EL PATOLOGO Y LOS BIOMARCADORES EN CANCER DE COLON

XXV Congreso de la SEAP

20 Mayo 2011

SéAP-IAP

sec

SEPAF

2011 ZARAGOZA

Biomarcadores

Los marcadores biológicos o biomarcadores son los cambios medibles, ya sean estos bioquímicos, fisiológicos o morfológicos, que se asocian a la exposición a un tóxico.

McCarthy & Shugart (1990)

Los biomarcadores son útiles para:

detectar la presencia de una exposición
determinar las consecuencias biológicas de la exposición
detectar los estados iniciales e intermedios de un proceso patológico
identificar a los individuos sensibles de una población

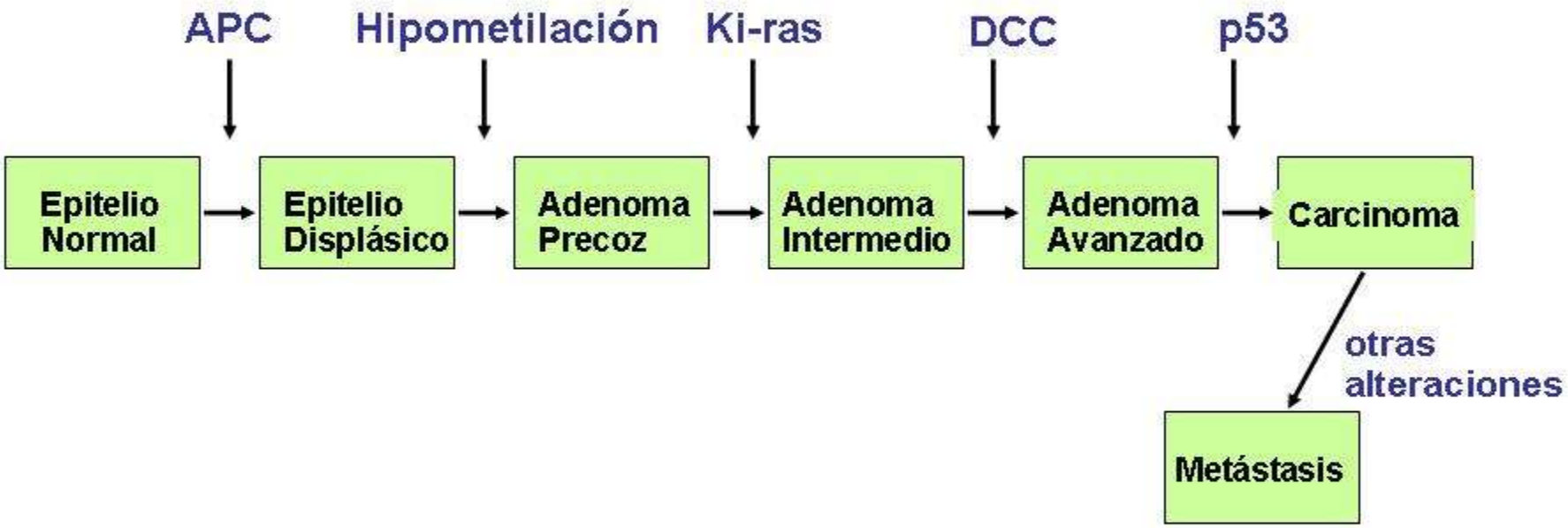
fundamentan la decisión de intervenir, tanto a nivel individual como

ambiental

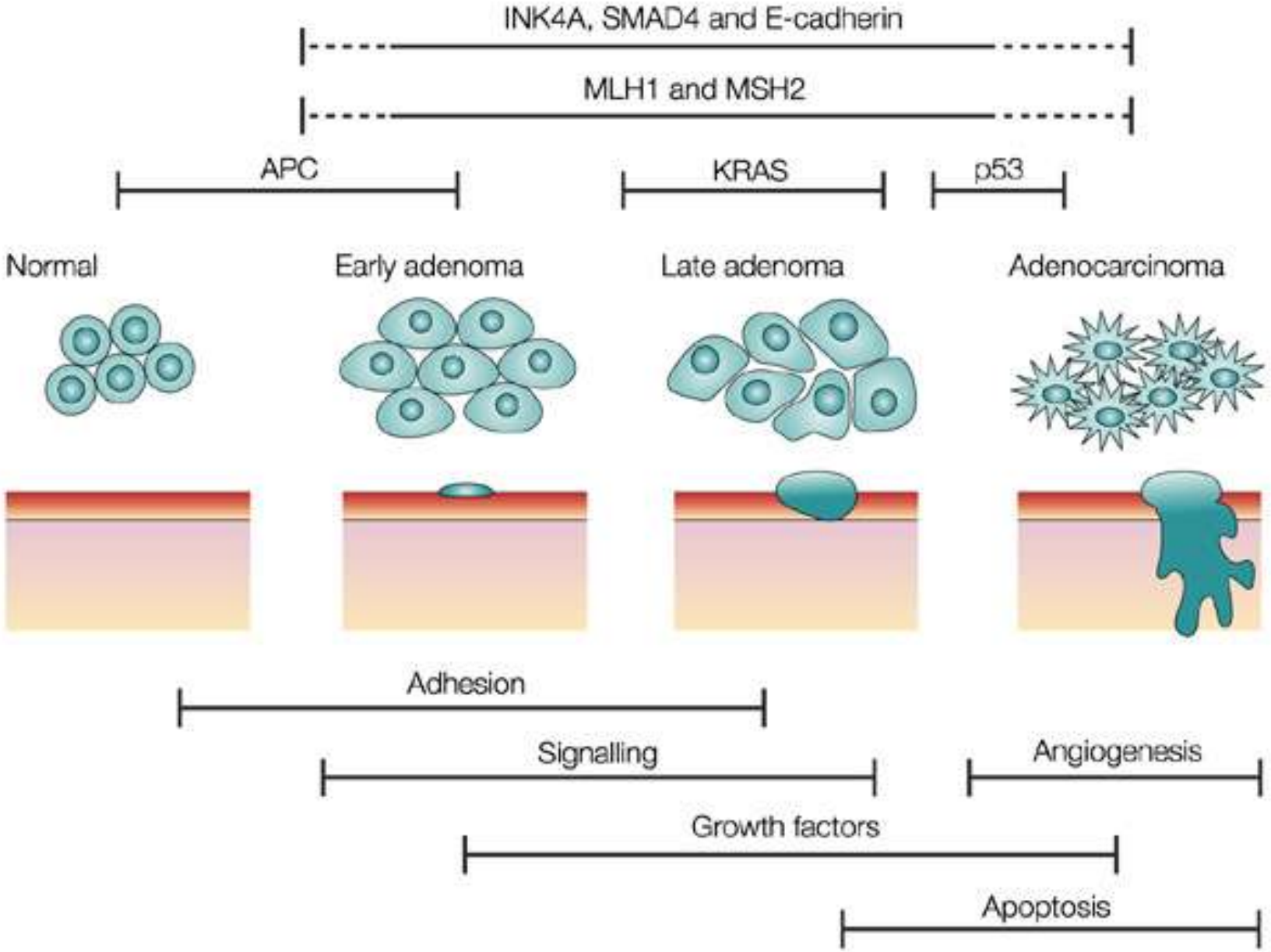
Biomarcadores en el cáncer

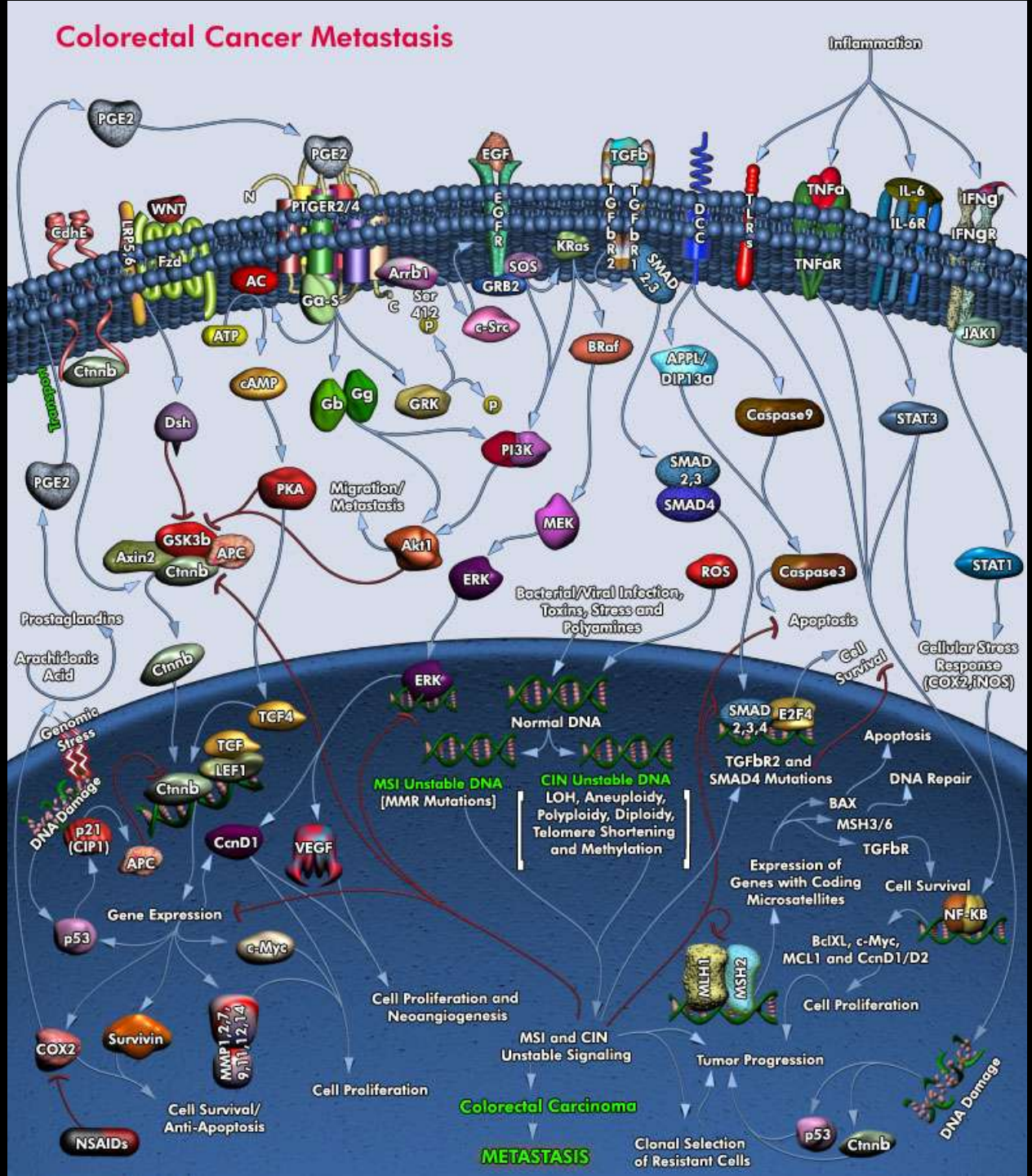
Genéticos	Mutaciones oncogenes Alteraciones en genes supresores
ADN	Amplificación genética Inestabilidad de microsatélites Alteraciones de secuencias repetitivas
Epigenéticos	Metilación de ADN
ARN	miARNs
Inmunológicos	Respuestas de células T y citoquinas

Bases biológicas del cáncer de colon



Hipótesis general de la carcinogénesis colorectal.
B. Vogelstein et al., 1995.


INK4A, SMAD4 and E-cadherin
MLH1 and MSH2
APC
KRAS
p53
Normal
Early adenoma
Late adenoma
Adenocarcinoma
Adhesion
Signalling
Angiogenesis
Growth factors
Apoptosis


Colorectal Cancer Metastasis
Inflammation
PGE2
PGE2
PTGER2/4
EGF
TGFb
TNFa
IL-6
IL-6R
IFNg
IFNgR
WNT
CdhE
LRP5/6
Fzd
AC
Ga-S
Arrb1
Ser 412 P
c-Src
KRas
SOS
GRB2
TGFbR2
TGFbR1
SMAD 2,3
DCC
TLRs
TNFaR
JAK1
Ctnnb
cAMP
Gb
Gg
GRK
P
BRaf
APPL/ DIP13a
Caspase9
STAT3
Dsh
PI3K
SMAD 2,3
SMAD4
PKA
Migration/ Metastasis
MEK
GSK3b
Axin2
APC
Ctnnb
Akt1
ERK
ROS
Caspase3
STAT1
Bacterial/Viral Infection, Toxins, Stress and Polyamines
Apoptosis
Prostaglandins
Arachidonic Acid
Cellular Stress Response (COX2,iNOS)
Cell Survival
Genomic Stress
DNA Damage
TCF4
TCF
LEF1
Normal DNA
SMAD 2,3,4
E2F4
Apoptosis
TGFbR2 and SMAD4 Mutations
DNA Repair
BAX
MSH3/6
TGFbR
MSI Unstable DNA [MMR Mutations]
CIN Unstable DNA LOH, Aneuploidy, Polyploidy, Diploidy, Telomere Shortening and Methylation
Expression of Genes with Coding Microsatellites
Cell Survival
NF-KB
p21 (CIP1)
APC
CcnD1
VEGF
Gene Expression
p53
c-Myc
BclXL, c-Myc, MCL1 and CcnD1/D2
MLH1
MSH2
Cell Proliferation and Neoangiogenesis
Cell Proliferation
COX2
Survivin
MMP1,2,7, 9,11,12,14
MSI and CIN Unstable Signaling
Tumor Progression
Cell Survival/ Anti-Apoptosis
Colorectal Carcinoma
NSAIDs
METASTASIS
Clonal Selection of Resistant Cells
p53
Ctnnb
DNA Damage

Desarrollo de Terapias Oncológicas Dirigidas

Anticuerpos Monoclonales empleados en el tratamiento del Cáncer

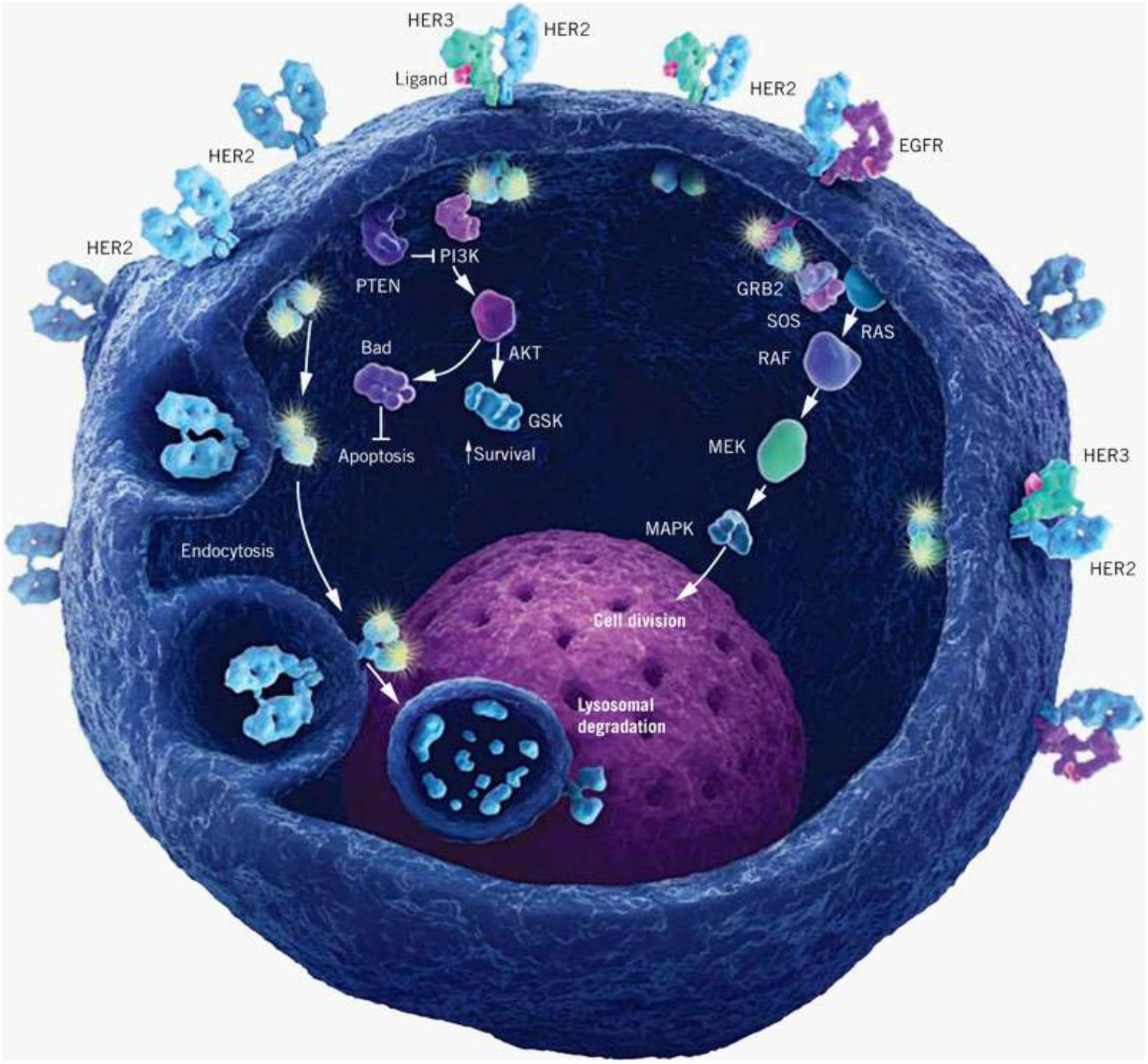
Ac	Nombre Comercial	Empleado en	Aprobado en	Diana	Determinación
rituximab	Mabthera®	Linfoma no-Hodgkin LNH	1998	CD20	IHQ
trastuzumab	Herceptin®	Cáncer de mama Cáncer de estómago	2000 2009	HER2	IHQ + FISH
alemtuzumab	Mabcampath®	LLC	2001	CD52	No
ibritumomab tiuxetan*	Zevalin®	LNH	2004	CD20	No
cetuximab	Erbitux®	Carcinoma colorrectal Cáncer de cabeza y cuello	2004 2006	EGFR	IHQ Molecular
bevacizumab	Avastin®	Carcinoma colorrectal Cáncer de pulmón NSCLC Cáncer de Mama Glioblastoma Cáncer renal	2005 2006 2008 2009 2009	VEGF	No
panitumumab	Vectibix®	Cancer colorrectal	2007	EGFR	IHQ Molecular
ofatumumab	Arzerra®	LLC	2010	CD20	IHQ

Inhibidores de Quinasas empleados en el tratamiento del Cáncer

TKI	Nombre Comercial	Empleado en	Aprobado en	Diana	Determinación
Imatinib	Glivec	LMA GIST	2001 2004	PDGFRa C-kit	IHQ + Molecular
gefitinib	Iressa	Cáncer de pulmón (NSCLC)	2009	EGFR	Molecular
erlotinib	Tarceva	Cáncer de pulmón (NSCLC) Cáncer de páncreas	2005	EGFR	Molecular
sunitinib	Sutent	Cáncer de Riñón GIST	2006	Multitarget (VEGFR)	No
sorafenib	Nexavar	Cáncer de Riñón Cáncer de Higado	2006	Multitarget (VEGFR)	No
dasatinib	Sprycel	LLA y LMC	2006 2009	Multitarget BCR-ABL, familia SRC (SRC, LCK, YES, FYN), c-kit, EPHA2, PDGFRß	No
temsirolimus	Torisel	Cáncer de Riñon Linfoma de células del manto	2007	mTOR	No
nilotinib	Tasigna	LMC	2007	Bcr-abl	Molecular

Dianas Terapéuticas en Cáncer Colorrectal Metastásico

- Epidermal growth factor receptor (EGFR)
- Vascular endothelial growth factor receptor (VEGFR)
- COX-2
- Otras dianas y biomarcadores
  - Antígeno Carcinoembrionario
  - Protein quinasa C
  - Metaloproteasas
  - Ras
  - Quinasas dependientes de ciclinas


HER3
HER2
Ligand
HER2
HER2
EGFR
HER2
PI3K
PTEN
GRB2
SOS
RAS
RAF
Bad
AKT
GSK
Apoptosis
Survival
MEK
HER3
MAPK
Endocytosis
HER2
Cell division
Lysosomal
degradation

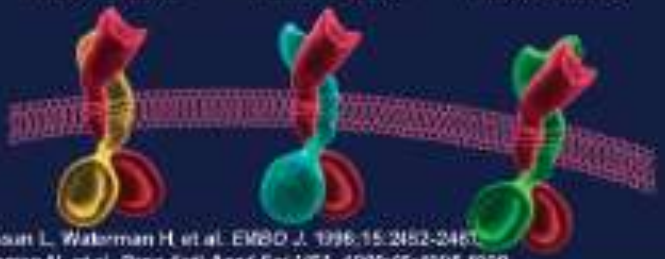
HER1/EGFR Dimerization

HER1 homodimer

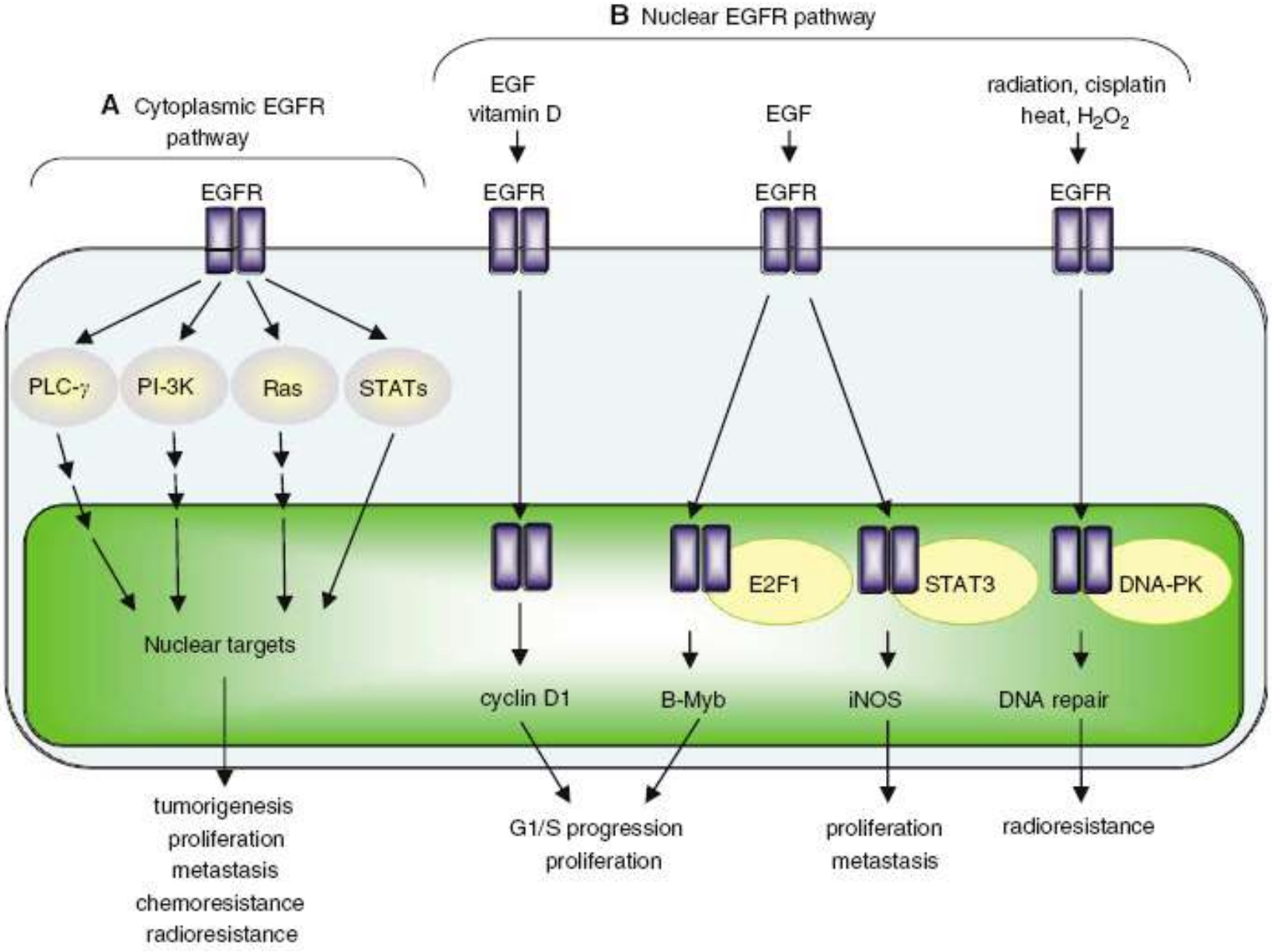
HER1-HER1

Three HER1-containing heterodimers

HER1-HER2 HER1-HER3 HER1-HER4



Pinkas-Kramarski R, Soussan L, Waterman H, et al. EMBO J. 1996;15:2452-2467.
Klapper LN, Glathe S, Vaisman N, et al. *Proc Natl Acad Sci USA*. 1999;96:4995-5000.


B Nuclear EGFR pathway
A Cytoplasmic EGFR pathway
EGF
vitamin D
EGF
radiation, cisplatin
heat, H_2O_2
EGFR
EGFR
EGFR
EGFR
PLC-γ
PI-3K
Ras
STATs
E2F1
STAT3
DNA-PK
Nuclear targets
cyclin D1
B-Myb
iNOS
DNA repair
tumorigenesis
proliferation
metastasis
chemoresistance
radioresistance
G1/S progression
proliferation
proliferation
metastasis
radioresistance

Inhibidores de EGFR en Cáncer Colorrectal

- Sobreexpresión de EGFR en más del 90% de tumores metastásicos
  - La activación de EGFR provoca inhibición de apoptosis, proliferación celular maligna, migración y angiogénesis
  - Tumores que expresan EGFR son más agresivos, con peor pronóstico
- Anticuerpos Monoclonales anti-EGFR
  - Cetuximab, Panitumumab
- Inhibidores Tyrosine kinase (TKIs) de EGFR
  - Gefitinib, Erlotinib

Venook A. Oncologist. 2005;10:250-261
Mayer A, et al. Cancer. 1993;71:2454-2560.

FDA News

FOR IMMEDIATE RELEASE
P04-20
February 12, 2004

Media Inquiries: 301-827-6242
Consumer Inquiries: 888-INFO-FDA

FDA Approves Erbitux for Colorectal Cancer

FDA today approved Erbitux (cetuximab) to treat patients with advanced colorectal cancer that has spread to other parts of the body. Erbitux is the first monoclonal antibody approved to treat this type of cancer and is indicated as a combination treatment to be given intravenously with irinotecan, another drug approved to fight colorectal cancer, or alone if patients cannot tolerate irinotecan.

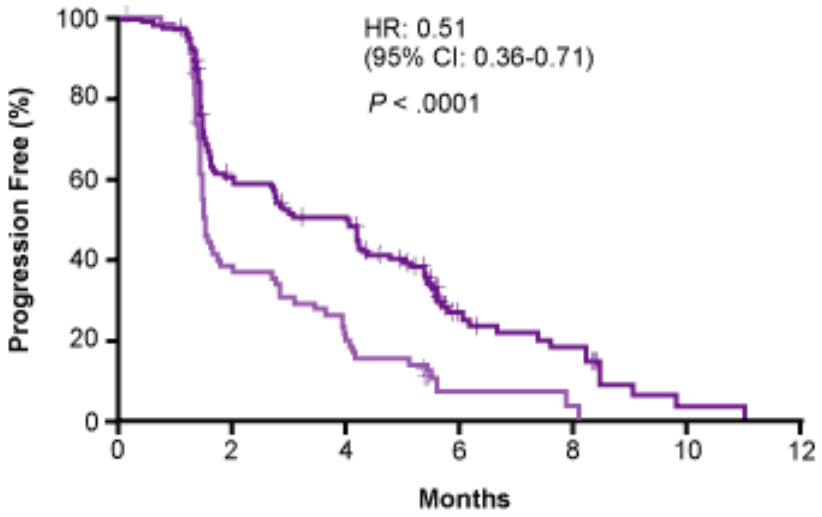
Erbitux was approved under FDA's accelerated approval program, which allows FDA to approve products for cancer and other serious or life-threatening diseases based on early evidence of a product's effectiveness. Although treatment with Erbitux has not been shown to extend patients' lives, it was shown to shrink tumors in some patients and delay tumor growth, especially when used as a combination treatment.

Erbitux is a genetically engineered version of a mouse antibody that contains both human and mouse components. (Antibodies in the body are substances produced by the immune system to fight foreign substances.) It can be produced in large quantities in the laboratory. This new monoclonal antibody is believed to work by targeting a natural protein called "epidermal growth factor receptor" (EGFR) on the surface of cancer cells, interfering with their growth.

For patients with tumors that express EGFR and who no longer responded to treatment with irinotecan alone or in combination with other chemotherapy drugs, the combination treatment of Erbitux and irinotecan shrank tumors in 22.9% of patients and delayed tumor growth by approximately 4.1 months. For patients who received Erbitux alone, the tumor response rate was 10.8% and tumor growth was delayed by 1.5 months.

Colorectal cancer -- cancer of the colon or rectum -- is the third most common cancer affecting men and women in the U.S. and, according to the Centers for Disease Control and Prevention (CDC), and is the second leading cause of cancer-related death. Colorectal cancer is also one of the most commonly diagnosed cancers in the U.S.; approximately 147,500 new cases were diagnosed in 2003.

Time to progression in the BOND study (Cetuximab ± Irinotecan)



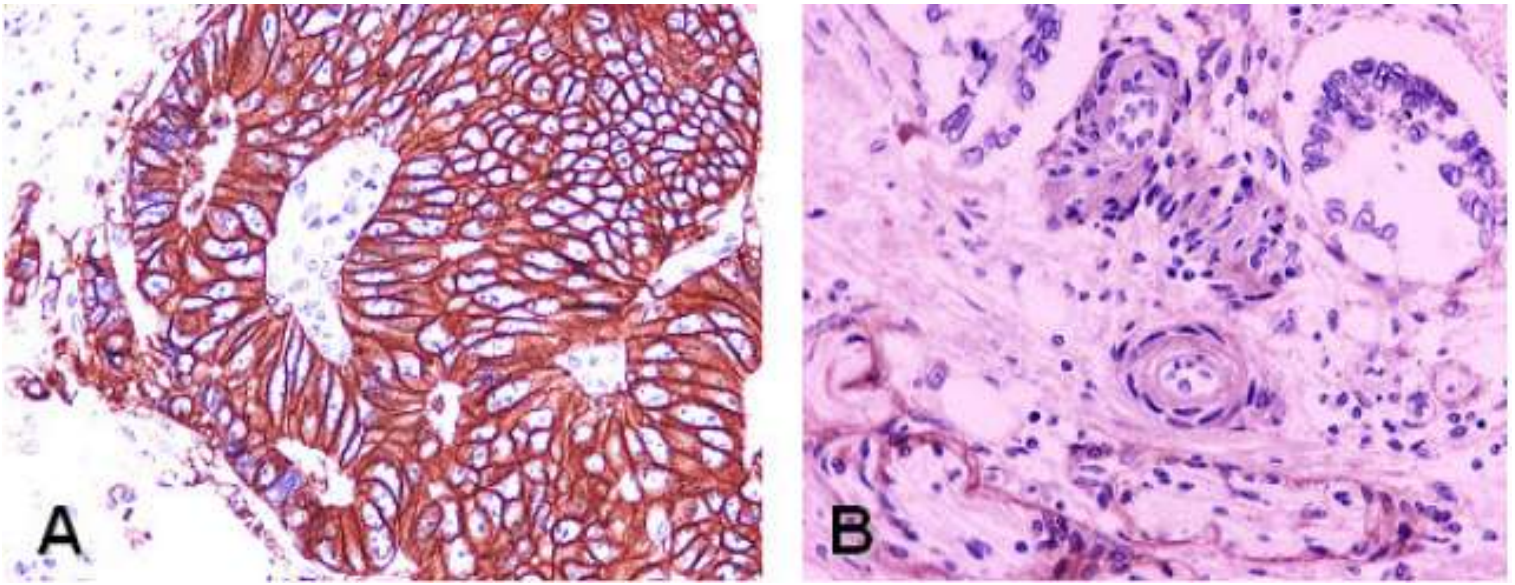
CI, confidence interval; HR, hazard ratio.

Cunningham D, et al. N Engl J Med. 2004;351:337-345.

Erbitux Q&A

- **What is Erbitux (Cetuximab)?**
  - **monoclonal antibody that targets EGFR**
  - **interfere with the growth of cancer cells by binding to EGFR so that the normal (natural) epidermal growth factors cannot bind and stimulate the cells to grow**
  - **approved label requires test for EGFR positivity (immunohistochemistry test)**

EXPRESION DE EGFR EN CANCER COLORRECTAL



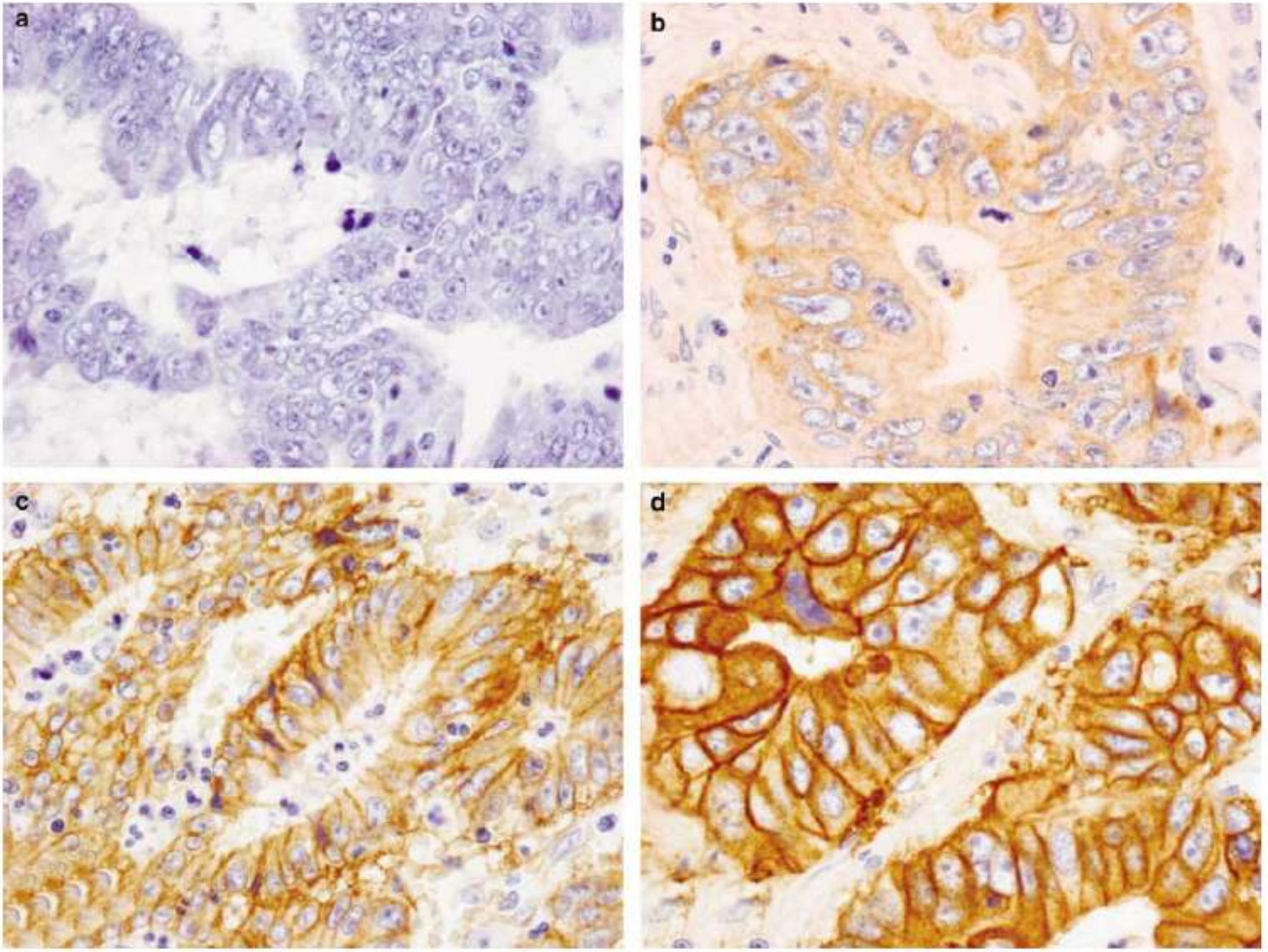


Figure 1 Immunohistochemical staining using the EGFR pharmDx kit showing negative (**a**), 1+ (**b**), 2+ (**c**) and 3+ (**d**) membrane labeling for EGFR in four different colorectal carcinomas.

KRAS Mutation Status Is Predictive of Response to Cetuximab Therapy in Colorectal Cancer

Astrid Lièvre,[1,3] Jean-Baptiste Bachet,[3] Delphine Le Corre,[1] Valérie Boige,[4] Bruno Landi,[2] Jean-François Emile,[3] Jean-François Côté,[1,2] Gorana Tomasic,[4] Christophe Penna,[3] Michel Ducreux,[4] Philippe Rougier,[3] Frédérique Penault-Llorca,[5] and Pierre Laurent-Puig[1,2]

[1]Université Paris-Descartes, Institut National de la Sante et de la Recherche Medicale UMR-775; [2]Assistance Publique-Hôpitaux de Paris, Hôpital Européen Georges Pompidou, Paris, France; [3]Assistance Publique-Hôpitaux de Paris, Hôpital Ambroise Paré, Boulogne Billancourt, France, Université de Versailles Saint-Quentin-en-Yvelines, Versailles, France; [4]Institut Gustave Roussy, Villejuif, France; and [5]Centre Jean Perrin, Clermont-Ferrand, France, Université Auvergne, Clermont-Ferrand, France

for *KRAS*, *BRAF*, and *PIK3CA* mutation by direct sequencing and for EGFR copy number by chromogenic *in situ* hybridization. Eleven of the 30 patients (37%) responded to cetuximab. A *KRAS* mutation was found in 13 tumors (43%) and was significantly associated with the absence of response to cetuximab (*KRAS* mutation in 0% of the 11 responder patients versus 68.4% of the 19 nonresponder patients; $P = 0.0003$). The overall survival of patients without *KRAS* mutation in their tumor was significantly higher compared with those patients with a mutated tumor ($P = 0.016$; median, 16.3 versus 6.9 months). An increased *EGFR* copy number was found in 3 patients (10%) and was significantly associated with an objective tumor response to cetuximab ($P = 0.04$). In conclusion, in this study, *KRAS* mutations are a predictor of resistance to cetuximab therapy and are associated with a worse prognosis. The *EGFR* amplification, which is not as frequent as initially reported, is also associated with response to this treatment. (Cancer Res 2006; 66(8): 3992-5)

British Journal of Cancer (2007) 96, 1166 – 1169

www.bjcancer.com

Clinical relevance of *KRAS* mutation detection in metastatic colorectal cancer treated by Cetuximab plus chemotherapy

F Di Fiore[*,1], F Blanchard[3], F Charbonnier[2], F Le Pessot[2,3], A Lamy[3], MP Galais[4], L Bastit[5], A Killian[2], R Sesboüé[2], JJ Tuech[2,6], AM Queuniet[7], B Paillot[1], JC Sabourin[2,3], F Michot[2,6], P Michel[1] and T Frebourg[2]

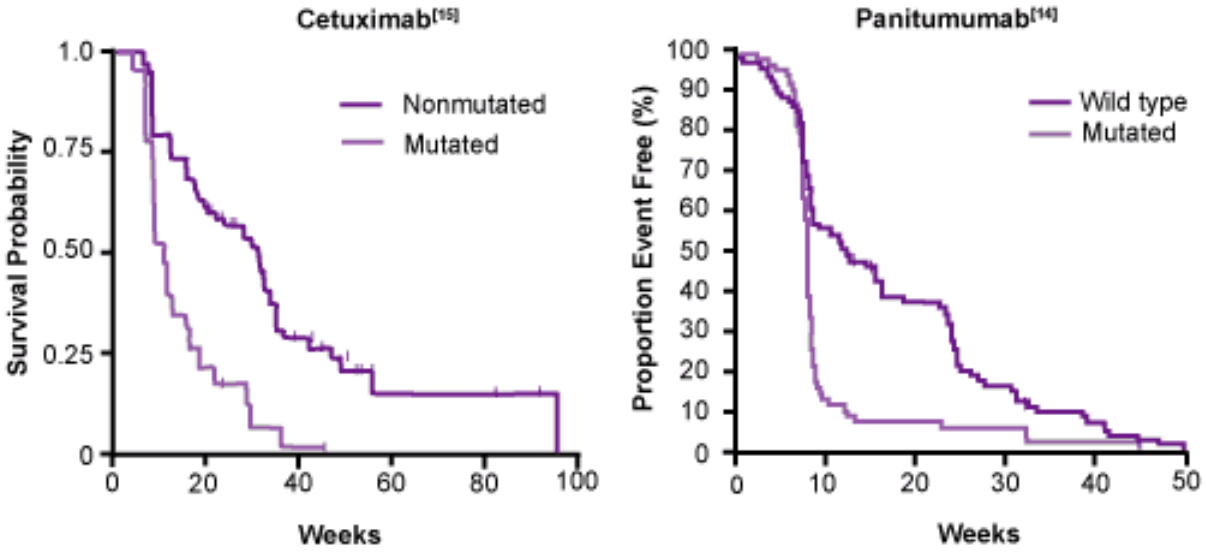
VOLUME 26 · NUMBER 10 · APRIL 1 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

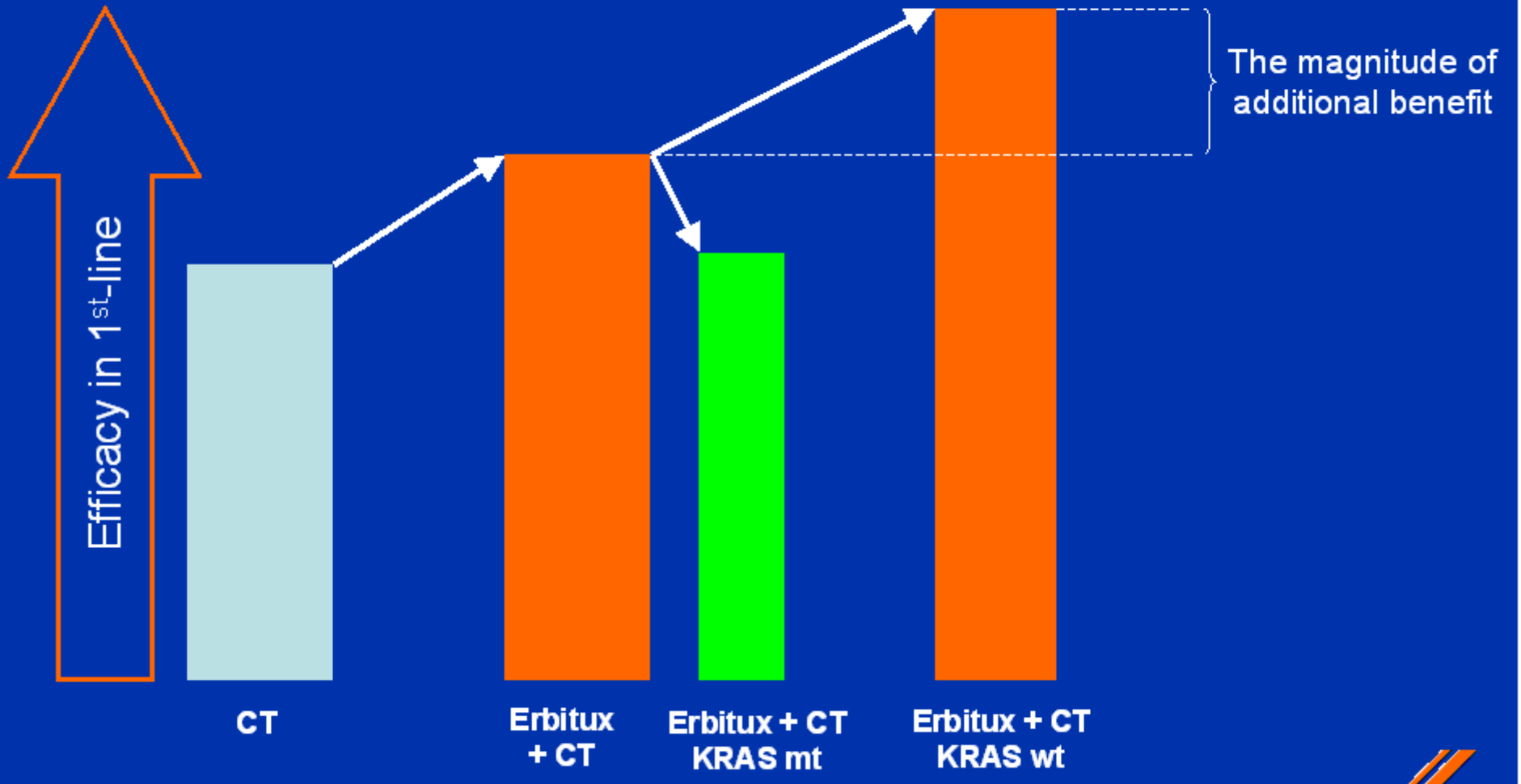
Wild-Type *KRAS* Is Required for Panitumumab Efficacy in Patients With Metastatic Colorectal Cancer

Rafael G. Amado, Michael Wolf, Marc Peeters, Eric Van Cutsem, Salvatore Siena, Daniel J. Freeman, Todd Juan, Robert Sikorski, Sid Suggs, Robert Radinsky, Scott D. Patterson, and David D. Chang

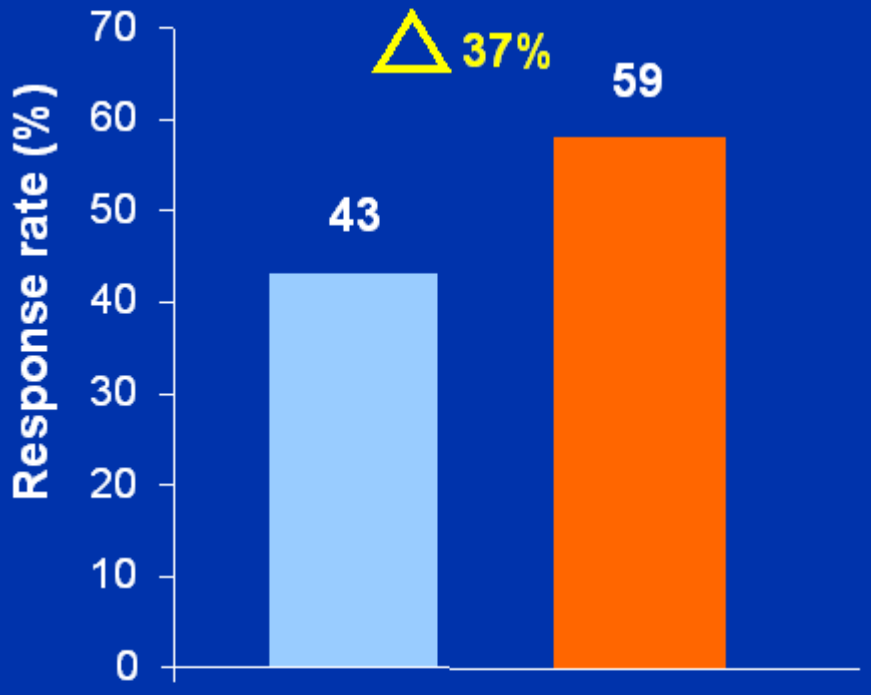


Lievre A, Bachet JB, Boige V, et al. KRAS mutations as an independent prognostic factor in patients with advanced colorectal cancer treated with cetuximab. J Clin Oncol. 2008;26:374-379. Reprinted with permission from the American Society of Clinical Oncology[15].

Does KRAS make a difference?



Relating KRAS status to efficacy: Response – KRAS wild-type patients



p=0.0025
Odds Ratio = 1.91
(95% CI: 1.245 -2.929)

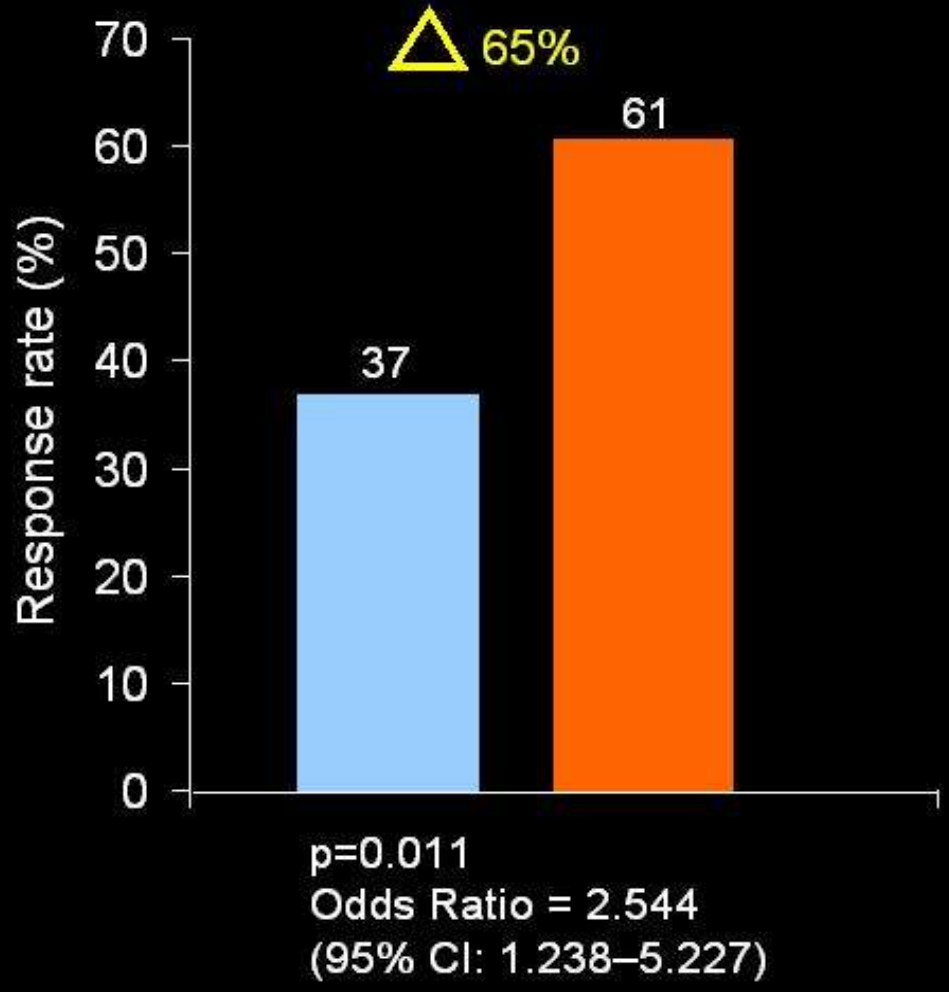
	FOLFIRI N=176	ERBITUX + FOLFIRI N=172
CR	0	1.2%
PR	43.2%	58.1%
SD	43.8%	30.8%
PD	9.1%	5.2%
Not evaluable	4.0%	4.7%
RR (CR+PR)	**43.2%**	**59.3%**
95% CI (exact)	[35.8%, 50.9%]	[51.6%, 66.7%]

based on Kaplan-Meier estimates

CRYSTAL

ERBITUX + FOLFIRI
FOLFIRI

Relating KRAS status to efficacy: Response – KRAS wild-type patients

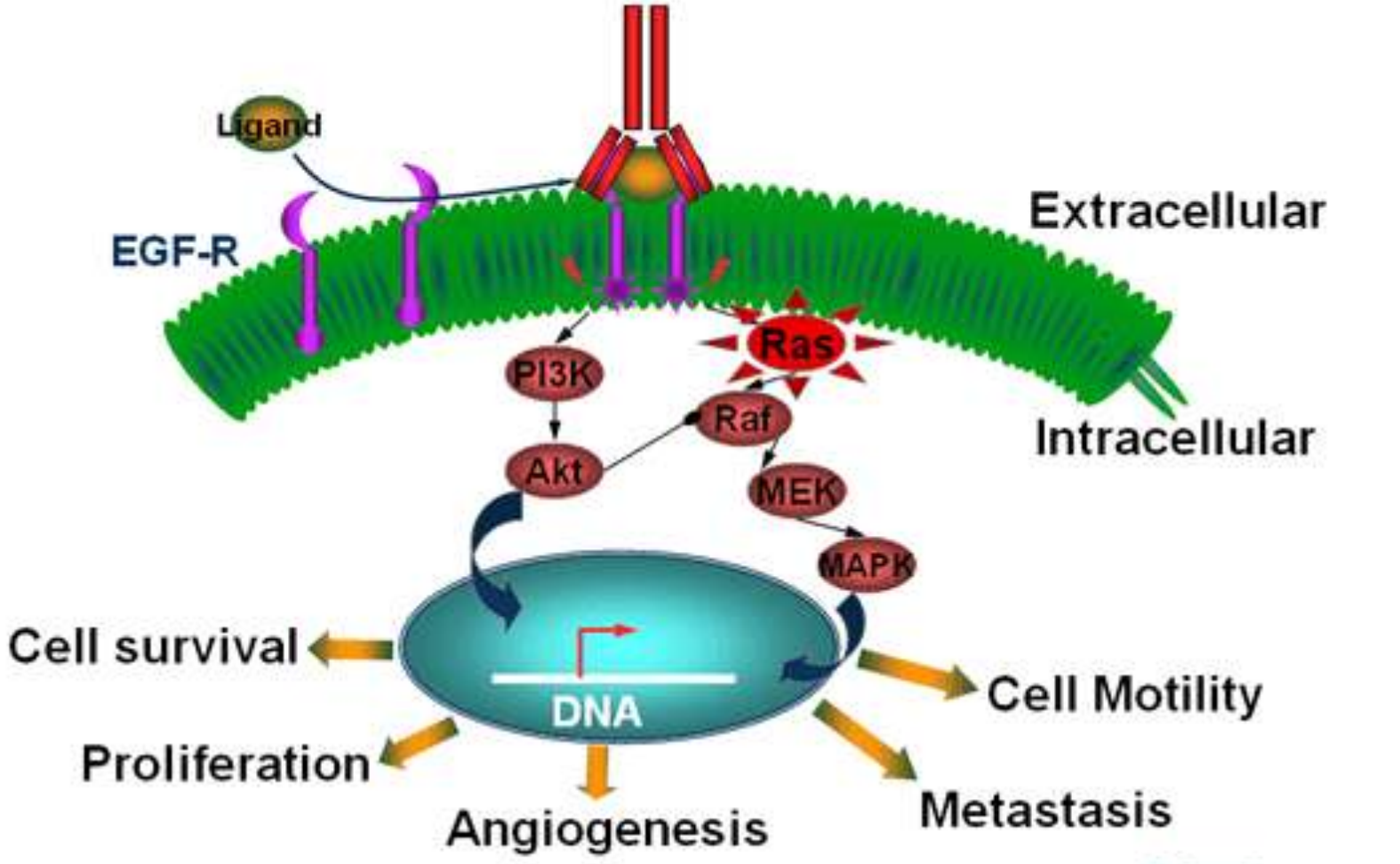


	FOLFOX N=73	ERBITUX + FOLFOX N=61
CR	1.4%	3.3%
PR	35.6%	57.4%
SD	41.1%	31.1%
PD	16.4%	4.9%
NE	5.5%	3.3%
RR	37.0%	60.7%
95% CI (exact)	[26.0%, 49.1%]	[47.3%, 72.9%]

OPUS

ERBITUX + FOLFOX
FOLFOX

mAbs Target Tumor Cell-Bound EGFR

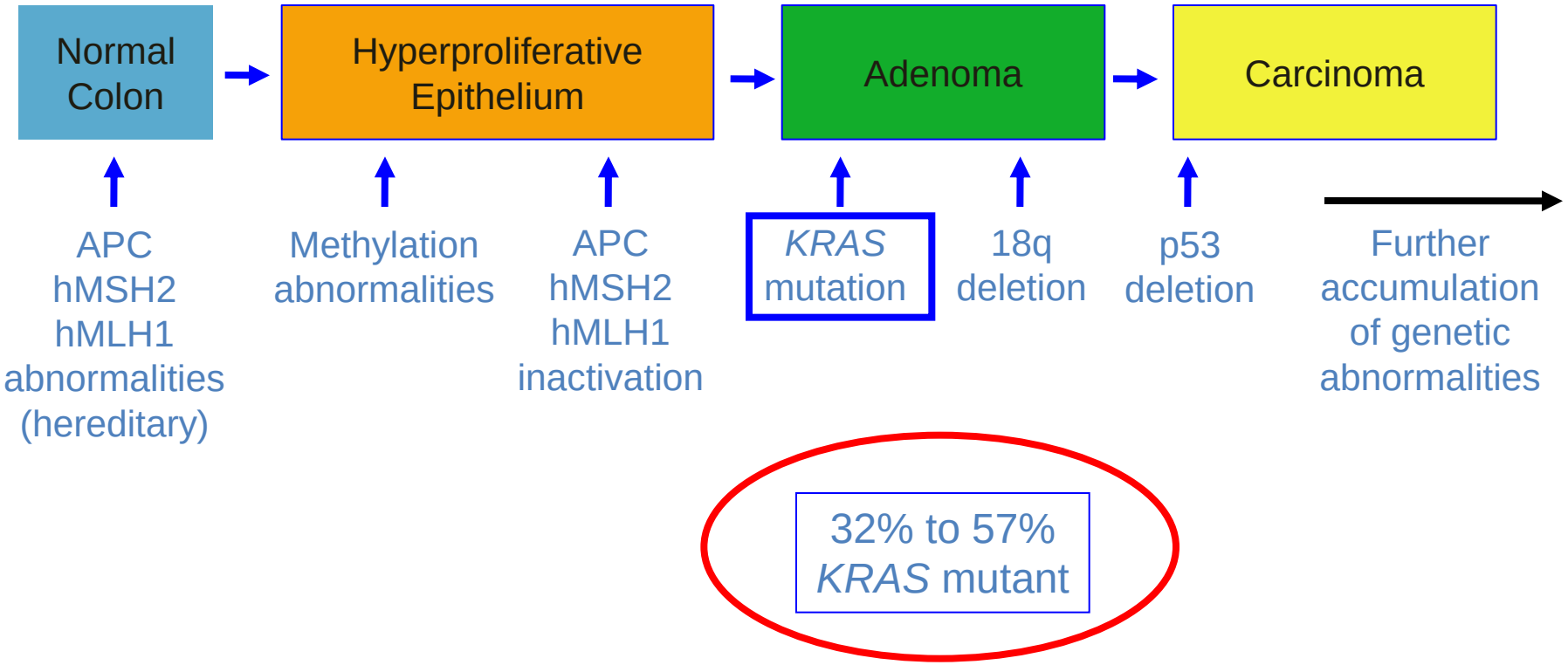


Medscape

Biomarcadores en Cáncer Colorrectal asociados a la vía de activación de EGFR

- Kras
- BRAF
- PIK3CA
- PTEN

Secuencia Adenoma-Carcinoma



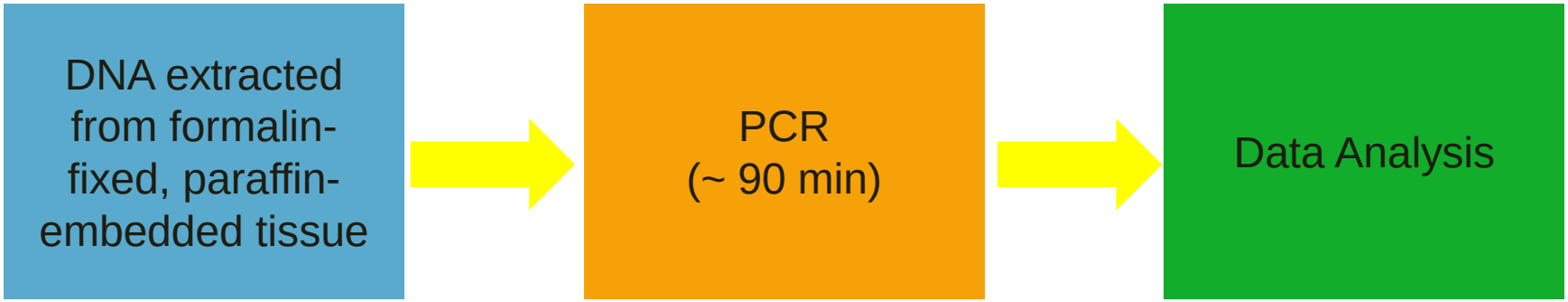
Indicación

- Desde Junio 2008 la indicación de Erbitux es:

Erbitux en combinación con quimioterapia está indicado para el tratamiento de pacientes con CCR metastásico KRAS nativo que expresa el EGFR

El test del KRAS debería hacerse a TODOS los pacientes con CCR metastásico

DNA-Based *KRAS* Testing



KRAS information

KRAS test centers

Argentina
Brazil
China
Columbia
Czech Republic
Ecuador
France
Germany
Hungary
Indonesia
Korea
Mexico
Peru
Singapore
Slovenia

CLÍNICA UNIVERSITARIA de NAVARRA
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Dr. Josep Mª Tabernero
Dr. Santiago Ramón y Cajal

HOSPITAL CLÍNICO SAN CARLOS
Martín Lagos, s/n
28040 Madrid
Prof. Eduardo Díaz-Rubio
Dra. Trinidad Caldés

HOSPITAL CARLOS HAYA
Avda. Carlos Haya s/n
29010 Málaga
Dr. Manuel Benavides
Dra. M. Dolores Bautista Ojeda

Hospital General Universitario de Valencia
Av. Tres Cruces s/n
46014 Valencia
Dr. Carlos Camps
Dr. Rafael Sirera

More info:
DxS Diagnostic Innovations
Deutsche Gesellschaft für Pathologie e.V.
Institut National du Cancer

THERASCREEN: K-RAS MUTATION TEST KIT

Corporate Cancer Mutation Products Molecular Diagnostic Technologies Genetic Analysis Services Contact Us News

DxS Diagnostic Innovations

- Clinical Diagnostic Kits
  - TheraScreen K-RAS
  - TheraScreen EGFR29
- Research Kits
  - EGFR29 Mutation Test Kit
  - K-RAS Mutation Test Kit
  - T790M EGFR Mutation Test Kit
  - B-RAF Mutation Test Kit
  - ABL-T3151 Mutation Test Kit

THERASCREEN: K-RAS MUTATION TEST KIT

The TheraScreen: K-RAS kit detects seven mutations in codons 12 and 13 of the K-RAS oncogene. This kit has been CE-marked for professional diagnostic use.

Background

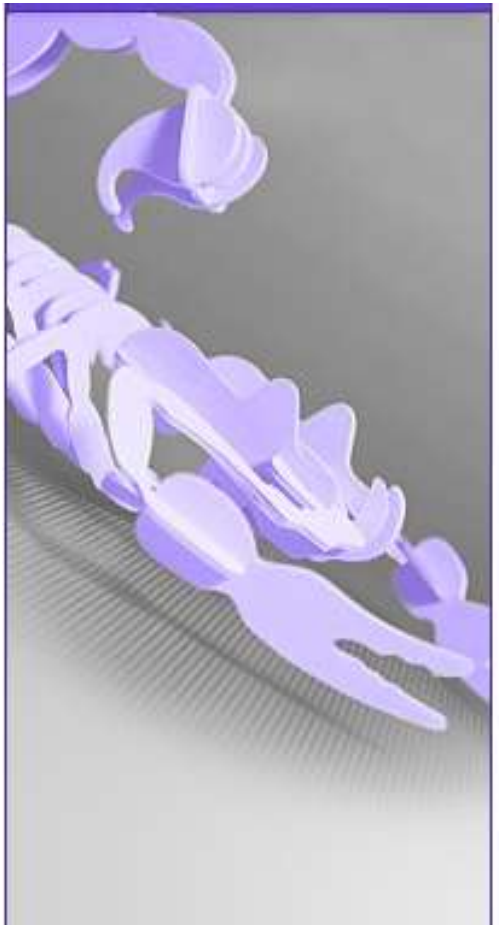
Mutations in the K-RAS oncogene are frequently found in human cancers. They are common in colorectal cancer, pancreatic cancer, lung adenocarcinoma, gall bladder cancer, bile duct cancer and thyroid cancer. These mutations can indicate prognosis and may be predictive of drug response. In particular, recent publications have shown that the successful treatment of metastatic Colorectal Cancer (mCRC), using monoclonal antibody therapies such as Panitumumab (Amgen) or Cetuximab (Erbitux, Merck), is directly linked to the oncogenic activation of the KRAS signalling pathway. (1-6).

AMPLIFICATION
REFRACTORY
MUTATION SYSTEM

ARMS®

+

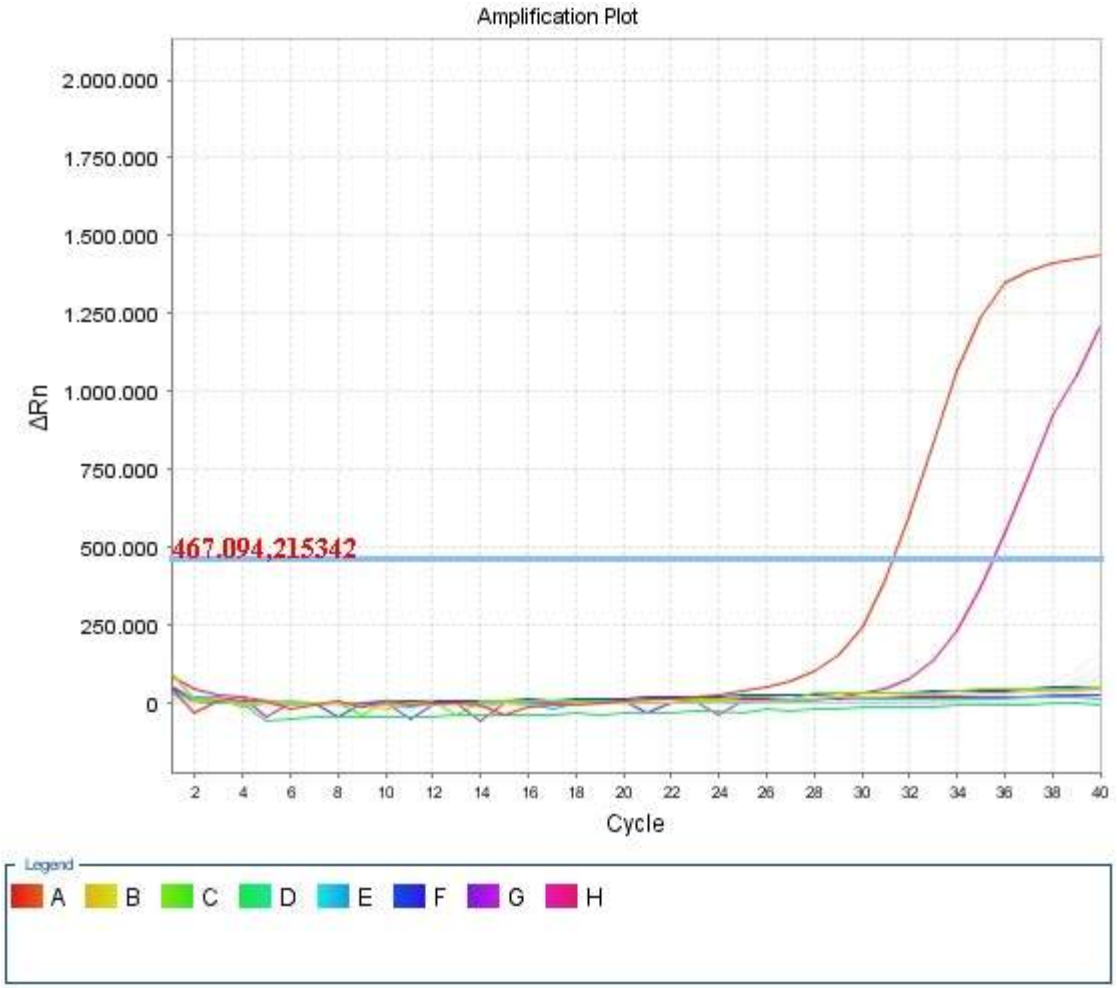
SCORPIONS

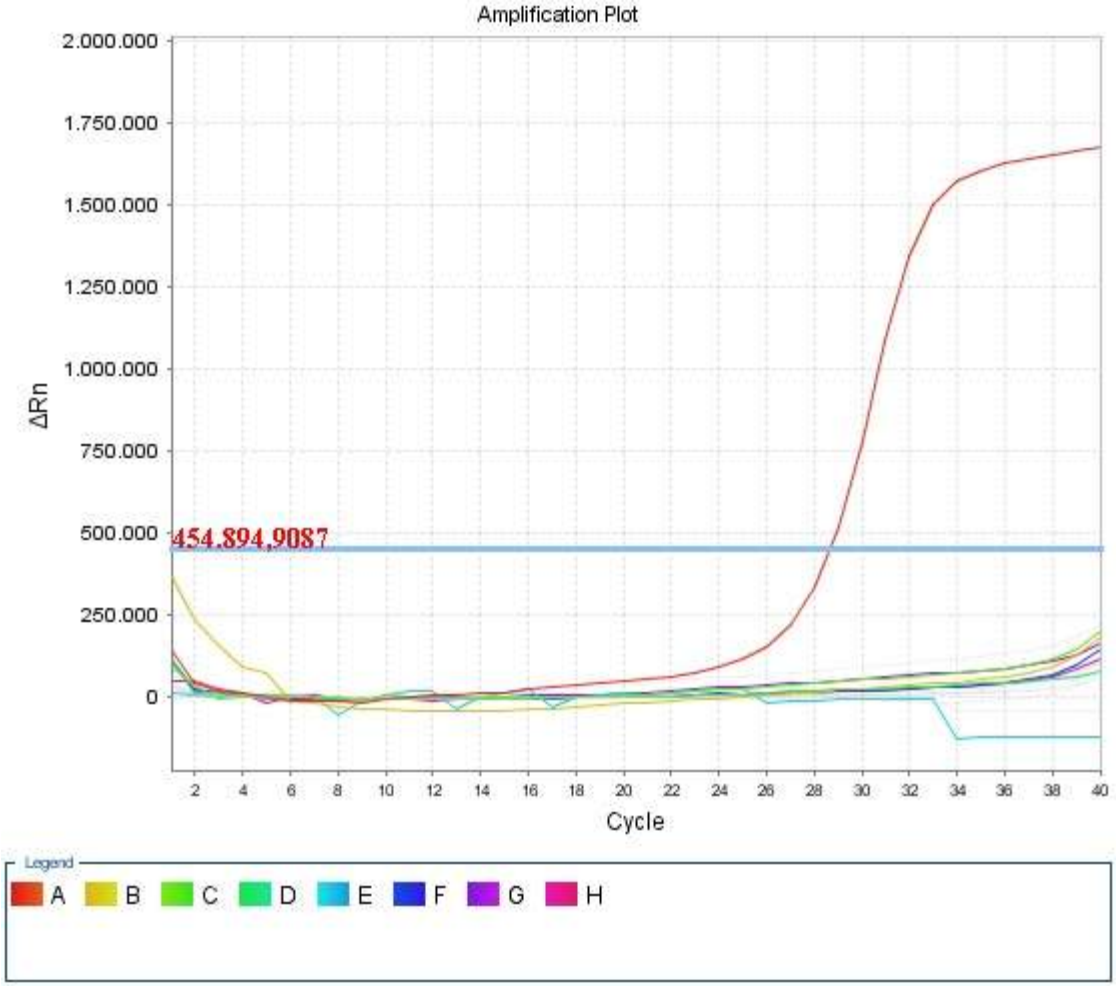


MUTACIONES DETECTADAS

1. **Gly12Asp** (GGT>GAT)
2. **Gly12Ala** (GGT>GCT)
3. **Gly12Val** (GGT>GTT)
4. **Gly12Ser** (GGT>AGT)
5. **Gly12Arg** (GGT>CGT)
6. **Gly12Cys** (GGT>TGT)
7. **Gly13Asp** (GGC>GAC)

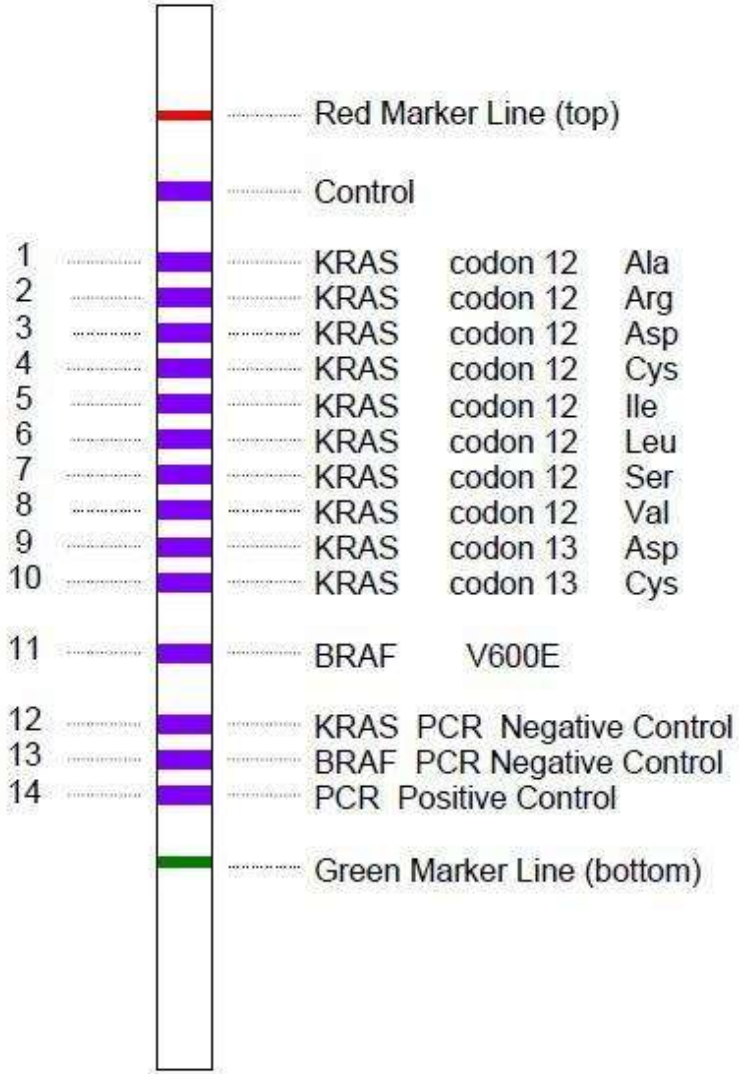
Detección de mutaciones por PCR a tiempo real

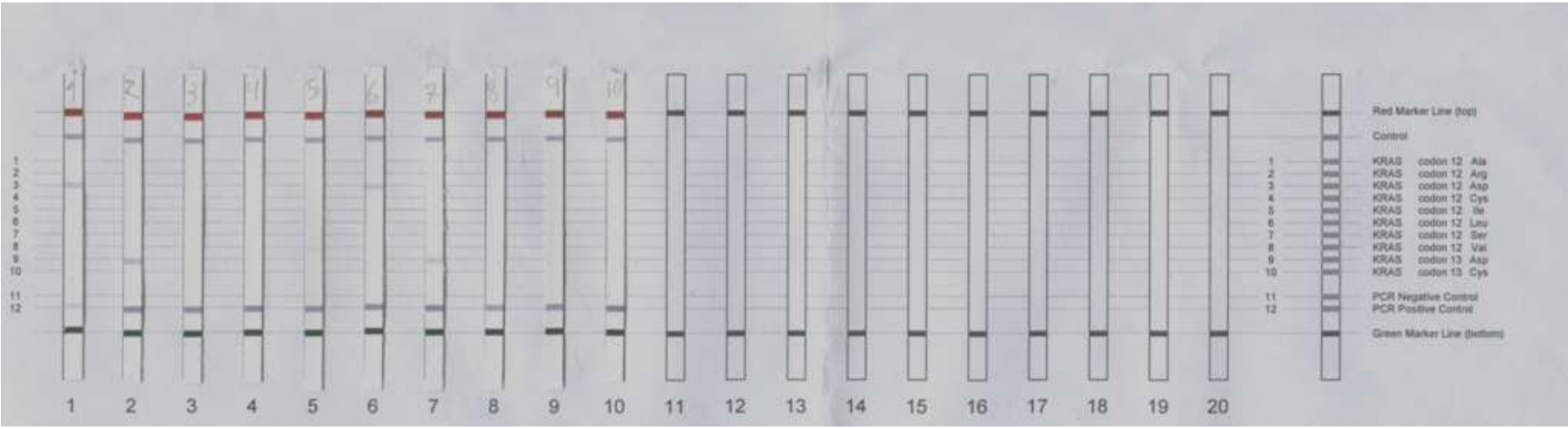



Amplification Plot
2.000.000
1.750.000
1.500.000
1.250.000
1.000.000
750.000
500.000
250.000
0
ΔRn
454.894,9087
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
32
34
36
38
40
Cycle
Legend
A
B
C
D
E
F
G
H

KRAS StripAssay

VIENNA LAB
ViennaLab Diagnostics GmbH


Red Marker Line (top)
Control
1 KRAS codon 12 Ala
2 KRAS codon 12 Arg
3 KRAS codon 12 Asp
4 KRAS codon 12 Cys
5 KRAS codon 12 Ile
6 KRAS codon 12 Leu
7 KRAS codon 12 Ser
8 KRAS codon 12 Val
9 KRAS codon 13 Asp
10 KRAS codon 13 Cys
11 BRAF V600E
12 KRAS PCR Negative Control
13 BRAF PCR Negative Control
14 PCR Positive Control
Green Marker Line (bottom)


1
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1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Red Marker Line (top)
Control
1 KRAS codon 12 Ala
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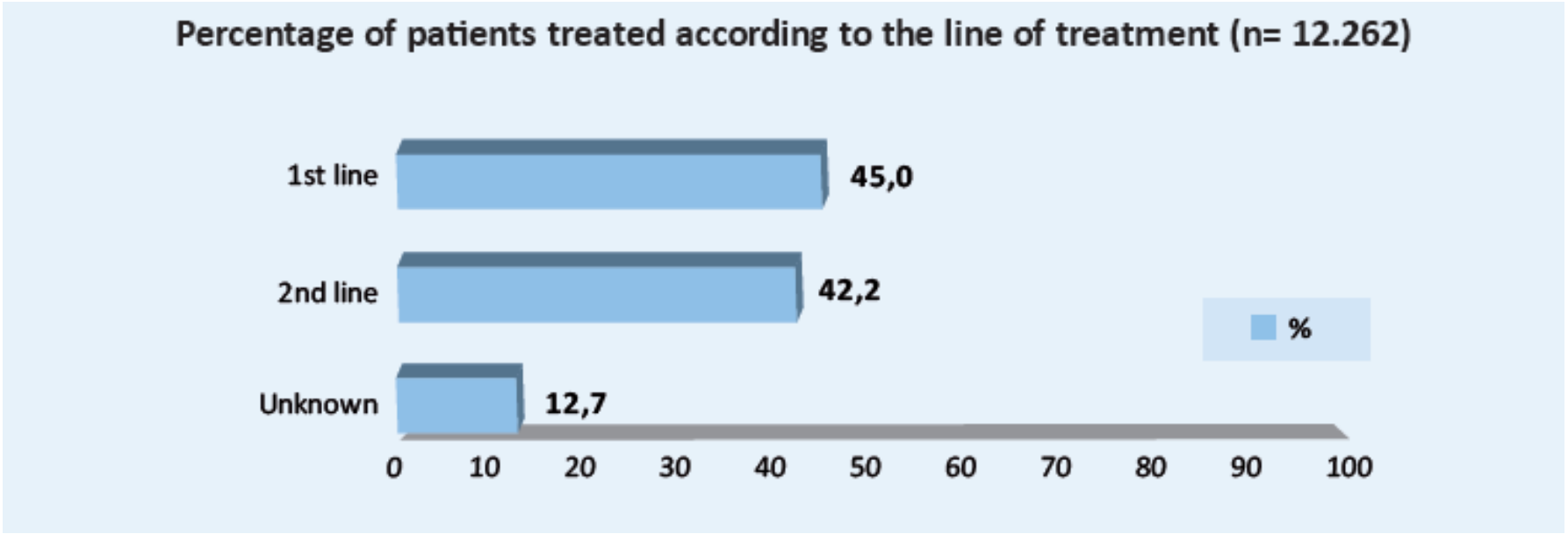
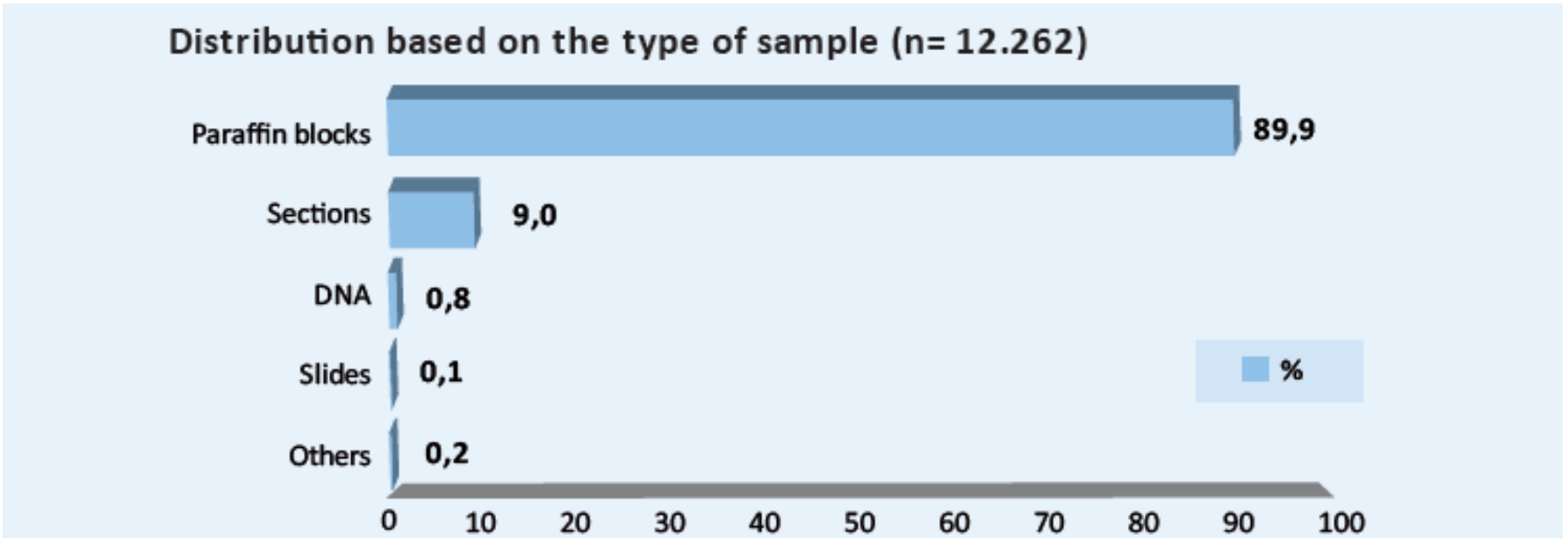
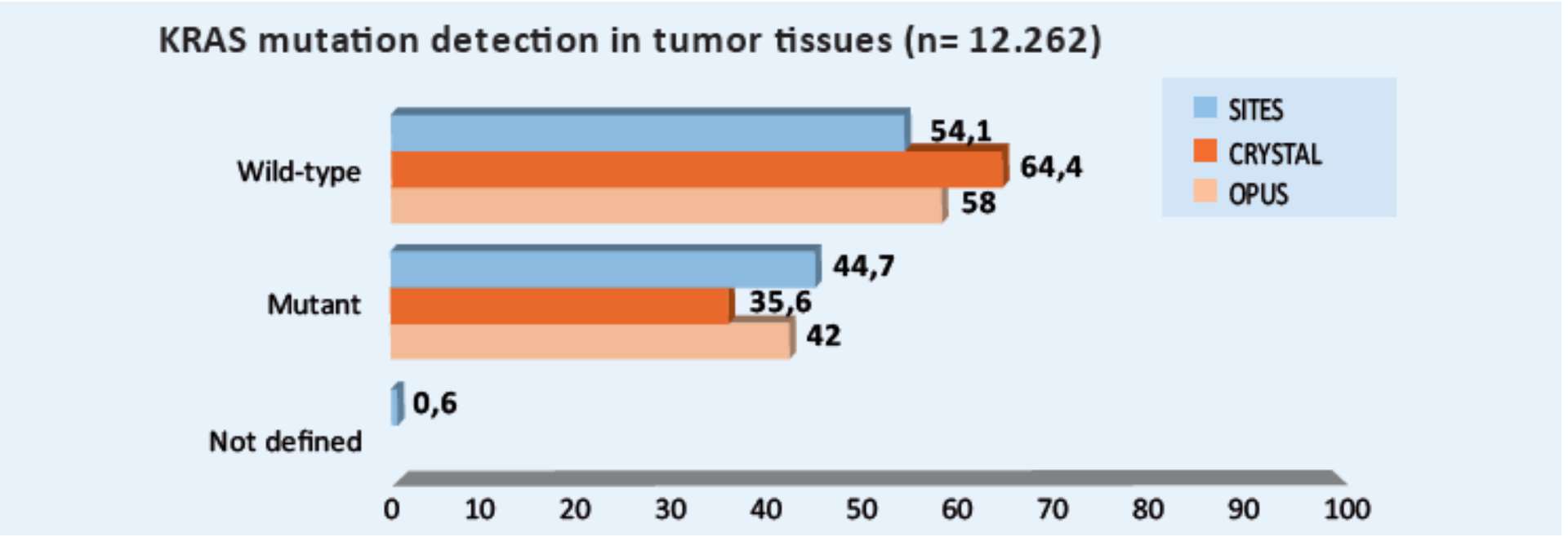
11 PCR Negative Control
12 PCR Positive Control
Green Marker Line (bottom)

Septiembre 2010





Septiembre 2010



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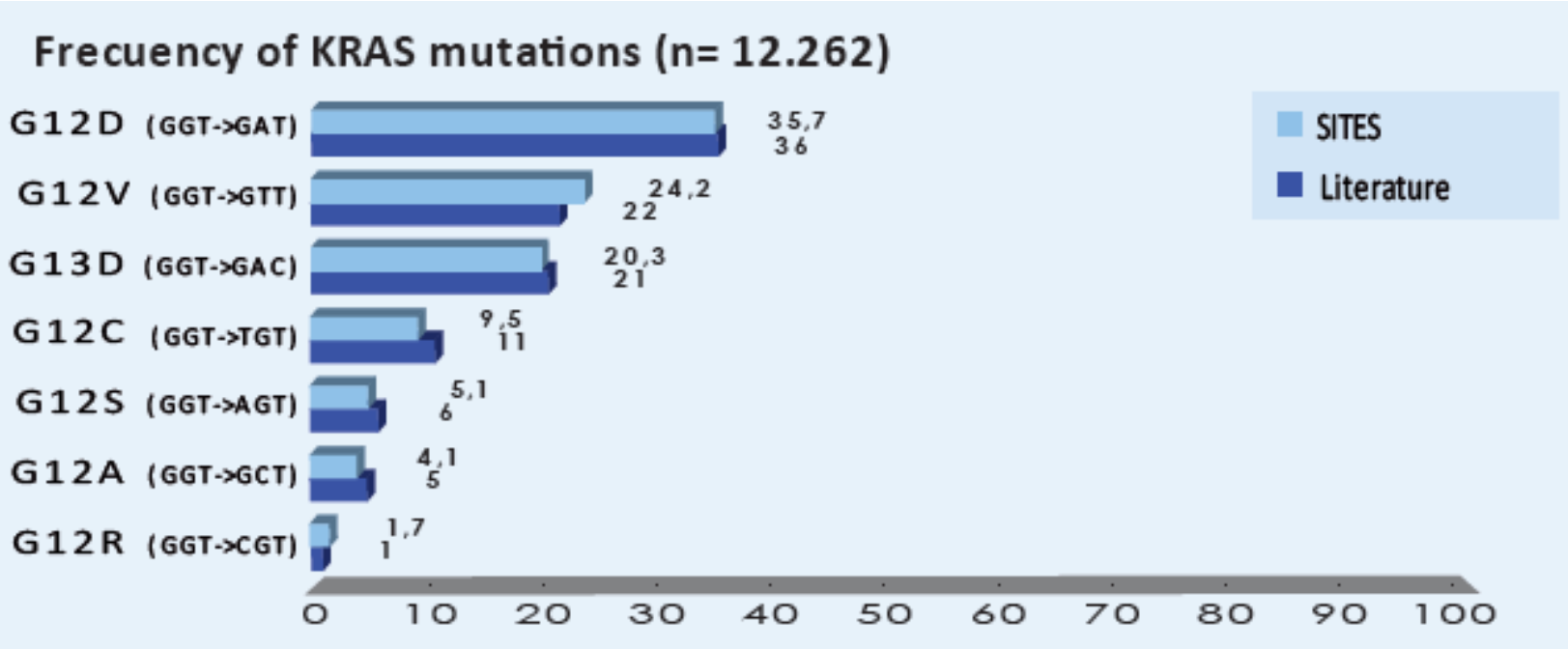


VOLUME 26 · NUMBER 35 · DECEMBER 10 2008

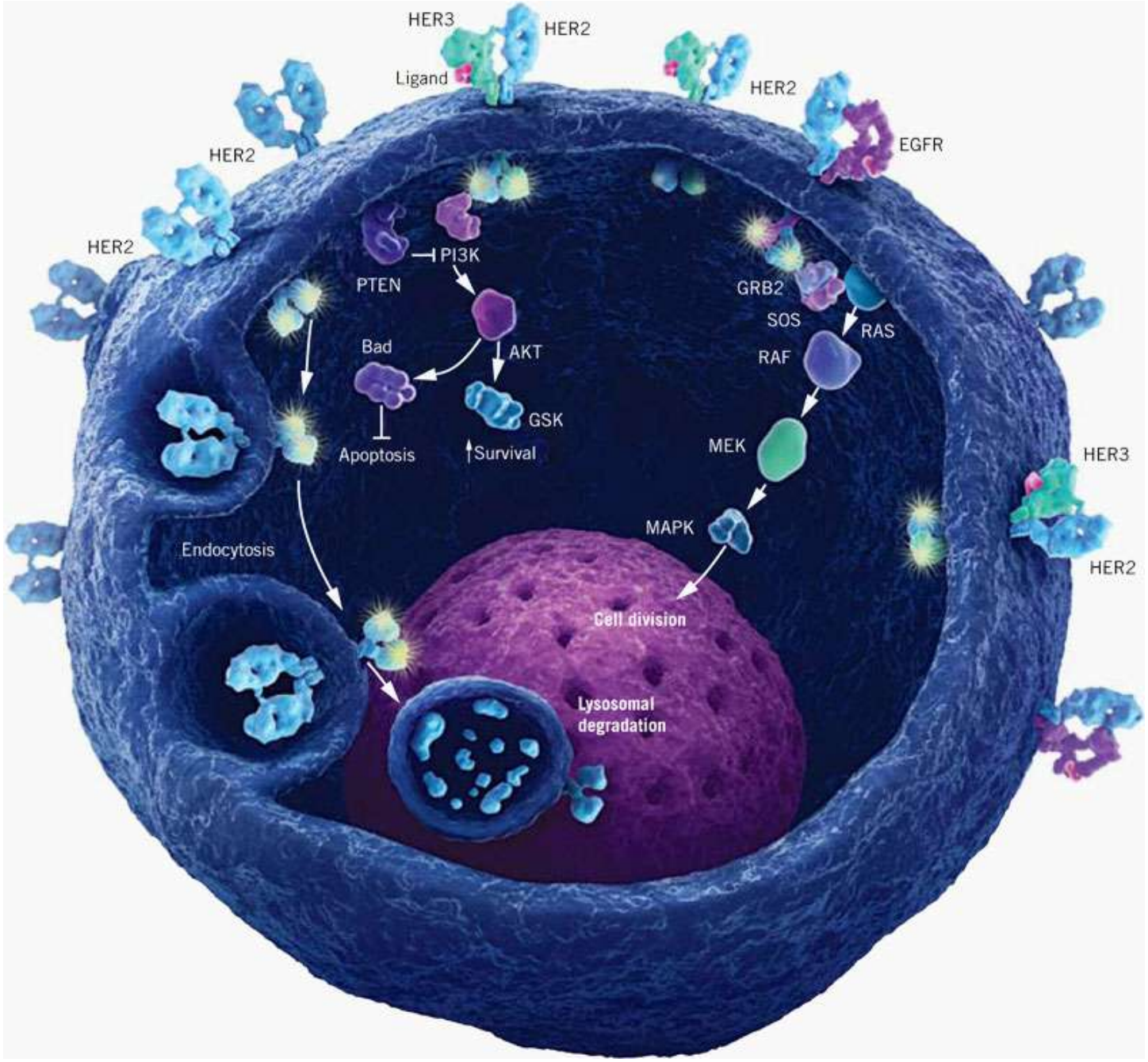
JOURNAL OF CLINICAL ONCOLOGY

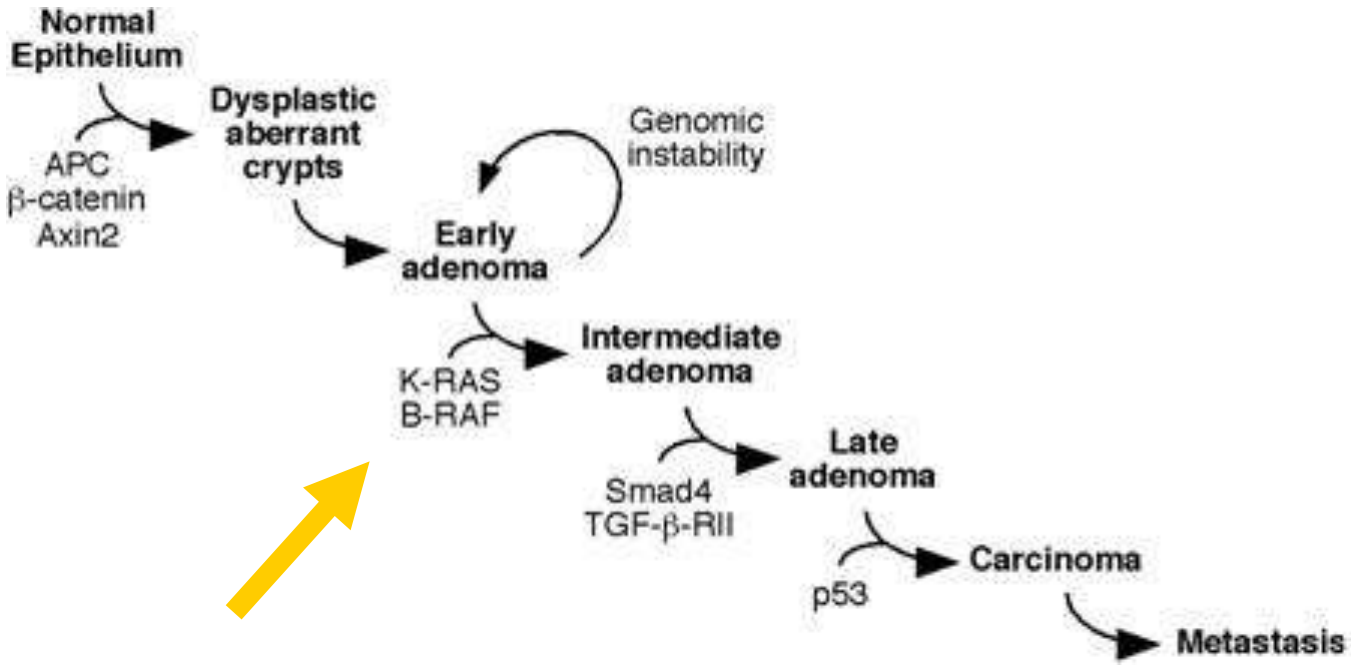
ORIGINAL REPORT

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

From the Laboratory of Molecular Genetics, The Oncogenomics Center,


HER3
HER2
Ligand
HER2
EGFR
HER2
HER2
PI3K
PTEN
GRB2
SOS
RAS
RAF
Bad
AKT
GSK
Apoptosis
Survival
MEK
HER3
MAPK
Endocytosis
HER2
Cell division
Lysosomal degradation


Normal Epithelium
APC
β-catenin
Axin2
Dysplastic aberrant crypts
Genomic instability
Early adenoma
K-RAS
B-RAF
Intermediate adenoma
Smad4
TGF-β-RII
Late adenoma
p53
Carcinoma
Metastasis

BRAF Mutation in Metastatic Colorectal Cancer

Jolien Tol, M.D.
Iris D. Nagtegaal, M.D., Ph.D.
Cornelis J.A. Punt, M.D., Ph.D.

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Table 1. Association of the Mutation Status of the *BRAF* Oncogene with Progression-free Survival, Overall Survival, and Response Rate.*

Variable	Wild-Type *BRAF*	Mutated *BRAF*	P Value
No. of patients			
CB group	243	17	
CBC group	231	28	
Median progression-free survival (mo)			
CB group	12.2	5.9	0.003
CBC group	10.4	6.6	0.010
Median overall survival (mo)			
CB group	24.6	15.0	0.002
CBC group	21.5	15.2	0.001
Response rate (%)			
CB group	50	35	0.32
CBC group	48	39	0.43

* *BRAF* denotes *B-type Raf kinase*, CB capecitabine, oxaliplatin, and bevacizumab, and CBC capecitabine, oxaliplatin, and bevacizumab plus cetuximab.

Effects of *KRAS*, *BRAF*, *NRAS*, and *PIK3CA* mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy-refractory metastatic colorectal cancer: a retrospective consortium analysis

Wendy De Roock, Bart Claes, David Bernasconi, Jef De Schutter, Bart Biesmans, George Fountzilas, Konstantine T Kalogeras, Vassiliki Kotoula, Demetris Papamichael, Pierre Laurent-Puig, Frédérique Penault-Llorca, Philippe Rougier, Bruno Vincenzi, Daniele Santini, Giuseppe Tonini, Federico Cappuzzo, Milo Frattini, Francesca Molinari, Piercarlo Saletti, Sara De Dosso, Miriam Martini, Alberto Bardelli, Salvatore Siena, Andrea Sartore-Bianchi, Josep Tabernero, Teresa Macarulla, Frédéric Di Fiore, Alice Oden Gangloff, Fortunato Ciardiello, Per Pfeiffer, Camilla Qvortrup, Tine Plato Hansen, Eric Van Cutsem, Hubert Piessevaux, Diether Lambrechts, Mauro Delorenzi, Sabine Tejpar

Lancet Oncol 2010; 11: 753–62

Published Online July 8, 2010 DOI:10.1016/S1470-

Summary

Background Following the discovery that mutant *KRAS* is associated with resistance to anti-epidermal growth factor receptor (EGFR) antibodies, the tumours of patients with metastatic colorectal cancer are now profiled for seven *KRAS* mutations before receiving cetuximab or panitumumab. However, most patients with *KRAS* wild-type tumours still do not respond. We studied the effect of other downstream mutations on the efficacy of cetuximab in, to our

BMC Cancer

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Research article

Open Access

Potential value of PTEN in predicting cetuximab response in colorectal cancer: An exploratory study

Evangelia Razis*[1], Evangelos Briasoulis[2], Eleni Vrettou[3], Dimosthenis V Skarlos[4], Dimitrios Papamichael[5], Ioannis Kostopoulos[3], Epaminont... Samantes[6], Ioannis Xanthakis[7], Matthaios Bobos[3], Eleni Galan... Georgia Ka...

stabilized. Lack of PTEN gene amplification was associated with more responses to cetuximab and longer time to progression (p = 0.042).

British Journal of Cancer (2007) 97, 1139 – 1145

www.bjcancer.com

PTEN loss of expression predicts cetuximab efficacy in metastatic colorectal cancer patients

M Frattini[*,1,3], P Saletti[2,3], E Romagnani[2,4], V Martin[1], F Molinari[1], M Ghisletta[1], A Camponovo[1], LL Etienne[1], F Cavalli[2] and L Mazzucchelli[1]

[1]Institute of Pathology, via in Selva 24, CH-6600 Locarno, Switzerland; [2]Oncology Institute of Southern Switzerland, Ospedale San Giovanni, CH-6500 Bellinzona, Switzerland

we demonstrate for the first time that the loss of PTEN protein expression is associated with nonresponsiveness to cetuximab.

Association of *KRAS* p.G13D Mutation With Outcome in Patients With Chemotherapy-Refractory Metastatic Colorectal Cancer Treated With Cetuximab

Wendy De Roock, MD
Derek J. Jonker, MD
Federica Di Nicolantonio, PhD
Andrea Sartore-Bianchi, MD
Dongsheng Tu, PhD
Salvatore Siena, MD
Simona Lamba, MSc
Sabrina Arena, PhD
Milo Frattini, PhD
Hubert Piessevaux, MD, PhD
Eric Van Cutsem, MD, PhD
Chris J. O'Callaghan, DVM, PhD
Shirin Khambata-Ford, PhD
John R. Zalcberg, MBBS, PhD
John Simes, MD
Christos S. Karapetis, MD
Alberto Bardelli, PhD
Sabine Tejpar, MD, PhD

Context Patients with metastatic colorectal cancer who have *KRAS* codon 12– or *KRAS* codon 13–mutated tumors are presently excluded from treatment with the anti–epidermal growth factor receptor monoclonal antibody cetuximab.

Objective To test the hypothesis that *KRAS* codon 13 mutations are associated with a better outcome after treatment with cetuximab than observed with other *KRAS* mutations.

Design, Setting, and Patients We studied the association between *KRAS* mutation status (p.G13D vs other *KRAS* mutations) and response and survival in a pooled data set of 579 patients with chemotherapy-refractory colorectal cancer treated with cetuximab between 2001 and 2008. Patients were included in the CO.17, BOND, MABEL, EMR202600, EVEREST, BABEL, or SALVAGE clinical trials or received off-study treatment. Univariate and multivariate analyses, adjusting for possible prognostic factors and data set, were performed. The effect of the different mutations was studied in vitro by constructing isogenic cell lines with wild-type *KRAS*, p.G12V, or p.G13D mutant alleles and treating them with cetuximab.

Main Outcome Measures The main efficacy end point was overall survival. Secondary efficacy end points were response rate and progression-free survival.

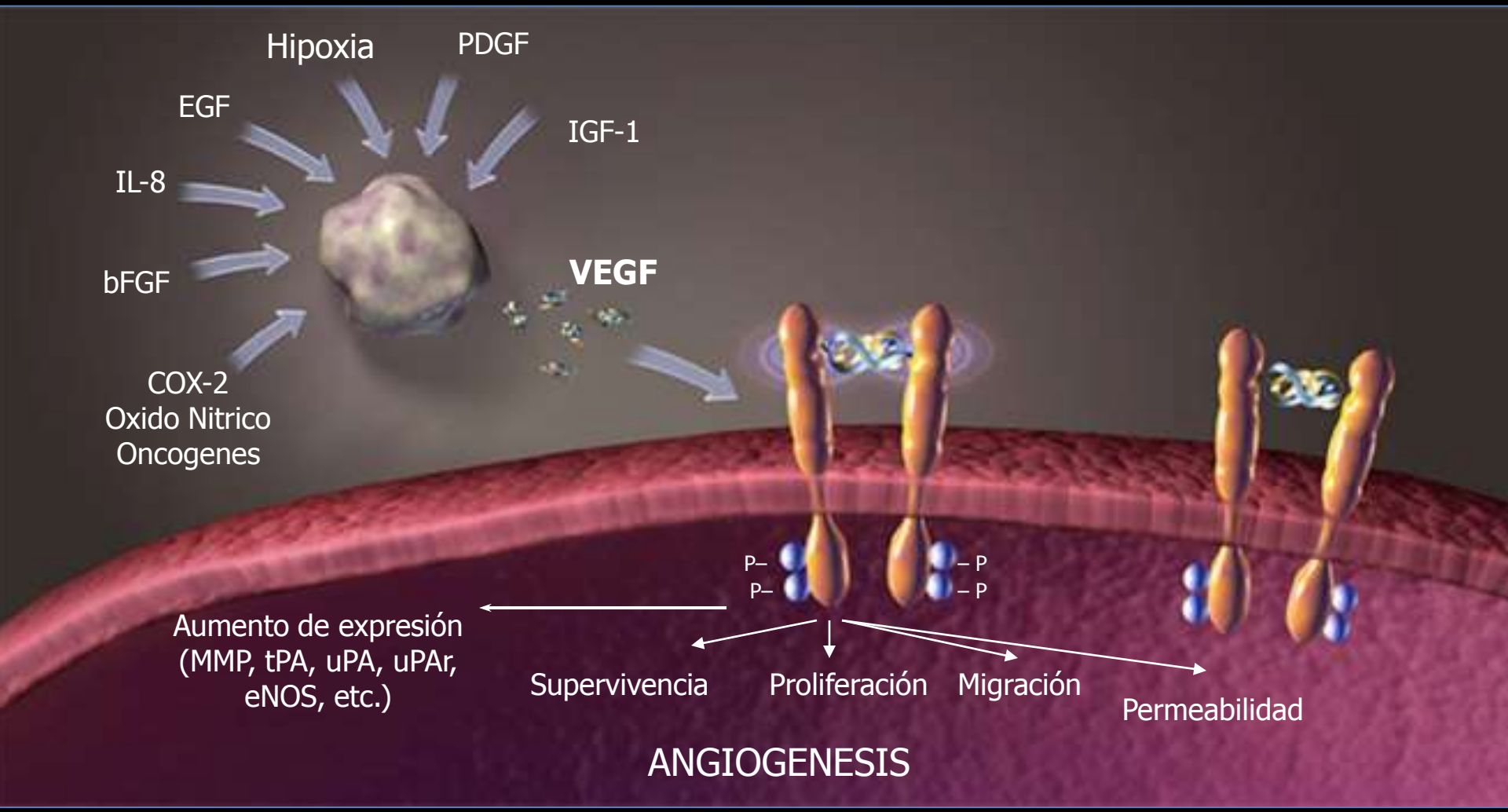
Results In comparison with patients with other *KRAS*-mutated tumors, patients with p.G13D-mutated tumors (n=32) treated with cetuximab had longer overall survival (median, 7.6 [95% confidence interval {CI}, 5.7-20.5] months vs 5.7 [95% CI, 4.9-6.8] months; adjusted hazard ratio [HR], 0.50; 95% CI, 0.31-0.81; *P*= .005) and longer progression-free survival (median, 4.0 [95% CI, 1.9-6.2] months vs 1.9 [95% CI, 1.8-2.8] months; adjusted HR, 0.51; 95% CI, 0.32-0.81; *P*=.004). There was a significant interaction between *KRAS* mutation status (p.G13D vs other *KRAS* mutations) and overall survival benefit with cetuximab treatment (adjusted HR, 0.30; 95% CI, 0.14-

Inhibidores de VEGF en Cáncer Colorrectal

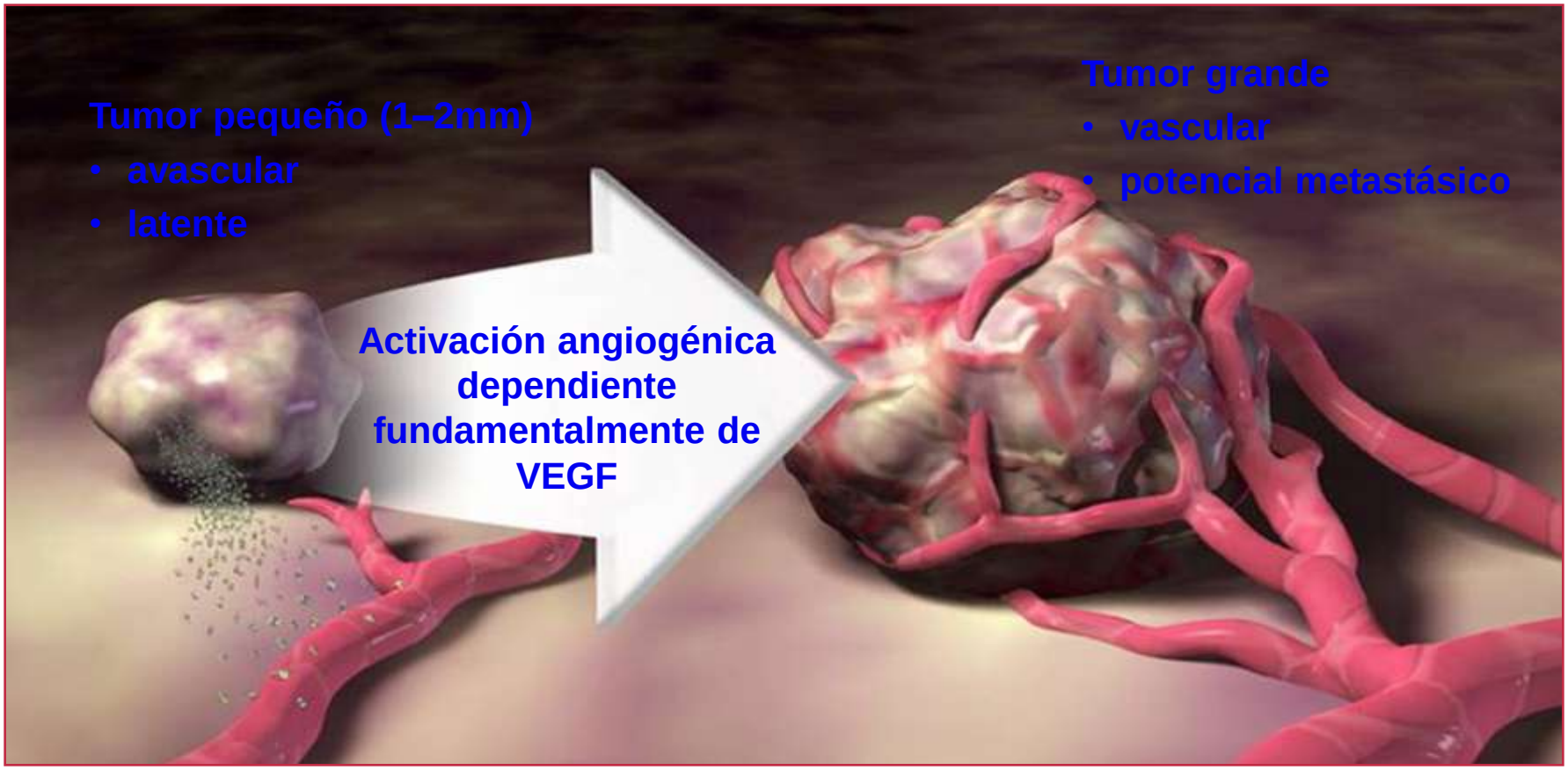
- Anticuerpos Monoclonales anti-VEGF
  - Bevacizumab (Avastin)

VEGF

- También se conoce como VEGF-A
- Existen cuatro especies moleculares
  - $VEGF_{121}$
  - $VEGF_{165*}$
  - $VEGF_{189}$
  - $VEGF_{206}$
- Moléculas relacionadas: VEGF-B, C y D, y el factor de crecimiento de la placenta (PlGF)
- Actúa sobre receptores localizados en la superficie celular


Hipoxia
PDGF
EGF
IGF-1
IL-8
VEGF
bFGF
COX-2
Oxido Nitrico
Oncogenes
P–
P–
– P
– P
Aumento de expresión
(MMP, tPA, uPA, uPAr,
eNOS, etc.)
Supervivencia
Proliferación
Migración
Permeabilidad
ANGIOGENESIS

VEGF factor clave de la angiogénesis tumoral



Etapa premaligna

(tumor avascular)

Tumor maligno

(activación angiogénica)

Crecimiento del tumor

(tumor vascularizado)

Invasión vascular

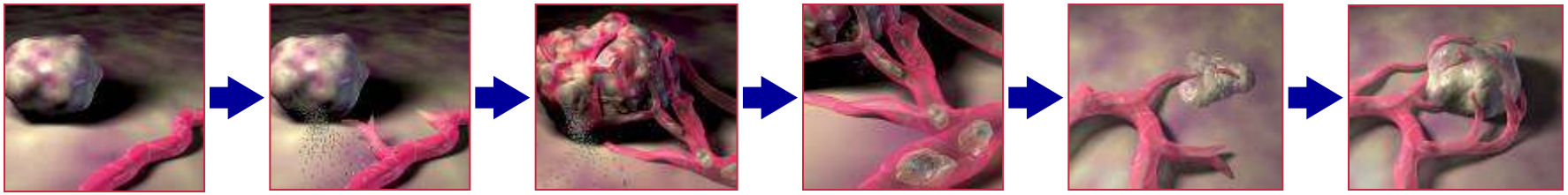
(intravasación del células tumorales)

Micrometástasis latente

(Diseminación a órganos distantes)

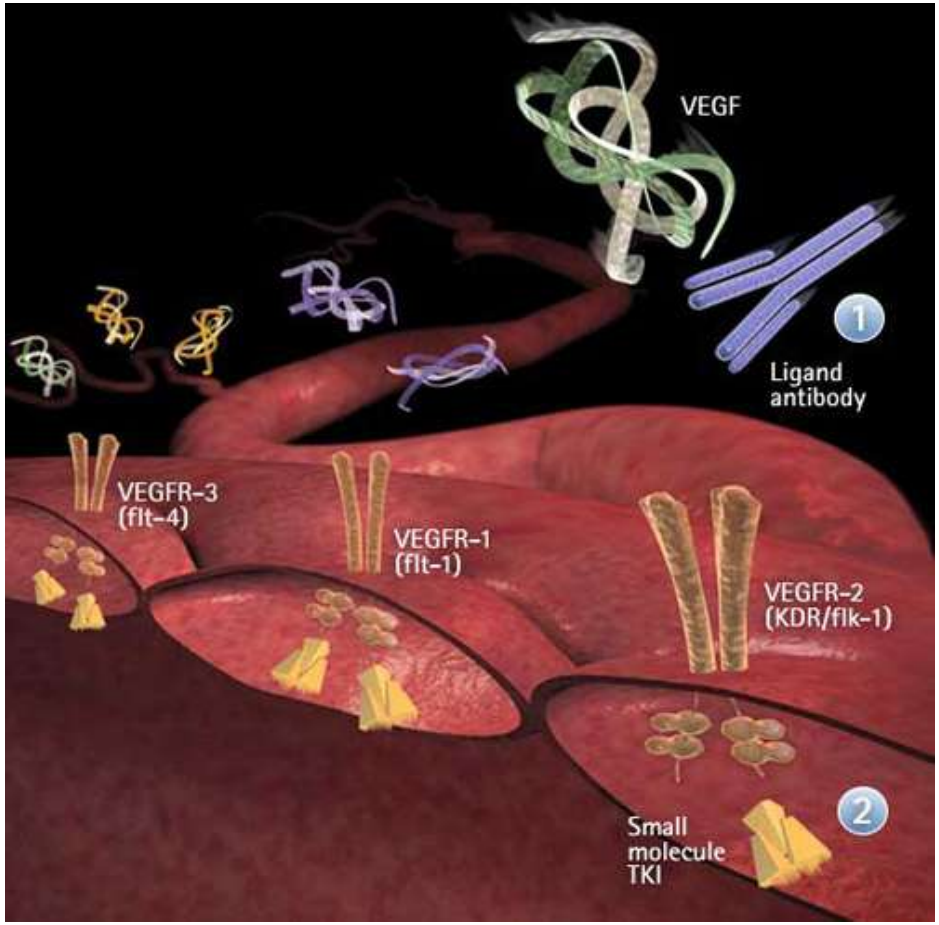
Metástasis franca

(angiogénesis secundaria)



Etapas en las cuales la angiogénesis desempeña un papel en la progresión tumoral

Vias de Inhibición de VEGF



- **Dirigidos a VEGF, como anticuerpos ligandos o receptores solubles**
  - **Inhiben la angiogenesis sin interferir otras vías**
  - **Ejemplos: bevacizumab, aflibercept (VEGF Trap)**

- **Dirigidos al receptor VEGFR, como inhibidores tirosinquinasas o anticuerpos anti VEGFR**
  - **Pueden tener otros efectos inhibidores e interferir en otras vías**
  - **Ejemplos:: cediranib, sunitinib**

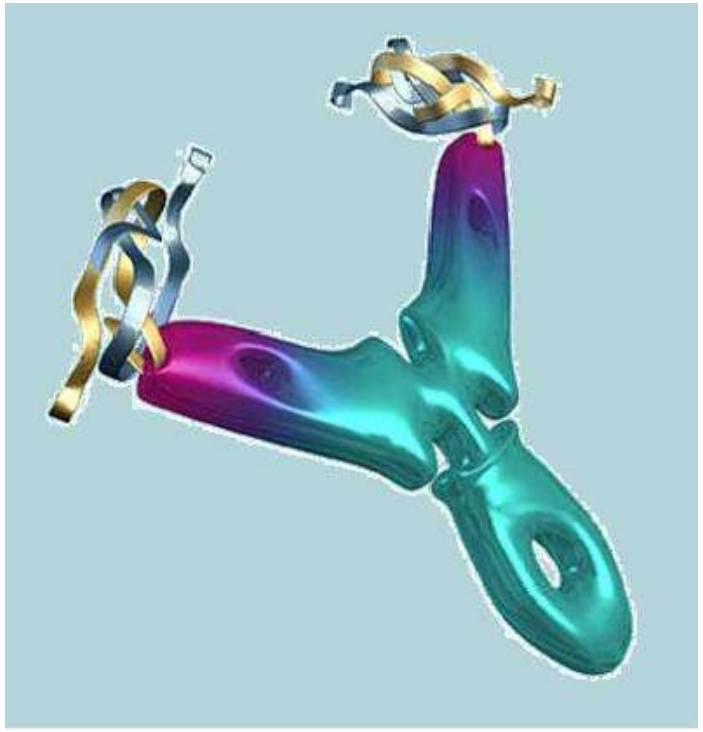
Bevacizumab

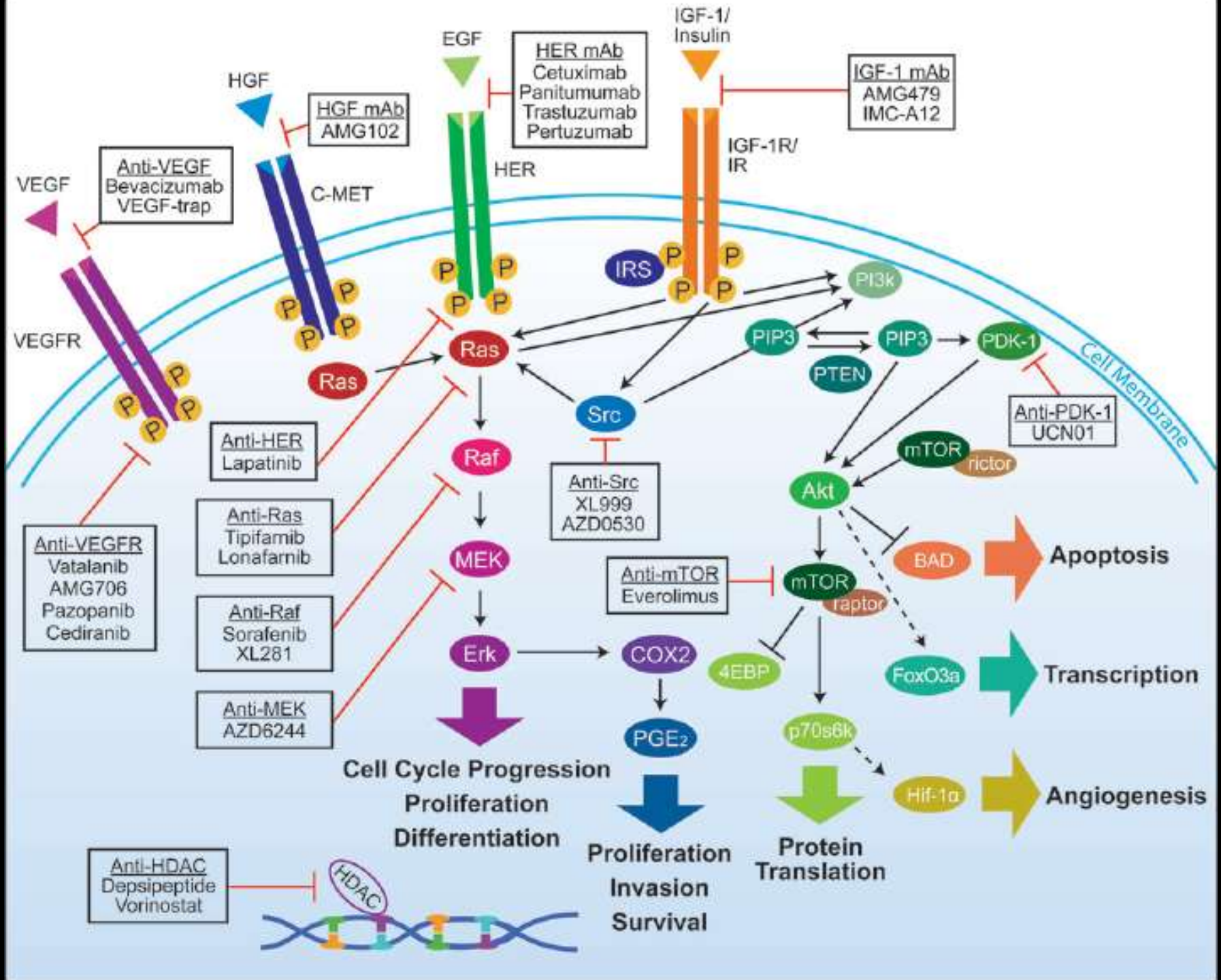
- **Anticuerpo recombinante humanizado dirigido frente al VEGF-A**

- **Reconoce todas las principales isoformas del VEGF-A humano**

- **Es el primer antiangiogénico específico aprobado en oncología (cáncer de colon, mama, pulmón, renal)**

No se ha identificado ningún marcador predictivo de respuesta




IGF-1/
Insulin
EGF
HER mAb
Cetuximab
Panitumumab
Trastuzumab
Pertuzumab
IGF-1 mAb
AMG479
IMC-A12
HGF
HGF mAb
AMG102
IGF-1R/
IR
HER
Anti-VEGF
Bevacizumab
VEGF-trap
VEGF
C-MET
IRS
PI3k
VEGFR
Ras
PIP3
PIP3
PDK-1
PTEN
Cell Membrane
Ras
Src
Anti-PDK-1
UCN01
Anti-HER
Lapatinib
mTOR
rictor
Raf
Anti-Src
XL999
AZD0530
Akt
Anti-Ras
Tipifamib
Lonafarnib
Anti-VEGFR
Vatalanib
AMG706
Pazopanib
Cediranib
MEK
BAD
Apoptosis
Anti-mTOR
Everolimus
mTOR
raptor
Anti-Raf
Sorafenib
XL281
Erk
COX2
4EBP
FoxO3a
Transcription
Anti-MEK
AZD6244
PGE2
p70s6k
Hif-1α
Angiogenesis
Cell Cycle Progression
Proliferation
Differentiation
Proliferation
Invasion
Survival
Protein
Translation
Anti-HDAC
Depsipeptide
Vorinostat
HDAC

miARNs como Biomarcadores en Cáncer Colorrectal

- Perfil de expresión de mARNs asociados a diagnóstico, pronóstico y/o predicción
- let-7 (regula ras)
- mR-21 (inhibición PTEN)
- mR-34
- mR-92 y mR-17-3
- Adenomas y adenocarcinomas mR-29a y mR92

LA IMPORTANCIA DEL PATÓLOGO EN LA ONCOLOGÍA[1,2]

- Cuando hablamos de cáncer, hay un especialista al que jamás ven los pacientes, pero que es la **pieza clave** en la **determinación de la firma molecular del tumor.**

- En los últimos años se ha experimentado un tremendo avance en el campo de la oncología, debido a que el diagnóstico del cáncer implica **la comprensión del comportamiento biológico del tumor.**

- Es fundamental que **el patólogo proporcione un diagnóstico** lo suficientemente **adecuado** y **preciso** como para que el oncólogo tome una decisión sobre el mejor tratamiento para el paciente.

RAS
Medicina Personalizada

IMPORTANCIA DEL PATÓLOGO EN EL TRATAMIENTO DEL CÁNCER COLORRECTAL[3]

- El cáncer colorrectal (CRC) es la segunda causa más importante de muerte por cáncer. La mayoría de estas muertes son atribuibles tanto a la recurrencia local como a las metástasis, frecuentemente en el hígado. Por lo tanto, la elección del mejor tratamiento es esencial en la reducción de esta mortalidad.

- El papel del patólogo en el CRC va creciendo día a día. Además de determinar el grado y estadio del tumor, han aparecido numerosos **marcadores de supervivencia y de respuesta al tratamiento**, tanto clínico-patológicos como biológicos, que también deben ser evaluados.

- Para que todos estos avances se aprovechen adecuadamente es fundamental que toda esta **información se transmita eficazmente al resto del equipo multidisciplinar** implicado en el tratamiento del paciente.

- El equipo de especialistas multidisciplinar es un componente esencial del tratamiento actual del cáncer, ya que permite una discusión abierta entre los diferentes especialistas para un manejo óptimo del paciente, así como una rápida transmisión de la información.

- Cada vez más, los patólogos tienen un **papel fundamental en la evaluación de la probabilidad de respuesta** de un paciente a un **tratamiento** en concreto, influenciando directamente en la **elección** del mismo.

- En el futuro veremos la producción de un **tratamiento personalizado** para cada paciente dependiendo de la firma molecular de su tumor.

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