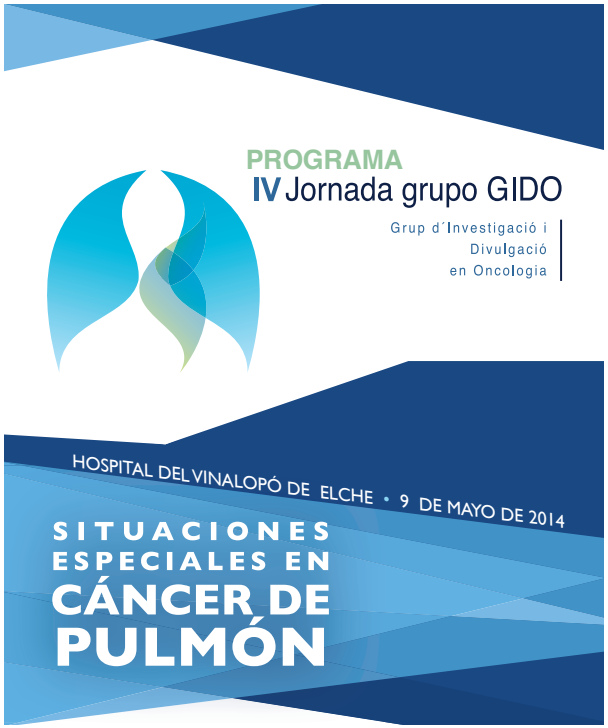

Segundas líneas de tratamiento: Nuevas dianas en carcinoma no microcitico de pulmón

Bartomeu Massutí
Hospital General Universitario Alicante
bmassutis@seom.org

ALACANT HOSPITAL GENERAL
DEPARTAMENT DE SALUT

GECP
Grupo Español de Cáncer de Pulmón
Spanish Lung Cancer Group
www.gecp.org

Contenido

- Datos epidemiológicos, magnitud del problema; resultados y evolución terapéutica
- Relevancia y búsqueda de subpoblaciones para tratamientos dirigidos: impacto terapéutico
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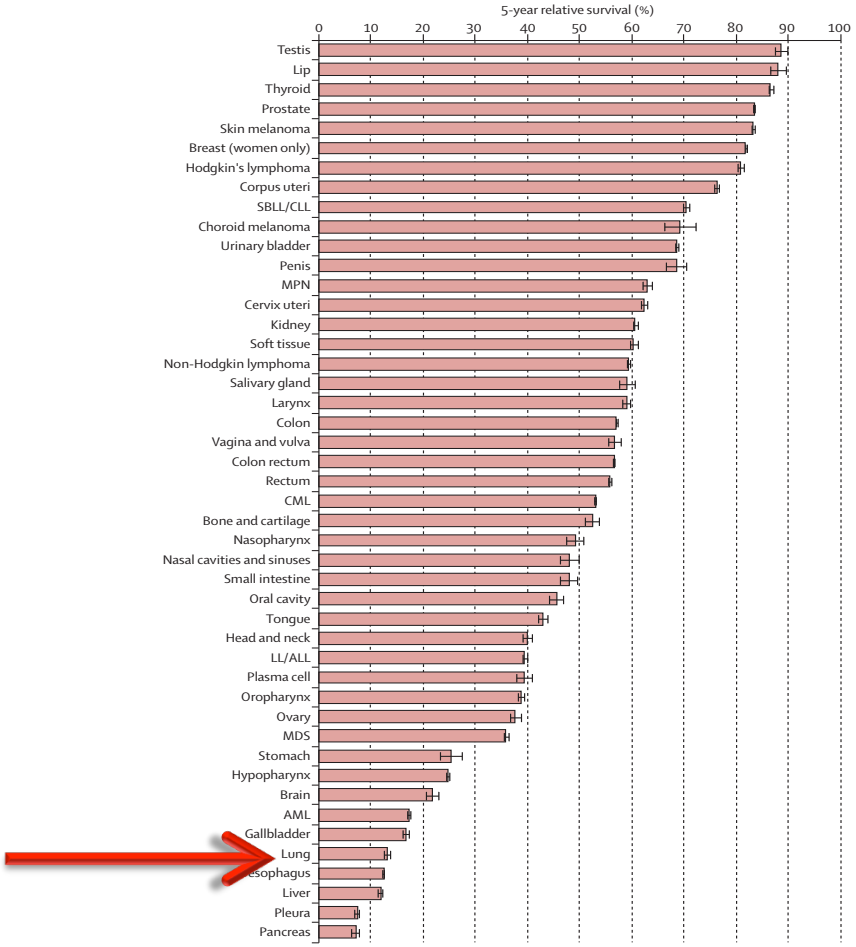
- Conclusiones


Sostenibilidad o retroceso?

Datos epidemiológicos Europa 2012-3



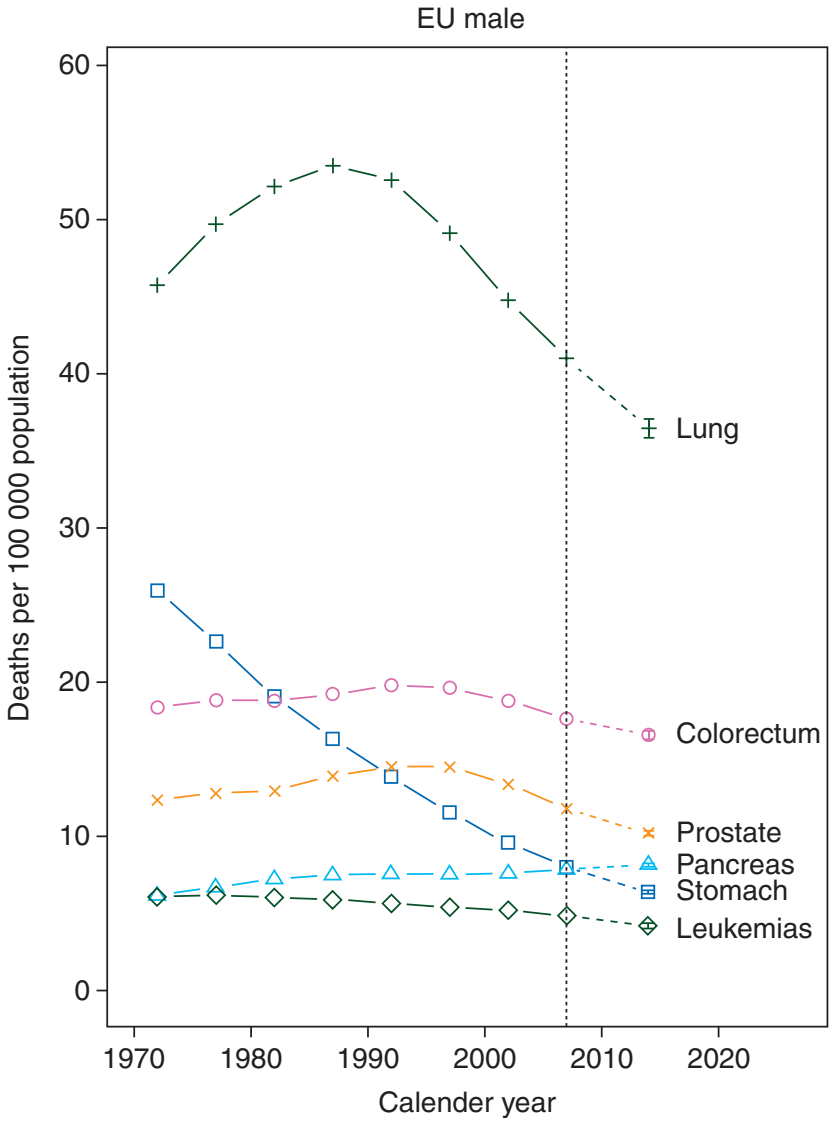
- EU-27:
  - Mortalidad total cáncer:
    - 1.314.230
    - Hombres: 737.747
    - Mujeres: 576.489
  - Mortalidad cáncer pulmón:
    - 269.610
    - Hombres: 186.970
    - Mujeres: 82.640

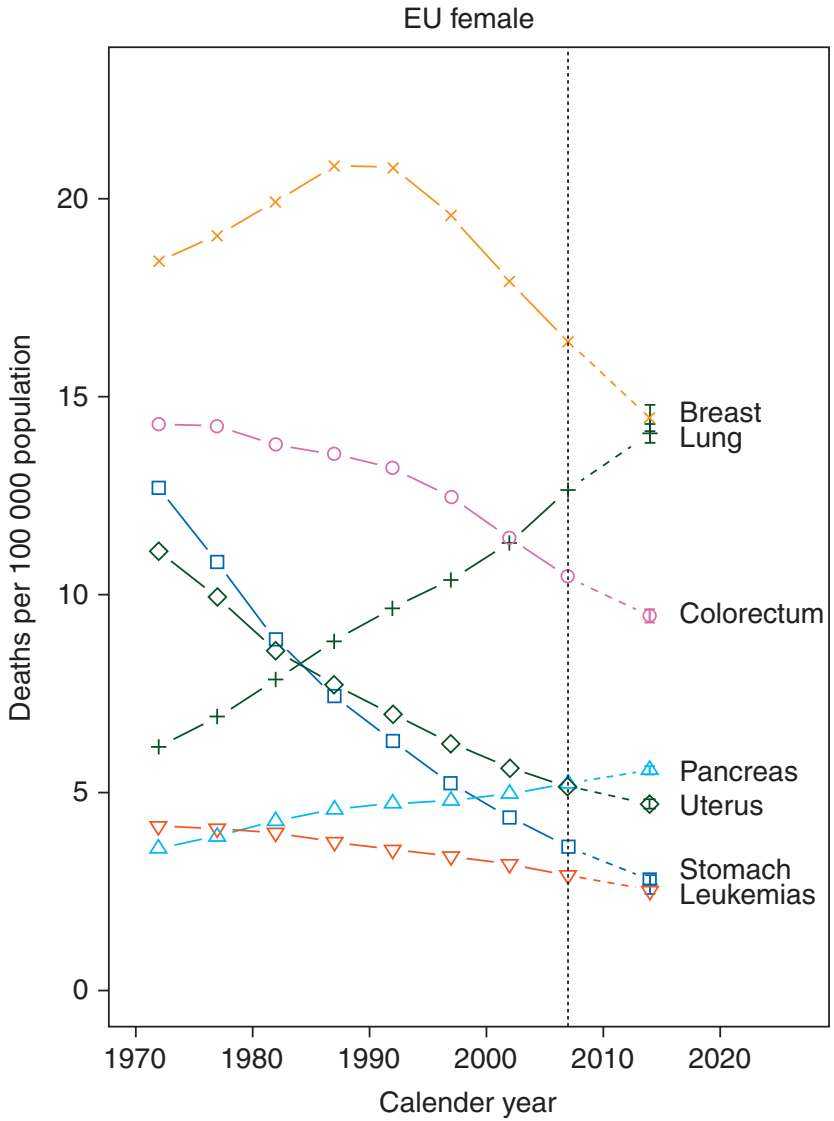
J. Ferlay et al. / European Journal of Cancer 49 (2013) 1374–1403

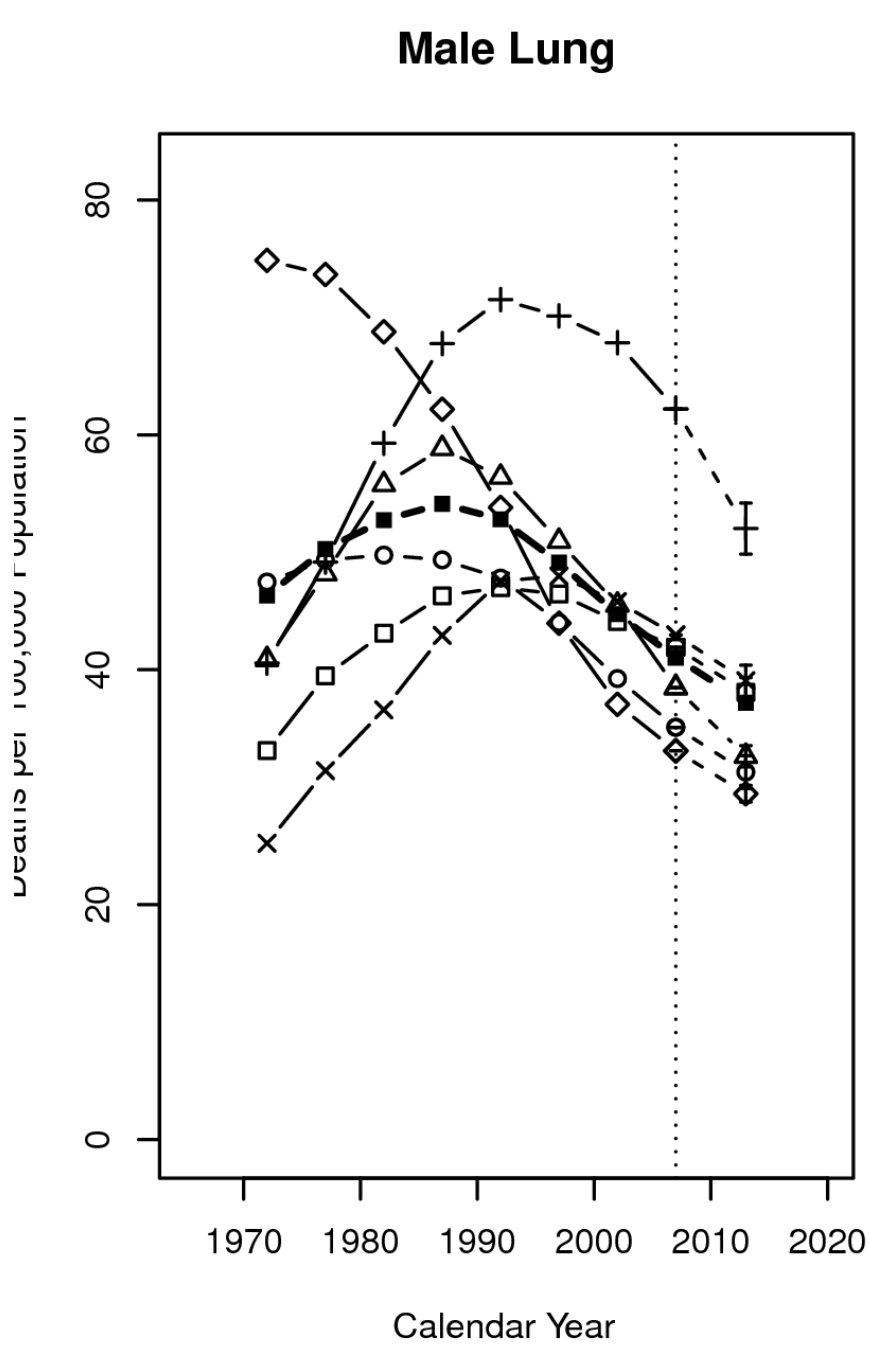
M.Malvezzi et al / Ann Oncology 2013; doi:10.1093/annonc/mdte010

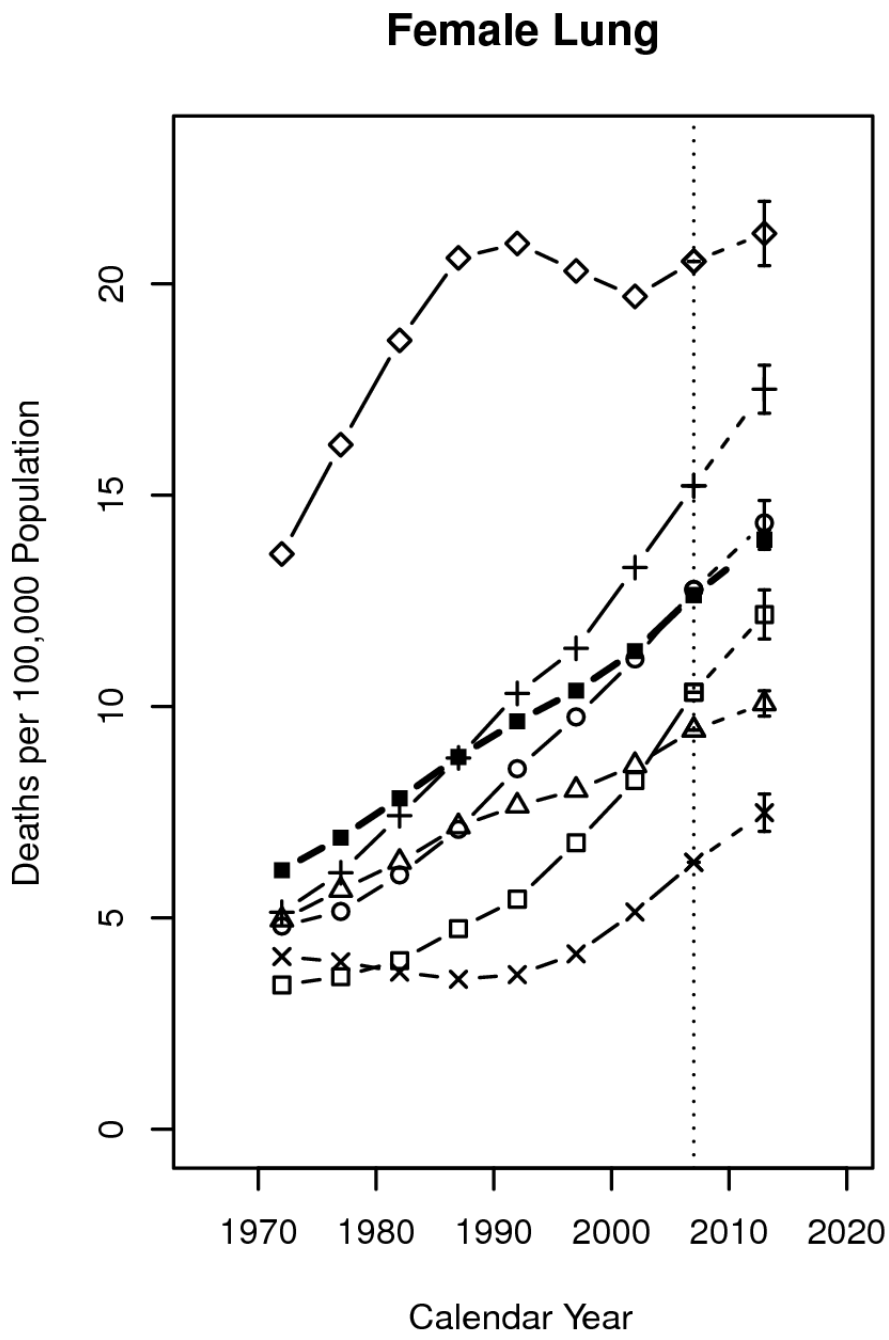
De Angelis:*Lancet Oncol* 2013. http://dx.doi.org/10.1016/S1470-2045(13)70546-1.

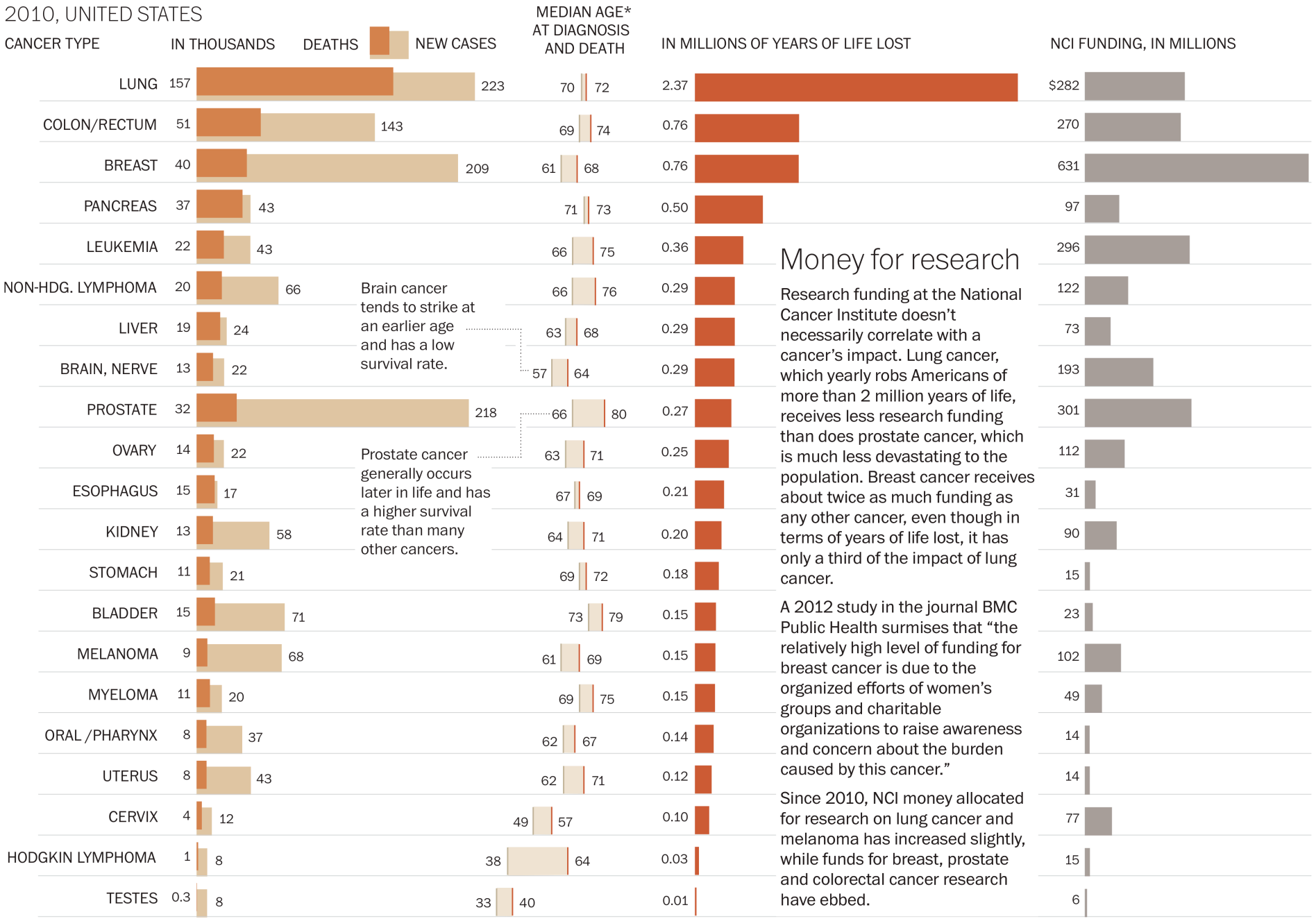
Evolución mortalidad hombres/mujeres






Male Lung
Deaths per 100,000 Population
0
20
40
60
80
1970
1980
1990
2000
2010
2020
Calendar Year


Female Lung
Deaths per 100,000 Population
0
5
10
15
20
1970
1980
1990
2000
2010
2020
Calendar Year



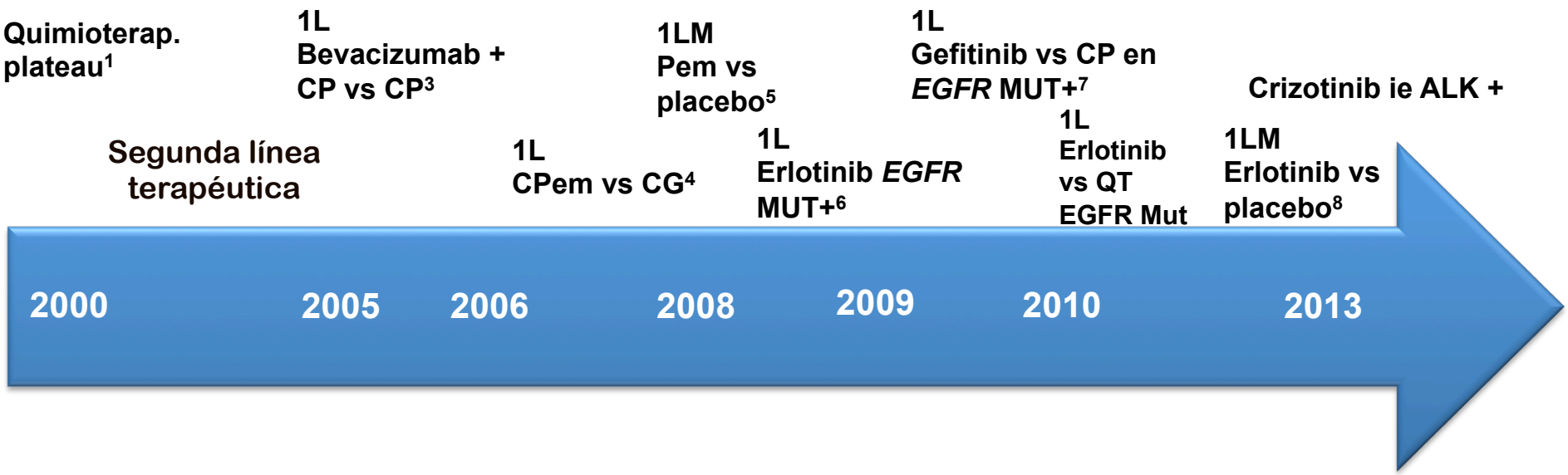
Money for research

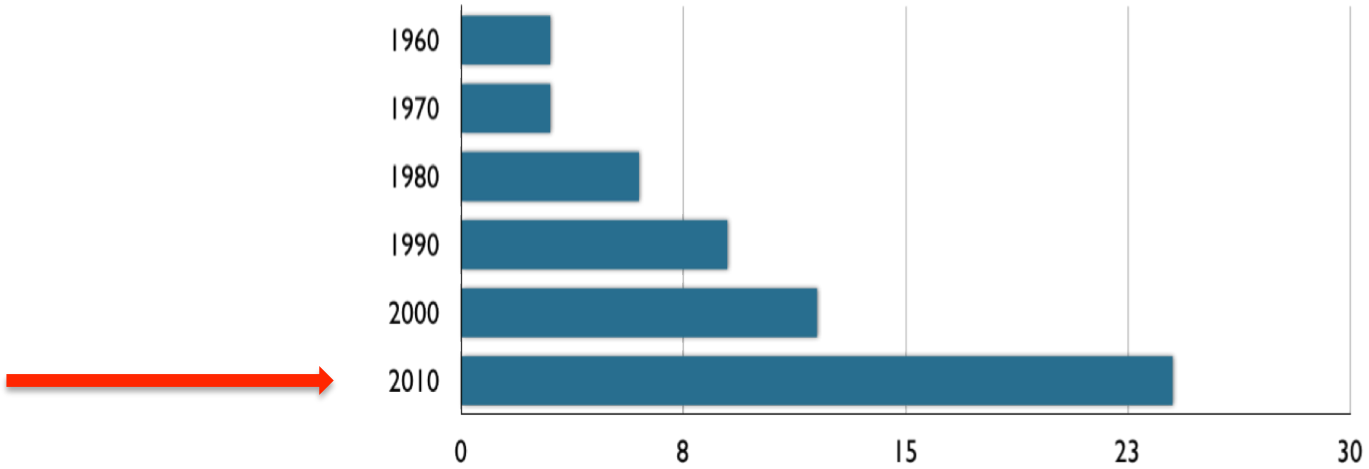
Research funding at the National Cancer Institute doesn't necessarily correlate with a cancer's impact. Lung cancer, which yearly robs Americans of more than 2 million years of life, receives less research funding than does prostate cancer, which is much less devastating to the population. Breast cancer receives about twice as much funding as any other cancer, even though in terms of years of life lost, it has only a third of the impact of lung cancer.

A 2012 study in the journal BMC Public Health surmises that "the relatively high level of funding for breast cancer is due to the organized efforts of women's groups and charitable organizations to raise awareness and concern about the burden caused by this cancer."

Since 2010, NCI money allocated for research on lung cancer and melanoma has increased slightly, while funds for breast, prostate and colorectal cancer research have ebbed.

Evolución terapéutica en Cáncer Pulmón avanzado: S XXI





CP = carboplatin paclitaxel
CPem = cisplatin pemetrexed
CG = cisplatin gemcitabine

1. Schiller, et al. NEJM 2002; 2. Sheppard, et al. NEJM 2005; 3. Sandler, et al. NEJM 2006
4. Scagliotti, et al. JCO 2008; 5. Ciuleanu, et al. Lancet 2009; 6. Rossell, et al. NEJM 2009
7. Mok, et al. NEJM 2009; 8. Cappuzzo, et al. Lancet Oncol 2010; 9. Sandler, et al. JTO 2010

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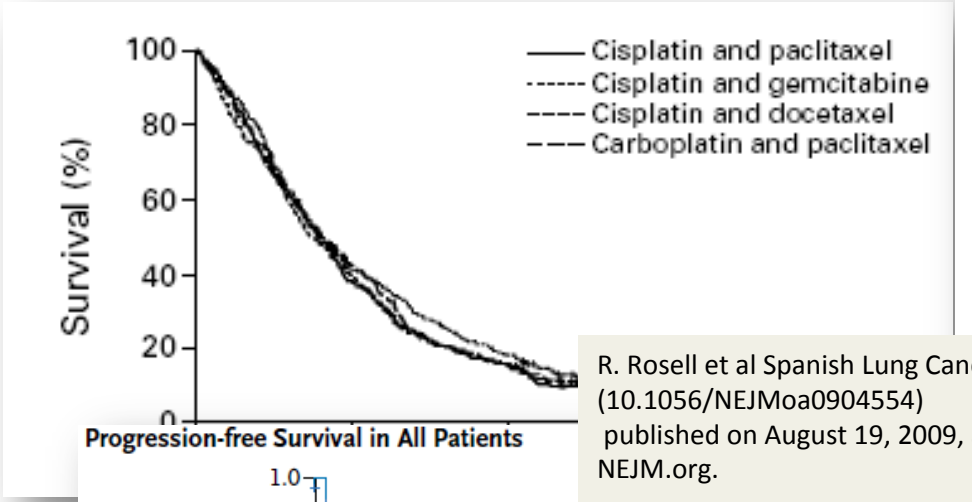
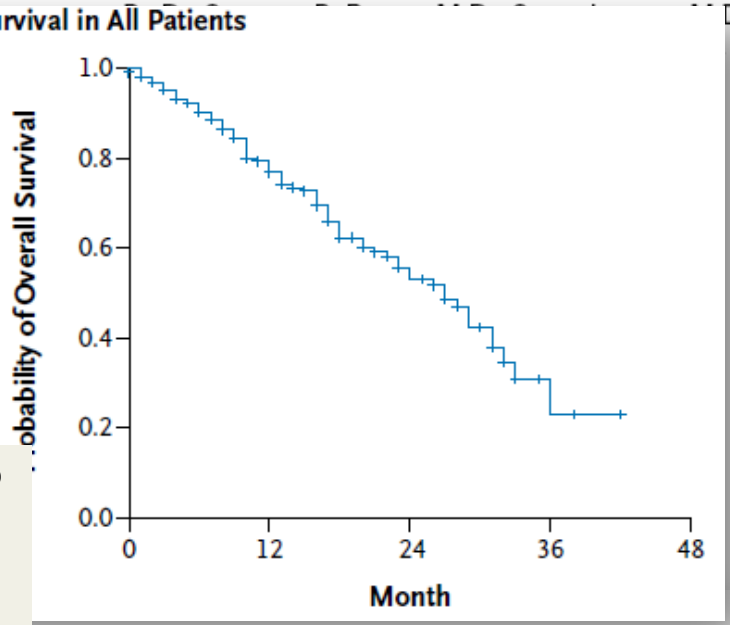
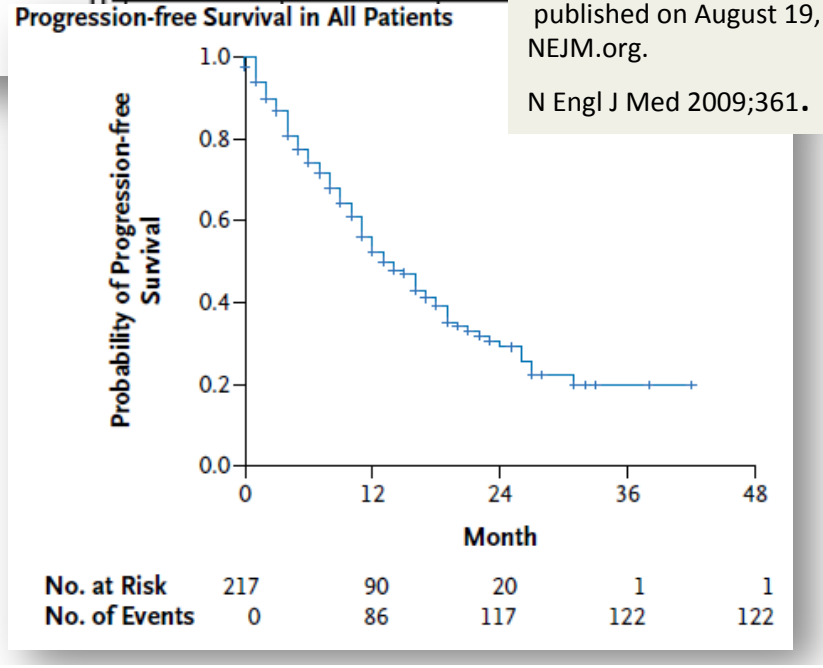
The NEW ENGLAND JOURNAL of MEDICINE

COMPARISON OF FOUR CHEMOTHERAPY REGIMENS FOR ADVANCED NON–SMALL-CELL LUNG CANCER

JOAN H. SCHILLER, M.D.
ALAN SANDLER, M.D.

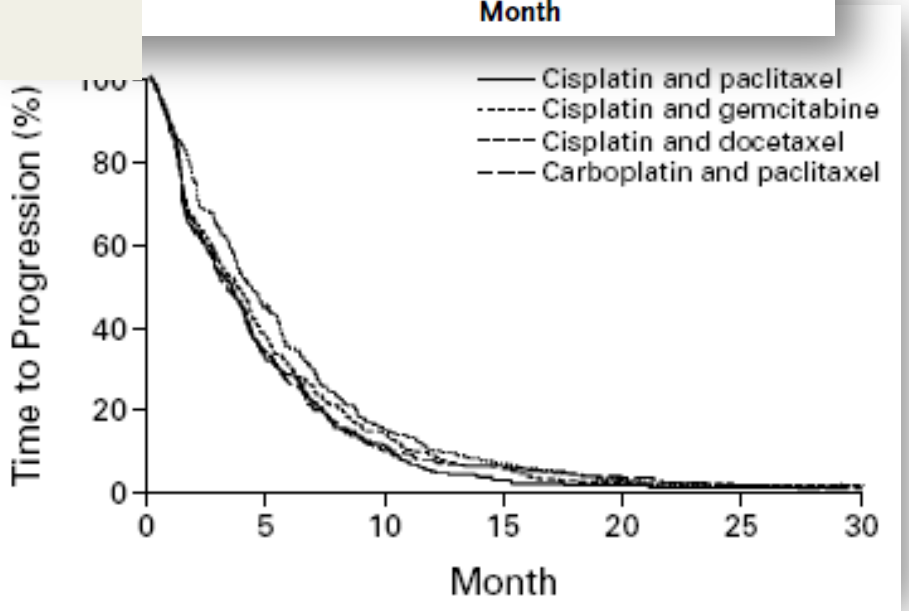






R. Rosell et al Spanish Lung Cancer Group (10.1056/NEJMoa0904554) published on August 19, 2009, at NEJM.org.

N Engl J Med 2009;361.



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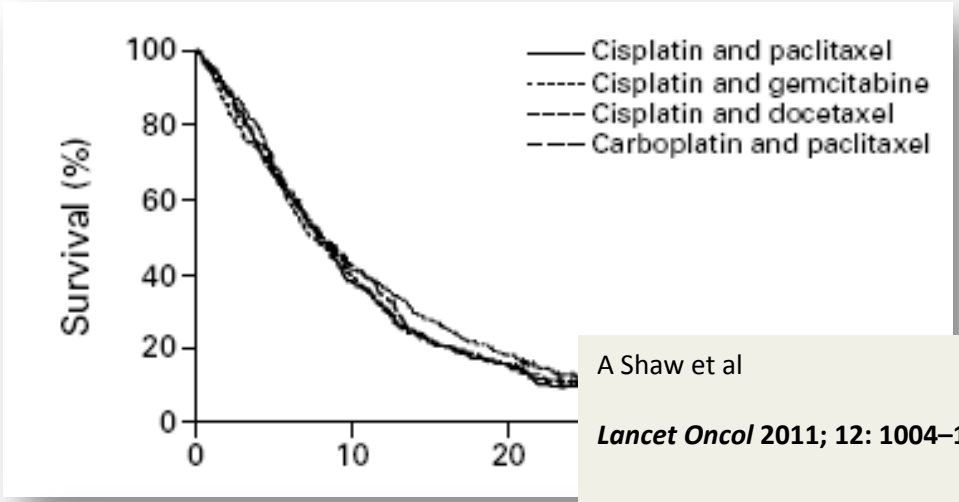
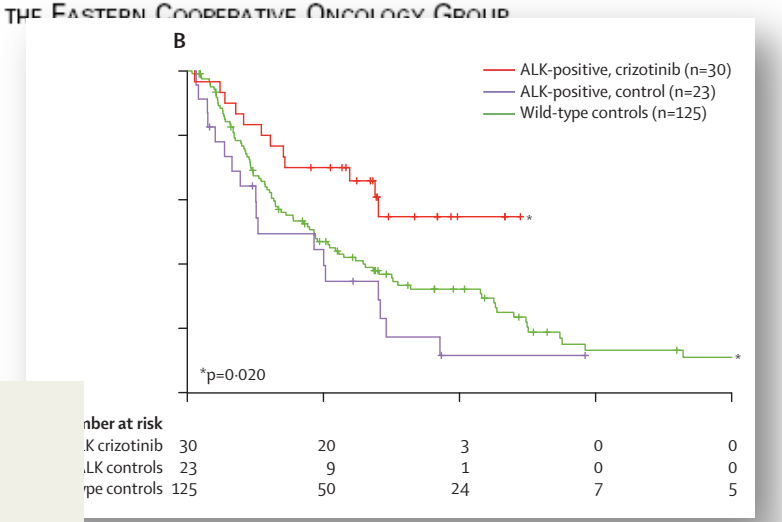
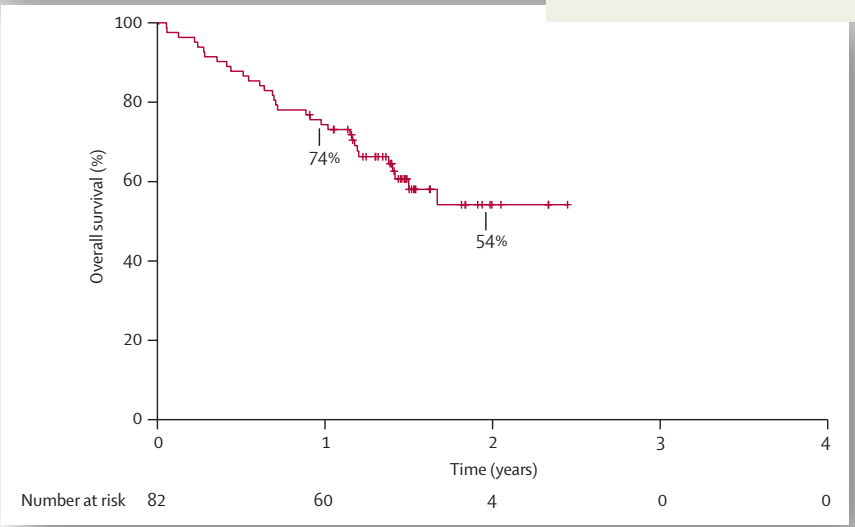
JOAN H. SCHILLER, M.D., DAVID HARRINGTON, PH.D., CHANDRA P. BELANI, M.D., COREY LANGER, M.D., ALAN SANDLER, M.D., JAMES KROOK, M.D., JUNMING ZHU, PH.D., AND DAVID H. JOHNSON, M.D., FOR THE EASTERN COOPERATIVE ONCOLOGY GROUP

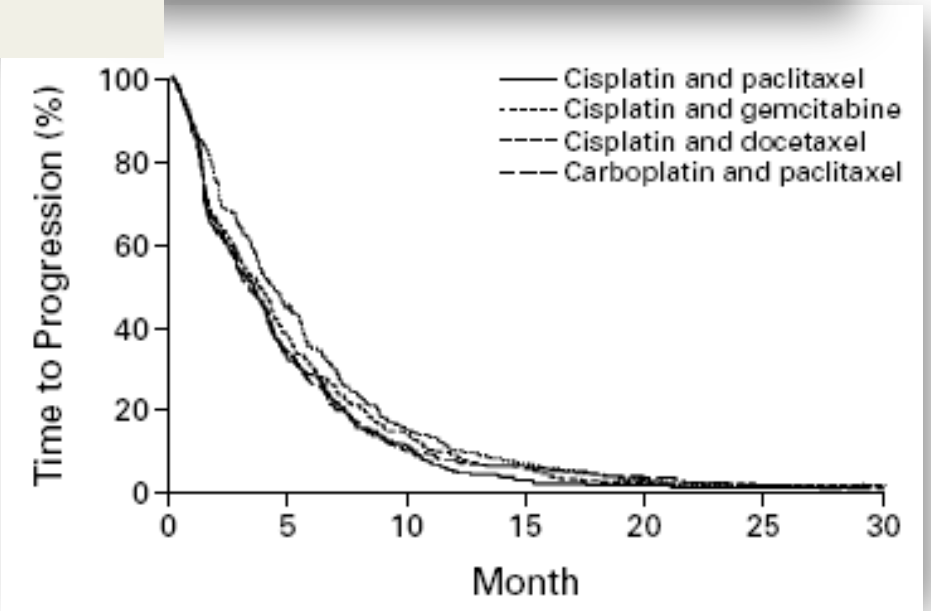


A Shaw et al

***Lancet Oncol* 2011; 12: 1004–12**

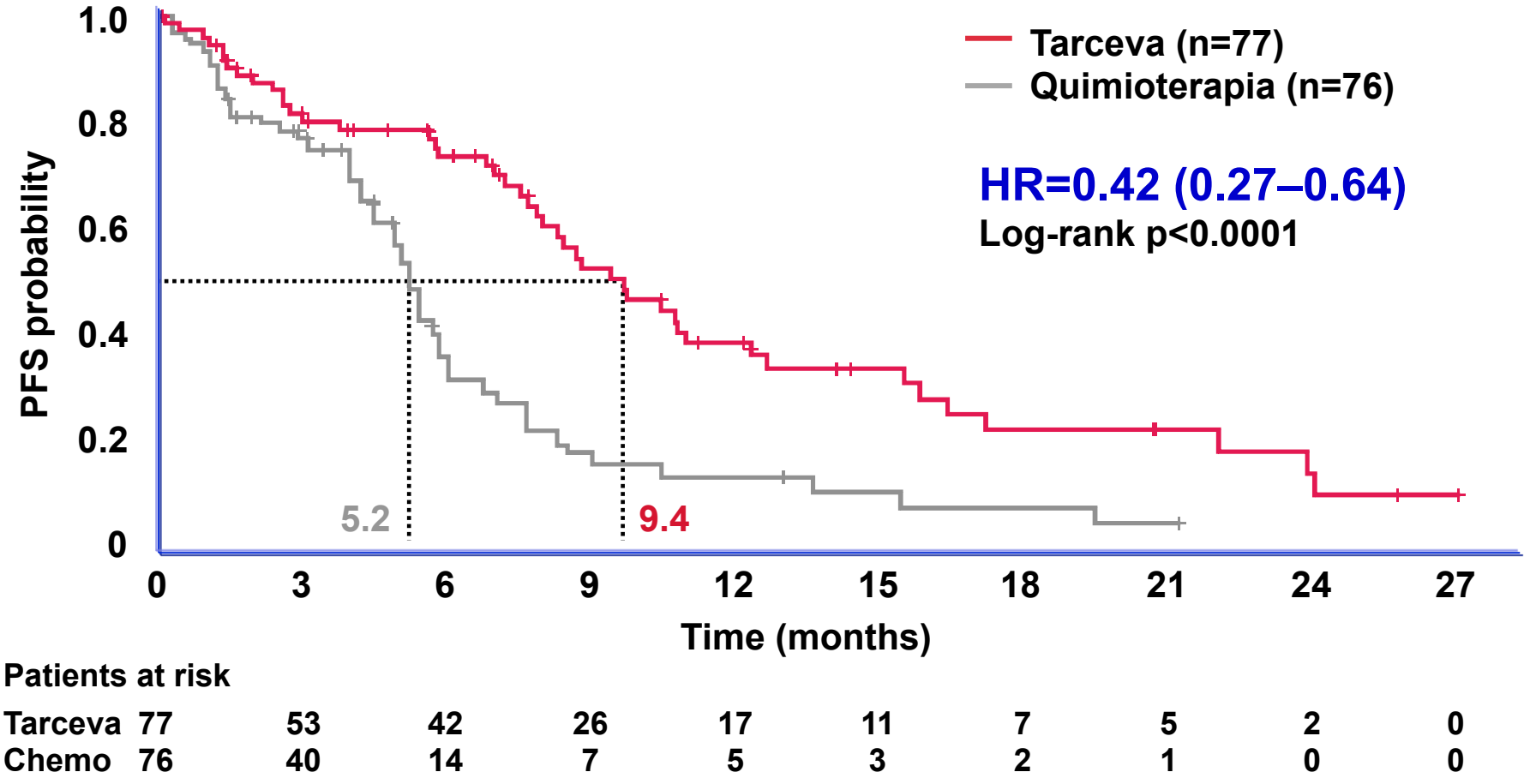






1ª línea EGFR mut: EURTAC

EURTAC : Erlotinib vs Quimioterapia basada en platino



Patients at risk

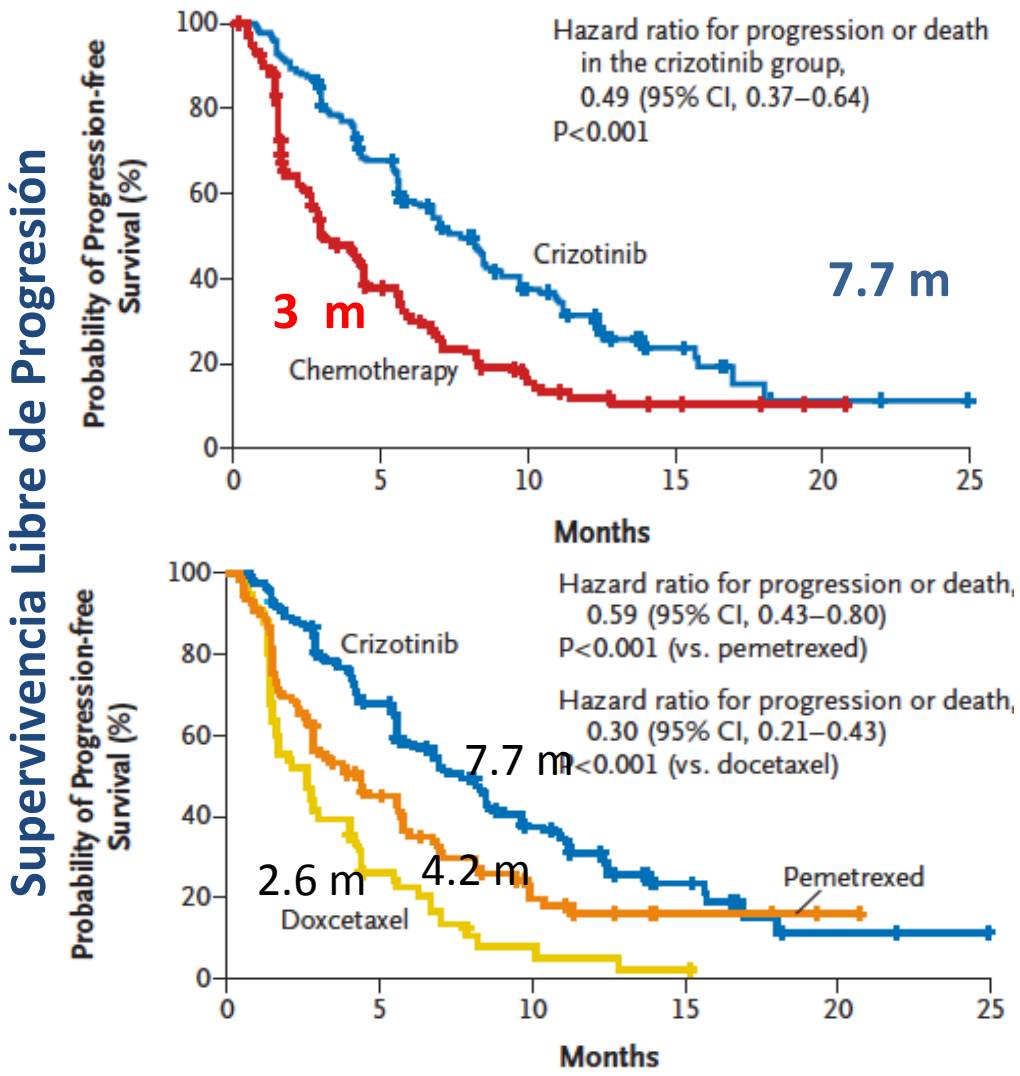
Tarceva	77	53	42	26	17	11	7	5	2	0
Chemo	76	40	14	7	5	3	2	1	0	0

Data cut-off: Gen 2011

Rosell et al Lancet Oncol 2012 Mar;13(3):239-46

2º linea ALK+: Crizotinib vs QT

PROFILE 1007



	Crizotinib (173)	Quimioterapia (174)
RESP. COMPLETA	1 (1%)	0 (0%)
RESP. PARCIAL	112 (65%)	34 (20%)
EN. ESTABLE	32 (18%)	63 (36%)
PROGRESIÓN	11 (6%)	60 (34%)
NO EVALUABLE	17 (10%)	17 (10%)

TRO 65% frente 20%

TCE 94% frente 66%

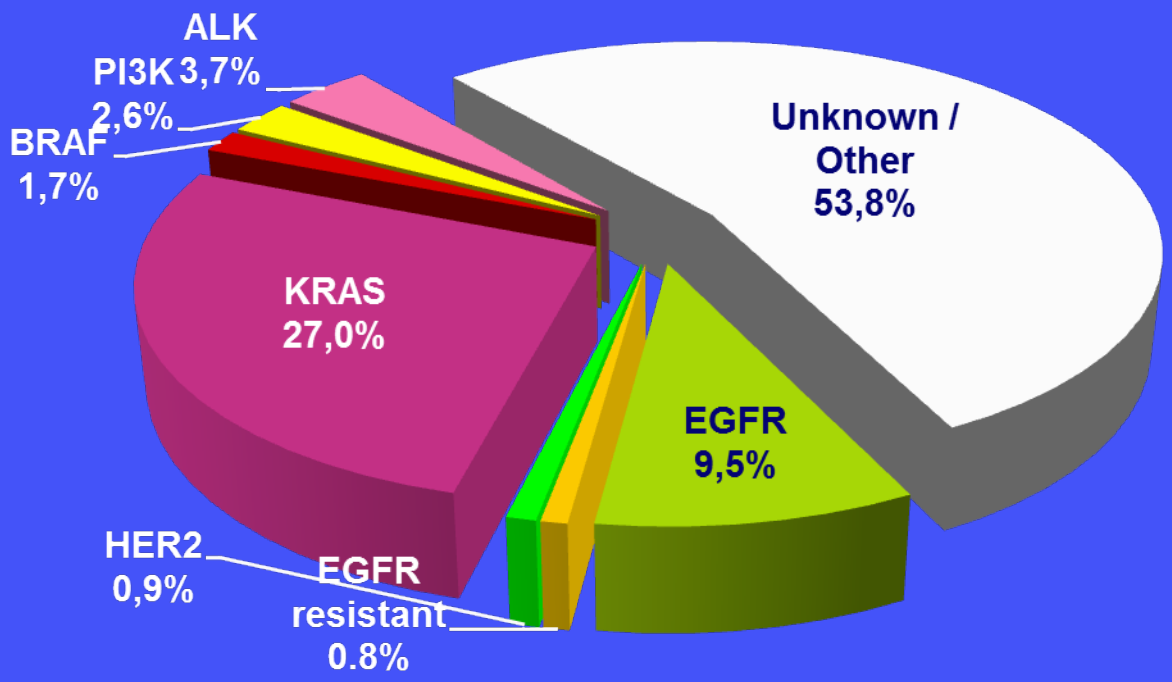
Shaw et al NEJM 2013

Evolution of lung cancer classification over time

M Reck, DF Heigener, T Mok, JC Soria, KF Rabe, 2013

Mutation driven therapy presently benefits only a subgroup of the overall population

BIOMARKERS FRANCE: driver mutations in 10,000 patients with non-squamous NSCLC

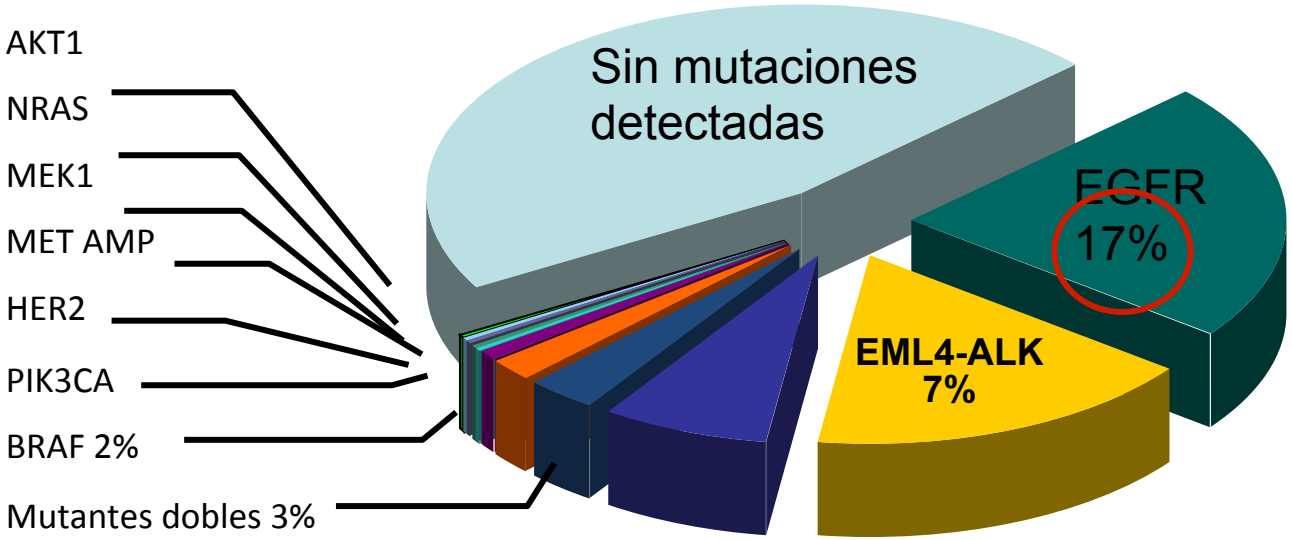


Of the alterations detected, only *EGFR* Mut and *EML4-ALK* can currently be targeted therapeutically

Results expressed in % on available analyses

Barlesi, et al. ASCO 2013

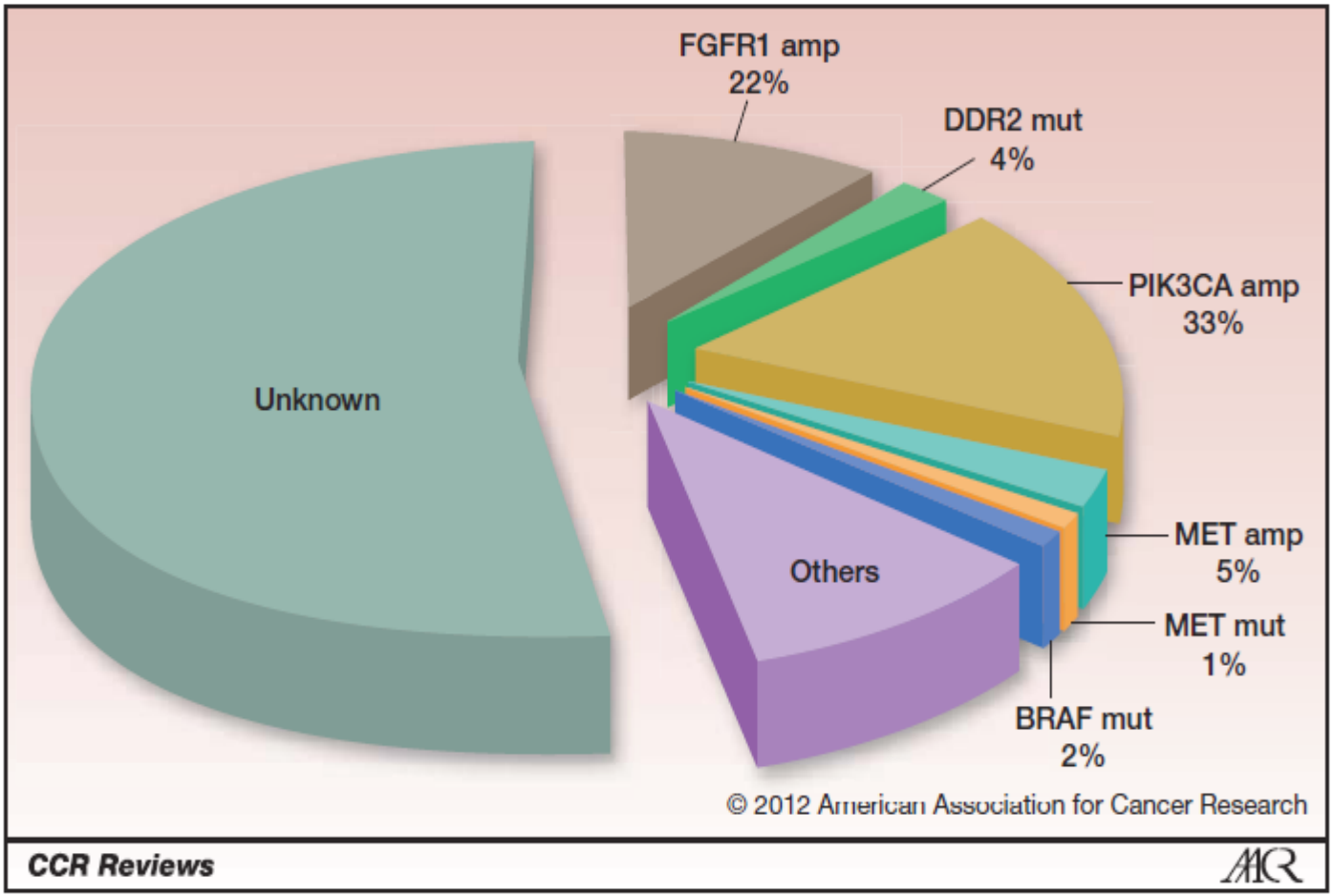
Mutaciones Adenocarcinoma



incidencia de mutaciones "*single driver*"

Lung Cancer Mutation Consortium

Genetic alterations in SCC 2012



Perez-Moreno et al. CCR 2012

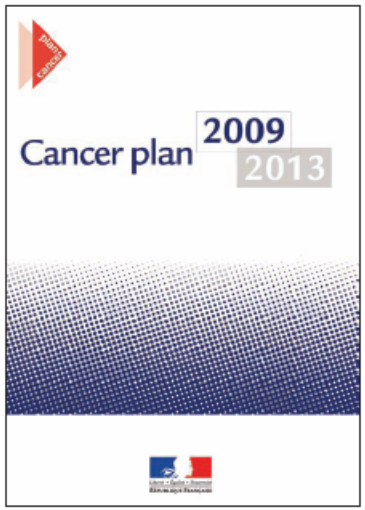
Dianas potencialmente tratables

- Mutaciones EGFR
- Translocaciones ALK
- Translocación ROS1

- Mutación EGFR2/HER2
- Mutación BRAF

- Kras
- MEK
- PI3K
- MET
- DDR2
- FGFR-2
- PD1/PDL1

National comitment to nation-wide provision of molecular tests



Measure 21.

Guarantee equal access to innovative and existing treatments.

21.2 Develop cancer molecular genetics hospital platforms and expand access to molecular testing.

INSTITUT NATIONAL DU CANCER

Courtesy JC Soria

Ensuring equity of access to innovation:
France organisation of molecular centres for personalized medicine

Provides nationwide molecular diagnostic tests

- **Objectives**
  - Perform molecular testing for all patients;
  - Whatever the healthcare institution status (public hospitals, private hospitals…);
  - Perform high quality tests;
  - leukemia, solid tumours

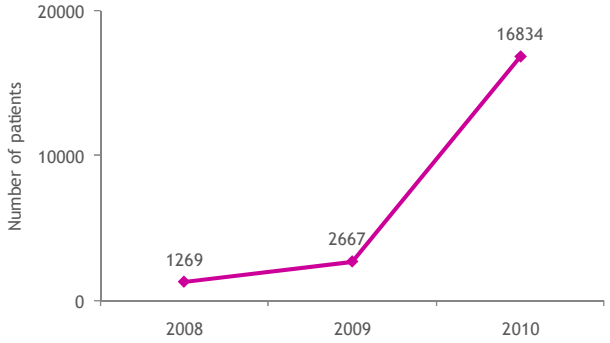
- **28 regional centres**
  - Partnerships between several laboratories located in University hospitals and cancer centres
  - Regional organization
  - Cooperation between pathologists and biologists

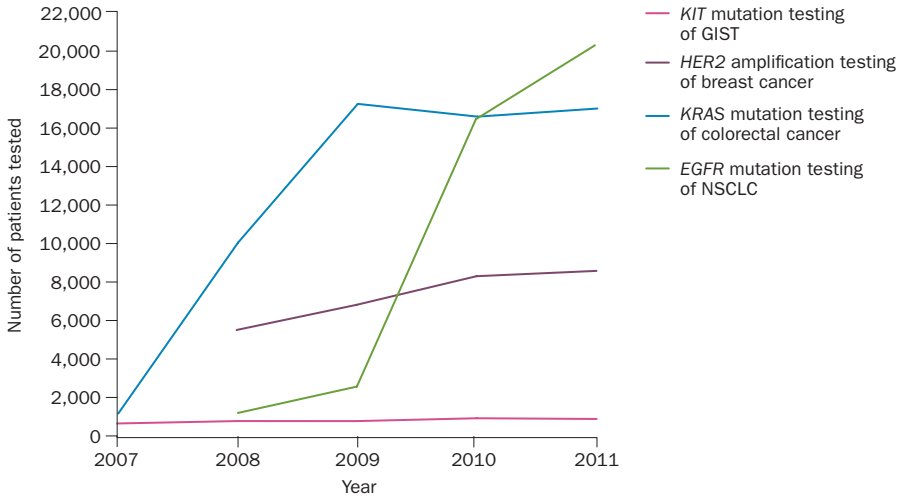
Courtesy JC Soria

INSTITUT NATIONAL DU CANCER

Evolución test moleculares Francia

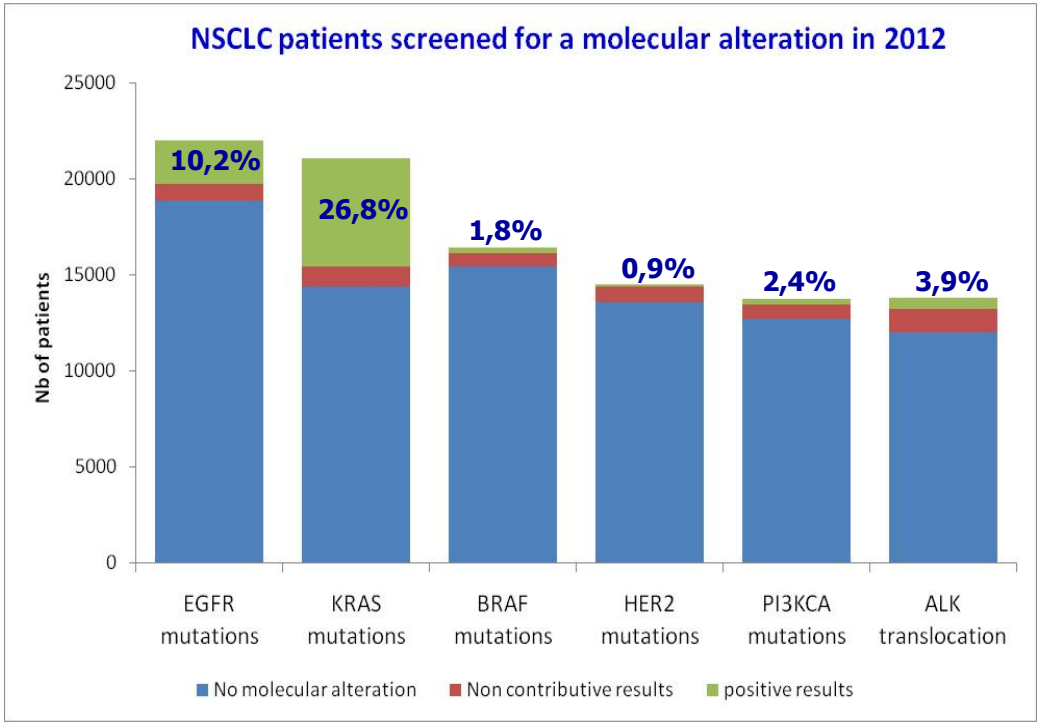
Figure 18 Evolution of the number of tests for *EGFR* mutations in lung cancer





Nowak, F. et al. Nat. Rev. Clin. Oncol. advance online publication 10 July 2012; doi:10.1038/nrclinonc.2012.42

2012 data



- *ALK* translocation : 13801 patients screened
  - IHC : 11539 tests
  - FISH : 8658 tests
    => Ongoing project in order to determine the strategy of analysis (IHC, FISH, RT-PCR)

- Median turn around time : 8,5 days for EGFR screening (upon receipt of the tumour block by the *ad hoc* centre)

INSTITUT NATIONAL DU CANCER

Courtesy JC Soria

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Limitations for personalized and targeted therapies

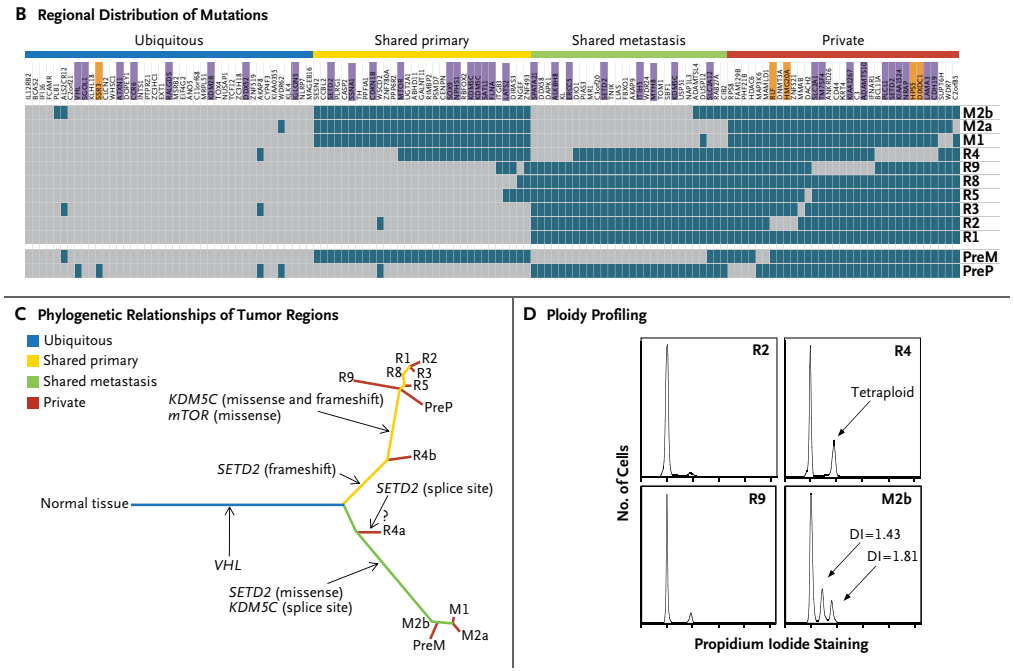
- Current anti-cancer treatments are dominated by **targeting genetic defects** such as oncogenes (EGFR, ALK, ROS) or non-oncogenic genetic defects (i.e. PARP inhibitors for BRCA1 deficiency).

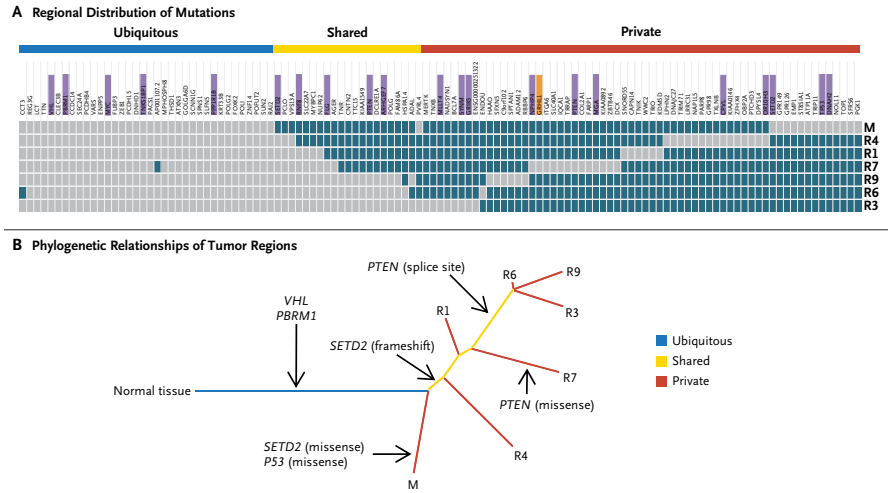
- Targeting genetic defects in a **personalized** strategy is limited by the high degree of **intra-tumor heterogeneity**, adaptation of genetic networks **resistance** and high **somatic mutation** rates in cancer.

- Some patients do not respond
- Response variability
- All patients progress

Representatividad vs Heterogeneidad

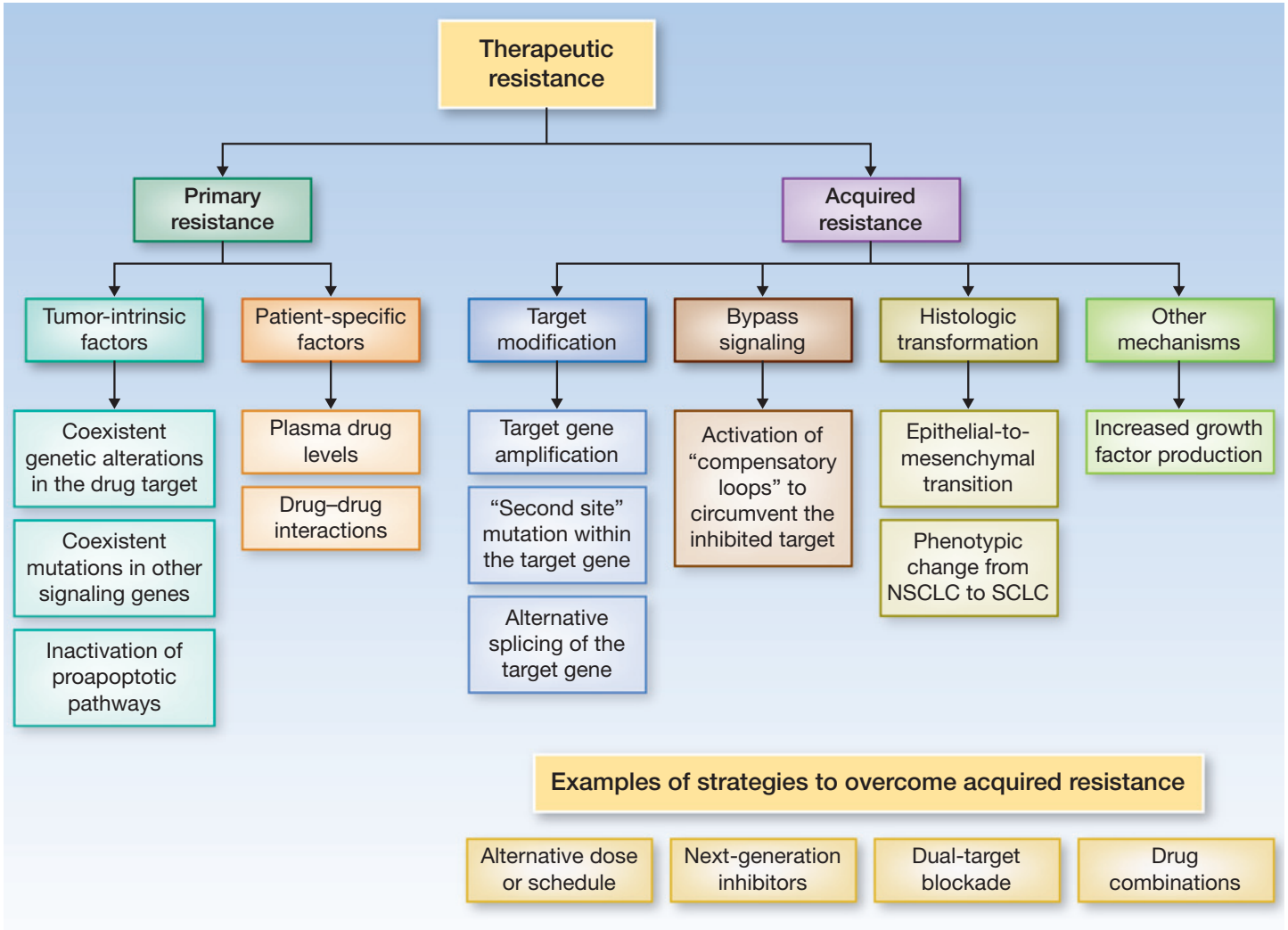
Gerlinger N Engl J Med 2012;366:883-92.





Mecanismos de resistencia a TKIs

Lovly Clin Cancer Res; 20 (9); 2249–56. !2014 AACR.



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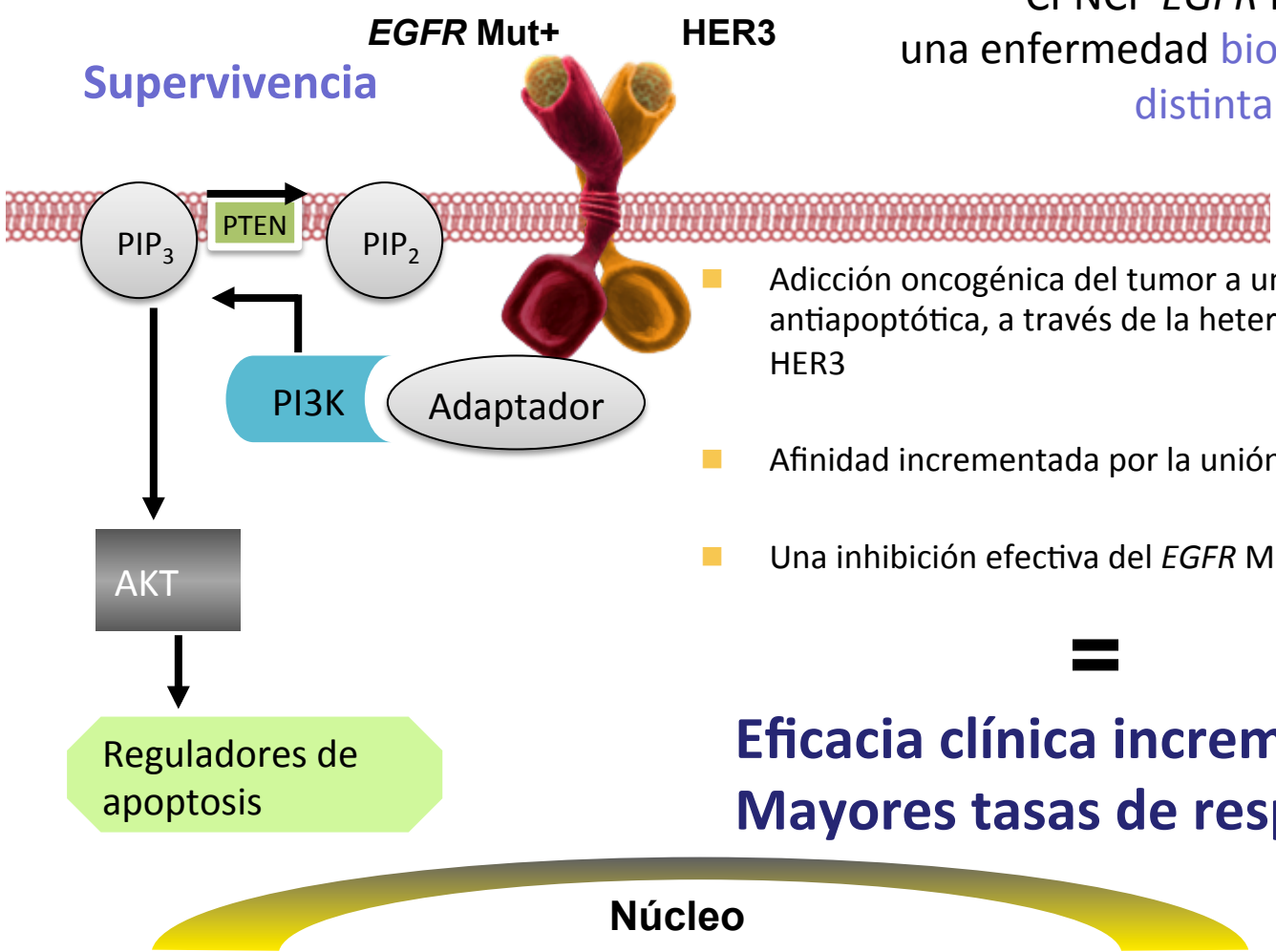
EGFR



CPNCP *EGFR* Mut+:
una enfermedad biológicamente distinta

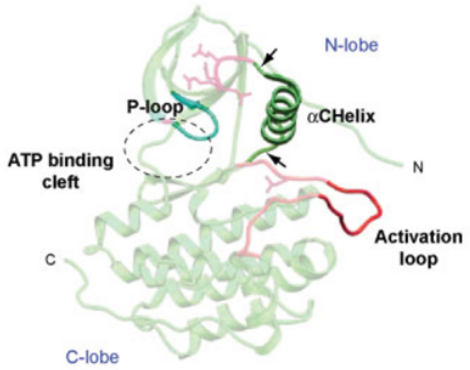
- Adicción oncogénica del tumor a una vía de señalización antiapoptótica, a través de la heterodimerización con HER3
- Afinidad incrementada por la unión de EGFR TKIs.
- Una inhibición efectiva del *EGFR* Mut+.

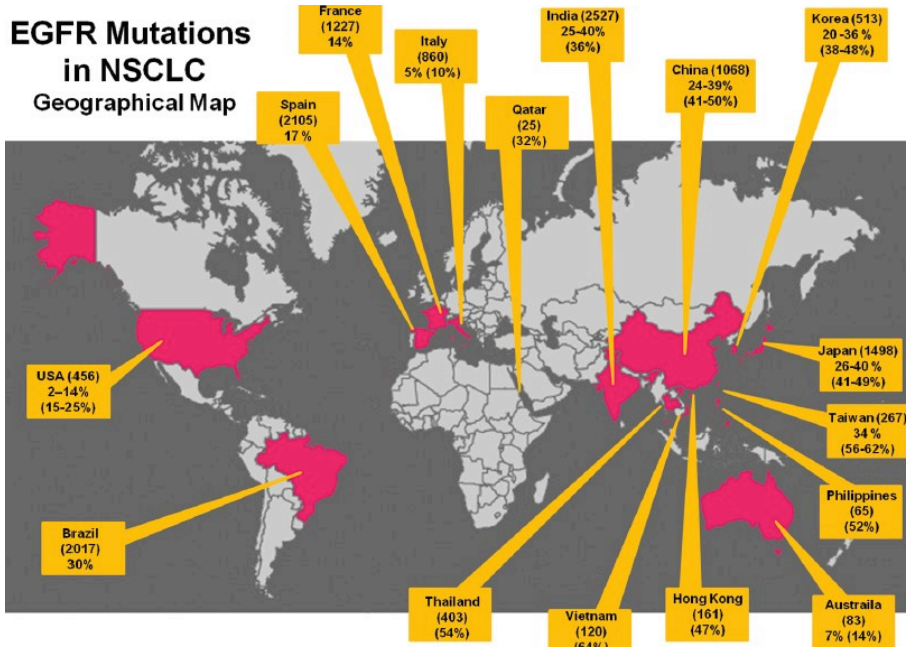
=

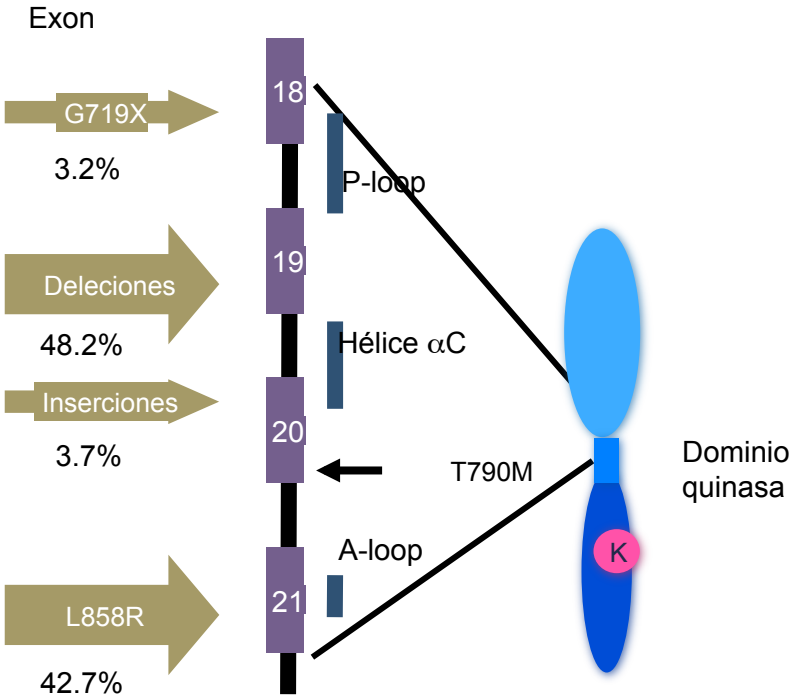
Eficacia clínica incrementada
Mayores tasas de respuesta

Carey, et al. Cancer Res 2006; Karaman, et al. Nat Biotechnol 2008 ; Yun, et al. Cancer Cell 2007; Eck, et al. Biochim Biophys Acta 2010

Mutaciones de EGFR



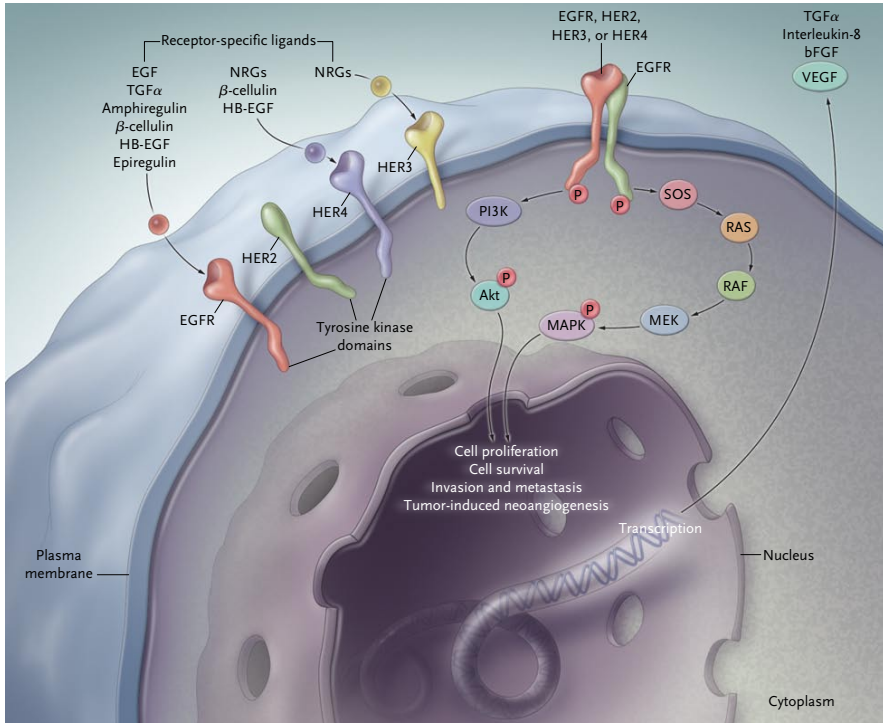


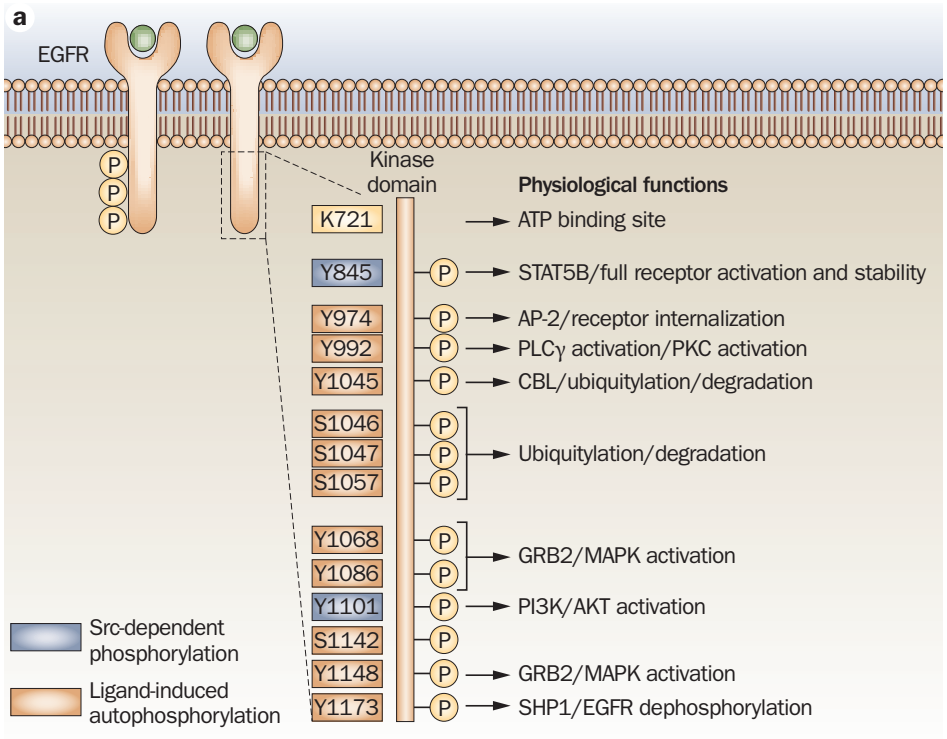


	Total, %	*Non-east Asian, %*	*East Asian, %*
All subgroups	19	10	30
Smokers	11	4	17
Nonsmokers	54	35	60
Adenocarcinoma	42	16	49
Non-adenocarcinoma	3	1	4
Male	16	1	22
Female	46	20	58

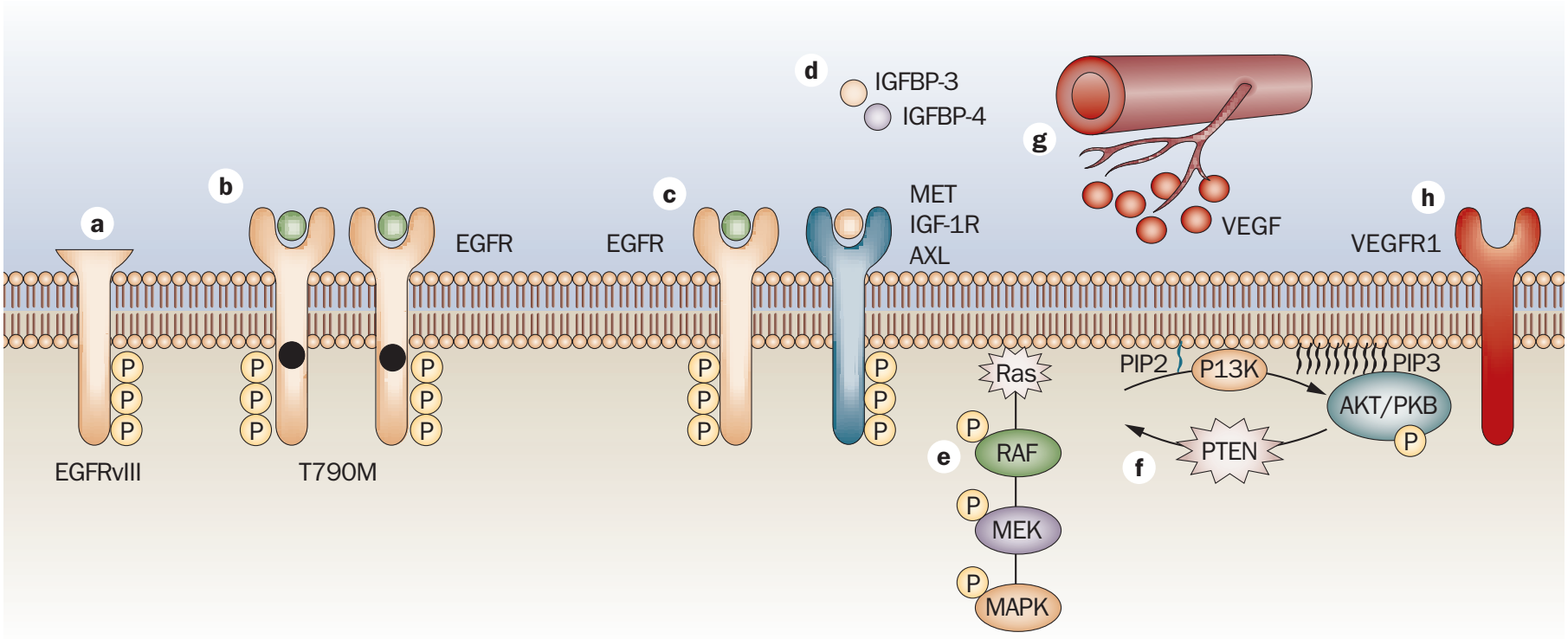
Mitsudomi, et al. Int J Clin Oncol 2006; Riely, et al. Clin Cancer Res 2006

Complejidad fisiológica





Mecanismos potenciales resistencia



Resistencia primaria/adquirida

Resistencia primaria

- Mutación Kras
- Mutación NF1 rasGAP
- Pérdida PTEN
- Mutación concomitante EGFR (T790M)
- Translocación concomitante EML4-ALK
- Mutación dominio quinasa HER2

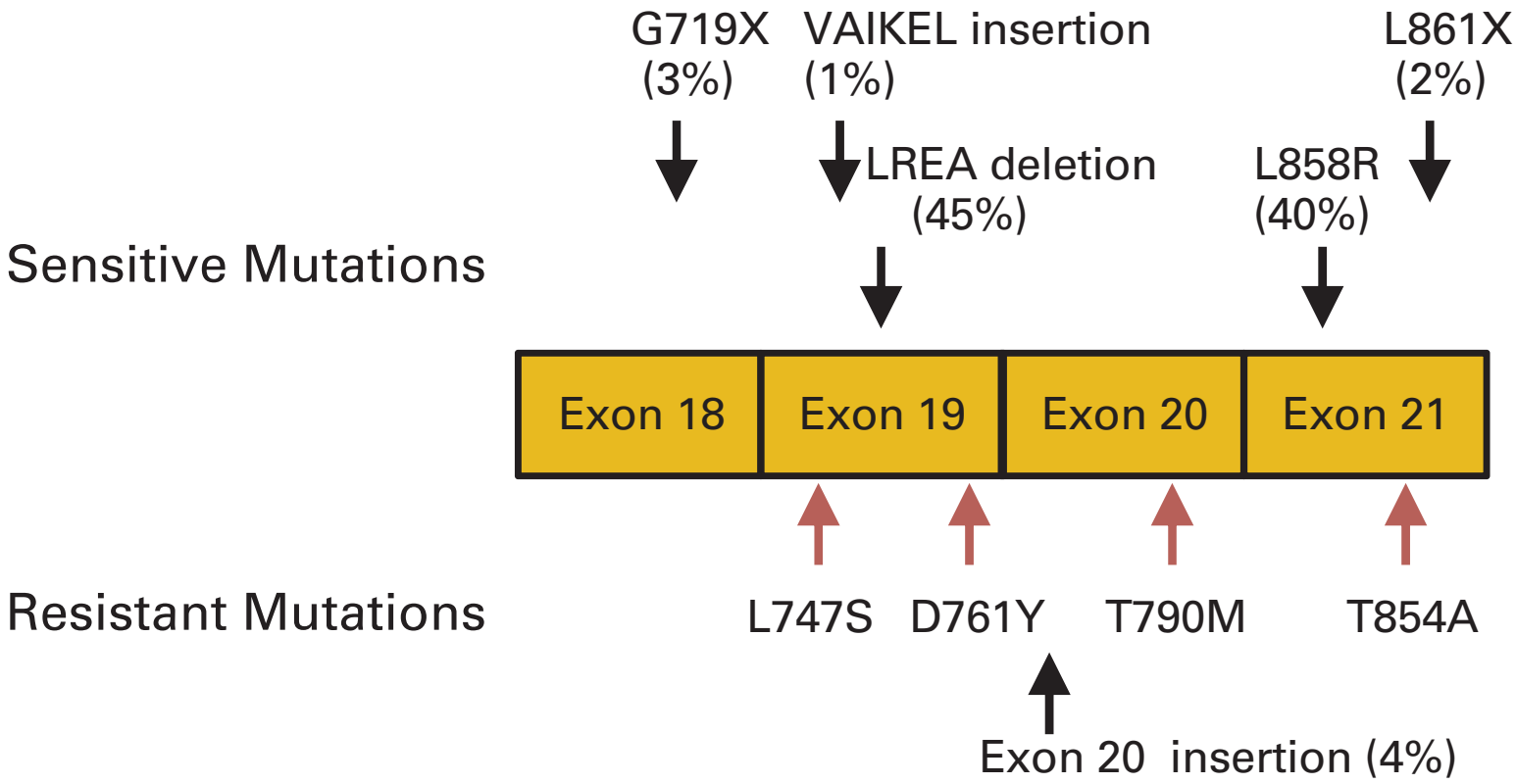
Resistencia adquirida

- Mutación secundaria EGFR (T790M)
- Amplificacion c-Met
- Mutaciones vía PI3KC
- Transformación fenotípica
- Mutación BRAF
- IGF1R-mTOR-HSP90
- Sobrexpresión VEGF

Clinical patterns resistance

- **Secondary EGFR mutations: T790M**
- **MET amplification**
- **HGF high levels**
- Downstream effectors: PTEN loss, PI3K mut.
- Small cell lung cancer (SCLC) transformation.
- Epithelial to Mesenchimal Transition (EMT).
- DRG: BRCA1 mRNA levels.
- FAS and NFKB signalling.
- VEGF/VEGFR.
- IGFR1, IGFBP.

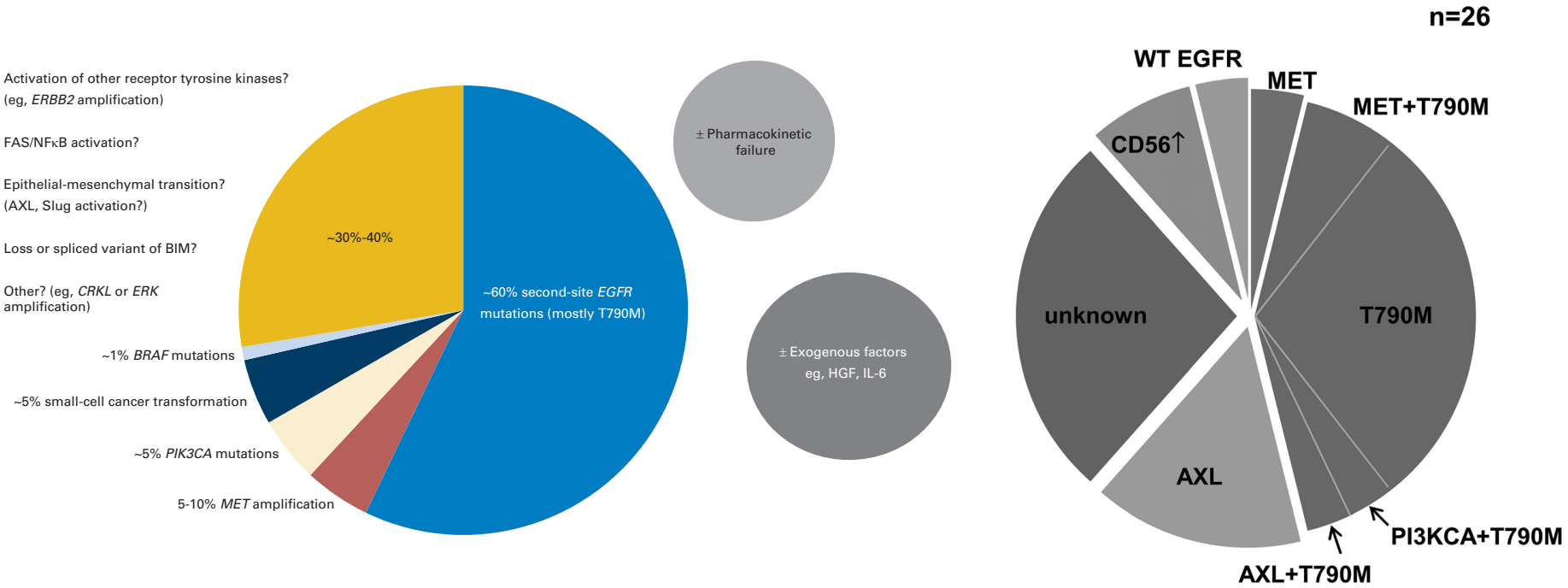
Not all mutations are created equal!!



Frecuencia de los mecanismos de resistencia

Ohashi J Clin Oncol 31:1070-1080. © 2013

Ji et al. BMC Cancer 2013, 13:606



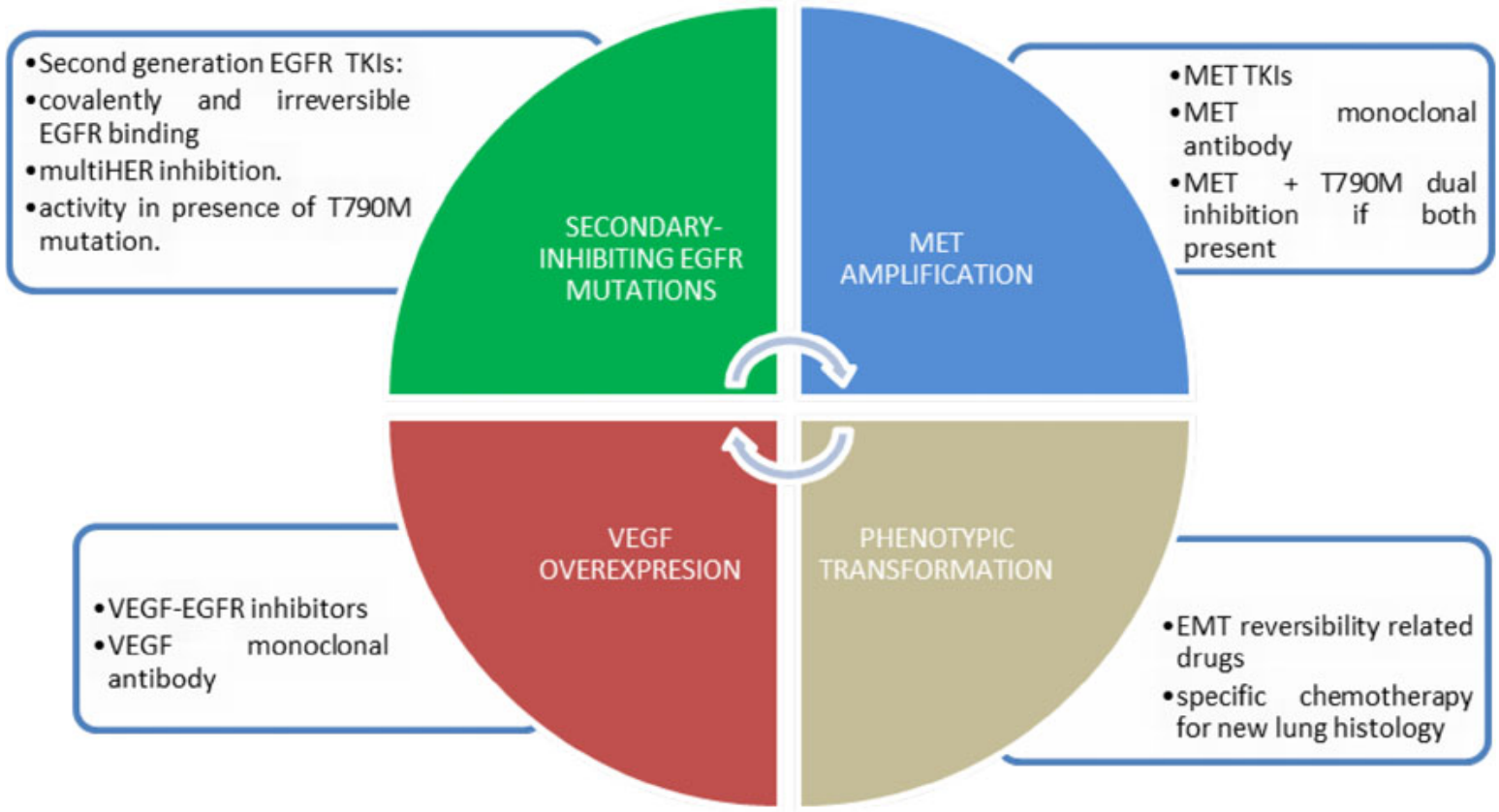
Progresión neoplásica durante anti-EGFR

Table 1. Criteria for Acquired Resistance to EGFR TKIs in Lung Cancer

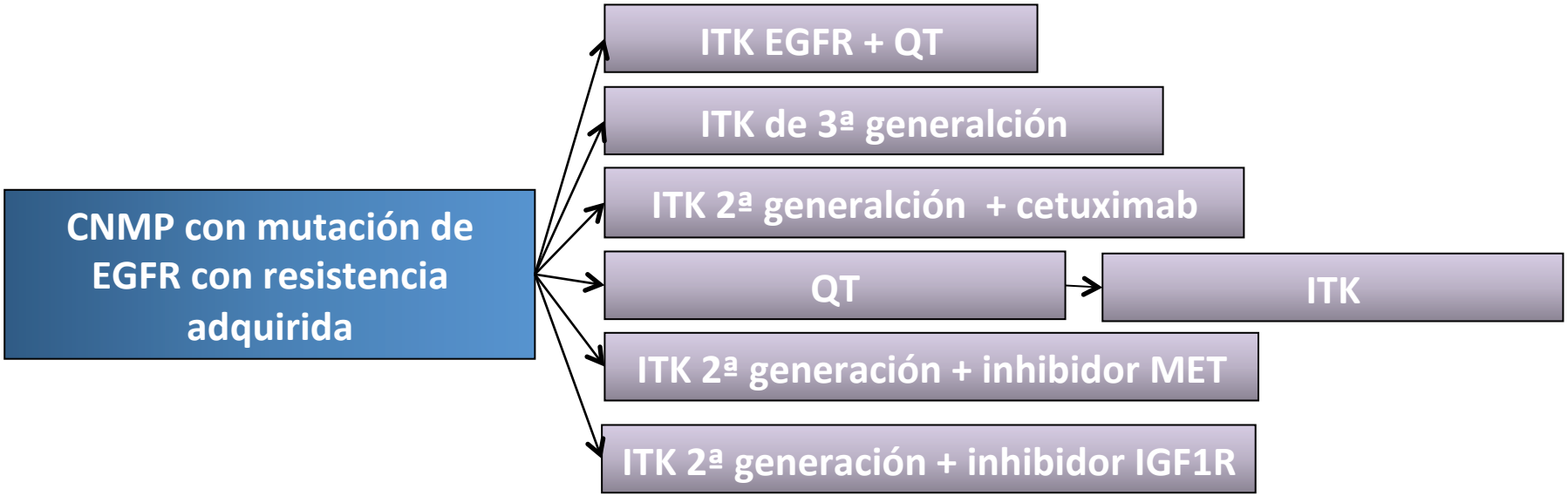
1. Previously received treatment with a single-agent EGFR TKI (eg, gefitinib or erlotinib)
2. Either of the following:
   - A. A tumor that harbors an *EGFR* mutation known to be associated with drug sensitivity (ie, G719X, exon 19 deletion, L858R, L861Q)
   - B. Objective clinical benefit from treatment with an EGFR TKI as defined by either:
     - i. Documented partial or complete response (RECIST or WHO), or
     - ii. Significant and durable (≥ 6 months) clinical benefit (stable disease as defined by RECIST or WHO) after initiation of gefitinib or erlotinib
3. Systemic progression of disease (RECIST or WHO) while on continuous treatment with gefitinib or erlotinib within the last 30 days
4. No intervening systemic therapy between cessation of gefitinib or erlotinib and initiation of new therapy

- Respuesta disociada
- Patrón de progresión
- Evolutividad de la progresión
- Opciones para tratamientos locales?

Circunventing resistance mechanisms in EGFR mut.

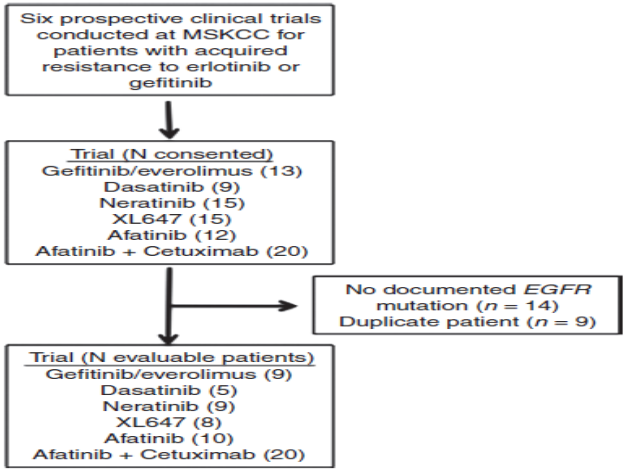


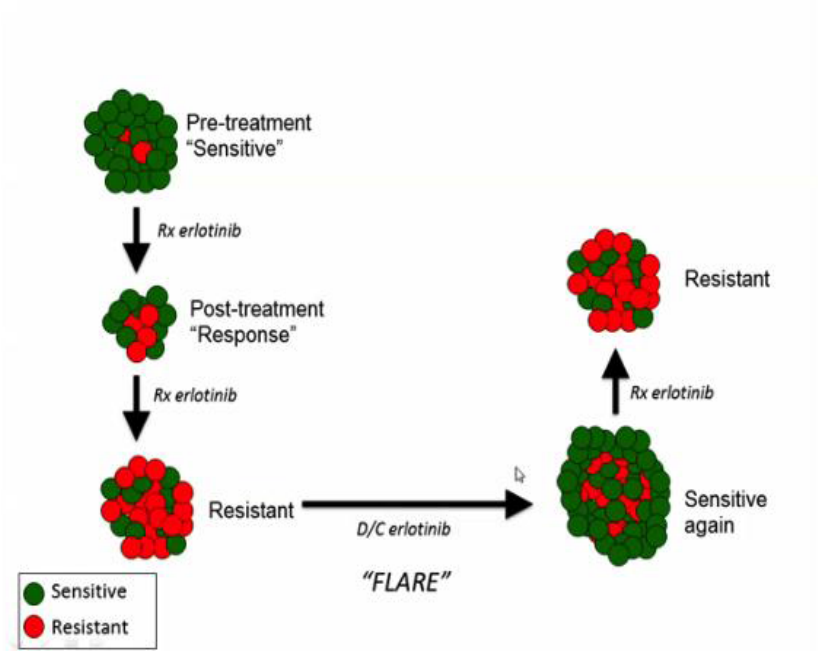
Posibles alternativas terapéuticas

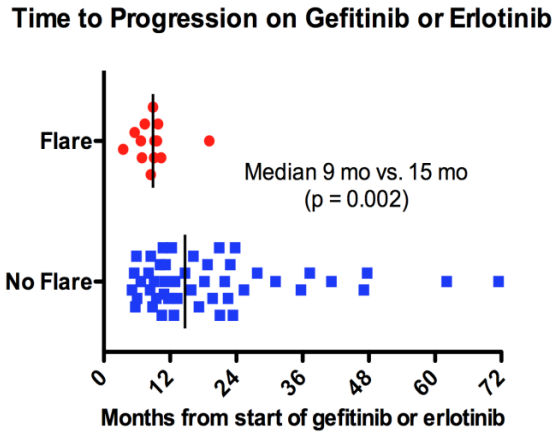


Pao W et al. Nat Rev Cancer 2010

El dilema de mantener anti-EGFR tras progresion





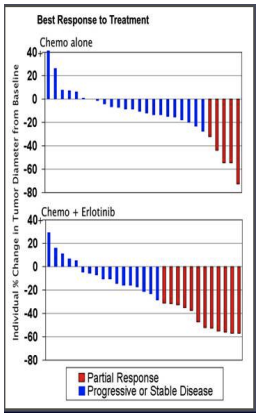


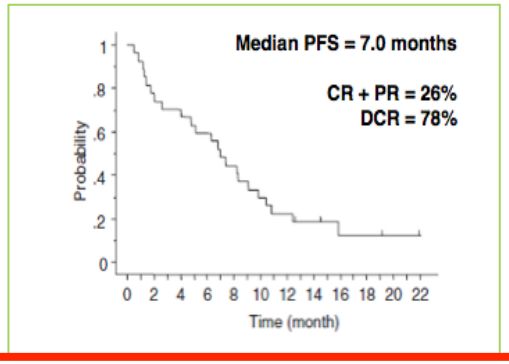
- 14/61 pacientes (23%,) con flare
- Medina de tiempo: 8 días (range 3-21)
- Características asociadas a flare:
  - TP corto con ITK (9 vs 15 mo, p=0.002)
  - Enfermedad pleural (p=0.02)
  - Enfermedad en SNC (p=0.01)
- Flare no asociado con mutación T790M o QT previa

Chaft JE, et al. Clin Cancer Res. 2011

Experiencia clínica de mantenimiento anti-EGFR tras progresión

- Estudio con 78 pacientes:
  - 44 QT y 34 QT + Erlotinib en pacientes con resistencia adquirida a ITK
    - TR 18% vs 41%
    - no diferencias en SLP (4,2 m vs. 4,4 m) ni SG
- Fase II: 27 pacientes con mutación EGFR.
  - A la progresión con erlotinib o gefitinib se añade Pemetrexed.



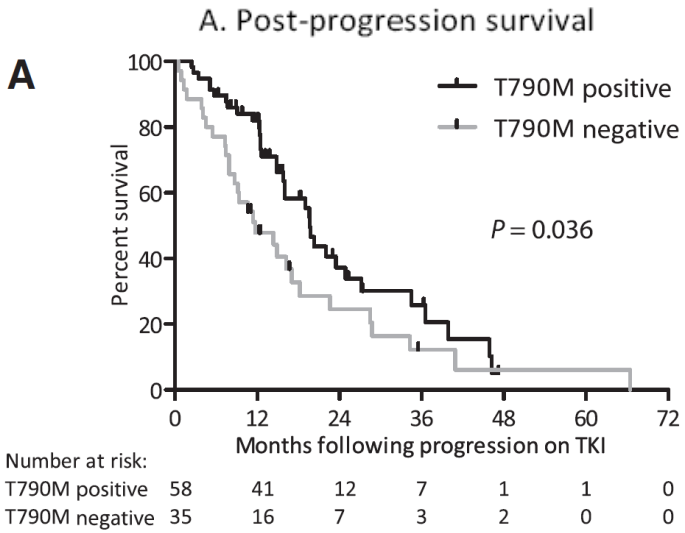


- Fase III IMPRESS: Cisplatino-Pemetrexed +/- Gefitinib tras progresión a gefitinib en pacientes con mutación EGFR (NCT01544179)
- Fase II: 120 pacientes con mutaciones EGFR y PE a TKI: Platino-Pemetrexed +/-Erlotinib (NCT01928160)

Goldberg SB et al. The Oncologist 2013
Yoshimura N et al. J Thorac Oncol 2013
Clinicaltrials.gov

T790M

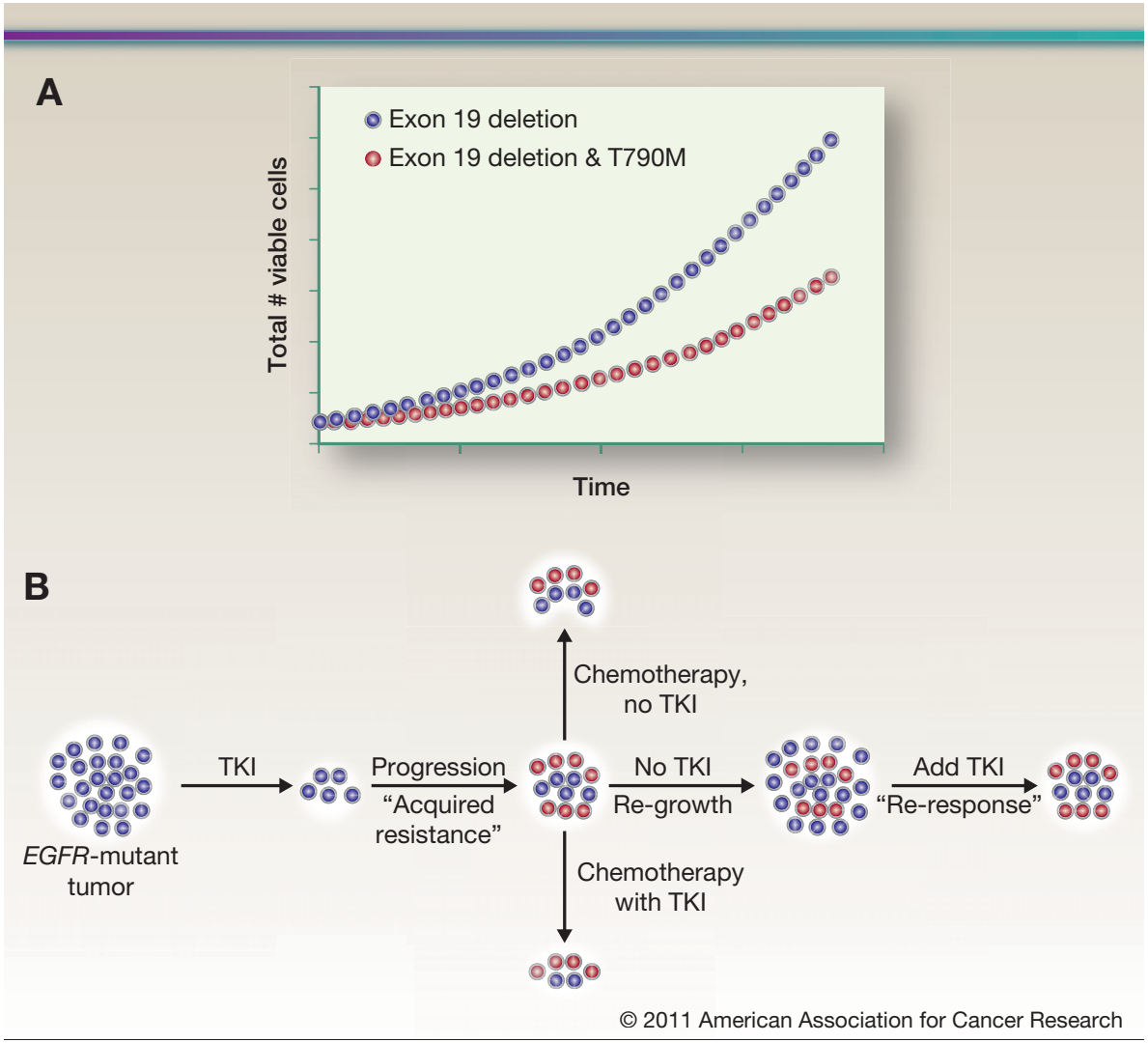
- The most common mechanism of resistance to EGFR TKIs (50-68%)
- Display surprisingly slow rates of growth (Chmielecki J Sci Transl Med 2011).
- May have a better prognosis than non-T790M mechanisms.



Oxnard et al CCR 2011

- The irreversible EGFR inhibitors CL387,785, EKB-569, PF299804, BIBW2992, and HKI-272 have all been shown to inhibit EGFR T790M and block the growth of NSCLC cell lines harboring T790M mutations.

Escenarios teóricos e influencia T790M



Trying to overcome T790M

HKI-272 (EGFR + Her2)

- RR **2%** in TKI-resistant patients.
- Intriguing responses in G719X patients. (Sequist, JCO 2010)

XL-647 (EGFR, Her2, VEGF)

- RR **3%** in TKI-resistant patients. (Pietanza, JTO 2011)

BIBW-2992 (EGFR + Her2)

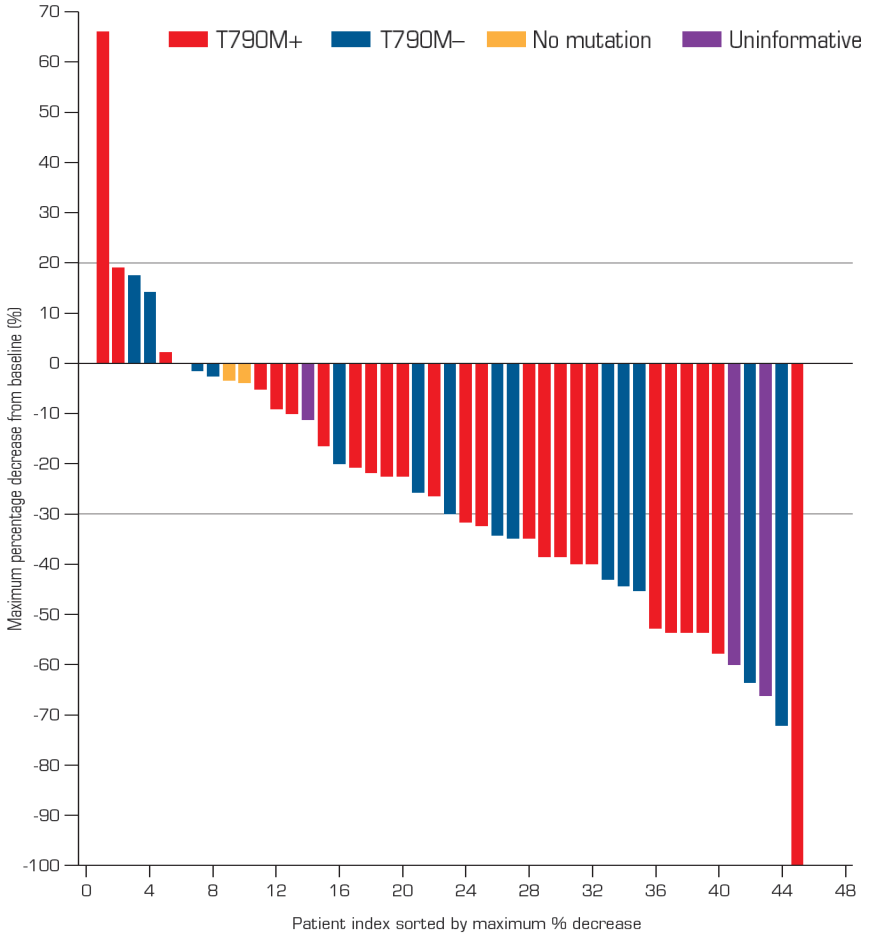
- RR **7%** in TKI-resistant patients, 2mo PFS advantage. (Miller, ESMO'10)
- RR 40% in Ph1 combining afatinib and cetuximab. (Janjigian, ASCO 2011)

PF-299804 (EGFR + Her2)

- RR **7%** in TKI-resistant patients. (Janne, ASCO '09)

Afatinib + Cetuximab

- NSCLC patients with clinically defined AR (Jackman JCO 2010) received oral afatinib 40 mg daily with escalating dose cohorts of biweekly cetuximab at 250 and 500 mg/m2.
- 47 of 80 patients have been enrolled and received the predefined maximum dose (RP2D):
  - afatinib 40 mg +
  - cetuximab 500 mg/m2)
- Confirmed PRs were observed in 18/45 evaluable patients (40%), including 9/26 PRs in patients with documented T790M mutations.

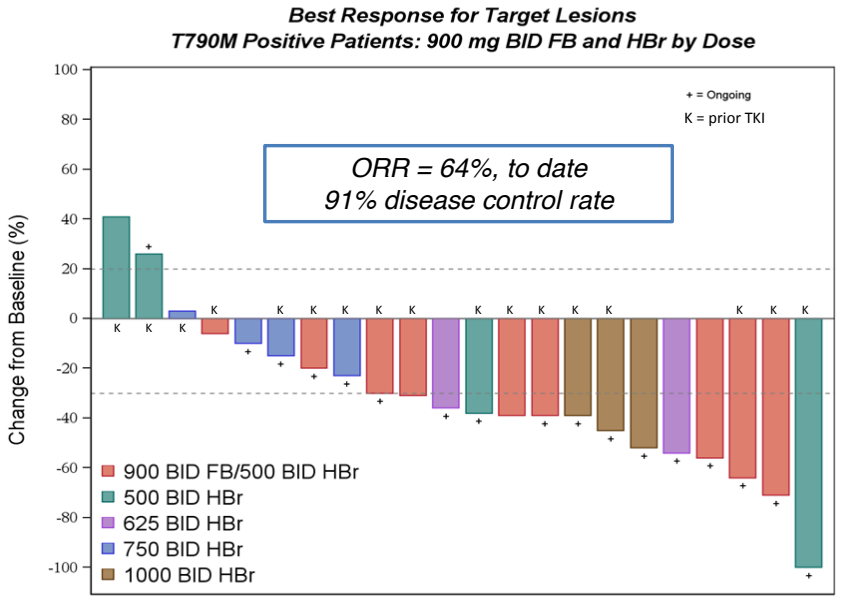


Resultados recientes

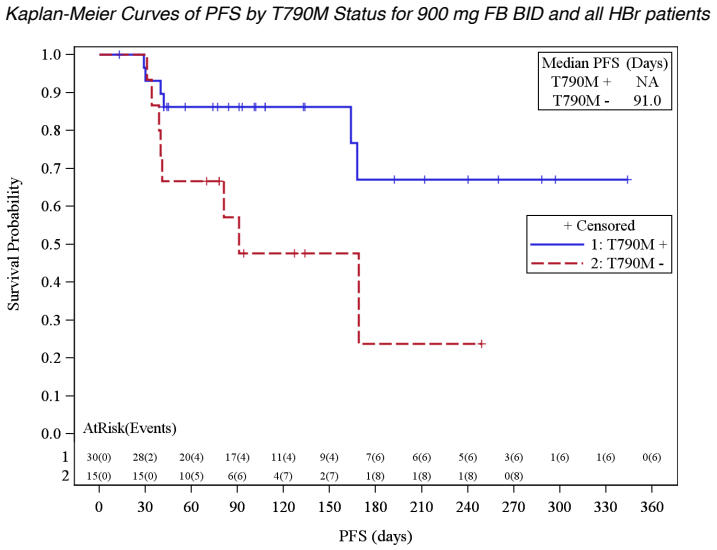
- Fase I AZD9291
- Fase I CO1686
- Fase II Ganetespib

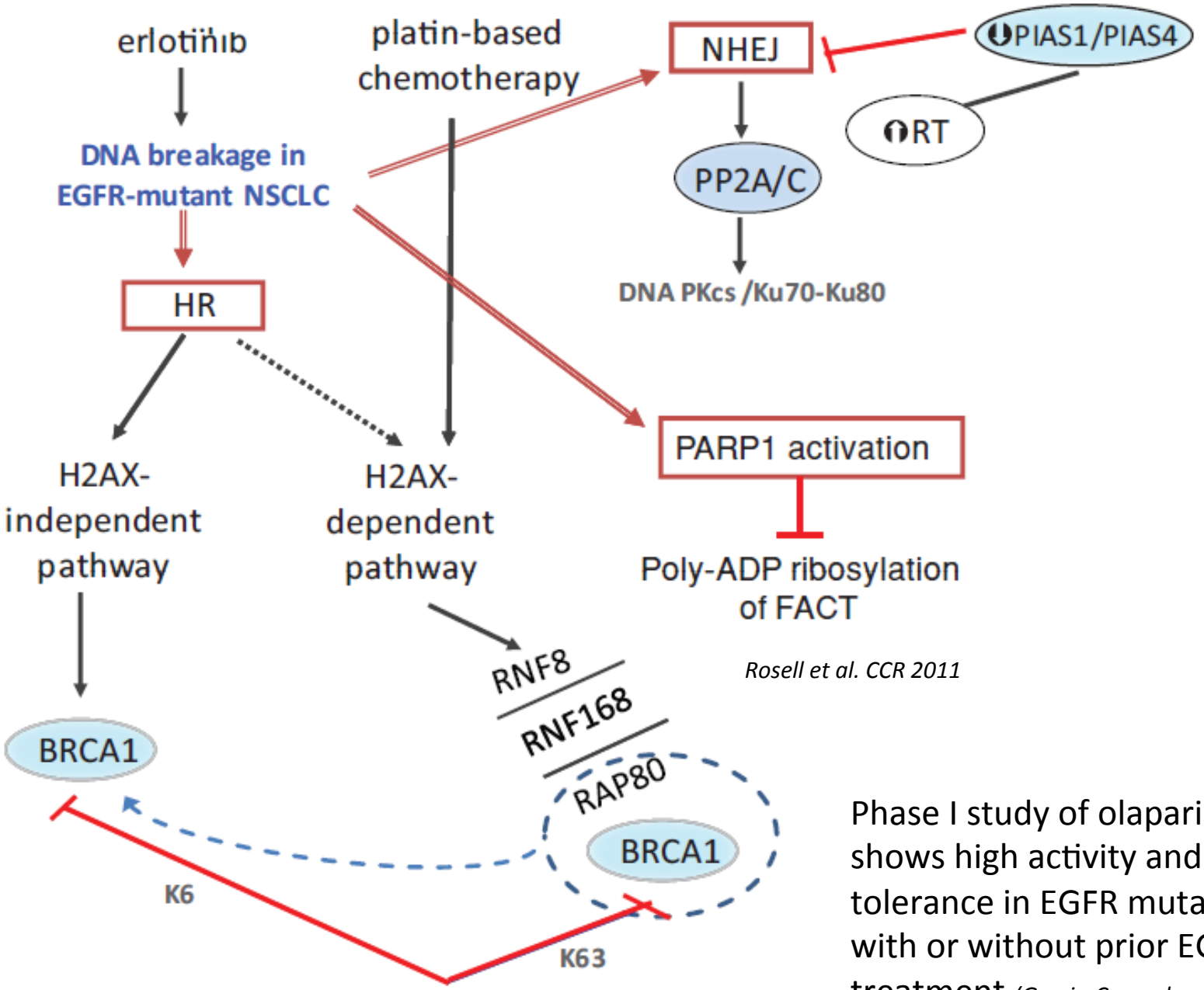
CO1686

Efficacy clear across dose levels in 22 centrally-confirmed T790M+ patients



Durable benefit: median PFS exceeds 6mo in T790M+ patients

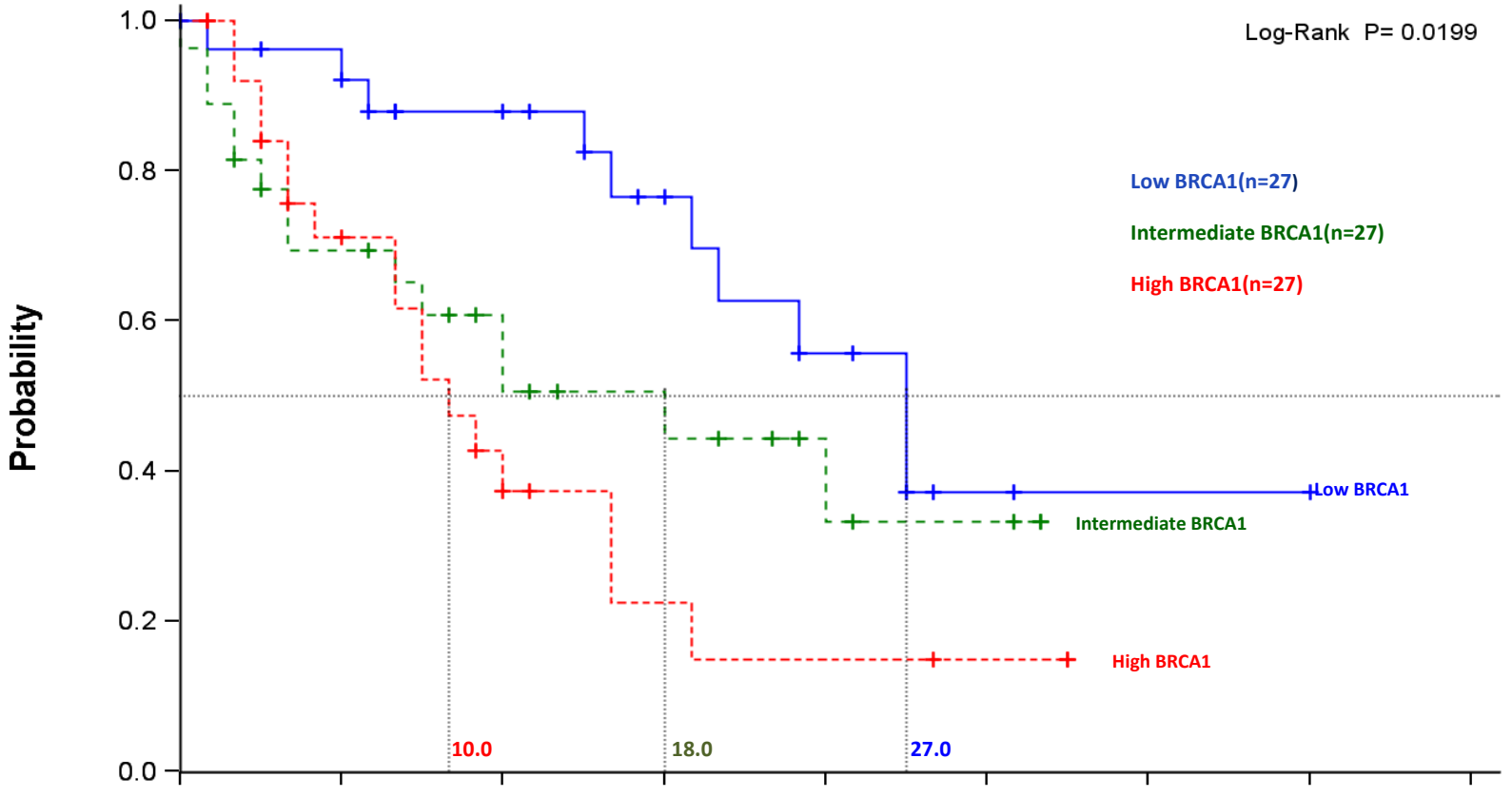




Rosell et al. CCR 2011

Phase I study of olaparib/gefitinib shows high activity and good tolerance in EGFR mutant patients with or without prior EGFR TKI treatment *(Garcia-Campelo et al. ASCO 2014)*

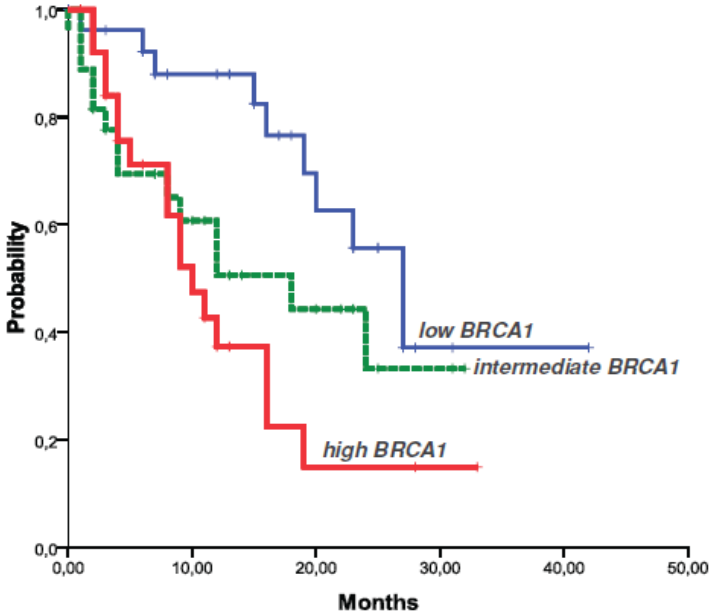
PFS in erlotinib treated EGFR mut pts by BRCA1



Patients at Risk

Low BRCA1	26	22	17	11	7	2	1	0	0
Interm. BRCA1	26	17	10	7	3	2	0	0	0
High BRCA1	27	15	6	3	2	1	0	0	0

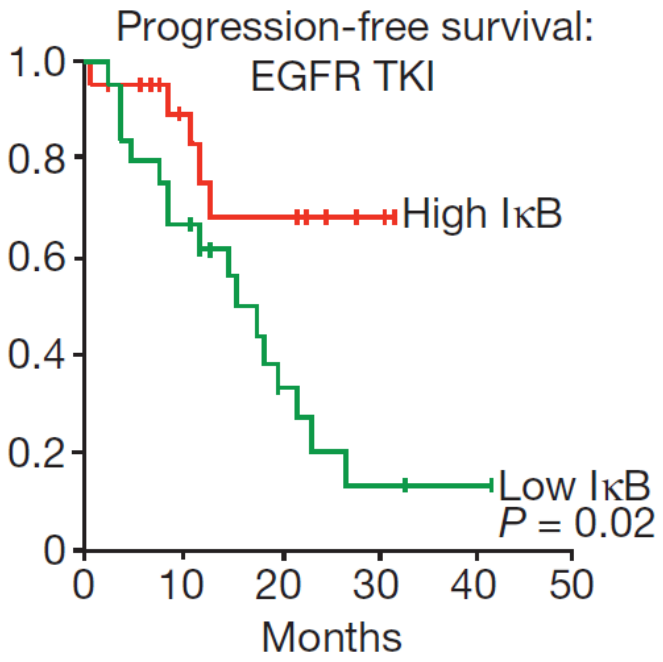
Rosell et al. CCR 2011



Rosell et al. CCR 2011

BRCA1	*n*	PFS	95% CI	*P*
4.92	27	27	21.3-32.7	0.02
4.92-10.7	27	18	6.3-29.7	
>10.7	27	10	6.7-13.3	

Figure 2. Kaplan–Meier curves of progression-free survival in 81 NSCLC patients with EGFR mutations, according to BRCA1 mRNA levels.



Bivona et al. Nature 2011

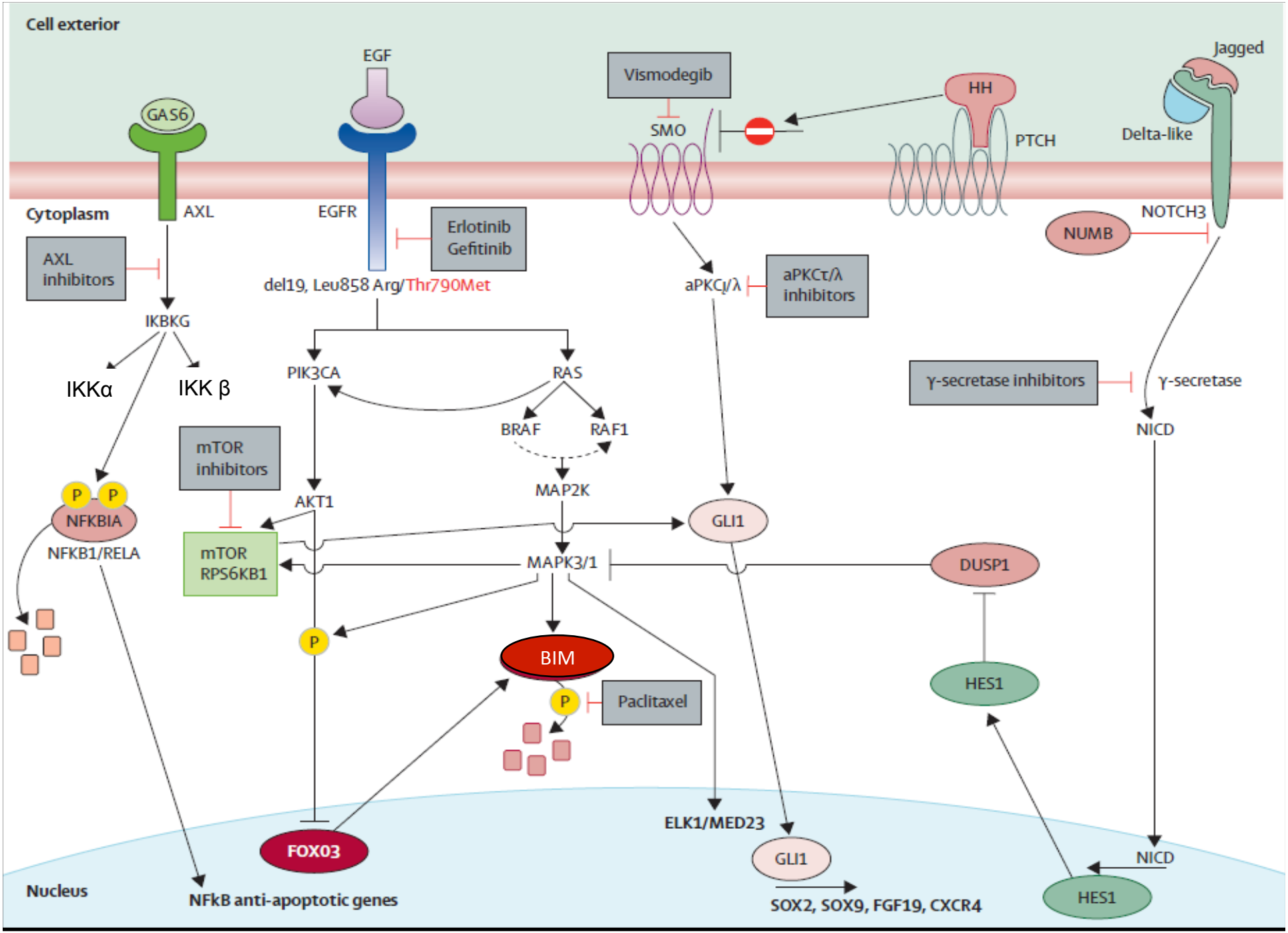
Hypoxia induces downregulation of BRCA1 and increases sensitivity to cisplatin but resistance to paclitaxel (Chan et al. Cancer Res 2008)

Oral topotecan inhibits HIF-1α (Kumar et al. CCR 2011)

Hypoxia-HIF-1α induces PDL-1. Glyceryl trinitate blocks HIF-1α (Barsoum et al. Cancer Res 2013)

BRCA1 is required for activation of NFkB and BRCA1 and NFkB cooperate to regulate expression of the NFkB anti-apoptotic targets Bcl2 and XIAP. NFkB inhibitors could sensitize BRCA1 WT tumors to DNA damaging chemotherapy. (Harte et al. Oncogene 2014)

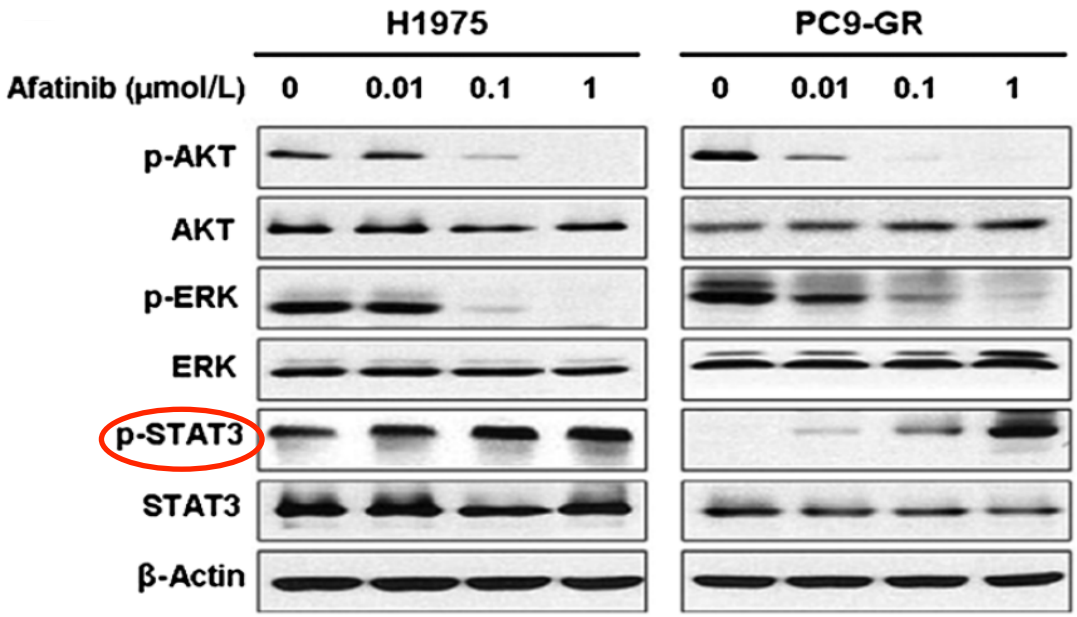
Zoledronic acid inhibits NFkB (Schech et al. Mol Cancer Ther. 2013)



Rosell, Bivona, Karachaliou. Lancet. 2013

The problem

STAT3 signaling is not inhibited with EGFR TKI monotherapy



Kim et al. Mol Cancer Ther. 2012

Ongoing research to solve the problem

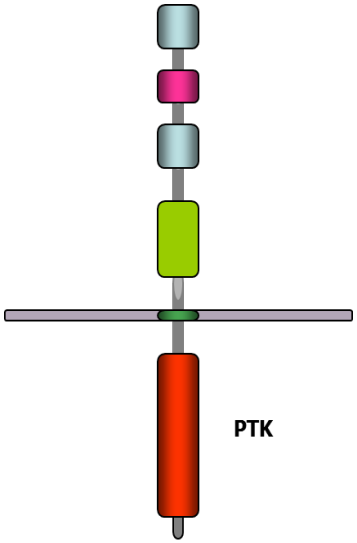
• Western blots with **CO-1686 , AZD9291 and dacomitinib**, with or without STAT3 inhibitors (*paclitaxel , niclosamide or AZD9139*).

• AXL inhibitors (*warfarin, sulfazalazine or S 49076*), BCL-XL inhibitors (TW37, ABT-273 [Sellekchem]).

Contenido

- Datos epidemiológicos, magnitud del problema; resultados y evolución terapéutica
- Relevancia y búsqueda de subpoblaciones para tratamientos dirigidos: impacto terapéutico
- Limitaciones de los tratamientos dirigidos
- Progresión durante anti-EGFR
- Progresión durante crizotinib
- Conclusiones

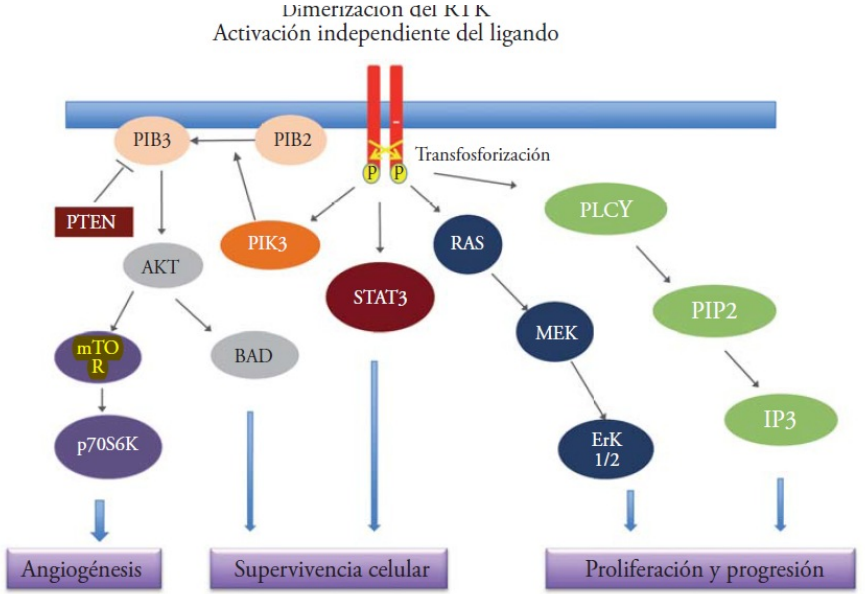
Translocación de ALK

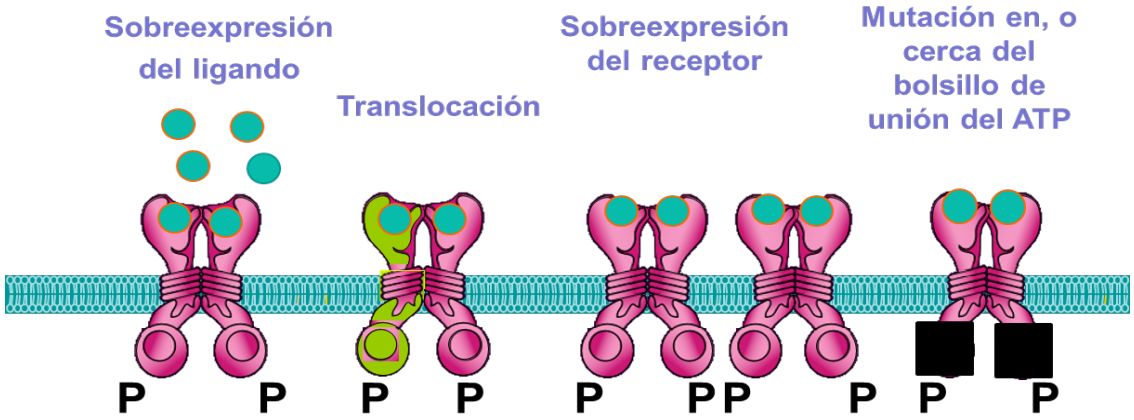


Cromosoma 2p32.2

Proteina transmembrana con actividad TK

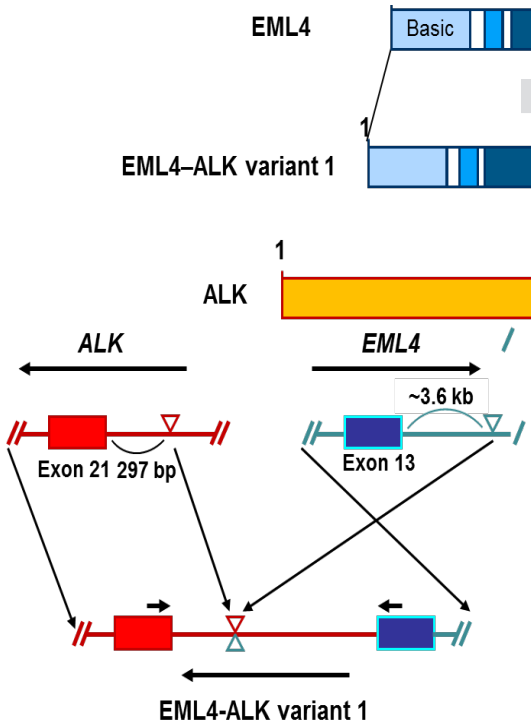
En adultos, la expresión normal se limita al sistema nervioso





Grande E et al. Mol Cancer Ther 2011
Bai et al. Mol Cell Biol 1998
Mossé et al. CCR 2009.

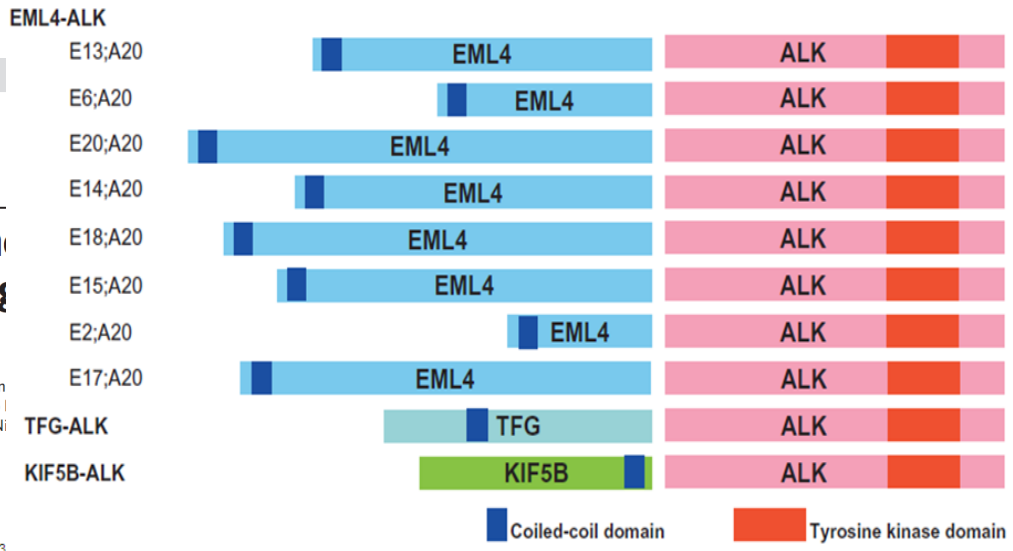
Translocación de ALK



Vol 448|2 August 2007|doi:10.1038/nature05945

Identification of th
EML4-ALK fusion g
lung cancer

Manabu Soda[1,2], Young Lim Choi[1], Munehiro Enom
Shin-ichiro Fujiwara[1], Hideki Watanabe[1], Kentaro
Yuichi Ishikawa[6], Hiroyuki Aburatani[5,7], Toshiro Ni

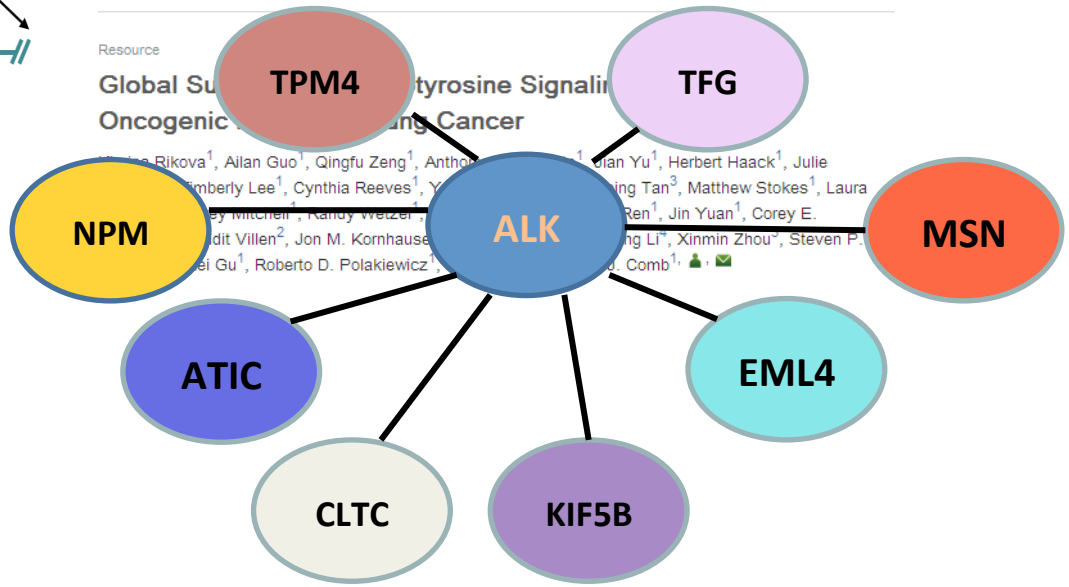


Cell
Volume 131, Issue 6, 14 December 2007, Pages 1190–1203

Resource

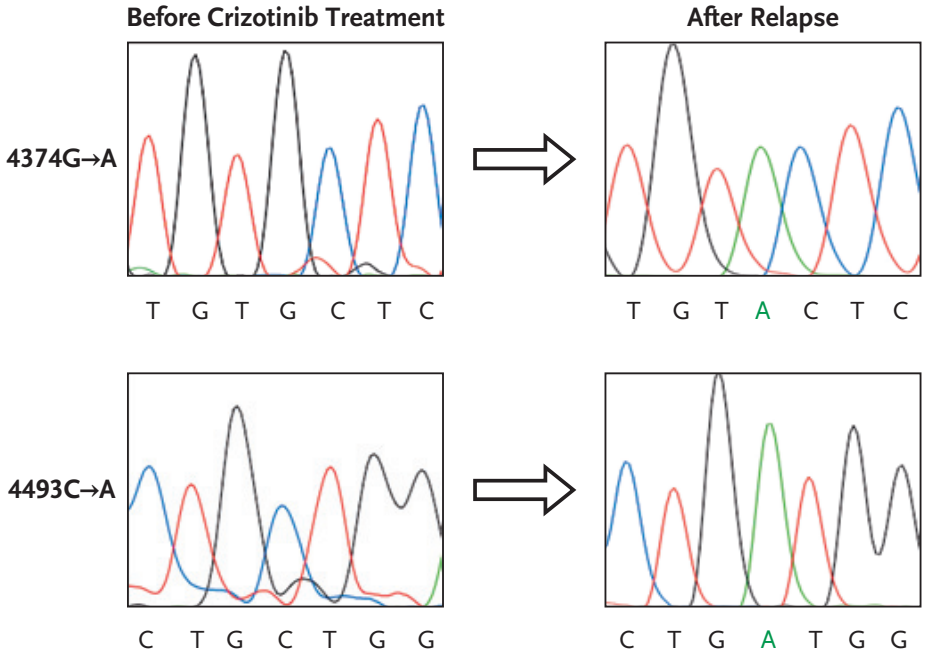
Global Su tyrosine Signali
Oncogenic ung Cancer

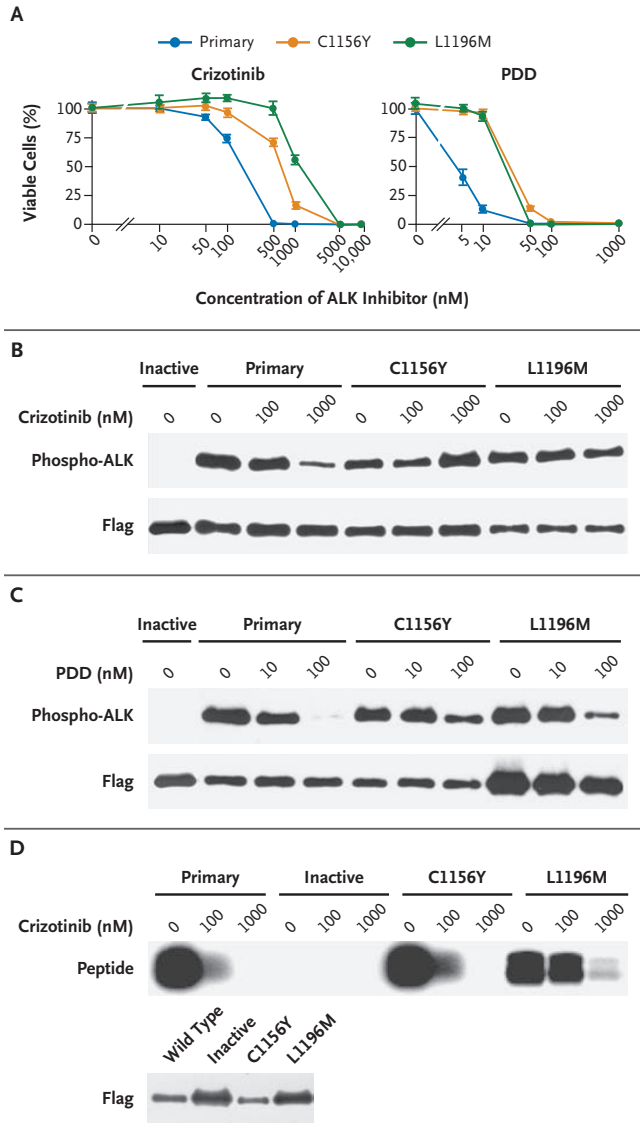
Rikova[1], Ailan Guo[1], Qingfu Zeng[1], Antho lan Yu[1], Herbert Haack[1], Julie
mberly Lee[1], Cynthia Reeves[1], Y ng Tan[3], Matthew Stokes[1], Laura
Ren[1], Jin Yuan[1], Corey E.
dit Villen[2], Jon M. Kornhause ng Li[4], Xinmin Zhou[4], Steven P.
ei Gu[1], Roberto D. Polakiewicz[1], Comb[1],



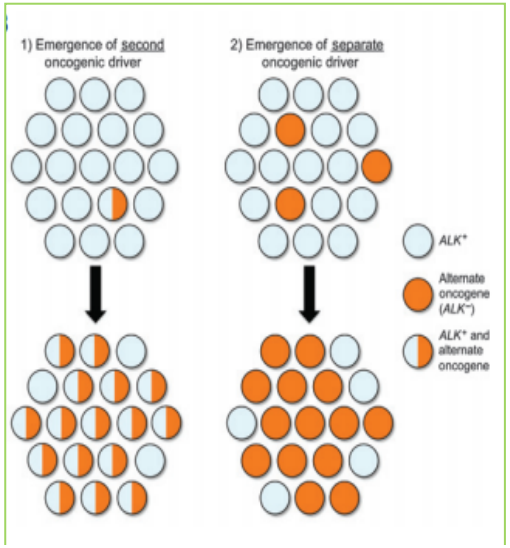
Soda et al Nature 2007
Rivoka et al Cell 2007
Choi et al Cancer Res 2008
Takeuchi CCR 2009

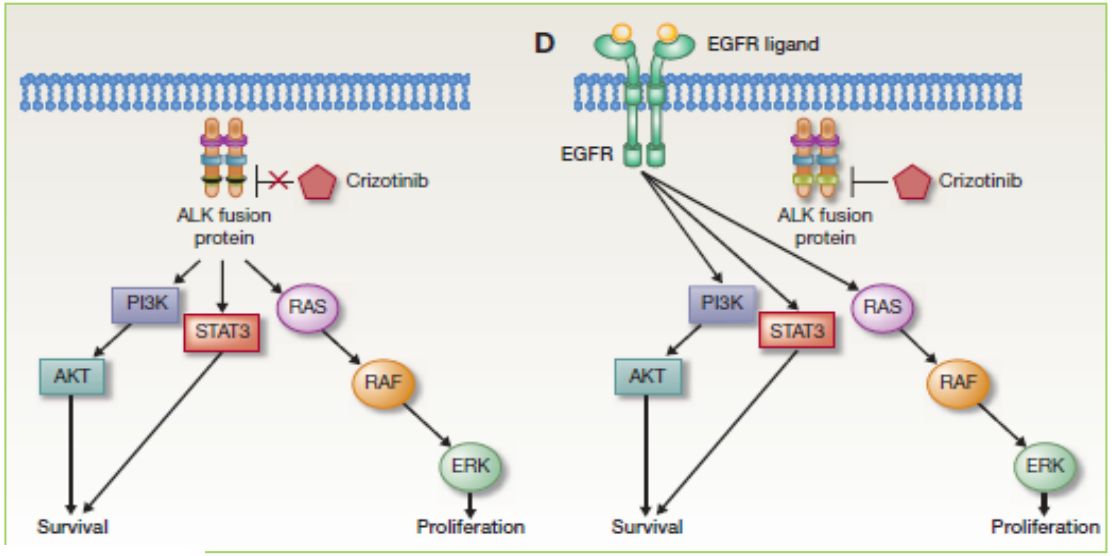
Mutaciones adicionales resistencia en EML4-ALK

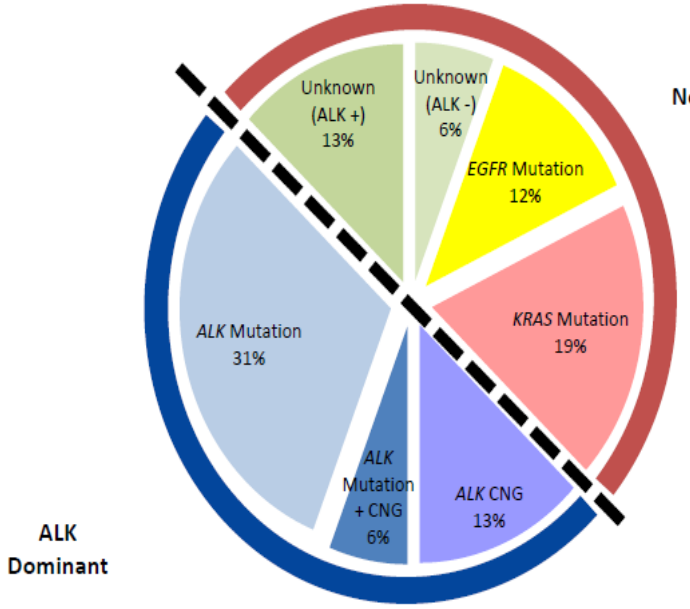




Mecanismos de resistencia adquirida a Crizotinib



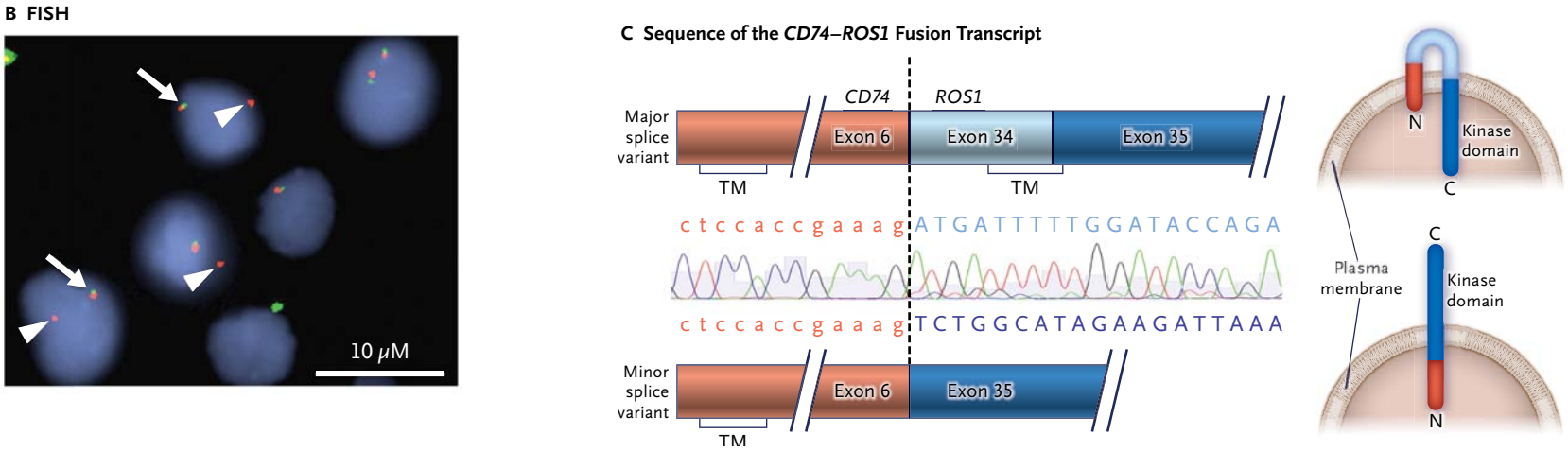


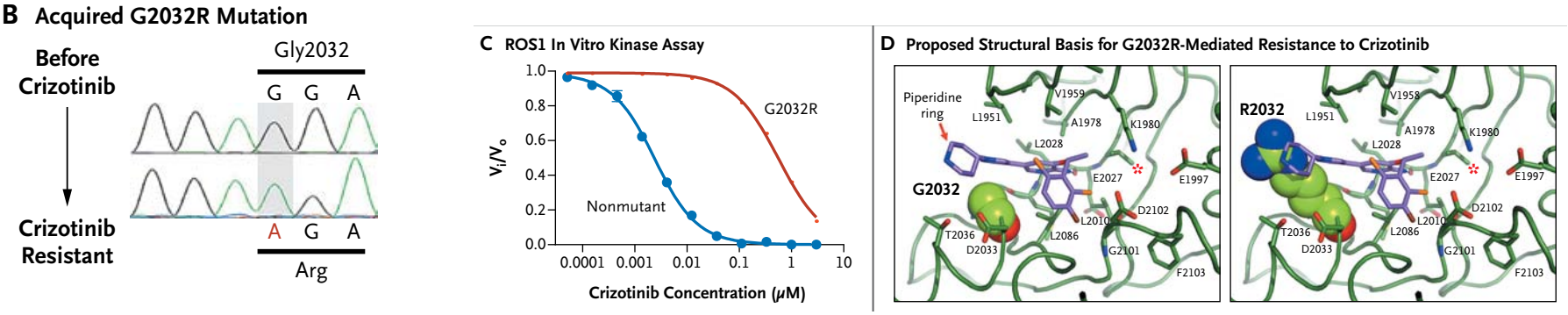


- Mutación o amplificación de ALK
- Activación de vias de señalización alternativas:
  - EGFR
  - K-ras
  - C-kit

Shaw AT J Clin Oncol2013
Sasaki T Clin Cancer Res 2011

Resistencias en ROS1 tratado con Crizotinib





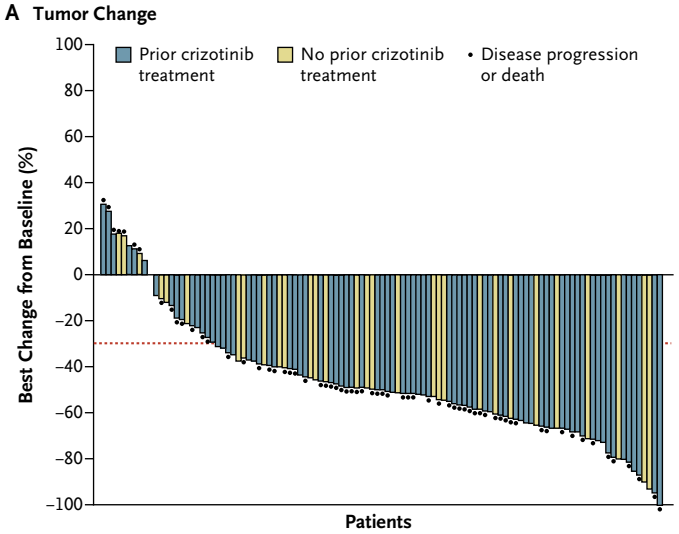
Ceritinib en pacientes pretratados con Crizotinib y translocación ALK

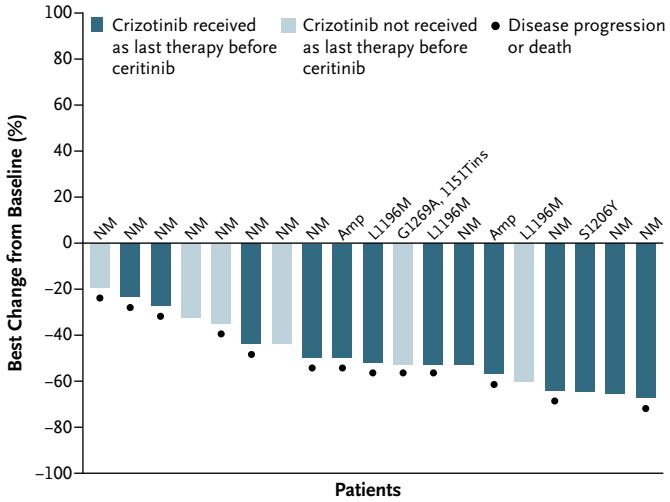
N Engl J Med 2014;370:1189-97.
DOI: 10.1056/NEJMoa1311107

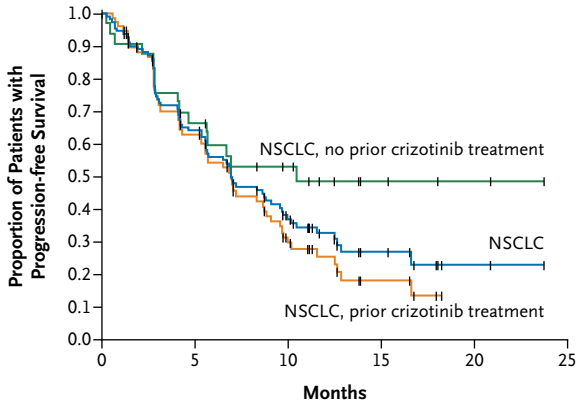
Characteristic	All Patients (N = 130)
Age — yr	
Median	53
Range	22–80
Female sex — no. (%)	78 (60)
Race — no. (%)*	
White	97 (75)
Asian	29 (22)
Other	4 (3)
Smoking status — no. (%)	
Never smoked	81 (62)
Former smoker	44 (34)
Current smoker	5 (4)
ECOG performance status score — no. (%)†	
0	25 (19)
1	89 (68)
2	15 (12)
3	1 (1)
Tumor type — no. (%)	
Non–small-cell lung cancer	122 (94)
Breast cancer	4 (3)
Alveolar rhabdomyosarcoma	1 (1)
Inflammatory myofibroblastic tumor	1 (1)
Anaplastic large-cell lymphoma	1 (1)
Rectal adenocarcinoma	1 (1)
Select sites of metastases — no. (%)	
Lung	101 (78)
Thoracic lymph nodes	73 (56)
Brain	64 (49)
Liver	51 (39)
Bone	49 (38)
Meninges	1 (1)
Prior crizotinib therapy for non–small-cell lung cancer — no./total no. (%)	
Yes	83/122 (68)
No	39/122 (32)

Respuesta y SLP con Ceritinib

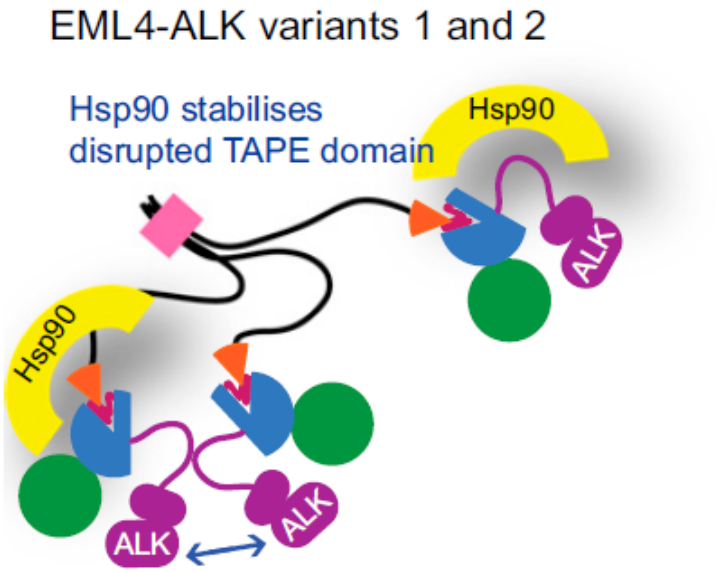
N Engl J Med 2014;370:1189-97.
DOI: 10.1056/NEJMoa1311107

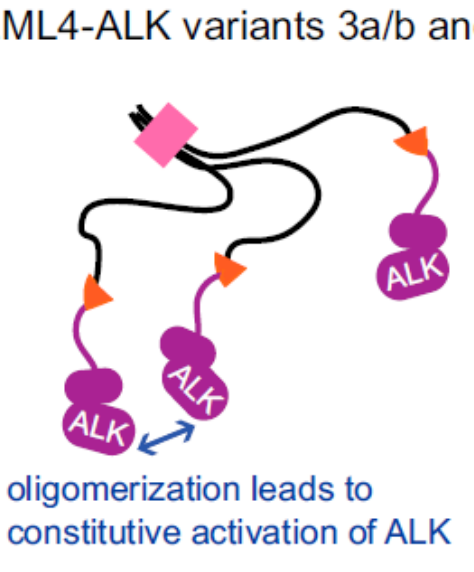






No. at Risk						
NSCLC, no prior crizotinib treatment	34	21	13	4	2	0
NSCLC	114	66	30	9	2	0
NSCLC, prior crizotinib treatment	80	45	17	5	0	

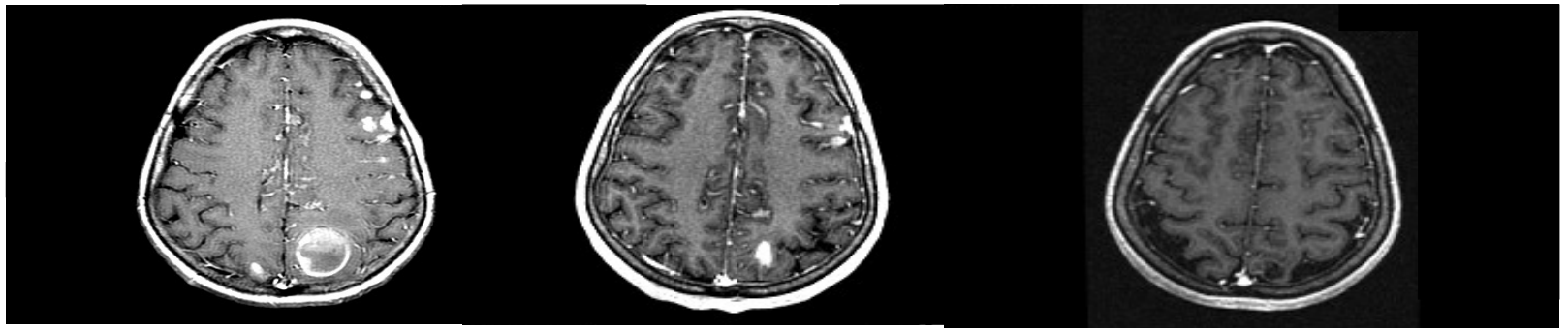




Richards et al. PNAS 2014

Sensitivity of variants to Hsp90 inhibitors differs depending on whether the breakpoint of the fusion protein interrupts the globular TAPE domain.

Dec 2011 Aug 2012 Feb 2014



Courtesy S Viteri

Progression
After 1yr crizotinib

Partial response
After 8m ganetespib

Almost CR
After 12m ceritinib (LDK378)

Contenido

- Datos epidemiológicos, magnitud del problema; resultados y evolución terapéutica
- Relevancia y búsqueda de subpoblaciones para tratamientos dirigidos: impacto terapéutico
- Limitaciones de los tratamientos dirigidos
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Conclusiones

- Los tratamientos dirigidos sobre mutaciones conductoras comportan la aparición de resistencias mediadas por diferentes mecanismos (mutaciones adicionales, vías de escape)
- La heterogeneidad característica de la transformación maligna puede ser relevante en la progresión clínica
- La inclusión de pacientes en EC debería ser prioritaria
- La continuación del tratamiento con ITKs es objeto de investigación clínica
- La posibilidad de combinaciones con quimioterapia citotóxica u otros fármacos biológicos son alternativas en la práctica clínica y en la investigacion clínica
- La posibilidad de adición de tratamientos locales y mantenimiento del tratamiento basal puede ser considerada en determinadas circunstancias clínicas
- El Ceritinib ha sido recientemente aprobado por la FDA para el tratamiento de pacientes con translocacion de ALK que progresan a Crizotinib

Muchas Gracias