BIOMARCADORES EN ONCOLOGÍA

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REINA SOFÍA

Análisis de biomarcadores, clave para el desarrollo de estrategias de Medicina de Precisión en Cáncer

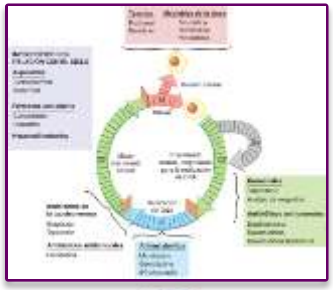
Con más de 8,2 millones de muertes ocasionadas en el mundo en 2012, el cáncer es un problema de salud de primera magnitud, por lo que estrategias que mejoren su abordaje son prioritarias

Su abordaje es complejo y está sometido a continuos cambios, debido al impacto de diversos factores de tipo epidemiológico, científicos o de política sanitaria.

Fuente OMS: Nota descriptiva 297. Febrero 2014.

AYER

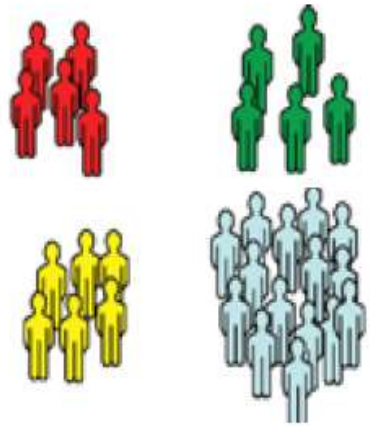
Pacientes con el mismo diagnóstico



QT

HOY

Pacientes con el mismo diagnóstico



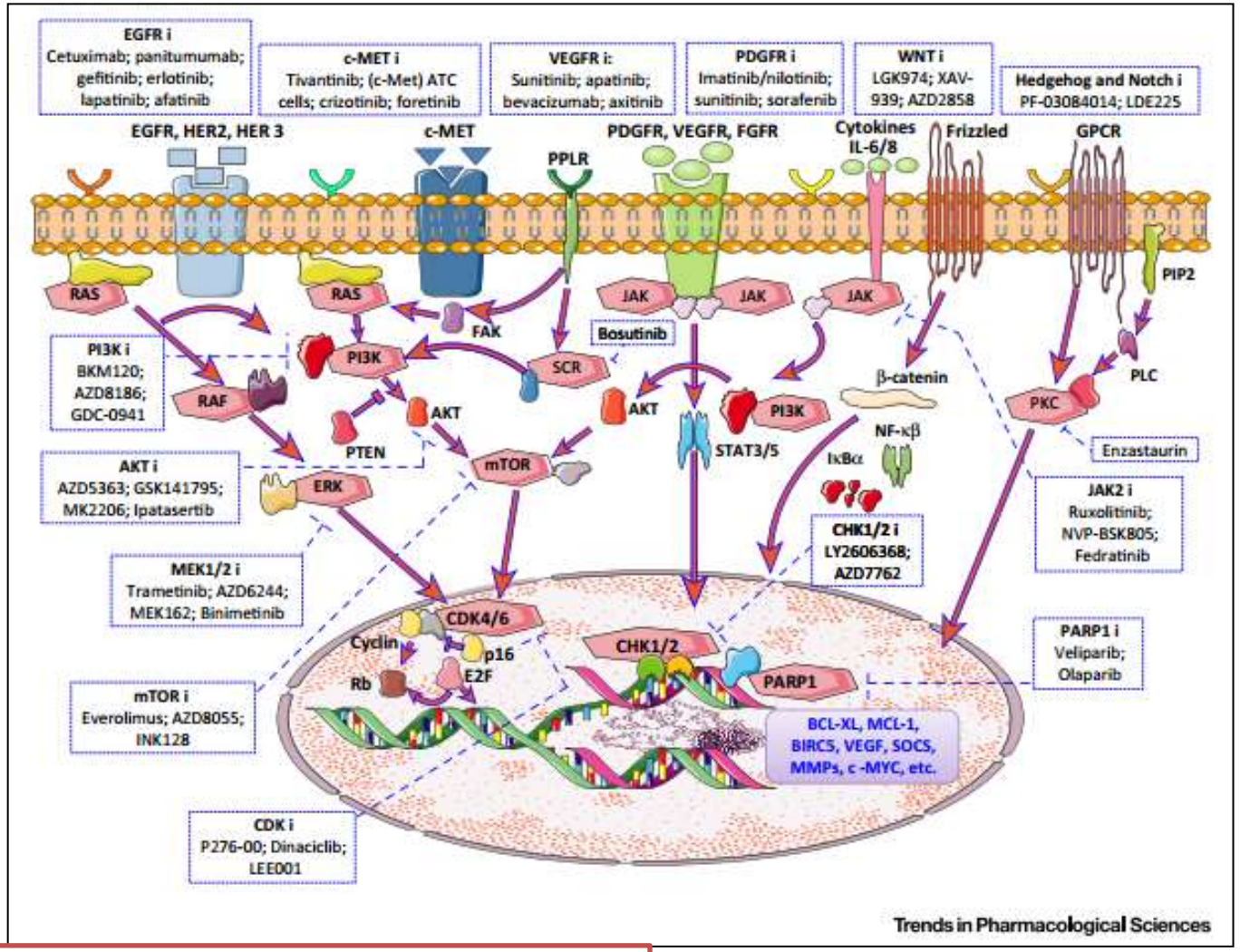
Biomarcadores

- Moleculares
- Clínicos

Tratamiento óptimo para cada paciente

Pronósticos
Predictores de respuesta
Predictores de toxicidad

Nuevos abordajes: inmunoterapia y dianas moleculares.



Murugan, Parsons et al. Trends in farmacologycal sciences

BIOMARCADORES = MEDICINA PERSONALIZADA

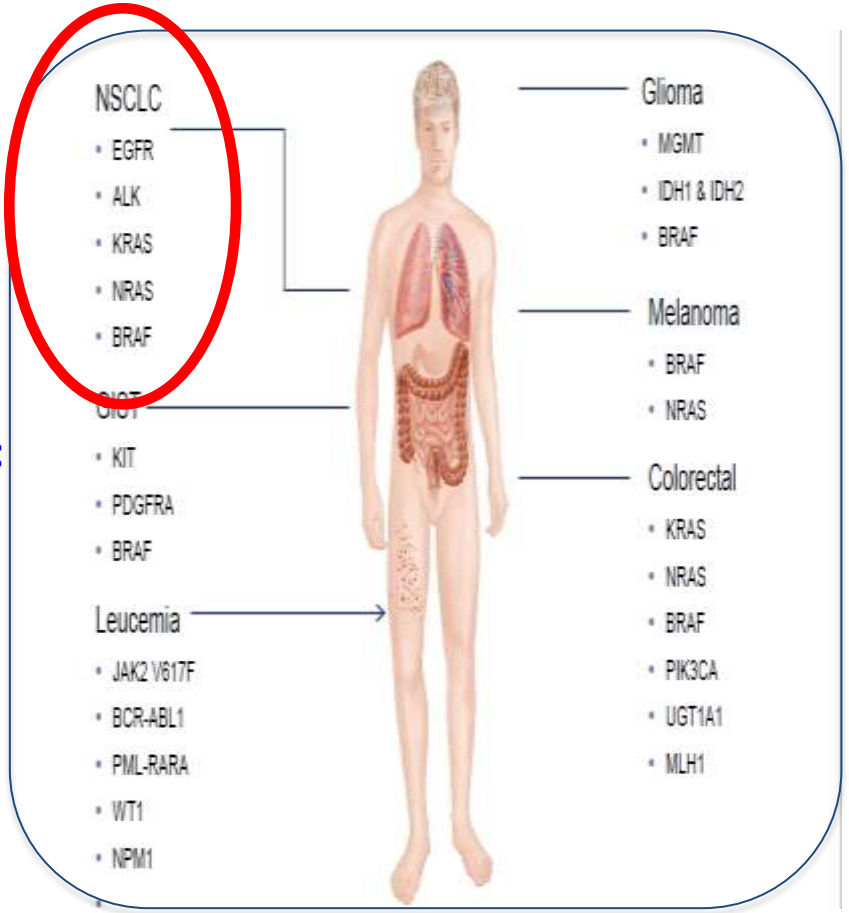
Identificar aquellos pacientes que puedan beneficiarse de una terapia concreta

CRITERIO DE EFICACIA : SG, SLP..

REDUCIR TOXICIDAD

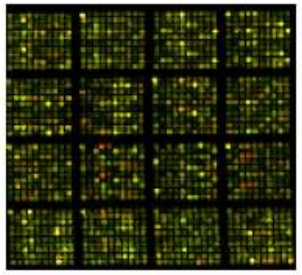
CRITERIOS DE EFICIENCIA

TERAPIAS DIRIGIDAS A UNA DIANA ESPECIFICA:



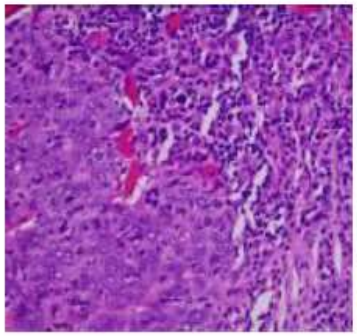
HISTORIA de los BIOMARCADORES EN CÁNCER

XXI century

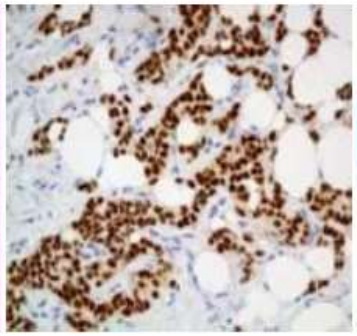


Genomics
- Microarrays
- qPCR
- miRNAs

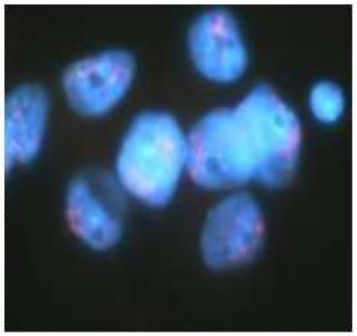
XIX century

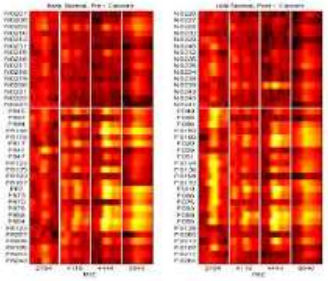


1980s



2000s

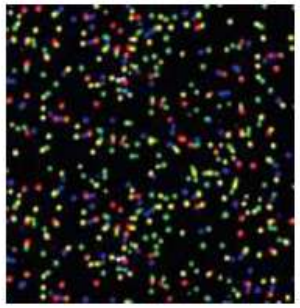




Proteomics
Metabolomics

Histology and patient clinical features

Unique gen/protein biomarkers



Next Gen Sequencing

Multiple gen/protein biomarkers profiling

¿ QUIEN ? ¿ COMO ? ¿CUÁNTO?

Servicio Murciano de Salud

Biomarker Point

Punto de encuentro para la determinación de biomarcadores oncológicos

Plataforma Diagnóstica

1DENTIFY EGFR M+

IDENTIFICANDO A LOS PACIENTES ADECUADOS DESDE LA PRIMERA LÍNEA

MODELO FRANCES DE IMPLEMENTACIÓN DE BIOMARCADORES

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

Provides nationwide molecular diagnostic tests

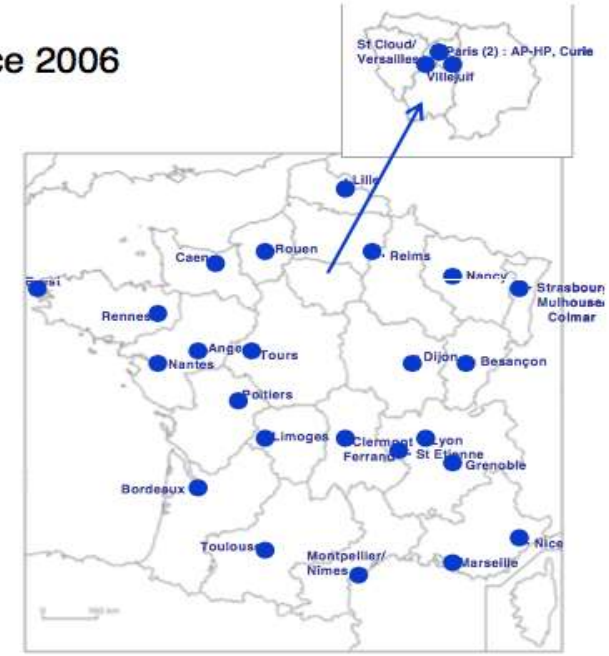
The programme is operated by the INCa/Ministry of Health since 2006

➢ 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 centres

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



Acuerdo SEOM - SEAP

Plataforma de Biomarcadores en Cáncer

ELSEVIER

Patología

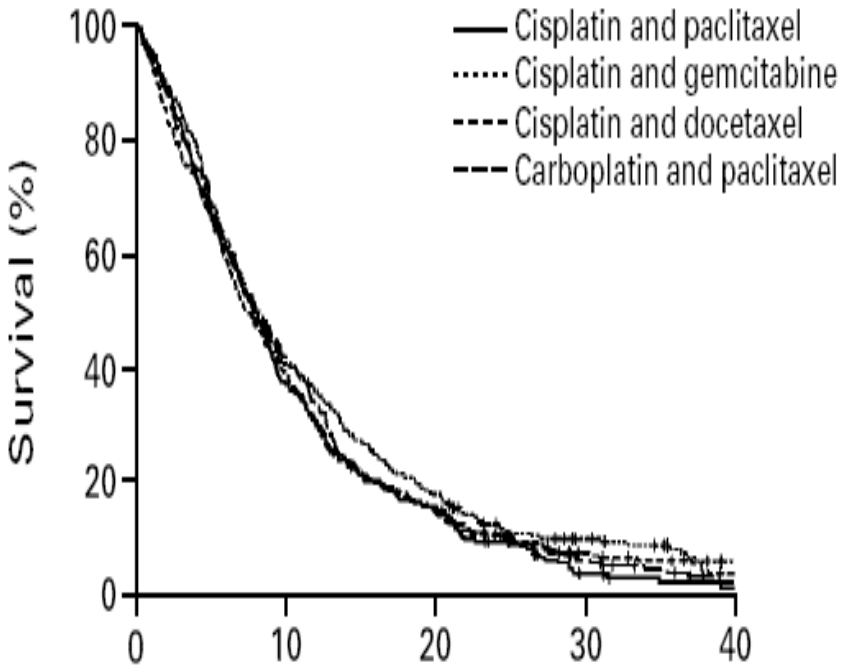
www.elsevier.es/patologia

REVISIÓN

Actualización de las recomendaciones para la determinación de biomarcadores en el carcinoma de pulmón avanzado de célula no pequeña. Consenso Nacional de la Sociedad Española de Anatomía Patológica y de la Sociedad Española de Oncología Médica

Fernando López-Ríos[a,*], Javier de Castro[b], Ángel Concha[c], Pilar Garrido[d], Javier Gómez-Román[e], Dolores Isla[f], José Ramírez[g], Luis Paz-Ares[h], Julián Sanz[i] y Enriqueta Felip[j]

2004: Tratamiento Ca Pulmón NM IV



RO 20 %

TTP 4 - 5 meses

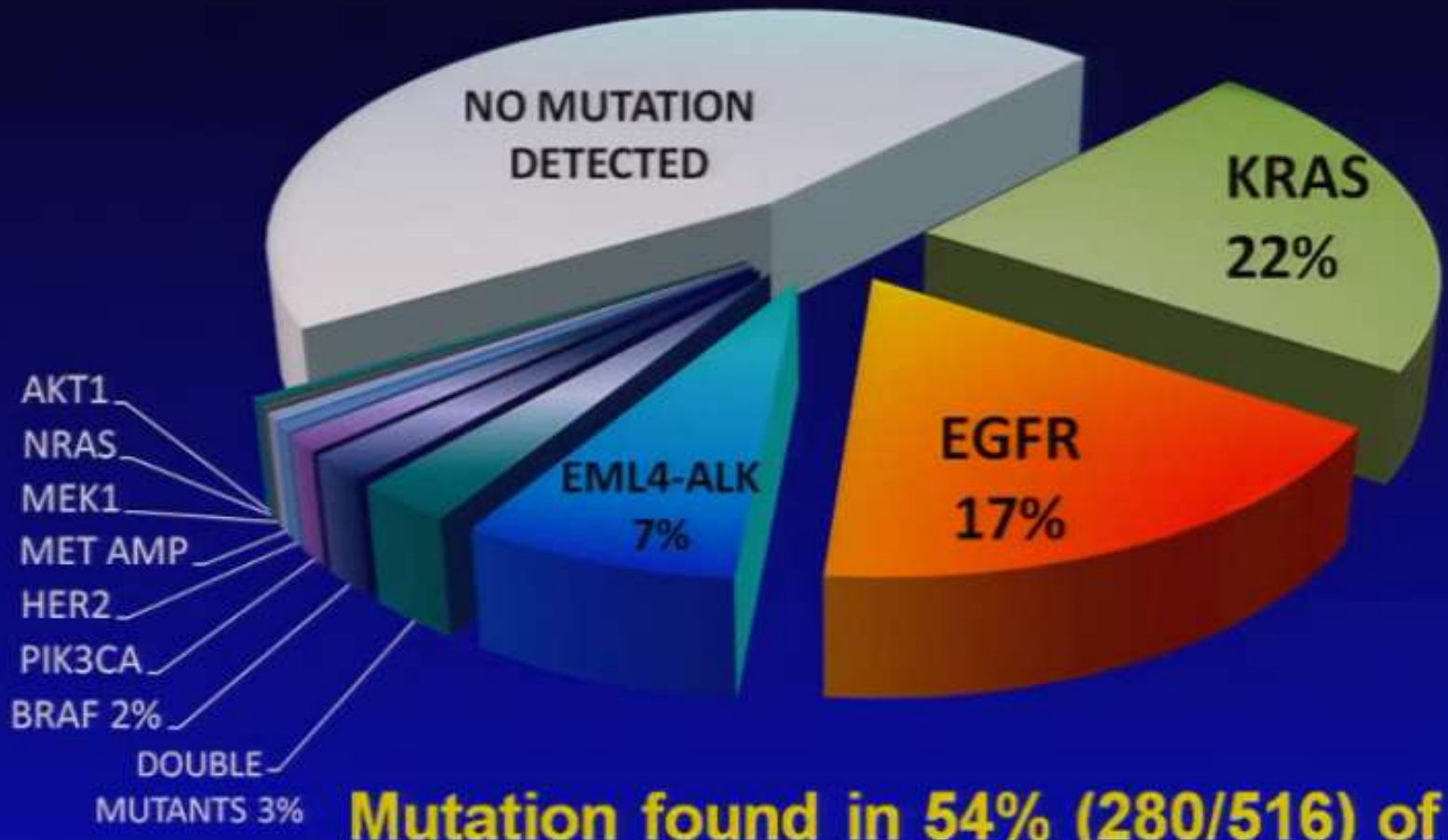
SG 9 meses

- El tratamiento estándar consiste en un doblete de Platino + (vnr, gemz, taxanos, etc.) que son comparables en términos de eficacia, aunque cada uno con un patrón de toxicidad diferente.
- El añadir un tercer fármaco al doblete de platino , aumenta toxicidad sin beneficio en la supervivencia
- Año 2004 : parece que se ha alcanzado un “plateau” en el tratamiento del CPNCP (con mediana de supervivencia 9 m.)

Schiller (ECOG),NEJM 2002

Lung Cancer Mutation Consortium

Incidence of Single Driver Mutations



Mutation found in 54% (280/516) of tumors completely tested (CI 50-59%)

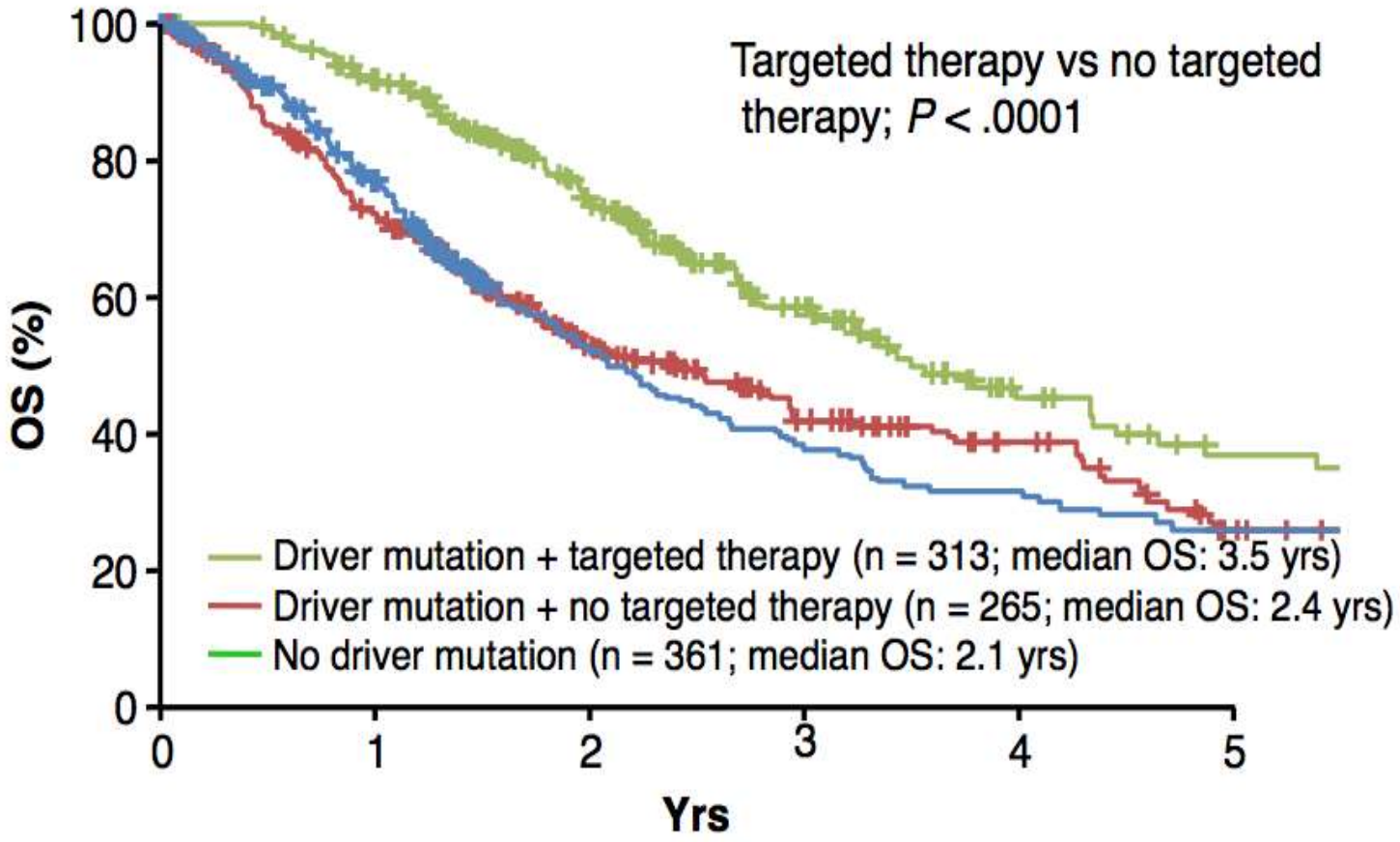
EDITORIAL

Divide and Conquer to Treat Lung Cancer

Bruce E. Johnson, M.D.

N Engl J Med 2016; 375

Lung Cancer Mutation Consortium: OS by Mutation and Treatment



Johnson B. ASCO 2013: Abstract 8019

EGFR

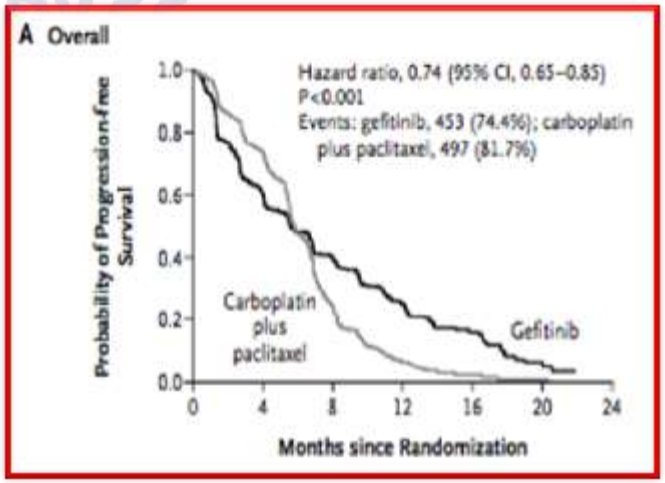
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 3, 2009 VOL. 361 NO. 10

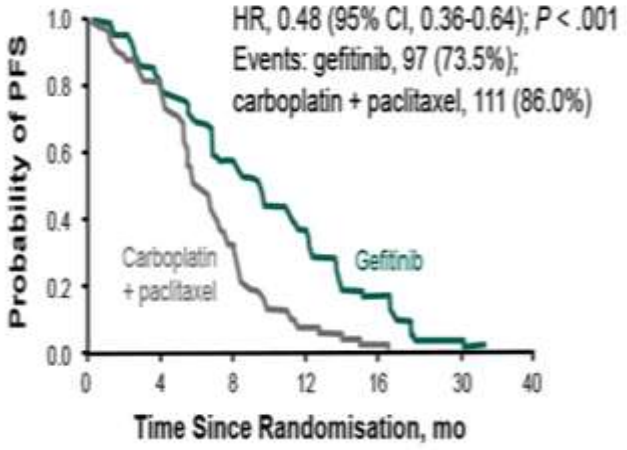
IPASS

Gefitinib or Carboplatin–Paclitaxel in Pulmonary Adenocarcinoma

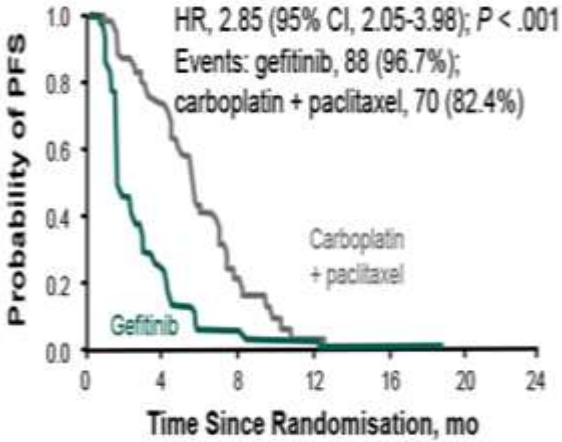
Tony S. Mok, M.D., Yi-Long Wu, M.D., F.A.C.S., Sumitra Thongprasert, M.D., Chih-Hsin Yang, M.D., Ph.D.,



EGFR-Mutation–Positive



EGFR-Mutation–Negative

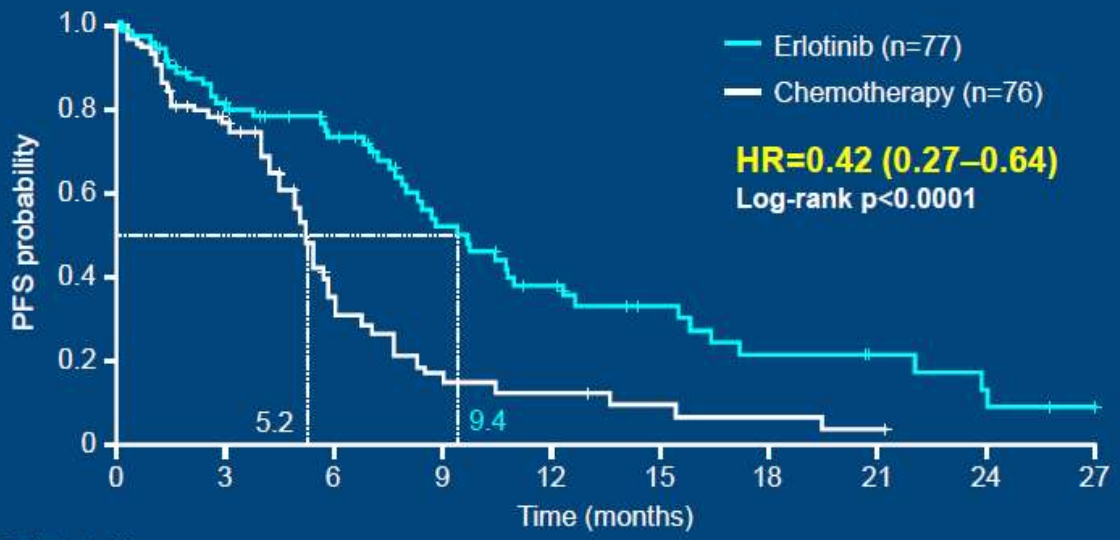


EURTAC

Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial

Rafael Rosell, Enric Carcereny, Radj Gervais, Alain Vergnenegre, Bartomeu Massuti, Enriqueta Felip, Ramon Palmero, Ramon Garcia-Gomez,

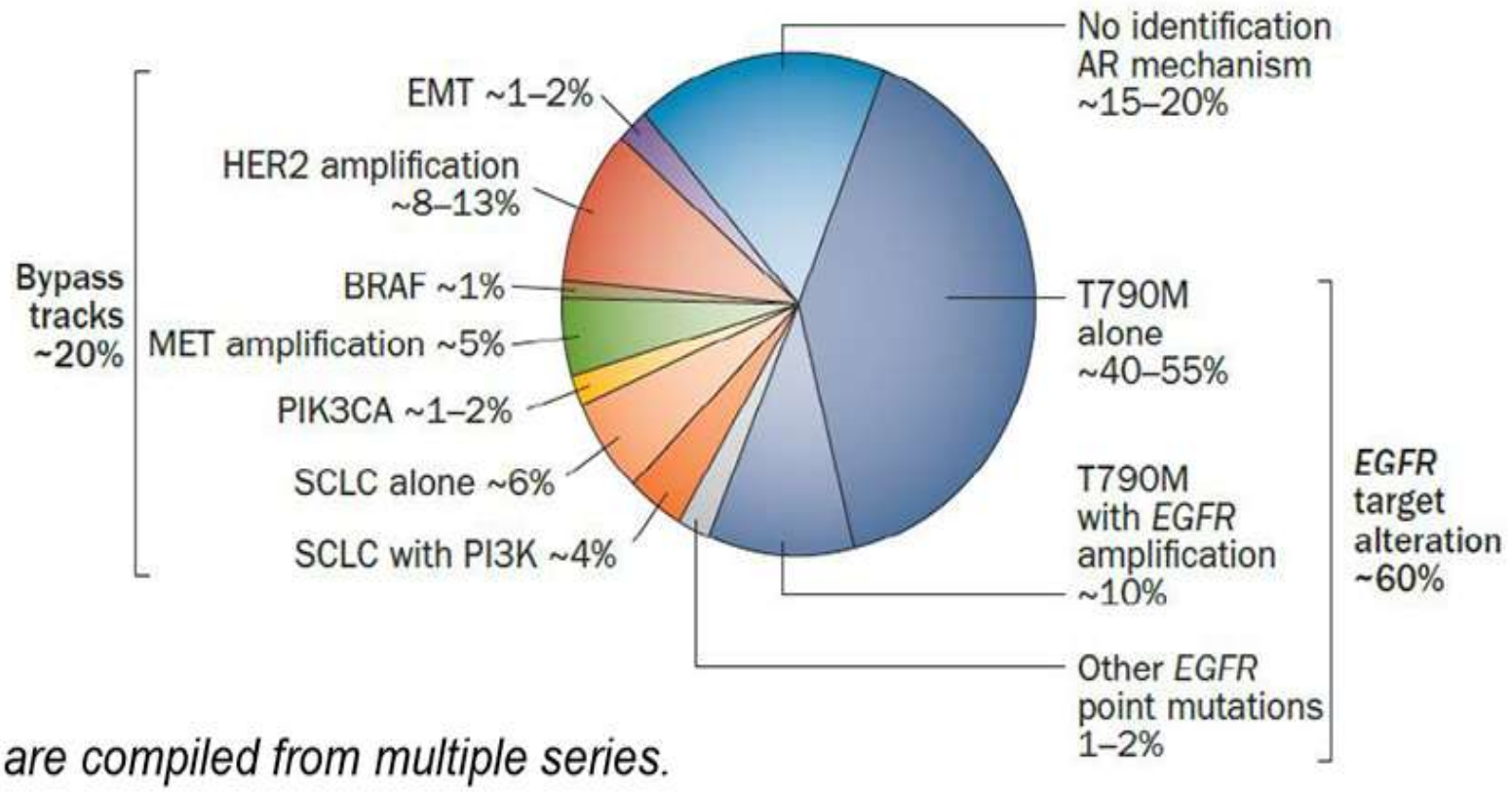
Primary endpoint: PFS



Data cut-off: 2 Aug 2010; reviewed by IDMC January 2011

PRESENTED AT: ASCO Annual '11 Meeting

MECANISMOS DE RESISTENCIA a los iTK de primera generación

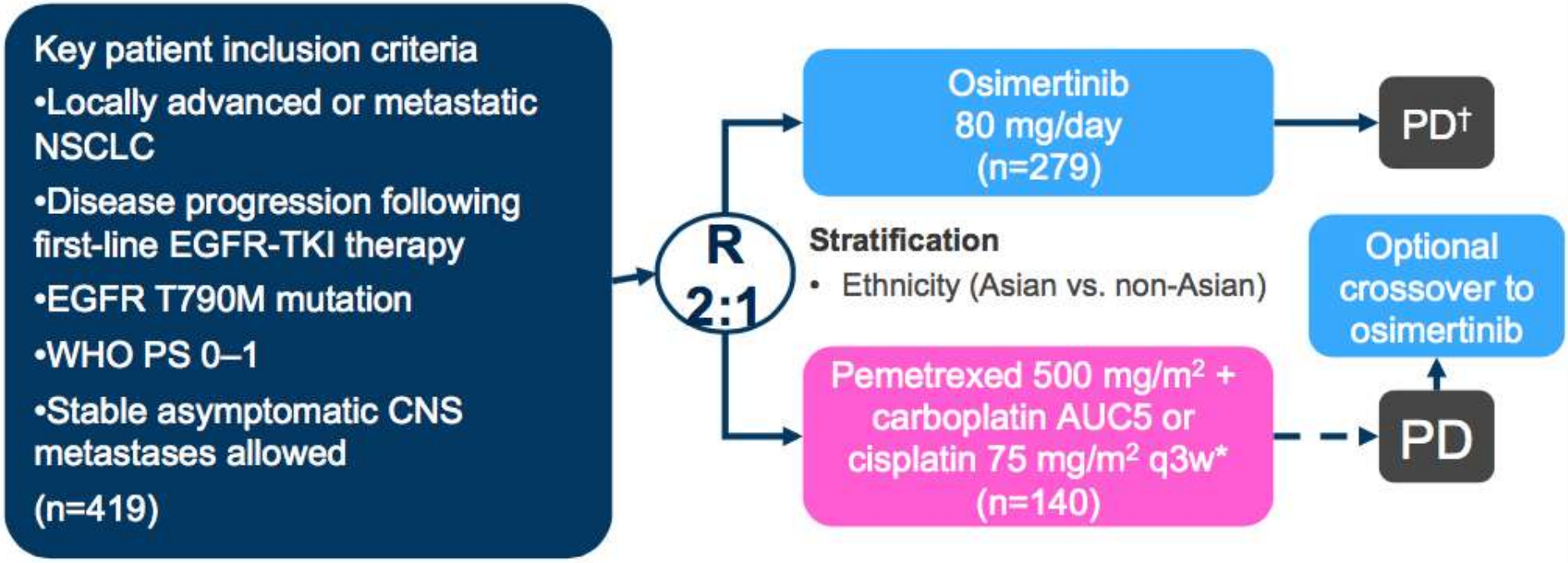


Data are compiled from multiple series.

Camidge, Nat Rev Clin Oncol 2014;11

Mutación de Resistencia T790M

- **AURA 3. Study objective**
  - To compare osimertinib to platinum-based doublet chemotherapy in patients with centrally-confirmed EGFR T790M-positive advanced NSCLC



Primary endpoint

•PFS by investigator assessment

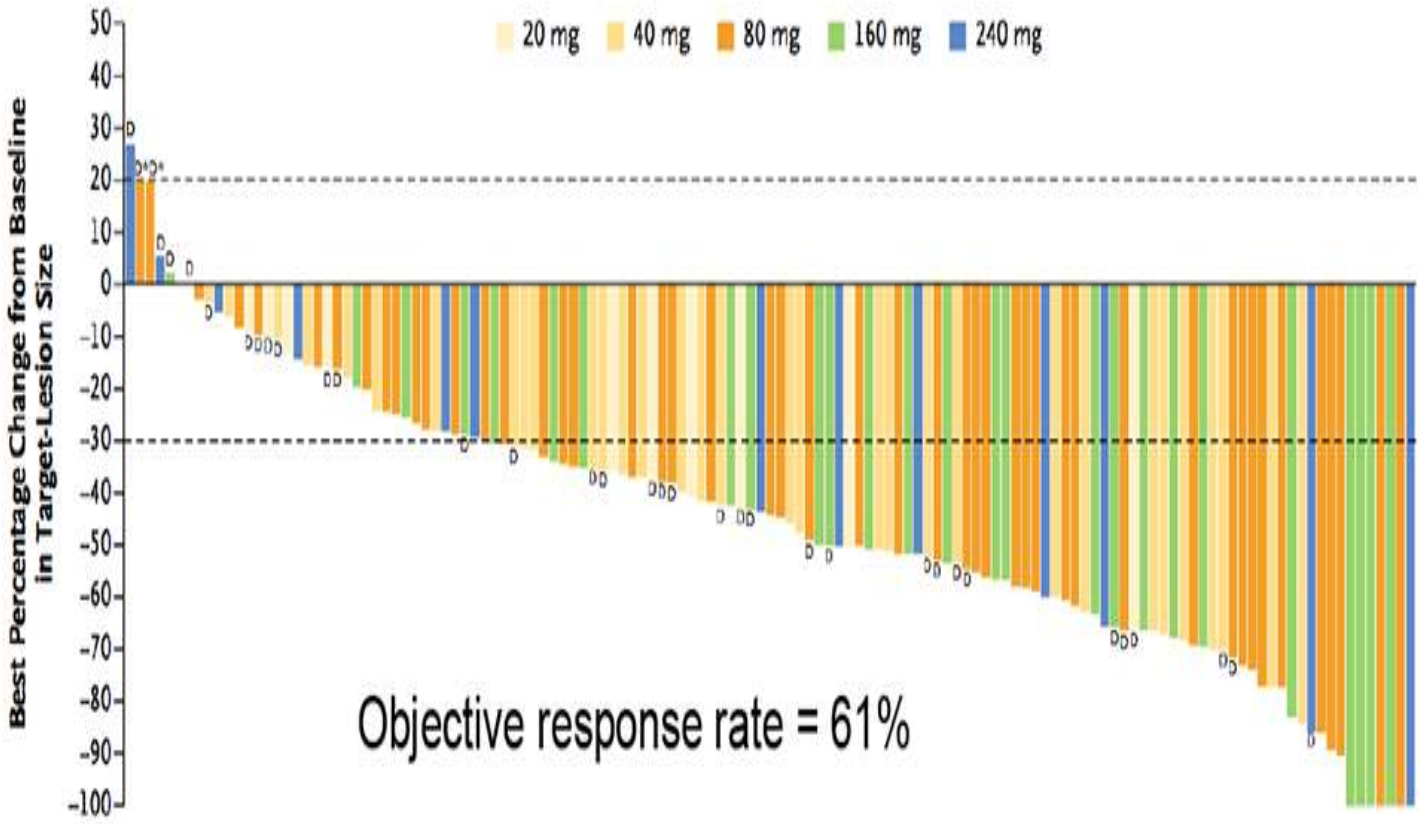
Secondary endpoints

- OS, ORR, DoR, DCR, BICR-assessed PFS

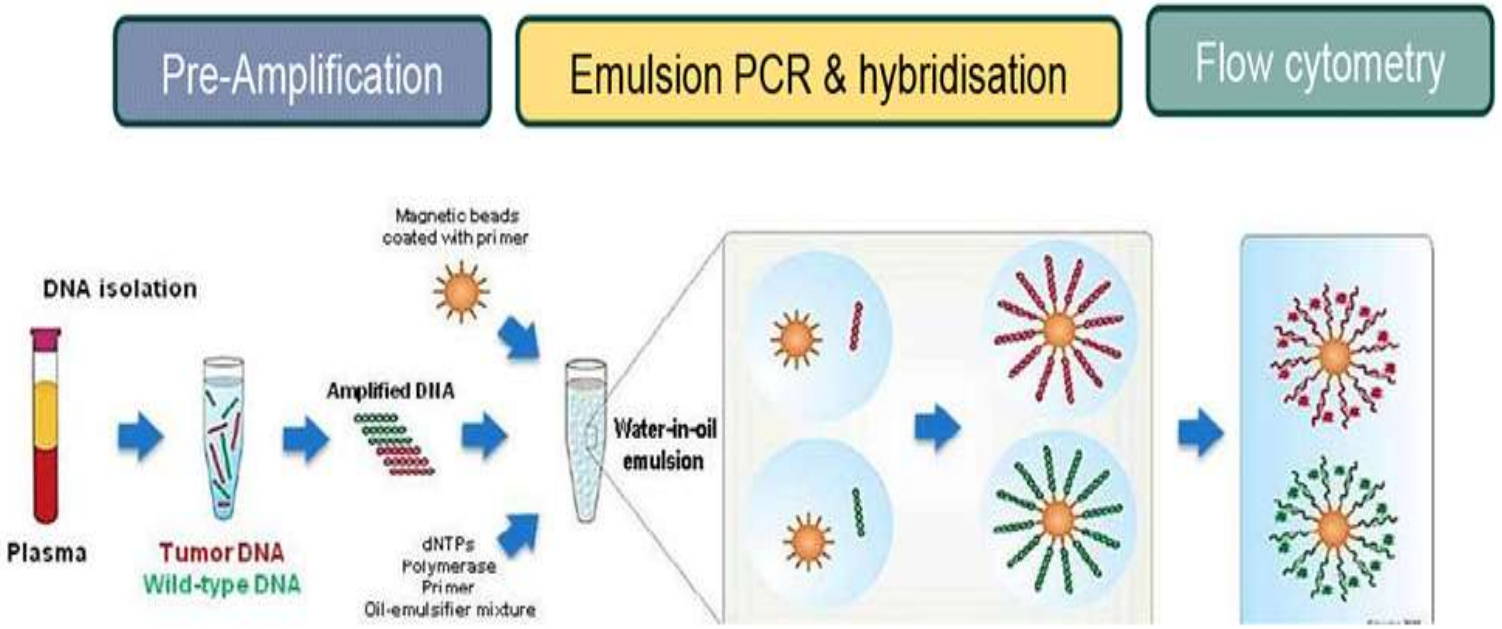
Papadimitrakopoulo V, WCLC 2016

Mutación de Resistencia T790M

AURA3: Key results



BIOPSIA LÍQUIDA: biomarcador en plasma



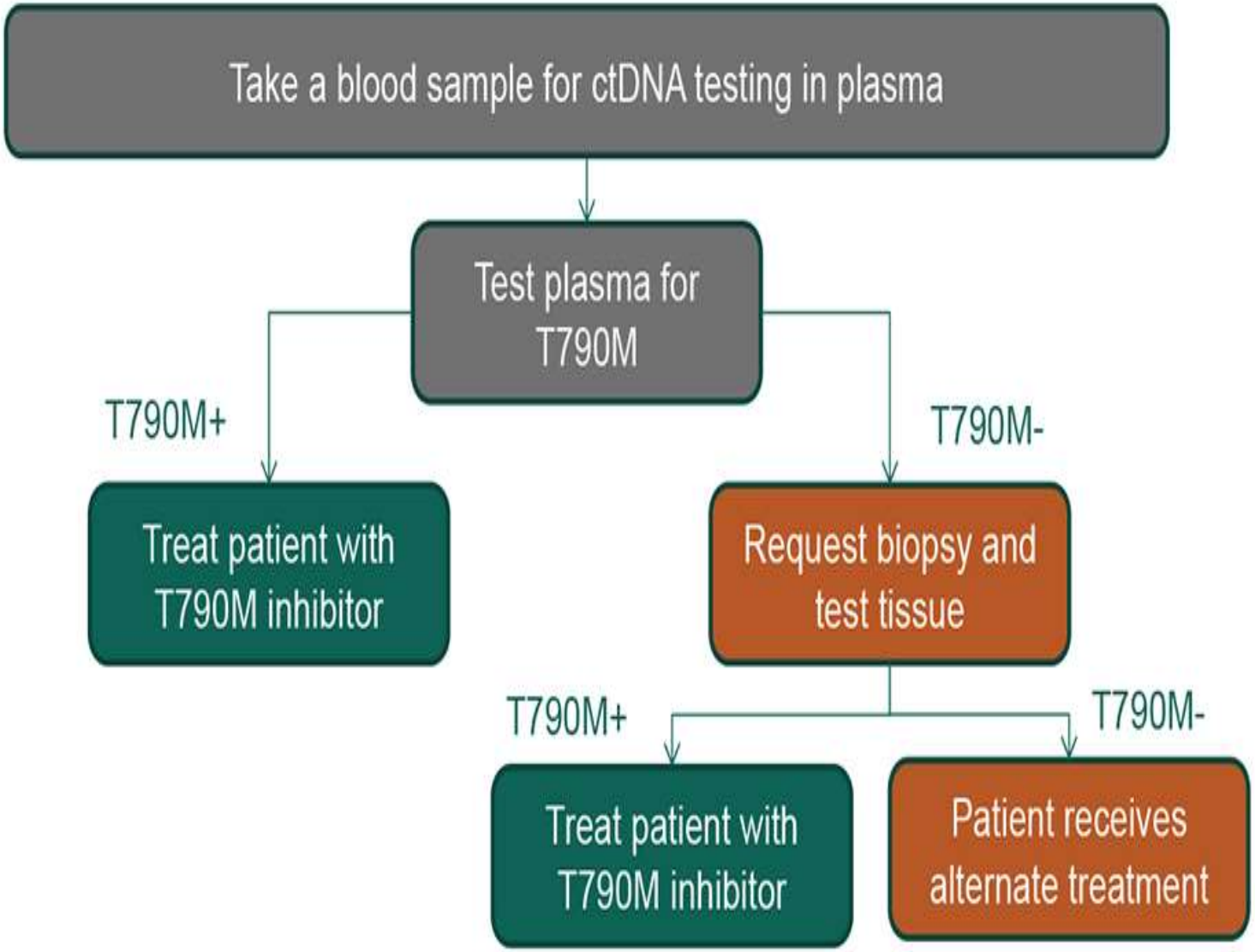
BEAMing is digital PCR followed by flow cytometry

- *EGFR* test identifies L858R, del19, and rare activating mutations plus T790M

EGFR+ y T790M en cDNA: sensibilidad y especificidad

	Pooled study of AURA: Cobas in cDNA (AURA extension AND AURA2)		
	L858R	**Exon 19 del**	**T790M**
Utilisation du test Cobas® tissu comme référence			
VPP /sensitivity	75,6 %	85,1 %	61,4 %
VPN / specificity	98,1 %	98,0 %	78,6 %
Concordance	90,9 %	90,0 %	65,4 %

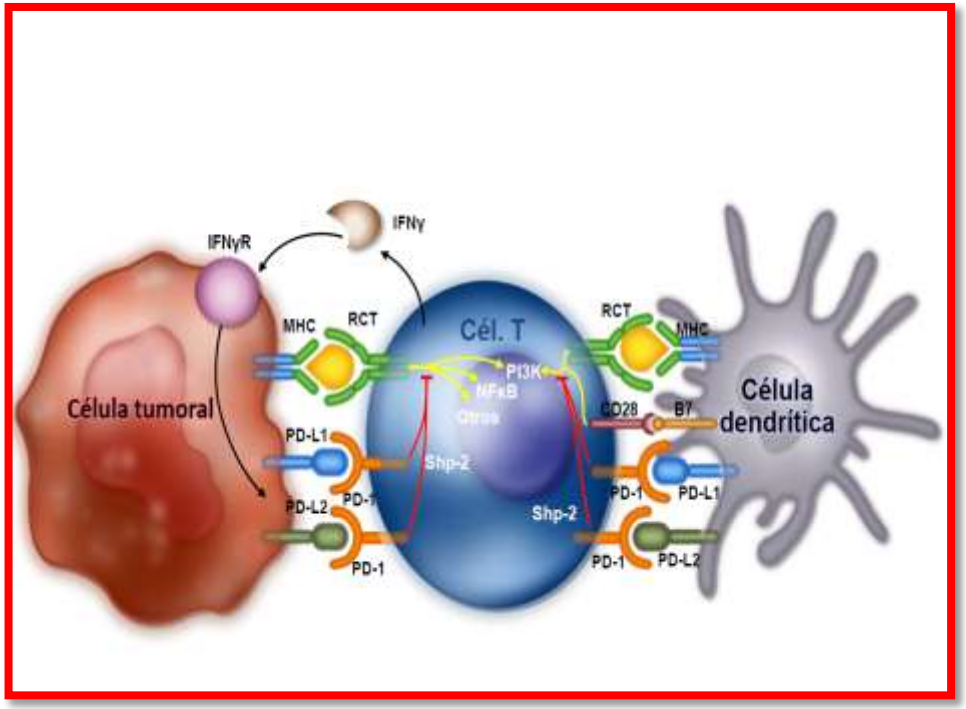
Oxnard, ELCC 2016

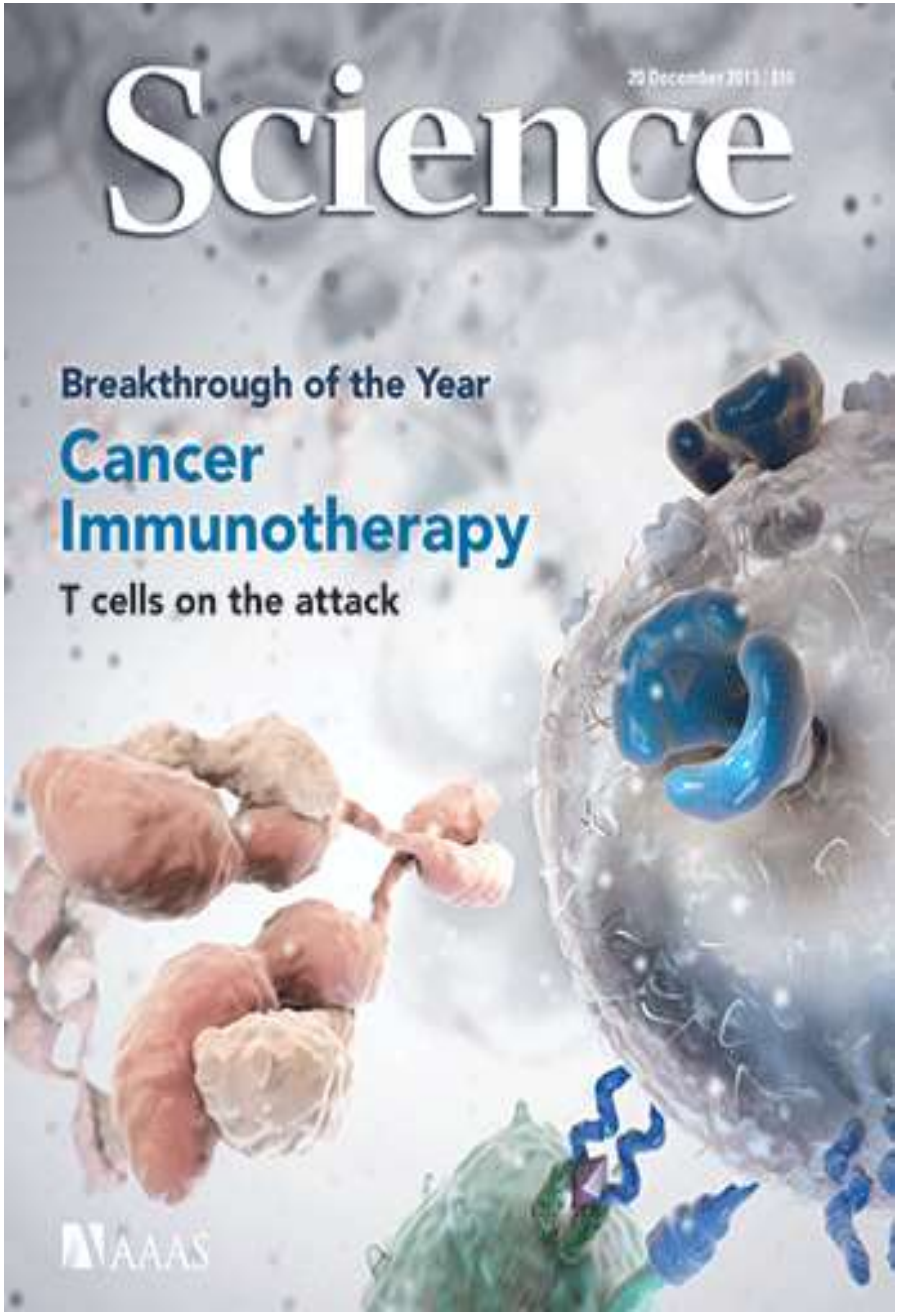


Según modelo de Oxnard, JCO 2016

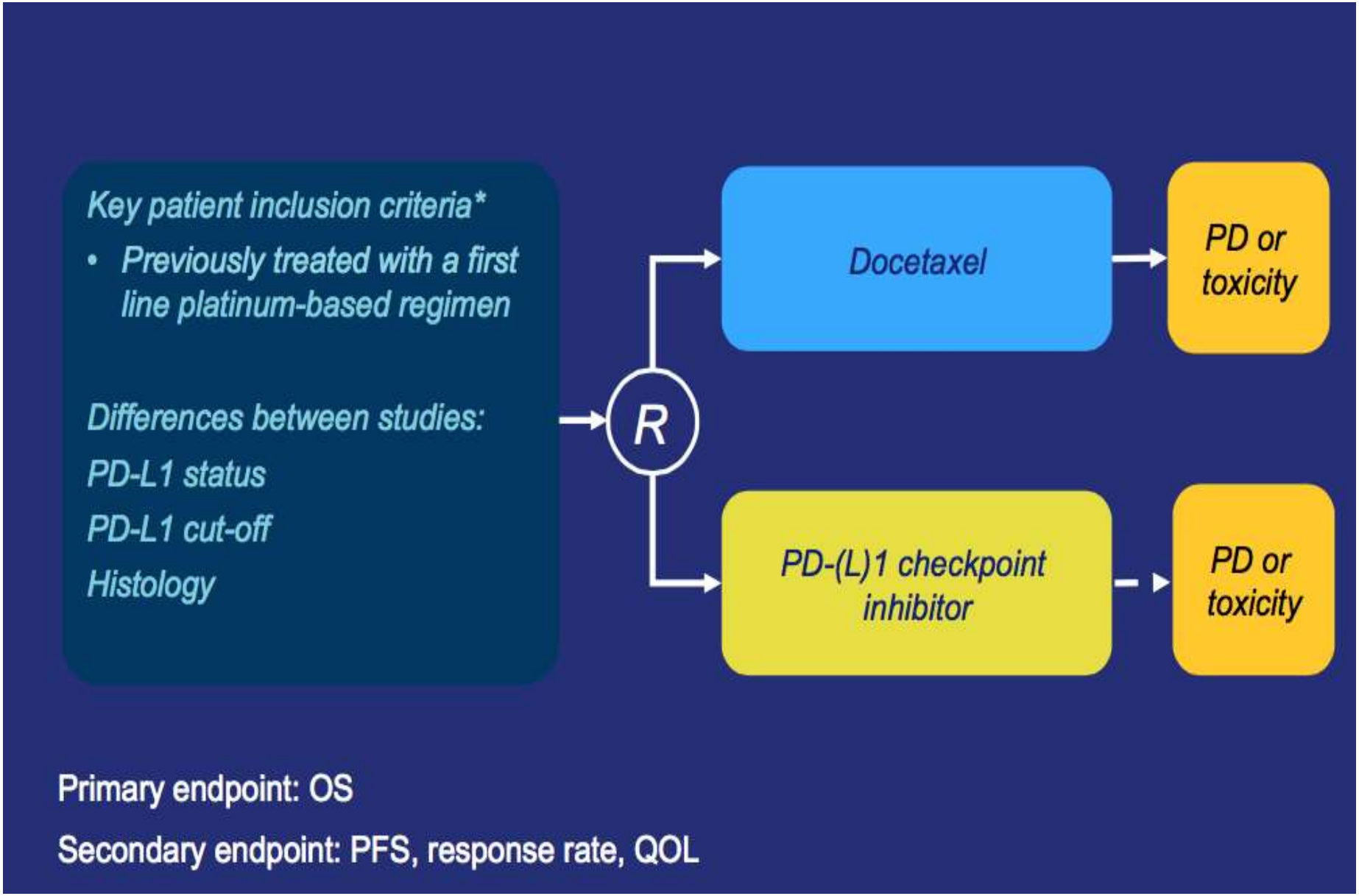
PD(L)-1


"PDLOMAS" ACTIVITY IN 2015
Mel
SCLC
RCC
NSCLC
Bladder
HNSCC
Gastric
Hodgkin
B Cell NHL
MSI High CRC
Ovarian
TNBC
Breast
HCC
Pancreatic
PD-1/PD-L1 Blockade


IFNγR
IFNγ
MHC
RCT
Cél. T
PI3K
NFκB
Célula tumoral
PD-L1
PD-L2
PD-1
Shp-2
RCT
MHC
CD28
B7
Célula dendrítica
PD-1
PD-L1
PD-1
PD-L2


Science
20 December 2013 | 339
Breakthrough of the Year
Cancer Immunotherapy
T cells on the attack
AAAS

¿ QUE DATOS TENEMOS DE INMUNOTERAPIA EN **SEGUNDA LÍNEA ?**



RESUMEN de los EC FASE III anti-PD(L)-1 en 2ªL CPNCP

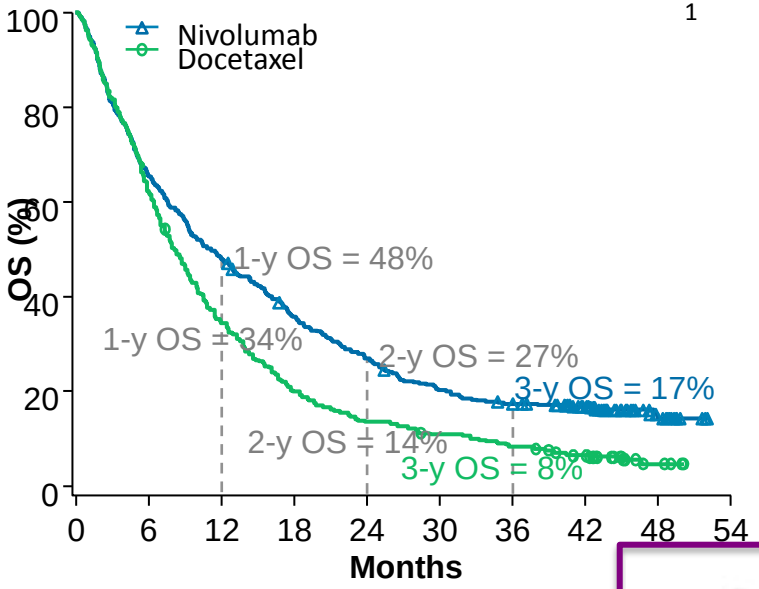
	CheckMate 017[1] Nivolumab vs docetaxel	CheckMate 057[1] Nivolumab vs docetaxel	KEYNOTE-010[2] Pembrolizumab (2mg/kg or 10mg/kg) vs docetaxel	OAK[3] Atezolizumab vs docetaxel
Phase of study	III	III	II/III	III
PD-L1 selected	No	No	Yes (TPS* ≥1%)	No
Study size, n	272 (135 vs 137)	582 (292 vs 290)	1,033 (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)

	CheckMate 017 phase 3***		CheckMate 057 phase 3***		KEYNOTE-010 phase 3***			POPLAR phase 2***	
	Nivolumab	Docetaxel	Nivolumab	Docetaxel	Pembrolizumab 2 mg/kg	Pembrolizumab 10 mg/kg	Docetaxel	Atezolizumab	Docetaxel
Patients (n)	135	137	292	290	345	346	343	144	143
Response rate (%)									
All patients	20	9	19	12	18	19	9	15	15
PD-L1 positive	21	8	36	13	30	29	8	38	13
PD-L1 negative	15	12	10	14	NA	NA	NA	8	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
PD-L1 positive	4·8	3·1	5·0	3·8	5·0	5·2	4·1	2·8	3·0
PD-L1 negative	4·2	2·9	2·1	4·2	NA	NA	NA	1·7	4·1
Median overall survival (months)									
All patients	9·2	6·0	12·2	9·4	10·4	12·7	8·5	12·6	9·7
PD-L1 positive	10	6·4	19·4	8·1	14·9	17·3	8·2	15·5	9·2
PD-L1 negative	8·5	6·1	9·8	10·1	NA	NA	NA	9·7	9·7

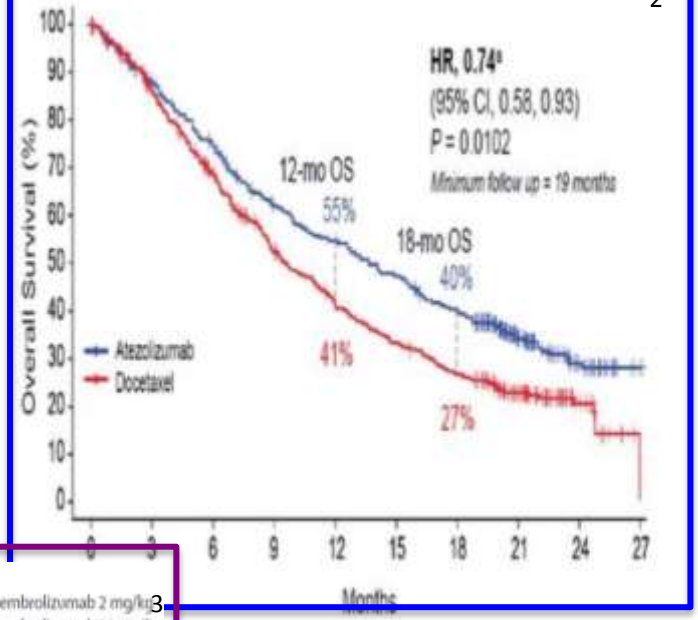
1.Brahmer NEJM2015
Borghaei NEJM 2015
2..Herbst , Lancet 2016
3. Barlesi Ann Oncol 2016

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

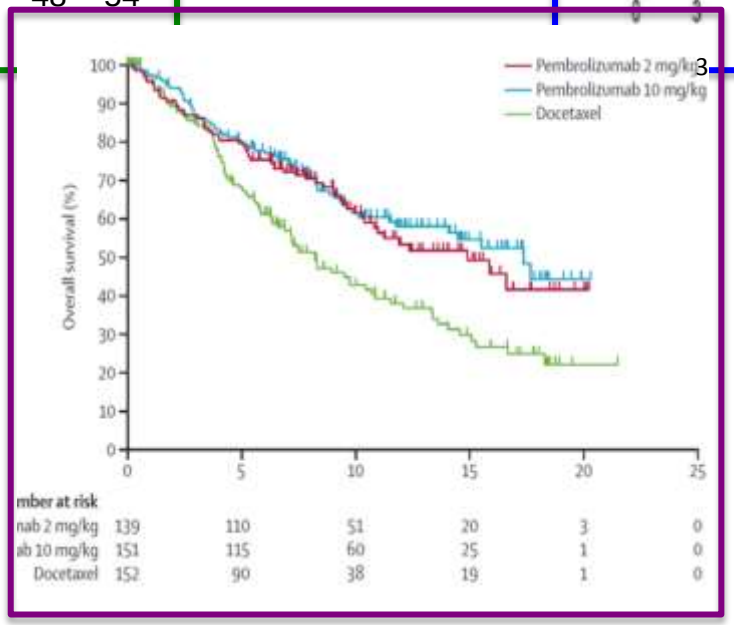
1



2



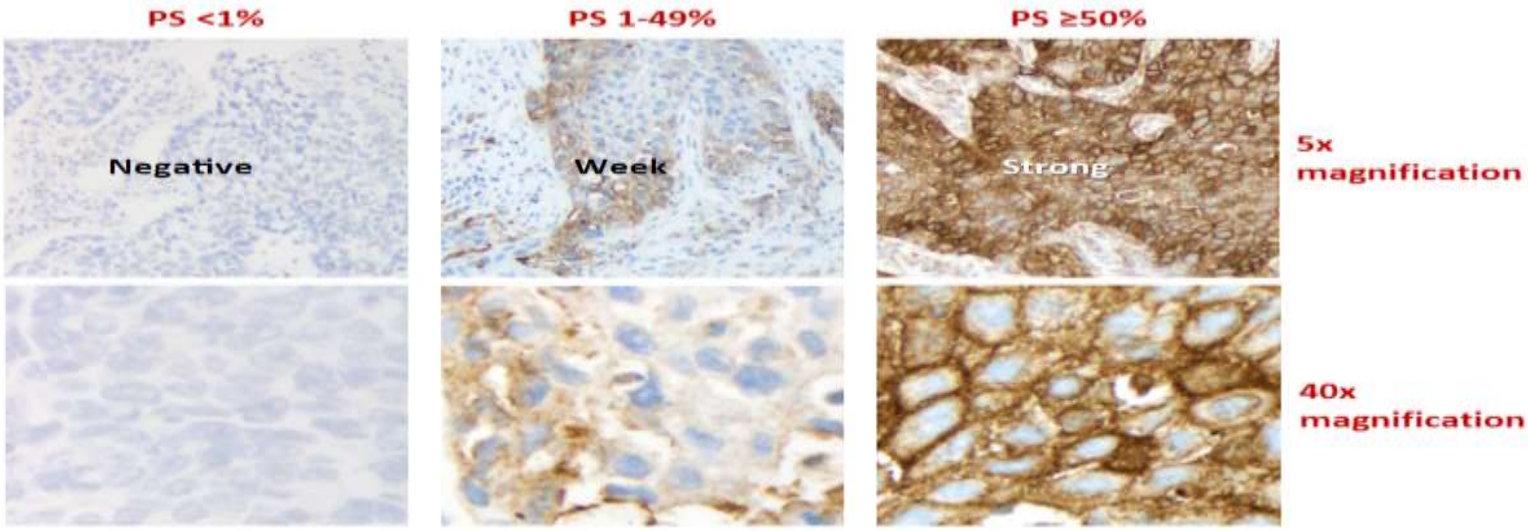
3



1.WLCC 2017
2.Herbst , Lancet 2016
3.Barlesi Ann Oncol 2016

Biomarcadores : IHQ en Inmunoterapia

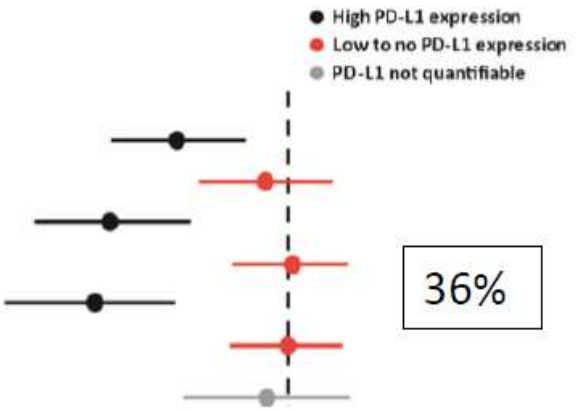
Drug	Nivolumab	Pembrolizumab	Atezolizumab	Durvalumab
Antibody clone	28-8- Dako	22C3 Dako	SP142 Ventana	SP263 Ventana
Interpretation	Tumor cell membrane	Tumor cell membrane	Tumor cell membrane Immune cells	Tumor cell membrane
Platform	Autostainer	Autostainer	Benchmark Ultra	Benchmark Ultra
Pharma	BMS	MSD	Genentech	Astra-Zeneca
FDA	Complementary	Companion		



PDL1 : biomarcador predictivo

En 2L CPNCP alta expresión PDL1 se correlaciona con mejores resultados

PD-L1 expression level	Nivolumab n	Docetaxel n	Unstratified HR (95% CI)	Interaction *P*-value
OS				
≥1%	123	123	0.59 (0.43, 0.82)	0.06
<1%	108	101	0.90 (0.66, 1.24)	
≥5%	95	86	0.43 (0.30, 0.63)	<0.001
<5%	136	138	1.01 (0.77, 1.34)	
≥10%	86	79	0.40 (0.26, 0.59)	<0.001
<10%	145	145	1.00 (0.76, 1.31)	
			0.91 (0.61, 1.35)	



36%

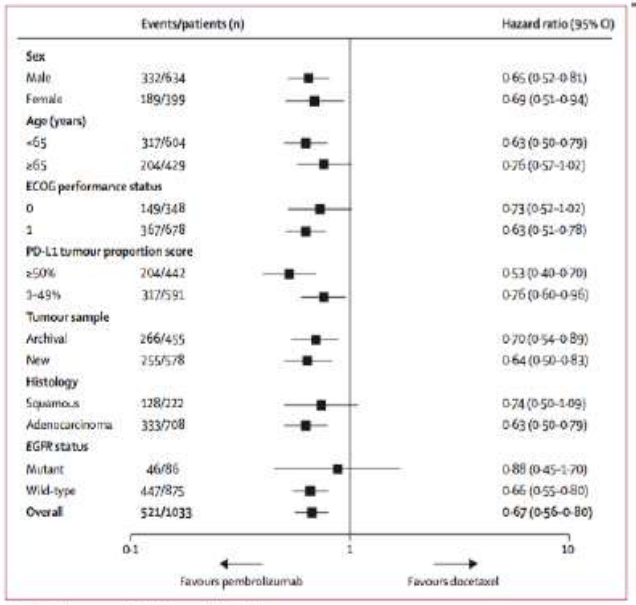
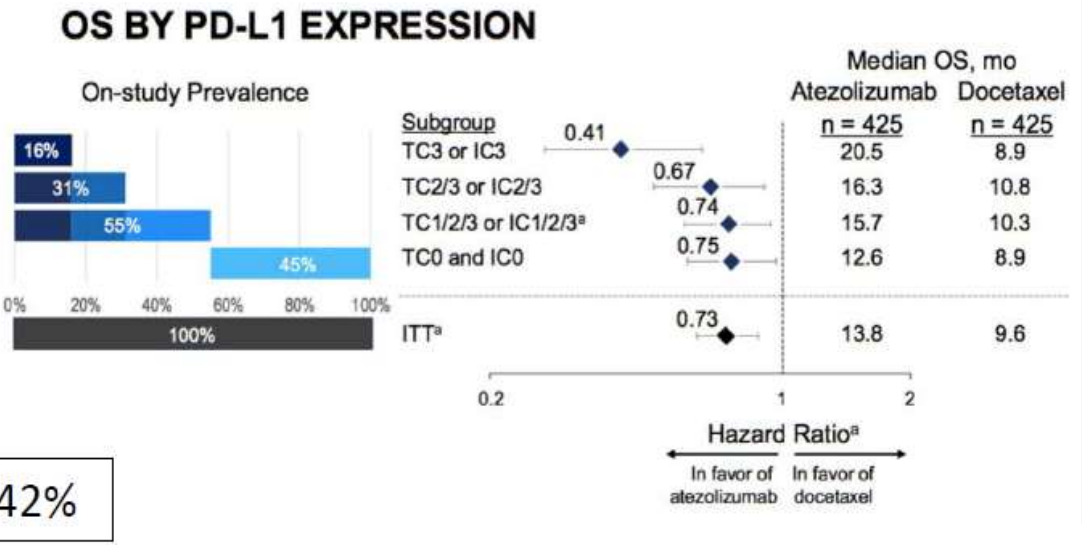
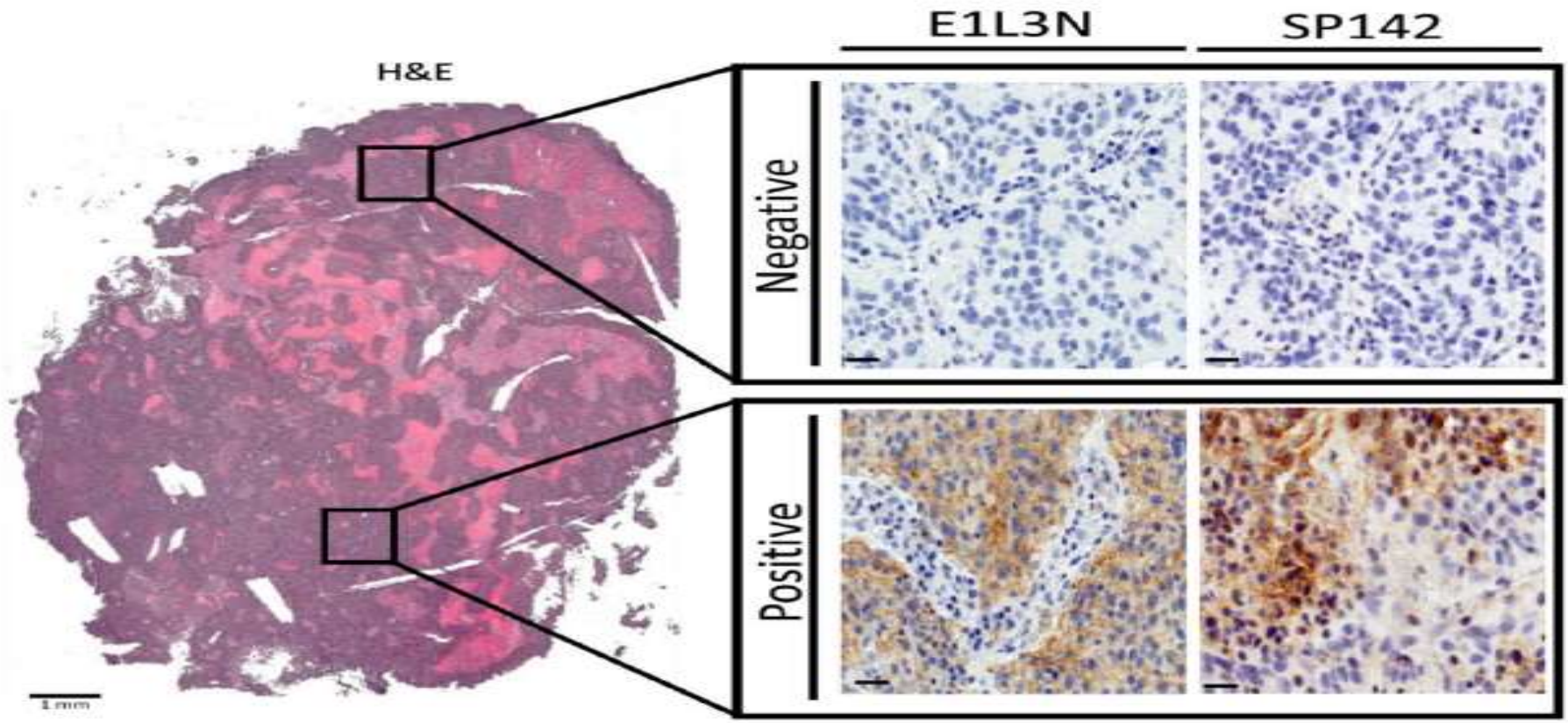


Figure 3: Subgroup analysis of overall survival
Shows the comparison of the pooled pembrolizumab doses versus docetaxel. ECOG=Eastern Cooperative Oncology Group.



42%

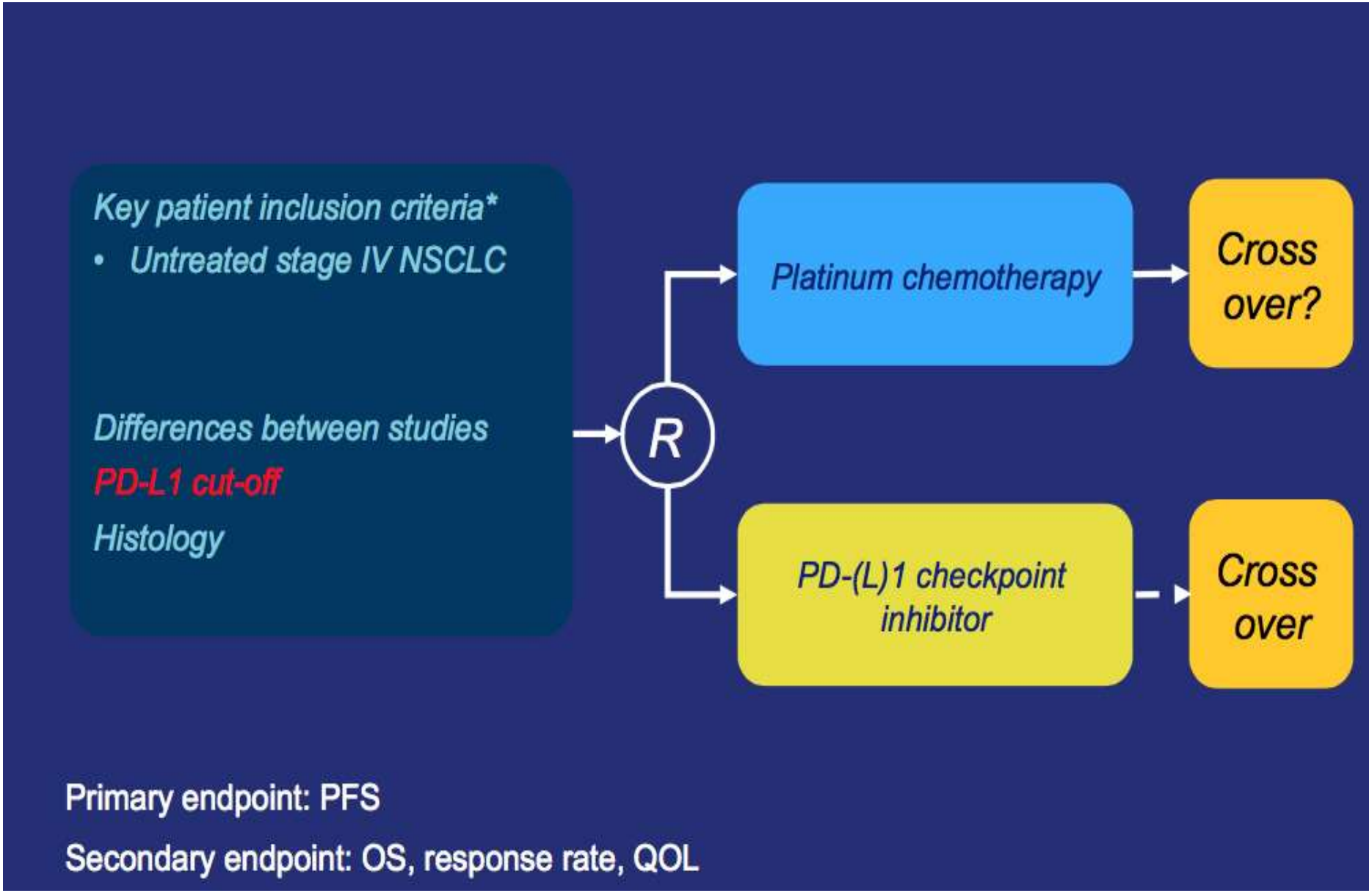
Gran heterogeneidad intratumoral



La expresión de PDL1 puede variar entre el tumor primario y las metástasis, entre diferentes metástasis o incluso dentro de la misma biopsia

McLaughlin JAMA Oncol 2016,2 81)

¿ QUE DATOS TENEMOS DE INMUNOTERAPIA EN **PRIMERA LINEA ?**

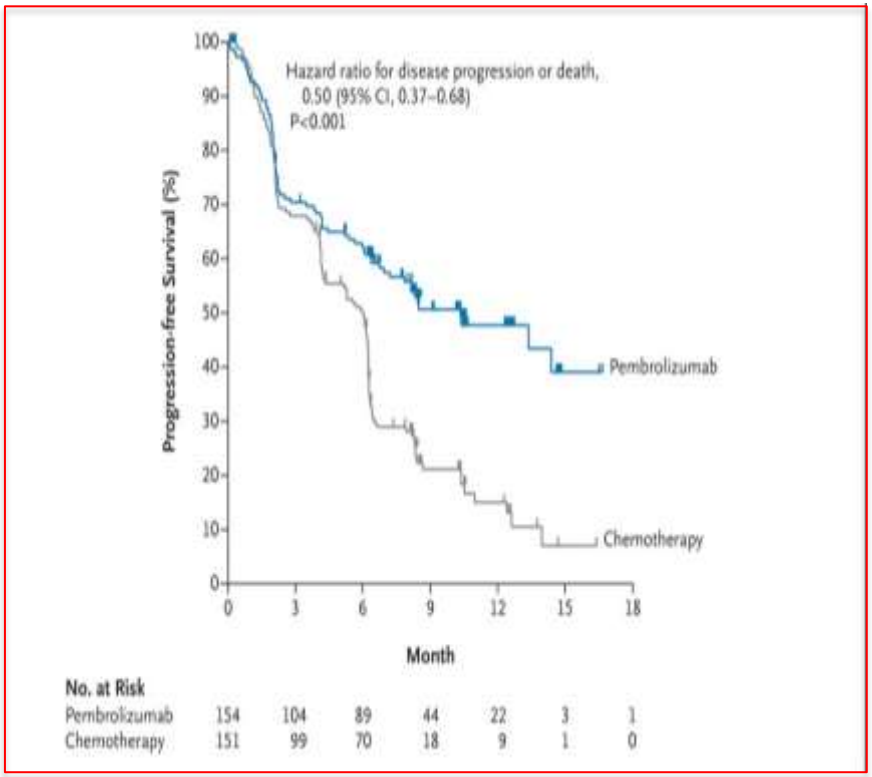


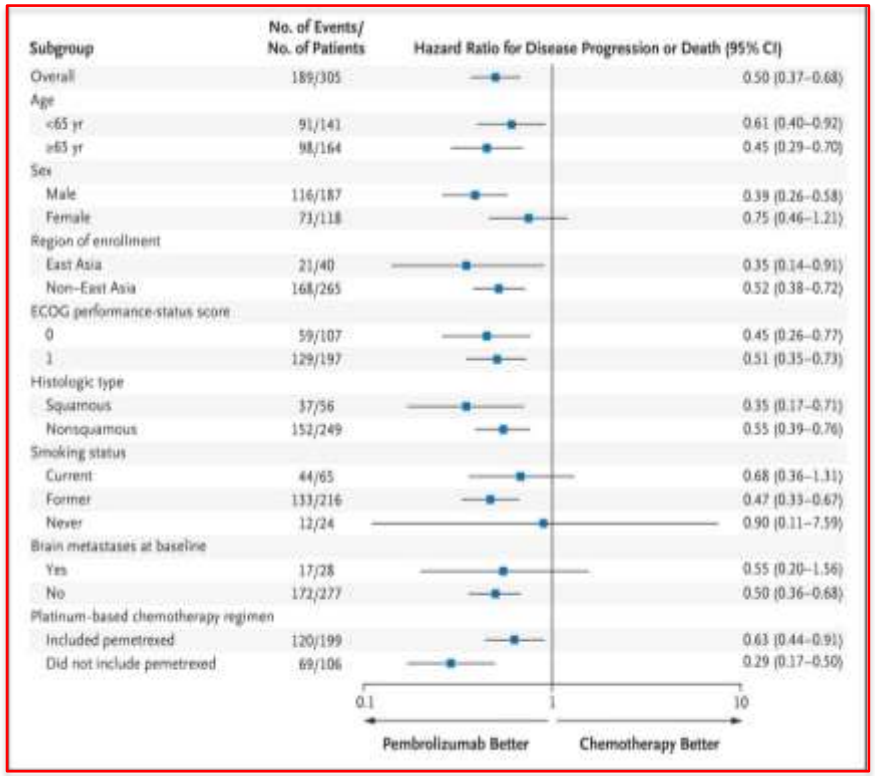
ORIGINAL ARTICLE

Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer

Martin Reck, M.D., Ph.D., Delvys Rodríguez-Abreu, M.D., Andrew G. Robinson, M.D., Rina Hui, M.B., B.S., Ph.D., Tibor Csőszi, M.D., Andrea Fülöp, M.D., Maya Gottfried, M.D., Nir Peled, M.D., Ph.D.,

Aproximadamente 28-30% de CPNCP tienen niveles elevados de expresión de PD-L1 en membrana **(>50% de cls tumorales +)**



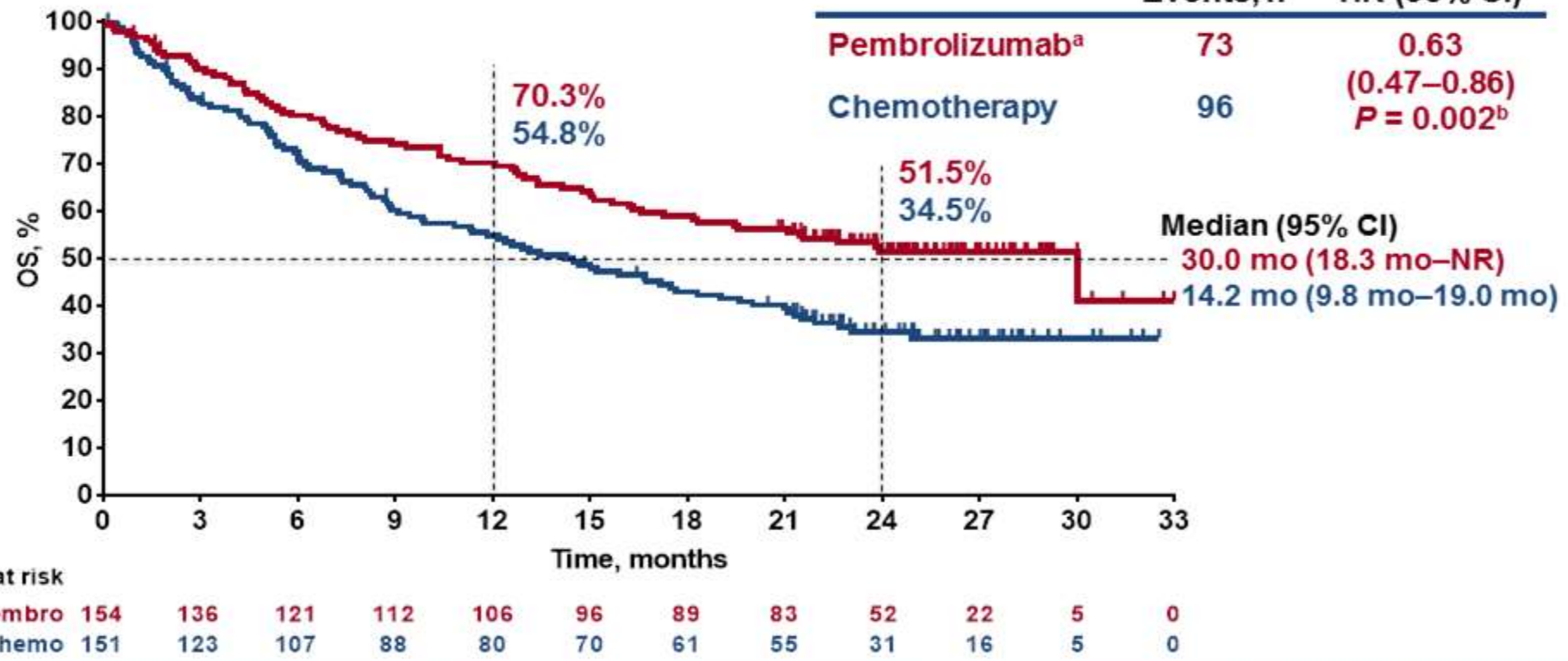


Reck , NEJM 2016

Updated Analysis of KEYNOTE-024: Pembrolizumab Versus Platinum-based Chemotherapy for Advanced NSCLC With PD-L1 TPS ≥50%

Julie R. Brahmer,[1] Delvys Rodríguez-Abreu,[2] Andrew G. Robinson,[3] Rina Hui,[4]

Overall Survival: Updated Analysis



[a]Effective crossover rate from chemotherapy to anti-PD-L1 therapy, 62.3% (82 patients crossed over to pembrolizumab during the study and 12 received anti-PD-L1 therapy outside of crossover). [b]Nominal *P* value. NR, not reached.
Data cutoff: July 10, 2017.

Phase 3 CheckMate 026 Study Design: Nivolumab vs Chemotherapy in First-line NSCLC

Key eligibility criteria:

- Stage IV or recurrent NSCLC
- No prior systemic therapy for advanced disease
- No *EGFR/ALK* mutations sensitive to available targeted inhibitor therapy
- ≥1% PD-L1 expression[a]
- CNS metastases permitted if adequately treated at least 2 weeks prior to randomization

Randomize 1:1

Nivolumab
3 mg/kg IV Q2W
n = 271

Chemotherapy
(histology dependent)[b]
Maximum of 6 cycles
n = 270

Tumor scans Q6W until wk 48 then Q12W

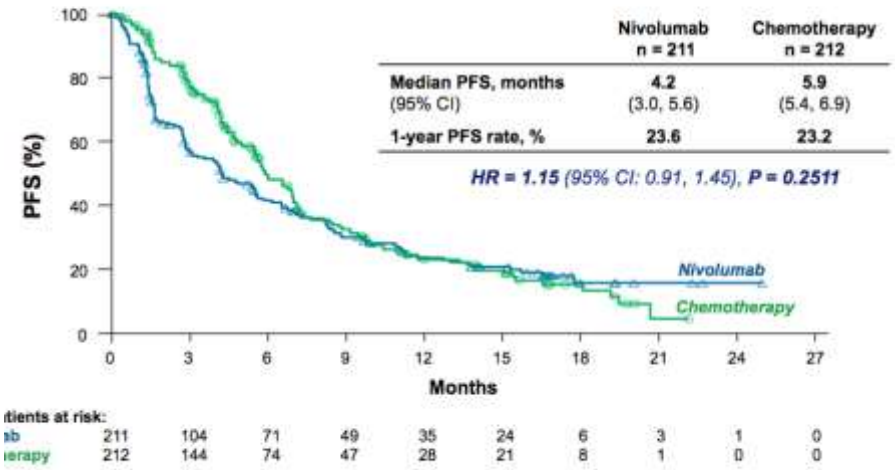
Disease progression or unacceptable toxicity

Disease progression

Crossover nivolumab[c] (optional)

Primary Endpoint (PFS per IRRC in ≥5% PD-L1+)

CheckMate 026: Nivolumab vs Chemotherapy in First-line NSCLC



	Nivolumab n = 211	Chemotherapy n = 212
Median PFS, months (95% CI)	4.2 (3.0, 5.6)	5.9 (5.4, 6.9)
1-year PFS rate, %	23.6	23.2

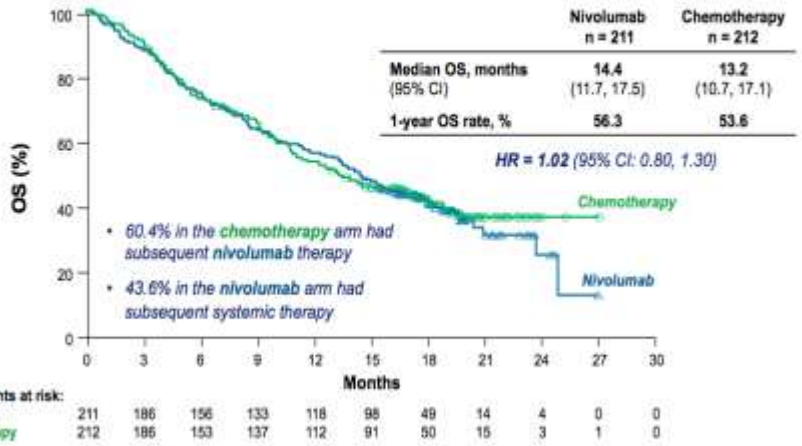
HR = 1.15 (95% CI: 0.91, 1.45), P = 0.2511

No. of patients at risk:											
Nivolumab	211	104	71	49	35	24	6	3	1	0	
Chemotherapy	212	144	74	47	28	21	8	1	0	0	

All randomized patients (≥1% PD-L1+): HR = 1.17 (95% CI: 0.95, 1.43)

OS (≥5% PD-L1+)

CheckMate 026: Nivolumab vs Chemotherapy in First-line NSCLC



	Nivolumab n = 211	Chemotherapy n = 212
Median OS, months (95% CI)	14.4 (11.7, 17.5)	13.2 (10.7, 17.1)
1-year OS rate, %	56.3	53.6

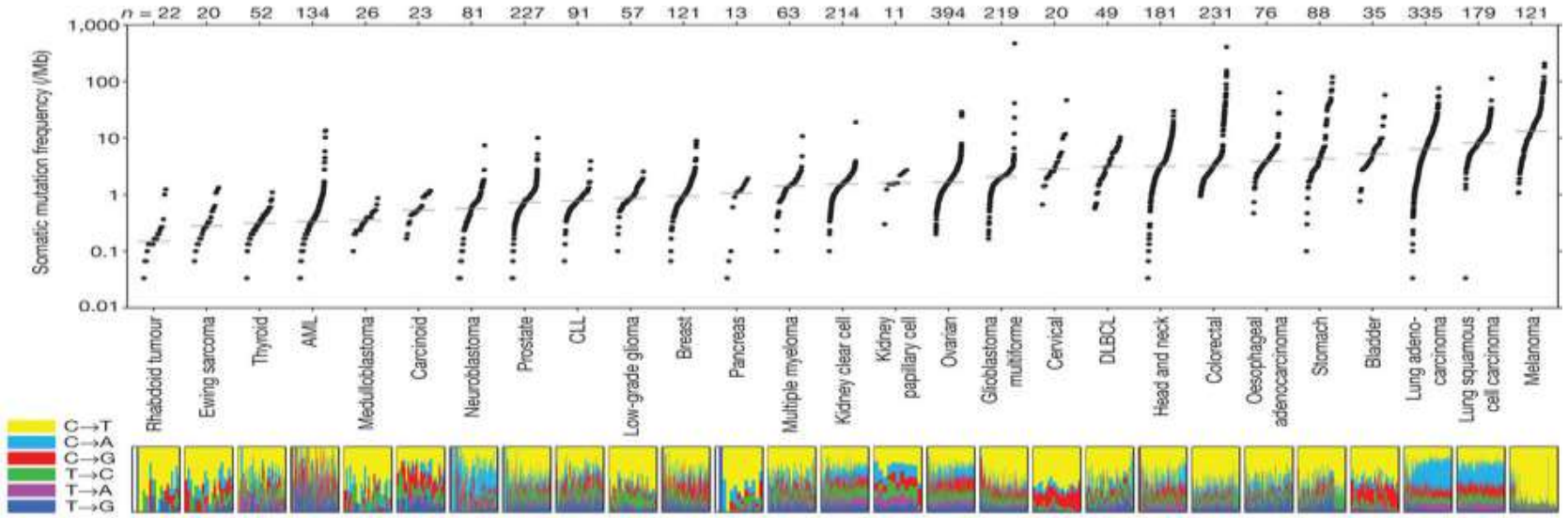
HR = 1.02 (95% CI: 0.80, 1.30)

No. of patients at risk:											
Nivolumab	211	186	156	133	118	98	49	14	4	0	0
Chemotherapy	212	186	153	137	112	91	50	15	3	1	0

All randomized patients (≥1% PD-L1+): HR = 1.07 (95% CI: 0.86, 1.33)

Tumor Mutation Burden TMB

CARGA MUTACIONAL

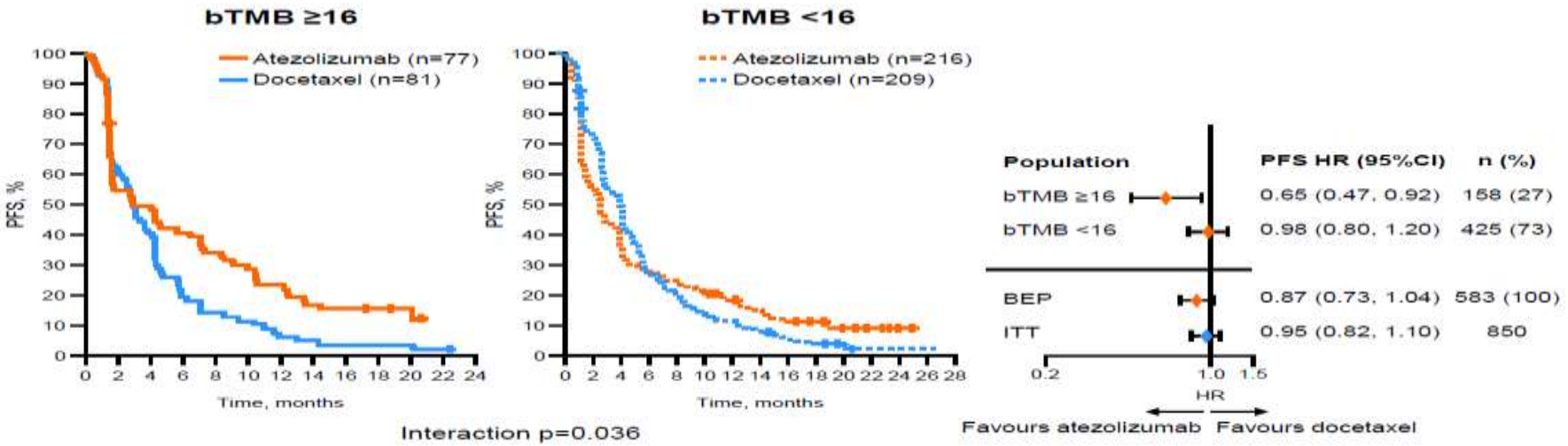


- Estudios en CP han mostrado como la carga mutacional se asocia con respuesta a los inhibidores inmuno-checkpoints
- Se ha sugerido que los neoantígeos predicen respuestas
- Los tumores con altas cargas mutacionales presentan también mayor nº de neoantígenos en moleculas HLA
- El Proyecto Atlas Cancer Genome demostró que casi el 60% de las biopsias de CP presentaban 5 o más neoantígenos

1295O: Blood-based biomarkers for cancer immunotherapy: Tumor mutational burden in blood (bTMB) is associated with improved atezolizumab (atezo) efficacy in 2L1 NSCLC (POPLAR and OAK) – Gandara DR, et al

- **Study objective**
  - To validate a novel assay to measure blood tumour mutational burden (bTMB) and evaluate the association between bTMB and efficacy of atezolizumab
- **Methods**
  - A 394 gene-based NGS assay was used to retrospectively test plasma samples for bTMB from the phase 2 POPLAR study and phase 3 OAK study
    - 211/273 samples from POPLAR and 583/797 samples from OAK were biomarker-evaluable
  - The association between bTMB and atezolizumab efficacy was analysed and the cut-point of bTMB ≥16 was selected based on POPLAR, and validated in OAK
- **Key results**

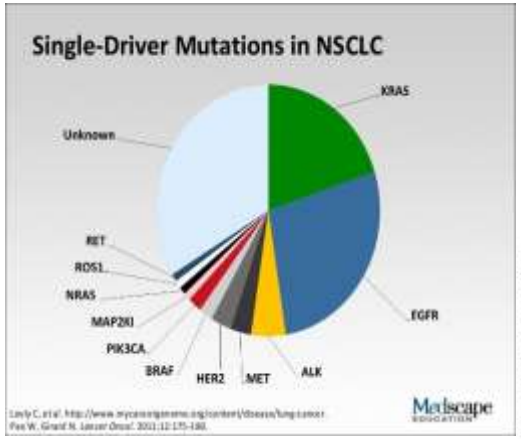
Atezolizumab PFS benefit in bTMB subgroups: OAK



BEP, biomarker-evaluable population

Gandara DR et al. Ann Oncol 2017;28(suppl 5):Abstr 1295O

ALK
ROS1

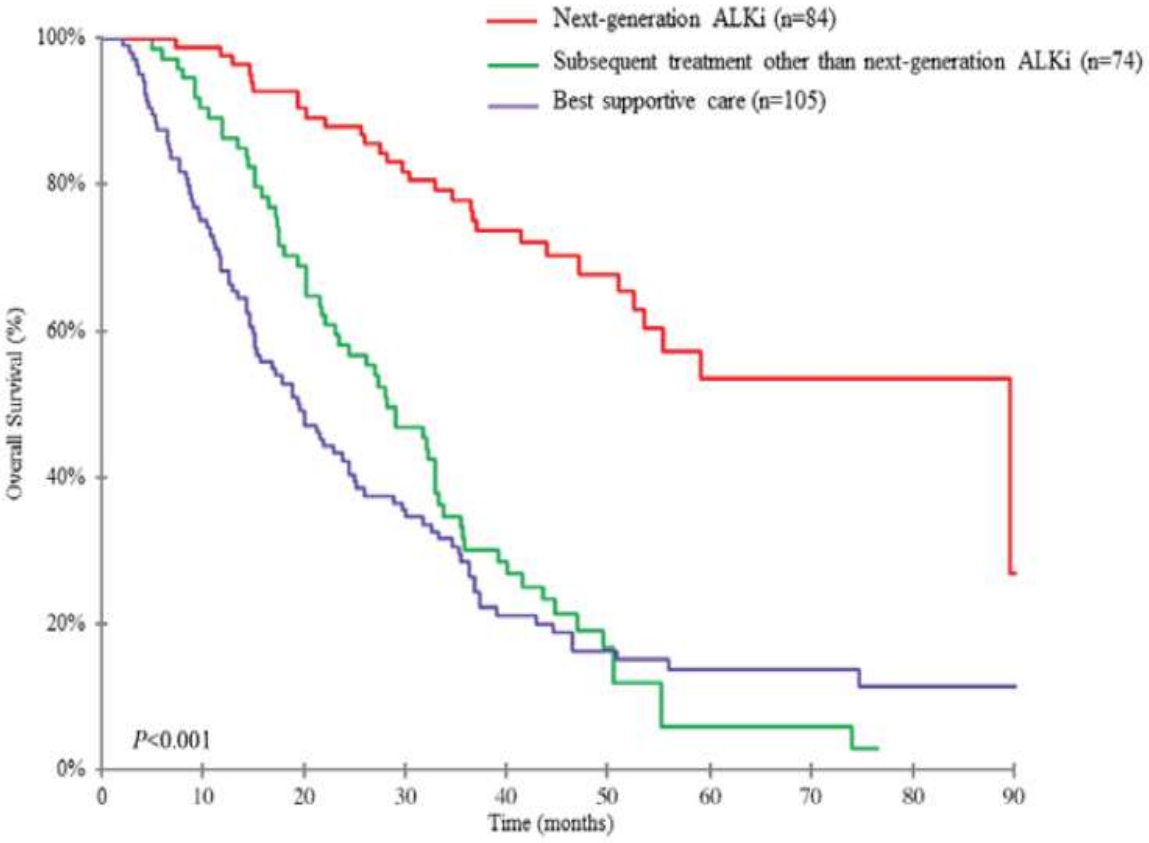


www.impactjournals.com/oncotarget/ Oncotarget, 2017, Vol. 8, (No. 13), pp: 21903-21917

Research Paper

Overall survival with crizotinib and next-generation ALK inhibitors in *ALK*-positive non-small-cell lung cancer (IFCT-1302 CLINALK): a French nationwide cohort retrospective study

Michaël Duruisseaux[1], Benjamin Besse[2], Jacques Cadranel[3], Maurice Pérol[4],



Number at risk

Next-generation ALKi	84	76	44	12	4
Subsequent treatment other than next-generation ALKi	74	51	17	2	0
Best supportive care	105	51	20	9	4

Mas allá de EGFR-ALK-ROS1

Paneles de secuenciación dirigidos

Panel GENERICOS: Panel de cáncer, regiones hotspot (sitios recurrentemente mutados, COSMIC) de 50 oncogenes y genes supresores

- Contiene 207 amplicones y se requiere **10 ng de DNA**
- Identificación de ~2.800 variantes (mutaciones/SNP) descritas e infinitas no descritas
- Selección de marcadores basadas en pronóstico y predicción

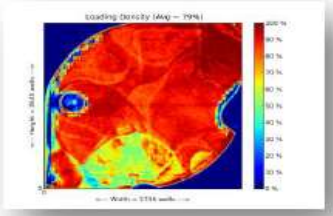
The Ion AmpliSeq™ Cancer Panel targets 50 genes

ABL1	*EZH2*	*JAK3*	*PTEN*
AKT1	*FBXW7*	*IDH2*	*PTPN11*
ALK	*FGFR1*	*KDR*	*RB1*
APC	*FGFR2*	*KIT*	*RET*
ATM	*FGFR3*	*KRAS*	*SMAD4*
BRAF	*FLT3*	*MET*	*SMARCB1*
CDH1	*GNA11*	*MLH1*	*SMO*
CDKN2A	*GNAS*	*MPL*	*SRC*
CSF1R	*GNAQ*	*NOTCH1*	*STK11*
CTNNB1	*HNF1A*	*NPM1*	*TP53*
EGFR	*HRAS*	*NRAS*	*VHL*
ERBB2	*IDH1*	*PDGFRA*	
ERBB4	*JAK2*	*PIK3CA*	

Panel ESPECIFICOS: Panel de cáncer de pulmón y colon

- Contiene 88 amplicones: hostspots y regiones (total de 14.6Kb) de 22 genes implicados en cáncer de colon y pulmón

- Genes incluidos: *KRAS, EGFR, BRAF,PIK3CA, AKT1, ERBB2, PTEN, NRAS, STK11, MAP2K1, ALK, DDR2, CTNNB1, MET, TP53, SMAD4, FBXW7, FGFR3, NOTCH1, ERBB4, FGFR1, FGFR2)*



Gen	Alteración	Frecuencia en Ca Pulmón NM
AKT1	Mutation	1%
ALK	Rearrangement	3–7%
BRAF	Mutation	1–3%
DDR2	Mutation	~4%
EGFR	Mutation	10–35%
FGFR1	Amplification	20%
HER2	Mutation	2–4%
KRAS	Mutation	15–25%
MEK1	Mutation	1%
MET	Amplification	2–4%
NRAS	Mutation	1%
PIK3CA	Mutation	1–3%
PTEN	Mutation	4–8%
RET	Rearrangement	1%
ROS1[a]	Rearrangement	1%

Drugs approved in NSCLC.

Drugs approved in NSCLC but for other molecular subtype.

Drugs approved in other cancer.

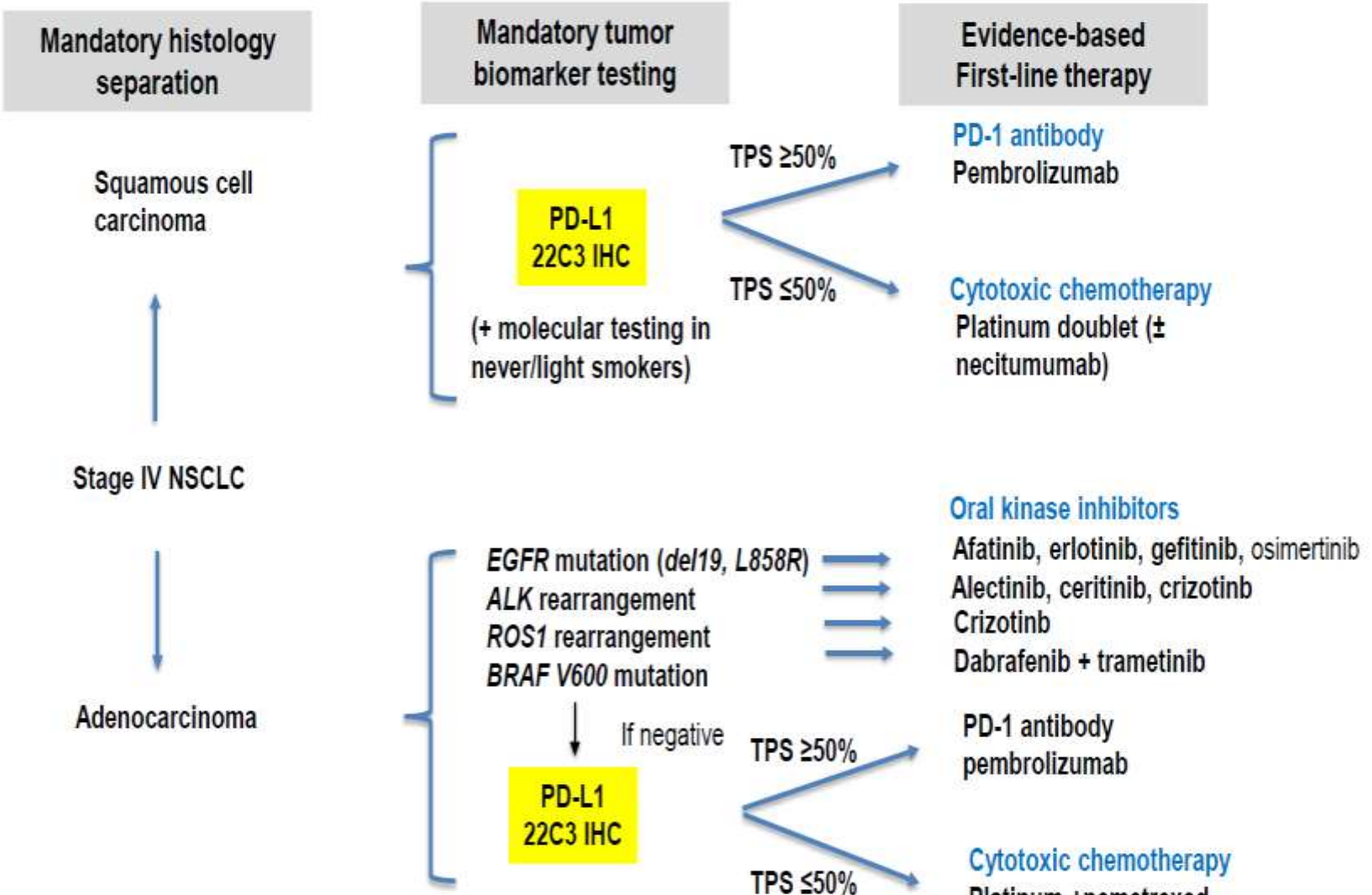
Drugs in clinical development

OA04.07: Clinical Characteristics of Lung Adenocarcinoma in the Young: Results from the Genomics of Young Lung Cancer Study

- **Study objective**
  - To assess the genomics of young lung cancer (GYLC) by examining lifestyle risk factors using specific genomic alteration to better characterize lung cancer in the young
- **Methods**
  - Patients diagnosed with a **bronchogenic lung cancer <40 years of age** were recruited to the GYLC study
- **Key results**
  - **114 patients <40 y**: median age at diagnosis of 34 years (range 16–39); 44% male; 80% stage IV
  - Among the patients with stage IV adenocarcinoma, **77% showed driver mutations by ALK, EGFR or ROS1 and 16% had other mutations including HER2, RET, ATM, TP53, BRCA2 and KRAS**
- **Conclusions**
  - Preliminary results revealed a **heavily enriched population for oncogenic drivers**
  - This study will enable a more comprehensive Epidemiology of Young Lung Cancer study to identify risk factors related to specific genomic alterations

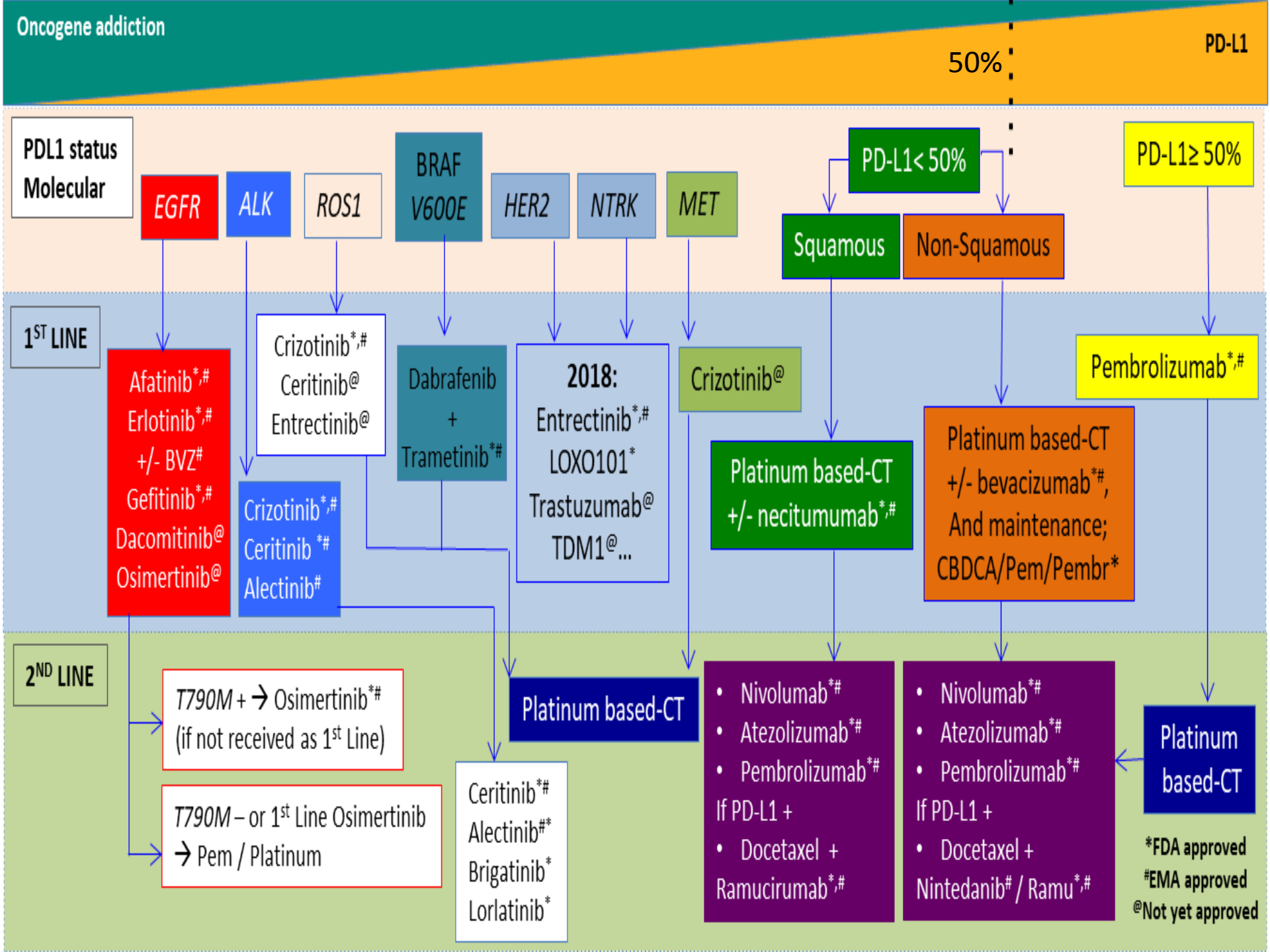
Gitlitz et al. J Thorac Oncol 2016; 11(suppl): abstr OA04.07

PD-L1 Testing and Molecular Testig Is Mandatory for First-Line Treatment Decison Making in Advanced NSCLC



IHC, immunohistochemistry; TPS, tumor proportion score

Rangachari D, et al. *Transl Cancer Res.* 2017;6(Suppl 1):S151-S157.


Oncogene addiction
50%
PD-L1
PDL1 status
Molecular
EGFR
ALK
ROS1
BRAF V600E
HER2
NTRK
MET
PD-L1< 50%
PD-L1≥ 50%
Squamous
Non-Squamous
1ST LINE
Afatinib*,#
Erlotinib*,#
+/- BVZ#
Gefitinib*,#
Dacomitinib@
Osimertinib@
Crizotinib*,#
Ceritinib@
Entrectinib@
Dabrafenib
+
Trametinib*#
2018:
Entrectinib*,#
LOXO101*
Trastuzumab@
TDM1@...
Crizotinib@
Pembrolizumab*,#
Platinum based-CT
+/- necitumumab*,#
Platinum based-CT
+/- bevacizumab*#,
And maintenance;
CBDCA/Pem/Pembr*
Crizotinib*,#
Ceritinib*#
Alectinib#
2ND LINE
T790M + → Osimertinib*#
(if not received as 1st Line)
T790M – or 1st Line Osimertinib
→ Pem / Platinum
Platinum based-CT
Ceritinib*#
Alectinib#*
Brigatinib*
Lorlatinib*
• Nivolumab*#
• Atezolizumab*#
• Pembrolizumab*#
If PD-L1 +
• Docetaxel +
Ramucirumab*,#
• Nivolumab*#
• Atezolizumab*#
• Pembrolizumab*#
If PD-L1 +
• Docetaxel +
Nintedanib# / Ramu*,#
Platinum
based-CT
*FDA approved
#EMA approved
@Not yet approved

MUCHAS GRACIAS POR SU ATENCIÓN