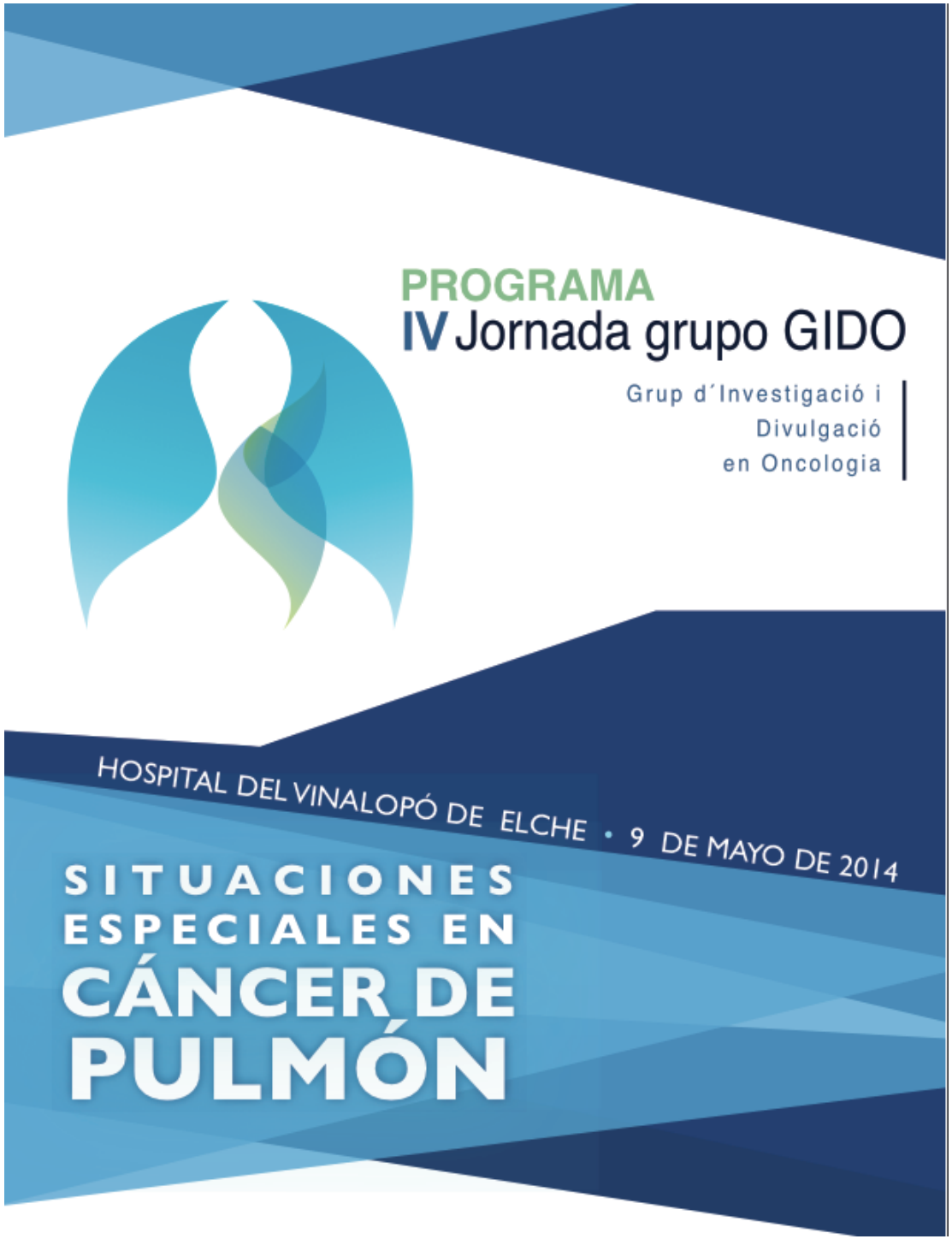


SEGUNDAS LINEAS DE TRATAMIENTO:

CARCINOMA ESCAMOSO

Dra. Elisa Gálvez
S. Oncología Médica
H.G.U. Elda

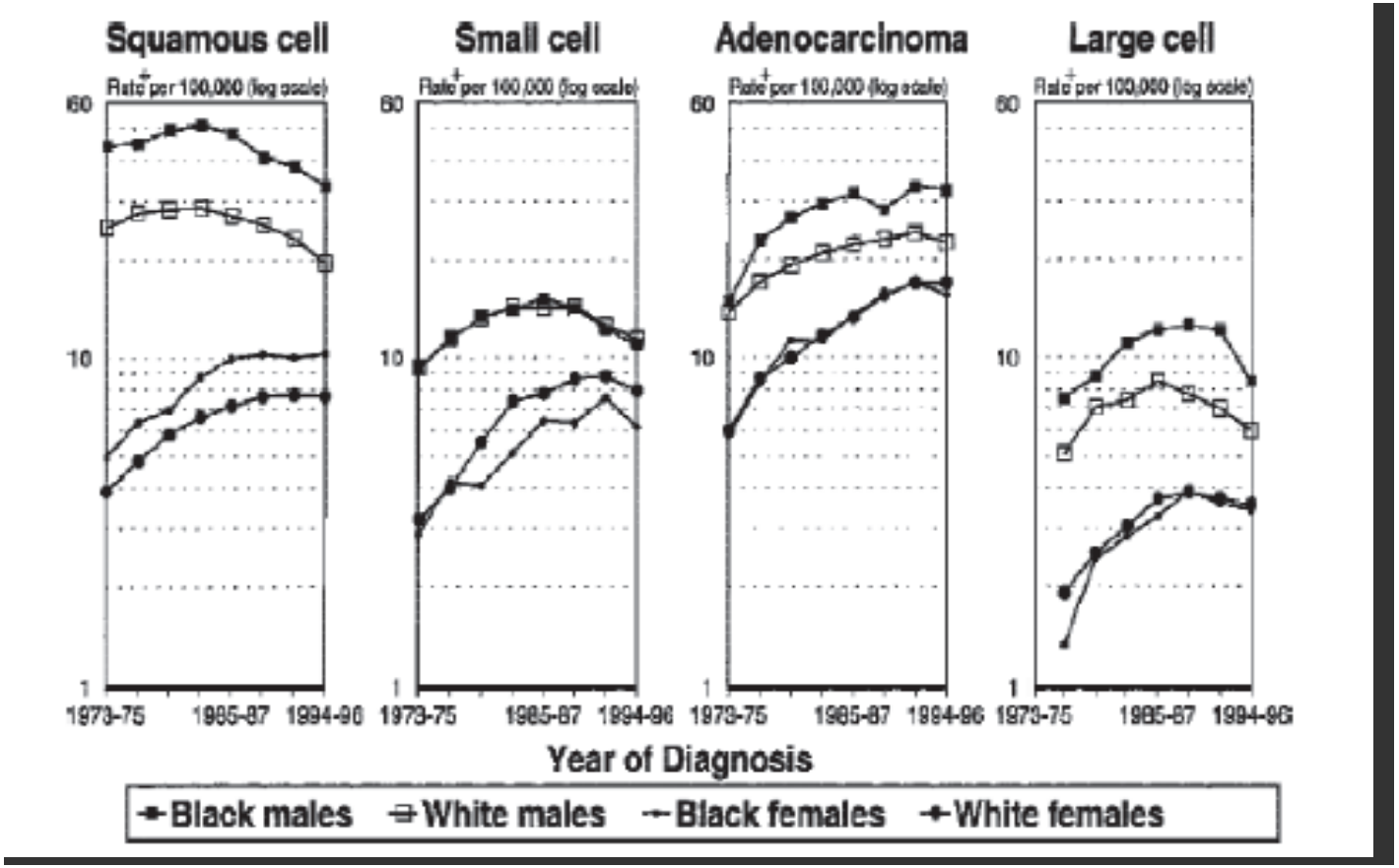
Introducción

- Ca. Pulmón:
  - Incidencia España: 23.211.
  - 1ª causa de muerte por cáncer: 20.327 (23.8/100000 hab).
- 85% C.P. No microcítico
  - 30% escamosos

GLOBOCAN 2008

C. P. Escamoso

- F. Riesgo:
  - Tabaquismo
  - Otros: *Ocupacional, EPOC …*



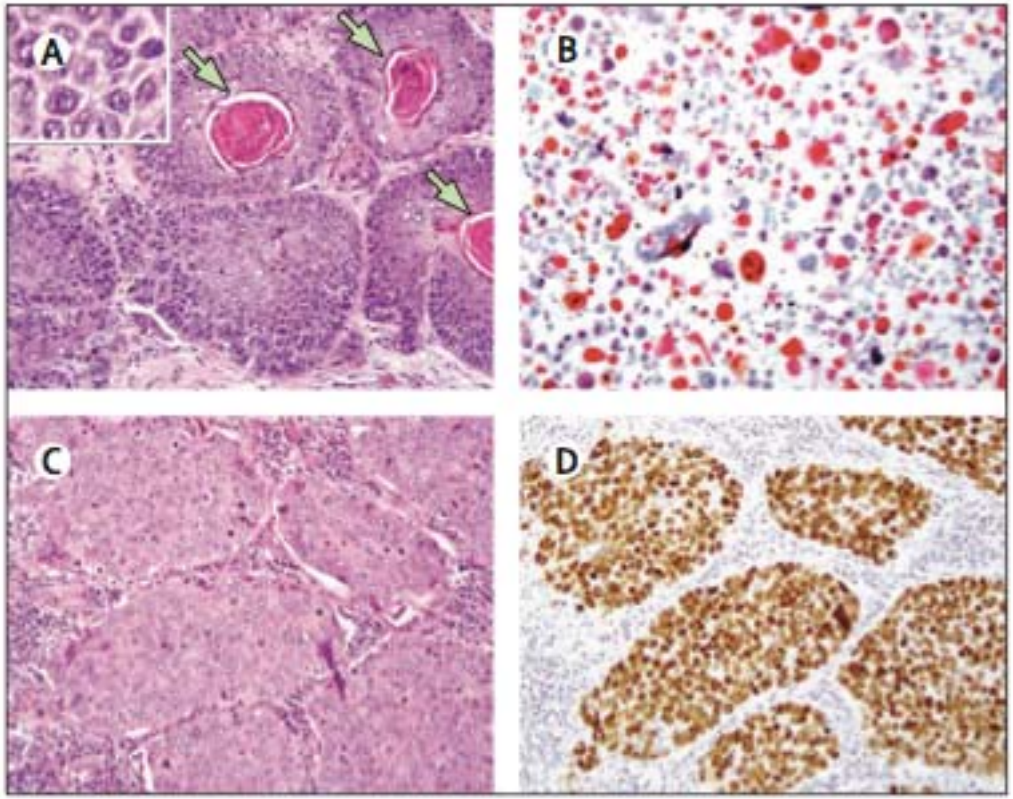
Características clínico/radiológicas

- Presentación clínica:
  - Tos, disnea esfuerzo, hemoptisis, neumonía obstructiva…
- Tumores centrales
- Cavitación
- Histología:
  - puentes intercelulares, queratinización, perlas escamosas….
- Dx: morfológico / IHQ

Chee-Keong Toh en: Methods of Molecular Biology, Cancer Epidemiology, vol 472. Chap 19. 2009

Diagnóstico

- Morfología / IHQ.



Patología

- Cambios mucosa de epitelio bronquial.

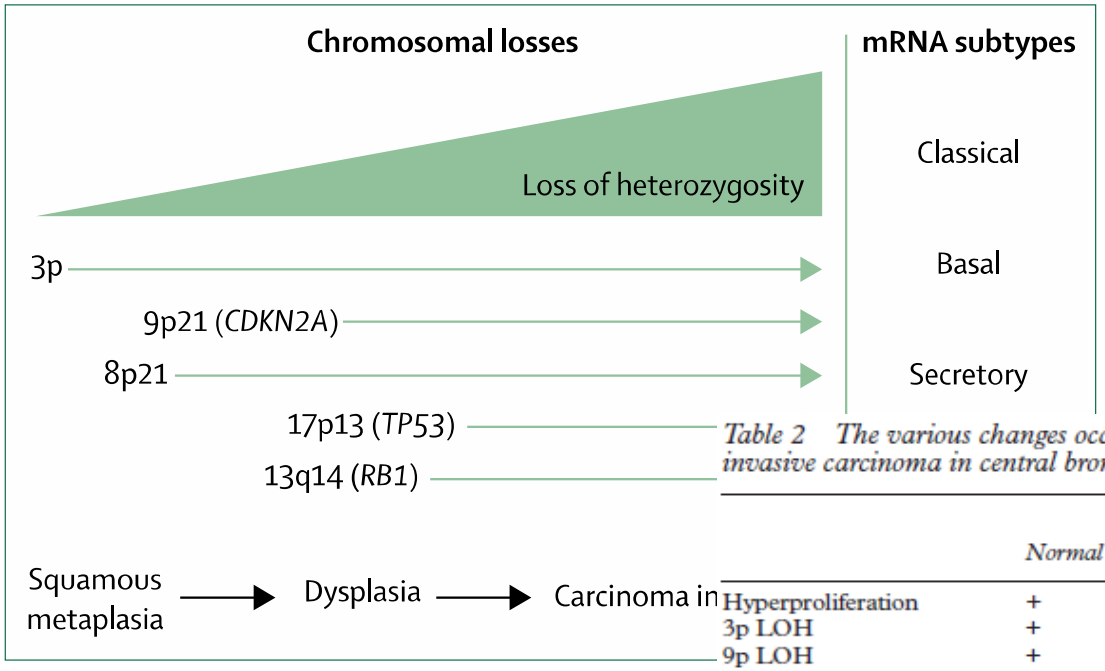


Table 2 The various changes occurring with progression from normal bronchial mucosa to invasive carcinoma in central bronchial carcinogenesis

	Normal	*Squamous metaplasia*	*Low grade dysplasia*	*High grade dysplasia*	*Carcinoma in situ*	*Invasive carcinoma*
Hyperproliferation	+	++	++	++	+++	+++
3p LOH	+	+	++	++	+++	+++
9p LOH	+	+	++	++	+++	+++
p53 overexpression	+	+	++	++	+++	+++
Rb expression	++	++	++	++	++	++
Cyclin D1 overexpression		+	+	++	++	
Telomerase overexpression		+	+	+	+	+++
bcl-2 overexpression			+	+	++	++
Aneuploidy			+	++	++	+++
p53 mutation				+		++
p16 loss			+		++	
FHIT loss				+	++	+++
13q and 17p LOH				+	+++	+++
5p and 5q LOH						+

Normal refers to morphologically normal epithelium in cigarette smokers. Data summarised from discussion in text and references.
LOH, loss of heterozygosity.

***Drilon A. Lancet Oncol* 2012; 13: e418–26**

Tratamiento

- 1ª línea: doblete de platino
- **2ª línea**:
  - " Debe ofrecerse tratamiento sistémico a todo paciente en estadio IV con PS 0-2 tras progresión a 1ª linea"
  - Mejora supervivencia y control de síntomas.
- Supervivencia a 5 años:
  - < 5%.

Tratamiento

- Elección tratamiento:
  - Edad
  - PS
  - Comorbilidad
  - Preferencias del paciente
  - Histología
  - Patología molecular

ESCENARIO ACTUAL

… 2014

Table 3. *Continued*

Topic	Recommendations
	Brain metastases treatment: • WBRT remains the standard treatment of limited-number metastatic brain lesions when local approaches are not possible. • Delaying WBRT after front-line cisplatin-based chemotherapy does not modify the OS according to a randomized phase III trial. • Systemic therapy is a reasonable option for patients with no or relatively minor symptoms from brain metastases with early radiotherapy intervention in the case of the development or progression of symptoms while on treatment [II, B].
Maintenance treatment	• In patients with a non-squamous histology, improvements in PFS and OS were observed with pemetrexed switch maintenance versus placebo following four cycles of platinum-based chemotherapy. • Switch maintenance with erlotinib versus placebo demonstrated PFS and OS benefit in all histologies, with a greatest benefit in efficacy in patients with stable disease (SD) after induction treatment leading to a label restriction for such patients. • Decisions about maintenance must take into account the histology, response to platinum-doublet chemotherapy, remaining toxicity after first-line chemotherapy, PS, and patient preference [I, B]. • Any patient with a tumor bearing an activating (sensitizing) EGFR mutation should receive an EGFR TKI as maintenance, if not received as the first-line therapy [II, A]. • Continuing pemetrexed following completion of first-line cisplatin plus pemetrexed chemotherapy is recommended in patients with a non-squamous histology [I, B].
Second-line treatment	• Patients clinically or radiologically progressing after first-line chemotherapy with PS 0–2 should be offered second-line chemotherapy. • Comparable options as the second-line therapy consist of pemetrexed—for a non-squamous histology only—or docetaxel [I, B]. Erlotinib is an additional option in EGFR WT patients with PS 0–3 [II, B]. • Any patient with a tumor bearing an activating (sensitizing) EGFR mutation should receive an EGFR TKI as the second-line therapy, if not received previously [I, A]. • Treatment may be prolonged if the disease is controlled and the toxicity acceptable [II, B].
Subsequent lines of treatment	• Erlotinib is indicated for EGFR WT patients who have not yet received EGFR TKIs, with PS 0–3 [II, B]. • Any patient with a tumor bearing an activating (sensitizing) EGFR mutation should receive an EGFR TKI in any line of therapy, if not received previously [I, A].
Role of minimally-invasive procedures in	• In case of symptomatic major airway obstruction or post-obstructive infection, endoscopic debulking by laser, cryotherapy, or stent placement may be helpful [III, C].
	prevention [II; B].
Role of palliative-care early intervention	Early palliative-care intervention is recommended, in parallel with standard oncologic care [I; A].
Response evaluation	• Response evaluation is recommended after two to three cycles of chemotherapy using the same initial radiographic investigation which demonstrated tumor lesions. • Follow-up with PET is not routinely recommended, due to its high sensitivity and relatively low specificity. • Measurements and response reporting should follow RECIST 1.1 criteria. However, the adequacy of RECIST in evaluating the response to EGFR or ALK TKI in respective genetically driven NSCLC is debatable.

Continued

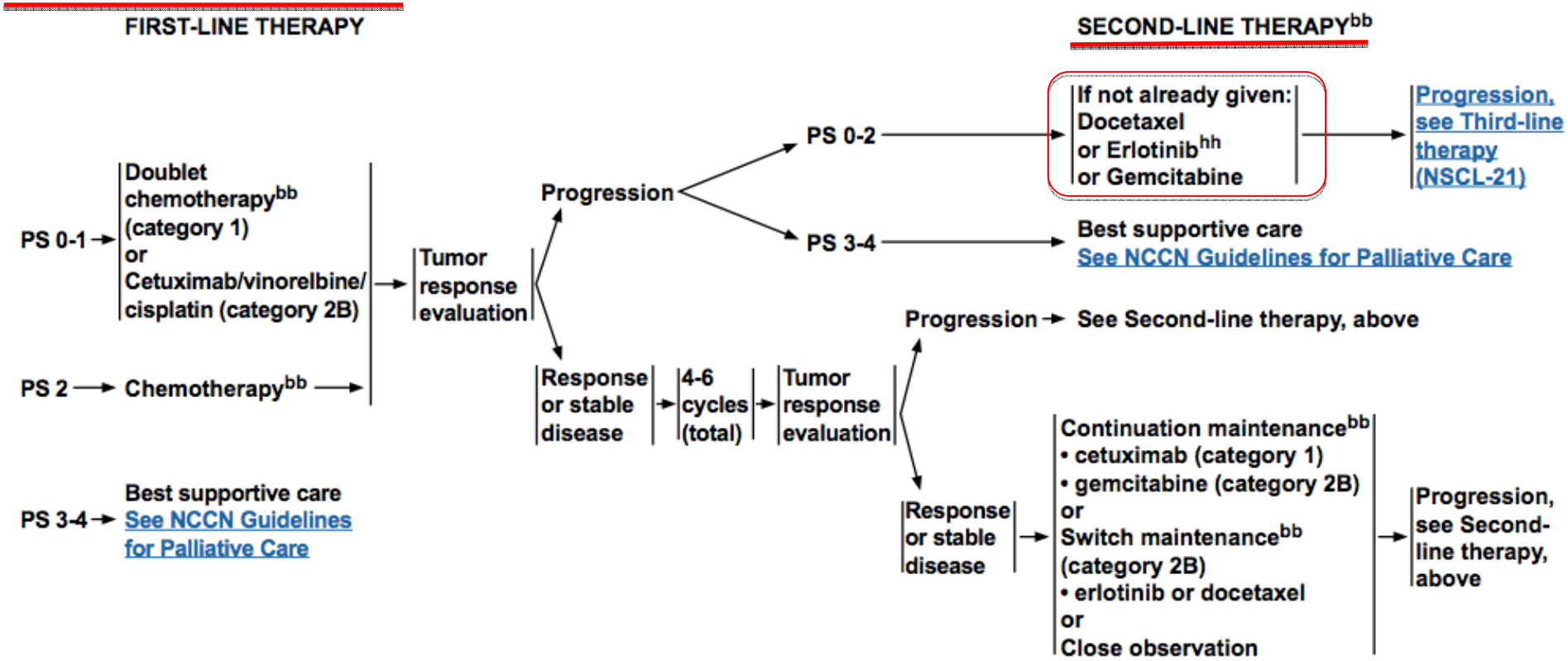
Second-line treatment
- Patients clinically or radiologically progressing after first-line chemotherapy with PS 0–2 should be offered second-line chemotherapy.
- Comparable options as the second-line therapy consist of pemetrexed—for a non-squamous histology only—or docetaxel [I, B]. Erlotinib is an additional option in EGFR WT patients with PS 0–3 [II, B].
- Any patient with a tumor bearing an activating (sensitizing) EGFR mutation should receive an EGFR TKI as the second-line therapy, if not received previously [I, A].
- Treatment may be prolonged if the disease is controlled and the toxicity acceptable [II, B].

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2014
Non-Small Cell Lung Cancer

NCCN Guidelines Index
NSCLC Table of Contents
Discussion

SQUAMOUS CELL CARCINOMA



2ª Línea C.P. Escamoso

- Docetaxel 75mg/m2/21 días.

J Clin Oncol. 2000 May;18(10):2095-103.

Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy.

Shepherd FA[1], Dancey J, Ramlau R, Mattson K, Gralla R, O'Rourke M, Levitan N, Gressot L, Vincent M, Burkes R, Coughlin S, Kim Y, Berille J.

J Clin Oncol. 2000 Jun;18(12):2354-62.

Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group.

Fossella FV[1], DeVore R, Kerr RN, Crawford J, Natale RR, Dunphy F, Kalman L, Miller V, Lee JS, Moore M, Gandara D, Karp D, Vokes E, Kris M, Kim Y, Gamza F, Hammershaimb L.

2ª Línea C.P. Escamoso

- Erlotinib 150 mg/día v.o.

N Engl J Med. 2005 Jul 14;353(2):123-32.

Erlotinib in previously treated non-small-cell lung cancer.

Shepherd FA[1], Rodrigues Pereira J, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, Campos D, Maoleekoonpiroj S, Smylie M, Martins R, van Kooten M, Dediu M, Findlay B, Tu D, Johnston D, Bezjak A, Clark G, Santabárbara P, Seymour L; National Cancer Institute of Canada Clinical Trials Group.

Lancet Oncol. 2012 Mar;13(3):300-8. doi: 10.1016/S1470-2045(11)70385-0. Epub 2012 Jan 24.

Efficacy and safety of erlotinib versus chemotherapy in second-line treatment of patients with advanced, non-small-cell lung cancer with poor prognosis (TITAN): a randomised multicentre, open-label, phase 3 study.

Ciuleanu T[1], Stelmakh L, Cicenas S, Miliauskas S, Grigorescu AC, Hillenbach C, Johannsdottir HK, Klughammer B, Gonzalez EE.

Erlotinib in advanced squamous cell carcinoma of the lung: P3-095

Isla, Dolores[1]; Jimenez, Ulpiano[2]; Valverde, Juan Jose[3]; Garcia, Javier[4]; Almenarez, Jose Alfredo[5]; Moreno, Jose Andres[6]; Valero, Pedro[7]; Bernabe, Reyes[8]; Amador, Maria Luz[9]; Paz, Ares Luis[10]

Journal of Thoracic Oncology:
August 2007 - Volume 2 - Issue 8 - p S719

2ª Línea C.P. Escamoso

- Erlotinib vs Docetaxel

The Lancet Oncology, Volume 14, Issue 10, Pages 981 - 988, September 2013

Erlotinib versus docetaxel as second-line treatment of patients with advanced non-small-cell lung cancer and wild-type *EGFR* tumours (TAILOR): a randomised controlled trial

Marina Chiara Garassino MD [a] [1], Olga Martelli MD [c], Massimo Broggini PhD [d], Gabriella Farina MD [a], Silvio Veronese PhD [e], Eliana Rulli PhD [d], Filippo Bianchi MD [b], Anna Bettini MD [f], Flavia Longo MD [g], Luca Moscetti MD [h], Maurizio Tomirotti MD [i], Mirko Marabese PhD [d], Monica Ganzinelli PhD [b], Calogero Lauricella PhD [e], Roberto Labianca MD [f], Irene Floriani PhD [d], Giuseppe Giaccone MD [j], Valter Torri MD [d], Alberto Scanni MD [a], Silvia Marsoni MD [k], on behalf of the TAILOR trialists

2ª Línea C. P. Escamoso

- Pemetrex ng/m2/21 d, i.v.

J Clin Oncol. 2004 May 1;22(9):1

Randomized phase III t pemetrexed vers cetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy.

Hanna N[1], Shepherd FA, Fossella FV, Pereira JR, De Marinis F, von Pawel J, Gatzemeier U, Tsao TC, Pless M, Muller T, Lim HL, Desch C, Szondy K, Gervais R, Shaharyar, Manegold C, Paul S, Paoletti P, Einhorn L, Bunn PA Jr.

J Clin Oncol. 2008 Jul 20;26(21):3543-51. doi: 10.1200/JCO.2007.15.0375. Epub 2008 M

Phase III study c aring cisplatin plu ncitabine latin plus pemetrexed in chemotherapy-naive patients with advan e non-sma ng c

Scagliotti GV[1], Parikh P, von Paw eier U, Digumarti R, Zukin M, Lee JS, Mellemgaard A, Park K, Patil S, Rolski J, Goksel T, de

Pemetrexed: indicado en no escamosos

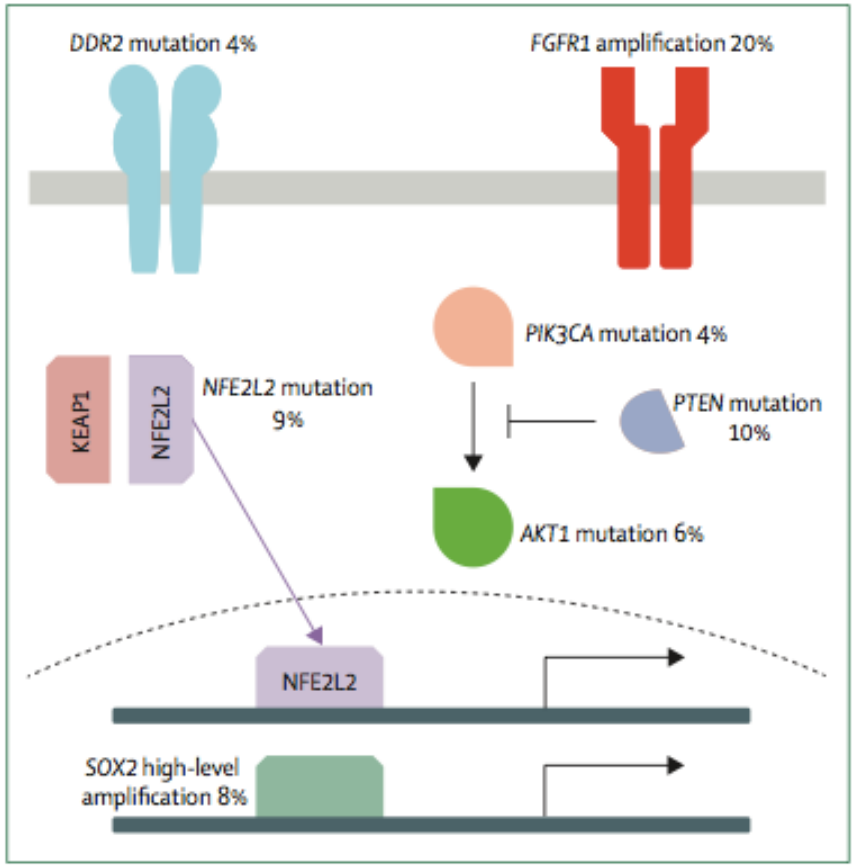
ESCENARIO FUTURO

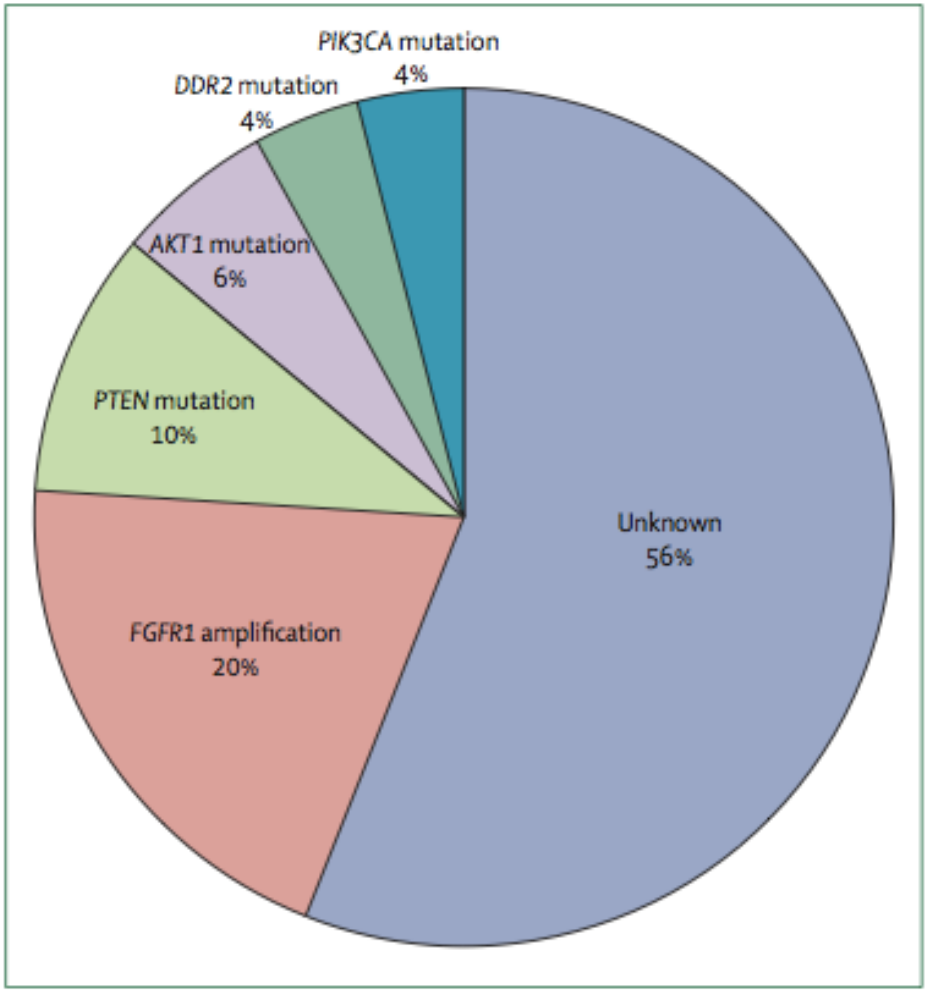
2014 ….

Biología Molecular

- Caracterización genómica: Perfiles genético.
- The Cancer Genome Atlas.
- Complejidad genómica del C. Escamoso.
- ….

Biología Molecular





Genetic abnormality	Gene location	Squamous Cell Carcinoma	Adenocarcinoma
TP53[36;71]	17p13.1	51%	36%
PIK3CA amplification[51;52;54]	3q26.3	33%	6%
SOX2 amplification[23;24]	3q26.3-q27	23%	Very rare
FGFR1 amplification[24;25]	8p12	22%	1%
PTEN mutation[36;61]	10q23.3	10%	2%
MET amplification[34;35]	7q31.1	3-21%	3-21%
PTEN loss[59;62]	10q23.3	8-20%	8-20%
KRAS mutation[36]	12p12.1	6%	21%

Perez-Moreno PD, et al. Clin Cancer Res 2012; 18: 2443

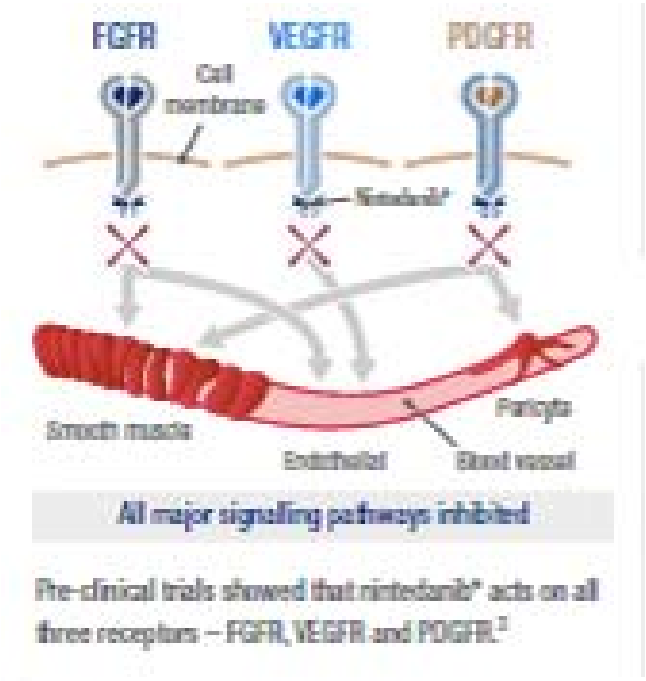
Inhibidores angiogénesis

- Grandes fracasos.
  - Bevacizumab[1]:
    - Hemorragia pulmonar º3.
    - Uso “investigacional”.
  - I. Tirosín-quinasa (ITK):
    - Sorafenib [2]
    - Motesanib [3]

(1) Johnson DH. J Clin Oncol 2004;22:2184-91.
(2) Scagliotti G. J Clin Oncol 2010;28:1835-42.
(3) Scagliotti G. MONET1. J Clin Oncol 2012;30:2829-36.

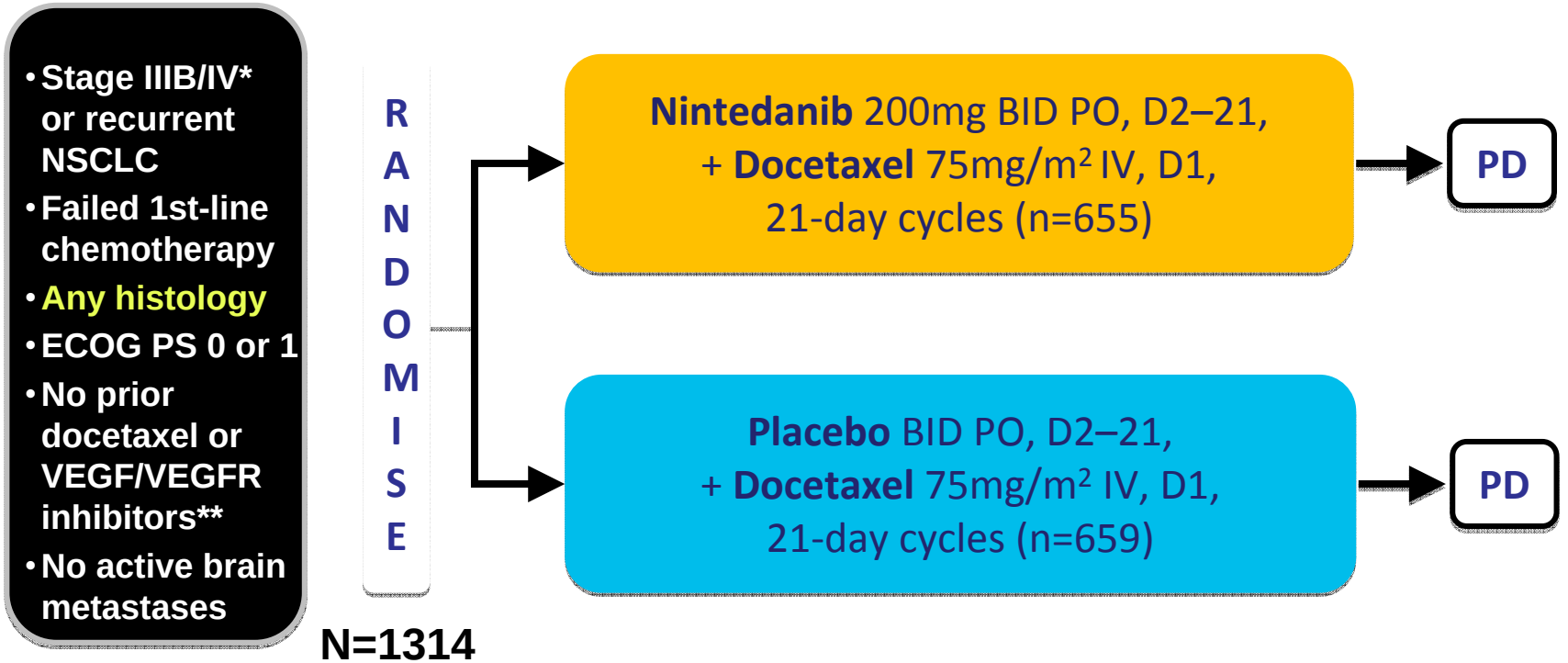
Inhibidores angiogénesis

- ITKs (cont):
  - Nintedanib: LUME-Lung1.



Reck M. *Lancet Oncol* 2014;15(2):143-155.

LUME-Lung 1 Study Design



N=1314

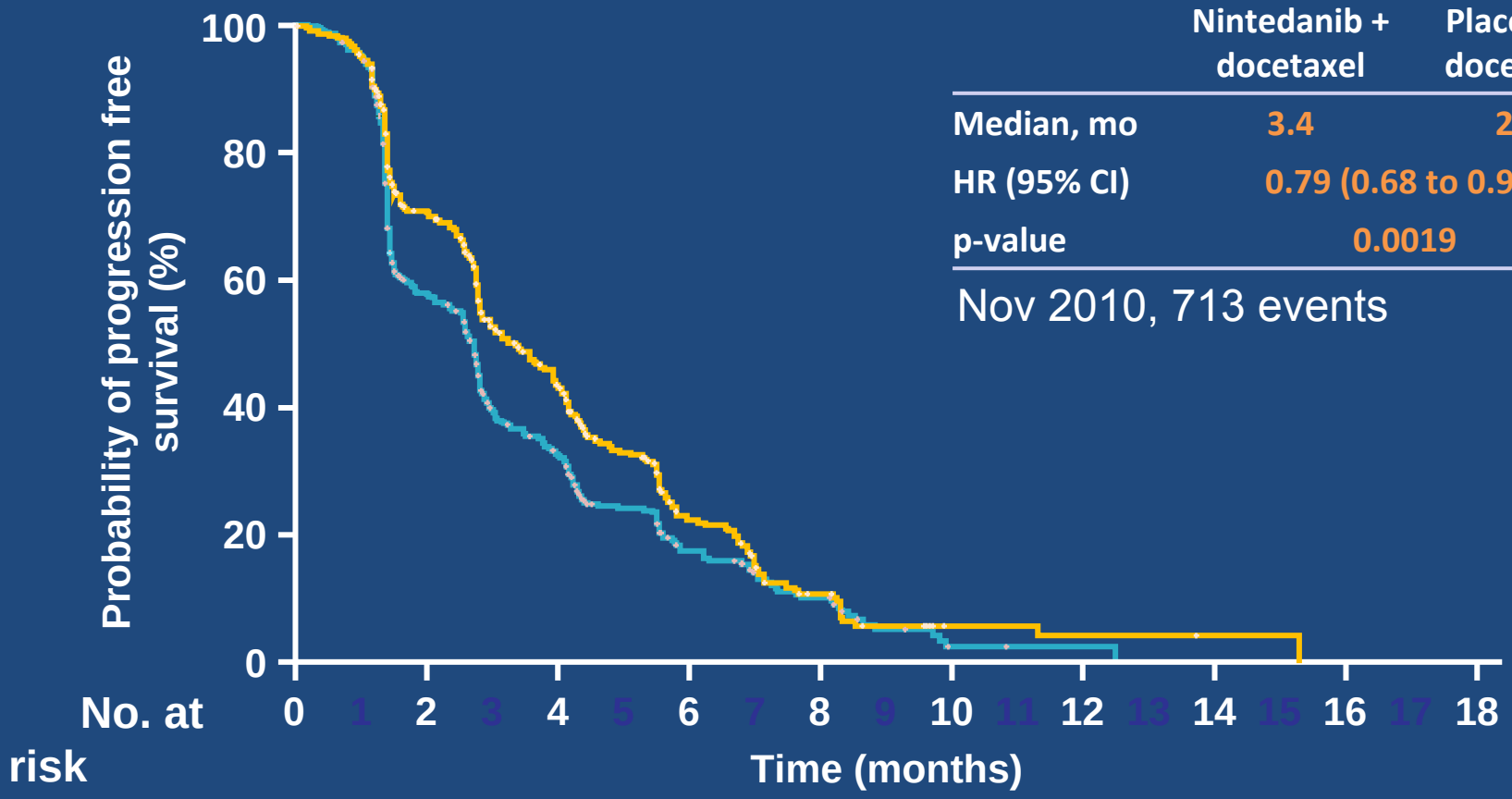
Number of docetaxel cycles not restricted
Monotherapy allowed after ≥4 cycles of combination therapy

Stratification: ECOG performance status (0 vs 1)
Prior bevacizumab (yes vs no)
Histology (squamous vs non-squamous)
Brain metastases (yes vs no)

Obj 1º: PFS
Obj 2º: OS, …

Primary Endpoint: PFS

Independent Central Review in All Patients



	Nintedanib + docetaxel	Placebo + docetaxel
Median, mo	3.4	2.7
HR (95% CI)	0.79 (0.68 to 0.92)	
p-value	0.0019	

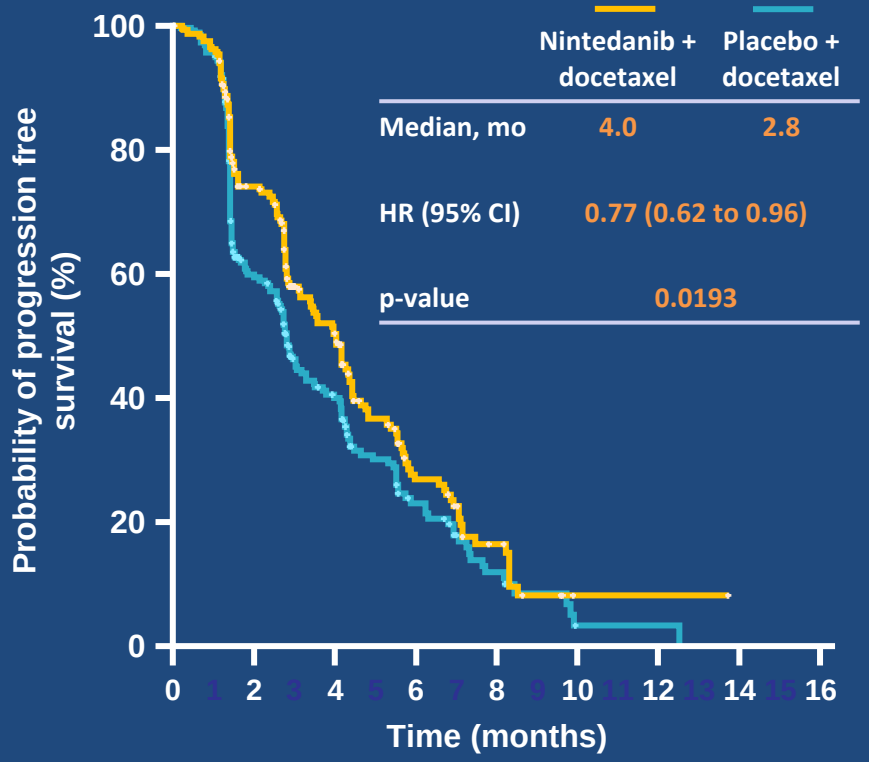
Nov 2010, 713 events

No. at risk									
Nintedanib	565	295	155	57	19	4	3	1	0
Placebo	569	250	116	43	21	2	1	0	0

PFS

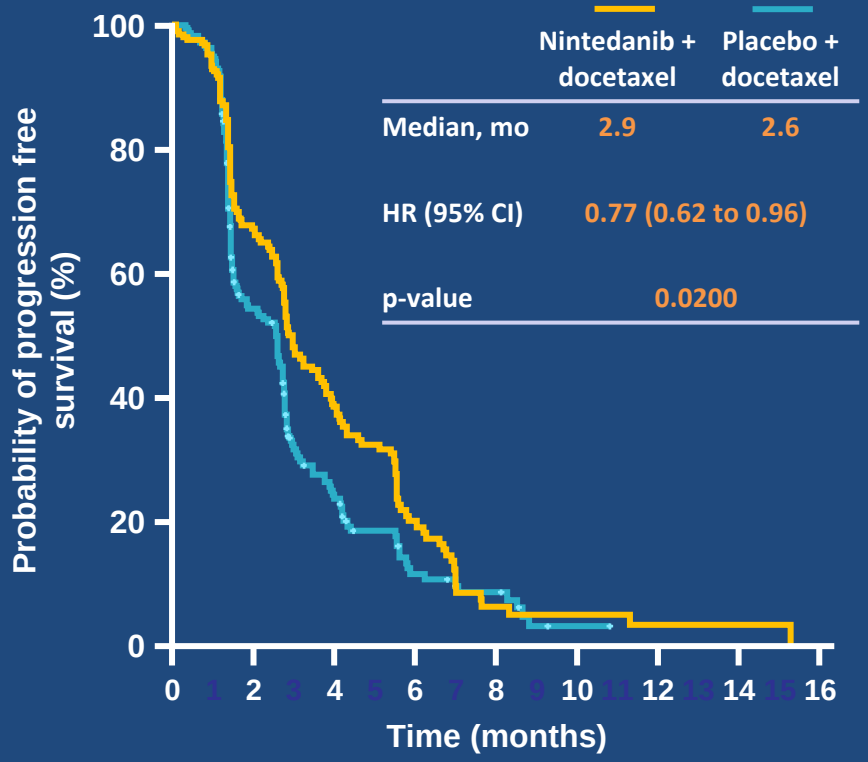
Independent Central Review in Major Histologies

Adenocarcinoma



No. at risk								
Nintedanib	277	150	86	32	13	1	1	0
Placebo	285	129	70	28	12	1	1	0

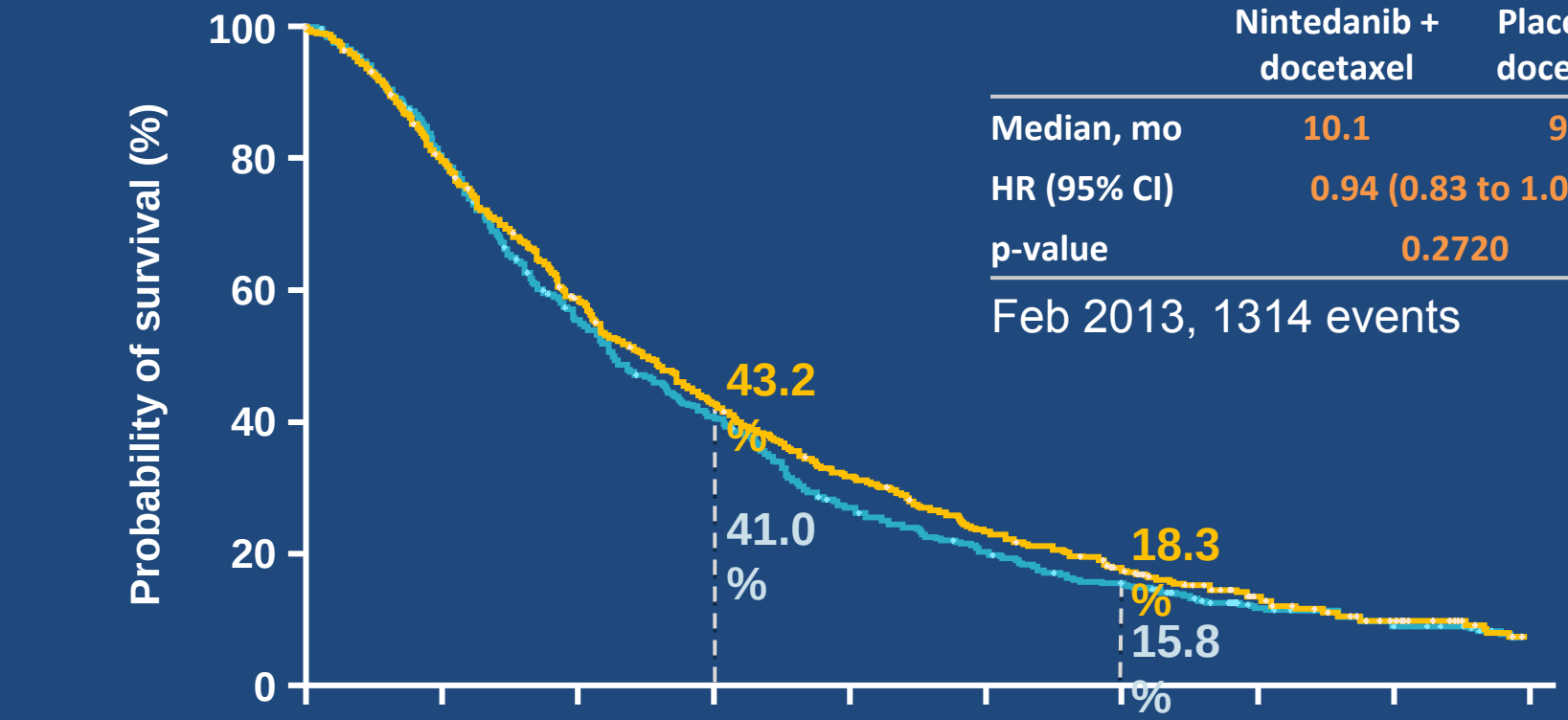
Squamous Cell Carcinoma



No. at risk									
Nintedanib	240	122	59	22	5	3	2	1	0
Placebo	247	101	36	13	8	1	0	0	0

Overall Survival

All Patients



	Nintedanib + docetaxel	Placebo + docetaxel
Median, mo	10.1	9.1
HR (95% CI)	0.94 (0.83 to 1.05)	
p-value	0.2720	

Feb 2013, 1314 events

Nintedanib	655	516	374	271	200	147	106	67	34	14
Placebo	659	511	344	250	162	120	91	58	28	13

OS Adeno T<9mo → OS Adeno → OS All pts

Lung Adenocarcinomas *vs* Squamous Carcinomas

- Tumor samples: NSCLC stage I – III; 41 ADC, 34 SCC
- Immunohistochemistry: PAL-E (vascular density), GLUT1 (glucose transporter), MCT4 (monocarboxylate transporter, lactate export)
- Results
  - Vascular density significantly higher in ADC
    75 versus 145 vascular structures per mm^2
  - GLUT1 expression significantly lower in ADC
    marker positive fraction 1.8% versus 24%
  - MCT4 expression similar in ADC and SCC
    Marker positive fraction 16% versus 17%
  - Transporter expression increasing with increasing distance from nearest vessel, more clearly observed in SCC (chronic hypoxia pattern of expression)

Conclusion: ADC rely mainly on aerobic glycolysis and may use lactate as a substrate for mitochondrial oxydation, whereas SCC are more hypoxic due to low vascular density and utilize anaerobic glycolysis to generate ATP

Differences in metabolism between adeno- and squamous cell non-small cell lung carcinomas: spatial distribution and prognostic value of GLUT1 and MCT4. Meijer TW et al 2012 Lung Cancer 76:316

Vía EGFR

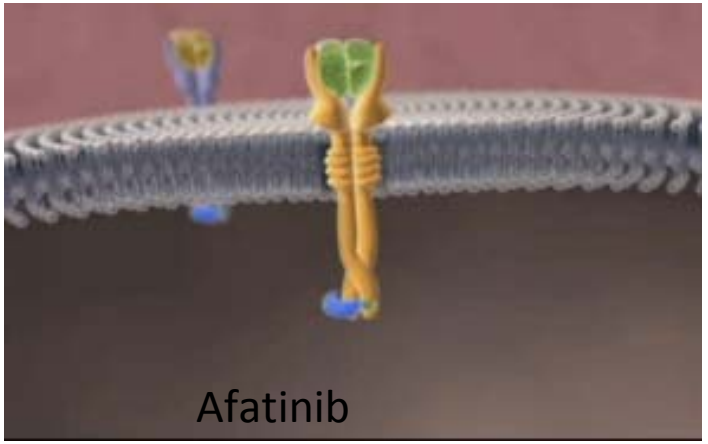
- Mutación EGFR: ≈ 0% en C.P. Escamoso.
- Sobreexpresión, amplificación EGFR y aumento número copias EGFR.

- A. Monoclonales: Cetuximab.
  - No datos en 2ª línea.
  - EC. FLEX (1ªL): CDDP/VNR + cetuximab.
    - ↑ supervivencia en EGFR+ (IHQ)

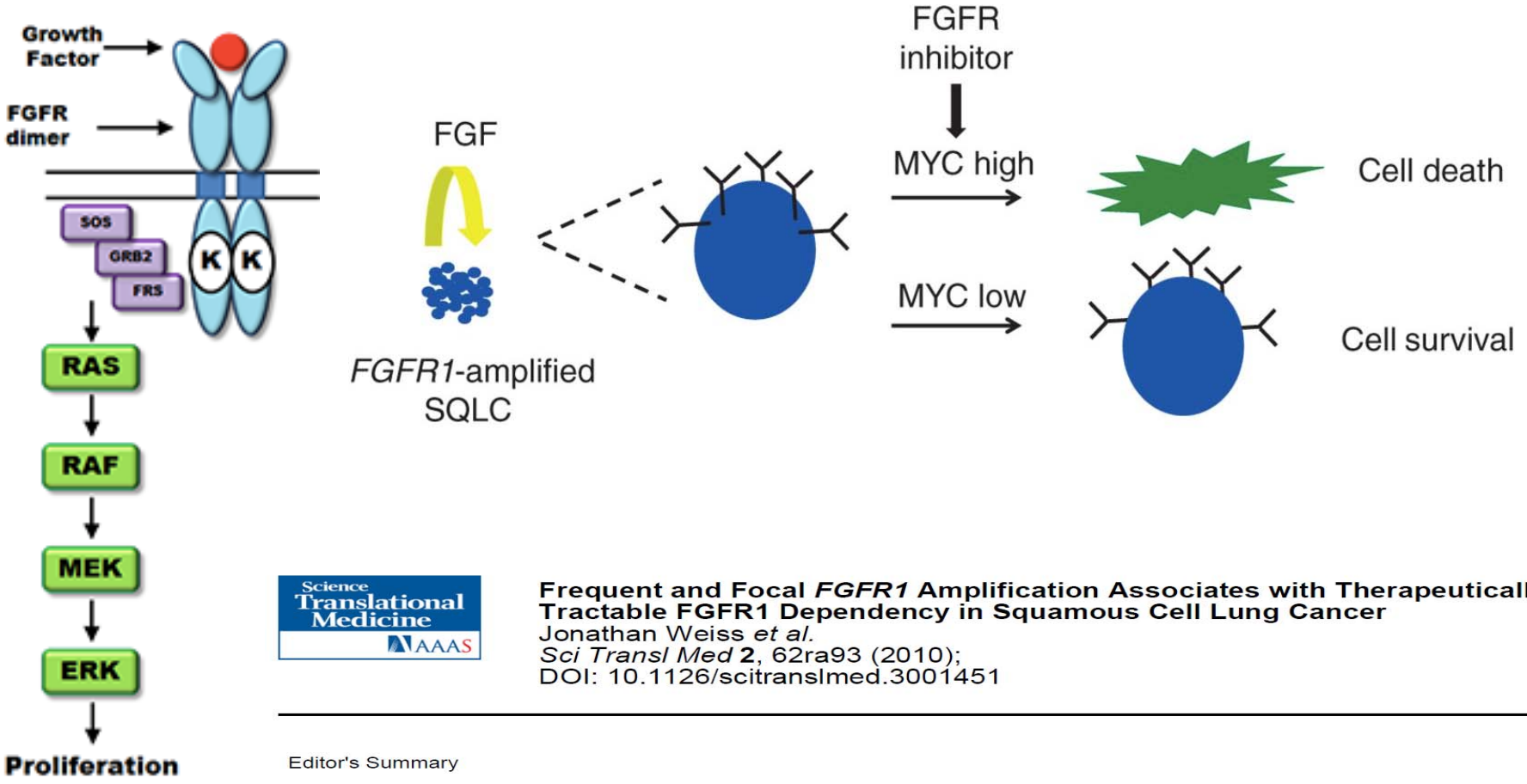
Vía EGFR

- ITKs:
  - Erlotinib
  - Afatinib
    - LUX-LUNG 8 (NCT01523587)
  - Gefitinib
    - F. II 2ªL C.P. Esc, EGFR mut. (NCT 01485809)

EGFR Mut



Vía FGFR1: FIBROBLAST GROWTH FACTOR RECEPTOR 1.



Science Translational Medicine AAAS

Frequent and Focal *FGFR1* Amplification Associates with Therapeutically Tractable FGFR1 Dependency in Squamous Cell Lung Cancer

Jonathan Weiss *et al.*

Sci Transl Med **2**, 62ra93 (2010);

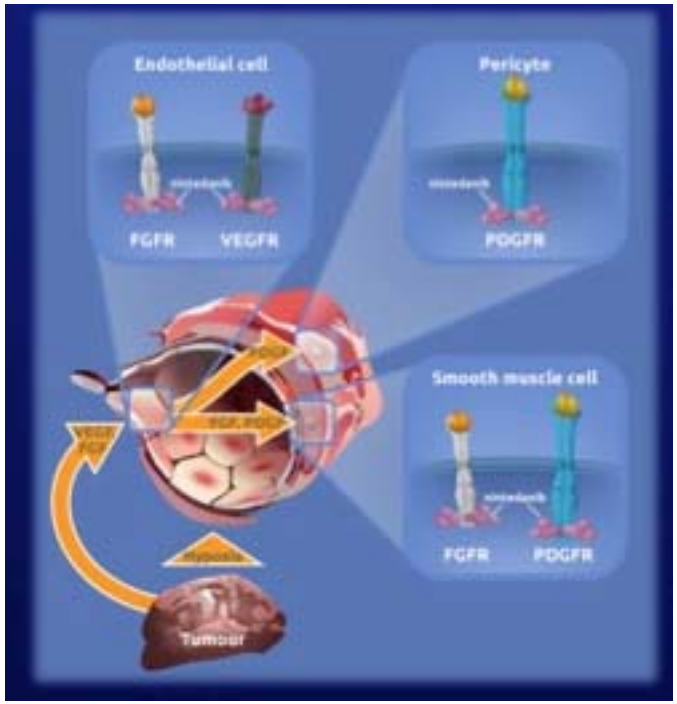
DOI: 10.1126/scitranslmed.3001451

Editor's Summary

A Smoking Gun for Lung Cancer

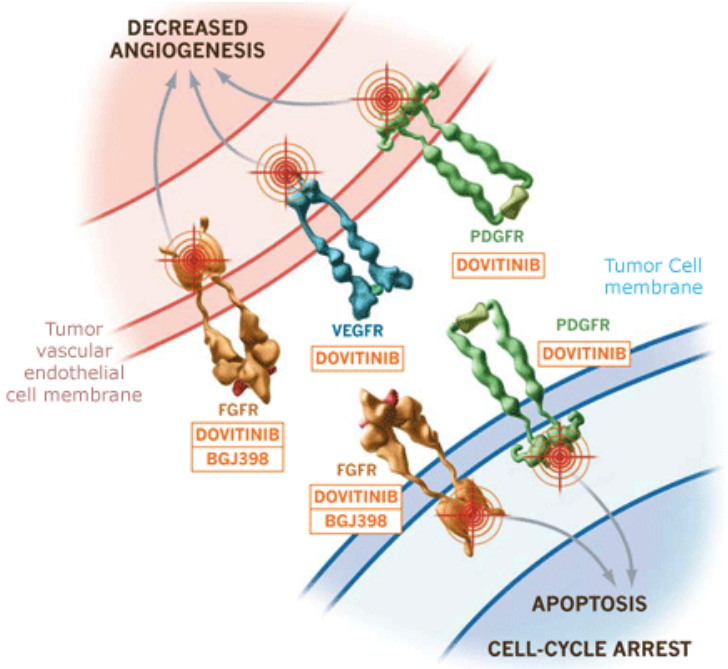
Vía FGFR1: FIBROBLAST GROWTH FACTOR RECEPTOR 1.

- Nintedanib

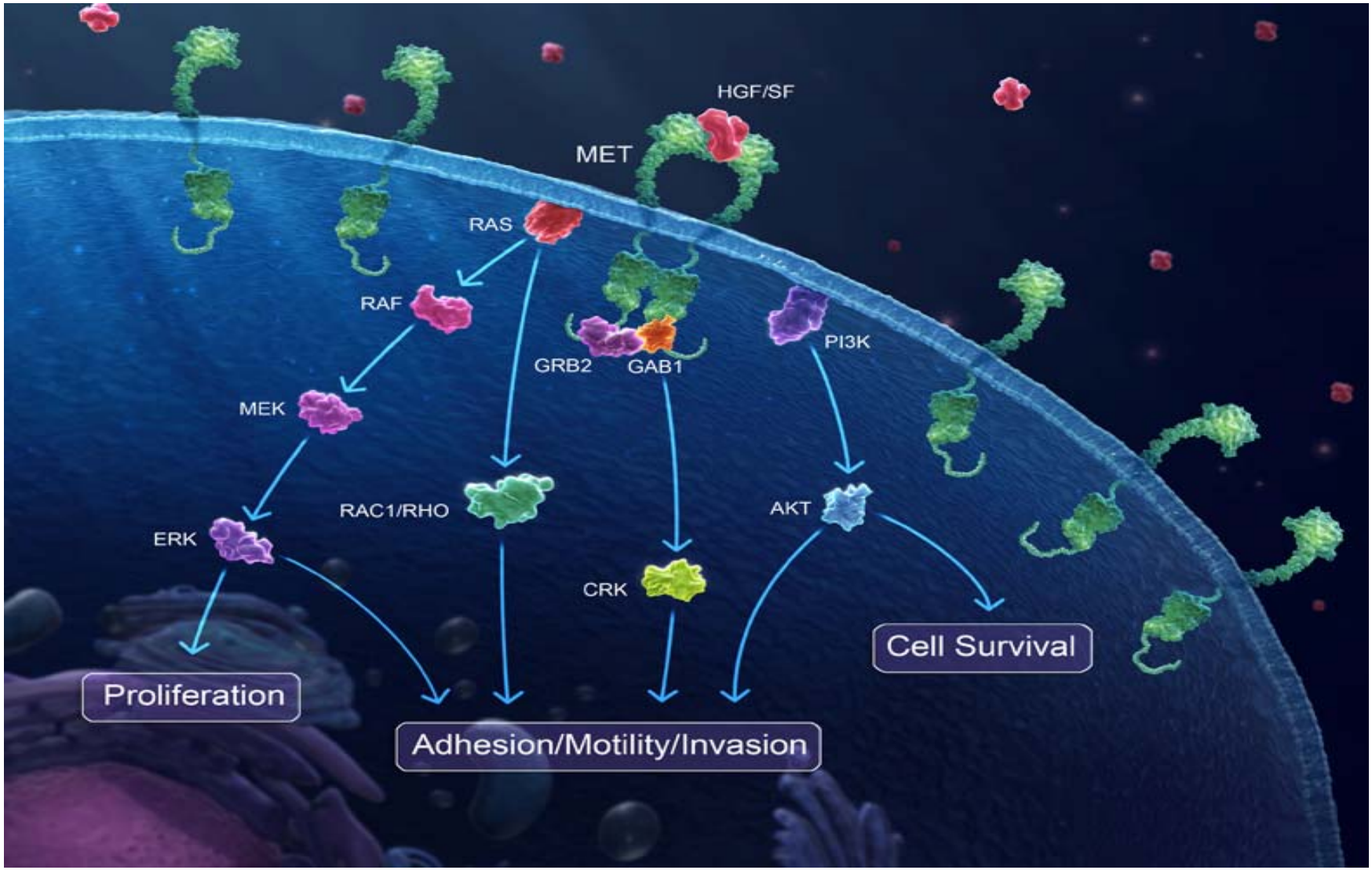


Ponatinib

Dovitinib

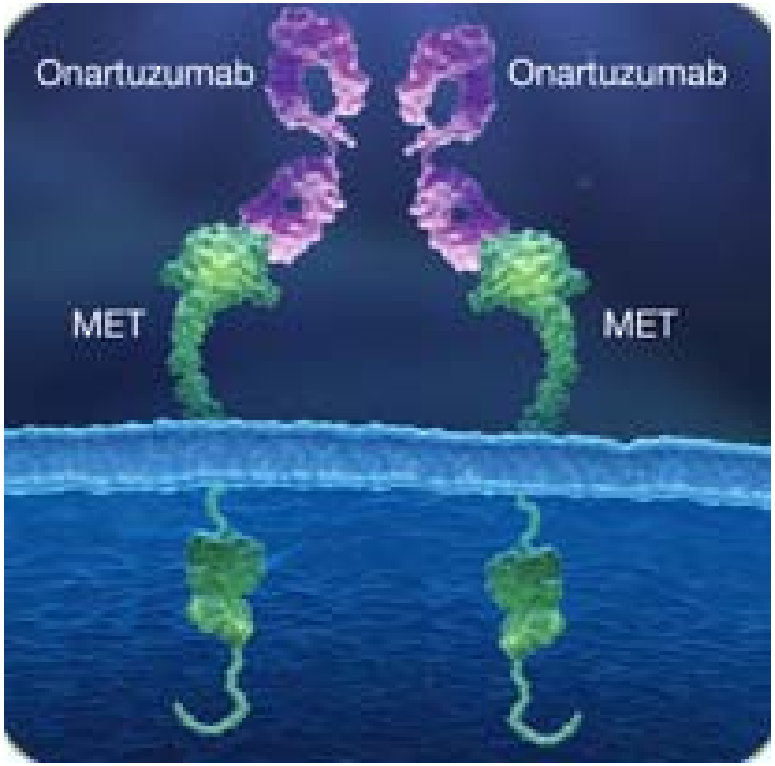


Vía Mesenchymal-Epithelial Transition Factor (MET)



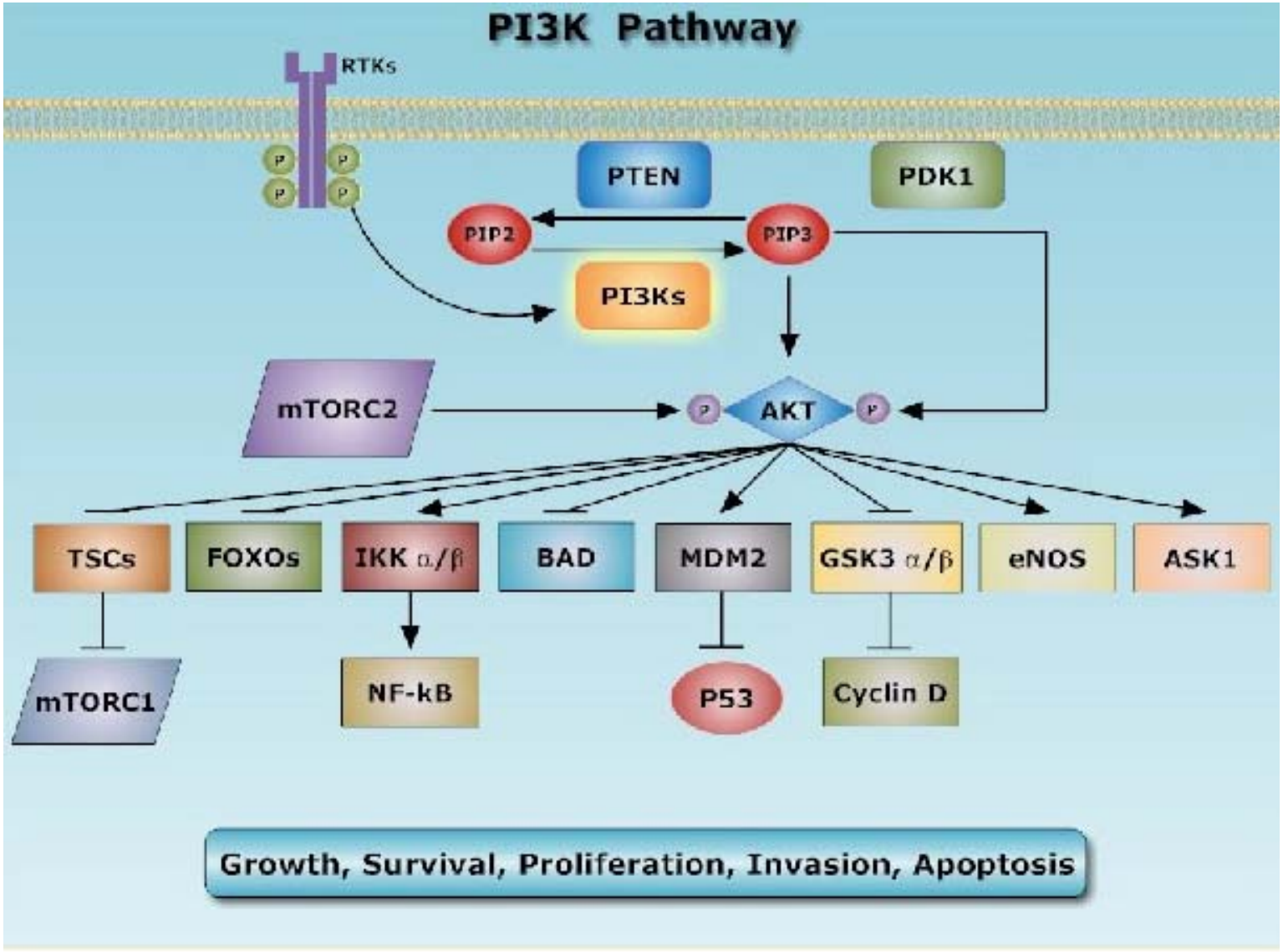
Vía Mesenchymal-Epithelial Transition Factor (MET)

- Onartuzumab:
  - EC. F. III, 2ªL C.P. No microcitico.
    - Erlotinib + onartuzumab vs Erlotinib.



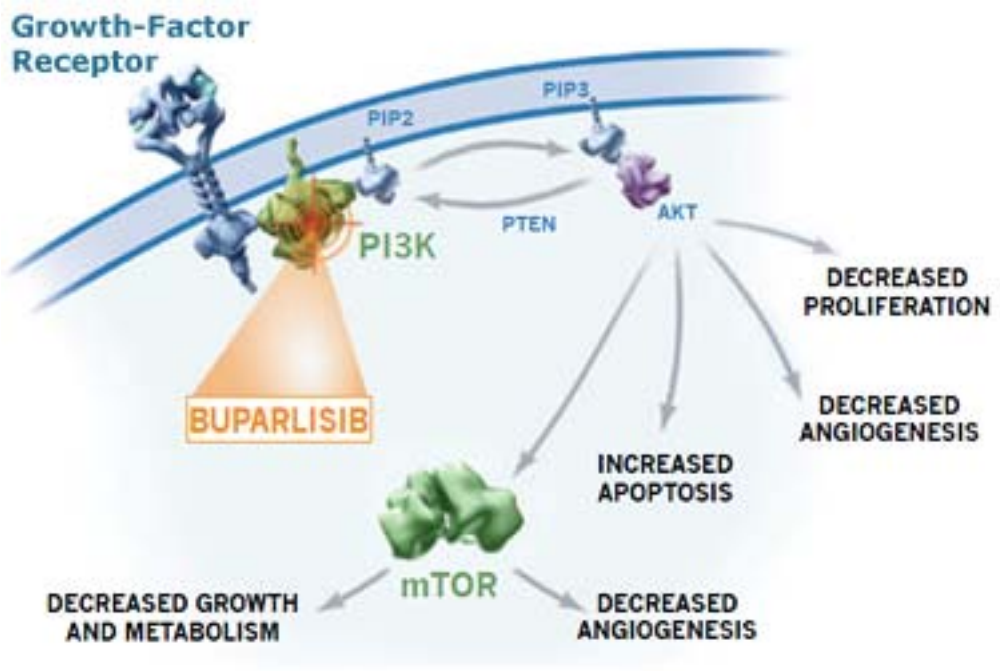
Gherardi E. Nat Rev Cancer 2012;12:89-103

Vía PI3K (Phosphatidylinositol 3-kinase)

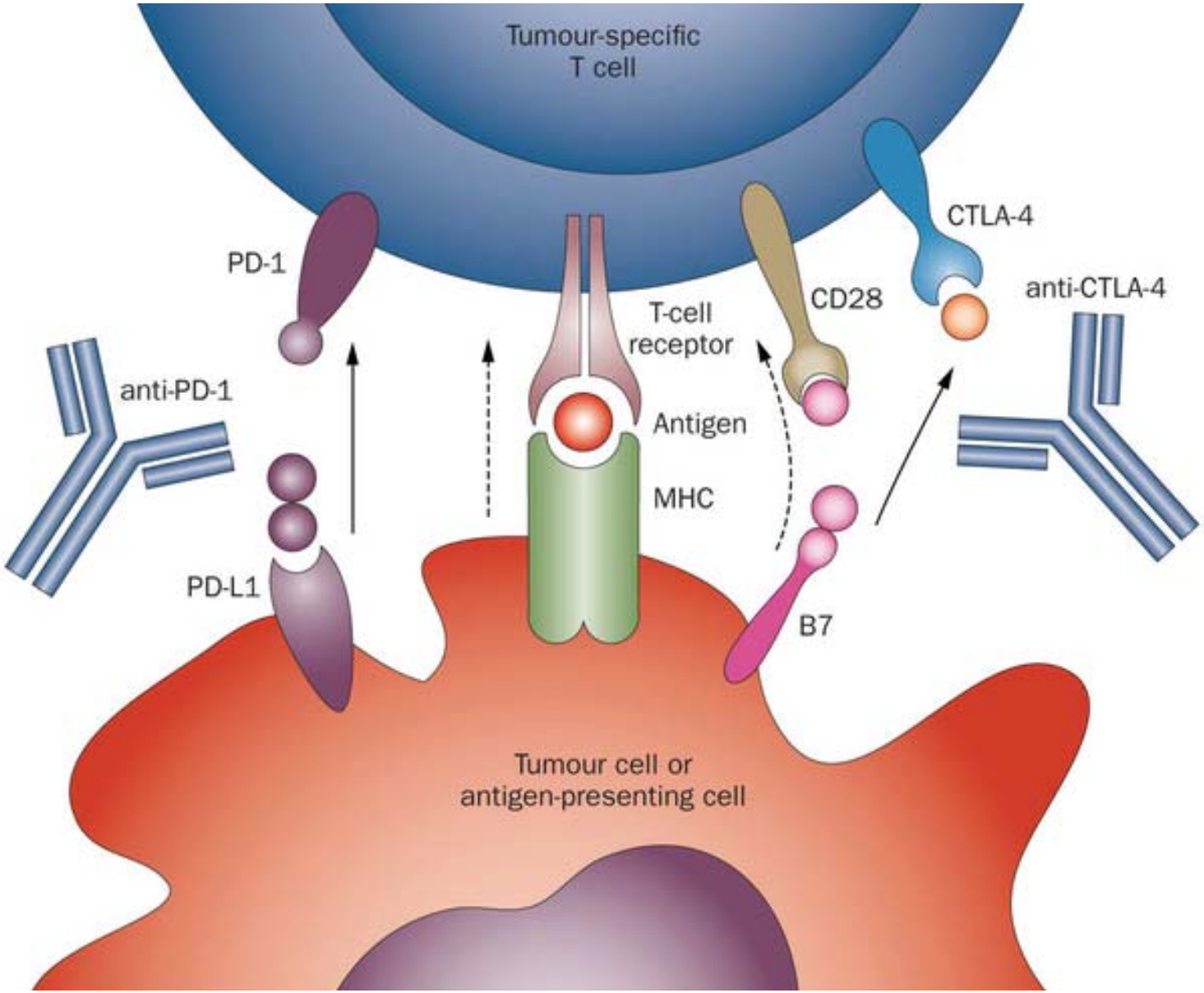


Vía PI3K (Phosphatidylinositol 3-kinase)

- Buparlisib (BMK120):

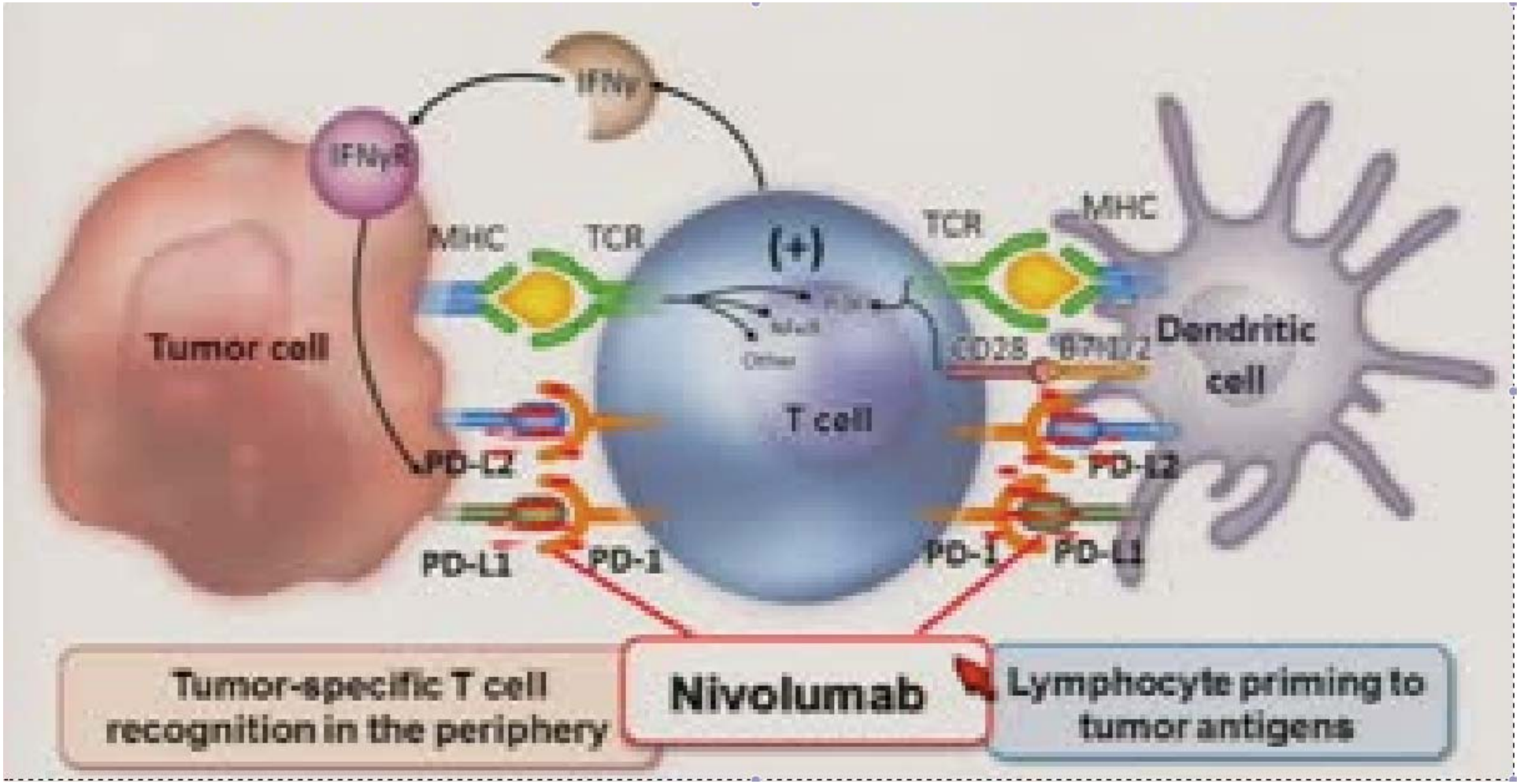


Inmunoterapia



Inmunoterapia

- PD1 (programmed cell death protein 1):
  - Nivolumab:

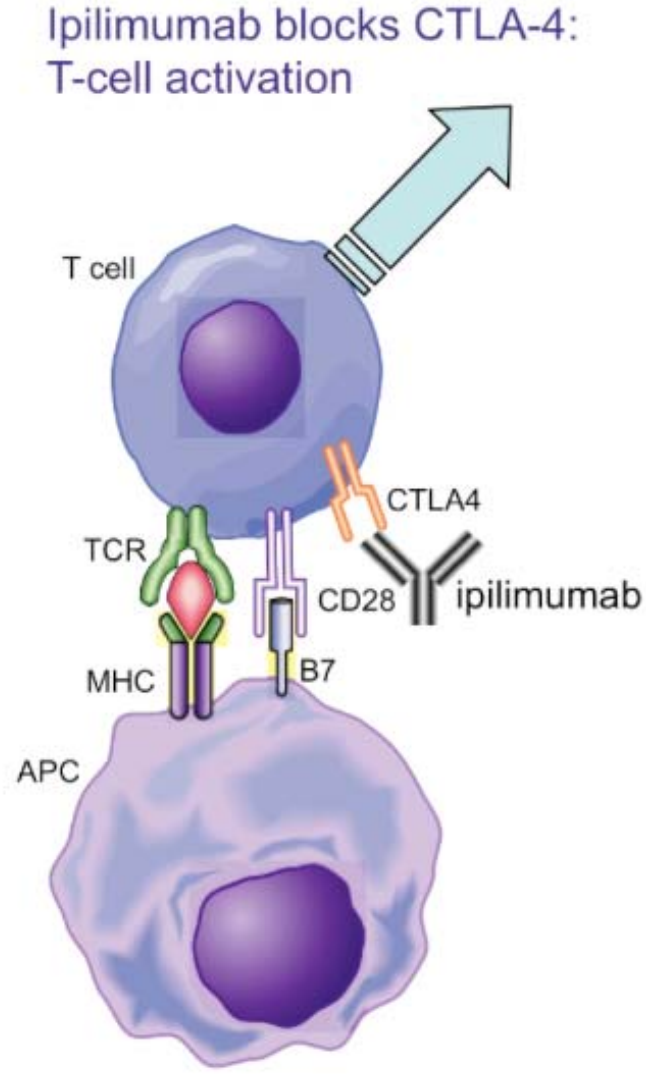


Inmunoterapia

- CTLA 4

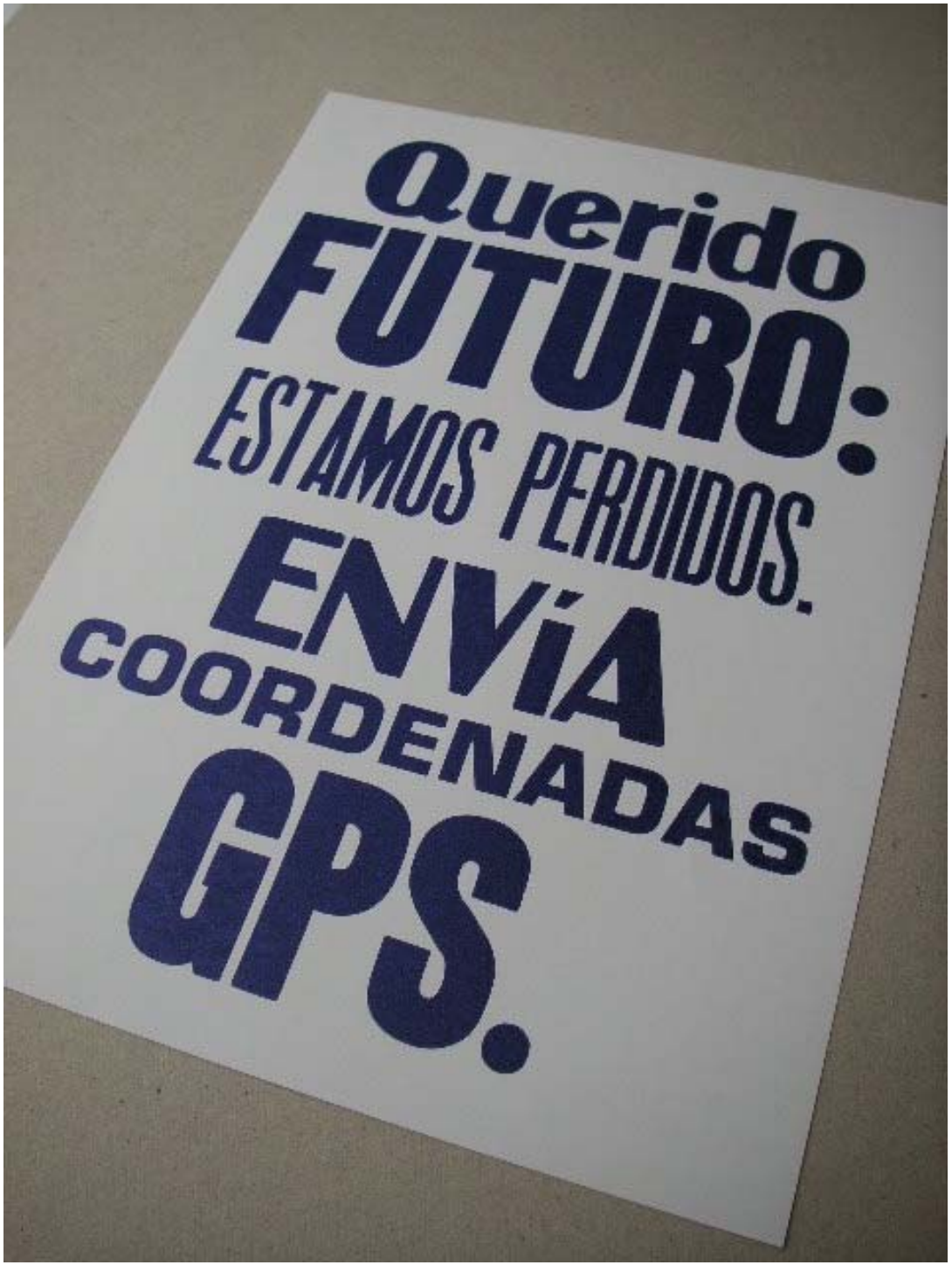
(cytotoxic T-Lymphocyte-associated antigen 4):

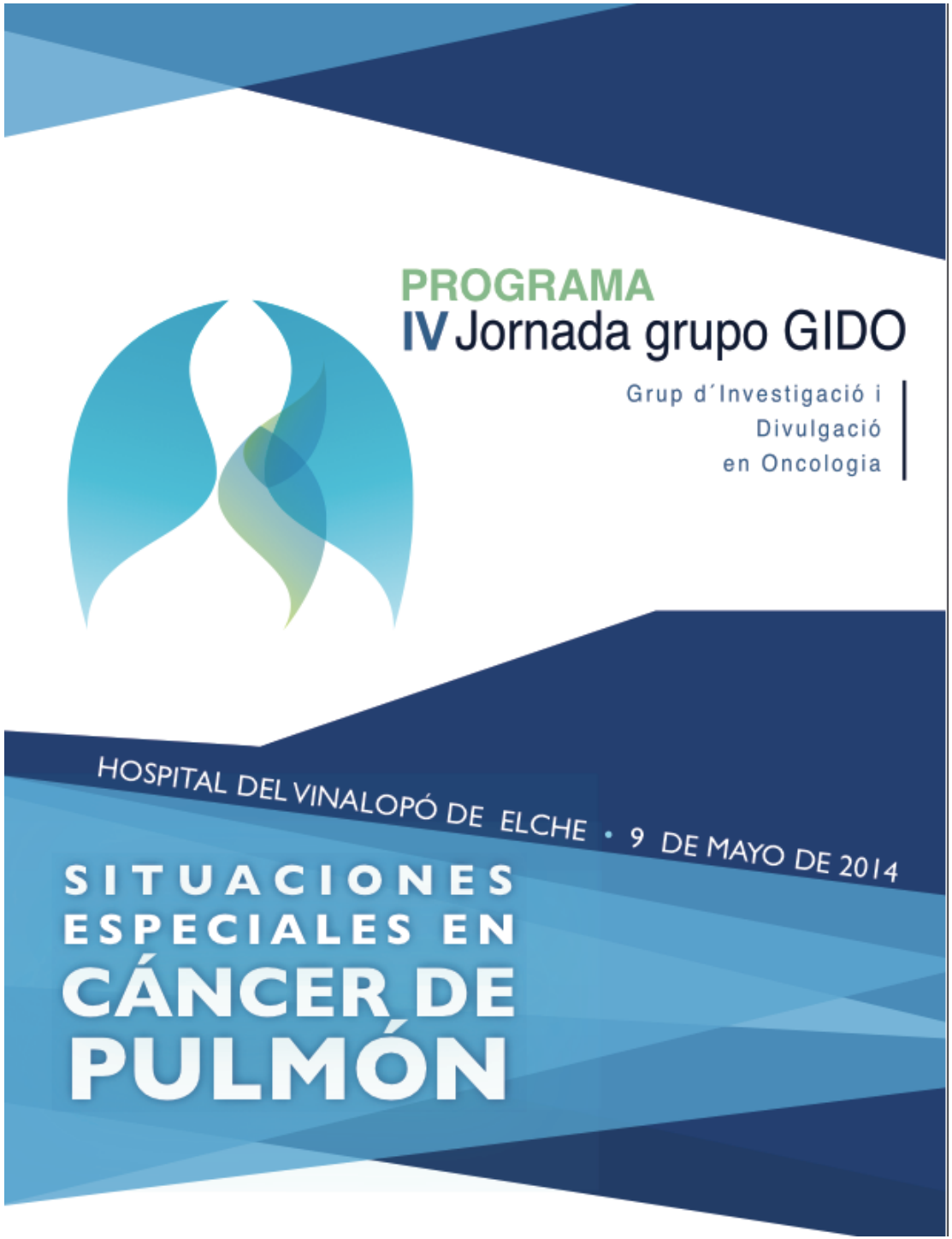
  – Ipilimumab.



CONCLUSIONES

- C.P. Escamoso: 1/3 de CPNCP.
- Retraso en el desarrollo terapéutico.
- Identificación alteraciones moleculares: “road map”. Complejo.
- Futuro: Inmunoterapia y ttos. Moleculares.
- Presente: 2ªL: Quimioterapia (docetaxel).


Querido
FUTURO:
ESTAMOS PERDIDOS.
ENVíA
COORDENADAS
GPS.



SEGUNDAS LINEAS DE TRATAMIENTO:

CARCINOMA ESCAMOSO

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