Leveraging Oncogene Addiction to Improve Therapies for Patients with Gastrointestinal Stromal Tumor (GIST)

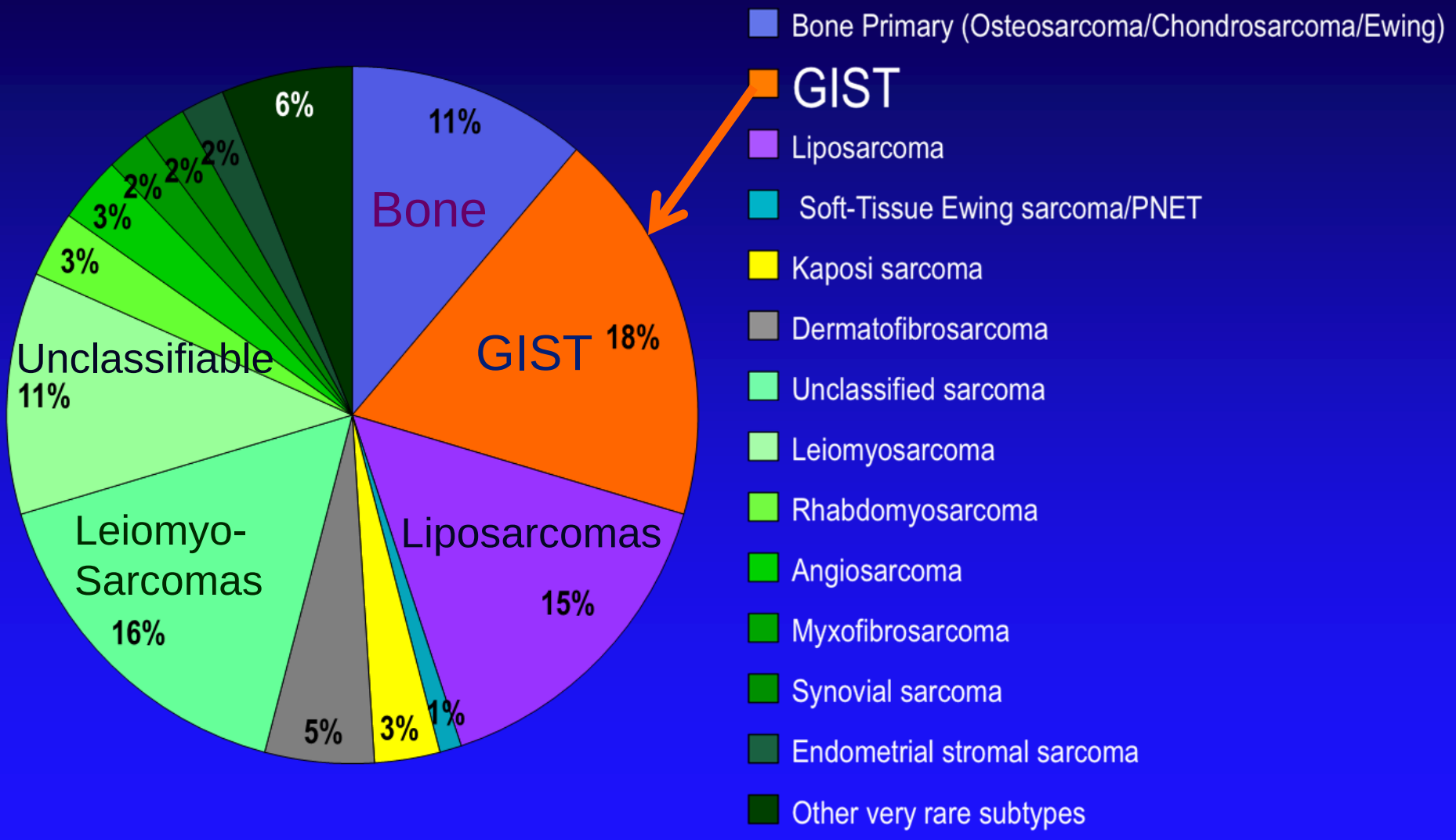
George D. Demetri, MD

Ludwig Center at Dana-Farber/Harvard Cancer Center

Harvard Medical School

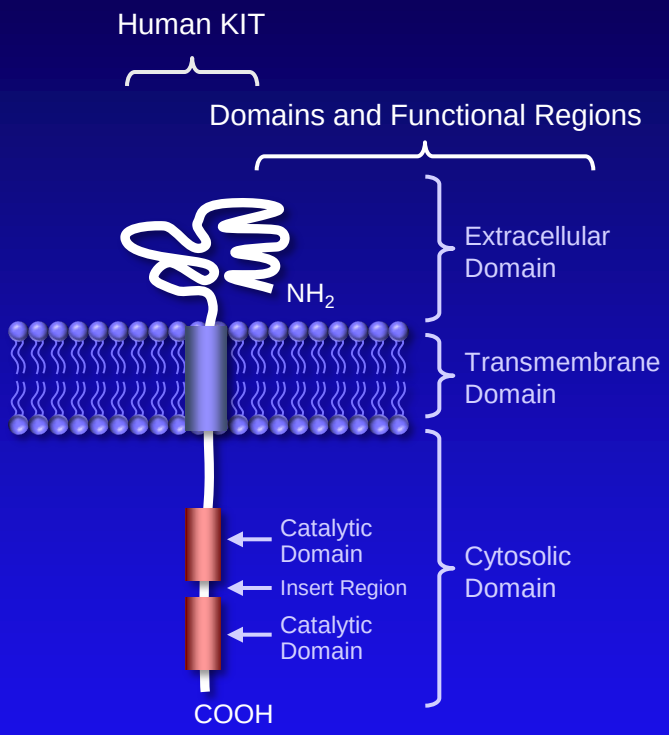
Boston, Massachusetts

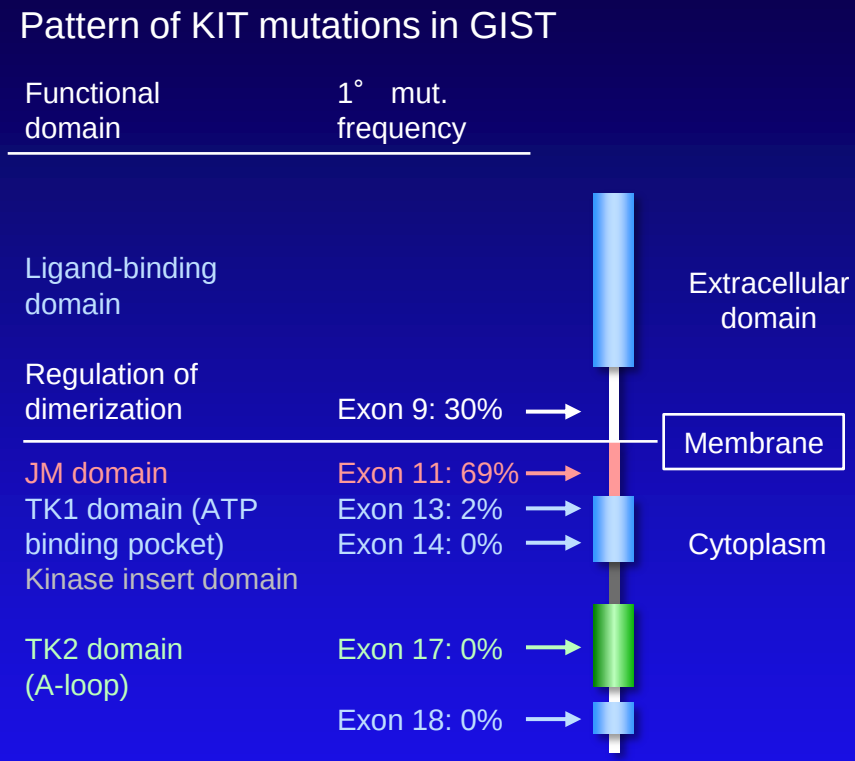
GIST Is the Most Common Subtype of All Sarcomas



Ducimetiere F, et al. *PLoS ONE.* 2011;6(8):e20294. doi:10.1371/journal.pone.0020294.

Mutant Kinases are DRIVERS in >90% of GIST

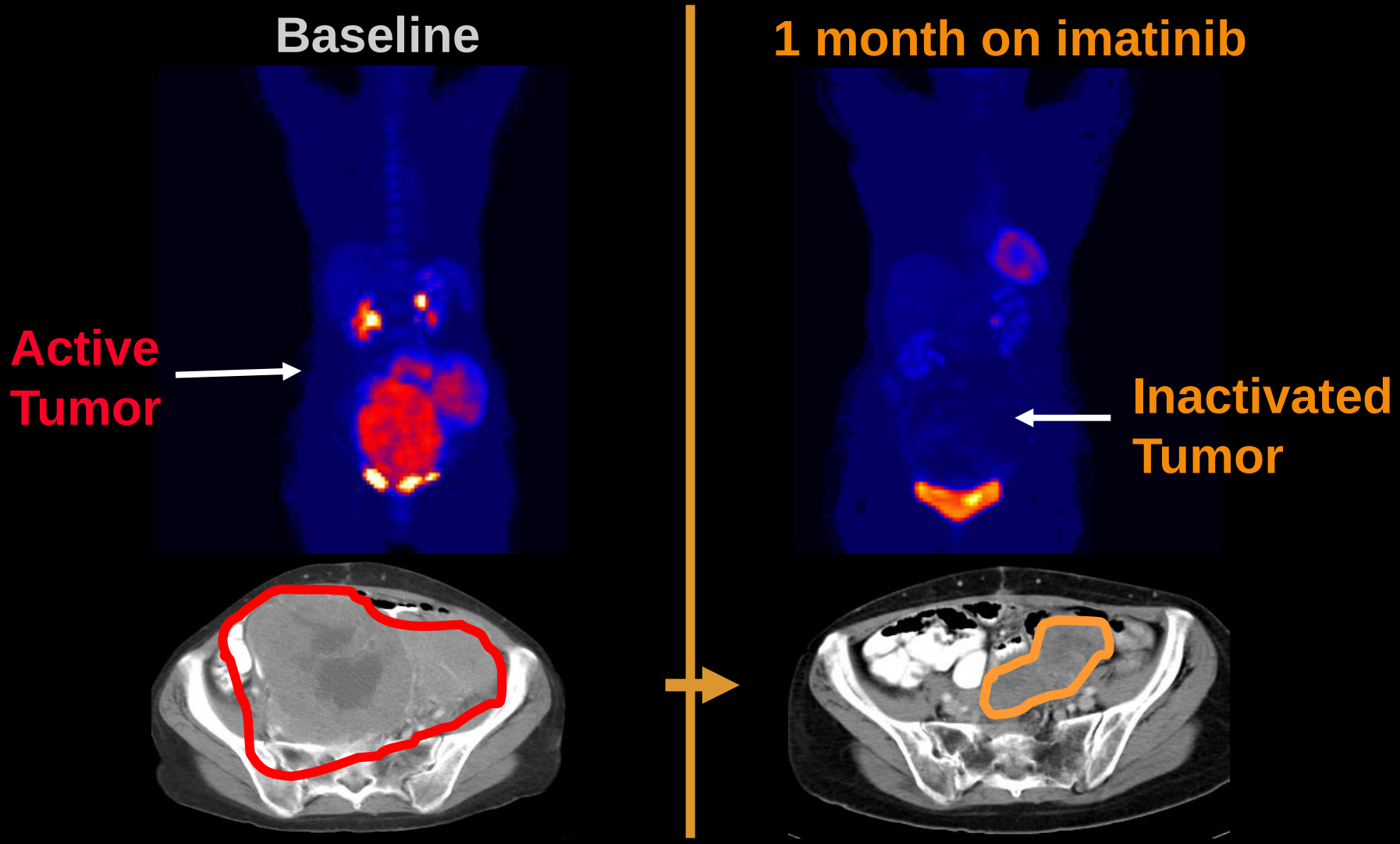




- At clinical presentation of disease, only one mutation is detectable in a given patient
  - Different patients harbor different mutations in *KIT* or *PDGFRA*
  - *The tumors are addicted to the signals from these mutant kinases*

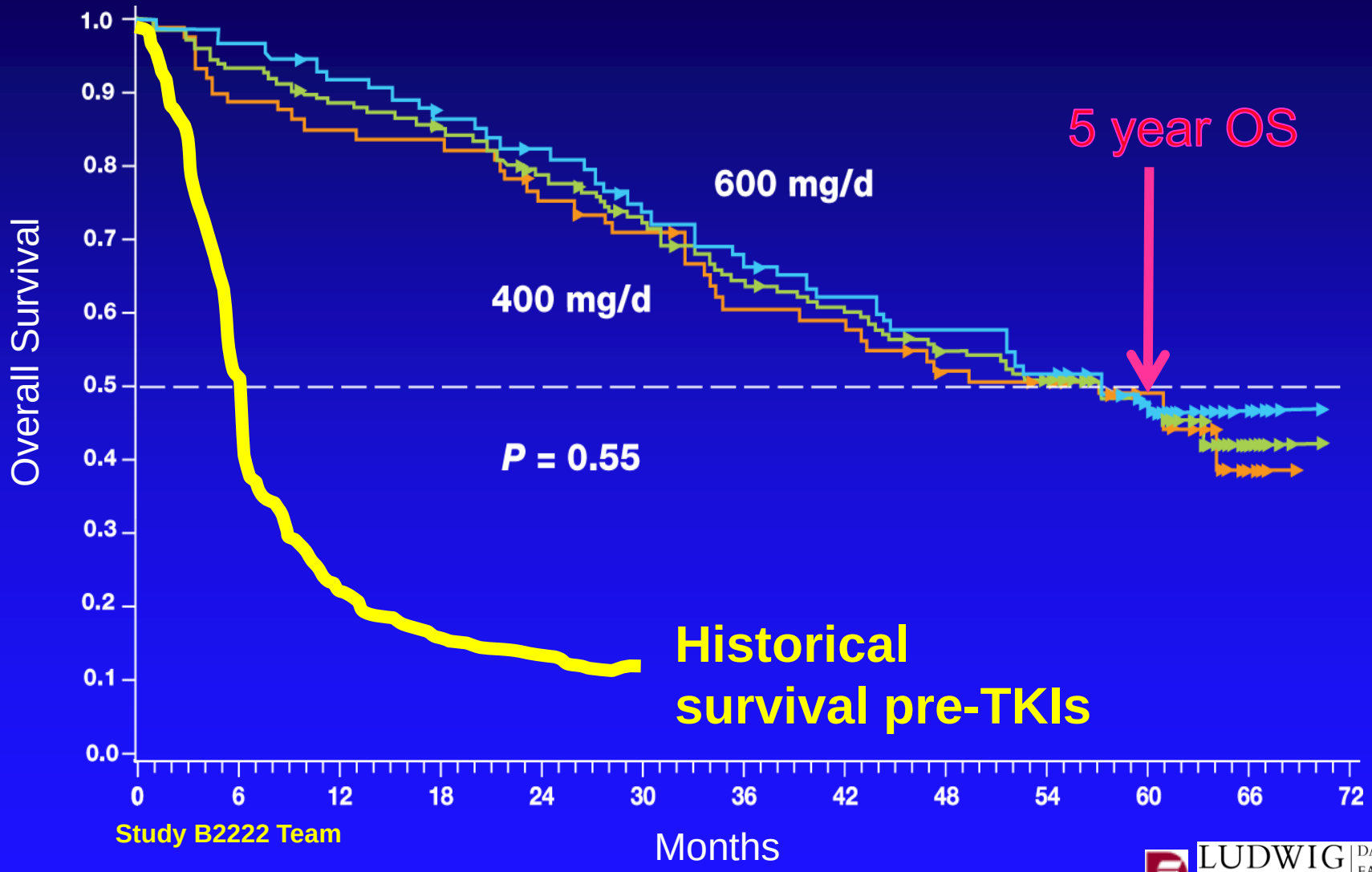
1. Jensen B, et al. *Br J Pharmacol.* 2008;154:1572-1582; 2. Gajiwala K, et al. *Proc Natl Acad Sci USA.* 2009;106:1542-1547.

The First US GIST Patient Treated with Imatinib: Dana-Farber Cancer Institute and Harvard Medical School



Demetri G. Medscape Education Oncology. 2011. http://www.medscape.org/viewarticle/747252.

300% Improvement in Overall Survival for Metastatic GIST Treated with Imatinib



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

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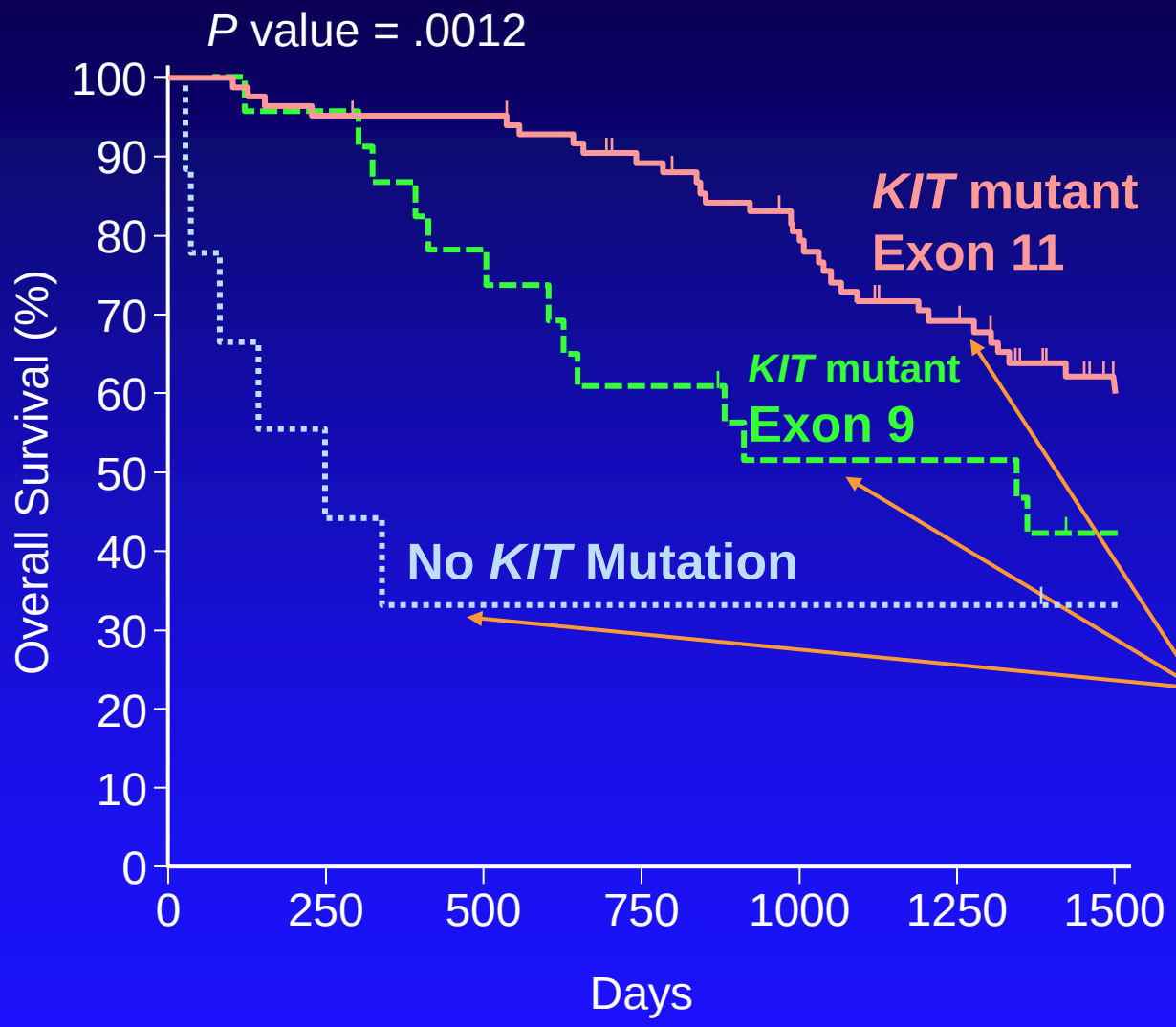
GIST with Different Mutations Behave Differently



Different Genotypic and Structural Variants Fail Imatinib Therapy at Different Rates

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

GIST Comprises Several Clinically Distinct Molecular Subtypes

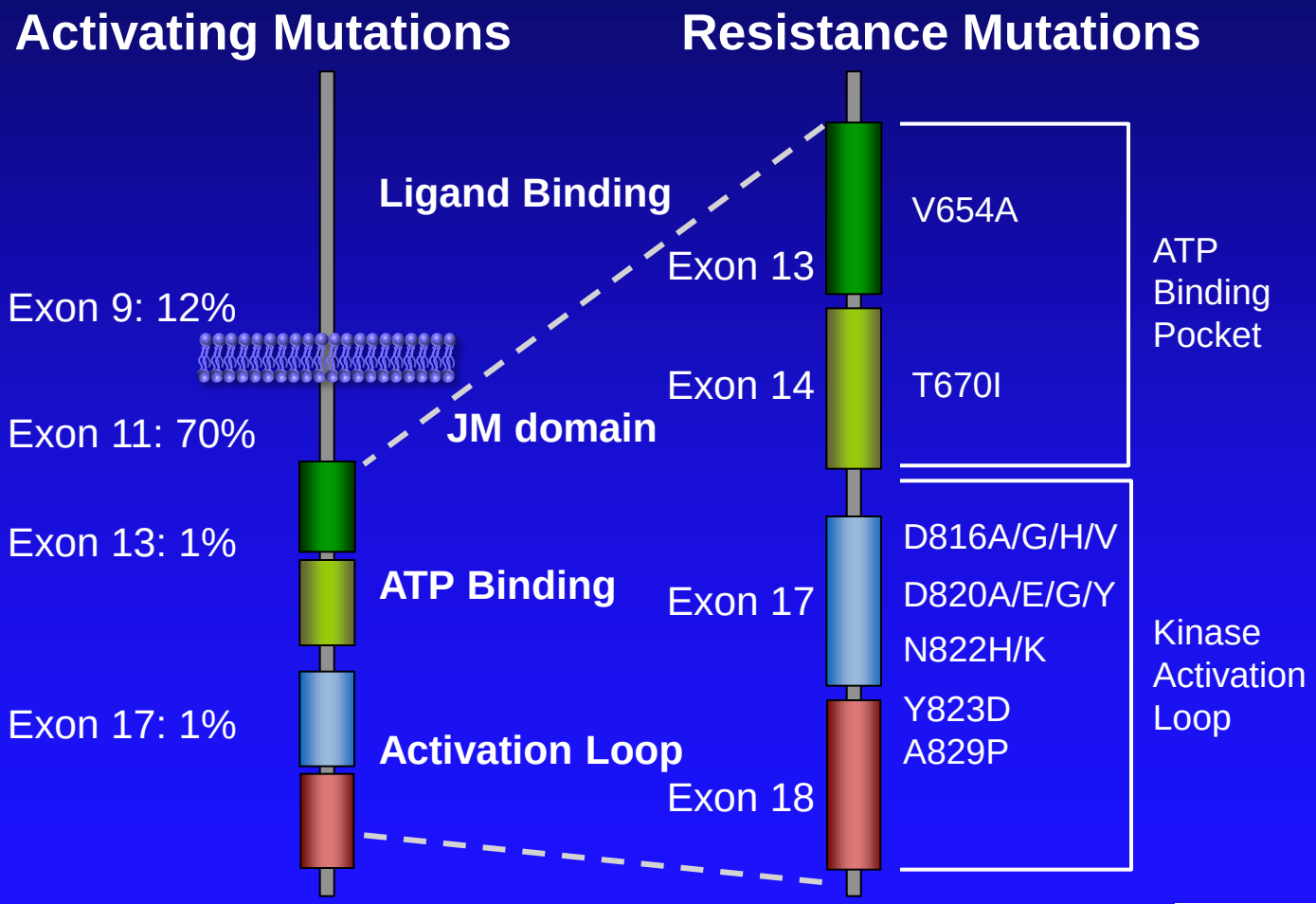
KIT mutant	
Exon 11	Most common site of mutation (67%)
Exon 9	2nd most common site of mutation (10%)
Exons 13 & 17	Rare (2%)
PDGFRA mutant	
Exons 12 & 14	Rare (1%)
Exon 18	Uncommon (6%)
BRAF mutant	Exceptionally rare (<1%)
"Wild-type"	No mutation in *KIT* or *PDGFRA* (14%): Often with deficiencies in metabolic pathways (SDH)
Familial GIST	Germline *KIT* or *PDGFRA* mutation
Pediatric	*KIT* & *PDGFRA* are generally "Wild type" (no mutation)
Carney's triad	*KIT* & *PDGFRA* are generally "Wild type" (no mutation)
Carney-Stratakis	Mutations in metabolism enzymes: Functional loss with defects in *SDH-B, SDH-C, or SDH-D*
NF-1-related	Etiology unclear: no mutations in *KIT, PDGFRA, or SDH*

Modified from http://www.liferaftgroup.org/news_sci_articles/KIT_&_PDGFRA_mutations_A_Z.html . Accessed September 2012

GIST Patients Identify with Molecular Medicine

GIST Mutations

- GIST is addicted to signals from the primary mutant kinase
- Secondary mutations arise to continue the aberrant signaling in TKI-resistant GIST

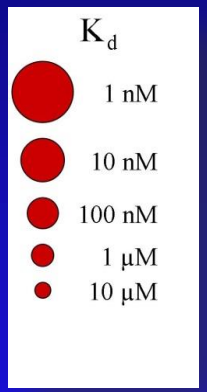


Gramza A, et al. *Clin Cancer Res*. 2009;15:7510-7518.

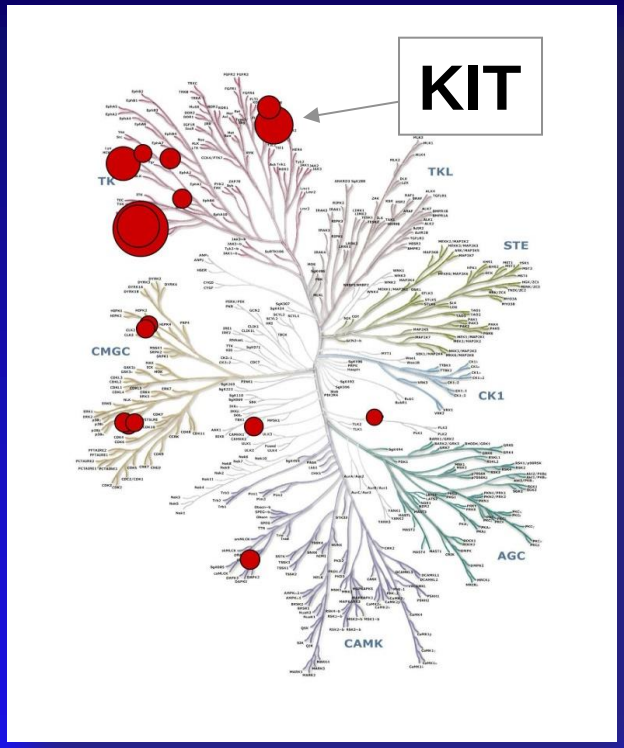
Understanding Resistance to Overcome the Problem

- Why is there only ONE mutation detectable at clinical presentation?
  - Double mutants MUST have an evolutionary disadvantage and be “less fit”
  - Double mutants only evolve to clinically detectable levels after single mutants are suppressed with kinase inhibitor therapy
- Structural biology of TKI resistance

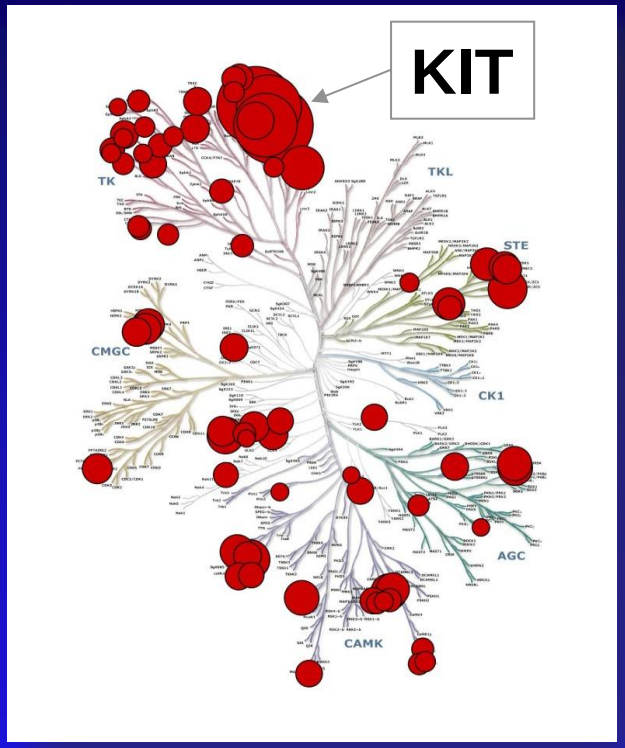
Imatinib vs Sunitinib: Profiling the Kinome



Size of bubble reflects binding affinity for target



Imatinib



Sunitinib

Fabian M, et al. *Nature Biotech*. 2005;23:329-336.

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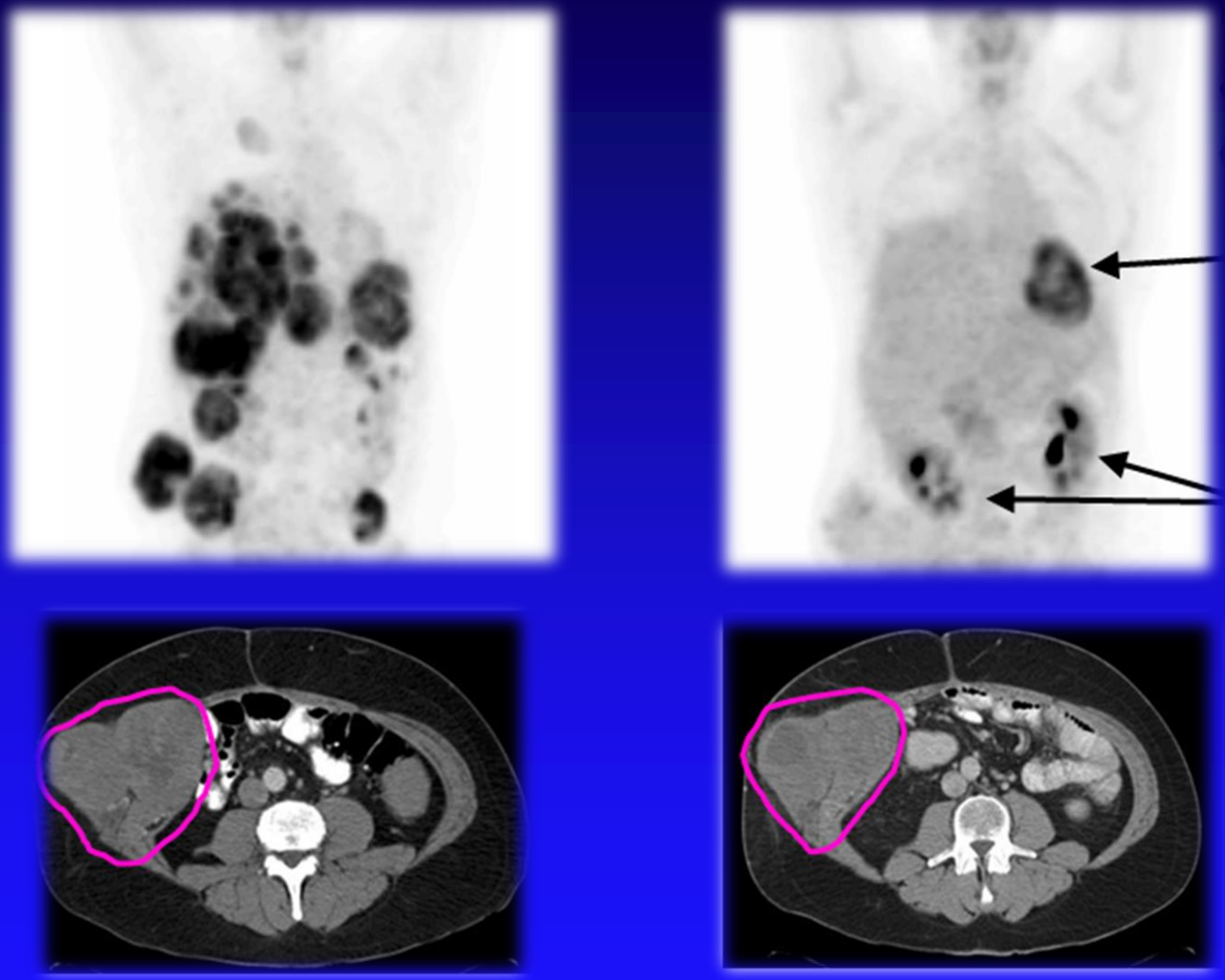
Sunitinib Benefit in Imatinib-Resistant GIST

Baseline **Day 7 PET**



PET scan after 7 days of sunitinib

Normal heart

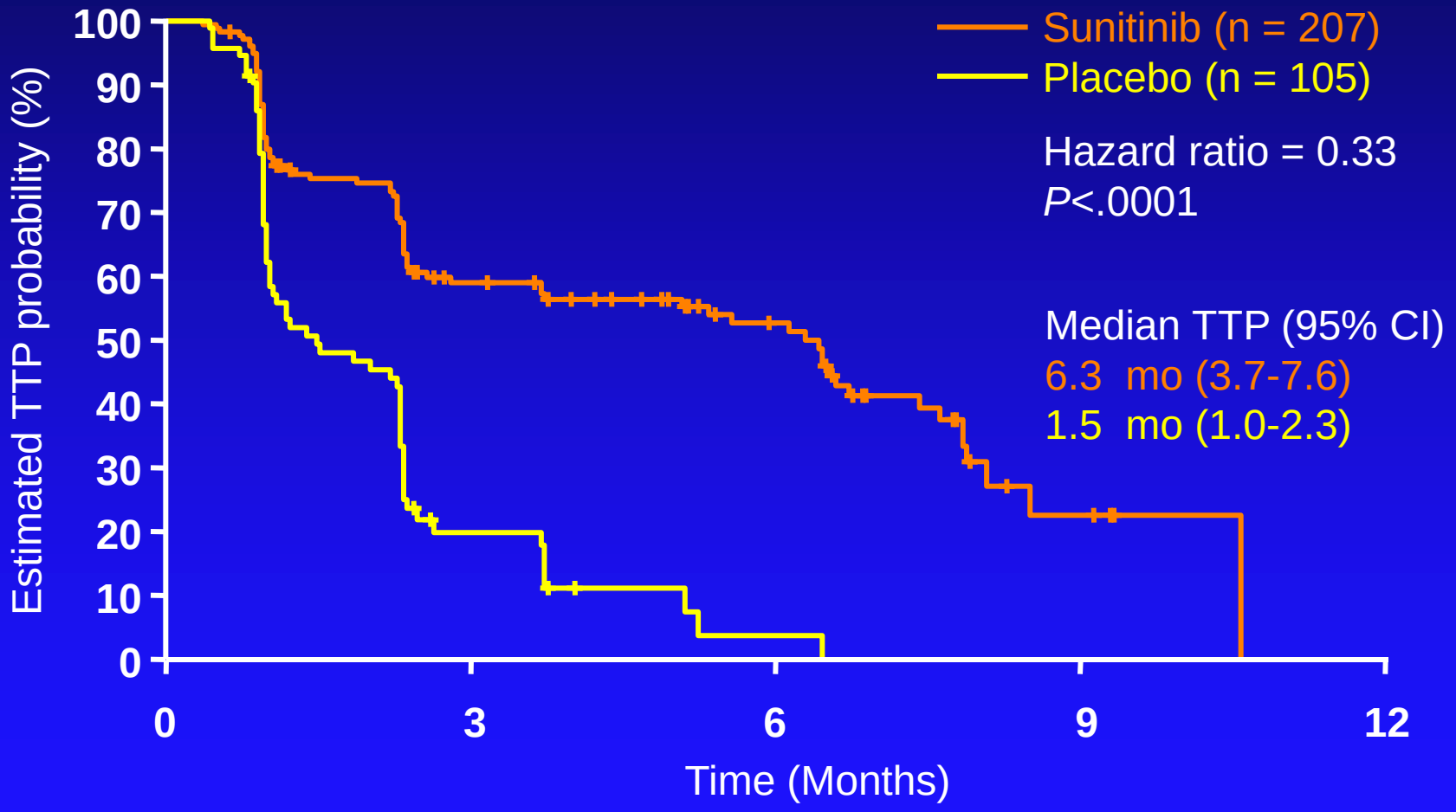
Normal kidneys

CT scan after 2 months of sunitinib

PET, positron emission tomography; CT, computed tomography

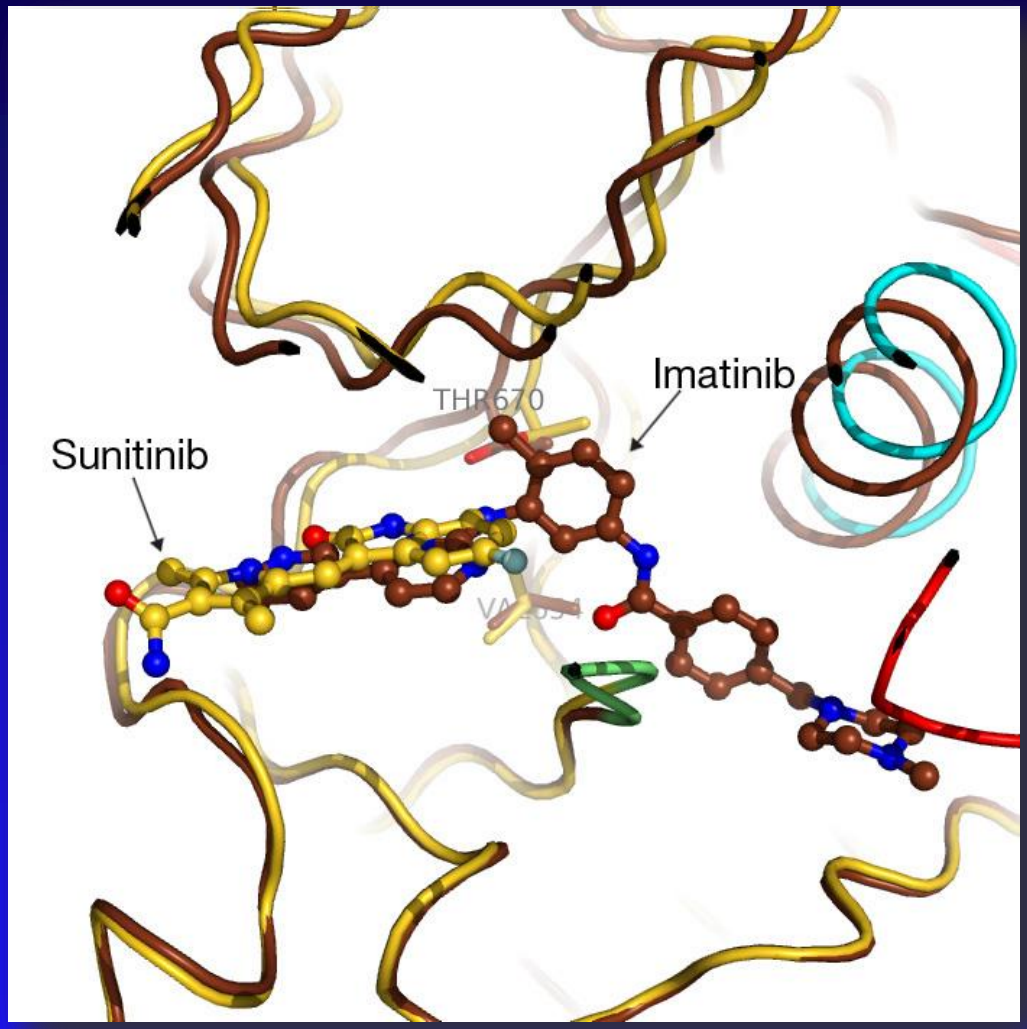
Demetri G, et al. *Clin Cancer Res.* 2009;15:5902.

Sunitinib Improves Progression-Free Survival in GIST Following Failure of Imatinib



Demetri G, et al. *Lancet.* 2006;368:1329-1338.

Structural Explanation for Why Sunitinib Works in Imatinib-Resistant GIST



Gajiwala K, Pfizer Oncology and Demetri G, Dana-Farber/Harvard.
1. Gajiwala K, et al. *Proc Natl Acad Sci USA.* 2009;106:1542-1547; 2. Mol C, et al. *J Biol Chem.* 2004;279:31655-31663.

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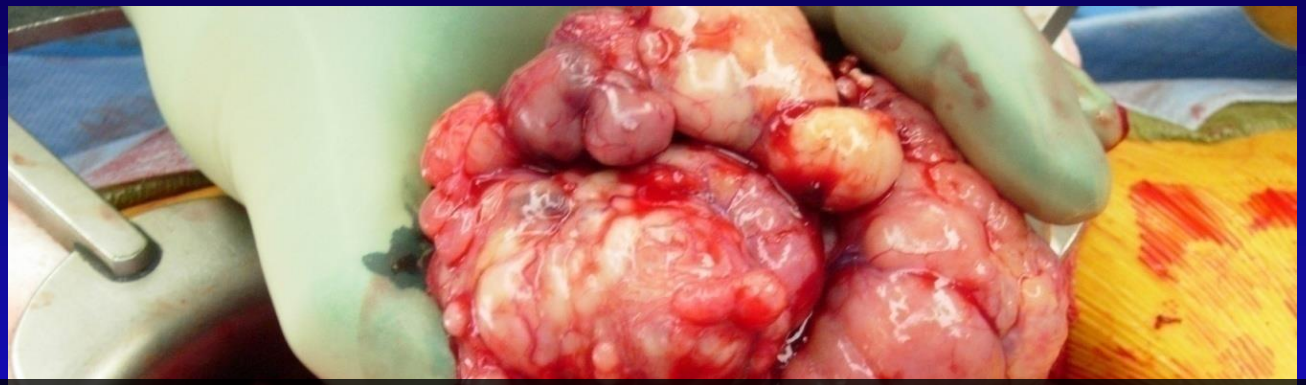
The Challenge of Multiple Progressing Tumors in Metastatic GIST Failing TKI Therapy



46 Tumors

All started with Exon 9 *KIT* Mutant but now demonstrate >10 different secondary resistance mutations in *KIT*

Courtesy of Drs Chan Raut, Yuexiang Wang, and Jon Fletcher, Dana-Farber/Harvard.

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The Emergence of GIST Clones Resistant to TKIs Complicates "Personalized Medicine"

How to Manage Patients with Metastatic GIST Progressing Despite Treatment with the 2 Approved TKI Drugs (Imatinib and Sunitinib)

Clinical trials…new agents

Guideline Recommendations After Failure of Imatinib and Sunitinib

Gastrointestinal stromal tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

P. G. Casali[1] & J.-Y. Blay[2]
On behalf of the ESMO/CONTICANET/EUROBONET Consensus Panel of Experts*

[1]Department of Cancer Medicine, Istituto Nazionale dei Tumori, Milan, Italy; [2]INSERM U590, Claude Bernard University and Department of Oncology, Edouard Herriot Hospital, Lyon, France

GIST: Extensive Disease Progression or Intolerance

Imatinib 400 mg → **Imatinib 800 mg** →

Imatinib 800 mg *[exon 9]* →

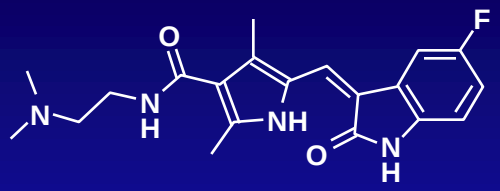
Sunitinib →

CLINICAL TRIAL

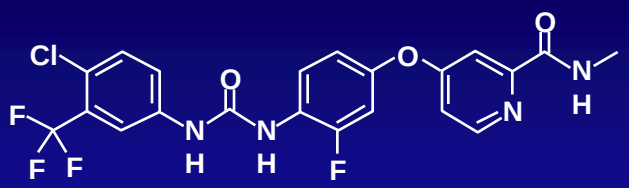
Casali PG, et al. *Ann Oncol*. 2010;21(suppl 5):v98-v102.

Regorafenib (BAY 73-4506) Is a Structurally Distinct Oral Inhibitor of Multiple Kinases Relevant to GIST and Other Cancers

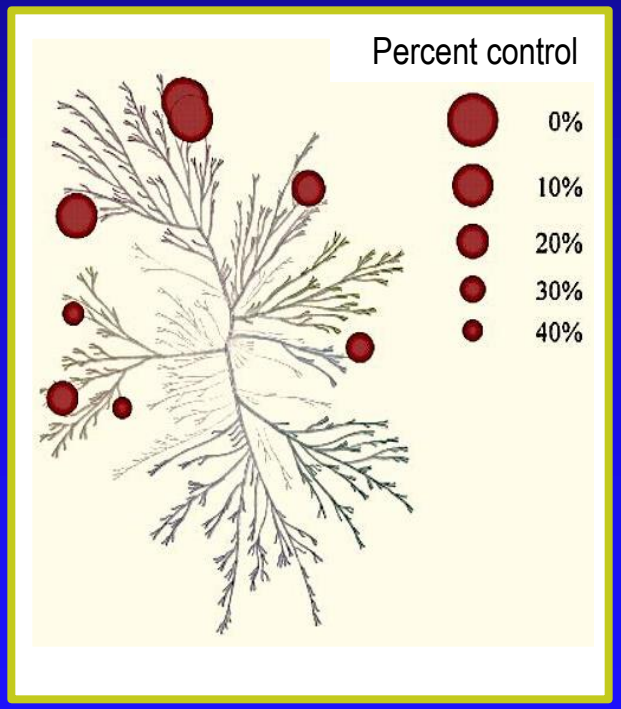
Imatinib

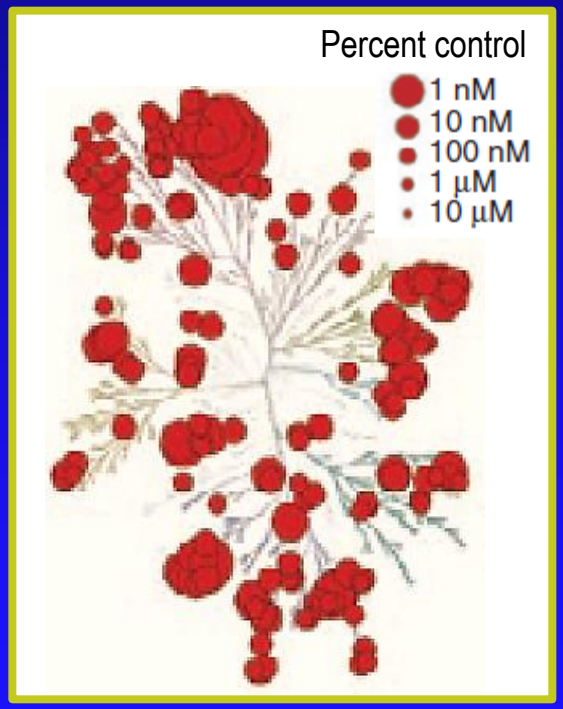


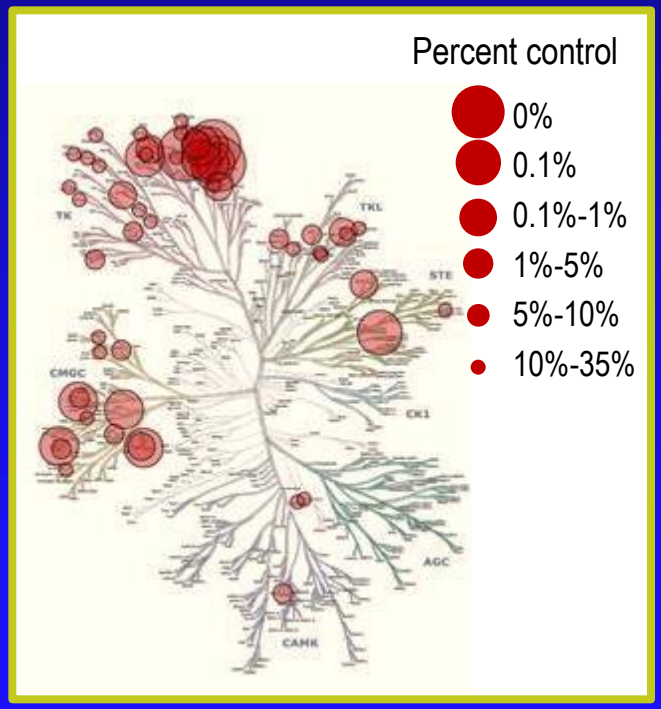
Sunitinib



Regorafenib







1. Wilhelm SM, et al. *Int J Cancer.* 2011;129:245-255; 2. Murphy EA, et al. *PNAS.* 2010;107:4299-4304; 3. Fabian M, et al. *Nature Biotech*. 2005;23:329-336; 4. Sutent® (sunitinib malate) [prescribing information] New York, NY: Pfizer, Inc; 2012.

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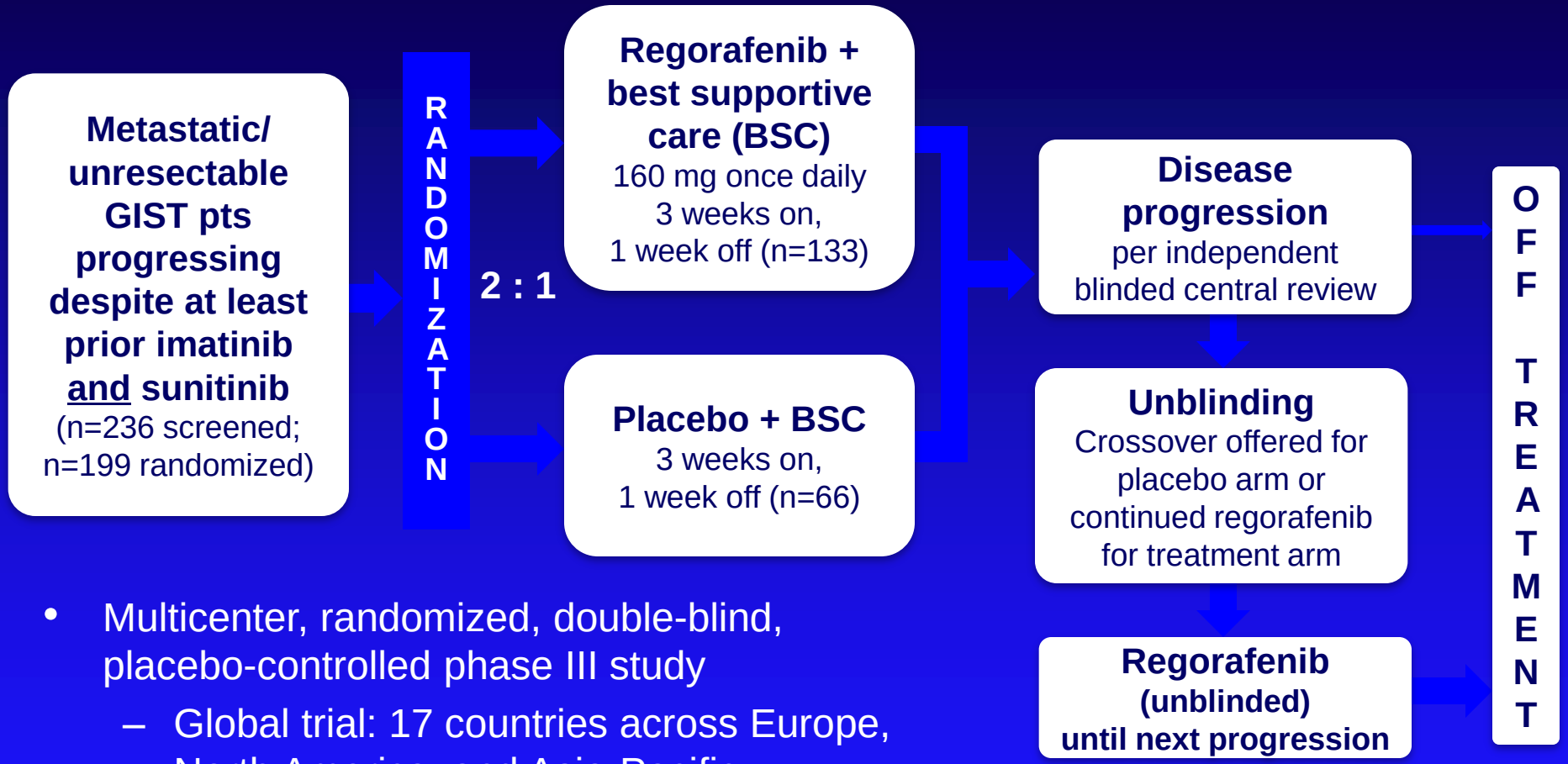
GIST – Regorafenib In Progressive Disease (GRID): Study Design



- 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. Oral abstract presented at ASCO 2012. *J Clin Oncol.* 2012;30: (suppl; abstr LBA10008).

GRID Study: Baseline Patient Demographics

		Regorafenib n = 133	Placebo n = 66
Age, median years (range)		58 (18-82)	58 (25-87)
Sex, n (%)	Male	85 (63.9)	42 (63.6)
	Female	48 (36.1)	24 (36.4)
Race, n (%)	White	90 (67.7)	45 (68.2)
	Black	0 (0.0)	1 (1.5)
	Asian	34 (25.6)	16 (24.2)
Prior lines of GIST therapies, n (%)	2 (imatinib and sunitinib *only*)	74 (55.6)	39 (59.1)
	>2 (imatinib, sunitinib, and others)	59 (44.4)	27 (40.9)
ECOG PS, n (%)	0	73 (54.9)	37 (56.1)
	1	60 (45.1)	29 (43.9)

ECOG PS, Eastern Cooperative Oncology Group performance status

Demetri G, et al. Oral abstract presented at ASCO 2012. *J Clin Oncol.* 2012;30: (suppl; abstr LBA10008).

GRID Study: Prior GIST Therapies at Entry

	Regorafenib (n = 133) n (%)	Placebo (n = 66) n (%)
Imatinib	133 (100.0)	66 (100.0)
Sunitinib	133 (100.0)	66 (100.0)
Nilotinib	29 (21.8)	20 (30.3)
Other tyrosine kinase inhibitors	2 (1.5)	1 (1.5)
mTOR inhibitor	3 (2.3)	1 (1.5)
Cytotoxic chemotherapy	13 (9.8)	2 (3.0)
Other	5 (3.8)	1 (1.5)

Demetri G, et al. Oral abstract presented at ASCO 2012. *J Clin Oncol.* 2012;30: (suppl; abstr LBA10008).

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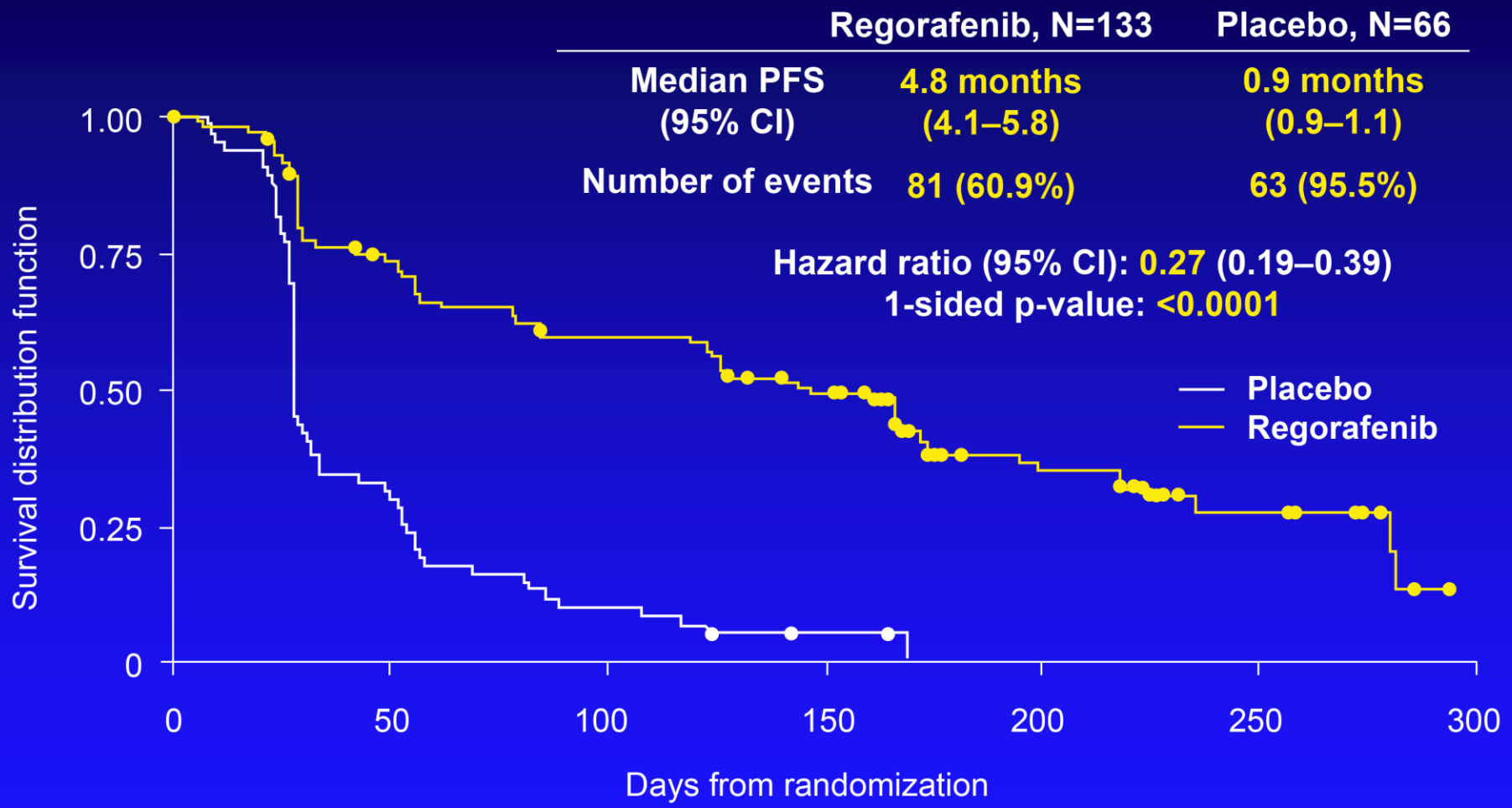
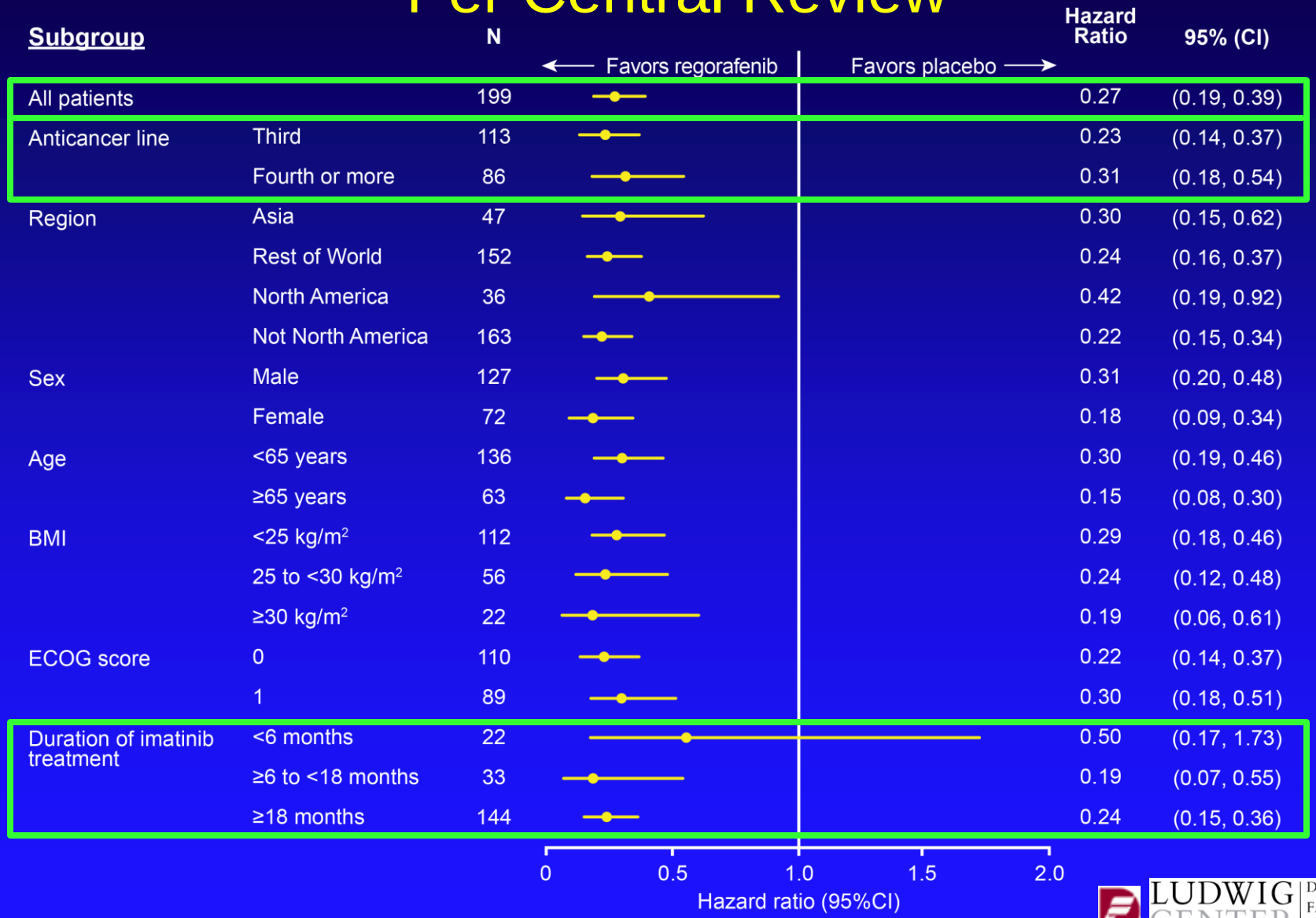
GRID Study: PFS (Primary Endpoint Per Blinded Central Review)



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

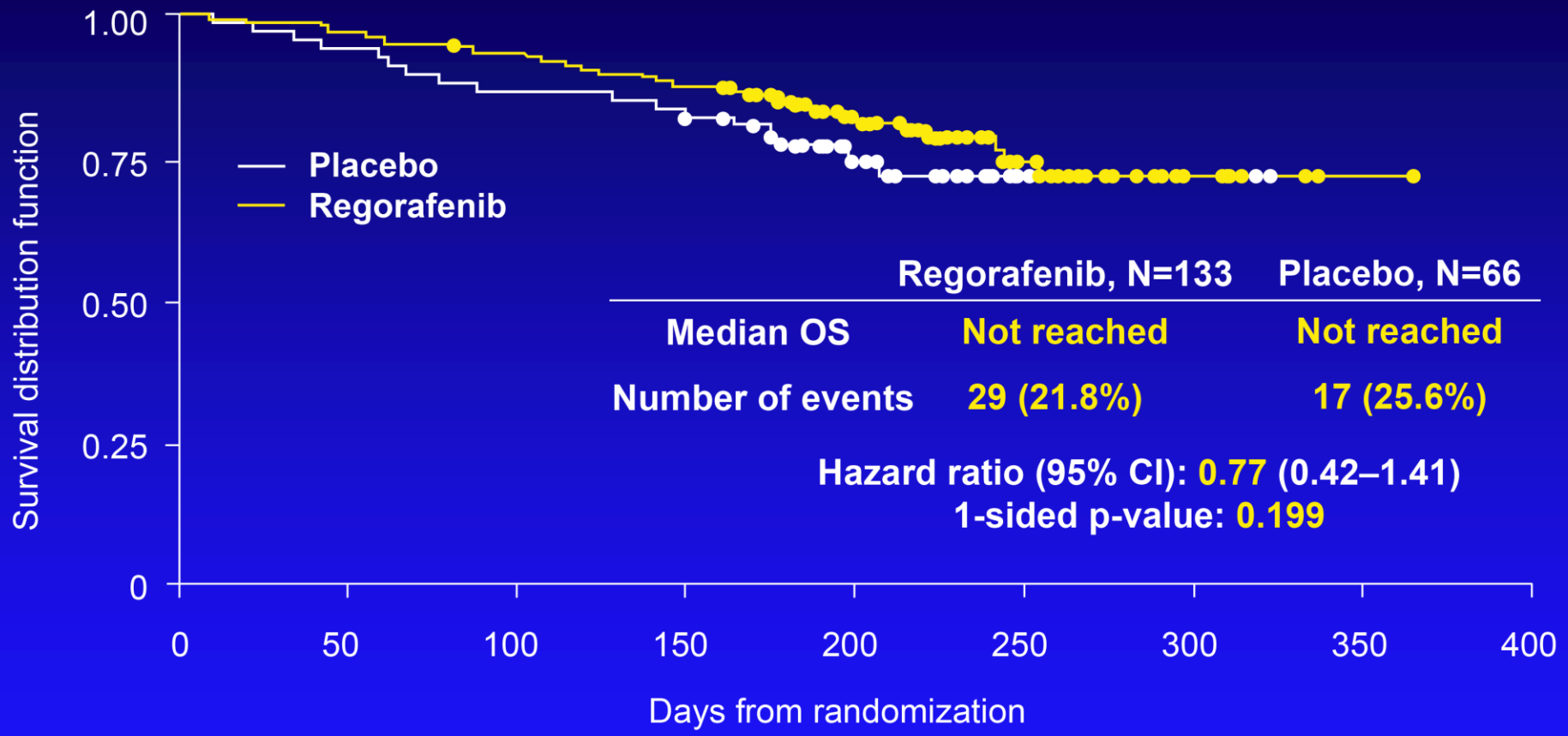
Demetri G, et al. Oral abstract presented at ASCO 2012. *J Clin Oncol.* 2012;30: (suppl; abstr LBA10008).

Prespecified Subgroup Analysis: PFS Per Central Review



Demetri G, et al. Oral abstract presented at ASCO 2012. *J Clin Oncol.* 2012;30: (suppl; abstr LBA10008).

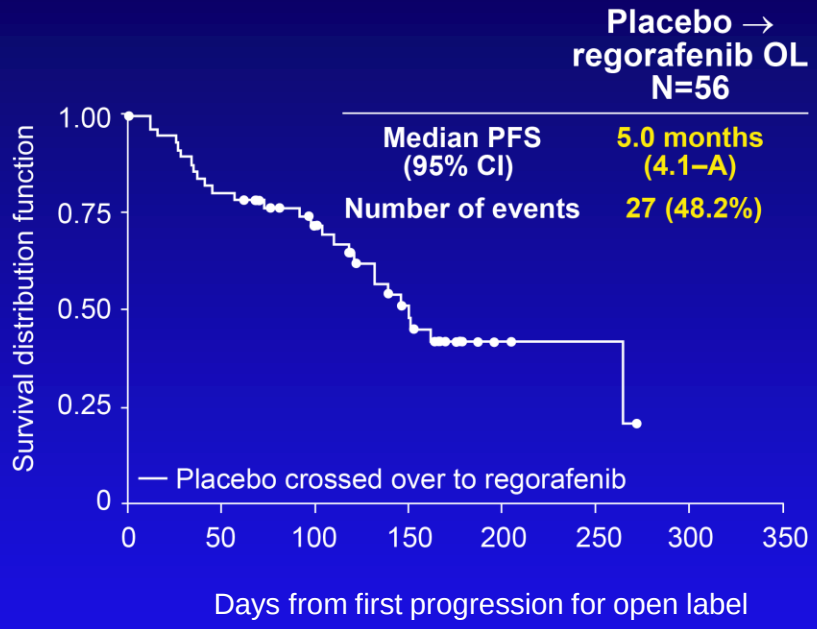
GRID Study: OS (Following 85% Crossover of Patients on Placebo Arm)



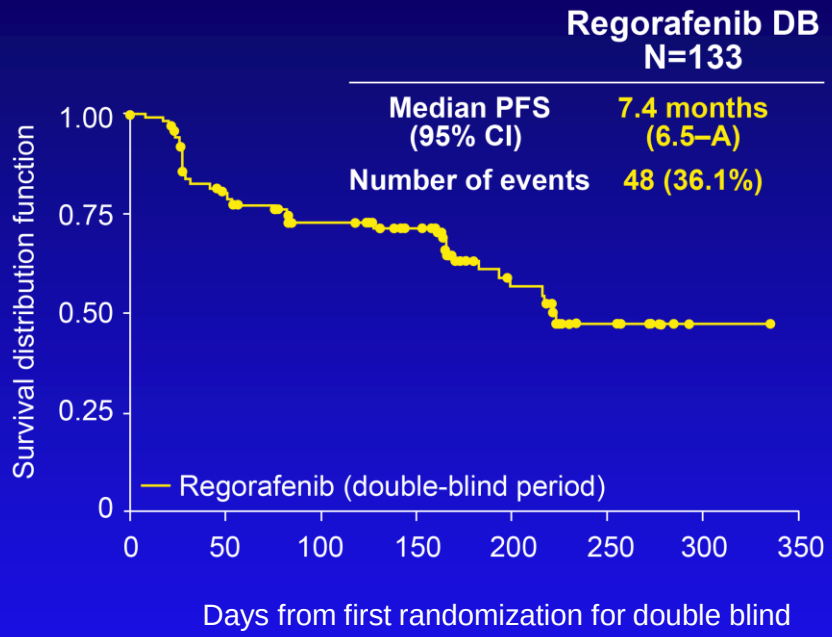
Because of the crossover design, lack of statistical significance between regorafenib and placebo was not unexpected

Demetri G, et al. Oral abstract presented at ASCO 2012. *J Clin Oncol.* 2012;30: (suppl; abstr LBA10008).

PFS Following Crossover (Per Investigator Assessment)



Substantial PFS benefit in patients initially randomized to placebo and subsequently crossed over to open-label regorafenib



PFS benefit in placebo arm after crossover to regorafenib is comparable to PFS benefit in patients initially randomized to regorafenib

Demetri G, et al. Oral abstract presented at ASCO 2012. *J Clin Oncol.* 2012;30: (suppl; abstr LBA10008).

Disease Control and Overall Response Rates

	Regorafenib (n = 133) n (%)	Placebo (n = 66) n (%)
Disease Control Rate CR + PR + durable SD (≥12wks)	**70 (52.6)**	**6 (9.1)**
Objective Response Rate	**6 (4.5)**	**1 (1.5)**
Complete response (CR)	0 (0.0)	0 (0.0)
Partial response (PR)	6 (4.5)	1 (1.5)
Stable disease (SD) (at any time)	95 (71.4)	22 (33.3)
Progressive disease (PD)	28 (21.1)	42 (63.6)

Responses based on modified RECIST v1.1

Regorafenib improved rates of disease control vs placebo

Demetri G, et al. Oral abstract presented at ASCO 2012. *J Clin Oncol.* 2012;30: (suppl; abstr LBA10008).

Drug-Related Treatment-Emergent Adverse Events in ≥10% of Patients During Double-Blind Treatment

	Regorafenib (n = 132), % Median 23 wks exposure				Placebo (n = 66), % Median 7 wks exposure			
Grade	**All**	**3**	**4**	**5**	**All**	**3**	**4**	**5**
Hand-foot skin reaction	56.1	**19.7**	0	0	15.2	**1.5**	0	0
Hypertension	48.5	**22.7**	0.8	0	16.7	**3.0**	0	0
Diarrhea	40.9	5.3	0	0	7.6	0	0	0
Fatigue	38.6	2.3	0	0	27.3	1.5	0	1.5
Mucositis, oral	37.9	1.5	0	0	9.1	1.5	0	0
Alopecia	23.5	1.5	0	0	3.0	0	0	0
Hoarseness	22.0	0	0	0	4.5	0	0	0

Treatment-Emergent Adverse Events Leading to Permanent Discontinuation of Study Treatment

Regorafenib	Placebo
8 (6.1%)	5 (7.6%)

Baseline GIST Genotype Per Site Reports: Exploratory Analysis of Outcomes

Tumor Genotype, n (%)	Placebo	Regorafenib	Total
Prior GIST genotype available and reported at study entry (% total study population)	36 (54.5%)	60 (45.1%)	96 (48.2%)
KIT exon 11 mutation	17 (47.2%)	34 (56.7%)	51 (53.1%)
KIT exon 9 mutation	6 (16.7%)	9 (15.0%)	15 (15.6%)
Wild type *KIT* and *PDGFRA*	2 (5.6%)	6 (10.0%)	8 (8.3%)
Unspecified or other exon mutant	11 (30.5%)	11 (18.3%)	22 (22.9%)

Mutation Biomarker	Progression-Free Survival					
	N	Events	HR	95% CI	Placebo, median months	Regorafenib, median months
KIT exon 11 mutation	51	40	0.212	0.098-0.458	1.1	5.6
KIT exon 9 mutation	15	11	0.239	0.065-0.876	0.9	5.4

Demetri G, et al. Oral abstract presented at ASCO 2012. *J Clin Oncol.* 2012;30: (suppl; abstr LBA10008).

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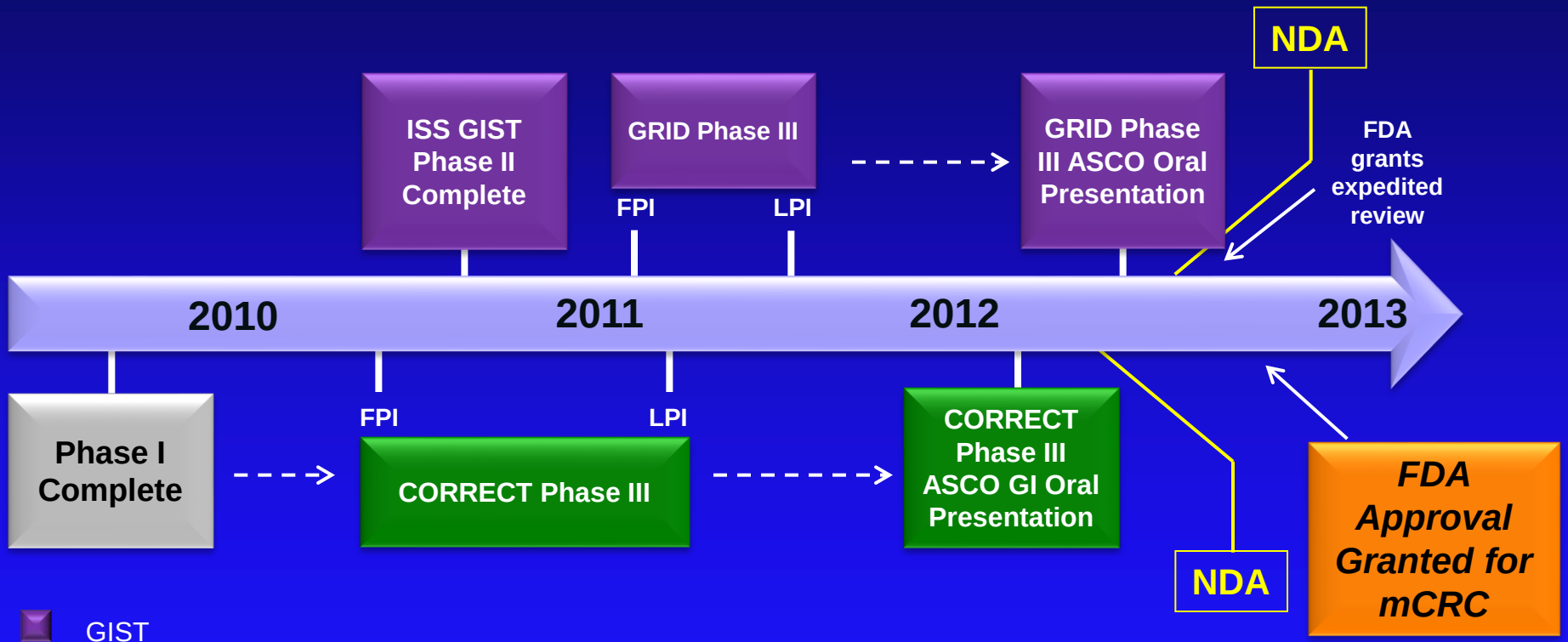
Regorafenib Clinical Development

Rapid and Effective Academia – Industry Collaborative Effort



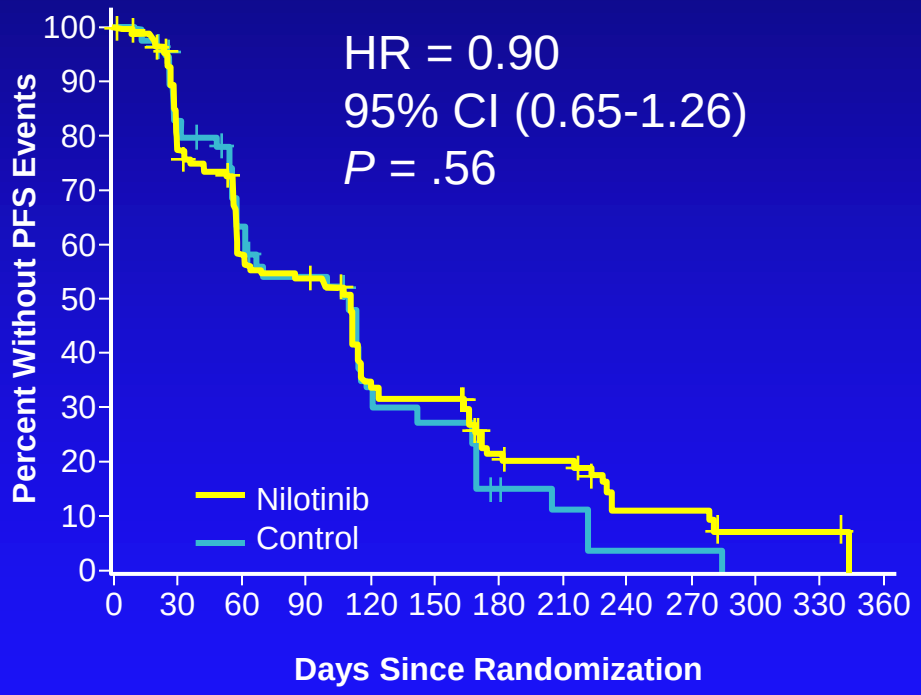
1. Mross K, et al. *Clin Cancer Res.* 2012;18(9):2658-2667; 2. Strumberg D, et al. *Br J Cancer*. 2012;106(11):1722-1727; 3. George S, et al. *J Clin Oncol*. 2012;30(19):2401-2407; 4. Grothey A, et al. GI Cancers Symposium; 2012. Abstract LBA385; 5. Demetri G, et al. ASCO; 2012. Abstract LBA10008; 6. http://www.press.bayer.com/baynews/baynews.nsf/id/en_home. 7. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm321271.htm

Other TKIs Tested or in Trials for GIST

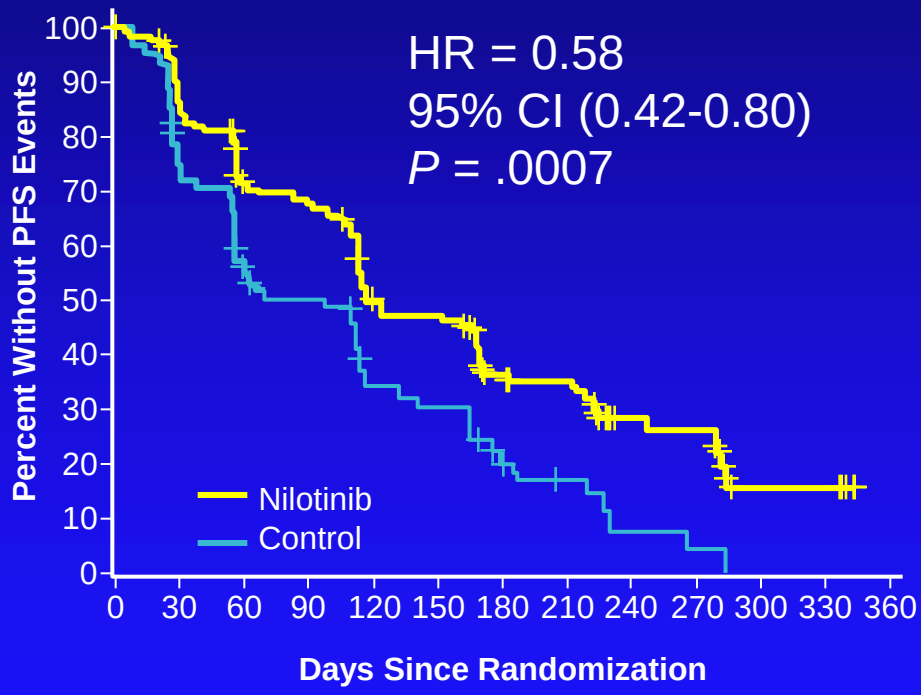
- Nilotinib
- Dasatinib
- Masitinib
- Pazopanib
- Sorafenib

Phase III Study of Nilotinib vs BSC With or Without a TKI in Patients with GIST Resistant to or Intolerant of Imatinib and Sunitinib

Primary Endpoint: Progression-Free Survival



Blinded Central Review



Unblinded Local Review

Reichardt P, et al. *Ann Oncol.* 2012;23:1680-1687.

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Summary

- To date, regorafenib is the only agent to demonstrate a significant improvement in PFS among GIST patients previously treated with imatinib and sunitinib, the only other two therapies approved for GIST by regulatory authorities
- If approved, regorafenib may offer patients with TKI-refractory GIST the opportunity for further active treatment

Thank You