RỐI LOẠN THỤ THỂ TYROSINE KINASE TRONG CÁC BỆNH UNG THƯ

TS.BS. HOÀNG ANH VŨ

Đại học Y Dược Thành phố Hồ Chí Minh

hoangvuxinh@yahoo.com

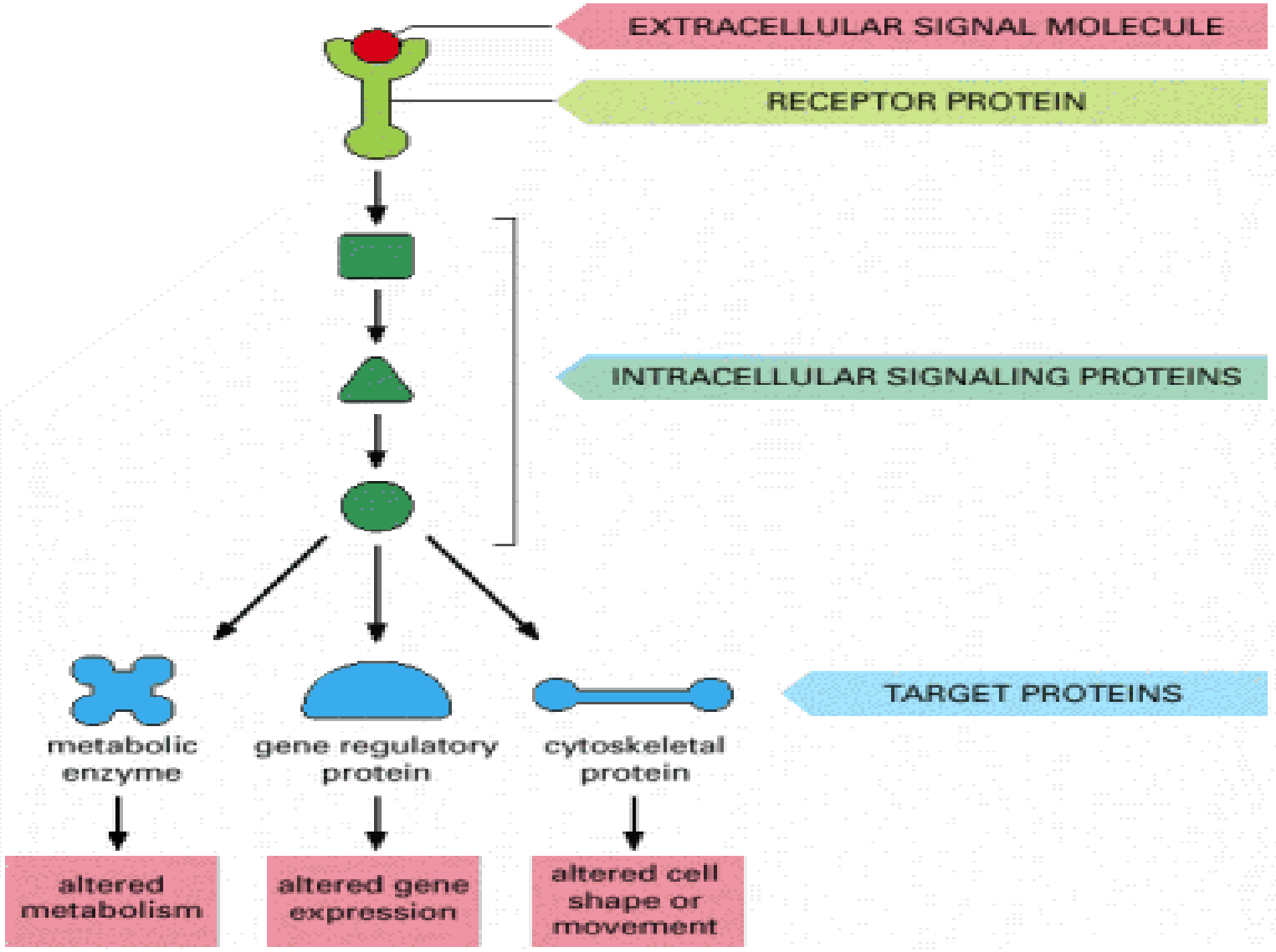
Nội dung:

1. **TỔNG QUÁT**
2. ***FLT3* TRONG UNG THƯ MÁU**
3. ***EGFR* TRONG UNG THƯ PHỔI VÀ UNG THƯ ĐẠI TRỰC TRÀNG**
4. ***HER-2/neu* TRONG UNG THƯ VÚ**
5. ***KIT* VÀ *PDGFRA* TRONG U MÔ ĐỆM ĐƯỜNG TIÊU HÓA**

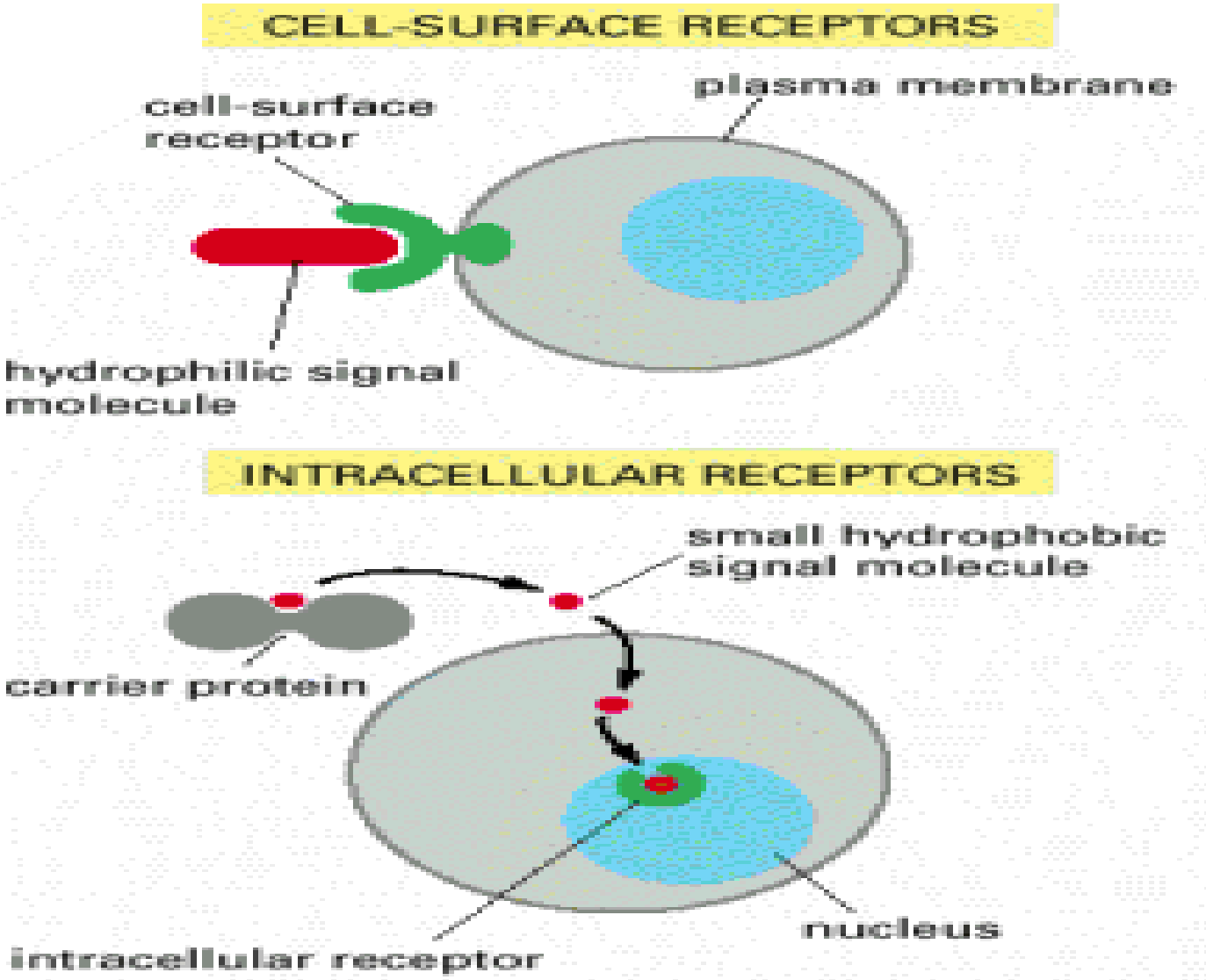
Nội dung:

1. **TỔNG QUÁT**
2. ***FLT3*** **TRONG UNG THƯ MÁU**
3. ***EGFR*** **TRONG UNG THƯ PHỔI VÀ UNG THƯ ĐẠI TRỰC TRÀNG**
4. ***HER-2/neu*** **TRONG UNG THƯ VÚ**
5. ***KIT*** **VÀ** ***PDGFRA*** **TRONG U MÔ ĐỆM ĐƯỜNG TIÊU HÓA**

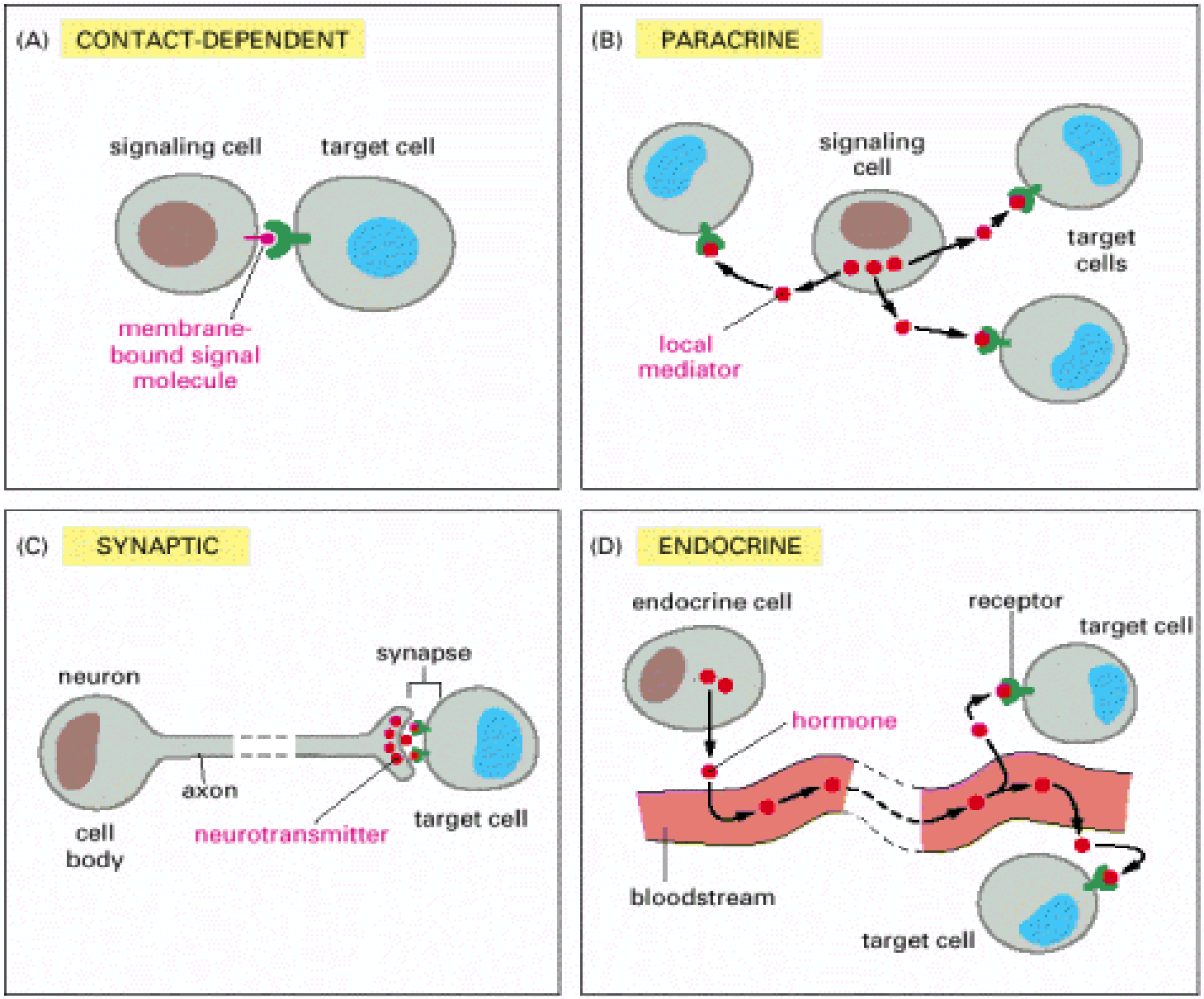
MÔ HÌNH ĐƠN GIẢN VỀ TRUYỀN TÍN HIỆU NỘI BÀO



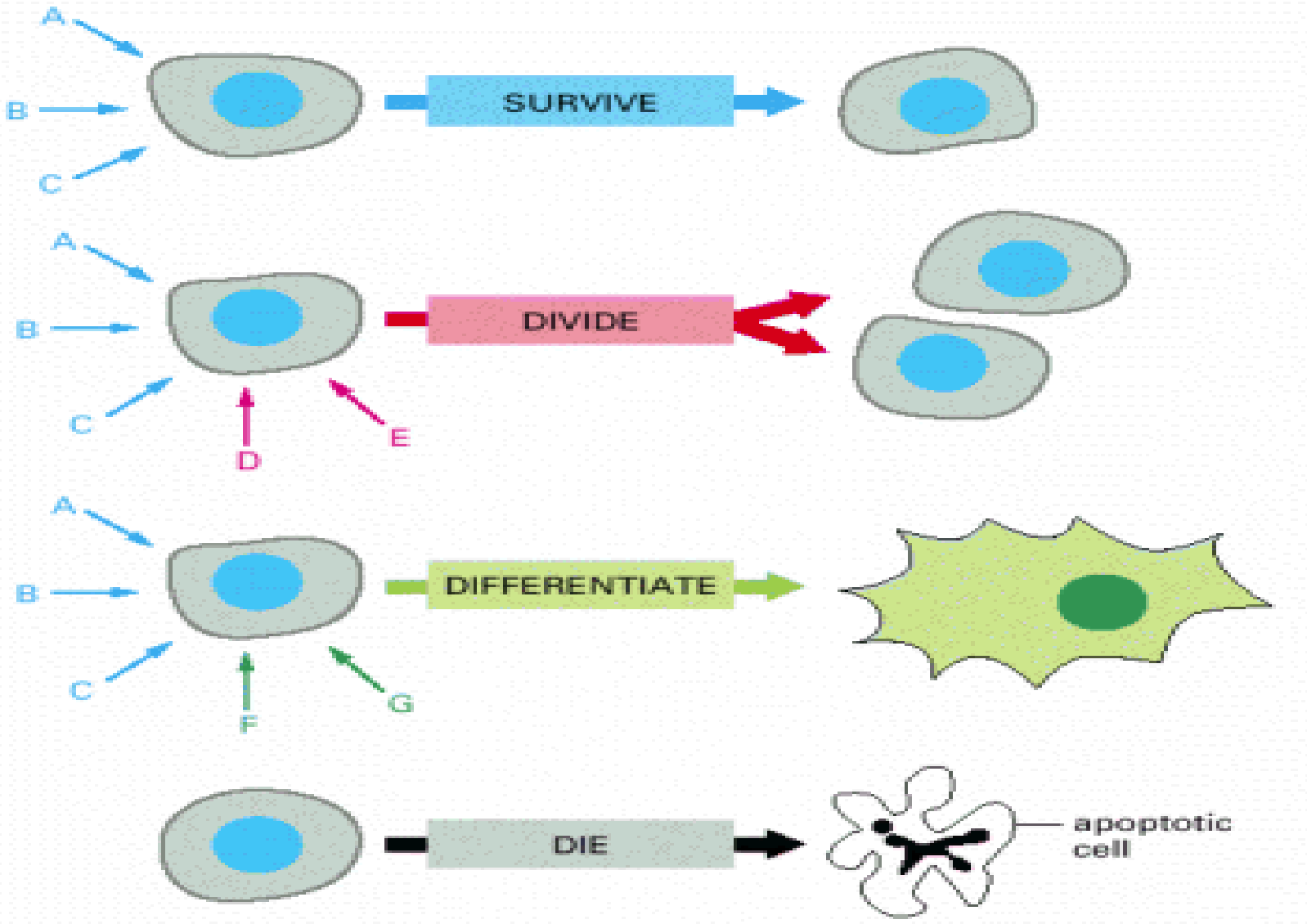
THỤ THỂ BỀ MẶT VÀ THỤ THỂ NỘI BÀO



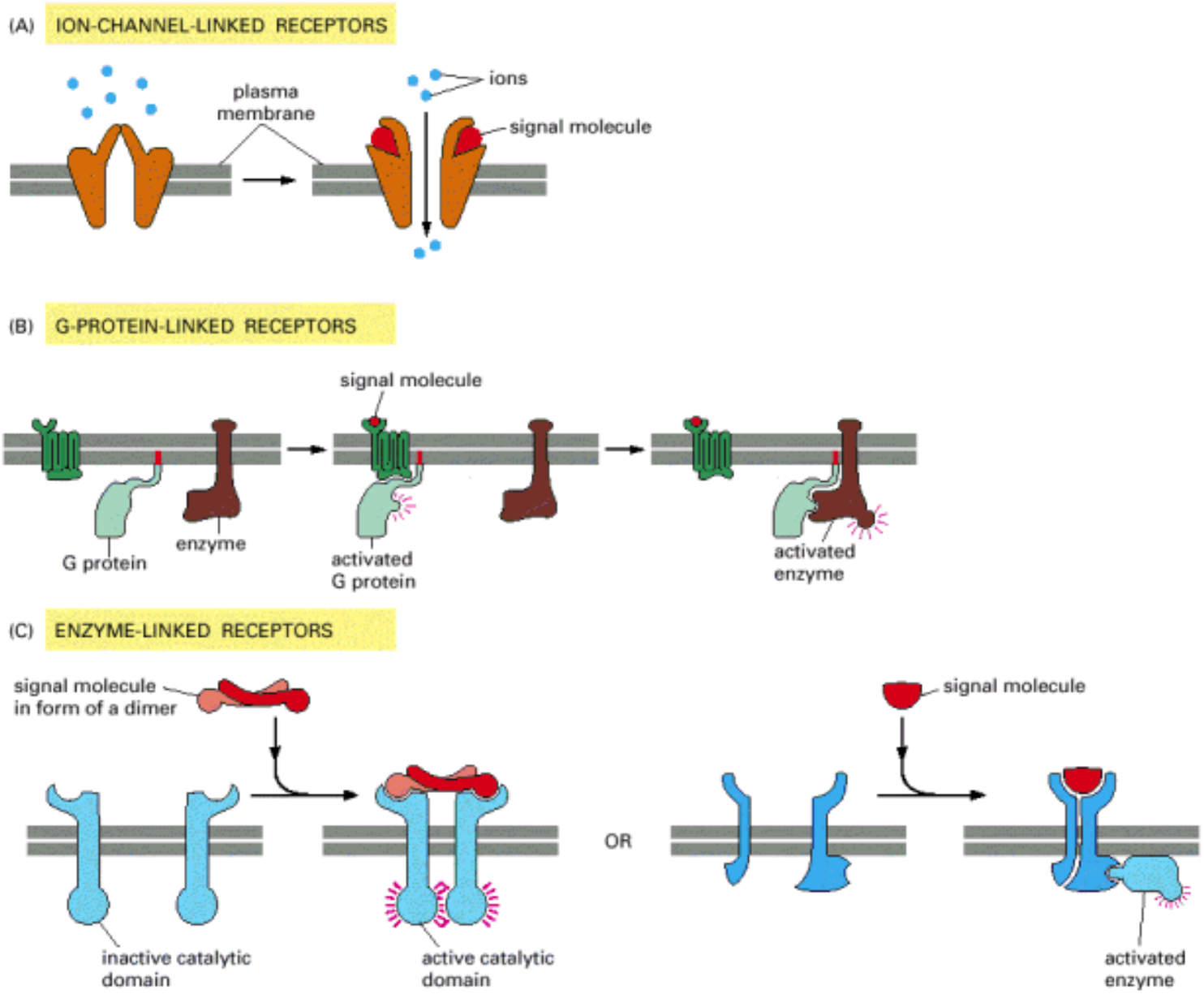
CÁC KIỂU TƯƠNG TÁC GIỮA LIGAND VÀ THỤ THỂ



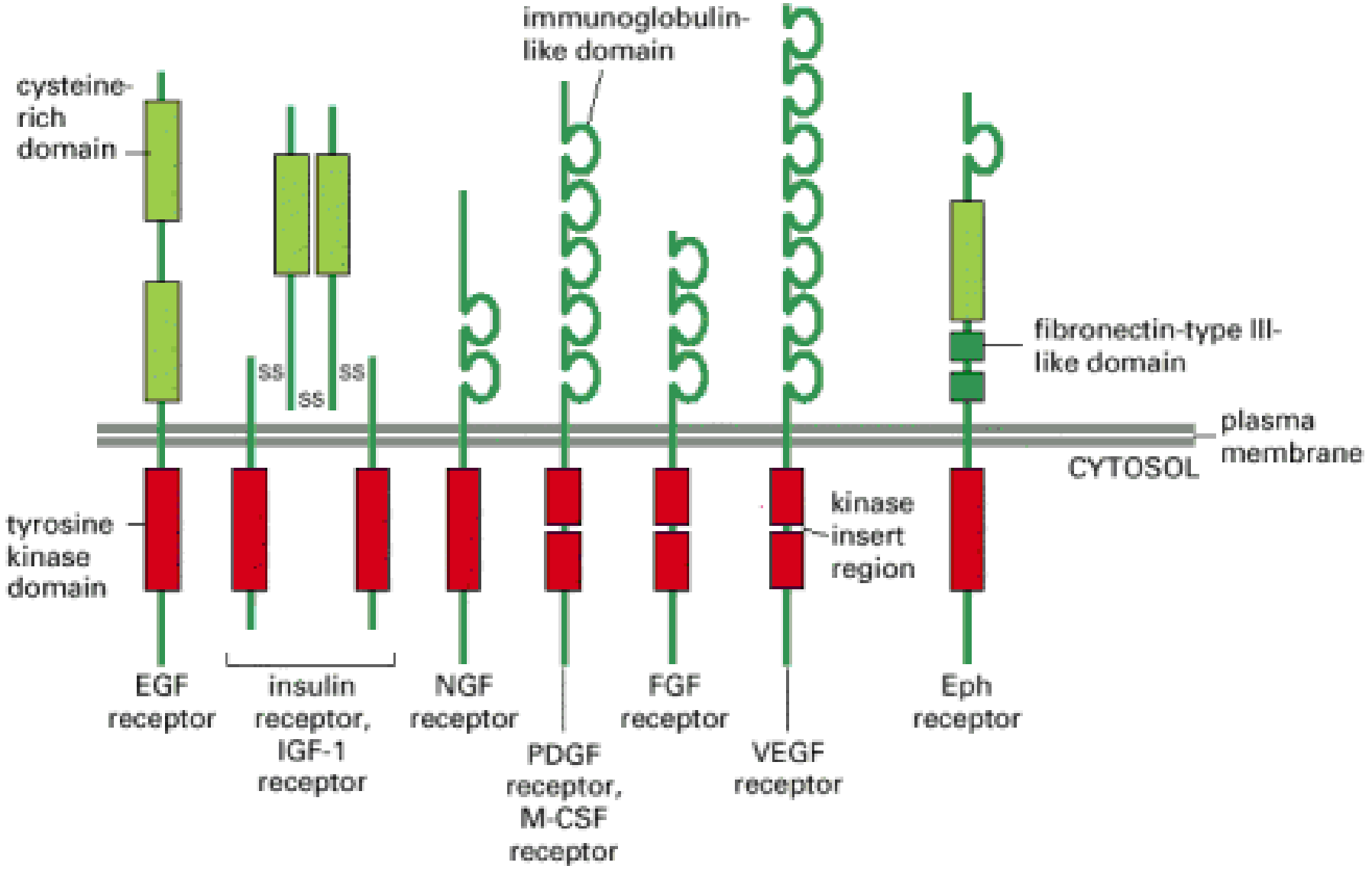
TẾ BÀO TỒN TẠI ĐƯỢC NHỜ TÍN HIỆU NGOẠI BÀO

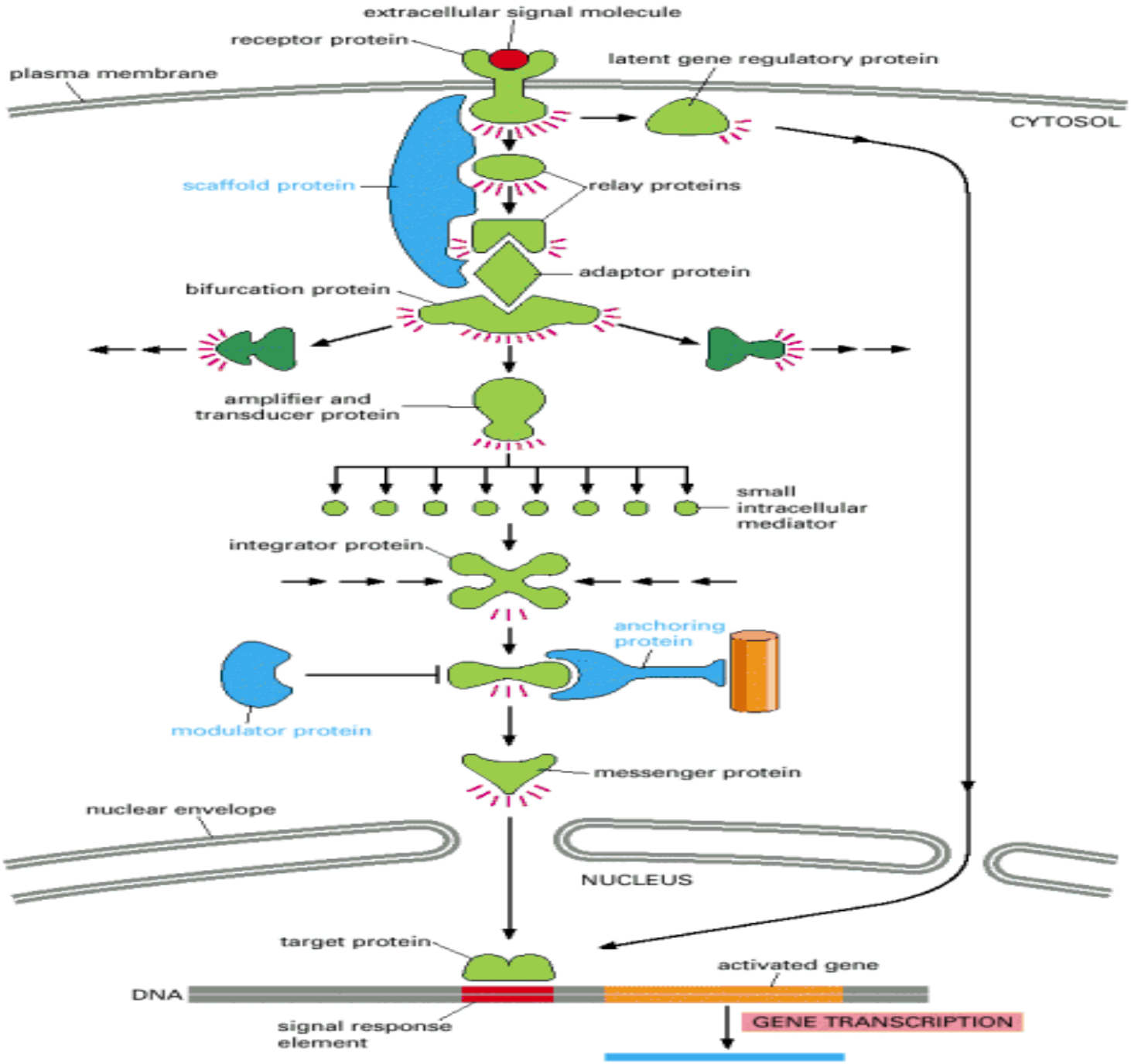


CÁC NHÓM THỤ THỂ BỀ MẶT



CÁC NHÓM THỤ THỂ TYROSINE KINASE



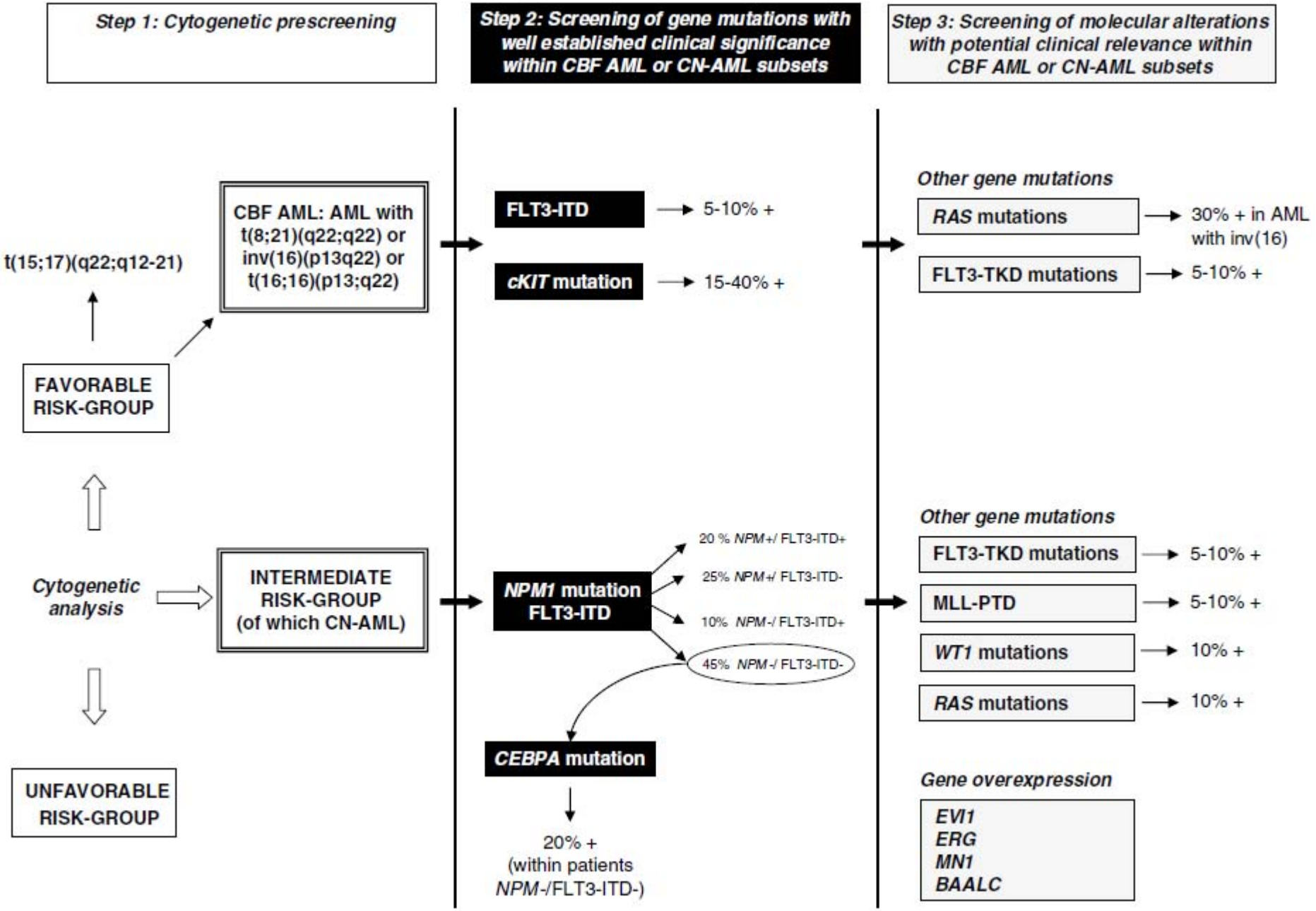

extracellular signal molecule
receptor protein
plasma membrane
latent gene regulatory protein
CYTOSOL
scaffold protein
relay proteins
adaptor protein
bifurcation protein
amplifier and
transducer protein
small
intracellular
mediator
integrator protein
anchoring
protein
modulator protein
messenger protein
nuclear envelope
NUCLEUS
target protein
activated gene
DNA
signal response
element
GENE TRANSCRIPTION

Nội dung:

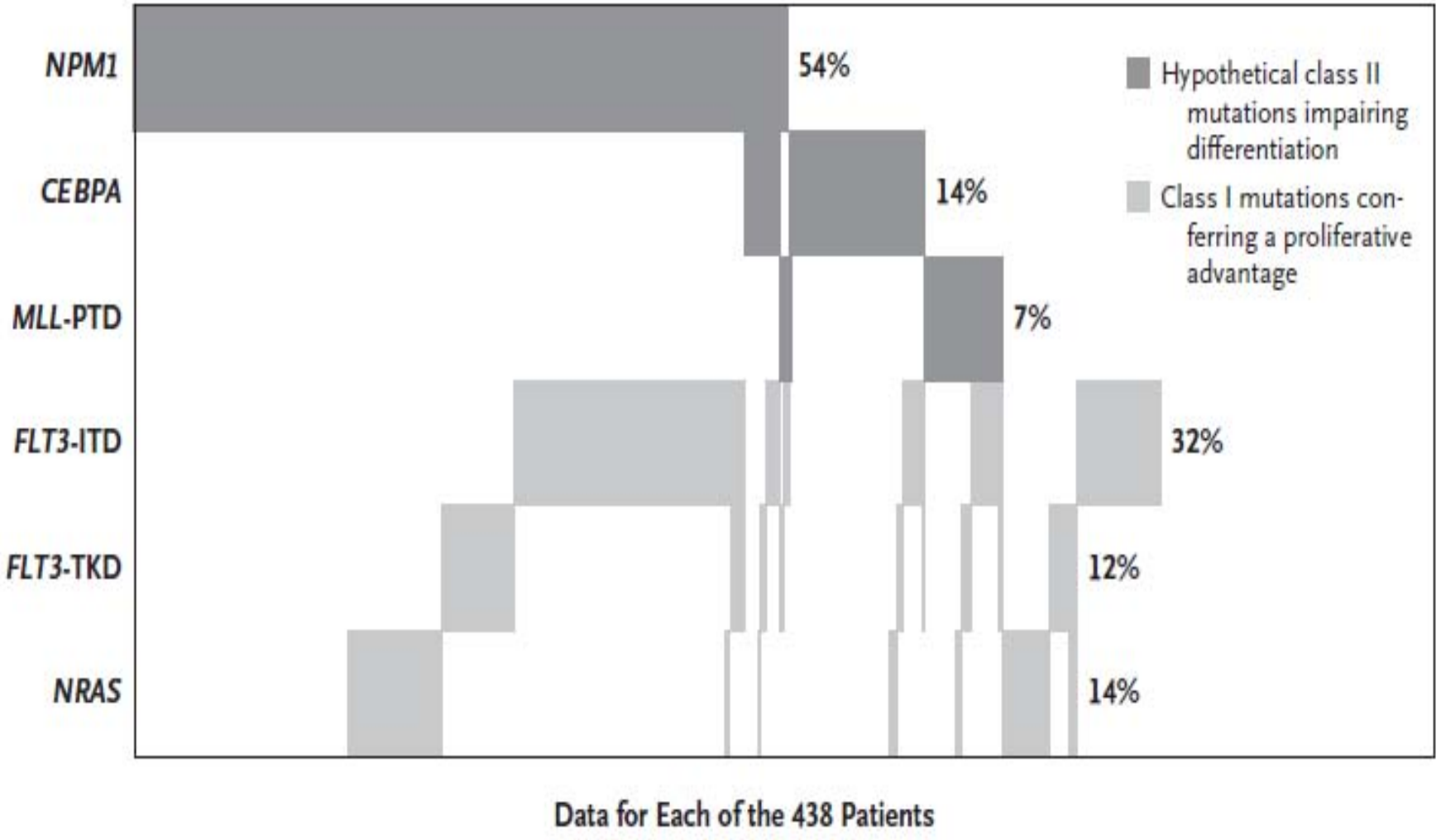
1. TỔNG QUÁT
2. ***FLT3*** **TRONG UNG THƯ MÁU**
3. ***EGFR*** TRONG UNG THƯ PHỔI VÀ UNG THƯ ĐẠI TRỰC TRÀNG
4. ***HER-2/neu*** TRONG UNG THƯ VÚ
5. ***KIT*** VÀ ***PDGFRA*** TRONG U MÔ ĐỆM ĐƯỜNG TIÊU HÓA

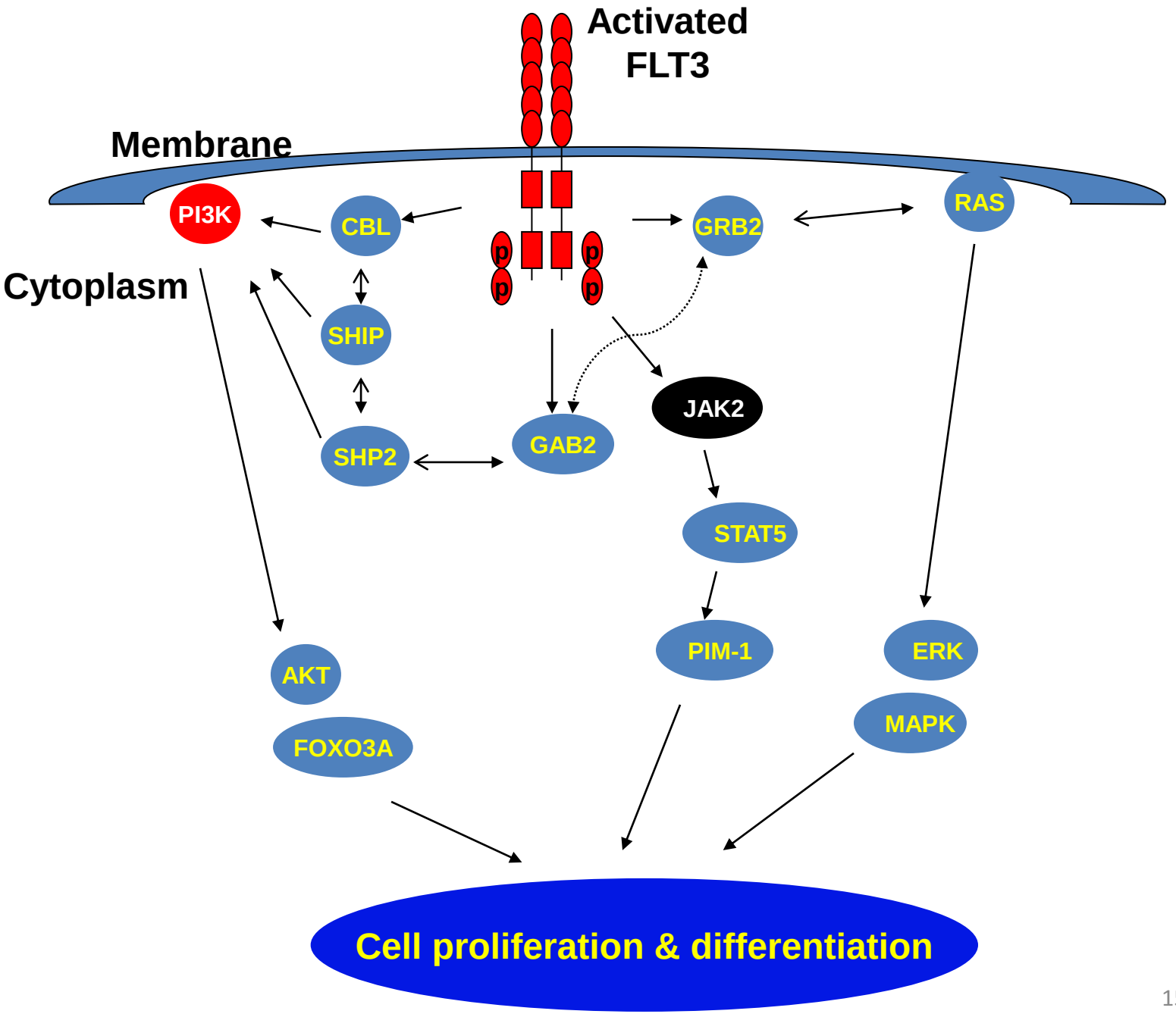
UNG THƯ MÁU DÒNG TỦY CẤP TÍNH

- Acute Myeloid Leukemia (AML): Là thể bệnh ung thư máu thường gặp nhất ở người lớn
- Rối loạn NST rất phổ biến, có ý nghĩa tiên lượng
- 30 – 40% có đột biến gen *FLT3*

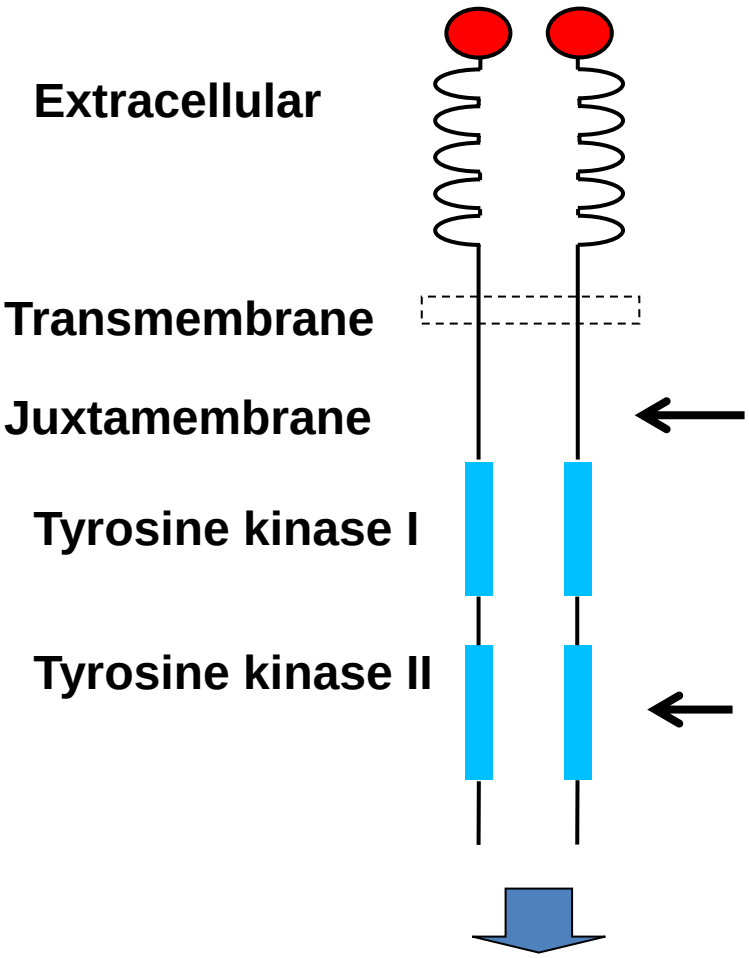

Step 1: Cytogenetic prescreening
Step 2: Screening of gene mutations with well established clinical significance within CBF AML or CN-AML subsets
Step 3: Screening of molecular alterations with potential clinical relevance within CBF AML or CN-AML subsets
t(15;17)(q22;q12-21)
CBF AML: AML with t(8;21)(q22;q22) or inv(16)(p13q22) or t(16;16)(p13;q22)
FAVORABLE RISK-GROUP
Cytogenetic analysis
INTERMEDIATE RISK-GROUP (of which CN-AML)
UNFAVORABLE RISK-GROUP
FLT3-ITD
5-10% +
cKIT mutation
15-40% +
NPM1 mutation FLT3-ITD
20 % NPM+/ FLT3-ITD+
25% NPM+/ FLT3-ITD-
10% NPM-/ FLT3-ITD+
45% NPM-/ FLT3-ITD-
CEBPA mutation
20% + (within patients NPM-/FLT3-ITD-)
Other gene mutations
RAS mutations
30% + in AML with inv(16)
FLT3-TKD mutations
5-10% +
Other gene mutations
FLT3-TKD mutations
5-10% +
MLL-PTD
5-10% +
WT1 mutations
10% +
RAS mutations
10% +
Gene overexpression
EVI1
ERG
MN1
BAALC

ĐỘT BIẾN GEN THƯỜNG GẶP TRONG UNG THƯ MÁU




Activated
FLT3
Membrane
Cytoplasm
PI3K
CBL
GRB2
RAS
p
p
p
p
SHIP
JAK2
SHP2
GAB2
STAT5
PIM-1
ERK
AKT
MAPK
FOXO3A
Cell proliferation & differentiation

ĐỘT BIẾN *FLT3* TRONG UNG THƯ MÁU



	Frequency		
	AML	ALL	MDS
1. Insertion (ITD)	15-35%	rare	5-10%
2. Point mutations			
3. Point mutations	5-10%	1-3%	2-5%

Cell proliferation and differentiation

FLT3 is target for selective inhibition

Divergent cytotoxic effects of PKC412 in combination with conventional antileukemic agents in FLT3 mutation-positive versus -negative leukemia cell lines

Y Furukawa[1], HA Vu[2], M Akutsu[3], T Odgerel[1], T Izumi[3], S Tsunoda[3], Y Matsuo[4], K Kirito[5], Y Sato[2], H Mano[6] and Y Kano[3]

Leukemia (2007) 21, 1005–1014

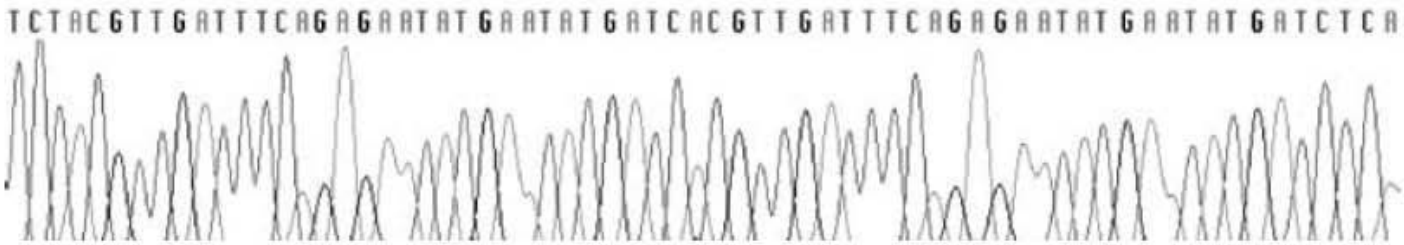
a

MOLM13/14

Wild-type sequence	AT	TTC	AGA	GAA	TAT	GAA	TAT	GAT	CTC	AAA	TGG	GAG	TTT	CCA	AGA	GAA	AAT	TTA
		594	595	596	597	598	599	600	601	602	603	604	605	606	607	608	609	610
		Phe	Arg	Glu	Tyr	Glu	Tyr	Asp	Leu	Lys	Trp	Glu	Phe	Pro	Arg	Glu	Asn	Leu
Internal duplication and point mutaton	AT	TTC	AGA	GAA	TAT	GAA	TTT	GAT	TTC	AGA	GAA	TAT	GAA	TAT	GAT	CTC	AAA	TGG
		Phe	Arg	Glu	Tyr	Glu	Phe	Asp	Phe	Arg	Glu	Tyr	Glu	Tyr	Asp	Leu	Lys	Trp

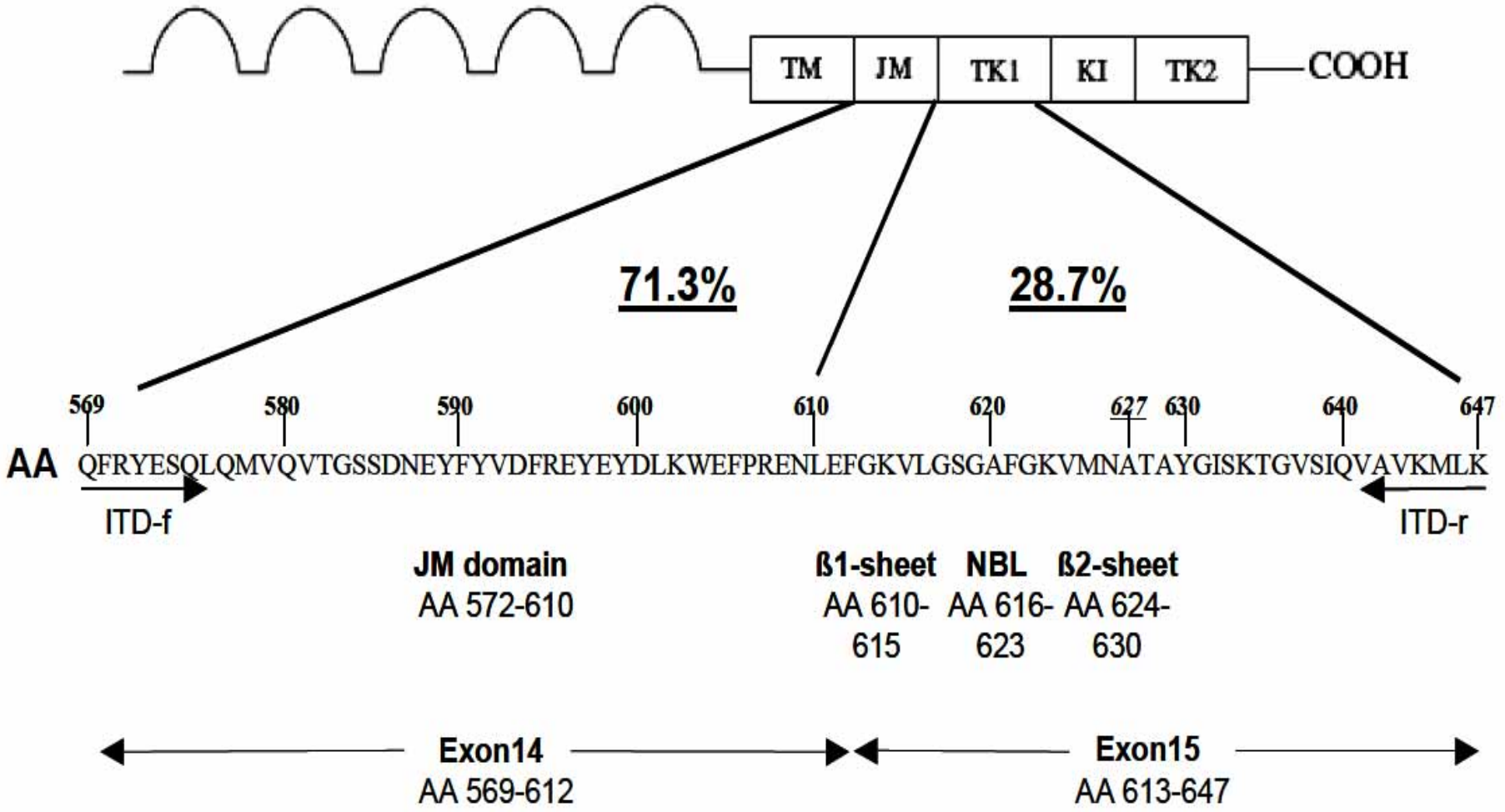
b

MV4-11



Internal duplication sequence	TC	TAC	GTT	GAT	TTC	AGA	GAA	TAT	GAA	TAT	GAT	CAC	GTT	GAT	TTC	AGA	GAA	TAT	GAA	TAT	GAT	CTC	A
	TC	591	592	593	594	595	596	597	598	599	600	#	592	593	594	595	596	597	598	599	600	601	
	TC	Tyr	Val	Asp	Phe	Arg	Glu	Tyr	Glu	Tyr	Asp	His	Val	Asp	Phe	Arg	Glu	Tyr	Glu	Tyr	Asp	Leu	

INTERNAL TANDEM DUPLICATION (ITD)

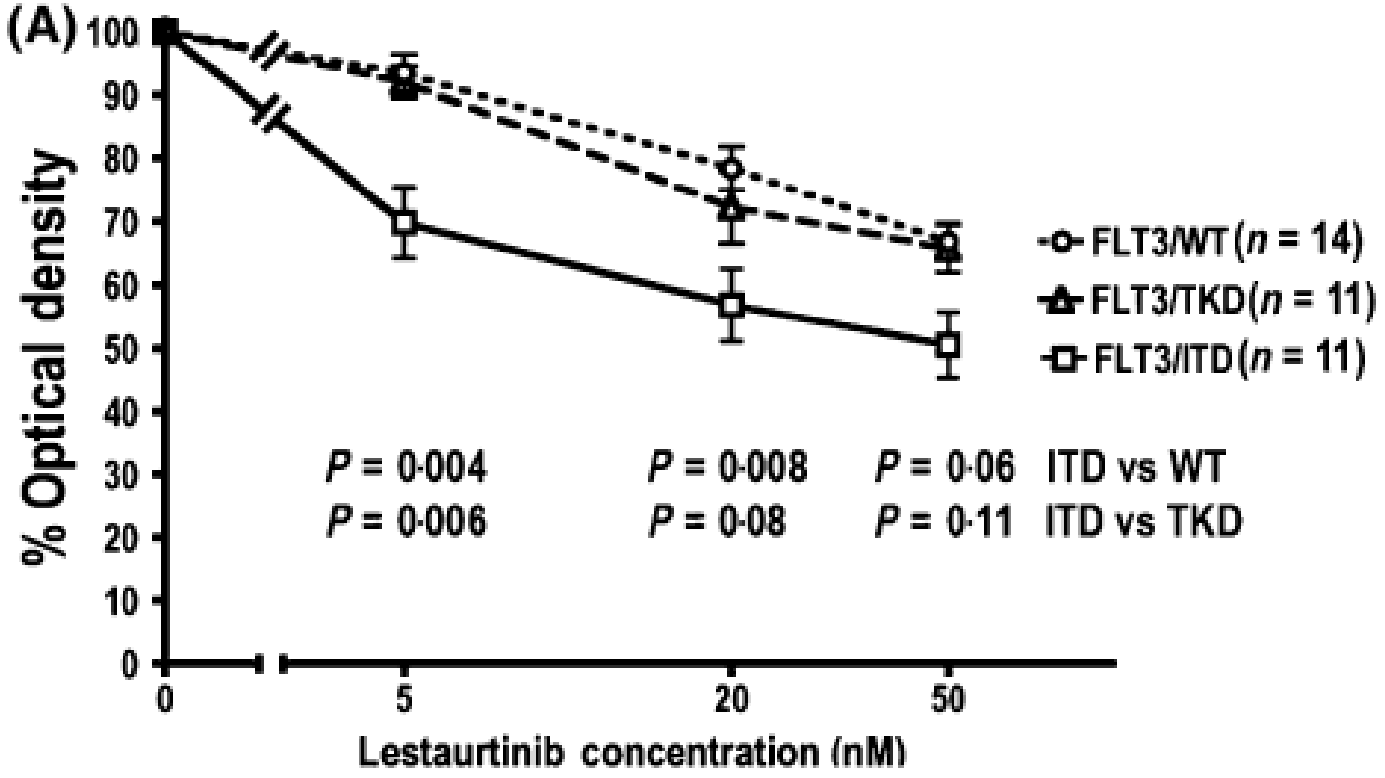


(Breitenbuecher F, *Blood* 2008;113:4074-7)

Acute myeloid leukaemia blast cells with a tyrosine kinase domain mutation of FLT3 are less sensitive to lestaurtinib than those with a FLT3 internal tandem duplication

Adam J. Mead, Rosemary E. Gale, Panagiotis D. Kottaridis, Satomi Matsuda, Asim Khwaja and David C. Linch

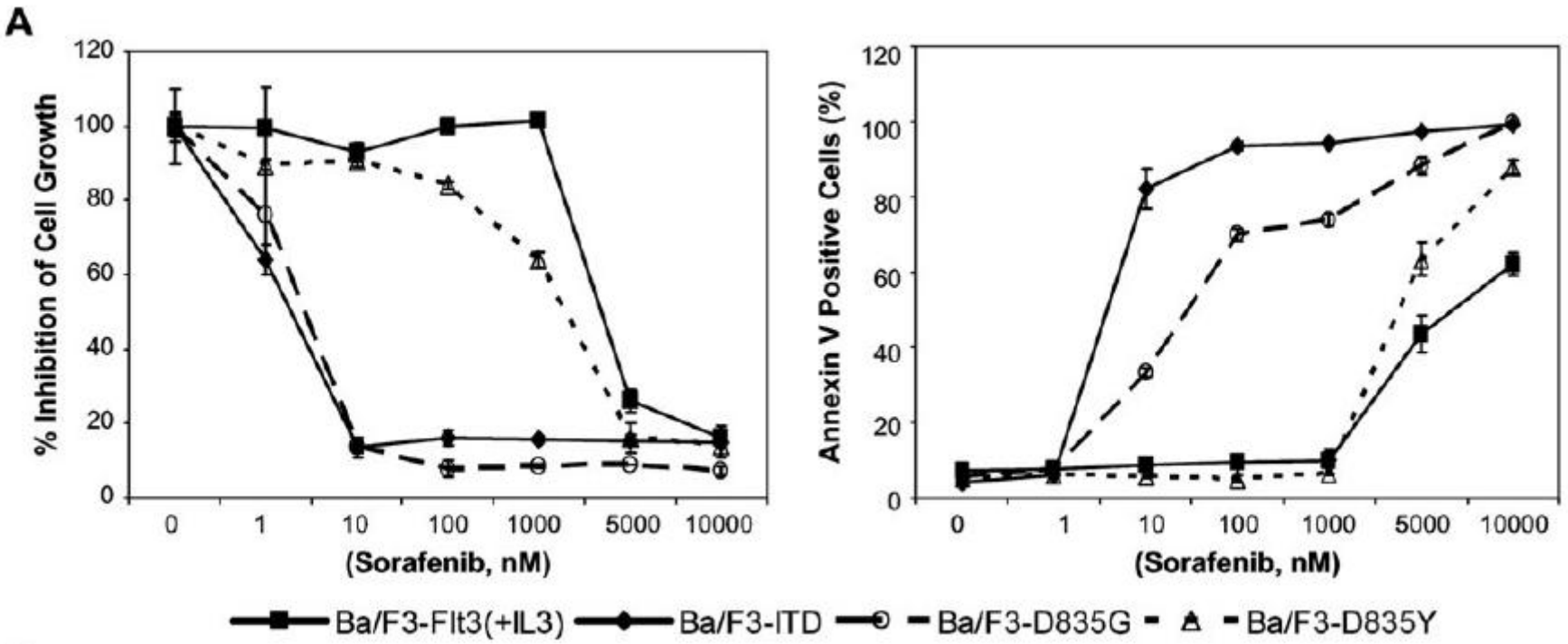
British Journal of Haematology, **141**, 454–460



Mutant FLT3: A Direct Target of Sorafenib in Acute Myelogenous Leukemia

Weiguo Zhang, Marina Konopleva, Yue-xi Shi, Teresa McQueen, David Harris, Xiaoyang Ling, Zeev Estrov, Alfonso Quintás-Cardama, Donald Small, Jorge Cortes, Michael Andreeff

J Natl Cancer Inst 2008;100:184–198

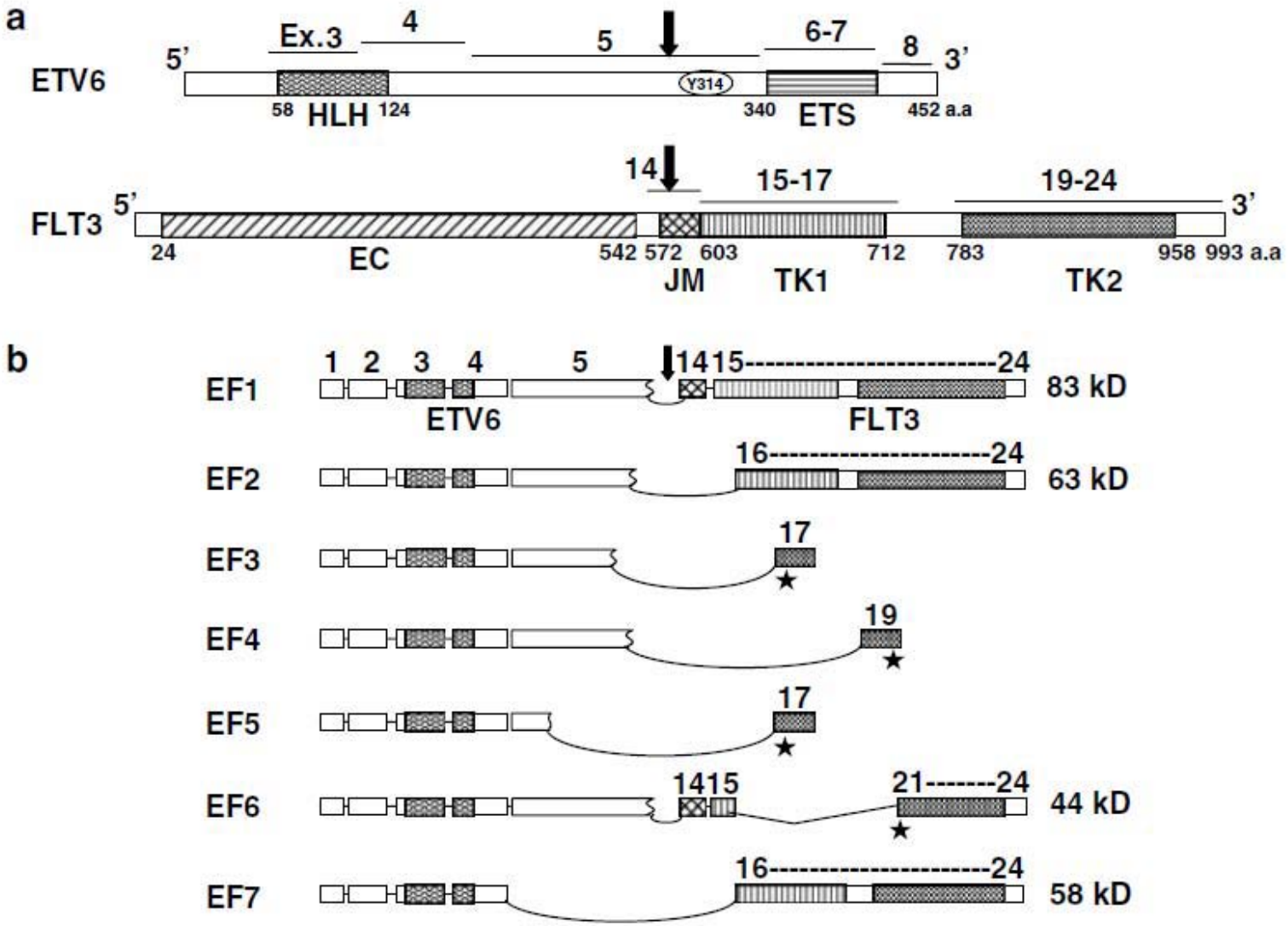


(D: Aspartic acid, G:Glycine, Y: Tyrosine)

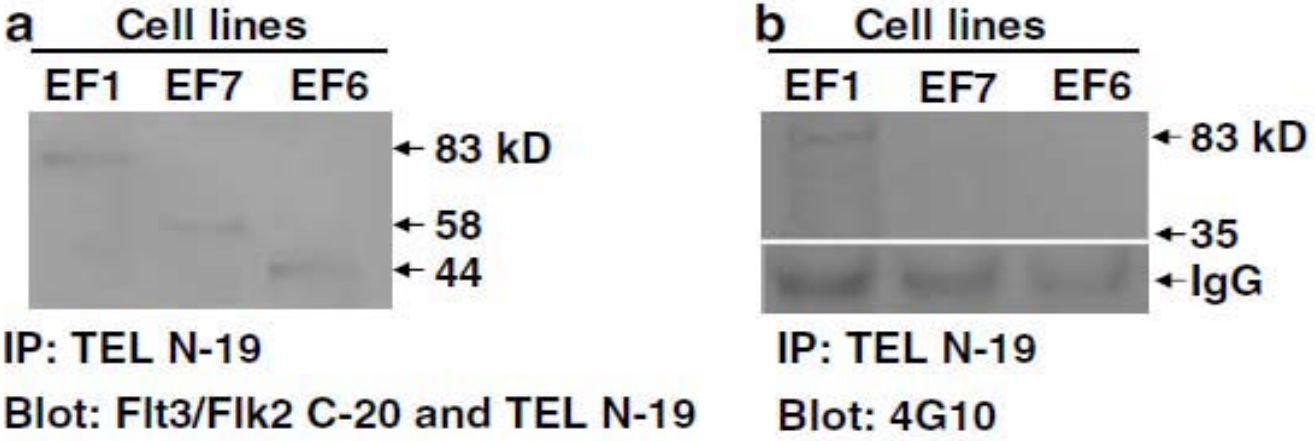
FLT3 is fused to *ETV6* in a myeloproliferative disorder with hypereosinophilia and a t(12;13)(p13;q12) translocation

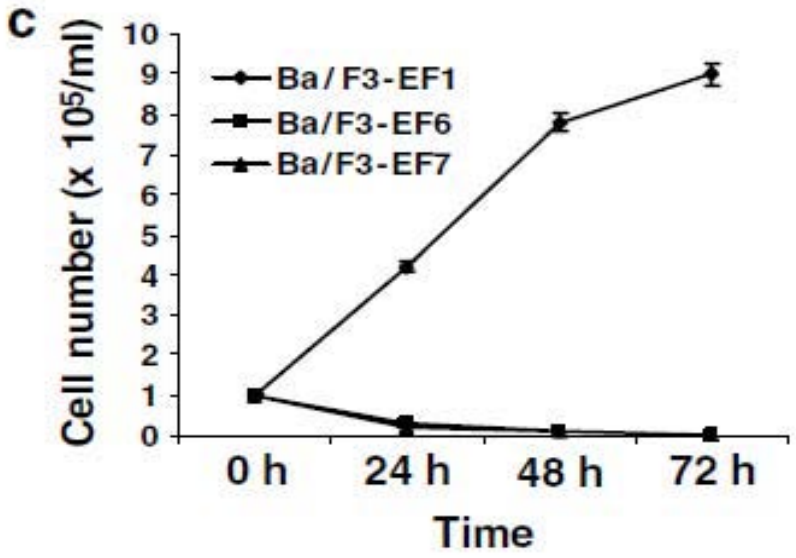
HA Vu[1,2], PT Xinh[1,2], M Masuda[3], T Motoji[3], A Toyoda[4], Y Sakaki[4], K Tokunaga[2] and Y Sato[1]

Leukemia (2006) 20, 1414–1421



ETV6/FLT3 GÂY CHUYỂN DẠNG TẾ BÀO

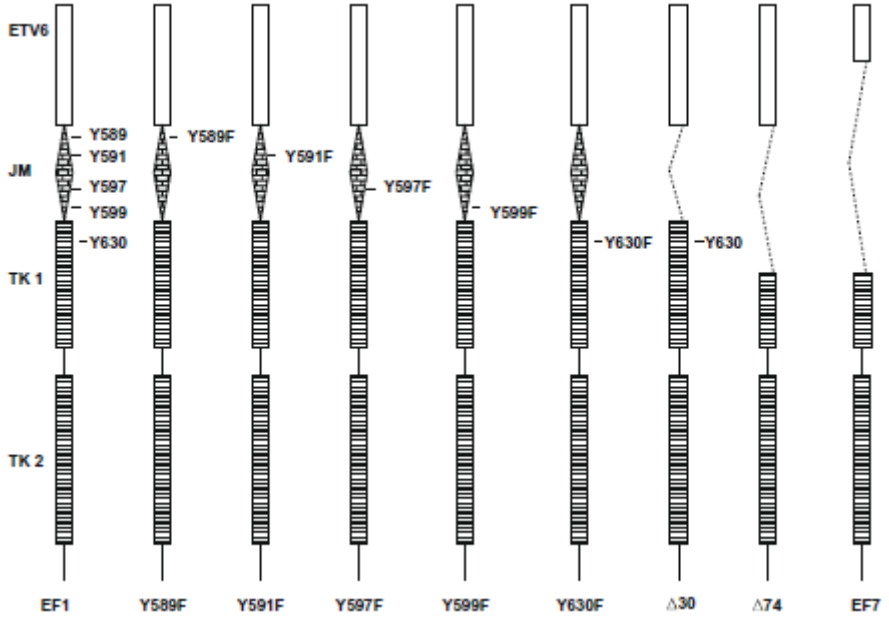


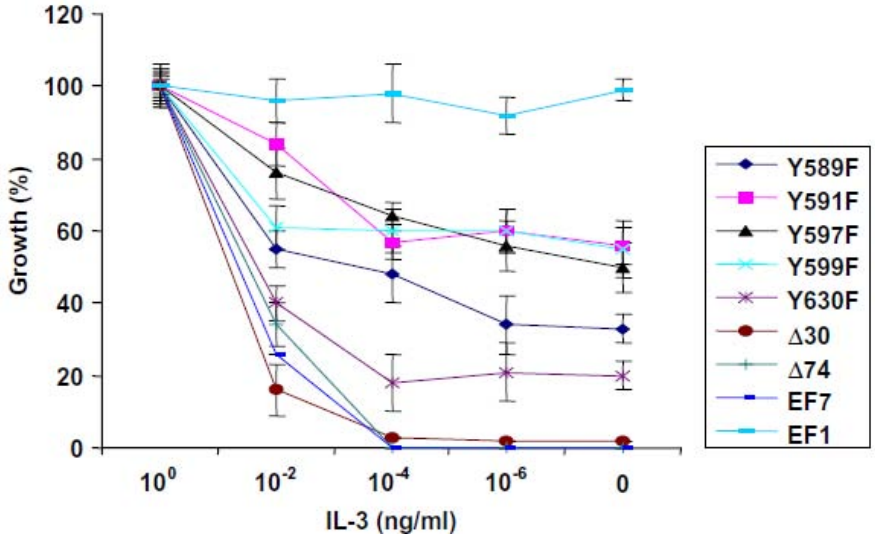


The juxtamembrane domain in ETV6/FLT3 is critical for PIM-1 up-regulation and cell proliferation

Hoang Anh Vu [a,b], Phan Thi Xinh [b], Yasuhiko Kano [d], Katsushi Tokunaga [c], Yuko Sato [b,*]

Biochemical and Biophysical Research Communications 383 (2009) 308–313

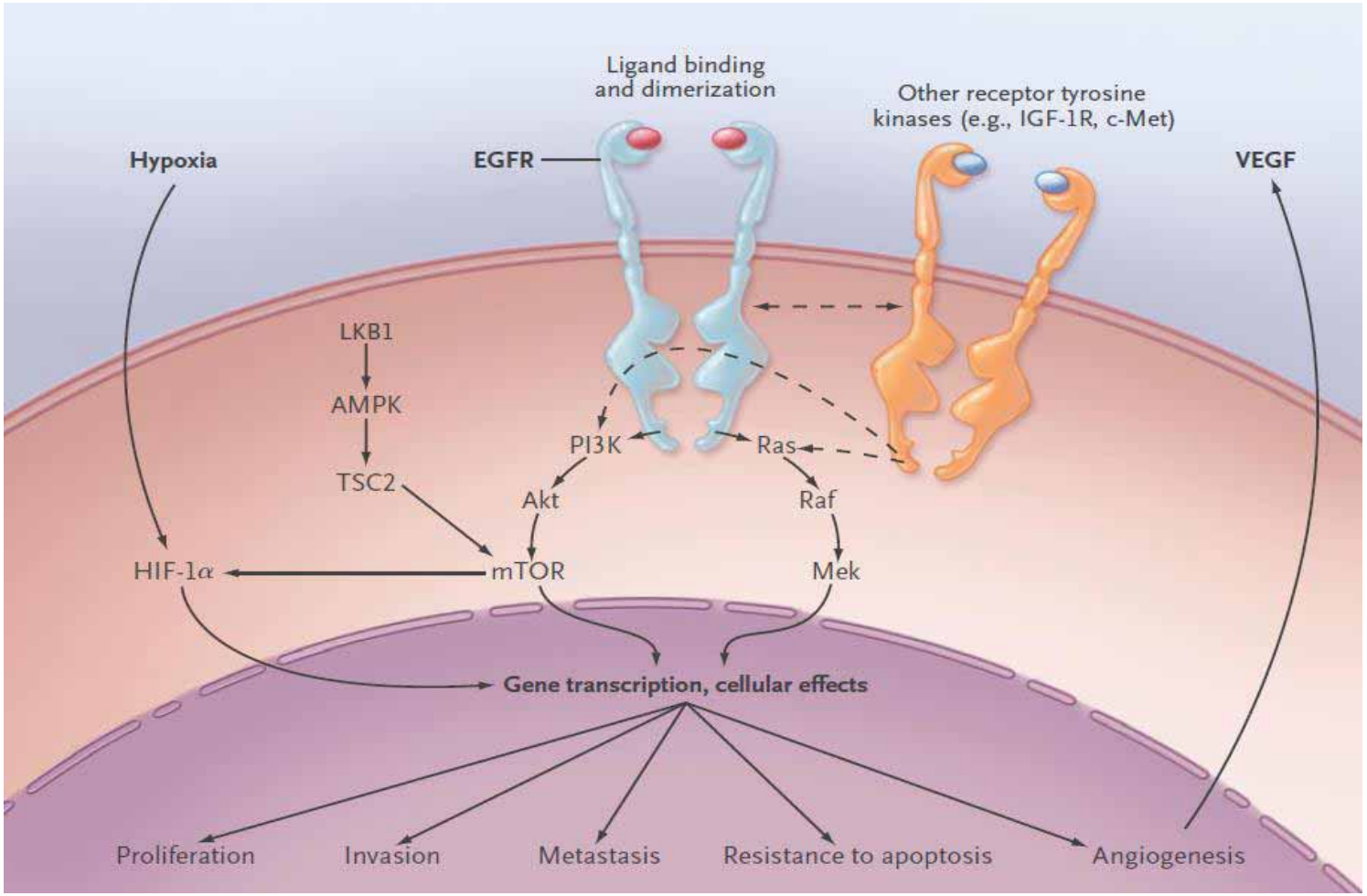




Nội dung:

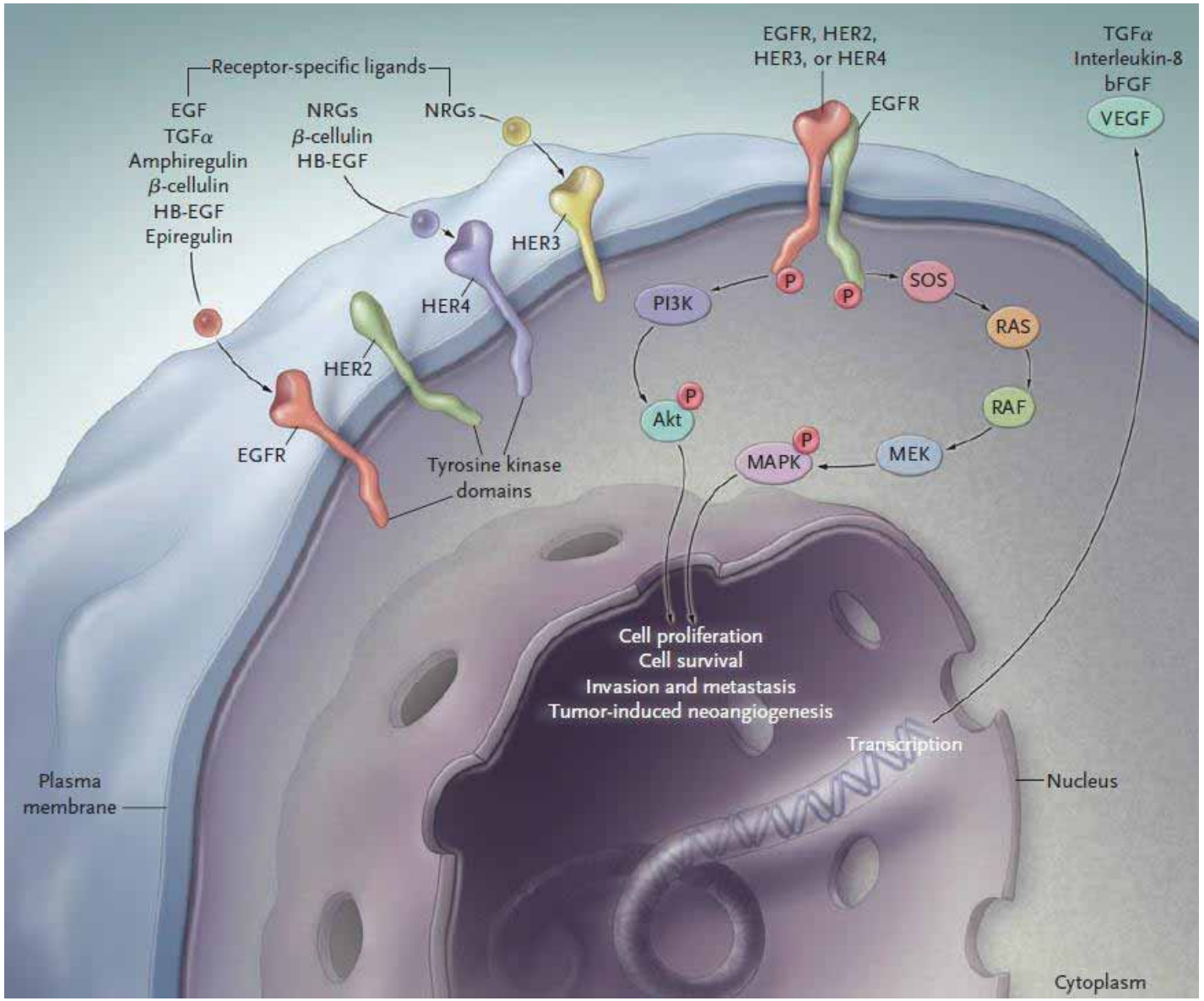
1. TỔNG QUÁT
2. *FLT3* TRONG UNG THƯ MÁU
3. ***EGFR*** **TRONG UNG THƯ PHỔI** VÀ UNG THƯ ĐẠI TRỰC TRÀNG
4. *HER-2/neu* TRONG UNG THƯ VÚ
5. *KIT* VÀ *PDGFRA* TRONG U MÔ ĐỆM ĐƯỜNG TIÊU HÓA

CƠ CHẾ HOẠT HÓA EGFR



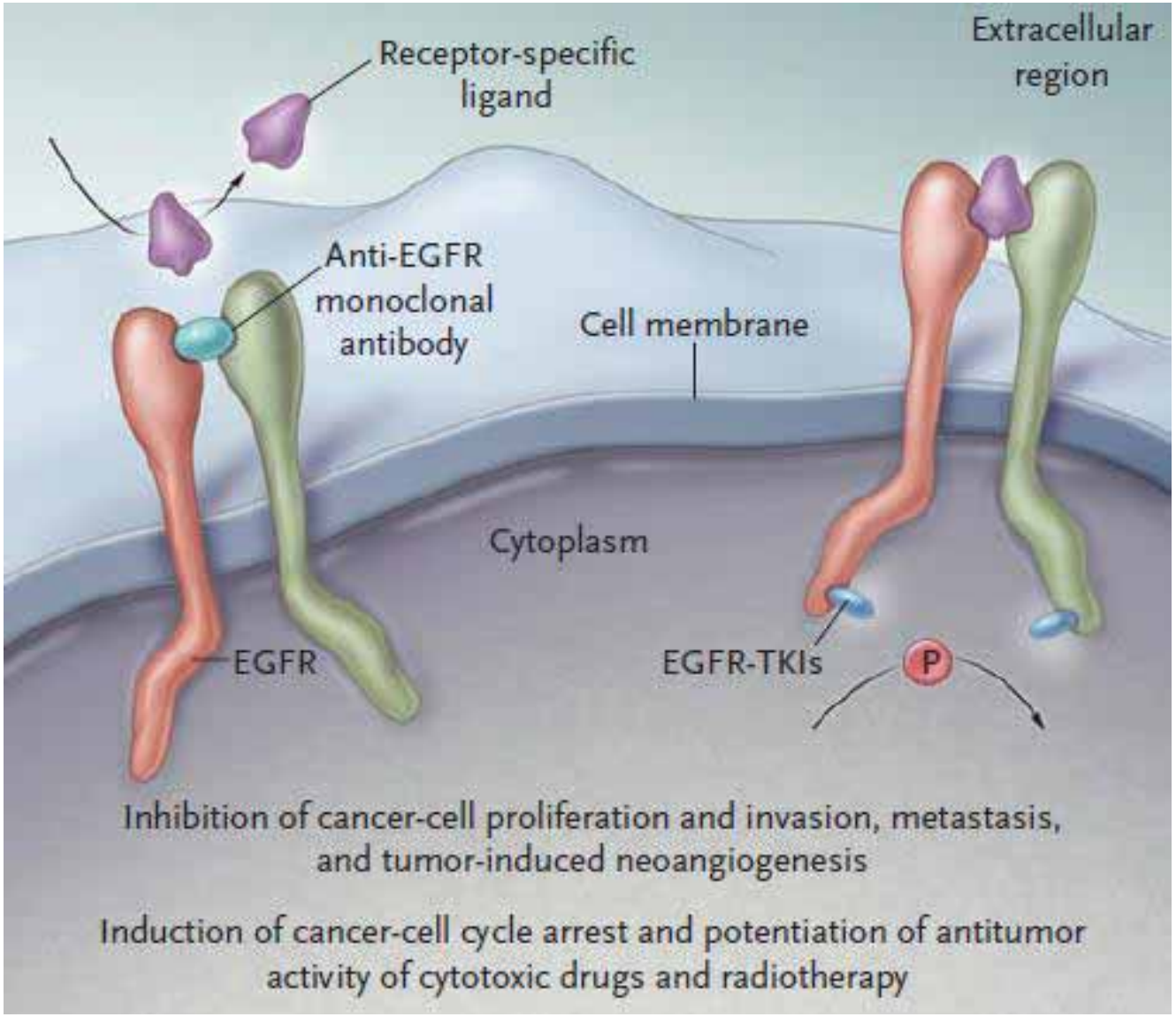
- **Epidermal Growth Factor Receptor**
- **NST số 7, 200 kb, 28 exon**
- **Receptor xuyên màng: tăng sinh và biệt hóa tế bào, di động, phát triển mô**

CÁC LOẠI THỤ THỂ HER



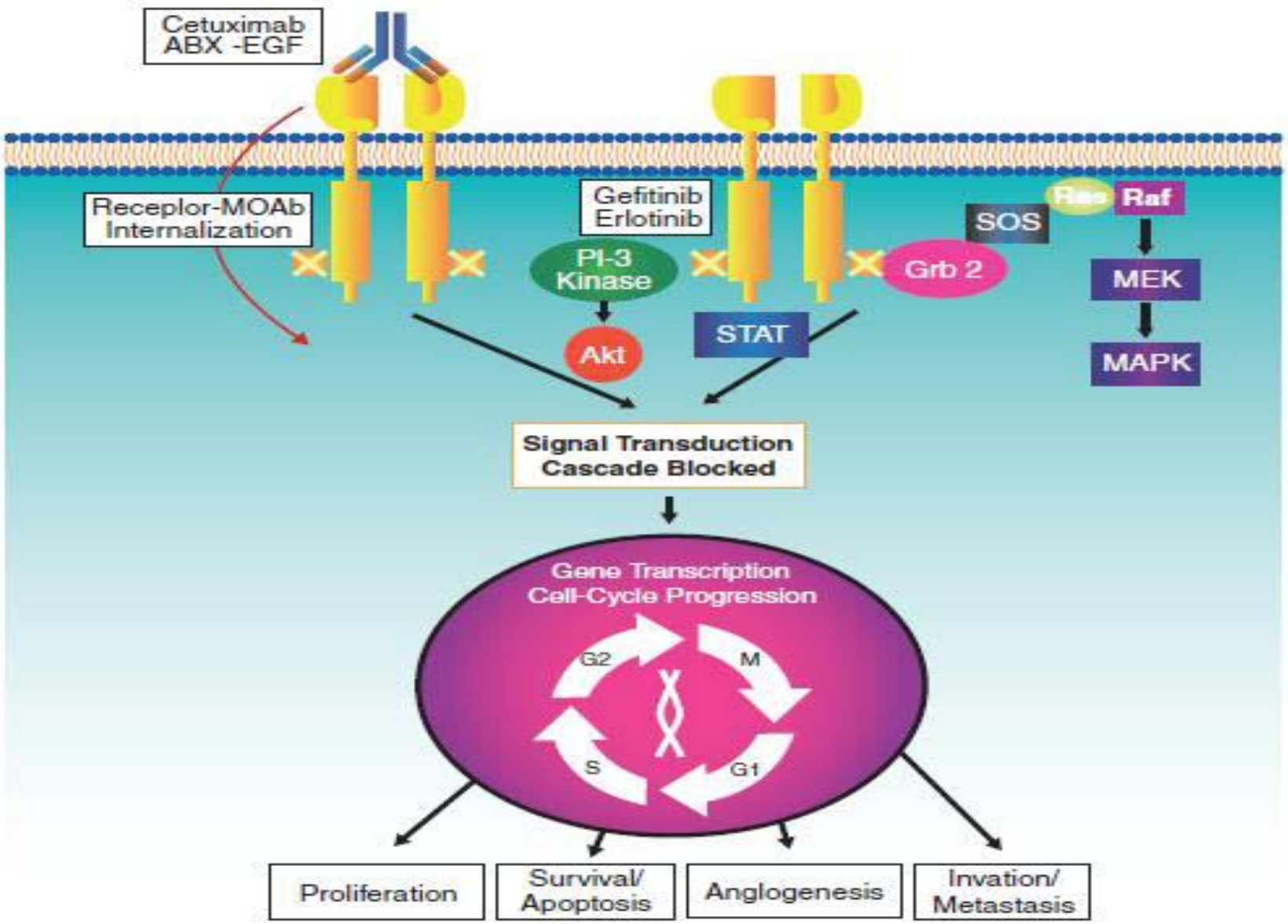
(Ciardiello F, N Engl J Med 2008;358:1160-74)

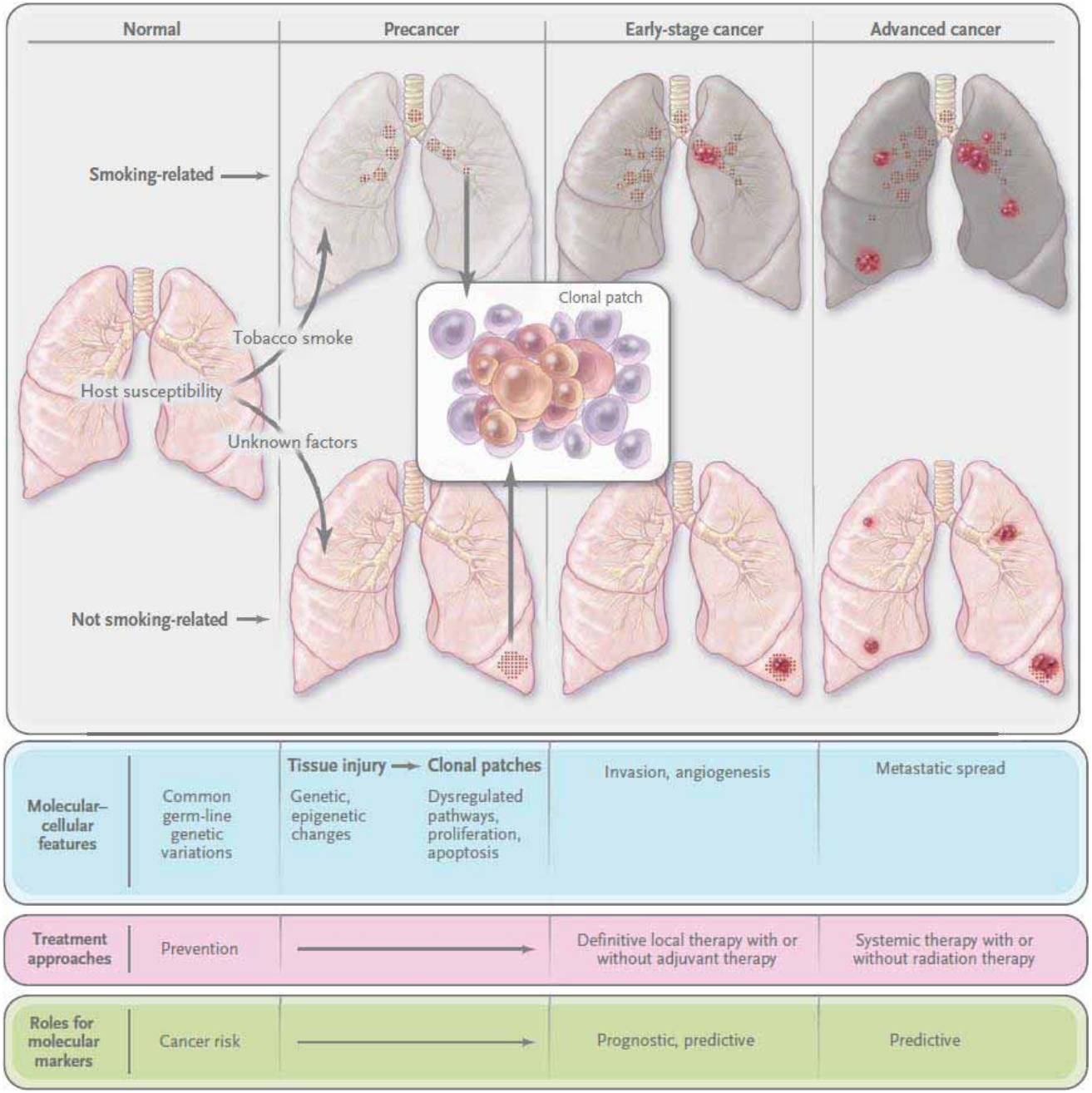
ỨC CHẾ HOẠT TÍNH EGFR BẰNG THUỐC



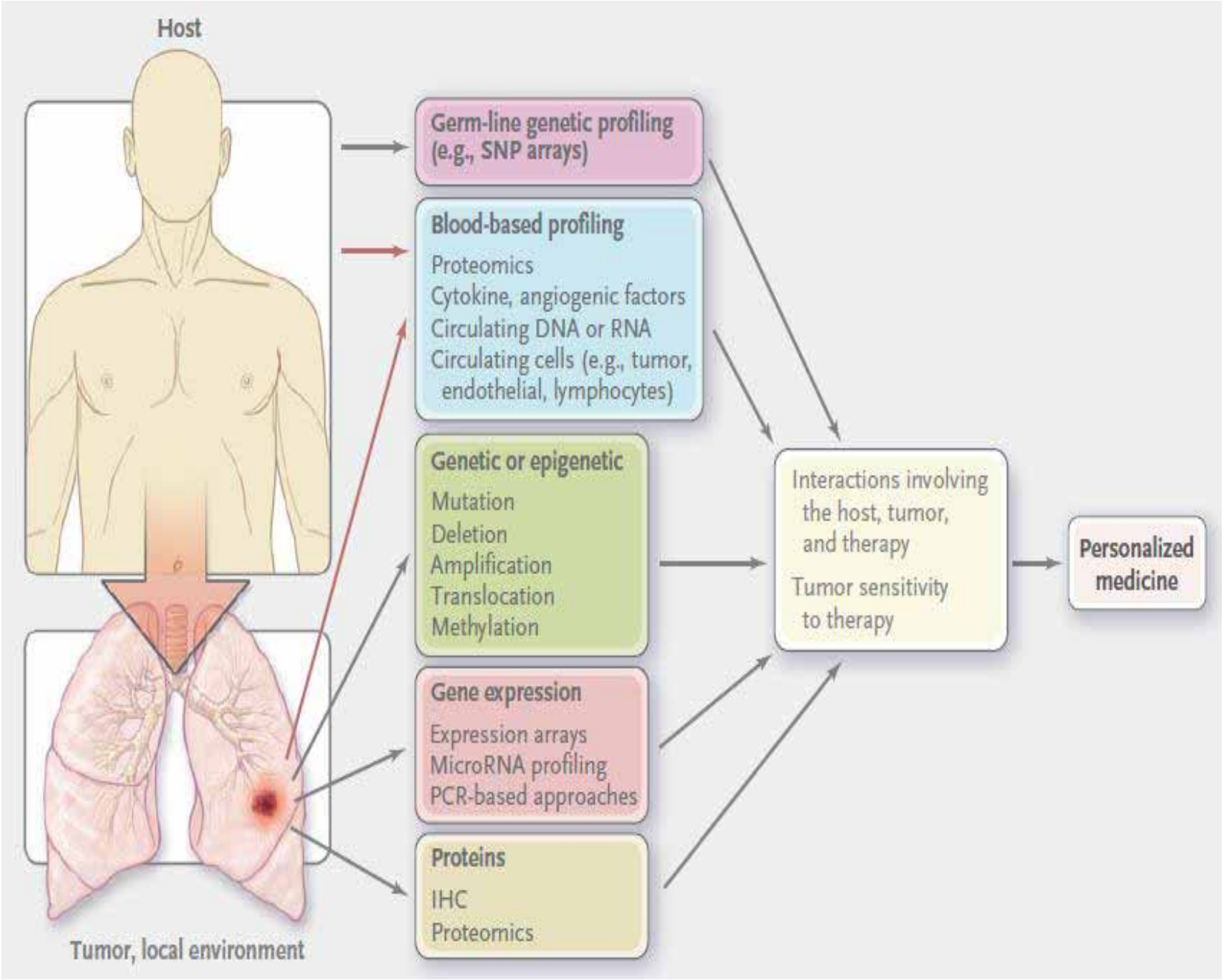
(Ciardiello F, N Engl J Med 2008;358:1160-74)

ỨC CHẾ HOẠT TÍNH EGFR BẰNG THUỐC



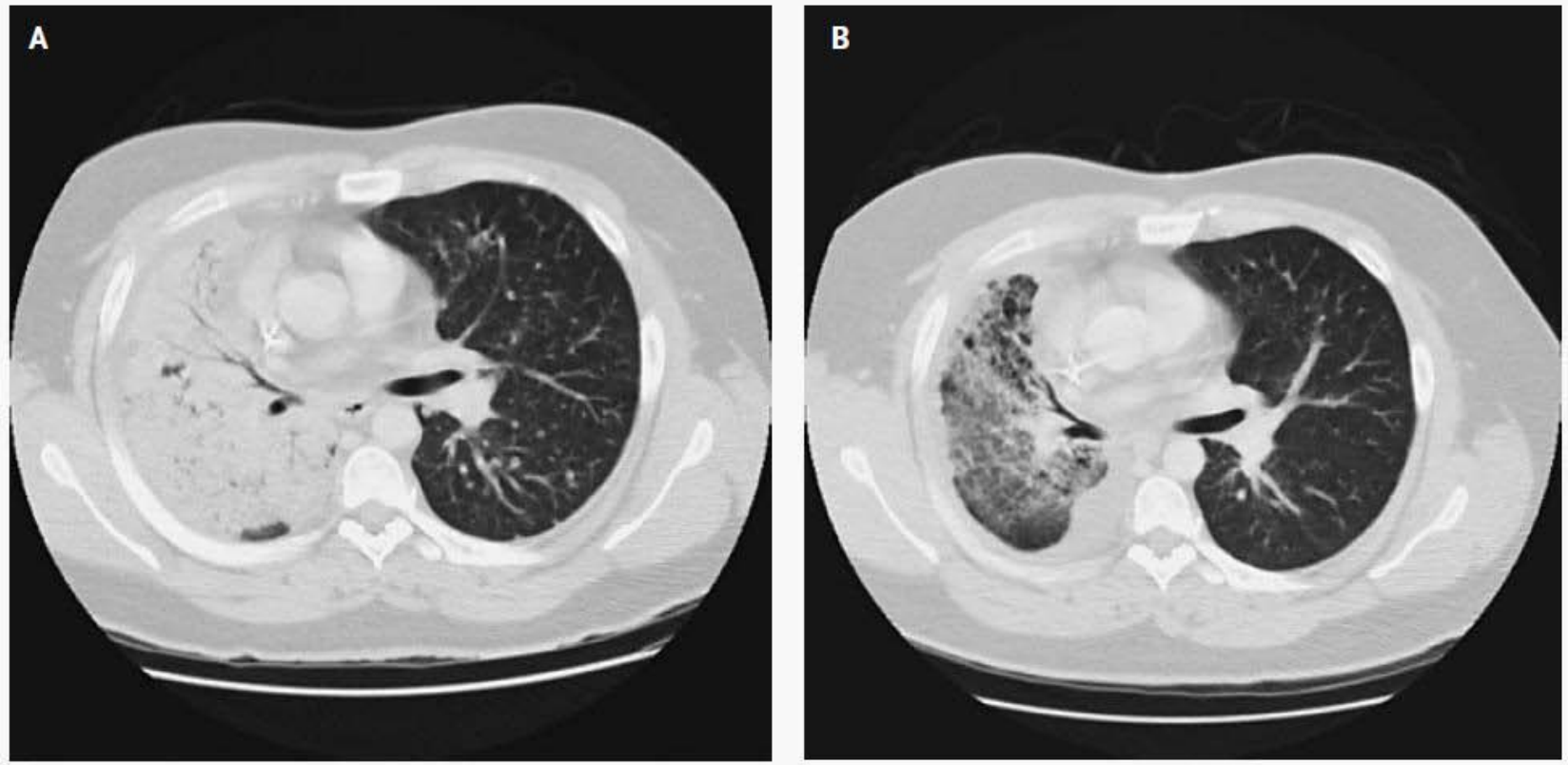


(Herbst RS, N Engl J Med 2008;359:1367-80)



(Herbst RS, N Engl J Med 2008;359:1367-80)

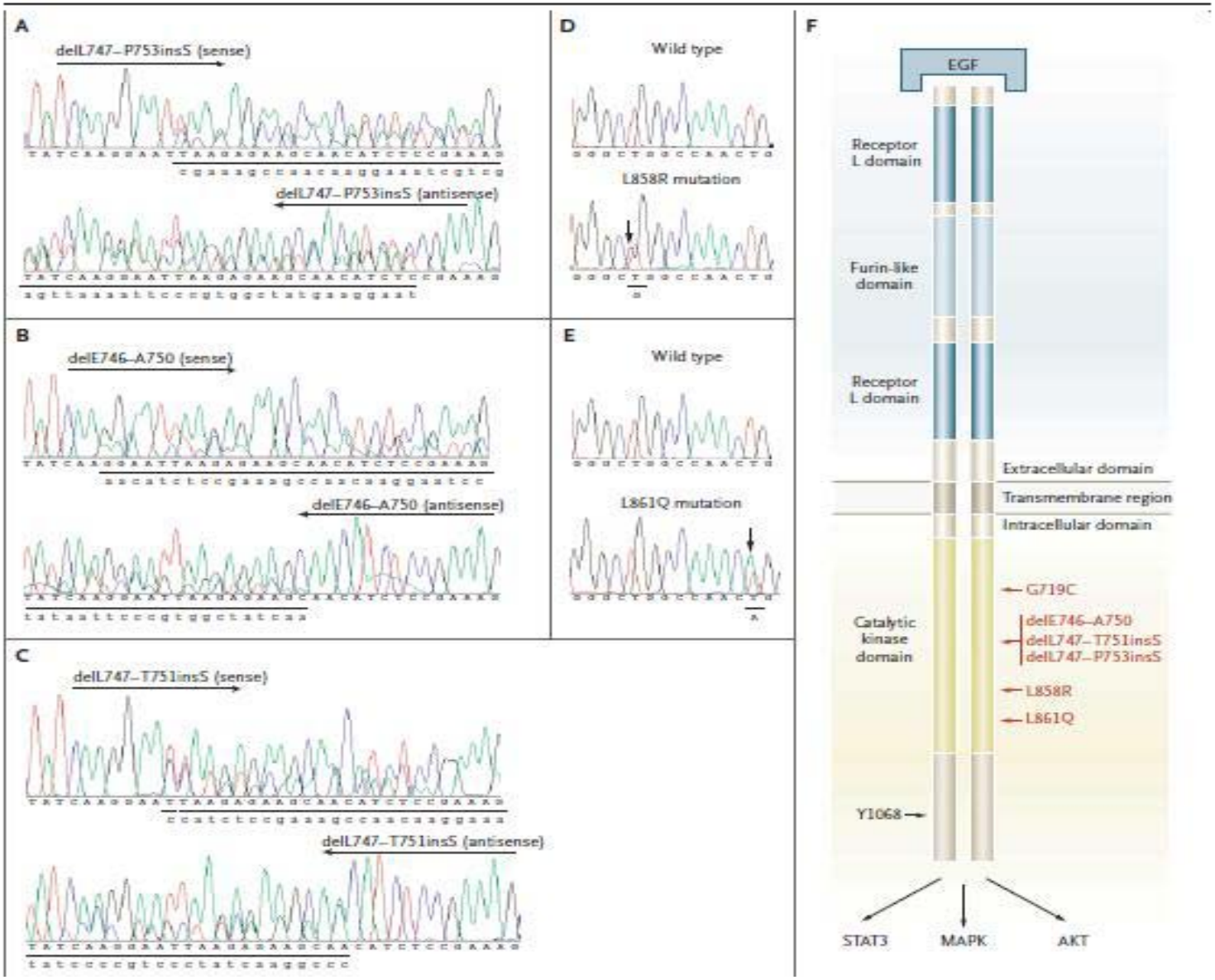
ĐiỀU TRỊ UNG THƯ PHỔI BẰNG GEFITINIB



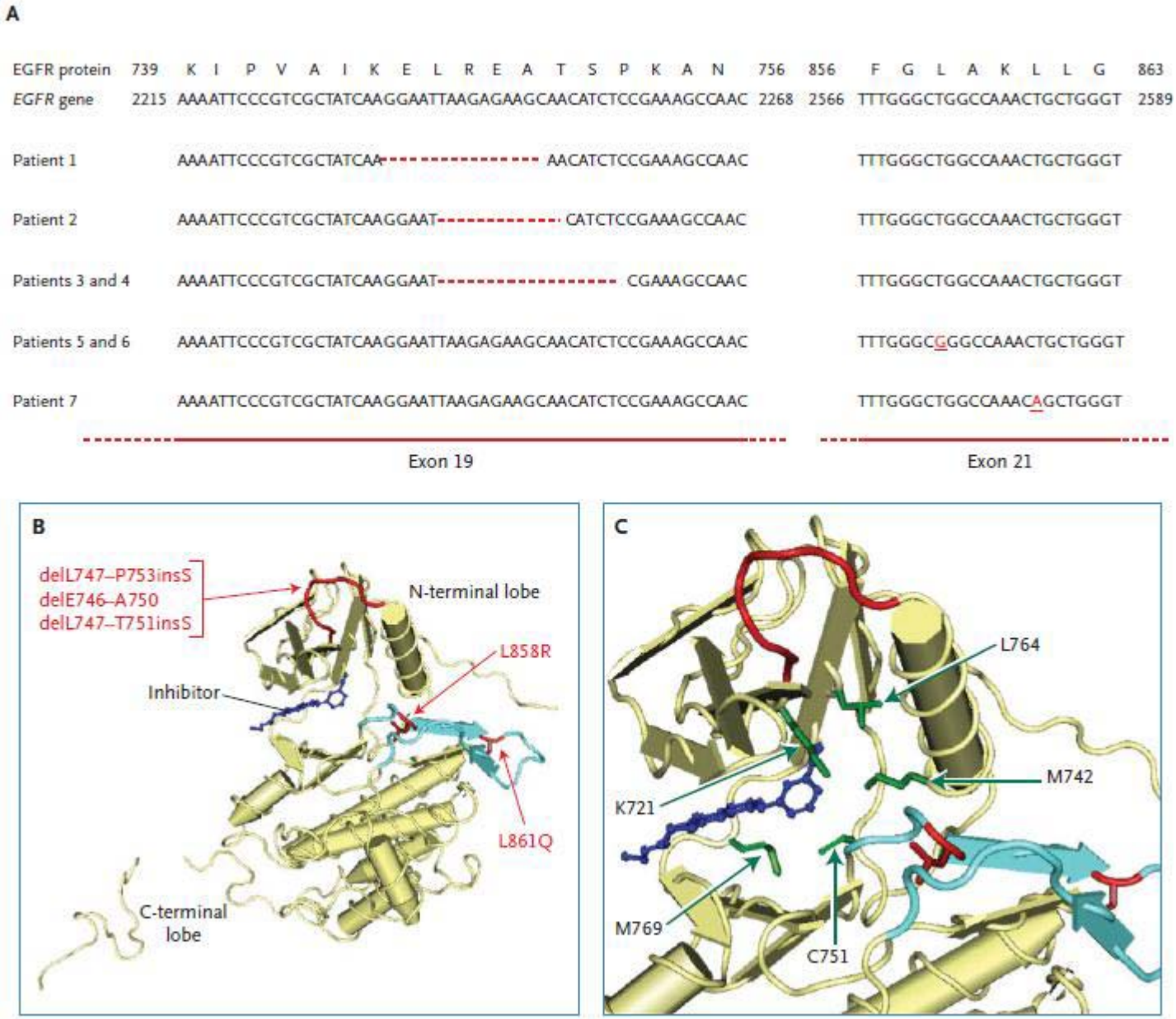
(Lynch TJ, N Engl J Med 2004;350:2129-39)

- ✓ EGFR tăng biểu hiện trong 40-80% NSCLC
- ✓ Gefitinib ức chế đặc hiệu EGFR
- ✓ Chỉ 10% bệnh nhân NSCLC có đáp ứng với gefitinib

ĐỘT BIẾN EGFR TRONG UNG THƯ PHỔI

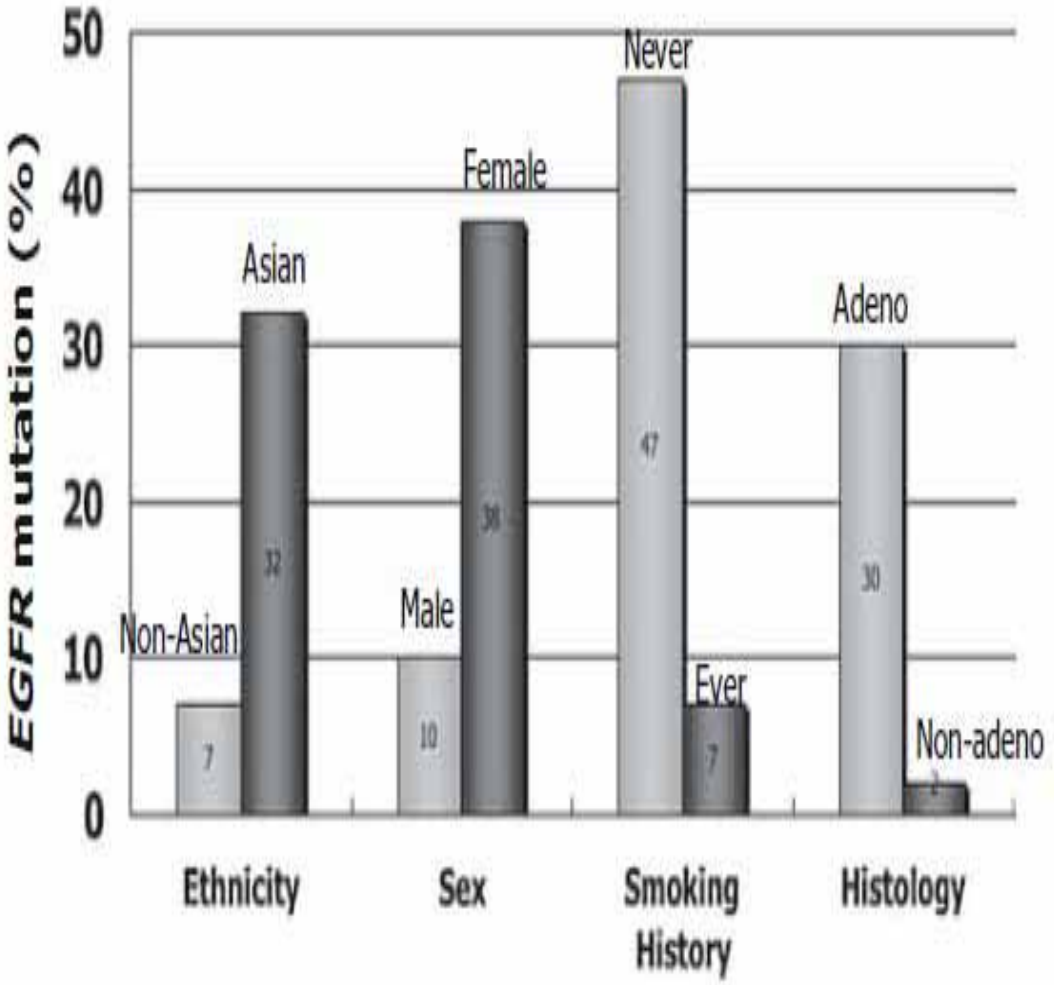


(Lynch TJ, N Engl J Med 2004;350:2129-39)



(Lynch TJ, N Engl J Med 2004;350:2129-39)

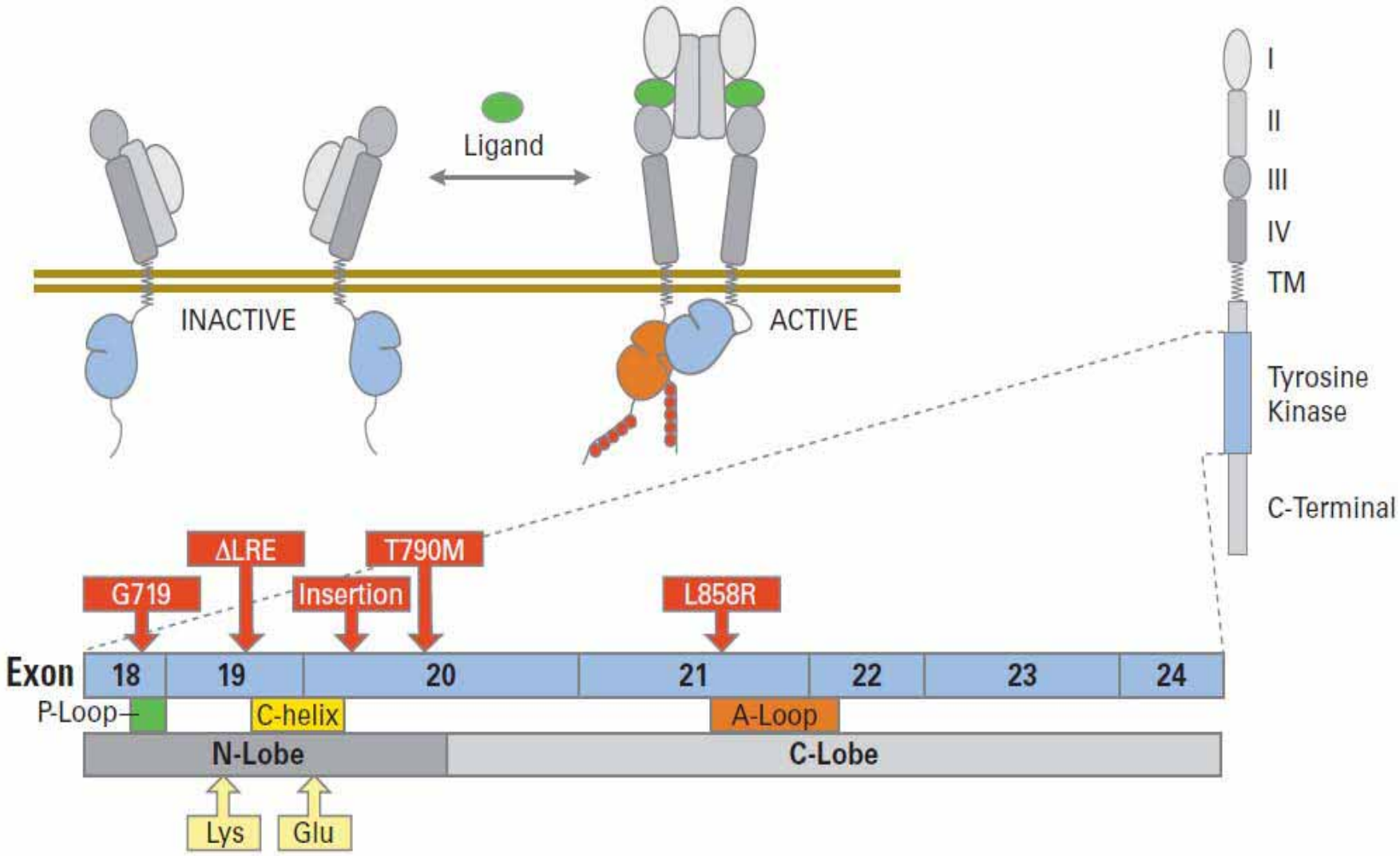
ĐẶC ĐIỂM ĐỘT BIẾN EGFR TRONG UNG THƯ PHỔI



(Fukui T, Gen Thorac Cardiovasc Surg 2008; 56:97–103)

- **Carcinôm tuyến > carcinôm gai-tuyến**
- **Nữ > nam**
- **Không hút thuốc lá > hút thuốc**
- **Theo chủng tộc:**
  - **Âu, Mỹ: 3 – 5%**
  - **Nhật: 32%**
  - **Hàn Quốc: 36.4%**
  - **Đài Loan: 55%**
  - **Thái Lan: 57.4%**
  - **Việt Nam ?**

VỊ TRÍ ĐỘT BIẾN EGFR TRONG UNG THƯ PHỔI

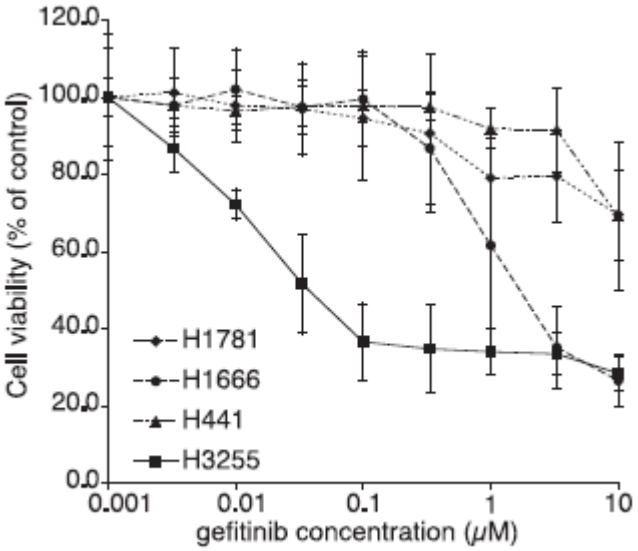


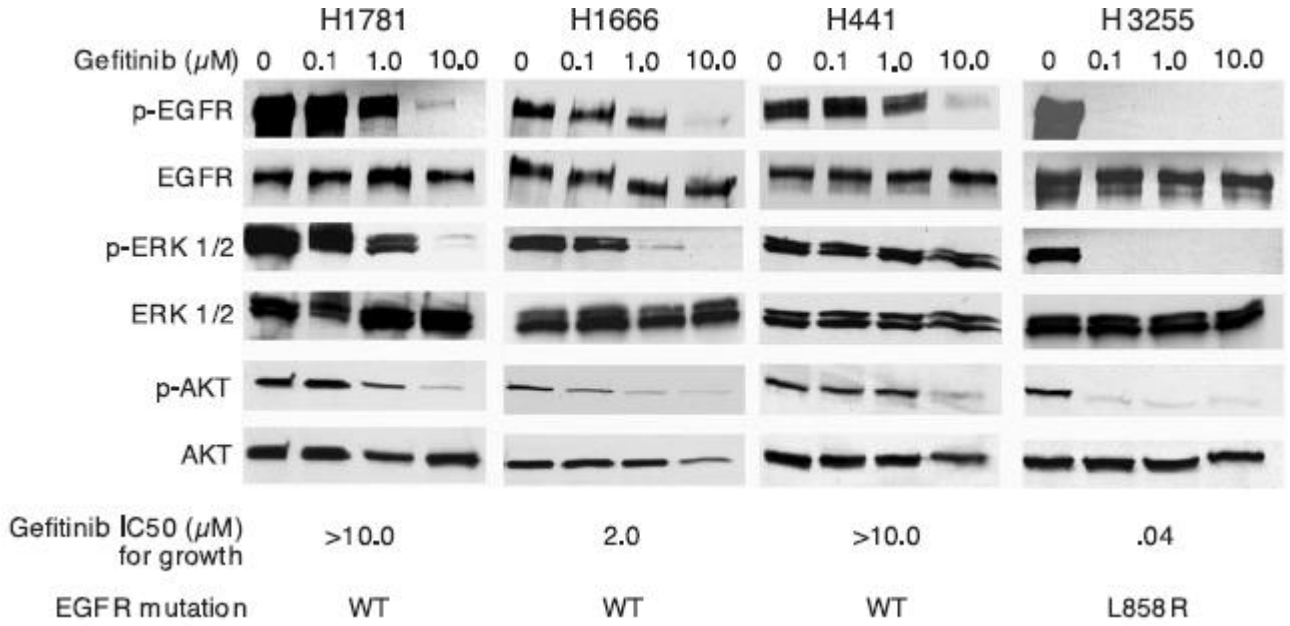
(Kumar A, *J Clin Oncol 2008;26:1742-1751)*

EGFR Mutations in Lung Cancer: Correlation with Clinical Response to Gefitinib Therapy

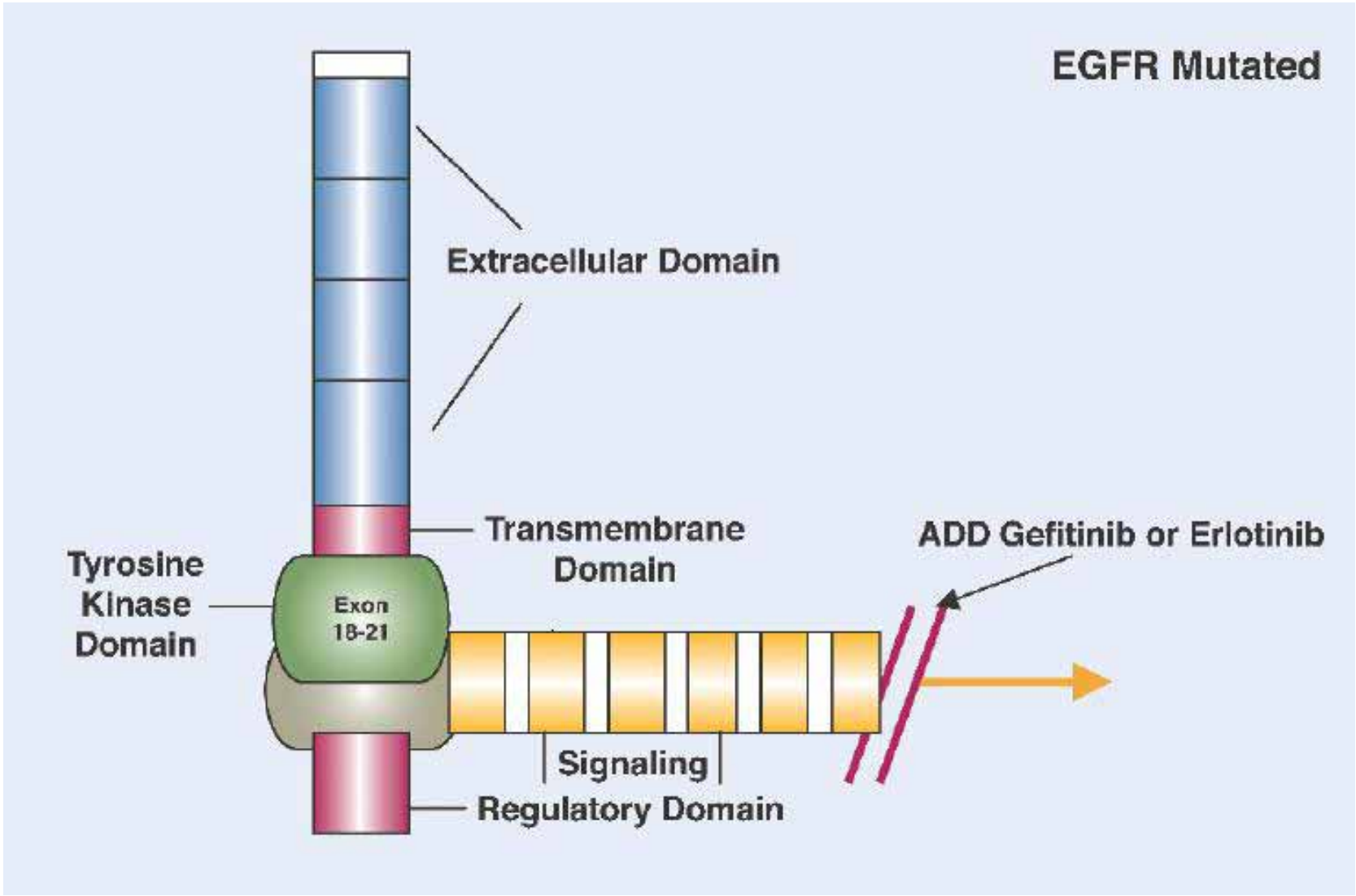
J. Guillermo Paez,[1,2]* Pasi A. Jänne,[1,2]* Jeffrey C. Lee,[1,3]* Sean Tracy,[1] Heidi Greulich,[1,2] Stacey Gabriel,[4] Paula Herman,[1] Frederic J. Kaye,[5] Neal Lindeman,[6] Titus J. Boggon,[1,3] Katsuhiko Naoki,[1] Hidefumi Sasaki,[7] Yoshitaka Fujii,[7] Michael J. Eck,[1,3] William R. Sellers,[1,2,4]† Bruce E. Johnson,[1,2]† Matthew Meyerson[1,3,4]†

(Science 2004;304:1497-1500)

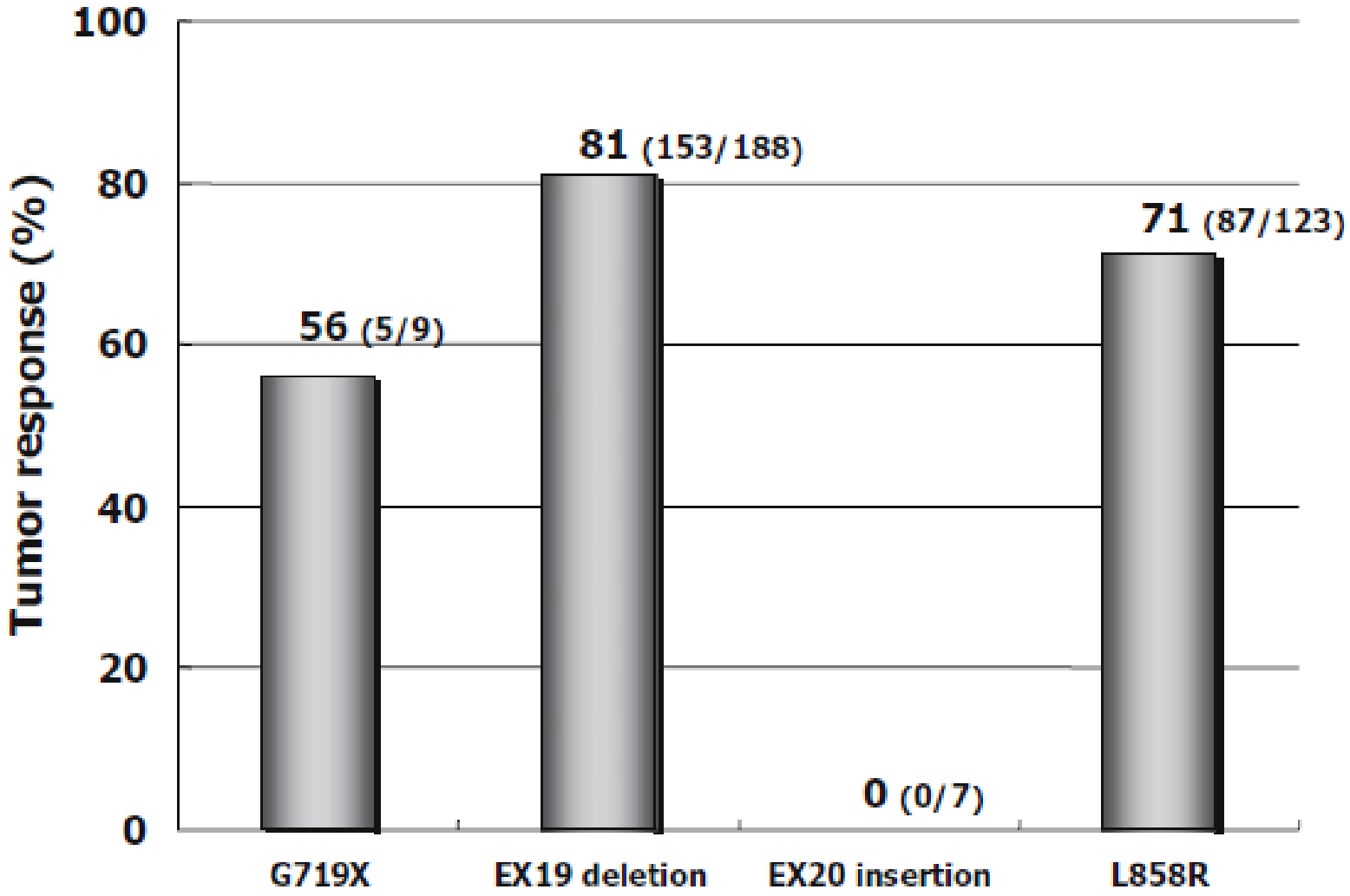




GEFITINIB VÀ ERLOTINIB NGĂN CHẶN TÍN HIỆU TỪ EGFR ĐỘT BIẾN



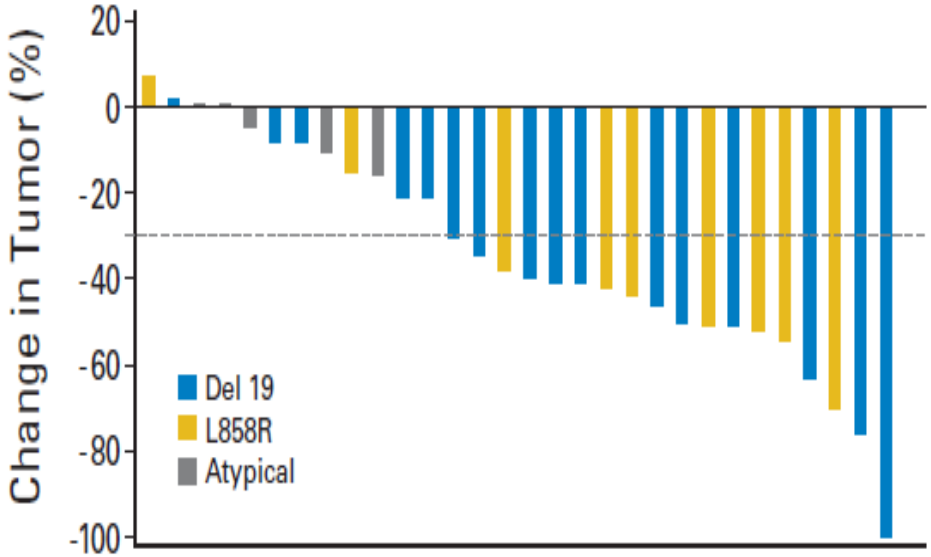
ĐÁP ỨNG VỚI THUỐC ỨC CHẾ EGFR PHỤ THUỘC KIỂU ĐỘT BIẾN



(Fukui T, Gen Thorac Cardiovasc Surg 2008; 56:97–103)

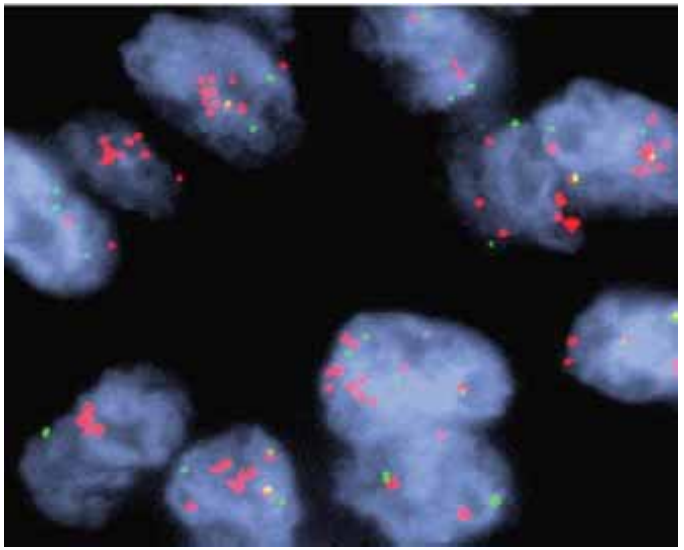
First-Line Gefitinib in Patients With Advanced Non–Small-Cell Lung Cancer Harboring Somatic *EGFR* Mutations

Lecia V. Sequist, Renato G. Martins, David Spigel, Steven M. Grunberg, Alexander Spira, Pasi A. Jänne, Victoria A. Joshi, David McCollum, Tracey L. Evans, Alona Muzikansky, Georgiana L. Kuhlmann, Moon Han, Jonathan S. Goldberg, Jeffrey Settleman, A. John Iafrate, Jeffrey A. Engelman, Daniel A. Haber, Bruce E. Johnson, and Thomas J. Lynch

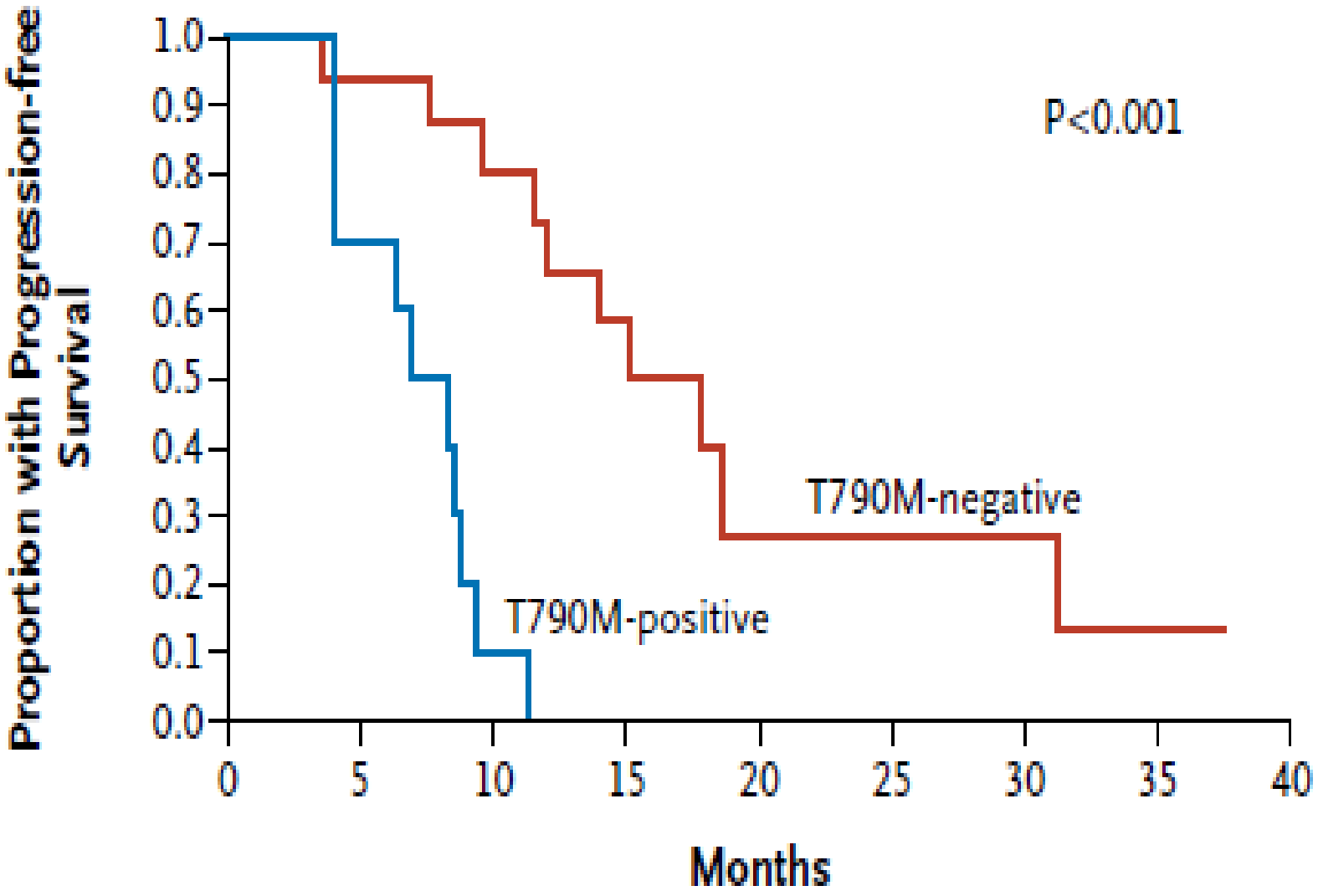


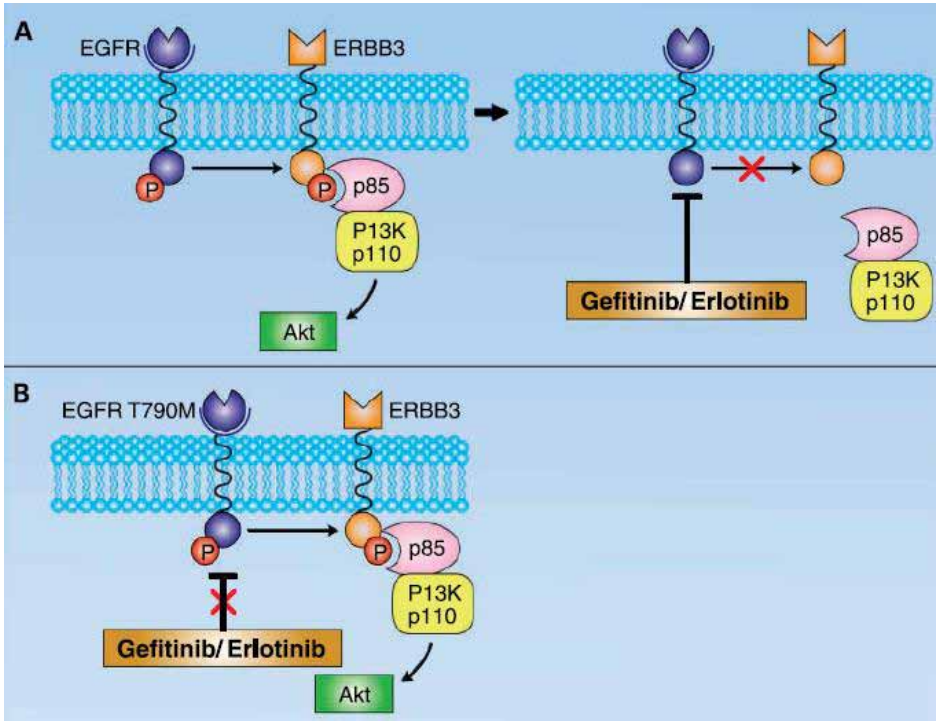
Đáp ứng với gefitinib phụ thuộc kiểu đột biến *EGFR*

Khuyếch đại gen *MET* (đỏ) trên bệnh nhân ung thư phổi có biểu hiện *EGFR* (xanh) nhưng kháng gefitinib



EGFR T790M: ĐỘT BIẾN KHÁNG THUỐC



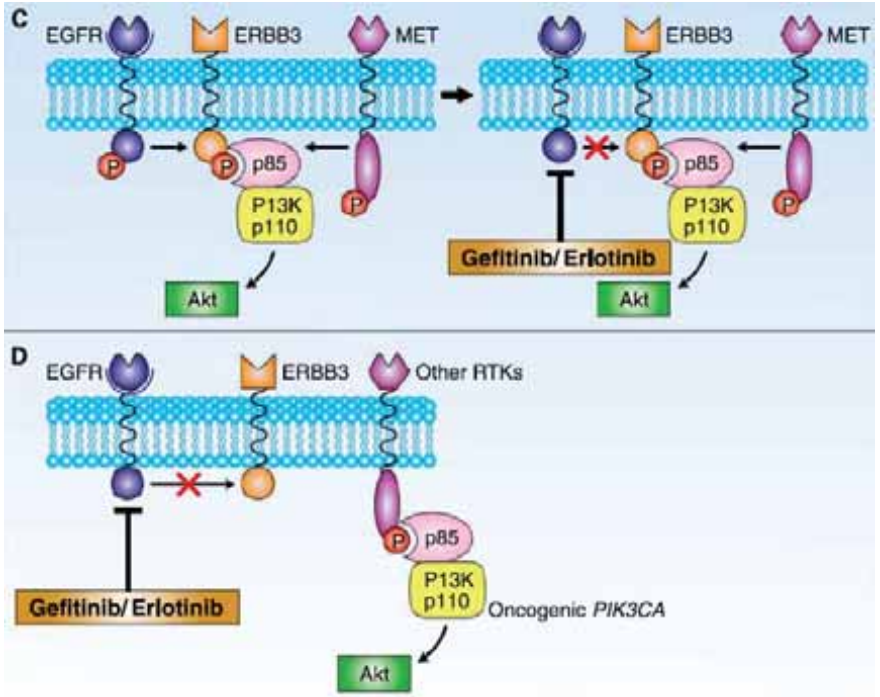


Kháng thuốc do đột biến

EGFR T790M

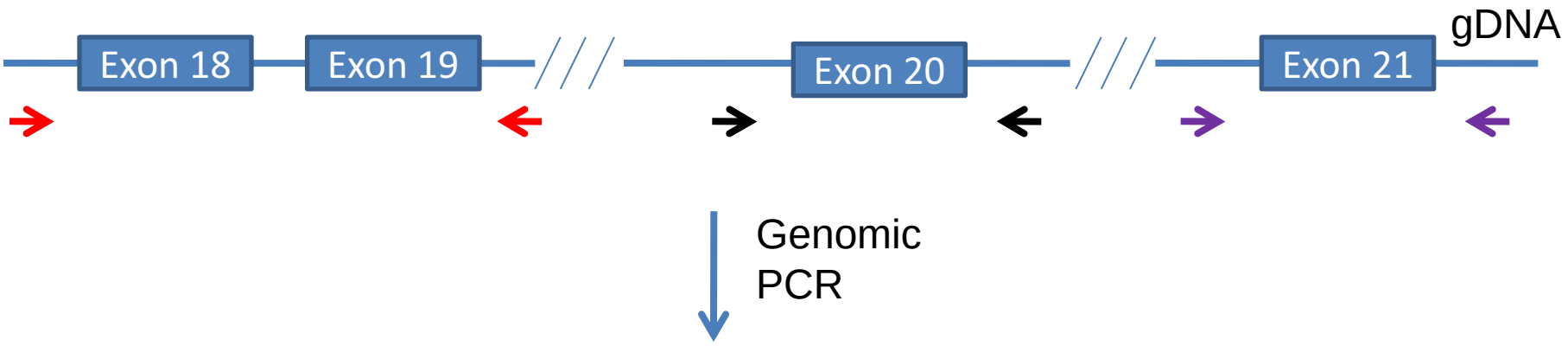
Kháng thuốc do

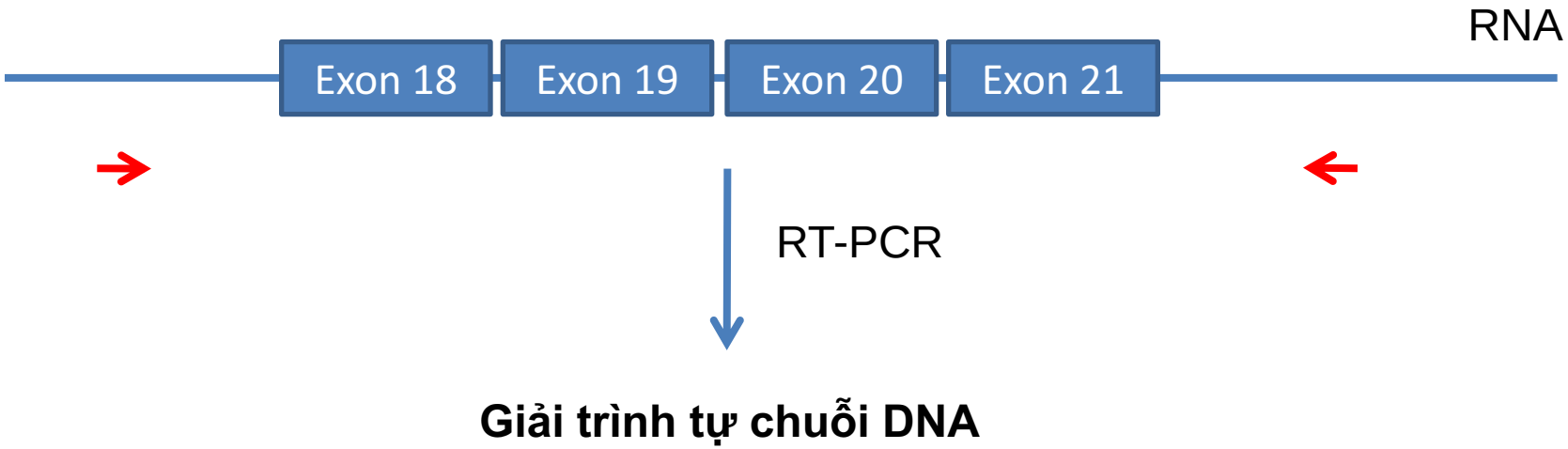
cơ chế khác



(Engelman JA, Clin Cancer Res 2008;14(10):2895-2899)

KHẢO SÁT ĐỘT BIẾN *EGFR*



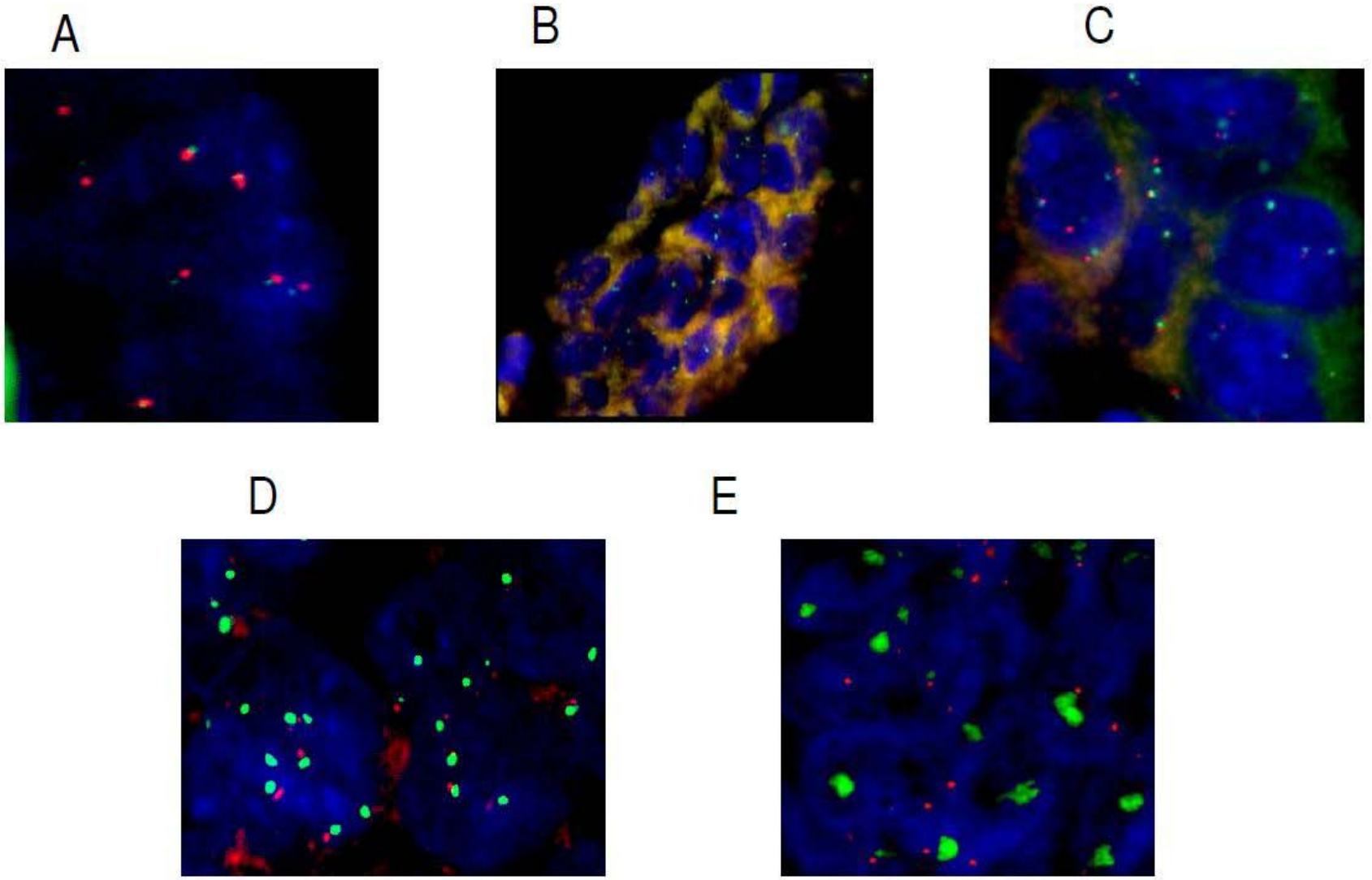


Nội dung:

1. TỔNG QUÁT
2. *FLT3* TRONG UNG THƯ MÁU
3. ***EGFR*** **TRONG UNG THƯ PHỔI VÀ UNG THƯ ĐẠI TRỰC TRÀNG**
4. *HER-2/neu* TRONG UNG THƯ VÚ
5. *KIT* VÀ *PDGFRA* TRONG U MÔ ĐỆM ĐƯỜNG TIÊU HÓA

- Đột biến *EGFR* trong ung thư đại trực tràng: rất hiếm.
- 70% - 80% có biểu hiện EGFR: Đích điều trị của kháng thể đơn dòng
- Cetuximab có hiệu quả hơn trên bệnh nhân có biểu hiện mạnh EGFR dạng hoạt động (pEGFR) hoặc có khuyếch đại gen *EGFR* qua khảo sát bằng FISH

KHẢO SÁT BIỂU HIỆN EGFR BẰNG FISH



Dual color FISH assays for probes of EGFR (green) and chromosome seven (CEP7, red). (A) Balanced disomy in healthy colorectal mucosa. (B) Balanced disomy in tumor of patient 15. (C) Balanced low polysomy in tumor of patient 4. (D) High polysomy in tumor of patient 1. (E) Amplification in a control tumor.

A polymorphism of *EGFR* extracellular domain is associated with progression free-survival in metastatic colorectal cancer patients receiving cetuximab-based treatment

(Goncalves A, *BMC Cancer* 2008;8:169)

Bệnh phẩm

↓

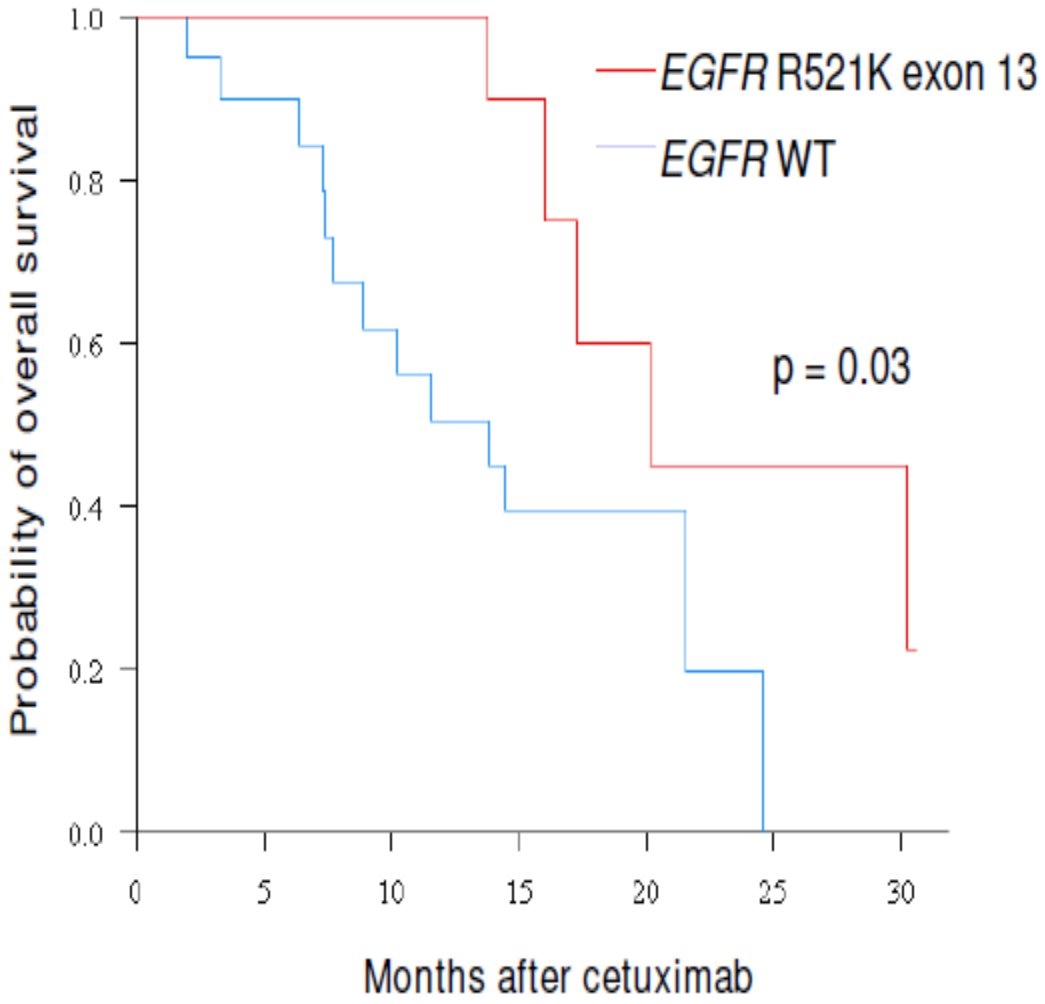
DNA

↓

PCR: EGFR exons 6 - 14

↓

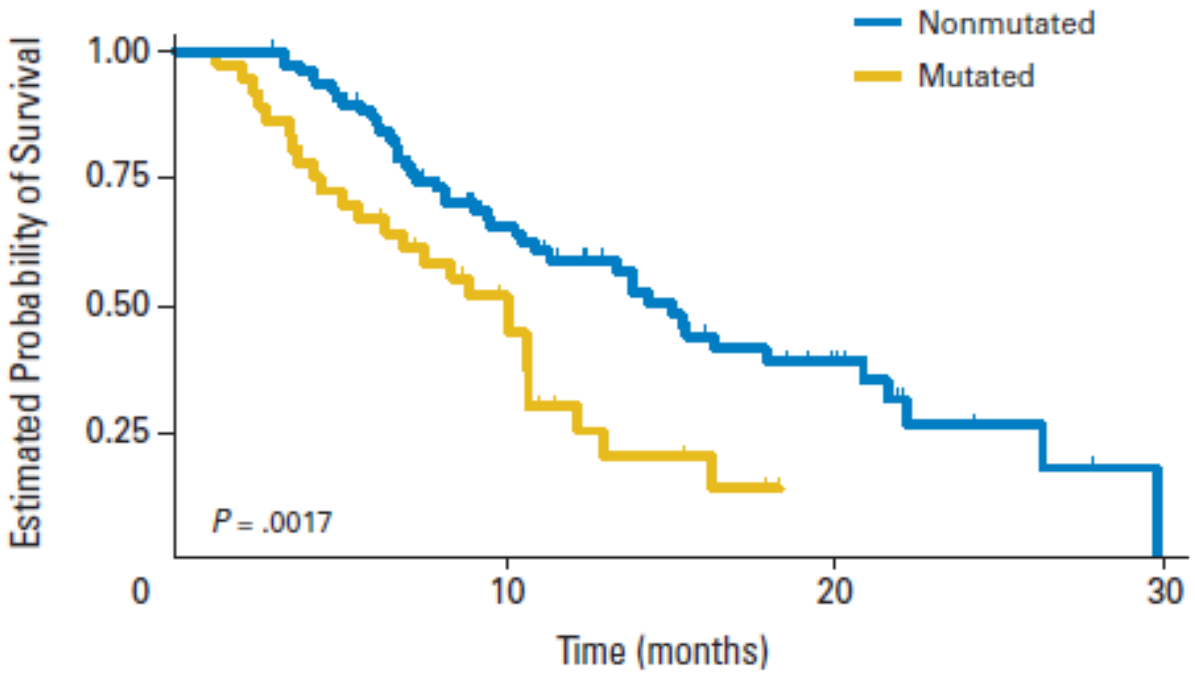
Sequencing



KRAS Mutations As an Independent Prognostic Factor in Patients With Advanced Colorectal Cancer Treated With Cetuximab

Astrid Lièvre, Jean-Baptiste Bachet, Valérie Boige, Anne Cayre, Delphine Le Corre, Emmanuel Buc, Marc Ychou, Olivier Bouché, Bruno Landi, Christophe Louvet, Thierry André, Fréderic Bibeau, Marie-Danièle Diebold, Philippe Rougier, Michel Ducreux, Gorana Tomasic, Jean-François Emile, Frédérique Penault-Llorca, and Pierre Laurent-Puig

J Clin Oncol 26:374-379. © 2008 by American Society of Clinical Oncology

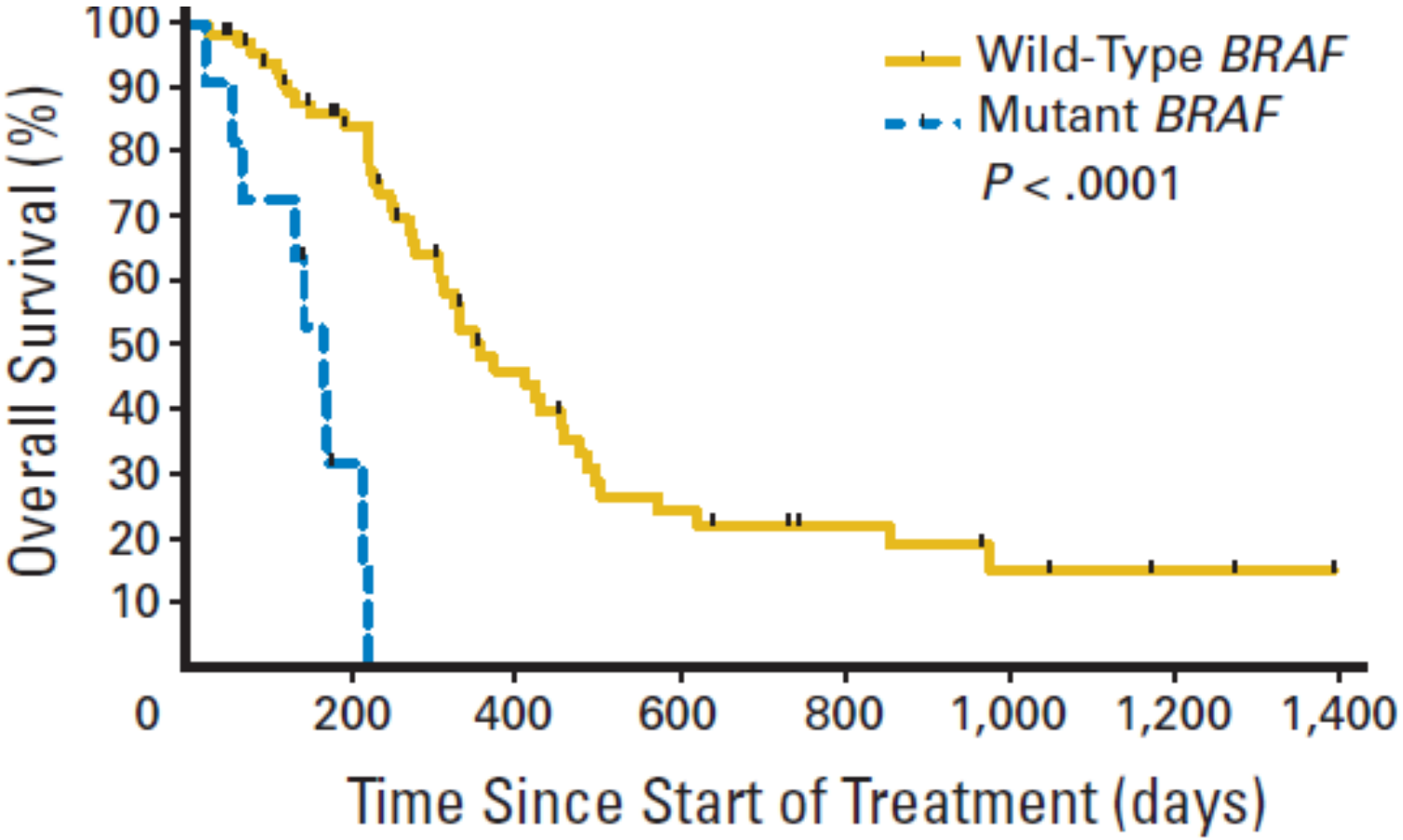


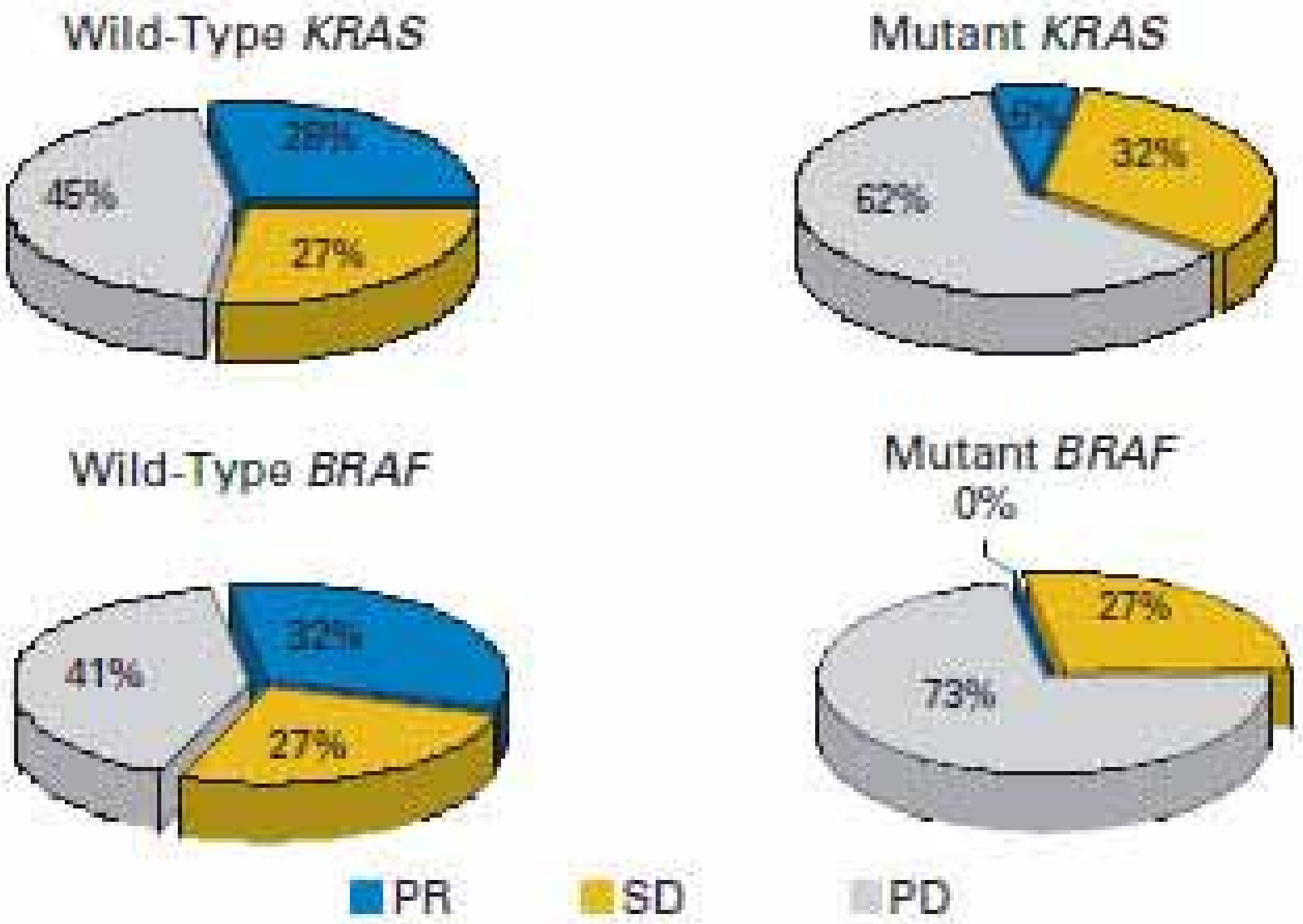
	Months				
	0	6	12	18	24
No. at risk					
KRAS nonmutated	77	65	32	17	4
KRAS mutated	36	25	7	1	0

Wild-Type *BRAF* Is Required for Response to Panitumumab or Cetuximab in Metastatic Colorectal Cancer

Federica Di Nicolantonio, Miriam Martini, Francesca Molinari, Andrea Sartore-Bianchi, Sabrina Arena, Piercarlo Saletti, Sara De Dosso, Luca Mazzucchelli, Milo Frattini, Salvatore Siena, and Alberto Bardelli

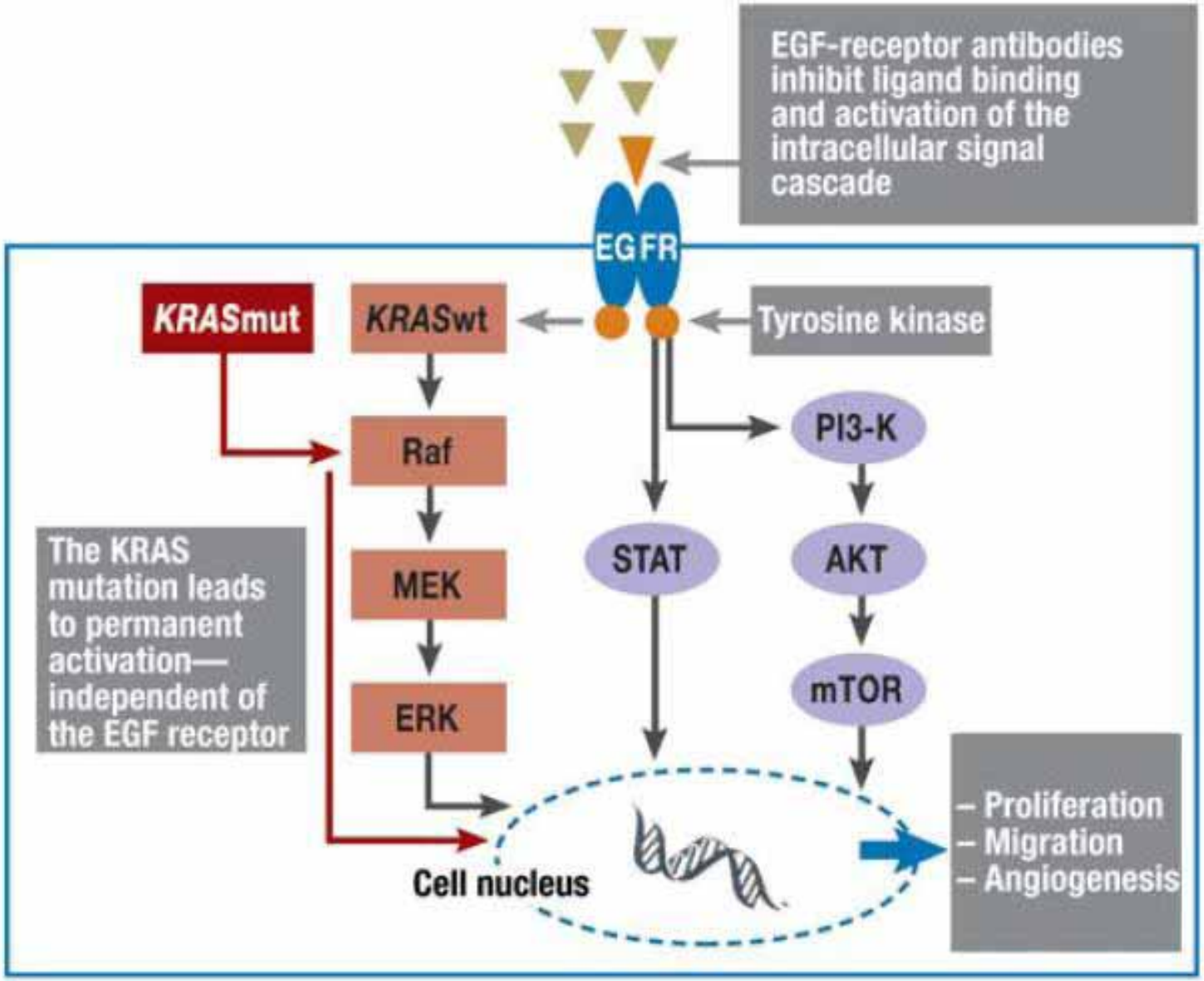
J Clin Oncol 26:5705-5712. © 2008 by American Society of Clinical Oncology



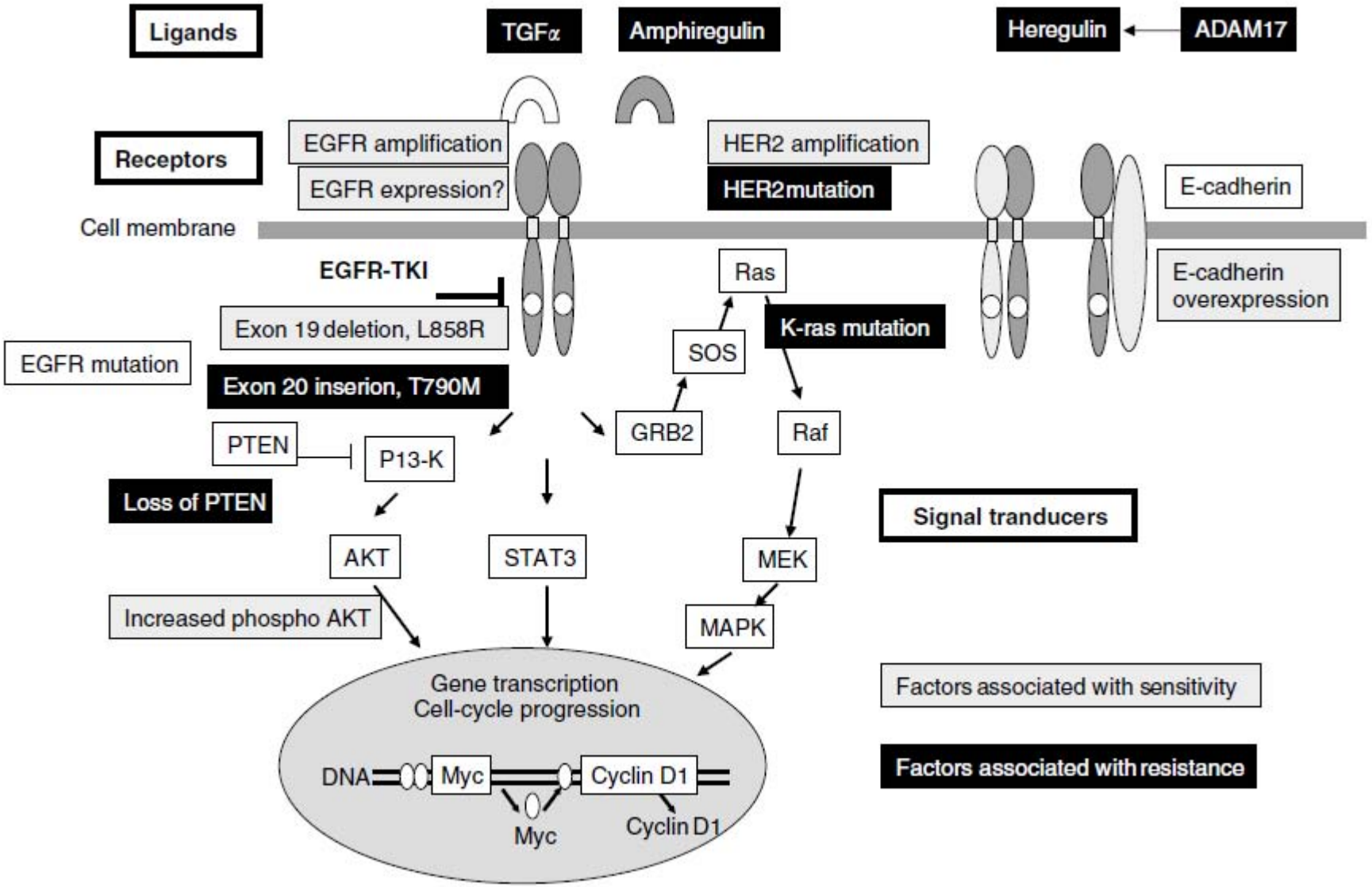


PR: partial response, SD: stable disease, PD: progressive disease

LIÊN HỆ GiỮA EGFR, KRAS VÀ BRAF



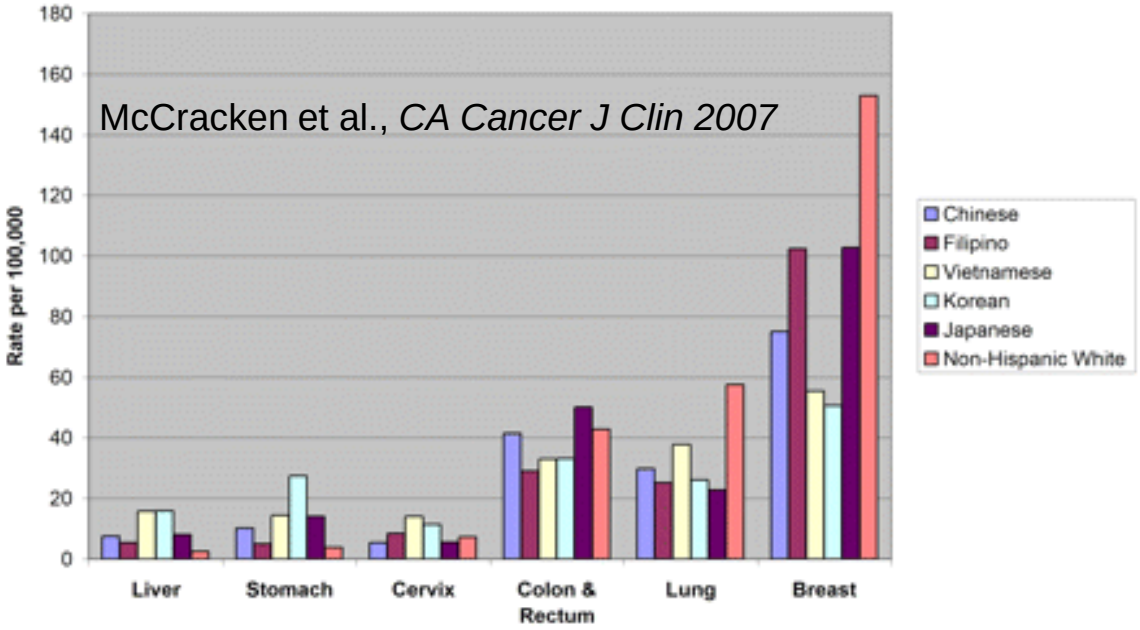
DỰ ĐOÁN ĐÁP ỨNG VỚI THUỐC ỨC CHẾ EGFR (Xám: nhạy, đen: kháng)



(Uramoto H, British Journal of Cancer 2007;96,857 – 863)

Nội dung:

1. TỔNG QUÁT
2. *FLT3* TRONG UNG THƯ MÁU
3. *EGFR* TRONG UNG THƯ PHỔI VÀ UNG THƯ ĐẠI TRỰC TRÀNG
4. ***HER-2/neu* TRONG UNG THƯ VÚ**
5. *KIT* VÀ *PDGFRA* TRONG U MÔ ĐỆM ĐƯỜNG TIÊU HÓA



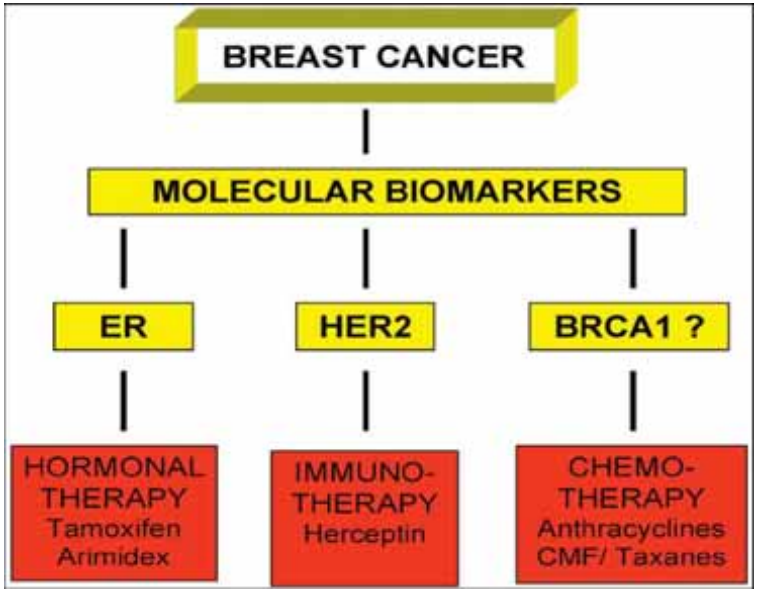
Ung thư vú đứng đầu trong số những ung thư thường gặp trên phụ nữ thuộc các chủng tộc khác nhau.

Theo cơ chế phân tử, ung thư vú có thể được xếp vào 3 nhóm, với những hướng điều trị khác nhau:

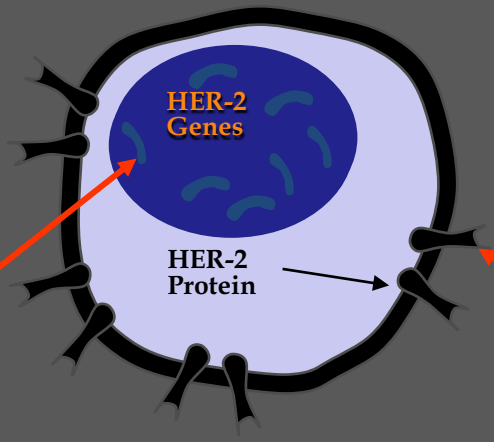
1. Nhóm có estrogen receptor (+): 60-70%

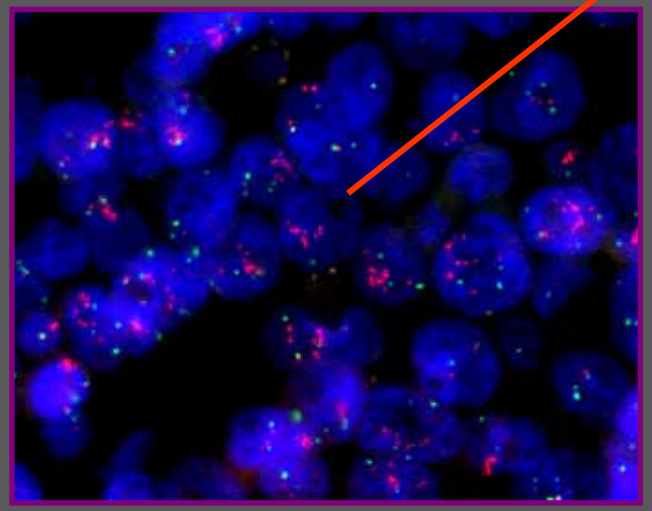
2. Nhóm HER-2/neu (+): 20-30%

3. Nhóm có mang đột biến *BRCA1/2*: 5-10%



TARGET

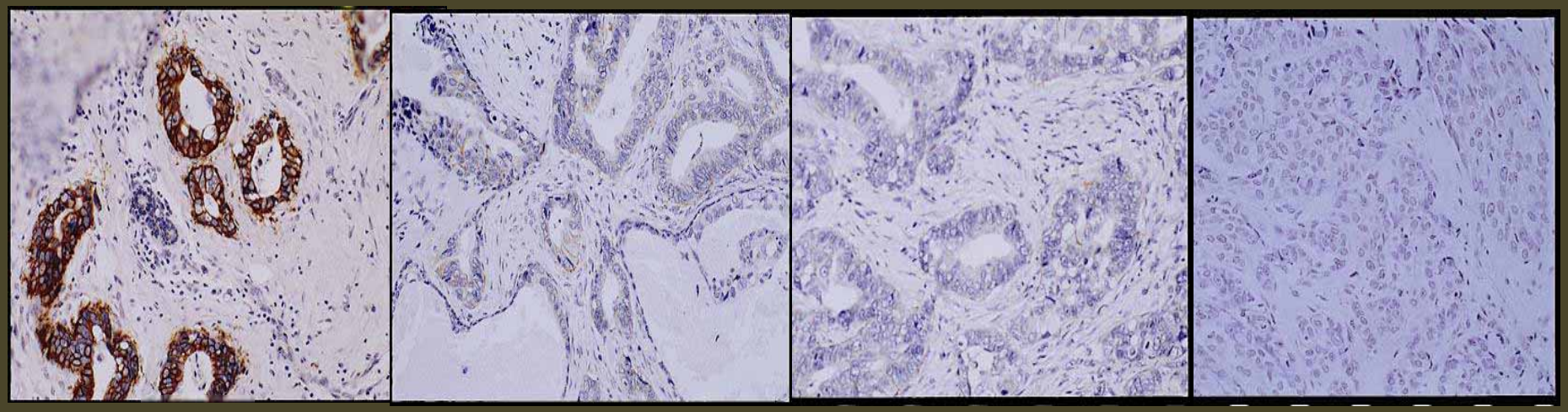




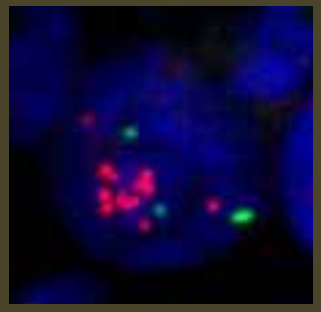
FISH : DNA

IHC : Protein

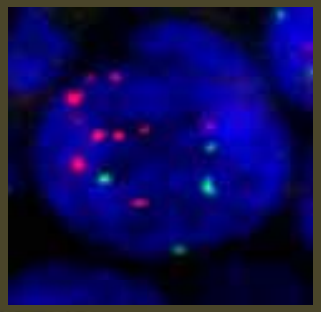
ĐÁNH GIÁ HER2 BẰNG IHC VÀ FISH



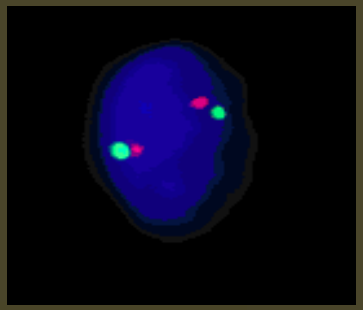
3+ 2+ 1+ Negative/0



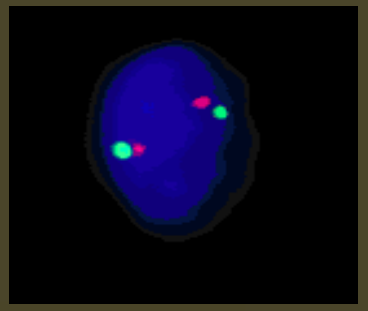
High amplification



Low amplification

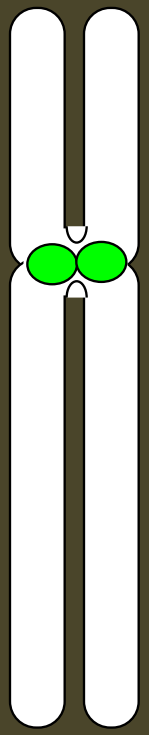


Normal

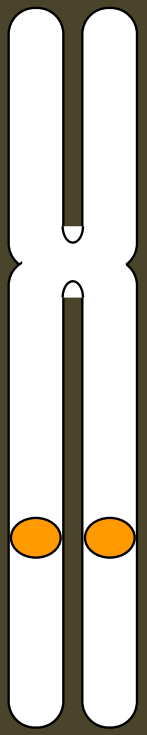


Normal

PathVysion HER2 DNA probe

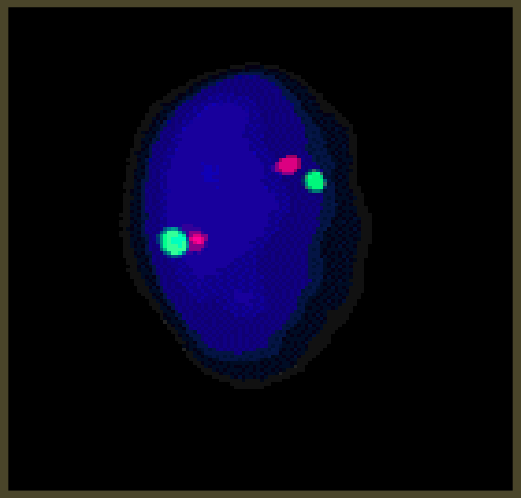


Chromosome 17
Centromere



Chromosome 17
HER2/*neu*

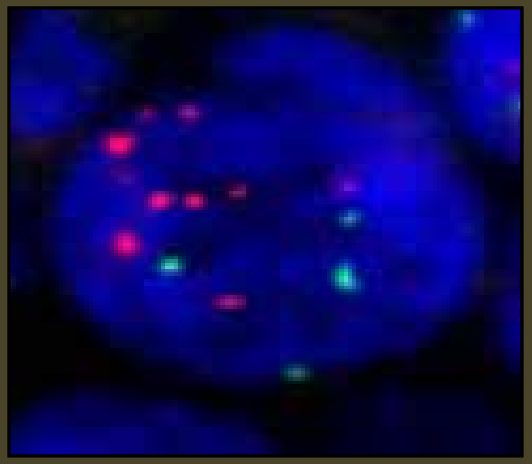
Signal Enumeration



HER-2 orange signal : 2

CEP 17 green signals : 2

Ratio = 1.0



HER-2 orange signal : 10

CEP 17 green signals : 4

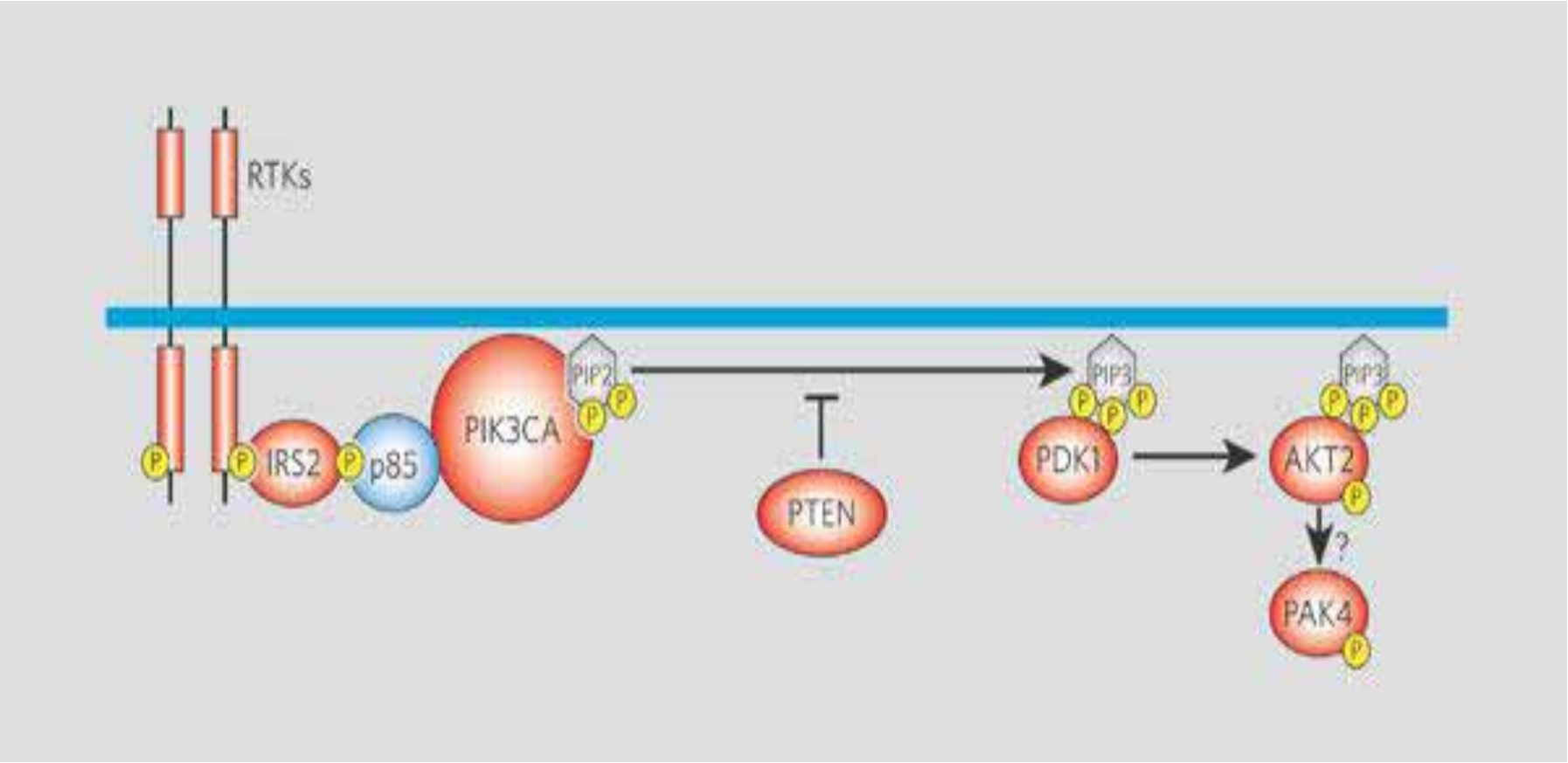
Ratio = 2.5

$$\frac{\text{HER2 signal \# X 20 nuclei}}{\text{CEP 17 signal \# X 20 nuclei}} \geq 2.0 \text{ (positive)}$$

Trastuzumab được khuyên dùng cho bệnh nhân ung thư vú có tăng biểu hiện HER-2/neu qua khảo sát bằng immunohistochemistry hoặc FISH

Chỉ có 30% bệnh nhân có đáp ứng với trastuzumab

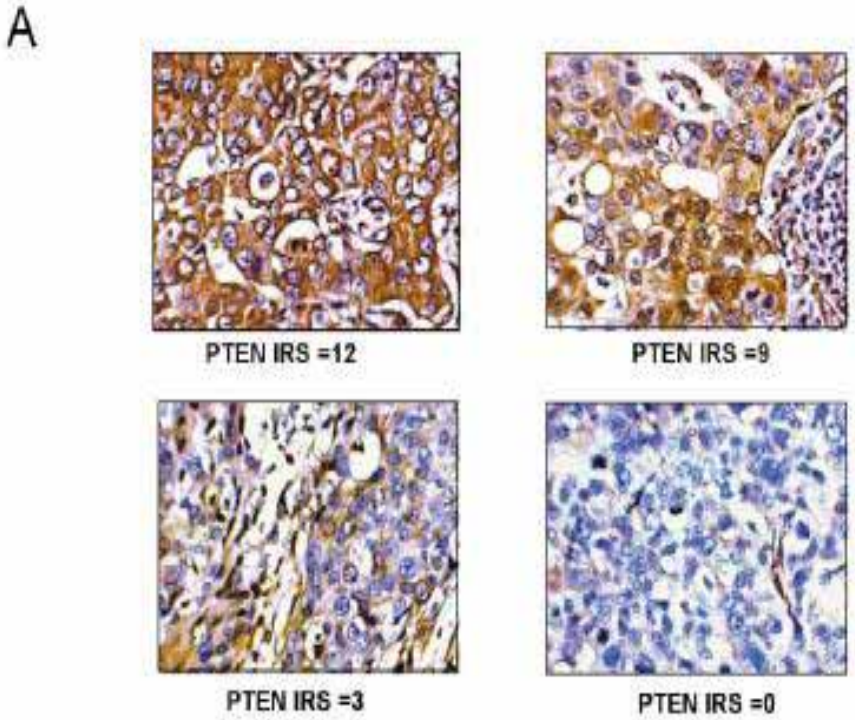
Ngoài HER-2/neu, yếu tố nào giúp dự đoán đáp ứng điều trị?



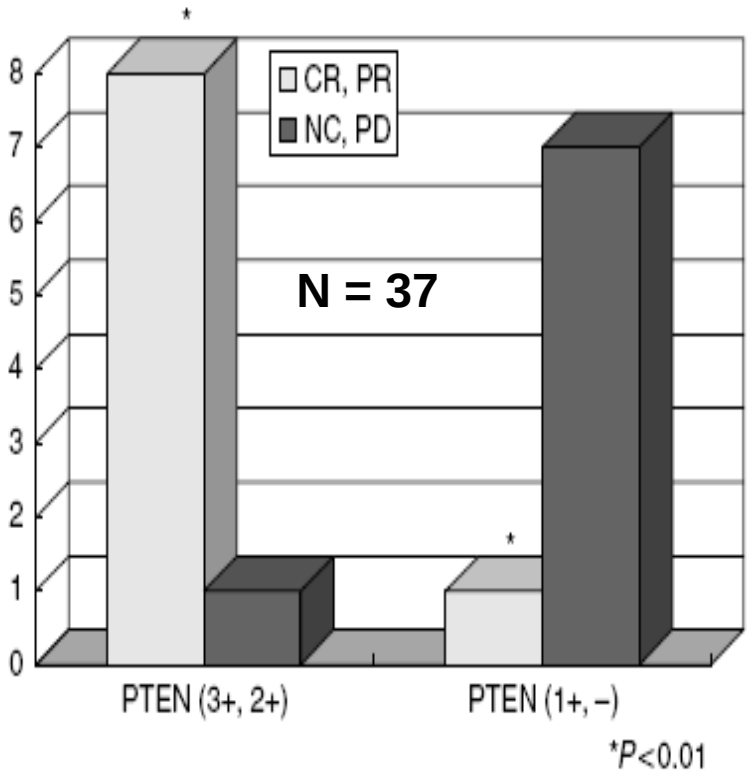
Một trong những dòng thác tín hiệu nội bào liên quan đến ung thư và receptor tyrosine kinase (HER-2/neu) là PTEN/PI3K/AKT.

Bình thường PTEN có chức năng ức chế nội tại trong con đường này.

Đột biến của PIK3CA gặp trong 25-30%, mất chức năng PTEN gặp trong 50% trường hợp ung thư vú.

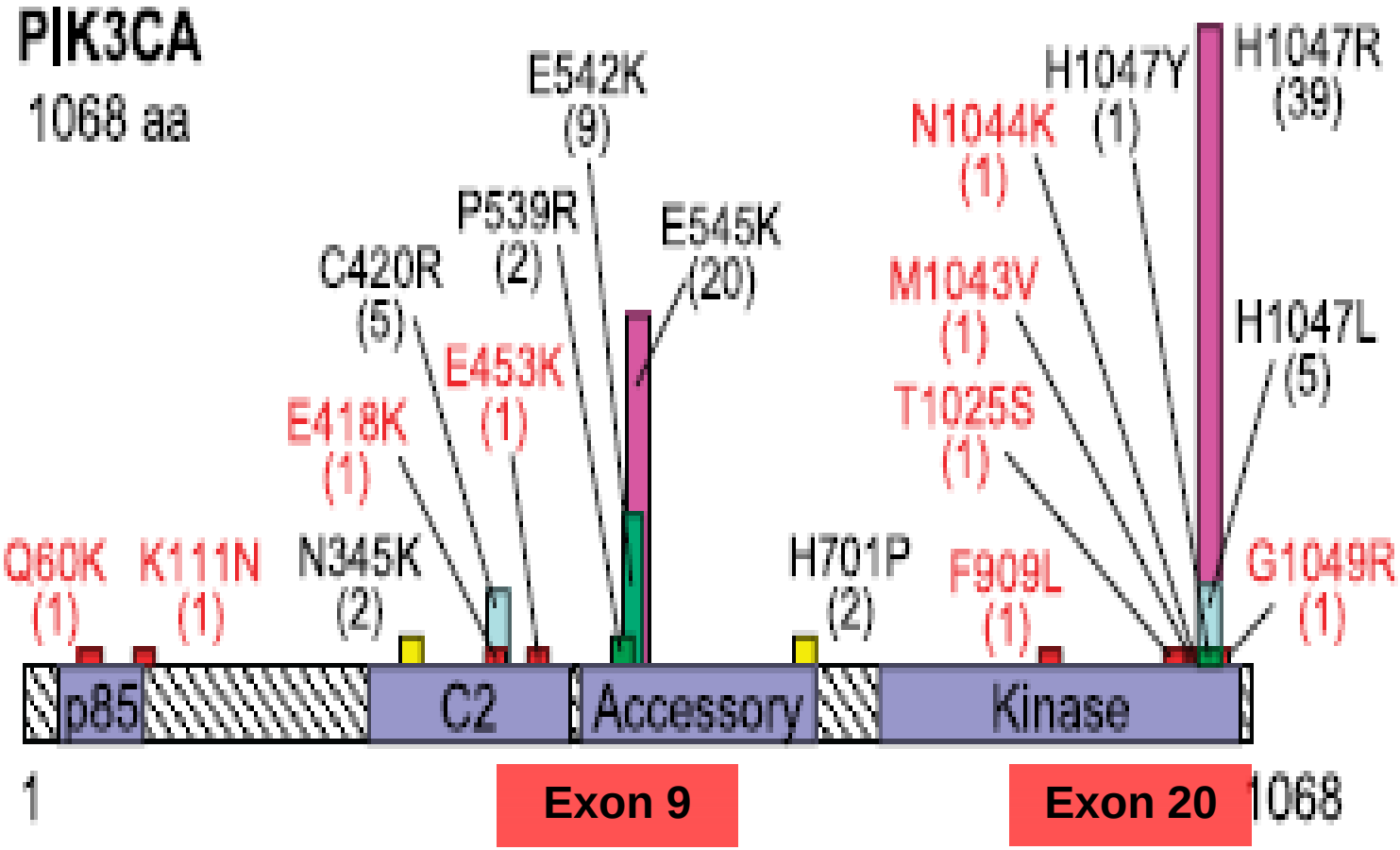


Nagata et al., *Cancer Cell* 2004



Fujita et al., *Brit J Cancer* 2006

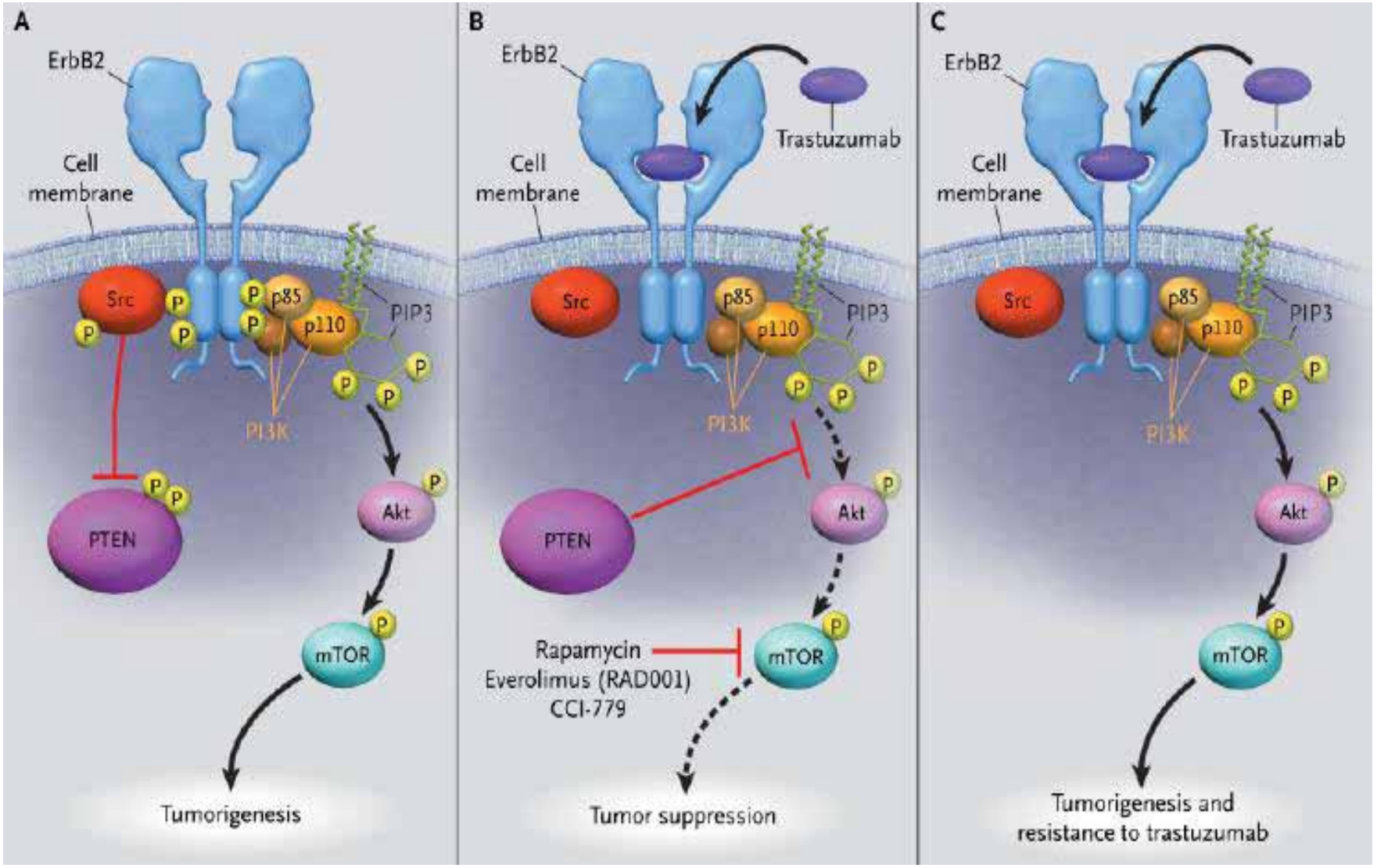
Mất biểu hiện PTEN là yếu tố tiên đoán đáp ứng kém với trastuzumab



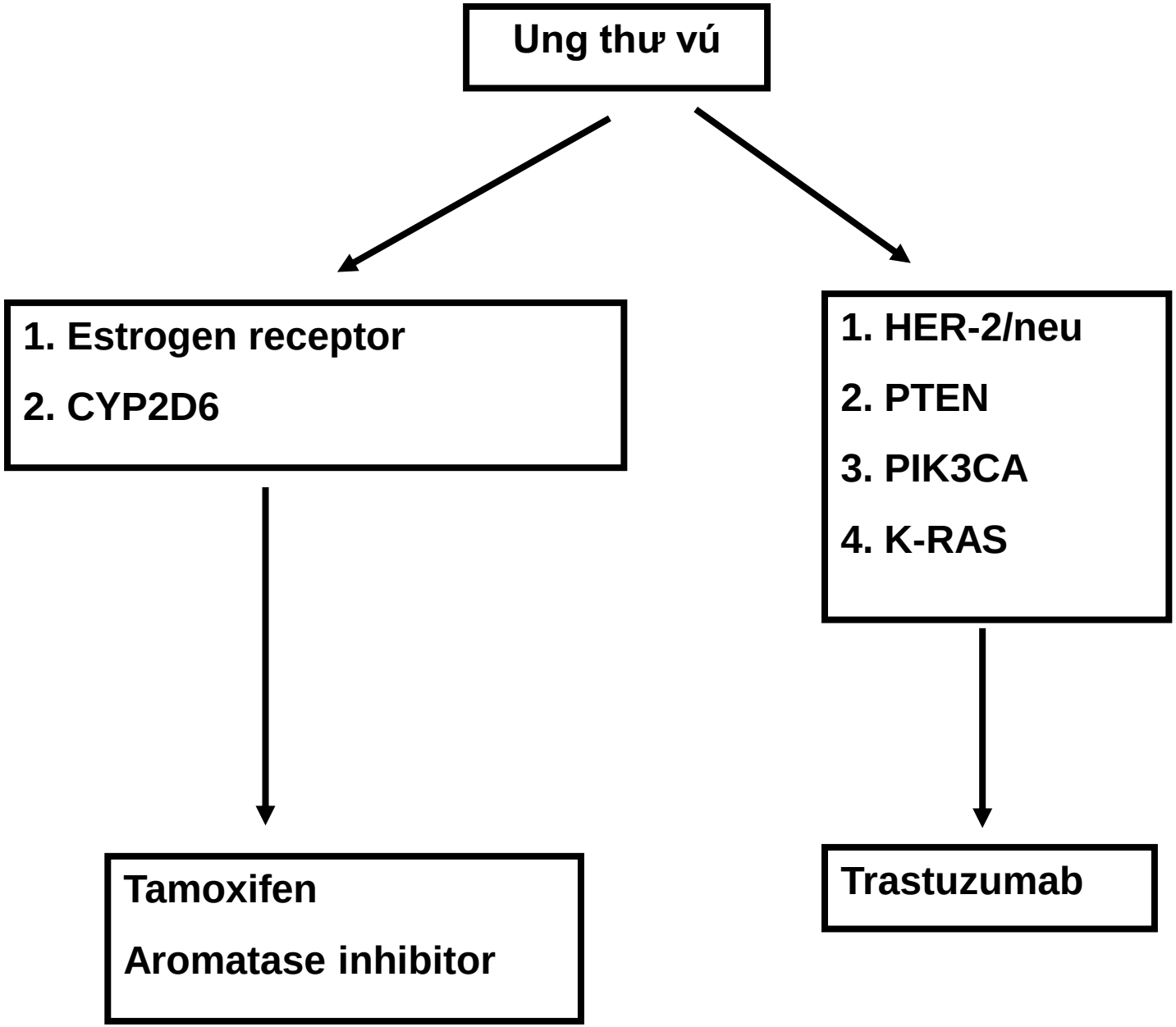
Phần lớn đột biến của PIK3CA xảy ra ở exon 9 và 20

Đột biến PIK3CA liên quan với tiên lượng xấu khi điều trị bằng trastuzumab

(Berns et al,. Cancer Cell 2007)



Pandolfi *et al,. N Engl J Med 2004*

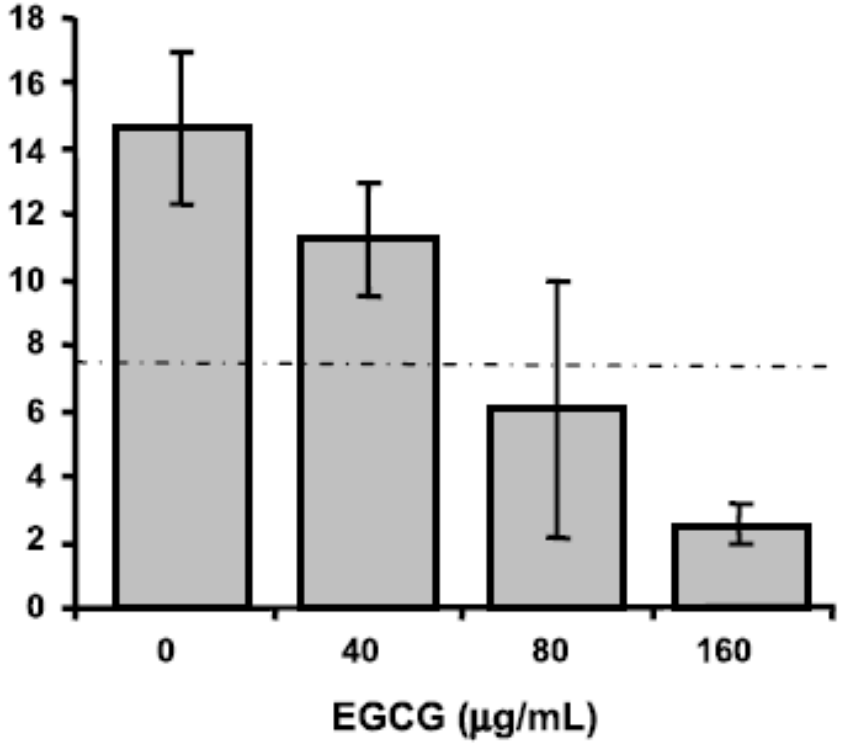

Ung thư vú
1. Estrogen receptor
2. CYP2D6
1. HER-2/neu
2. PTEN
3. PIK3CA
4. K-RAS
Tamoxifen
Aromatase inhibitor
Trastuzumab

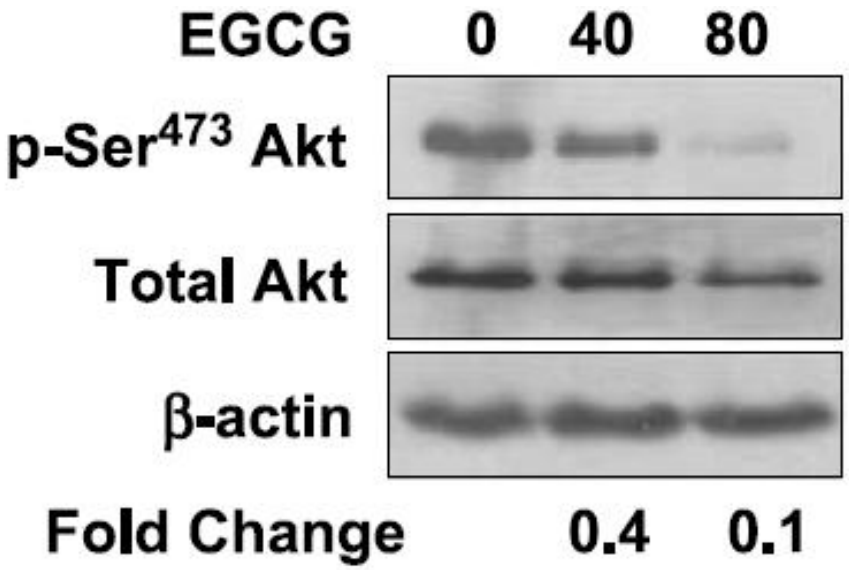
Trastuzumab-Resistant HER2-Driven Breast Cancer Cells Are Sensitive to Epigallocatechin-3 Gallate

Sean F. Eddy,[1] Susan E. Kane,[2] and Gail E. Sonenshein[1]

[1]Department of Biochemistry and Women's Health Interdisciplinary Research Center, Boston University School of Medicine, Boston, Massachusetts and [2]Division of Molecular Medicine, Beckman Research Institute of the City of Hope, Duarte, California

Cancer Res 2007; 67: (19). October 1, 2007





EGCG có ức chế trực tiếp HER-2 không?

Nội dung:

1. TỔNG QUÁT
2. *FLT3* TRONG UNG THƯ MÁU
3. *EGFR* TRONG UNG THƯ PHỔI VÀ UNG THƯ ĐẠI TRỰC TRÀNG
4. *HER-2/neu* TRONG UNG THƯ VÚ
5. ***KIT*** **VÀ** ***PDGFRA*** **TRONG U MÔ ĐỆM ĐƯỜNG TIÊU HÓA**

U mô đệm đường tiêu hóa:

- Gastrointestinal Stromal Tumor (GIST)
- Điều trị chính: phẫu thuật
- Kháng với các phương thức hóa trị cổ điển
- Khoảng 95% có mang đột biến gen *KIT* hoặc *PDGFRA*: Đáp ứng với imatinib

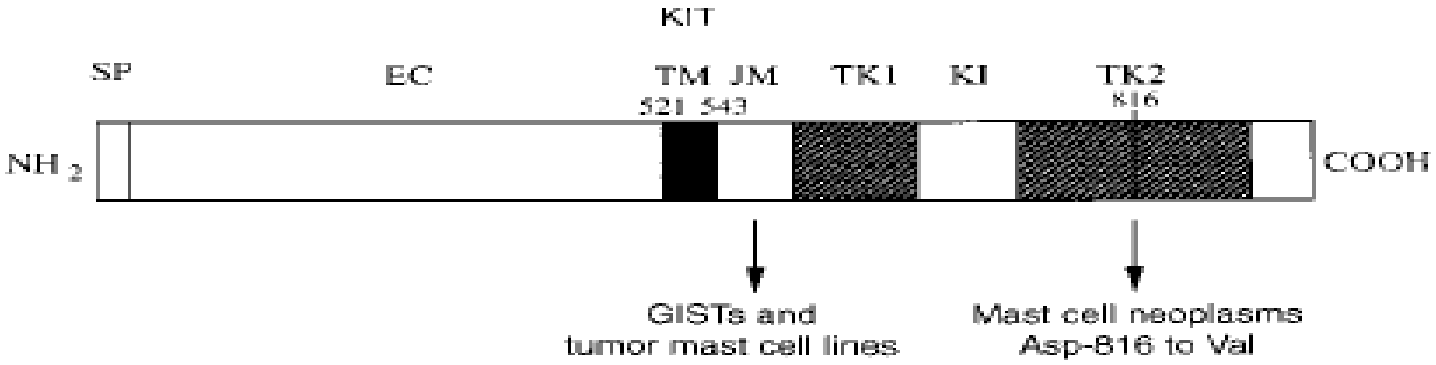
Đột biến gen *KIT:*

- Gastrointestinal Stromal Tumor (GIST)
- U tế bào mầm (buồng trứng hoặc tinh hoàn)
- Ung thư máu cấp

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†

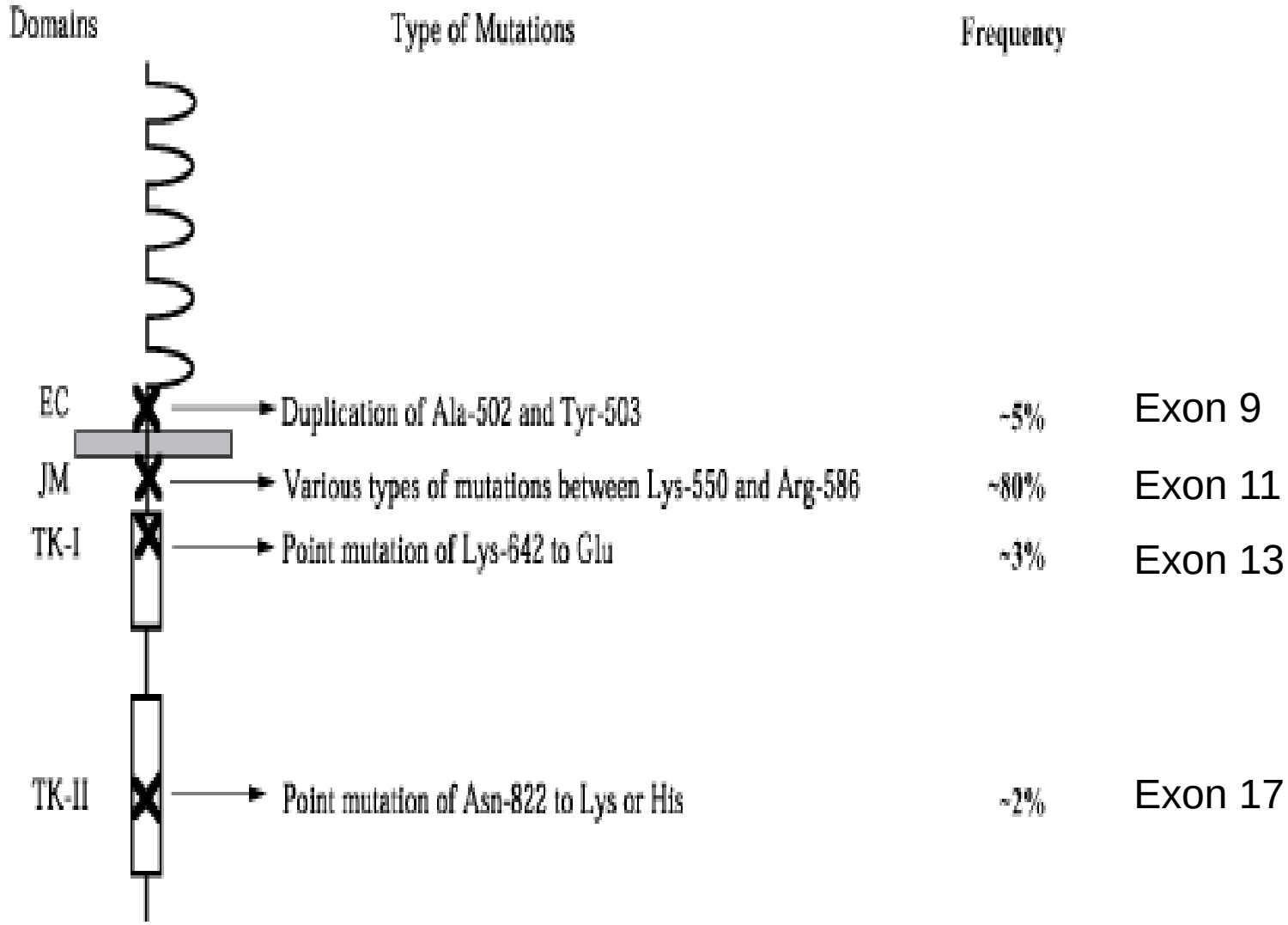
SCIENCE • VOL. 279 • 23 JANUARY 1998



	549									560									570									581
Wild type	Q	K	P	M	Y	E	V	Q	W	K	V	V	E	E	I	N	G	N	N	Y	V	Y	I	D	P	T	Q	L	P	Y	D	H	K
GISTs																																	
1	Q	K	P	M	Y	E	V	Q	W	K	-	-	E	E	I	N	G	N	N	Y	V	Y	I	D	P	T	Q	L	P	Y	D	H	K
2	Q	K	-	-	-	-	-	Q	W	K	V	V	E	E	I	N	G	N	N	Y	V	Y	I	D	P	T	Q	L	P	Y	D	H	K
3	Q	[I]	-	-	-	-	-	Q	W	K	V	V	E	E	I	N	G	N	N	Y	V	Y	I	D	P	T	Q	L	P	Y	D	H	K
4	Q	K	P	M	Y	E	V	Q	W	K	[D]	V	E	E	I	N	G	N	N	Y	V	Y	I	D	P	T	Q	L	P	Y	D	H	K
5	Q	-	-	-	-	-	-	-	-	-	-	V	V	E	E	I	N	G	N	N	Y	V	Y	I	D	P	T	Q	L	P	Y	D	H	K
HMC-1	Q	K	P	M	Y	E	V	Q	W	K	V	[G]	E	E	I	N	G	N	N	Y	V	Y	I	D	P	T	Q	L	P	Y	D	H	K

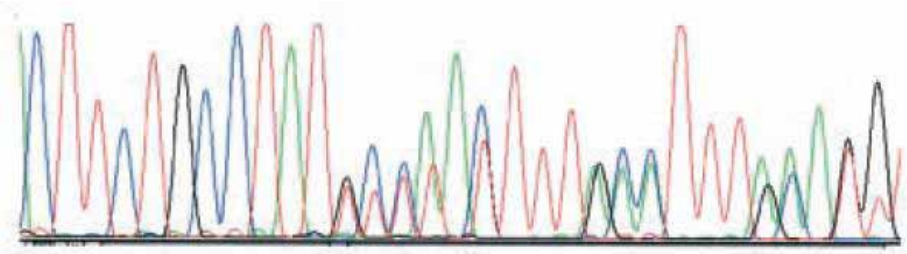
	548									560									570									580
FMA3	Q	K	P	M	Y	E	V	Q	W	K	V	V	E	E	I	N	G	N	N	Y	V	Y	I	D	P	-	-	-	-	-	-	-	-	K

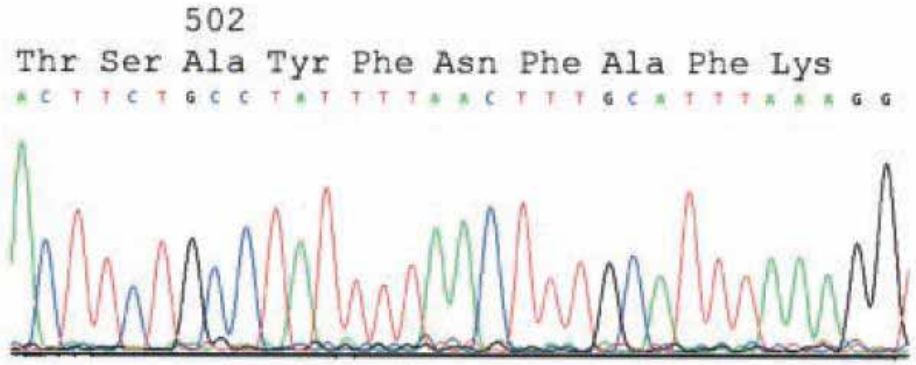
PHÂN BỐ ĐỘT BIẾN *KIT* TRONG GIST

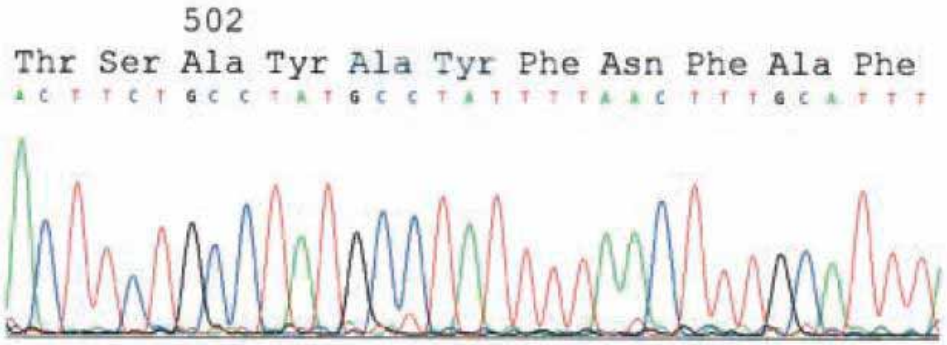


(Kitamura Y, **Cancer Sci 2003; 94: 315–320)**

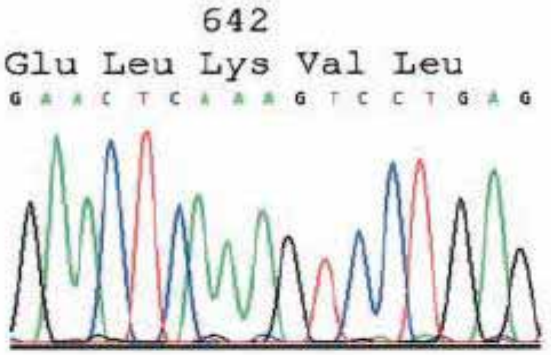
Thêm 6 bp ở exon 9

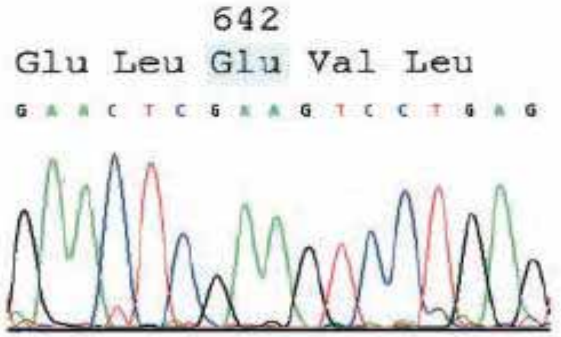






Đột biến ở exon 13





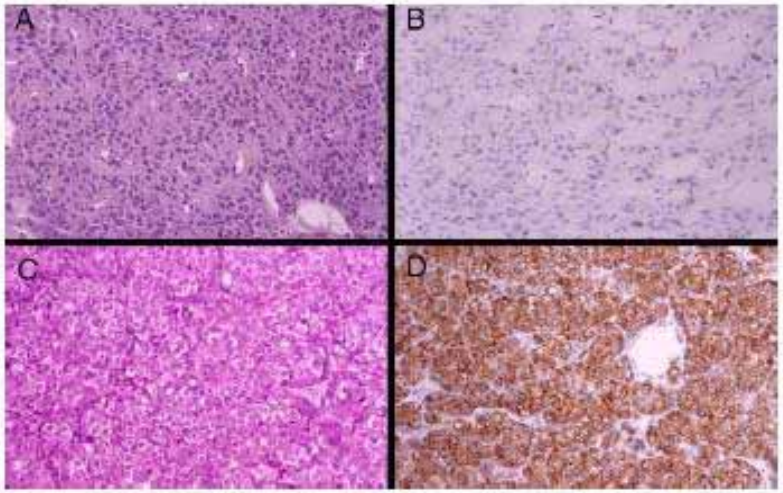
PDGFRA Activating Mutations in Gastrointestinal Stromal Tumors

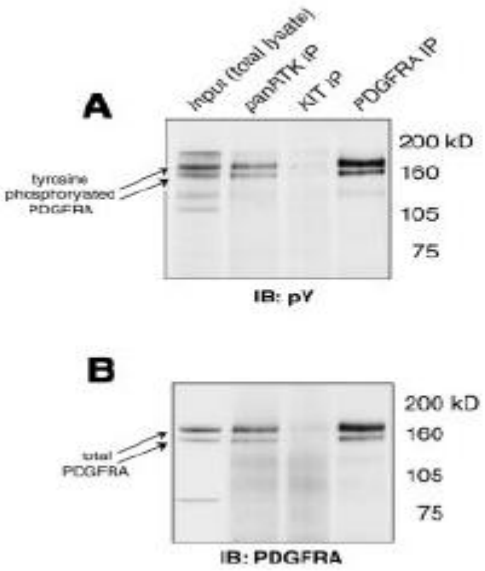
Michael C. Heinrich,[1]* Christopher L. Corless,[2] Anette Duensing,[3] Laura McGreevey,[1] Chang-Jie Chen,[3] Nora Joseph,[3] Samuel Singer,[4] Diana J. Griffith,[1] Andrea Haley,[1] Ajia Town,[1] George D. Demetri,[5] Christopher D. M. Fletcher,[3] Jonathan A. Fletcher[3,5]*

Science 2003;299:708-710

KIT-WT

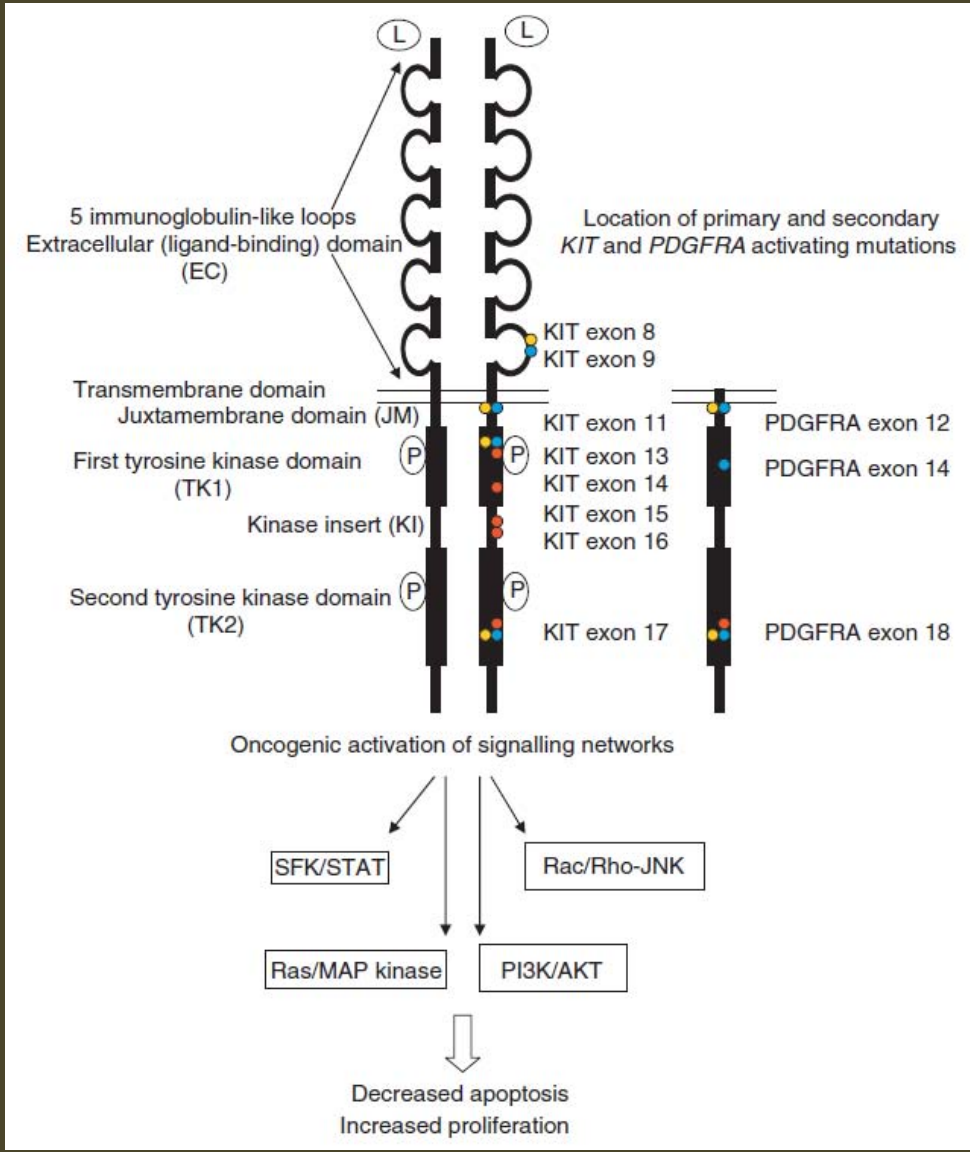
KIT-mt





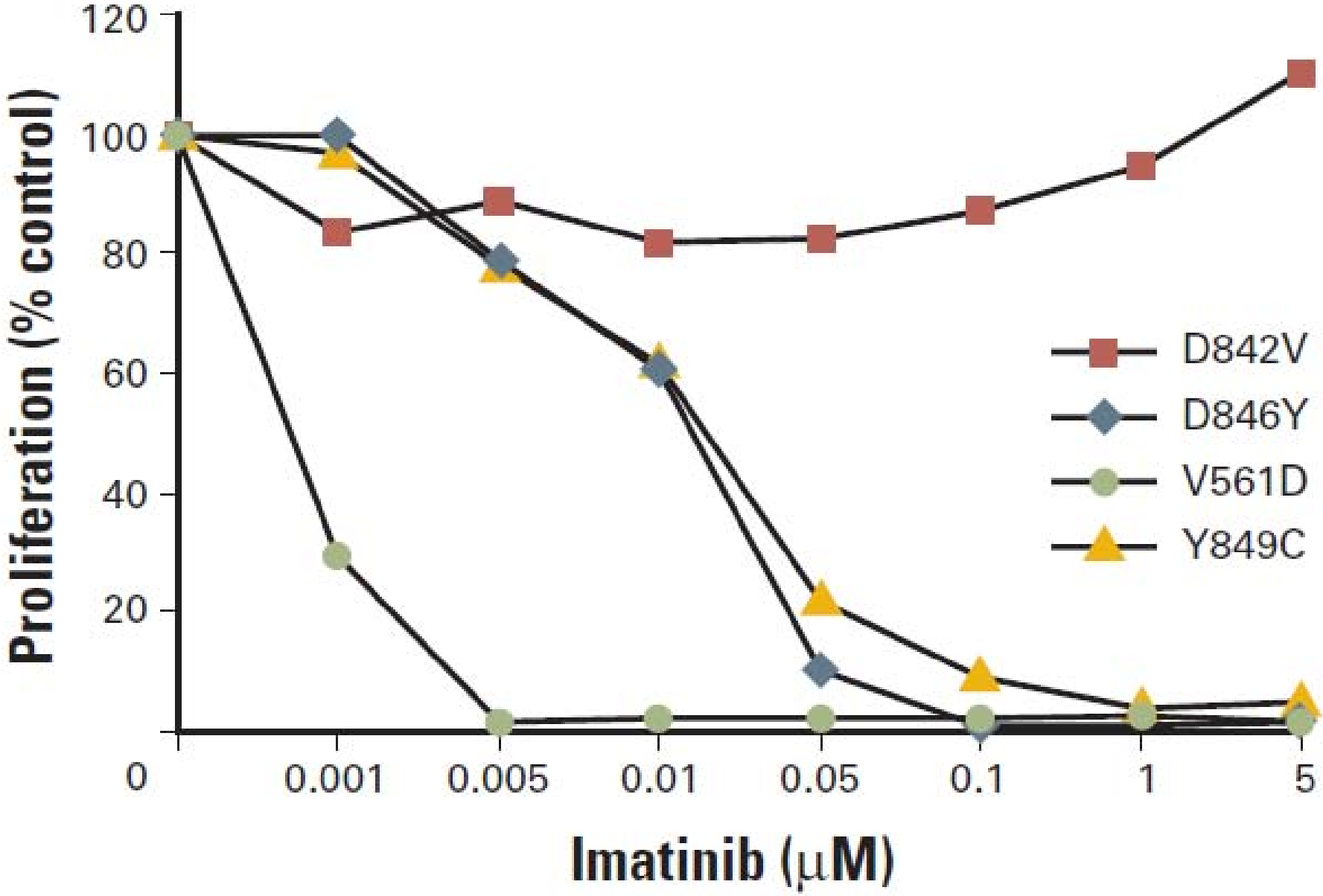
PDGFRA region	Mutation	Number of GISTs
Activation loop (exon 18)	D842V	8
	Del DIMH842-845	1
	Del HDSN845-848P	1
Juxtamembrane (exon 12)	V561D	1
	Ins ER561-562	1
	Del RVIES560-564	1
	Del SPDGHE566-571R	1

PHÂN BỐ ĐỘT BIẾN *KIT* VÀ PDGFRA TRONG GIST



Gene	Exon	Primary *KIT* and *PDGFRA* mutations identified in GISTs from imatinib clinical trials (*n*)	Sensitivity to imatinib mesylate
KIT	9	Ala502_Tyr503dup	Sensitive to imatinib *in vitro*[29] Complete remission in 5%, partial response in 29%, stable disease in 47%, progressive disease in 17% as reported by EORTC phase III trial[84] A high-dose regimen increased progression-free survival[84]
	11	Deletion/deletion–insertion Substitution Duplication	Most common mutants sensitive to imatinib *in vitro*[29] Rare Val559Ile mutant resistant to imatinib *in vitro*[77] Complete remission in 6%, partial response in 61%, stable disease in 25%, progressive disease in 3% as reported by EORTC phase III trial[84]
	13	Lys642Glu (8) Glu635Lys (1)	Sensitive to imatinib *in vitro*[29] Partial response or stable disease reported in all nine cases[29,35,84]
	17	Asp820Tyr (1) Asn822Lys (2) Asn822His (2)	Asn822Lys and Asn822His sensitive to imatinib *in vitro*[29] Partial response reported in four mutants including Asn820Tyr, Asn822Lys, Asn822His[29,84] Primary resistance reported in Asn822Lys mutant[27]
PDGFRA	12	Asp561Val (4) Deletion/deletion–insertion Duplication, insertion	Asp561Val and some other exon 12 mutants tested sensitive to imatinib *in vitro*[30,117] Objective response reported in the majority of a few cases treated with imatinib[29,84]
	14	Asn659Lys	This mutant tested sensitive to imatinib *in vitro*[30] No clinical experience
	18	Asp842_His845del (2) Asp842_Met844del (1) Ile843del (1) Ile843_His845del (1) Asp842Val (7) Asp846Val (1)	Some of these and similar mutants tested sensitive to imatinib *in vitro*[30,117] Objective response reported in the majority of a few cases treated with imatinib[29,84] Asp842Val resistant to imatinib *in vitro*[29,30,117] Resistance reported in seven cases including Asp846Val[29,35,84]; stable disease in one case after 5 months of imatinib treatment[35]
KIT PDGFRA	9, 11, 13, 17 12, 14, 18	Wild-type Wild-type	Partial response in 23%, stable disease in 50%, and progressive disease in 19% as reported by EORTC phase III trial[84]

(Lasota J, *Histopathology* 2008)


Proliferation (% control)
120
100
80
60
40
20
0
0.001
0.005
0.01
0.05
0.1
1
5
Imatinib (μM)
D842V
D846Y
V561D
Y849C

Trước điều trị

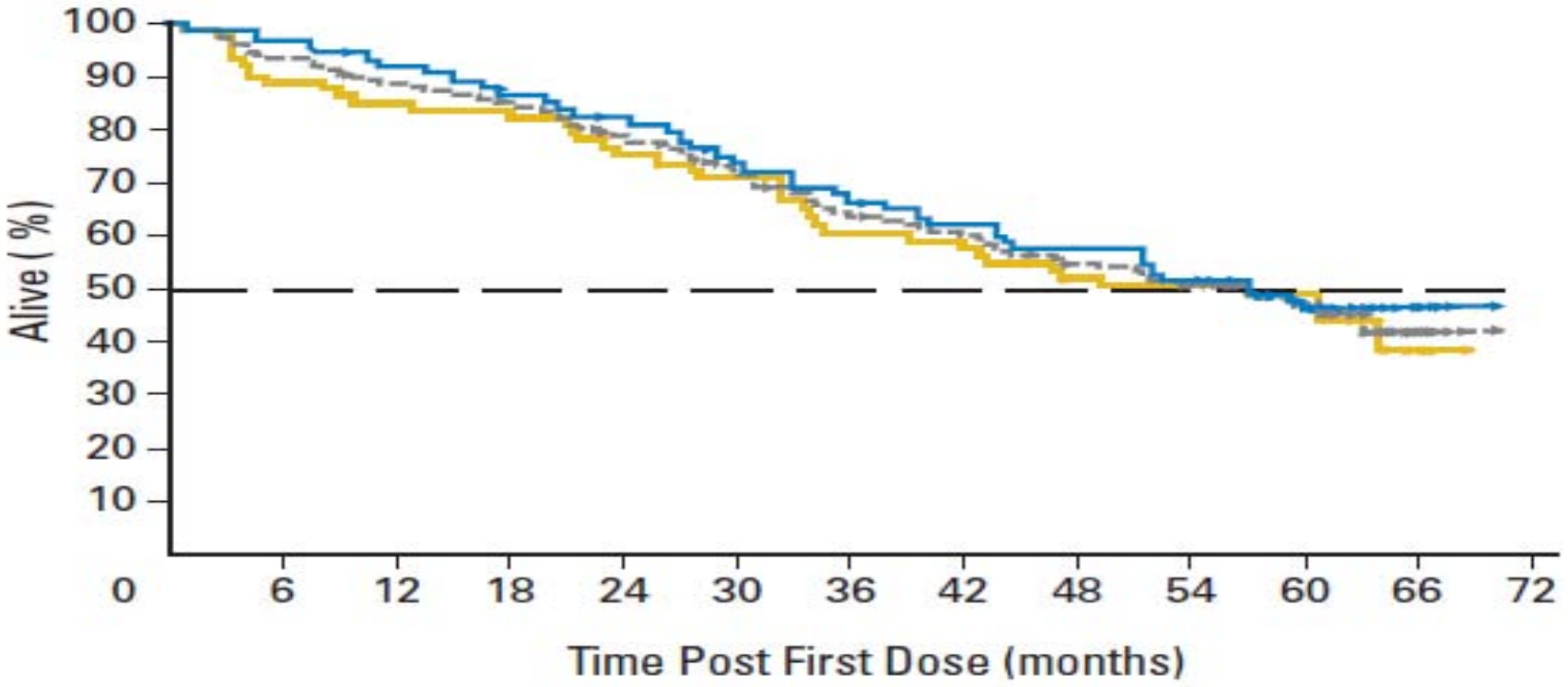
September 14, 2000

Imatinib (2 tuần)

September 27, 2000

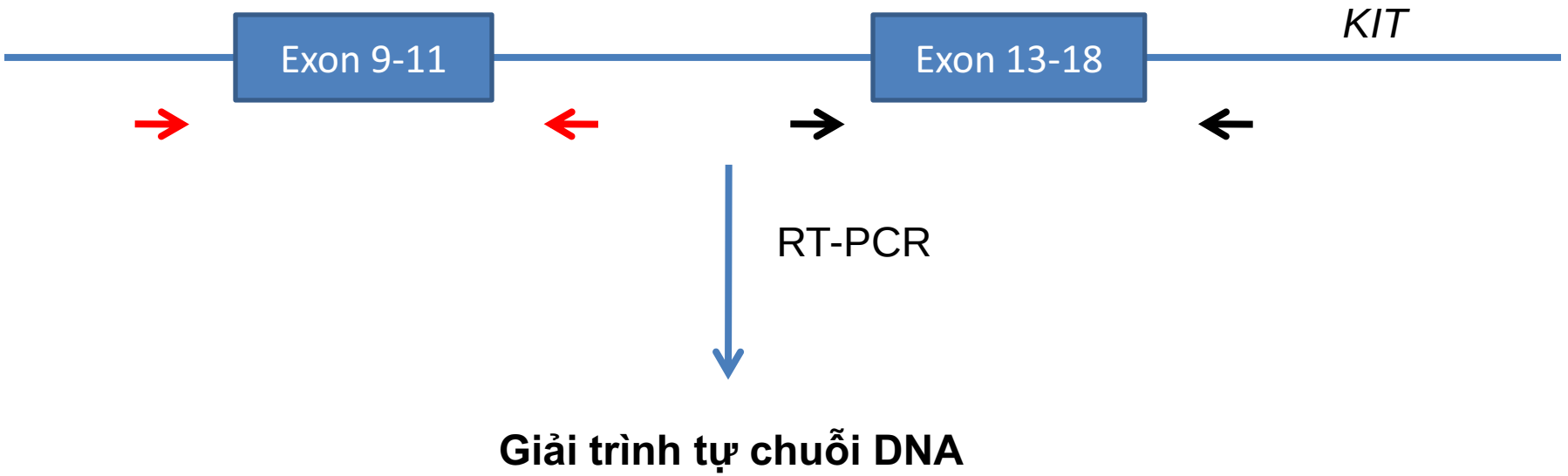
HIỆU QUẢ ĐIỀU TRỊ GIST BẰNG IMATINIB

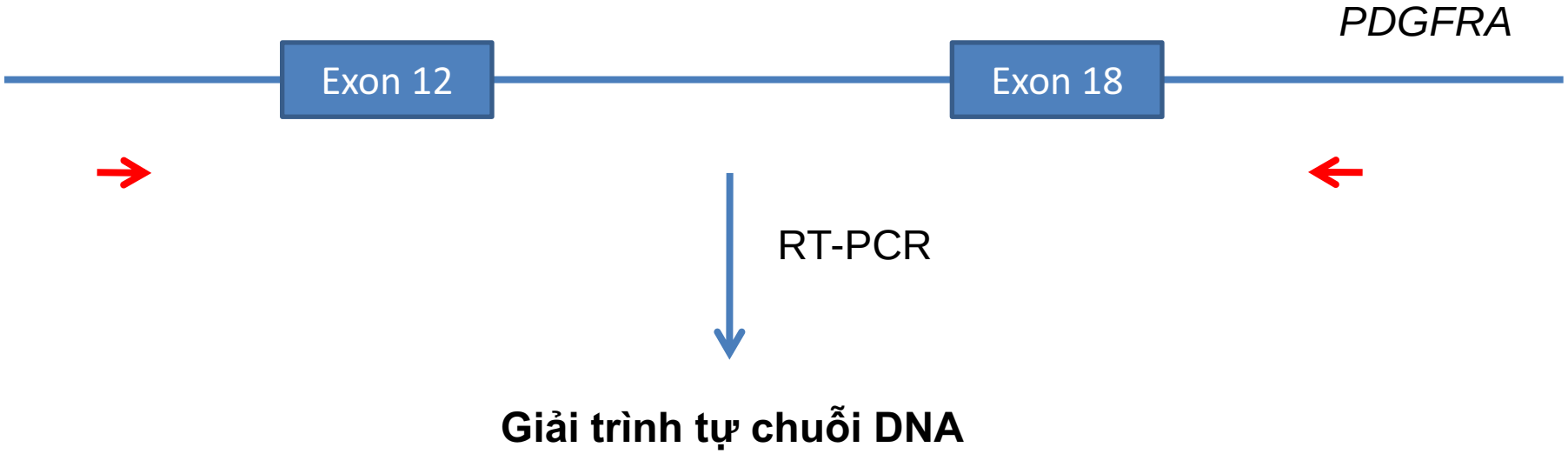
Treatment	Months: 0	12	24	36	48	60	Median duration (months)	95% CI LL	95% CI UL
	No. at risk								
400mg	73	62	54	42	34	26	57	35	N/A
600mg	74	67	58	46	39	28	57	44	N/A
Pooled	147	129	112	88	73	54	57	44	N/A



(Blanke CD, J Clin Oncol 2008;26:620-625)

KHẢO SÁT ĐỘT BIẾN *KIT* VÀ *PDGFRA*



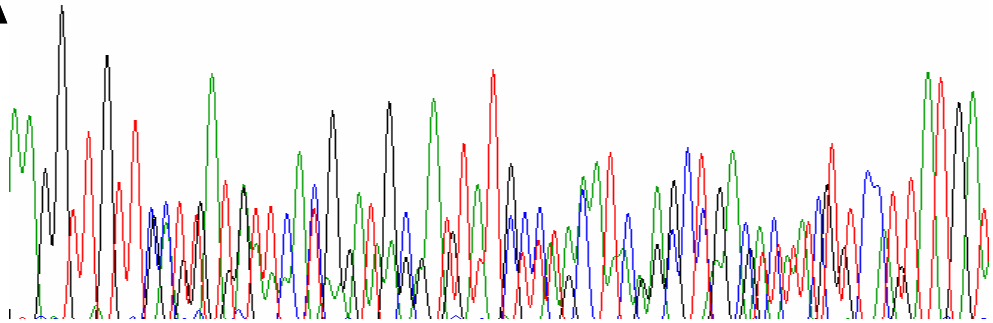


A Recurrent Duodenal Gastrointestinal Stromal Tumor with a Frameshift Mutation Resulting in a Stop Codon in *KIT* Exon 13

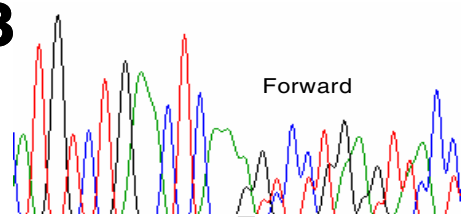
Hoang Anh Vu,[1,2] Phan Thi Xinh,[1,2] Makoto Kikushima,[1] Yi Zhu,[1] Makoto Tokuhara,[3] Masayoshi Tani,[3] Toshio Shimizu,[3] Kiyoshi Saito,[4] Katsushi Tokunaga,[2] and Yuko Sato[1*]

GENES, CHROMOSOMES & CANCER 42:179–183 (2005)

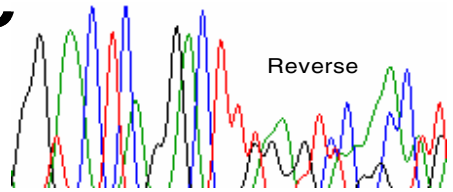
A



B



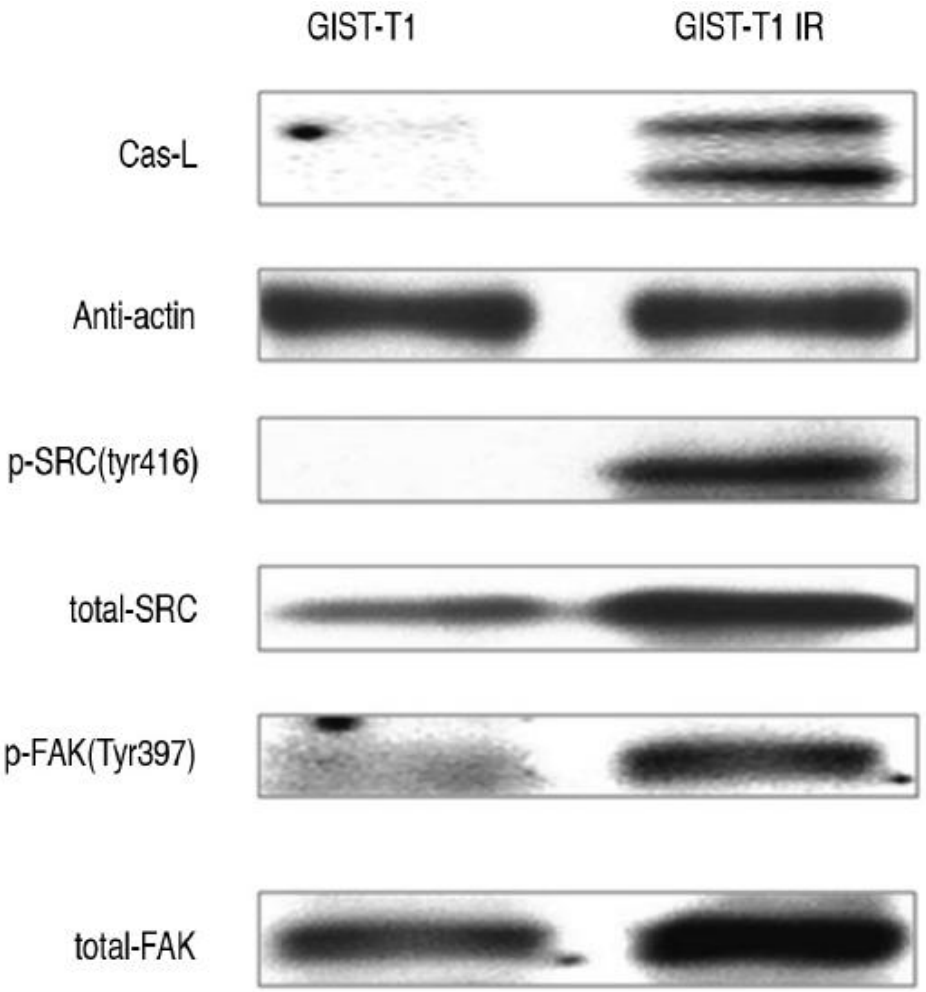
C



Cas-L was overexpressed in imatinib-resistant gastrointestinal stromal tumor cells

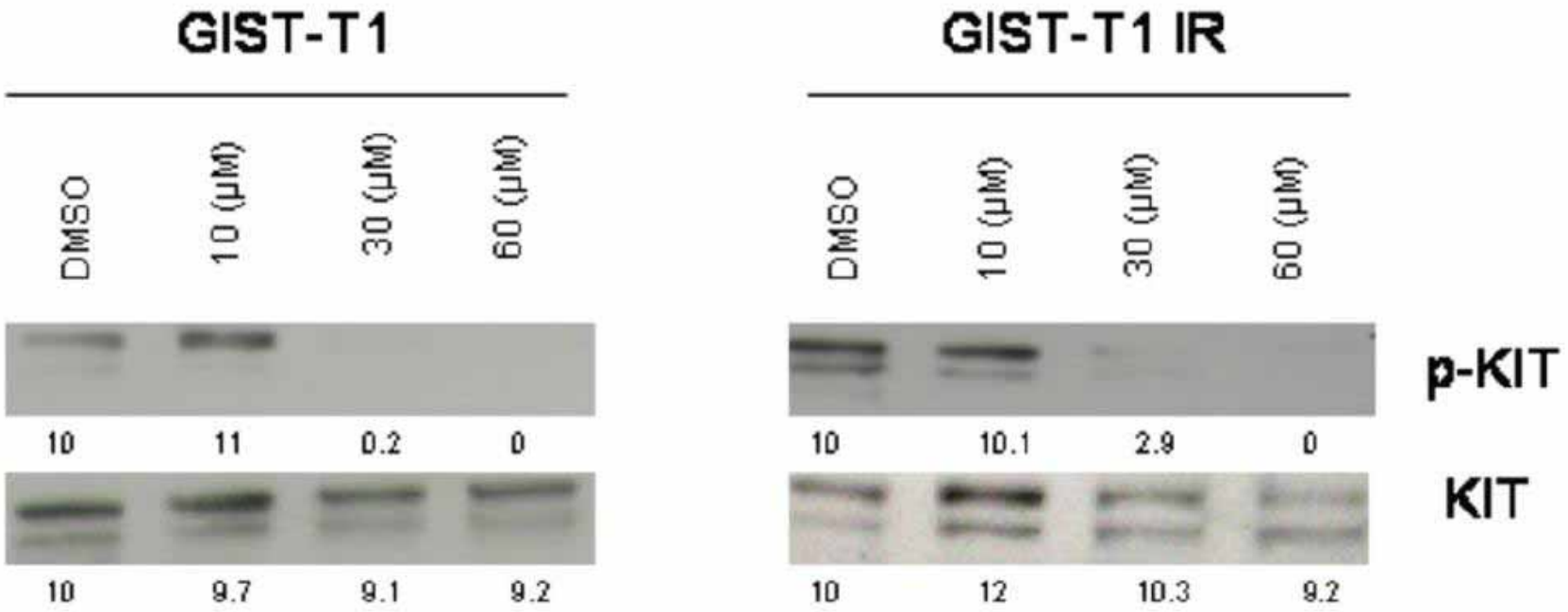
[Cancer Biology & Therapy 8:8, 683-688; 15 April 2009]

Le Ba Thao,[1,2] Hoang Anh Vu,[1] Kazuki Yasuda,[3] Shigeki Taniguchi,[3] Fumiharu Yagasaki,[4] Takahiro Taguchi,[5] Toshiki Watanabe[2] and Yuko Sato[1,*]



Green Tea (-)-Epigalocatechin-3-gallate Inhibits KIT Activity and Causes Caspase-Dependent Cell Death in Gastrointestinal Stromal Tumor Including Imatinib-resistant Cells

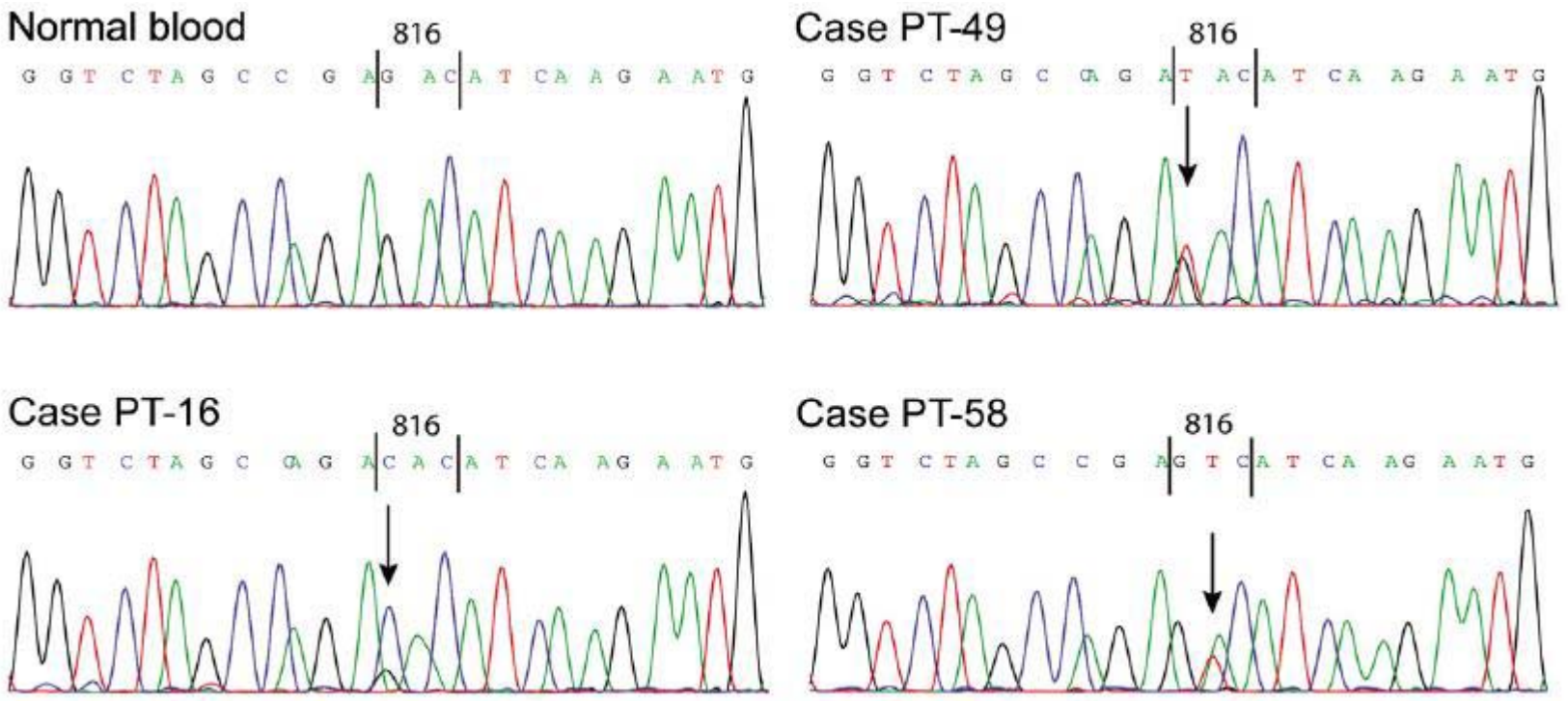
Hoang Thanh Chi[1,2], Hoang Anh Vu[1], Reo Iwasaki[1,2], Le Ba Thao[1,2], Yukihiko Hara[3], Takahiro Taguchi[4], Toshiki Watanabe[2], Yuko Sato[1]



Ovarian dysgerminomas are characterised by frequent *KIT* mutations and abundant expression of pluripotency markers

Christina E Hoei-Hansen*†[1], Sigrid M Kraggerud†[2,5], Vera M Abeler[3], Janne Kærn[4], Ewa Rajpert-De Meyts[1] and Ragnhild A Lothe[2,5]

Molecular Cancer 2007, **6**:12



MÔ HÌNH XUẤT HIỆN U TẾ BÀO MẦM Ở BUỒNG TRỨNG VÀ TINH HOÀN