Squamous NSCLC: Where do EGFR TKIs Fit In?

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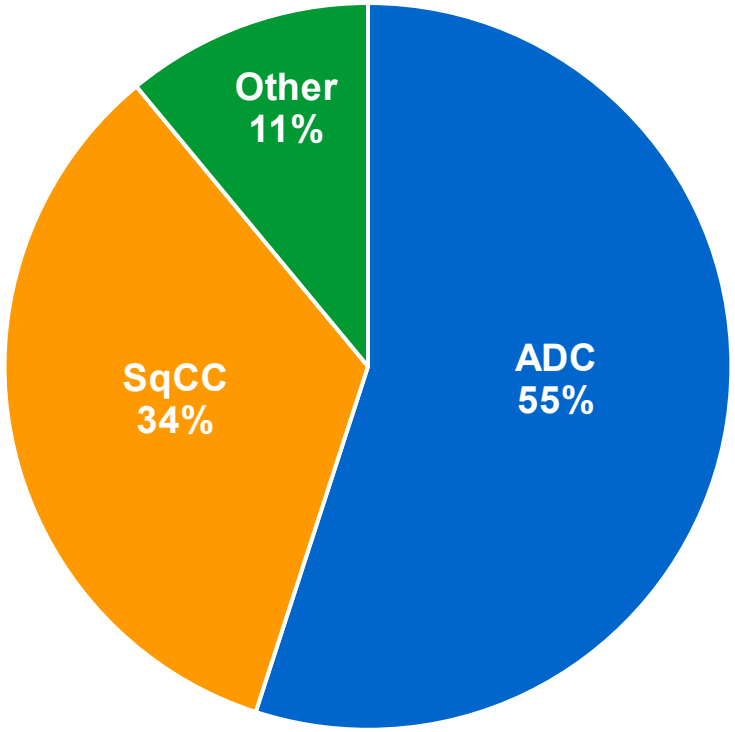
Disclosures

- Has been a consultant or advisor to Boehringer Ingelheim, MSD, Roche, Boehringer Ingelheim, Guardant Health, Pfizer, Takeda, Novartis, Astra-Zeneca, Lilly
- Has received trial funding from Novartis, Pfizer

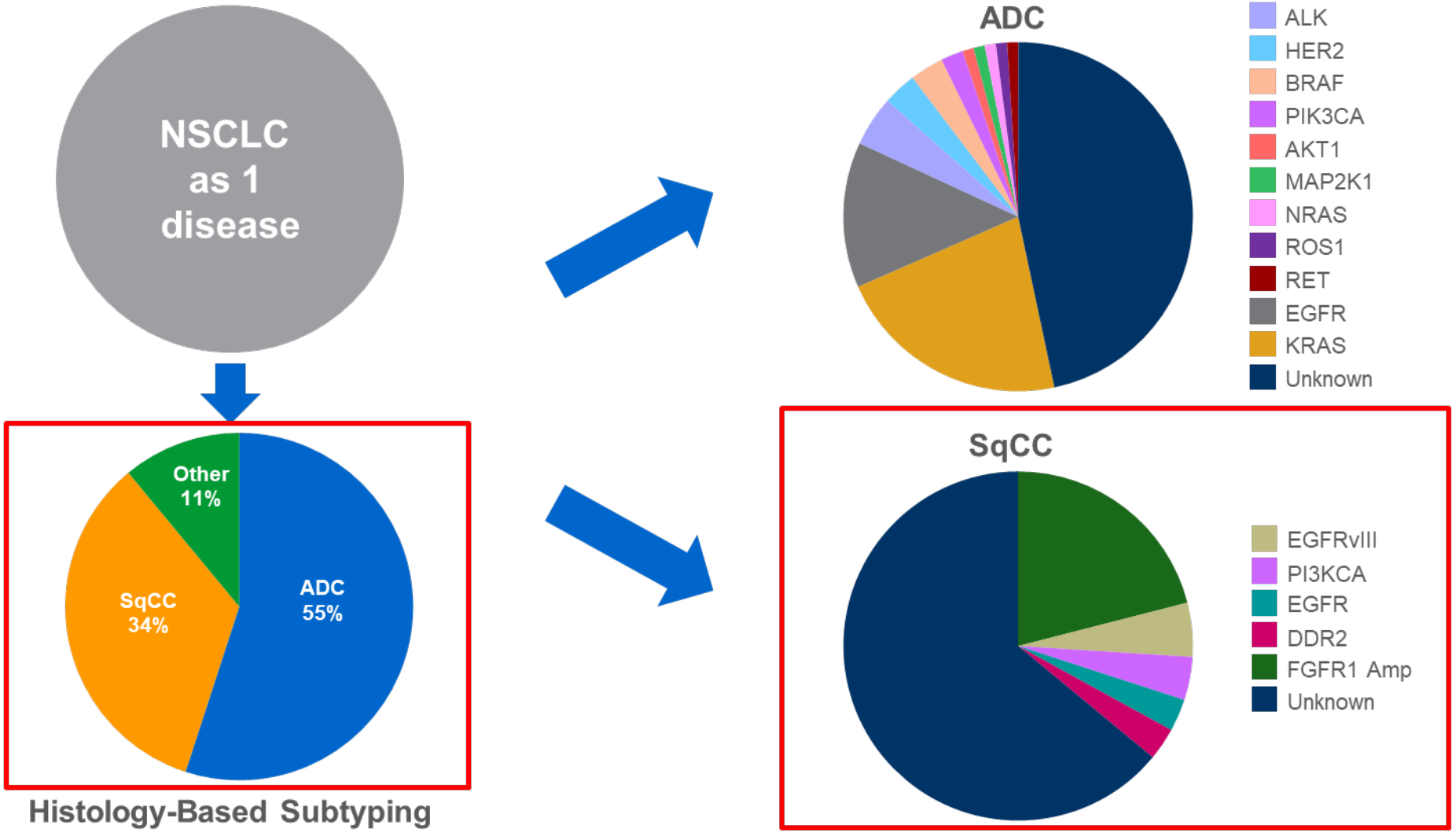
Differences Between NSCLC Histologic Subsets: ADC vs SqCC of the Lung[1,2]



	ADC	SqCC
Age	Bimodal with younger subset	~Older
Male/female	↑ Females	↑ Males
Smoking	Never-smoker subset	~Smokers
Therapies contraindicated	No	Yes (pemetrexed, bevacizumab)
Biomarker-driven targeted therapy as SOC	Yes	No
Good candidate: PD-L1 therapy	Yes[a]	Yes[a]

[a]Advances in 2015.
ADC = adenocarcinoma; PD-L1 = programmed death-ligand 1; SOC = standard of care.
1. Gandara DR et al. *Clin Cancer Res*. 2015;21:2236-2243; 2. Li T et al.. *J Clin Oncol*. 2013;31:1039-1049.

Evolution of NSCLC Subtyping From Histologic to a Multitude of Genomically Defined Subsets



AKT1 = protein kinase B1; ALK = anaplastic lymphoma kinase; DDR = discoidin domain receptor; FGFR = fibroflast growth factor receptor; HER2 = human epidermal growth factor receptor 2; KRAS = Kirsten rat sarcoma; MAP2K1 = mitogen-activated protein 2 kinase 1; NRAS = neuroblastoma RAS; PIK = phosphatidylinositol kinase; RET = rearranged during transfection; ROS1 = ROS Proto-Oncogene

1. Li T et al. *J Clin Oncol*. 2013;31:1039-1049.

First-Line Immunotherapy Trials in Patients With SqCC of the Lung Are Rapidly Changing the Treatment Landscape

Trial Name	Histology	Treatment Arms
KEYNOTE-024[1]	Mixed (N=305) Squamous (N=56)	Pembrolizumab *vs* chemotherapy (PD-L1 ≥50%)
KEYNOTE-042[2]	Mixed (N=1274) Squamous (N=492)	Pembrolizumab *vs* chemotherapy (PD-L1 ≥1%)
KEYNOTE-407[3]	Squamous (N=560)	Pembrolizumab + chemotherapy vs chemotherapy
IMpower131[4]	Squamous (N=1021)	Arm A: atezolizumab + carboplatin + paclitaxel Arm B: atezolizumab + carboplatin + nab-paclitaxel Arm C: carboplatin + nab-paclitaxel
Checkmate 227 Part 1[5-7]	Mixed (N=1739) Squamous (N=487[a])	Part 1a (PD-L1 ≥1%): Nivolumab + ipilimumab; chemotherapy; or nivolumab
		Part 1b (PD-L1 <1%): Nivolumab + ipilimumab; chemotherapy; or nivolumab + chemotherapy

[a]Squamous histology in 28% of all randomised patients.

1. Reck M et al. *N Engl J Med*. 2016;375:1823-1833; 2. Lopes G et al. *J Clin Oncol*. 2018;36(suppl 18):LBA4 (oral presentation); 3. Paz-Ares L et al. *N Engl J Med*. 2018;379:2040; 4. Jotte R et al. *J Clin Oncol*. 2018;36(suppl):LBA9000 (oral presentation); 5. Hellmann MD et al. *Cancer Res*. 2018;78(suppl 13):CT077 (oral presentation); 6. Borghaei H et al. *J Clin Oncol*. 2018;36(suppl):9001 (oral presentation); 7. Hellmann MD et al. *N Engl J Med*. 2018;378:2093-2104.

Current Treatment Landscape for Stage IV SqCC NSCLC: ESMO Guidelines

First-line treatments

- IO monotherapy
- IO + Carbo/pac
- IO + Carbo/nab-pac
- Chemotherapy

Second-line treatments

- Nivolumab
- Atezolizumab
- Pembrolizumab if PDL1 >1%
- Docetaxel
- Ramucirumab/docetaxel
- Erlotinib
- Afatinib

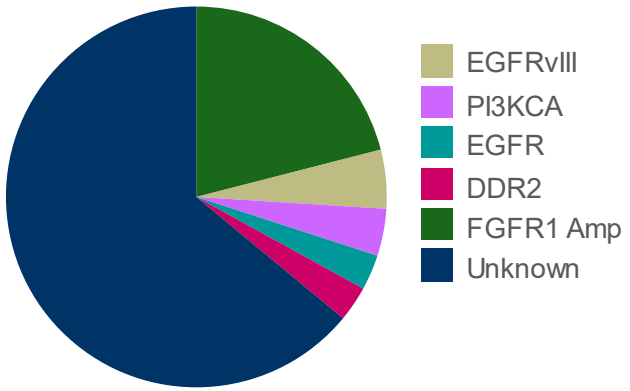
IO = immuno-oncology; nab-pac = albumin-bound paclitaxel; pac = paclitaxel.
Planchard D et al. *Ann Oncol.* (2018) 29 (suppl 4): iv192–iv237 (Updated 18 September 2019 by the ESMO Guidelines Committee).

The ErbB Receptor Family Is a Valid Therapeutic Target for SqCC of the Lung

- Dysregulation of the ErbB pathway is frequently observed in SqCC of the lung
  - EGFR overexpression and gene amplification aberrations of other ErbB receptors and dysregulation of the downstream pathways have been implicated in the pathobiology of SqCC[1,2]
  - These findings likely account for the benefits these patients derive from erlotinib[11-13] and other EGFR-directed therapies in different treatment settings,[14-16] despite the low frequency of EGFR-activating mutations[17]

ErbB Receptor	Frequency (%)
EGFR overexpression[2-5]	25-86
EGFR amplification[2,5]	15-27
EGFRvIII mutation[6]	5
EGFR kinase domain mutation[7]	<5%
ERBB2 mutation/amplification[2]	5
ERBB3 mutation[8]	1
ERBB3 overexpression[9]	10
ERBB4[10]	8

Frequency of known genetic drivers in SqCC[17]



1. Hirsch FR et al. *J Clin Oncol*. 2003;21:3798-3807; 2. Lopez-Malpartida AV et al. *Lung Cancer*. 2009;65:25-33; 3. Lee HJ et al. *Lung Cancer*. 2010;68:375-382; 4. Gately K et al. *Clin Lung Cancer*. 2014;15:58-66; 5. Dacic S et al. *Am J Clin Pathol*. 2006;125:860-865; 6. Ji H et al. *Proc Natl Acad Sci U S A*. 2006;103:7817-7822; 7. Dearden S et al. *Ann Oncol*. 2013;24:2371-2376; 8. Jaiswal BS et al. *Cancer Cell*. 2013;23:603-617; 9. Gorgoulis V et al. *Pathol Res Pract*. 1995;191:973-981; 10. Kan Z et al. *Nature*. 2010;466:869-873; 11. Shepherd FA et al. *N Engl J Med*. 2005;353:123-132; 12. Clark GM et al. *Clin Lung Cancer*. 2006;7:389-394; 13. Tsao et al. ESMO 2008. N Engl J Med. 200;353:133-44; 14. Pirker R et al. *Lancet*. 2009;373:1525-1531; 15. Pirker R et al. *Lancet Oncol*. 2012;13:33-42; 16. Thatcher et al. ASCO 2014. Abstract 8008; 17. Li T et al. *J Clin Oncol*. 2013;31:1039-1049.

LUX-Lung 8 Study Design: Randomized, Phase III Trial of Afatinib[a] vs Erlotinib in SqCC of the Lung

- Advanced SqCC NSCLC (stage IIIB/IV)
- PD after ≥4 cycles of a first-line platinum doublet
- ECOG PS 0 or 1
- No prior anti-EGFR therapy
- No active brain metastases

Randomisation 1:1 (N=795)

Afatinib (n=398) 40 mg QD

Erlotinib (n=397) 150 mg QD

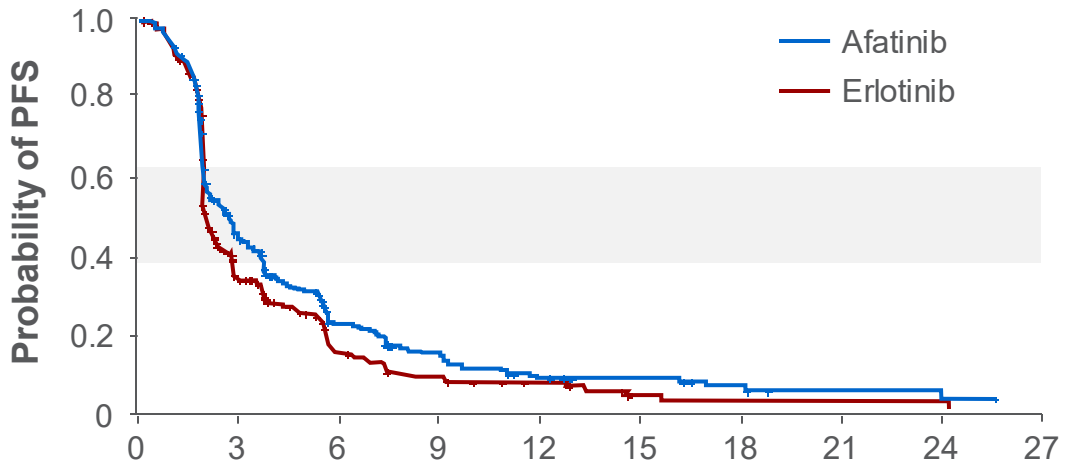
Treatment until disease progression or unacceptable AEs

- Primary endpoint: PFS; key secondary endpoint: OS
- Stratification: East Asian vs non–East Asian
- Tumour tissue collected for correlative science
- Radiographic tumour assessment at baseline; Weeks 8, 12, 16; every 8 weeks thereafter

[a]Esta indicación no está financiada en España por el Sistema Nacional de Salud. This indication is not reimbursed by the Spanish National Health System.
AE = adverse event; ECOG PS = Eastern Cooperative Oncology Group performance status; PD = progressive disease.
Soria JC et al. *Lancet Oncol*. 2015;16:897-907.

LUX-Lung 8: Significant Improvement in PFS and OS With Afatinib Compared With Erlotinib

Updated PFS Analysis by Independent Review (n=795)

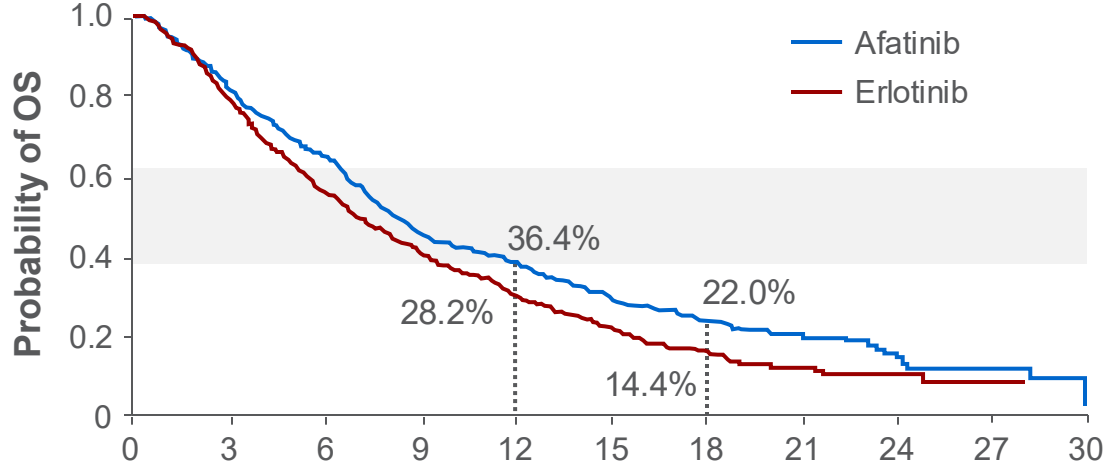


No. at risk

398	139	50	30	14	10	5	2	2	0
397	99	34	17	10	2	1	1	1	0

	Afatinib 40 mg QD (n=398)	Erlotinib 150 mg QD (n=397)
Patients progressed or died, n (%)	299 (75.1)	306 (77.1)
Median PFS (mo)	2.6	1.9
	HR, 0.81; 95% CI, 0.69-0.96; *P*=0.0103	

Primary Analysis of OS (key secondary endpoint) (n=795)



No. at risk

398	316	249	170	124	82	47	28	10	4	0
397	305	210	150	94	54	30	11	4	2	0

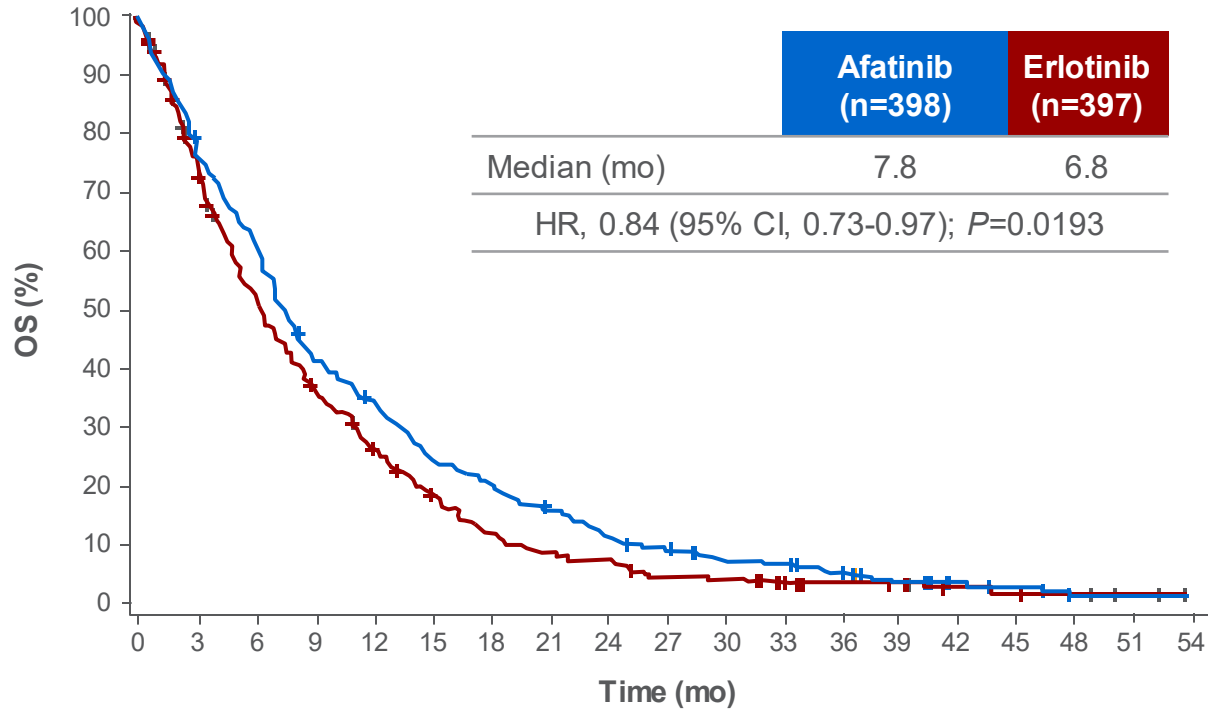
	Afatinib 40 mg QD (n=398)	Erlotinib 150 mg QD (n=397)
Patients died, n (%)	307 (77.1)	325 (81.9)
Median OS (mo)	7.9	6.8
	HR, 0.81; 95% CI, 0.69-0.95; *P*=0.0077	

HR = hazard ratio.

Soria JC et al. *Lancet Oncol*. 2015;16:897-907.

Retrospective Analysis of LUX-Lung 8 Patients Deriving Long-Term Benefit

OS: Final Analysis (ITT population)



	Afatinib (n=398)	Erlotinib (n=397)
Median (mo)	7.8	6.8
HR, 0.84 (95% CI, 0.73-0.97); *P*=0.0193		

Number at risk

Afatinib	398	317	250	170	138	107	85	68	49	40	31	29	22	13	8	6	2	2	0
Erlotinib	397	305	210	150	108	75	51	37	32	22	19	15	11	10	5	3	2	0	0

OS and PFS in Patients Deriving Long-Term Benefit

- 21 of 398 (5%) patients in the afatinib arm received ≥12 months of treatment
  - Median treatment duration was 19.0 months (range, 12.3-51.3 months)

	Afatinib ITT (n=398)	Afatinib LTB Subgroup (n=21)
Median OS, mo	7.8	27.5 (range, 16.2-53.6)
Median PFS, mo	2.6	12.9 (range, 2.8-25.8)

ITT = intent-to-treat; LTB = long-term benefit.

Goss D et al. *Ann Oncol*. 2018;29(suppl 8):viii493-viii547 (poster presentation; abstract 1442P).

Association of *ERBB* Mutations With Clinical Outcomes of Afatinib- or Erlotinib-Treated Patients With Lung Squamous Cell Carcinoma: Secondary Analysis of the LUX-Lung 8 Randomized Clinical Trial

- Association of LUX-Lung 8 trial outcomes with *ERBB* gene family member aberrations was assessed in an ad hoc, secondary analysis
- Tumour specimens from 245 patients were eligible for NGS (TGA subset: afatinib n=132; erlotinib n=113)

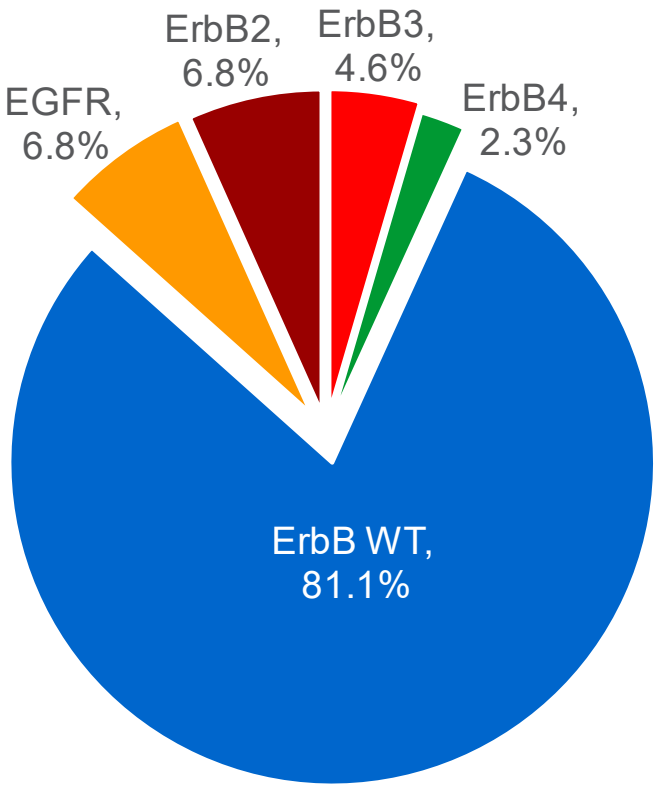
Gene	TGA[a] subset, % (n) (n=245)
ERBB wild-type	78.4 (192)
ERBB mutation	21.6 (53)
EGFR	6.5 (16)
HER2	4.9 (12)
HER3	6.1 (15)
HER4	5.7 (14)

- 1 patient (0.4%) had EGFR, HER2, and HER3 mutations
- 2 patients (0.8%) had HER3 and HER4 mutations

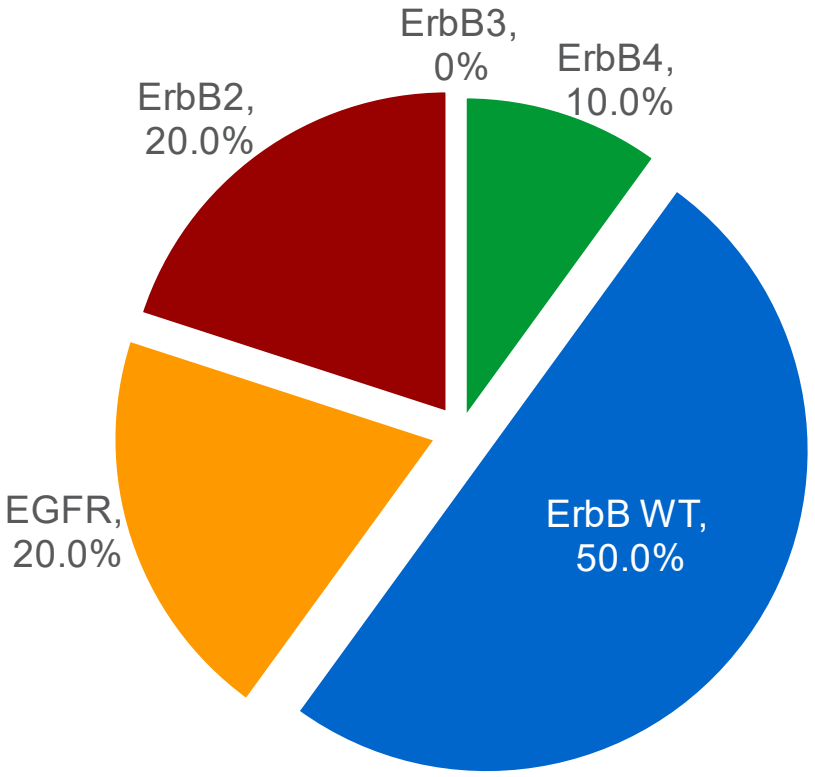
[a]TGA was performed using NGS in a cohort enriched for patients with PFS of ≥2 months. Tumour specimens from 245 patients were eligible for NGS (TGA subset: 132 patients treated with afatinib; 113 patients treated with erlotinib).
TGA = tumor genetic analysis; NGS = next-generation sequencing.
Goss GD et al. *JAMA Oncol*. 2018;4:1189-1197.

ERBB Mutations in Tumours of Patients Deriving Long-term Benefit

All Afatinib-Treated Patients (n=132[a])



Afatinib-Treated LTBs (n=10[a])

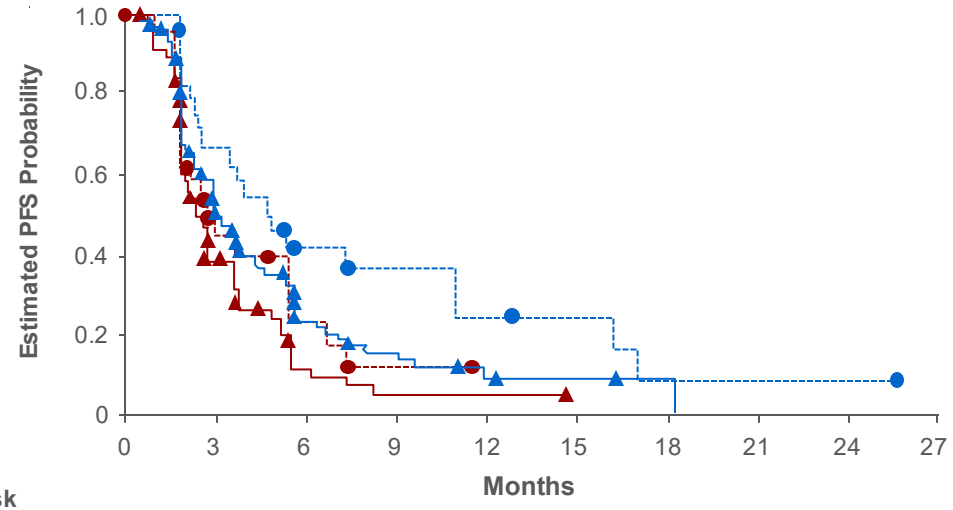


[a]NGS was undertaken in 10/21 LTRs and 132/398 afatinib-treated patients overall. ErbB family mutations were more frequent in LTBs than in the overall afatinib-treated population.
Yang J et al. *Ann Oncol*. 2017;28(suppl 2):ii28-ii51 (poster presentation; abstract 102P).

LUX-Lung 8: PFS and OS Benefit With Afatinib Was Greater in Patients With Cancers Harbouring ERBB Mutations

PFS

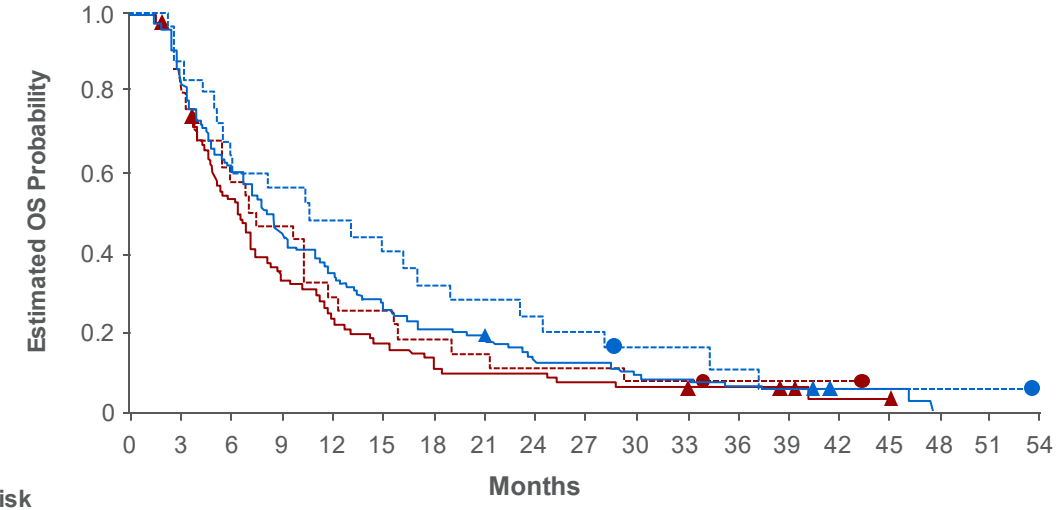
	Afatinib Present vs Absent	Erlotinib Present vs Absent
Median PFS	4.9 vs 3.0 mo	2.7 vs 2.4 mo
HR (95% CI); *P* value	0.62 (0.37-1.02) 0.06	0.76 (0.46-1.26) 0.29



No. at risk										
Afatinib: absent	107	47	15	8	3	2	1	0	0	0
Afatinib: present	25	16	8	6	4	3	1	1	1	0
Erlotinib: absent	85	26	5	2	2	0	0	0	0	0
Erlotinib: present	28	9	4	1	0	0	0	0	0	0

OS

	Afatinib Present vs Absent	Erlotinib Present vs Absent
Median OS	10.6 vs 8.1 mo	7.2 vs 6.4 mo
HR (95% CI); *P* value	0.75 (0.47-1.17) 0.21	0.84 (0.54-1.32) 0.46



No. at risk																			
Afatinib: absent	107	88	65	48	37	28	22	20	13	12	9	8	6	5	2	2	0	0	0
Afatinib: present	25	22	15	14	12	10	8	7	6	5	3	3	2	1	1	1	1	1	0
Erlotinib: absent	85	69	44	27	19	14	11	8	8	6	5	5	4	3	1	1	0	0	0
Erlotinib: present	28	23	16	13	8	7	5	4	3	3	2	2	1	1	1	0	0	0	0

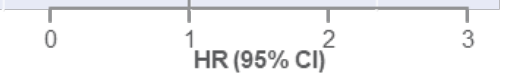
▲ Afatinib: ERBB Family mutation absent
● Afatinib: ERBB Family mutation present
▲ Erlotinib: ERBB Family mutation absent
● Erlotinib: ERBB Family mutation present

Goss GD et al. *JAMA Oncol*. 2018;4:1189-1197.

ERBB Family Mutation-Positive vs Negative Cancers in LUX-Lung 8

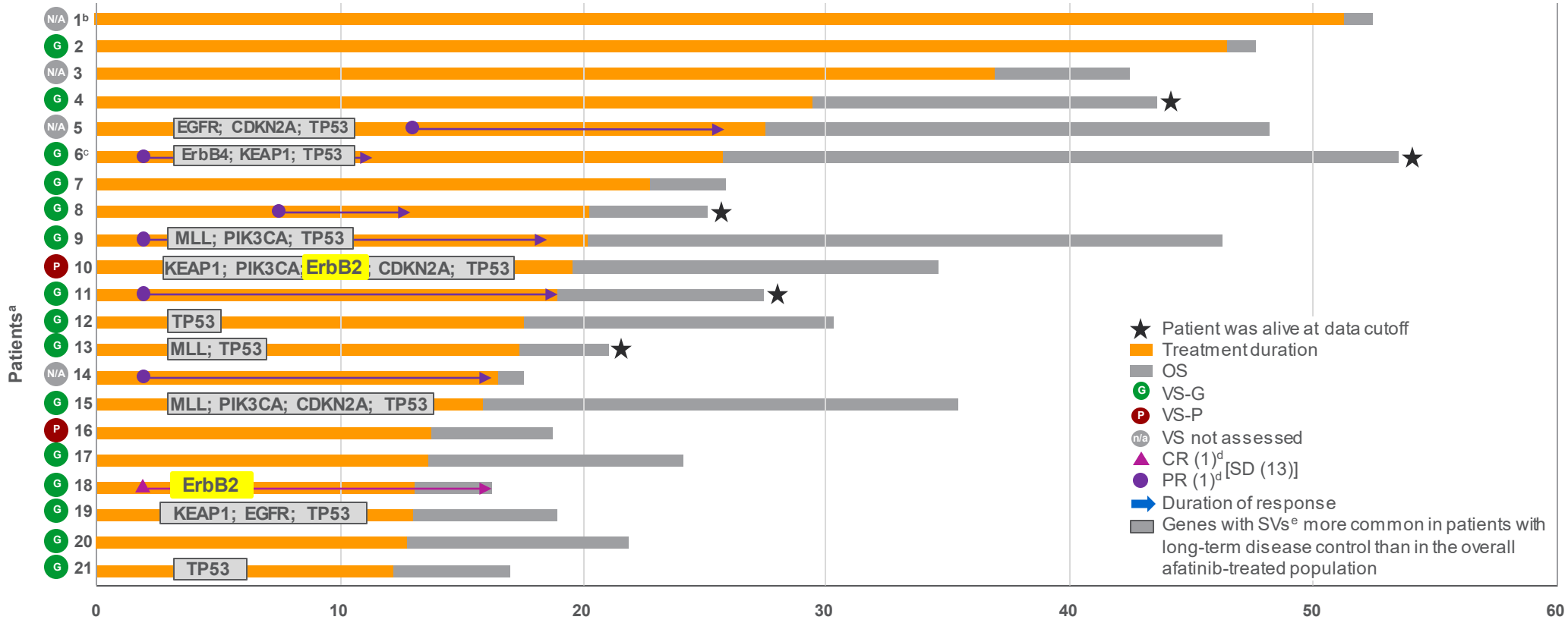
PFS

Variable	No. of patients	HR (95% CI)	Favours afatinib treatment	Favours erlotinib treatment	Interaction *P* value
LL8	795	0.81 (0.69-0.96)			
TGA	245	0.69 (0.51-0.92)			
***EGFR* mutation**					0.98
Present	16	0.64 (0.17-2.44)			
Absent	229	0.67 (0.50-0.91)			
***HER2* mutation**					0.006
Present	12	0.06 (0.01-0.59)			
Absent	233	0.72 (0.54-0.97)			
***HER3* mutation**					0.69
Present	15	0.52 (0.16-1.72)			
Absent	230	0.69 (0.51-0.94)			
***HER4* mutation**					0.91
Present	14	0.21 (0.02-1.94)			
Absent	231	0.67 (0.50-0.91)			
***ERBB* network mutation**					0.72
Present	53	0.56 (0.29-1.08)			
Absent	192	0.70 (0.50-0.97)			
***HER2, 3, 4* mutation**					0.54
Present	38	0.44 (0.19-0.99)			
Absent	207	0.71 (0.52-0.98)			



Goss GD et al. *JAMA Oncol*. 2018;4:1189-1197.

LUX-Lung 8 Long-Term Benefiters: Treatment Response



- Median OS, 27.5 mo (range, 16.2-53.6 mo); median PFS, 12.9 mo (range, 2.8-25.8 mo)
- **2 of the 10 long-term benefitters with TGA data available had a HER2 mutation**

[a]Patients were ordered and numbered by treatment duration (at data cut-off), with patient 1 being on treatment longest; [b]Patient transferred to commercial drug on discontinuation from study drug; [c]Patient also had rearrangements in two genes; [d]First observed response at time of tumour measurement; [e]≥1 SV present in at least 3/10 patients with long-term disease control, or part of the ErbB family (EGFR, ErbB2, ErbB3, ErbB4).

CR = complete response; MLL = mixed-linkage leukaemia; PR = partial response; SD = stable disease; SV = structural variation; VS = VeriStrat; VS-G = VeriStrat-good; VS-P = VeriStrat-poor.

Goss D et al. *Ann Oncol*. 2018;29(suppl 8):viii493-viii547 (poster presentation; abstract 1442P).

Summary and Conclusions

- Major differences exist between SqCC of the lung and ADC, including identification of treatable oncogene subsets[1,2]
- Immune checkpoint inhibitors have emerged as promising novel treatment options for advanced SqCC. Increased use of IO in 1L creates a need to optimize 2L decisions[3]
- ErbB receptor family is a rational therapeutic target for SqCC of the lung[4]
- LUX-Lung 8
  - Afatinib[a] significantly improved PFS (HR, 0.81; *P*=0.0103) and OS (HR, 0.84; *P*=0.0193) vs erlotinib[5,6]
  - In patients achieving LTB (defined as afatinib treatment for ≥12 months), a mOS of 27.5 months was seen and ErbB family mutations were more frequent in this group[6]
  - Patients with ErbB mutation–positive tumours showed a more pronounced PFS and OS benefit with afatinib over erlotinib[7]
- In the treatment of advanced SqCC, afatinib should be considered:
  - As a treatment option in patients who have failed previous treatment with chemotherapy and immunotherapy
  - In the second-line setting in patients who are not eligible for immune checkpoint inhibitors

[a]Esta indicación no está financiada en España por el Sistema Nacional de Salud. This indication is not reimbursed by the Spanish National Health System.

1. Gandara DR et al. *Clin Cancer Res*. 2015;21:2236-2243; 2. Li T et al.. *J Clin Oncol*. 2013;31:1039-1049; 3. Planchard D et al. *Ann Oncol*. (2018) 29 (suppl 4): iv192–iv237 (Updated 18 September 2019 by the ESMO Guidelines Committee); 4. The Cancer Genome Atlas Research Network. *Nature*. 2012;489:519-525; 5. Soria JC et al. *Lancet Oncol*. 2015;16:897-907; 6. Goss D et al. *Ann Oncol*. 2018;29(suppl 8):viii493-viii547 (poster presentation; abstract 1442P); 7. Goss GD et al. *JAMA Oncol*. 2018;4:1189-1197.