GIOTRIF® (afatinib) for Squamous Cell Carcinoma of the Lung

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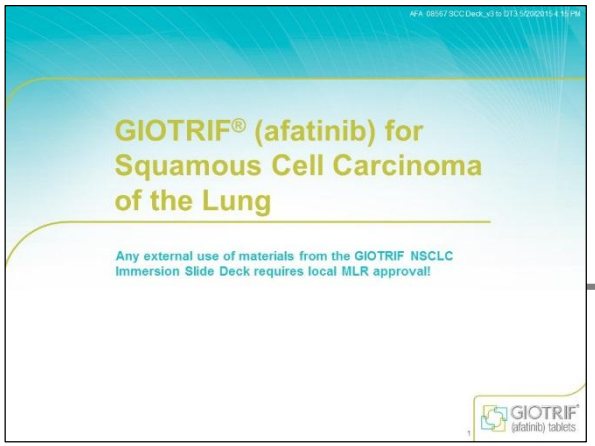

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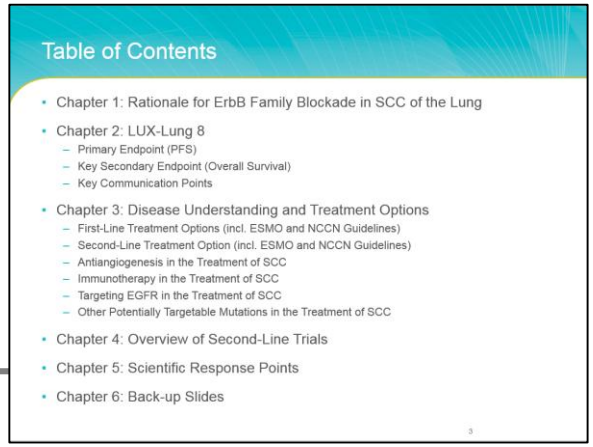

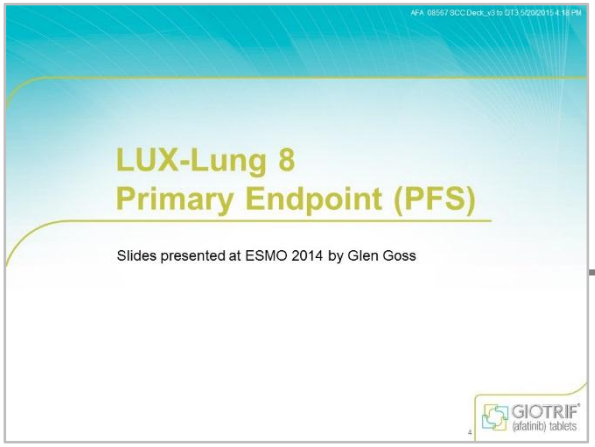

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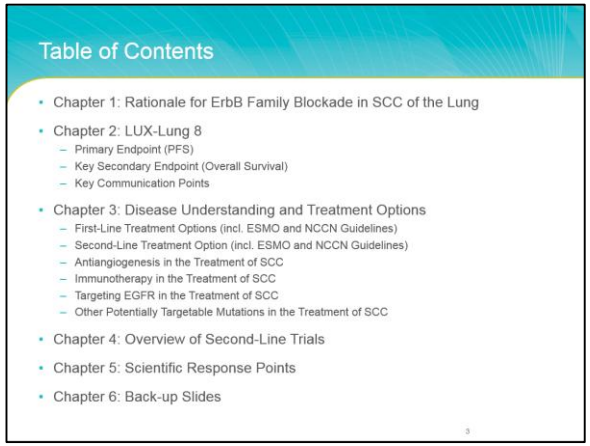

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Rationale for ErbB Receptors Blockade in SCC of the Lung

Alterations of ErbB Pathway in SCC of the Lung

EGFR overexpression and/or gene amplification

Aberrations of other ErbB receptors

Dysregulation of downstream pathway

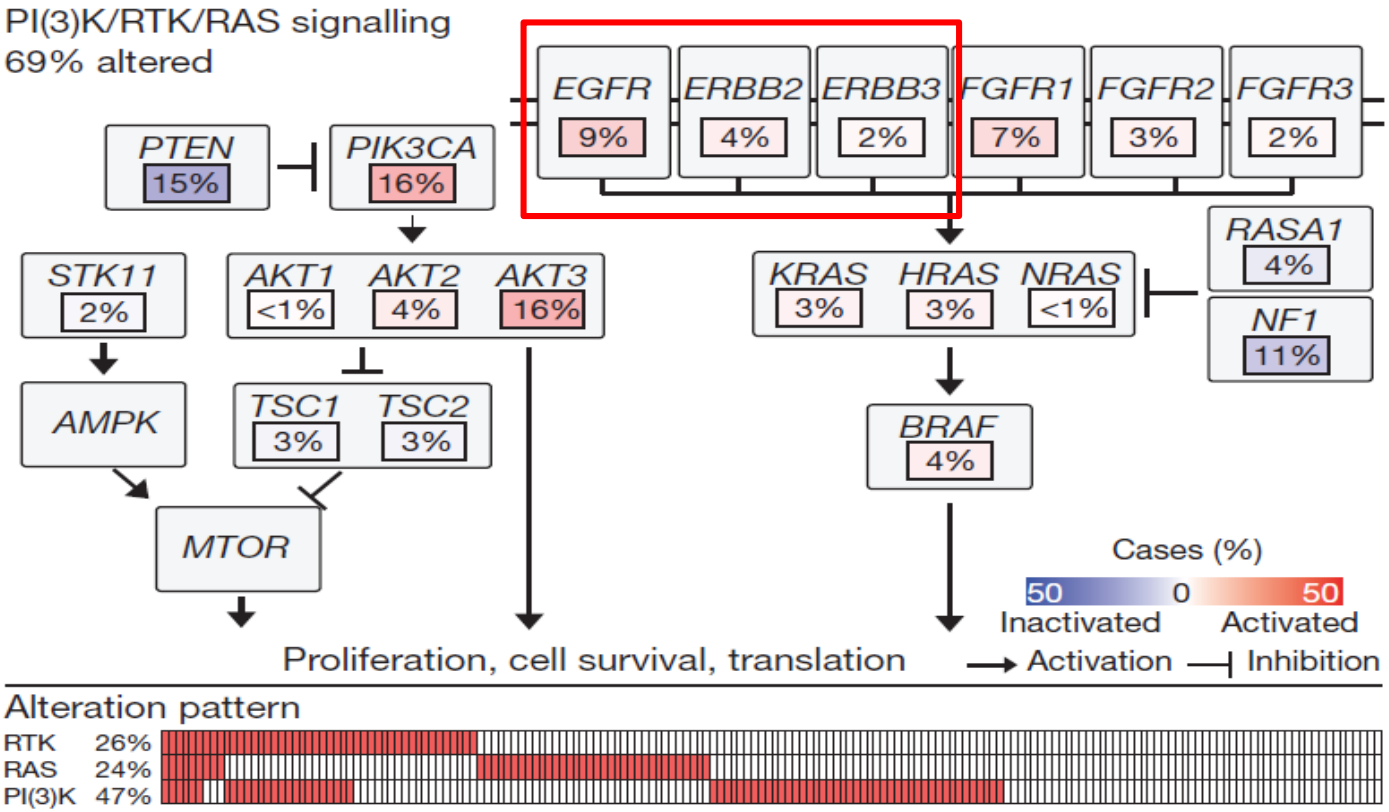
Implicated in the pathobiology of SCC

ErbB Receptor	Frequency (%)
EGFR overexpression	57-82
EGFR amp	7-26
*EGFR*vIII mut	3-5
EGFR kinase domain mut	1-3
ERBB2 mut/amp	4
ERBB3 mut	1-2
ERBB3 overexpression	28
ERBB4	1-2

1. D'Arcangelo et al. *Future Oncol.* 2013;9:699; 2. Jaiswal et al. *Cancer Cell.* 2013;23:603; 3. Kan et al. *Nature.* 2010;466:869; 4. Hirsch et al. *J Clin Oncol*. 2003;21:3798; 5. Dacic et al. *Am J Clin Pathol*. 2006;125:860; 6. Lopez-Malpartida et al. *Lung Cancer.* 2009;65:25; 7. Lee et al. *Lung Cancer.* 2010;68:375; Gately K et al Clin Lung Cancer 2014; 15:58.

Cancer Genome Atlas Research Network
Alterations in Targetable Oncogenic Pathways in SCC tumors

- **Analysis of 178 patients with SCC tumours**
- *EGFR* mutations in two cases, although these were different from those found in ADC
- Alterations in the PI3K/AKT pathway genes were mutually exclusive with *EGFR* alterations



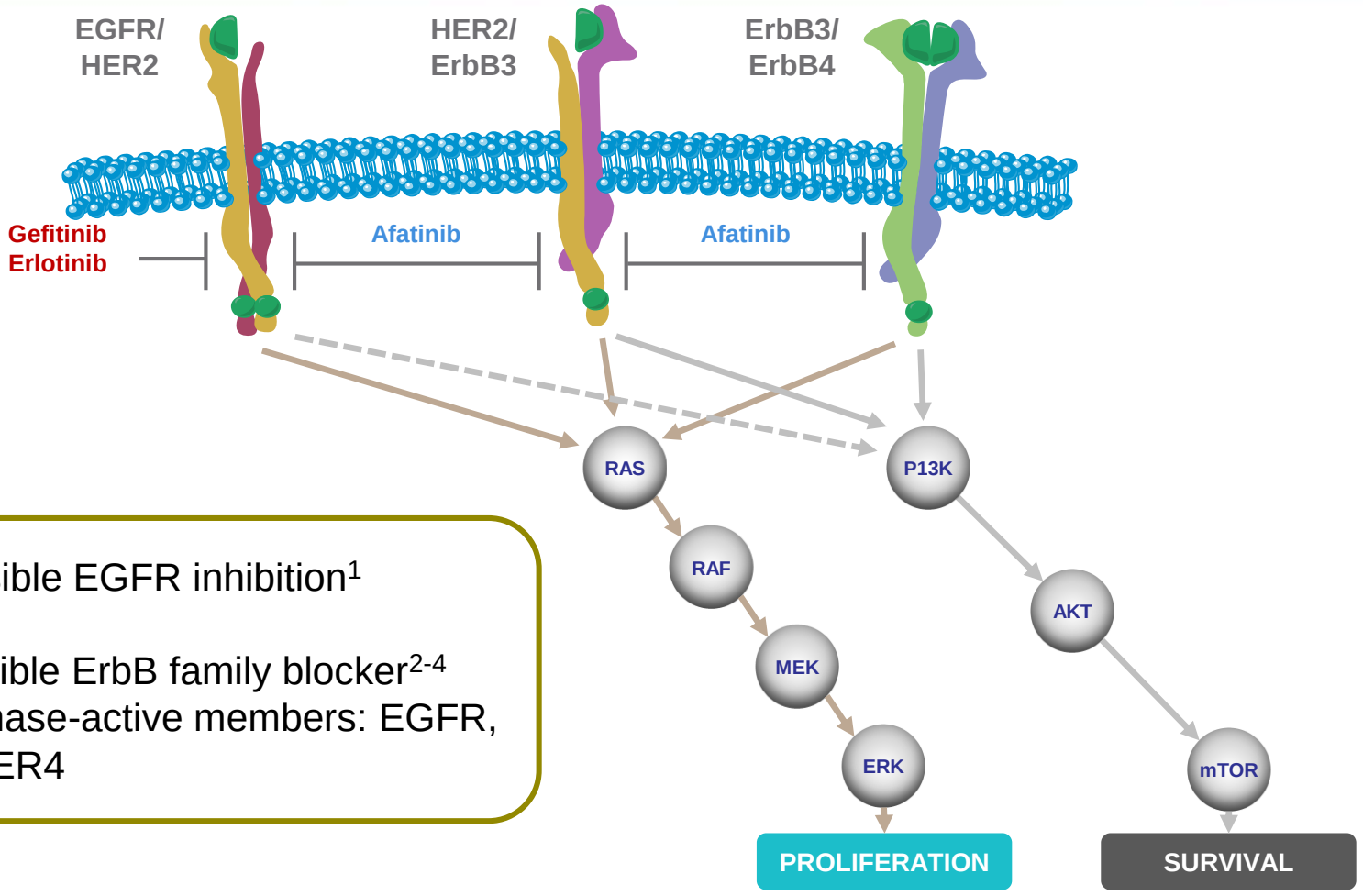
Cancer Genome Atlas Research Network. *Nature*. 2012;489:519-25.

Rationale for ErbB Family Inhibition in the Treatment of SCC of the Lung

- SCC of the lung is known to have high EGFR overexpression and gene amplification, aberrations of other ErbB receptors, and dysregulation of downstream pathway has been implicated in pathobiology of SCC[1,2]
- These findings likely account for the benefits these patients derive from erlotinib[3-5] and other EGFR-directed therapies in different treatment settings[6-8], despite the low frequency of EGFR-activating mutations[9]
- Erlotinib is an approved treatment for second-line locally advanced or metastatic NSCLC[10]
- Afatinib showed anti-tumour activity when investigated in patients with SCC of the lung (ORR=4.4%; DCR=60.4%; LUX-Lung 5)[11] and head & neck cancer[12,13]

1. Hirsch et al. *J Clin Oncol*. 2003;21:3798; 2. Lopez-Malpartida et al. *Lung Cancer*. 2009;65:25; 3. Shepherd et al. *N Engl J Med*. 2005;352:123;
4. Clark et al. *Clin Lung Cancer*. 2006;7:389; 5. Leon et al. ESMO 2008. 1277P; 6. Pirker et al. *Lancet*. 2009;373:1525-31;
7. Pirker et al. *Lancet Oncol*. 2012;13:33; 8. Thatcher et al. ASCO 2014. Abstract 8008; 9. Dearden et al. *Ann Oncol*. 2013;24:2371;
10. Tarceva Prescribing Information; 11. D'Arcangelo et al. *Future Oncol*. 2013;9:699; 12. Seiwert et al. *Ann Oncol.* 2014;25:1813;
13. Machiels et al. *Lancet Oncol*. 2015;16:583.

Targeting ErbB Pathway



Erlotinib: Reversible EGFR inhibition[1]

Afatinib: Irreversible ErbB family blocker[2-4]

- Inhibits all kinase-active members: EGFR, HER2 and HER4

EGFR = epidermal growth factor receptor; HER2 = human epidermal growth factor receptor-2; ; ErbB3 = human epidermal growth factor receptor-3 ErbB4 = human epidermal growth factor receptor-4

1. Schettino et al. Expert Rev Respir Med. 2008;2:167-78; 2. Li D, et al. Oncogene 2008;27:4702–11; 3. Solca F, et al. J Pharmacol Exp Ther 2012;343:342–50; 4. Yarden Y, Pines. G Nat Rev Cancer. 2012;12:553.

LUX-Lung 8
Primary Endpoint (PFS)

Goss et al. ESMO 2014 Abstract 12220

Background

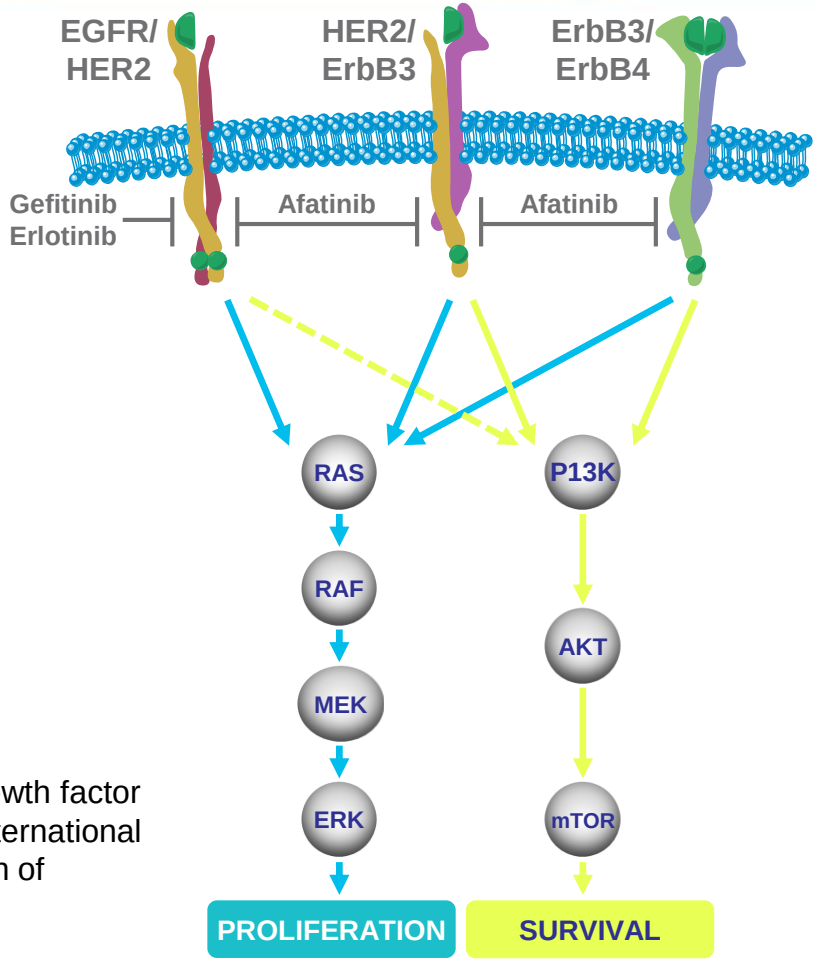
- Squamous histology represents approximately 30% of NSCLC[1,2]
- Limited progress and therapeutic options for patients in second-line setting
  - Targetable oncogenic alterations are limited and have not yet translated to a therapeutic paradigm
  - Patients often have extensive comorbidities
  - Erlotinib – last drug approved (in 2005)[3]
    - Based on efficacy vs placebo in second-/third-line setting[4]
    - Survival benefit confirmed in subset analysis of male ever-smokers with squamous cell carcinoma[5]

NSCLC = non–small cell lung cancer.

1. Heighway and Betticher. *Atlas Genet Cytogenet Oncol Haematol*. 2004;8:133.
2. Bryant and Cerfolio. *Chest*. 2007;132:185.
3. Tarceva EPAR assessment EMA 2007. http://www.ema.europa.eu. Accessed September 5, 2014.
4. Shepherd et al. *N Engl J Med.* 2005;353:123.
5. Clark et al. *Clin Lung Cancer*. 2006;7:389.

Afatinib: Irreversible ErbB Family Inhibition

- Afatinib is an irreversible ErbB-family blocker[1,2]
  - 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[a] in the major ICH regions of US,[3] EU[4] and Japan[5] for the treatment of patients with NSCLC harbouring distinct types of EGFR-activating mutations

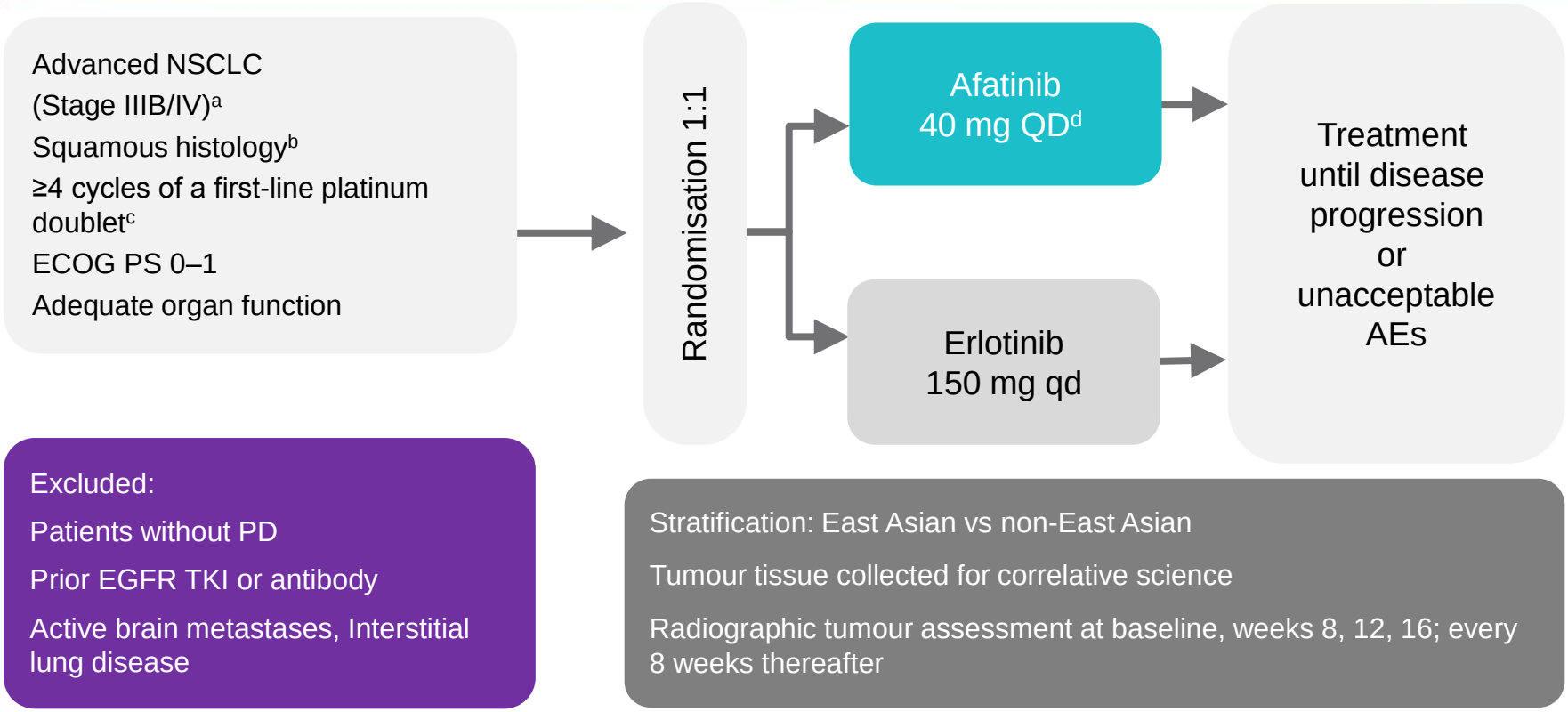


EGFR = epidermal growth factor receptor; HER2 = human epidermal growth factor receptor-2; HER4 = human epidermal growth factor receptor-4; ICH = International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

[a]Indications differ between countries.

1. Li et al. *Oncogene.* 2008;27:4702.
2. Solca et al. *J Pharmacol Exp Ther.* 2012;343:342.
3. Gilotrif Prescribing Information 2013.
4. Giotrif EPAR Assessment EMA 2013.
5. PMDA Japan New Drug Approvals 2013.

LUX-Lung 8: Study Design



[a]American Joint Committee on Cancer Staging Manual, 7th edition.
[b]As determined by the investigator, tumours with mixed histology allowed.
[c]Patients progressing within 6 months of receiving adjuvant/neoadjuvant chemo/chemoradiotherapy were allowed (as long as ≥4 cycles criterion was met).
[d]Dose escalation to 50 mg at cycle 2 for patients meeting adverse event criteria.
ECOG = Eastern Cooperative Oncology Group; PS = performance status; AE = adverse events; PD = progressive disease; TKI = tyrosine kinase inhibitor.

Goss et al. ESMO 2014. Abstract 12220.

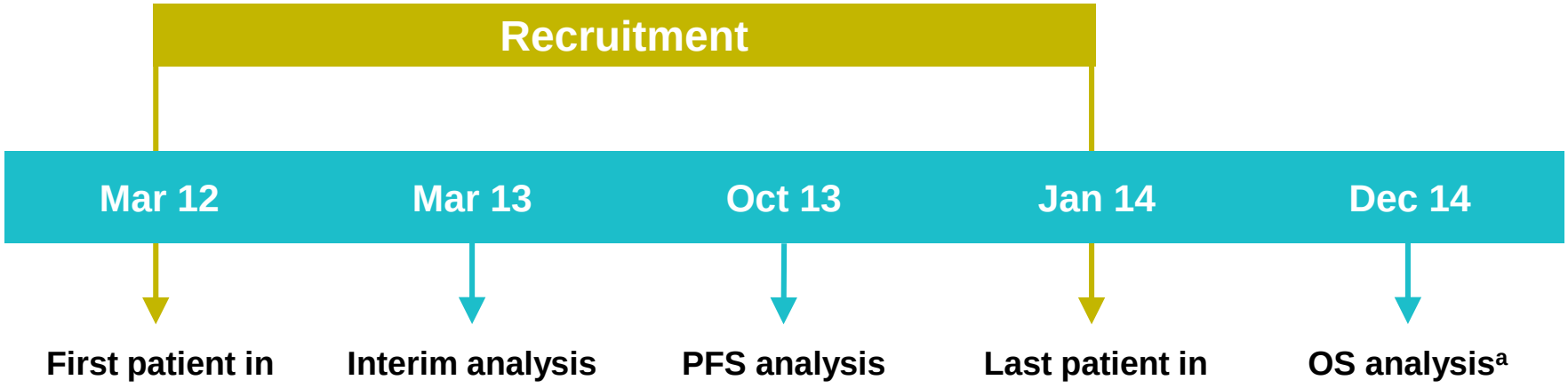
Endpoints

- Primary endpoint – Progression-free survival by central independent radiology review (RECIST 1.1)
- Key secondary endpoint – Overall survival
- Secondary endpoints
  - Objective response rate
  - Disease control rate
  - Tumour shrinkage
  - Health-related quality of life
  - Safety in both treatment groups

RECIST = Response Evaluation Criteria in Solid Tumours.

Goss et al. ESMO 2014. Abstract 12220.

Timelines and Interim Futility Analysis



- An interim futility analysis was performed by an independent DMC and the trial was allowed to accrue to the planned 800 patients
- The PFS primary analysis was conducted when trial recruitment was ongoing

DMC = data monitoring committee; OS = overall survival; PFS = progression-free survival.
[a]Event-dependent.

Goss et al. ESMO 2014. Abstract 12220.

Statistical Assumptions

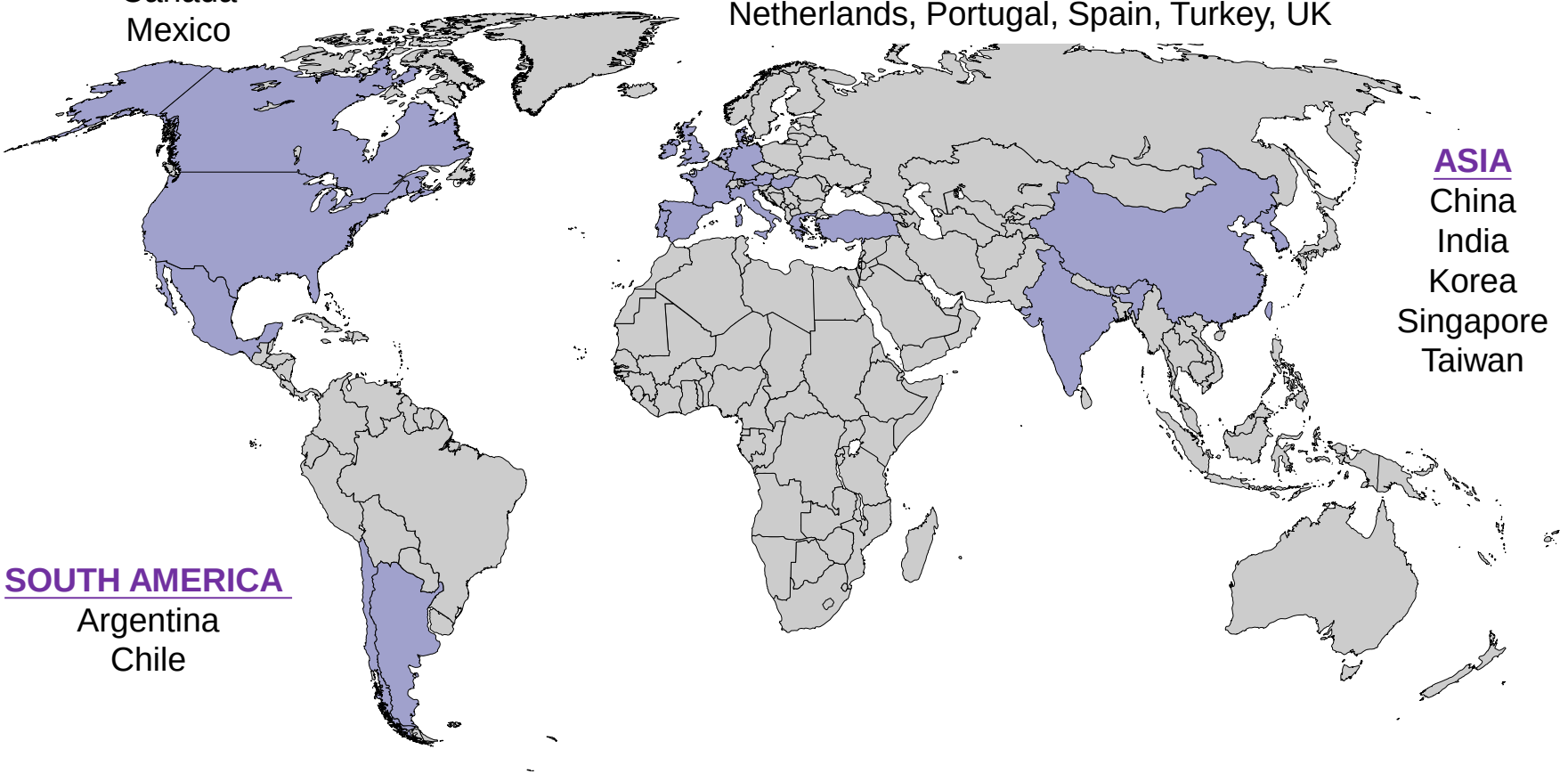
- Primary endpoint – PFS by Independent Radiology Review (RECIST 1.1)
  - Assuming a median PFS of 14 weeks in the afatinib arm and 10 weeks in the erlotinib arm, ≥372 events and a sample size of 500 were required for 90% power to detect a hazard ratio of 0.714 using a two-sided level test
- Key secondary endpoint – OS to be tested only if PFS showed statistical significance (P<0.05, two-sided)
  - A median OS of 8.75 months with afatinib and 7 months with erlotinib required ≥632 events and a sample size of 800 for 80% power to detect a hazard ratio of 0.8 (two-sided)

Goss et al. ESMO 2014. Abstract 12220.

LUX-Lung 8: Global Randomised Phase 3 Trial

NORTH AMERICA
USA
Canada
Mexico

EUROPE
Austria, Denmark, France, Germany, Greece, Hungary, Ireland, Italy, Netherlands, Portugal, Spain, Turkey, UK



ASIA
China
India
Korea
Singapore
Taiwan

SOUTH AMERICA
Argentina
Chile

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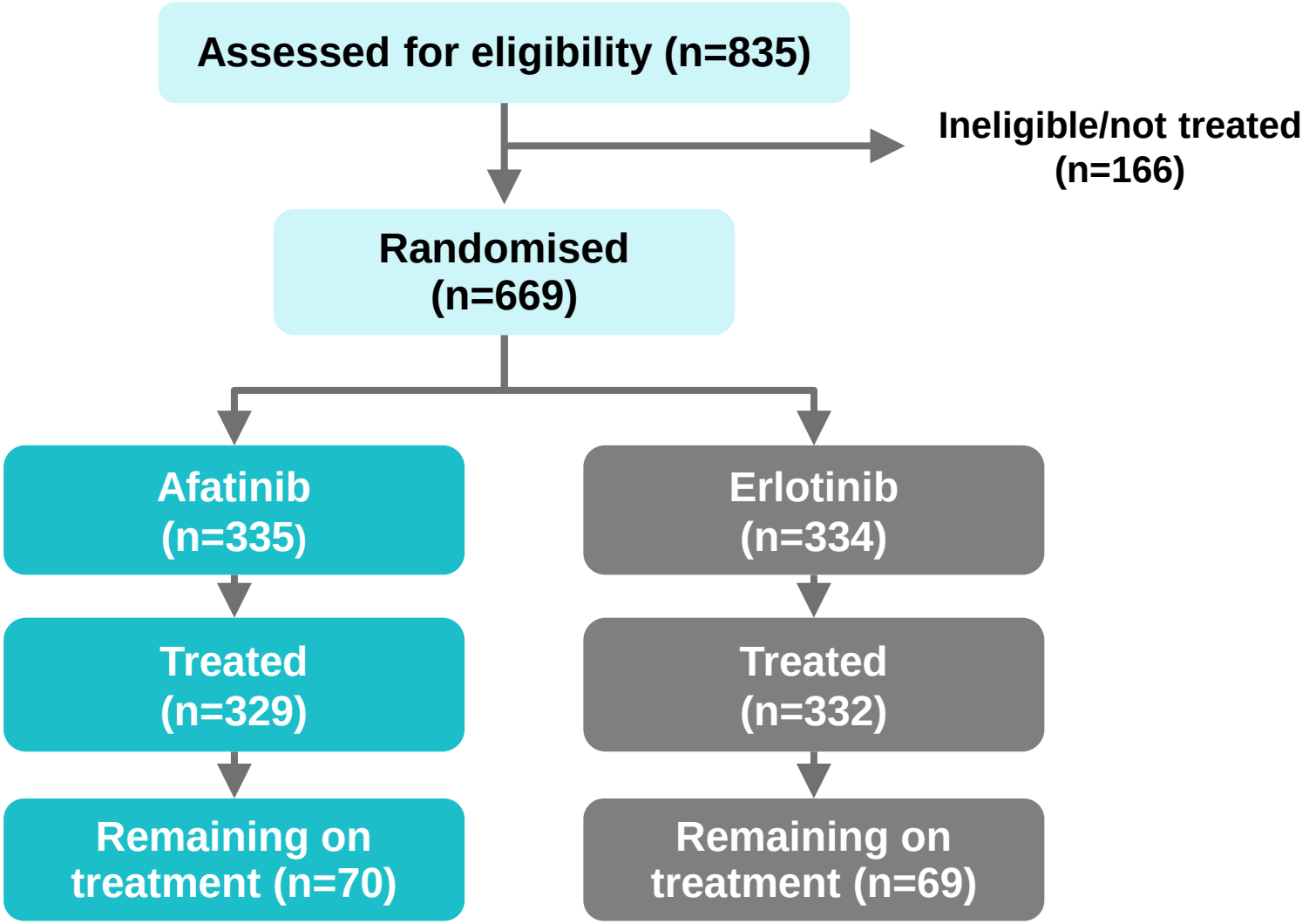
Primary PFS Analysis



Goss et al. ESMO 2014. Abstract 12220.

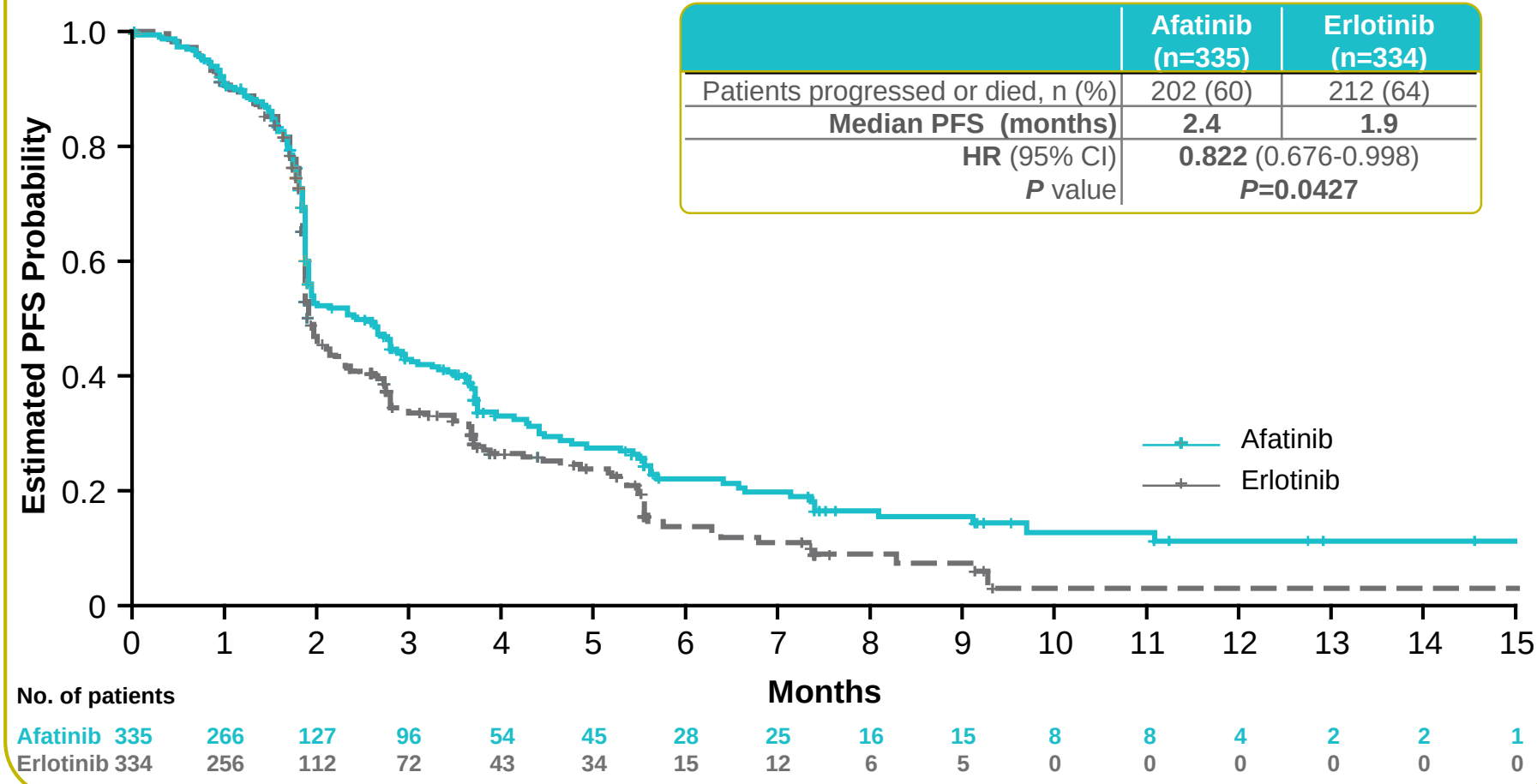
Demographics and Baseline Characteristics

		Afatinib[g]	Erlotinib[g]	Total
Number randomised		335	334	669
ECOG[a], %	0	33	35	34
	1	66	65	66
Male, %		85	84	85
Race (for stratification), %	Non-East Asian	78	78	78
	East Asian	22	23	22
Median age, years		65	64	65
Smoking history, %	Never smoker	8	3	5
	Ex-smoker[e]	7	6	7
	Smoker	85	91	88
Median time since diagnosis, years		0.7	0.8	0.8
Clinical stage[b], %	IIIB	13	12	12
	IV	88	87	87
Histology[c], %	Squamous	96	96	96
	Mixed type[f]	5	3	4
Prior chemotherapy, %	Platinum-doublet	100	100	100
Best response to first-line chemotherapy[d], %	CR/PR	47	46	46
	SD	41	43	42
	Unknown	13	11	12

CR = complete response; PR = partial response; SD = stable disease. [a]<1% were ECOG PS 2; [b]<1% were stage IIIA; [c]<1% were undifferentiated (considered to be of squamous histology); [d]<1% had PD; [e]<15 pack years and stopped >1 year before diagnosis; [f]considered to be of squamous histology; [g]percentages may not total 100 due to rounding.

Goss et al. ESMO 2014. Abstract 12220.

LUX-Lung 8: PFS (Independent Review)



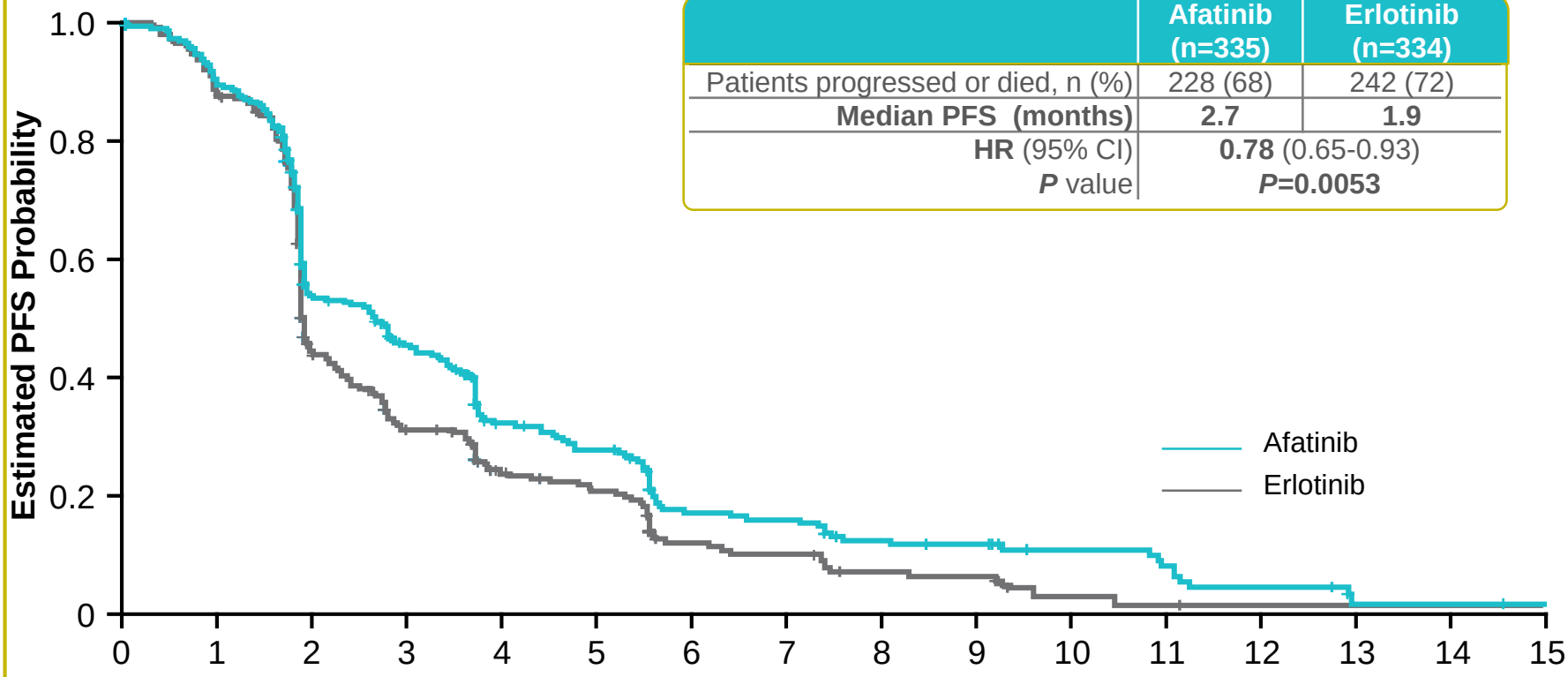
	Afatinib (n=335)	Erlotinib (n=334)
Patients progressed or died, n (%)	202 (60)	212 (64)
Median PFS (months)	**2.4**	**1.9**
HR (95% CI)	**0.822** (0.676-0.998)	
P value	***P*=0.0427**	

CI = confidence interval; HR = hazard ratio.

Goss et al. ESMO 2014. Abstract 12220.

LUX-Lung 8: PFS (Investigator Review)

	Afatinib (n=335)	Erlotinib (n=334)
Patients progressed or died, n (%)	228 (68)	242 (72)
Median PFS (months)	**2.7**	**1.9**
HR (95% CI)	**0.78** (0.65-0.93)	
P value	***P*=0.0053**	



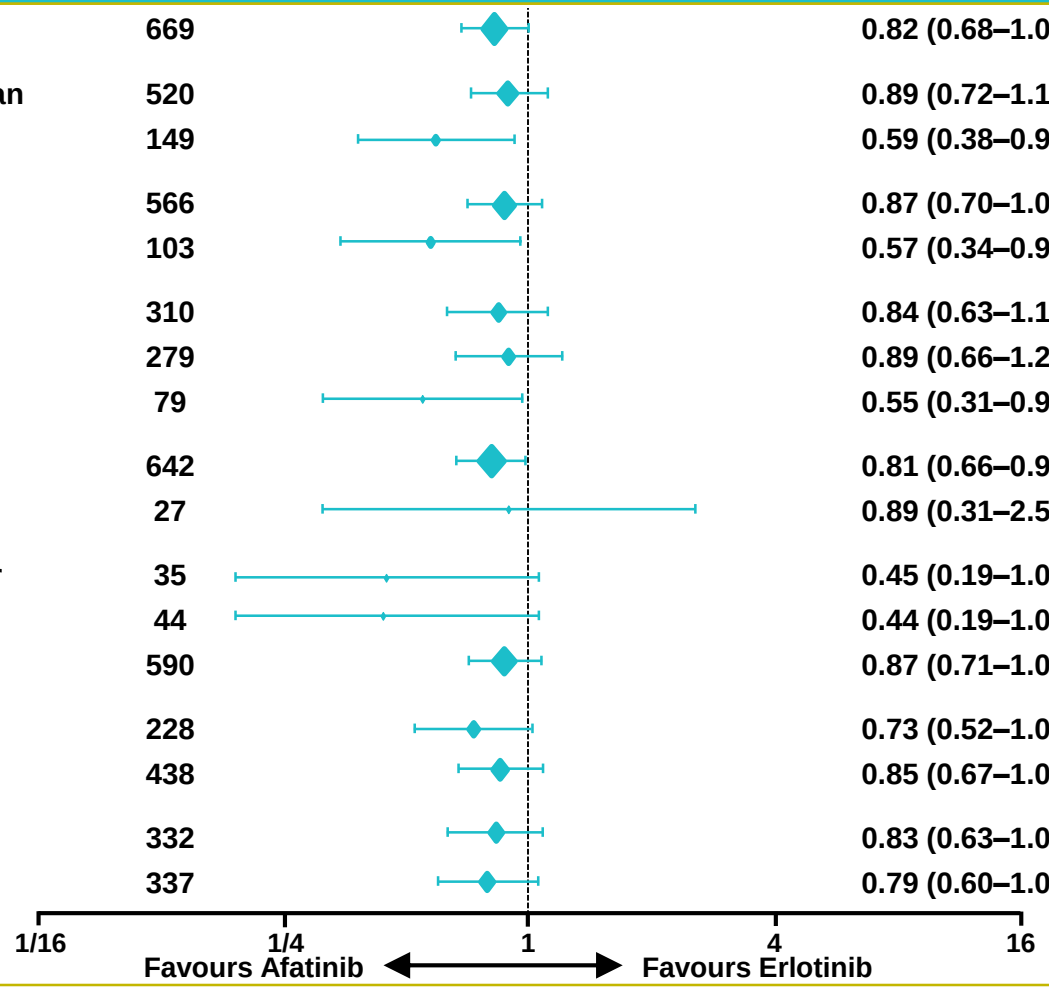
No. of patients

Afatinib	335	260	137	110	66	56	30	28	19	17	12	9	5	1	1	0
Erlotinib	334	252	119	78	49	40	18	15	9	8	2	1	0	0	0	0

Goss et al. ESMO 2014. Abstract 12220.

PFS Subgroups: Independent Review

Factors		Number of Patients	Hazard Ratio (95% CI)
Overall		669	0.82 (0.68–1.00)
Race	Non-East Asian	520	0.89 (0.72–1.11)
	East Asian	149	0.59 (0.38–0.92)
Gender	Male	566	0.87 (0.70–1.07)
	Female	103	0.57 (0.34–0.95)
Best response to first-line chemotherapy	CR/PR	310	0.84 (0.63–1.11)
	SD	279	0.89 (0.66–1.21)
	Unknown	79	0.55 (0.31–0.96)
Histology	Squamous	642	0.81 (0.66–0.98)
	Mixed	27	0.89 (0.31–2.57)
Smoking history	Never smoker	35	0.45 (0.19–1.05)
	Ex-smoker[a]	44	0.44 (0.19–1.05)
	Smoker	590	0.87 (0.71–1.07)
ECOG at baseline	0	228	0.73 (0.52–1.02)
	1	438	0.85 (0.67–1.08)
Age	<65 years	332	0.83 (0.63–1.08)
	≥65 years	337	0.79 (0.60–1.05)



[a]<15 pack years and stopped >1 year before diagnosis.

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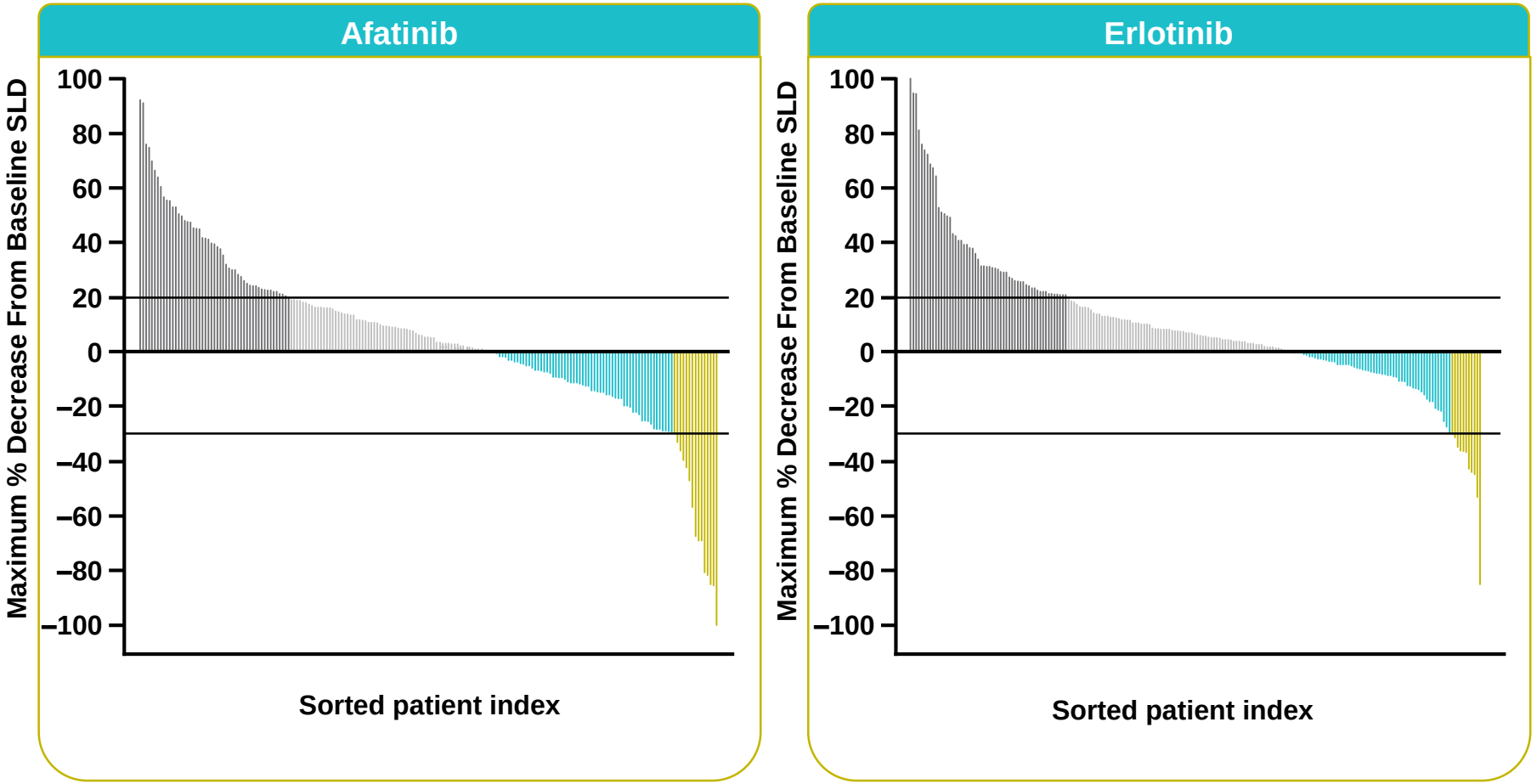
Tumour Shrinkage



SLD = sum of target lesion diameters.

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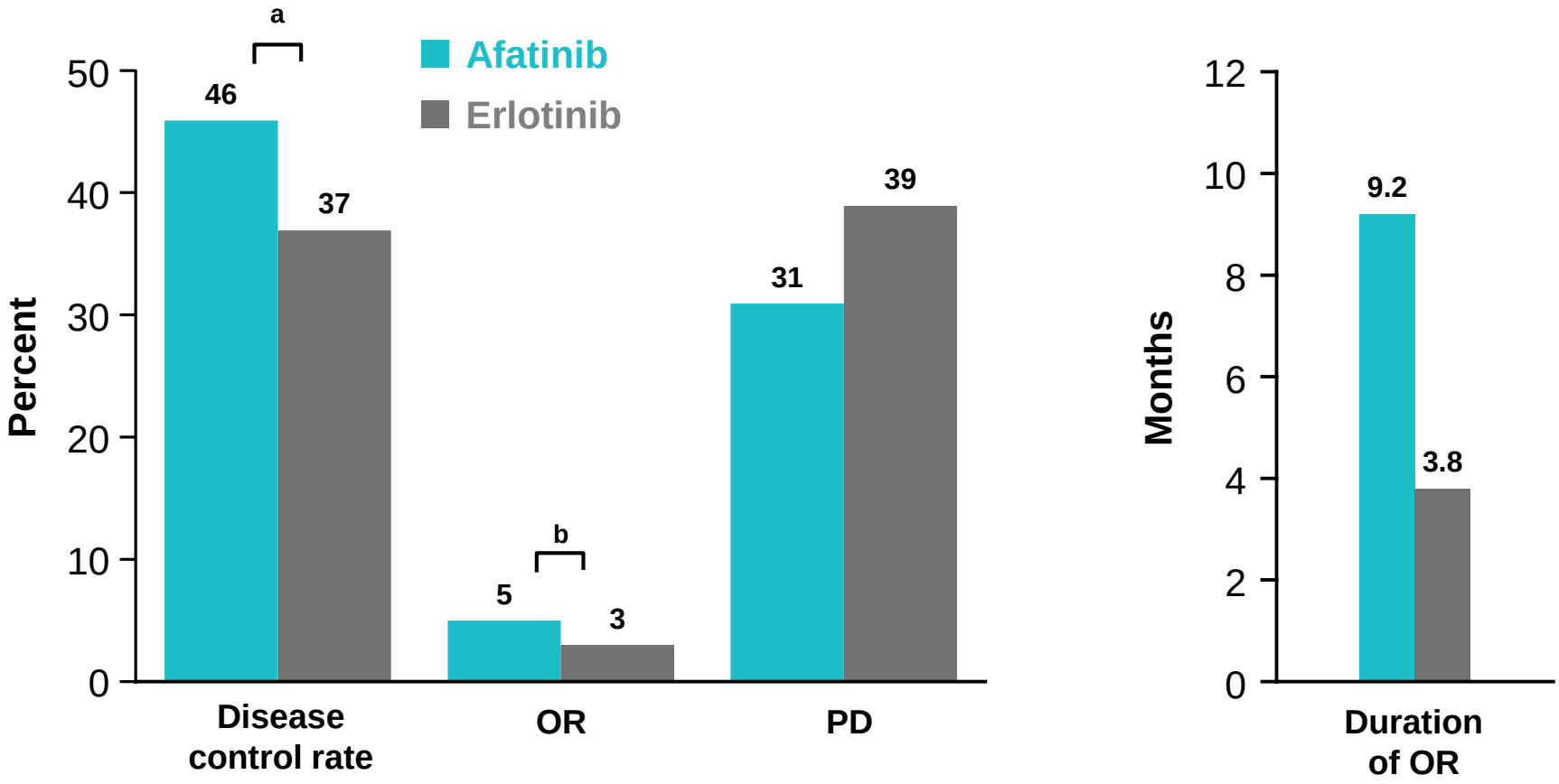
LUX-Lung 8:
Objective Response (Independent Review)



[a]Odds ratio: 1.44; 95% CI, 1.06–1.96; *P* value 0.0203.

[b]Odds ratio: 1.63; 95% CI, 0.73–3.66; *P* value 0.2332.

Goss et al. ESMO 2014. Abstract 12220.

LUX-Lung 8: Adverse Events Overall Summary

	Afatinib (n=329) (%)	Erlotinib (n=332) (%)
Any AE	98	96
Drug-related AEs	91	80
CTCAE grade 3 or higher	50	49
AEs leading to dose reduction	24	12
AEs leading to discontinuations excluding PD-related	15	12
SAEs	39	38
Fatal (all cause, excluding PD)	12	11

CTCAE = Common Terminology Criteria for Adverse Events; SAEs = serious adverse events.

Goss et al. ESMO 2014. Abstract 12220.

LUX-Lung 8: Drug-Related AEs (>5%)

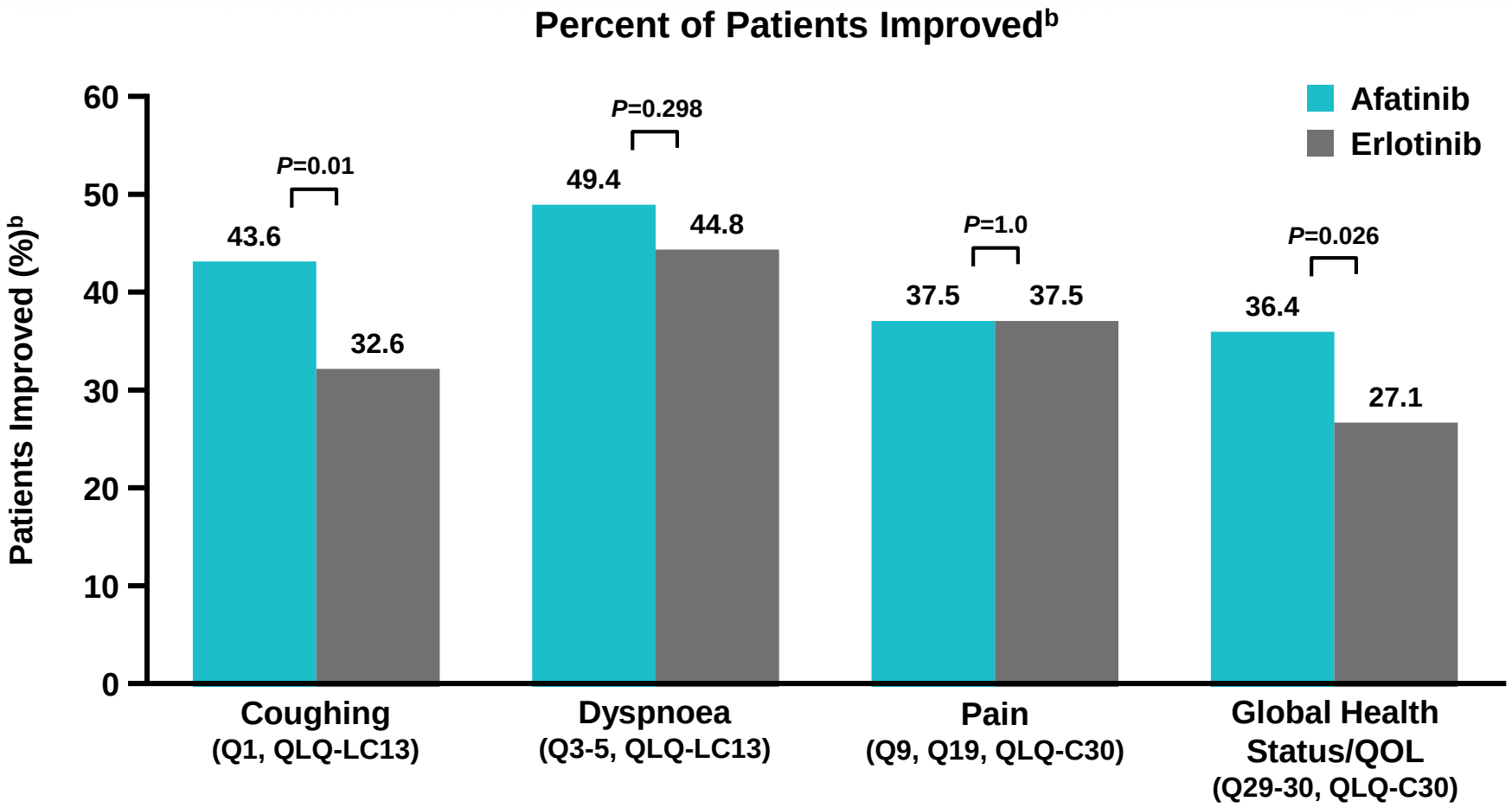
Grouped categories by CTCAE grades

	Afatinib (N=329) n, (%)			Erlotinib (N=332) n, (%)		
AE Category	All	Grade 3	Grade 4[d]	All	Grade 3	Grade 4[e]
Total with related AEs	298 (91)	75 (23)	4 (1)	266 (80)	48 (15)	1 (<1)
Diarrhoea	218 (66)	30 (9)	2 (<1)	103 (31)	7 (2)	1 (<1)
Rash/acne[a]	208 (63)	18 (6)		221 (67)	30 (9)	
Stomatitis[a]	90 (27)	11 (3)		28 (8)		
Fatigue[a]	44 (13)	3 (1)		43 (13)	6 (2)	
Decreased appetite	38 (12)	3 (1)		34 (10)	2 (<1)	
Nausea	38 (12)	3 (1)		24 (7)	3 (1)	
Paronychia[a]	35 (11)	1 (<1)		14 (4)	1 (<1)	
Pruritus	29 (9)	1 (<1)		36 (11)		
Dry skin	27 (8)[b]	2 (<1)		34 (10)		
Vomiting	25 (8)[c]	2 (<1)		10 (3)	2 (<1)	

[a]Grouped terms; [b]8.2; [c]7.6; [d]Six patients (1.8%) in the afatinib treatment group had drug-related fatal AEs: interstitial lung disease (2 patients) and pneumonia, respiratory failure, acute renal failure, and general physical health deterioration (1 patient each); [e]Two patients (0.6%) in the erlotinib treatment group had drug-related fatal AEs: intersitial lung disease and peritonitis (1 patient each).

Goss et al. ESMO 2014. Abstract 12220.

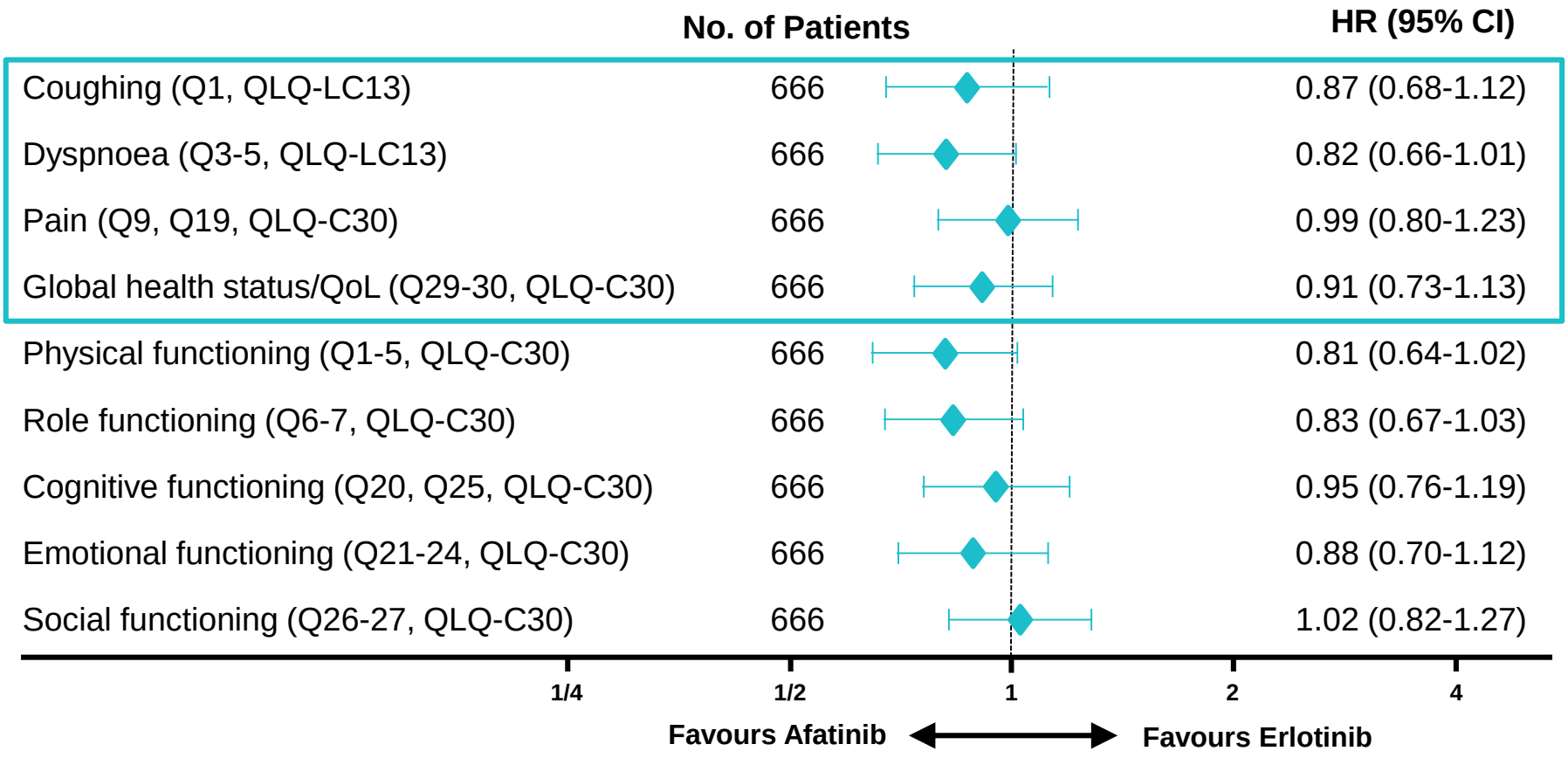
LUX-Lung 8: Patient-Reported Outcomes[a]



[a]Further PRO data will be presented at a later date.
[b]Based on EORTC QLQ-C30 and QLQ-LC13.
PRO = patient-reported outcomes; EORTC = European Organisation for Research and Treatment of Cancer; QLQ-Q30 = Core Quality of Life Questionnaire; LC13 = Lung Cancer Module; QoL = quality of life.
Goss et al. ESMO 2014. Abstract 12220.

LUX-Lung 8: Patient-Reported Outcomes[a] (cont'd)

Time to deterioration of lung cancer symptoms and quality of life[b]



[a]Further PRO data will be presented at a later date.
[b]Based on EORTC QLQ-C30 and QLQ-LC13.

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LUX-Lung 8: Conclusions

- Afatinib significantly improved PFS when compared with erlotinib
  - Independent and investigator reviews were consistent
- Tumour shrinkage was greater, response rate higher, and disease control rate significantly higher in the afatinib arm compared with the erlotinib arm
- Overall AE profile was consistent with mechanistic profile and was manageable
  - Rate of SAEs and grade ≥3 AEs similar for both drugs
- Patient-reported outcomes favoured afatinib vs erlotinib
- OS data are awaited

Goss et al. ESMO 2014. Abstract 12220.

LUX-Lung 8
Key Secondary Endpoint (Overall Survival)

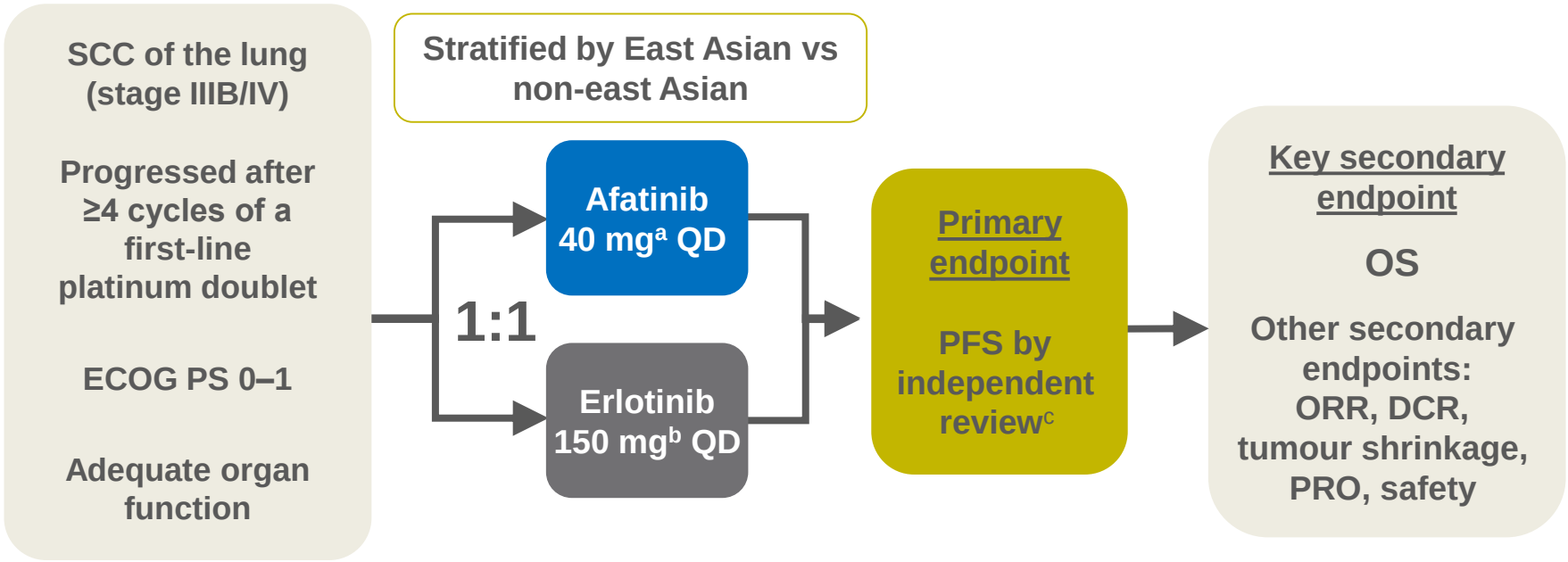
Soria et al. ASCO 2015 Abstract 8002

Background

- SCC of the lung remains a disease with high unmet medical need
- ErbB pathway dysregulation is frequently observed in SCC[1-3]
- Erlotinib, a reversible EGFR TKI, is an approved second-line therapy for these patients
  - Improved tolerability over docetaxel[4] yet similar survival in second-line unselected and *EGFR*wt NSCLC[5]
- Afatinib could confer additional benefit over erlotinib
  - Irreversible inhibition of signaling from ErbB1(EGFR), HER2 to HER4[6]

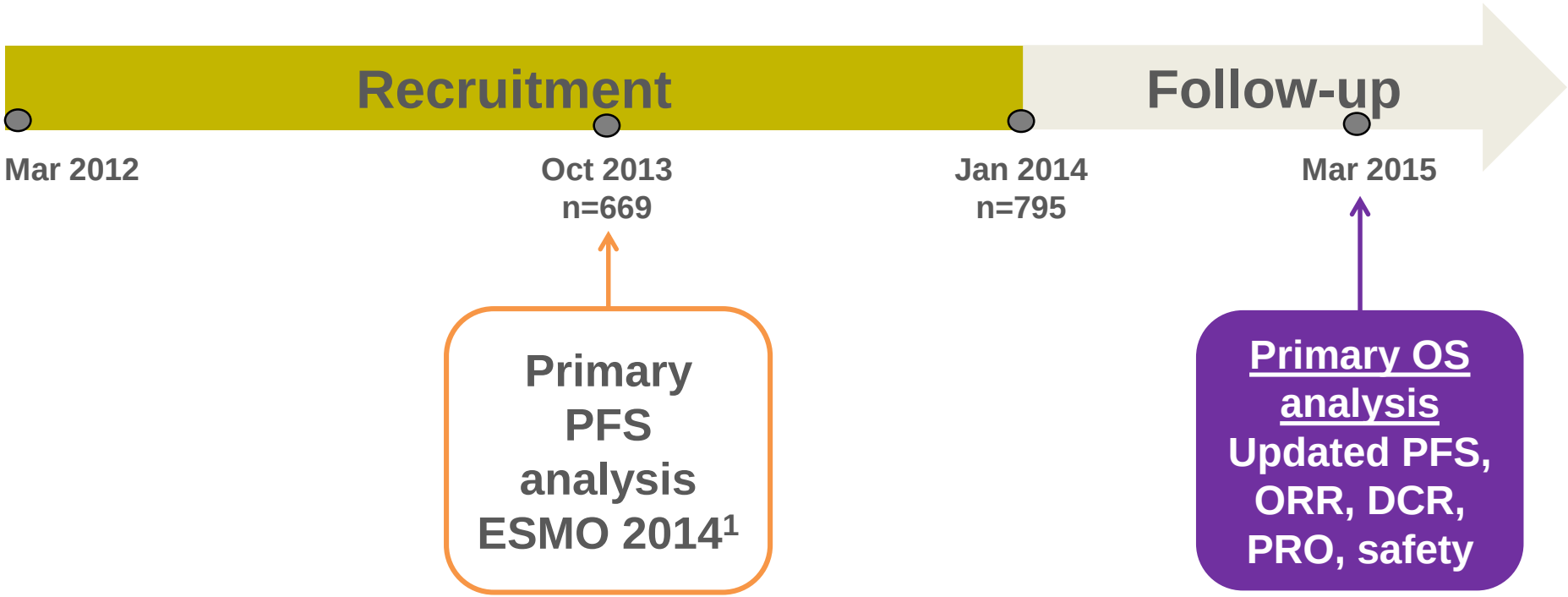
1. Heinmoller et al. *Clin Cancer Res*. 2003;9:5238; 2. Ugocsai et al. *Anticancer Res*. 2005;25:3061; 3. Cancer Genome Atlas Research Network. *Nature*. 2012;489:519; 4. Lee et al. *J Natl Cancer Inst*. 2013;105:595; 5. Li et al. *PLoS One*. 2014;9(7):e102777; 6. Solca et al. *J Pharmacol Exp Ther*. 2012;343:342.

Study Design



[a]Dose escalation to 50 mg and dose reduction to 30 or 20 mg permitted.
[b]Dose reduction to 100 or 50 mg permitted.
[c]Tumour assessment at baseline and weeks 8, 12, and 16; every 8 weeks thereafter.

Timelines



1. Goss et al. ESMO 2014. Abstract 12220.

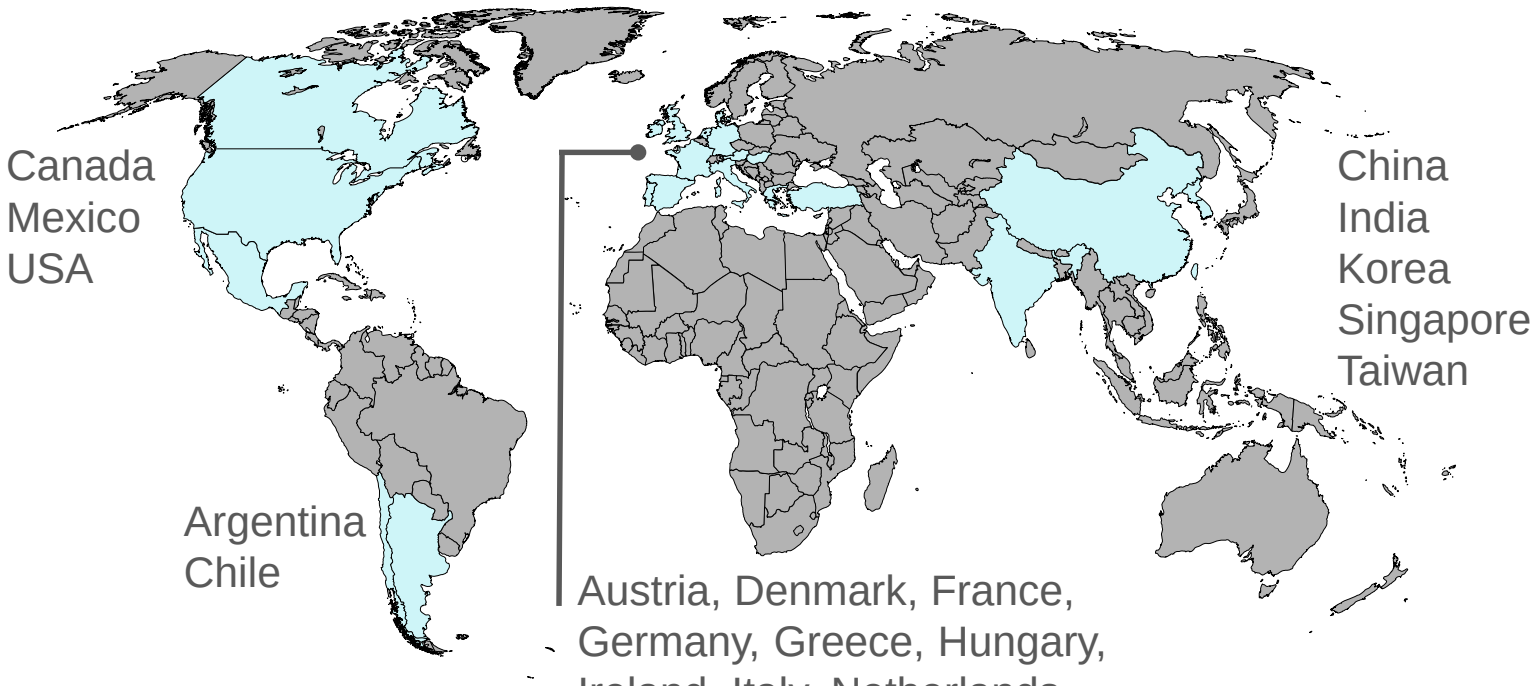
Statistical Assumptions

- **Primary endpoint**: PFS by independent radiology review (RECIST version 1.1)
  - Required ≥372 PFS events (90% power; HR=0.714[a]; median PFS 10 vs 14 weeks)
  - **endpoint was met: afatinib significantly improved PFS; HR=0.82; 95% CI, 0.68-1.00; *P*=0.0427; median 2.4 vs 1.9 months[1]**
- **Key secondary endpoint**: OS
  - Required 632 death events (80% power to detect HR of 0.80[a])
    - Increase in median OS from 7.0 to 8.75 months

[a]Two-sided 5% significance level.

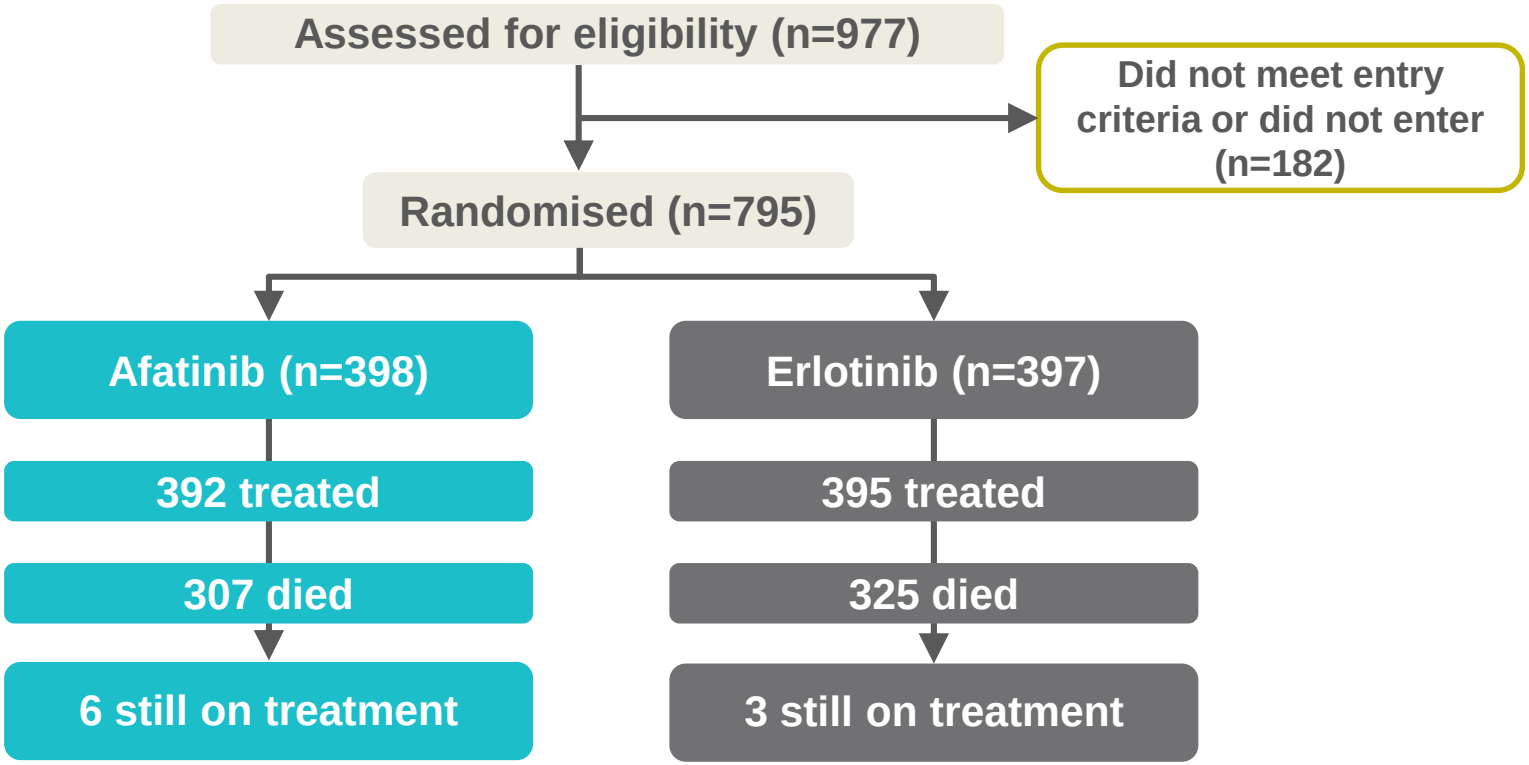
1. Goss et al. ESMO 2014. Abstract 12220.

Recruitment



Soria et al. ASCO 2015. Abstract 8002

Patient Disposition



Soria et al. ASCO 2015. Abstract 8002

Demographics and Baseline Characteristics

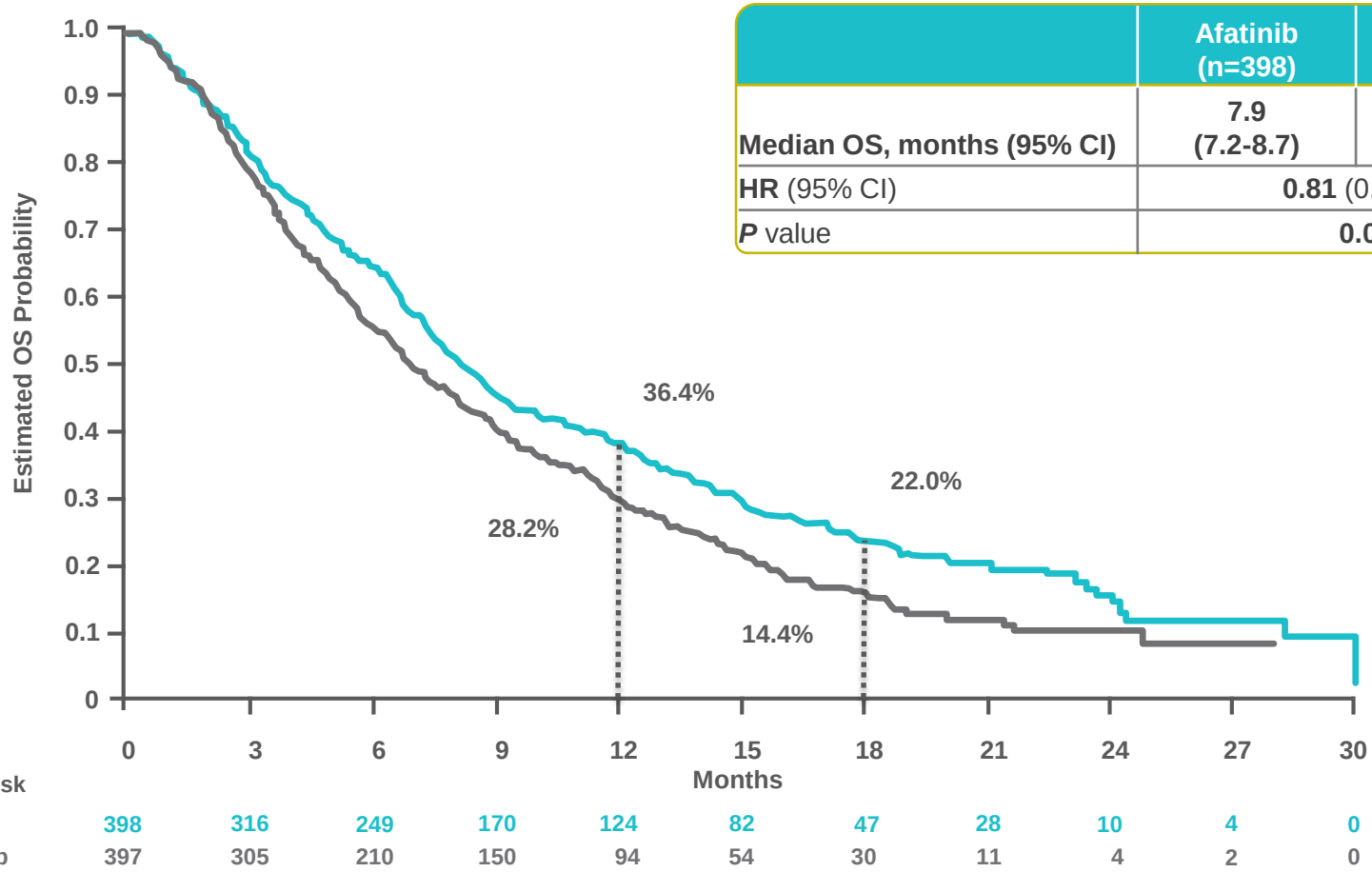
		Afatinib[g] (n=398)	Erlotinib[g] (n=397)
Median age, years		65	64
Male, %		84	83
Race, %	Asian	24	24
	East Asian	22	22
	White	72	73
	Other[d]	2	3
Smoking history, %	Never smoker	7	5
	Light ex-smoker[e]	3	3
	Current and other ex-smoker[f]	91	92
ECOG,[a] %	0/1	32/68	34/66
Clinical stage,[b] %	IIIB/IV	12/88	12/87
Histology,[c] %	Squamous	96	96
	Mixed	4	4
Best response to first-line chemotherapy, %	CR/PR	47	47
	SD	41	42
	Unknown	12	11

[a]<1% were ECOG PS 2; [b]≤1% were stage IIIA; [c]<1% were undifferentiated (considered to be of squamous histology); [d]Includes black/African American and American Indian/Alaska Native; [e]Fifteen pack-years and stopped >1 year before diagnosis; [f]Seventy-one (17.8%) and 85 (21.4%) patients were current smokers, respectively; [g]Percentages may not total 100 due to rounding.

Soria et al. ASCO 2015. Abstract 8002

Primary Analysis of OS (n=795)

	Afatinib (n=398)	Erlotinib (n=397)
Median OS, months (95% CI)	**7.9 (7.2-8.7)**	**6.8 (5.9-7.8)**
HR (95% CI)	**0.81** (0.69-0.95)	
P value	**0.0077**	

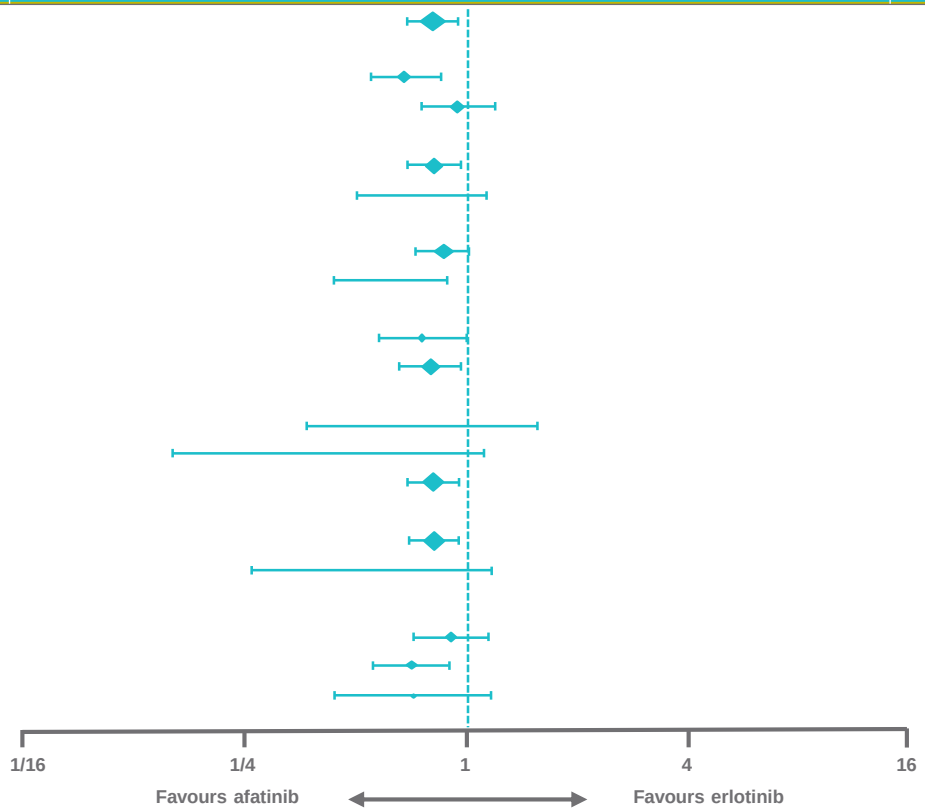


Median follow-up time: 18.4 months.

Soria et al. ASCO 2015. Abstract 8002

OS Subgroup Analysis

Factors	No. of Patients	Hazard Ratio (95% CI)
Overall	795	0.81 (0.69–0.95)
Age		
<65 years	399	0.68 (0.55–0.85)
≥65 years	396	0.95 (0.76–1.19)
Gender		
Male	666	0.82 (0.69–0.97)
Female	129	0.77 (0.51–1.14)
Race		
Non-East Asian	623	0.87 (0.73–1.03)
East Asian	172	0.62 (0.44–0.88)
ECOG at baseline		
0	260	0.76 (0.58–1.01)
1	531	0.80 (0.66–0.97)
Smoking history		
Never smoker	44	0.77 (0.37–1.57)
Light ex-smoker	23	0.43 (0.16–1.12)
Current and other ex-smoker	728	0.81 (0.69–0.96)
Histology		
Squamous	763	0.82 (0.70–0.96)
Mixed	32	0.55 (0.26–1.17)
Best response to first-line chemotherapy		
CR/PR	371	0.91 (0.72–1.15)
SD	328	0.71 (0.56–0.90)
Unknown	89	0.72 (0.44–1.17)



Soria et al. ASCO 2015. Abstract 8002

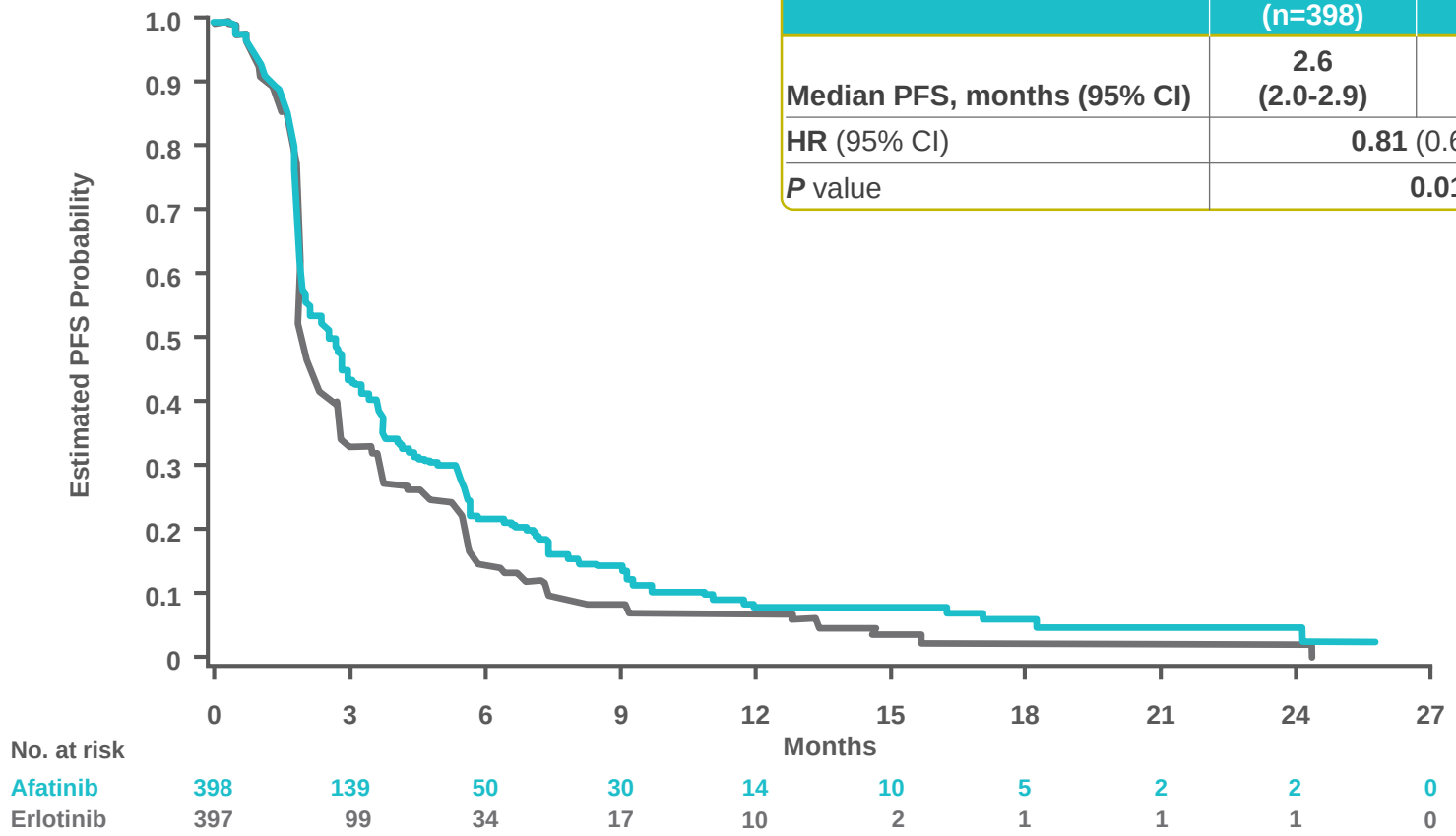
Post-Progression Therapies

	Percent	
	Afatinib (n=392)	Erlotinib (n=395)
Subsequent systemic treatment	46.4	48.6
Chemotherapy	44.9	46.8
Docetaxel	23.7	26.1
Platinum-based doublet	11.2	10.9
Gemcitabine	10.5	10.9
Vinorelbine	9.4	8.6
EGFR-targeted	3.1	2.0
Erlotinib	2.3	2.0
Afatinib	0.5	0.0
Immune checkpoint inhibitor	0.3	0.0
Other	1.3	2.8

Soria et al. ASCO 2015. Abstract 8002

PFS: Independent Review—Updated With All Randomised Patients (N=795)

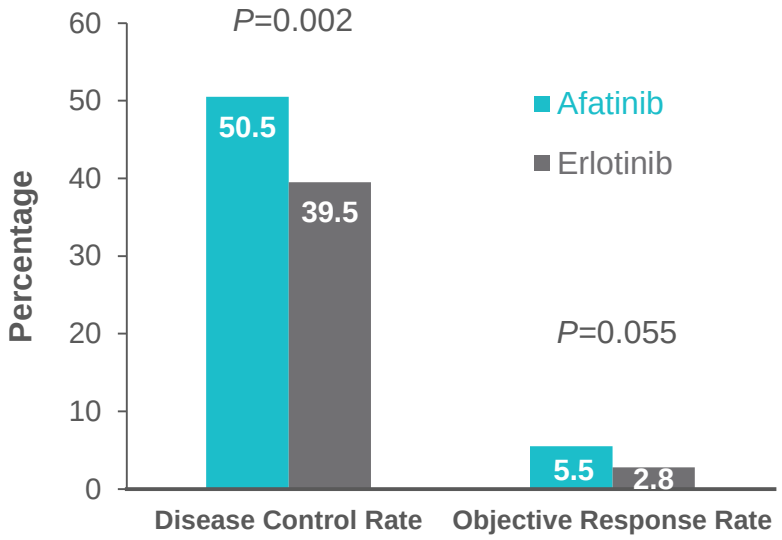
	Afatinib (n=398)	Erlotinib (n=397)
Median PFS, months (95% CI)	**2.6 (2.0-2.9)**	**1.9 (1.9-2.1)**
HR (95% CI)	**0.81** (0.69-0.96)	
P value	**0.0103**	



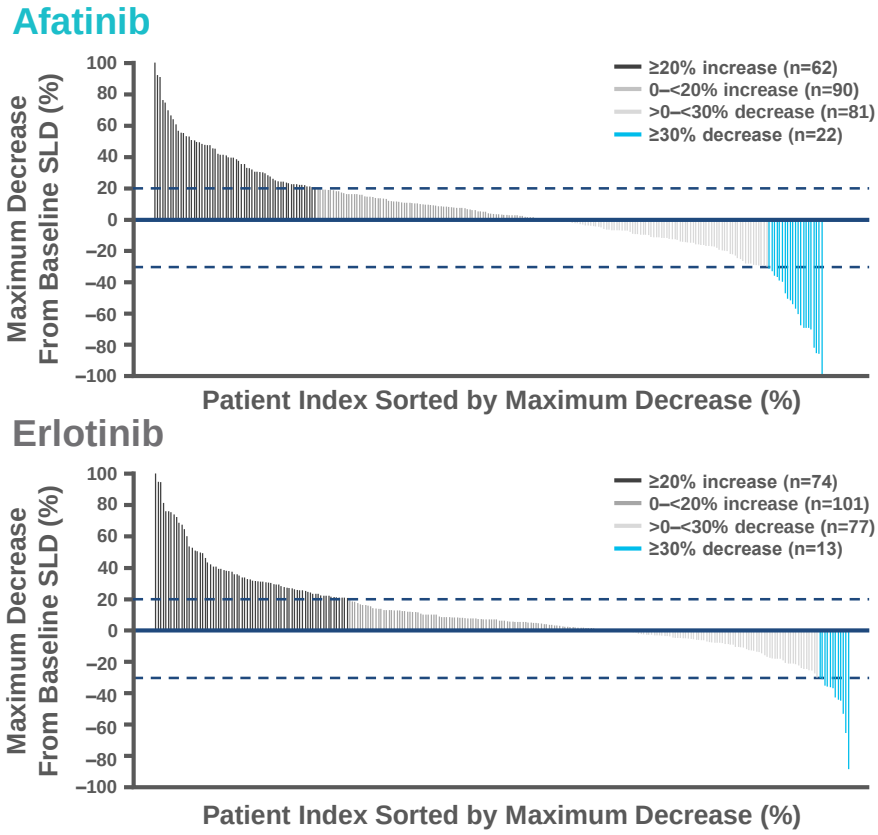
Data cut-off February 2, 2015.

Soria et al. ASCO 2015. Abstract 8002

Objective Response and Tumour Shrinkage



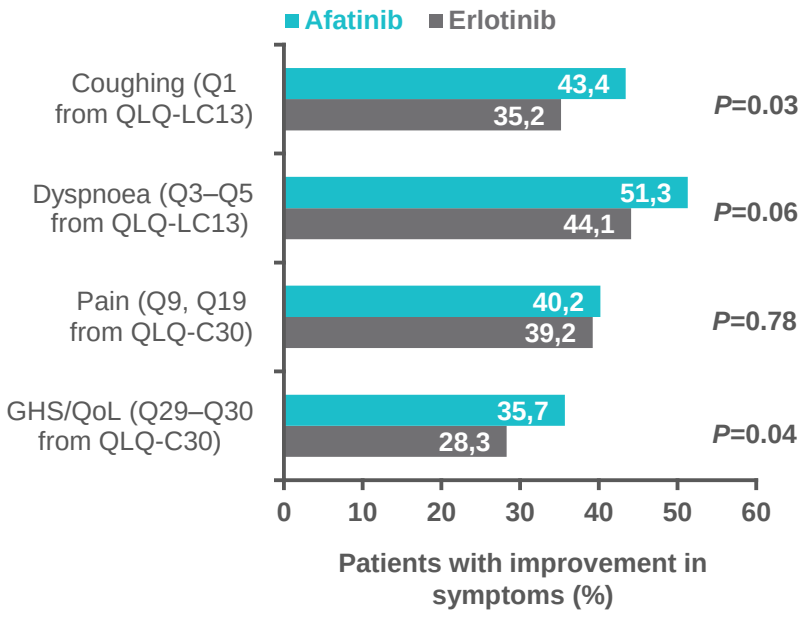
- Duration of response was 7.29 months for afatinib and 3.71 months for erlotinib



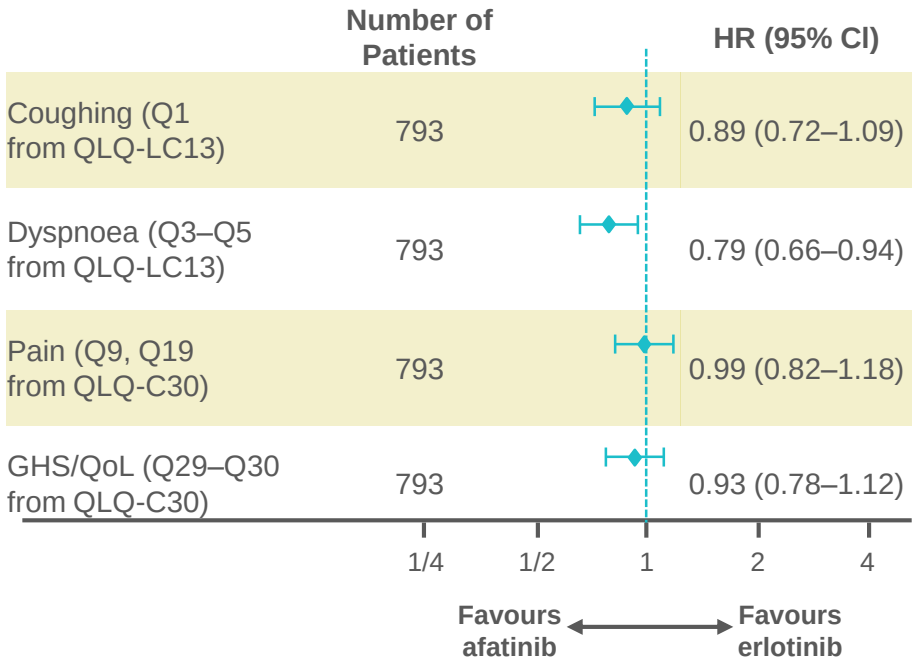
Soria et al. ASCO 2015. Abstract 8002

Patient-Reported Outcomes

Symptom Improvement



Time to Deterioration



GHS = global health status.

Gadgeel et al. ASCO 2015. Abstract 8100, Poster 425.

Adverse Events: Overall Summary

Events	Afatinib (n=392) (%)	Erlotinib (n=395) (%)
Any AE	99.5	97.5
Drug-related AEs	93.4	81.3
AEs leading to dose reduction	26.5	14.2
AEs leading to discontinuations	20.2	17.0
CTCAE grade 3 or higher	57.1	57.4
Serious AEs	44.1	44.1
Drug-related fatal AEs	1.5[a]	1.3[b]

[a]Interstitial lung disease (n=2), pneumonia, respiratory failure, acute renal failure, and general physical health deterioration (1 patient each).
[b]Interstitial lung disease, pneumonitis, pneumonia, intestinal obstruction, and peritonitis (1 patient each).

Soria et al. ASCO 2015. Abstract 8002

Drug-Related AEs (>10%)

	Afatinib (n=392) (%)			Erlotinib (n=395) (%)		
AE Category	All	Grade 3	Grade 4	All	Grade 3	Grade 4
Diarrhoea	70	10	1	33	2	<1
Rash/acne[a]	67	6	0	67	10	0
Stomatitis[a]	29	4	0	9	0	0
Fatigue[a]	15	2	0	12	2	0
Nausea	13	1	0	7	1	0
Decreased appetite	13	1	0	10	1	0
Paronychia[a]	11	1	0	4	<1	0
Dry skin	9	1	0	10	0	0
Pruritus	8	<1	0	12	0	0
Vomiting	8	1	0	3	1	0
Dehydration	4	1	1	1	1	0

[a]Grouped terms.

Soria et al. ASCO 2015. Abstract 8002

Ongoing Tumour Genomic Analysis

- FoundationOne™ NGS platform used to assess 300 genes
- 238 patient samples analysed
- *EGFR* aberrations infrequent and balanced between arms
  - *EGFR*m+ n=14, not concentrated in East Asian patients
  - CNA n=15
  - No correlation of *EGFR* aberrations with PFS/OS
- Results to be presented at an upcoming congress

NGS = next-generation sequencing; CNA = copy number alteration.

Soria et al. ASCO 2015. Abstract 8002

Summary

- LUX-Lung 8 is the largest phase 3 trial in the second-line treatment for SCC of the lung
- In this head-to-head trial, afatinib showed a significant reduction in the risk of death and disease progression by 19% when compared to erlotinib
- Consistent advantage across all endpoints and subgroups
- Overall symptom relief and QoL measures favouring afatinib
- Pattern of AEs consistent with EGFR inhibition in both arms with similar rate of severe, serious, and fatal AEs
- Afatinib should be the TKI of choice in second-line treatment of patients with SCC of the lung

Soria et al. ASCO 2015. Abstract 8002

LUX-Lung 8
Patient-Reported Outcomes

Gadgeel et al. ASCO 2015 Abstract 8100

Poster 425

Introduction

- Quality of Life (QoL) and symptom control are important components of cancer care[1] and consideration of these aspects of patients' experience of their condition is important

- LUX-Lung 8, a prospective, randomized, Phase III global trial, compared afatinib and erlotinib in patients with squamous cell carcinoma (SCC) of the lung following failure of platinum-based chemotherapy[2]

- Here we report results from LUX-Lung 8 with emphasis on pre-specified patient-reported outcome (PRO) endpoints

1. Peppercorn JM, et al. J Clin Oncol 2011;29:755–60;

2. Goss G, et al. Ann Oncol 2014;25(Suppl.4):iv426–70 (abstract 1222O)

LUX-Lung 8 Study Design

Open-label, Global Phase III study

- **Stage IIIB/IV NSCLC with squamous histology**
- **Progressed after ≥4 cycles of a first-line platinum-doublet**
- **ECOG PS 0–1**
- **Adequate organ function**

Afatinib 40 mg QD

1:1

Erlotinib 150 mg QD

Stratified by east Asian vs non-east Asian

Primary endpoint

- **PFS**

Key secondary endpoint

- **OS**

Secondary endpoints

- **ORR**
- **DCR**
- **Tumor shrinkage**
- **Patient-reported outcomes**

EORTC QLQ-C30 and QLQ-LC13 completed once every cycle and at end of treatment

Status change, TTD and change in scores over time assessed for pre-specified symptoms: Cough, dyspnea, pain

ECOG PS, Eastern Cooperative Oncology Group performance status; QD, once daily; PFS, progression-free survival; OS, overall survival; ORR, objective response rate; DCR, disease control rate; TTD, Time to deterioration

Assessment of Patient-Reported Outcomes

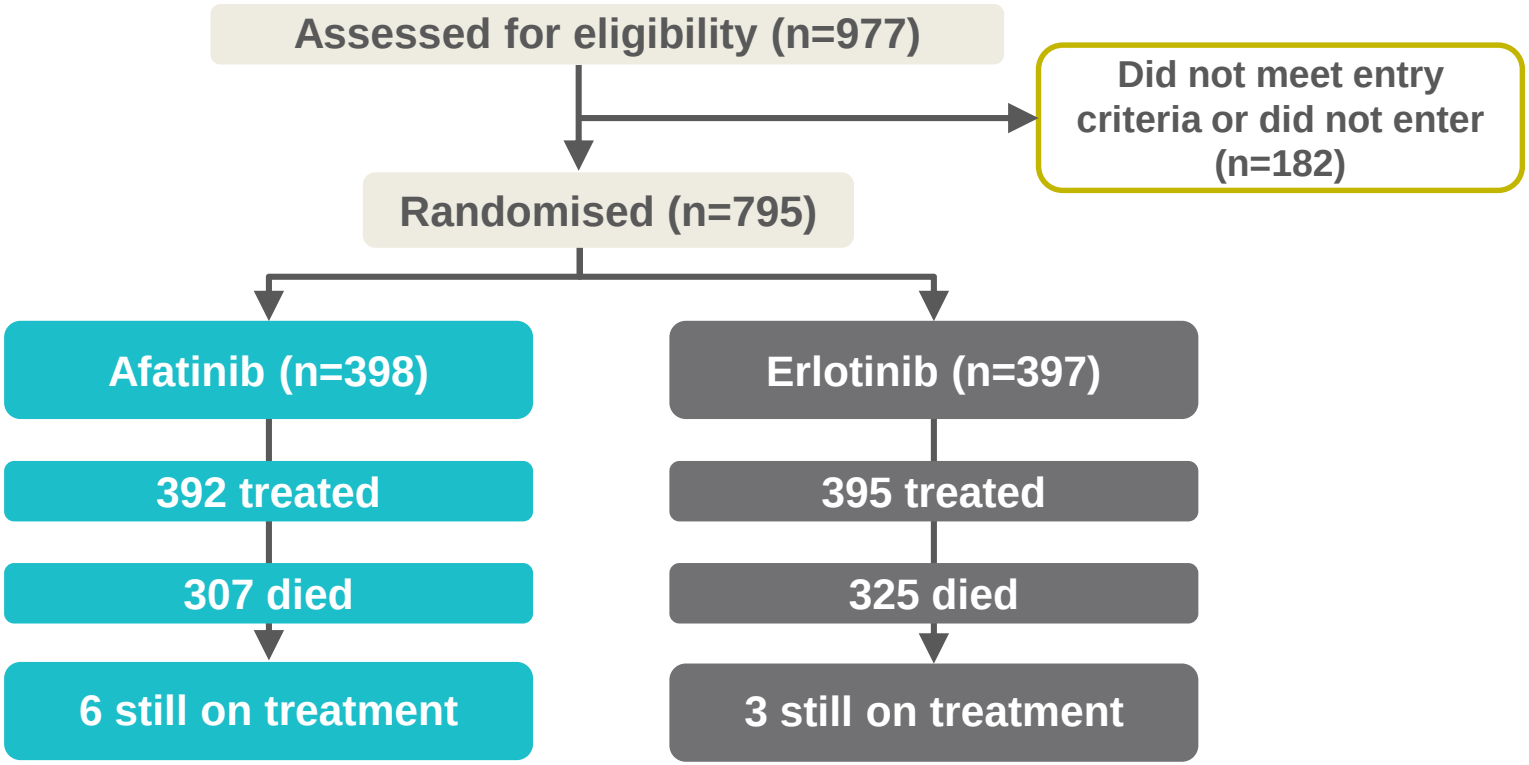
- Assessed using the European Organisation for Research and Treatment of Cancer (EORTC) core quality of life questionnaire (QLQ-C30) and its lung-cancer specific module (QLQ-LC13)[1,2]
  - At the first visit of each treatment course,
  - And, at the end of treatment
- Scores were converted to a 0–100 scale and analysed in line with EORTC scoring algorithms[1]
- Pre-specified symptoms relevant to lung cancer (cough, dyspnoea and pain) were analysed alongside global health status/ quality of life (GHS/QoL) for status change, TTD and change in scores over time
  - Cough: Question (Q)1 from QLQ-LC13
  - Dyspnoea: Q3-5 from QLQ-LC13
  - Pain: Q9 and 19 from QLQ-C30
  - GHS/QoL: Q29-30 from QLQ-C30

GHS, global health status; QoL, quality of life; TTD, time to deterioration

1. Aaronson NK, et al. J Natl Cancer Inst 1993;5:365–76

2. Bergman B, et al. Eur J Cancer 1994;30A:635–42

Patient Disposition



Soria JC, et al. J Clin Oncol 2015;33(suppl; abstr 8002)

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Soria JC, et al. J Clin Oncol 2015;33(suppl; abstr 8002)

Key study outcomes

	Afatinib	Erlotinib	HR/ OR (95% CI)	p-value
Median OS (months)	7.9	6.8	0.81 (0.69-0.95)	0.008
Median PFS (months)	2.6	1.9	0.81 (0.69-0.96)	0.010
DCR (%)	50.5	39.5	1.56 (1.18-2.06)	0.002
ORR (%)	5.5	2.8	2.06 (0.98-4.32)	0.055

HR, hazard ratio; OR, odds ratio

Soria JC, et al. J Clin Oncol 2015;33(suppl; abstr 8002)

Primary Analysis of OS (n=795)

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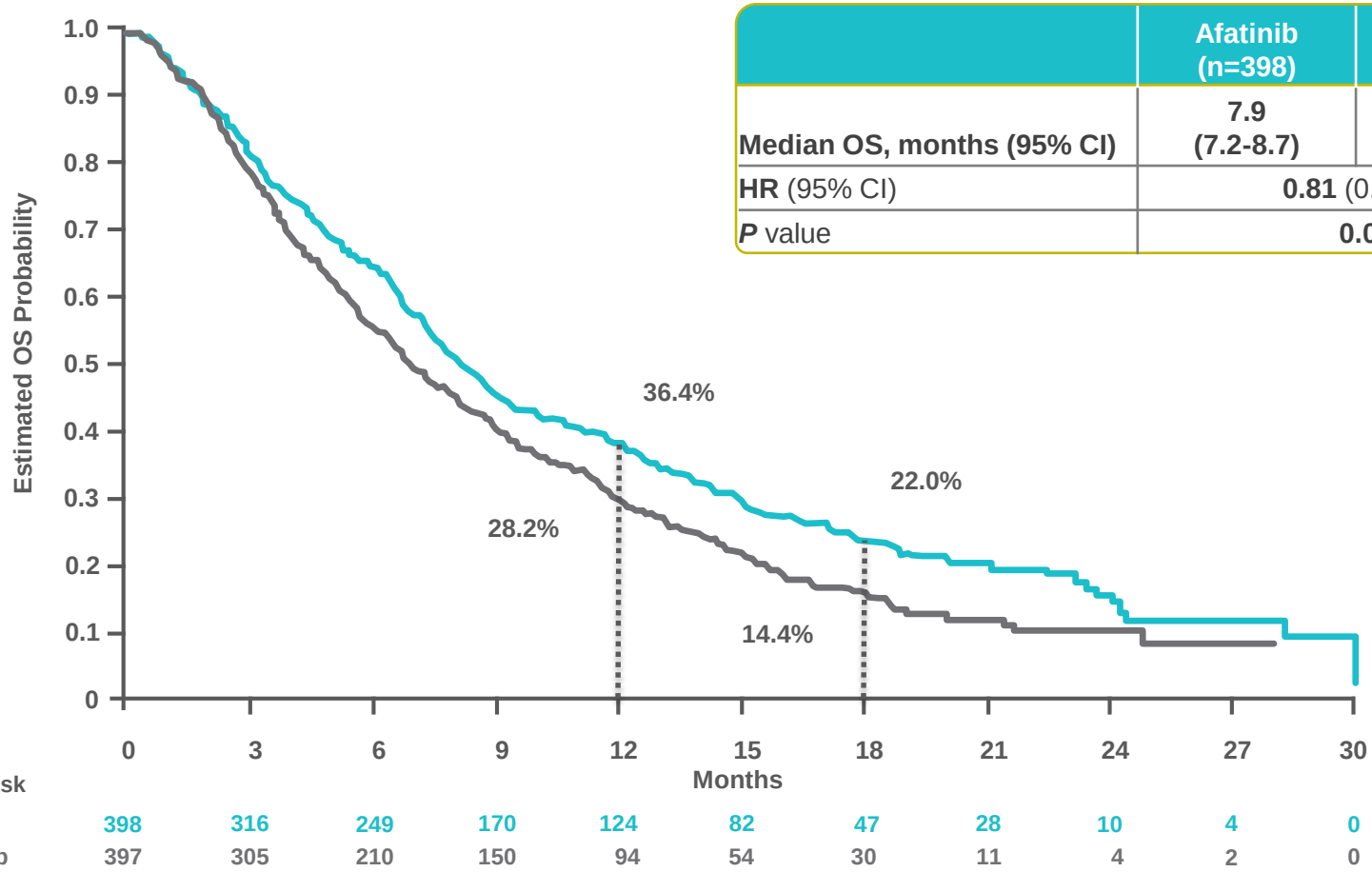


Median follow-up time: 18.4 months.

Soria JC, et al. J Clin Oncol 2015;33(suppl; abstr 8002)

Symptom burden at baseline

Scale	Mean (SD)	
	Afatinib	Erlotinib
Cough (Q1 from QLQ-LC13)	39.7 (29.5)	37.8 (26.3)
Dyspnea (Q3–Q5 from QLQ-LC13)	28.8 (23.5)	29.7 (23.5)
Pain (Q9, Q19 from QLQ-C30)	26.9 (29.2)	29.7 (28.5)
GHS/QoL*	60.8 (21.0)	60.2 (21.6)

Baseline symptom scores were low for cough, dyspnea and pain

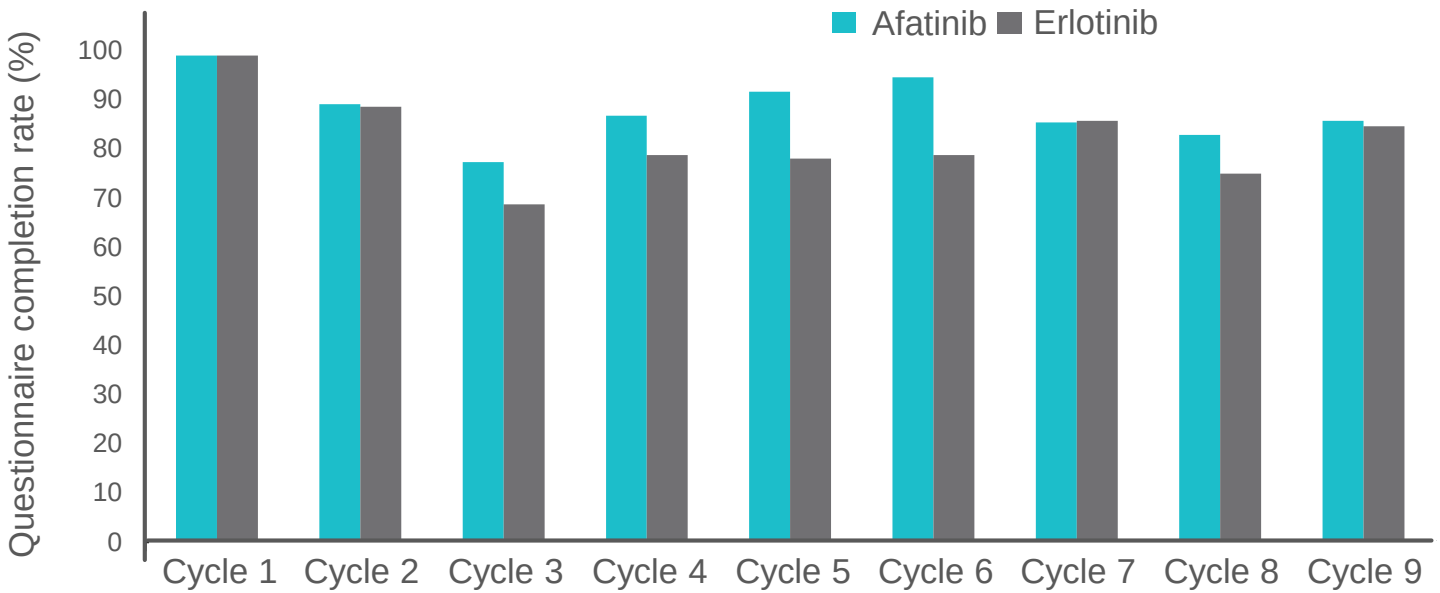
*For GHS/QoL, higher scores reflect better status

SD, standard deviation

Gadgeel et al. ASCO 2015. Abstract 8100, Poster 425.

Questionnaire completion rate

- Completion rates for the EORTC questionnaire were high throughout treatment
  - Afatinib range: 77.3–99.0%; erlotinib range: 68.7–99.0%

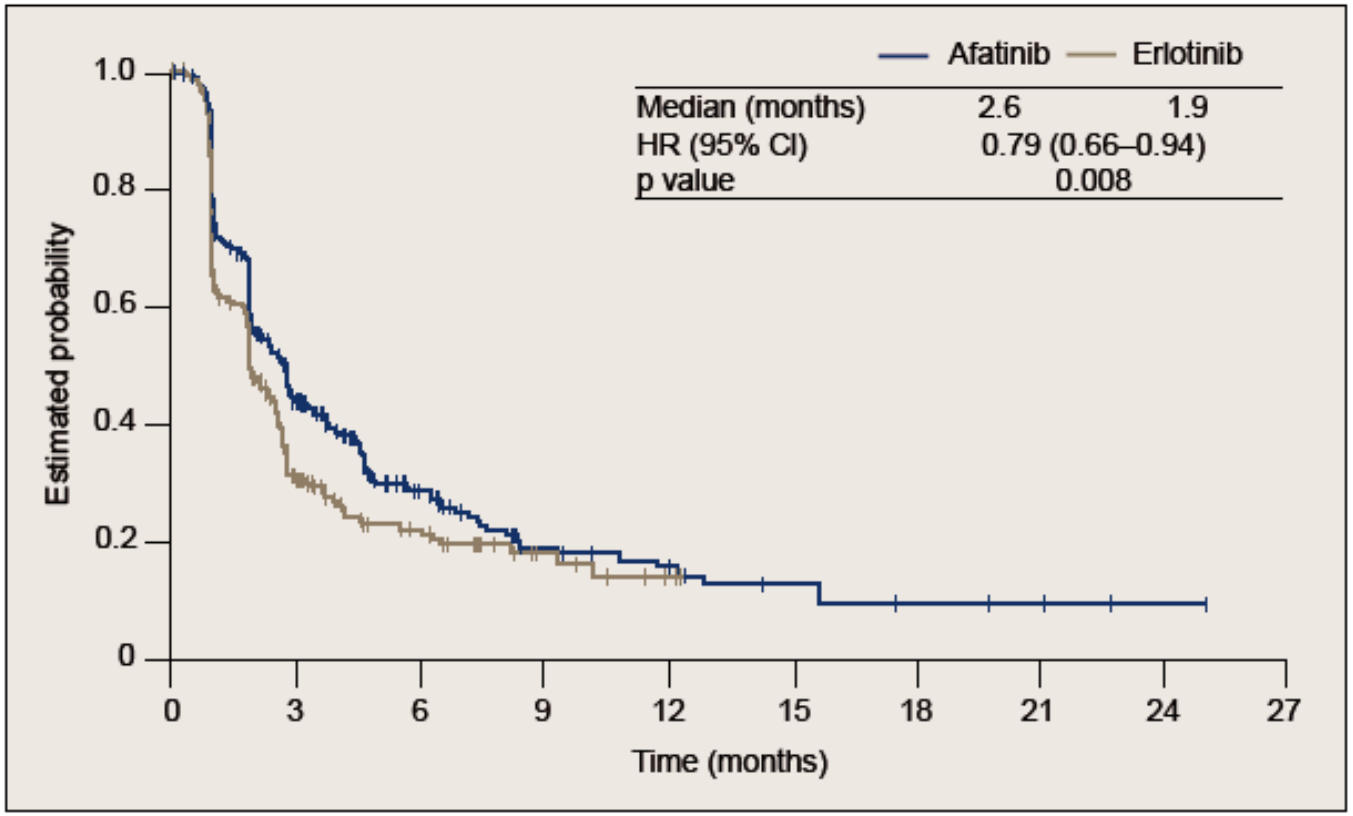


	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 8	Cycle 9
Afatinib expected responses (n)	398	348	282	174	108	55	41	35	21
Erlotinib expected responses (n)	397	350	259	141	82	47	28	20	13

Gadgeel et al. ASCO 2015. Abstract 8100, Poster 425.

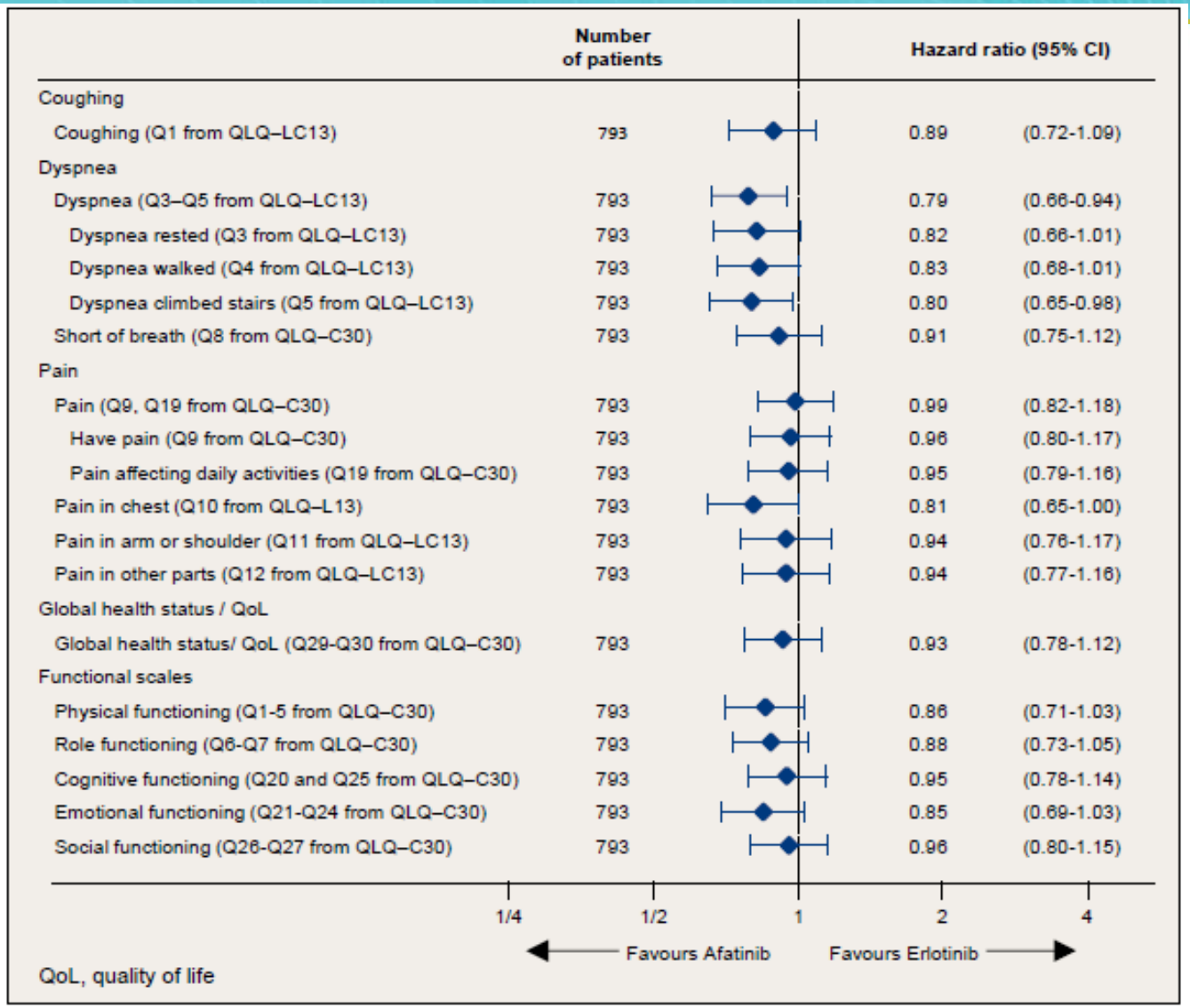
Time to deterioration of dyspnea

- Afatinib significantly delayed TTD of dyspnoea compared to erlotinib (median 2.6 vs 1.9 months, p=0.008)



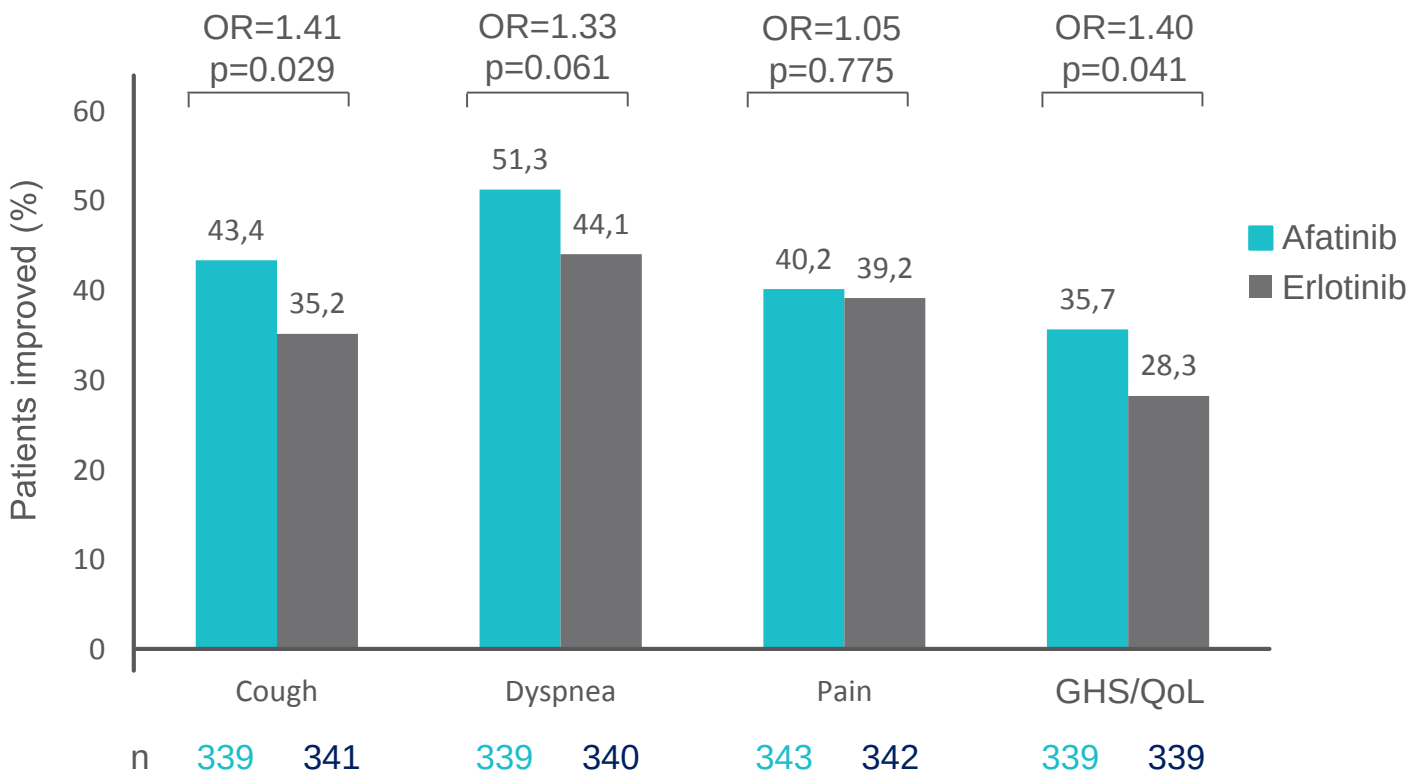
Gadgeel et al. ASCO 2015. Abstract 8100, Poster 425.

Time to deterioration of symptoms: Sub-categories



Gadgeel et al. ASCO 2015. Abstract 8100, Poster 425.

Status change

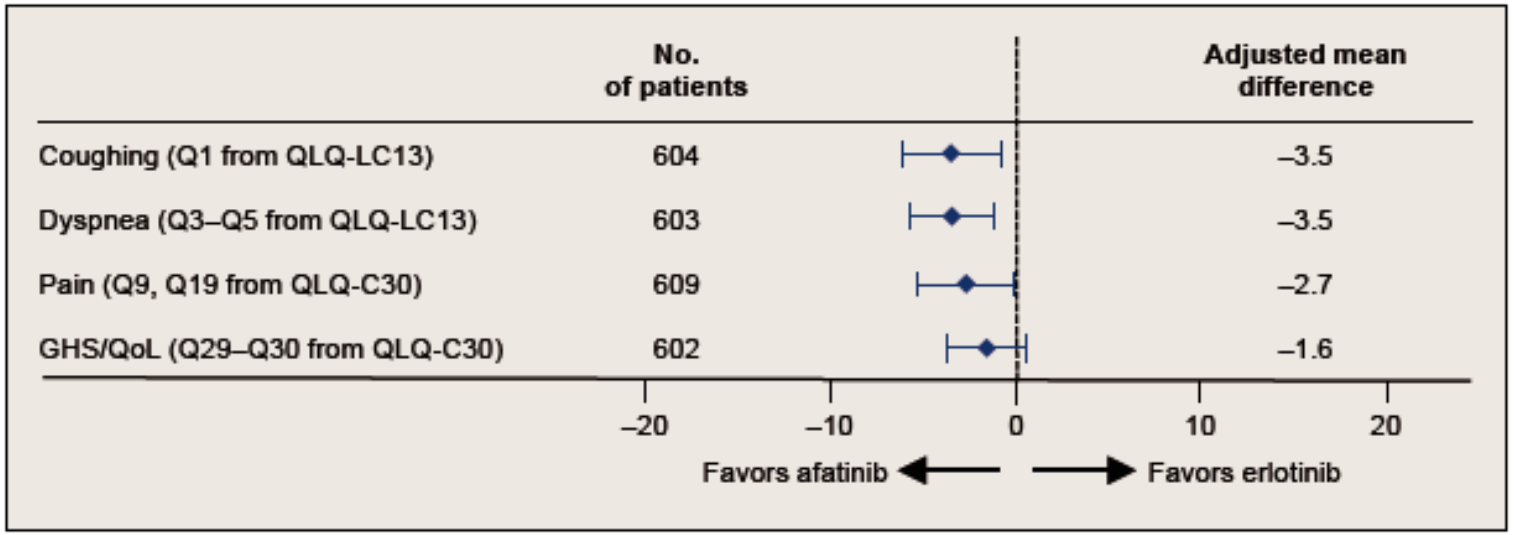


- Dyspnea walked: 34.6% vs 26.5%, p=0.022

GHS = global health status..

Gadgeel et al. ASCO 2015. Abstract 8100, Poster 425.

Change in scores over time



- There were no significant differences between afatinib and erlotinib for changes in GHS/QoL over time but, with the exception of social functioning, changes in functional scales over time significantly favored afatinib

GHS = global health status..

Gadgeel et al. ASCO 2015. Abstract 8100, Poster 425.

Conclusions

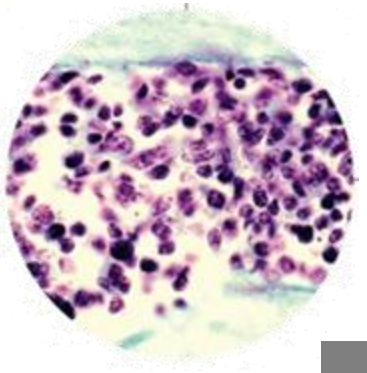
- In LUX-Lung 8, significant improvement in OS and PFS achieved with afatinib compared to erlotinib in second-line treatment of SCC was complemented by improvements in PROs
- Improvements in several PRO parameters that included GHS/QoL and key lung cancer-associated symptoms were observed across three key analyses
- These analyses confirm the clinical meaningfulness of the improvements observed for PFS, OS and tumor response with afatinib compared with erlotinib in LUX-Lung 8
- With better efficacy and PROs over erlotinib and a manageable adverse event profile, afatinib should be considered the tyrosine kinase inhibitor of choice for second-line treatment of SCC of the lung

GHS = global health status..

Gadgeel et al. ASCO 2015. Abstract 8100, Poster 425.

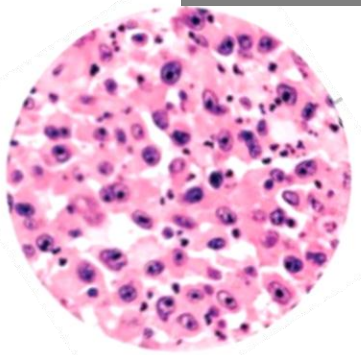
Disease Understanding and Treatment Options

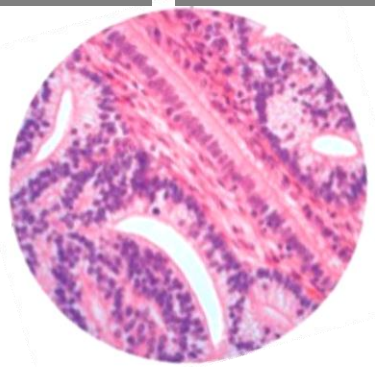
SCC Is a Histologically Distinct NSCLC Subtype

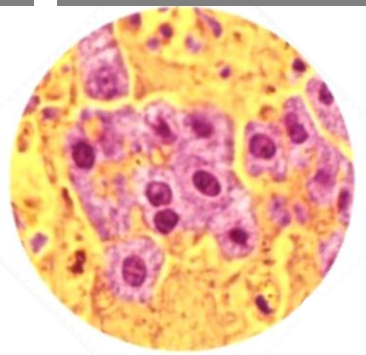


Lung Cancer

- Small Cell (≈10%-15%)
- NSCLC (85%-90%)[1]
  - Large Cell (15%)
  - Adenocarcinoma (50%)
    - TTF-1 (+)
    - p63 (-)
    - CK7 (+)
    - CK20 (-)
  - SCC (**20%-30%**)
- Others (<5%) (eg, carcinoid)







Typical immunoprofile[2,3]
- TTF-1 (-)
- p63 (+)
- CK7 (-)
- CK20 (-)
- CK5/6 (+)

Higher likelihood:
- Smoker
- Central tumour growth
- Cavitation

1. Statistics from the American Cancer Society. http://www.cancer.org/cancer/lungcancer-non-smallcell/. Accessed March 9, 2015.
2. NCCN Clinical Practice Guidelines in Oncology–NSCLC. Version 5.2015.
3. Rekhtman et al. *Mod Pathol*. 2011;24:1348.
Images adapted from Nature Outlook. http://blogs.nature.com/ofschemesandmemes/2014/09/11/the-dominant-malignancy-lung-cancer. Accessed March 9, 2015.

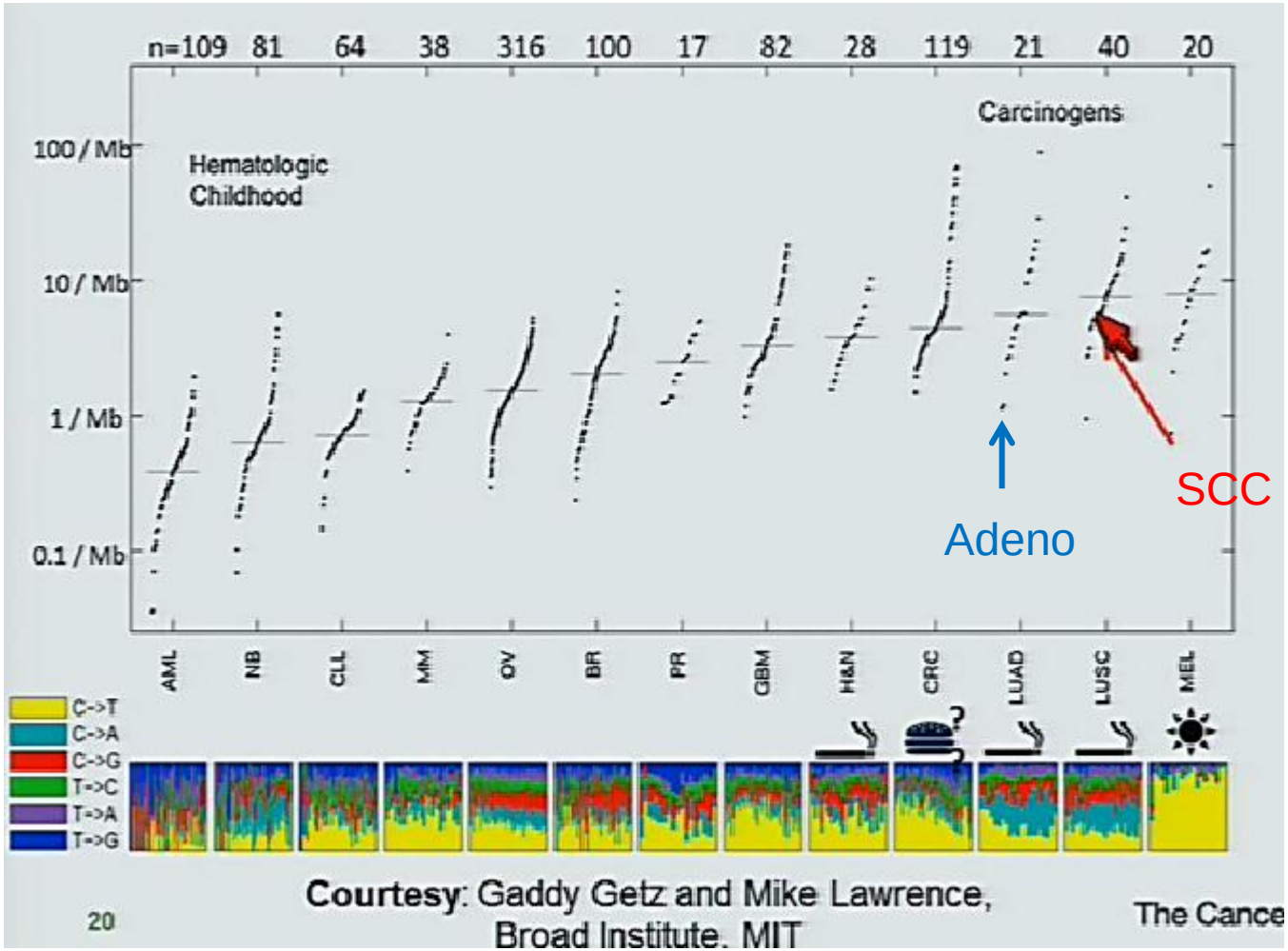
Squamous Cell Carcinoma of the Lung

- Type of NSCLC formed from reserve cells—round cells that replace injured or damaged cells in the lining of the bronchi, the lung's major airways[1]
- Usually occurs in the lung's central portions or in one of the main airway branches, leading to symptoms of cough, dyspnoea, atelectasis, obstructive pneumonia and haemoptysis[1]
- Treatment options are limited and SCC of the lung is associated with a poor prognosis[2,3]:
  - Median OS after diagnosis of advanced disease is around 4 months[3]
  - The 5-year survival is ≈1.6%[3]

1. Oliver et al. *Am J Clin Oncol*. 2015;38:220.
2. *Cancer Monthly*. Lung Cancer (NSCLC). http://www.cancermonthly.com/cancer_basics/lung.asp. Accessed April 20, 2015.
3. Cetin et al. *Clin Epidemiol*. 2011;3:139.

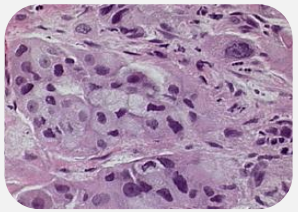
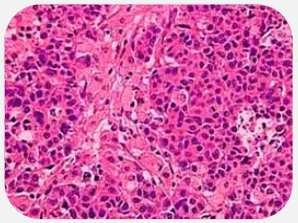
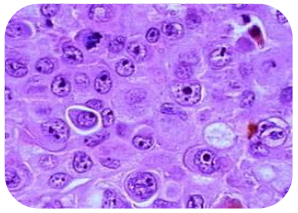
SCC of the Lung Is a Genetically Complex Tumour

SCC has a very high rate of somatic mutations



Siddhartha et al. ASCO 2014. Abstract e22195.

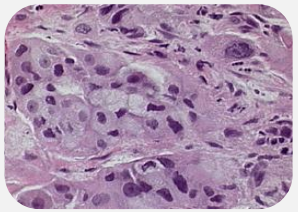
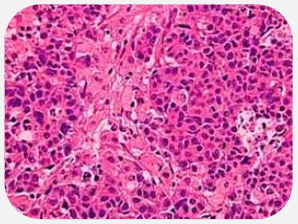
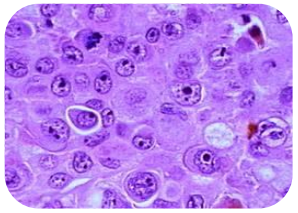
SCC of the Lung Accounts for 20-30% of NSCLC

	Classification		Charatheristics[1]
Non squamous[c]	**Adenocarcinoma 50%[a]**		• Malignant epithelial tumours with glandular differentiation • IASLC classification of invasive ADC[2]: – Lepidic, acinar, papillary, micropapillary, or solid pattern predominant – Variants: invasive mucinous ADC, colloid, fetal, and enteric
	Large cell carcinoma 15%[a]		• Involves large cells (subtypes are giant cell, clear cell) with large nuclei • No evidence of squamous or glandular differentiation
Squamous	**Squamous cell carcinoma 20%-30%[b]**		• Involves cells of the squamous epithelium • Two variants of clinicopathologic significance[3] – Papillary variant – Basaloid variant

[a]Images from www.surgical-pathology.com.
[b]Image from http://www.lmp.ualberta.ca/resources/pathoimages/PC-S.htm.
[c]Other less common subtypes of nonsquamous NSCLC include adenosquamous carcinoma and sarcomatoid carcinoma.[3]

1. Langer et al. *J Clin Oncol.* 2010;28:5311; 2. Travis et al. *J Thorac Oncol.* 2011;4:244; 3. WHO 2004.

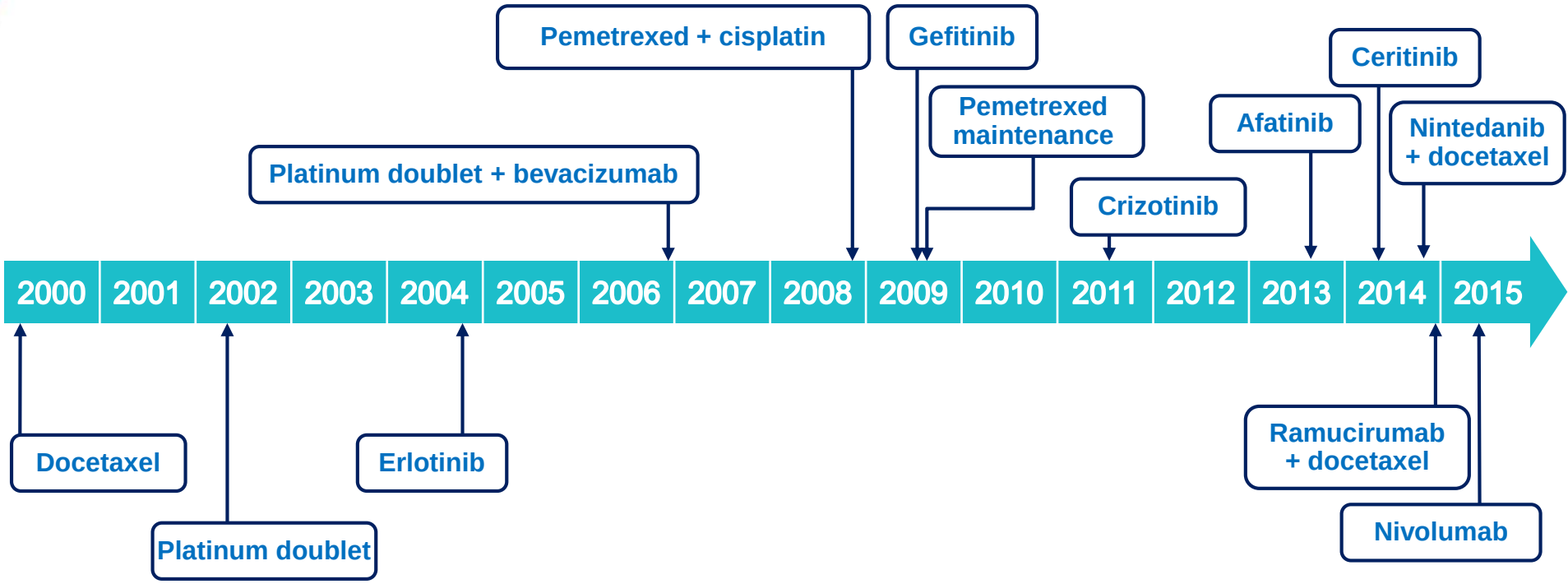
NSCLC: Patient Profile and Treatment Options[1-3]

	Classification		Patient Profile and Treatment Options
Non squamous[c]	**Adenocarcinoma 50%[a]**		• Younger • Also non-/light smokers • Better performance status/less comorbidities
	Large cell carcinoma 15%[a]		• Treatment options include pemetrexed and bevacizumab • Defined oncogene drivers → targeted therapies
Squamous	**Squamous cell carcinoma 20%-30%[b]**		• Older and often with major comorbidities • Usually (heavy) Smokers • **NO** pemetrexed or bevacizumab • **NO** approved targeted therapies for any established oncogenic drivers

[a]Images from www.surgical-pathology.com.
[b]Image from http://www.lmp.ualberta.ca/resources/pathoimages/PC-S.htm.
[c]Other less common subtypes of nonsquamous NSCLC include adenosquamous carcinoma and sarcomatoid carcinoma.[3]

1. Langer et al. *J Clin Oncol.* 2010;28:5311; 2. Travis et al. *J Thorac Oncol.* 2011;4:244; 3. WHO 2004.

Treatments for NSCLC Approved* after 2000

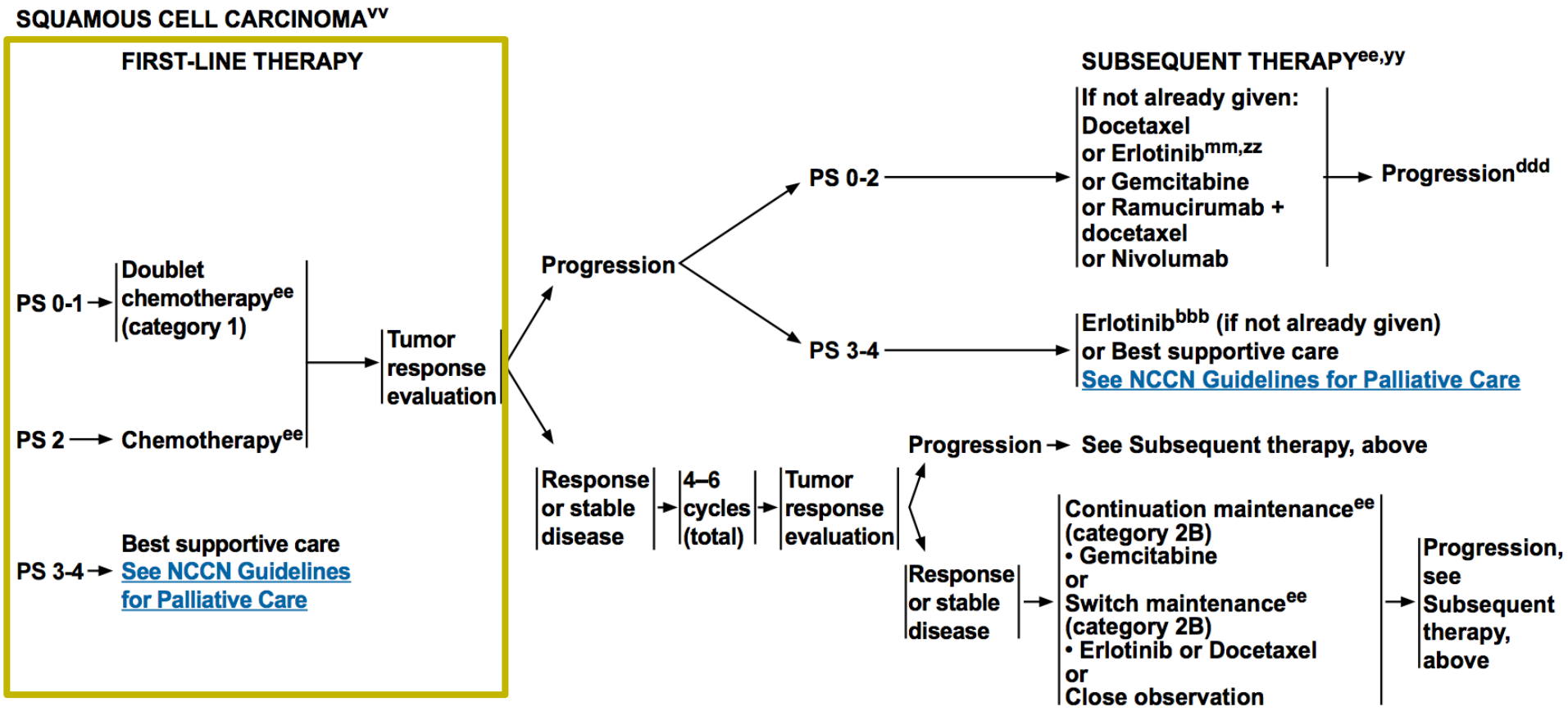


*According to FDA or European Commission approval dates

Registration conditions differ internationally. Thus, the approved indication may not be the same and there may not be an approved SCC indication in all countries. Country-specific information is contained in the locally approved registration documents.

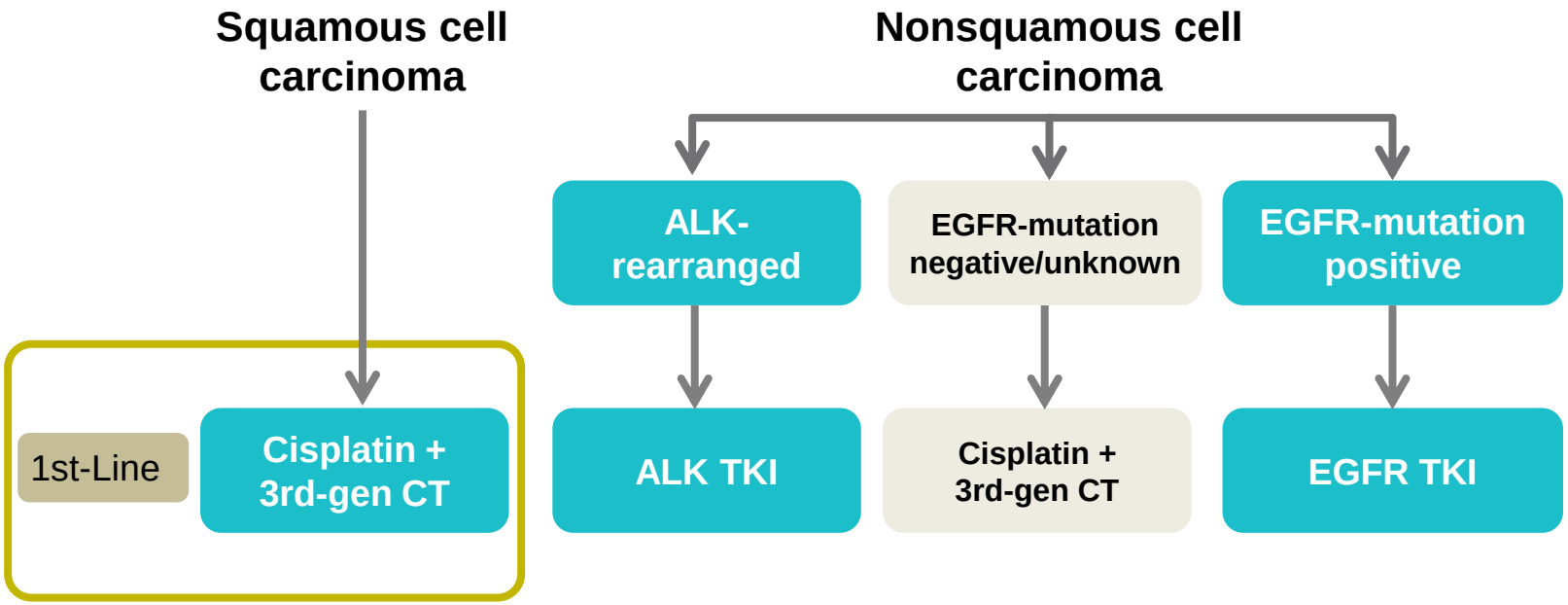
FDA: Food and Drug Administration
Approval information available at: http://www.fda.gov/Drugs/InformationOnDrugs/ucm279174.htm and http://www.ema.europa.eu/

First-Line Treatment of Metastatic SCC of the Lung: NCCN Guidelines



NCCN = National Comprehensive Cancer Network.
NCCN Clinical Practice Guidelines. NSCLC. Version 6.2015.

First-Line Treatment of Metastatic SCC of the Lung: ESMO Guidelines



ESMO = European Society for Medical Oncology; CT = chemotherapy; ALK = anaplastic lymphoma kinase; TKI = tyrosine kinase inhibitor.

Modified from Reck et al. *Ann Oncol.* 2014;25(suppl 3):iii27 and Besse et al. *Ann Oncol.* 2014;25:1475.

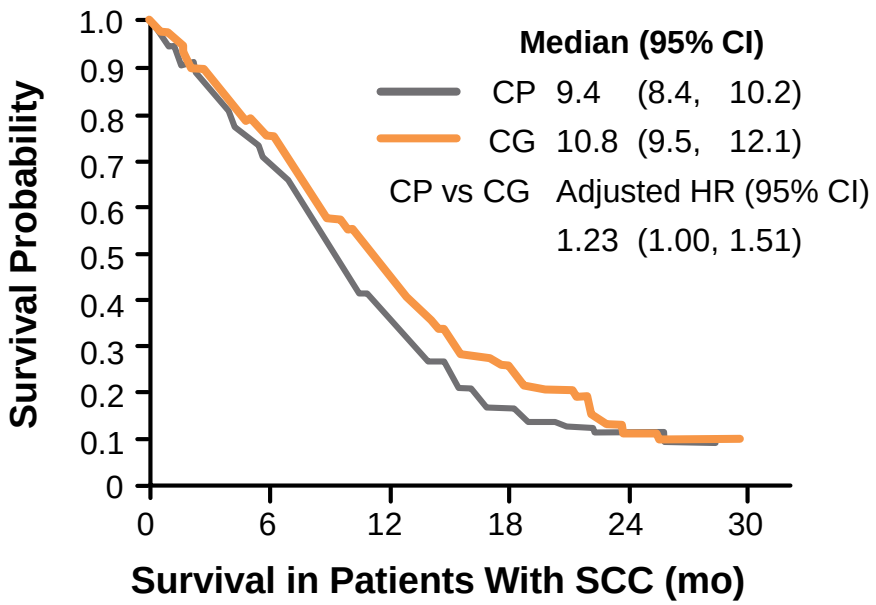
First-Line Treatment for SCC of the Lung: Platinum-Based Doublet Chemotherapy

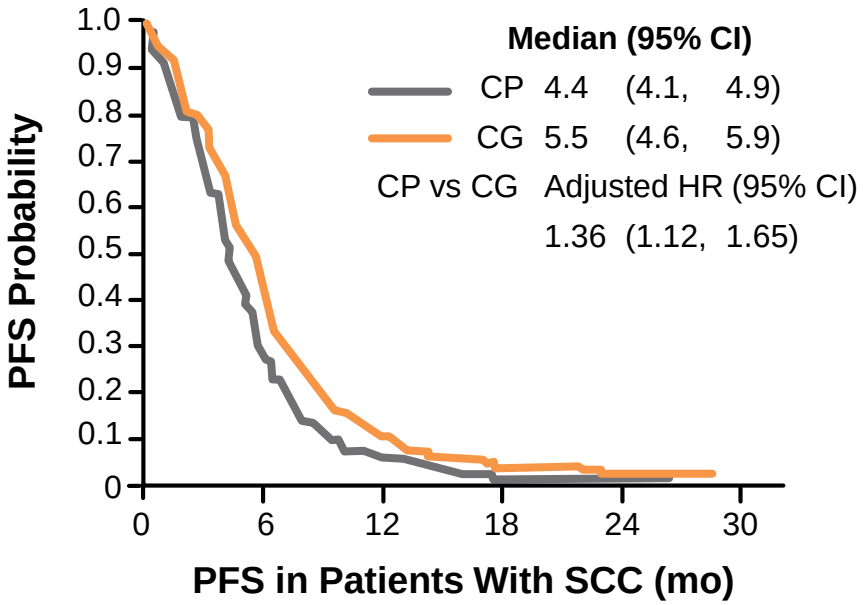
- Platinum-based CT (carboplatin or cisplatin plus third-generation CT[a]) has been the recommended first-line treatment for advanced NSCLC
  - Meta-analysis in 1995 showed a 10% improvement in survival at 1 year compared with BSC[1,2]
  - Equivalent efficacy in nonsquamous vs squamous[3-5]
- Another meta-analysis (9 trials, 2968 patients) showed improved radiologic response rates for cisplatin compared with carboplatin-based regimens, but only showed an increase in OS if used in nonsquamous histologic subtypes or in combination with third-generation CT [a,6]
- Cisplatin-based regimens were associated with a higher rate of nausea, vomiting and nephrotoxicity, whereas carboplatin was associated with increased thrombocytopenia[6]

[a]Paclitaxel, docetaxel, gemcitabine or vinorelbine.
BSC = best supportive care.

1. Travis et al. WHO Classification of Tumours. 2004:9.2. Reck et al. *Ann Oncol*. 2014;25(suppl 3);iii27; 3. Schiller et al. *N Engl J Med*. 2002;346:92.
4. Kelly et al. *J Clin Oncol*. 2001;19:3210; 5. Pilkington et al. *Thorax*. 2015;70:359; 6. Ardizzoni et al. *J Natl Cancer Inst*. 2007;99:847.

First-Line Treatment for SCC of the Lung: Platinum-Based Doublet Chemotherapy (*cont'd*)





CP = cisplatin + pemetrexed; CG = cisplatin + gemcitabine.

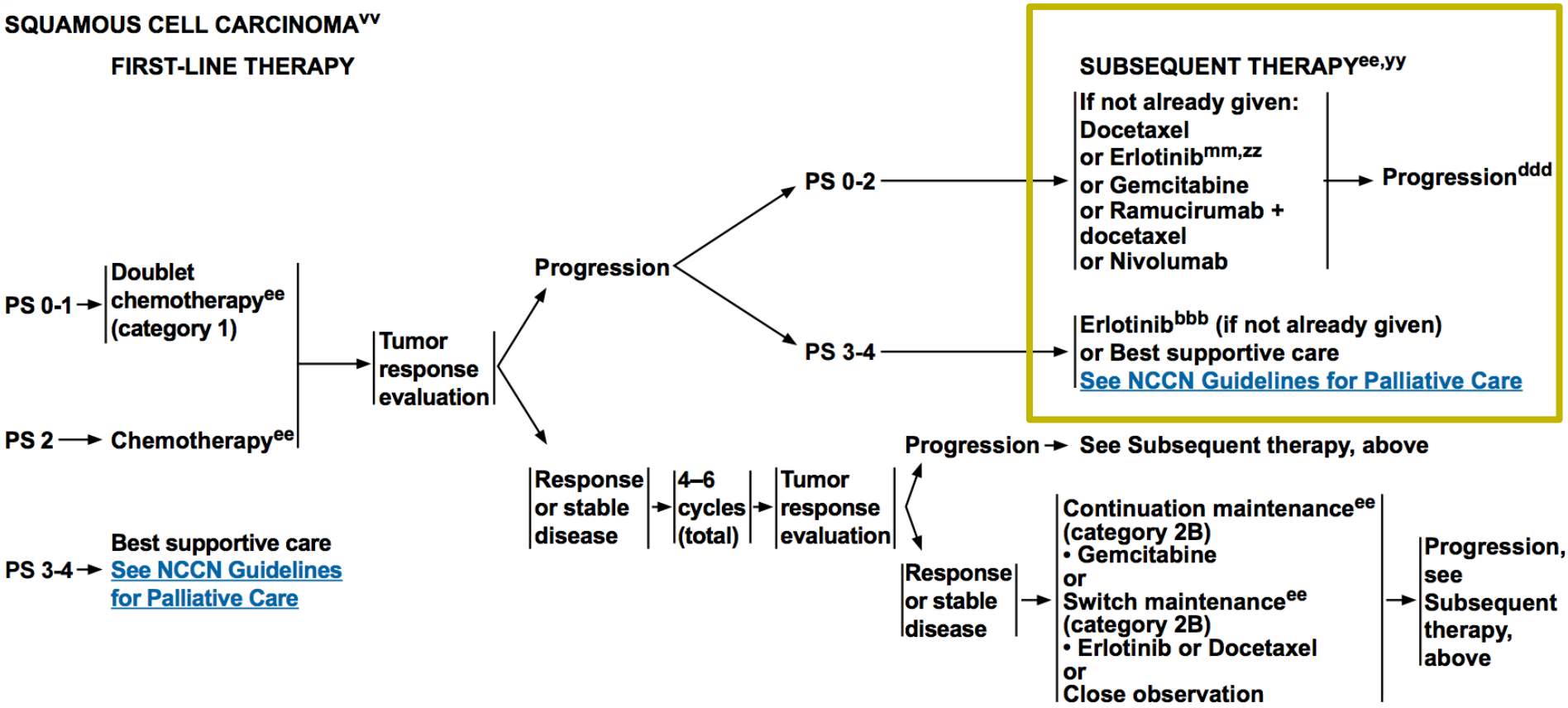
Scagliotti et al. *J Clin Oncol*. 2008;26:3543.

Pemetrexed-Based CT in SCC of the Lung

- Pemetrexed-based CT is only recommended for non-SCC
  - First line: cisplatin/pemetrexed provided a significant OS benefit of 1.7-3.7 months compared with cisplatin/gemcitabine for non-SCC, whereas SCC had a significantly longer OS of 1.4 months with cisplatin/gemcitabine[1]
  - Second line: pemetrexed provided an OS advantage for non-SCC (HR 0.78, *P*=0.047), whereas SCC had a shorter OS (HR 1.56; *P*=0.018) (vs docetaxel)[2]
- A potential explanation for the different clinical behaviour of pemetrexed is that SCC tumours express higher levels of thymidylate synthase, the main target of pemetrexed, with higher expression levels being associated with resistance[3,4]
  - As such, pemetrexed-based chemotherapy is not recommended in any setting for SCC

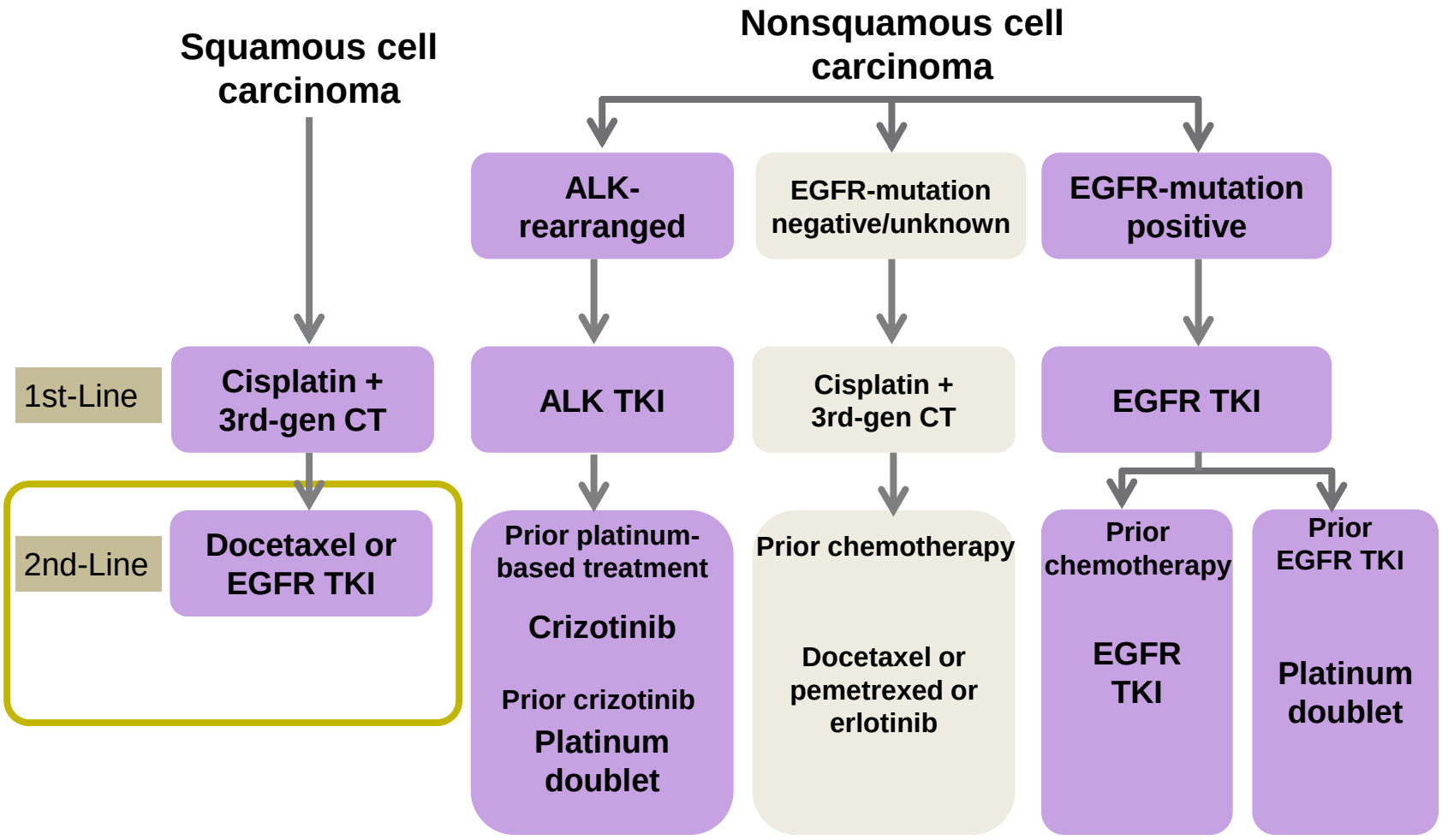
1. Scagliotti et al. *J Clin Oncol*. 2008;26:3543; 2. Scagliotti et al. *Oncologist*. 2009;14:253.
3. Ceppi et al. *Cancer*. 2006;107:1589; 4. Shih et al. *Cancer Res*. 1997;57:1116.

Second-Line Treatment of Metastatic SCC of the Lung: NCCN Guidelines



NCCN Clinical Practice Guidelines. NSCLC. Version 6.2015.

Second-Line Treatment of Metastatic SCC of the Lung: ESMO Guidelines



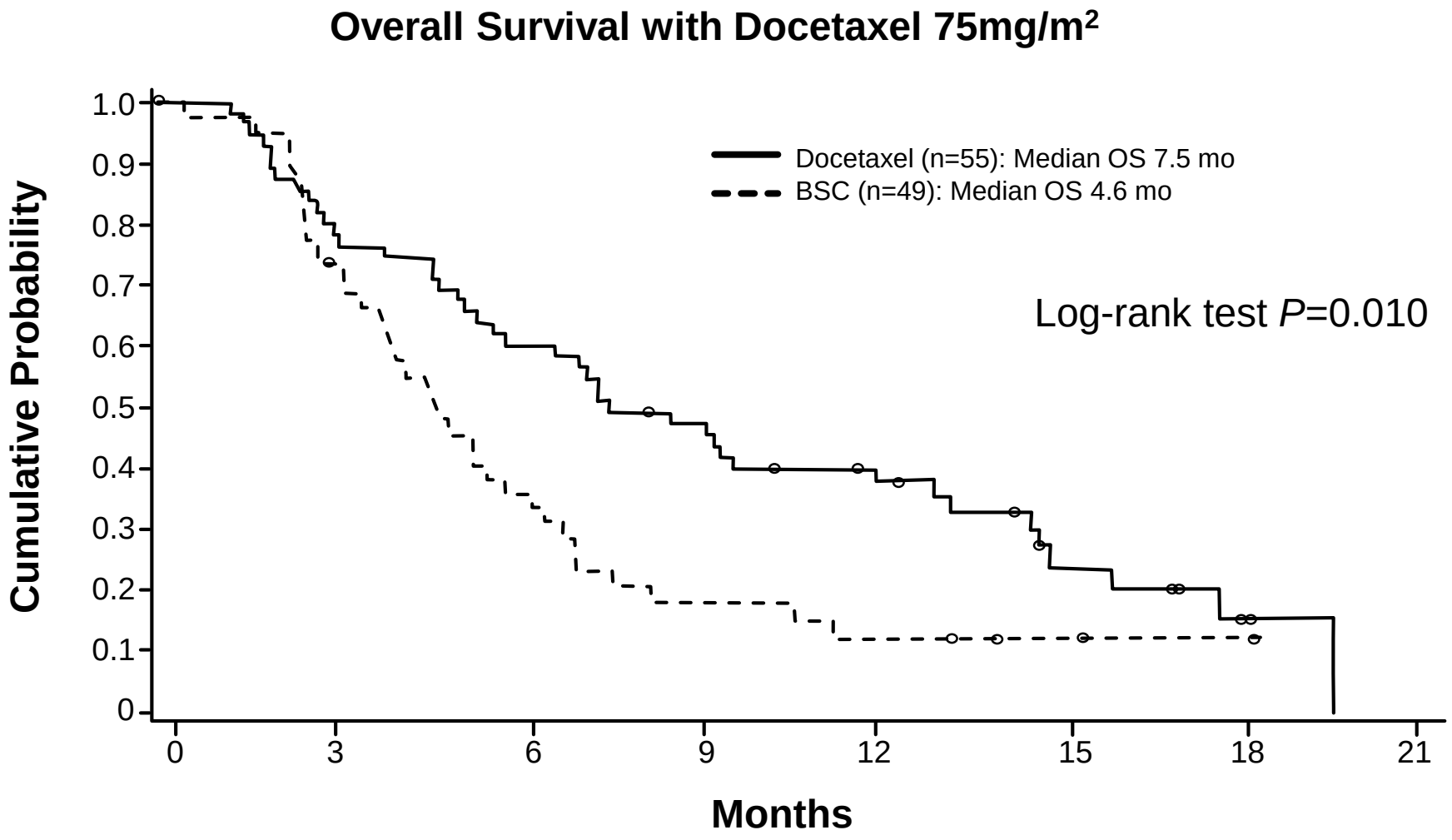
Modified from Reck et al. *Ann Oncol.* 2014;25(suppl 3):iii27 and Besse et al. *Ann Oncol.* 2014;25:1475.

Second-Line Chemotherapy for advanced NSCLC

- Doublet CT fails to improve OS and increases toxicity compared with single agent[1]
- Docetaxel vs BSC in NSCLC: TAX317 trial[2]:
  - Docetaxel vs BSC upon progression after platinum-based CT as first-line, showed a significant improvement in OS (7.5 vs 4.6 months, *P*=0.010) as well disease-related symptoms with docetaxel
  - Docetaxel was associated with significant toxicity
  - Docetaxel vs vinorelbine or ifosfamide—TAX320 trial[3]:
    - Similar results to docetaxel as in TAX317
  - In contrast to pemetrexed, the efficacy of docetaxel has not been found to vary by histologic subtype[4]

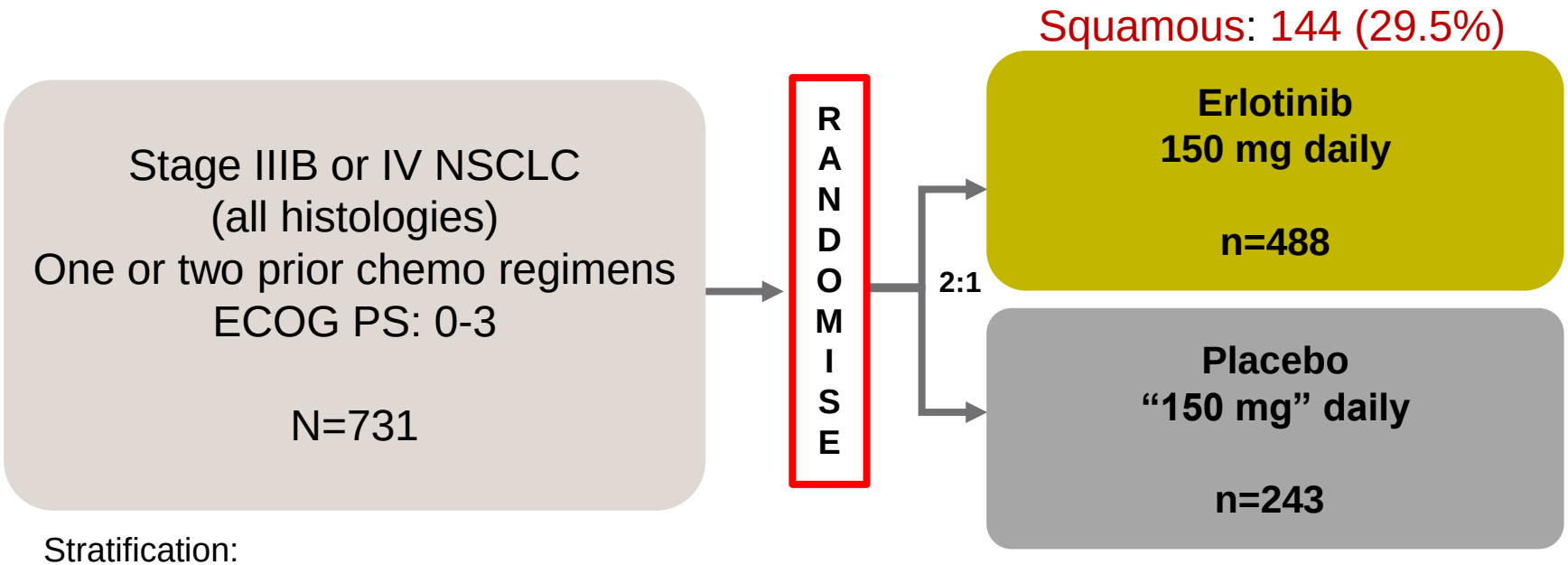
1. Di Maio et al. *J Clin Oncol*. 2009;27:1836.
2. Shepherd et al. *J Clin Oncol*. 2000;18:2095.
3. Fossella et al. *J Clin Oncol*. 2000;18:2354.
4. Scagliotti et al. *Oncologist*. 2009;14:253.

TAX 317: Docetaxel vs BSC in Second-Line Treatment for advanced NSCLC



Shepherd et al. *J Clin Oncol.* 2000;18:2095.

BR 21: Trial Design



Stratification:

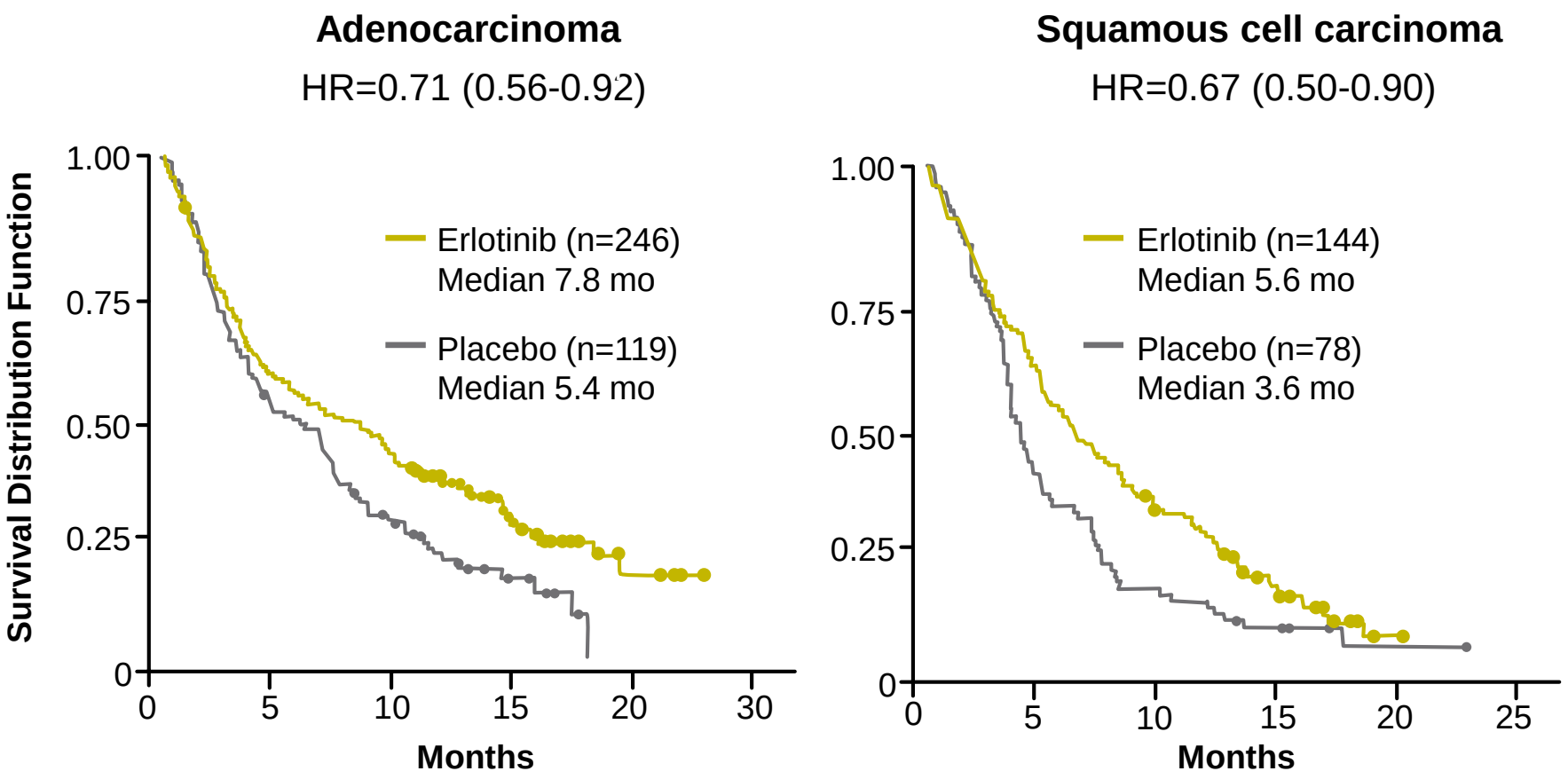
- Center
- PS: 0/1 vs 2/3
- Response to prior Rx: CR/PR vs SD vs PD
- Prior regimens: 1 vs 2
- Prior platinum therapy: Yes vs no

- Primary endpoint: OS
- Secondary endpoints: PFS, ORR, DOR, toxicity and QoL

Shepherd et al. *N Engl J Med*. 2005;352:123

BR 21: Erlotinib vs Placebo in Second-Line Treatment for advanced NSCLC

Overall Survival



Shepherd et al. *N Engl J Med*. 2005;352:123.
Clark et al. *Clin Lung Cancer.* 2006;7:389.

Label of Approved Drugs in Second Line Treatment At the time of Trial Design in 2011

- **Docetaxel**
  - As a single agent is indicated for the treatment of patients with locally advanced or metastatic NSCLC after failure of prior platinum-based CT
- **Erlotinib**
  - Treatment of locally advanced or metastatic NSCLC after failure of ≥1 prior CT regimen
  - Maintenance treatment of patients with locally advanced or metastatic NSCLC whose disease has not progressed after 4 cycles of platinum-based, first-line CT

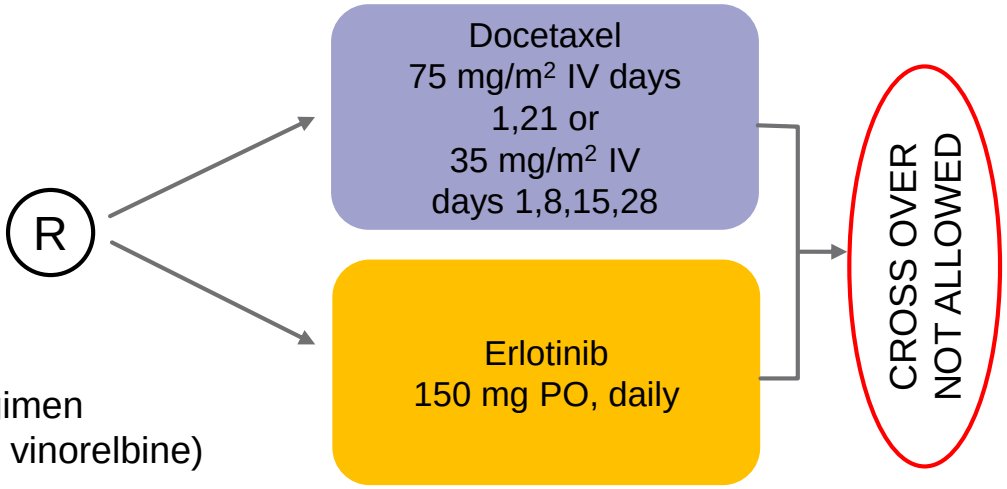
- ✓ Both drugs were approved on the basis of placebo-controlled trials that included all histologies, and both showed OS improvement
- ✓ Erlotinib mechanistic profile of targeting EGFR and oral posology, similar efficacy but better tolerability comparing to docetaxel, made it the obvious choice for comparing with afatinib in LUX-Lung 8

Any new evidence after 2011 regarding Erlotinib vs Docetaxel?

TAILOR (2012): Erlotinib vs Docetaxel in Second Line Treatment in NSCLC

- Advanced/recurrent NSCLC
- Previous platinum-based doublet
- EGFR wild-type
- *KRAS* determined
- ECOG PS 0-2

STRATIFICATION
- Centre
- Recurrent/progressed
- Type of prior chemotherapy regimen (pemetrexed vs gemcitabine vs vinorelbine)
- ECOG PS (0-1 vs 2)
- Adequacy of tissue sample (optimal vs suboptimal)



Results in 222 pts (ITT): OS improvement with docetaxel vs erlotinib
(8.2 vs 5.4m; HR 0.73, 95% CI 0.53-1.00, p=0.05)

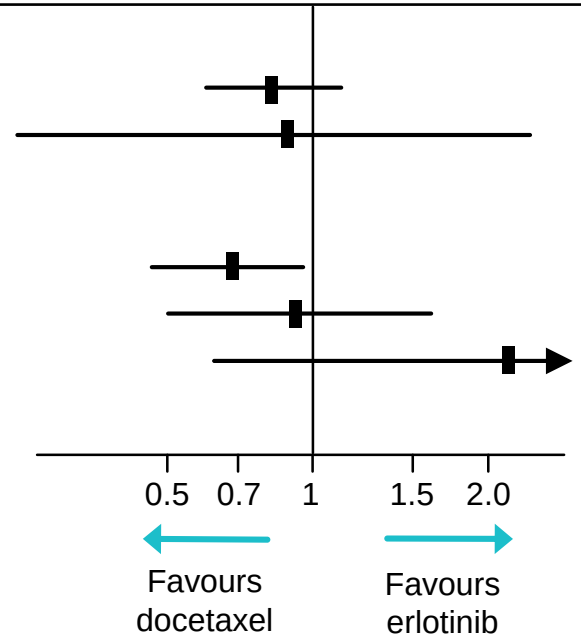
Conclusion of the trial:
Chemotherapy is more effective than erlotinib for second-line treatment for previously treated patients with NSCLC who have wild-type EGFR tumours

Garassino et al. *Lancet Oncol*. 2013;14:981.

TAILOR: Erlotinib vs Docetaxel in Second Line Treatment in NSCLC (cont'd)

OS: ADC vs SCC Histology

	Docetaxel Group	Erlotinib Group	Hazard Ratio (95% CI)	$P_{interaction}$
Performance status				
0-1	85/103	86/100	0.80 (0.59-1.07)	0.81
2	7/7	9/9	0.87 (0.31-2.47)	
Histology				
Adenocarcinoma	69/83	63/69	0.67 (0.48-0.95)	0.14
Squamous	19/23	25/31	0.90 (0.49-1.65)	
Other	4/4	7/9	2.32 (0.62-8.74)	



In the subgroup of patients with squamous histology the OS did not differ between treatment groups

Garassino et al. *Lancet Oncol*. 2013;14:981.

Meta-analysis (2014): EGFR TKIs vs Chemotherapy as Second-Line Treatment in Advanced NSCLC

Clinical trials available through PubMed, Embase, Cochrane (CENTRAL), ASCO, ESMO, and World Conference of Lung Cancer were screened

Selection criteria
- EGFR-TKI vs standard second-line CT (docetaxel or pemetrexed)
- Prospective randomised trial
- Patients previously treated with platinum compounds
- Sufficient data to calculate effect measure

10 randomised trials were identified composed of 3825 NSCLC patients

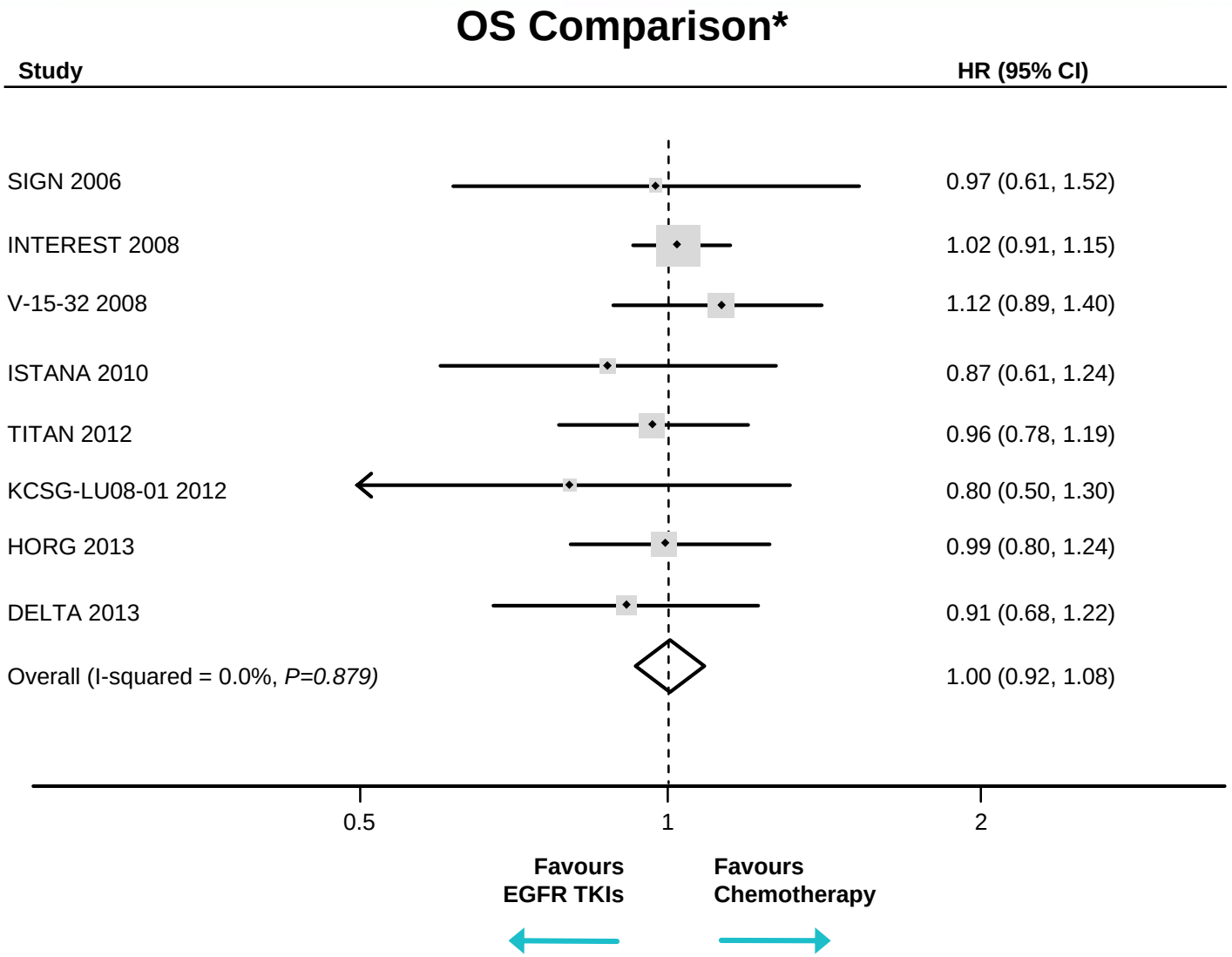
Data were analysed on an ITT basis
Outcome measures:

PFS[a] | OS[a] | ORR | RR | Grade 3-4 toxicities

[a]EGFR mutation–positive and EGFR mutation–negative subgroups were pooled.
ITT = intention-to-treat; ORR = objective response rate; RR = response rate.

Li et al. *PLoS One.* 2014;9:e102777.

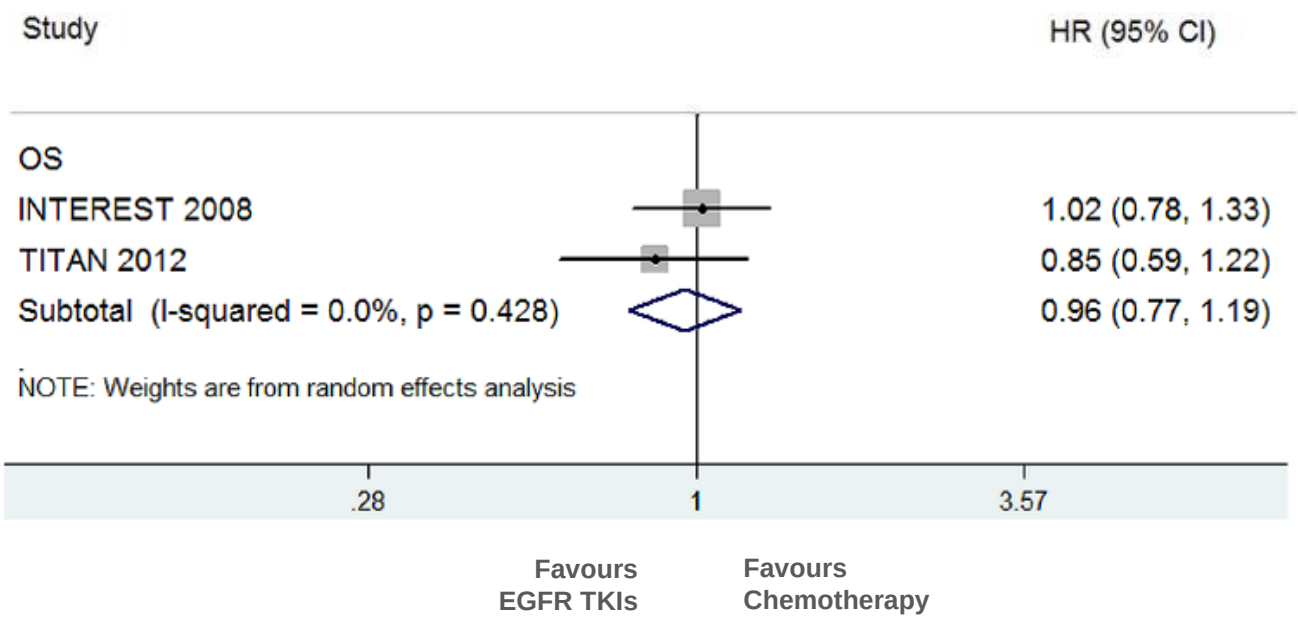
Meta-analysis (2014): EGFR TKIs vs Chemotherapy as Second-Line Treatment (cont'd)



Li et al. *PLoS One.* 2014;9:e102777.

Meta-analysis (2014): EGFR TKIs vs Chemotherapy as Second-Line Treatment (cont'd)

OS Comparison in the subgroup of EGFR wild type patients*



*TAILOR was not included in the OS comparison at that time the OS data hadn't been reported yet

Li et al. *PLoS One.* 2014;9:e102777.

Label of Approved Drugs in Second Line Treatment

- Docetaxel
  - As a single agent is indicated for the treatment of patients with locally advanced or metastatic NSCLC after failure of prior platinum-based CT
- Erlotinib
  - Treatment of locally advanced or metastatic NSCLC after failure of ≥1 prior CT regimen
  - Maintenance treatment of patients with locally advanced or metastatic NSCLC whose disease has not progressed after 4 cycles of platinum-based, first-line CT

Recent additions (US)

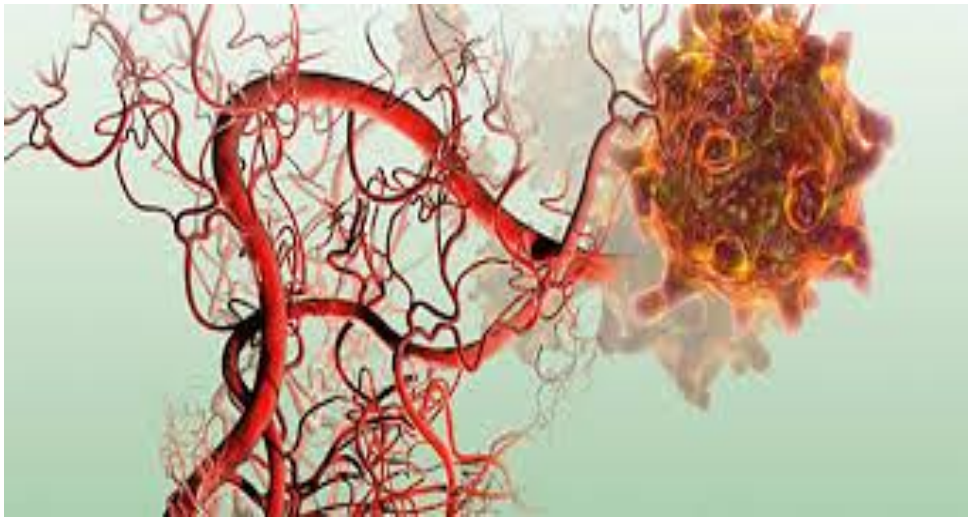
- **Ramucirumab + docetaxel** (Dec 12, 2014)
  - Treatment of metastatic NSCLC with disease progression on or after platinum-based CT
- **Nivolumab** (Mar 5, 2015)
  - Treatment of metastatic squamous NSCLC with progression on or after platinum-based CT

Antiangiogenesis in the Treatment of SCC Lung

Antiangiogenesis in the Treatment of NSCLC

- Angiogenesis is important for the development and growth of tumours beyond a certain size[1]
- Signaling cascades involved in angiogenesis include VEGF and PDGF as well as other pathways[2]
- Antiangiogenic approaches have been demonstrated to be active in a number of solid tumors including NSCLC[3]

Angiogenesis in tumour growth and development[4]



1. www.cancer.gov/about-cancer/treatment/types/immunotherapy/angiogenesis-inhibitors-fact-sheet. Accessed May 19, 2015.
2. Rolfo et al. *Expert Opin Investig Drugs*. 2013;22:1081.
3. Sandler et al. *N Engl J Med*. 2006;355:2542.
4. http://www.nyas.org/Publications/EBriefings/Detail.aspx?cid=6fe7e173-b02e-4b8f-a8cb-7c0e3de1d5ed. Accessed January 26, 2015.

Antiangiogenic Approaches in the Treatment of SCC of the Lung

	No. of Patients With SCC	Regimen	Results
Johnson et al.[1]	Total: 13 7.5 mg/kg: 10 15 mg/kg: 3	Bevacizumab (7.5 or 15 mg/kg) + CP vs CP	• 6 patients experienced a major life-threatening bleeding described as haemoptysis or haematemesis; 4 events were fatal; 4 of the severe haemorrhages occurred in 13 patients with SCC
Scagliotti et al.[2]	Total: 223 Treatment: 109 (23%) Control: 114 (25%)	Sorafenib + CP vs Placebo + CP	• The study was terminated because it was highly unlikely to meet its primary endpoint of OS • Patients with SCC had greater risk for mortality in sorafenib arm than in control arm (HR 1.85; 95% CI, 1.22-2.81) • SCC may be associated with a greater incidence of fatal bleeding events (including fatal pulmonary haemorrhage), irrespective of treatment
Scagliotti et al.[3]	Total: 223 Treatment: NA Control: NA	Motesanib + CP vs Placebo + CP	• In November 2008, the DMC recommended that enrollment of all patients be halted and treatment of SCC be discontinued because of higher early mortality and a higher incidence of gross haemoptysis compared with placebo

C = carboplatin; P = paclitaxel; NA = not available; DMC = Data Monitoring Committee.

1. Johnson et al. *J Clin Oncol*. 2004;22:2184.
2. Scagliotti et al. *J Clin Oncol*. 2010;28:1835.
3. Scagliotti et al. *J Clin Oncol*. 2012;30:2829.

Antiangiogenic Approaches in the Treatment of SCC of the Lung (cont'd)

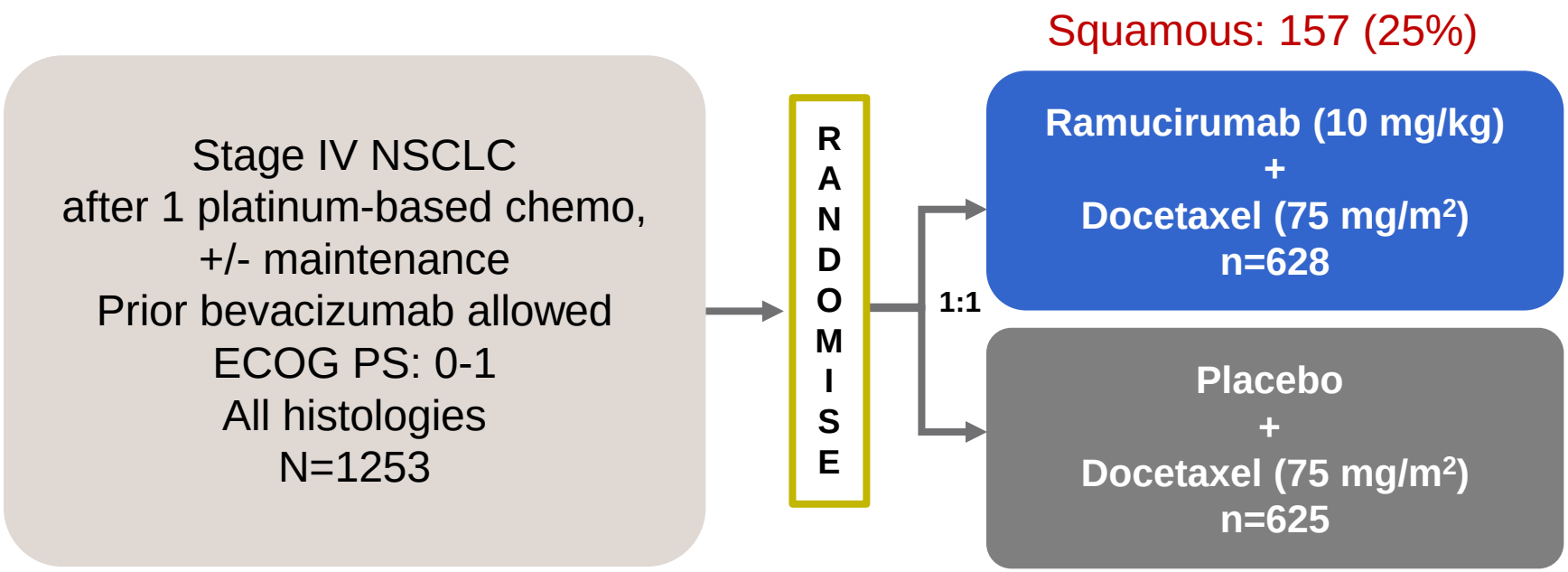
	No. of Patients With SCC	Regimen	Results
Reck et al.[1]	Total: 555 Treatment: 276 (42.1%) Control: 279 (42.3%)	Nintedanib + D vs Placebo + D	• PFS (by central independent review) was significantly longer in the nintedanib + D group than in the placebo + D group (Adeno: HR=0.77; 95% CI, 0.62-0.96, *P*=0.0193; SCC: HR 0.77; 95% CI, 0.62-0.96, *P*=0.02) • There was no difference in OS between the 2 groups for patients with SCC (HR 1.01; 95% CI, 0.85-1.21, *P*=0.8907) • There was a low incidence of class effects typically associated with antiangiogenic agents, such as hypertension, bleeding, perforation, and thromboembolism, which have been noted with other antiangiogenic agents in NSCLC

D = docetaxel

1. Reck et al. *Lancet Oncol*. 2014;15:143.

REVEL: Ramucirumab + Docetaxel in Second-Line Treatment for NSCLC

Ramucirumab: A fully human IgG1 mAb targets extracelluar domain of VEGFR-2



Stratification Factors:

- ECOG PS: 0-1
- Gender
- Prior maintenance
- East Asia vs ROW

Primary endpoint: OS

Secondary endpoints: PFS, ORR, safety, PRO

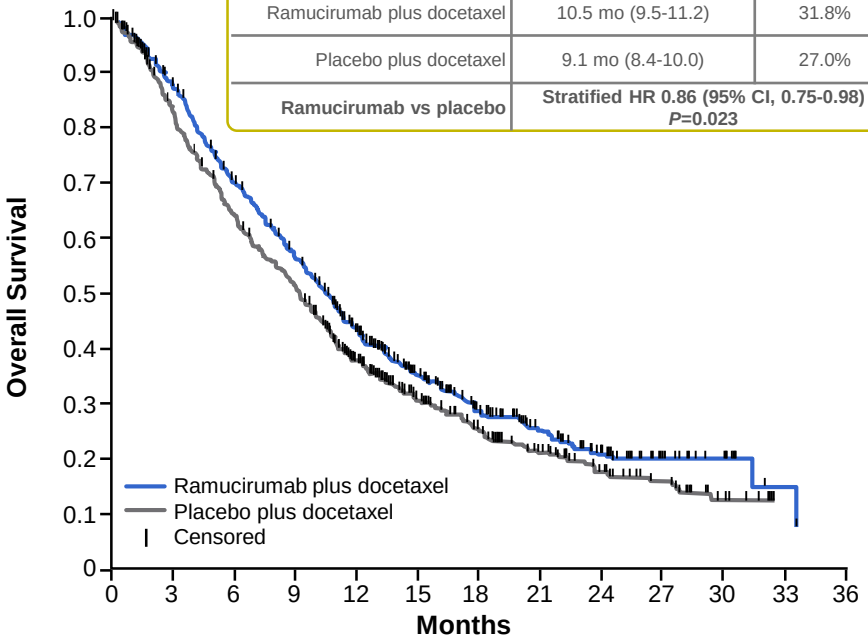
mAb = monoclonal antibody; VEGFR-2 = VEGF receptor 2; ROW = rest of world; PRO = patient-reported outcomes.

Garon et al. *Lancet*. 2014;384:665.

REVEL: OS and PFS (ITT)

OS

	Median (95% CI)	Censoring Rate
Ramucirumab plus docetaxel	10.5 mo (9.5-11.2)	31.8%
Placebo plus docetaxel	9.1 mo (8.4-10.0)	27.0%
Ramucirumab vs placebo	**Stratified HR 0.86 (95% CI, 0.75-0.98) *P*=0.023**	

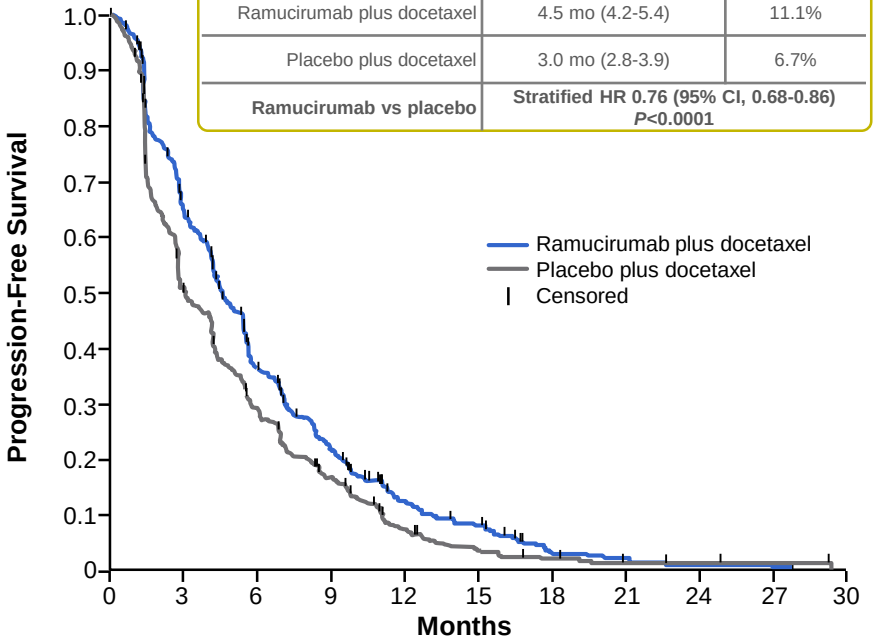


Number at risk

Ramucirumab plus docetaxel	628	527	415	329	231	156	103	70	45	23	11	2	0
Placebo plus docetaxel	625	501	386	306	197	129	86	56	36	23	9	0	0

PFS

	Median (95% CI)	Censoring Rate
Ramucirumab plus docetaxel	4.5 mo (4.2-5.4)	11.1%
Placebo plus docetaxel	3.0 mo (2.8-3.9)	6.7%
Ramucirumab vs placebo	**Stratified HR 0.76 (95% CI, 0.68-0.86) *P*<0.0001**	



Number at risk

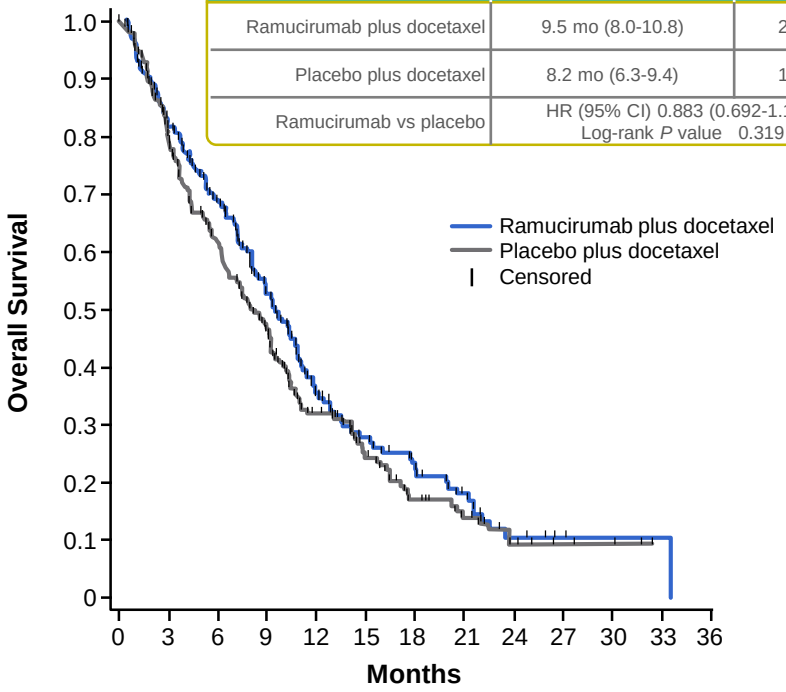
Ramucirumab plus docetaxel	628	383	204	120	59	38	11	7	3	3	0		
Placebo plus docetaxel	625	301	172	95	37	17	9	4	3	2	0		

Garon et al. *Lancet*. 2014;384:665.

REVEL: OS and PFS in SCC subgroup

OS

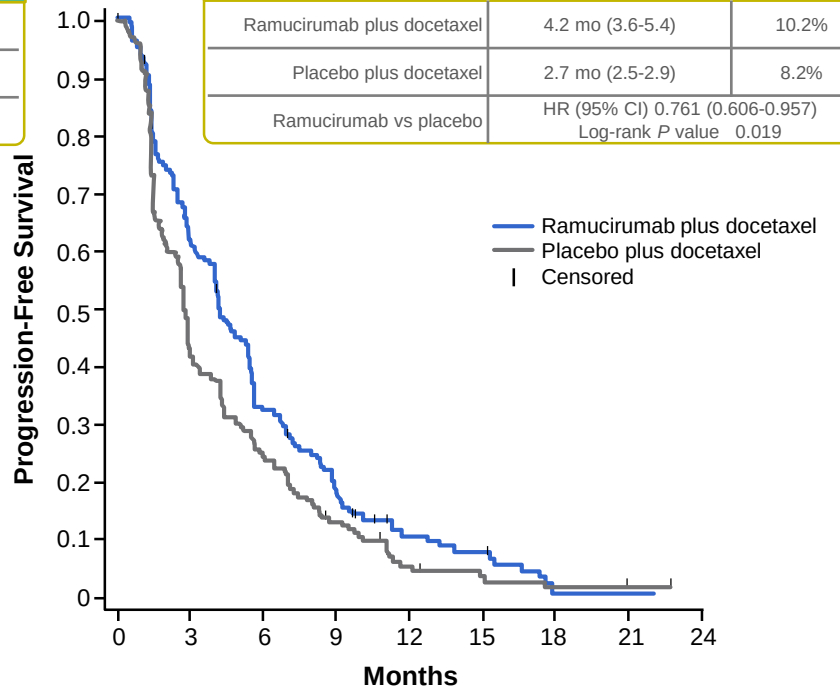
	Median (95% CI)	Censoring Rate
Ramucirumab plus docetaxel	9.5 mo (8.0-10.8)	21.7%
Placebo plus docetaxel	8.2 mo (6.3-9.4)	19.9%
Ramucirumab vs placebo	HR (95% CI) 0.883 (0.692-1.127) Log-rank *P* value 0.319	



Patients at risk													
Ramucirumab plus docetaxel	157	124	103	78	49	31	23	16	6	2	1	1	0
Placebo plus docetaxel	171	132	99	75	48	31	20	14	8	5	4	0	0

PFS

	Median (95% CI)	Censoring Rate
Ramucirumab plus docetaxel	4.2 mo (3.6-5.4)	10.2%
Placebo plus docetaxel	2.7 mo (2.5-2.9)	8.2%
Ramucirumab vs placebo	HR (95% CI) 0.761 (0.606-0.957) Log-rank *P* value 0.019	



Patients at risk									
Ramucirumab plus docetaxel	157	91	47	26	11	8	1	1	0
Placebo plus docetaxel	171	68	39	20	7	4	2	1	0

Garon et al. *Lancet*. 2014;384:665.

REVEL: Haematologic AEs by Histology

Treatment Emergent Adverse Events	Grade	Nonsquamous		Squamous	
		Ramucirumab (n=465)	Placebo (n=441)	Ramucirumab (n=157)	Placebo (n=170)
Haematologic Adverse Events					
Neutropenia[a]	Any	253 (54.4)[b]	196 (44.4)	88 (56.1)	83 (48.8)
	3/4/5	224 (48.2)[b]	171 (38.8)	78 (49.7)	70 (41.2)
Leukopenia[a]	Any	93 (20.0)	82 (18.6)	40 (25.5)	32 (18.8)
	3/4/5	56 (12.0)	52 (11.8)	29 (18.5)	23 (13.5)
Anaemia[a]	Any	93 (20.0)[b]	117 (26.5)	37 (23.6)	53 (31.2)
	3/4/5	14 (3.0)	25 (5.7)	4 (2.5)	9 (5.3)
Febrile neutropenia	Any	75 (16.1)[b]	42 (9.5)	25 (15.9)	20 (11.8)
	3/4/5	75 (16.1)[b]	42 (9.5)	25 (15.9)	20 (11.8)
Thrombocytopenia[a]	Any	53 (11.4)[b]	21 (4.8)	31 (19.7)[b]	11 (6.5)
	3/4/5	12 (2.6)[b]	3 (0.7)	6 (3.8)	1 (0.6)

[a]Consolidated AE category comprising synonymous MedDRA preferred terms.
[b]*P*<0.05 for between-treatment group; comparison based on Fisher's exact test.

Garon et al. *Lancet*. 2014;384:665.

REVEL: AEs of Interests by Histology

Treatment Emergent Adverse Events	Grade	Nonsquamous		Squamous	
		Ramucirumab (n=465)	Placebo (n=441)	Ramucirumab (n=157)	Placebo (n=170)
Adverse Events of Special Interest					
Bleeding/ haemorrhage[a]	Any	145 (31.2)[b]	60 (13.6)	36 (22.9)	33 (19.4)
	3/4/5	11 (2.4)	8 (1.8)	4 (2.5)	5 (2.9)
Epistaxis	Any	97 (20.9)[b]	30 (6.8)	19 (12.1)[b]	9 (5.3)
	3/4/5	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal haemorrhage[a]	Any	14 (3.0)	7 (1.6)	3 (1.9)	3 (1.8)
	3/4/5	3 (0.6)	1 (0.2)	1 (0.6)	1 (0.6)
Pulmonary haemorrhage[a]	Any	34 (7.3)	25 (5.7)	15 (9.6)	21 (12.4)
	3/4/5	5 (1.1)	4 (0.9)	3 (1.9)	4 (2.4)
Haemoptysis	Any	25 (5.4)	16 (3.6)	11 (7.0)	16 (9.4)
	3/4/5	3 (0.6)	2 (0.5)	1 (0.6)	2 (1.2)
Hypertension[a]	Any	54 (11.6)[b]	23 (5.2)	14 (8.9)	6 (3.5)
	3/4/5	27 (5.8)[b]	13 (2.9)	8 (5.1)[b]	0 (0.0)
Infusion-related reaction[a]	Any	18 (3.9)	20 (4.5)	5 (3.2)	8 (4.7)
	3/4/5	4 (0.9)	3 (0.7)	1 (0.6)	1 (0.6)
Proteinuria	Any	15 (3.2)[b]	5 (1.1)	6 (3.8)[b]	0 (0.0)
	3/4/5	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)

[a]Consolidated AE category comprising synonymous MedDRA preferred terms.
[b]*P*<0.05 for between-treatment group; comparison based on Fisher's exact test.

Garon et al. *Lancet*. 2014;384:665.

REVEL: AEs of Interests by Histology (cont'd)

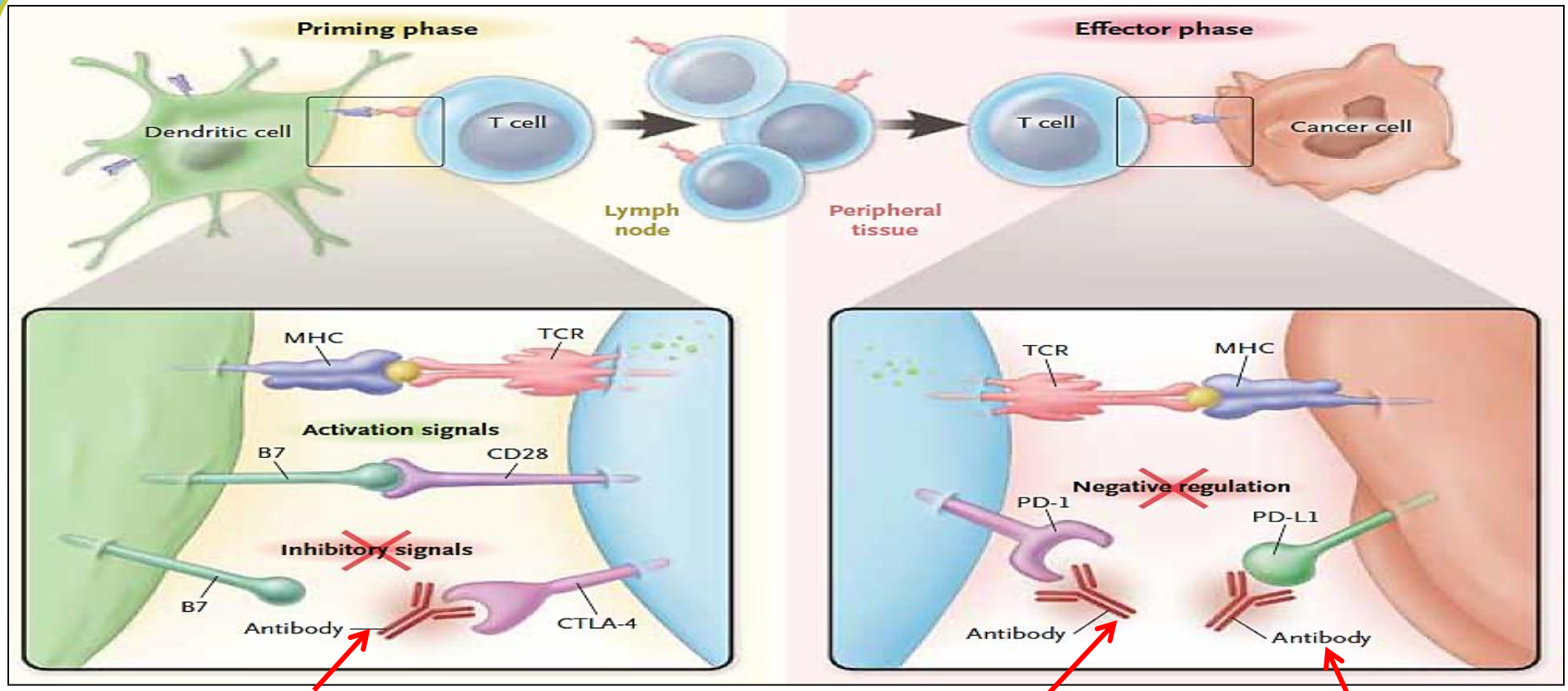
Treatment Emergent Adverse Events	Grade	Nonsquamous		Squamous	
		Ramucirumab (n=465)	Placebo (n=441)	Ramucirumab (n=157)	Placebo (n=170)
Adverse Events of Special Interest					
Venous thromboembolic[a]	Any	9 (1.9)[b]	27 (6.1)	7 (4.5)	8 (4.7)
	3/4/5	7 (1.5)	15 (3.4)	4 (2.5)	3 (1.8)
Renal failure[a]	Any	11 (2.4)	11 (2.5)	3 (1.9)	3 (1.8)
	3/4/5	2 (0.4)	1 (0.2)	1 (0.6)	1 (0.6)
Arterial thromboembolic[a]	Any	6 (1.3)	10 (2.3)	4 (2.5)	2 (1.2)
	3/4/5	3 (0.6)	7 (1.6)	3 (1.9)	0 (0.0)
Congestive heart failure[a]	Any	6 (1.3)	3 (0.7)	0 (0.0)	1 (0.6)
	3/4/5	5 (1.1)	0 (0.0)	0 (0.0)	1 (0.6)
Gastrointestinal perforation[a]	Any	5 (1.1)	1 (0.2)	1 (0.6)	1 (0.6)
	3/4/5	4 (0.9)	1 (0.2)	1 (0.6)	1 (0.6)

[a]Consolidated AE category comprising synonymous MedDRA preferred terms.
[b]$P<0.05$ for between-treatment group; comparison based on Fisher's exact test.

Garon et al. *Lancet*. 2014;384:665.

Immunotherapy in the Treatment of SCC Lung

Immunotherapy in the Treatment of NSCLC: Immune Checkpoint Inhibitors



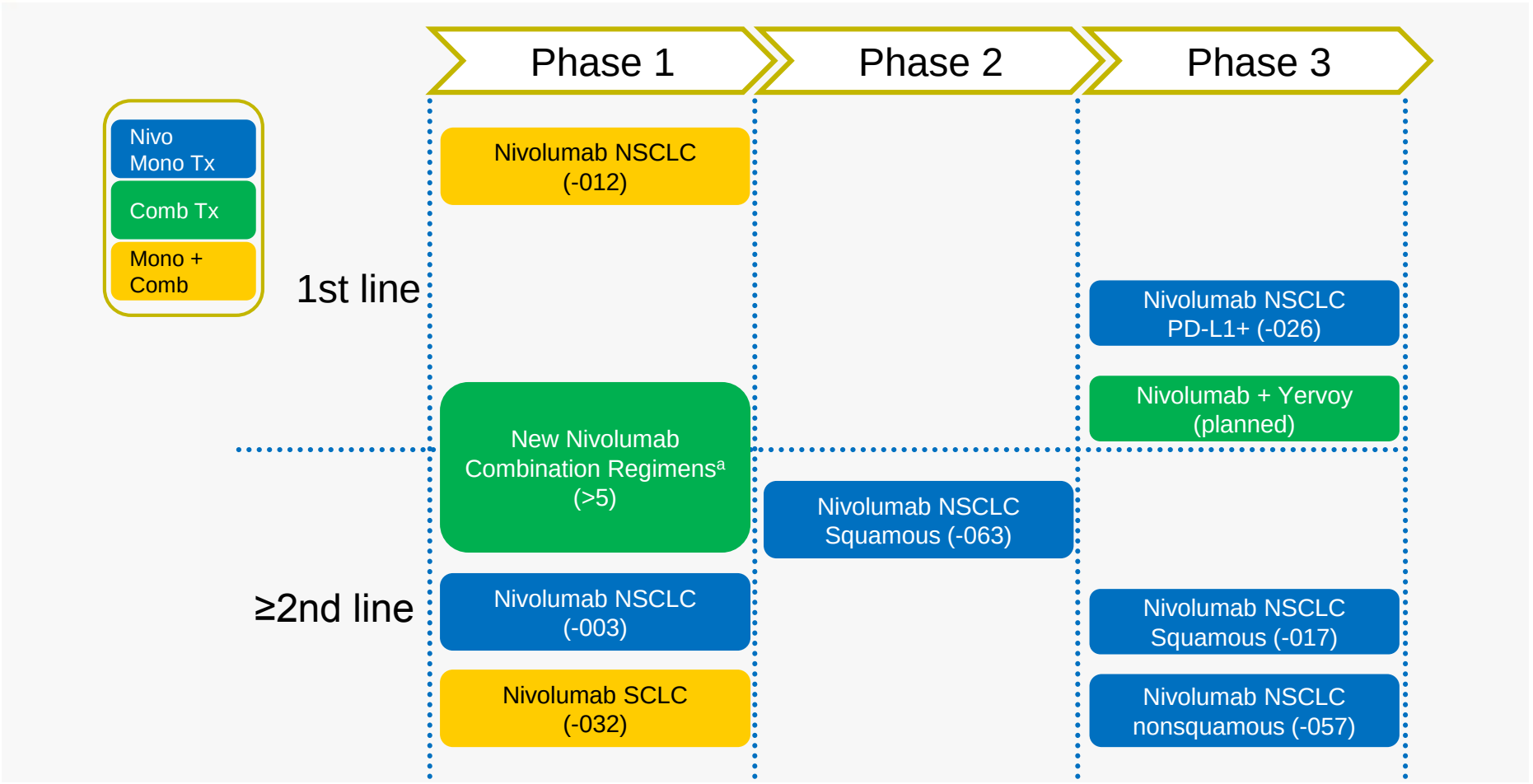
Ipilimumab

Nivolumab
Pembrolizumab

MPDL3280A
MEDI4736

Ribas. *N Engl J Med.* 2012;366:2517.

Nivolumab Lung Cancer Development Programme

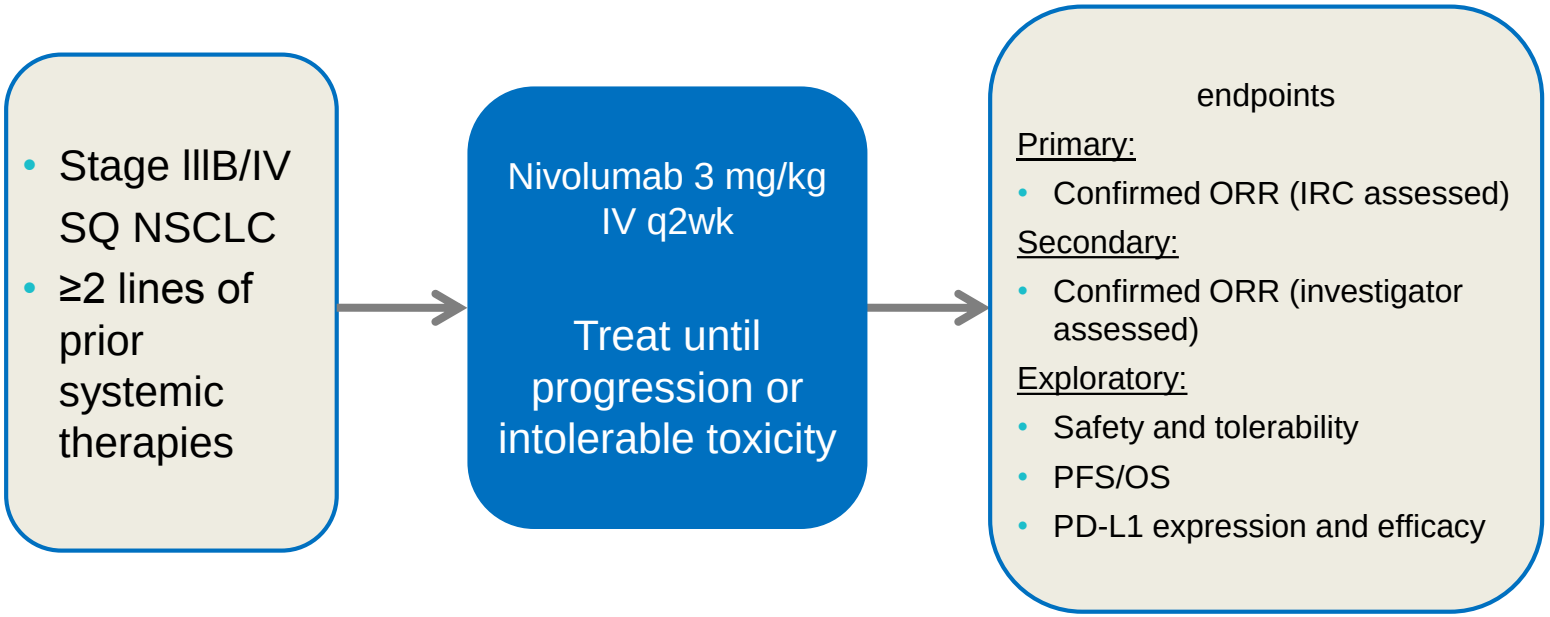


[a]Includes collaborations.

Ramalingam. CMSTO 2014.

CheckMate-063: Trial Design

Phase 2 Nivolumab in Advanced, Third-Line + Squamous Cell Lung Cancer

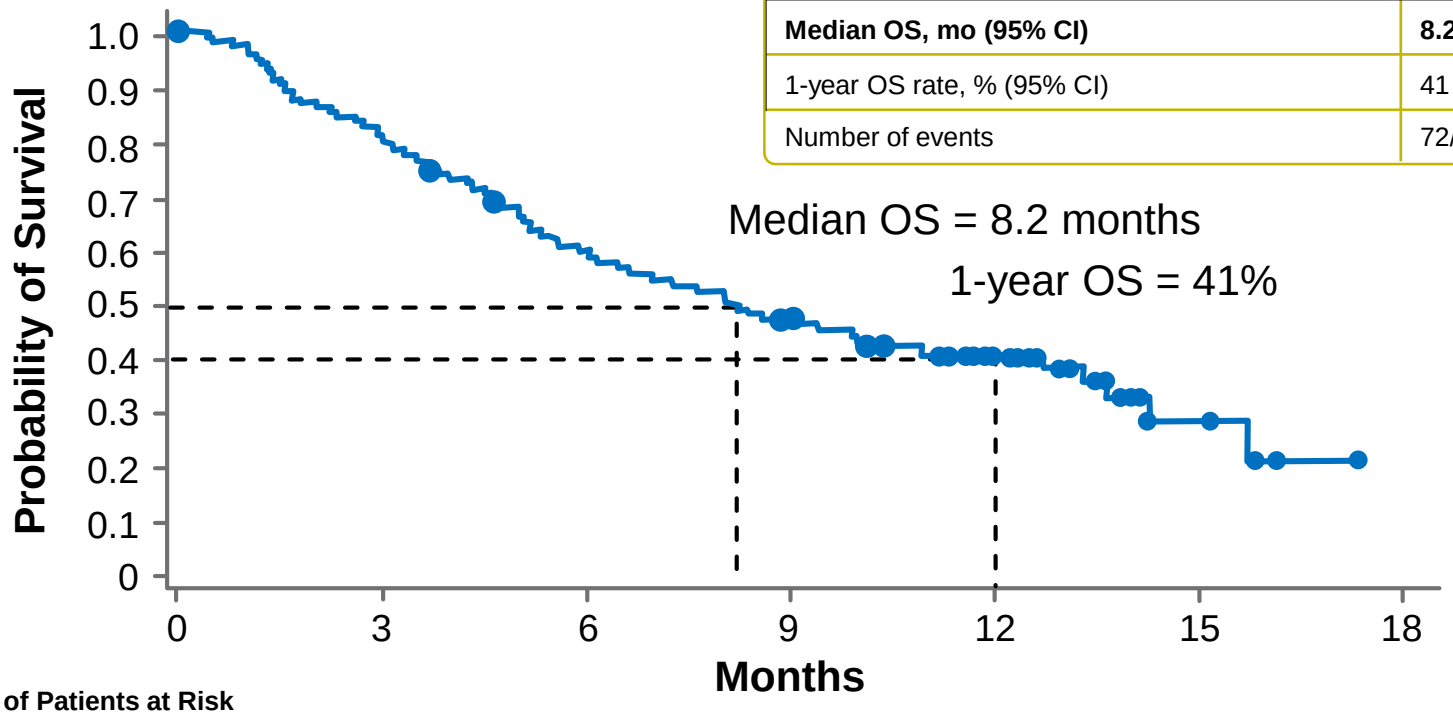


- Tumour assessments (per RECIST v1.1) performed at week 8 and every 6 weeks
- Minimum of 11 months of follow-up for response
- Median OS fellow-up was 8 months (range, 0-17.3)

Ramalingam. CMSTO 2014.

CheckMate-063: Overall Survival

Median OS, mo (95% CI)	**8.2 (6.1-11)**
1-year OS rate, % (95% CI)	41 (32-50)
Number of events	72/117



Number of Patients at Risk

Nivolumab 3 mg/kg	117	93	68	51	28	5	0

◆ Median follow-up for OS: 8 months (range, 0-17)

Green circles represent censored observations.

Ramalingam. CMSTO 2014.

CheckMate-063: Other Endpoints

	IRC Assessed (per RECIST 1.1)[a]
ORR, % (n) [95% CI]	15 (17) [9-22]
Disease control rate, % (n)	40 (47)
Median DOR, mo (range)	NR (2+ to 12+)
Ongoing responders, % (n)	76 (13)
Median time to response, mo (range)	3 (2-9)
Median PFS, mo (95% CI)	2 (2-3)
PFS rate at 1-year, % (95% CI)	20 (13-29)

ORR by PD-L1 Expression (IRC Assessed)

76 evaluable samples[a]

Subgroups		ORR, % (n/N)
Overall		15 (17/117)
PD-L1	≥1%	20 (9/45)
	<1%	13 (4/31)
	≥5%	24 (6/25)
	<5%	14 (7/51)
	Indeterminate/NE[b]	30 (3/10)

Safety:

- Discontinued due to adverse reactions: 27%
- Drug delay for an adverse reaction: 29%
- Serious adverse reactions: 59%
- Most frequent serious adverse reactions reported in at least 2% of patients were:
  - Dyspnoea, pneumonia, chronic obstructive pulmonary disease exacerbation, pneumonitis, hypercalcemia, pleural effusion, hemoptysis, and pain

[a]July 2014 DBL.
[b]No quantifiable PD-L1 expression.
NR = not reached; DOR = duration of response; NE = not evaluable.

Opdivo (nivolumab) prescribing information.
Rizvi et al. *Lancet Oncol.* 2015;16:257.

CheckMate-017: Trial Design

An open-label randomised phase 3 trial of BMS-936558 (nivolumab) vs docetaxel in previously treated advanced or metastatic squamous cell NSCLC

Patients with:

- Confirmed squamous cell NSCLC
- Stage IIIB/IV disease or recurrent or progressive disease following multimodal therapy (radiation therapy, surgical resection, or chemoradiation therapy for locally advanced disease)
- Disease recurrence or progression after 1 prior platinum doublet-based CT regimen for advanced or metastatic disease
- No prior treatment with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or docetaxel
- ECOG PS 0-1
- Pre-treatment (archival or fresh) tumor samples required for PD-L1 analysis

Randomise

Stratification by region and prior paclitaxel use

1:1

Nivolumab (3 mg/kg)
IV q2wk
(n=135)

Docetaxel (75 mg/m^2)
IV q3wk
(n=137)

Primary endpoints: OS
Secondary endpoints: ORR, PFS (by IRR), correlation between PD-L1 expression and efficacy, QoL (LCSS)

Spigel et al. ASCO 2015 Abstract 8009
Brahmer et al. N Engl J Med published on May 31, 2015

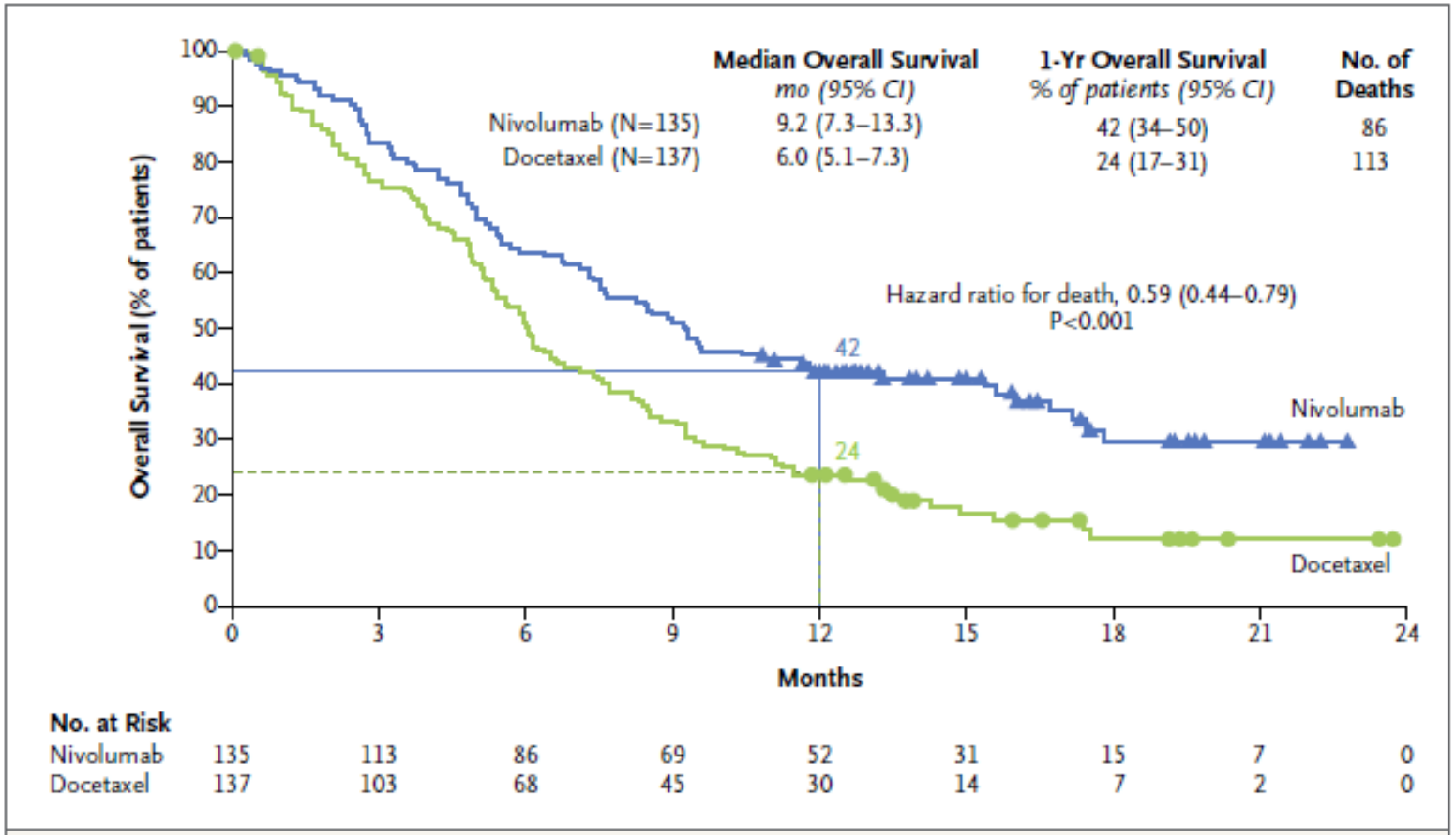
CheckMate-017: Baseline Characteristics

Table 1. Baseline Characteristics, Stratification Factors, and Prior Therapy.*

Characteristic	Nivolumab (N=135)	Docetaxel (N=137)	Total (N=272)
Age — yr			
Median	62	64	63
Range	39–85	42–84	39–85
Age category — no. (%)			
<65 yr	79 (59)	73 (53)	152 (56)
≥65 to <75 yr	45 (33)	46 (34)	91 (33)
≥75 yr	11 (8)	18 (13)	29 (11)
Sex — no. (%)			
Male	111 (82)	97 (71)	208 (76)
Female	24 (18)	40 (29)	64 (24)
Race — no. (%)†			
White	122 (90)	130 (95)	252 (93)
Black	6 (4)	2 (1)	8 (3)
Asian	4 (3)	2 (1)	6 (2)
Other	1 (1)	2 (1)	3 (1)
Not reported	2 (1)	1 (1)	3 (1)
Disease stage — no. (%)			
IIIB	29 (21)	24 (18)	53 (19)
IV	105 (78)	112 (82)	217 (80)
Not reported	1 (1)	1 (1)	2 (1)
ECOG performance-status score — no. (%)‡			
0	27 (20)	37 (27)	64 (24)
1	106 (79)	100 (73)	206 (76)
Not reported	2 (1)	0	2 (1)
Central nervous system metastasis — no. (%)			
Yes	9 (7)	8 (6)	17 (6)
No	126 (93)	129 (94)	255 (94)
Smoking status — no. (%)			
Current or former smoker	121 (90)	129 (94)	250 (92)
Never smoked	10 (7)	7 (5)	17 (6)
Unknown	4 (3)	1 (1)	5 (2)
Geographic region — no. (%)			
United States or Canada	43 (32)	43 (31)	86 (32)
Europe	77 (57)	78 (57)	155 (57)
Rest of world§	15 (11)	16 (12)	31 (11)
Other systemic cancer therapy — no. (%)¶			
Bevacizumab	1 (1)	1 (1)	2 (1)
Cetuximab	0	2 (1)	2 (1)
Etoposide	17 (13)	11 (8)	28 (10)
Fluorouracil	1 (1)	0	1 (<1)
Gemcitabine	60 (44)	71 (52)	131 (48)
Paclitaxel	46 (34)	46 (34)	92 (34)
Pemetrexed	3 (2)	3 (2)	6 (2)
Vinorelbine	20 (15)	24 (18)	44 (16)

Spigel et al. ASCO 2015 Abstract 8009
Brahmer et al. N Engl J Med published on May 31, 2015

CheckMate-017: Overall Survival

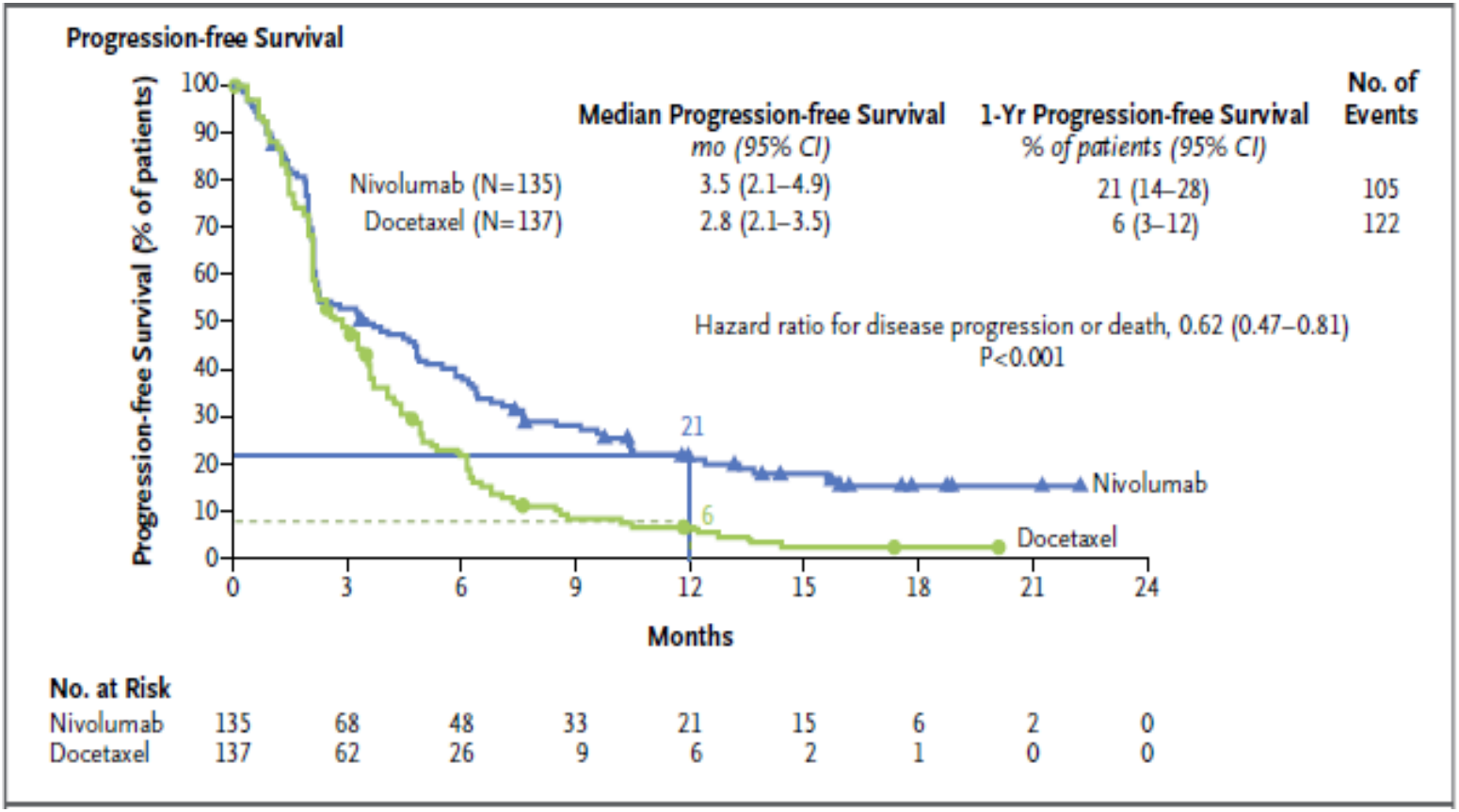


At time of DBL (Dec 15, 2014), 199 deaths were reported (86% of deaths required for final analysis)

Spigel et al. ASCO 2015 Abstract 8009

Brahmer et al. N Engl J Med published on May 31, 2015

CheckMate-017: Progression Free Survival



PFS defined as the time from randomization to the date of the first documented event of tumor progression, death or last tumor assessment that could be evaluated (data-censoring date).
The analysis included all the patients who underwent randomization.

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Brahmer et al. N Engl J Med published on May 31, 2015

CheckMate-017: Objective Response Rate

28 pts in the nivolumab arm were treated beyond RECIST v1.1-defined progression

Non-conventional benefit was observed in 9 pts (not included in ORR)

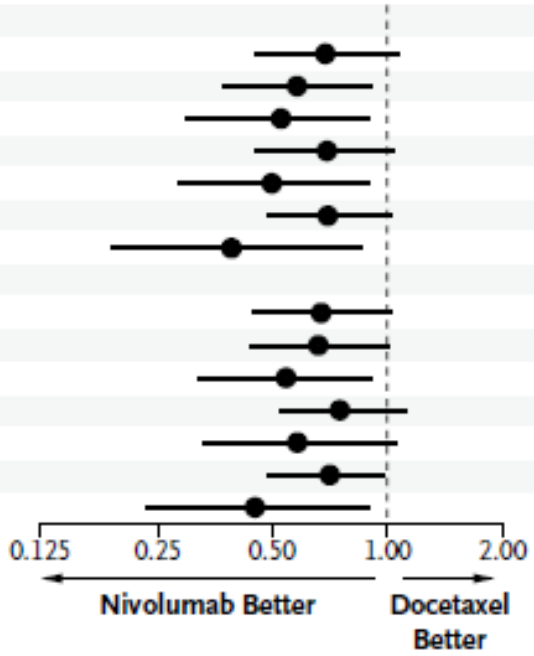
Variable	Nivolumab (N=135)	Docetaxel (N=137)
Objective response†		
No. of patients	27	12
% of patients (95% CI)	20 (14–28)	9 (5–15)
Estimated odds ratio (95% CI)	2.6 (1.3–5.5)	
P value	0.008	
Best overall response — no. (%)		
Complete response	1 (1)	0
Partial response	26 (19)	12 (9)
Stable disease	39 (29)	47 (34)
Progressive disease	56 (41)	48 (35)
Could not be determined	13 (10)	30 (22)
Time to response — mo‡§		
Median	2.2	2.1
Range	1.6–11.8	1.8–9.5
Duration of response — mo‡¶		
Median	NR	8.4
Range	2.9 to 20.5+	1.4+ to 15.2+

Spigel et al. ASCO 2015 Abstract 8009
Brahmer et al. N Engl J Med published on May 31, 2015

CheckMate-017: OS, PFS and ORR by PD-L1 Expression Level

Overall and Progression-free Survival According to PD-L1 Expression Level

PD-L1 Expression Level	Nivolumab	Docetaxel	Unstratified Hazard Ratio (95% CI)
	no. of patients		
Overall survival			
≥1%	63	56	0.69 (0.45–1.05)
<1%	54	52	0.58 (0.37–0.92)
≥5%	42	39	0.53 (0.31–0.89)
<5%	75	69	0.70 (0.47–1.02)
≥10%	36	33	0.50 (0.28–0.89)
<10%	81	75	0.70 (0.48–1.01)
Not quantifiable at baseline	18	29	0.39 (0.19–0.82)
Progression-free survival			
≥1%	63	56	0.67 (0.44–1.01)
<1%	54	52	0.66 (0.43–1.00)
≥5%	42	39	0.54 (0.32–0.90)
<5%	75	69	0.75 (0.52–1.08)
≥10%	36	33	0.58 (0.33–1.02)
<10%	81	75	0.70 (0.49–0.99)
Not quantifiable at baseline	18	29	0.45 (0.23–0.89)



ORR by PD-L1 Expression Level

	≥1%	<1%	≥5%	<5%	≥10%	<10%	NA
Nivolumab ORR, % (n/N)	**18** (11/63)	**17** (9/54)	**21** (9/42)	**15** (11/75)	**19** (7/36)	**16** /13/81)	**39** (7/18)
Docetaxel ORR, % (n/N)	**11** (6/56)	**10** (5/52)	**8** (3/39)	**12** (8/69)	**9** (3/33)	**11** (8/75)	**3** (1/29)
Interaction p-value	0.94		0.29		0.64		

Spigel et al. ASCO 2015 Abstract 8009
Brahmer et al. N Engl J Med published on May 31, 2015

CheckMate-017: Treatment and Safety Summary

	Nivolumab N=131		Docetaxel n-=129	
	Any Grade	Grade 3-5[a]	Any Grade	Grade 3-5
Treatment-related AEs, %	58	7	86	57
Treatment-related AEs leading to discontinuation, %	3[b]	2	10[c]	7
Treatment-related deaths, %	0		2[d]	

- Median number of doses was 8 (range, 1-48) for nivolumab and 3 (range, 1-29) for docetaxel

[a] No grade 5 events were reported with nivolumab. [b] 1% patients had increased ALT/AST, increased lipase, myasthenic syndrome, or rash, and 2% patients had pneumonitis. [c] Peripheral neuropathy (3%) and fatigue (2%). [d] Interstitial lung disease, pulmonary hemorrhage, and sepsis (1 patient each).

Spigel et al. ASCO 2015 Abstract 8009
Brahmer et al. N Engl J Med published on May 31, 2015

CheckMate-017: Treatment-related AEs (≥5% of patients)

Event	Nivolumab (N=131)		Docetaxel (N=129)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients with an event (percent)			
Any event	76 (58)	9 (7)	111 (86)	71 (55)
Fatigue	21 (16)	1 (1)	42 (33)	10 (8)
Decreased appetite	14 (11)	1 (1)	25 (19)	1 (1)
Asthenia	13 (10)	0	18 (14)	5 (4)
Nausea	12 (9)	0	30 (23)	2 (2)
Diarrhea	10 (8)	0	26 (20)	3 (2)
Arthralgia	7 (5)	0	9 (7)	0
Pyrexia	6 (5)	0	10 (8)	1 (1)
Pneumonitis	6 (5)	0	0	0
Rash	5 (4)	0	8 (6)	2 (2)
Mucosal inflammation	3 (2)	0	12 (9)	0
Myalgia	2 (2)	0	13 (10)	0
Anemia	2 (2)	0	28 (22)	4 (3)
Peripheral neuropathy	1 (1)	0	15 (12)	3 (2)
Leukopenia	1 (1)	1 (1)	8 (6)	5 (4)
Neutropenia	1 (1)	0	42 (33)	38 (30)
Febrile neutropenia	0	0	14 (11)	13 (10)
Alopecia	0	0	29 (22)	1 (1)

Spigel et al. ASCO 2015 Abstract 8009
Brahmer et al. N Engl J Med published on May 31, 2015

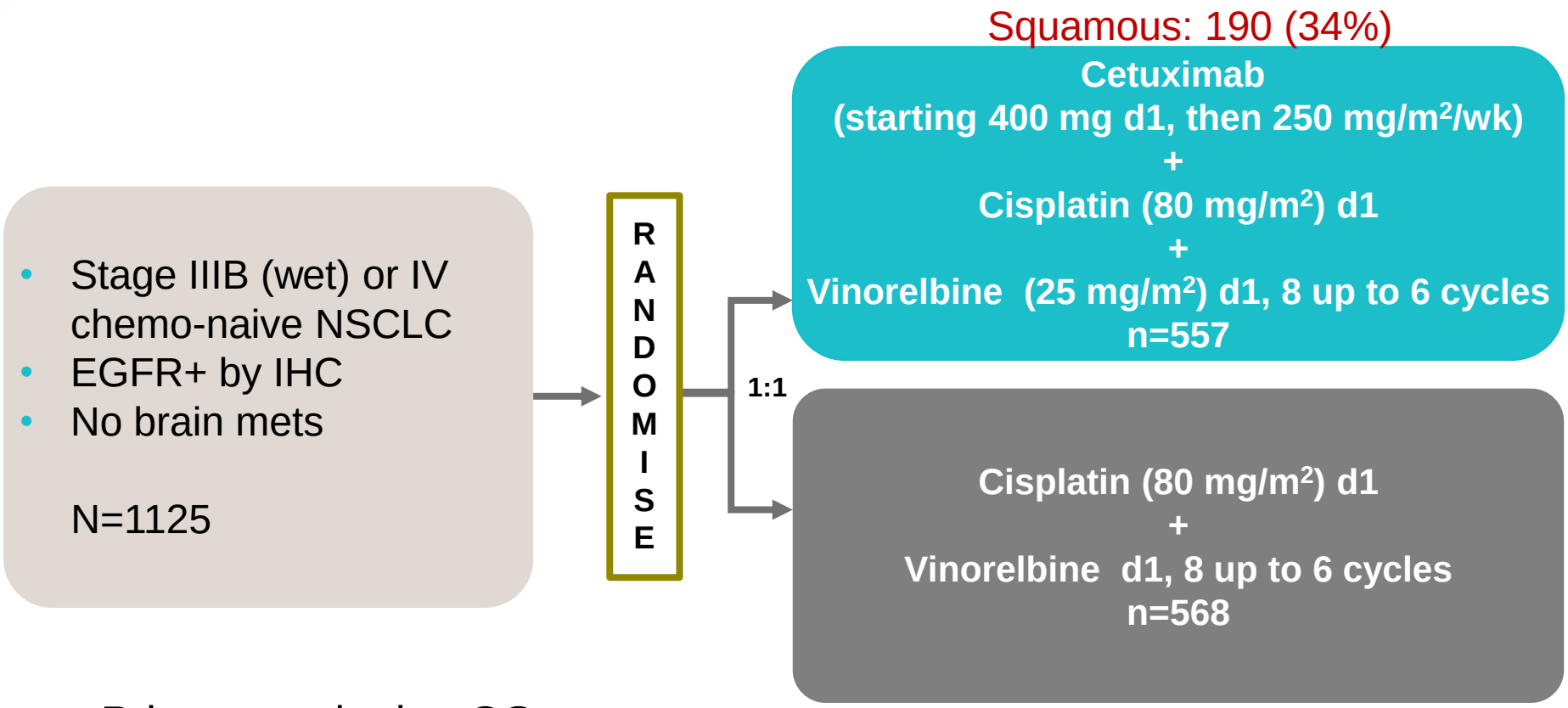
CheckMate-017: Summary

- Nivolumab is the first PD-1 inhibitor to demonstrate a survival benefit versus standard-of-care docetaxel in previously-treated patients with advanced SQ NSCLC
  - 41% reduction in risk of death (HR 0.59; *P*=0.00025)
  - 1-yr OS: 42% vs 24%
  - mOS: 9.2m vs 6.0m
- Nivolumab demonstrated superiority over docetaxel across all secondary efficacy endpoints
  - ORR: 20% vs 9% (P=0.0083)
- Nivolumab benefit was independent of PD-L1 expression
- The safety profile of nivolumab was favourable versus docetaxel and consistent with prior studies
- Nivolumab received FDA approval in the US on March 4, 2015 for metastatic SQ-NSCLC with progression on or after platinum-based chemotherapy

Spigel et al. ASCO 2015 Abstract 8009

Targeting EGFR in the Treatment of SCC Lung

FLEX: Cetuximab Plus Chemotherapy in First-Line NSCLC

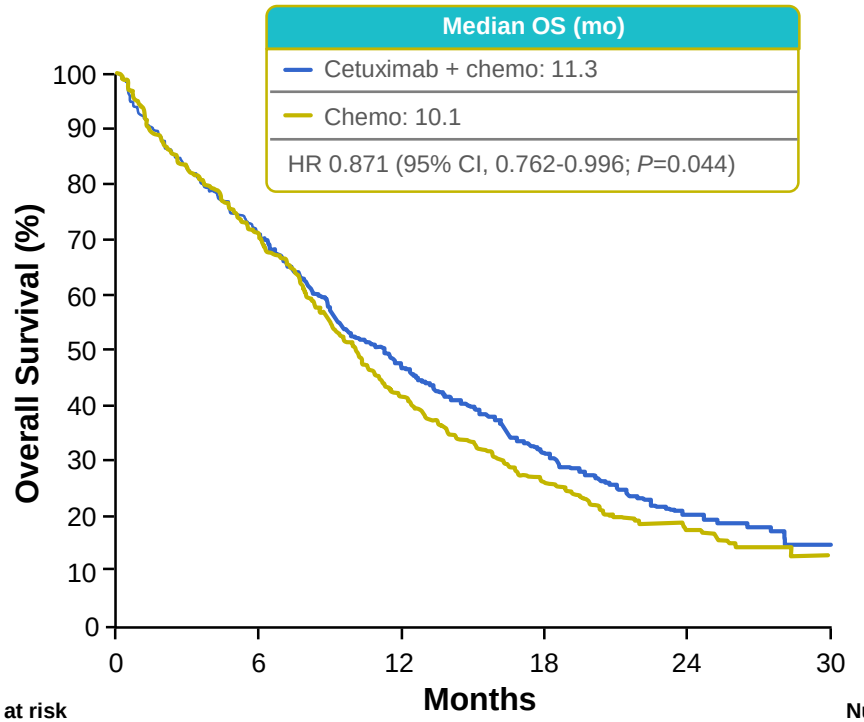


- Primary endpoint: OS
- Secondary endpoints: PFS, ORR, QoL, and safety

Pirker et al. *Lancet*. 2009;373:1525.

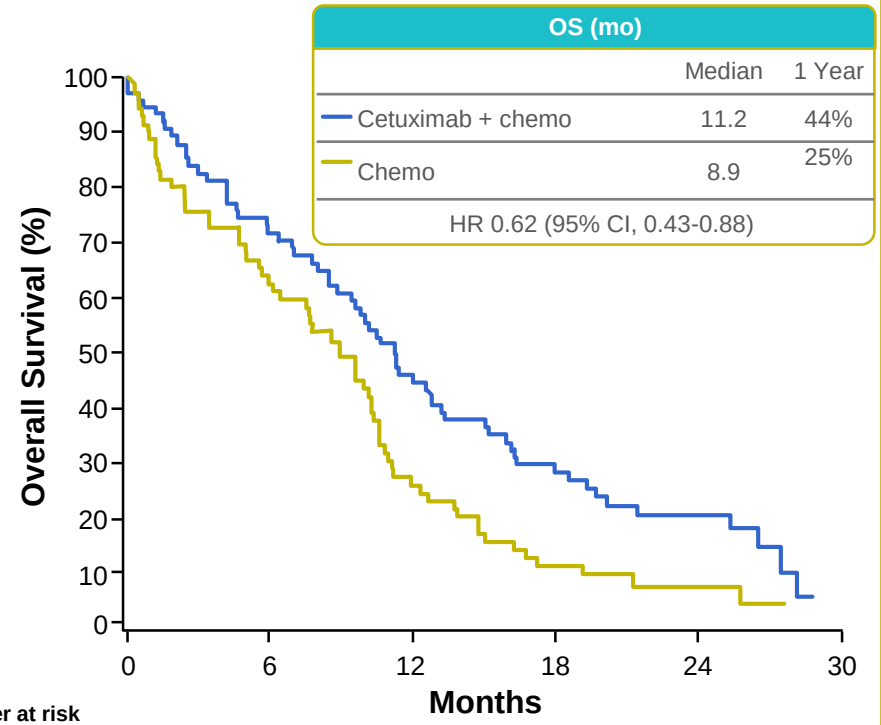
FLEX: OS (ITT) and in High EGFR-Expressing SCC

ITT



Number at risk						
Chemotherapy plus cetuximab	557	383	251	155	53	3
Chemotherapy	568	383	225	134	48	0

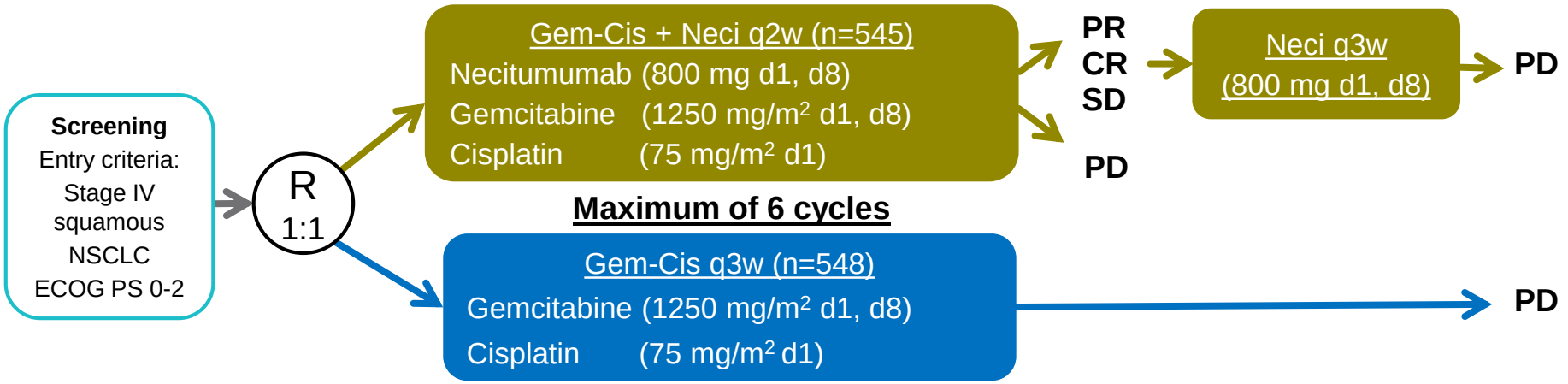
High EGFR-expressing SCC



Number at risk						
Chemotherapy plus cetuximab	75	52	32	19	10	0
Chemotherapy	69	42	17	7	2	0

Pirker et al. *Lancet*. 2009;373:1525.
Pirker et al. *Lancet Oncol*. 2012;13:33.

SQUIRE: Necitumumab plus Gemcitabine-Cisplatin in First-Line in SCC of the Lung

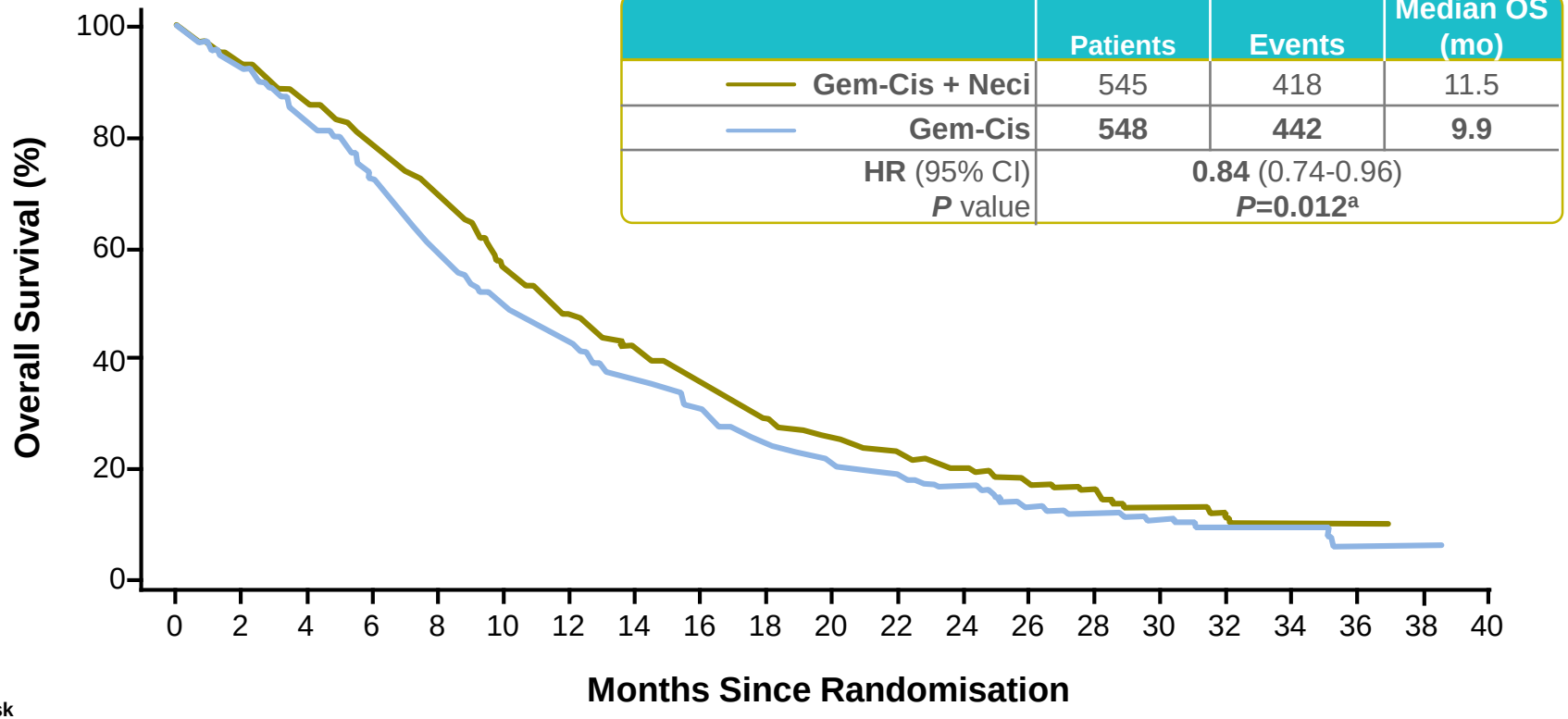


Randomisation (R) stratified by: ECOG PS (0-1 vs 2) and geographic region (North America, Europe, and Australia vs South America, South America, South Africa, and India vs East Asia)

- Patient selection not based on EGFR protein expression
- Radiographic tumour assessment (investigator read): at baseline and every 6 weeks until PD
- Mandatory tissue collection
- Primary endpoint: OS
- Secondary endpoints: PFS, ORR, and safety

Thatcher et al. ASCO 2014. Abstract 8008.

SQUIRE: OS (ITT)



	Patients	Events	Median OS (mo)
Gem-Cis + Neci	545	418	11.5
Gem-Cis	**548**	**442**	**9.9**
HR (95% CI)	**0.84** (0.74-0.96)		
P value	***P*=0.012**[a]		

No. at risk

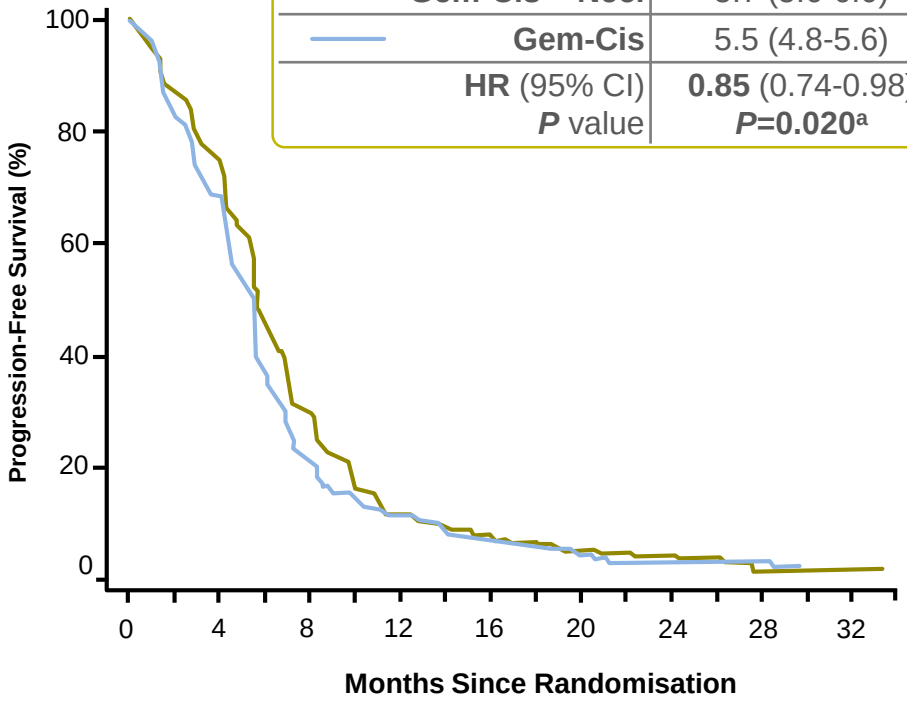
Gem-Cis + Neci	545	496	450	407	358	291	243	208	176	130	101	84	61	42	32	20	11	3	3	0	0
Gem-Cis	548	494	435	379	308	254	219	182	153	115	80	63	49	33	27	19	9	7	3	1	0

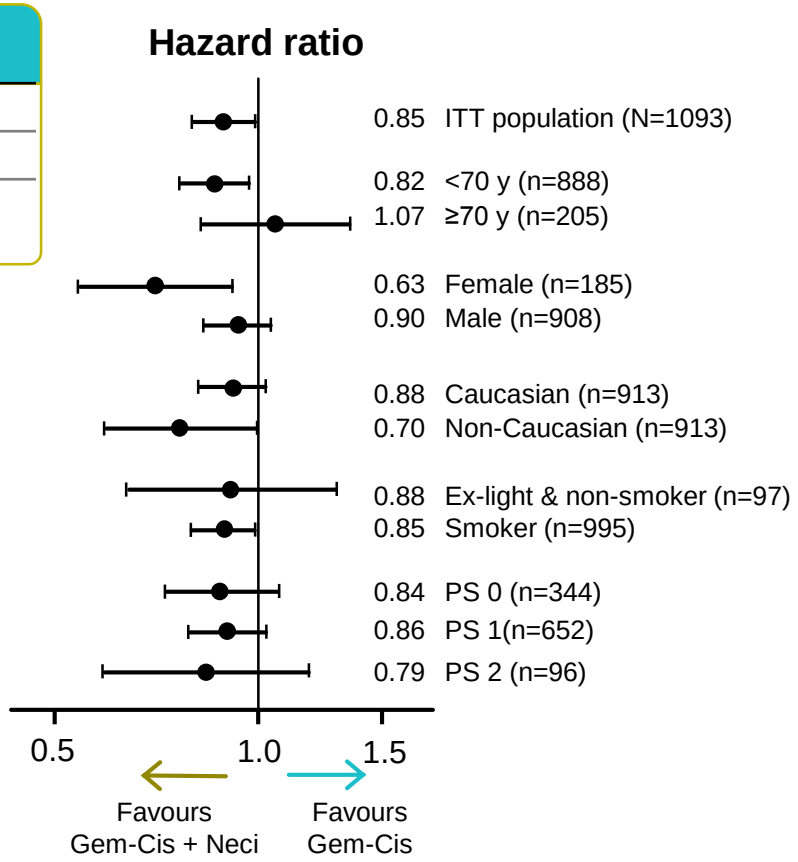
[a]Log-rank test (stratified).

Thatcher et al. ASCO 2014. Abstract 8008.

SQUIRE: PFS by Investigator (ITT)

Median PFS, mo (95% CI)	
Gem-Cis + Neci	5.7 (5.6-6.0)
Gem-Cis	5.5 (4.8-5.6)
HR (95% CI)	**0.85** (0.74-0.98)
P value	***P*=0.020**[a]





[a]Log-rank test (stratified).

Thatcher et al. ASCO 2014. Abstract 8008.

SQUIRE: Adverse Events

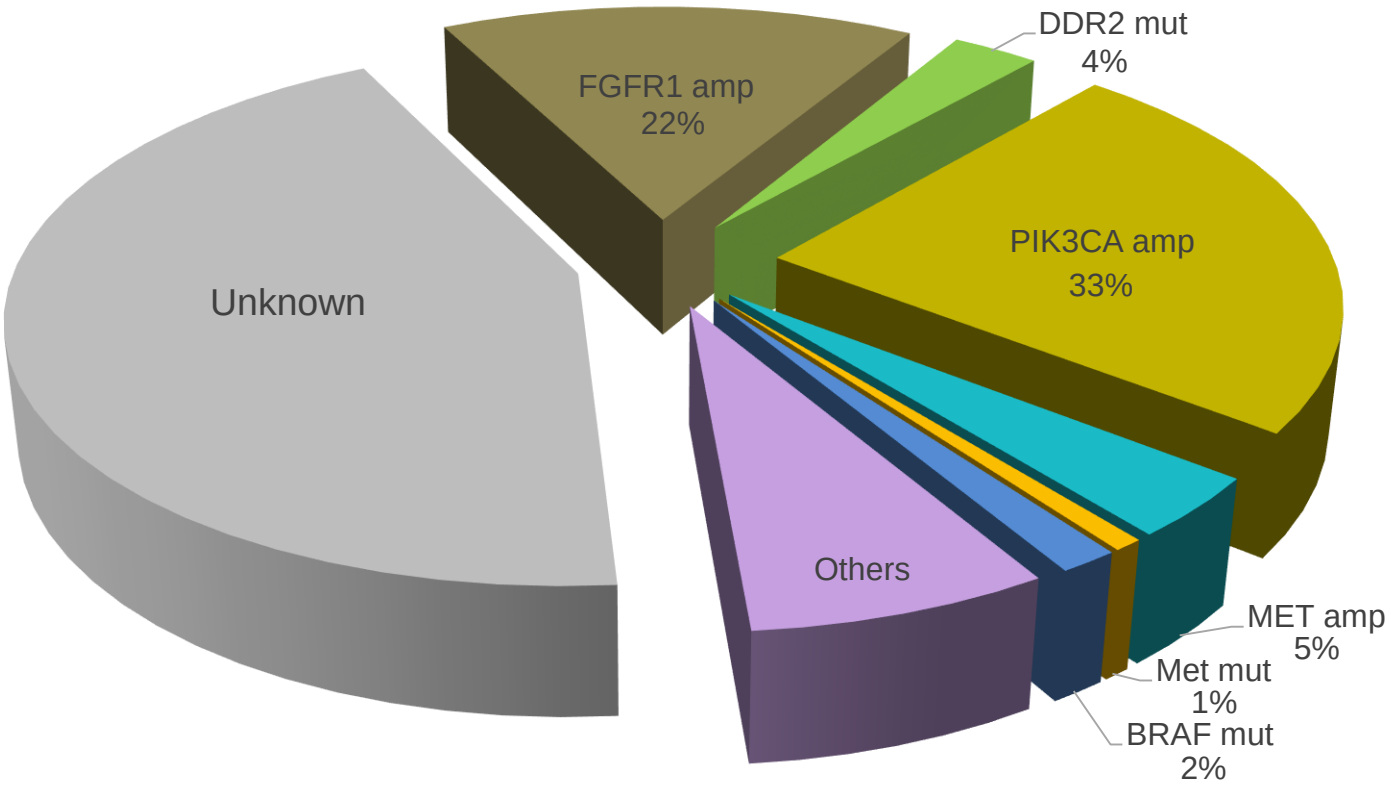
	% of Patients			
	Gem-Cis + Neci (n=538)		Gem-Cis (n=541)	
Event Category[a]	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Neutropenia	43.7	24.3	45.8	27.5
Febrile neutropenia	1.1	0.7	1.5	1.3
Anaemia	41.8	10.6	45.8	10.9
Thrombocytopenia	21.7	10.2	27.0	10.7
Fatigue	42.6	7.2	42.5	7.0
Hypomagnesaemia	31.2	9.3	15.7	1.1
Skin rash	76.2	7.1	10.2	0.4
Hypersensitivity/infusion-related reaction	1.5	0.4	2.0	0
Conjunctivitis	7.4	0.4	2.2	0
Interstitial lung disease (pneumonitis)	0.9	0.4[b]	0.7	0.6
Arterial thromboembolic events	5.4	3.9[c]	3.9	2.0[c]
Venous thromboembolic events	9.1	5.0[d]	5.4	2.6[d]

[a]Adverse events grouped by medical concept, selected according to treatment relevance.
[b]Includes 1 fatal event of pneumonitis (0.2%).
[c]Fatal arterial thromboembolic events, n(%): Gem-Cis + Neci 3 (0.6%), Gem-Cis 1 (0.2%).
[d]Fatal venous thromboembolic events, n(%): Gem-Cis + Neci 1 (0.2%), Gem-Cis 1 (0.2%).

Thatcher et al. ASCO 2014. Abstract 8008.

Other Potentially Targetable Mutations in the Treatment of SCC

Frequency of Other Potentially Targetable Mutations in SCC of the Lung



Perez-Moreno et al. *Clin Cancer Res*. 2012;18:2443.

FGFR Inhibition: BGJ398

- Phase 1 dose-escalation study enrolled patients ≥18 years of age with any *FGFR* genetically altered tumour, progressed after at least 1 line of therapy, including platinum (SCC cohort: N=21)
  - FGFR 1-amplified tumours were identified by FISH/CISH
- BGJ398: 100-150 mg once daily in 28-day cycles
- Results: 17 evaluable patients
  - 2 PR, lasting about 8 and 3 months
  - 2 additional PRs after the data cutoff date
  - 3 additional patients had SD with tumour regression (up to 11% reduction)
- Safety
  - Manageable and reversible hyperphosphatemia, stomatitis, alopecia, decreased appetite, and fatigue
- Conclusion
  - These data encourage further development of BGJ398 in FGFR1-amplified SCC and efforts to optimise predictive biomarkers for FGFR inhibitor sensitivity

FISH/CISH = fluorescence in situ hybridisation/chromogenic in situ hybridisation.

Nogova et al. ASCO 2014. Abstract 8034.

FGFR Inhibition: AZD4547

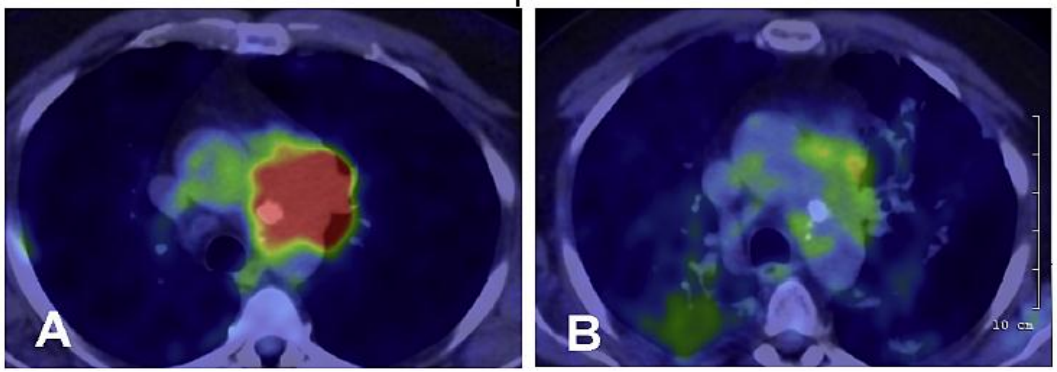
- A multicentre phase 1 expansion of AZD4547 in patients with previously treated stage IV FGFR1-amplified SCC
  - FGFR1 amplification was confirmed through central FISH (n=13) or review of local results (n=2)
- AZD4547 80 mg PO twice daily continuously in a q3wk cycle
- Results
  - 15 patients were treated. 1 PR, 4 SD, 9 PD (7 progressions and 2 deaths)
    - The 1 PR was observed in a patient with high FGFR1 amplification
- Safety
  - The most common related AEs were gastrointestinal and dermatologic
  - Grade ≥3 related AEs occurred in 3 patients (20%) (central serous retinopathy, hyponatremia, dehydration)
- Conclusions
  - AZD4547 was well tolerated in patients with FGFR1-amplified squamous cell lung cancer but did not meet its prespecified efficacy endpoint in terms of ORR for continuation

Paik et al. ASCO 2014. Abstract 8035.

c-Met Inhibition: Crizotinib

Case report of 73-year-old Caucasian male with advanced SCC

Before c-Met amplified SCC After



- Tumour biopsy[1]
  - Wild-type EGFR, KRAS, PIK3CA, and no ALK or ROS1 rearrangement
  - c-Met amplified shown by FISH
- Rationale for c-Met inhibition[1]
  - c-Met amplification: 3.9-21% of SCC cases; high copy number associated with worse prognosis and shorter OS
  - Secondary c-Met amplification as a potential resistant mechanism to EGFR-targeted TKIs
- Treatment: Crizotinib monotherapy at standard dose (250 mg 2× per day)[1]
- Result: PR (confirmed by chest and PET/CT after 8 weeks)[1]
  - c-Met inhibitors might be an effective treatment option for SCC patients
- Development of c-Met inhibitor in SCC: Phase 1 combination trial of crizotinib and dacomitinib in patients with NSCLC including SCC was terminated[2]

PET/CT = positron emission tomography/computed tomography.

1. Schwab et al. *Lung Cancer.* 2014;83:109.
2. https://www.clinicaltrials.gov/ct2/show/NCT01441128?term=c-Met&cond=Squamous+Cell+Non-small+Cell+Lung+Cancer & rank=1. Accessed May 2015.

DDR2 Inhibition: Dasatinib

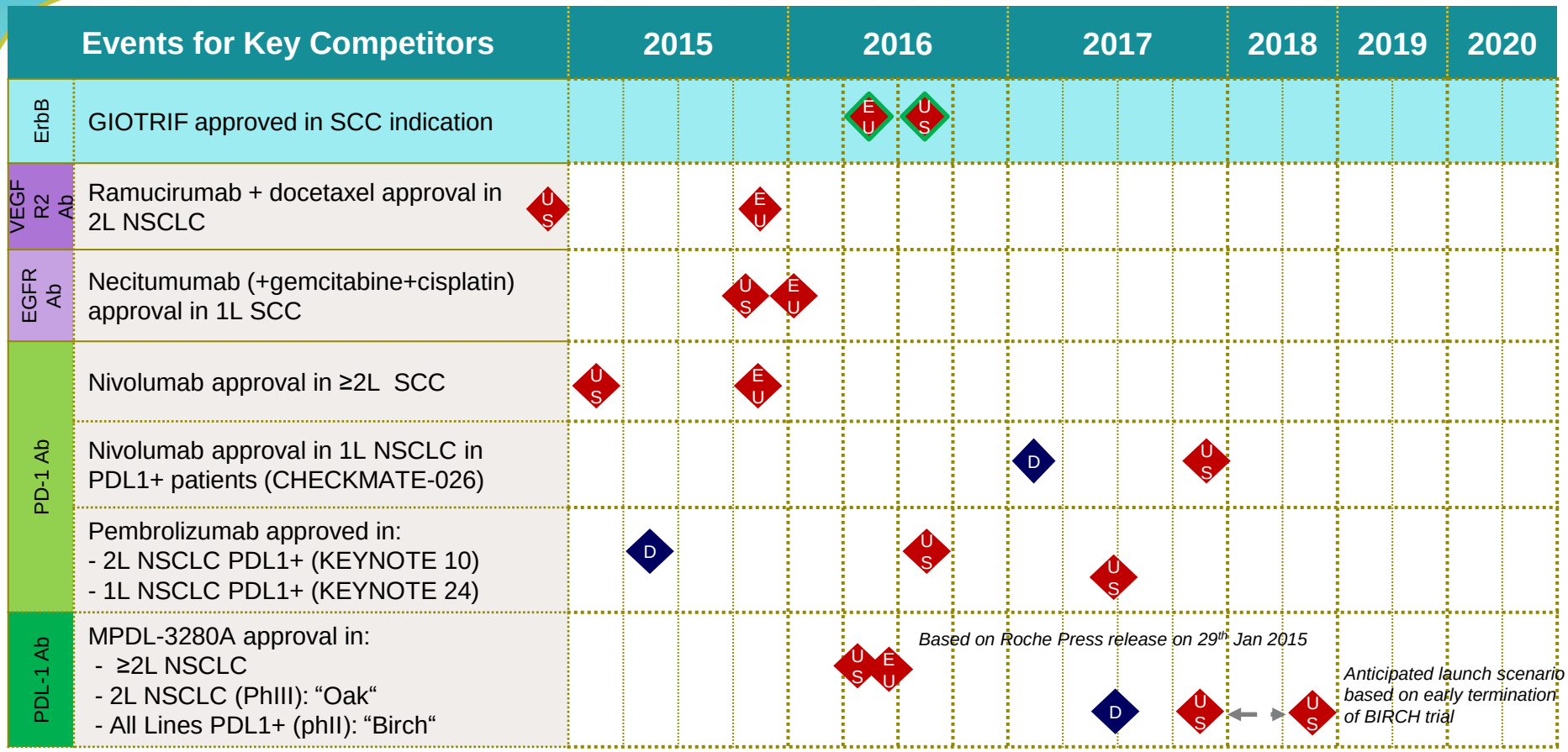
- An open-label, phase 2 study of dasatinib in patients with advanced stage lung SCC who had failed standard chemotherapy
- Dasatinib 140 mg daily in 28-day cycles
- Results
  - The study was halted after enrolling 5 patients, all of whom were discontinued from the trial due to excess toxicity
- Safety
  - 3 of 5 (60%) patients experienced grade ≥3 toxicities (dyspnoea, fatigue, AST elevation, anorexia, nausea)
  - Intolerable grade 2 pleural effusions were noted in 2 of 5 patients
- Conclusions
  - Dasatinib administered at 140 mg/d for the treatment of advanced SCC is associated with excess AEs, similar to other studies, so is not recommended in unselected patients

DDR2 = discoidin domain receptor tyrosine kinase 2; AST = aspartate aminotransferase.

Brunner et al. *J Thorac Oncol*. 2013;8:1434.

Overview of Key Competitors Timelines

Key Competitors - Timelines



- Nivolumab had an early launch in 2L/3L SCC; PD1 inhibitors are anticipated to have a major impact on treatment algorithm
- Necitumumab U.S. launch is expected mid 2015; it may have a positive effect on the relevance of ErbB inhibition in this disease. Acceptance of subsequent ErbB inhibition needs to be ascertained
- Several combination trials of above compounds have been either already initiated or are planned to begin in 2015.

D Data L Launch

Overview of Trials in Second Line Treatment

Trials in Second Line Treatment Chemo/chemo-backbone

Trial	Treatment	Median PFS (mo)	HR for PFS	Median OS (mo)	HR for OS	ORR (%)	Safety profile
JMEI	**Pemetrexed vs doce (n=571)**	**2.9 vs 2.9**	**0.97**	**8.3 vs 7.9**	**0.99**	**9.1 vs 8.8**	13% FN; 24% hospitalization
	Squamous *(n=172)*	2.3 vs 2.7	1.4*	6.2 vs 7.4	1.56*	2.8 vs. 8.1	
ZODIAC	**Vandetanib + doce vs doce (n=727)**	**4.0 vs 3.2**	**0.79**	**10.6 vs 10.0**	**0.91**	**17 vs 10**	9% FN
	Squamous *(n=344)*		0.79		0.98		
ZEAL	**Vandetanib + pem vs pem (n=1391)**	**4.1 vs 2.8**	**0.86**	**10.5 vs 9.2**	**0.86**	**19 vs 8**	52% grade ≥ 3 AEs
	Squamous *(n=114)*		1.04		1.08		
LUME-Lung 1	**Nintedanib + doce vs doce (n=1314)**	**3.4 vs 2.7**	**0.79**	**10.1 vs 9.1**	**0.94**	**4.4 vs. 3.3**	>70% grade ≥ 3 AEs; 7% FN
	Squamous (n=487)	2.9 vs 2.6	0.77*	8.6 vs 8.7	1.01	4.7 vs. 2.2	
REVEL	**Ramucimurab + doce vs doce (n=1253)**	**4.5 vs 3.0**	**0.76**	**10.5 vs 9.1**	**0.86**	**23.0 vs 13.6**	>70% grade ≥ 3 AEs; 16% FN;
	Squamous (n=328)	4.2 vs 2.7	0.76*	9.5 vs 8.2	0.88	26.7 vs 10.5	

FN: febrile neutropenia

Hanna N et al. *J Clin Oncol. (2004)* 1;22(9):1589-97.; Scagliotti G et al. *The Oncologist (2009);* 14(3):253-263.
Herbst RS et al. *The Lancet Oncology (2010)*; 11(7):619-626; De Boer RH et al. *J Clin Oncol. (2011*);29(8):1067-74
Reck M et al. *Lancet Oncology (2014):* 143-155; Garon E et al Lancet Oncology (2014):epub

Trials in Second Line Treatment
EGFR TKI

Trial	Treatment	Median PFS (mo)	HR for PFS	Median OS (mo)	HR for OS	ORR (%)	Safety profile
BR.21	**Erlotinib vs placebo (n=727)** Squamous *(n=222)*	**2.2 vs 1.8**	**0.61**	**6.7 vs 4.7** 5.6 vs. 3.6	**0.70** 0.67*	9 vs 1 4 vs ?	
ZEST	**Vandetanib vs erlotinib (n=1240)** Squamous *(n=272)*	**2.6 vs 2.0**	**0.98** 1.09	**6.9 vs 7.8**	**1.01** 1.25	12vs12	50% grade ≥ 3
BETA	**Erlotinib + bev vs erlotinib (n=636)** Squamous *(n=28)*	**3.4 vs 1.7**	**0.62**	**9.3 vs 9.2**	**0.97** 0.91	13 vs 6	60% grade ≥ 3
TITAN	**Doce/pem vs erlotinib, fast PD (n=304)** Squamous *(n=154)*	**2.2 vs 1.6**	**1.19**	**5.5 vs 5.3**	**0.96** 0.86	8 vs 6	31% grade ≥ 3
SUN1087	**Sunitinib + erlotinib vs erlotinib (n=960)** Squamous *(n=270)*	**3.6 vs 2.0**	**0.81** 0.8	**9.0 vs 8.5**	**0.92** 0.94	11 vs 7	
TAILOR	**Doce vs erlotinib, EGFR wt (n=222)** Squamous *(n=54)*	**2.9 vs 2.4**	**0.72*** 0.57	**8.2 vs 5.4**	**0.78** 0.90	15 vs 3	5% FN
DELTA	**Erlotinib vs doce (n=301)** Squamous *(n=61)*	**2.0 vs 3.2**	**1.22** 1.60*	**14.8 vs 12.2**	**0.91**	17 vs18	15% FN
ARCHER 1009	**Dacomitinib vs erlotinib (n=878)**	**2.6 vs 2.6**	**0.94**	**7.9 vs 8.4**	**1.08**	11 vs 8	11% G3 diarrhoea

Shepherd FA et al. *N Engl J Med (2005);* 353(2):123-132
Natale RB et al. *J Clin Oncol. (2011)* Mar 10;29(8):1059-66
Herbst RS et al. *Lancet. (2011)*;377(9780):1846-54.
Ciuleanu T et al. *Lancet Oncol. (2012):* (3):300-8
Scagliotti GV, at el. *J Clin Oncol. (2012*);30(17):2070-8
Garrassino et al *Lancet Oncol* (2013)
Kawaguchi T et al. *J Clin Oncol* (2014); 32; 1902-1908
Ramalingam S et al. *J Clin Oncol* 32:5s, 2014 (suppl; abstr 8018)

Clinical Trials in NSCLC Immunotherapies

Trial	Treatment	Median PFS (mo)	HR for PFS	Median OS (mo)	HR for OS	ORR (%)	Safety profile
CHECKMATE-063 (phII)	Nivolumab (single arm) All squamous; ≥3L (n=117)	2.0	-	8.2 (1yr OS=41%)	-	15%	17% Grade≥3
CHECKMATE-017 (phIII)	Nivolumab vs doce All squamous (n=272)	3.5 vs 2.8	0.62	9.2 vs 6.0	0.59	20 vs 9	7% Grade≥3

Ramalingam. CMSTO 2014.
Brahmer et al. N Engl J Med published on May 31, 2015

JMEI Trial

Trial	Treatment	Median PFS (mo)	HR for PFS	Median OS (mo)	HR for OS	ORR (%)	Safety profile
JMEI	**Pemetrexed vs doce (n=571)**	**2.9 vs 2.9**	**0.97**	**8.3 vs 7.9**	**0.99**	**9.1 vs 8.8**	See below additional information
	Squamous *(n=172)*	2.3 vs 2.7	1.4*	6.2 vs 7.4	1.56*	2.8 vs. 8.1	

Trial Population:
Patients with stage III or IV disease not amenable to curative therapy
PS 0 to 2
Previous treatment with one prior chemotherapy regimen for advanced NSCLC
Patients received pemetrexed 500 mg/m2 IV day 1 or docetaxel 75 mg/m2 IV day 1

Patient stratification:
PS (0 or 1 *v* 2), prior platinum or paclitaxel use, number of prior CT regimens (1 or 2), time since last chemotherapy (<3 *v* ≥ 3 months), best response to last chemotherapy (DCR versus PD/unknown), stage (III *v* IV), …

Primary endpoint : OS

Results:
571 patients randomized; 28% in pemetrexed and 32% in docetaxel were SCC
1 year survival rate for each arm was 29.7%
Safety: docetaxel arm with higher frequence of grade 3 or 4 neutropenia (40.2% *v* 5.3%; *P* .001), FN (12.7% *v* 1.9%; *P* .001), neutropenia with infections (3.3% *v* 0.0%; *P* .004), hospitalizations for neutropenic fever (13.4% *v* 1.5%; *P* .001), hospitalizations due to other DRAE (10.5% *v* 6.4%; *P* .092), use of granulocyte colony-stimulating factor support (19.2% *v* 2.6%, *P* .001) and all grade alopecia (37.7% *v* 6.4%; *P* .001) compared with pemetrexed arm.

Hanna N et al. *J Clin Oncol. (2004)* 1;22(9):1589-97.

TAILOR (Italian trial)

Trial	Treatment	Median PFS (mo)	HR for PFS	Median OS (mo)	HR for OS	ORR (%)	Safety profile
TAILOR	**Doce vs erlotinib, EGFR wt (n=222)**	**2.9 vs 2.4**	**0.72***	**8.2 vs 5.4**	**0.78**	15 vs 3	5% FN
	Squamous *(n=54)*		0.57		0.90		

Trial Population:
Patients with advanced NSCLC, wild-type EGFR, with prior platinum-based chemotherapy
PS 0 to 2

Patient stratification:
PS (0 or 1 *v* 2), centre, stage, type of 1L (pemetrexed vs gemcitabine vs vinorelbine)

Primary endpoint: OS

Results/Comments docetaxel/erlotinib:
48% PS0, 44-45% PS1 and 6-8% PS2; 21-28% Squamous histology; 27-17% never smokers
In erlotinib group grade 3-4 skin Aes were not associated with OS, PFS or RR (the low number of events might also have reduced the size of the association)
Docetaxel was better than erlotinib in never smokers (HR 0.50, ss) and adenocarcinoma (HR

Scientific Response Points (SRPs)

Scientific Response Points

Trial Design and Baseline Characteristics

1. What is the rationale for studying EGFR TKIs in SCC of the lung? Does SCC have a low incidence of EGFR mutations?
2. Why was erlotinib chosen as the control arm, since it is not used that much in this setting?
3. Why is the total patient population different in the primary analysis than in the overall survival analysis?
4. Why was the randomisation stratified by East Asian vs non-East Asian patients?

Efficacy

5. I believe that these data are mainly driven by the imbalances in never-smokers (probably those with *EGFR* mutations).
6. I think erlotinib is underdosed, as plasma levels are lower in heavy smokers.
7. PFS and OS differences are marginal. Data are not clinically meaningful.

Safety

8. Safety profile is not that comparable, since the nature of the AEs is quite different.
9. The trial just confirmed what we already know: afatinib is a little better but more toxic.
10. How many patients escalated to 50 mg? Was the safety profile different from the overall population?
11. What was the starting dose? Why did you allow an increase to 50 mg?
12. Afatinib is more toxic; more patients needed a dose reduction than with erlotinib.

Scientific Response Points (cont'd)

Biomarkers and subgroups

13. Is the effect on OS/PFS primarily driven by patients with EGFR mutation positive tumours?
14. Is there a different clinical/molecular feature in the early vs late progressing population?
15. Patients with SD as best response to first line had a more pronounced OS benefit. Can you explain?

Trials/Competitors comparison

16. Docetaxel is more efficacious than erlotinib, so I will continue using reserve a TKI for later lines.
17. How relevant are these data in light of the TAILOR/DELTA trials?
18. Nivolumab is/will be available, so TKIs are relegated to third or fourth line as a last option.
19. Ramucirumab plus docetaxel showed even better data in the subgroup of patients with squamous histology.

Efficacy of afatinib in other SCC

20. Are there afatinib data in other squamous cell carcinomas?

SRP 1: What is the rationale for studying EGFR TKIs in SCC of the lung? Does SCC have a low incidence of EGFR mutations?

- SCC of the lung is known to have high EGFR overexpression and gene amplification, aberrations of other ErbB receptors (including *ErbB3* overexpression in 30%), and dysregulation of downstream pathway has been implicated in pathobiology of SCC[1,2]
- These findings likely account for the benefits these patients derive from erlotinib[3-5] and other EGFR-directed therapies[a] in various treatment settings, despite the low frequency of EGFR-activating mutations[6]

Supportive evidence:

1) The incidence of ErbB alterations in SCC of the lung[1-12]: High EGFR gene copy-number and protein overexpression, EGFR mutations = 1%–5%; EGFRvIII mutants = 5%–8% , ErbB4 mutations = ≈2%–3%, ErbB3 mutations = ≈1%

2) Other EGFR-targeted agents provided OS benefit: [a]cetuximab[13,14] or [a]necitumumab[15] when added to first-line platinum doublet chemotherapy vs doublet chemotherapy only.

1. Hirsch et al. *J Clin Oncol*. 2003;21:3798; 2. Lopez-Malpartida et al. *Lung Cancer*. 2009;65:25; 3. Shepherd et al. *N Engl J Med*. 2005;352:123;
4. Clark et al. *Clin Lung Cancer*. 2006;7:389; 5. Leon et al. ESMO 2008. 1277P; 6. Dearden et al. *Ann Oncol*. 2013;24:2371;
7. D'Arcangelo et al. *Future Oncol.* 2013;9:699; 8. Jaiswal et al. *Cancer Cell.* 2013;23:603; 9. Kan et al. *Nature.* 2010;466:869;
10. Dacic et al. *Am J Clin Pathol*. 2006;125:860; 11. Lee et al. *Lung Cancer.* 2010;68:375; 12. Gately et al. *Clin Lung Cancer*. 2014;15:58;
13. Pirker et al. *Lancet*. 2009;373:1525-31; 14. Pirker et al. *Lancet Oncol*. 2012;13:33; 15. Thatcher et al. ASCO 2014. Abstract 8008.

SRP 2: Why was erlotinib chosen as the control arm, since it is not used that much in this setting?

- At the time of study design (2011), erlotinib and docetaxel were the only approved treatment options for patients who had progressed after platinum-based CT, on the basis of placebo-controlled trials (incl. all histologies), and both showed OS benefit[1-3]
  - Also, erlotinib and docetaxel are in international guidelines for second-line SCC[4]
- Owing to similar efficacy but improved tolerability compared with docetaxel, the EGFR inhibitory mode of action and oral posology made erlotinib the obvious choice for comparing with afatinib in LUX-Lung 8
- Based on the above, BI decided to start the first head-to-head trial comparing afatinib with erlotinib as second-line treatment in advanced SCC

If needed, it could be added:

While the trial was running, additional data became available, confirming that erlotinib could be considered comparable with chemotherapy in second-line squamous histology:

- *TAILOR trial (2012): OS in patients with SCC did not differ between erlotinib and docetaxel*[5]
- *A meta-analysis (2014) assessed second-line EGFR TKIs vs CT and confirmed comparable OS between groups with better tolerability in the EGFR TKI group, both in unselected NSCLC patients and in the EGFR wt population*[6]

1. Shepherd et al. *J Clin Oncol*. 2000;18:2095; 2. Shepherd et al. *N Engl J Med*. 2005;352:123; 3. Clark et al. *Clin Lung Cancer*. 2006;7:389;
4. Reck et al. *Ann Oncol*. 2014;25(suppl 3):iii27; 5. Garassino et al. *Lancet Oncol*. 2013;14:981; 6. Li et al. *PLoS One*. 2014;9:e102777.

SRP 3: Why is the total patient population different in the primary analysis than in the overall survival analysis?

- The trial was design to be powered to detect difference in OS, which required 632 deaths and approximately 800 patients
- However, the primary endpoint of PFS required 372 PFS events by independent review, and this number was reached while the trial had recruited 669 patients and recruitment continued

SRP 4: Why was the randomisation stratified by East Asian vs non-East Asian patients?

- Since the overall incidence of *EGFR* mutations (in particular in adenocarcinoma) in East Asians is higher than in Caucasians,[1] randomisation was stratified by race (East Asian vs non-East Asian) to eliminate any potential bias in EGFR mutation frequency across groups

1. Dearden et al. *Ann Oncol*. 2013;24:2371.

SRP 5: I believe that these data are mainly driven by the imbalances in never-smokers (probably those with *EGFR* mutations)

- The numbers of never-smoker patients are small (26 [6.5%] in afatinib and 18 [4.5%] in erlotinib) and it is rather unlikely that they had a major impact on the outcome
- In addition, the biomarker analysis reports low incidence of *EGFR* mutations and amplification, suggesting that the PFS and OS benefit is not driven by these *EGFR* aberrations
- The superiority of afatinib over erlotinib in patients with SCC of the lung could reflect its higher potency and the relevance of broader irreversible ErbB blockade in this setting compared with *EGFR* inhibition only.

SRP 6: I think that erlotinib is underdosed, as plasma levels are lower in heavy smokers

- This global trial was fully adhering to the Tarceva US PI,[1] and the recommended dosing regimen
  - The efficacy and long-term safety of a dose higher than the recommended starting doses have not been established in patients who continue to smoke cigarettes. Therefore, current smokers should be advised to stop smoking, as plasma concentrations of erlotinib in smokers as compared with nonsmokers are reduced
- The double-blind CurrentS trial compared erlotinib 300 mg qd with erlotinib 150 mg qd in heavy smokers in second line. No difference in PFS was observed, nor in OS[2] (see more details on next slide)

1. Tarceva (erlotinib) Prescribing Information.
2. Smit et al. ASCO 2014. Abstract 8046.

SRP 6: Supporting Evidence: CurrentS Trial

Double blind, randomised phase 3 trial of second-line erlotinib (150 vs 300 mg) in current smokers with advanced NSCLC

- Primary endpoint: PFS
- Secondary endpoints: OS, DCR, safety
- Sample size/assumption:
  - 300 randomised pts
  - 277 PFS events, HR 0.714
  - mPFS 10 vs 14 wk
  - 80% power; 5% 2-sided α

Conclusions:

- First and largest trial in active smokers with NSCLC
- No statistically significant increase in PFS with erlotinib 300 mg vs 150 mg
- OS: no difference between the arms
- Numeric increase in AESIs with 300-mg dose

		E150	E300
	ITT Population	n=154	n=159
Ethnicity n (%)	Caucasian	97 (63.0)	99 (62.3)
	Asian	46 (29.9)	49 (30.8)
	Other/not reported	11 (7.1)	11 (6.9)
Histology, n (%)	Adenocarcinoma	100 (64.9)	96 (60.4)
	Squamous cell carcinoma	42 (27.3)	48 (30.2)
	Large cell carcinoma	6 (3.9)	7 (4.4)
	Other	6 (3.9)	8 (5.0)
ECOG PS, n (%)	0-1	145 (94.2)	148 (93.1)
	2	9 (5.8)	11 (6.9)
Smoking status	Median pack yrs	31.3	30.0
PFS	Events, n (%)	143 (92.9)	140 (88.1)
	Median, wks	6.9	7.0
	[a]HR (95% CI)	1.05 (0.83-1.33)	
	[a]Log-rank *P*	0.671	
OS	Events, n (%)	122 (79.2)	123 (77.4)
	Median, mo	6.8	6.8
	[a]HR (95%CI)	1.03 (0.80-1.32)	
	[a]Log-rank *P*	0.846	
DCR, % (95% CI)		40.3 (32.4-48.5)	36.5 (29.0-44.5)

	Safety population	n=154	n=158
Relative dose intensity (% of planned: mean SD)		98.6 (5.9)	97.1 (8.4)
AEs of special interest (AESI; all grades), n (%)	Rash	63 (40.9)	97 (61.4)
	Diarrhoea	30 (19.5)	47 (29.7)
	Interstitial lung disease	0 (0.0)	2 (1.3)

[a]Unstratified.

Smit et al. ASCO 2014. Abstract 8046.

SRP 7: PFS and OS differences are marginal. Data are not clinically meaningful

- Up until recently, erlotinib and docetaxel were the only approved treatment options in the second-line setting.[1]
- Afatinib reduced the risk of death by 19% in this difficult-to-treat population
  - Significant OS improvement was consistent throughout the observation period
  - The 1-year survival rate for afatinib was 36.4% (vs 28.2% for erlotinib), and the survival probability was significantly higher
- PFS and OS improvement with afatinib were associated with improvements in lung cancer–related symptoms and global health status/QoL

1. Reck et al. *Ann Oncol*. 2014;25(suppl 3):iii27.

SRP 8: Safety profile is not that comparable, since the nature of the AEs is quite different

- The pattern of AEs was consistent with EGFR inhibition in both arms with similar rates of severe, serious, and fatal AEs
- Indeed, there were some differences in terms of incidence of specific AEs:
  - Higher incidence of grade ≥3 diarrhoea was seen with afatinib
  - Higher incidence of grade 3 rash/acne with erlotinib
- Nevertheless, overall symptom relief and Global Health Status/QoL measures favoured afatinib

If needed:

The low frequency of treatment discontinuation due to diarrhoea and rash (4% and 3%) suggests that the recommended dose reduction scheme and supportive care measures were generally sufficient to allow patients to remain on afatinib therapy for as long as they experienced clinical benefit

SRP 9: The trial just confirmed what we already know: afatinib is a little better but more toxic

- The consistent benefit in all endpoints of this head-to-head trial indeed supports superiority of afatinib and should be preferred vs erlotinib as a treatment option for patients with SCC of the lung
- The PRO/QoL data, reflecting the general health status during the treatment with both agents showed better results with afatinib reflecting acceptable tolerability
- The AEs that were higher for afatinib included mainly diarrhoea and stomatitis, both of which can be managed

If needed:

The low frequency of treatment discontinuation due to diarrhoea and rash suggests that the recommended dose reduction scheme and supportive care measures were generally sufficient to allow patients to remain on afatinib therapy for as long as they experienced clinical benefit

SRP 10: How many patients escalated to 50 mg? Was the safety profile different from the overall population?

- A total of 39 (10%) patients in the afatinib arm received the escalated dose of 50 mg with a mean exposure of 106 days vs 121 days in the overall population
- The safety profile in the patients who dose-escalated to 50 mg after 28 days was very similar to the overall population

SRP 11: What was the starting dose? Why did you allow an increase to 50 mg?

- The recommended starting dose of afatinib for second-line SCC of the lung is 40 mg
- To potentially maximise the benefit of afatinib, dose escalation to 50 mg (MTD) was considered to be appropriate in patients with advanced SCC who tolerated the starting dose of 40 mg
  - 10% of patients dose-escalated after 28 days
- This dose scheme is in line with the recommended dosing regimen for afatinib in pivotal EGFR mutation–positive trials and was derived on the basis of PK observations and MTDs derived in a phase 1 trial

MTD = maximum tolerated dose.

SRP 12: Afatinib is more toxic; more patients needed a dose reduction than with erlotinib

- Overall rate of dose reductions due to AEs will also include the patients who reduced after escalation (from 50 mg to 40 mg)
- Three quarters of patients received the full dose of 40 mg or 50 mg throughout their treatment, and of the 25% of patients who required a dose below 40 mg daily, the majority had only one dose reduction (90%)
- Overall, dose reduction led to a lower frequency of common AEs, and this adaptive dosing has the potential to provide “truly individualised targeted treatment,” allowing patients to remain on afatinib therapy, and this translated into a clinically meaningful OS benefit

SRP 13: How many patients had an *EGFR* mutation–positive tumour?

- Using the Foundation Medicine FoundationOne™ platform, next-generation sequencing (300 genes) was performed in patients, enriched for patients with PFS >2 months and appropriate controls (PFS ≤2 months)
- The incidence of *EGFR* mutations/amplification was low in these patients and was balanced between the two treatment arms, and results suggest that the benefit of afatinib over erlotinib does not seem to be driven by the presence of these EGFR aberrations[a]
- The superiority of afatinib over erlotinib in patients with SCC of the lung could reflect its higher potency and the relevance of broader irreversible ErbB blockade in this setting compared with EGFR inhibition only

[a]Results will be presented at WCLC.

SRP 14: Is there a different clinical/molecular feature in the early vs late progressing population?

- Biomarker analysis was performed on 238 (≈30%) patients; samples from patients with PFS >2 months and appropriate controls (PFS ≤2 months) were retrospectively enriched
- Overall, the incidence of *EGFR* mutations and EGFR amplification identified in this trial is low, and the PFS and OS improvement conferred by afatinib does not appear to be driven by the presence of these EGFR aberrations
- The superiority of afatinib over erlotinib in patients with SCC of the lung could reflect its higher potency and the relevance of broader irreversible ErbB blockade in this setting compared with EGFR inhibition only
- The trial team will continue to analyse the data characterising relevant subgroups

SRP 15: Patients with SD as best response to first line had a more pronounced OS benefit. Can you explain?

- A lower HR of 0.71 was observed for these 328 patients vs the overall population (HR 0.81)
- This is an interesting observation, but the trial was not powered to detect differences in subgroups so no final conclusions can be drawn

SRP 16: Docetaxel is more efficacious than erlotinib, so I will continue using docetaxel in patients fit for chemo and reserve a TKI for later lines

- TAILOR trial directly compared second-line docetaxel and erlotinib and indicated that docetaxel is superior in patients with NSCLC and wild-type EGFR. This benefit appeared to be driven by patients with adenocarcinoma since OS in patients with squamous histology did not differ significantly between treatment groups[1]
- In addition, a meta-analysis of trials assessed second-line EGFR TKIs vs CT and confirmed comparable OS between groups with better tolerability in the EGFR TKI group, both in unselected NSCLC patients and in the EGFR wild-type population[2]
- In LUX-Lung 8, afatinib reported a median OS of 7.9 months and was associated with overall symptom relief and improvement in GHS/QoL measures
- Efficacy of afatinib in this setting has been proven with a favourable route of administration compared with IV administration

1. Garassino et al. *Lancet Oncol*. 2013;14:981.
2. Li et al. *PLoS One*. 2014;9:e102777.

SRP 17: How relevant are these data in light of the TAILOR/DELTA trials?

- Cross-trial comparisons should be done very cautiously as trial parameters differ
- LUX-Lung 8 only recruited patients with squamous histology, whereas TAILOR[1] and DELTA[2] had only ≈20%-25% patients with squamous histology
- TAILOR trial indicated that second-line docetaxel is superior to erlotinib in patients with NSCLC and wild-type EGFR, and this benefit appeared to be driven by patients with adenocarcinoma; OS in patients with squamous histology did not differ significantly between treatment groups[1]
  - More recently, a meta-analysis assessed second-line EGFR TKIs vs CT and confirmed comparable OS between groups with better tolerability in the EGFR TKI group, both in unselected NSCLC patients and in the EGFR wild-type population[3]
- DELTA trial did not report OS data by histology[2]
- LUX-Lung 8 OS improvement confirms the clinical relevance of the ErbB receptors and downstream pathway in the pathobiology of SCC

1. Garassino et al. *Lancet Oncol*. 2013;14:981.
2. Kawaguchi et al. *J Clin Oncol.* 2014;32:1902.
3. Li et al. *PLoS One*. 2014;9:e102777.

SRP 18: Nivolumab is/will be available, so TKIs are relegated to third or even to fourth line as a last option

- Indeed, nivolumab showed interesting data in CheckMate-017,[1] with a mOS of 9.2 months vs 6.0 months on docetaxel.
- There is no head-to-head data comparing afatinib and nivolumab. We therefore cannot speculate on the efficacy of one compound over the other.
- SCC of the lung remains a disease with high unmet medical need, where there is a role for multiple treatment options in the continuum of care, so even patients who either do not receive or do not benefit from nivolumab still be in need of efficacious treatments
- Efficacy of afatinib in this setting has been proven with a favourable route of administration compared to IV administration.

1. Opdivo (nivolumab) Prescribing Information.

SRP 19: Ramucirumab in combination with docetaxel showed even better data in the subgroup of patients with squamous histology

- Cross-trial comparisons should be done very cautiously as trial parameters differ
- The REVEL[1] trial was not powered for subgroup analyses. Nevertheless, in the subgroup of patients with squamous histology the HR was 0.88 with no statistical difference.
- OS improvement with afatinib in this setting has been proven with a favourable route of administration compared to IV administration.

1. Garon et al. *Lancet*. 2014;384:665.

SRP 20: Are there afatinib data in other squamous cell carcinomas?

- Afatinib demonstrated robust clinical activity in HNSCC patients (1200.28, and LUX-HN1)[1,2]
- Afatinib also showed activity in NSCLC patients with tumours displaying squamous cell histology (LUX-Lung 1, LUX-Lung 5)[3]
- Afatinib showed clear antiproliferative effects on lung SCC cells in vitro and antitumour activity in tumour models of human SCC in vivo (eg, FaDu cells)[4]

1. Seiwert et al. *Ann Oncol.* 2014;25:1813.
2. Machiels et al. *Lancet Oncol*. 2015;16:583.
3. D'Arcangelo et al. *Future Oncol*. 2013;9:699.
4. Schütze et al. *Strahlenther Onkol*. 2007;182:256.

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