Clinical Considerations in *EGFR* Mutation–Positive NSCLC: Does Treatment Sequence Matter?

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Faculty Disclosure

- Honoraria: AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Merck, Novartis, Pfizer

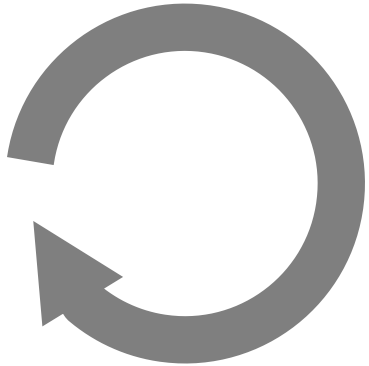
Choosing the Sequence in *EGFR*-Mutant NSCLC

Evidence #1

TKIs are standard up front but they are not equal

Evidence #3

Sequence affects survival



Evidence #2

Mutational subgroup/ resistance pattern determines treatment choice

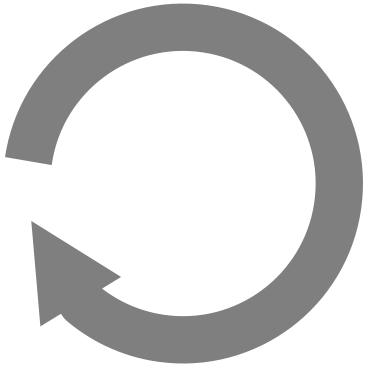
NSCLC = non–small cell lung cancer; TKI = tyrosine kinase inhibitor.

Girard. *Future Oncol*. 2018;14:1117.

Choosing the Sequence in *EGFR*-Mutant NSCLC

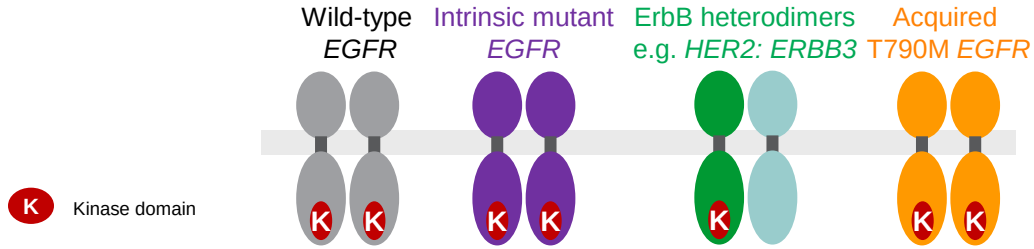
Evidence #1

TKIs are standard up front but they are not equal



Girard. *Future Oncol.* 2018;14:1117.

First-, Second-, and Third-Generation *EGFR* TKIs Are Not Equal: Activity Against *EGFR* Mutations



Erlotinib
Gefitinib

1st-generation TKI

EGFR inhibition

Activity range

- **Reversible** binding to wild-type and mutant EGFR
- **Inactive on T790M** mutant

Afatinib
Dacomitinib

2nd-generation TKI

ErbB family blockade

Activity range

- **Irreversible covalent binding** to EGFR, ErbB2 and ErbB4 to inhibit **all ErbB** family signalling
- Broader activity to overcome *EGFR* TKI-resistant mutations

Osimertinib

3rd-generation TKI

EGFR mutant-specific inhibitor

Activity range

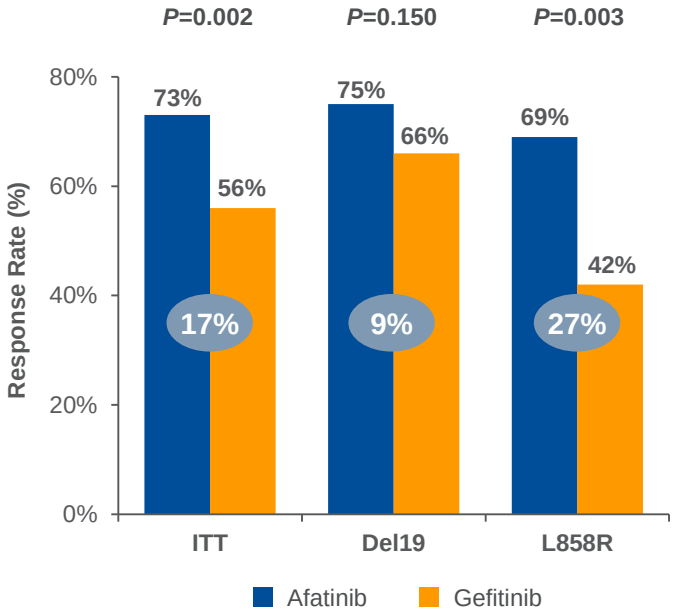
- Irreversible covalent binding to mutant EGFR
- Specificity for **EGFR T790M mutant**; EGFR **wild-type sparing**

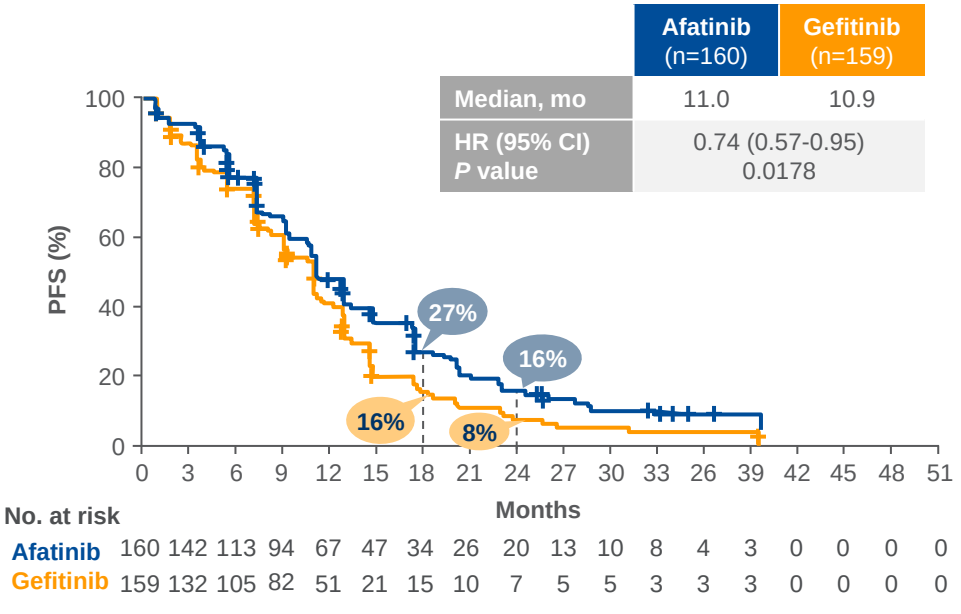
Drug	Metabolised by CYP Enzymes	Possible Drug-Drug Interactions
Erlotinib	✓	✓
Gefitinib	✓	✓
Afatinib	X	X
Dacomitinib	✓	✓
Osimertinib	✓	✓

Girard. *Future Oncol*. 2018;14:1117; Cross et al. *Cancer Discov*. 2014;4:1046; Li et al. *Oncogene*. 2008;27:4702; Peters et al. *Cancer Treat Rev*. 2014;40:917; TAGRISSO Prescribing Information. March 2017.

First- and Second-Generation EGFR TKIs Are Not Equal: LUX-Lung 7

LUX-Lung 7: Afatinib vs gefitinib as first-line treatment of patients with *EGFR* mutation–positive NSCLC: a phase 2B, open-label, randomised controlled trial





	Afatinib (n=160)	Gefitinib (n=159)
Median, mo	11.0	10.9
HR (95% CI) *P* value	0.74 (0.57-0.95) 0.0178	

PFS = progression-free survival; HR = hazard ratio; CI = confidence interval.

Corral et al. *Ann Oncol*. 2017;28 (suppl 2):ii28.

First- and Second-Generation EGFR TKIs Are Not Equal: ARCHER 1050

ARCHER 1050: Dacomitinib vs gefitinib as first-line treatment of patients with EGFR mutation–positive NSCLC: a phase 3, open-label, randomised trial (excluding CNS metastases)

- Advanced NSCLC with *EGFR*-activating mutation(s)
- No prior systematic treatment of advanced NSCLC
- No CNS metastasis
- No prior *EGFR* TKI or other TKI
- ECOG PS 0, 1

→ **R 1:1** (N=452)

- **Dacomitinib 45 mg PO QD** (n=227)
- **Gefitinib 250 mg PO QD** (n=225)

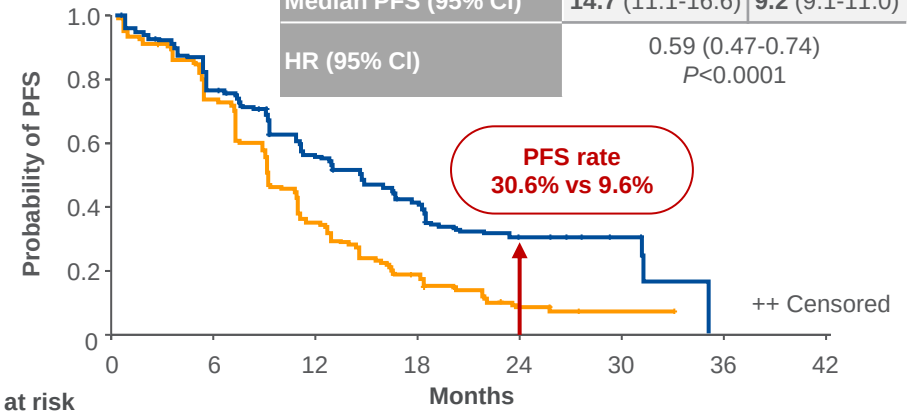
Primary end point

PFS by blinded independent review

- ≥256 PFS events
- PFS HR ≤0.667 (50%↑)
- 90% power
- 1-sided α=0.025
- mPFS: 14.3 vs 9.5 months

PFS: Blinded Independent Review (ITT Population)

	Daco (n=227)	**Gef** (n=225)
Events, n (%)	136 (59.9%)	179 (79.6%)
Median PFS (95% CI)	**14.7** (11.1-16.6)	**9.2** (9.1-11.0)
HR (95% CI)	0.59 (0.47-0.74) *P*<0.0001	



No. at risk								
Dacomitinib	227	154	106	73	20	6	0	0
Gefitinib	225	155	69	34	7	1	0	0

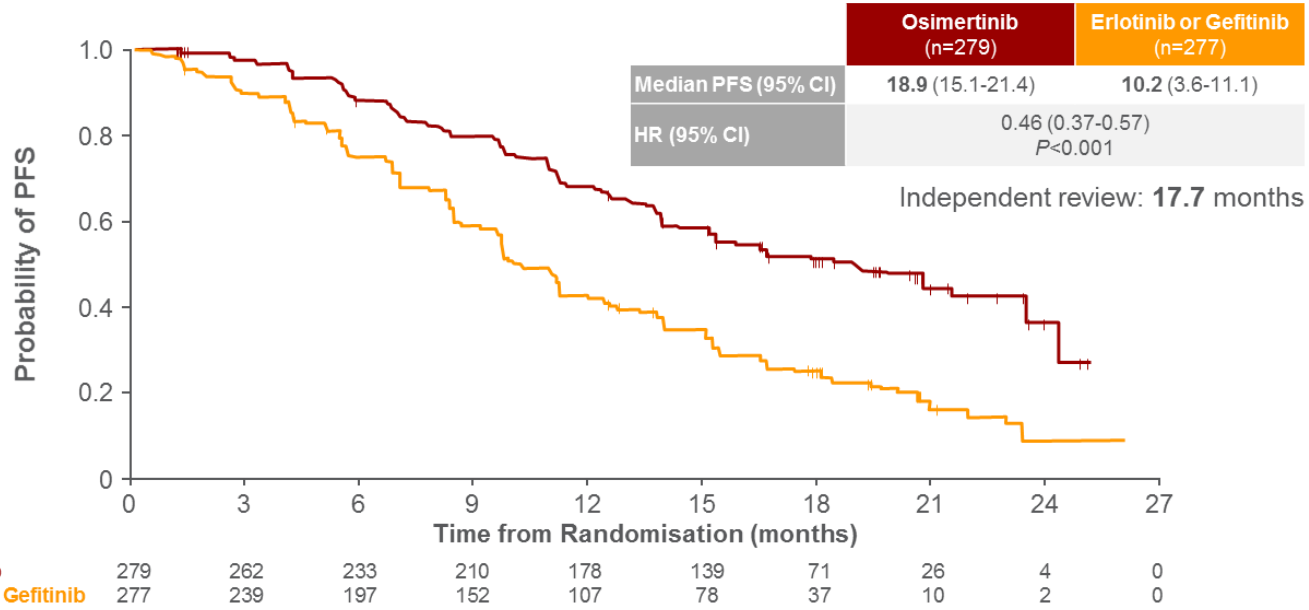
CNS = central nervous system; ECOG PS = Eastern Cooperative Oncology Group performance status; R = randomised; PO = orally; QD = once daily; mPFS = median progression-free survival; ITT = intent-to-treat.

ClinicalTrials gov. https://clinicaltrials.gov/ct2/show/NCT01774721. Accessed March 16, 2018; Mok et al. *J Clin Oncol*. 2017;35(suppl 18):LBA9007; Wu et al. *Lancet Oncol*. 2017;18:1454.

First- and Second-Generation EGFR TKIs Are Not Equal: FLAURA

FLAURA: Osimertinib vs erlotinib or gefitinib as first-line treatment of patients with *EGFR* mutation–positive NSCLC: a phase 3, double-blind, randomised trial

Primary endpoint: PFS (By investigator assessment)



Date cut-off 12 Jun 2017. Tick marks indicate censored data. "For statistical significance, *P*-value of less than 0.0015, determined by O'Brien Planning approach was required.
CI = confidence interval; DCO = data cut-off; HR = hazard ratio; NS = not significant; PFS = progression-free survival.
Soria J-C et al. *N Engl J Med*. 2018;378:113.

First-, Second-, and Third-Generation EGFR TKIs Are Not Equal: Safety

Second- or Third-Generation TKIs vs First-Generation TKIs

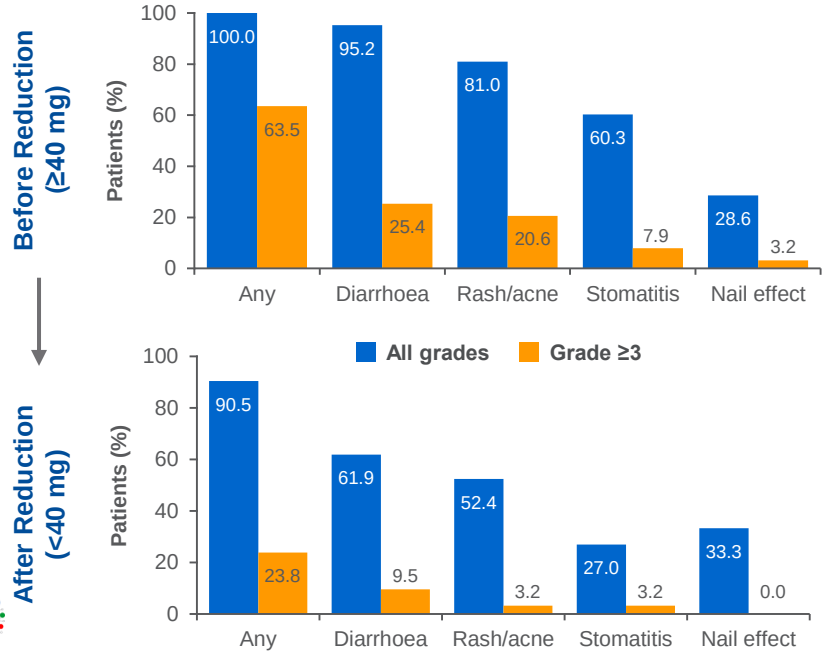
	LUX-Lung 7[1,2]		ARCHER 1050[3]		FLAURA[4]	
	Afatinib (n=160)	**Gefitinib** (n=159)	**Dacomitinib** (n=227)	**Gefitinib** (n=225)	**Osimertinib** (n=279)	**First-gen TKI** (n=277)
Treatment discontinuation rate	**6%**	**6%**	**10%**	**7%**	**10%**	**14%**
Most common grade ≥3 AEs	Diarrhoea, 12% Rash/acne, 9%	Liver enzyme elevation, 9% Rash/acne, 3%	Acne, 14% Diarrhoea, 8% Paronychia, 7%	Liver enzyme elevation, 12% Dyspnoea, 3%	Diarrhoea, 2% Decreased appetite, 2%	Rash/acne, 7% Liver enzyme elevation, 12%

AE = adverse event.

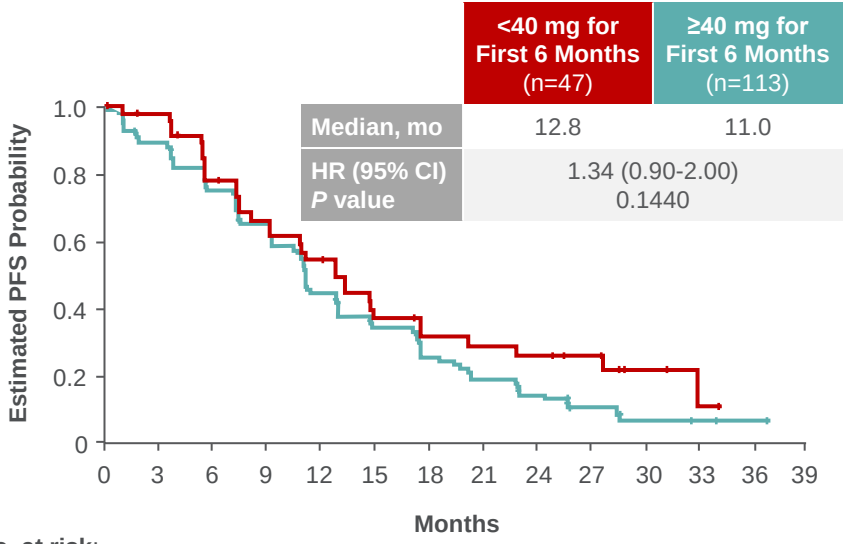
1. Park et al. *Lancet Oncol*. 2016;17:577; 2. Paz-Ares et al. *Ann Oncol*. 2017;28:270; 3. Wu et al. *Lancet Oncol*. 2017;18:1454; 4. Soria et al. *N Engl J Med*. 2018;378:113.

Dose Reduction of Afatinib Reduced Drug-Related AEs Without Compromising Efficacy

Treatment-Related AEs in Patients Who Had a Dose Reduction From 40 mg (n=63)



PFS in Patients Who Received a Dose Reduction Within the First 6 Months of Treatment



	<40 mg for First 6 Months (n=47)	≥40 mg for First 6 Months (n=113)
Median, mo	12.8	11.0
HR (95% CI) *P* value	1.34 (0.90-2.00) 0.1440	

No. at risk:

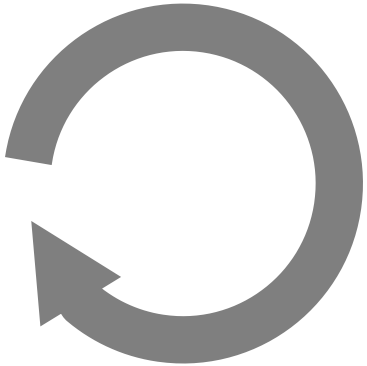
<40 mg	47	45	34	28	22	15	11	10	9	7	3	1	0	0
≥40 mg	113	97	78	66	45	32	23	17	12	6	3	2	1	0

Hirsh et al. *J Clin Oncol*. 2016;34(suppl 15):9046.

Choosing the Sequence in *EGFR*-Mutant NSCLC

Evidence #1

TKIs are standard up front but they are not equal



Evidence #2

Mutational subgroup/ resistance pattern determines treatment choice

Girard. *Future Oncol.* 2018;14:1117.

First-Line: PFS Efficacy of TKIs Is Different in *EGFR* del19/L858R Mutations

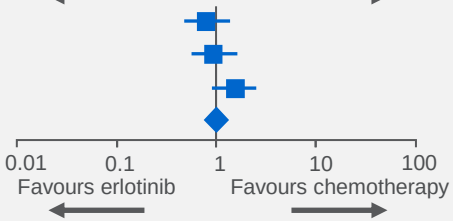
- Impact of specific *EGFR* mutations and clinical characteristics on outcomes after treatment with *EGFR* TKIs vs chemotherapy in *EGFR* M+ lung cancer: a meta-analysis

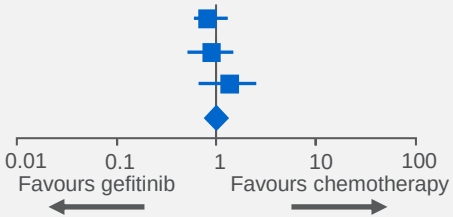
Trial	HR	95% CI	HR	95% CI
	Exon 19 deletion		Exon 21 L858R substitution	
ENSURE	0.20	0.12-0.33	0.54	0.32-0.91
EURTAC	0.27	0.17-0.43	0.53	0.29-0.97
LUX-Lung 3	0.28	0.18-0.44	0.73	0.46-1.16
LUX-Lung 6	0.20	0.13-0.32	0.32	0.19-0.54
NEJ002	0.24	0.15-0.38	0.33	0.20-0.54
OPTIMAL	0.13	0.07-0.24	0.26	0.14-0.48
WJTOG 3405	0.42	0.26-0.66	0.69	0.44-1.07
All	0.24	0.20-0.29	0.48	0.39-0.58

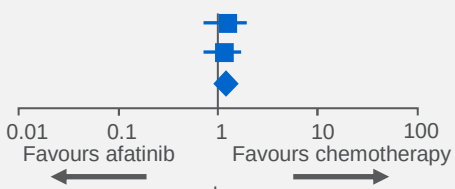
Lee et al. *J Clin Oncol*. 2015;33:1958.

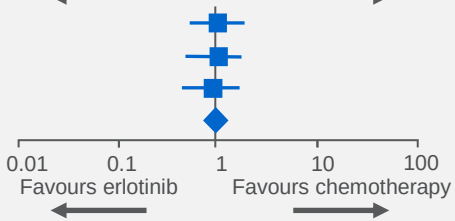
First-Line: OS Efficacy of TKIs Is Different in *EGFR* del19/L858R Mutations

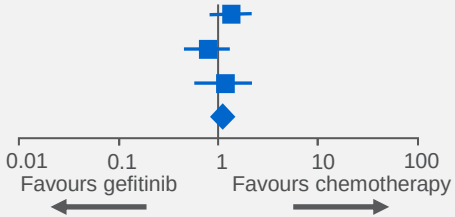
Agent	Study	HR (95% CI)	Del19	HR (95% CI)	L858R
Afatinib	LUX-Lung 3	0.53 (0.36-0.79)		1.30 (0.80-2.11)	
	LUX-Lung 6	0.64 (0.44-0.94)		1.22 (0.81-1.83)	
	Total	**0.59 (0.45-0.77)**		**1.25 (0.91-1.71)**	
Erlotinib	ENSURE	0.79 (0.48-1.30)		1.05 (0.60-1.84)	
	EURTAC	0.94 (0.57-1.54)		1.00 (0.56-1.79)	
	OPTIMAL	1.52 (0.91-2.52)		0.92 (0.55-1.54)	
	Total	**1.04 (0.71-1.51)**		**0.98 (0.72-1.35)**	
Gefitinib	IPASS	0.86 (0.61-1.22)		1.40 (0.91-2.15)	
	NEJ002	0.83 (0.52-1.34)		0.82 (0.49-1.38)	
	WJTOG3405	1.19 (0.65-2.18)		1.11 (0.60-2.05)	
	Total	**0.90 (0.70-1.17)**		**1.11 (0.81-1.54)**	











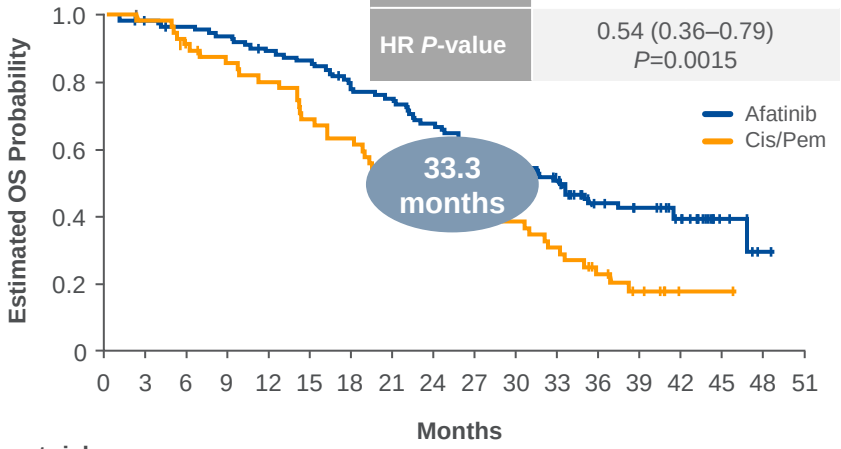
OS = overall survival.

Kato et al. *Value Health.* 2015;18:A436.

LUX-Lung 3 and LUX-Lung 6: OS in Del19 Subgroup (Prespecified Endpoint)

LUX-Lung 3

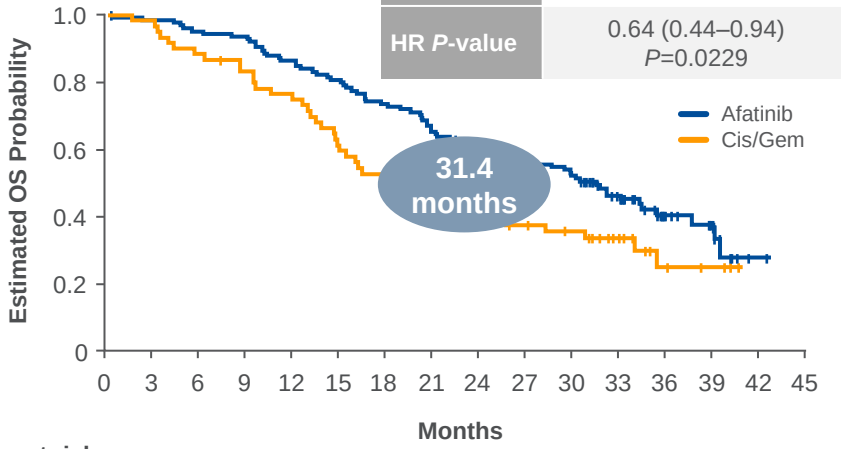
	Afatinib (n=112)	Cis/Gem (n=57)
Median, mo	33.3	21.1
HR *P*-value	0.54 (0.36–0.79) *P*=0.0015	



No. at risk:																	
Afatinib	112	108	105	102	96	93	83	80	72	62	58	51	34	30	21	6	1	0
Cis/Gem	57	55	50	46	43	37	33	27	25	22	20	16	10	6	1	1	0	0

LUX-Lung 6

	Afatinib (n=124)	Cis/Gem (n=62)
Median, mo	31.4	18.4
HR *P*-value	0.64 (0.44–0.94) *P*=0.0229	

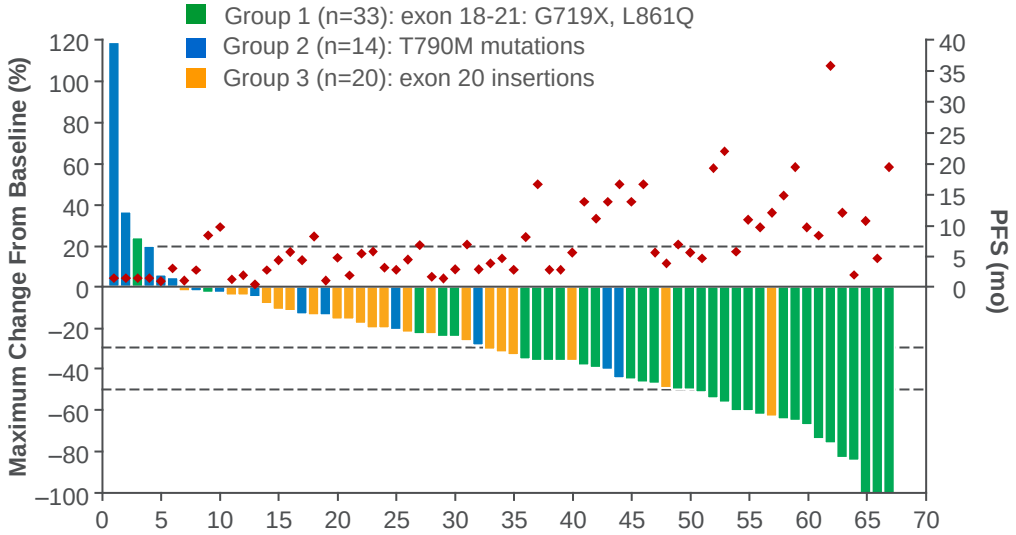


No. at risk:																	
Afatinib	124	122	118	115	106	99	90	80	73	69	59	39	16	8	1	0	
Cis/Gem	62	58	53	49	44	35	30	28	26	21	18	11	4	3	0	0	

Yang et al. *Lancet Oncol*. 2015;16:141-151.

First-Line: Afatinib Is Effective for Uncommon *EGFR* Mutations

- Clinical activity of afatinib in patients with advanced NSCLC harbouring uncommon *EGFR* mutations: a combined post hoc analysis of LUX-Lung 2, 3, and 6



Patient index sorted by maximum % decrease in descending order

	T790M (n=14)	Exon 20 Ins (n=23)	Mut/Dup Exon 18-21 (n=38)	G719X (n=18)	L861Q (n=16)	S768I (n=8)
Response rate (%)	14.3	8.7	71.1	77.8	56.3	100.0
PFS (mo)	2.9	2.7	10.7	13.8	8.2	14.7
OS (mo)	14.9	9.2	19.4	26.9	17.1	NE

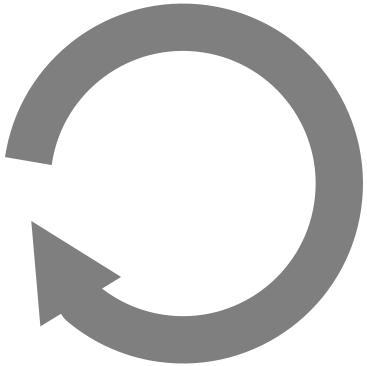
Note: A patient may be presented in more than 1 category.

Yang et al. *Lancet Oncol*. 2015;16:830.

Choosing the Sequence in *EGFR*-Mutant NSCLC

Evidence #1

TKIs are standard up front but they are not equal



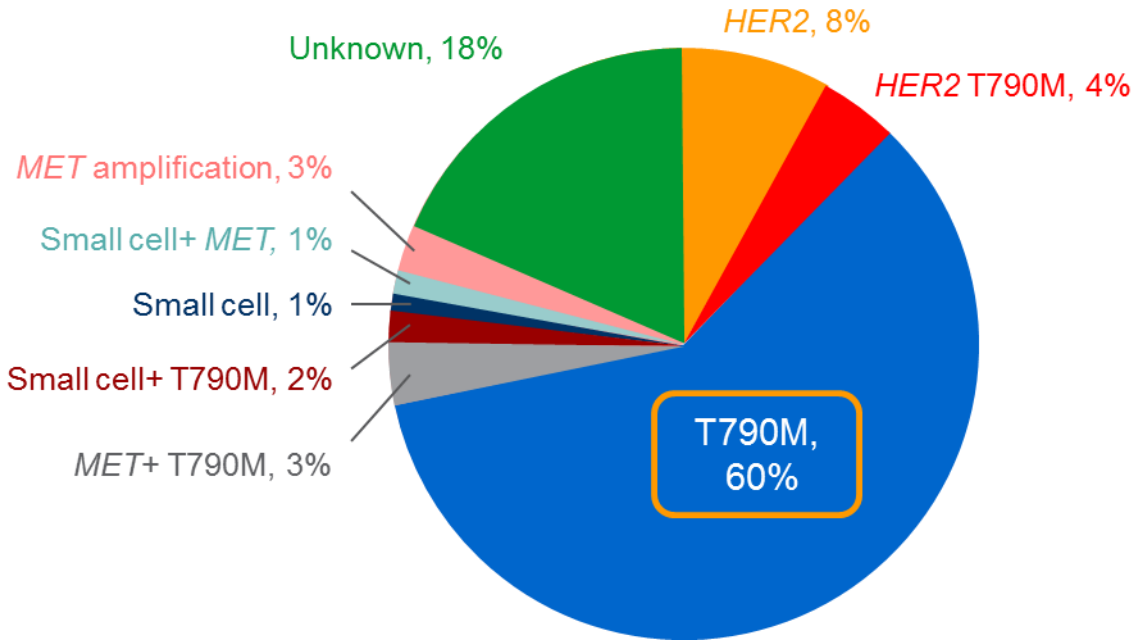
Evidence #2

Mutational subgroup/ resistance pattern determines treatment choice

Girard. *Future Oncol.* 2018;14:1117.

Molecular Mechanisms of Acquired Resistance to First- and Second-Generation EGFR TKIs

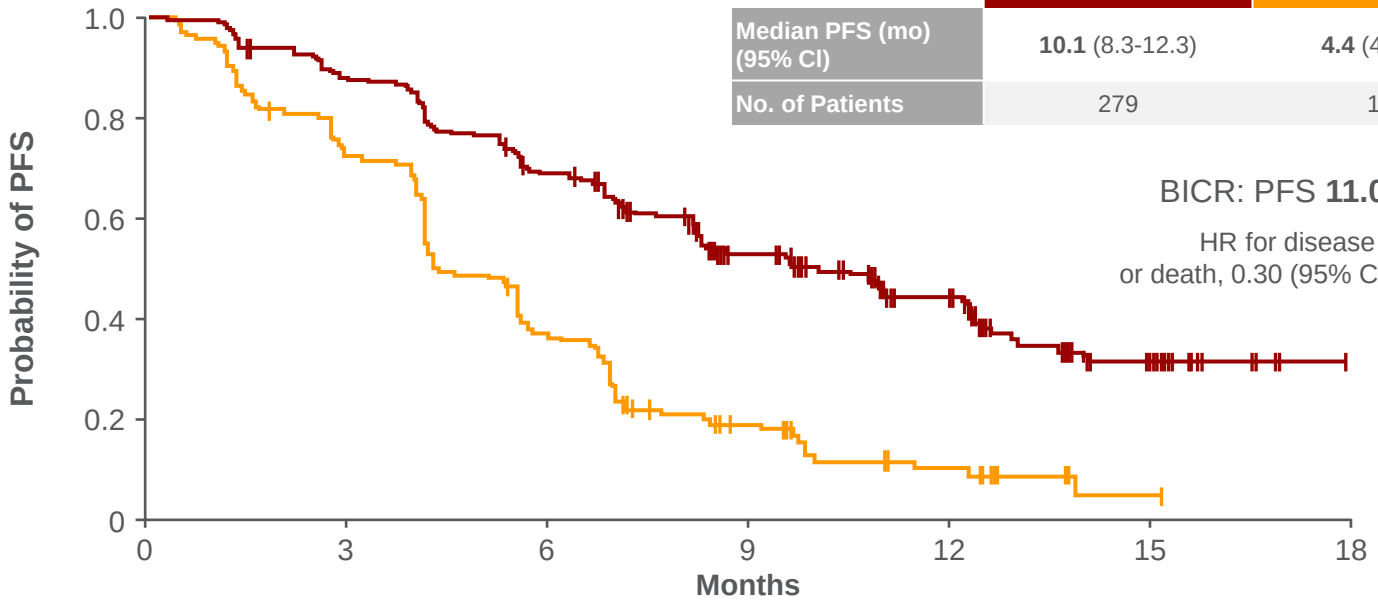
- 155 *EGFR*-mutant NSCLC, acquired resistance after TKI
- Molecular analyses on rebiopsy specimen



Yu et al. *Clin Cancer Res*. 2013;19:2240.

AURA 3: Osimertinib Standard of Care for T790M+ Acquired Resistance to First- and Second-Generation *EGFR* TKIs

	Osimertinib	Platinum/pemetrexed
Median PFS (mo) (95% CI)	**10.1** (8.3-12.3)	**4.4** (4.2-5.6)
No. of Patients	279	140



BICR: PFS **11.0** months

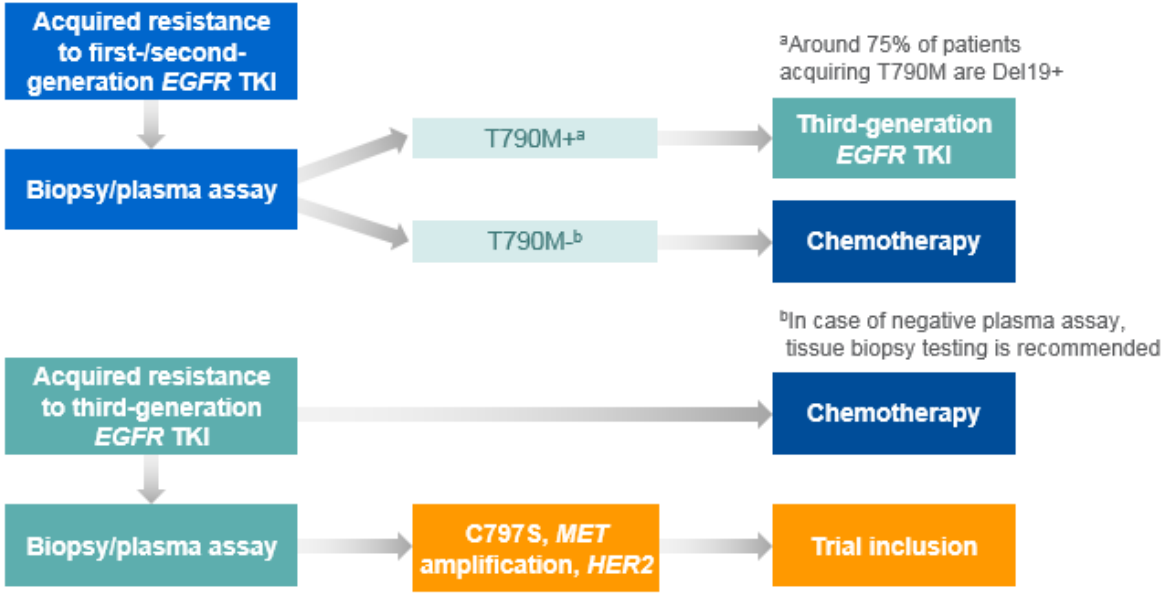
HR for disease progression or death, 0.30 (95% CI, 0.23-0.41)

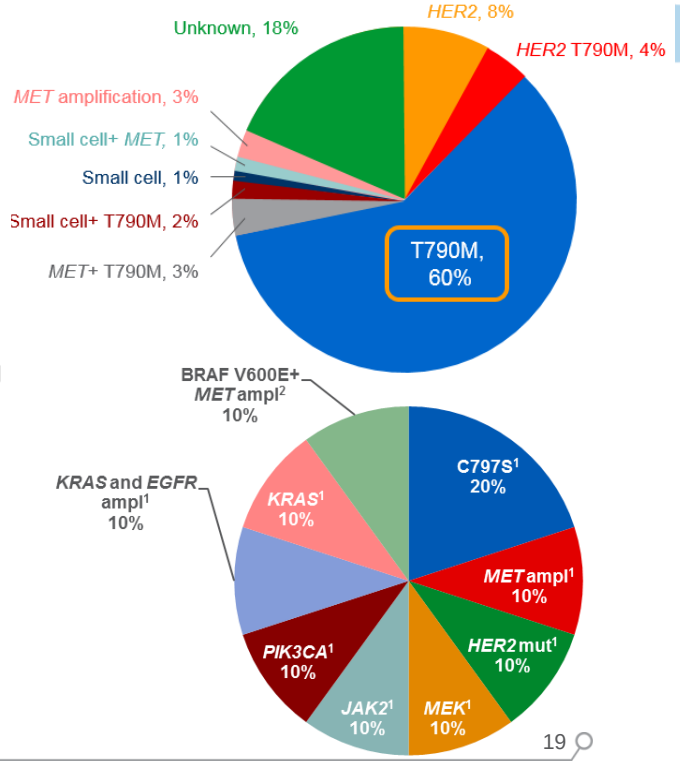
P<0.001

No. at risk							
Osimertinib	279	240	162	88	50	13	0
Platinum/pemetrexed	140	93	44	17	7	1	0

Mok et al. *N Engl J Med*. 2017;376:629.

Biopsy or Plasma May be Used to Determine *EGFR* T790M Status





Oxnard et al. *J Clin Oncol.* 2016;34:3375; Jenkins S et al. *J Thorac Oncol*. 2017;12:1061.

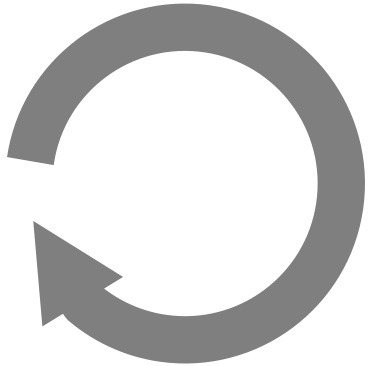
Choosing the Sequence in *EGFR*-Mutant NSCLC

Evidence #1

TKIs are standard up front but they are not equal

Evidence #3

Sequence affects survival

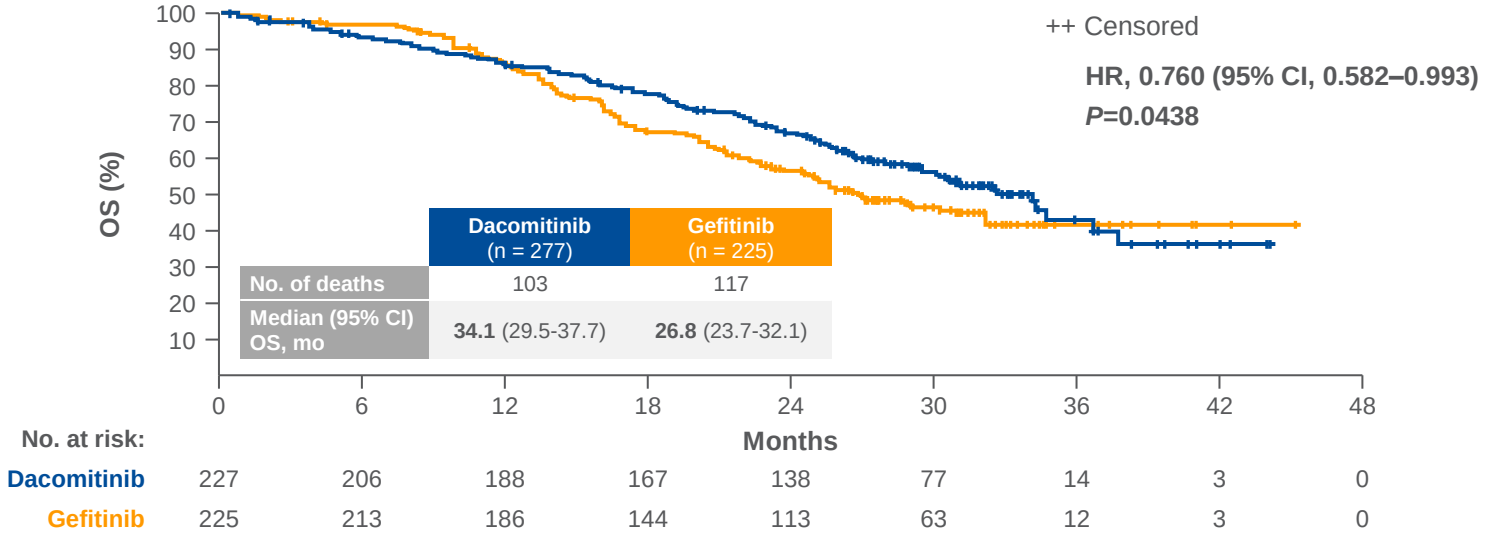


Evidence #2

Mutational subgroup/ resistance pattern determines treatment choice

Girard. *Future Oncol*. 2018;14:1117.

OS in *EGFR*-Mutant NSCLC: ARCHER 1050 Trial (Excluding Brain Metastases)

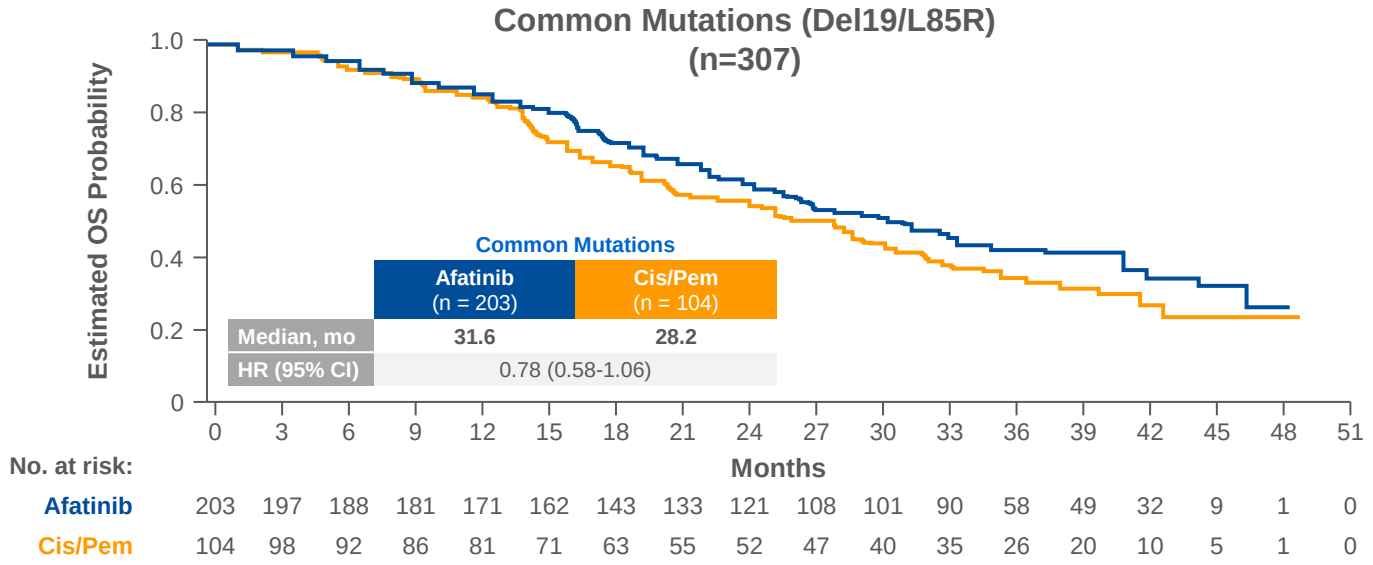


- Third-generation *EGFR* TKIs were used as a first subsequent therapy in 22 patients (9.7%) in the dacomitinib arm and in 25 patients (11.1%) in the gefitinib arm
- Median OS in patients subsequently treated with third-generation TKIs was **36.7** (95% CI: 30.1-NR) months in the dacomitinib arm

NR = not reported.

Mok et al. *J Clin Oncol*. 2018;36:2244.

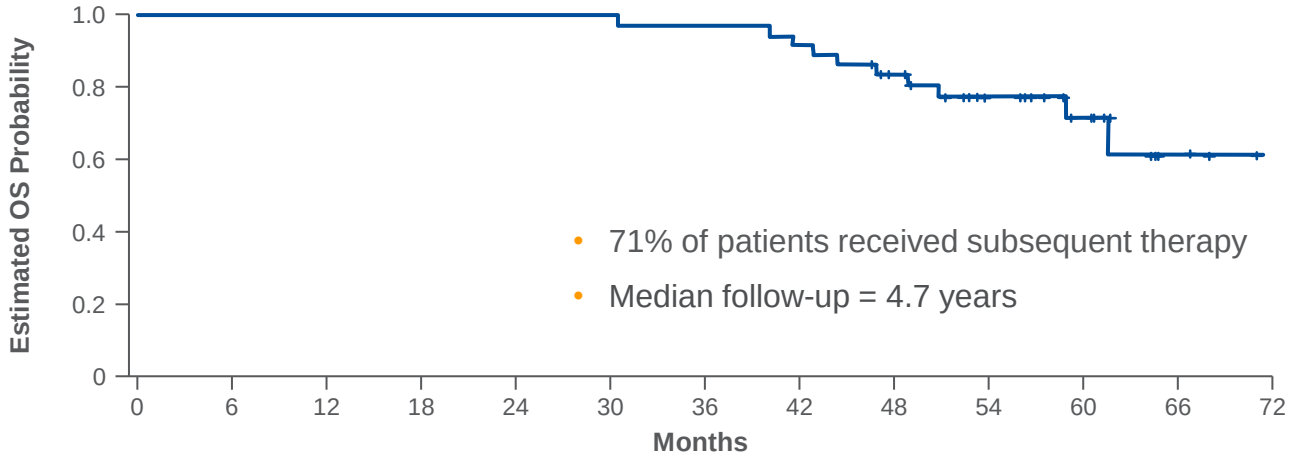
OS in *EGFR*-Mutant NSCLC: LUX-Lung 3 Trial



- OS was up to **41.5 months in del19** patients in countries with a **universal healthcare reimbursement** policy

Yang et al. *Lancet Oncol*. 2015;16:141.

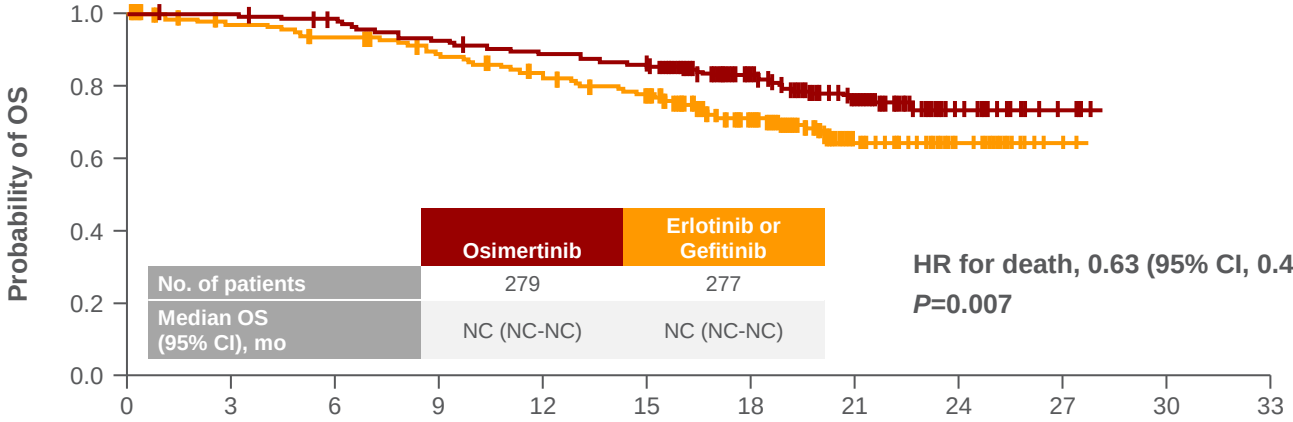
OS in Patients in LUX-Lung 3, 6, and 7 Treated Subsequently With Osimertinib



No. at risk:												
Afatinib	37	37	37	37	37	37	36	35	28	20	12	3	0

Sequist et al. *Ann Oncol*. 2017;28(suppl 2):ii28.

OS in Patients Treated With First-Line Osimertinib

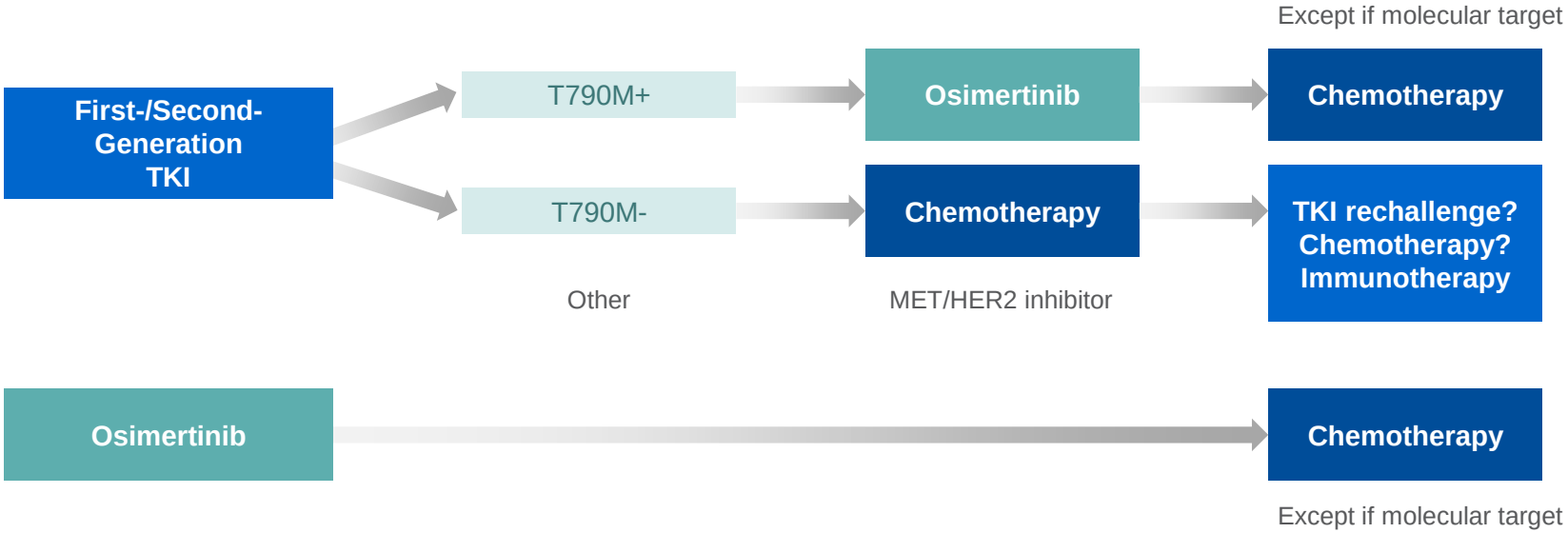


FLAURA OS DATA ARE IMMATURE (25% MATURITY)

NC = not calculable.

Soria et al. *N Engl J Med*. 2018;378:113.

Treatment Sequences in *EGFR*-Mutant NSCLC After First-Line *EGFR* TKI



NEED MATURE OS AND TREATMENT SEQUENCES FROM FLAURA and AURA 3

Girard. *Future Oncol*. 2018;14:1117.

How Do We Optimise Sequence?

Clinical factors

- CNS disease and progression
  - Data for afatinib and osimertinib show delay in onset and progression of CNS metastases
- Loss of patients from one line to another
- Treatment of oligoprogression, treatment beyond PD

Optimisation of treatments

- Antiangiogenics
- Anti-*EGFR* antibodies
- Chemotherapy + TKI

Understanding of biology

- *EGFR* mutational subgroups (eg, del19, L858R, uncommon mutations) determine treatment choice
- Resistance mechanisms impact subsequent therapy choice

PD = disease progression.

Choosing the Sequence in *EGFR*-Mutant NSCLC

Evidence #1

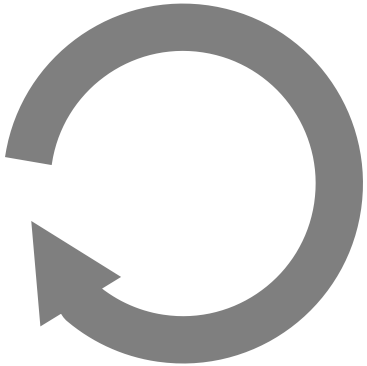
TKIs are standard up front but they are not equal

Evidence #2

Mutational subgroup/ resistance pattern determines treatment choice

Evidence #3

Sequence makes survival



Girard. *Future Oncol*. 2018;14:1117.