EGFR-TKIs for metastatic NSCLC

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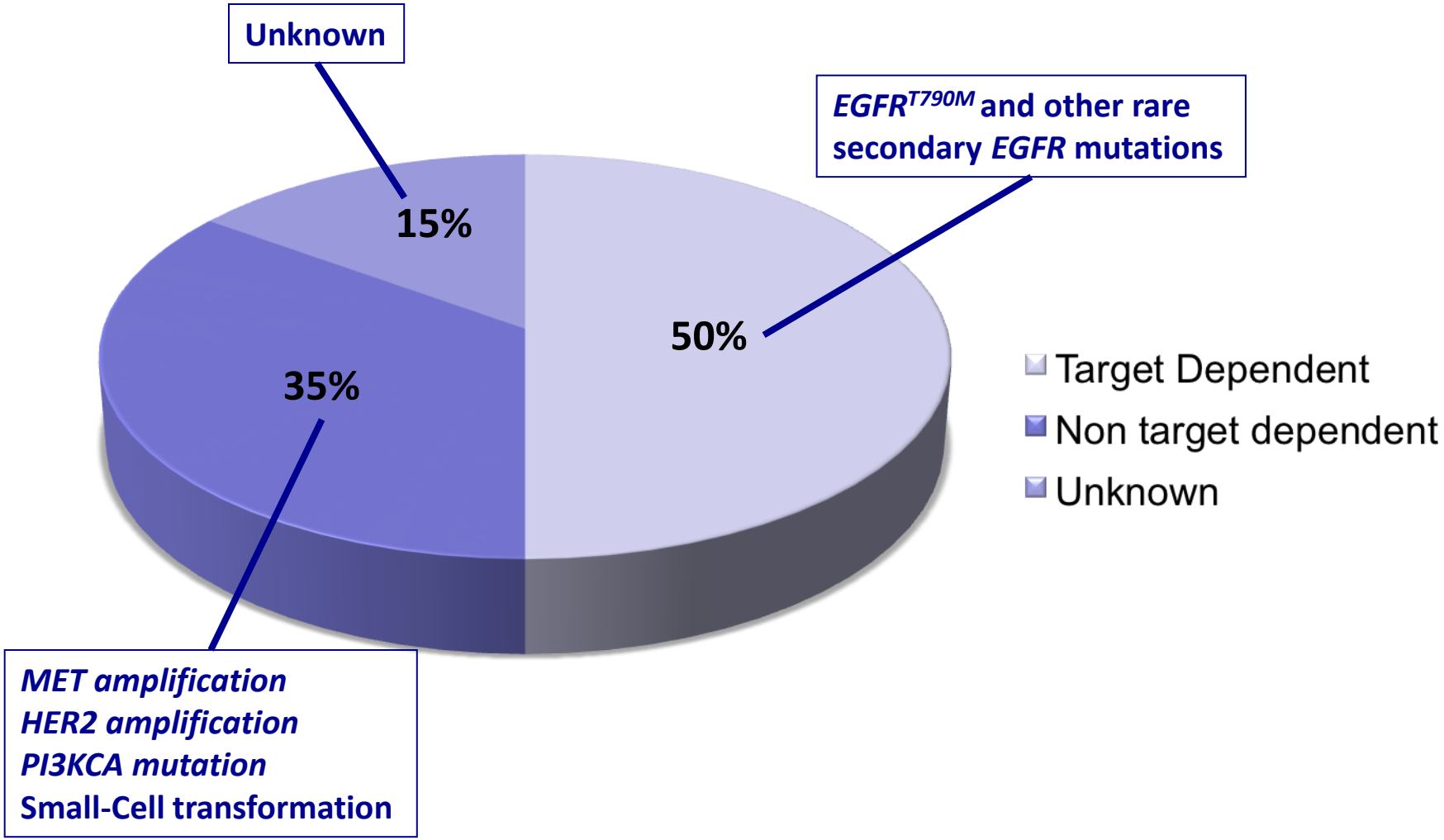
Studies of EGFR TKIs versus chemotherapy as first-line therapy in *EGFR*$^{mut+}$ NSCLC

Study	#	Treatment	RR %	PFS		OS	
				mPFS (mos)	HR P-value	mOS (mos)	HR P-value
IPASS *	97	Gefitinib	71.2	9.5	0.48	21.6	1.00
	111	CBDCA + TXL	47.3	6.3	<0.0001	21.9	0.99
First SIGNAL *	159	Gefitinib	84.6	8.0	0.54	27.2	1.04
	150	CDDP+ GEM	37.5	6.3	0.008	25.6	NR
WJTOG 3405	88	Gefitinib	62.1	9.2	0.48	36.0	1.18
	89	CDDP + TXT	32.2	6.3	<0.001	39.0	NR
NEJ 002	114	Gefitinib	73.7	10.4	0.36	27.7	0.89
	114	CBDCA + TXL	30.7	5.5	<0.001	26.6	0.48
OPTIMAL	82	Erlotinib	83.0	13.1	0.16	22.6	1.06
	72	CBDCA + GEM	36.0	4.6	<0.0001	28.8	0.68
EURTAC	84	Erlotinib	54.5	9.4	0.34	19.3	1.04
	82	Platinum Doublet	10.5	5.2	<0.0001	19.5	0.87
ENSURE	110	Erlotinib	68.2	11.1	0.43	NR	NR
	107	CDDP + GEM	39.3	5.7	<0.0001	NR	NR
LUX Lung 3	230	Afatinib	56.0	11.1	0.58	16.6	1.12
	115	CDDP + PEM	23.0	6.9	0.0004	14.8	0.60
LUX Lung 6	242	Afatinib	66.9	11.0	0.28	22.1	0.95
	122	CDDP + GEM	23.0	5.6	<0.0001	22.2	0.76

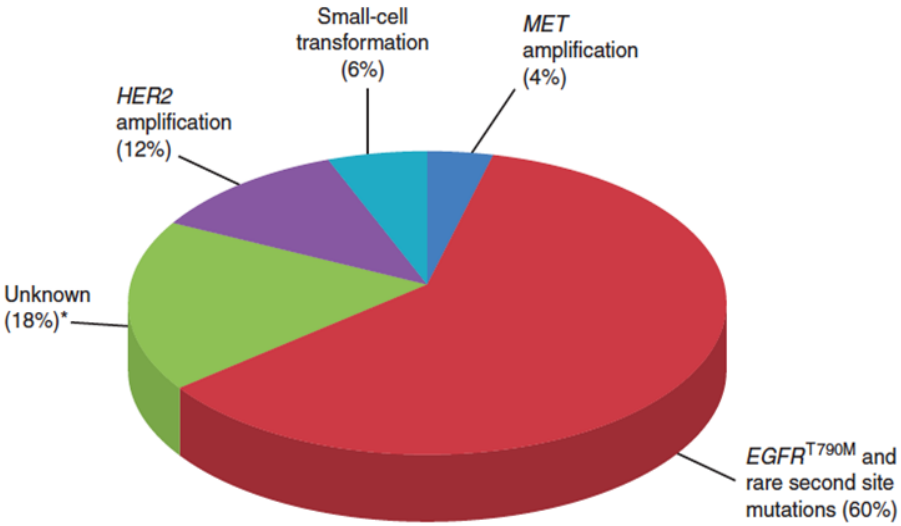
* Shown data are restricted to *EGFR*$^{mut+}$ population

Mechanisms of acquired resistance to first-generation EGFR-TKIs



Overcoming Acquired Resistance in *EGFR* $^{T790M+}$

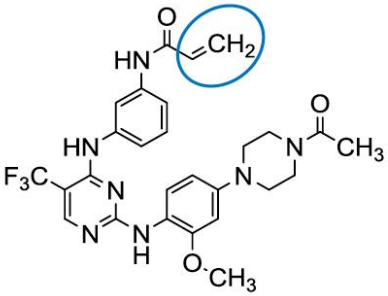
EGFR-TKI resistance

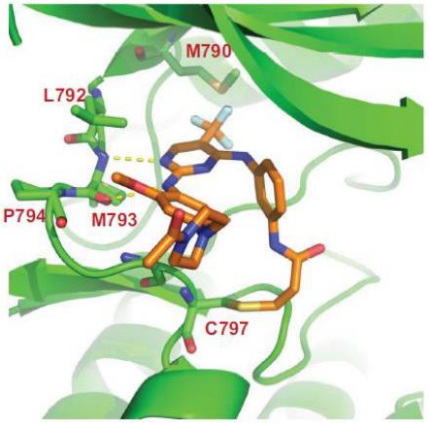


Takezawa et al. Cancer Discovery 2012

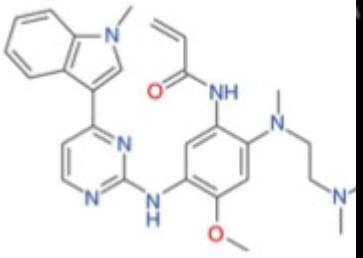
Rociletinib

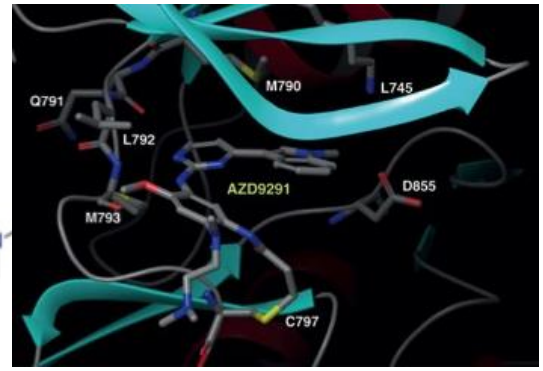
rociletinib (CO-1686)



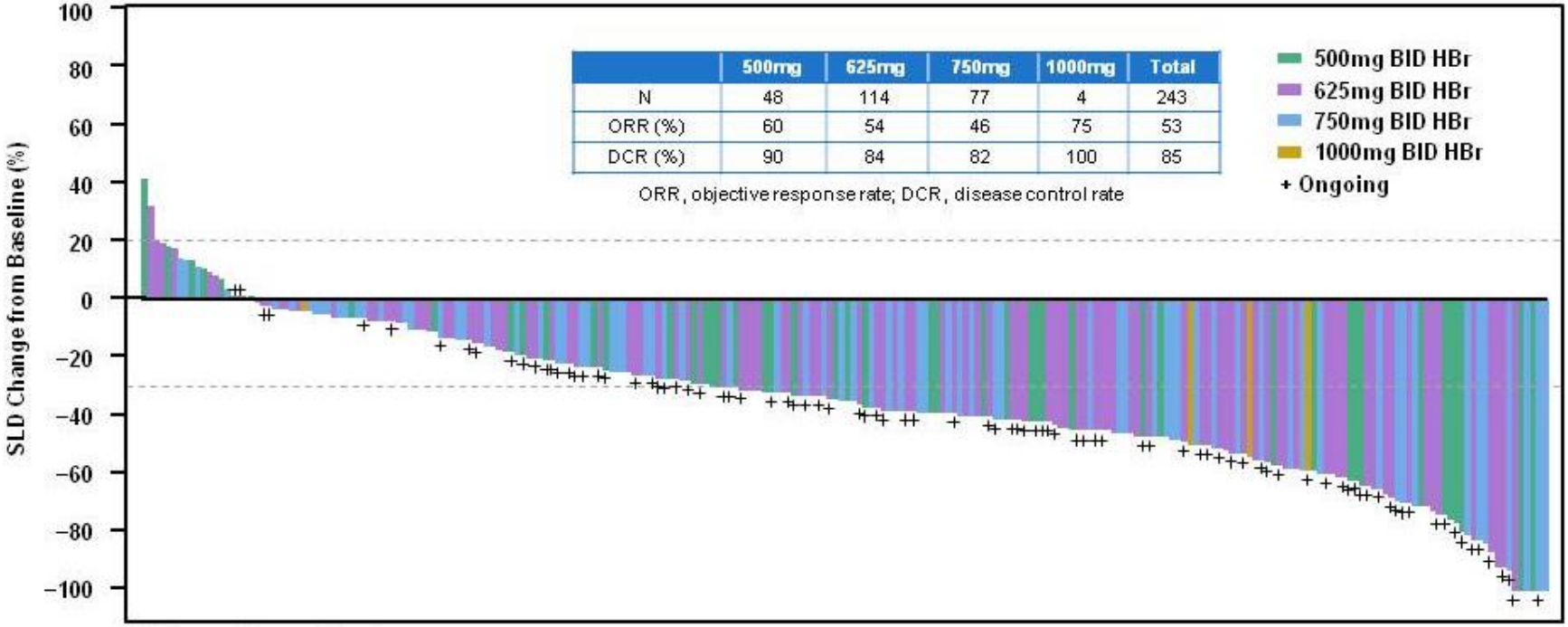


Mereletinib





Best response to rociletinib in 243 centrally confirmed *T790M+* patients



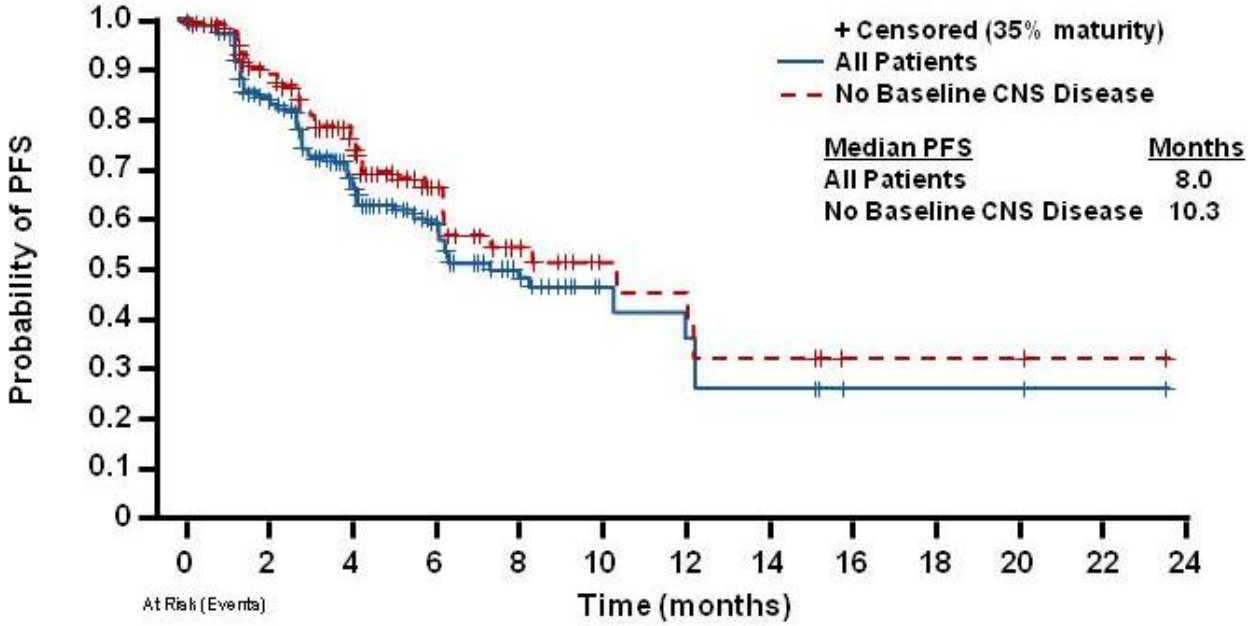
	500mg	625mg	750mg	1000mg	Total
N	48	114	77	4	243
ORR (%)	60	54	46	75	53
DCR (%)	90	84	82	100	85

ORR, objective response rate; DCR, disease control rate

SLD, sum of longest diameters

Sequist L, et al. ASCO 2015

PFS in 270 centrally confirmed *T790M+* patients

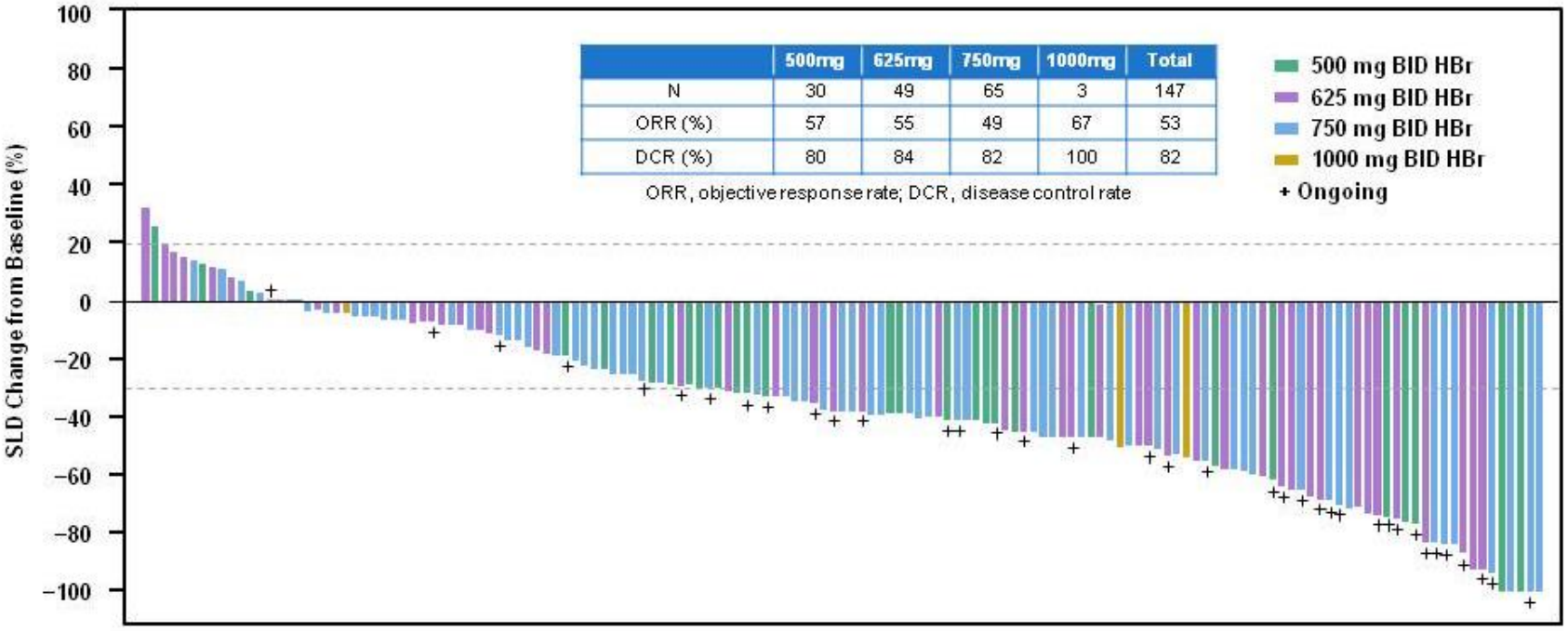


At Risk (Events)

All patients	270 (0)	187 (39)	104 (71)	57 (80)	29 (89)	9 (90)	8 (92)	5 (94)	2 (94)	2 (94)	2 (94)	1 (94)	0 (94)
No baseline CNS disease	163 (0)	118 (16)	68 (32)	37 (38)	20 (44)	8 (45)	7 (47)	5 (48)	2 (48)	2 (48)	2 (48)	1 (48)	0 (48)

Sequist L, et al. ASCO 2015

Best response to rociletinib in plasma *T790M+* patients



	500mg	625mg	750mg	1000mg	Total
N	30	49	65	3	147
ORR (%)	57	55	49	67	53
DCR (%)	80	84	82	100	82

ORR, objective response rate; DCR, disease control rate

SLD, sum of longest diameters

Sequist L, et al. ASCO 2015

T790M plasma testing is a viable alternative to tissue testing

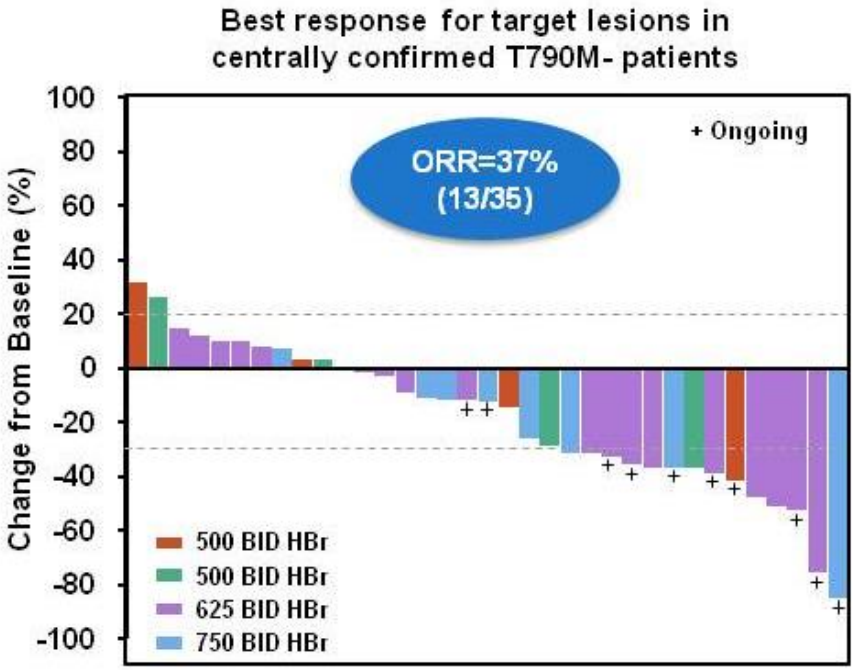
Objective response rate for 188 evaluable patients with both central T790M tissue test result and plasma T790M result

		Plasma T790M		
		+	-	
Tissue T790M	+	55% (72/130)	43% (13/30)	53% (85/160)
	-	35% (6/17)	27% (3/11)	32% (9/28)
		53% (78/147)	39% (16/41)	

- Similar ORR observed when detecting T790M in either tissue or plasma
- Not all patients with progression on first-line TKI are candidates for tissue re-biopsy

Sequist L , et al. ASCO 2015

Rociletinb activity observed in central *T790M* negative patients



Hypotheses to explain this activity

1. Tissue heterogeneity
2. Assay sensitivity
3. IGF1-R/IR activity
4. TKI retreatment effect
   - 86% patients directly off TKI

Sequist L, et al. ASCO 2015

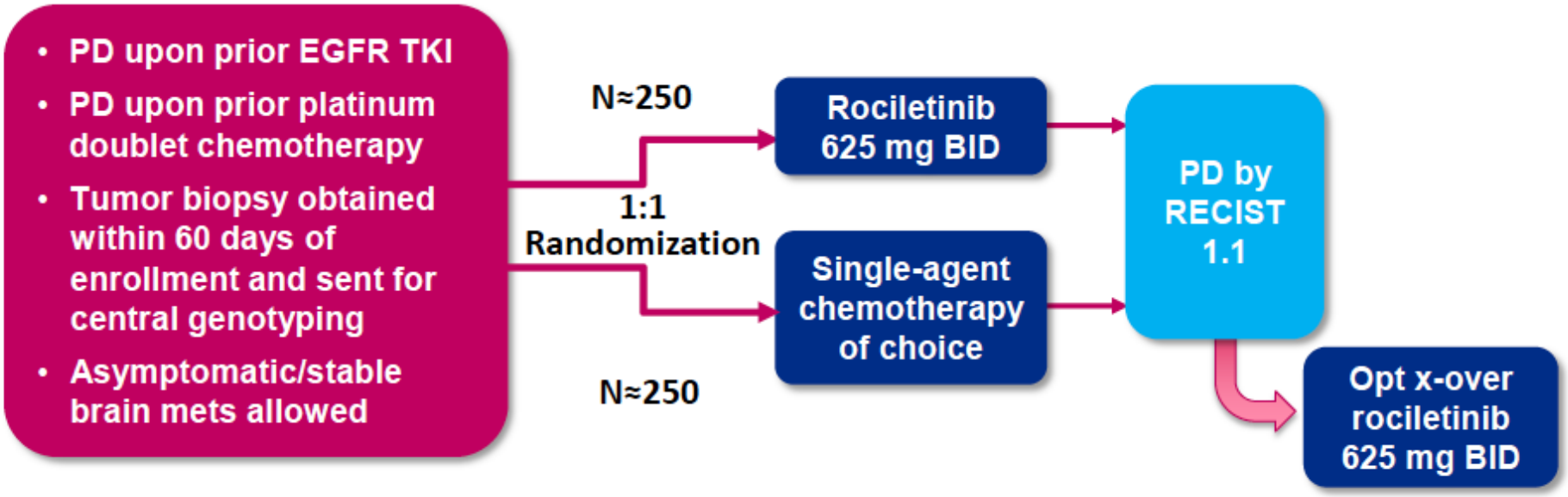
Treatment-related AEs occurring in patients receiving Rociletinib at therapeutic dose

Event	Any Grade	Grade 1	Grade 2	Grade 3
		number (percent)		
Hyperglycemia†	43 (47)	14 (15)	9 (10)	20 (22)
Nausea	32 (35)	16 (17)	14 (15)	2 (2)
Fatigue	22 (24)	9 (10)	9 (10)	4 (4)
Diarrhea	20 (22)	16 (17)	4 (4)	0
Decreased appetite	18 (20)	10 (11)	7 (8)	1 (1)
Vomiting	13 (14)	9 (10)	2 (2)	2 (2)
QTc prolongation	11 (12)	3 (3)	3 (3)	5 (5)
Muscle spasms	10 (11)	9 (10)	0	1 (1)

Sequist L, et al. NEJM 2015

TIGER 3 trial design

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



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

Mets=metastases; PD=progressive disease.

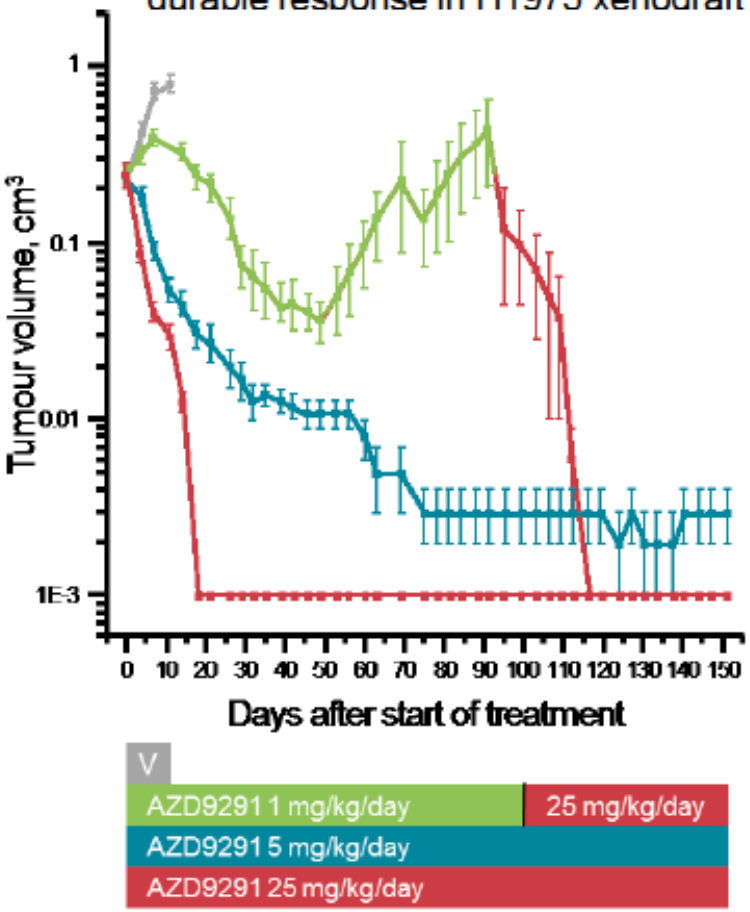
Soria JC, et al. Chicago 2014

AZD9291: another irreversible EGFR-TKI potentially effective against T790M

- AZD9291 is a potent oral, irreversible inhibitor of *EGFR* that contains EGFR-TKI-sensitising (*EGFR*m+) and resistance mutations (T790M)
- Good potency and high selectivity demonstrated in enzymatic and cellular *in vitro* assays

Model	Wild-type LoVo cells	*EGFR*m+ PC9 cells	*EGFR*m+/ T790M H1975 cells
AZD9291 phospho-EGFR IC_{50} µM	0.480	0.017	0.0115

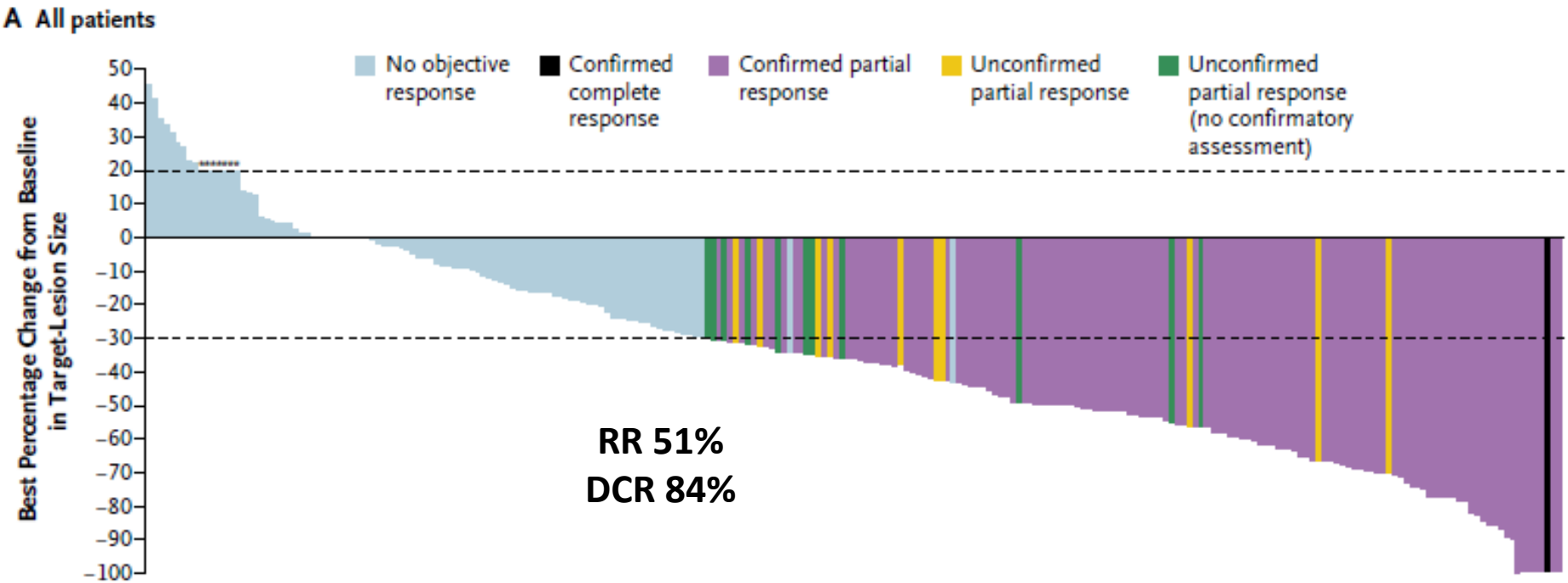
AZD9291 achieved complete and durable response in H1975 xenograft



AstraZeneca data on file

V, vehicle

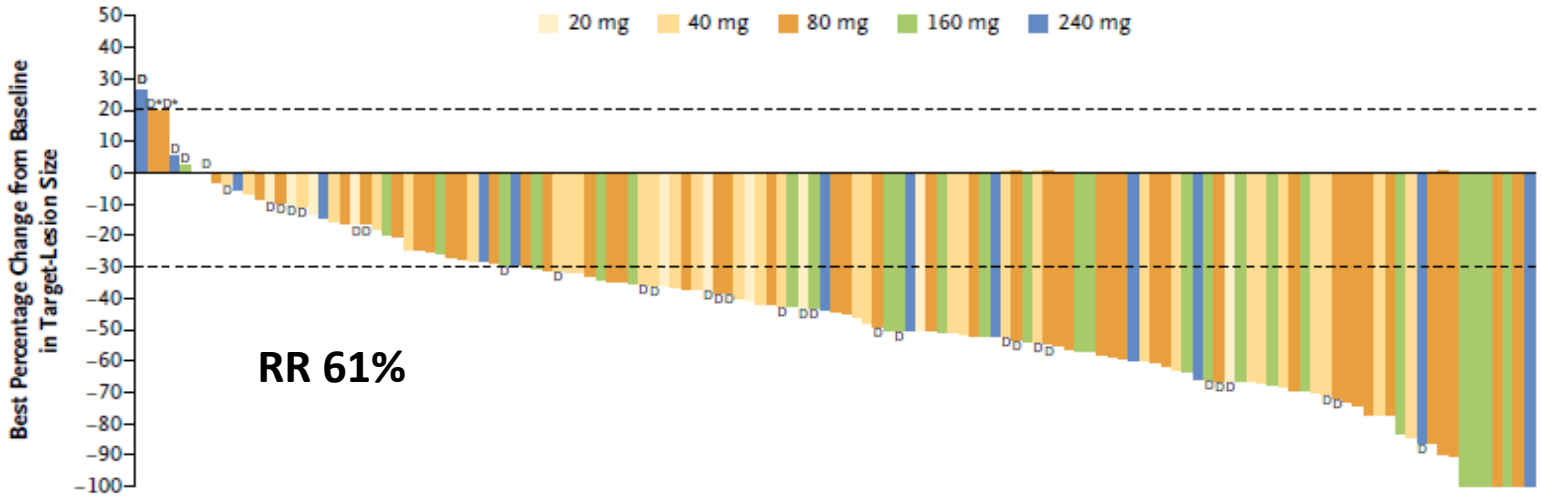
Activity of AZD9291 in overall study population



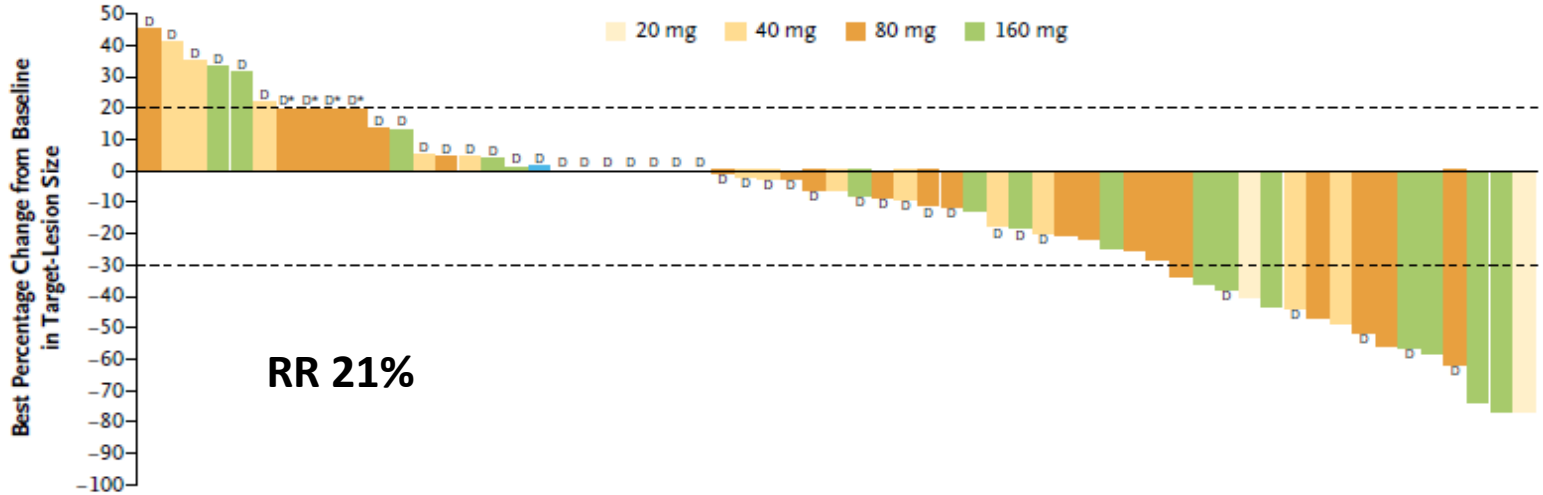
Janne PA, et al. NEJM 2015

Activity of AZD9291 according to *EGFR* ^{T790M} status

EGFR $^{T790M+}$

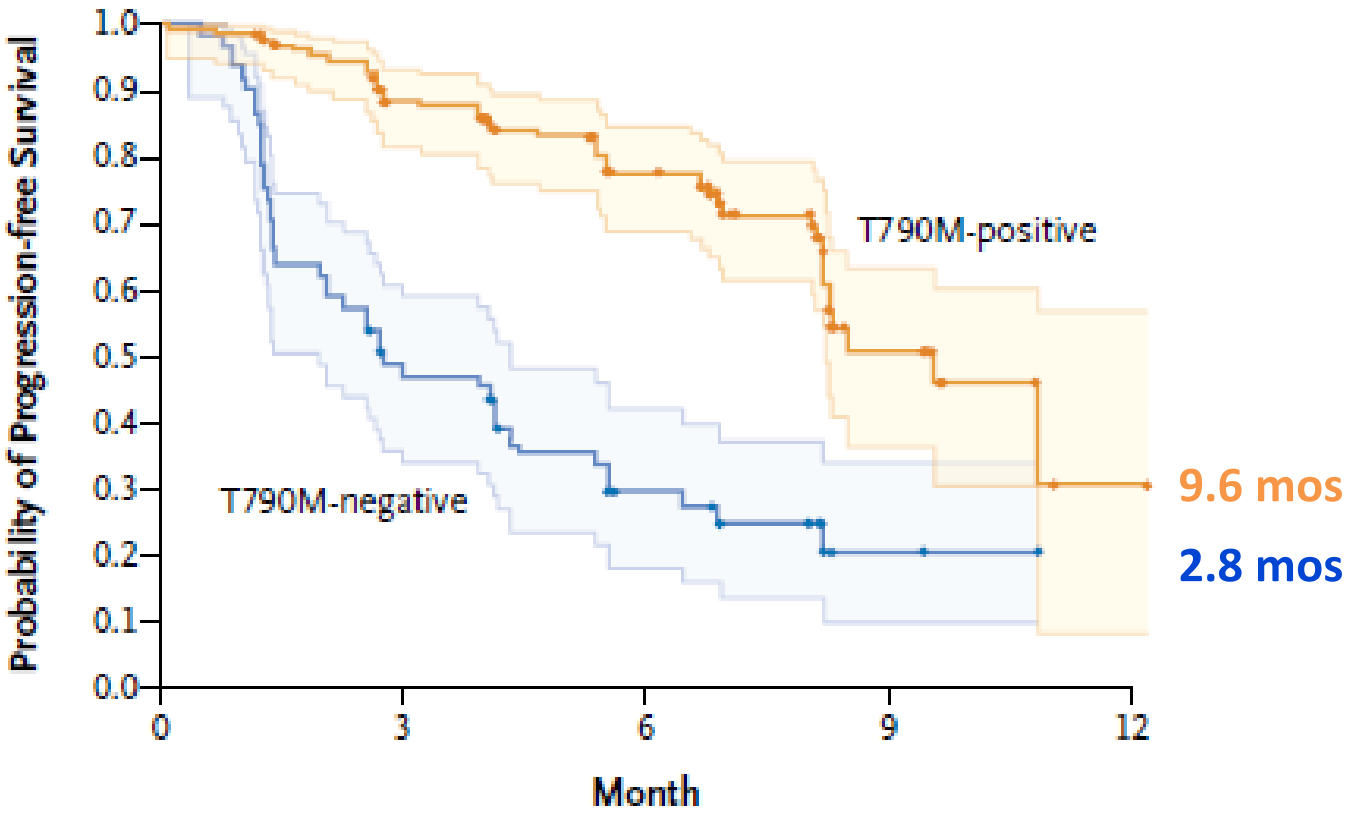


EGFR $^{T790M-}$



Janne PA, et al. NEJM 2015

PFS with AZD9291 according to *EGFR* ^{T790M} status



Janne PA, et al. NEJM 2015

AZD9291 Toxicity Profile

Event	20 mg (N=21)	40 mg (N=58)	80 mg (N=90)	160 mg (N=63)	240 mg (N=21)	Total (N=253)
	number of patients (percent)					
Diarrhea						
Any grade	5 (24)	24 (41)	30 (33)	43 (68)	16 (76)	118 (47)
Grade 3–5	0	1 (2)	1 (1)	1 (2)	1 (5)	4 (2)
Rashes and acne‡						
Any grade	5 (24)	13 (22)	29 (32)	40 (63)	15 (71)	102 (40)
Grade 3–5	0	0	0	2 (3)	0	2 (1)
Nausea						
Any grade	3 (14)	10 (17)	16 (18)	19 (30)	7 (33)	55 (22)
Grade 3–5	1 (5)	0	0	0	0	1 (<0.5)
Decreased appetite						
Any grade	7 (33)	11 (19)	14 (16)	16 (25)	6 (29)	54 (21)
Grade 3–5	1 (5)	0	1 (1)	0	0	2 (1)
Dry skin						
Any grade	2 (10)	9 (16)	10 (11)	25 (40)	5 (24)	51 (20)
Grade 3–5	0	0	0	0	0	0
Pruritus						
Any grade	2 (10)	11 (19)	15 (17)	12 (19)	7 (33)	47 (19)
Grade 3–5	0	0	0	0	0	0

Janne PA, et al. NEJM 2015

Practical questions with EGFR-TKIs

What is the best inhibitor ?

Gefitinib versus erlotinib as second line treatment in unselected NSCLC: Phase III trial

- Stage III-IV Adenocarcinoma
- Evaluable disease
- 2° line & after
- Age >20 years
- No interstitial lung disease

→ **R** →

Erlotinib 150 mg/die

Gefitinib 250 mg/die

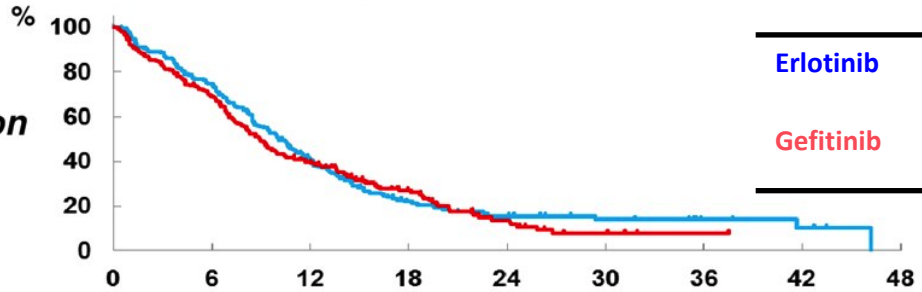
Stratification factors:
Gender, PS, Stage, Smoking history, Mutation status,Institution, Prior regimen

Non-Inferiority trial

Katakami N, et al. ASCO 2014

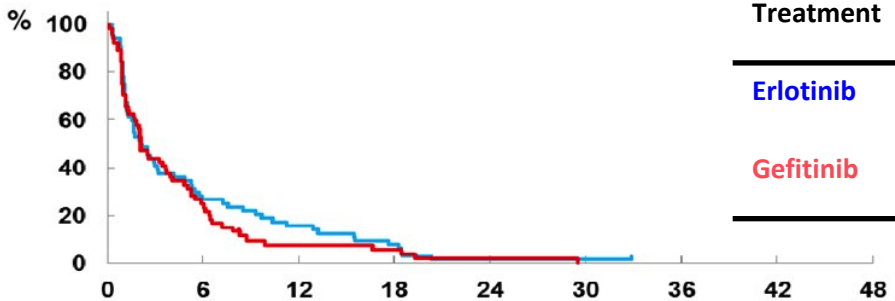
Gefitinib versus Erlotinib: PFS according to EGFR status

***EGFR mutation* (+)**



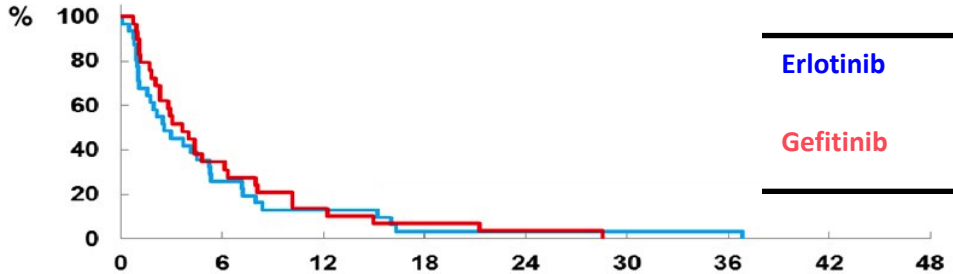
Treatment	mPFS (mos)	p value
Erlotinib	10.09	0.532
Gefitinib	8.90	

***EGFR mutation* (-)**



Treatment	mPFS (mos)	p value
Erlotinib	2.10	0.221
Gefitinib	2.07	

***EGFR mutation* unknown**



Treatment	mPFS (mos)	p value
Erlotinib	2.53	0.878
Gefitinib	2.27	

Katakami N, et al. ASCO 2014

Dacomitinib versus Erlotinib as 2/3 line in NSCLC: the ARCHER1009 trial:

- Advanced or metastatic NSCLC
- 1 or 2 prior chemotherapy lines
- Tissue required
- Measurable Disease

→ **R 1:1**

N=800

→ **Dacomitinib 45 mg/die**

→ **Erlotinib 150 mg/die**

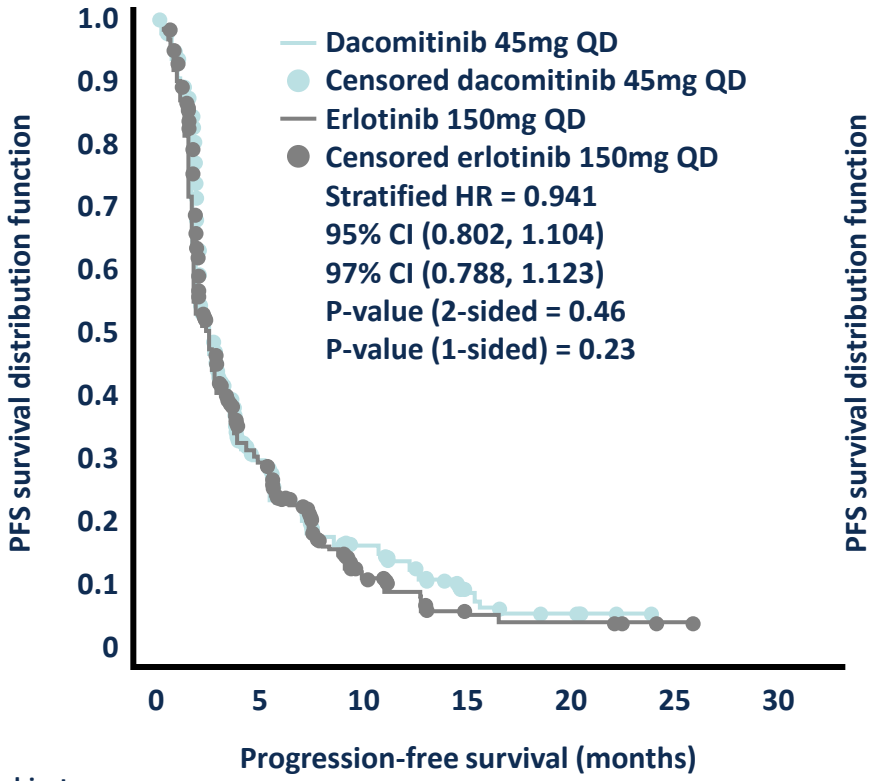
Co-primary end-point2 : PFS in ITT population and *in KRAS wild type* population

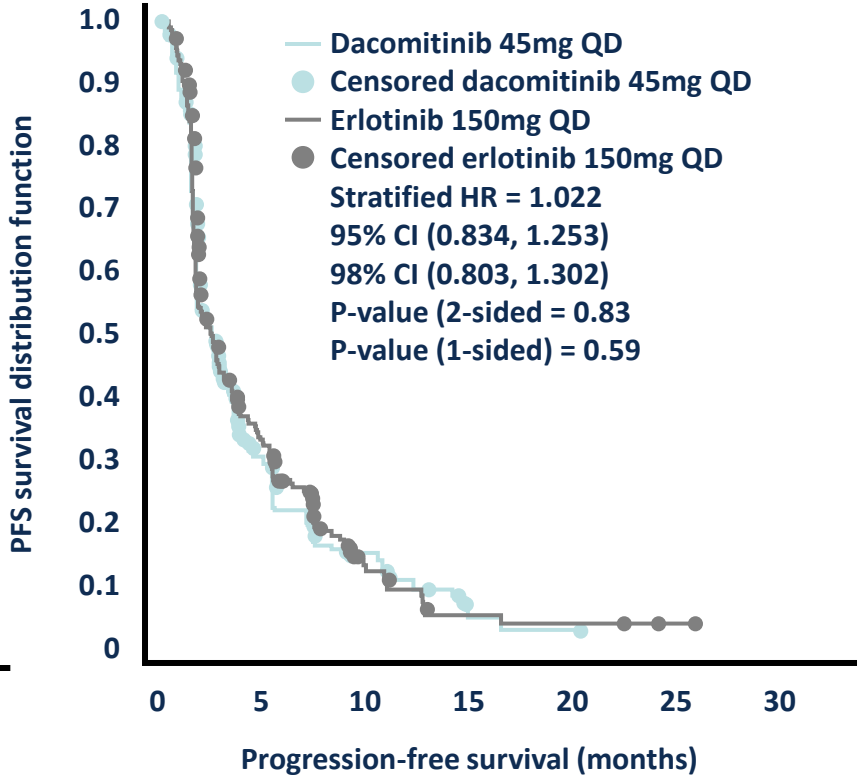
Secondary end points: OS, RR, PFS by Investigators , Safety, PRO

Ramalingam SS, et al. Lancet Oncol 2014

Dacomitinib versus erlotinib:

PFS by independent review in all patients and *KRAS*^{wt} patients





# of subjects at risk													
Dacomitinib	439	88	36	11	5	0	0	256	51	18	3	1	0	0
Erlotinib	439	89	21	5	4	1	0	263	63	14	4	3	1	0

Ramalingam SS, et al. Lancet Oncol 2014

LUX Lung 3 and 6 trials 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

Stratification by EGFR mutation type: Del19/L858R/other
and by race (LUX-Lung 3 only): Asian/non-Asian

Afatinib
40 mg orally once daily

LUX-Lung 3[1]:
Cisplatin + pemetrexed
up to 6 cycles

LUX-Lung 6[2]:
Cisplatin + gemcitabine
up to 6 cycles

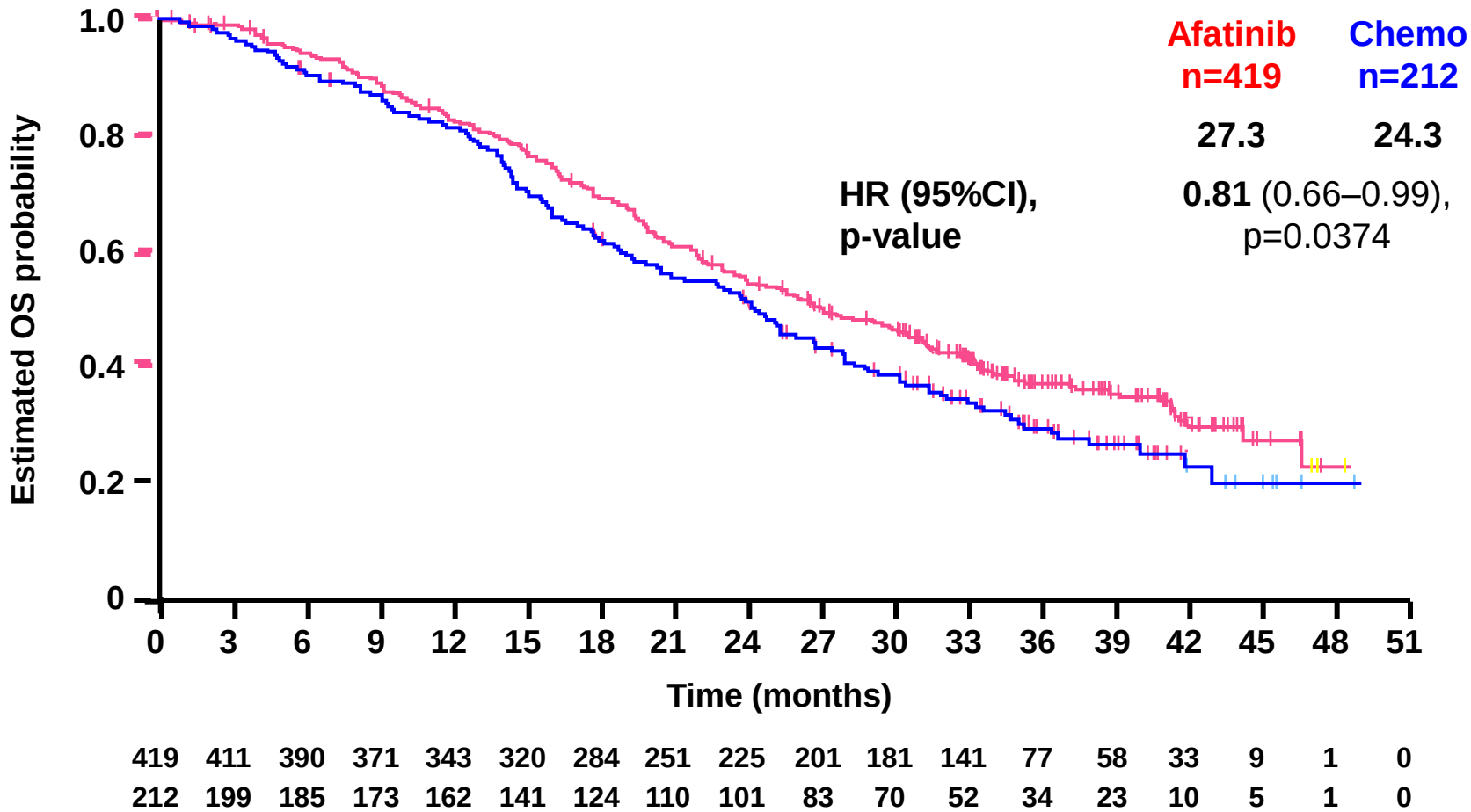
Primary endpoint: PFS (independent review)
Secondary end points: ORR, DCR, OS, PRO, safety

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

1. Sequist et al. *J Clin Oncol*. 2013;31:3327; 2. Wu et al. *Lancet Oncol*. 2014;15:213.

Yang J. et al, Lancet Oncol 2014

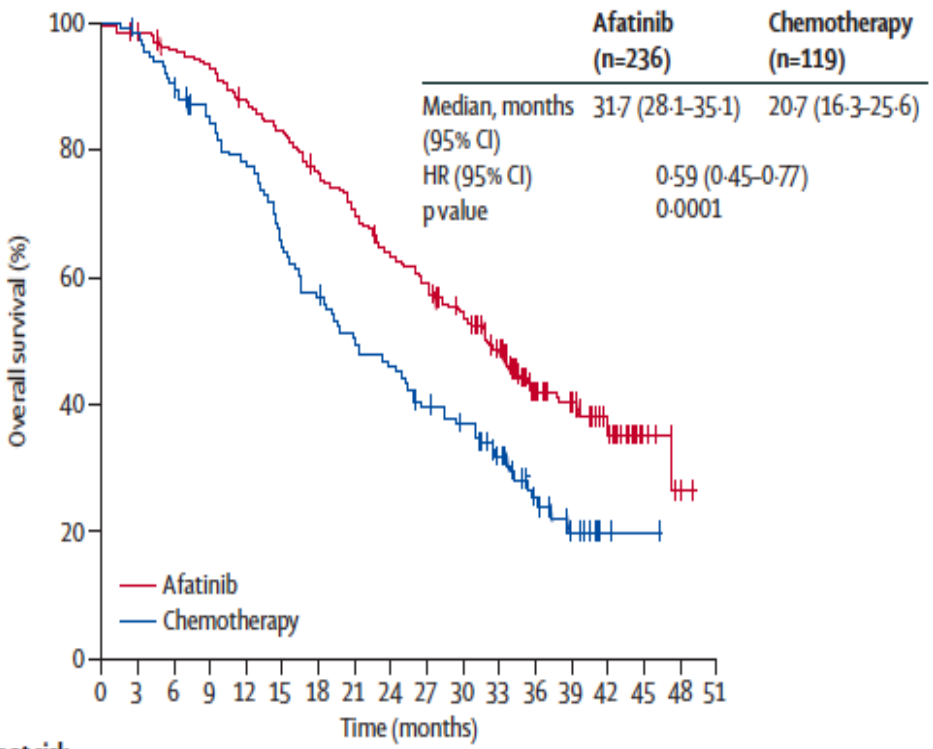
Combined OS analysis: common mutations (n=631)



Yang J. et al, ASCO 2014

Combined OS analysis: mutation categories

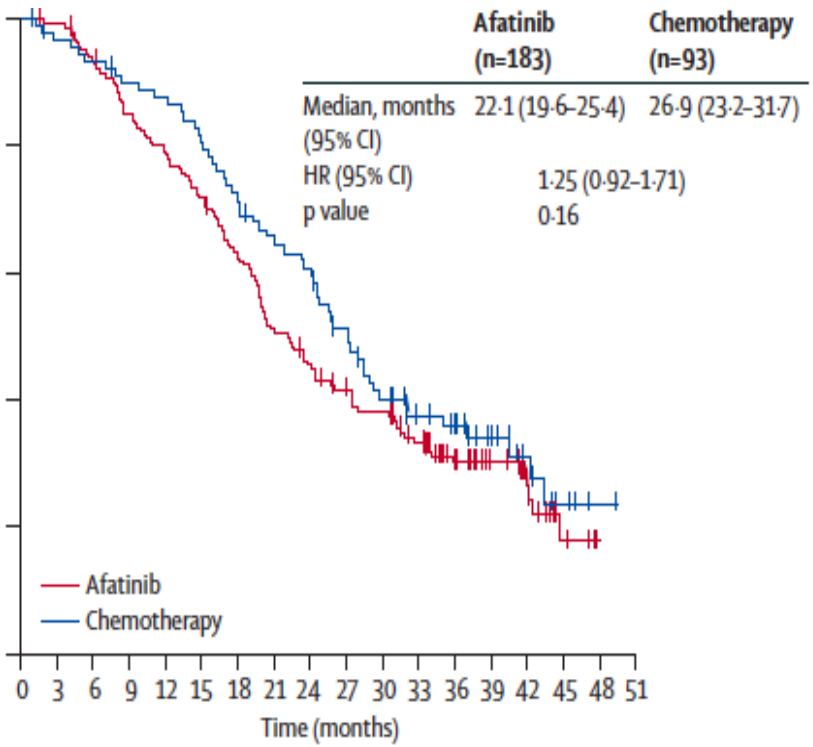
Exon 19



Number at risk

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

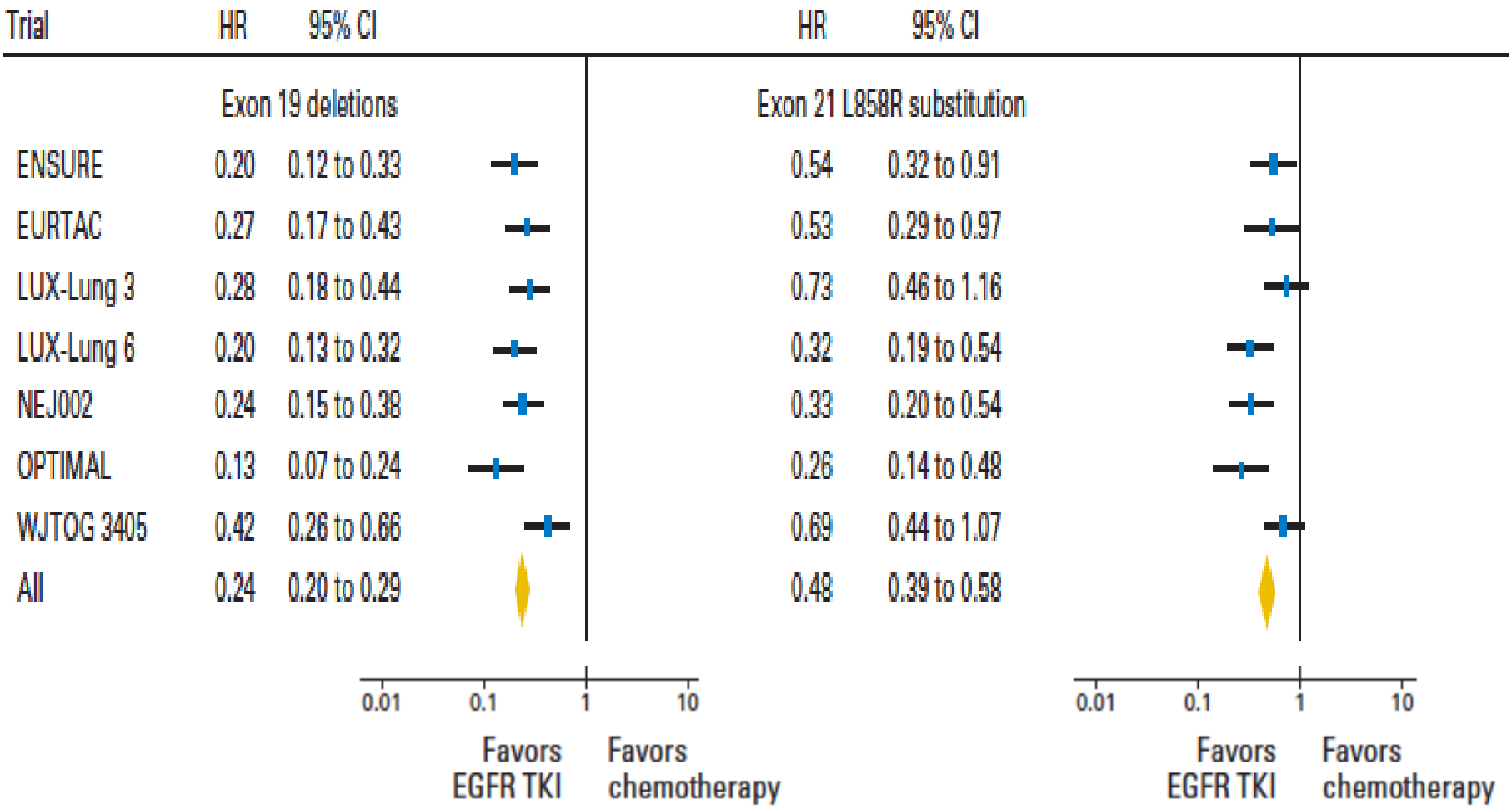
Exon 21



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

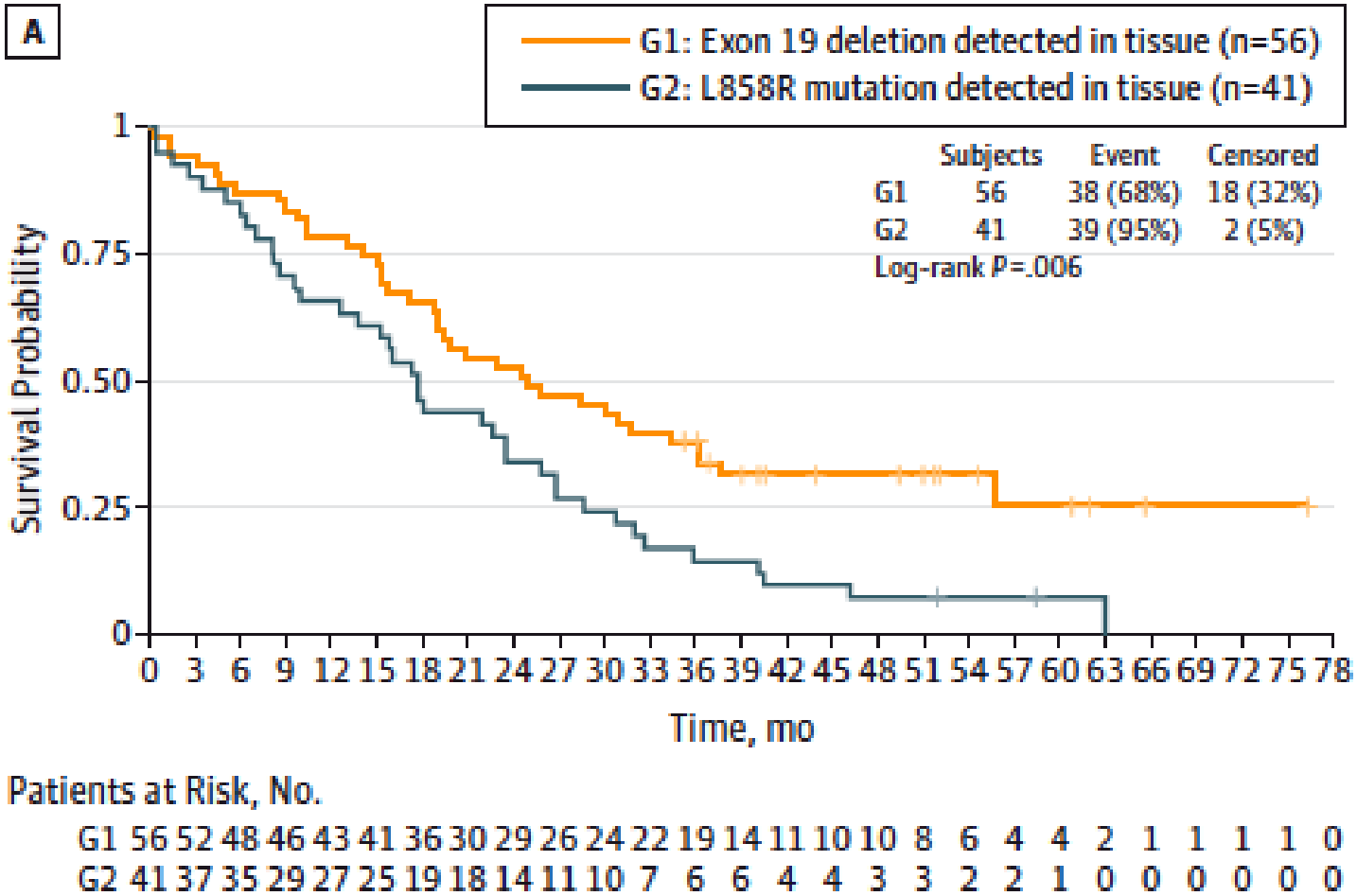
Yang J C-H, et al. Lancet Oncol 2015

All EGFR-TKIs are more effective in patients with *EGFR*^{del19}



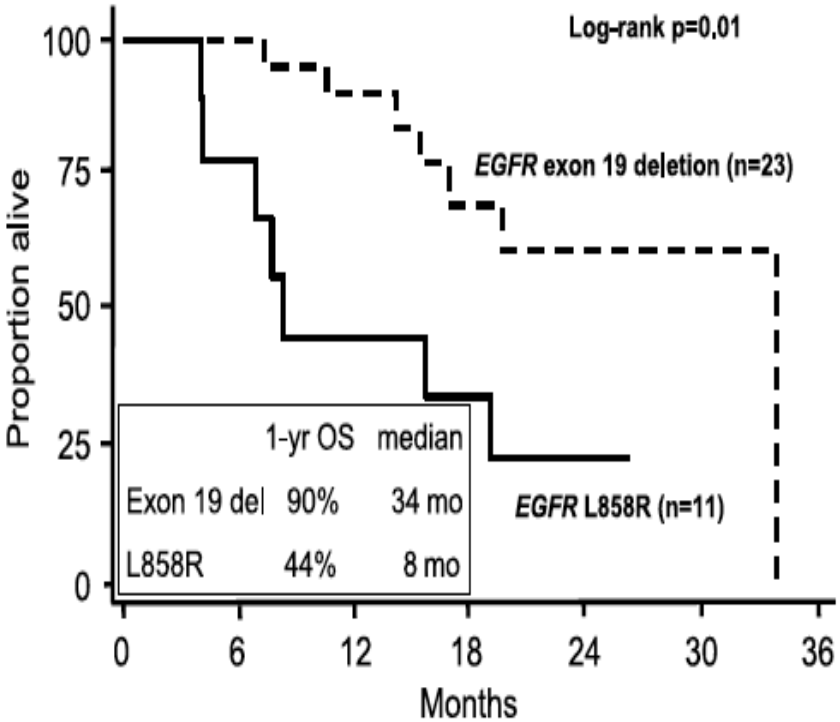
Lee et al. JCO 2015

Prolonged PFS in patients harbouring *EGFR* ^{del19}: Results of the EURTAC trial

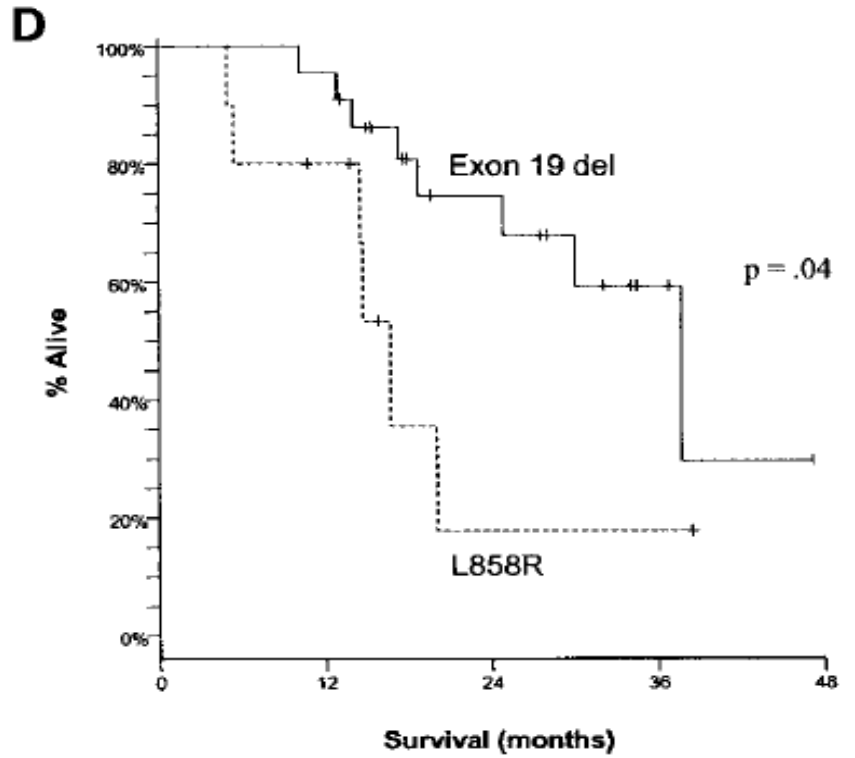


Karachaliou N , et al. JAMA Oncol 2015

EGFR^{del19} is associated with prolonged survival in NSCLC patients treated with erlotinib or gefitinib



Riely G, et al. CCR 2006



	n	1-yr OS	Median
Exon 19 deletion	22	95%	38 months
L858R mutation	10	80%	17 months

Jackman DM, et al . CCR 2006

Indirect comparison of toxicities reported with gefitinib or erlotinib or afatinib

	Gefitinib				Erlotinib		Afatinib	
	IPASS* [48] n = 607	First SIGNAL* [49] n = 159	WJTOG 3405 [50] n = 87	NEJ002 [51] n = 114	OPTIMAL [52] n = 83	EURTAC [53] n = 84	LUX-Lung 3 [54] n = 230	LUX-Lung 6 [55] n = 239
Rash	66.2 (3.1)	72.4 (29.3)	85.0 (2.3)	71.0 (5.3)	73.0 (2)	79.7 (13.0)	89.1 (16.2)	80.8 (14.2)
Diarrhoea	46.6 (3.8)	49.7 (2.5)	54.0 (1.1)	34.2 (0.9)	25.0 (1)	57.1 (5)	95.2 (14.4)	88.3 (5.4)
Fatigue	16.8 (0.3)	28.3 (10.0)	39 (2.2)	10.5 (2.6)	5.0 (0)	57.1 (0)	17.5 (1.3)	10 (0.4)
Anorexia	21.9 (1.5)	44.6 (13.8)	NR	14.9 (5.3)	NR	31 (0)	20.5 (3.1)	10 (1.3)
Stomatitis	17.0 (0.2)	40.2 (1.9)	21.8 (0)	NR	13.0 (1)	NR	72.1 (8.7)	51.9 (5.4)
Paronychia	13.5 (0.3)	NR	32.1 (1.1)	NR	4.0 (0)	NR	56.8 (11.4)	32.6 (0)
Vomiting	12.9 (0.2)	18.9 (0)	NR	NR	1.0 (0)	NR	17.0 (3.1)	9.6 (0.8)

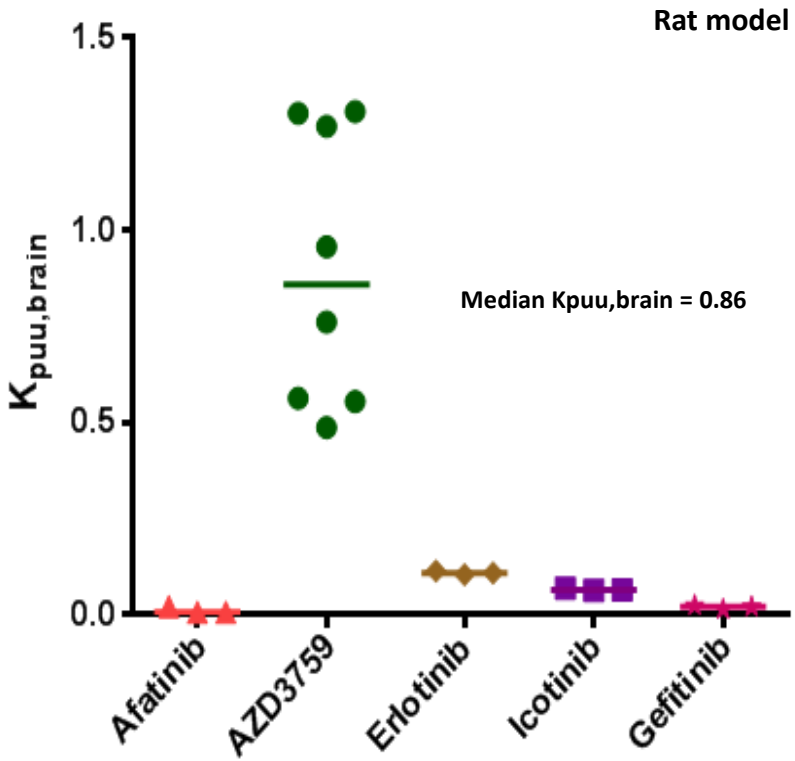
***Shown data include all patients treated with gefitinib**
Data are reported as percentage of AEs of any grade and, in parenthesis, of grade 3

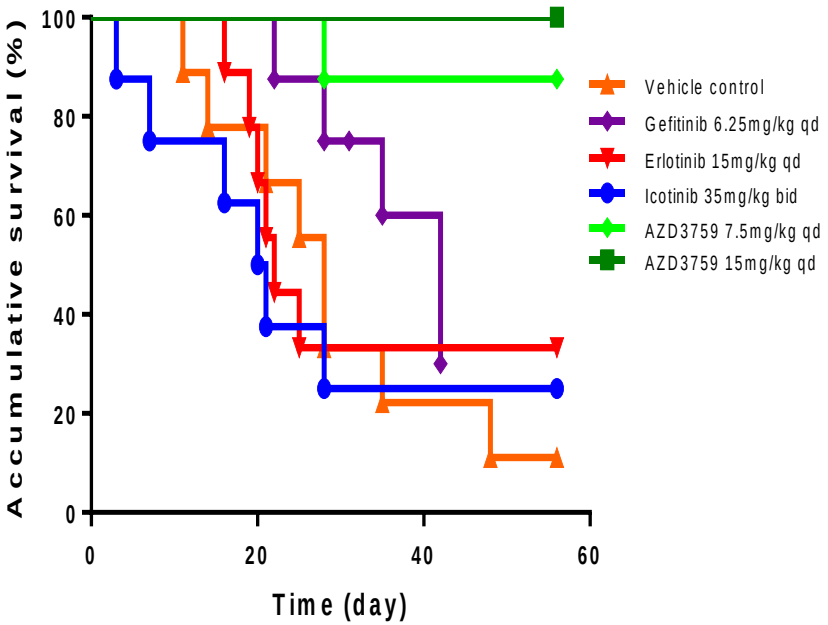
Landi L , Expert Opin Pharmacother 2014

Practical questions with EGFR-TKIs

Do we need new first-generation EGFR-TKIs?

AZD3759 outstanding BBB characteristics





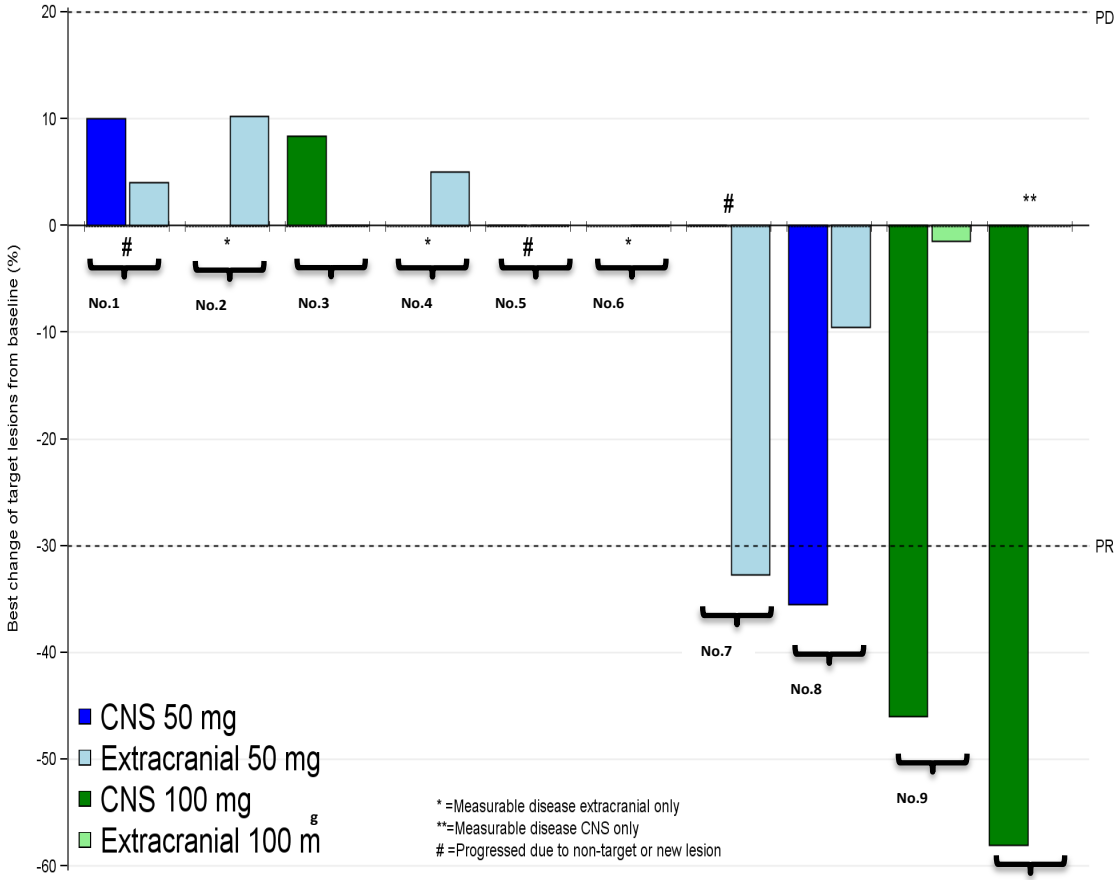
AZD3759 is not a substrate

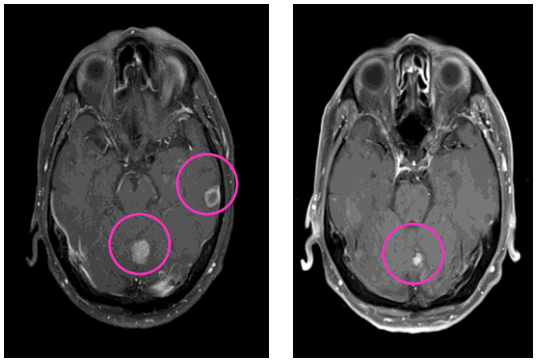
- **of PGP**
- **or BCRP efflux transporters**

Significantly prolonged animal survival in PC-9 BM model, compared with gefitinib, erlotinib, icotinib

Kim DW, et al. ASCO 2015

AZD3759 preliminary clinical data





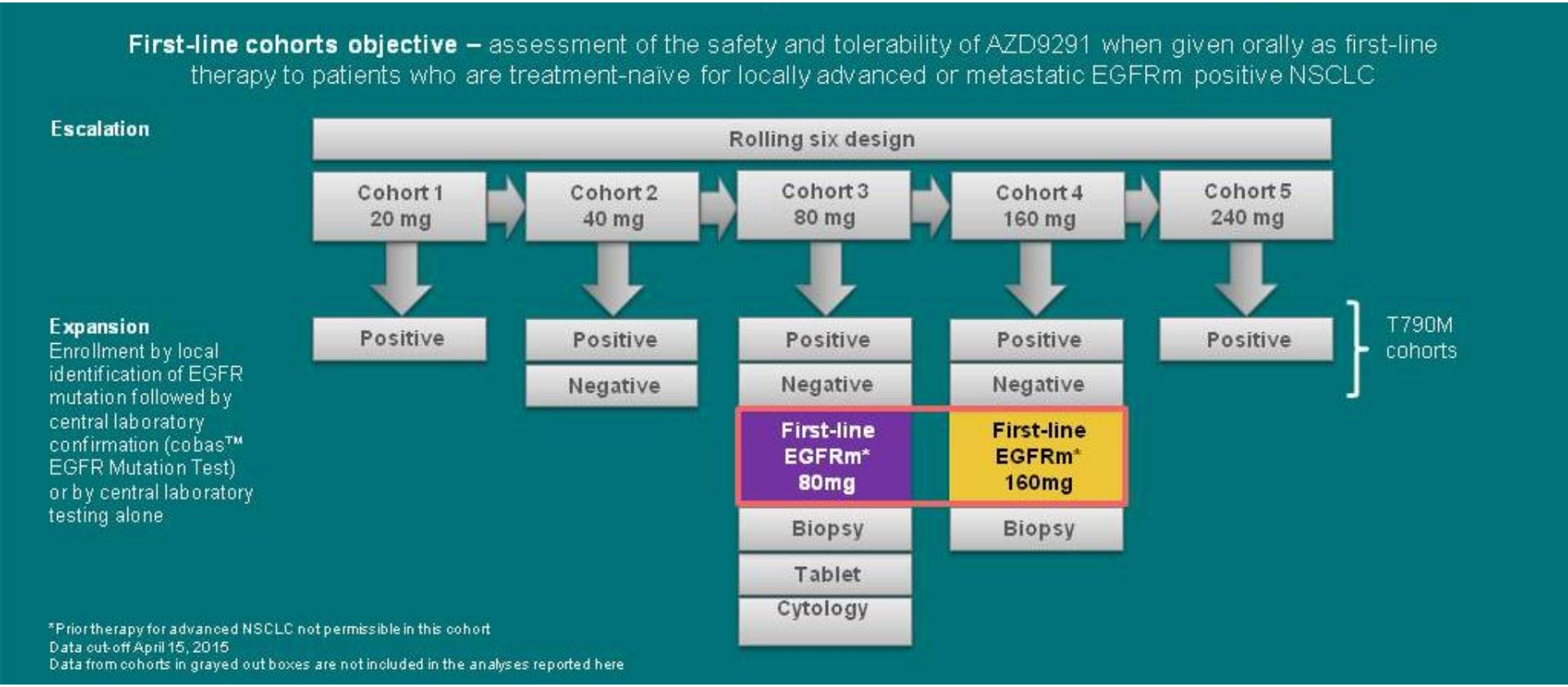
	Cohort			
	50mg bid (n=5)		100mg bid (n=7)	
Grade	1	2	1	2
Skin rash	1	0	3	1
Diarrhea	0	0	1	0
Constipation	0	0	1	0
Fatigue	0	0	1	0

Kim DW, et al. ASCO 2015

Practical questions with EGFR-TKIs

Are third-generation EGFR-TKIs the best option in first-line *EGFR* mutant?

AZD9291: expansion cohort data in first-line setting at two different dose levels



Ramalingam S, et al. , ASCO 2015

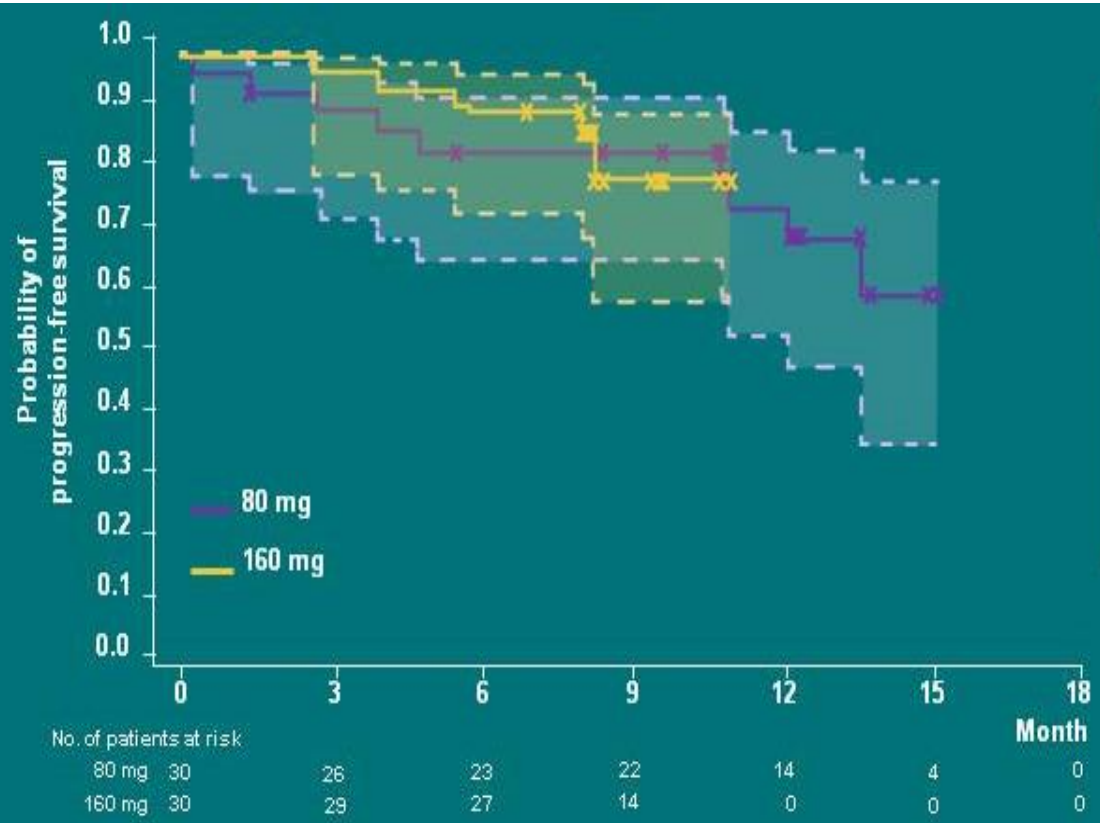
Response to AZD9291 in first-line patients

	80 mg N=30	160 mg N=30	Total N=60
Objective response rate#	**63% (95% CI 44, 80)**	**83% (95% CI 65, 94)**	**73% (95% CI 60, 84)**
Disease control rate	93% (95% CI, 78, 99)	100% (95% CI 88, 100)	97% (95% CI 89, 100)
Best objective response			
Complete response#	0	1	1
Partial response#	19	24	43
Stable disease	9	5	14
Progressive disease	2	0	2

Population: evaluable for response, data cut-off April 15, 2015
Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1), programmatically calculated from investigator-recorded tumor measurement
*Considered a complete response because target lesion <10mm (lymph node) with complete response in non-target-lesions and no new lesions
#Confirmed responses only

Ramalingam S, et al. , ASCO 2015

PFS to AZD9291 in first-line patients



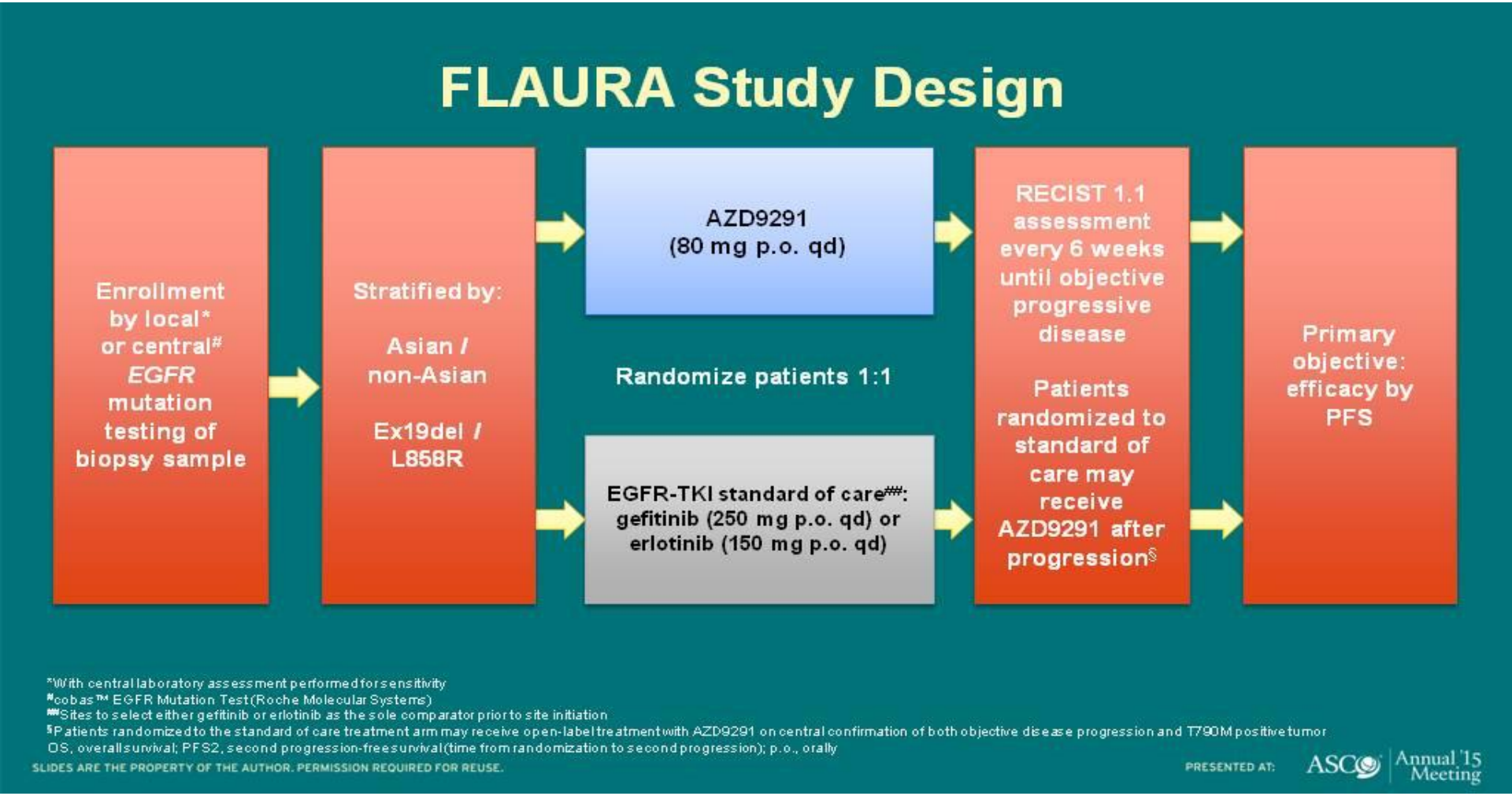
Percentage remaining progression-free,* % (95% CI)	80 mg N=30	160 mg N=30	Total N=60
3 months	90 (72, 97)	97 (79, 100)	93 (83, 97)
6 months	83 (64, 93)	90 (72, 97)	87 (75, 93)
9 months	83 (64, 93)	78 (57, 89)	81 (68, 89)
12 months	73 (51, 87)	NC	72 (55, 84)

Data are too immature to estimate median PFS; only 15 events have occurred

Population: all dosed patients, data cut-off April 15, 2015
NC, not calculable
Progression events that do not occur within 14 weeks of the last evaluable assessment (of first dose) are censored. Crosses indicate censored observations

Ramalingam S, et al. , ASCO 2015

Preliminary data support phase III trial against standard of care



Ramalingam S, et al. ASCO 2015

Molecular mechanisms responsible for acquired resistance to third-generation EGFR-TKIs

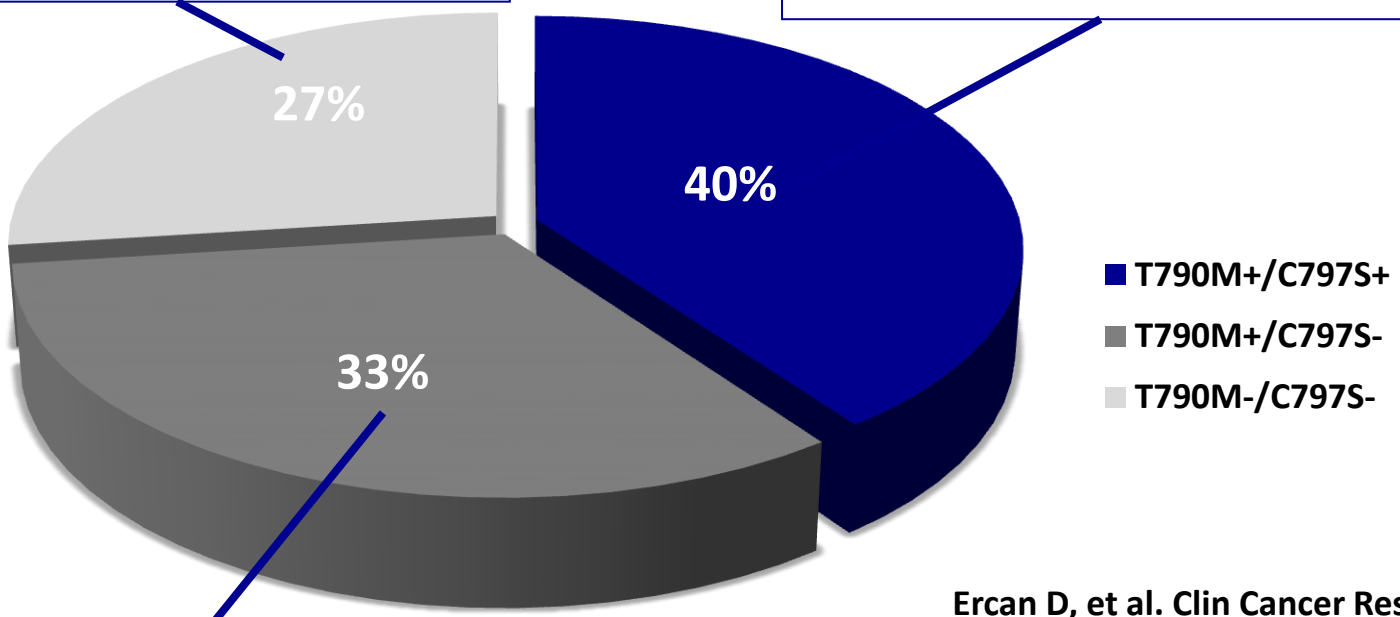
EGFR $^{T790M-}$

- ***Small-cell transformation***
- ***Activation of other pathway (i.e NRAS pathway, MET amplification, FGFR3 mutation)***

EGFR $^{DEL19+/T790M+/C797S+}$

So far reported for AZD9291 only

Resistance to all EGFR-TKIs



EGFR$^{T790M+/C797S-}$

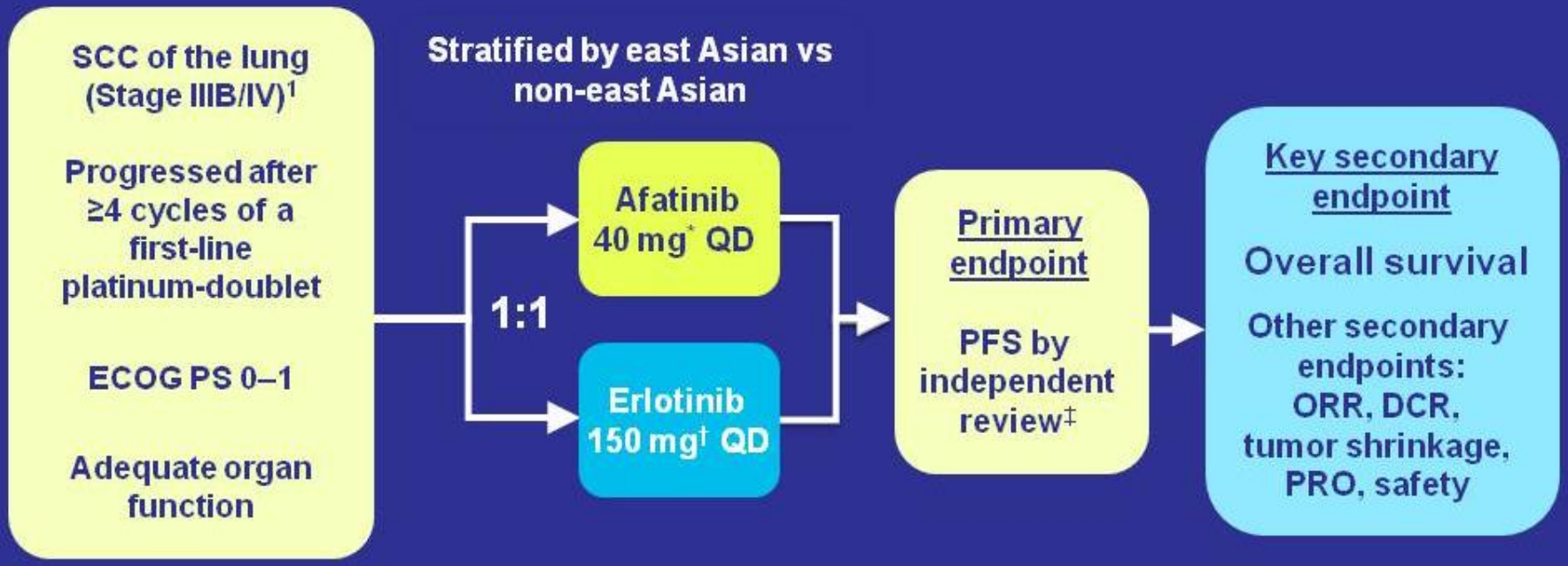
- **Additional *EGFR* mutation (i.e L718Q or L844V)**

Ercan D, et al. Clin Cancer Res 2015
Thress KS, et al. Nature Med 2015
Piotrowska Z, et al. Cancer Discov 2015
Eberlein CA, et al. Cancer Res 2015

Practical questions with EGFR-TKIs

Any role of EGFR-TKIs in *EGFR*^{wt} in 2015?

Afatinib versus erlotinib in second-line in squamous-cell carcinoma

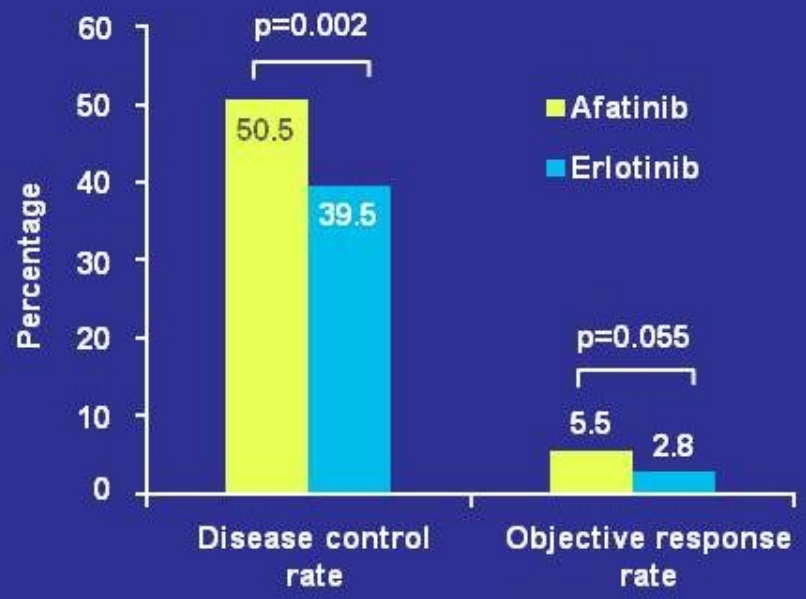


*Dose escalation to 50 mg and dose reduction to 30 or 20 mg permitted
†Dose reduction to 100 or 50 mg permitted
‡Tumor assessment at baseline, Weeks 8, 12, 16; every 8 weeks thereafter

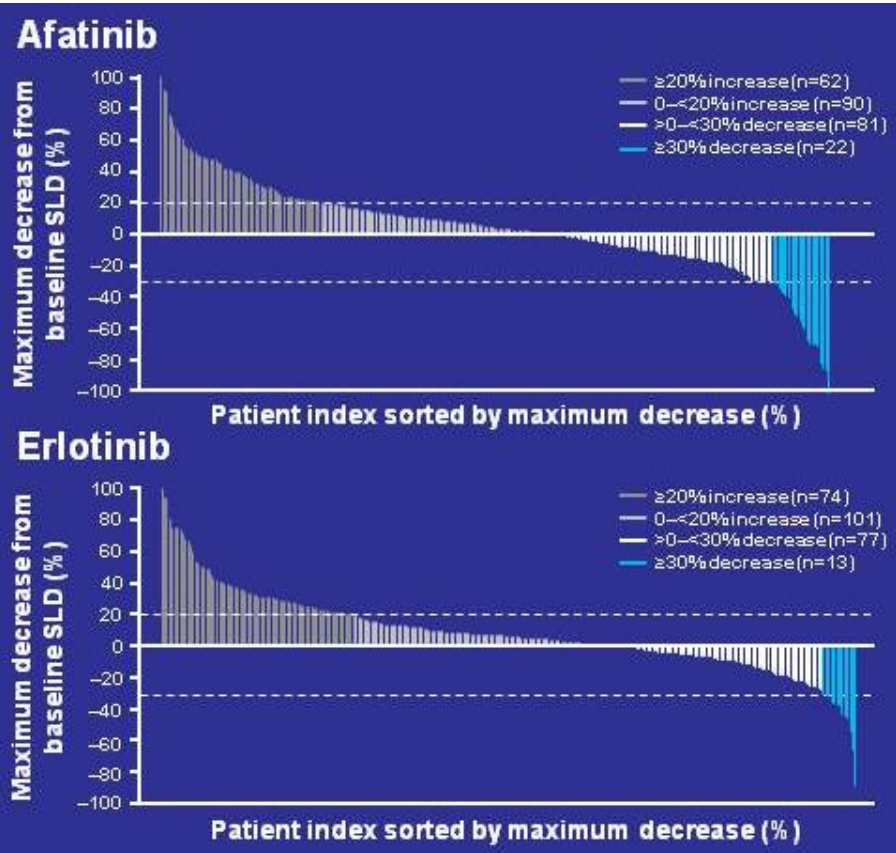
1. Edge S, et al. (Editor). AJCC Cancer Staging Manual. 7th ed. New York: Springer-Verlag New York, 2010.

Soria JC, et al. ASCO 2015

Response rate of afatinib versus erlotinib as second-line in squamous-cell carcinoma

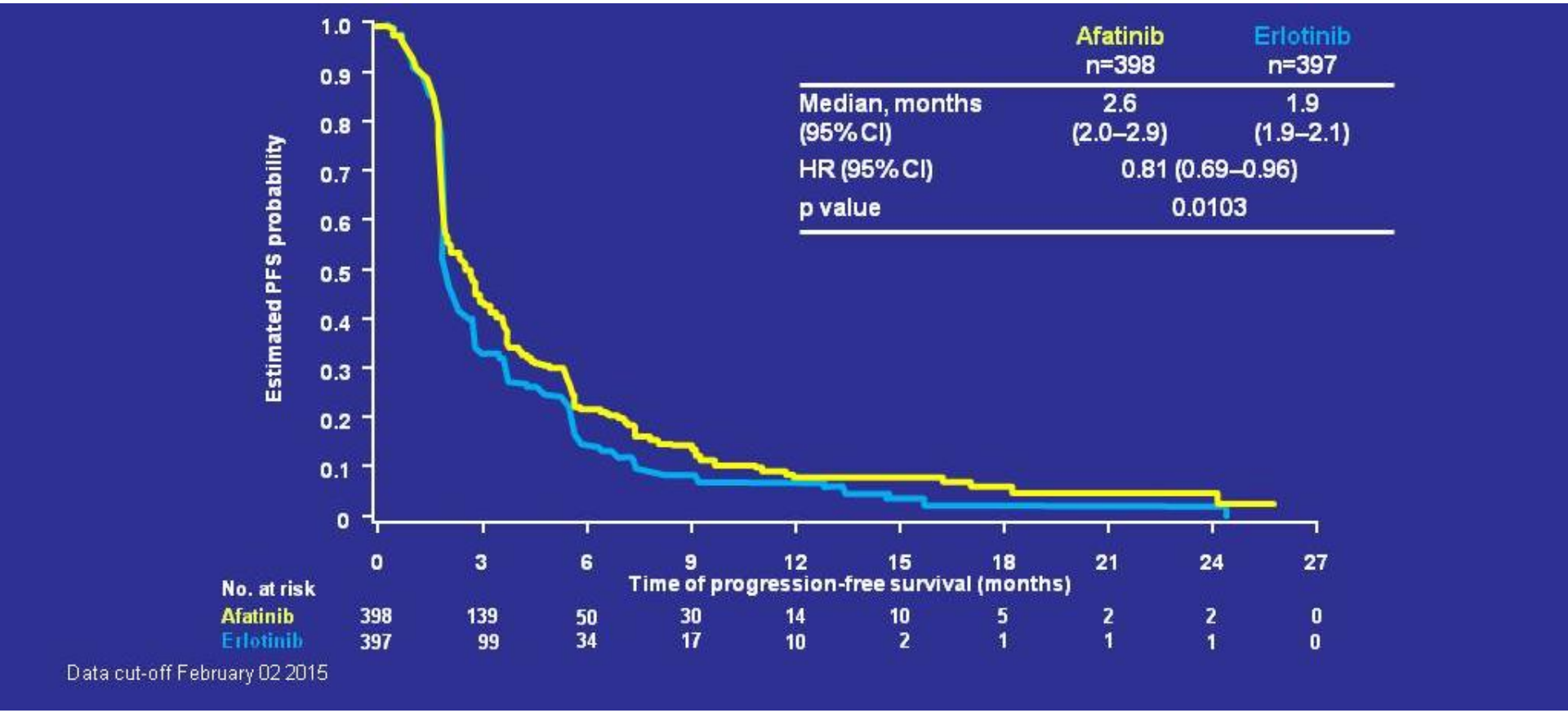


- Duration of response was 7.29 months for afatinib and 3.71 months for erlotinib



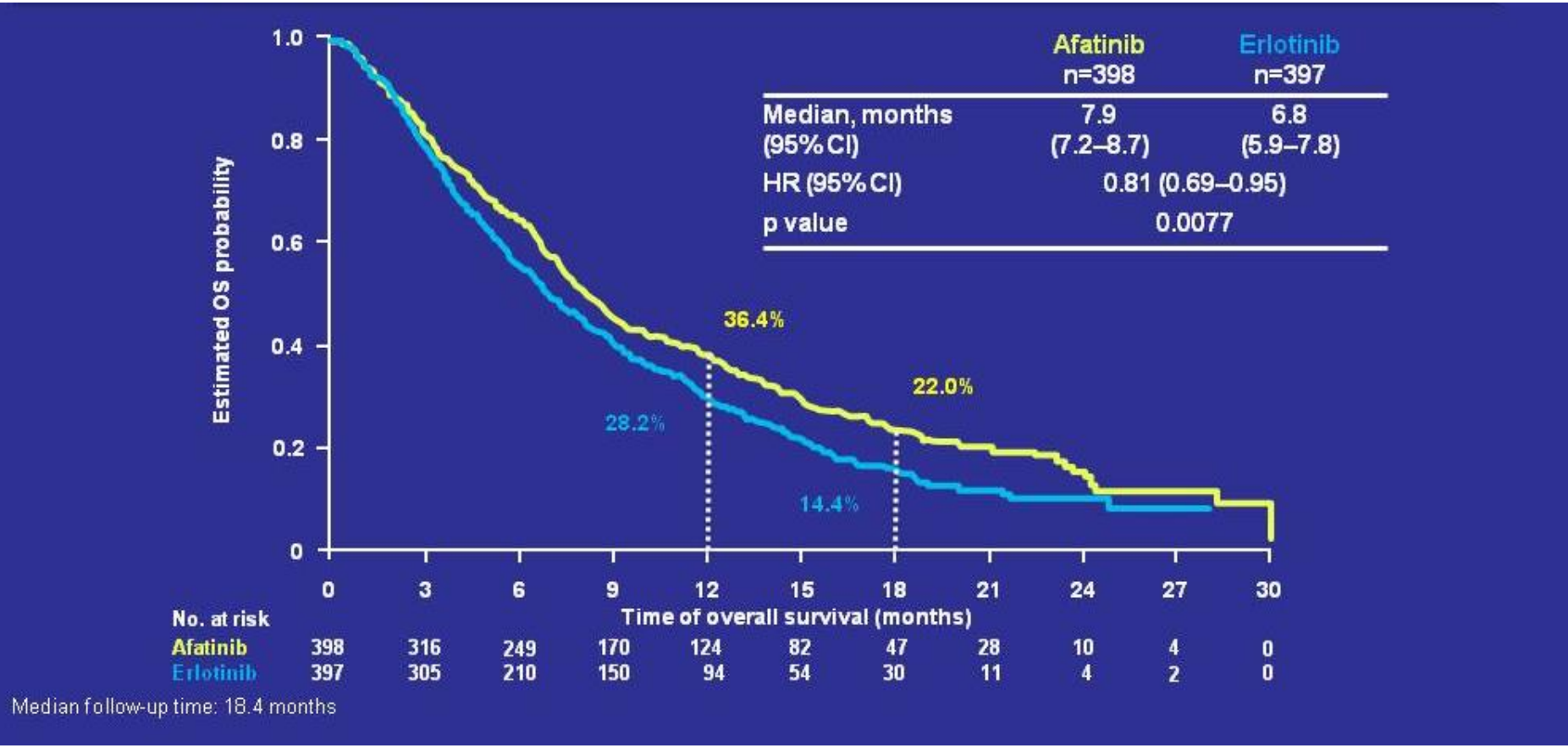
Soria JC, et al. ASCO 2015

PFS of afatinib versus erlotinib as second-line in squamous-cell carcinoma



Soria JC, et al. ASCO 2015

Overall survival of afatinib versus erlotinib as second-line in squamous-cell carcinoma

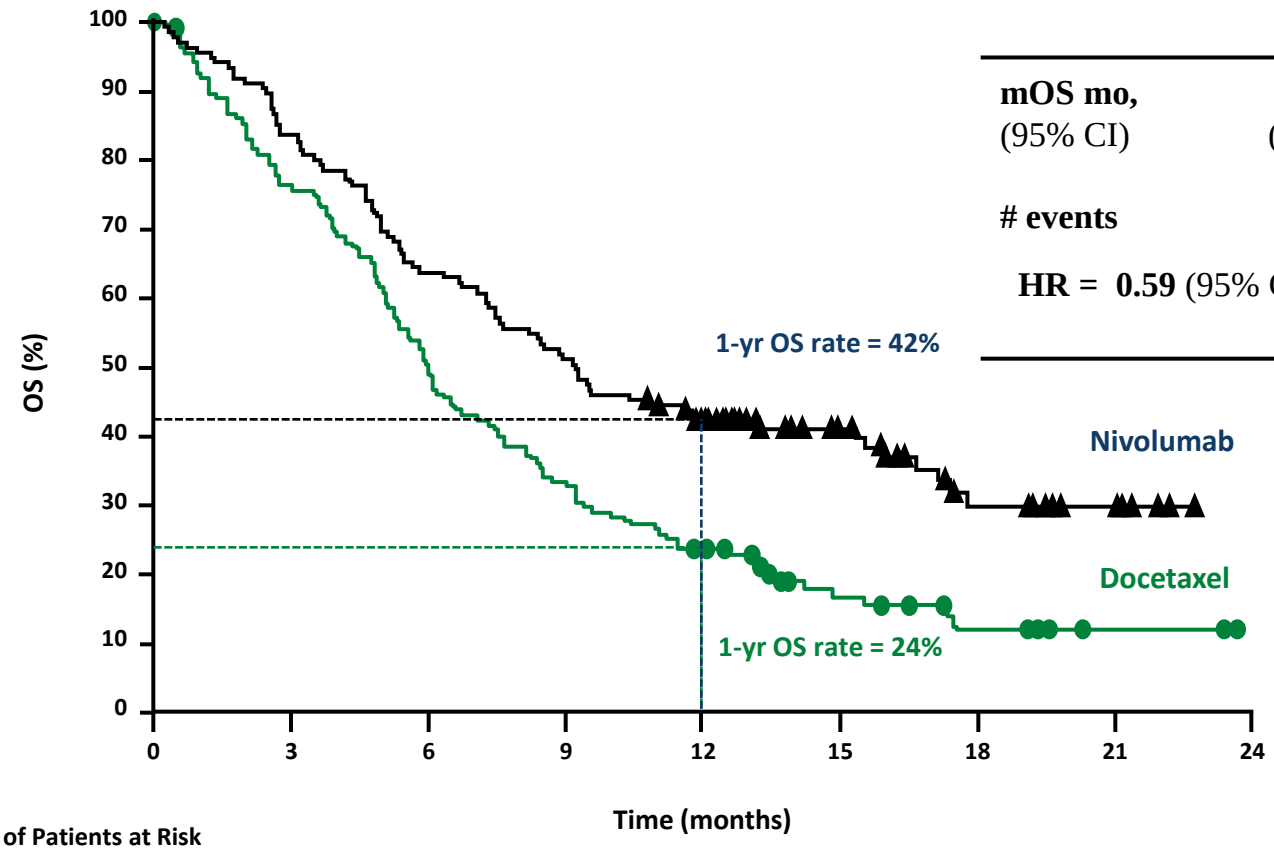


Soria JC, et al. ASCO 2015

Overall survival of nivolumab versus docetaxel in squamous-cell carcinoma

	Nivolumab n = 135	Docetaxel n = 137
mOS mo, (95% CI)	**9.2** (7.3, 13.3)	**6.0** (5.1, 7.3)
# events	86	113

HR = 0.59 (95% CI: 0.44, 0.79), ***P* = 0.00025**



Number of Patients at Risk

Nivolumab	135	113	86	69	52	31	15	7	0
Docetaxel	137	103	68	45	30	14	7	2	0

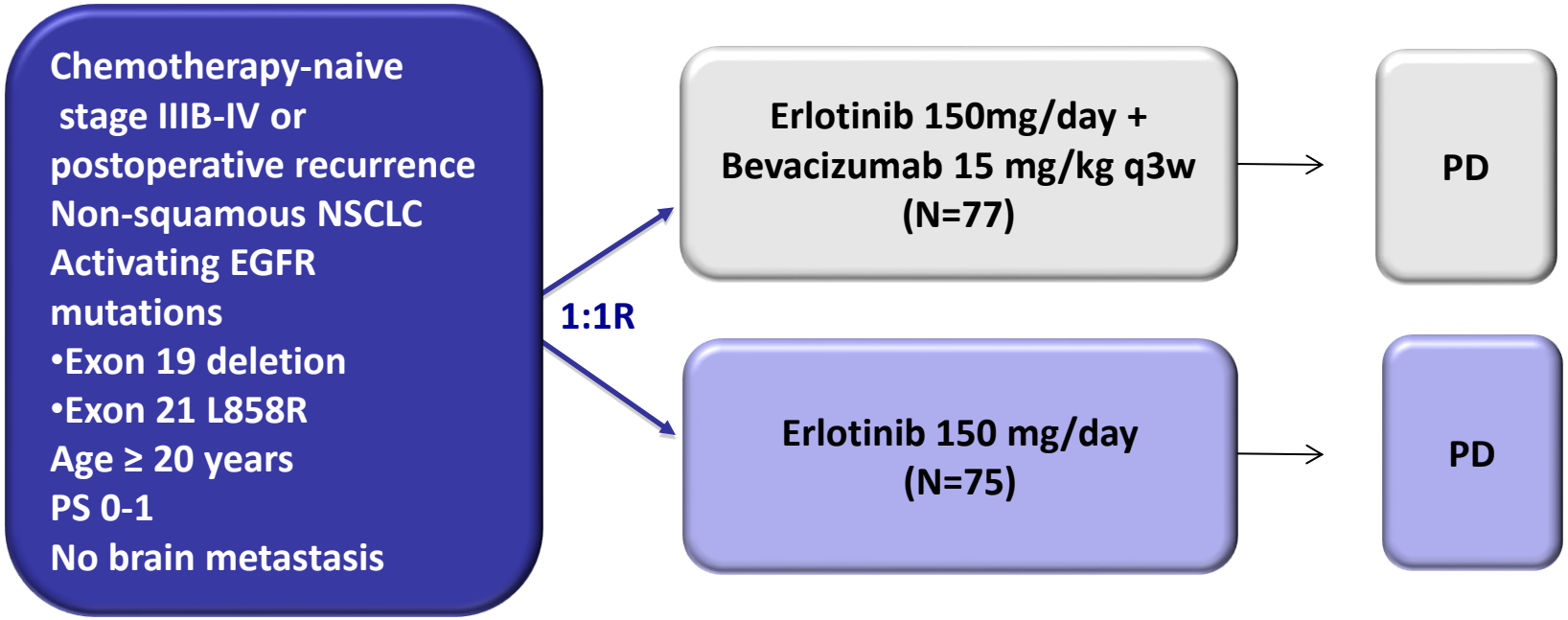
Symbols represent censored observations

Brahmer J, et al. NEJM 2015

Practical questions with EGFR-TKIs

EGFR-TKIs in combination with other agents

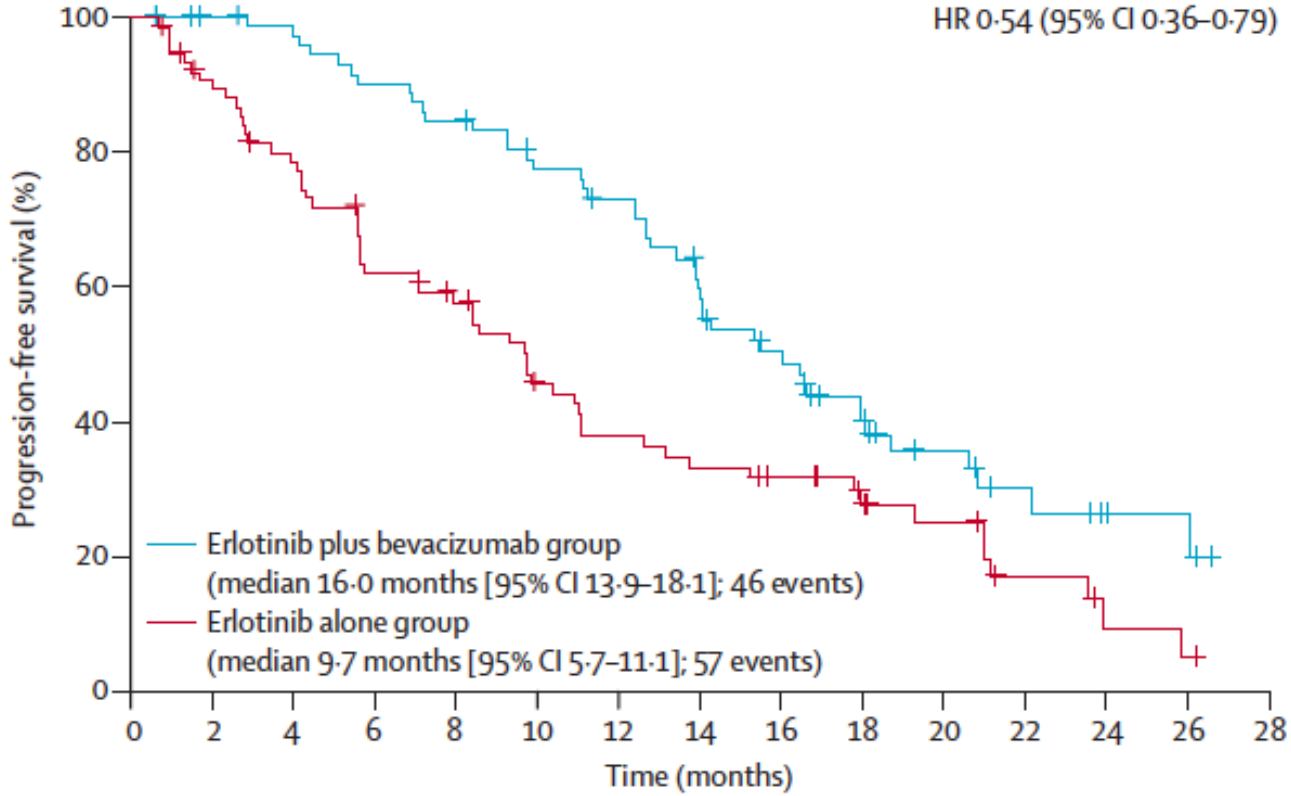
Erlotinib versus erlotinib+bevacizumab as first-line therapy in *EGFR*$^{mut+}$ NSCLC: phase IIR study



Primary end-point: PFS
Secondary End points: OS, ORR, QoL, symptoms improvement FACT-L scale and safety

Seto T, et al. Lancet Oncol 2014

Erlotinib versus erlotinib+bevacizumab as first-line therapy in *EGFR*$^{mut+}$ NSCLC: PFS



Number at risk

Erlotinib plus bevacizumab group	75	72	69	64	60	53	49	38	30	20	13	8	4	4	0
Erlotinib alone group	77	66	57	44	39	29	24	21	18	12	10	5	2	1	0

Seto T, et al. Lancet Oncol 2014

Nivolumab plus erlotinib in *EGFR*$^{mut+}$ NSCLC

- Chemotherapy-naive pts with stage IIIB/IV NSCLC
- *EGFR* mut. Positive
- Pretreated with erlotinib

→

Nivolumab 3 mg/kg iv Q2W
+ Erlotinib 150 mg/day orally
Until disease progression or unacceptable toxicity

Primary end point: safety and tolerability

Secondary end points: ORR and PFS rate at 24 wks

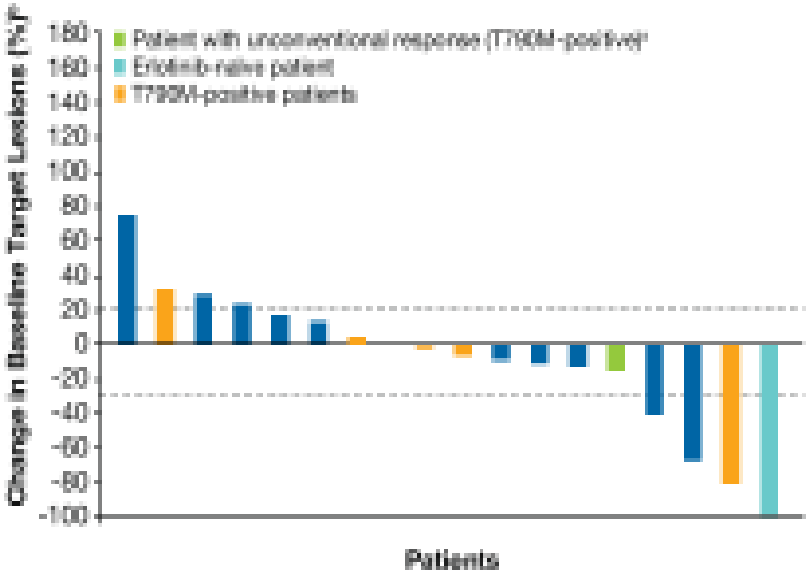
- 20 patients refractory after prior treatment with EGFR-TKI, one patient EGFR-TKI naive
- Mutation status: Exon 19: 12 pts, L858R: 9 pts, T790M: 7 pts, S76B1: 1 pt.

Rizvi NA, et al. ASCO 2014

Nivolumab plus erlotinib: safety and RR

- Treatment-related AEs (all grades) reported in all 21 patients, most frequently rash (48%)
- No pneumonitis (any grade) was observed
- Grade 3 treatment-related AEs reported in 5 patients (24%): increased AST or ALT, diarrhea, and weight decrease (no grade 4 AEs reported)
- 4 patients (19%) discontinued due to AEs related to any study medication
- 8 patients died (all due to disease progression)

Tumor responses	Prior erlotinib n = 20	No prior erlotinib n = 1
ORR, n (%) [95% CI]	4 (19) [5.4, 41.9]	
Best response, n (%)		
PR	3 (15)	1 (100)
SD [ongoing, n]	9 (45) [3]	0
PD	8 (38)	0
DOR by patient, weeks	60.1, 64.6+, 70+	72.3+



Rizvi NA, et al. ASCO 2014

Conclusions

- **EGFR-TKIs are the best option in first-line NSCLC harbouring activating *EGFR* mutations**
- **Gefitinib, erlotinib and afatinib:**
  - **Are equally effective**
  - **Evidence of higher efficacy in *EGFR*^{del19} versus *EGFR*^{ex21} mutation <u>FOR ALL</u> EGFR-TKIs**
  - **Suggestion of greater impact on survival for second-generation EGFR-TKIs in *EGFR*^{del19}**
- **Third-generation EGFR-TKIs very effective in acquired resistance**
- **Best sequencing of EGFR-TKIs not yet defined**
- **No role in second-line in squamous-cell carcinoma**
- **Combination of EGFR-TKIs with other agents under investigation**