Breakout Session 2

Multi-disciplinary management of advanced GIST

Talks

1. **How I treat advanced GIST?**
   - by *Dr Richard Quek*

2. **Advanced molecular toolkit in advanced GIST**
   - by *Dr Nagavalli DO Somasundaram*

2. **When would I offer surgery in metastatic GIST?**
   - by *Dr Melissa Teo*

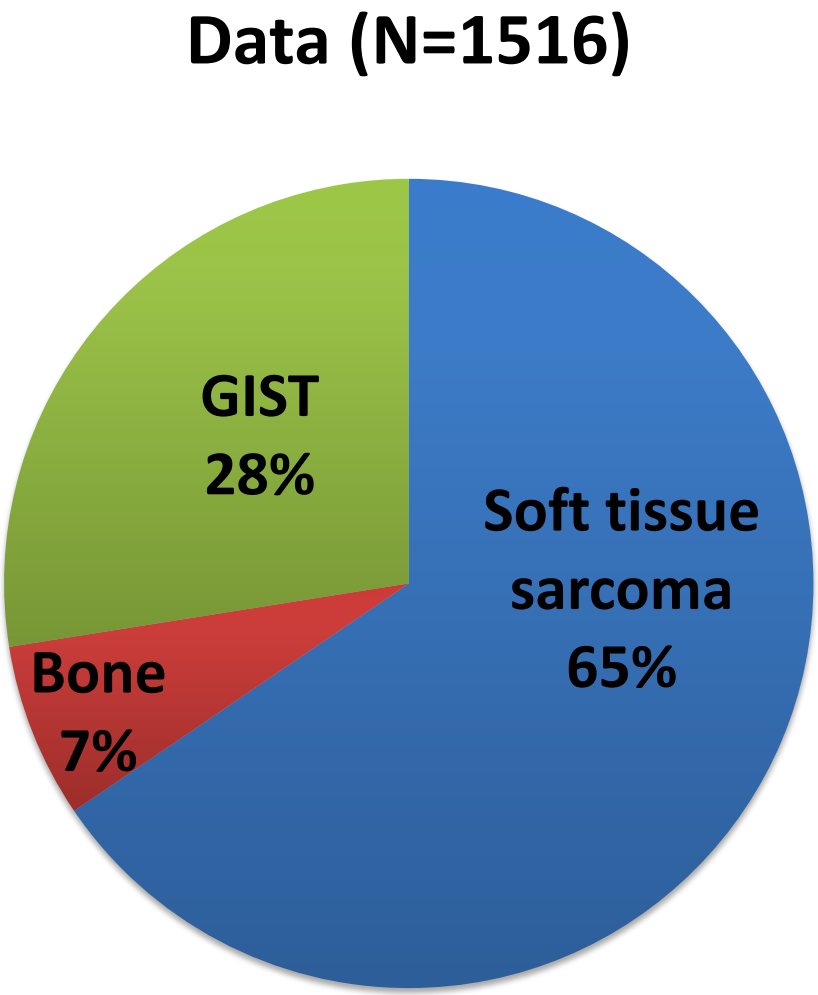
How I Treat Advanced GIST ?

Speaker: Dr Richard Quek
Organization: National Cancer Centre Singapore
Date: 15 Jul 2015

Gastrointestinal Stromal Tumor (GIST)

- GIST is one of the most common forms of sarcoma
- Originate from the same lineage as the interstitial cells of Cajal
- Characterized by the presence of KIT/ PDGFRA activating mutations
- 10-15% of GIST are wild type for KIT/ PDGFRA mutations
- Mutations result in abnormal constitutively active tyrosine kinases

Distribution of Soft Tissue Sarcoma
NCC Singapore Sarcoma Database

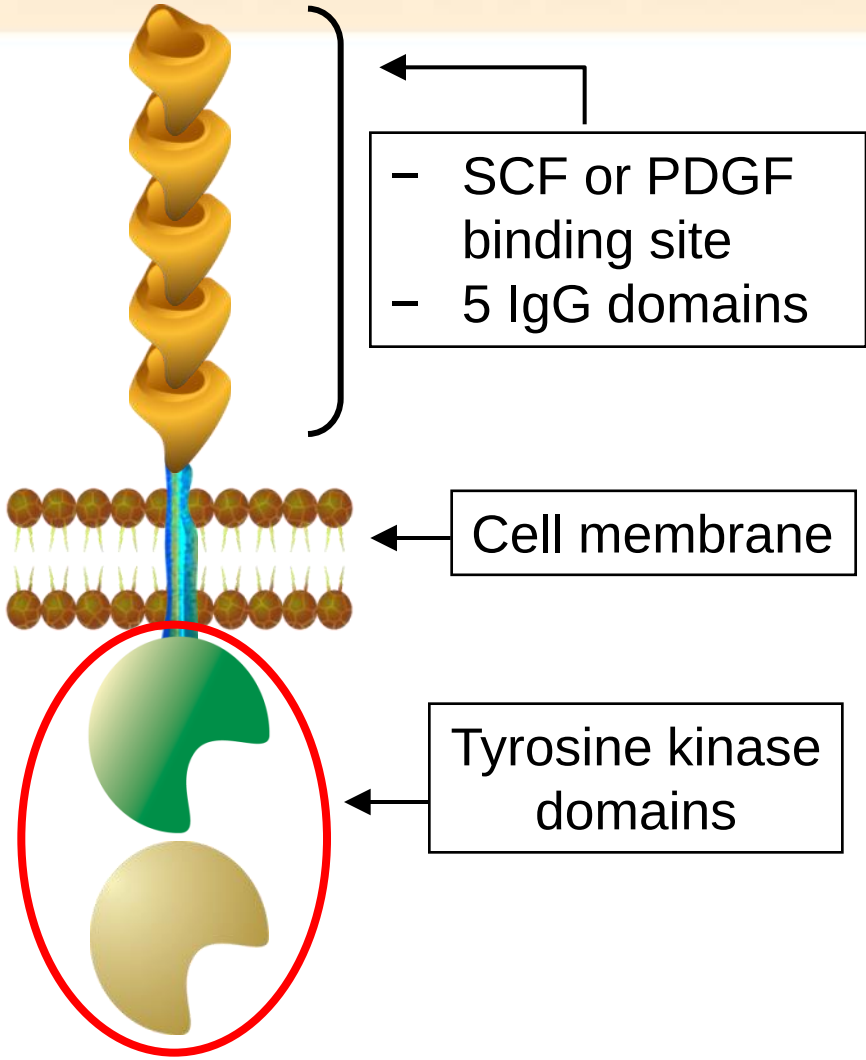


Partners in Academic Medicine

SingHealth DUKE NUS GRADUATE MEDICAL SCHOOL SINGAPORE

KIT and PDGFRA Receptor Structures

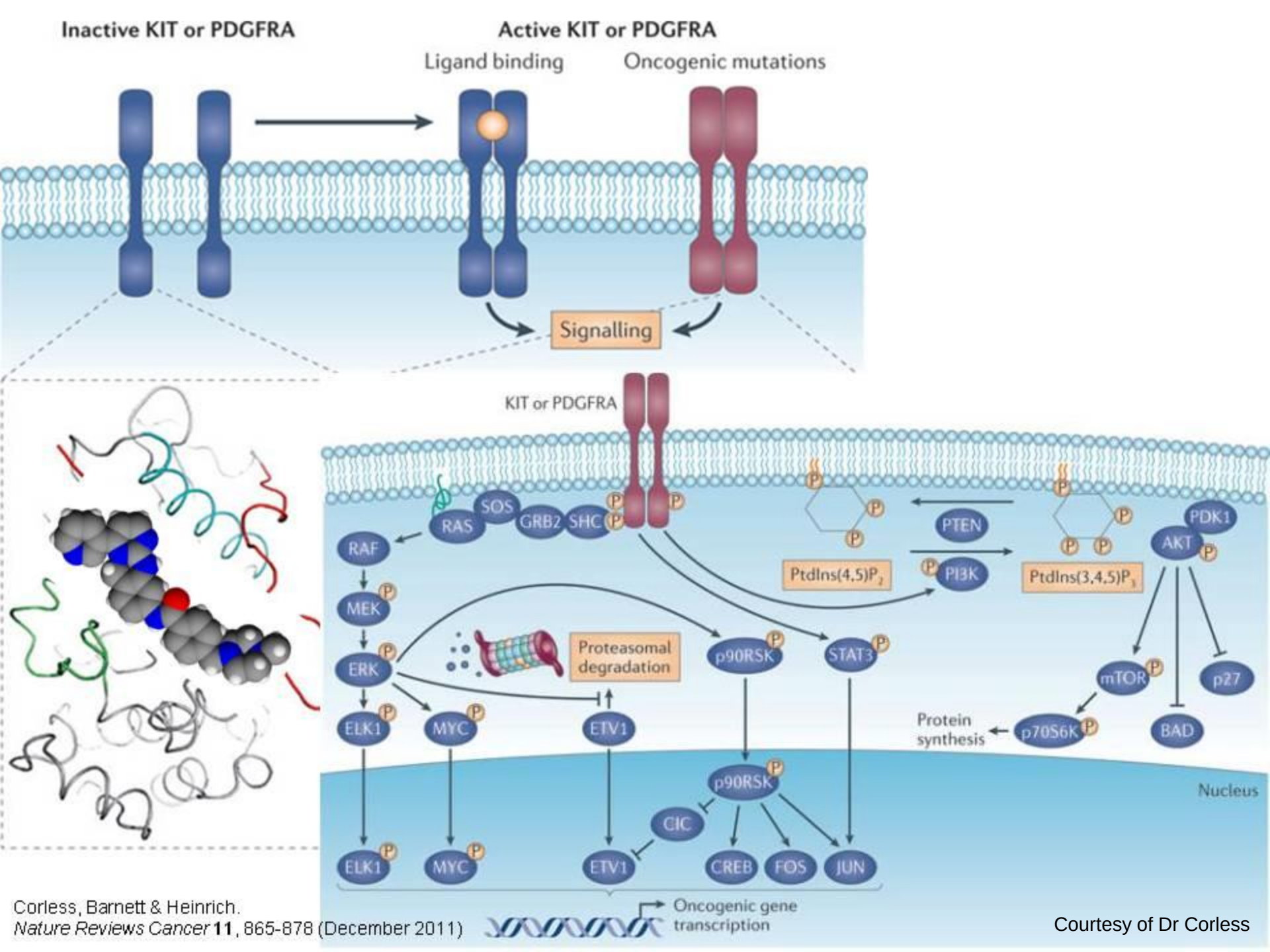
- Type 3 receptor tyrosine kinases
- Extracellular domain binds ligand
  - SCF for KIT
  - PDGF for PDGFRA
- Downstream effects of ligand binding to KIT or PDGFRA are proliferative and antiapoptotic
- Intracellular domain has
  - 2 tyrosine kinase domains
  - Multiple autophosphorylation sites



SCF, stem cell factor; PDGF, platelet-derived growth factor; IgG, immunoglobulin G., ATP, adenosine triphosphate.

Taylor ML et al. Hematol Oncol Clin North Am. 2000;14:517-535.
Corless CL et al. Annu Rev Pathol. 2008;3:557-586.
Figure adapted with permission from Trent JC et al. Curr Opin Oncol. 2006;18:386-395.

Courtesy of Eva Wardelmann



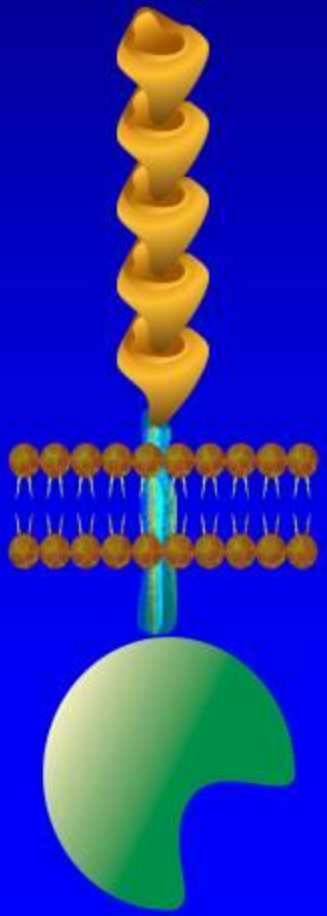
Corless, Barnett & Heinrich.
Nature Reviews Cancer **11**, 865-878 (December 2011)

Courtesy of Dr Corless

KIT and *PDGFRA* Mutations in >2000 GISTs (Heinrich & Corless Labs)

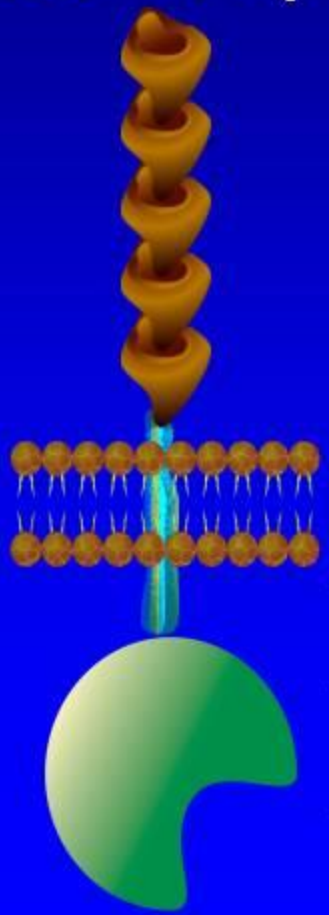
Wild-type tumors: 14%

KIT (78.5%)



- Exon 9 (9%)
- Exon 11 (67%)
- Exon 13 (1%)
- Exon 17 (1%)

PDGFRA (7.5%)

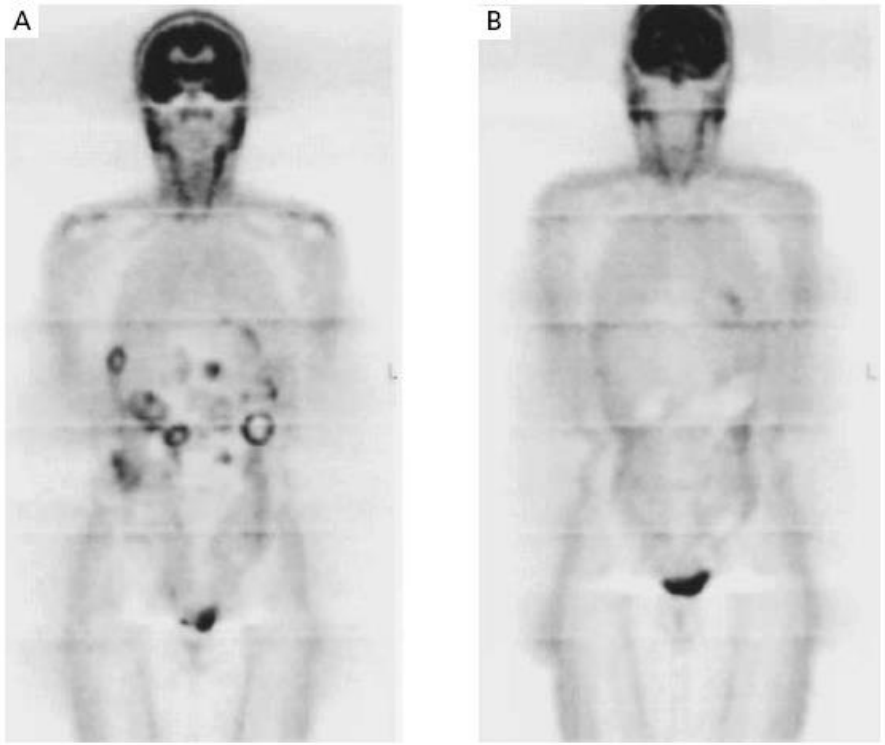


- Exon 12 (2%)
- Exon 14 (rare)
- Exon 18 (5.5%)

Courtesy of Dr Corless

Joensuu et al. N Engl J Med. 2001;344(14):1052-6

- **Imatinib**, tyrosine kir



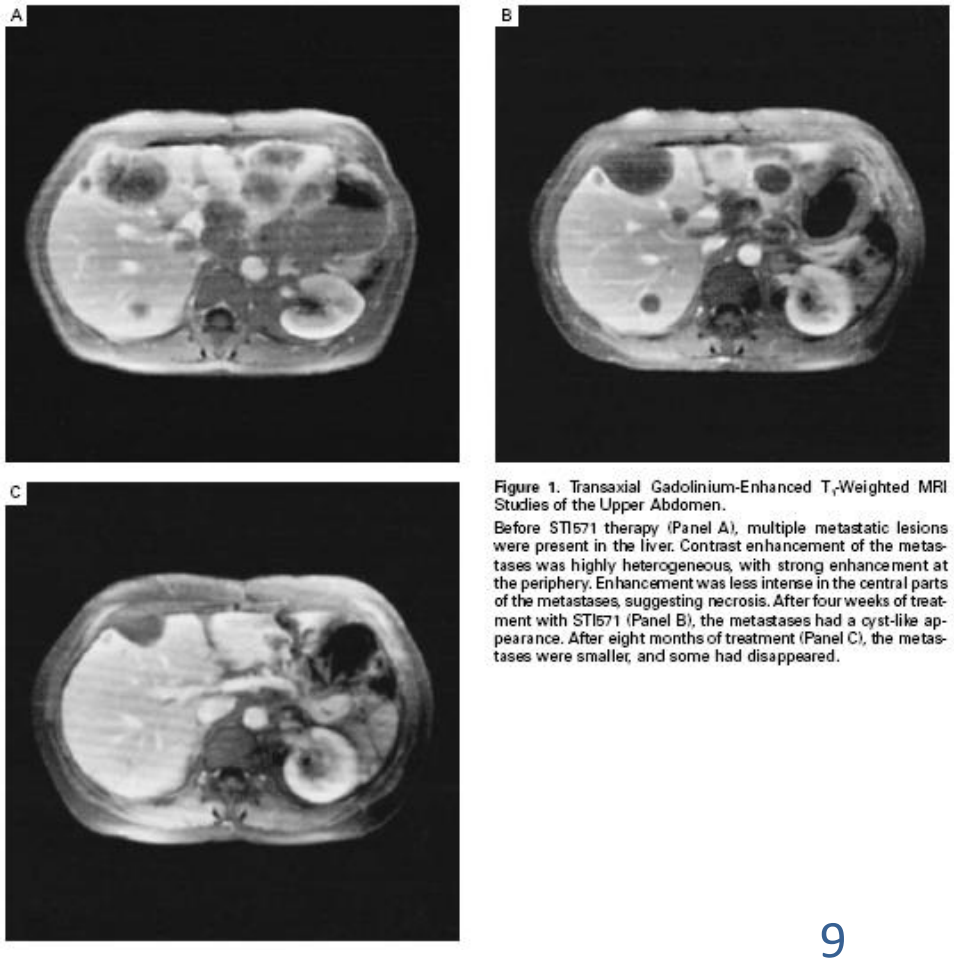


Figure 1. Transaxial Gadolinium-Enhanced T_1-Weighted MRI Studies of the Upper Abdomen.

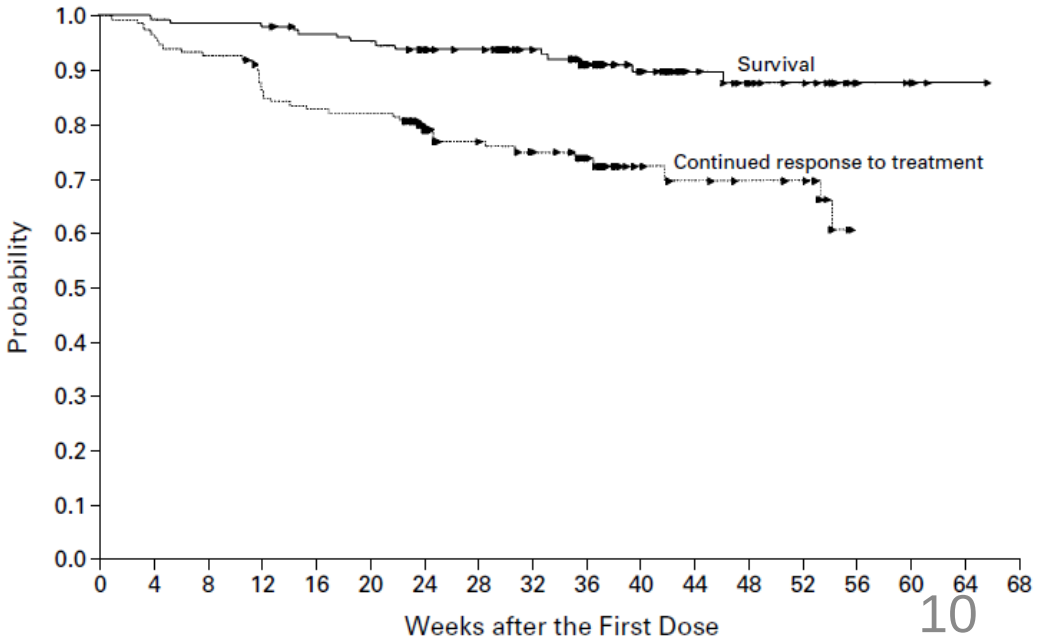
Before STI571 therapy (Panel A), multiple metastatic lesions were present in the liver. Contrast enhancement of the metastases was highly heterogeneous, with strong enhancement at the periphery. Enhancement was less intense in the central parts of the metastases, suggesting necrosis. After four weeks of treatment with STI571 (Panel B), the metastases had a cyst-like appearance. After eight months of treatment (Panel C), the metastases were smaller, and some had disappeared.

SingHealth DUKE NUS GRADUATE MEDICAL SCHOOL SINGAPORE

EFFICACY AND SAFETY OF IMATINIB MESYLATE IN ADVANCED GASTROINTESTINAL STROMAL TUMORS

GEORGE D. DEMETRI, M.D., MARGARET VON MEHREN, M.D., CHARLES D. BLANKE, M.D., ANNICK D. VAN DEN ABBEELE, M.D., BURTON EISENBERG, M.D., PETER J. ROBERTS, M.D., MICHAEL C. HEINRICH, M.D., DAVID A. TUVESON, M.D., PH.D., SAMUEL SINGER, M.D., MILOS JANICEK, M.D., PH.D., JONATHAN A. FLETCHER, M.D., STUART G. SILVERMAN, M.D., SANDRA L. SILBERMAN, M.D., PH.D., RENAUD CAPDEVILLE, M.D., BEATE KIESE, M.SC., BIN PENG, M.D., PH.D., SASA DIMITRIJEVIC, PH.D., BRIAN J. DRUKER, M.D., CHRISTOPHER CORLESS, M.D., CHRISTOPHER D.M. FLETCHER, M.D., AND HEIKKI JOENSUU, M.D.

- B-2222 study
- Randomized phase II: 400mg vs 600mg IM/day
- N=147
- Outcome
  - **PR: 54%**
  - SD: 28%
  - PD: 14%
- Time to 1st response 3mths



Demetri. N Engl J Med 2002;347:472-80

Long-Term Results From a Randomized Phase II Trial of Standard- Versus Higher-Dose Imatinib Mesylate for Patients With Unresectable or Metastatic Gastrointestinal Stromal Tumors Expressing *KIT*

Charles D. Blanke, George D. Demetri, Margaret von Mehren, Michael C. Heinrich, Burton Eisenberg, Jonathan A. Fletcher, Christopher L. Corless, Christopher D.M. Fletcher, Peter J. Roberts, Daniela Heinz, Elisabeth Wehre, Zariana Nikolova, and Heikki Joensuu

- Median OS 57 mths
- Approx 1/3 remained on long-term drug
- Best Response
  - CR: 1%
  - PR: 67%
  - SD: 16%
  - PD: 12%

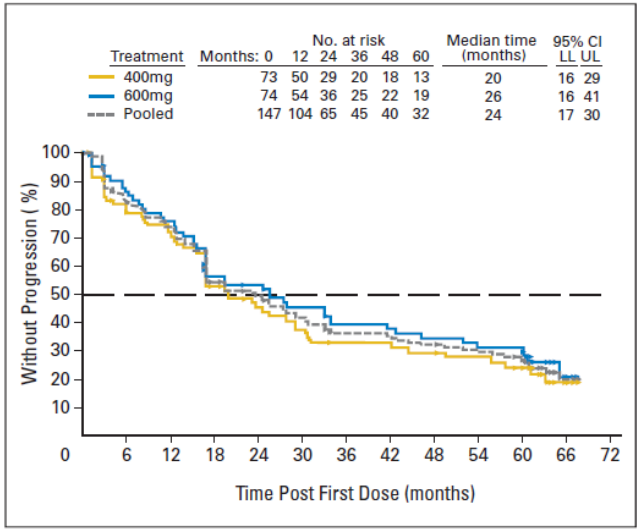


Fig 1. Time to progression. LL, lower limit; UL, upper limit.

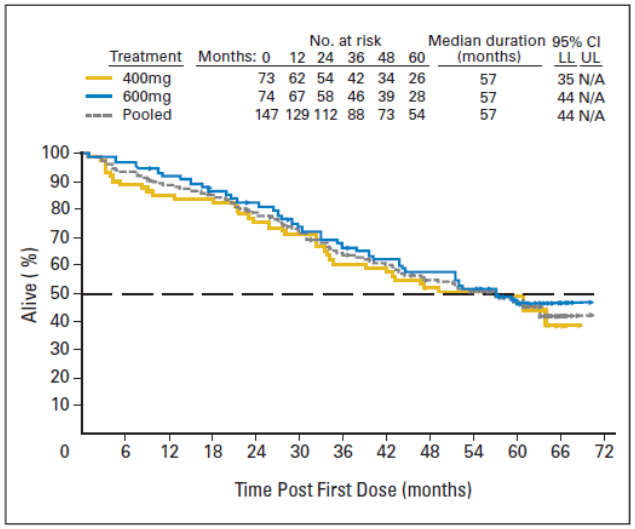


Fig 2. Overall survival. LL, lower limit; UL, upper limit; N/A, not available.

Partners in Academic Medicine

SingHealth DUKE NUS

Blanke. J Clin Oncol. 2008;26:620-5

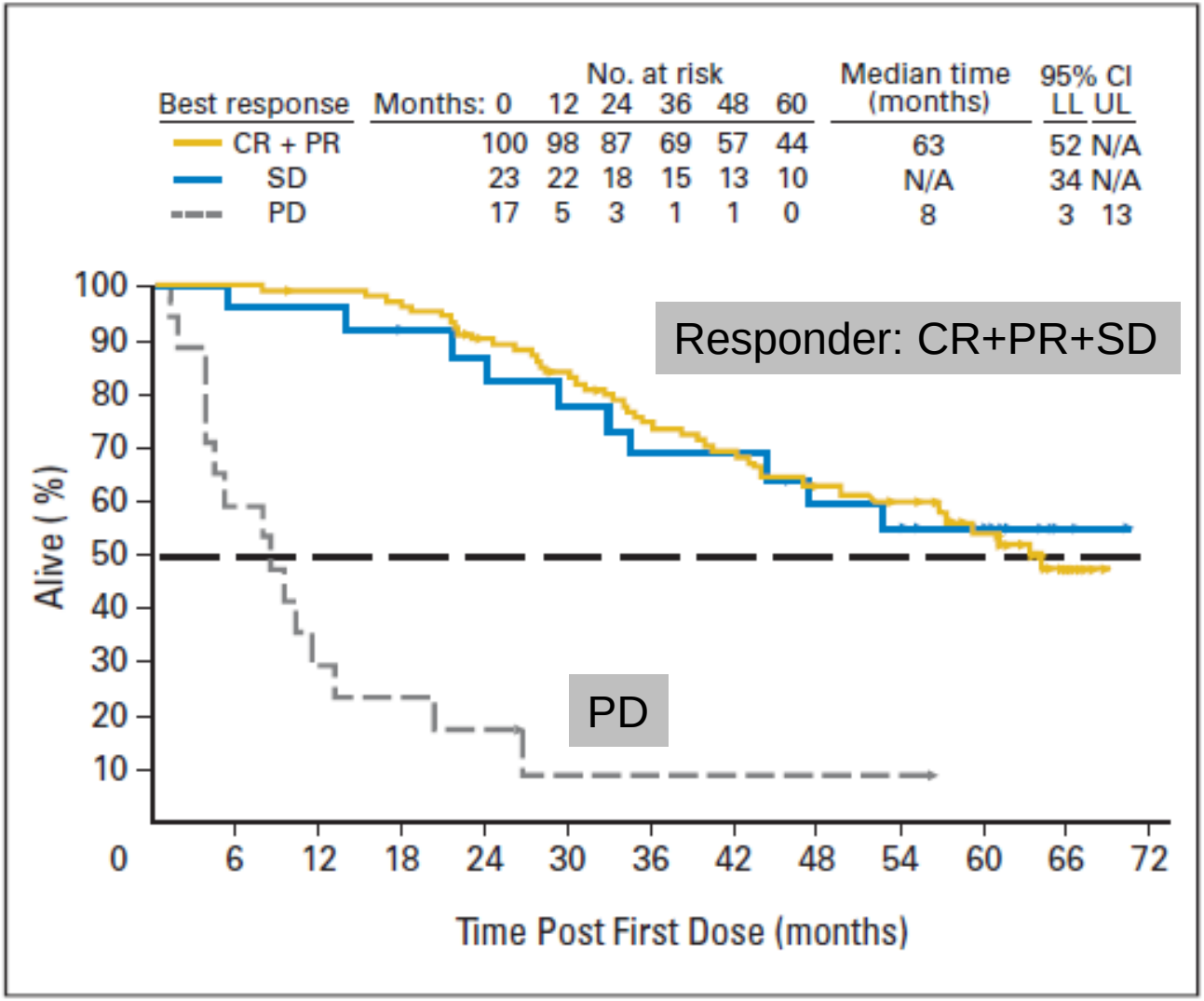


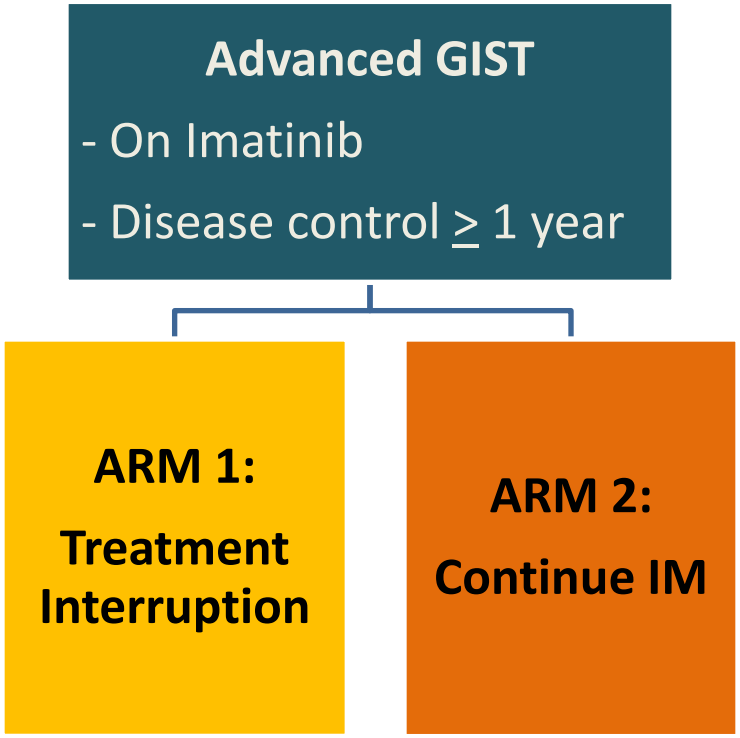
Fig 3. Overall survival according to best response. LL, lower limit; UL, upper limit; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; N/A, not available.

Partners in Acade

SingHealth DUKE NUS GRADUATE MEDICAL SCHOOL SINGAPORE

Blanke. J Clin Oncol. 2008;26:620-5

Duration of IM in Metastatic GIST: BFR 14



- Phase III
- Relapse 81% vs 31%
- PFS 6 mth vs 18 mth
- 92% regained disease control
- Longer f/u 25% (2nd relapse) vs 31% (p=ns)
- OS identical

Partners in Academic Medicine

SingHealth DUKE NUS GRADUATE MEDICAL SCHOOL SINGAPORE

Blay. J Clin Oncol. 2007;25(9):1107-13

Primary Mutational Status & Imatinib

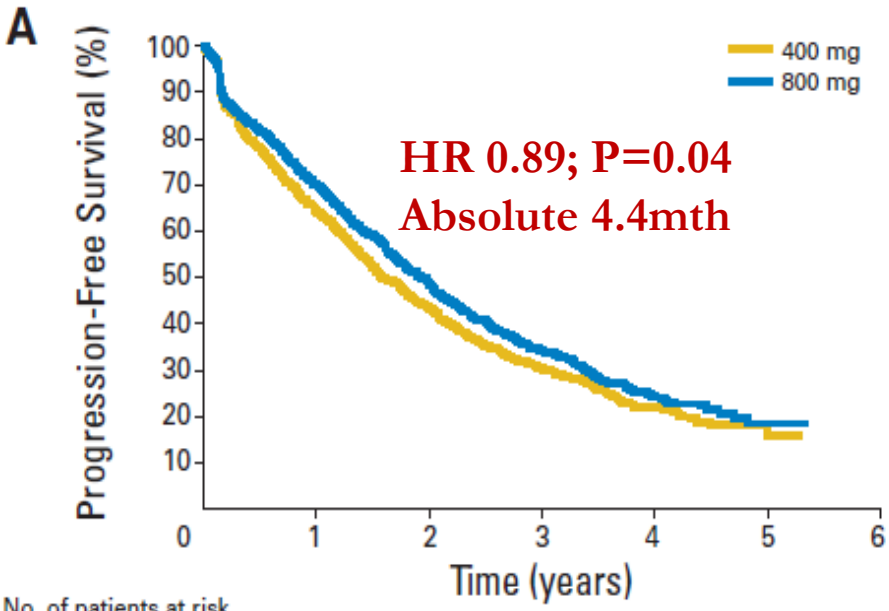
- Randomized phase II Imatinib 400mg vs 600mg daily[1]

	KIT Ex 11	KIT Ex 9	Wild Type
Partial Response	84%	48%	0%
		P=0.0006	P<0.0001
Event Free Survival	687 days	200 days	82 days

[1] Demetri et al. N Engl J Med. 2002;347(7):472-80
[2] Heinrich et al. J Clin Oncol. 2003;21(23):4342-9

Imatinib Dosing: 400mg or 800mg daily?

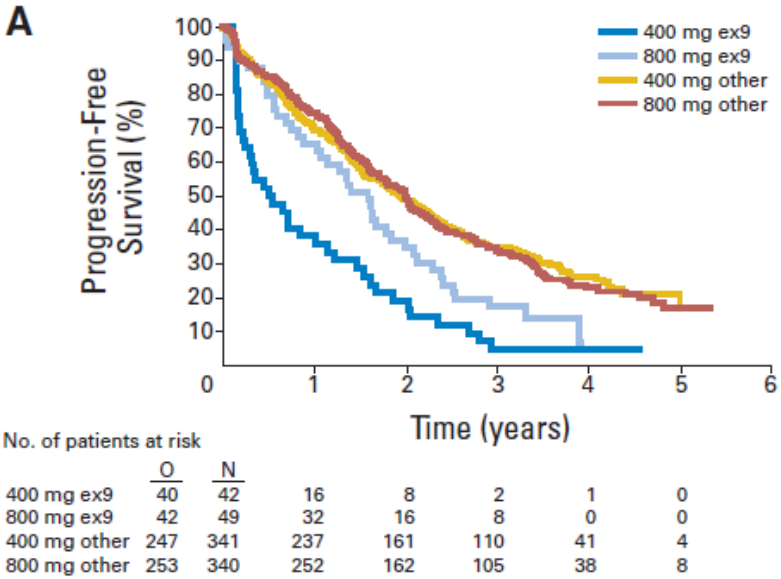
Overall Cohort



No. of patients at risk

Dose	O	N					
400 mg	610	818	520	333	219	62	7
800 mg	591	822	572	374	247	74	11

Exon 9 mutants



No. of patients at risk

	O	N					
400 mg ex9	40	42	16	8	2	1	0
800 mg ex9	42	49	32	16	8	0	0
400 mg other	247	341	237	161	110	41	4
800 mg other	253	340	252	162	105	38	8

Exon 9 mutants	IM 400mg	IM 800mg
Median PFS	6 mths	19 mths
3 year estimate	5%	17%
P-value		0.017

Partners in Academic Medicine

SingHealth DUKE NUS GRADUATE MEDICAL SCHOOL SINGAPORE

MetaGIST. J Clin Oncol. 2010;28:1247-1253
Verweij, et al. Lancet 2004; 364: 1127–134
Blanke et al. J Clin Oncol. 2008;26:626-632

Sunitinib: Approved 2nd line therapy in GIST

- Tyrosine kinase inhibitor with activity against:
  - KIT
  - PDGFRs
  - all 3 isoforms of the vascular endothelial growth factor receptors (VEGFR-1, VEGFR-2, VEGFR-3)
  - Fms-like tyrosine kinase-3 receptor (FLT3)
  - RET

Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial

George D Demetri, Allan T van Oosterom, Christopher R Garrett, Martin E Blackstein, Manisha H Shah, Jaap Verweij, Grant McArthur, Ian R Judson, Michael C Heinrich, Jeffrey A Morgan, Jayesh Desai, Christopher D Fletcher, Suzanne George, Carlo L Bello, Xin Huang, Charles M Baum, Paolo G Casali

- Pivotal Phase III study
- Sunitinib vs placebo
- Intermittent Dosing 4wks on/2wks off
- TTP 6.8 mth vs 1.6 mth

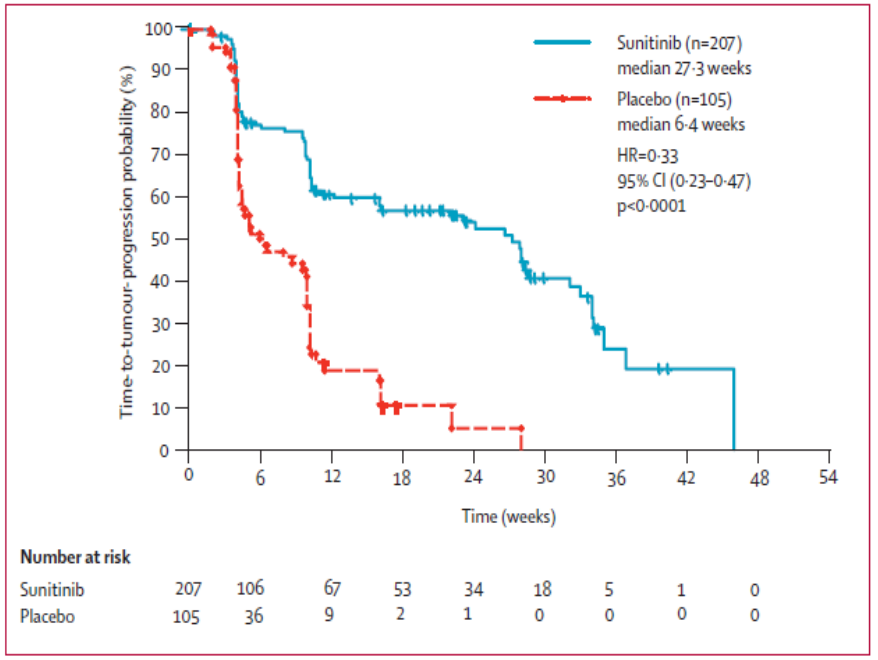


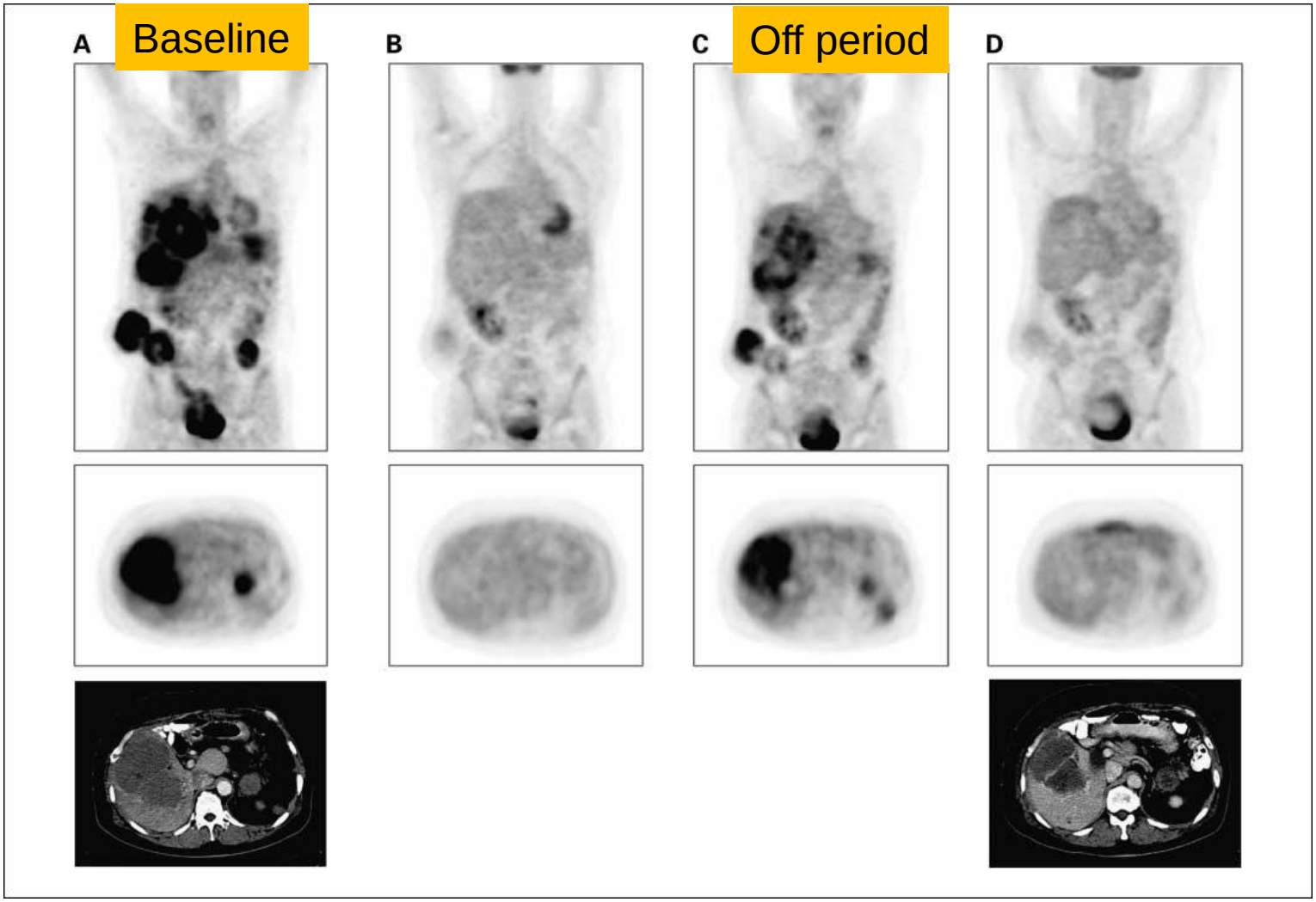
Figure 2: **Kaplan-Meier estimates of time to tumour progression**
Results represent central radiology assessment of ITT population.

Partners in Academic Medicine

SingHealth DUKE NUS GRADUATE MEDICAL SCHOOL SINGAPORE

Demetri. Lancet. 2006;368(9544):1329-38

Initial Sunitinib phase I/II study
n=97 GIST pts
Approximately 60% had serial PET done



Demetri et al. Clin Cancer Res 2009;15(18):5902-5909

EUROPEAN JOURNAL OF CANCER 45 (2009) 1959–1968

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Clinical evaluation of continuous daily dosing of sunitinib malate in patients with advanced gastrointestinal stromal tumour after imatinib failure

S. George[a,*], J.Y. Blay[b,c], P.G. Casali[d], A. Le Cesne[e], P. Stephenson[f], S.E. DePrimo[g], C.S. Harmon[g], C.N.J. Law[g], J.A. Morgan[a], I. Ray-Coquard[h], V. Tassell[g], D.P. Cohen[g], G.D. Demetri[a]

- Phase II
- Sunitinib 37.5mg daily without breaks
- N=60, progressed on imatinb
- Median PFS 34 weeks (8.5mths)
- No new toxicity signals

George et al. EJC 2009; 45:1959-68

Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial

*George D Demetri, Peter Reichardt, Yoon-Koo Kang, Jean-Yves Blay, Piotr Rutkowski, Hans Gelderblom, Peter Hohenberger, Michael Leahy, Margaret von Mehren, Heikki Joensuu, Giuseppe Badalamenti, Martin Blackstein, Axel Le Cesne, Patrick Schöffski, Robert G Maki, Sebastian Bauer, Binh Bui Nguyen, Jianming Xu, Toshirou Nishida, John Chung, Christian Kappeler, Iris Kuss, Dirk Laurent, Paolo G Casali, on behalf of all GRID study investigators**

- Phase III study
- Jan 04, 2011 - Aug 18, 2011
- N=199 randomized
- 57 countries involved

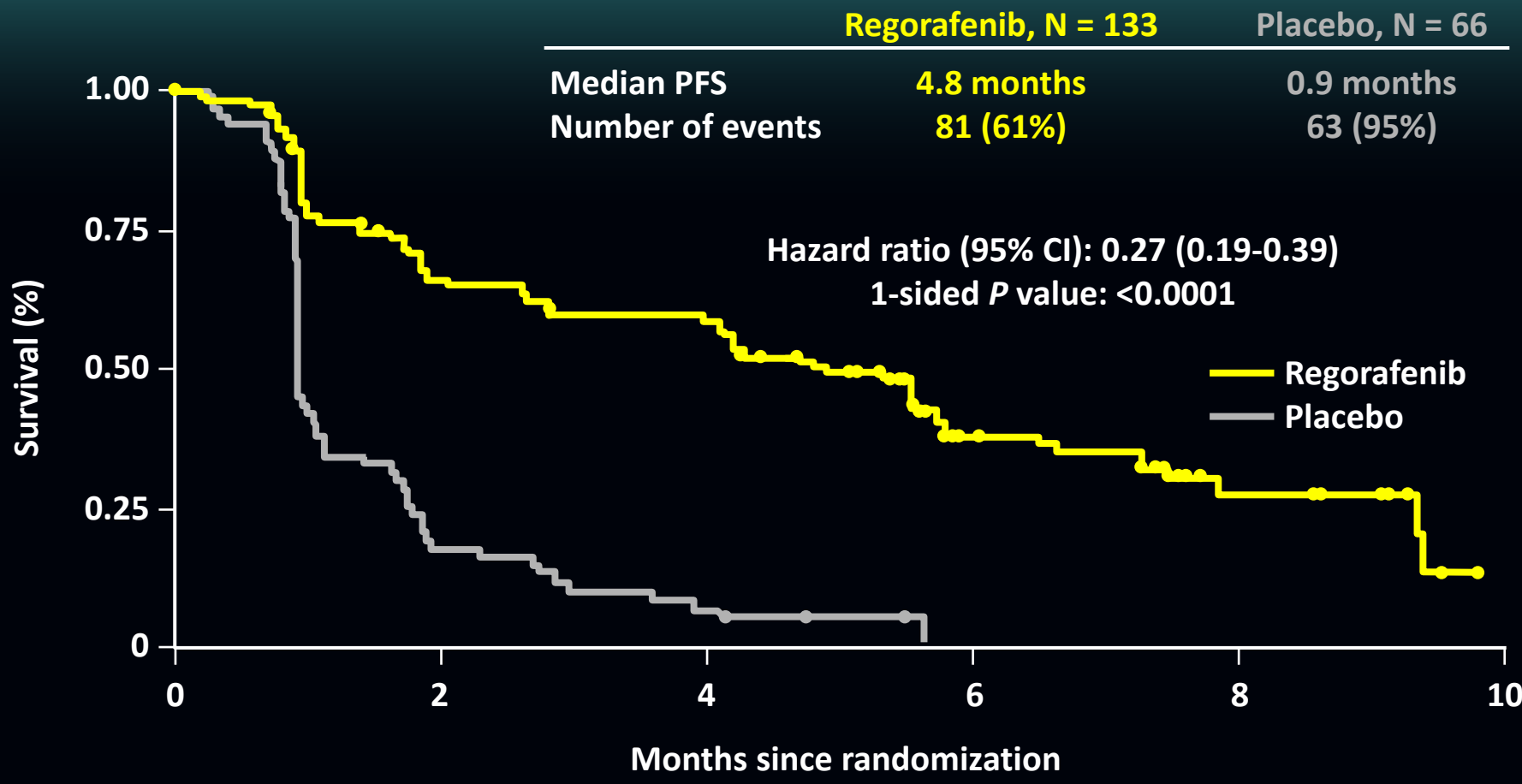
Lancet. 2013;381(9863):295-302

Eligibility and Methods

- Failure of at least previous imatinib and sunitinib
- Patients could have received other systemic therapies, including investigational agents, except any VEGFR inhibitors other than sunitinib
- Randomised 2:1 to Oral regorafenib 160 mg once daily or matching placebo, 3 weeks on, 1 week off
- Cross over permitted

Lancet. 2013;381(9863):295-302

73% Reduction in the Risk of Progression or Death with Regorafenib vs Placebo in GRID Study



Regorafenib significantly improved PFS vs placebo (*P* <.0001); primary endpoint met

Demetri GD, et al. Lancet. 2013;381:295-302.

Adverse events on-study occurring in ≥20% of patients during double-blind treatment

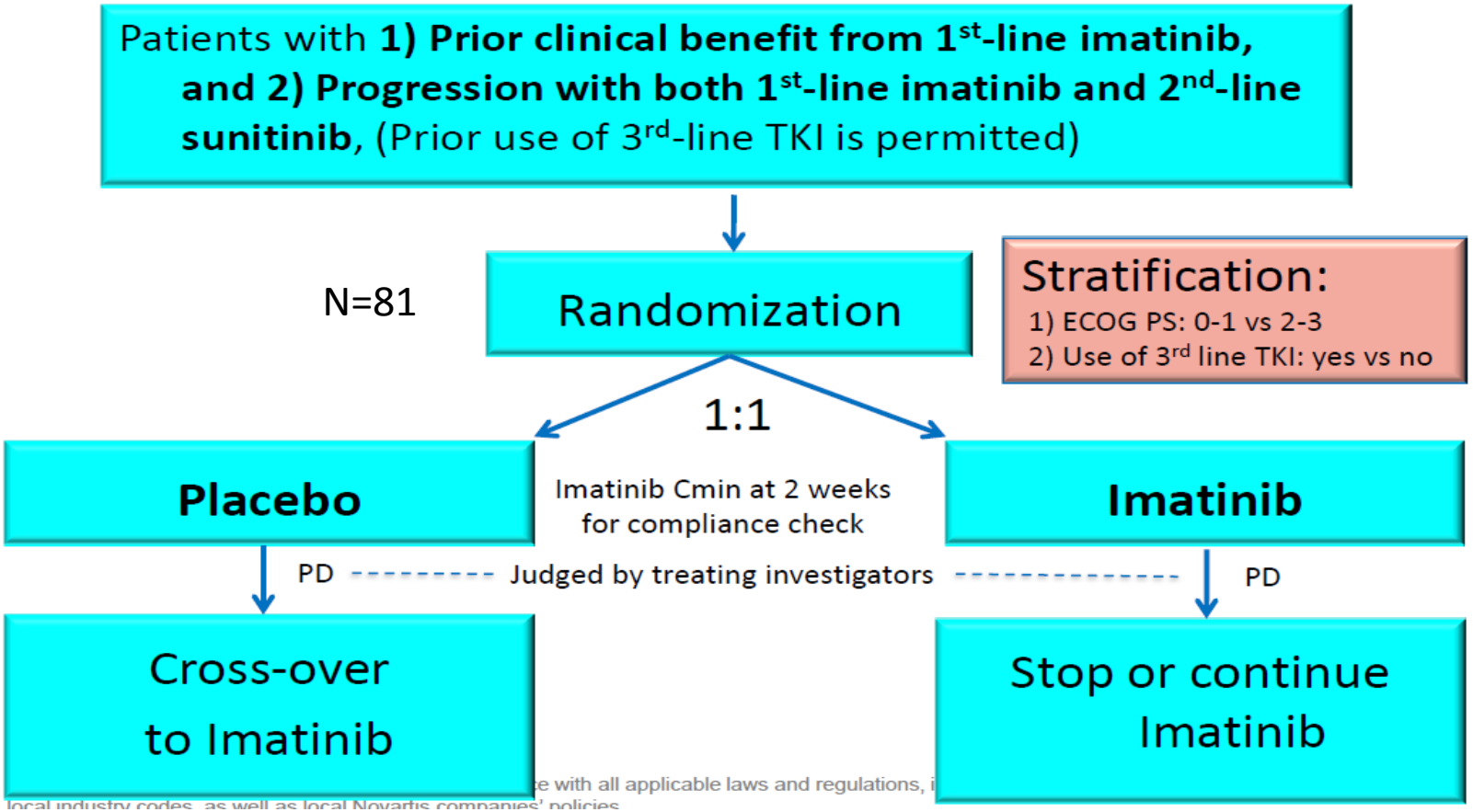
NCI-CTCAE v4.0 term	Regorafenib (N=132), %				Placebo (N=66), %			
	All Grades	G3	G4	G5	All Grades	G3	G4	G5
Hypertension	59.1	27.3	0.8	0	27.3	4.5	0	0
HFSR	56.8	20.5	0	0	13.6	0	0	0
Fatigue	50.0	3.0	0	0	37.9	1.5	0	1.5
Diarrhea	46.2	7.6	0	0	9.1	0	0	0
Oral mucositis	40.9	1.5	0	0	9.1	1.5	0	0

On-study adverse events resulted in permanent discontinuation of study treatment, n (%)	Regorafenib	Placebo
	8 (6.1%)	5 (7.6%)

NCI-CTCAE: National Cancer Institute-Common Terminology Criteria for Adverse Events
HFSR: Hand-foot skin reaction

Resumption of imatinib to control metastatic or unresectable gastrointestinal stromal tumours after failure of imatinib and sunitinib (RIGHT): a randomised, placebo-controlled, phase 3 trial

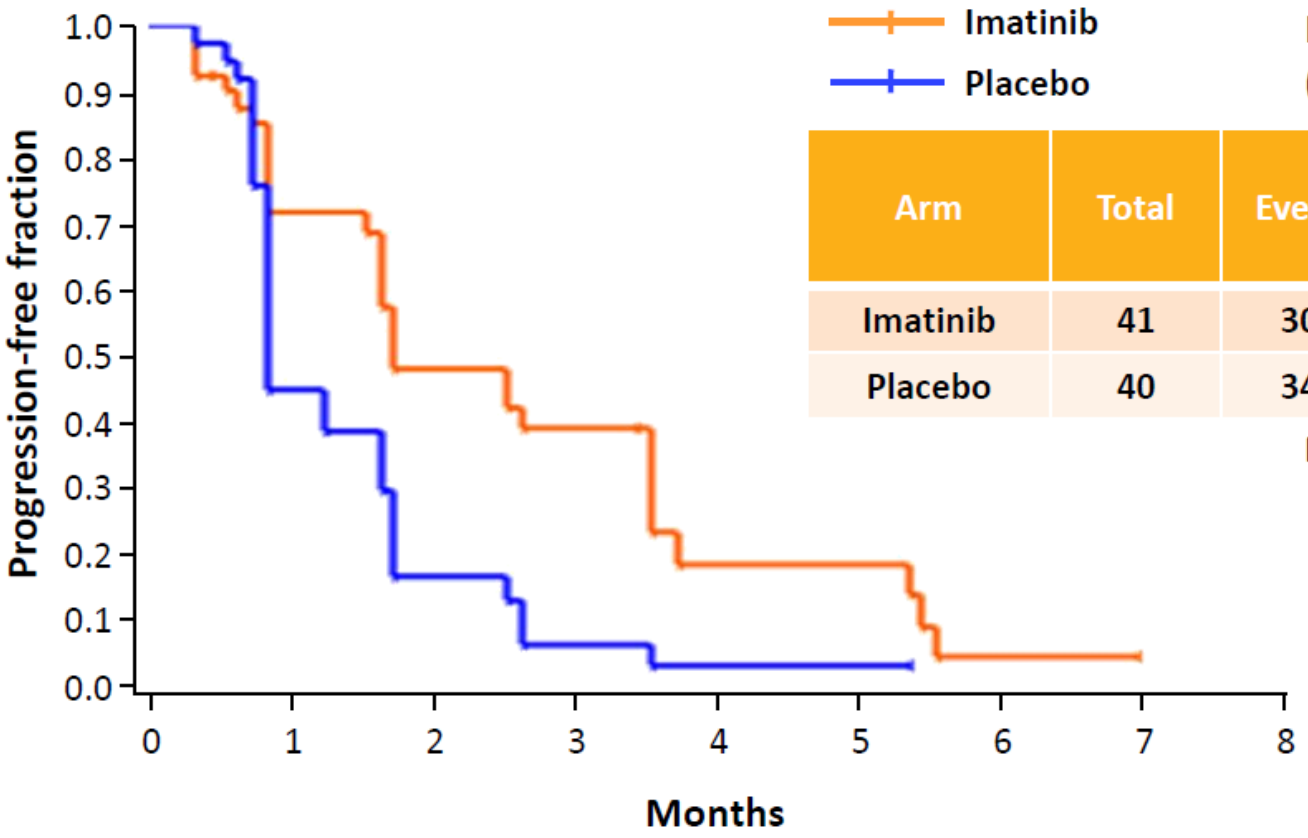
Yoon-Koo Kang, Min-Hee Ryu, Changhoon Yoo, Baek-Yeol Ryoo, Hyun Jin Kim, Jong Jin Lee, Byung-Ho Nam, Nikhil Ramaiya, Jyothi Jagannathan, George D Demetri



Lancet Oncol 2013; 14: 1175–82

Results

N=81



HR: 0.45
(95% CI, 0.27-0.76)

Arm	Total	Event	Median PFS, months (95% CI)
Imatinib	41	30	1.8 (0.9-2.8)
Placebo	40	34	0.9 (0.8-0.9)

P = 0.00075 (1-sided)

Implication
1st prospective evidence for continuation of TKI beyond progression in GIST
Provide a new standard for a comparator arm in new GIST trials

Lancet Oncol 2013; 14: 1175–82

Pazopanib salvage therapy (after failure of imatinib and sunitinib)

PAZOGIST (ASCO 2015)

Study design

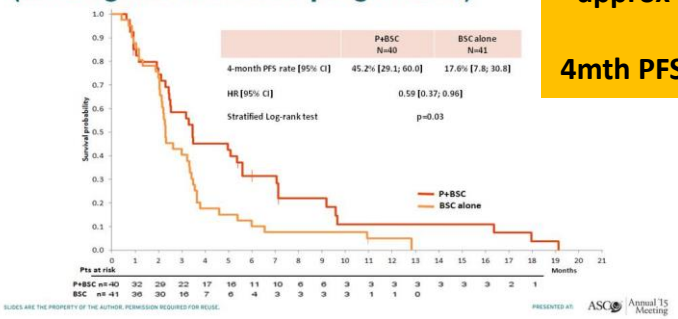
N=81

- Randomized, open-label, multicenter phase II study
- Stratification criterion : number of prior different drugs (2 drugs *versus* more than 2 drugs)

* Switch to pazopanib allowed for patients randomized in Arm B with disease progression

PRESENTED AT: ASCO Annual '15 Meeting

Progression-Free Survival
(investigator-assessed progression)



PRESENTED AT: ASCO Annual '15 Meeting

Median PFS on Pazopanib - approx 3.5mths

4mth PFS rate 45% vs 17%

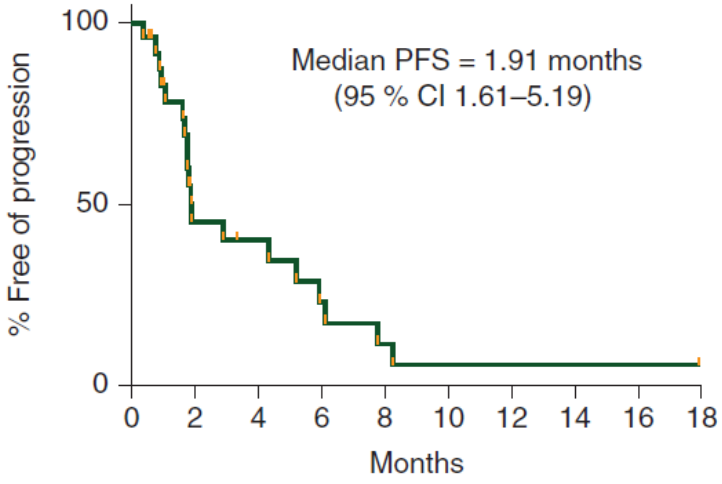
Presented By Jean-Yves Blay at 2015 ASCO Annual Meeting

A multicenter phase II study of pazopanib in patients with advanced gastrointestinal stromal tumors (GIST) following failure of at least imatinib and sunitinib

K. N. Ganjoo[1*], V. M. Villalobos[1], A. Kamaya[1], G. A. Fisher[1], J. E. Butrynski[2], J. A. Morgan[2], A. J. Wagner[2], D. D'Adamo[2], A. McMillan[1], G. D. Demetri[2,3] & S. George[2]

[1]Stanford Cancer Institute, Stanford; [2]Center for Sarcoma and Bone Oncology, Dana Farber Cancer Institute, Boston; [3]Ludwig Center at Dana-Farber/Harvard Cancer Center and Harvard Medical School, Boston, USA

- Phase II
- N=25
- Approx 70% had prior regorafenib/ sofarenib



Ganjoo et al. Annals of Oncology 25: 236–240, 2014

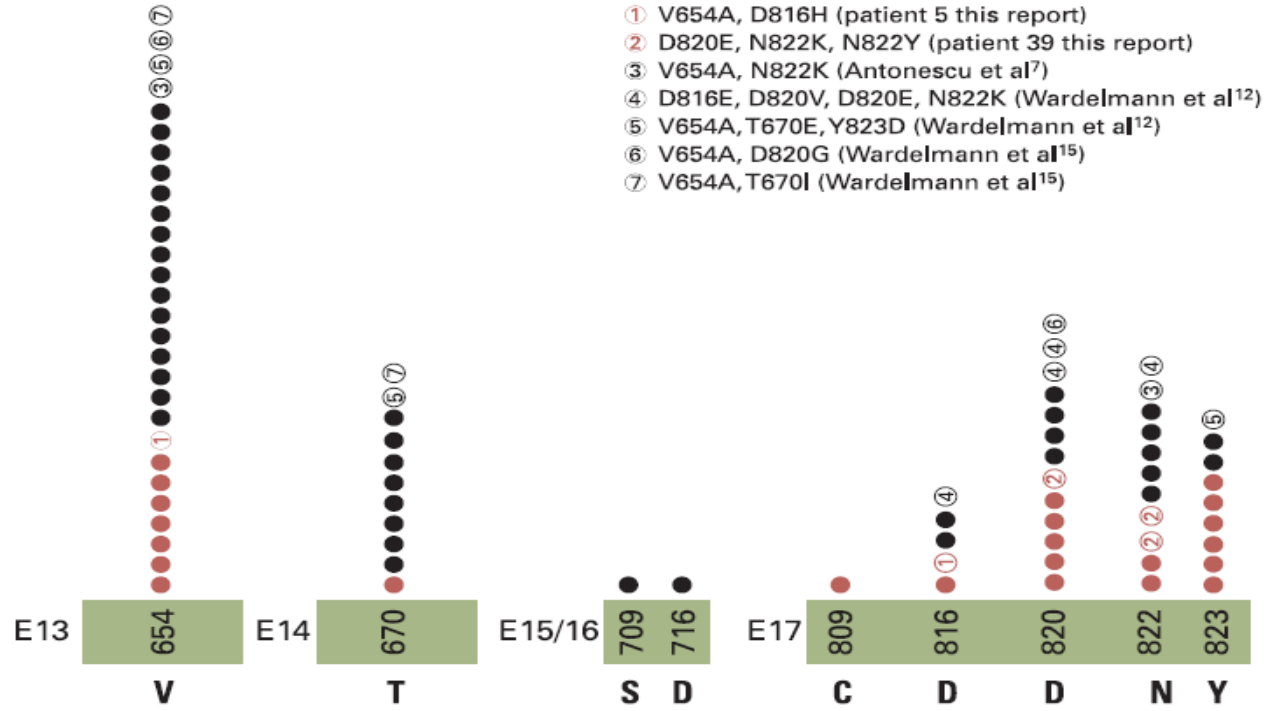
Tyrosine Kinase Inhibitor Resistance

Main mechanism through development of secondary mutations

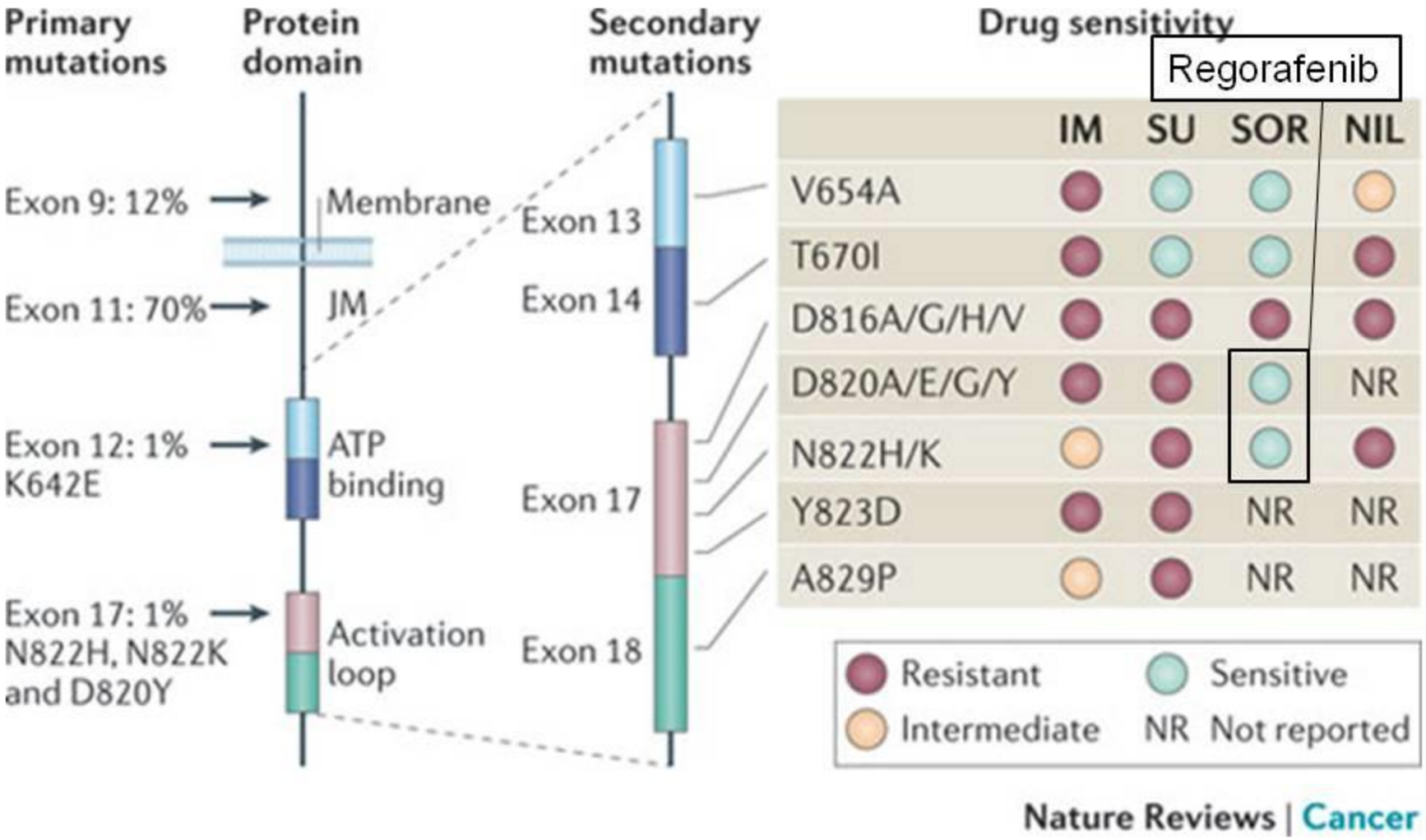
Clonal Evolution under Pharmacological Pressure

Secondary Mutations

- Non-randomly distributed
  - ATP binding pocket (Ex 13/14)
  - Kinase activation loop (Ex 17/18)



Heinrich et al. J Clin Oncol. 2006;24:4764-4774

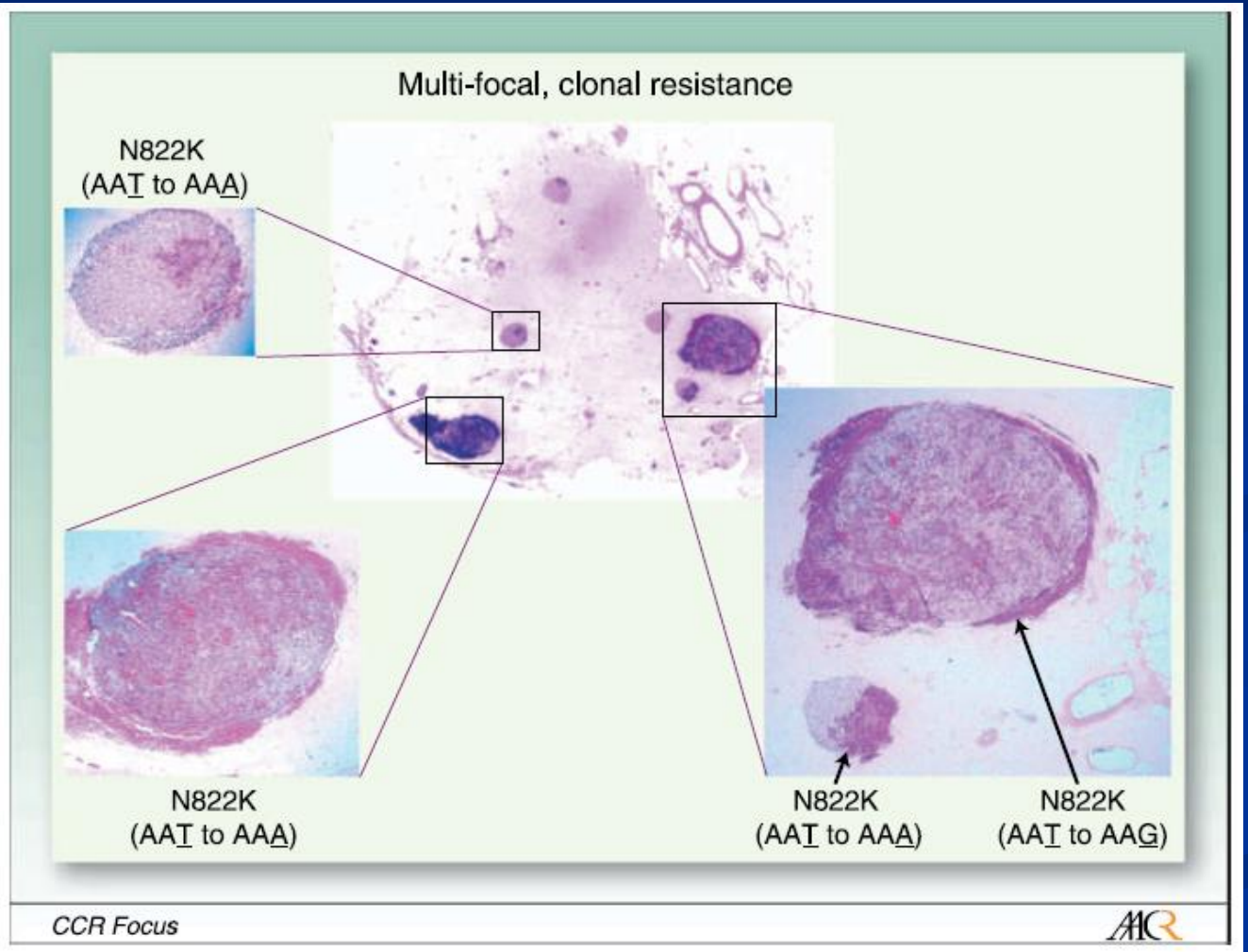


George et al. J Clin Oncol. 2012 May 21. [Epub ahead of print]

Corless, Barnett & Heinrich. *Nature Reviews Cancer* **11**, 865-878 (December 2011)

Courtesy of Dr Corless

Resistance is molecularly heterogeneous



Gramza, Corless and Heinrich. Clin Cancer Res 2009;15(24):7510-8

In Summary

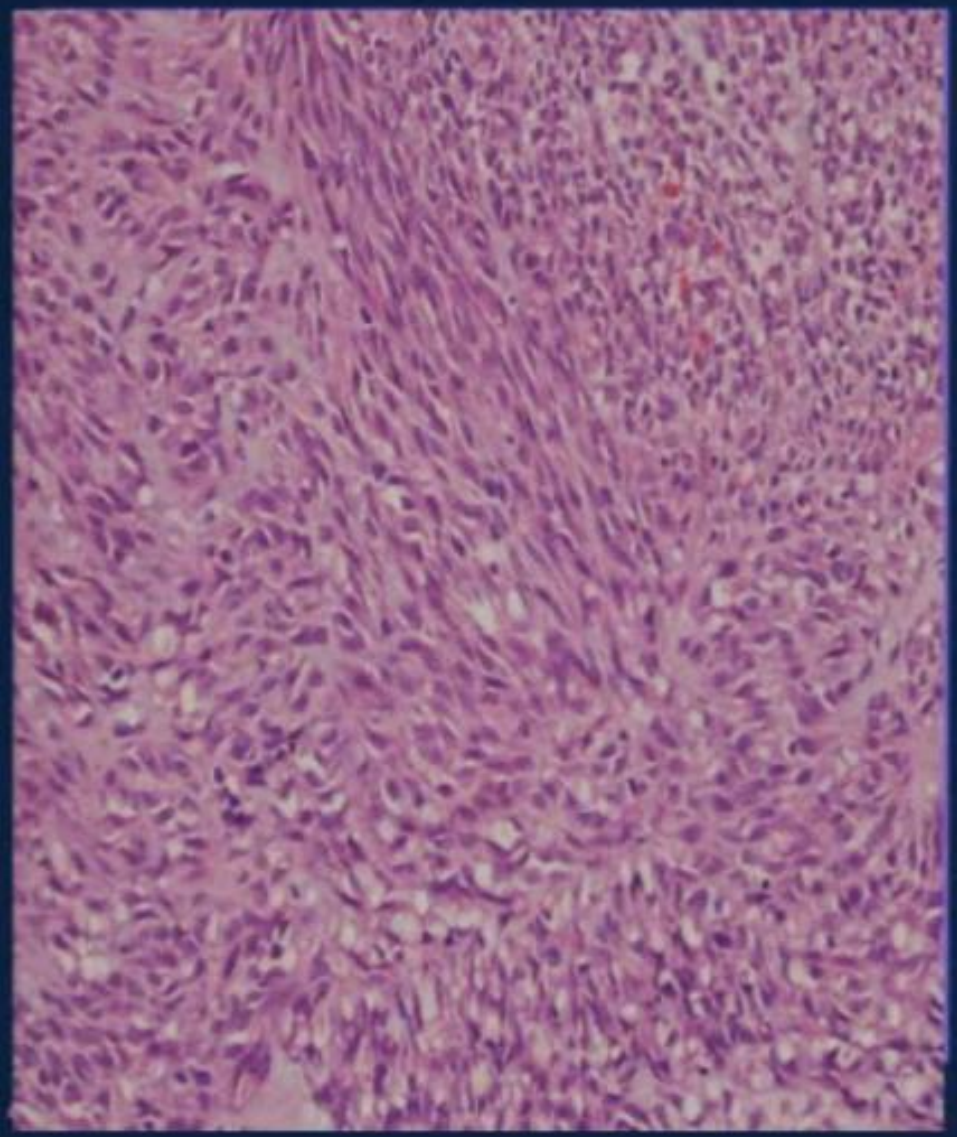
- Reviewed the pathogenesis of GIST
- Discussed the approved 1st to 3rd line treatment in advanced GIST
- GIST mutations: Detection and utility

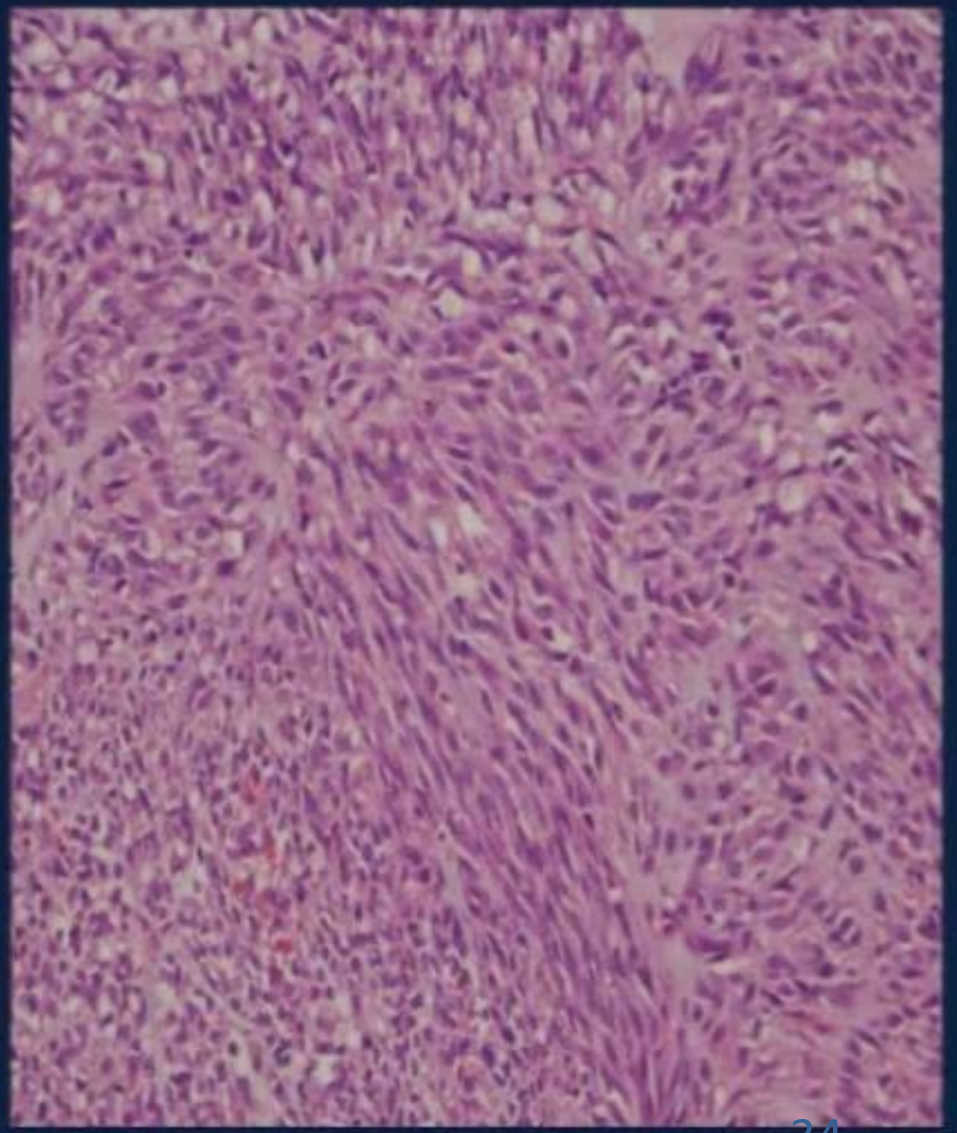
- Central role of KIT mutation and its impacts on primary treatment and resistance

- Novel strategies following failure of standard approved treatment

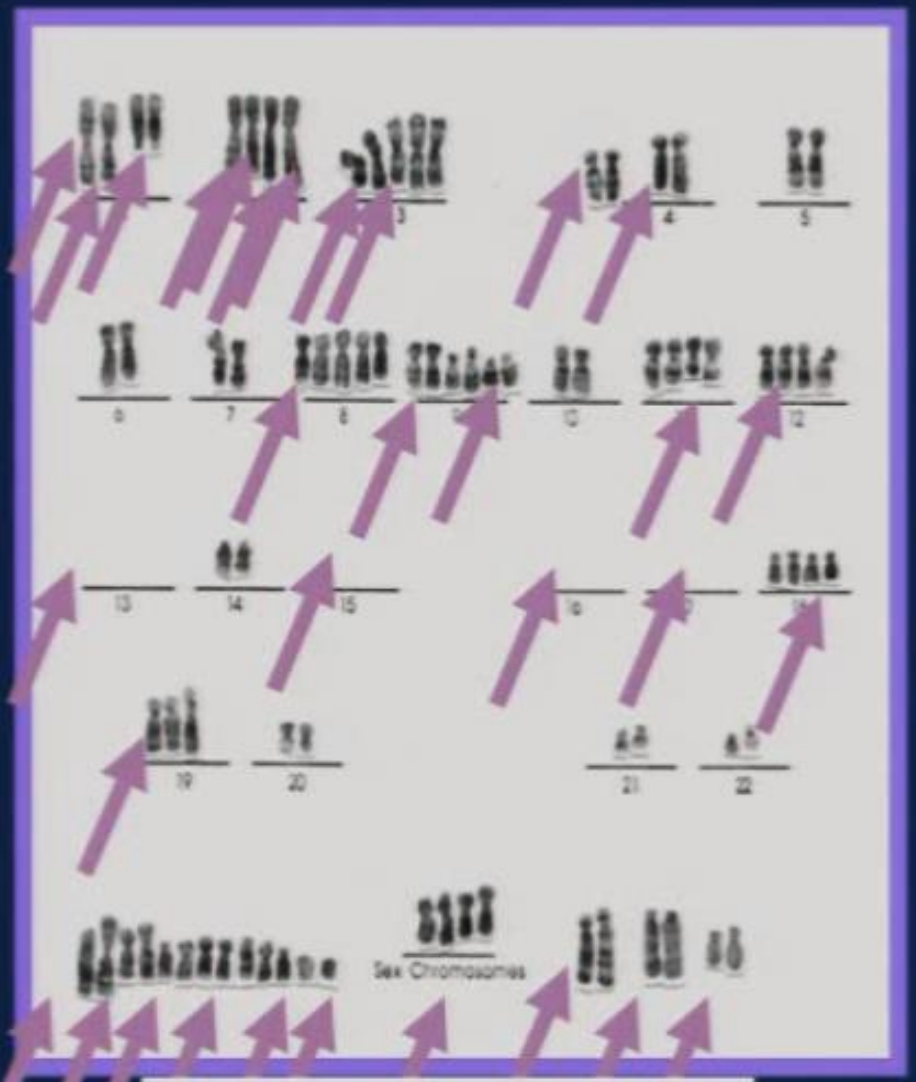
Thank you

Same Disease? Or Completely Different?

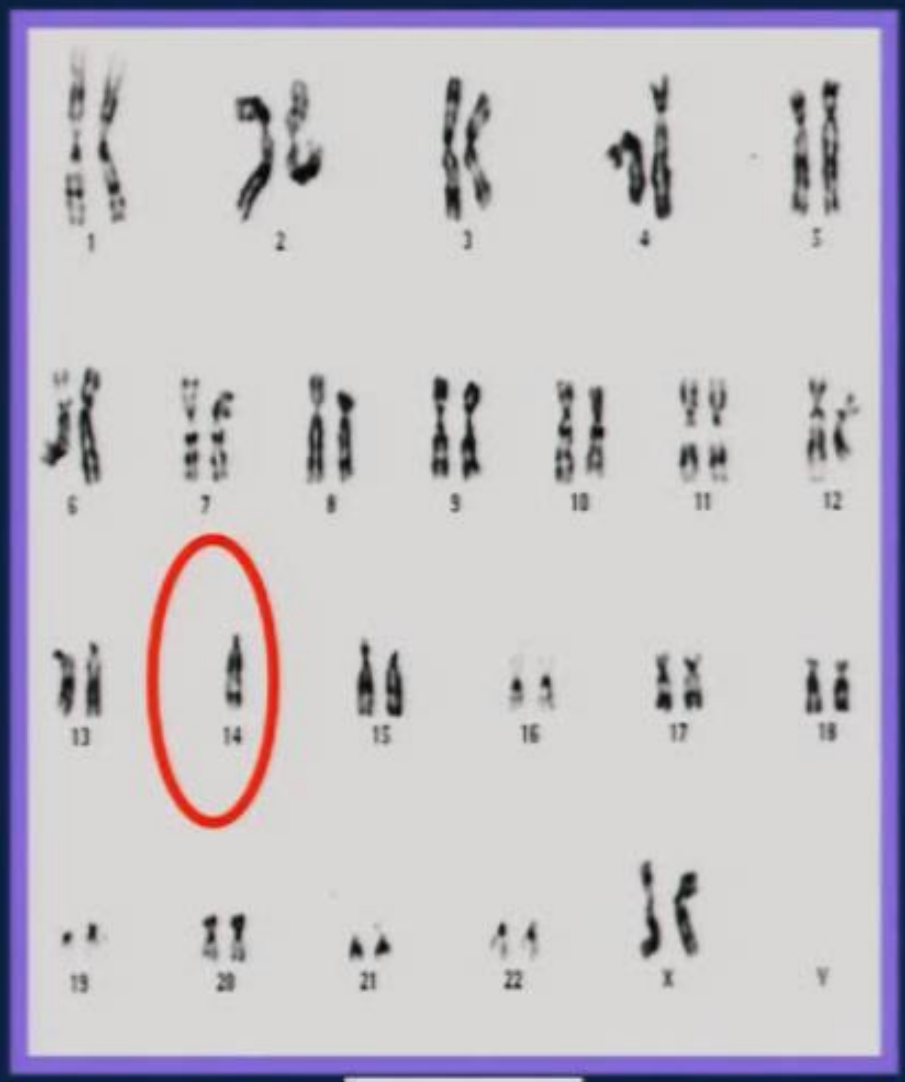




Same Disease? Or Completely Different?



Leiomyosarcoma



GIST

Response to Imatinib (Glivec)