2019台灣胸腔暨重症加護醫學會

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OA02

Factors Associated with Osimertinib Effectiveness in Advanced Non-small Cell Lung Cancer with Acquired T790M Mutation

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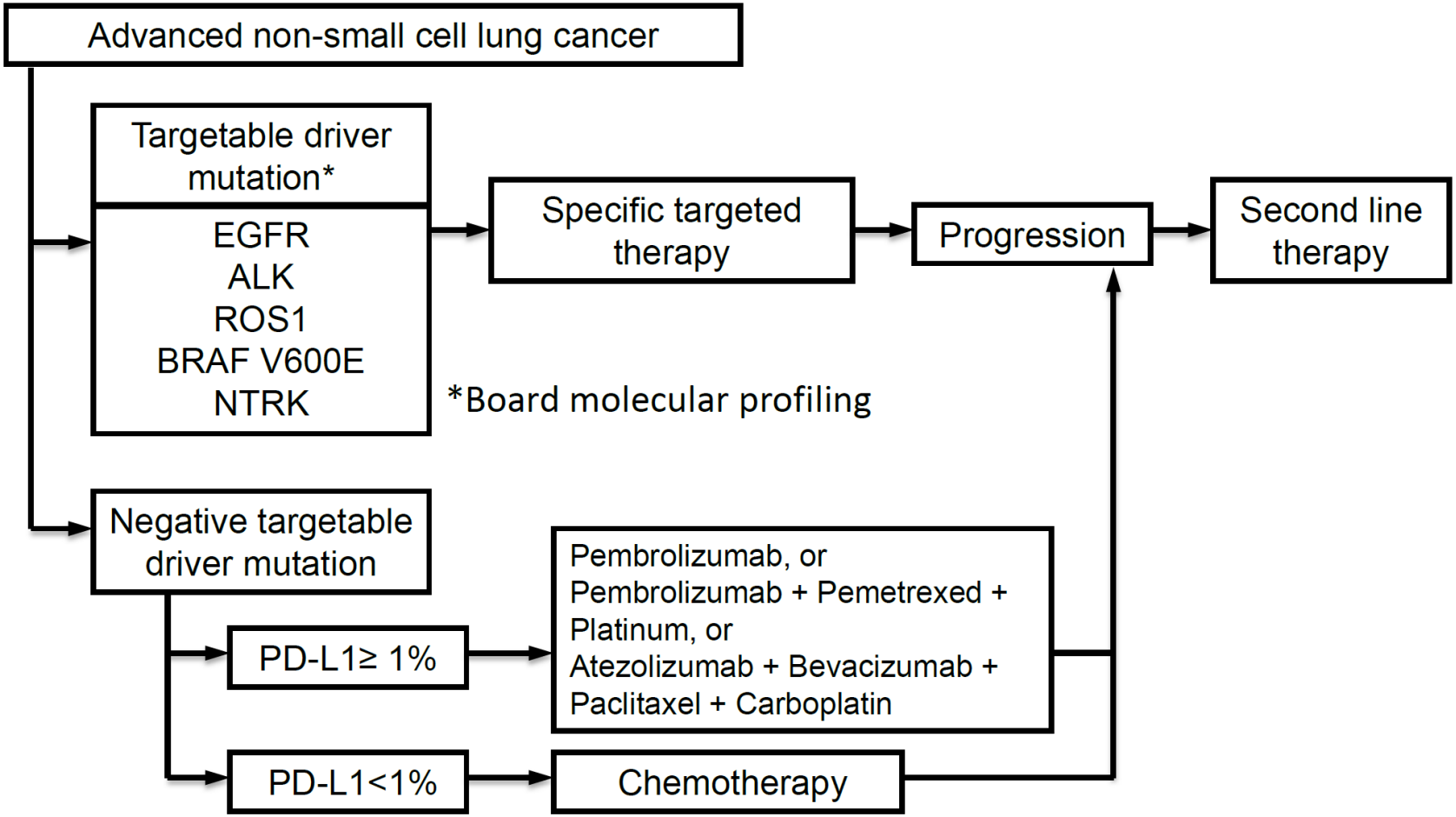
Precision Medicine in Non-small Cell Lung Cancer



Adapted from NCCN Guideline - NSCLC 2019 Ver 7. 2019 Aug 30

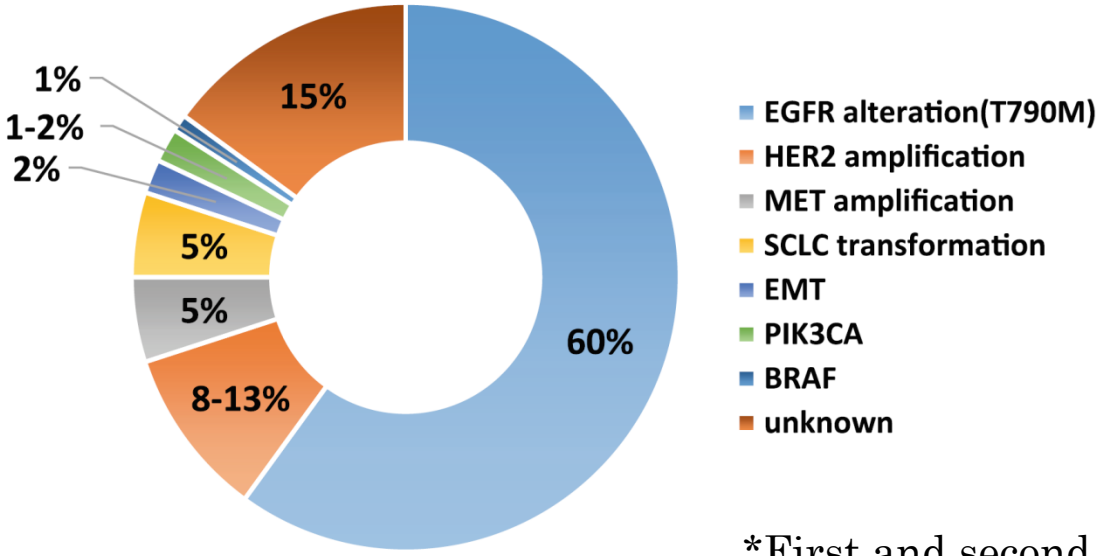
Resistance Mechanism for EGFR TKI*

- Acquired T790M accounts for around 50% EGFR TKI* resistance.
  - Gefitinib
  - Erlotinib
  - Afatinib

Kobayashi S et al. *N Engl J Med*. 2005 Feb 24;352(8):786-92.

Pao W et al. *PLoS Med*. 2005 Mar;2(3):e73.

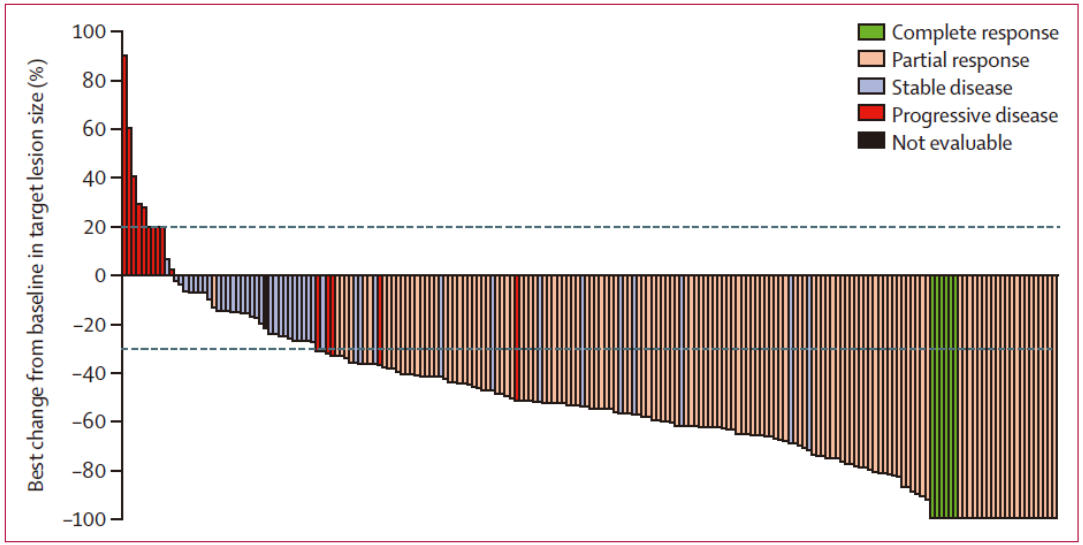
Wu SG et al. *Oncotarget*. 2016 Mar 15;7(11):12404-13.



*First and second generation EGFR TKI

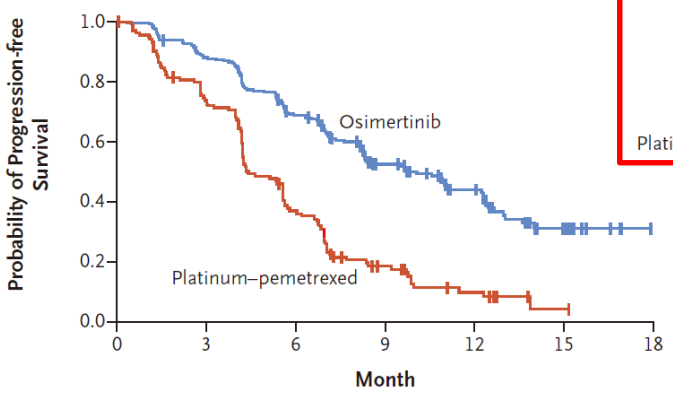
Wu SG et al. *Mol Cancer*. 2018 Feb 19;17(1):38.

Osimertinib is Effective to Control Lung Cancer with Acquired EGFR T790M mutation.



AURA2 (n=199)
ORR 70%

A Patients in Intention-to-Treat 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 Progression-free Survival *mo (95% CI)*
Osimertinib	279	10.1 (8.3–12.3)
Platinum–pemetrexed	140	4.4 (4.2–5.6)

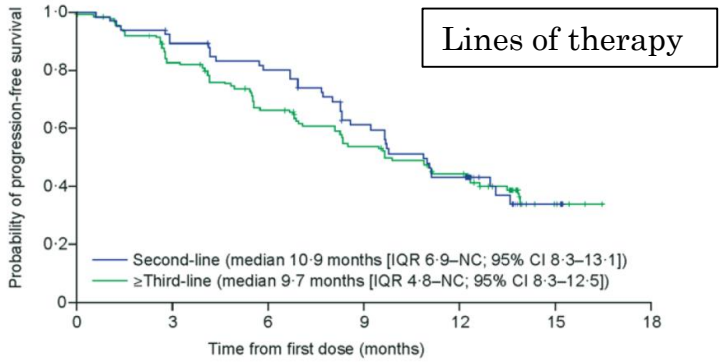
Hazard ratio for disease progression or death, 0.30 (95% CI, 0.23–0.41)
P<0.001

AURA3 (n=419)
Osimertinib vs Chemotherapy (2:1)

Goss G et al. *Lancet Oncol*. 2016 Dec;17(12):1643-1652.
Mok TS et al. *N Engl J Med.* 2017 Feb 16;376(7):629-640.

Factors for Osimertinib Efficacy in AURA2

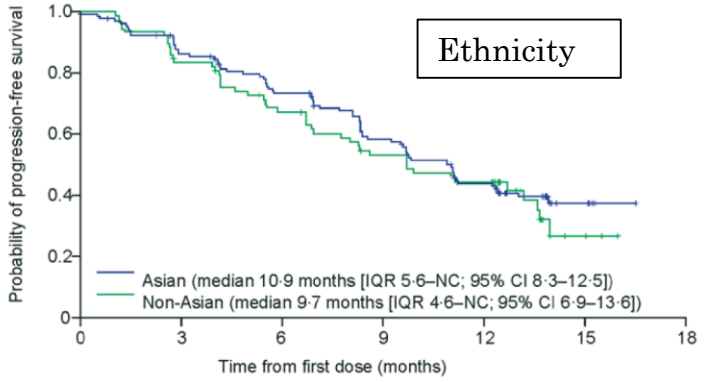
Lines of therapy



No. of patients at risk (No. censored)

Second-line:	68 (0)	59 (2)	52 (3)	37 (6)	26 (6)	5 (24)	0 (29)
≥Third-line:	142 (0)	114 (4)	88 (8)	69 (11)	53 (15)	8 (53)	0 (61)

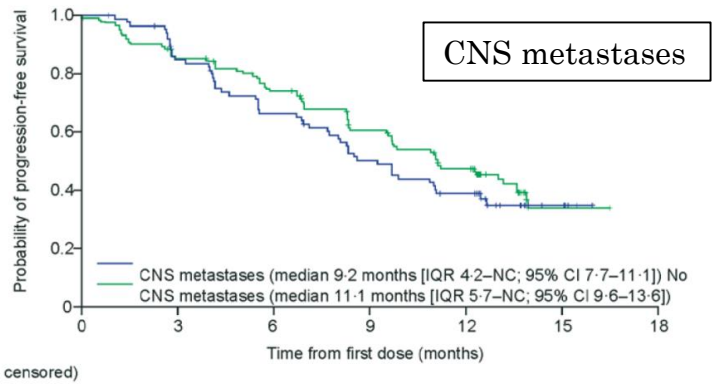
Ethnicity



No. of patients at risk (No. censored)

Asian:	132 (0)	110 (4)	91 (7)	70 (10)	50 (13)	11 (47)	0 (58)
Non-Asian:	78 (0)	63 (2)	49 (4)	36 (7)	29 (8)	2 (30)	0 (32)

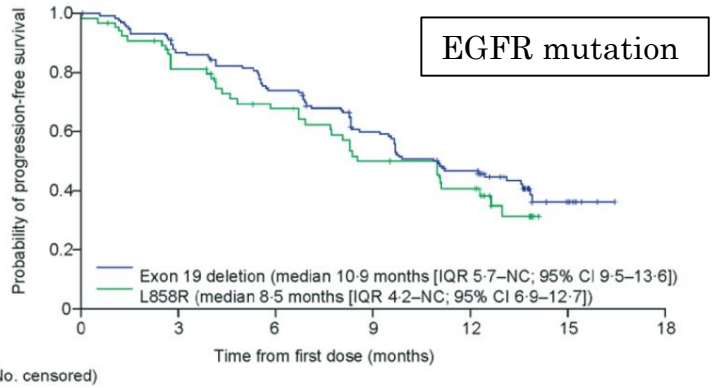
CNS metastases



No. of patients at risk (No. censored)

CNS metastases:	87 (0)	71 (3)	54 (5)	40 (6)	30 (7)	5 (30)	0 (35)
No CNS metastases:	123 (0)	102 (3)	86 (6)	66 (11)	49 (14)	8 (47)	0 (55)

EGFR mutation



No. of patients at risk (No. censored)

Exon 19 deletion:	137 (0)	117 (2)	99 (3)	76 (8)	56 (11)	13 (47)	0 (60)
L858R:	66 (0)	51 (3)	39 (7)	28 (8)	22 (9)	0 (28)	0 (28)

Goss G et al. *Lancet Oncol*. 2016 Dec;17(12):1643-1652.

Factors for Osimertinib Efficacy in AURA3

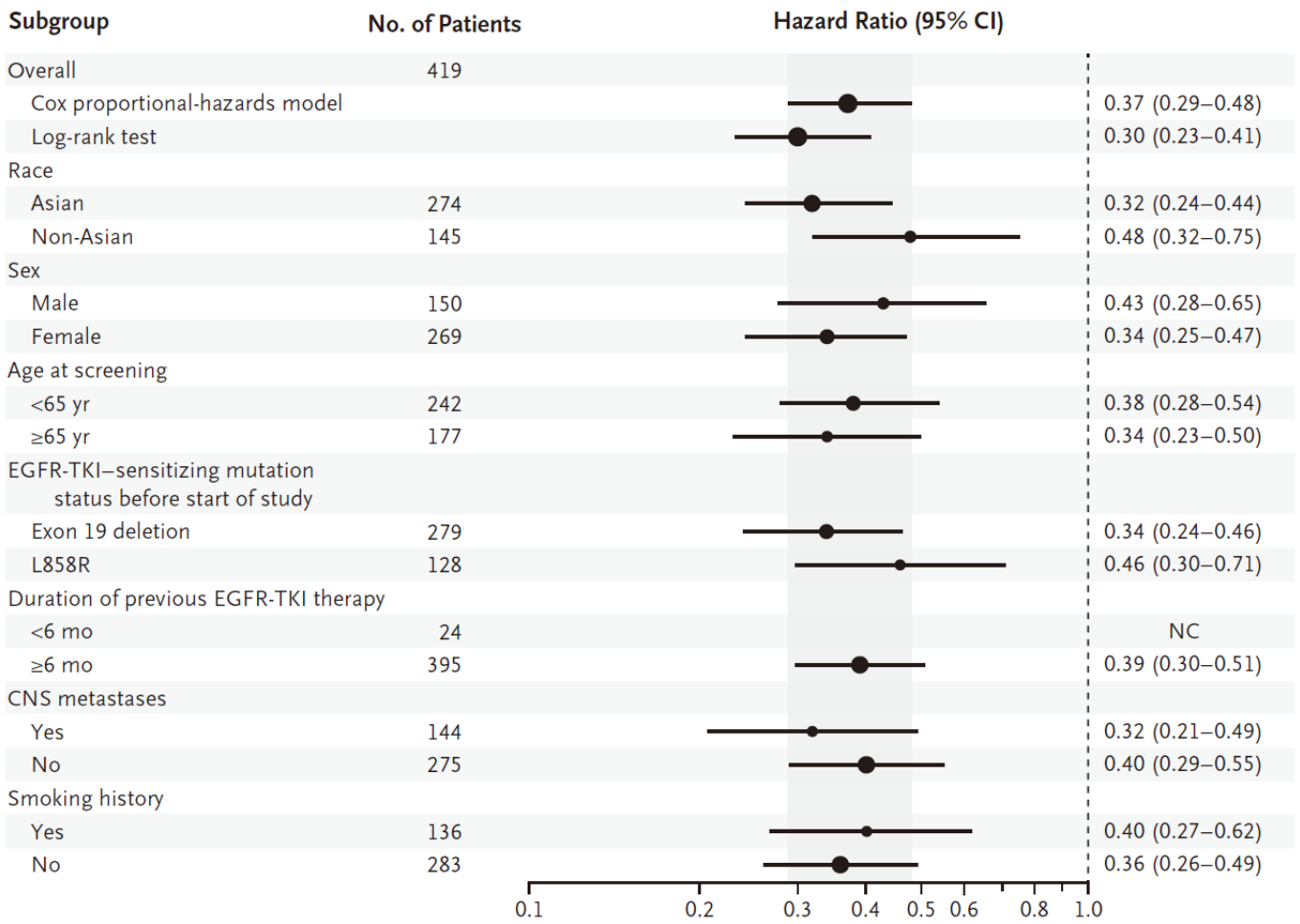


Figure 2. Subgroup Analyses of Progression-free Survival.

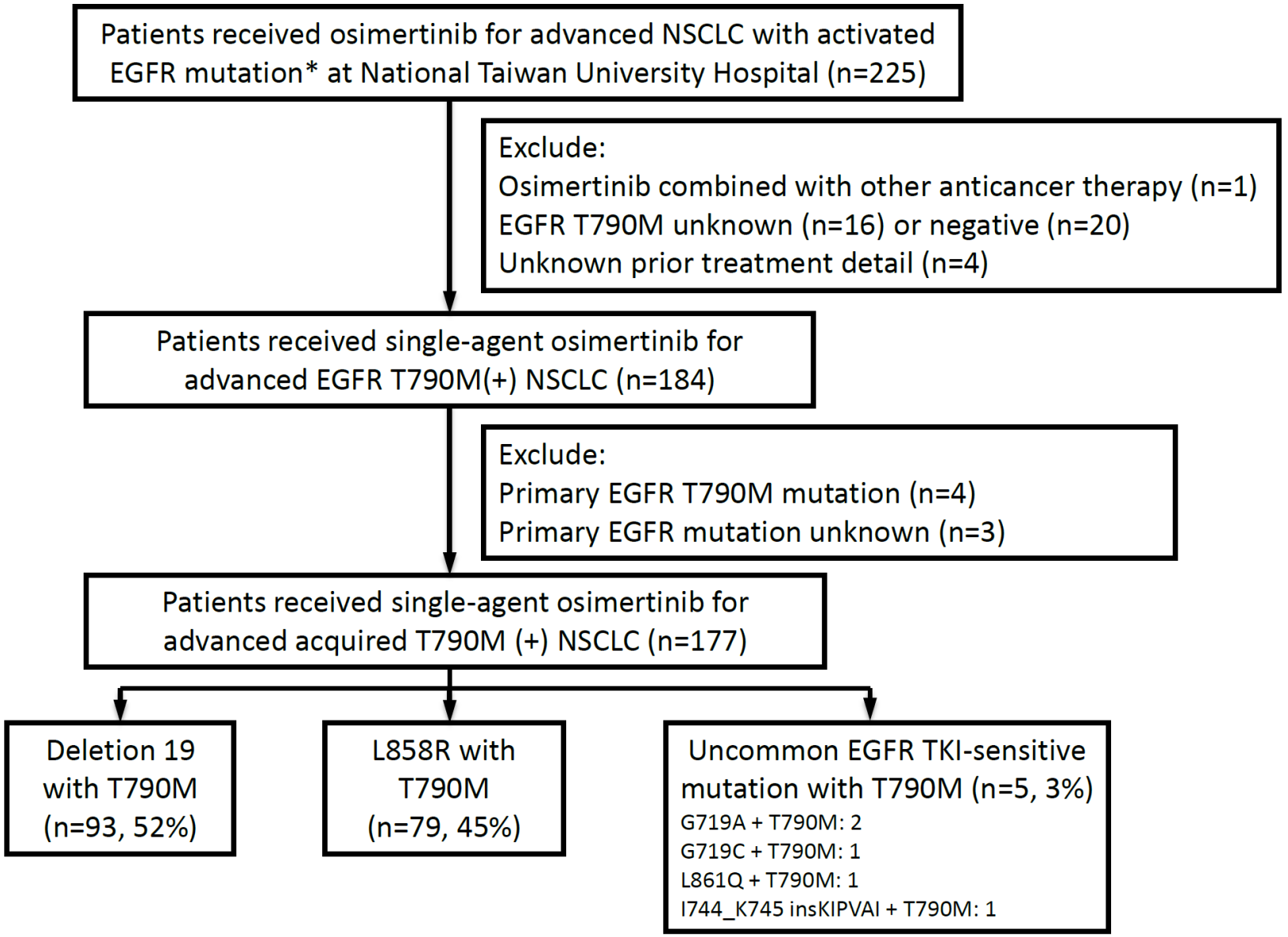
Mok TS et al. *N Engl J Med.* 2017 Feb 16;376(7):629-640.

Clinical Problems

- Osimertinib is effective to control NSCLC with acquired T790M after EGFR TKI therapy.
- Factors associated with osimertinib effectiveness are still not well known.

Study Aim

- To evaluate osimertinib effectiveness in terms of progression-free survival (PFS) and overall survival (OS) in acquired T790M NSCLC

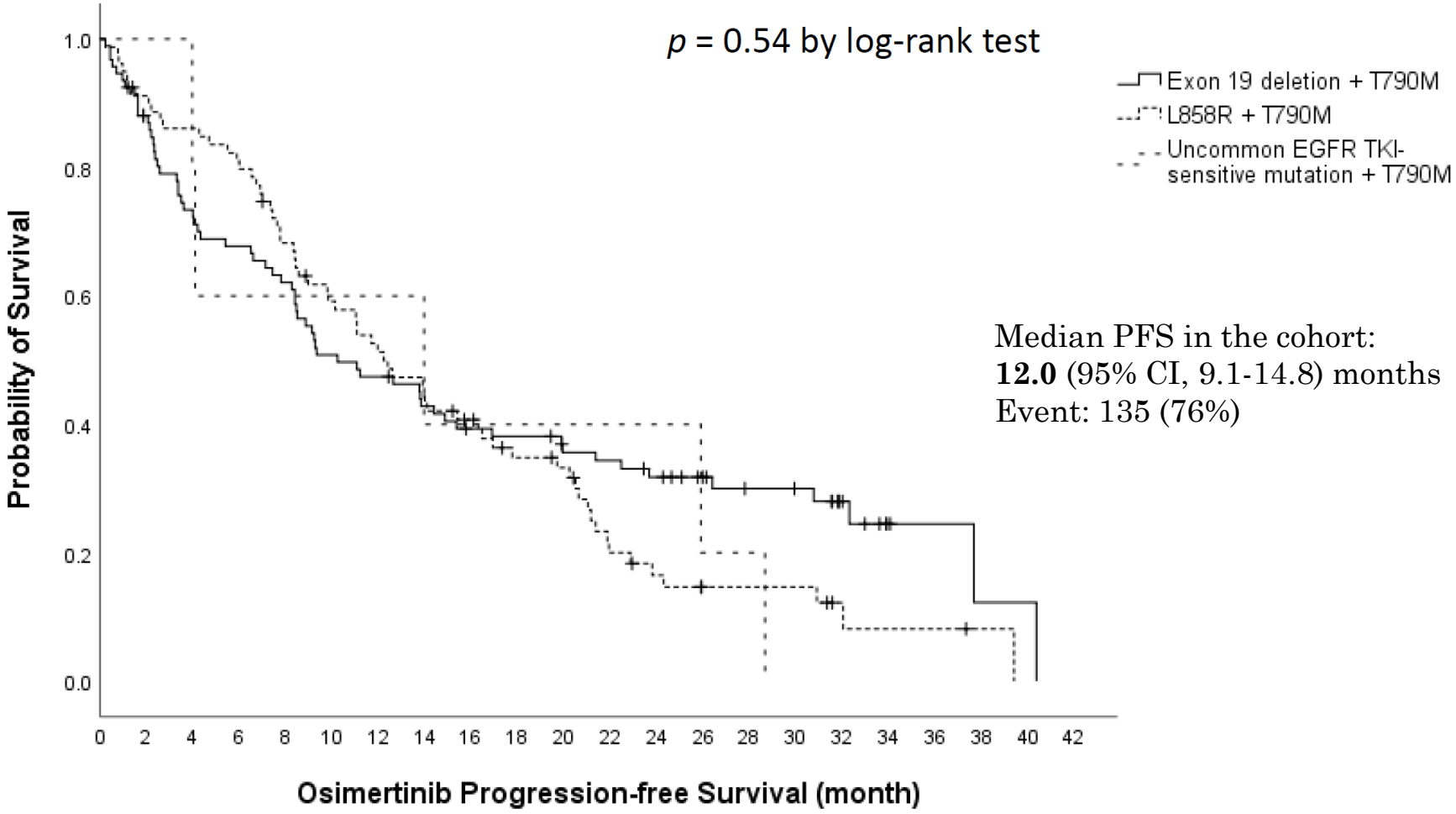


*Activated EGFR mutation = EGFR exon 19 deletion, L858R, G719X, L861Q and exon 19 insertion

Demogarphic Data

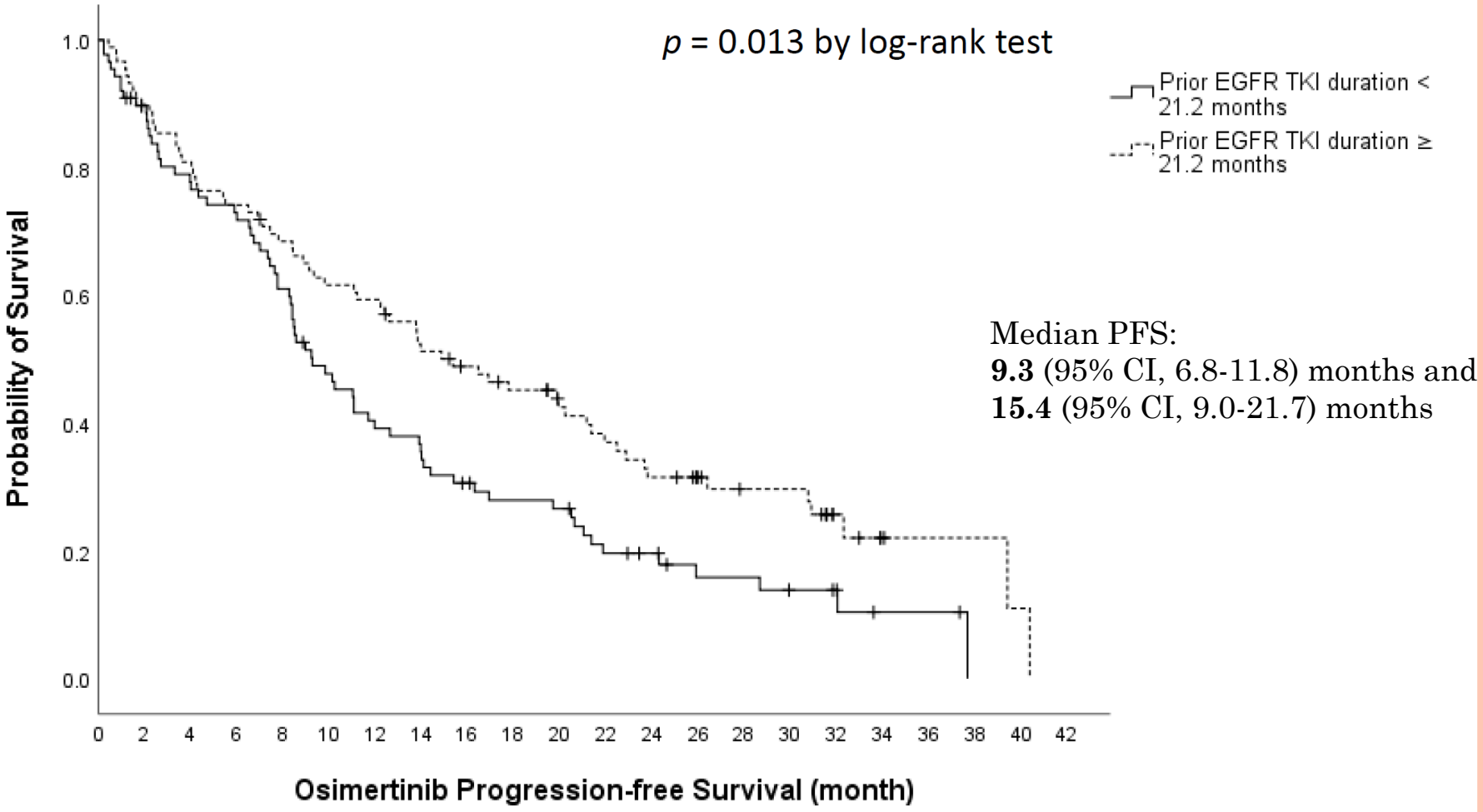
	Total study cohort (n=177)	EGFR Del 19 + T790M (n=93)	EGFR L858R + T790M (n=79)	Uncommon EGFR + T790M (n=5)	*p* value
Median age in years (IQR)	**60 (53-71)**	60 (52-69)	63 (54-71)	53 (49-77)	0.42
Male	**64 (36%)**	32 (34%)	29 (37%)	3 (50%)	0.51
Never-smoker	**138 (79%)**	72 (77%)	63 (82%)	4 (67%)	0.45
Adenocarcinoma	**176 (99%)**	93 (100%)	78 (99%)	6 (100%)	0.54
First-line systemic treatment					0.77
EGFR TKI	**149 (84%)**	78 (84%)	67 (84%)	5 (83%)	
Chemotherapy	**21 (12%)**	12 (13%)	8 (10%)	1 (17%)	
EGFR TKI with chemotherapy	**2 (1%)**	0 (0%)	2 (3%)	0 (0%)	
Others	**5 (3%)**	3 (3%)	2 (3%)	0 (0%)	
Prior anticancer therapy (line) (IQR)	**3 (2-5)**	3 (2-5)	3 (2-4)	1 (1-3)	0.049
Prior EGFR TKI treatment duration in months (IQR)	**21.2 (13.9 – 33.6)**	23.1 (14.6 – 38.9)	18.8 (13.6 – 27.0)	16.5 (8.5 – 22.3)	0.10
Prior T790M EGFR TKI exposure	**10 (6%)**	5 (5%)	5 (6%)	0 (0%)	0.83
ECOG ≥ 2 before osimertinib	**37 (21%)**	20 (22%)	16 (20%)	1 (17%)	0.98
Brain metastasis before osimertinib	**83 (47%)**	44 (48%)	39 (49%)	0 (0%)	0.10
Median follow-up time after osimertinib (month) (IQR)	**19.5 (10.0 – 29.1)**	19.4 (9.3 – 30.5)	19.9 (12.9 – 27.5)	19.4 (7.9 – 31.5)	0.98

OSIMERTINIB PFS



Median PFS in the cohort:
12.0 (95% CI, 9.1-14.8) months
Event: 135 (76%)

OSIMERTINIB PFS



Median PFS:
9.3 (95% CI, 6.8-11.8) months and
15.4 (95% CI, 9.0-21.7) months

Cox Regression Analysis for Factors for PFS

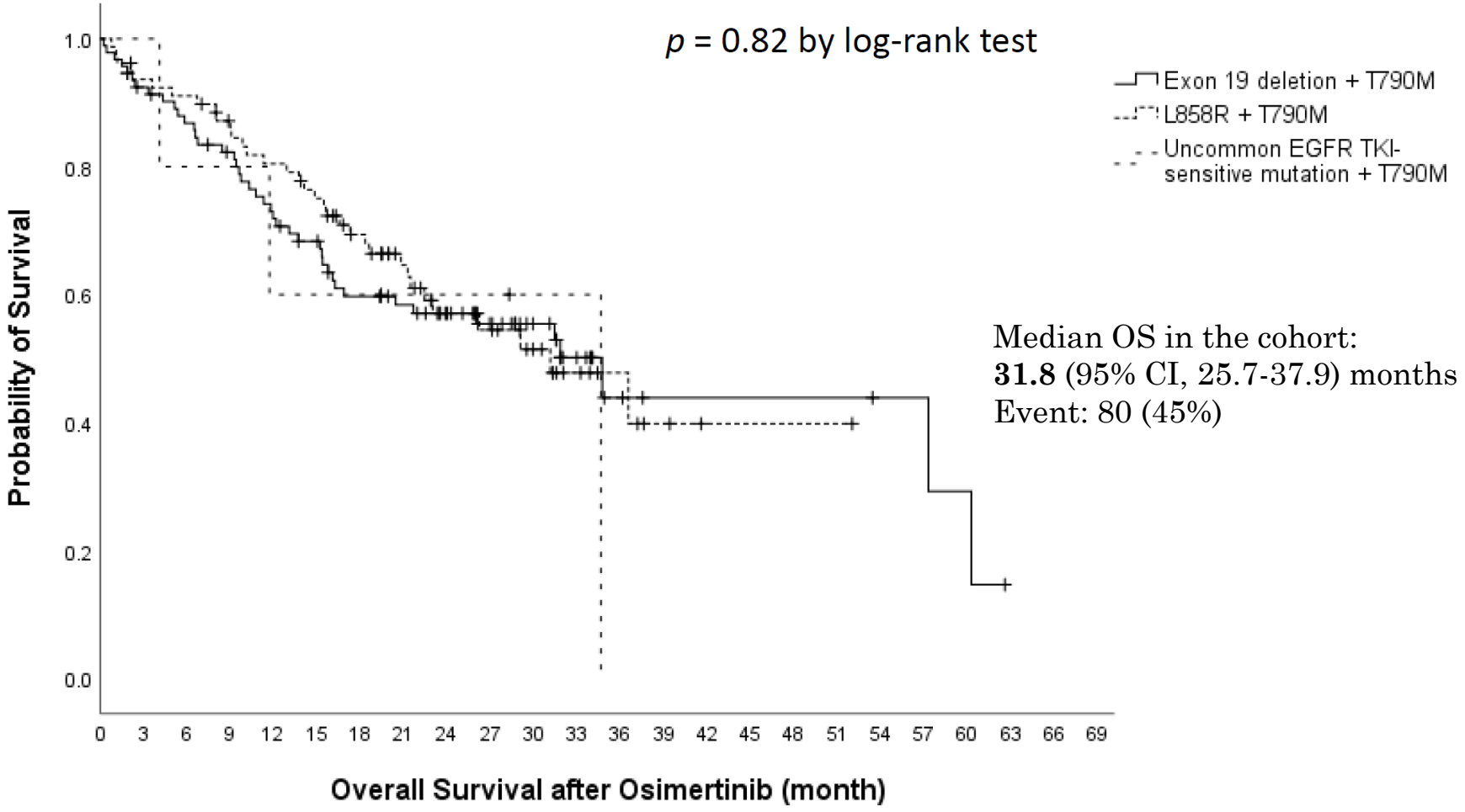
	Hazard ratio	95% CI	*p* value	Adjusted hazard ratio#	95% CI	*p* value
Age (≥ 65)	0.99	0.70-1.42	0.98			
Male sex	1.06	0.74-1.51	0.77			
Never-smoker	0.89	0.59-1.36	0.60			
EGFR mutation			0.55			
Del 19 + T790M*	1.00*					
L858R + T790M	1.20	0.85-1.70	0.30			
Uncommon + T790M	1.30	0.52-3.25	0.57			
Previous anticancer therapy (per line)	1.10	1.02-1.18	0.013	1.09	1.01-1.18	0.027
First-line treatment as an EGFR TKI	0.74	0.48-1.15	0.18			
Prior T790M EGFR TKI exposure	1.44	0.70-2.95	0.32			
Prior EGFR TKI treatment duration (per month)	0.98	0.97-0.99	<0.001	0.98	0.97-0.99	0.001
ECOG ≥ 2 before osimertinib	2.12	1.41-3.20	<0.001	1.96	1.29-2.98	0.002
Brain metastasis at osimertinib initiation	1.39	0.99-1.96	0.06			

Acronyms: CI, confidence interval; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; ECOG, Eastern Cooperative Oncology Group performance scale

*As a reference compared to other T790M mutations

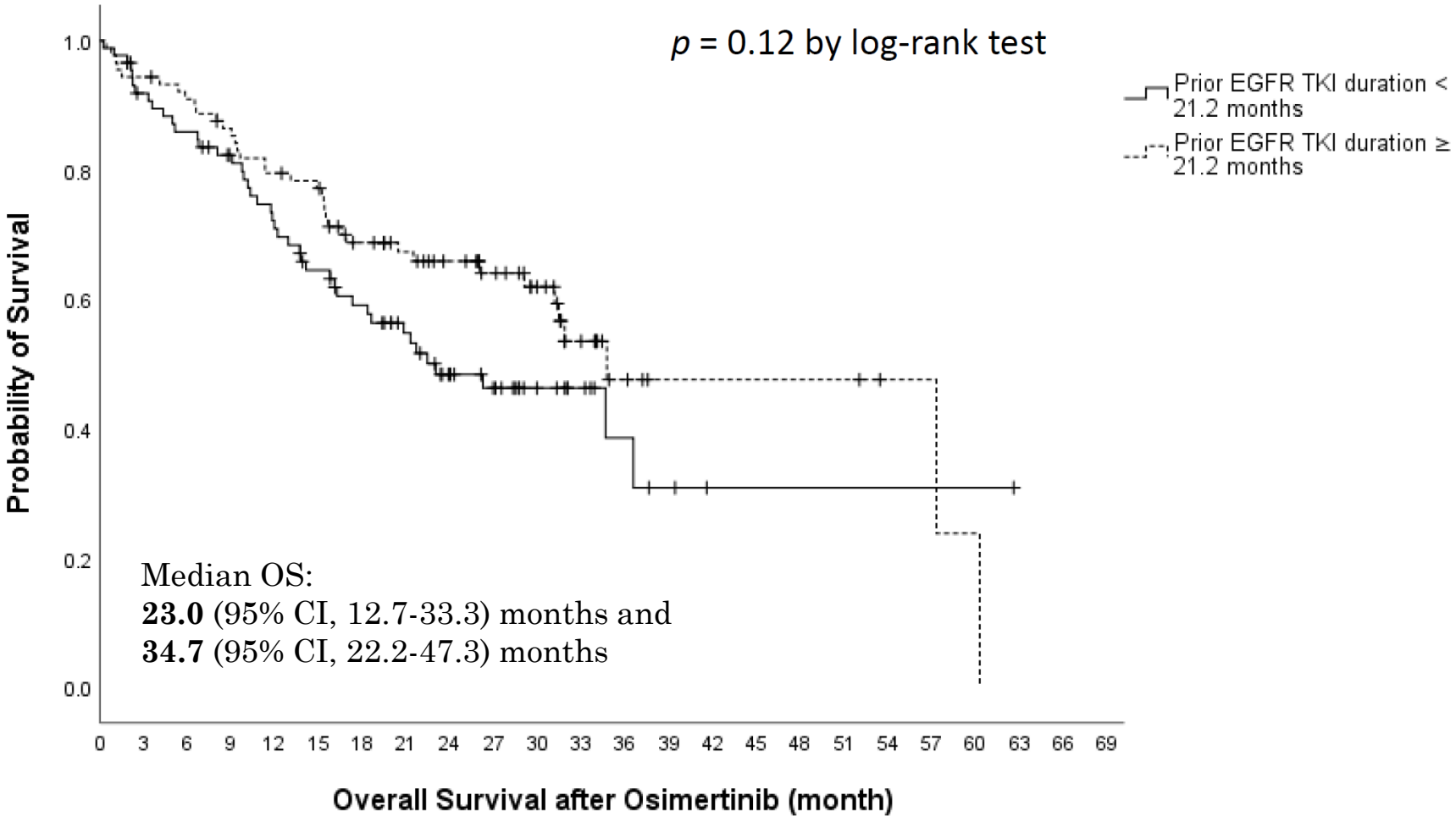
#Multivariate backward LR analysis

OS AFTER OSIMERTINIB



Median OS in the cohort:
31.8 (95% CI, 25.7-37.9) months
Event: 80 (45%)

OS AFTER OSIMERTINIB



Cox Regression Analysis for factors for OS

	Hazard ratio	95% CI	*p* value	Adjusted hazard ratio#	95% CI	*p* value
Age (≥ 65)	1.01	0.64-1.61	0.96			
Male sex	1.16	0.73-1.84	0.53			
Never-smoker	0.82	0.48-1.39	0.45			
EGFR mutation			0.82			
Del 19 + T790M*	1.00*					
L858R + T790M	0.94	0.59-1.48	0.77			
Uncommon + T790M	1.36	0.42-4.39	0.61			
Previous anticancer therapy (per line)	1.09	0.99-1.19	0.09			
First-line treatment as an EGFR TKI	0.69	0.40-1.20	0.19			
Prior T790M EGFR TKI exposure	1.39	0.56-3.45	0.48			
Prior EGFR TKI treatment duration (per month)	0.97	0.95-0.99	<0.001	0.97	0.96-0.99	0.001
ECOG ≥ 2 before osimertinib	3.21	1.98-5.22	<0.001	2.92	1.79-4.76	<0.001
Brain metastasis at osimertinib initiation	1.33	0.86-2.06	0.21			

Acronyms: CI, confidence interval; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; ECOG, Eastern Cooperative Oncology Group performance scale

*As a reference compared to other T790M mutations

#Multivariate backward LR analysis

FINDINGS FROM THE STUDY

- Prior EGFR TKI treatment duration, ECOG scale ≥ 2, and more prior anticancer therapies may be associated with osimertinib effectiveness.
- There was no PFS difference among EGFR exon 19 deletion with T790M, L858R with T790M and uncommon EGFR TKI-sensitive mutation (G719X, L861Q and exon 19 insertion) with T790M.
- Exon 19 insertion (I744_K745 insKIPVAI) can also acquire T790M.

Strength of the study

- First large osimertinib cohort (n=177) in East Asia
- Comparable PFS and OS with RCTs
- Matured data
  - Median follow up 19.5 months
  - PFS event 76%
- First report:
  - Longer prior EGFR TKI treatment duration is associated with longer osimertinib PFS in a large cohort.
  - Exon 19 insertion can acquire T790M.

Limitation of the Study

- It is a retrospective cohort in East Asia (EGFR mutation rate around 50%).
- There were various methods to test EGFR mutation.
- Only small numbers of patients underwent re-biopsy after osimertinib resistance.

Thank you