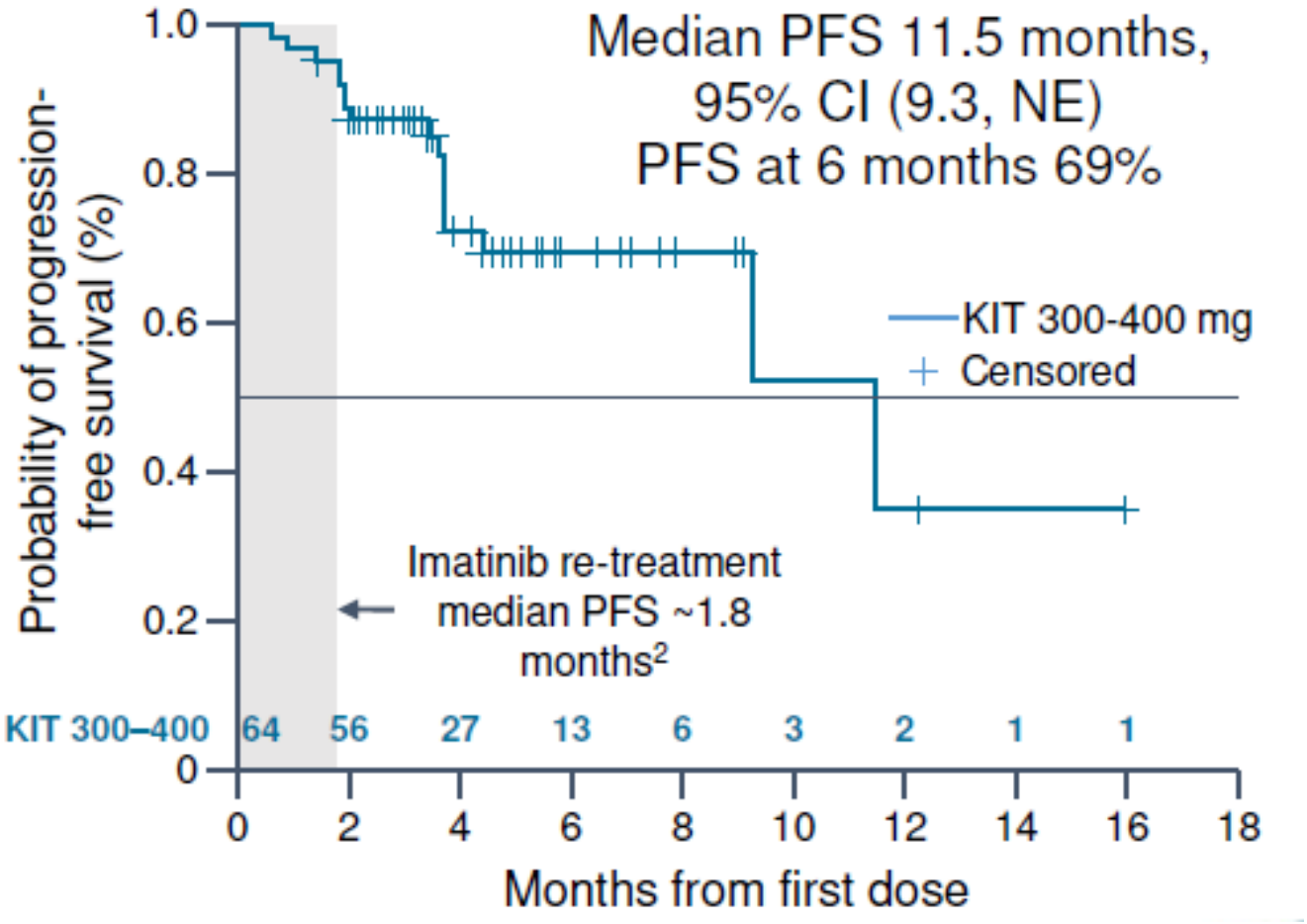
Class	Agent	Trial Phase	Results
KIT Inhibitors	Sorafenib	II	PR=13%, SD=58% PFS=5 months
	Dasatinib	II	PR=22%, SD=24% PFS= 2 months
	Nilotinib	I/II/III	PR=10%, SD=37% PFS=3 months
	Pazopanib	II	PazoGIST, PFS-1.9 months
	Ponatinib	II	Exon 11 CBR 37%, PFS 4.3 months
	Axitinib	ND	ND
mTOR Inhibitors	Everolimus	II	PR=2%, SD=43% PFS=3.5 months
	Temsirolimus	ND	ND

Other TKIs

Ongoing Trials

BLU-285 (avapritinib)

Now in phase III (vs. regorafenib)



Heinrich et al. CTOS 2017.

Other TKIs

Ongoing Trials

DCC-2618 (Ripretinib)

In phase III vs. placebo (4th line)

Enrollment complete

In phase III vs. sutent (2nd line)

Lines	N	mPFS	Number Censored	Active Patients
2	38	42 weeks	22 (58%)	61%
3	29	40 weeks	15 (52%)	59%
4+	111	24 weeks	40 (36%)	44%

George, et al. ESMO 2018

Other Clinical Trials

- KIT/PDGFR inhibitors
- KIT/PDGFR inhibitors plus Other
- Other
  - Downstream inhibitors
  - Immunotherapy including cellular therapy

Molecular Decision-Making in GIST

- Optimal therapy for GIST patients ***requires*** molecular decision-making
  - Kit exon 9: Imatinib 800mg (or tolerated dose)
  - PDGFR D842V: anti-PDGFR trial
  - SDH-B deficiency: Sunibitnib or Regorafenib
  - BRAF V600E: Raf inhibitor?
  - NF-1, Ras: Raf inhibitor?
  - KIT secondary mutations
    - Exon 13 (ATP binding site): Sunitinib 37.5 mg daily
    - Exon 17 (A-loop): Regorafenib 120 mg daily

  - **TRK fusion – LOXO-101 (Larotrectinib)**

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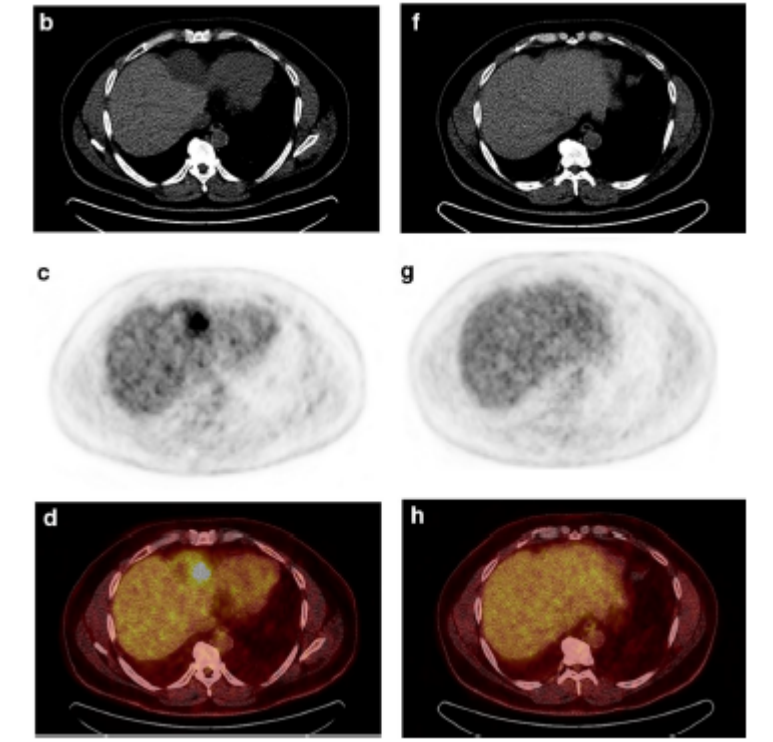
CASE REPORT Open Access

Response to sunitinib of a gastrointestinal stromal tumor with a rare exon 12 *PDGFRA* mutation

Andrew S. Brohl[1*], Elizabeth G. Demicco[2], Karen Mourtzikos[3] and Robert G. Maki[4]



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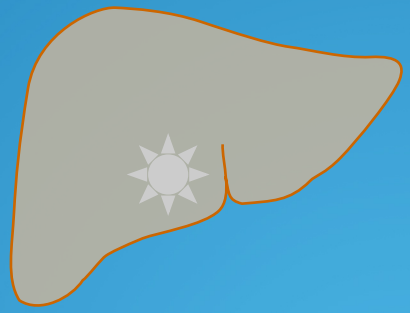
Patterns of Metastasis

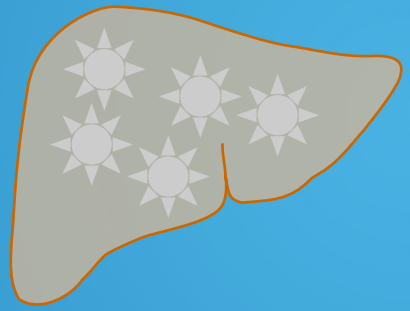
Oligometastasis



Systemic Therapy

Local Therapy

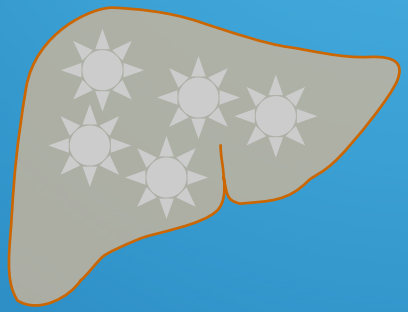
Single Organ Metastases

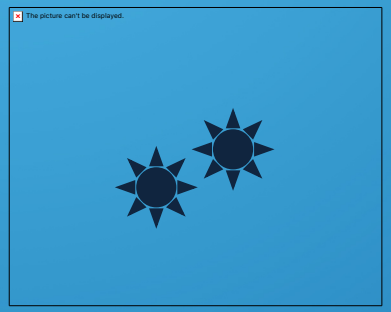


Systemic Therapy

Local Therapy

Multi-Organ Metastases





Systemic Therapy

Metastatic lesion

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Future of GIST treatment

- Increasing TKI options
- Increased personalization of therapy
  - Genetics-based TKI selection
  - Real time disease monitoring blood-based DNA testing
- Continued exploration of novel treatments (downstream TKIs, immunotherapies, combination approaches)

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