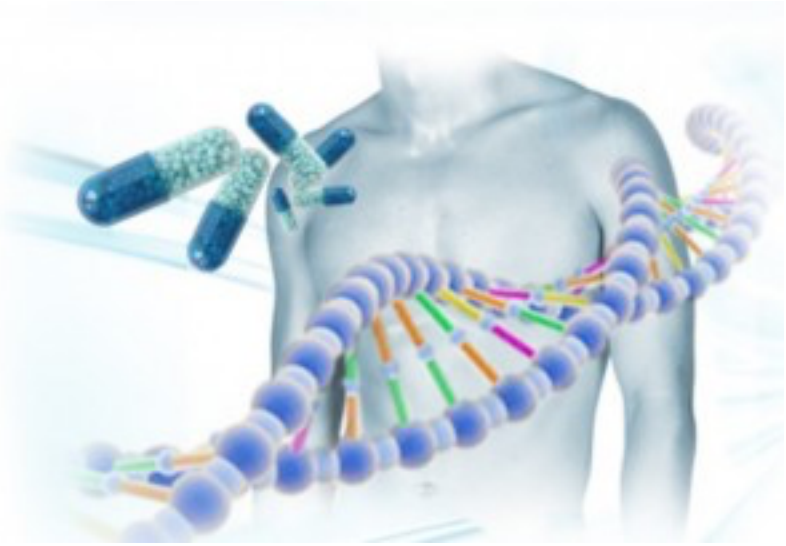
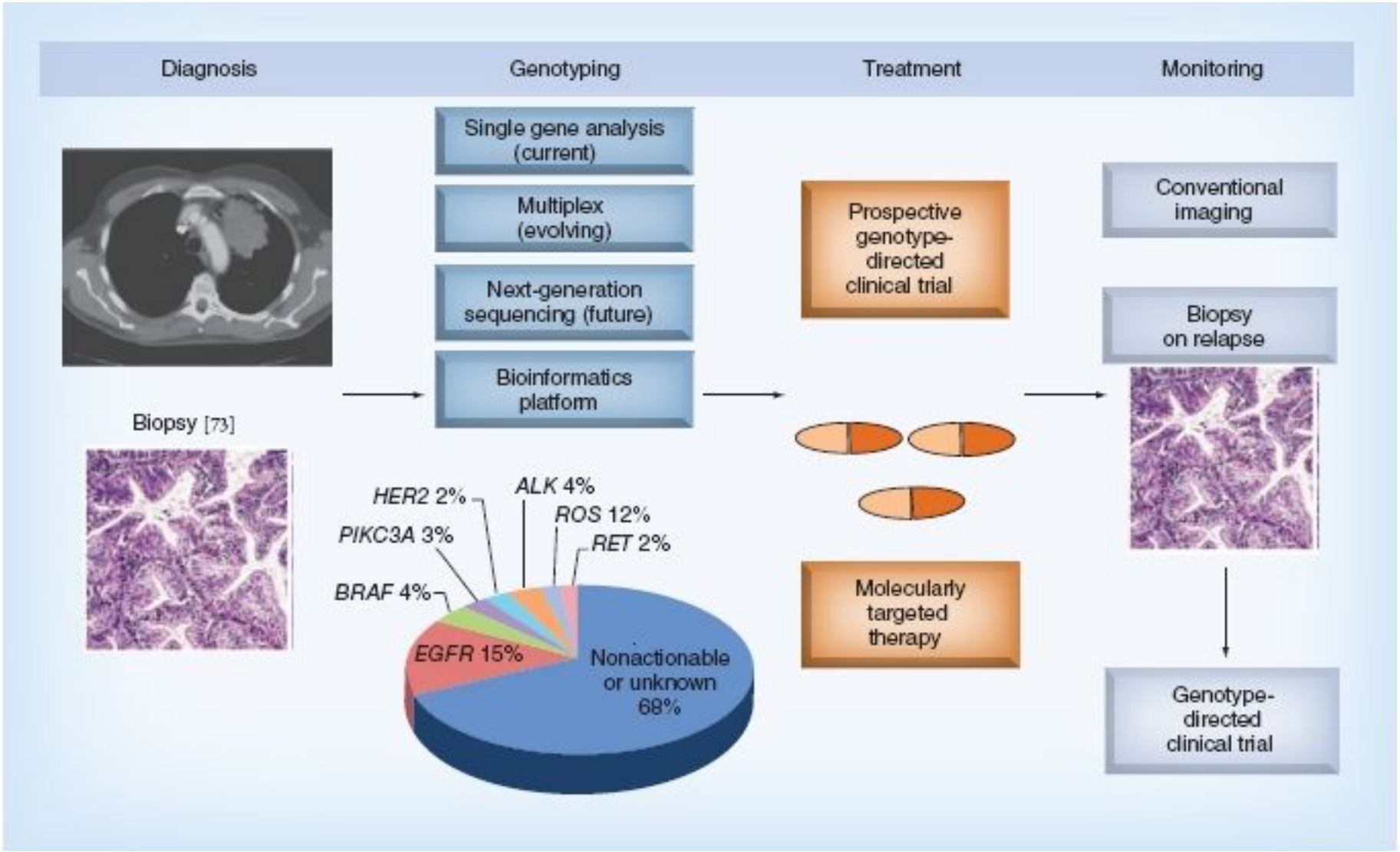
Terapias diana

Carcinoma no microcítico de pulmón avanzado



Eugenio Palomares García
Oncólogo Médico
Hospital Vinalopó Elche
4 de Marzo de 2016

Del diagnóstico al tratamiento dirigido



Oncogénesis en CNMP

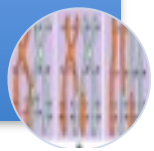
Tipo de alteración molecular

Mutaciones puntuales

- EGFR
- HER2
- KRAS
- BRAF
- NRAS

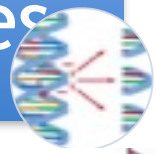
Reordenamientos

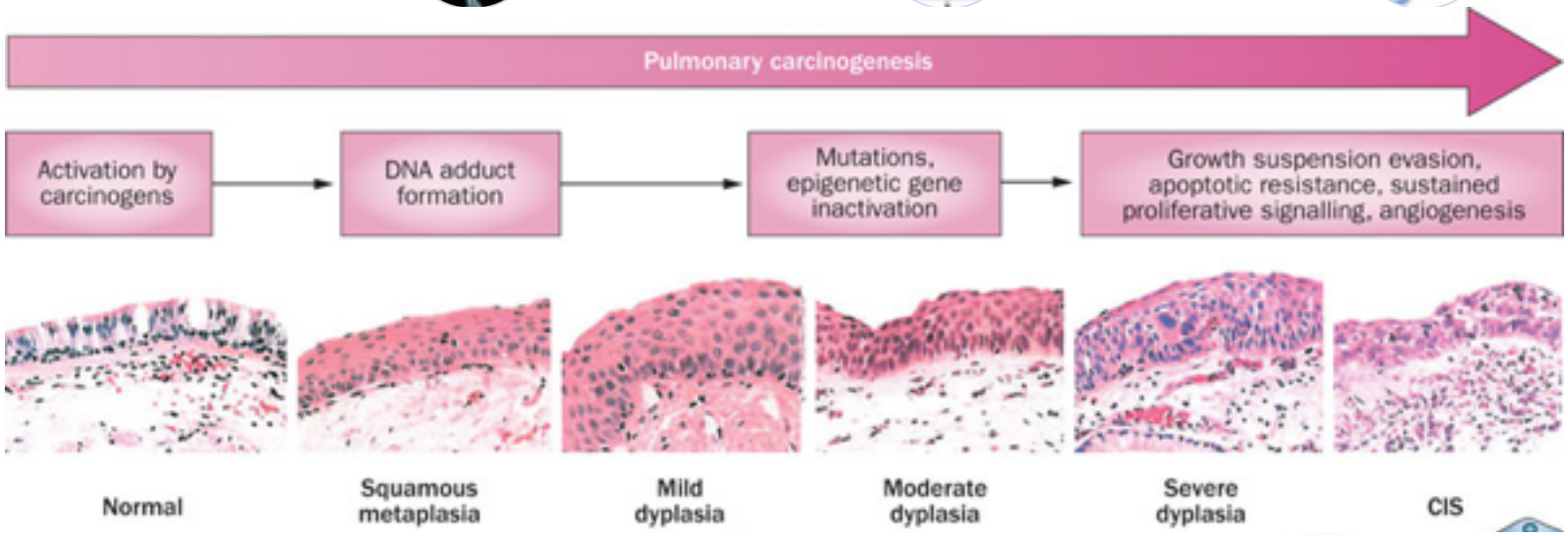
- ALK
- ROS
- RET



Amplificaciones y sobreexpresiones

- MET





Oncogénesis en CPNM: Driver mutations

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genoma de
la línea

crecimiento
y
supervivenc
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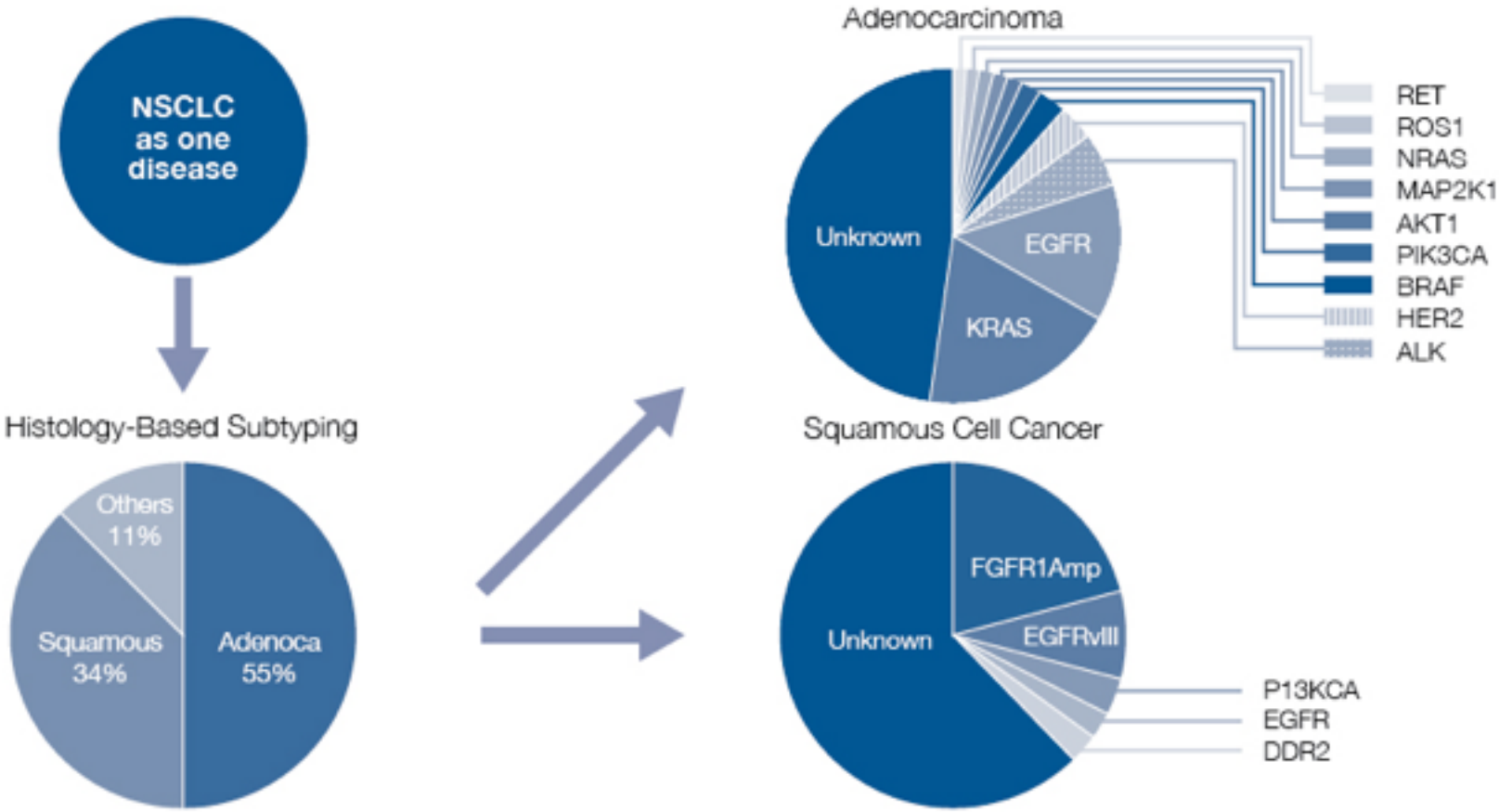
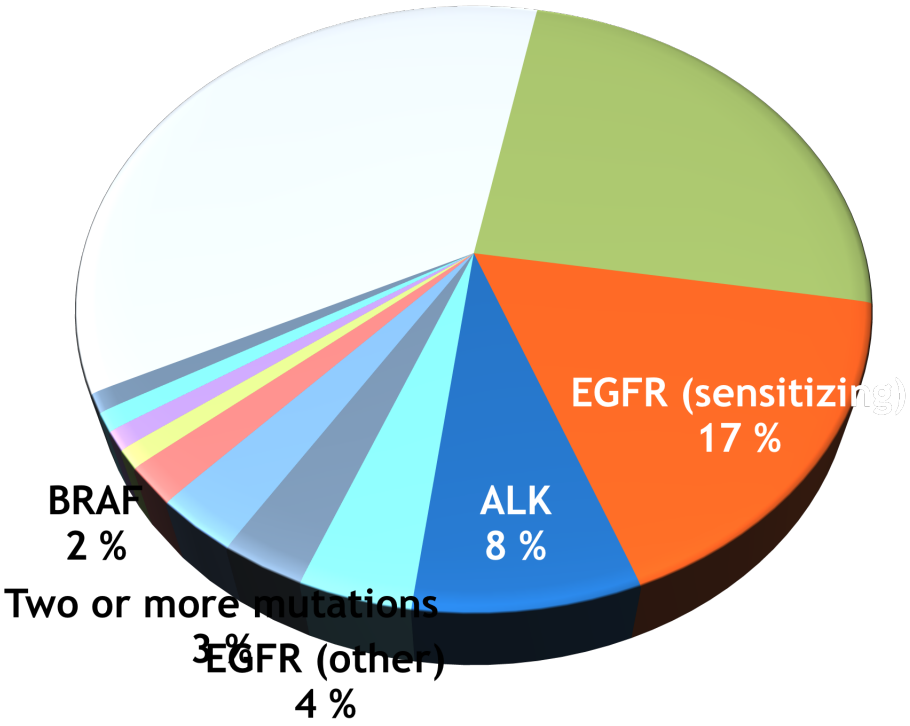
Son los **biomarcadores** más útiles para predecir la eficacia de las terapias dirigidas en CNMP avanzado, facilitando el tratamiento personalizado

Evolución de la clasificación: del subtipo histológico al subtipo molecular

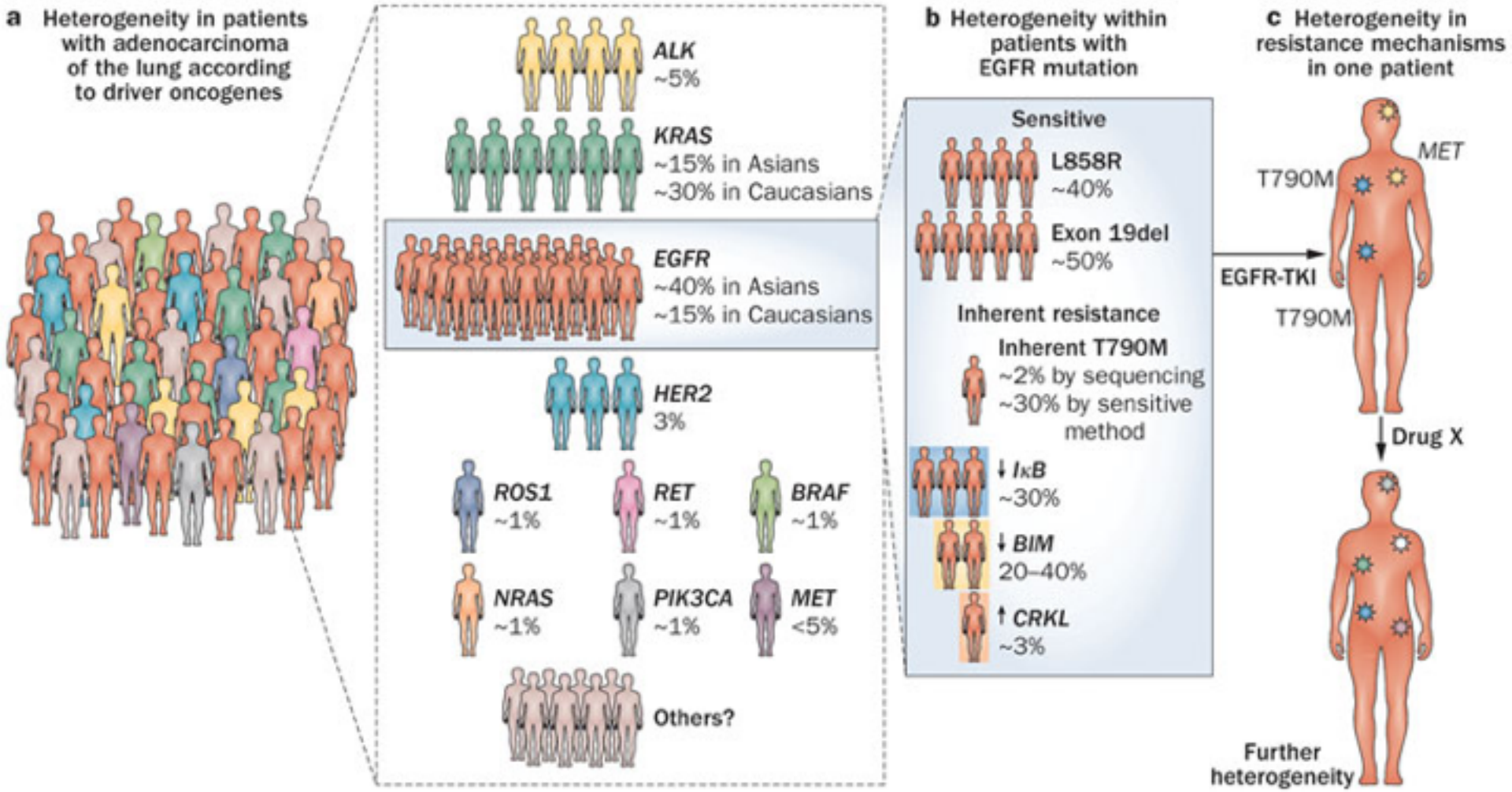


Incidencia de mutaciones driver en Adenocarcinoma de pulmón avanzado

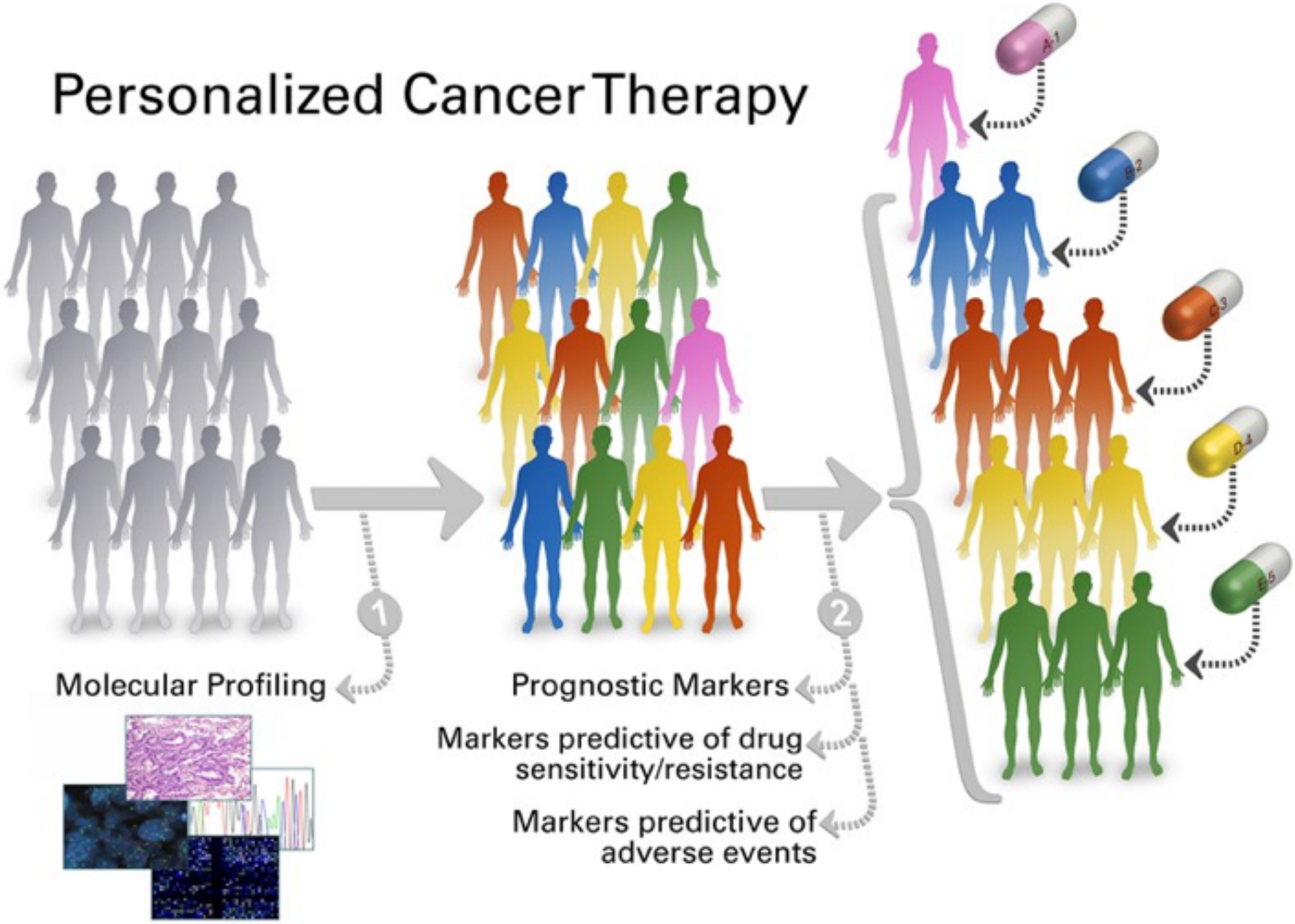


Kris MG et al. JAMA 2014;311(19):1998-2006

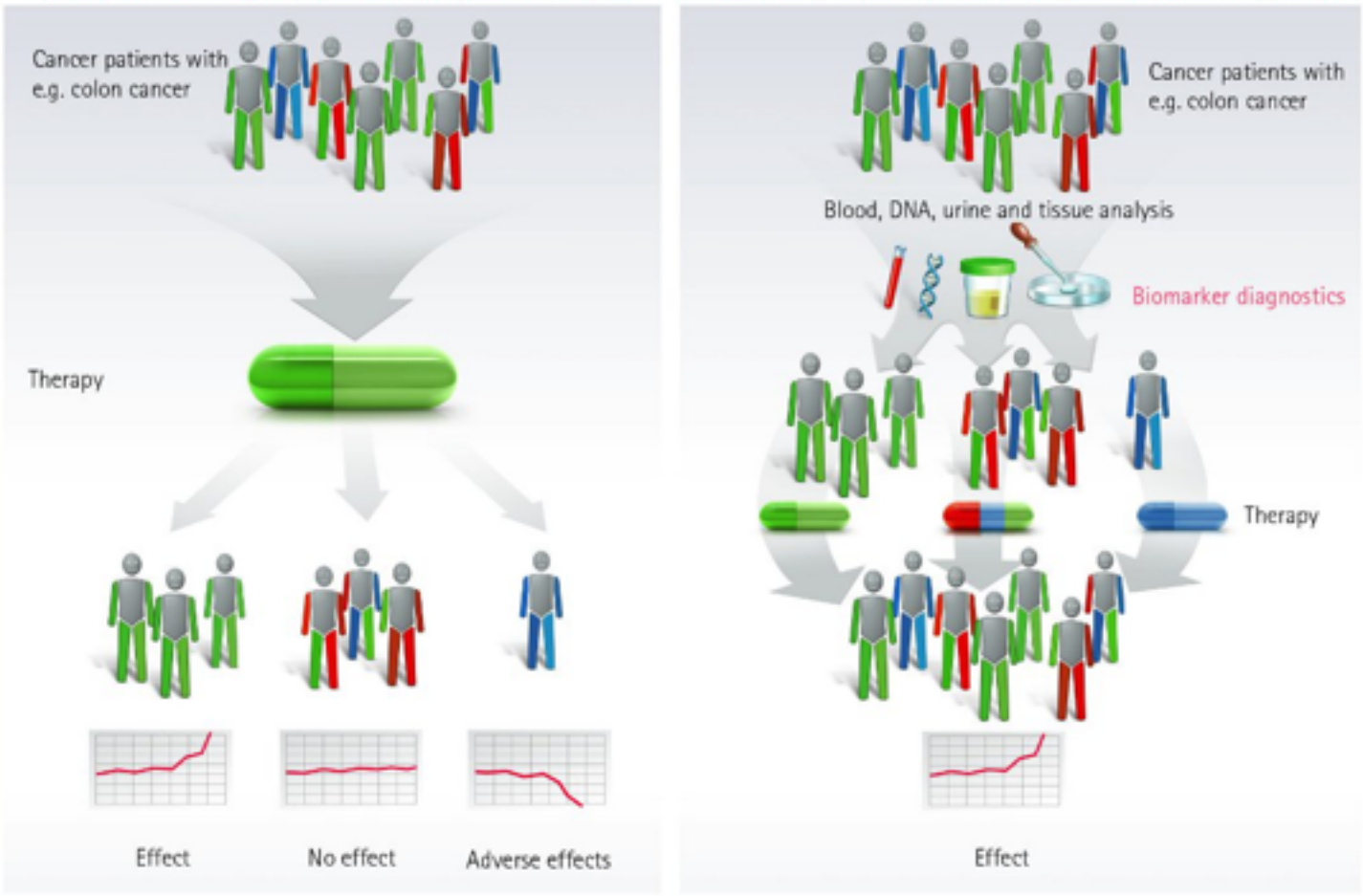
Heterogeneidad: driver mutations y mecanismos de resistencia



Personalized Cancer Therapy



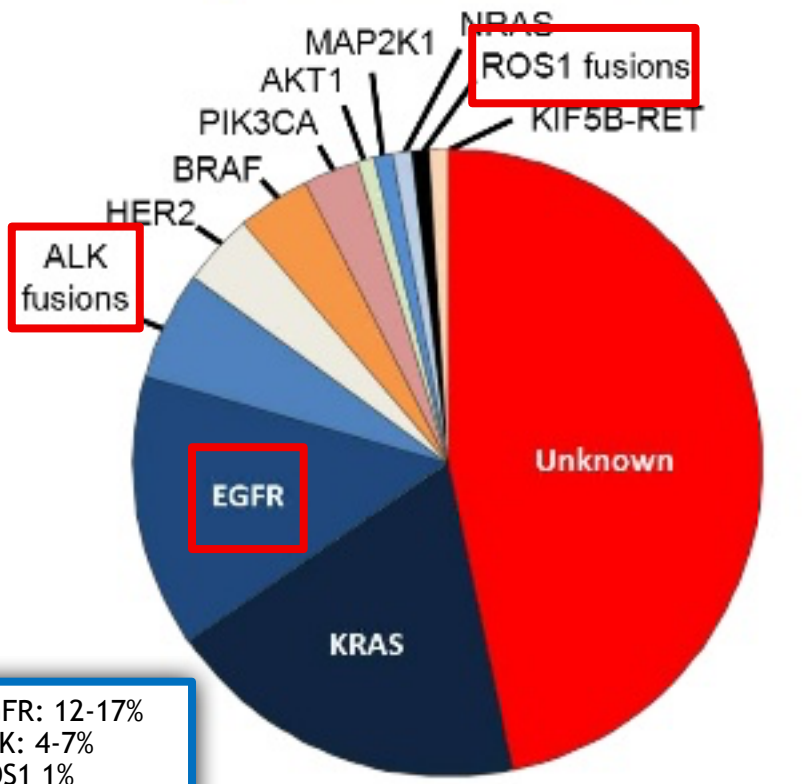
Personalized medicine: tailored treatments



Different people respond differently to the same therapy: while one treatment brings about the desired success in one group of patients with e.g. colon cancer, it does not change the condition of other groups at all, or even leads to adverse effects (left). The reason: the genetic makeup and metabolic profile of each individual patient influences the effect of a drug. Personalized medicine takes these individual patterns of cellular and metabolic products into account in the diagnostic phase: biomarker diagnostics separates patients into groups with similar characteristics, and provides information on the best individual treatment. This should enable all patients to benefit from their own, "personal" therapy.

Potential Oncogenic Drivers in NSCLC

Adenocarcinoma



EGFR: 12-17%
ALK: 4-7%
ROS1 1%

Total: 17 – 25%

Squamous Cell Carcinoma

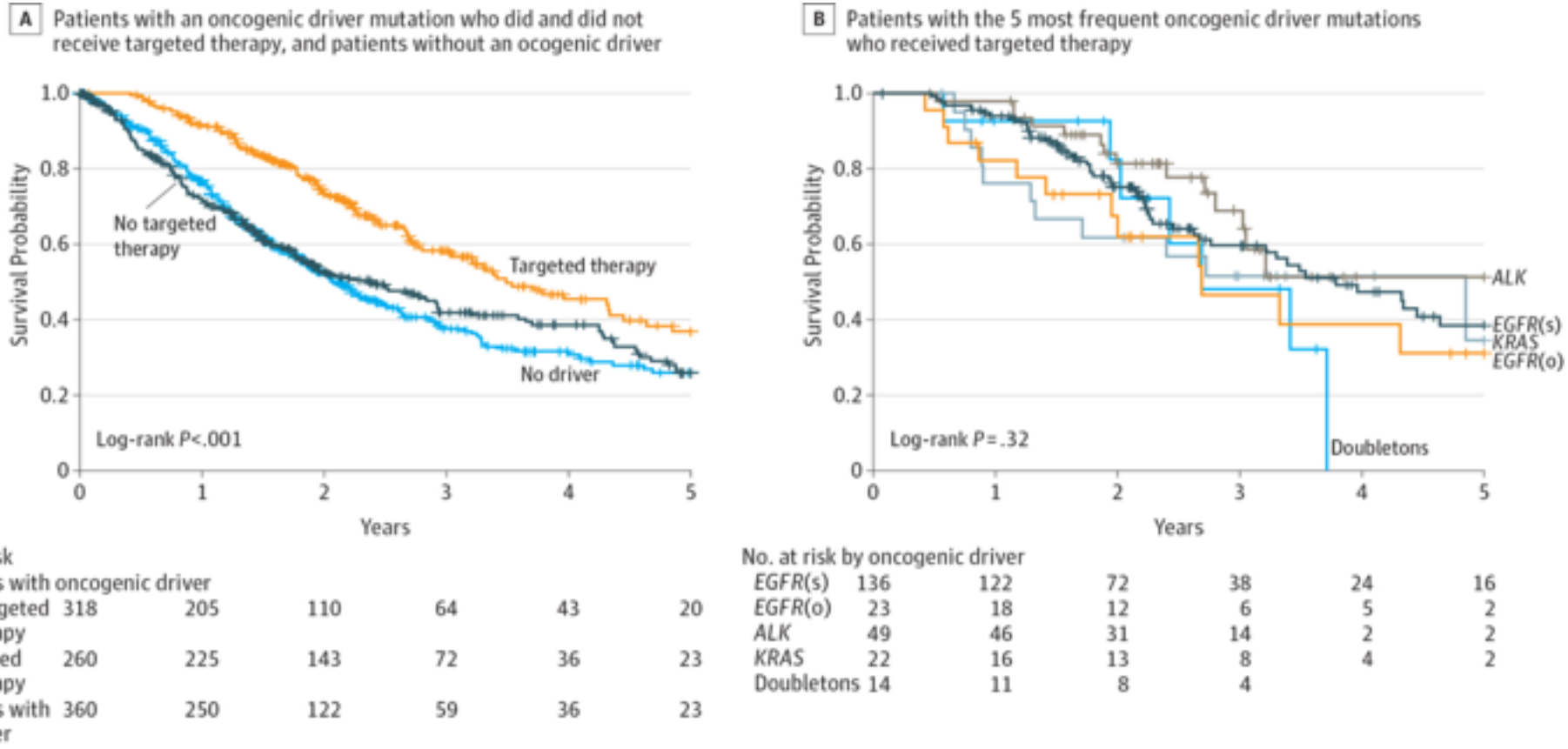
Gene	Event Type	Frequency, %
FGFR1	Amplification	20-25
FGFR2	Mutation	5
PIK3CA	Mutation	9
PTEN	Mutation deletion	18
CCND1	Amplification	8
CDKN2A	Deletion/mutation	45
PDGFRA	Amplification mutation	9
EGFR	Amplification	10
MCL1	Amplification	10
BRAF	Mutation	3
DDR2	Mutation	4
ERBB2	Amplification	2

Hammerman P, et al. IASLC WCLC 2011. Abstract PRS.1

Terapias diana aprobadas

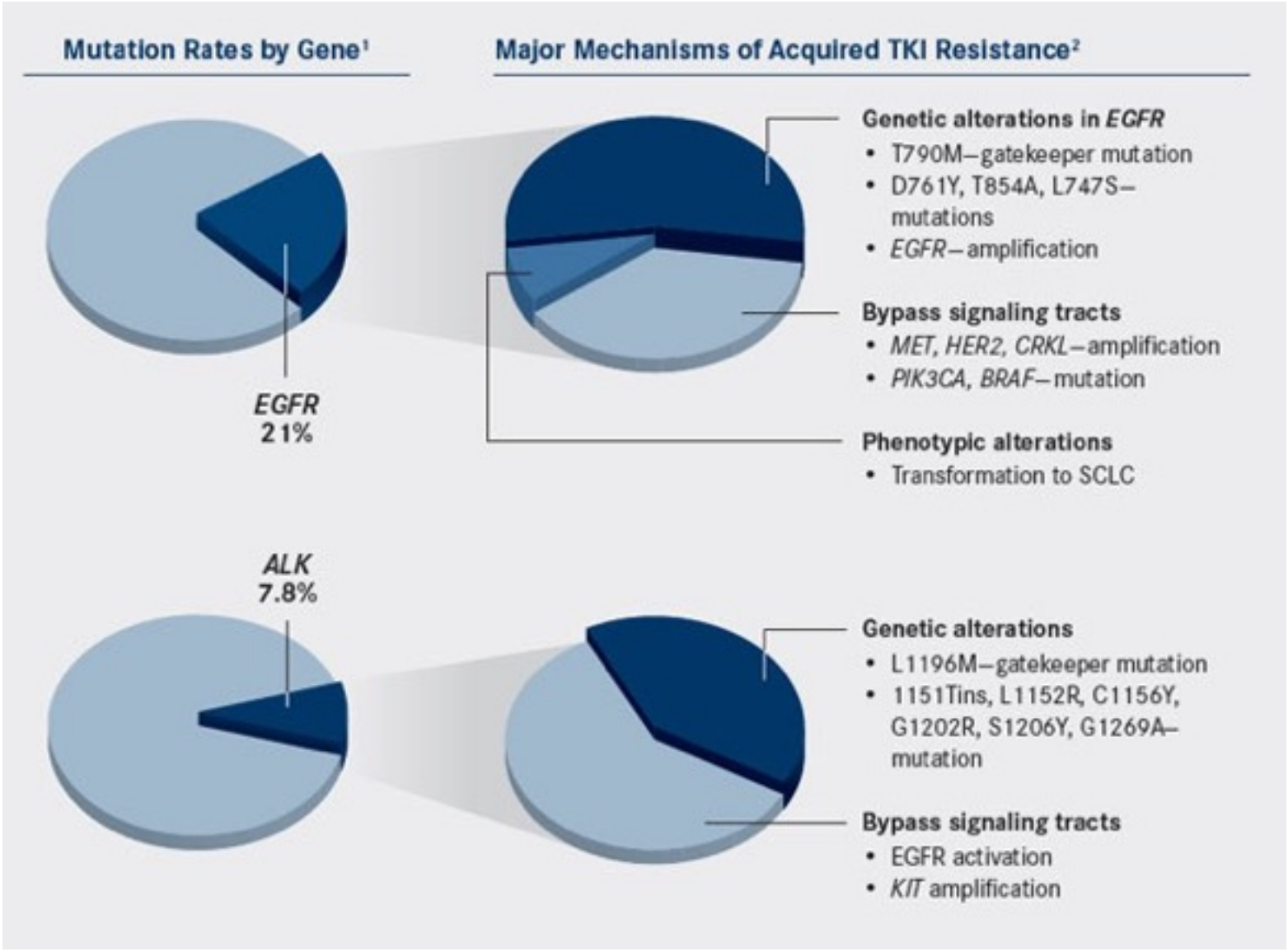
Diana	Frecuencia	Tratamiento aprobado
EGFR	12%-17%	1ªG: Gefitinib y Erlotinib (FDA y EMA) 2ªG: Afatinib (FDA y EMA) 3ª G: Osimertinib (FDA y EMA)
ALK	3-7%	1ªG: Crizotinib (FDA, EMA) 2ªG: Ceritinib (FDA, EMA) 2ªG: Alectinib (FDA)
ROS1	1%	1ª G: Crizotinib (FDA)

Using Multiplexed Assays of Oncogenic Drivers in Lung Cancers to Select Targeted Drugs

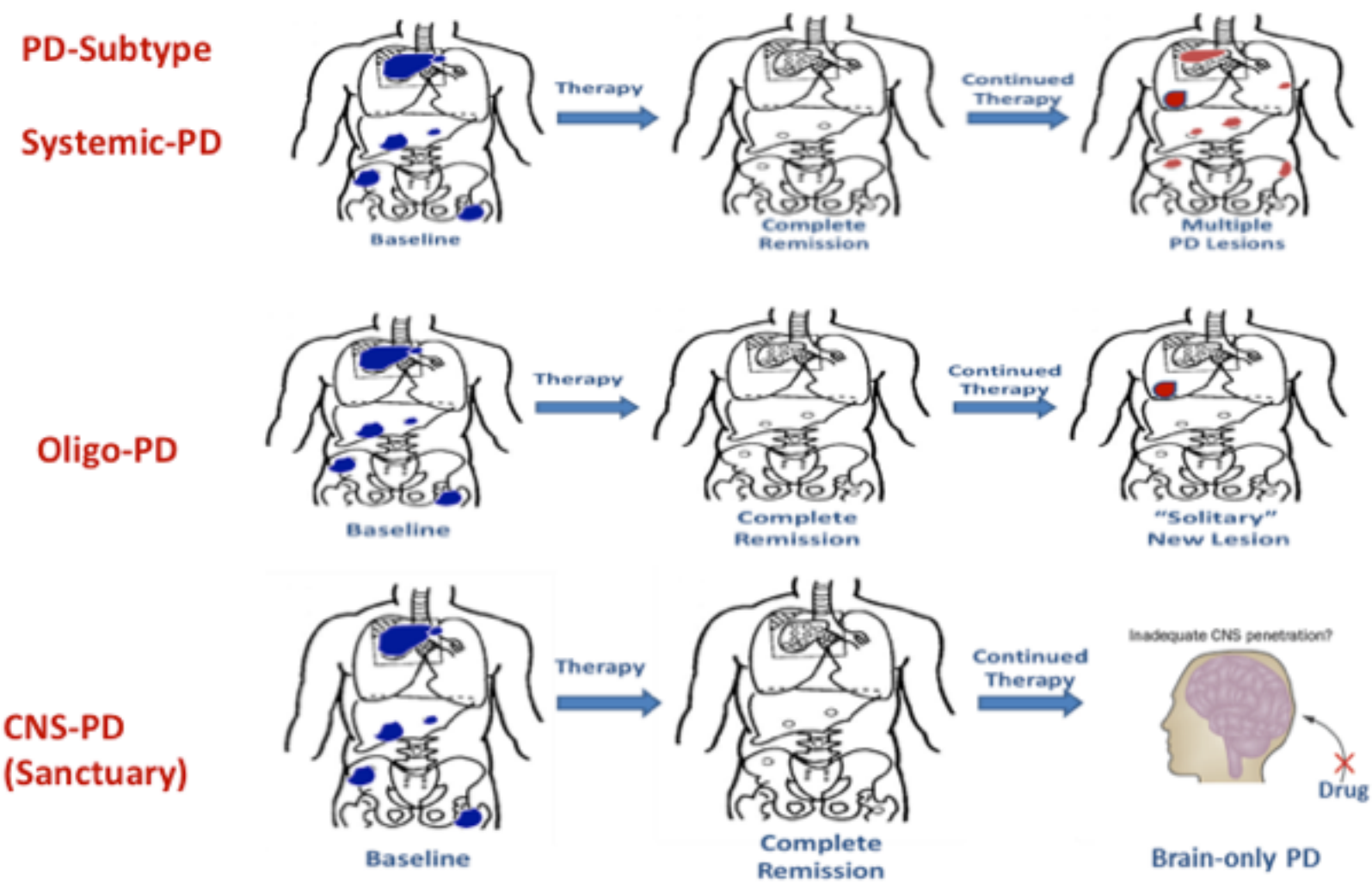


260 pts con mutación driver conocida y tratada con terapia dirigida: SGm 3.5 años
318 pts con mutación driver conocida y no tratada con terapia dirigida: SGm 2.4 años
360 pts sin mutación driver: SGm 2.1 años JAMA. 2014;311(19):1998-2006. doi:10.1001/jama.2014.3741

Mecanismos de resistencia adquirida a ITKs



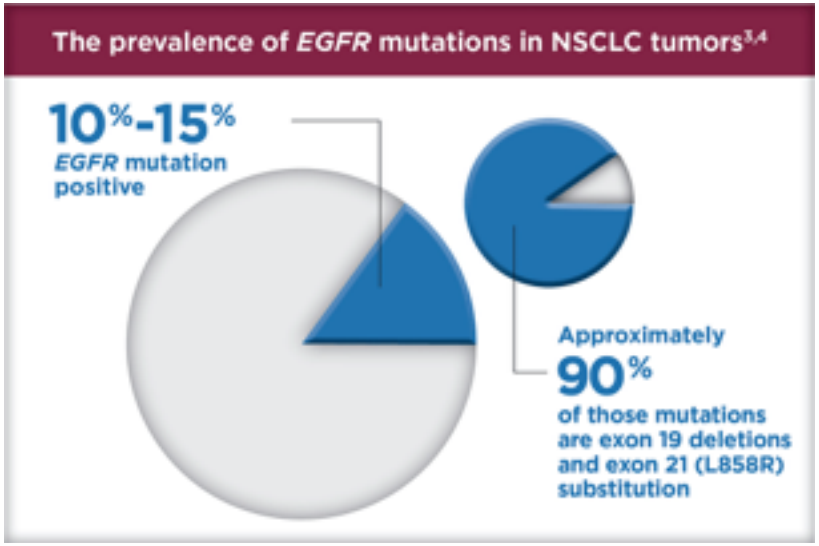
Not all Patients with Acquired Resistance to Targeted TKIs are Created Equal: Three PD Subtypes



Gandara D. - Educational ASCO 2013

EGFR m+

Carcinoma no microcítico de pulmón avanzado



EGFR m+

EGFR ITK + Quimioterapia

- No demostrado papel relevante en 1ªL en EGFRm+
  - 4 EC negativos (pacientes no seleccionados)

- F II: FASTACT-2
  - n=451 1ª línea carbo + gem vs carbo + gem + erlotinib. En 97 EGFRm+:
    - SLP 7.6m vs 6m
    - SG 18.3 vs 15.2m
  - No beneficio en EGFRwt

- F III IMPRESS. EGFRm+ tratados con gefitinib
  - n=265 1ª línea cis + pem + gefitinib vs cis + pem:
    - SLP 5.4m vs 5.4m
    - HR 0.86

EGFR m+

Author	Study	Agent	N (EGFR mut +)	RR	Median PFS (mo)	PFS HR	OS (mo)	OS HR	Crossover (%)
Mok et al	IPASS	**Gefitinib** (vs carbo/pacli)	261	71.2% vs 47.3%	9.8 vs 6.4	0.48 (0.36-0.64)	21.6 vs 21.9	1.00 (0.76-1.33)	40
Han et al	First-SIGNAL	**Gefitinib** (vs cim/gem)	42	84.6% vs 37.5%	8.0 vs 6.3	0.54 (0.27-1.1)	27.2 vs 25.6	1.04 (0.50-2.18)	75
Mitsudomi et al	WJTOG 3405	**Gefitinib** (vs carbo/pacli)	172	62.1% vs 32.2%	9.2 vs 6.3	0.49 (0.34-0.71)	30.9 vs NR	1.25 (0.88-1.78)	60
Maemondo et al	NEJGSG002	**Gefitinib**	230	73.7% vs	10.8 vs 5.4	0.30	30.5 vs 23.6	0.89	94.6
Zhou et									
Rosell									
Wu et a									
Sequist		(cis/pem)				(0.43-0.78)		(0.58-1.06)	
Wu et al	LUX-Lung 6	**Afatinib** (cis/gem)	364	67% vs 23%	11 vs 5.6	0.28 (0.20-0.39)	23.6 vs 23.5	0.83 (0.62-1.09)	56
Park et al	LUX-Lung 7	Afatinib vs Gefitinib	319	70% vs 56%	11 vs 10.9	0.73 (0.57-0.95)	Datos inmaduros	-	-

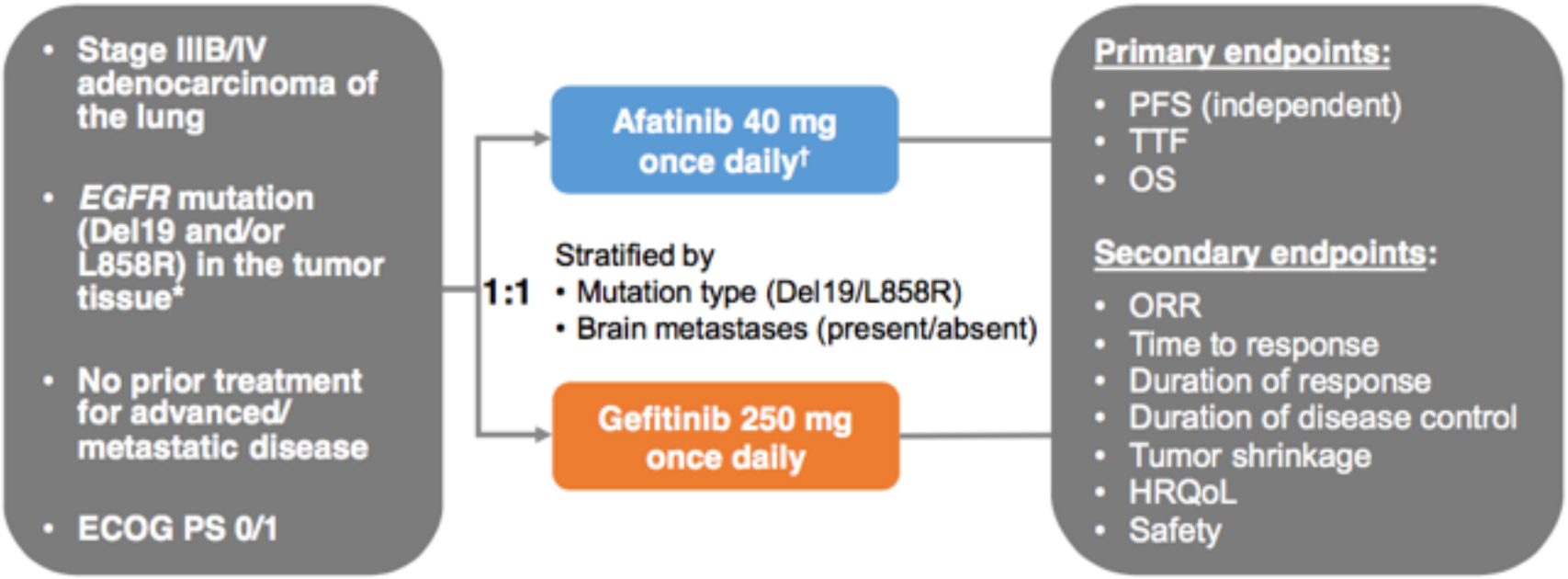
En el tratamiento de 1ª línea en CNMP EGFRm+, los EGFR ITKs de 1ª generación (erlotinib, gefitinib) y 2ª generación (afatinib) **mejoran claramente la SLP** frente a QT basada en platino.

En estos ensayos no han demostrado beneficio en SG debido al empleo de estos ITKs en **2ª línea tras progresión a quimioterapia**

EGFR m+

LUX-Lung 7

Primer estudio randomizado que compara dos ITKs EGFR en 1ª

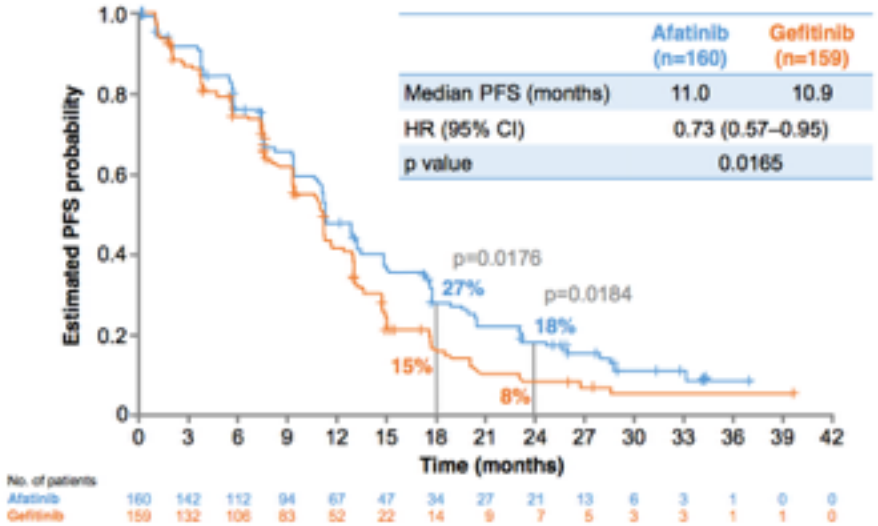


- Treatment beyond progression allowed if deemed beneficial by investigator
- RECIST assessment performed at Weeks 4, 8 and every 8 weeks thereafter until Week 64, and every 12 weeks thereafter

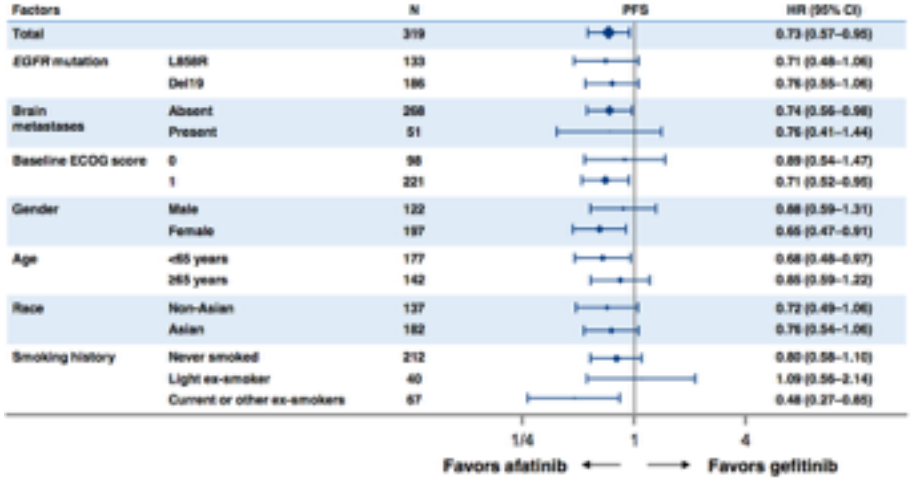
*Central or local test
†Dose modification to 50, 30, 20 mg permitted in line with prescribing information

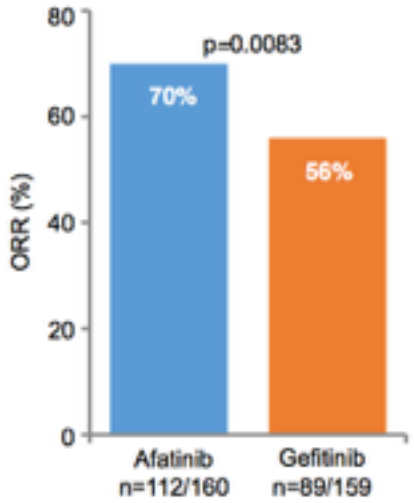
EGFR m+

LUX-Lung 7: SLP



	Afatinib (n=160)	Gefitinib (n=159)
Median PFS (months)	11.0	10.9
HR (95% CI)	0.73 (0.57–0.95)	
p value	0.0165	



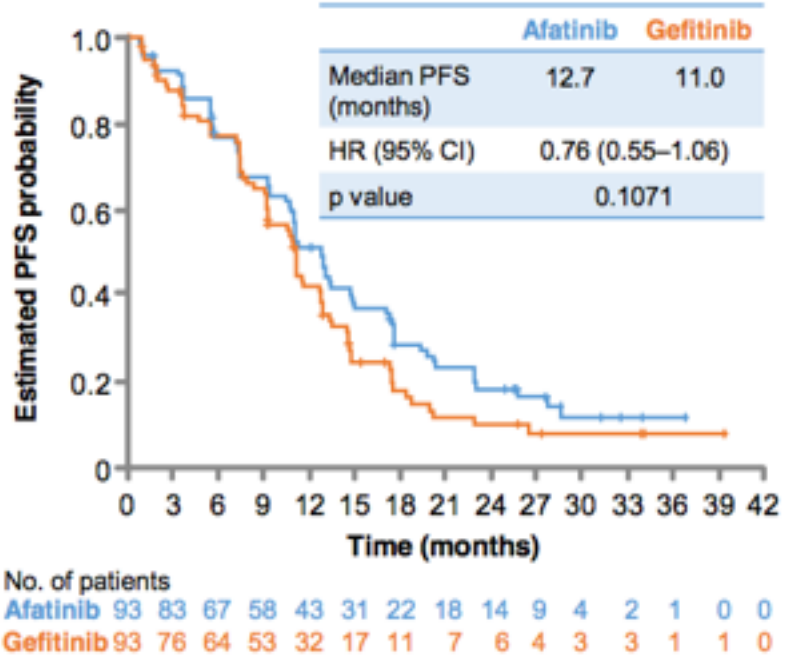


	Afatinib (n=112)	Gefitinib (n=89)
Median DoR (months)	10 .1	8.4
95% CI	(7.8–11.1)	(7.4–10.9)

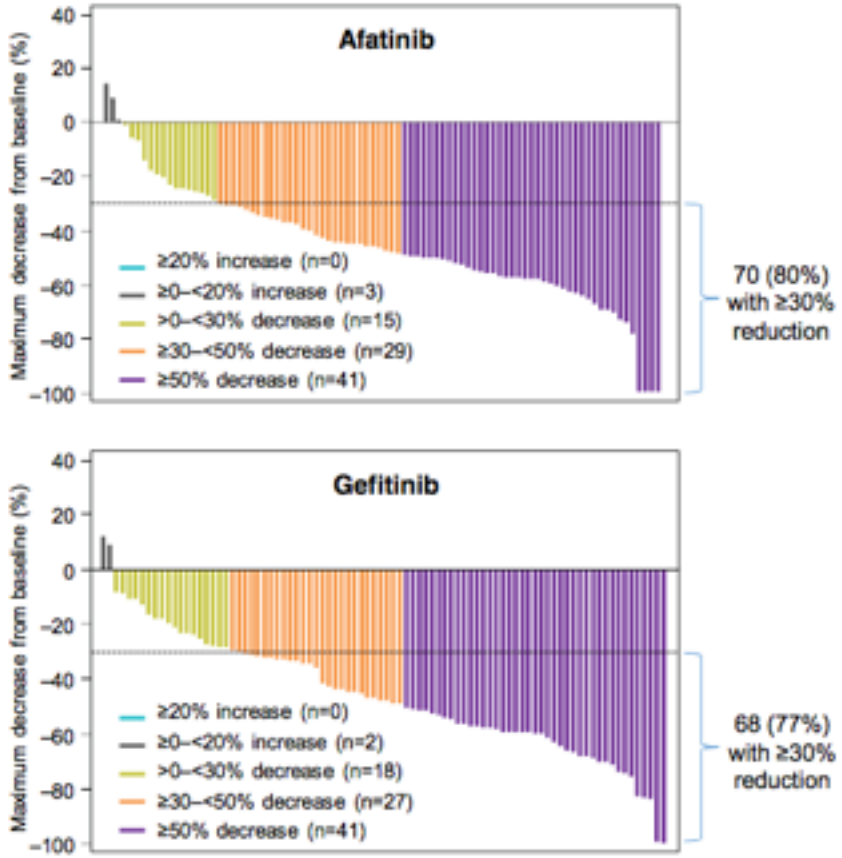
EGFR m+

LUX-Lung 7

Efficacy in patients with Del19 mutation



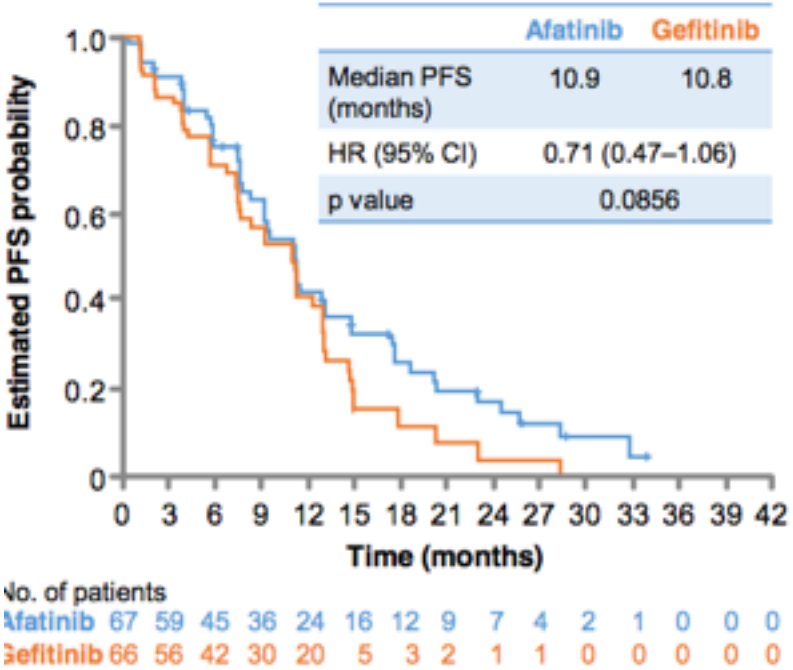
	Afatinib (n=93)	Gefitinib (n=93)
ORR	73%	66%



EGFR m+

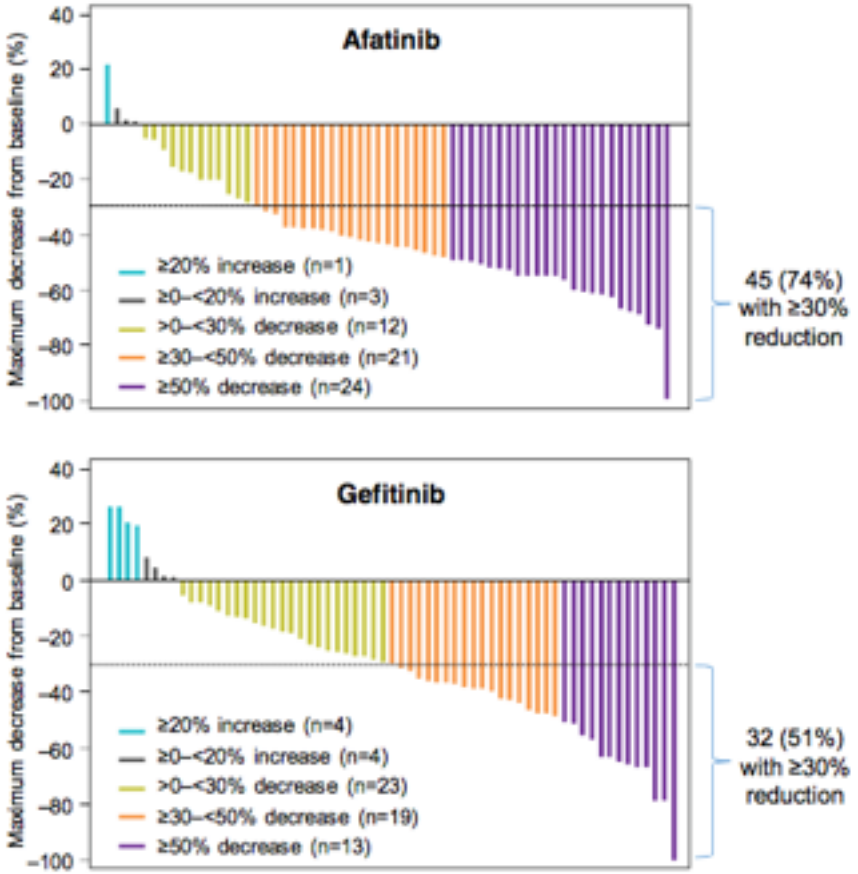
LUX-Lung 7

Efficacy in patients with L858R mutation



	Afatinib	Gefitinib
Median PFS (months)	10.9	10.8
HR (95% CI)	0.71 (0.47–1.06)	
p value	0.0856	

	Afatinib (n=67)	Gefitinib (n=66)
ORR	66%	42%



EGFR m+

LUX-Lung 7

Events, %	Afatinib (n=160)	Gefitinib (n=159)
Any AE	98.8	100.0
Drug-related AEs	97.5	96.2
AEs leading to dose reduction*	41.9	1.9*
Drug-related AEs leading to discontinuation	6.3	6.3
Serious AEs	44.4	37.1
Drug-related serious AEs	10.6	4.4†
Drug-related fatal AE	-	0.6‡

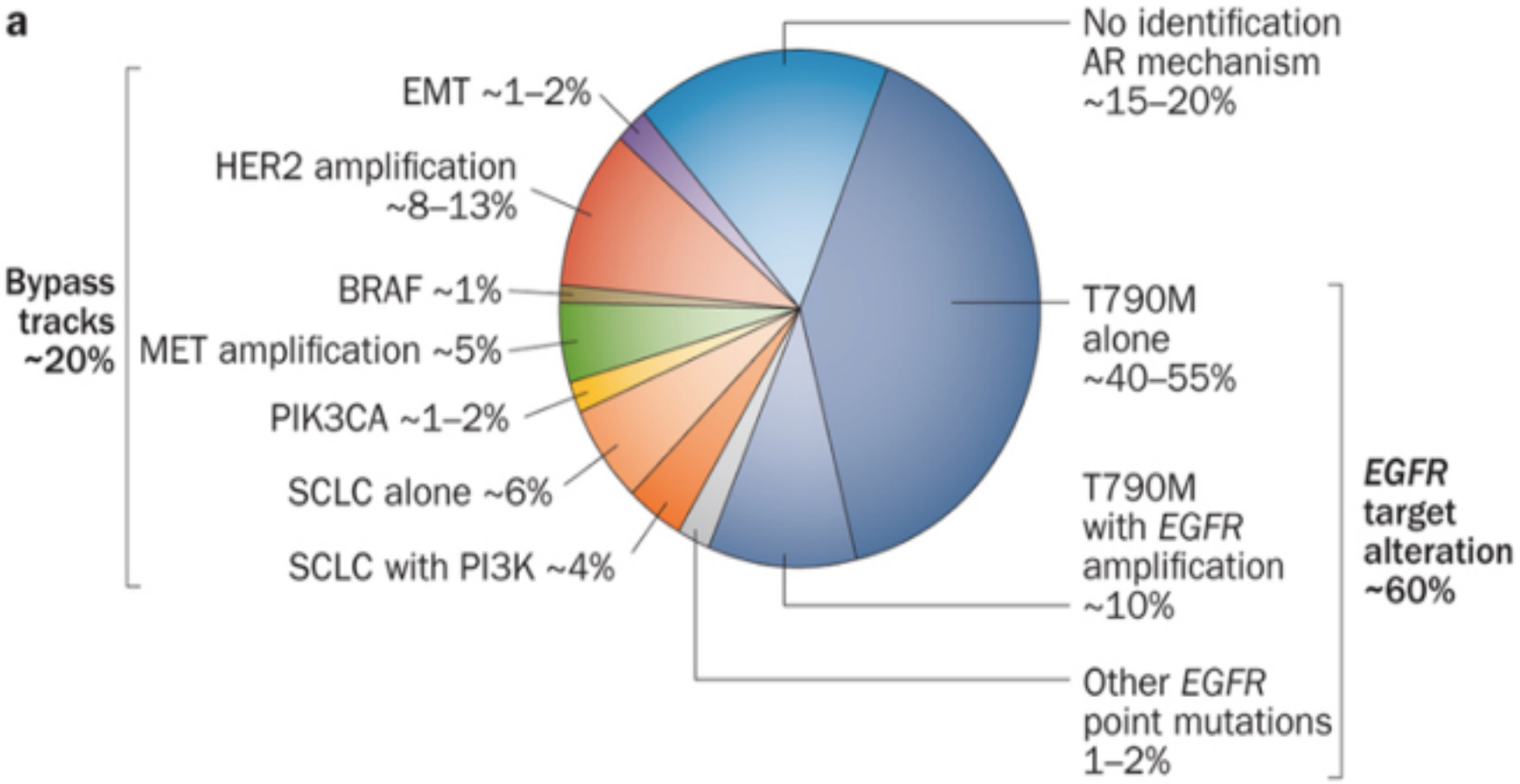
*No dose reductions foreseen for gefitinib according to prescribing information
†Including four patients with drug-related ILD (no drug-related ILD on afatinib)
‡One patient died of hepatic failure

	Afatinib (n=160)		Gefitinib (n=159)	
AE category, %	All	Grade 3	All	Grade 3
Diarrhea	90.0	11.9†	61.0	1.3
Rash/acne*	88.8	9.4	81.1	3.1
Stomatitis*	64.4	4.4	23.9	-
Paronychia*	55.6	1.9	17.0	0.6
Dry skin	32.5	-	37.1	-
Pruritus	23.1	-	22.6	-
Fatigue*	20.6	5.6	14.5	-
Decreased appetite	16.3	0.6	11.9	-
Nausea	16.3	1.3	13.8	-
Alopecia	10.6	-	15.1	-
Vomiting	10.6	-	3.8	0.6
ALT increased	9.4	-	23.9	7.5‡
AST increased	6.3	-	20.8	2.5

*Grouped terms of AEs

EGFR m+ Resistencia a EGFR ITKs

Ocurre tras 9-13 m de tratamiento con EGFR ITKs



Nature Reviews Clinical Oncology 11, 473–481 (2014)

Resistencia EGFR m+
Quimioterapia

Manejo asistencial de la resistencia: quimioterapia

Poca evidencia de la eficacia de la QT en EGFRm + que progresan a ITK

Probablemente comparable a la 1ªL de QT en EGFRm+ (no tratados previamente)

Estudio	Tratamiento	N	RR	Diseño
Gridelli JCO 2012	Cis/Gem	13	15%	Prospectivo
Wu IJC 2010	Varios	41	15%	Retrospectivo
Goldberg ASCO 2012	Varios	28	18%	Retrospectivo
Yoshimura JCO 2012	Pem/TKI	27	26%	Prospectivo

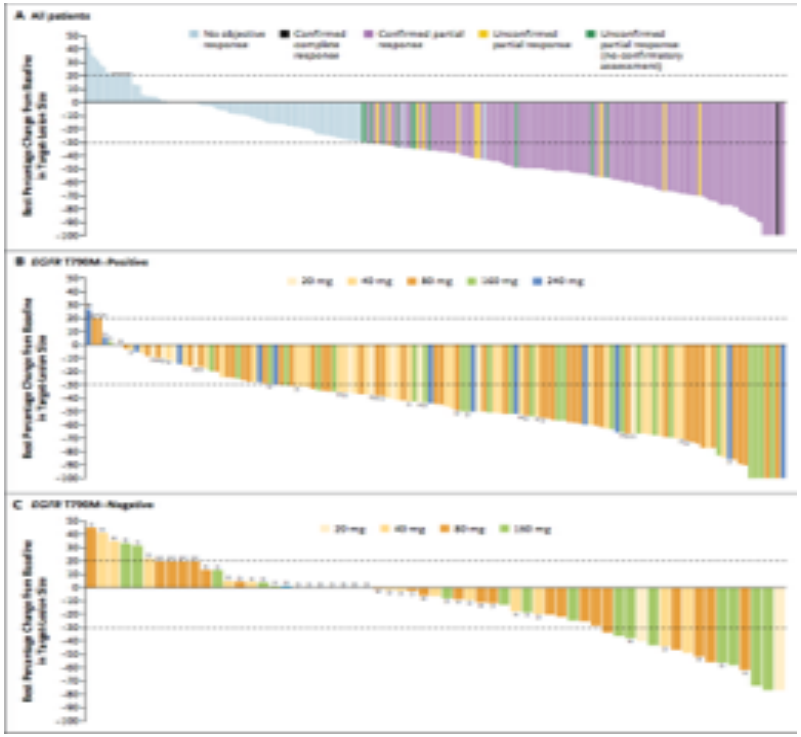
Resistencia EGFR m+ ITKs 3ºG

Osimertinib (3ªG): Activo frente T790M EGFRm+

Fase I/II n= 253 EGFRm+ con R a IKT

TR 61% y SLP 9.6 m si T790M (127 ptes)
TR 21% y SLP 2.8 m si no T790M (61 ptes)

80 mg al día
Aprobado FDA



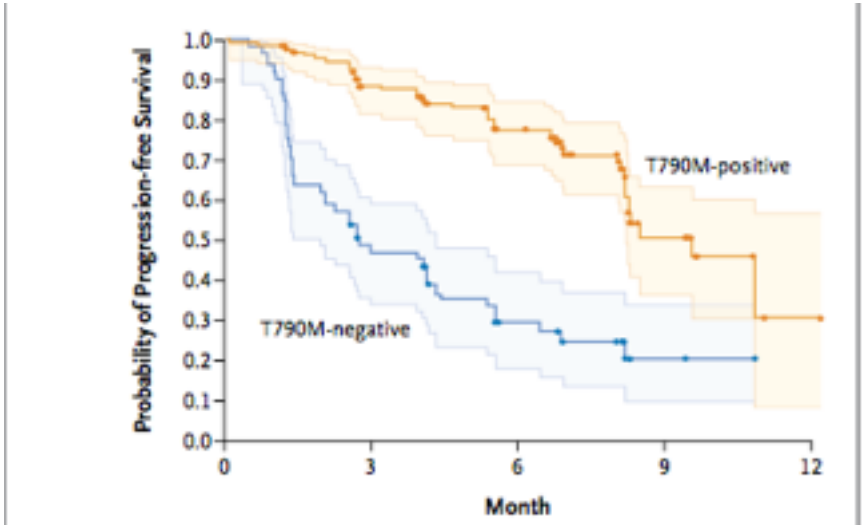


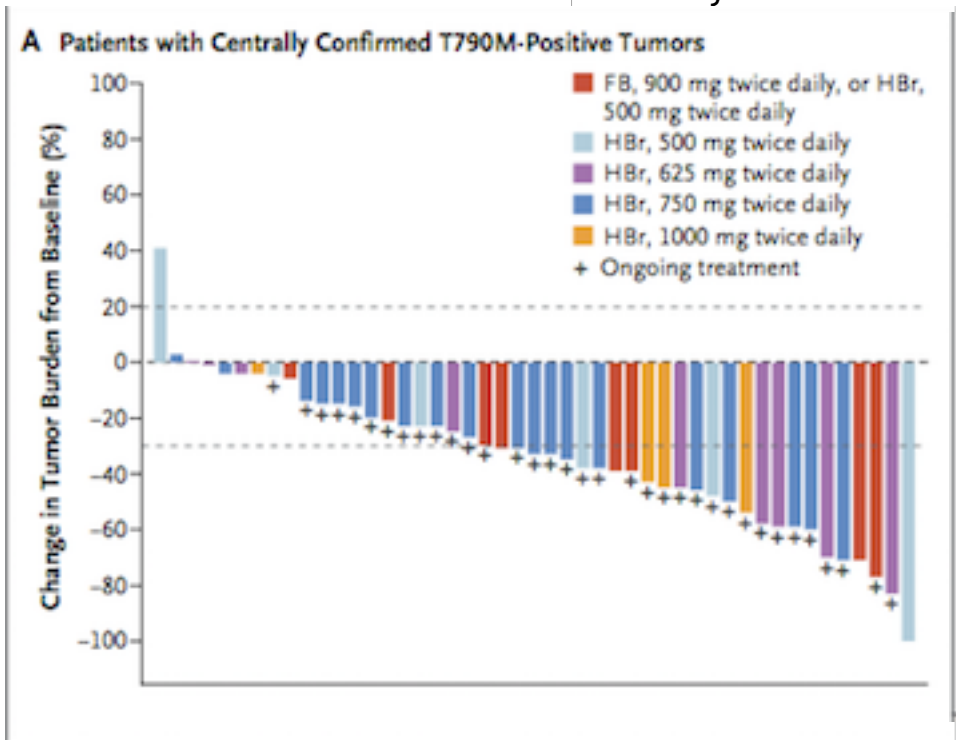
Figure 3. Progression-free Survival According to Status with Respect to *EGFR* T790M.

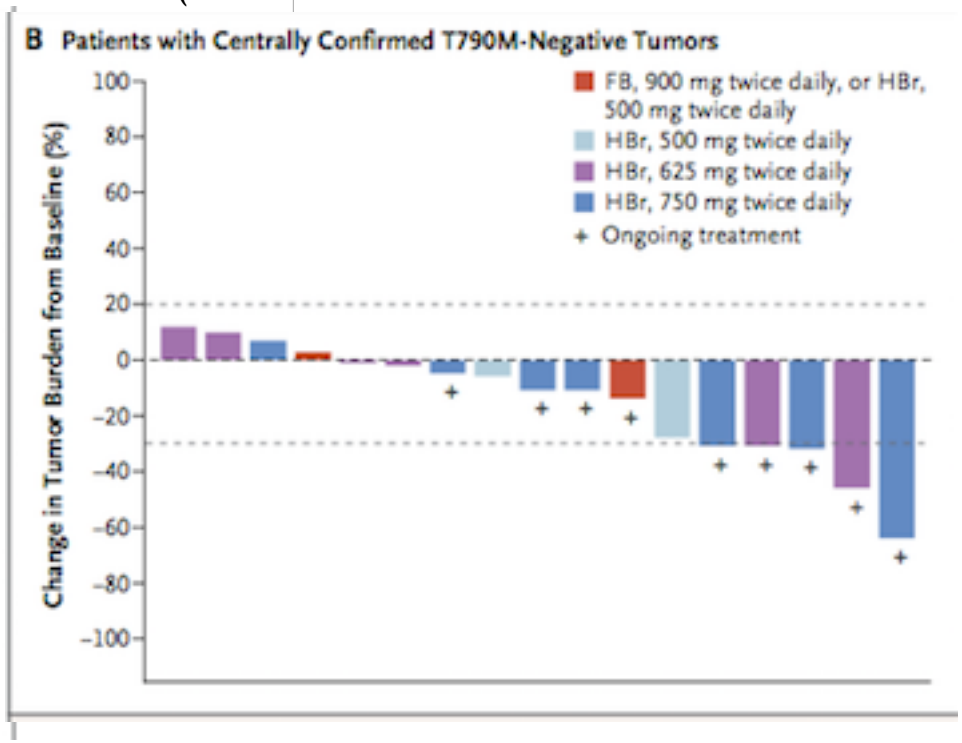
Resistencia EGFR m+ ITKs 3ºG

Rociletinib (3ªG): Activo frente T790M EGFRm+

Fase I/II n= 130 EGFRm+ con R a IKT

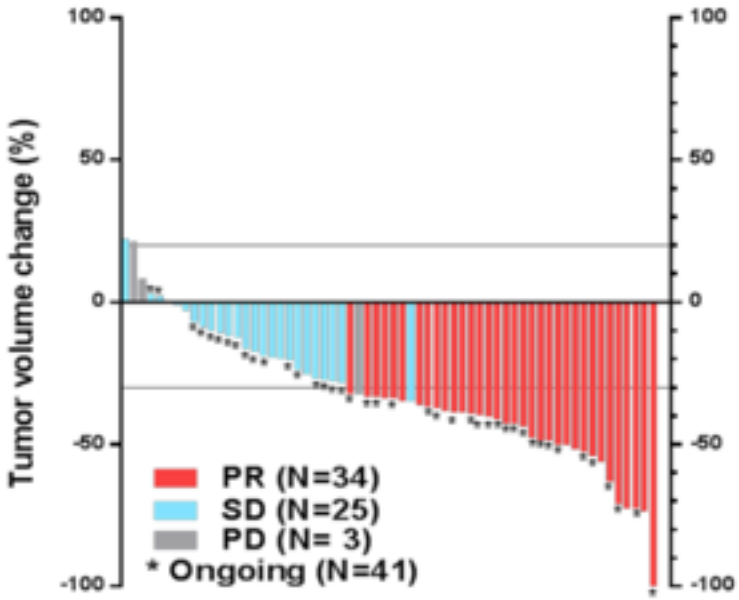
TR 59% y SLP 13.1 m si T790M (46 ptes)
TR 29% y SLP 5.6 m si no T790M (17

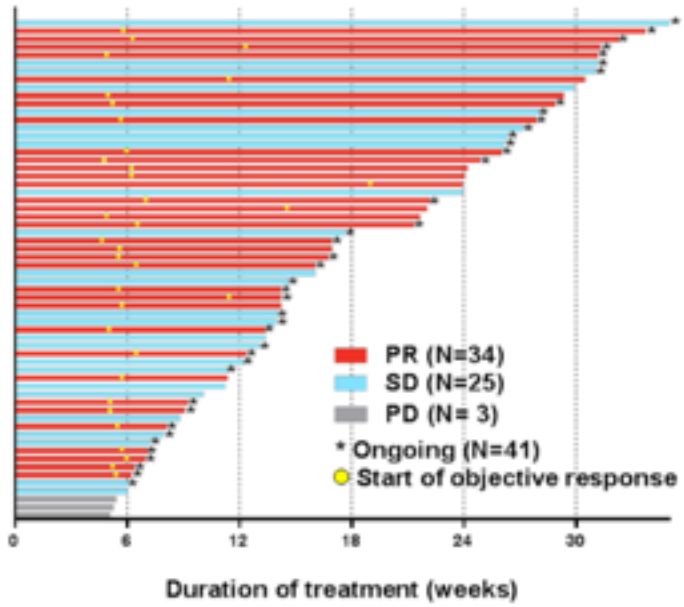




Resistencia EGFR m+ ITKs 3ºG

HM61713 (3ªG): Activo frente T790M EGFRm+



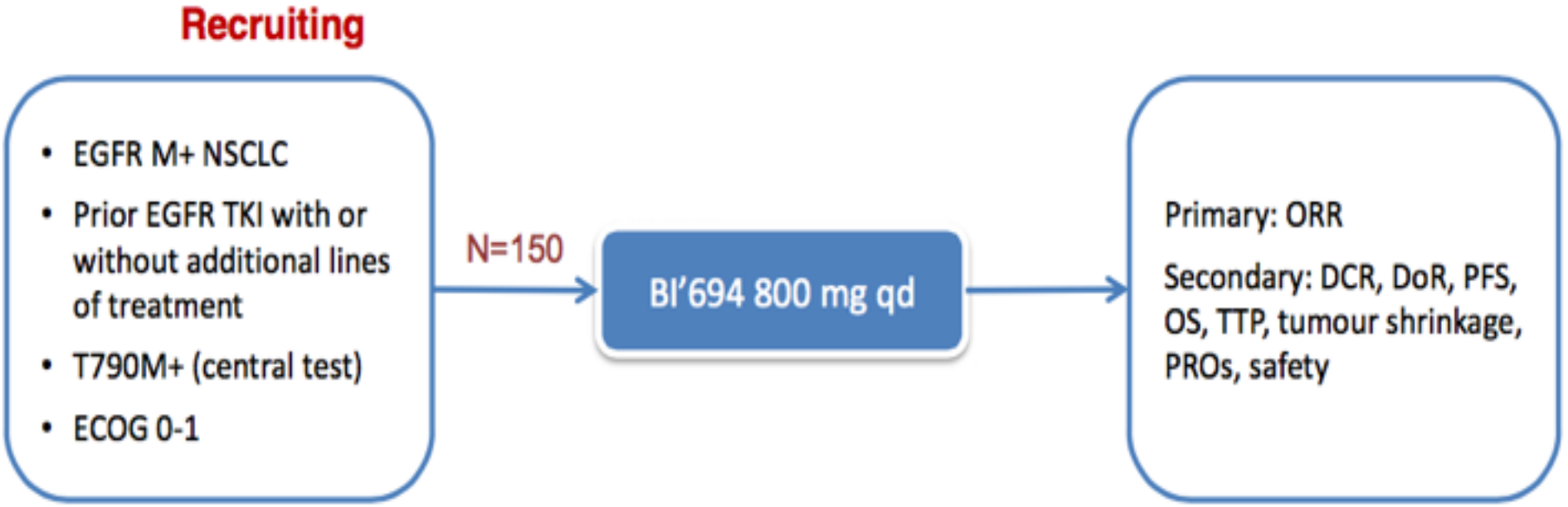


	ORR (%)	DCR (%)	Median PFS
N=62	54.8	95.2	Not reached

>70% of responders still continue on treatment

Lee JS, et al. ESMO Asia 2015; #425PD

ELUXA 1: Phase II study in T790M+ NSCLC



- Countries: USA, Korea, Taiwan, Malaysia, Philippines, Italy, Spain; Canada, Australia, Germany
- Coordinating Investigators: Prof. K. Park and Dr. P. Janne
- FPI – July 2015 (Korea)

Lee JS, et al. ESMO Asia 2015; #425PD

1ª línea EGFR m+ Erlotinib + BVZ

Erlotinib plus bevacizumab versus erlotinib alone as first-line treatment for advanced *EGFR* mutation-positive non-squamous non-small-cell lung cancer: an open-label, randomized trial

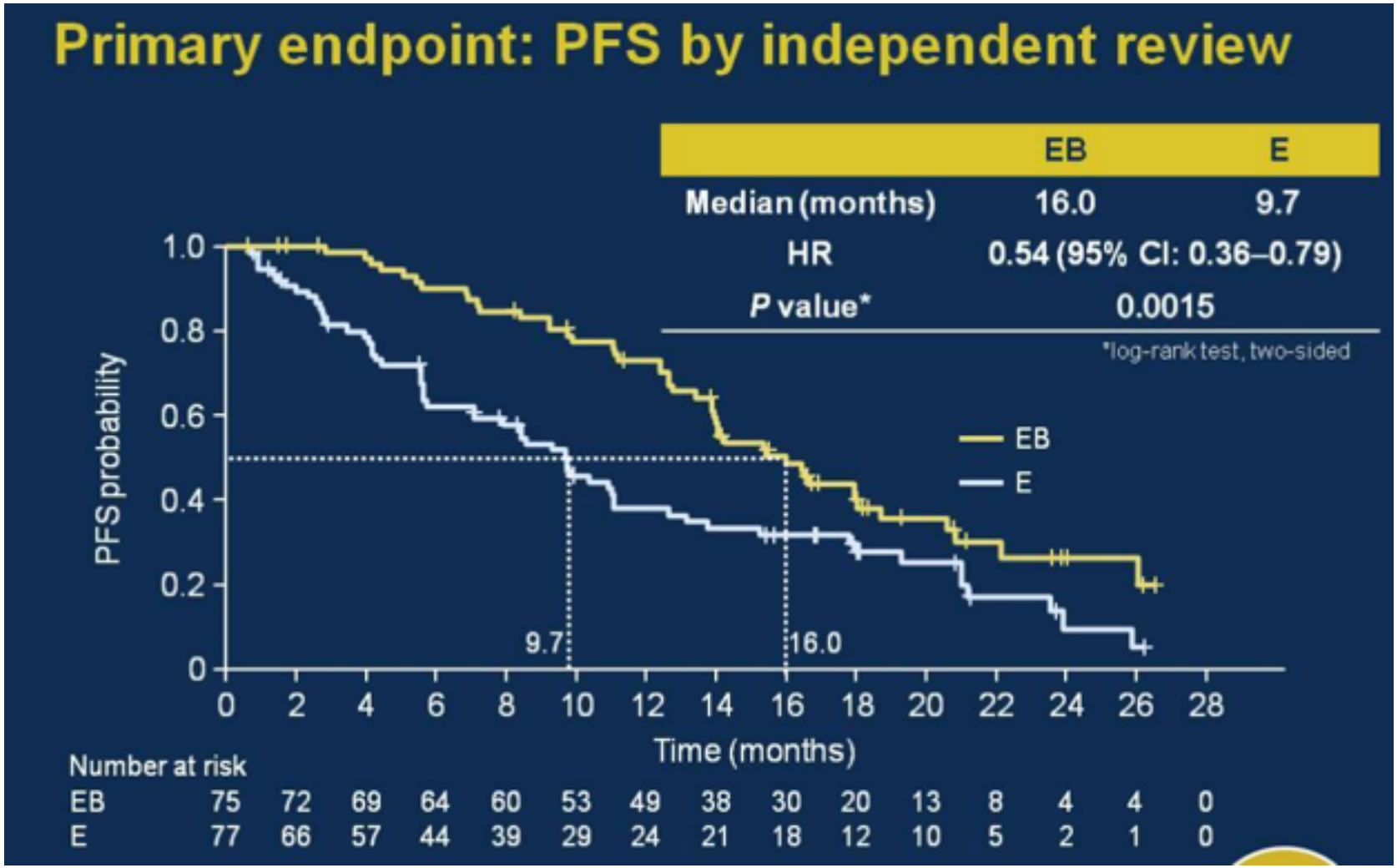
Terufumi KATO, Takashi SETO, Makoto NISHIO, Koichi GOTO
Shinji ATAGI, Yukio HOSOMI, Noboru YAMAMOTO, Toyoaki HIDA
Makoto MAEMONDO, Kazuhiko NAKAGAWA, Seisuke NAGASE
Isamu OKAMOTO, Takeharu YAMANAKA
Ryosuke HARADA, Masahiro FUKUOKA
and Nobuyuki YAMAMOTO

A phase II trial of erlotinib (E) and bevacizumab (B) in patients with advanced non-small-cell lung cancer with activating epidermal growth factor receptor mutations with and without T790M mutation.

Spanish Lung Cancer Group and the European Thoracic Oncology Platform BELIEF trial

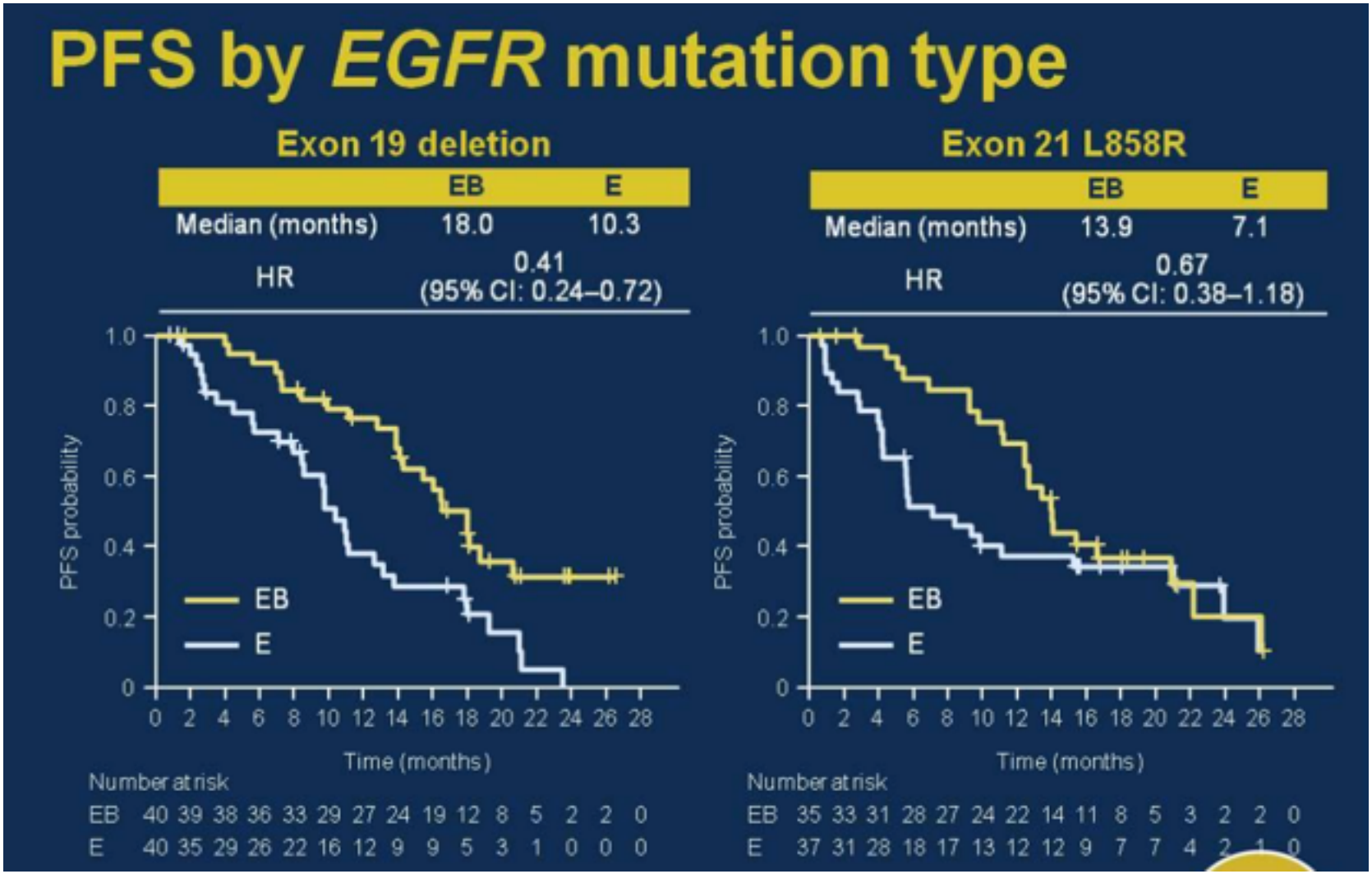
1ª línea EGFR m+ Erlotinib + BVZ

II JO25567 Phase II trial



1ª línea EGFR m+ Erlotinib + BVZ

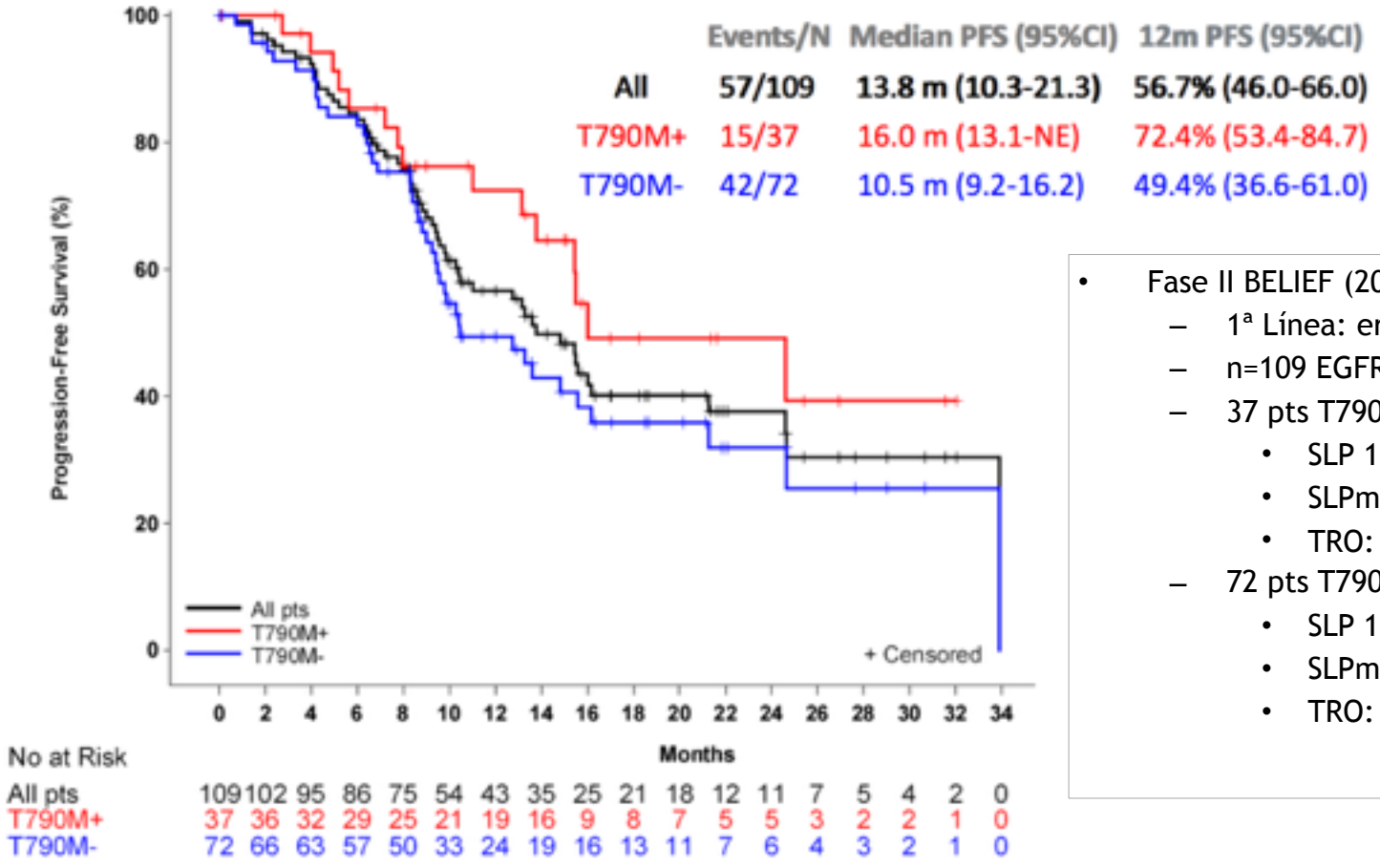
II JO25567 Phase II trial



1ª línea EGFR m+ Erlotinib + BVZ

BELIEF Phase II trial

13 | ETOP 2-11 BELIEF: PFS by T790M mutation (N=109)

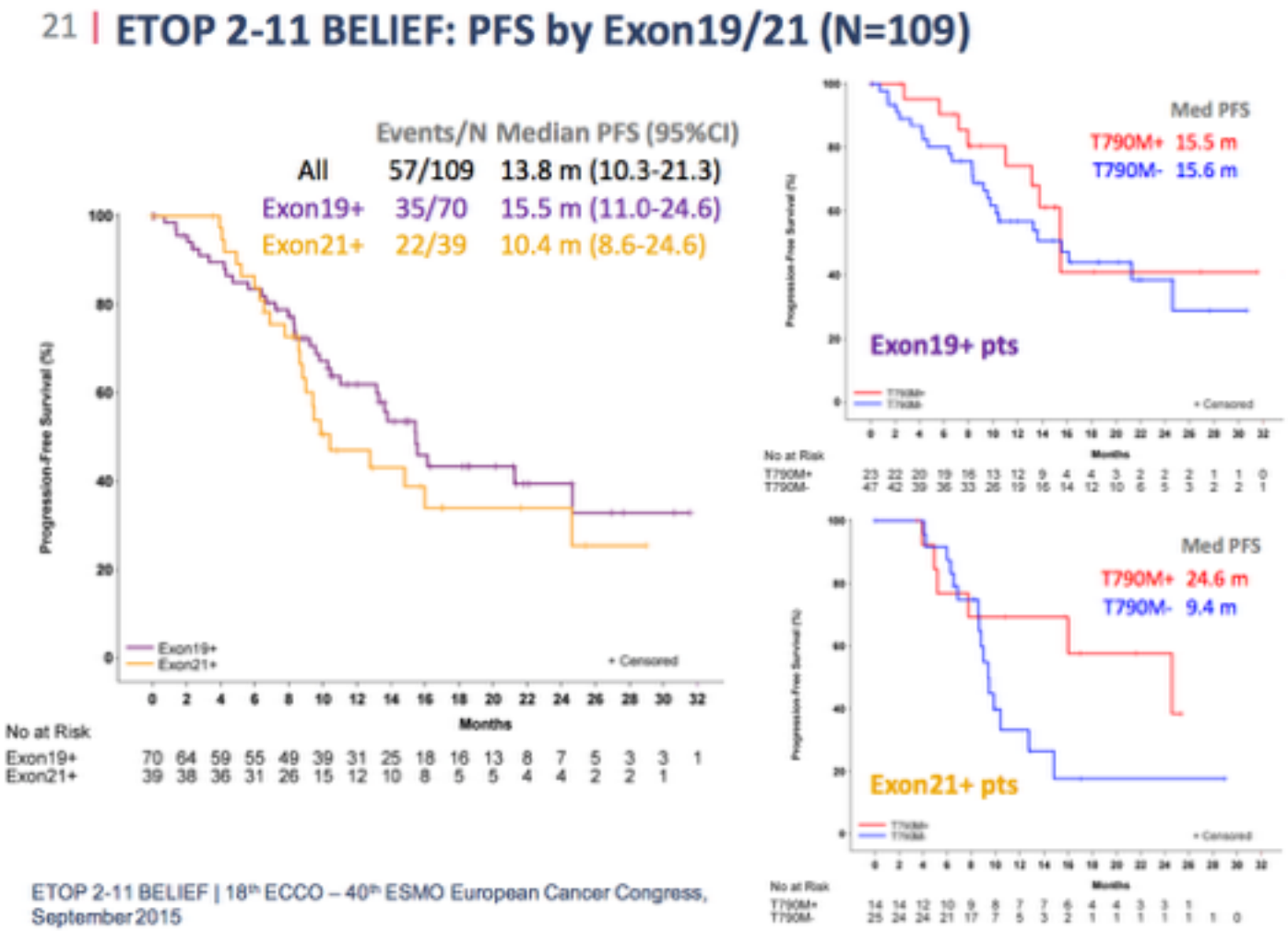


ETOP 2-11 BELIEF | 18th ECCO – 40th ESMO European Cancer Congress, September 2015

- Fase II BELIEF (2015 ECC)
  - 1ª Línea: erlotinib + BVZ
  - n=109 EGFRm+ (Del 19, L858R)
  - 37 pts T790m+ pretratamiento
    - SLP 1a: 72.4%
    - SLPm 16m
    - TRO: 70.3%
  - 72 pts T790m- pretratamiento
    - SLP 1a: 49.4%
    - SLPm: 10.5m
    - TRO: 79.2%

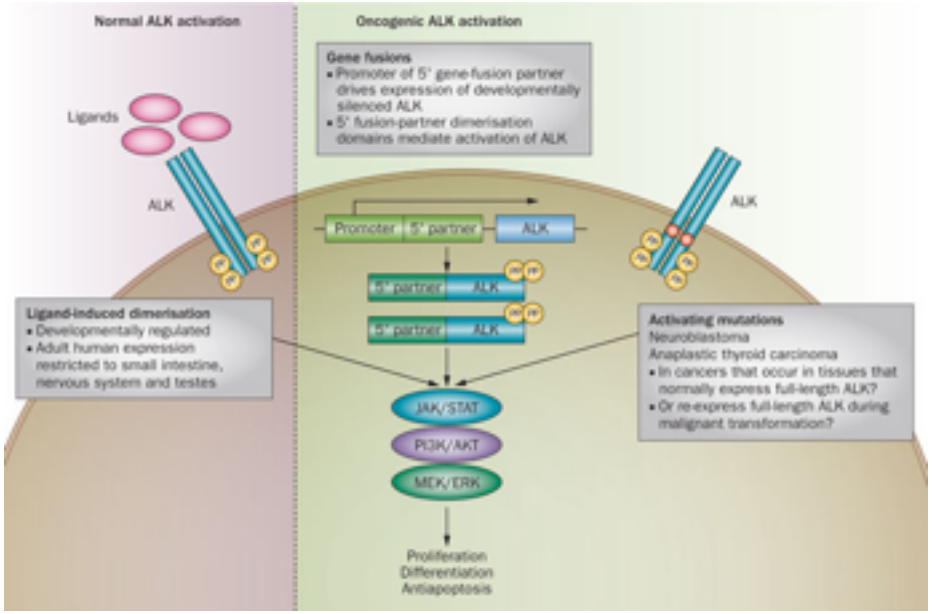
1ª línea EGFR m+ Erlotinib + BVZ

BELIEF Phase II trial



ALK+

Carcinoma no microcítico de pulmón avanzado

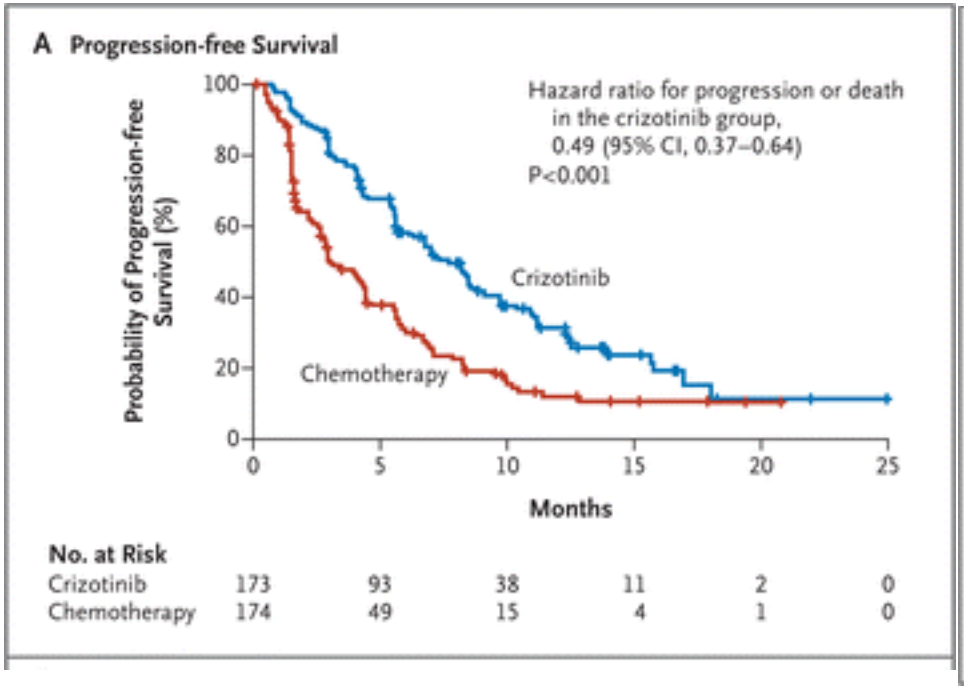


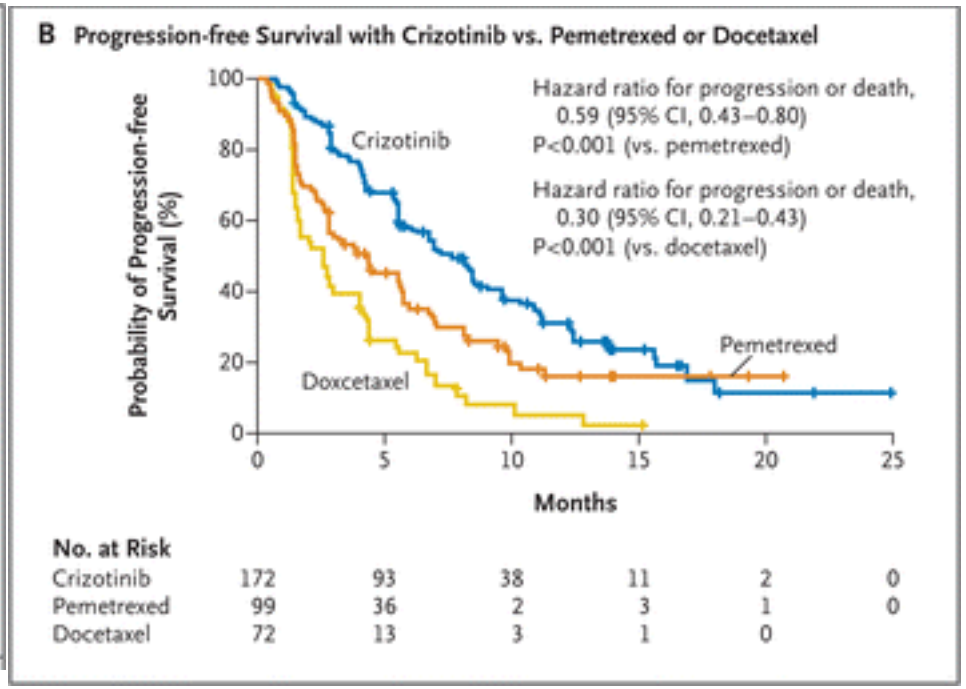
ALK+ Eficacia de crizotinib

Study	Phase	n	Design	ORR	Median duration of response (wks)	Median duration of treatment (wks)	Median PFS (mo)	PFS HR	OS HR	Median OS (mo)	Crossover (%)
PROFILE 1001	I	143	Single-arm Dose escalation from 50 qd – 300 BID	60.8%	49.1	43.1	9.7				
PROFILE 1005	II	439	Single-arm Administered 250 mg BID	59.8%	45.6	N/A	8.1				
PROFILE 1007	III	347	**Crizotinib** (vs pem or doce) in 2ªL	65% vs 20%	32.1	15.9	7.7 vs 3.0	0.49	1.02	20.3 vs 22.8	64%
PROFLE 1014	III	343	**Crizotinib** (vs cis-carbo + pem) in 1ªL	74% vs 45%	11.3 (mo) vs 5.3 (mo)	-	10.9 vs 7.0	0.45	0.82 No sig.	NA	70%

OS 1y 84% vs 79%

Crizotinib versus Chemotherapy in Advanced ALK-Positive Lung Cancer (PROFILE 1007). Phase III 2º-line

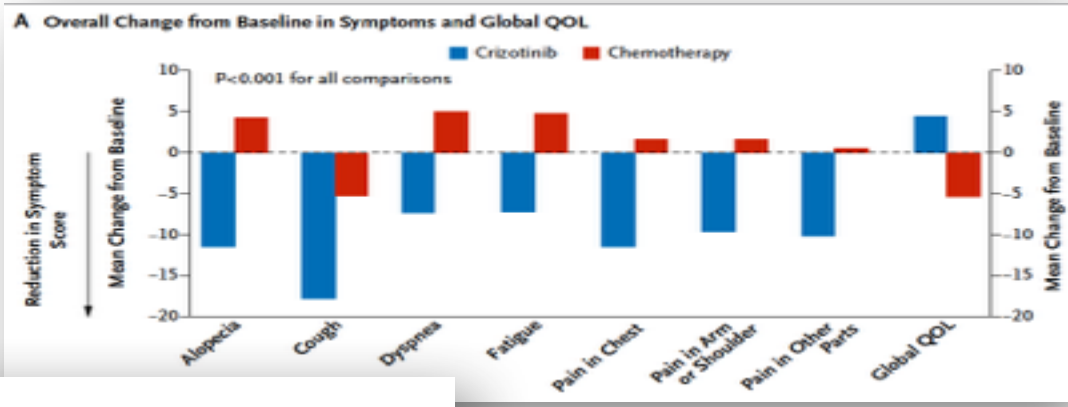


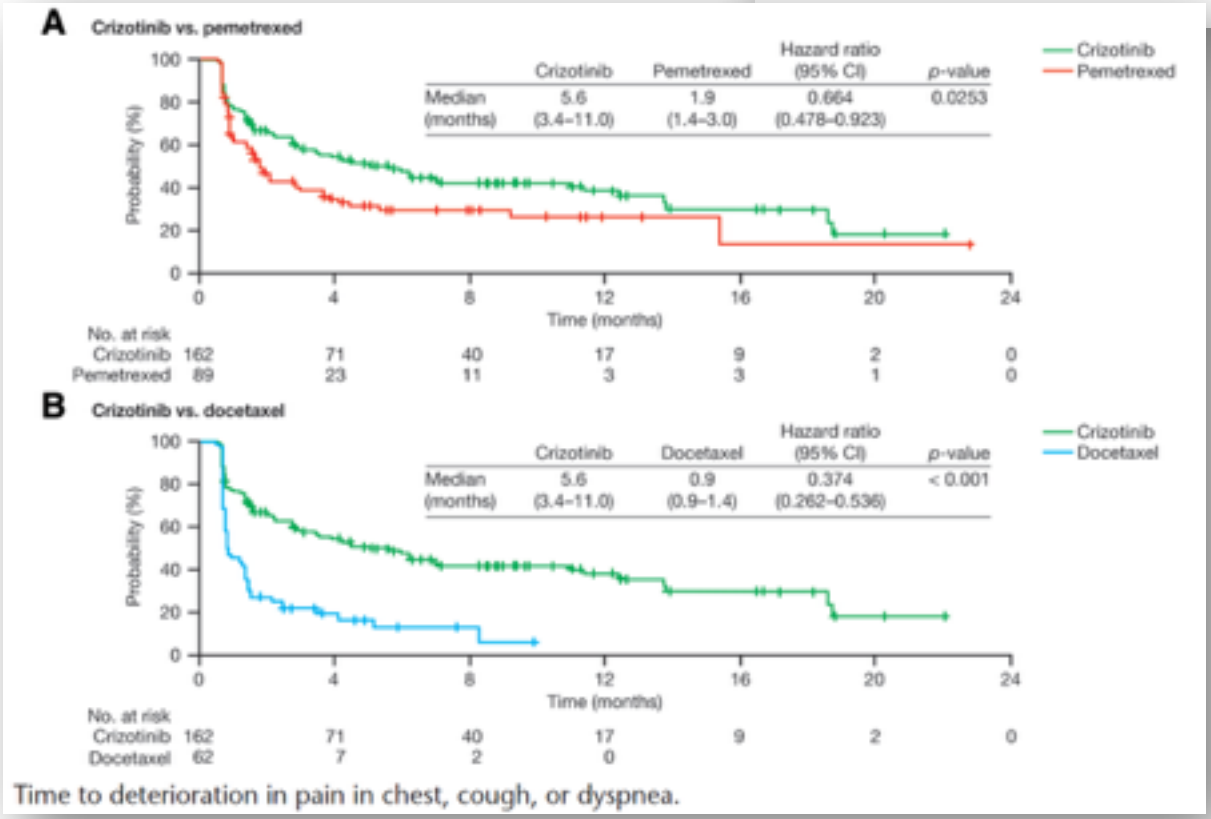


Study	Phase	Design	ORR	Median duration of response (wks)	Median duration of treatment (wks)	Median PFS (mo)	PFS HR	OS HR	Median OS (mo)	Crossover (%)
PROFILE 1007	III	**Crizotinib** (vs pem or doce) in 2ªL	65% vs 20%	32.1	15.9	7.7 vs 3.0	0.49	1.02	20.3 vs 22.8	64%

Shaw et al. N Engl J Med 368, 2385-2394, 2013

Crizotinib vs chemotherapy: impact on QoL

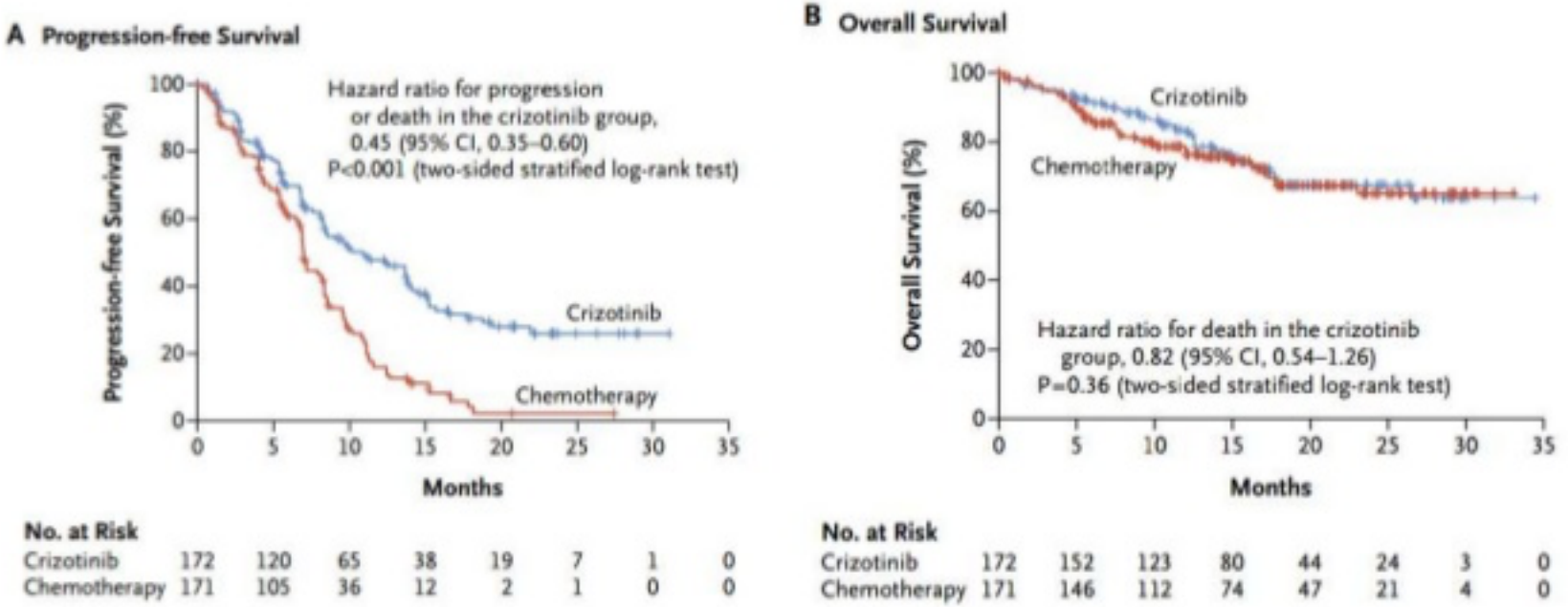




Time to deterioration in pain in chest, cough, or dyspnea.

Shaw AT et al. N Engl J Med.2013 Jun 20;368(25):2385-94.
Blackhall F et al. J Thorac Oncol. 2014 Nov;9(11):1625-33.

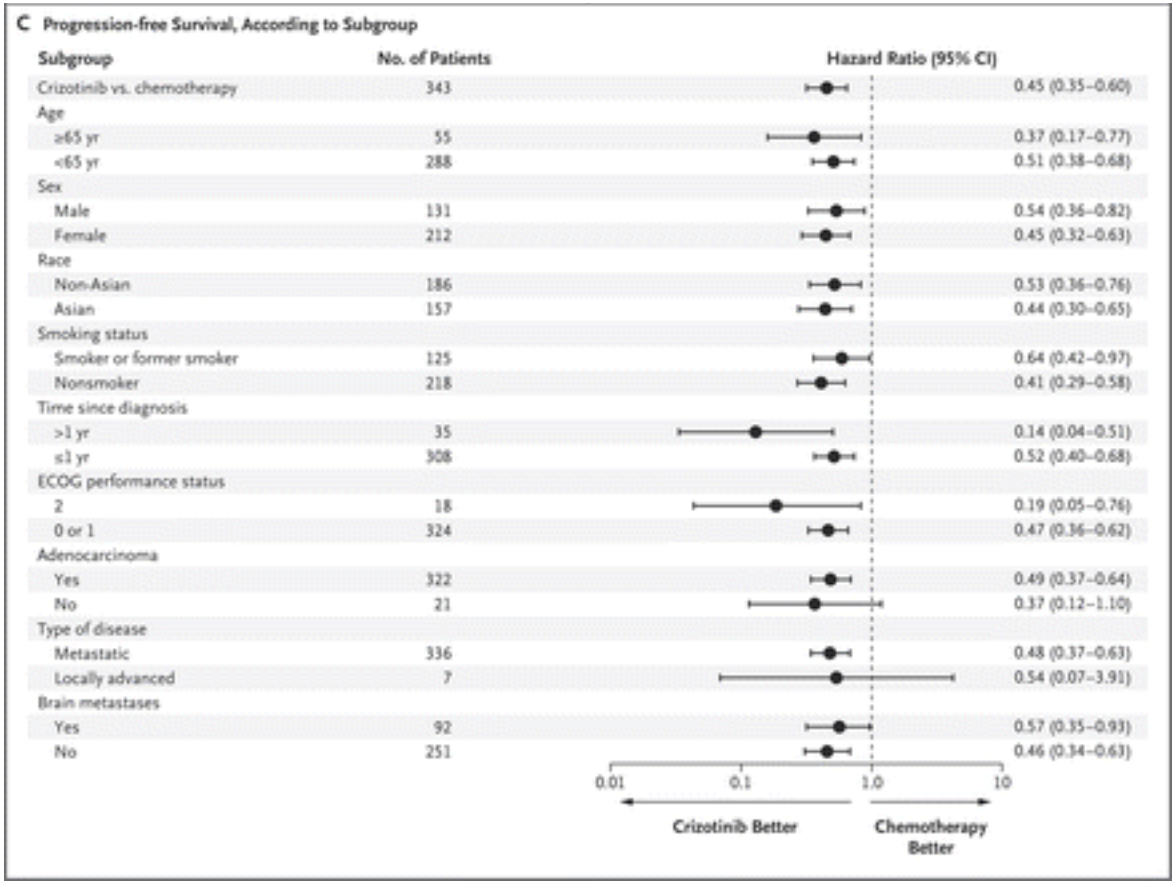
Phase III First-line Study of Crizotinib versus platinum-based chemotherapy in Advanced ALK-Positive Lung Cancer (PROFILE 1014)



Study	Phase	Design	ORR	Median duration of response (wks)	Median duration of treatment (wks)	Median PFS (mo)	PFS HR	OS HR	Median OS (mo)	Crossover (%)
PROFLE 1014	III	**Crizotinib** (vs cis-carbo + pem) in 1ªL	74% vs 45%	11.3 (mo) vs 5.3 (mo)	-	10.9 vs 7.0	0.45	0.82 No sig.	NA	70%

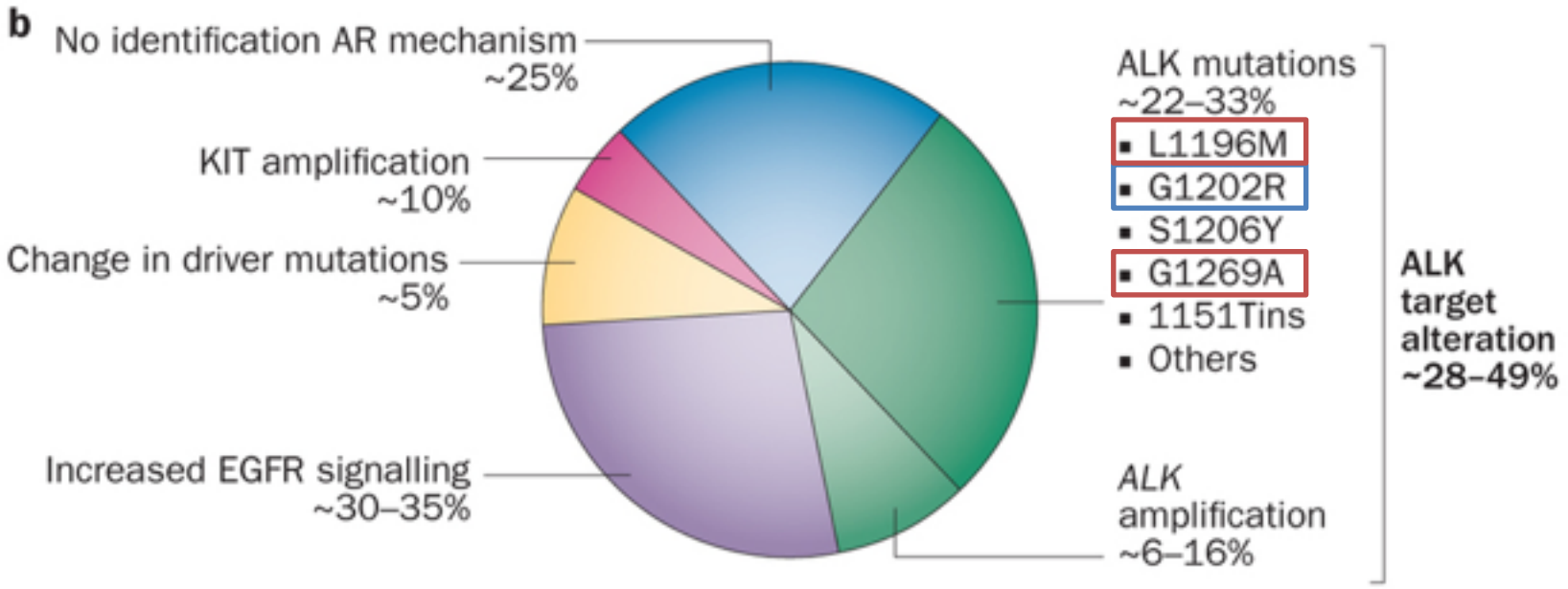
Solomon et al. N Engl J Med 2014, 371: 2167-77

Phase III First-line Study of Crizotinib versus platinum-based chemotherapy in Advanced ALK-Positive Lung Cancer (PROFILE 1014)



Solomon et al. N Engl J Med 2014, 371: 2167-77

ALK+ Resistencia a ALK ITKs



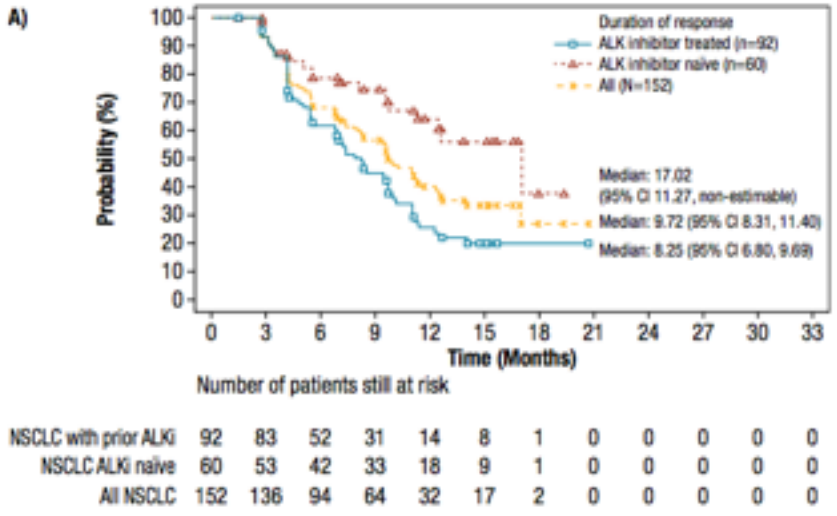
Nature Reviews Clinical Oncology 11, 473–481 (2014)

ALK+ Eficacia de ITKs 2ªG

Study	Phase	n	Population	Agent	Design	ORR	Median duration of response (wks)	Median PFS (mo)	PFS HR
Shaw et al 2014	I	130	ALK positive (68% progressed on Crizotinib)	Ceritinib	Single-arm	All 61.8% ALK ITK naïve 72.3% Pretreated 56.4%	All 9.7 ALK ITK naïve 17.2 Pretreated 8.7	All 7.0 ALK ITK naïve 18.4 Pretreated 6.9	NA
Seto et al 2013	I/II	58	ALK positive- 1st line setting	Alectinib	Single-arm	93.5%	x	27.7	NA

Ceritinib in Patients with Advanced Anaplastic Lymphoma Kinase (ALK)-rearranged (ALK+) Non-small Cell Lung Cancer (NSCLC): An Update of ASCEND-1

DURACIÓN DE RESPUESTA



SLP

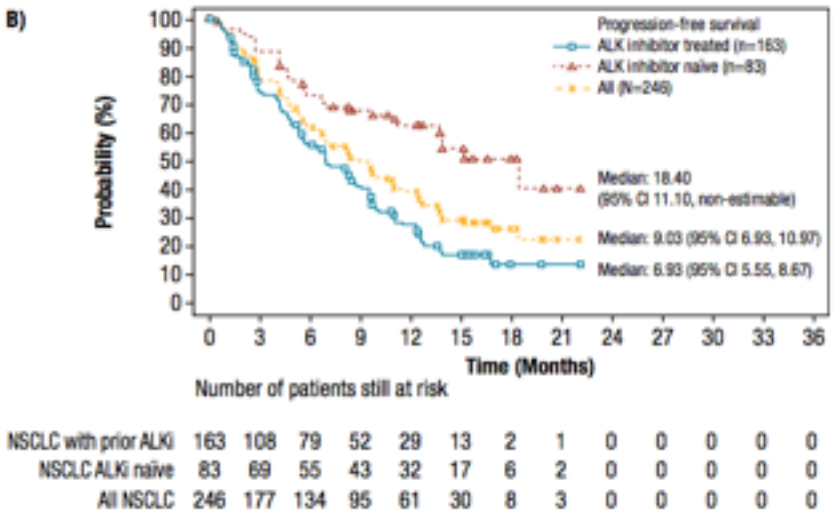
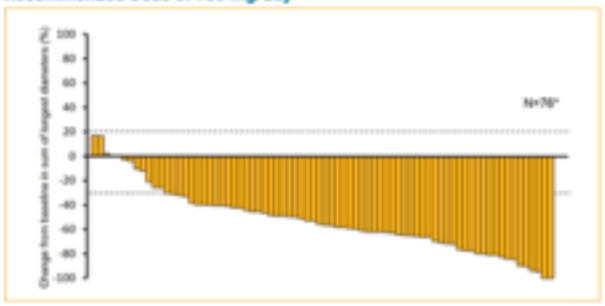


Figure 2. Waterfall Plot of Best Percentage Change from Baseline for ALK Inhibitor Naive Patients with ALK+ NSCLC Treated with Ceritinib at the Recommended Dose of 750 mg/day



*Patients with measurable disease at baseline and at least 1 post baseline assessment without unknown response for target lesion or overall response

Poster Presented at European Society of Medical Oncology (ESMO), Madrid, Spain 26 – 30 September 2014.

Ceritinib in Patients with Advanced Anaplastic Lymphoma Kinase (ALK)-rearranged (ALK+) Non-small Cell Lung Cancer (NSCLC): An Update of ASCEND-1

Table 3. Key Investigator-Assessed Efficacy Outcomes for Patients with ALK+ NSCLC

Efficacy Parameter	NSCLC with Prior ALK inhibitor n=163	NSCLC ALK Inhibitor Naïve Patients n=83	All NSCLC Patients N=246
Complete response, n (%)	3 (1.8)	1 (1.2)	4 (1.6)
Partial response, n (%)	89 (54.6)	59 (71.1)	148 (60.2)
Stable disease, n (%)	29 (17.8)	14 (16.9)	43 (17.5)
Progressive disease, n (%)	16 (9.8)	0	16 (6.5)
Unknown, n (%)	26 (16.0)	9 (10.8)	35 (14.2)
Overall response rate, n (%) [95% CI]	92 (56.4) [48.5, 64.2]	60 (72.3) [61.4, 81.6]	152 (61.8) [55.4, 67.9]

Poster Presented at European Society of Medical Oncology (ESMO), Madrid, Spain 26 – 30 September 2014.

ASCEND-2: A single-arm, open-label, multicenter phase II study of ceritinib in adult patients (pts) with ALK-rearranged (ALK+) non-small cell lung cancer (NSCLC) previously treated with chemotherapy and crizotinib (CRZ)

Investigator-assessed efficacy outcomes.

	BM N=100	No BM N=40	All N=140
WB ORR (CR+PR), n (%) [95% CI]	33 (33.0) [23.9, 43.1]	21 (52.5) [36.1, 68.5]	54 (38.6) [30.5, 47.2]
WB DCR (CR+PR+SD), n (%) [95% CI]	74 (74.0) [64.3, 82.3]	34 (85.0) [70.2, 94.3]	108 (77.1) [69.3, 83.8]
Median Duration of Response, Mos [95% CI]	9.2 [5.5, 11.1]	10.3 [7.4, 16.6]	9.7 [7.1, 11.1]
Median Progression Free Survival (PFS) Mos [95% CI]	5.4 [4.7,7.2]	11.3 [5.7,15.6]	5.7 [5.4, 7.6]

Conclusions: Ceritinib provided durable responses and safety outcomes in CRZ-pretreated patients with or without BM consistent with those seen in ASCEND-1

2015 ASCO Annual Meeting

ASCEND-3: A single-arm, open-label, multicenter phase II study of ceritinib in ALKi-naïve adult patients (pts) with ALK-rearranged (ALK+) non-small cell lung cancer (NSCLC)

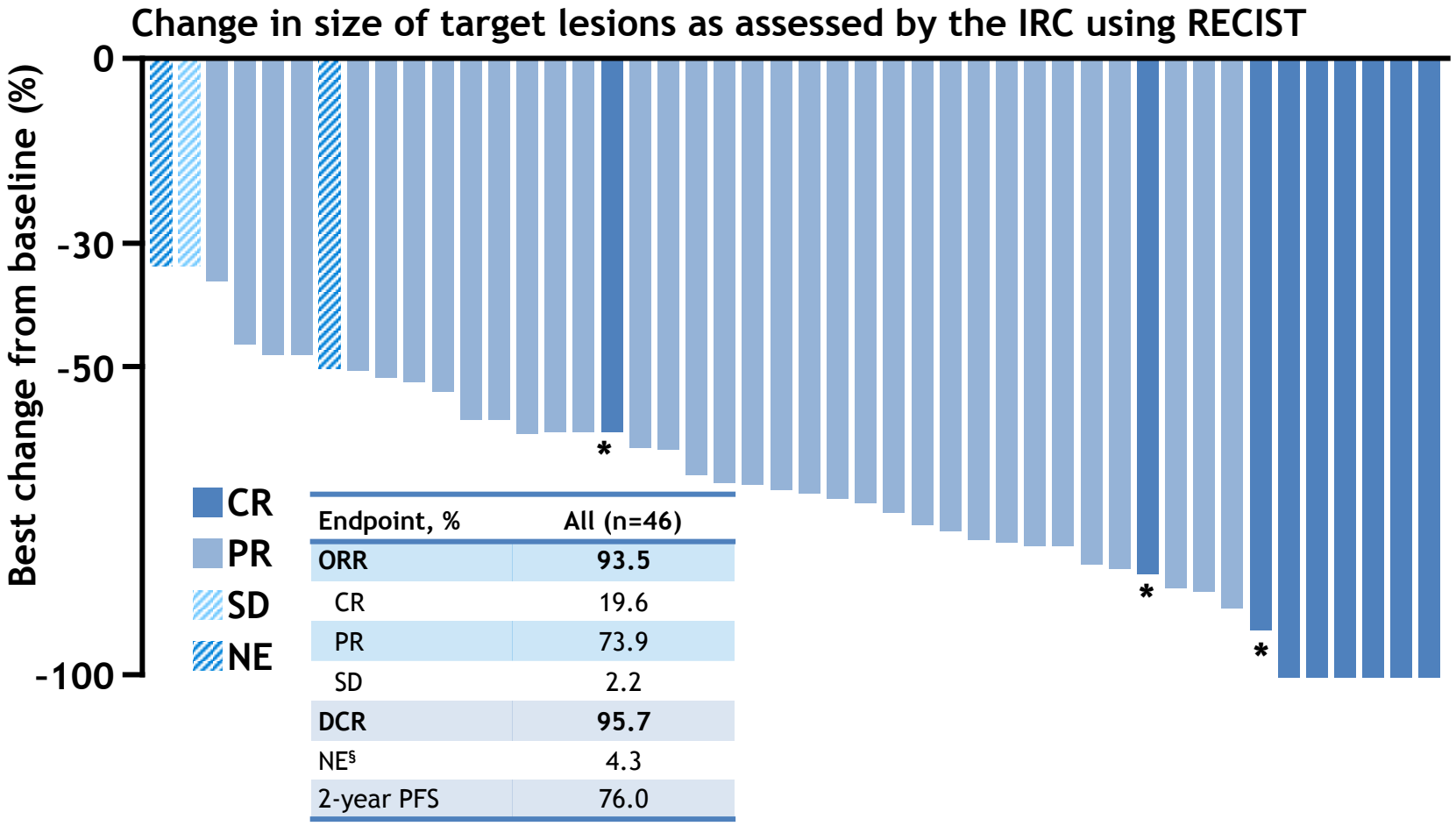
	BM N=50	No BM N=74	All N=124
WB ORR (CR+PR), n (%) [95% CI]	29 (58.0) [43.2, 71.8]	50 (67.6) [55.7, 78.0]	79 (63.7) [54.6, 72.2]
WB DCR (CR+PR+SD), n (%) [95% CI]	43 (86.0) [73.3,94.2]	68 (91.9) [83.2,97.0]	111 (89.5) [82.7, 94.3]
Median Duration of Response (DOR), Mos [95% CI]	9.1 [7.5, NE]	10.8 [9.3, 10.8]	9.3 [9.1, NE]
Median Progression Free Survival (PFS)* Mos [95% CI]	10.8 [7.3, NE]	11.1 [9.2, 12.8]	11.1 [9.3, NE]

NE = Not Estimable *Follow-up ongoing: 84 (67.7%) pts censored; 77 (62.1%) ongoing without event.

Conclusions: Ceritinib achieved robust ORR and promising DOR/PFS in pts with and without baseline BM. Ceritinib showed brain responses even in pts with no prior BRT. Safety outcomes were similar to the ASCEND-1 trial.

2015 ASCO Annual Meeting

AF-001JP study (phase II portion)
Percentage change in tumour size from baseline by IRC

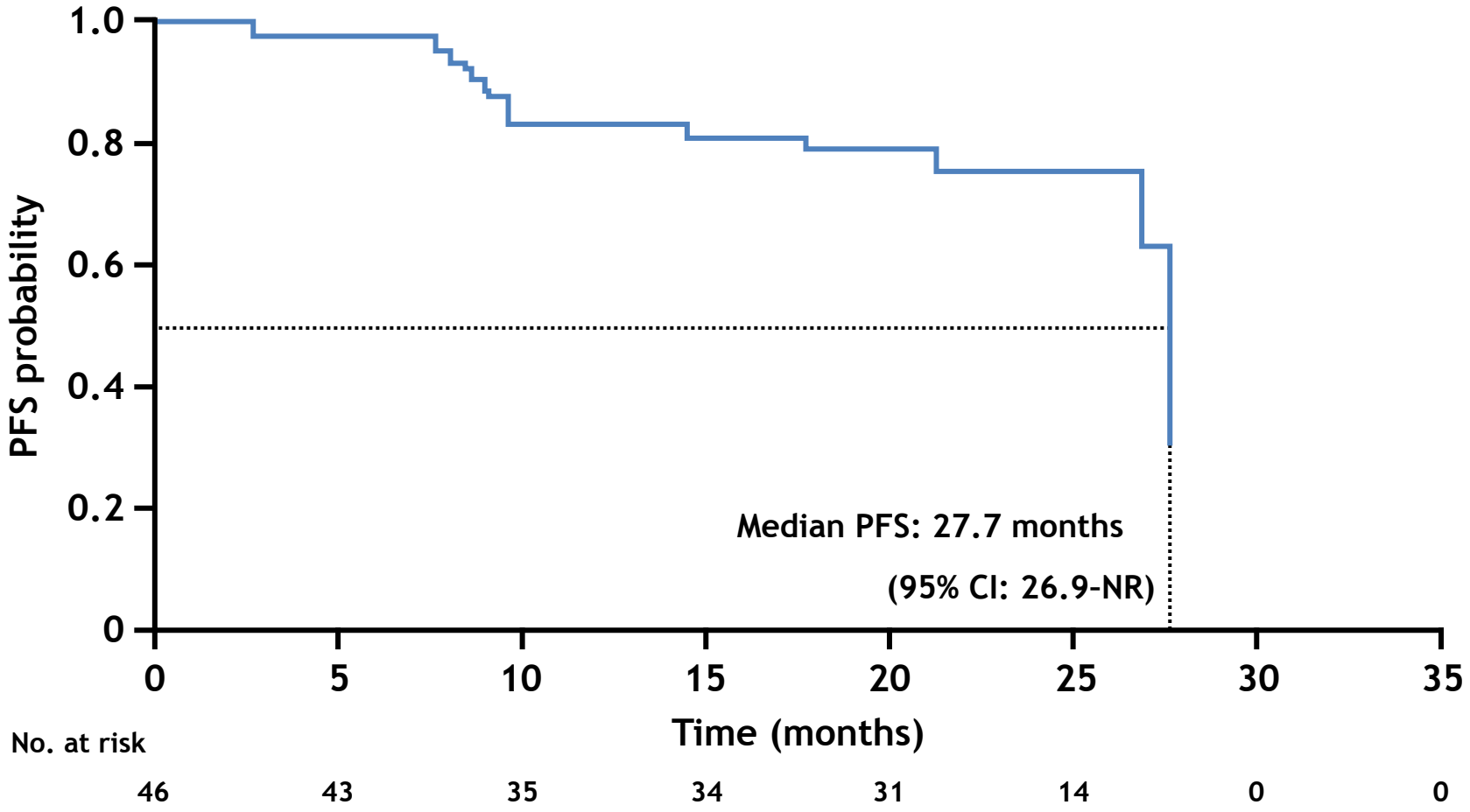


Endpoint, %	All (n=46)
ORR	**93.5**
CR	19.6
PR	73.9
SD	2.2
DCR	**95.7**
NE§	4.3
2-year PFS	76.0

Data cut-off: 31 Jan 2014
CR = complete response; NE = not evaluated; PR = partial response; SD = stable disease; RECIST = Response Evaluation Criteria in Solid Tumors
*Lymph nodes identified as target lesion for RECIST evaluation
§For best overall response evaluation, one patient withdrew early due to an adverse event (no response data); one patient had investigator-assessed PD not confirmed by the IRC

Tamura, et al. CMSTO 2014

AF-001JP study (phase II portion)
PFS by IRC

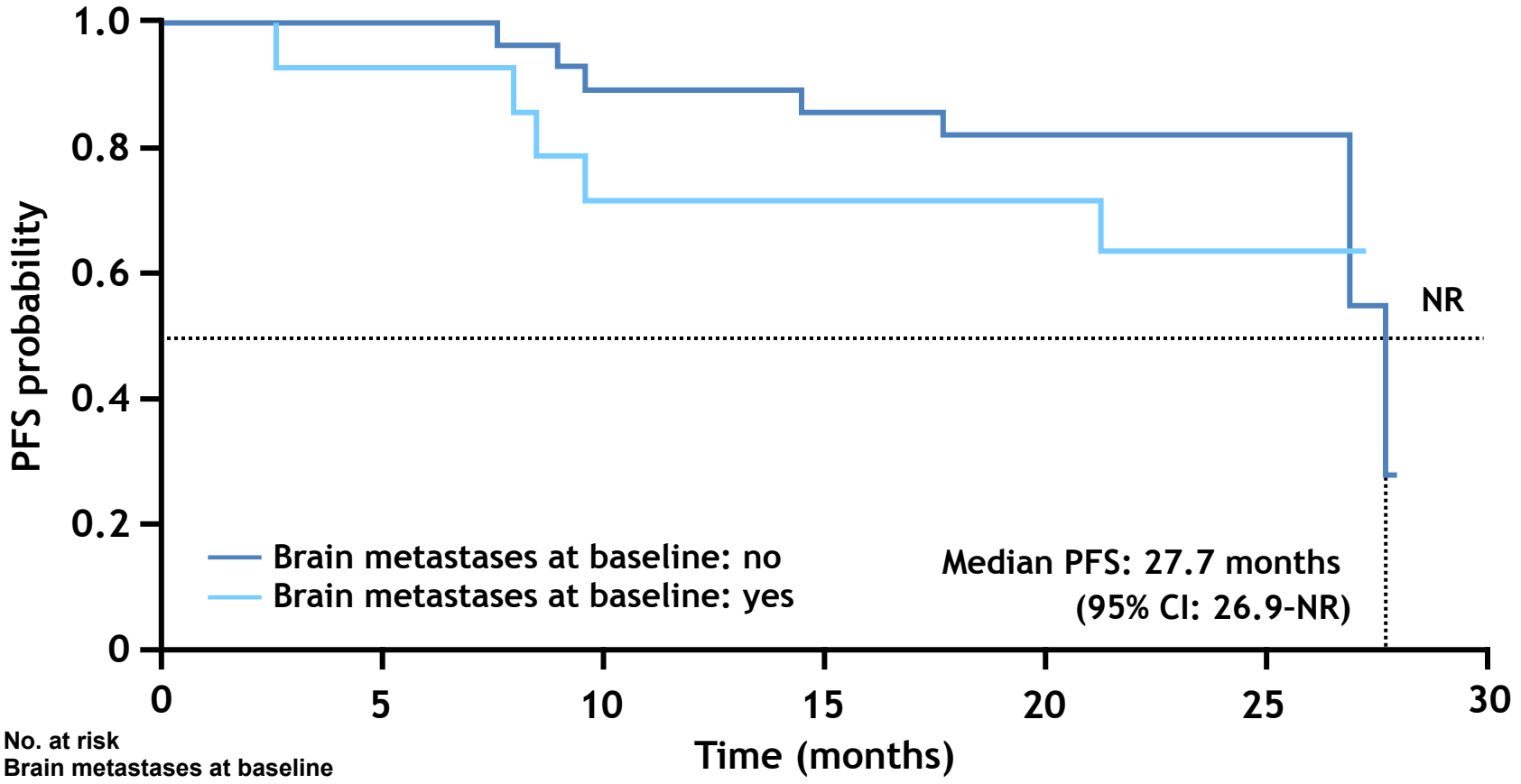


Median duration of follow up: 22 months (range 1-28)

Data cut-off: 31 Jan 2014
CI = confidence interval; NR = not reached

Tamura, et al. CMSTO 2014

AF-001JP study (phase II portion)
PFS by presence or absence of brain metastases at baseline



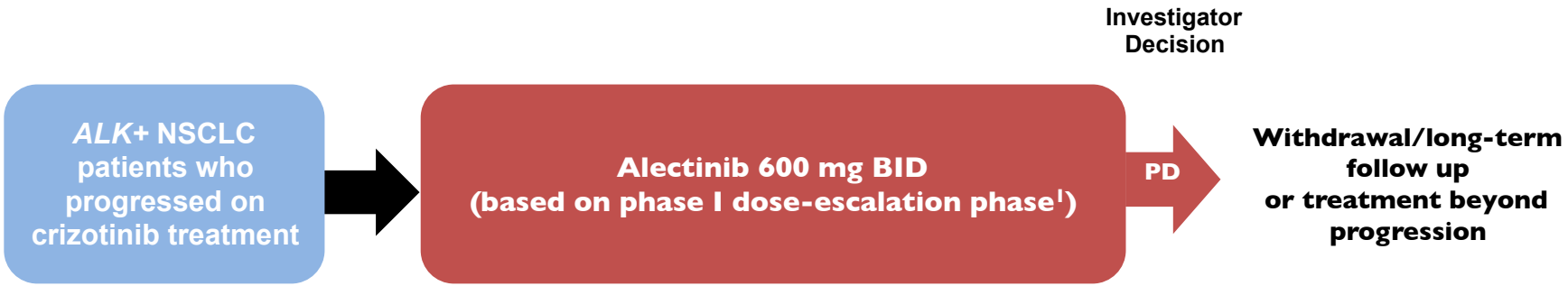
No. at risk
Brain metastases at baseline

No	32	30	25	24	21	9	0
Yes	14	13	10	10	10	5	0

Data cut-off: 31 Jan 2014

Tamura, et al. CMSTO 2014

Updated efficacy/safety data from the phase 2 NP28761 study of alectinib in ALK+ NSCLC



- Key inclusion criteria
  - *ALK*+ NSCLC (by FDA-approved FISH test)
  - Disease progression following first-line crizotinib
  - ECOG PS ≤2
  - 1-week minimum washout between crizotinib and alectinib
  - Untreated or treated CNS metastases allowed, as long as asymptomatic and neurologically stable

- Primary endpoint
  - ORR by IRC according to RECIST v1.1
- Key secondary endpoints
  - CNS ORR by IRC
- Additional secondary endpoints
  - Patient-reported outcomes
  - Disease control rate
  - Duration of response
  - PFS
  - Safety

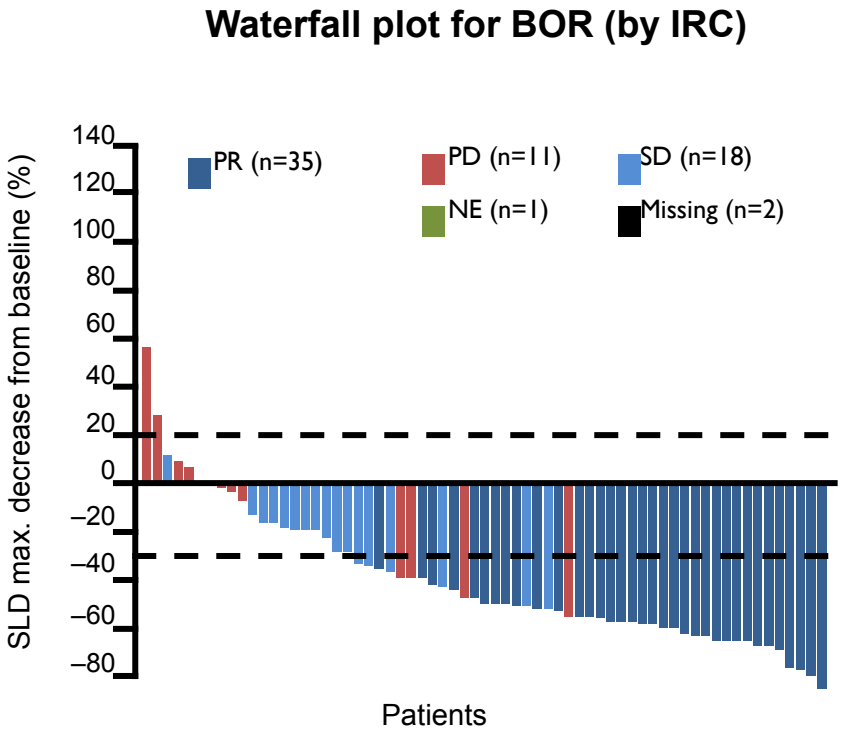
BID = twice daily; ORR = overall response rate; IRC = Independent Review Committee; PFS = progression-free survival; ECOG PS = Eastern Cooperative Oncology Group performance status

1. Gadgeel SM, et al. Lancet Oncol 2014

Updated efficacy/safety data from the phase 2 NP28761 study of alectinib in ALK+ NSCLC

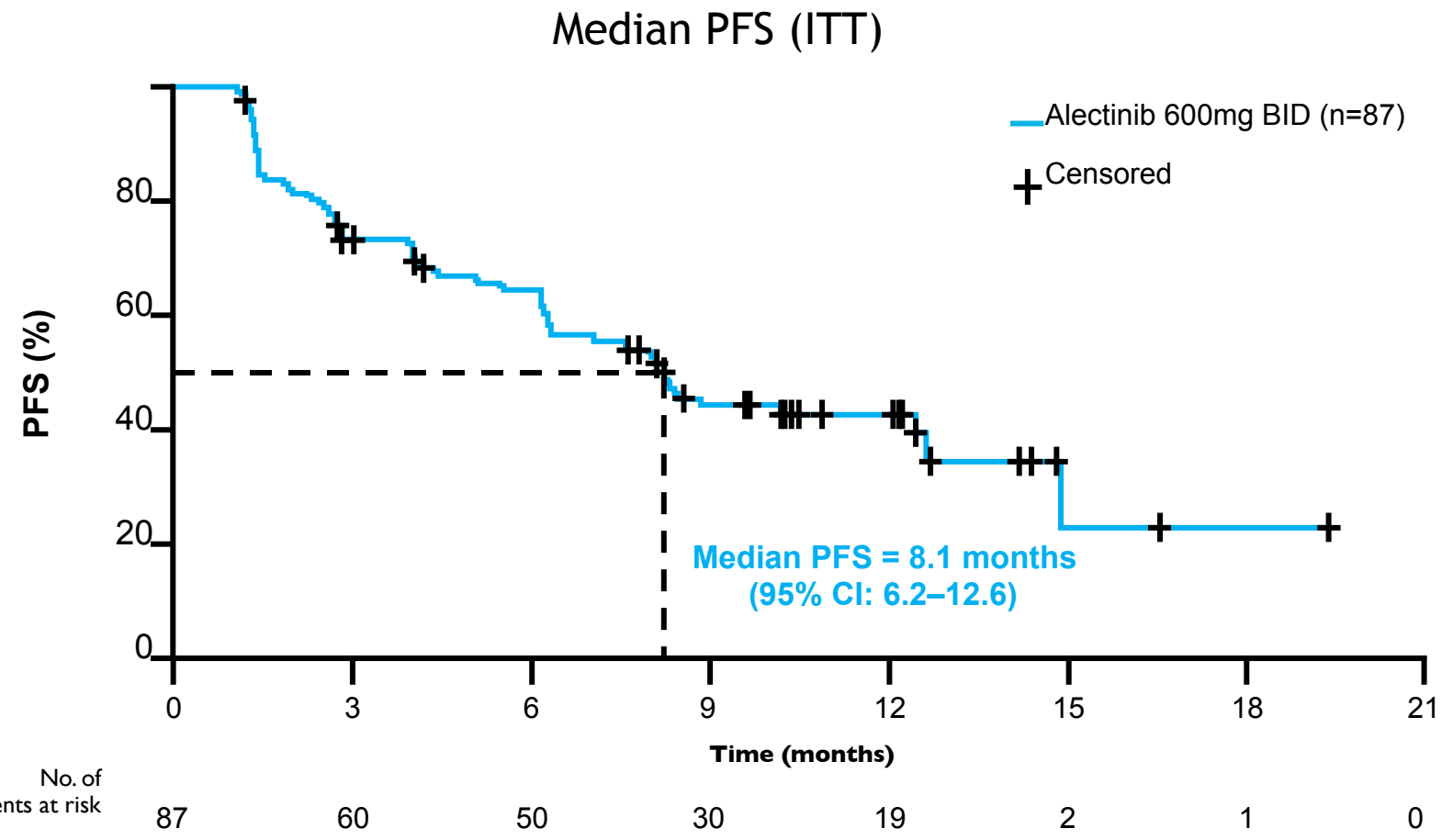
Objective response rate by IRC

	Response-evaluable population (n=67*)
Median follow-up, months [range]	**9.9 [1.1–19.8]**
Responders (ORR, %)	35 (52.2)
[95% CI]	[39.7; 64.6]
Complete response, n (%)	0 (0.0)
Partial response, n (%)	35 (52.2)
Stable disease, n (%)	18 (26.9)
Progressive disease, n (%)	11 (16.4)
Disease control rate, n (%)	**53 (79.1)**
[95% CI]	[67.4; 88.1]
Median duration of response, months (95% CI)	**13.5 (6.7; NE)**



CI = confidence interval; SLD = sum of longest diameters; Data cut-off = 27 April 2015; For duration of response data, 40% of responders had an event; * 2 patients had missing data or were not evaluable

Updated efficacy/safety data from the phase 2 NP28761 study of alectinib in ALK+ NSCLC

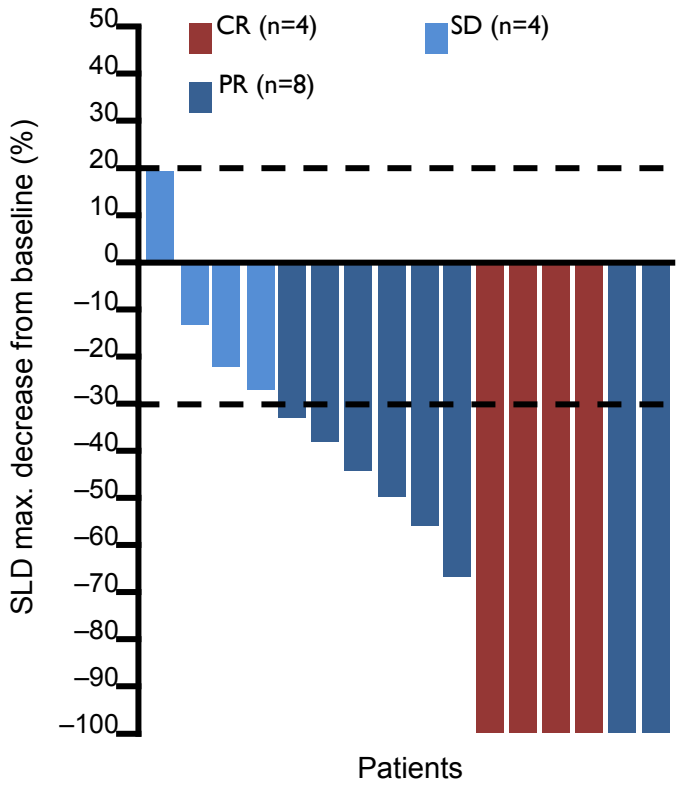


OS = overall survival; ITT = intent-to-treat; Data cut-off = 27 April 2015

Updated efficacy/safety data from the phase 2 NP28761 study of alectinib in ALK+ NSCLC

CNS ORR by IRC

Alectinib (600mg BID)	Measurable disease (n=16)	Measurable and non-measurable disease (n=52)
Responders (ORR, %)	**12 (75.0)**	**21 (40.4)**
[95% CI]	[47.6; 92.7]	[27.0; 54.9]
Complete response, n (%)	4 (25.0)	13 (25.0)
Non-CR / non-PD, n (%)	12 (75.0)	33 (63.5)*
Disease control rate, n (%)	**16 (100.0)**	**46 (88.5)**
[95% CI]	[79.4; 100.0]	[76.6; 95.6]
Median duration of response, months (95% CI)	**11.1 [5.8; 11.1]**	**11.1 [10.8; NE]**



*Includes partial response only observed in patients with measurable disease
Data cut-off = 27 April 2015; 1 patient with non-measurable disease had missing data or was not evaluable; 50% and 33% of responders , respectively, had an event at data cut-off

Updated efficacy/safety data from the phase 2 NP28761 study of alectinib in ALK+ NSCLC

CNS ORR by prior radiation

Alectinib (600 mg BID)	All patients with CNS metastases* (n=52)	
	Prior radiation (n=34)	No prior radiation (n=18)
Responders (ORR %)	26.5	66.7
[95% CI]	[12.9; 44.4]	[41.0; 86.7]
Complete response, n (%)	**3 (8.8)**	**10 (55.6)**
Partial response, n (%)	6 (17.6)	2 (11.1)
Stable disease, n (%)	20 (58.8)	5 (27.8)
Progressive disease, n (%)	4 (11.8)	1 (5.6)

ALK+

Metástasis cerebrales

Para el año que viene…

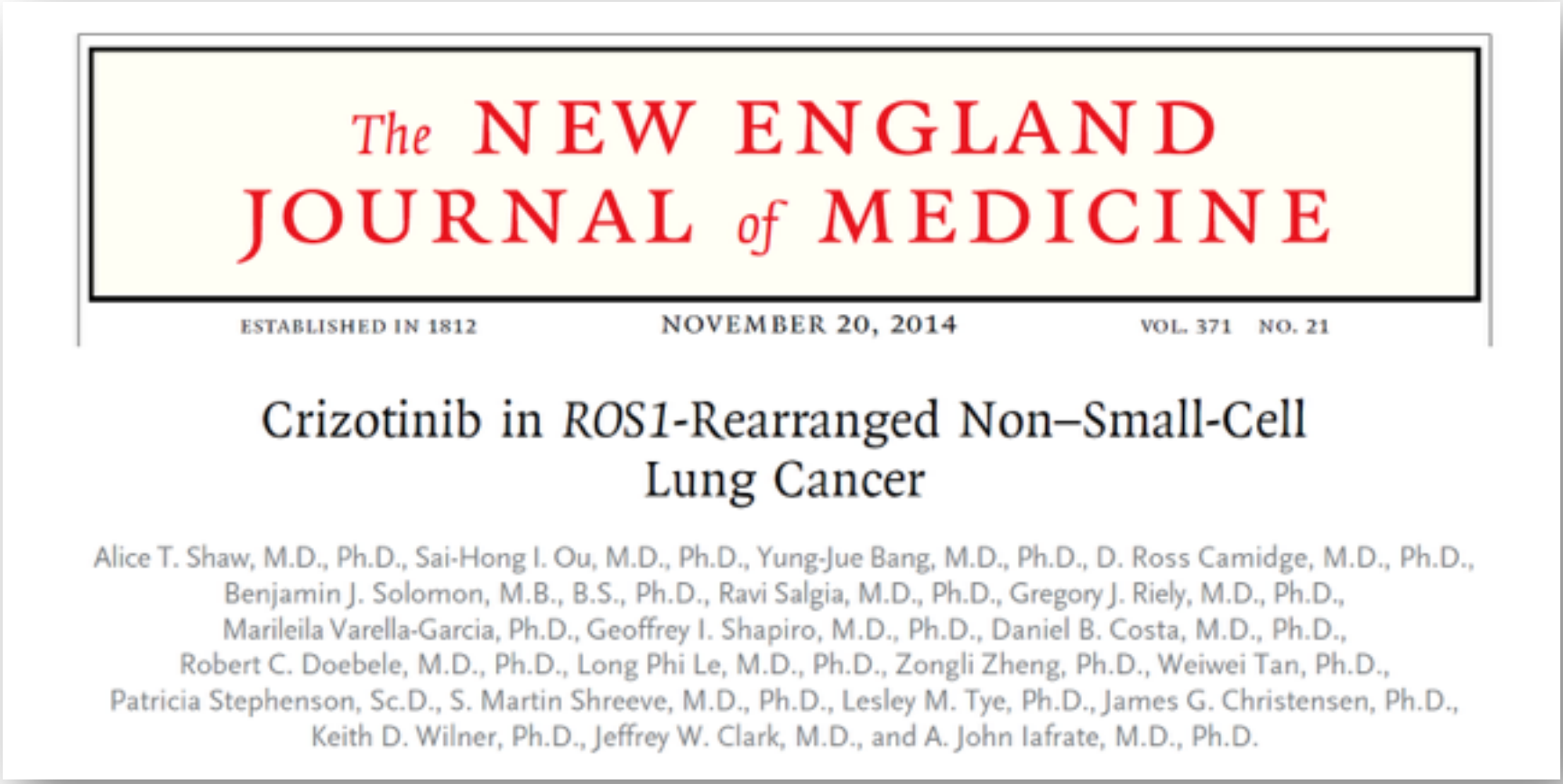
ALK+ Fármacos en investigación

Novel ALK Inhibitors in Development	Company	Other Targets	Activity Against Mutations Mediating Crizotinib	Highlights
ASP26113	Ariad	ROS1 EGFR (including mutant EGFR)	Yes-*L1196M*	Ongoing phase 1/2 study:12/16 patients resistant to crizotinib responded to doses between 60 mg/d: 240 mg/d; duration of response >40 weeks 4 TKI-naïve patients: 2 with response, 2 with stable disease 4/5 patients with CNS metastases showed improvement in imaging TRAEs: fatigue (40%), nausea (36%), diarrhea (33%), headaches (18%) Early onset pulmonary symptoms were seen on days 1/2 after receiving 180 mg/d doses. Hence recommended to start with 90 mg/d for 1 week then increase to 180 mg/d if no pulmary events.
ASP3026	Astellas	ROS1 ACK	Yes-*L1196M*	Ongoing phase I trials with advanced solid tumors Maximal tolerated dose = 525 mg/d GI side effects most common; grade 3 rash and increases in AST/ALT were also observed
TSR-011	Tesaro	TRK-A TRK-B TRK-C	Yes-*L1196M*	Phase I trial: 65% of 17 evaluable patients with advanced solid tumors had stable disease or partial response at 8 weeks. Of the 3 evaluable patients with NSCLC who had progressed on crizotoinib, 1 had partial response and 2 had stable disease Dose-limiting toxicities included QTc prolongation, dysesthesias
PF-06463922	Pfizer	ROS1 EGFR31	All known *ALK* and *ROS* mutants	Good CNS activity seen in mice models with improved overall survival and regression of intracranial lesions Clinical trials ongoing
RXDX-101	Ignyta	ROS1	Yes-*L1196M* *C1156Y23*	CNS activity seen in mice models with tumor regression Phase I trials ongoing; so far the drug is well tolerated
X-376 and X-39652	Xcovery	cMET	Yes-*L1196M*	Antitumor activity in vitro and in vivo Synergistic activity in combination with mTOR inhibitors
CEP28122	Teva	RSK2, RSK3, RSK4	Unknown	In vivo efficacy seen in mouse models with ALK-driven tumors Complete tumor regression see in 1-2 days of Rx initiation
CEP37440	Teva	FAK	Unknown	In development phase

Driver mutations

Gene	Alteration	Frequency (%)	Targeted therapies	Current clinical trials†
EGFR	Mutation	10–15	Erlotinib, gefitinib, afatinib, CO-1686, AZD9291	NCT01836341, NCT01542437, NCT01953913, NCT01931306, NCT01526928, NCT01802632
BRAF	Mutation	3–4	Dabrafenib, trametinib, dasatinib	NCT01336634, NCT01362296 NCT01514864
PI3KCA	Mutation	1–3	BKM120, XL147	NCT01297452, NCT01570296, NCT01297491, NCT01723800, NCT01390818
HER2	Mutation	1–4	Afatinib, neratinib, dacomitinib	NCT01542437, NCT01827267, NCT01858389, NCT00818441
EML4-ALK, KIF5B-ALK, TFG-ALK	Fusion	3–5	Crizotinib, LDK378, CH5424802	NCT00932451, NCT01639001, NCT01685060, NCT01685138, NCT01828112, NCT01828099, NCT01579994, NCT01871805
ROS1	Fusion	1–2	Crizotinib	NCT01945021
RET	Fusion	1–2	Cabozantinib, vandetanib	NCT01639508, NCT01823068

†Trials can be accessed via the ClinicalTrials.gov website.



The NEW ENGLAND JOURNAL of MEDICINE

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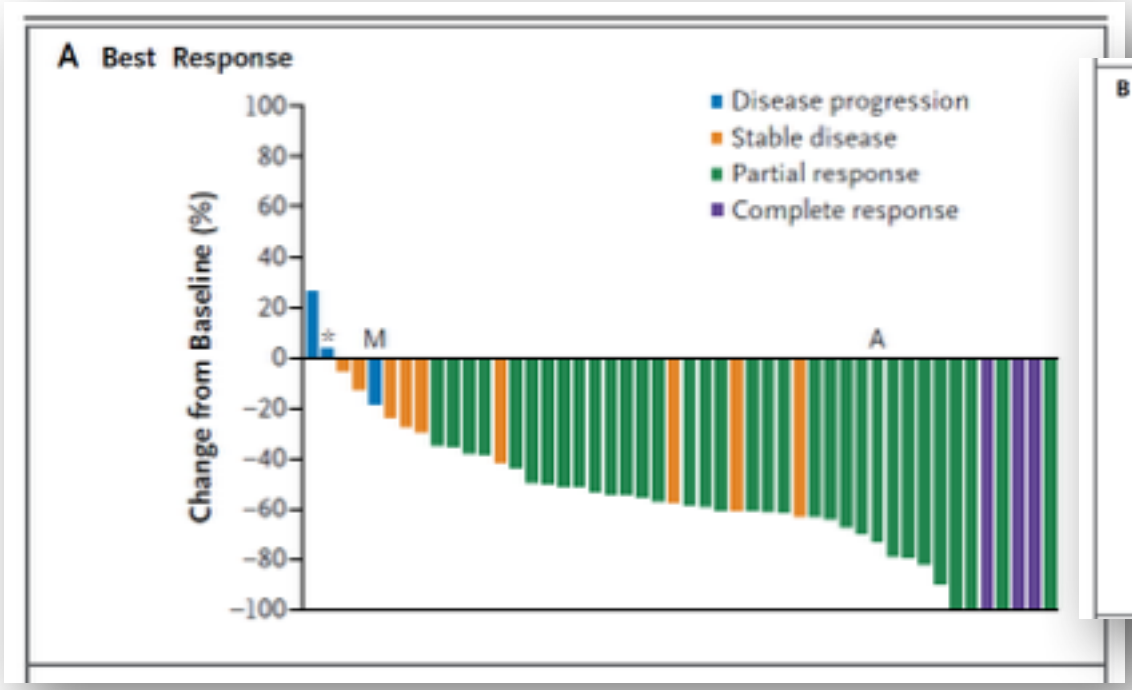
Crizotinib in *ROS1*-Rearranged Non–Small-Cell Lung Cancer

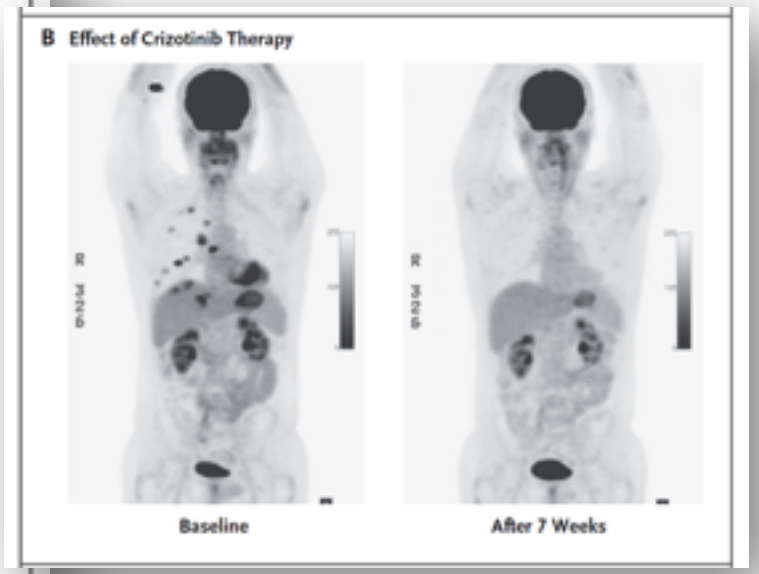
Alice T. Shaw, M.D., Ph.D., Sai-Hong I. Ou, M.D., Ph.D., Yung-Jue Bang, M.D., Ph.D., D. Ross Camidge, M.D., Ph.D., Benjamin J. Solomon, M.B., B.S., Ph.D., Ravi Salgia, M.D., Ph.D., Gregory J. Riely, M.D., Ph.D., Marileila Varella-Garcia, Ph.D., Geoffrey I. Shapiro, M.D., Ph.D., Daniel B. Costa, M.D., Ph.D., Robert C. Doebele, M.D., Ph.D., Long Phi Le, M.D., Ph.D., Zongli Zheng, Ph.D., Weiwei Tan, Ph.D., Patricia Stephenson, Sc.D., S. Martin Shreeve, M.D., Ph.D., Lesley M. Tye, Ph.D., James G. Christensen, Ph.D., Keith D. Wilner, Ph.D., Jeffrey W. Clark, M.D., and A. John Iafrate, M.D., Ph.D.

- 50 patients
- Median age 53 (range 25-77)
- Female 56%, never smokers 78%, adenocarcinoma 98%

Shaw AT et al, N Engl J Med 2014;371:1963-71.

Tumor responses to crizotinib in ROS1-rearranged NSCLC

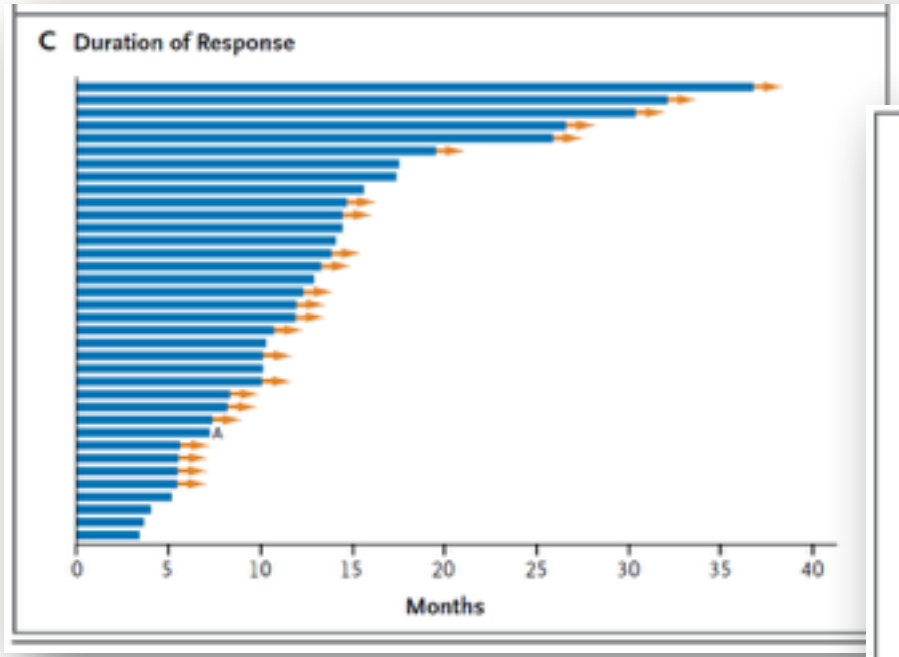


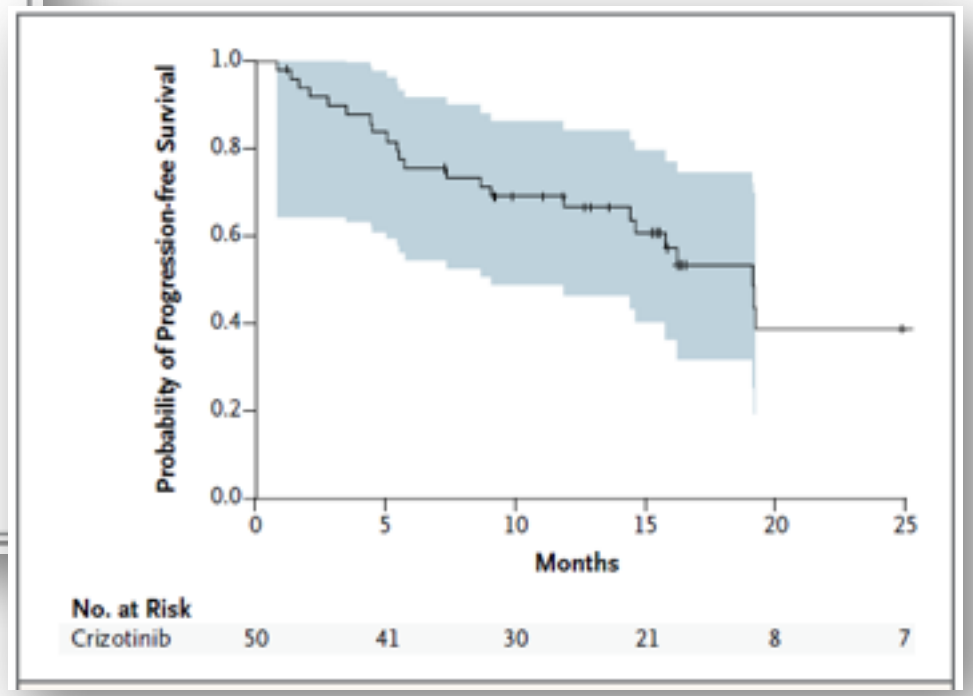


Overall response rate 72% (6% CR, 66% PR).
Median time to response 7.9 weeks (range, 4.3 - 32.0)

Shaw AT et al, N Engl J Med 2014;371:1963-71.

Tumor responses to crizotinib in ROS1-rearranged NSCLC





Median duration of response:
17.6 months (95%CI 14.5 – not reached)
Median progression-free survival:
19.2 months (95%CI 14.4 – not reached)

Shaw AT et al, N Engl J Med 2014;371:1963-71.

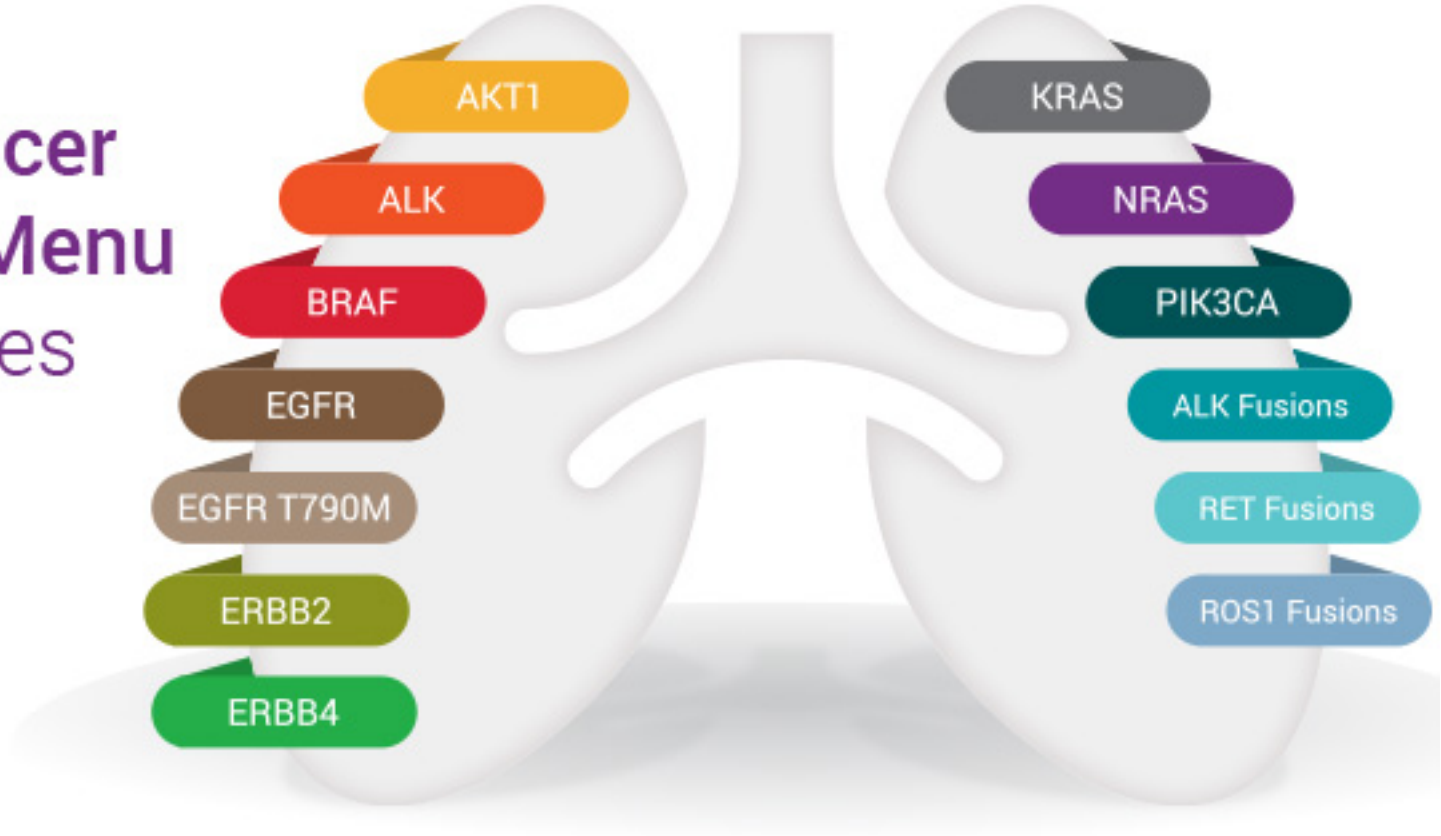
ROS1 — Targeting the One Percent in Lung Cancer

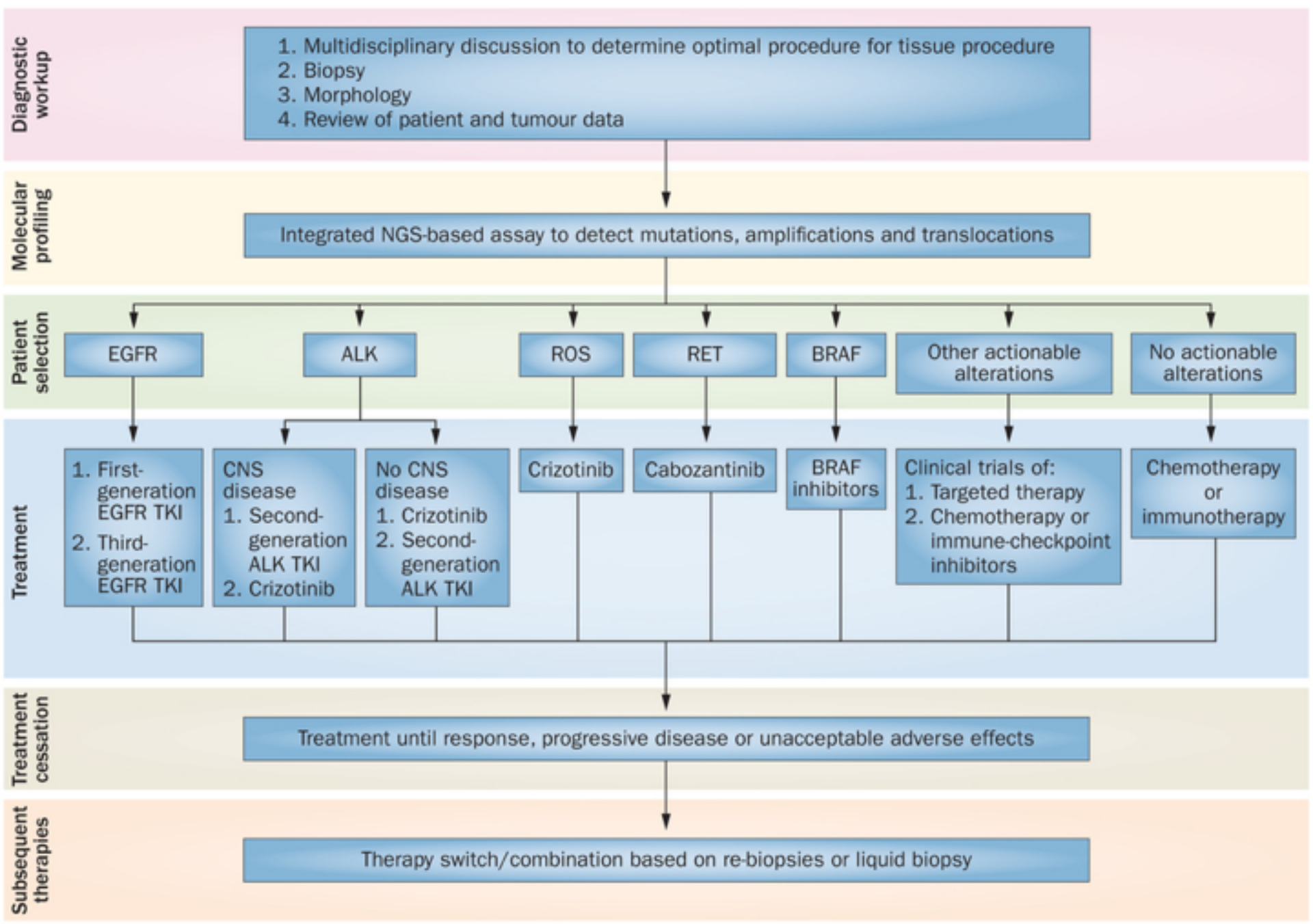
Kathryn A. Gold, M.D.

[…]
The study by Shaw et al. proves that it is possible to conduct trials in ***small subgroups*** *of patients with NSCLC and demonstrate* ***big results****.*
[…]

N ENGL J MED 371;21 NEJM.ORG NOVEMBER 20, 2014

Our **Lung Cancer Testing Menu** Includes




Diagnostic workup
1. Multidisciplinary discussion to determine optimal procedure for tissue procedure
2. Biopsy
3. Morphology
4. Review of patient and tumour data
Molecular profiling
Integrated NGS-based assay to detect mutations, amplifications and translocations
Patient selection
EGFR
ALK
ROS
RET
BRAF
Other actionable alterations
No actionable alterations
Treatment
1. First-generation EGFR TKI
2. Third-generation EGFR TKI
CNS disease
1. Second-generation ALK TKI
2. Crizotinib
No CNS disease
1. Crizotinib
2. Second-generation ALK TKI
Crizotinib
Cabozantinib
BRAF inhibitors
Clinical trials of:
1. Targeted therapy
2. Chemotherapy or immune-checkpoint inhibitors
Chemotherapy or immunotherapy
Treatment cessation
Treatment until response, progressive disease or unacceptable adverse effects
Subsequent therapies
Therapy switch/combination based on re-biopsies or liquid biopsy