Maximising the Clinical Potential of TKIs for Patients With Squamous NSCLC

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Disclosures

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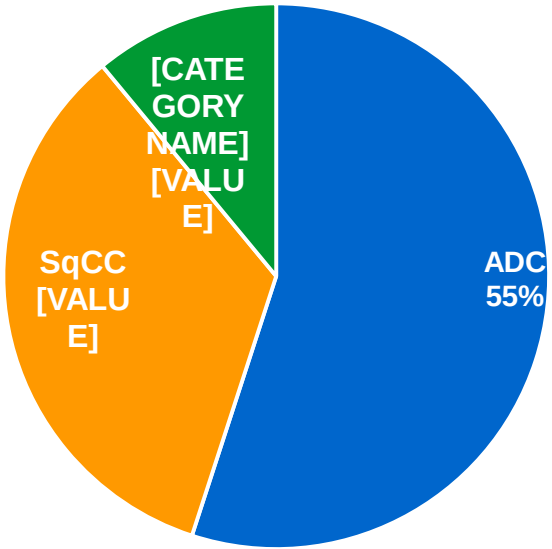
- Consultant: AstraZeneca, BMS, Boehringer Ingelheim, Celgene, CellMax, Genentech, Guardant Health, IO Biotech, Lilly, Liquid Genomics, Merck

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; NSCLC = non–small cell lung cancer; SOC = standard of care; SqCC = squamous cell carcinoma; 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, Kung HJ, Mack PC, Gandara DR. *J Clin Oncol*. 2013;31:1039–1049.

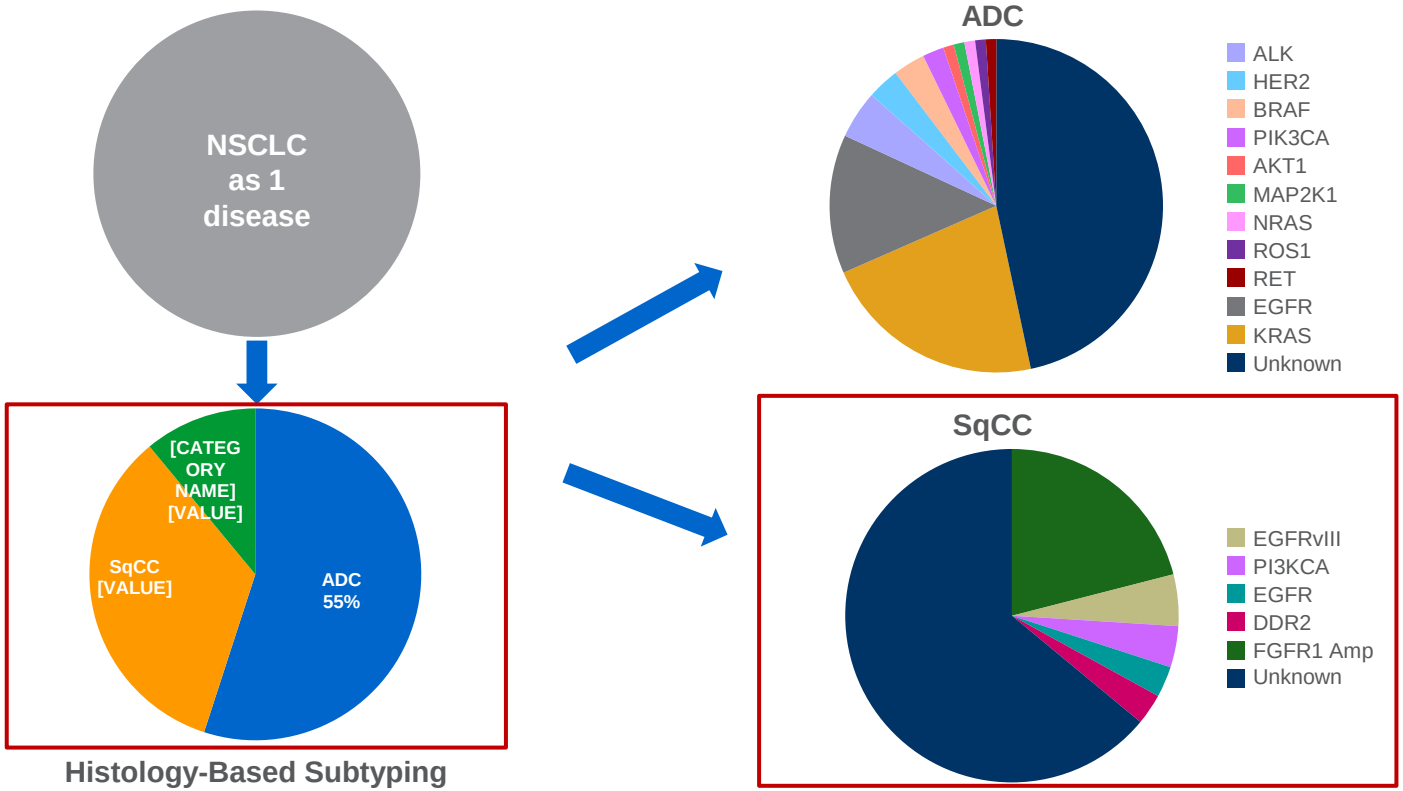
First-line Immunotherapy Trials in Patients With SqCC of the Lung Are Rapidly Changing the Treatment Landscape

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=559)	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 randomized 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; 3. Paz-Ares L. et al. *J Clin Oncol*. 2018;36(suppl):105; 4. Jotte R et al. *J Clin Oncol*. 2018;36(suppl):LBA9000; 5. Hellmann MD et al. *Cancer Res.* 2018; 78 (suppl 13): CT077; 6. Borghaei H et al. *J Clin Oncol*. 2018;36(suppl):9001; 7. Hellmann MD et al. *N Engl J Med*. 2018;378:2093–2104.

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



ADC = adenocarcinoma; SqCC = squamous cell carcinoma.

Li T, Kung HJ, Mack PC, Gandara DR. *J Clin Oncol*. 2013;31:1039–1049.

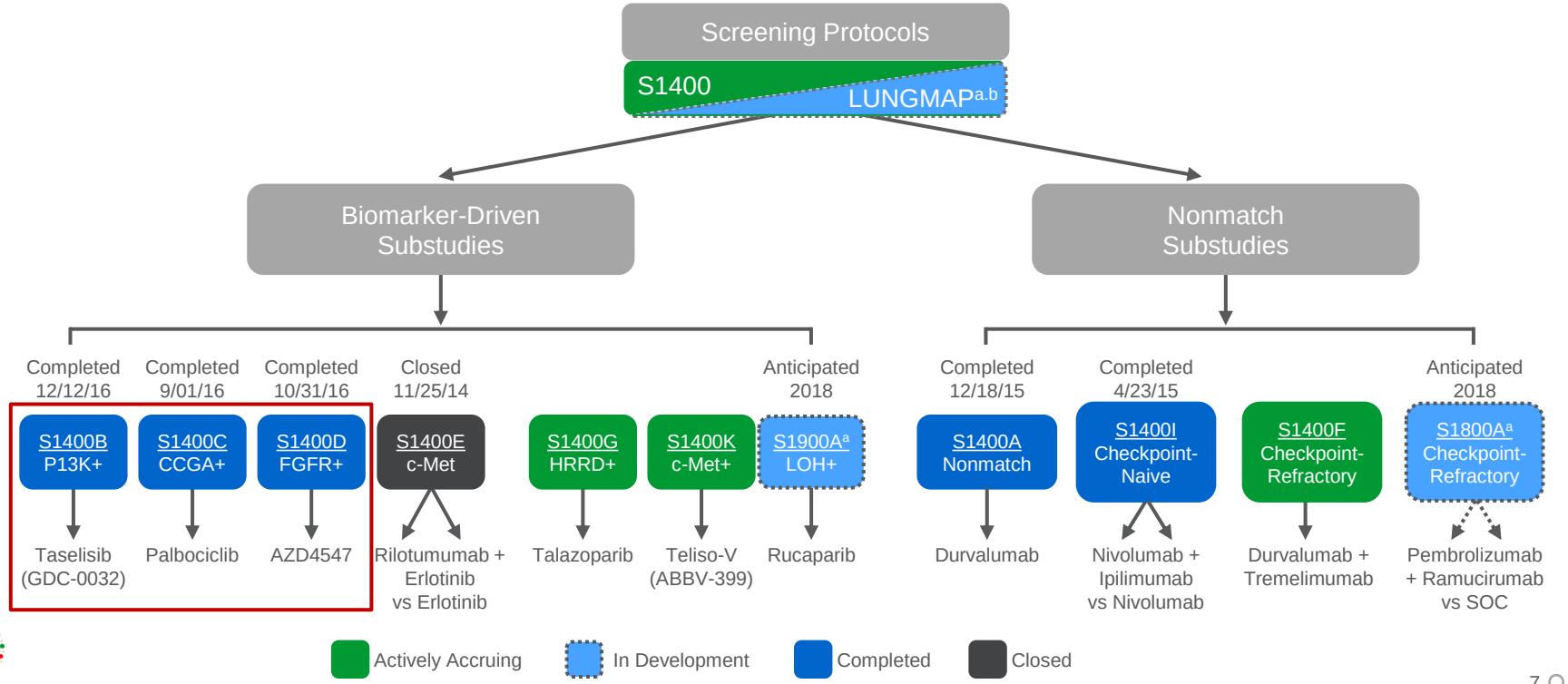
“Druggable Targets”: Genetic Alterations in SqCC of the Lung

Genetic Alterations	Prevalence	Clinical Trials
RTK amplification	>30% with *EGFR* and *FGFR1* most common	EGFR mAbs, FGFR TKIs, FGFR mAbs, FGFR ligand traps
RTK mutations/fusions	Rare (<10%), most common in *FGFR2* and *FGFR3 (FGFR3-TACC3)*, rare *DDR2* mutations	FGFR TKIs, FGFR mAbs, FGFR ligand traps, dasatinib
RAS	10%-20%, most commonly loss of NF1 or RASA1, RAS mutations rare	MEK and ERK inhibitors, direct RAS inhibitors
PI3K	Common ~50% alterations in PIK3A, PTEN, and PIK3R1	PI3K and mTOR inhibitors
TP53 and *CDKN2A/RB1*	Genomic loss in nearly all cases, amplification of *CDK4/CDK6/ CCND1* in *CDKN2A* intact tumors	CDK inhibitors?
Oxidative stress regulation	Common mutation of *NFE2L2/KEAP1/CUL3* (25%)	PI3K inhibitors?
Differentiation	Common loss of NOTCH1; *TP63* and *SOX2* gain	?
Immune evasion	Rare *HLA* and *B2M* mutations, <10%	Immune checkpoint inhibitors, vaccines

B2M = beta-2 microglobulin; CCND = cyclin D gene; CDK = cyclin D-dependent kinase; CUL3 = cullin 3; DDR = DNA damage response; ERK = extracellular signal-regulated kinase; FGFR = fibroblast growth factor receptor; HLA = human leukocyte antigen; KEAP 1 = Kelch-like ECH-associated protein 1; mAb = monoclonal antibody; MEK = MAP kinase-ERK kinase; mTOR = mechanistic target of rapamycin; NFE2L2 = nuclear factor, erythroid 2 like 2; PI3K = phosphatidylinositol-4,5-bisphosphate 3-kinase; PTEN = phosphatase and tensin homolog; RAS = rat sarcoma; RB = retinoblastoma; RTK = receptor tyrosine kinase; SOX = sex determining region Y-box; TP53 = tumor protein 53; TP63 = tumor protein 63.

Gandara DR et al. *Clin Cancer Res*. 2015;21:2236–2243.

Current Lung-MAP Schema (May 2018)



[a]Only new substudies will be one to al NSCLC histologies. The rest of the current substudies are for patients only with squamous cell carcinoma.
[b]New screening protocol will include all NSCLC histologies. The new umbrella screening protocol will simply be referred to as LUNGMAP.
Lung-MAP. Available at http://www.lung-map.org/healthcare-provider. Accessed September 14, 2018.

Lung-MAP Genotypic Substudy Results

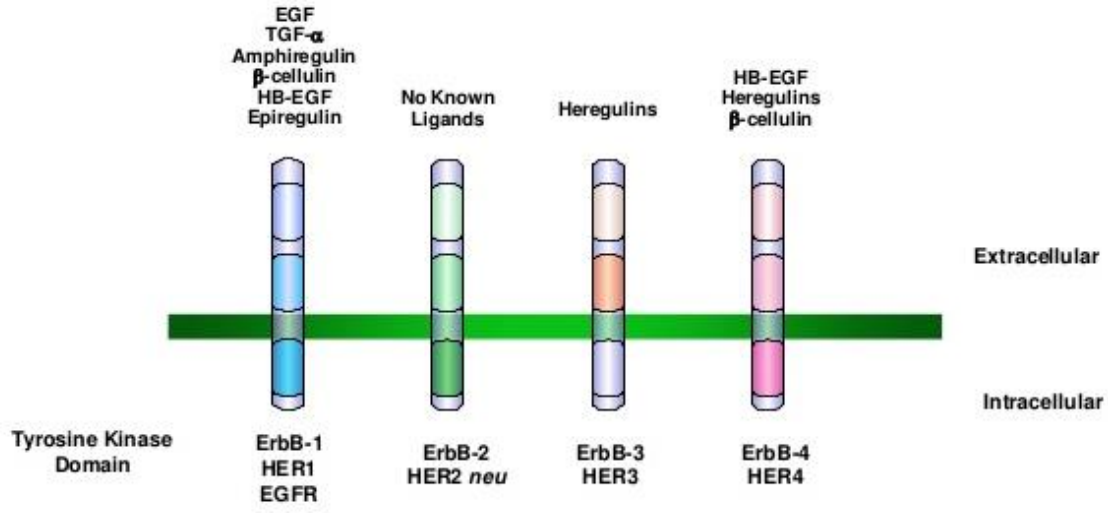
	Patients (N)	Best Objective Response		Response N (%)	PFS Median (95% CI)	OS Median (95% CI)
S1400B (Taselisib)	39	1 PR	17 SD 6 PD 2 NASS	1 (4%)	2.8 (1.7, 4.0)	5.9 (4.1, 11.5)
S1400C (Palbociclib)	54	2 PR	12 SD 16 PD 2 NASS	2 (6%)	1.8 (1.6, 2.9)	7.2 (4.0, 14.6)
S1400D (AZD4547)	45	1 PR 1 UPR	13 SD 10 PD 2 NASS	2 (7%)	2.7 (1.4, 4.5)	7.5 (3.6, 9.3)
Docetaxel	73	2 PR 1 UPR	29 SD 13 PD 11 NASS	3 (5%)	2.7 (1.9, 2.9)	7.7 (6.7, 9.2)

CI = confidence interval; NASS = not adequately assessed; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; SD = stable disease; UPR = unconfirmed partial response.

Herbst R et al. *J Thorac Oncol*. 2017;12(suppl 2):S1783–S1784.

In Search of an Oncogene Driver for SqCC of the Lung

Targeting ErbB (HER) Family Alterations in NSCLC



Adapted from Gandara R et al. *JAMA Oncol.* doi:10.1001/jamaoncol.2018.0774

EGFR (HER1, ErbB-1):

- Well-established as therapeutic target (not the subject of this talk)

HER2 (ErbB-2):

- No known ligand
- No ligand required for activation
- Mutations, amplification, over-expression

HER3 (ErbB-3):

- Heregulin is ligand
- Mutations identified
- Induces PI3K-AKT pathway
- Heterodimerization with HER family receptors (EGFR and ErbB2/HER2)

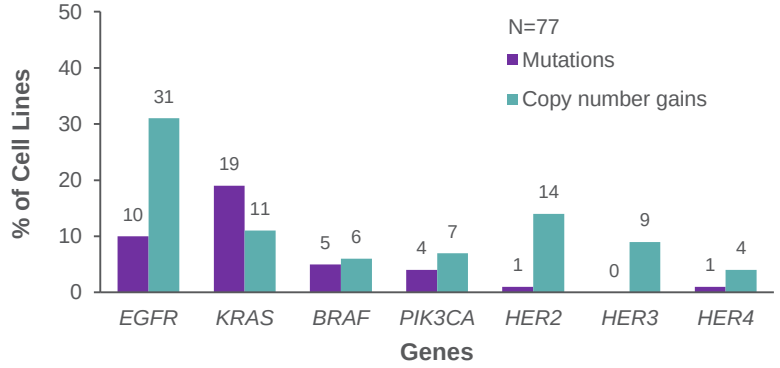
HER4 (ErbB-4):

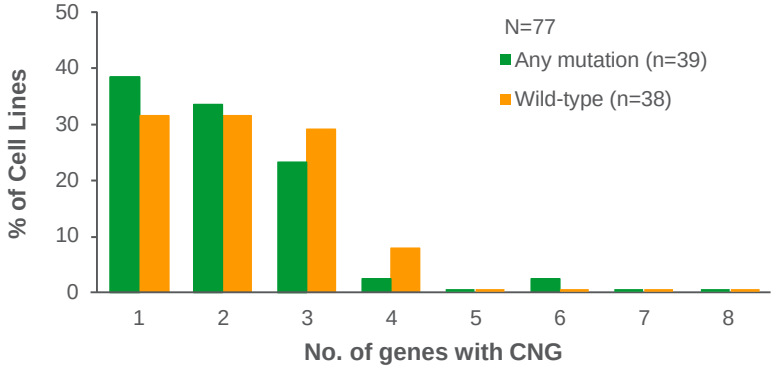
- Multiple ligands (EGF, epiregulin, neuroregulin 3 and 4)
- Mutations identified

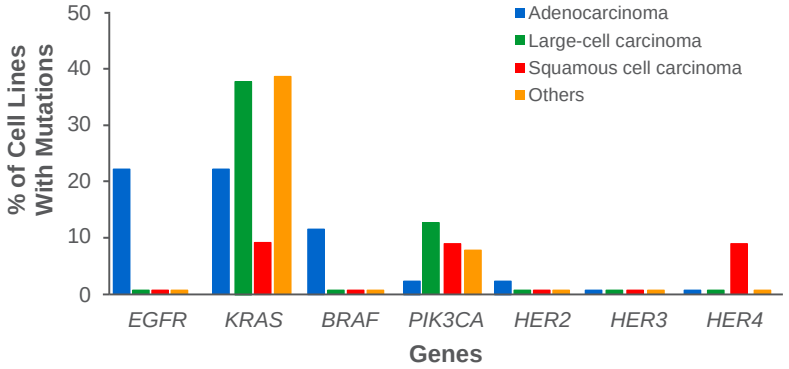
HB = heparin-binding; TGF = transforming growth factor.

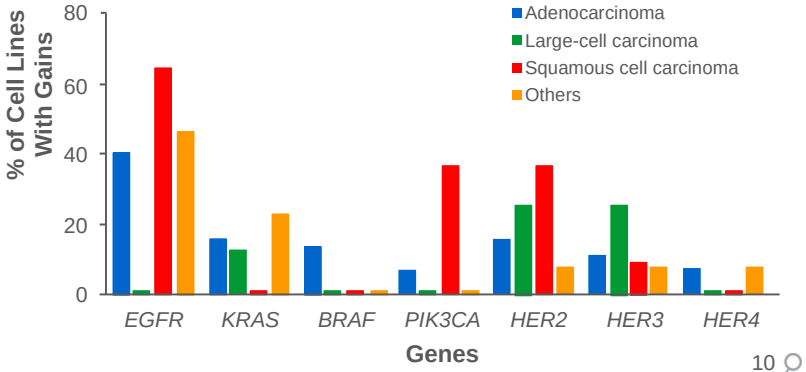
1. Gandara DR et al. *JAMA Oncol*. doi:10.1001/jamaoncol.2018.0774; 2. Olayioye MA et al. *EMBO J*. 2000;19:3159–3167.

Prevalence of *ERBB* Family Mutations and Gene Copy Number Alterations





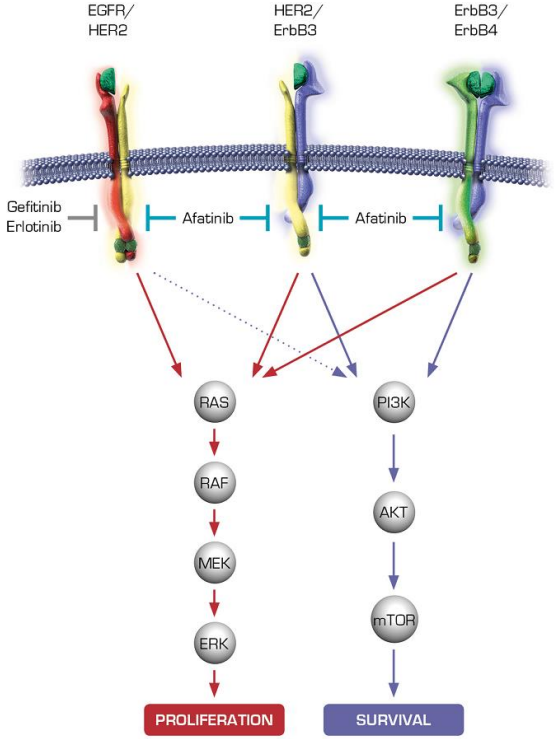




CNG = cyclic nucleotide-gating channel.

Gandhi J et al. *PLoS One*. 2009;4(2):e4576. doi: 10.1371/journal.pone.0004576.

Afatinib Is the First Irreversible ErbB Family Blocker



- Afatinib covalently binds and irreversibly blocks EGFR, HER2, and ErbB4[2,3]
- Targeting the whole ErbB Family enhances the effect on important signaling pathways[2]

1. Hirsh. *BioDrugs*. 2015;29(3):167-83; 2. Li D et al. *Oncogene*. 2008;27:4702; 3. Solca F et al. *J Pharmacol Exp Ther*. 2012;343:342–350.

LUX-Lung 8 Study Design: Afatinib 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**

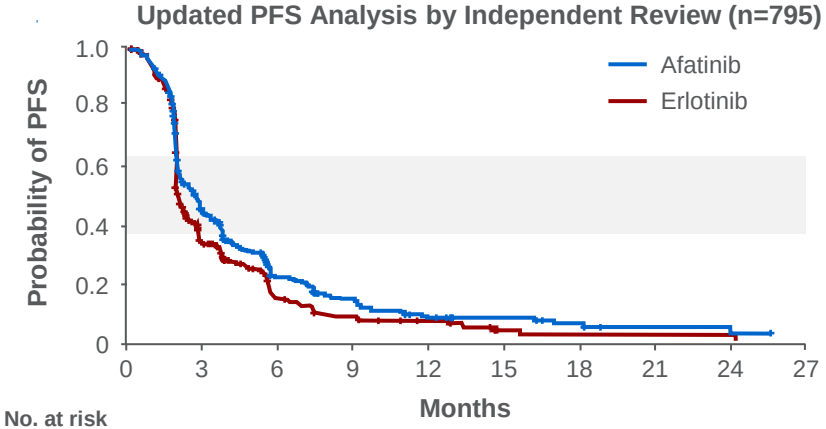
→ Treatment until disease progression or unacceptable AEs

- 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
- Primary endpoint: PFS; key secondary endpoint: OS

AE = adverse event; EGFR = epidermal growth factor receptor; ECOG PS = Eastern Cooperative Oncology Group performance status; QD = once daily.

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

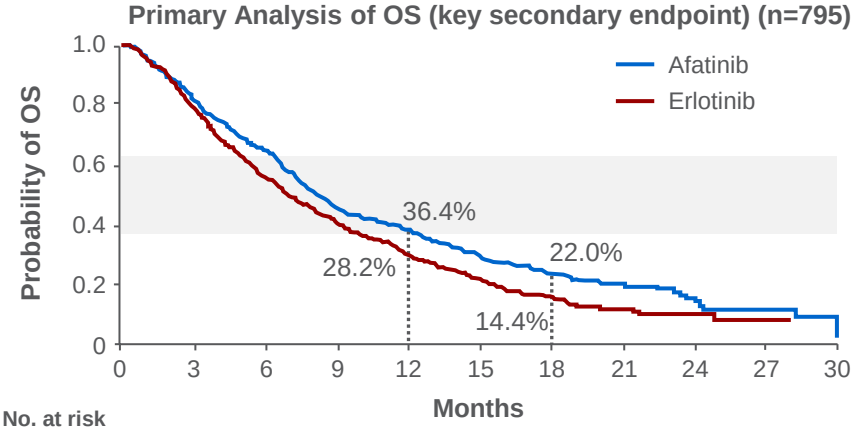
LUX-Lung 8: Significant Improvement in PFS and OS With Afatinib Compared With Erlotinib



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 (months)	2.6	1.9
	HR 0.81; 95% CI: 0.69–0.96; *P*=0.0103	



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

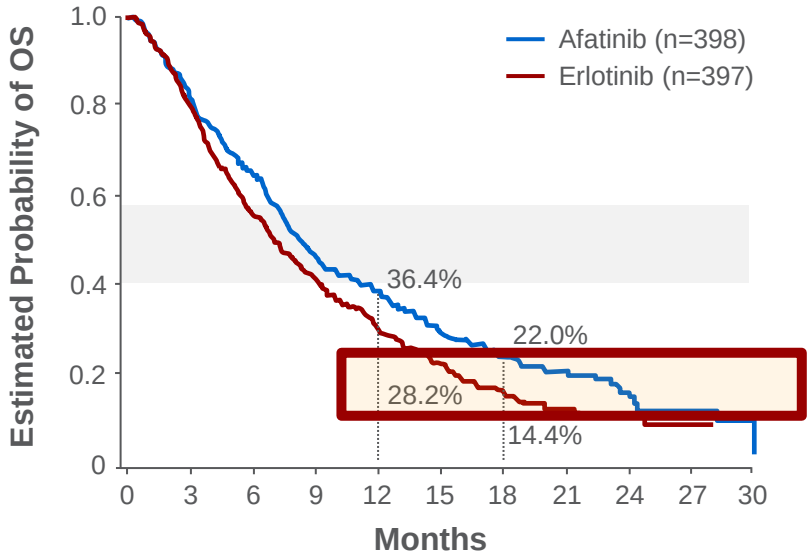
	Afatinib 40 mg QD (n=398)	Erlotinib 150 mg QD (n=397)
Patients died, n (%)	307 (77.1)	325 (81.9)
Median OS (months)	7.9	6.8
	HR 0.81; 95% CI: 0.69–0.95; *P*=0.0077	

HR = hazard ratio.

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

Retrospective Analysis of LUX-Lung 8 Patients Deriving Long-term Benefit[1]

OS: Primary Analysis (ITT population)



OS and PFS in Patients Deriving Long-term Benefit

- 21 patients received ≥12 months of afatinib treatment
  - Median treatment duration was 17.6 months (range: 12.3–27.6 months)

	Afatinib ITT (n=398)	Afatinib LTB (n=21)
Median OS, months	7.9	21.1 (range: 12.9–31.6)
Median PFS, months	2.6	16.6 (range: 2.8–25.8)

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

Yang J et al. *Ann Oncol*. 2017;28(suppl 2):ii28-ii51.

ERBB Family Mutations in SqCC of the Lung in the LUX-Lung 8 Trial

22% of Patients in the TGA Had *ERBB* Mutations

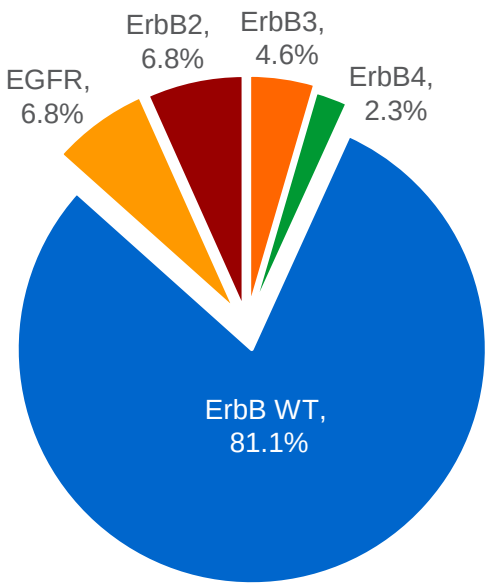
Gene	TGA subset, % (n) (n=245)
ERBB wild-type	78.4 (192)
ERBB mutation	21.6 (53)
EGFR	6.5 (16)
HER2	4.9 (12)
HER3	6.1 (15)
HER4	5.7 (14)

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

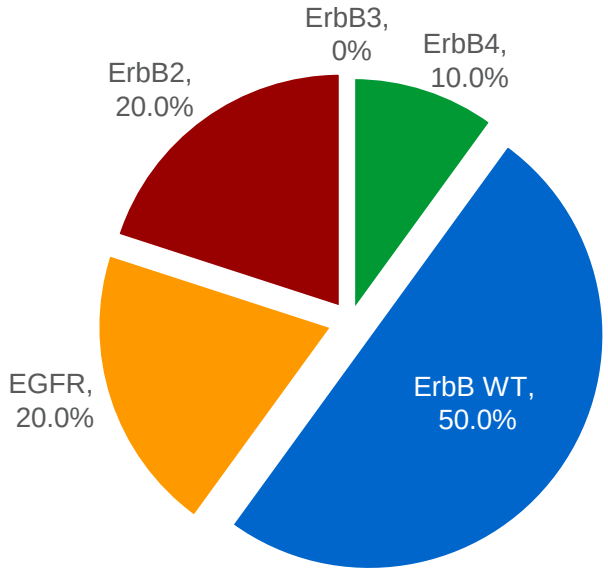
Goss GD et al. *JAMA Oncol*. 2018 doi: 10.1001/jamaoncol.2018.0775.

Genomic Aberrations in Patients Deriving Long-term Benefit

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

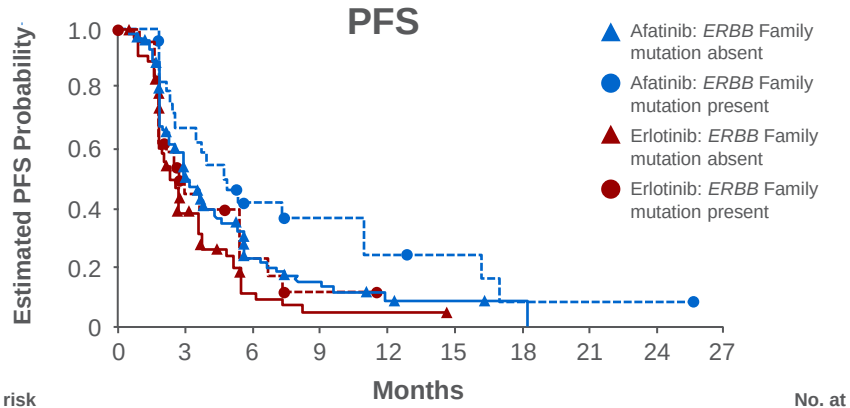


Afatinib-Treated LTBs (n=10[a])



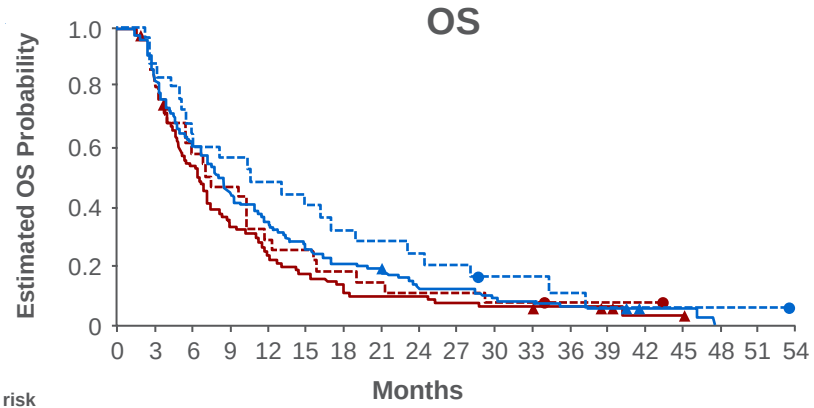
[a]Next-generation sequencing was undertaken in 10/21 LTRs and 132/398 afatinib-treated patients overall; WT = wild-type.
ErbB family mutations were more frequent in LTBs than in the overall afatinib-treated population.
Yang J et al. *Ann Oncol*. 2017;28(suppl 2):ii28-ii51.

PFS and OS Benefit With Afatinib Was Greater in Patients Harbouring *ERBB* Mutations



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

	Afatinib Present vs Absent	Erlotinib Present vs Absent
Median PFS	4.9 mo vs 3 mo	2.7 mo 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	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	

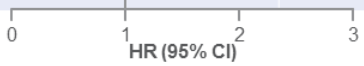
	Afatinib Present vs Absent	Erlotinib Present vs Absent
OS	10.6 mo vs 8.1 mo	7.2 mo vs 6.4 mo
HR (95% CI); *P* value	0.75 (0.47-1.17) 0.21	0.84 (0.54–1.32) 0.46

Goss GD et al. *JAMA Oncol*. doi: 10.1001/jamaoncol.2018.0775.

PFS and OS Were Longer in Patients With *HER* (*ERBB*) Mutation–Positive Tumours vs Those Without

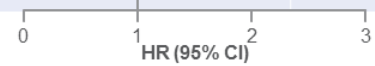
PFS

Variable	No. of patients	HR (95% CI)	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)	



OS

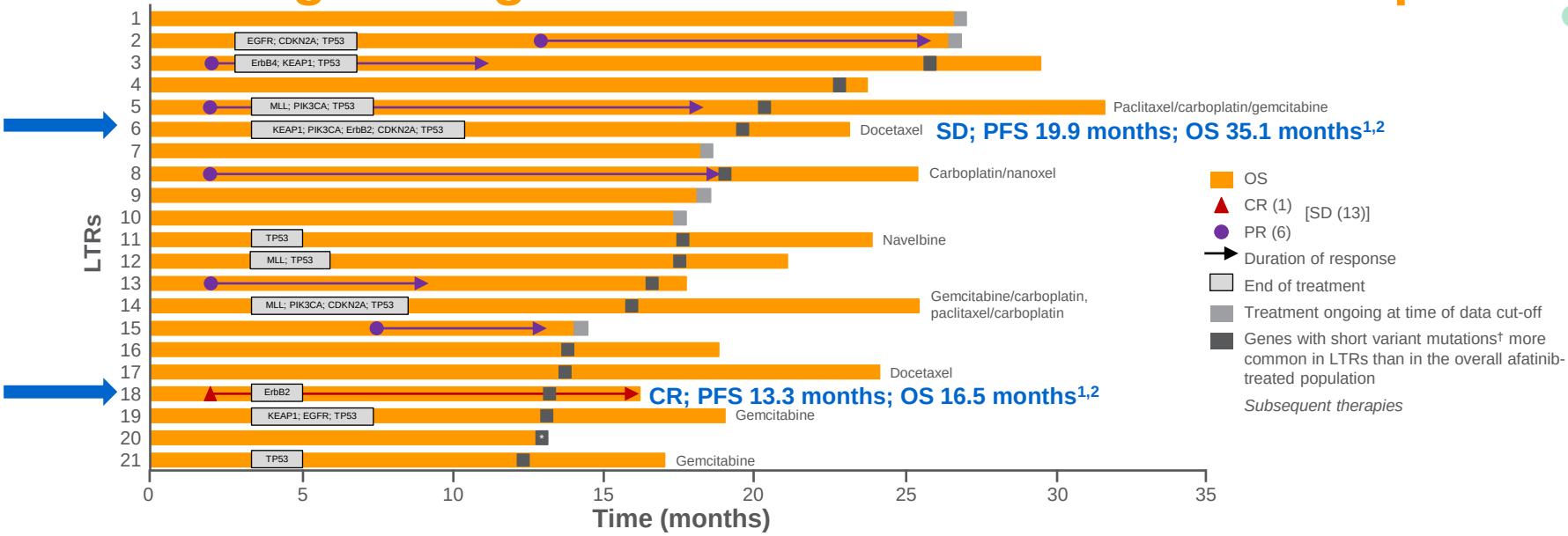
Variable	No. of patients	HR (95% CI)	Interaction *P* value
LL8	795	0.84 (0.73-0.98)	
TGA	245	0.81 (0.62-1.05)	
EGFR mutation			0.25
Present	16	1.35 (0.45-4.06)	
Absent	229	0.77 (0.59-1.01)	
HER2 mutation			0.003
Present	12	0.06 (0.01-0.57)	
Absent	233	0.83 (0.64-1.09)	
HER3 mutation			0.89
Present	15	0.84 (0.27-2.59)	
Absent	230	0.81 (0.62-1.06)	
HER4 mutation			0.13
Present	14	0.22 (0.05-1.04)	
Absent	231	0.82 (0.63-1.08)	
ERBB network mutation			0.67
Present	53	0.72 (0.41-1.26)	
Absent	192	0.81 (0.60-1.09)	
HER2, 3, 4 mutation			0.18
Present	38	0.48 (0.24-0.97)	
Absent	207	0.86 (0.64-1.14)	



LL8 = LUX-Lung 8; TGA = tumour genetic analysis.

Goss GD et al. *JAMA Oncol*. doi: 10.1001/jamaoncol.2018.0775.

LUX-Lung 8 Long-Term Benefiters: Treatment Response



- Median OS was 21.1 mo (range: 12.9–31.6 mo); median PFS (independent central review) was 16.6 mo (range: 2.8–25.8 mo)[1]
- **2 of the 10 long-term benefiters with tumor genetic analysis data available had a HER2 mutation[1]**

*Treatment ongoing until death; †≥1 mutation present in at least 3/10 LTRs, or part of the ErbB family (EGFR, ErbB2, ErbB3, ErbB4).

1. Yang J et al. *Ann Oncol*. 2017;28(suppl 2):ii28-ii51. 2. Data on file. Boehringer Ingelheim.

Recent Additional Trial on Activity of Afatinib in HER2 Exon 20-Mutated NSCLC

	All *HER2* Mutation-Positive Patients	Patients With p.A775_G776insYVMA in Exon 20	Patient With M774dup in Exon 20
n (%)	28 (100)	10 (36)	2 (7)
TTF			
Median TTF, months	2.9	9.6	1.9
TTF >1 year	8 (29)	4 (40)	0 (0)
Tumour response			
Patients with response data available	16 (57)	6 (60)	0 (0)
ORR	3 (19)	2 (33)	ND
DCR	11 (69)	6 (100)	ND
PR	3 (19)	2 (33)	ND
SD	8 (50)	4 (67)	ND

DCR = disease control rate; ORR = objective response rate; TTF = time to treatment failure.
Peters S et al. *J Thorac Oncol*. doi: 10.1016/j.jtho.2018.07.093.

Summary and Conclusions

- Major differences exist between SqCC of the lung and ADC, including identification of treatable oncogene subsets

- LUX-Lung 8[1]
  - Afatinib significantly improved PFS (HR 0.81; *P*=0.0427) and OS (HR 0.81; *P*=0.0077) vs erlotinib
  - Survival rates at 12 and 18 months favored afatinib
    - 12 months (afatinib vs erlotinib): 36% vs 28% (*P*=0.016)
    - 18 months: 22% vs 14% (*P*=0.013)
  - In patients on afatinib for ≥12 months, a median survival benefit of nearly 2 years was seen
    - ErbB family mutations were more frequent in this group[2]
  - Patients with *ErbB* mutation–positive tumours showed a more pronounced PFS and OS benefit with afatinib over erlotinib[3]

1. Soria JC et al. *Lancet Oncol*. 2015;16:897–907; 2. Yang J et al. *Ann Oncol*. 2017;28(suppl 2):ii28-ii51; 3. Goss GD et al. *JAMA Oncol*. doi: 10.1001/jamaoncol.2018.0775

Summary and Conclusions (*cont'd*)

- 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