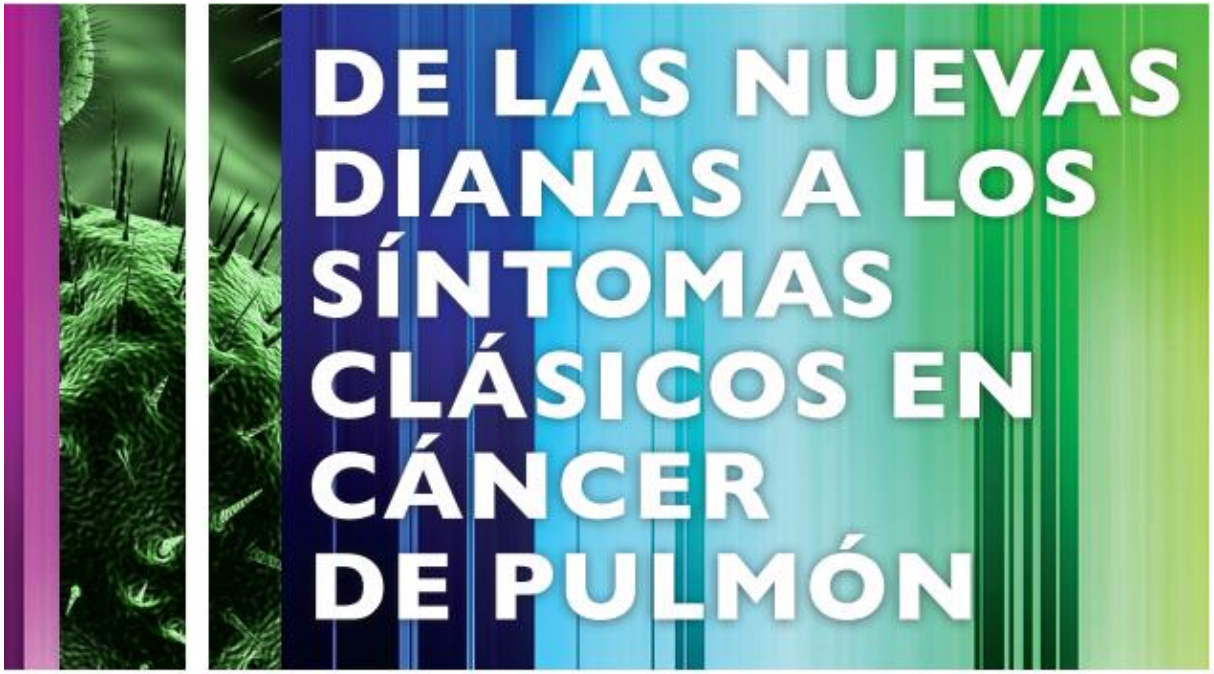
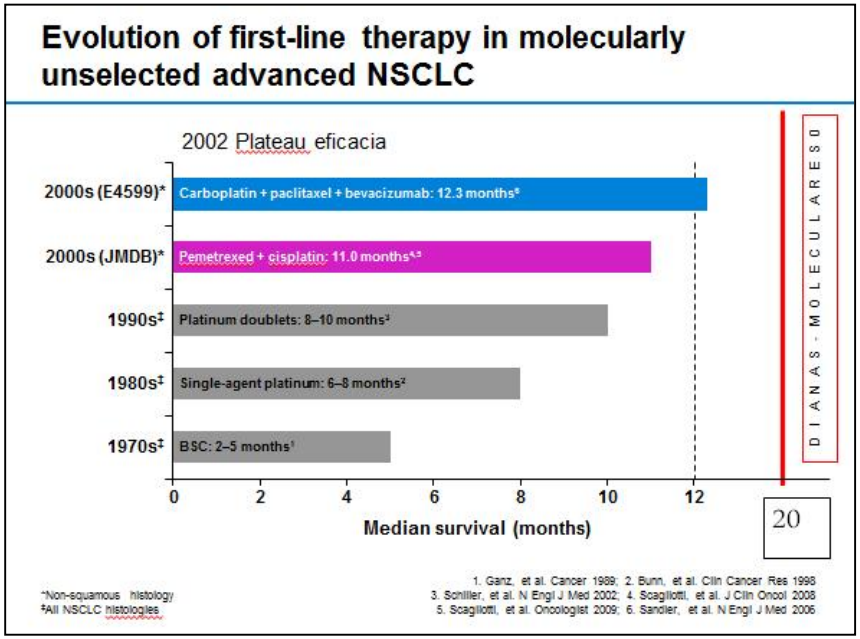
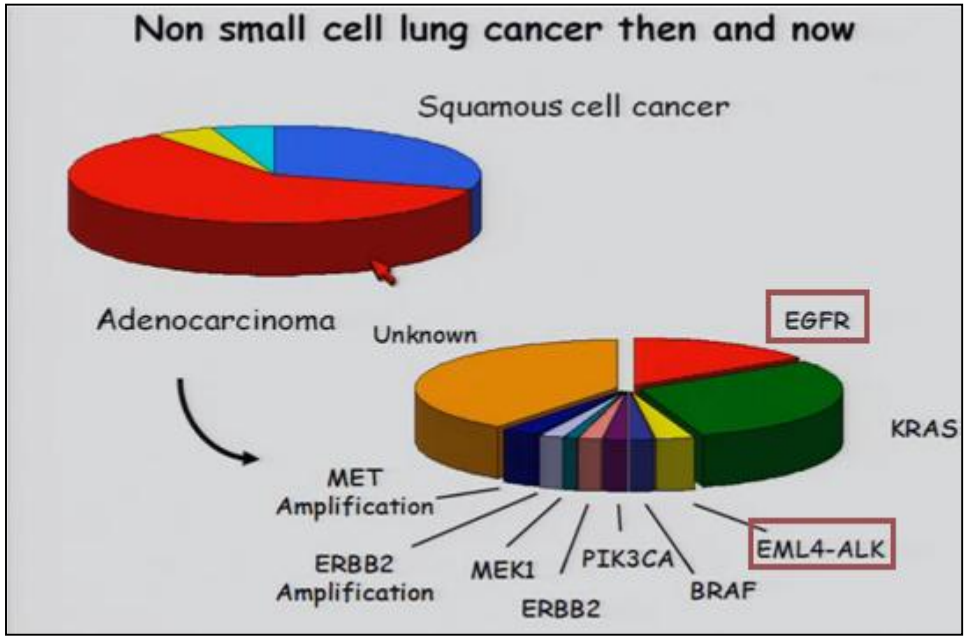


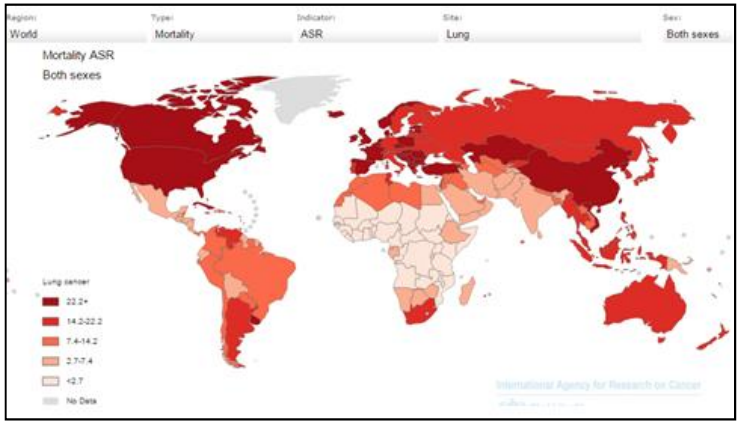
EGFR

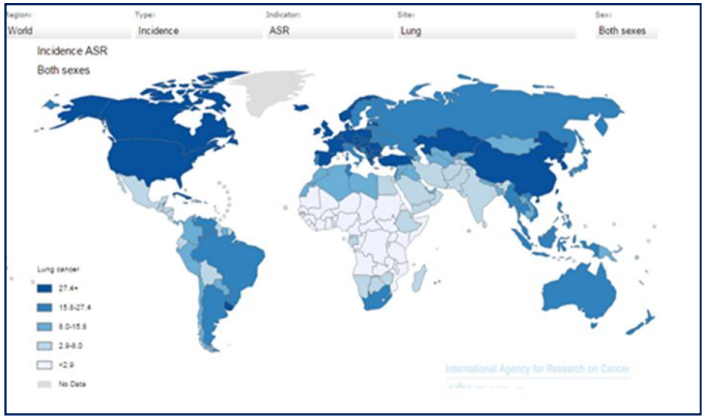
Dra. Mar Llorente . Hospital General de Elda.

Introducción

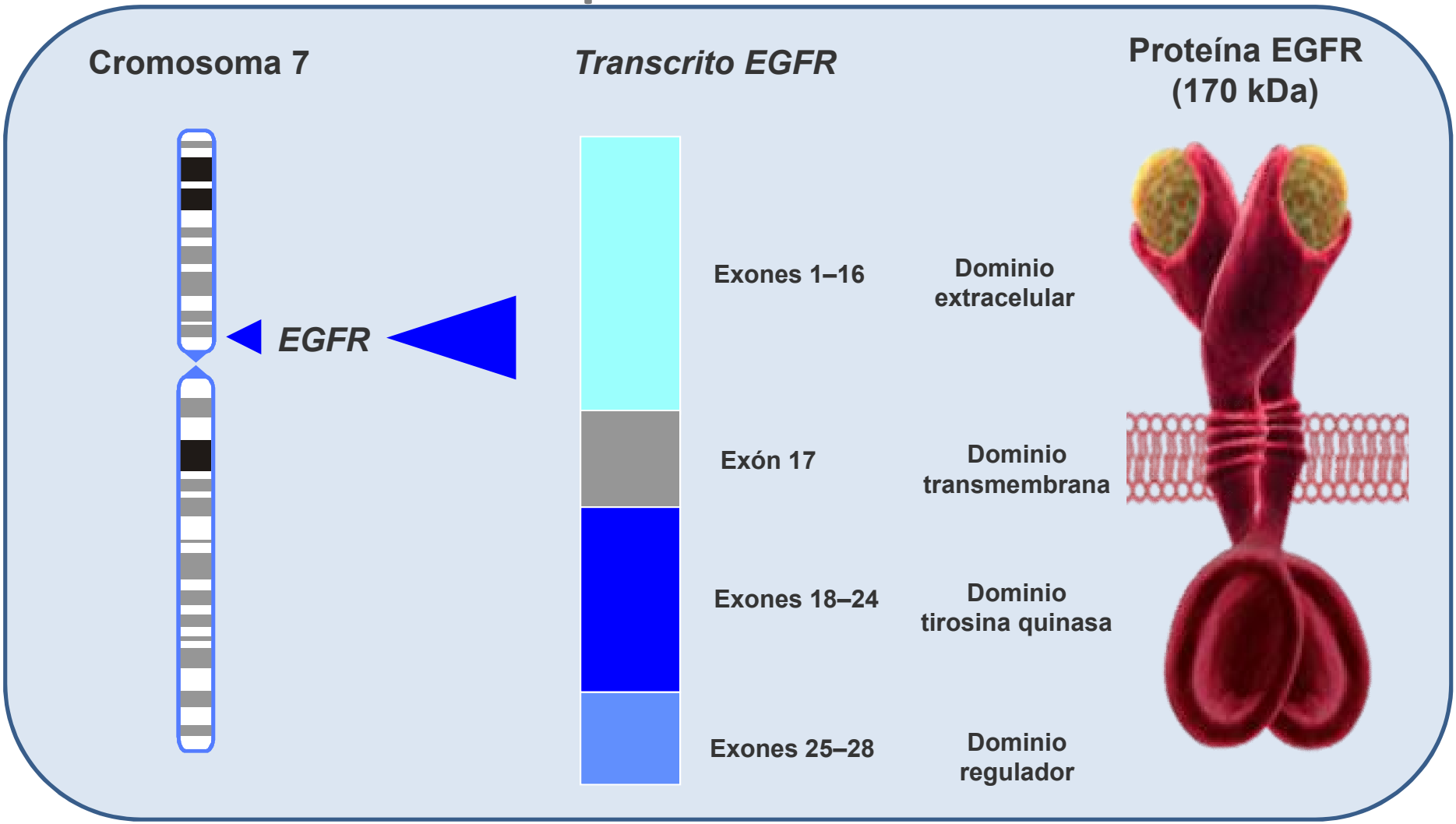






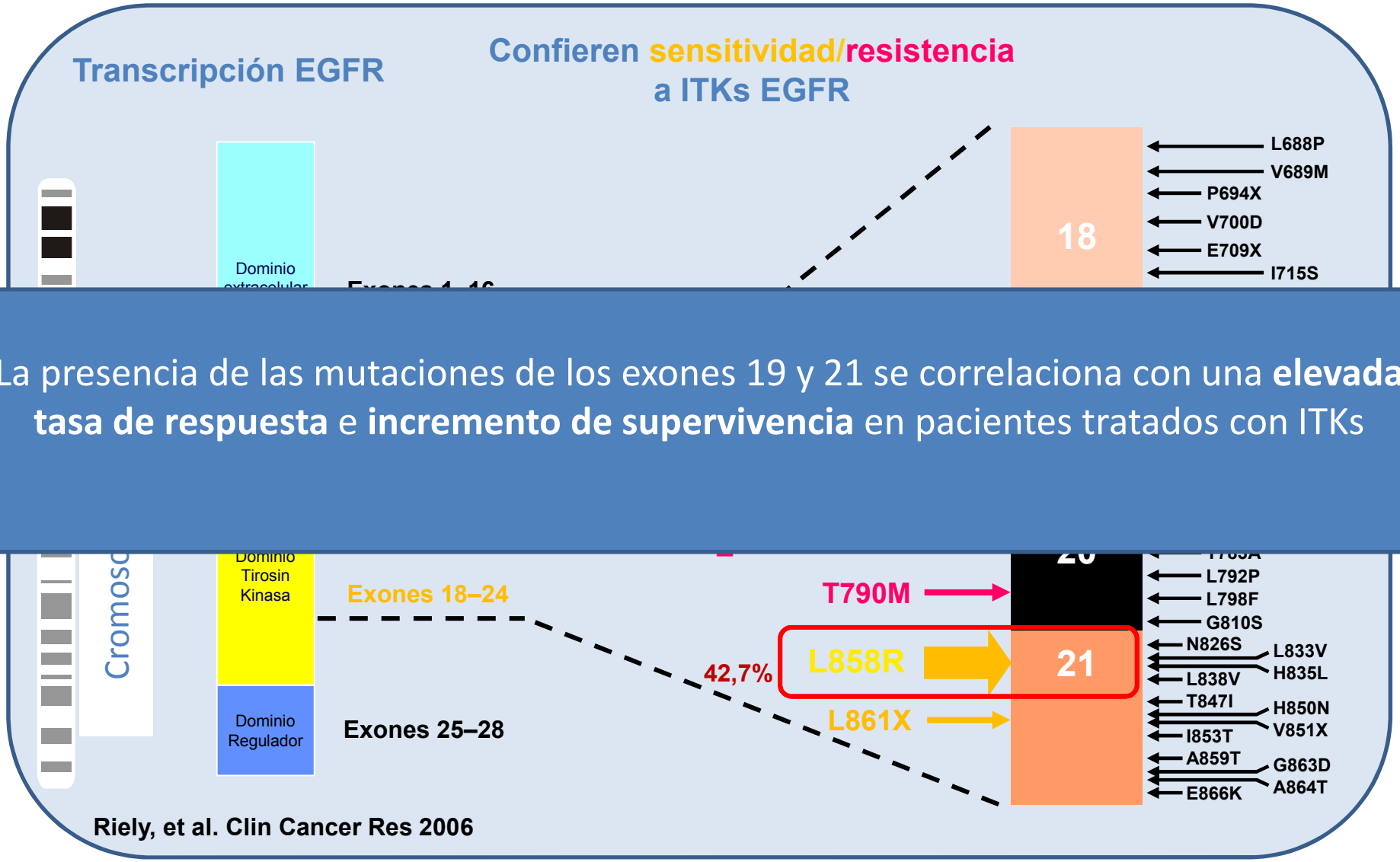


Localización del EGFR, gen y proteína



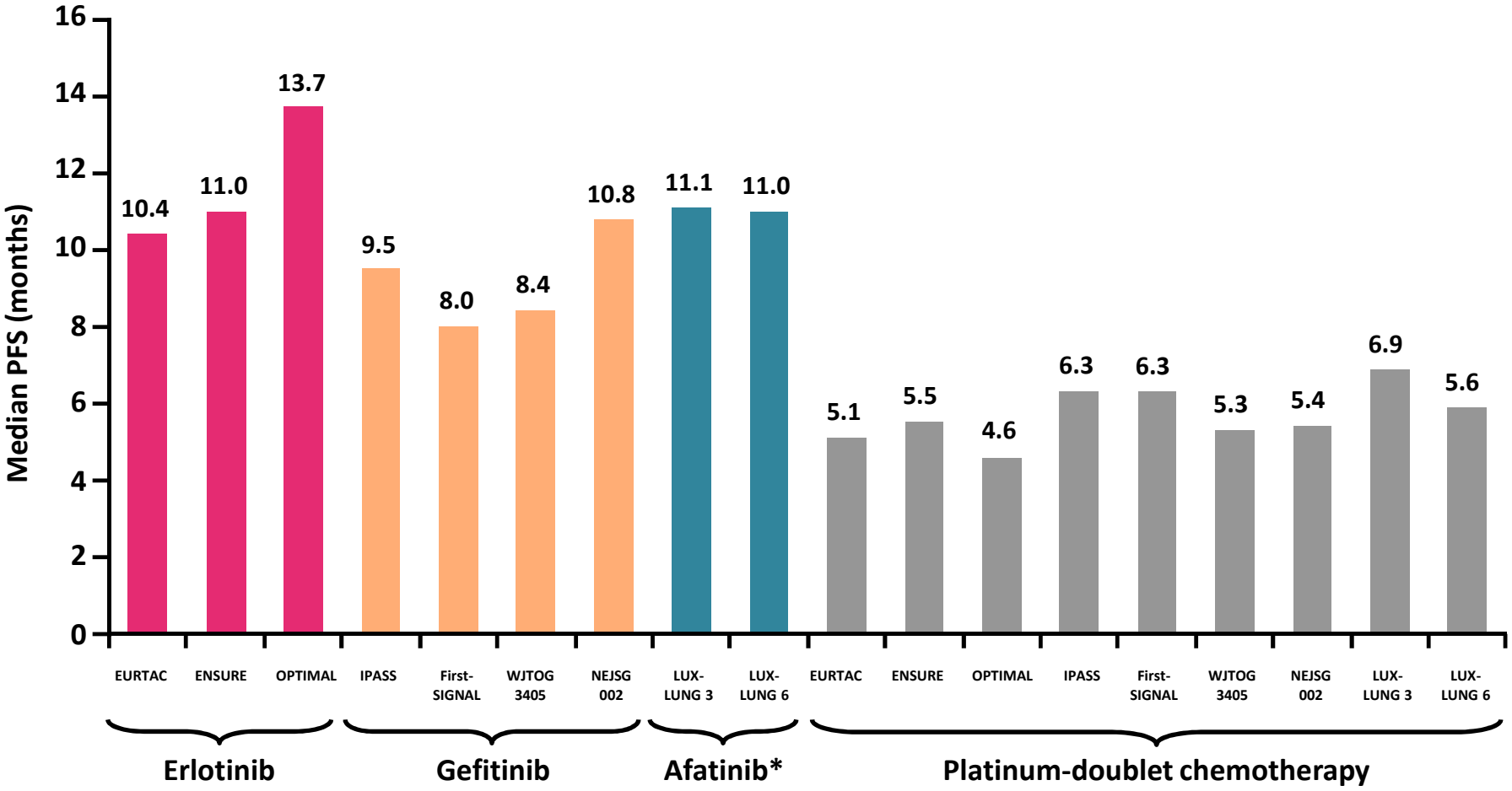
Mitsudomi, et al. Int J Clin Oncol 2006; Riely, et al. Clin Cancer Res 2006

Mutaciones identificadas en el gen EGFR



La presencia de las mutaciones de los exones 19 y 21 se correlaciona con una **elevada tasa de respuesta** e **incremento de supervivencia** en pacientes tratados con ITKs

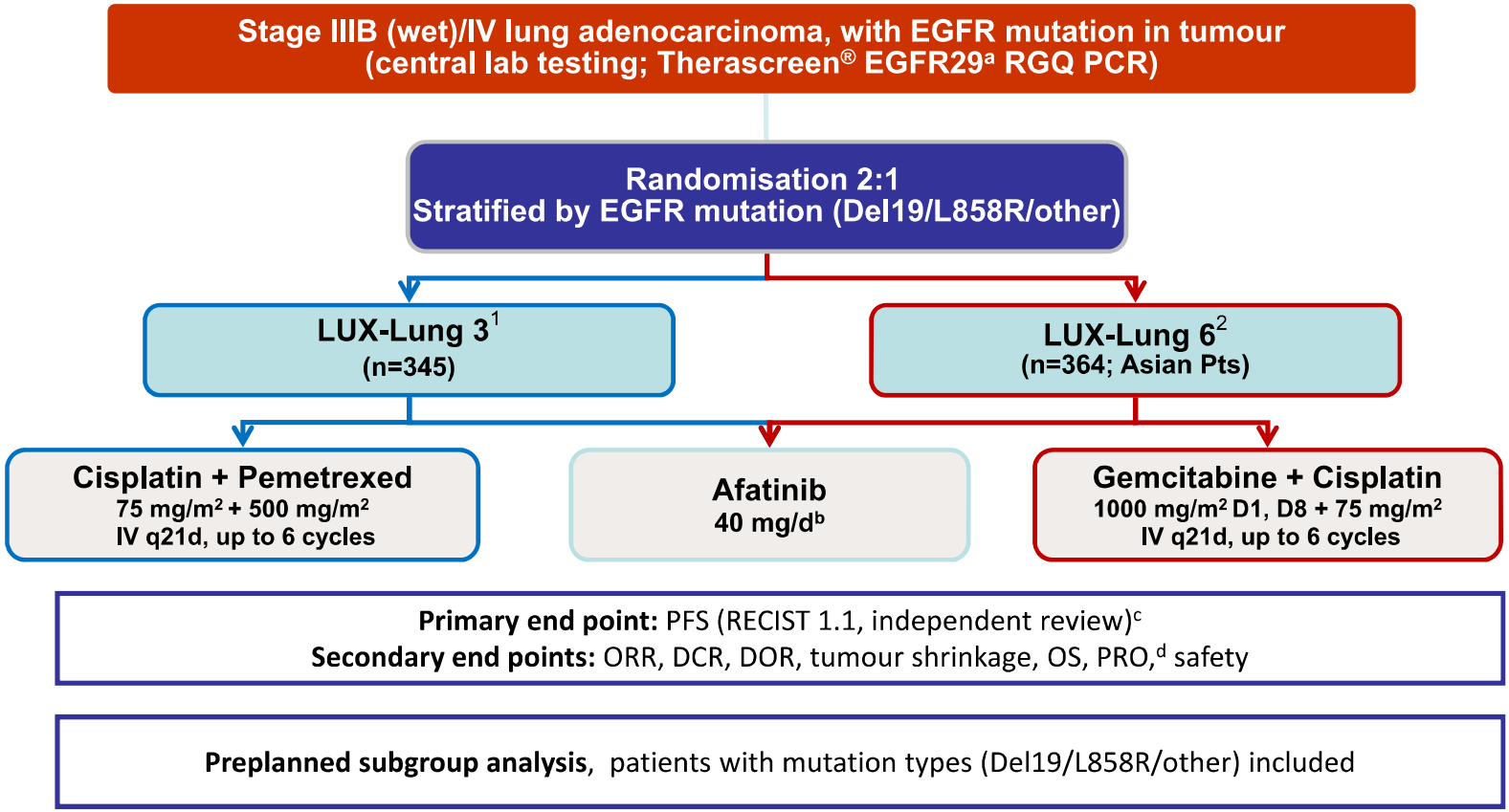
First-line EGFR TKIs demonstrate improved PFS vs chemotherapy in EGFR Mut+ NSCLC



Cross-trial comparison. Data should be interpreted with caution
*All *EGFR* mutations

Costa, et al. Clin Cancer Res 2014; Wu, et al. WCLC 2013; Chen, et al. Ann Oncol 2013
Gefitinib SmPC 2010; Han, et al. J Clin Oncol 2012; Mitsudomi, et al. Lancet Oncol 2010
Maemondo, et al. N Engl J Med 2010; Sequist, et al. J Clin Oncol 2013; Wu, et al. Lancet Oncol 2014

Diseño de LUX-Lung 3 y 6



Primary end point: PFS (RECIST 1.1, independent review)[c]
Secondary end points: ORR, DCR, DOR, tumour shrinkage, OS, PRO,[d] safety

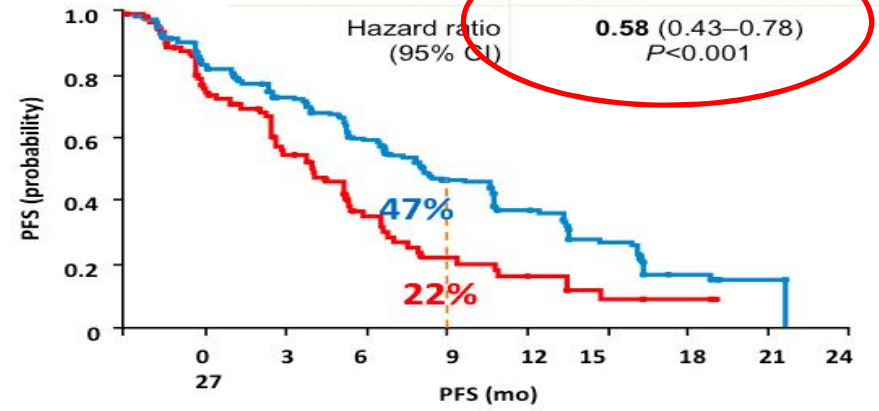
Preplanned subgroup analysis, patients with mutation types (Del19/L858R/other) included

1. Sequist et al. J Clin Oncol. 2013.
2. Wu et al. Lancet Oncol, 2014

LUX-Lung 3: PFS

PFS in Overall Population

	Afatinib (n=230)	Cis/Pem (n=115)
PFS event, n (%)	152 (66)	69 (60)
Median PFS (mo)	**11.14**	**6.90**
Hazard ratio (95% CI)	**0.58** (0.43–0.78) *P*<0.001	

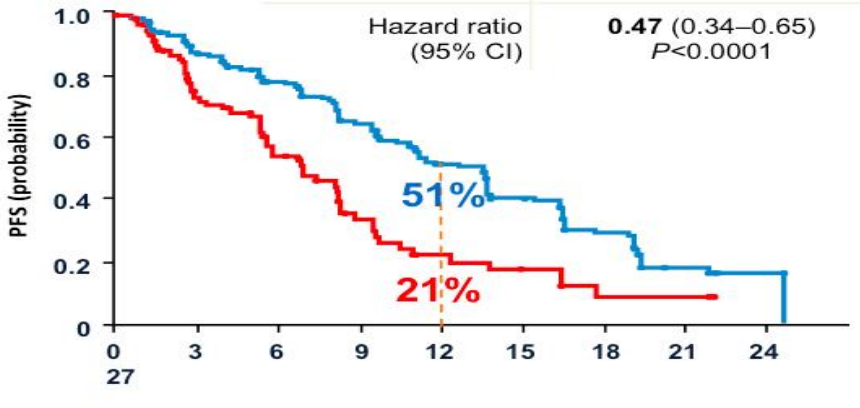


Number at risk:

Afatinib	230	180	151	120	77	50	31	10	3	0
Cis/Pem	115	72	41	21	11	7	3	2	0	0

PFS in Patients With Common Mutations

	Afatinib (n=204)	Cis/Pem (n=104)
PFS event, n (%)	130 (64)	61 (59)
Median PFS (mo)	**13.6**	**6.9**
Hazard ratio (95% CI)	**0.47** (0.34–0.65) *P*<0.0001	



Number at risk:

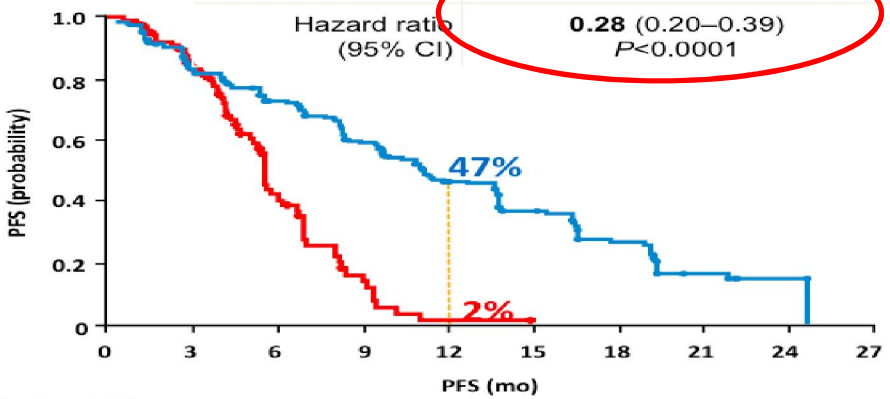
Afatinib	204	169	143	115	75	49	30	10	3	0
Cis/Pem	104	62	35	17	9	6	2	2	0	0

Sequist et al. *J Clin Oncol*. 2013;31:3327.

LUX-Lung 6: PFS

PFS by Independent Review

	Afatinib (n=242)	Gem/Cis (n=122)
Median PFS (mo)	**11.0**	**5.6**
Hazard ratio (95% CI)	**0.28** (0.20–0.39) *P*<0.0001	

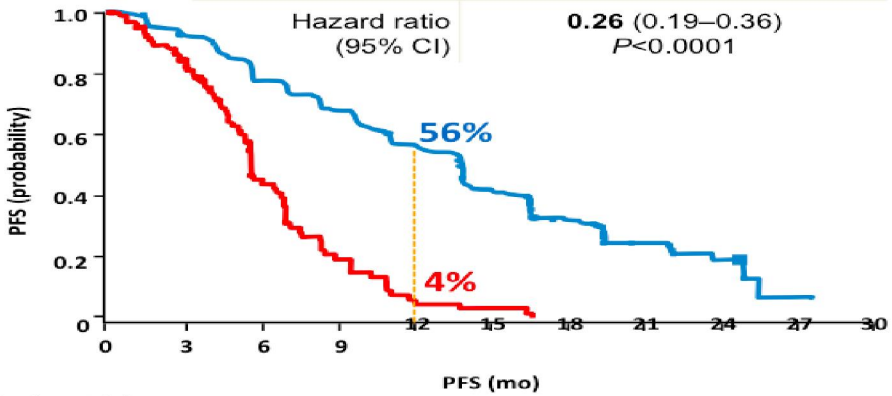


Number at risk:

Afatinib	242	208	166	126	89	60	35	12	4	0
Gem/Cis	122	70	25	8	1	0	0	0	0	0

PFS by Investigator Review

	Afatinib (n=242)	Gem/Cis (n=122)
Median PFS (mo)	**13.7**	**5.6**
Hazard ratio (95% CI)	**0.26** (0.19–0.36) *P*<0.0001	

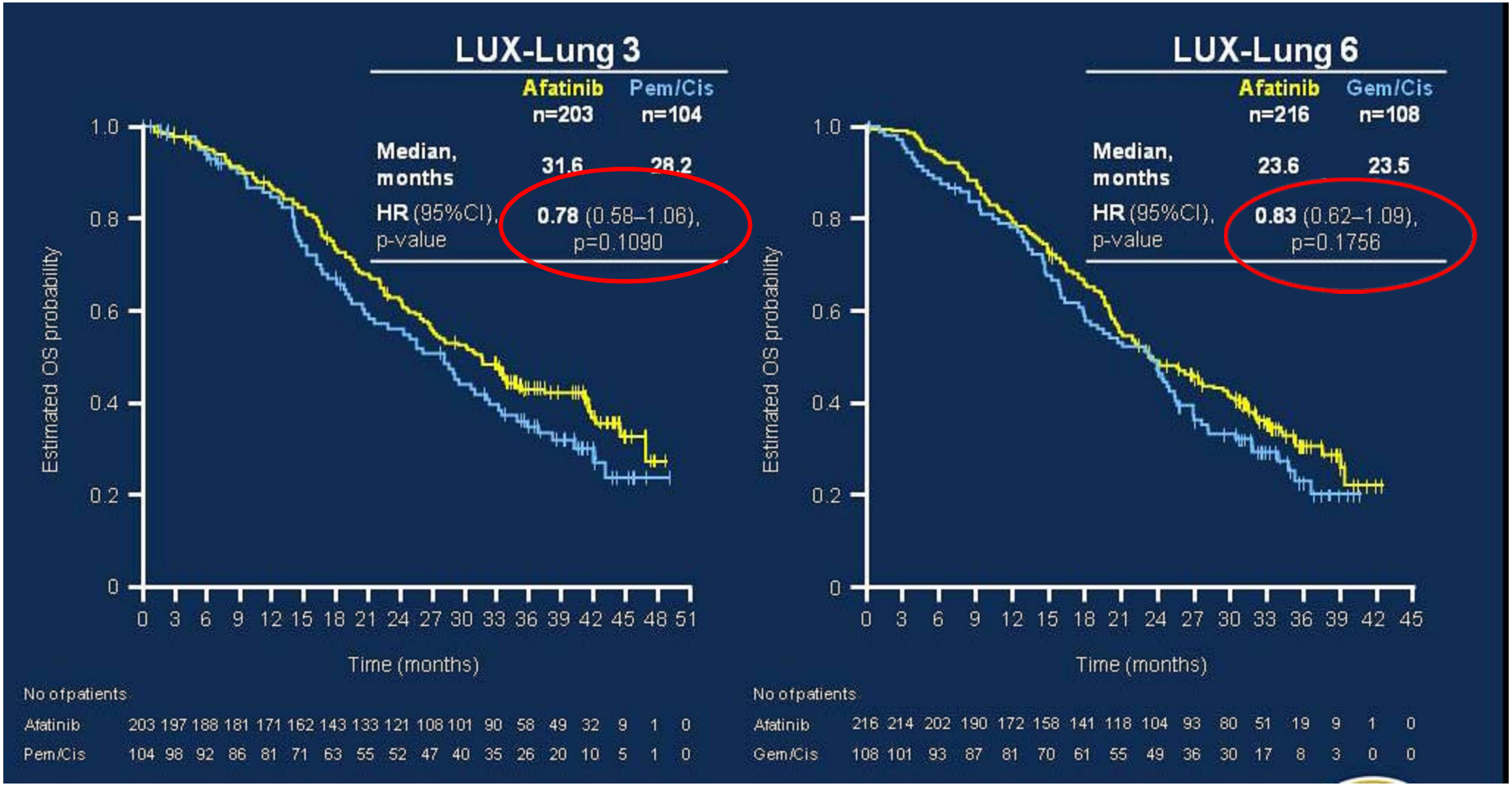


Number at risk:

Afatinib	242	211	178	157	124	87	49	23	10	1	0
Gem/Cis	122	75	31	13	3	2	0	0	0	0	0

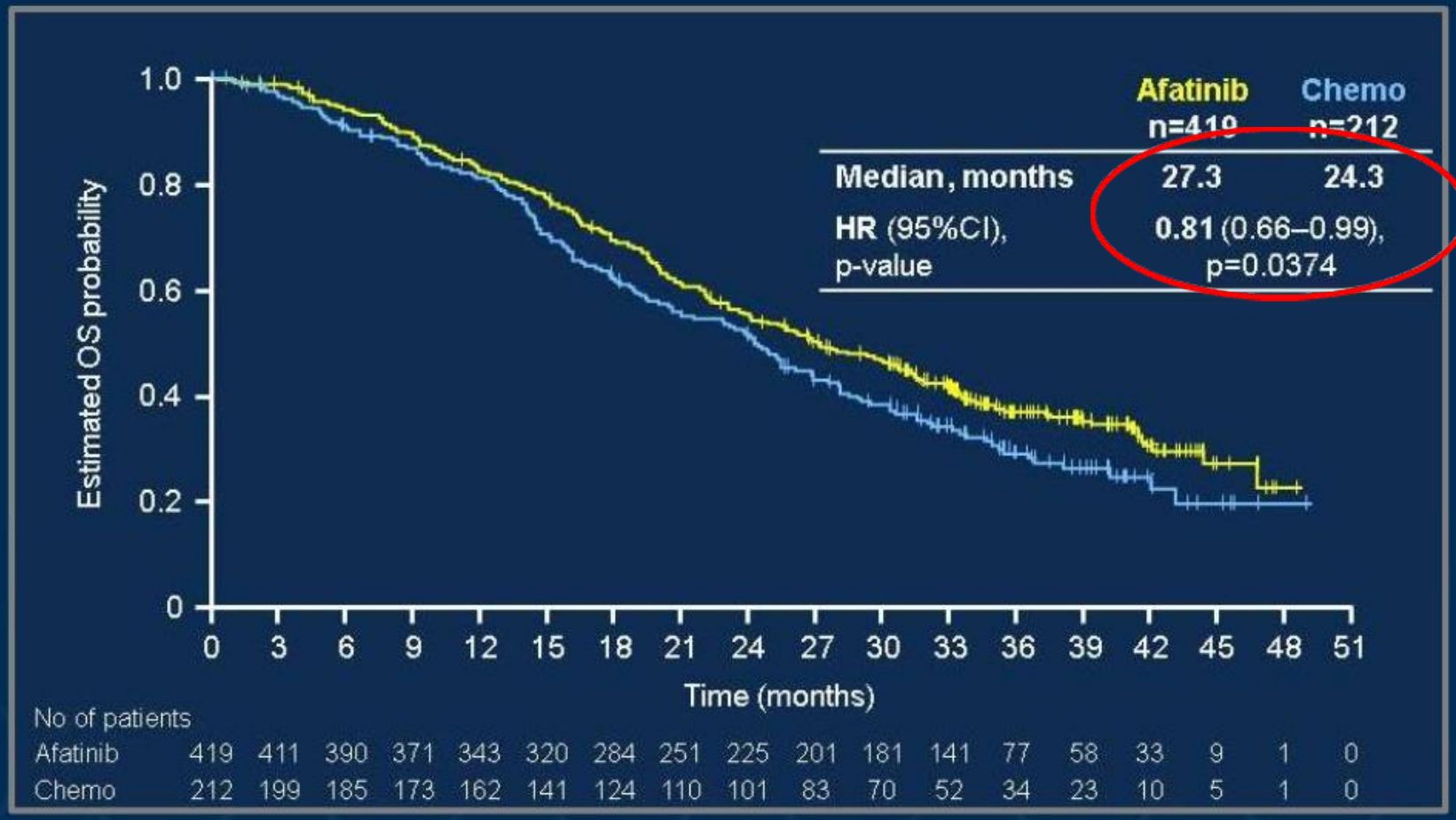
Wu et al. Lancet Oncol. 2014;15:213

SG: LUX Lung 3 y 6. Mutaciones comunes



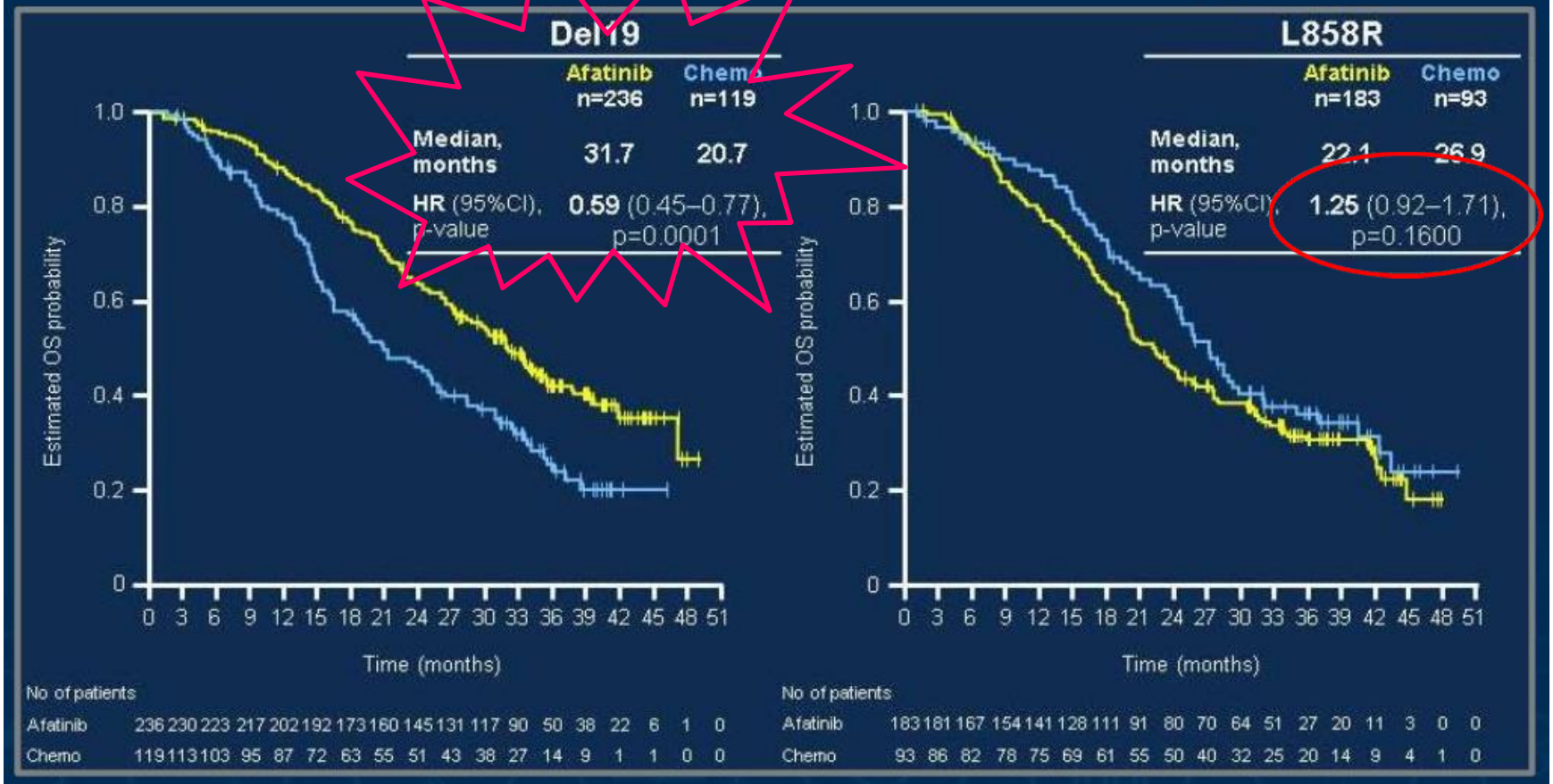
Yang J, ASCO, 2014

Combined OS Analysis: LUX-Lung 3, LUX-Lung 6 (Del 19 and L858R only)



Yang, A#8004

Combined OS Analysis: LUX-Lung 3, LUX-Lung 6 by Mutation Subtype



Yang, A#8004

Comparativa ITKs

	% of Patients			
	LUX-Lung 3 Afatinib (n=229)	**LUX-Lung 6 Afatinib (n=239)**	**EURTAC[1] Erlotinib (n=84)**	**IPASS[2] Gefitinib (n=607)**
Treatment-related AEs	99.6	98.7	93	NR
Any grade ≥3	60.7	46.9	45	28.7
Dose reduction due to AE	**57.2**	**32.2**	21	16.1 (modification)
Discontinuation due to AE	7.9 (related)	5.9 (related)	6 (related)	6.9
Any serious AE	28.8	15.1	32	16.3
Fatal serious AE	1.7 (related)	0.4 (related)	1 (related)	3.8
ILD-like	1.3	0.4	1	2.6

1. Rosell et al. *Lancet Oncol.* 2012;13:239;
2. Mok et al. *N Engl J Med.* 2009;361:947.

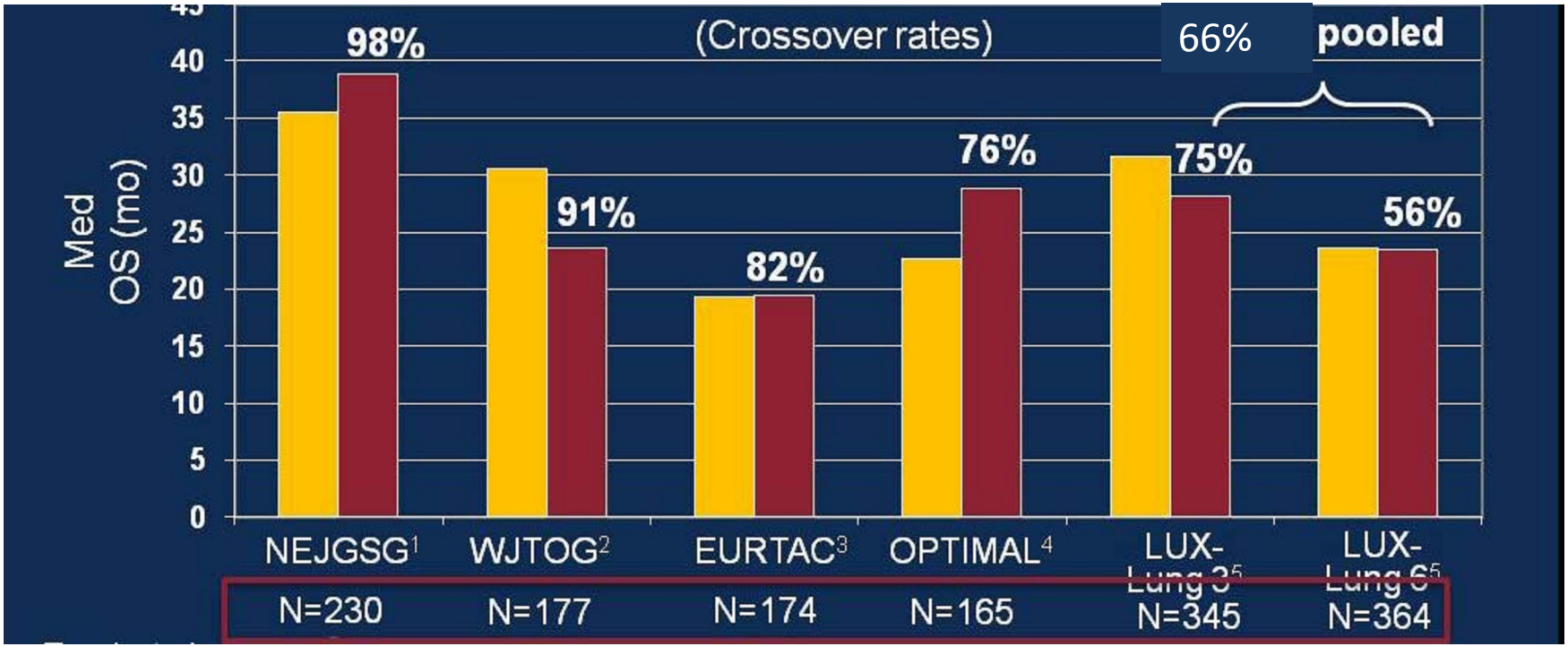
Table 3. Selected Toxicities in Phase III Erlotinib and Afatinib Trials

		Diarrhea		Rash		Paronychia		Stomatitis		
Trial	Agent	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)	Tx D/C
EURTAC	Erlotinib	57	5	80	13	NR		NR		6
OPTIMAL	Erlotinib	25	1	61	2	4	0	13	1	0
LUX-Lung 3	Afatinib	95	14	89	16	57	11	72	8.7	8
LUX-Lung 6	Afatinib	**88**	5.4	**81**	14.6	**33**	**0**	**52**	5.4	5.9

Abbreviations: EURTAC, European Tarceva versus Chemotherapy; N … t reported; Tx D/C, treatment discontinuation because of drug-related adverse event.

Langer, J Clin Oncol, 2013

LUX Lung 3/6: Tratamientos de segunda línea



West, ASCO, 2014

¿Qué ITK utilizamos en 1º Linea?

Últimas revisiones sistemáticas publicadas

1. Haaland et al

Meta-Analysis of First-Line Therapies in Advanced Non–Small-Cell Lung Cancer Harboring *EGFR*-Activating Mutations

Benjamin Haaland, PhD,† Pui San Tan, MPharm,‡ Gilberto de Castro, Jr, MD, PhD,§ and Gilberto Lopes, MD, MBA, FAMS‖¶*

2. Haspinger et al

Is there evidence for different effects among EGFR-TKIs? Systematic review and meta-analysis of EGFR tyrosine kinase inhibitors (TKIs) *versus* chemotherapy as first-line treatment for patients harboring EGFR mutations

Table 2
Overall results of comparisons between TKIs and chemotherapy (CT) and overall results of indirect comparisons among TKIs.

Outcome	Gefitinib *versus* Chemotherapy	Conclusion	Erlotinib *versus* Chemotherapy	Conclusion	Afatinib *versus* chemotherapy	Conclusion	Gefitinib *versus* Afatinib (ind. comp.)	Conclusion	Erlotinib *versus* Afatinib (ind. comp.)	Conclusion	Gefitinib *versus* Erlotinib (ind. comp.)	Conclusion
Progression-free survival												
Hazard ratio (HR) (95% CI)	HR = 0.43 (0.32, 0.56) I^2 = 54%	Gefitinib better	HR = 0.32 (0.16, 0.65) I^2 = 54%	Erlotinib better	HR = 0.41 (0.20, 0.82) I^2 = 90%	Afatinib better	HR = 1.05 (0.61, 1.81)	No difference	HR = 0.78 (0.39, 1.55)	No difference	HR = 1.34 (0.63, 2.86)	No difference
Progression-free survival (exon 19 deletion)												
Hazard ratio (HR) (95% CI)	HR = 0.40 (0.29, 0.55) I^2 = 0%	Gefitinib better	HR = 0.20 (0.09, 0.46) I^2 = 76%	Erlotinib better	HR = 0.24 (0.17, 0.33) I^2 = 4%	Afatinib better	HR = 1.67 (1.05, 2.64)	Afatinib better	HR = 0.83 (0.35, 2.01)	No difference	HR = 2.00 (0.83, 4.80)	No difference
Progression-free survival (L858R mutation)												
Hazard ratio (HR) (95% CI)	HR = 0.53 (0.38, 0.76) I^2 = 0%	Gefitinib better	HR = 0.38 (0.18, 0.79) I^2 = 64%	Erlotinib better	HR = 0.49 (0.22, 1.10) I^2 = 54%	No difference	HR = 1.08 (0.45, 2.60)	No difference	HR = 0.78 (0.26, 2.32)	No difference	HR = 1.39 (0.62, 3.16)	No difference
Overall survival												
Hazard ratio (HR) (95% CI)	HR = 1.00 (0.83, 1.20) I^2 = 0%	No difference	HR = 1.11 (0.83, 1.50) I^2 = 0%	No difference	HR = 1.01 (0.77, 1.32) I^2 = 0%	No difference	HR = 0.91 (0.65, 1.26)	No difference	HR = 1.10 (0.74, 1.64)	No difference	HR = 0.90 (0.68, 1.19)	No difference
Objective response rate												
Risk ratio (RR) (95% CI)	RR = 2.45 (2.03, 2.95) I^2 = 0%	Gefitinib better	RR = 2.54 (1.80, 3.59) I^2 = 28%	Erlotinib better	RR = 2.70 (2.12, 3.45) I^2 = 0%	Afatinib better	RR = 0.91 (0.67, 1.23)	No difference	RR = 0.94 (0.65, 1.35)	No difference	RR = 0.96 (0.69, 1.34)	No difference
Diarrhea												
Risk ratio (RR) (95% CI)	RR = 2.00 (1.40, 2.85) I^2 = 80%	Chemoth. better	RR = 2.55 (1.42, 4.56) I^2 = 75%	Chemoth. better	RR =6.98 (4.97, 9.81) I^2 = 91%	Chemoth. better	RR = 0.29 (0.20, 0.41)	Gefitinib better	RR = 0.36 (0.25, 0.54)	Erlotinib better	RR = 0.80 (0.63, 1.01)	No difference
Rash												
Risk ratio (RR) (95% CI)	RR = 4.42 (2.82, 6.92) I^2 = 84%	Chemoth. better	RR = 4.42 (1.57, 12.44) I^2 = 93%	Chemoth. better	RR = 10.90 (6.89, 17.24) I^2 = 91%	Chemoth. better	RR = 0.41 (0.25, 0.65)	Gefitinib better	RR = 0.41 (0.25, 0.66)	Erlotinib better	RR = 1.00 (0.82, 1.22)	No difference

ClinicalTrials.gov

A service of the U.S. National Institutes of Health

LUX-Lung 7: A Phase IIb Trial of Afatinib(BIBW2992) Versus Gefitinib for the Treatment of 1st Line EGFR Mutation Positive Adenocarcinoma of the Lung

This study is ongoing, but not recruiting participants.

Sponsor:
Boehringer Ingelheim

Information provided by (Responsible Party):
Boehringer Ingelheim

ClinicalTrials.gov Identifier:
NCT01466660

First received: November 4, 2011
Last updated: February 4, 2015
Last verified: February 2015
History of Changes

ARCHER-1050: A Study of Dacomitinib vs. Gefitinib in 1st-Line Treatment Of Advanced NSCLC. (ARCHER 1050)

This study is currently recruiting participants. (see Contacts and Locations)

Verified January 2015 by SFJ Pharmaceuticals, Inc.

Sponsor:
SFJ Pharmaceuticals, Inc.

Collaborator:

ClinicalTrials.gov Identifier:
NCT01774721

First received: January 21, 2013
Last updated: January 7, 2015
Last verified: January 2015
History of Changes

ARCHER 1009 : A Study Of Dacomitinib (PF-00299804) Vs. Erlotinib In The Treatment Of Advanced Non-Small Cell Lung Cancer

This study is ongoing, but not recruiting participants.

Sponsor:
Pfizer

Information provided by (Responsible Party):
Pfizer

ClinicalTrials.gov Identifier:
NCT01360554

First received: April 12, 2011
Last updated: February 16, 2015
Last verified: February 2015
History of Changes

Study With Gefitinib in Combination With Olaparib (AZD2281) Versus Gefitinib Alone (GOAL)

This study is currently recruiting participants. (see Contacts and Locations)

Verified March 2013 by Spanish Lung Cancer Group

Sponsor:
Spanish **Lung Cancer** Group

Information provided by (Responsible Party):
Spanish Lung Cancer Group

ClinicalTrials.gov Identifier:
NCT01513174

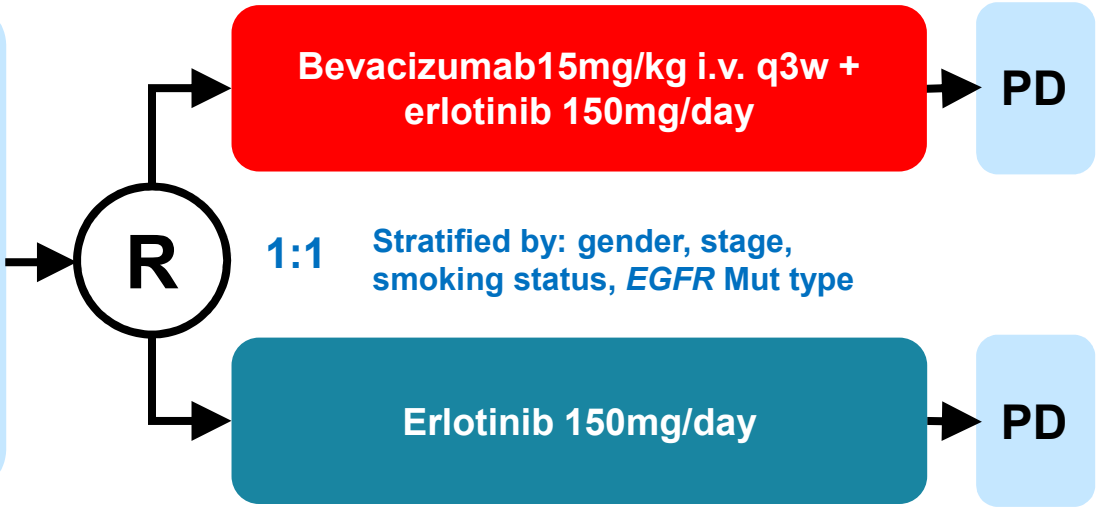
First received: December 11, 2011
Last updated: November 18, 2014
Last verified: March 2013
History of Changes

Improving the standard of care: new combinations

JO25567 phase II study of 1L erlotinib ± bevacizumab in *EGFR* Mut+ NSCLC

- Stage IIIB/IV or recurrent NSCLC
- Non-squamous histology
- *EGFR* Mut+
  - exon 19 deletion / L858R*
- No prior treatment
- ECOG PS 0–1

(n=152)



Primary endpoint
- PFS by independent review

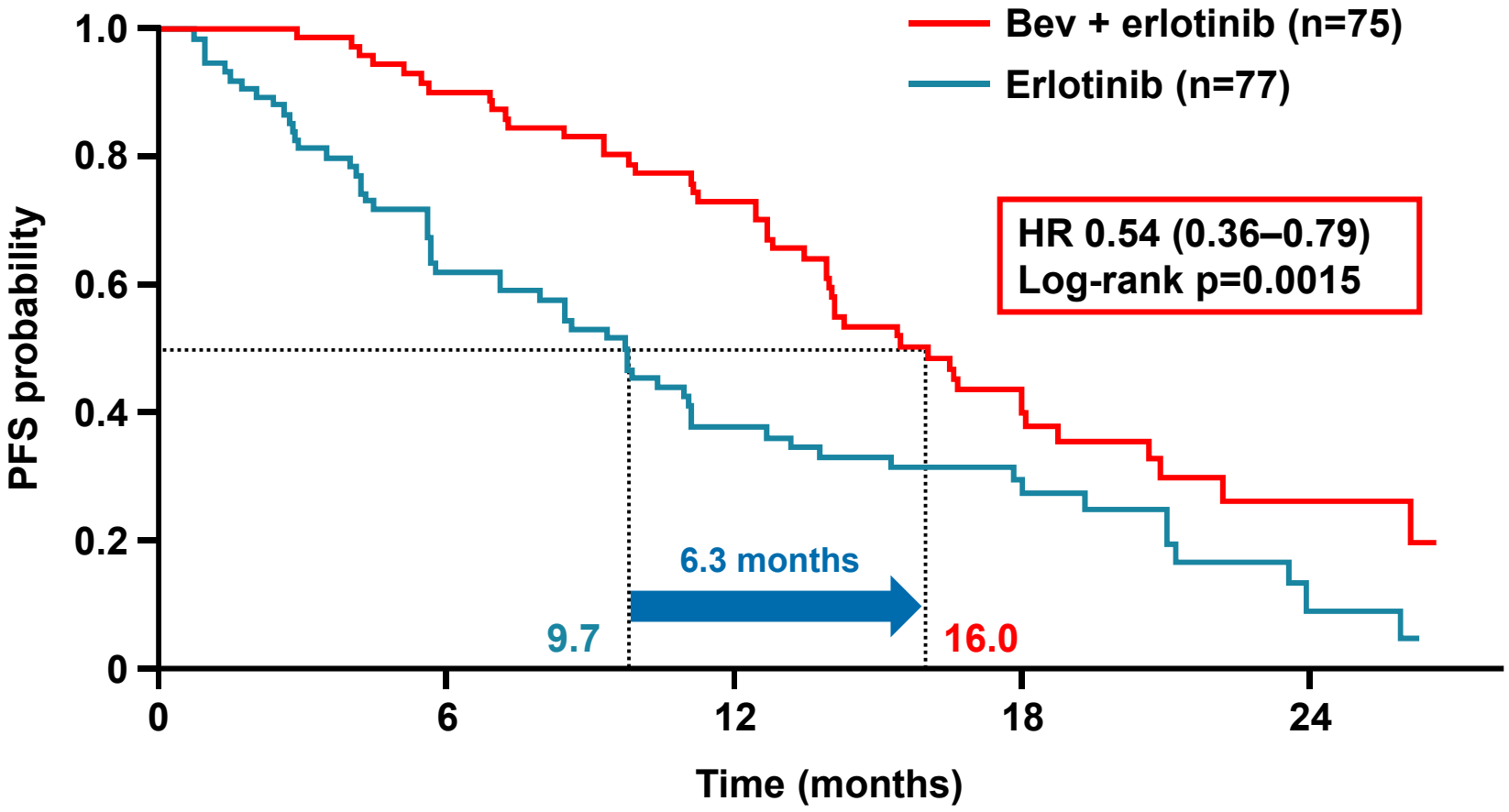
Secondary endpoints
- OS
- ORR
- DCR
- Response duration
- QoL
- Safety

Exploratory endpoints
- Biomarkers

*T790M excluded; *EGFR* mutation assays performed at investigational site using: PNA LNA PCR Clamp PCR-Invader, Cycleave or 'Other' methods
This study involves the off-label use of erlotinib. In Malaysia, erlotinib monotherapy is indicated for first-line treatment of patients with locally advanced or metastatic NSCLC with activating *EGFR* mutations

JapicCTI-111390
Seto, et al. Lancet Oncol 2014

JO25567: PFS by independent review in all patients (primary endpoint)



This study involves the off-label use of erlotinib. In Malaysia, erlotinib monotherapy is indicated for first-line treatment of patients with locally advanced or metastatic NSCLC with activating *EGFR* mutations

Seto, et al. Lancet Oncol 2014

JO25567:
toxicity (AEs occurring in >20% patients)

	Bev + erlotinib (n=75)		Erlotinib (n=77)	
%	All grades	Grade ≥3	All grades	Grade ≥3
Rash	99	25	99	19
Diarrhoea	81	1	78	1
Hypertension	76	60	13	10
Paronychia	76	3	65	4
Dry skin	75	3	58	0
Hemorrhagic event	72	3	29	0
Stomatitis	63	1	60	3
Proteinuria	52	8	4	0
Pruritus	45	1	42	0
Hepatic dysfunction	44	8	51	18
Decreased weight	44	0	25	0
Decreased appetite	35	1	34	1
Dysgeusia	27	0	22	0
Nasopharyngitis	27	0	19	0
Constipation	23	0	19	1

This study involves the off-label use of erlotinib. In Malaysia, erlotinib monotherapy is indicated for first-line treatment of patients with locally advanced or metastatic NSCLC with activating *EGFR* mutations

Seto, et al. Lancet Oncol 2014

Erlotinib/Bevacizumab vs. Erlotinib for EGFR Mutation-Positive Adv NSCLC

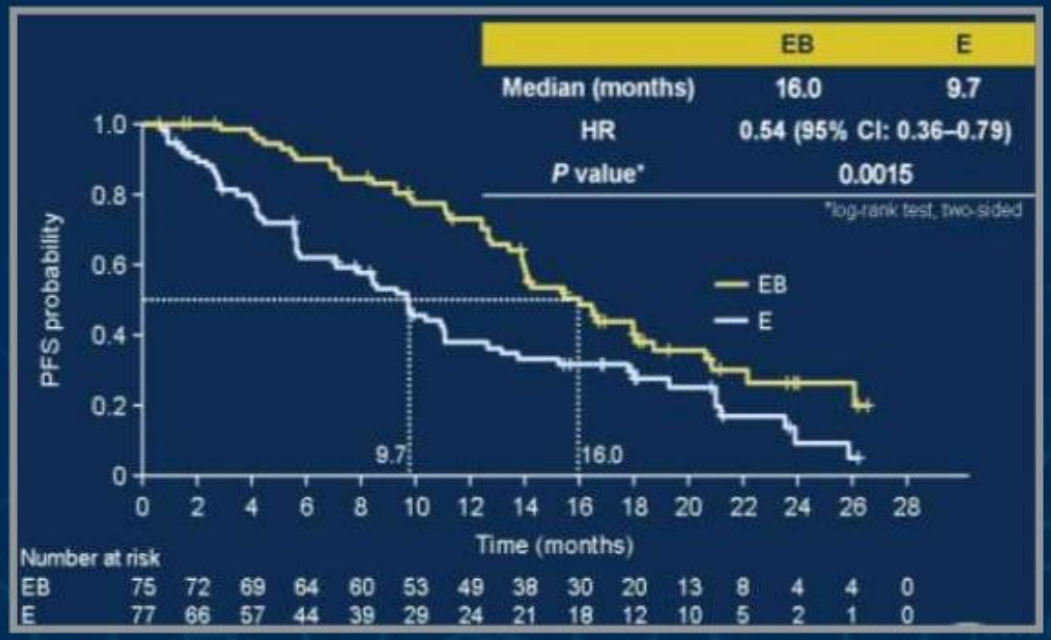
Adv NSCLC
EGFR Mut'n (exon 19/21)
Treatment-naïve
N = 154

RAND

Erlotinib 150 mg/day
+ bevacizumab 15 mg/kg IV Q21 days
until progression or prohibitive toxicity

Erlotinib 150 mg/days
until progression or prohibitive toxicity

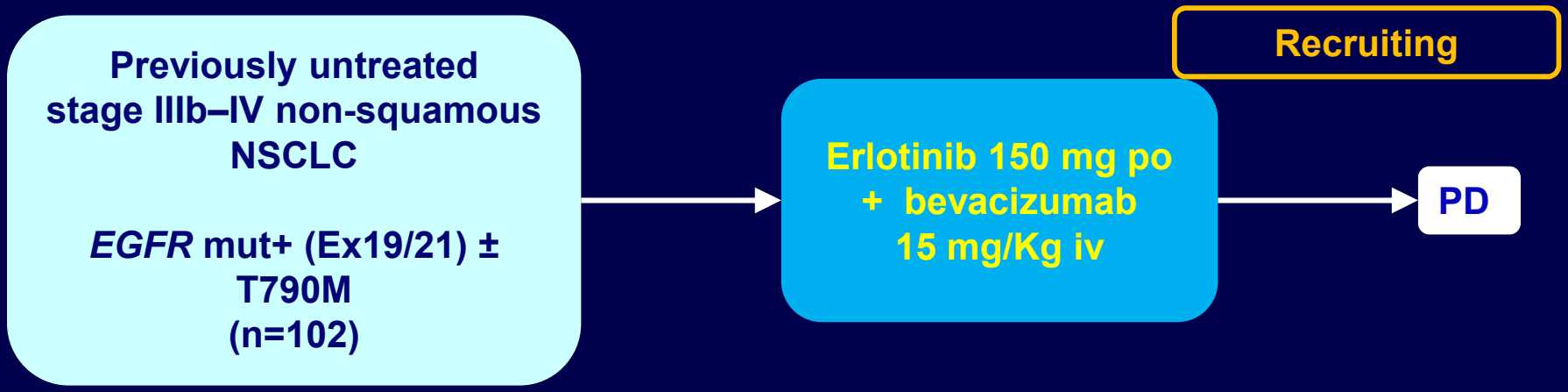
Primary endpoint: PFS



	EB	E	P
ORR (CR/PR)	69%	64%	ns
DCR (CR/PR/SD)	99%	88%	0.018

Kato, A#8005

BELIEF (MO29711): phase II study

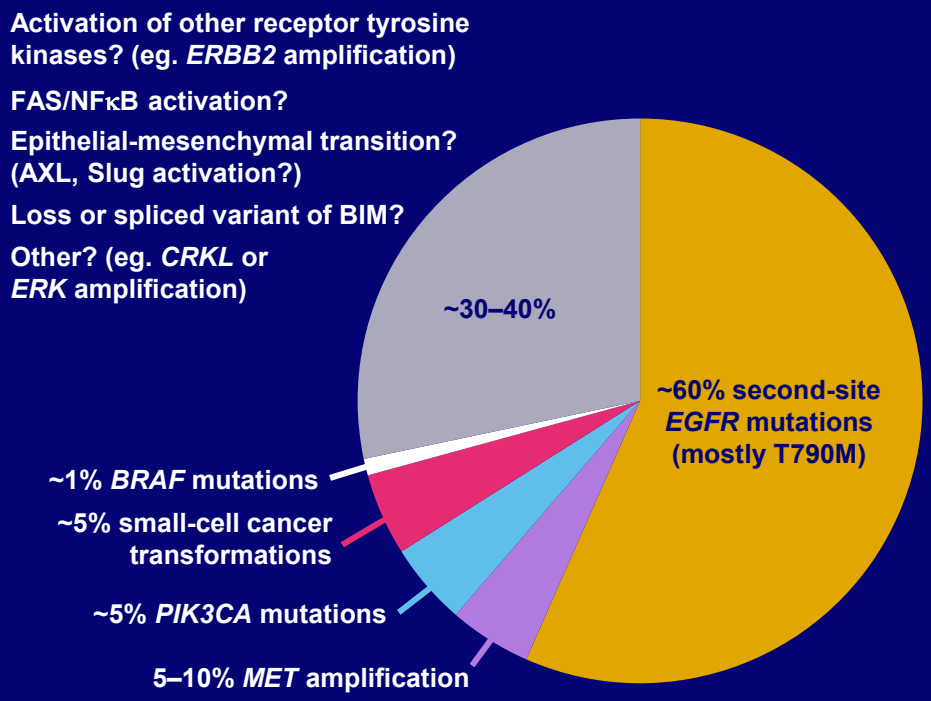


- Sponsor: ETOP
- FPI: Q3 2011; 12 m estimated recruitment time
- Primary objective
  - PFS
- Secondary objectives
  - OS
  - RR
  - Safety
  - QoL
  - Additional translational research (TBD)

NCT01562028

Acquired resistance in *EGFR* Mut+ NSCLC

Mechanisms of acquired resistance to EGFR TKIs



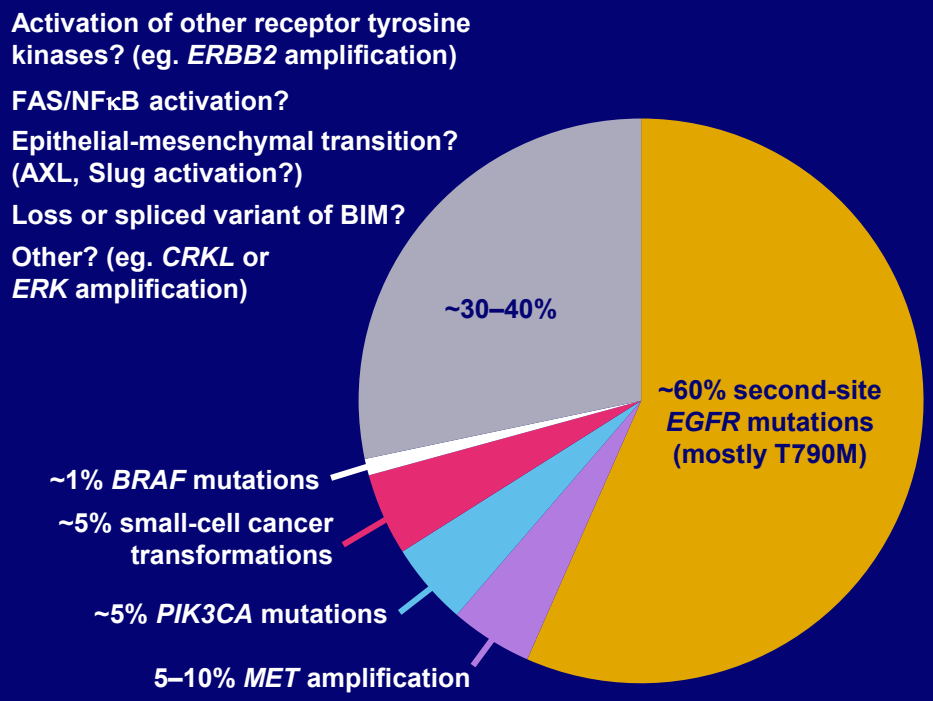
- Acquired resistance to EGFR TKIs in metastatic setting is inevitable
- The average PFS is 8–13 months

CRITERIOS DE JACKMAN DE RESISTENCIA ADQUIRIDA A EGFR-TKIs (3)

1. Previously received treatment with a single-agent EGFR TKI (eg, gefitinib or erlotinib)
2. Either of the following:
   A. A tumor that harbors an EGFR mutation known to be associated with drug sensitivity (ie, G719X, exon 19 deletion, L858R, L861Q)
   B. Objective clinical benefit from treatment with an EGFR TKI as defined by either:
      i. Documented partial or complete response (RECIST of WHO), or
      ii. Significant and durable (≥ 6 months) clinical benefit (stable disease as defined by RECIST or WHO) after initiation of gefitinib or erlotinib
3. Systemic progression of disease (RECIST or WHO) while on continuous treatment with gefitinib or erlotinib within the last 30 days
4. No intervening systemic therapy between cessation of gefitinib or erlotinib and initiation of new therapy

Acquired resistance in *EGFR* Mut+ NSCLC

Mechanisms of acquired resistance to EGFR TKIs



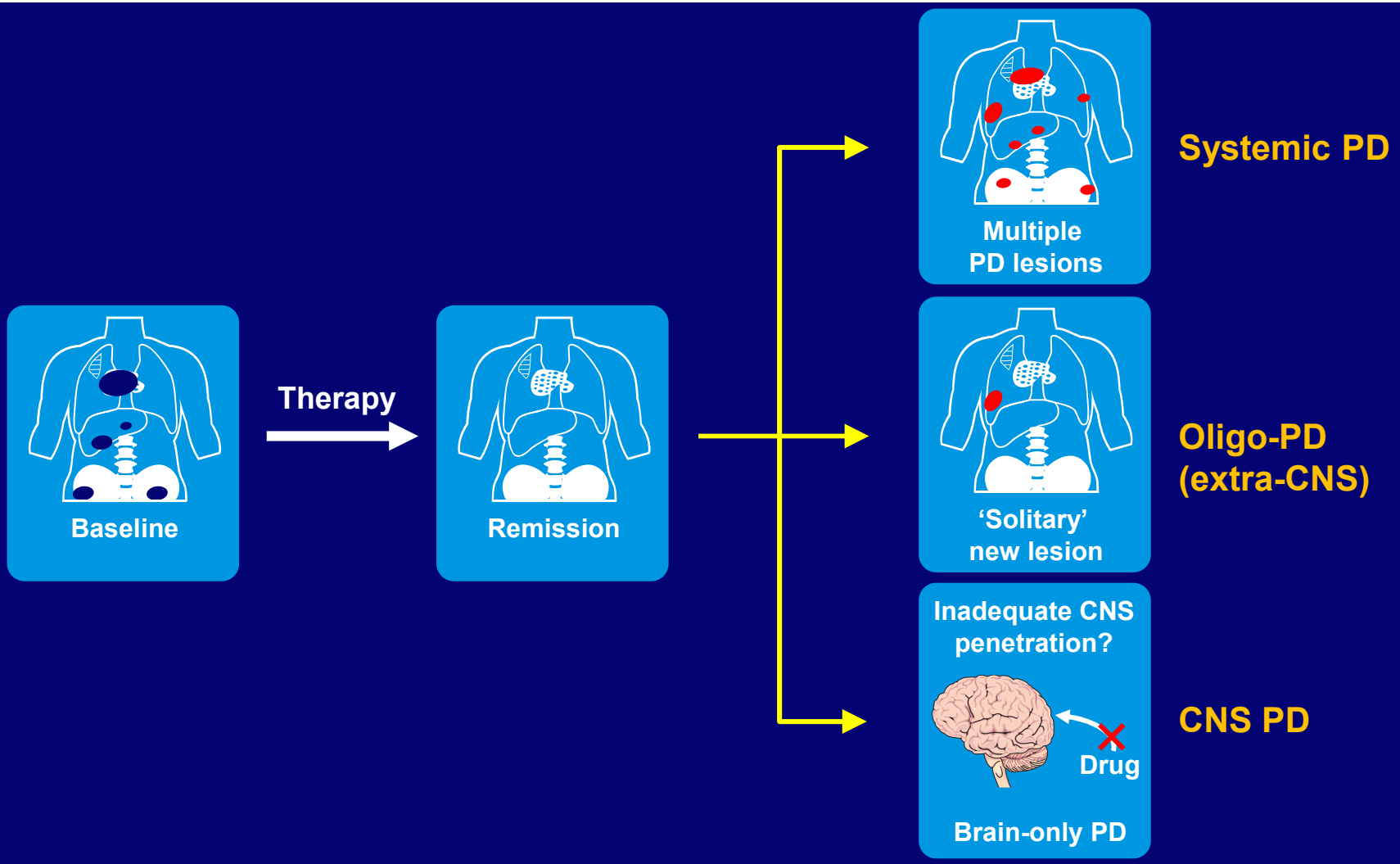
- Acquired resistance to EGFR TKIs in metastatic setting is inevitable
- The average PFS is 8–13 months

What options are under investigation to address this area of unmet need?

- Continuing TKIs beyond progression
- Irreversible TKIs

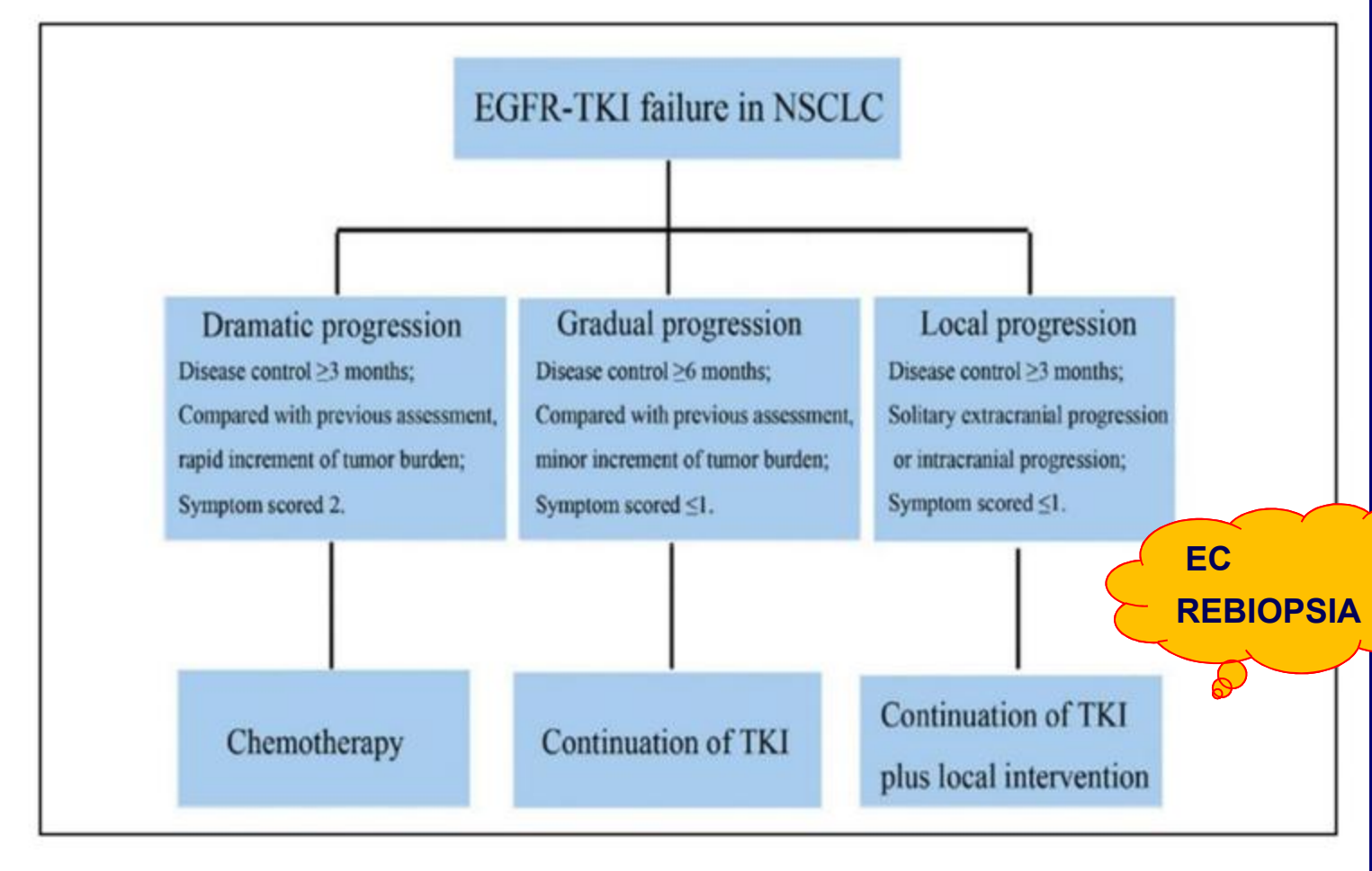
Ohashi et al, J Clin Oncol 2013

Scenarios for progression on TKI therapy



Adapted from Gandara. ASCO 2013

Algoritmo de tratamiento



Yang, Lung Cancer 2013

Rebiopsiar

RESULTADOS DE DIFERENTES ESTUDIOS EN PACIENTES EGFR MUTADOS CON RESISTENCIA ADQUIRIDA A TKIs EN LOS QUE SE REALIZA REBIOPSIA

Study	*Year*	*Patients*	*Type of study*	*Incidence of most prevalent resistance mechanisms*	*Other findings*
Sequist et al. (1)	2011	39	Retrospective	T790M = 49 % MET = 5 % SCLC transformation = 14 % PIK3CA = 5 %	Changing T790M status at longitudinal biopsies
Arcilla et al. (2)	2011	99	Prospective	T790M = 68 % MET amplifications = 11 %	
Yu et al. (3)	2013	155	Prospective	T790M = 63 % MET = 5 % SCLC transformation = 3 %	No mutations in PID3CA, AKT1, BRAF, ERBB2, KRAS, MEK1 or NRAS were detected at adquired resistance
Hata et al. (4)	2013	78	Retrospective	T790M: CNS lesions = 17 % Non CNS lesions = 41 %	Emergence of T790M in CNS lesions was rare. T790M+ patients had a better prognosis than T790M- patients
Sun et al. (5)	2013	70	Prospective	T790M = 51 % SCLC transformations = 1 %	No prognostic or predictive role for T790M mutation

1. Sequist et al. Sci Transl Med 2011;3:75ra26. 2. Arcilla et al. Clin Cancer 2011;17:1169. 3. Yu et al. Clin Cancer Res 2013;19:2240. 4. Hata et al. Cancer 2013;119:4325. 5. Sun et al. Lung Cancer 2013;82:294.

LETTER

nature International weekly journal of science

doi:10.1038/nature12065

Non-invasive analysis of acquired resistance to cancer therapy by sequencing of plasma DNA

Muhammed Murtaza[1]*, Sarah-Jane Dawson[1,2]*, Dana W. Y. Tsui[1]*, Davina Gale[1], Tim Forshew[1], Anna M. Piskorz[1], Christine Parkinson[1,2], Suet-Feung Chin[1], Zoya Kingsbury[3], Alvin S. C. Wong[4], Francesco Marass[1], Sean Humphray[3], James Hadfield[1], David Bentley[3], Tan Min Chin[4,5], James D. Brenton[1,2,6], Carlos Caldas[1,2,6] & Nitzan Rosenfeld[1]

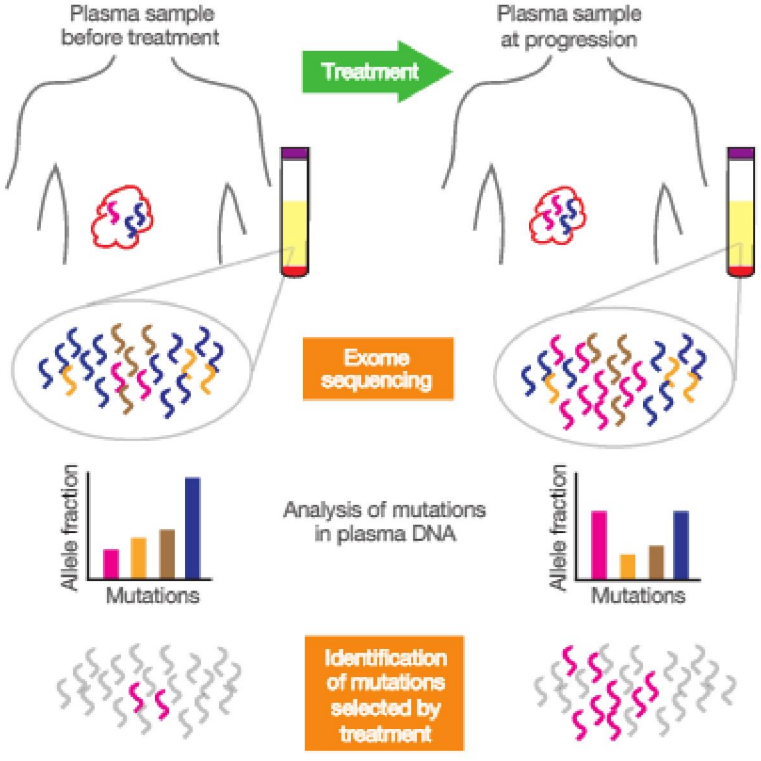


Figure 1 | Identification of treatment-associated mutational changes from exome sequencing of serial plasma samples. Overview of the study design:

Opciones terapéuticas

CONTINUAR TKI

- ASPIRATION

CONTINUAR TKI + QT

- IMPRESS
- LUX-LUNG 5

QT

TKI + AC MONOCLONAL

- AFATINIB + CETUXIMAB

EGFR-ITK IRREVERSIBLE

- 2º GENERACIÓN
  - AFATINIB: LUX-LUNG 1
  - DACOMITINIB: ARCHER
- 3º GENERACIÓN
  - CO-1686
  - AZD9291

ENSAYO CLÍNICO

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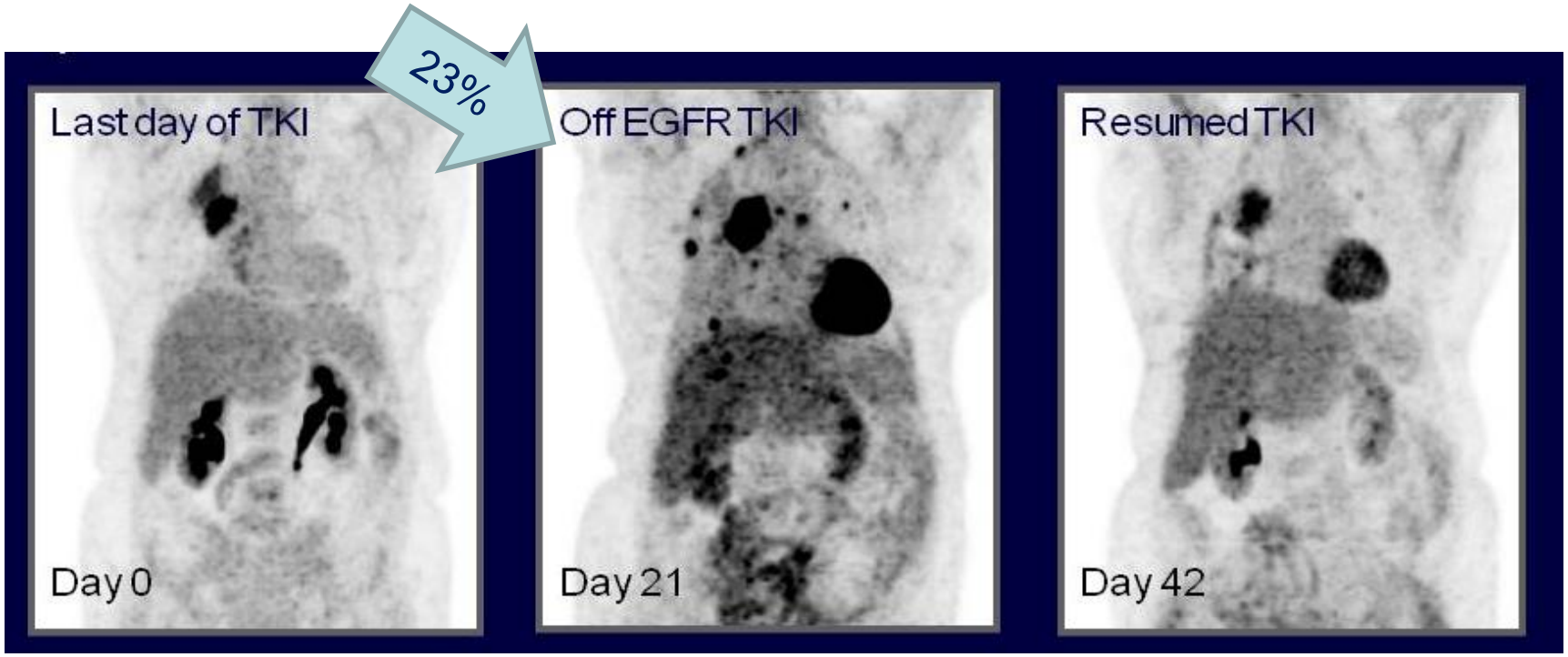
ENSAYO CLÍNICO

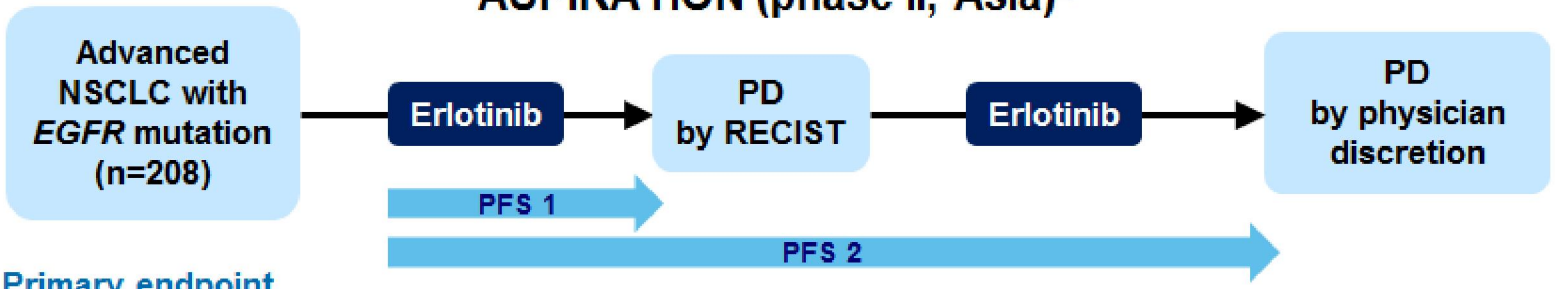
Flare of Disease after EGFR TKI discontinuation in acquired resistance



Rápido crecimiento que conduce a hospitalización y / o muerte atribuible a la PE por el cese de EGFR TKI hasta en un 23% (n=14) de los pacientes CPNM EGFRm y R.Adquirida.

Riely et al. Clinical Cancer Research 2007, Chaft et al. CCR 17 (19): 6298-6303, 2011

ASPIRATION (phase II, Asia)[2]

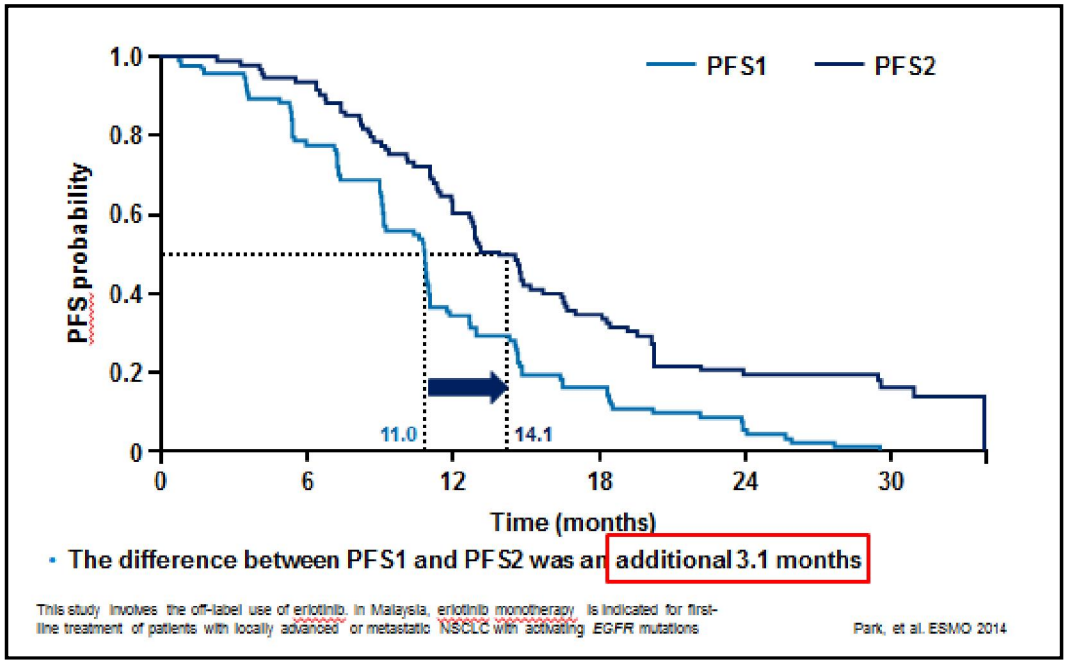


Primary endpoint

PFS 1

These studies involve the off-label use of EGFR TKIs. In Malaysia, erlotinib and gefitinib monotherapy are indicated for first-line treatment of patients with locally advanced or metastatic NSCLC with activating *EGFR* mutations

1. Mok, et al. ESMO 2014; 2. Park, et al. ESMO 2014



Opciones terapéuticas

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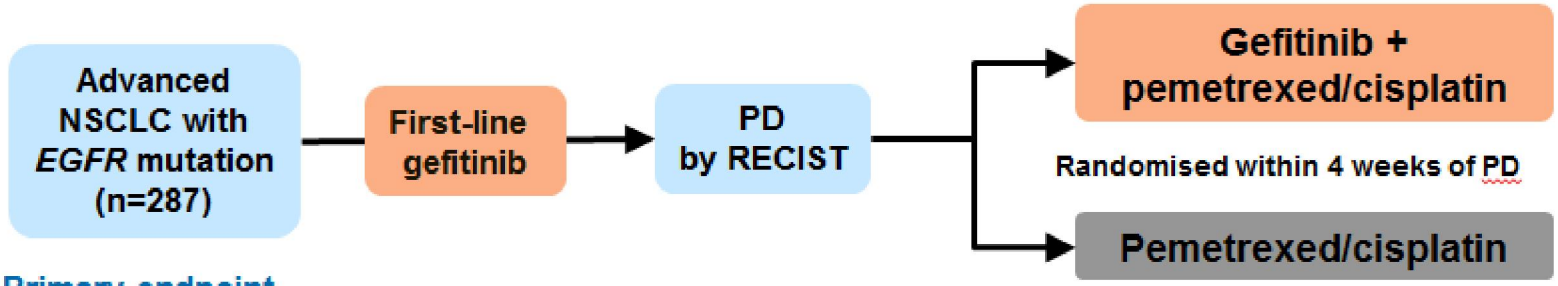
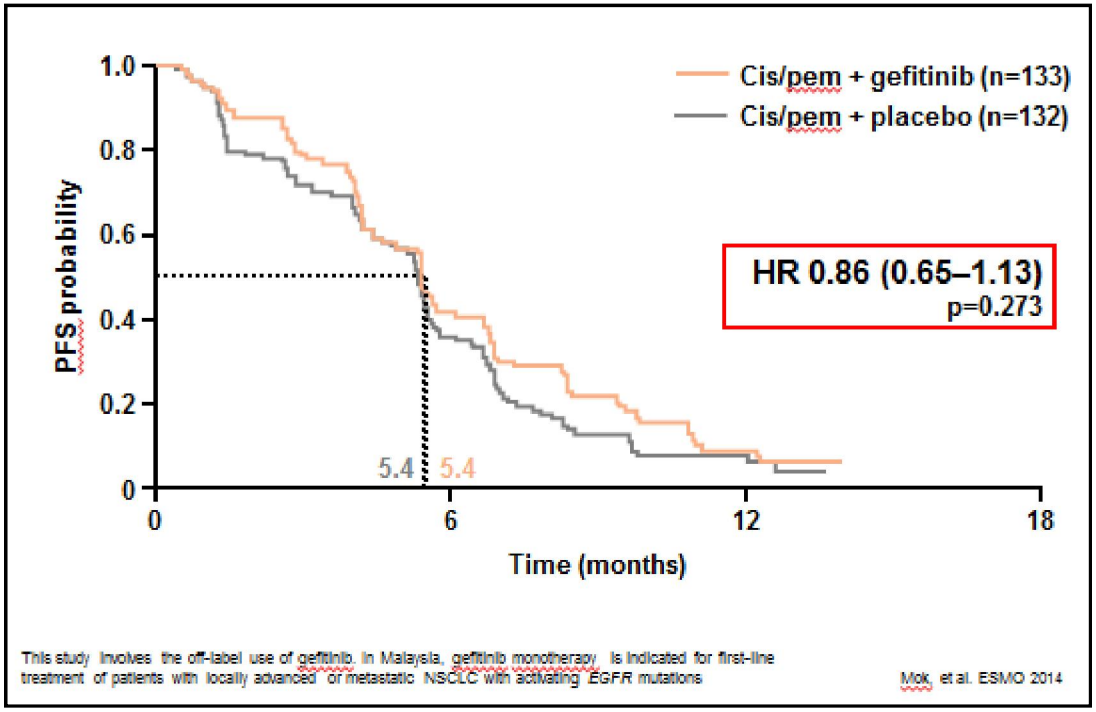
ENSAYO CLÍNICO

IMPRESS (phase III, Europe/Japan/Asia)[1]



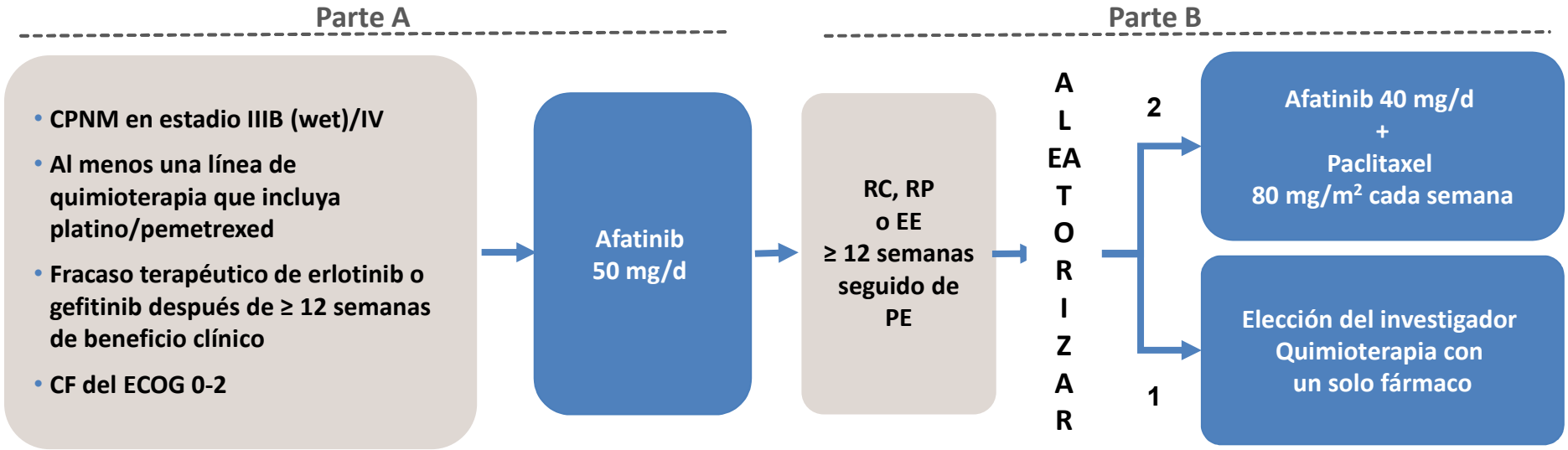
Primary endpoint
PFS

1. Mok, et al. ESMO 2014; 2. Park, et al. ESMO 2014



LUX-Lung 5: diseño del estudio

- Estudio abierto, global realizado en 115 centros de 23 países
- Reclutamiento de la parte A: Entre abril de 2010 y mayo de 2011
- Análisis principal: la parte B aleatorizada se ha presentado (cierre de la base de datos en noviembre de 2013)
- La parte A no aleatorizada se publicó con anterioridad (Schuler et al, ASCO 2012)

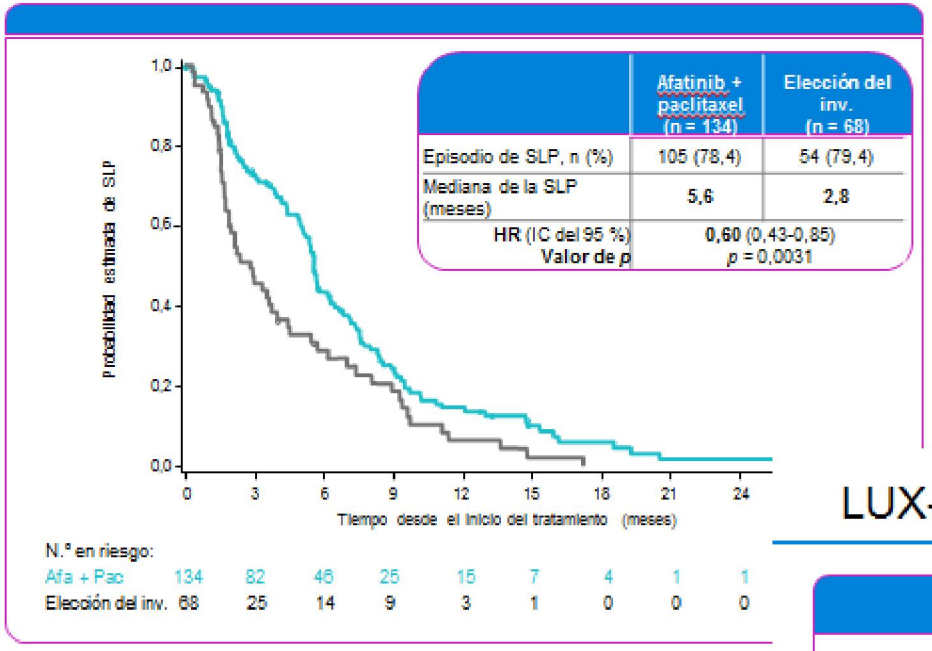


Criterio principal de valoración: SLP en la parte B (revisión del investigador)
Criterios secundarios de valoración: SG en la parte B, SLP en la parte A, TRO en las partes A y B

RC, respuesta completa, CF ECOG, categoría funcional del *Eastern Cooperative Oncology Group*, PE, progresión de la enfermedad, RP = respuesta parcial; EE = enfermedad estable

1.Schuler M. et al. J Clin Oncol 2014; 32(15) (suppl), 5S, abstr. 8019; 2. Schuler M. et al. J Clin Oncol 2012; 30(15S) (suppl), abstr. 7557

SLP en la revisión del investigador



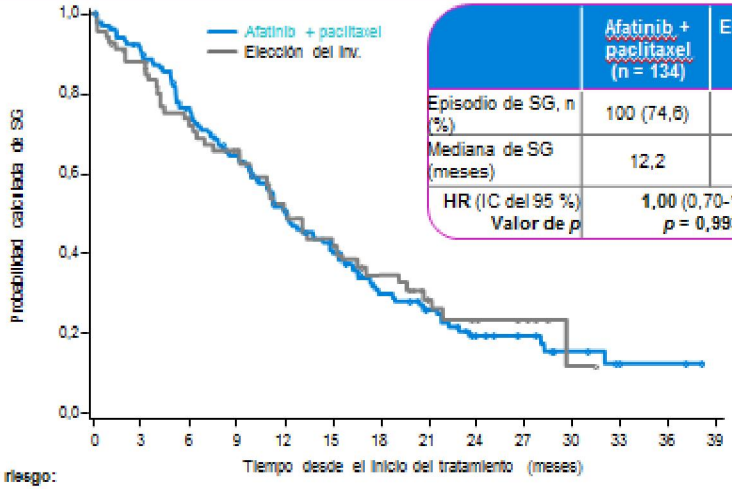
	Afatinib + paclitaxel (n = 134)	Elección del inv. (n = 68)
Episodio de SLP, n (%)	105 (78,4)	54 (79,4)
Mediana de la SLP (meses)	5,6	2,8
HR (IC del 95 %)	0,60 (0,43-0,85)	
Valor de *p*	*p* = 0,0031	

1.Schuler M. et al. J Clin Oncol 2014; 32(15) (suppl), 5S, abstr. 8019;

Beneficio SLP del bloqueo continuado del EGFR con afatinib en pacientes con CPNM tratados previamente con ITK

LUX-Lung 5: Supervivencia global

SG



	Afatinib + paclitaxel (n = 134)	Elección del inv. (n = 68)
Episodio de SG, n (%)	100 (74,6)	46 (67,6)
Mediana de SG (meses)	12,2	12,2
HR (IC del 95 %)	1,00 (0,70-1,43)	
Valor de *p*	*p* = 0,9936	

1.Schuler M. et al. J Clin Oncol 2014; 32(15) (suppl), 5S, abstr. 8019;

CONTINUAR ITK + QT

Trial	Patients	Continued EGFR TKI + chemo
Goldberg et al.	- 34 chemo + E - 44 chemo	**RR improved (41% vs 18%; OR: 0'31, p=0'08)** No PFS or OS difference
Faehling et al.	- 27 chemo + EGFR TKI - 14 chemo	**Improved OS**
Yoshimura et al.	27 pemetrexed + EGFR TKI	**ORR 26%, DCR 78%** Median PFS 7 months Median OS 11.4 months
Janne PA et al.	- EGFR TKI + QT (CARBO o PACLITAXEL - ERLOTINIB	38'5 vs 31 months OS

Goldberg et al. ASCO 2012 Abstract 7524, Yoshimura N. et al. JTO 8 (1):96-101, 2013; Faehling et al. ASCO 2012 Abstract 7572; Oxnard et al. ASCO 2012 Abstract 7547

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ENSAYO CLÍNICO

Opciones terapéuticas

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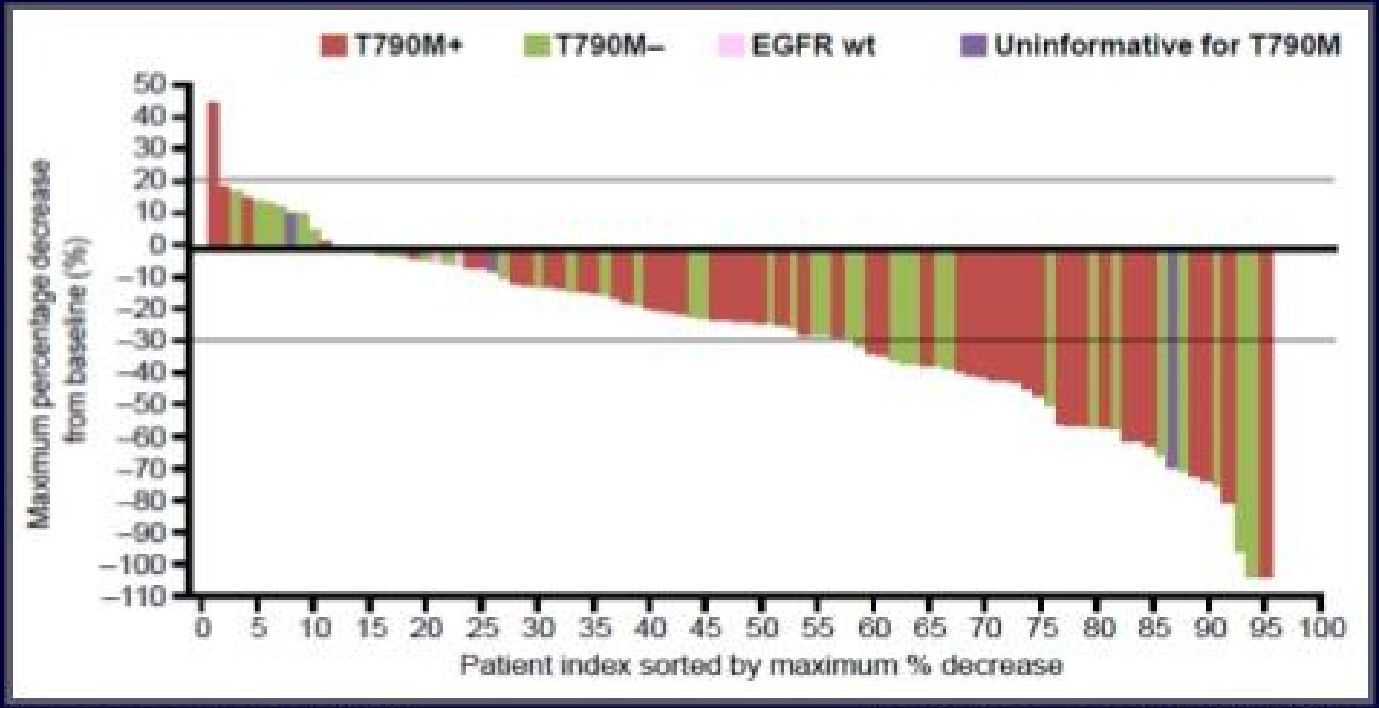
ENSAYO CLÍNICO

Afatinib + Cetuximab in EGFR-mutated NSCLC refractory to EGFR TKI

N = 60



Response rate: 30%

Clinical benefit (DCR): 75%

Janjigian, et al. ESMO 2012

- This is specific for afatinib combination:
  Erlotinib/cetuximab had RR 0/13 (Janjigian, CCR 2011)

Opciones terapéuticas

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CONTINUAR TKI + QT

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ENSAYO CLÍNICO

LUX-Lung 1: Trial design

Patients with:
- Adenocarcinoma of the lung
- Stage IIIB/IV
- Progressed after one or two lines of chemotherapy (incl. one platinum-based regimen) and ≥12 weeks of treatment with erlotinib or gefitinib
- ECOG 0–2

N=585

Randomization 2:1 (Double Blind)

- Oral afatinib (BIBW2992) 50 mg once daily plus BSC
- Oral placebo once daily plus BSC

Primary endpoint: Overall survival (OS)

Secondary: PFS, RECIST response, QoL (LC13 & C30), safety

- Radiographic assessments at 4, 8, 12 wks and every 8 wks thereafter
- Exploratory biomarkers:
  - Archival tissue testing for EGFR mutations (optional; central lab)
  - Serum EGFR mutational analysis (all patients)

Miller, ESMO 2010

SLP:3.3 m vs 1,1m
HR: 0,38

	Independent review	
	Afatinib* arm	Placebo arm
Partial response (PR) regardless of confirmation	13%	0.5%
Partial response (PR) confirmed	7%	0.5%
Stable disease (SD)	51%	18%
Disease control rate (DCR)	58%	19%

Third-generation TKIs in EGFR Mut+ NSCLC

	CO-1686[1]	AZD9291[2]
ORR, %	[illegible]	21% in T790M- pts 61% in T790M+ pts
Median PFS	[illegible]	2.8 months (T790M-) 9.6 months (T790M+)
Any drug-related AE, %	[illegible]	80
Any drug-related AE grade ≥3, %	[illegible]	13
Most frequent AEs	Hyperglycaemia and IGT (53%), nausea (35%) and diarrhoea (24%)	Diarrhoea (47%), rash* (40%) and nausea (22%)

Studies are ongoing

*Grouped term
NR = not reported; IGT = impaired glucose tolerance
Cross-trial comparison. Data should be interpreted with caution
CO-1686 and AZD9291 are not approved in Malaysia for the treatment of patients with NSCLC

1. Sequist, et al. ASCO 2104; 2. Yang, et al. ESMO 2014

Improving the standard of care: third-generation TKIs

Third-generation TKIs have been designed to target resistance mutants

CO-1686 (phase I/II)[1]

Advanced or metastatic *EGFR* Mut+ NSCLC

Previously treated with EGFR TKI

(n=170)

→ **Phase I**
Dose escalation

→ **Phase II**
Expansion in T790M+

Primary endpoints

Incidence of grade 3/4 AEs, PK, ORR and DoR

AZD9291 (phase I)[2,3]

Advanced NSCLC with confirmed radiological PD on prior EGFR TKI

Dose escalation based on safety and PK
(rolling 6 design, with cohort expansion up to n=30)

20mg	40mg	80mg	160mg	240mg
T790M+	T790M+	T790M+	T790M+	T790M+
	T790M–	T790M–	T790M–	

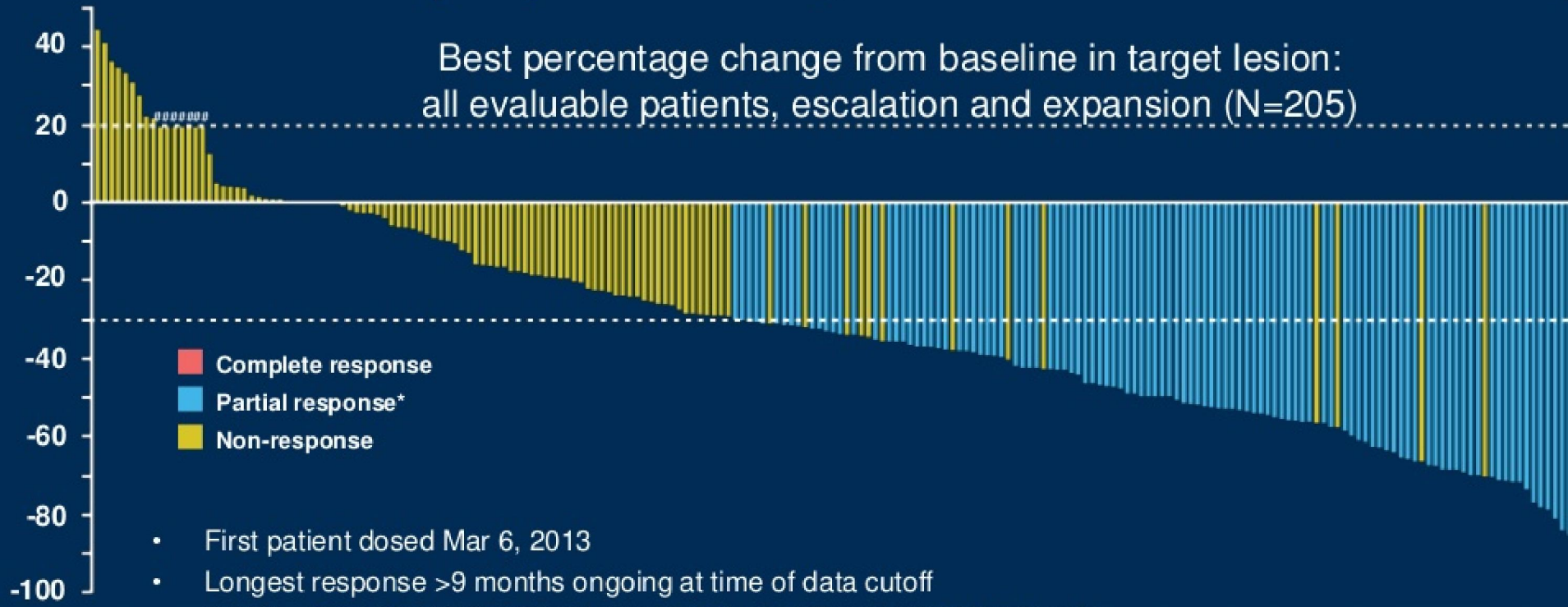
Primary endpoints

Safety and tolerability in EGFR TKI-resistant patients

CO-1686 and AZD9291 are not approved in Malaysia for the treatment of patients with NSCLC

1. Sequist, et al. ASCO 2014
2. Janne, et al. ASCO 2014; 3. Yang, et al. ESMO 2014

AZD9291: Response rate* in overall population(T790M+ and T790M-)

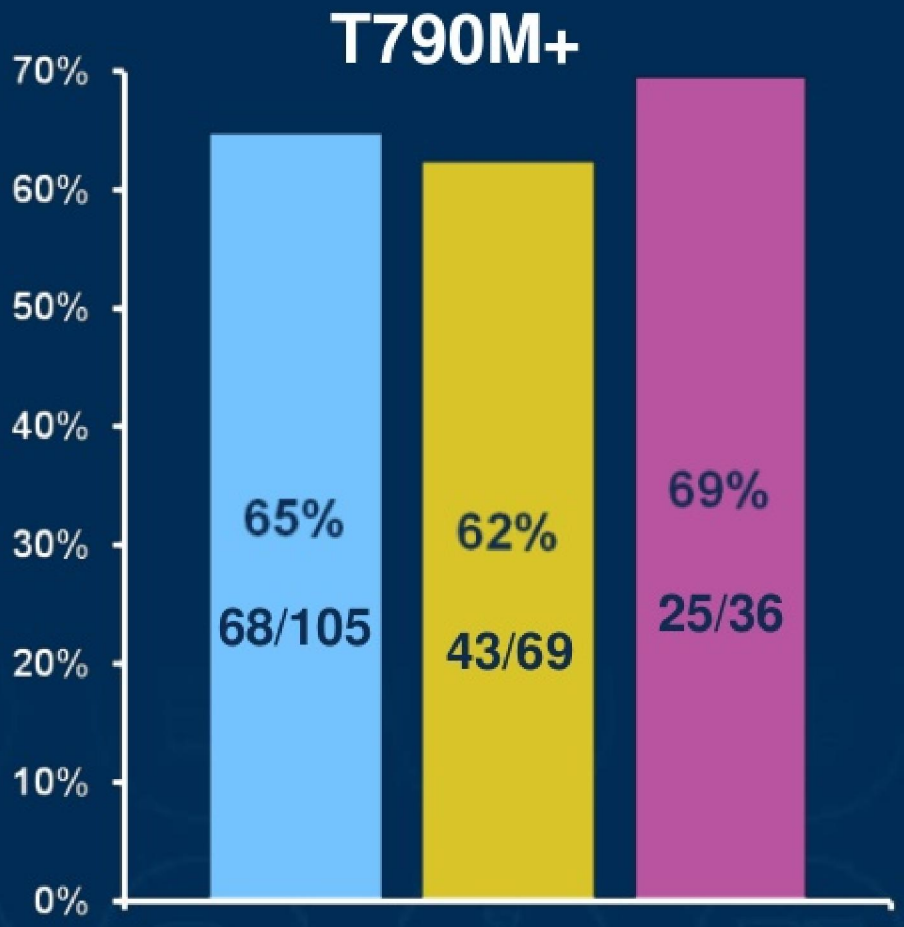


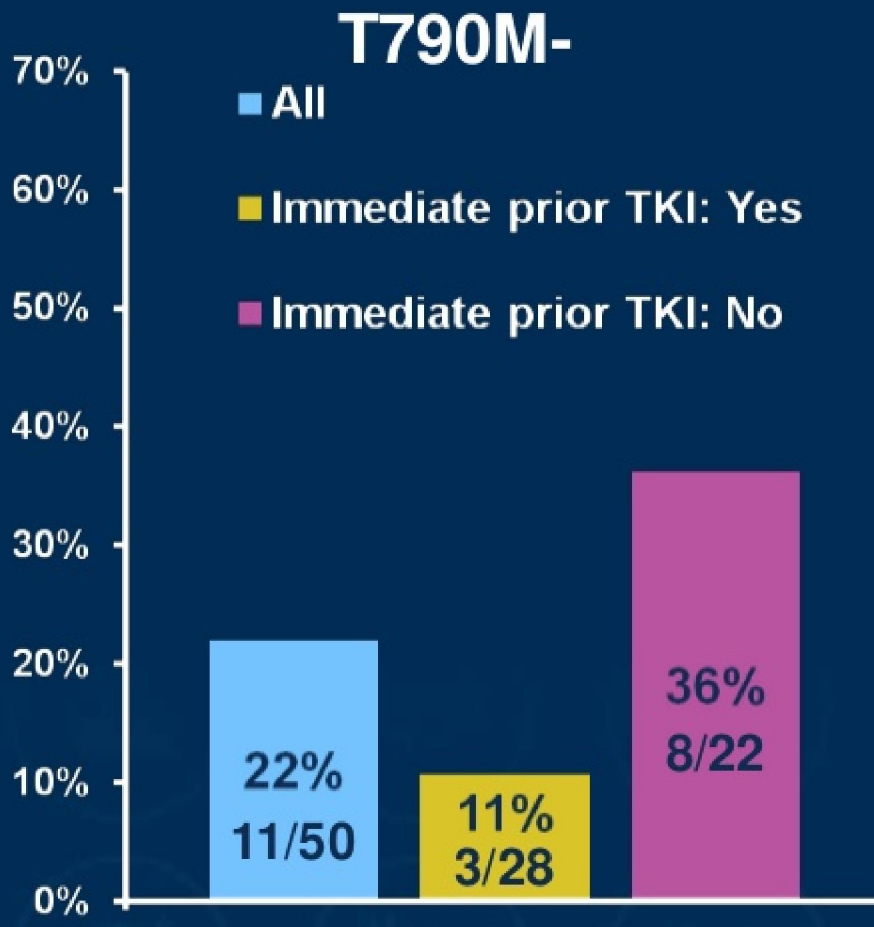
- First patient dosed Mar 6, 2013
- Longest response >9 months ongoing at time of data cutoff
- ORR* = 53% (109/205; 95% CI 46%, 60%); no difference in ORR by race
- Overall disease control rate (CR+PR+SD) = 83% (171/205; 95% CI 78%, 88%)

	20 mg	40 mg	80 mg	160 mg	240 mg
N (205)	20	57	61	55	12
ORR	55%	44%	54%	58%	67%

*Includes confirmed responses and responses awaiting confirmation; #represents imputed values. Population: all dosed patients with a baseline RECIST assessment and an evaluable response (CR, PR, SD, or PD), N=205 (from 232 dosed patients, 27 patients with a current non-evaluable response are not included). CI, confidence interval; CR, confirmed complete response; ORR, overall response rate; PD, progressive disease; PR, confirmed partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease

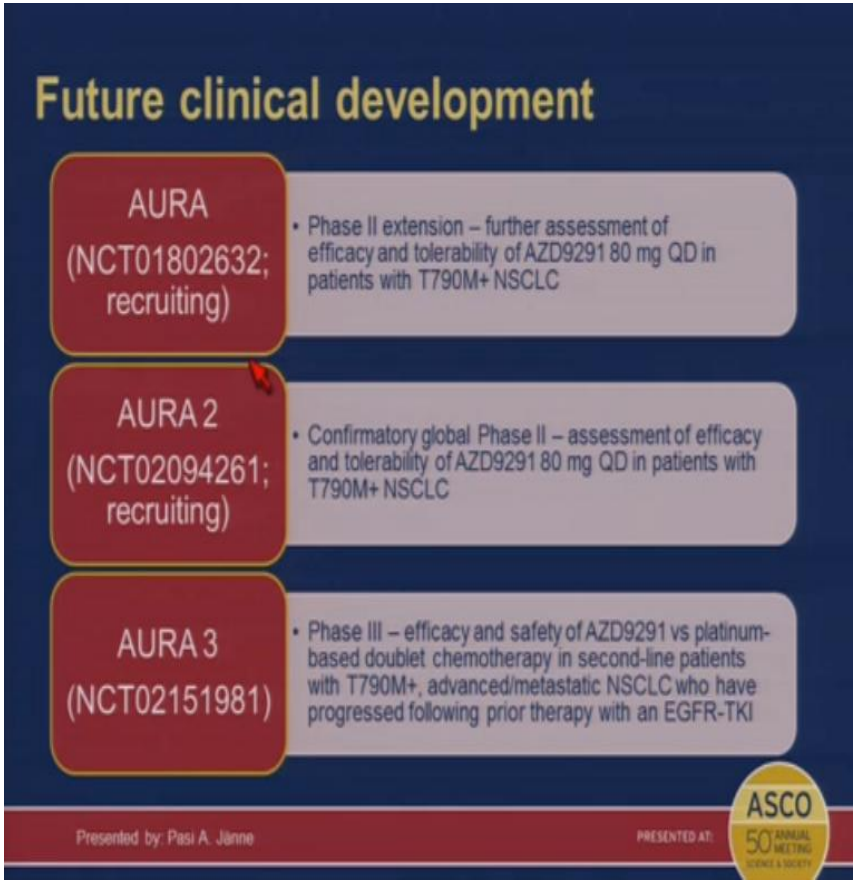
Response rate* according to T790M (central test) status: immediate prior EGFR-TKI,# yes vs no





*Includes confirmed responses and responses awaiting confirmation; #TKI therapy is defined as being immediately prior if TKI was the last regimen taken prior to the study, with no subsequent therapy. Population: all dosed centrally confirmed T790M+ and T790M- patients with a baseline RECIST assessment and an evaluable response, T790M+ N=105 (from 107 T790M+ patients with response data; two patients not included as subgroup missing), T790M- N=50

AZD9291 EGFRm T790M



CO-1686 EGFRm T790M

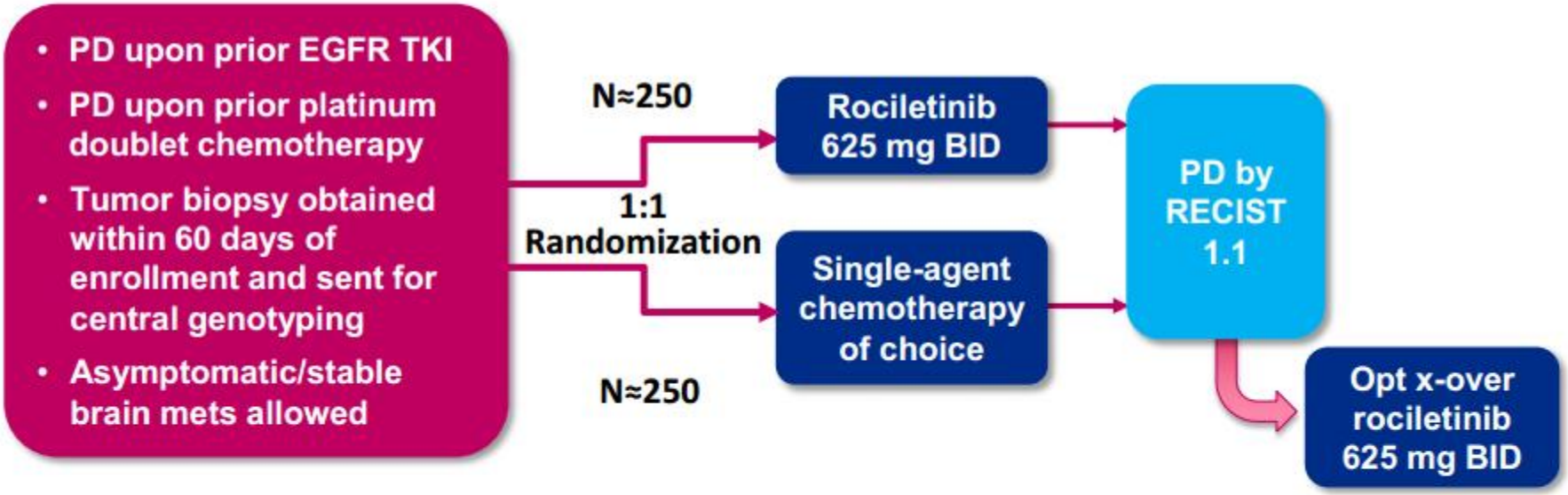
Comprehensive development program underway – first NDA planned mid 2015

TIGER Program

TIGER-X (Ph 2)	• Single arm – expansion cohorts • ≥2nd-line mutant EGFR NSCLC, T790M+
TIGER-1 (Ph 2/3)	• Randomized rociletinib vs erlotinib • 1st-line, treatment-naïve • Mutant EGFR (not screened for T790M status)
TIGER-2 (Ph 2)	• Single-arm • 2nd-line mutant EGFR NSCLC, T790M+ • Patients progressing on 1st-line EGFR TKI
TIGER-3 (Ph 3)	• Randomized rociletinib vs chemotherapy • >2nd-line mutant EGFR NSCLC, T790M+ and T790M– (sequential analysis)

T790M+ and T790M– patients to be studied in TIGER-3 phase 3 trial

TIGER-3: International, randomized, phase 3 study in ≥3rd line mutant EGFR NSCLC, both T790M+ and T790M–



Primary endpoint is PFS; step-down primary efficacy analysis – initially in central T790M+ patients, then all-comers

Mets=metastases; PD=progressive disease.

Opciones terapéuticas

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ENSAYO CLÍNICO

MECANISMOS DE RESISTENCIA ADQUIRIDA Y TERAPIAS EN INVESTIGACIÓN

Mecanismo	*Prevalencia*	*Terapia potencial*
EGFR T790M	50-60 %	AZD9291 CO-1686 HM61713
CPM	3-14 %	CDDP+VP-16
Amplificación MET	5-11 %	Cabozantinib + erlotinib, LY2875358 erlotinib INC280 + gefitinib
Amplificación HER2	12 %	Dacomitinib Dacomitinib intermitente Afatinib (dosis altas intermitentes)
Mutación PIK3CA	0-5 %	BKM120 + gefitinib BKM120 + erlotinib
BRAF V600E	1 %	Inh. BRAF+EGFR
Amplificación CRKL	?	?
Sobreexpresión AXL	?	?

CPM: cáncer de pulmón microcítico.

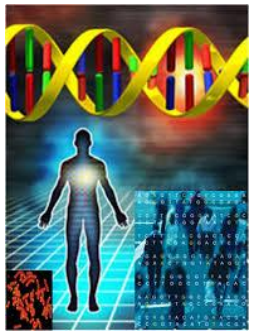
TKI
12m

QT
6m

QT 2ªL
4m

BSG
2m

24
meses



¿Cómo podríamos mejorarlo?

TKI +Anti-VEGFR
16m

TKI
3m

T790M+
10m

QT
6m

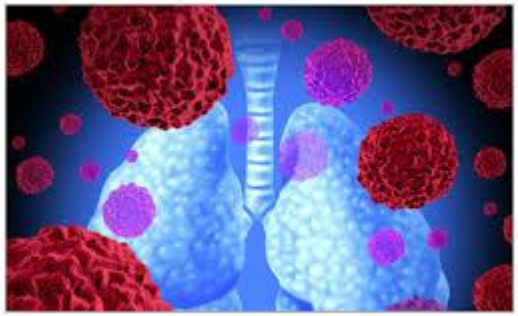
QT 2ªL
4m

BSG

41
meses

CONCLUSIONES

- ✓ ITK-EGFR 1º LINEA EGFRm+. Tto personalizado.
- ✓ Del19 Y L858R subtipos de comportamiento diferente
- ✓ Mutación 2ª T790M
- ✓ Nuevos enfoques para prolongar la sv
  - ✓ Continuar ITK
  - ✓ 3 º generación ITK. CO-1686 Y AZD 9291
  - ✓ Nuevas combinaciones
- ✓ Valorar re-biopsia y EC



ORGANIZA:

GIDO
grup de investigació i divulgació en oncologia

EGFR

Dra. Mar Llorente .

Hospital General de Elda.