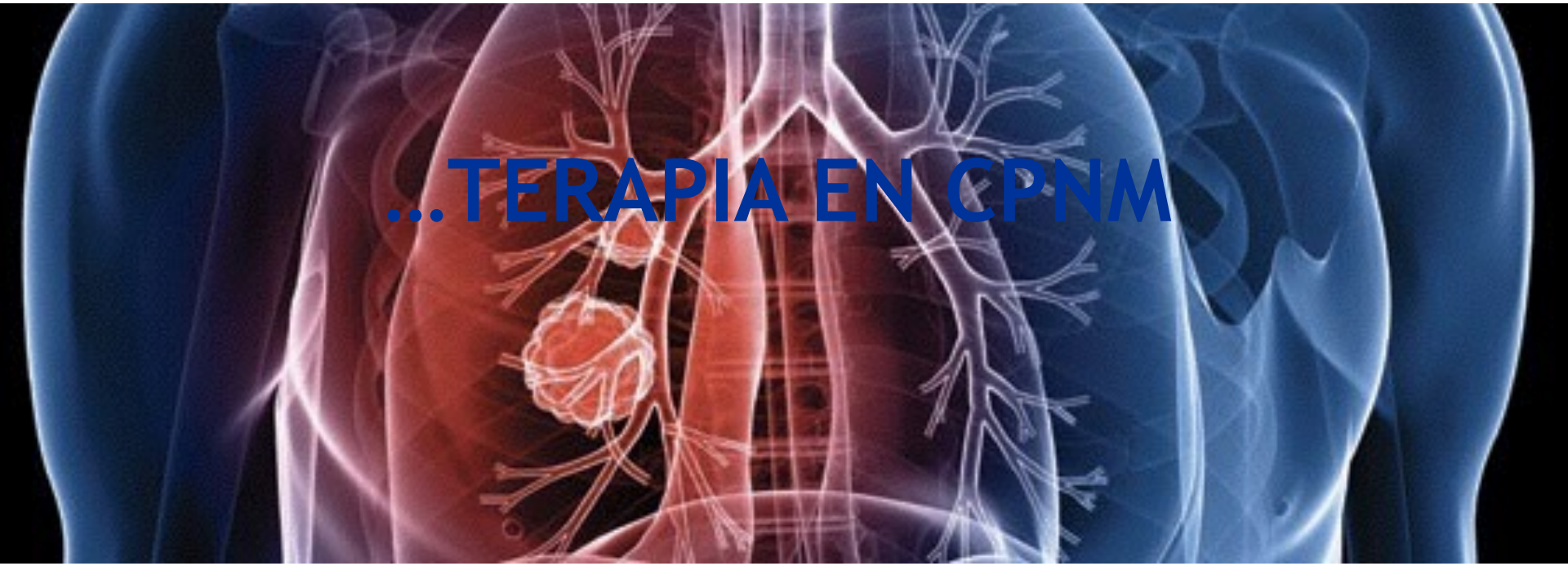
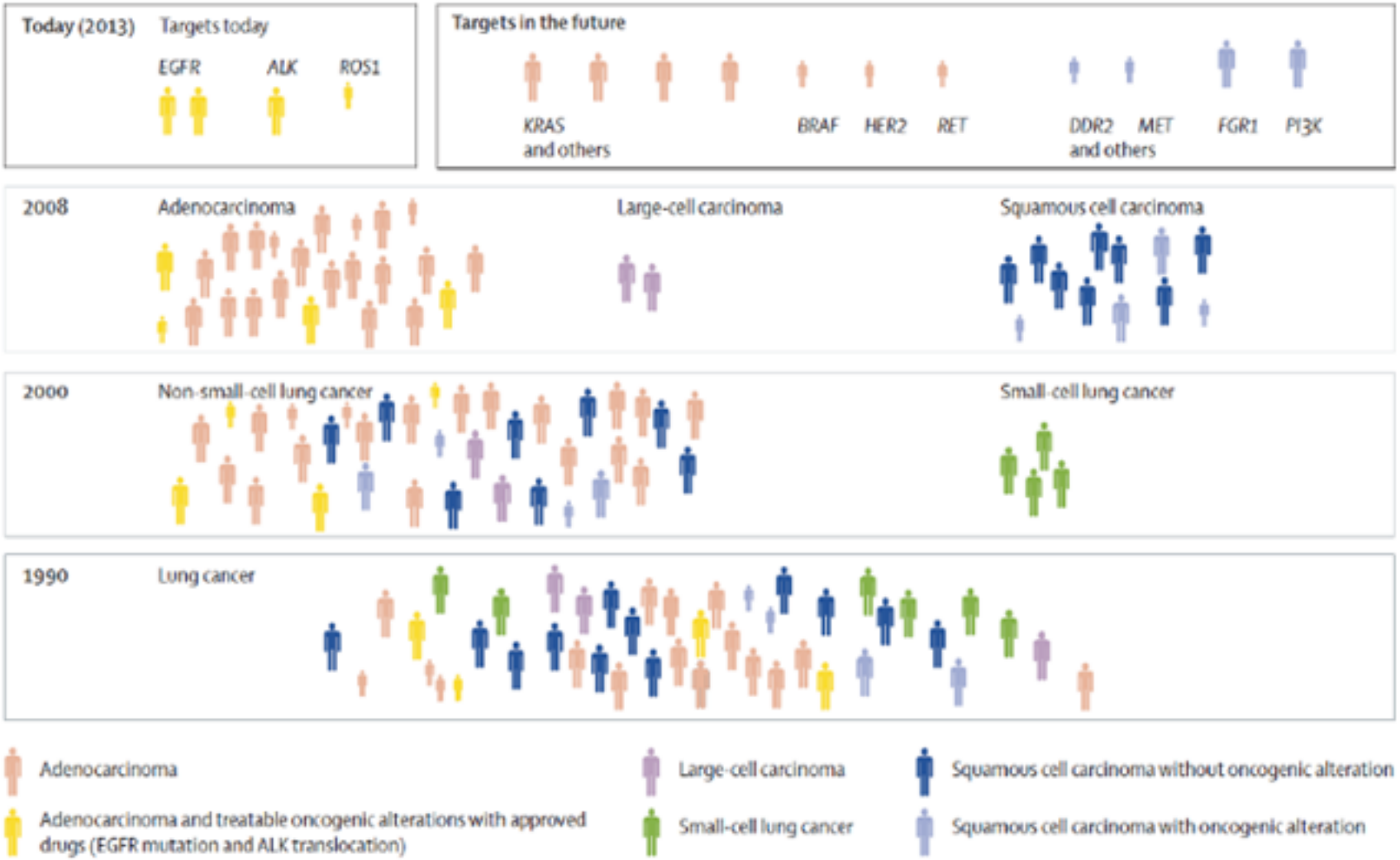


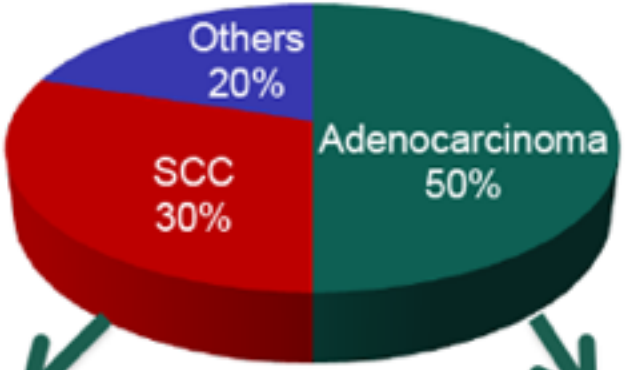
...TERAPIA EN CPNM

Dra Ana Blasco
Oncología Médica
Hospital General Universitario Valencia

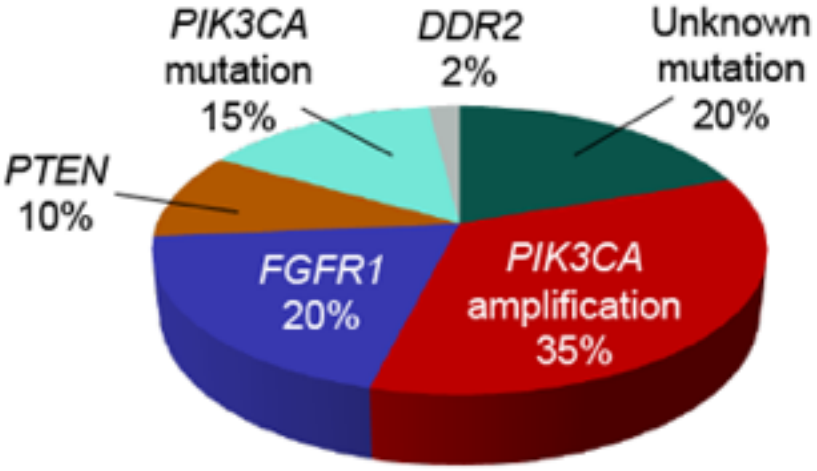


Reck M et al. *Lancet*. 2013;382:709-719.

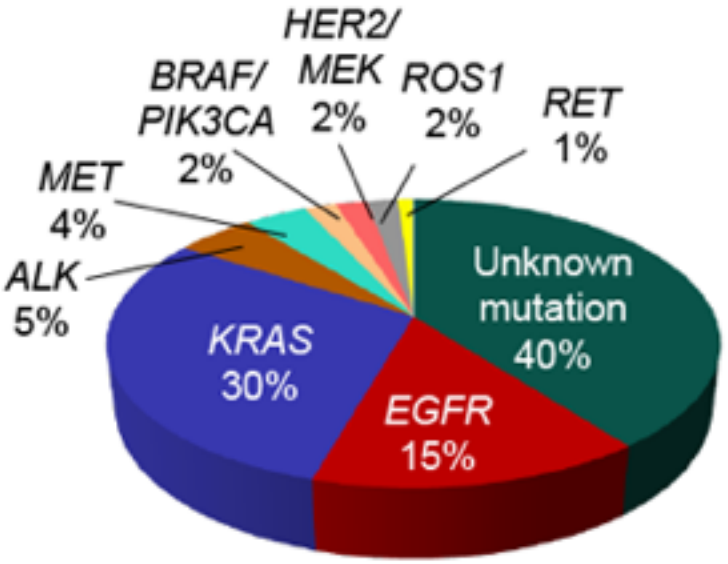
NSCLC by Histology



SCC



Adenocarcinoma



Chan BA et al. *Transl Lung Cancer Res*. 2015;4:36-54.

Mutaciones conocidas en CPNM

Biomarkers	Gender, Age	Prevalence, %	Tobacco	Ethnicity	ADC vs SqCC/Distinctive Histologic Characteristics	Clinically Relevant Genetic Abnormality	Examples of Targeting Agent (Available or in Development)
EGFR	Female, younger	10-40	Non-smokers	Asian	ADC/Non-mucinous bronchioalveolar (lepidic)	M (most common in-frame deletions of e19 and point M in e21)	Gefitinib, Erlotinib, Afatinib, Dacomitinib, Neratinib
ALK	Younger	2-6	Non-smokers	Not distinctive	ADC/solid pattern, signet-ring cells	Translocation, inversion (*EML4-ALK* most common)	Crizotinib, Ceritinib
HER2/ERBB2	Female	1-4	Non-smokers	Asian	ADC	In-frame insertions in e20	Trastuzumab, Pertuzumab, Lapatinib
ROS1	Female, younger	0.5-2	Non-smokers	Und.	ADC	Translocation (*ROS1-FIG*)	Crizotinib
RET	Younger	1-2	Non-smokers	Not distinct	ADC/ Adenosquamous	KIF5B-RET and CCDC6-RET fusion genes	Vandetanib, Cabozantinib
KRAS	Not distinct	15-30	Smokers	Caucasian	ADC/mucinous, particularly with lepidic (bronchioalveolar) pattern	Ms in codon 12 (majority) and 13	Selumetinib (via inhibition of MEK)
BRAF	Not distinct	3 (ADCs)	Smokers	Not distinct	ADC	Ms in *V600E* (50%), *G469A* (39%), *D594G* (11%)	Dabrafenib, Vemurafenib, XL281, Selumetinib

e: exon; M: mutation; Und: undetermined.

Brega E, Brandao G. *Front Oncol*. 2014;4:182.

..... +++ Mutaciones CPNM

Biomarkers	Gender, Age	Prevalence, %	Tobacco	Ethnicity	ADC vs SqCC/Distinctive Histologic Characteristics	Clinically Relevant Genetic Abnormality	Examples of Targeting Agent (Available or in Development)
NRAS	Und.	0.5-1	Smokers	Und.	ADC	Ms in codon Q61 in e3 (80%) and G12 (e2)	Selumetinib, Trametinib
FGFR1	Not distinct	22 (of SqCC)	Smokers	Not distinct	SqCC	Amplification	PD173074
PTEN	Not distinct	4-8	Smokers	Not distinct	SqCC	Various Ms in e5-8	GSK2636771
DDR2	Und.	2.5-3.8	Und.	Und.	SqCC	Missense Ms	Imatinib, Dasatinib
MAP2K1/ MEK1	Und.	1	Unclear	Und.	ADC	Ms *in Q56P, K57N, D67M*	AZD6244, Pimasertib, Refametinib, others
PIK3CA	Not distinct	2-4	Mixed reports	Not distinct	ADC and SqCC	Ms in *E545K, H1047R* (most common), also *E542K, H1o47L*	Everolimus, Temsirolimus, GDC-0941, XL-147, others
AKT1	Und.	1	Und.	Und.	ADC and SqCC	M in *E17K*	MK-2206
MET	Not distinct	1-5	Not distinct	Und.	ADC	Amplification, protein overexpression/M	Vandetanib, Cabozantinib

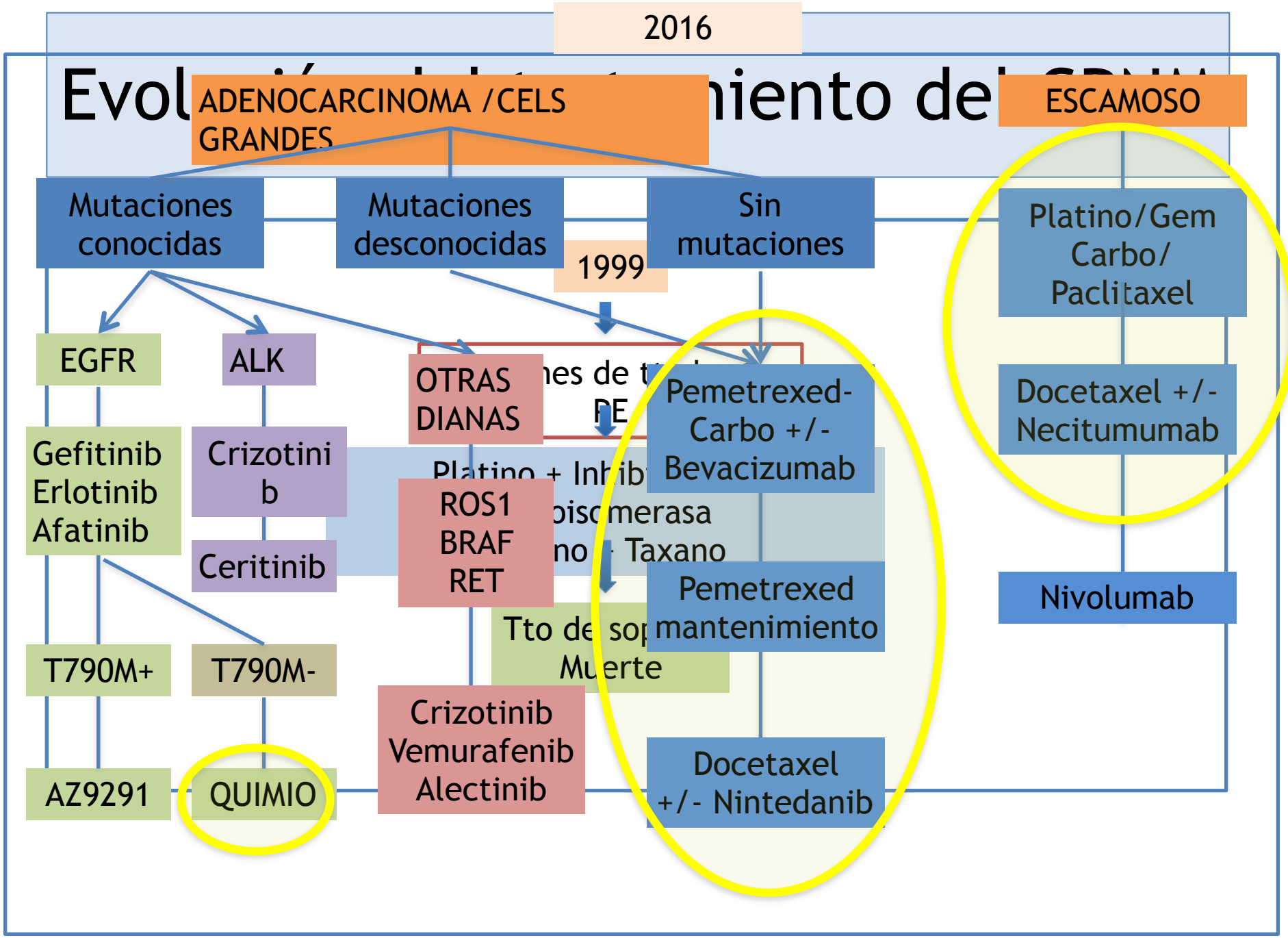
Brega E, Brandao G. *Front Oncol*. 2014;4:182.

“Literatura traslacional”

Mutación	EGFR	ALK	HER2	BRAF	KRAS	PI3K	AKT1	MAP2k1	MET
Adenocarcinoma	15-15%								
Escamoso	2-5%								

Blasco A, et al.

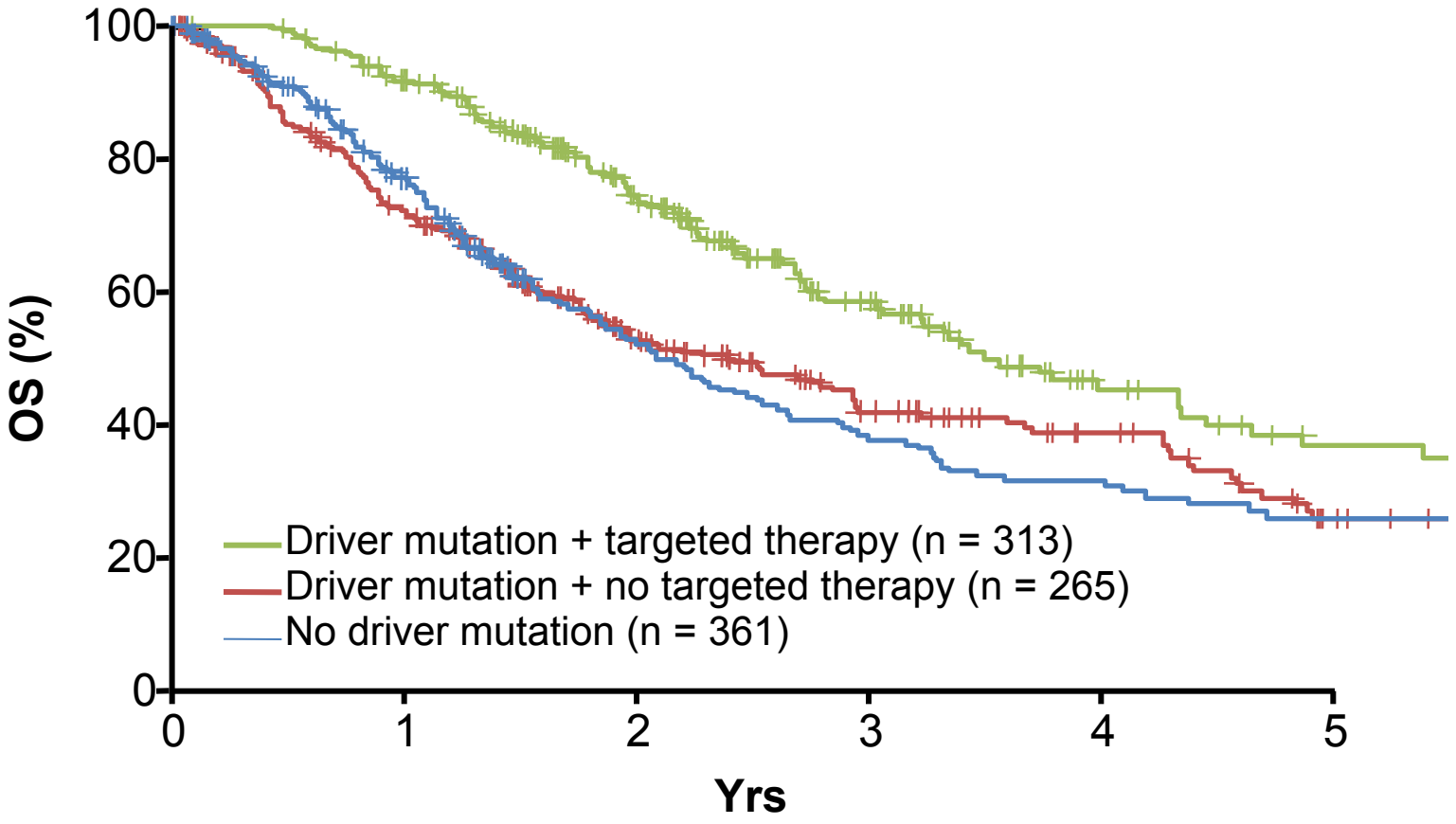
From Pao W, et al.


2016
Evol iento de
ADENOCARCINOMA /CELS GRANDES
ESCAMOSO
Mutaciones conocidas
Mutaciones desconocidas
Sin mutaciones
1999
Platino/Gem Carbo/ Paclitaxel
Docetaxel +/- Necitumumab
EGFR
ALK
OTRAS DIANAS
Pemetrexed-Carbo +/- Bevacizumab
Gefitinib Erlotinib Afatinib
Crizotinib
Ceritinib
ROS1 BRAF RET
Taxano
Pemetrexed mantenimiento
Nivolumab
T790M+
T790M-
Crizotinib Vemurafenib Alectinib
AZ9291
QUIMIO
Docetaxel +/- Nintedanib


barranc
1h 25min
de l'Infern

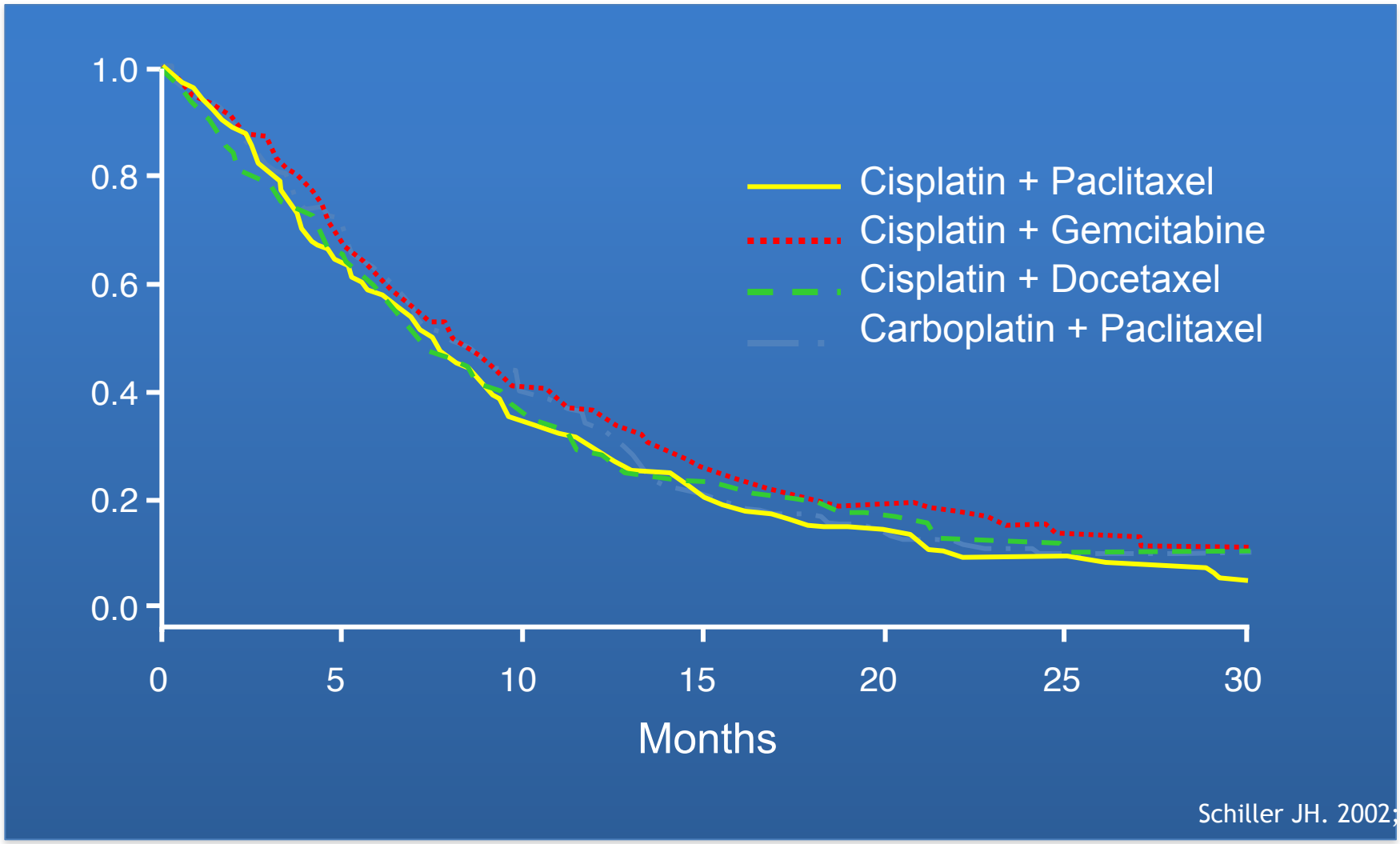
¿Esto es relevante?

Lung Cancer Mutation Consortium: OS/ttos



Johnson B. 2013

ECOG 1594: SG en función de esquema

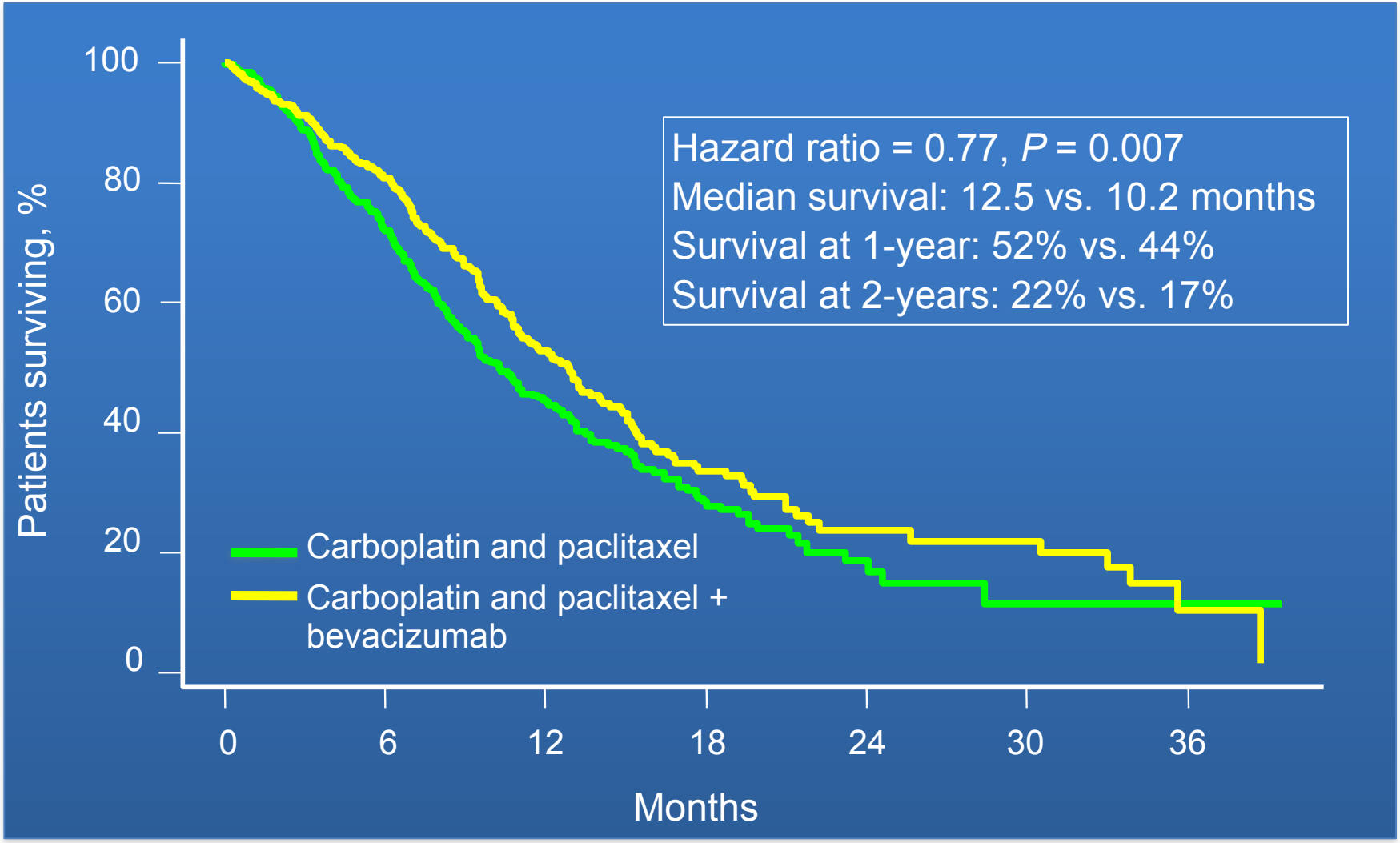


Schiller JH. 2002;

Esquemas “clásicos” sin selección

Estudio	N	ORR(%)	MST (mos)
SWOG 9509			
Carbo-Pac	208	25	8.0
Cis-Vino	202	28	8.0
EGOG 1594			
Cis-Pac	292	21.3	8.1
Cis-Gem	288	21	8.1
Cis-Doce	293	17.3	7.4
Italian Study			
Carbo-Pac	290	15.3	8.3
Cis-Gem	205	30	9.8
Carbo-Pac	201	32	9.9
Cis-Vino	201	30	8.1
EORTC 08975			
Cis-Pac	159	31	8.1
Cis-Gem	160	36	8.8
Gem-Pac	161	27	6.9
TAX 326			
Doce-Cis	408	NA	10.9
Doce-Carbo	406	NA	9.1
Cis-Vino	404	NA	10.0

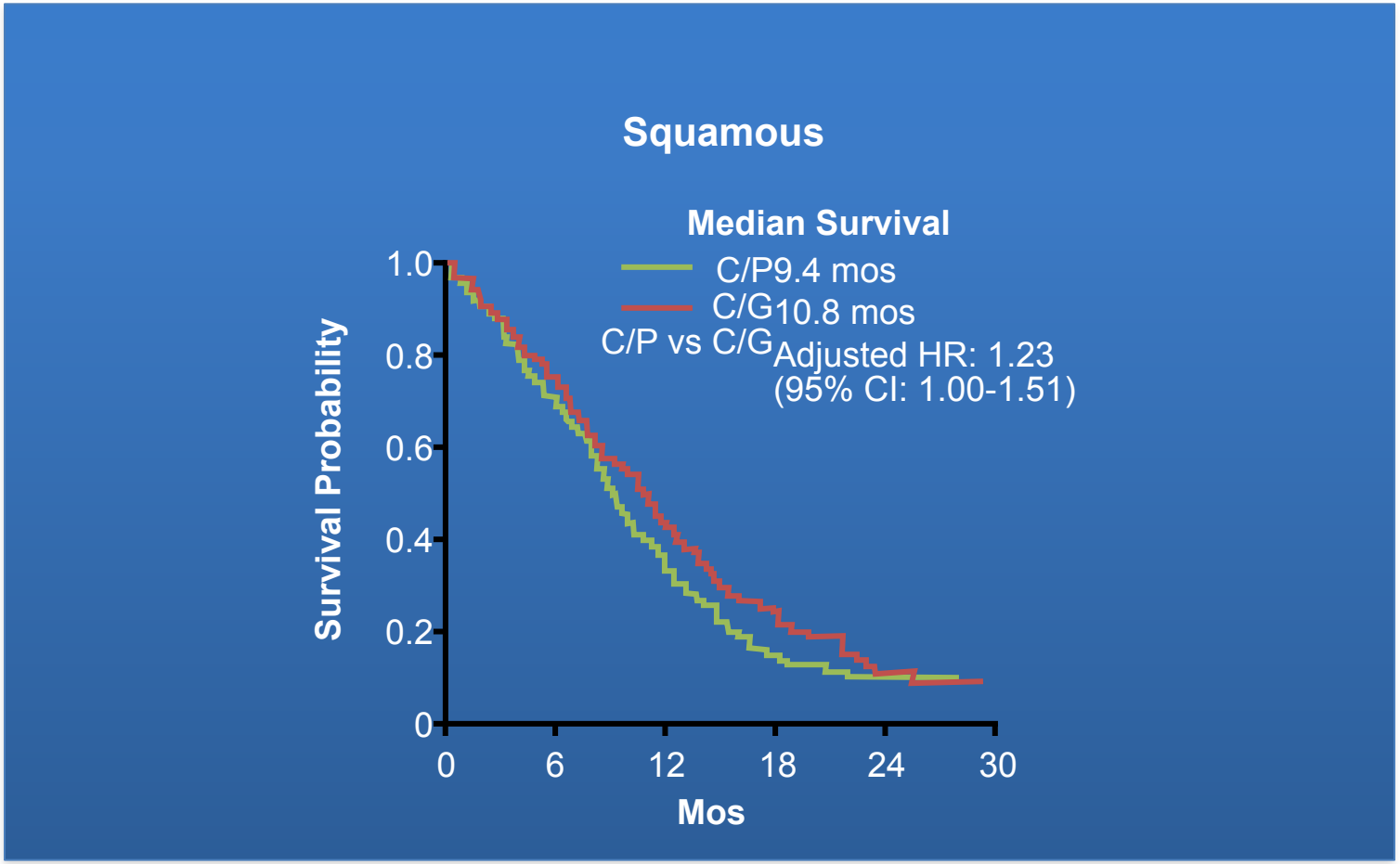
Pequeñas victorias hacen camino..



Sandler 2006

Se hace camino al andar..

Superioridad del doblete platino-pemetrexed en tumores no escamosos



Scagliotti GV,. 2008

ADENOCARCINOMA, LARGE CELL, NSCLC NOS[tt]

FIRST-LINE THERAPY

PS 0-1 → Doublet chemotherapy[ff] (category 1) or Bevacizumab + chemotherapy[ff,uu,vv] (if criteria met)[ww]

PS 2 → Chemotherapy[ff]

PS 3-4 → Best supportive care. See NCCN Guidelines for Palliative Care

→ Tumor response evaluation

- **Progression** → PS 0-2 → **SUBSEQUENT THERAPY[ff]**
  - If not already given:
  - Systemic immune checkpoint inhibitors (preferred)
    - Nivolumab (category 1) or Pembrolizumab[xx] (category 1)
  - or
  - Other systemic therapy
  - Docetaxel or Pemetrexed or Erlotinib[yy] or Gemcitabine or Ramucirumab + docetaxel
  - → Progression[ccc]
- **Progression** → PS 3-4 → Erlotinib[zz] or afatinib[zz] or gefitinib[zz] or crizotinib[aaa] (if not already given) or Best supportive care. See NCCN Guidelines for Palliative Care
- Response or stable disease → 4–6 cycles (total) → Tumor response evaluation
  - **Progression** → See Subsequent therapy, above
  - Response or stable disease → **Continuation maintenance[ff]**
    - Bevacizumab (category 1)[uu]
    - Pemetrexed (category 1)
    - Bevacizumab + pemetrexed[bbb]
    - Gemcitabine (category 2B)
    - or
    - **Switch maintenance[ff]** (category 2B)
    - Pemetrexed or Erlotinib
    - or
    - Close observation
    - → Progression, see Subsequent therapy, above

[ff] See Systemic Therapy for Advanced or Metastatic Disease (NSCL-F).

[tt] Consider additional mutational testing if only EGFR and ALK were performed. See Emerging Targeted Agents for Patients With Genetic Alterations (NSCL-H).

[uu] Bevacizumab should be given until progression.

[vv] Any regimen with a high risk of thrombocytopenia and the potential risk of bleeding should be used with caution in combination with bevacizumab.

[ww] Criteria for treatment with bevacizumab: non-squamous NSCLC, and no recent history of hemoptysis. Bevacizumab should not be given as a single agent, unless as maintenance if initially used with chemotherapy.

[xx] Pembrolizumab is approved for patients with NSCLC tumors with PD-L1 expression, as determined by an FDA-approved test for PD-L1 with use of pembrolizumab.

[yy] Recommend proteomic testing for patients with NSCLC and wild-type EGFR or with unknown EGFR status. A patient with a "poor" classification should not be offered erlotinib in the second-line setting. Gregorc V, Novello S, Lazzari C, et al. Lancet Oncol 2014; 15:713-21.

[zz] May be considered for PS 3 and 4 patients with sensitizing EGFR mutations.

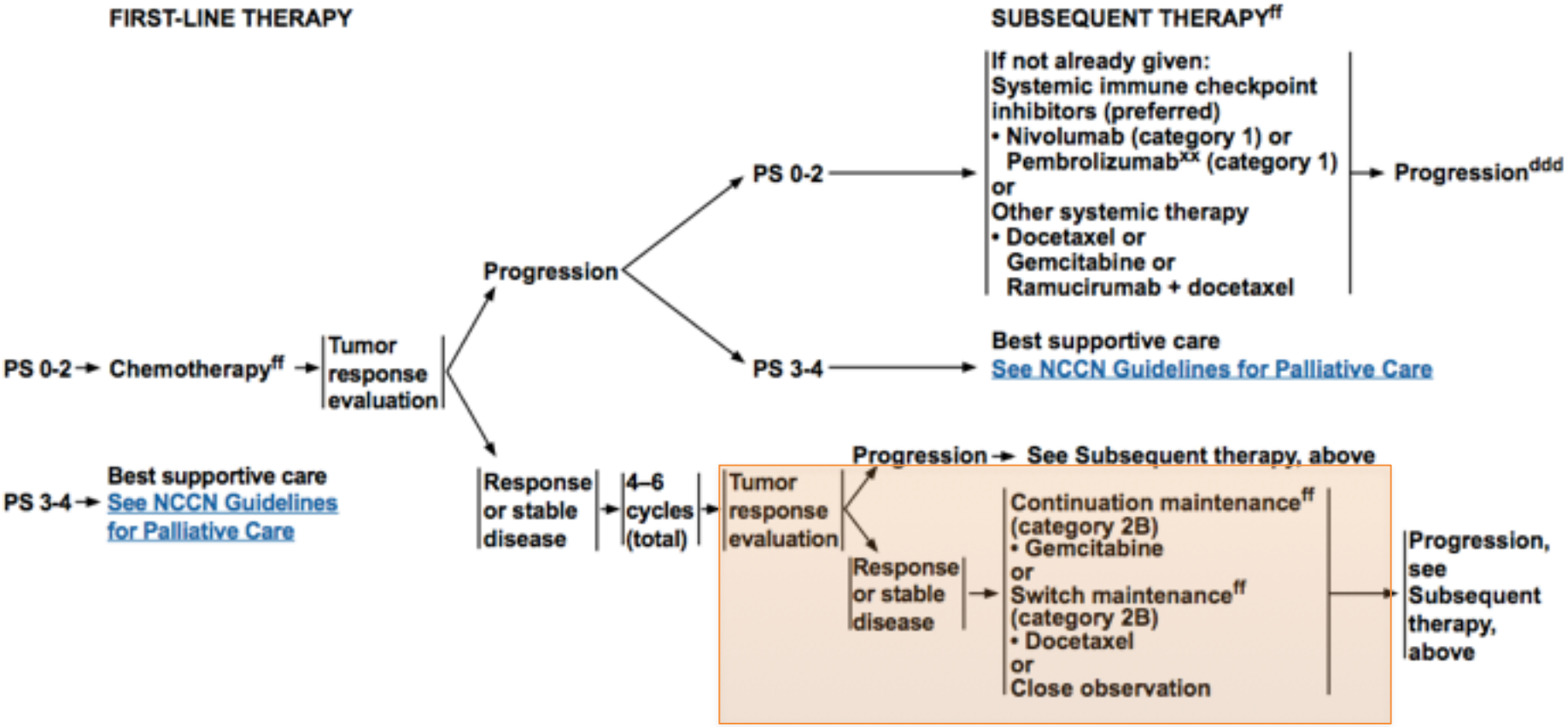
[aaa] May be considered for PS 3 and 4 patients if positive for the ALK rearrangement.

[bbb] If bevacizumab was used with a first-line pemetrexed/platinum chemotherapy regimen.

[ccc] If not already given, options for PS 0-2 include erlotinib, nivolumab, pembrolizumab, docetaxel (category 2B), pemetrexed (category 2B), gemcitabine (category 2B), or ramucirumab + docetaxel (category 2B); options for PS 3-4 include erlotinib or best supportive care. Options for further progression are best supportive care or clinical trial.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

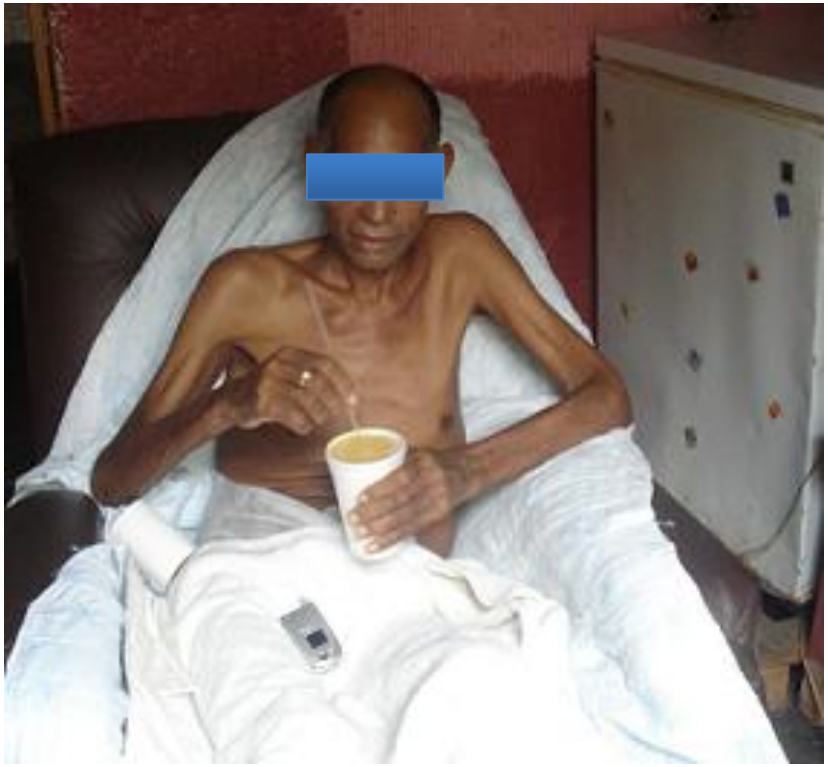
SQUAMOUS CELL CARCINOMA[tt]



[ff] See Systemic Therapy for Advanced or Metastatic Disease (NSCL-F).
[tt] Consider additional mutational testing if only EGFR and ALK were performed. See Emerging Targeted Agents for Patients With Genetic Alterations (NSCL-H).
[xx] Pembrolizumab is approved for patients with NSCLC tumors with PD-L1 expression, as determined by an FDA-approved test for PD-L1 with use of pembrolizumab.
[ddd] If not already given, options for PS 0-2 include nivolumab, pembrolizumab, docetaxel (category 2B), gemcitabine (category 2B), or ramucirumab + docetaxel (category 2B); options for PS 3-4 include best supportive care. Options for further progression are best supportive care or clinical trial.

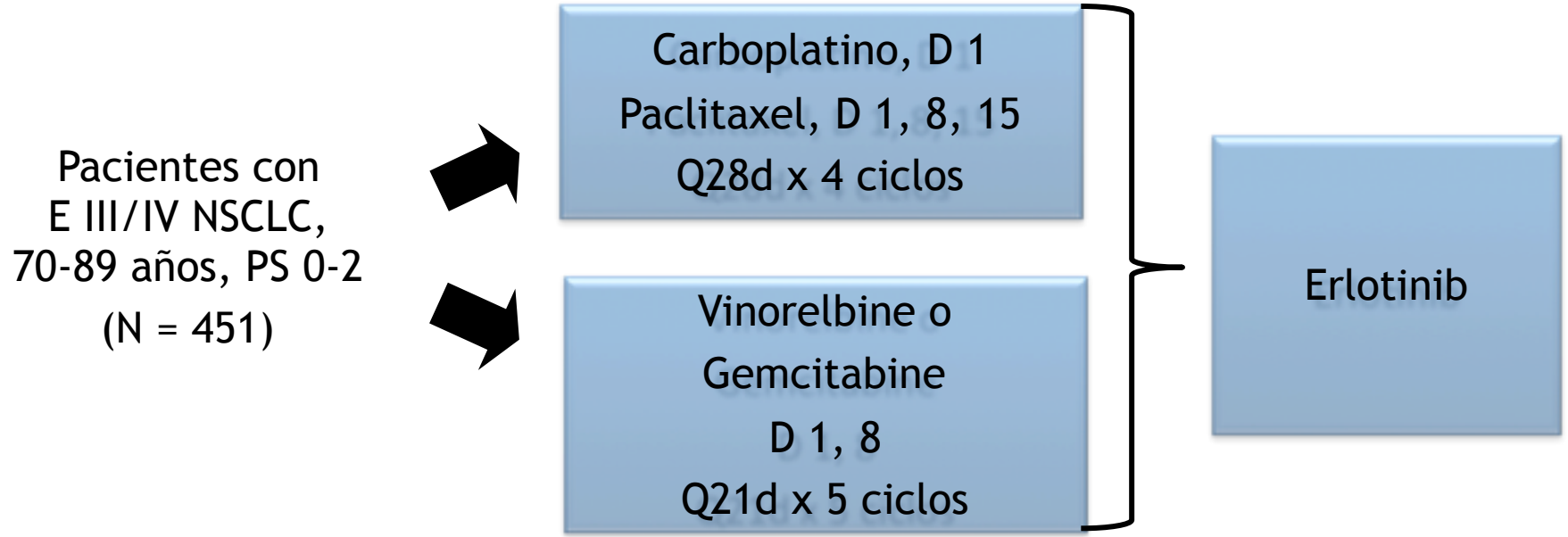
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

…Además hemos aprendido:



Dobletes en ancianos

IFCT-0501: Dobletes de platino en ancianos



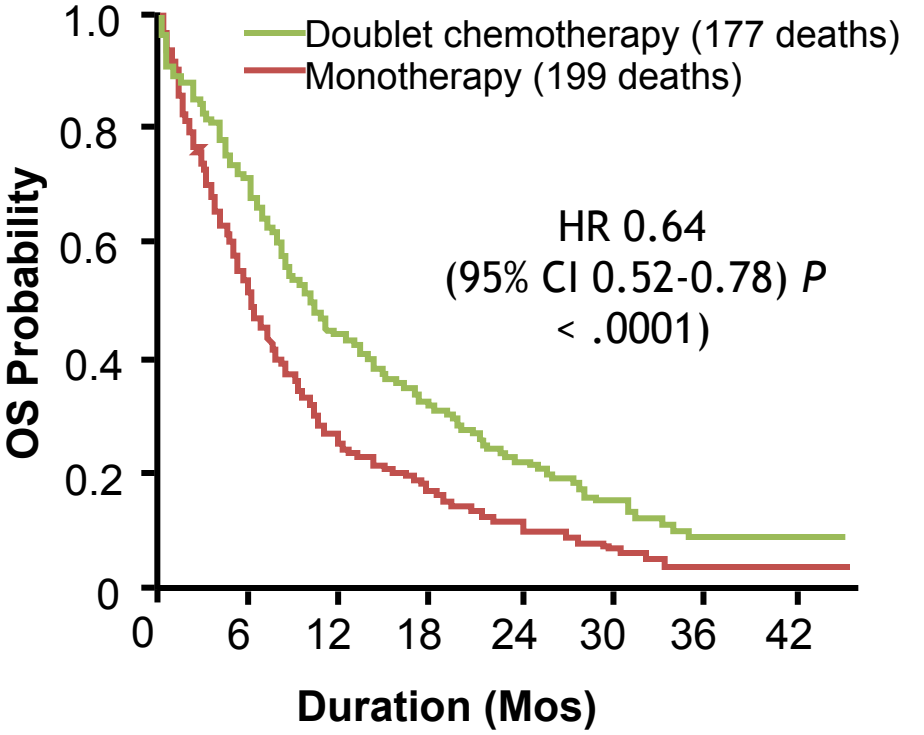
- Objetivo primario SG

Quoix E,2011.

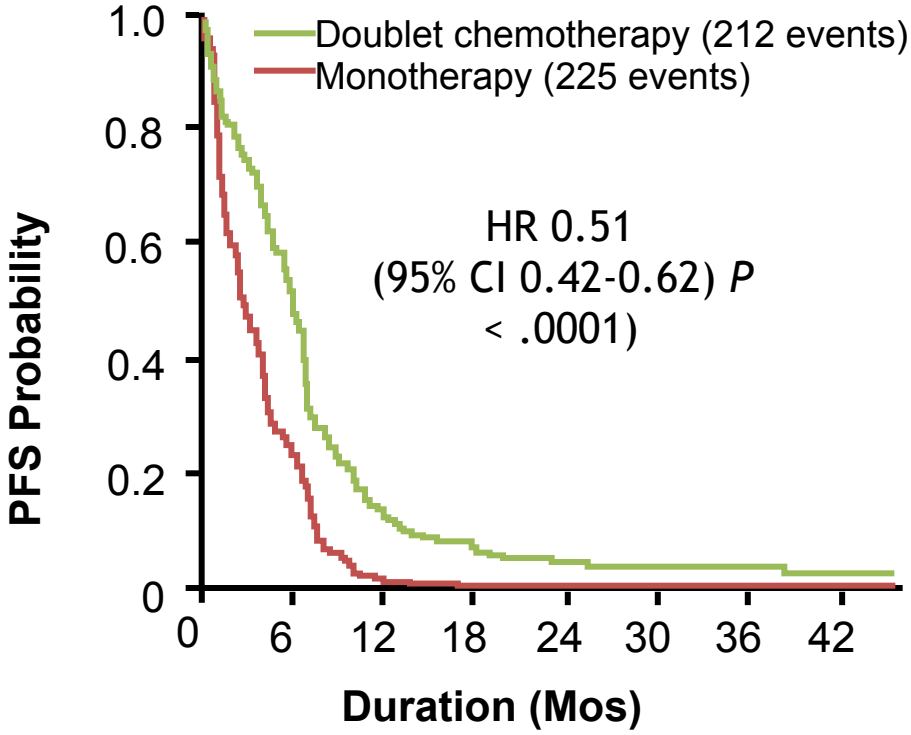
Dobletes en ancianos: OS y PFS

	P	CP
Median OS, mo	6.1	8.3
PFS at 6 mo, %	50	65
PFS at 12 mo, %	22	43

OS



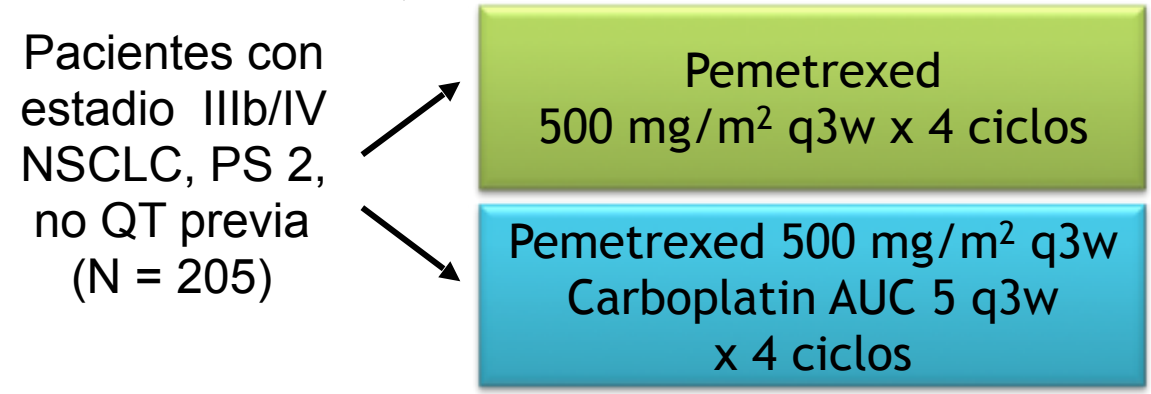
PFS



Quoix E,2011.

Dobletes y PS 2

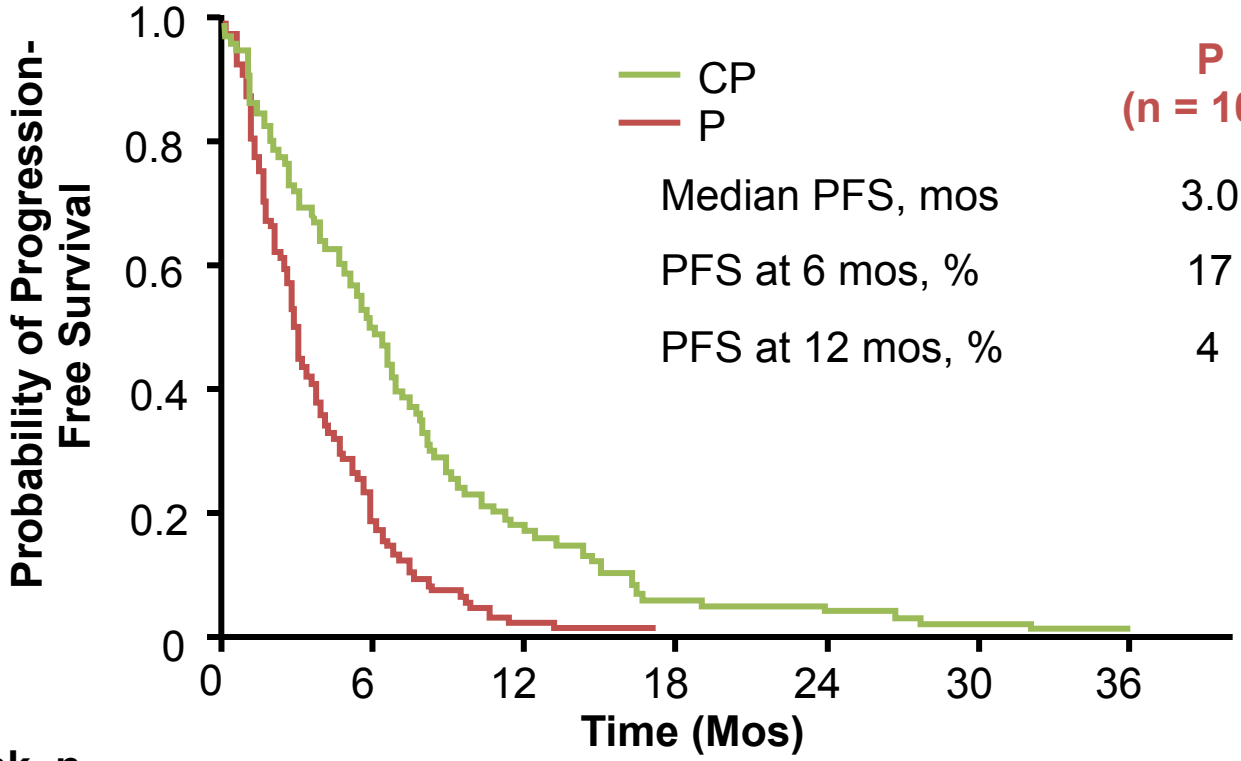
Estratificados por estadio (IIIb vs IV), edad (≥ vs < 70), pérdida de peso (≥ vs < 5%)



- Objetivo primario: OS
- Objetivos secundarios: PFS, ORR, seguridad

Zukin M. 2013.

PS 2 y PFS

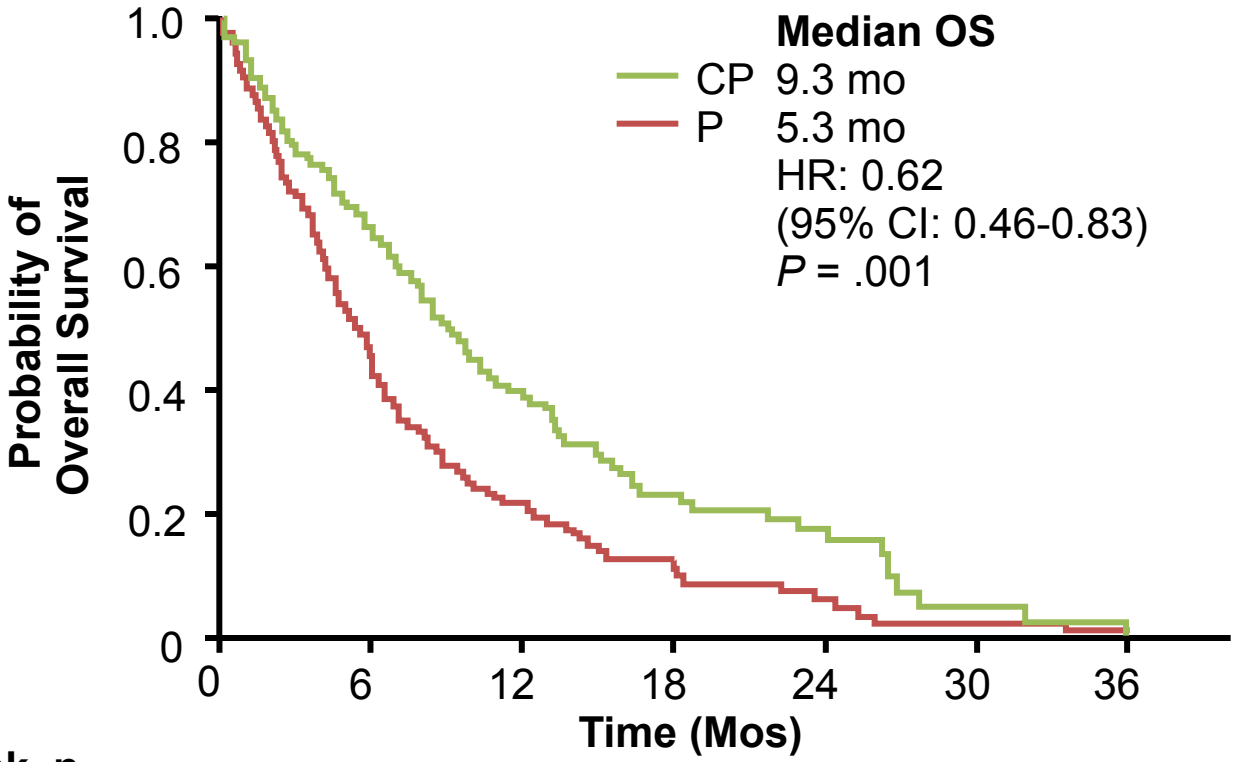


	P (n = 102)	CP (n = 103)
Median PFS, mos	3.0	5.9
PFS at 6 mos, %	17	47
PFS at 12 mos, %	4	18

At Risk, n							
CP arm	103	49	17	6	4	2	0
P arm	98	18	2	0	0	0	0

Zukin M. 2013.

PS2 y OS

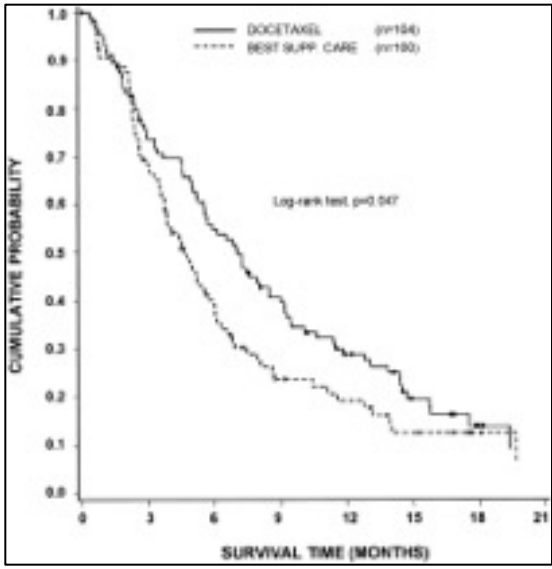


At Risk, n							
CP arm	103	68	39	20	10	2	0
P arm	98	45	20	10	5	2	0

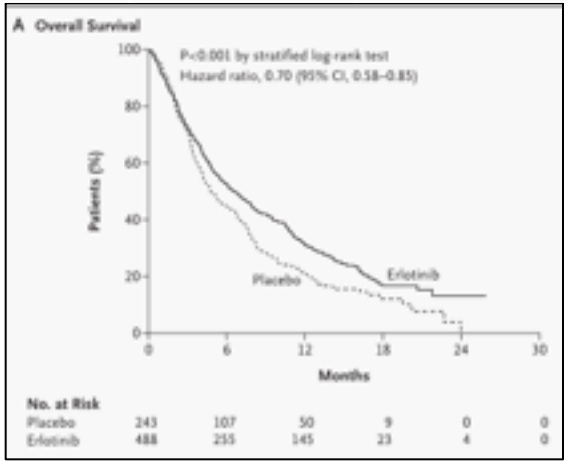
Zukin M. 2013.

Segunda línea

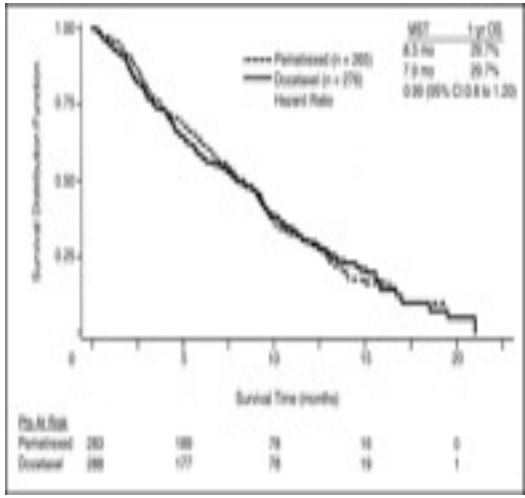
Study	Treatment Arms	Median OS (mos)	1-Year Survival
TAX 317[a]	Docetaxel (N = 103)	7.0	37.0%
	Best supportive care (N = 100)	4.6	12.0%
Hanna et al. 2004[b]	Pemetrexed (N = 283)	8.3	29.7%
	Docetaxel (N = 288)	7.9	29.7%
INTEREST[c]	Gefitinib (N = 723)	7.6	32.0%
	Docetaxel (N = 710)	8.0	34.0%
TITAN[d]	Erlotinib (N = 203)	5.3	26.0%
	Chemotherapy (N = 221: 116 docetaxel, 105 pemetrexed)	5.5	24.0%



Shepherd F A et al. JCO 2000



Shepherd F A et al. Nejm 2005

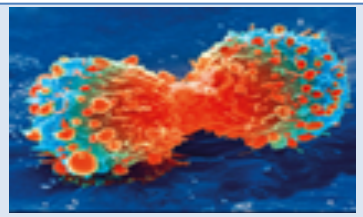


Hanna N et al. JCO 2004

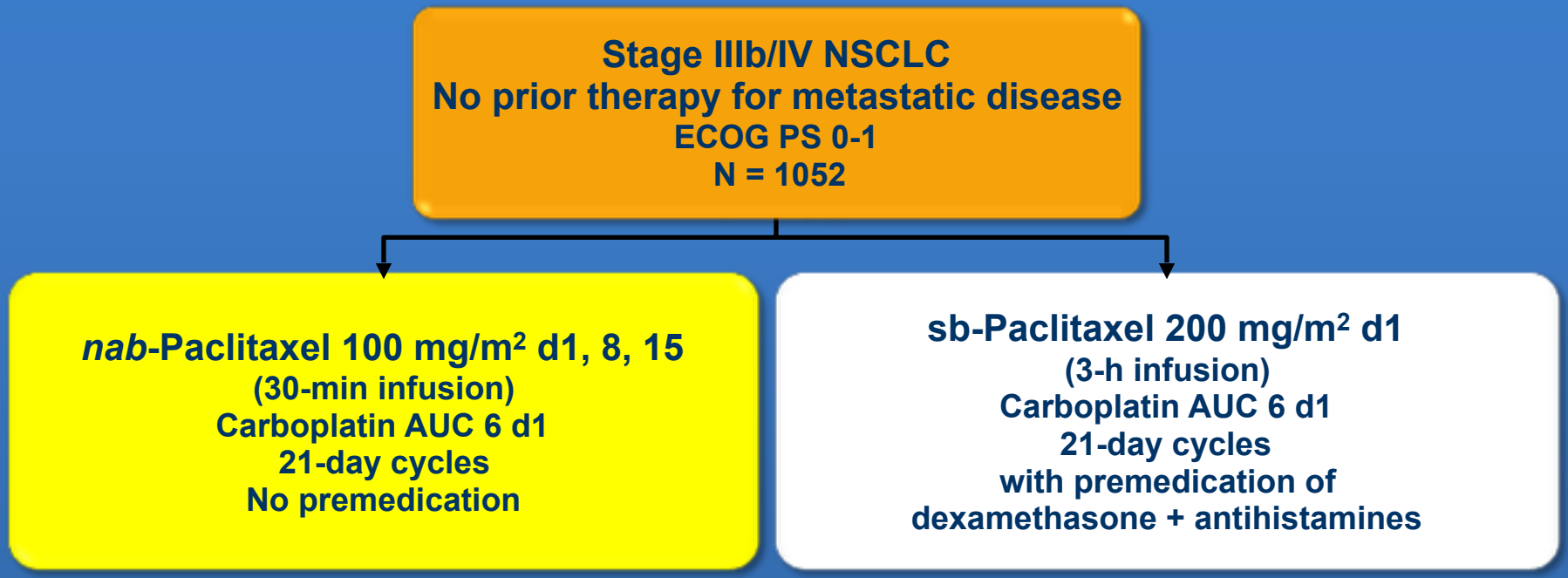
a. Shepherd FA, et al. *J Clin Oncol*. 2000;18:2095-2103.
b. Hanna N, et al. *J Clin Oncol*. 2004;22:1589-1597.
c. Kim ES, et al. *Lancet*. 2008;372:1809-1818.
d. Ciuleanu T, et al. *Lancet Oncol*. 2012;13:300-308.

¿Qué hay de nuevo?

Nab-Paclitaxel en CPNM



- ABRAXANE… Sistema a base de nanopartículas de albumina diseñado para vehiculizar paclitaxel
- Permite administrar mayores dosis de Paclitaxel evitando los efectos secundarios de los excipientes

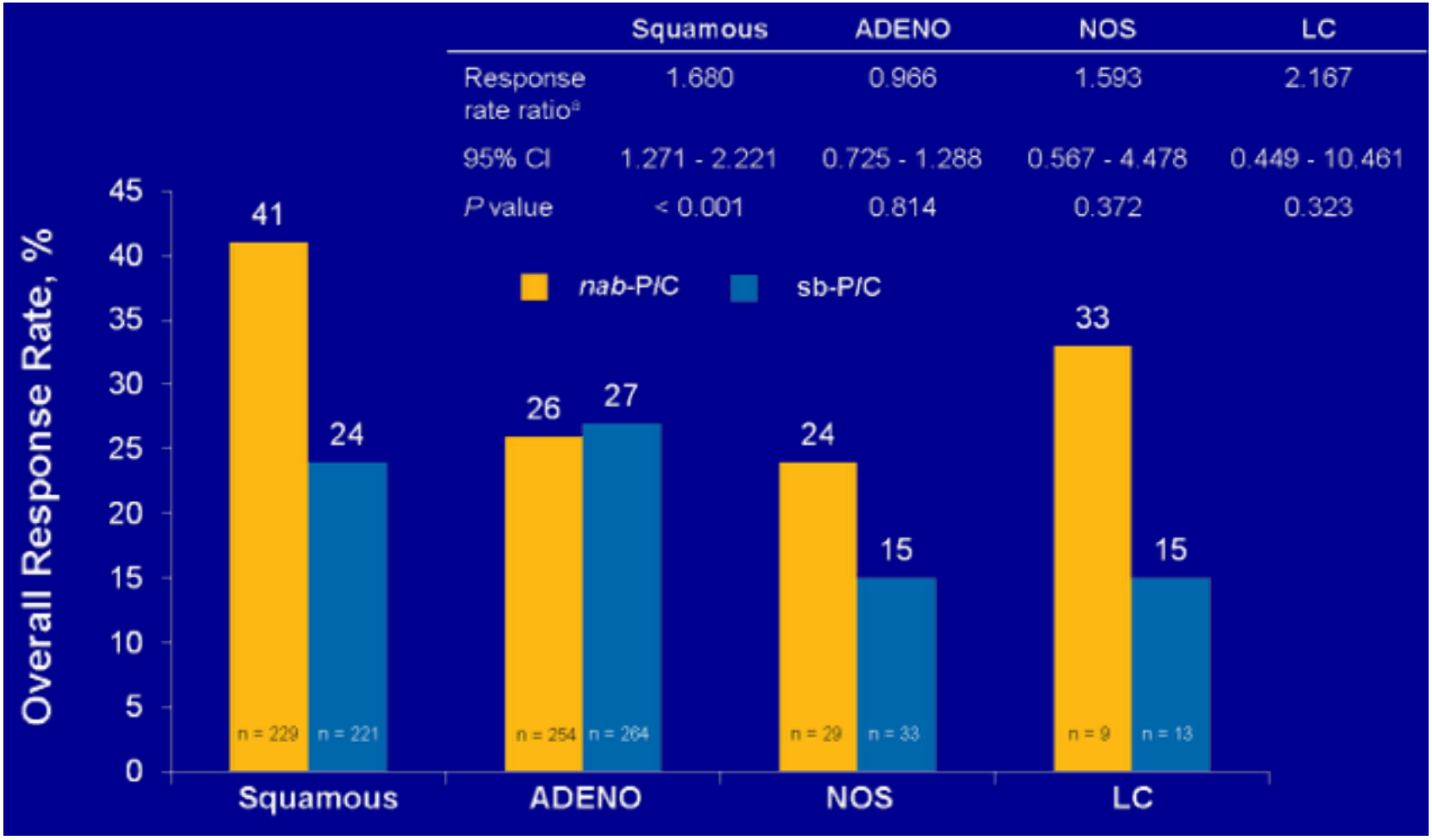


Stratification factors: Stage (IIIb vs IV); age; (< 70 vs ≥ 70); sex; histology (adenocarcinoma vs squamous cell vs other); geographic region

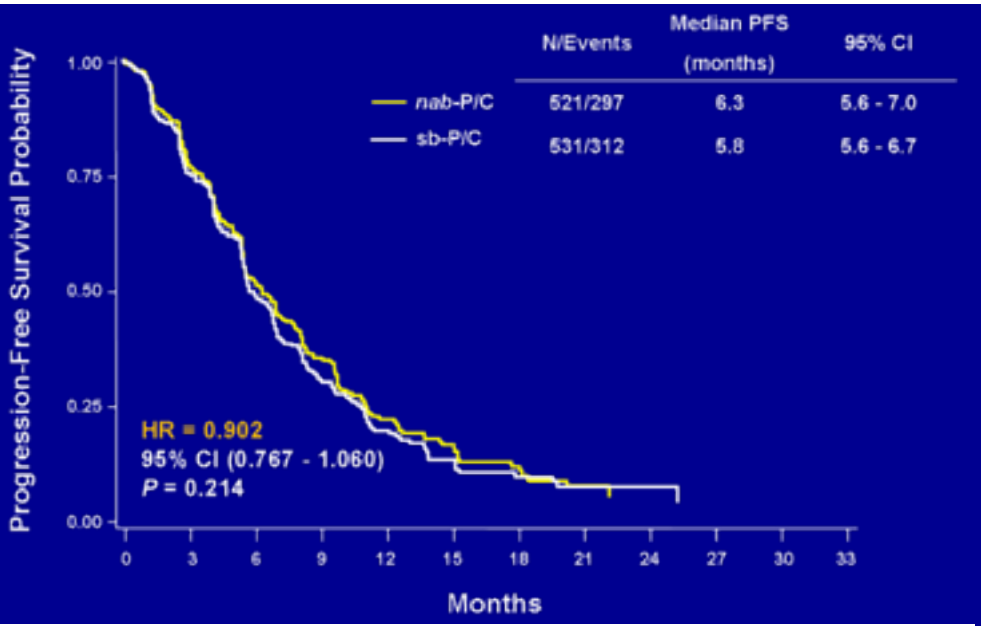
- Objective: To compare the efficacy and safety of *nab*-paclitaxel plus carboplatin vs sb-paclitaxel plus carboplatin in advanced NSCLC
- Primary endpoint: ORR by independent radiological review (CR + PR)
- Secondary endpoints: PFS, OS, DCR (CR + PR + SD), and safety

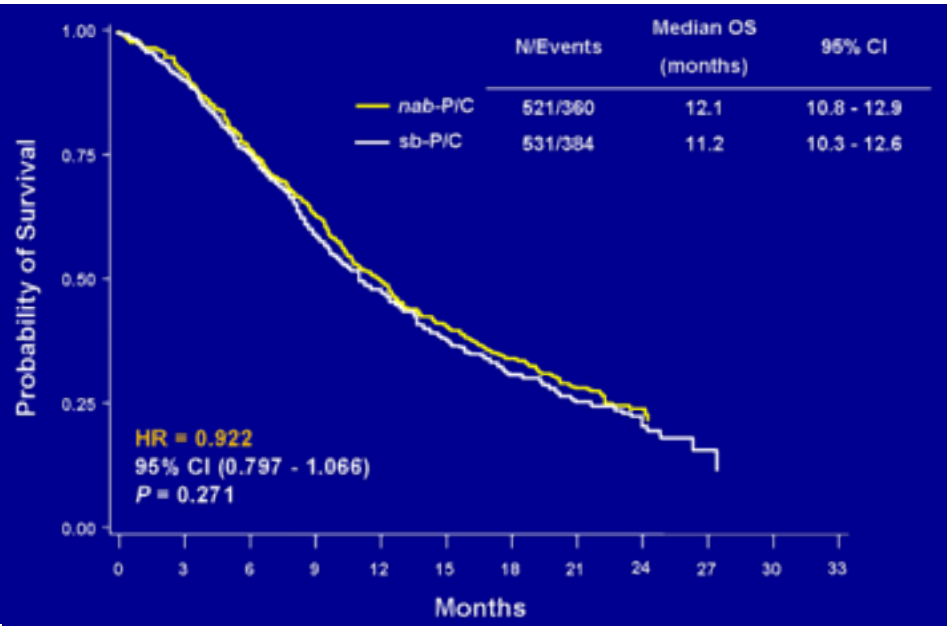
Socinski. 201

Nab-Paclitaxel: RR e histología



Nab-Paclitaxel: PSF y OS





Conclusiones Nab-Paclitaxel

- *Nab*-P/C en primera línea en pacientes con CPNM es eficaz :
  - 68% mejora en la tasa de respuesta, 1 mes de beneficio en OS
  - ORR 41% en escamosos
- Tiene un perfil tóxico manejable
- Menor incidencia y gravedad de neuropatía
- Estudios demuestran buen perfil toxico en ancianos y PS2

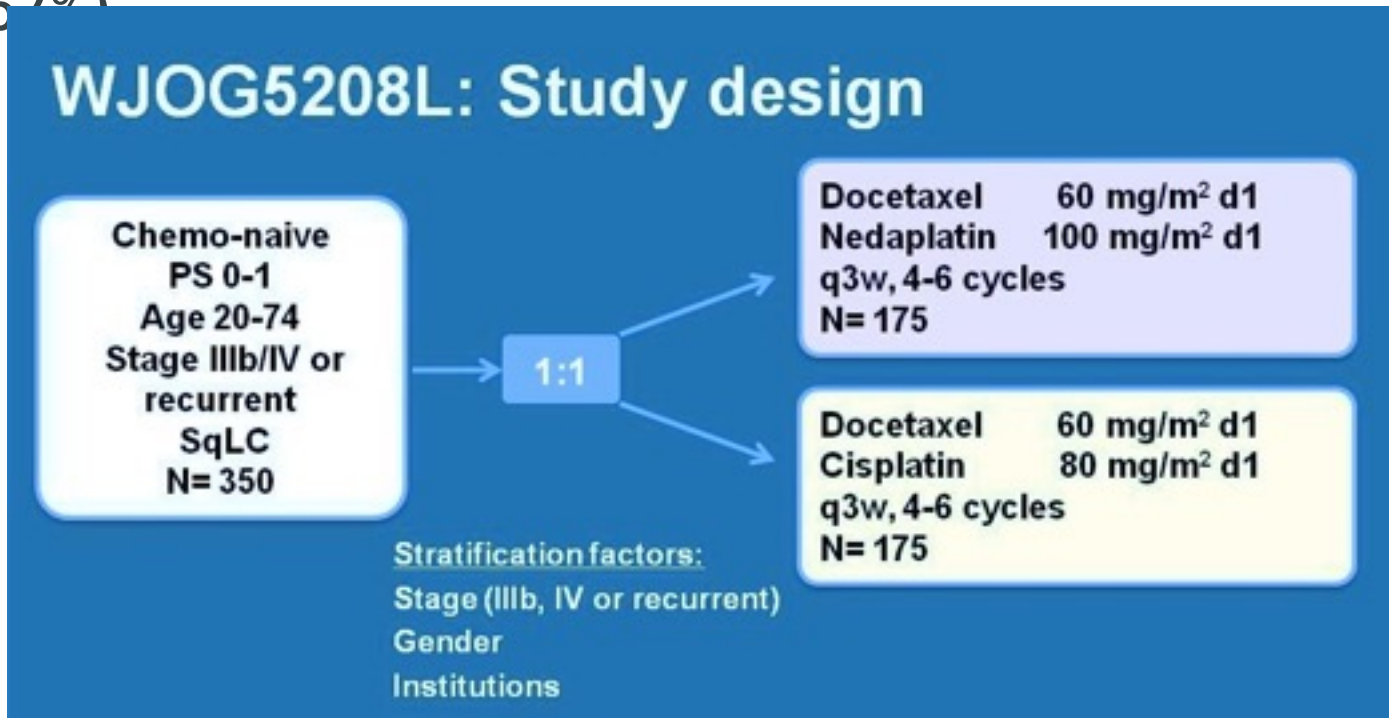
Nedaplatin

- Compuesto platino de segunda generación
- Menos nauseas/vómitos y nefrotoxicidad
- Toxicidad limitante de dosis neutropenia y trombopenia
- Estudio fase II eficaz en escamosos (mPFS 7.4m, MST 16.1m , RR 62%)

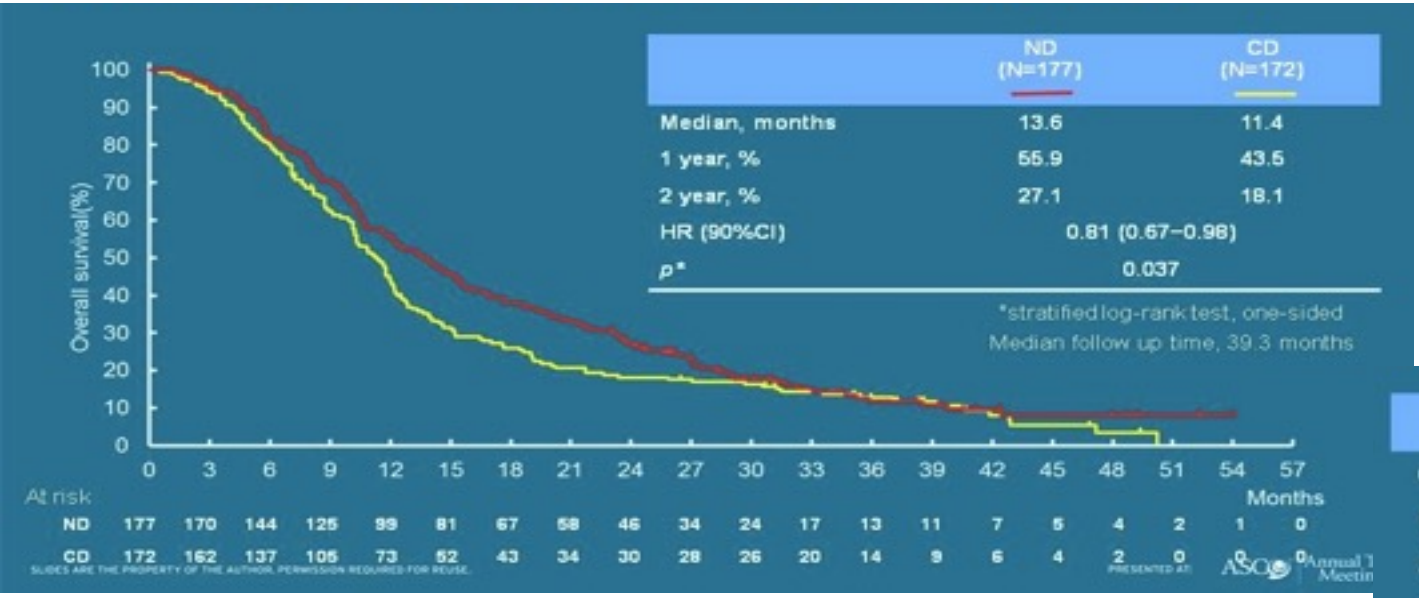
OBJETIVO PRIMARIO: SG

OBJETIVOS SECUNDARIOS: PFS, RR, AES

Shukuya 2015



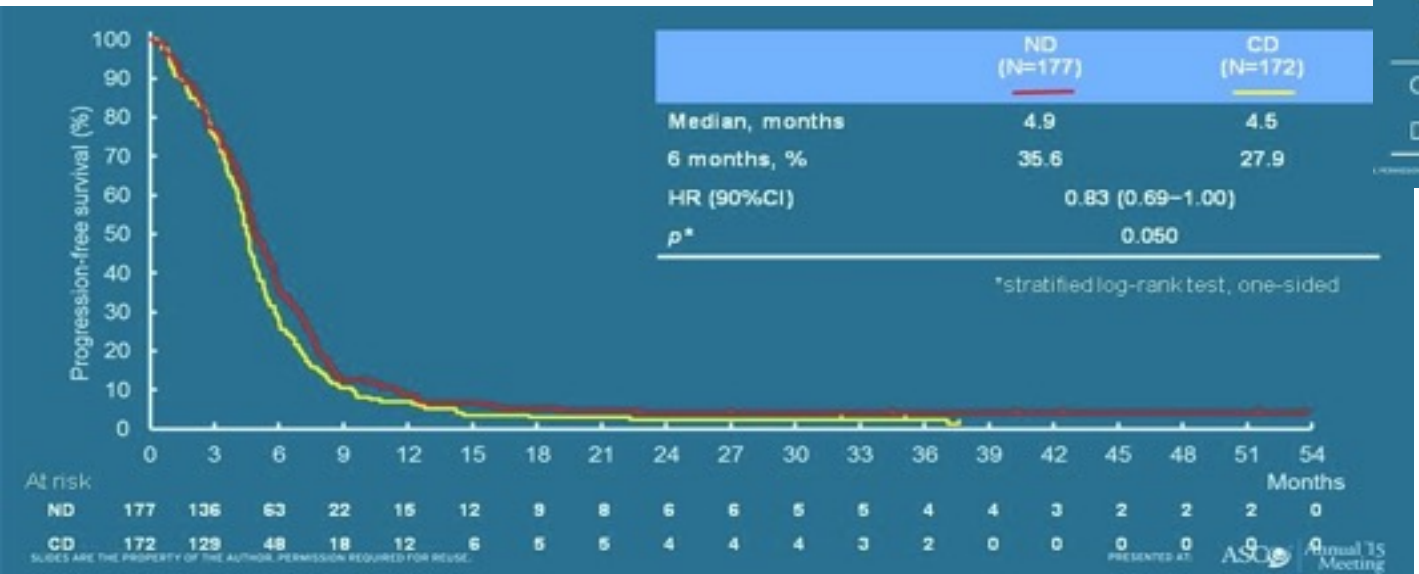
Nedaplatin OS y TTP



RECIST ver. 1.1

	ND (N=172)	CD (N=168)	*p value
CR	3 (1.7%)	1 (0.6%)	–
PR	93 (54.1%)	88 (52.4%)	–
SD	50 (29.1%)	47 (28.0%)	–
PD	24 (14.0%)	27 (16.1%)	–
NE	2 (1.2%)	5 (3.0%)	–
ORR	55.8%	53.0%	0.663
DCR	84.9%	81.0%	0.387

*Fisher's exact test



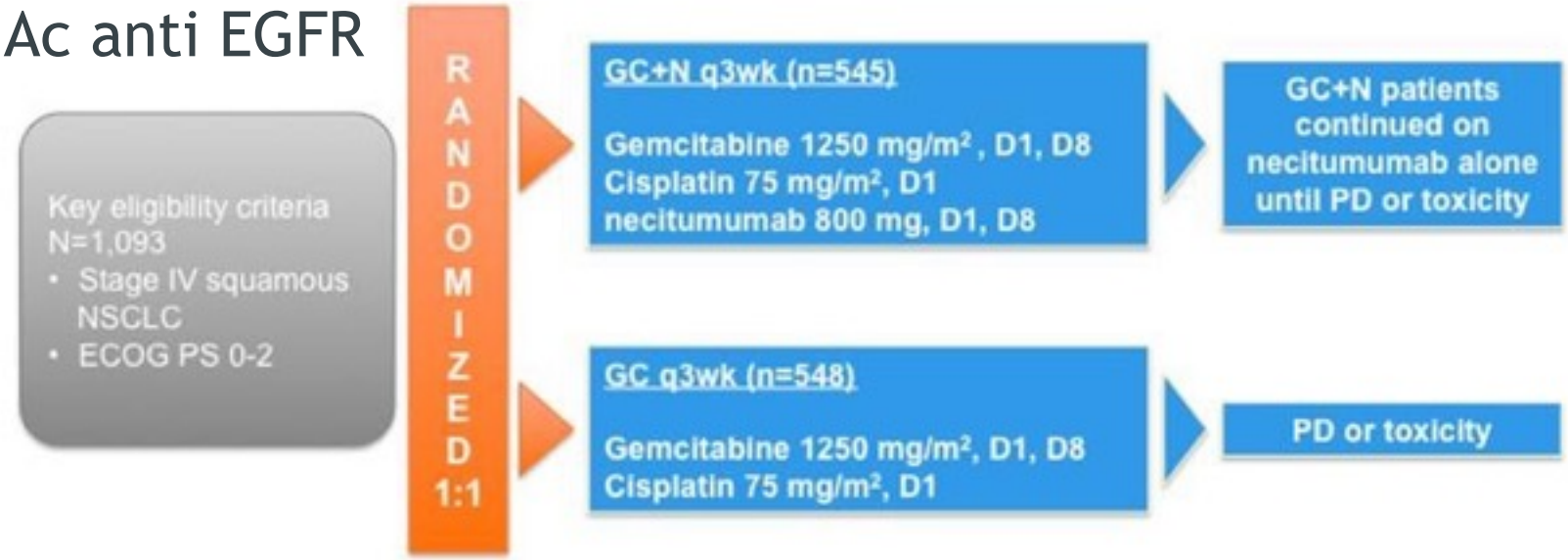
Conclusiones Nedaplatin

- Nedaplatin tiene mayor PFS y SG que Cisplatino.
- Menos nauseas y alteraciones hidroelectrolíticas con mayor toxicidad hematológica

Los datos necesitan confirmación en población no asiática

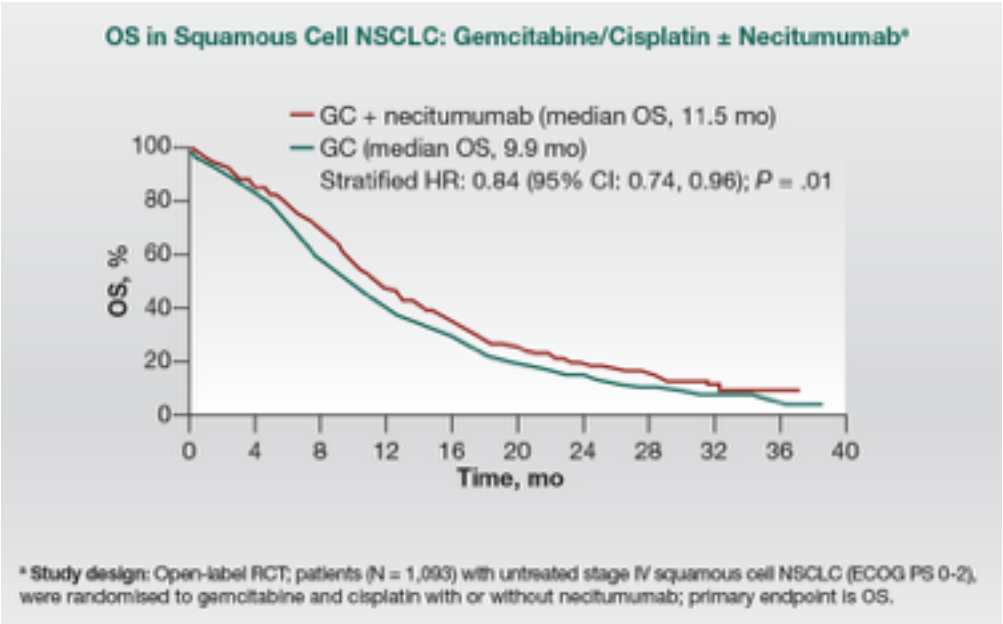
Necitumumab CPNM escamoso

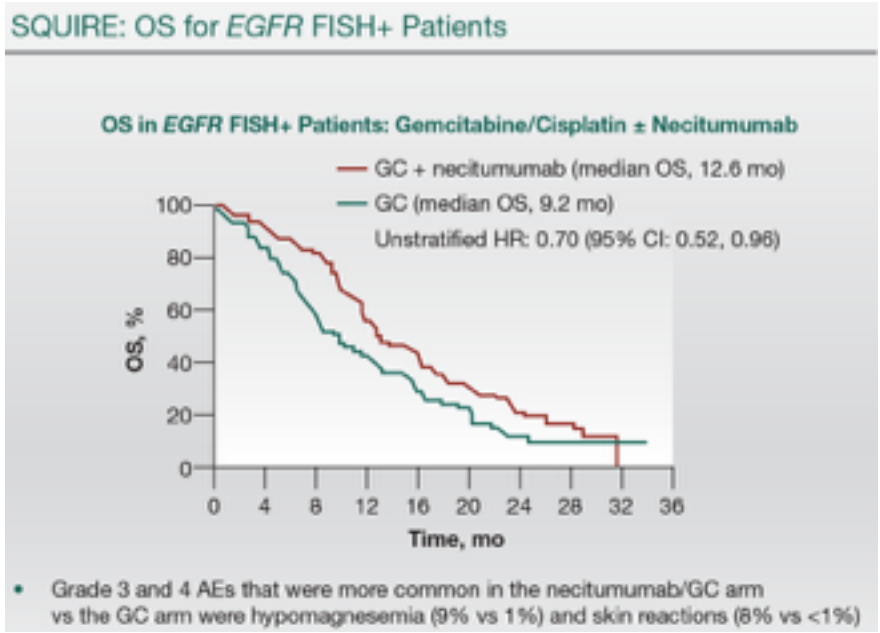
- Ac anti EGFR



Cohort (N=1093)	GC + N[a] n=545	GC n=548	HR (95% CI)	P Value
Median OS, months	11.5	9.9	0.84 (0.74, 0.96)	0.012
Median PFS, months	5.7	5.5	0.85 (0.74, 0.98)	0.020
ORR, %	31.2	28.8	—	0.400

Necitumumab





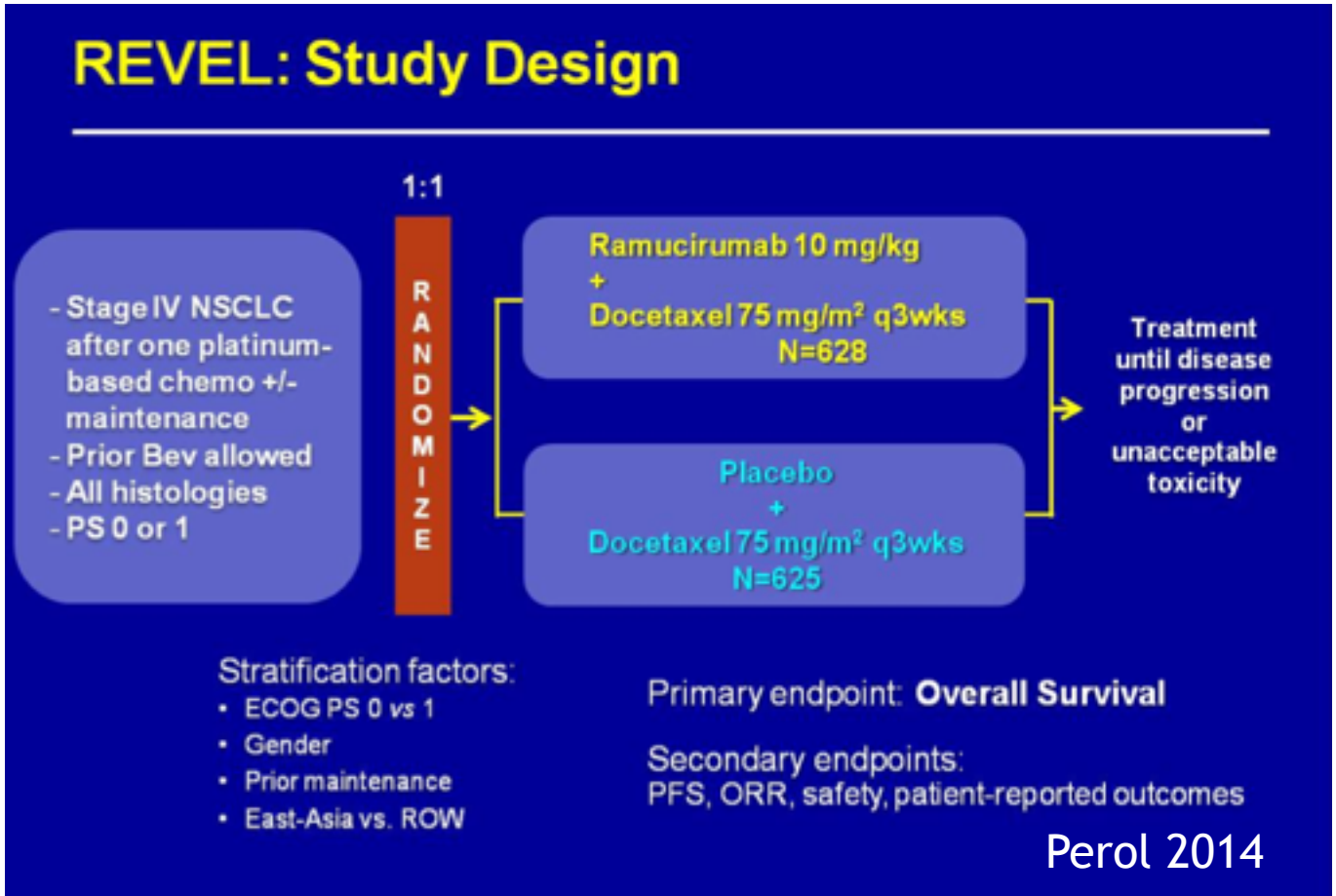
- Modesto beneficio en SG
- Valor del mantenimiento en CPNM escamoso
- Perfil toxicidad

Ciuleanu 2015

Ramucirumab

•Ramucirumab (RAM) es un Ac monoclonal humano IgG1 especialmente vinculado al dominio extracelular de VEGFR-2

•Aprobado en cáncer gástrico pretratado



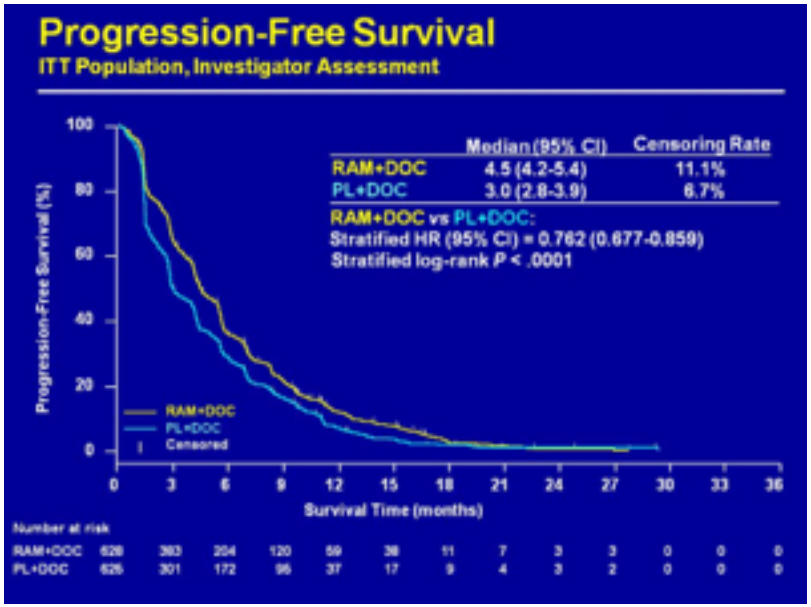
Ramicirumab RR

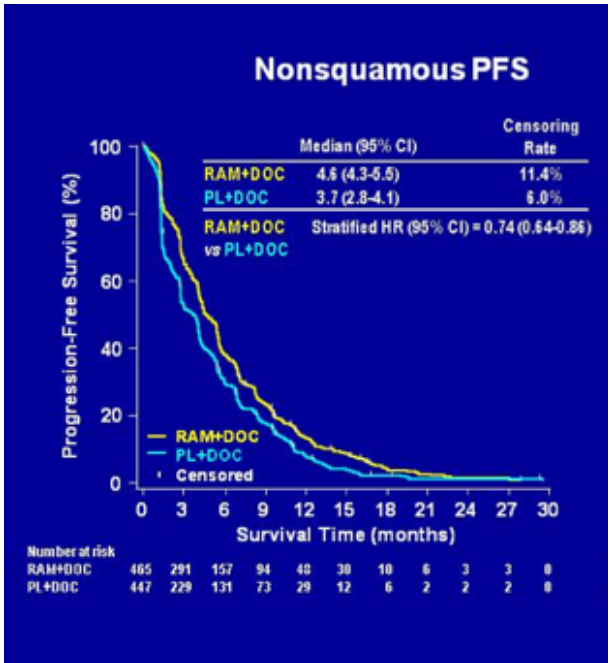
Tumor Response by RECIST v1.1

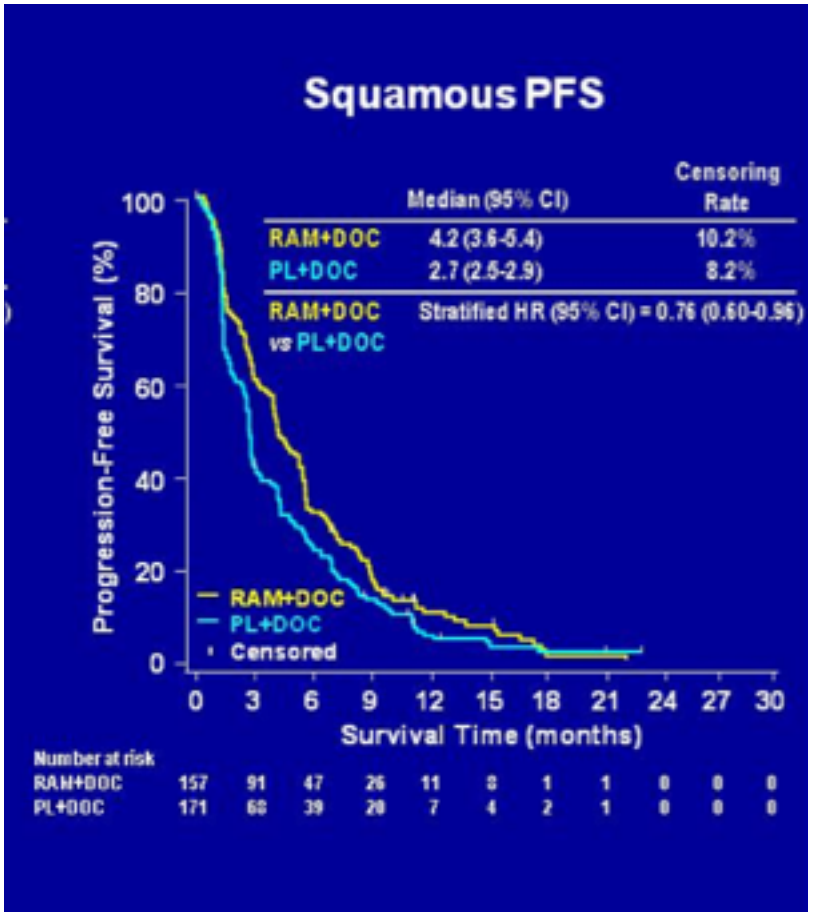
ITT Population, Investigator Assessment

	RAM+DOC N=628	PL+DOC N=625	*P*-value
Response, n (%)			
CR	3 (0.5)	2 (0.3)	
PR	141 (22.5)	83 (13.3)	
SD	258 (41.1)	244 (39.0)	
PD	128 (20.4)	206 (33.0)	
Unknown/not assessed	98 (15.6)	90 (14.4)	
ORR (CR+PR), % (95% CI)	*22.9 (19.7-26.4)*	*13.6 (11.0-16.5)*	*<.001*
DCR (CR+PR+SD), % (95% CI)	*64.0 (60.1-67.8)*	*52.6 (48.6-56.6)*	*<.001*

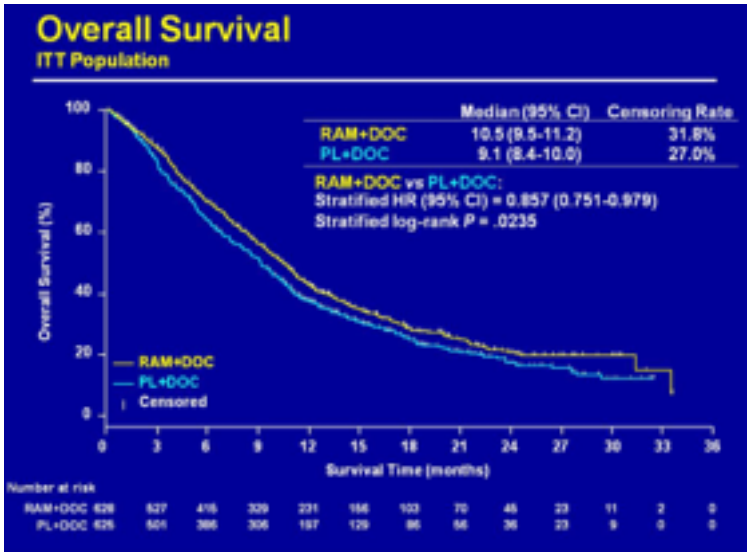
Ramucirumab y PFS

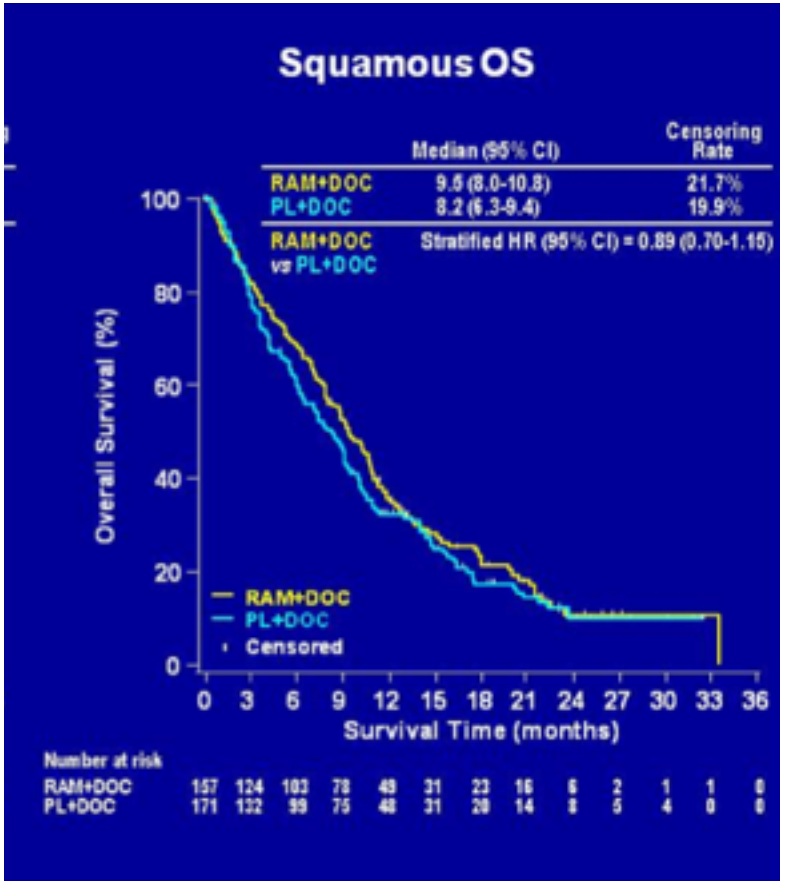


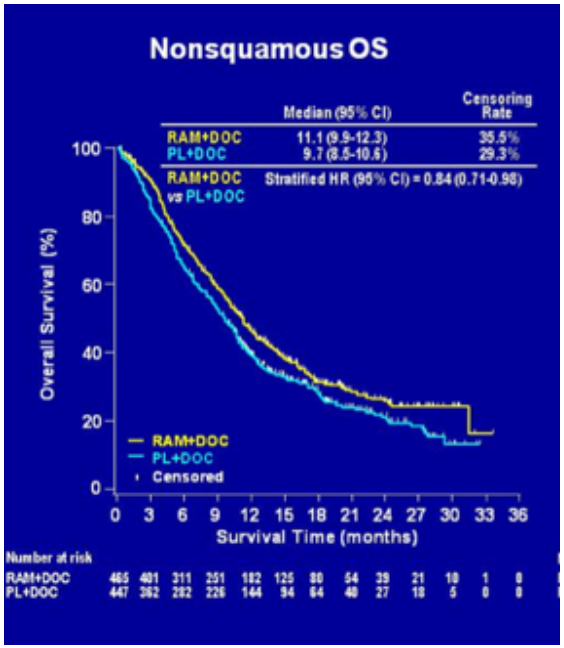




Ramucirumab: OS



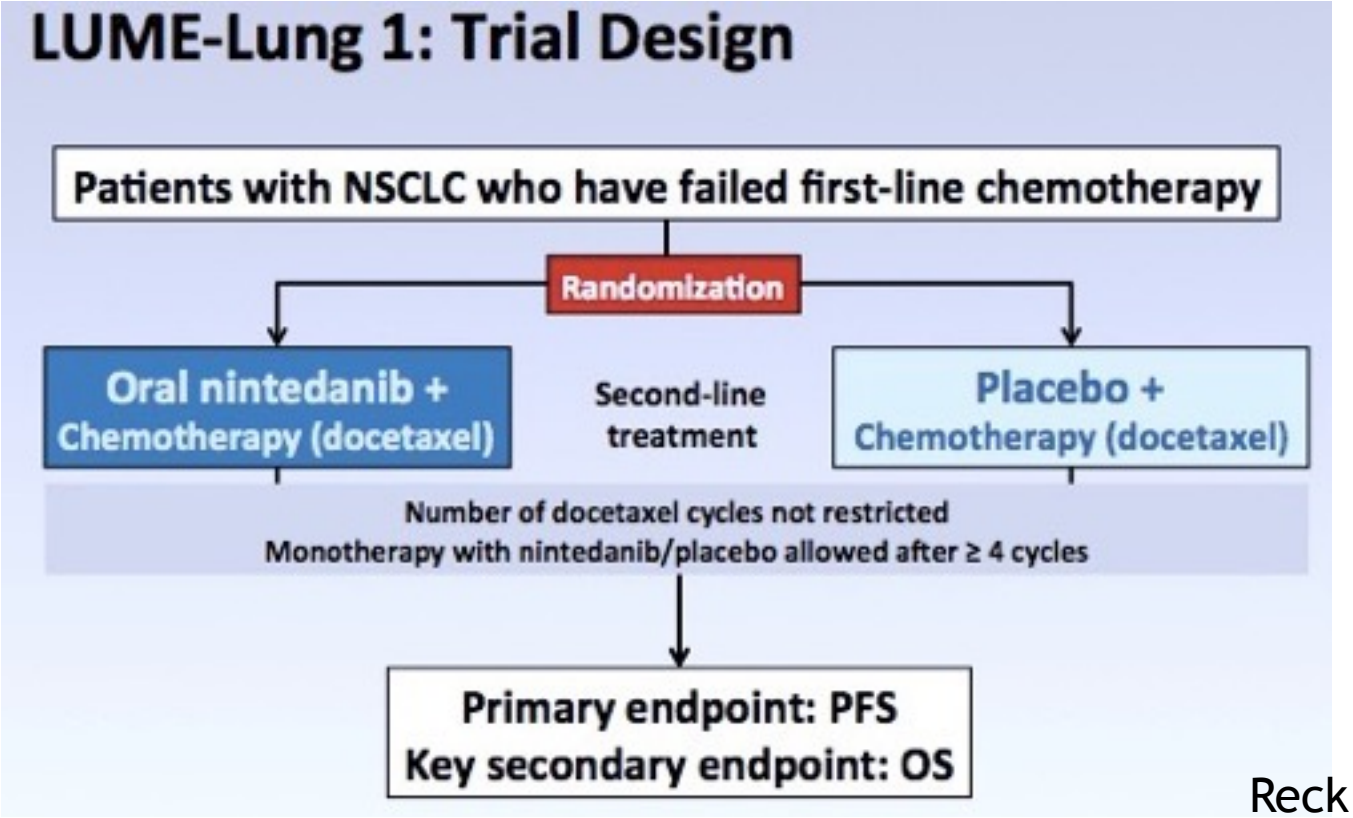




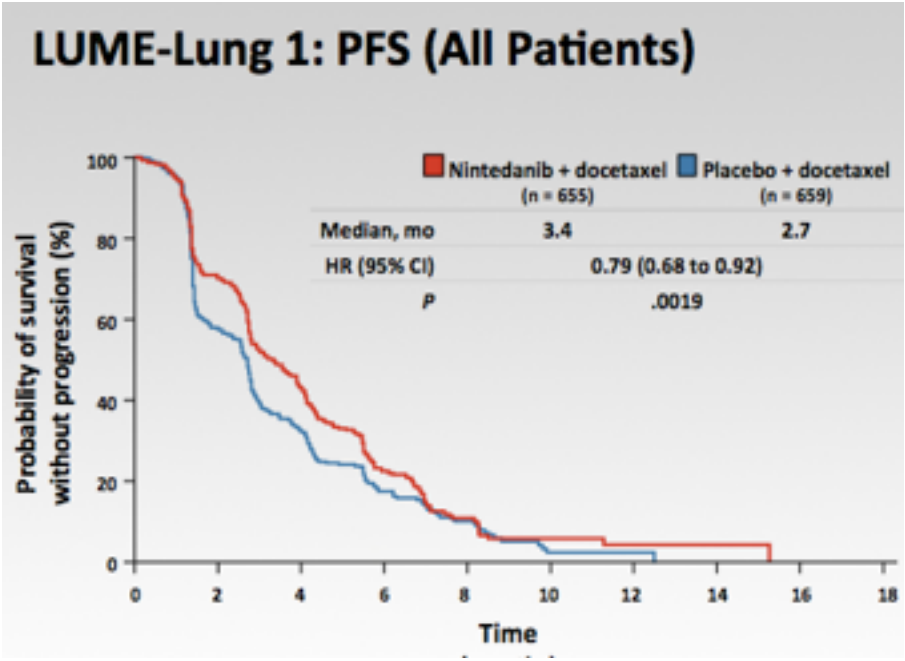
- Primer estudio que demuestra que la asociación de un nuevo agente a la quimioterapia mejora la SG en pacientes con CPNM en segunda línea.
- 1.4 meses de incremento en SG
- Es el primer inhibidor VEGF que muestra beneficio en pacientes con carcinomas escamosos
- Perfil tóxico aceptable: HTA, epistaxis y reacciones en punto de infusiones.

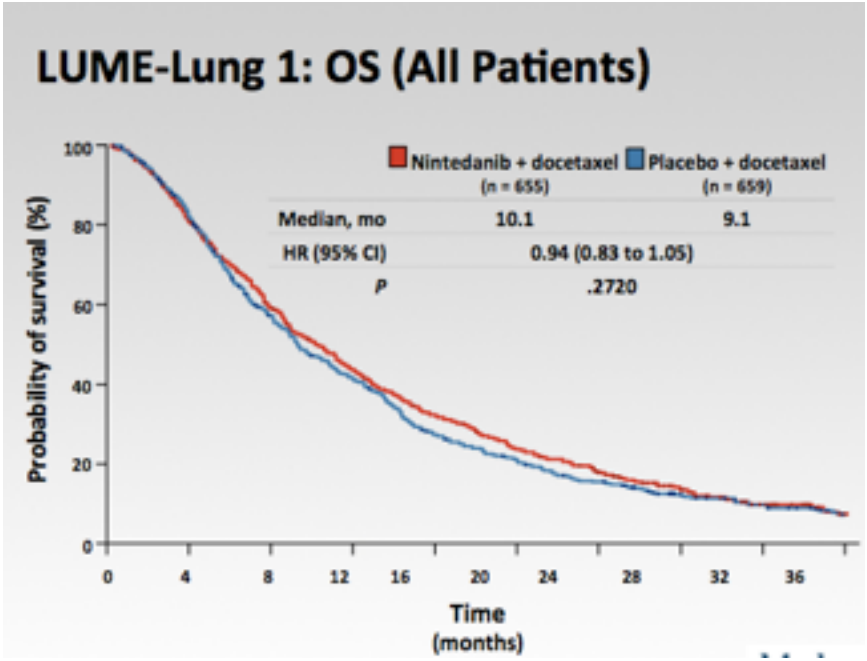
Nintedanib: 2º Línea CPNM

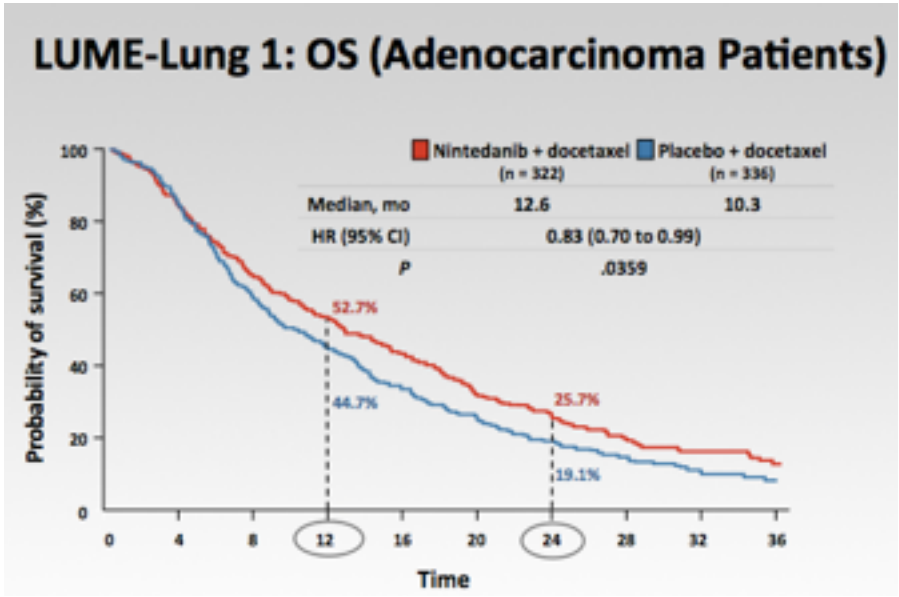
- Inhibidor tirosinkinasa, que ejerce su efecto antitumoral bloqueando VEGFR 1-3, PDGFR α and ß y FGFR 1-3
- Vía oral



Reck 2014







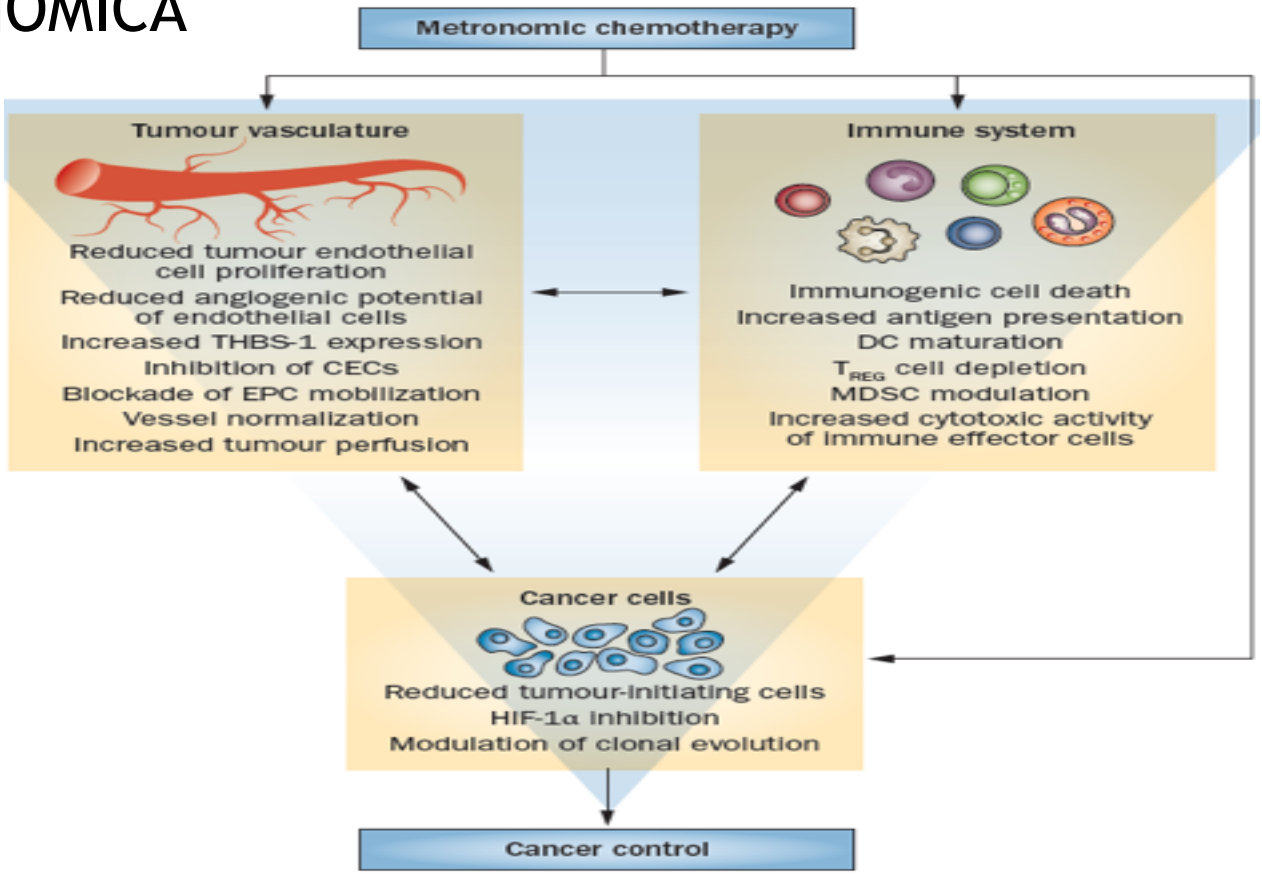
- La combinación mejora PFS en pacientes con CPNM refractario, en ambos subtipos histológicos
- ***Prolonga OS en pacientes con adenocarcinoma , incluso en los pacientes de mal pronóstico*** (progresión en los primeros 9 meses de inicio de primera línea)
- Principal efecto secundario: Diarrea y elevación enzimas hepáticas

¿Podemos mejorar los resultados?

- ¿Sigue siendo la quimioterapia la base del tratamiento del CPNM?
- ¿Disponemos de factores predictivos de respuesta?
  - Expresión ERCC1 es un factor predictivo de beneficio de Qt en pacientes con Qt adyuvante basada en platino
  - ERCC1 juega un papel fundamental en mecanismos de resisitencia a QT y susceptibilidad de cáncer
  - La diferente expresión de Timidilato sintetasa puede determinar la respuesta a pemetrexed
  - RRM1, relacionada con la sensibilidad a Gemcitabina

¿Podemos mejorar más?

- Nuevas fórmulas de tratamientos ya conocidos: QT METRONÓMICA



VNR oral metromómica 1º línea ancianos

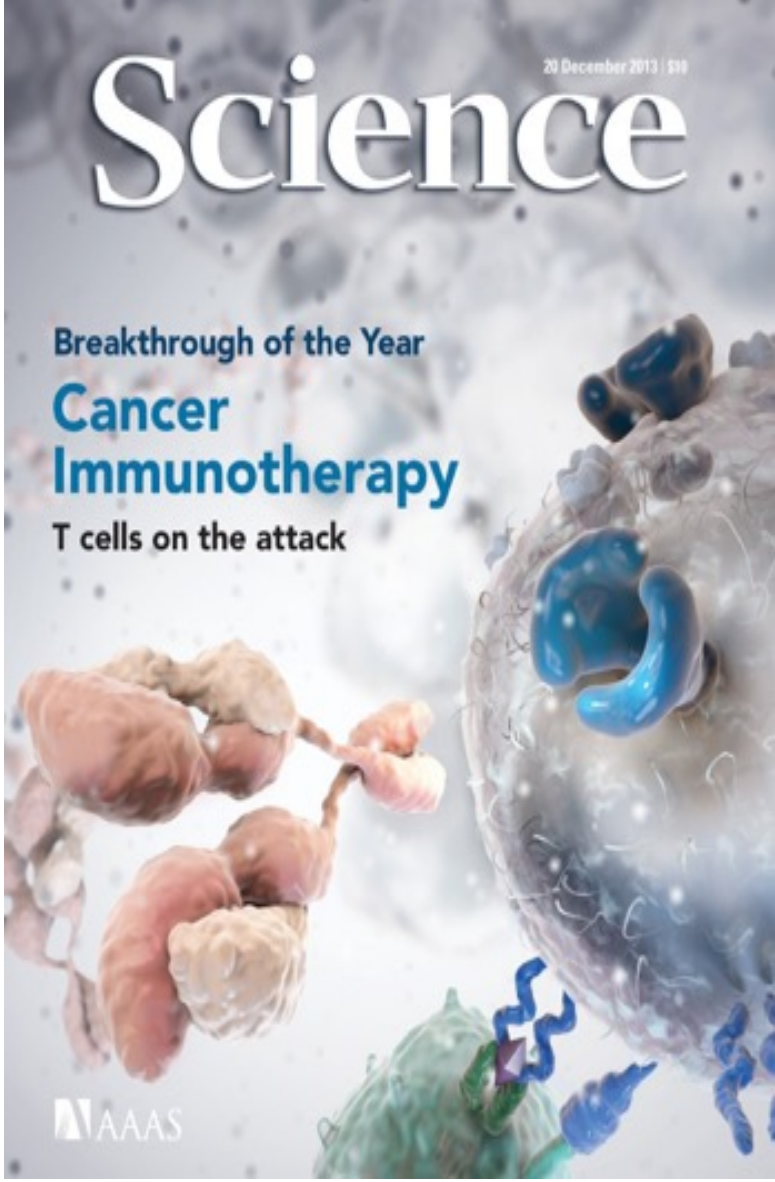
- Edad mediana: 80 [70-92] años
- ECOG PS 0/1/2: 0/16/27 pacientes
- Dosis: 50 mg 3 días/semana (lunes, miércoles, viernes). Ciclos de 3 semanas
- Duración: mediana 5 ciclos [rango 1–21 ciclos]

Respuesta Clínica (N=43)	n (%)
Respuesta Completa	1 (2,3)
Respuesta Parcial	7 (16,3)
Respuesta Global	8 (18,6)
EE >12 semanas	17(39,5)
Beneficio clínico	25 (58,1)
Mediana TTP	5 [2–21] meses
Mediana SG	9 [3–29] meses

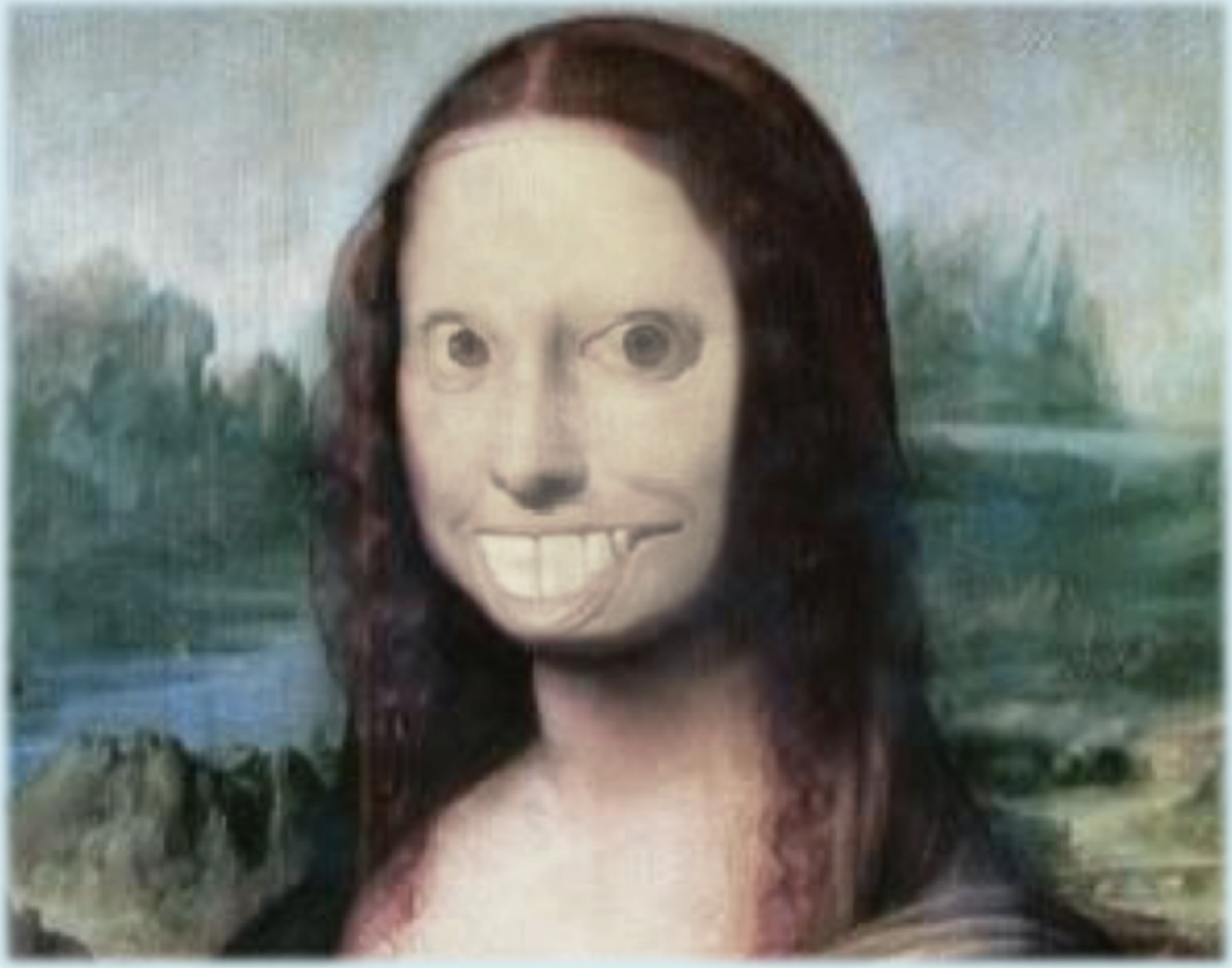
	Todos los grados(%)	Grado 3/4 (%)
Anemia	44	0,1
Neutropenia	4,0	0,1
Leucopenia	3,2	0
Náuseas	8	0
Vómitos	5	0
Fatiga	32,4	0,1
Diarrea	10,5	0,1
Neurotoxicidad	2,4	0

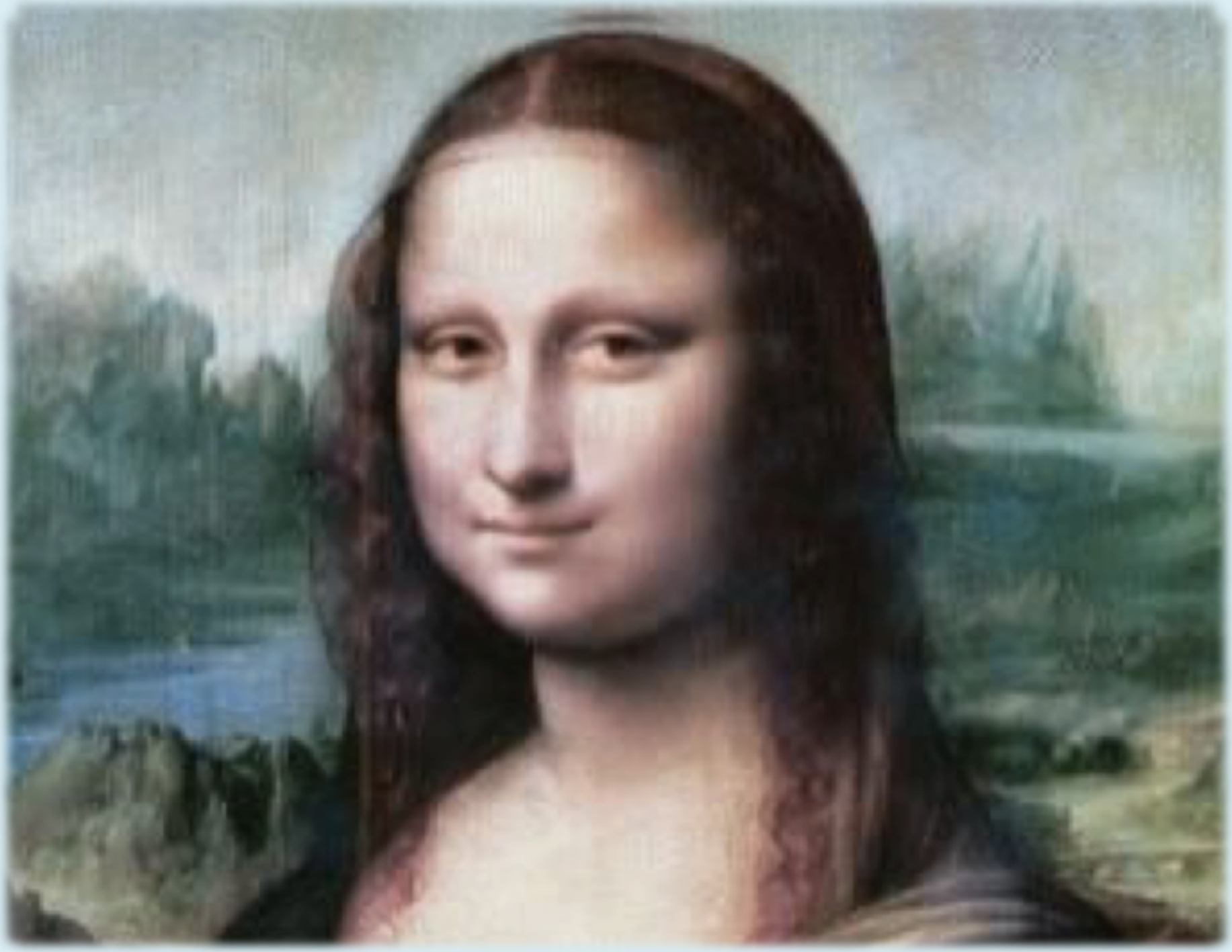
Camerini A. 2015

Los tumores crean el Caos

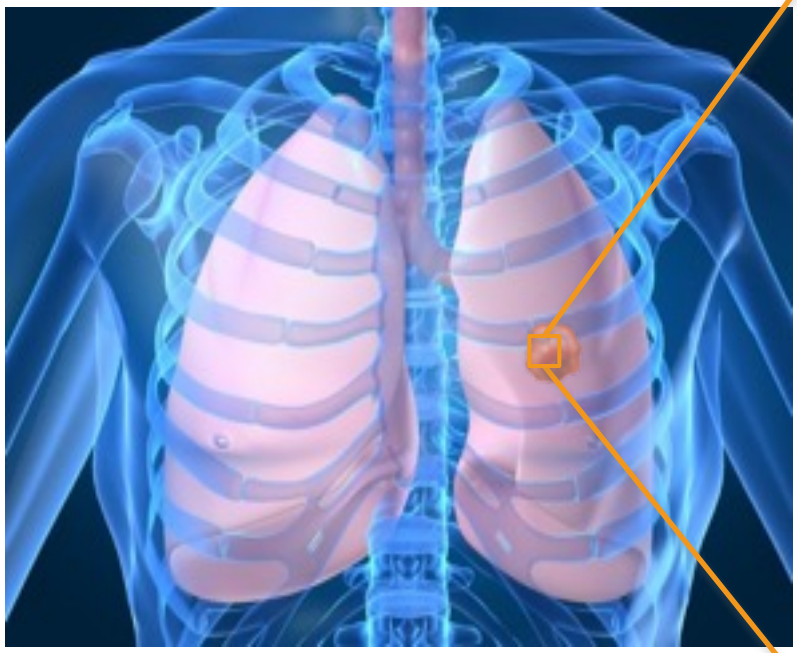


Los tumores hacen todo lo posible por evadir la respuesta inmune





Células inmunes y su impacto pronóstico en el CPNM



Pronostico Favorable

- **Dendritic cells**
  OS, disease-specific survival, disease-free survival[1]
- **CD3⁺ cells**
  NSCLC survival and lower risk of disease recurrence[2–4]
- **CD8⁺ cells**
  OS[5–8]
- **CD4⁺ cells**
  OS[6,9]
- **Macrophages**
  OS[7]
- **NK cells**
  NSCLC-specific survival[10]

Pronóstico Desfavorable[1]

- **NK Cells (immature / impaired)**
  Disease progression[11]
- **Tregs**
  OS, relapse- and recurrence-free survival[12,13]

OS = overall survival.

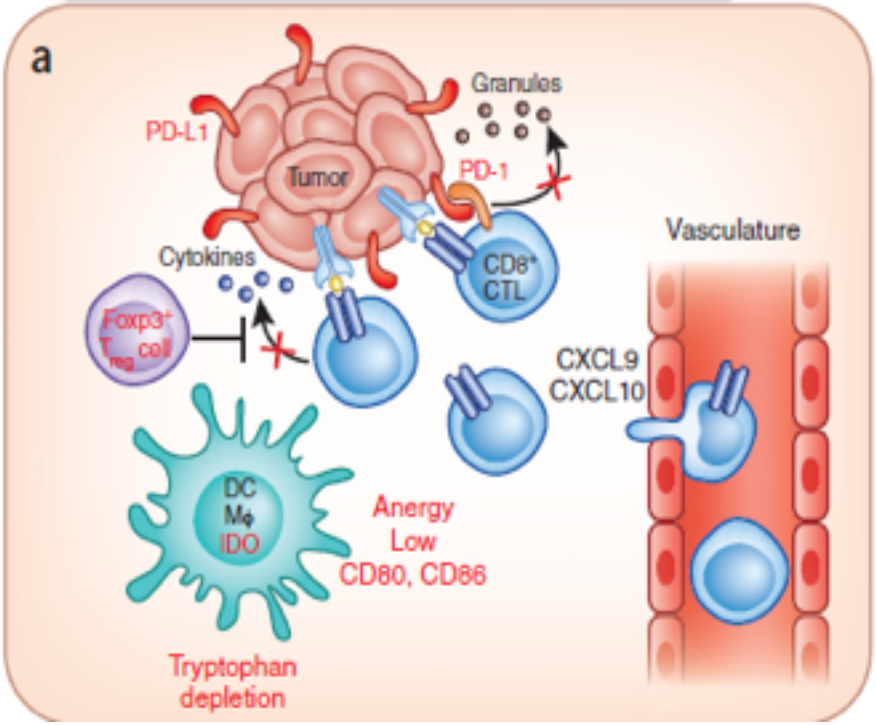
1. Dieu-Nosjean M, et al. *J Clin Oncol*. 2008;26:4410–4117; 2. Petersen R, et al. *Cancer*. 2006;107:2866–2872;
3. Al-Shibli K, et al. *APMIS*. 2010;118:371–382; 4. Ruffini E, et al. *Ann Thorac Surg*. 2009;87:365–372;
5. Zhuang X, et al. *Appl Immunohistochem Mol Morphol*. 2010;18:24–28; 6. Hiraoka K, et al. *Br J Cancer*. 2006;94:275–280;
7. Kawai O, et al. *Cancer*. 2008;113:1387–1395; 8. McCoy M, et al. *Br J Cancer*. 2012;107:1107–1115;
9. Wakabayashi O, et al. *Cancer Sci*. 2003;11:1003–1009; 10. Al-Shibli K, et al. *Histopathol*. 2009;55:301–312;
11. Jin J, et al. *PLoS One*. 2013;8:e61024; 12. Tao H, et al. *Lung Cancer*. 2012;75:95–101; 13. Shimizu K, et al. *J Thorac Oncol*. 2010;5:585–590.

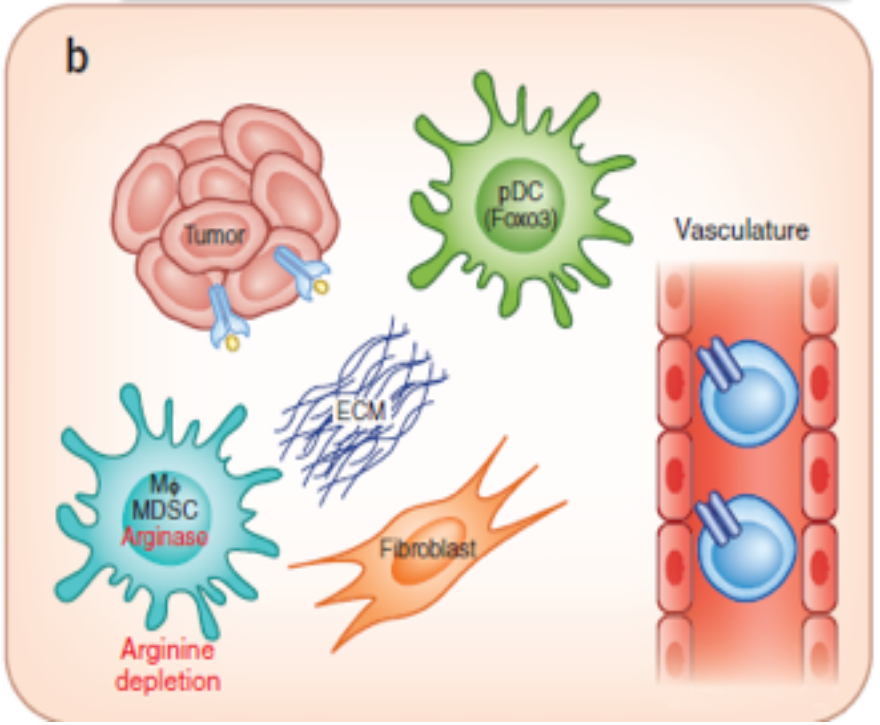
¿Son todos los tumores iguales inmunologicamente?

Segregation of tumors based on immune infiltrates in the tumor microenvironme

T cell-infiltrated tumors

non-T cell-infiltrated tumors





T cell recruitment : High levels of innate immune signals, chemokine expression (influx of CD8+T cells)

BUT, negative immune regulators dominate:

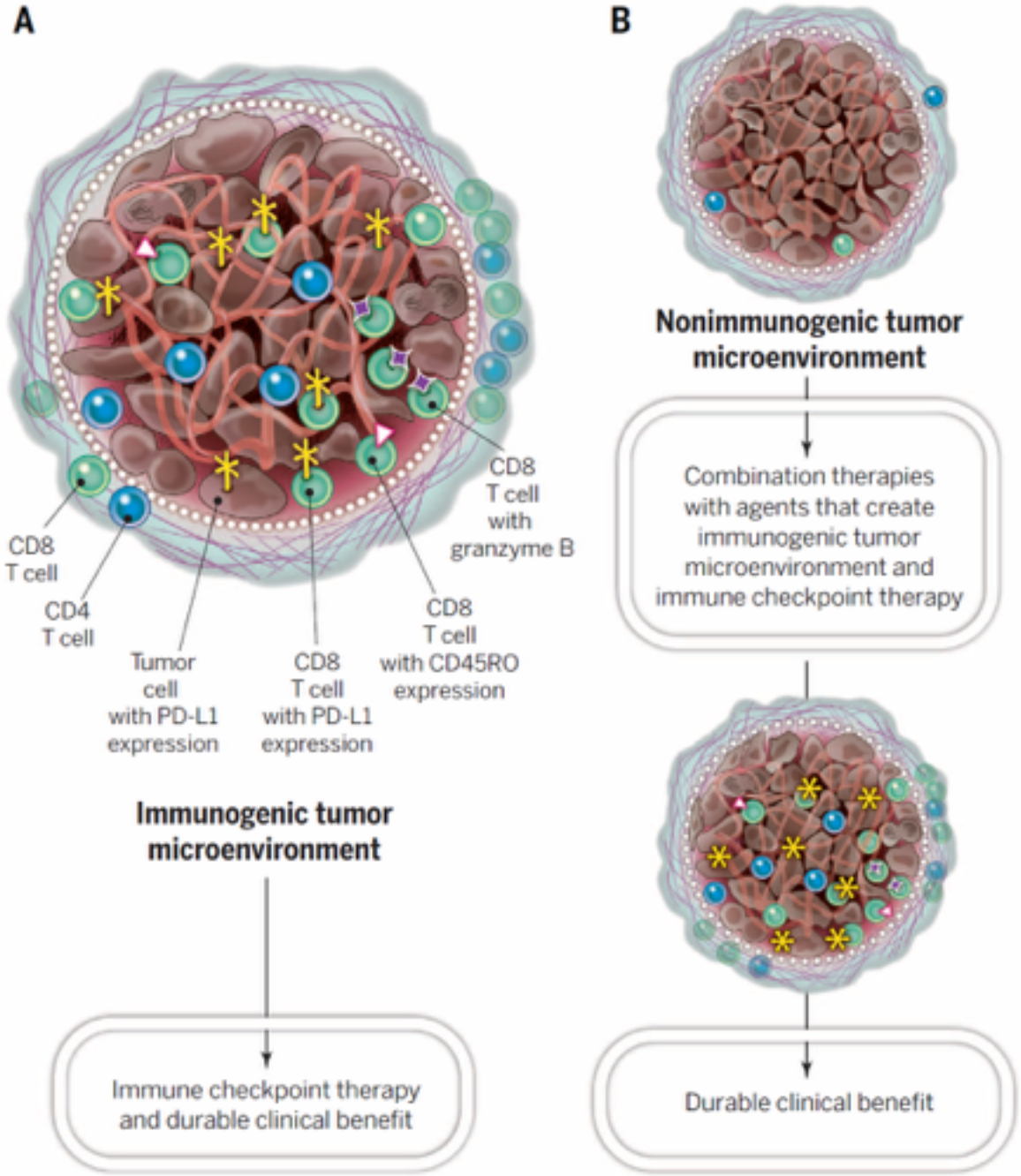
- Inhibitory receptors
- Suppressive cells
- Suppressive enzymes (IDO, arginase)

Poor effector cell trafficking due to:

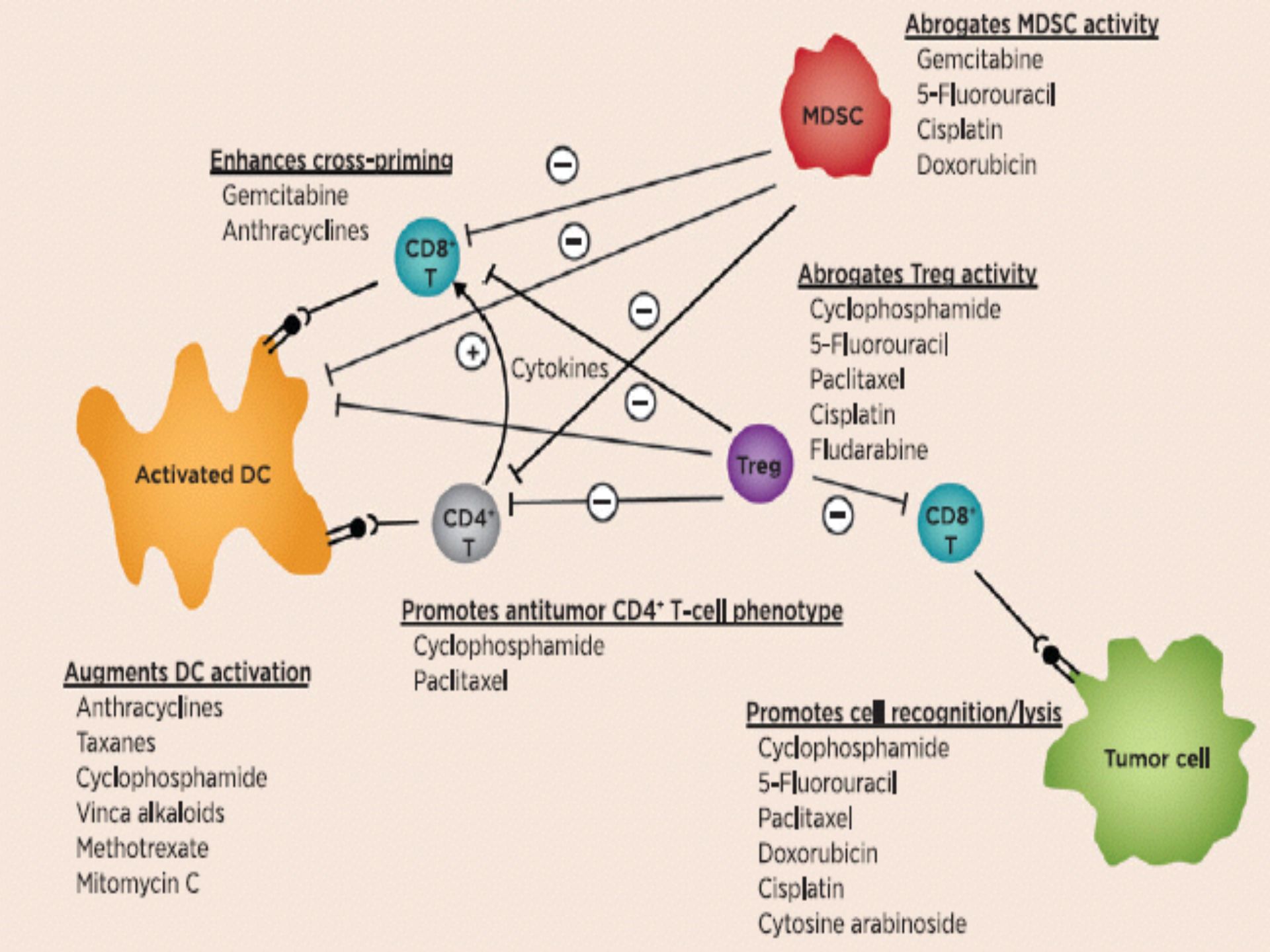
High expression of vascular markers, macrophages, fibroblasts

Low inflammation and chemokine expression, few lymphocyte

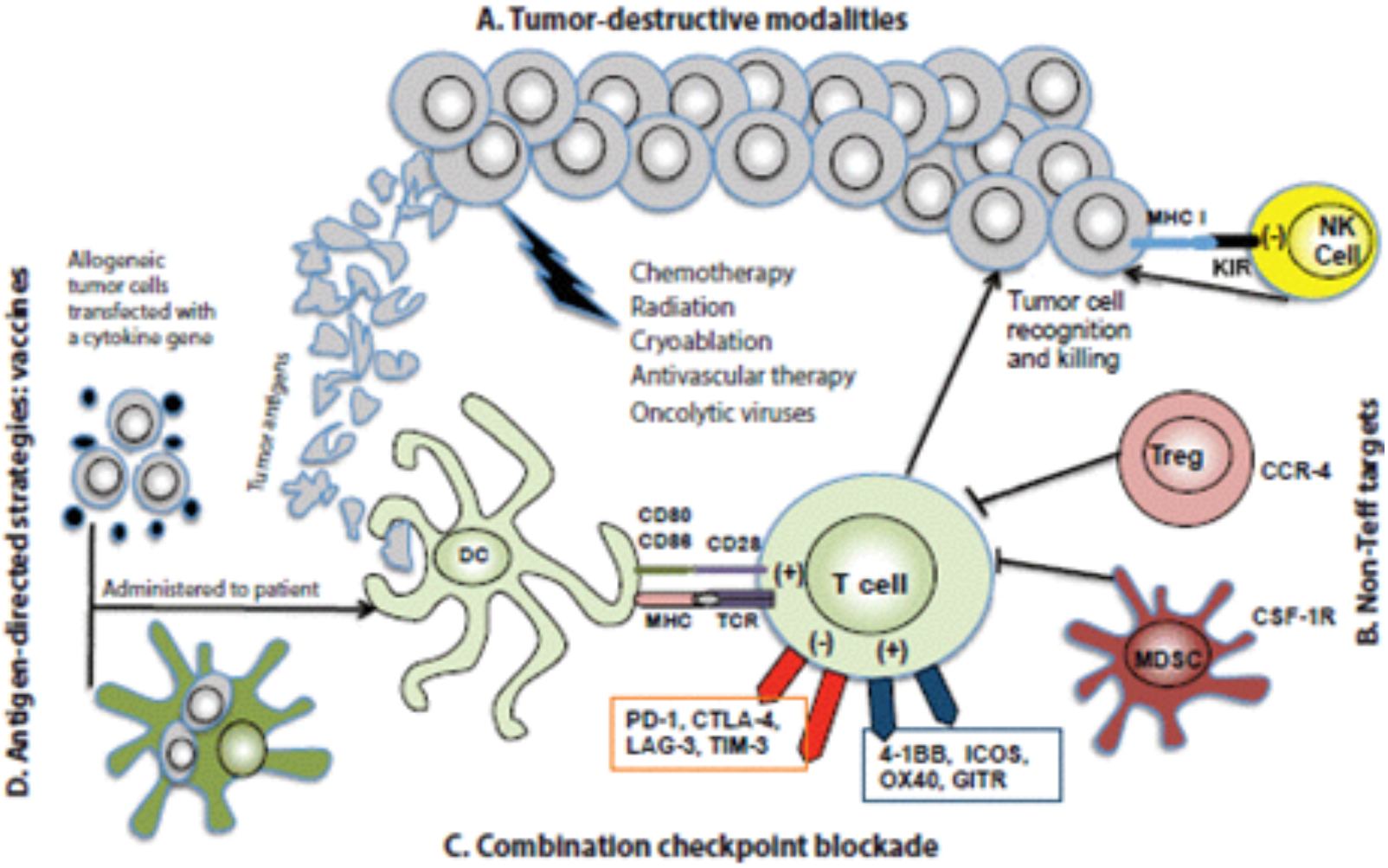
Gajewski TF, et al. *Nature immunology* 2013:1014-1022; Tumeh et al *Nature* 2014: 568-571



Padmanee Sharma[1,2]* and James P. Allison[1]* Science, 2015


Abrogates MDSC activity
Gemcitabine
5-Fluorouracil
Cisplatin
Doxorubicin
MDSC
Enhances cross-priming
Gemcitabine
Anthracyclines
CD8+ T
Abrogates Treg activity
Cyclophosphamide
5-Fluorouracil
Paclitaxel
Cisplatin
Fludarabine
Cytokines
Activated DC
Treg
CD4+ T
CD8+ T
Promotes antitumor CD4+ T-cell phenotype
Cyclophosphamide
Paclitaxel
Augments DC activation
Anthracyclines
Taxanes
Cyclophosphamide
Vinca alkaloids
Methotrexate
Mitomycin C
Promotes cell recognition/lysis
Cyclophosphamide
5-Fluorouracil
Paclitaxel
Doxorubicin
Cisplatin
Cytosine arabinoside
Tumor cell

Combination strategies with citotoxic TL associated antigens(CTL4) blockade



Conclusiones finales

- El tratamiento de precisión del cáncer de pulmón es ya una realidad.
- La quimioterapia tiene un papel definido, pero veremos un cambio en la intención de los tratamientos
- El algoritmo terapéutico en pacientes “pan-negativos” es también complejo, siendo preciso definir factores predictivos.
- Estos factores dependerán de tratamientos previos, tipo de respuesta, perfil tóxico y características intrínsecas de los pacientes.
- La ***combinación***, ***secuenciación*** e incluso la ***alternancia*** o incluso la ***repetición*** de los tratamientos mejorará los resultados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de l'Infern