Progress in EGFR Tyrosine Kinase Targeted Therapies in NSCLC

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Disclosures

Honoraria for advisory board work or speaker bureau activites from Pfizer, Roche, AZD, BI, BMS, Lilly, MSD

Abstract 338

A7471009: Updates for PFS and OS for Relevant EGFR Mutants Subsets

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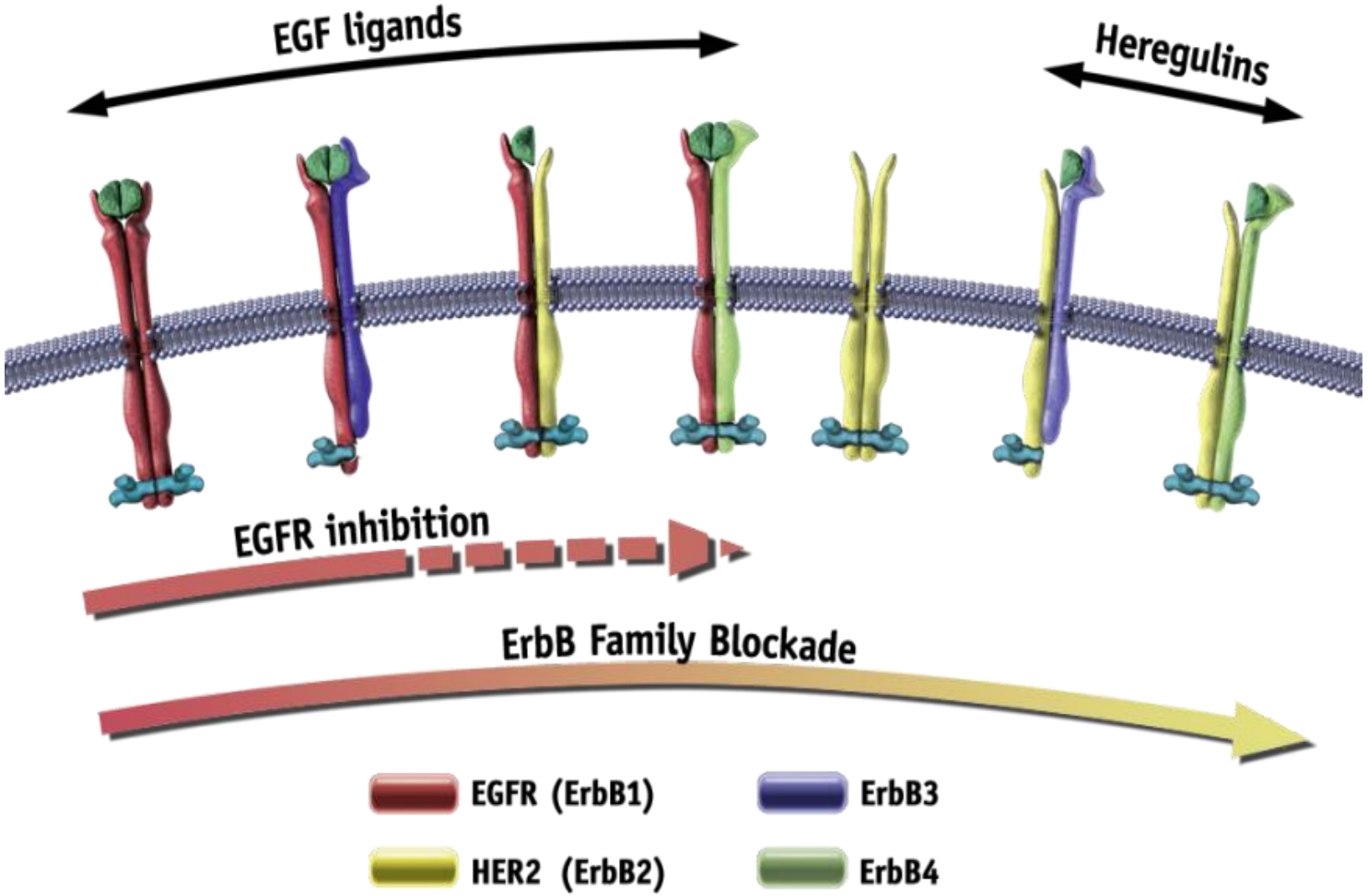
5th European Lung Cancer Conference 2015,
April 15–18, 2015, Geneva Switzerland

Dacomitinib: a 2nd Generation EGFR TKI - an irreversible ErbB Family Blocker



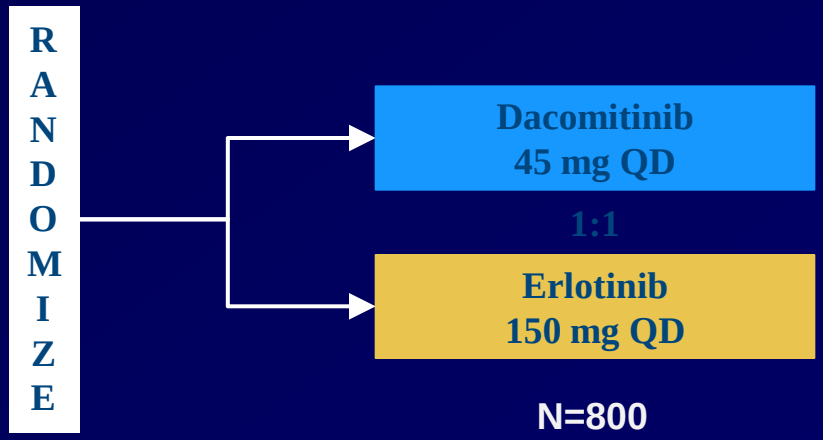
Li D, et al. *Oncogene* 2008;27:4702–11;
Solca F, et al. *J Pharmacol Exp Ther* 2012;343:342–50.

ARCHER 1009 Study Design

Trial design	Endpoints	Study sites
Randomized, double-blind, double-dummy	Primary: PFS (independent review) Secondary: OS, OR, PFS per investigator review, PRO (also powered for OS)	Global (US, EU, Latin America, Australia, and Asia – 25 countries)

Populations
- Co-primary = all and *KRAS* wild-type

Advanced NSCLC, measurable disease
- 1–2 prior chemo
- Tissue required from all subjects

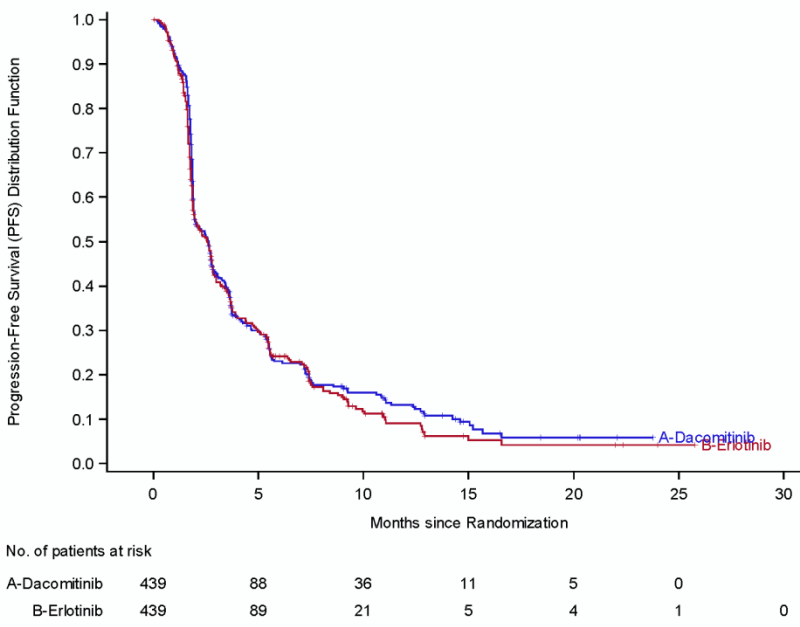


Stratifcation at baseline based on:
- Histology (adenocarcinoma vs. nonadenocarcinoma)
- Race (Asian vs. non-Asian and Indian sub-continent)
- ECOG PS 0–1 vs. 2
- Smoking status (never smoker, defined as ≤100 cigarettes, cigars, or pipes in lifetime vs. ever-smoker)

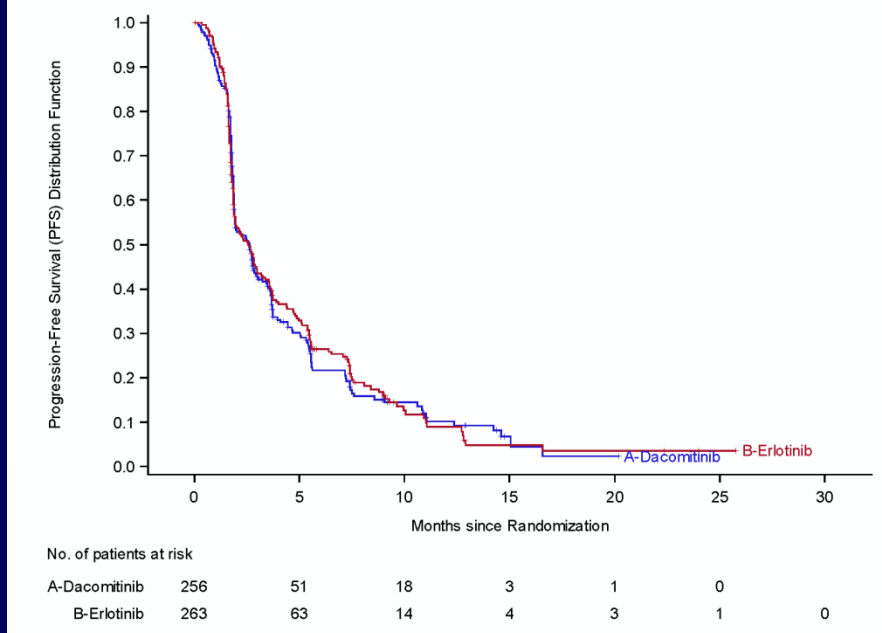
Ramalingam SS, et al. *Lancet Oncol* 2014;15:1369–78

ARCHER 1009: Kaplan-Meier curves for PFS (co-primary endpoints)

Full intent-to-treat population



KRAS WT subpopulation



Ramalingam SS, et al. *Lancet Oncol* 2014 [Epub ahead of print]

EGFR Mutant Subgroups

	Dacomitinib n (%)	Erlotinib n (%)	Total n (%)
EGFR mutant	47	44	91
Treated	46 (97.9)	44 (100)	90 (98.9)
Ongoing on treatment	*10 (21.3)*	*7 (15.9)*	*17 (18.7)*
Ongoing on study[1]	24 (51.1)	21 (47.7)	45 (49.5)
Activating mutant (exon 19 or 21)	37	39	76
Treated	36 (97.3)	39 (100)	75 (98.7)
Ongoing on treatment	*9 (24.3)*	*6 (15.4)*	*15 (19.7)*
Ongoing on study[1]	20 (54.1)	18 (46.2)	38 (50.0)

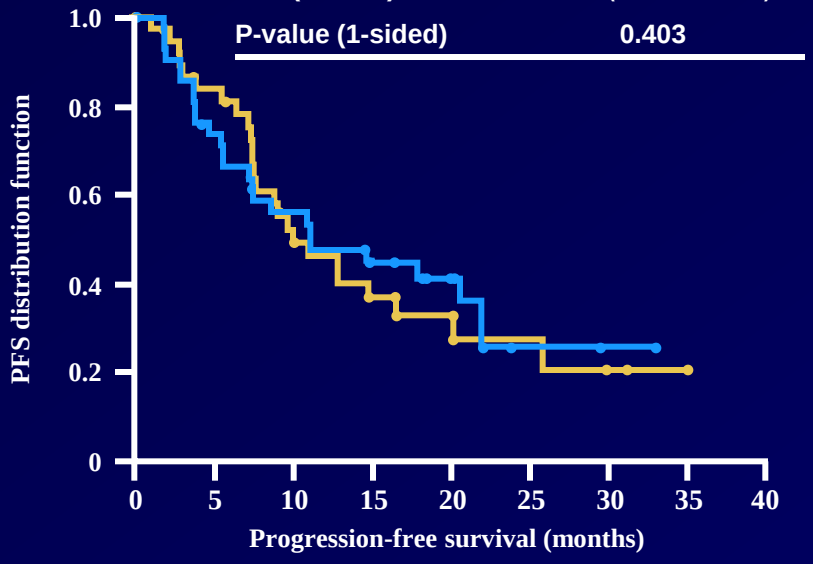
Data cut-off July 31, 2014

[1]On study means either still on treatment or being followed for OS and/or AE

PFS for All EGFR Mutations (n=91)

Per independent review

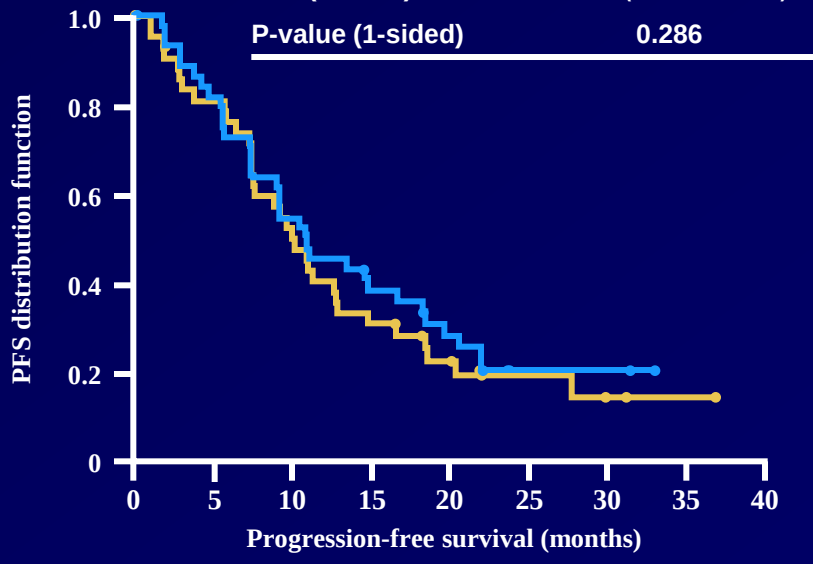
	Dacomitinib (N=47)	Erlotinib (N=44)
Events (%)	26 (55.3)	25 (56.8)
Median, mo (95% CI)	11.1 (5.6–21.9)	10.0 (7.4–16.6)
HR* (95% CI)	0.935 (0.539–1.624)	
P-value (1-sided)	0.403	



No. of patients at risk									
Dacomitinib	47	30	20	14	10	2	1	0	0
Erlotinib	44	30	17	11	7	4	2	1	0

Per investigator's assessment

	Dacomitinib (N=47)	Erlotinib (N=44)
Events (%)	34 (72.3)	34 (77.3)
Median, mo (95% CI)	10.9 (7.5–18.2)	10.0 (7.4–12.8)
HR* (95% CI)	0.874 (0.542–1.408)	
P-value (1-sided)	0.286	



No. of patients at risk									
Dacomitinib	47	36	24	16	11	2	2	0	0
Erlotinib	44	34	21	13	8	4	2	1	0

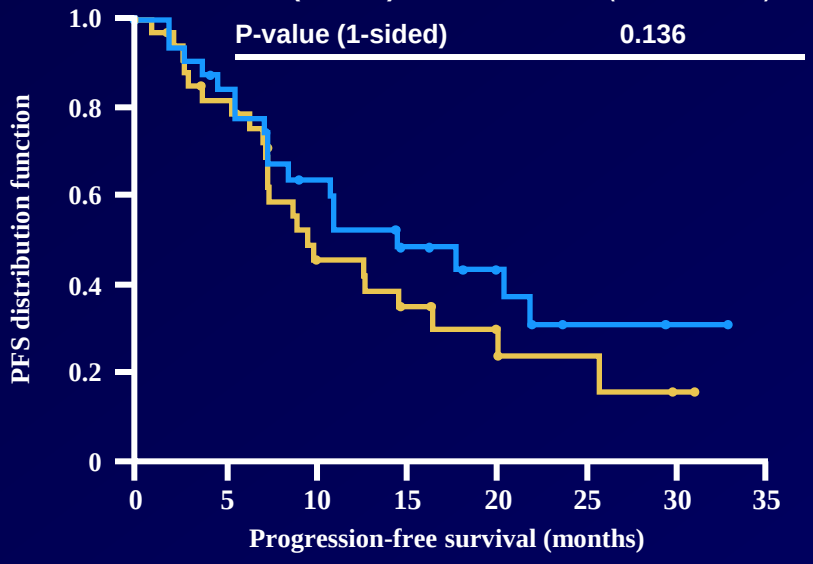
*Unstratified

PFS per independent review was still NOT mature with 56% event rate

PFS for Activating EGFR Mutations in Exon 19 or 21 (n=76)

Per independent review

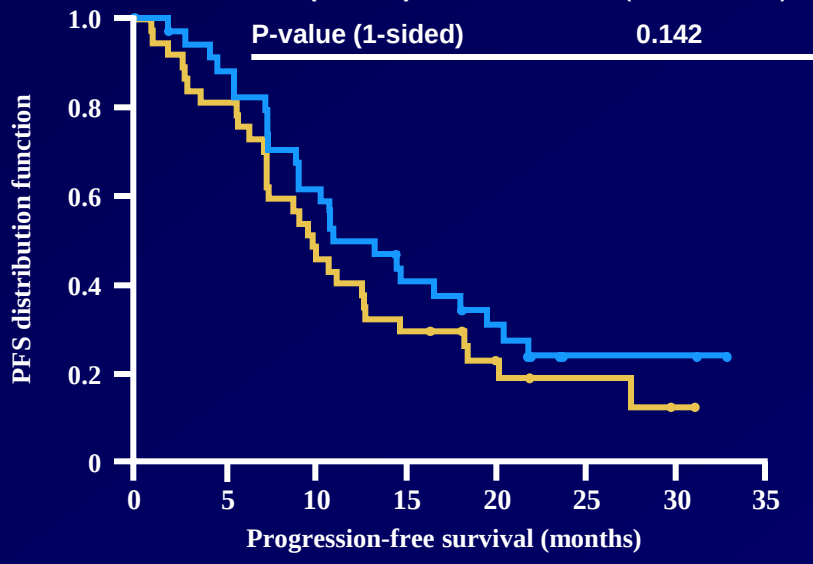
	Dacomitinib (N=37)	Erlotinib (N=39)
Events (%)	18 (48.6)	25 (59.0)
Median, mo (95% CI)	14.6 (7.6–NR)	9.6 (7.3–16.6)
HR* (95% CI)	0.707 (0.380–1.315)	
P-value (1-sided)	0.136	



No. of patients at risk								
Dacomitinib	37	26	17	11	8	2	1	0
Erlotinib	39	26	14	9	6	3	1	0

Per investigator's assessment

	Dacomitinib (N=37)	Erlotinib (N=39)
Events (%)	25 (67.6)	30 (76.9)
Median, mo (95% CI)	13.4 (9.0–19.6)	10.0 (7.4–12.8)
HR* (95% CI)	0.749 (0.440–1.275)	
P-value (1-sided)	0.142	



No. of patients at risk								
Dacomitinib	37	30	21	13	9	2	2	0
Erlotinib	39	30	18	11	7	3	1	0

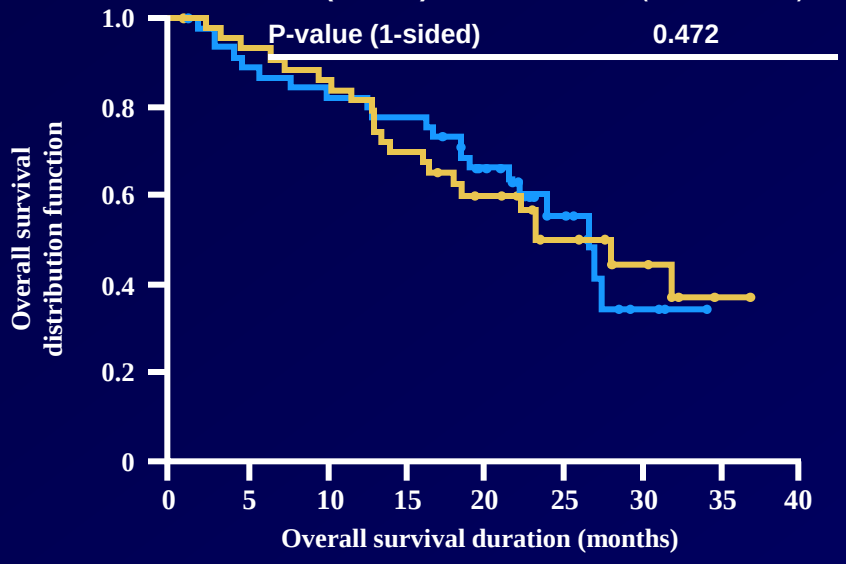
*Unstratified

PFS per independent review was still NOT mature with 56% event rate

OS for EGFR Mutations and Exon 19 and 21

EGFR mu

	Dacomitinib (N=47)	Erlotinib (N=44)
Events (%)	21 (44.7)	22 (50.0)
Median, mo (95% CI)	26.6 (21.6–NR)	28.0 (16.4–NR)
HR* (95% CI)	0.976 (0.534–1.786)	
P-value (1-sided)	0.472	

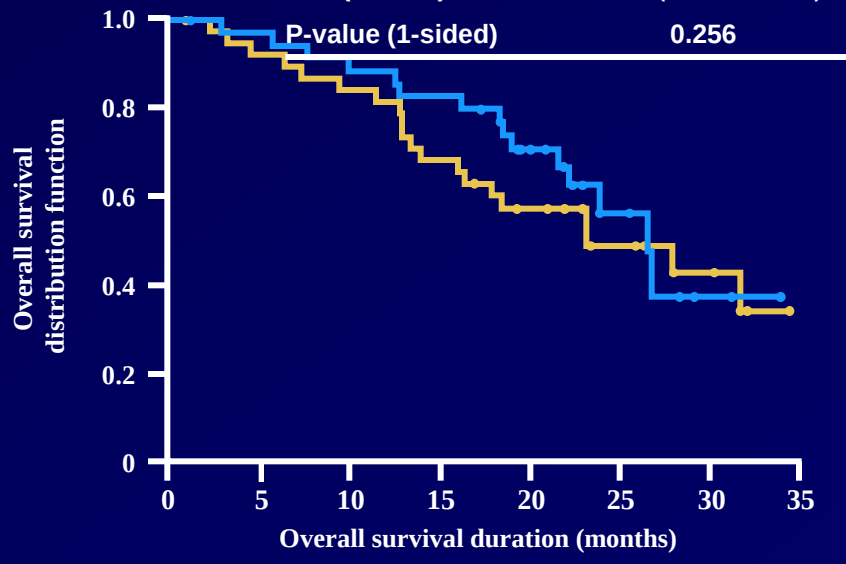


No. of patients at risk

Dacomitinib	47	40	37	35	25	11	3	0	0
Erlotinib	44	40	37	30	22	12	7	1	0

Activating mutation in exon 19 or 21

	Dacomitinib (N=37)	Erlotinib (N=39)
Events (%)	15 (40.5)	20 (51.3)
Median, mo (95% CI)	26.6 (21.6–NR)	23.2 (16.0–NR)
HR* (95% CI)	0.796 (0.405–1.565)	
P-value (1-sided)	0.256	



No. of patients at risk

Dacomitinib	37	34	31	29	20	8	2	0
Erlotinib	39	35	32	28	18	10	8	0

*Unstratified

OS was not mature with <50% deaths

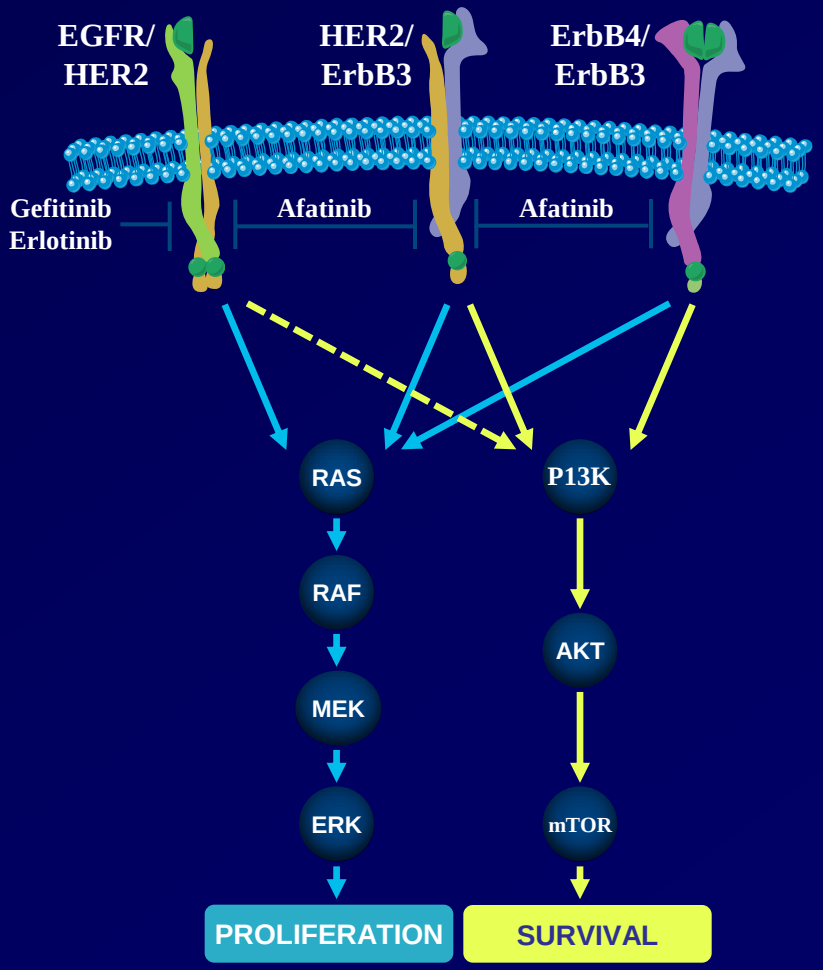
Most Frequent Treatment-related Adverse Events by MedDRA Preferred Term (or CLUSTERED Term) in Patients with Activating Mutation in Exon 19 or 21

AE preferred term	Dacomitinib (%)	Erlotinib (%)
Diarrhea	88.9	66.7
PARONYCHIA (CLUSTER)	58.3	38.5
Paronychia	55.6	33.3
STOMATITIS (CLUSTER)	52.8	46.2
Rash	50.0	66.7
Dry skin	33.3	30.8
Stomatitis	33.3	30.8
Decreased appetite	27.8	17.9
DERMATITIS ACNEIFORM (CLUSTER)	25.0	30.8
Dermatitis acneiform	22.2	28.2

DERMATITIS ACNEIFORM is any event having a PT of dermatitis acneiform, acne, acne pustular, acne conglobata, acne cystic or acne fulminans
PARONYCHIA is any event having a PT of paronychia or nail disorder
STOMATITIS is any event having a PT of stomatitis, mouth ulceration, glossodynia, glossitis, cheilitis, oral pain, oropharyngeal pain, oropharyngeal discomfort or mucosal inflammation

Afatinib: irreversible ErbB-family inhibition

- Afatinib is an irreversible ErbB-family blocker[1–3]
  - Inhibits all kinase-active members: EGFR, HER2 and HER4
  - Proof of concept in squamous histology in various trials in lung, and head and neck cancer
  - Approved* in the major ICH regions of US,[4] EU[5] and Japan[6] for the treatment of patients with NSCLC harbouring distinct types of EGFR-activating mutations



EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor-2; HER4, human epidermal growth factor receptor-4; ICH, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
*Indications differ between countries

1. Li D, et al. Oncogene 2008;27:4702–11; 2. Solca F, et al. J Pharmacol Exp Ther 2012;343:342–50;
3. Yarden Y, Pines. G *Nat Rev Cancer*. 2012;12:553;
4. Gilotrif prescribing information 2013. http://www.accessdata.fda.gov (Accessed: 05 Sept 2014);
5. Giotrif EPAR assessment EMA 2013. http://www.ema.europa.eu (Accessed 05 Sept 2014);
6. PMDA Japan new drug approvals 2013. http://www.pmda.go.jp (Accessed 05 September 2014)

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

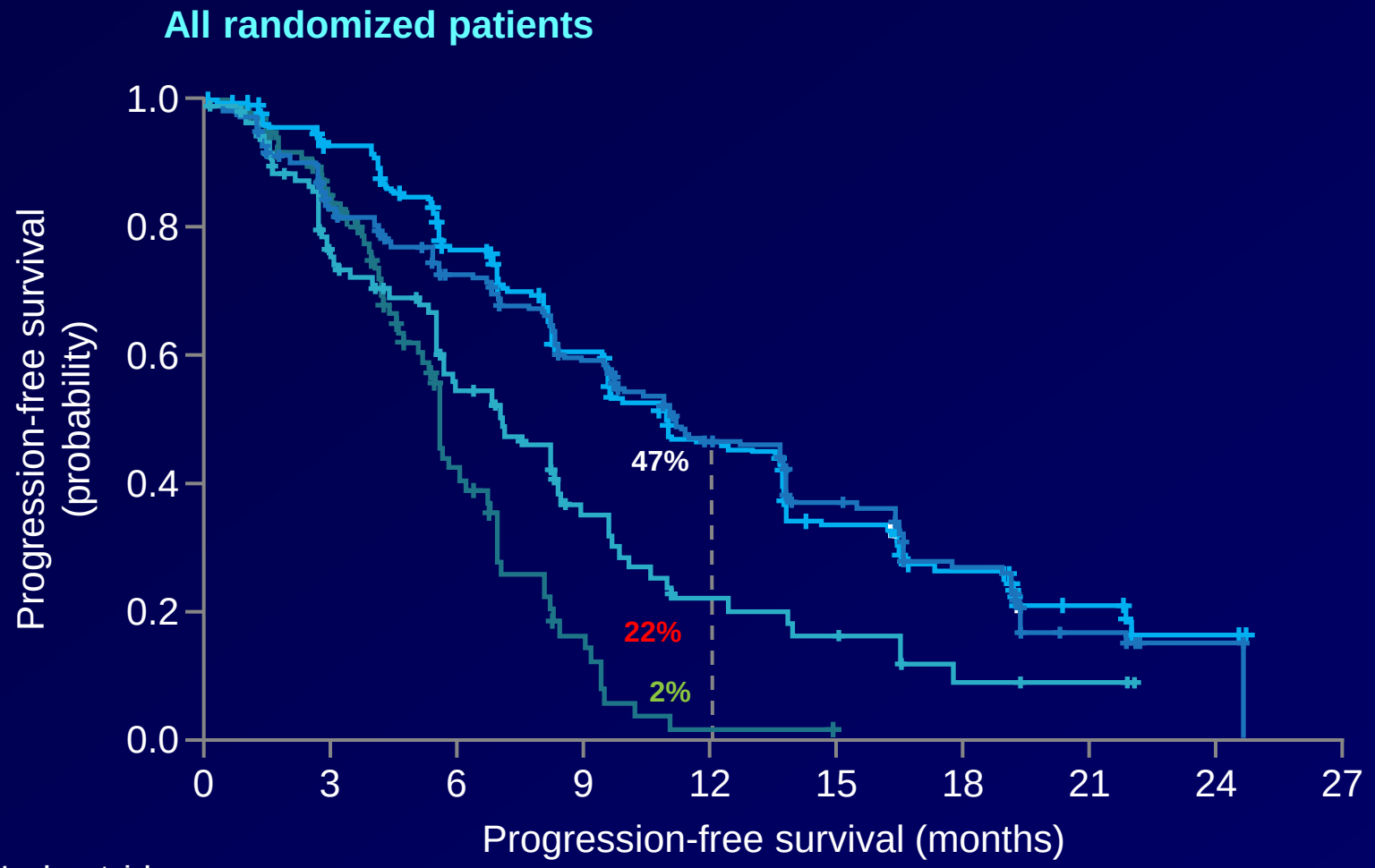
LUX-Lung 6:
Cisplatin + gemcitabine
up to 6 cycles

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.

LUX-Lung 3 and 6

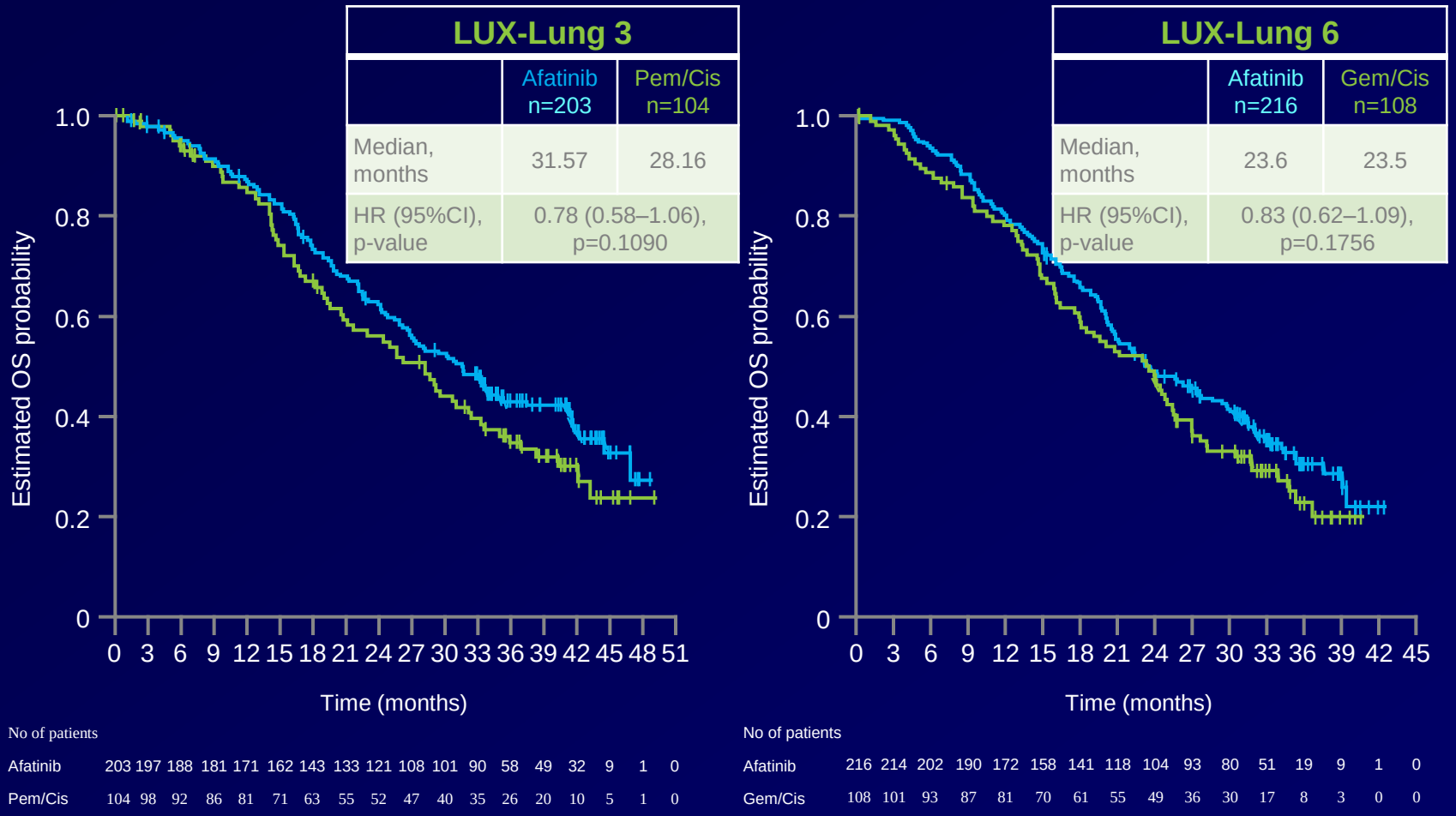
- **Significant improvement over chemotherapy in PFS (primary endpoint)[1,2]**

	Common mutations (Del19/L858R)			
	LUX-Lung 3 (n=307)		LUX-Lung 6 (n=324)	
	Afatinib	Pem/Cis	Afatinib	Gem/Cis
Median PFS, mo	13.6	6.9	11.1	5.6
HR, p-value	HR=0.47, p<0.0001		HR=0.25, p<0.0001	

- **Activity in some types of uncommon mutations (L861Q, G719X, S768I)[3]**
- **Improved symptom control and delay in worsening of cancer-related cough and dyspnea[4]**

1. Sequist et al. *J Clin Oncol*. 2013;31:3327; 2. Wu et al. *Lancet Oncol*. 2014;15:213; 3. Yang et al. *J Thorac Oncol*. 2013;8:suppl 2 (O03.05); 4. Sequist et al. *J Thorac Oncol*. 2013;8:suppl 2 (P3.11-023).

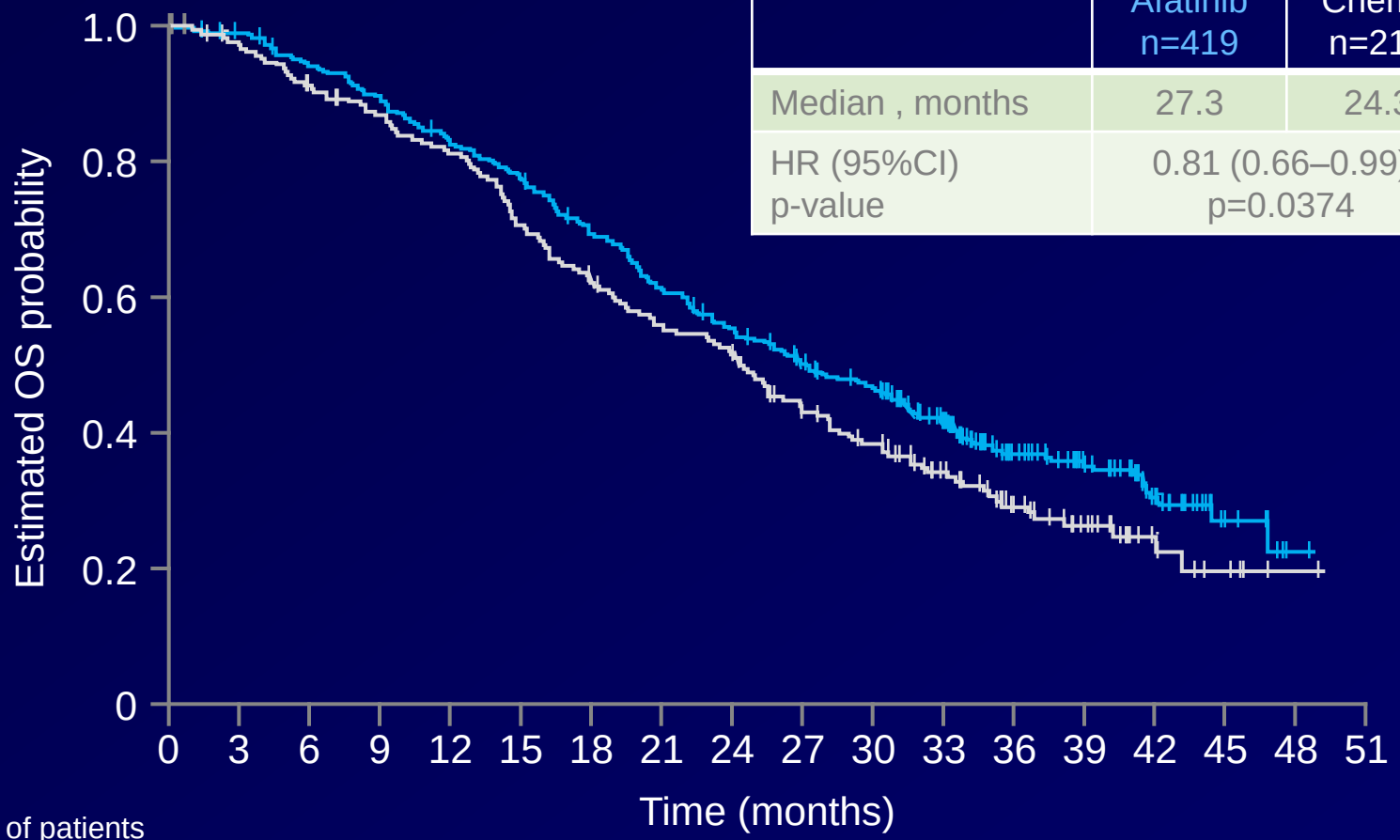
OS in common mutations LUX-Lung 3 and 6



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

Combined OS analysis

	Afatinib n=419	Chemo n=212
Median , months	27.3	24.3
HR (95%CI) p-value	0.81 (0.66–0.99) p=0.0374	



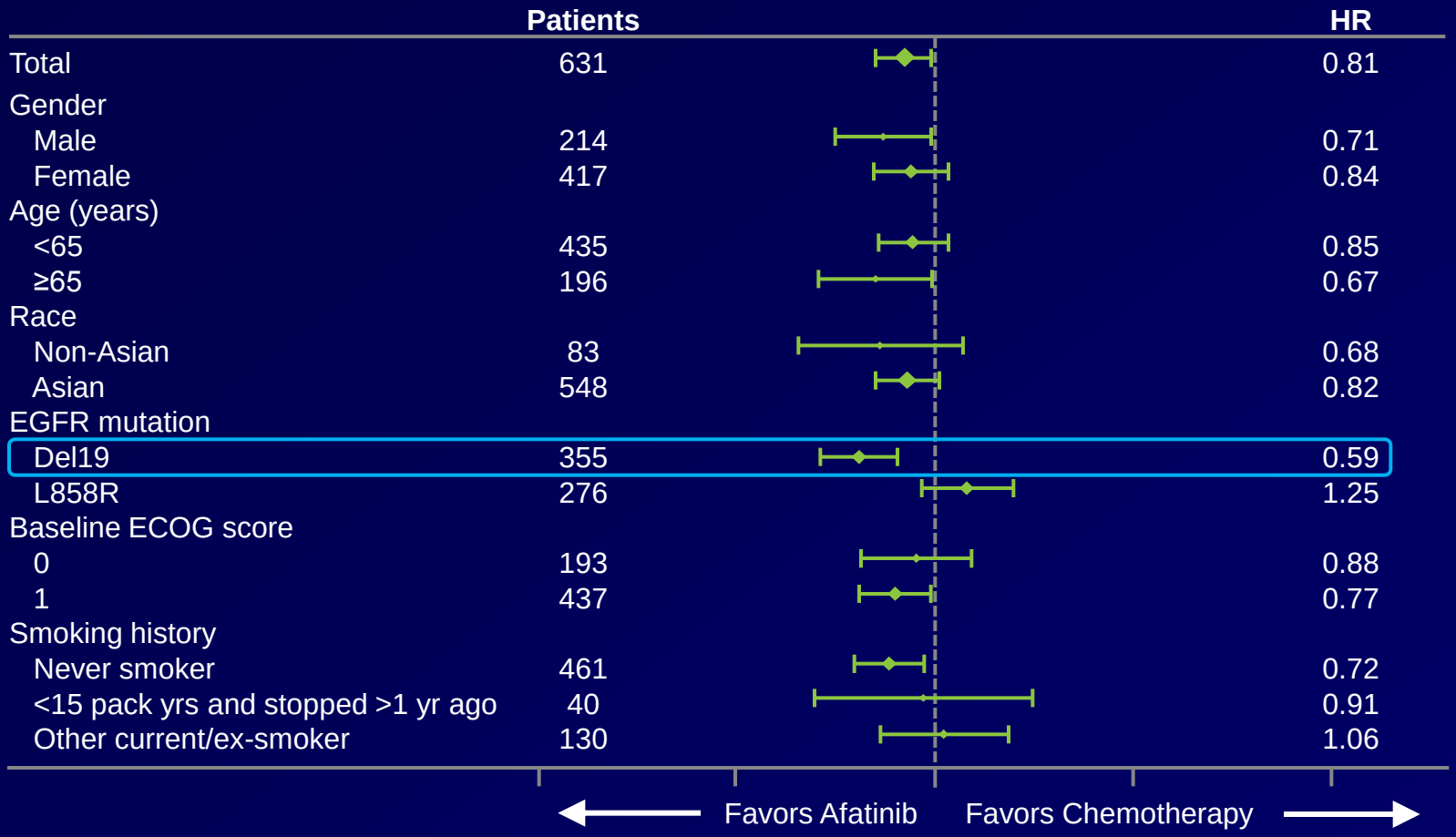
No of patients

Afatinib	419	411	390	371	343	320	284	251	225	201	181	141	77	58	33	9	1	0
Chemo	212	199	185	173	162	141	124	110	101	83	70	52	34	23	10	5	1	0

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

Combined OS analysis in common mutations

Subgroups



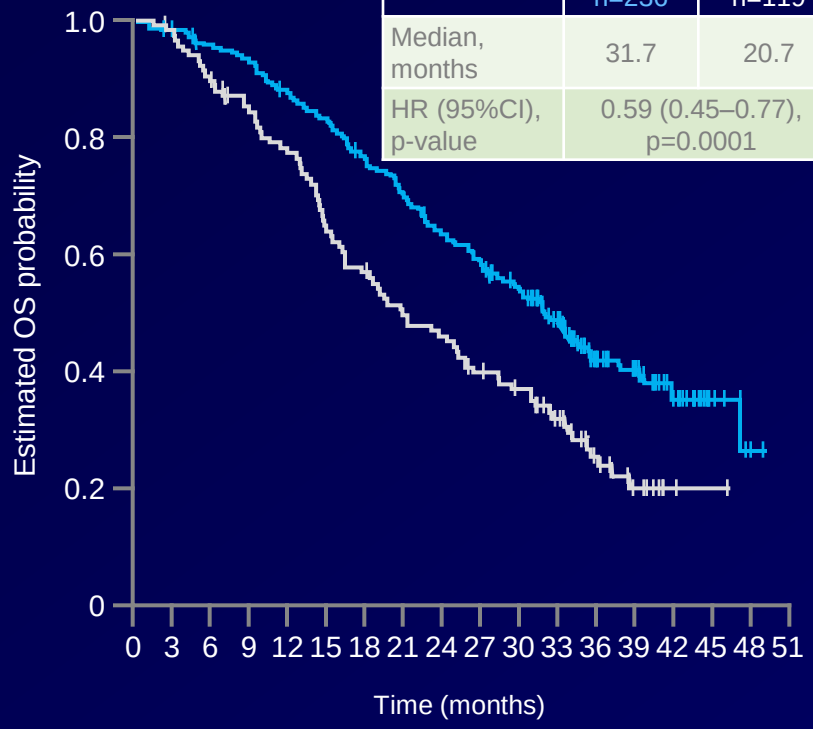
Yang JCH, et al. ASCO 2014: abstract 8004 and oral presentation.

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	

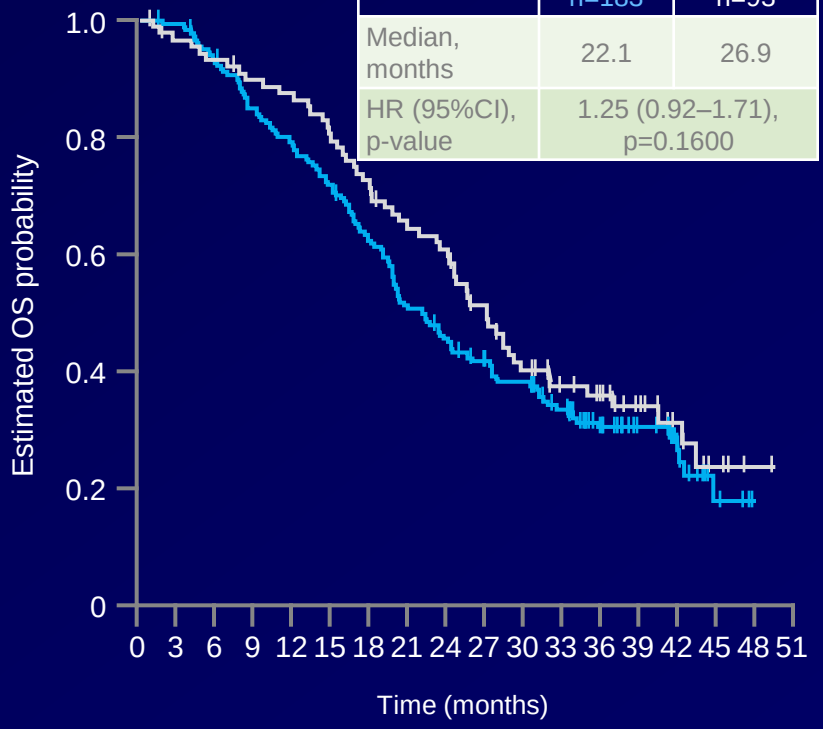


No of patients

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

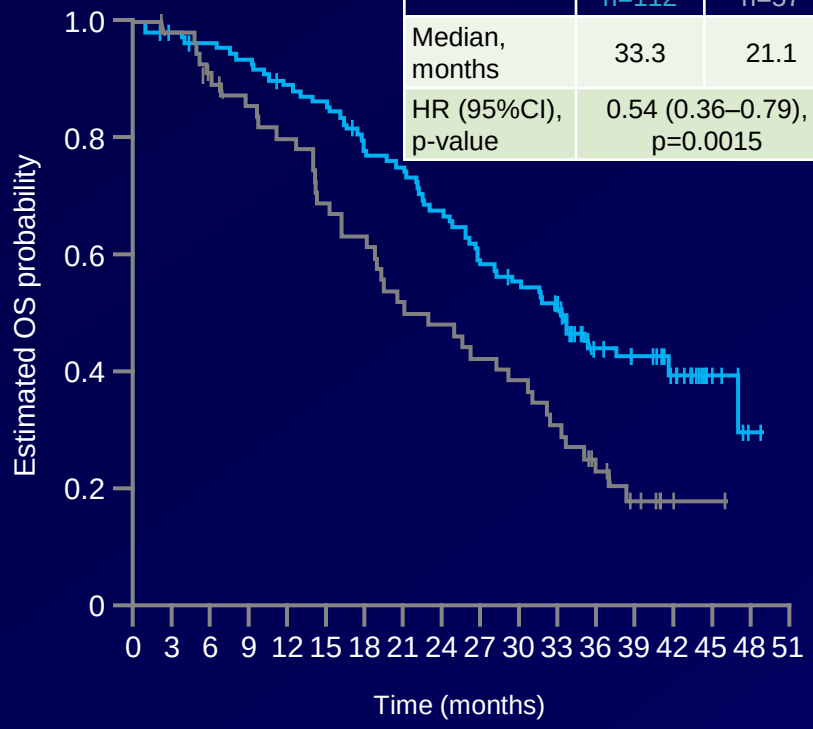
Yang JCH, et al. ASCO 2014: abstract 8004 and oral presentation.

OS in Del19 subgroup

Mutation categories

LUX-Lung 3

	Afatinib n=112	Pem/Cis n=57
Median, months	33.3	21.1
HR (95%CI), p-value	0.54 (0.36–0.79), p=0.0015	

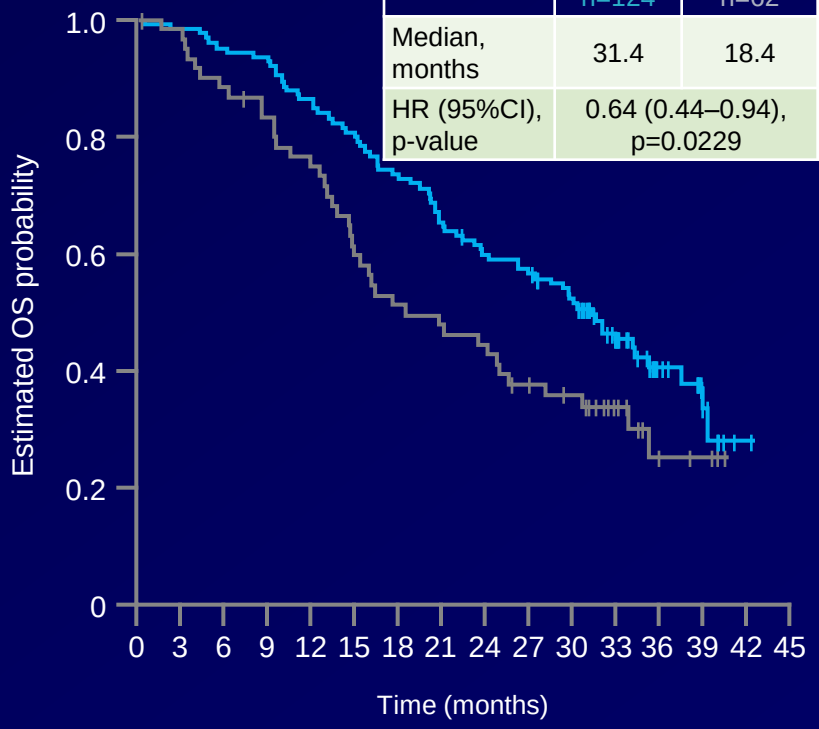


No of patients

Afatinib	112	108	105	102	96	93	83	80	72	62	58	51	34	30	21	6	1	0
Pem/Cis	57	55	50	46	43	37	33	27	25	22	20	16	10	6	1	1	0	0

LUX-Lung 6

	Afatinib n=124	Gem/Cis n=62
Median, months	31.4	18.4
HR (95%CI), p-value	0.64 (0.44–0.94), p=0.0229	

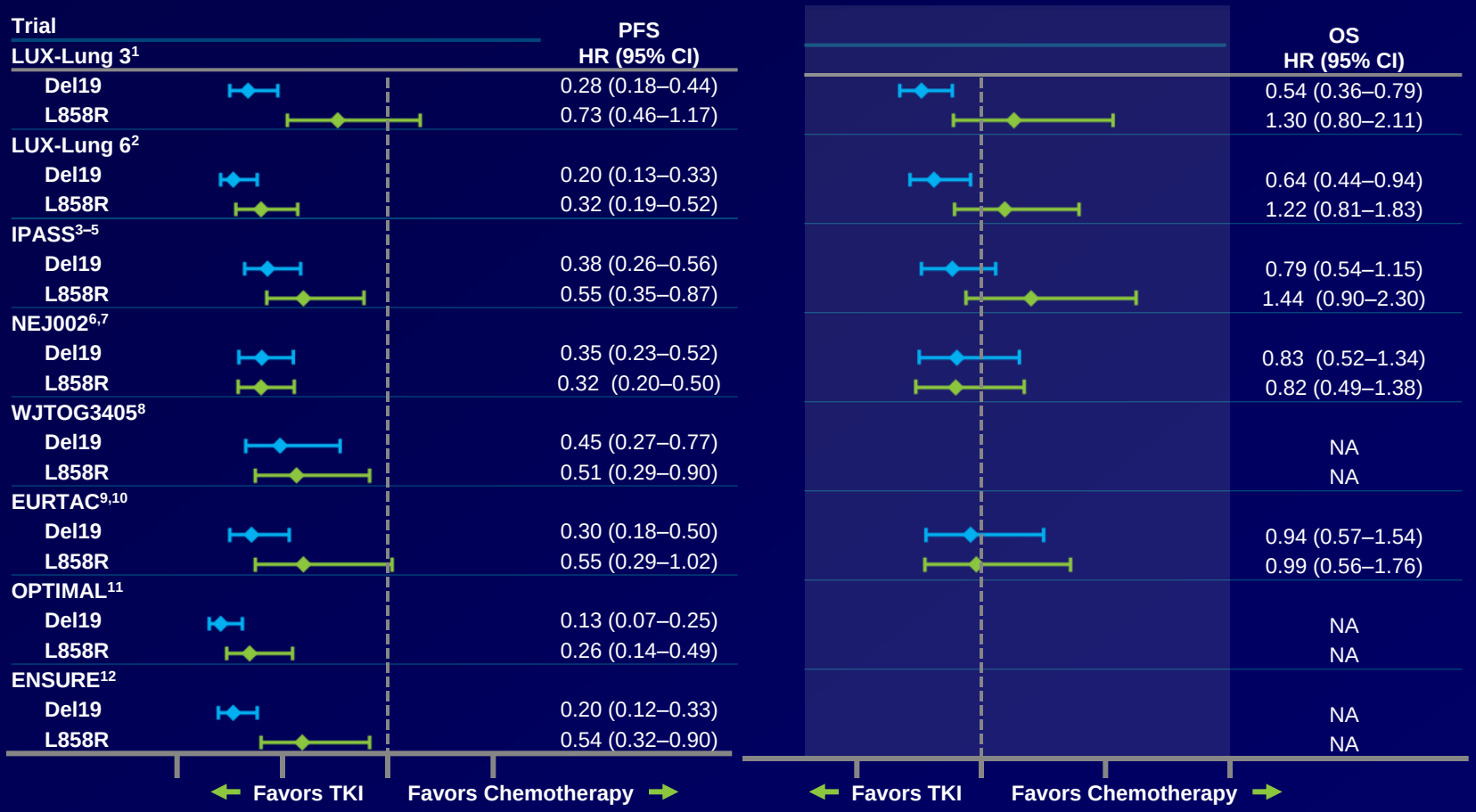


No of patients

Afatinib	124	122	118	115	106	99	90	80	73	69	59	39	16	8	1	0
Gem/Cis	62	58	53	49	44	35	30	28	26	21	18	11	4	3	0	0

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

HRs for PFS and OS in Del19 and L858R patients



1. Sequist et al. *J Clin Oncol*. 2013;31:3327; 2. Wu et al. *Lancet* Oncol. 2014;15:213; 3. Mok et al. *N Engl J Med*. 2009;361:947; 4. Fukuoka et al. *J Clin Oncol*. 2011;29:2866; 5. Yang et al. *Eur J of Cancer*. 2011 (suppl1;S633); 6. Maemondo et al. *N Engl J Med*. 2010;362:2380; 7. Inoue et al. *Ann Oncol*. 2013;24:54; 8. Mitsudomi et al. *Lancet Oncol*. 2010;11:121; 9. Rosell et al. *Lancet Oncol*. 2012;13:239; 10. TARCEVA® (erlotinib) prescribing information, 2013; 11. Zhou et al. *Lancet Oncol*. 2011;12:735; 12. Wu et al. *J Thorac Oncol*. 2013;8:suppl 2 (P1.11-021).

Conclusions

- First comparison of a 1st and 2nd generation EGFR TKI within the context of a randomised phase III study
- PFS data for dacomitinib consistent with afatinib
- PFS data for erlotinib consistent with reported outcomes
  - Suggests that 2nd generation EGFR TKIs may be superior to 1st generation agents at least in terms of PFS

Randomised studies indicating benefit from first line EGFR TKI in EGFR mutation positive patients

Study (n)	Comparison	Eligible Mutations	ORR (%)	PFS (M)	HR
LUX-lung 6 (n=364)	Afatinib v Cis/Gem	19del/L858R EGFR 29	67 v 23%	11.0 v 5.6	0.28[0.20,0.39]
LUX-lung 3 (n=345)	Afatinib v. Cis/Pem	19del/L858R EGFR 29	61 v 22% 56 v 23%	13.6 v 6.9 11.1 v 6.9	0.47 [0.34,0.65] 0.58 [0.34, 0.65]
EURTAC (n=174)	Erlotinib v. Chemotherapy	19del/L858R	58 v 15%	10.4 v 5.4	0.47 [0.28,0.78]
OPTIMAL (n=165)	Erlotinib v. Carbo/Gem	19del/L858R	83 v 36%	13.1 v 4.6	0.16 [0.10,0.26]
WJOTG (n= 172)	Geftinib v. Cis/Docet	19del/L858R	62 v 32%	9.2 v 6.3	0.49 [0.34,0.71]
NEJ002 (n=230)	Gefitinib v. Carbo/Pac	19del/L858R + other (6.1%)	74 v 31%	10.8 v.5.4	0.30 [0.22,0.41]
IPASS (n=261)	Gefitinib v. Carbo/Pac	19del/L858R EGFR 29	71 v 47%	9.5 v 6.3	0.48 [0.36,0.64]
First Signal (n= 313/96)	Gefitinib v. Cis/Gem	19del/L858R	85 v 38%	8 v 6.3	0.544 [0.269,1.10]

LUX-Lung 7

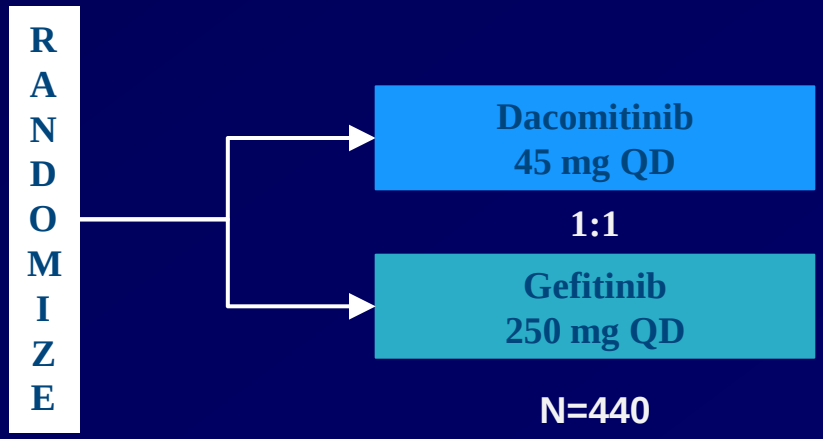
- Afatinib vs Gefitinib 1st line in EGFR mutation positive cases
- Overall survival primary endpoint
- Recruitment completed and read out within next 12 months

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)

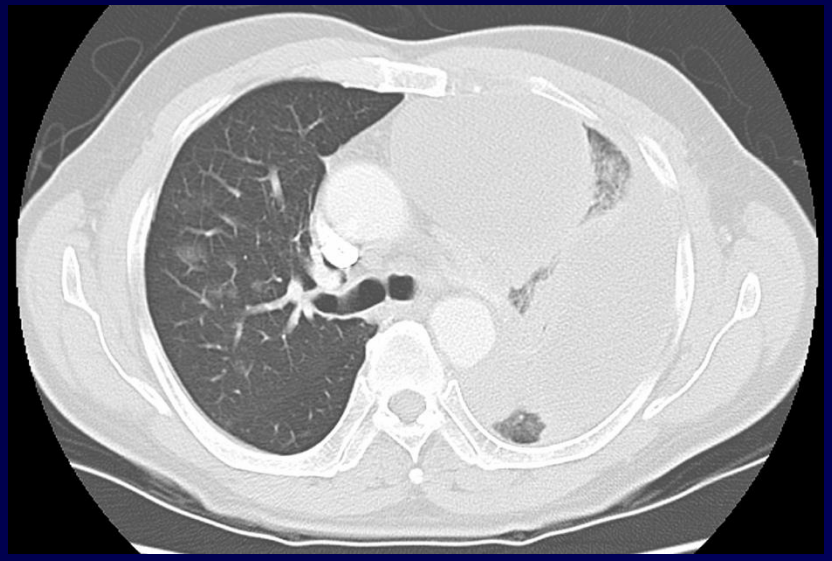
Stage IIIb/IV NSCLC with EGFR activating mutation(s)

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

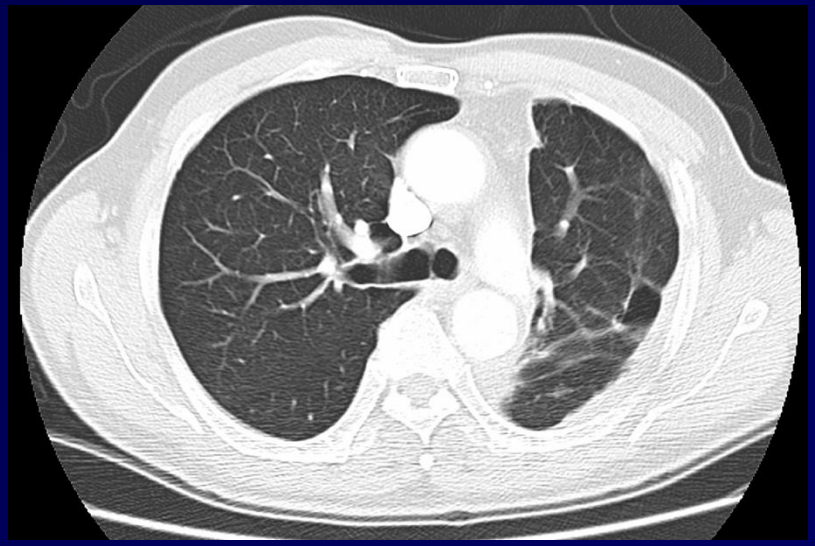


Acquired resistance to EGFR TKIs

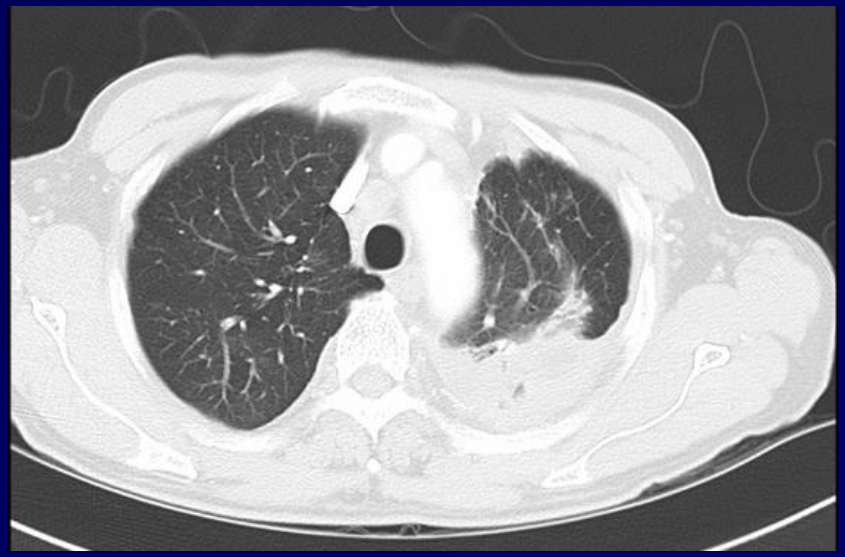
Pre-Erlotinib



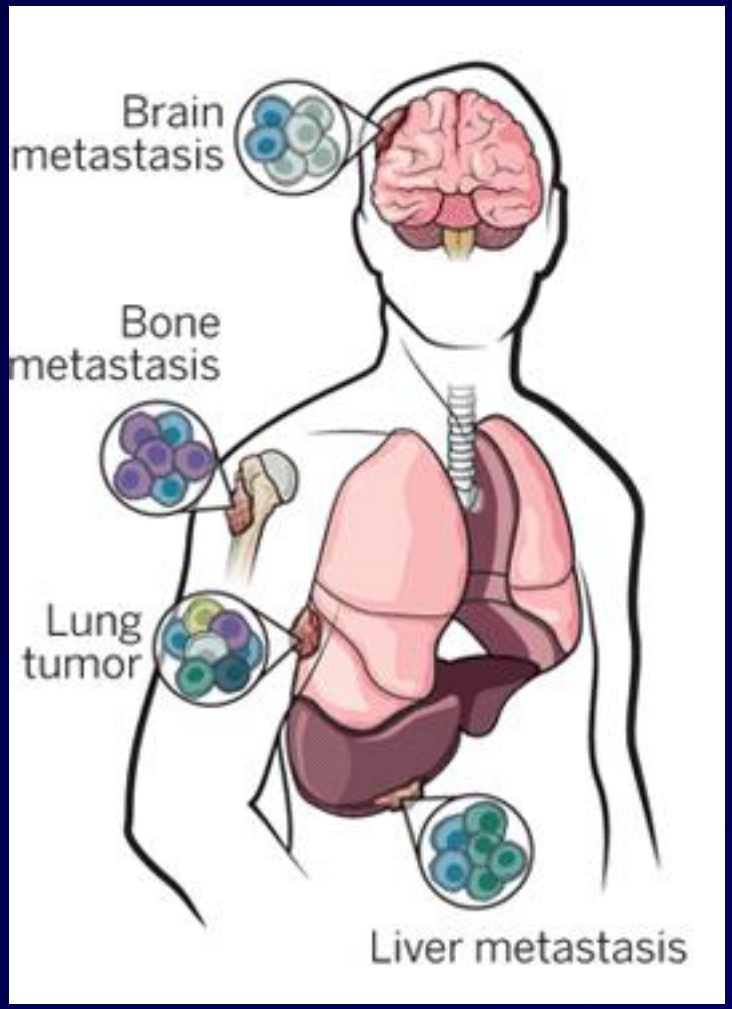
After 6 months Erlotinib

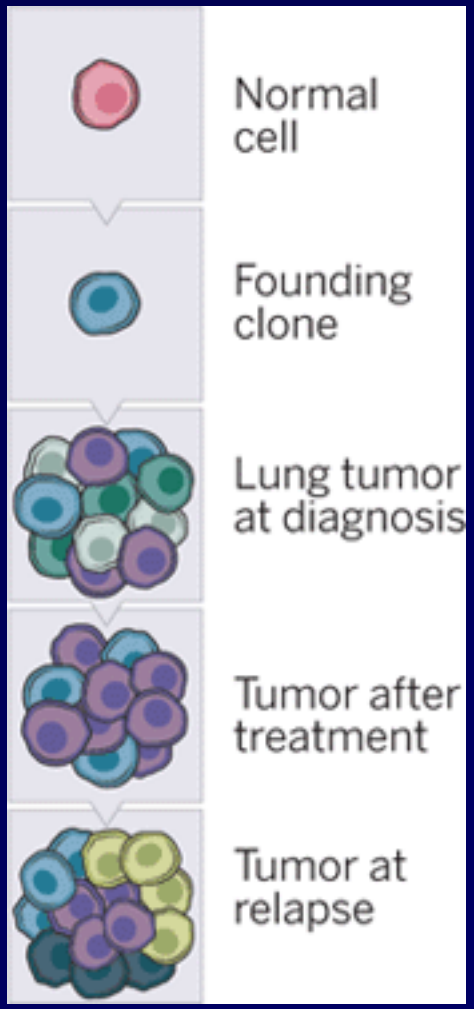


Progression after 18 months Erlotinib



Intrapatient Heterogeneity



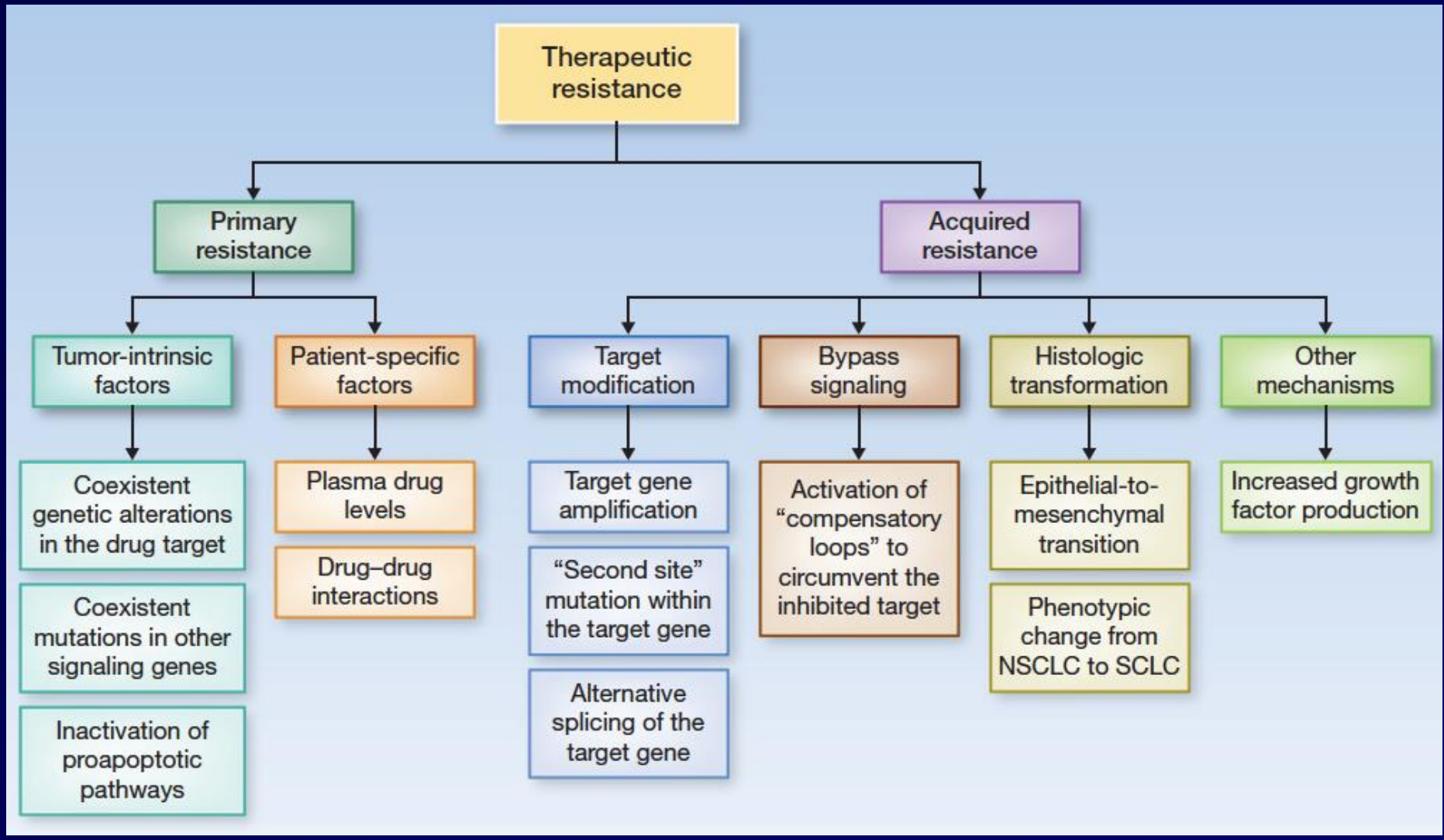


Courtesy Ben Solomon: Govindan, Science 2014; De Brouin Science 2014; Zhang Science 2014

Spatial Heterogeneity

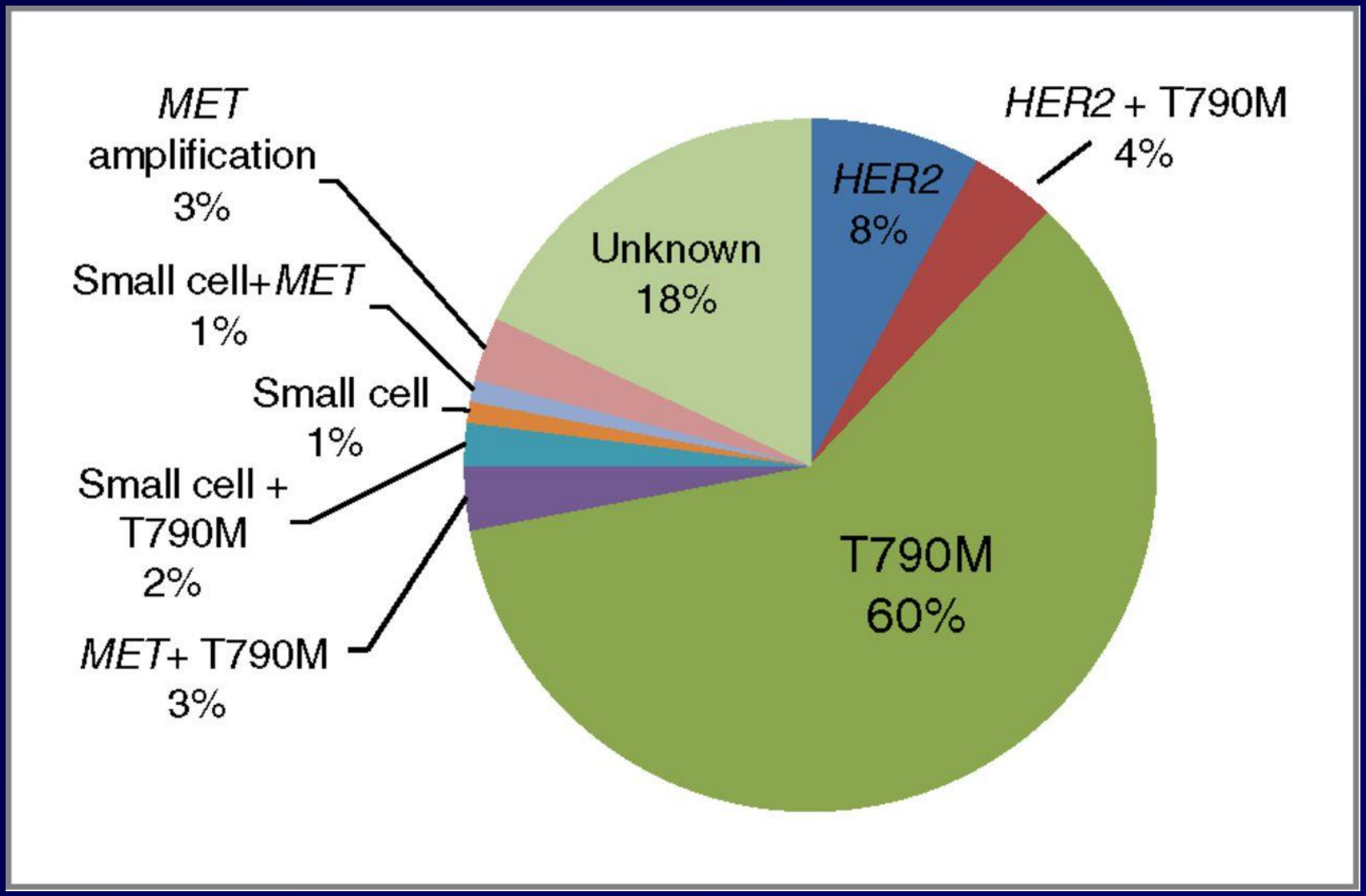
Temporal Heterogeneity

Mechanisms of Resistance to Targeted Therapies



Lovly and Shaw, Clin Cancer Res 20(9):2249-56, 2014

Mechanism of acquired resistance to EGFR TKIs in NSCLC



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

Third Generation EGFR TKIs

- **Currently available EGFR TKI have 2 important limitations**
  - **Wild-type inhibition results in cutaneous toxicity and diarrhea**
  - **Efficacy is limited by emergence of the T790M resistance mutation in ≈60% of patients**

- **3rd generation EGFR TKIs are mutation specific inhibitors that inhibit T790M as well as the classical mutations**
  - **AZD9291**
  - **CO1686 (Rocelitinib)**

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

Key inclusion and exclusion criteria

Key inclusion criteria

- Measurable disease at baseline
- Radiological documentation of disease progression while on a previous continuous treatment with an EGFR-TKI. No limit on prior EGFR-TKI or systemic regimens
- EGFRm positive tumour or clinical benefit from EGFR-TKI according to Jackman criteria[1]
- Dose expansion: confirmation of tumour T790M mutation status (confirmed positive or negative) from a new biopsy sample taken after disease progression on the most recent treatment regimen (EGFR-TKI or chemotherapy)
- Patients with stable, asymptomatic brain metastases (not requiring steroids for ≥4 weeks) were allowed

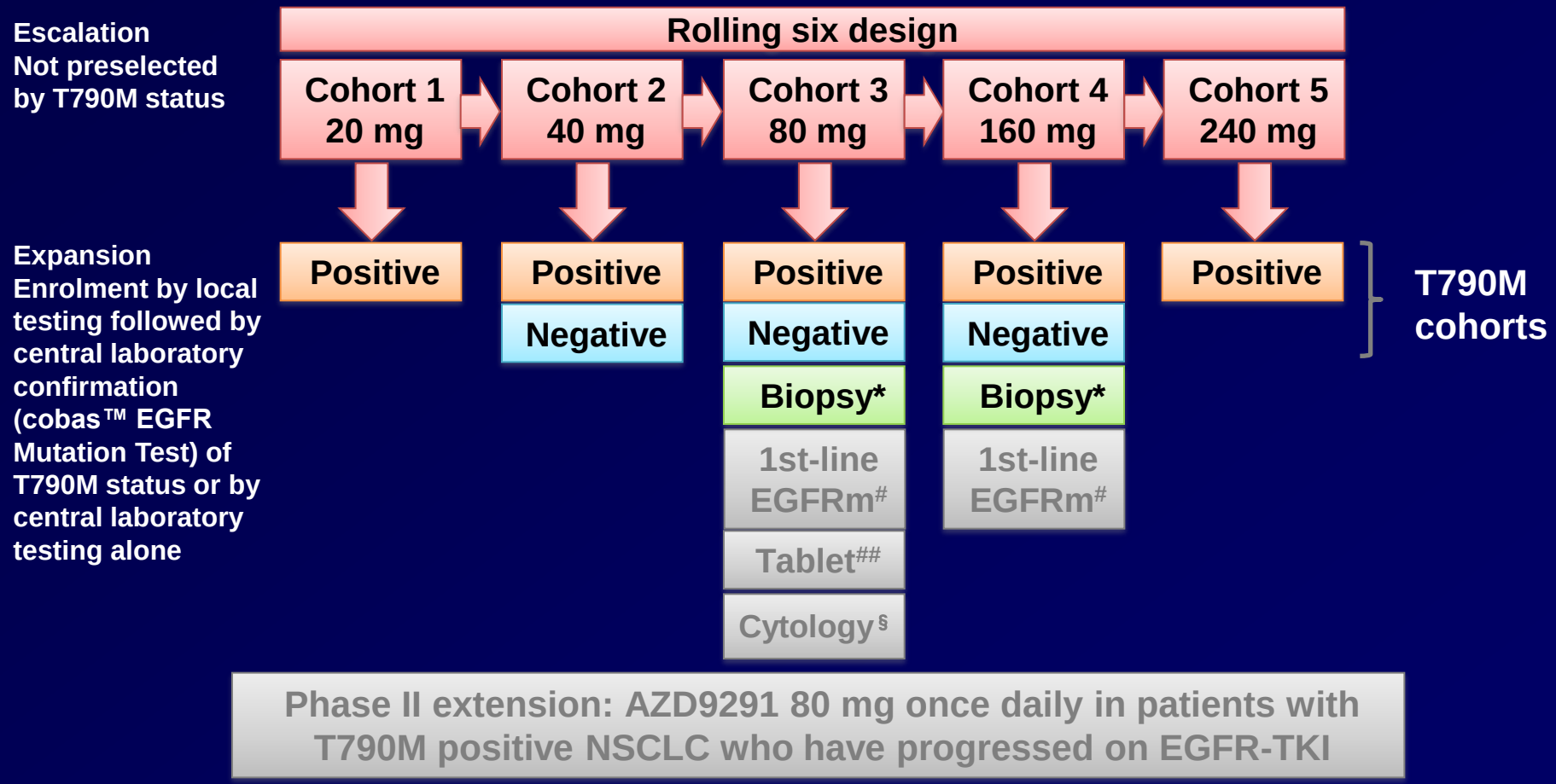
Key exclusion criteria

- Prior history of ILD
- Symptomatic brain metastases

1. Jackman et al. J Clin Oncol 2010;28:357–360
ILD, interstitial lung disease

Phase I / II dose escalation / expansion and extension study design

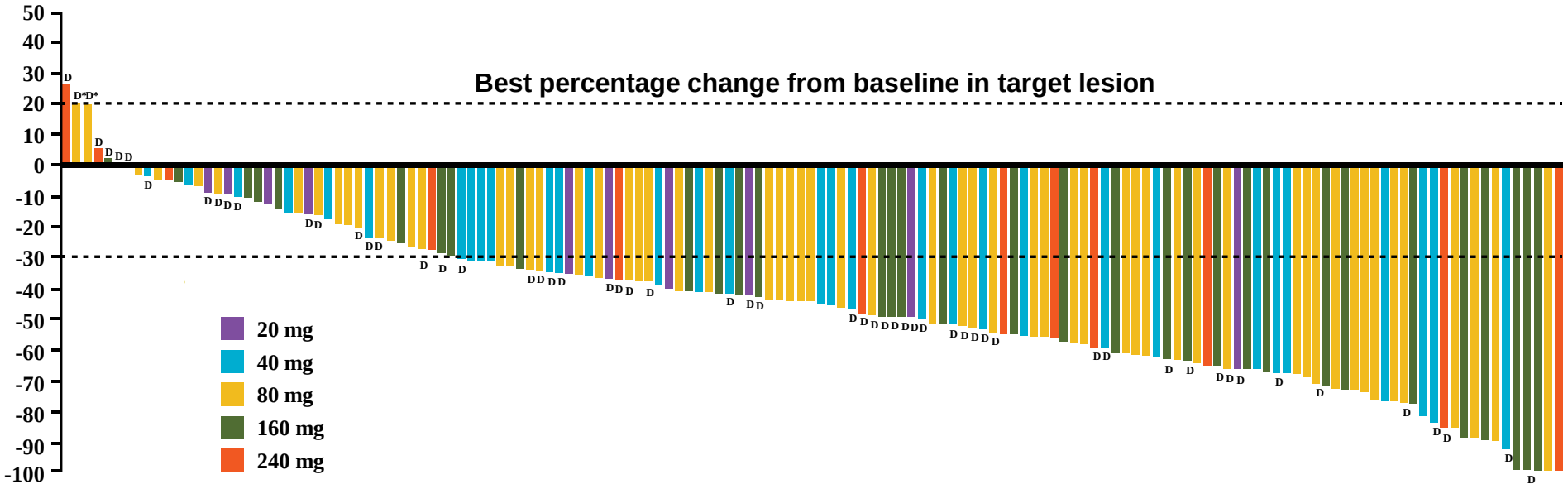
Primary objective – assessment of the safety, tolerability and efficacy (ORR) of AZD9291 in patients with acquired resistance to EGFR-TKIs



*Paired biopsy cohort patients with T790M positive tumours; safety and efficacy data only reported here
#Prior therapy not permissible in this cohort
##Not selected by mutation status, US only
§T790M positive from cytology specimen, Japan only
ORR, objective response rate

Data from cohorts in greyed out boxes are not included in the analyses of p.o. 2 Dec 2014

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

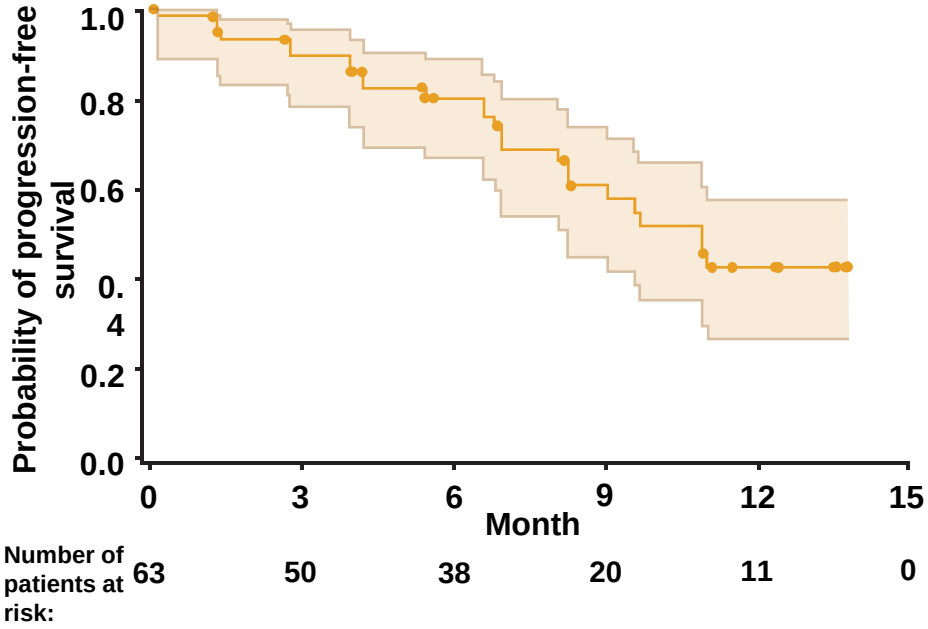
T790M positive (central test) 80 mg cohort – best objective response

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

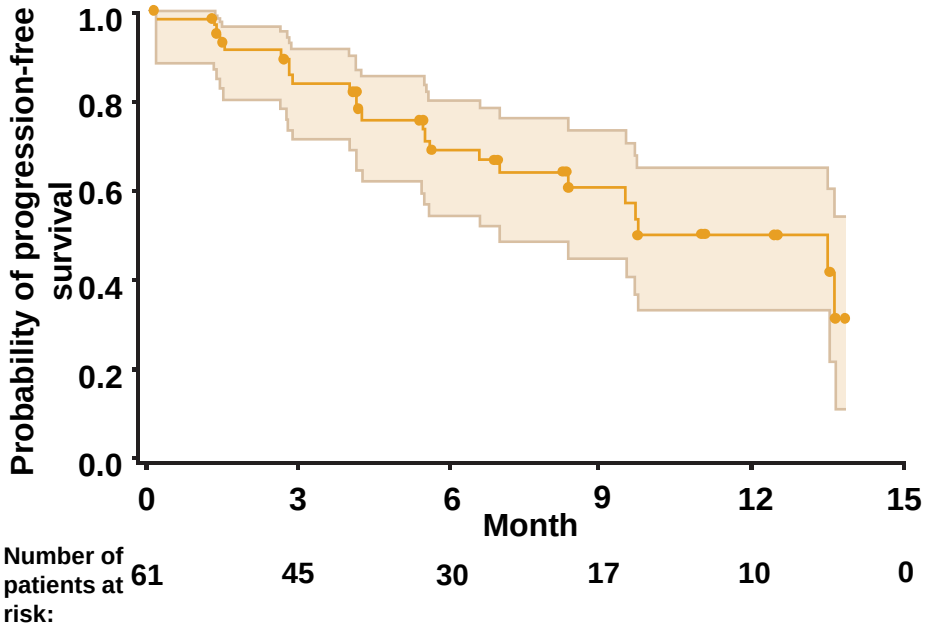
T790M positive (central test) 80 mg cohort – progression-free survival

Investigator assessed



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

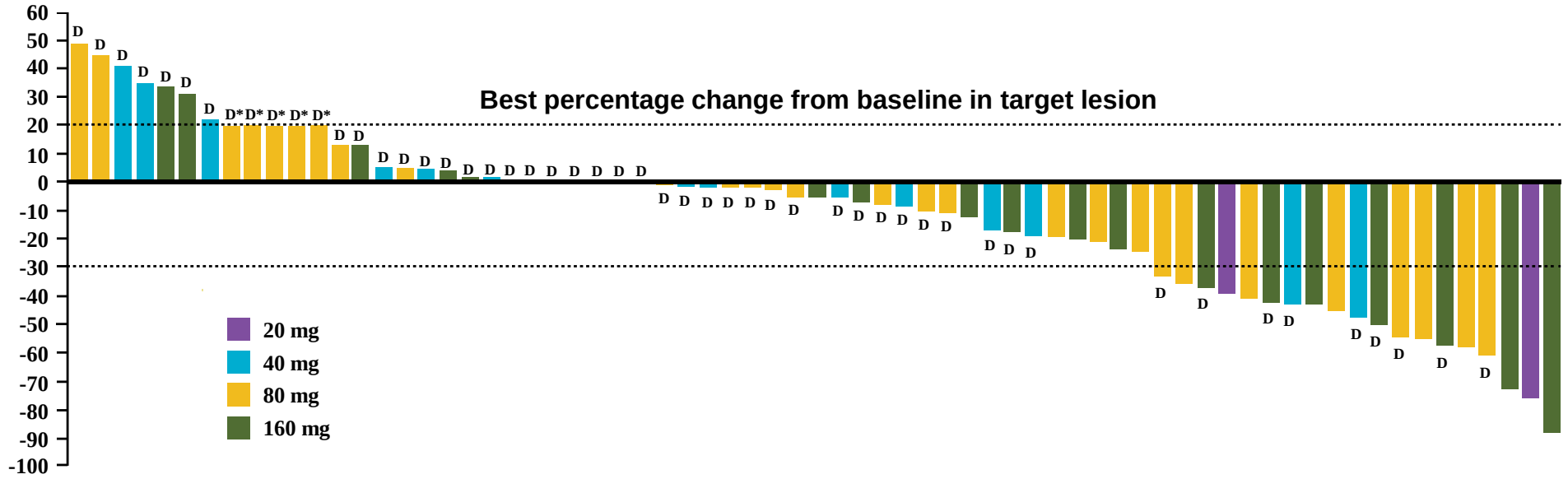
Independent review



- **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)

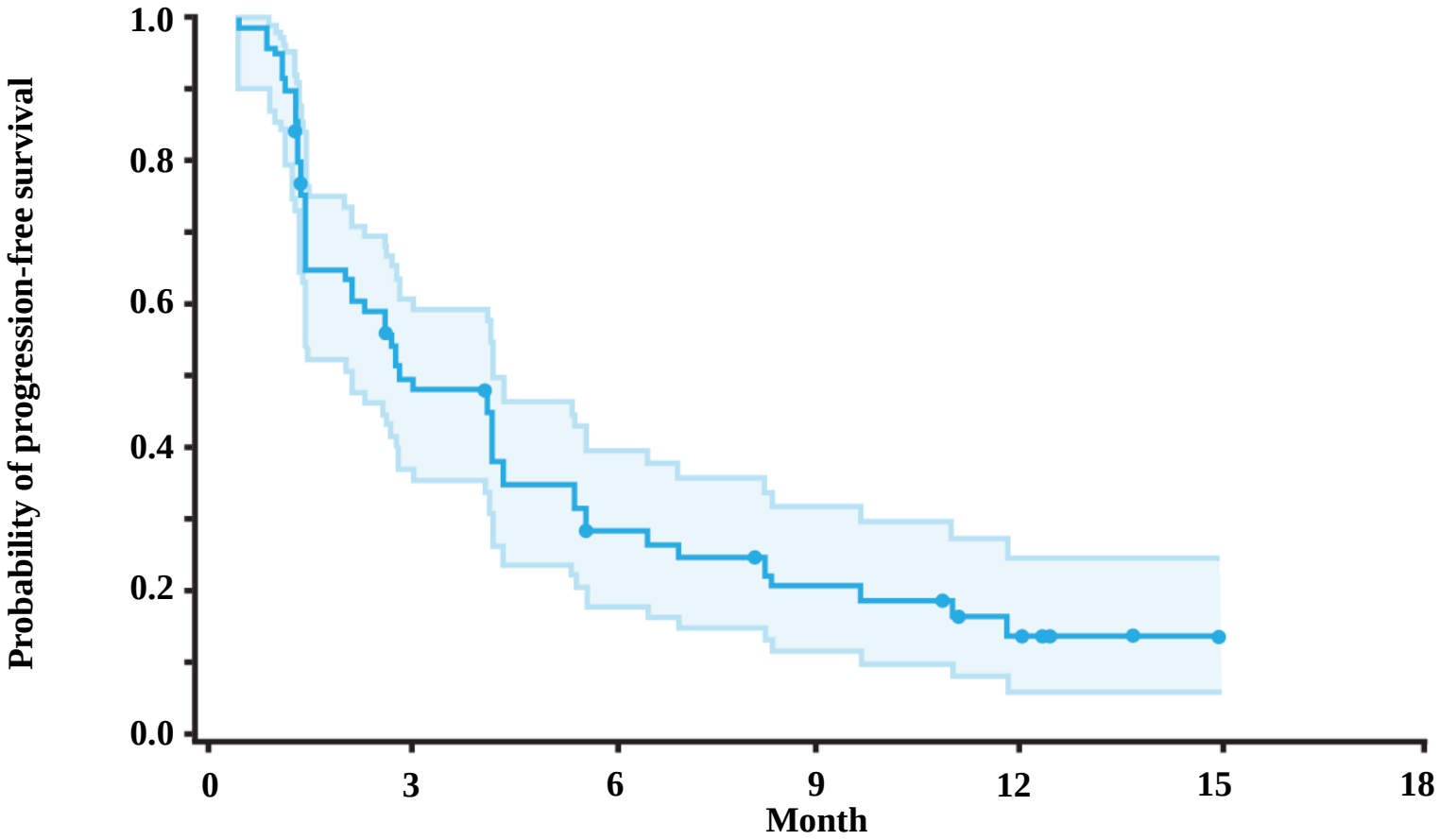


DCR (CR+PR+SD) in patients with centrally tested T790M positive tumours was 64% (44 / 69; 95% CI 51, 75)

	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

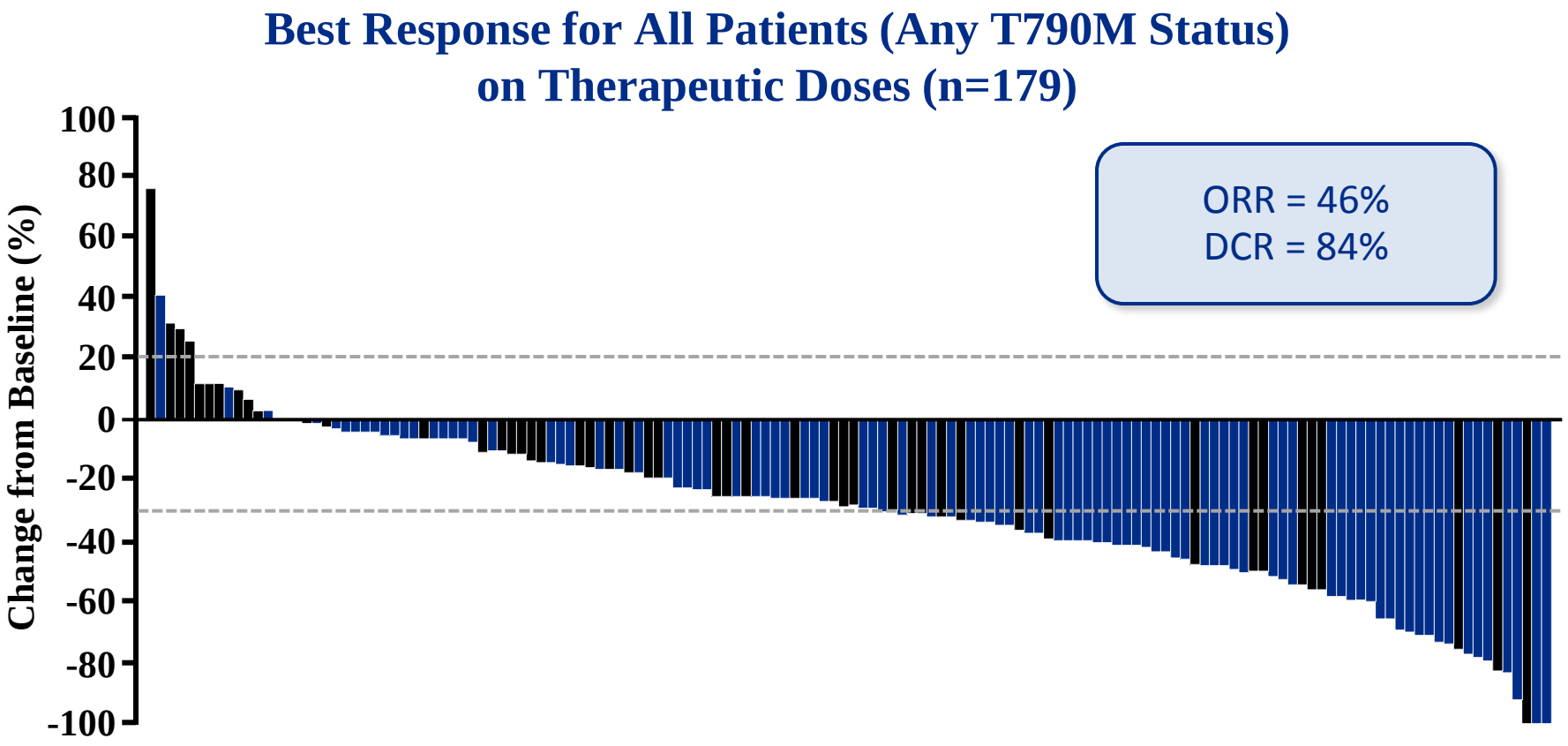
26TH EORTC-NCI-AACR SYMPOSIUM ON
MOLECULAR TARGETS AND CANCER THERAPEUTICS
18-21 NOVEMBER 2014
BARCELONA, SPAIN

Interim phase 2 results with the irreversible, mutant selective, EGFR inhibitor rociletinib (CO-1686)

Jean-Charles Soria,[1] Lecia Sequist,[2] Jonathan Goldman,[3] Heather Wakelee,[4] Shirish Gadgeel,[5] Andreea Varga,[1] Helena Yu,[6] Benjamin Solomon,[7] Sai-Hong Ou,[8] Vassiliki Papadimitrakopoulou,[9] Geoffrey Oxnard,[10] Leora Horn,[11]
Rafal Dziadziuszko,[12] Bo Chao,[13] Alexander Spira,[14] Stephen Liu,[15] Tarek Mekhail,[16] Shannon Matheny,[17] Jason Litten,[17] Ross Camidge[18]

[1]Institut Gustave-Roussy, Paris; [2]Massachusetts General Hospital, Boston; [3]UCLA, Los Angeles; [4]Stanford University, Palo Alto; [5]Karmanos Cancer Institute, Detroit; [6]Memorial Sloan Kettering Cancer Center, New York; [7]Peter MacCallum Cancer Centre, Melbourne; [8]UC Irvine, Orange; [9]MDACC, Houston; [10]Dana Farber Cancer Institute, Boston; [11]Vanderbilt University, Nashville; [12]Medical University of Gdansk, Gdansk; [13]Ohio State University, Columbus; [14]Virginia Cancer Specialists, Fairfax; [15]Georgetown University, Washington DC; [16]Florida Hospital Cancer Institute, Orlando; [17]Clovis Oncology, Boulder; [18]University of Colorado Cancer Center, Aurora

Combined responses from TIGER-X Phase 1/2



DCR=disease control rate; ORR=overall response rate.

Rocelitinib (CO1686) – Adverse events

Treatment-related adverse events (all grades) seen in >10% of patients

Adverse event	Frequency, %
Hyperglycemia	32
Diarrhea	25
Nausea	25
Reduced appetite	20
Fatigue	14
Muscle spasm	13
Vomiting	11

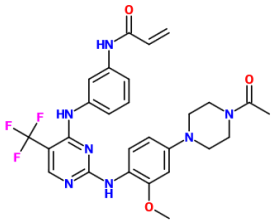
Grade 3/4 treatment-related adverse events seen in >5% of patients*

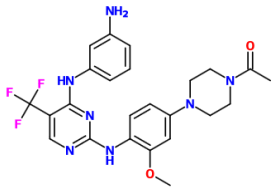
Adverse event	Frequency, %
Hyperglycemia	14

*21% of patients had a grade 3/4 treatment-related adverse event and only hyperglycemia was observed in ≥5% of patients

Observed hyperglycemia relates to metabolite of rociletinib

- **Rociletinib metabolite M502 is an inhibitor of IGF1R and accumulates in humans causing hyperglycemia**
  - **No hyperglycemia observed in toxicology studies of rociletinib**
- **Like rociletinib, M502 is wild-type EGFR sparing**



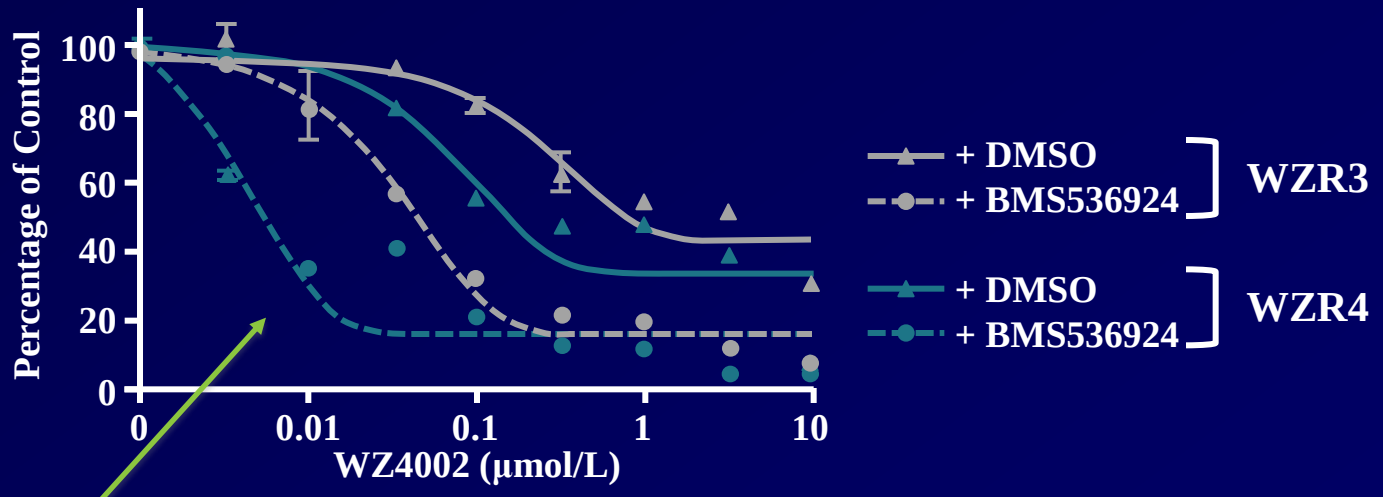


Assay	Rociletinib	M502
A431 (IC_{50}, nM) Cellular (wild-type EGFR)	903	907
NCI-H1975 (IC_{50}, nM) Cellular (T790M EGFR)	36	961
IGF1R (IC_{50}, nM) Kinase	477	57
IGF1R (IC_{50}, nM) Cellular	458	58

IC_{50}=half maximal inhibitory concentration; IGF1R=insulin-like growth factor 1 receptor.

IGF1R pathway activation may play a role in acquired resistance to EGFR TKI

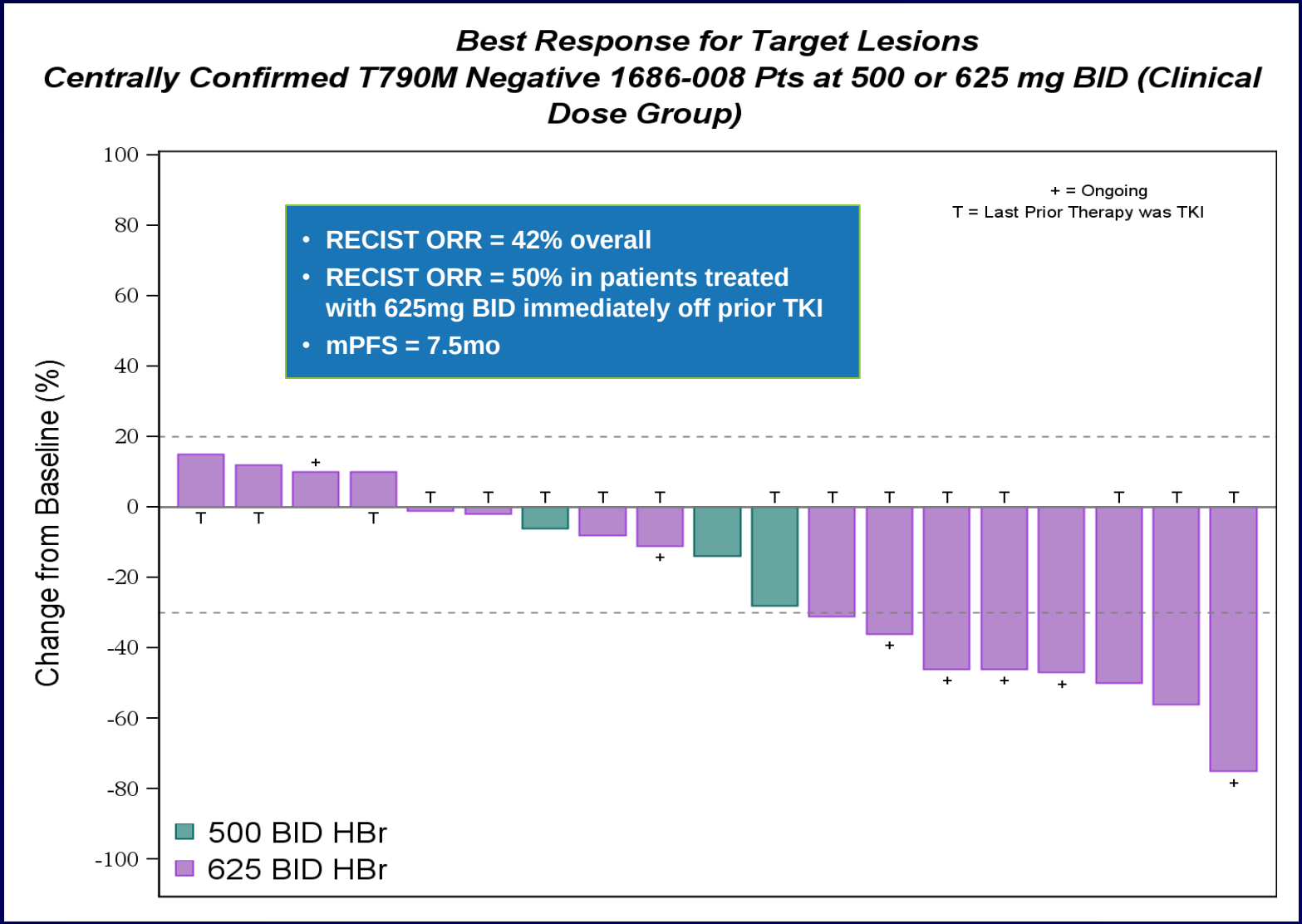
- Multiple publications have demonstrated a role for IGF1R signaling in mediating resistance to EGFR inhibitors in NSCLC models
  - Resistance to WZ4002 (a third-generation EGFR inhibitor structurally related to CO-1686) is mediated by IGF1R signaling and can be reversed by the addition of an IGF1R inhibitor (data from Janne lab)



WZ4002 + IGF1R inhibitor BMS536924 restores activity in resistant cell lines with IGF1R pathway activation

Cortot AB et al. *Cancer Res*. 2013;73:834-843; Sharma SV et al. *Cell*. 2010;141:69-80; Vazquez-Martin A et al. *Sci Rep*. 2013;3:2560.

Striking Activity in T790M-negative Patients



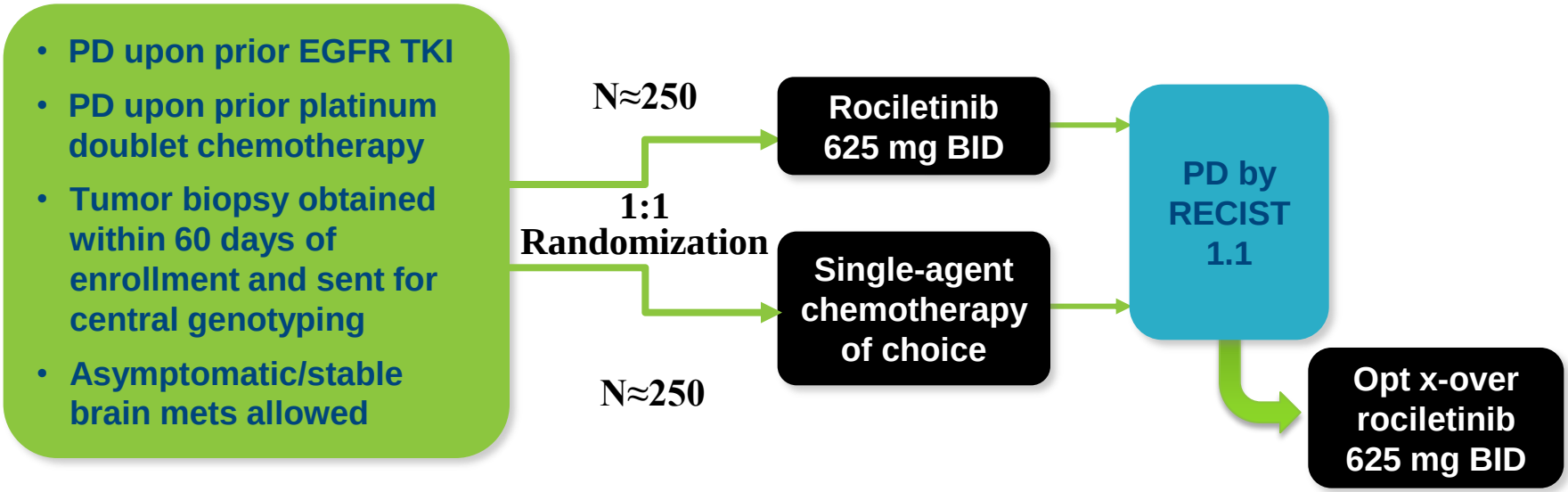
**Database as of January 2nd 2015*

Ongoing confirmatory studies

AURA3 Phase III (NCT0215198; recruiting)	• Phase III study designed to compare the efficacy and safety of AZD9291 vs platinum-based doublet chemotherapy in patients with EGFRm and T790M positive advanced NSCLC whose disease has progressed following prior therapy with an EGFR-TKI
AURA extension, Phase II (NCT01802632; active, not recruiting)	• Phase II study designed to assess the effects of AZD9291 in patients with advanced NSCLC with disease progression following prior therapy with an EGFR-TKI; prospective central confirmation of T790M positive status is a requirement
AURA2 Phase II (NCT02094261; active, not recruiting)	• Phase II, global, pivotal study designed to assess the efficacy and safety of AZD9291 after previous EGFR-TKI therapy in patients with EGFRm and T790M positive advanced NSCLC

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

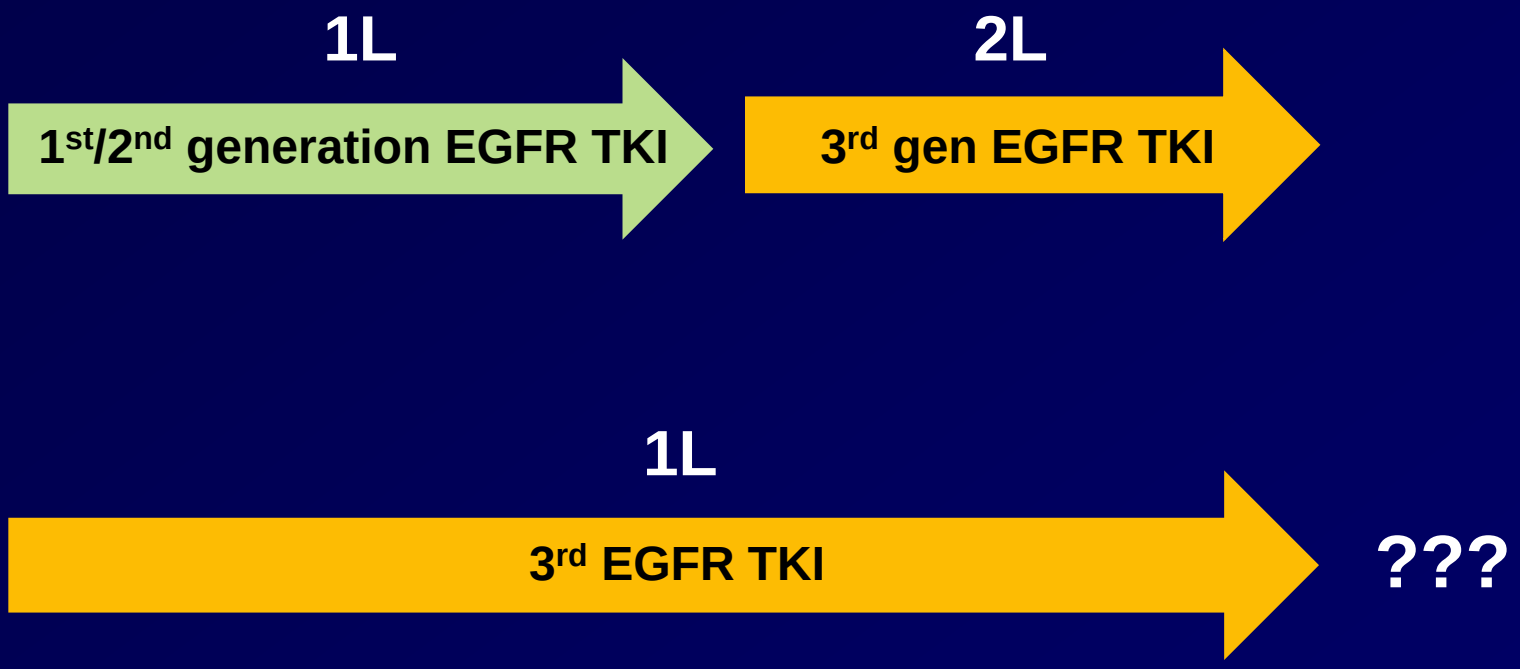
TIGER-3: International, randomized, phase 3 study in ≥3rd line mutant EGFR NSCLC, both T790M+ and T790M–



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

Mets=metastases; PD=progressive disease.

What is Optimal First-Line Therapy for EGFR mut NSCLC



Conclusions

- 2nd gen pan-HER TKIs have consistent impressive activity in EGFR mu disease - ?superior to 1st gen agents
- 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!

Physician's Dilemma…..

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