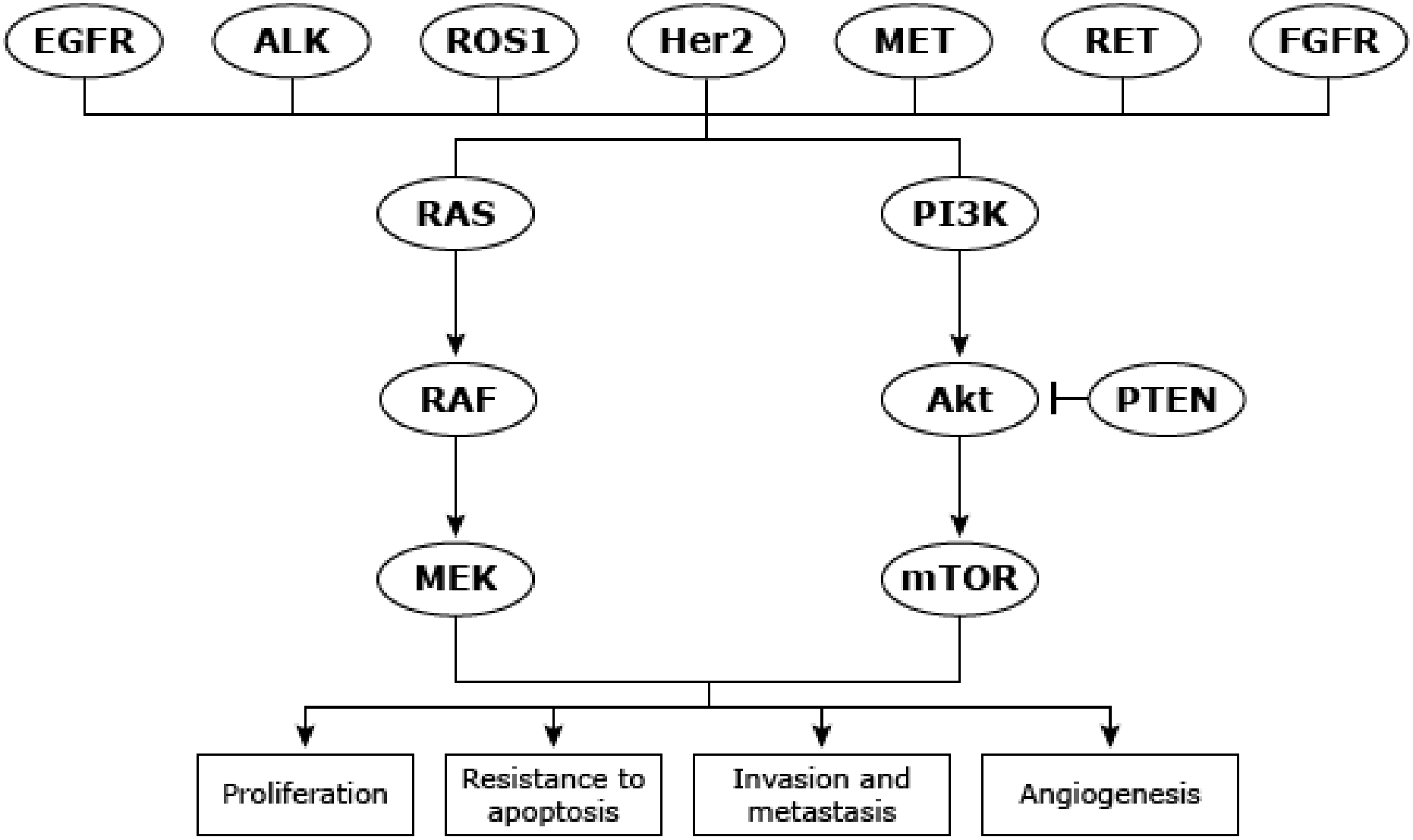
Comparison of 2nd versus 1st generation TKIs in 1st line treatment of EGFR and ALK positive advanced/metastatic NSCLC

Dr Puneet Saxena


EGFR
ALK
ROS1
Her2
MET
RET
FGFR
RAS
PI3K
RAF
Akt
PTEN
MEK
mTOR
Proliferation
Resistance to apoptosis
Invasion and metastasis
Angiogenesis

Mutations in the EGFR TK

- 15 % of NSCLC adenocarcinoma in the US
- More frequently in women and nonsmokers
- Asian populations – incidence higher
- Predominantly located in *EGFR* exons 18-21
  - 85% of *EGFR* mutations are either deletions in exon 19 or a single point mutation in exon 21 (L858R)
- The specific *EGFR* mutation identified is important
  - There are sensitive mutations, primary resistance mutations (often exon 20), and acquired resistance mutations (T790M)

Pao W, et al. J Clin Oncol. 2005;23:2556-2568.
Wu YL, et al. J Thorac Oncol. 2007;2:430-439.

PIONEER study

- Analysis of 1482 pts with adenocarcinoma
- 7 Asian regions (China, Hong Kong, India, Philippines, Taiwan, Thailand, Vietnam)
- Incidence of EGFR mutations -22 to 62 %
  - lower in patients from India (22.2%) compared with other areas (47.2%-64.2%)
- More common in nonsmokers
- 37 % in regular smokers
- Frequency higher in women
  - Difference not significant after considering the frequency of smoking

Shi Y. J Thorac Oncol. 2014;9(2):154

Impact of EGFR inhibitor in NSCLC on progression-free and overall survival: a meta-analysis

- 23 eligible trials (13 front-line, 7 second-line, 3 maintenance; n = 14570)
- 13 phase III trials in which an EGFR TKI was compared with platinum-based chemotherapy
- 2620 patients (1475 EGFR mutation positive and 1145 mutation negative
- PFS significantly prolonged (HR 0.43, 95% CI 0.38-0.49)
- No effect on survival was observed (HR 1.01, 95% CI 0.87-1.18)

J Natl Cancer Inst. 2013;105(9):595

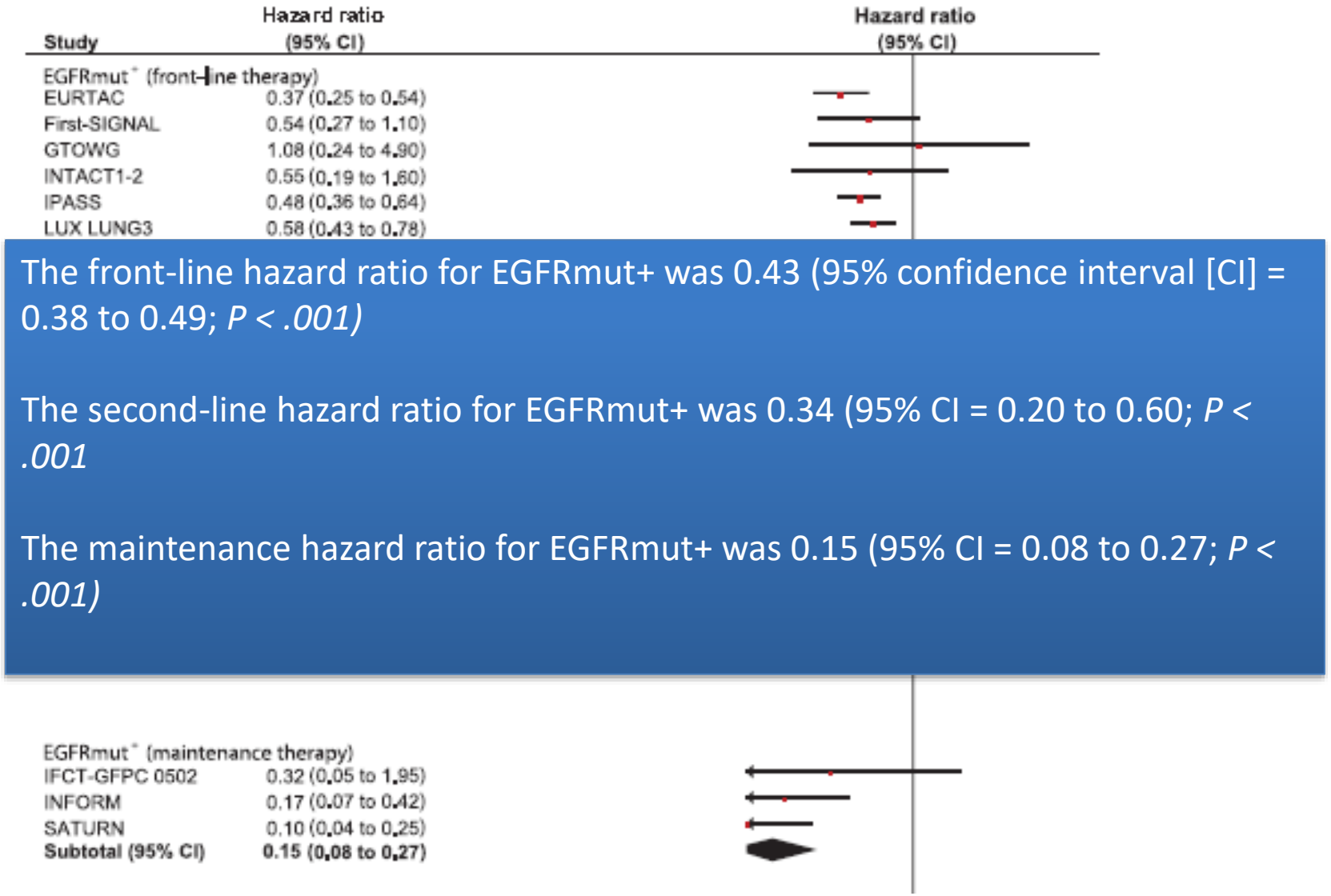
Table 1. Demographic characteristics of patients*

Study name (year) (reference)	Treatment comparison	EGFR mutation assessment method	No. of EGFR+ patients (%)	No. of EGFR- patients (%)	No. of EGFR unknown patients (%)	Age, y, median	Asian, %	Males, %	Present/ former smokers, %	Adeno-carcinoma, %
Front-line treatment										
INTACT 1 (2004) (24,43)	Gefitinib + CisG vs CisG	Direct sequencing	32 (2)	280 (13)	1818 (85)	60	6	74	NK	46
INTACT 2 (2004) (25,43)	Gefitnib + CP vs CP					62	NK	60	NK	55
TRIBUTE (2005) (22)	Erlotinib + CP vs CP	Direct sequencing	29 (3)	198 (18)	851 (79)	63	3	61	89	61
TALENT (2007) (26,37)	Erlotinib + CisG vs CisG	NK	NK	NK	NK	61	4	77	NK	38
IPASS (2009) (19,20)	Gefitinib vs CP	ARMS	261 (21)	176 (15)	780 (64)	57	100	21	6	96
NEJ002 (2010) (17,38)	Gefitinib vs CP	PCR clamp	228 (100)	0	0	63‡	100	36	38	94
GTOWG† (2010) (27)	Erlotinib vs CV	Direct sequencing	10 (4)	75 (26)	199 (70)	76	NK	68	83	50
TOPICAL (2010) (36,43)	Erlotinib vs placebo	SequenomOncoCarta Panel	28 (4)	362 (54)	280 (42)	77	2	61	95	38
WJTOG3405* (2010) (21,33)	Gefitinib vs CisD	Direct sequencing, PCR clamp	172 (100)	0	0	64	100	31	31	97
OPTIMAL* (2011) (16,35)	Erlotinib vs CG	Direct sequencing	154 (100)	0	0	58	100	41	29	87
First-SIGNAL (2012) (23)	Gefitinib vs CisG	Direct sequencing	43 (14)	54 (17)	212 (69)	57	100	11	NK	NK
EURTAC* (2012) (18)	Erlotinib vs platinum-G or platinum-D	Direct sequencing	173 (100)	0	0	65	0	27	31	92
LUX Lung 3† (2012) (34)	Afatinib vs CisPem	TheraScreen EGFR29	345 (100)	0	0	61	72	35	32	100
Maintenance therapy										
IFCT-GFPC 0502* (2010) (32)	Erlotinib or G vs placebo	NK	8 (3)	106 (34)	196 (63)	58	0	73	90	65
SATURN (2010) (13)	Erlotinib vs placebo	Direct sequencing	49 (6)	388 (44)	452 (50)	60	15	74	83	45
INFORM (2011) (30)	Gefitinib vs placebo	NK	30 (10)	49 (17)	217 (73)	55	100	59	46	71
Second-line/subsequent treatment										
ISEL (2005) (41)	Gefitinib vs placebo	Direct sequencing, ARMS	26 (2)	189 (11)	1477 (87)	62	20	67	78	45
BR21 (2005) (39,40)	Erlotinib vs placebo	Direct sequencing, ARMS	34 (5)	170 (23)	527 (72)	61	13	65	75	50
INTEREST (2008) (28,29)	Gefitinib vs D	Direct sequencing	44 (3)	253 (17)	1169 (80)	61	22	65	80	54
V-15–32 (2009) (31)	Gefitinib vs D	Direct sequencing	31 (6)	26 (6)	432 (88)	NK	100	62	68	78
TITAN (2012) (12)	Erlotinib vs pemetrexed or D	Direct sequencing	11 (3)	149 (35)	264 (62)	59	13	76	83	50
TAILOR† (2012) (14)	Erlotinib vs D	Direct sequencing	0	219 (100)	0	67	0	68	77	69
KCSG-LU08-01 (2012) (42)	Gefitinib vs Pem	Direct sequencing	33 (24)	38 (28)	64 (48)	61	100	15	0	100

* ARMS = amplification refractory mutation system; CG = carboplatin-gemcitabine; CisD = cisplatin-docetaxel; CisG = cisplatin-gemcitabine; CisPem = cisplatin-pemetrexed; CP = carboplatin-paclitaxel; CV = carboplatin-vinorelbine; D = docetaxel; EGFR+ = presence of epidermal growth factor receptor mutation; EGFR- = absence of epidermal growth factor receptor mutation; G = gemcitabine; NK = not known; PCR = polymerase chain reaction; PEM = pemetrexed.

J Natl Cancer Inst. 2013;105(9):595

HR comparing PFS in subgroups of EGFR positive



The front-line hazard ratio for EGFRmut+ was 0.43 (95% confidence interval [CI] = 0.38 to 0.49; *P < .001)*

The second-line hazard ratio for EGFRmut+ was 0.34 (95% CI = 0.20 to 0.60; *P < .001*

The maintenance hazard ratio for EGFRmut+ was 0.15 (95% CI = 0.08 to 0.27; *P < .001)*

J Natl Cancer Inst. 2013;105(9):595

TKIs for EGFR

1st generation

- Erlotinib
- Geftinib

2nd generation

- Afatinib
- Dacomitinib
- Neratinib

3rd generation

- Osimertinib
- Rociletinib
- Olmutinib
- EGF816
- ASP8273

2nd versus 1st generation EGFR TKIs

- Preclinical studies showed superior activity of *afatinib* over first-generation TKIs
  - Irreversible binding, which confers stronger binding affinity and potency
  - ability to circumvent first-generation TKI resistance mechanism T790M mutation in exon 20
  - effectiveness against multiple HER-endothelial growth factor receptors (EGFR/ErbB1, HER2/ErbB2, ErbB3, and ErbB4)

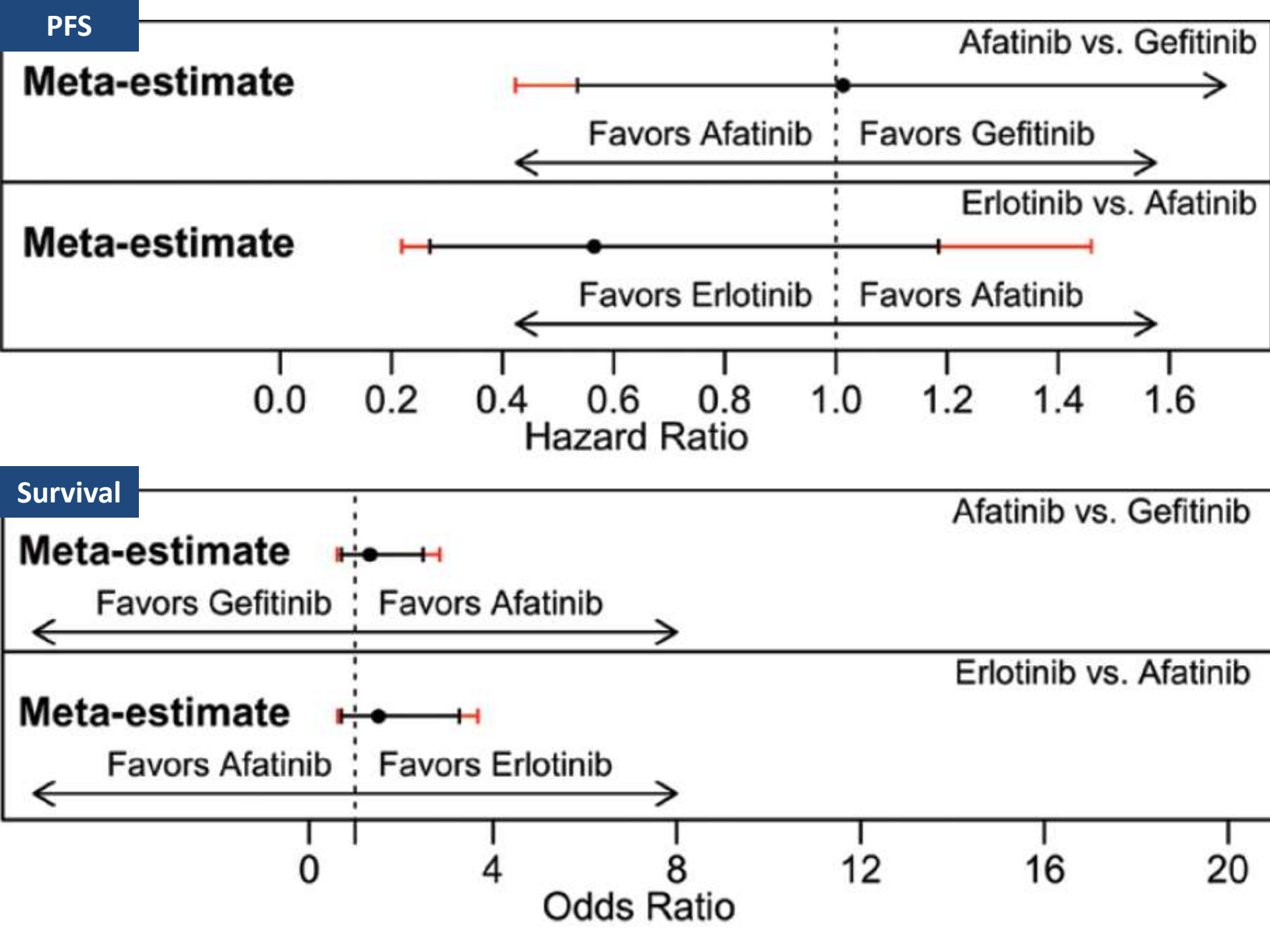
Oncogene 2008;27:4702–4711

Meta-Analysis of First-Line Therapies in Advanced NSCLC Harboring *EGFR-Activating Mutations*

- 8 randomized phase 3 clinical trials comparing gefitinib, erlotinib, or afatinib

	Progression-Free Survival	Response	Disease Control	Overall Survival
Comparison	**HR (95% CI; 95% PI)**	**OR (95% CI; 95% PI)**	**OR (95% CI; 95% PI)**	**HR (95% CI; 95% PI)**
Gefitinib vs. chemotherapy	0.44 (0.31–0.63; 0.22–0.88)	4.1 (2.7–6.3; 2.3–7.6)	2.1 (1.3–3.5; 1.2–3.7)	0.99 (0.81–1.21; 0.81–1.21)
Erlotinib vs. chemotherapy	0.25 (0.15–0.42; 0.11–0.55)	8.2 (4.5–15.1; 3.9–17.5)	2.5 (1.4–4.7; 1.3–4.9)	1.06 (0.82–1.37; 0.82–1.37)
Afatinib vs. chemotherapy	0.44 (0.26–0.75; 0.20–0.98)	5.5 (3.4–8.8; 2.9–10.5)	2.9 (1.8–4.6; 1.7–4.8)	1.01 (0.78–1.31; 0.78–1.31)
Erlotinib vs. gefitinib	0.57 (0.30–1.08; 0.24–1.36)	2.0 (0.9–4.1; 0.8–4.7)	1.2 (0.5–2.7; 0.5–2.8)	1.07 (0.77–1.47; 0.77–1.47)
Afatinib vs. gefitinib	1.01 (0.53–1.92; 0.42–2.42)	1.3 (0.7–2.5; 0.6–2.8)	1.4 (0.7–2.7; 0.7–2.8)	1.02 (0.73–1.41; 0.73–1.41)
Erlotinib vs. afatinib	0.56 (0.27–1.18; 0.22–1.46)	1.5 (0.7–3.3; 0.6–3.7)	0.9 (0.4–1.9; 0.4–2.0)	1.05 (0.73–1.51; 0.73–1.51)

J Thorac Oncol 2014; 9: 805–11

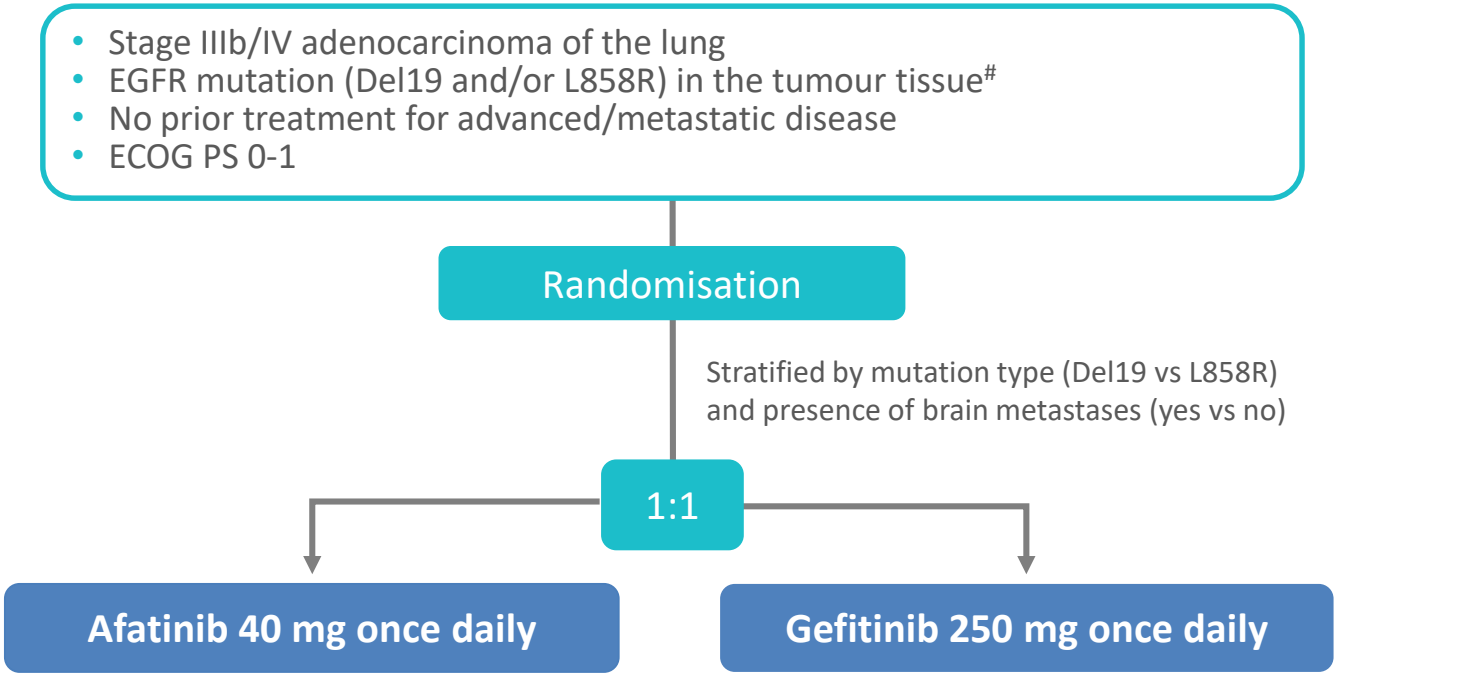

PFS
Afatinib vs. Gefitinib
Meta-estimate
Favors Afatinib
Favors Gefitinib
Erlotinib vs. Afatinib
Meta-estimate
Favors Erlotinib
Favors Afatinib
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1.6
Hazard Ratio
Survival
Afatinib vs. Gefitinib
Meta-estimate
Favors Gefitinib
Favors Afatinib
Erlotinib vs. Afatinib
Meta-estimate
Favors Afatinib
Favors Erlotinib
0
4
8
12
16
20
Odds Ratio

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

- 9 trials
- 3 TKIs similar in terms of PFS and OS
- RR for diarrhea
  - *Gefitinib vs afatinib 0.29(95% CI 0.20–0.41)*
  - *Erlotinib vs afatinib 0.36 (95% CI 0.25–0.54)*
- RR for rash
  - *Gefitinib vs afatinib 0.41(95% CI 0.25–0.65)*
  - *Erlotinib vs afatinib 0.41 (95% CI 0.25–0.66)*

Crit Rev Oncol Hematol 2015; 94: 213–27

LUX-Lung 7 – Phase IIb, open-label



Primary endpoints: PFS (independent review)#, **TTF, OS**

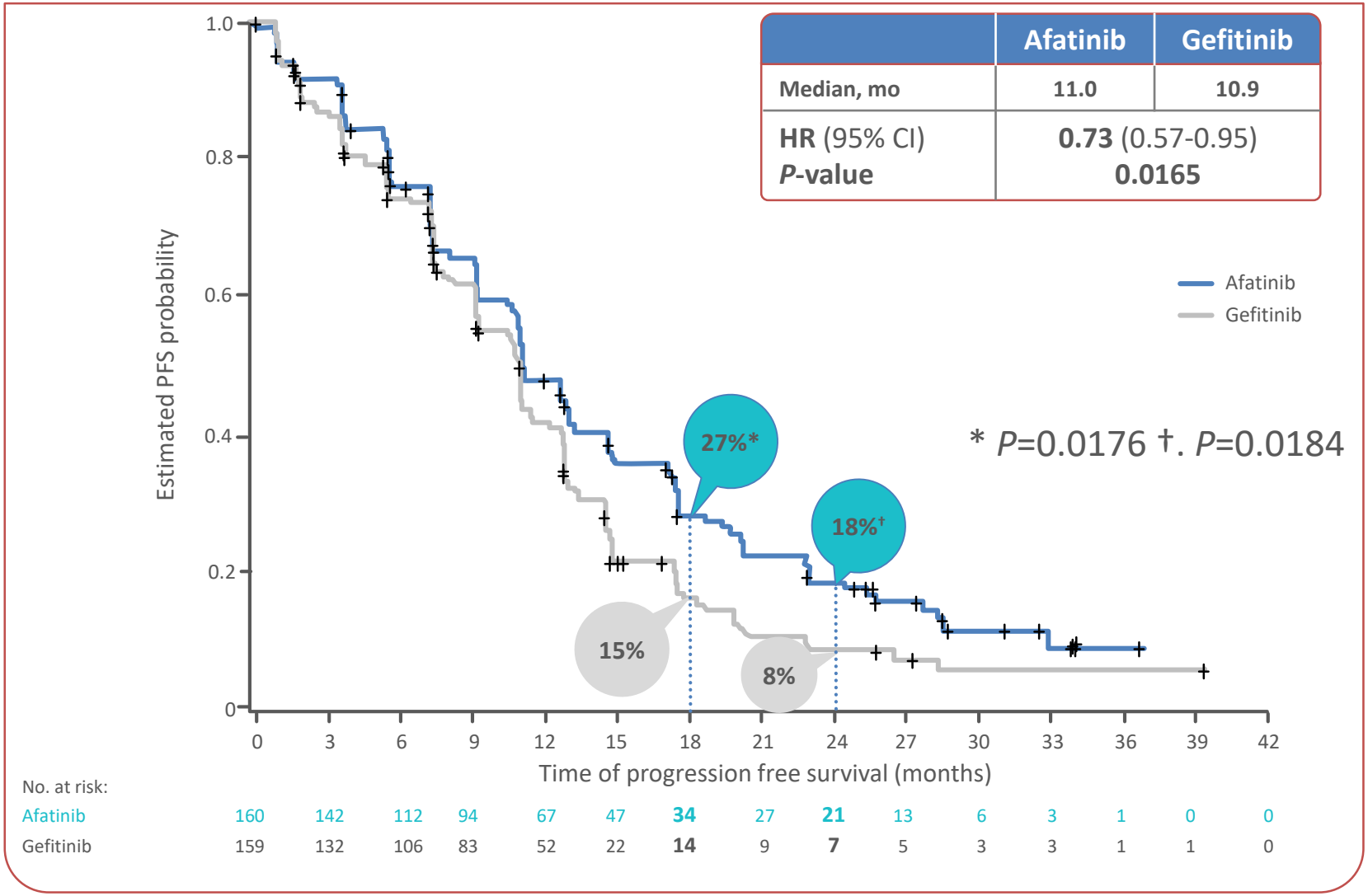
Secondary endpoints: ORR, time to and duration of response, duration of disease control, tumour shrinkage, HRQoL, safety

local or central test

Tumor assessment performed at week 4, 8, every 8 weeks until w64 and every 12 weeks thereafter

Treatment beyond progression allowed if deemed beneficial by investigator.

Lancet Oncol. 2016;17(5):577



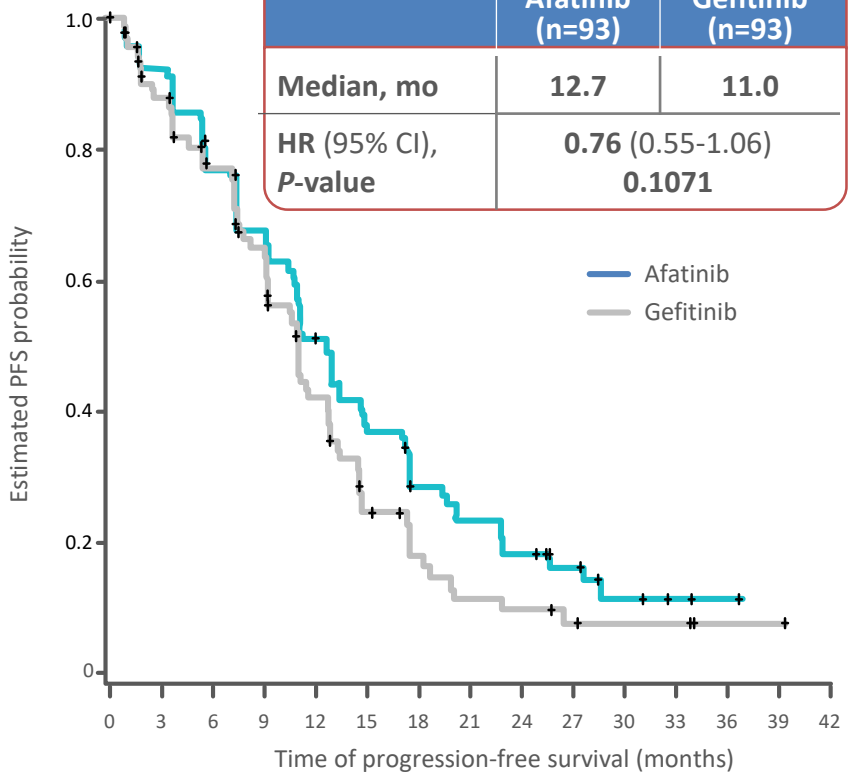
- Serious treatment-related adverse events occurred in 17 (11%) patients in the afatinib group and seven (4%) in the gefitinib group

Lancet Oncol. 2016;17(5):577

PFS by Mutation Type

Del19

	Afatinib (n=93)	Gefitinib (n=93)
Median, mo	12.7	11.0
HR (95% CI), ***P*-value**	**0.76** (0.55-1.06) **0.1071**	

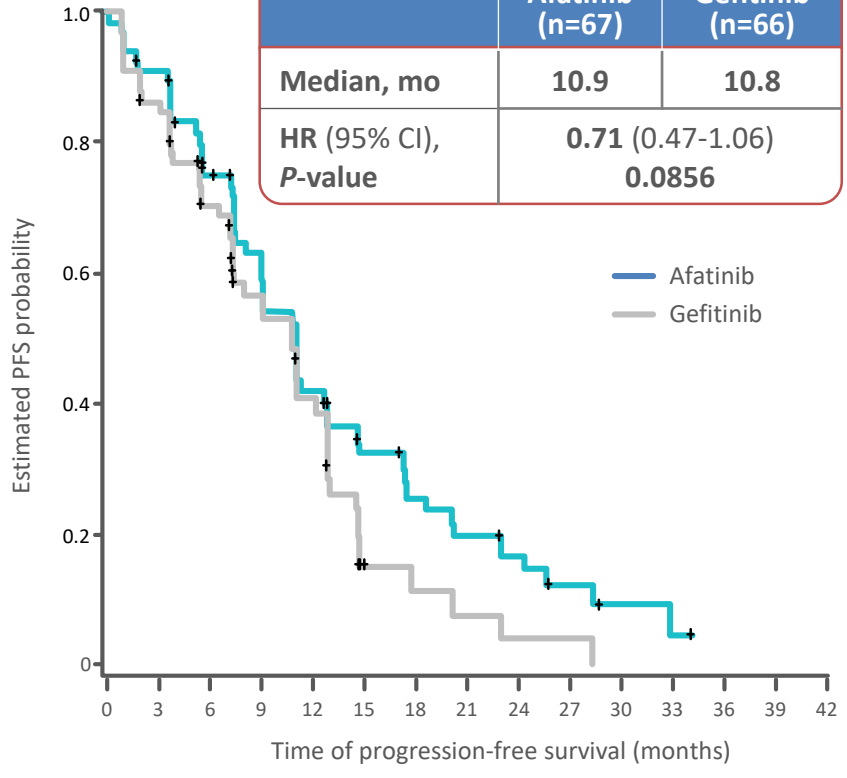


No. at risk:

Afatinib	93	83	67	58	43	31	22	18	14	9	4	2	1	0	0
Gefitinib	93	76	64	53	32	17	11	7	6	4	3	3	1	1	0

L858R

	Afatinib (n=67)	Gefitinib (n=66)
Median, mo	10.9	10.8
HR (95% CI), ***P*-value**	**0.71** (0.47-1.06) **0.0856**	

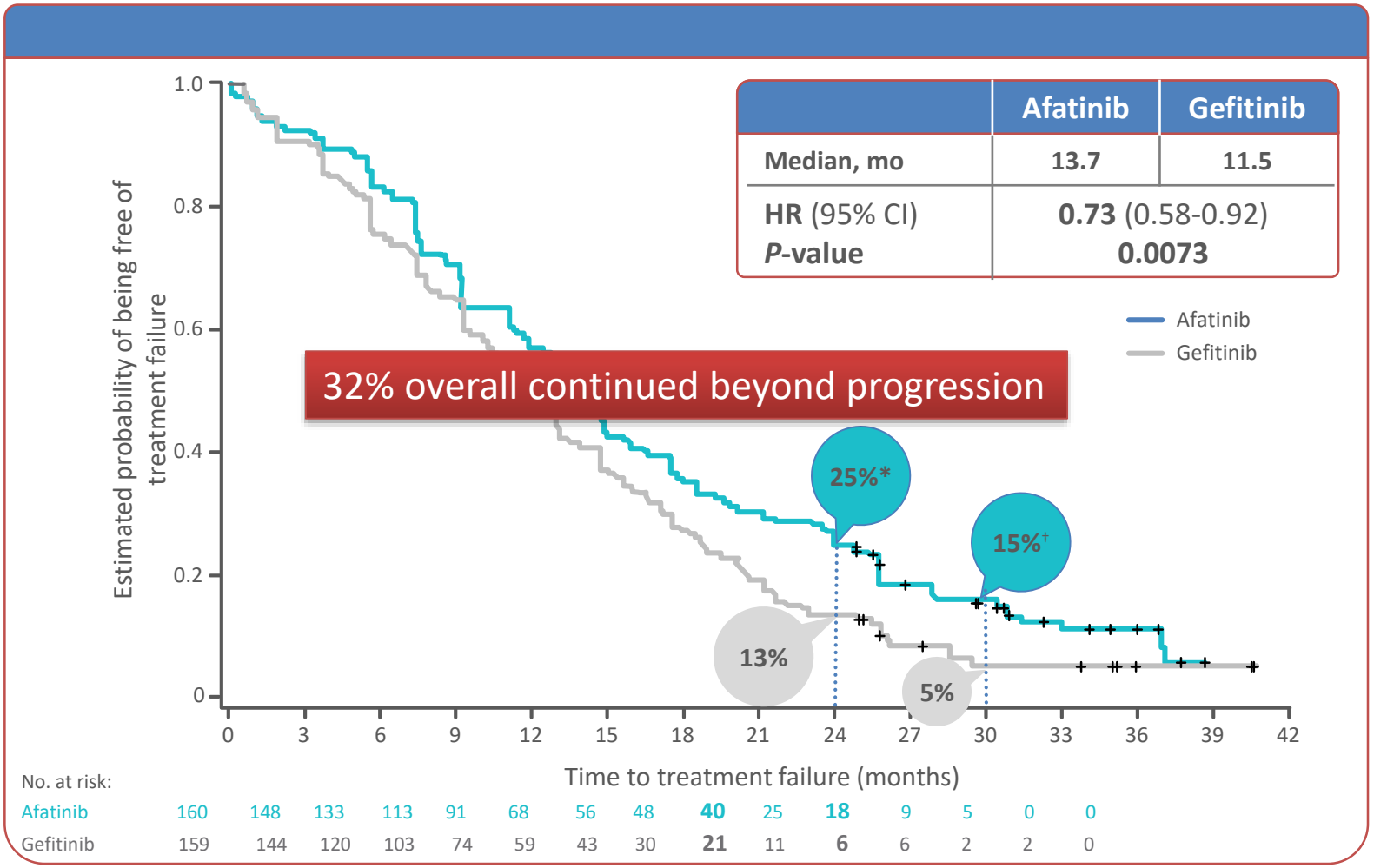


No. at risk:

Afatinib	67	59	45	36	24	16	12	9	7	4	2	1	0	0	0
Gefitinib	66	56	42	30	20	5	3	2	1	1	0	0	0	0	0

Lancet Oncol. 2016;17(5):577

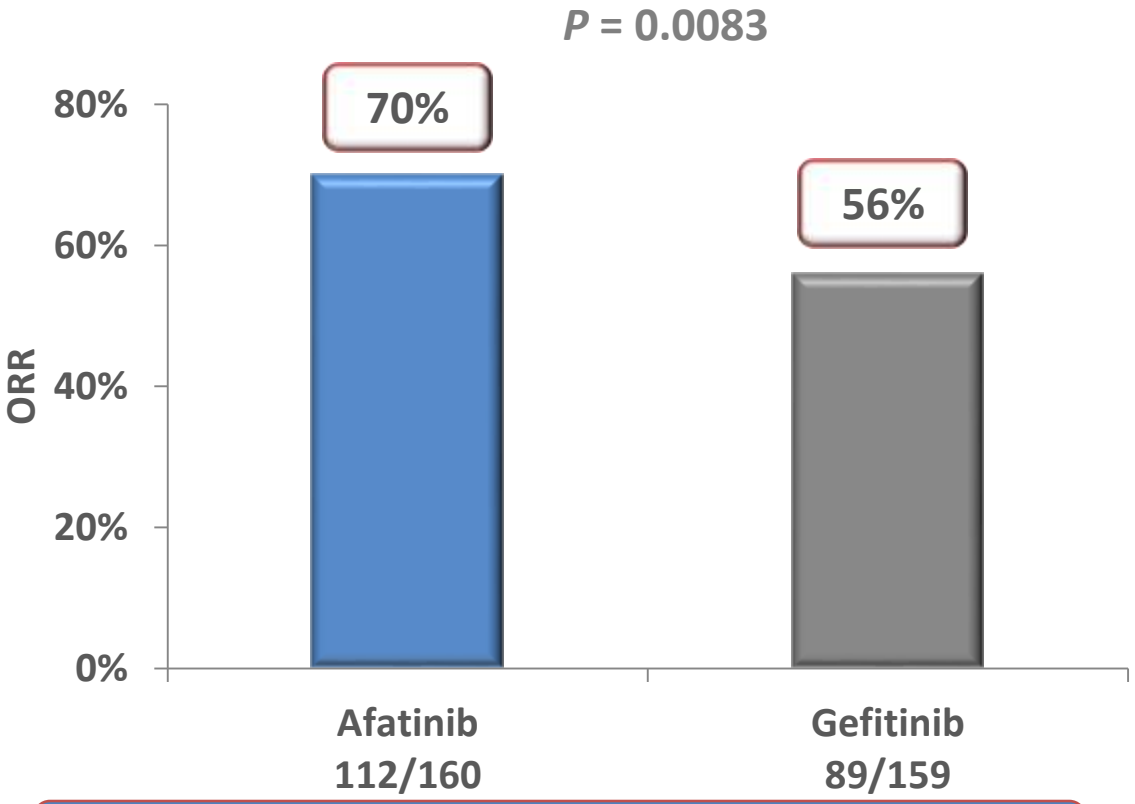
Time to Treatment Failure



TTF = time from randomization to discontinuation for any reason

Lancet Oncol. 2016;17(5):577

Objective Response and Disease Control Rate by Independent Review



Median DoR , months (95% CI)	10.1 (7.8, 11.1)	8.4 (7.4 – 10.9)
Disease control rate (N)	91.3% (146)	87.4% (139)

Lancet Oncol. 2016;17(5):577

Adverse Events Overall Summary

	Afatinib, 160 N (%)	Gefitinib, 159 N (%)
Pts with any AE	158 (98.8)	159 (100.0)
Pts with related AEs	156 (97.5)	153 (96.2)
AEs leading to dose reduction**	67 (41.9)	3 (1.9)**
Related AEs leading to discontinuation	10 (6.3)	10 (6.3)
SAEs	71 (44.4)	59 (37.1)
Related SAEs	17 (10.6)	7 (4.4)
Related fatal SAE	0	1 (0.6)*

***hepatic failure (reported as DILI case)**

** Dose modification for afatinib according to label.

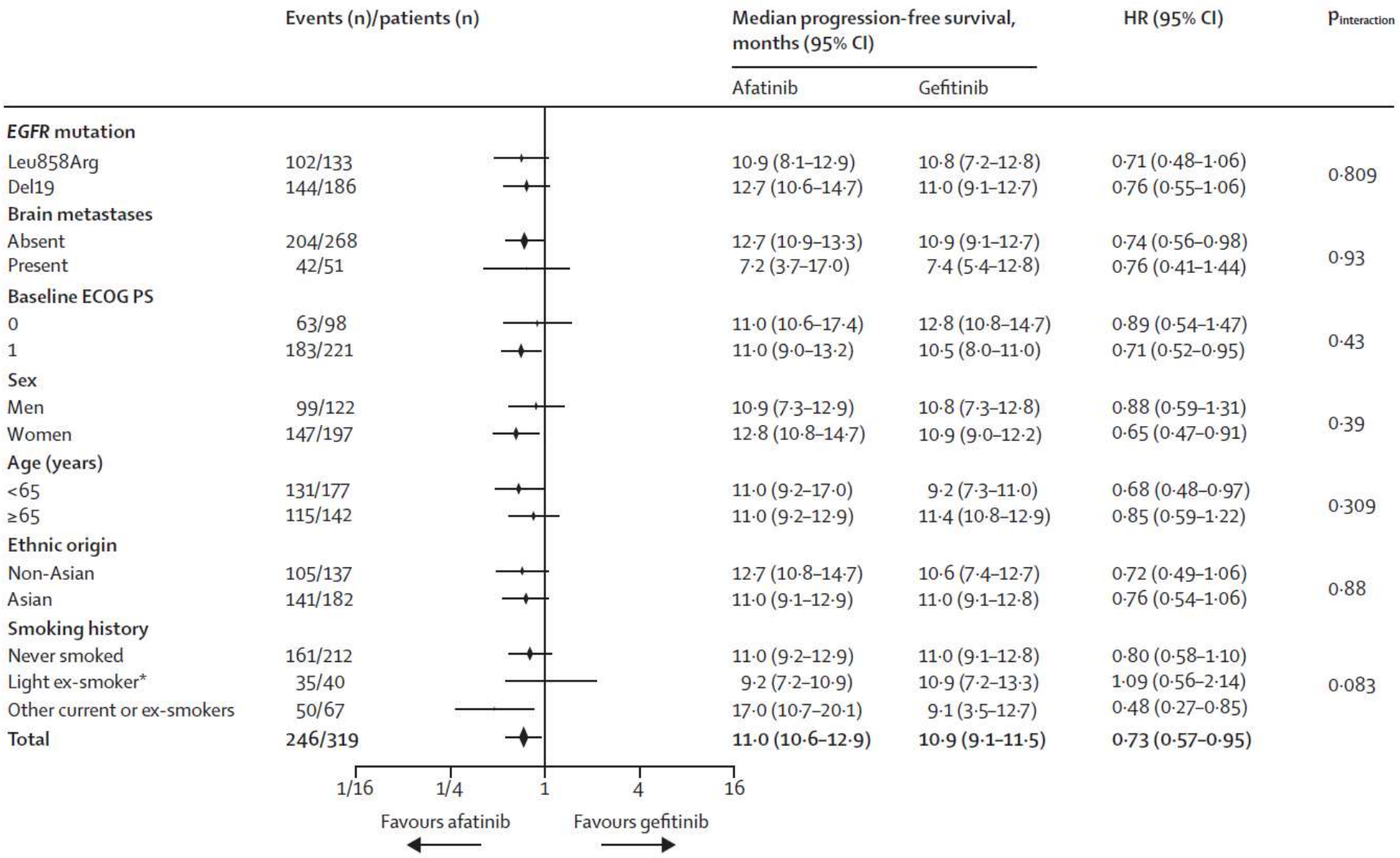
Lancet Oncol. 2016;17(5):577

Related AEs Occuring with >10%

	Afatinib			Gefitinib		
	All Gr	Gr3	Gr4	All Gr	Gr3	Gr4
Diarrhoea	144 (90.0)	19 (11.9)	1 (0.6)	97 (61.0)	2 (1.3)	
Rash/Acne*	142 (88.8)	15 (9.4)		129 (81.1)	5 (3.1)	
Stomatitis*	103 (64.4)	7 (4.4)		38 (23.9)		
Paronychia*	89 (55.6)	3 (1.9)		27 (17.0)	1 (0.6)	
Dry skin	52 (32.5)			59 (37.1)		
Pruritus	37 (23.1)			36 (22.6)		
Fatigue*	33 (20.6)	9 (5.6)		23 (14.5)		
Decr. appetite	26 (16.3)	1 (0.6)		19 (11.9)		
Nausea	26 (16.3)	2 (1.3)		22 (13.8)		
Alopecia	17 (10.6)			24 (15.1)		
Vomiting	17 (10.6)			6 (3.8)	1 (0.6)	
ALT increase	15 (9.4)			38 (23.9)	12 (7.5)	1 (0.6)
AST increase	10 (6.3)			33 (20.8)	4 (2.5)	

4 cases of ILD with gefitinib, 3 of them ≥ grade 3
No case of ILD with afatinib.

Lancet Oncol. 2016;17(5):577



Lancet Oncol. 2016;17(5):577

Afatinib versus gefitinib in patients with *EGFR* mutation-positive advanced non-small-cell lung cancer: overall survival data from the phase IIb LUX-Lung 7 trial

- Primary OS analysis was planned after 213 OS events and 32-month follow-up
- After a median follow-up of 42.6 months, median OS (afatinib versus gefitinib) was 27.9 versus 24.5 months [HR 0.86, 95% CI 0.66–1.12, P=0.2580]

Ann Oncol. 2017;28(2):270-277

Would 2nd generation TKIs be useful in mutations conferring resistance to 1st generation TKIs?

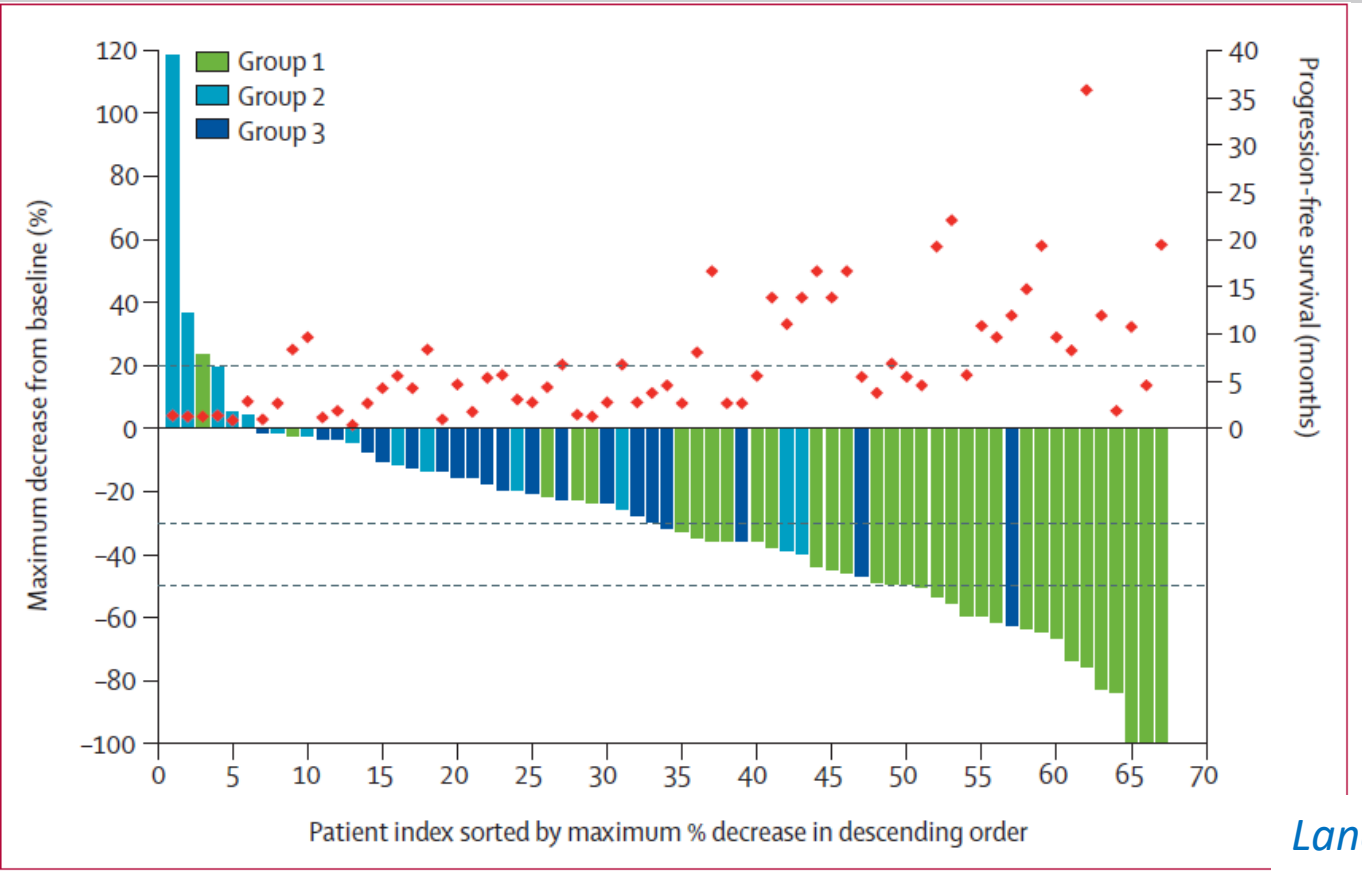
Clinical activity of afatinib in patients with advanced non-small-cell lung cancer harbouring uncommon *EGFR* mutations: a combined post-hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6

James C-H Yang, Lecia V Sequist*, Sarayut Lucien Geater, Chun-Ming Tsai, Tony Shu Kam Mok, Martin Schuler, Nobuyuki Yamamoto, Chong-Jen Yu, Sai-Hong I Ou, Caicun Zhou, Daniel Massey, Victoria Zazulina, Yi-Long Wu*

- Combined post hoc, ITT analysis of data on pts with uncommon *EGFR* mutations (n = 100) prospectively collected from the LUX-Lung 2, 3, and 6 trials
  - Afatinib: n = 75; chemotherapy: n = 25

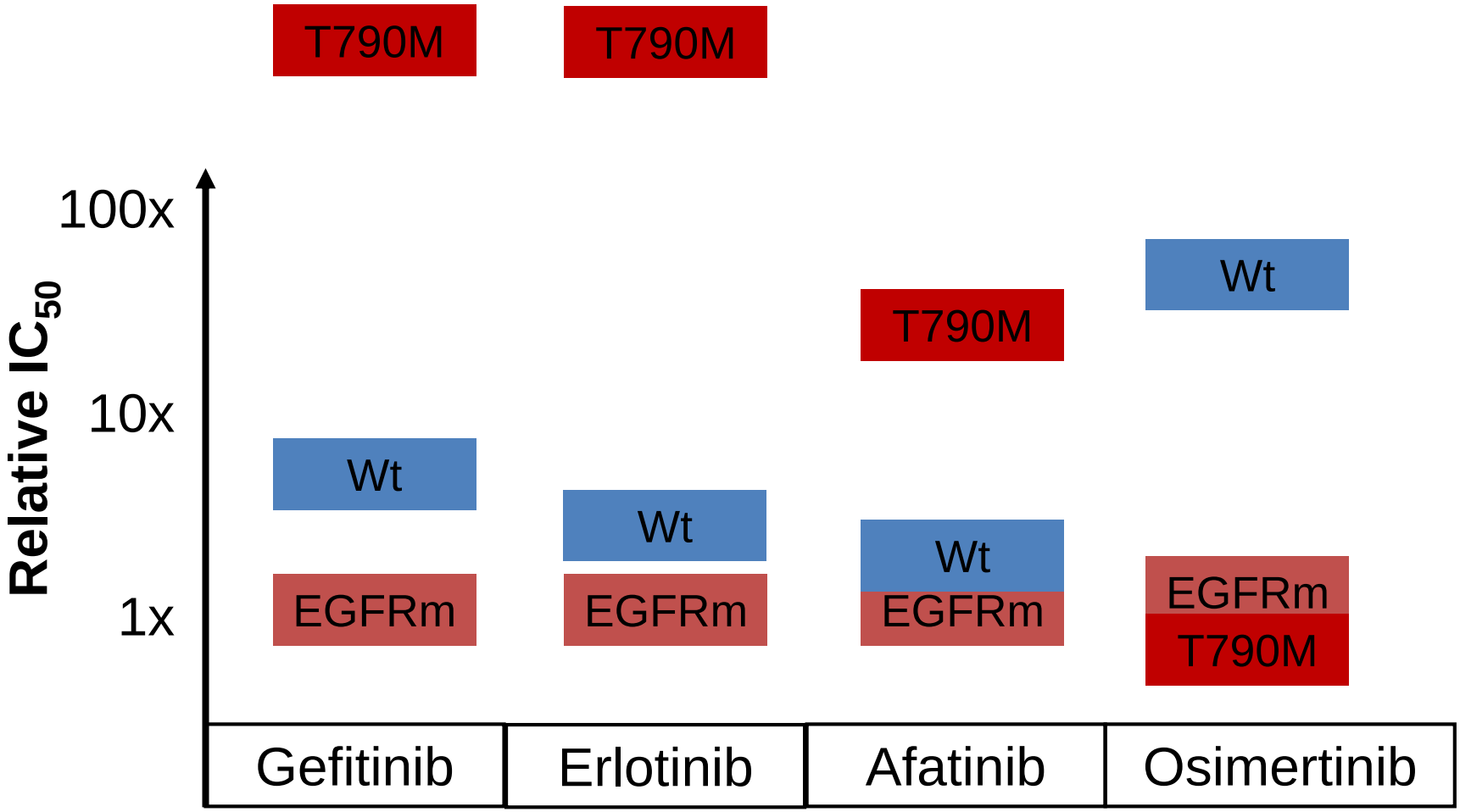
Lancet Oncol 2015; 16: 830–38

Cohort	n	Uncommon Mutations
Group 1	38	Point mutations or duplications in exons 18-21 (L861Q, G719S, G719A, G719C, S768I, rare others) alone or in combination with each other
Group 2	14	De novo T790M mutations in exon 20 alone or in combination with other mutations
Group 3	23	Exon 20 insertions



Lancet Oncol 2015; 16: 830–38

3 Generations of EGFR TKIs



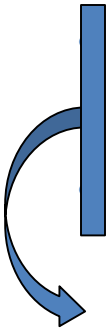
Li D, et al. Oncogene. 2008;27:4702-4711. Ranson M, et al. WCLC 2013. Abstract MO21.12. Moyer JD, et al. Cancer Res. 1997;57:4838-4848. Kancha RK, et al. Clin Cancer Res. 2009;15:460-467.

LUX-LUNG 8: Afatinib versus erlotinib as second-line treatment of patients with advanced squamous cell carcinoma

- Open-label randomised controlled phase 3 trial
- Stage IIIB or IV squamous cell carcinoma of the lung who had progressed after at least 4cycles of platinum-based-chemotherapy
- Randomly assigned (1:1) to receive afatinib (40 mg per day) or erlotinib (150 mg per day) until disease progression

Lancet Oncol;16(8):897-907

Alterations of ErbB Pathway in SCC-NSCLC



EGFR overexpression and/or gene amplification

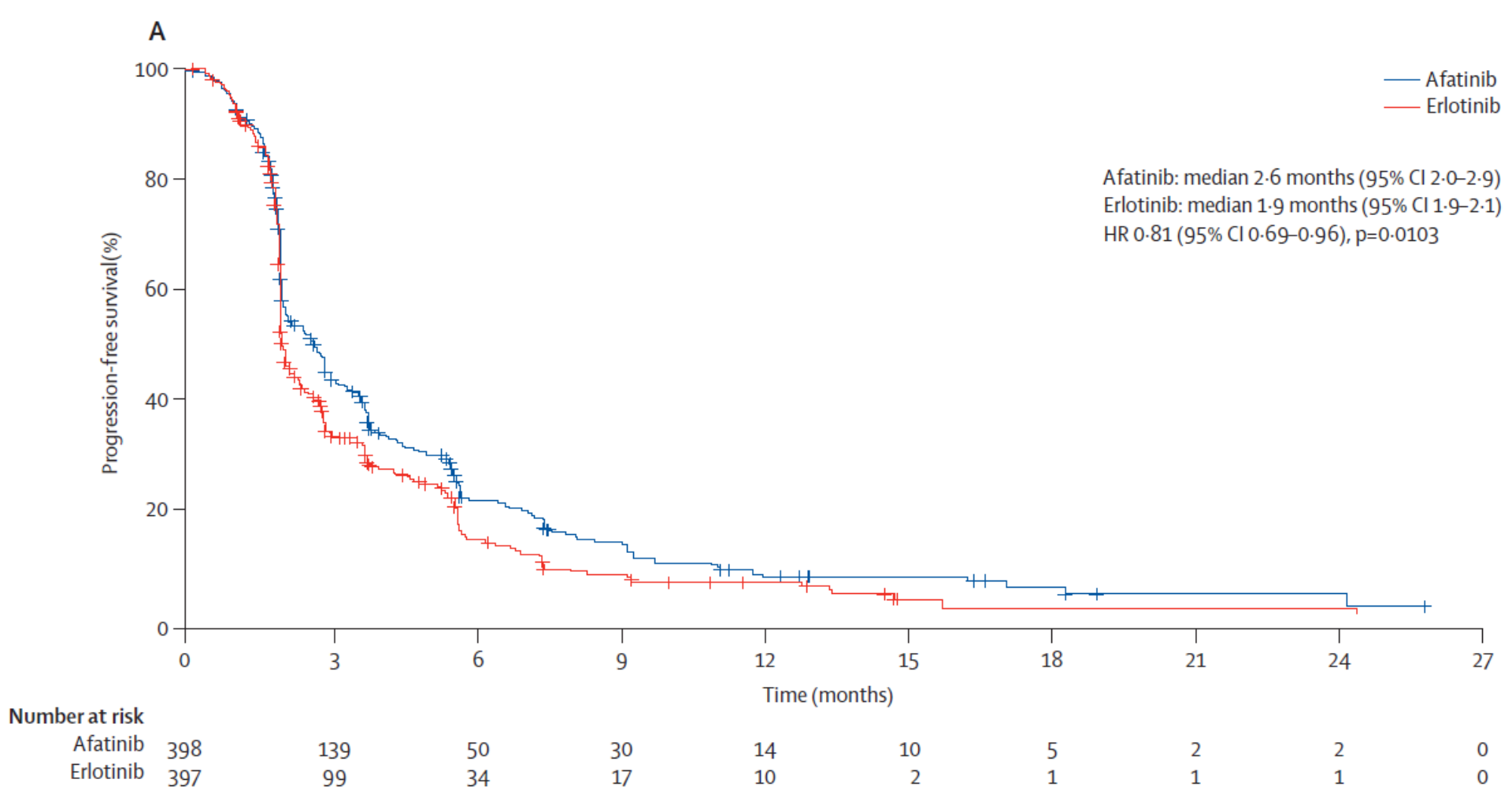
Aberrations of other ErbB receptors

Dysregulation of downstream pathway

Implicated in the pathobiology of SCC

ErbB Receptor	Frequency (%)
EGFR amp	7-26
*EGFR*vIII mut	3-5
EGFR overexpression	57-7
EGFR kinase domain mut	1-3
ERBB2	4
ERBB3	1-2
ERBB3 overexpression	≈30
ERBB4	1-2

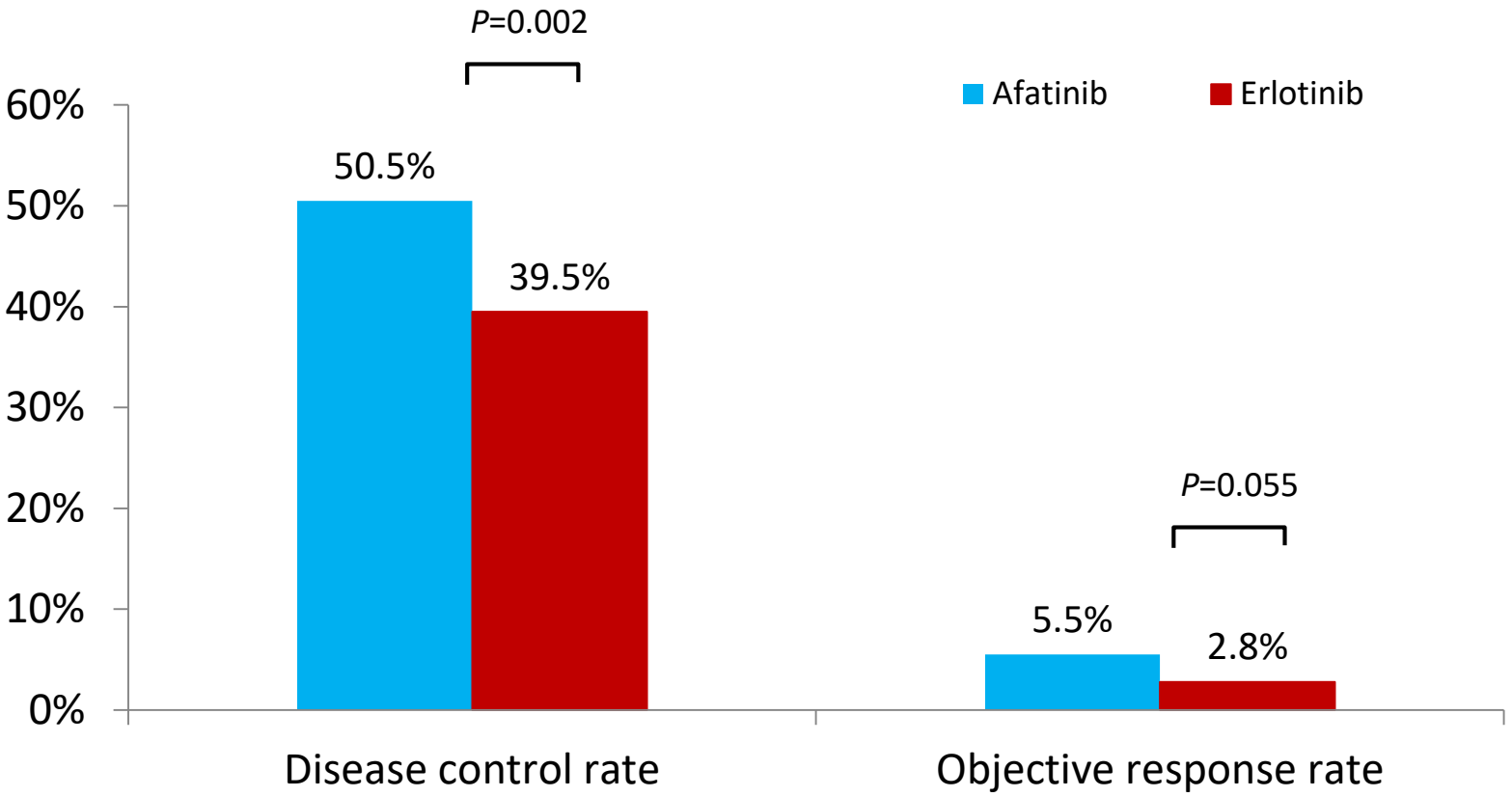
Gately K et al Clin Lung Cancer 2014; 15:58



- 795 patients
- PFS significantly longer with afatinib (median 2·4 months [95% CI 1·9-2·9] vs 1·9 months [1·9-2·2]; HR 0·82 [95% CI 0·68-1·00], p=0·0427)

Lancet Oncol;16(8):897-907

Tumour response (independent review)



Duration of response:

- Afatinib: 7.29 months
- Erlotinib: 3.71 months

Lancet Oncol;16(8):897-907

Dacomitinib

- Dacomitinib versus gefitinib for the first-line treatment of advanced EGFR mutation positive NSCLC
- ARCHER 1050: A randomized, open-label phase III trial
- Newly diagnosed stage IIIB/IV/ recurrent NSCLC harboring an EGFR- activating mutation (exon 19 del or exon 21 L858R mu +/- exon 20 T790M mu)
- Randomized 1:1 to D 45 mg PO QD or G 250mg PO QD
- 452 pts

J Clin Oncol. 2017;35(suppl; abstr LBA9007)

ITT Population

	Dacomitinib (D) N=227 Median (months)	Gefitinib (G) N=225 Median (months)	
PFS per IRC	14.7 [95% CI: 11.1,16.6]	9.2 [95% CI: 9.1,11.0]	Stratified HR = 0.59 [95% CI: 0.47,0.74] 1-sided p-value <0.0001
PFS per INV	16.6 [95% CI: 12.9,18.4]	11.0 [95% CI: 9.4,12.1]	Stratified HR = 0.62 [95% CI: 0.50,0.78] 1-sided p-value <0.0001
DR per IRC in responders	14.8	8.3	Stratified HR = 0.40 [95% CI: 0.31,0.53] -sided p-value <0.0001

66% of patients requiring a dose reduction, compared to 8% for those receiving gefitinib

- Reduced the risk of disease progression by more than 40%
- 6.5-month improvement in response duration
- PFS was similar in both arms at 6-months
  - Became apparent by 24-months

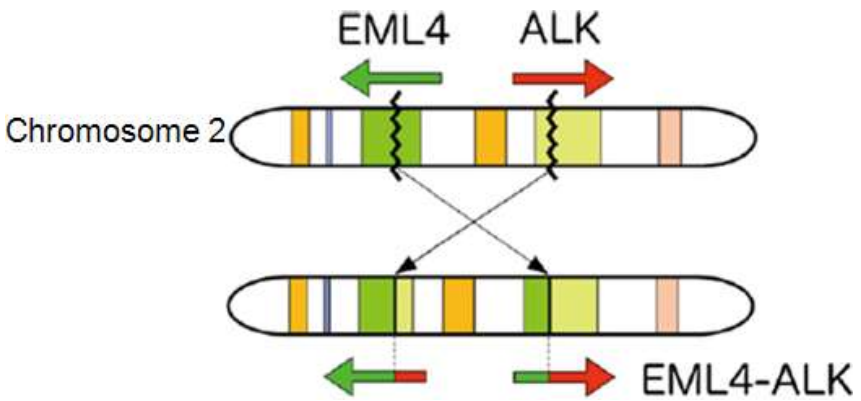
J Clin Oncol. 2017;35(suppl; abstr LBA9007)

Take home message (1^{st} vs 2^{nd} generation EGFR TKIs)

- Afatinib may yield the strongest disease outcomes
- Also cause the most side effects
- 1^{st} generation may be tolerated better
- 2^{nd} generation not effective in resistance to 1^{st} generation

Fusion Oncogene *EML4-ALK*

- The echinoderm microtubule associated protein like-4 (EML4) anaplastic lymphoma kinase (ALK) fusion oncogene
- Inv(2)(p21p23) that joins exons 1-13 of EML4 to exons 20-29 of ALK
- Oncogene “addiction” hypothesis



Lung Cancer. 2013;82(2):179.

Epidemiology

- About 4% in non selected NSCLC
- Tend to be independent of EGFR or RAS mutation
- Increased prevalence in never/light smokers
- Younger patients
- 97% adenocarcinomas, rarely in squamous

Lung Cancer. 2013;82(2):179.

Crizot

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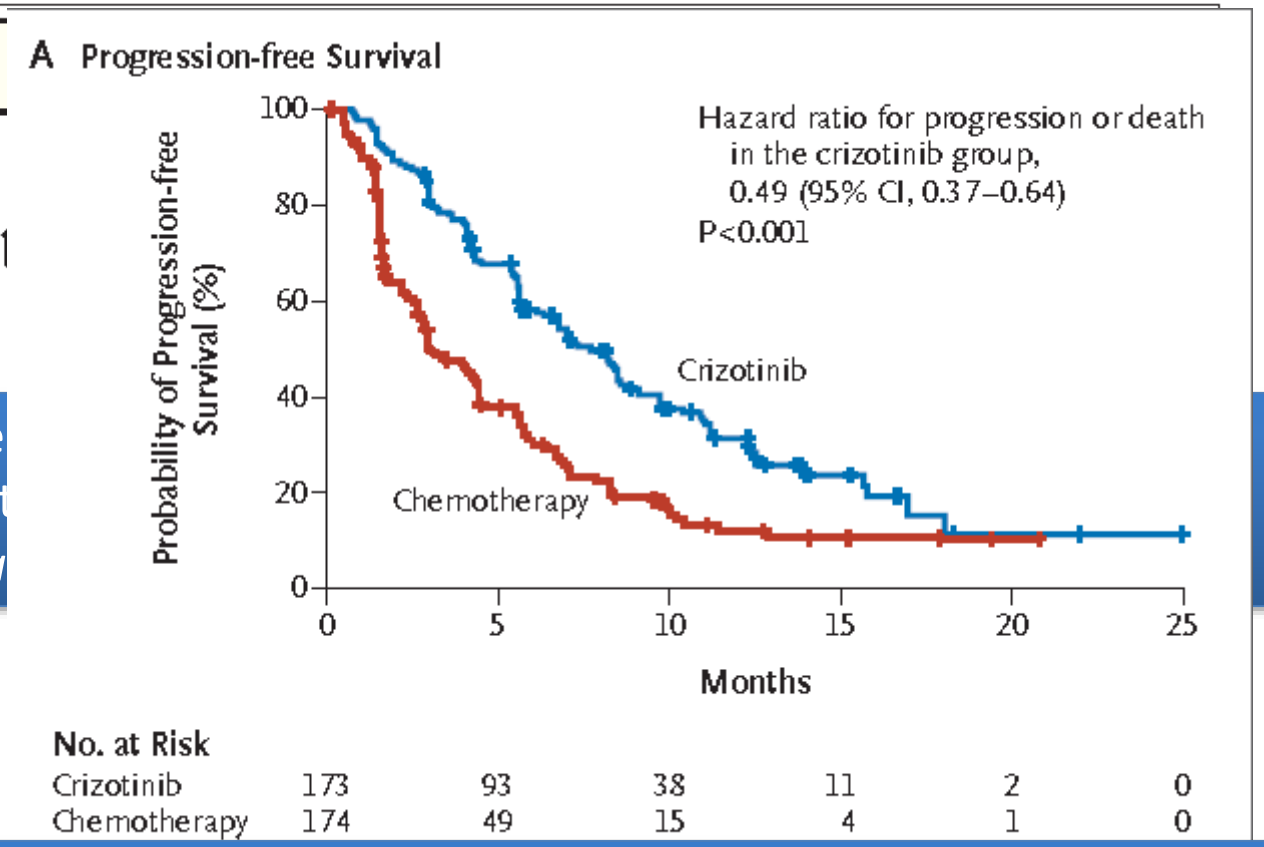

The median progression-free survival was 7.7 months in the crizotinib group and 3.0 months in the chemotherapy group
Crizotinib superior to standard chemotherapy in patients with previously treated, advanced non–small-cell lung cancer with *ALK rearrangement*

PROFILE 1007

N Engl J Med. 2013 ;368(25):2385-94

First-l

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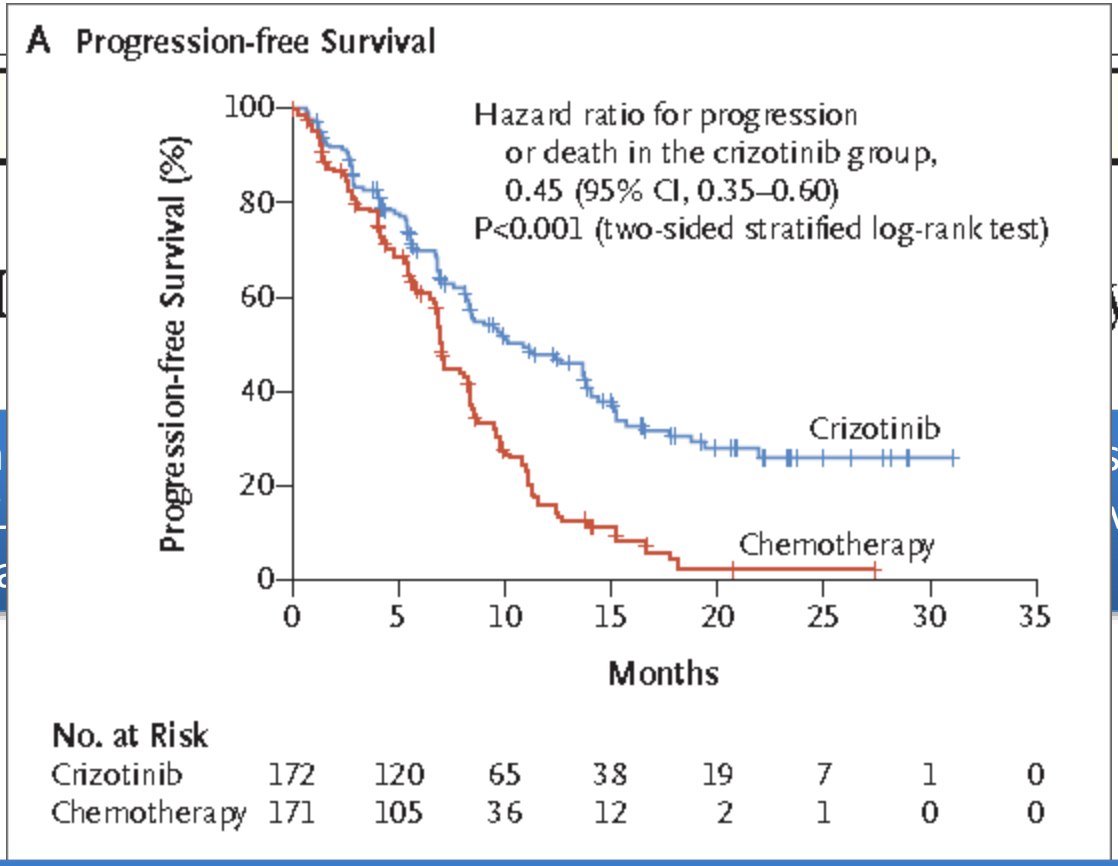


Progression-free survival was significantly longer with crizotinib than with chemotherapy (median, 10.9 months vs. 7.0 months)
Crizotinib was superior to standard first-line pemetrexed-plus-platinum chemotherapy in patients with previously untreated advanced *ALK-positive NSCLC.*

PROFILE 1014

N Engl J Med. 2014 ;371(23):2167-77

TKIs for ALK

First generation

- Crizotinib (XALKORI®, Pfizer),

Second Generation

- Ceritinib (Zykadia®, Novartis Pharmaceuticals)
- Alectinib (Alecensa®, Roche/Genentec)
- Brigatinib (Ariad Pharmaceuticals)

Third Generation

- Lorlatinib

Crizotinib beyond disease progression

- NSCLC inevitably develops progressive disease
- Oligoprogressive disease
- CBDP
  - crizotinib-refractory disease still maintains dependence on ALK signaling
- Disease flare following discontinuation of crizotinib upon disease progression
- More likely to have brain as a site of progression (twice compared to TKI naïve)

G. Metro et al. Lung Cancer. 2017; 106 : 58–66

CNS relapse on Crizotinib

- Poor activity of crizotinib in the CNS
  - Low CSF-to-serum ratios (0.06% and 0.26%)
  - Substrate of P-glycoprotein, a drug-efflux pump
- CBDP is a reasonable choice for patients with isolated CNS relapse on crizotinib
  - controlled extra-cranial disease
  - brain metastases are amenable to local ablative treatment

Tang et al. Int. J. Cancer. 2014;134: 1484–1494

Oligo-progression at extra-cranial site(s)

- Median post-progression PFS - 4months
  - Additional 5.5 months if ≤ 4 newly growing lesions outside the CNS with local ablative approaches

- Decision to manage these patients with CBDP and local ablative therapy should be discussed within a multidisciplinary team

- Role of 2nd and 3rd generation ALK inhibitors

2nd vs 1st generation ALK TKIs

- Highly selective ALK-I
- Block the ALK-tyrosine kinase more effectively than crizotinib
- Potential to overcome most of the secondary mutations
  - L1196M gatekeeper mutation
  - Differential in-vivo sensitivity to a 2nd gen ALK-TKI

2nd Generation TKIs in Crizotinib refractory disease

Variable	Ceritinib (750 mg/d)			Alectinib (600 mg BD)		Brigatinib (90 mg/d × 7 days → 180 mg/d)
	ASCEND−1	ASCEND-2	ASCEND−5	NP28763	NP28761	ALTA
No. of pts	163	140	115	138	87	110
ORR (%)	56.4	38.6	39.1	50	52.2	54
DCR (%)	74.2	77.1	76.5	78.7	79.1	86
DoR	8.3	9.7	NR	11.2	13.5	NR
PFS (mos)	6.9	5.7	5.4	8.9	8.1	12.9

DCR, disease control rate; DoR, duration of response; No., number; NR, not reported; ORR, overall response rate

G. Metro et al. Lung Cancer. 2017; 106 : 58–66

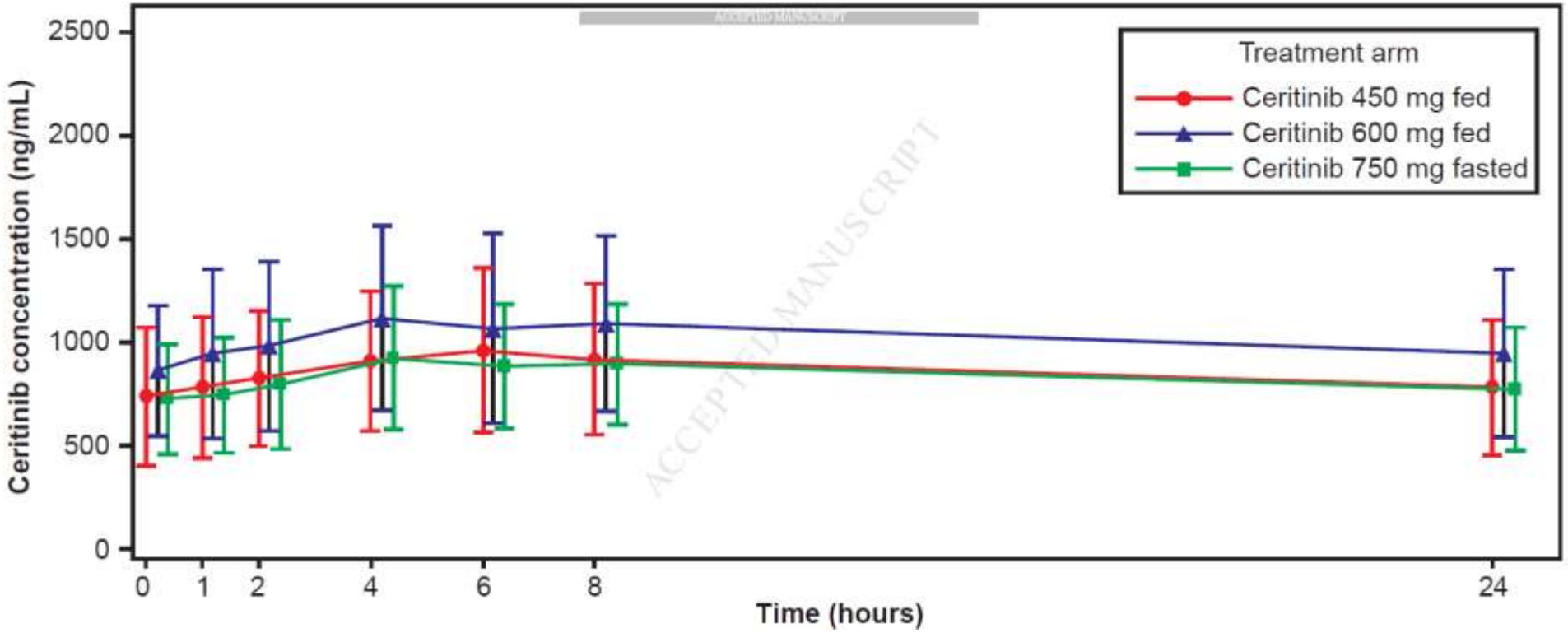
Ceritinib

- 20-fold greater potency than crizotinib in enzymatic assays
- Overcomes several ALK mutations
- Does not inhibit MET, but it does target ROS1 and insulin-like growth factor 1 receptor kinases
- Particularly active against brain metastases
- ‘ASCEND’ clinical trials

ASCEND 8

- Multicenter, randomized, open-label, phase 1 study
- Part 1 investigated the steady-state pharmacokinetics (PK) and safety of ceritinib 450 mg or 600 mg taken with a low-fat meal versus 750 mg fasted
- Patient subset - advanced *ALK+ NSCLC* patients, treatment naïve or pretreated with chemotherapy and/or crizotinib
- Part 2 will assess efficacy and safety of ceritinib in treatment-naïve patients

J Thorac Oncol. 2017 Jul 17. pii: S1556-0864(17)30578-6



- Ceritinib 450 mg with food had similar exposure and a more favorable GI safety profile vs ceritinib 750 mg fasted in patients with *ALK+ NSCLC*

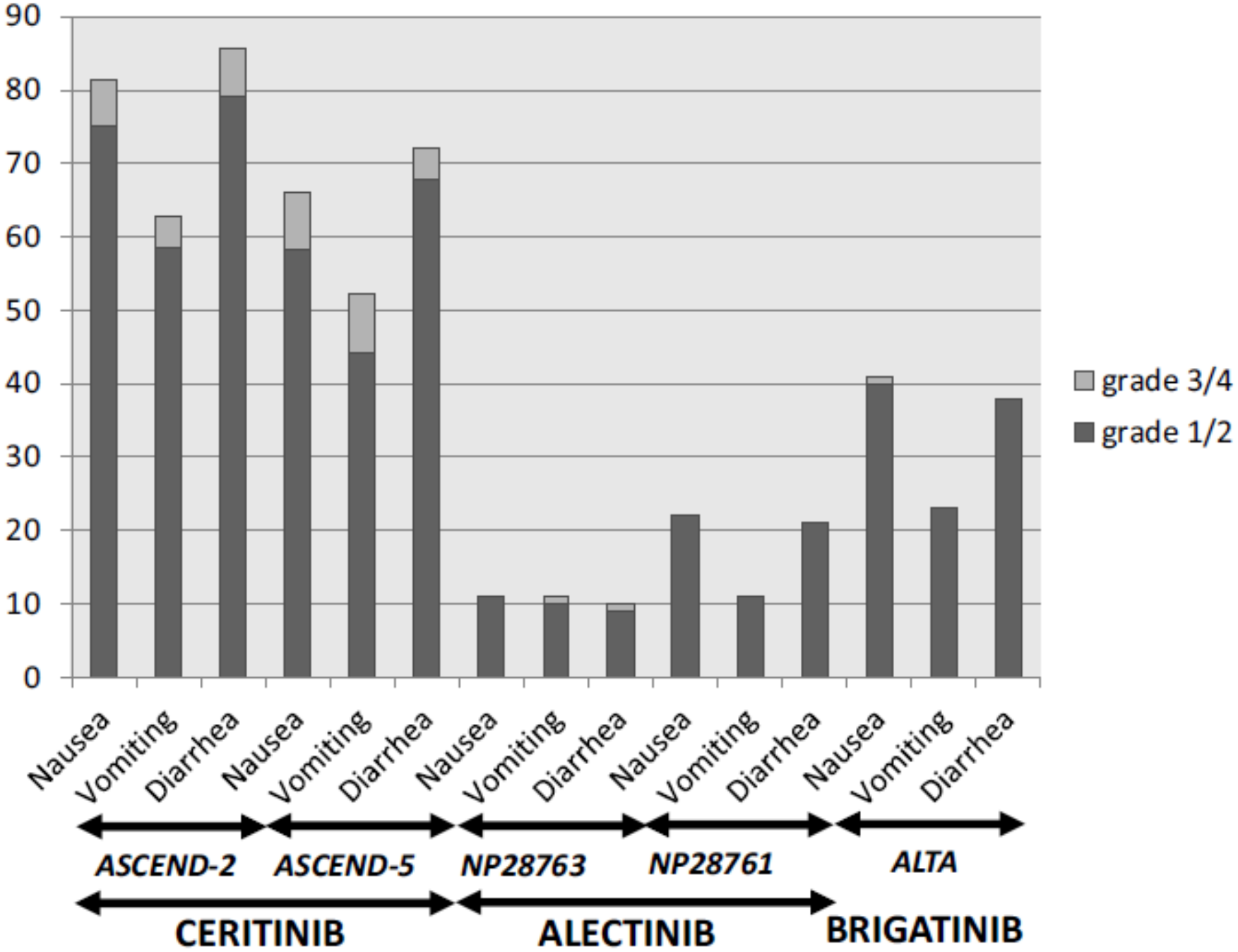
J Thorac Oncol. 2017 Jul 17. pii: S1556-0864(17)30578-6

Alectinib

- 5 times more potent than crizotinib
- Overcomes most ALK mutations
- Does not inhibit the kinase activity of MET and has only low inhibitory activity against ROS1,while it exerts anti-proliferative activity against RET kinase
- Highly active against CNS metastases including leptomeningeal carcinomatosis

Brigatinib

- 12-fold greater potency than crizotinib
- Inhibits ROS1kinase with potency similar to that of ALK
- Overcomes several mutations
- High CNS activity

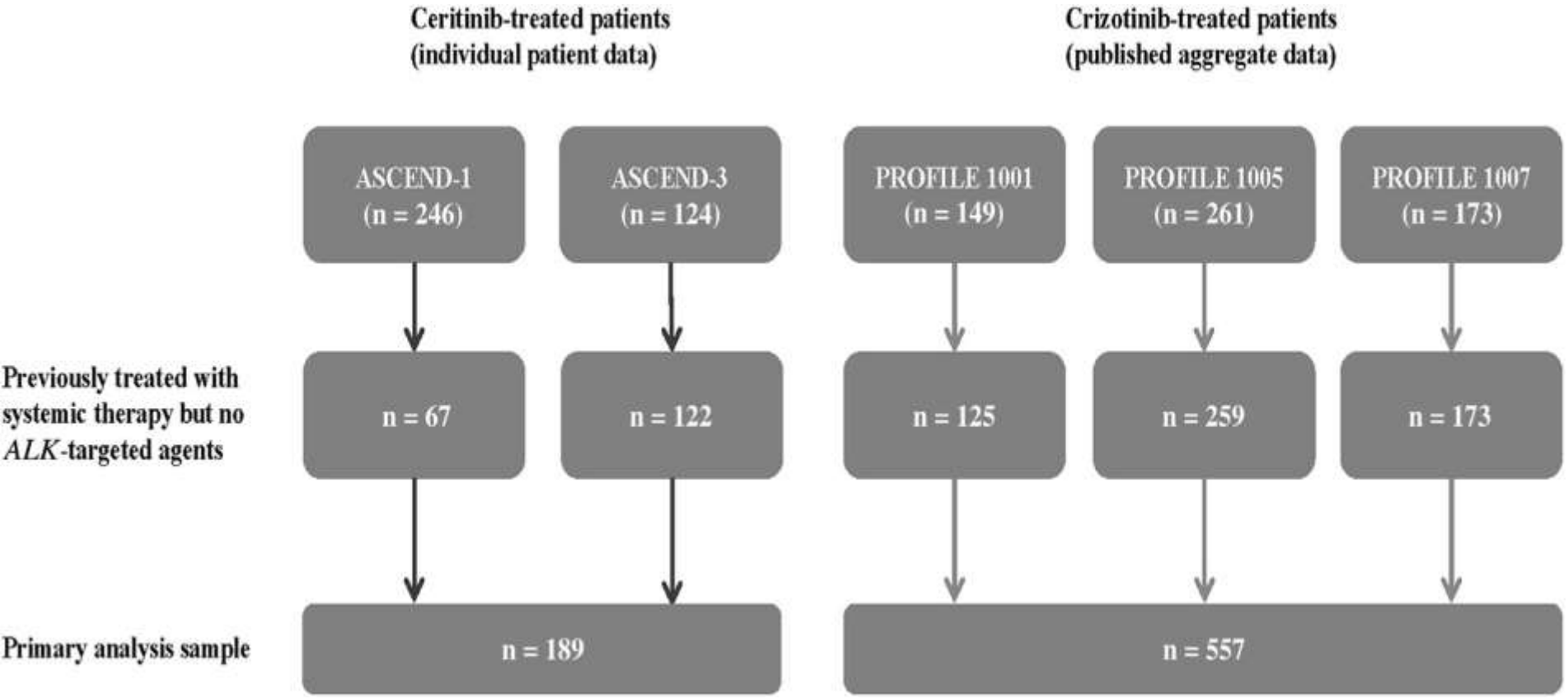


G. Metro et al. Lung Cancer. 2017; 106 : 58–66

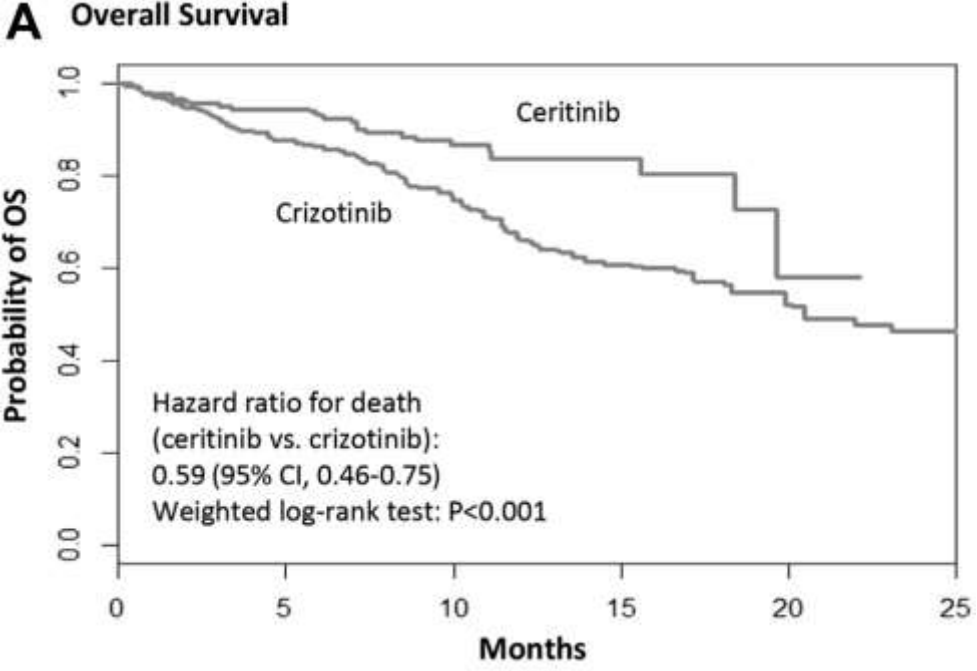
Comparative Efficacy of Ceritinib and Crizotinib as Initial *ALK*-Targeted Therapies in Previously Treated Advanced NSCLC: An Adjusted Comparison with External Controls

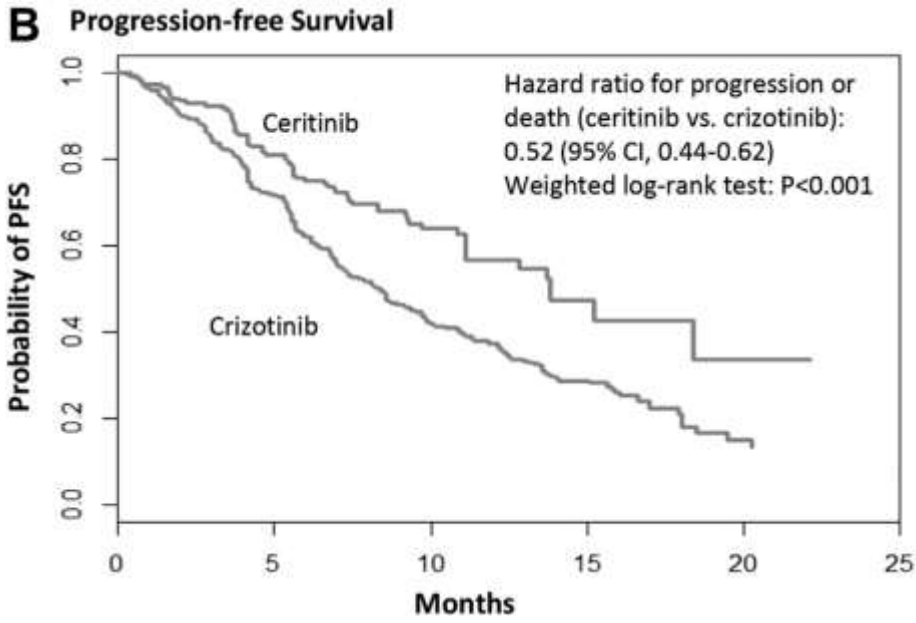
- Individual patient data were drawn from
  - Ceritinib- two single-arm trials (ASCEND-1 and ASCEND-3)
  - Crizotinib- PROFILE 1001, PROFILE 1005, PROFILE 1007
- To adjust for cross-trial differences, average baseline characteristics were matched using propensity score weighting

Tan DS et al. J Thorac Oncol. 2016;11(9):1550-7.



Tan DS et al. J Thorac Oncol. 2016;11(9):1550-7.





- The median OS was not reached with ceritinib as compared with 20.5 months with crizotinib
- The median PFS was 13.8 months with ceritinib as compared with 8.3 months with crizotinib.

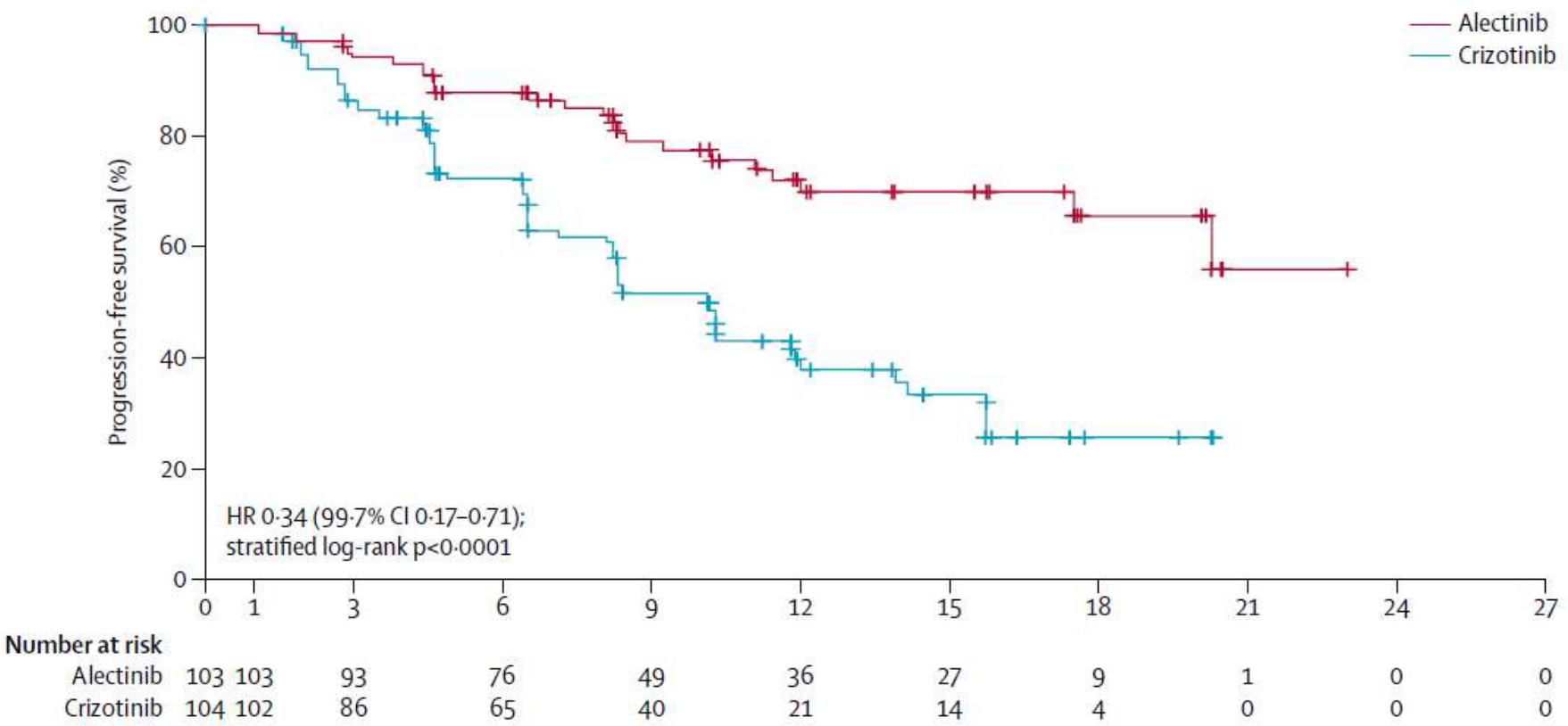
Tan DS et al. J Thorac Oncol. 2016;11(9):1550-7.

Alectinib versus crizotinib in patients with *ALK*-positive non-small-cell lung cancer (J-ALEX): an open-label, randomised phase 3 trial

- ALK inhibitor-naive Japanese patients with ALK-positive NSCLC, who were chemotherapy-naive or had received one previous chemotherapy regimen

- Randomly assigned (1:1) to receive
  - oral alectinib 300 mg twice daily (n=103)
  - crizotinib 250 mg twice daily (n=104)
  - until progressive disease, unacceptable toxicity, death, or withdrawal

Hida et al. Lancet 2017; 390: 29–39



- Median progression-free survival had not yet been reached with alectinib (95% CI 20·3–not estimated) and was 10·2 months (8·2–12·0) with crizotinib
- Similar results when stratified by line of treatment or stage of disease
- Significantly favourable adverse effect profile with Alectinib

Hida et al. Lancet 2017; 390: 29–39

	Alectinib	Crizotinib
Assessed by IRF		
Total	83	90
Objective response	92% (85·6–97·5)	79% (70·5–87·3)
Complete response	2 (2%)	2 (2%)
Partial response	74 (89%)	69 (77%)
Stable disease	4 (5%)	12 (13%)
Time to response (months)	1·0 (1·0–1·1)	1·0 (1·0–1·0)
Duration of response (months)	NE (NE–NE)	11·1 (7·5–13·1)
Assessed by investigators		
Total	103	104
Objective response	85% (78·6–92·3)	70% (61·4–79·0)
Complete response	5 (5%)	2 (2%)
Partial response	83 (81%)	71 (68%)
Stable disease	13 (13%)	19 (18%)
Time to response (months)	1·0 (1·0–1·1)	1·0 (1·0–1·0)
Duration of response (months)	NE (16·7–NE)	11·2 (8·5–13·9)

Data are n, % (95% CI), n (%), or median (95% CI). IRF=independent review facility. NE=not estimable.

Hida et al. Lancet 2017; 390: 29–39

Alectinib versus Crizotinib in Untreated *ALK*-Positive Non–Small-Cell Lung Cancer

ALEX Trial

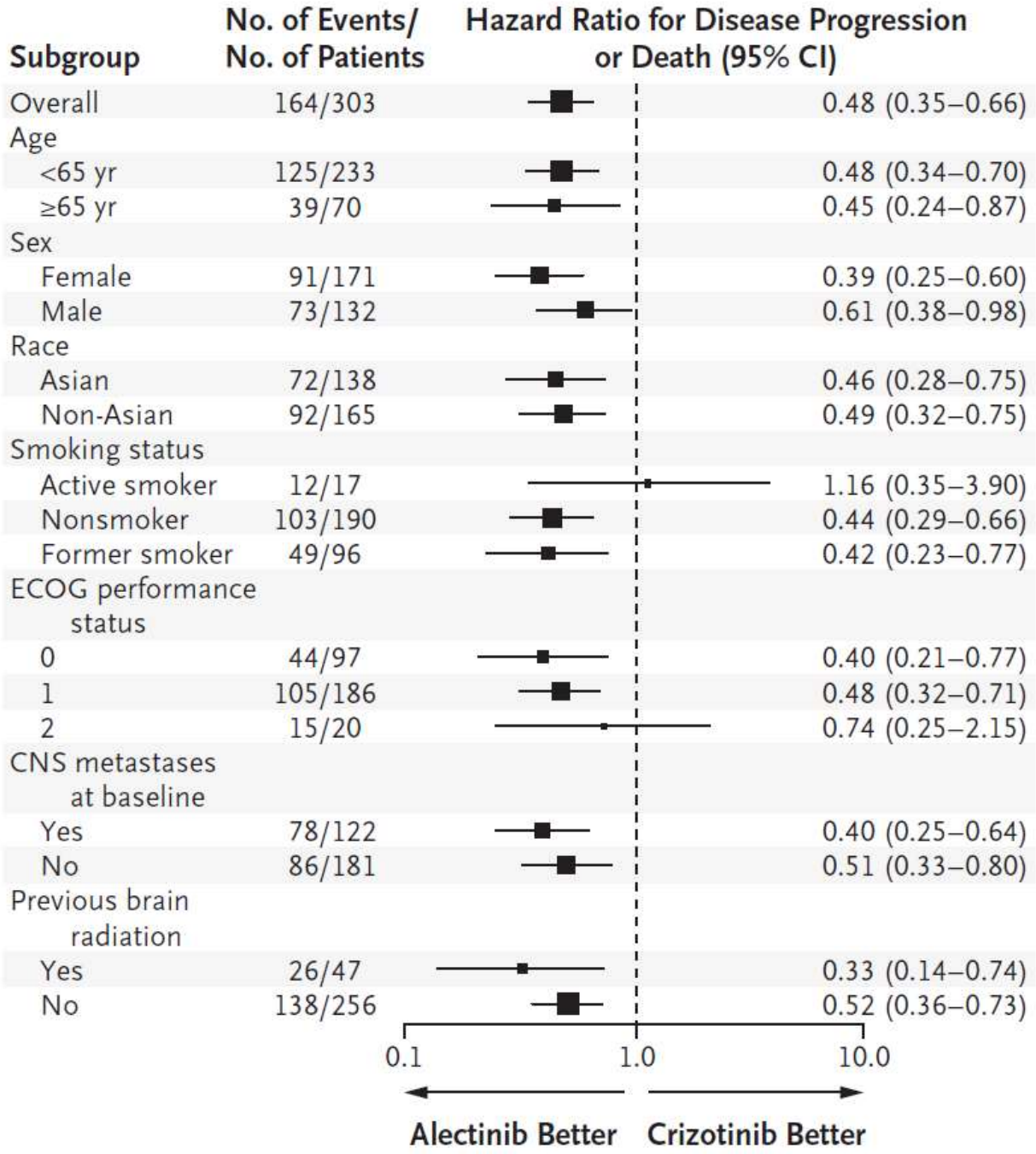
- Randomized, open-label, phase 3 trial
- Randomly assigned 303 patients with previously untreated, advanced ALK-positive NSCLC
  - alectinib (600 mg twice daily)
  - crizotinib (250 mg twice daily)
- Primary end point - investigator-assessed PFS
- Secondary end points
  - IRC-assessed PFS
  - time to CNS progression
  - objective response rate
  - overall survival

N Engl J Med. 2017 Jun 6. doi: 10.1056/NEJMoa1704795.

Results

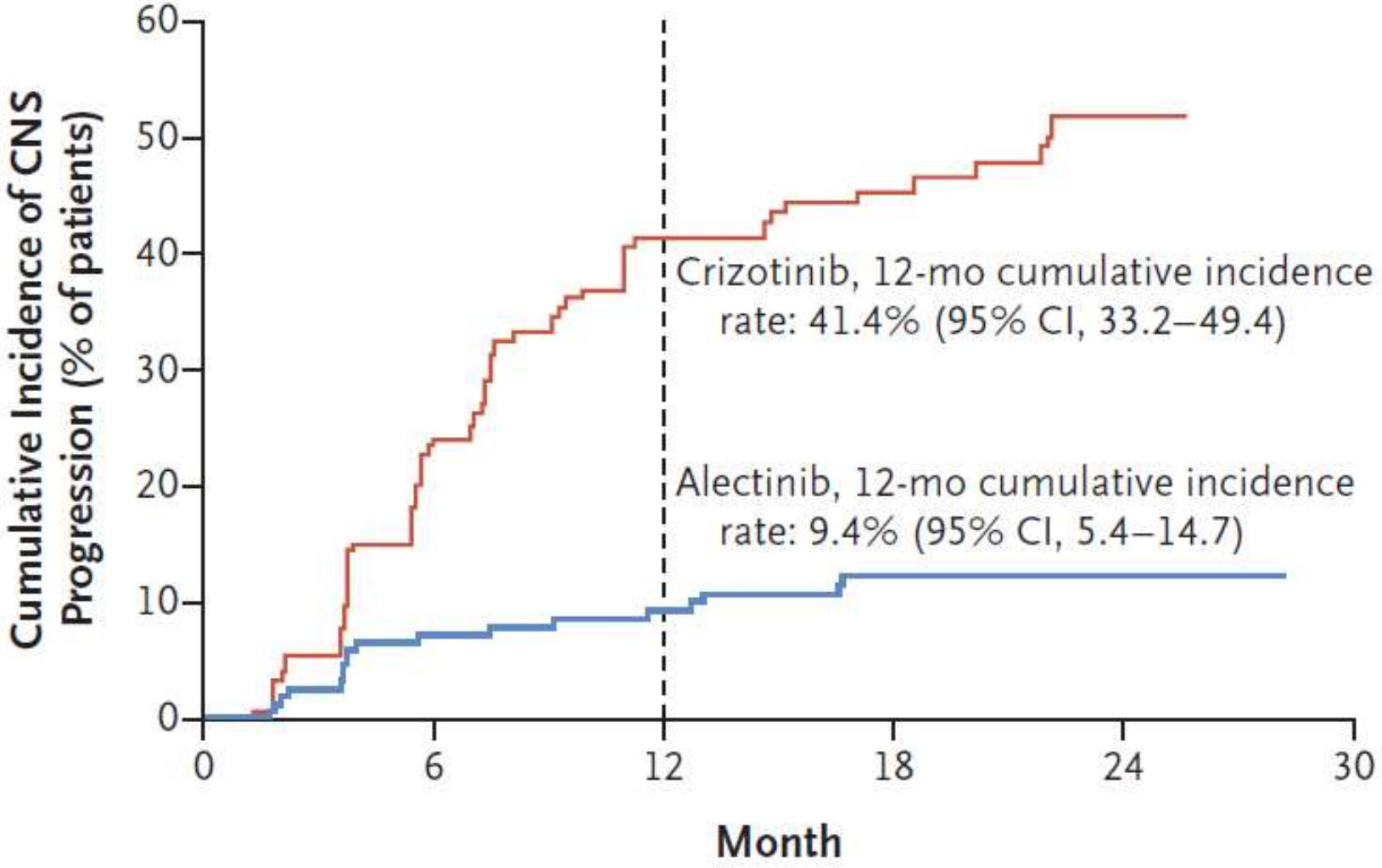
- Median follow-up of 17.6 months (crizotinib) and 18.6 months (alectinib)
- An event of disease progression or death
  - 62 of 152 patients (41%) in the alectinib group
  - 102 of 151 patients (68%) in the crizotinib group
- PFS was significantly higher with alectinib than with crizotinib
  - 12-month event-free survival rate, 68.4% [95% CI, 61.0 to 75.9] with alectinib 48.7% [95% CI, 40.4 to 56.9] with crizotinib
  - HR for disease progression or death, 0.47 [95% CI, 0.34 to 0.65]; P<0.001)
  - Median PFS with alectinib was not reached
- Grade 3 to 5 adverse events were less frequent with alectinib (41% vs. 50% with crizotinib)

N Engl J Med. 2017 Jun 6. doi: 10.1056/NEJMoa1704795.



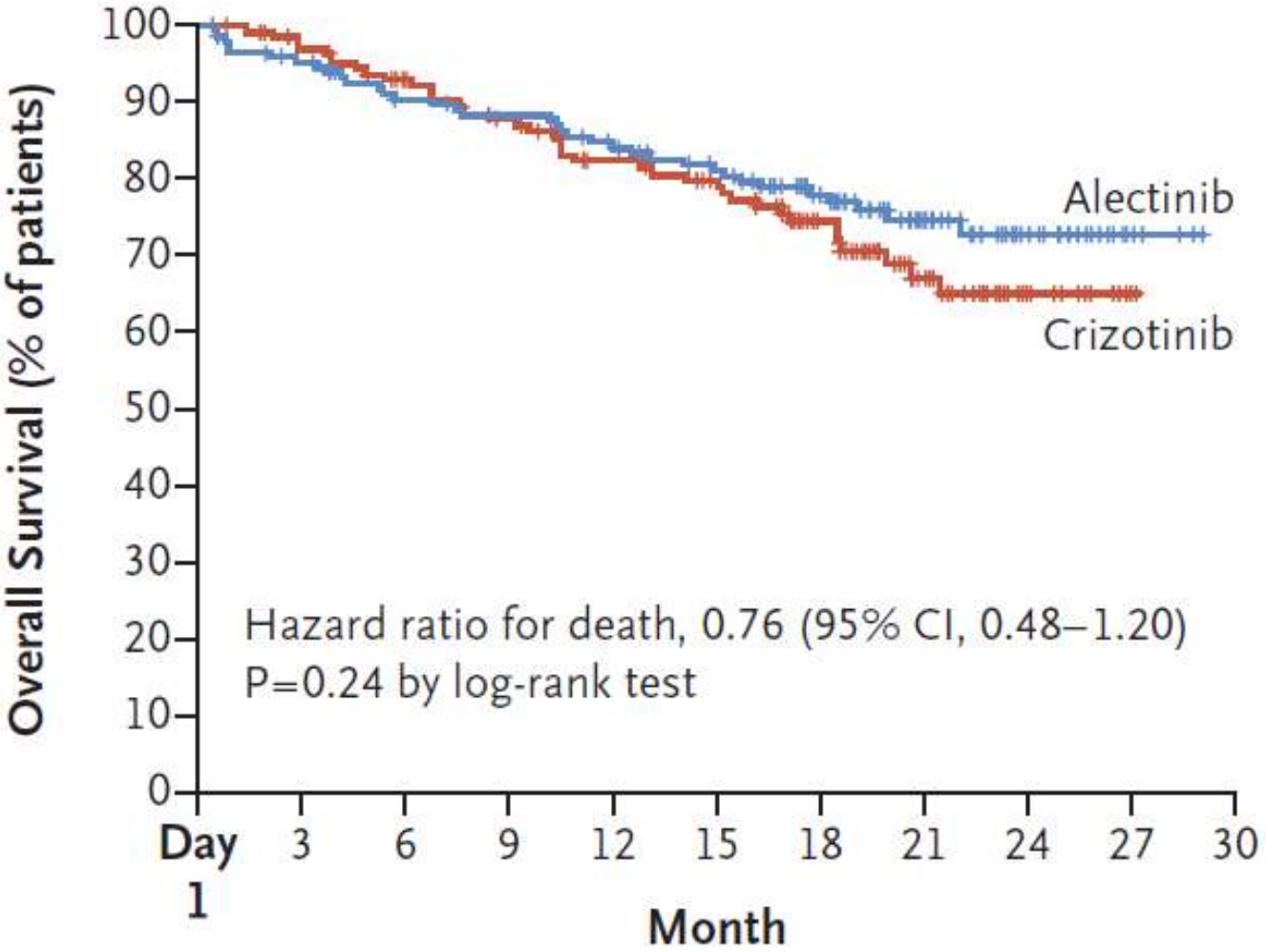
N Engl J Med. 2017 Jun 6. doi: 10.1056/NEJMoa1704795.

CNS Progression



N Engl J Med. 2017 Jun 6. doi: 10.1056/NEJMoa1704795.

Overall Survival



No. at Risk

Alectinib	152	142	131	127	119	107	87	51	24	5
Crizotinib	151	141	127	115	103	95	73	33	13	1

N Engl J Med. 2017 Jun 6. doi: 10.1056/NEJMoa1704795.

Take home message (1st vs 2nd generation ALK TKIs)

- For those with newly diagnosed ALK-positive NSCLC, alectinib is recommended as first-line treatment
- Improved efficacy (both systemic and intracranial) as well as a more favorable side effect profile compared with crizotinib
- Second generation agents are preferred in CNS mets
- Second generation agents have superior tolerance
- Cost factor and availability in developing nations