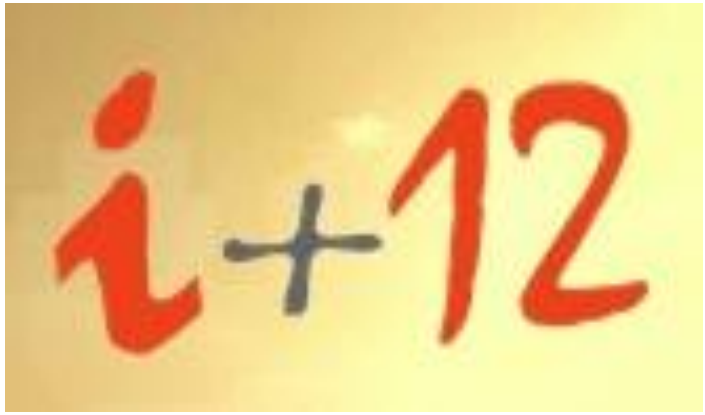


cnio
Centro Nacional de Investigaciones Oncológicas

UNIVERSIDAD COMPLUTENSE MADRID

Medicina Personalizada en Oncología: el Ejemplo del Cáncer de Pulmón

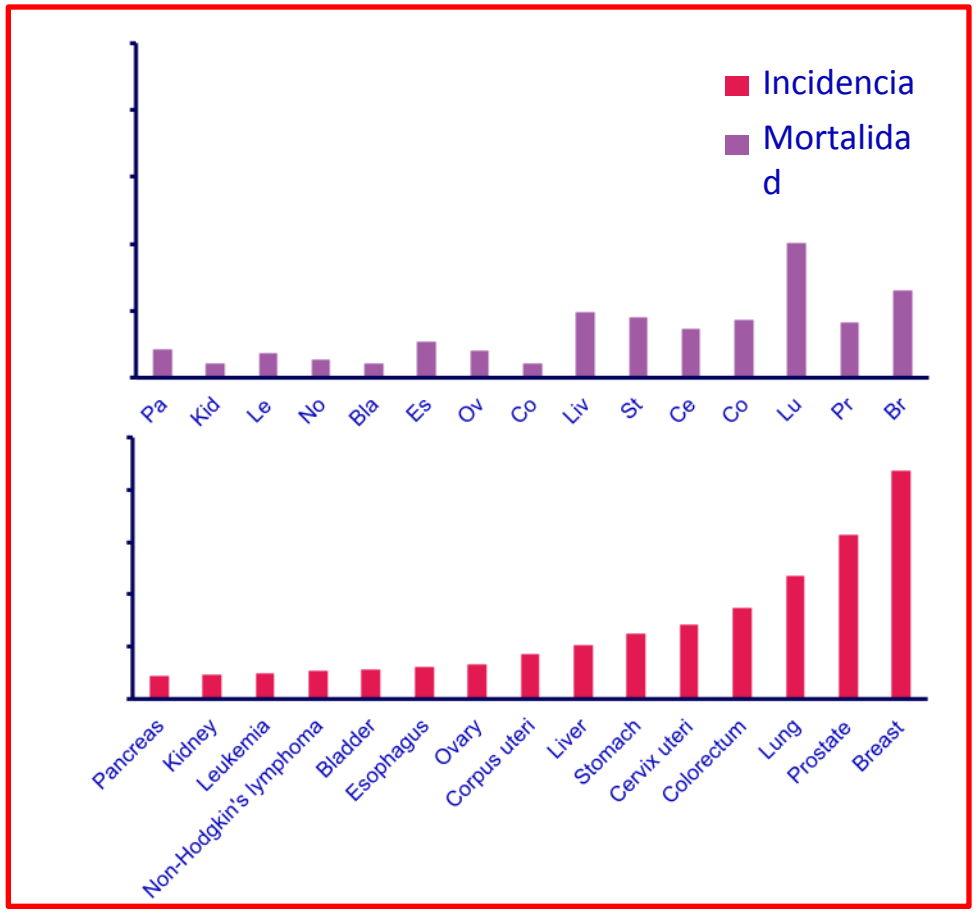
Luis Paz-Ares

Hospital Universitario Doce de Octubre,

Madrid, Spain

El Cáncer de pulmón es tumor más letal

Tasas de Incidencia y Mortalidad ajustadas por edad (GLOBOCAN database[1], 2012)



- Mortalidad actual >1,6 millones/año
- Se expera un aumento de la mortalidad por cáncer de pulmón de 1,8 en los siguientes 20 years[1]

1. Ferlay J et al. GLOBOCAN 2012. http://globocan.iarc.fr/Pages/fact_sheets_population.aspx.

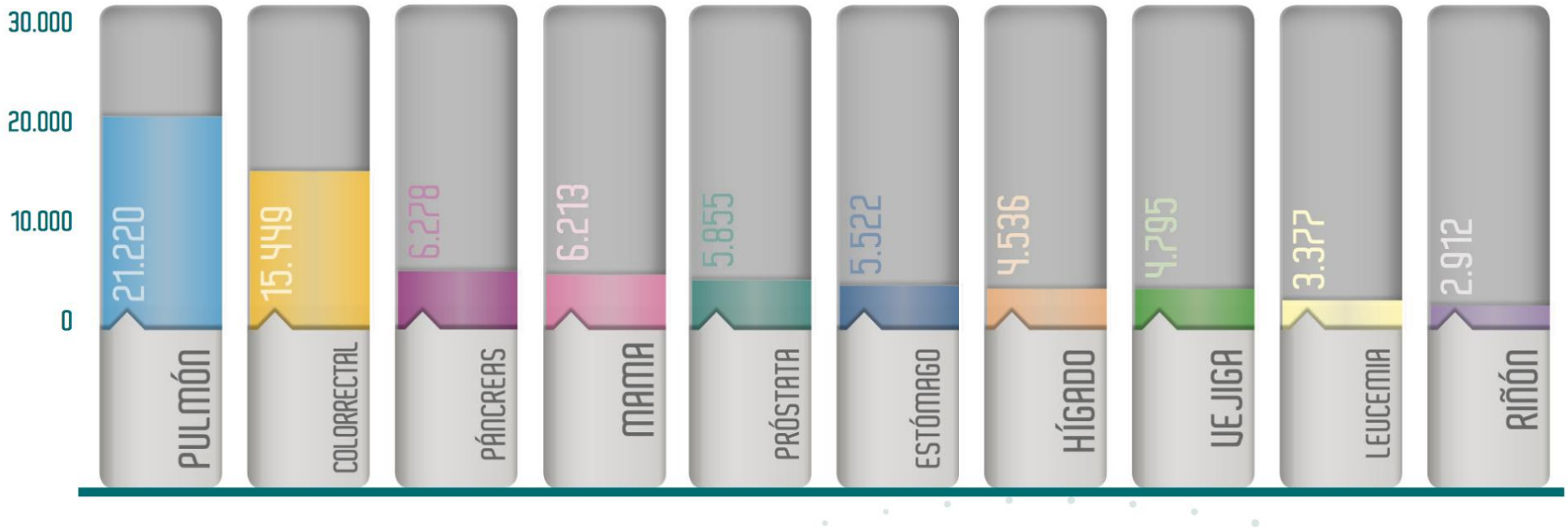
Epidemiología del cáncer

Incidencia Mundial (2012)

Incidencia en España (2015)

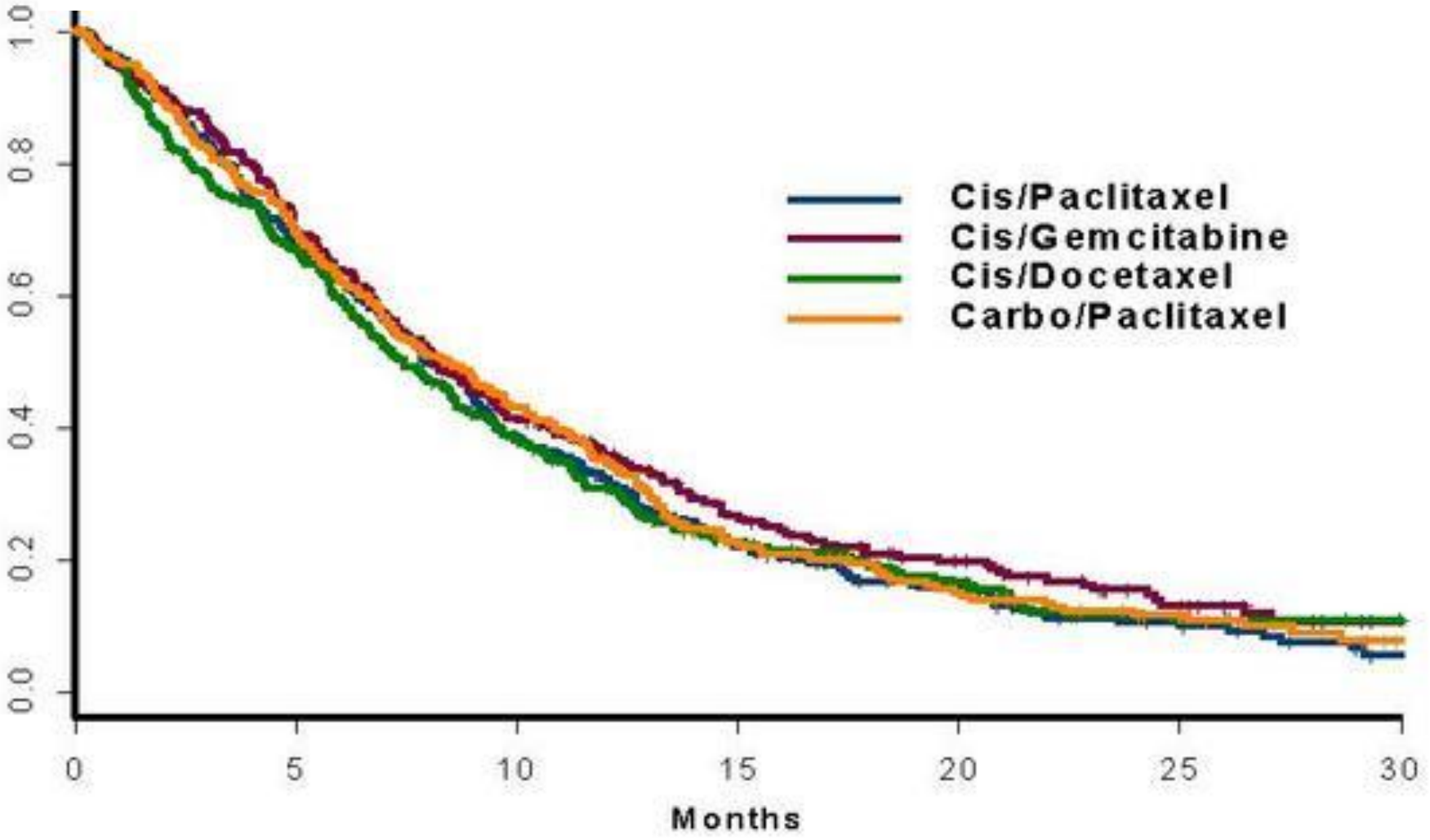
Epidemiología del cáncer

Mortalidad en España (2014)



El pasado! – solo quimioterapia!

Ensayo ECOG 1594 - Supervivencia



Agenda

- Conocimiento y tecnología
- Adicción oncogénica
- Subgrupos difíciles
- Estrategias prometedoras
- Perspectivas

Agenda

- **Conocimiento y Tecnología**
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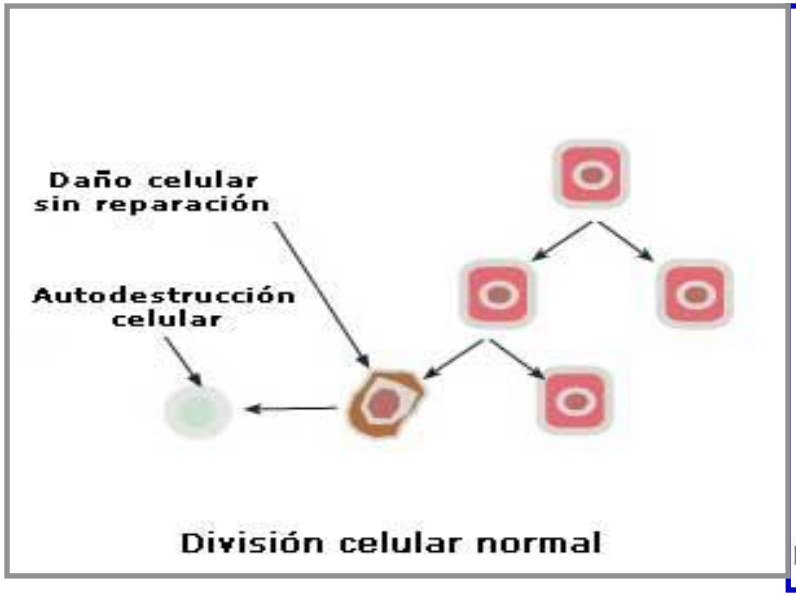
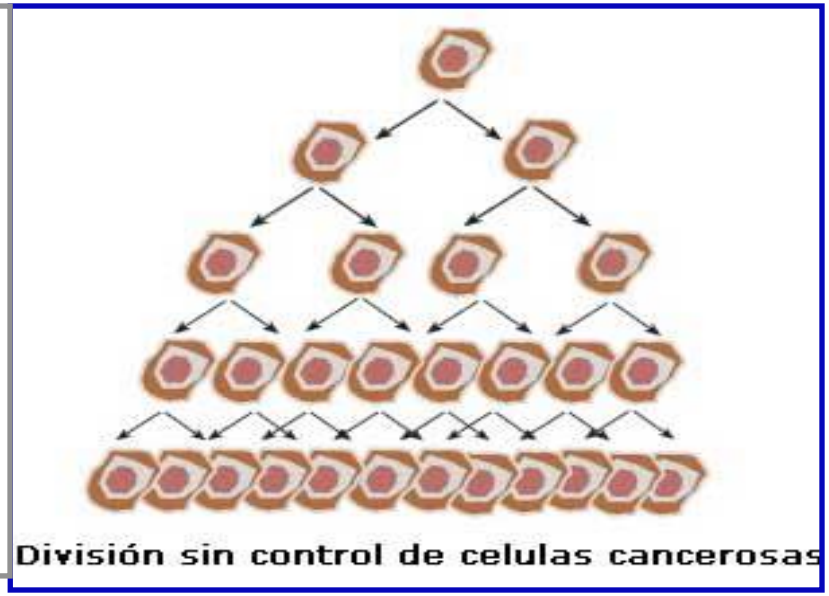
¿Qué es el cáncer?

¿Cómo se produduce el cáncer?

Grupo de enfermedades que se caracterizan por el **crecimiento incontrolado y la diseminación de las células**.

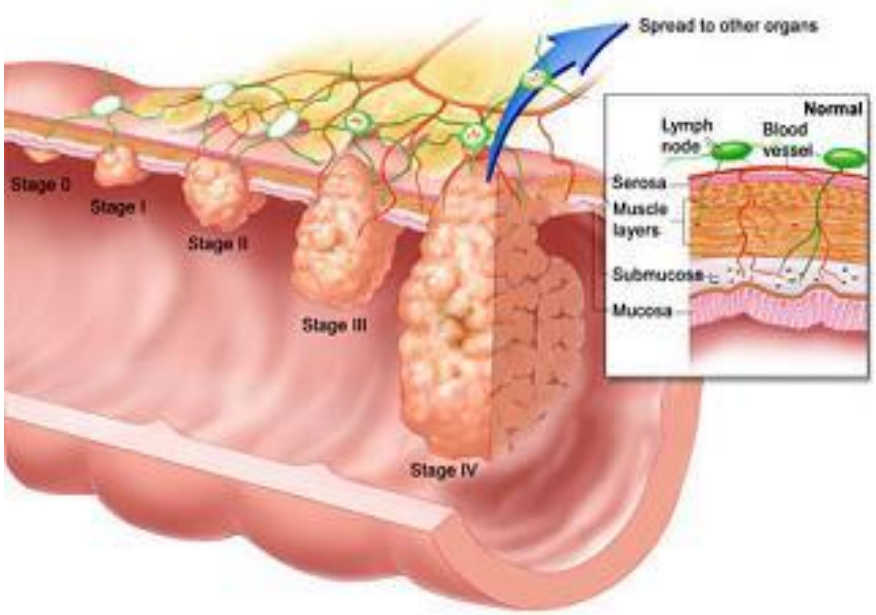
El cáncer es una **enfermedad genética**. Ocurre como consecuencia de cambios en la composición del material genético de las células, que alteran su división y funcionalidad (Mutaciones, alt. en reparación, etc.)

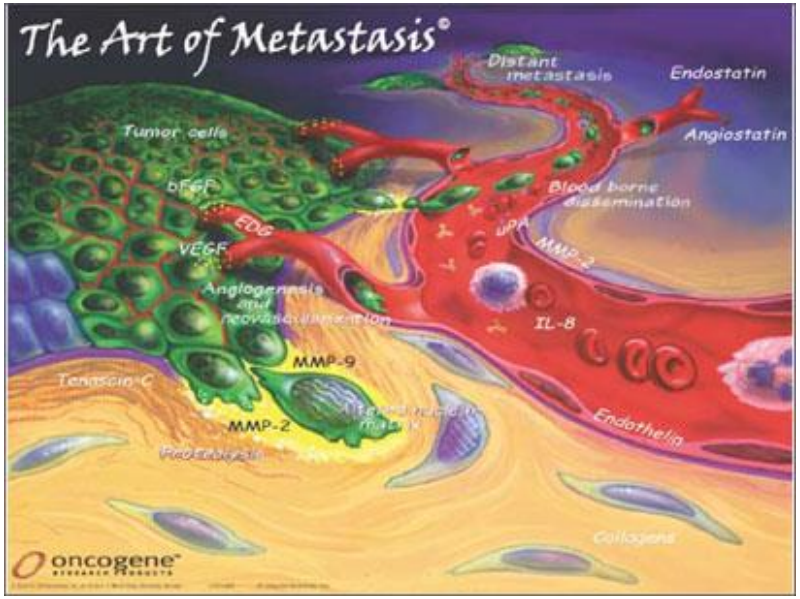




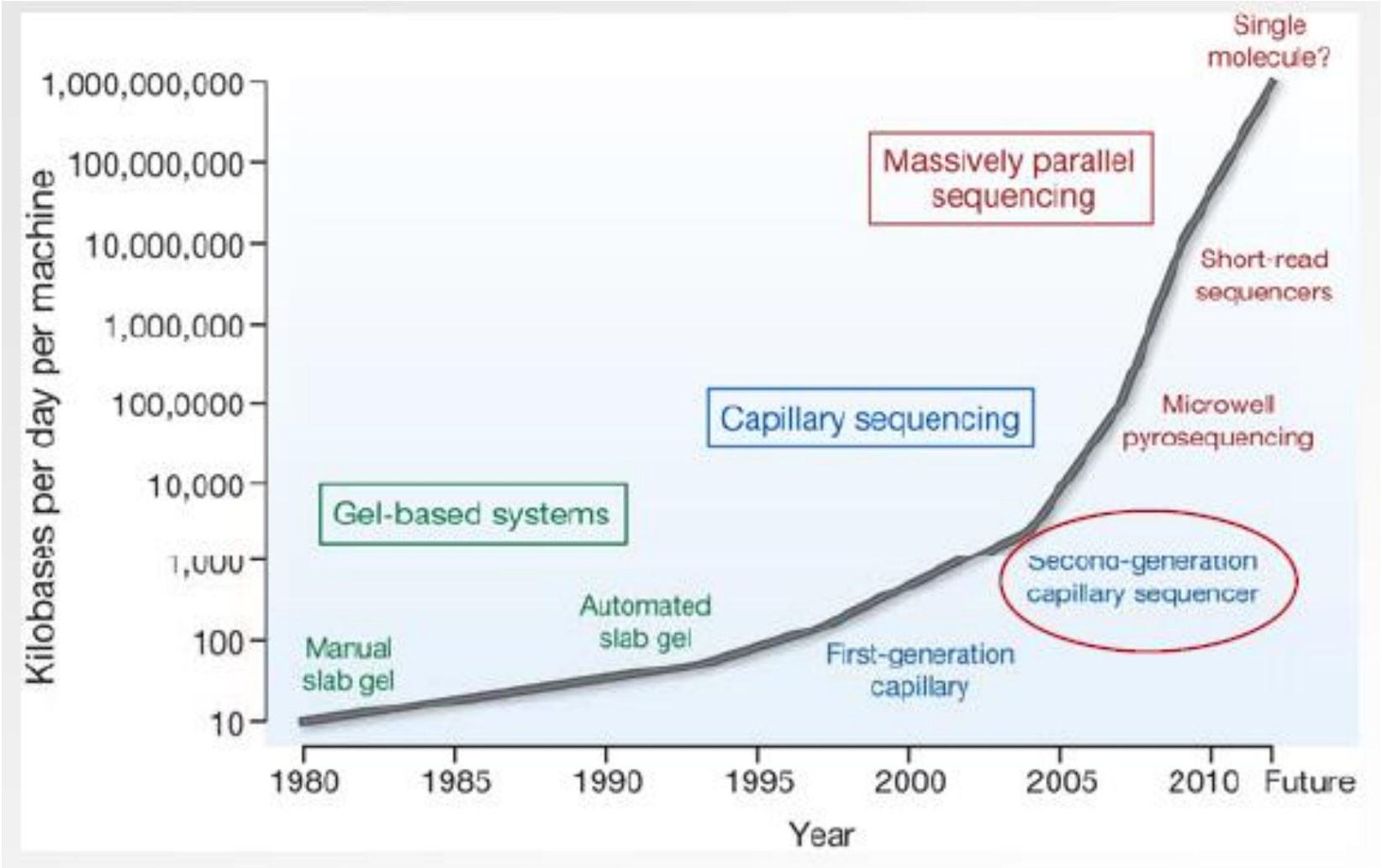
Historia natural del cáncer

Para que se produzca un cáncer es necesario que **los factores cancerígenos actúen de forma continuada** y se produzcan **alteraciones celulares acumulativas durante un largo periodo de tiempo**, generalmente años.

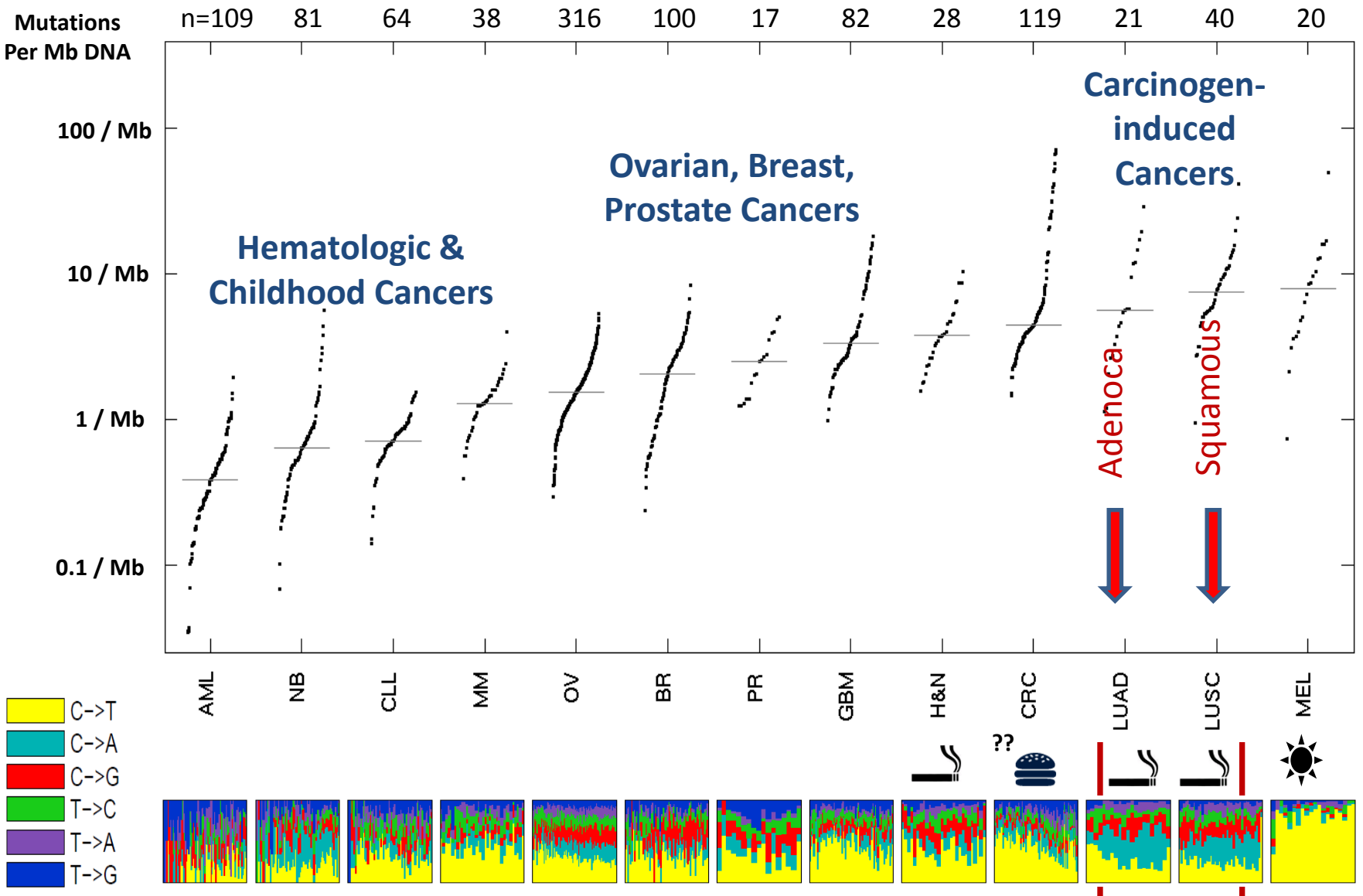




Evolución de la tecnología genómica
El ejemplo de la NGS

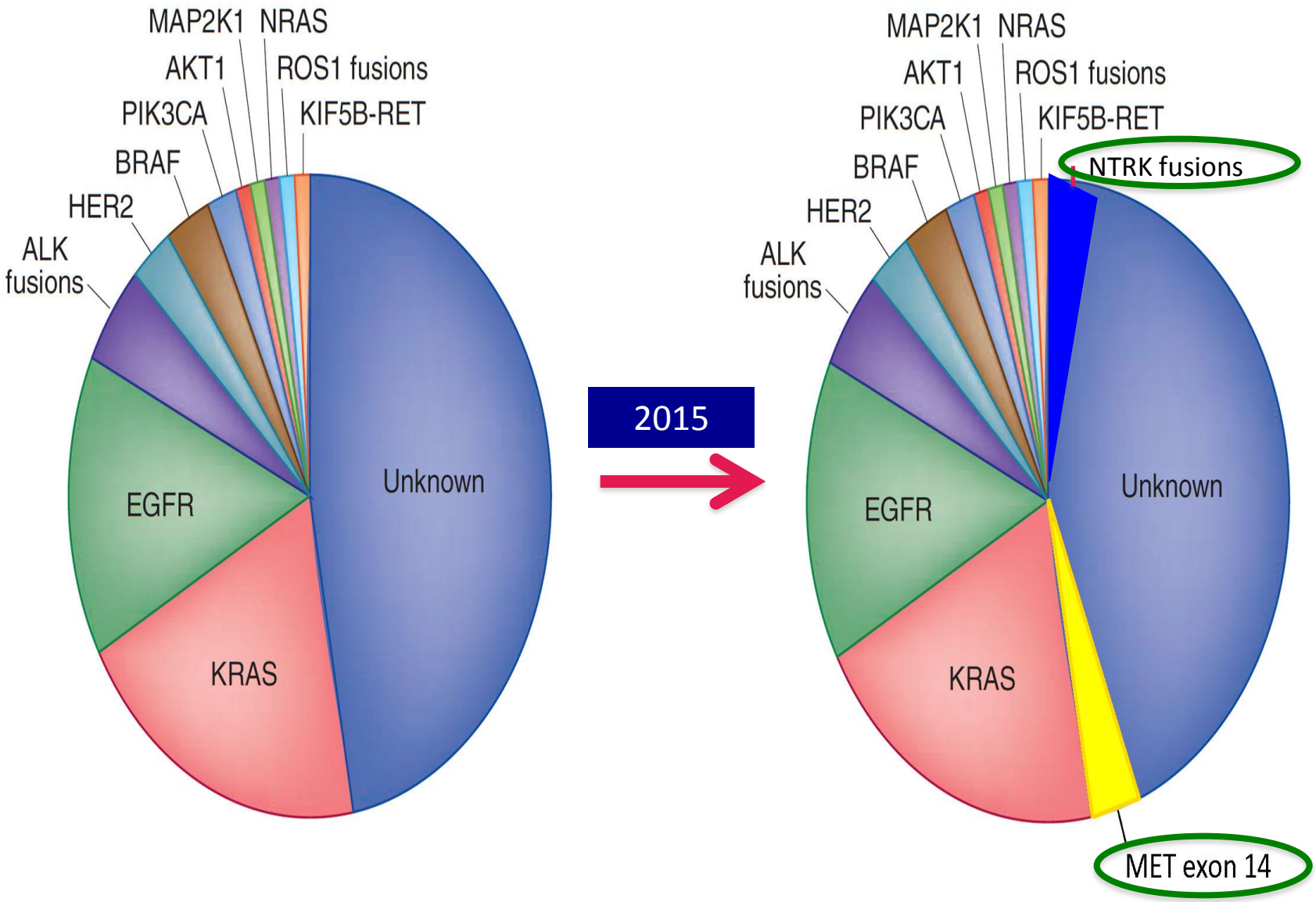


Las aberraciones genómicas son muy frecuentes en cáncer de pulmón



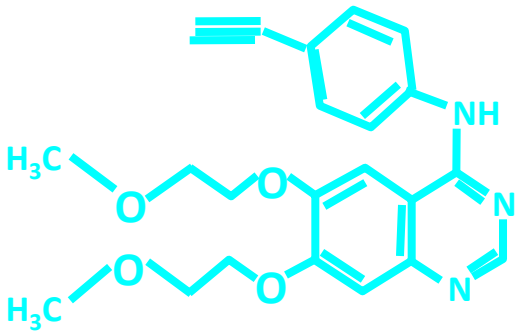
From The Cancer Genome Atlas Project: Govindan R. J Clin Oncol. 2012 (Proc ASCO Annual Meeting);30 (suppl): abstr 7006.

Adenocarcinoma de pulmón - Genotipo



Agentes dirigidos a dianas moleculares

Pequeñas Moléculas

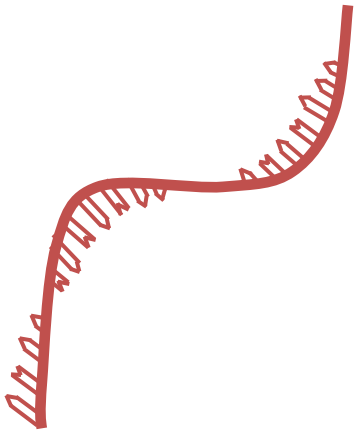


Intracellular action
c 0.5–2kDa
Orally available

Anticuerpos Monoclonales

Extracellular action
c 150kDa
i.v. infusion

Oligonucleótidos antisentido



Intracellular action
c 10kDa
i.v. infusion

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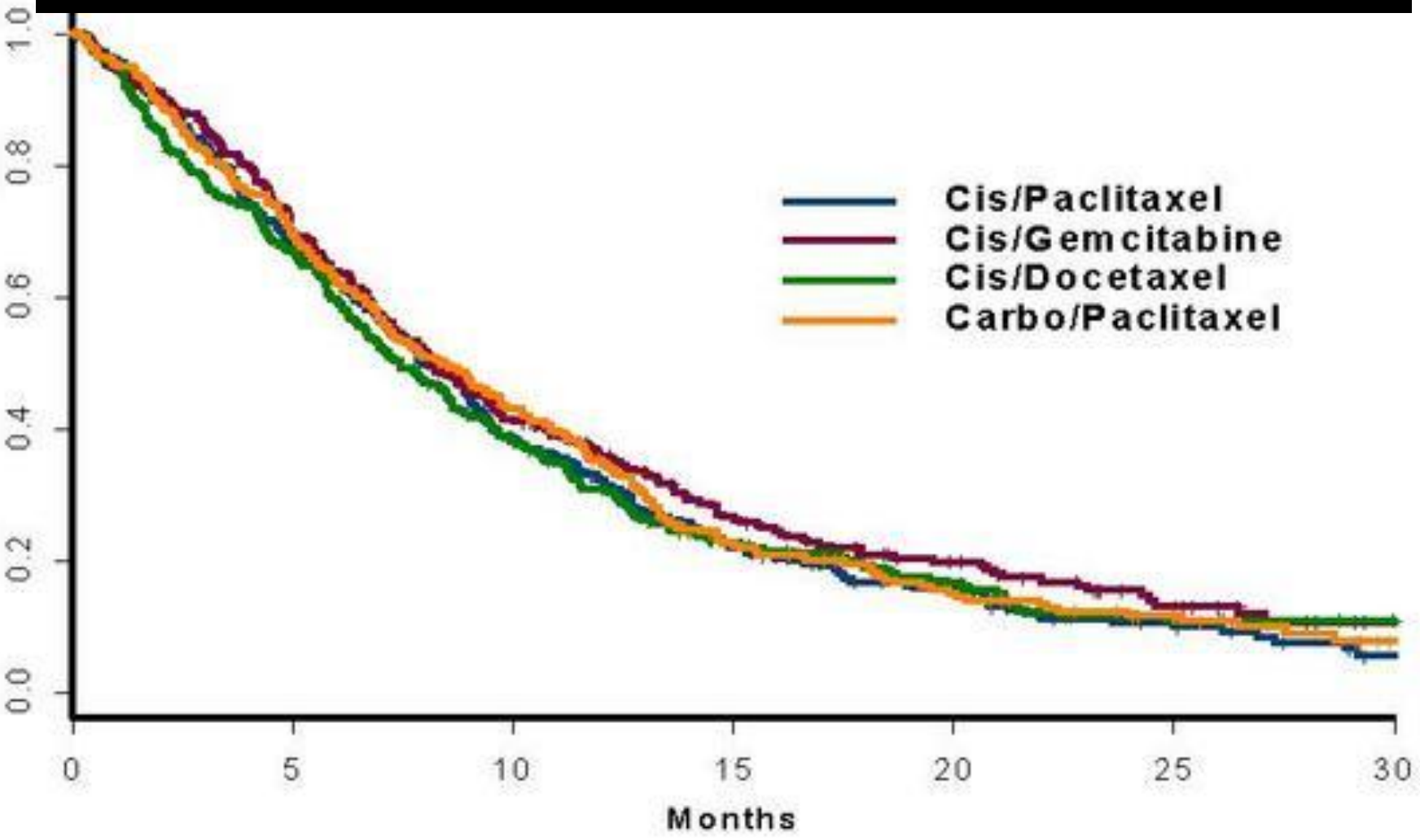
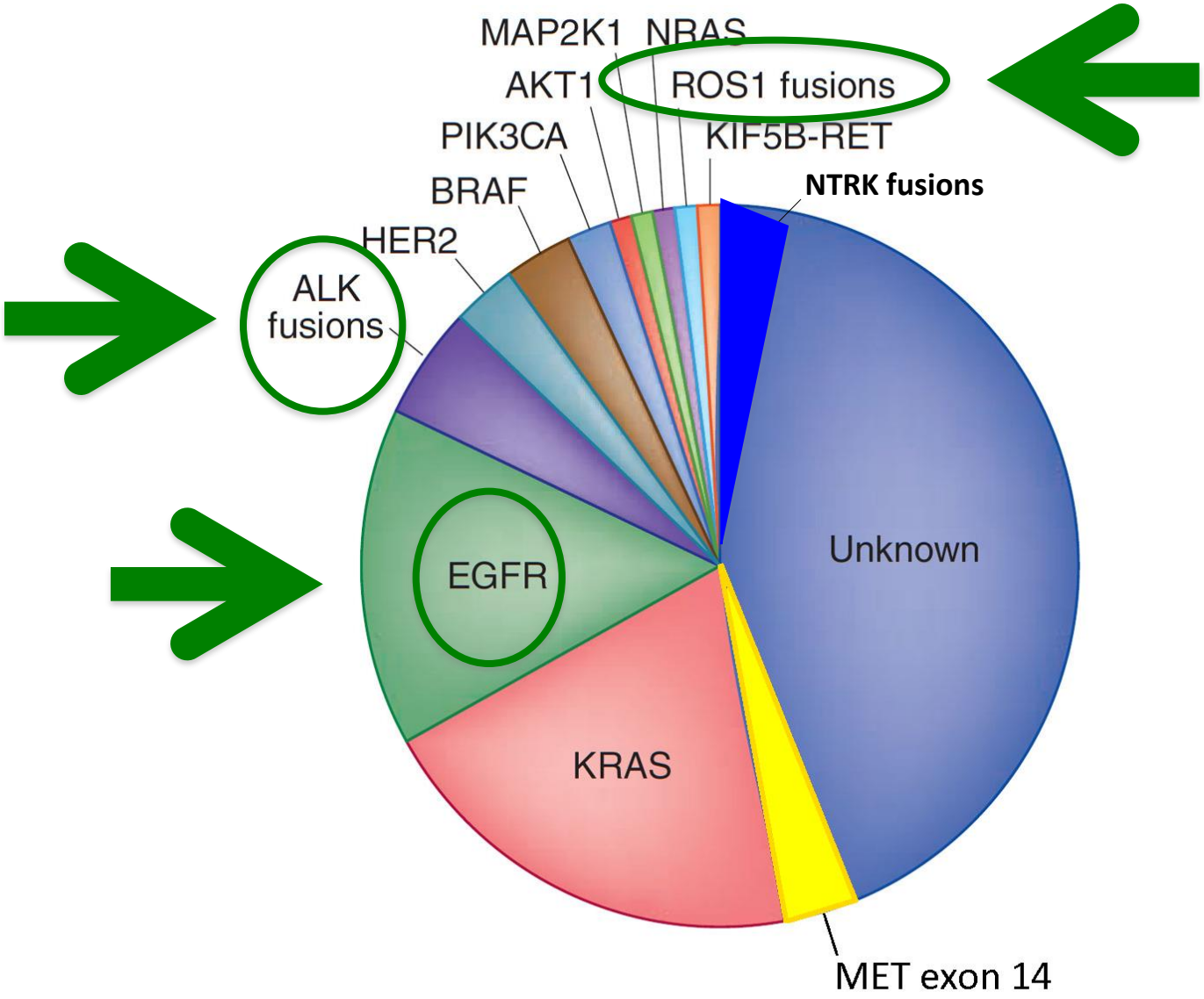
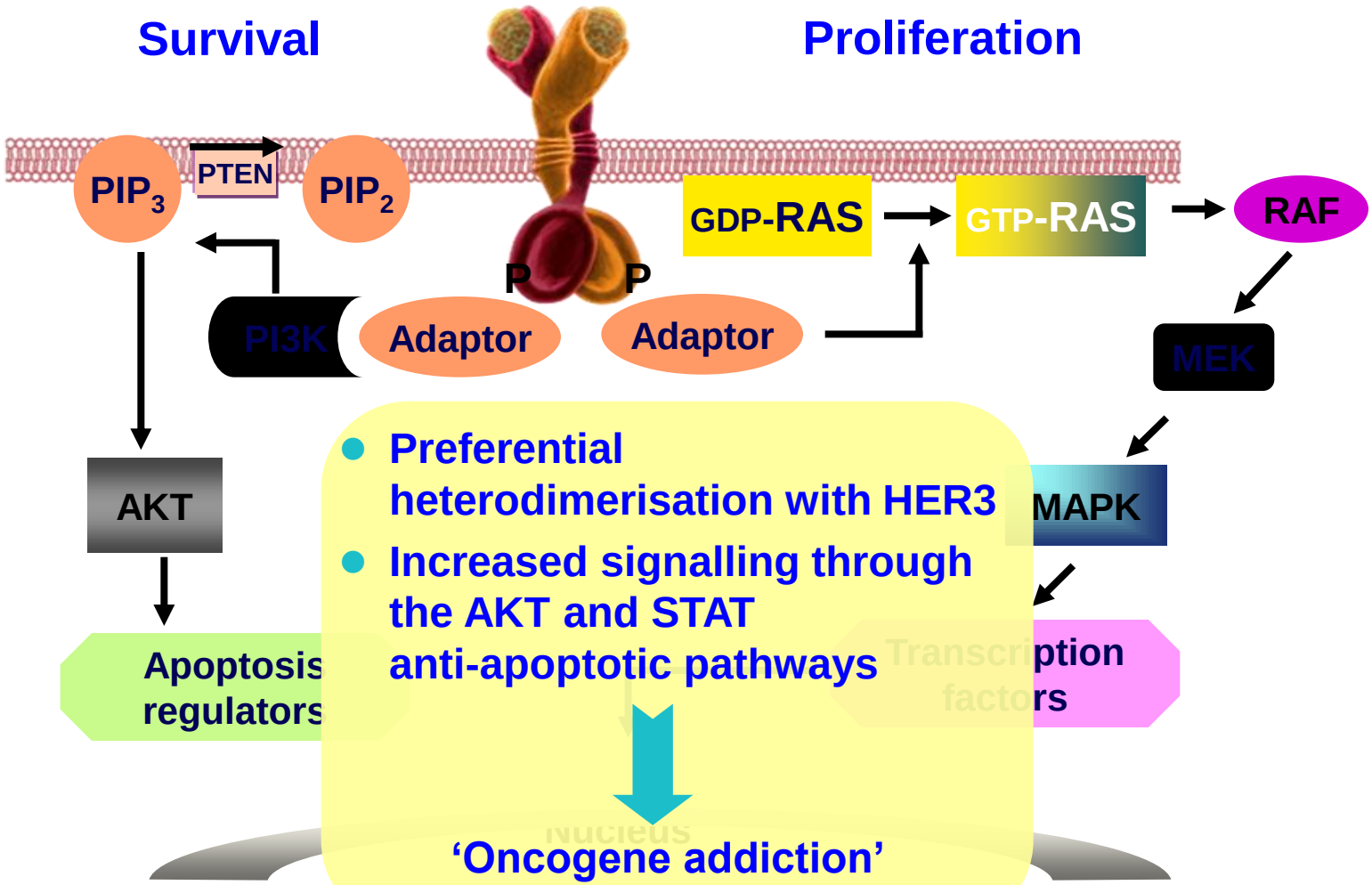


Adenocarcinoma de pulmón
Subtipos con tratamientos específicos



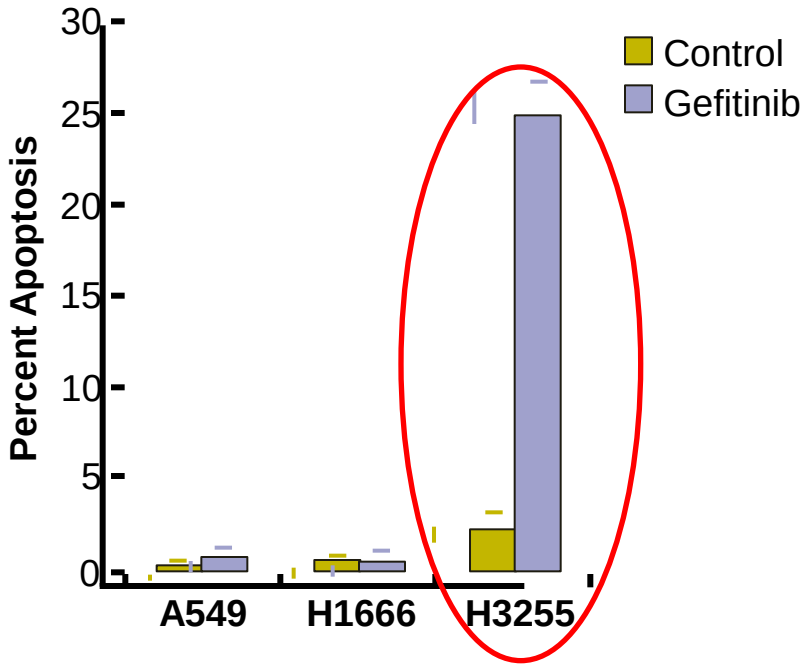
Cáncer de pulmón con mutación EGFR
una enfermedad biológicamente distinta



Sordella, et al. Science 2004

Efecto citotóxico vs Citostático Inhibidores de TK de EGFR (Erlotinib)

- **Efecto citotóxico (apoptosis) restringido a tumores *EGFR* Mt+ (respuesta objetiva)**
- **Efecto citostatico (prarada en el crecimiento) en tumores sin mutación *EGFR* (estabilización)**



Jänne PA ,et al. Clin Cancer Res. 2006;12:4416s-4420s.

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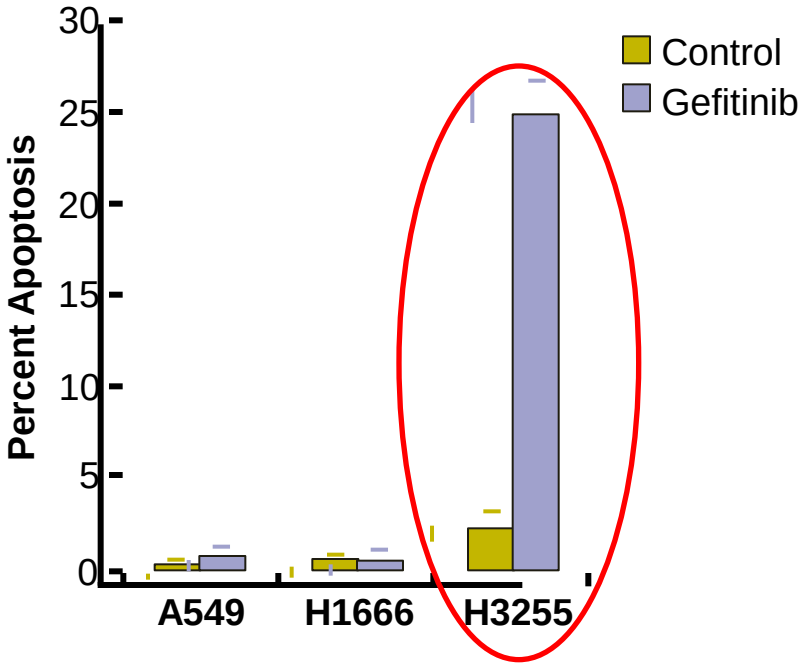
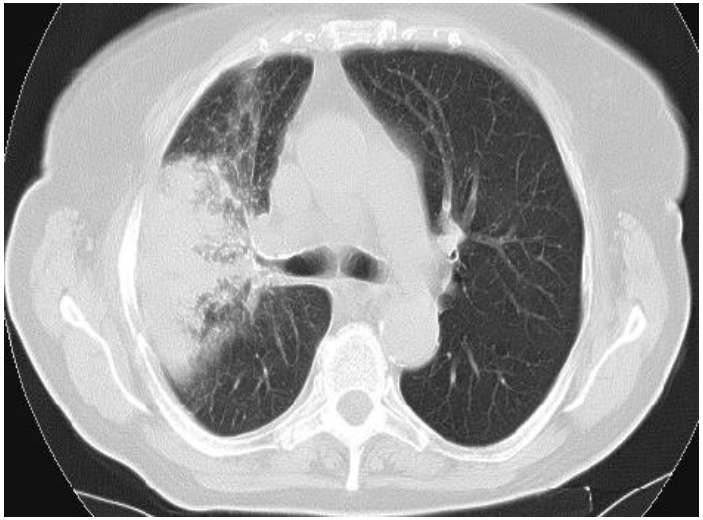
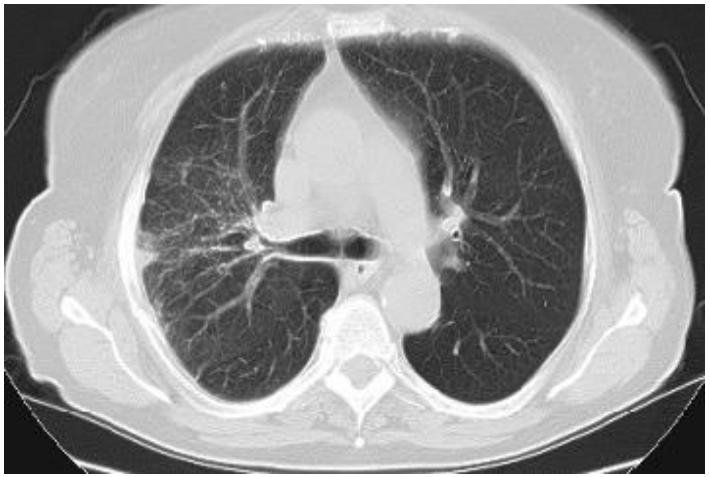


Jänne PA ,et al. Clin Cancer Res. 2006;12:4416s-4420s.

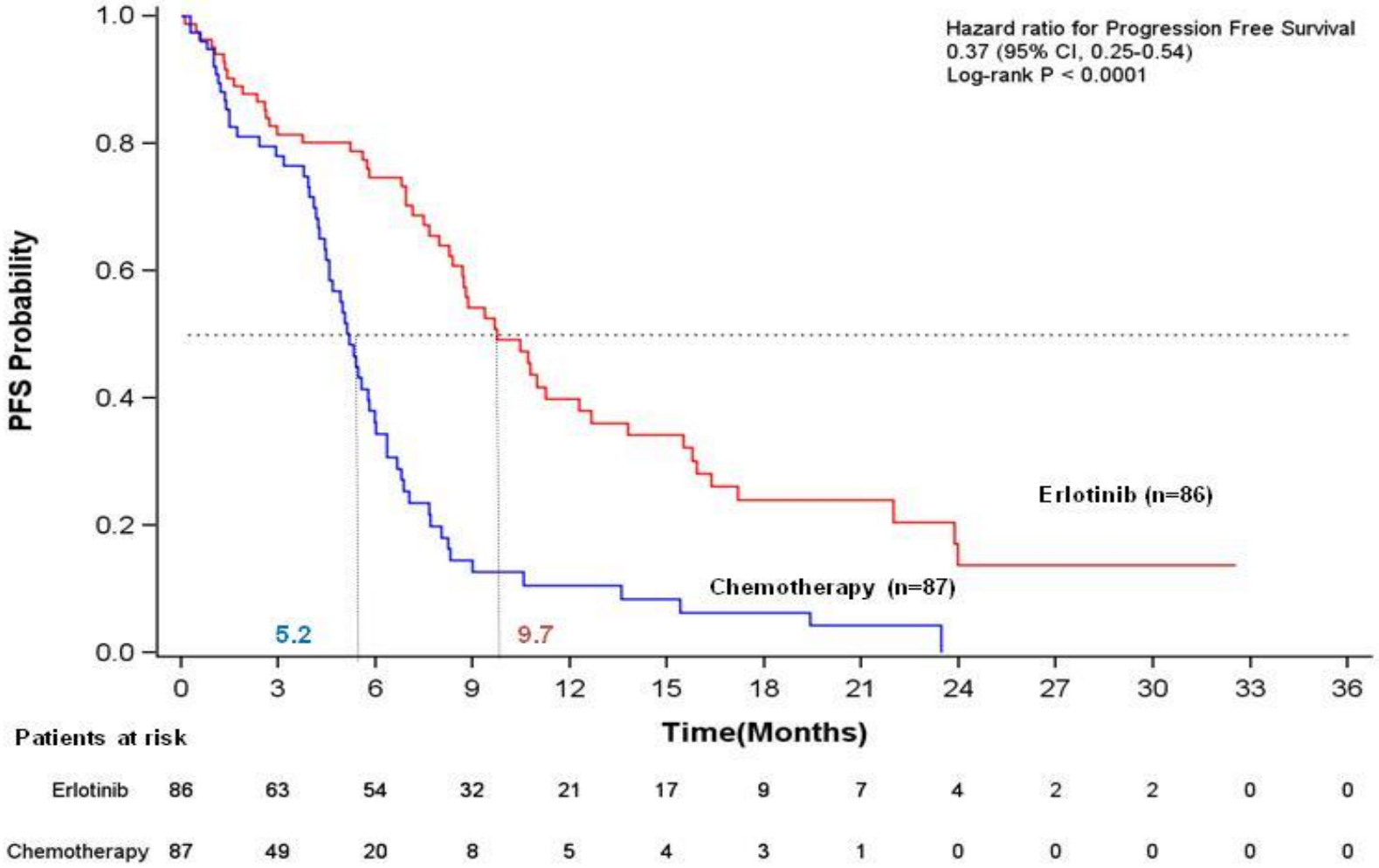


24.03.2005 (Comienzo del tratamiento)



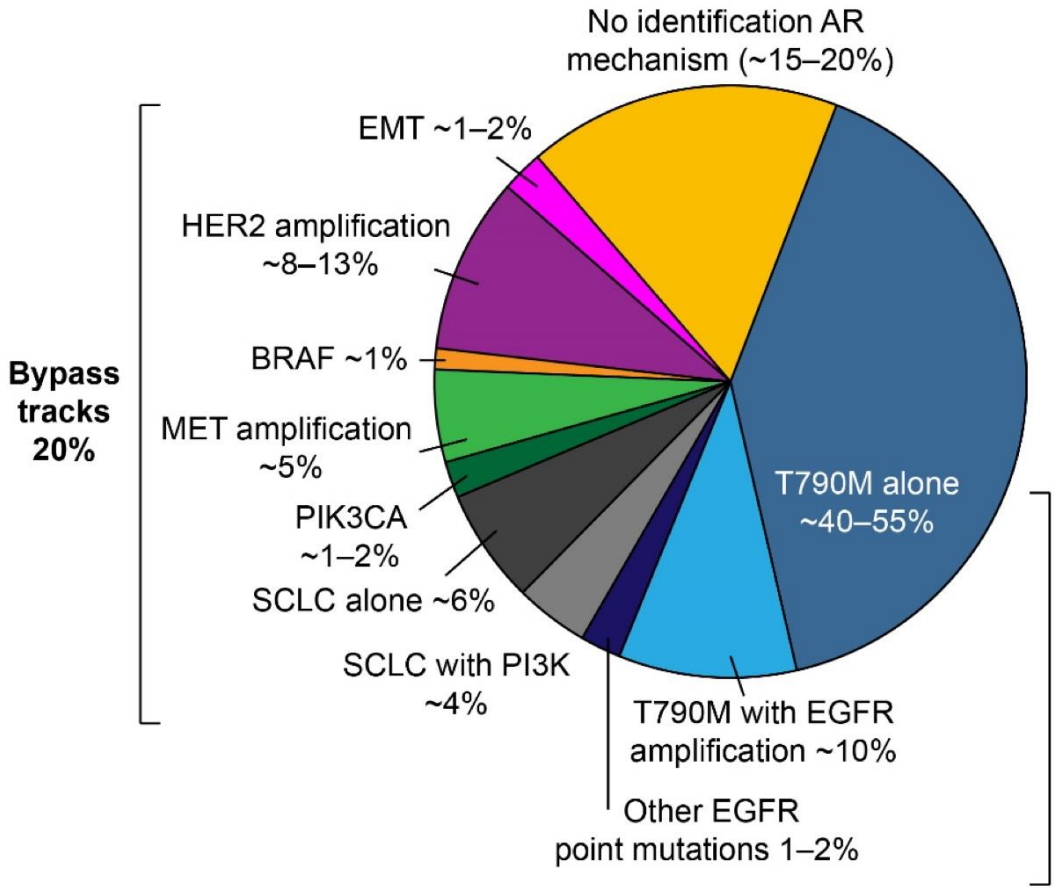
16.05.2005 (Remisión completa)

Ensayo EURTAC : Erlotinib *v* Quimioterapia

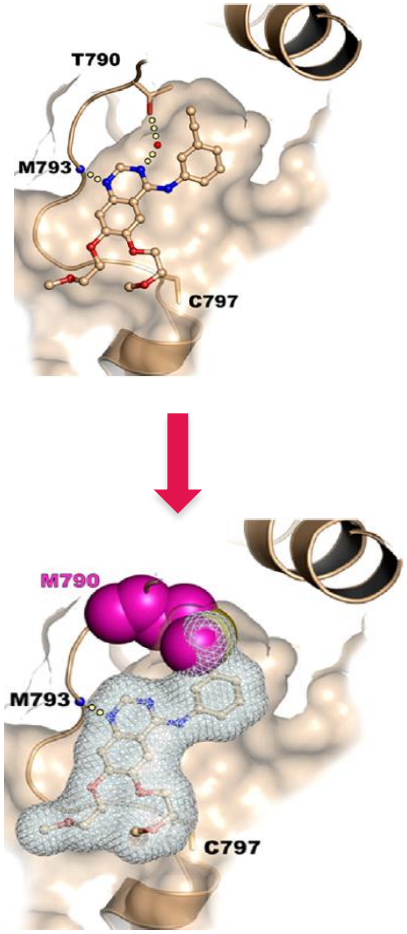


Rosell, …Paz-Ares. Lancet Oncol 2012

CNMP EGFR M+: Resistencia Adquirida



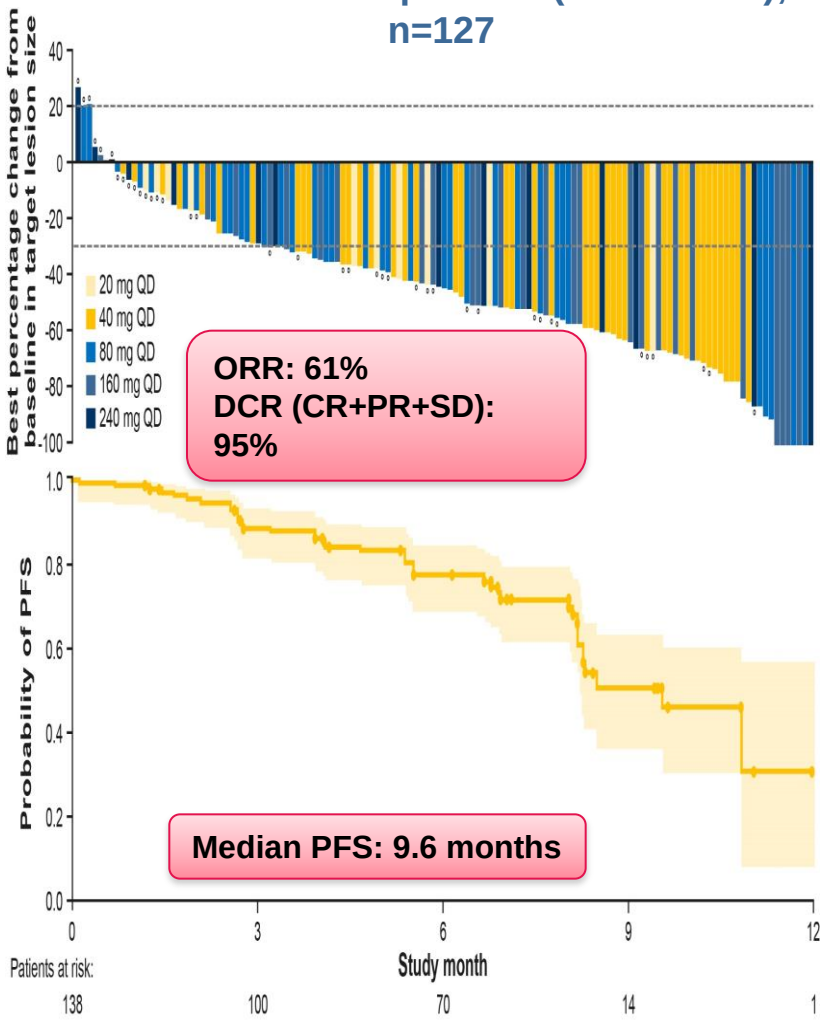
T790M - Exon 20

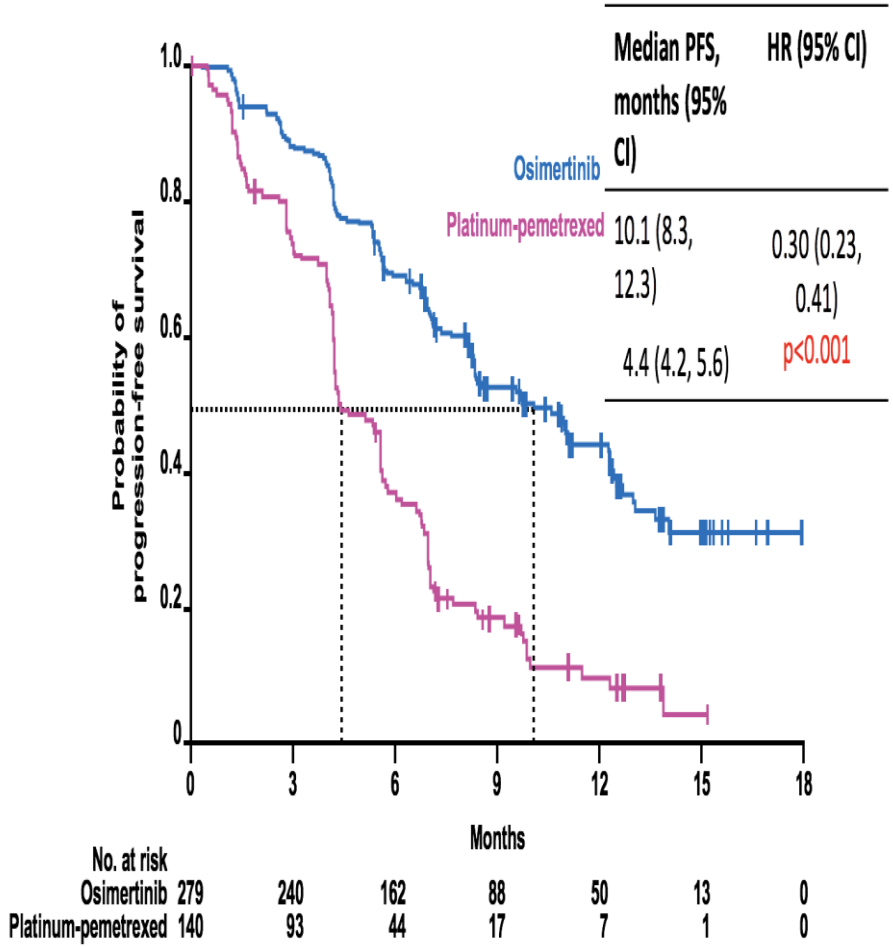


Michalczyk A et al. Bioorg Med Chem. 2008 Apr 1;16(7):3482-8.

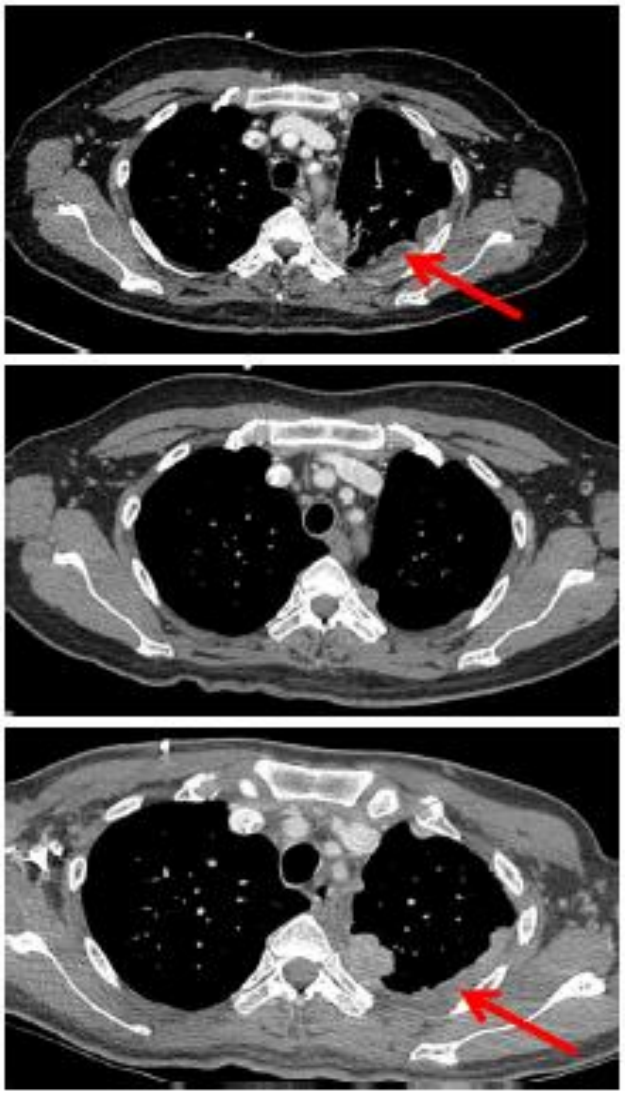
Osimertinib en Cáncer de pulmón EGFR-T790M +

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

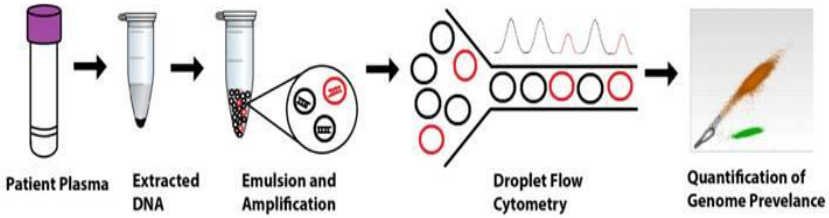


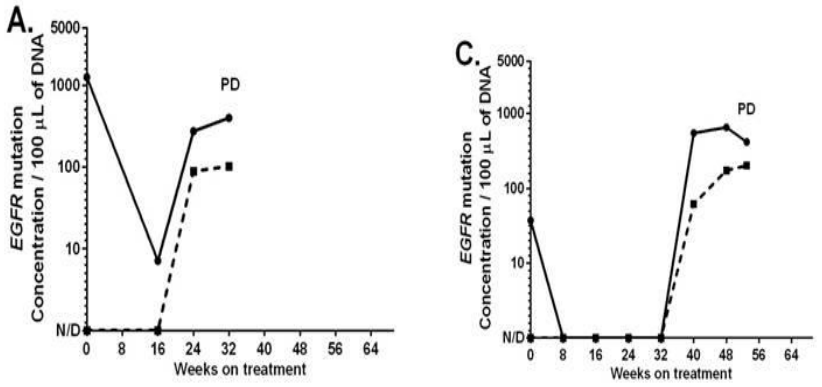


Monitorización de la Resistancia Biopsia Líquida



Non-invasive genotyping and disease monitoring





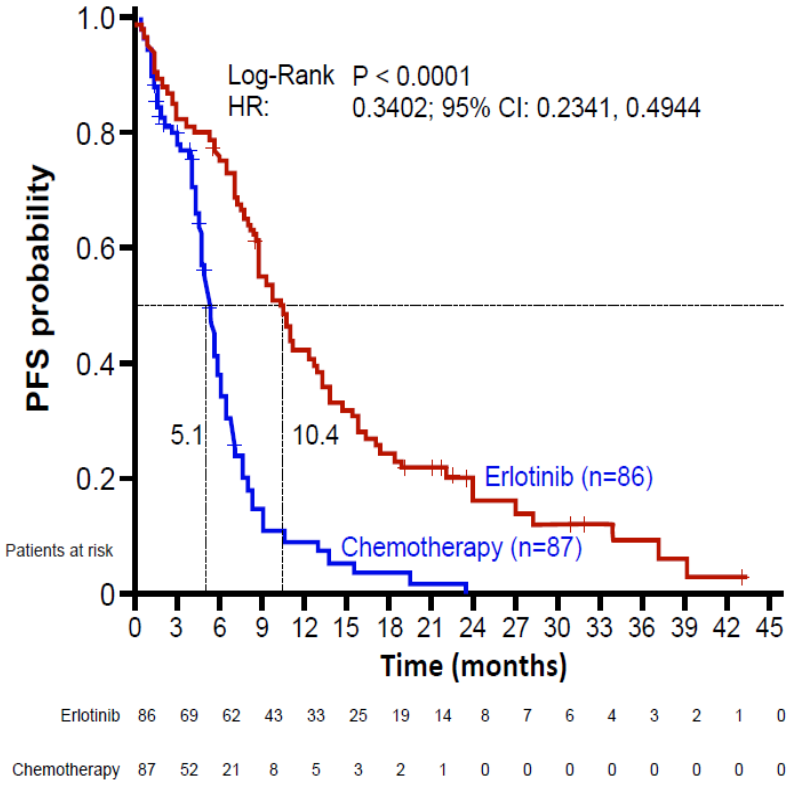
Serial monitoring for EGFR activating and EGFR T790M resistance mutation in erlotinib treated EGFR mutant patients

Oxnard et al. CCR 2014

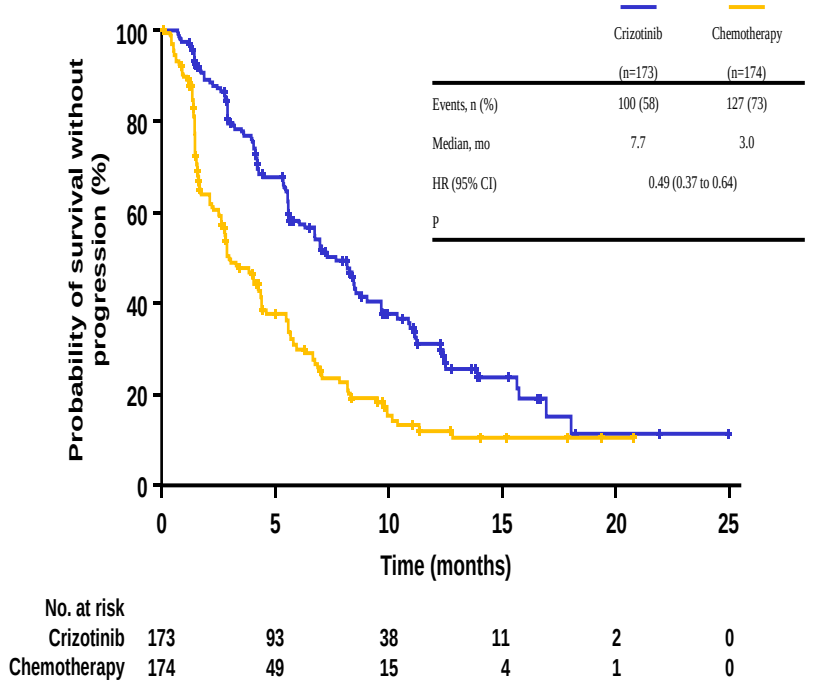
Sacher et al. ASCO 2014; Abstract 8059

Cáncer de pulmón con Adicción Oncogénica: Tratamiento presonalizado

Erlotinib versus Quimioterapia CNMP EGFR+



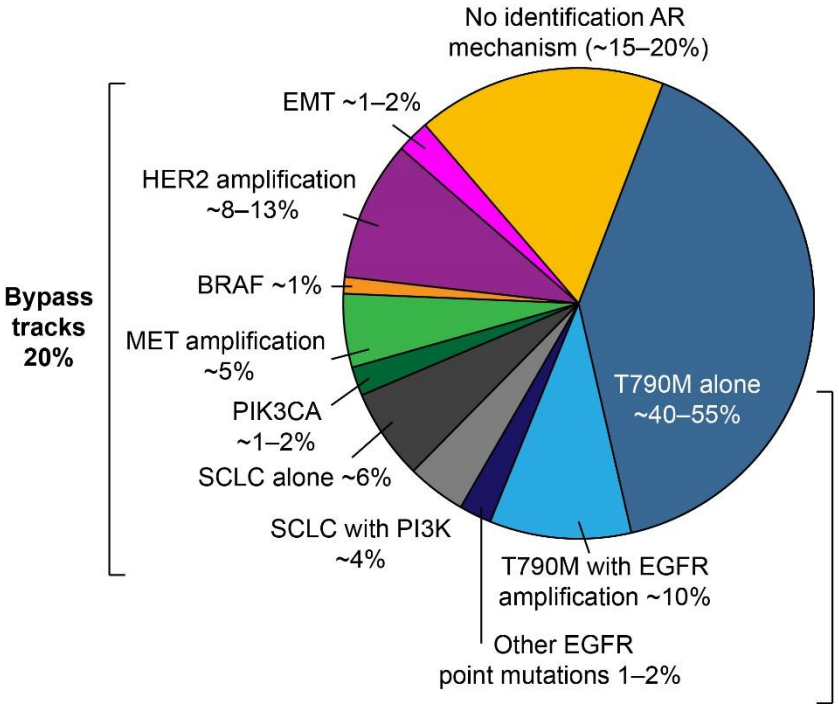
Crizotinib versus Quimioterapia CNMP ALK+



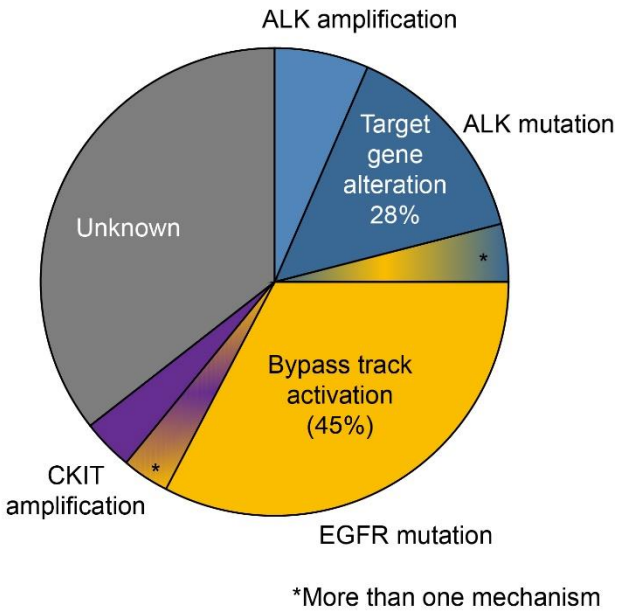
Shaw et al., NEJM 2012

Resistencia Adquirida a TKI
Paralelismo EGFR - ALK

EGFR mutant



ALK positive

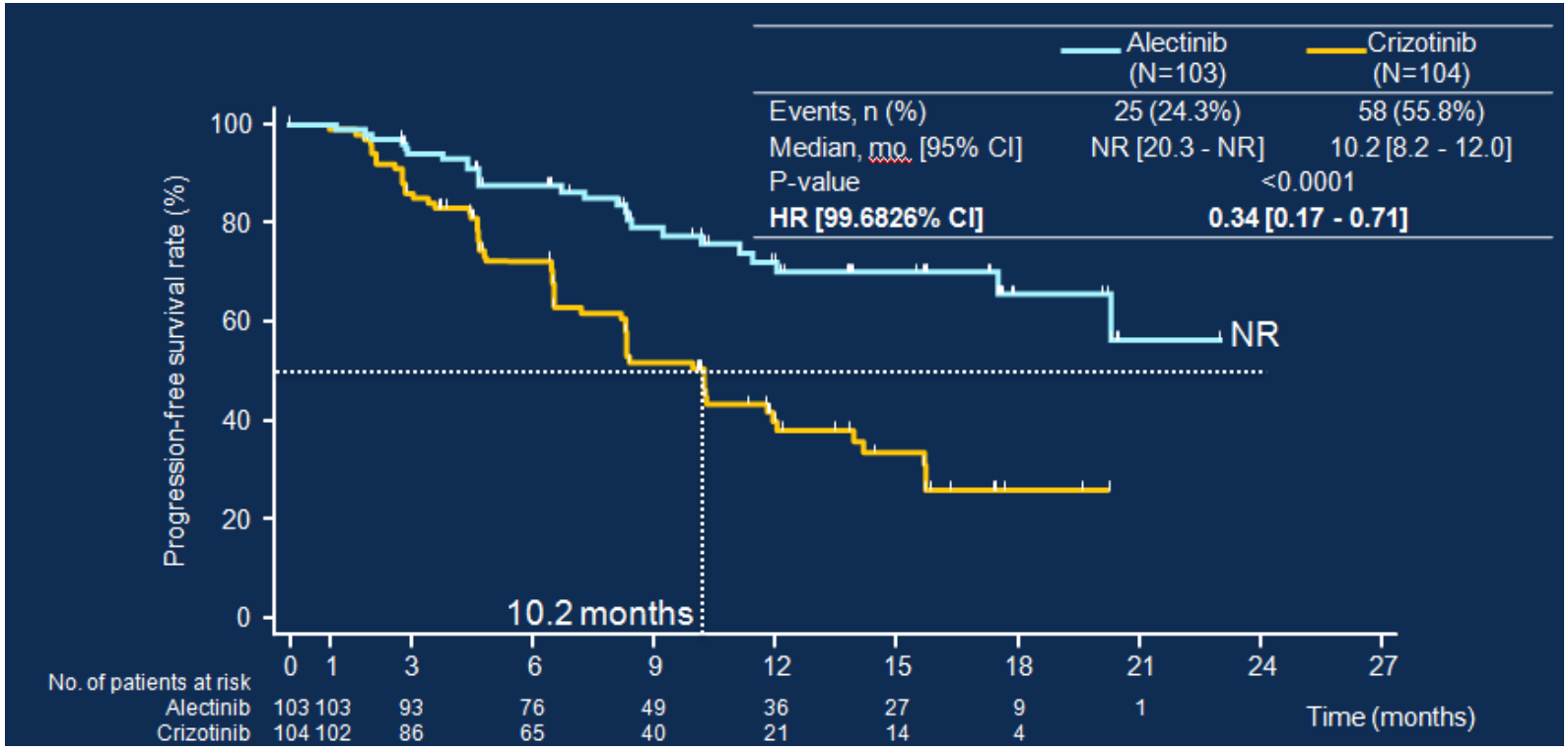


Common themes

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

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

Estudio J-ALEX : Alectinib vs Crizotinib



ORR* assessed by IRF

	Alectinib (n=83)	Crizotinib (n=90)
ORR [95%CI]	**91.6% [85.6 - 97.5]**	**78.9% [70.5 - 87.3]**
CR or PR	76	71

* In patients with measurable lesion assessed by IRF at baseline

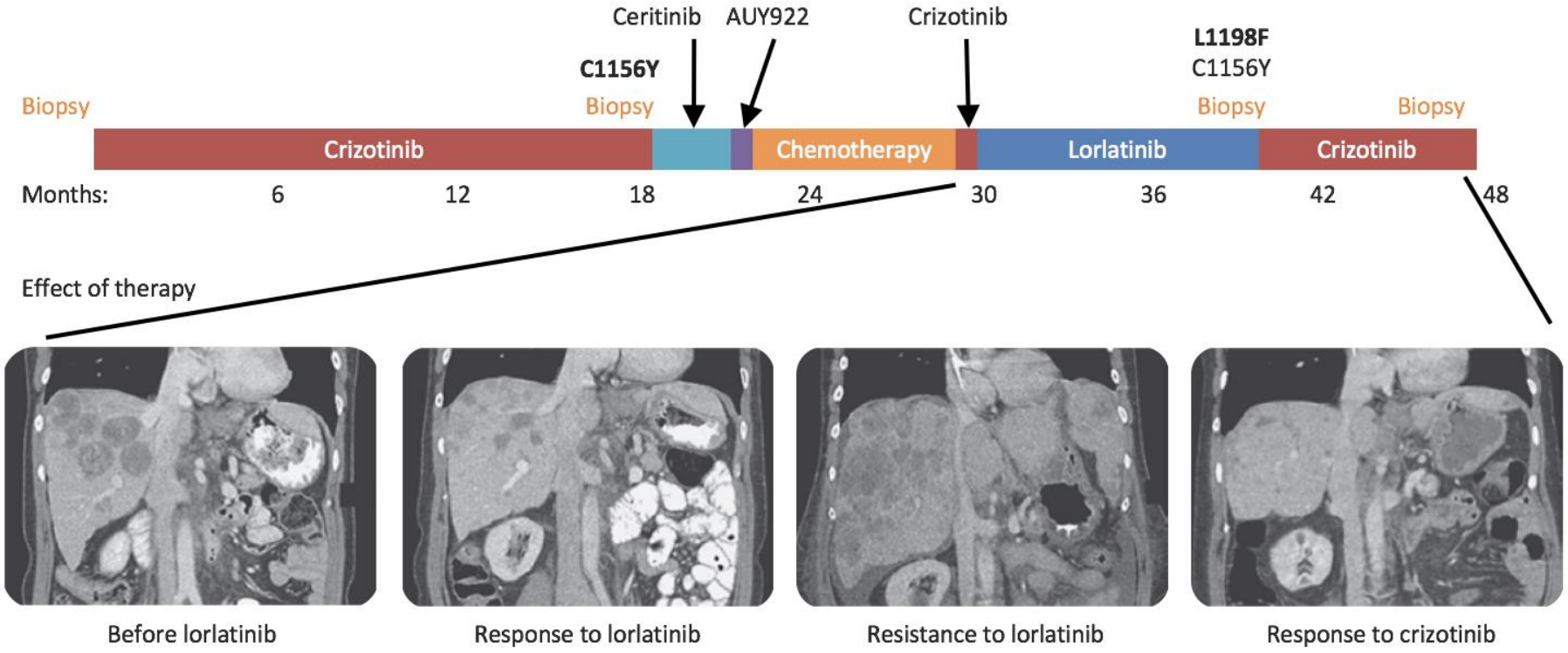
CNMP ALK+
TKI 1ª/2ª vs 3ª Generación

1st/2nd Gen TKI – 11 m

3rd Gen TKI – 9-10m

3rd Gen TKI – >26 m

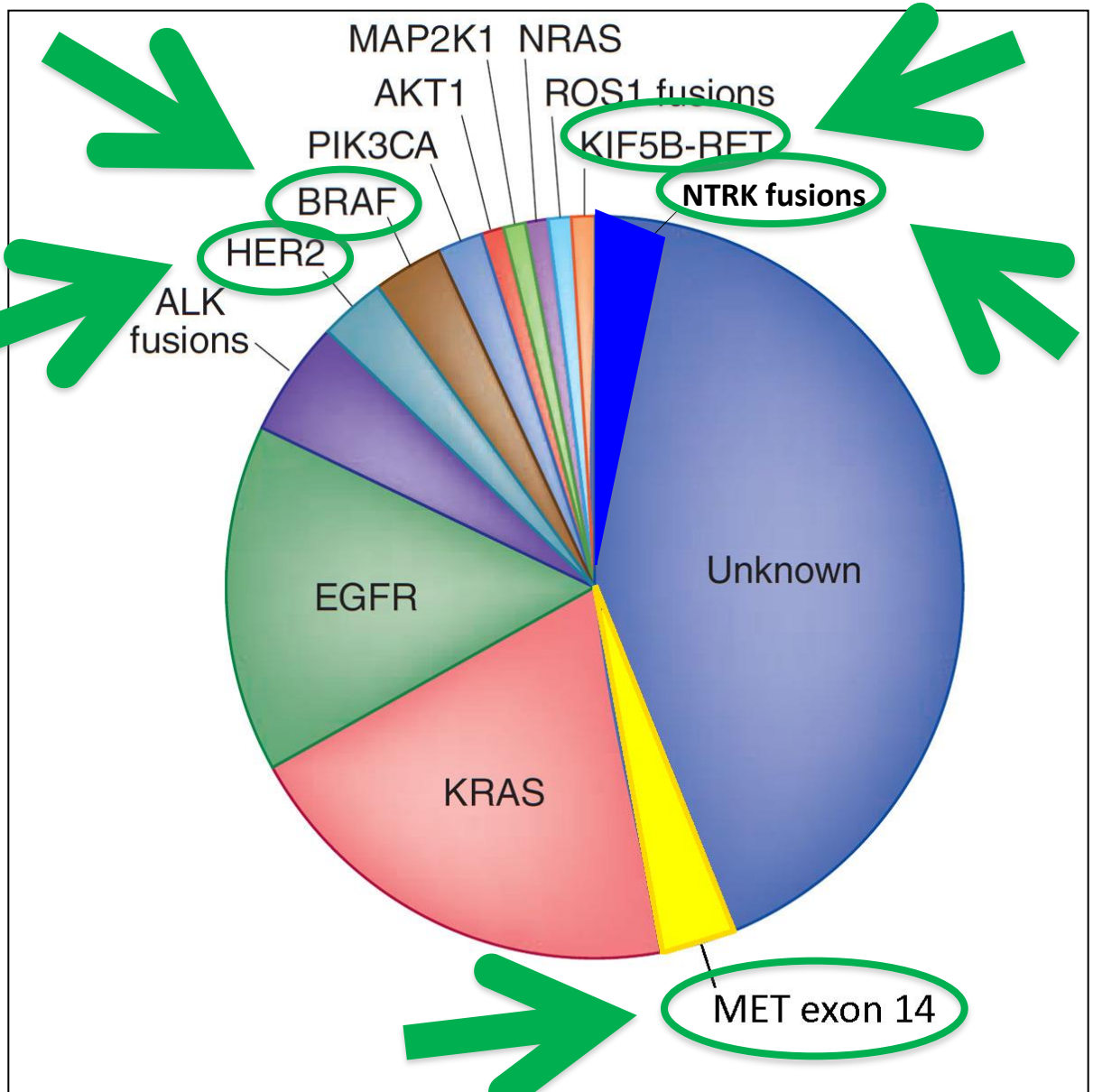
Monitorización del genotipo
Guía de tratamientos sucesivos



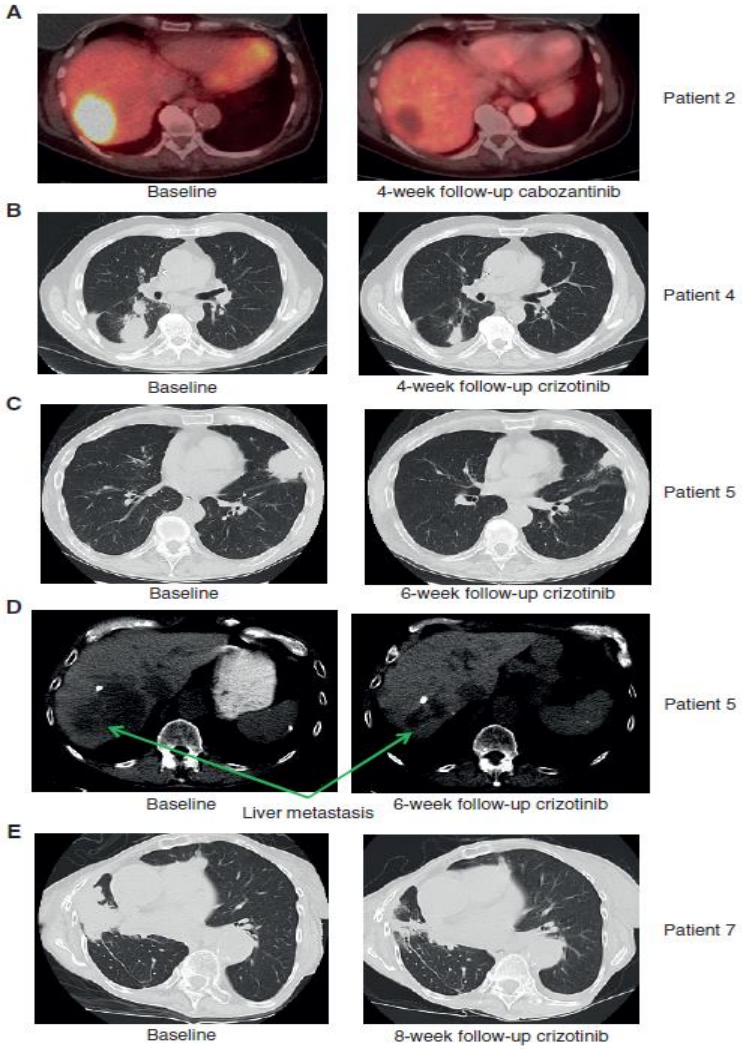
- Sequencing strategies should be flexible; in some cases revisiting previous agents may be the best approach

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

Adenocarcinoma de pulmón
Subtipos con tratamientos específicos



CNMP con mutación de MET
Inhibidores selectivos de MET



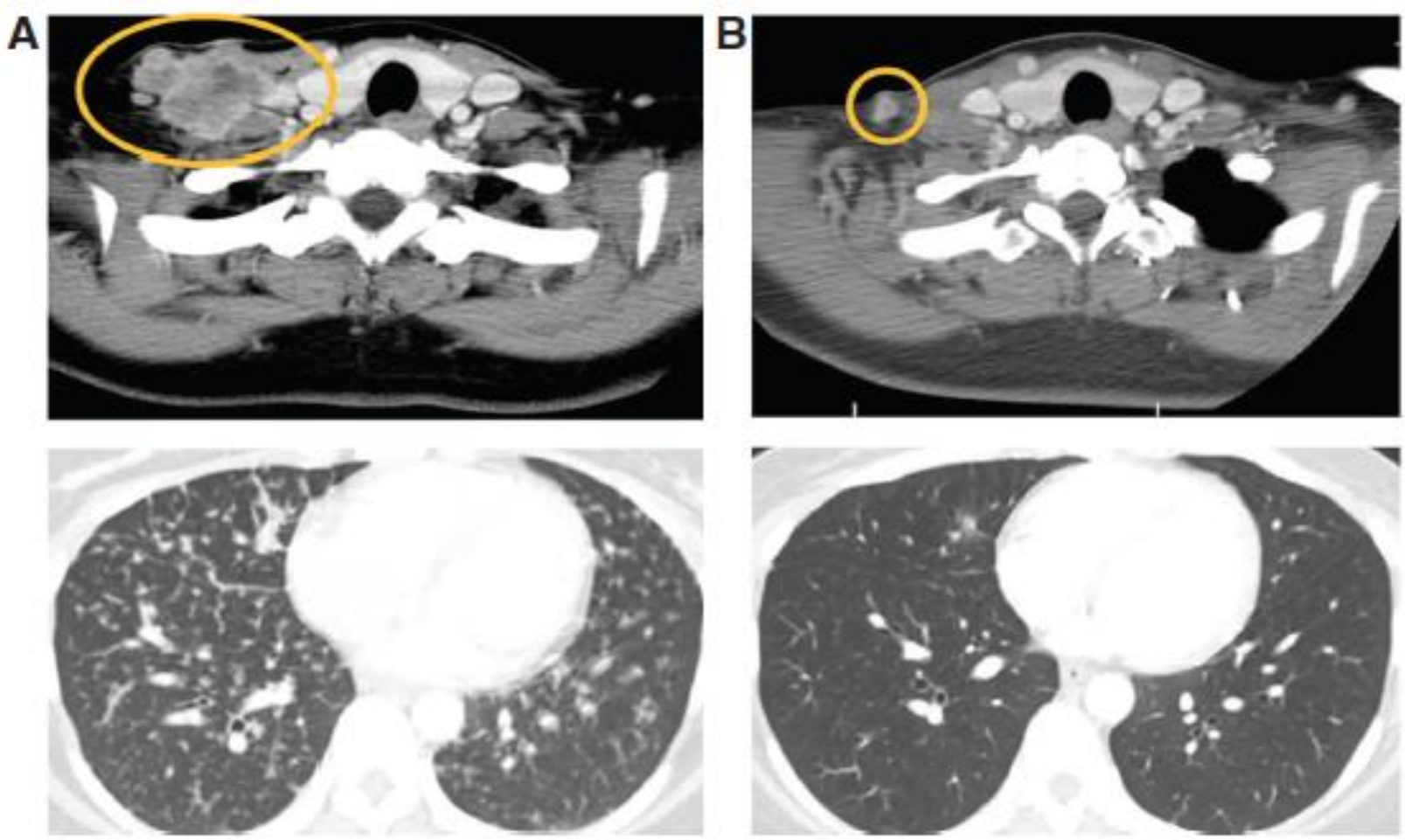
Pt 2 (A)
***MET*ex14 alteration (*MET* c.3028G>C) and multiple others**
GCN =6
MET IHC H-score 300
Cabozantinib SD 5.1+ (CR by PERCIST)

Pt 4 (B)
***MET*ex14 alteration (*MET* c.3024_3028del) and multiple others**
MET not amplified
MET IHC H-score 300
Crizotinib 3.6 months, PR

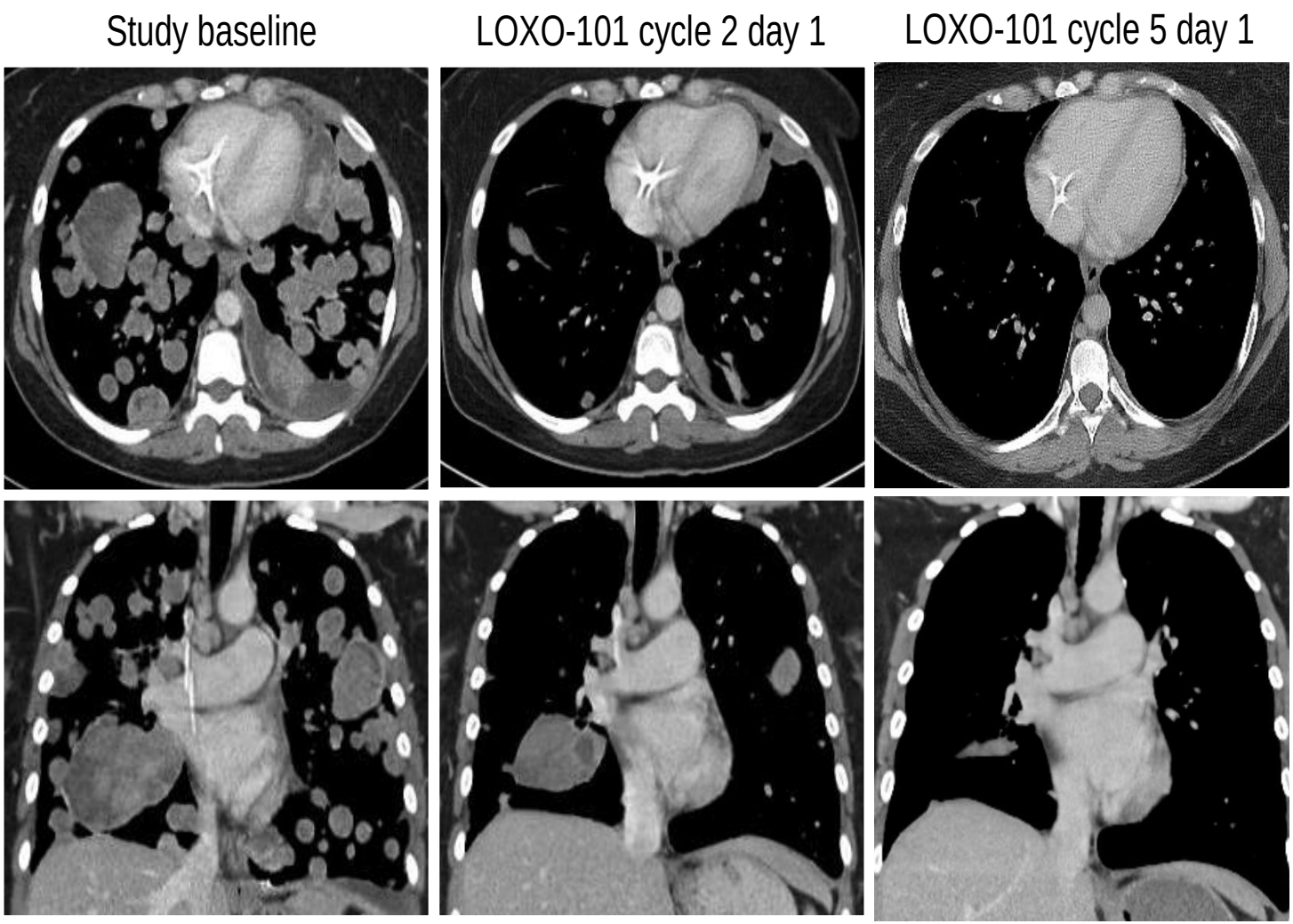
Pt 5 (C&D)
***MET*ex14 alteration (*MET* c.3001_3021del) and multiple others**
GCN = 3.8
Crizotinib 4.6+ months, PR

Pt 7 (E)
***MET*ex14 alteration (*MET* c.3001_3021del)**
MET not amplified
MET IHC H-score 300
Crizotinib 3.1+ months, PR

CNMP con Traslocación RET
Inhibidores selectivos de RET

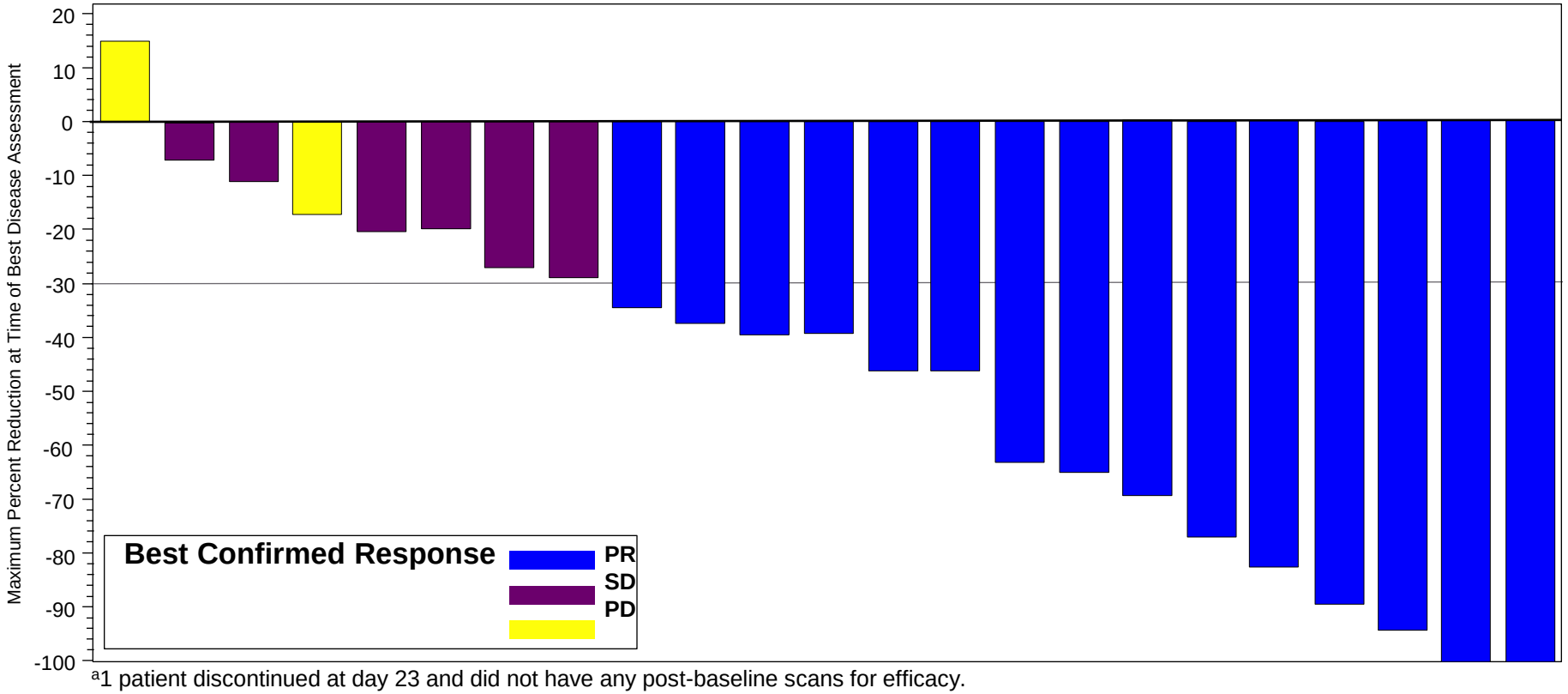


CNMP con Traslocación NTRK
Inhibidores selectivos de NTRK



Doebele et al. Cancer Discovery 2015

CNMP con mutación BRAF V600E
Dabrafenib + Trametinib



[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

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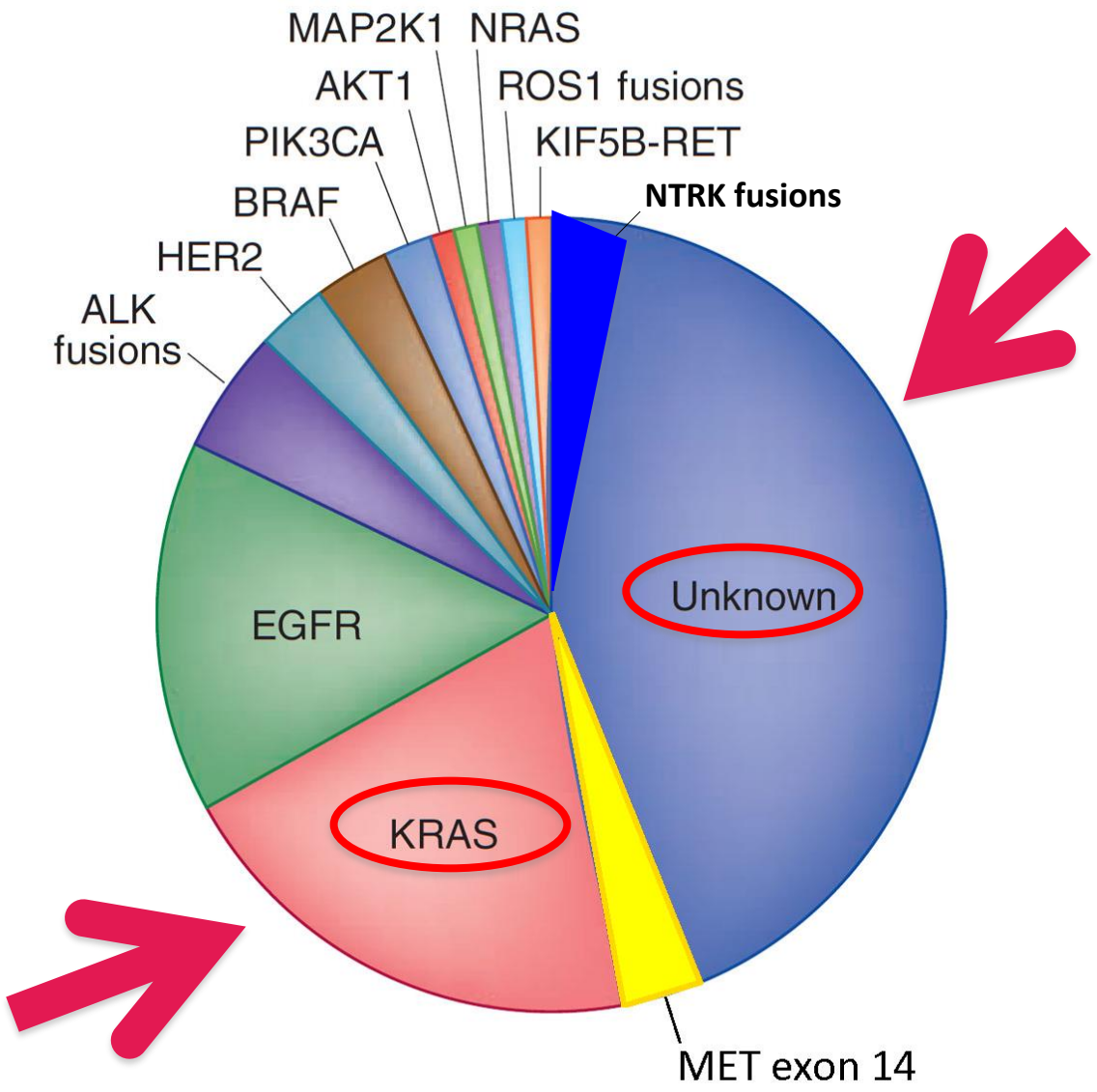
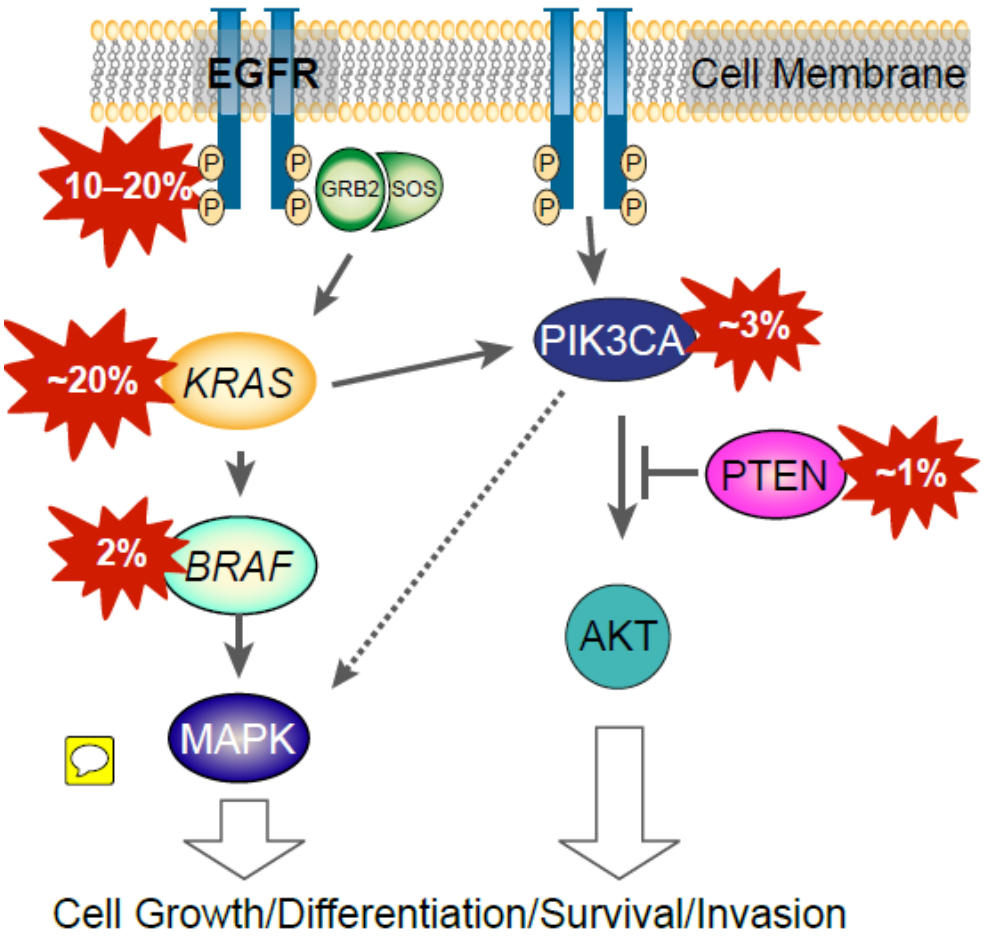
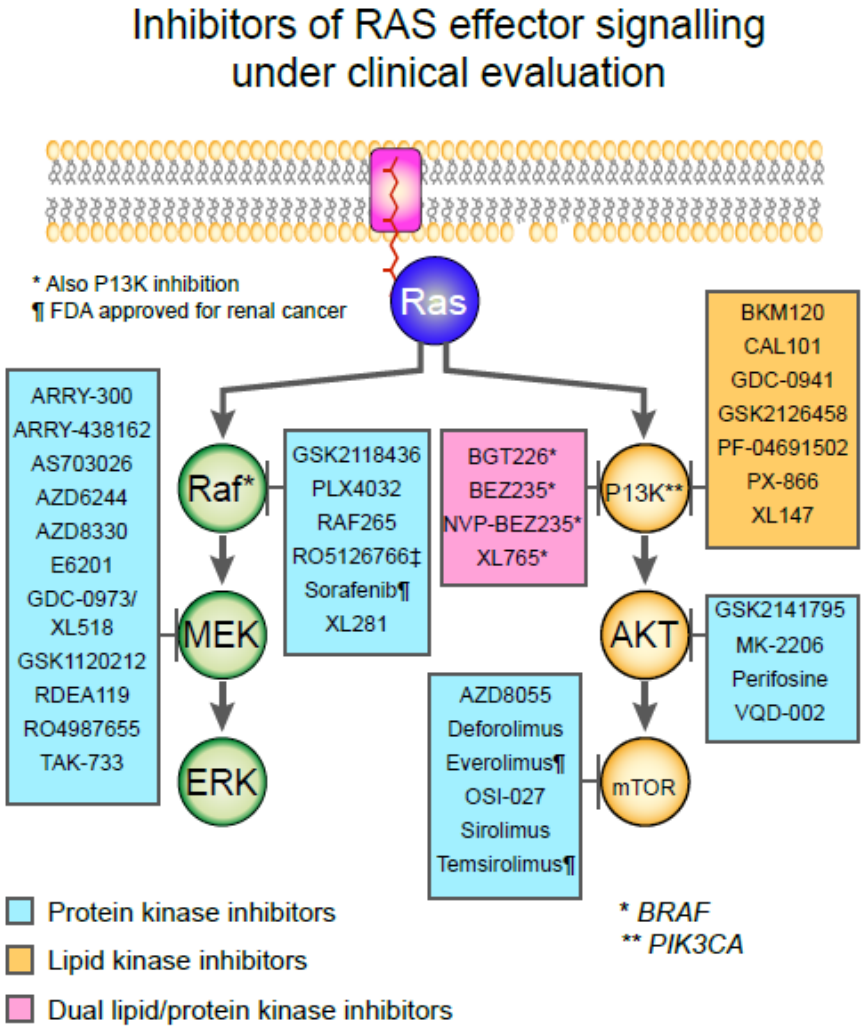
Adenocarcinoma de pulmón
Subtipos con tratamientos específicos



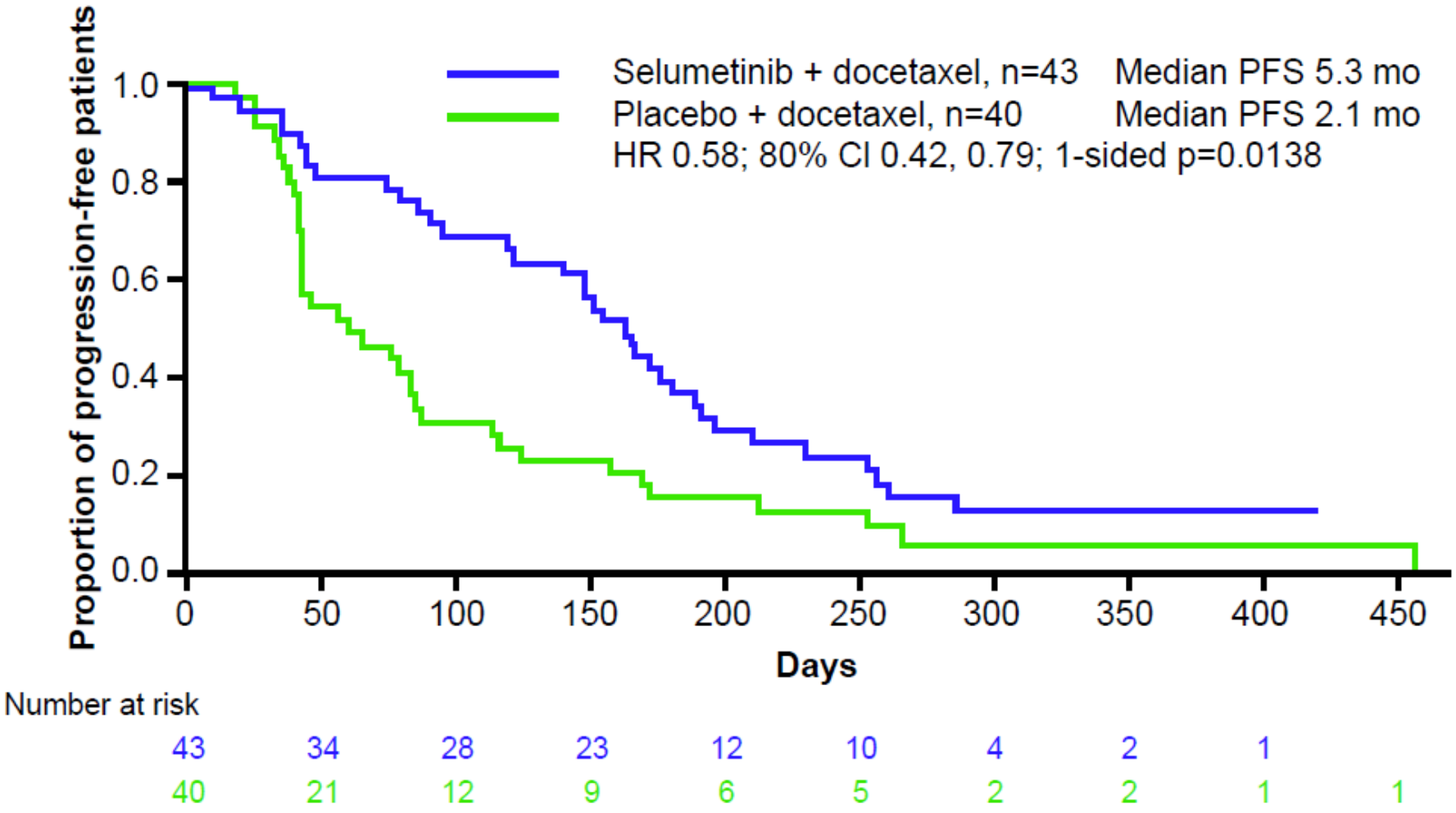
Targeting KRAS^{MUT} NSCLC





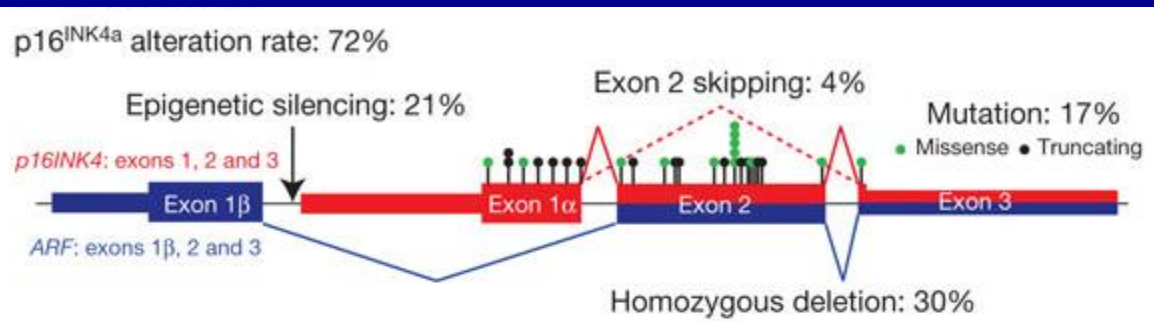
Adapted from Pritchard & Grady. Gut 2011;60:116–19

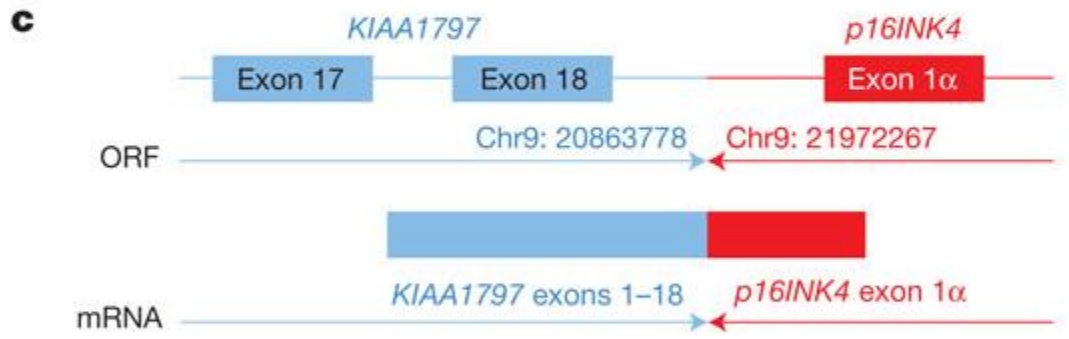
Targeting KRAS^{MUT} NSCLC
MEK 1/2 inhibition: PFS

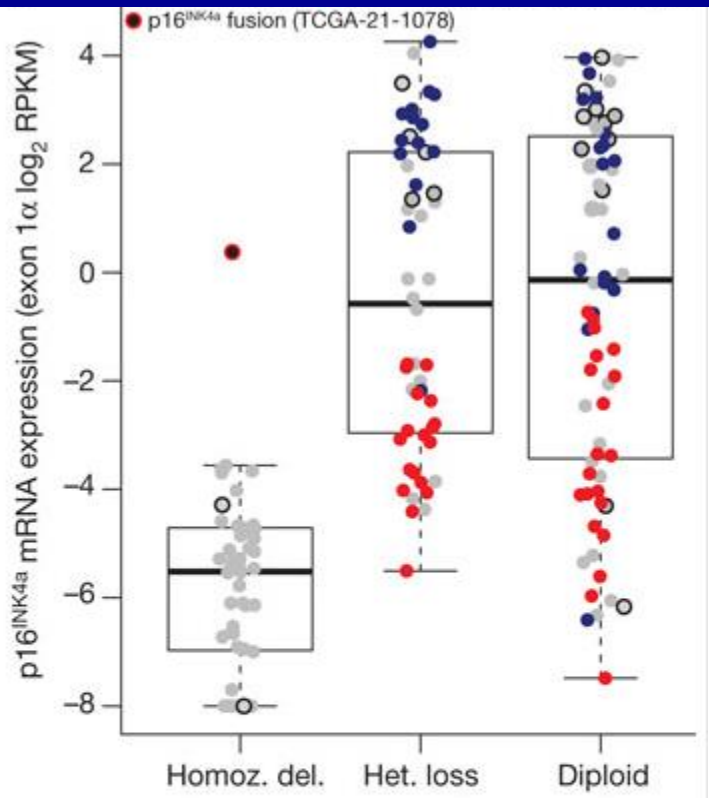


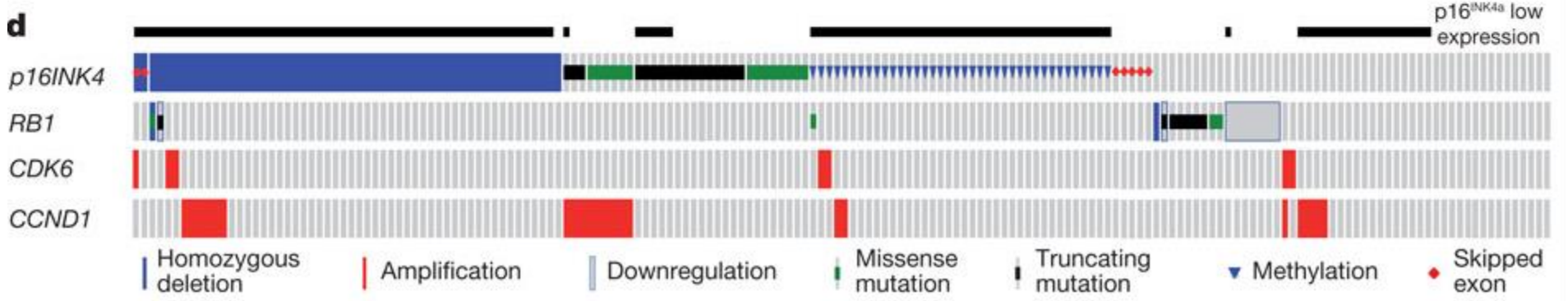
Janne PA, et al. J Clin Oncol 2012;30(suppl):abstract 7503

CDKN2A is predominantly deleted in squamous NSCLC





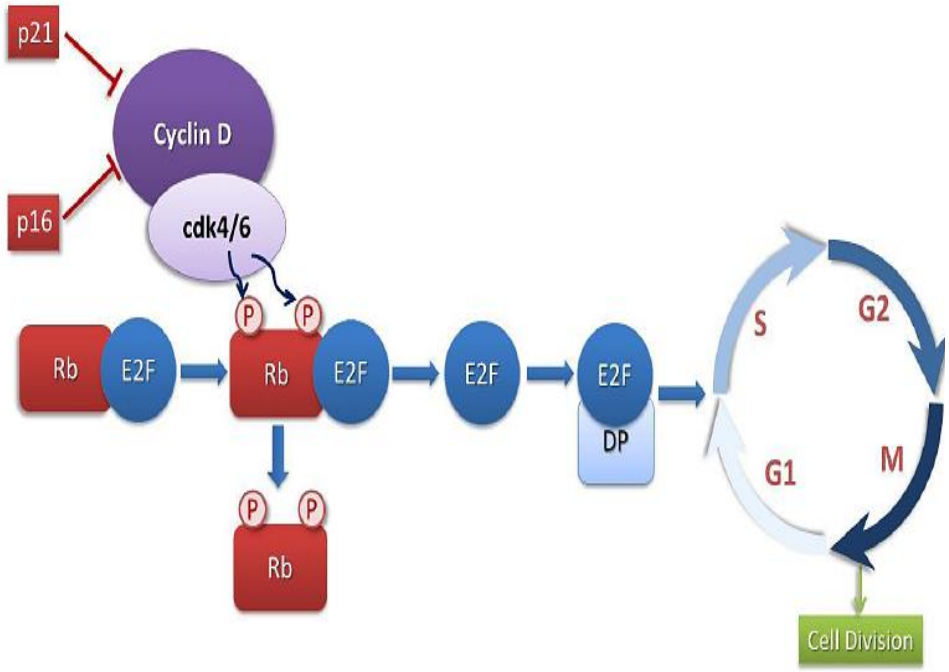




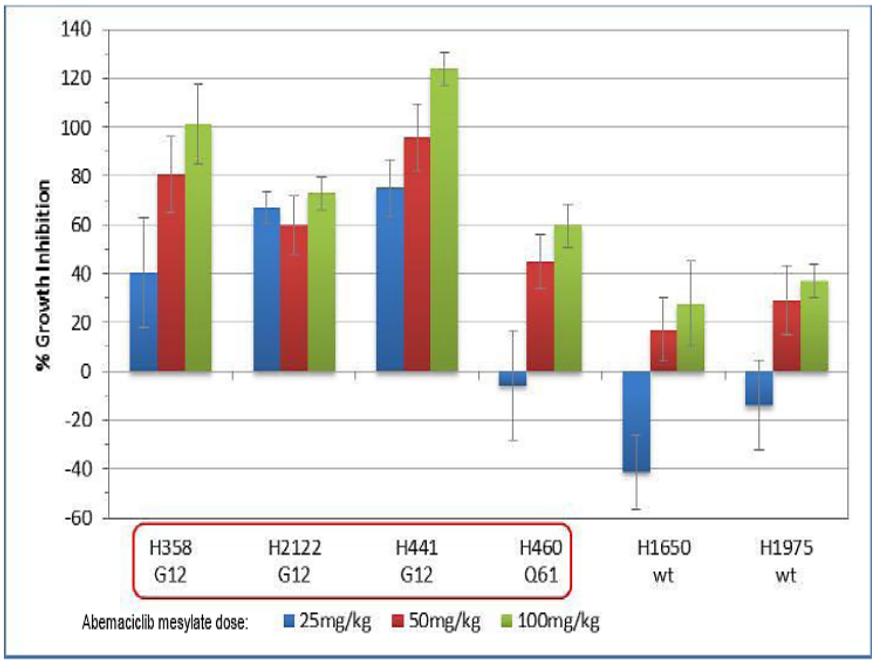
Cancer Genome Atlas Research Network. Nature 2012;489:519–25

Targeting CDK4

CDK4/6 Regulates G1→S Cell Cycle Progression



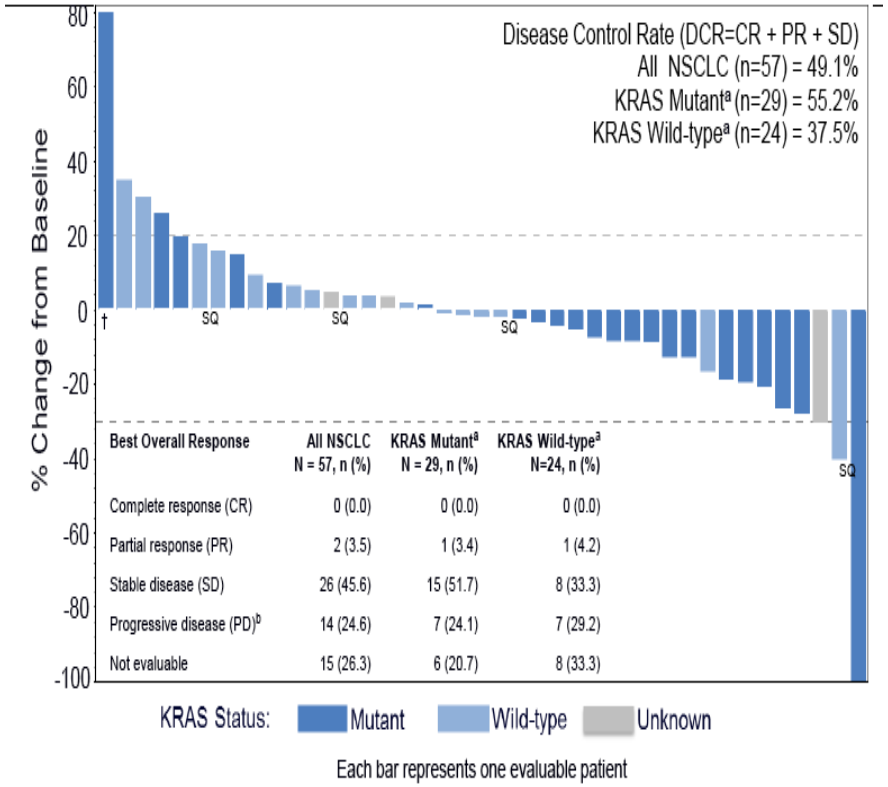
NSCLC Models with Activated KRAS: Evidence for Greater Sensitivity to Abemaciclib



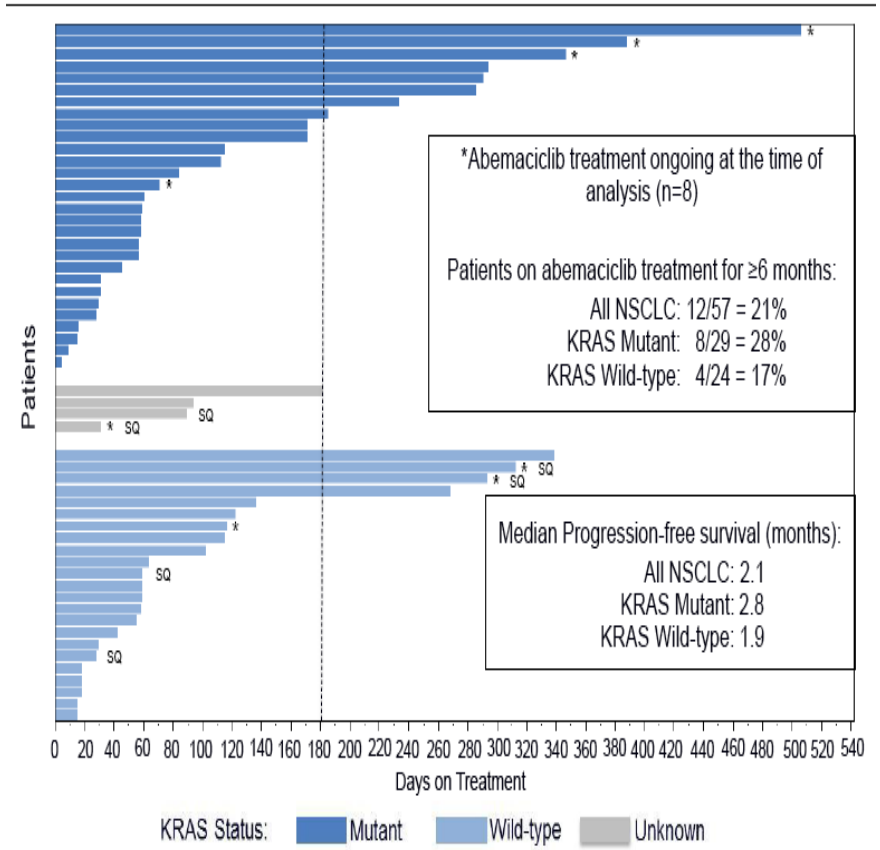
Goldman JW, et al. J Clin Oncol 2014;32(suppl):abstract 8026

Abemaciclib in NSCLC

Change in tumour size at best response for the NSCLC cohort

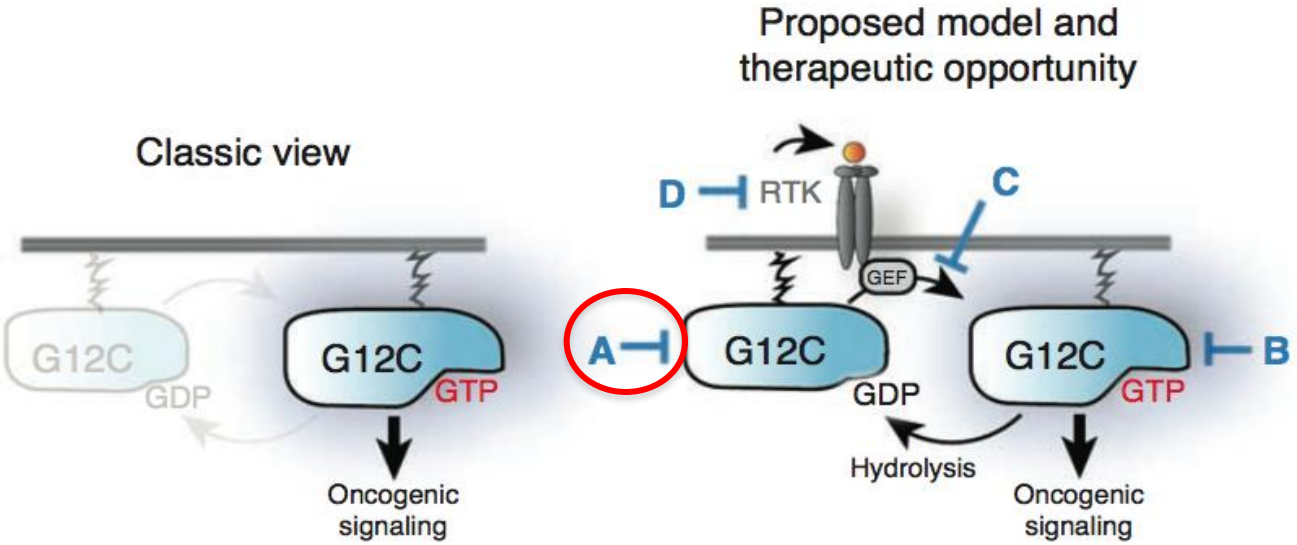


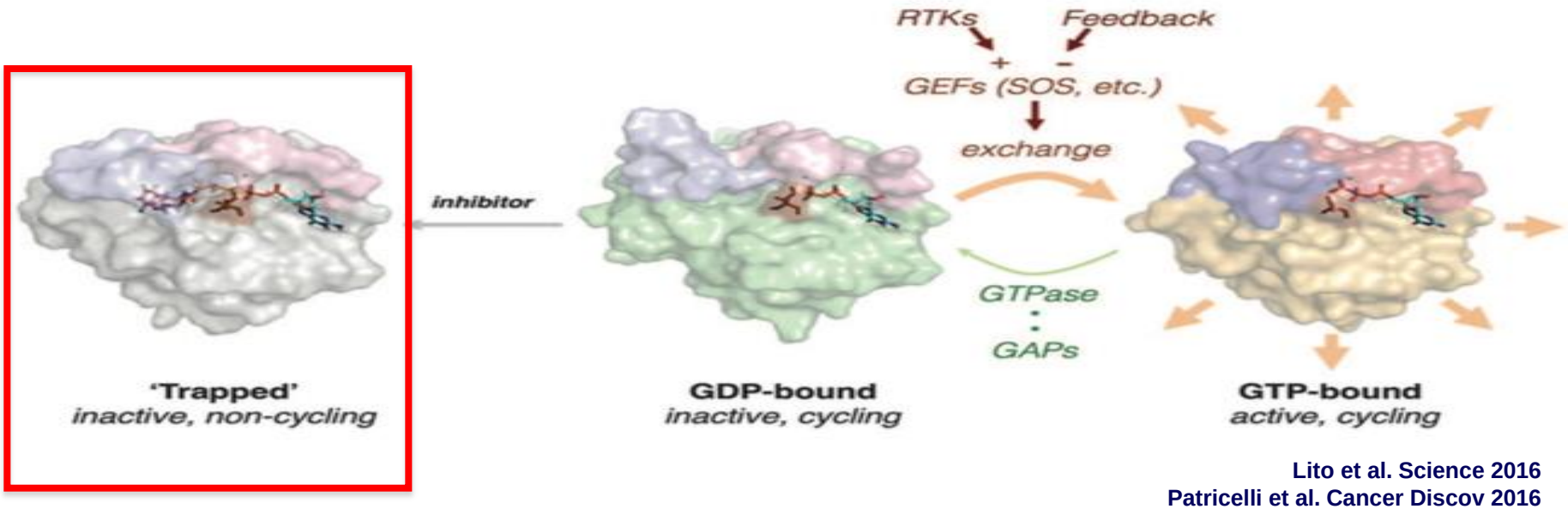
Treatment duration for NSCLC patients



Goldman JW, et al. J Clin Oncol 2014;32(suppl):abstract 8026

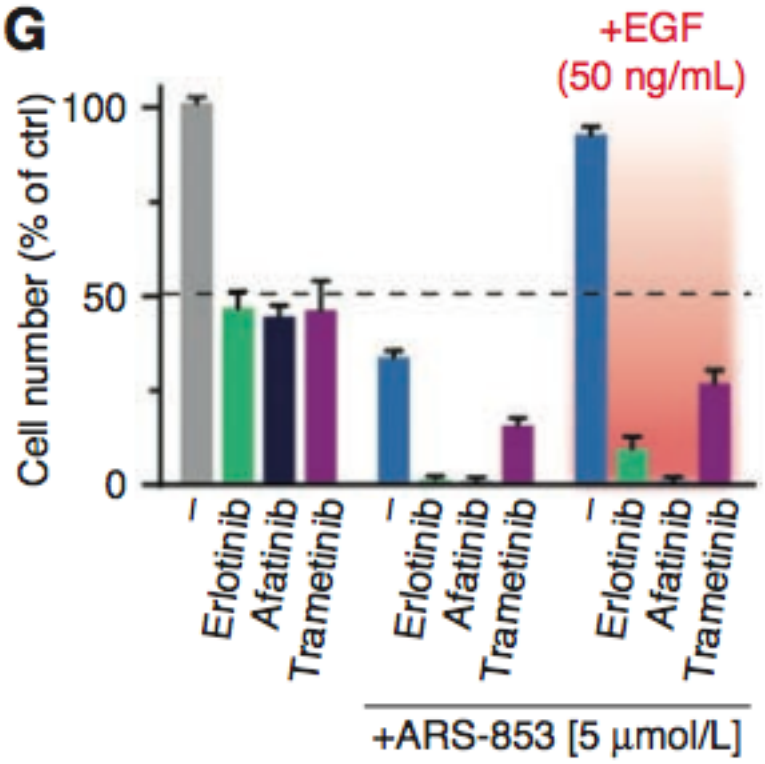
KRAS G12C Covalent Inhibitors

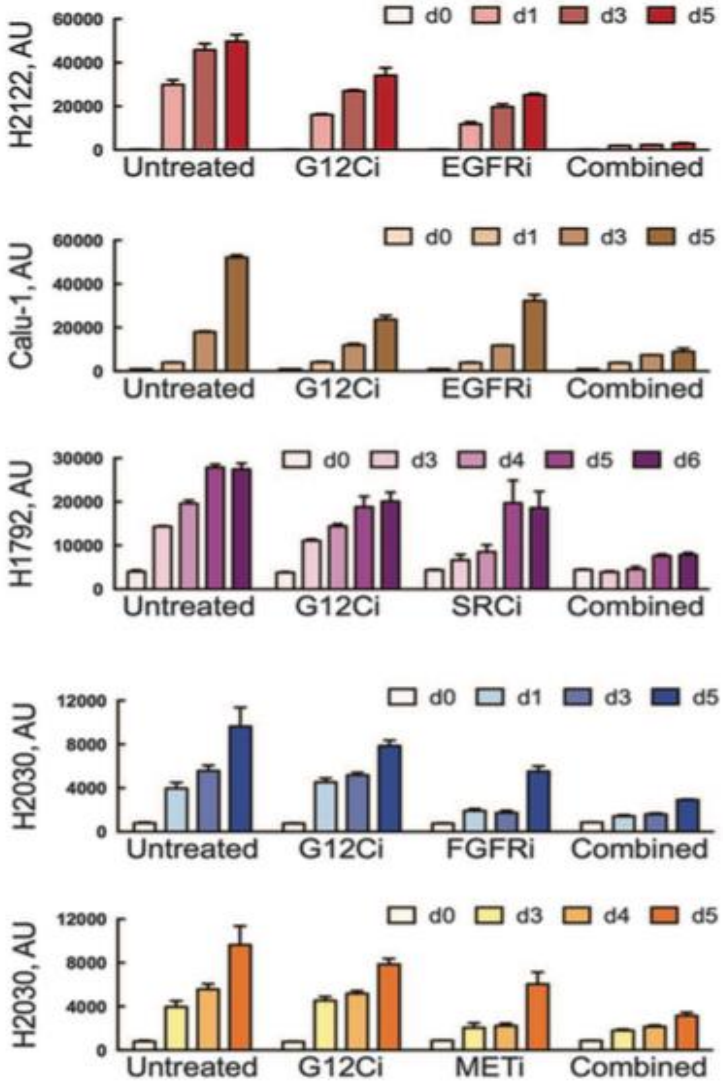




Lito et al. Science 2016
Patricelli et al. Cancer Discov 2016

KRAS G12C Covalent Inhibitors





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

Juniper Randomized Phase III Trial
Abemaciclib vs Erlotinib

- Stage IV or Relapsed NSCLC
- Kras mutation
- 1-2 lines of prior Chemo

Abemaciclib

Erlotinib

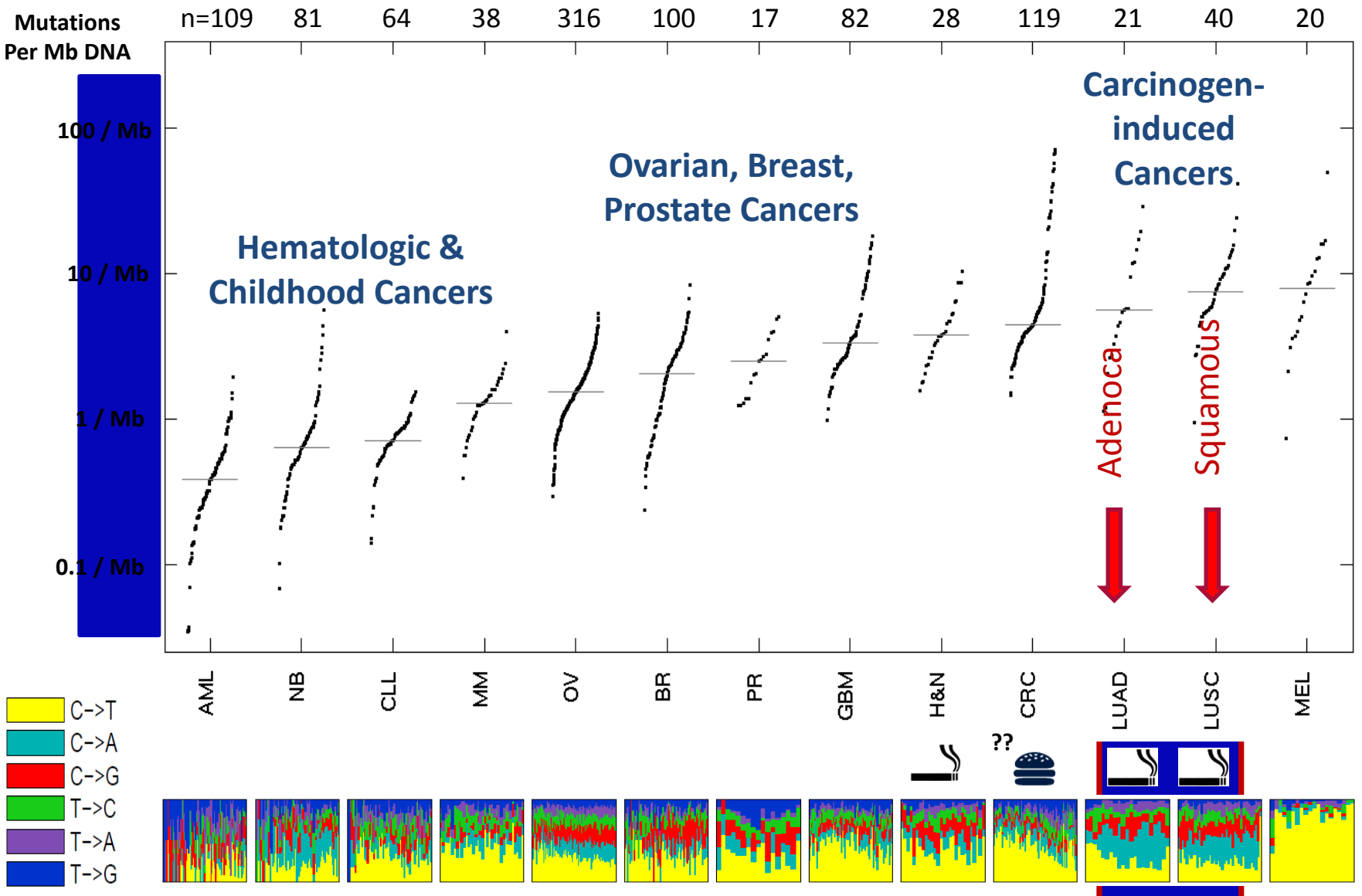
N= 550

Stratification factors

- ECOG PS (0 versus 1)
- Kras (12C vs Other)
- Prior chemo lines (1 versus 2)
- Male versus Female

PIs: JW Goldman & L Paz-Ares

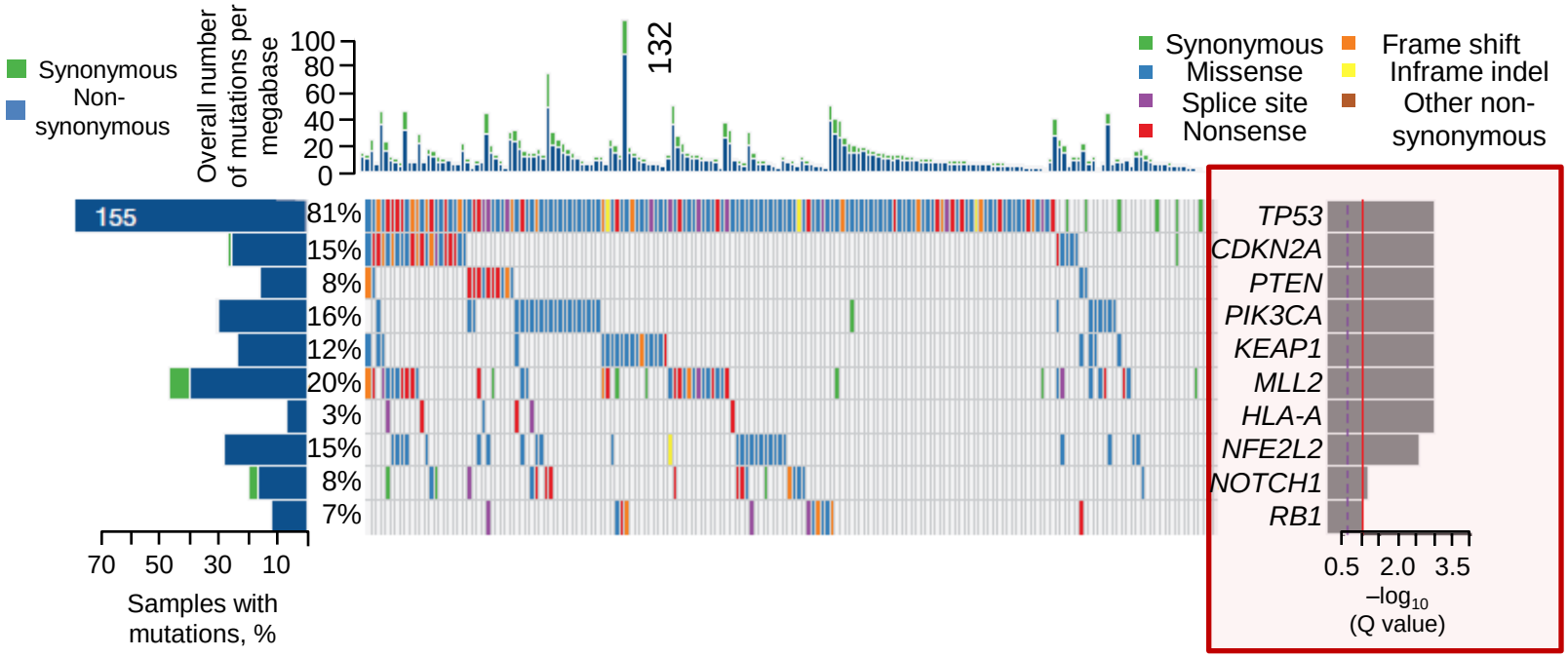
Las aberraciones genómicas son muy frecuentes en cáncer de pulmón



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

Squamous cell carcinomas frequently have genetic mutations in multiple pathways

Significantly mutated genes in squamous NSCLC[1]

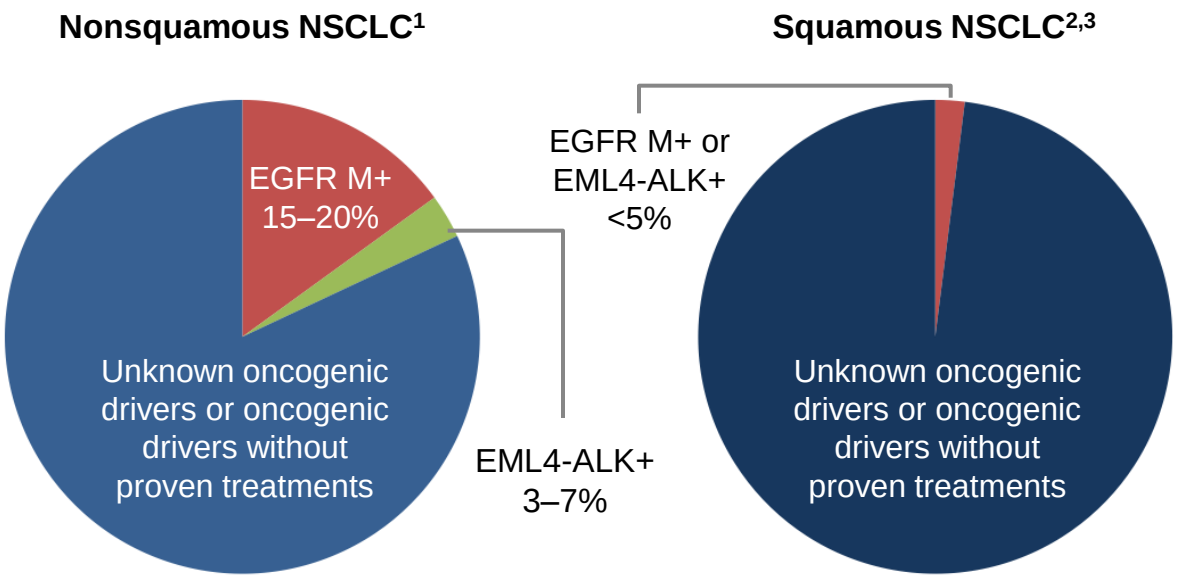


Statistically significant recurrent mutations found in 10 genes, including mutation of TP53 in nearly all specimens

CDKN2A, cyclin-dependent kinase inhibitor 2A; HLA-A, human leukocyte antigen A; KEAP1, kelch-like ECH-associated protein 1; MLL2, mixed lineage leukemia 2; NFE2L2, nuclear factor (erythroid derived 2)-like 2; NOTCH1, neurogenic locus notch homolog protein 1; NSCLC, non-small cell lung cancer; PIK3CA, phosphatidylinositol 3-kinase catalytic subunit; PTEN, phosphatase and tensin homolog; RB1, retinoblastoma 1; TP53, tumor protein 53

1. The Cancer Genome Atlas Research Network. *Nature* 2012;489:519–25

Oncogenic drivers with effective treatments are rare in squamous vs nonsquamous NSCLC[1-3]

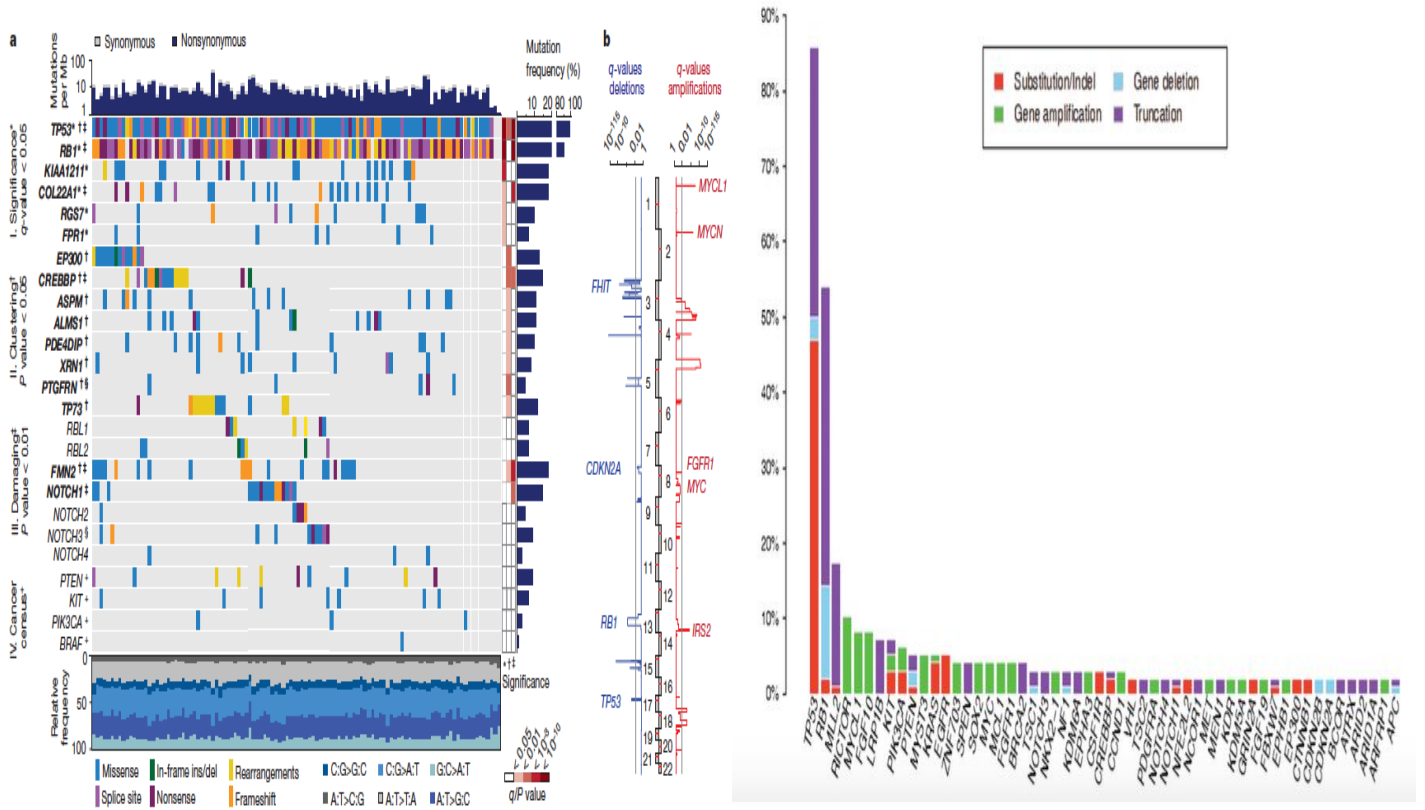


ALK, anaplastic lymphoma kinase;
EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer

1. Gerber DE et al. *Am Soc Clin Oncol Educ Book* 2014:e353–65;
2. Pao W, Girard N. *Lancet Oncol* 2011;12:175–80;
3. Perez-Moreno P et al. *Clin Cancer Res* 2012;18:2443–51

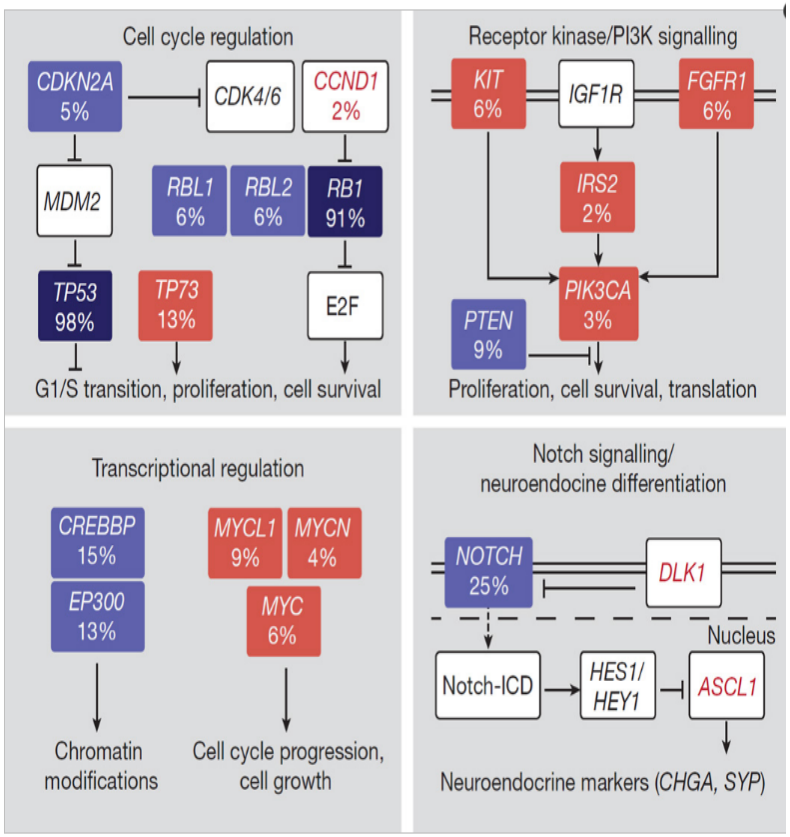
Biological Characteristics of SCLC

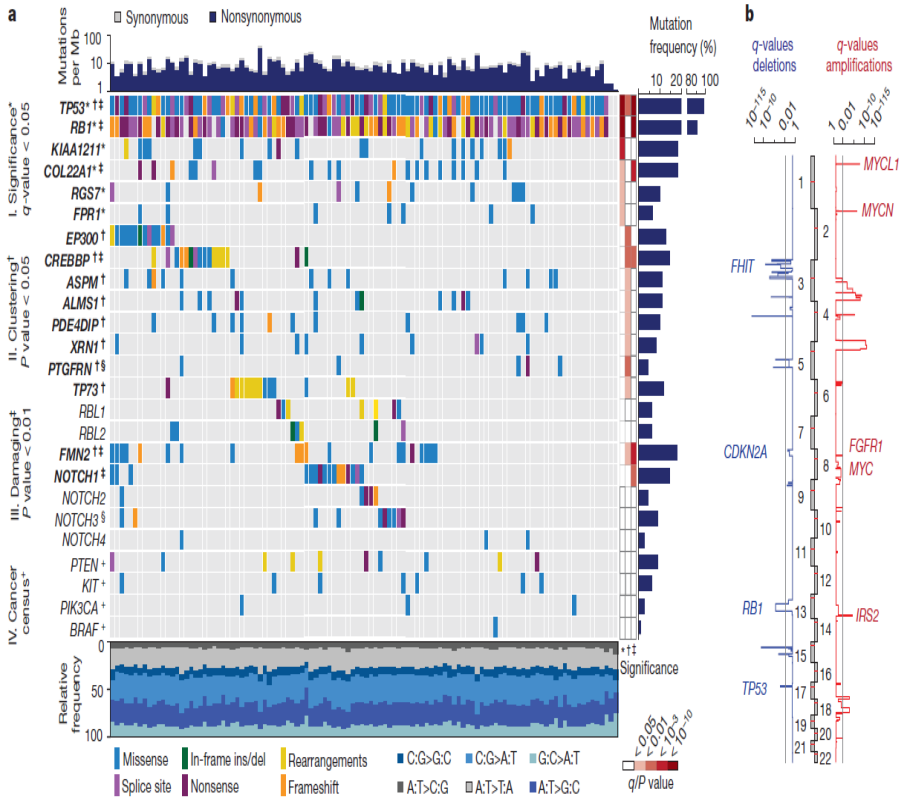
- SCLC sequencing on 110 whole genomes found evidence for a nearly universal and biallelic loss of TP53 and RB1 (left panel).
- SCLC sequencing on 98 patient samples revealed 53% had $\geq$ 1 actionable mutation (right panel)
- Low frequency targetable mutations: NOTCH1, BRAF, PIK3CA, and KIT.
- Amplification of FGFR1 and MYC family genes.
- Mutation frequency is high.



George J et al, Nature 2015, 524:47-53.;Ross JS et al; J Clin Path 2014

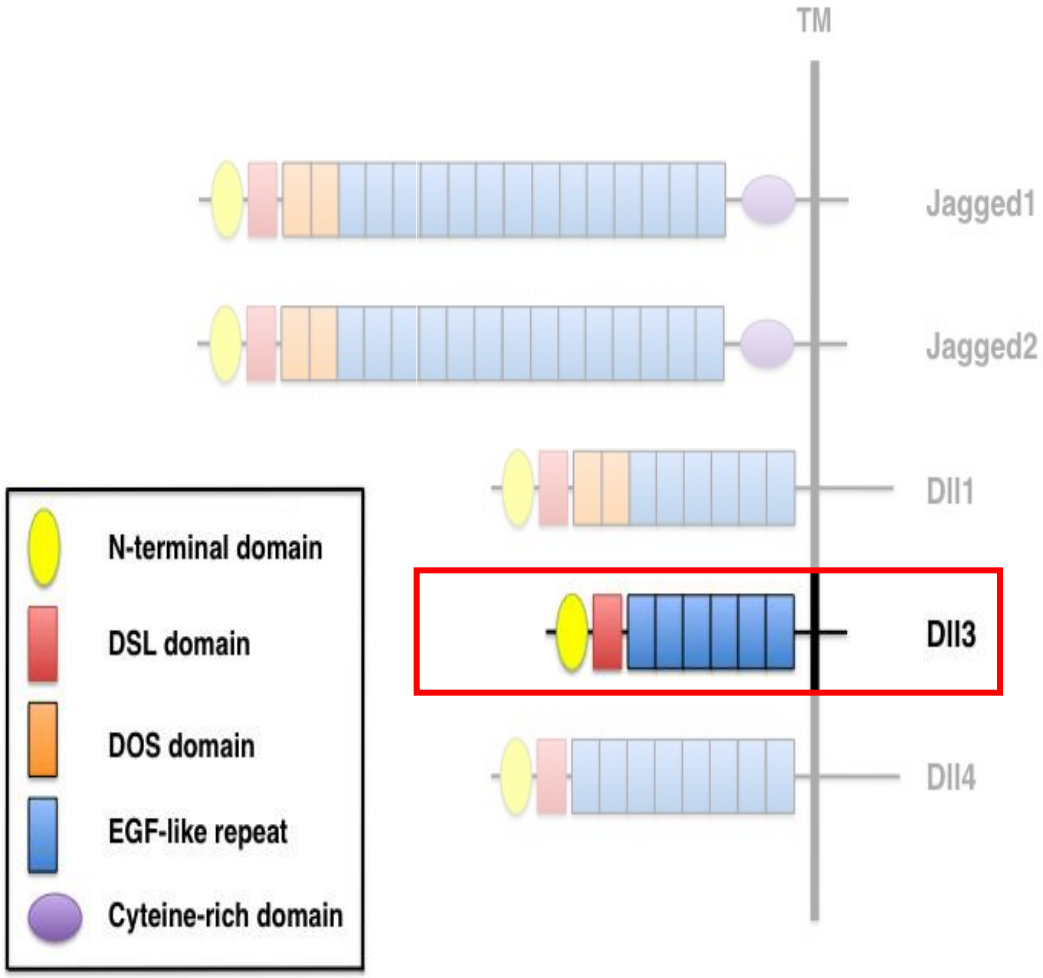
SCLC Genomic Landscape





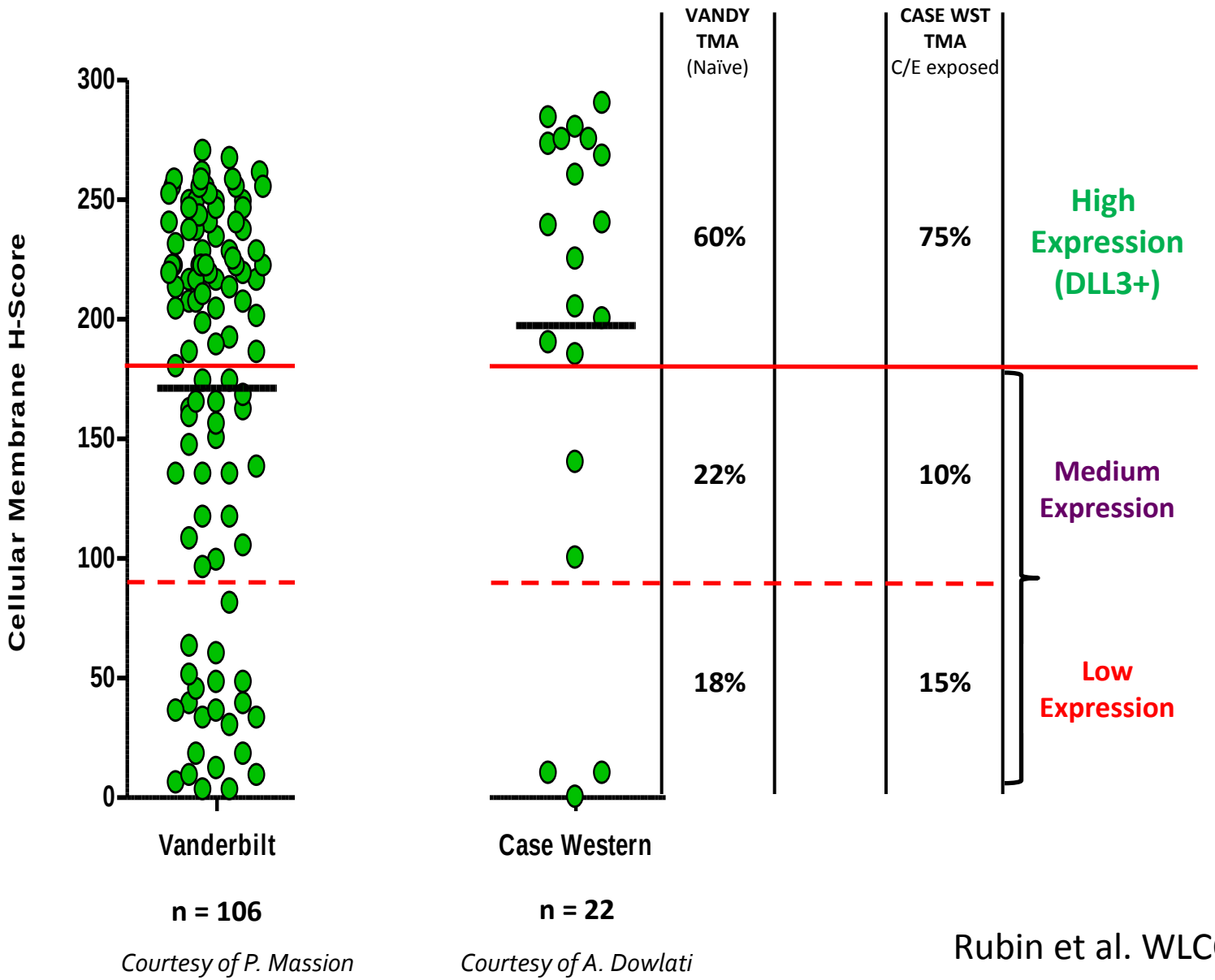
J. Gorge et al..Nature.2015 524(7563): 47–53

DLL3 is a dominant inhibitor of Notch signaling



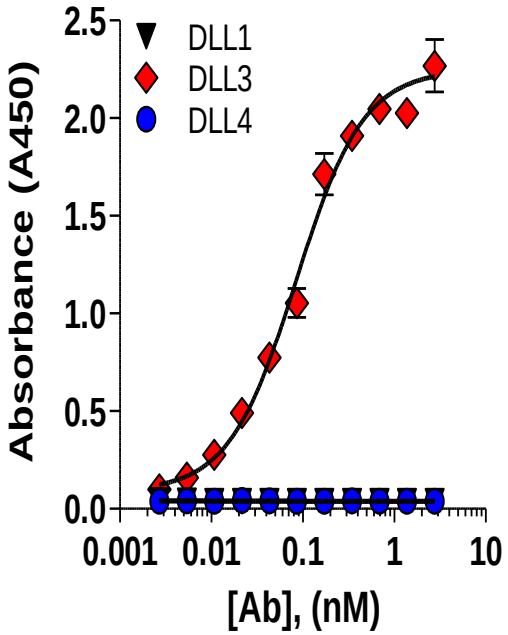
- Normally expressed during development in the Golgi
- Aberrantly expressed in SCLC tumor-initiating cells
- Interacts with and inhibits Notch1 in *cis*
- May mediate Notch inhibition downstream of ASCL1

DLL3 expression by IHC in SCLC

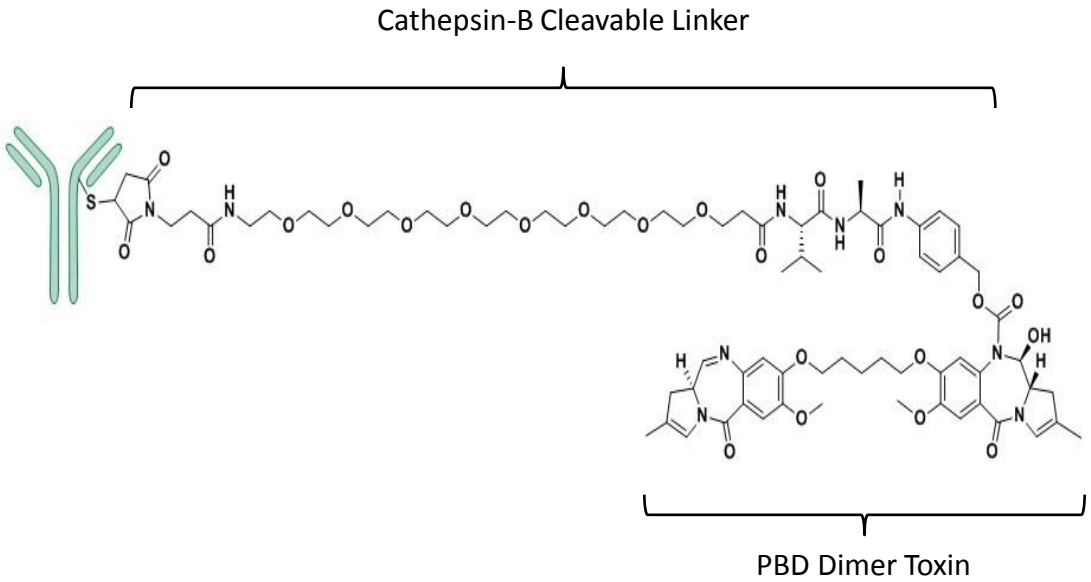


Rubin et al. WLCC 2015

Rovalpituzumab Tesirine (Rova-T™; SC16LD6.5)



Drug-to-Antibody Ratio (DAR) = 2

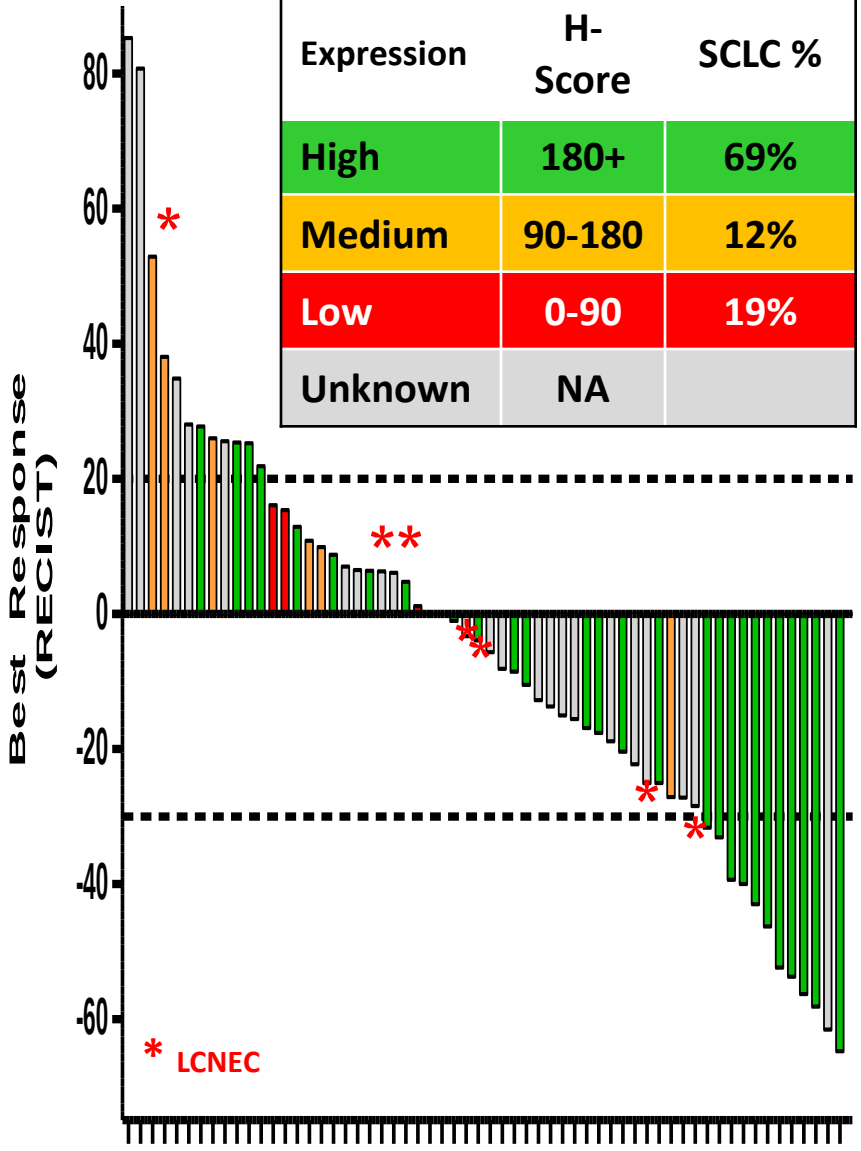


Rubin et al. WLCC 2015

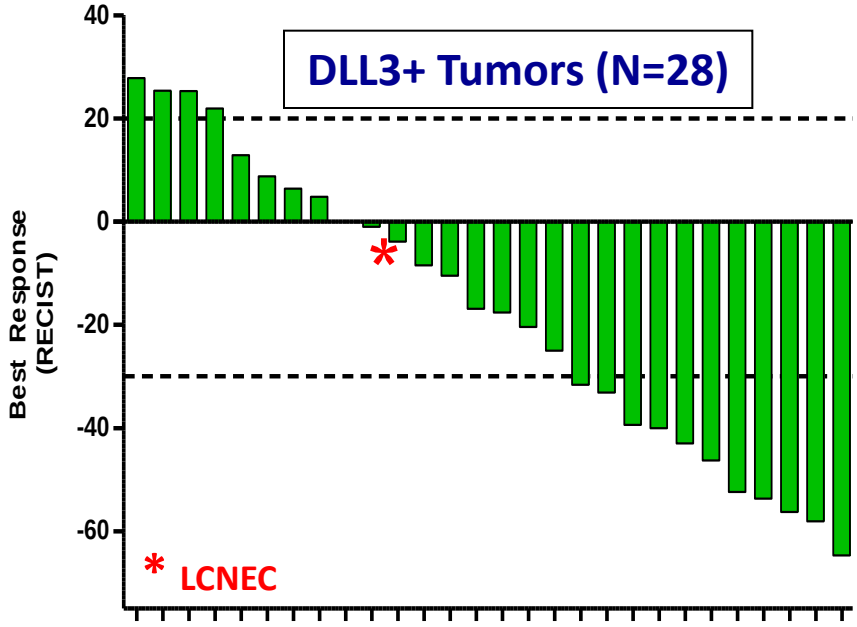
Rova-T: best response in evaluable patients

0.2 mg/kg q3w and 0.3 mg/kg q6w cohorts (n=60)

Expression	H-Score	SCLC %
High	180+	69%
Medium	90-180	12%
Low	0-90	19%
Unknown	NA	



	Topotecan†	All Pts & dose levels	DLL3+ Ph 1b Cohorts
2nd Line	17%	22%	40%
3rd Line	No Approved Drug	17%	38%

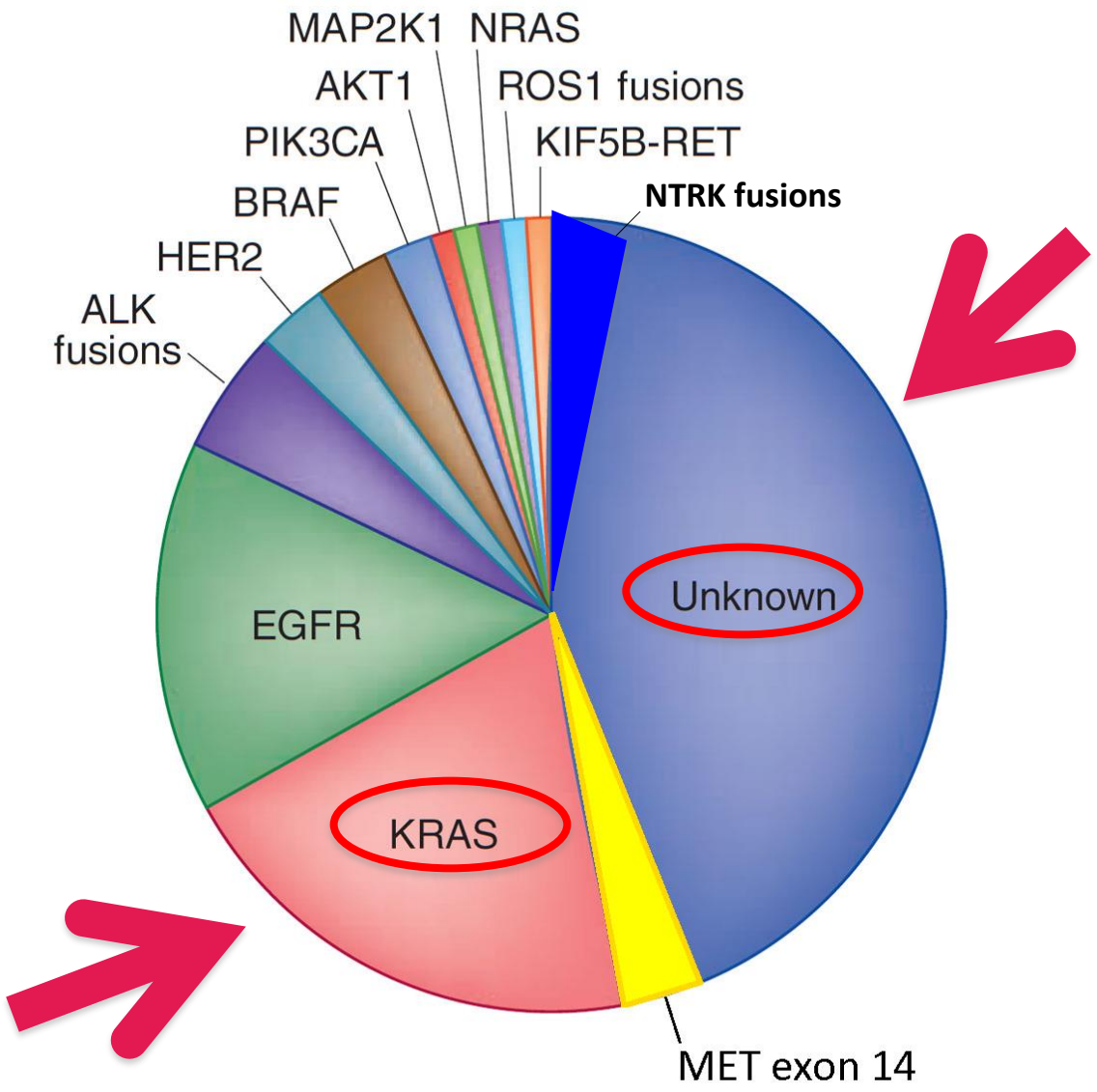


Rubin et al. WLCC 2015

Agenda

- Conocimiento y tecnología
- Adicción oncogénica
- Subgrupos difíciles
- **Estrategias prometedoras**
- Perspectivas

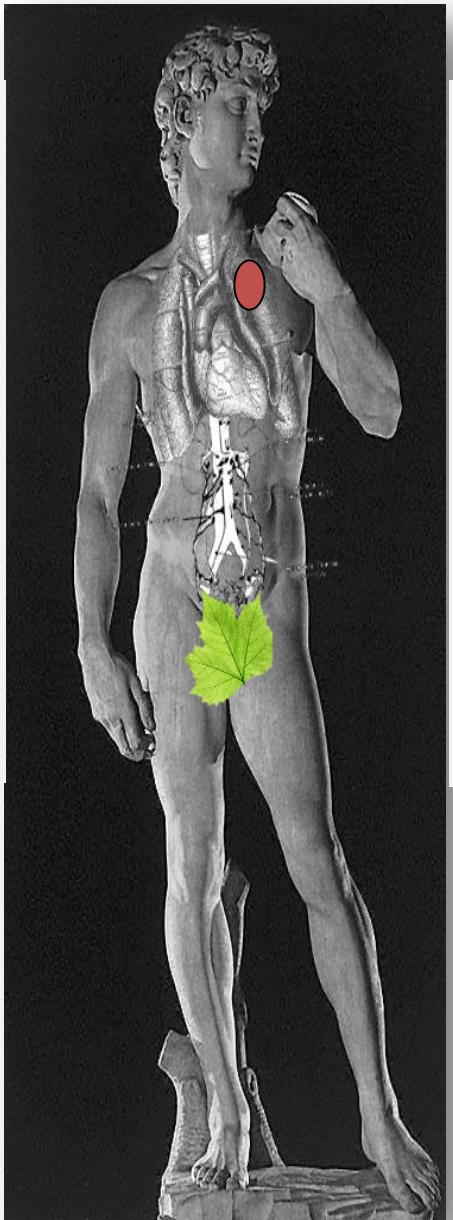
Adenocarcinoma de pulmón
Subtipos con tratamientos específicos



Una visión diferente del cáncer…

Visión de la Oncología Tradicional

Un CANCER que crece

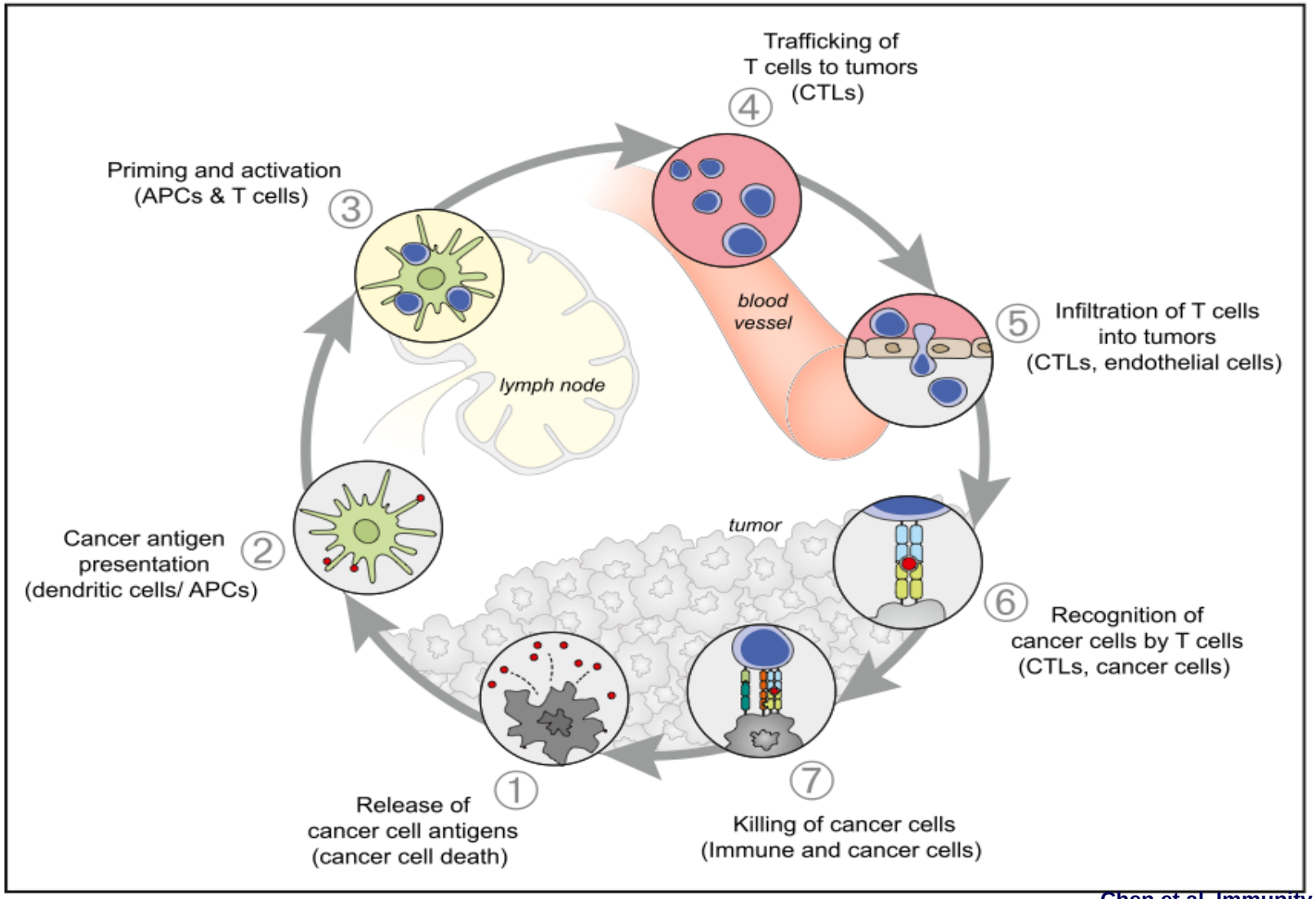


Visión de la Inmuno-Oncologia

Un CUERPO Que deja crecer el cáncer

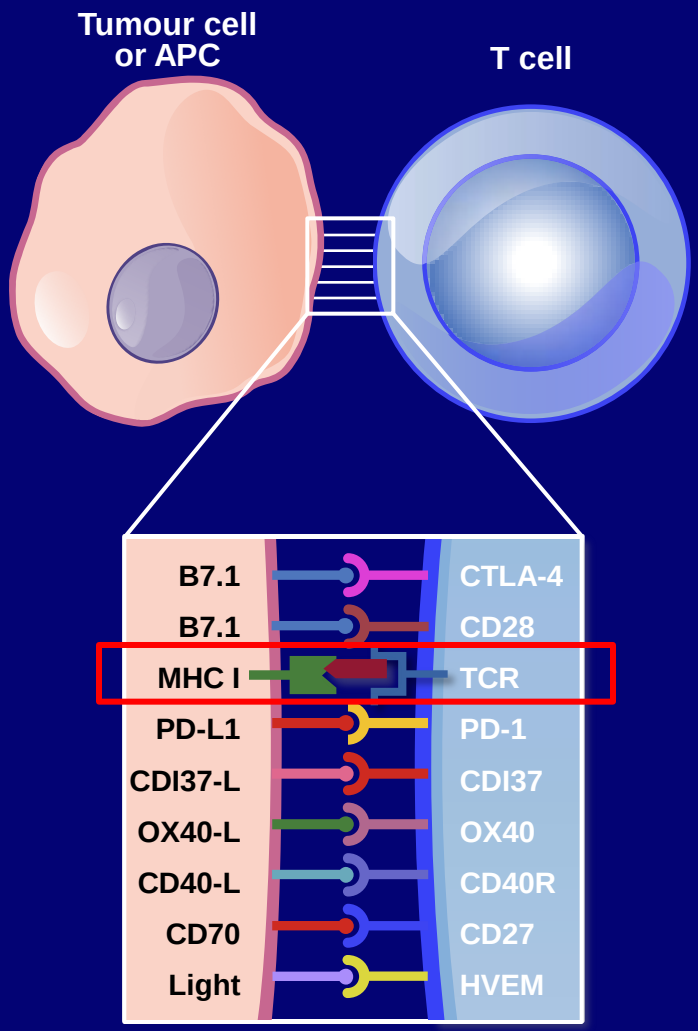
Michel-Ange 1500

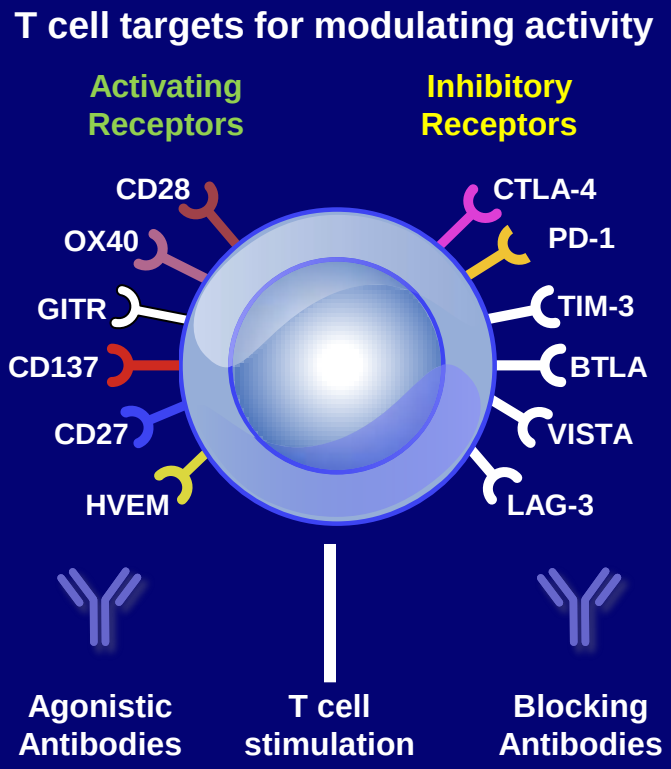
Ciclo de Inmunidad Tumoral



Chen et al. Immunity 2013

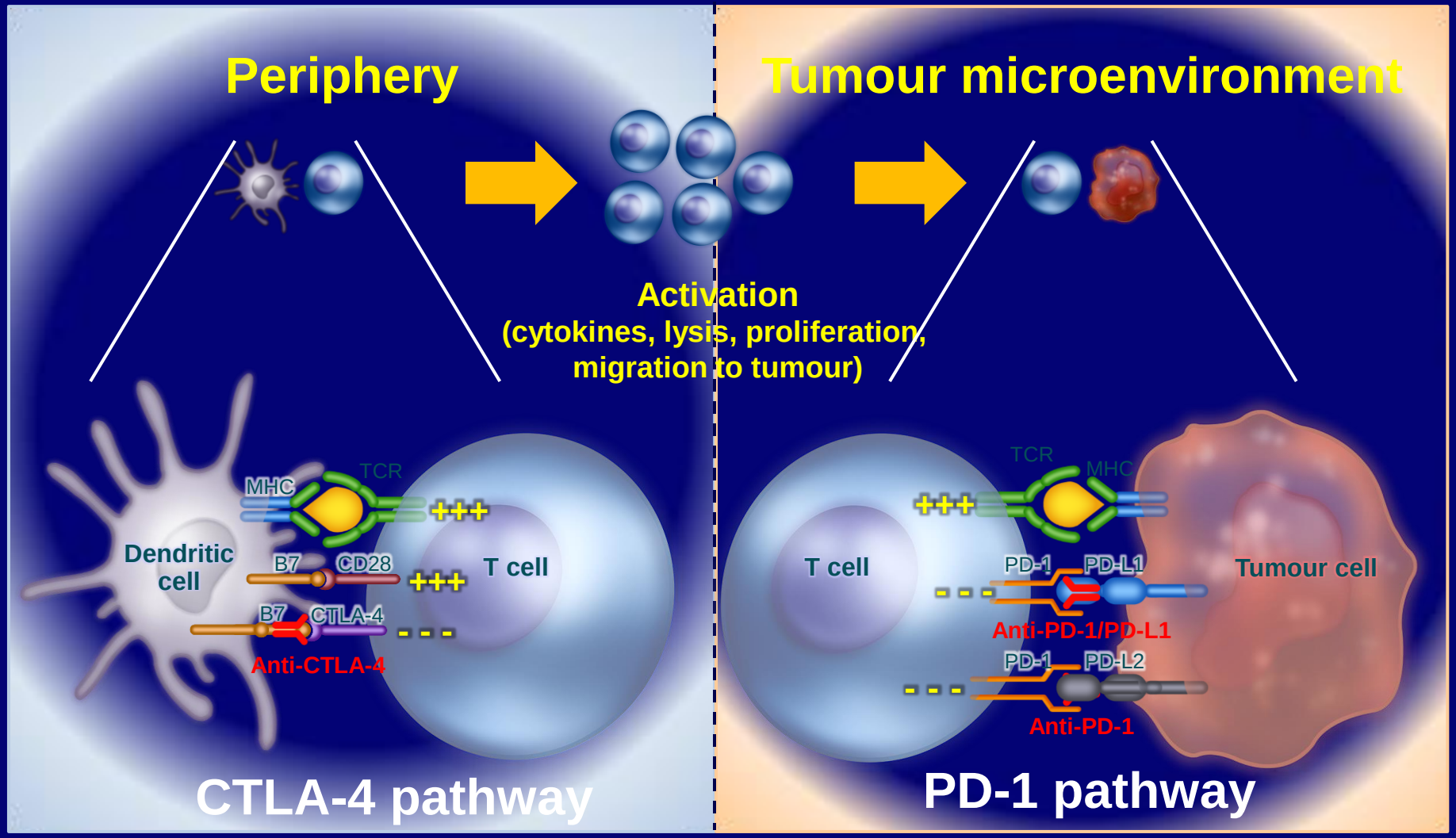
Inmunidad del cáncer: Balance entre señales estimuladoras e inhibitorias





Mellman Nature 2011; Pardoll Nat Rev Cancer 2012

Inhibición de la evasión inmune
Receptores CTLA-4 and PD-1



Wolchock J, et al. *J Clin Oncol* 2013;31(Issue 15_suppl); abstr 9012^

Inhibidores de PDL1/PD1 en Desarrollo

	Nivolumab	Pembrolizumab	Atezolizumab	Durvalumab	Avelumab
Company	Bristol-Myers Squibb	MSD	Roche	AstraZeneca	Merck KGaA/Pfizer
Brand name	OPDIVO®	KEYTRUDA®	TECENTRIQ®	IMFINZI™	BAVENCIO®
Target	PD-1	PD-1	PD-L1	PD-L1	PD-L1
Class	mAb (IgG4)	mAb (IgG4)	mAb (IgG1)	mAb (IgG1)	mAb (IgG1)
Dosing	3mg/kg q2w (EU) or 240mg q2w (US)	2mg/kg q3w (EU in ≥2L) or 200mg q3w (EU in 1L; US 1L and ≥2L)	1200mg q3w	20mg/kg q4w	10mg/kg q2w
Administration	Intravenous infusion	Intravenous infusion	Intravenous infusion	Intravenous infusion	Intravenous infusion
Indications /approvals in metastatic NSCLC	**FDA/EMA**: metastatic NSCLC after prior CT*	**FDA/EMA**: previously untreated, metastatic NSCLC with high PD-L1 expression [§] **FDA/EMA**: metastatic PD-L1+[¶] NSCLC after prior CT*	**FDA**: metastatic NSCLC after prior CT*	Not yet approved	Not yet approved
Pivotal trials in NSCLC	**Previously treated** CheckMate 017[‡], CheckMate 057[‡] **Treatment-naïve** CheckMate 026[‡], CheckMate 227	**Previously treated** KEYNOTE-010[‡] **Treatment-naïve** KEYNOTE-024[‡], KEYNOTE-042, KEYNOTE-021[‡], KEYNOTE-189, KEYNOTE-407	**Previously treated** POPLAR[‡], OAK[‡] **Treatment-naïve** IMpower110, IMpower130, IMpower131, IMpower132, IMpower150	**Previously treated** ATLANTIC ARCTIC **Treatment-naïve** NEPTUNE MYSTIC	**Previously treated** JAVELIN Lung 200 **Treatment-naïve** JAVELIN Lung 100
Diagnostic assay	28-8 (Dako platform)	22C3 (Dako platform)	SP142 (Ventana platform)	SP263 (Ventana platform)	73-10 (Dako platform)

*And approved therapy for *EGFR* Mut+ or *ALK*+ NSCLC; [‡]Study data reported; [§]TPS ≥50%; [¶]TPS ≥1%
TPS = tumour proportion score, the proportion of viable tumour cells showing partial or complete membrane PD-L1 expression

Inhibidores de PD-1/PD-L1 en CNMP Pretratado

	CheckMate 017 phase 3[125]		CheckMate 057 phase 3[126]		KEYNOTE-010 phase 3[127]			POPLAR phase 2[128]		Durvalumab phase 1b[129]	Avelumab phase 1b[130]
	Nivolumab	Docetaxel	Nivolumab	Docetaxel	Pembrolizumab 2 mg/kg	Pembrolizumab 10 mg/kg	Docetaxel	Atezolizumab	Docetaxel	Durvalumab	Avelumab
Patients (n)	135	137	292	290	345	346	343	144	143	198	184
Response rate (%)											
All patients	20	9	19	12	18	19	9	15	15	16	14
PD-L1 positive	21	8	36	13	30	29	8	38	13	27	16
PD-L1 negative	15	12	10	14	NA	NA	NA	8	10	5	10
Median progression-free survival (months)											
All patients	3·5	2·8	2·3	4·2	3·9	4·0	4·0	2·7	3·0	NA	2·9
PD-L1 positive	4·8	3·1	5·0	3·8	5·0	5·2	4·1	2·8	3·0	NA	3·0
PD-L1 negative	4·2	2·9	2·1	4·2	NA	NA	NA	1·7	4·1	NA	1·4
Median overall survival (months)											
All patients	9·2	6·0	12·2	9·4	10·4	12·7	8·5	12·6	9·7	NA	8·9
PD-L1 positive	10	6·4	19·4	8·1	14·9	17·3	8·2	15·5	9·2	NA	8·4
PD-L1 negative	8·5	6·1	9·8	10·1	NA	NA	NA	9·7	9·7	NA	4·6
Histology	SCC	SCC	Non-SCC	Non-SCC	All comers	All comers	All comers	All comers	All comers	All comers	All comers
Setting	Second line	Second line	Second line	Second line	Second line	Second line	Second line	Second line	Second line	Pre-treated	Pre-treated
PD-L1 expression											
Positive	≥5%	≥5%	≥5%	≥5%	Highly positive ≥50%; positive ≥1%	Highly positive ≥50%; positive ≥1%	Highly positive ≥50%; positive ≥1%	Tumour cell 1–3 or tumour-infiltrating immune cells 1–3		≥25%	≥1%
Negative	<5%	<5%	<5%	<5%	<1% (not included)	<1% (not included)	<1% (not included)	Tumour cell 0 and tumour-infiltrating immune cells 0		<25%	<1%

Percentages rounded. PD-1=programmed death-1. PD-L1=programmed death ligand-1. SCC=squamous cell cancer. NA=not available.

Table 4: **Trials of anti-PD-1/PD-L1 inhibitors in patients with advanced NSCLC who were pre-treated with chemotherapy**

Hirsch et al. Lancet 2016

Inhibidores de PD-1/PD-L1 en CNMP Pretratado

	CheckMate 017 phase 3[125]		CheckMate 057 phase 3[126]		KEYNOTE-010 phase 3[127]			POPLAR phase 2[128]		Durvalumab phase 1b[129]	Avelumab phase 1b[130]
	Nivolumab	Docetaxel	Nivolumab	Docetaxel	Pembrolizumab 2 mg/kg	Pembrolizumab 10 mg/kg	Docetaxel	Atezolizumab	Docetaxel	Durvalumab	Avelumab
Patients (n)	135	137	292	290	345	346	343	144	143	198	184
Response rate (%)											
All patients	20	9	19	12	18	19	9	15	15	16	14
PD-L1 positive	21	8	36	13	30	29	8	38	13	27	16
PD-L1 negative	15	12	10	14	NA	NA	NA	8	10	5	10
Median progression-free survival (months)											
All patients	3·5	2·8	2·3	4·2	3·9	4·0	4·0	2·7	3·0	NA	2·9
PD-L1 positive	4·8	3·1	5·0	3·8	5·0	5·2	4·1	2·8	3·0	NA	3·0
PD-L1 negative	4·2	2·9	2·1	4·2	NA	NA	NA	1·7	4·1	NA	1·4
Median overall survival (months)											
All patients	9·2	6·0	12·2	9·4	10·4	12·7	8·5	12·6	9·7	NA	8·9
PD-L1 positive	10	6·4	19·4	8·1	14·9	17·3	8·2	15·5	9·2	NA	8·4
PD-L1 negative	8·5	6·1	9·8	10·1	NA	NA	NA	9·7	9·7	NA	4·6
Histology	SCC	SCC	Non-SCC	Non-SCC	All comers	All comers	All comers	All comers	All comers	All comers	All comers
Setting	Second line	Second line	Second line	Second line	Second line	Second line	Second line	Second line	Second line	Pre-treated	Pre-treated
PD-L1 expression											
Positive	≥5%	≥5%	≥5%	≥5%	Highly positive ≥50%; positive ≥1%	Highly positive ≥50%; positive ≥1%	Highly positive ≥50%; positive ≥1%	Tumour cell 1–3 or tumour-infiltrating immune cells 1–3		≥25%	≥1%
Negative	<5%	<5%	<5%	<5%	<1% (not included)	<1% (not included)	<1% (not included)	Tumour cell 0 and tumour-infiltrating immune cells 0		<25%	<1%

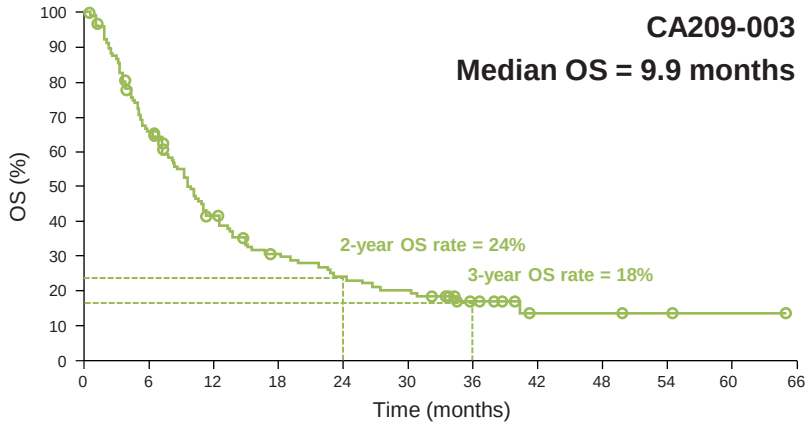
Percentages rounded. PD-1=programmed death-1. PD-L1=programmed death ligand-1. SCC=squamous cell cancer. NA=not available.

Table 4: **Trials of anti-PD-1/PD-L1 inhibitors in patients with advanced NSCLC who were pre-treated with chemotherapy**

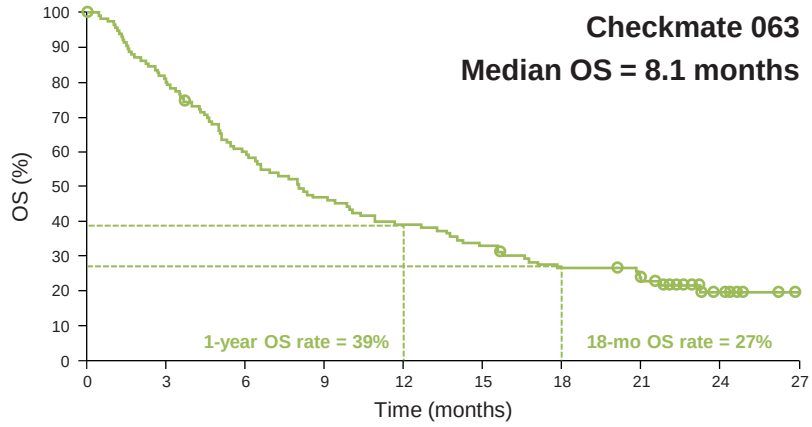
Hirsch et al. Lancet 2016

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

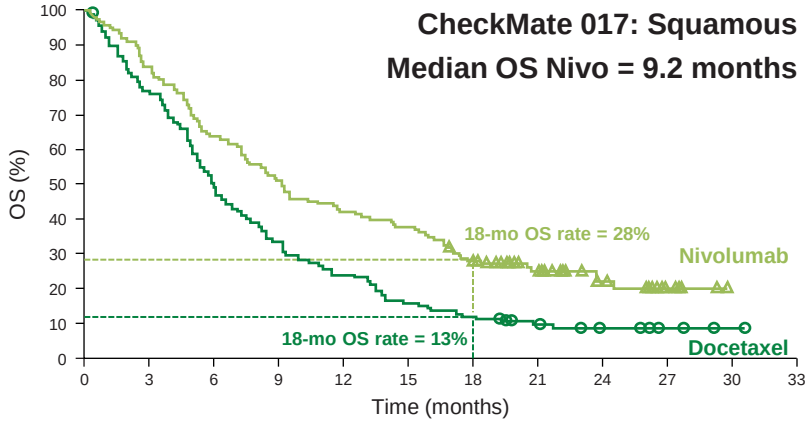
Phase 1 Data[1]

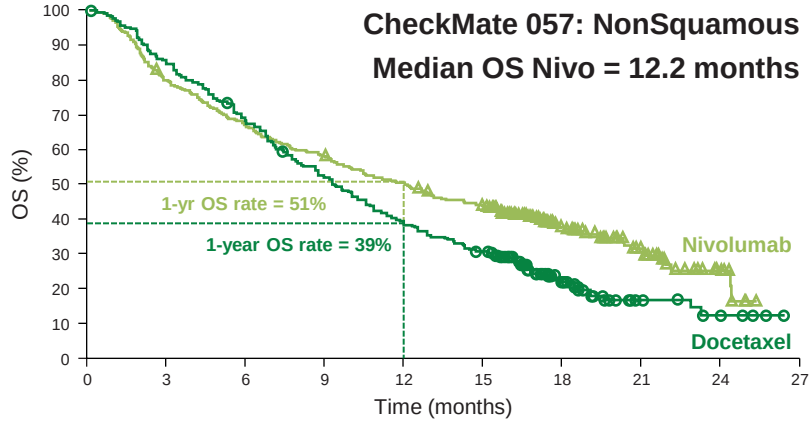


Phase 2 Data[2]



Phase 3 Data[3,4]

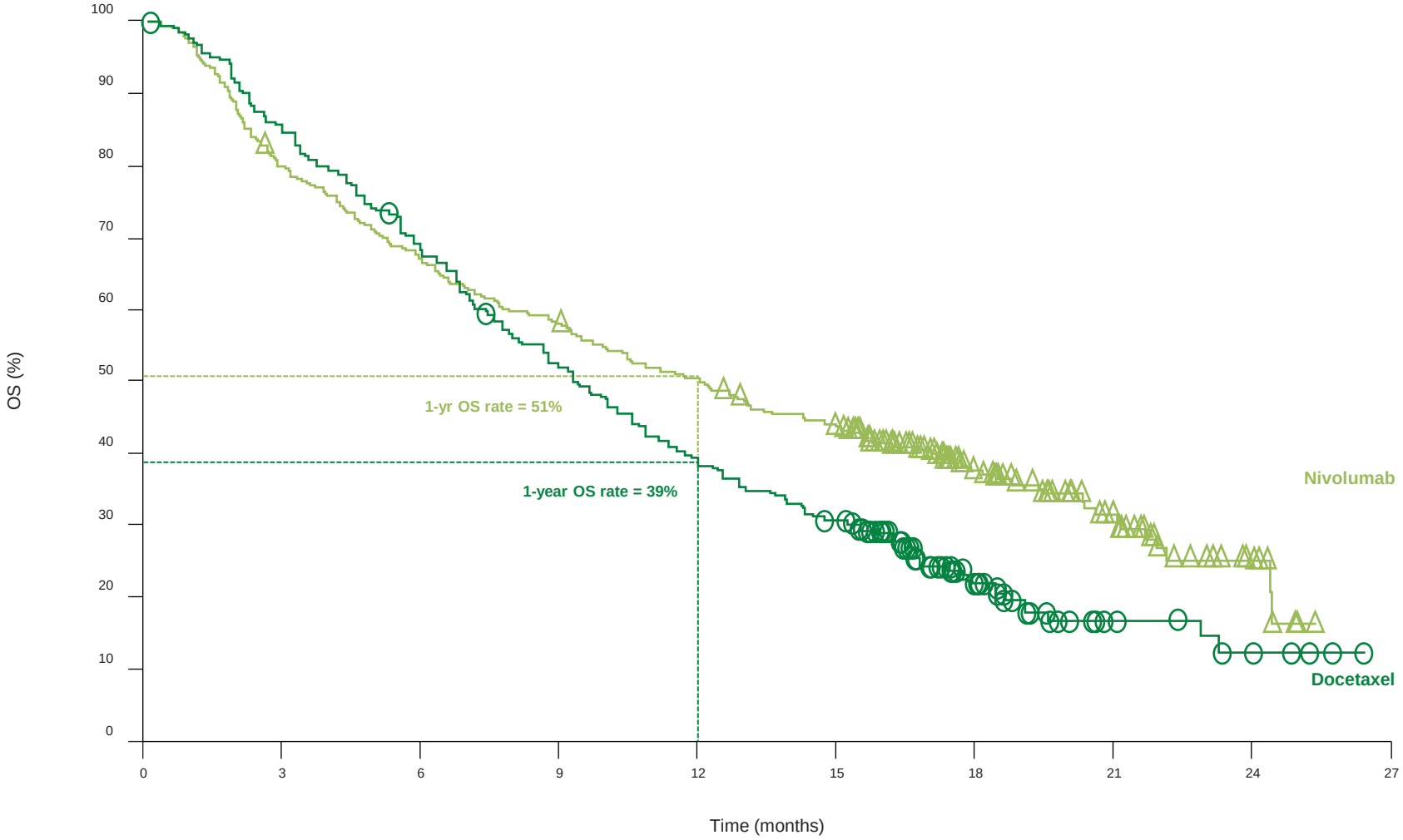




Gettinger S, JCO 2015, Brahmer J et al NEJM 2015

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

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



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

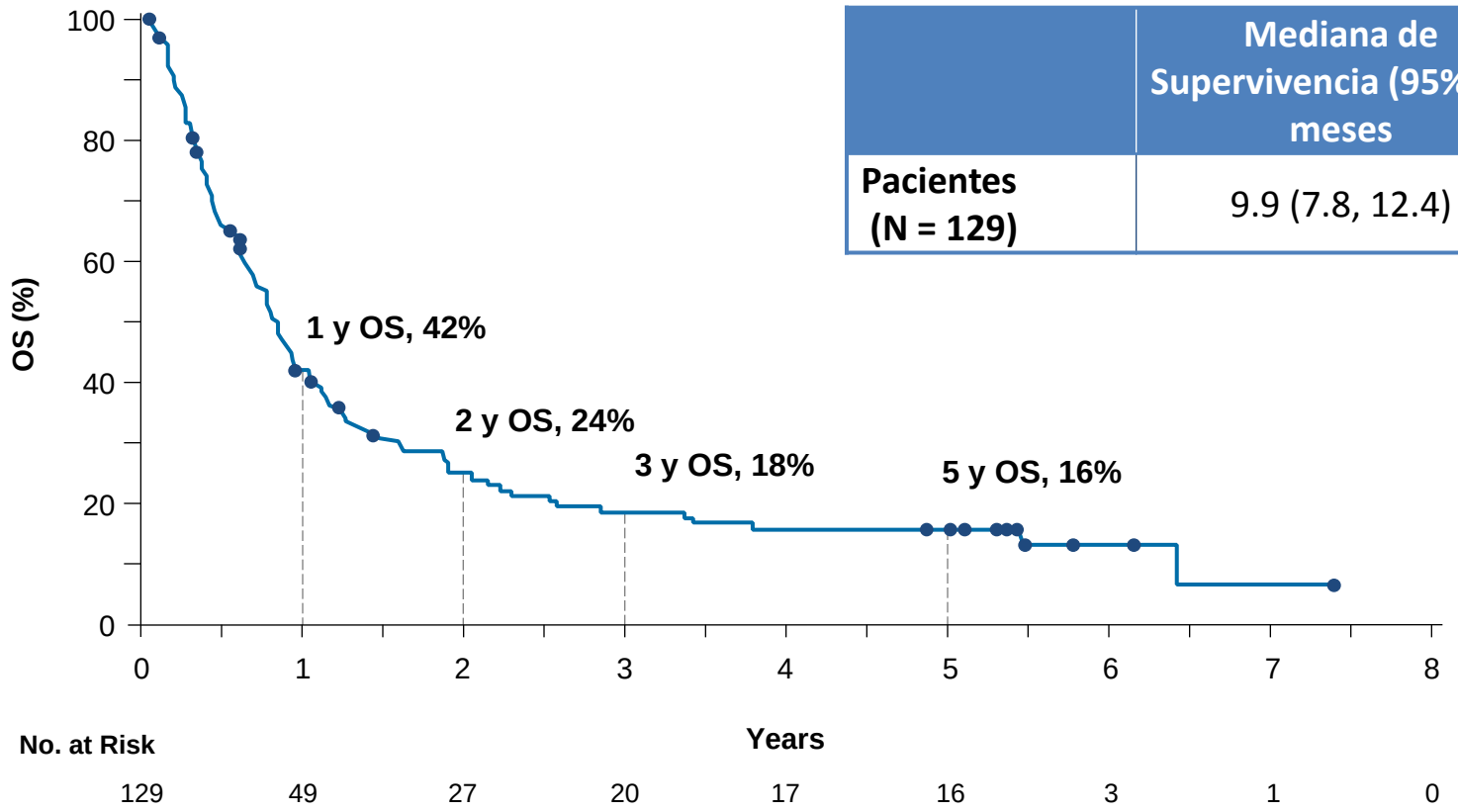
Inhibidores de PD-1/PD-L1 en CNMP Pretratado
Estudios de Fase III

	CheckMate 017[1] Nivolumab vs docetaxel	CheckMate 057[1] Nivolumab vs docetaxel	KEYNOTE-010[2] Pembrolizumab (2mg/kg or 10mg/kg) vs docetaxel	OAK[3] Atezolizumab vs docetaxel
Phase of study	**III**	**III**	**II/III**	**III**
PD-L1 selected	**No**	**No**	**Yes (TPS* ≥1%)**	**No**
Study size, n	**272 (135 vs 137)**	**582 (292 vs 290)**	**1,033 (344 vs 346 vs 343)**	**1,225 (425 vs 425)***
Histology	**Squamous**	**Non-squamous**	**All-comers**	**All-comers**
Line of therapy, % **2L** **3L** **>3L** **Other/unknown**	 **100** **0** **0** **0**	 **88** **11** **<1** **0**	 **69** **20** **9** **<1**	 **75** **25** **0** **0**
Subsequent CIT (immunotherapy arm vs chemo arm), %	**<1 vs 2**	**1 vs 2**	**0.6 vs 1.7 vs 13.1**	**4.5 vs 17.2**
Crossover from chemo arm to study immunotherapy, %	**4**	**6**	**Not permitted**	**Not permitted**
Median OS, months **HR vs docetaxel (p value)**	**9.2 vs 6.0** **0.62 (p=0.0004)**	**12.2 vs 9.5** **0.75 (p<0.001)**	**10.4 vs 12.7 vs 8.5** **2mg/kg: 0.71 (p=0.0008)** **10mg/kg: 0.61 (p<0.0001)**	**13.8 vs 9.6** **0.73 (p=0.0003)**

*850 in primary population
NR = not reached

1. Borghaei, et al. ASCO 2016
2. Herbst, et al. Lancet 2015; 3. Barlesi, et al. ESMO 2016

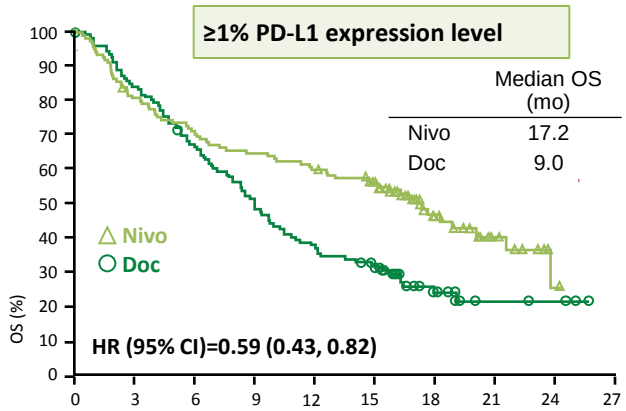
Cáncer de Pulmón Tratado con Nivolumab
Supervivencia a 5 años

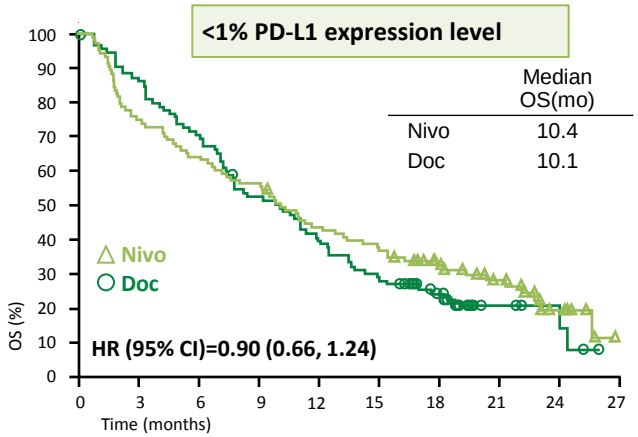


	Mediana de Supervivencia (95% CI), meses
Pacientes (N = 129)	9.9 (7.8, 12.4)

Brahmer et al. AACR 2017

Expresión de PD-L1 en el tumor: Predictiva del beneficio con Nivolumab

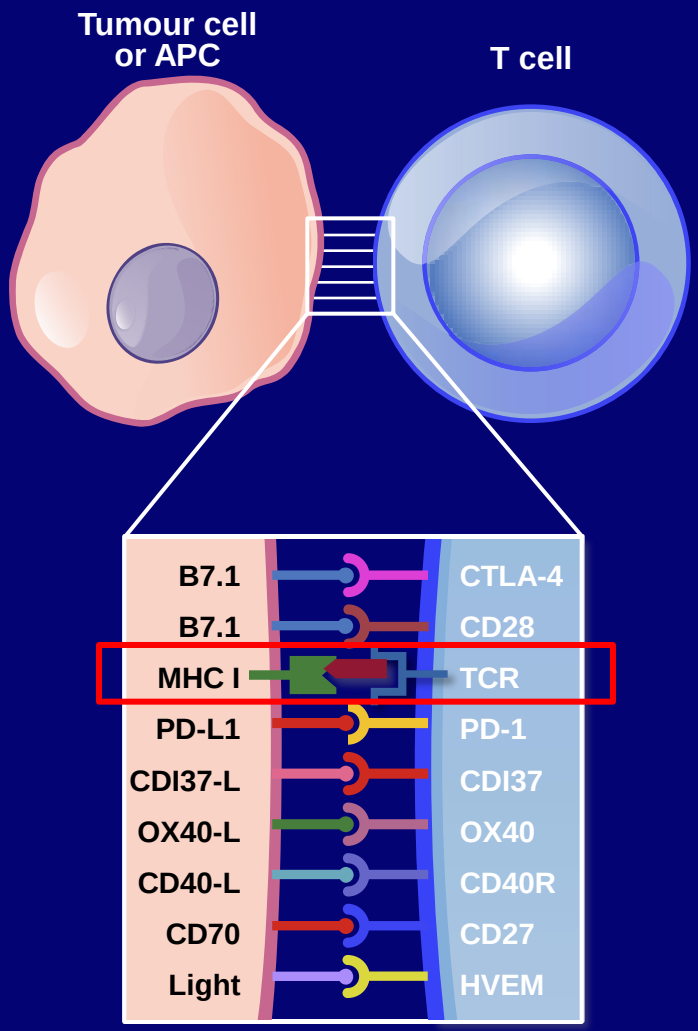


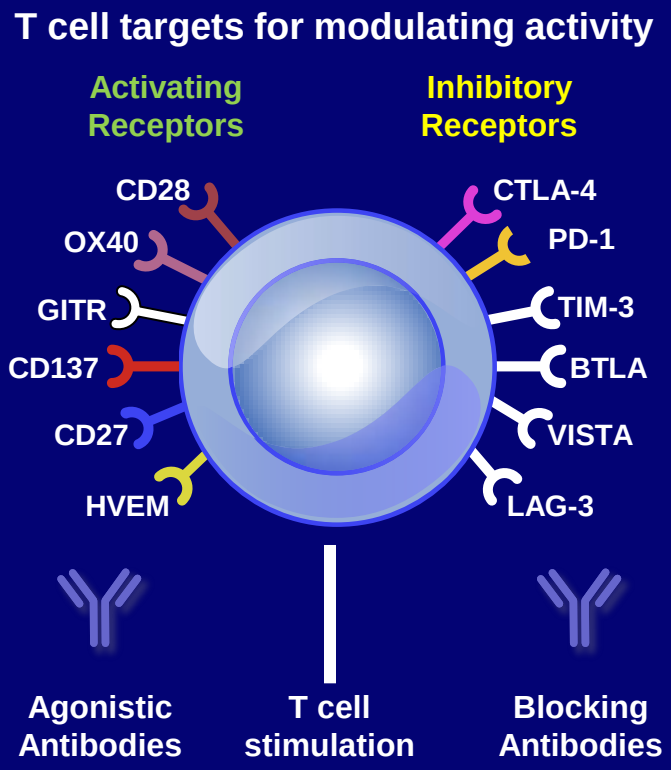


PD-L1 expression level	Median OS (mo)		HR
	Nivolumab	Docetaxel	
≥5%	18.2	8.1	HR (95% CI) = 0.43 (0.30, 0.63)
<5%	9.7	10.1	HR (95% CI) = 1.01 (0.77, 1.34)
≥10%	19.4	8.0	HR (95% CI) = 0.40 (0.26, 0.59)
<10%	9.9	10.3	HR (95% CI) = 1.00 (0.76, 1.31)

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

Inmunidad del cáncer: Balance entre señales estimuladoras e inhibitorias





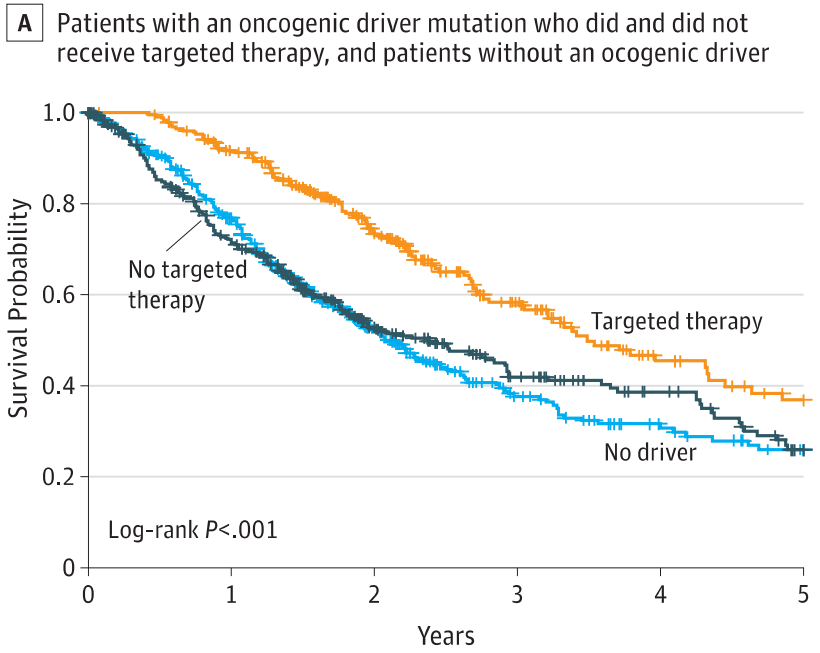
Mellman Nature 2011; Pardoll Nat Rev Cancer 2012

Agenda

- Conocimiento y tecnología
- Adicción oncogénica
- Subgrupos difíciles
- Estrategias prometedoras
- **Perspectivas**

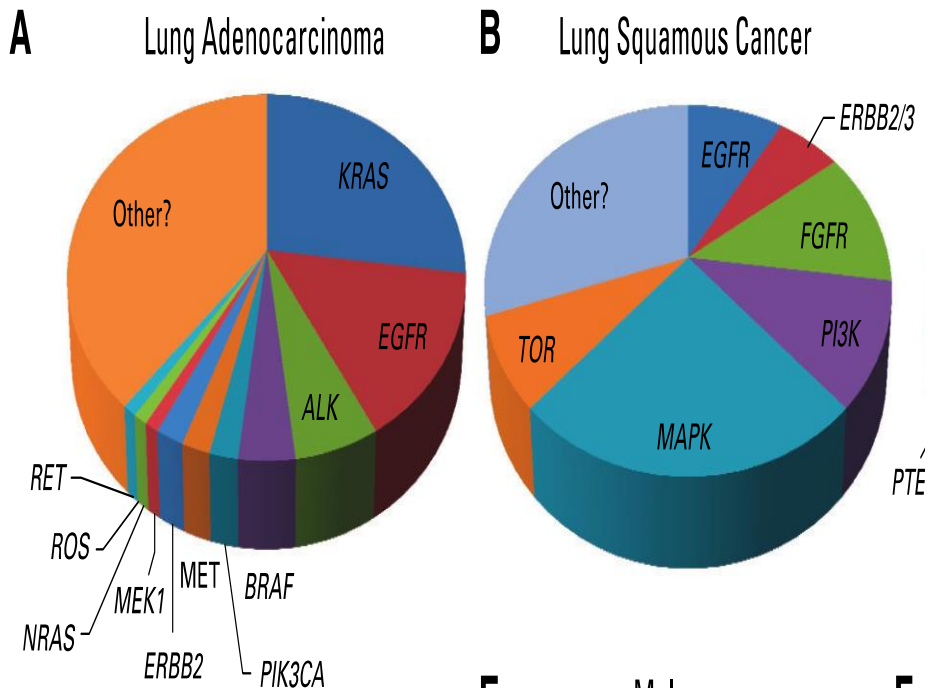
Algoritmo Terapéutico
Cáncer de Pulmón en 2020

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.

Algoritmo Terapéutico
Cáncer de Pulmón en 2020

Gracias

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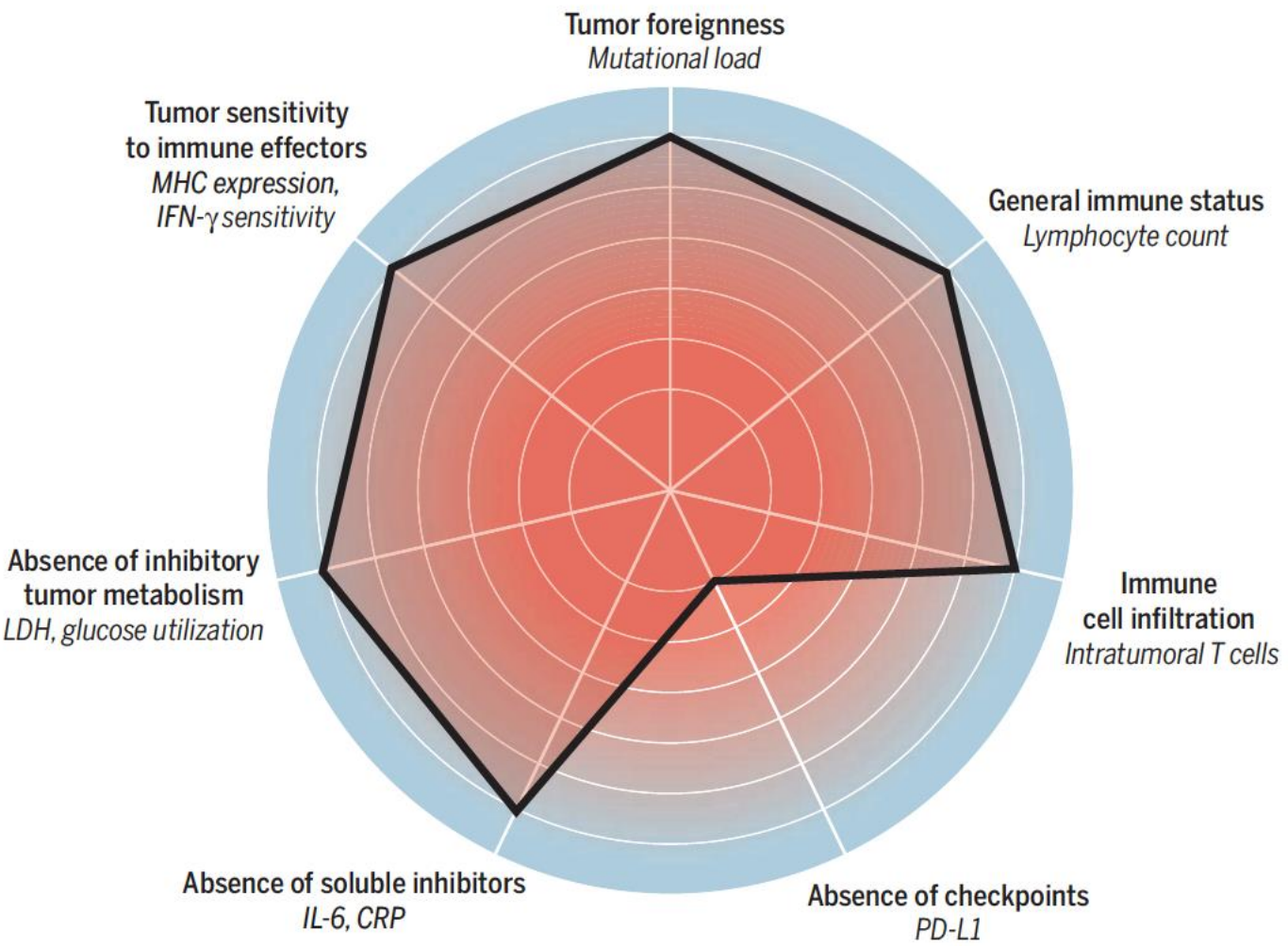
Immunograma del Cáncer



Vansteenkiste J. et al., atezolizumab in NSCLC (POPLAR)