GIST:

Medical and Multidisciplinary Therapy

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DISCLOSURES FOR GEORGE D. DEMETRI, MD

Consulting fees received from Janssen, Bayer, EMD-Serono (Merck KGA), Lilly, Sanofi, Daiichi-Sankyo, Pfizer, Novartis, Ziopharm, Ariad, Polaris, KyMab, Genocea, Nektar, Caris Life Sciences, WCG

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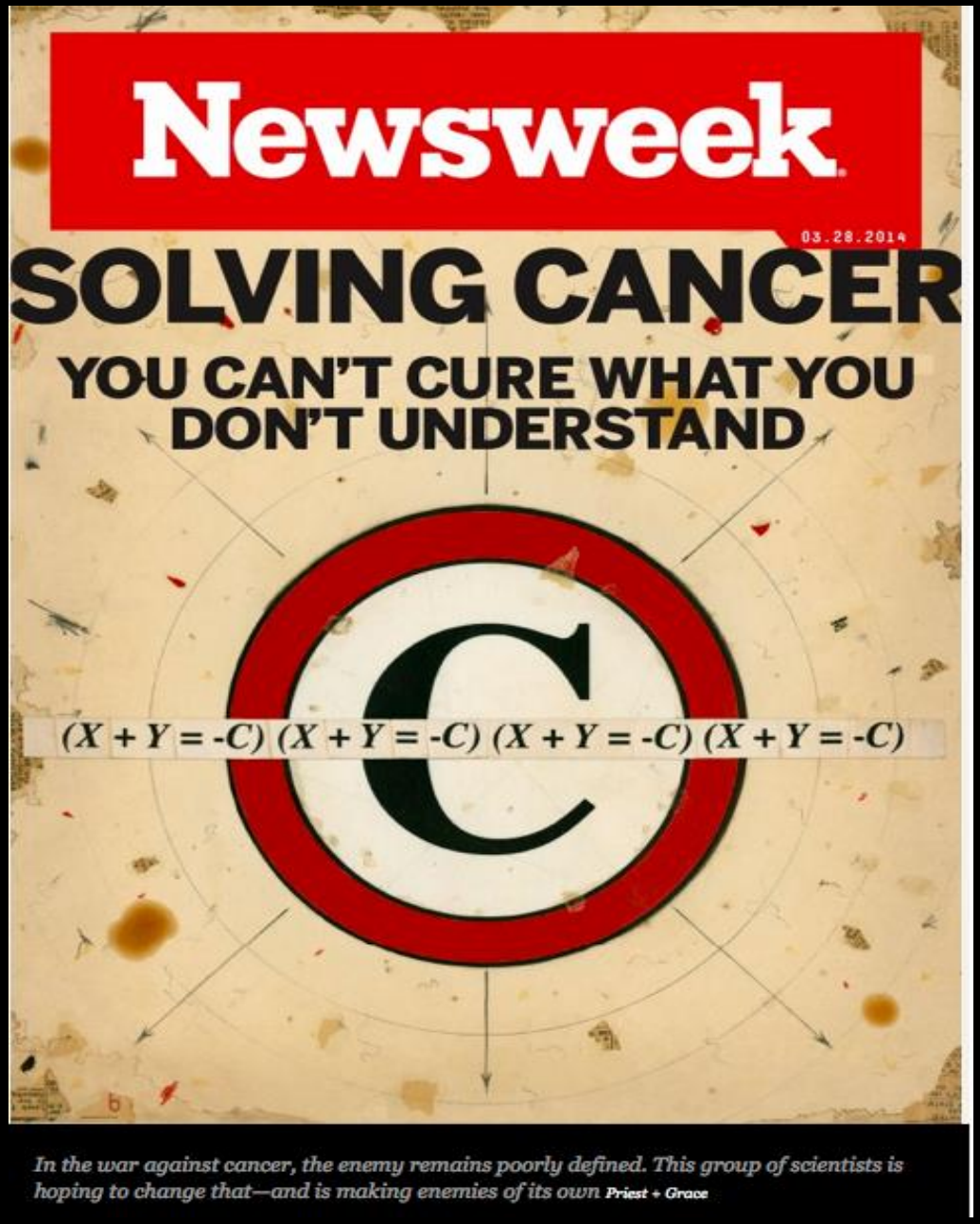
Patent licensed to Novartis from Dana-Farber Cancer Institute with royalties paid directly to DFCI

Equity in Blueprint Medicines, Kolltan, and G1 Therapeutics

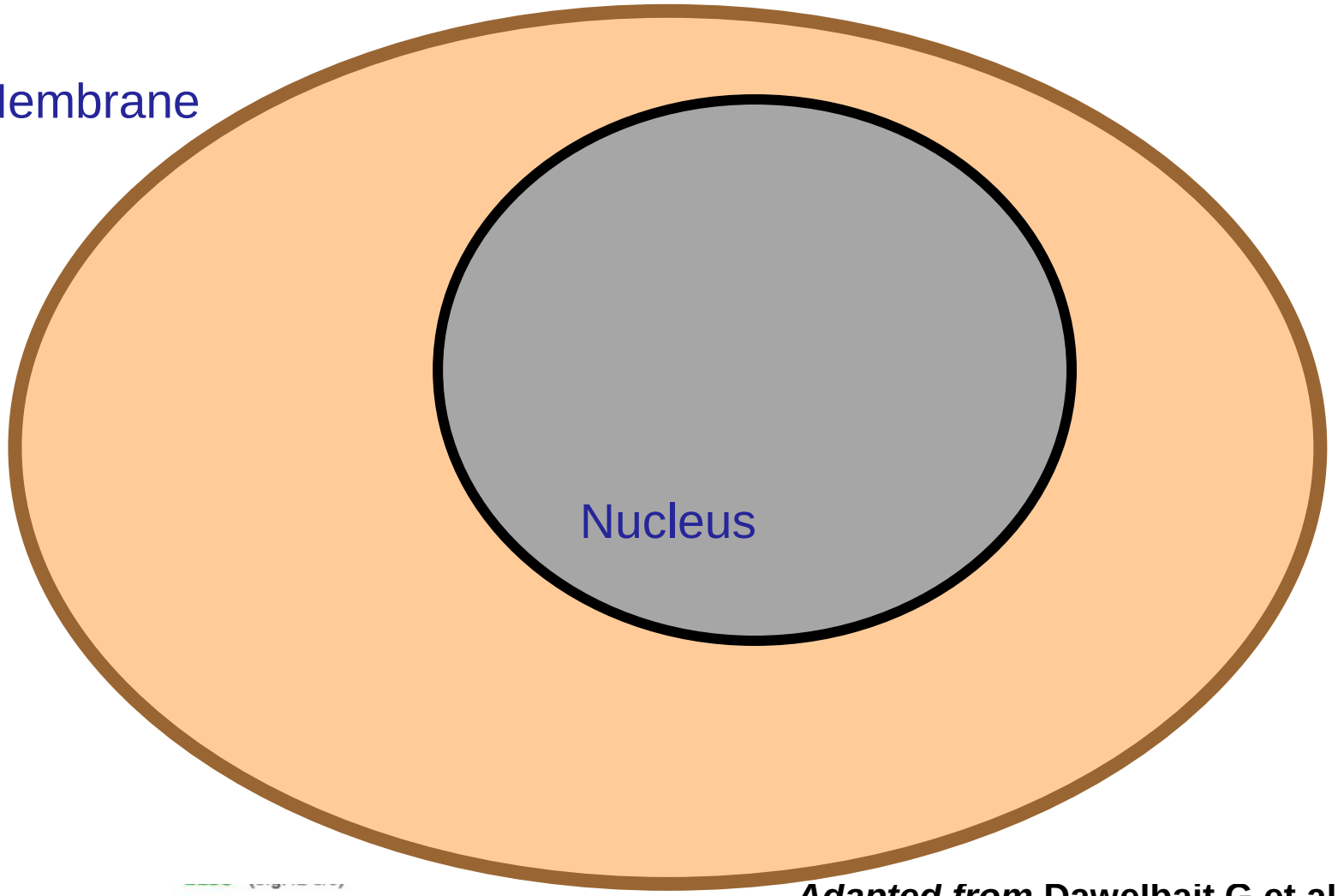
Board of Directors of Blueprint Medicines


Newsweek
03.28.2014
SOLVING CANCER
YOU CAN'T CURE WHAT YOU DON'T UNDERSTAND
(X + Y = -C) (X + Y = -C) (X + Y = -C) (X + Y = -C)
In the war against cancer, the enemy remains poorly defined. This group of scientists is hoping to change that—and is making enemies of its own Priest + Grace

The Disease is the Medium, The *Mechanism* is the Message

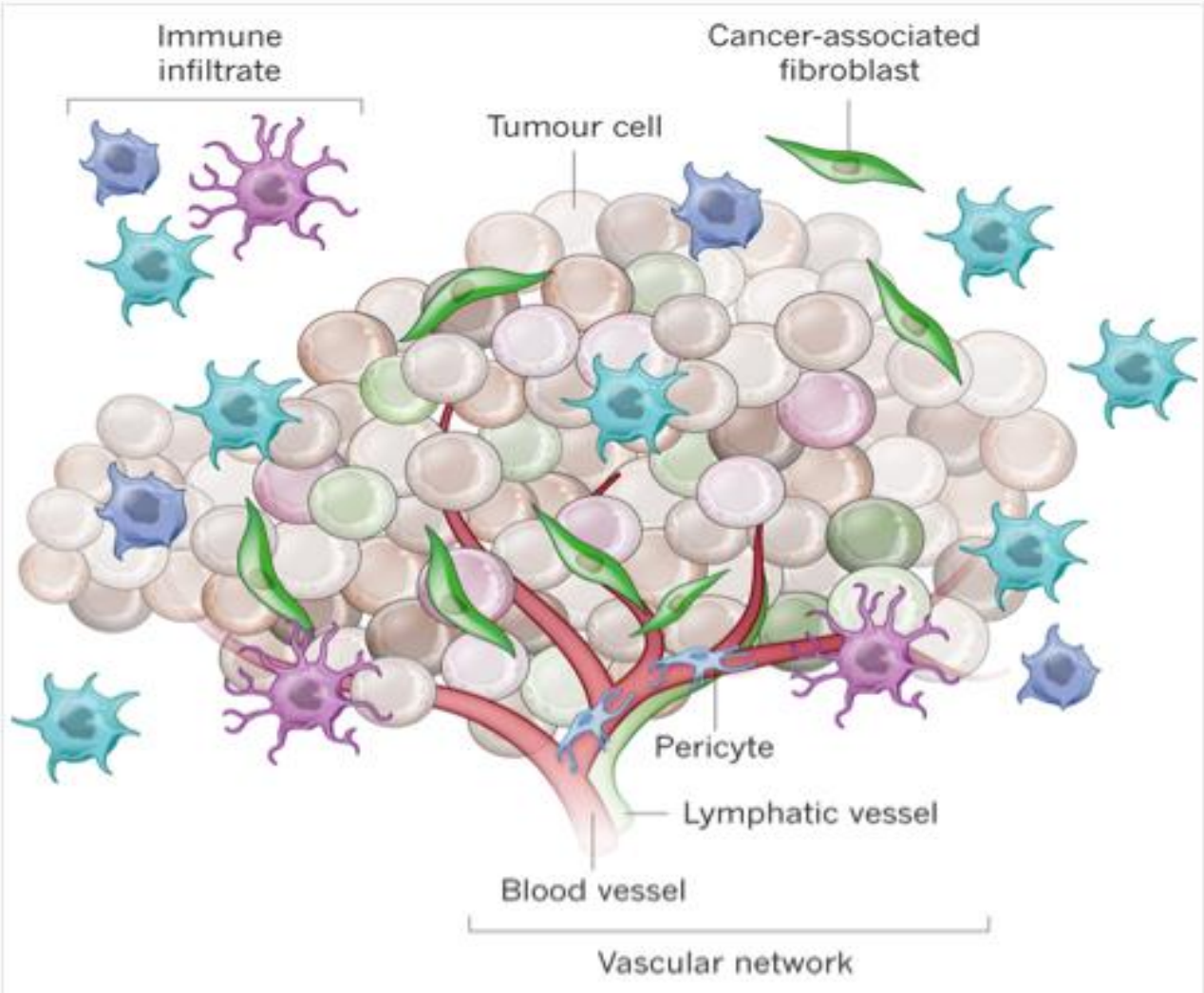
- Understanding the basic mechanisms of GIST at the molecular level
- Diagnosing patients correctly
- Understanding clinically relevant GIST variations
- Understanding resistance to overcome barriers to cure

Research has helped us to understand which mechanisms drive cancer cells



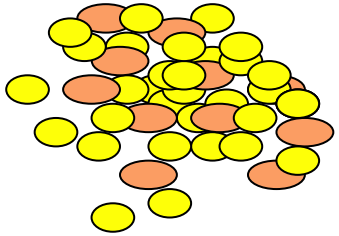
Adapted from Dawelbait G et al. Bioinformatics 2007;23:i115-i124

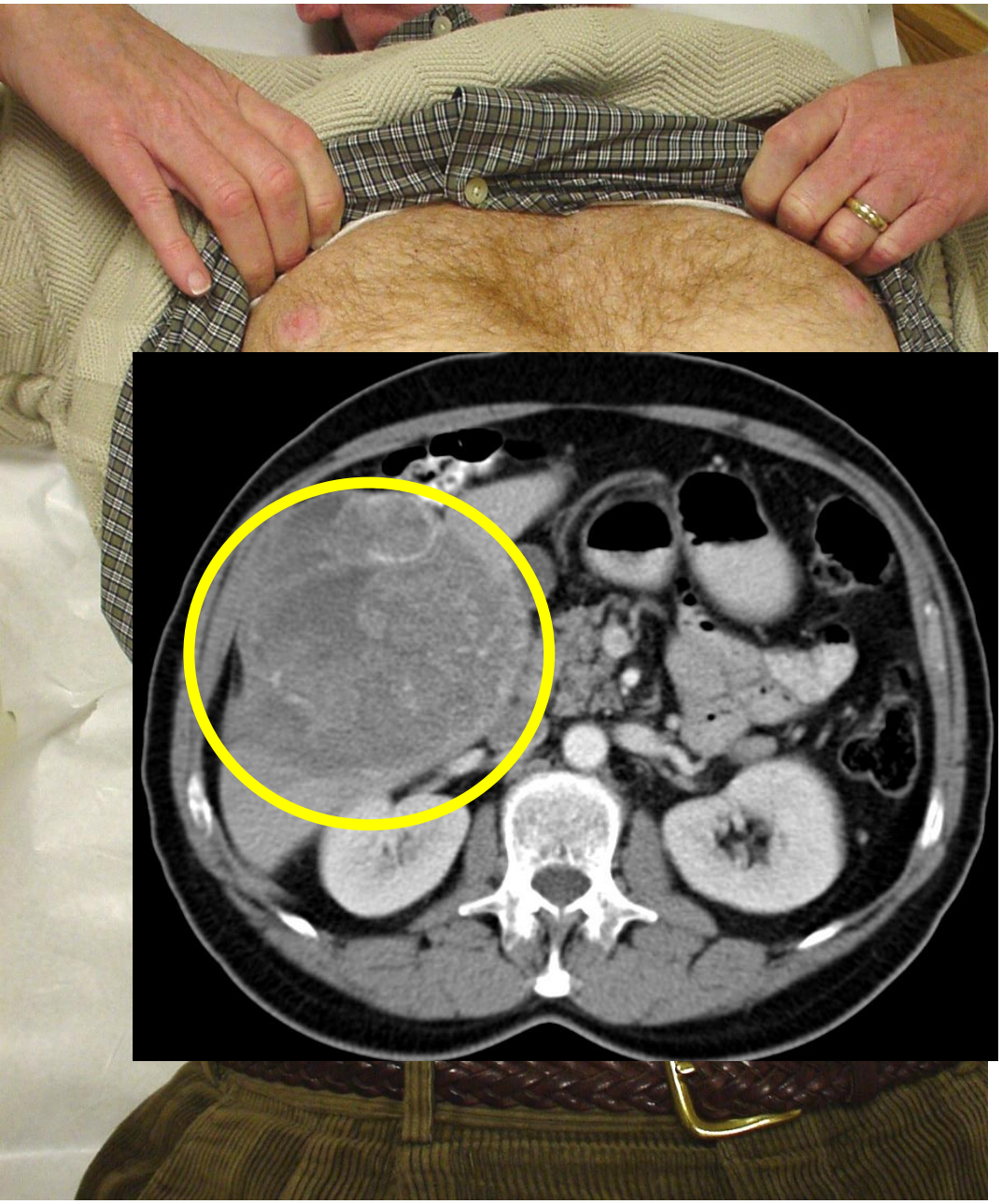
Tumor cells are only one part of an ecosystem – How to make the whole ecosystem extinct?



We need to identify the switches that sustain cancer cell survival and growth

ON





There was no effective systemic medical therapy for GIST prior to Kinase Inhibitors

The Enabling Discovery Linking KIT to GIST

Gain-of-Function Mutations of c-*kit* in Human Gastrointestinal Stromal Tumors

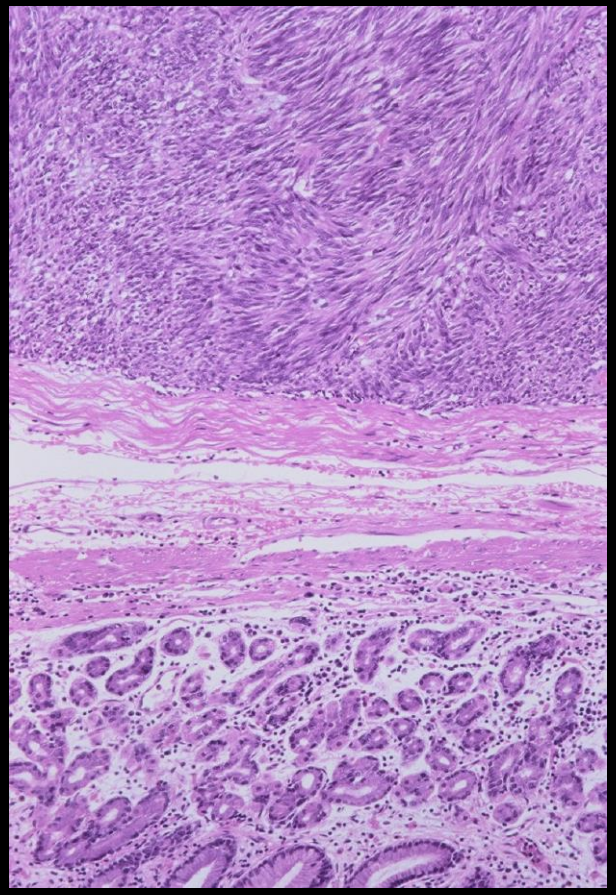
Seiichi Hirota,* Koji Isozaki,* Yasuhiro Moriyama, Koji Hashimoto, Toshirou Nishida, Shingo Ishiguro, Kiyoshi Kawano, Masato Hanada, Akihiko Kurata, Masashi Takeda, Ghulam Muhammad Tunio, Yuji Matsuzawa, Yuzuru Kanakura, Yasuhisa Shinomura, Yukihiko Kitamura†

Science 279:577-580, 1998

Detection of KIT by Immunohistochemical Staining in GIST

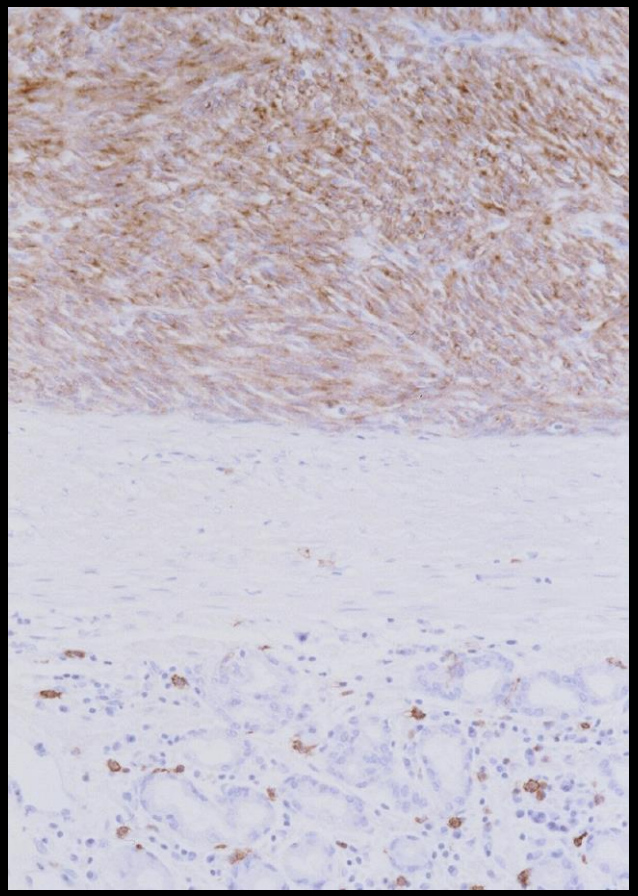
H+E Stain

CD117 IHC Stain



TUMOR
GIST

Normal
Small
Intestine



CDM Fletcher, MD

The first GIST patient on imatinib: January 2000

NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey

Clinical Development

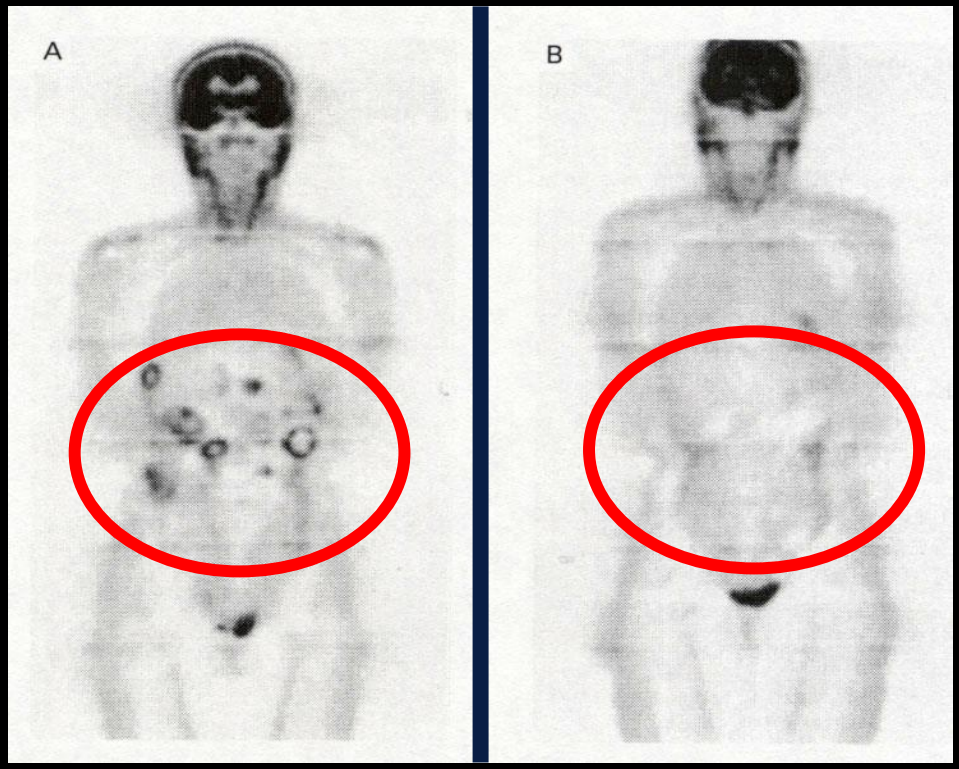
STI571/STI571B

Protocol No. CSTI571B2221

An Individual Supply, Pilot Study to Determine the Efficacy and Safety of STI571 in a Patient with a Progressing Metastatic Gastrointestinal Stromal Tumour

Document Type:	Clinical Study Protocol
Development Phase:	I
Document Status:	Final
Release Date:	February 18 2000

Imatinib Induces Major Response in the First Patient with Metastatic GIST

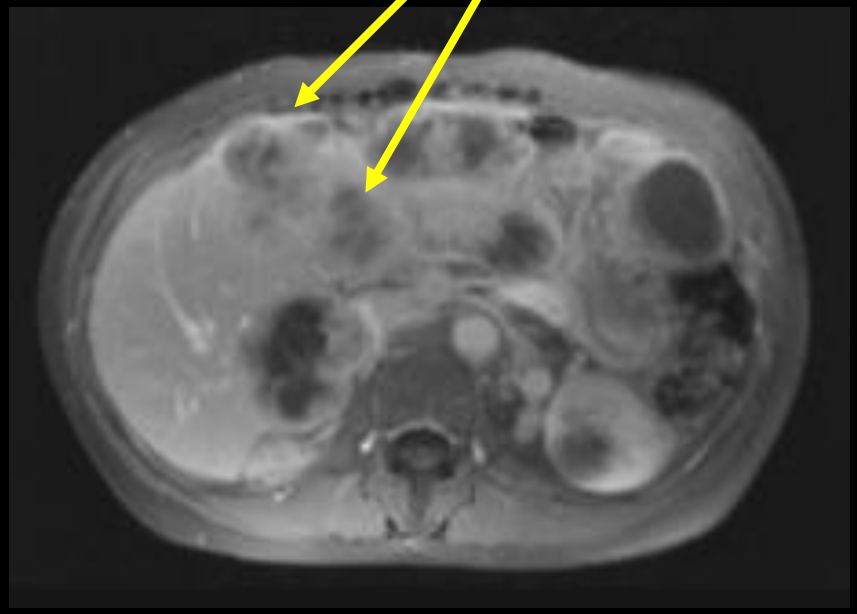


March 3, 2000

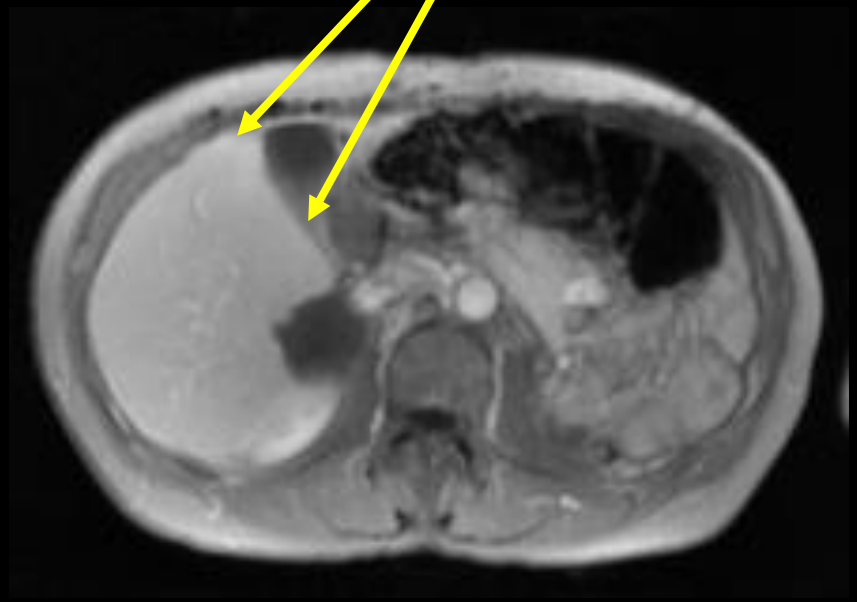
April 5, 2000

Joensuu H, et al. NEJM 2001; 344: 1052-6

GIST liver metastases disappear after 4 weeks of treatment with STI571 (imatinib, Glivec)



BASELINE



AFTER 4 weeks Rx

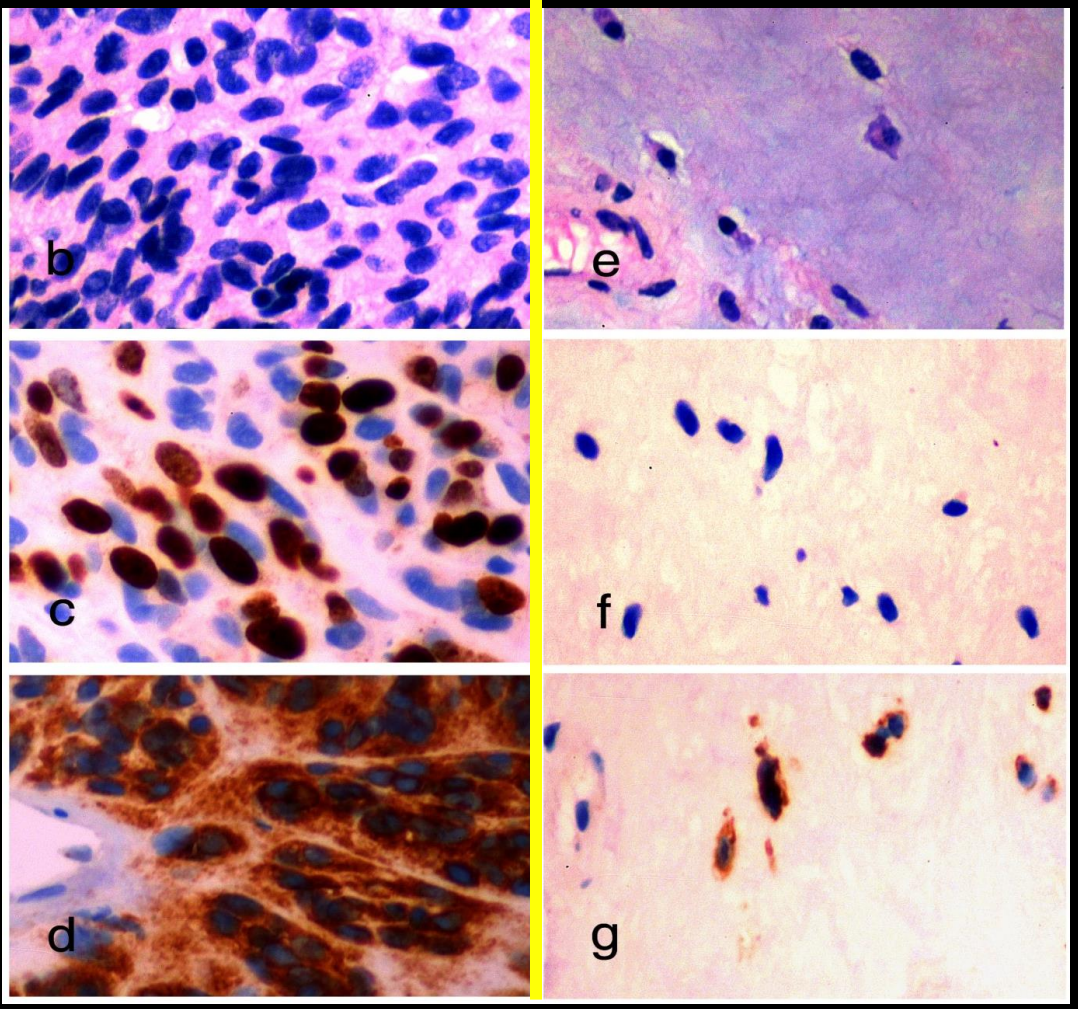
GIST Biopsy
Before Imatinib

GIST Biopsy
After Imatinib

H+E

Ki-67
(proliferation)

CD117
(KIT)



H+E

Ki-67

CD117

Joensuu, et al. N Engl J Med.2001; (344): 1052-1056

Rapid movement to the next big step: April 2000

NOVARTIS

Novartis Pharma AG
Basel, Switzerland

Clinical Development

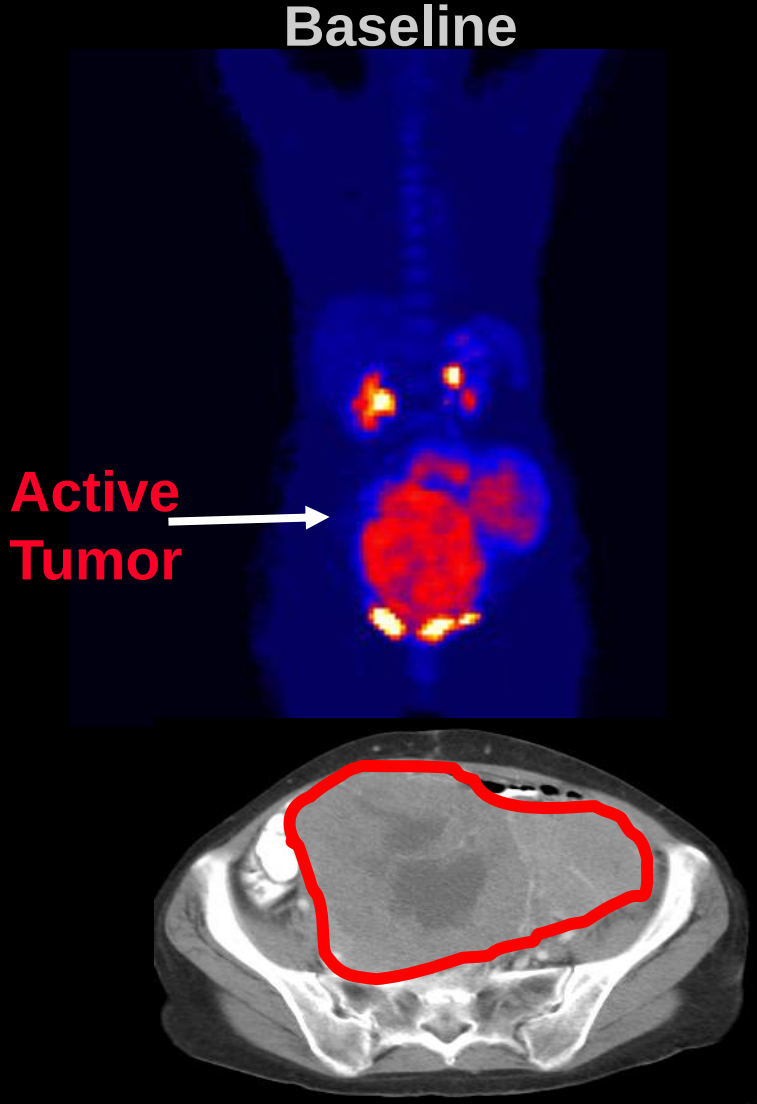
Compound STI 571

Protocol No. CSTI571B2222

A Phase II Study of STI571 in Patients with Unresectable or Metastatic Malignant Gastrointestinal Stromal Tumors Expressing c-kit

Author(s): George D. Demetri, M.D.; Renaud Capdeville M.D.; Sasa Dimitrijevic, Ph.D.

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



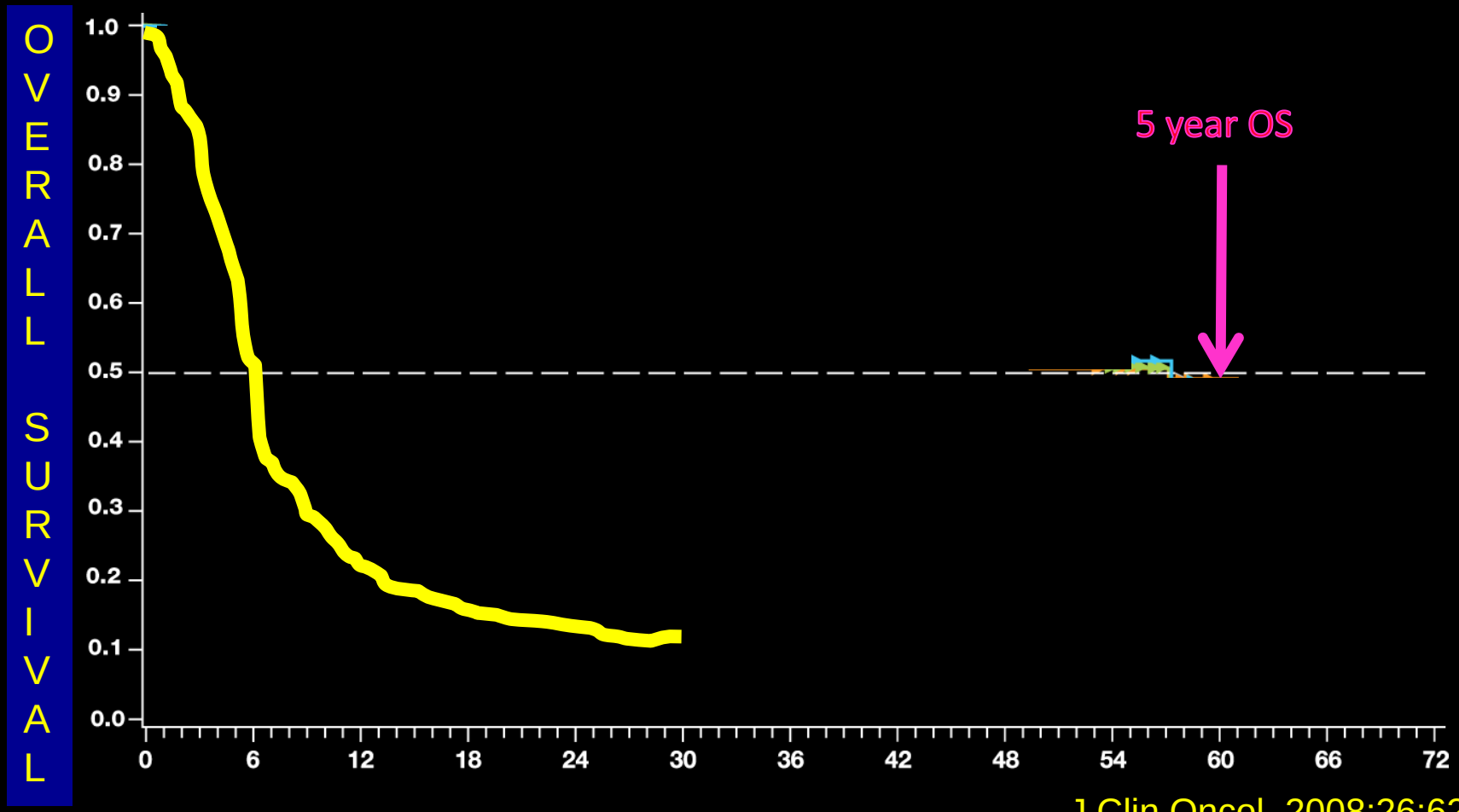
Imatinib Benefits the Majority of Patients with Metastatic GIST

Best Response	All patients N = 147 (%)
Partial Response	**97 (66%)**
Stable Disease	**25 (17%)**
Progression or Non-evaluable	25 (17%)

83% Benefit

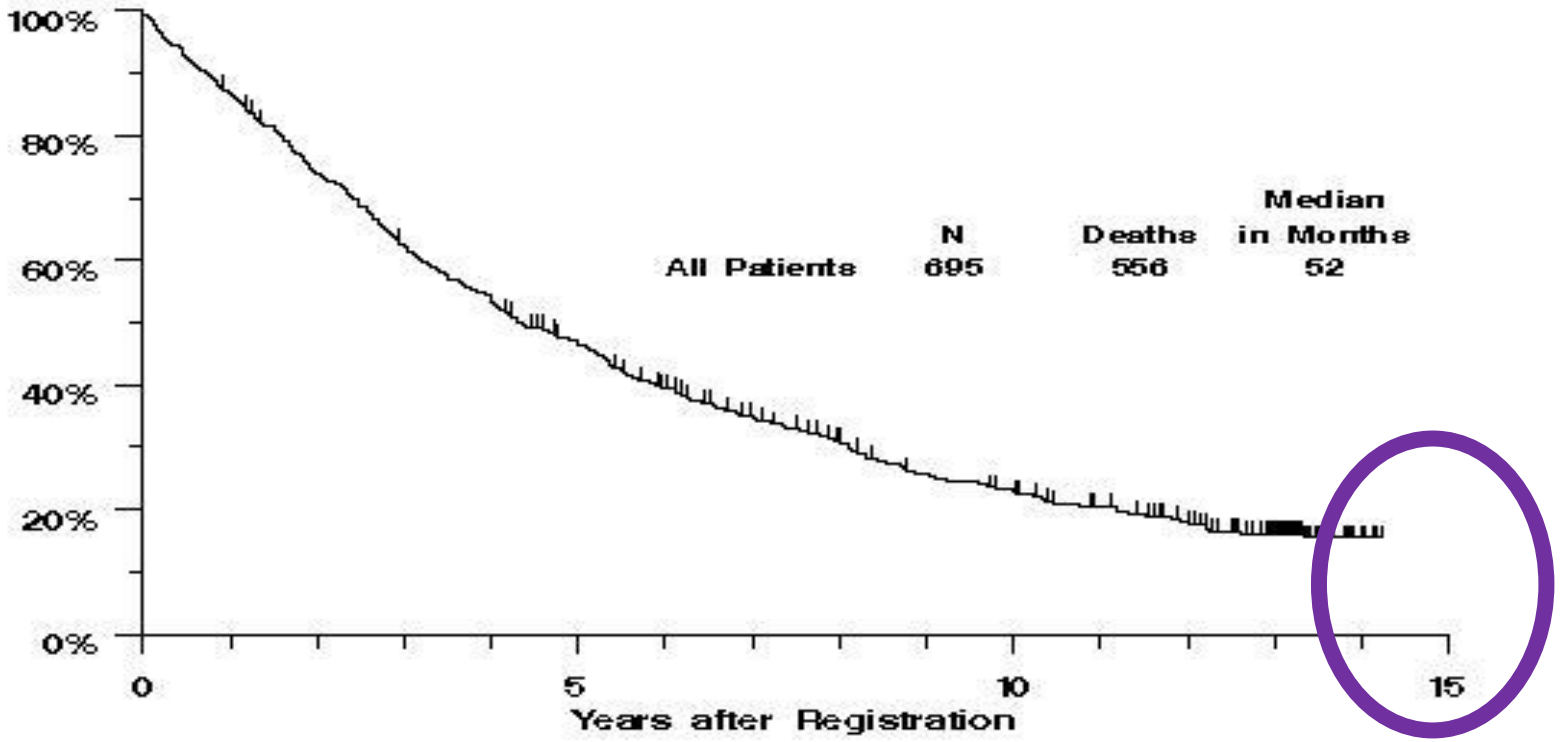
Demetri et al. Update from N Engl J Med 2002

Significant improvement in overall survival for metastatic GIST patients treated with imatinib

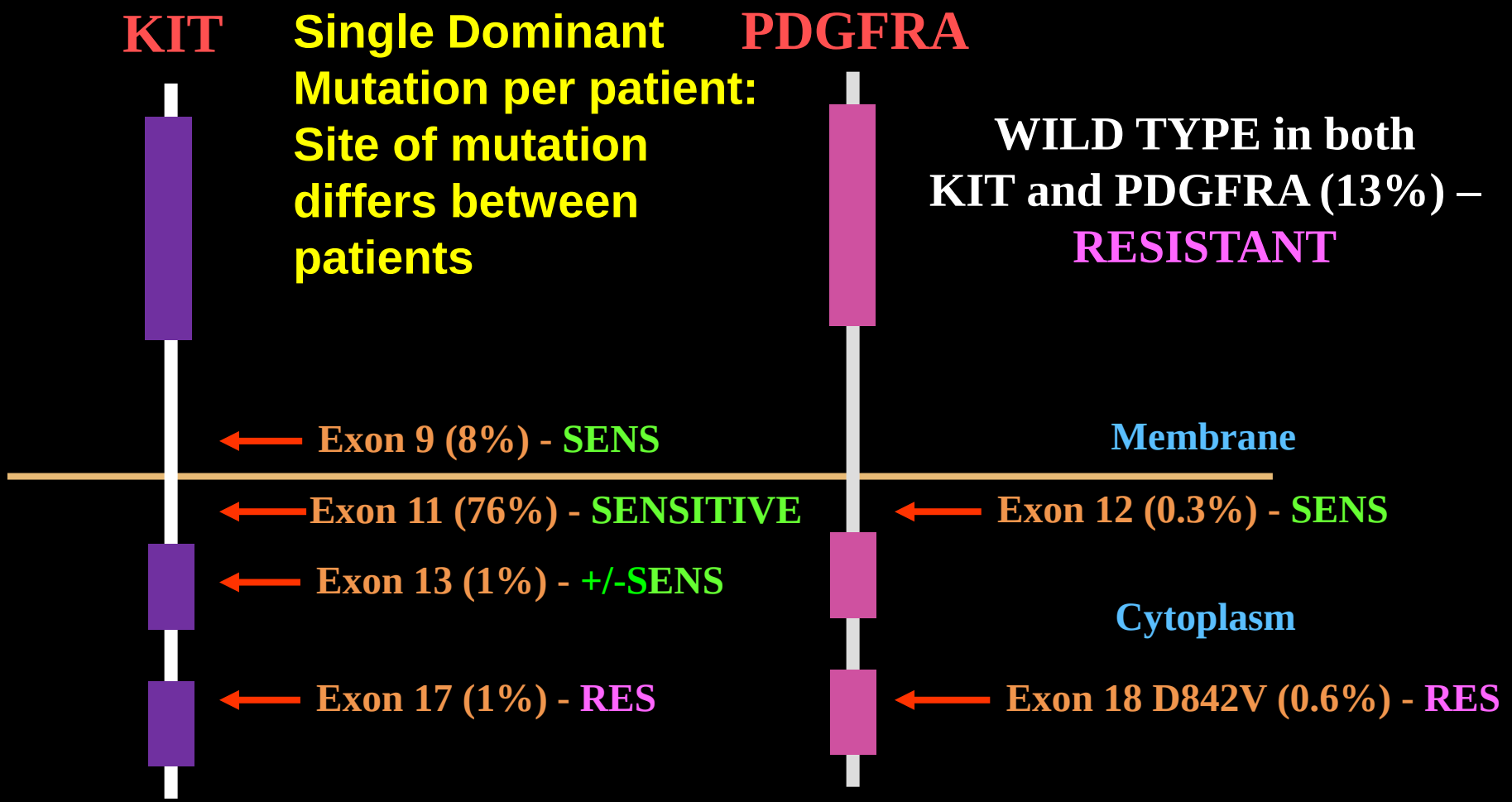


J Clin Oncol. 2008;26:620-625

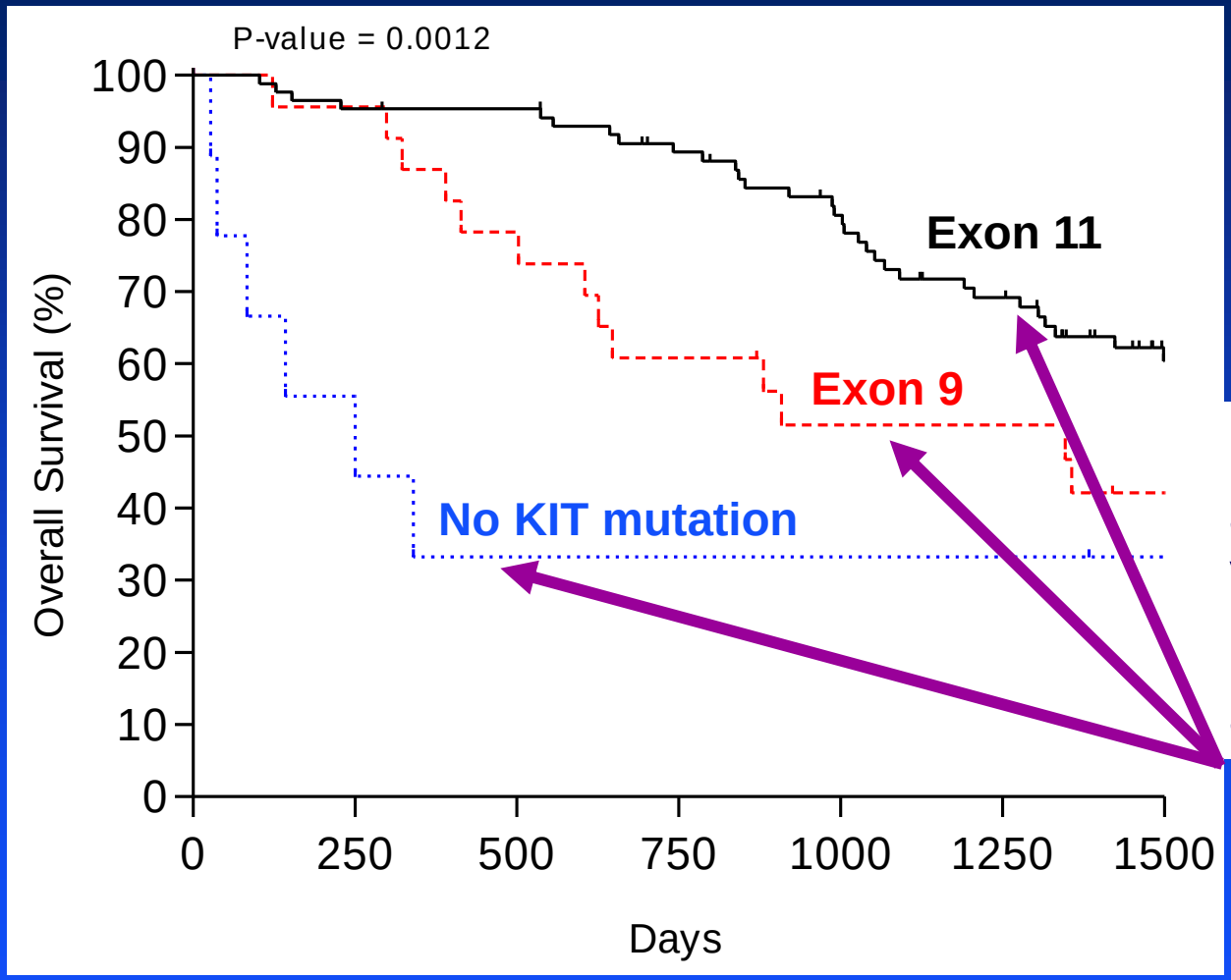
Long Term Survival in GIST Patients:
S0033 Intergroup US-Canada Trial



Different Structural Variants of Kinase Targets in GIST



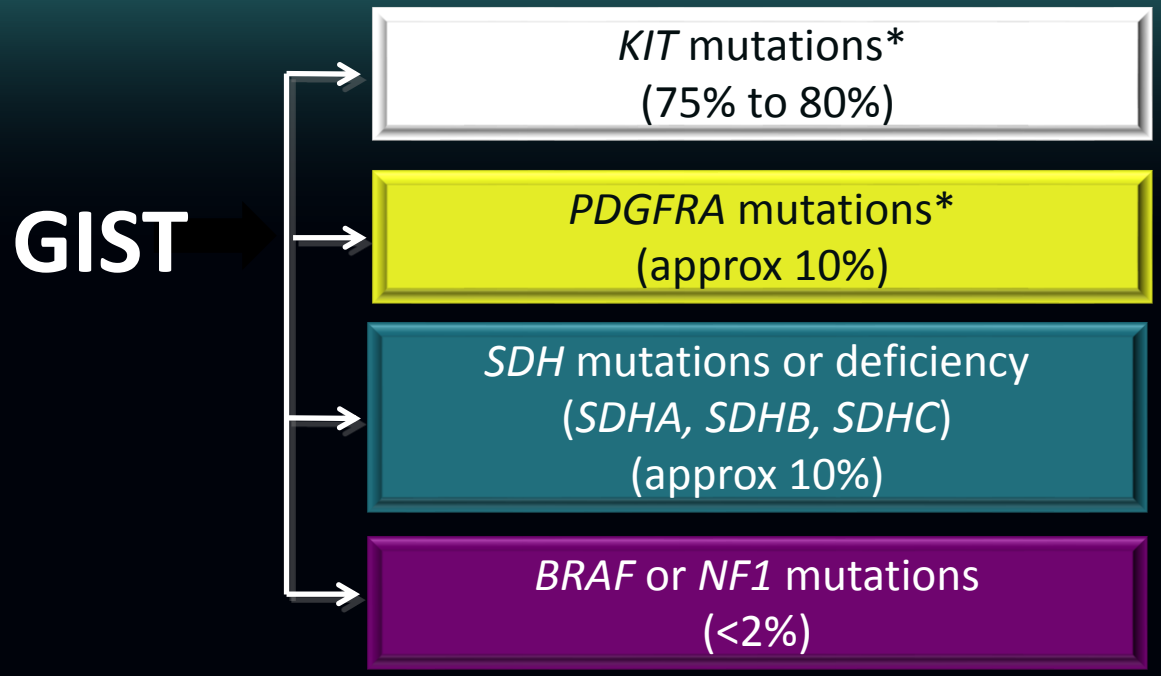
Describing and Dissecting Imatinib Failure



Different Genotypic and Structural Variants Fail ImatinibTherapy at Different Rates

Heinrich, Corless, Blanke, Joensuu, von Mehren, Demetri 2006

There are clinically important differences in GIST between patients



* SPECIFIC MUTATIONAL SUBTYPES can impact patient outcomes

KIT exon 11 mutations predict most benefit with imatinib

KIT exon 9 mutations may progress faster on standard dose imatinib

PDGFRA D842V mutation:
good risk in primary localized GIST , worse outcomes in metastatic GIST

Corless CL, et al. *Nat Rev Cancer*. 2011;11(12):865-878.

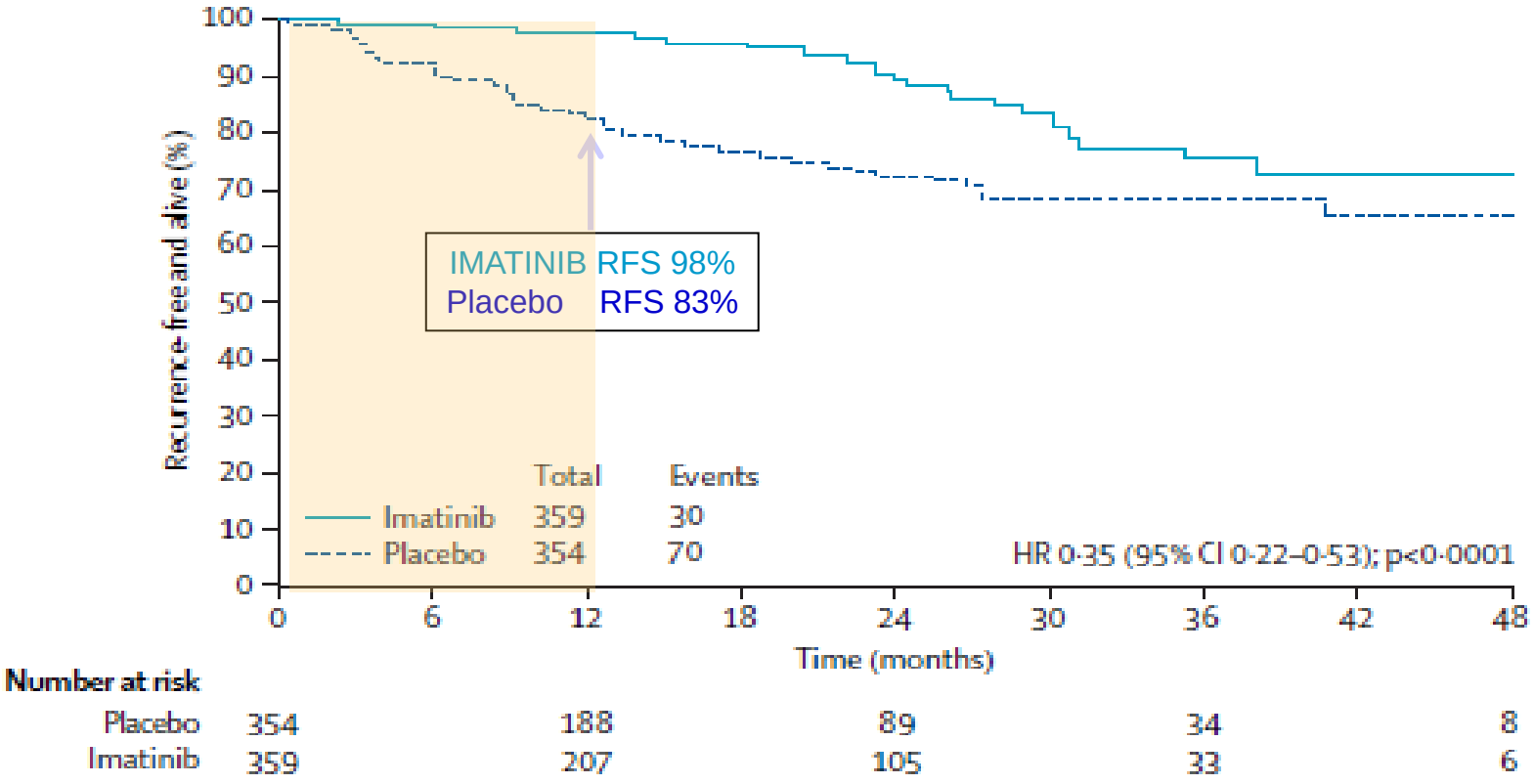
Variable Affecting RISK of Recurrence for Primary Localized GIST

Tumor Parameters		RISK OF RECURRENCE (%)			
Size	**Mitotic Count**	**Stomach**	**Duodenum**	**Jejunum / Ileum**	**Rectum**
≤ 2 cm	≤ 5 per 50 HPFs	0	0	0	0
> 2, ≤ 5 cm		2	8	4	9
> 5, ≤ 10 cm		4	} 34	24	} 57
> 10 cm		12		52	
≤ 2 cm	> 5 per 50 HPFs	0*	*	50*	54
> 2, ≤ 5 cm		16	50	73	52
> 5, ≤ 10 cm		55	} 86	85	} 71
> 10 cm		86		90	

* Too few cases

Adapted from Miettinen and Lasota. *Sem Diag Pathol.* 2006; 23(2):70-83.

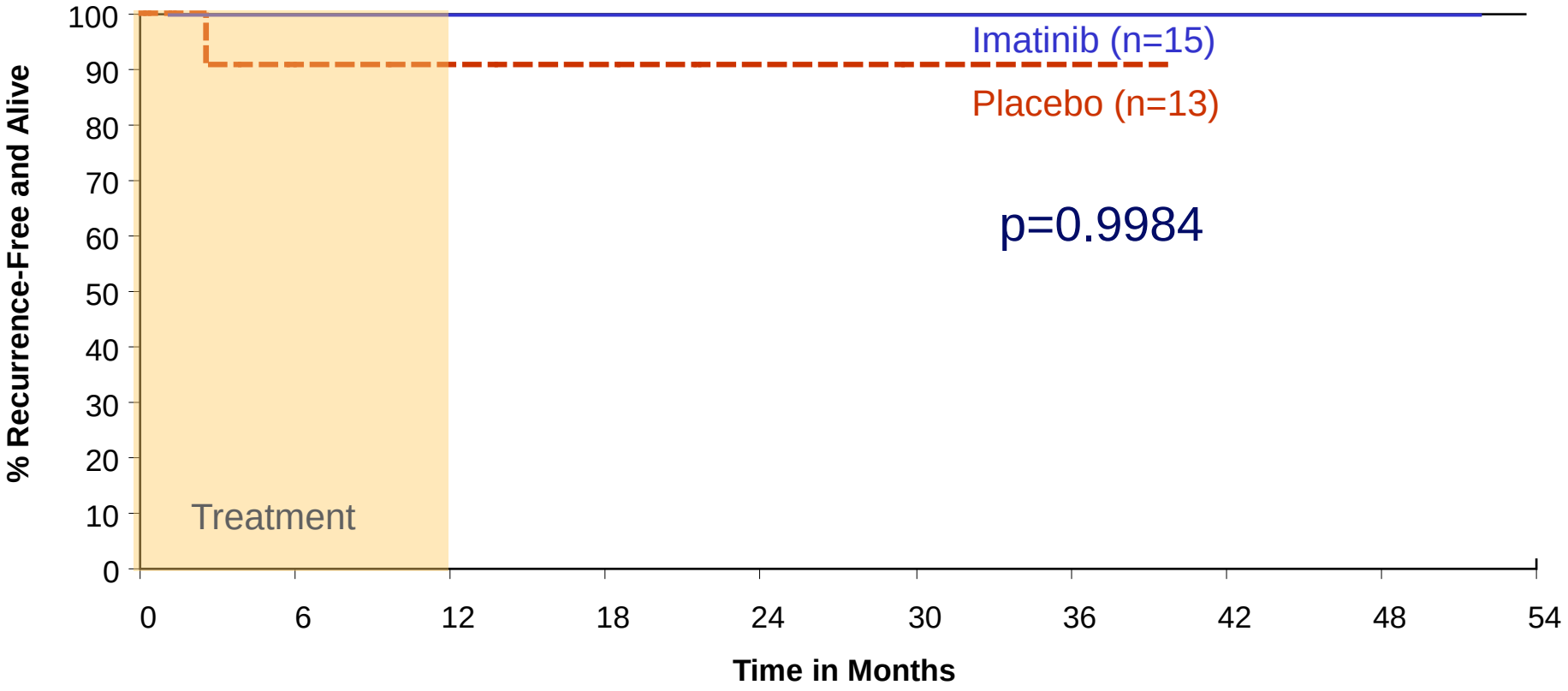
Adjuvant Imatinib Improves Recurrence-Free Survival in Primary GIST: ACOSOG Z9001



DeMatteo et al. *Lancet.* 2009; 373(9669):1097-104.

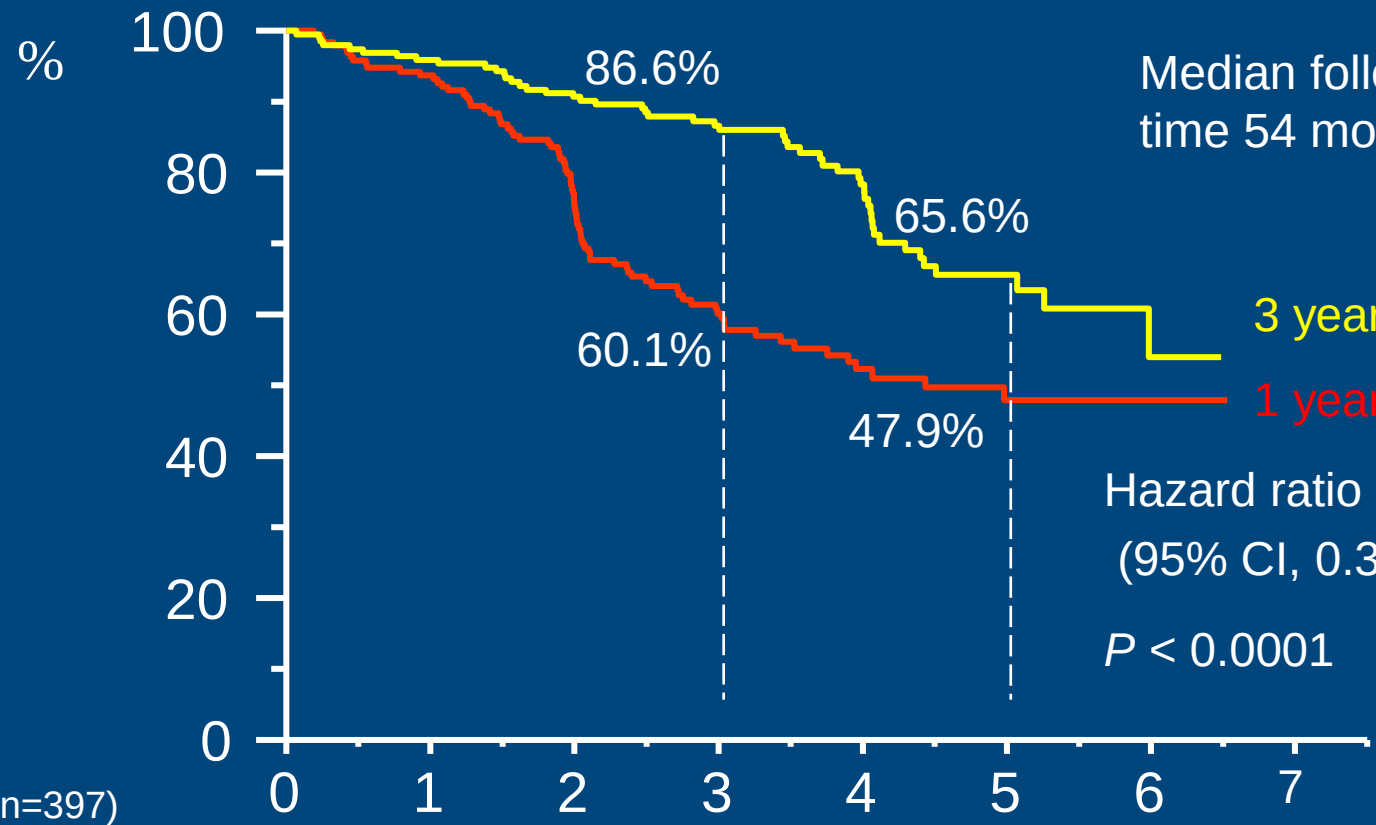
Not all GIST patients benefit from adjuvant imatinib

NO IMATINIB BENEFIT for GIST with PDGFRA D842V Mutation



Corless et al. ASCO 2010 and JCO online March 17, 2014; DOI:10.1200/JCO.2013.51.2046.

Improved Recurrence-Free Survival with 3 yrs vs. 1 yr of Adjuvant Imatinib in GIST



Median follow-up time 54 months

Hazard ratio 0.46
(95% CI, 0.32-0.65)

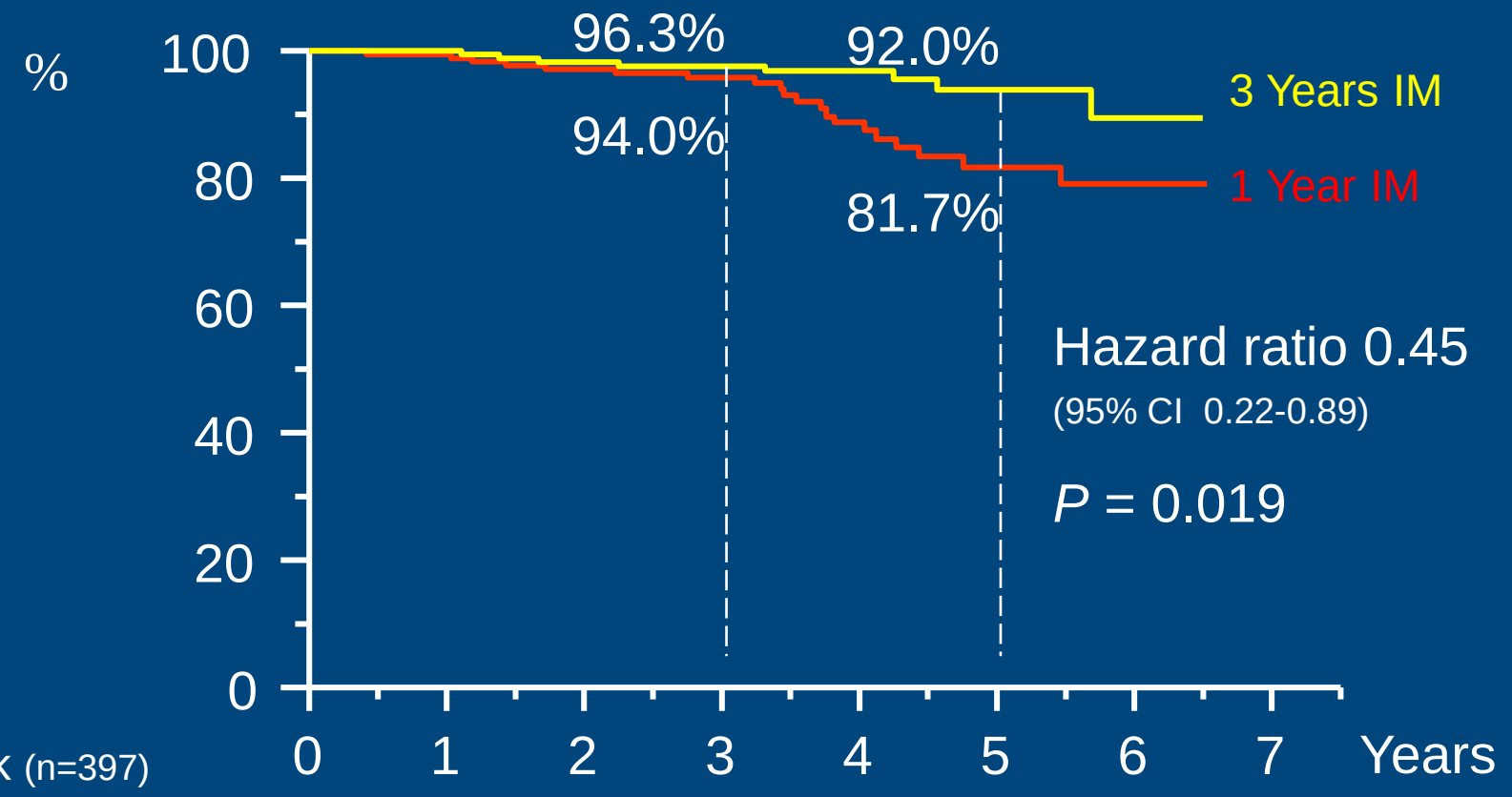
P < 0.0001

No. at risk (n=397)								
36 Months of imatinib	198	184	173	133	82	39	8	0
12 Months of imatinib	199	177	137	88	49	27	10	0

Joensuu H, et al

JAMA. 2012;307(12):1265-1272

Improved Overall Survival with 3 yrs vs. 1 yr of Adjuvant Imatinib in GIST



No. at risk (n=397)								
36 Months of imatinib	198	192	184	152	100	56	13	0
12 Months of imatinib	199	188	176	140	87	46	20	0

Joensuu H, et al

JAMA. 2012;307(12):1265-1272

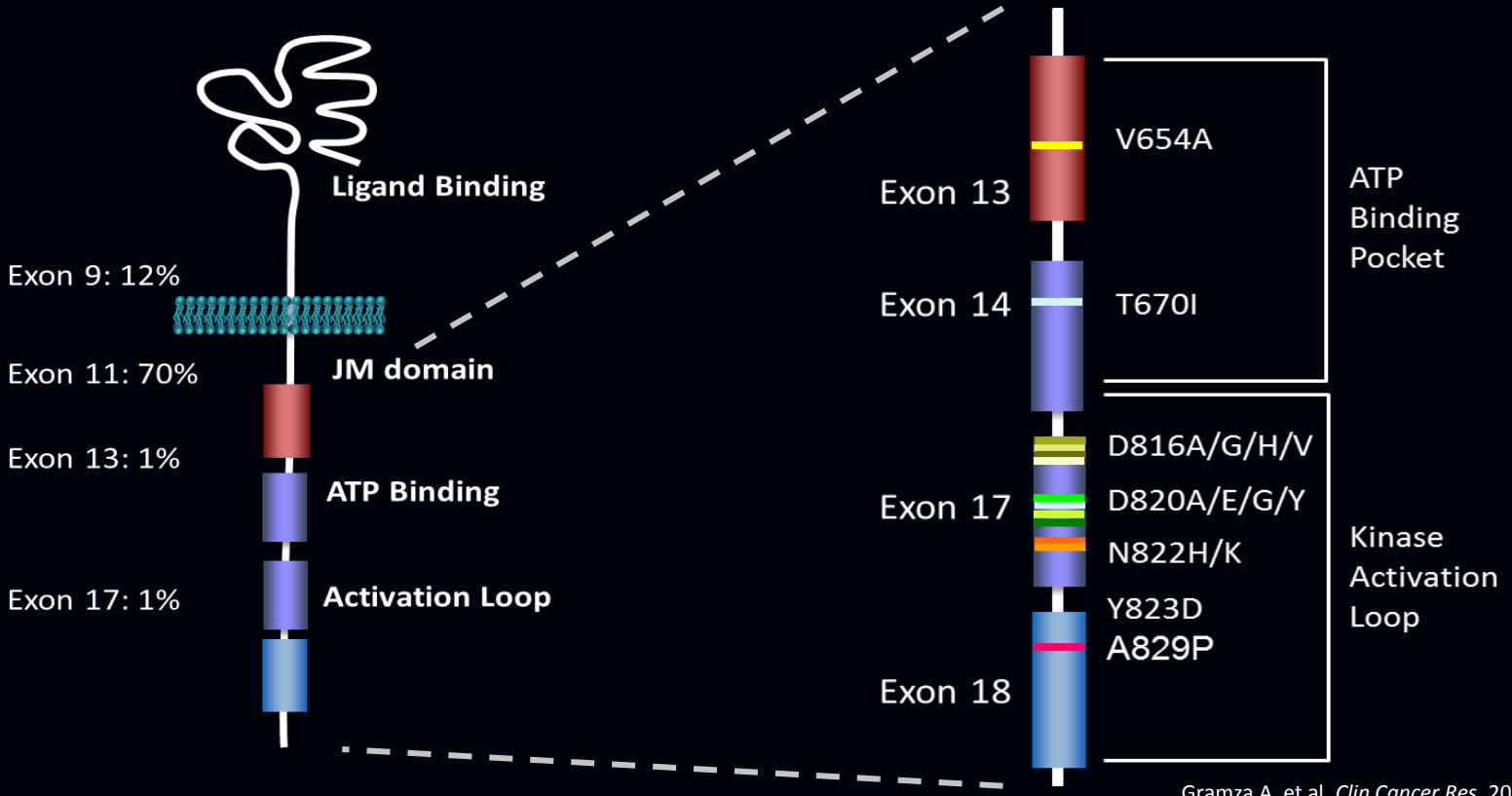
Resistance to Kinase Inhibition in *KIT*-Mutant GIST Is Generally Caused by Secondary *KIT* Mutations

PRIMARY *KIT* Activating Mutations

GIST is addicted to signals from the primary mutant kinase

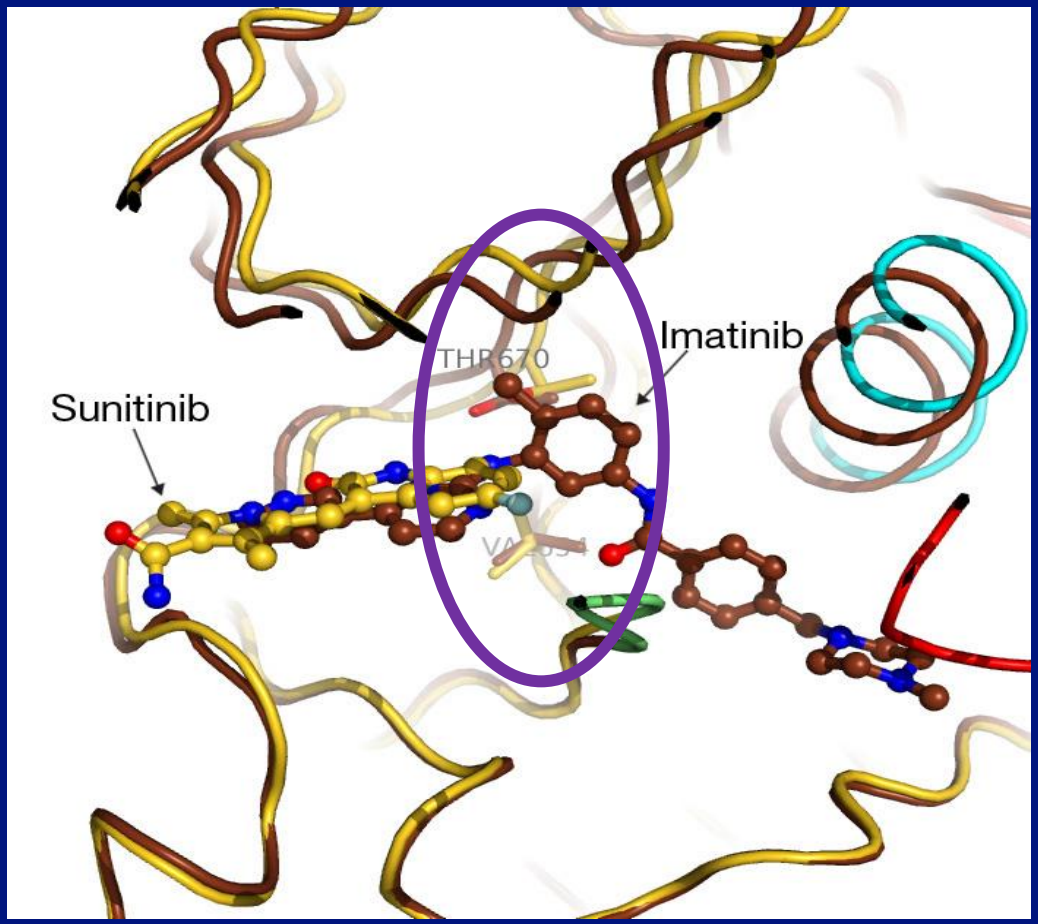
KIT Resistance Mutations

Clonal expansion of multiple secondary mutations in TKI-resistant GIST



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

Sunitinib overcomes resistance to imatinib by fitting into the mutated KIT binding pocket



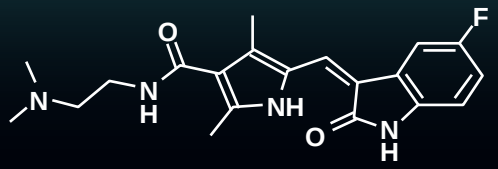
Courtesy of
K Gajiwala,
Pfizer Oncology

[1]Gajiwala et al. *Proc Natl Acad Sci USA* 2009;106:1542

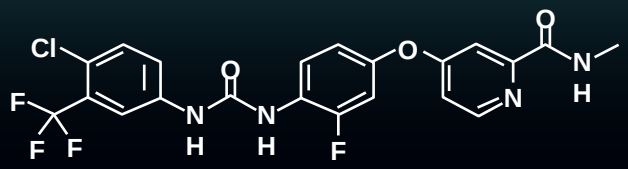
[2]Mol et al. *J Biol Chem* 2004;279:31655

There are now 3 different Tyrosine Kinase Inhibitors (TKIs) approved for therapy of metastatic GIST

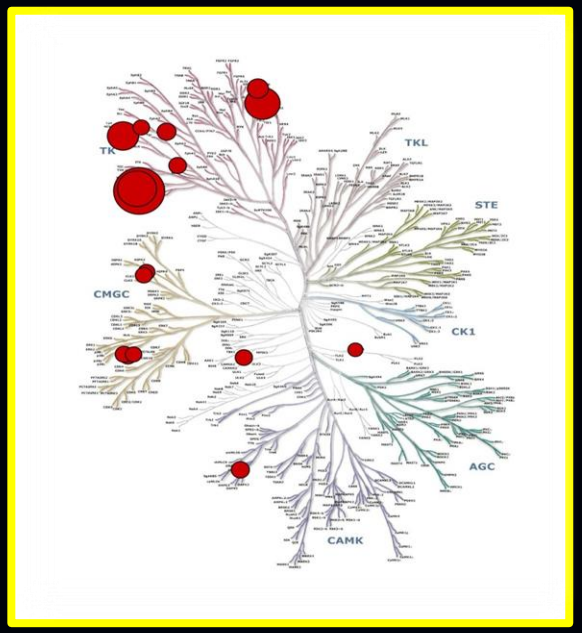
Imatinib

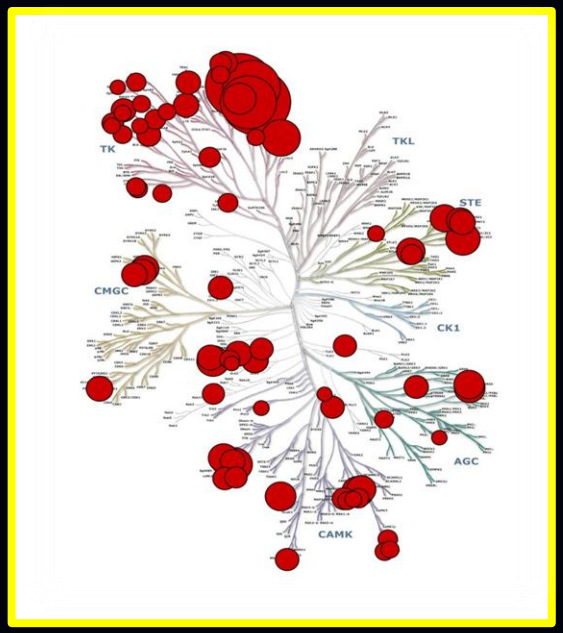


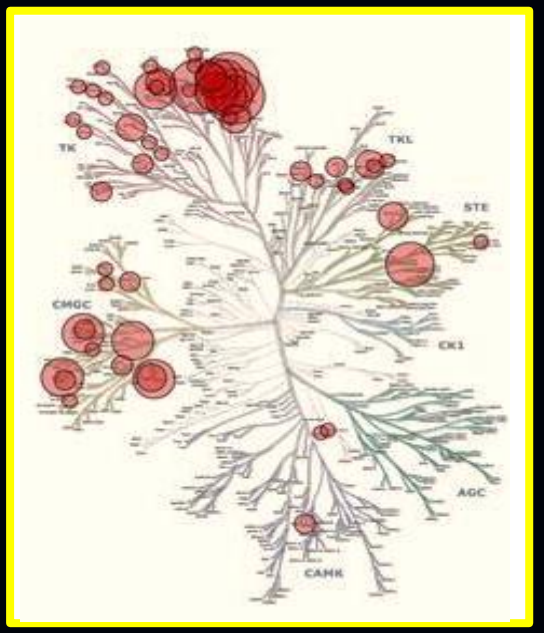
Sunitinib



Regorafenib

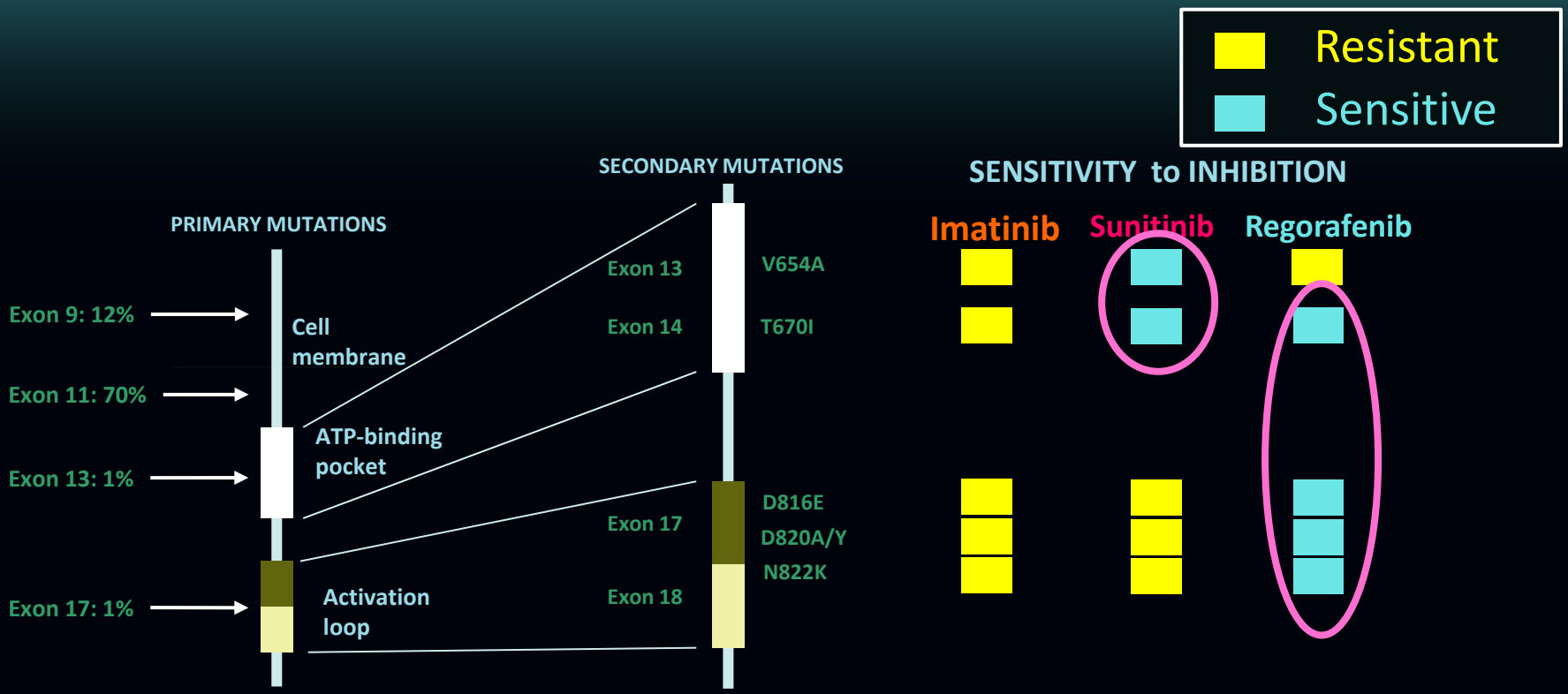






Wilhelm SM, et al. *Int J Cancer.* 2011;129:245-255; Murphy EA, et al. *PNAS.* 2010;107:4299-4304; Fabian M, et al. *Nat Biotechnol*. 2005;23:329-336; Sutent® (sunitinib malate) [prescribing information] New York, NY: Pfizer, Inc; 2012.

Overcoming dual resistance to imatinib and sunitinib with regorafenib



Regorafenib has activity in GIST cells with KIT *primary* exon 11 mutations and secondary KIT exon 17 imatinib-resistant mutations, but is less active against KIT exon 13 (V654A) mutations compared to sunitinib

Serrano-García C, et al. ASCO 2013. Abstract 10510.

Why are GIST patients not cured with TKI Therapy?

- We do not really know…
  - D842V *PDGFRA*-specific and Exon 17 *KIT*-specific inhibitors
  - BRAF-specific drugs
  - Metabolic targeting of SDH-mutant GIST
- Insufficient kinase inhibition?
  - BRAF mutants need >95% inhibition for activity
- Other GIST cell survival pathways?

Other New Options for Metastatic GIST

- Mutation-specific therapies
  - D842V *PDGFRA*-specific and Exon 17 *KIT*-specific inhibitors
  - BRAF-specific drugs
  - Metabolic targeting of SDH-mutant GIST
- Anti-KIT targeting monoclonal antibodies
- New combinations with TKIs
  - Inhibitors of MEK, FGFR
  - Immuno-oncology approaches

- Consider referral to clinical trials at every step in GIST management

OTHER LEARNINGS

GIST Management has been a model for translational and clinical oncology multidisciplinary research

- The global sarcoma community has worked together effectively to advance research and improve patient outcomes
- Collaborations with regulatory agencies, national groups, patient advocacy groups and biopharma have accelerated progress
- Costs remain a concern for sustainability of cancer care in the era of combinations
- Rapid and focused trials have been the model for efficient development of new therapies
- Thanks to everyone who has been a part of this over nearly two decades!