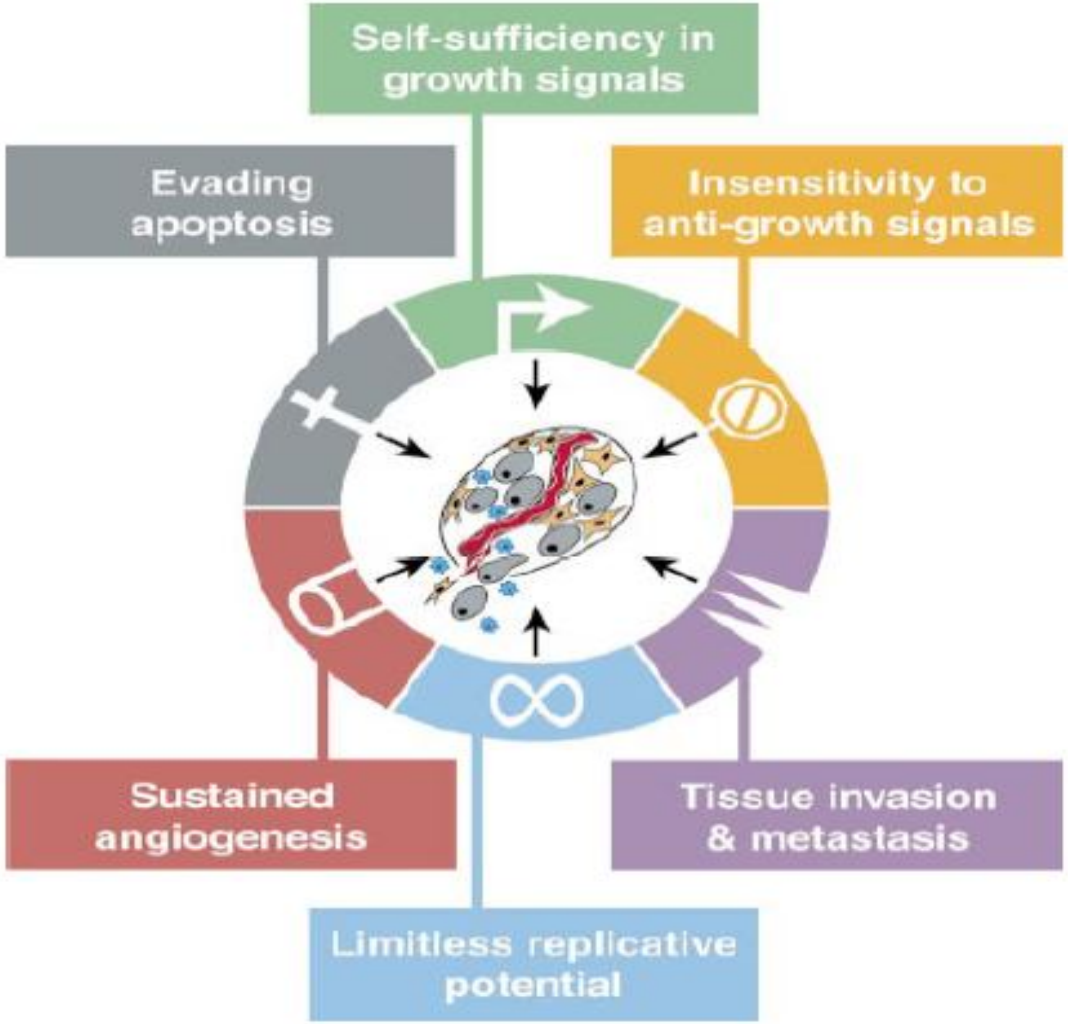
Avances y Retos en Oncologica

Manuel Hidalgo, M.D., Ph.D.

Agenda

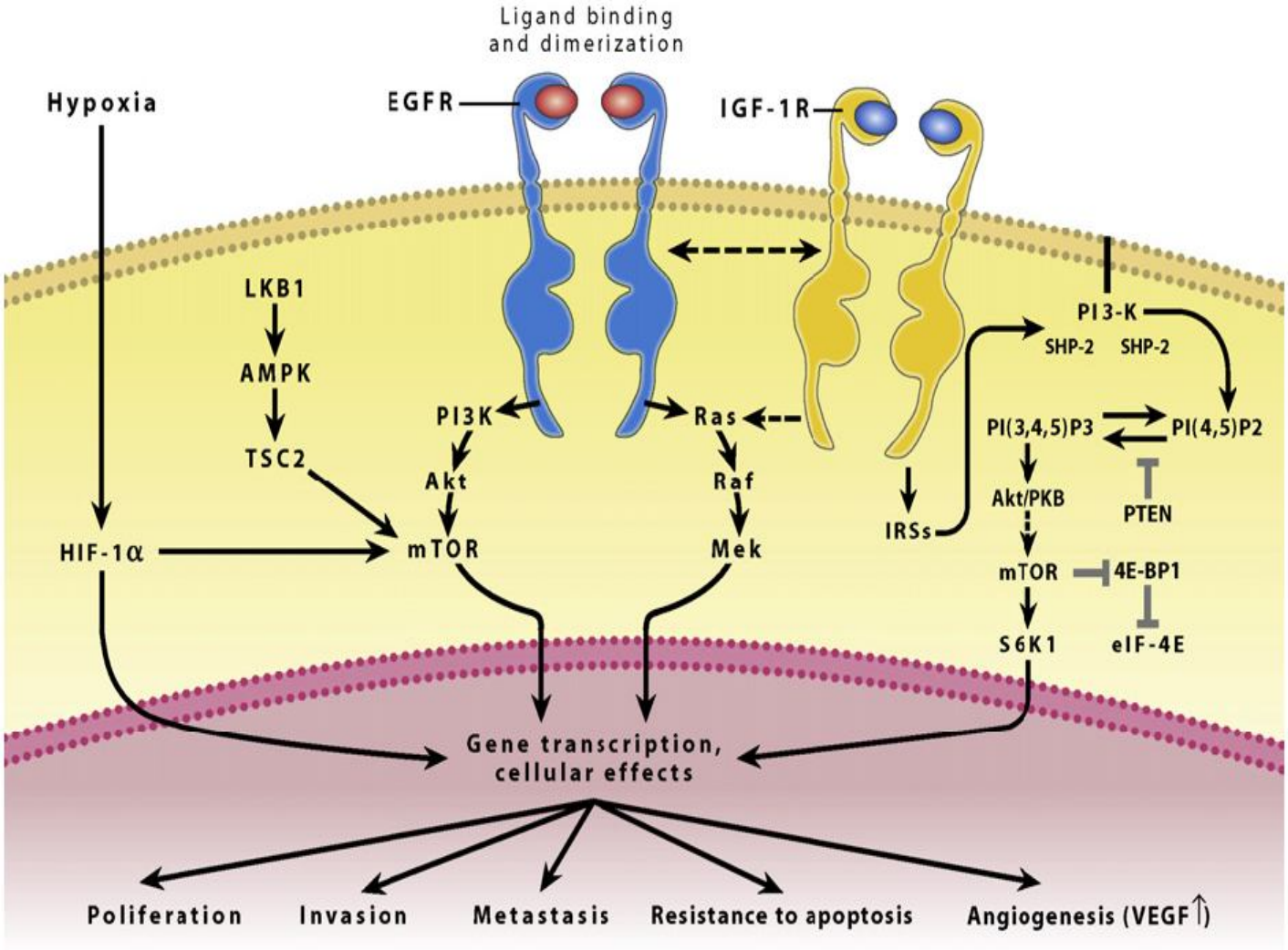
- Conocimiento basico.
- Prevencion.
- Diagnostico.
- Tratamiento.

The Hallmarks of Cancer



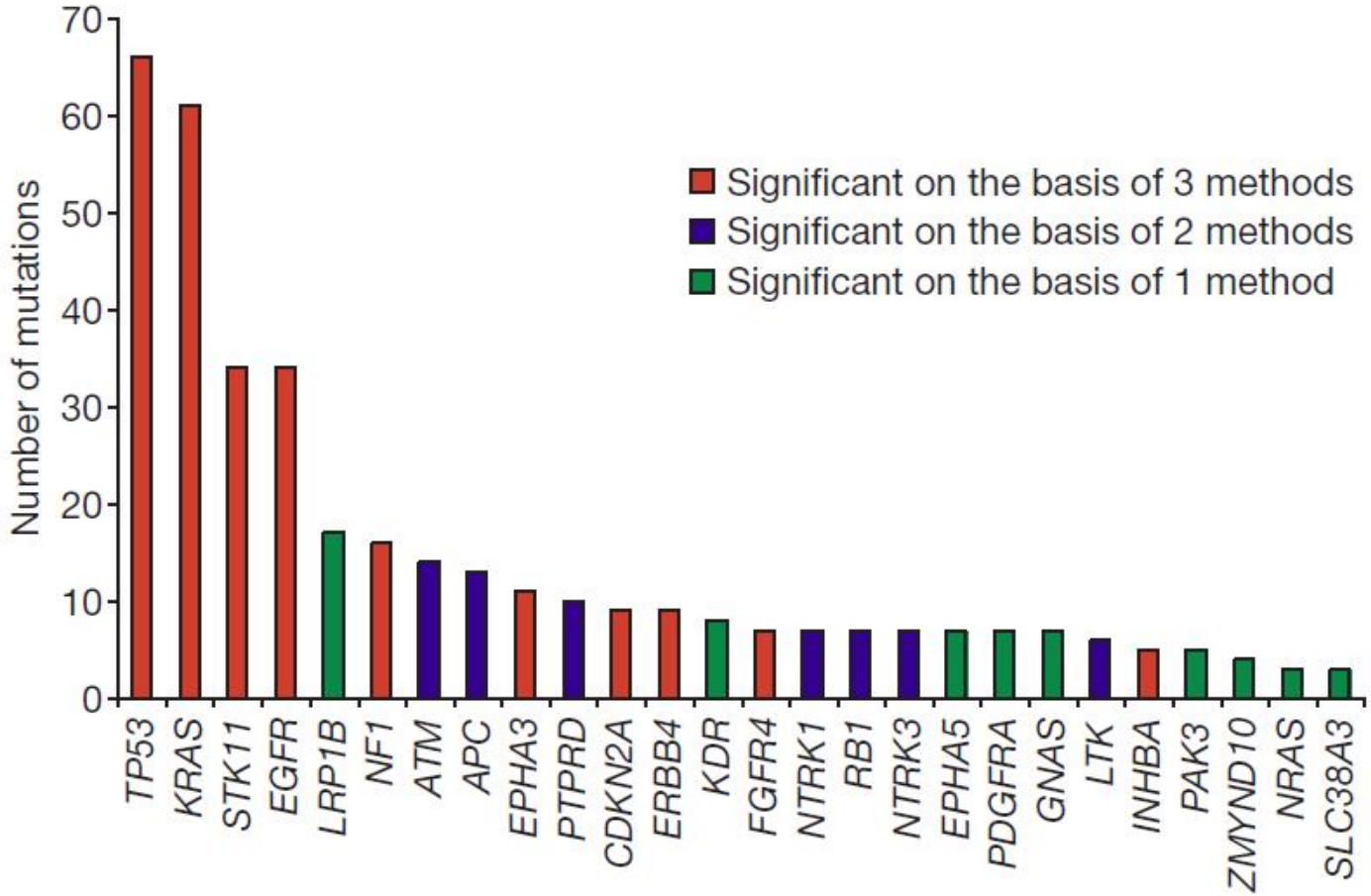
Hanahan and Weinberg, Cell 2000

Simplified view of EGFR Pathway



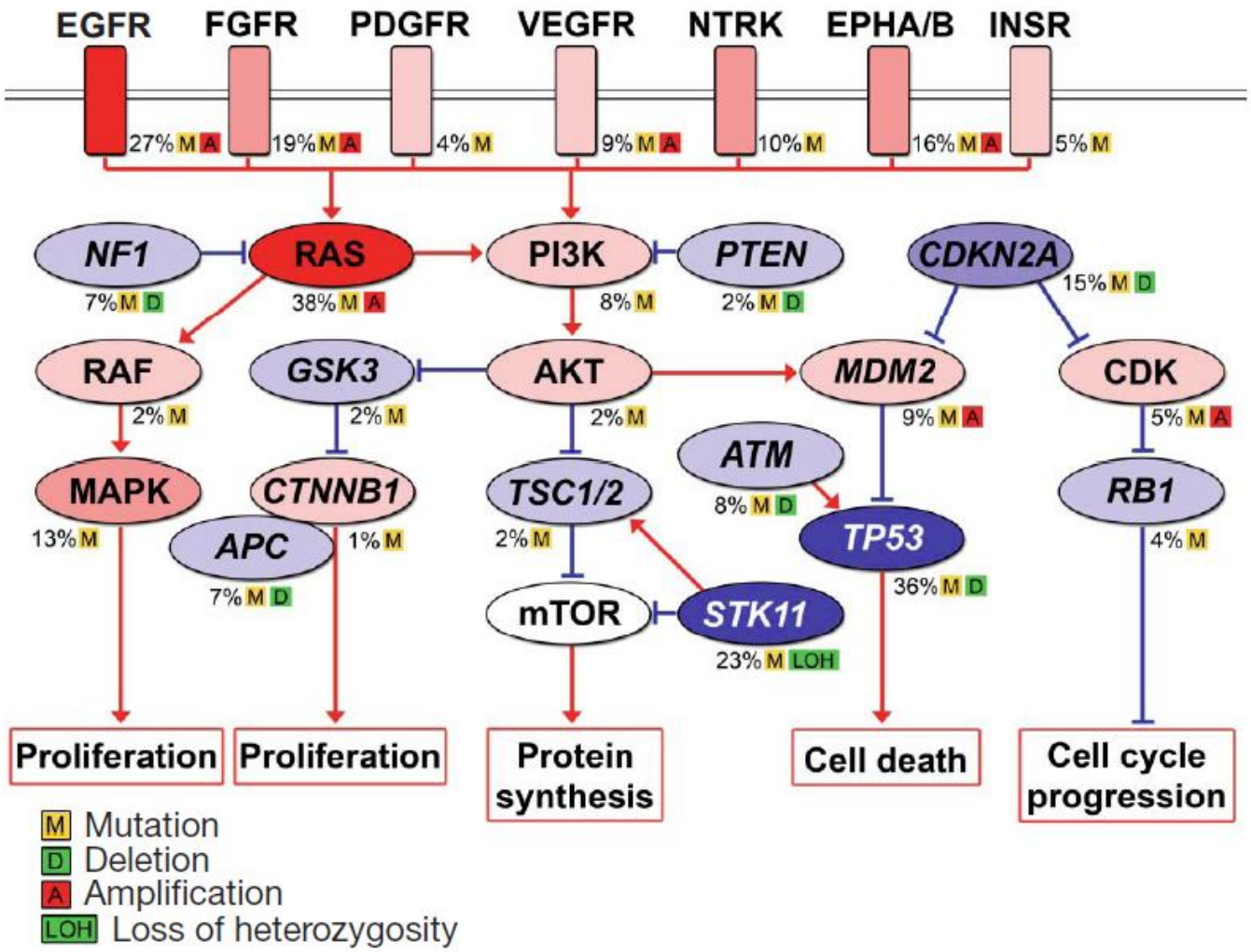
Dempke et al, Lung Cancer 2009

Genomic Landscape of Lung Adenocarcinoma



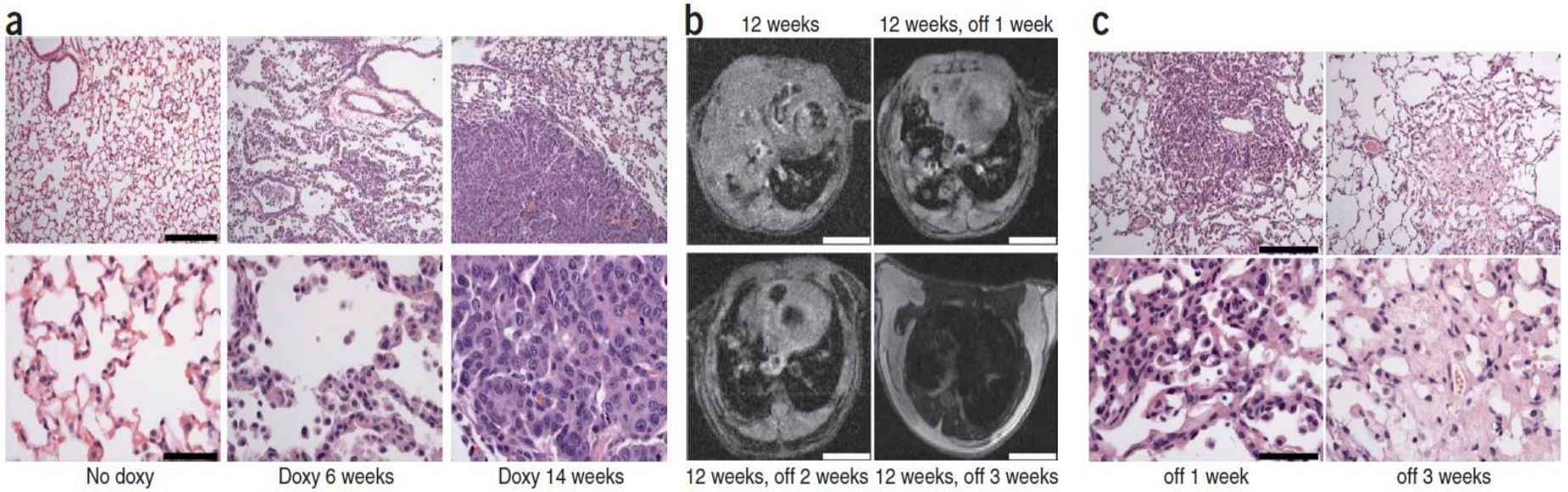
Ding et al, Nat 2008

Genomic Landscape of Lung Adenocarcinoma



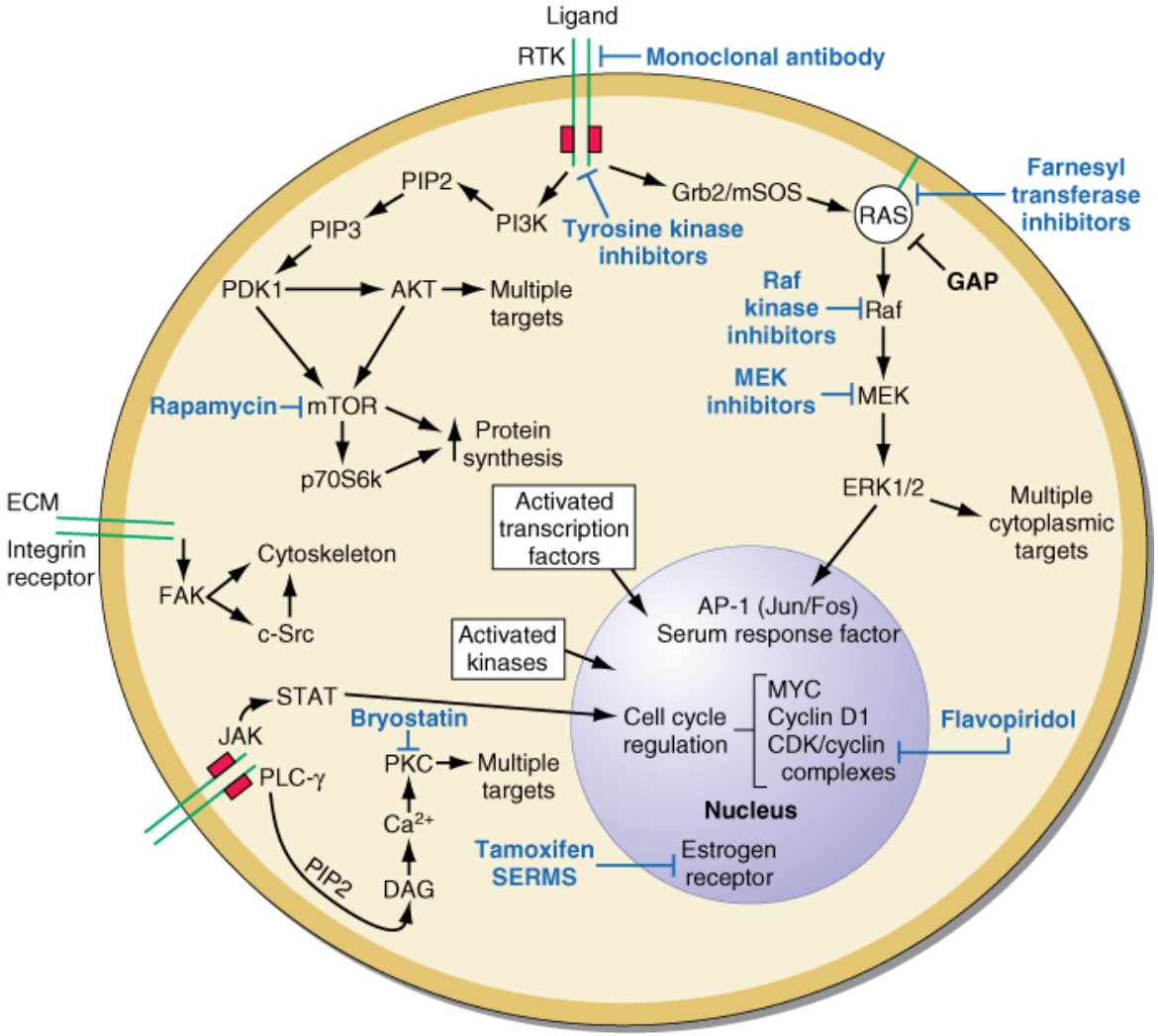
Ding et al, Nat 2008

Induccion de Cancer en Ratones



Engelman et al, Nat Med 2008

Oportunidades Terapeuticas



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

Prevencion Primaria

- Segunda causa de muerte.
- Causas modificable responsables 30 % tumores.
  - Prohibicion fumar.
  - Regulacion dieta.
  - Exposicion al UV.
- El factor mas importante es la edad.
  - Aun no modificable.

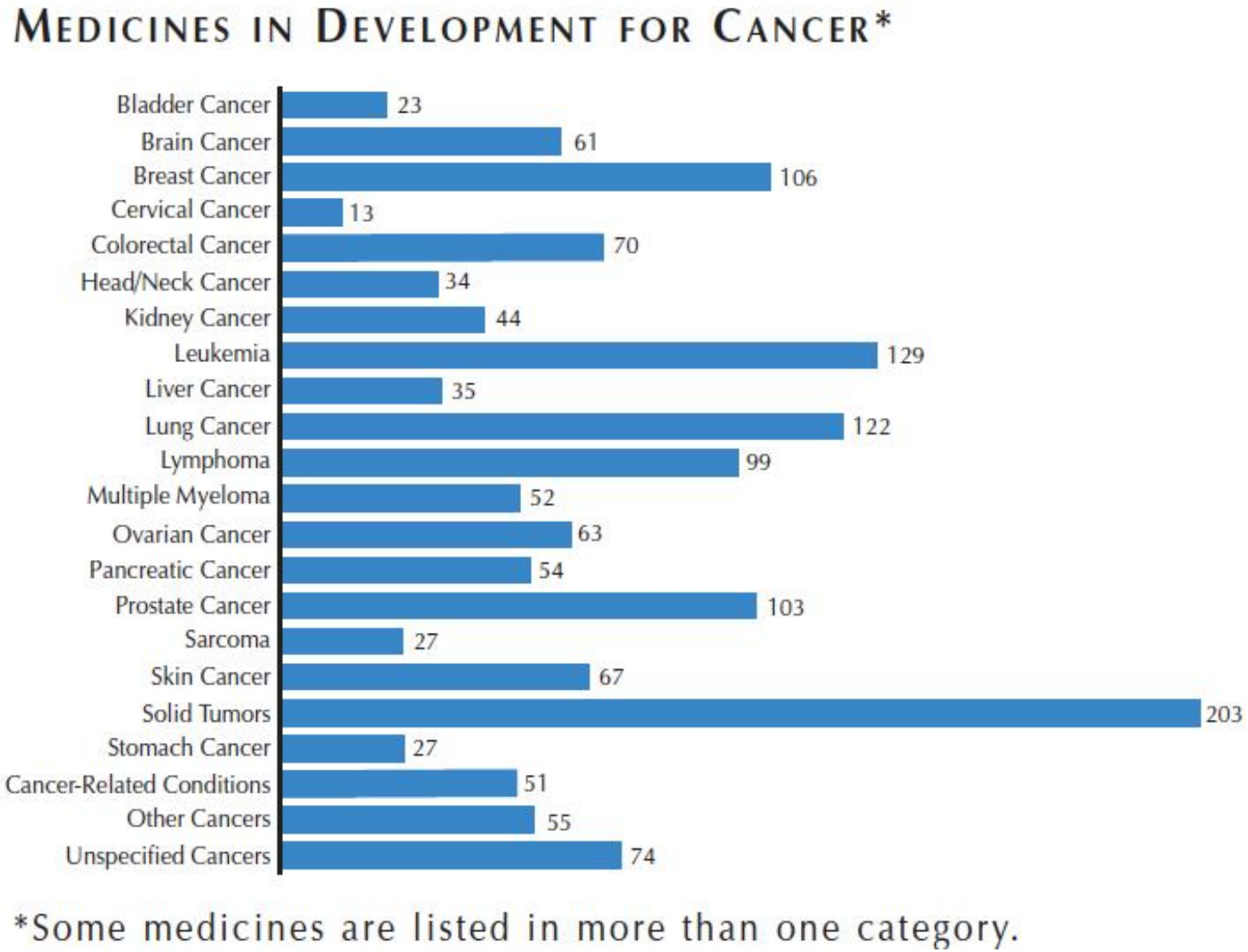
Prevencion Secundaria

- Definicion grupos de riesgo.
- Recomendaciones de screening.
  - Mamografia.
  - Colonoscopia.
- No se cumplen.
- Importante descubrimiento de mediadores sericos.

Avances Terapeuticos

- **Tratamiento multidisciplinario:**
  - Curacion 50-60 % tumores.
  - Centro Oncologico.
  - No es, desgraciadamente, el modelo en España.
- **Nuevos farmacos diana moleculares.**
  - Aumento supervivencia.
  - Menos toxicidad.
  - Eficaces en grupos pequeños de pacientes.
  - Necesidad de incorporar biomarcadores.

Muchos Agentes en Desarrollo

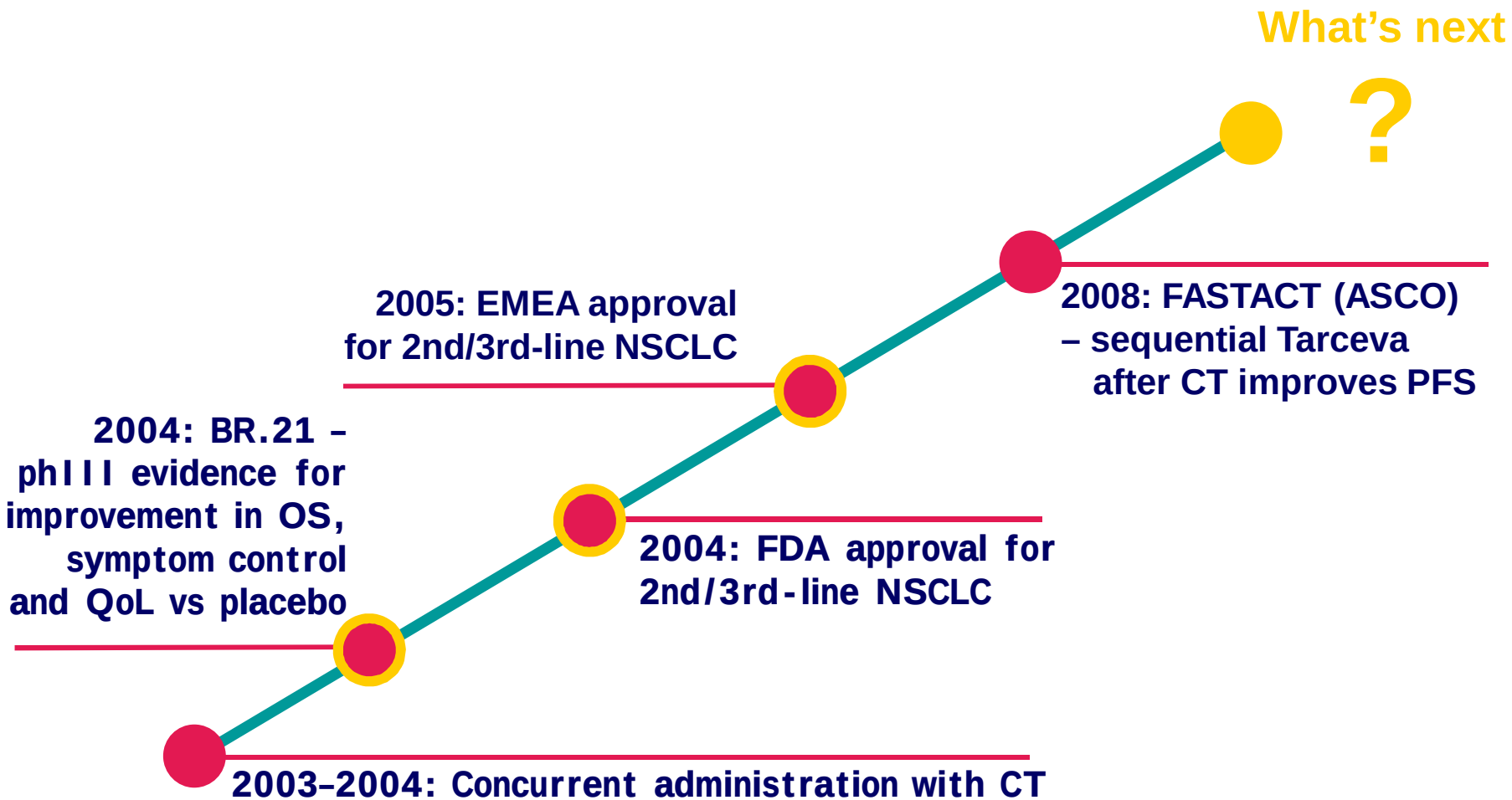


Currently Approved EGFR Inhibitors

Drug	Molecular properties	Approved uses
Tarceva	Reversible EGFR TKI	Monotherapy in refractory NSCLC With gemcitabine first-line in pancreatic cancer
Gefitinib	Reversible EGFR TKI	Available in Asia for refractory NSCLC (third line) Investigational use only in ROW
Cetuximab	Human-mouse chimeric MoAB	Monotherapy (USA) or combination therapy for refractory CRC (EU in patients with wild-type *K-RAS*) Approved in head and neck cancer with radiotherapy or as monotherapy in second line
Panitumumab	Fully human MoAB	Monotherapy (third line) in refractory CRC in the USA (EU in patients with wild-type *K-RAS*)

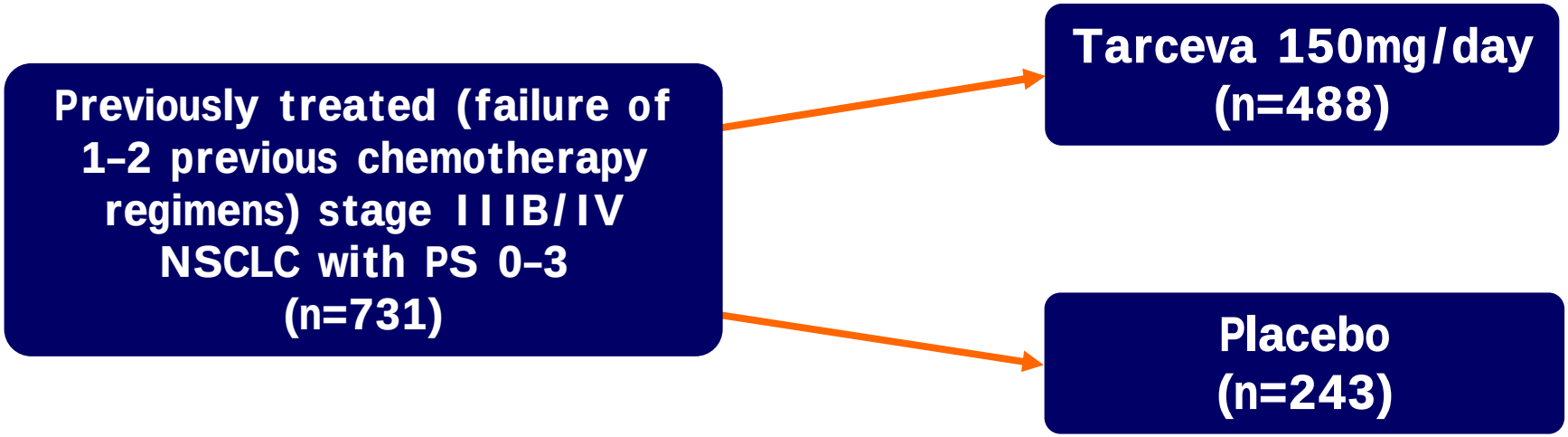
Ciardiello, et al. NEJM 2008

EGFR inhibitors in NSCLC: Tarceva as monotherapy and in combination



Ciardiello, et al. NEJM 2008
Lee, et al. ASCO 2008

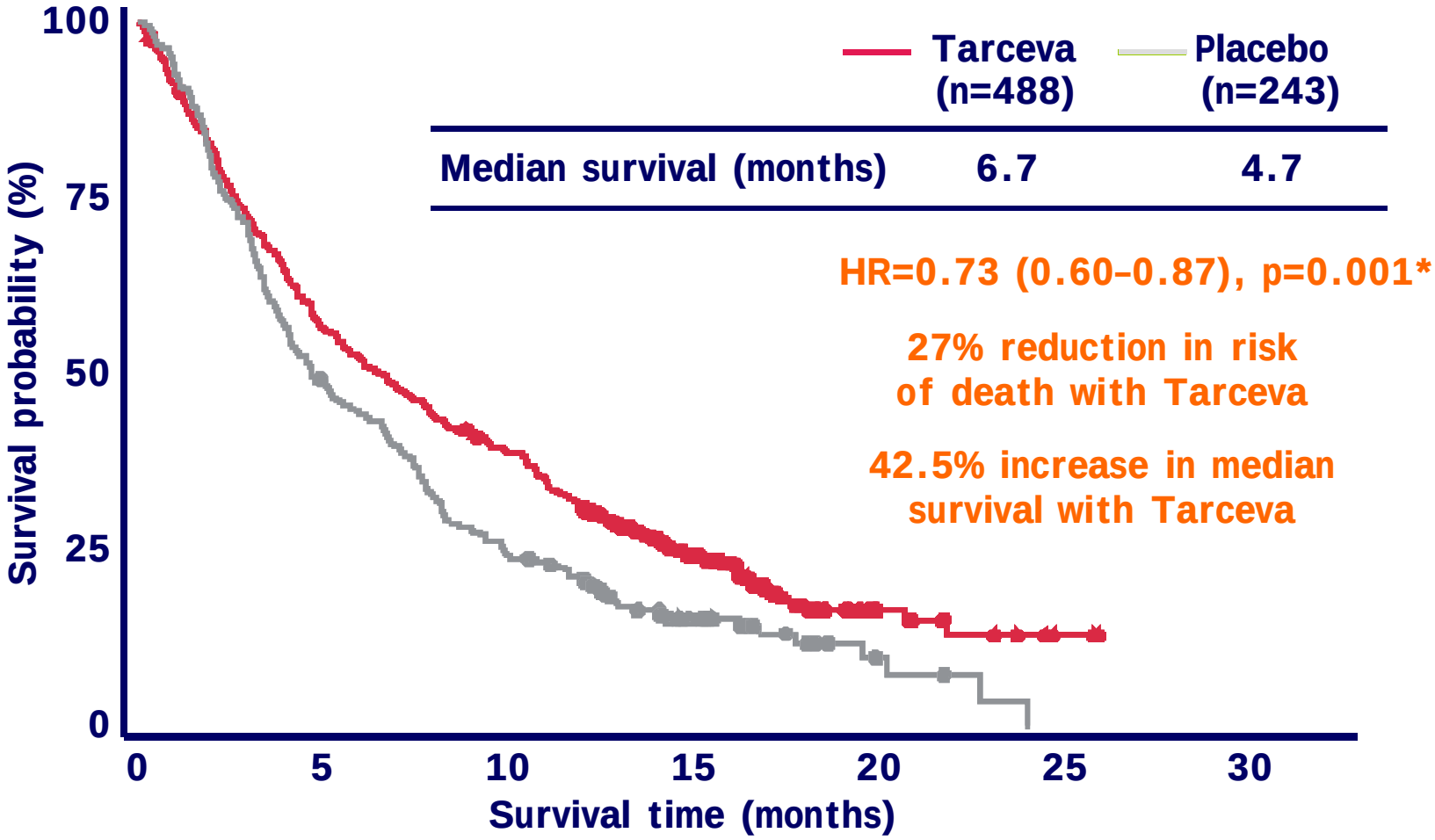
Pivotal Clinical Trial: NCIC-CTG BR.21



- Primary endpoint: OS
- Secondary endpoints: PFS, RR, safety, QoL, duration of response

NCIC-CTG = National Cancer Institute of Canada – Clinical Trials Group

Phase III trial BR.21 demonstrated improvement in OS versus placebo



*HR and p (log-rank test) adjusted for stratification factors at randomisation and EGFR status

Shepherd, et al. NEJM 2005
Tarceva Summary of Product Characteristics

EGFR Mutations Confers High Susceptibility to EGFR Inhibitors

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†]

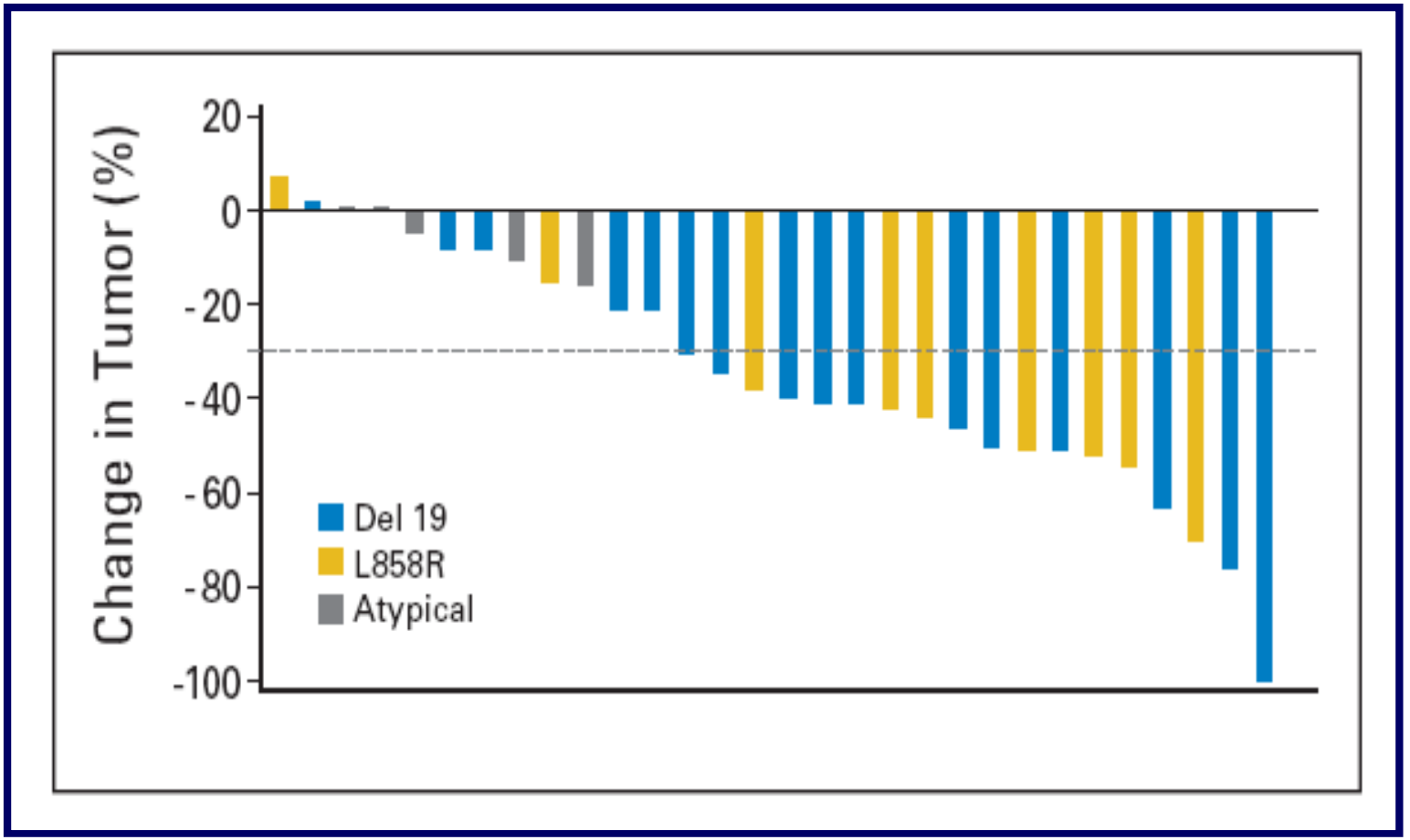
Science 2004

Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non–Small-Cell Lung Cancer to Gefitinib

Thomas J. Lynch, M.D., Daphne W. Bell, Ph.D., Raffaella Sordella, Ph.D., Sarada Gurubhagavatula, M.D., Ross A. Okimoto, B.S., Brian W. Brannigan, B.A., Patricia L. Harris, M.S., Sara M. Haserlat, B.A., Jeffrey G. Supko, Ph.D., Frank G. Haluska, M.D., Ph.D., David N. Louis, M.D., David C. Christiani, M.D., Jeff Settleman, Ph.D., and Daniel A. Haber, M.D., Ph.D.

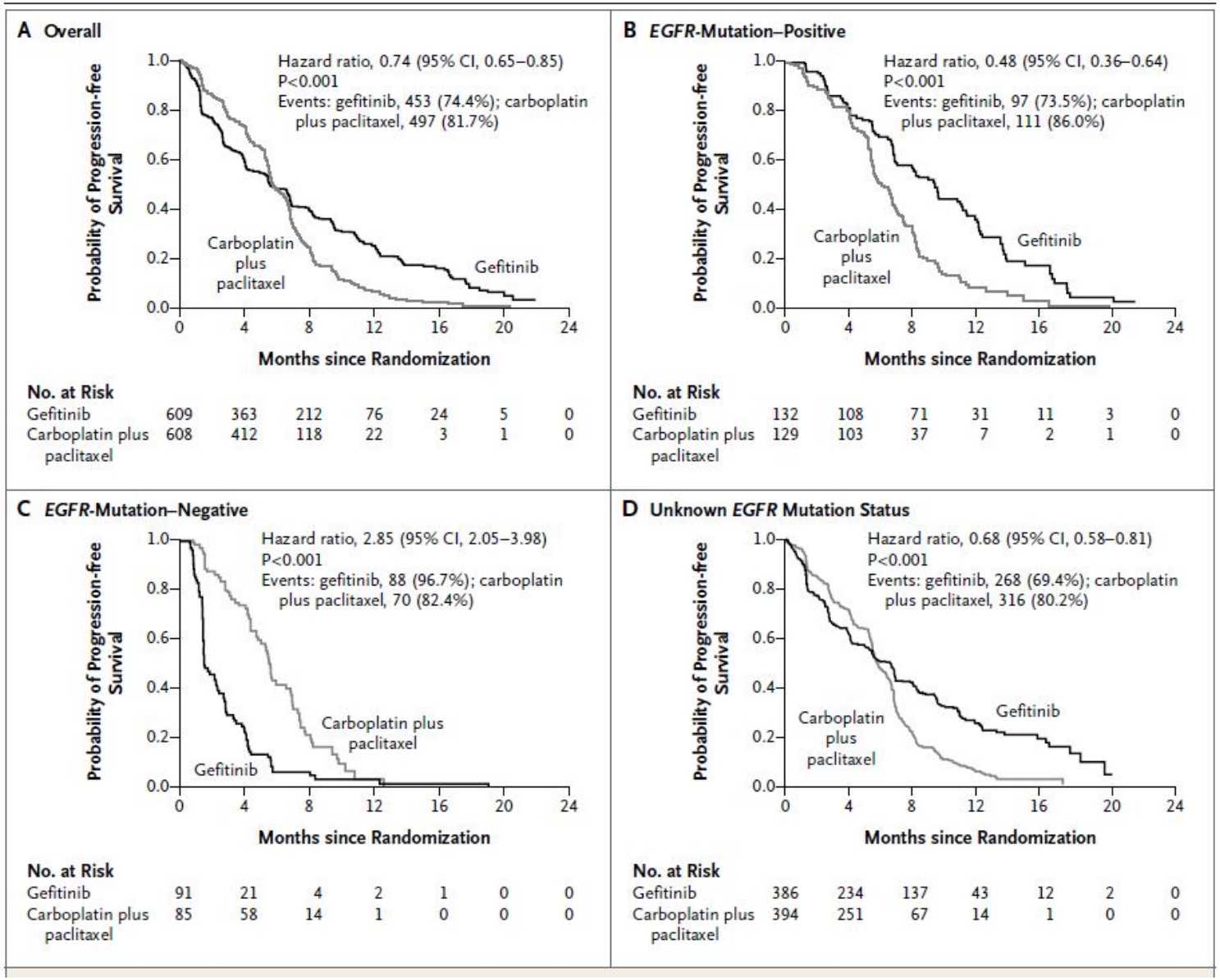
NEJM 2004

First Line Gefitinib in EGFR mut Patients



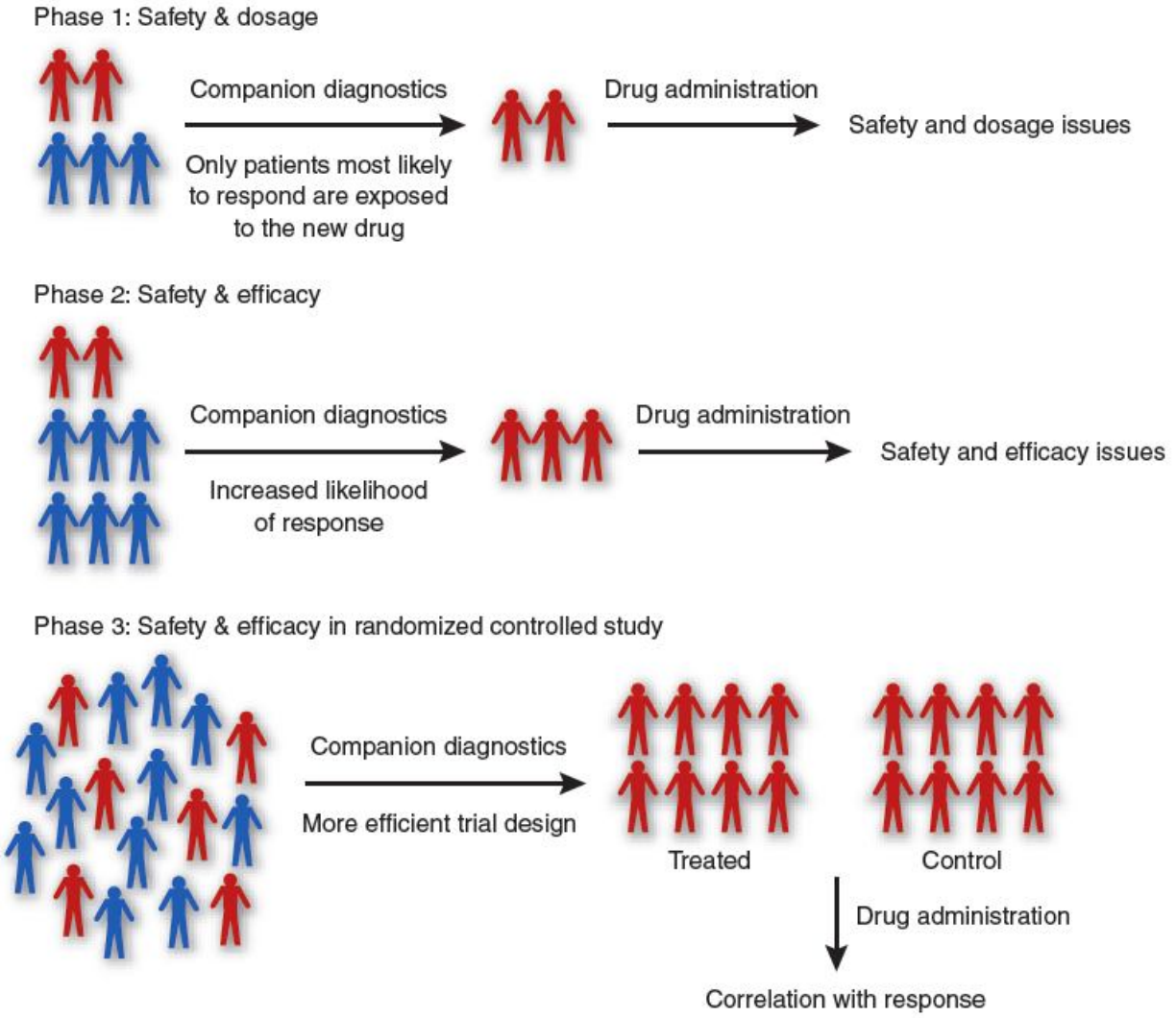
Sequist et al, JCO 2008

Gefitinib in NSCLC



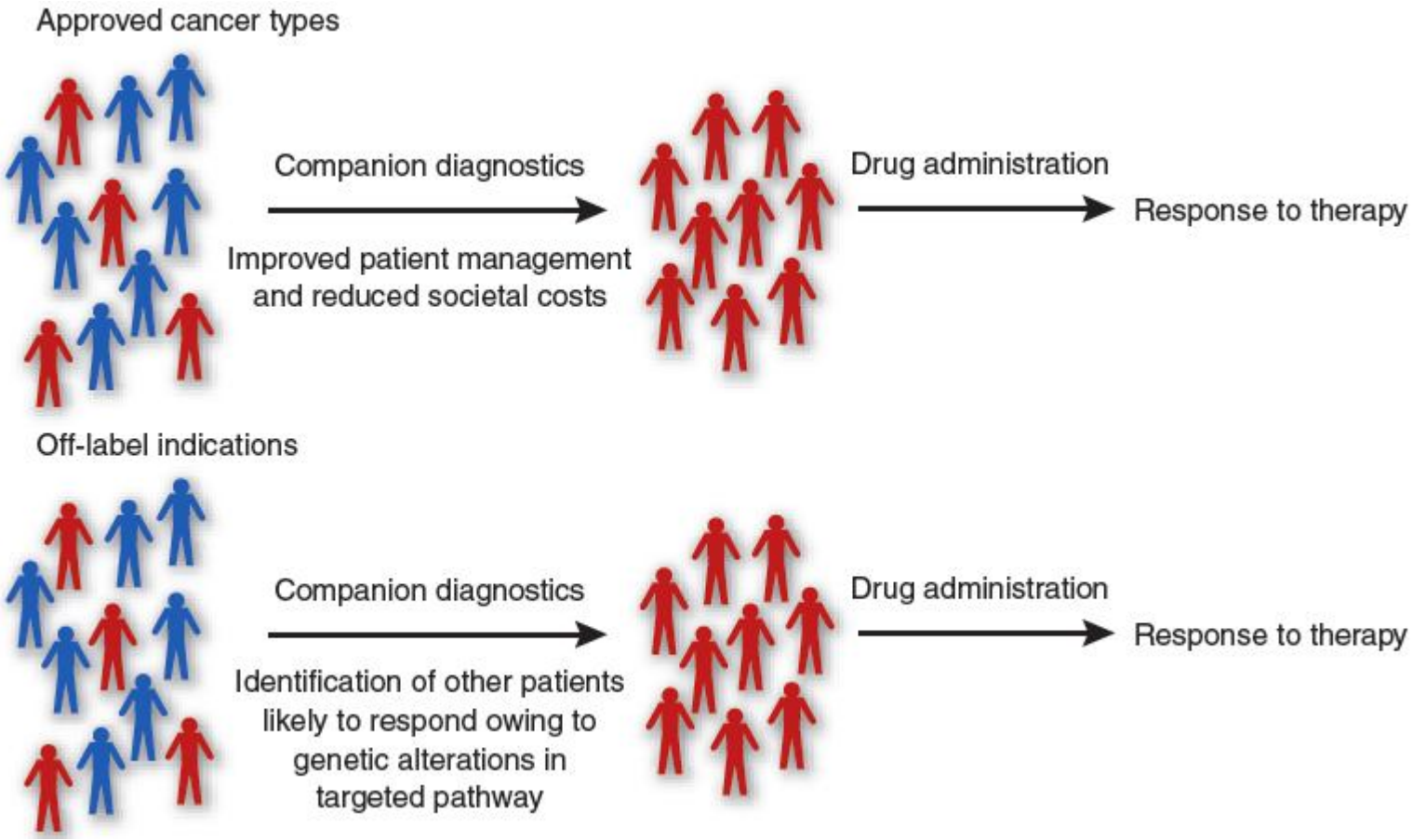
Mok et al, NEJM 2009

Aplicaciones de Marcadores Moleculares en Drug Development



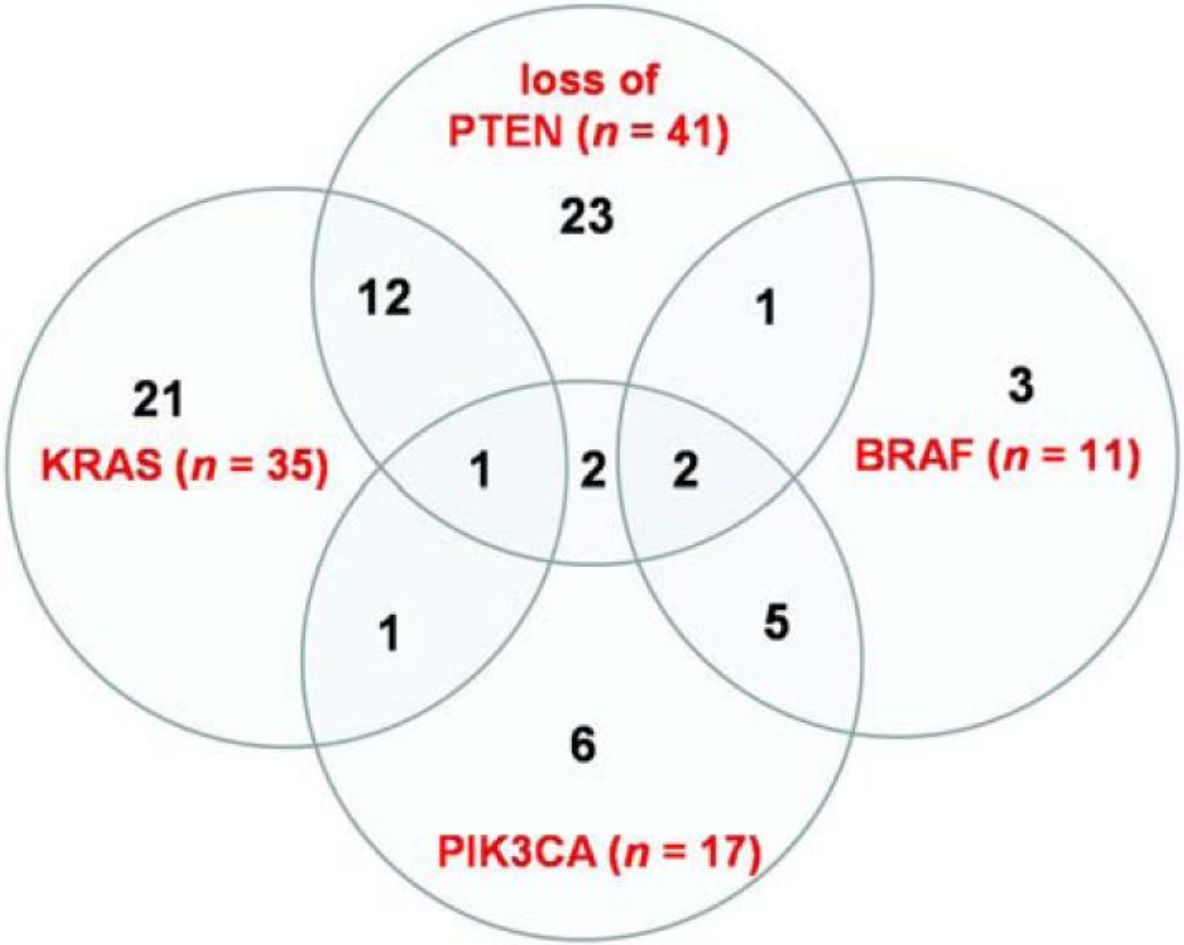
Papadopoulos et al, 2006

Aplicaciones de Marcadores Moleculares en Drug Development



Papadopoulos et al, 2006

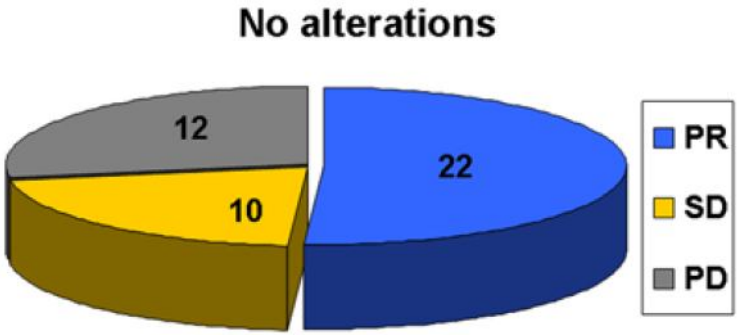
Genomic Alterations in Colon Cancer

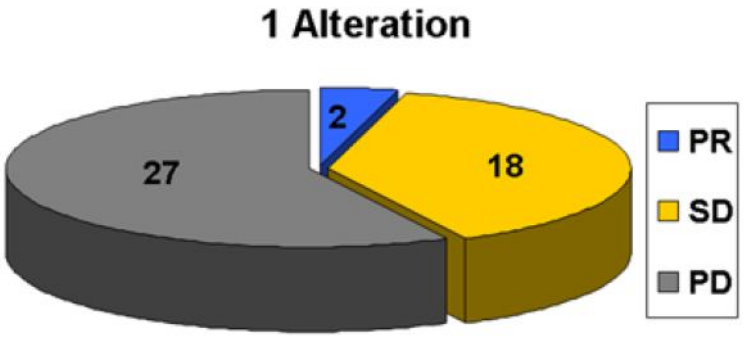


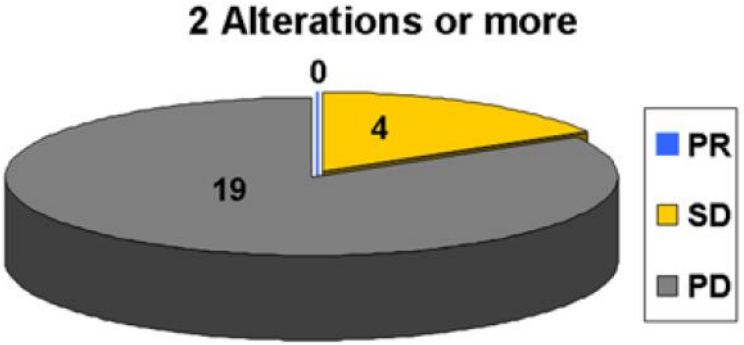
Sartore-Bianchi et al. PlosOne 2009

Genomic Alterations in Colon Cancer

# Alterations	# Patients (%)
0	44 (39%)
1	47 (41%)
2+	23 (20%)

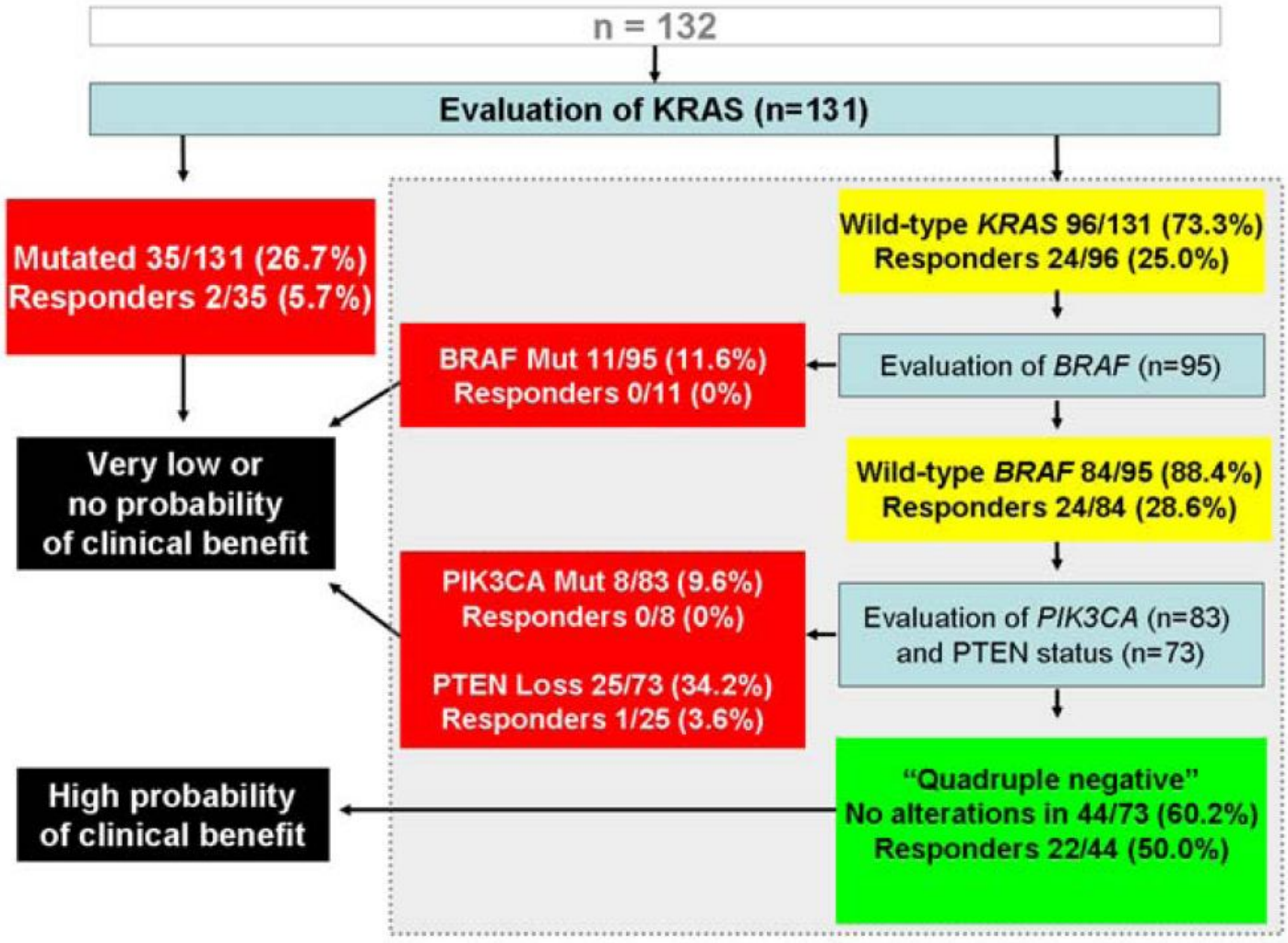






Sartore-Bianchi et al. PlosOne 2009

Flow Chart of Molecular Markers for EGFR inhibitors in in Colon Cancer

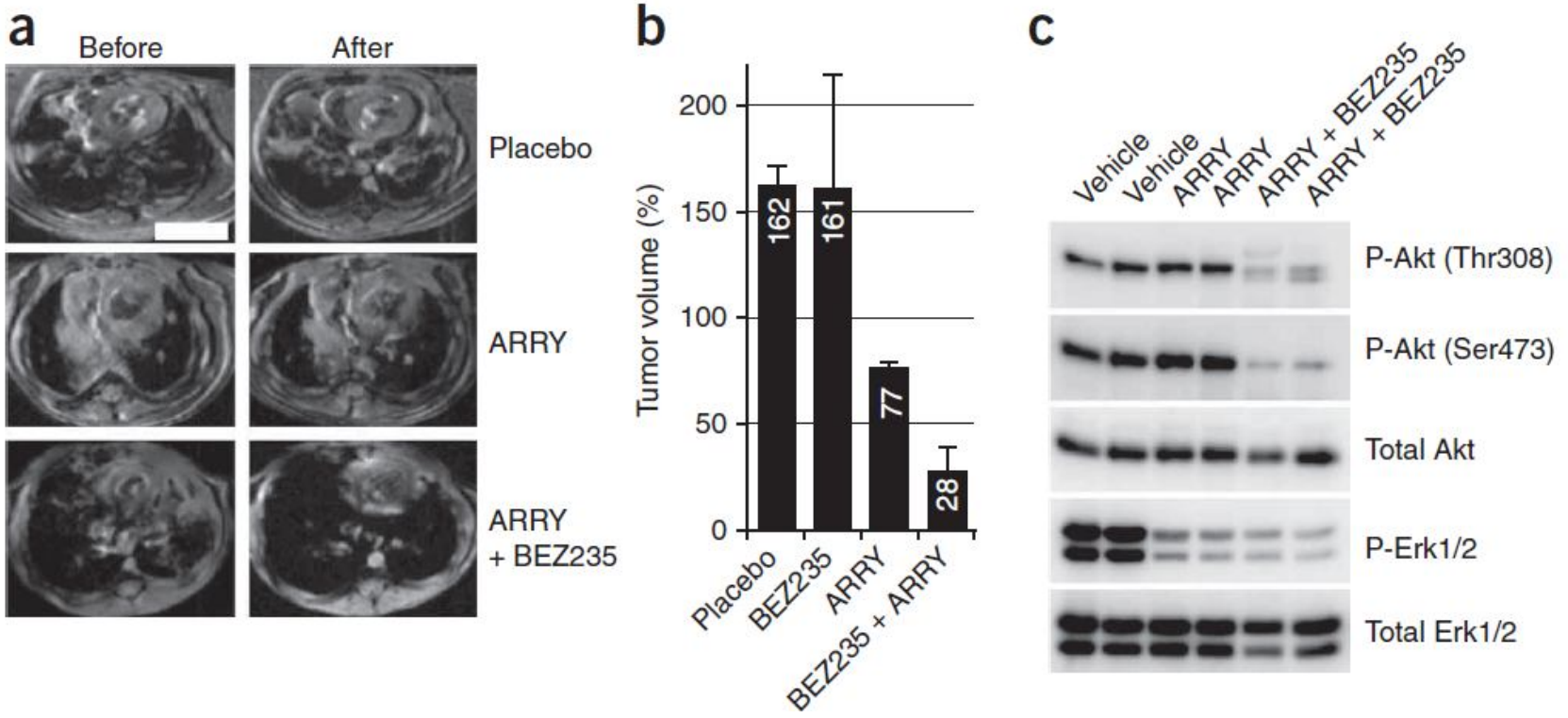


Sartore-Bianchi et al. PlosOne 2009

Retos Desarrollo de Farmacos

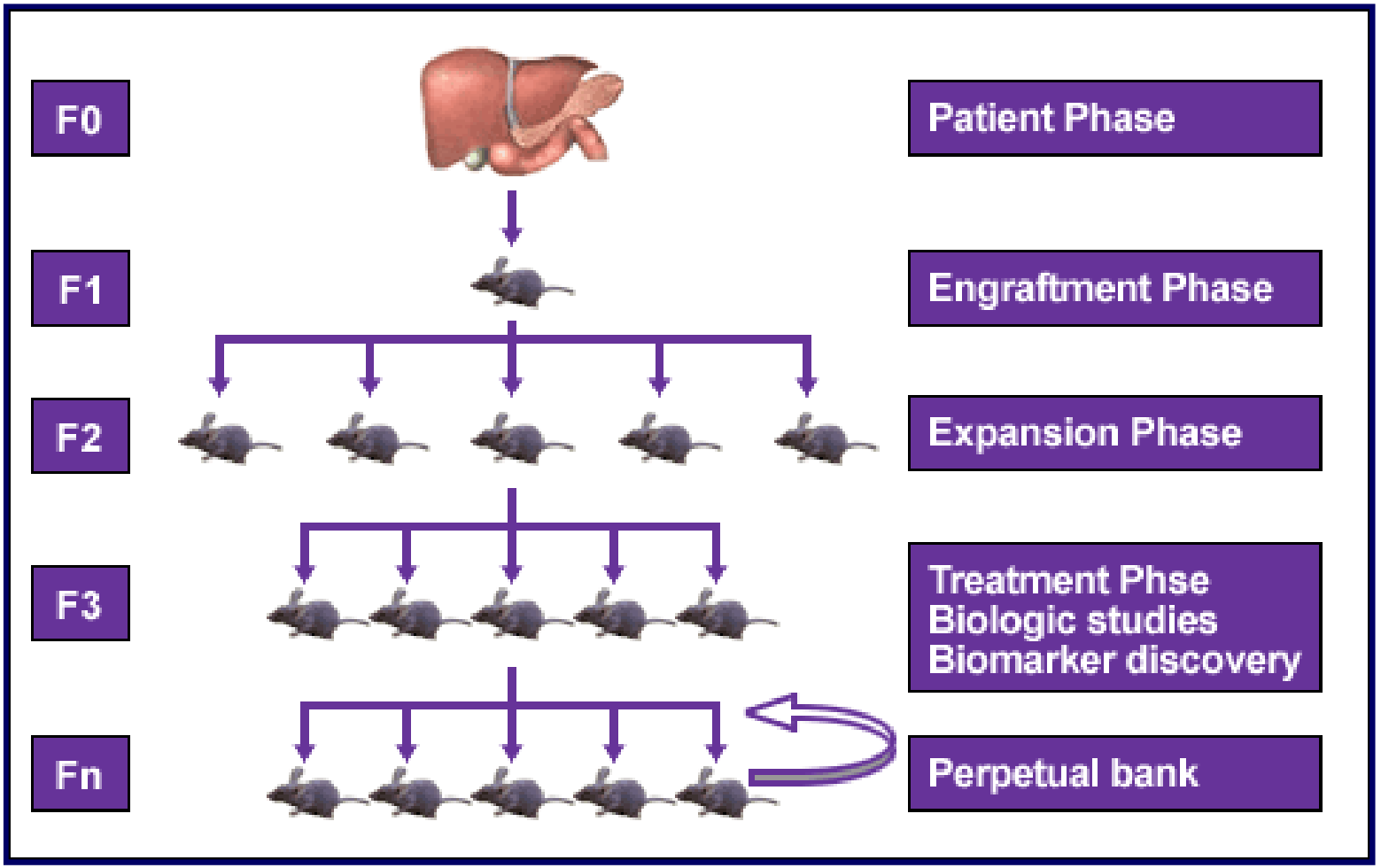
- Farmacos selectivos y especificos.
- Grupos de pacientes reducidos.
- Incorporacion de biomarcadores desde fases tempranas.
- Desarrollo preclinico.

Teraputica Frente a Dianas Moleculares



Engelman et al, Nat Med 2008

Generation of Personalized Xenograft



Overall Results

Tumor Type	Number of Drugs Tested	Predicted Clinical Sensitivity (Yes/No)	Predicted Clinical Resistance (Yes/No)	Treatment Course & Duration of Response
PDA	17	Yes, three times	Yes, once	2nd line, CR, 46 + mo
PDA	5	No active agent	Yes, once	1st line, PD
PDA	4	Yes, once	Not tested	1st line, SD, 6 mo
PDA	1	Yes, once	Not tested	1st line, SD, 6 mo
LMS	28	Yes, twice	Yes, twice	4th line, PR, 9 mo
MCS	21	Yes, once	Yes, once	3rd line, PR, 9 mo
NSCLC	25	Yes, once	Yes, twice	3rd line, PR, 9 mo
Esophageal	24	Yes, three times	Not tested	3rd, 4th, & 5th, PR 48 + mo
Myoepithelioma	13	No active agent	Yes, twice	1st and 2nd line, PD
CRC	16	Yes, once	Not tested	3rd line, PR, 12 + mo
Breast Cancer	12	Yes, once	Not tested	Not treated
11	**166**	**14/14**	**9/9**	**N/A**

JH033 Pancreatic Cancer

Patient

63 year-old male with metastatic Stage IV pancreatic cancer.

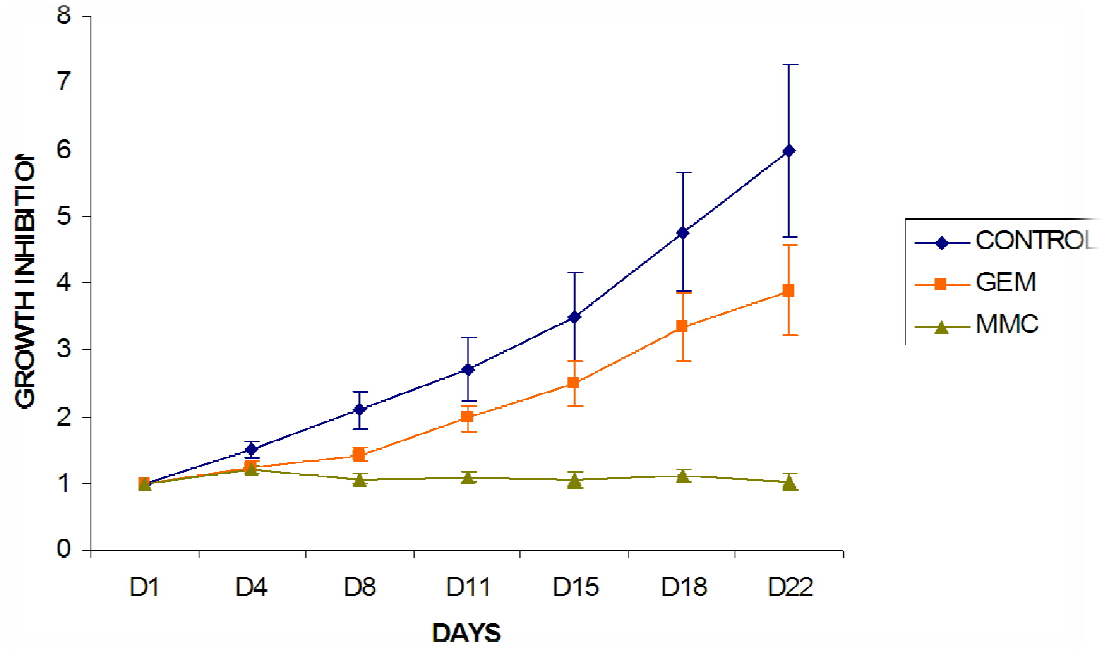
Tumorgraft results

17 drugs in 26 treatment groups were tested

Treatment with Mitomycin C resulted in tumor growth inhibition

Clinical results

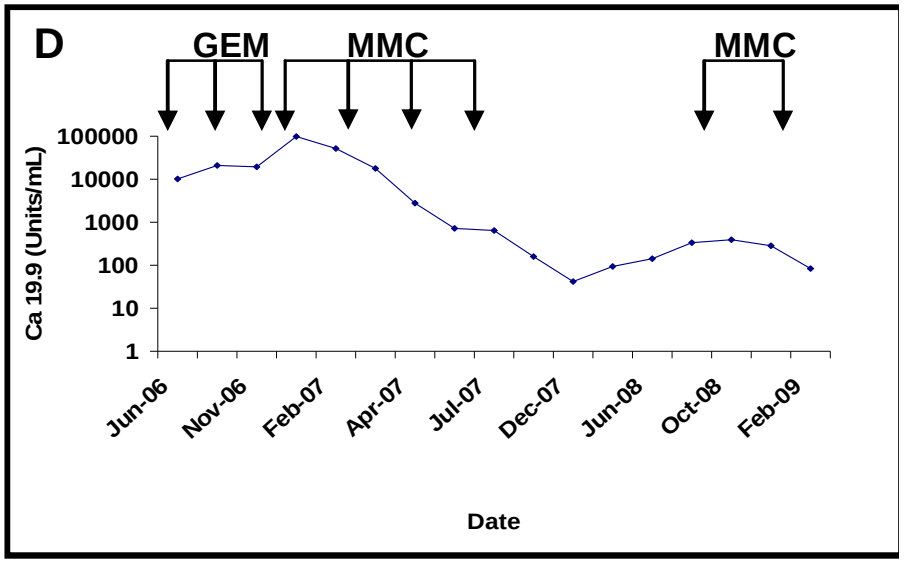
Responded to treatment with normalization of CA199 marker.




A


H
B
F


C


D
GEM
MMC
MMC
Ca 19.9 (Units/mL)
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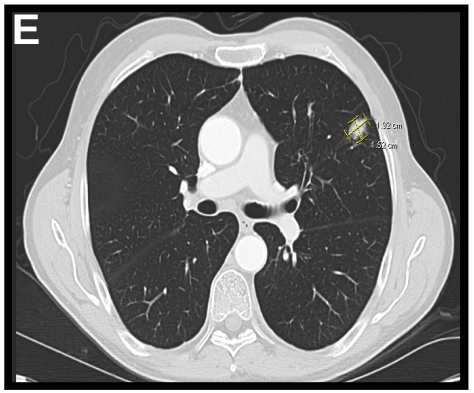
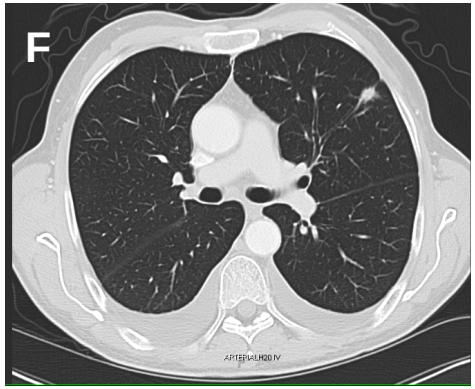
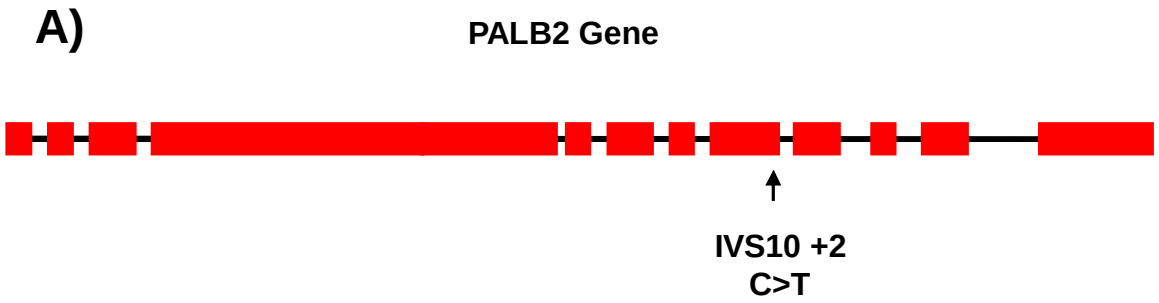
Oct-08
Feb-09
Date

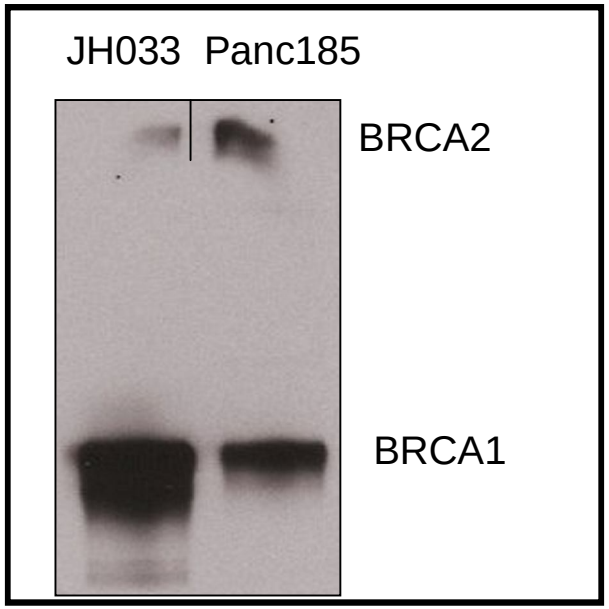

E


F

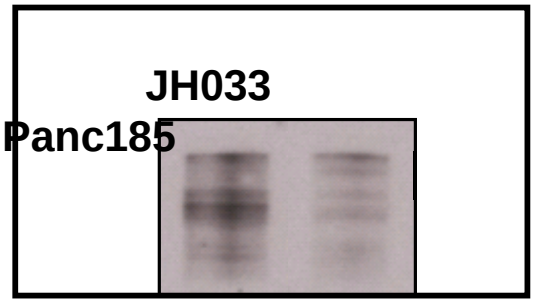
A)


PALB2 Gene
IVS10 +2
C>T

B)


JH033
Panc185
BRCA2
BRCA1

C)


JH033
Panc185

Conclusions

- El conocimiento basico de cancer avanza de forma rapida.
- Se pueden prevenir y curar muchos casos si se aplica lo que se conoce.
- El cancer es una enfermedad compleja y heterogenea.
- El desarrollo, aprobacion y utilizacion de farmacos tendra que adaptarse a esa realidad.