cnio
Centro Nacional de Investigaciones Oncológicas

UNIVERSIDAD COMPLUTENSE MADRID

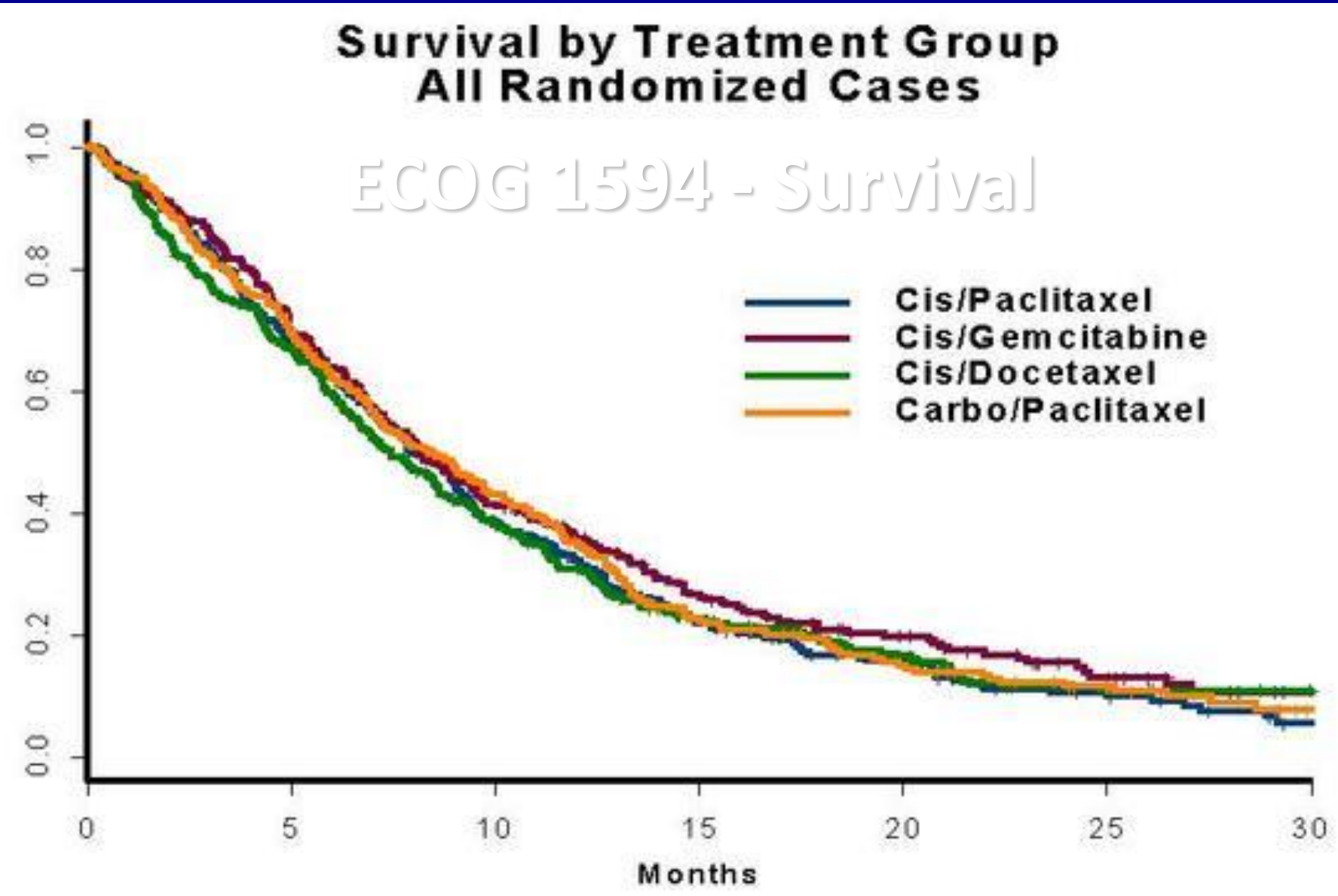
Medicina Personalizada en Oncología:
El Ejemplo del Cáncer de Pulmón

Luis Paz-Ares

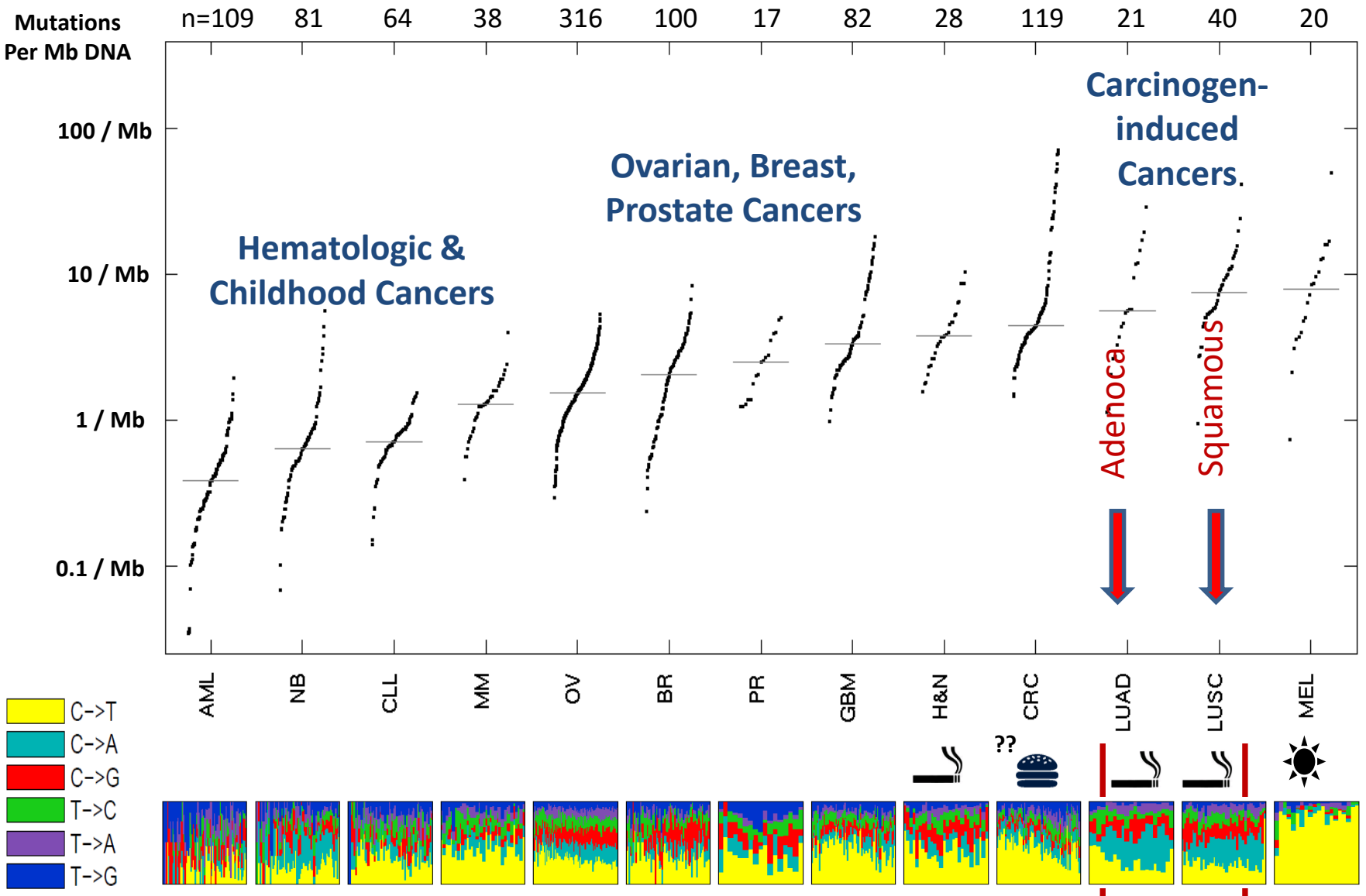
Hospital Universitario Doce de Octubre,

Madrid, Spain

El Pasado (hopefully !!)

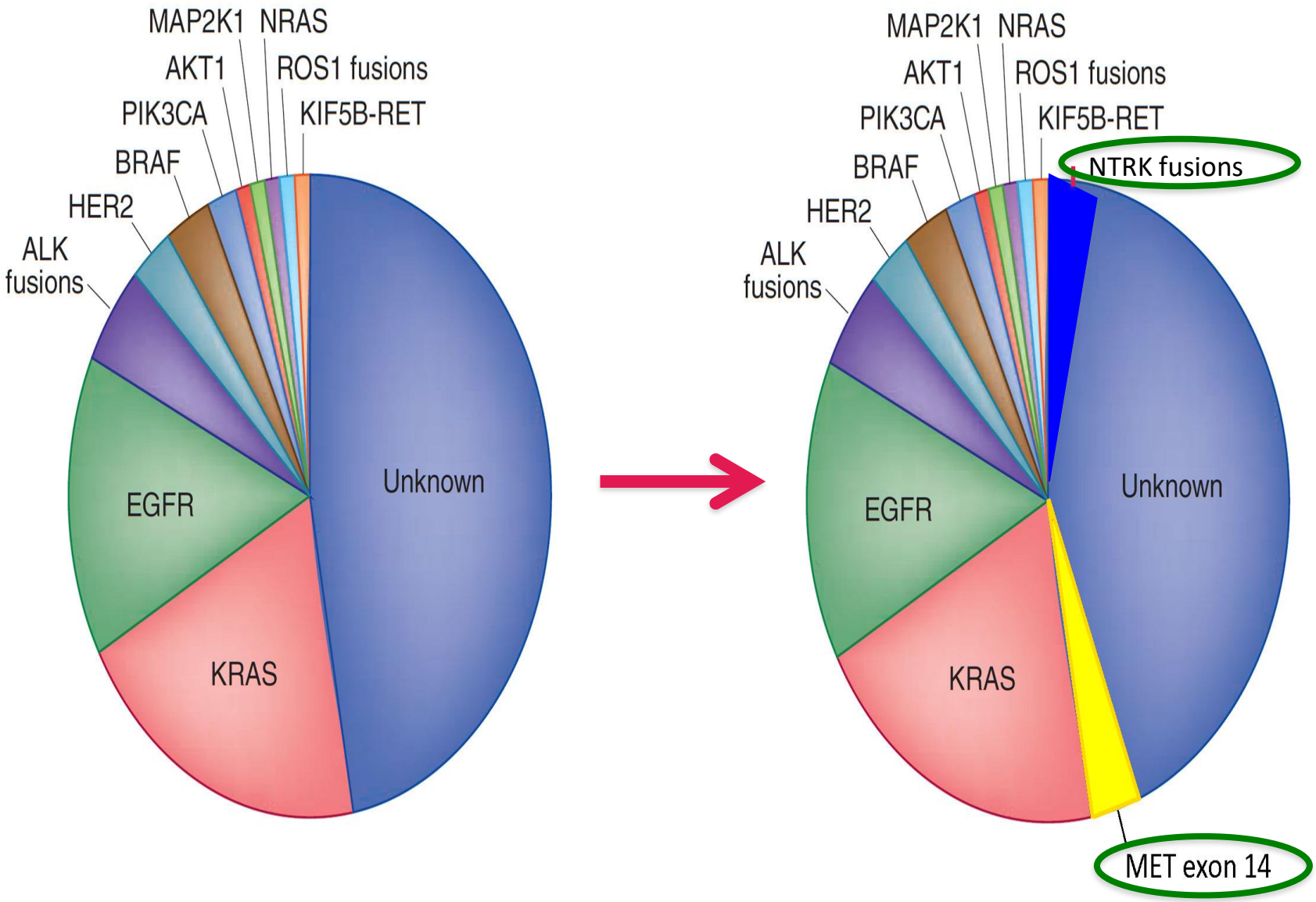


Las aberraciones genómicas son muy frecuentes en cáncer de pulmón



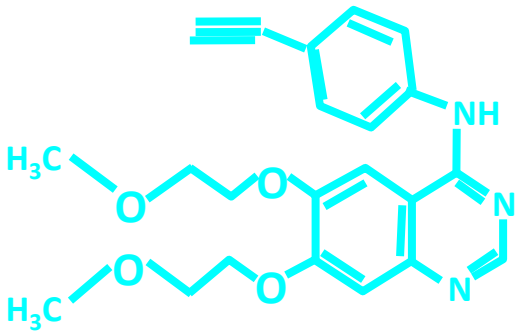
From The Cancer Genome Atlas Project: Govindan R. J Clin Oncol. 2012 (Proc ASCO Annual Meeting);30 (suppl): abstr 7006.

Adenocarcinoma de pulmón - Genotipo



Agentes dirigidos a dianas moleculares

Pequeñas Moléculas

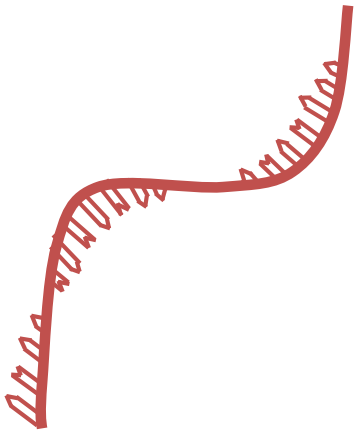


Intracellular action
c 0.5–2kDa
Orally available

Anticuerpos Monoclonales

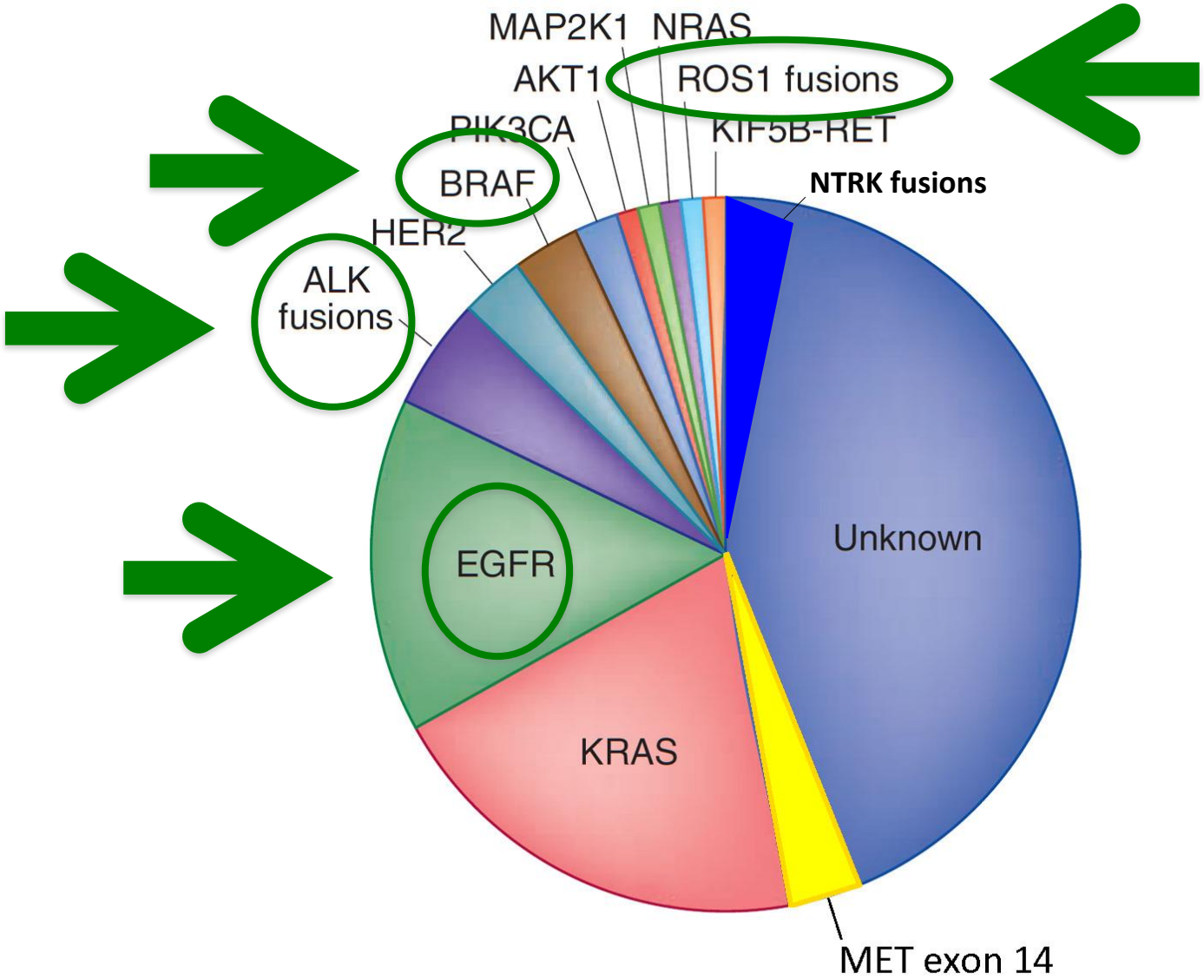
Extracellular action
c 150kDa
i.v. infusion

Oligonucleótidos antisentido

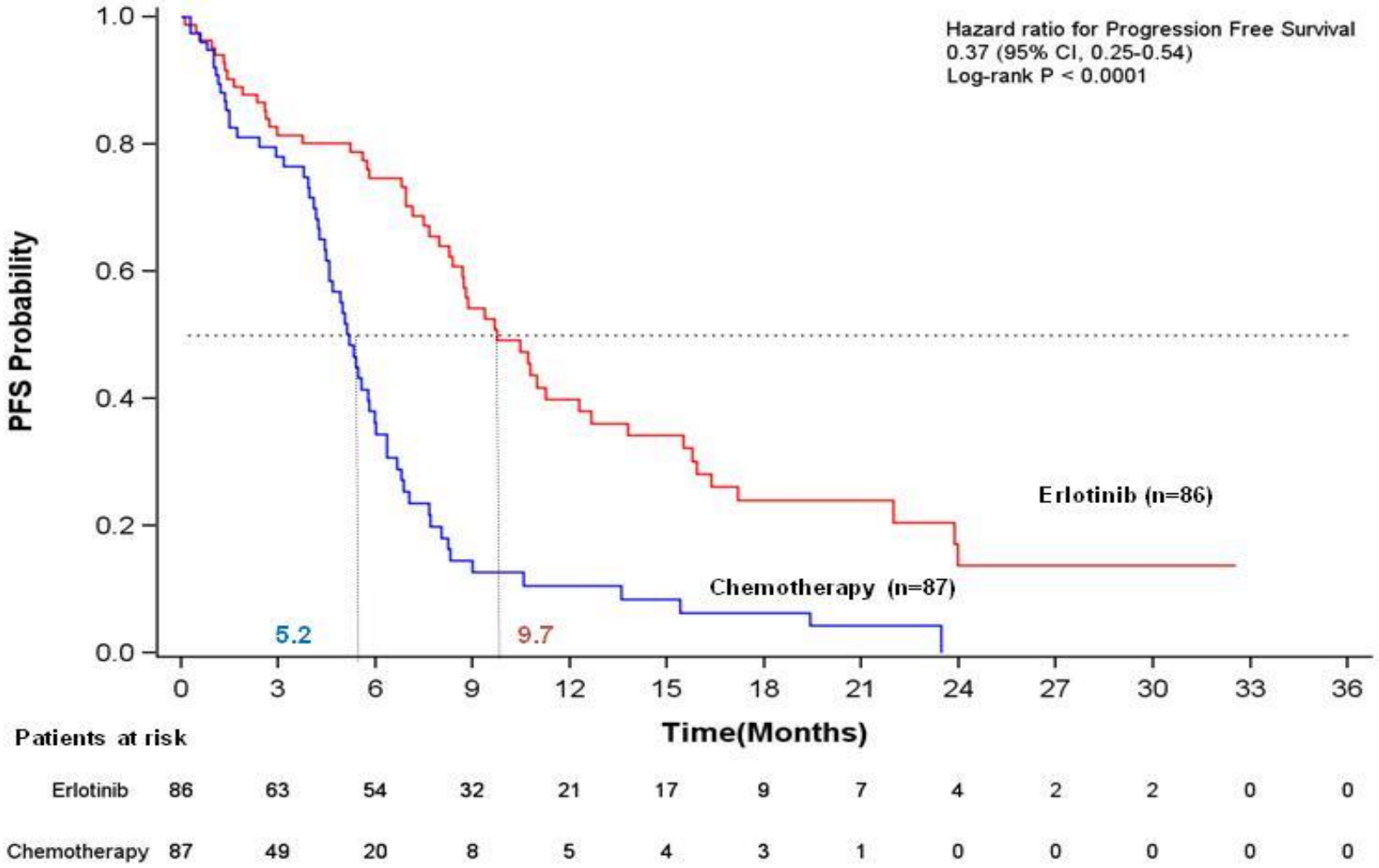


Intracellular action
c 10kDa
i.v. infusion

Adenocarcinoma de pulmón
Subtipos con tratamientos específicos

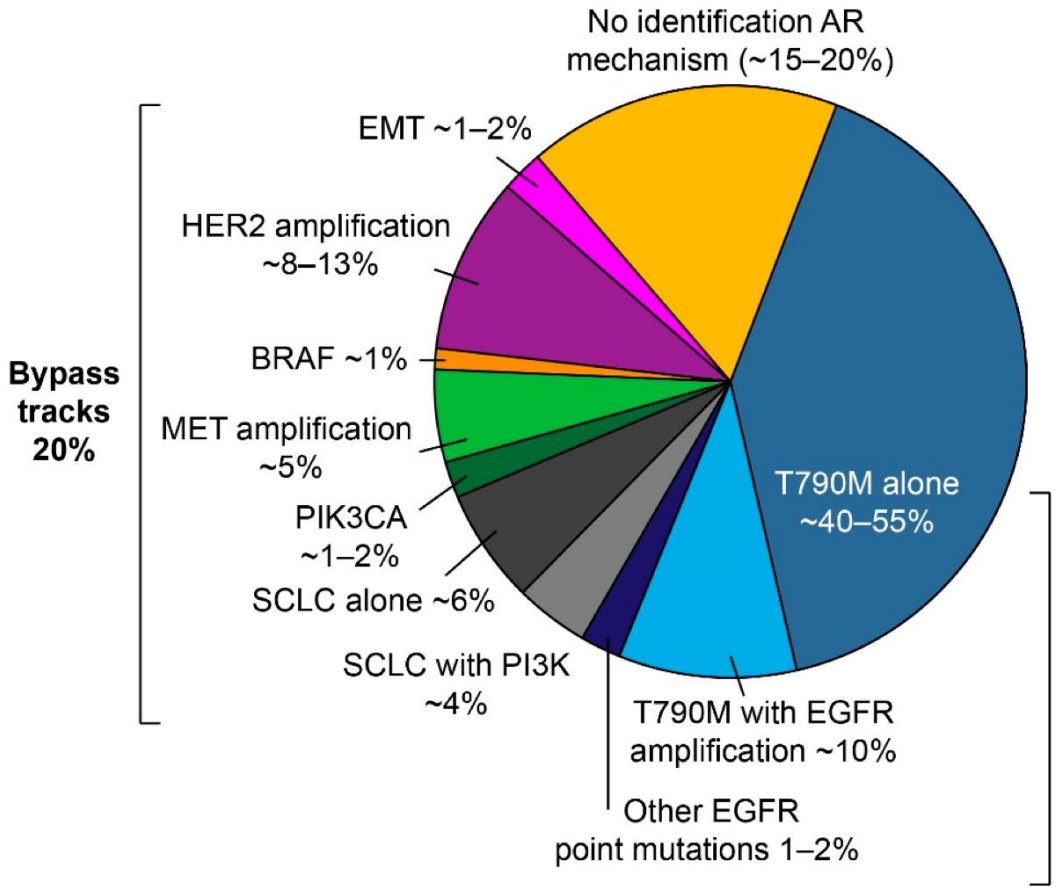


Ensayo EURTAC : Erlotinib *v* Quimioterapia

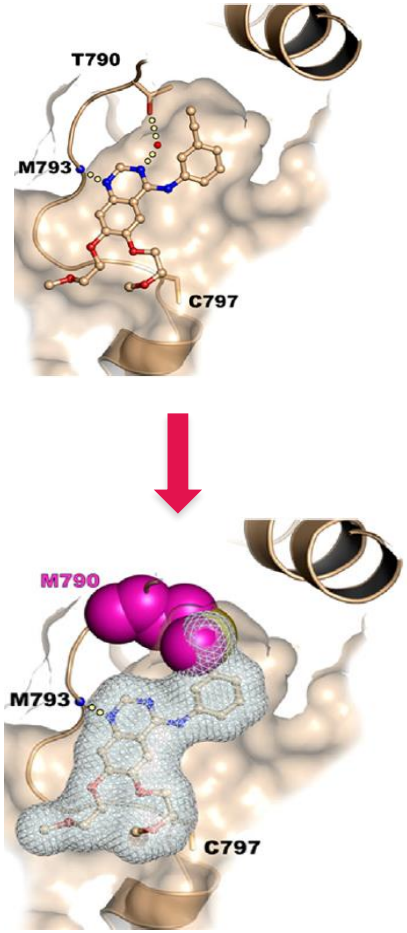


Rosell, …Paz-Ares. Lancet Oncol 2012

CNMP EGFR M+: Resistencia Adquirida

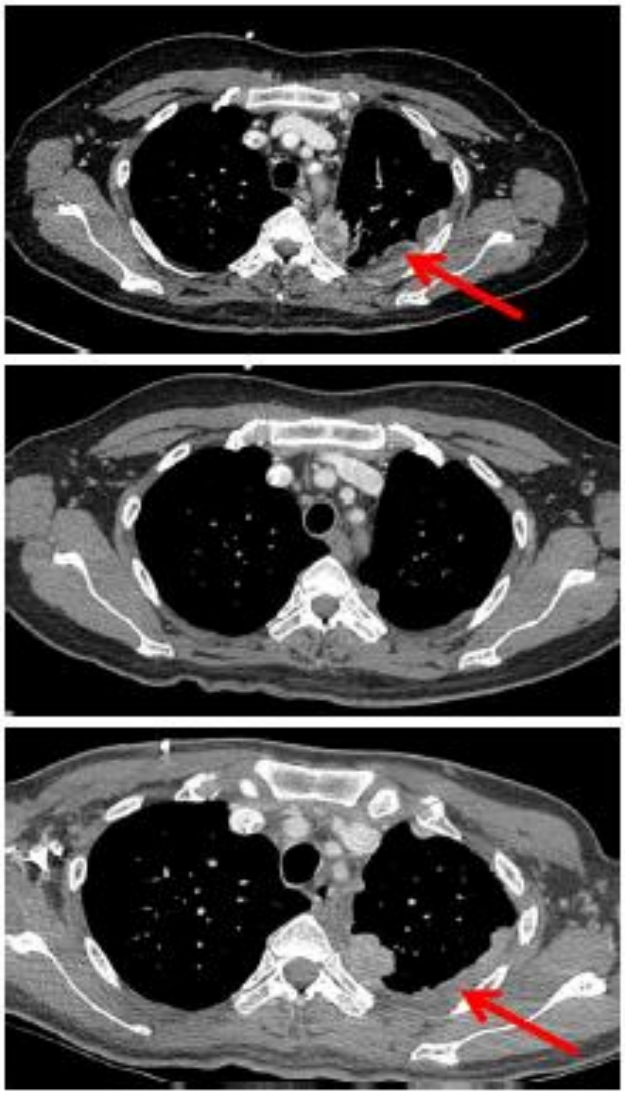


T790M - Exon 20

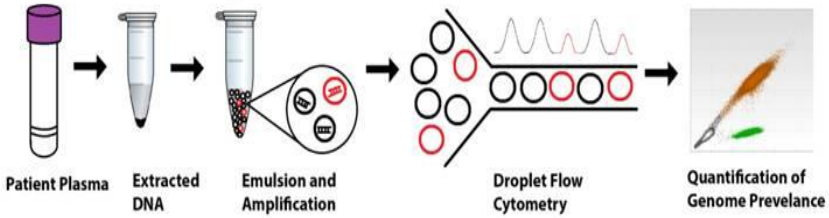


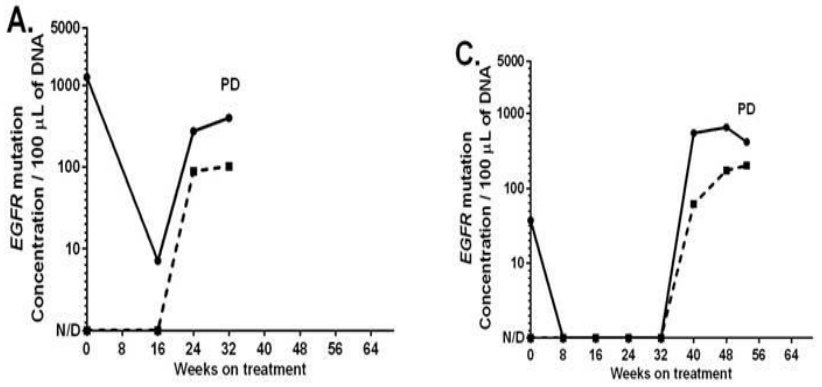
Michalczyk A et al. Bioorg Med Chem. 2008 Apr 1;16(7):3482-8.

Monitorización de la Resistancia Biopsia Líquida



Non-invasive genotyping and disease monitoring





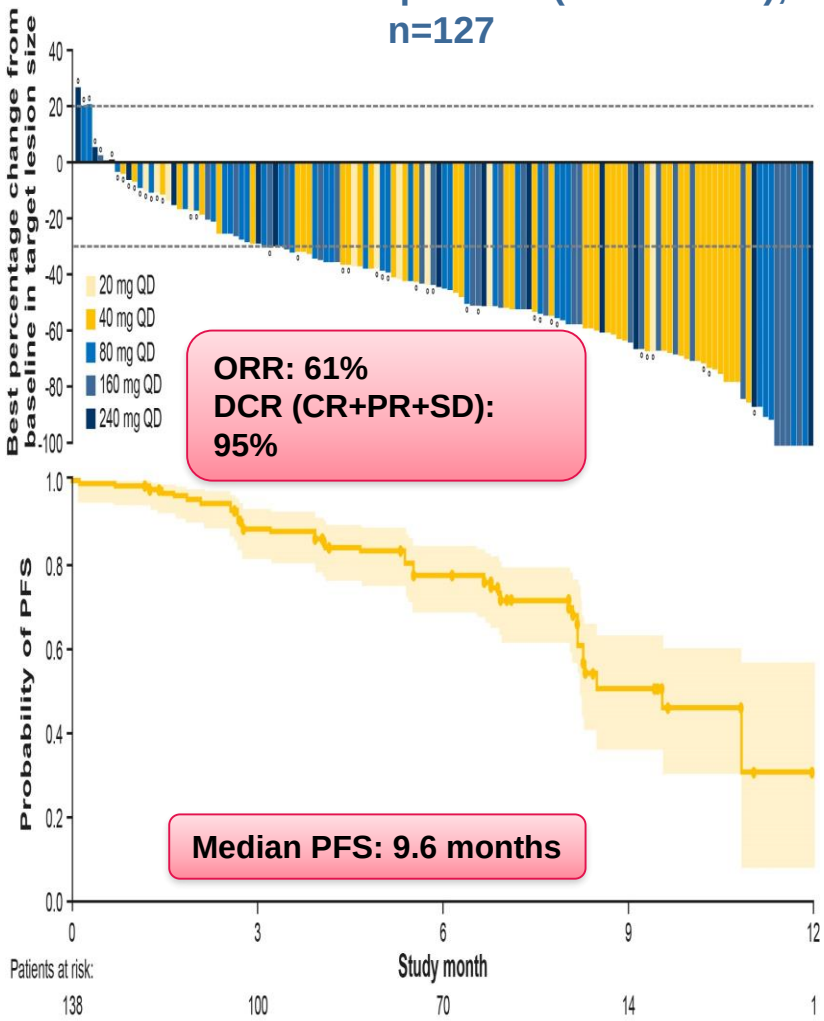
Serial monitoring for EGFR activating and EGFR T790M resistance mutation in erlotinib treated EGFR mutant patients

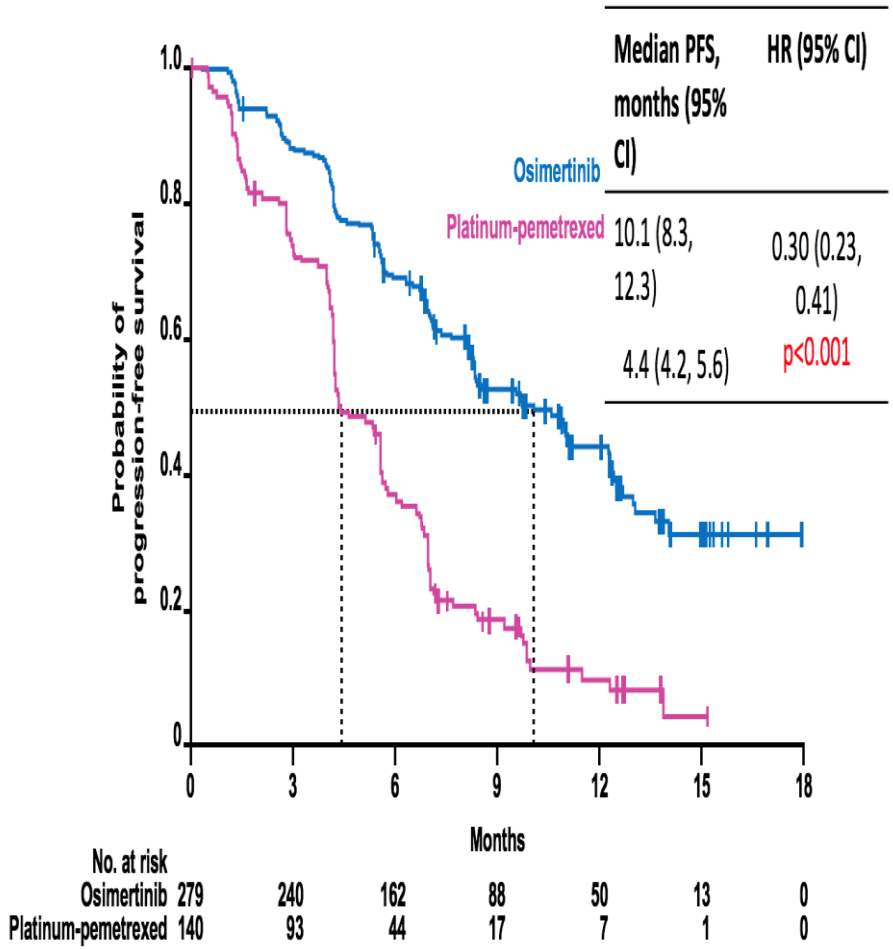
Oxnard et al. CCR 2014

Sacher et al. ASCO 2014; Abstract 8059

Osimertinib en Cáncer de pulmón EGFR-T790M +

Best change in target lesion and ORR in T790M evaluable patients (central test); n=127



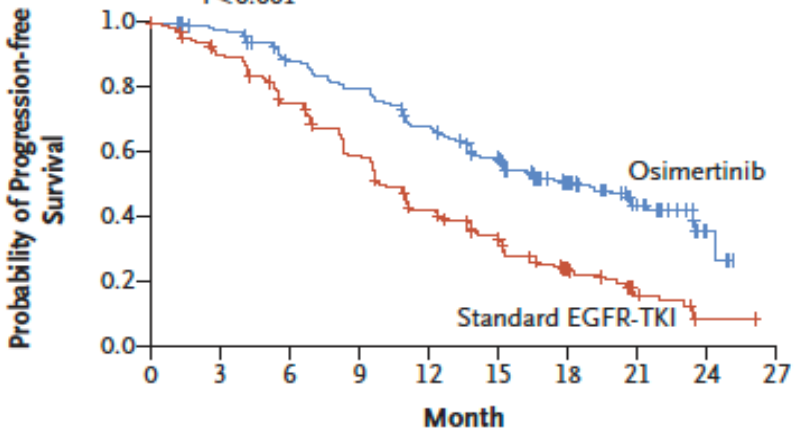


Ensayo Flaura
Gefitinib v Omimertinib

Progression-Free Survival

	No. of Patients	Median Progression-free Survival (95% CI)
		mo
Osimertinib	279	18.9 (15.2–21.4)
Standard EGFR-TKI	277	10.2 (9.6–11.1)

Hazard ratio for disease progression or death, 0.46 (95% CI, 0.37–0.57)
P<0.001

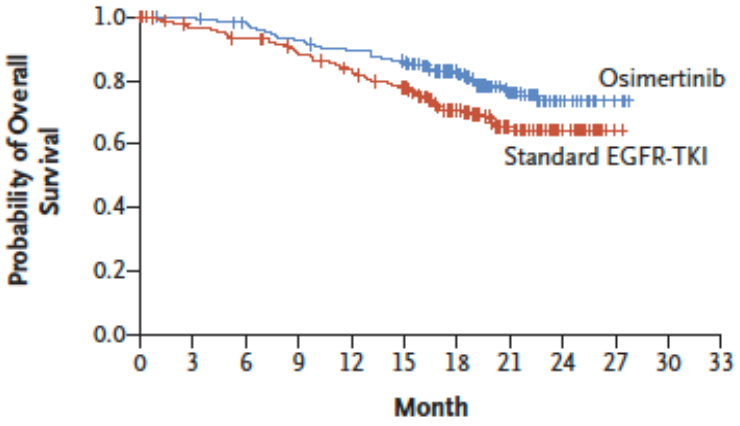


No. at Risk										
Osimertinib	279	262	233	210	178	139	71	26	4	0
Standard EGFR-TKI	277	239	197	152	107	78	37	10	2	0

Overall Survival

	No. of Patients	Median Overall Survival (95% CI)
		mo
Osimertinib	279	NC (NC–NC)
Standard EGFR-TKI	277	NC (NC–NC)

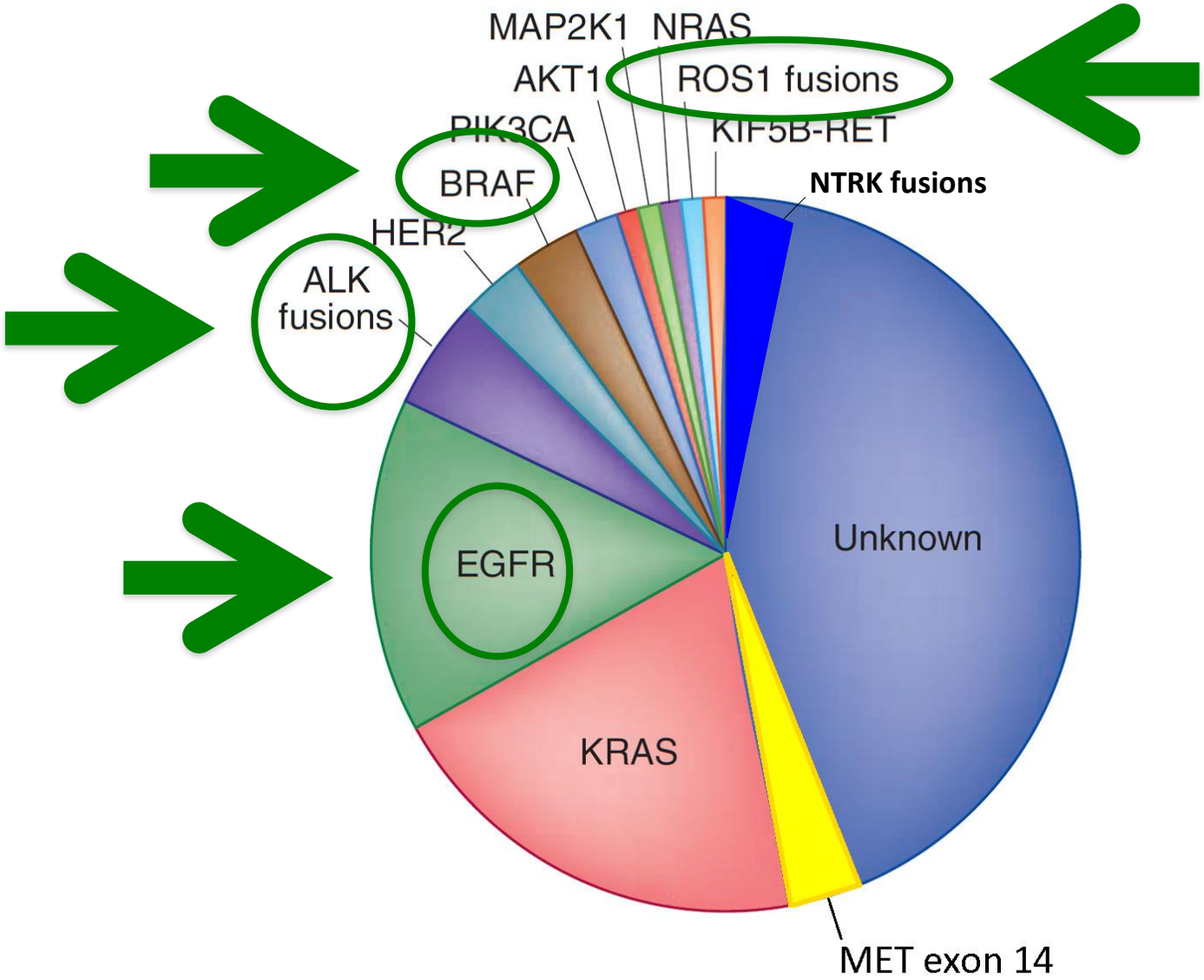
Hazard ratio for death, 0.63 (95% CI, 0.45–0.88)
P=0.007



No. at Risk												
Osimertinib	279	276	269	253	243	232	154	87	29	4	0	0
Standard EGFR-TKI	277	263	252	237	218	200	126	64	24	1	0	0

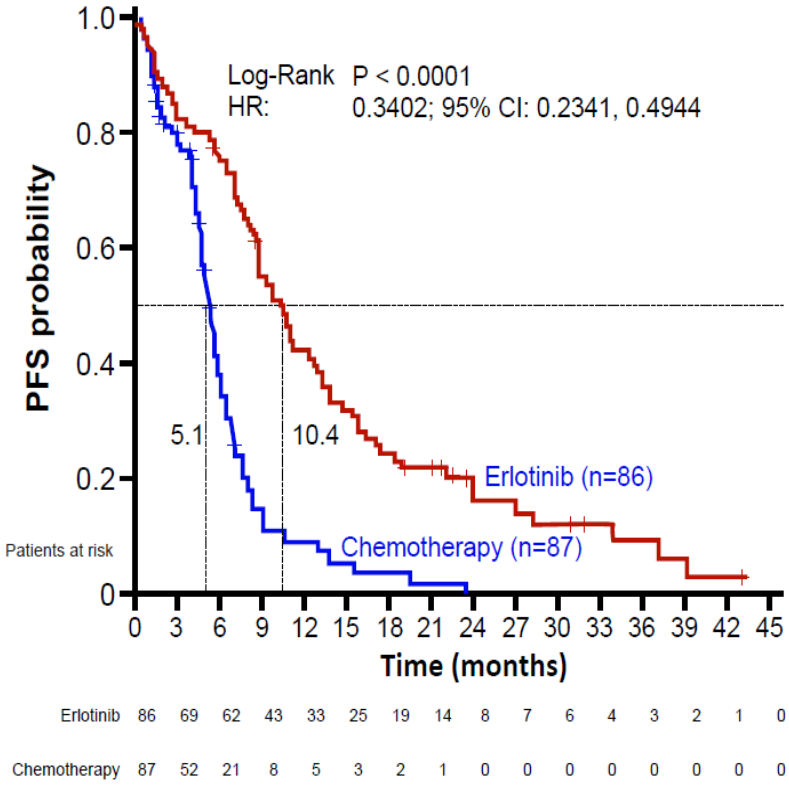
Soria et al. NEJM 2018

Adenocarcinoma de pulmón
Subtipos con tratamientos específicos

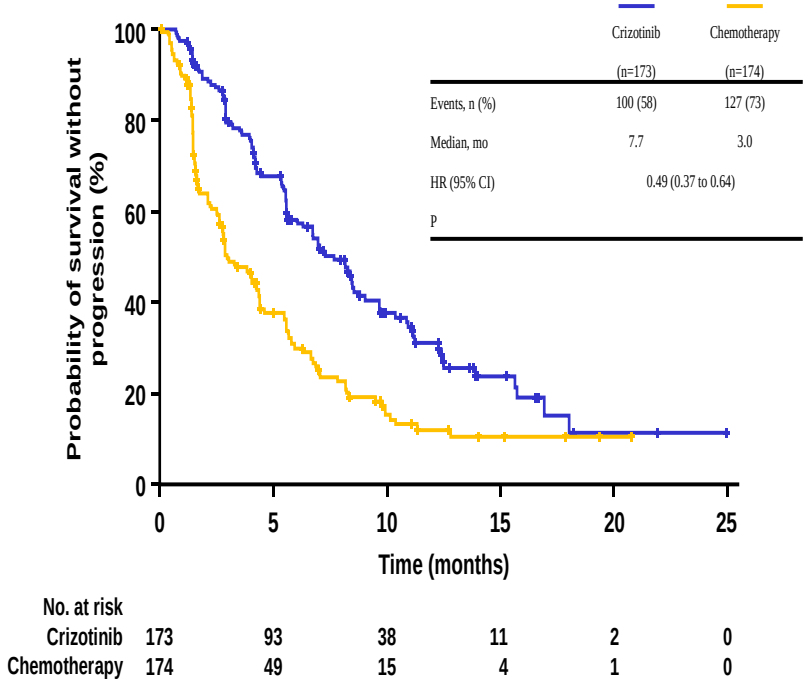


Adenocarcinoma Pulmón
Adicción a EGFR - ALK

Erlotinib versus chemotherapy in EGFR-driven advanced NSCLC[1]



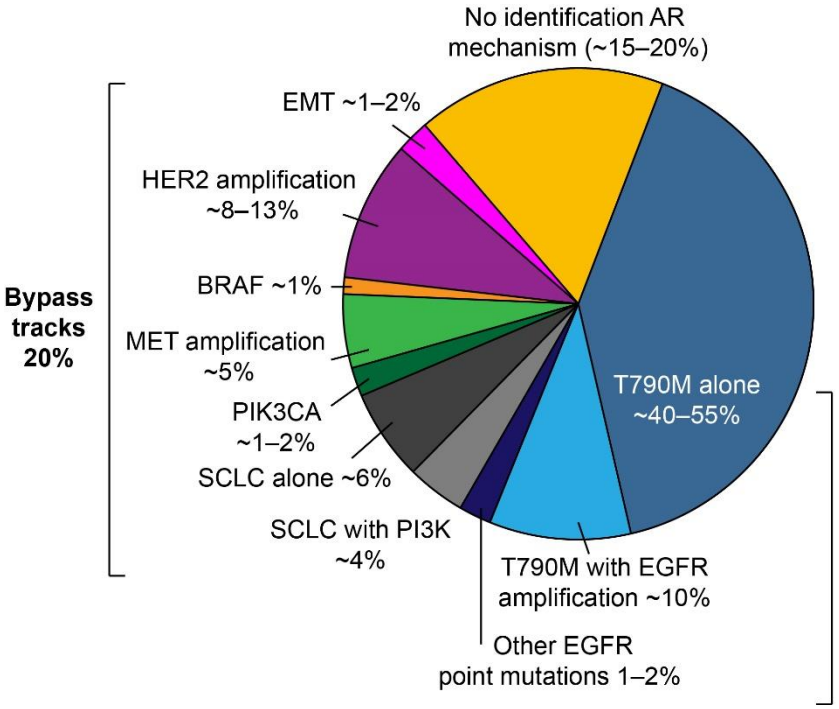
Crizotinib *v* Chemotherapy in ALK + NSCLC



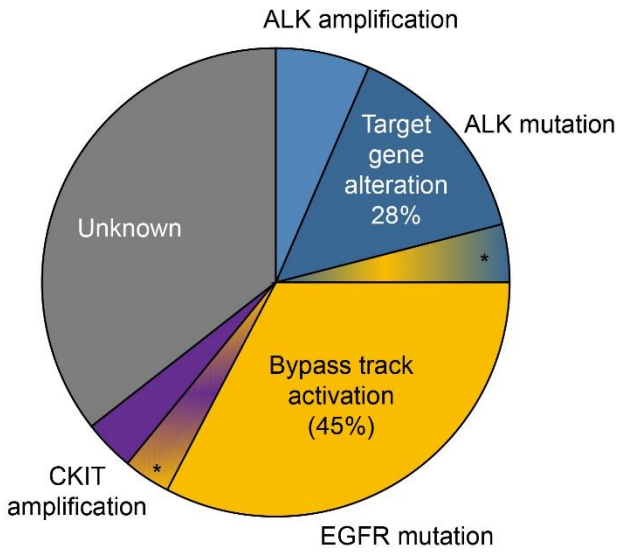
Shaw et al., NEJM 2012

Resistencia Adquirida
CNMP EGFR mutado y ALK positivo

EGFR mutant



ALK positive



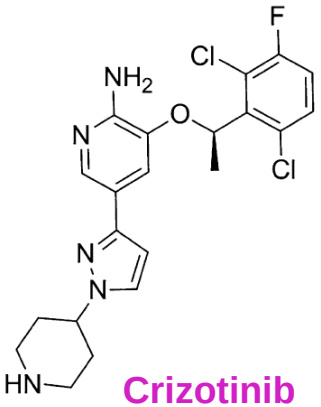
*More than one mechanism

Common themes

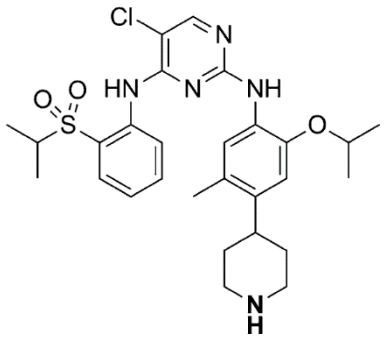
Second site mutations in target (e.g. T790M / L1196M)

Use of alternative signalling pathways (e.g. MET / EGFR)

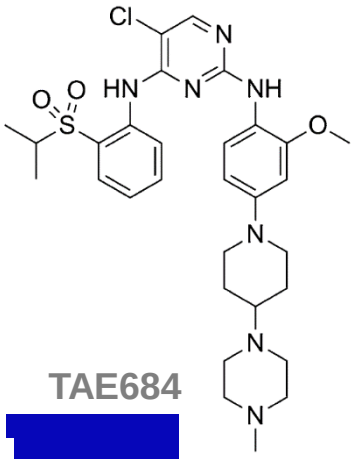
Siguiente generación Inhibidores de4 ALK



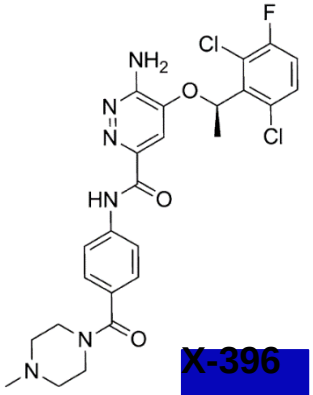
Crizotinib



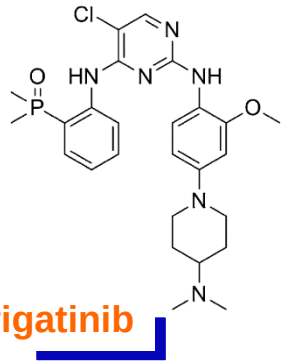
Ceritinib



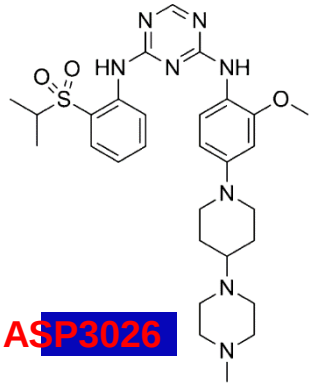
TAE684



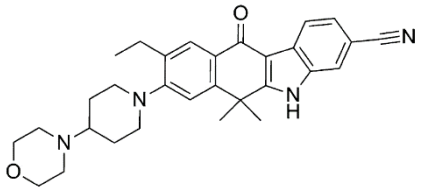
X-396



Brigatinib



ASP3026



Alectinib

New ALK inhibitors should be active against resistance mutations, have proven CNS activity, improved systemic efficacy and have an acceptable safety profile

Resistencia Adquirida a TKIs de ALK

Cellular ALK phosphorylation mean IC_{50} (nmol/L)

Mutation status	Crizotinib	Ceritinib	Alectinib	Brigatinib	Lorlatinib
Parental Ba/F3	763.9	885.7	890.1	2774.0	11293.8
EML4–ALK V1	38.6	4.9	11.4	10.7	2.3
EML4–ALK C1156Y	61.9	5.3	11.6	4.5	4.6
EML4–ALK I1171N	130.1	8.2	397.7	26.1	49.0
EML4–ALK I1171S	94.1	3.8	177.0	17.8	30.4
EML4–ALK I1171T	51.4	1.7	33.6[a]	6.1	11.5
EML4–ALK F1174C	115.0	38.0[a]	27.0	18.0	8.0
EML4–ALK L1196M	339.0	9.3	117.6	26.5	34.0
EML4–ALK L1198F	0.4	196.2	42.3	13.9	14.8
EML4–ALK G1202R	381.6	124.4	706.6	129.5	49.9
EML4–ALK G1202del	58.4	50.1	58.8	95.8	5.2
EML4–ALK D1203N	116.3	35.3	27.9	34.6	11.1
EML4–ALK E1210K	42.8	5.8	31.6	24.0	1.7
EML4–ALK G1269A	117.0	0.4	25.0	ND	10.0
EML4–ALK D1203N+F1174C	338.8	237.8	75.1	123.4	69.8
EML4–ALK D1203N+E1210K	153.0	97.8	82.8	136.0	26.6

$IC_{50} \leq 50$ nmol/L

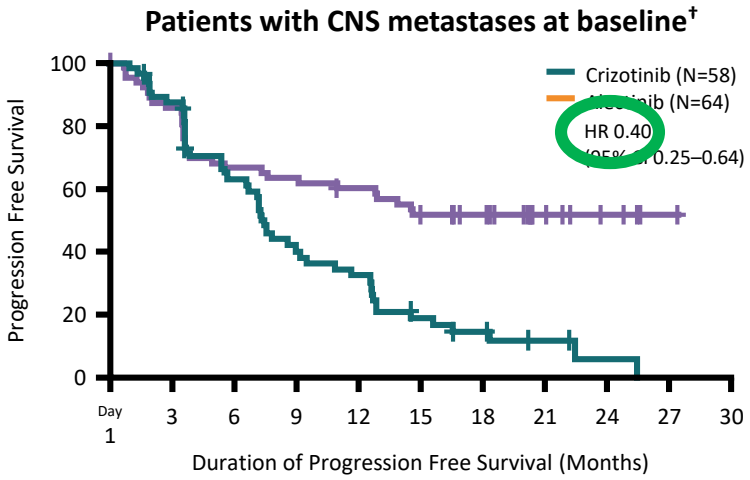
$IC_{50} > 50 < 200$ nmol/L

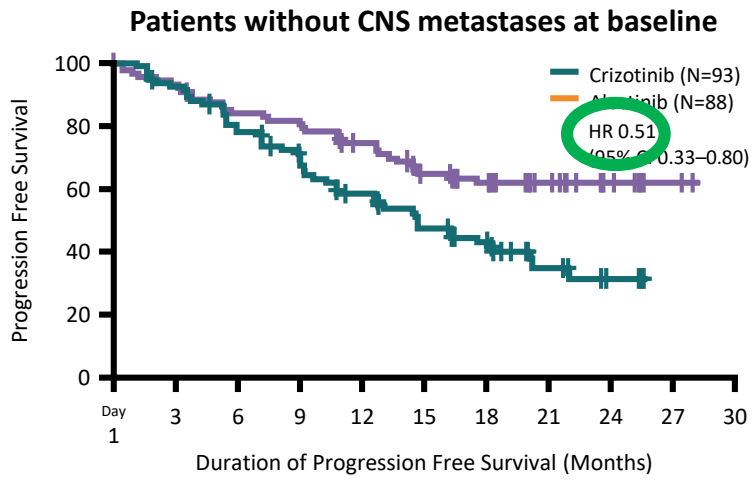
$IC_{50} \geq 200$ nmol/L

Gainor et al. Cancer Discov 2016

Ensayo Alex
Primera Línea: Alectinib v Crizotinib

PFS by baseline CNS metastases status*





Patients at Risk										
Crizotinib	5	4	6	2	1	9	6	3	1	
Alectinib	6	5	4	3	3	3	2	1	4	1
	4	4	1	9	6	1	4	0		

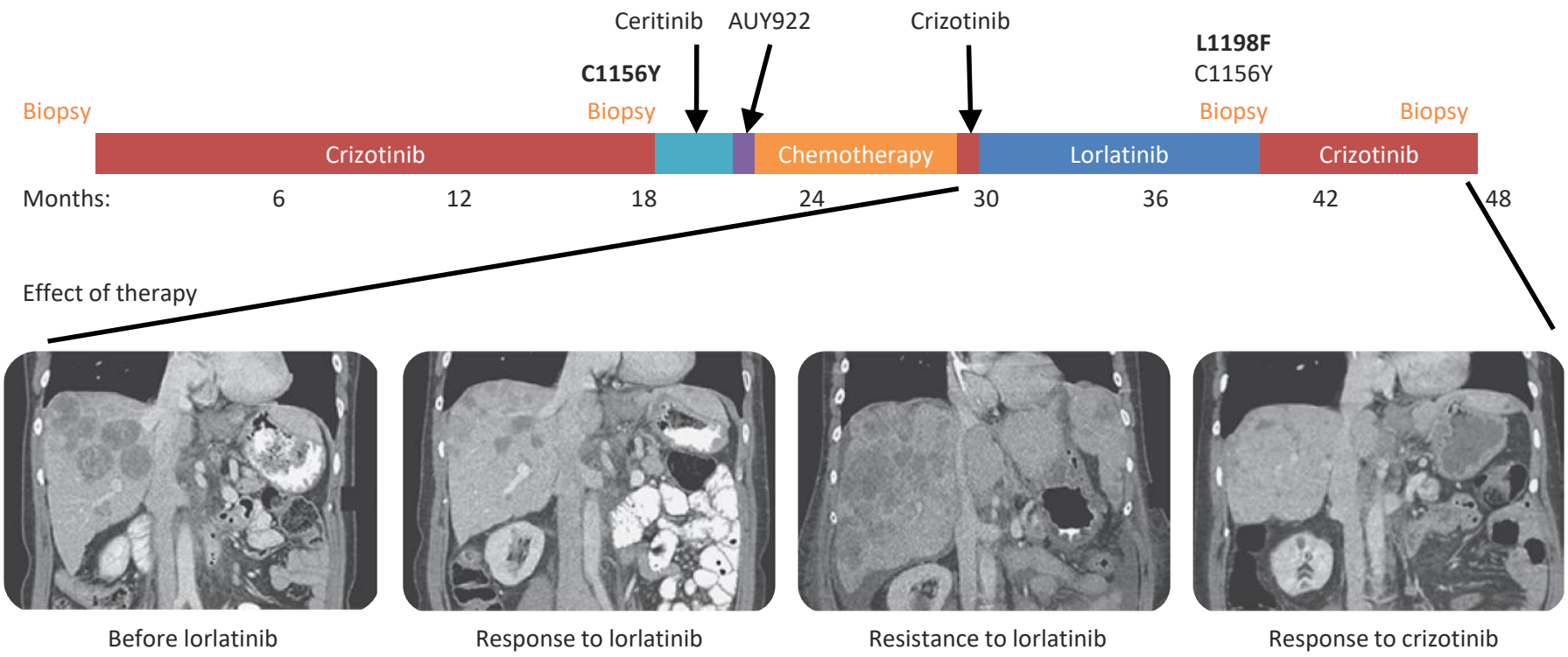
Patients at Risk										
Crizotinib	9	8	7	6	4	3	2	1	4	
Alectinib	8	4	1	2	6	5	4	3	1	2
	8	1	2	0	1	0	3	5	1	

*investigator-assessed; †All patients with CNS metastases at baseline, irrespective of radiotherapy

Shaw, et al. ASCO 2017

Perters S et al., NEJM 2017

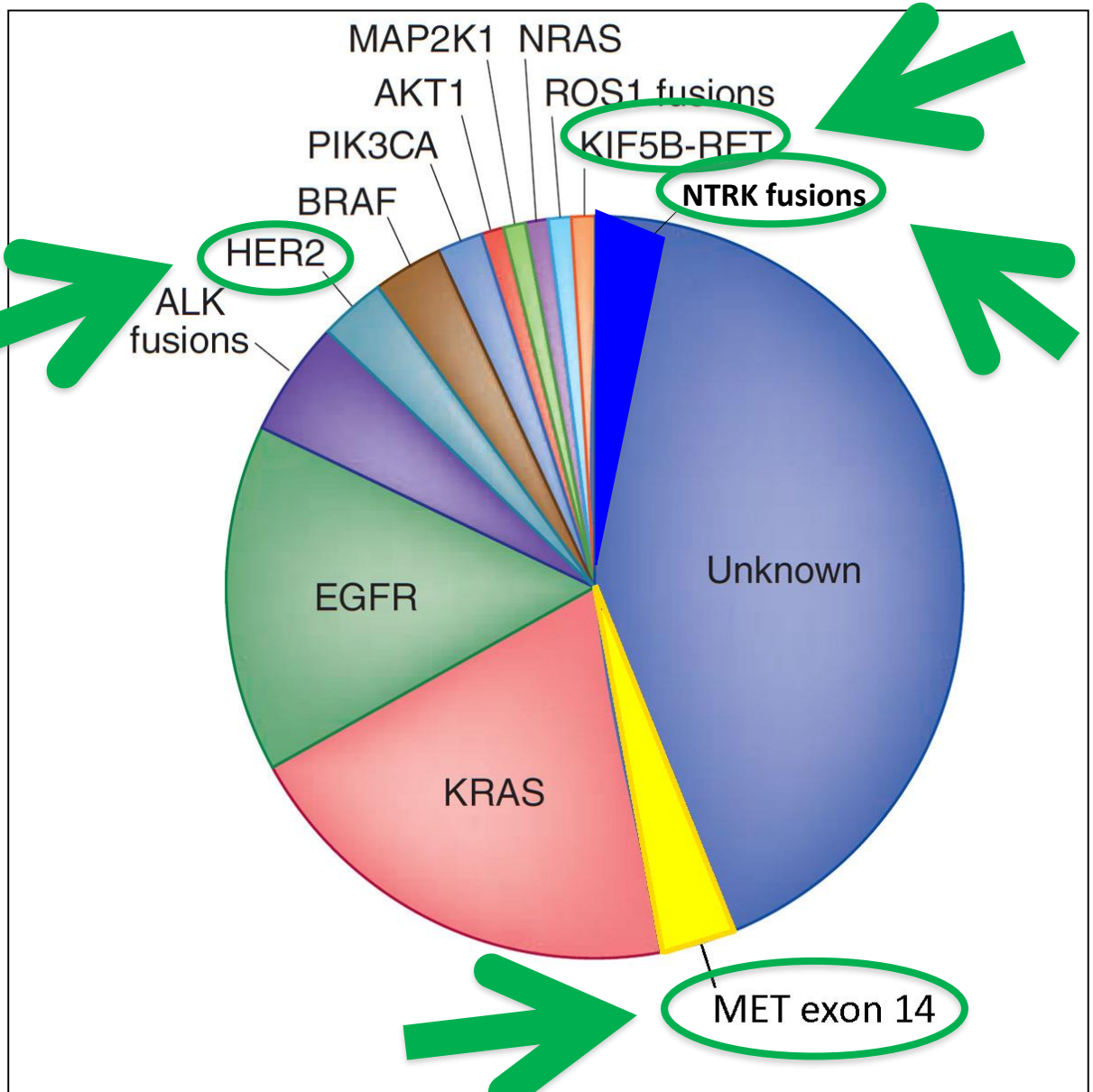
Genotipado repetido a lo largo de la enfermedad



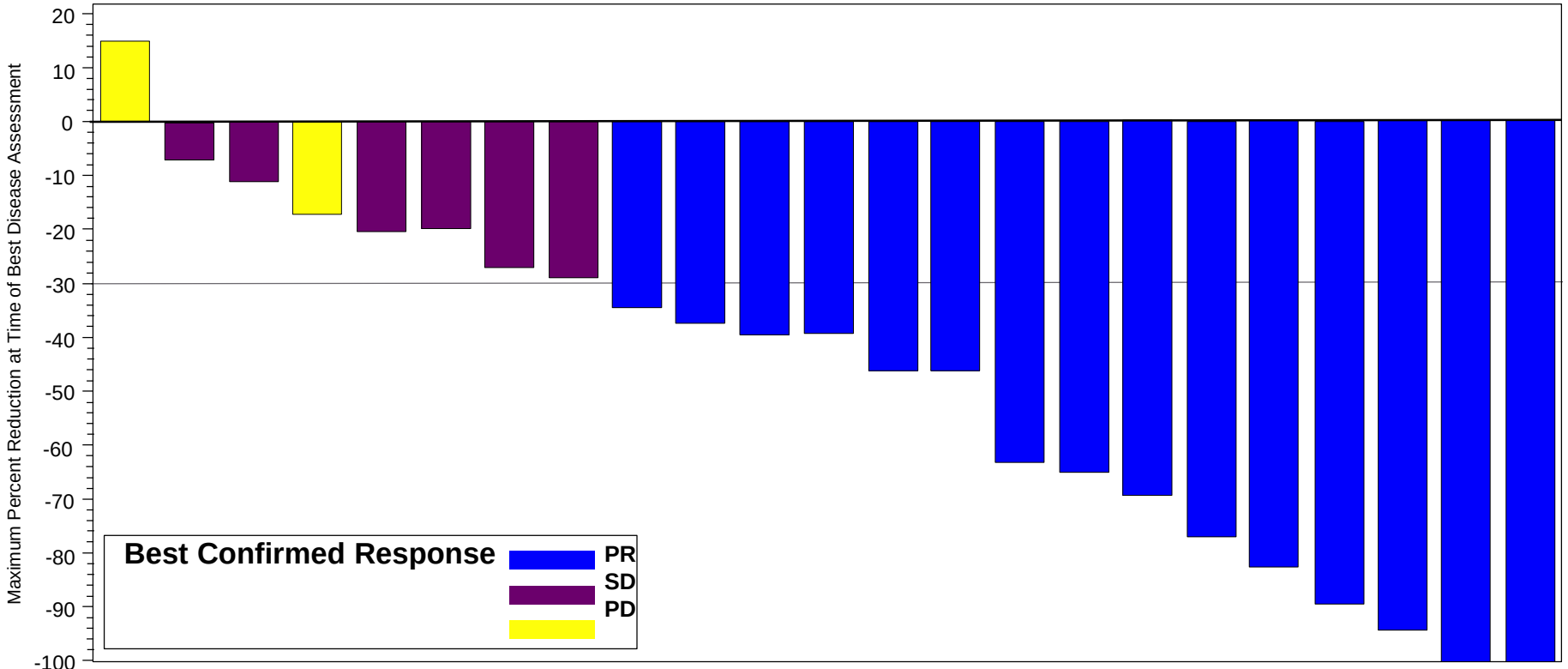
- Sequencing strategies should be flexible; in some cases revisiting previous agents may be the best approach

Shaw AT, et al. N Engl J Med 2016;374:54–61.

Adenocarcinoma de pulmón
Subtipos con tratamientos específicos



Phase 2 study of dabrafenib + trametinib in previously-treated BRAF V600E Mut+ NSCLC



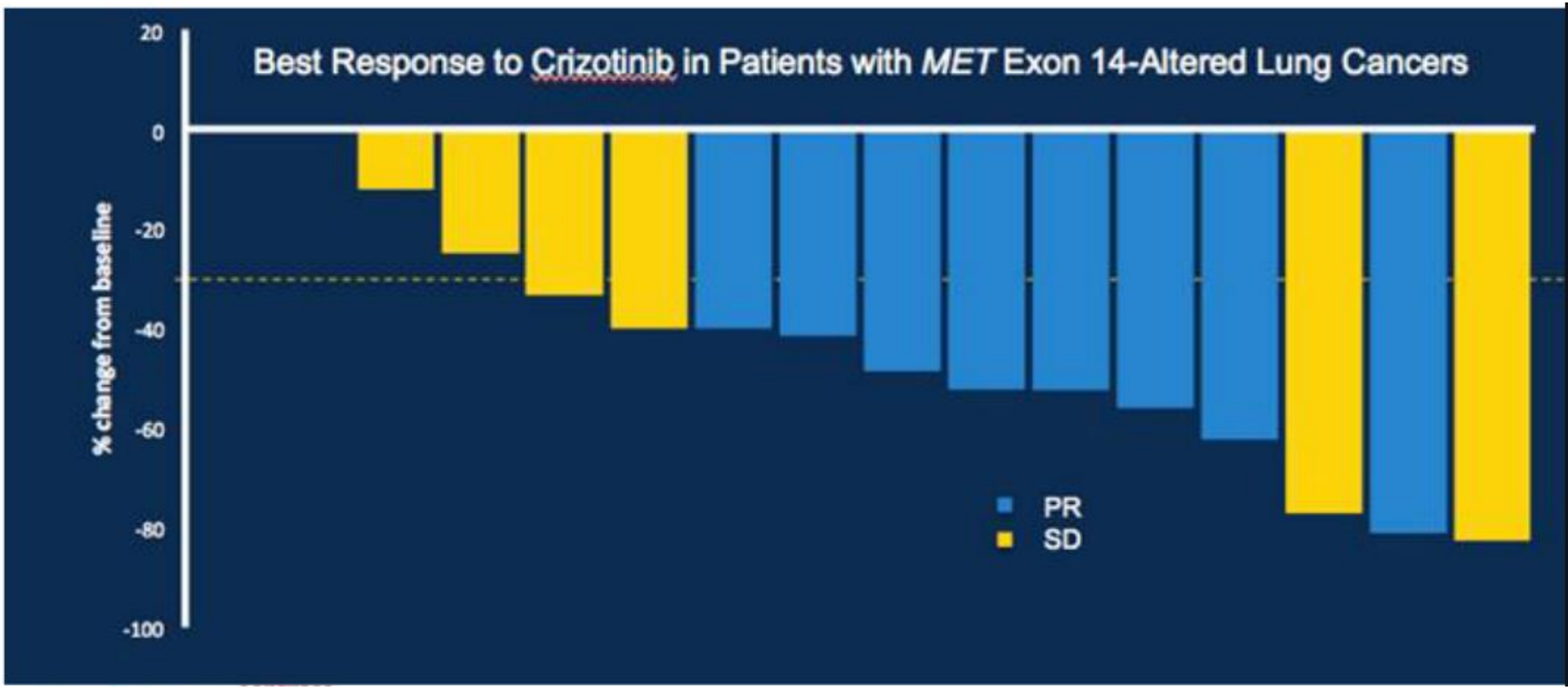
[a]1 patient discontinued at day 23 and did not have any post-baseline scans for efficacy.

- The median duration of response was not reached

D Planchard et al. J Clin Oncol 2015

MET mut+ NSCLC
Crizotinib Phase II Trial (Korea)

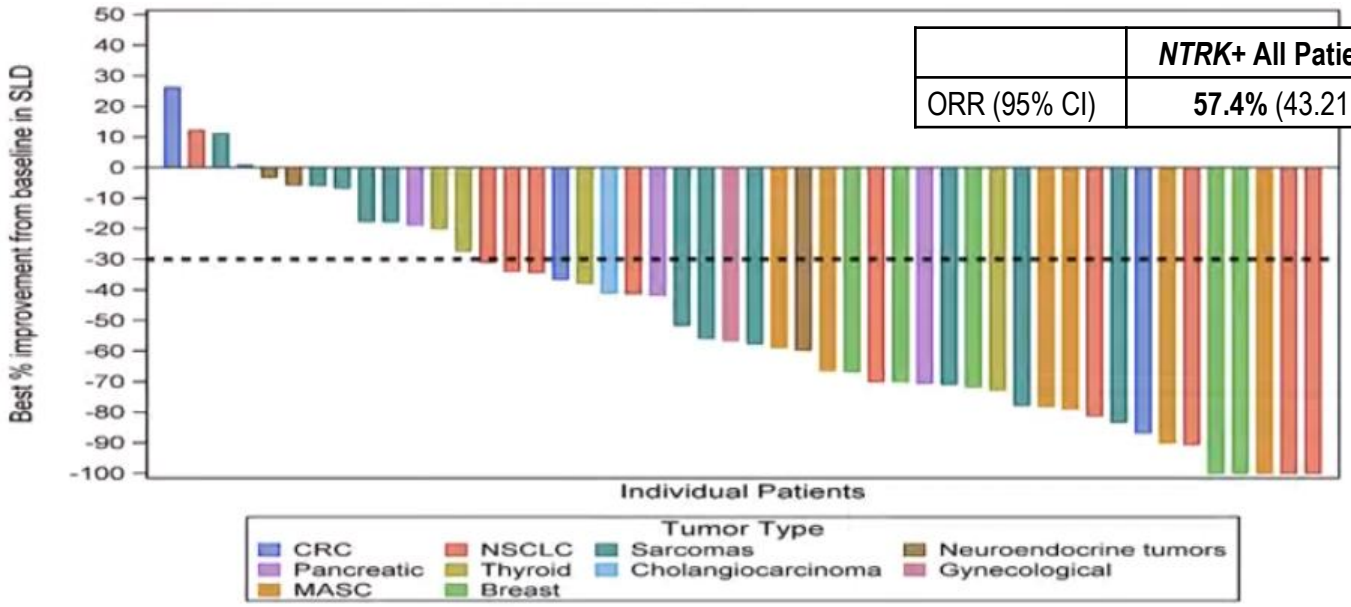
N= 21; RR= 44%



Drilon et al., ASCO 2016

Objective response rate by tumour type: patients with *NTRK* fusion-positive solid tumours (integrated analysis population; BICR)

Best percent change in tumour sum
(BICR, *NTRK* tumour agnostic)



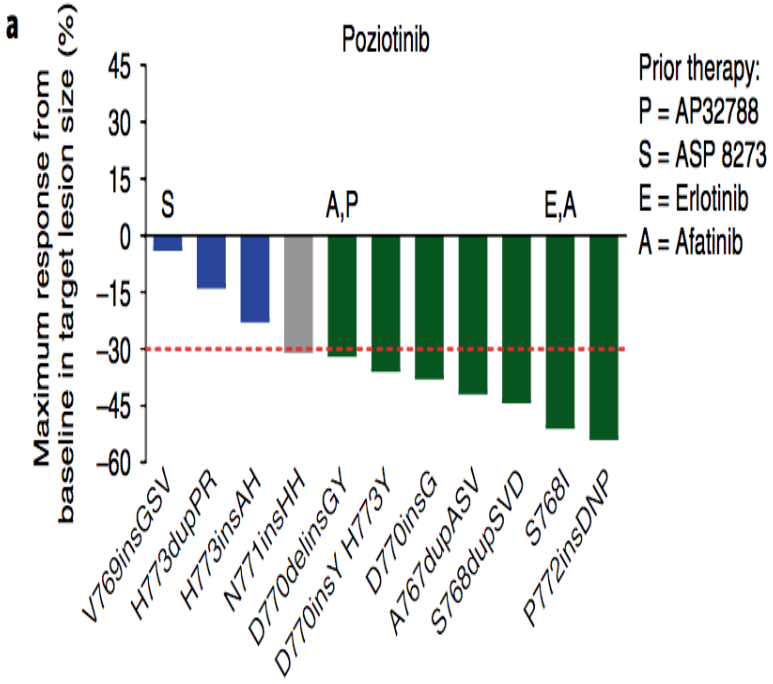
	NTRK+ All Patients (N=54)
ORR (95% CI)	**57.4%** (43.21, 70.77)*

Cut-off date: 31 May 2018
*Non-CR/PD, missing or unevaluable, n=6

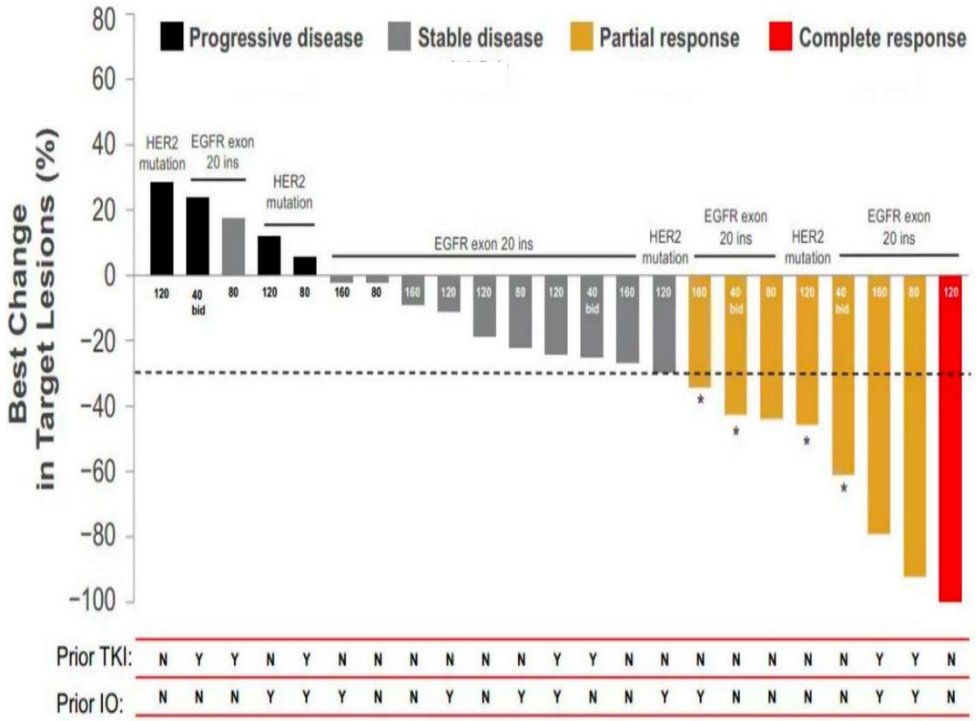
Mas Eficacia en Tumores con Adicción Oncogénica

The case of EGFR Exon 20 NSCLC

Poziotinib



TAK-788

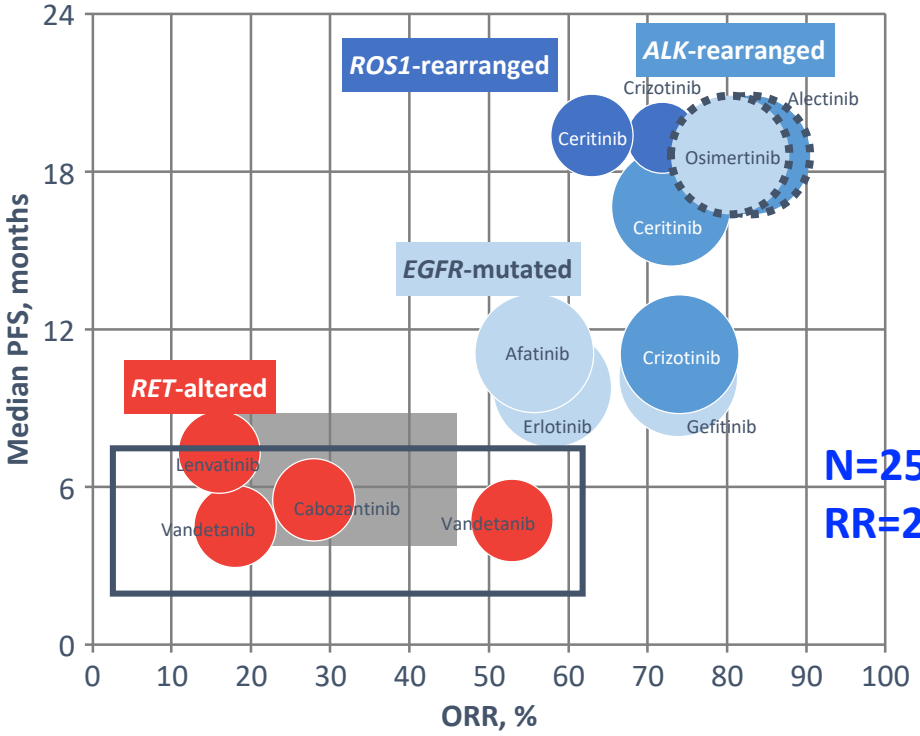


Robichaux JP, et al.Nat Med. 2018

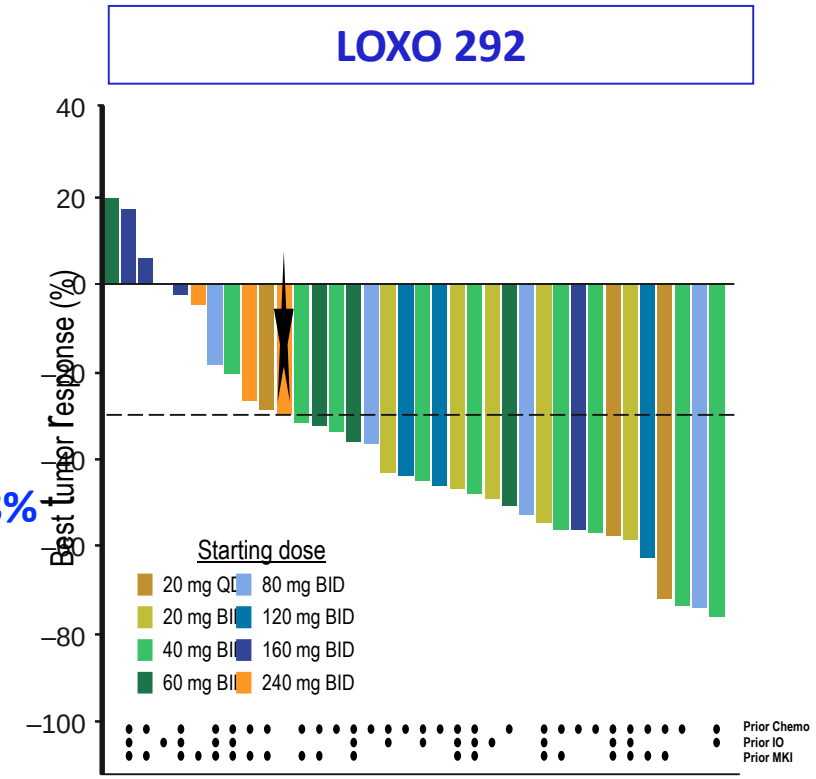
Doebele,ASCO 2018

Mas Eficacia en Tumores con Adicción Oncogénica

The case of RET+ NSCLC



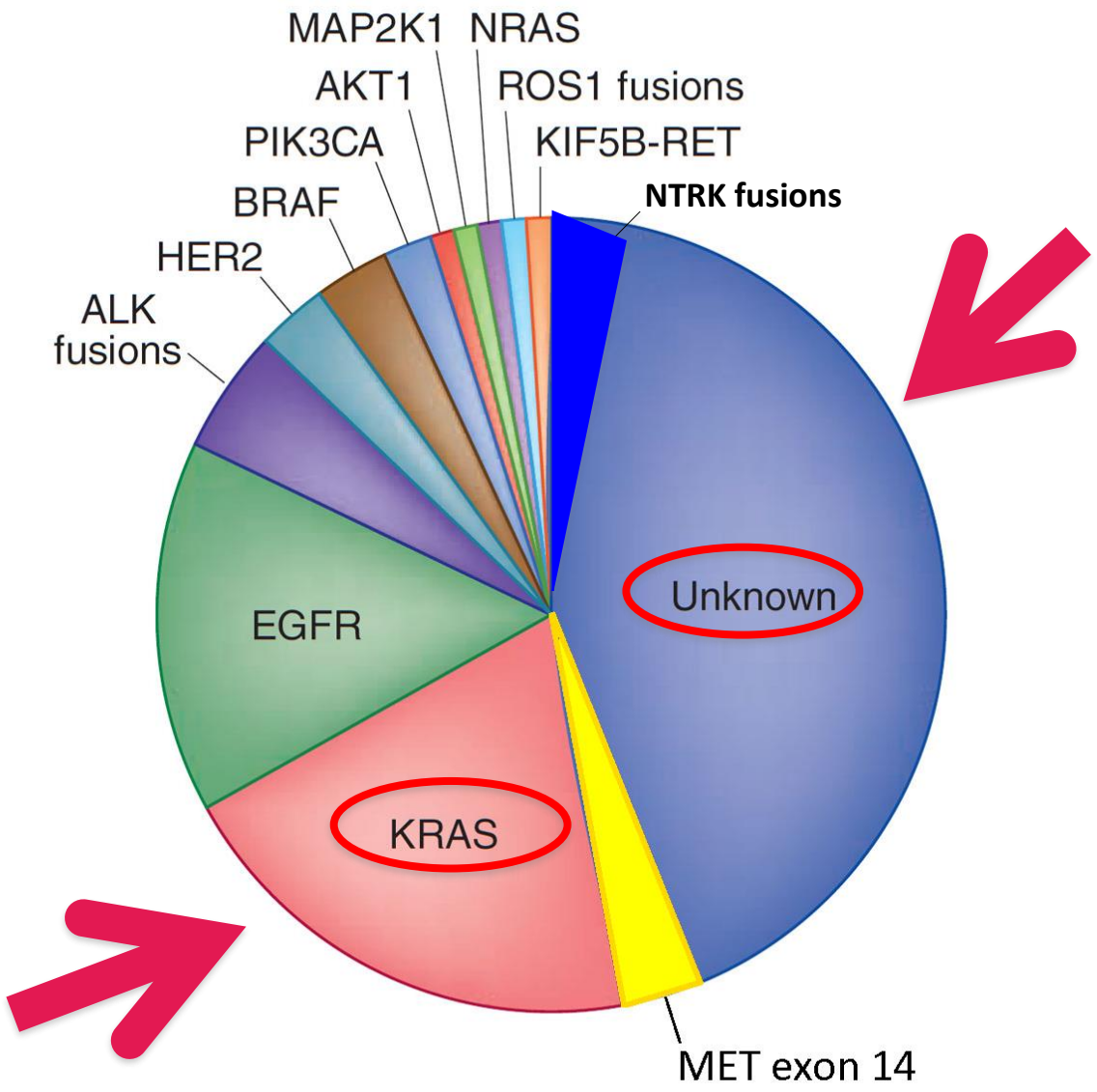
N=25
RR=28%



Drilon A et al. *Nat Rev Clin Oncol*. 2018;15(3):151-167.
Herbst RS et al. *Nature*. 2018;553(7689):446-454.

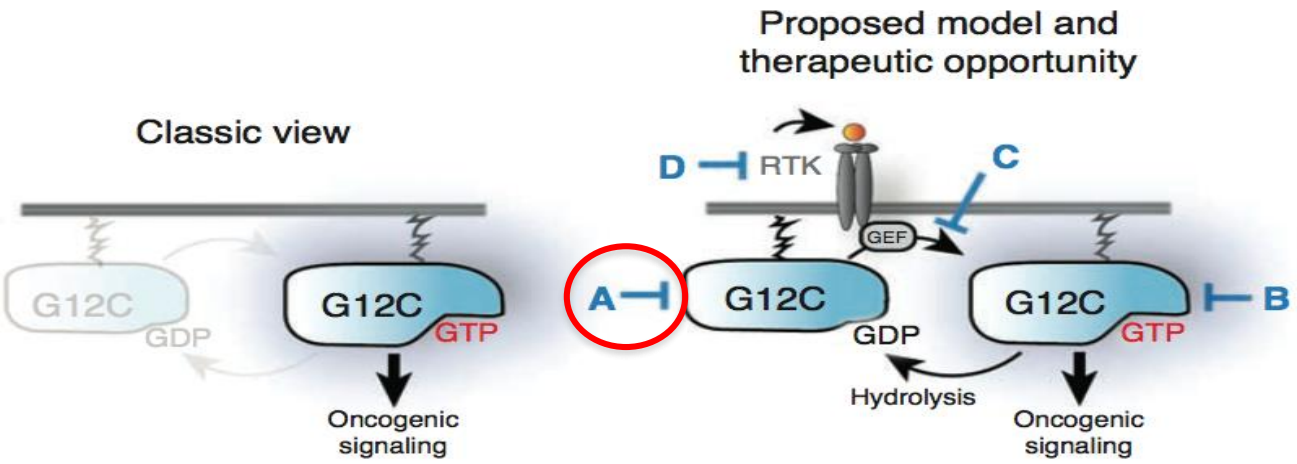
Oxnard et al. WLCC 2018.

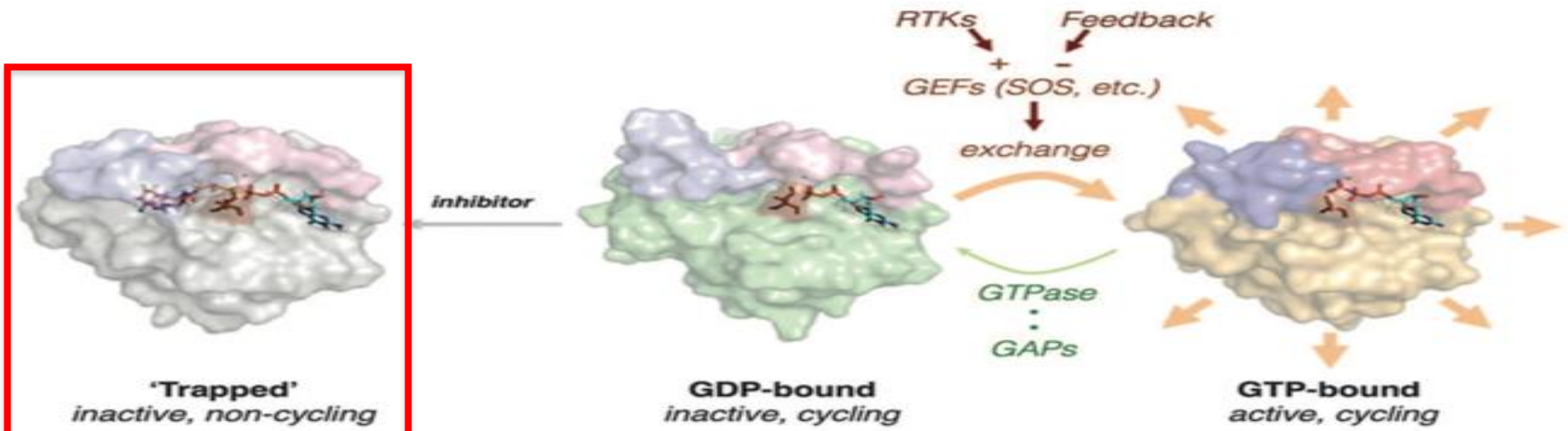
Adenocarcinoma de pulmón
Subtipos con tratamientos específicos



Targeting Kras…

The case of G12C KRAS covalent inhibitors





Lito et al. Science 2016
Patricelli et al. Cancer Discov 2016

Genes supresores de tumores…

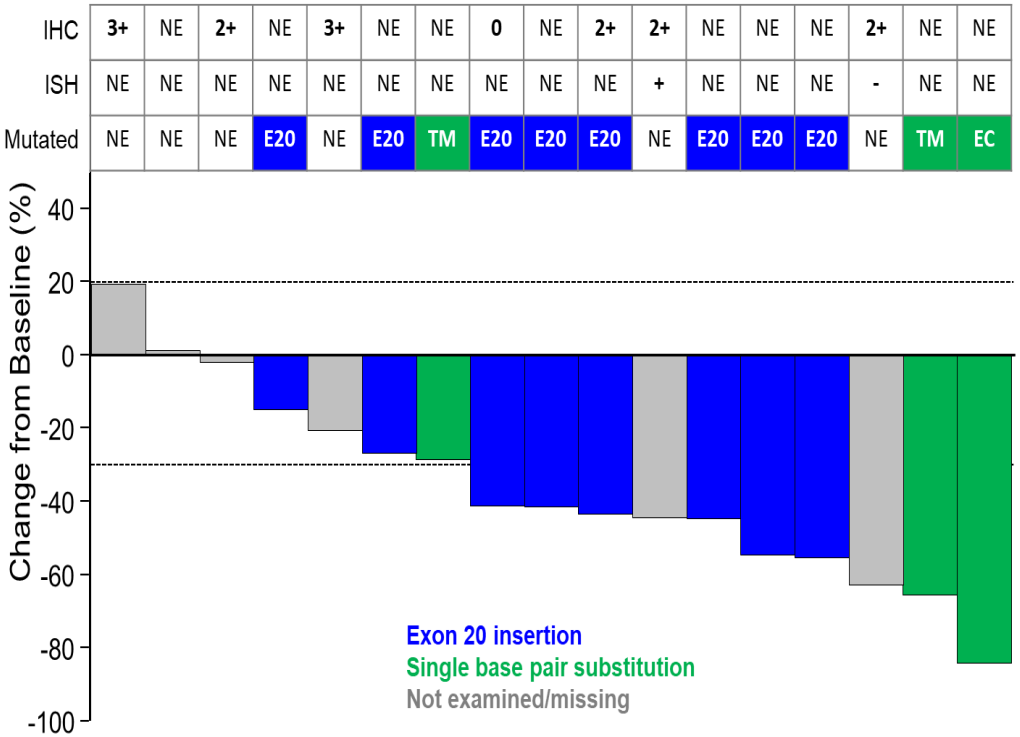
- KRAS
- P53 pathway
- LKB1(STK11)
- Oxidative stress pathway…KEAP1/NFE2L2
- Nucleosome remodeling…ARID1A/ARID1B/ARID2/SMARCA4
- Histone modifiers…SETD2, KMT2D/C

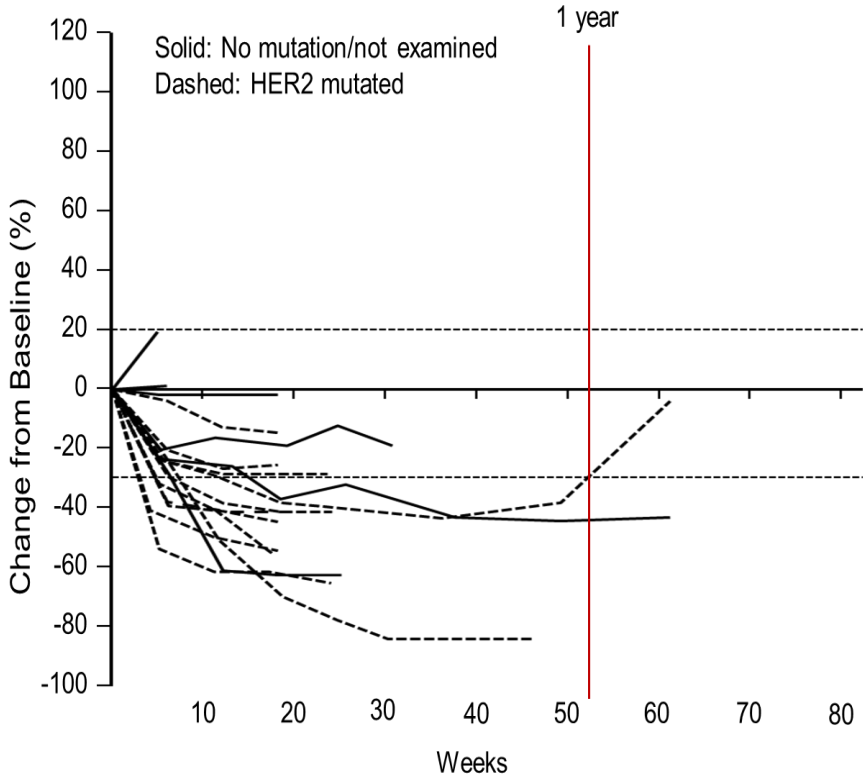
Cys-targeting compounds			
CP-31398	Protein screen	Styrylquinazoline	Michael acceptor
PRIMA-1	Cellular screen	Quinuclidinone	Converted to MQ, which binds p53 by Michael addition
APR-246	Cellular screen	Quinuclidinone	Converted to MQ, which binds p53 by Michael addition
MIRA-1	Cellular screen	Maleimide	Michael acceptor
STIMA-1	Cellular screen	Styrylquinazoline	Michael acceptor
3-Benzoylacrylic acid	Protein screen based on p53 thermostability	Benzoylacrylate	Binds p53 by Michael addition
KSS-9	Rational design	Piperlongumine	Microtubule poison; redox; Michael acceptor
PK11007	Protein screen	Sulfonylpyrimidine	Binds p53 by nucleophilic aromatic substitution
Zn^{2+} chelators			
ZMC1	Database analysis	Thiosemicarbazone	Zn^{2+} chelator
COTI-2	*In silico* screen	Thiosemicarbazone	Zn^{2+} chelator
Peptides			
pCAPs	Phage display	Peptides	Bind p53; promote refolding
Reacp53	Rational design	Peptide	Disrupts mutant-p53 aggregates
Other types of compounds			
RETRA	Cellular screen	2-(4,5-Dihydro-1,3-thiazol-2-ylthio)-1-(3,4-dihydroxyphenyl) ethanone	Disrupts mutant-p53–p73 complexes
PK083	Molecular docking and/or rational design	Carbazole	Binds and stabilizes p53-Y220C
P53R3	DNA-binding assay	Quinazoline	Restores DNA binding to mutant p53
SCH529074	DNA-binding assay	Piperazinylquinazoline	Binds p53
PK7088	Rational design	Pyrazole	Binds and stabilizes p53-Y220C
Stictic acid	Modelling	1,4-Dihydroxy-10-methoxy-5,8-dimethyl-3,7-dioxo-1,3-dihydro-7H-2,6,12-trioxabenzo [5,6]cyclohepta[1,2-e] indene-11-carbaldehyde	Binds p53 *in silico*
Chetomin	Cellular reporter screen	Epidithiodioxopiperazine	HSP40-mediated refolding of p53-R175H

Bykov, Eriksson, Bianchi and Wiman, Nature Rev Cancer, 2018

En el Fúturo Utilizaremos mas ADCs…

DS-8201 - Tumor Shrinkage by HER2 Status





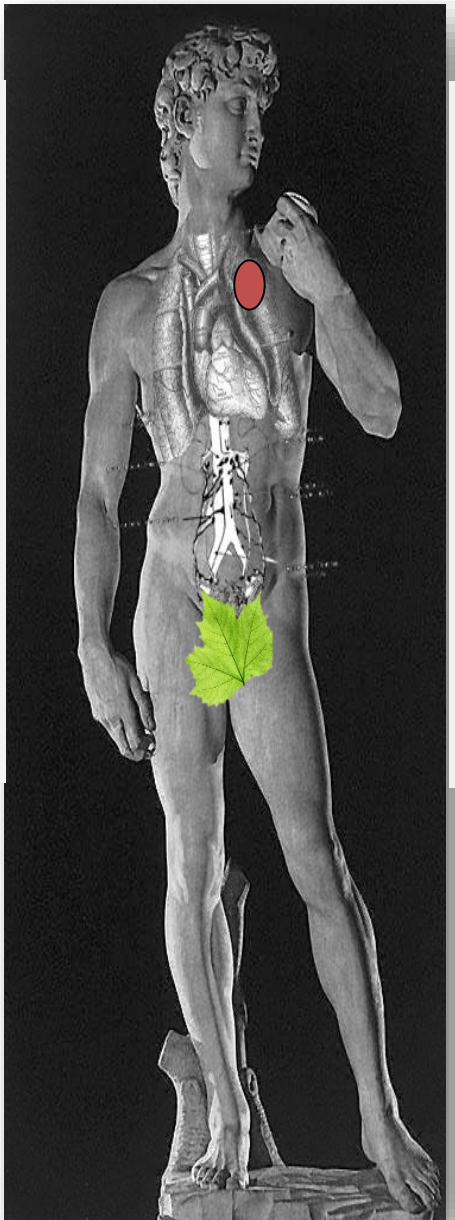
IHC by local laboratory testing.
E20, exon 20 insertion; EC, single base pair substitution at extracellular domain; IHC, immunohistochemistry; ISH, in situ hybridization; NSCLC, non-small cell lung cancer; NE, not examined or missing; TM, single base pair substitution in transmembrane domain.

Tsurutani et al. WLCC 2018

Una visión diferente del cáncer…

Visión de la Oncología Tradicional

Un CANCER que crece



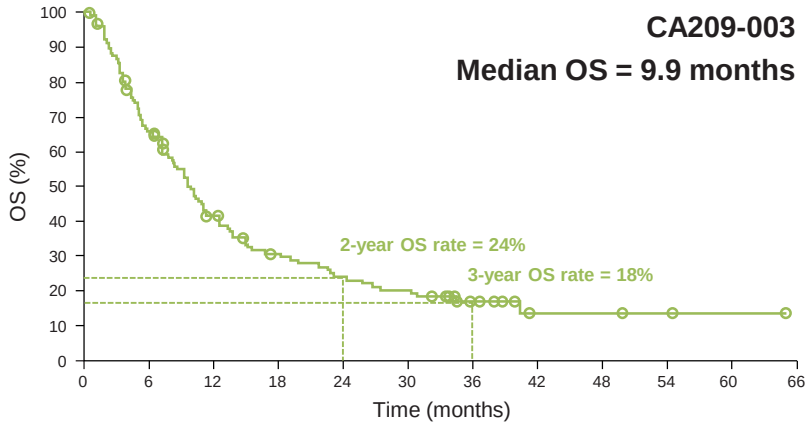
Visión de la Inmuno-Oncologia

Un CUERPO Que deja crecer el cáncer

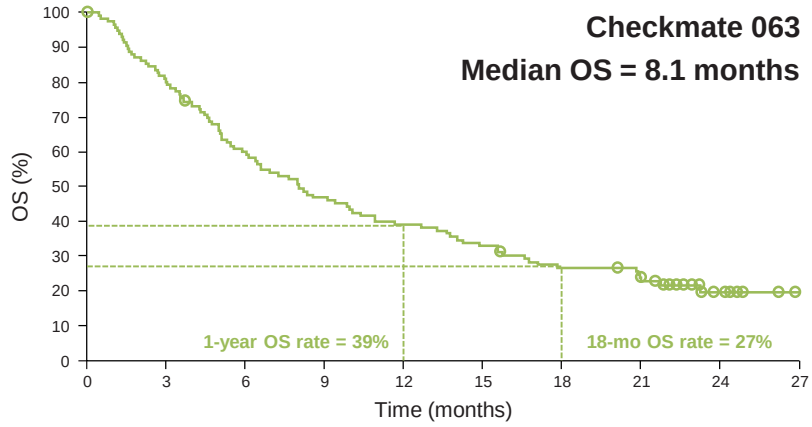
Miguel Angel 1500

Inhibidores de PD-1/PD-L1: Nivolumab
Impacto en Supervivencia en CNMP

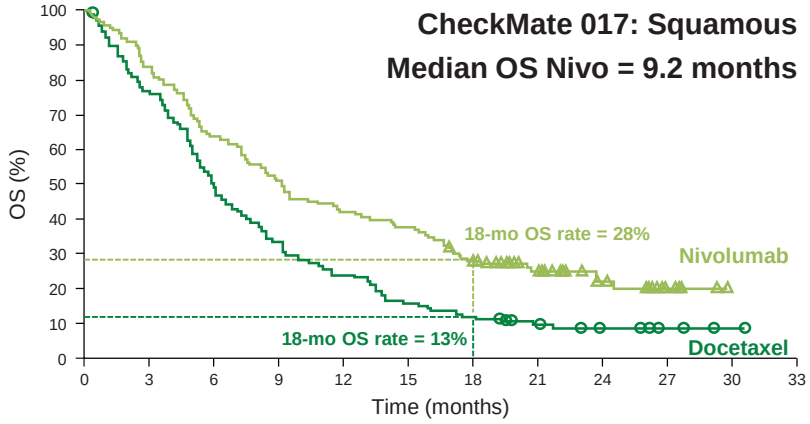
Phase 1 Data[1]

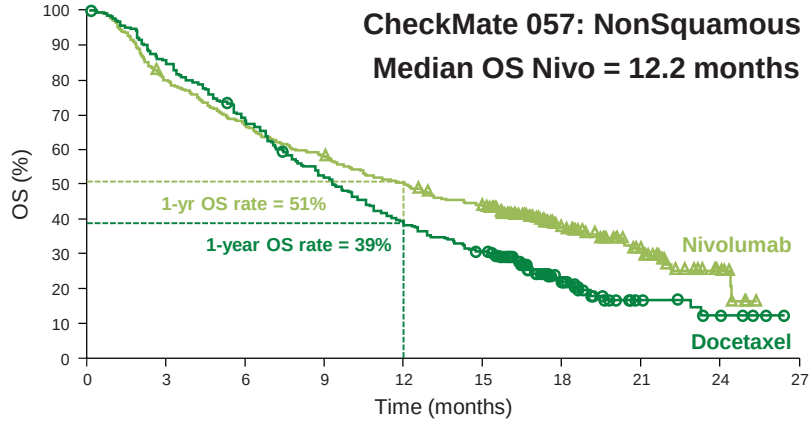


Phase 2 Data[2]



Phase 3 Data[3,4]

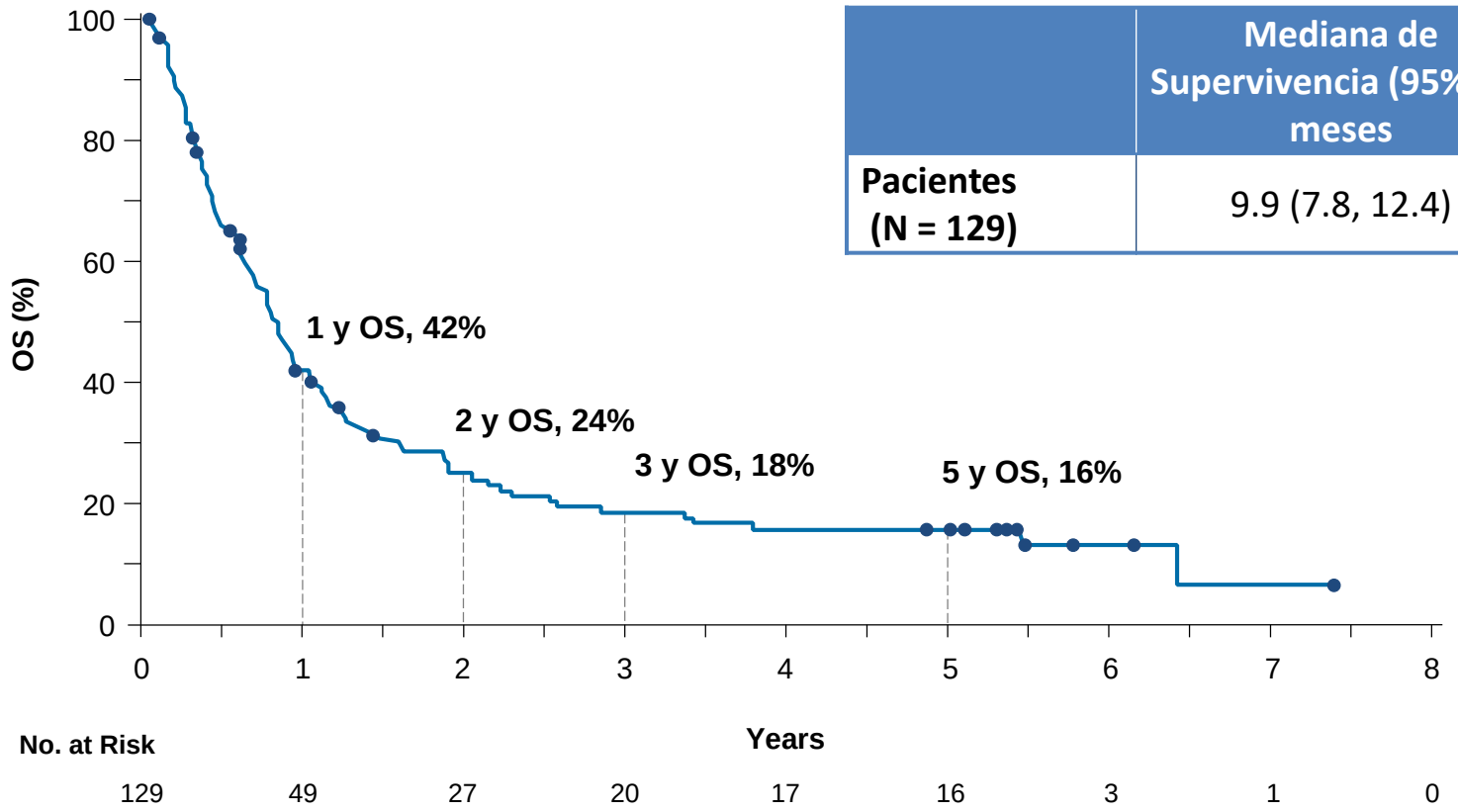




Gettinger S, JCO 2015, Brahmer J et al NEJM 2015

Paz-Ares L, et al. ASCO 2015,. Borghaei , Paz-Ares L et al. NEJM 2015

Cáncer de Pulmón Tratado con Nivolumab
Supervivencia a 5 años

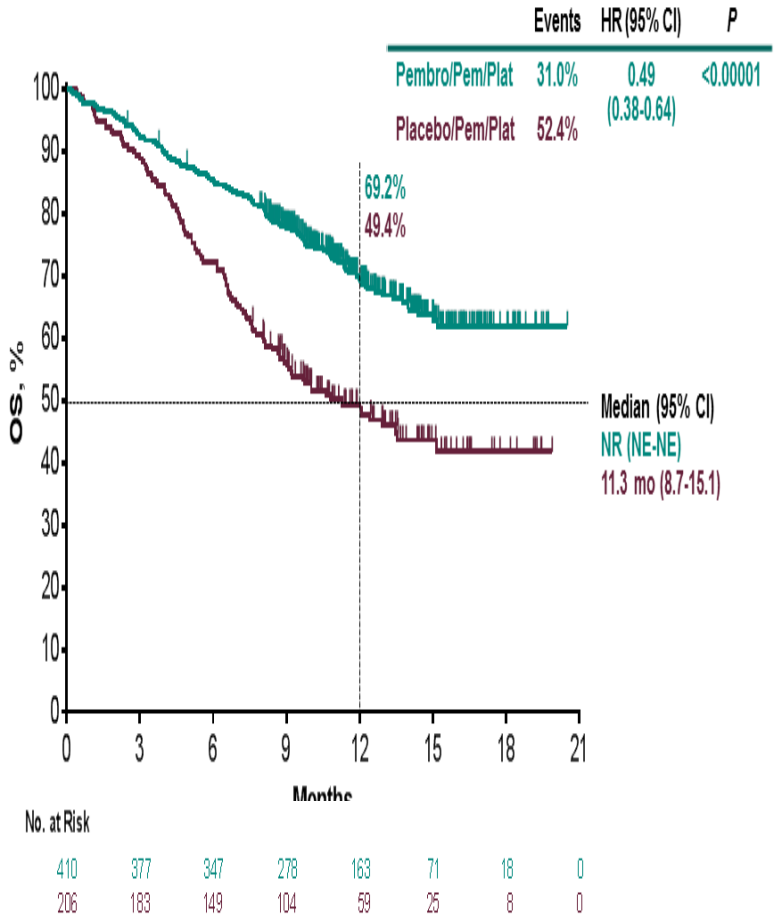


	Mediana de Supervivencia (95% CI), meses
Pacientes (N = 129)	9.9 (7.8, 12.4)

Brahmer et al. AACR 2017

Chemo ± Pembrolizumab in NSCLC

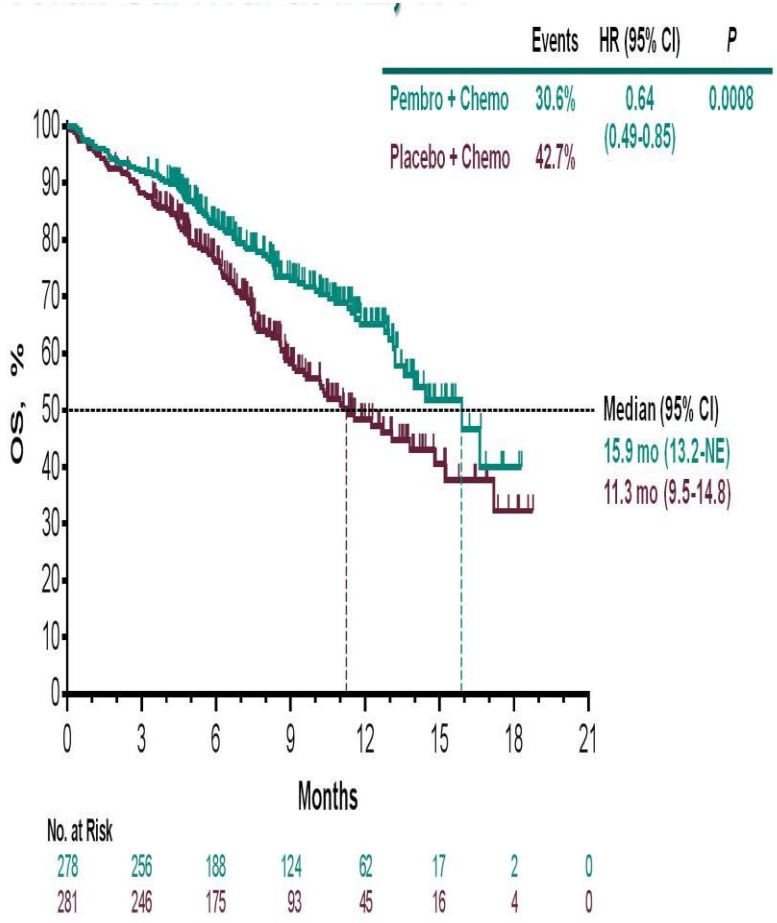
Non SCC KeyNote 189 Trial



Data cutoff date: Nov 8, 2017.

Ghandi et al., NEJM 2018

SCC KeyNote 407 Trial



Data cutoff date: Apr 3, 2018.

Paz-Ares et al., NEJM 2018

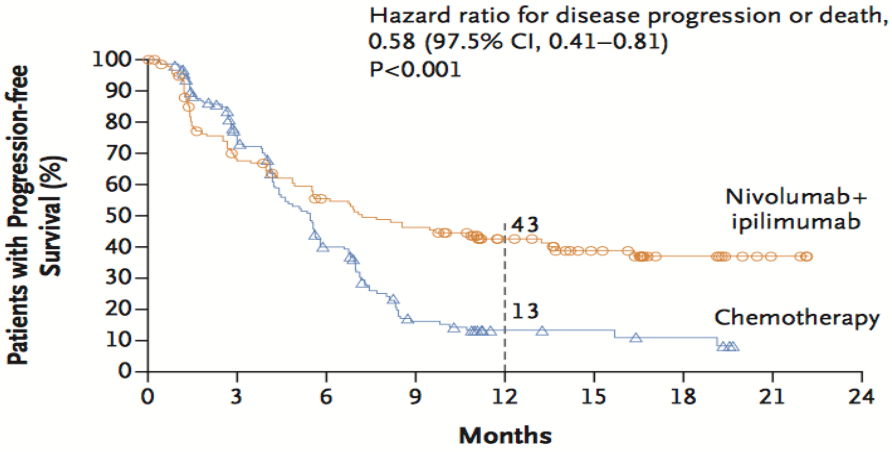
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab plus Ipilimumab in Lung Cancer with a High Tumor Mutational Burden

M.D. Hellmann, T.-E. Ciuleanu, A. Pluzanski, J.S. Lee, G.A. Otterson, C. Audigier-Valette, E. Minenza, H. Linardou, S. Burgers, P. Salman, H. Borghaei, S.S. Ramalingam, J. Brahmer, M. Reck, K.J. O'Byrne, W.J. Geese, G. Green, H. Chang, J. Szustakowski, P. Bhagavatheeswaran, D. Healey, Y. Fu, F. Nathan, and L. Paz-Ares

ABSTRACT



No. at Risk									
Nivolumab + ipilimumab	139	85	66	55	36	24	11	3	0
Chemotherapy	160	103	51	17	7	6	4	0	0

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Hellmann at the Thoracic Oncology Service, Division of Solid Tumor Oncology, Department of Medicine, Memorial Sloan Kettering Cancer Center, 885 2nd Ave., New York, NY 10017, or at hellmanm@mskcc.org; or to Dr. Paz-Ares at the Medical Oncology Department, Hospital Universitario 12 de Octubre, Av. de Córdoba SN, 280141 Madrid, Spain, or at lpazaresr@seom.org.

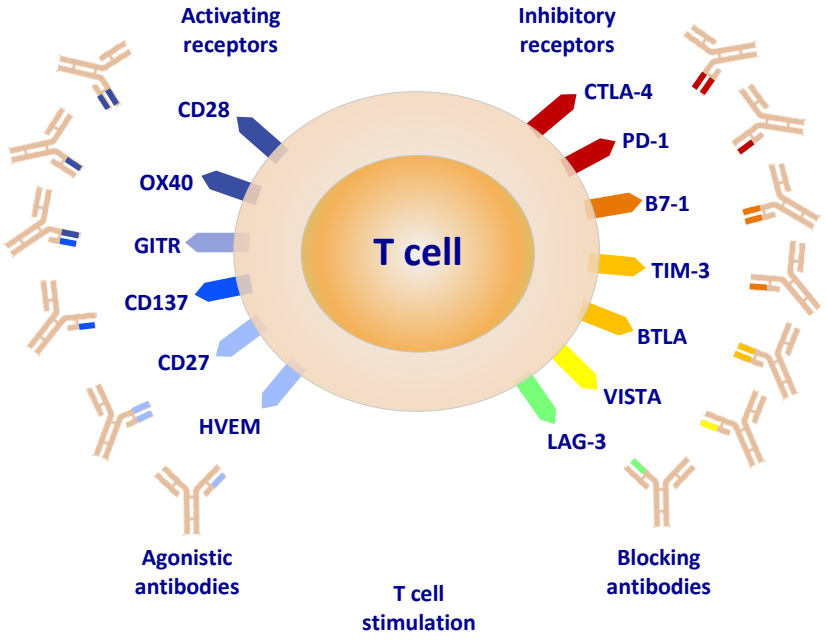
A list of investigators in part 1 of the CheckMate 227 trial is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on April 16, 2018, at NEJM.org.

DOI: 10.1056/NEJMoa1801946

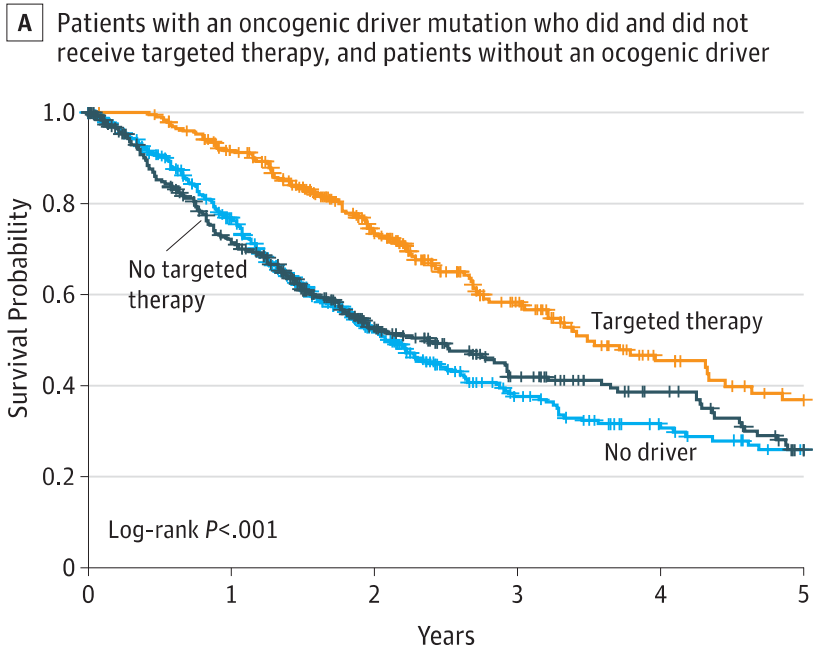
Nuevas Inmunoterapias

- Immune checkpoint inhibitors
- Angiogenesis
- CAR T-cells
- Dendritic cells
- Tumor-associated macrophages
- Regulatory immune cells
- Cytokines and chemokines
- Combination therapies



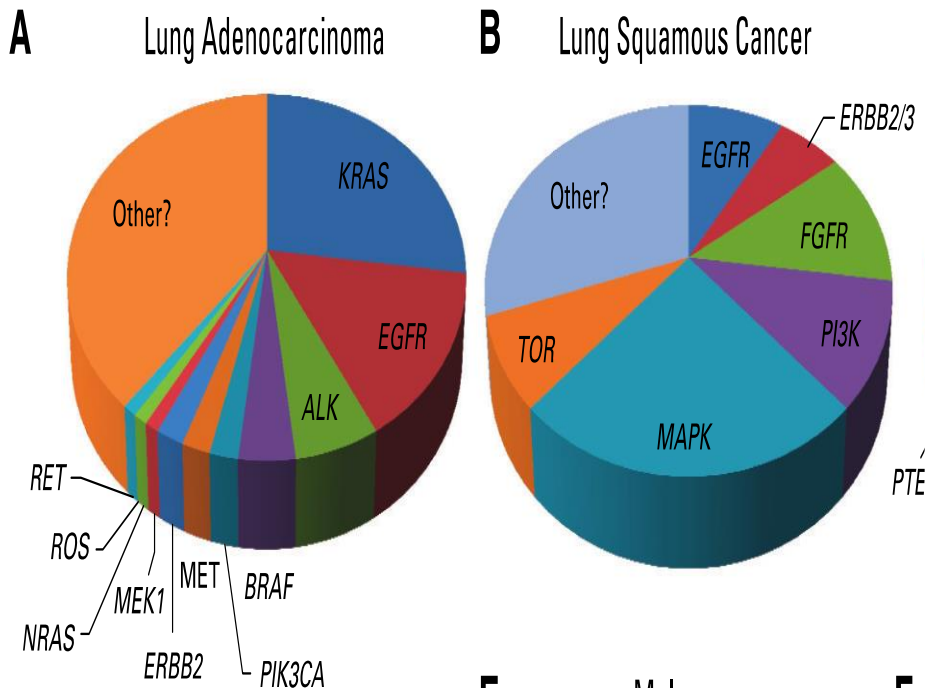
Tang H et al. Cancer Lett 2015;370(1):85-90 ; Pitt JM et al. Ann Oncol 2016;27(8);1482-1492

Adicción Oncogénica y Tratamiento Selectivo Cáncer de Pulmón



No. at risk

Patients with oncogenic driver						
No targeted therapy	318	205	110	64	43	20
Targeted therapy	260	225	143	72	36	23
Patients with no driver	360	250	122	59	36	23



Kris et al., JAMA 2015.

Oncología Personalizada
Como hacerla llegar a todos los pacientes?

- Muestras adecuadas de tumor
- Equipos expertos
- Tecnología
- Bioinformáticos clínicos
- Respuesta adecuada en tiempo
- Programas de control de calidad
- Programa innovador de EECC

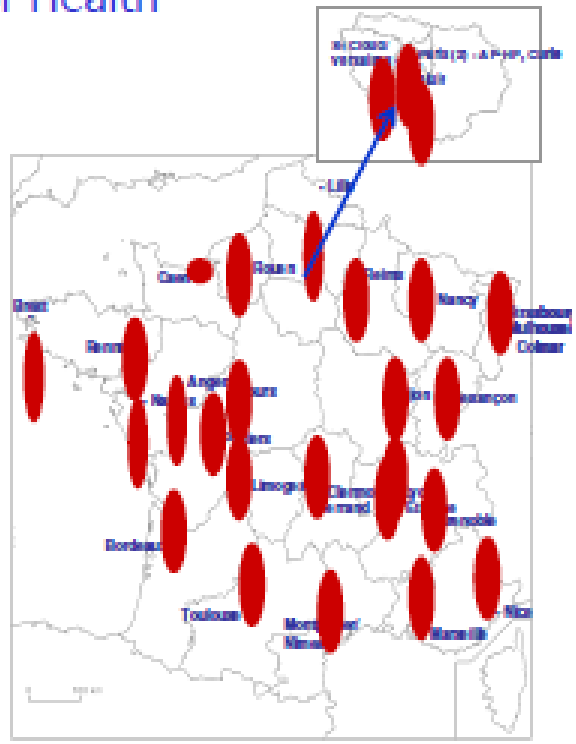
Ensuring equity of access to innovation: France organisation of molecular platforms for personalised medicine

Provides nation-wide molecular diagnostic tests

The programme is operated by the INCa/Ministry of Health since 2006

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

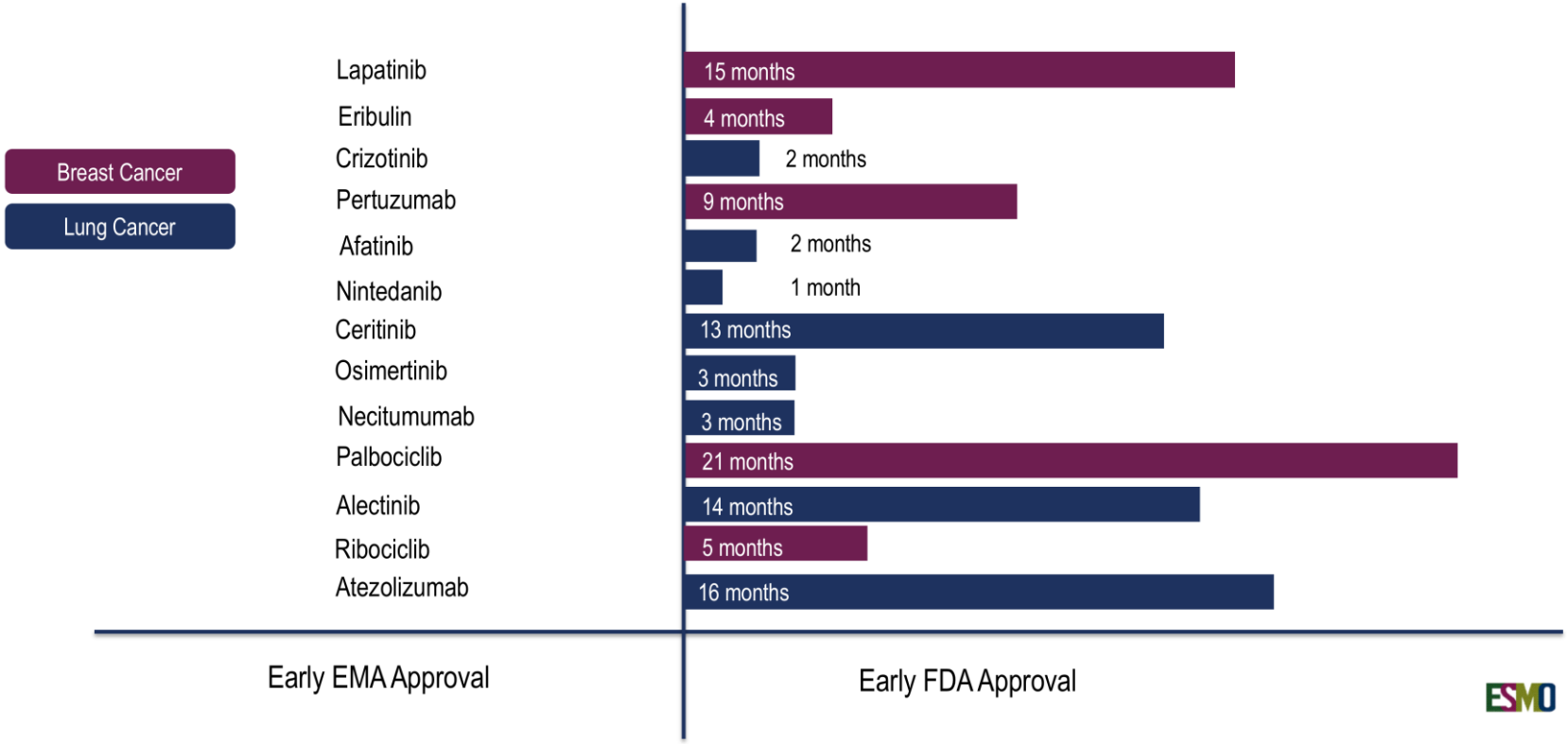
- **28 regional platforms**
  - Partnerships between several laboratories located in University hospitals and cancer centres
  - Regional organization
  - Cooperation between pathologists and biologists



Gracias

lpazaresr@seom.org

New medicine approval speed: FDA vs EMA 2007-2017

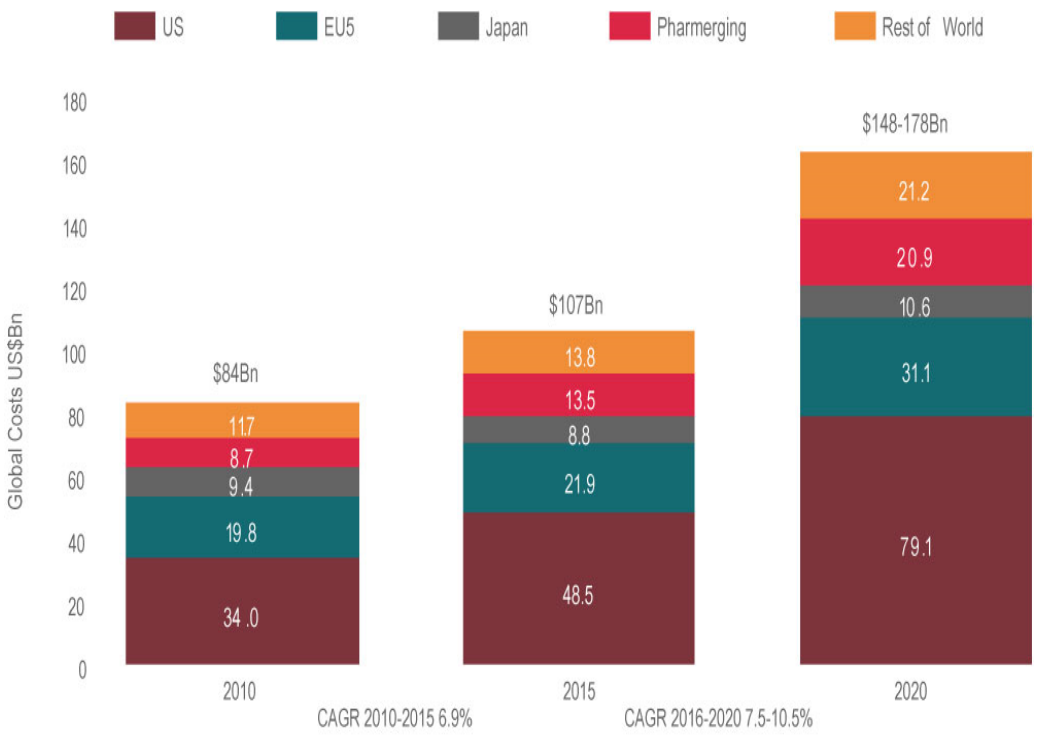


Where we are today
Global cancer costs

In the last 5 years:

- Costs of cancer medicines increased by 72% over 2010 in the US
- By 50% in countries other than the US

Global Oncology Costs and Growth, 2010 – 2020



IMS Health, MIDAS, Dec 2015; Market Prognosis, Mar 2016; IMS Institute for Healthcare Informatics, May 2016, Tabernero, ESMO 2017

Availability of NSCLC targeted agents (EU)

ESMO Survey : NSCLC Targeted Agents

Western Europe

Country:	LUNG CANCER : Biological and Bone Formulary and Cost					
	Erlotinib	Gefitinib	Crizotanib	Pamidronate	Zolederonate	Denosumab
Austria						
Belgium						
Cyprus						
Denmark						
Finland						
France						
Germany						
Greece						
Holland						
Ireland						
Israel						
Italy						
Luxembourg						
Norway						
Portugal						
Spain						
Sweden						
Switzerland						
Turkey						
United Kingdom						

Free
<25% cost
25-50% cost
Discount <50%
Full cost
Not available

Eastern Europe

Country:	LUNG CANCER : Biological and Bone Formulary and Cost					
	Erlotinib	Gefitinib	Crizotanib	Pamidronate	Zolederonate	Denosumab
Albania						
Armenia						
Belarus						
Bosnia and Herzegovina						
Bulgaria						
Croatia						
Czech Republic						
Estonia						
Georgia						
Hungary						
Kosovo, Republic of						
Kyrgyzstan						
Latvia						
Lithuania						
Macedonia						
Malta						
Montenegro						
PolandR						
Romania						
Russian Federation						
SerbiaR						
Slovenia						
Slovakia						
Ukraine						
Uzbekistan						

Cherny N, et al. Ann Oncol 2016.

Algoritmo Terapéutico
Cáncer de Pulmón en 2020