Optimal sequencing of EGFR Mutation-Driven NSCLC

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University of Athens Medical School

29 November 2019

The therapeutic landscape is changing rapidly..

EGFR +: 1st line treatment options

Erlotinib

Gefitinib

Afatinib

Dacomitinib

Osimertinib

APPROVED

TARGETED THERAPY FOR ADVANCED OR METASTATIC DISEASE

Sensitizing *EGFR* Mutation Positive

- First-line therapy
  - Afatinib[1]
  - Erlotinib[2]
  - Dacomitinib[3]
  - Gefitinib[4,5]
  - Osimertinib
- Subsequent therapy
  - Osimertinib[7]

All category I

Which 1st line treatment choice would be the best ..

..what would be the ideal sequencing ?

Choosing the right sequencing

TKIs are standard upfront

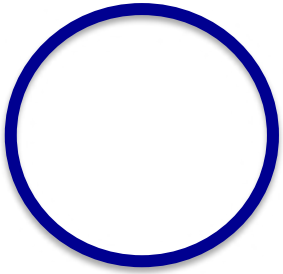
TKIs vs chemotherapy ?

	TKI	Study	RR (%)		PFS (mo)		OS (mo)	
			TKI	Chemo	TKI	Chemo	TKI	Chemo
	Gefitinib	IPASS[1,2]	71	47	9.5	6.3	21.6	21.9
	Gefitinib	F-Signal[3]	55	46	5.8	6.4	22.3	22.9
	Gefitinib	WJTOG[4]	62	32	9.2	6.3	30.9	NR
	Gefitinib	NEJ002[5,6]	73	31	10.8	5.4	27.7	26.6
	Erlotinib	EURTAC[7]	58	15	9.7	5.2	19.3	19.5
	Erlotinib	ENSURE[8]	63	34	11.0	5.5	26.3	25.5
	Erlotinib	OPTIMAL[9,10]	83	36	13.7	4.6	22.8	27.2
	Afatinib[a]	LL3[11,12]	56	23	13.6	6.9	[illegible].6	28.2
	Afatinib[a]	LL6[12,13]	66	23	11.0	[illegible].6		23.5

TKIs superiority

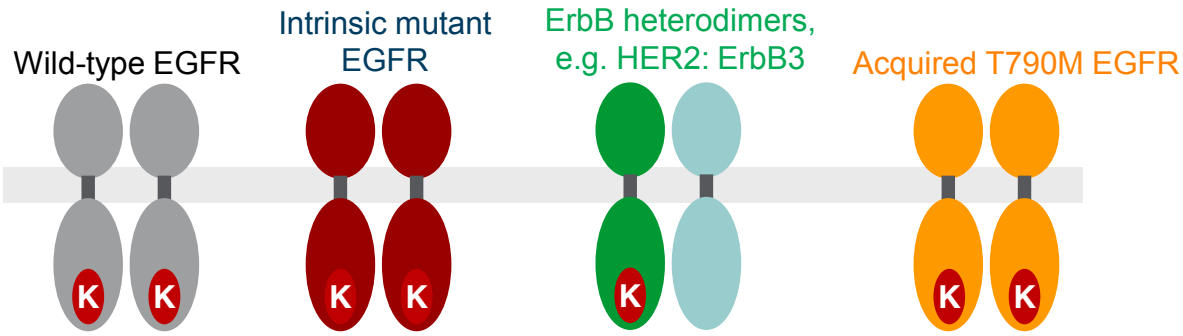
Choosing the right sequencing

TKIs are standard upfront



Not all TKIs are the same

Not ALL TKIs are not the same:
Activity against EGFR mutations



Erlotinib
Gefitinib

First-generation TKI

EGFR inhibition

Activity range

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

Afatinib
Dacomitinib

Second-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

Third-generation TKI

EGFR mutant-specific inhibitor

Activity

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

Range

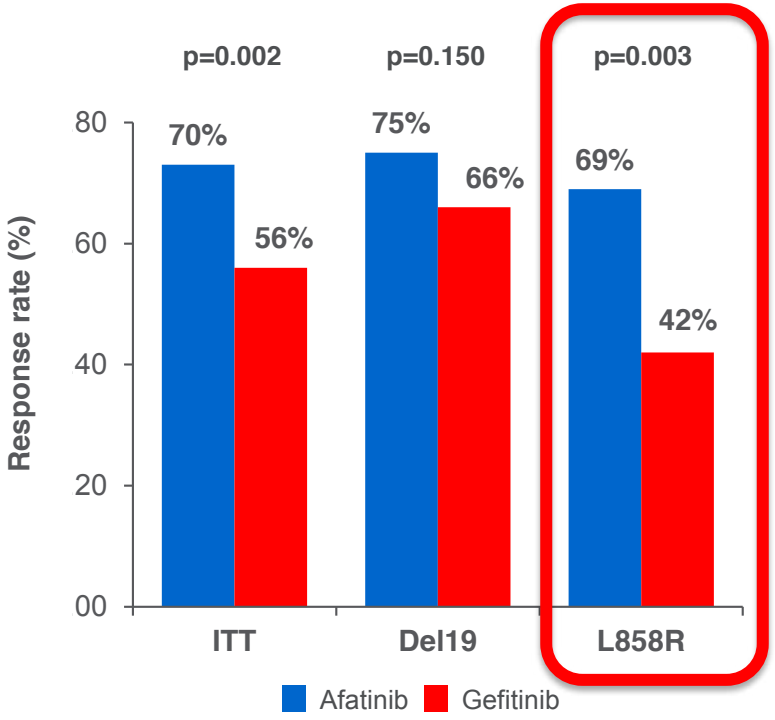
K Kinase domain

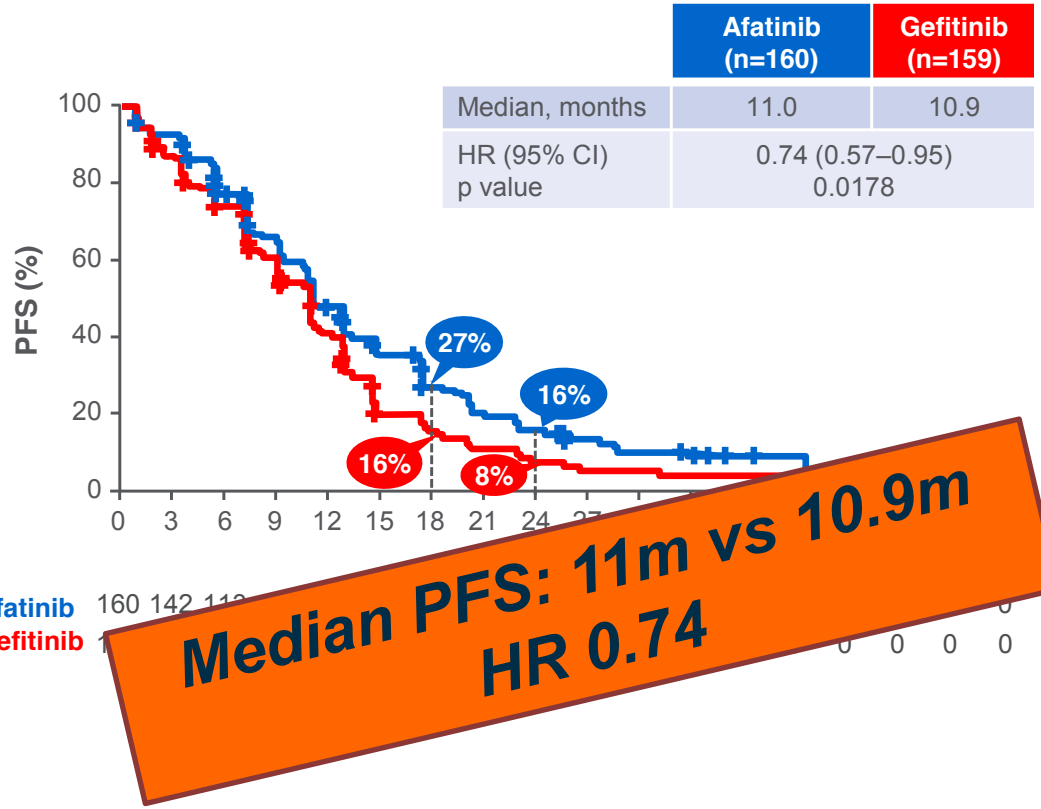
Not ALL TKIs are not the same:

Antitumor Activity

1st vs 2nd generation TKI

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





	Afatinib (n=160)	Gefitinib (n=159)
Median, months	11.0	10.9
HR (95% CI) p value	0.74 (0.57–0.95) 0.0178	

Median PFS: 11m vs 10.9m
HR 0.74

Not ALL TKIs are not the same:

Antitumor Activity

1st vs 2nd generation TKI

ARCHER 1050: Dacomitinib vs Gefitinib (excluding CNS metastases)

ARCHER 1050: study design

Phase III, randomised, 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 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)

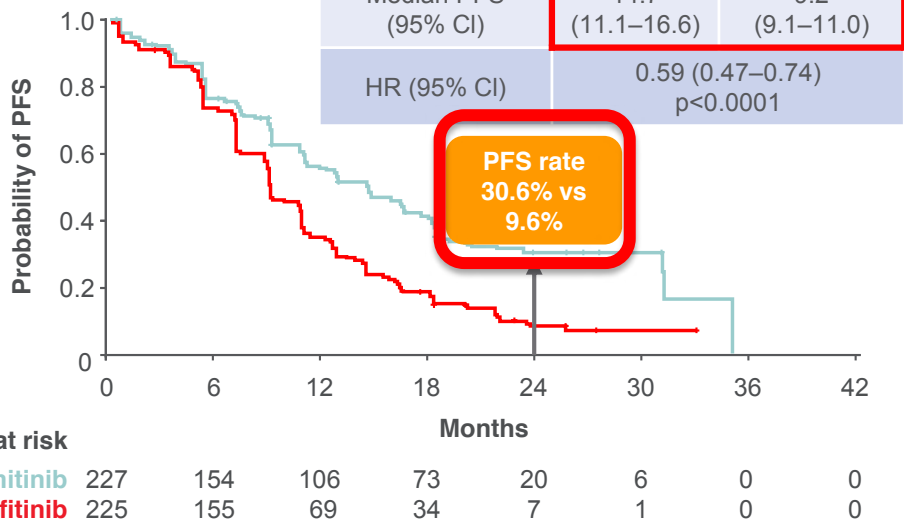
Primary endpoint
PFS by blinded independent review
- ≥256 PFS events
- PFS HR ≤0.667 (50%↑)
- 90% power
- 1-sided α=0.025
- mPFS: 14.3 vs 9.5 months

Satisfaction factors
Race (including Asian vs non-Asian)
EGFR mutation type (exon 19 vs 21)

Secondary endpoints
PFS (investigator assessed), ORR, DOR, TTF, OS, safety, PROs

PFS: blinded independent review (ITT population)

	Daco (n=227)	Gef (n=225)
Number of 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	

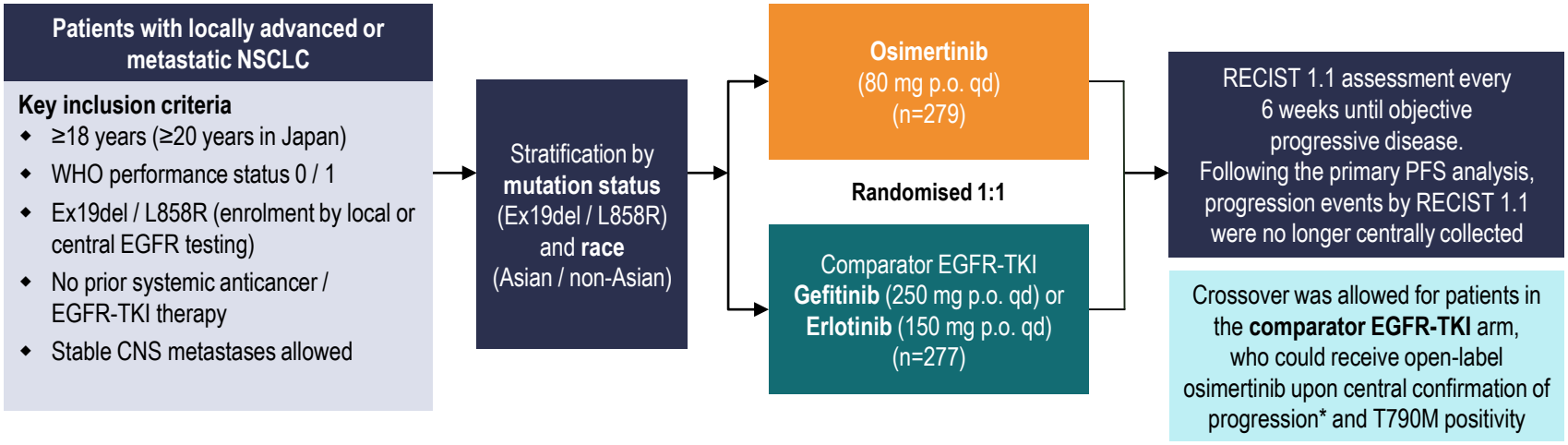


Not ALL TKIs are not the same:

Antitumor Activity

1st vs 3rd generation TKI

FLAURA DOUBLE-BLIND STUDY DESIGN



OS was a key secondary endpoint

- Final OS analysis planned for when approximately 318 death events had occurred
- For statistical significance, a p-value of less than 0.0495, determined by O'Brien-Fleming approach, was required
  - Alpha spend for interim OS analysis was 0.0015
- At data cut-off, 61 patients (22%) in the osimertinib arm and 13 patients (5%) in the comparator arm were ongoing study treatment

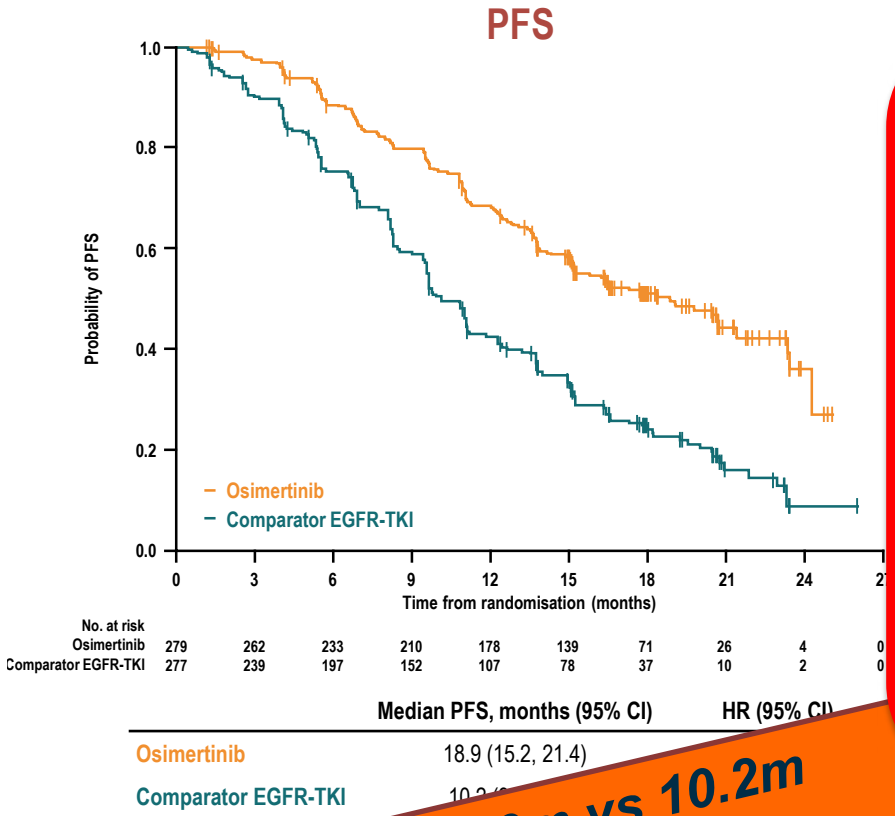
Data cut-off: 25 June 2019

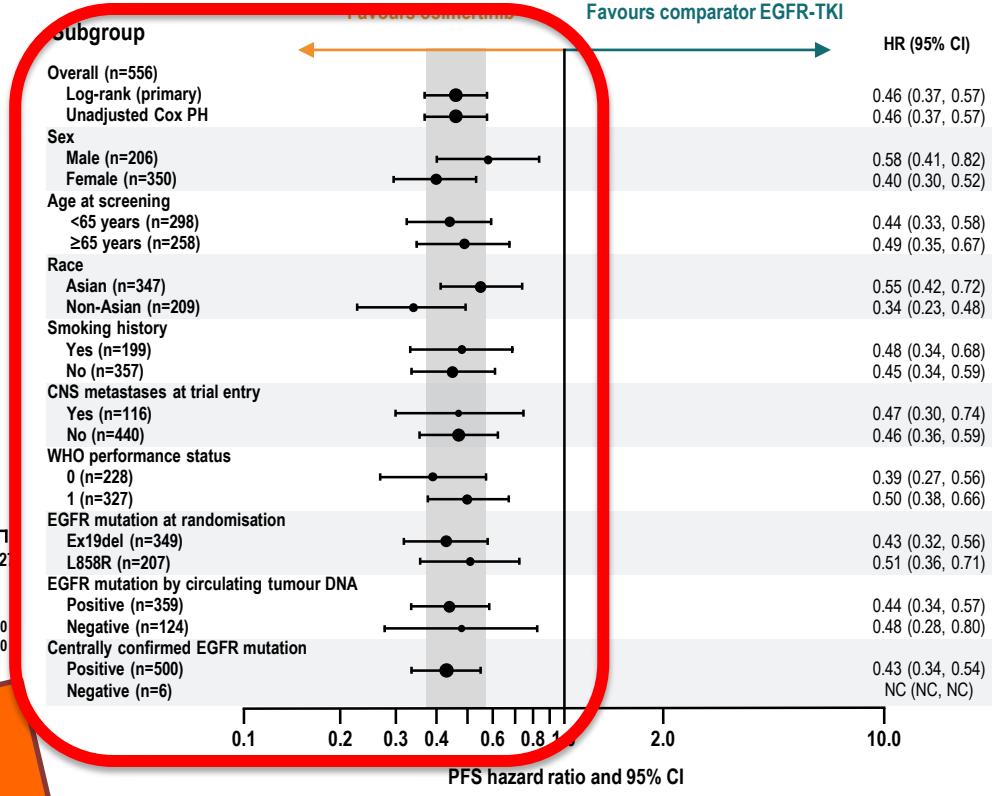
Soria et al. N Engl J Med 2018;378:113-25

*By investigator assessment if disease progression occurred after the primary analysis data cut-off

p.o., orally; qd, once daily; RECIST 1.1, Response Evaluation Criteria In Solid Tumors version 1.1; WHO, World Health Organization

PRIMARY ANALYSIS: PROGRESSION-FREE SURVIVAL





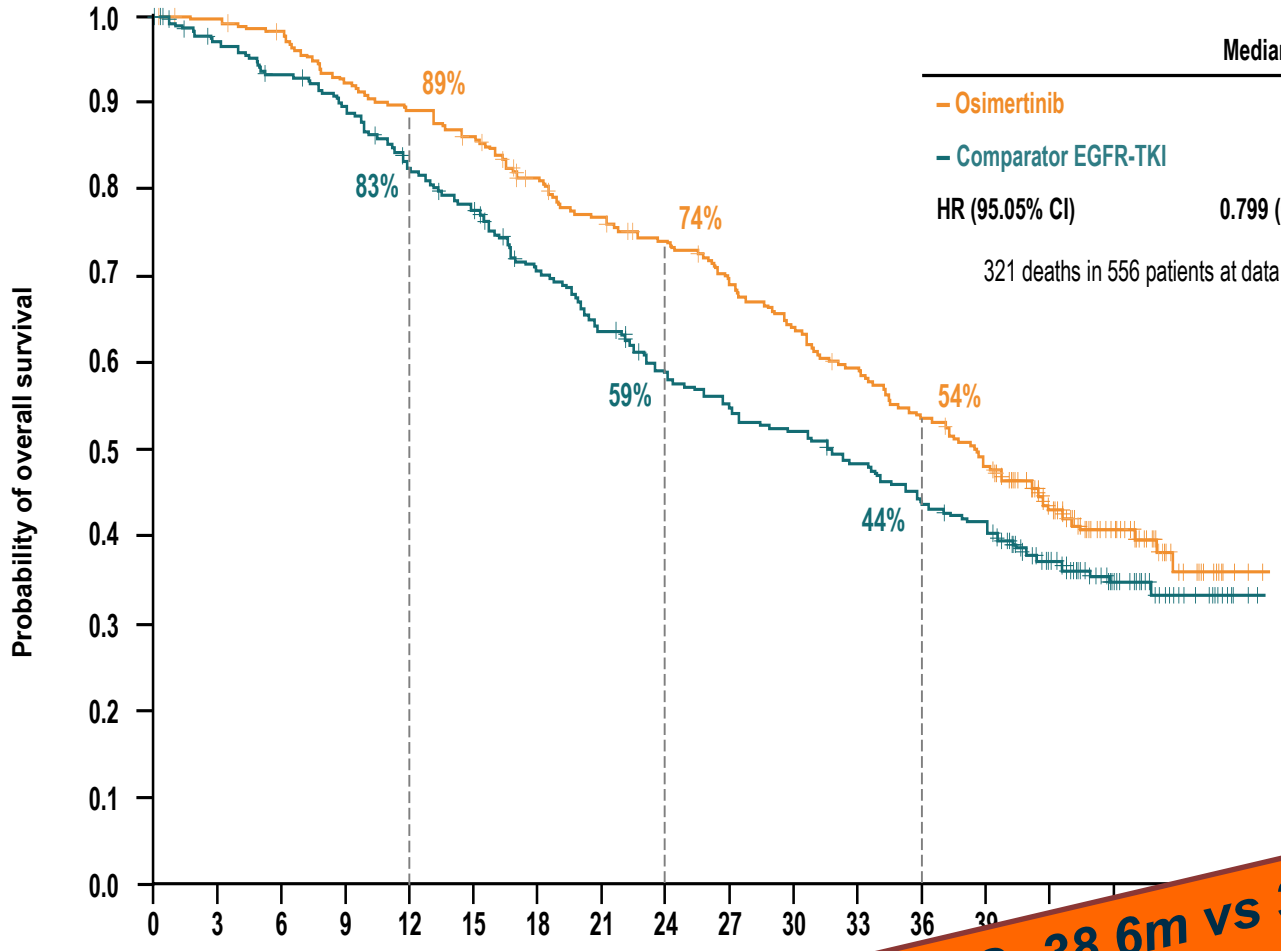
Median PFS: 18.9m vs 10.2m
HR 0.49

Data cut-off: 12 June 2017

Soria et al. N Engl J Med 2018;378:113-25

CI, confidence interval; ctDNA, circulating tumour DNA; NC, not calculable; PH, proportional-hazards

FINAL ANALYSIS: OVERALL SURVIVAL



Median OS: 38.6m vs 31.8m
HR 0.799

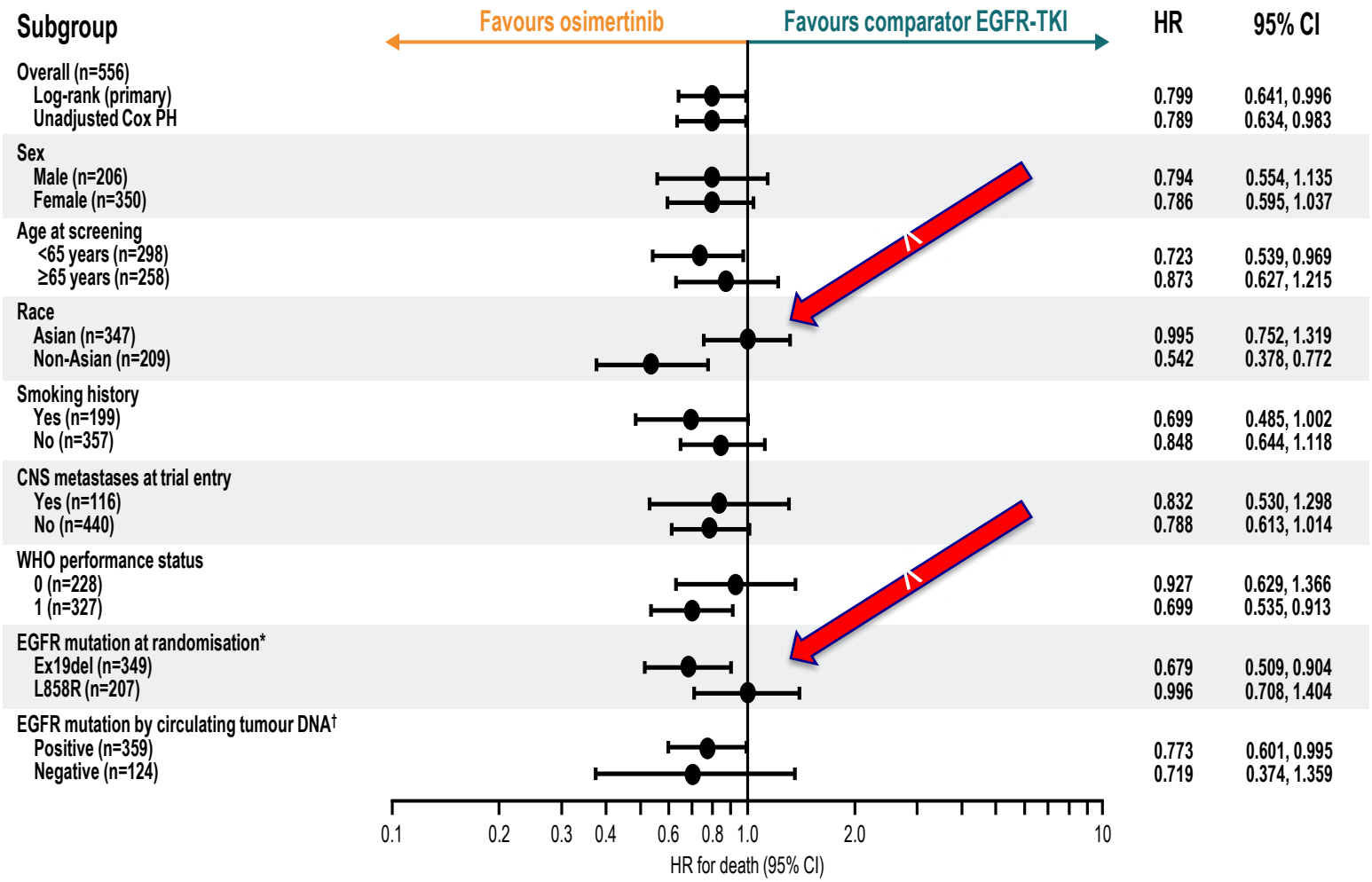
UNCONTR

BARCELONA 2019 ESMO congress

Data cut-off: 25 June 2019

For statistical significance, a p-value of less than 0.0495, determined by O'Brien-Fleming approach, was required

OVERALL SURVIVAL ACROSS SUBGROUPS



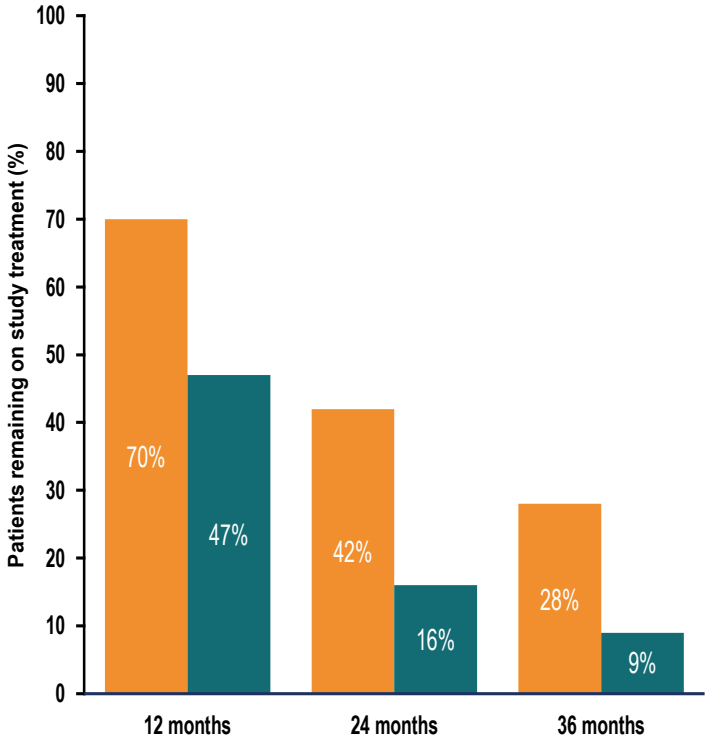
Data cut-off: 25 June 2019

Hazard ratio <1 implies a lower risk of death on osimertinib

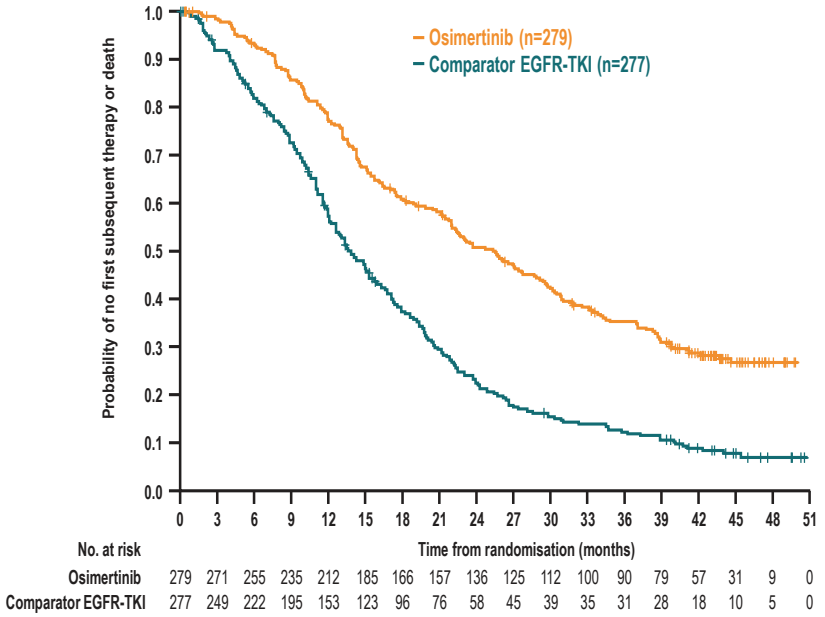
*Local or central test; †Result missing for 36 patients in the osimertinib arm and 37 patients in the comparator EGFR-TKI arm

PATIENTS REMAINING ON STUDY TREATMENT AND TIME TO FIRST SUBSEQUENT TREATMENT OR DEATH

Patients remaining on study treatment



Time to first subsequent treatment*



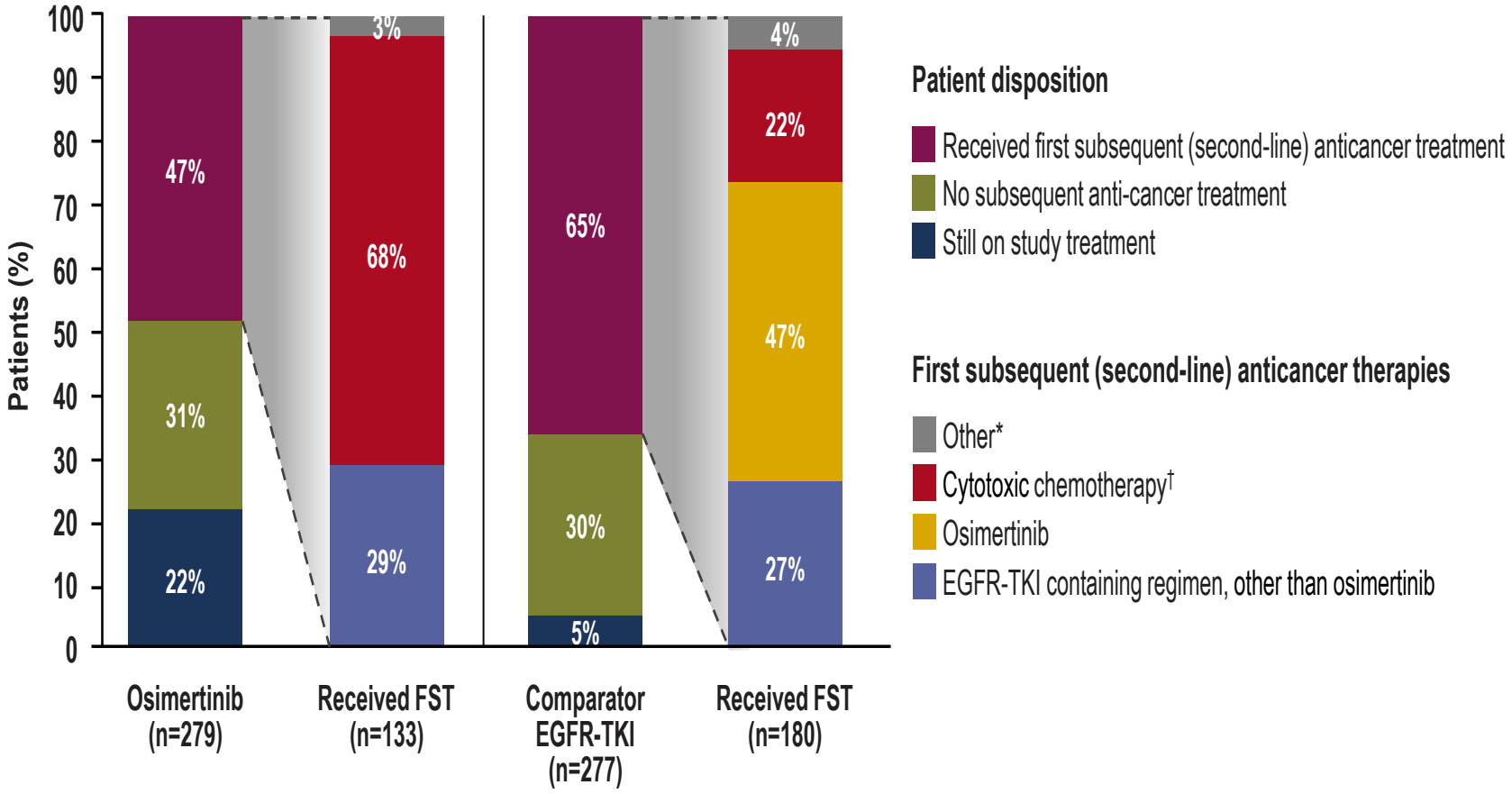
Time to first subsequent therapy or death	Events	Median, months (95% CI)
Osimertinib	194	25.5 (22.0, 29.1)
Comparator EGFR-TKI	242	13.7 (12.3, 15.7)
HR (95% CI)		**0.478 (0.393, 0.581) p<0.0001**

Data cut-off: 25 June 2019

*Time from the date of randomisation to the earlier of the date of anti-cancer therapy start date following study drug discontinuation or death

SECOND-LINE TREATMENT FOLLOWING PROGRESSION

- Of the 180 patients in the comparator EGFR-TKI arm who received a first subsequent treatment, **85 patients (47%) crossed over to osimertinib** (31% of all patients randomised from the comparator EGFR-TKI arm)



Data cut-off: 25 June 2019

*Refers to those patients who did not receive either chemotherapy or an EGFR-TKI; †The majority of patients who received cytotoxic chemotherapy received a platinum-based chemotherapy regimen

FST, first subsequent treatment

Not ALL TKIs are not the same:

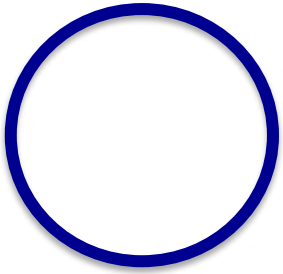
Toxicity profile

	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)	Erlotinib or gefitinib (n=277)
Treatment discontinuation rate	6.2%	6.3%	9.7%	6.7%	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	Rash/acne 7%

PROMs in favor of TKIs

Choosing the right sequencing

TKIs are standard upfront



Not all TKIs are the same

Biology drives sequence

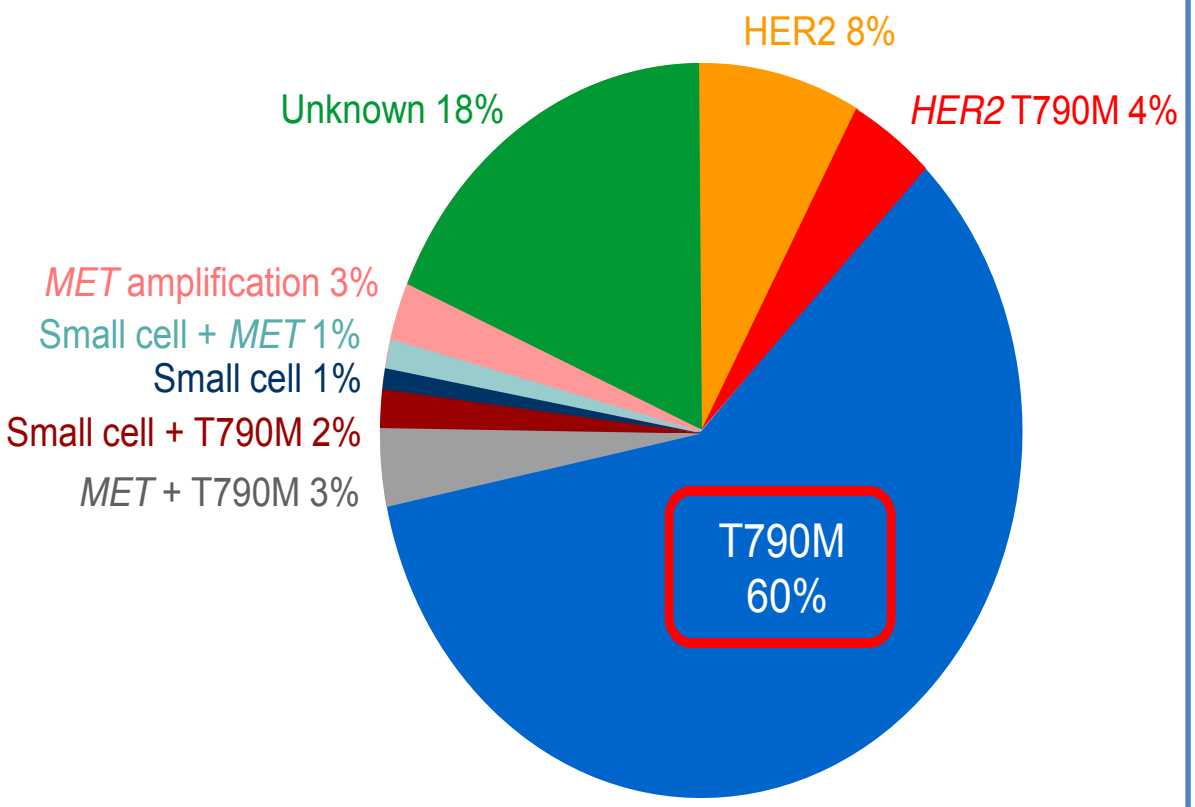
Biology drives sequencing:

Mechanisms of resistance

After 1st or 2nd generation TKI

155 EGFR-mutant NSCLC patients, acquired resistance after TKI

Molecular analyses on re-biopsy specimen

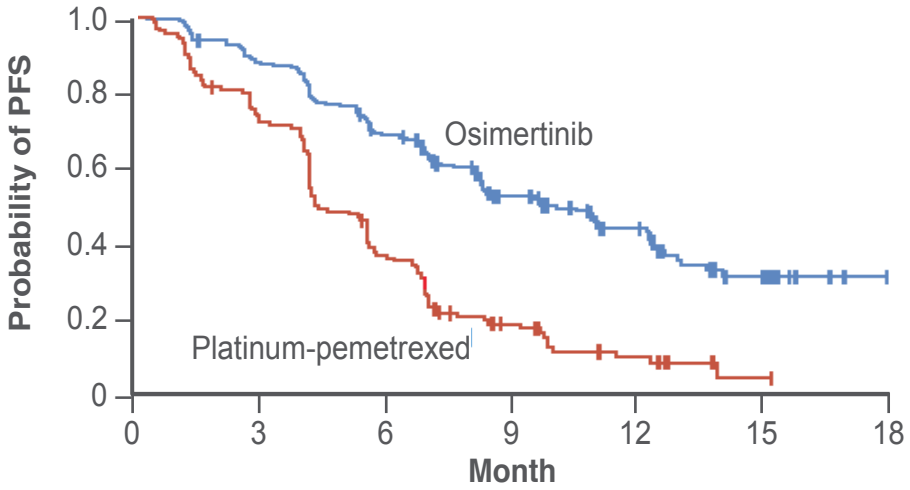


Biology drives sequencing:

Mechanisms of resistance

After 1st or 2nd generation TKI

Patients in the population



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

	No. of patients	Median PFS (months) (95% CI)
Osimertinib	279	10.1 (8.3-12.3
Platinum-pemetrexed	140	4.4 (4.2-5.6)

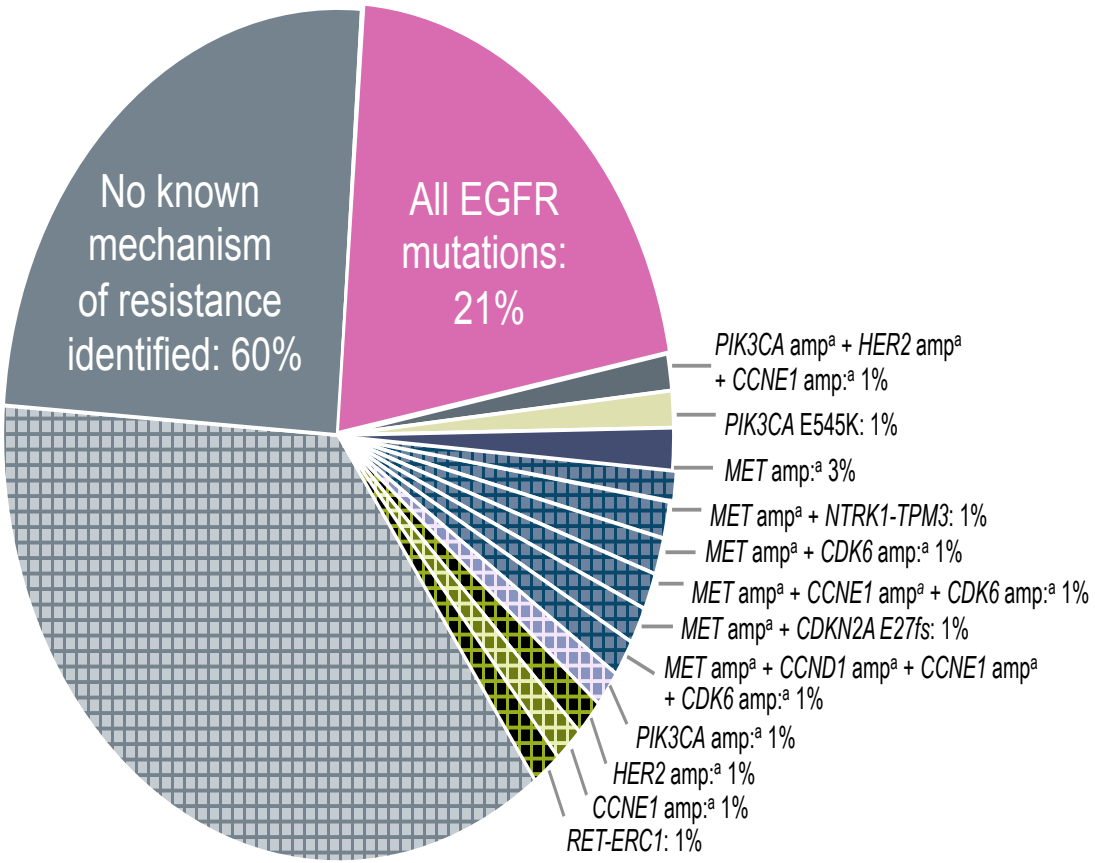
HR for PD or death, 0.30 (95% CI: 0.23–0.41)
p<0.001

Biology drives sequencing:

Mechanisms of resistance

After osimertinib

Patients receiving osimertinib (n=73)



Acquired Alterations

- Acquired EGFR mutations: 21%
- *MET* amp:[a] 19%
- Cell-cycle gene alterations: 12%
- *HER2* amp:[a] 5%
- *PIK3CA* amp[a]/mutation: 5%
- Oncogenic fusion: 4%
- *BRAF* V600E: 3%
- Loss of T790M: 49%

Any acquired EGFR mutation (-/+ other alterations)

MET amplification (-/+ other alterations except EGFR)

No known resistance mechanism

T790M loss

Amp = amplification; *BRAF* = v-Raf murine sarcoma viral oncogene homolog B; CAST = calpastatin; *CCND1* = cyclin-D1; *CCNE1* = cyclin-E1; *CDK6* = cyclin-dependent kinase 6; *CDKN2A* = cyclin-dependent kinase inhibitor 2A; EGFR = epidermal growth factor receptor; *ERC1* = ELKS/Rab6-interacting/CAST family member 1; fs = frameshift; *HER2* = human epidermal growth factor receptor 2; *MET* = met proto-oncogene (hepatocyte growth factor receptor); *NTRK1* = neurotrophic tyrosine kinase receptor 1; *PIK3CA* = phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha; *RET* = rearranged during transfection proto-oncogene; *TPM3* = tropomyosin 3.

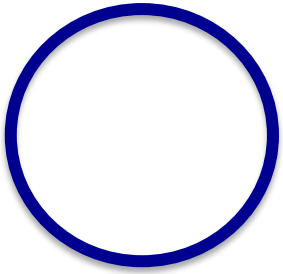
[a]Amplification events may be underrepresented in plasma analyses.

Papadimitrakopoulou V et al. Presented at: ESMO Congress; October 19-23, 2018; Munich, Germany.

Choosing the right sequencing

TKIs are standard upfront

Sequencing senarios



Not all TKIs are the same

Biology drives sequence

22-24 months for T790M +ve

1st or 2nd gen TKI up to 12-14 mos → 3rd gen TKI 10 mos

17-19 months for T790M -ve

1st or 2nd gen TKI up to 12-14 mos → Chemo 5 mos

24 months

Osimertinib as the 1st line treatment 19 mos → Chemo 5 mos

Median OS 38.6m

Thoughts & concerns

CNS metastases

CNS response to osimertinib in patients with T790M-positive advanced NSCLC: data from a randomized Phase III trial (AURA3)

Tony Mok[1], Myung-Ju Ahn[2], Ji-Youn Han[3], Jin-Hyoung Kang[4], Nobuyuki Katakami[5], Hye Ryun Kim[6], Rachel Hodge[7], Dana Ghiorghiu[7], Mireille Cantarini[8*], Yi-Long Wu[9], Vassiliki A Papadimitrakopoulou[10], Marina Chiara Garassino[11]

[1]State Key Laboratory in Oncology in South China, Sir YK Pao Centre for Cancer, Department of Clinical Oncology, Chinese University of Hong Kong, Hong Kong; [2]Samsung Medical Centre, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [3]Center for Lung Cancer, National Cancer Center, Goyang, Republic of Korea; [4]Catholic University Seoul St Mary's Hospital, Seoul, Republic of Korea; [5]Institute of Biomedical Research and Innovation, Kobe, Japan; [6]Department of Internal Medicine, Division of Medical Oncology, Yonsei University College of Medicine, Seoul, Republic of Korea; [7]AstraZeneca, Cambridge, UK; [8]AstraZeneca, Macclesfield, UK; [9]Guangdong Lung Cancer Institute, G
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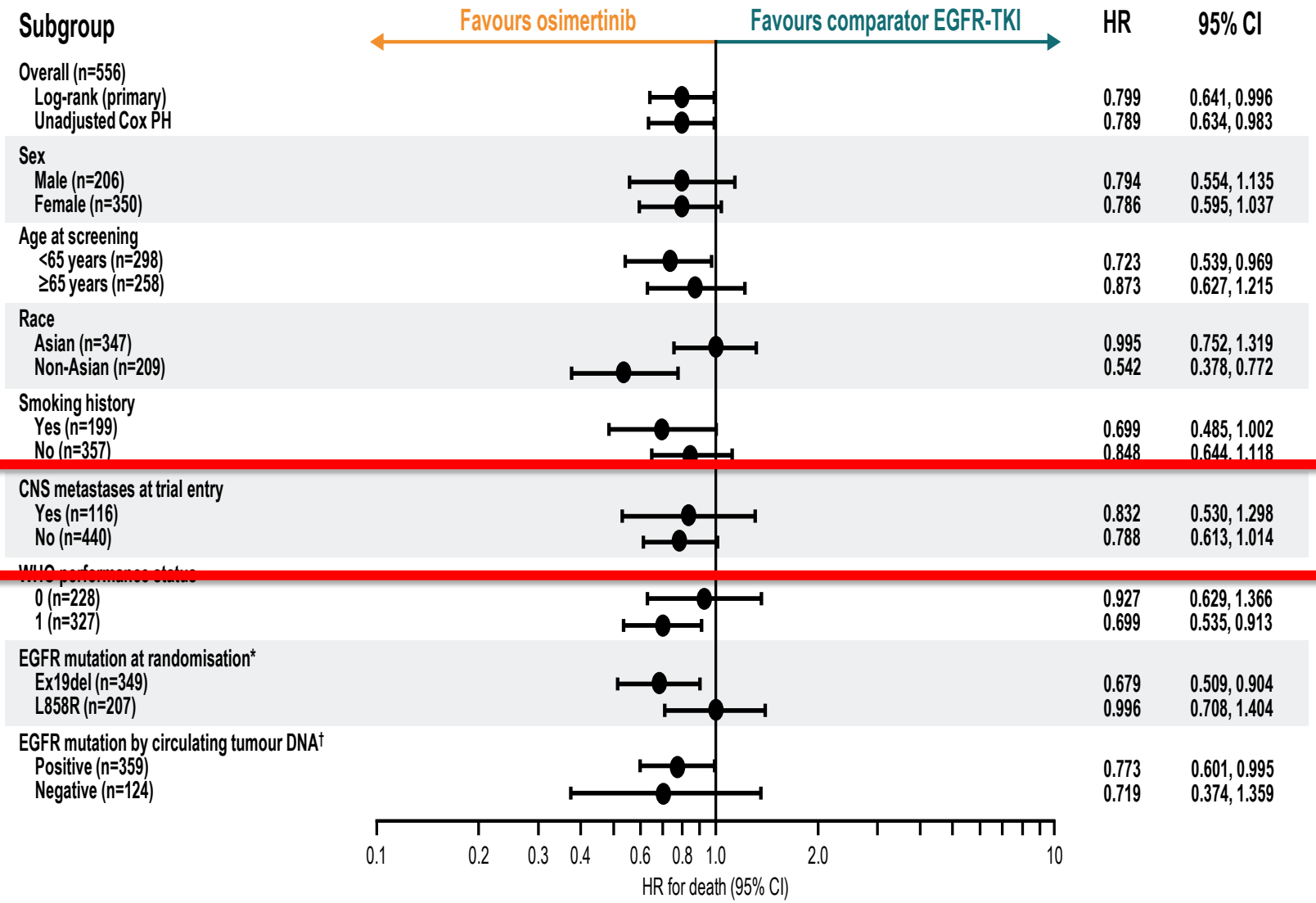
	Osimertinib 80 mg n=30	Chemotherapy n=16
CNS ORR (95% CI)	**70% (51, 85)**	**31% (11, 59)**
Odds ratio (95% CI)	5.13 (1.44, 20.64); p=0.015	
Median time to response, weeks	6.1	6.1
Median DoR, months (95% CI)	**8.9 (4.3, NC)**	**5.7 (NC, NC)**
DCR (95% CI)	**93% (78, 99)**	**63% (35, 85)**

OVERALL SURVIVAL ACROSS SUBGROUPS



Data cut-off: 25 June 2019

Hazard ratio <1 implies a lower risk of death on osimertinib

*Local or central test; †Result missing for 36 patients in the osimertinib arm and 37 patients in the comparator EGFR-TKI arm

Can we make EGFR TKIs better ?

International Journal of
Radiation Oncology
biology • physics
Official Journal of the American Society for Radiation Oncology
ASTRO
Non-Men

< Previous Article | October 1, 2017 Volume 99, Issue 2, Supplement, Page E458 | Next Article >

Chemotherapy plus *EGFR*-TKIs versus *EGFR*-TKIs Alone in Non–small Cell Lung Cancer with *EGFR*-Activating M

G. H
3088

DOI:

AACR ANNUAL MEETING 2019 ATLANTA

TATTON Phase Ib expansion cohort: osimertinib plus savolitinib for patients with EGFR-mutant, MET-amplified NSCLC after progression on prior epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI)

Ph
er
NSCLC harboring activating EGFR mutations:
NEJ026.

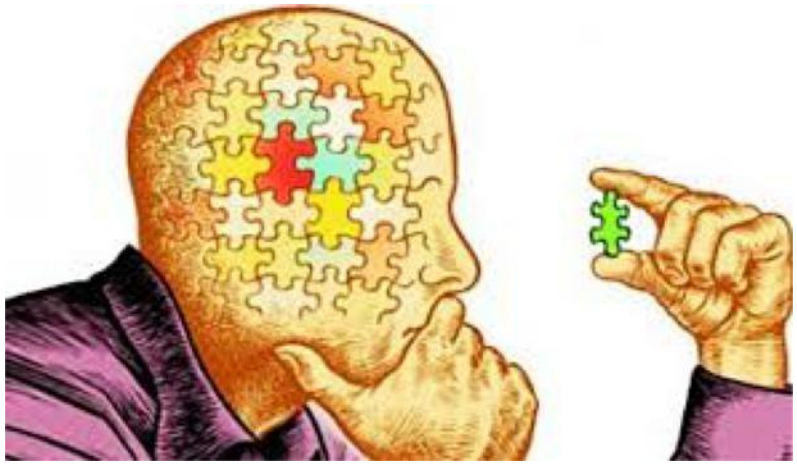
Naoki Furuya, Tatsuro Fukuhara, Haruhiro Saito, Kana Watanabe, Shunichi Sugawara, Shunich

Lancet Oncol. 2019 Oct 4. pii: S1470-2045(19)30634-5. doi: 10.1016/S1470-2045(19)30634-5. [Epub ahead of print]

Ramucirumab plus erlotinib in patients with untreated, EGFR-mutated, advanced non-small-cell lung cancer (RELAY): a randomised, double-blind, placebo-controlled, phase 3 trial.

Nakagawa K[1], Garon EB[2], Seto T[3], Nishio M[4], Ponce Aix S[5], Paz-Ares L[5], Chiu CH[6], Park K[7], Novello S[8], Nadal E[9], Imamura F[10], Yoh K[11], Shih JY[12], Au KH[13], Moro-Sibilot D[14], Enatsu S[15], Zimmermann A[16], Frimodt-Moller B[17], Visseren-Grul C[18], Reck M[19]; RELAY Study Investigators.

What about beyond TKIs?



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC

M.A. Socinski, R.M. Jotte, F. Cappuzzo, F. Orlandi, D. Stroyakovskiy, N. Nogami, D. Rodríguez-Abreu, D. Moro-Sibilot, C.A. Thomas, F. Barlesi, G. Finley, C. Kelsch, A. Lee, S. Coleman, Y. Deng, Y. Shen, M. Kowanetz, A. Lopez-Chavez, A. Sandler, and M. Reck, for the IMpower150 Study Group*

This article was published on June 4, 2018, at NEJM.org.

DOI: 10.1056/NEJMoa1716948

Atezolizumab in the 1st line setting

Atezolizumab + carbo + paclitaxel + bevacizumab

vs

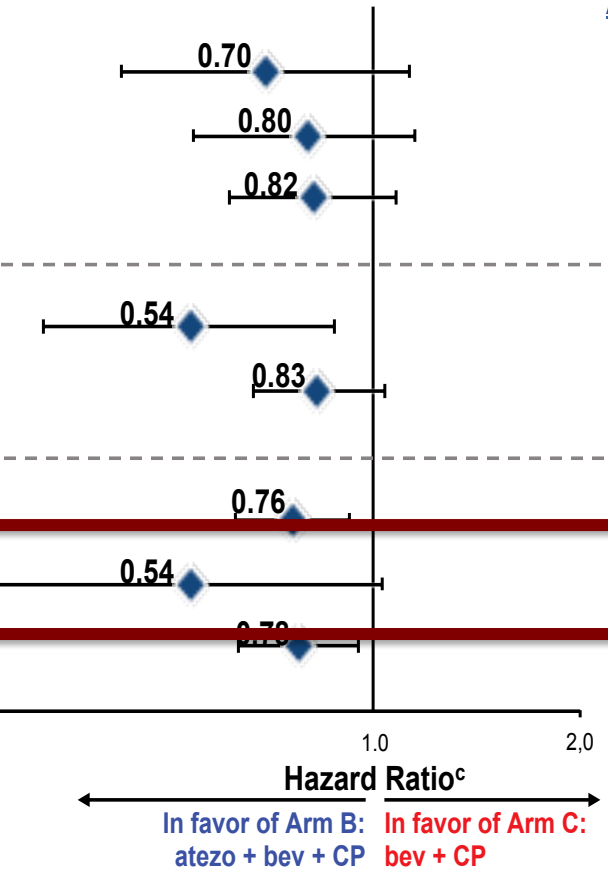
chemotherapy

- **OS:** 19.2m vs 14.7m *p=0.0164*

(regardless PDL1)

OS in Key Subgroups (Arm B vs Arm C)

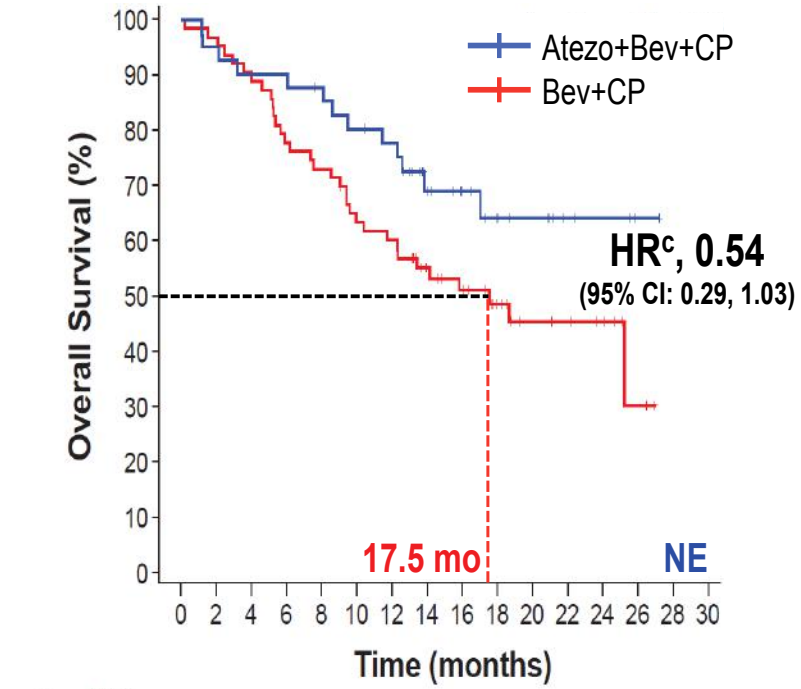
Subgroup	n (%)[a]	Median OS, mo: Arm B	Arm C
PD-L1–High (TC3 or IC3) WT	136 (20%)	25.2	15.0
PD-L1–Low (TC1/2 or IC1/2) WT	226 (32%)	20.3	16.4
PD-L1–Negative (TC0 and IC0) WT	339 (49%)	17.1	14.1
Liver Metastases WT	94 (14%)	13.2	9.1
No Liver Metastases WT	602 (86%)	19.8	16.7
ITT (including *EGFR/ALK*+)	800 (100%)	19.8	14.8
EGFR/ALK+ only	104[b] (13%)	NE	17.5
ITT-WT	696 (87%)	19.2	14.7



NE, not estimable.
[a] Prevalence % for PD-L1 IHC and liver metastases subgroups out of ITT-WT (n=696); prevalence of ITT, *EGFR/ALK*+, and ITT-WT out of ITT (n=800).
[b] One patient had *EGFR* exon 19 deletion and also tested *ALK* positive per central lab.
[c] Stratified HR for ITT and ITT-WT; unstratified HR for all other subgroups. Data cutoff: January 22, 2018

Addition of Bevacizumab to Atezolizumab and Chemotherapy Prolongs Survival of *EGFR/ALK*+ Patients[a]

Arm B[b] vs Arm C



OS: Not reached vs 17.5m
HR: 0.54

[a] Patients with a sensitizing *EGFR* mutation or *ALK* translocation must have disease progression or intolera… …oved targeted therapies.
[b] One patient had *EGFR* exon 19 deletion and also tested *ALK* positive per central lab. [c] Unstratified HR.
Data cutoff: January 22, 2018

To take home...

To take home..

- **Starting with 1st or 2nd gen EGFR TKIs**:
  - Physicians are familiar with 1st & 2nd gen EGFR-TKIs
  - If patients develop T790M then sequencing with 3rd gen
    - **Cons**: 40-60% of patients develop T790M that cannot be predicted
    - 30-40% of patients don't have a chance to receive 2nd line treatment

- **Starting with 3rd gen EGFR TKIs**:
  - OS benefit at 38.6 months
  - Better CNS penetration and efficacy in CNS metastases
  - Better PFS in patients whom will not develop T790M
    - **Cons**: Resistance mechanism
    - What next if patients fail 3rd gen EGFR TKI upfront ?

Biology is the key..

Thank you for your attention..