Understanding and Tracking Resistance to Mechanism-Targeted Therapies in GIST:

A look to the future

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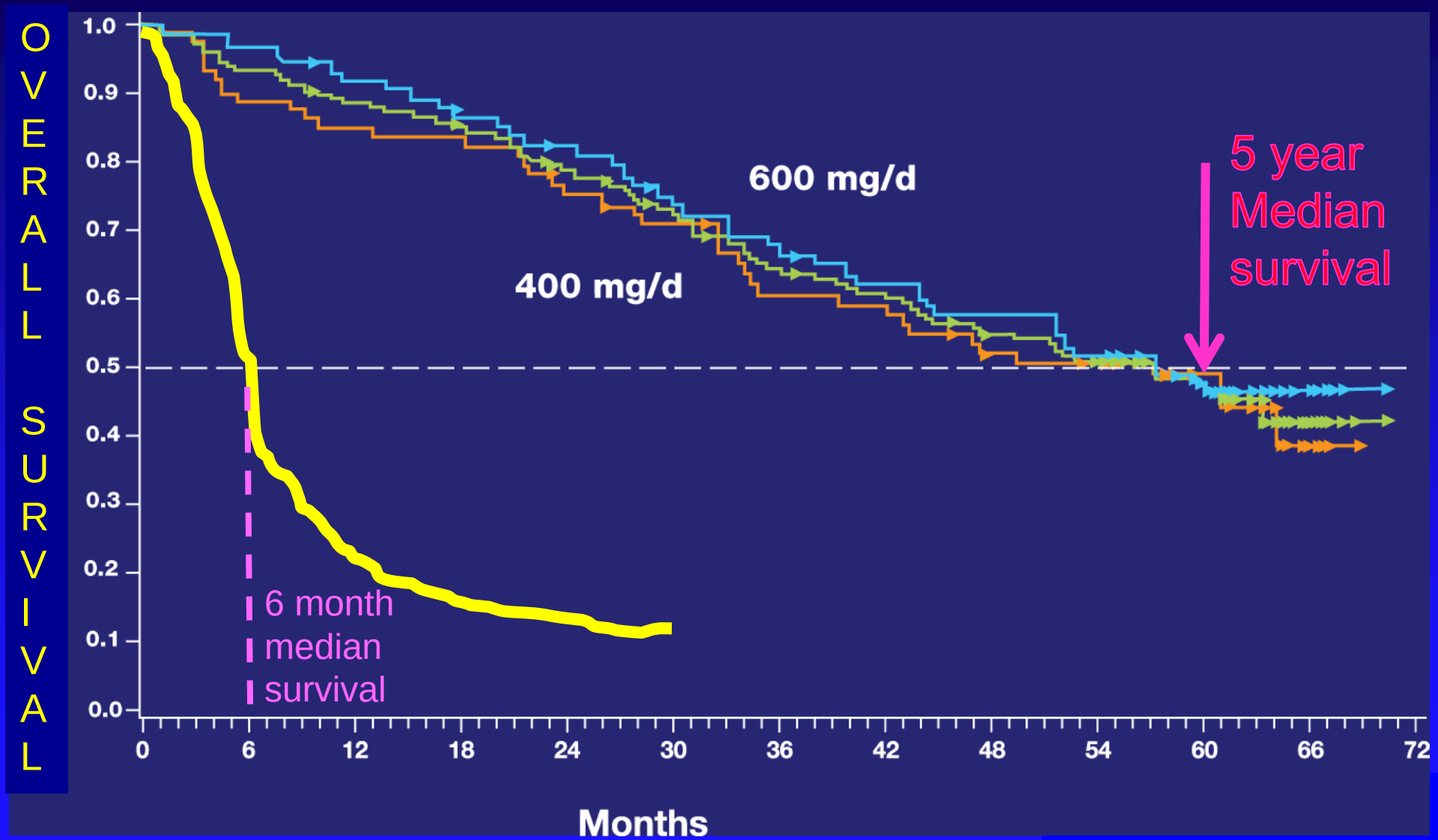
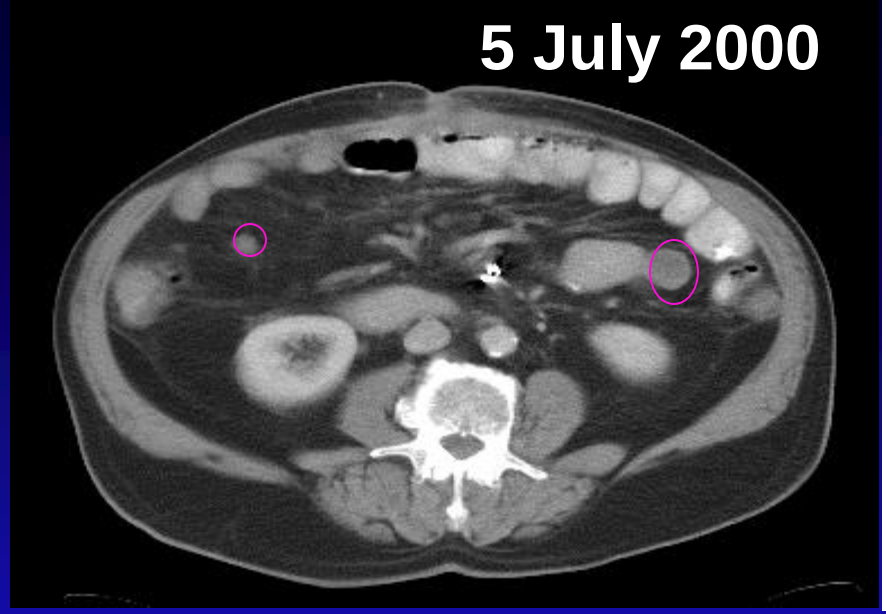
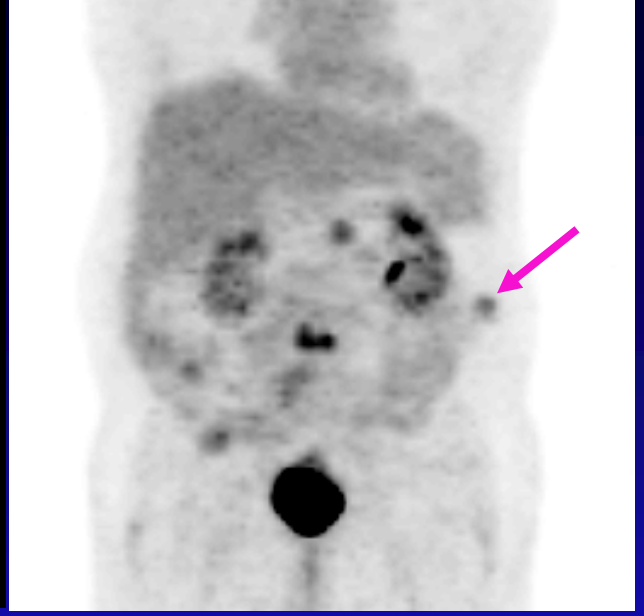
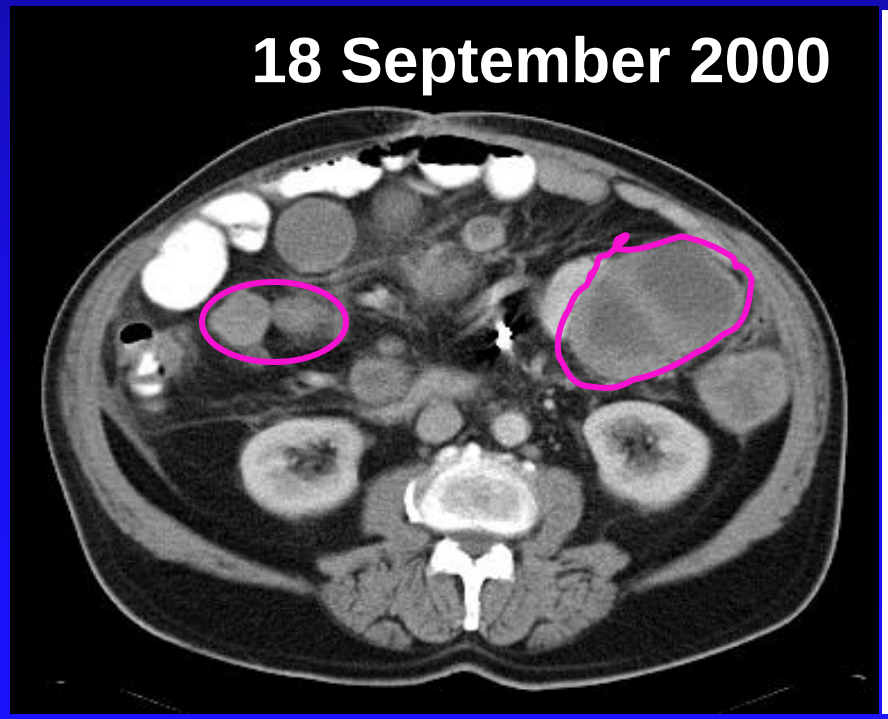
10-fold improvement in overall survival for patients with metastatic GIST treated with TKI therapies

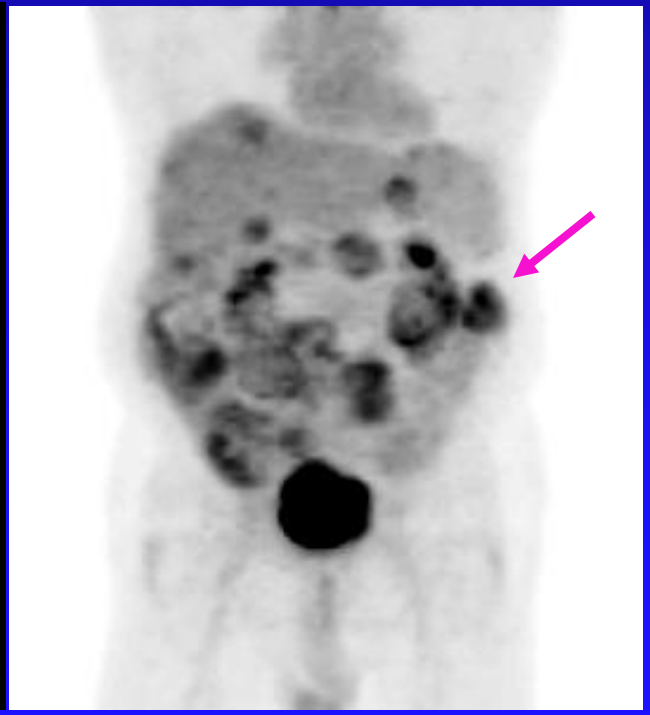






Primary Resistance to Imatinib in GIST





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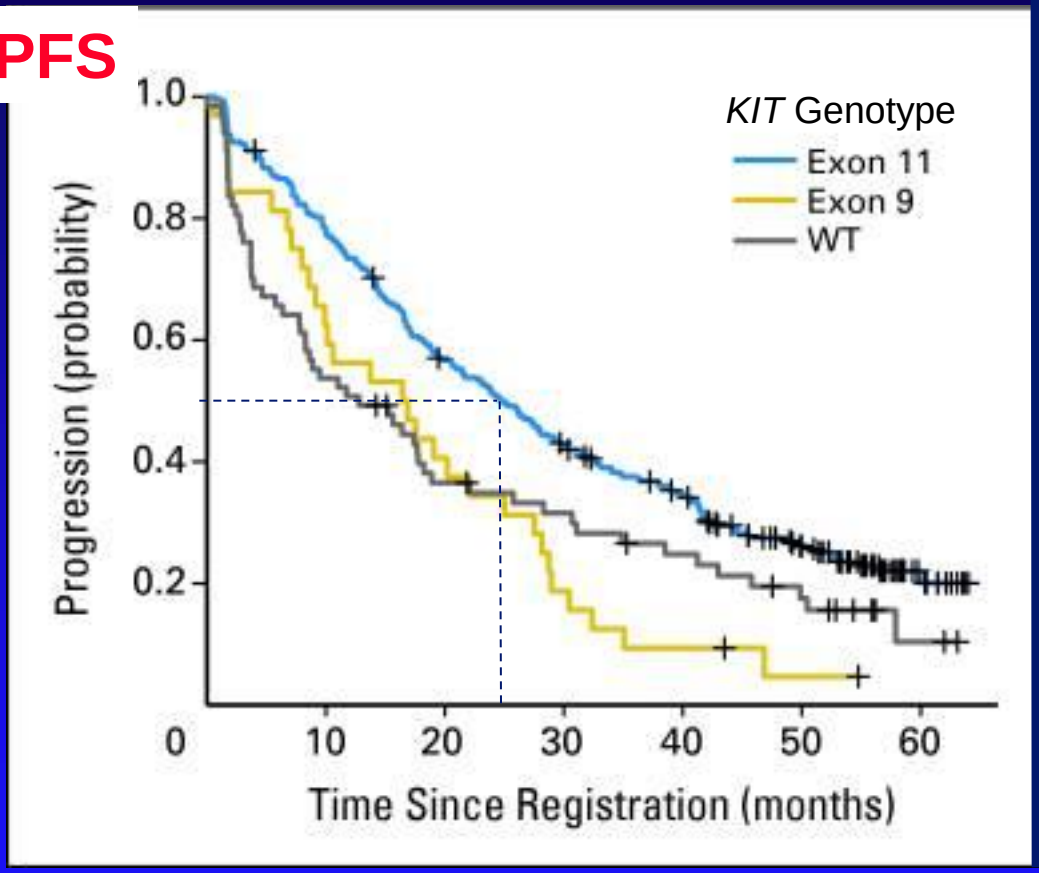
GIST is one “cancer diagnosis” with several distinct molecular subtypes occuring with different frequencies

GIST GENOTYPE	Metastatic GIST Frequency	Primary Localized GIST Frequency
KIT Exon 11 mutation	67%	60%
KIT Exon 9 mutation	10%	7%
Wild-type *KIT* + *PDGFRA* with *SDH* mutation	14%	12%
PDGFRA mutant	0%	20%
PDGFRA Exon 18 mutation	6%	N/A
Rare mutants at first presentation – *KIT* mutant: Exons 13 & 17 – *PDGFRA* mutant : Exons 12 & 14 – *BRAF* mutant V600E	 2% 1% <1%	 2% 1% <1%

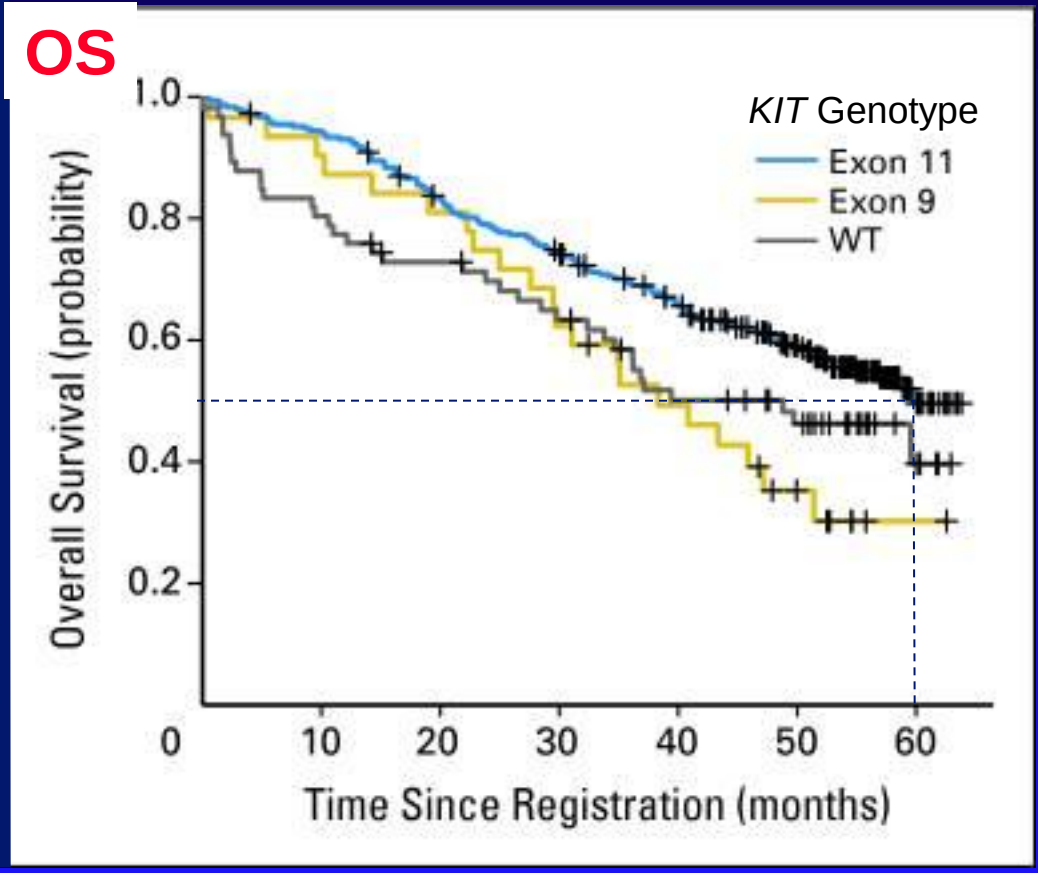
SDH, succinate dehydrogenase.

Patients Identify with Molecular Medicine

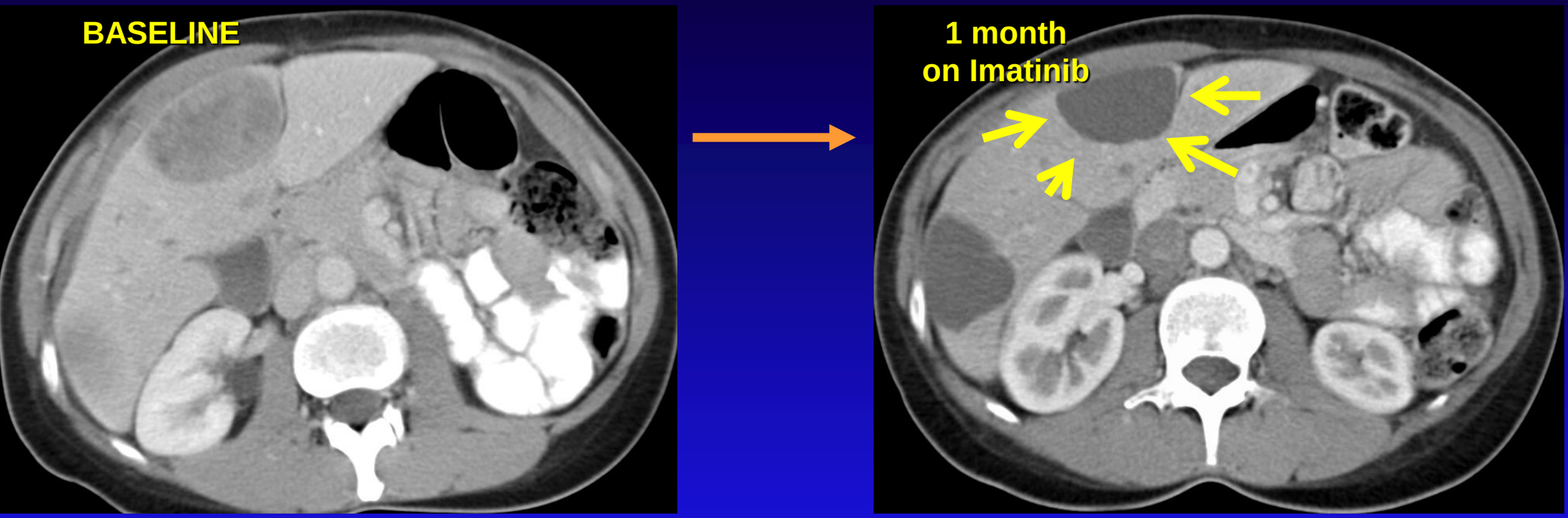
PFS



OS



Heinrich *et al.* S0033 trial; J Clin Oncol 2008



- Why do we not obtain more complete responses with TKI therapy in GIST?
- What preserves the shape of the residual hypocellular tumor mass?
  - Tumor cell heterogeneity and stromal interactions?
  - Functional resistance to TKI therapy

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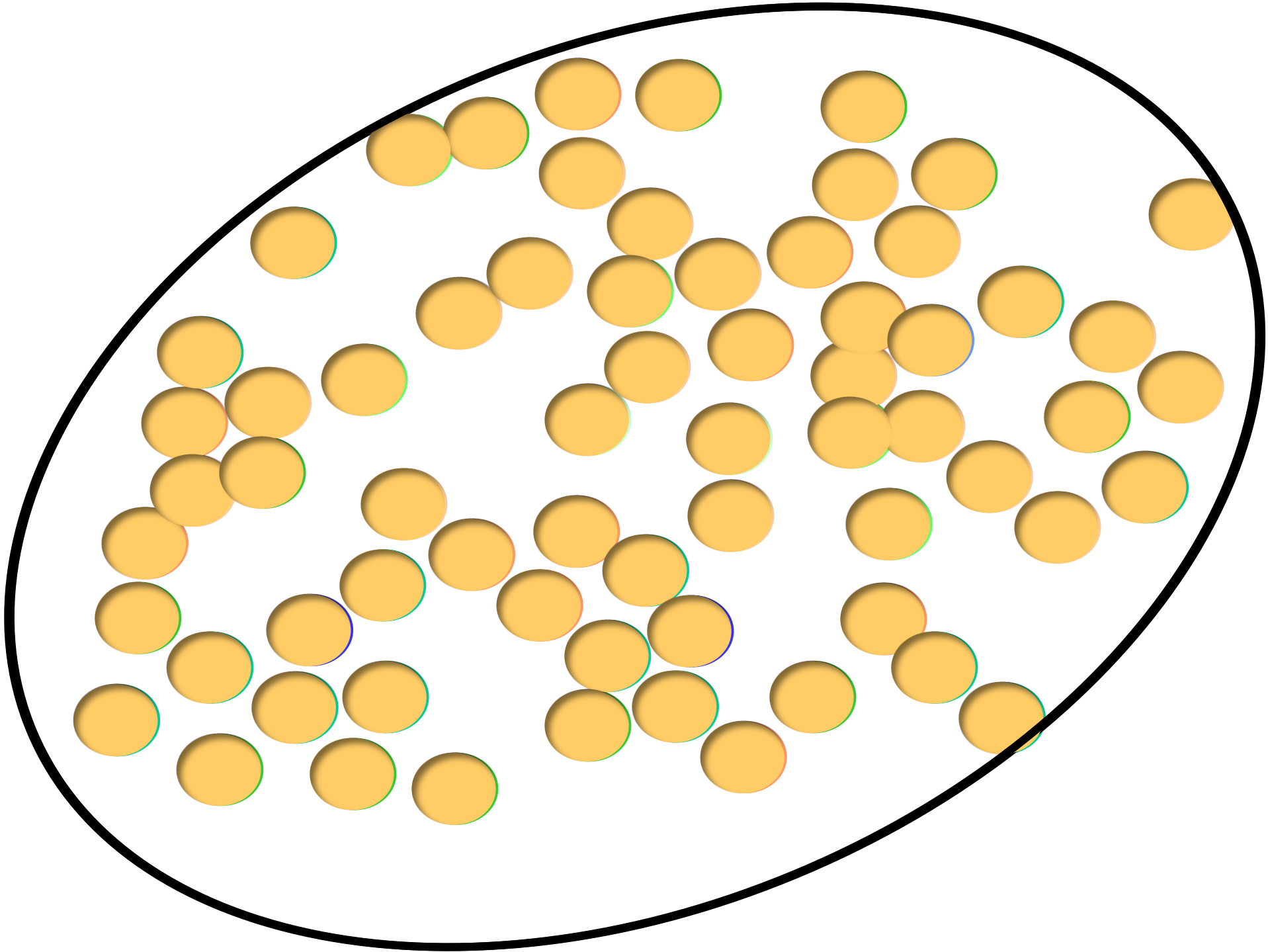
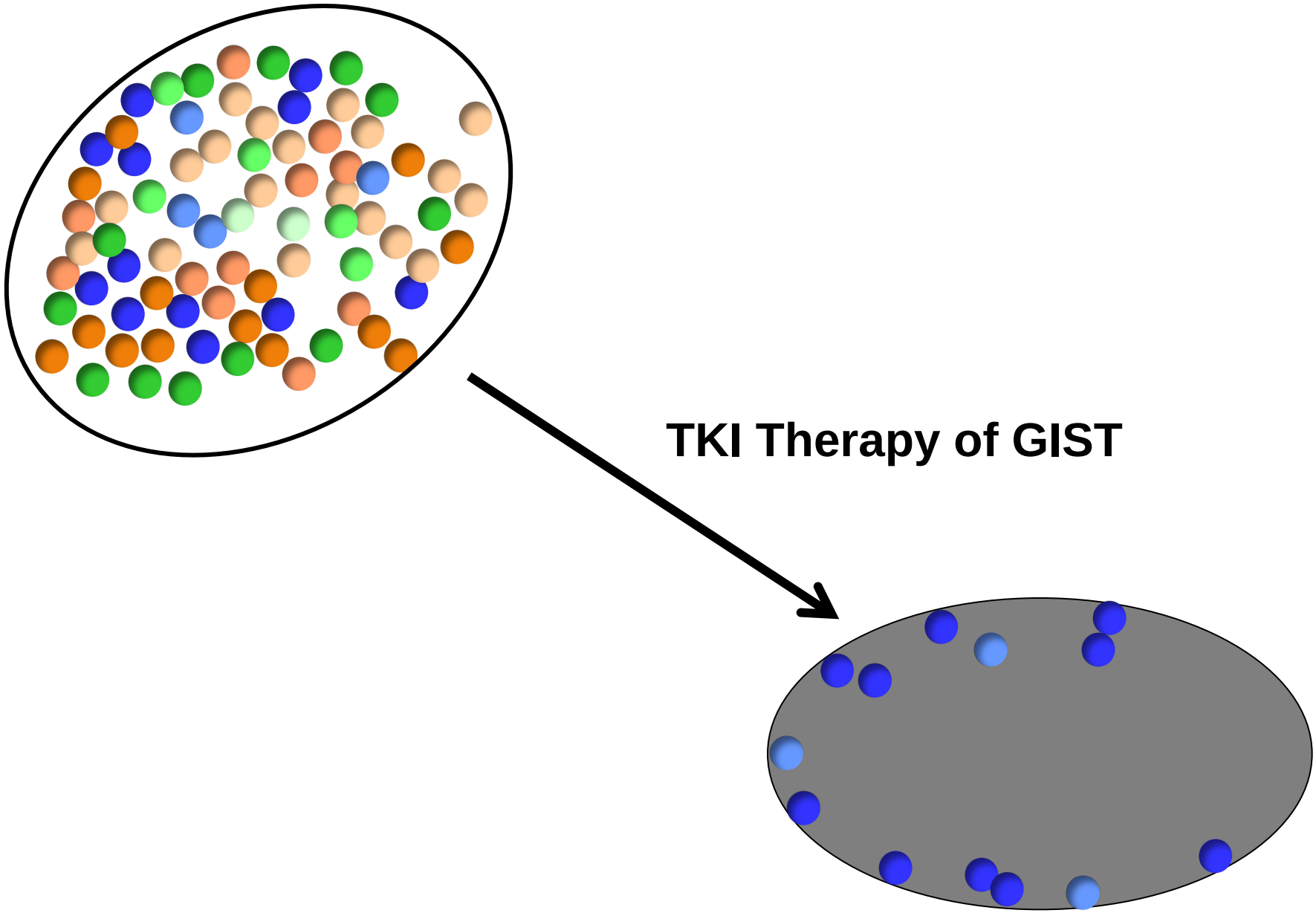
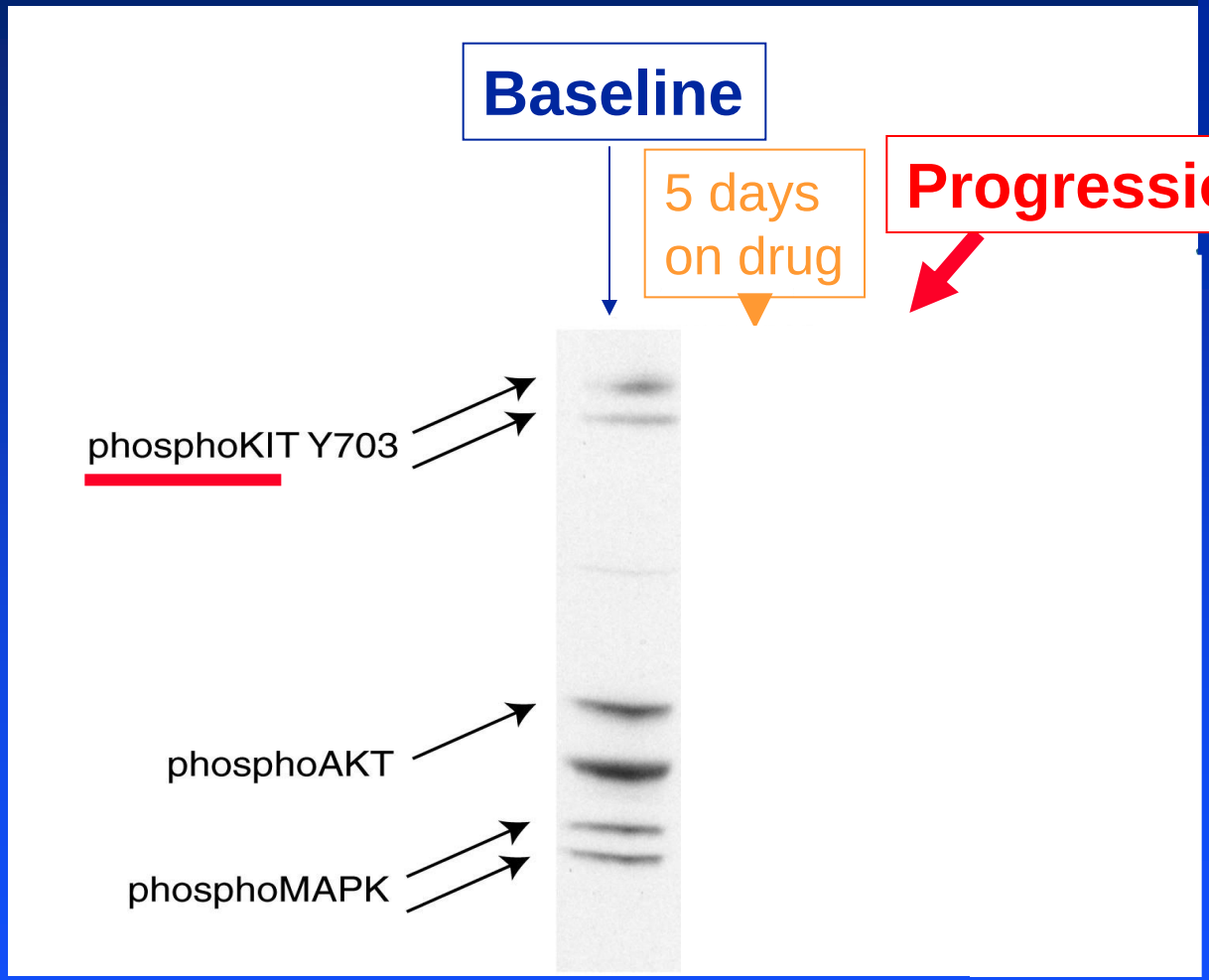
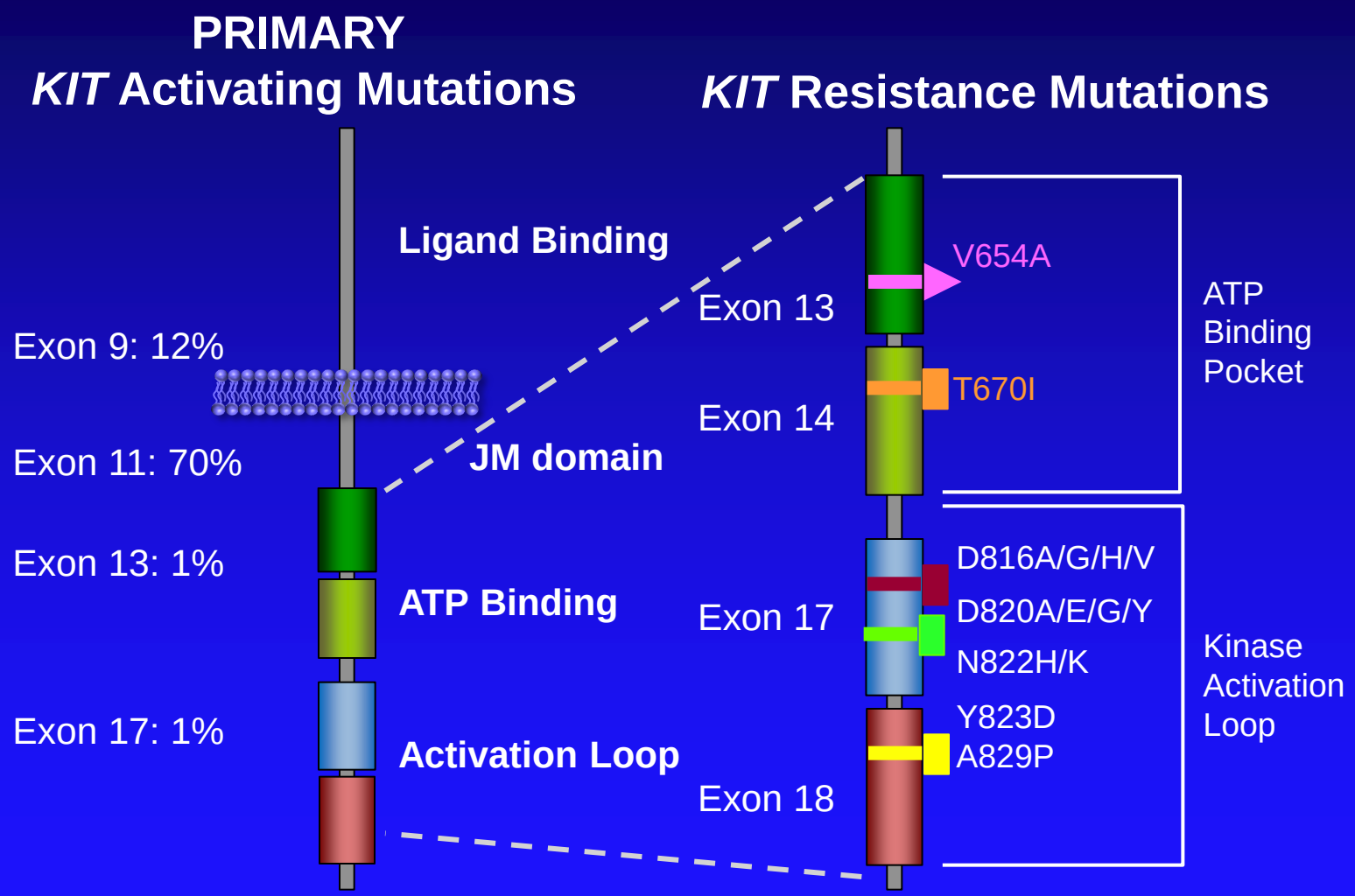



TKI Therapy of GIST

KIT Activation Is Rapidly Inhibited in GIST Patients Receiving Imatinib Treatment – but REACTIVATES with Progression



TKI Resistance in *KIT*-mutant GIST is generally caused by secondary *KIT* mutations



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

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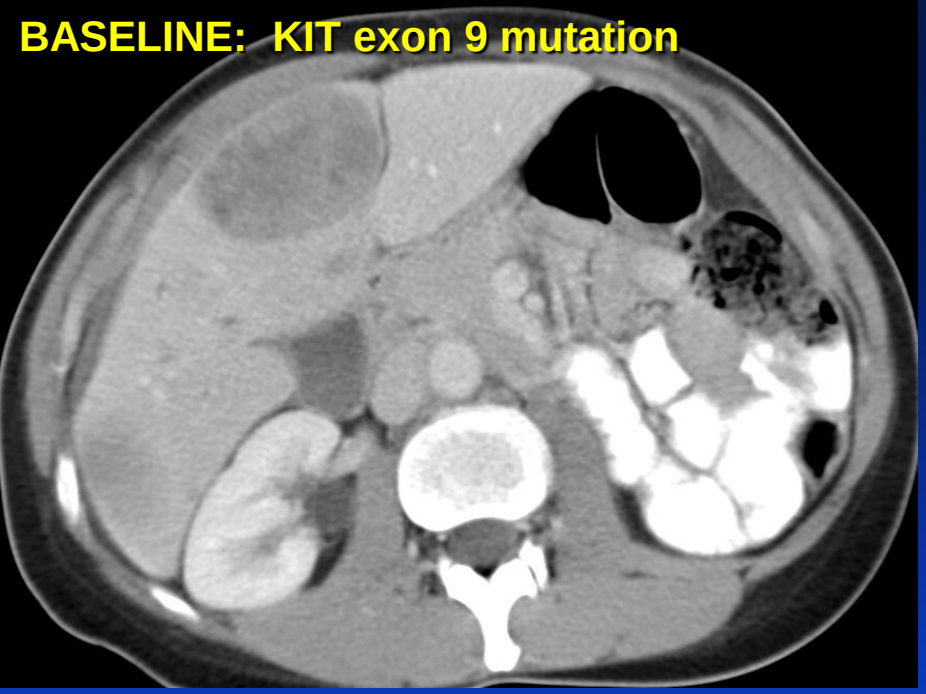
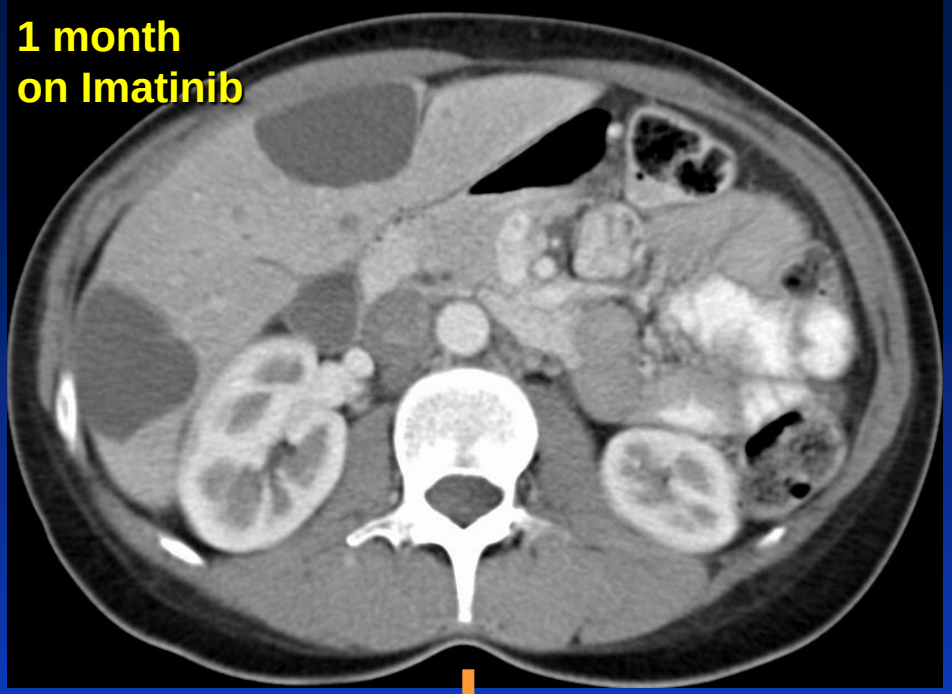
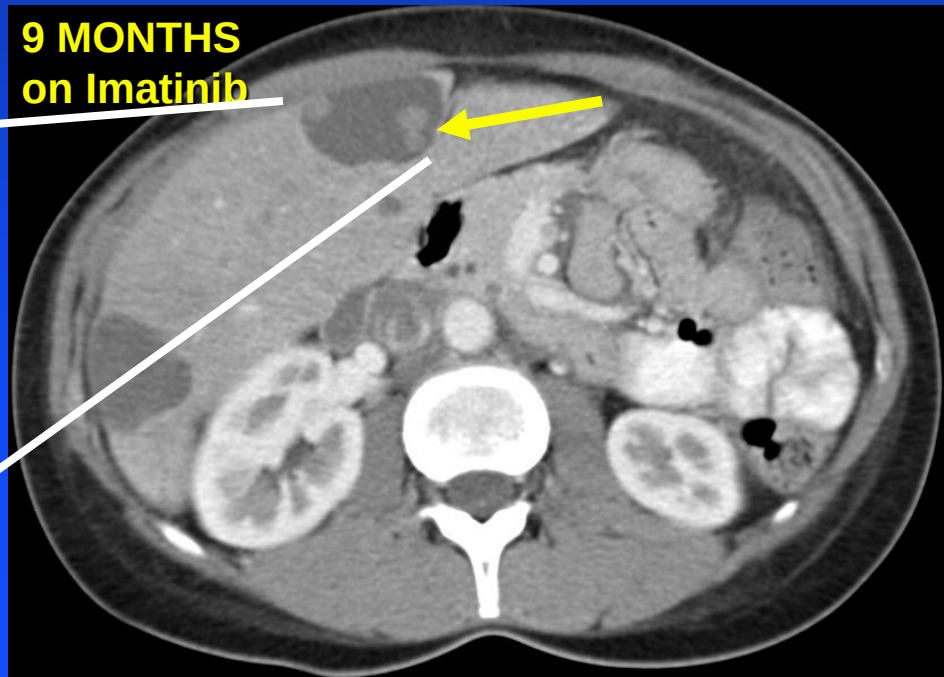




Response in GIST followed by polyclonal evolution

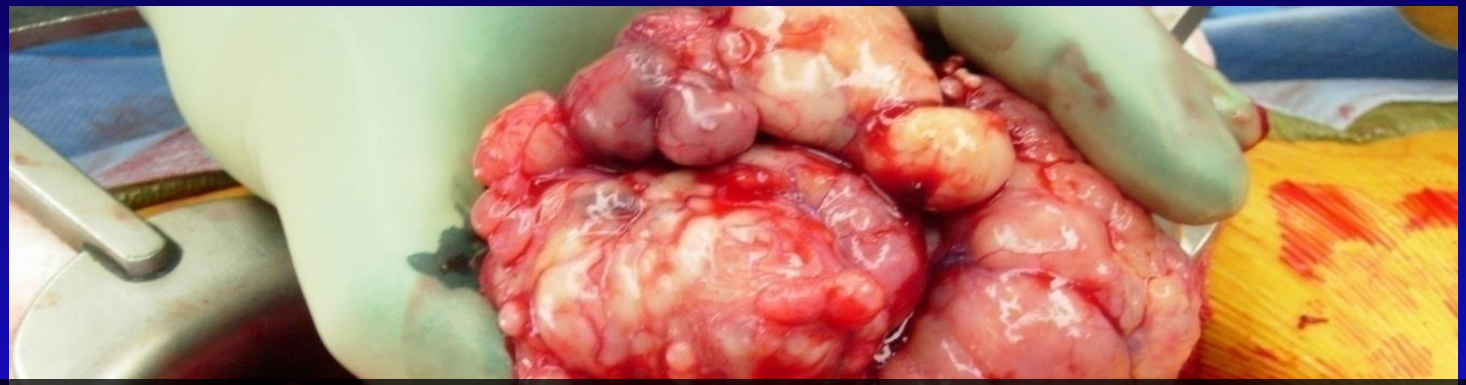


Exon 9 + Resistance Mutation #1

Exon9+Resist Mutation #2

Exon 9+Resist Mutation #3

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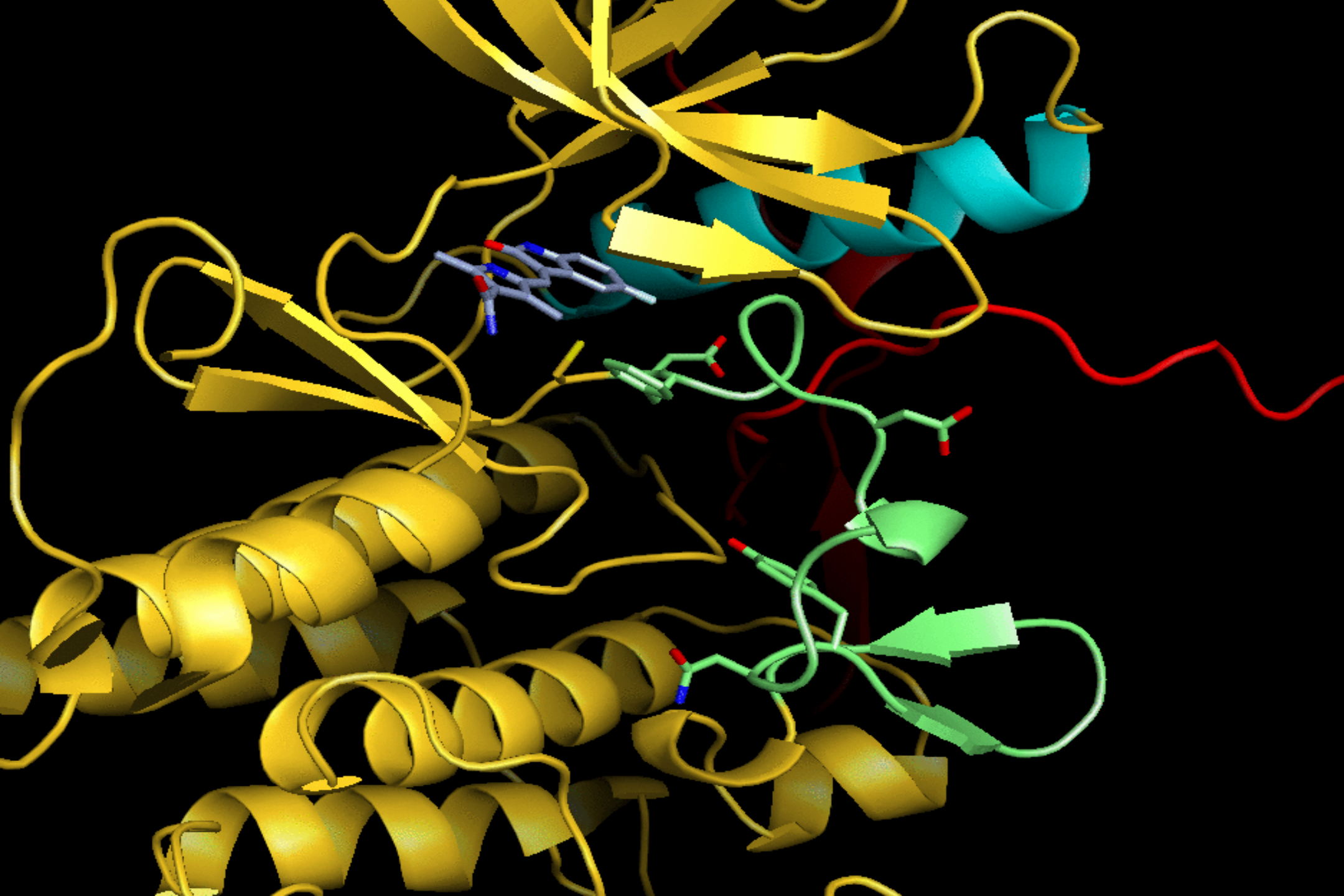
The Emergence of GIST Clones Resistant to TKIs Complicates "Personalized Medicine"

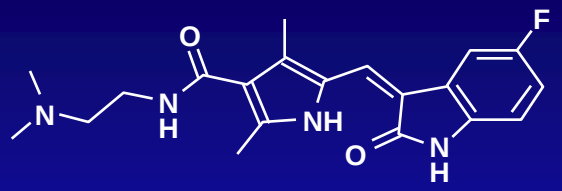
Limitations of Tumor Biopsies – and a Possible New Solution

- Tumor (“tissue”) biopsies may be problematic, because tumors are heterogeneous and only certain tumors (or even only certain parts of any given tumor) are sampled
- Tumor biopsies are invasive in patients with most solid tumors which are deep in internal organs
- Tumor cells are constantly dying and “leaking” DNA into the bloodstream
- A sophisticated assay of blood may be able to document a comprehensive picture of all the mutations in any given patient
- The “Liquid Biopsies” provide a potential alternative that may circumvent the limitations and risks of traditional tumor biopsies

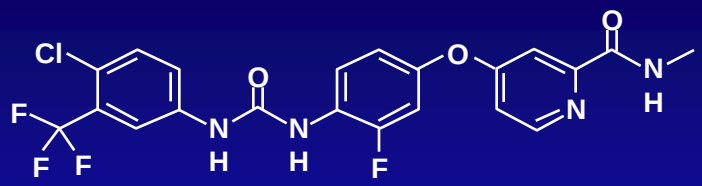


KIT inhibitors

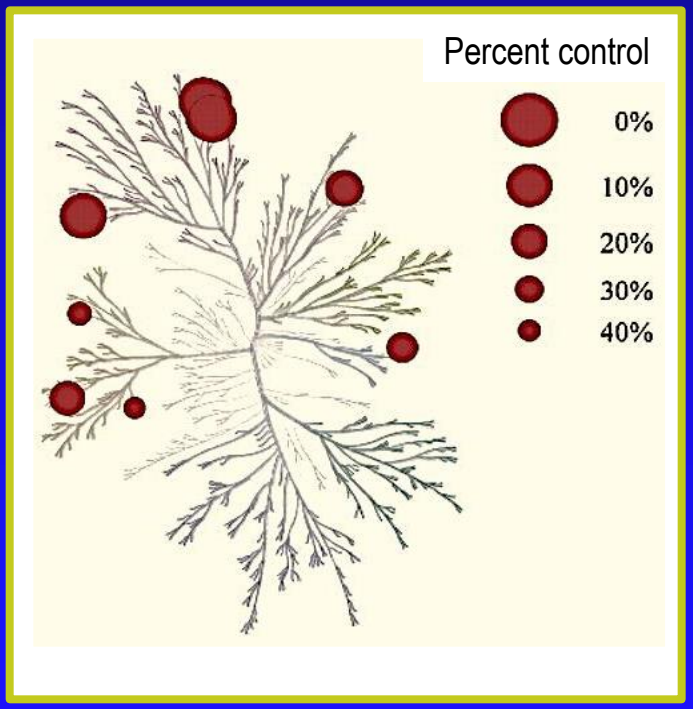
Imatinib

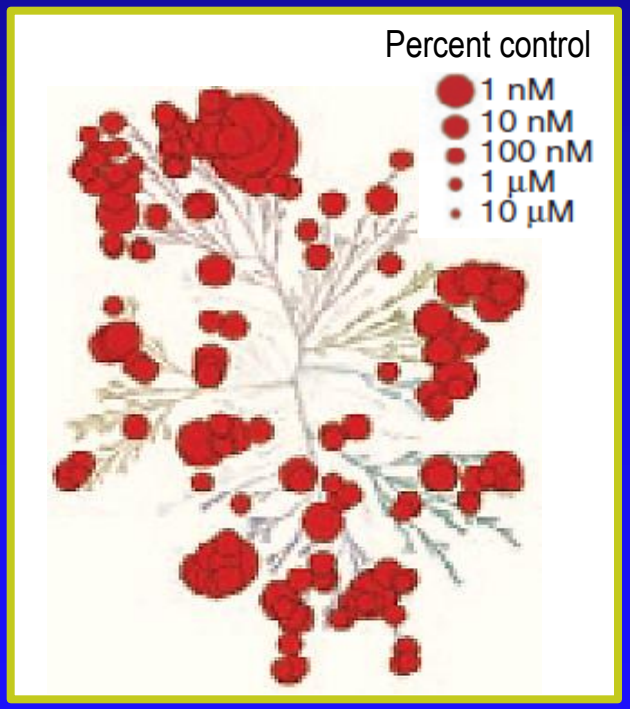


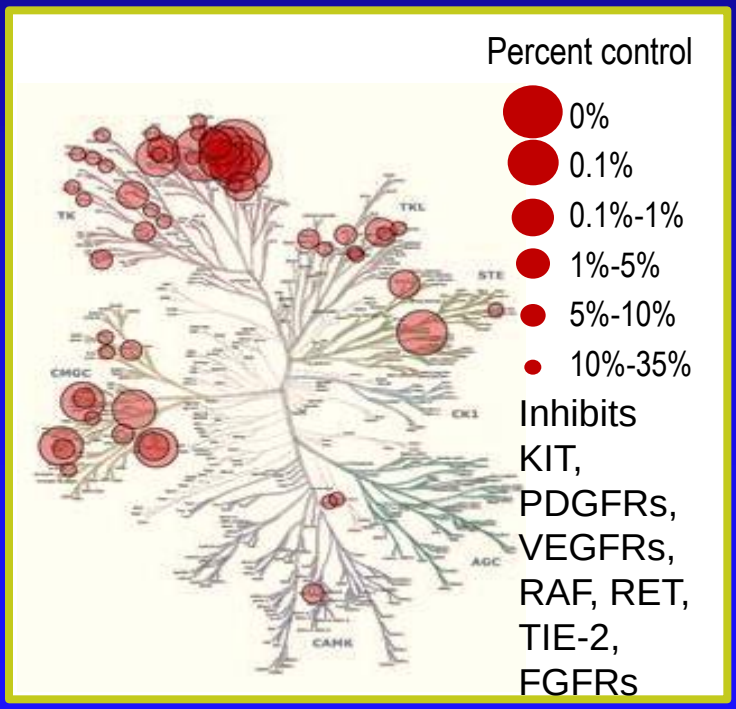
Sunitinib



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;

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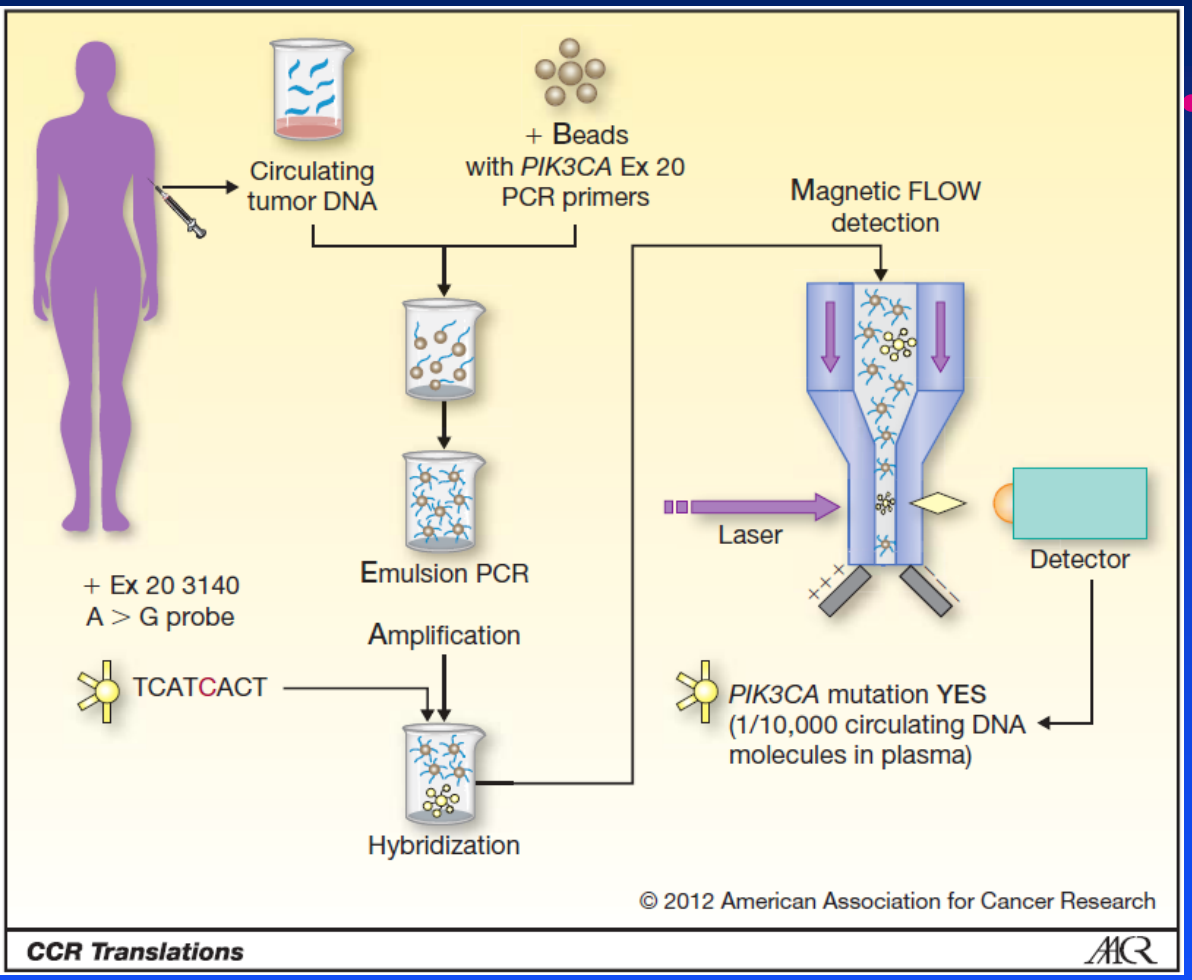
Mutational Analysis of Circulating DNA in Plasma via BEAMing Technology

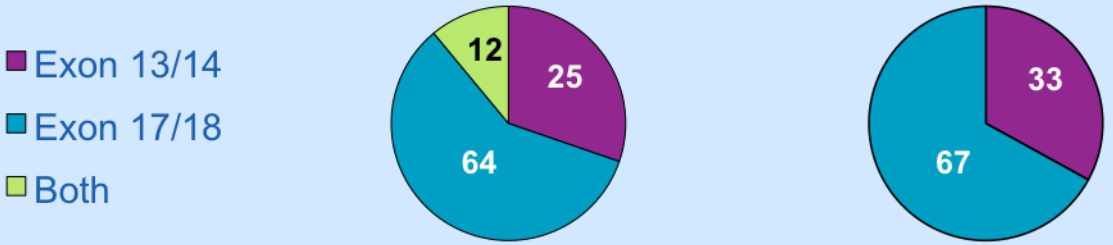


Richardson and Iglehart, Clinical Cancer Research, May 2012

- **B**eads, **E**mulsions, **A**mplification, **M**agnetics (done with *Inostics*):
  - *laboratory steps: pre-amplification, emulsion PCR, hybridization, flow cytometry*
  - *detection of tumor-associated mutations using circulating free DNA from **plasma***
  - *Exquisitely sensitive detection:*
    1 mutant allele in 10,000 normal alleles
  - *BEAMing can be used for multiple genes:*
    - *cancers: colorectal, breast, lung, GIST*
    - *genes: KRAS, BRAF, EGFR, PIK3CA*
    - *over 2,000 samples analyzed*
  - *Ideal concept to detect emergence of gene mutations which can make tumors resistant to targeted therapies*

Mutational analysis of DNA from plasma (BEAMing) and tumor tissue (sequencing)

	Plasma (BEAMing)	Tumor tissue
Patients with data, n (%)	163 (82)	102 (51)
Any *KIT* mutation (primary or secondary) detected, % of samples	58	66
Primary *KIT* mutations, % of samples		
Exon 9	15	18
Exon 11	12*	43
Secondary *KIT* mutations, % of samples	47	12
Other mutations detected, % of samples		
PDGFRA	1	3
KRAS	(1 of 2 samples)	2
BRAF	0	0



* BEAMing assays were not designed to detect most common primary *KIT* exon 11 deletion mutations

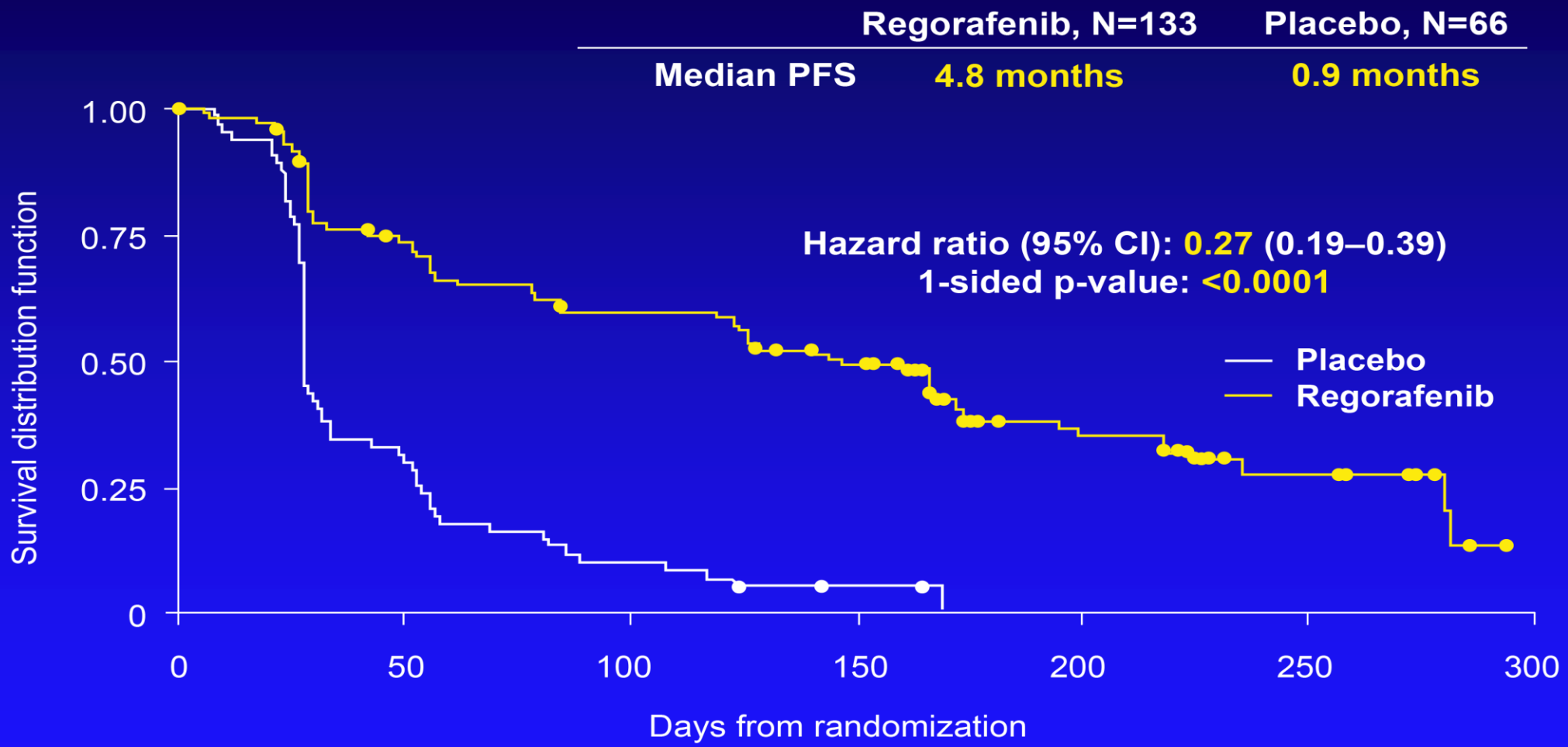
High Concordance of Mutation Detection in patient-matched plasma and tissue samples

- 100% concordance for primary *KIT* exon 9 mutations
  - 18 patients with subject-matched data*
- 79% concordance for primary *KIT* exon 11 mutations
  - 11 of 14 patients
- 91% overall concordance for primary *KIT* exons 9 and 11
  - 29 of 32 patients

Plasma or Tumor detection of *KIT* exon 9 or other mutations		
Patient no.	*KIT* mutation detected	
	Plasma BEAMing	*Tissue sequencing*
1	Exon 9 INS	Exon 9 INS
2	Exon 9 INS	Exon 9 INS
3	Exon 9 INS + exon 17 MUT	Exon 9 INS + exon 17 MUT
4	Exon 9 INS	Exon 9 INS
5	Exon 9 INS + exon 17 MUT	(external: exon 9 MUT)
6	Exon 9 INS + exon 17 MUT	Exon 9 INS
7	Exon 9 INS + exon 17 MUT	Exon 9 INS
8	Exon 9 INS	Exon 9 INS
9	Exon 9 INS	Exon 9 INS
10	Exon 9 INS	Exon 9 INS
11	Exon 9 INS + exon 17 MUT	(external: exon 9 MUT)
12	Exon 9 INS	Exon 9 INS
13	Exon 9 INS	Exon 9 INS
14	Exon 9 INS + exons 17 & 18 MUT	Exon 9 INS
15	Exon 9 INS	Exon 9 INS
16	Exon 9 INS + exon 17 MUT	Exon 9 INS
17	Exon 9 INS + exon 17 MUT	Exon 9 INS
18	Exon 9 INS + exon 17 MUT	Exon 9 INS

*Two discordant cases were confirmed to have exon 9 insertions by external testing

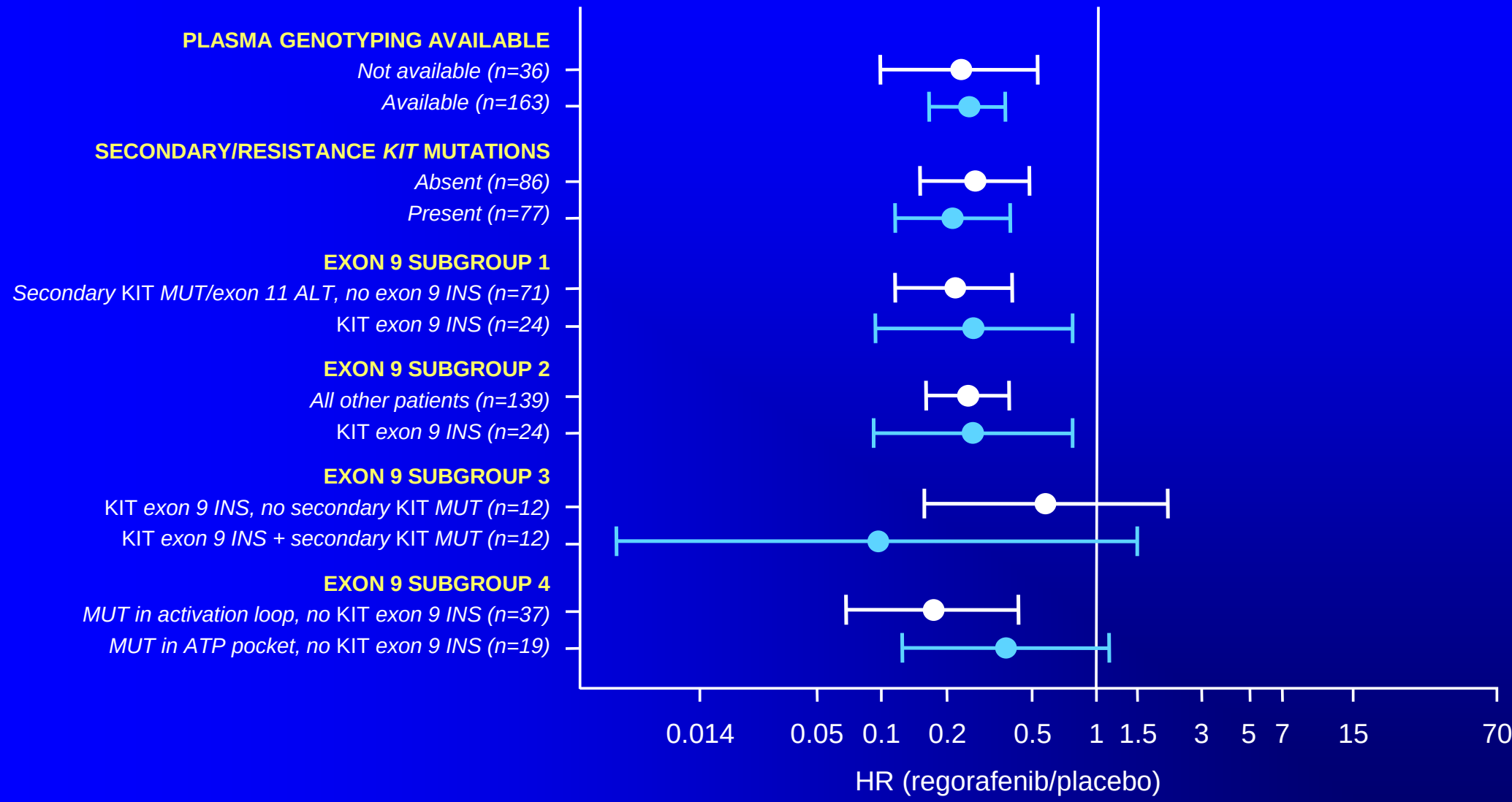
Phase III data supporting regorafenib FDA registration in GIST



Regorafenib significantly improved PFS *vs* placebo (p<0.0001); primary endpoint met

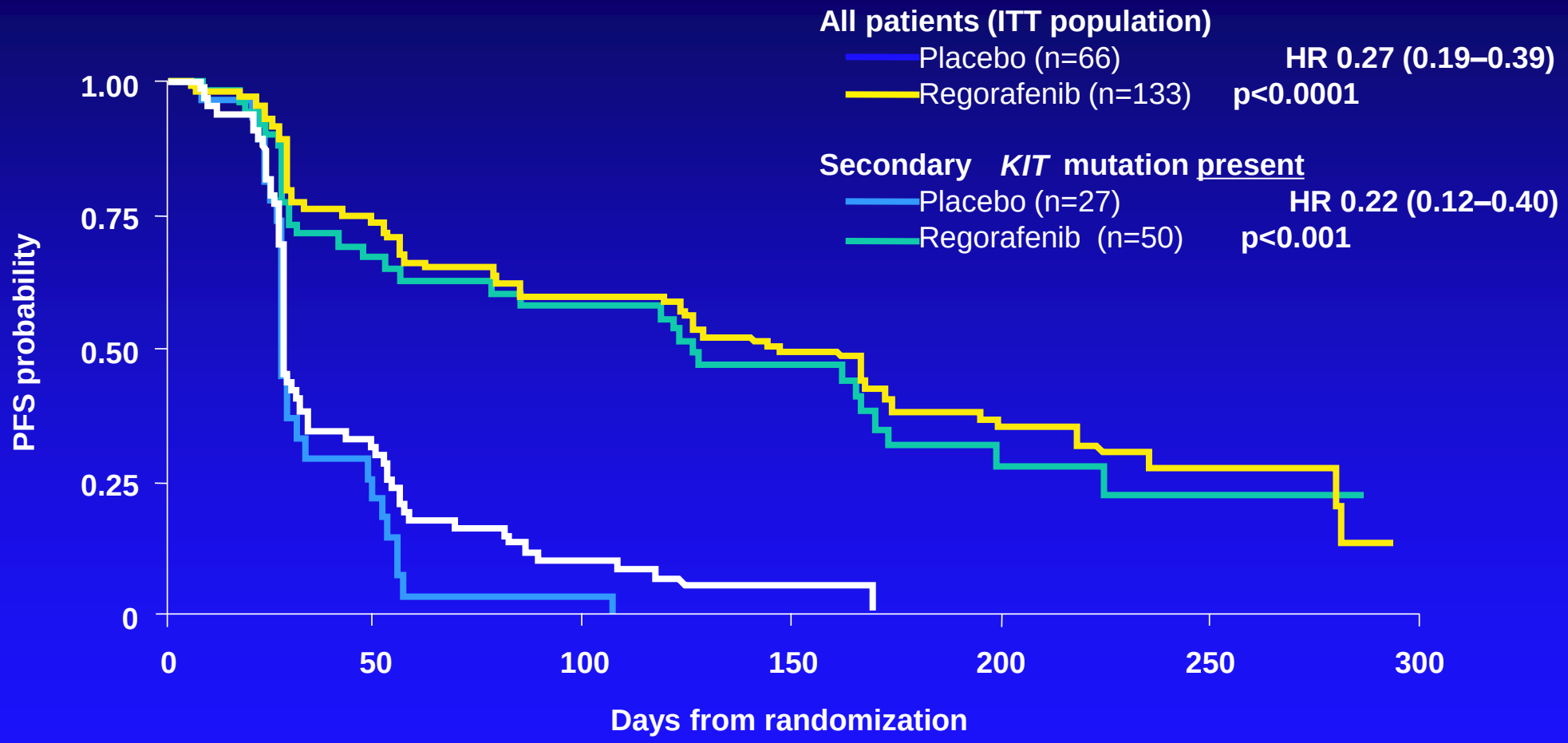
Demetri G, et al. Oral abstract presented at ASCO 2012, published *Lancet* 2013

Correlating Mutations detected in plasma DNA with Clinical Outcomes (benefit with regorafenib)



Regorafenib shows disease control benefit (improved PFS) over placebo in all mutation subgroups

Regorafenib shows benefit over placebo in GIST **with** secondary *KIT* mutations detectable in circulating free DNA assay



ITT curves from Demetri GD *et al. Lancet* 2013; 381: 295–302

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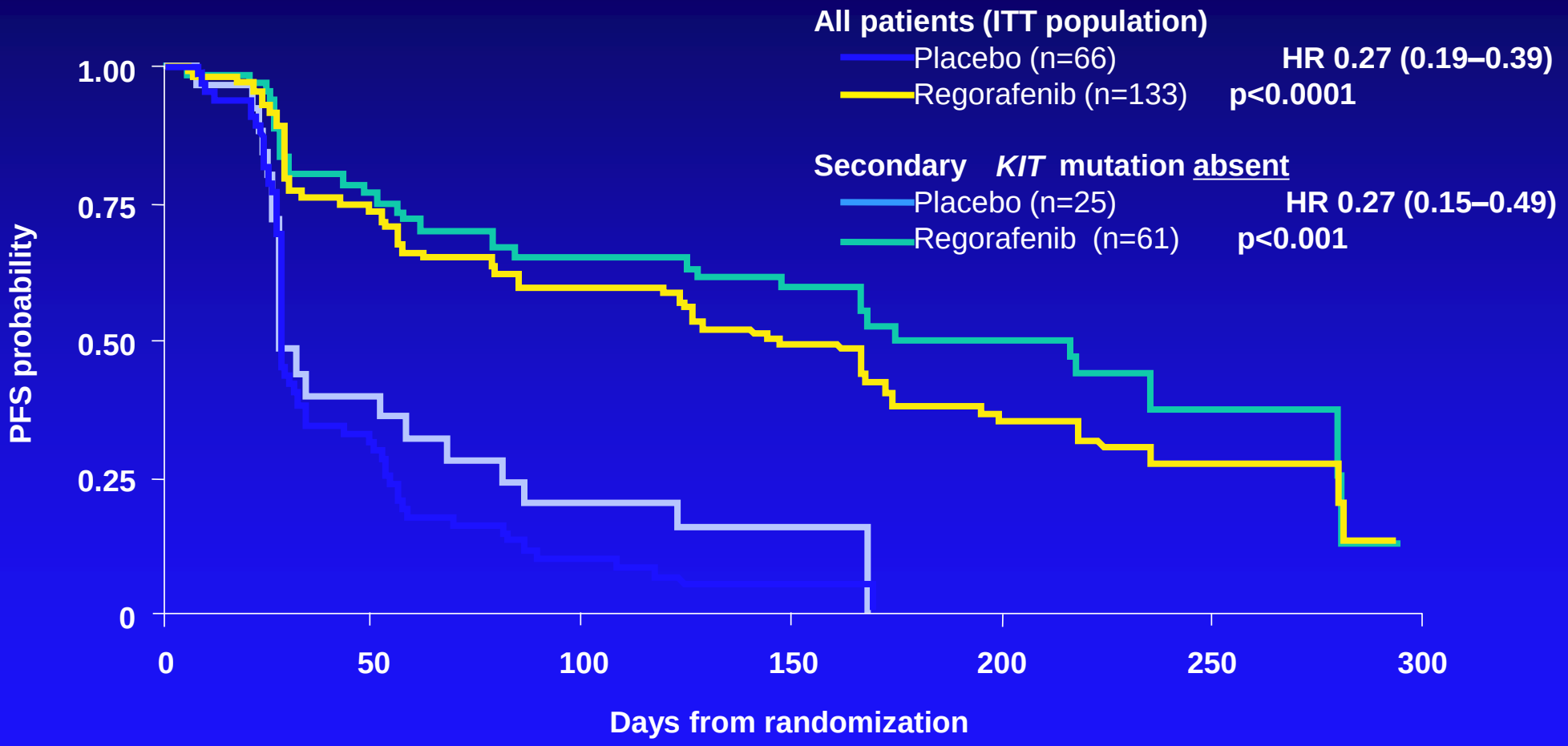
Regorafenib shows benefit over placebo in GIST **with no** secondary *KIT* mutations detectable in circulating free DNA assay



ITT curves from Demetri GD *et al. Lancet* 2013; 381: 295–302

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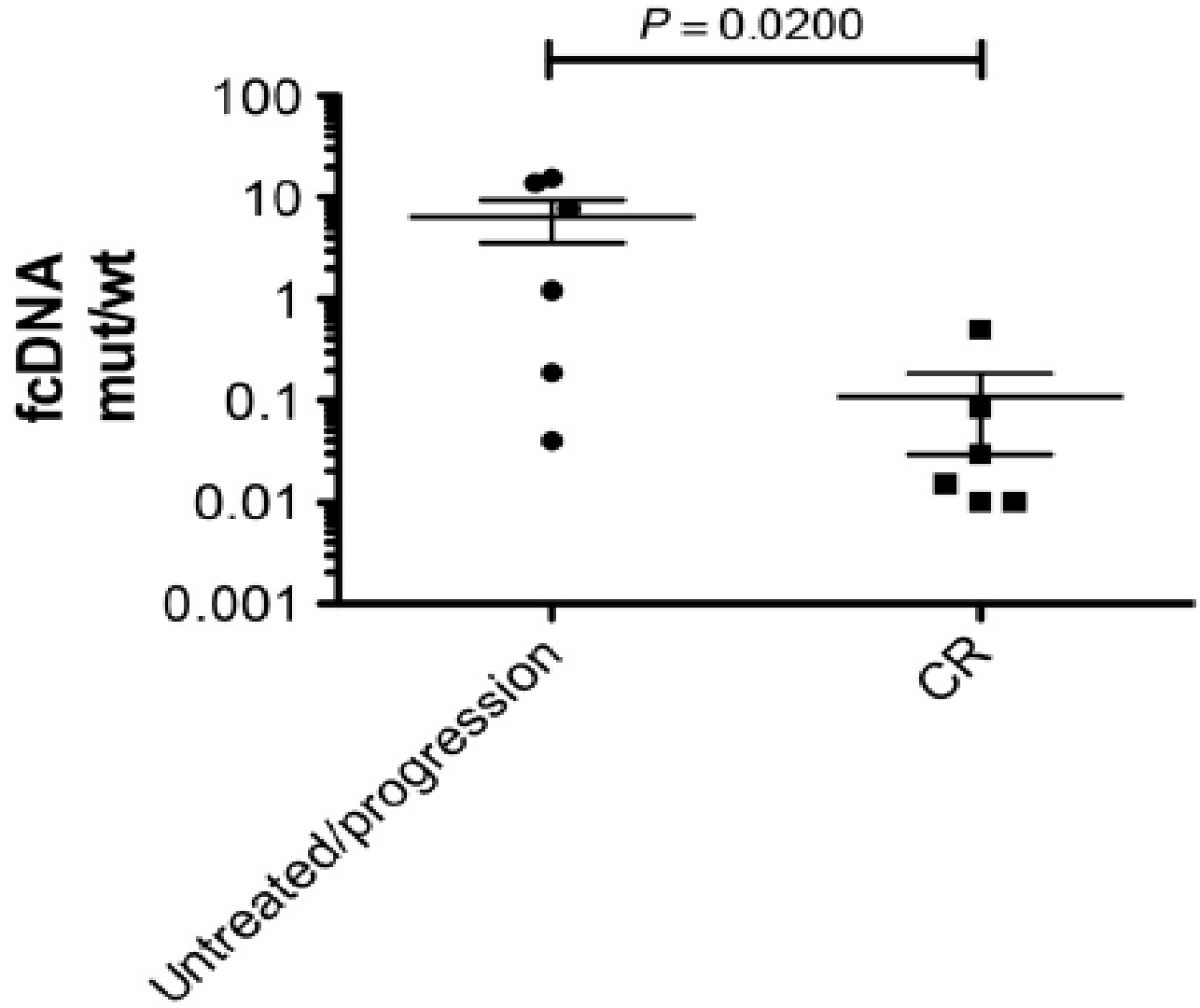
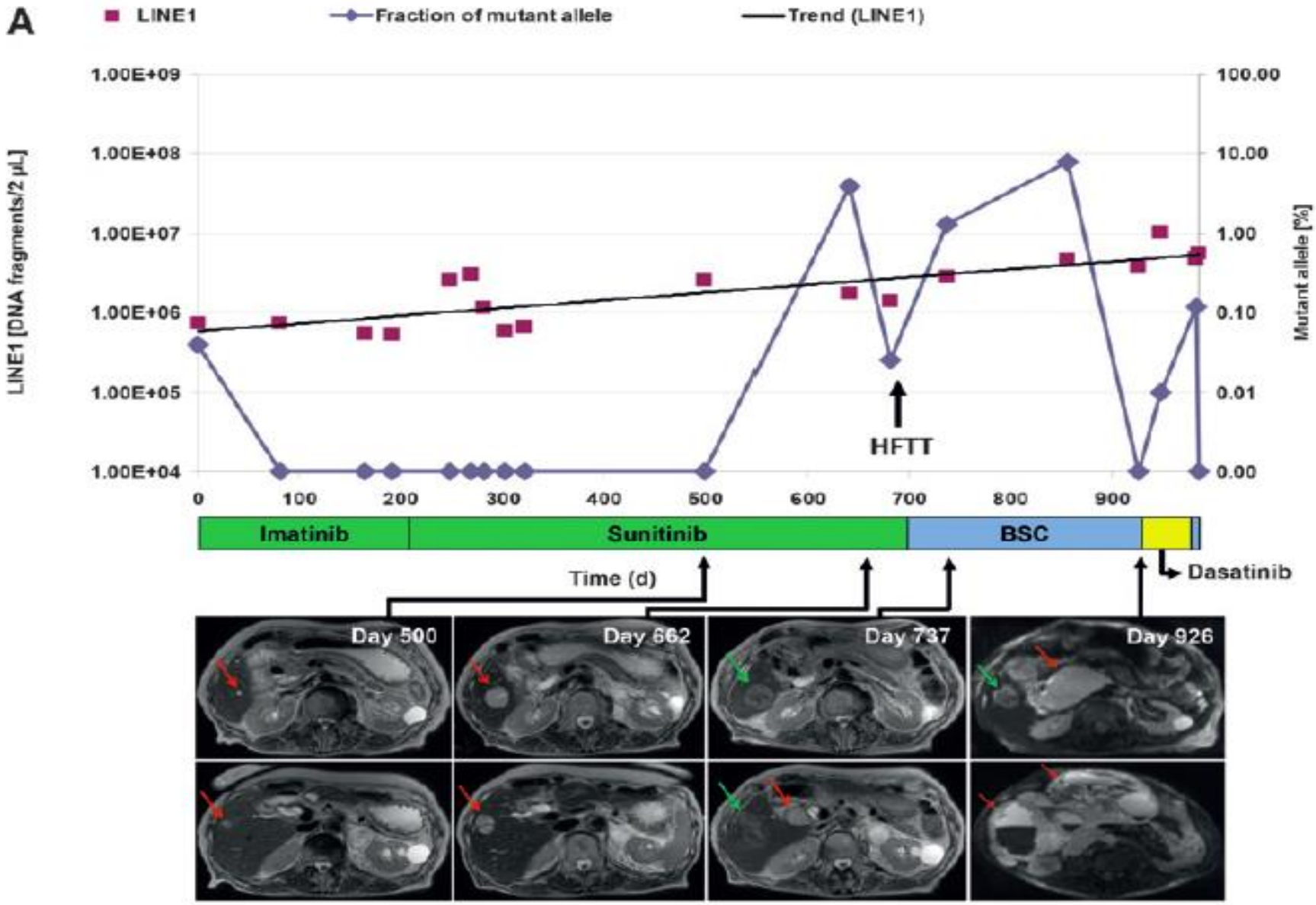
Mutant fcDNA correlates with clinical disease status (active/resistant vs. “CR”)



Maier J et al. Clin Cancer Res 2013;19:4854-4867

Clinical Cancer Research

Mutant fcDNA in correlation with clinical response in individual patients over time.



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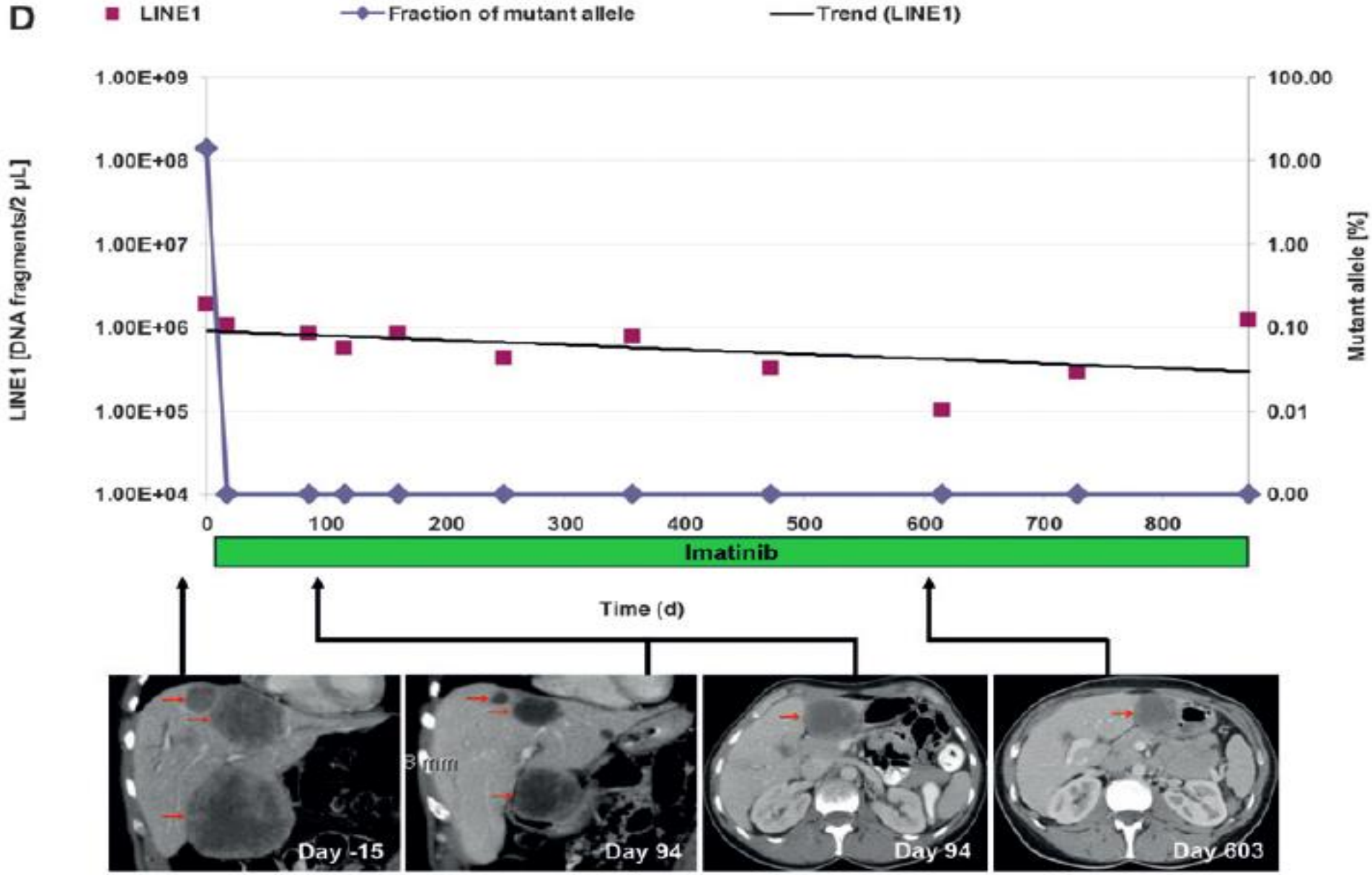

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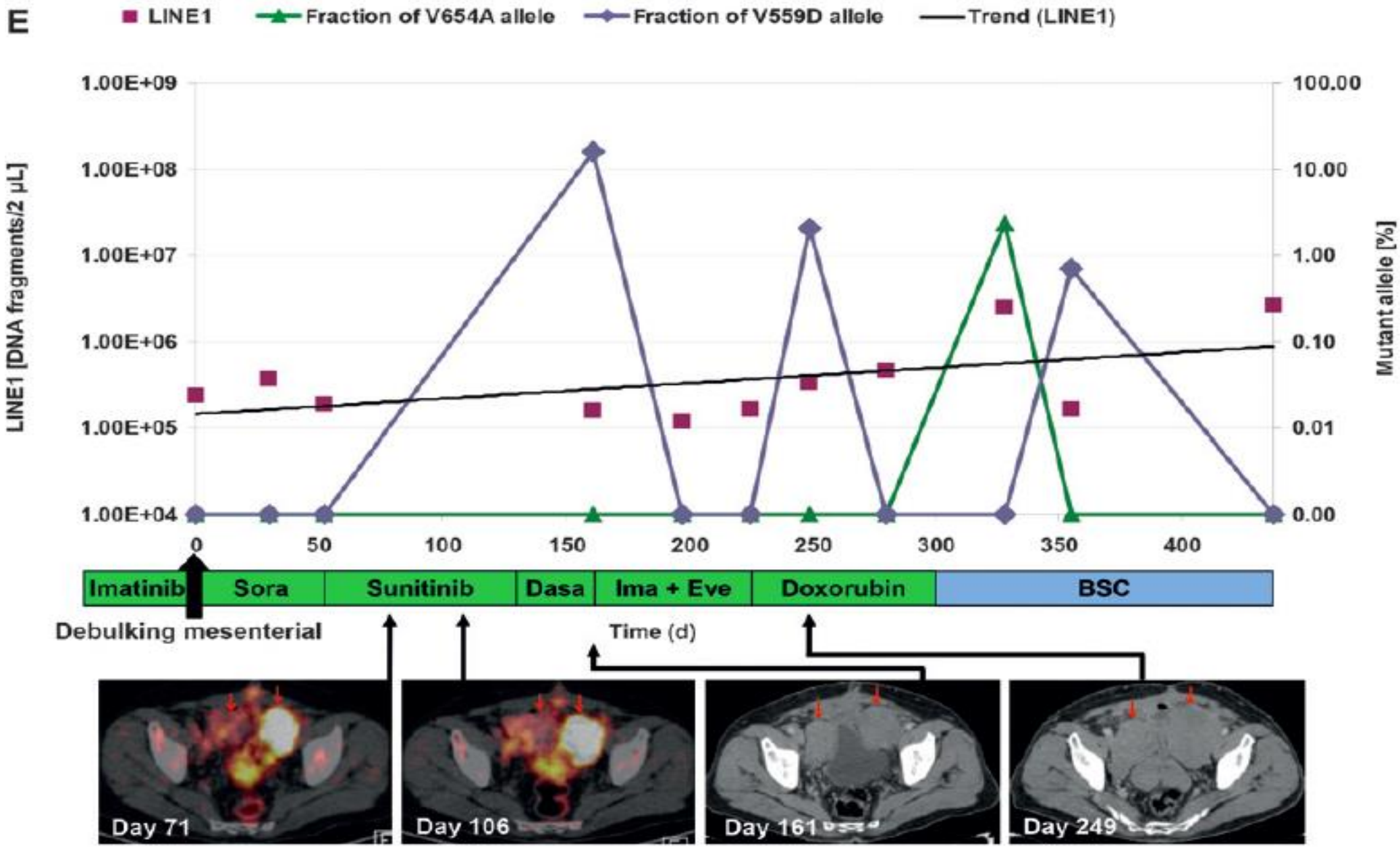
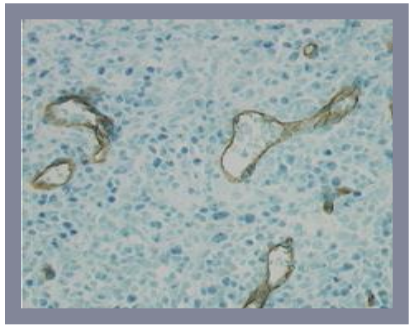


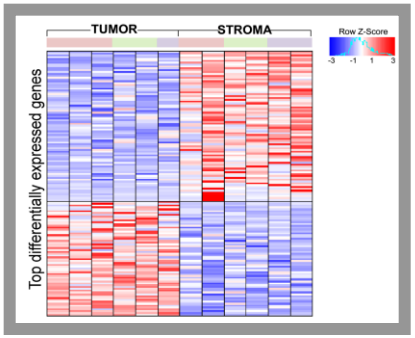
Maier J et al. Clin Cancer Res 2013;19:4854-4867

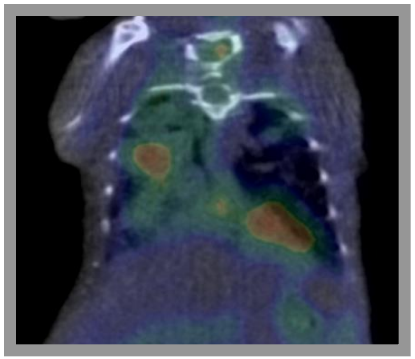
Clinical Cancer Research

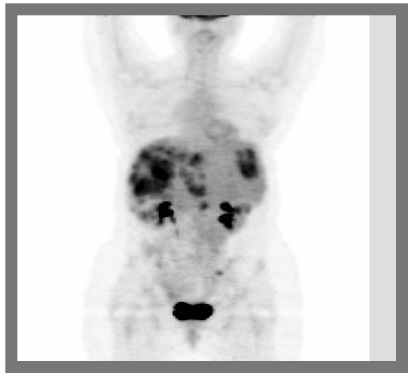
Next steps forward

- *Continuing research to expand free plasma DNA sensitivity*
- *Next-gen sequencing (NGS) on plasma for discovery detection of new mutations (rather than* previously identified mutations)
- Other biomarkers of resistance to be identified
  - For research use
  - For clinical use









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Thanks to all the patients, their families and all our collaborative colleagues worldwide!