8TH ANNUAL PUERTO RICO WINTER CANCER SYMPOSIUM

IMMUNOTHERAPY AND TARGETED THERAPY:
"Moving Forward In The Oncology Practice"

"New Landscape of Mutant *EGFR* & *ALK* Lung Cancer Patients"

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Speaker's Disclosure

Speaker Bureau: Genentech, Merck, Pfizer, Novartis, Takeda, Celgene, Astrazeneca, Boehringer-Ingelheim, Amgen

Consultancy: None

Royalties: None

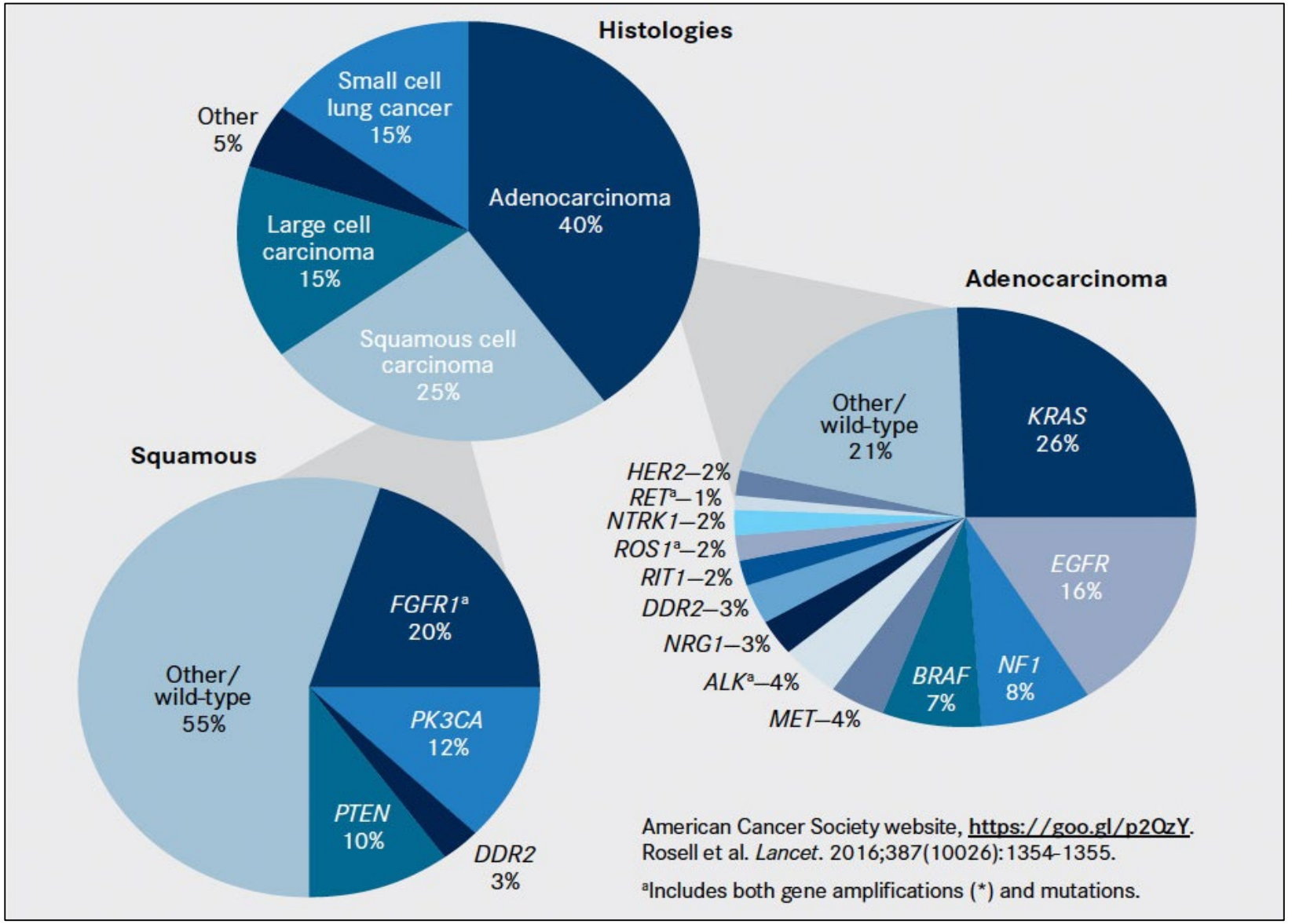
Research: None

Employment: None

Stocks: None

Other: None

Lung Cancer Subtypes and Molecular Drivers



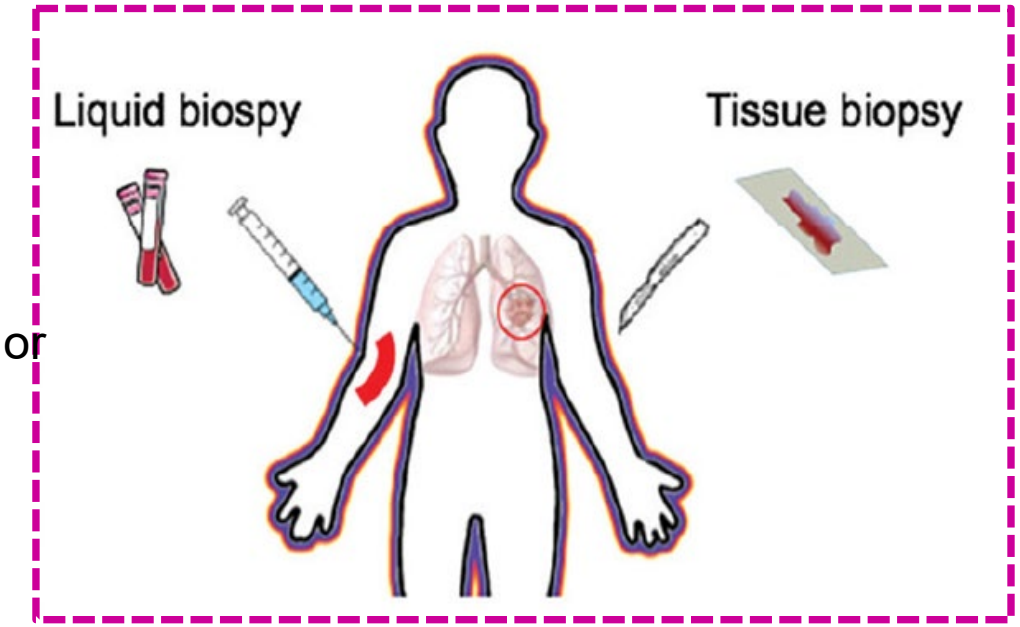
American Cancer Society website, https://goo.gl/p2QzY.
Rosell et al. *Lancet*. 2016;387(10026):1354-1355.

[a]Includes both gene amplifications (*) and mutations.

Comprehensive Genomic Profiling— Is Key!!
Liquid or Tissue

Liquid Biopsy

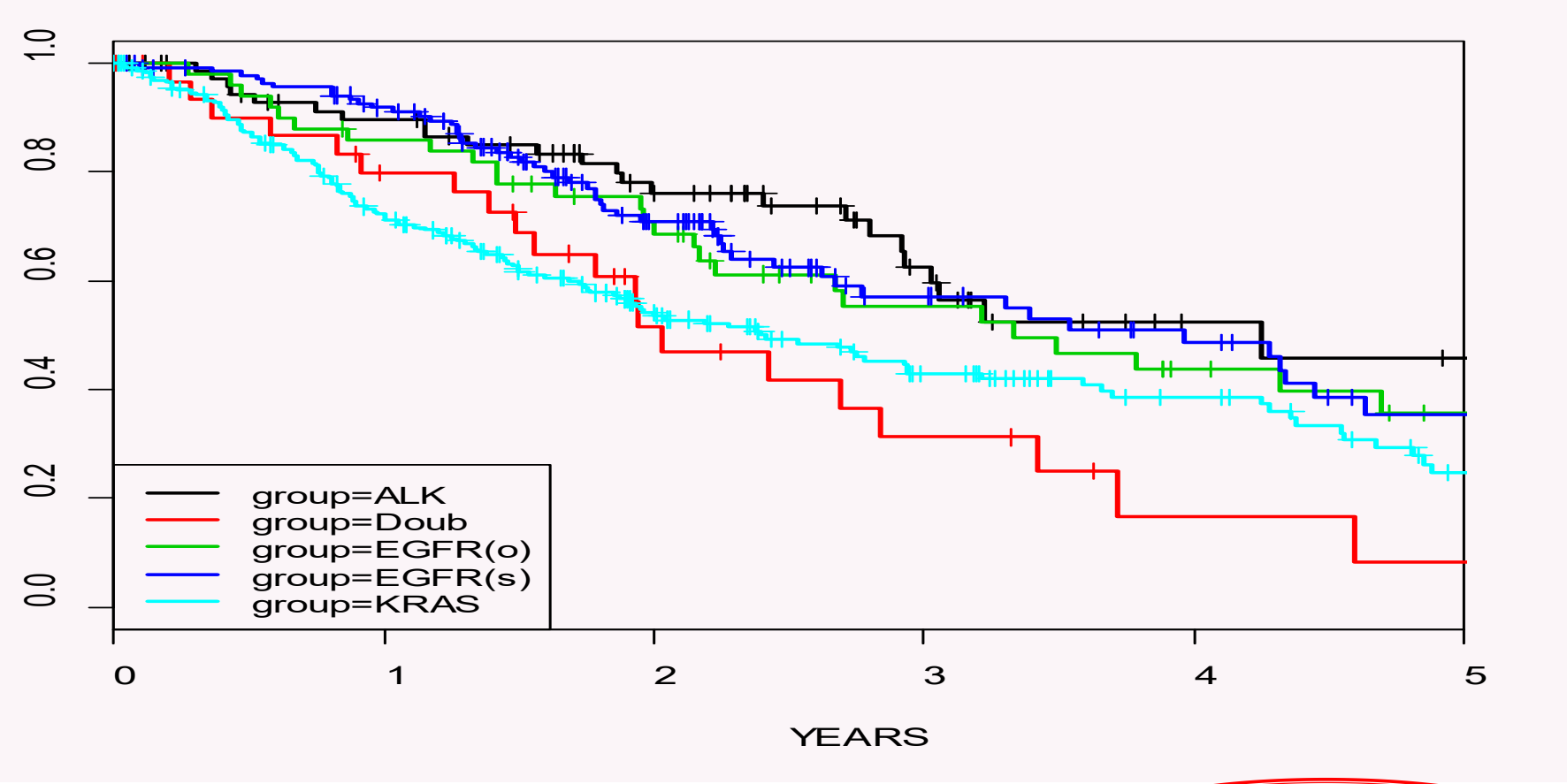
- Non-invasive blood test
- "Summation" of tumor heterogeneity
- Potential for periodic monitoring for response or resistance
- Speed



Tissue Biopsy

- Gold standard
- Invasive procedure
- Tissue accessibility
- Limited to biopsied tissue only
- Clinical complications
- Cost
- Time

NSCLC Survival with the 5 Most Frequent Oncogenic Drivers



LUNG CANCER MUTATION CONSORTIUM

Matching Patients with the Best Possible Therapies

Kris and Johnson; JAMA 2014

Altered Gene	N	Median Survival (95% CI)
EGFR (sensitizing)	140	4.0 years (2.7 to 5.4)
EGFR (other)	50	3.3 years (2.2 to 6.2)
ALK	73	4.3 years (3.0 to NA)
KRAS	231	2.4 years (1.9 to 3.6)
Drivers in Two Genes	32	2.0 years (1.6 to 4.6)

EGFR

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Randomized Studies of First Line EGFR TKI in Patients with EGFR Mutations

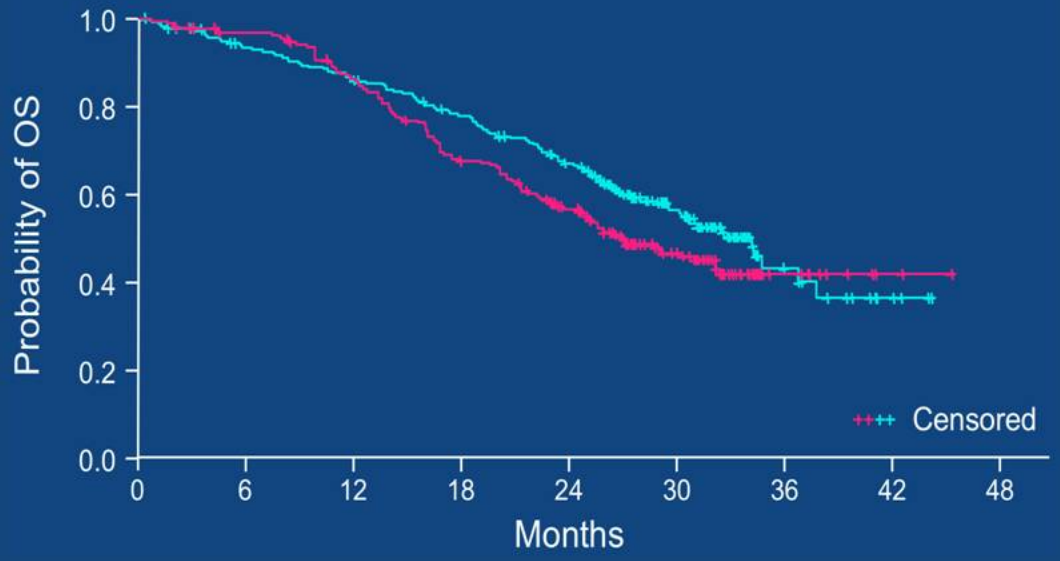
Author	Study	Agent	N (EGFRm+)	RR	Median PFS (months)	Median OS (months)
Mok et al.	IPASS	Gef	261	71.2% vs 47.3%	9.8 vs 6.4	21.6 vs 21.9
Lee et al.	First-SIGNAL	Gef	42	84.6% vs 37.5%	8.4 vs 6.7	27.2 vs 25.6
Mitsudomi et al.	WJTOG 3405	Gef	177	62.1% vs 32.2%	9.2 vs 6.3	35.5 vs 38.8
Maemondo et al.	NEJGSG002	Gef	230	73.7% vs 30.7%	10.8 vs 5.4	30.0 vs 23.6
Zhou et al.	OPTIMAL	Erl	154	83% vs 36%	13.1 vs 4.6	22.6 vs 28.8
Rosell et al.	EURTAC	Erl	154	54.5% vs 10.5%	9.2 vs 5.4	19.3 vs 19.5
Yang et al.	LUX-Lung 3	Afat	345	56% vs 23%	13.6 vs 6.9	31.6 vs 28.2
Wu et al.	LUX-Lung 6	Afat	364	67% vs 23%	11.0 vs 5.6	23.6 vs 23.5

Mok et al. *N Engl J Med*. 2009;361:947-57
Lee et al. WCLC 2009
Mitsudomi et al. *Lancet Oncol*. 2010;11;121-8
Maemondo et al. *N Engl J Med*. 2010;262:2380-88
Zhou et al. ESMO 2010
Rosell et al. ASCO 2011
Yang et al. ASCO 2012, Sequist IASLC 2012
Wu et al. ASCO 2013

Cross-over to an EGFR TKI in the control groups felt to reduce detectability of any possible OS benefit (all mutations)

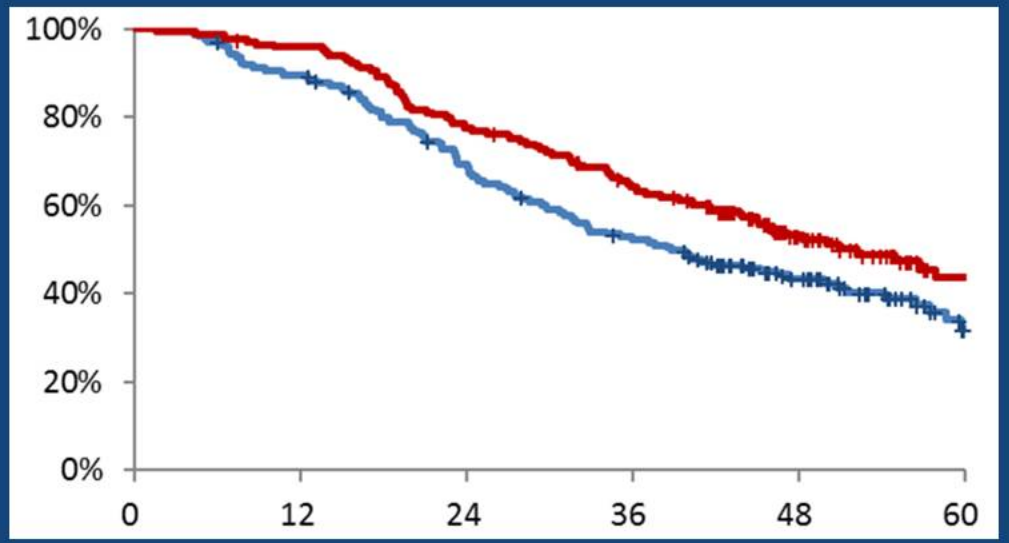
First phase III trials demonstrating OS benefit in EGFR M+ NSCLC
with an EGFR TKI control

ARCHER 1050 (n=452)
Median f/u 31.3 m



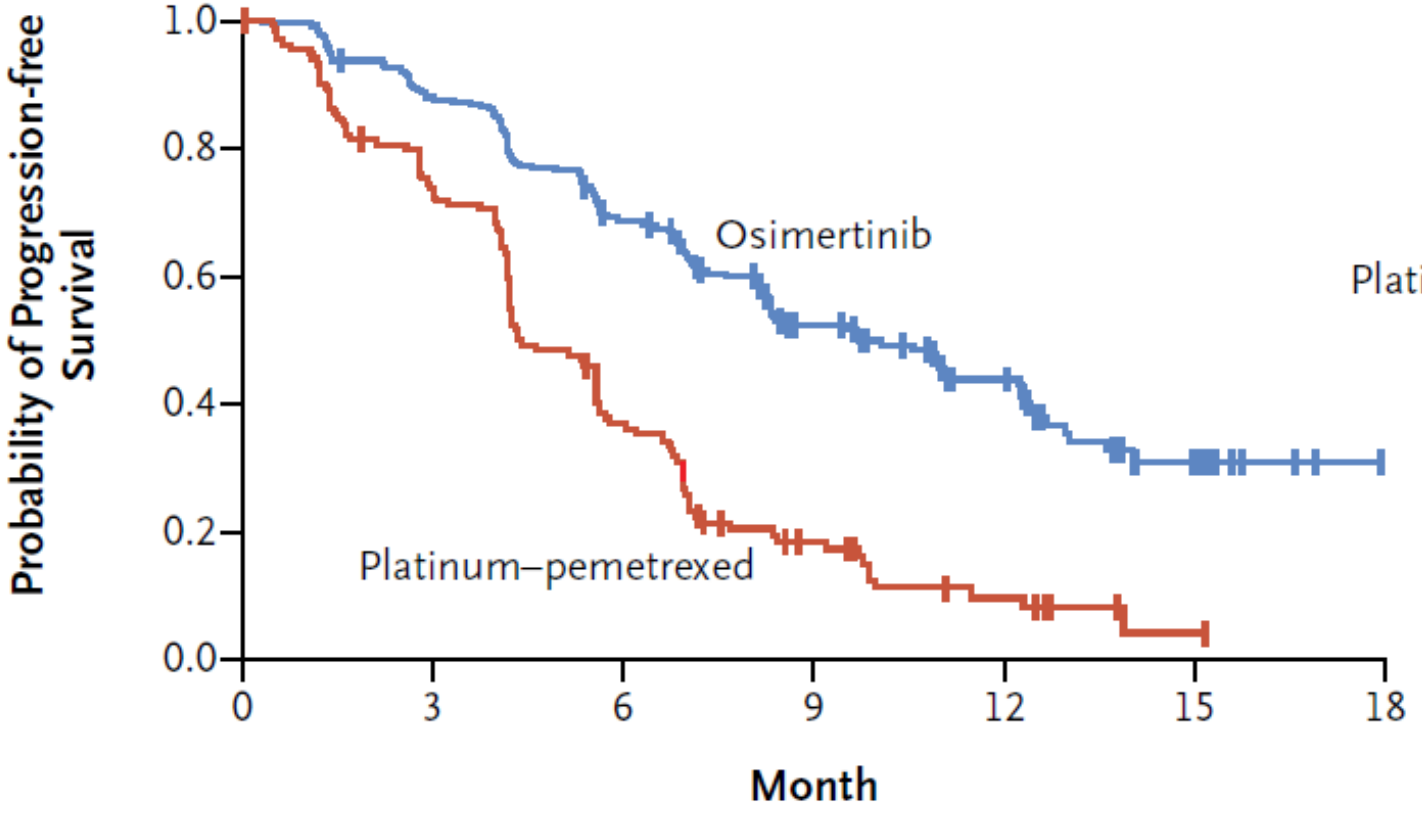
	Median OS	95% CI
Gefitinib	26.8 m	23.7 - 32.1
Dacomitinib	34.1 m	29.5 - 37.7
	HR 0.76 (95%CI 0.582 - 0.993) p=0.0219	

NEJ009 (n=345)
Median f/u minimum 42 m



	Median OS	95% CI
Gefitinib	38.8 m	31.1 - 50.8
Gefitinib + PemCb	52.2 m	44.0 - NR
	HR 0.695 (95%CI 0.520 - 0.927) p=0.013	

AURA3: Osimertinib *vs.* Platinum-Pemetrexed



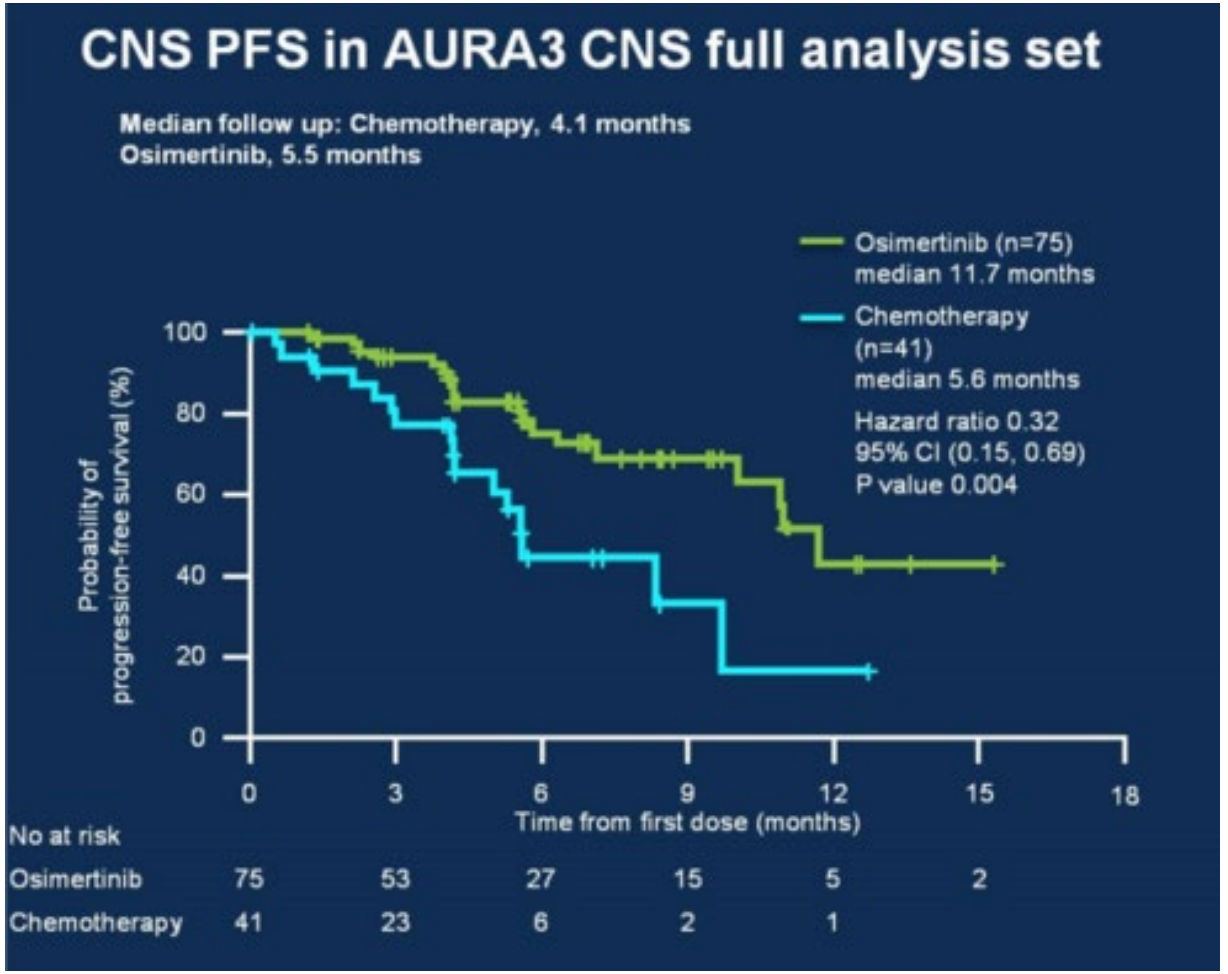
	No. of Patients	Median Progression-free Survival
		mo (95% CI)
Osimertinib	279	10.1 (8.3–12.3)
Platinum–pemetrexed	140	4.4 (4.2–5.6)

Hazard ratio for disease progression or death, 0.30 (95% CI, 0.23–0.41)
P<0.001

ORR: 71% (osimertinib) vs. 31% (chemotherapy); $P < .001$

AURA3: CNS EFFICACY

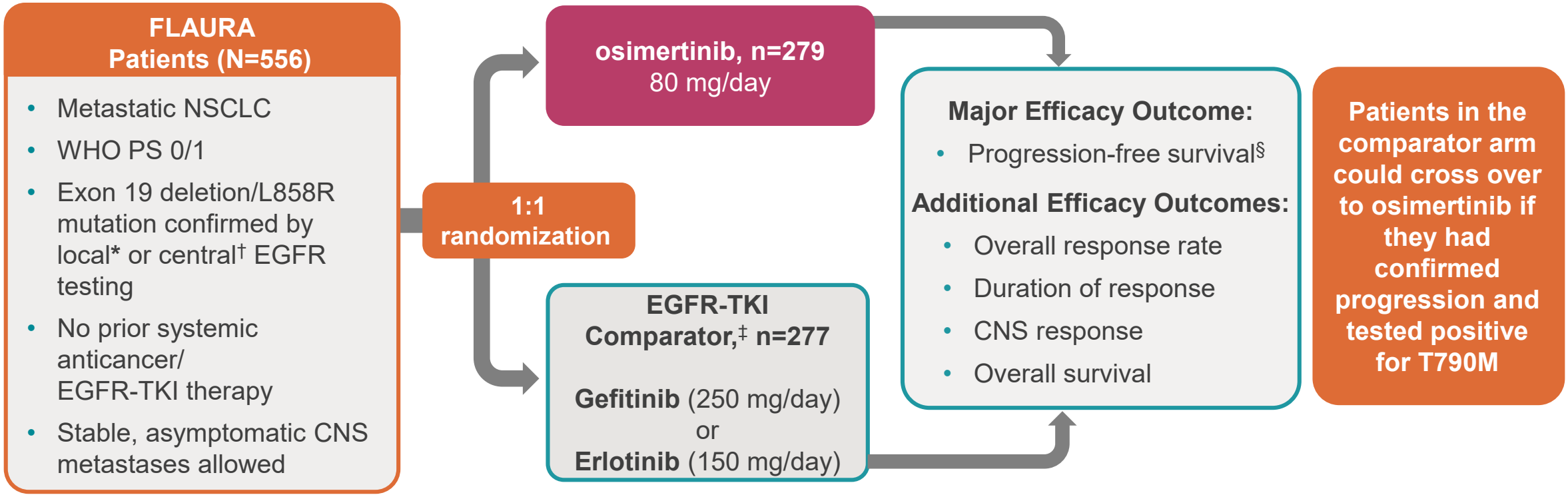
	Osimertinib 80 mg n=30	Chemotherapy n=16
CNS ORR (95% CI)	**70% (51, 85)**	**31% (11, 59)**
Odds ratio (95% CI)	5.13 (1.44, 20.64); p=0.015	
Median time to response, weeks	6.1	6.1
Median DoR, months (95% CI)	**8.9 (4.3, NC)**	**5.7 (NC, NC)**



Mok et al., ASCO 2017; Abstract 9005

OSIMERTINIB APPROVAL AS FIRST-LINE TREATMENT IS BASED ON THE FLAURA TRIAL[1,2]

FLAURA Is a Phase 3, Randomized, Double-Blind Trial in Patients With Previously Untreated EGFR Mutation-Positive Metastatic NSCLC

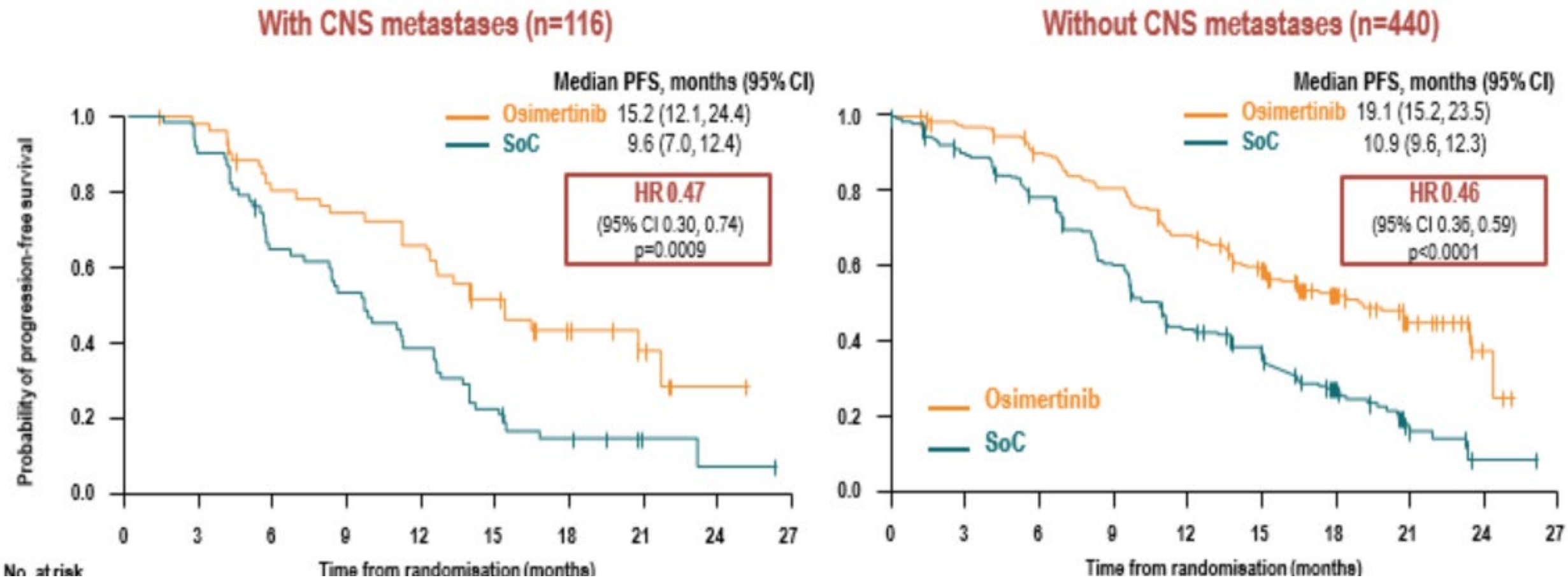


*With central laboratory assessment performed for sensitivity. †cobas® EGFR Mutation Test (Roche Molecular Systems). ‡Sites to select either gefitinib or erlotinib as the sole comparator prior to site initiation. All US patients in the EGFR-TKI comparator arm received erlotinib. §By investigator assessment according to RECIST version 1.1.

CNS, central nervous system; mg, milligram; PS, performance status; RECIST, Response Evaluation Criteria In Solid Tumors; WHO, World Health Organization.

1. TAGRISSO® (osimertinib) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2018. 2. Soria JC, et al. *N Engl J Med*. 2018;378(2):113-125.

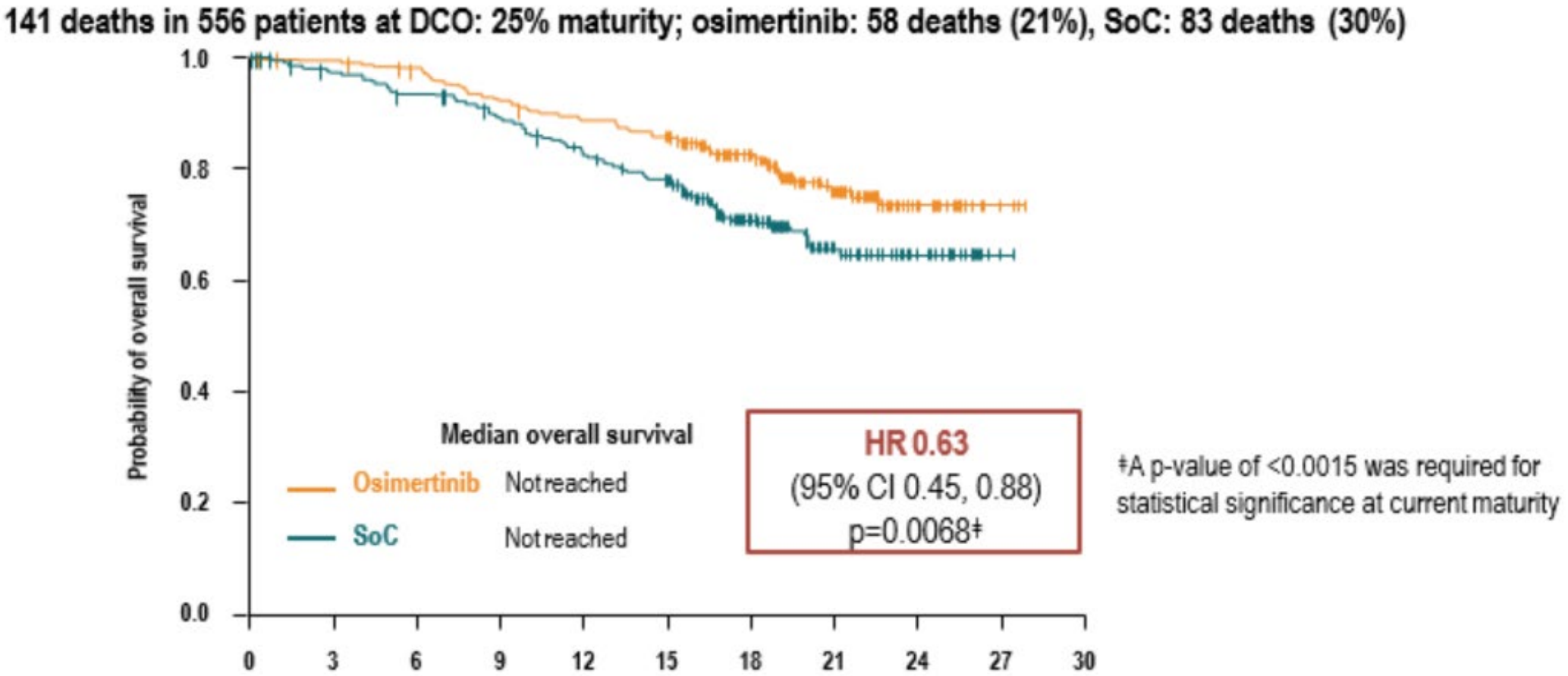
FLAURA Study



CNS progression events occurred in 17 (6%) vs 42 (15%) patients receiving osimertinib vs SoC (all patients)

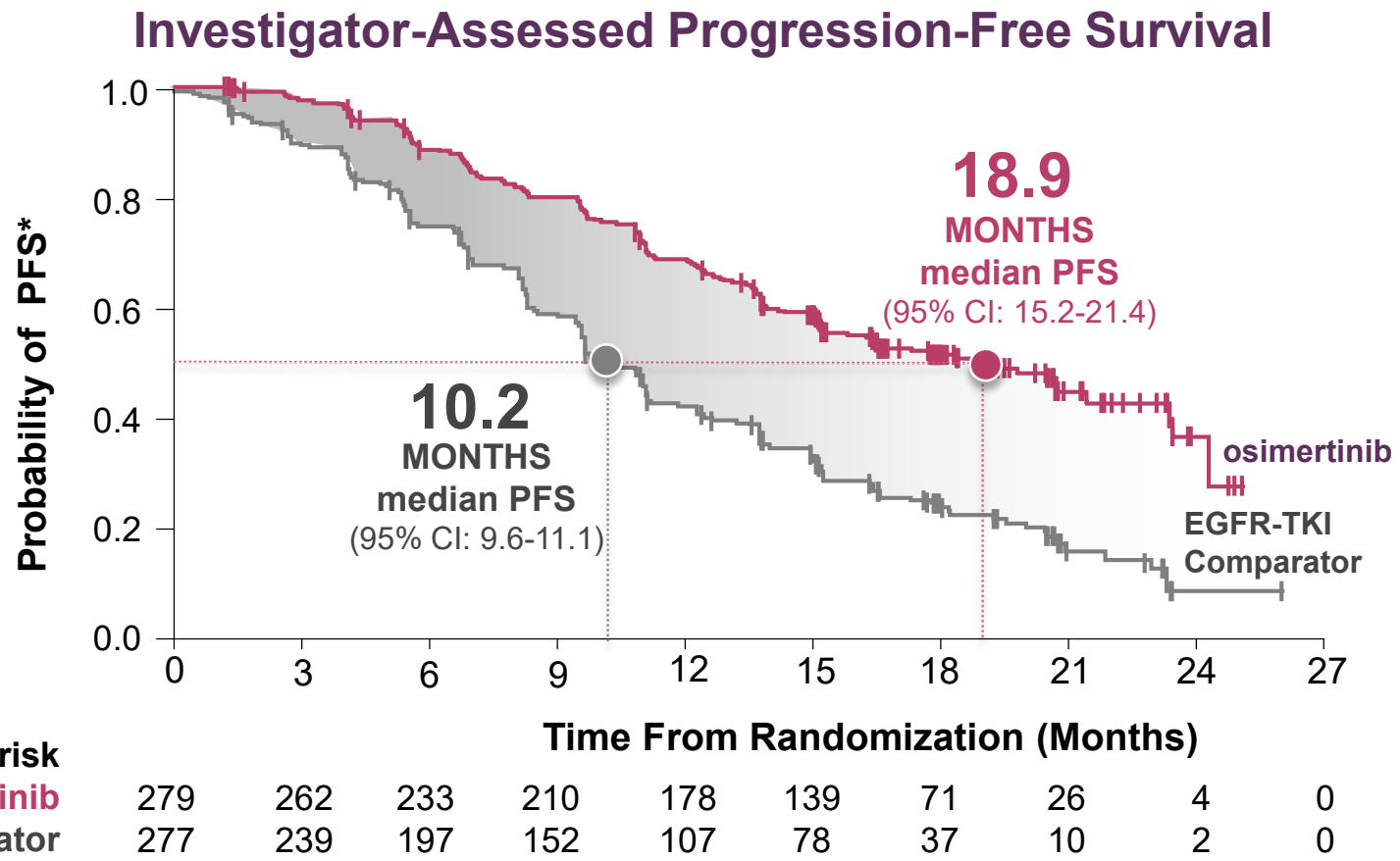
FLAURA data cut-off: 12 June 2017

1st *vs* 3rd Generation: FLAURA OS



Potential advantages of 1st line osimertinib: longer PFS, less toxicity, fewer brain mets, ? longer survival

1st vs 3rd Generation: FLAURA PFS



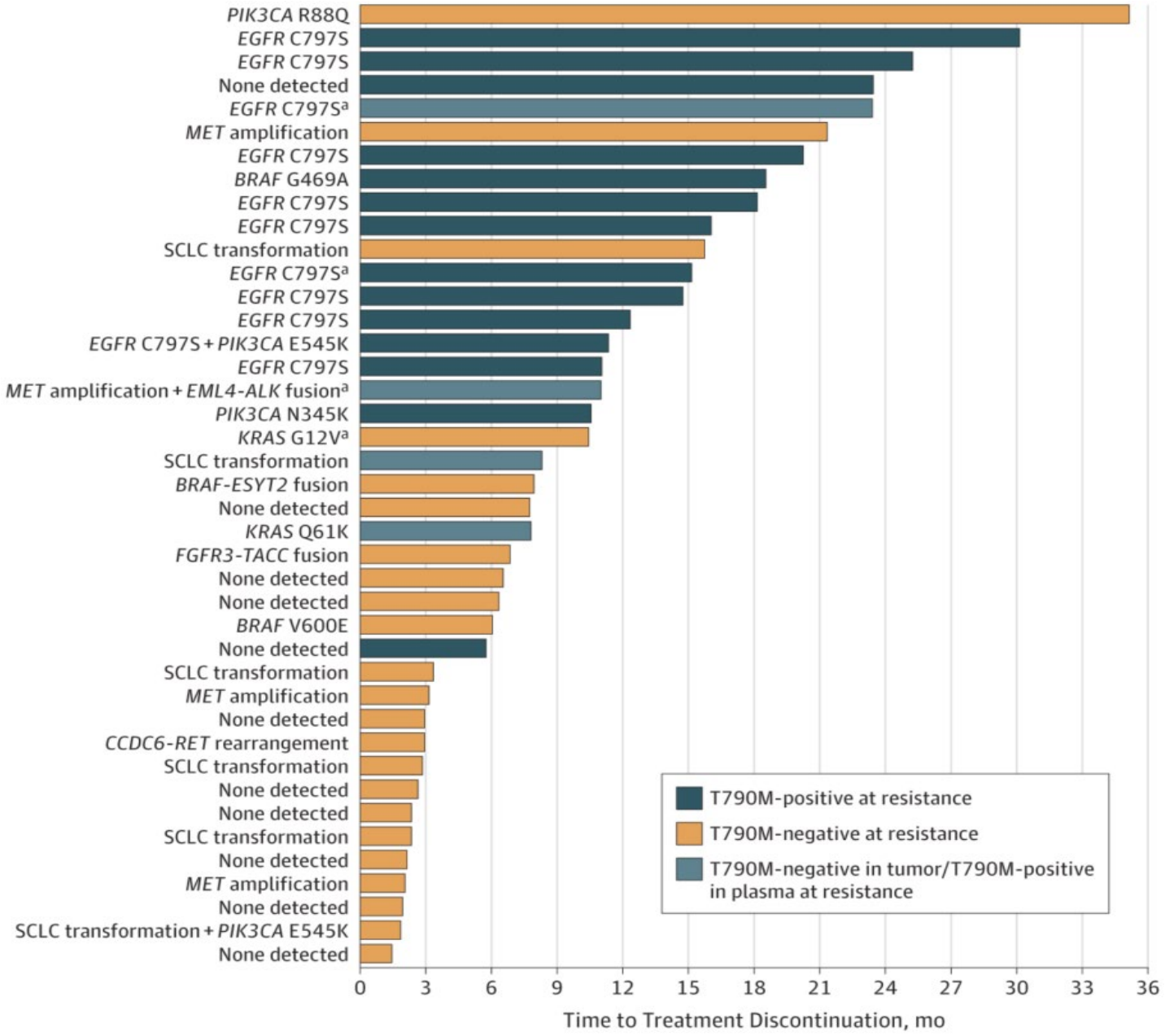
Hazard ratio=0.46
(95% CI: 0.37-0.57;
P<0.0001)

*PFS as determined by investigator assessment, defined as time from randomization until date of objective disease progression or death. Progression included deaths in absence of RECIST progression.[2] Tick marks indicate censored data.

CI, confidence interval; PFS, progression-free survival.

1. TAGRISSO® (osimertinib) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2018. 2. Soria JC, et al. *N Engl J Med*. 2018;378(2):113-125.

Acquired Resistance Mechanisms to Osimertinib



ARCHER 1050: Study Design

- Phase 3 randomized open-label study to evaluate dacomitinib as an alternative first-line treatment for patients with advanced NSCLC with an *EGFR*-activating mutation

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

N = 452

R
1:1

Dacomitinib 45 mg
PO QD
(n = 227)

Gefitinib 250 mg
PO QD
(n = 225)

Primary endpoint

PFS by blinded independent review (IR)

- Target HR ≤0.667 (50%↑)
- 90% power
- 1-sided α = 0.025
- Assumed median PFS: 14.3 vs 9.5 months

Stratification factors

Race (including Asian vs non-Asian)

EGFR mutation type (exon 19 vs 21)

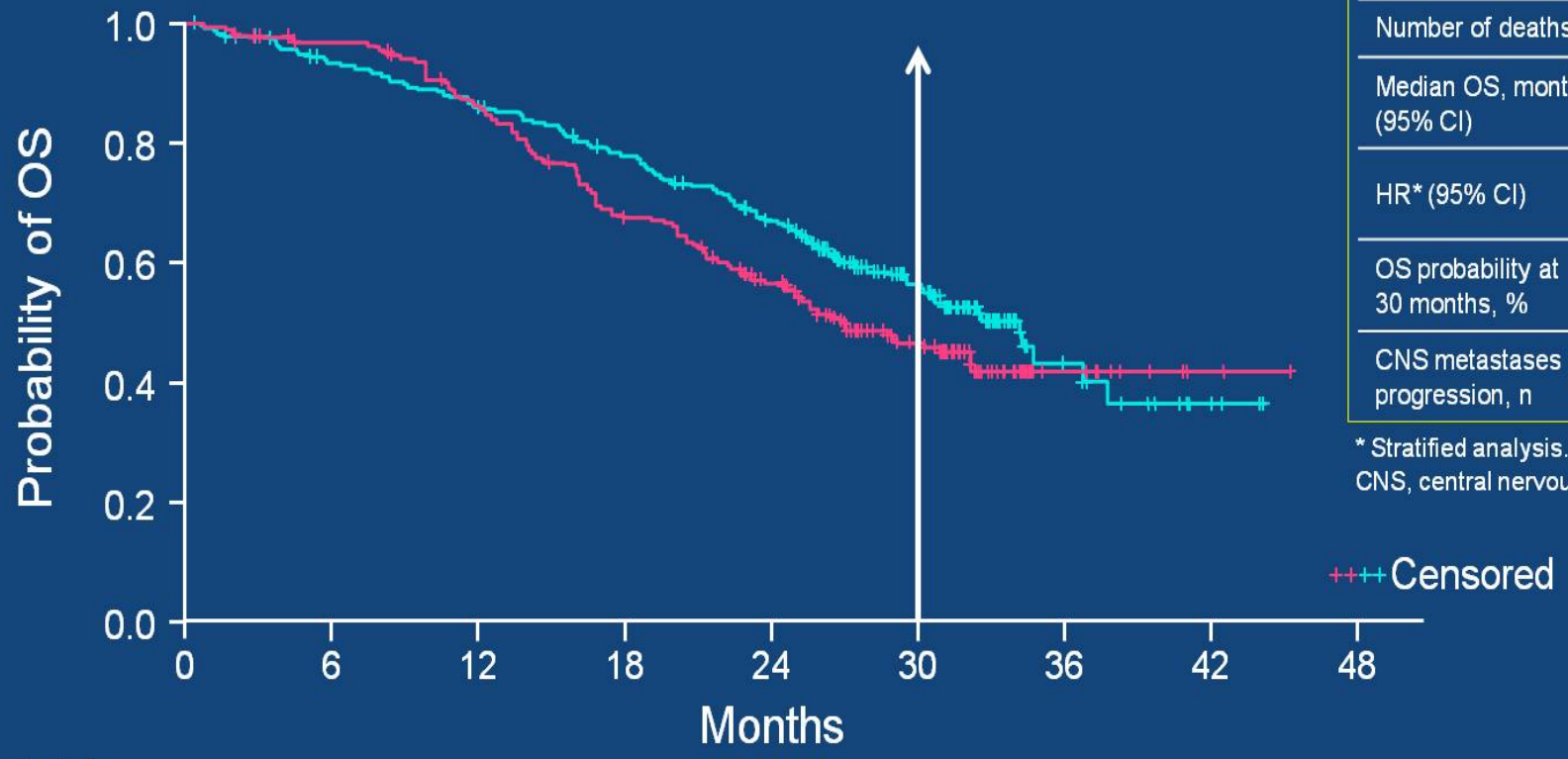
Secondary endpoints

OS

PFS (investigator assessed), ORR, DOR, TTF, Safety, PROs

ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show/NCT01774721.
CNS, central nervous system; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; ORR, objective response rate; PO, orally; PROs, patient-reported outcomes; PS, performance status; QD, once daily; R, randomized; TTF, time to treatment failure.

Final OS (Primary Analysis)



	Dacomitinib (n = 227)	Gefitinib (n = 225)
Number of deaths, n (%)	103 (45.4)	117 (52.0)
Median OS, months (95% CI)	34.1 (29.5, 37.7)	26.8 (23.7, 32.1)
HR* (95% CI)	0.760 (0.582, 0.993) 2-sided *P** = 0.0438	
OS probability at 30 months, %	56.2	46.3
CNS metastases at progression, n	1	11

* Stratified analysis.
CNS, central nervous system.

No. at risk:

Dacomitinib	227	206	188	167	138	77	14	3	0
Gefitinib	225	213	186	144	113	63	12	3	0

Updated Long-Term Adverse Events

Adverse Event,[a] n (%)	Dacomitinib (n = 227)			Gefitinib (n = 224)		
	Grade 1	Grade 2	≥ Grade 3[b]	Grade 1	Grade 2	≥ Grade 3[b]
Diarrhea[c]	113 (49.8)	65 (28.6)	20 (8.8)	103 (46.0)	20 (8.9)	2 (0.9)
Paronychia	46 (20.3)	77 (33.9)	17 (7.5)	30 (13.4)	12 (5.4)	3 (1.3)
Dermatitis acneiform	37 (16.3)	43 (18.9)	31 (13.7)	43 (19.2)	21 (9.4)	0
Stomatitis	51 (22.5)	40 (17.6)	8 (3.5)	33 (14.7)	6 (2.7)	1 (0.4)
Decreased appetite	40 (17.6)	23 (10.1)	7 (3.1)	48 (21.4)	6 (2.7)	1 (0.4)
Dry skin	42 (18.5)	18 (7.9)	3 (1.3)	35 (15.6)	3 (1.3)	0
Weight decreased	31 (13.7)	22 (9.7)	5 (2.2)	22 (9.8)	14 (6.3)	1 (0.4)
Alopecia	41 (18.1)	11 (4.8)	1 (0.4)	26 (11.6)	2 (0.9)	0
Cough	39 (17.2)	9 (4.0)	0	36 (16.1)	5 (2.2)	1 (0.4)
Pruritus	27 (11.9)	17 (7.5)	1 (0.4)	24 (10.7)	4 (1.8)	3 (1.3)
ALT increased	37 (16.3)	5 (2.2)	2 (0.9)	45 (20.1)	24 (10.7)	19 (8.5)
Conjunctivitis	27 (11.9)	16 (7.0)	0	6 (2.7)	3 (1.3)	0
Nausea	32 (14.1)	8 (3.5)	3 (1.3)	46 (20.5)	2 (0.9)	1 (0.4)
AST increased	41 (18.1)	1 (0.4)	0	56 (25.0)	16 (7.1)	9 (4.0)
Rash	19 (8.4)	11 (4.8)	10 (4.4)	22 (9.8)	2 (0.9)	0
Back pain	15 (6.6)	3 (1.3)	0	28 (12.5)	6 (2.7)	1 (0.4)

[a]Adverse events occurring in at least 15% of patients in either study group in the safety population. [b]There were no grade 4 events in either arm and one grade 5 event in the dacomitinib arm. [c]One patient (0.4%) in the dacomitinib arm had grade 5 diarrhea.
ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Dose Modification

Dacomitinib

- First dose reduction: 30 mg/day
- Second dose reduction: 15 mg/day

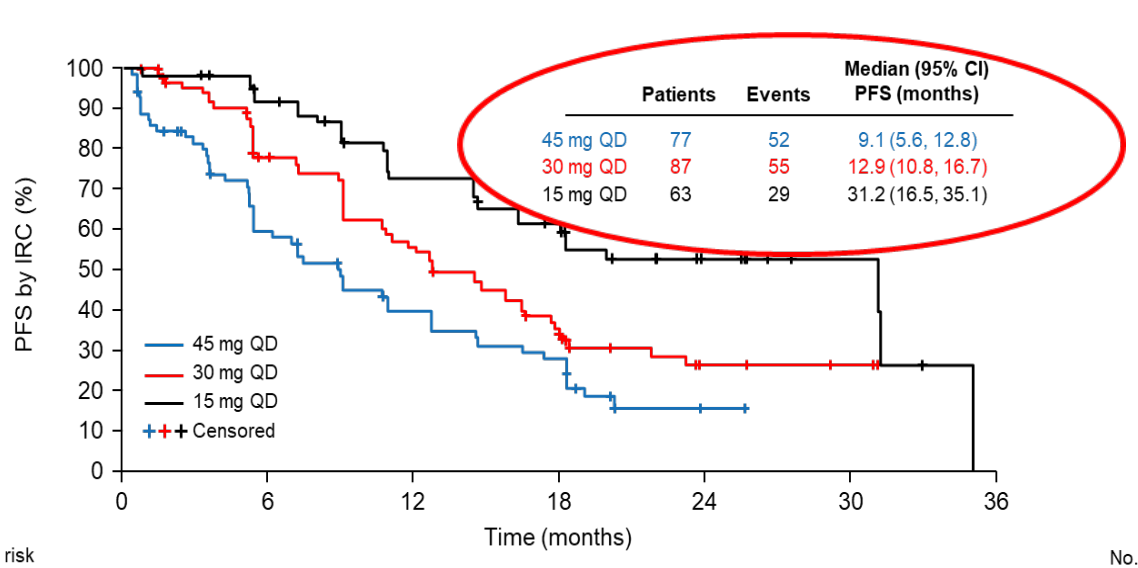
Gefitinib

- 250 mg every 2 days

	Dacomitinib (n = 227)	Gefitinib (n = 224)
Median time to dose reduction, months (range)	2.8 (0.3–20.3)	3.3 (1.2–25.7)
Median duration of dose reduction, months (range)	11.3 (0.1–33.6)	5.2 (0.3–17.8)
Reduction to 30 mg daily, n (%)	88 (38.8)	NA
Reduction to 15 mg daily, n (%)	63 (27.8)	NA
Total number of patients with dose modification, n (%)	151 (66.5)	18 (8.0)

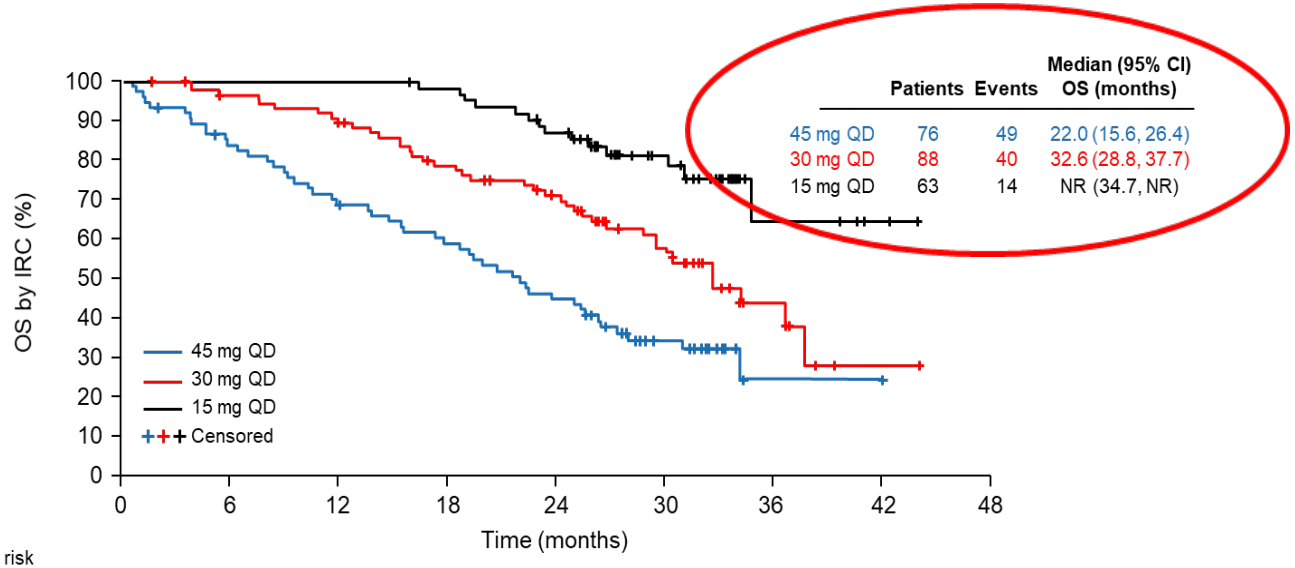
NA, not applicable.

Efficacy is preserved with dacomitinib dose reduction



	Patients	Events	Median (95% CI) PFS (months)
45 mg QD	77	52	9.1 (5.6, 12.8)
30 mg QD	87	55	12.9 (10.8, 16.7)
15 mg QD	63	29	31.2 (16.5, 35.1)

No. at risk							
45 mg QD	77	38	23	16	2	0	0
30 mg QD	87	61	43	25	5	2	0
15 mg QD	63	55	40	32	13	4	0



	Patients	Events	Median (95% CI) OS (months)
45 mg QD	76	49	22.0 (15.6, 26.4)
30 mg QD	88	40	32.6 (28.8, 37.7)
15 mg QD	63	14	NR (34.7, NR)

No. at risk									
45 mg QD	76	61	50	42	32	16	1	0	0
30 mg QD	88	82	75	64	54	33	7	1	0
15 mg QD	63	63	63	61	52	28	6	2	0

The separation of the curves is bit alarming, but keep in mind….

- All patients received 45 mg/d as a starting dose; Not protected by randomization.
- Non-responding patients with short treatment durations were less likely to undergo dose reduction.
- Likely censoring due to treatment discontinuation at 45 mg/d d/t toxicity, in the absence of disease progression.
- Speaks to the inevitability of dose reduction in patients with long treatment durations.

Liza C. Villaruz, MD; UPMC Hillman Cancer Center, Pittsburgh, PA. 19TH WCLC, Toronto, Canada. September 23-26, 2019.

What do these data mean in the era of 3rd Generation TKIs?

Osimertinib is preferred 1st line TKI as per NCCN

Inhibition of EGFR Phosphorylation *in vitro*:

A

	H1975 (L858R/ T790M)	PC-9 VanR (ex19del/ T790M)	PC-9 (ex19del)	H3255 (L858R)	H1650 (ex19del)	LoVo (WT)	A431 (WT)	NCI-H2073 (WT)
AZD9291	15 (10, 20)	6 (3, 13)	17 (13, 22)	60, 49	14, 12	480 (320, 720)	2376, 1193	1865 (872, 3988)
Dacomitinib	40 (24, 65)	6 (2, 17)	0.7 (0.5, 1)	1.2, 1.3	0.04, 0.06	12 (8, 17)	51, 22	26 (7, 99)
Afatinib	22 (15, 31)	3 (2, 6)	0.6 (0.5, 0.8)	1, 0.8	0.6, 3	15 (10, 24)	27, 40	25 (5, 129)
Gefitinib	3102 (1603, 6001)	741 (484, 1136)	7 (5, 11)	11, 12	16, 19	59 (42, 82)	60, 88	61 (34, 110)
Erlotinib	6073 (3634, 10150)	1262 (588, 2711)	6 (4, 7)	8, 11	5, 8	91 (53, 156)	244, 260	108 (52, 223)

Dose reductions in:				
LL3	**LL6**	**LL7**	**ACHER1050 (dacomitinib)**	**FLAURA (osimertinib)**
53%	28%	42%	66%	4%

Cross Cancer Discov 2014; Wu Lancet Oncol 2014; Wu Lancet Oncol 2014; Paz-Ares Ann Oncol 2017; Soria N Engl J Med 2018

Is overall survival benefit still a relevant endpoint?

- Has traditionally been the gold standard endpoint... together with quality of life

- Some commonly cited limitations:
  - Crossover effect
    - Chemotherapy → TKI
  - Long duration of follow up required

- RR & PFS have been an acceptable surrogate endpoint in targeted therapies in NSCLC
  - Threshold of surrogacy is highly context dependent e.g. type of intervention

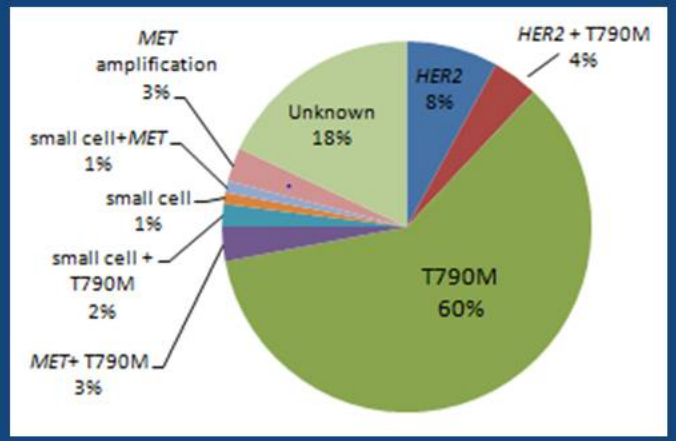
Acquired Resistance to Osimertinib

EGFR TKI

Gefitinib
Erlotinib
Afatinib
Dacominitib

→ **Acquired Resistance** →

EGFR TKI
Osimertinib



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Acquired Resistance #2

EGFR TKI
Osimertinib

→ **??**

Acquired *EGFR* mutations
Acquired alterations
Tumor heterogeneity
Histologic transformation

EGFR Sequencing *vs* Non-Sequencing

- Osimertinib > Gefitinib/Erlotinib (FLAURA study; phase III)
- Dacomitinib > Gefitinib (ARCHER 1050; phase III trial; OS +)
- Afatinib > Gefitinib (LUX-Lung 7; phase IIb)
- Afatinib vs Osimertinib? (no data)
- Dacomitinib vs Osimertinib (no data)
- Gefitinib/Carbo/Pem > Gefitinib (NEJ 009; phase III trial; OS +)

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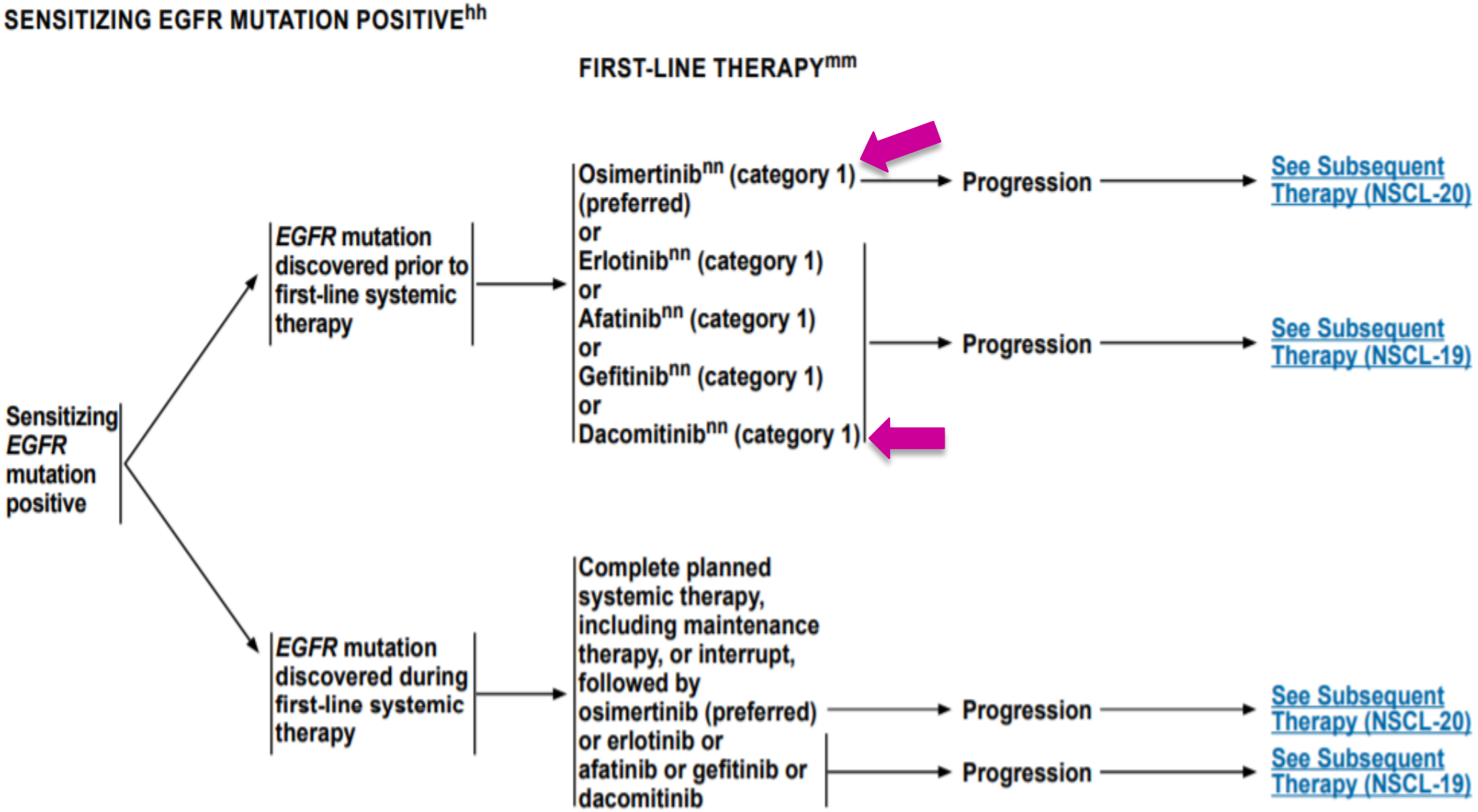
THIS IS NOW! MARCH 2, 2019



NCCN Guidelines Version 8.2018
Non-Small Cell Lung Cancer
August 17, 2018

Afatinib: Only FDA Approved Drug for Uncommon *EGFR* Mutations

	Mutation	Objective response	Progression-free survival (months)	Overall survival (months)
Gly719Xaa (n=18)	Gly719Xaa (n=8) Gly719Xaa+Thr790Met (n=1) Gly719Xaa+Ser768Ile (n=5) Gly719Xaa+Leu861Gln (n=3) Gly719Xaa+Thr790Met+Leu858Arg (n=1)	14 (77·8%, 52·4–93·6)	13·8 (6·8–NE)	26·9 (16·4–NE)
Leu861Gln (n=16)	Leu861Gln (n=12) Leu861Gln+Gly719Xaa (n=3) Leu861Gln+Del19 (n=1)	9 (56·3%, 29·9–80·2)	8·2 (4·5–16·6)	17·1 (15·3–21·6)
Ser768Ile (n=8)	Ser768Ile (n=1) Ser768Ile+Gly719Xaa (n=5) Ser768Ile+Leu858Arg (n=2)	8 (100·0%, 63·1–100·0)	14·7 (2·6–NE)	NE (3·4–NE)

Data are n (%, 95% CI) or median (95% CI). NE=not estimable. Uncommon mutation categories overlap for those with compound mutations, so individual patients might appear in more than one category.

Table 3: **Activity of afatinib in specific compound uncommon mutations**

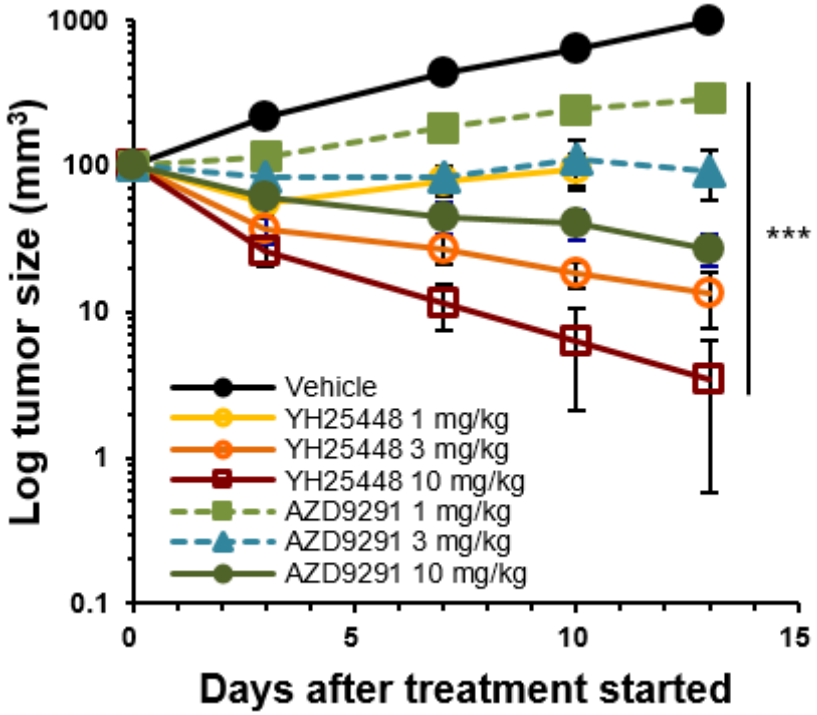
Afatinib is active in NSCLC tumours that harboured certain types of uncommon EGFR mutations, especially G719X, L861G, and S768I, but less active in other mutations types. Clinical benefit is lower in patients with de-novo T790M and exon 20 insertion mutations.

James C-H Yang et al. Lancet Oncol 2015; 16:830-8.

Emergent EGFR TKI Inhibitors

Lazertinib (YH25448): an irreversible covalent binding to C797

Enhanced antitumor effect in H1975 (L858R/T790M) xenograft and less cutaneous toxicity



YH25448

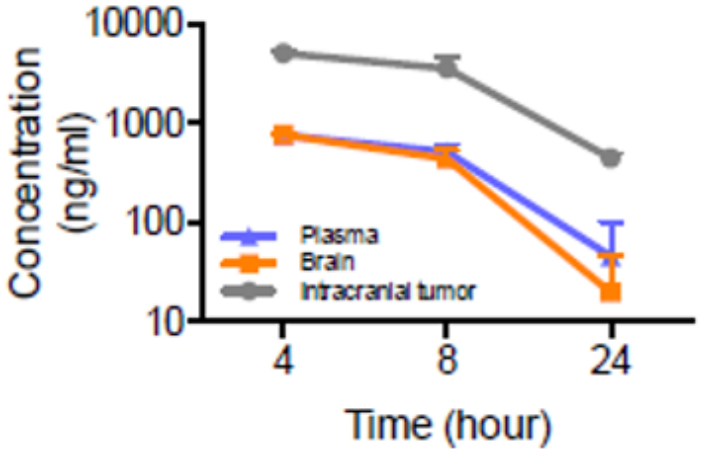
Osimertinib

Yun AACR 2018

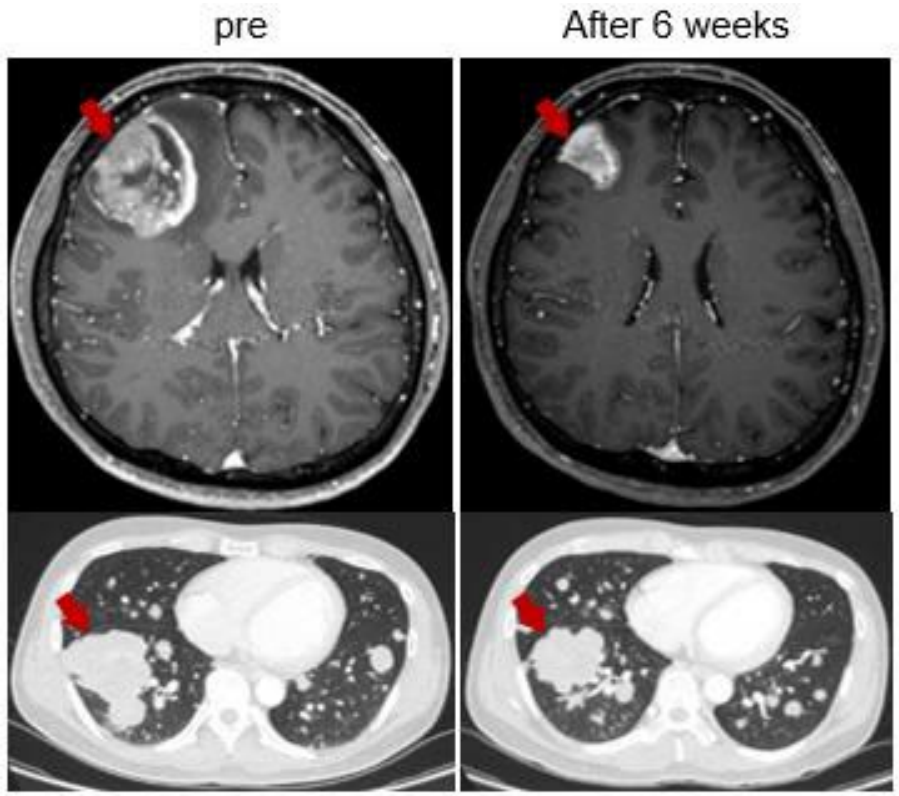
Lazertinib: CNS Penetration & Response

Uptake in intracranial tumor notably higher than brain and plasma

Relative exposure ratio (AUC_{last} based)	10 mg/kg
Brain/Plasma	0.9
Intracranial tumor/Plasma	7.0
Intracranial tumor/Brain	7.9



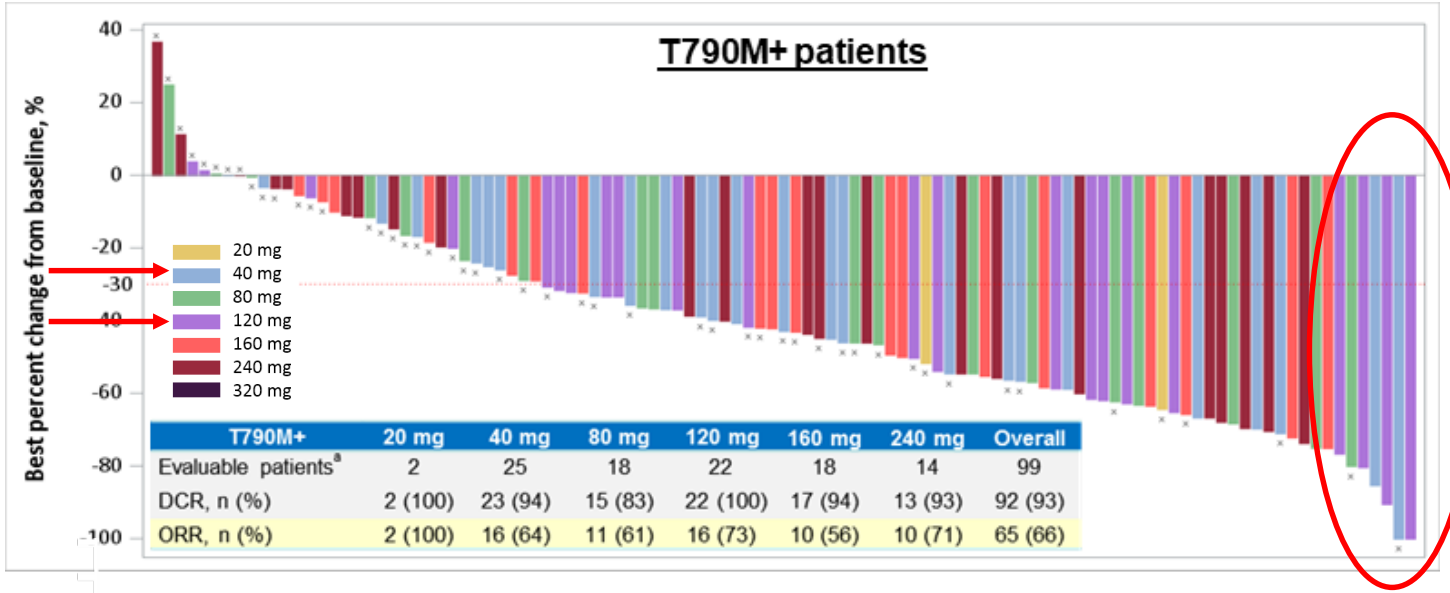
Intra- and Extracranial response in Del19/T790M mediated disease



Yun AACR 2018

Responses in Phase I Dose Escalation

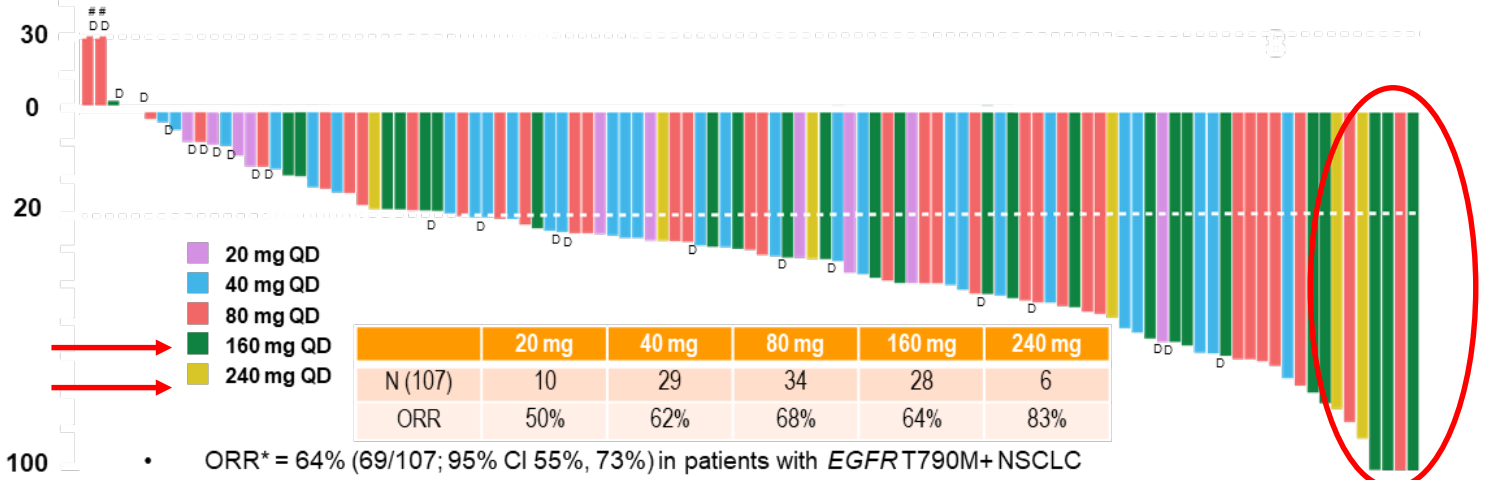
Lazertinib



T790M+	20 mg	40 mg	80 mg	120 mg	160 mg	240 mg	Overall
Evaluable patients[a]	2	25	18	22	18	14	99
DCR, n (%)	2 (100)	23 (94)	15 (83)	22 (100)	17 (94)	13 (93)	92 (93)
ORR, n (%)	2 (100)	16 (64)	11 (61)	16 (73)	10 (56)	10 (71)	65 (66)

T790M- patients		
	Osimertinib n=50	Lazertinib n=20
ORR n (%)	**11 (22)**	**7 (35)**

Osimertinib (AURA)



	20 mg	40 mg	80 mg	160 mg	240 mg
N (107)	10	29	34	28	6
ORR	50%	62%	68%	64%	83%

- ORR* = 64% (69/107; 95% CI 55%, 73%) in patients with *EGFR* T790M+ NSCLC
- Overall disease control rate (CR+PR+SD) = 94% (101/107; 95% CI 88%, 98%)

Hint of deep responses at lower doses, numerically higher RR in T790M- pts…

Janne N Engl J Med 2015

Safety and Tolerability

Lazertinib

Patients with TEAEs, n (%)	20mg (n=3)	40mg (n=27)	80mg (n=20)	120mg (n=25)	160mg (n=23)	240mg (n=24)	320mg (n=5)	Overall (N=127)
TEAEs	3 (100)	24 (89)	17 (85)	23 (92)	20 (87)	21 (88)	5 (100)	**113 (89)**
Drug related TEAEs	2 (67)	17 (63)	11 (55)	20 (80)	15 (65)	18 (75)	4 (80)	**87 (69)**
Serious TEAEs	1 (33)	4 (15)	4 (20)	6 (24)	4 (17)	1 (4)	2 (40)	**22 (17)**
Drug related serious TEAEs	0	2 (7)	1 (5)	2 (8)	0	1 (4)	0	**6 (5)**

Osimertinib (AURA)

Patients with TEAEs, n (%)	20mg (n=21)	40mg (n=58)	80mg (n=90)	160mg (n=63)	240mg (n=21)	Overall (N=253)
TEAEs	21 (100)	56 (97)	83 (92)	63 (100)	21 (88)	**244 (96)**
Drug related TEAEs	14 (67)	38 (66)	71 (79)	59 (94)	21 (100)	**203 (80)**
Serious TEAEs	6 (29)	21 (36)	26 (29)	24 (38)	5 (24)	**82 (32)**
Drug related serious TEAEs	2 (10)	2 (3)	10 (11)	16 (25)	3 (14)	**13 (13)**

Hints of better tolerability, though rates of serious drug related AEs low overall…..

Patients with TEAEs, n (%)	Lazertinib (N=127)	Osimertinib (AURA) (N=253)
Pruritus	**32 (25)**	**47 (19)**
Rash	**25 (20)**	**102 (40)**
Constipation	**22 (17)**	**40 (16)**
Decreased appetite	**22 (17)**	**54 (21)**
Diarrhoea	**16 (13)**	**118 (47)**
Nausea	**15 (12)**	**55 (22)**

Janne N Engl J Med 2015

CK-101 (RX518)

Novel, Oral, 3rd Generation, Irreversible TKI Targeting Mutant EGFR

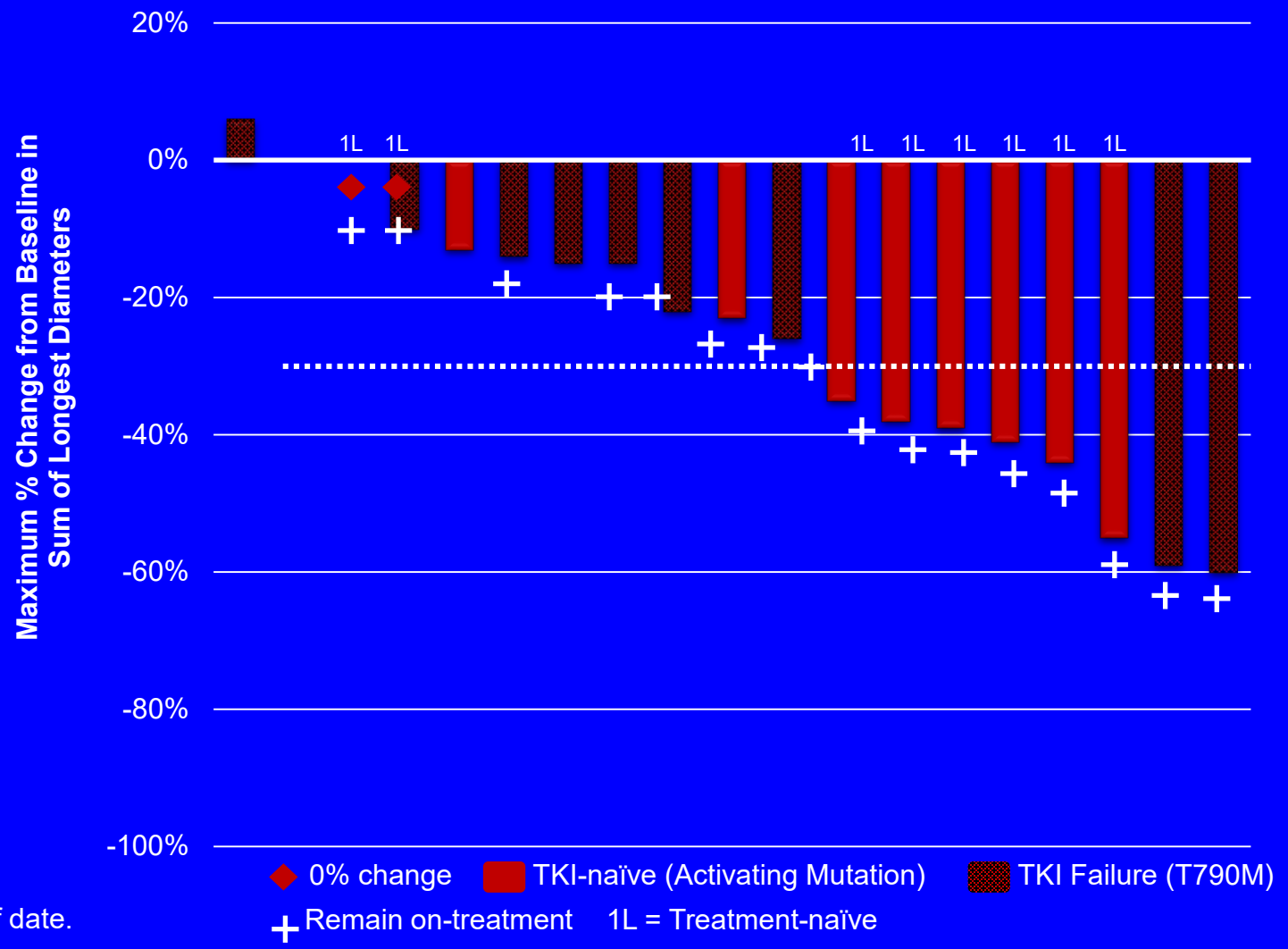
Inhibition of Cancer Cell Proliferation (IC_{50}, nM)[1]

Cell Line	EGFR Mutation	CK-101	osimertinib	afatinib
NCI-H1975	L858R/T790M	5	2	23
HCC827	Exon 19 del	10	3	1
A431	WT	689	280	34

- Selectively inhibits both EGFR-TKI-sensitizing mutations and T790M resistance mutation
- Minimal activity on wild-type EGFR
  - *In vitro*, CK-101 was over 100-fold less potent against wild-type EGFR than against L858R/T790M double mutation

Preliminary Responses of CK-101
EGFR Mutant NSCLC Expansion Cohort: 400mg BID

- 42% ORR (8/19 pts)[1]
  - 75% ORR (6/8 pts) in treatment-naïve pts
- 84% (16/19) pts had target lesion reductions versus baseline
- 3/5 patients with baseline brain metastasis had intracranial disease response
- Median DoR and PFS were not reached



[1] Includes 7 confirmed PRs, 1 pending.
Does not include additional PR (T790M pt) achieved post-data cutoff date.

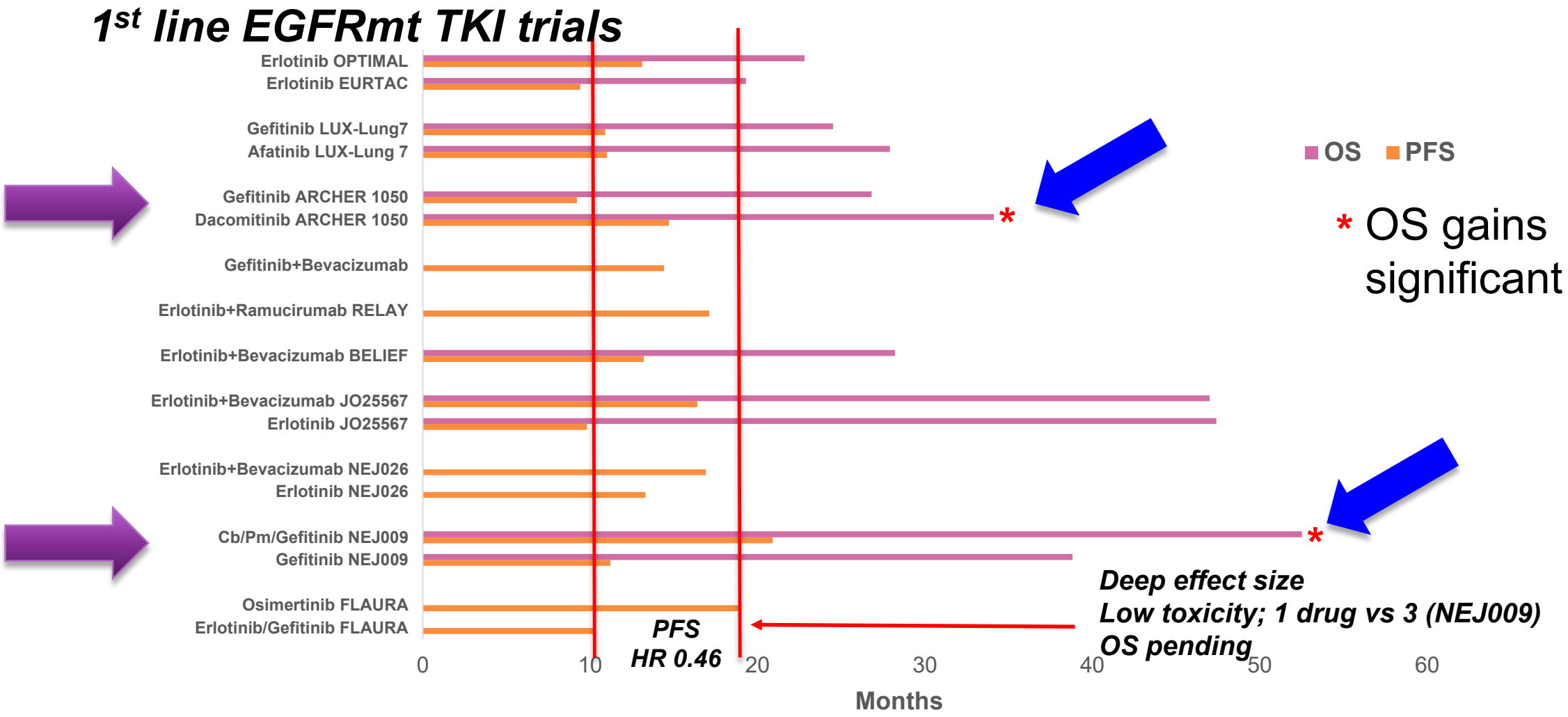
Presenter: Melissa L. Johnson, MD, Sarah Cannon Research Institute

Data cutoff date: 25 June 2018.

Conclusions

- CK-101 was well-tolerated across multiple dose groups
  - Maximum-tolerated dose not defined (no DLTs or treatment-related SAEs to date)
- CK-101 demonstrates preliminary activity in EGFR mutation-positive NSCLC
  - ORR of 75% (6 of 8) in treatment-naïve patients
- Soft gel capsule dosage form has been introduced to replace hard shell capsule; study ongoing to determine optimal dose, targeting higher serum concentrations
- Phase 3 trial in treatment-naïve EGFRm+ NSCLC planned for 2019

The Bar is High for Drug Development…

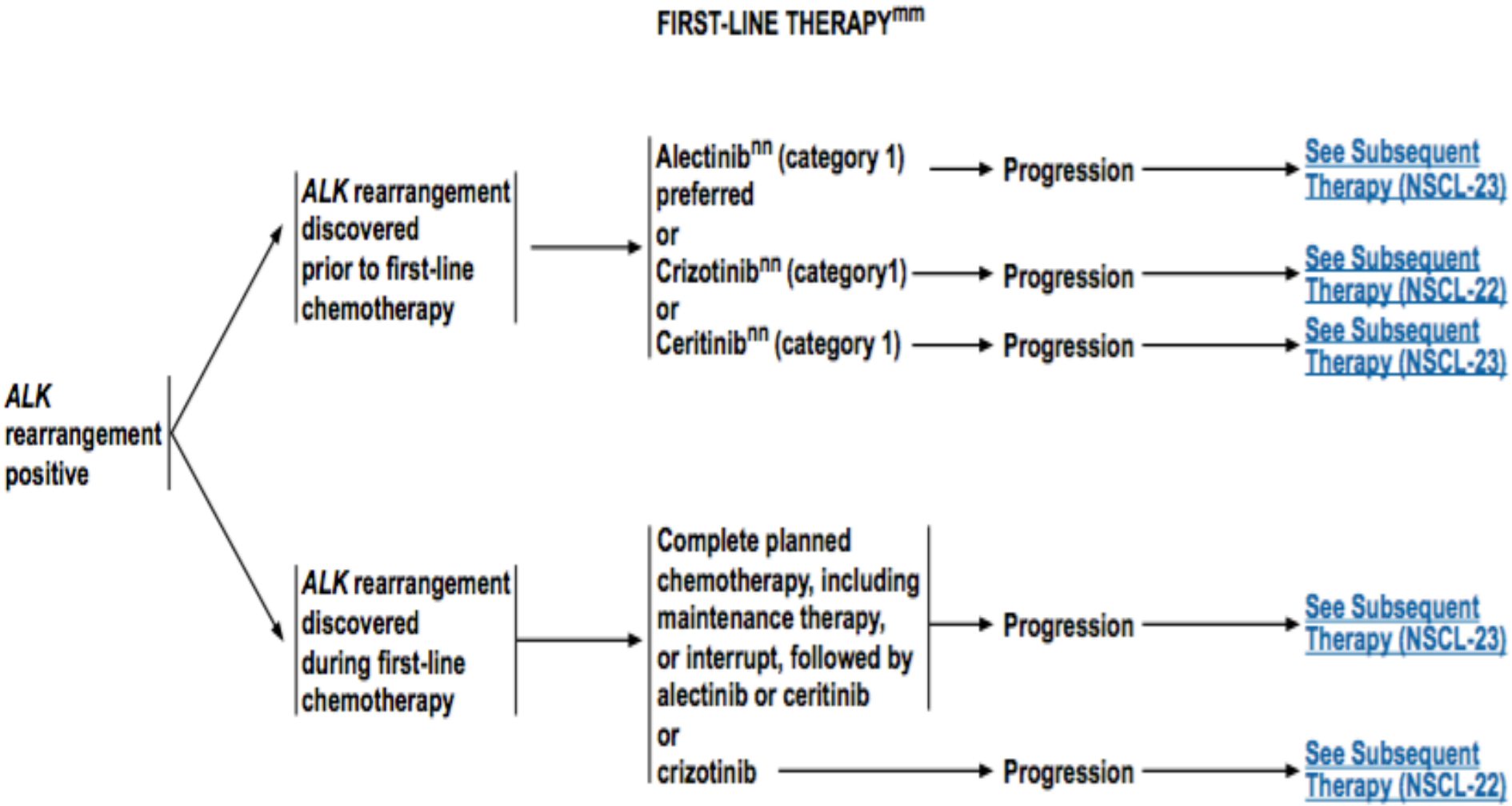


ALK

Oncology Latin American Association

OLA

ALK REARRANGEMENT POSITIVE[hh]



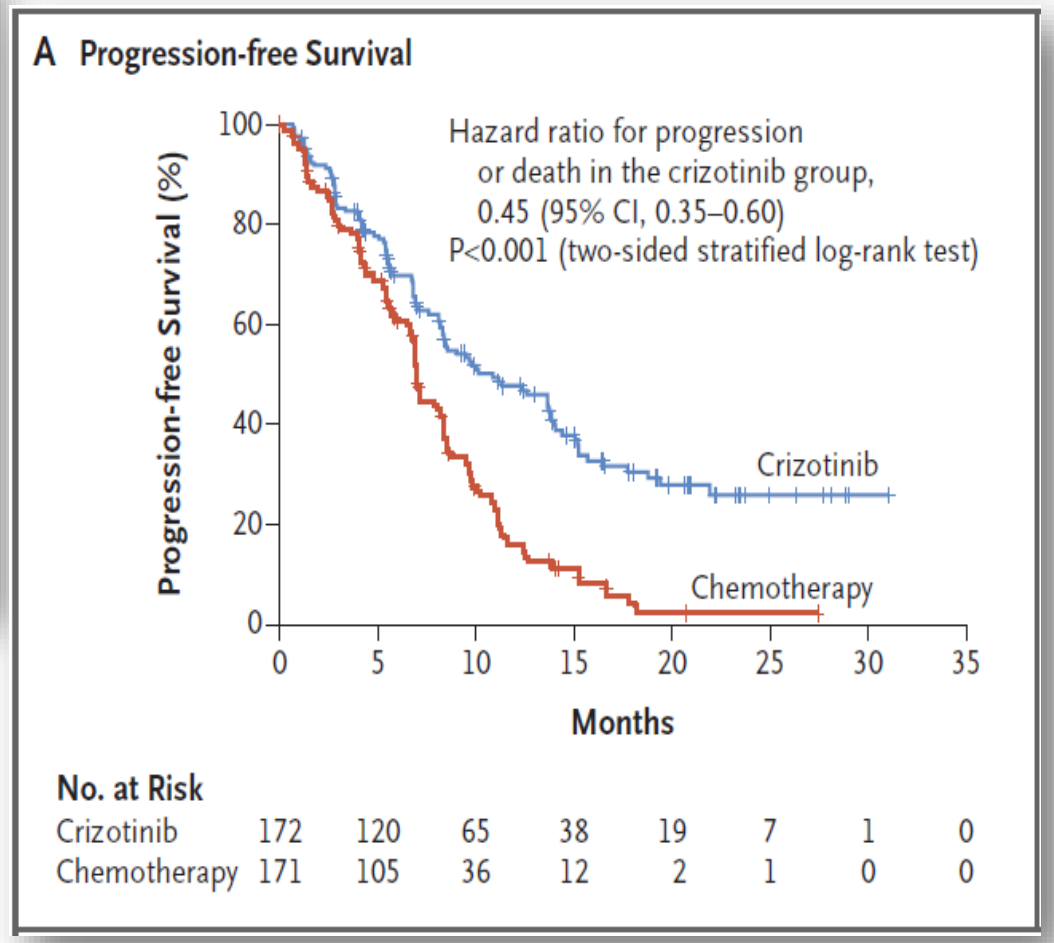
ALK+, Crizotinib as First Line

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

First-Line Crizotinib versus Chemotherapy in *ALK*-Positive Lung Cancer

Benjamin J. Solomon, M.B., B.S., Ph.D., Tony Mok, M.D., Dong-Wan Kim, M.D., Ph.D., Yi-Long Wu, M.D., Kazuhiko Nakagawa, M.D., Ph.D., Tarek Mekhail, M.D., Enriqueta Felip, M.D., Ph.D., Federico Cappuzzo, M.D., Jolanda Paolini, B.Sc., Tiziana Usari, B.Sc., Shrividya Iyer, Ph.D., Arlene Reisman, M.P.H., Keith D. Wilner, Ph.D., Jennifer Tursi, M.Sc., and Fiona Blackhall, M.D., Ph.D., for the PROFILE 1014 Investigators*



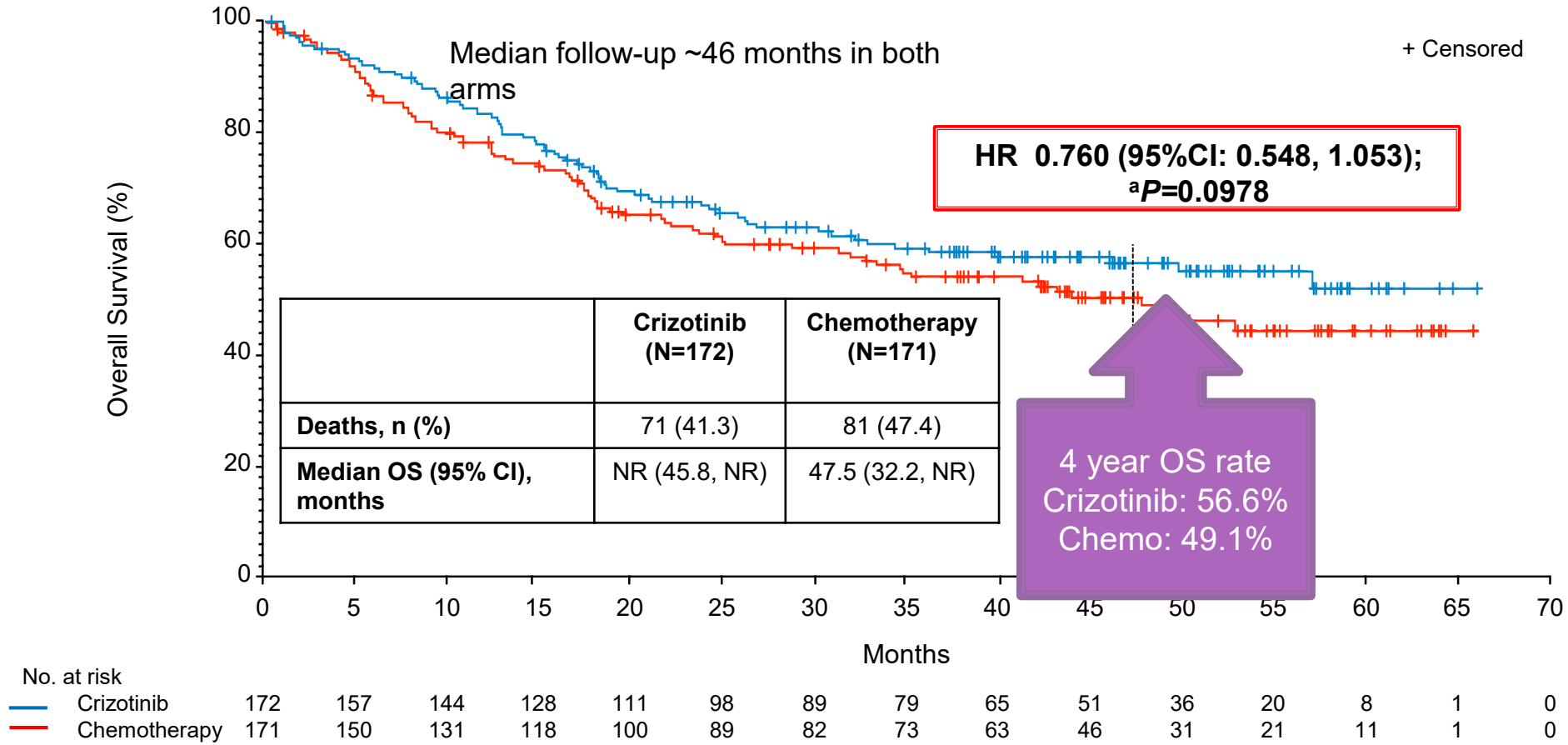
Significantly better efficacy to CT (platin/pem)

mPFS 10.9 *vs* 7.0 mo

(HR=0.45, P<0.0001)

Felip E. World Conference on Lung Cancer, Sept 23-26, 2018

Final primary OS analysis (ITT population)



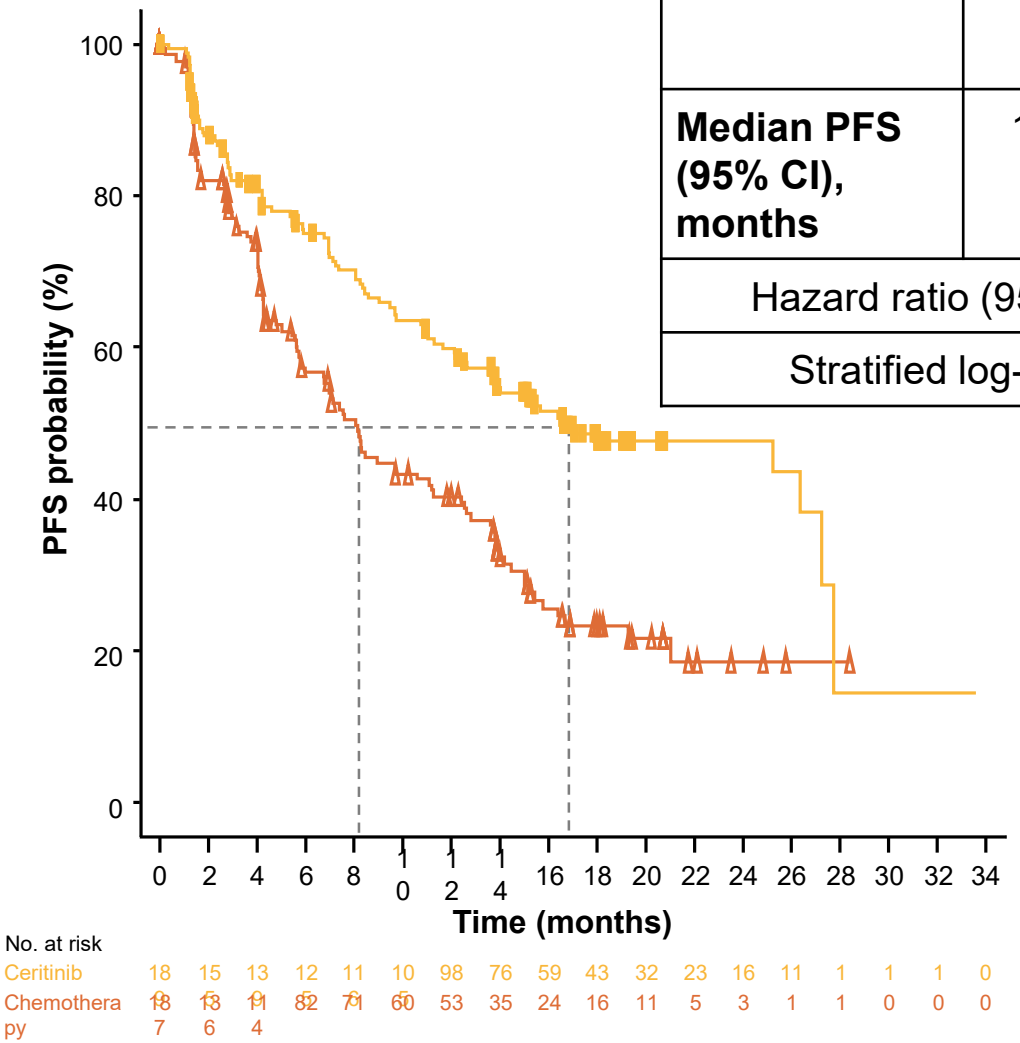
	Crizotinib (N=172)	Chemotherapy (N=171)
Deaths, n (%)	71 (41.3)	81 (47.4)
Median OS (95% CI), months	NR (45.8, NR)	47.5 (32.2, NR)

[a]2-sided p-value from the log-rank test stratified by ECOG PS, race, brain metastases.

Mok JCO 18

ALK+, Ceritinib as First Line

Significantly better efficacy to CT (platin/pem, pem maintenance)
mPFS 16.6 *vs* 8.1 mo
(HR=0.45, P<0.0001)

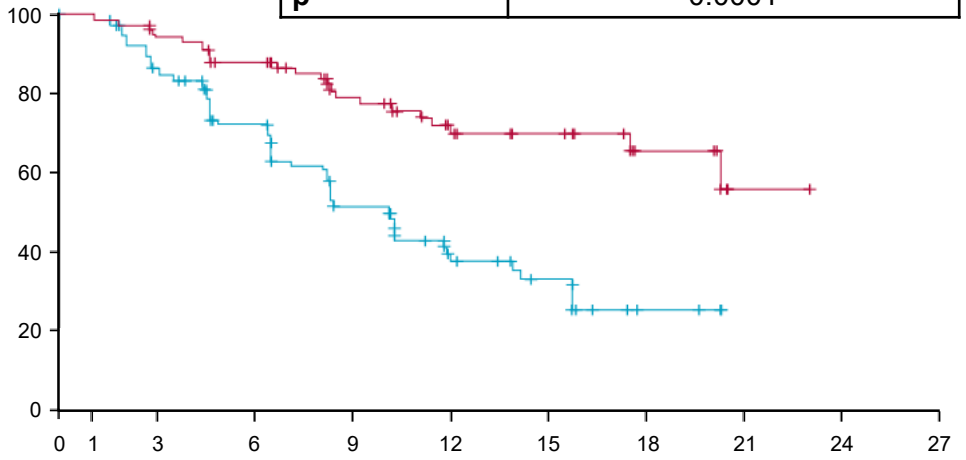


	Ceritinib (N=189)	Chemotherapy (N=187)
Median PFS (95% CI), months	16.6 (12.6, 27.2)	8.1 (5.8, 11.1)
Hazard ratio (95% CI) = 0.55 (0.42, 0.73)		
Stratified log-rank *P* value <0.00001		

Soria Lancet 17

ALK+, Alectinib as First Line

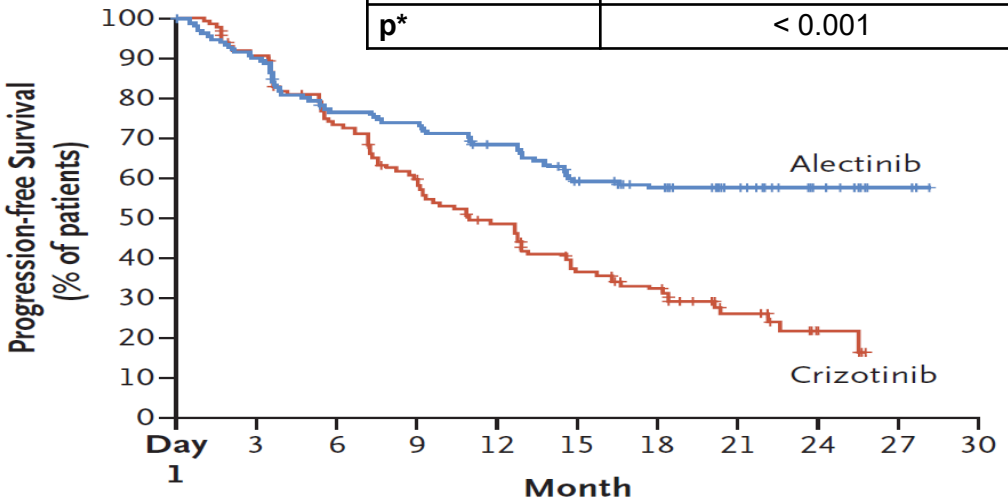
	Alectinib (n = 103)	Crizotinib (n = 104)
Events, n (%)	25 (24.3)	58 (55.8)
Median, mo	25.9	10.2
HR (99.7% CI)	0.38 (0.26–0.55)	
p*	0.0001	



J-ALEX: PFS

Hida Lancet 17 (updated ASCO 17)

	Crizotinib (n = 151)	Alectinib (n = 152)
Events, n (%)	102 (68)	62 (41)
Median, mo	11.1	NR
HR (95% CI)	0.47 (0.34–0.65)	
p*	< 0.001	

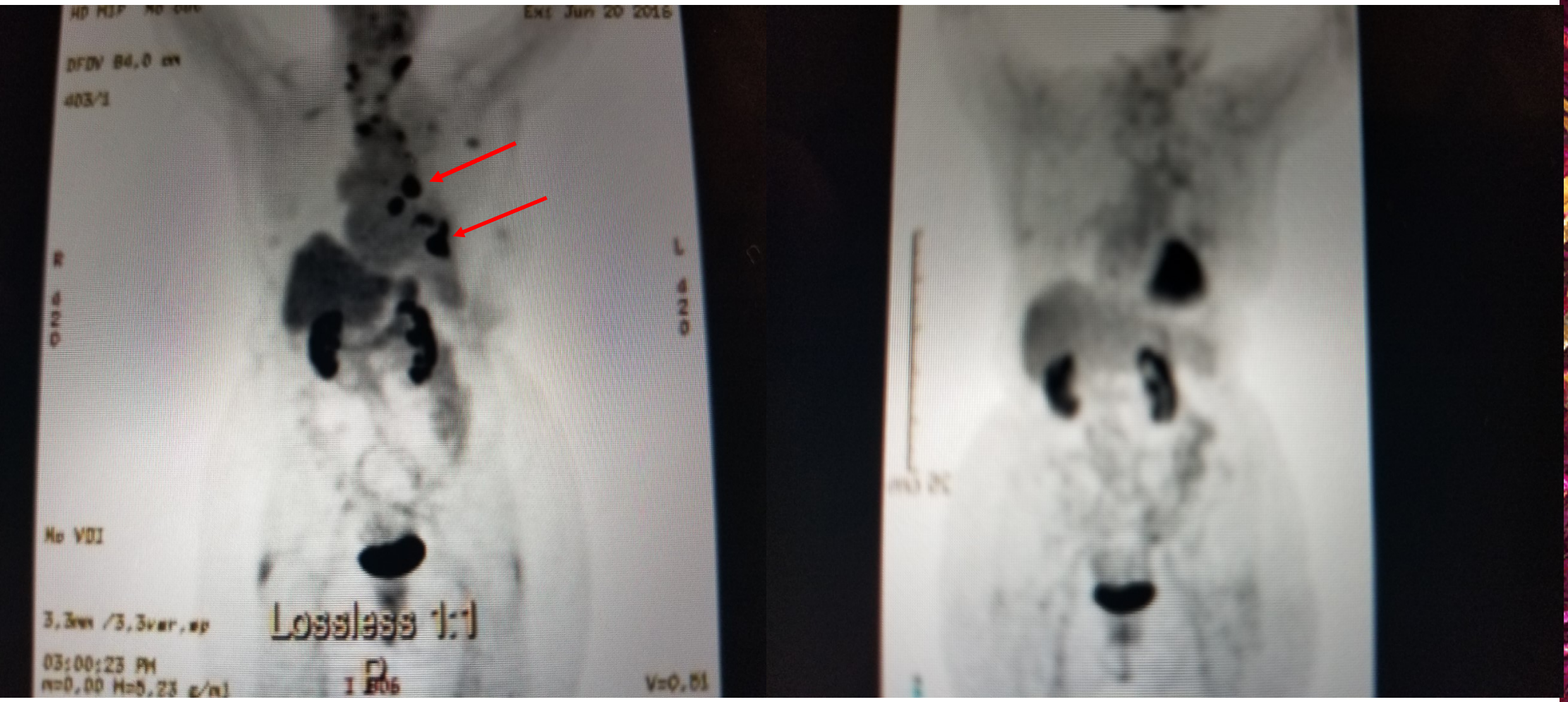


ALEX: PFS

Peters NEJM 2017

ALK/EML4+ Lung Adenocarcinoma Patient, Stage IV

June 2016 — crizotinib | alectinib → August 2018



ALTA-1L: Phase 3, Open-label, Randomized, Multicenter, Study (NCT02737501)

- Stage IIIB/IV ALK+ NSCLC
  - Enrollment based on local ALK testing
- No prior ALK inhibitor
- ≤1 prior systemic therapy for locally advanced/metastatic NSCLC

→ Randomized 1:1

- → Brigatinib 180 mg qd with 7-day lead-in at 90 mg
- → Crizotinib 250 mg bid

Stratified by:
- Brain metastases at baseline (y/n)
- Prior chemotherapy for locally advanced or metastatic disease (y/n)

→
- BIRC-assessed PD*
- Intolerable toxicity
- Other reasons for discontinuation

*Arm B crossover to brigatinib permitted at BIRC-assessed PD

Disease assessment every 8 weeks, including brain MRI for all patients

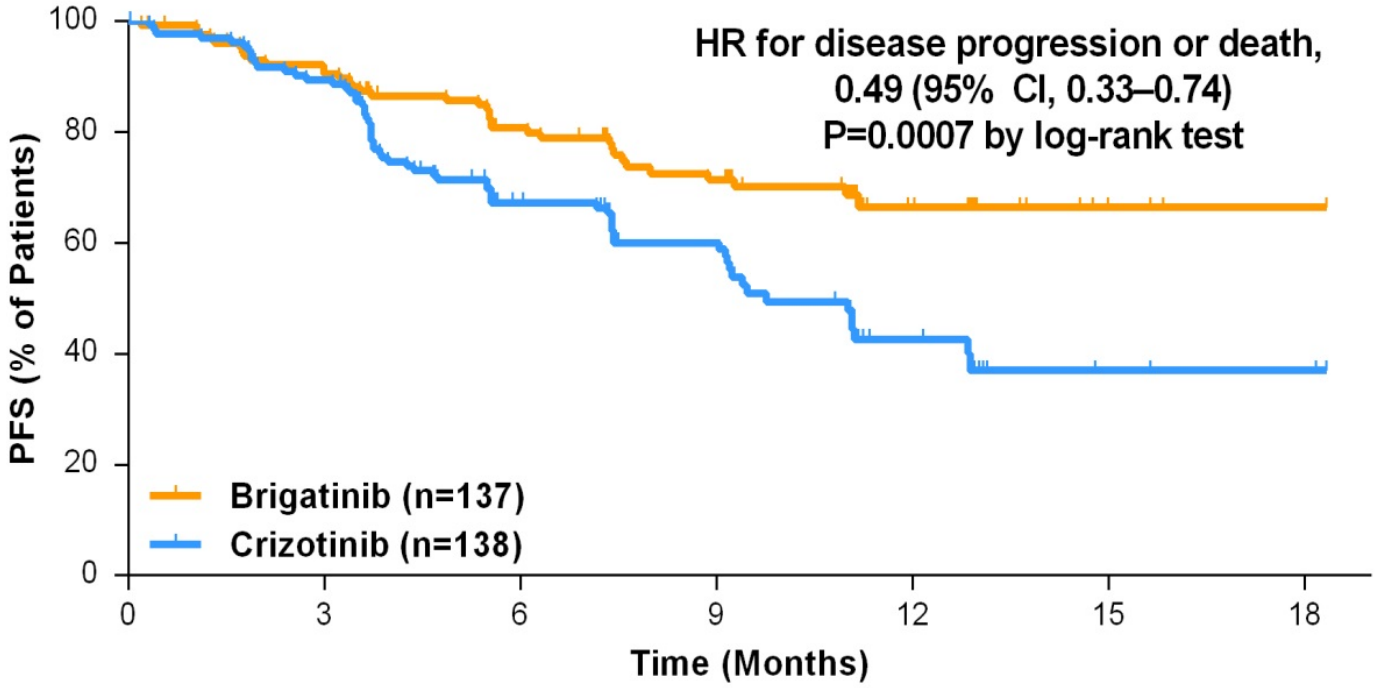
- Primary endpoint: Blinded independent review committee (BIRC)–assessed PFS per RECIST v1.1
- Key secondary endpoints: Confirmed ORR, confirmed intracranial ORR, intracranial PFS, OS, safety, and tolerability
- Statistical considerations: ~270 total patients (198 events); 135 in each arm to detect a 6-month improvement in PFS (HR=0.625), assuming:
  - 10-month PFS in crizotinib arm
  - 2 planned interim analyses at 99 (50%) and 149 (75%) total expected events

Trial fully accrued in August 2017 (N=275)

First Interim Analysis:
- A total of 99 PFS events are included
- According to the pre-specified O'Brien Flemming Lan-DeMets alpha spending function, a 2-sided P-value of 0.0031 will be used to define the threshold for significance

Primary Endpoint: BIRC-Assessed PFS

- **Brigatinib met the prespecified threshold for statistical superiority vs crizotinib**



Treatment	No. (%) of Patients With Events	Median PFS (95% CI)	1-Year PFS, % (95% CI)
Brigatinib (n=137)	36 (26)	NR (NR–NR)	67 (56–75)
Crizotinib (n=138)	63 (46)	9.8 months (9.0–12.9)	43 (32–53)

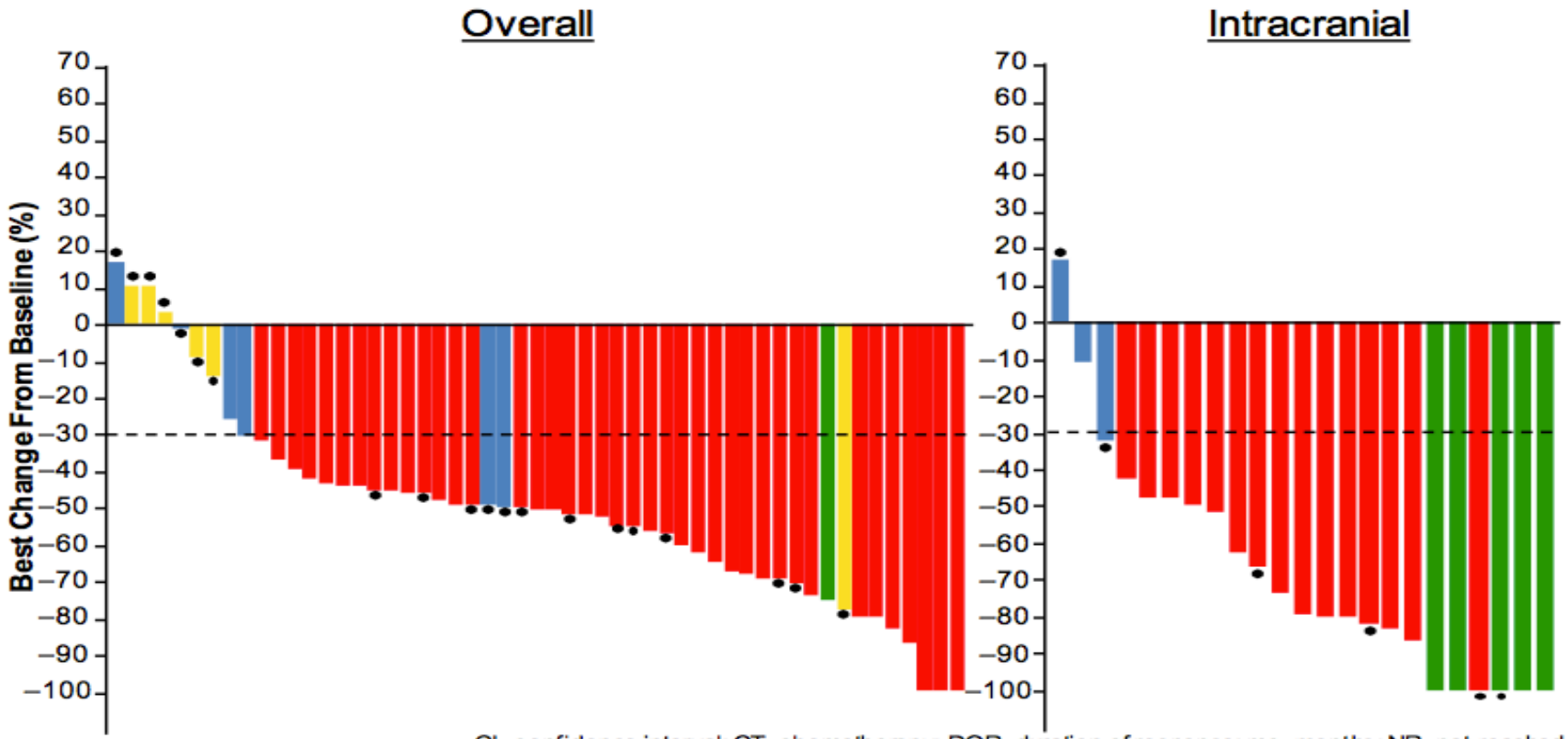
- Investigator-assessed median PFS was NR (95% CI, NR–NR) in the brigatinib arm and 9.2 months (95% CI, 7.4–12.9 months) in the crizotinib arm (HR, 0.45 [95% CI, 0.30–0.68]; log-rank P=0.0001)
- 1-year OS probability: brigatinib, 85% (95% CI, 76%–91%); crizotinib, 86% (77%–91%)

Lorlatinib Phase I/II Study: Crizotinib-Pretreated Patients

Efficacy in EXP2 (ALK+, Crizotinib Only) and EXP3A (ALK+, Crizotinib + CT)

	EXP2+3A (n=59)
ORR, n/N (%) (95% CI)	41/59 (69) (56, 81)
IC ORR, n/N (%) (95% CI)	25/37 (68) (50, 82)
Median DOR, mo (95% CI)	NR (11.1, NR)
DOR ≥6 mo, n°/n (%)	20/41 (49)
Median PFS, mo (95% CI)	NR (12.5, NR)

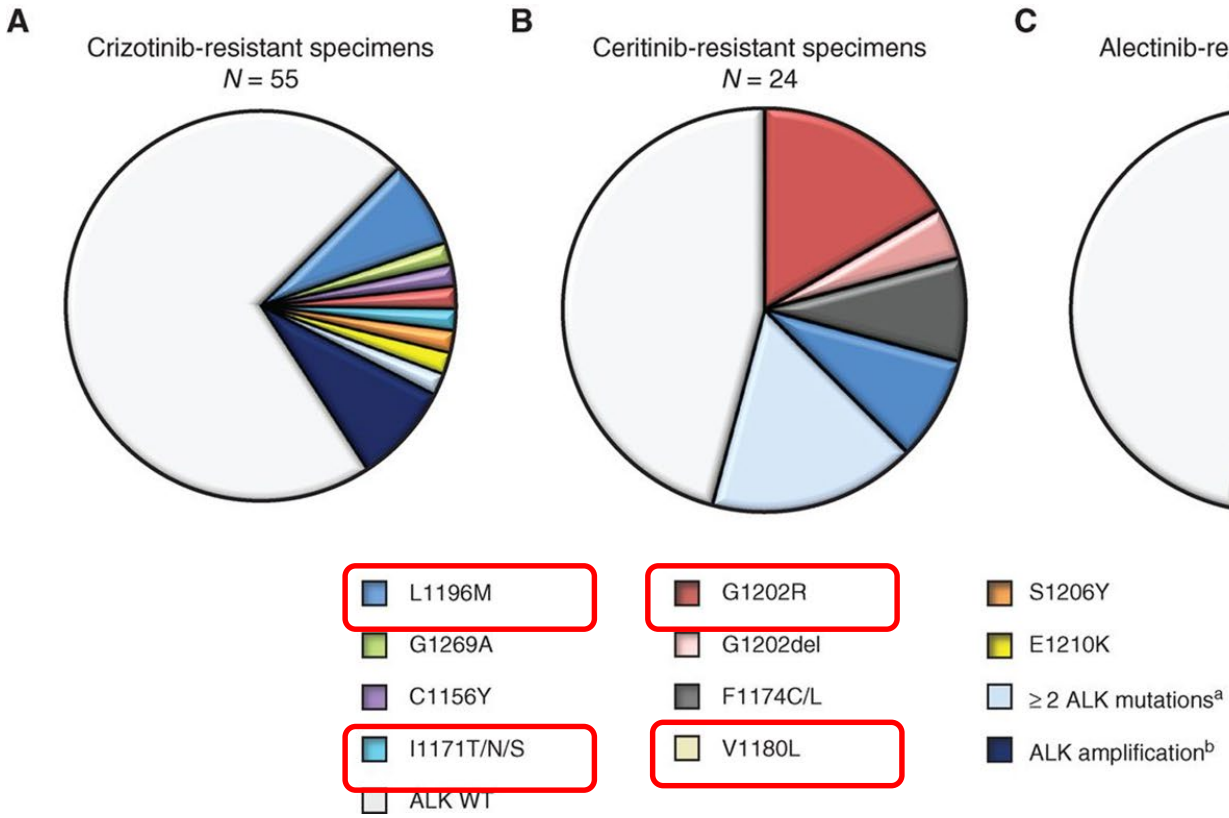
- 37 patients (63%) had brain metastases at baseline.



CI, confidence interval; CT, chemotherapy; DOR, duration of response; mo, months; NR, not reached.

Solomon et al. World Conference on Lung Cancer; Yokohama, Japan, 2017

Genetic diagnosis is needed!!!
Will the Choice of 1st Line ALKi TKI Impact on Patterns of Progression & Mechanism of Resistance?



G1202R → Lorlatinib

I1171T → Ceritinib/ Brigatinib/Lorlatinib

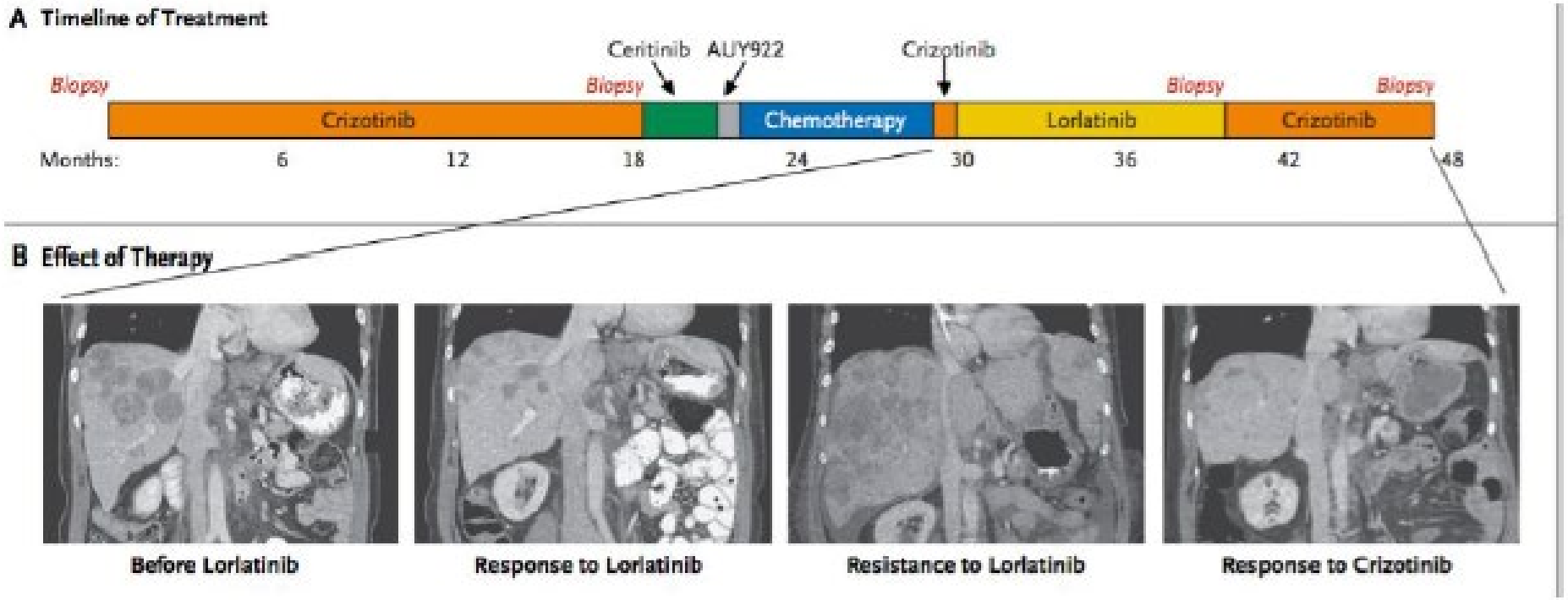
V1180L → Chemo? Other TKI?

L1196M → Ceritinib/ Brigatinib/Lorlatinib

Justin F. Gainor et al. Cancer Discov 2016;6:1118-1133

IASLC 2017

The Art of Precision Medicine



Resensitization to Crizotinib by the Lorlatinib *ALK* Resistance Mutation L1198F

Shaw et al.
NEJM 2016

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2019
Non-Small Cell Lung Cancer

NCCN Guidelines Index
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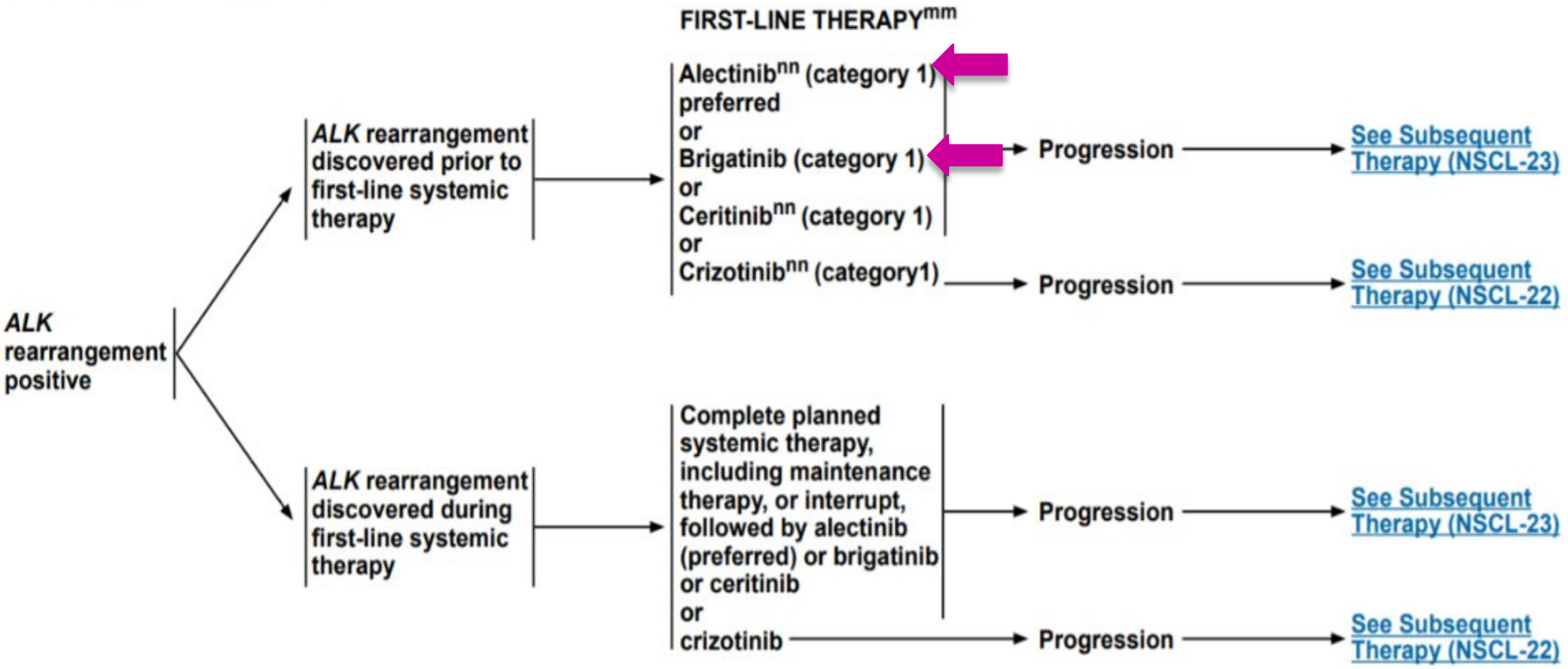
Discussion

ALK REARRANGEMENT POSITIVE[hh]



NCCN Guidelines Version 3.2019
Non-Small Cell Lung Cancer
January 18, 2019

Conclusion…

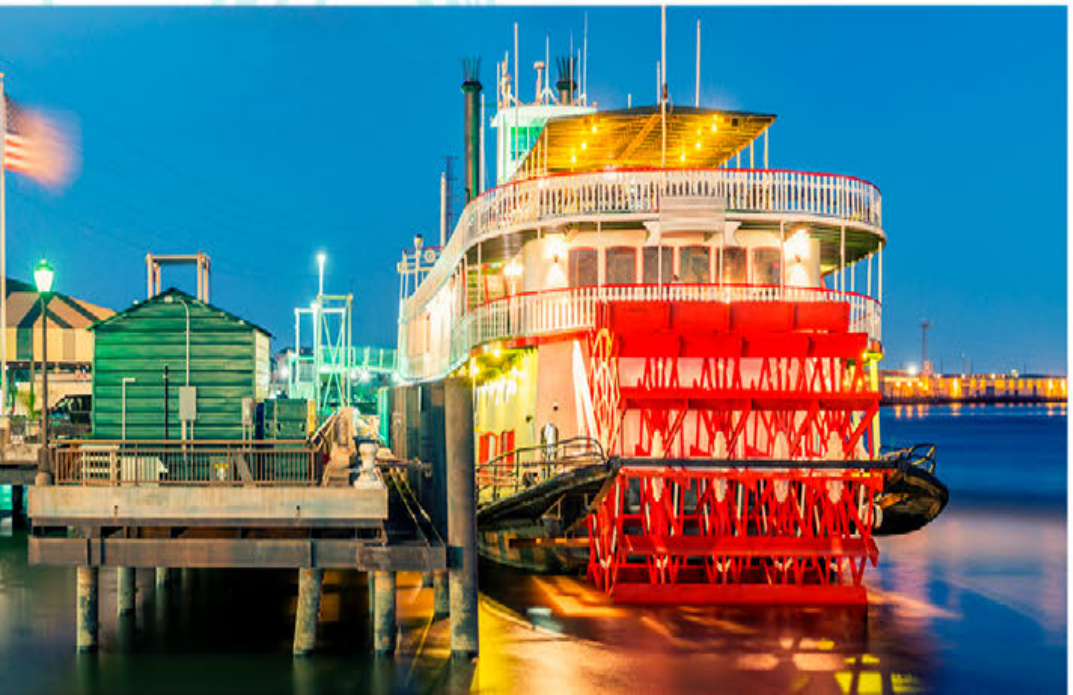
- All Non-Squamous NSCLC should have a Molecular Tumor Profile analysis.
- Targeted therapy precedes immunotherapy regardless of PD-L1 expression.
- For NSCLC patients w/o driver mutations, IO or chemo-IO is the new standard of care.
- Developing data suggests that liquid biopsy and tissue molecular profile are complementary, and give us the entire molecular picture of lung cancer.

NOSCM

NEW ORLEANS SUMMER CANCER MEETING

July 19-21, 2019

14th ANNUAL NEW ORLEANS SUMMER CANCER MEETING



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