Treatment of EGFR Mutant Patients

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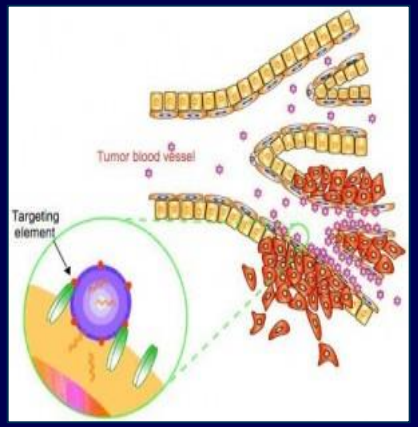
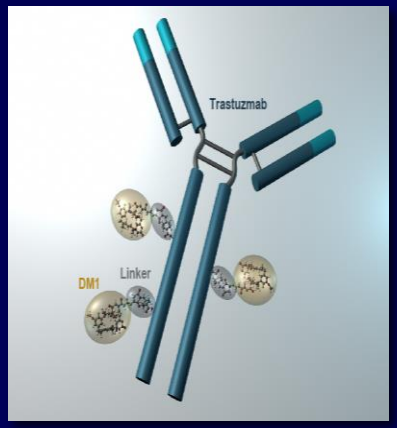
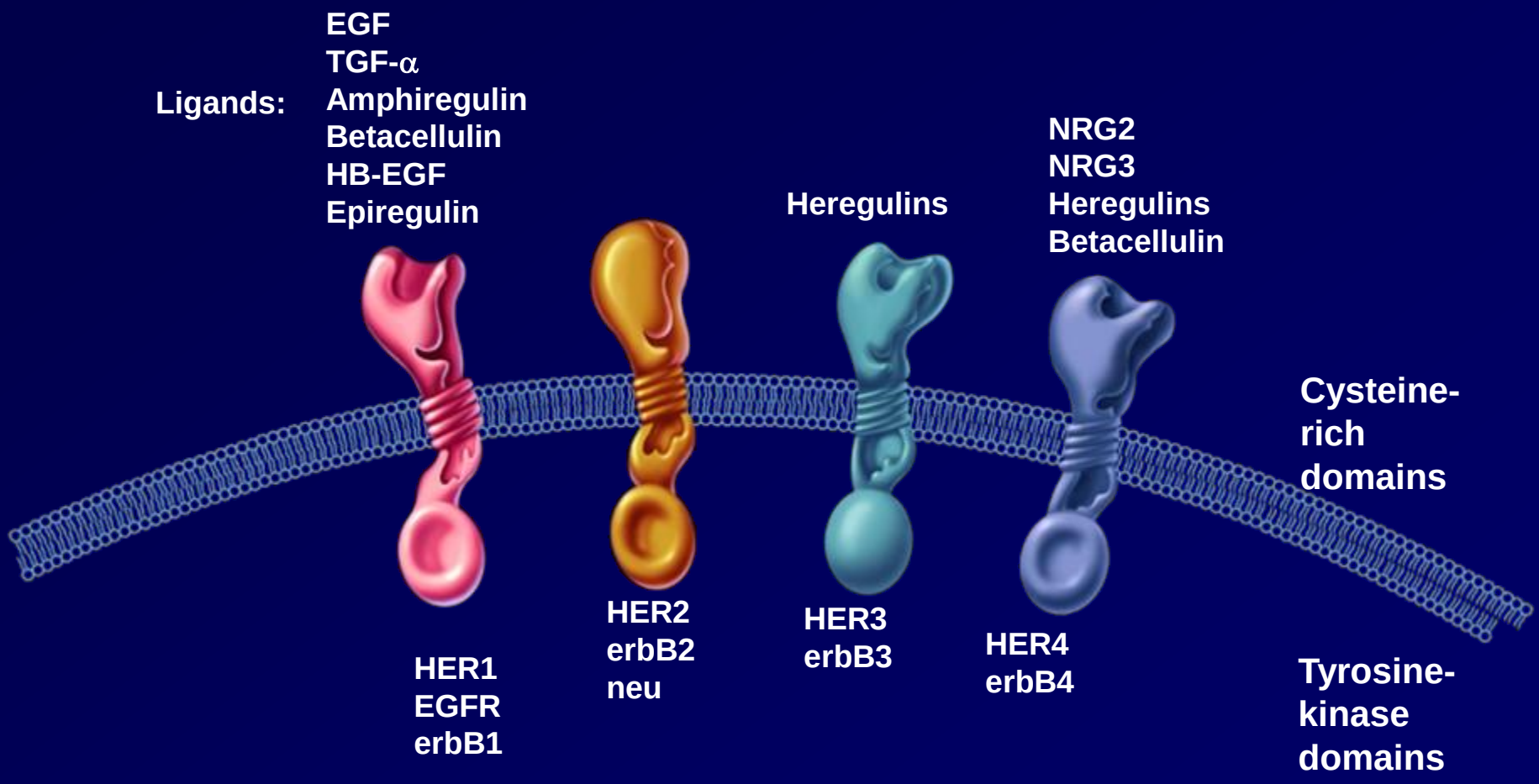
Disclosures

Honoraria for advisory board work, speaker bureau activites and/or travel grants from Pfizer, Roche, AZD, Boehringer, BMS, MSD, Lilly Oncology and Novartis

How Does This Enable Personalized Medicine?

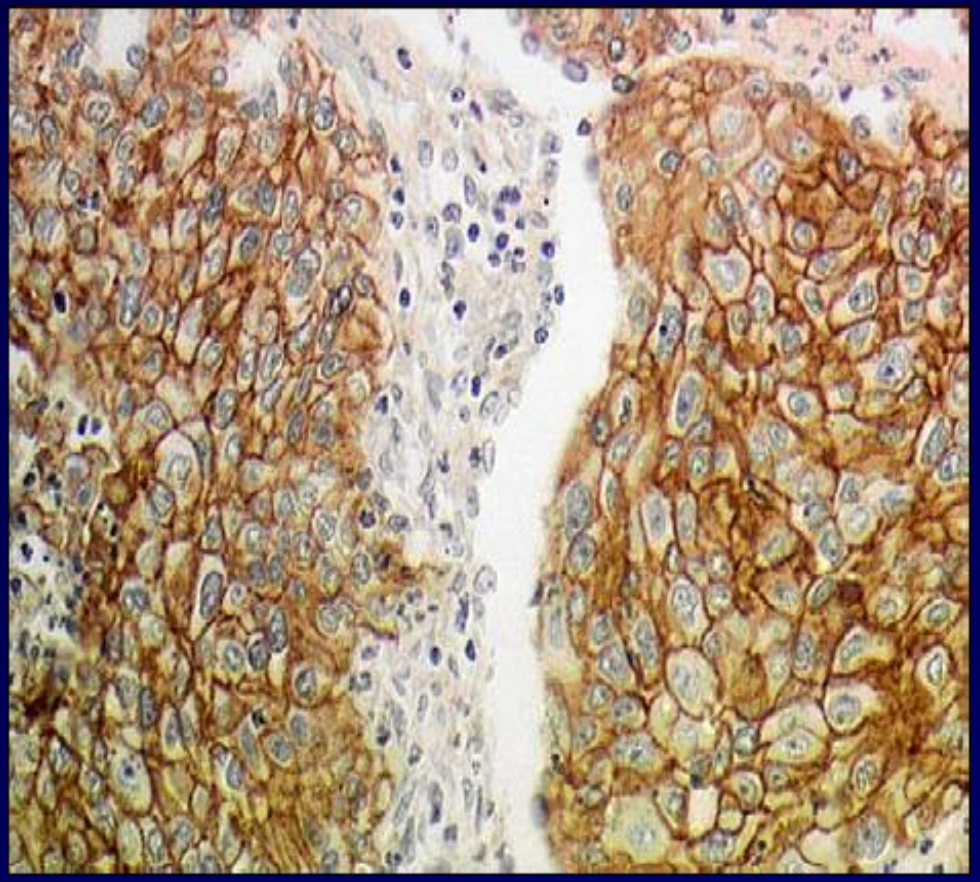
Right Target	Right Drug (or Combinations)	Right Patient
		
Genetic validation; Rare phenotypes	*Selective design and delivery; Combinations for complex diseases*	*Phenotyping and genotyping*

The HER family of receptors



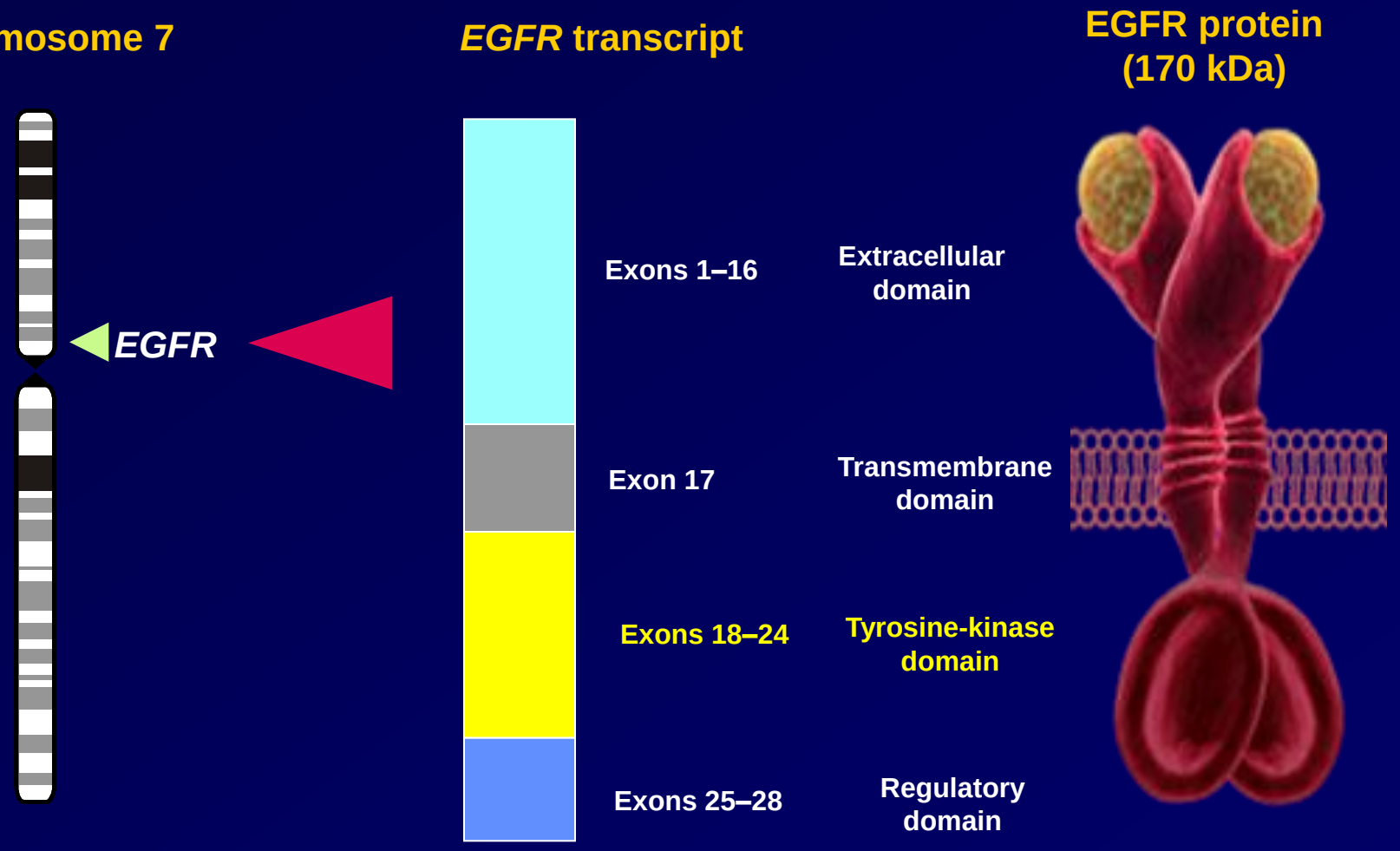
Salomon, et al. Crit Rev Oncol Hematol 1995
Woodburn. J Pharmacol Ther 1999

EGFR Protein Expression
Immunohistochemistry

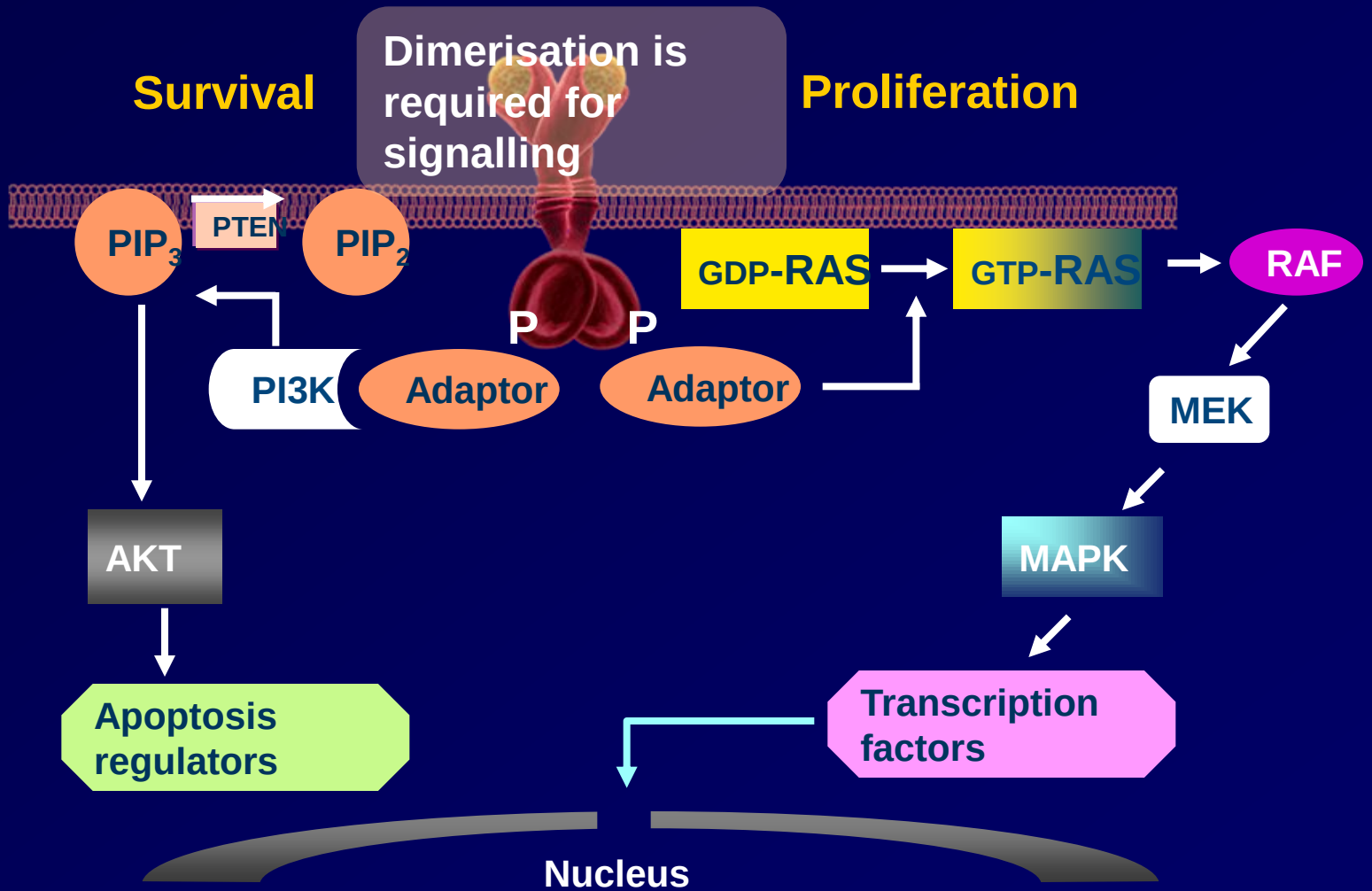


Representative example of a case of squamous cell carcinoma with high **EGFR expression (3+)** (original magnification 400x); Cut-off value of ≥10% positive cell (2+, 3+).

EGFR: molecular biology

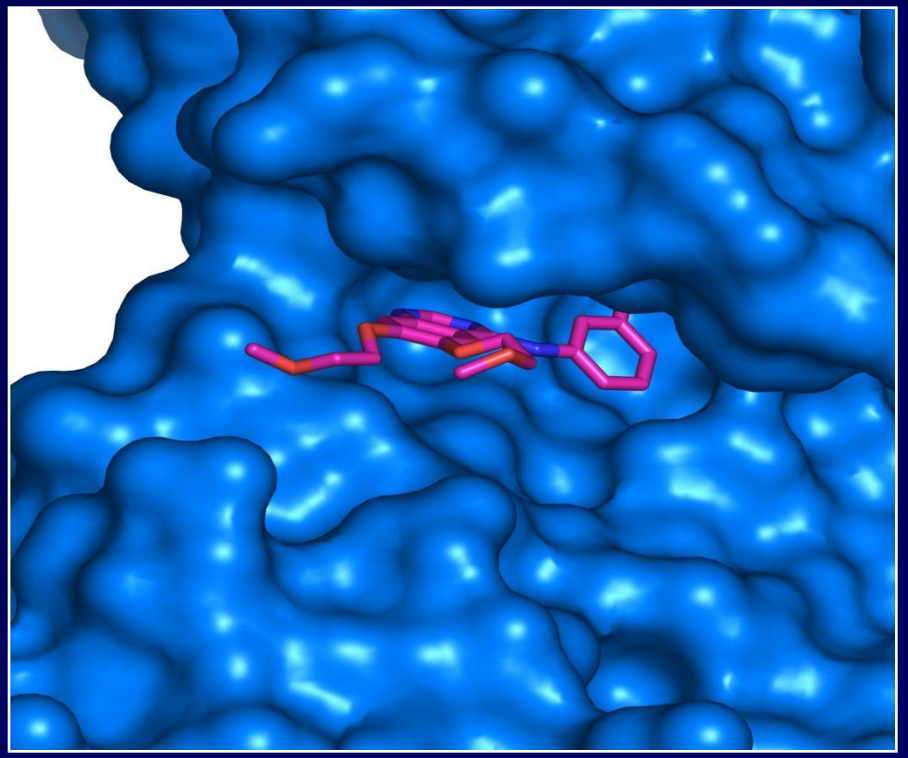


EGFR signalling pathways



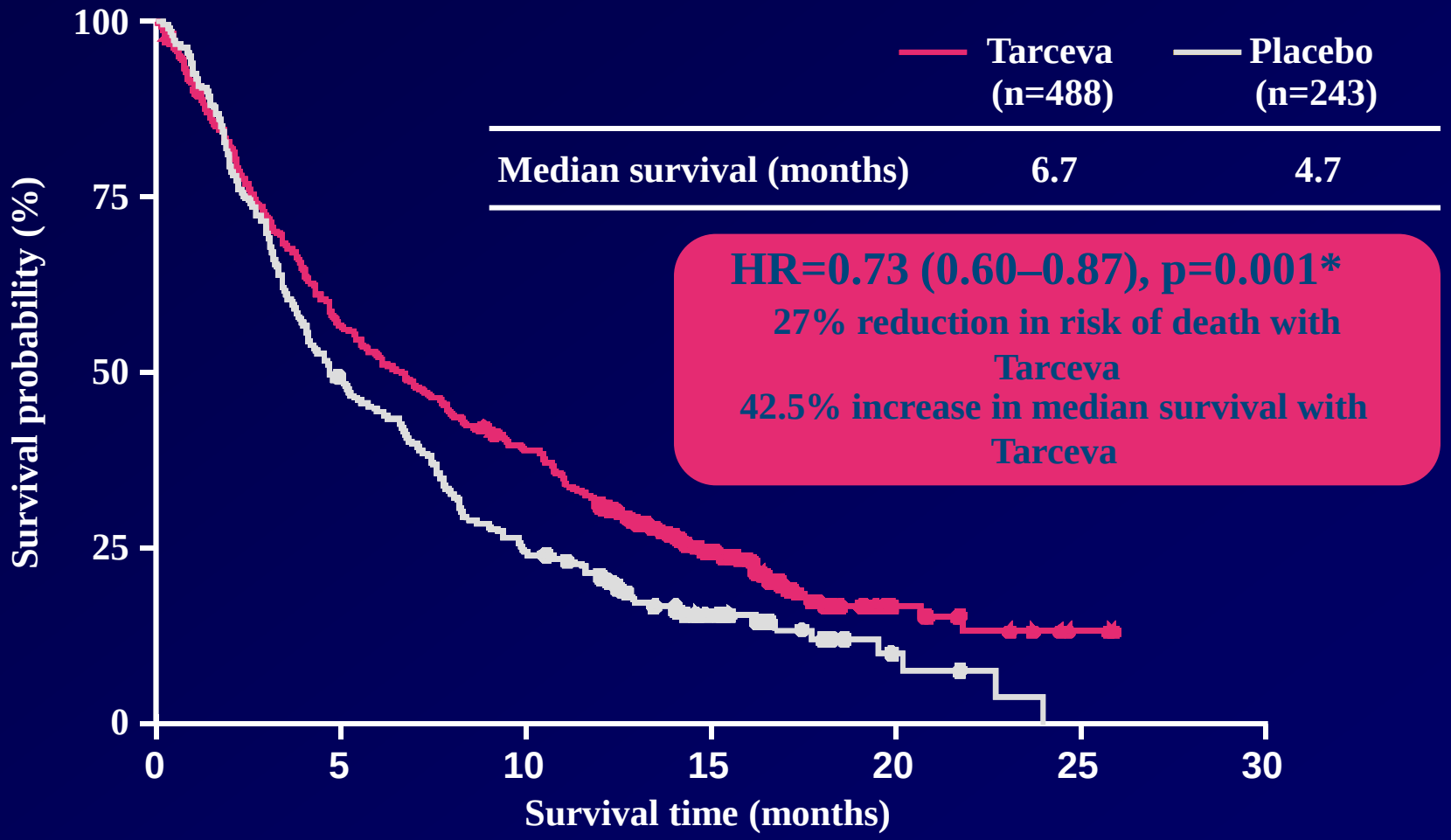
EGFR Tyrosine Kinase Inhibitors (TKI)

- Mutated EGFR has increased binding for ATP, thus higher affinity (5–10 fold) to gefitinib or erlotinib than wild-type
- Functional inhibition of EGFR signal-dependent cancer cell induces dramatic tumour response



Eck *et al. Biochim. Biophys. Acta* 2010;1804:559–66

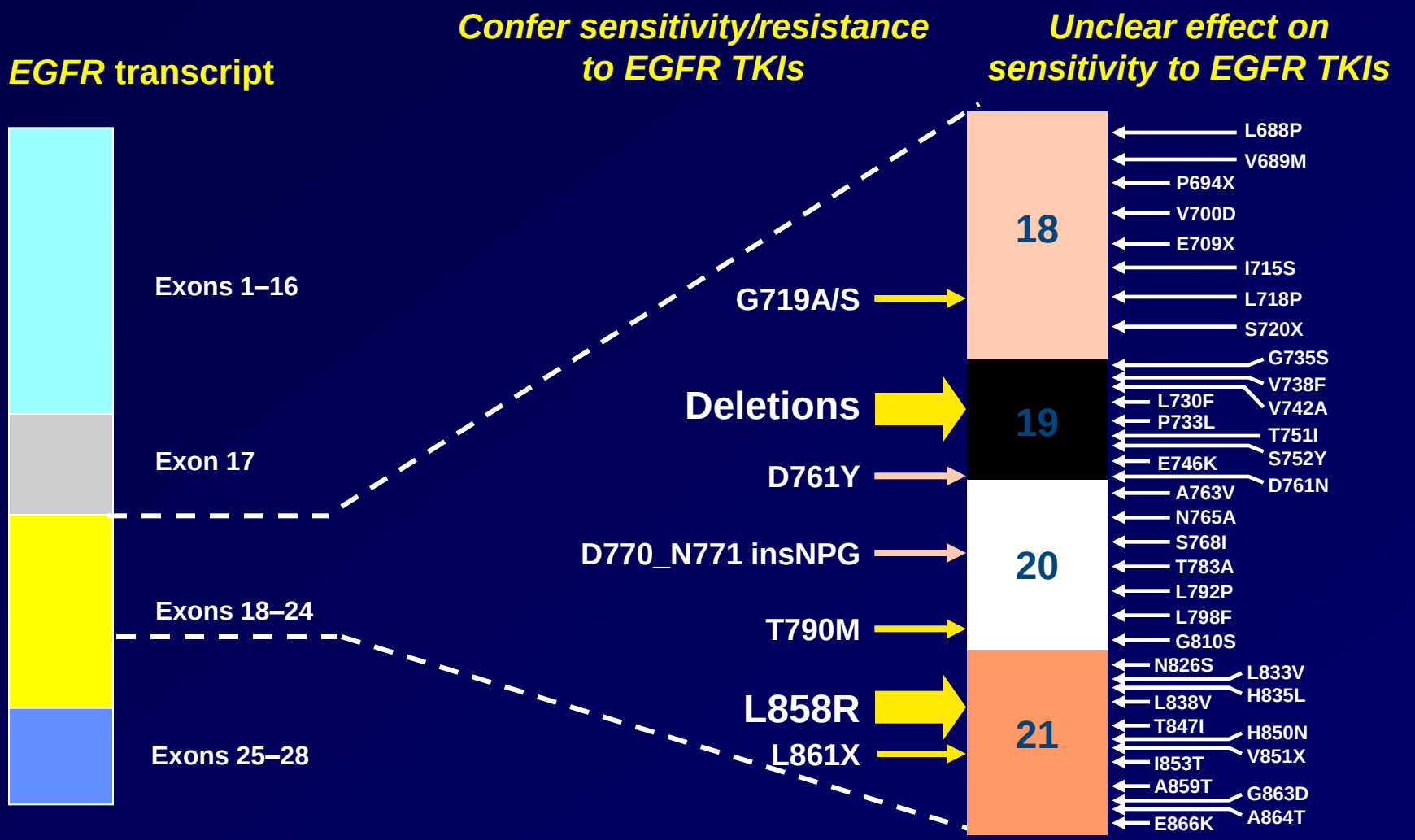
BR.21 demonstrated significant improvement in OS versus placebo



*HR and p (log-rank test) adjusted for stratification factors at randomisation and EGFR status

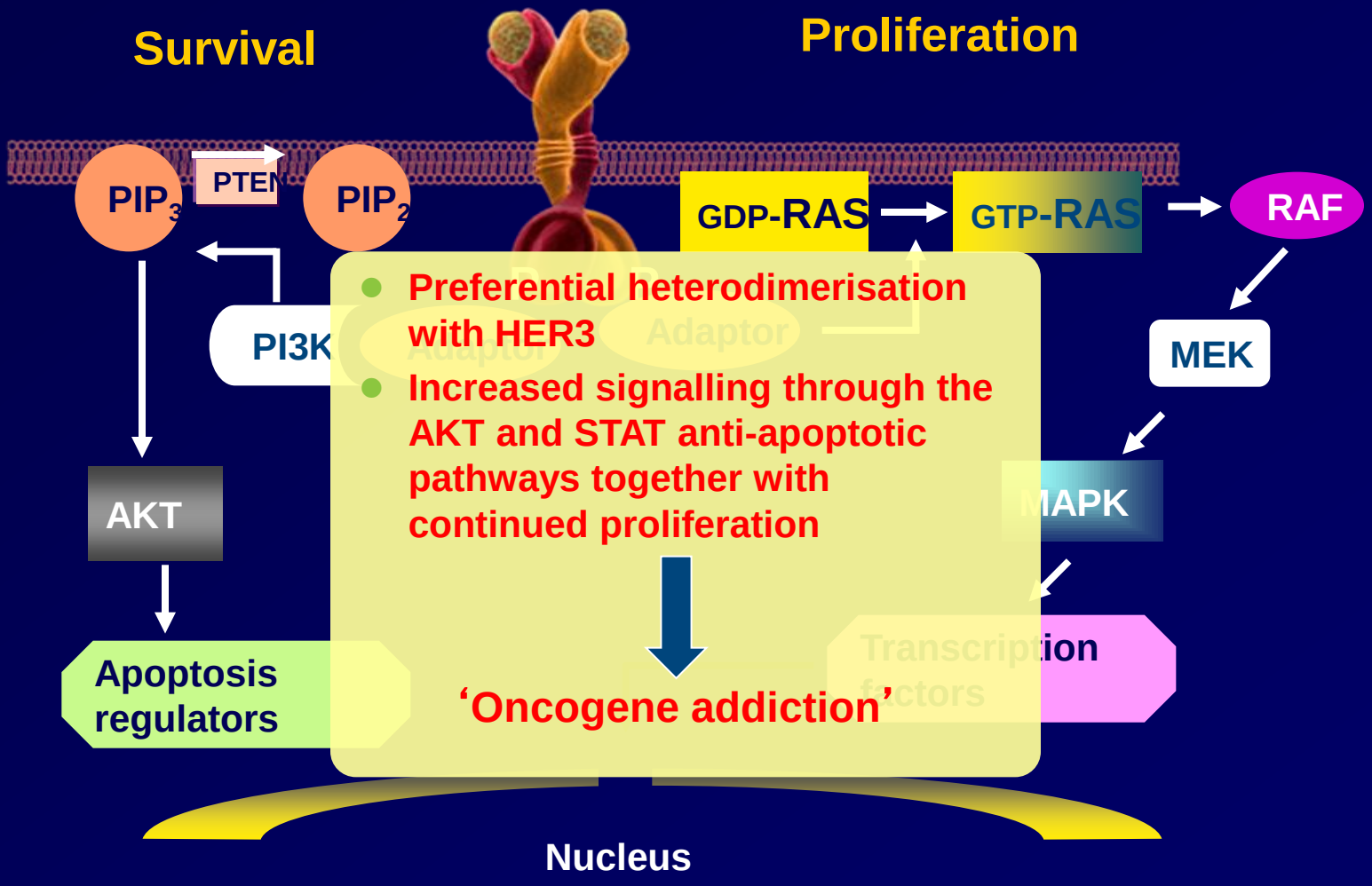
Shepherd, et al. NEJM 2005
Tarceva Summary of Product Characteristics

Mutations identified in *EGFR* gene



Riely, et al. Clin Cancer Res 2006

EGFR mutation-positive disease: a biologically distinct subtype of NSCLC



Sordella, et al. Science 2004

IPASS: patient selection based on clinical criteria

Chemotherapy-naïve Stage IIIb/IV NCSLC (adenocarcinoma)
Never smokers or ex-light smokers*

(N = 1217)

1:1 randomization

Gefitinib 250 mg/day
(n = 609)

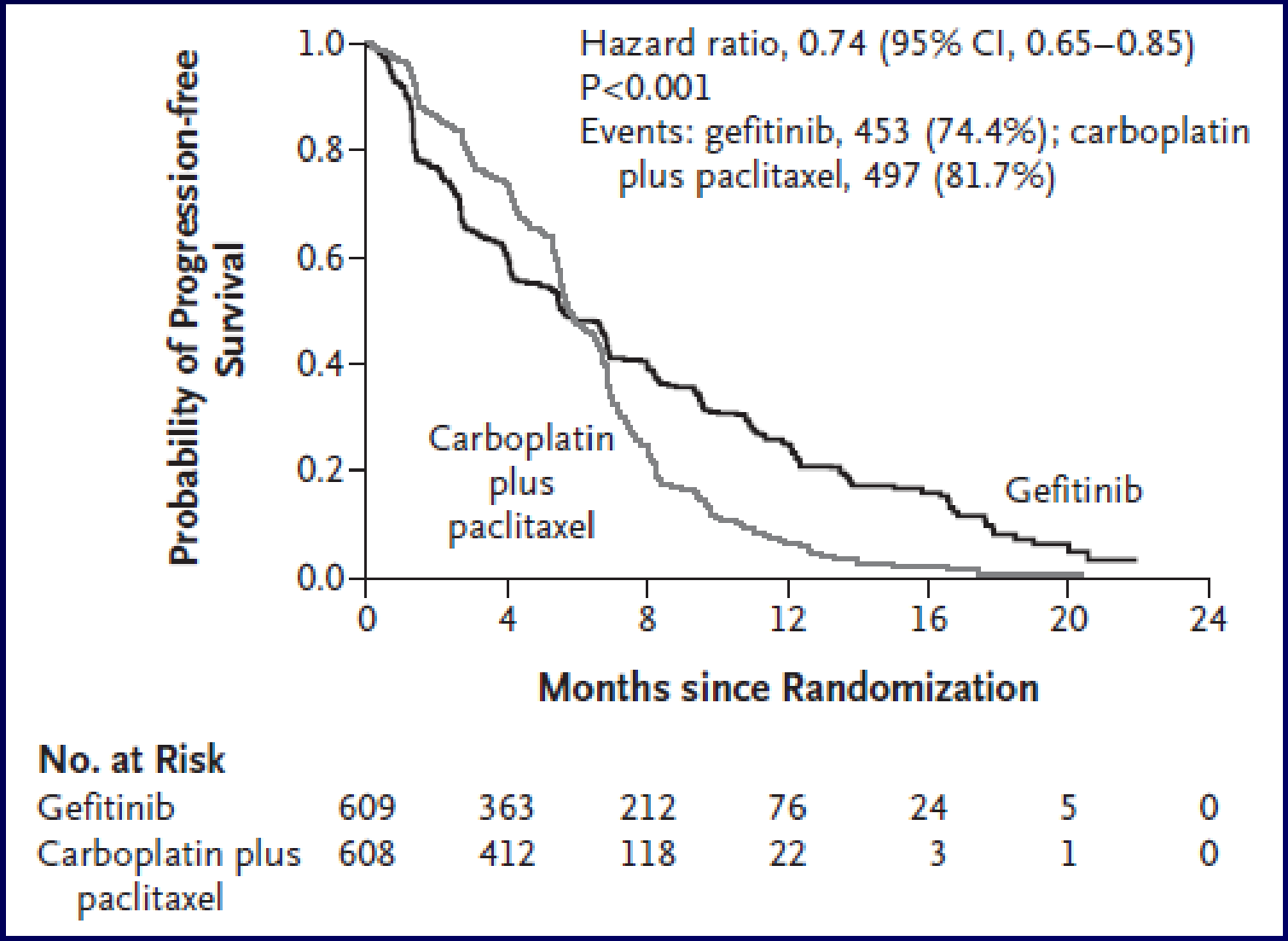
Carboplatin AUC 5 or 6 plus
Paclitaxel 200 mg/m^2
Every 3 weeks†
(n = 608)

- Primary endpoint: PFS
- Secondary endpoints: OS, ORR, QoL, disease-related symptoms, safety, tolerability
- Biomarker analysis: EGFR mutation, expression, and gene copy number

*patients had smoked < 100 cigarettes in their lifetime
†≤ 6 cycles.

Mok T et al. *New Engl J Med* 2009; 361:947–957

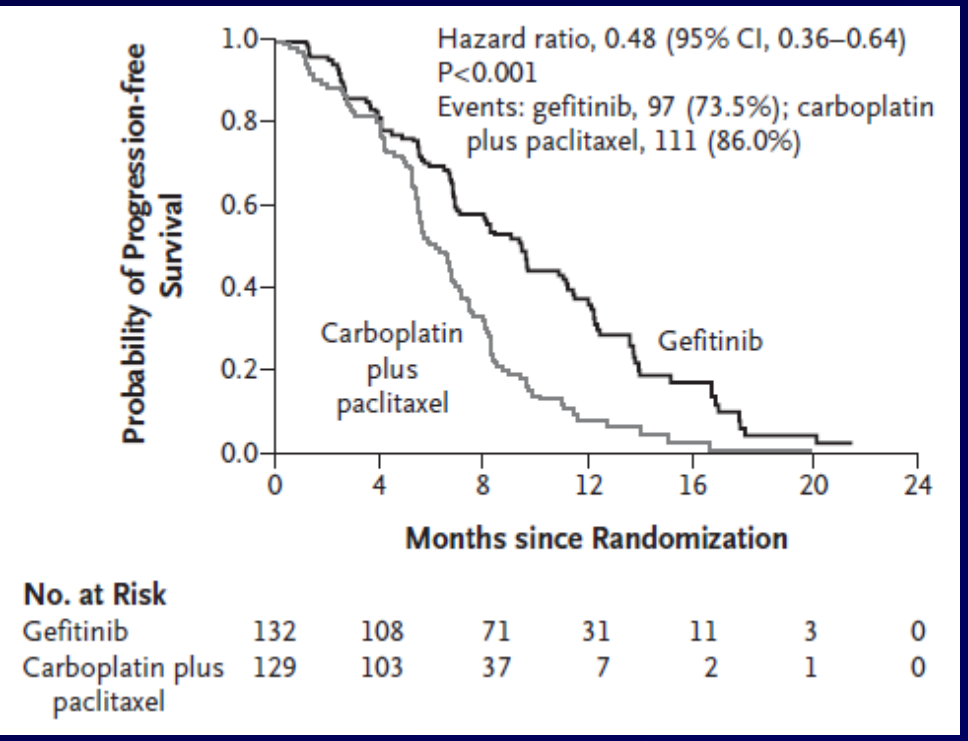
IPASS: gefitinib significantly improved PFS vs. carboplatin/paclitaxel



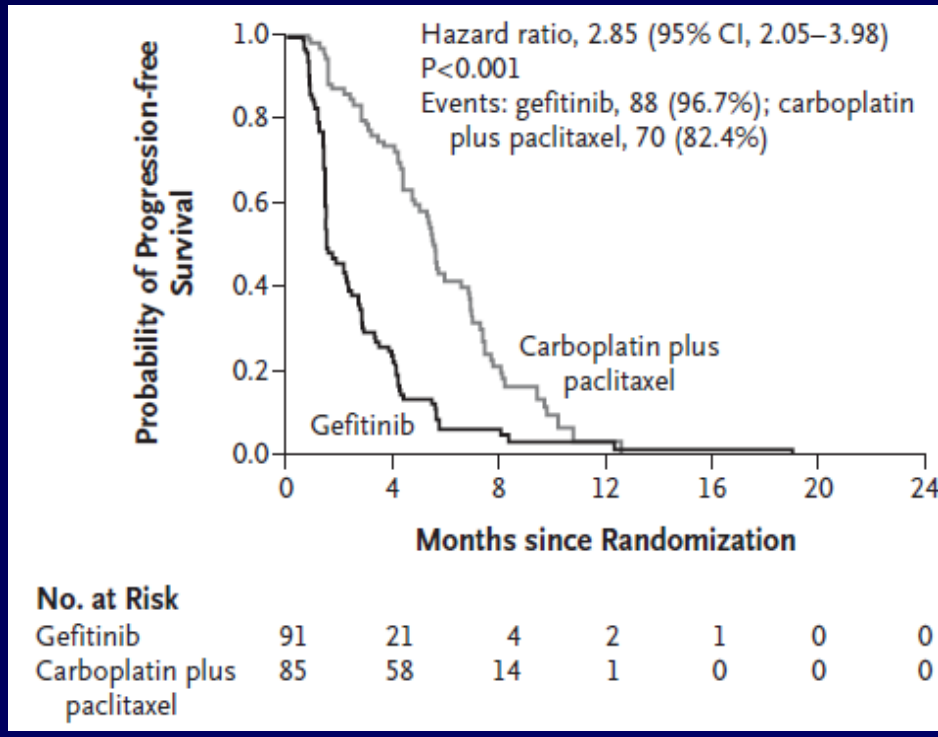
Mok T et al. *New Engl J Med* 2009; 361:947–957

IPASS: gefitinib benefit dependent on EGFR mutation status

EGFR mutation positive



EGFR mutation negative



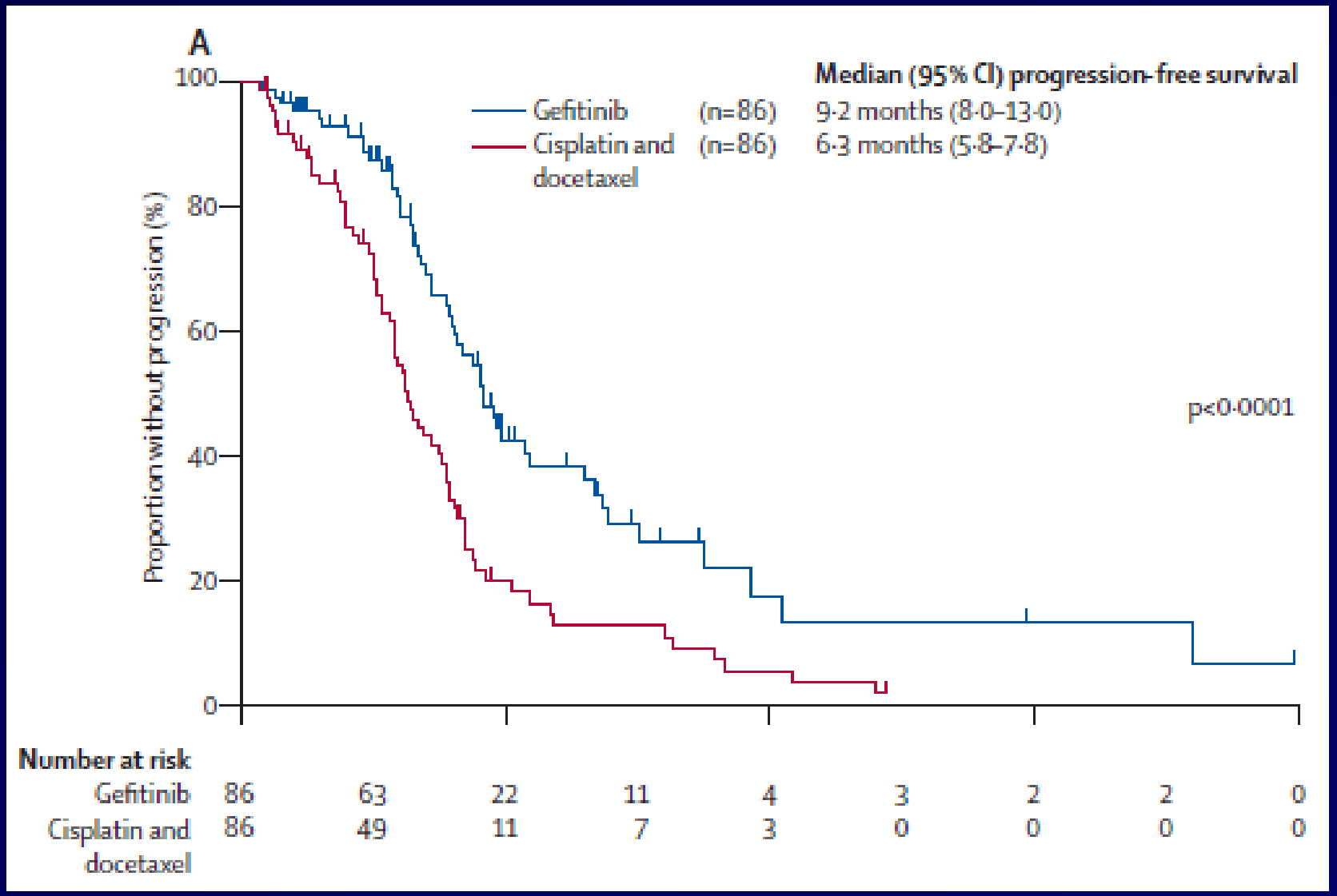
Mok T et al. *New Engl J Med* 2009; 361:947–957

Study of first-line gefitinib vs. chemotherapy in patients prospectively selected for EGFR mutations

- Primary endpoint in this study was to assess efficacy of gefitinib treatment in molecularly selected patients, not in demographically/clinically selected patients as in IPASS
- Inclusion criteria: patients screening positive for EGFR mutations L858R (Cycleave method and direct sequencing) or exon 19 deletion (fragment analysis)
- Patients randomized to receive first-line gefitinib or cisplatin/docetaxel

Mitsudomi T et al. *Lancet Oncol* 2010; 11:121–128

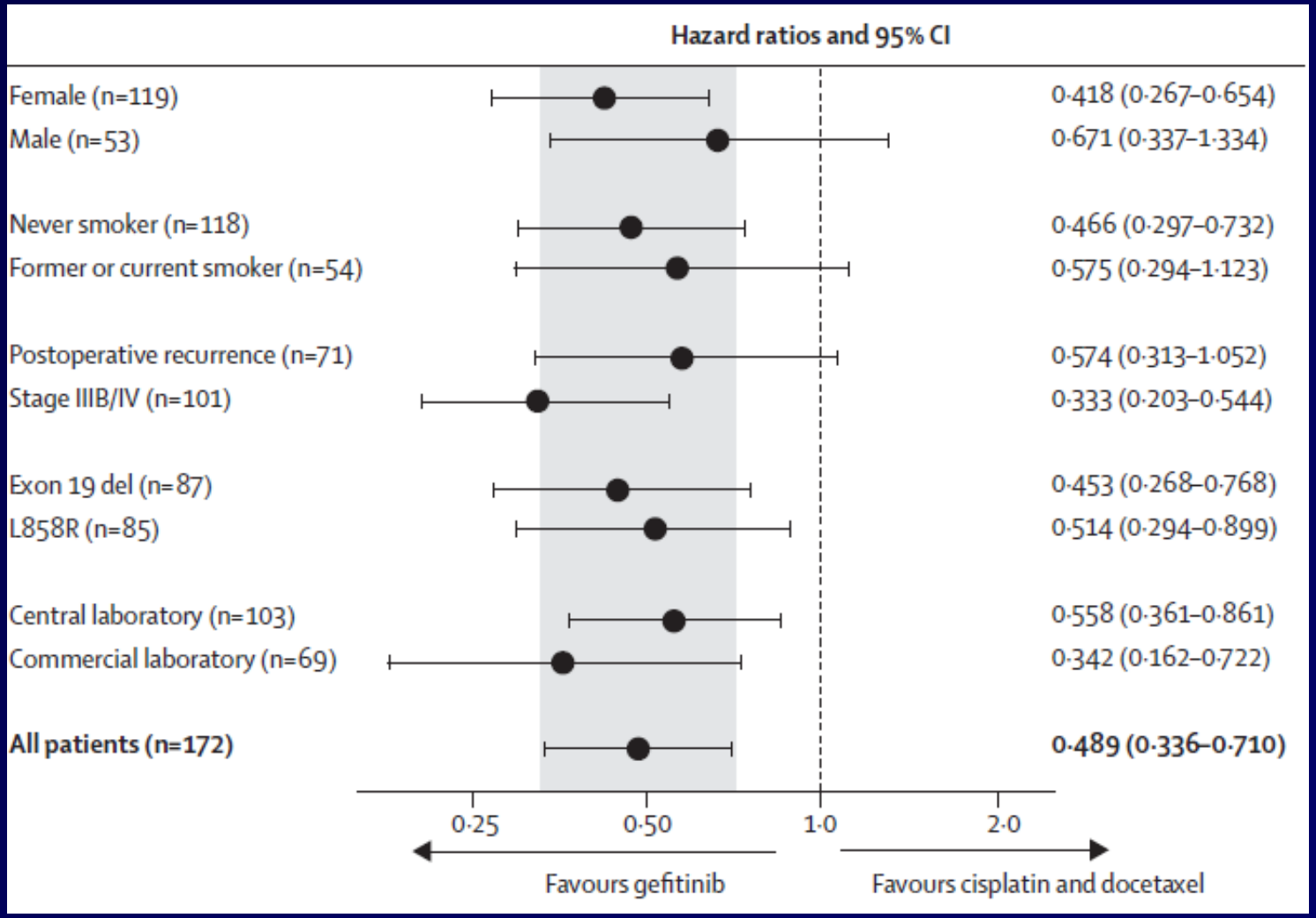
Gefitinib prolongs PFS vs. chemotherapy in patients selected for EGFR mutations



Mitsudomi T et al. *Lancet Oncol* 2010; 11:121–128

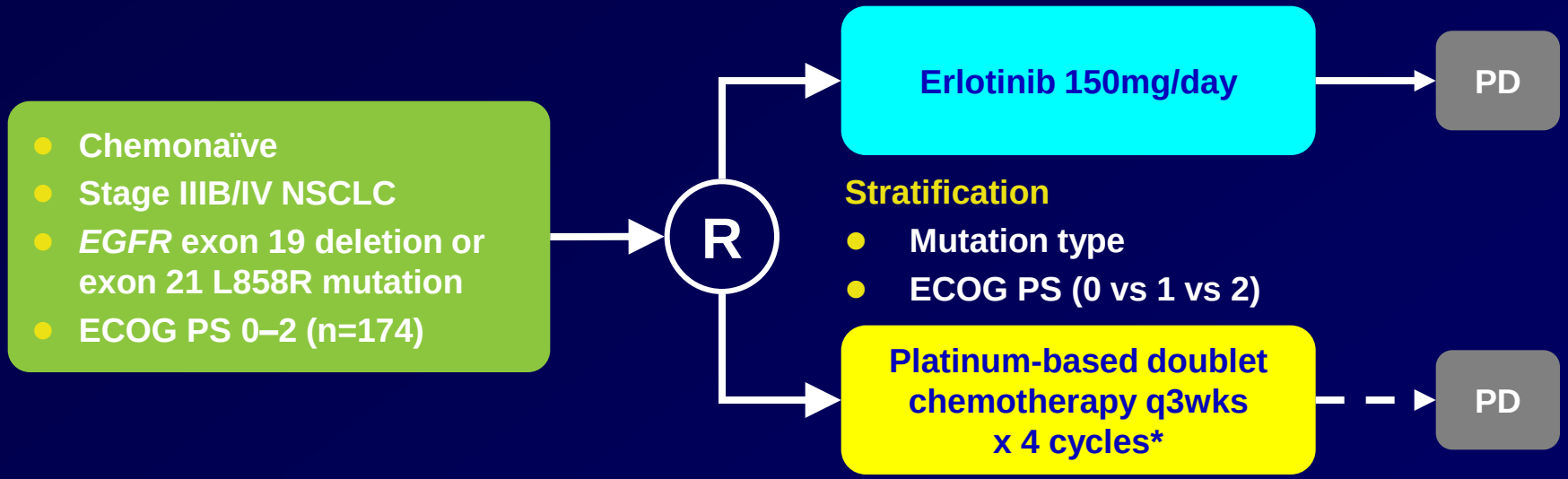
Gefitinib: prolonged PFS in all clinical subgroups

Hazard ratios for PFS by subgroup (overall population)



Mitsudomi T et al. *Lancet Oncol* 2010; 11:121–128

EURTAC study design



Primary endpoint

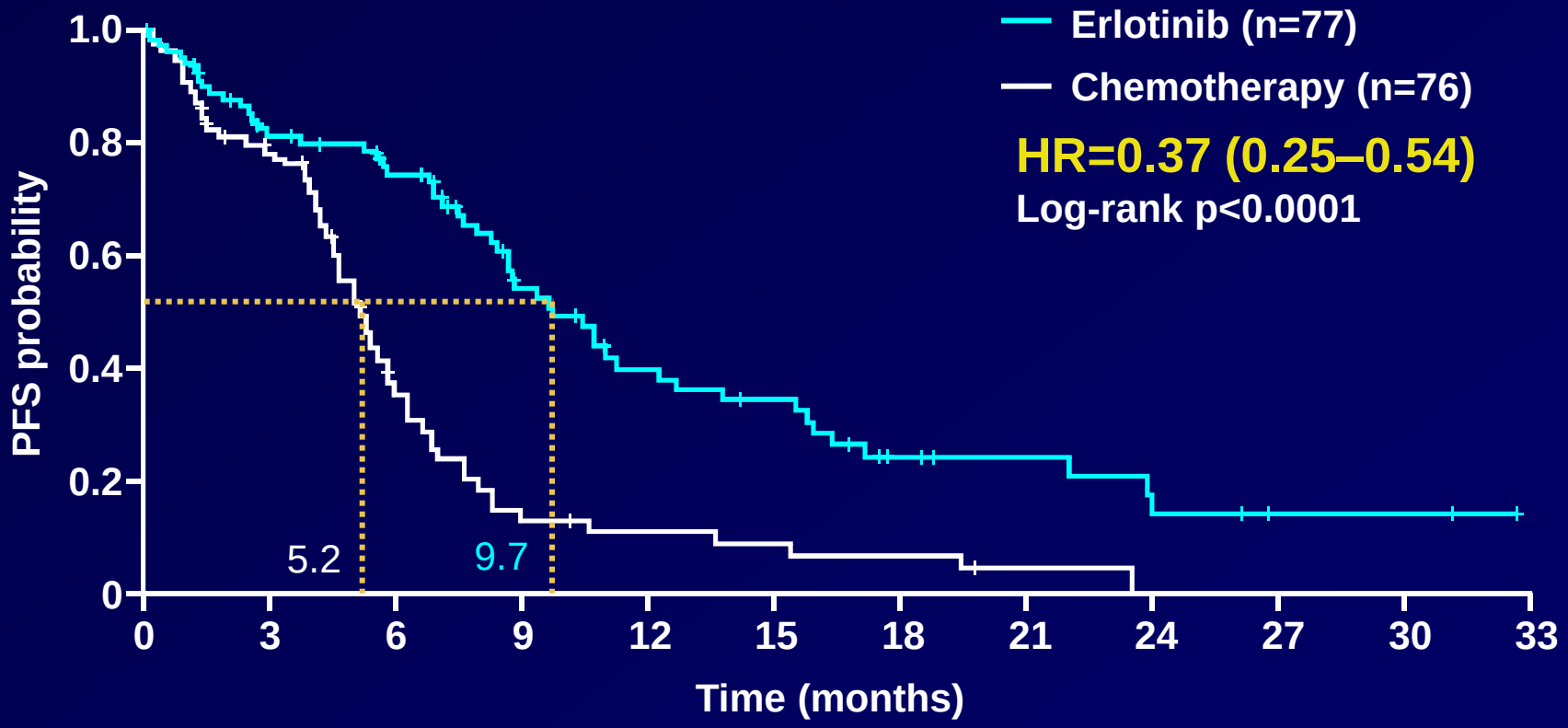
- Progression-free survival (PFS)
  - interim analysis planned at 88 events

Secondary endpoints

- Objective response rate
- Overall survival (OS)
- Location of progression
- Safety
- EGFR mutation analysis in serum
- Quality of life

ECOG = Eastern Cooperative Oncology Group; PS = performance status; PD = progressive disease
*Cisplatin 75mg/m^2 d1 / docetaxel 75mg/m^2 d1; cisplatin 75mg/m^2 d1 / gemcitabine 1250mg/m^2 d1,8; carboplatin AUC6 d1 / docetaxel 75mg/m^2 d1; carboplatin AUC5 d1 / gemcitabine 1000mg/m^2 d1,8

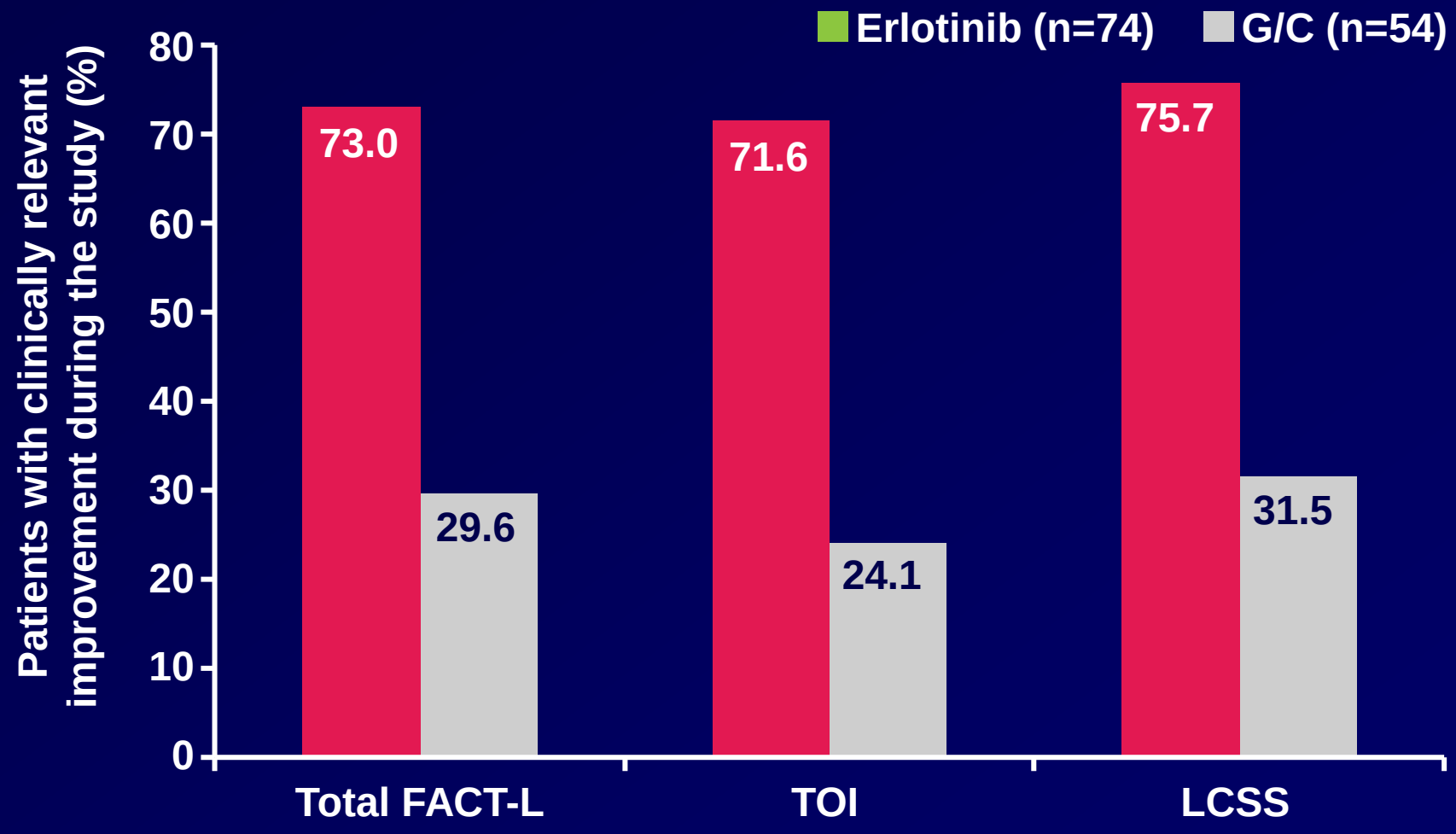
PFS in ITT population



Patients at risk												
Erlotinib	86	63	54	32	21	17	9	7	4	2	2	0
Chemo	87	49	20	8	5	4	3	1	0	0	0	0

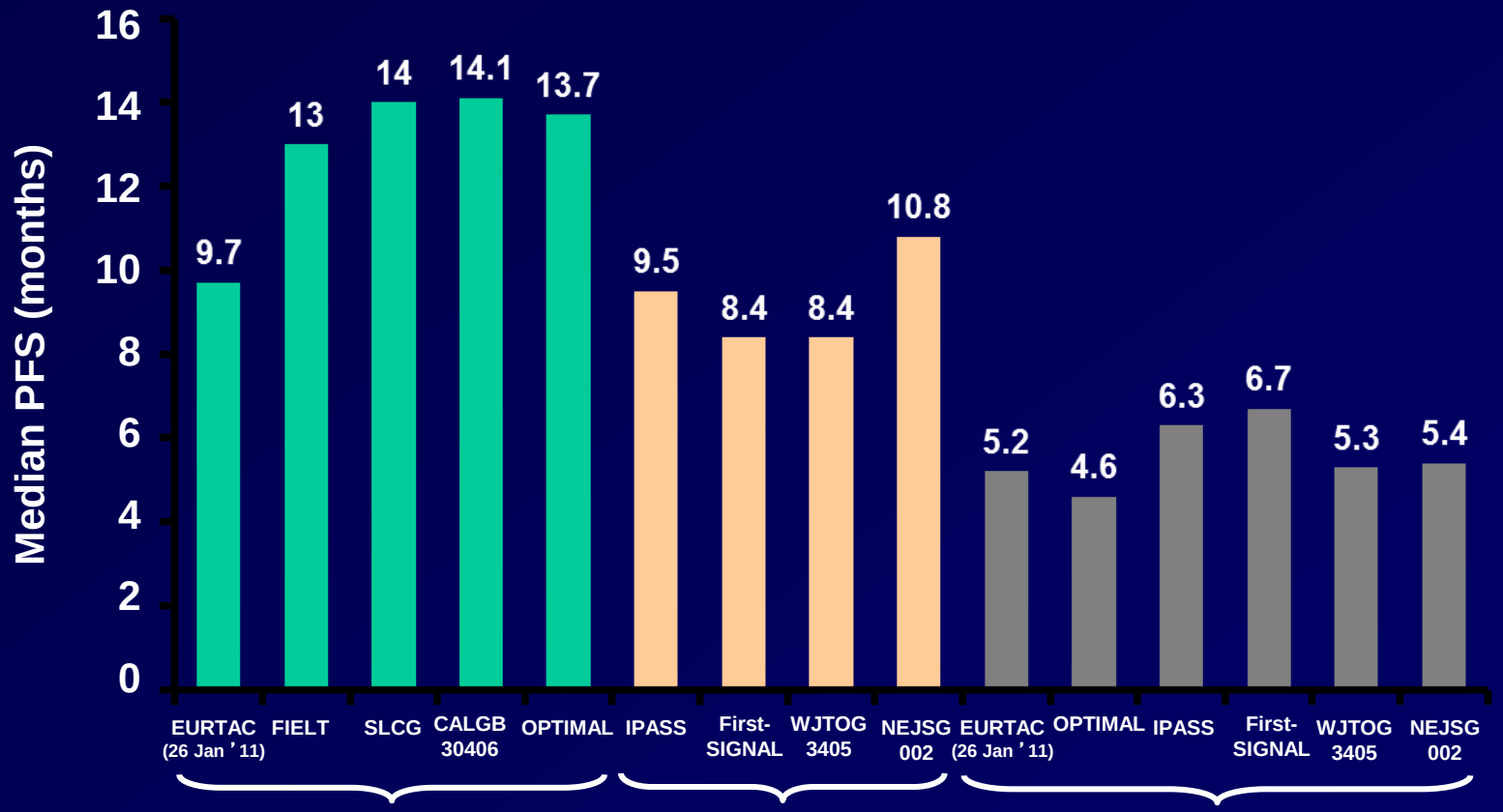
Data cut-off: 26 Jan 2011

Clinically relevant improvements in QoL



Includes all patients with a baseline and ≥1 post-baseline QoL assessment

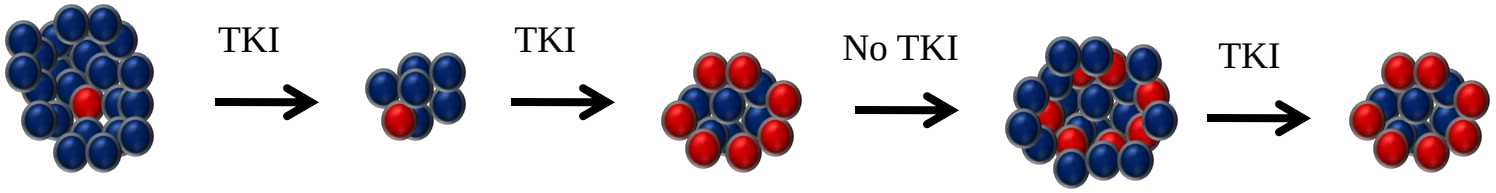
Tarceva is the only EGFR TKI to extend PFS beyond 1 year in *EGFR* Mut+



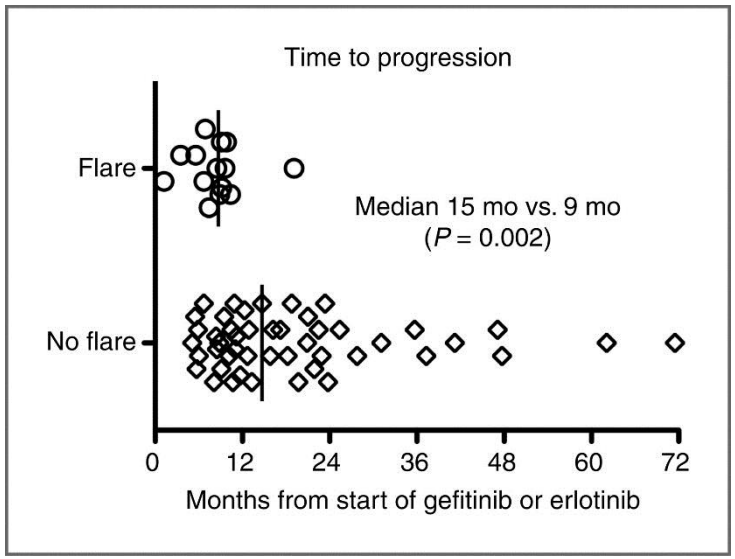
WJTOG3405: stage IIIB/IV pts (median PFS in overall population = 9.2 vs 6.3 mos)

Rosell et al. ASCO 2011; De Greve et al. ASCO 2011; Rosell, et al. NEJM 2009; Janne, et al. WCLC 2011; Zhou, et al. ASCO 2011; Mok, et al. NEJM 2009; Lee, et al. WCLC 2010; Mitsudomi, et al. Lancet Oncol 2010; Maemondo, et al. NEJM 2010

Response and Resistance to Kinase Inhibitors in Oncogene Addicted Lung Cancer



Drug Sensitive tumor | Clinical Response | Acquired Resistance | Re-growth or "flare" | Re-response



Severe flare – 14/61 (23%)
Median time to flare: 8 days (3 – 21)

Implications for Trial Design

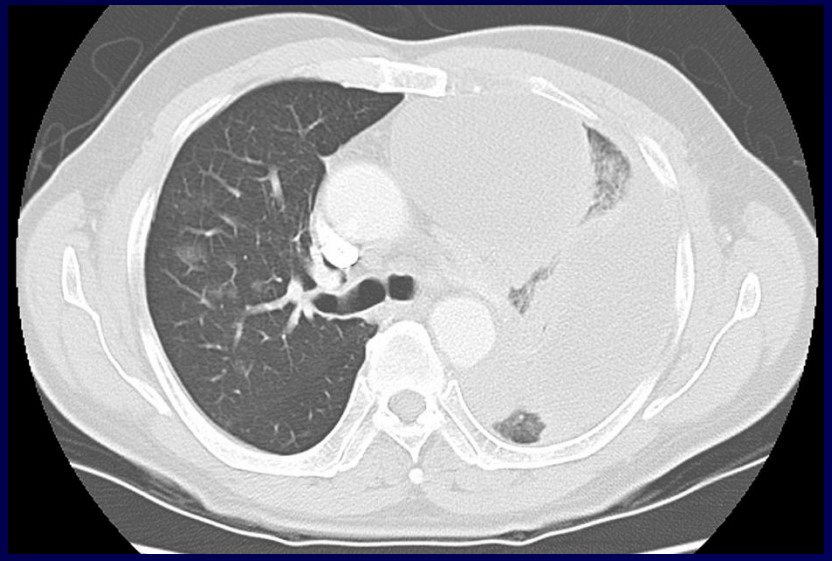
-Continuation of TKI beyond progression
- Add new agent to TKI

-Short washout for new agent
- e.g erlotinib 3 days
- depends on drug $T_{1/2}$

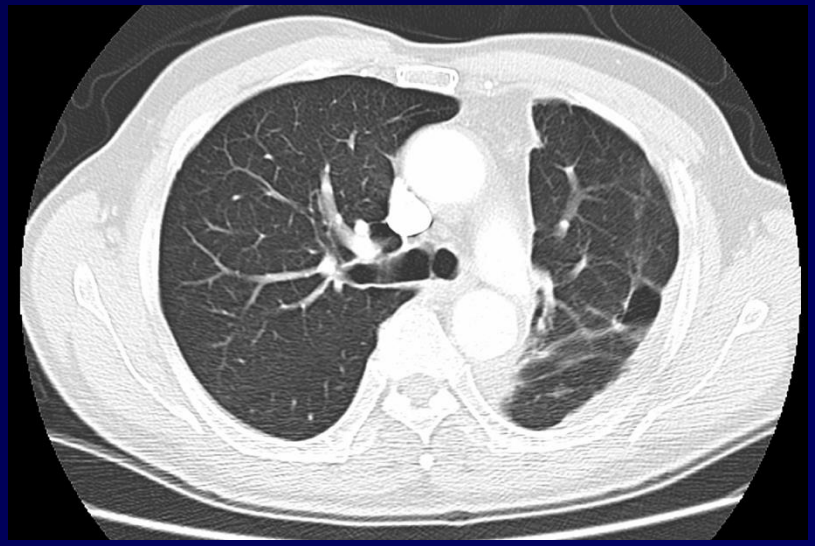
Chaft J E et al. Clin Cancer Res 2011;17:6298-6303

Acquired resistance to EGFR TKIs

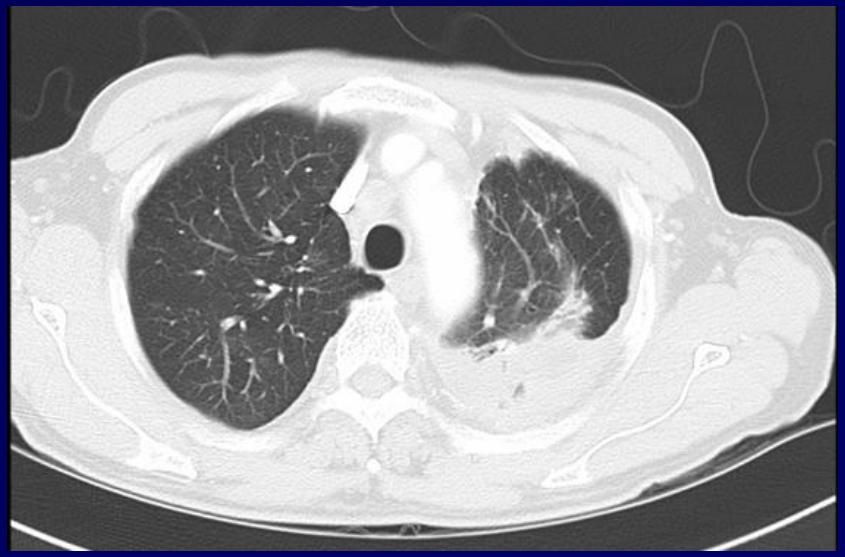
Pre-Erlotinib



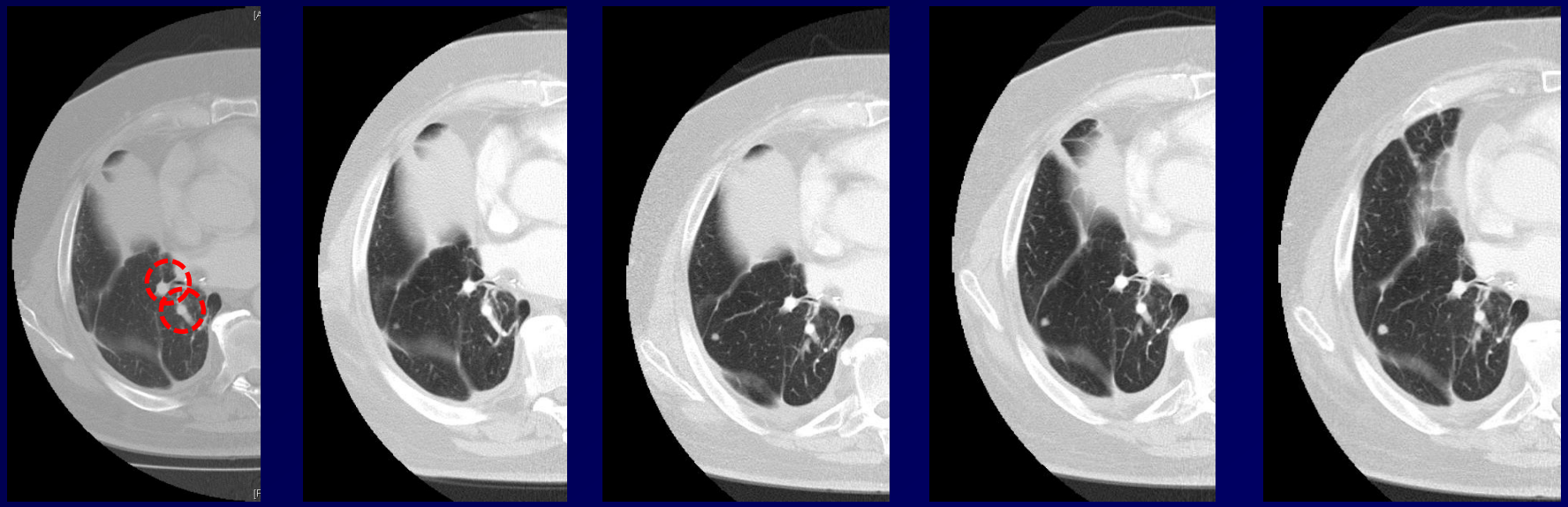
After 6 months Erlotinib



Progression after 18 months Erlotinib



Continued therapy with erlotinib beyond RECIST progression

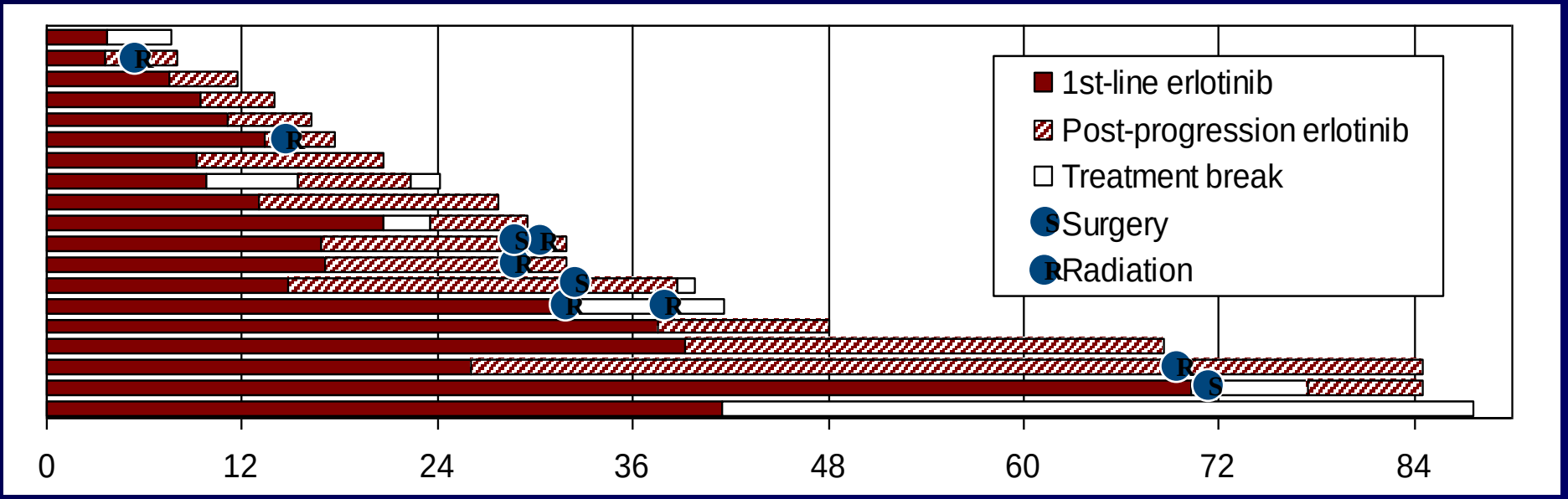


Dec 2009 Feb 2010 Apr 2010 Jun 2010 Aug 2010

RECIST Progression

Post-Progression Erlotinib

- Oxnard et al studied 42 pts with EGFR-mutant lung cancer receiving 1st-line erlotinib on 3 clinical trials
- 19 patients (45%) could delay alternate systemic therapy for >3 months after RECIST progression using erlotinib, local therapies, and observation
- 9 patients (21%) delayed treatment change for >12 months



Months from start of 1st-line erlotinib

Oxnard et al. ASCO 2012

ASPIRATION study

- First line treatment with Erlotinib until and beyond disease progression
- 208 pts enrolled to the phase II study
  - 176 progressed
  - At patient and clinician discretion treatment continued in 93 pts
- In the 93 continuing patients
  - PFS1 (time to PD) = 11.0 (95% CI, 9.2-11.1) months
  - PFS2 (time to discontinue erlotinib) =14.1 (95% CI, 12.2-15.9) months
- Treatment beyond progression is feasible and may delay salvage therapy in selected patients.

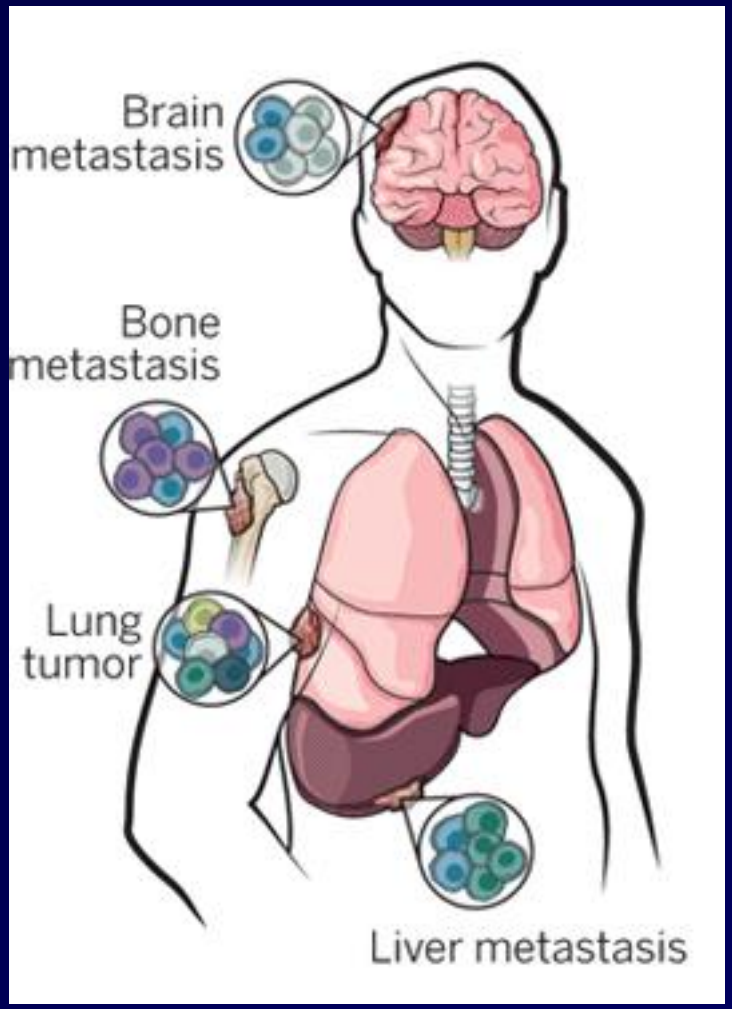
Park K et al. JAMA Oncol. 2015 Dec 30:1-8

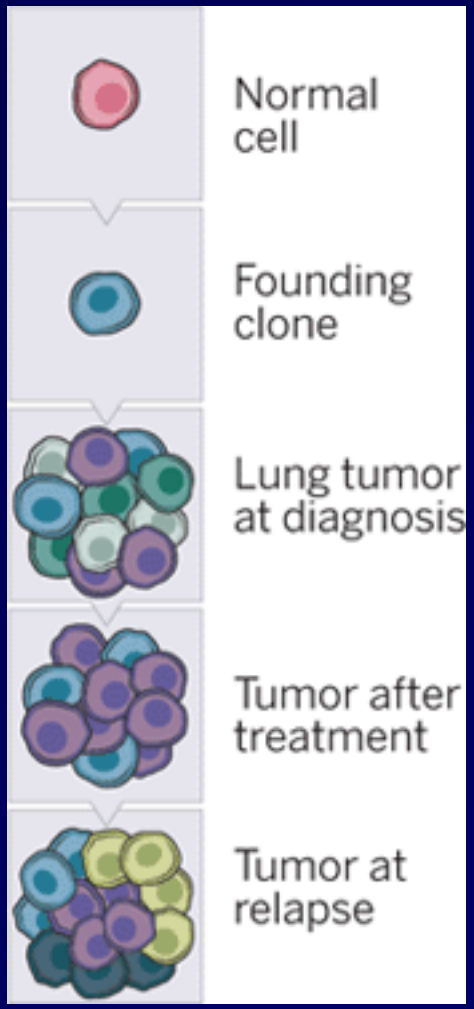
IMPRESS trial

- Post progression on EGFR TKI
  - 265 patients were randomly assigned: 133 to the gefitinib group and 132 to the placebo group
  - All patients received cisplatin and pemetrexed
- Continuation of gefitinib after radiological disease progression on first-line gefitinib did not prolong progression-free survival
- Platinum-based doublet chemotherapy remains a standard of care in this setting

Soria JC et al Lancet Oncol. 2015 Aug;16(8):990-8.

Intrapatient Heterogeneity



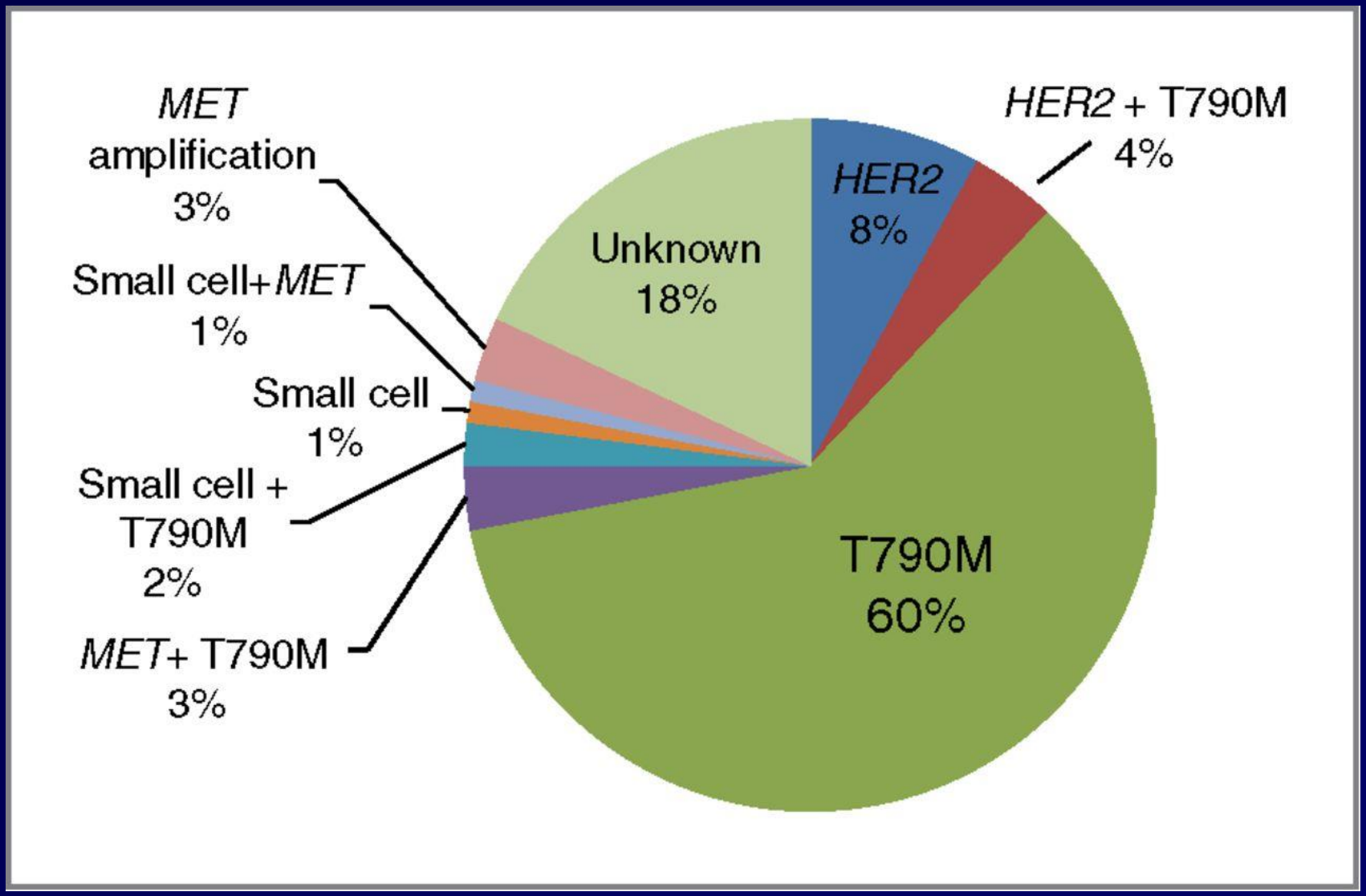


Courtesy Ben Solomon: Govindan, Science 2014; De Brouin Science 2014; Zhang Science 2014

Spatial Heterogeneity

Temporal Heterogeneity

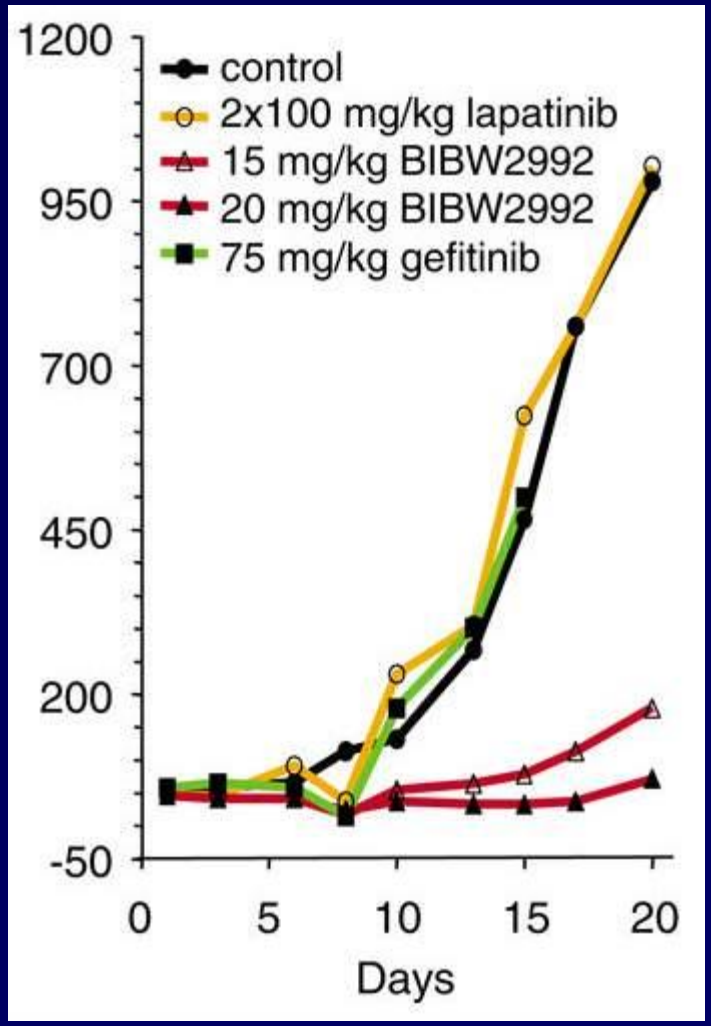
Mechanism of acquired resistance to EGFR TKIs in NSCLC



Yu H A et al. Clin Cancer Res 2013;19:2240-2247

Afatinib: active against tumour cells bearing T790M

- Afatinib was more effective than gefitinib or lapatinib in controlling xenograft tumours established from L858R/T790M-expressing H1975 cells



Li et al. *Oncogene* 2008;27:4702–11

LUX-Lung 3 and 6: design

- Stage IIIB/IV adenocarcinoma of the lung
- Presence of *EGFR* mutation in the tumor tissue*
- No prior treatment with chemotherapy for advanced/metastatic disease or EGFR inhibitors
- ECOG PS 0 or 1

Randomization

2:1

Afatinib
40 mg orally once daily

LUX-Lung 3:
Cisplatin + pemetrexed
up to 6 cycles

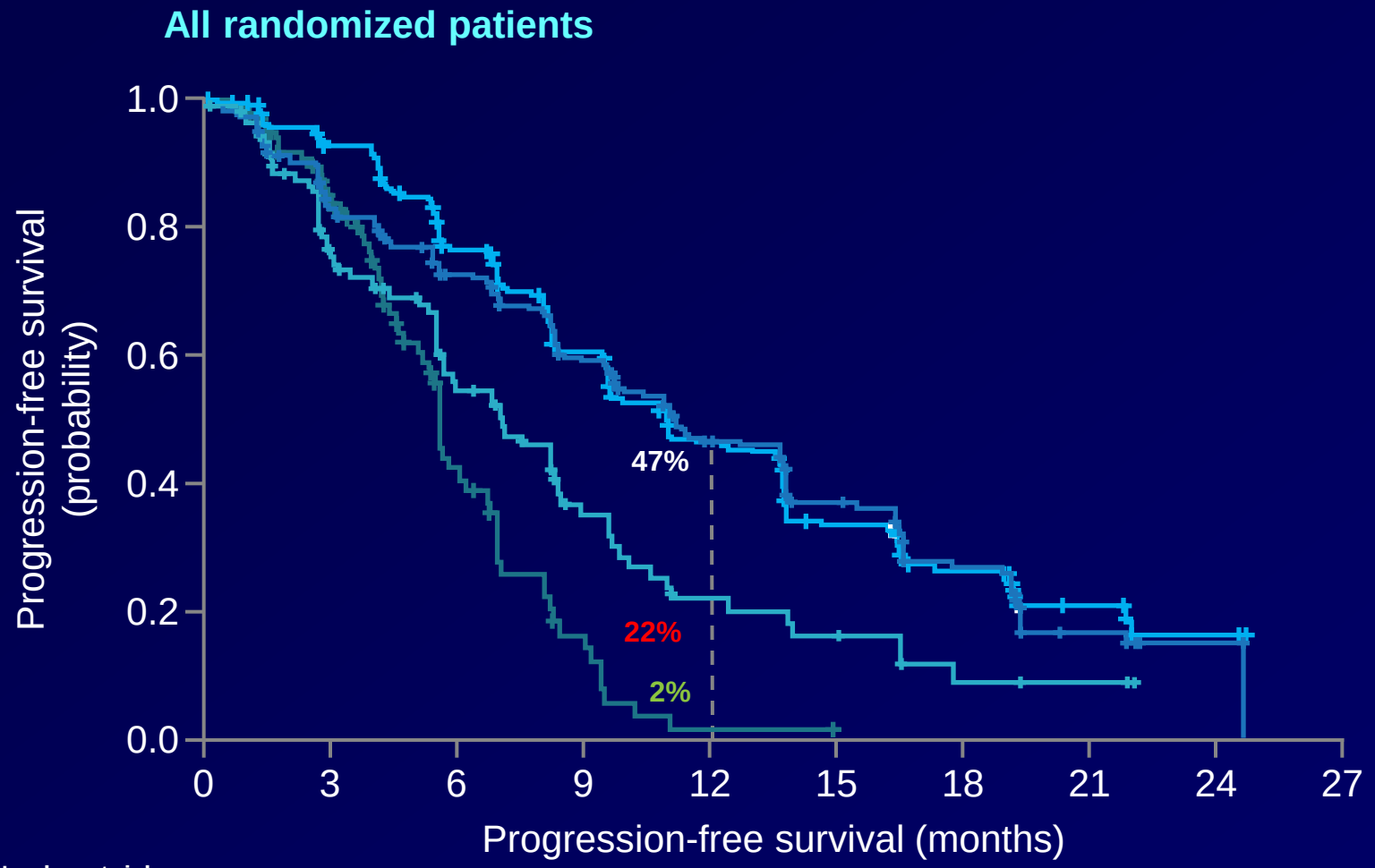
LUX-Lung 6:
Cisplatin + gemcitabine
up to 6 cycles

Primary endpoint: PFS (independent review)
Secondary end points: ORR, DCR, **OS**, PRO, safety

***EGFR29: 19 deletions in exon 19, 3 insertions in exon 20, L858R, L861Q, T790M, G719S, G719A and G719C (or G719X), S768I.**

**Sequist et al. *J Clin Oncol*. 2013;31:3327;
Wu et al. *Lancet Oncol*. 2014;15:213.**

Primary endpoint: PFS LL3 and LL6 superimposed Independent review



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

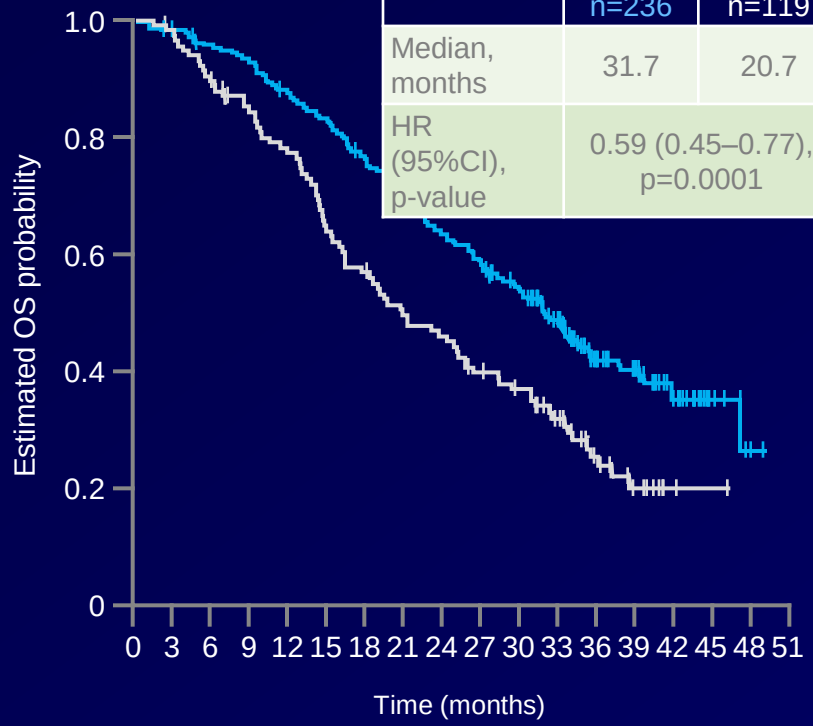
Sequist et al. *J Clin Oncol*. 2013;31:3327; Wu et al. *Lancet Oncol*. 2014;15:213.

Combined OS analysis

Mutation categories

Del19

	Afatinib n=236	Chemo n=119
Median, months	31.7	20.7
HR (95%CI), p-value	0.59 (0.45–0.77), p=0.0001	

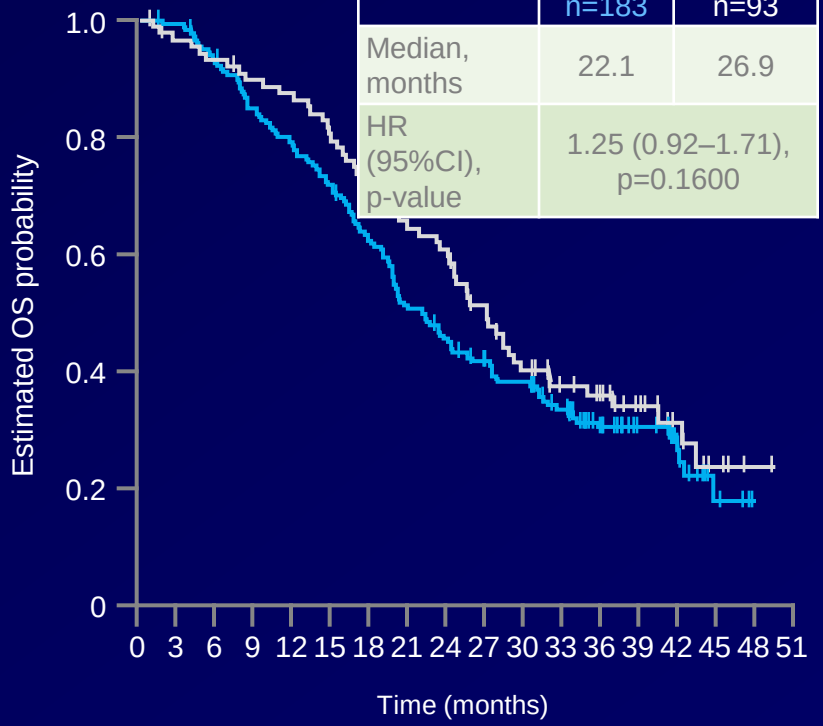


No of patients

Afatinib	236	230	223	217	202	192	173	160	145	131	117	90	50	38	22	6	1	0
Chemo	119	113	103	95	87	72	63	55	51	43	38	27	14	9	1	1	0	0

L858R

	Afatinib n=183	Chemo n=93
Median, months	22.1	26.9
HR (95%CI), p-value	1.25 (0.92–1.71), p=0.1600	



No of patients

Afatinib	183	181	167	154	141	128	111	91	80	70	64	51	27	20	11	3	0	0
Chemo	93	86	82	78	75	69	61	55	50	40	32	25	20	14	9	4	1	0

Yang JCH, et al. ASCO 2014: abstract 8004 and oral presentation.

Are 2nd Generation Irreversible HER Targeted Therapies Superior to 1st Generation Agents?

Afatinib versus gefitinib as first-line treatment of patients with *EGFR* mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial

Keunchil Park, Eng-Huat Tan, Ken O'Byrne, Li Zhang, Michael Boyer, Tony Mok, Vera Hirsh, James Chih-Hsin Yang, Ki Hyeong Lee, Shun Lu, Yuankai Shi, Sang-We Kim, Janessa Laskin, Dong-Wan Kim, Catherine Dubos Arvis, Karl Kölbeck, Scott A Laurie, Chun-Ming Tsai, Mehdi Shahidi, Miyoung Kim, Dan Massey, Victoria Zazulina, Luis Paz-Ares

www.thelancet.com/oncology **Published online April 12, 2016** **http://dx.doi.org/10.1016/S1470-2045(16)30033-X**

Study design

- Stage IIIB/IV adenocarcinoma of the lung
- *EGFR* mutation (Del19 and/or L858R) in the tumor tissue*
- No prior treatment for advanced/ metastatic disease
- ECOG PS 0/1

1:1

Afatinib 40 mg once daily†

Stratified by
- Mutation type (Del19/L858R)
- Brain metastases (present/absent)

Gefitinib 250 mg once daily

Primary endpoints:
- PFS (independent)
- TTF
- OS

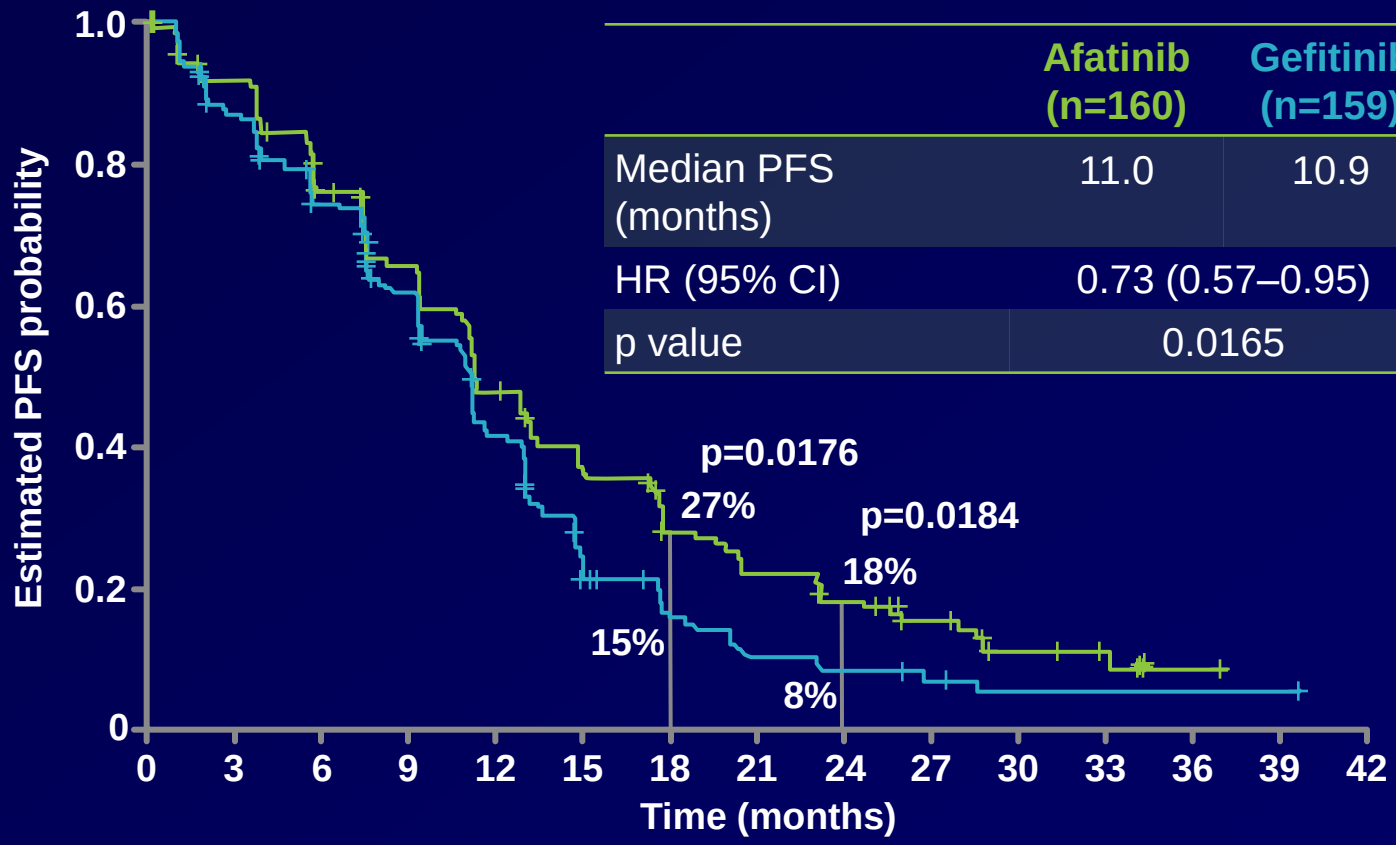
Secondary endpoints:
- ORR
- Time to response
- Duration of response
- Duration of disease control
- Tumor shrinkage
- HRQoL
- Safety

- 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

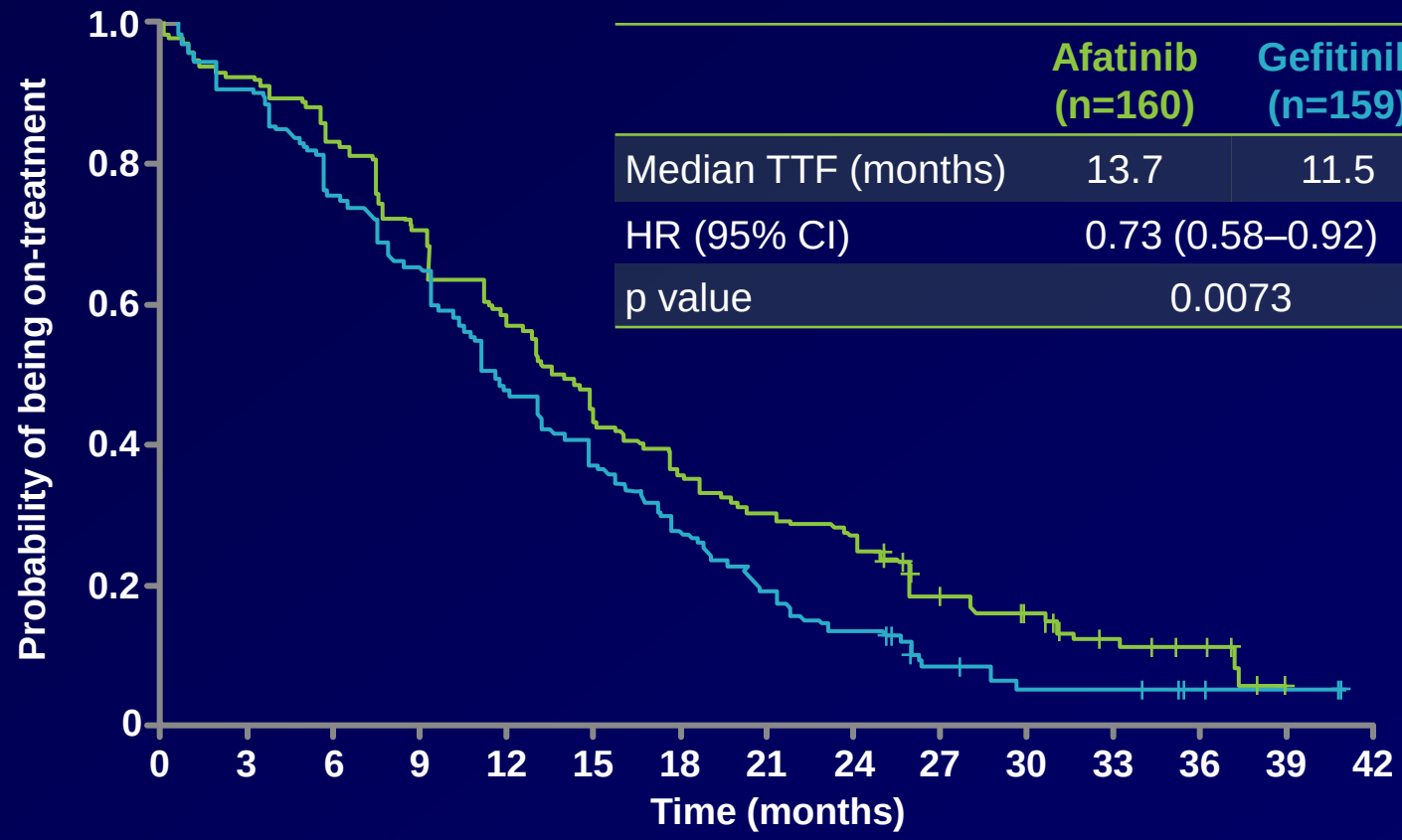
ECOG PS, Eastern Oncology Cooperative Group performance status; HRQoL, health-related quality of life; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumors; TTF, time to treatment failure

PFS by independent review



	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	

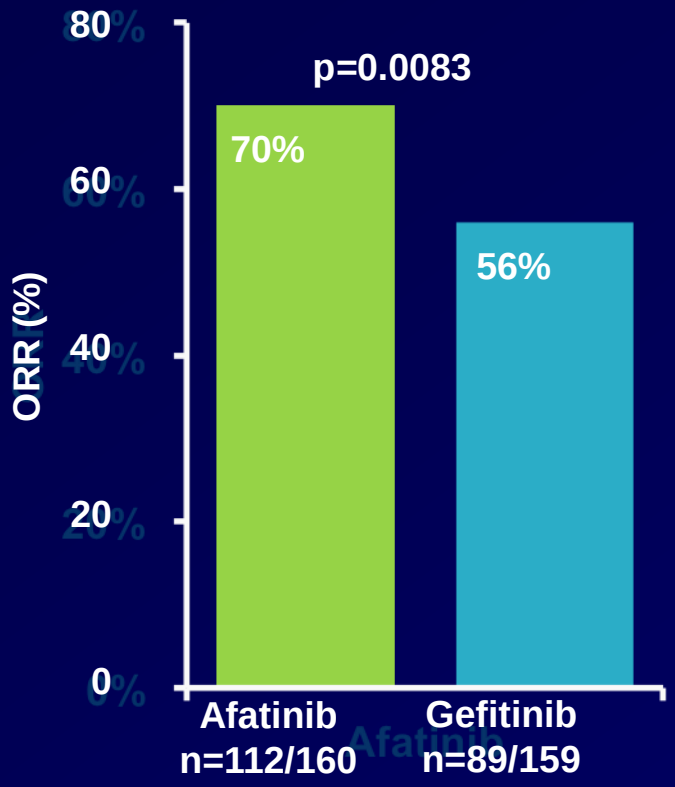
Time to treatment failure



	Afatinib (n=160)	Gefitinib (n=159)
Median TTF (months)	13.7	11.5
HR (95% CI)	0.73 (0.58–0.92)	
p value	0.0073	

No. of patients														
Afatinib	160	148	133	113	91	68	56	48	40	25	18	9	5	0	0
Gefitinib	159	144	120	103	74	59	43	30	21	11	6	6	2	2	0

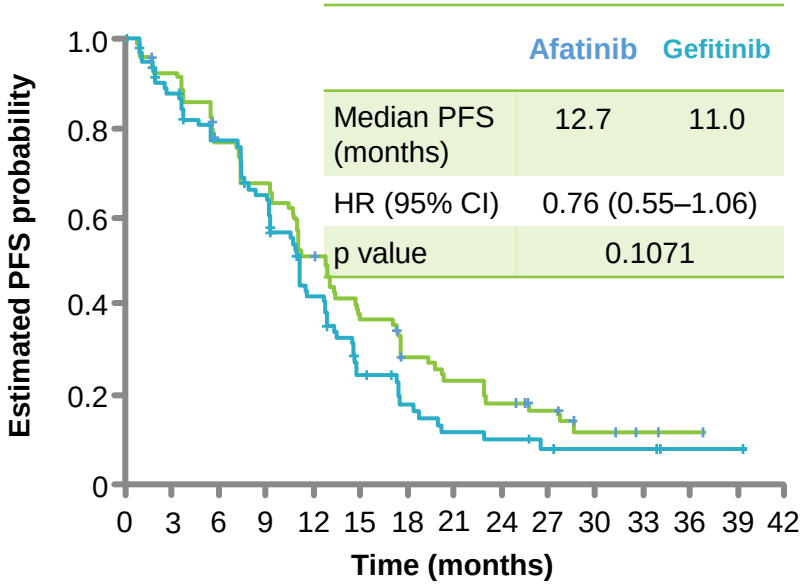
Objective response and duration of response (independent review)



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

DoR, duration of response

Efficacy in patients with Del19 mutation

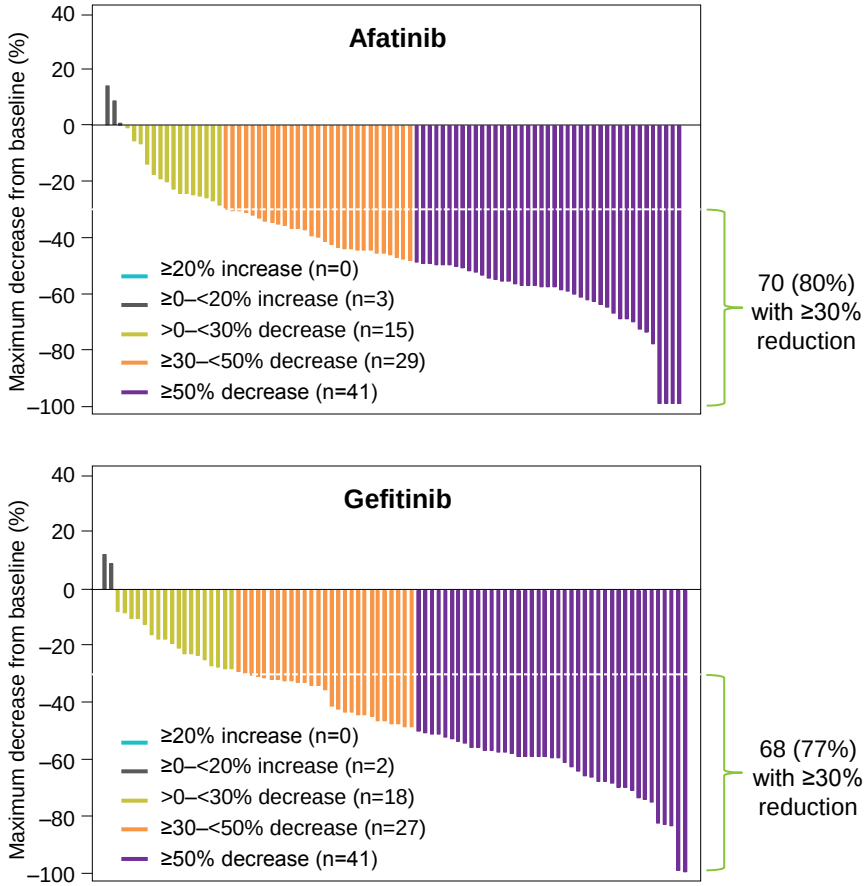


	Afatinib	Gefitinib
Median PFS (months)	12.7	11.0
HR (95% CI)	0.76 (0.55–1.06)	
p value	0.1071	

No. of patients

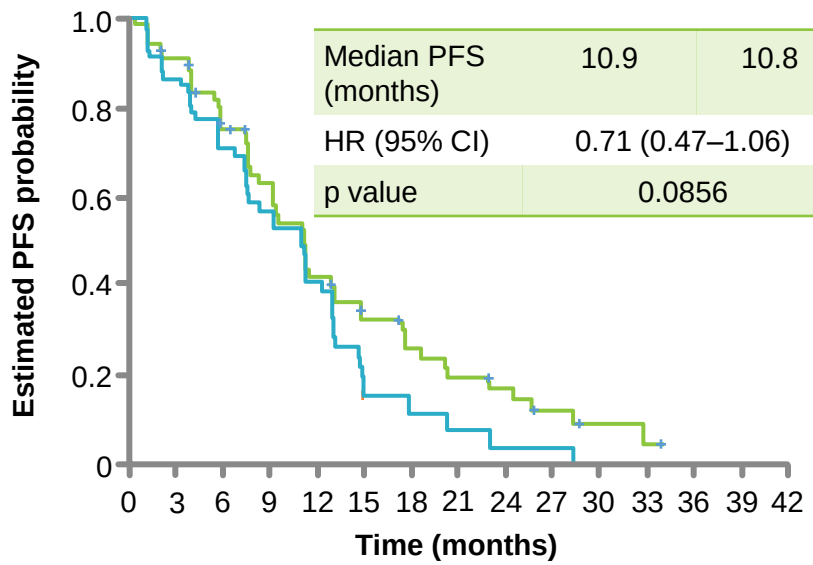
Afatinib	93	83	67	58	43	31	22	18	14	9	4	2	1	0	0
Gefitinib	93	76	64	53	32	17	11	7	6	4	3	3	1	1	0

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



Efficacy in patients with L858R mutation

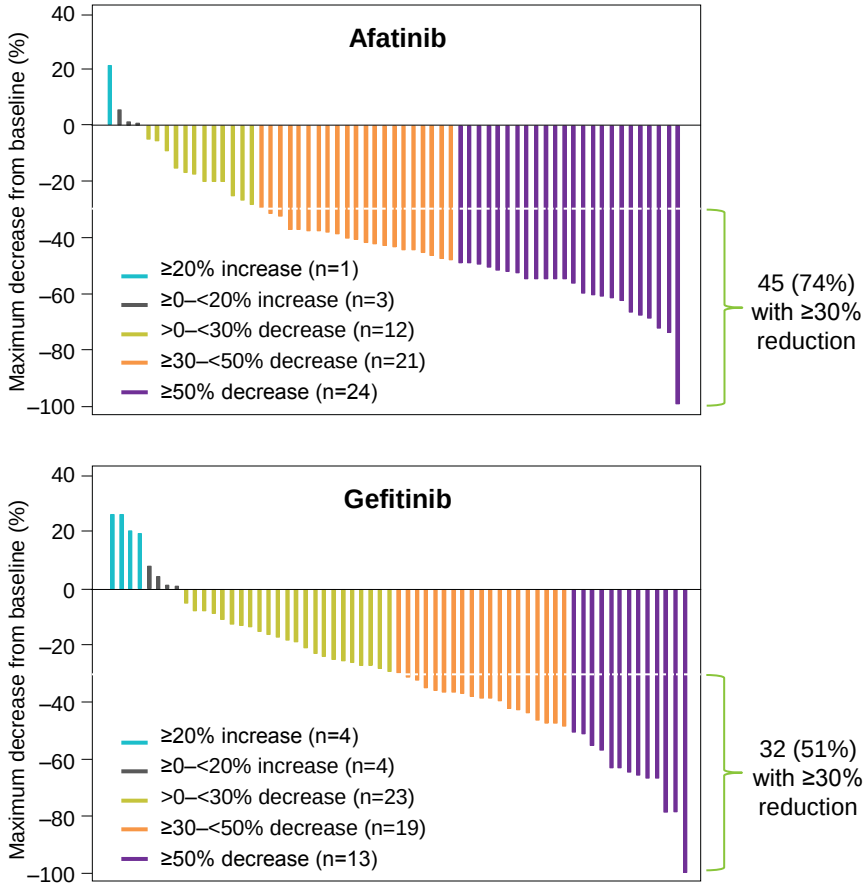
	Afatinib	Gefitinib
Median PFS (months)	10.9	10.8
HR (95% CI)	0.71 (0.47–1.06)	
p value	0.0856	



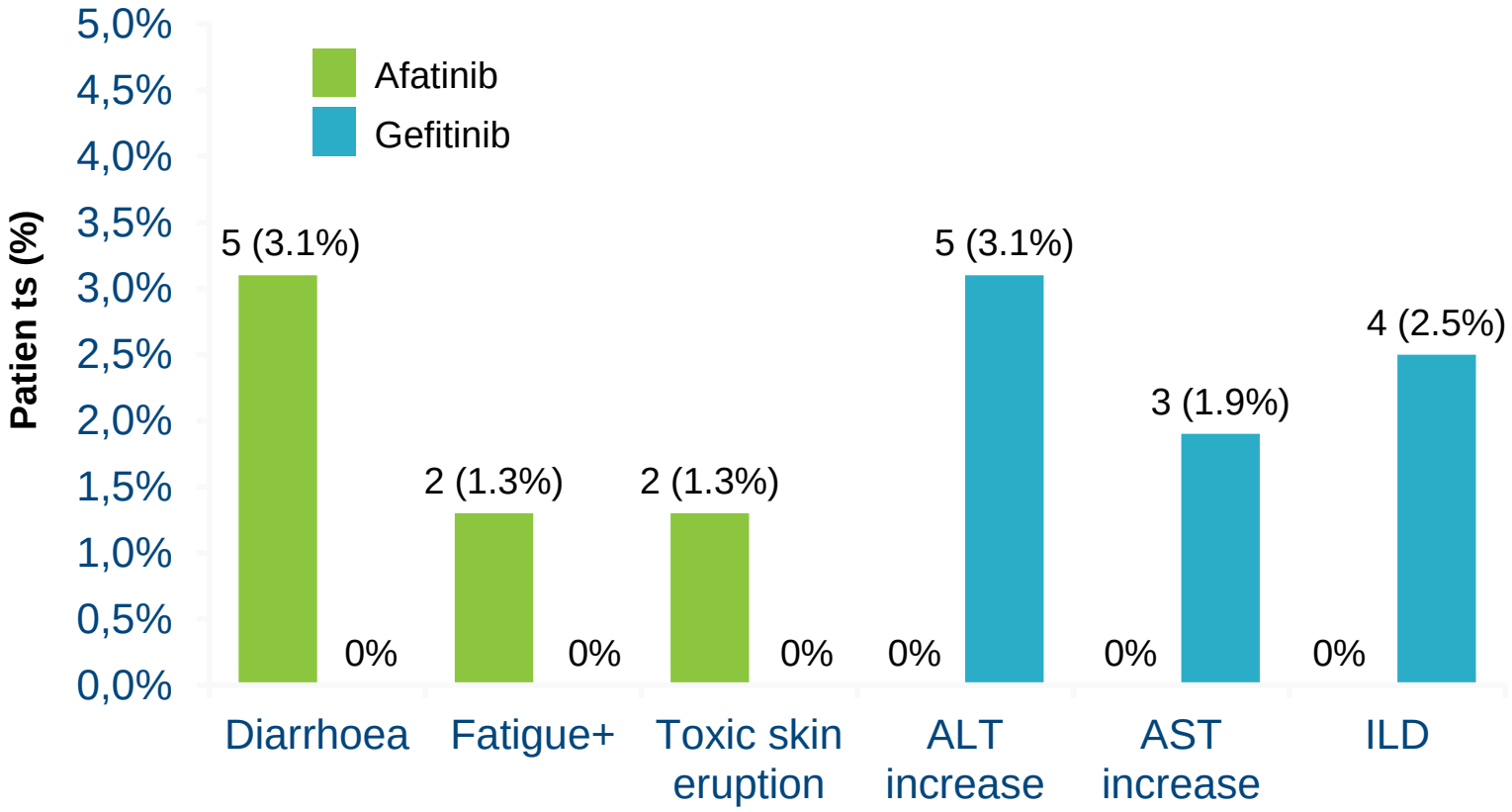
No. of patients

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

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



Drug-related AEs leading to discontinuation in >1 patient



Summary and conclusion

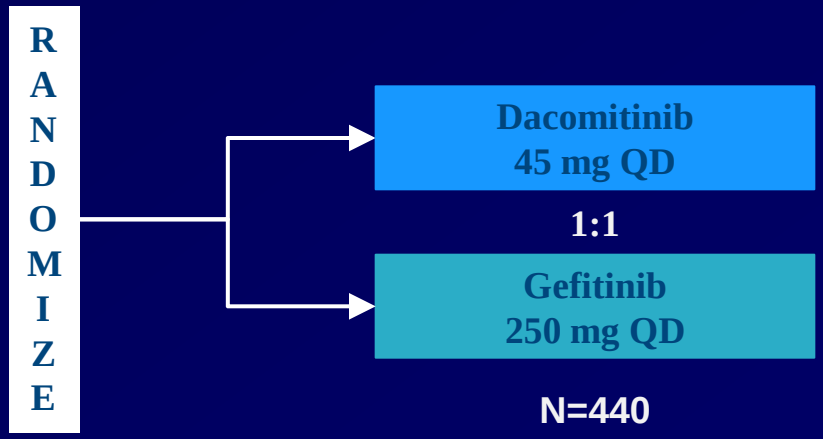
- Afatinib significantly improved PFS of patients with *EGFR*m+ NSCLC relative to gefitinib. Results are consistent across subgroups
- Afatinib treatment was associated with a significant improvement in response rate and TTF
- The improvement in efficacy was observed in both Del19 and L858R populations
- OS data immature (current HR: 0.87, 95%CI: 0.66–1.15)
- AEs in both groups were consistent with previous experience, and were manageable leading to equally low rates of treatment discontinuation
- LUX-Lung 7 confirms the benefit of irreversible ErbB blockade with afatinib over reversible EGFR inhibition with gefitinib in treatment of *EGFR*m+ NSCLC

Protocol DP312804 (A7471050) Study Design

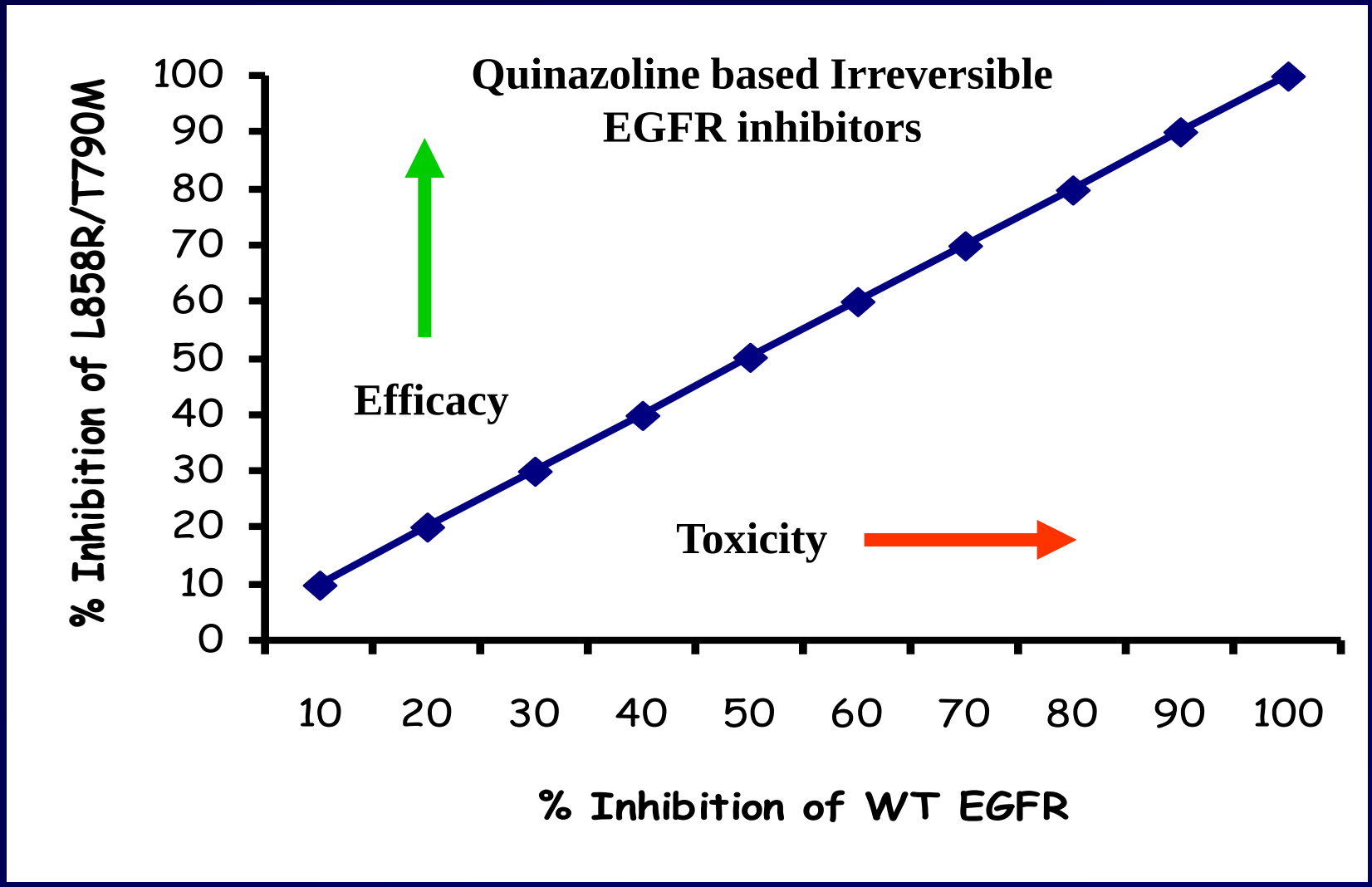
Trial design	Endpoints	Study sites
Phase 3 randomized, open-label, 1st line treatment of locally advanced or metastatic NSCLC with EGFR activating mutation(s)	Primary: PFS as per blinded IRC review Ha: HR≤ 0.667(50%↑) One-sided α = 0.025 Power = 90% Secondary: OS, OS_{30m}, PFS per INV, BOR, DR, PRO & PK	Global (Asia, EU)

Stage IIIb/IV NSCLC with EGFR activating mutation(s)

- First line treatment
- Stratification factors: race, mutation status



Quinazoline based Irreversible inhibitors are not selective for EGFR L858R/T790M over WT EGFR



Dose escalation of Irreversible EGFR inhibitors limited by diarrhea and rash (wild type EGFR)

Strategies to Inhibit EGFR T790M

- Intermittent pulse dosing of existing drugs
  - Even transient but complete inhibition of EGFR T790M maybe sufficient
  - Avoid/minimize WT EGFR inhibition
- Combinations of EGFR targeted therapies
  - EGFR TKIs & EGFR directed antibodies
- Develop mutant selective EGFR inhibitors
  - More potent against EGFR T790M vs. WT EGFR

Phase Ib study of Afatinib & Cetuximab

Pathology confirmed NSCLC with

EGFR mutation[1]

OR

SD ≥6 months on erlotinib/gefitinib

OR

Partial or complete response to erlotinib/gefitinib

ECOG PS 0-2
Age ≥ 18 years

Disease progression[2]

Stop erlotinib/ gefitinib for ≥72 hours[3]

Dose escalation schema 3–6 patients per cohort

Afatinib p.o. daily + escalating doses of i.v. cetuximab q 2 weeks

Dose levels starting at:
afatinib 40 mg +
cetuximab 250 mg/m^2

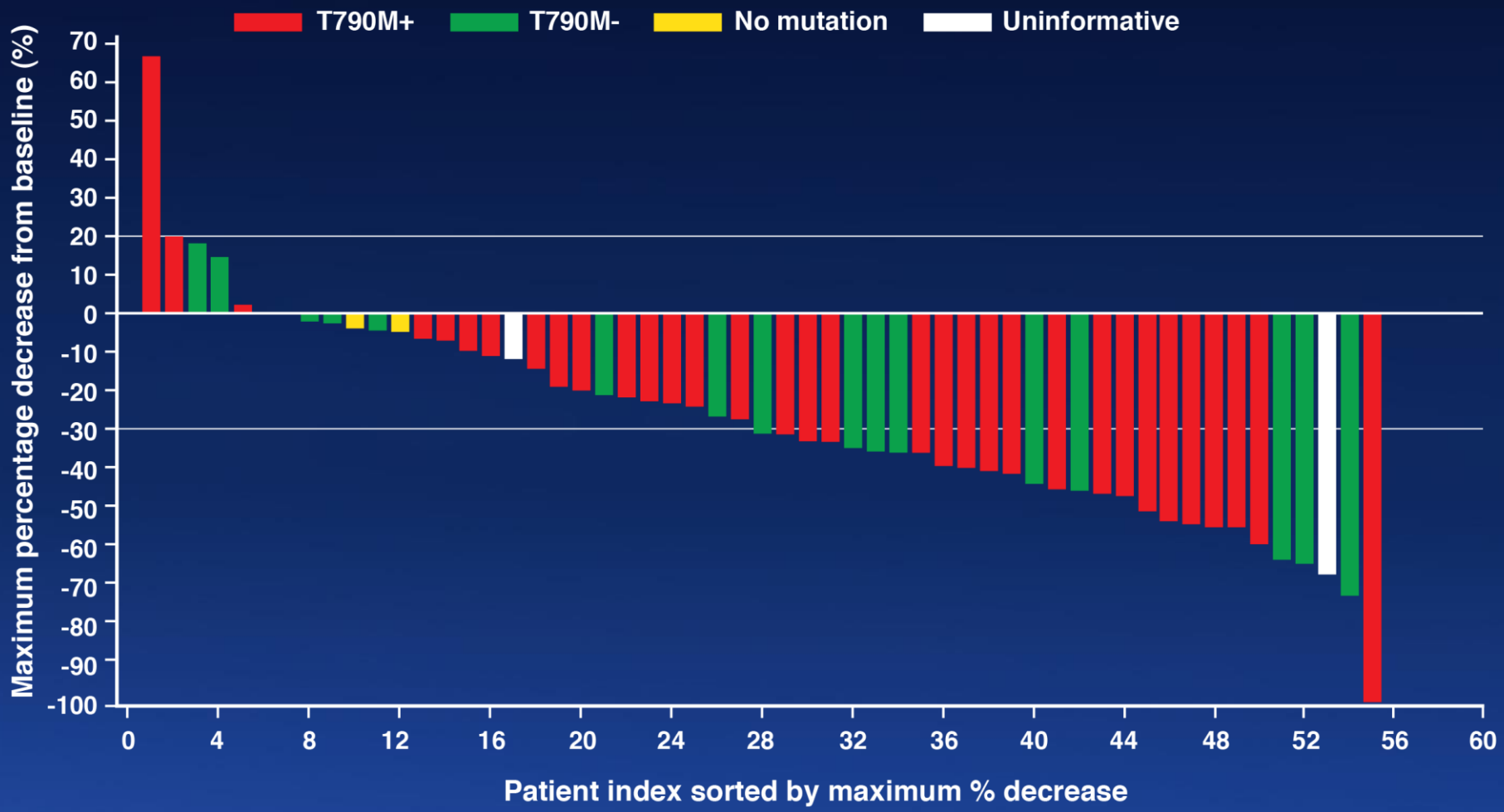
Predefined maximum dose:
afatinib 40 mg +
cetuximab 500 mg/m^2

MTD cohort expanded up to 80 *EGFR* mutation-positive patients[4]:
40 T790M+ and 40 T790M–

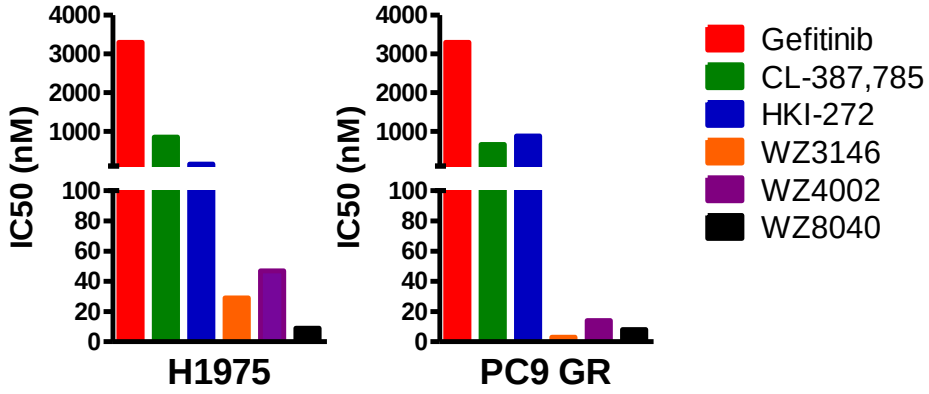
[1]EGFR G719X, exon 19 deletion, L858R, L861Q; [2]Progression of disease (Response Evaluation Criteria in Solid Tumors v1.1) on continuous treatment with erlotinib or gefitinib within the last 30 days; [3]Amended from original 14-day interval; [4]Acquisition of tumor tissue after the emergence of acquired resistance was mandated.
i.v.=intravenous; MTD=maximum tolerated dose; NSCLC=non-small cell lung cancer; SD=stable disease.

Tumor Regression by T790M Mutation Status

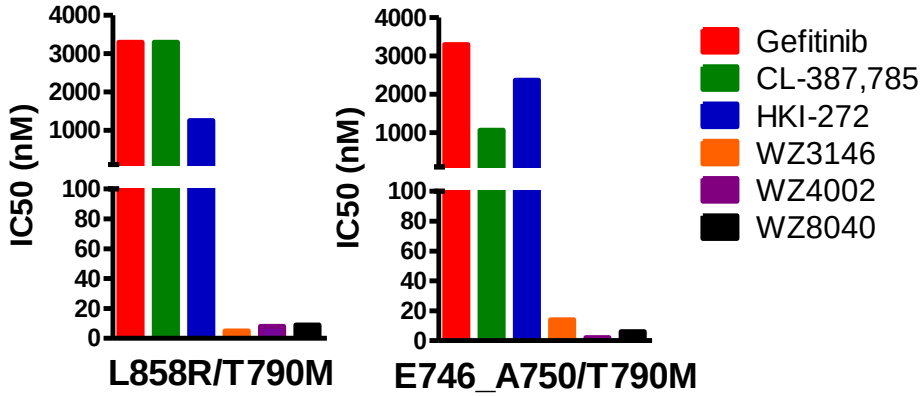
at Recommended Dose



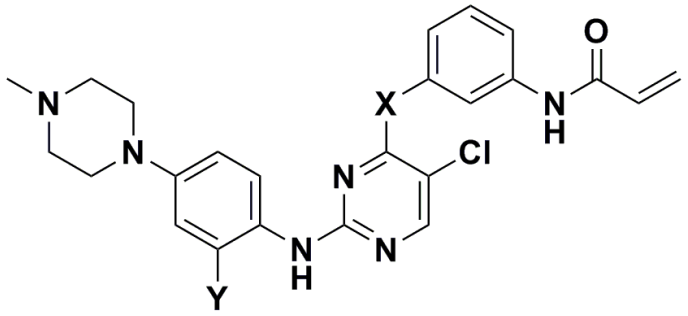
Horn at al. IASLC 2011



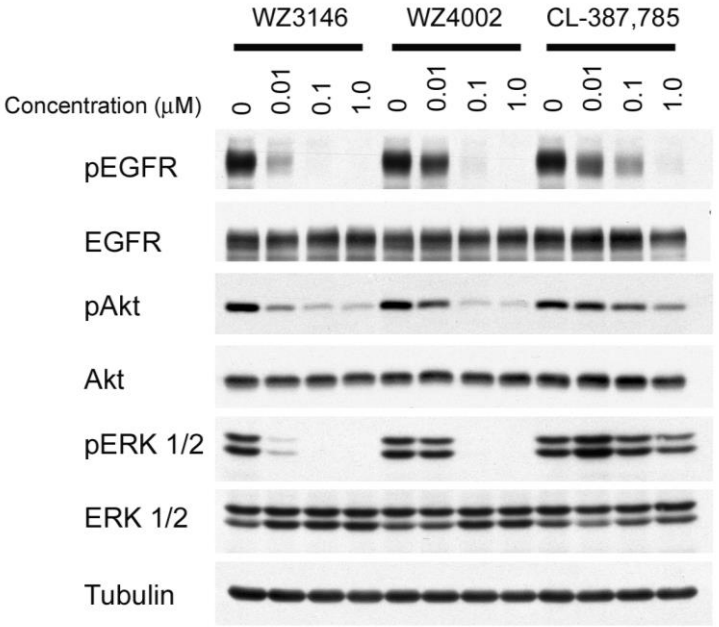
NSCLC cell lines



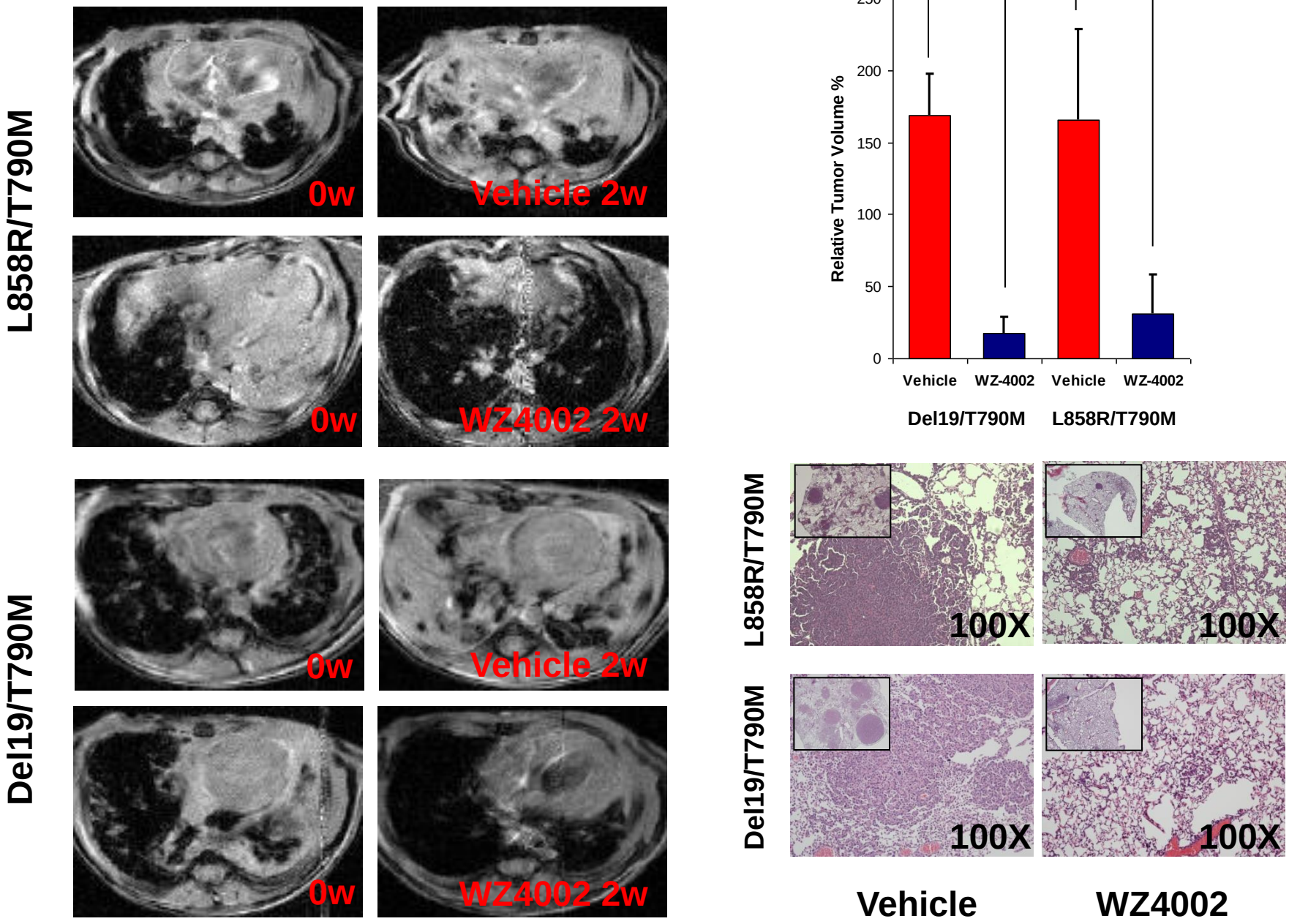
Ba/F3 cells



WZ3146 X=O, Y=H
WZ4002 X=O, Y=OMe
WZ8040 X=S, Y=H

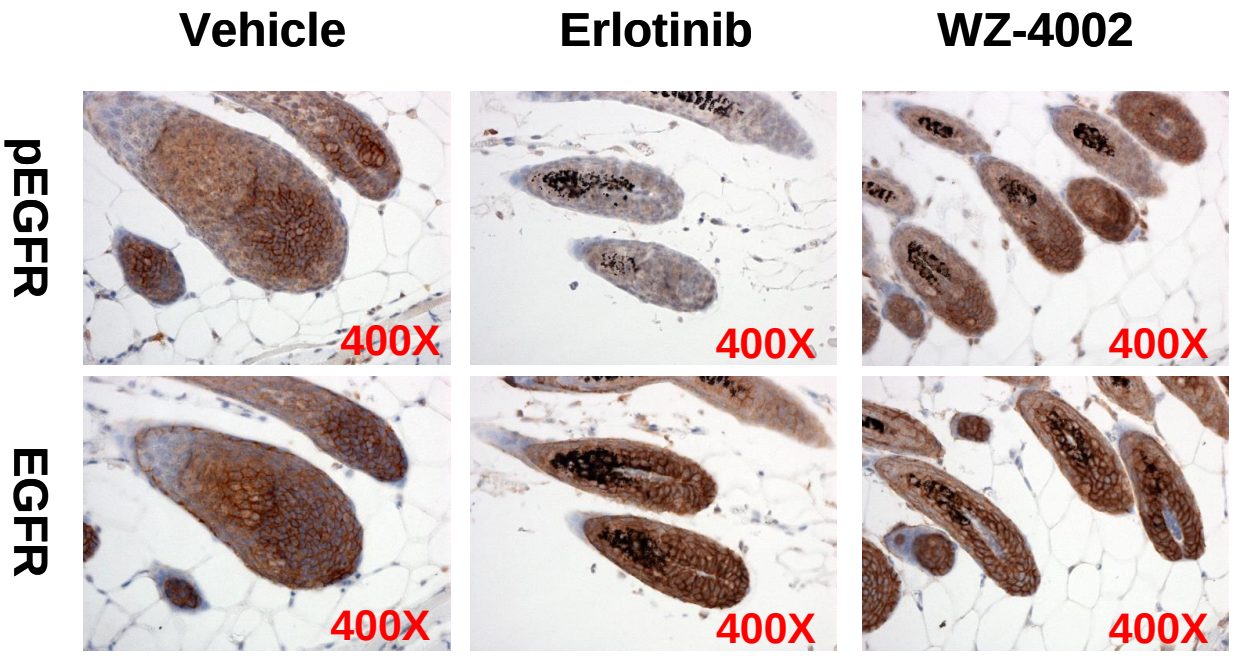


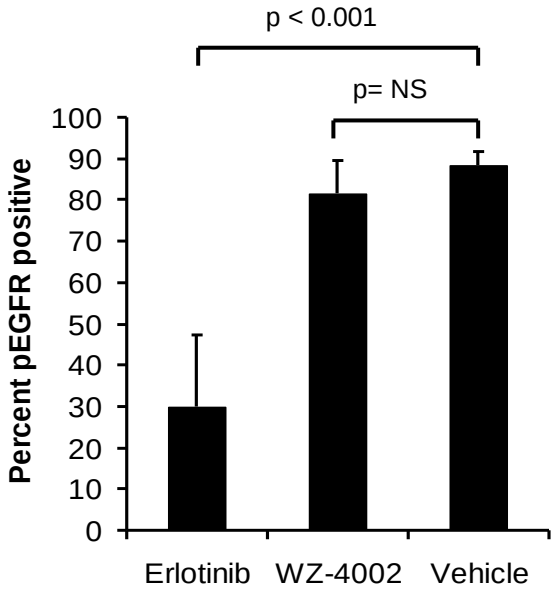
Zhou et al. Nature 2009


L858R/T790M
0w
Vehicle 2w
0w
WZ4002 2w
Del19/T790M
0w
Vehicle 2w
0w
WZ4002 2w
p = 0.001
p = 0.018
Relative Tumor Volume %
250
200
150
100
50
0
Vehicle
WZ-4002
Vehicle
WZ-4002
Del19/T790M
L858R/T790M
L858R/T790M
100X
100X
Del19/T790M
100X
100X
Vehicle
WZ4002

Is there a difference on WT EGFR in vivo ?

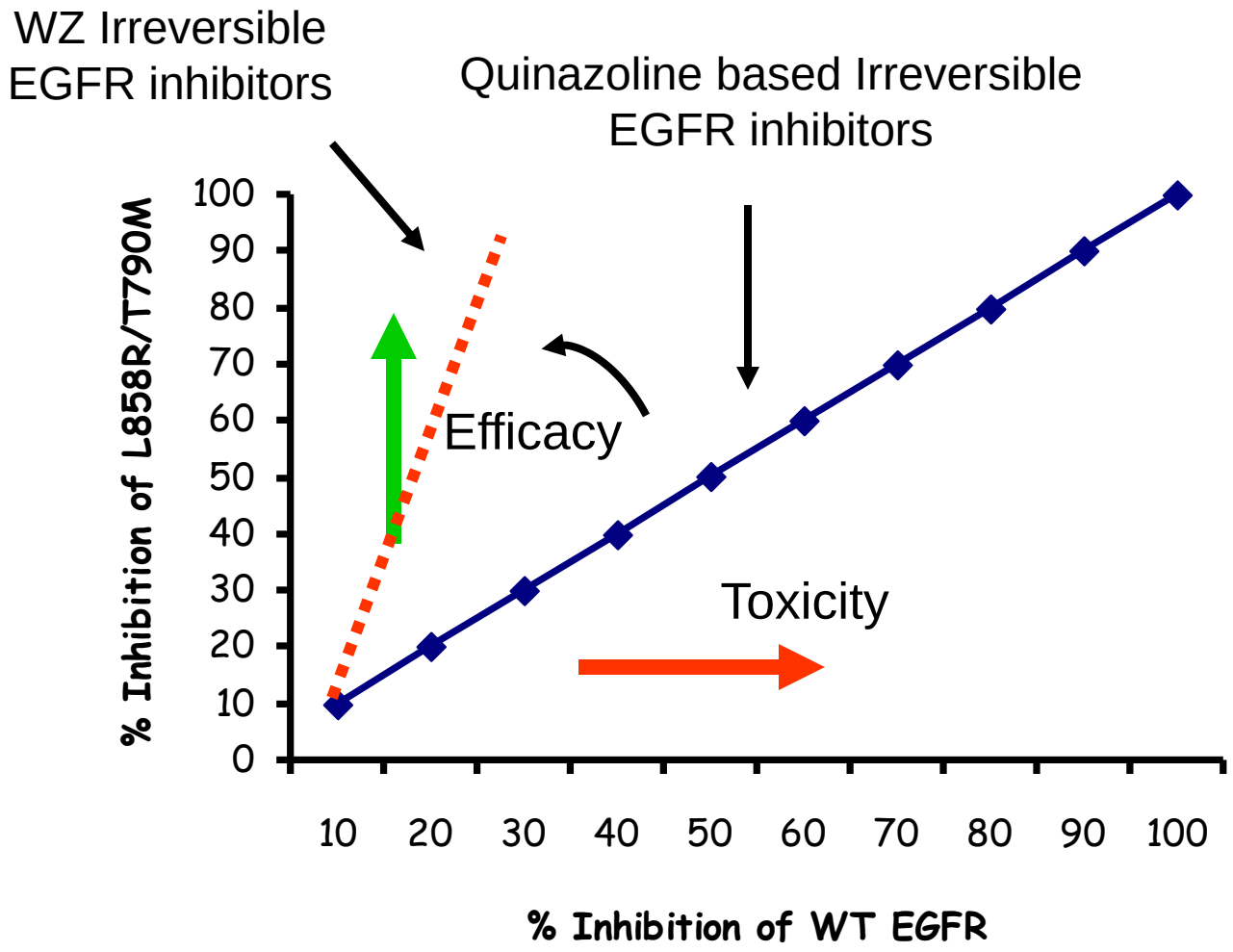
Evaluation of EGFR phosphorylation in hair follicle bulb





Zhou et al. Nature 2009

Quinazoline based Irreversible inhibitors are not selective for EGFR L858R/T790M over WT EGFR



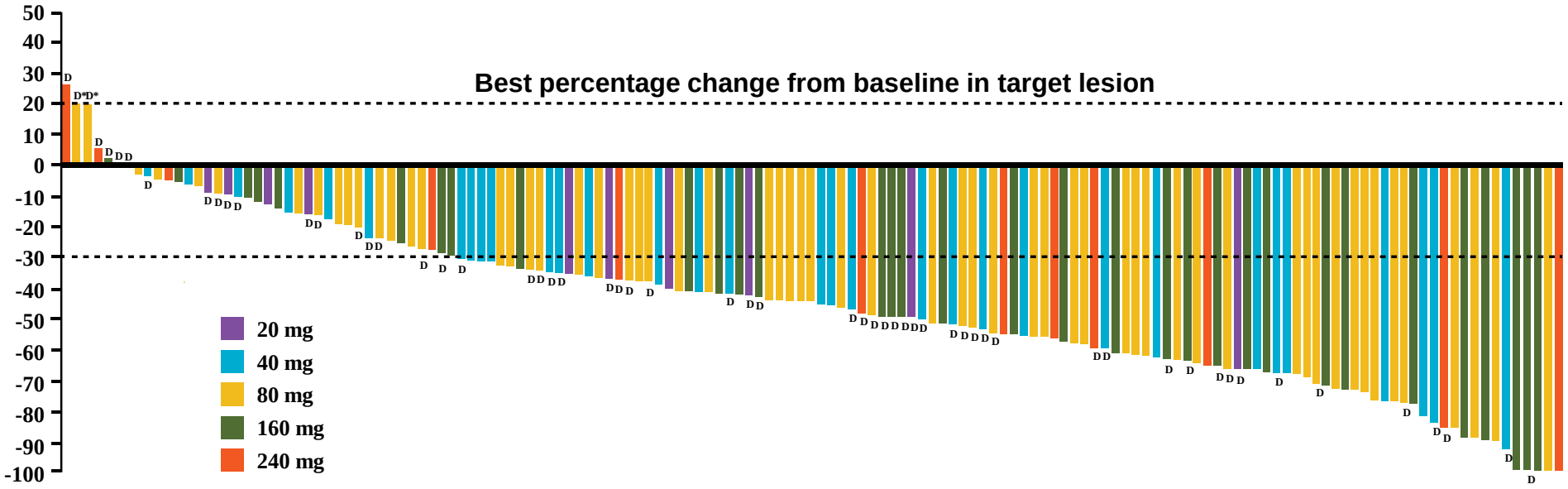
Dose escalation of Irreversible EGFR inhibitors limited by diarrhea and rash (wild type EGFR)

A Phase I study of AZD9291 in patients with EGFR-TKI-resistant advanced NSCLC – updated progression-free survival and duration of response data

Pasi A. Jänne[1], Myung-Ju Ahn[2], Dong-Wan Kim[3], Sang-We Kim[4], David Planchard[5], Suresh S. Ramalingam[6], Paul Frewer[7], Mireille Cantarini[7], Serban Ghiorghiu[7], James Chih-Hsin Yang[8]

[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]Samsung Medical Center, Seoul, Republic of Korea; [3]Seoul National University Hospital, Seoul, Republic of Korea; [4]Asan Medical Center, Seoul, Republic of Korea; [5]Gustave Roussy, Villejuif, France; [6]Emory University, Winship Cancer Institute, Atlanta, GA, USA; [7]AstraZeneca, Alderley Park, Macclesfield, UK; [8]National Taiwan University Hospital, Taipei, Taiwan

Response rate in T790M positive cohorts (central test)



DCR (CR+PR+SD) in patients with centrally tested T790M positive tumours was 90% (141 / 157; 95% CI 84, 94)

	20 mg	40 mg	80 mg	160 mg	240 mg	Total
N (157)	10	32	61	41	13	157
ORR (95% CI)	50% (19, 81)	59% (41, 76)	66% (52, 77)	51% (35, 67)	54% (25, 81)	59% (51, 66)

*Imputed values for patients who died within 14 weeks (98 days) of start of treatment and had no evaluable target lesion assessments
Nine patients (seven in the 160 mg cohort) currently have a best overall response of not evaluable, as they have not yet had a 6-week follow-up RECIST assessment
Patients are evaluable for response if they were dosed and had a baseline RECIST assessment. Data cut-off 2 Dec 2014
CI, confidence interval; CR, complete response; D, discontinued; DCR, disease control rate; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease

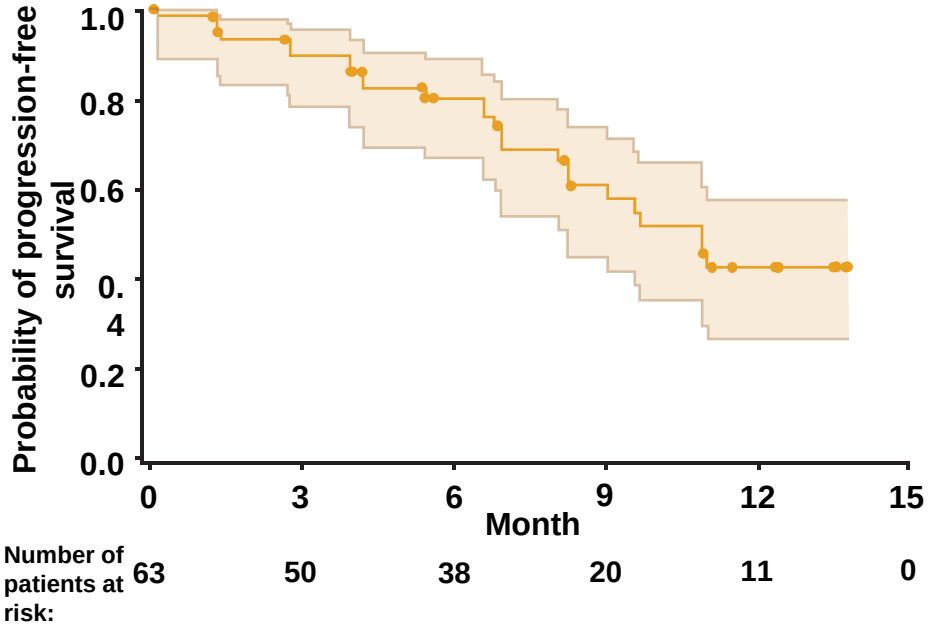
T790M positive (central test) 80 mg cohort – best objective response

Best objective response, n (%)	Investigator assessed N=61	Independent review[#] N=59
Partial response*	40 (66%) 95% CI 52, 77	32 (54%) 95% CI 41, 67
Stable disease	16 (26%)	22 (37%)
Progressive disease	4 (7%)	4 (7%)
Not evaluable	1 (2%)	1 (2%)

Population evaluable for response
***Confirmed responses only; one patient had a complete response**
[#]One patient did not have measurable disease; one patient's scan was not sent for independent review
T790M status at entry by central test result
Data cut-off 2 Dec 2014

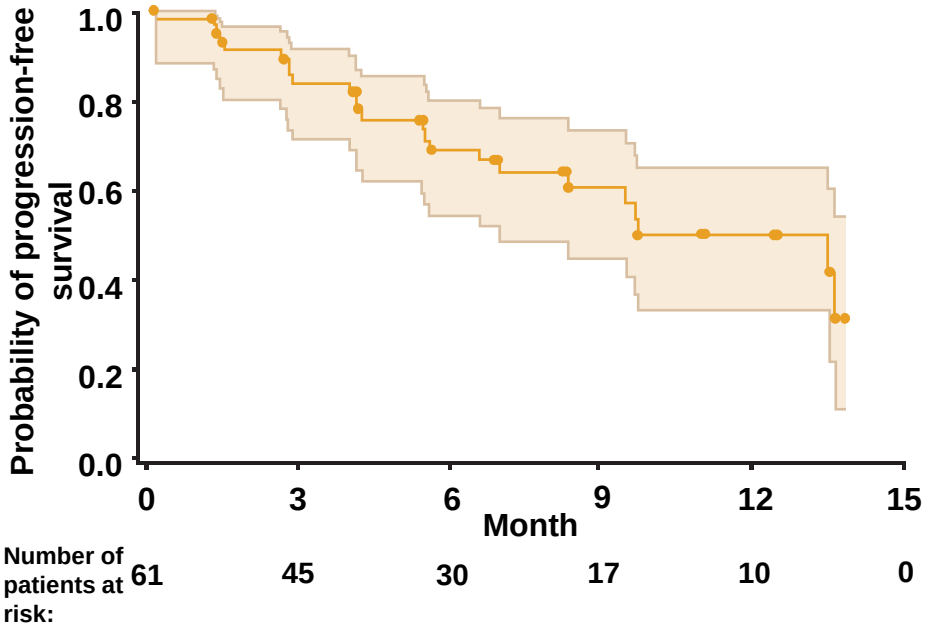
T790M positive (central test) 80 mg cohort – progression-free survival

Investigator assessed



- **Median progression-free survival, 10.9 months (95% CI 8.3, not calculable; 40% maturity, 25/63 events)**

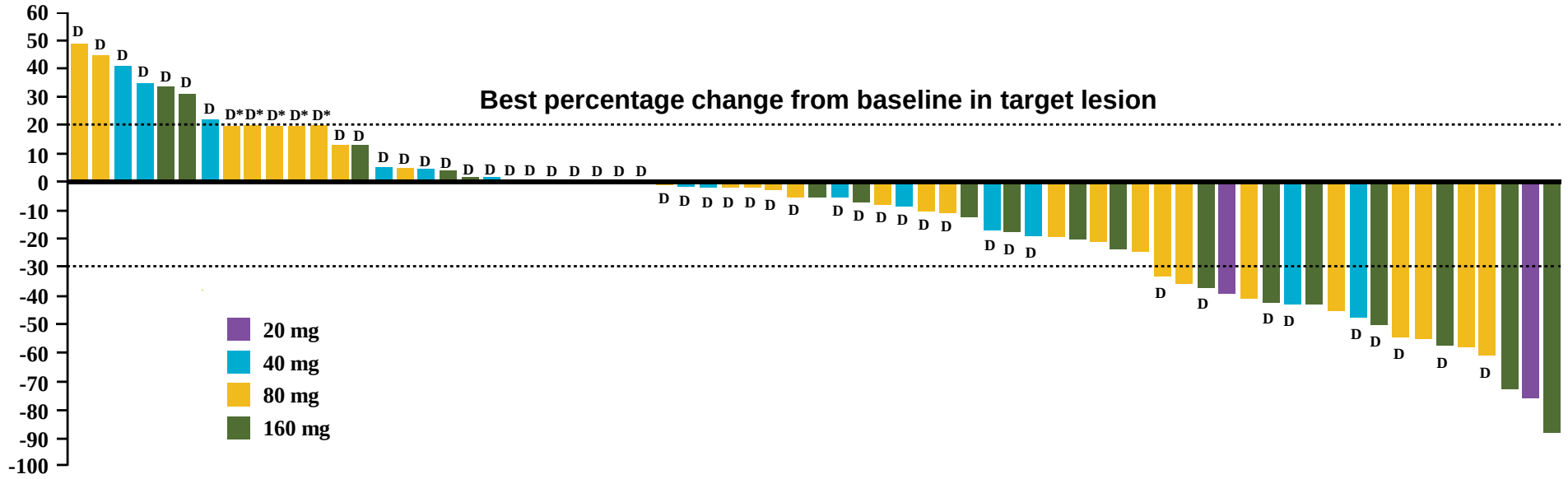
Independent review



- **Median progression-free survival, 13.5 months (95% CI 8.3, not calculable; 38% maturity, 24/63 events)**

Dots indicate censored observations, shaded area represents 95% CIs. Progression based on RECIST 1.1; progression events that do not occur within 14 weeks of the last evaluable assessment (or first dose) are censored
Population: 80 mg centrally confirmed T790M positive patients (n=63)
Data cut-off 2 Dec 2014

Response rate in T790M negative cohorts (central test)

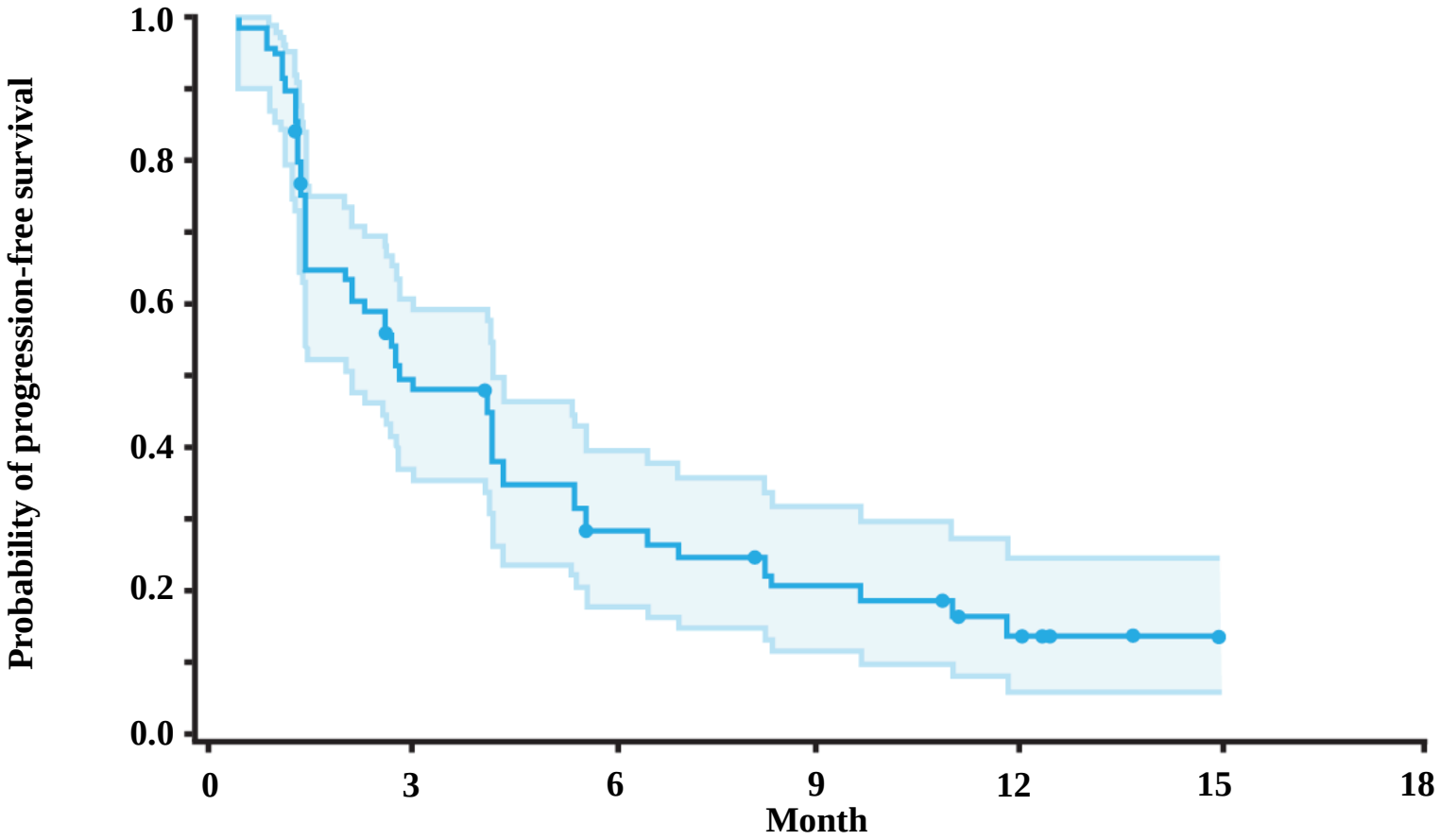


DCR (CR+PR+SD) in patients with centrally tested T790M positive tumours was 64% (44 / 69; 95% CI 51, 75)

	20 mg	40 mg	80 mg	160 mg	Total
N (69)	3	17	29	20	69
ORR (95% CI)	67% (9, 99)	12% (2, 36)	21% (8, 40)	30% (12, 54)	23% (14, 35)

***Imputed values for patients who died within 14 weeks (98 days) of start of treatment and had no evaluable target lesion assessments**
Patients are evaluable for response if they were dosed and had a baseline RECIST assessment. Data cut-off 2 Dec 2014

Progression-free survival – T790M negative (central test)



Median progression-free survival: 2.8 months
(95% CI 2.1, 4.2; 78% maturity, 54 / 69 events)

Dots indicate censored observations, shaded area represents 95% CIs. Progression based on RECIST 1.1; progression events that do not occur within 14 weeks of the last evaluable assessment (or first dose) are censored
Population: all dosed centrally confirmed T790M negative (n=69) patients. Investigator assessed data
T790M status at entry by central test result

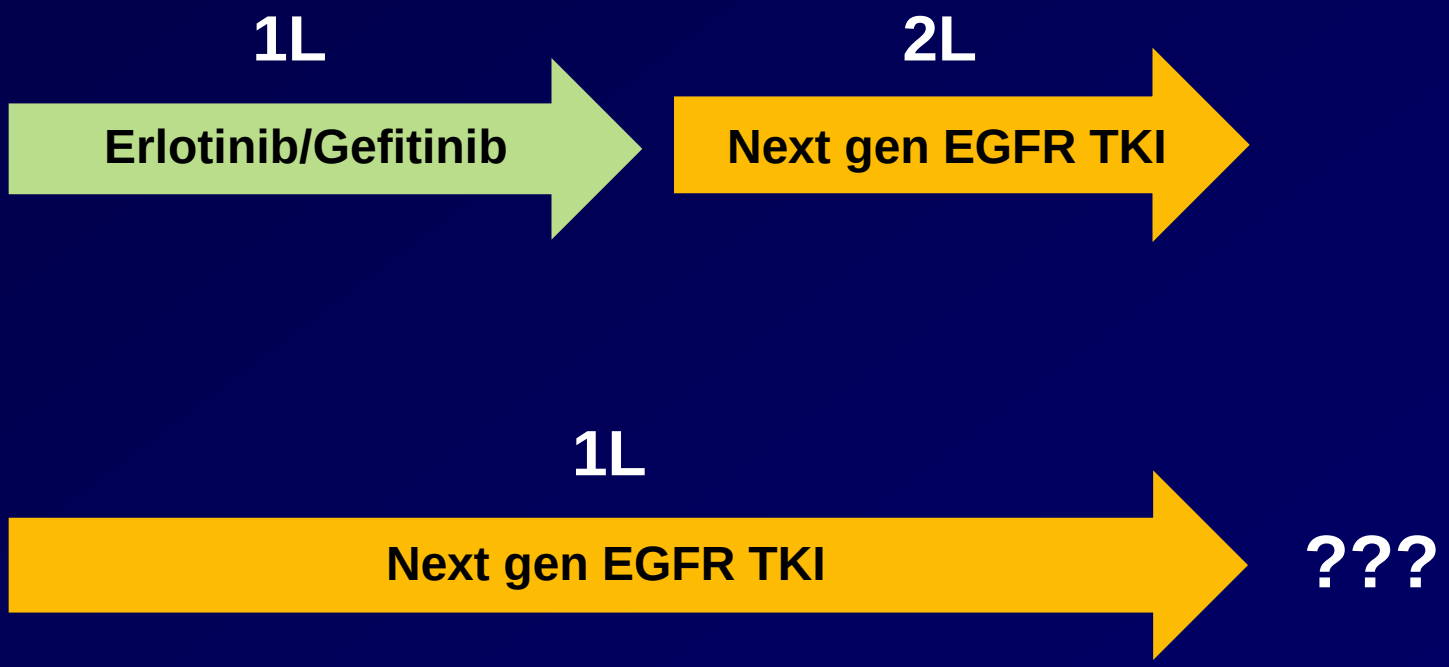
All-causality adverse events

Patients with an AE, %	20 mg (N=21)		40 mg (N=58)		80 mg (N=103)		160 mg (N=80)		240 mg (N=21)		Total (N=283)	
	Any Gr	Gr ≥3	Any Gr	Gr ≥3	Any Gr	Gr ≥3	Any Gr	Gr ≥3	Any Gr	Gr ≥3	Any Gr	Gr ≥3
AE by preferred term, occurring in >15% of patients overall												
Diarrhoea	29	0	47	2	36	1	68	3	76	5	50	2
Rash, grouped terms	24	0	33	0	38	0	63	3	76	5	46	1
Decreased appetite	38	10	19	0	26	3	24	0	33	0	25	2
Nausea	14	5	17	0	18	1	34	1	43	0	24	1
Dry skin	14	0	16	0	15	0	36	0	24	0	22	0
Paronychia	14	0	9	0	21	2	29	4	38	5	22	2
Pruritus	14	0	21	0	19	0	20	0	38	0	21	0
Fatigue	24	5	26	0	16	0	19	0	19	5	19	1
Constipation	5	0	26	0	21	0	18	0	14	0	19	0
Cough	19	0	17	0	13	0	21	0	0	0	16	0
Select AEs of interest												
Hyperglycaemia (n=8)	0	0	3	0	4	0	3	0	0	0	3	0
QT prolongation (n=10)	0	0	2	0	4	1	5	0	5	0	4	0.4
ILD-like events* (n=8)	0	0	0	0	3	2	6	4	0	0	3	2

Population: pre-treated, capsule-dosed patients (excluding Japanese-cytology cohort). Data cut-off 2 Dec 2014
***All ILD-like events are undergoing full investigation and subject to change**

As of 19th March 2015, of more than 1000 patients across all studies dosed with AZD9291, ILD grouped term events reported in approx 2.7% of patients (27 events): 12 grade 1–2; 13 grade ≥3; 2 currently ungraded. Of these, a total of 3 patients are reported to have died due to ILD (Grade 5).
CTCAE, Common Toxicity Criteria for Adverse Events; Gr, Grade

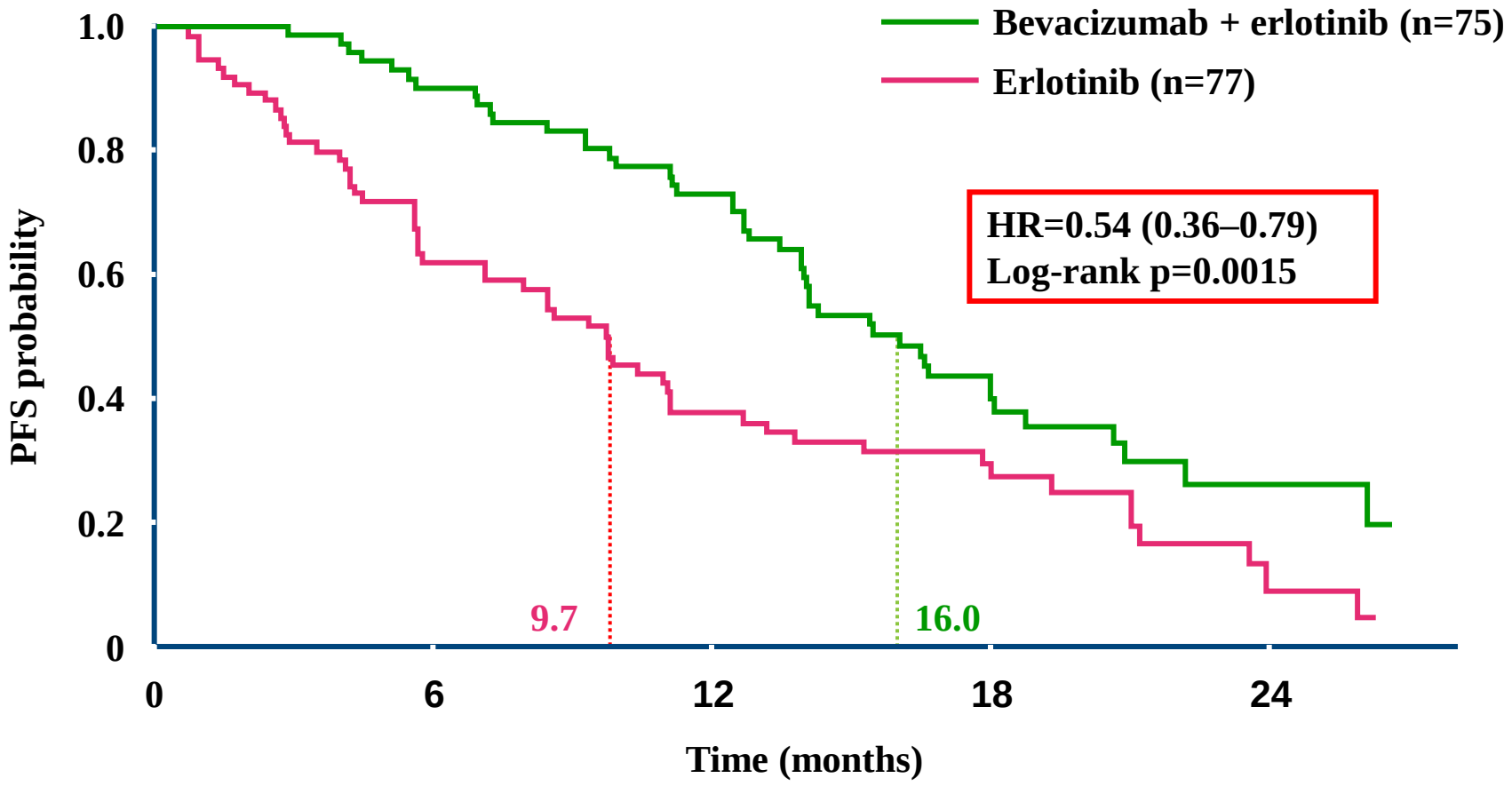
What is Optimal First-Line Therapy for EGFR mut NSCLC



Conclusions

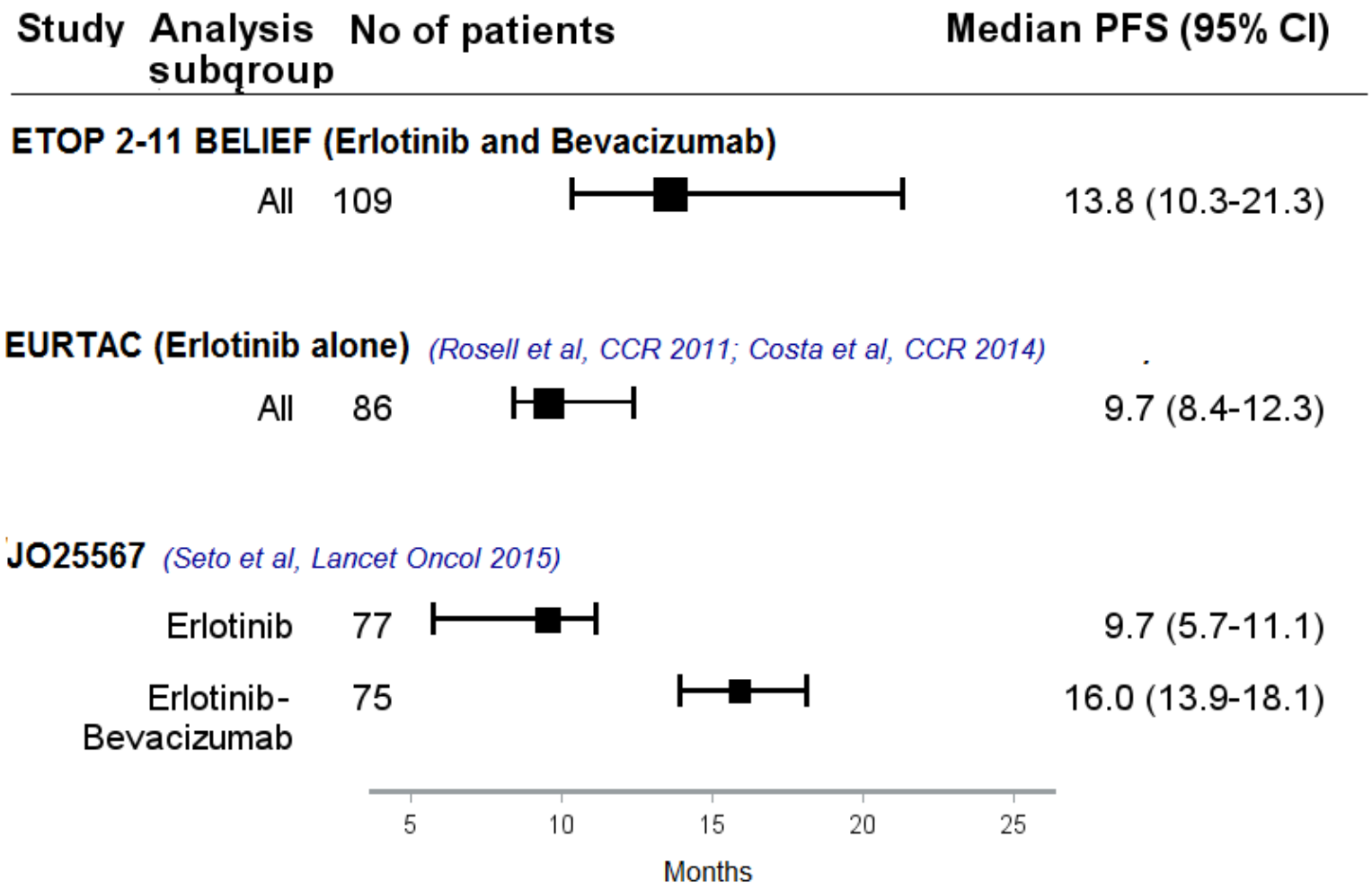
- Acquired resistance to EGFR inhibitors remains a clinical challenge
- Mechanisms responsible for acquired resistance can be identified through biopsy on progression
- Potential strategies to overcome resistance include mutation selective EGFR TKIs active against T790M (e.g. CO1686 and AZD929)
- Phase 3 studies of novel EGFR TKIs, with less toxicity, in first line setting are under-investigation in ongoing
  - And what next after resistance to 3rd generation TKIs develops?
  - Tissue and liquid biopsies required!

JO25567: PFS



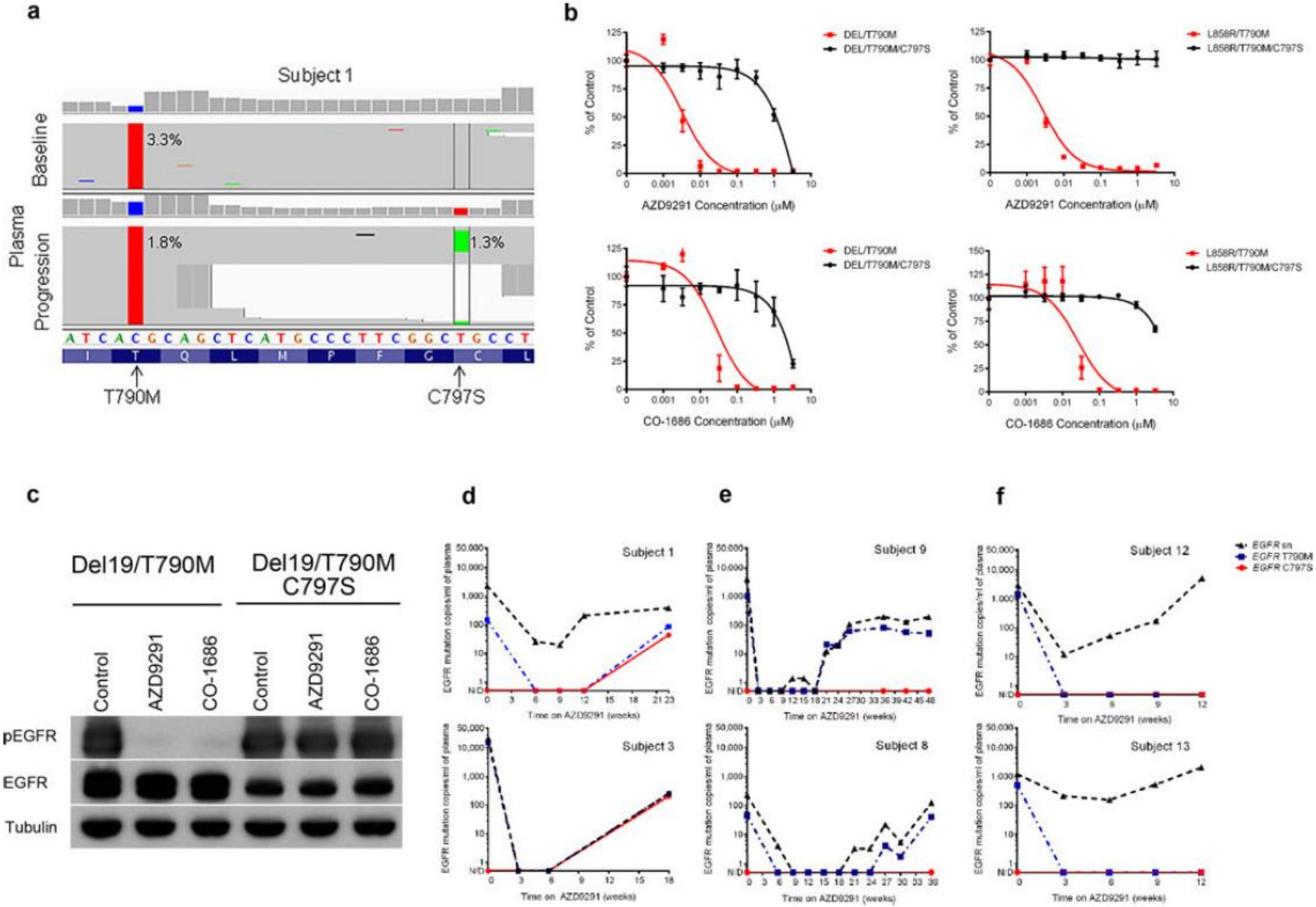
Seto, et al. Lancet Oncol 2014

BELIEF: data in context with other studies



Stahel, et al. ECC 2015

T790M resistance – C797S Mutation

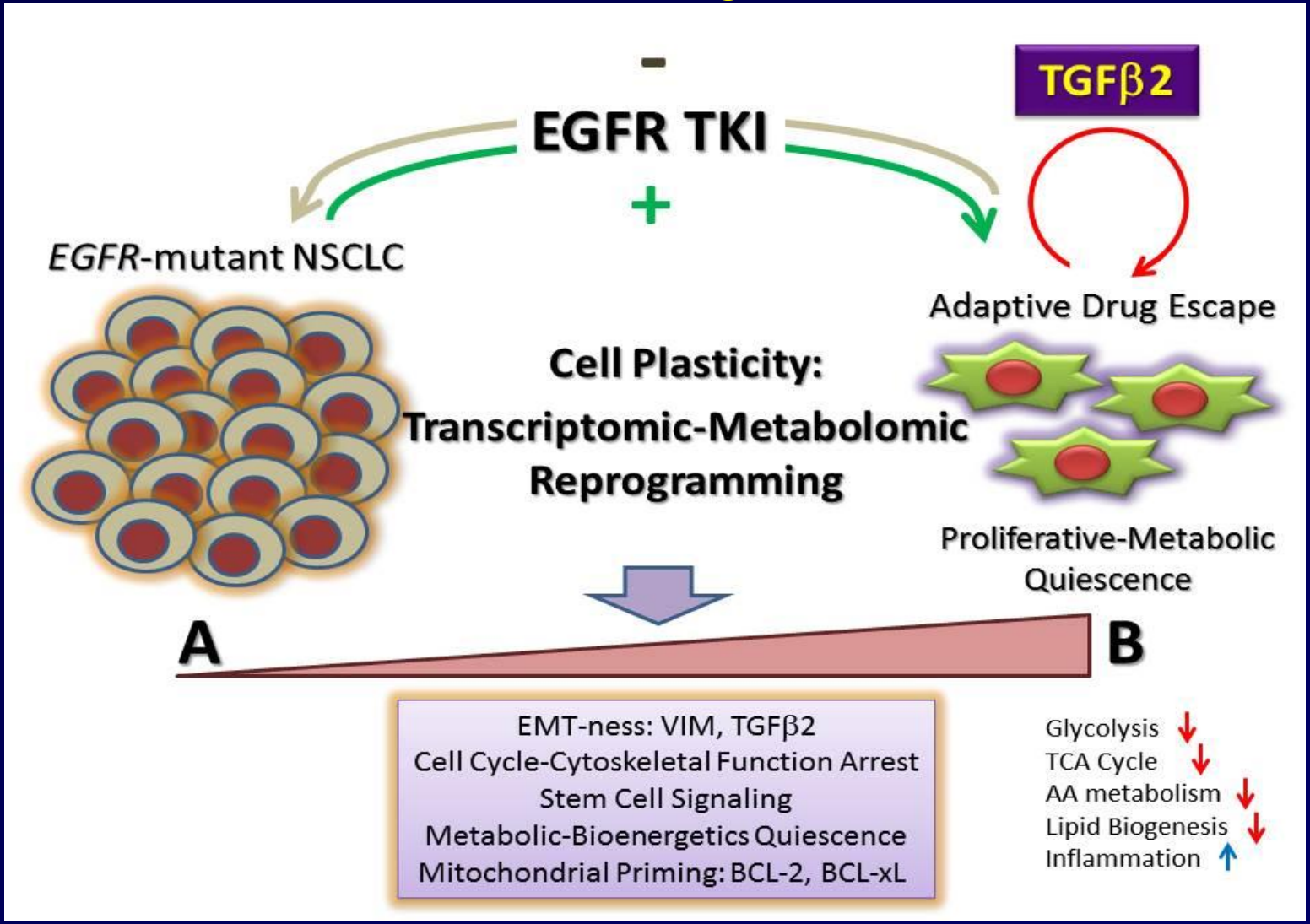


Acquired Resistance to AZD9291 and Increased Dependence on RAS Signaling in Preclinical Models

- NRAS mutations, including a novel E63K mutation, and gain of copy number of WT NRAS or WT KRAS can occur in cells resistant to gefitinib, afatinib, WZ4002, or AZD9291
- Compared with parental cells, a number of resistant cell populations were more sensitive to inhibition by the MEK inhibitor selumetinib (AZD6244; ARRY-142886) when treated in combination with the originating EGFR inhibitor
- In vitro, AZD9291 plus selumetinib prevented emergence of resistance in PC9 cells and delayed resistance in NCI-H1975 cells
- In vivo, concomitant AZD9291 and selumetinib caused regression of AZD9291-resistant tumors in an EGFRm/T790M transgenic model.

Eberlein et al, Cancer Res, 2015

Transcriptome-Metabolome Reprogramming of *EGFR*-mutant NSCLC Contributes to Early Adaptive Drug-Escape via BCL-xL Mitochondrial Priming



Presentation No. MINI09.02 : **Transcriptome-metabolome reprogramming of *EGFR*-mutant NSCLC contributes to early adaptive drug-escape via BCL-xL mitochondrial priming – *Patrick C Ma***

T790M Targeted Therapy Resistance

- EGFR(T790M) gatekeeper mutation resistance
  - selection of pre-existing EGFR(T790M)-positive clones
  - genetic evolution of initially EGFR(T790M)-negative
- those that evolve from drug-tolerant cells had a diminished apoptotic response to third-generation EGFR inhibitors
- Navitoclax, an inhibitor of BCL-xL and BCL-2 restores sensitivity

Hata AN et al, Nat Med, 2016

Inhibiting tankyrase prevents EMT and synergizes with EGFR-inhibition in NSCLC lines

- **Tankyrase inhibition stabilises Axin, reduces ß-catenin-dependent transcription and can prevent Wnt-driven EMT**
- **Inhibition of tankyrase enhances growth inhibition mediated by EGFR-inhibition in cell lines with a Wnt-responsive phenotype *in vitro* and *in vivo***
- ***Suggest tankyrase as a possible target in the subset of NSCLC with known dependencies on signaling through the canonical Wnt pathway***

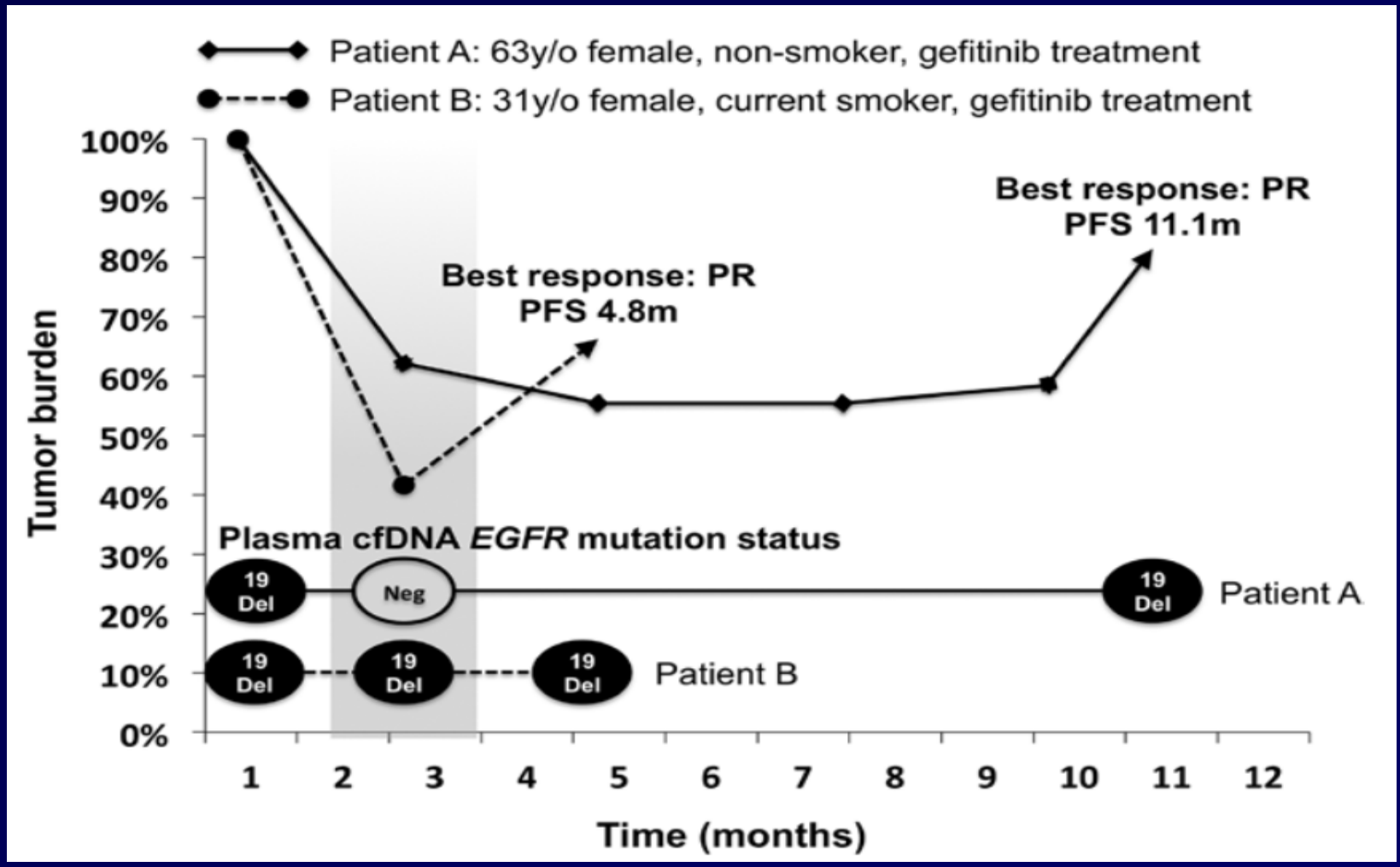
Other Mechanisms

- Loss of T790M expression;
- Met amplification
- BRAFV600E mutation
- HER Amplification
- PIK3CA mutations

Combination with PD1/PDL1 Agents

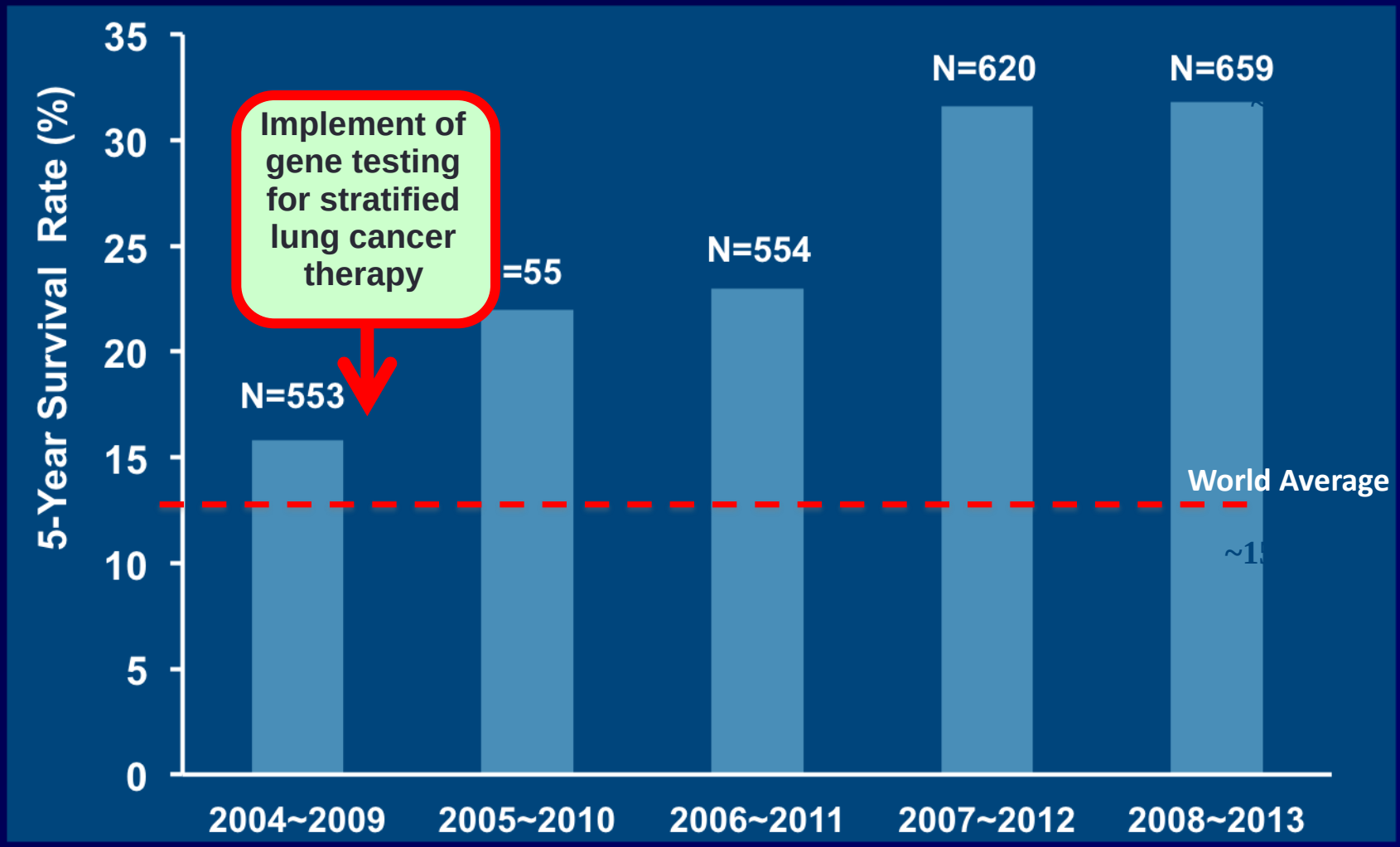
- Responses seen with combination
- Significant toxicity
  - Pneumonitis in 3/23 patients reported (to be presented here)
  - CAURAL study held

Monitoring of Tumor Response to EGFR-TKI by ctDNA



Tseng JS et al. JTO 2015

NSCLC 5-Year Survival (All Stages, NTUH)



Yang PC et al

Physician's Dilemma…..

so much to choose from but which one and for which patient?!