New Trends in Cancer Management: Signal Transduction and Drug Sensitivity

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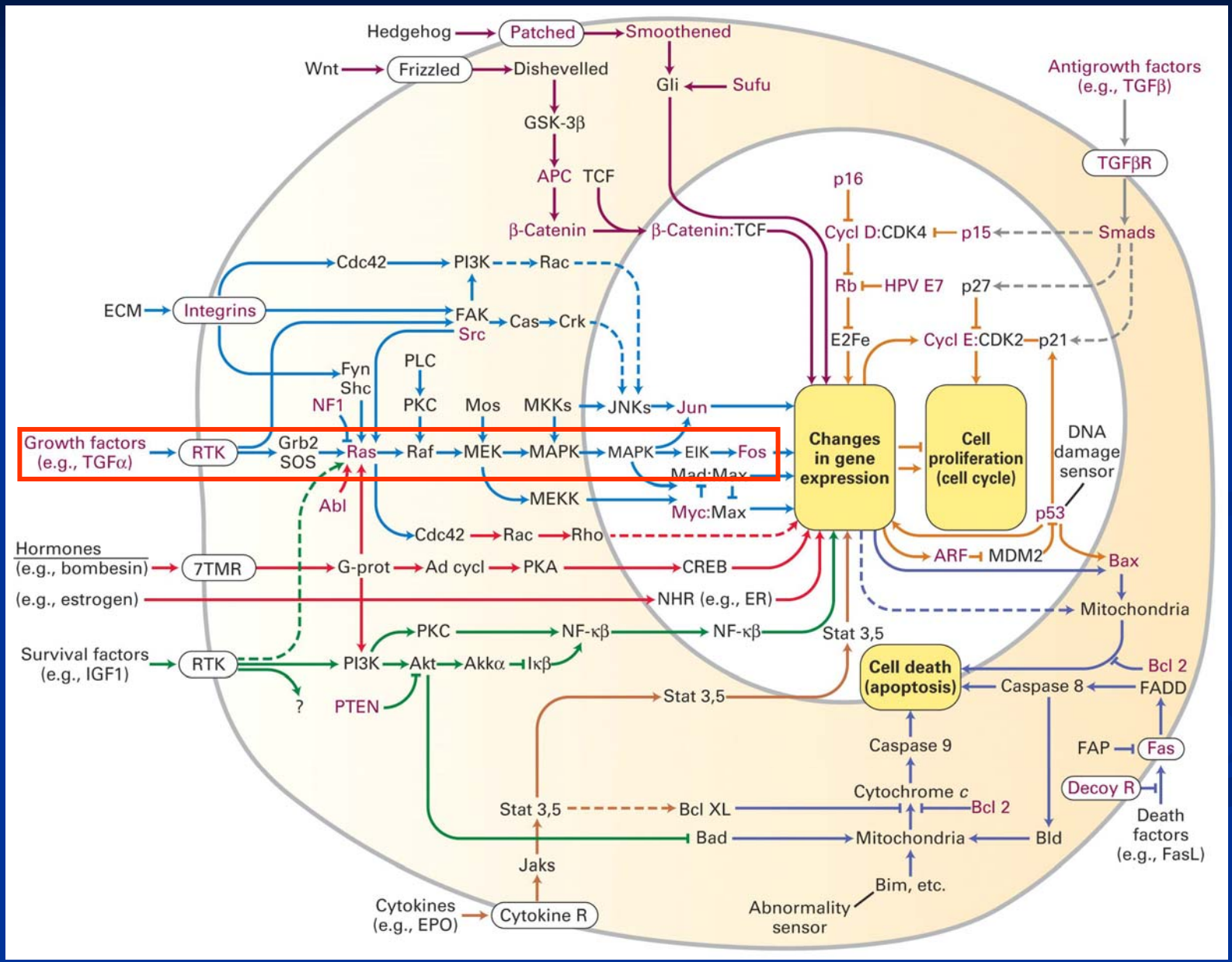
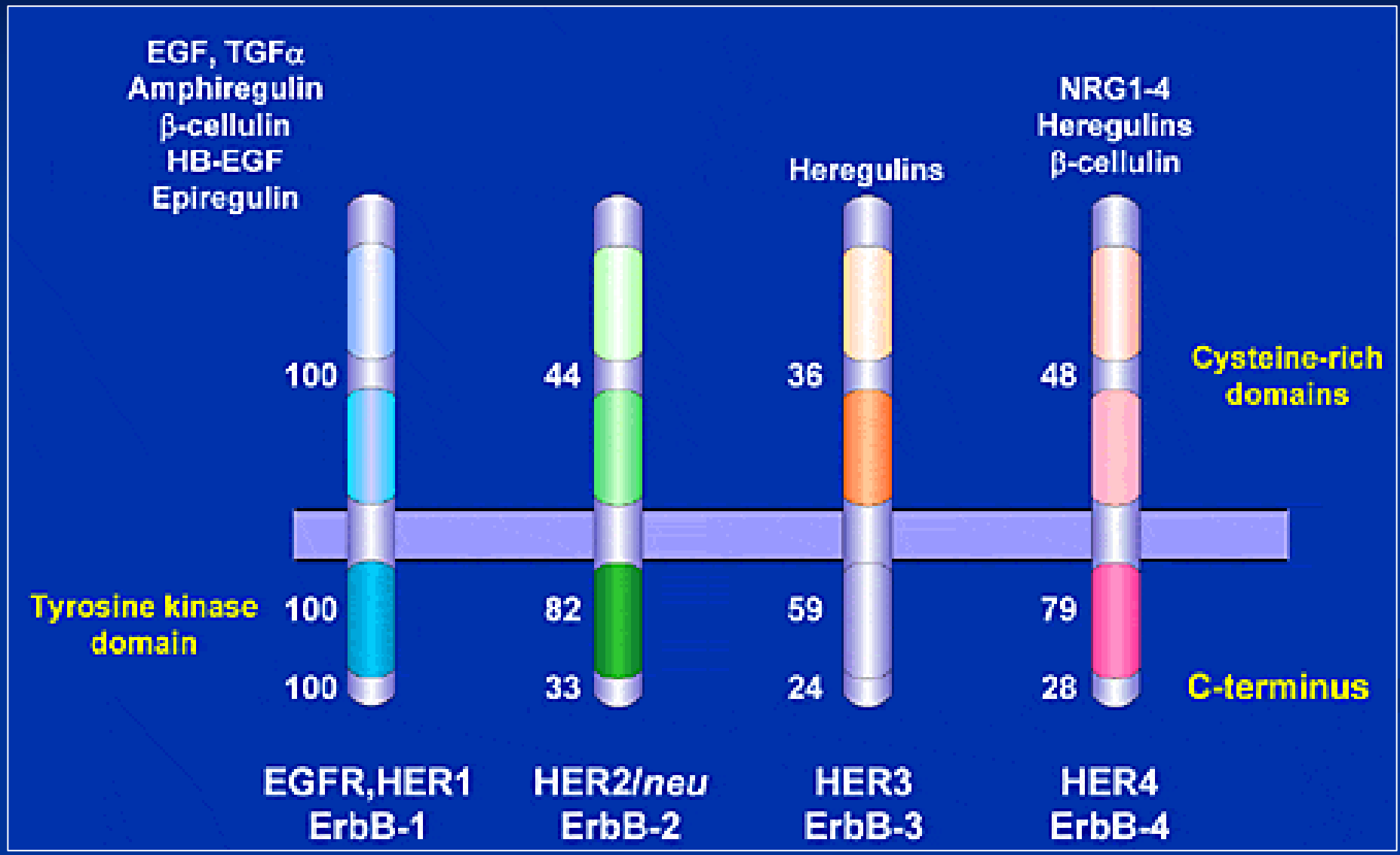
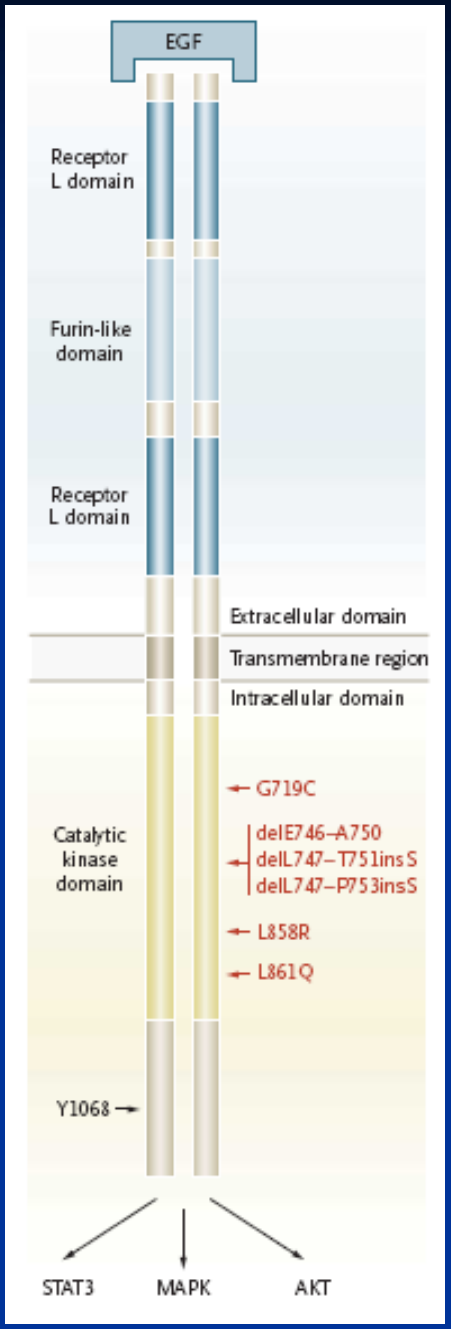
Cell circuitry that is affected by cancer-causing mutations



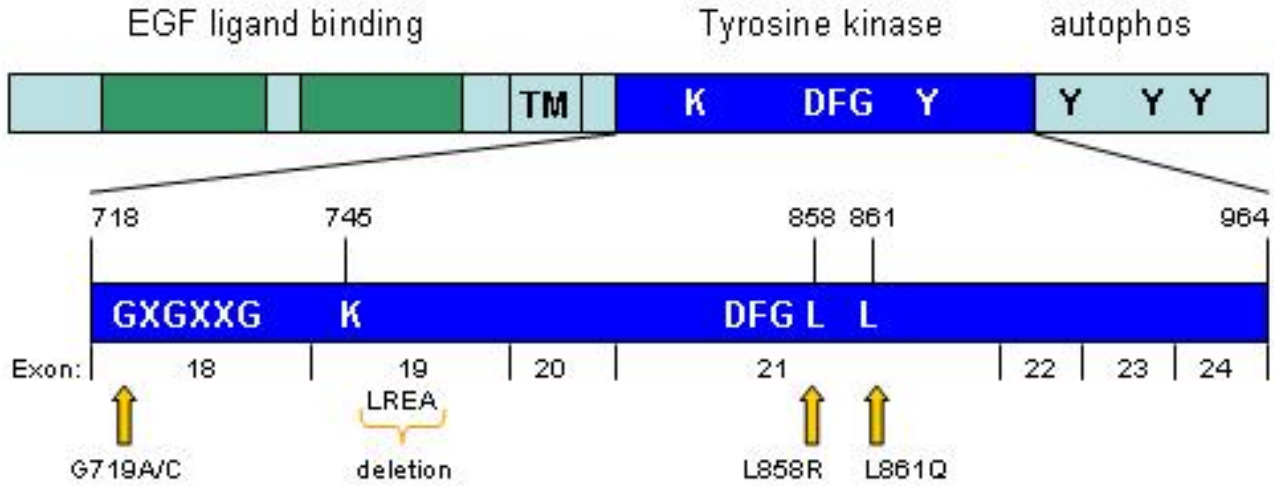
The Epidermal Growth Factor Receptor (EGFR) family and ligands



EGFR signaling pathway

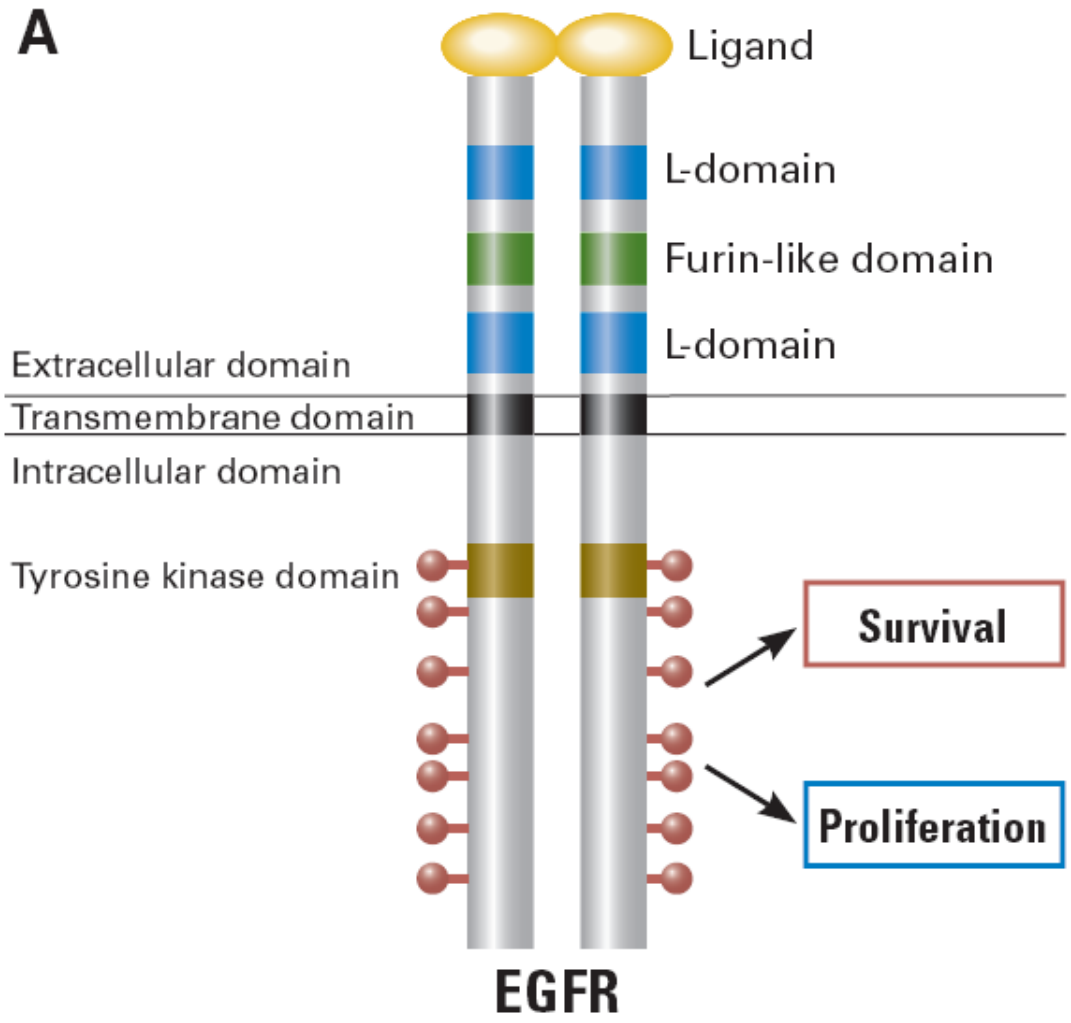


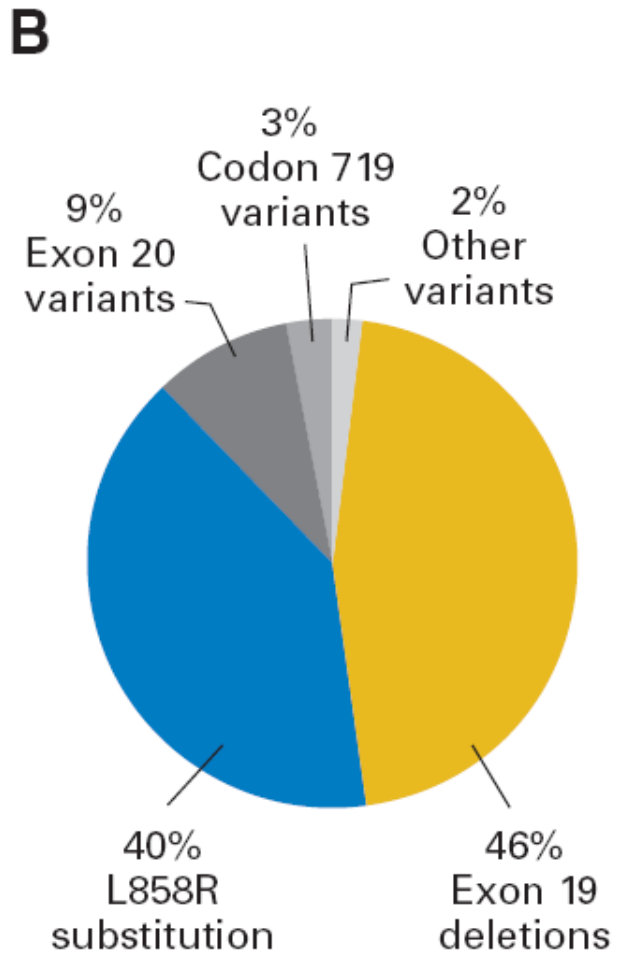
EGFR mutations associated with sensitivity to EGFR-TKIs



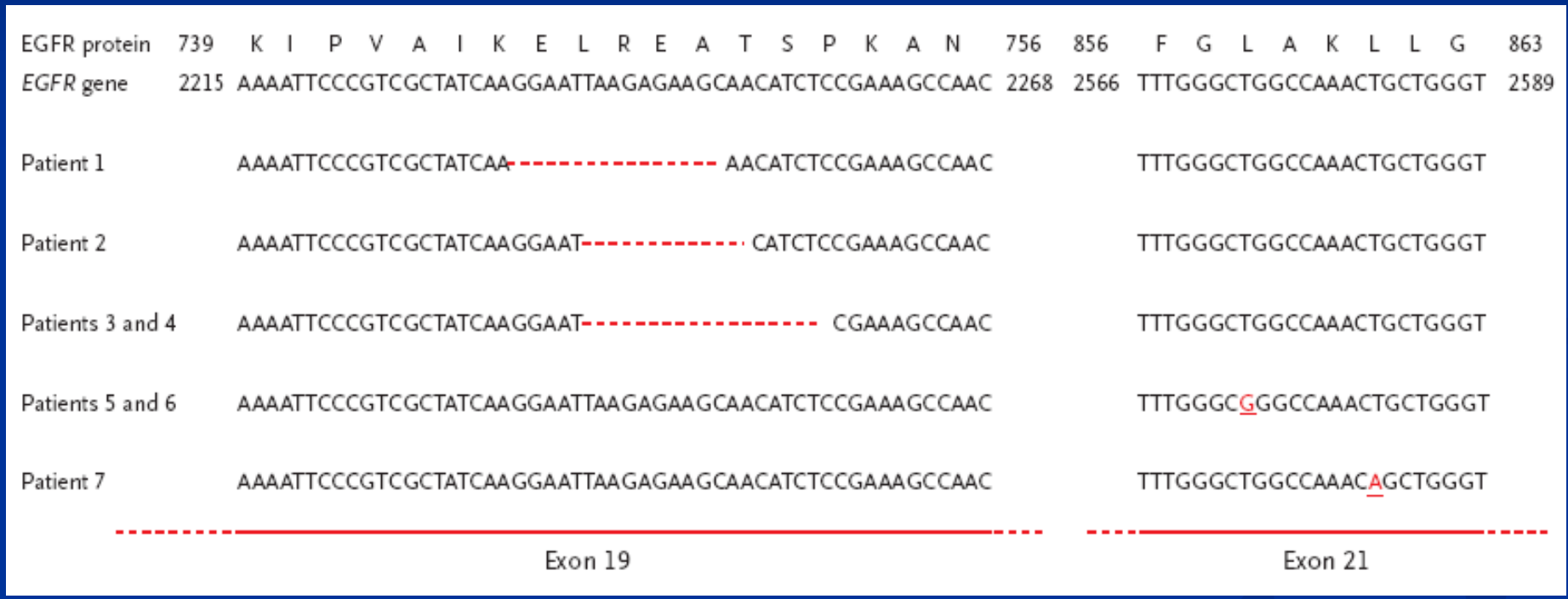
Thus far, only exon 19 dels and L858R reliably predict sensitivity

EGFR mutations



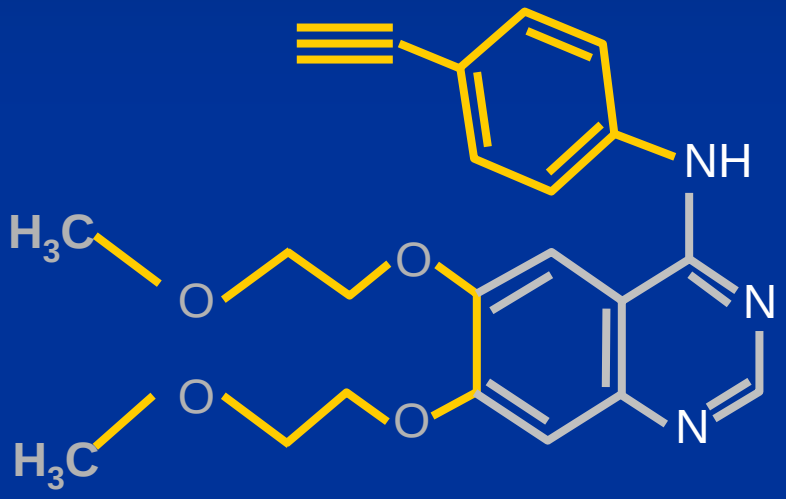


Clustering of Mutations in the *EGFR* Gene at Critical Sites within the ATP-Binding Pocket



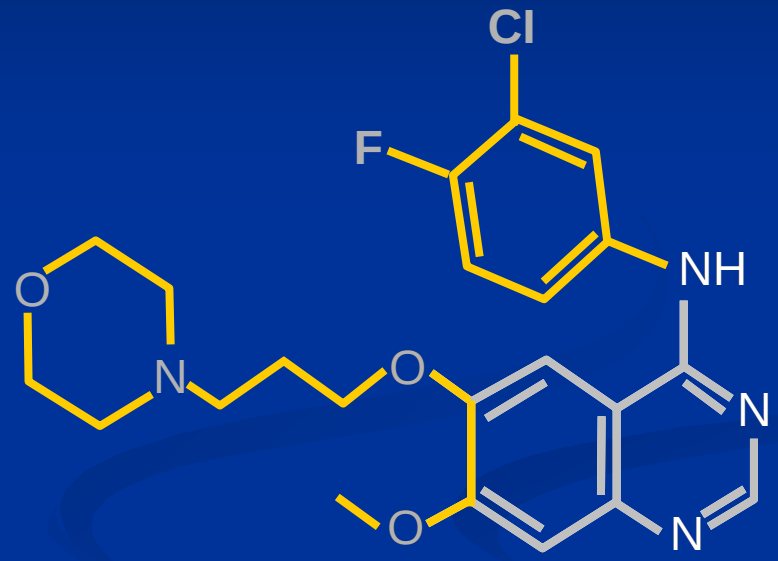
Lynch, N Engl J Med 2004;350:2129-39.

Erlotinib and Gefitinib: structural differences



Erlotinib

IC_{50} = 2nM[1]

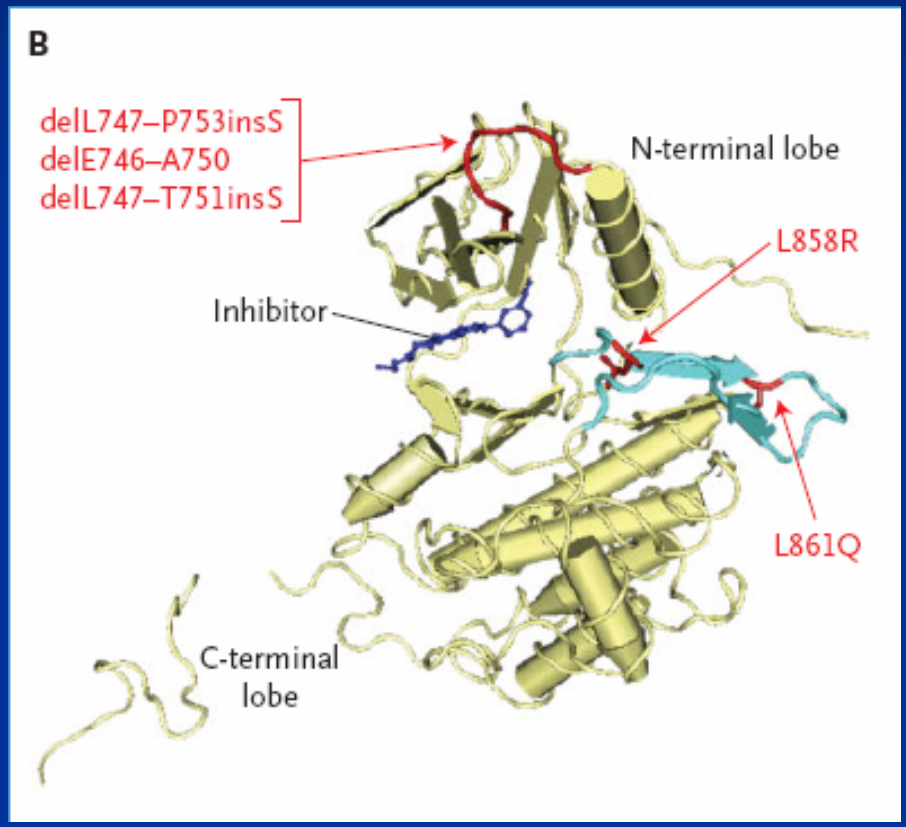


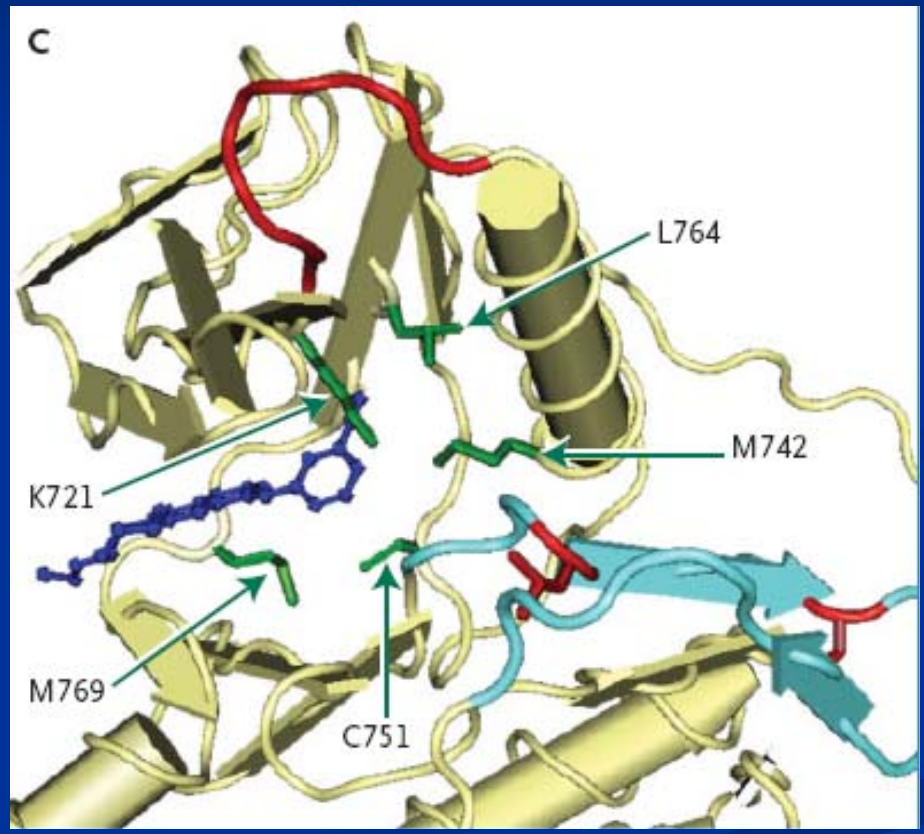
Gefitinib

IC_{50} = 23-79nM[2]

[1]Moyer J, et al. Cancer Res 1997;57:4838-48
[2]Woodburn J, et al. AACR 2000; Abs. 2552

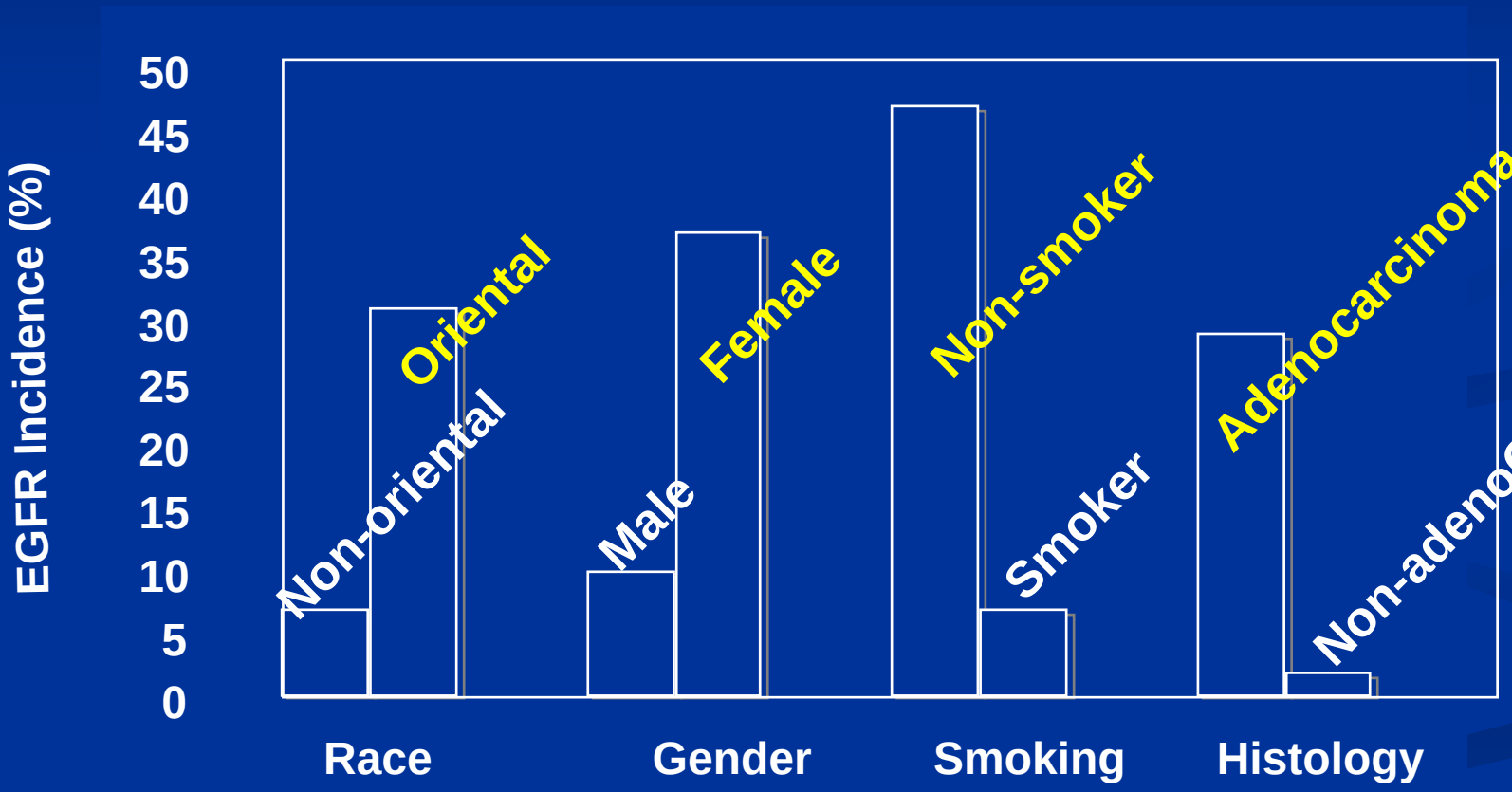
The three-dimensional structure of the EGFR ATP cleft in kinase domain



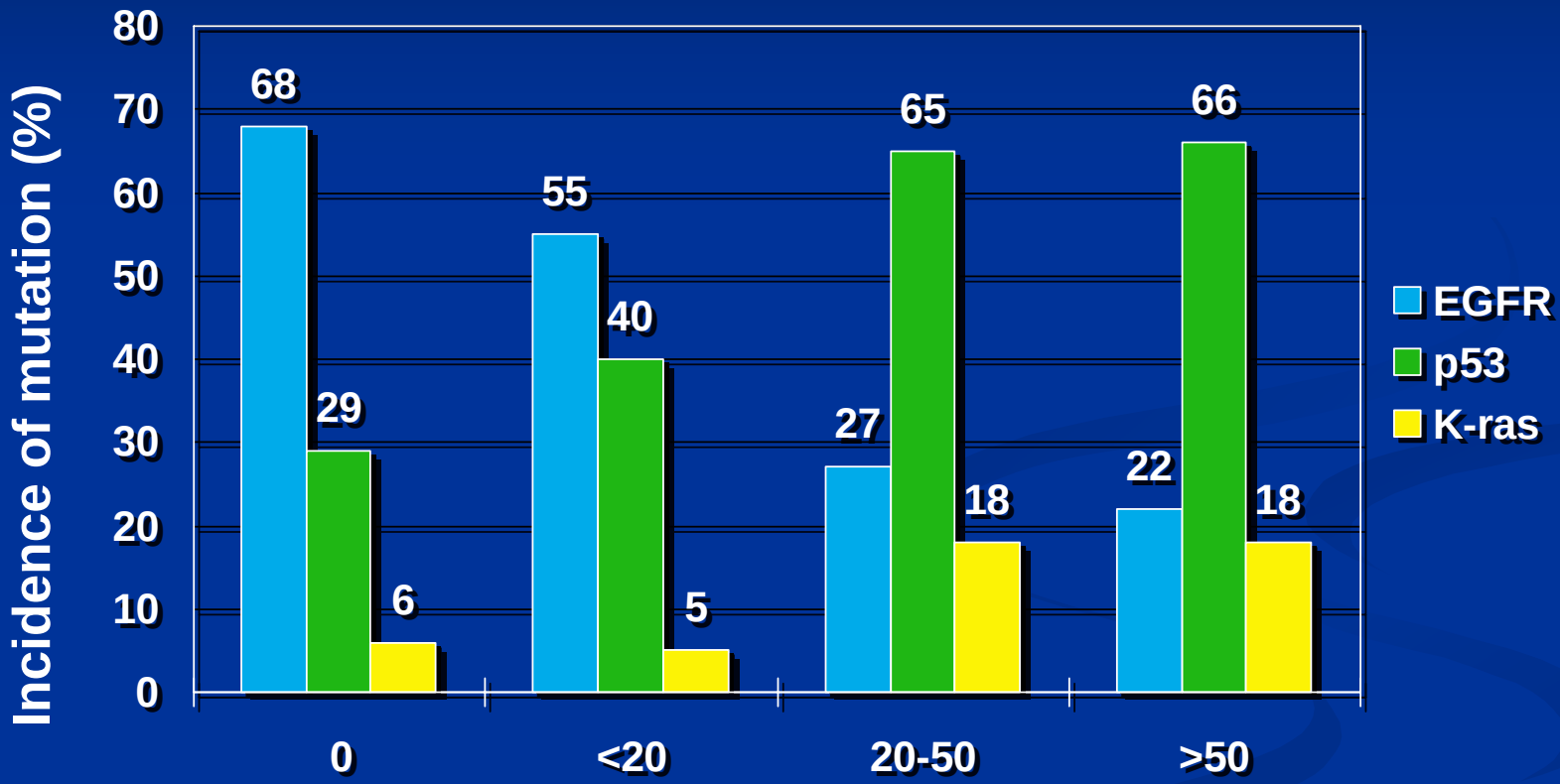


Lynch, N Engl J Med 2004;350:2129-39.

Incidence of EGFR mutations by race, gender, smoking status and histologic types (N=2530)



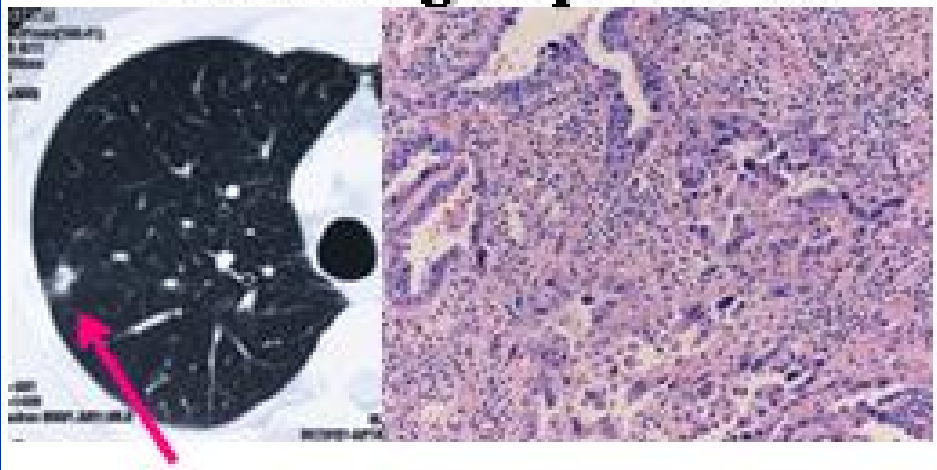
EGFR, p53 and K-ras mutation and smoking dose in patients with adenocarcinoma

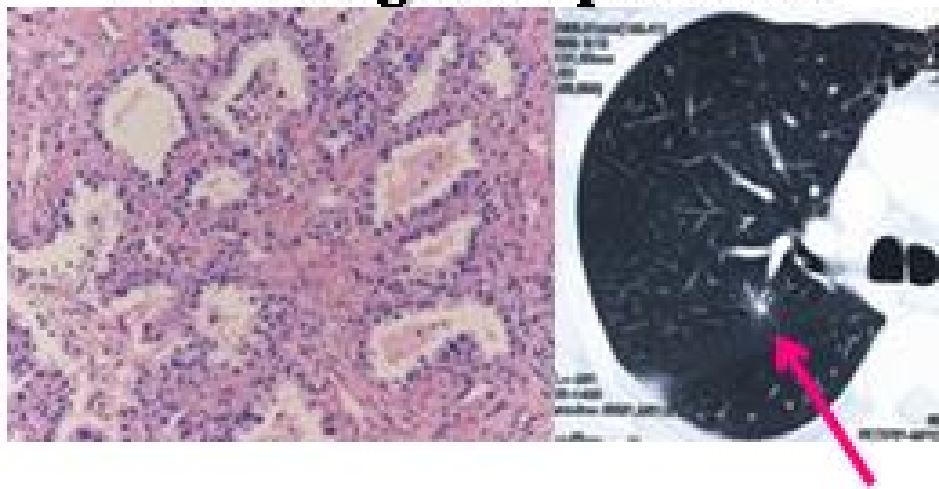


Kosaka et al., Cancer Res.64, 8919-8923, 2004

Synchronous smoking-dependent and -independent carcinogenesis in a 60 y/o male with heavy smoking history (95 PY)

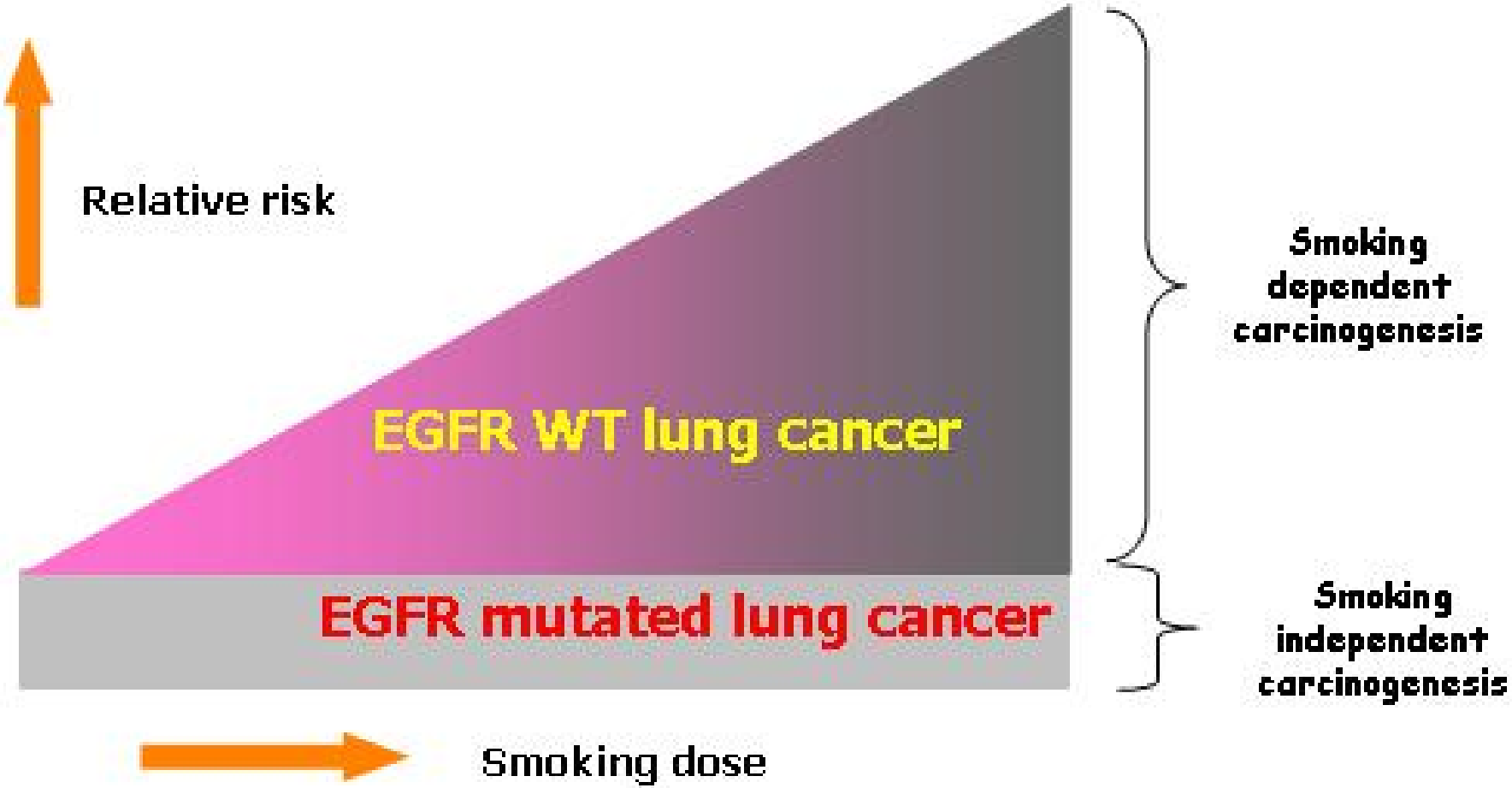
Smoking dependent | **Smoking independent**



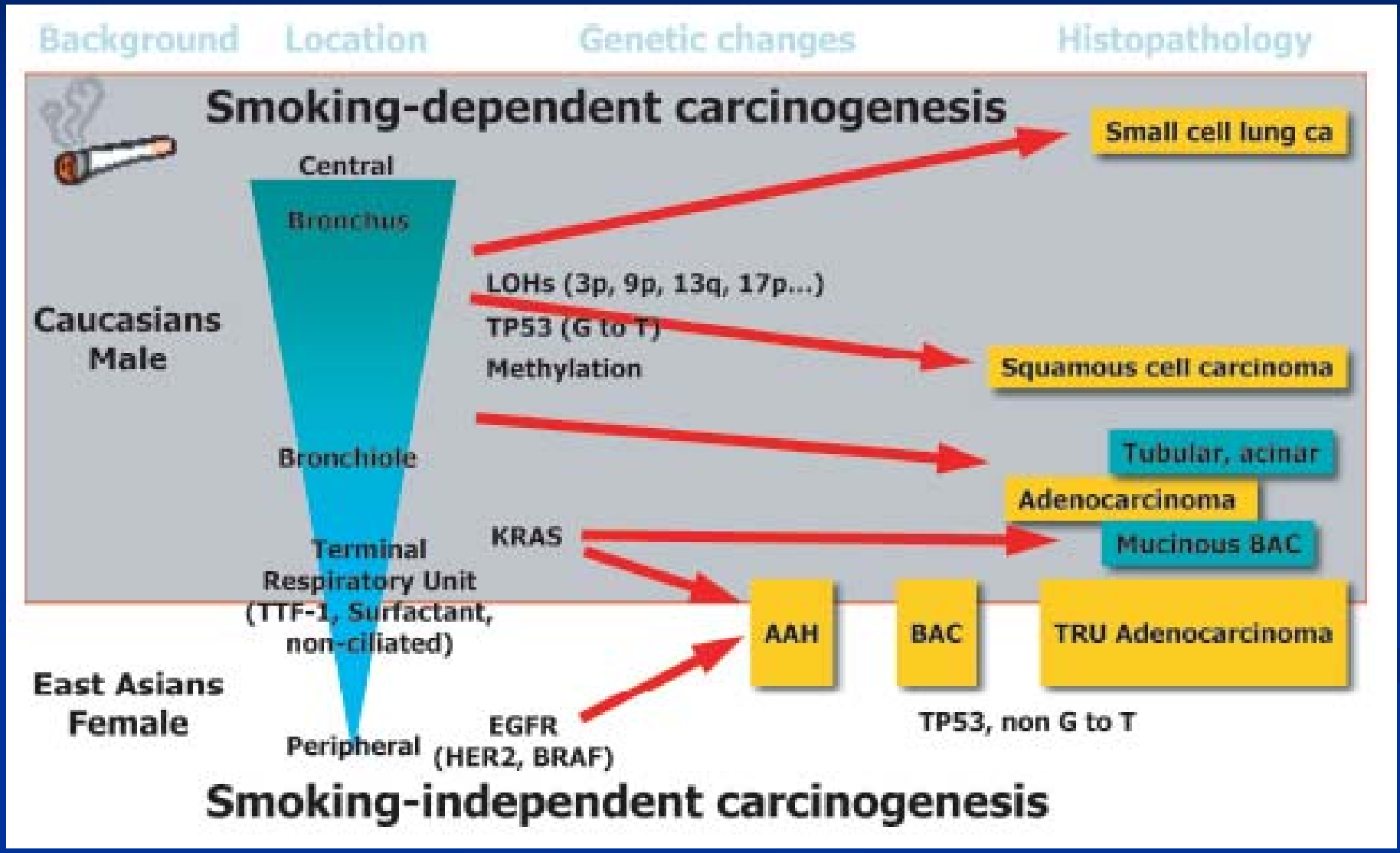


P53 IHC	+	-
TTF1 IHC	+	+
P53 gene	codon 214 CAT-CGT	WT
EGFR gene	WT	codon 858 CTG-CGG
K-ras gene	codon 13 GGT-TGT	WT

Smoking dependent and independent lung carcinogenesis

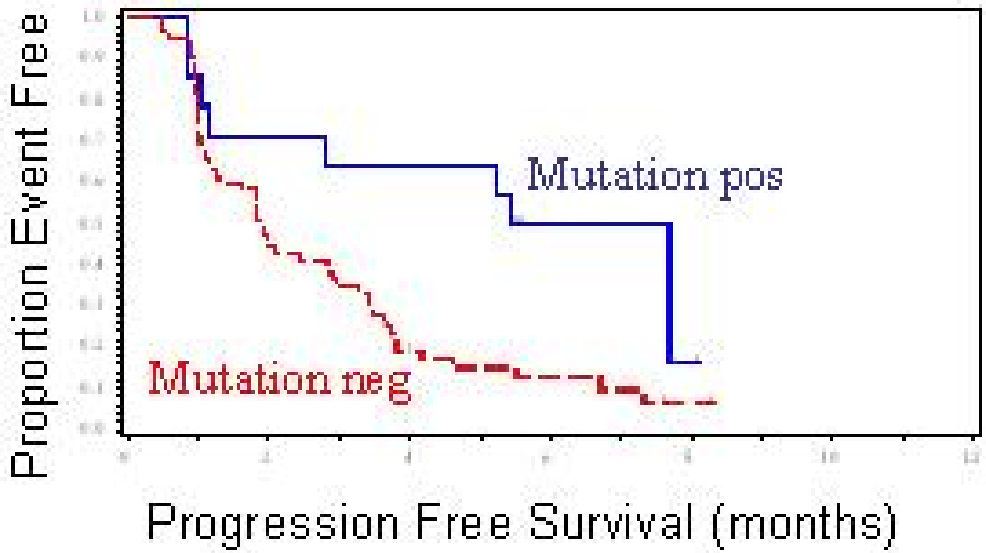


The current understanding of the relationship between lung carcinogenesis and tobacco smoking



Molecular analysis of IDEAl/INTACT trials

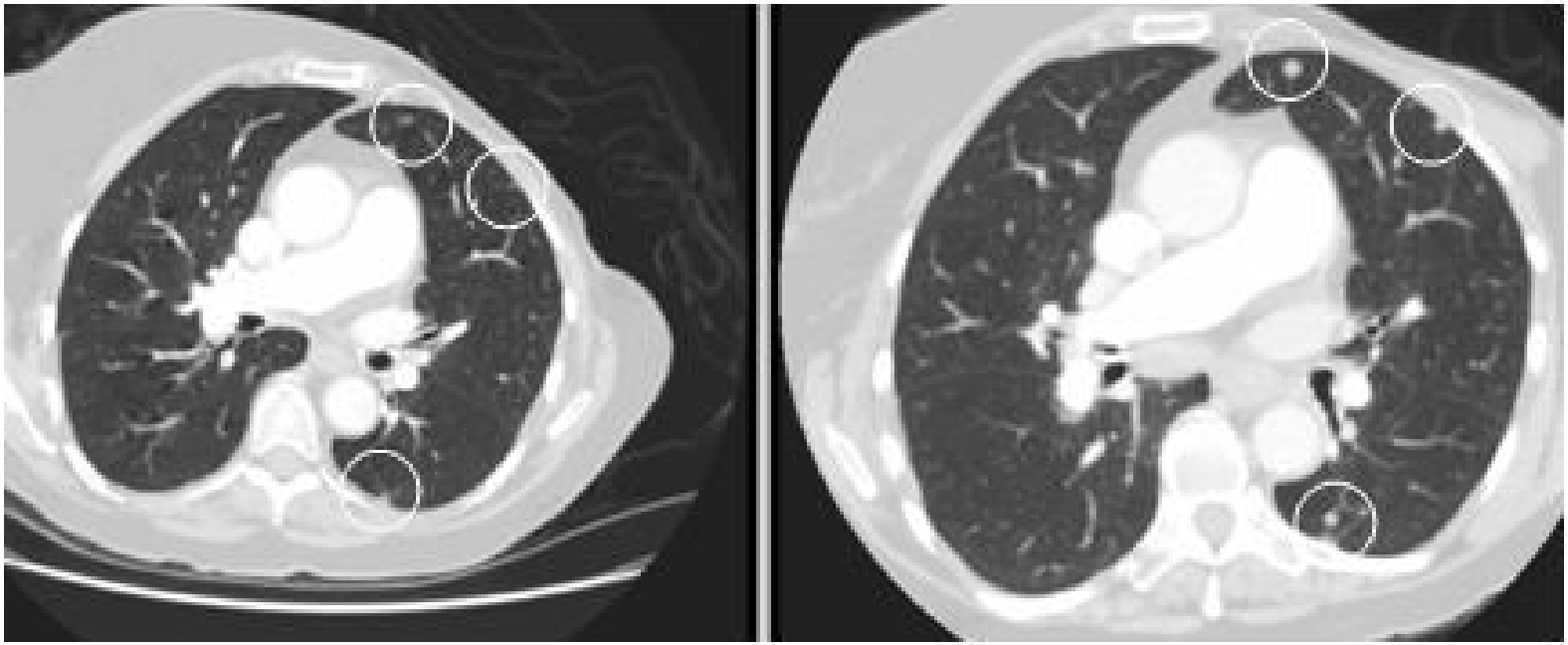
		Gefitinib response	
EGFR Mutation	+	6/13 (46%)	
	-	6/61 (10%)	P=0.005
EGFR Amplification	+	2/7 (29%)	
	-	12/79 (15%)	P=0.32



IDEAL Trial of
Gefitinib
as third line in NSCLC

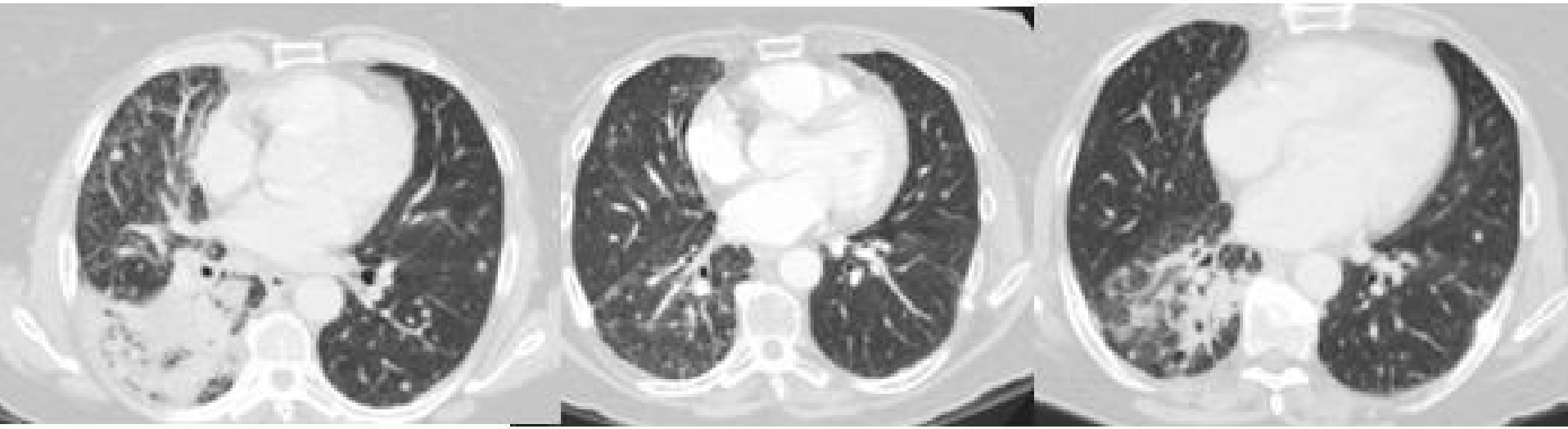
De Novo Resistance Mechanisms (2)

- 1 patient with both T790M and L858R had a best response of SD and remained on treatment for 55 days



Acquired Resistance

- 2 patients with del 19 mutations had initial PR but eventually progressed and acquired T790M was identified through analysis of circulating tumor cells from peripheral blood samples



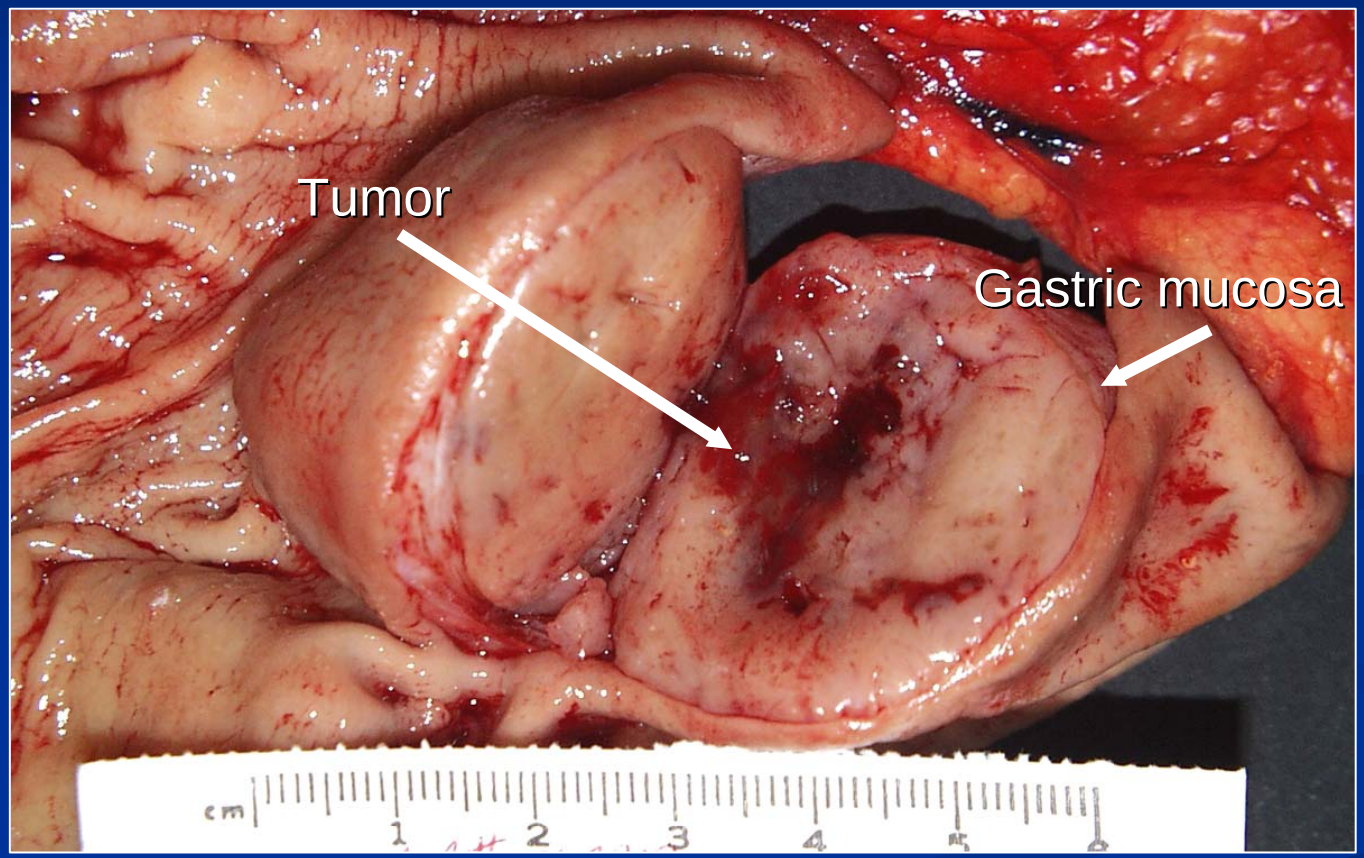
Baseline Response Progression

Summary of EGFR Inhibitors Tested Against $EGFR^{L858R/T790M}$

Compound	IC_{50} (nm)
Gefitinib	6600
Erlotinib	10000

(Inhibition of H1975 cell proliferation)

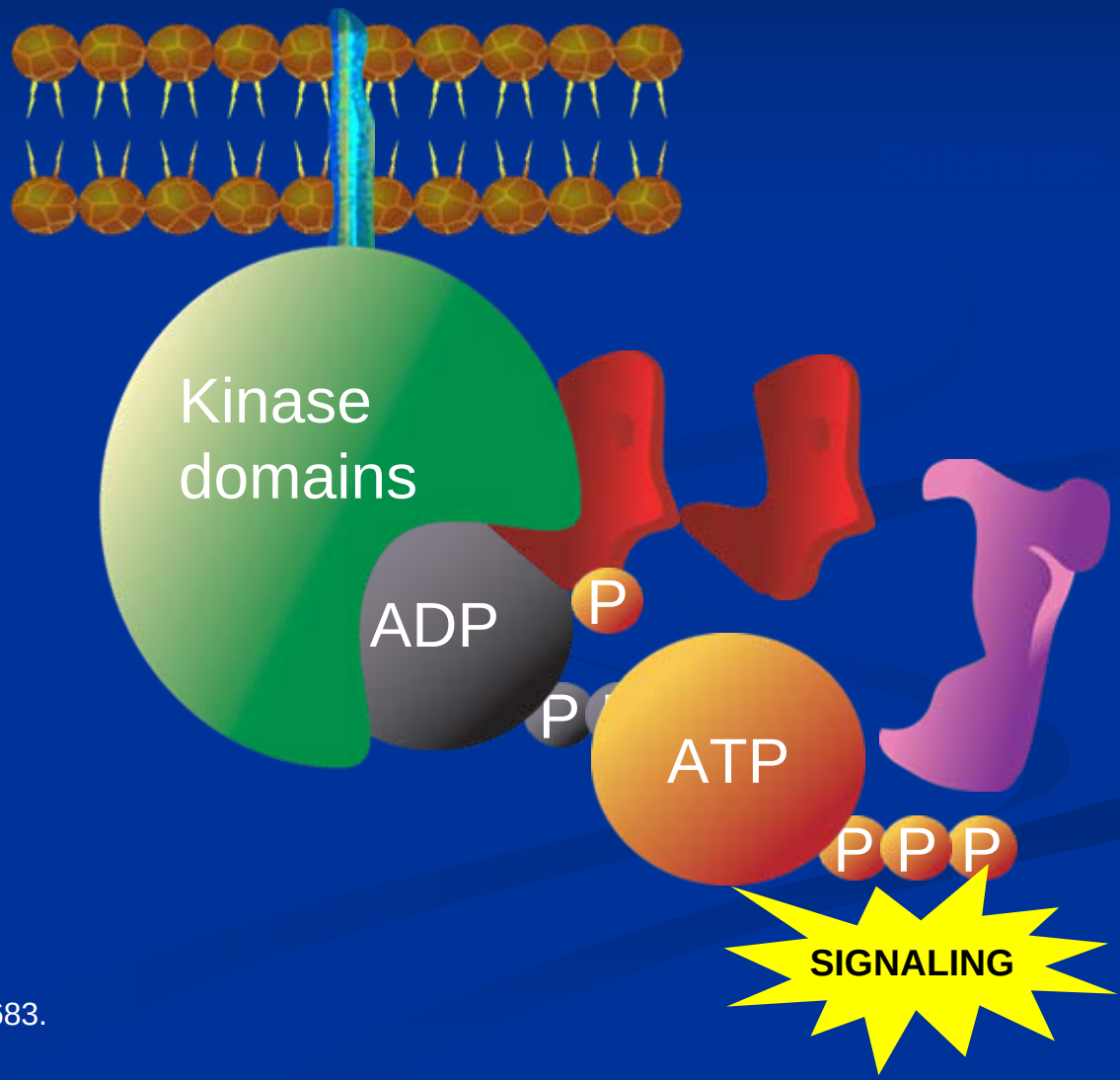
GIST: Primary Tumor



Gross pathology of primary GIST

Normal KIT Signaling

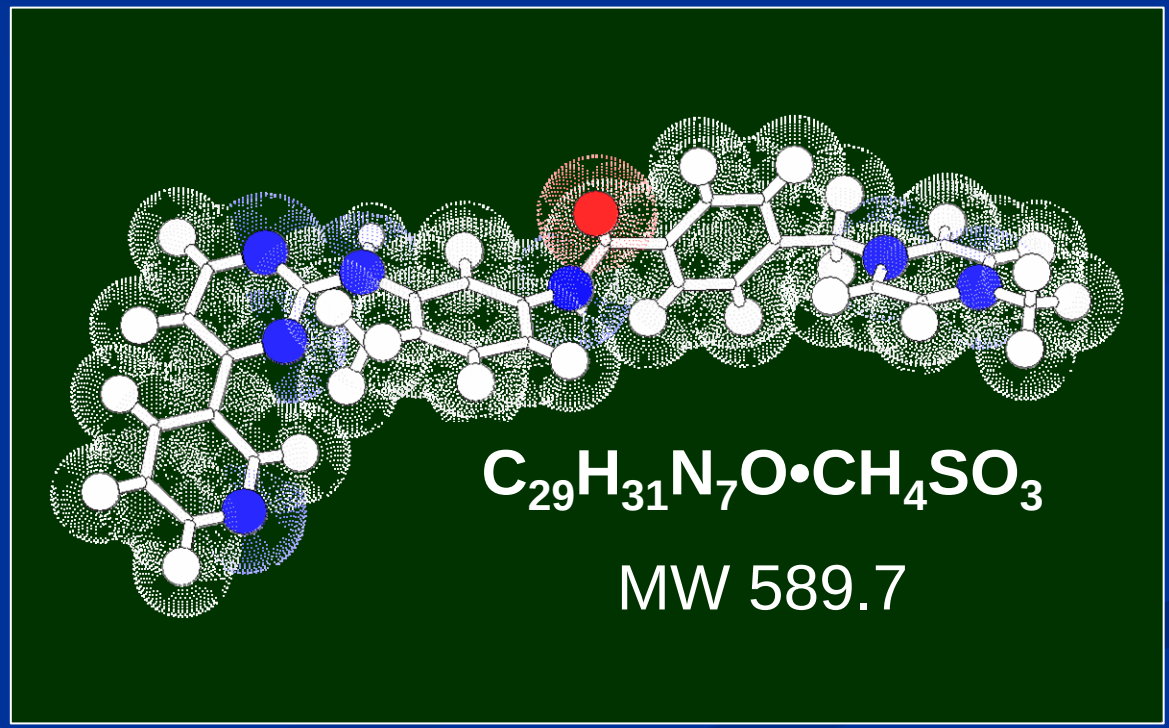
- The KIT kinase domain activates a substrate protein, eg, PI3 kinase, by phosphorylation
- This activated substrate initiates a signaling cascade culminating in cell proliferation and survival



Savage and Antman. *N Engl J Med.* 2002;346:683.
Scheijen and Griffin. *Oncogene*. 2002;21:3314.

Imatinib Mesylate: Background

- A selective tyrosine kinase inhibitor of
  - KIT
  - Bcr-Abl
  - PDGFRA/B
- First used in Philadelphia chromosome–positive (Ph+) CML

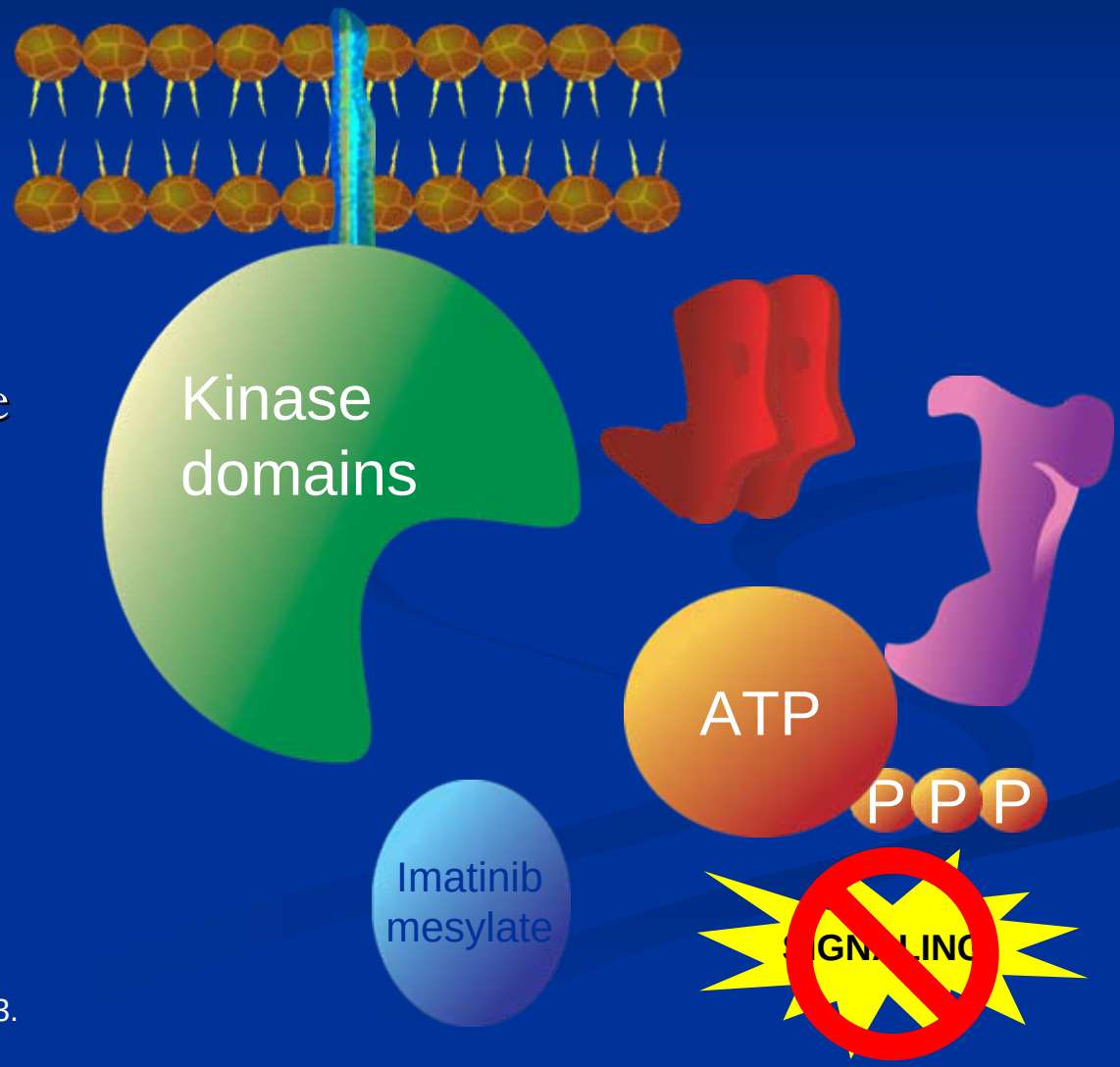


Class: Phenylaminopyrimidines

Druker et al. *Nat Med.* 1996;2:561.

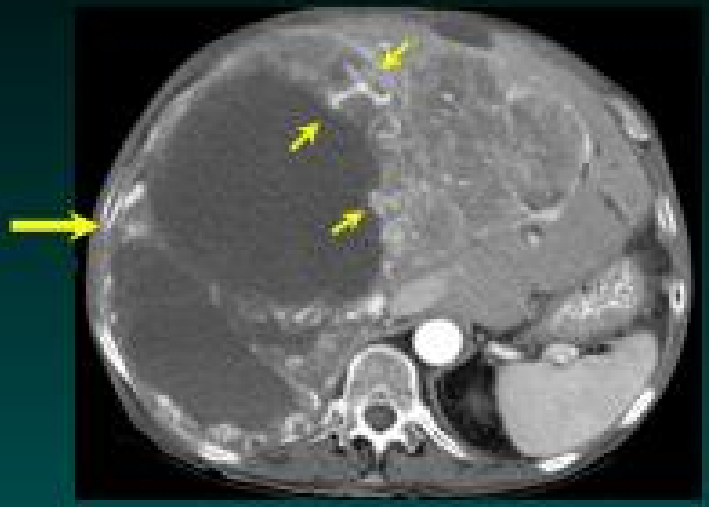
Imatinib Mesylate: Mechanism of Action

- Imatinib mesylate occupies the ATP binding pocket of the KIT kinase domain
- This prevents substrate phosphorylation and signaling
- A lack of signaling inhibits proliferation and survival

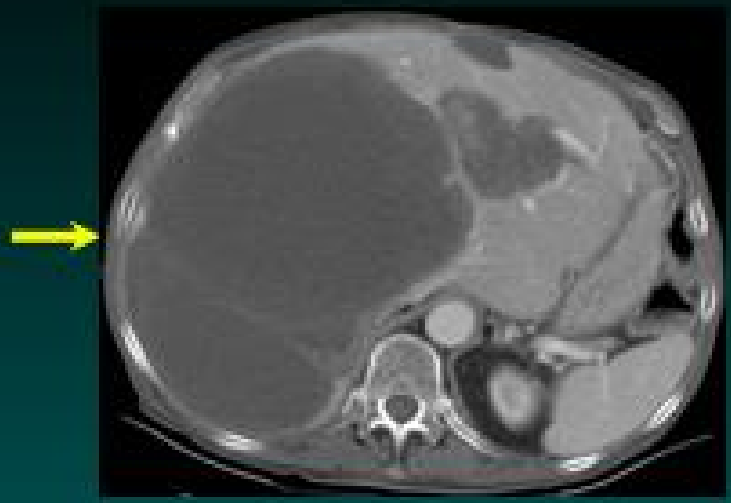


Savage and Antman. *N Engl J Med.* 2002;346:683.
Scheijen and Griffin. *Oncogene*. 2002;21:3314.

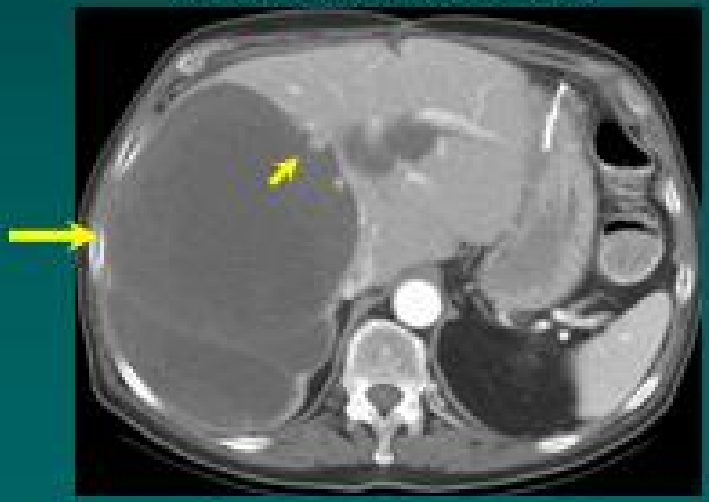
Response and Relapse



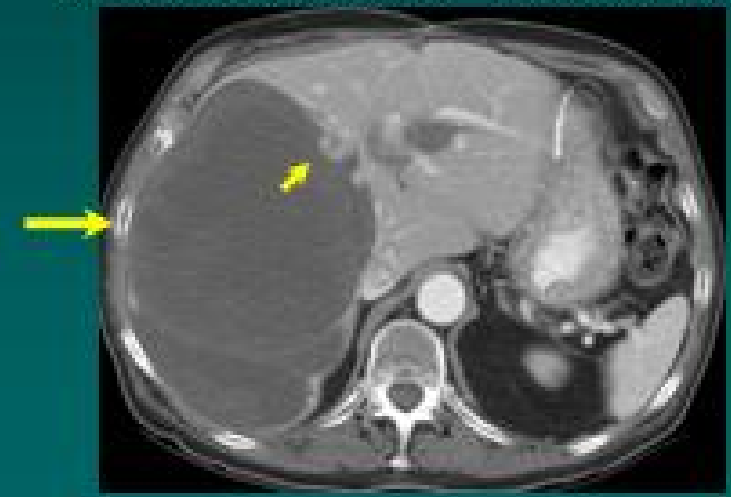
Pre-Treatment



2 Months Post-Treatment



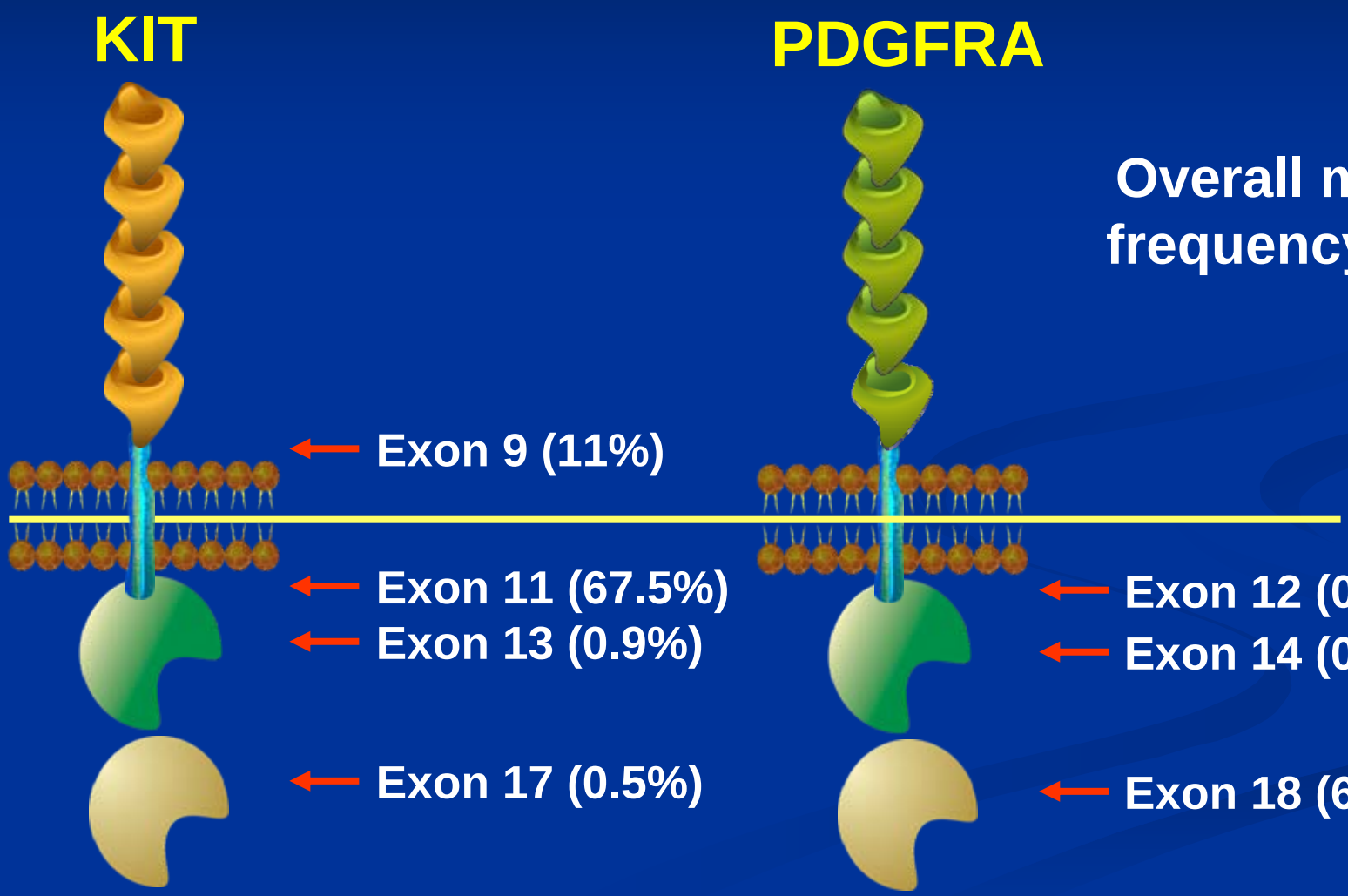
24 Months Post-Treatment



27 Months Post-Treatment

Choi et al. *AJR* 2004; 183:1619-1628

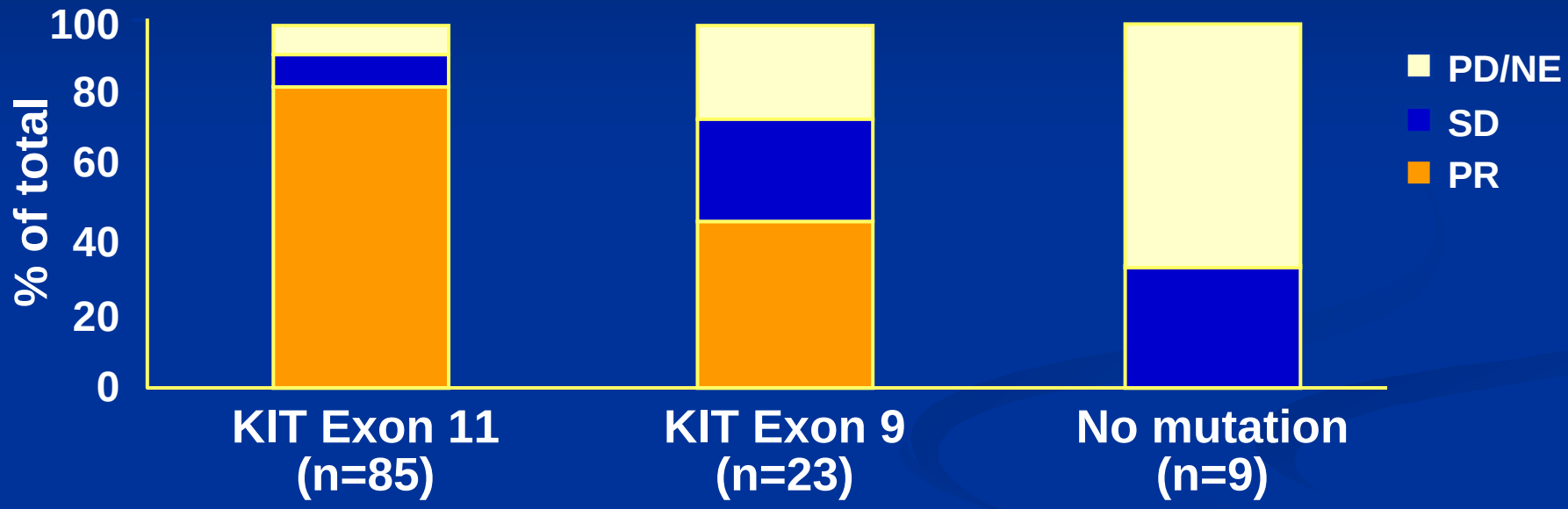
KIT and PDGFRA Mutations in GIST



Overall mutation frequency: 87.4%

Heinrich et al. *Hum Pathol.* 2002;33:484. Corless et al. *Proc Am Assoc Cancer Res.* 2003;44. Abstract R4447.

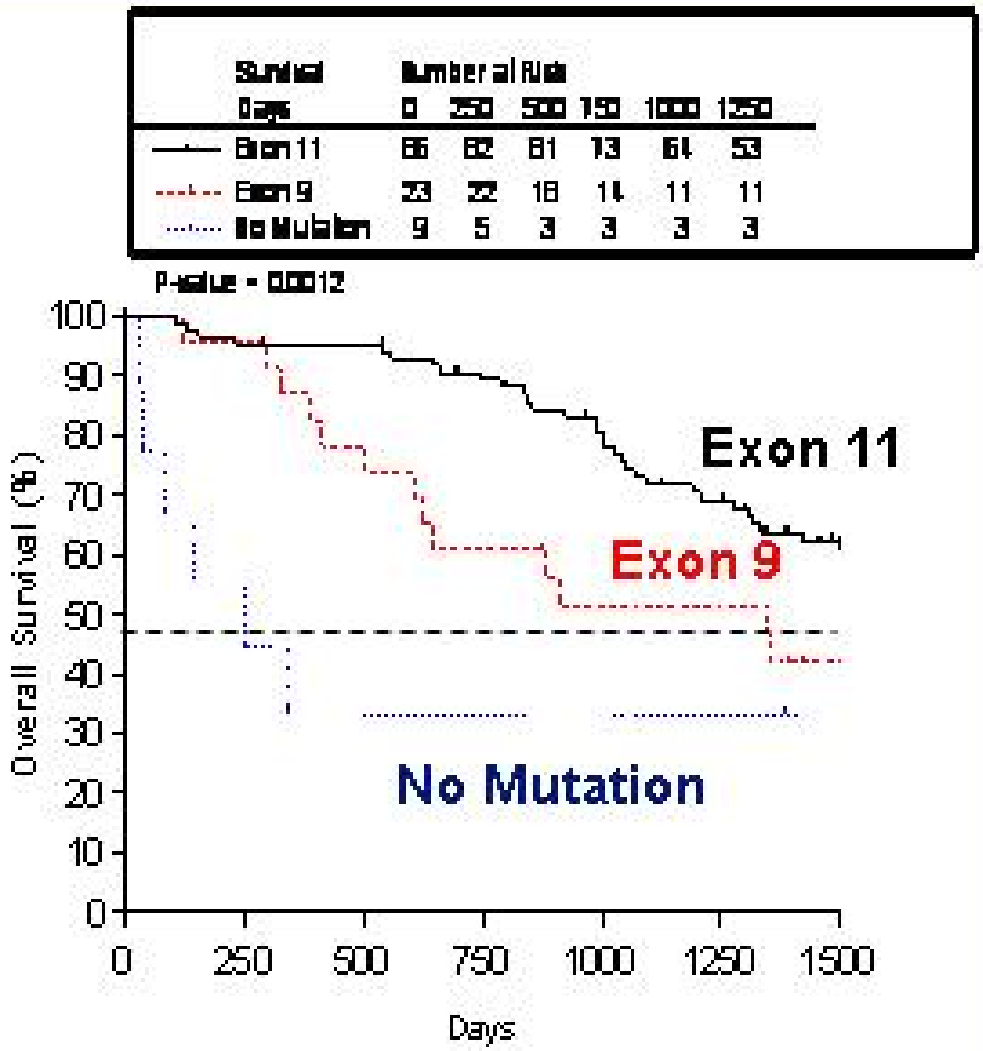
GIST: KIT Mutation Location Predicts Imatinib Mesylate Responsiveness



- KIT mutations are predictive of response to imatinib mesylate
- Exon 11 mutants respond best

Blanke et al. ASCO 2004 Gastrointestinal Cancers Symposium. Abstract 2.

Imatinib: Overall Survival by Genotype



Genotype	Median survival
Exon 11	Not reached
Exon 9	1347 days (192 wks)
No mutation	250 days (36 wks)

Blanke CD, et al. *Proc Am Soc Clin Oncol* 2006. Abstract 9528. In press