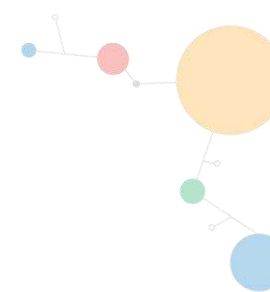


Maximising the Clinical Potential of TKIs for Patients With Squamous NSCLC

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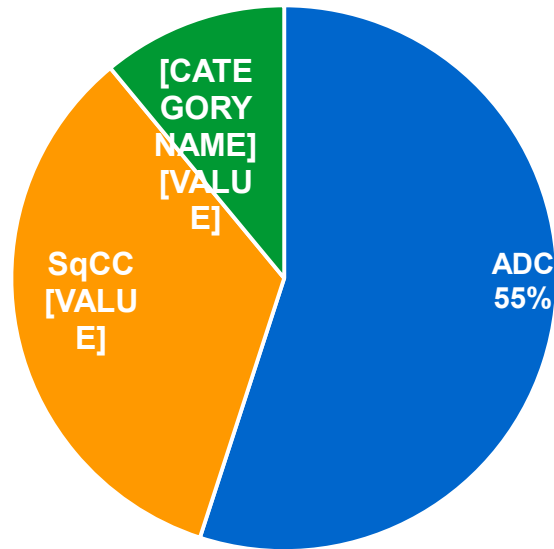
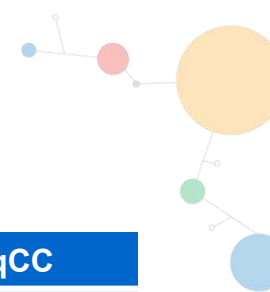


Disclosures

- Research grants: AstraZeneca, Roche-Genentech
- 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



^aAdvances 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

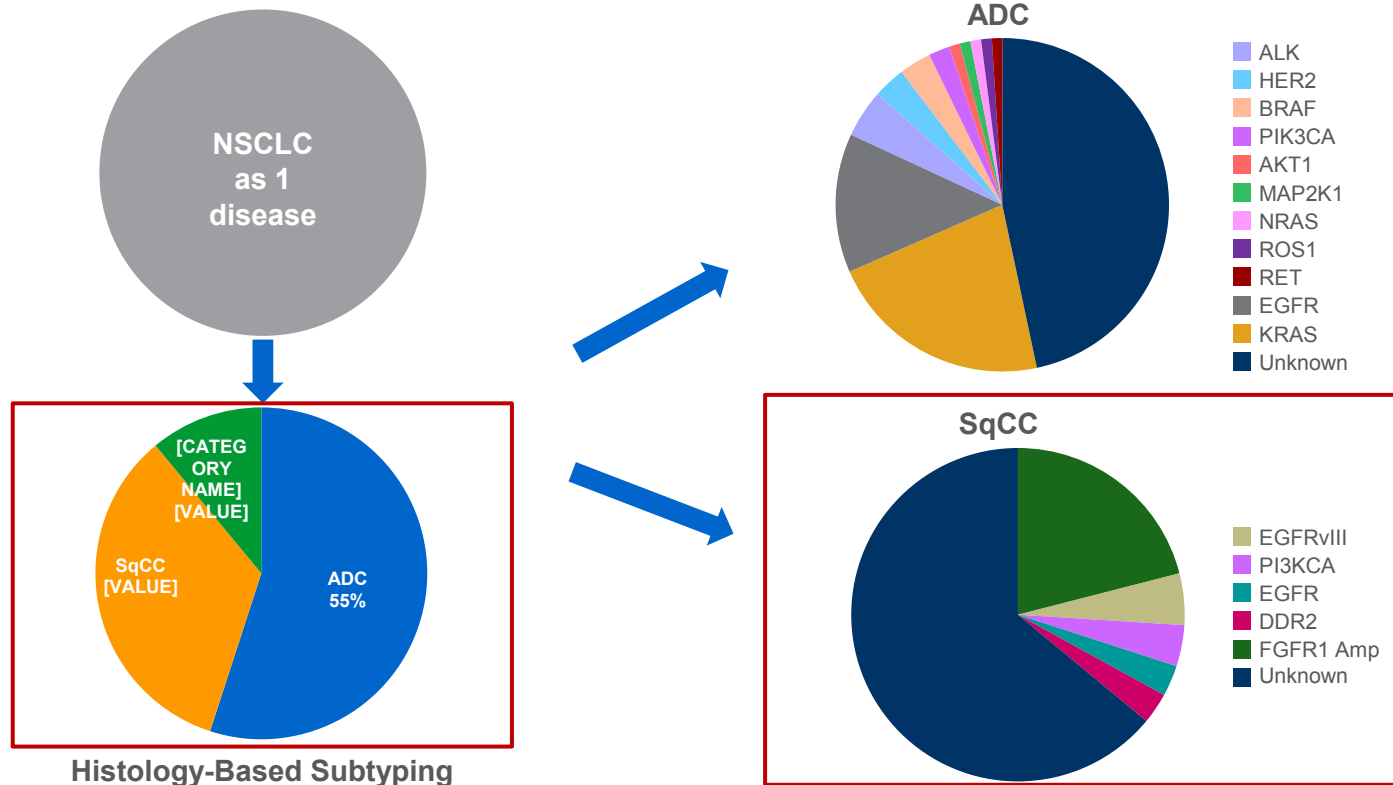
Trial Name	Histology	Treatment Arms
KEYNOTE-024 ¹	Mixed (N=305) Squamous (n=56)	Pembrolizumab vs chemotherapy (PD-L1 ≥50%)
KEYNOTE-042 ²	Mixed (N=1274) Squamous (n=492)	Pembrolizumab vs chemotherapy (PD-L1 ≥1%)
KEYNOTE-407 ³	Squamous (N=559)	Pembrolizumab + chemotherapy vs chemotherapy
IMpower131 ⁴	Squamous (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



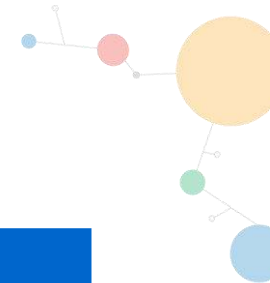
^aSquamous histology in 28% of all randomized patients.

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



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



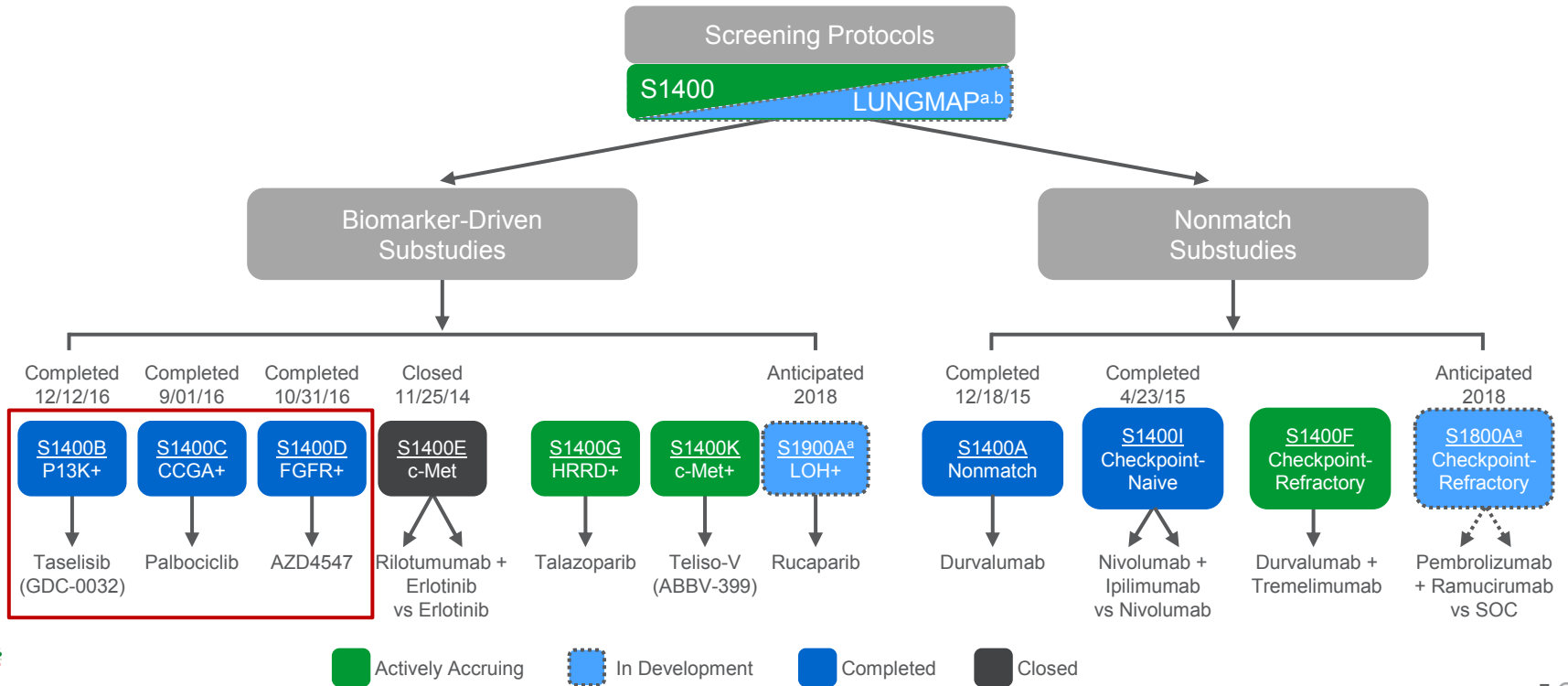
Genetic Alterations	Prevalence	Clinical Trials
<i>RTK</i> amplification	>30% with <i>EGFR</i> and <i>FGFR1</i> most common	<i>EGFR</i> mAbs, <i>FGFR</i> TKIs, <i>FGFR</i> mAbs, <i>FGFR</i> ligand traps
<i>RTK</i> mutations/fusions	Rare (<10%), most common in <i>FGFR2</i> and <i>FGFR3</i> (<i>FGFR3-TACC3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



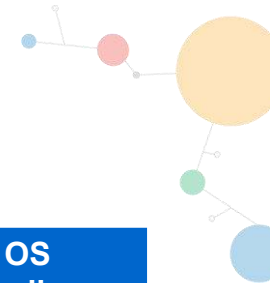
Current Lung-MAP Schema (May 2018)



^aOnly new substudies will be one to all NSCLC histologies. The rest of the current substudies are for patients only with squamous cell carcinoma.

^bNew 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)

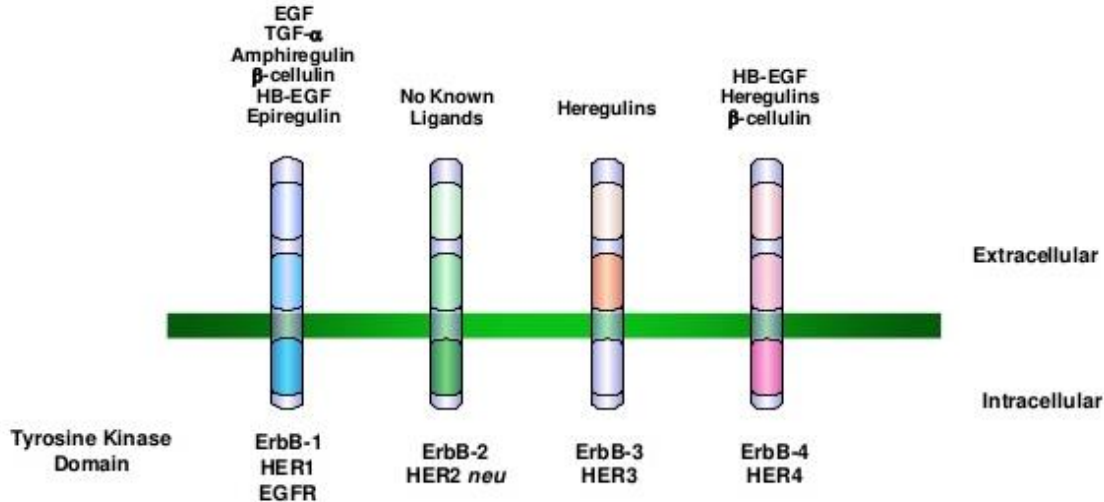
CI = confidence interval; NASS = not adequately assessed; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; SD = stable disease; UPR = unconfirmed partial response.

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



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

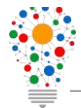
HER3 (ErbB-3):

- 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

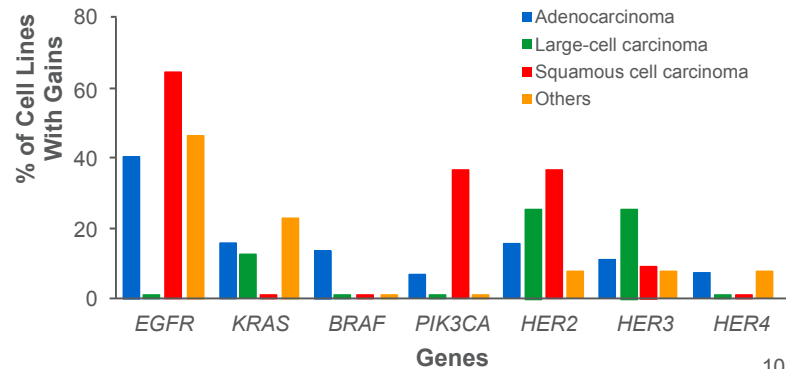
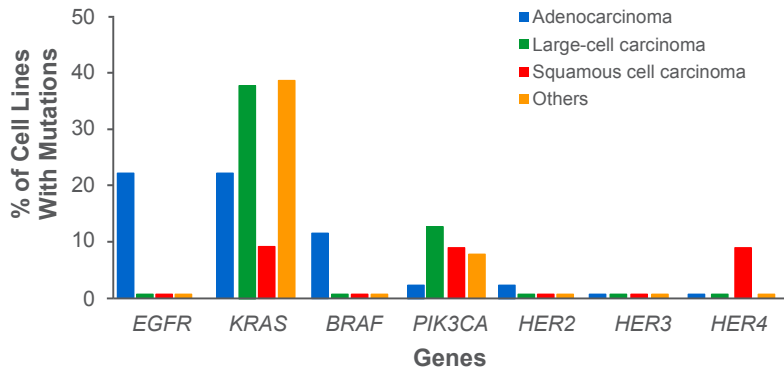
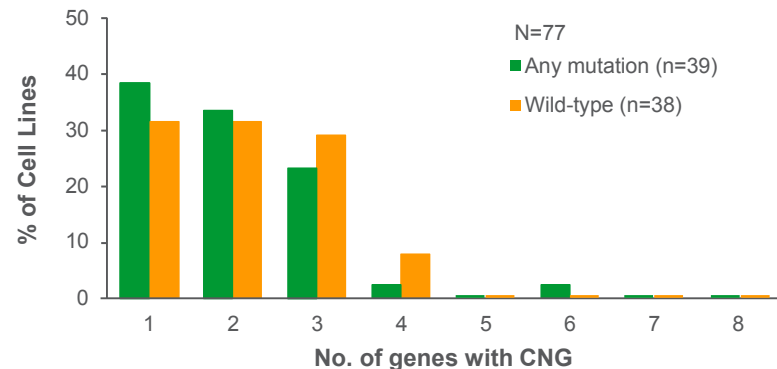
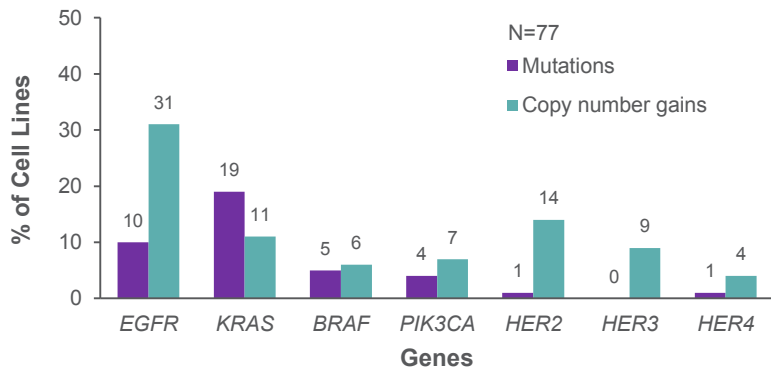
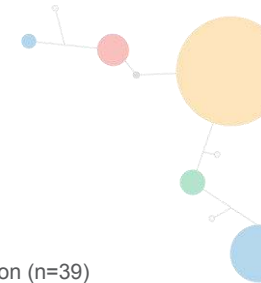
Adapted from Gandara R et al. *JAMA Oncol*. doi:10.1001/jamaoncol.2018.0774



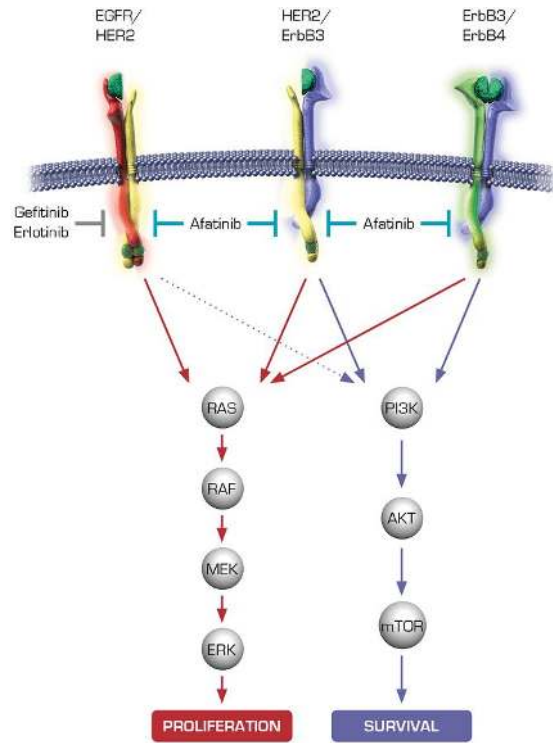
HB = heparin-binding; TGF = transforming growth factor.

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



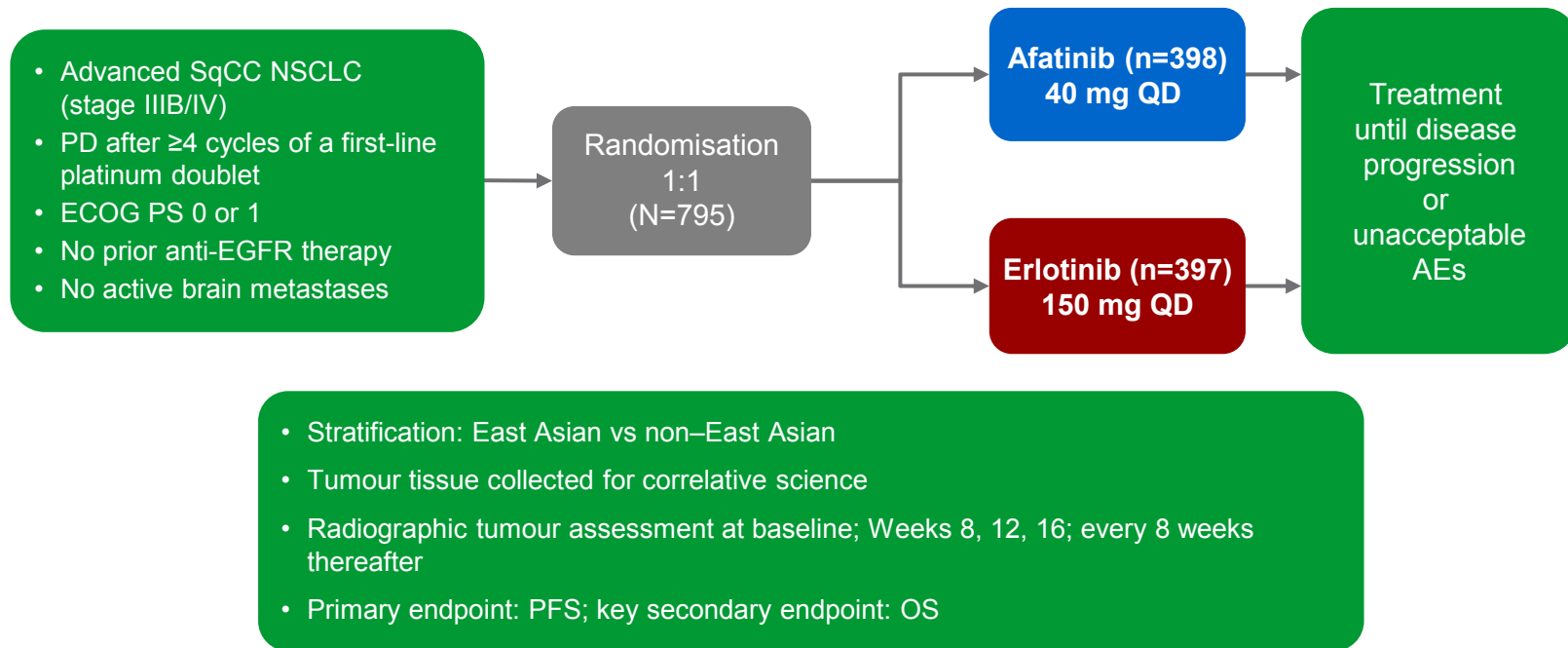
Afatinib Is the First Irreversible ErbB Family Blocker



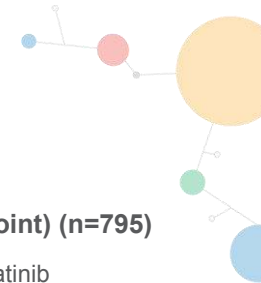
- Afatinib covalently binds and irreversibly blocks EGFR, HER2, and ErbB4^{2,3}
- Targeting the whole ErbB Family enhances the effect on important signaling pathways²



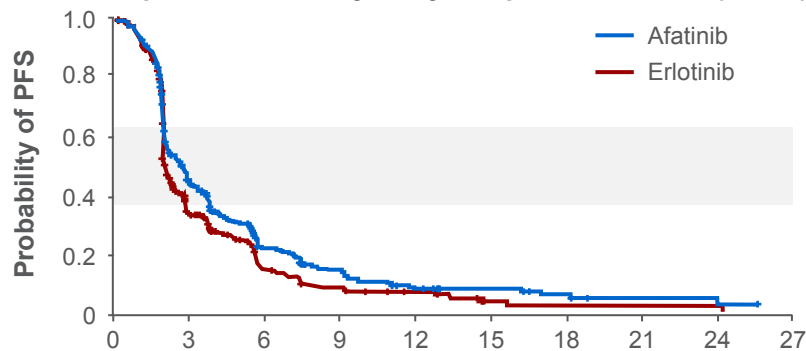
LUX-Lung 8 Study Design: Afatinib vs Erlotinib in SqCC of the Lung



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



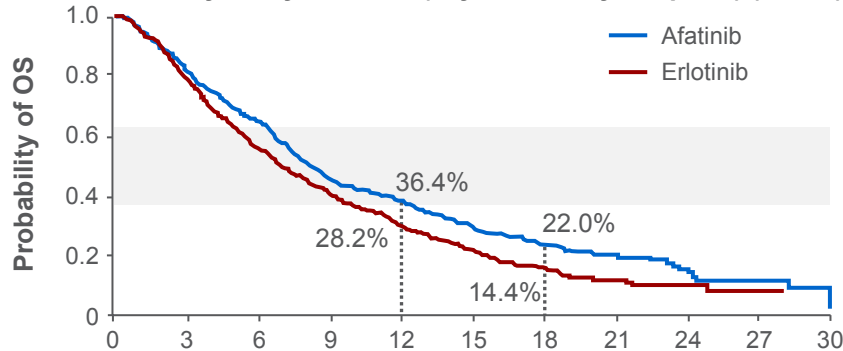
Updated PFS Analysis by Independent Review (n=795)



No. at risk	Months									
398	139	50	30	14	10	5	2	2	2	0
397	99	34	17	10	2	1	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	

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



No. at risk	Months									
398	316	249	170	124	82	47	28	10	4	0
397	305	210	150	94	54	30	11	4	2	0

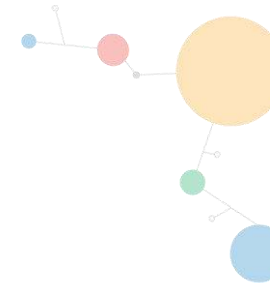
	Afatinib 40 mg QD (n=398)	Erlotinib 150 mg QD (n=397)
Patients died, n (%)	307 (77.1)	325 (81.9)
Median OS (months)	7.9	6.8
	HR 0.81; 95% CI: 0.69–0.95; P=0.0077	



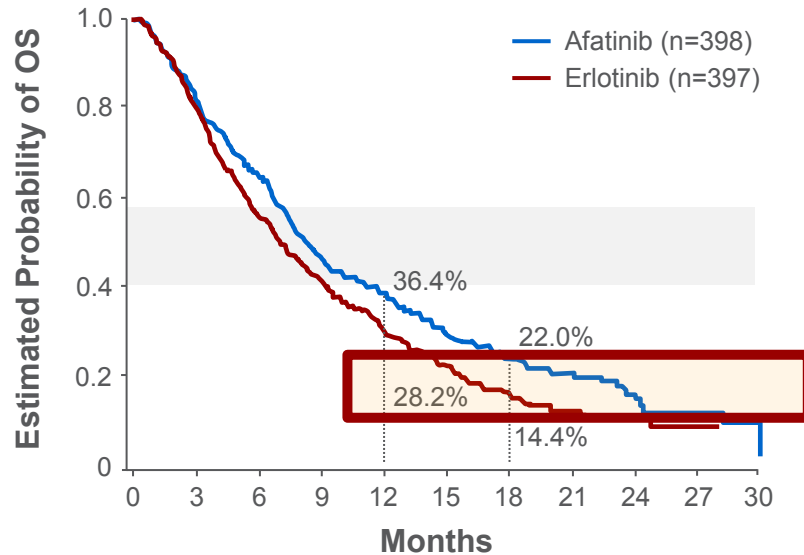
HR = hazard ratio.

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

Retrospective Analysis of LUX-Lung 8 Patients Deriving Long-term Benefit¹



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



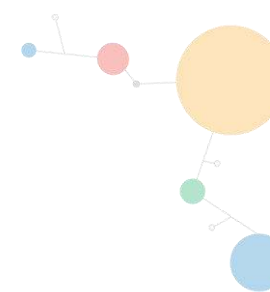
22% of Patients in the TGA Had *ERBB* Mutations

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

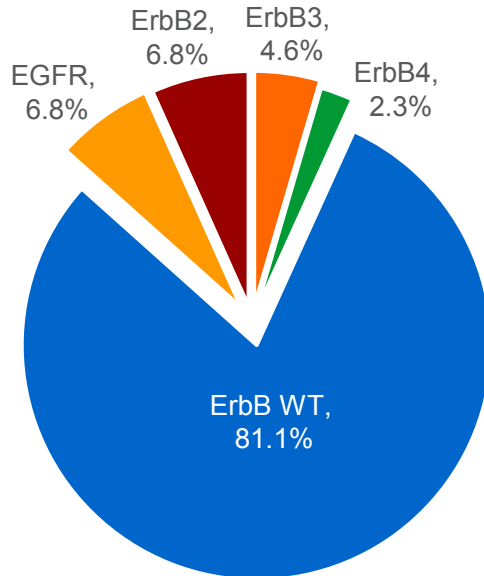
- 1 patient (0.4%) had EGFR, HER2, and HER3 mutations
- 2 patients (0.8%) had HER3 and HER4 mutations



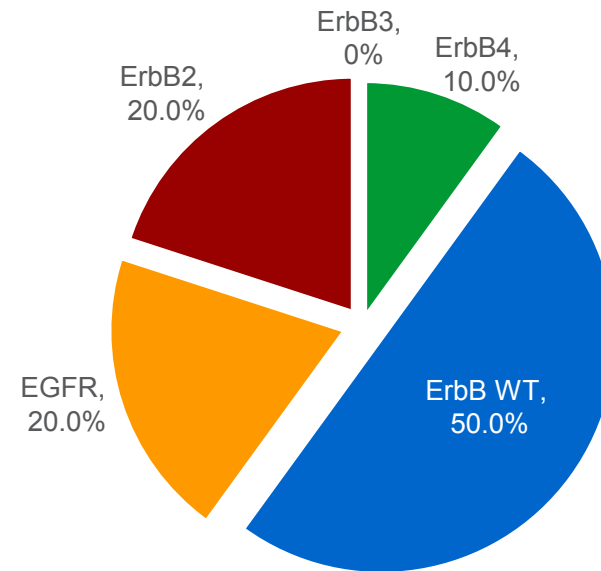
Genomic Aberrations in Patients Deriving Long-term Benefit



All Afatinib-Treated Patients (n=132^a)



Afatinib-Treated LTBs (n=10^a)

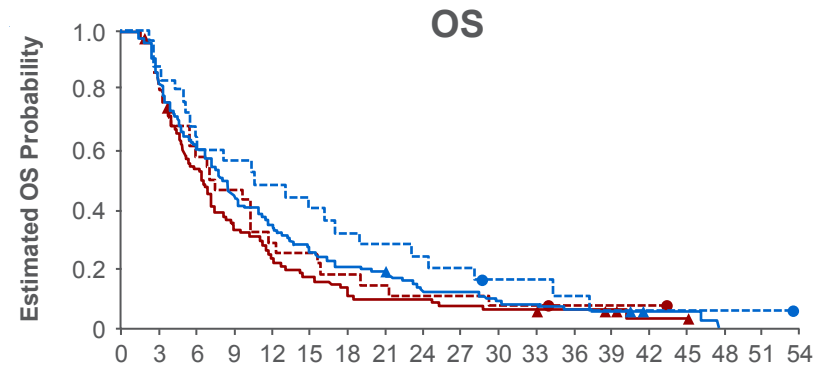
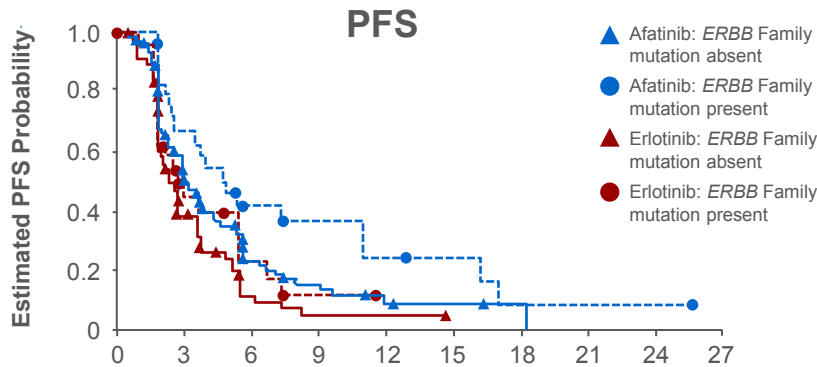
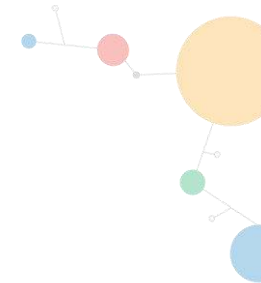


^aNext-generation sequencing was undertaken in 10/21 LTRs and 132/398 afatinib-treated patients overall; WT = wild-type.

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 Harboring *ERBB* Mutations



No. at risk

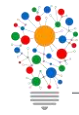
	0	3	6	9	12	15	18	21	24	27
Afatinib: absent	107	47	15	8	3	2	1	0	0	0
Afatinib: present	25	16	8	6	4	3	1	1	1	0
Erlotinib: absent	85	26	5	2	2	0	0	0	0	0
Erlotinib: present	28	9	4	1	0	0	0	0	0	0

No. at risk

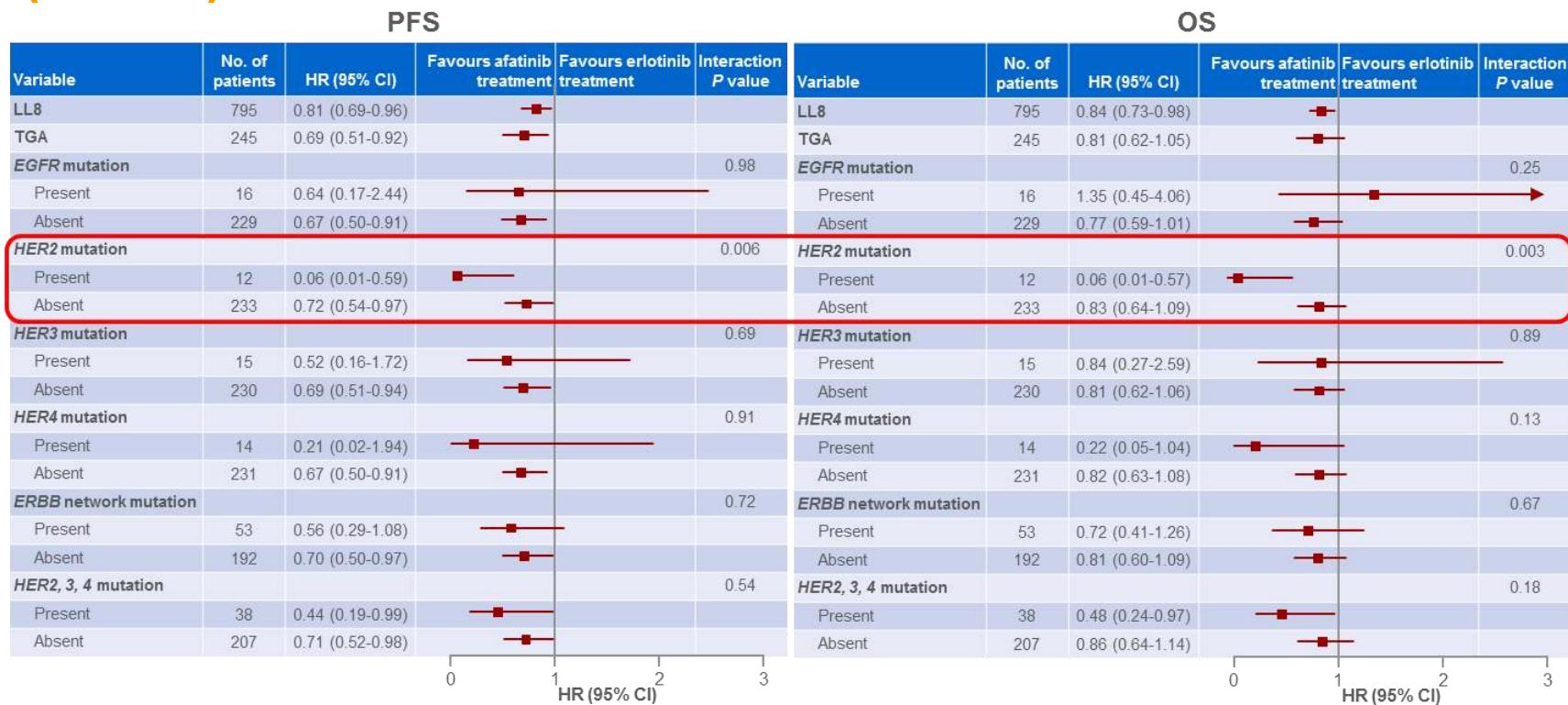
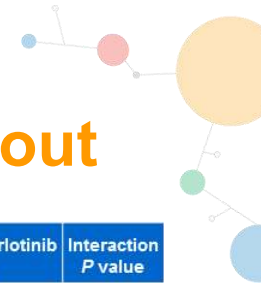
	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54
Afatinib: absent	107	88	65	48	37	28	22	20	13	12	9	8	6	5	2	2	0	0	0
Afatinib: present	25	22	15	14	12	10	8	7	6	5	3	3	2	1	1	1	1	1	0
Erlotinib: absent	85	69	44	27	19	14	11	8	8	6	5	5	4	3	1	1	0	0	0
Erlotinib: present	28	23	16	13	8	7	5	4	3	3	2	2	1	1	1	0	0	0	0

	Afatinib Present vs Absent	Erlotinib Present vs Absent
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

	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

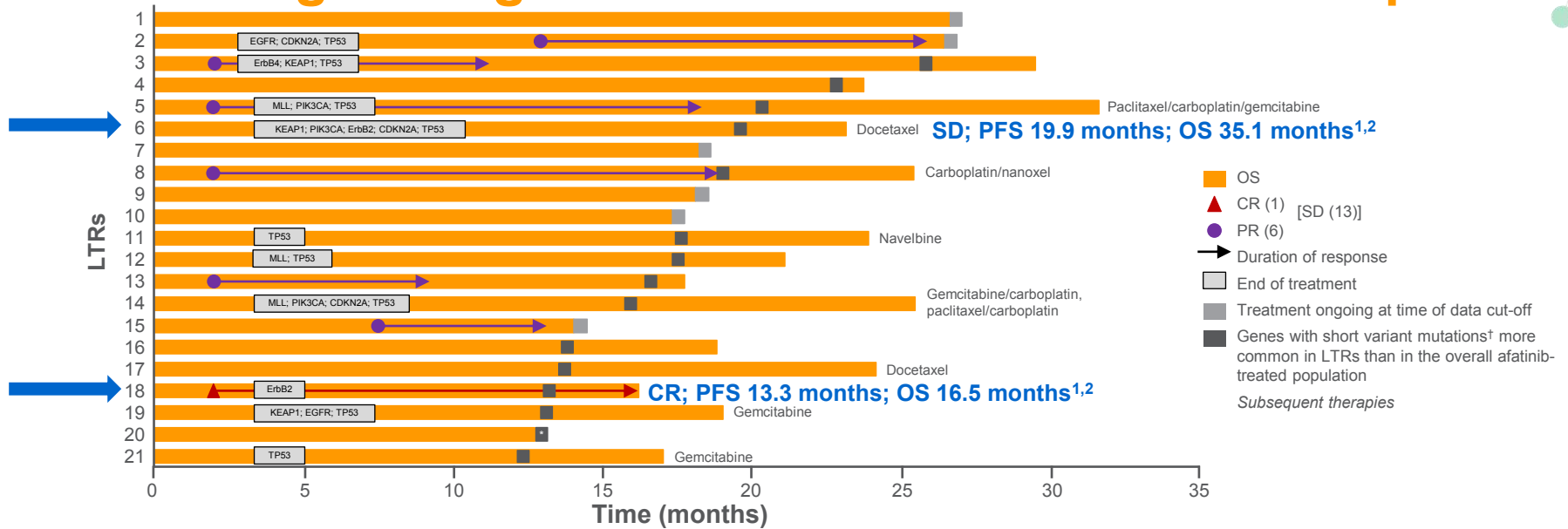


PFS and OS Were Longer in Patients With *HER* (*ERBB*) Mutation–Positive Tumours vs Those Without



LL8 = LUX-Lung 8; TGA = tumour genetic analysis.
 Goss GD et al. *JAMA Oncol*. doi: 10.1001/jamaoncol.2018.0775.

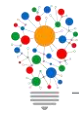
LUX-Lung 8 Long-Term Benefitters: Treatment Response



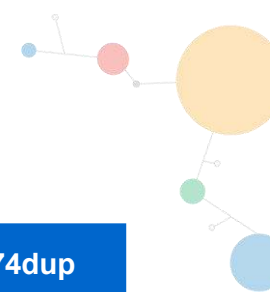
- Median OS was 21.1 mo (range: 12.9–31.6 mo); median PFS (independent central review) was 16.6 mo (range: 2.8–25.8 mo)¹
- **2 of the 10 long-term benefitters with tumor genetic analysis data available had a HER2 mutation¹**

*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.

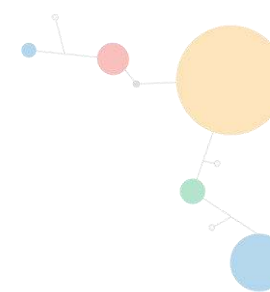


Recent Additional Trial on Activity of Afatinib in HER2 Exon 20-Mutated NSCLC



	All <i>HER2</i> 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

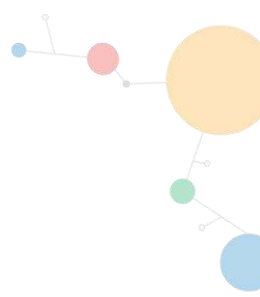




Summary and Conclusions

- Major differences exist between SqCC of the lung and ADC, including identification of treatable oncogene subsets
- LUX-Lung 8¹
 - 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 group²
 - Patients with *ErbB* mutation–positive tumours showed a more pronounced PFS and OS benefit with afatinib over erlotinib³





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

