Rebiopsy and Sequential Therapy

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KATRD EGFR Cohort 연구 제안

주제	연구제목
Rebiopsy and sequential therapy	1L Osimertinib efficacy 분석
	T790M 발현 비율 및 발현 예후 인자
	rebiopsy method에 의한 T790M 발현 차이
	rebiopsy 에서 PD-L1 status 변동 및 ICI 반응
	적절한 rebiosy 검사 시기
	EGFR 변이 환자에서의 ICI 투여 현황, 효과, 독성 분석
	Definitive CCRTx vs. 1st line EGFR-TKI 치료 성적 비교
	CCRT followed by durvalumab의 real-world data

Contents

1. Rebiopsy

1) Spatiotemporal heterogeneity
2) Clinical factors predicting detection of T790M mutation
3) Post PD-L1 change after EGFR-TKI treatment

2. Sequential therapy

1) Optimal sequence of EGFR-TKI therapy
2) Treatment options for patients with unresectable stage III EGFR-mutant NSCLC
3) Immunotherapy in EGFR-mutant NSCLC patients

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Spatial heterogeneity

Spatiotemporal T790M Heterogeneity in Individual Patients with *EGFR*-Mutant Non–Small-Cell Lung Cancer after Acquired Resistance to EGFR-TKI

Journal of Thoracic Oncology® • Volume 10, Number 11, November 2015

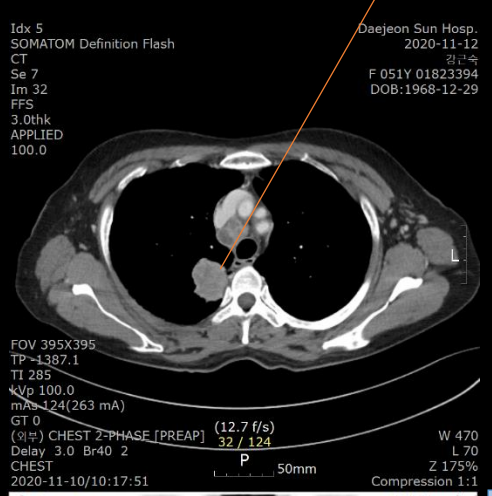
Biopsy site 1 / T790M(+/-)	Biopsy site 2 / T790M(+/-)	
Lung tumor / +	CSF / -	1 case
Pleural effusion / +	CSF / -	9 cases
Lung (primary) / +	Lung (meta) / -	1 case
Lung tumor / -	Pleural effusion / +	2 cases

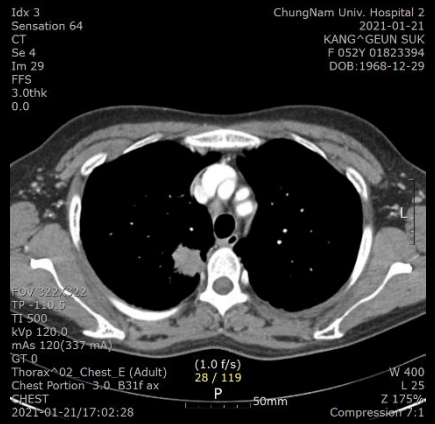
30 patients underwent multiple site rebiopsies

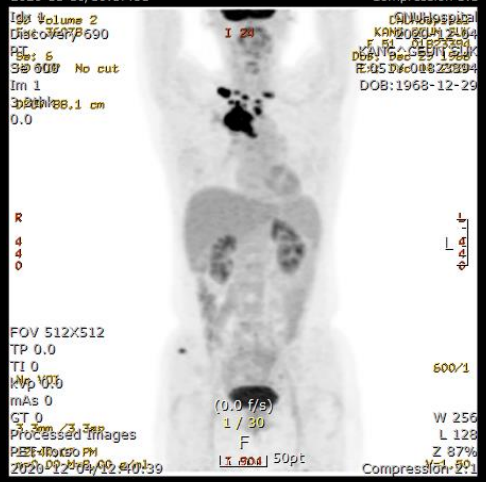
Hata, Akito, et al. *Journal of thoracic oncology* 10.11 (2015): 1553-1559.

Case #1 53/F, Lung cancer (adeno, RUL, N3M1b, lung to lung, bone)

RUL PCNB ; Exon 19 del



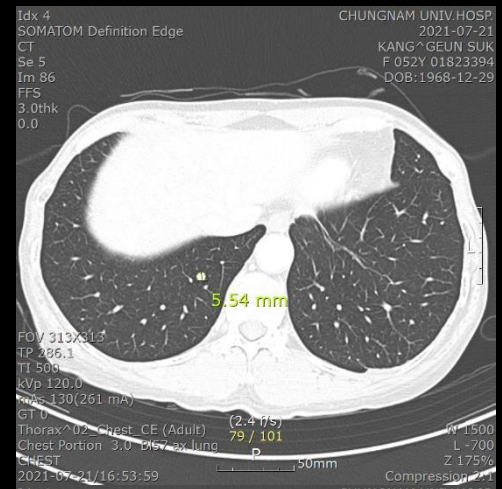


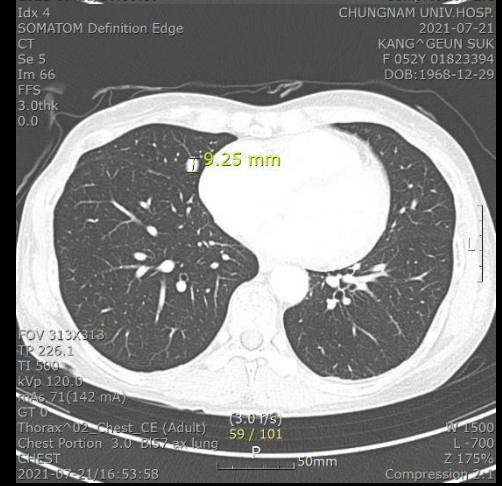


2020.12.8

Decreased SD
(38→30mm)

Afatinib (7 months)

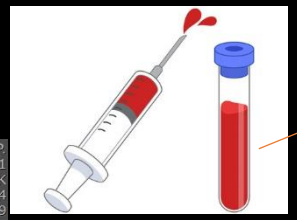




2021.7.21

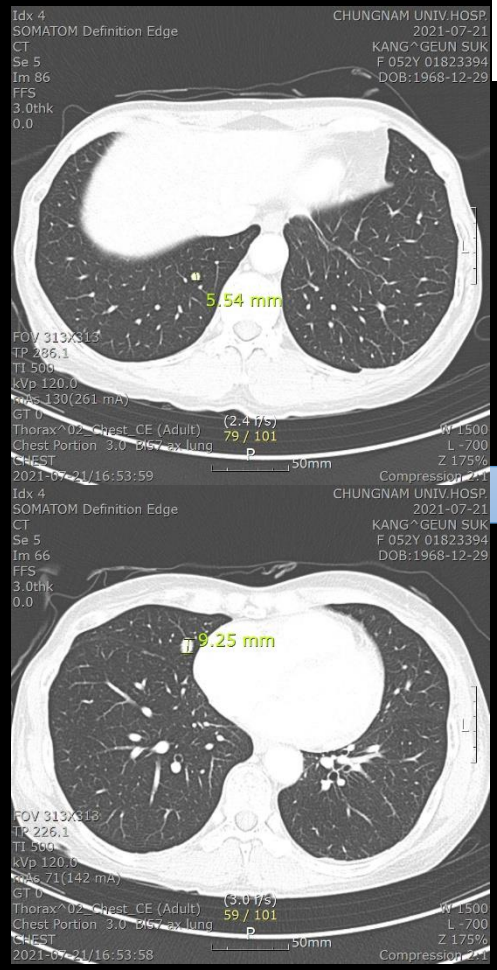
Case #1 53/F, Lung cancer (adeno, RUL, N3M1b, lung to lung, bone)

EGFR(cell free DNA) ; Exon 19 del

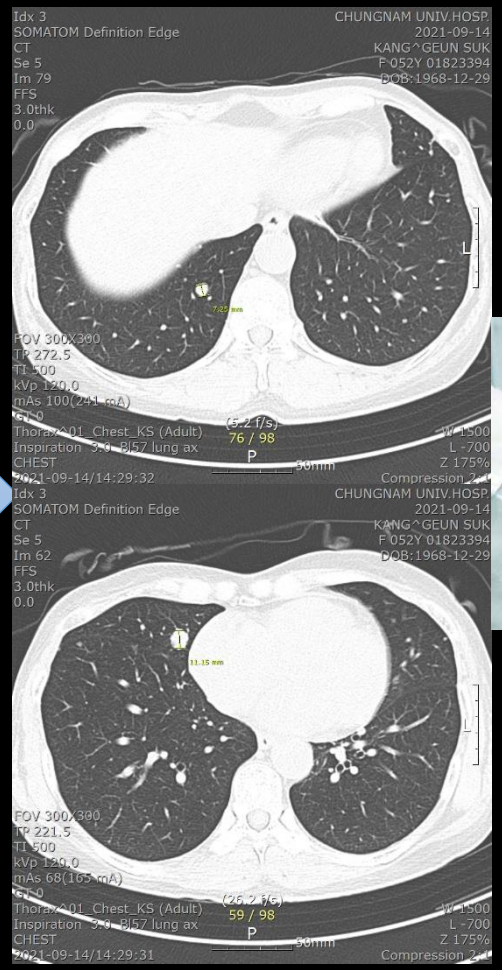


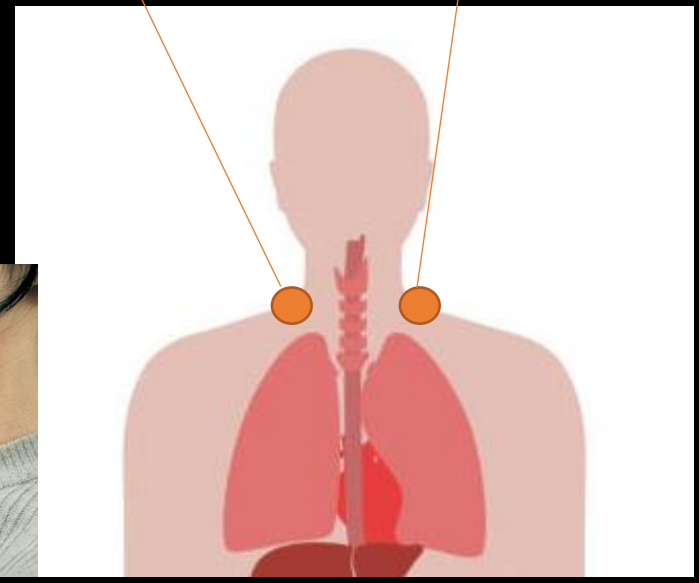
Exon 19 del
Exon 20 T790M

Exon 19 del



Pemetrexed #2





2021.7.14

2021.9.14

Temporal heterogeneity

Spatiotemporal T790M Heterogeneity in Individual Patients with *EGFR*-Mutant Non–Small-Cell Lung Cancer after Acquired Resistance to EGFR-TKI

Journal of Thoracic Oncology® • Volume 10, Number 11, November 2015

T790M status	
+ → - → + → - → +	1 patient
+ → - → +	2 patients
+ → -	2 patients
- → +	1 patient

24 received repeated rebiopsies at the same lesion

Hata, Akito, et al. *Journal of thoracic oncology* 10.11 (2015): 1553-1559.

Spatiotemporal heterogeneity

Case	First try			Second try			Third try			Fourth try		
	M	Site	Result	M	Site	Result	M	Site	Result	M	Site	Result
1	1	Lung	No malignancy	2	lung	No malignancy	3	Muscle	ADC D19+/T790M+			
2	1	Lung	No malignancy	1.5	lung	ADC insufficient	2	Pleura	ADC D19+/T790M+			
3	0.5	Lung	No malignancy	3	lung	No malignancy	4	Bone	ADC D19+/T790M+			
4	1	LN	No malignancy	2	lung	No malignancy	2.5	LN	ADC D19+/T790M+			
5	0.5	Lung	ADC D19+/T790M-	11	lung	ADC D19+/T790M-	30	Pleura	No malignancy	31	LN	ADC D19+/T790M+
6	1	Lung	No malignancy	2	LN	No malignancy	3	Lung	ADC L858R+/T790M-			
7	0.5	LN	No malignancy	1	Bone	Metastatic carcinoma	1.5	Lung	ADC L858R+/T790M-			
8	1	Lung	ADC insufficient	1.5	lung	No malignancy	2	LN	ADC D19+/T790M+			

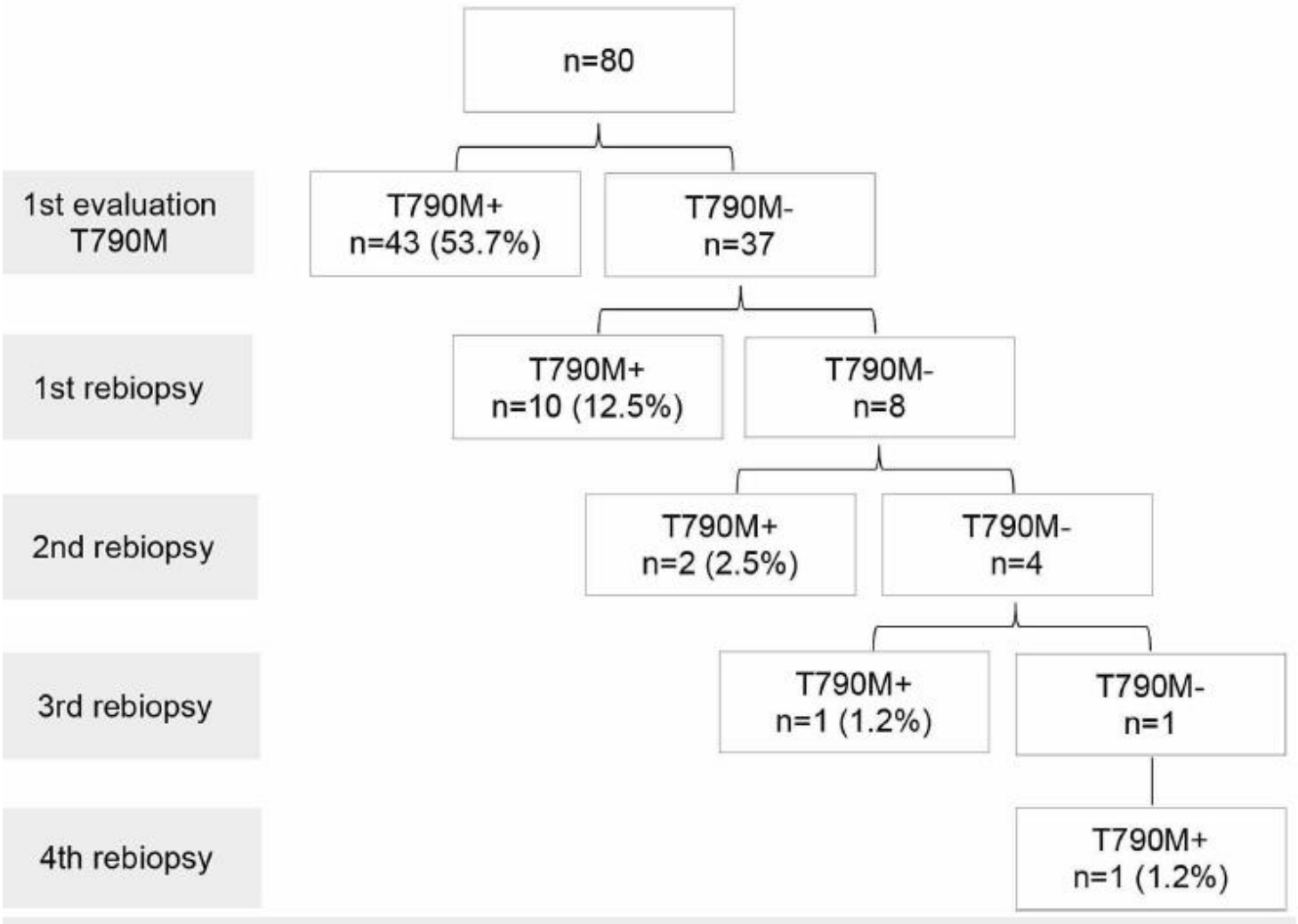
Spatial heterogeneity

Temporal heterogeneity

Lee, Kangkook, et al. *Lung Cancer* 130 (2019): 87-92.

Repeated biopsy

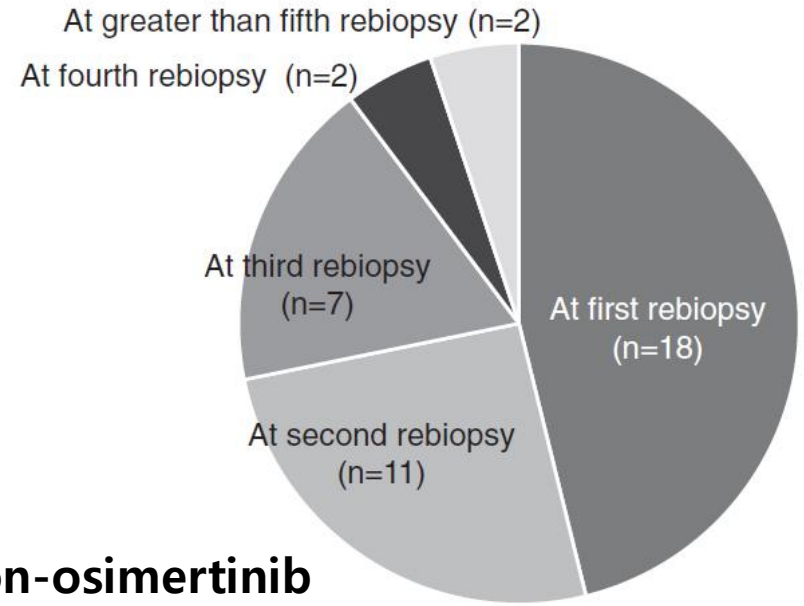
T790M mutation (+)
53.7% → 71.1%



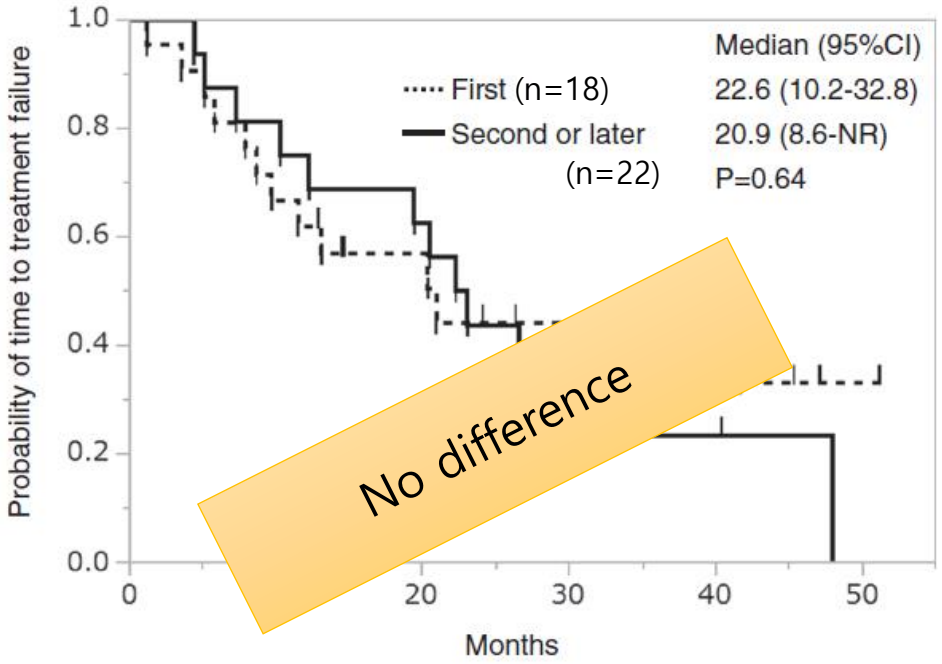
Pereira, Isabel, et al. *Cureus* 12.12 (2020).

Repeated biopsy

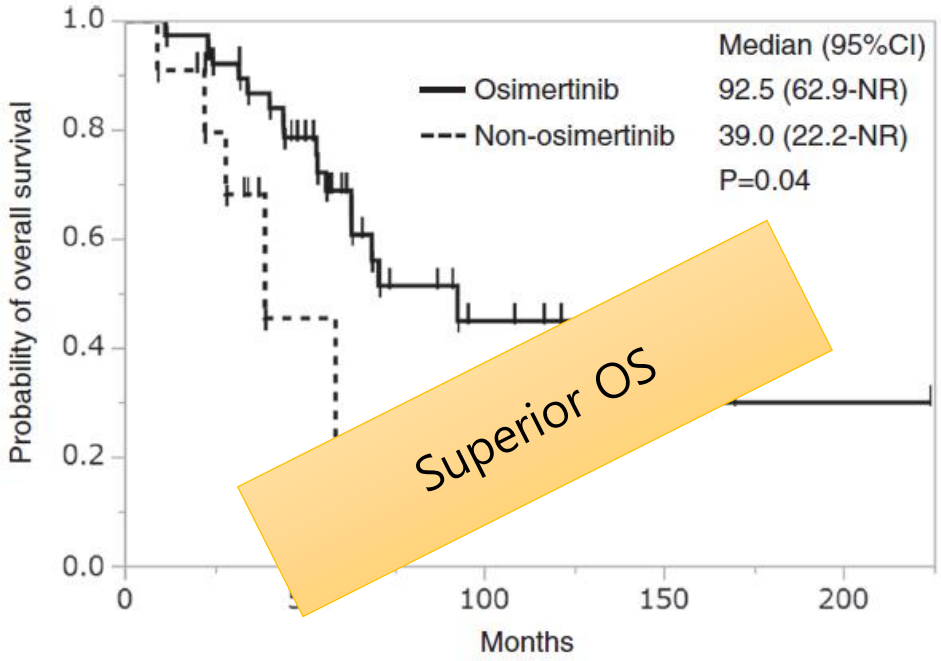
Treatment during biopsy interval: EGFR-TKIs, cytotoxic chemotherapies, combination therapies of EGFR-TKI an angiogenesis inhibitors, immune-check point inhibitors



First rebiopsy vs. Second or later rebiopsy

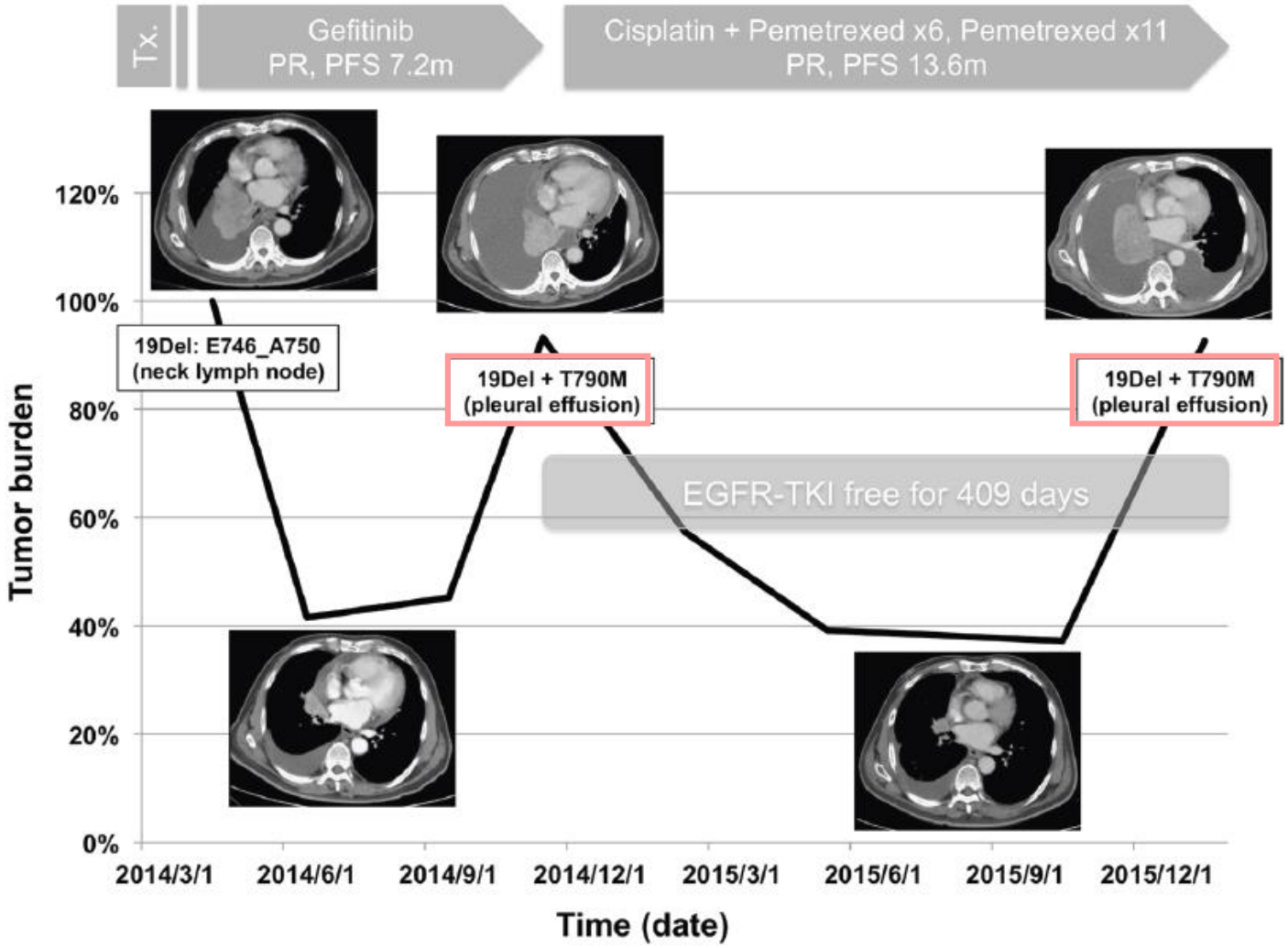


Osimertinib vs. Non-osimertinib



Ninomaru, Taira, et al. *Thoracic Cancer* 12.6 (2021): 746-751.

Repeated biopsy

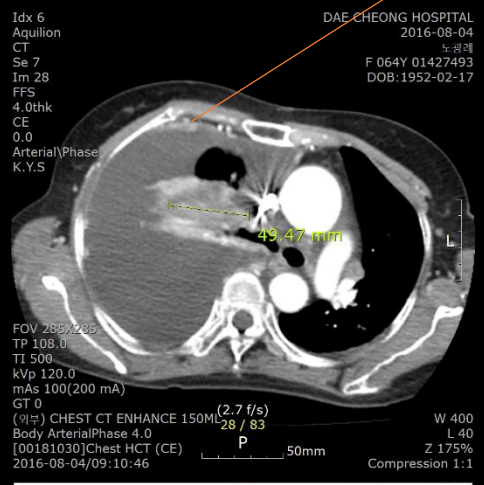


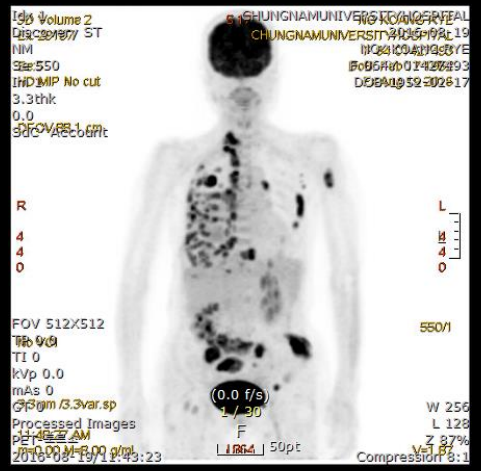
Mutation could be identified in patients with a **long EGFR-TKI free interval**.
For patients without suitable lesions for rebiopsy at the time of EGFR-TKI progression, an **attempt to rebiopsy** should be considered during the **subsequent treatment**.

Tseng, Jeng-Sen, et al. *Oncotarget* 7.30 (2016): 48059.

Case #2 63/F, Lung cancer (adeno, RUL, T4N3M1b, pleura, bone)

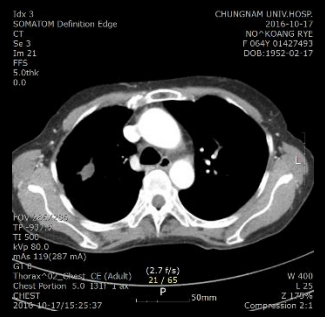
Pleura ; Exon 21 L858R or L861Q



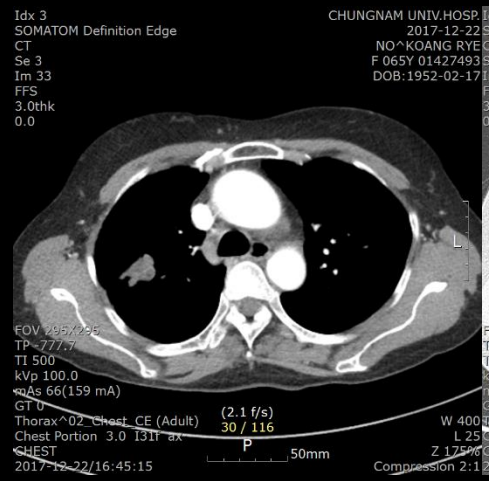


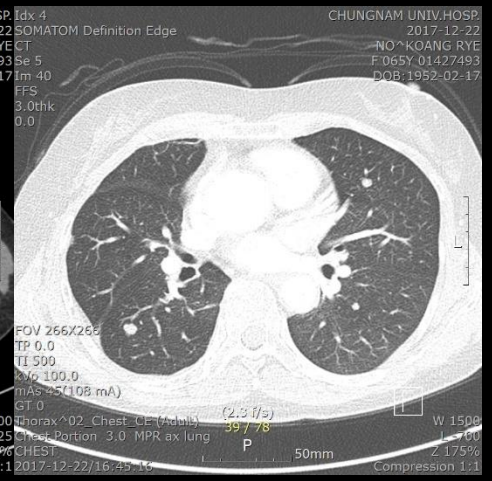
2016.8.19

PR (49→22mm)



Gefitinib (16 months)





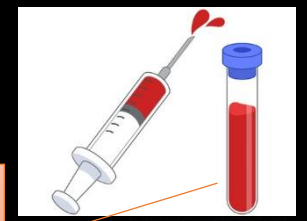
2017.12.22

Case #2 63/F, Lung cancer (adeno, RUL, T4N3M1b, pleura, bone)

Rebiopsy refuse

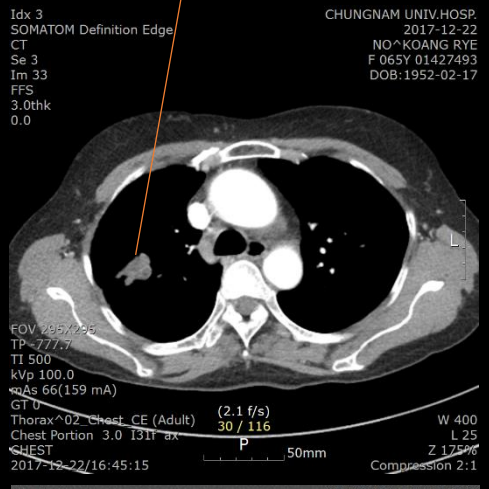
RUL PCNB; Exon 21 L858R

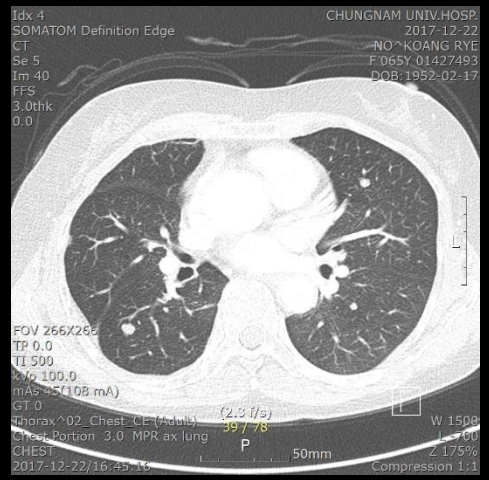
EGFR(cell free DNA) ;
Exon 21 L858R, Exon 20 T790M



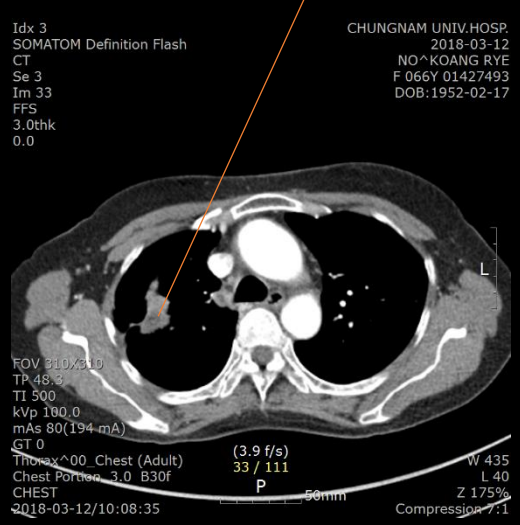
Pemetrexed #3

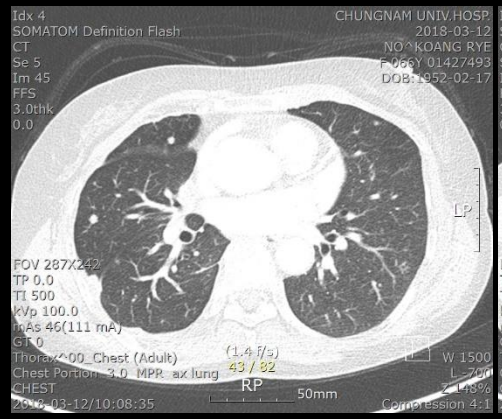
FU loss

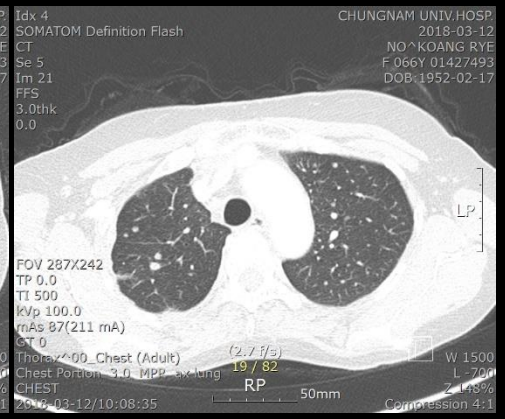




2017.12.22





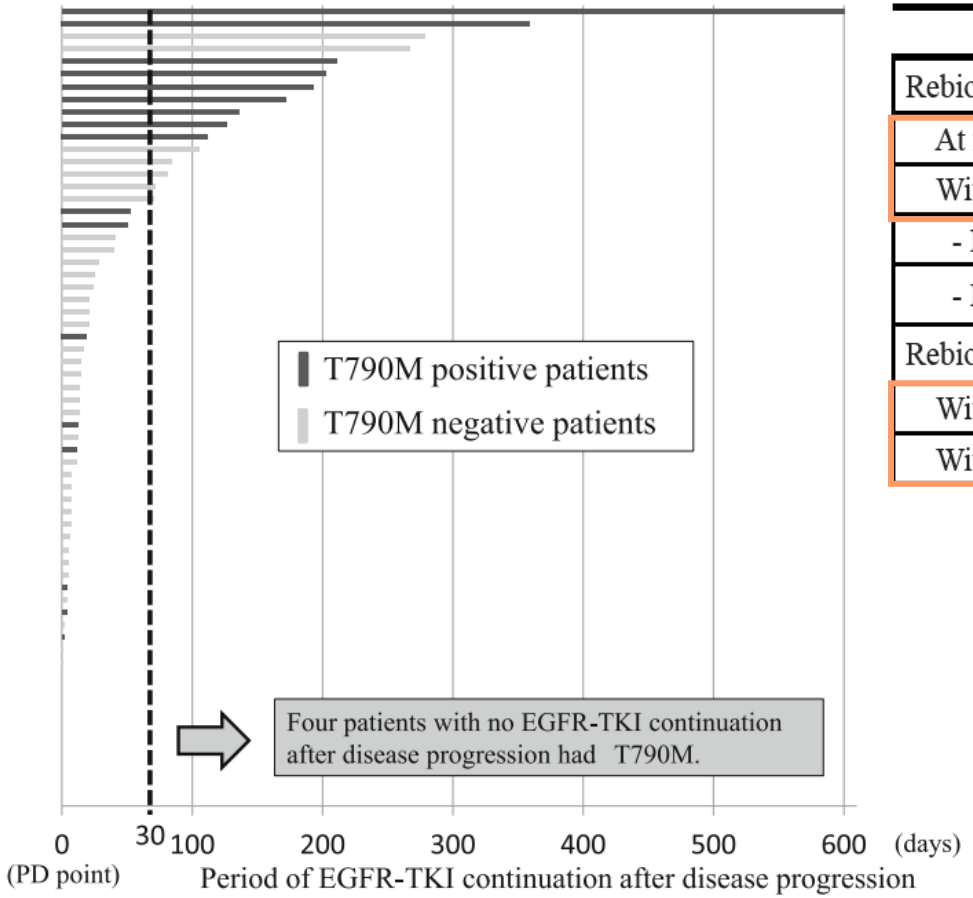


2018.3.2

2018.7.11

Treatment during re-biopsy interval

Continued treatment with EGFR-TKI after progression might promote T790M



Rebiopsy timing did not influence the detection rate of T790M

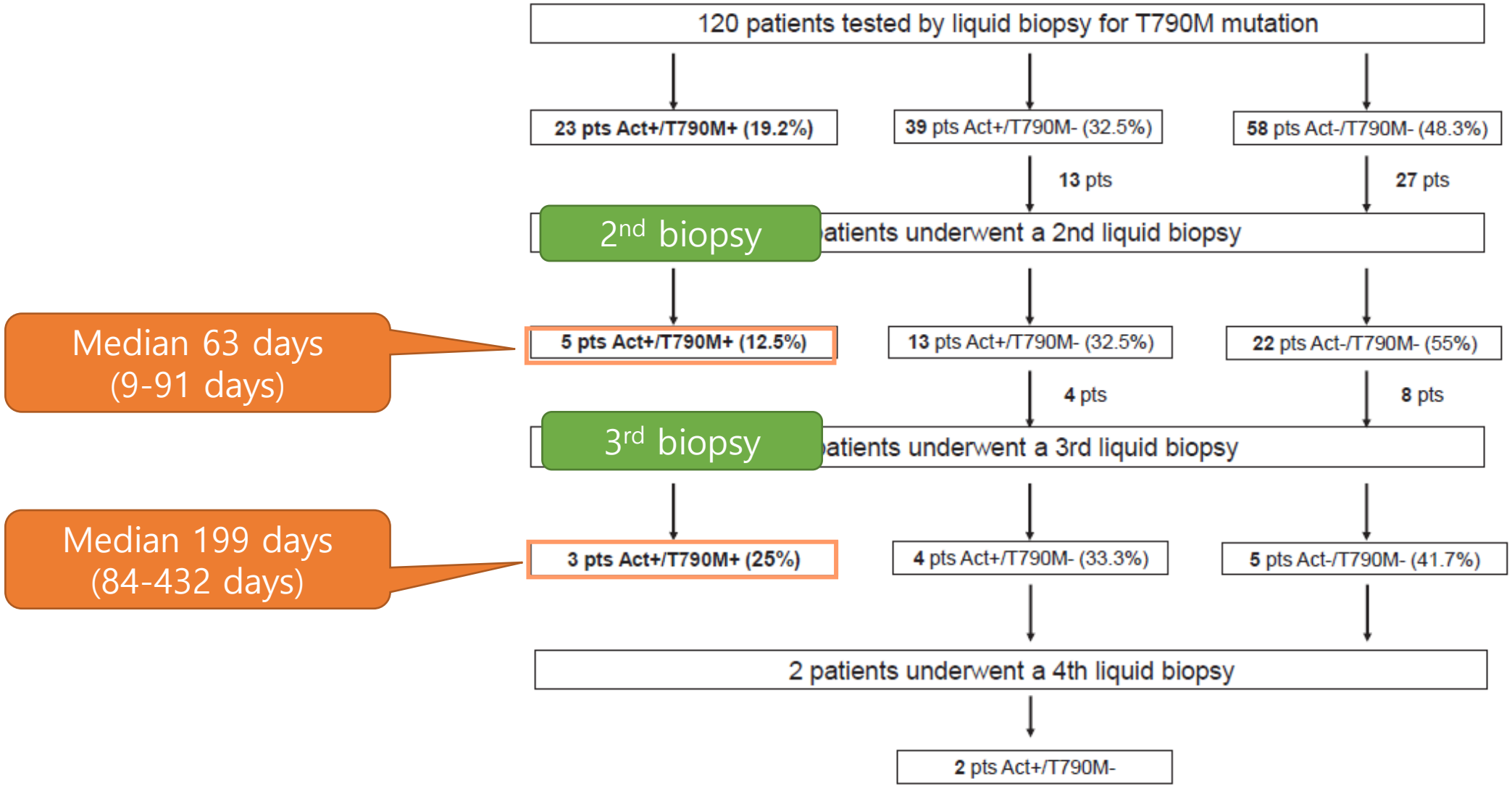
Characteristics	*n*	T790M mutation (%)	*P* value[a]
Rebiopsy timing (1)[b]			1.000
At first EGFR-TKI progression	54	55.6	
With interval from first EGFR-TKI PD	44	54.5	1.000[c]
- Post-PD best response PR	− 11	− 54.5	
- Post-PD best response SD/PD	− 33	− 54.5	
Rebiopsy timing (2)			0.802
With EGFR-TKI treatment at rebiopsy	78	53.8	
Without EGFR-TKI treatment at rebiopsy	20	60.0	

Controversial

Ko, Ryo, et al. *BMC cancer* 16.1 (2016): 1-8.

Tseng, Jeng-Sen, et al. *Oncotarget* 7.30 (2016): 48059.

Repeated liquid biopsy



Minari, Roberta, et al. *Clinical Lung Cancer* 21.5 (2020): e464-e473.

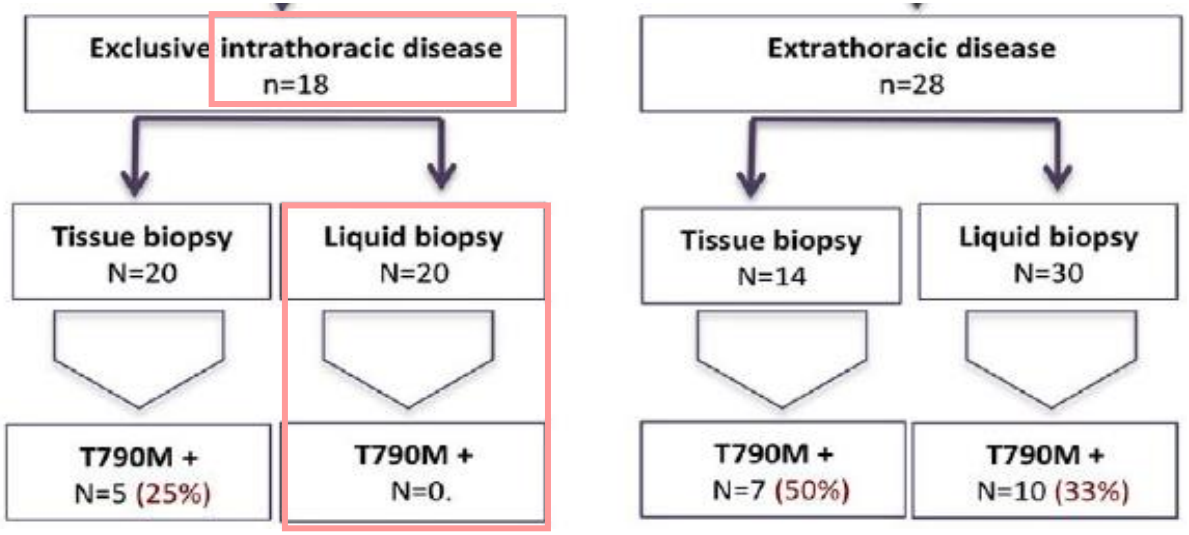
Liquid biopsy timing

Table 2 Timing of the First Liquid Biopsy and the Results

Liquid Biopsy Before Disease Progression According to RECIST Criteria	T790M		Overall	*P*
	Negative, n (%)	Positive, n (%)		
No	76 (76.8)	23 (23.2)	99	.012
Yes	21 (100)	0	21	
Overall	97 (80.8)	23 (19.2)	120	

T790M
all negative before RECIST-PD

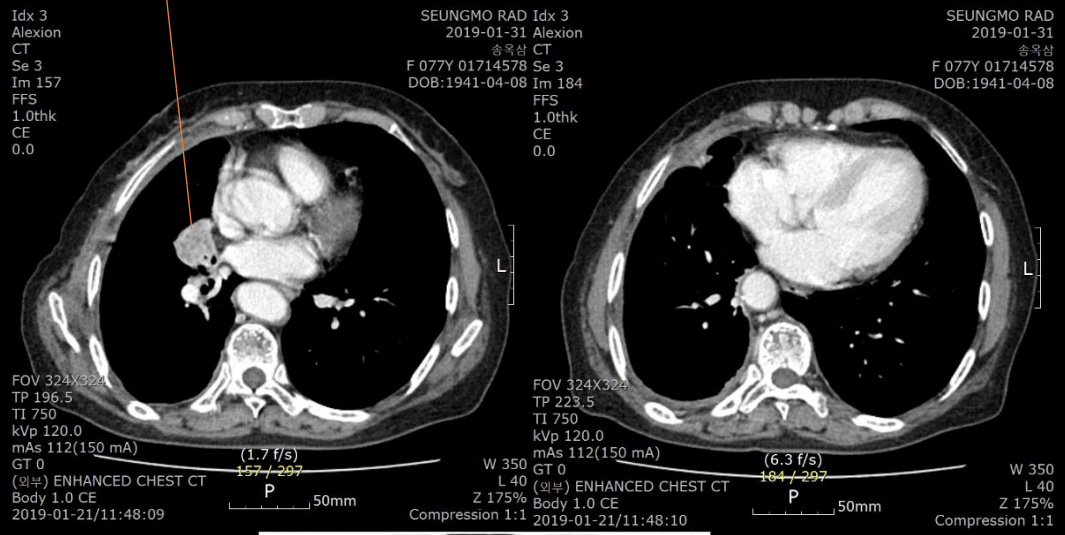
T790M
all negative in intrathoracic disease

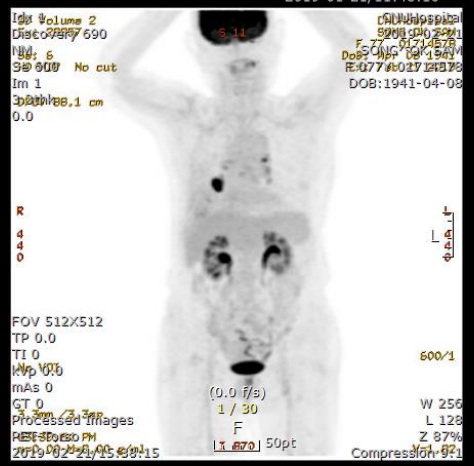


Minari, Roberta, et al. *Clinical Lung Cancer* 21.5 (2020): e464-e473.
Seto, Takashi, et al. *Oncology and therapy* 6.2 (2018): 203-215.

Case #3 78/F, Lung cancer (adeno, RML, T2N3M1b, pleura, brain)

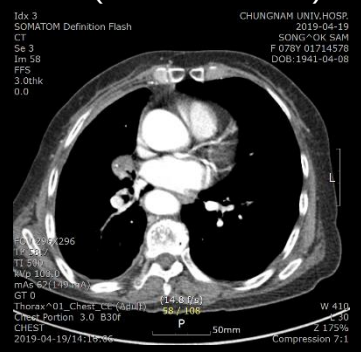
RML PCNB ; Exon 21 L858R



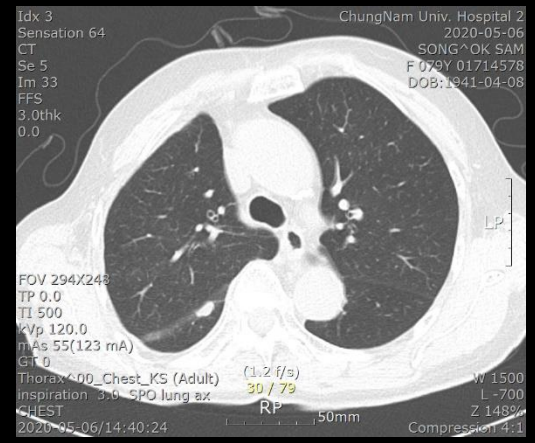


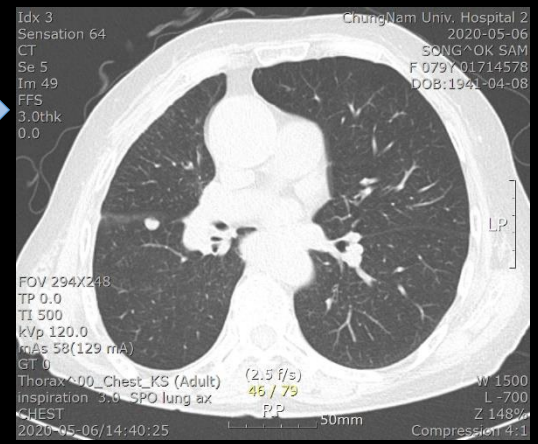
2019.2.21

PR (29→18mm)



Gefitinib (14 months)



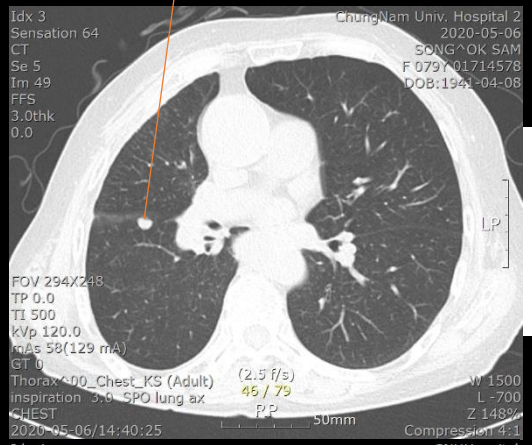


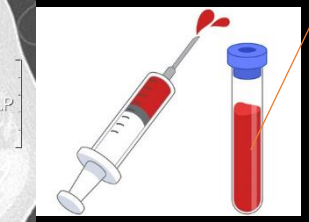
2020.5.6

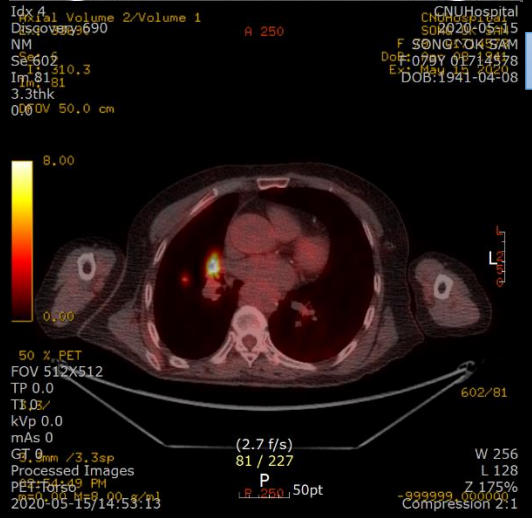
Case #3 78/F, Lung cancer (adeno, RML, T2N3M1b, pleura, brain)

EGFR(cell free DNA) ; Not Detected

Fissural nodule ; malignancy (-)



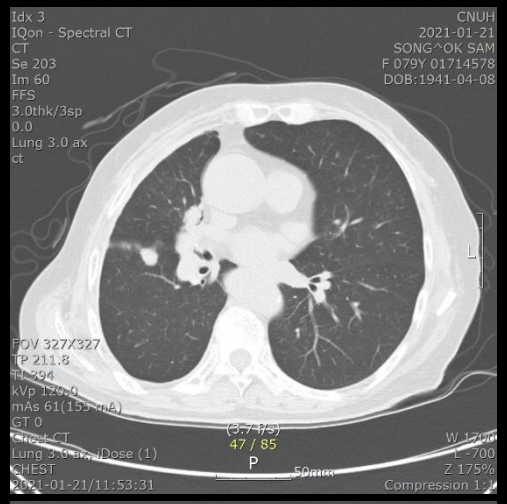


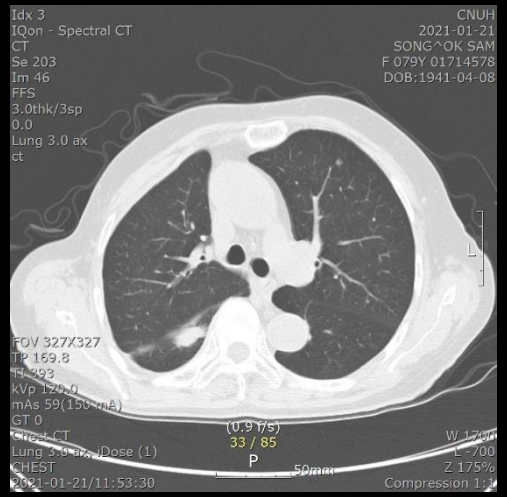


2020.5.6

observation

new brain mets – GKS (2회)

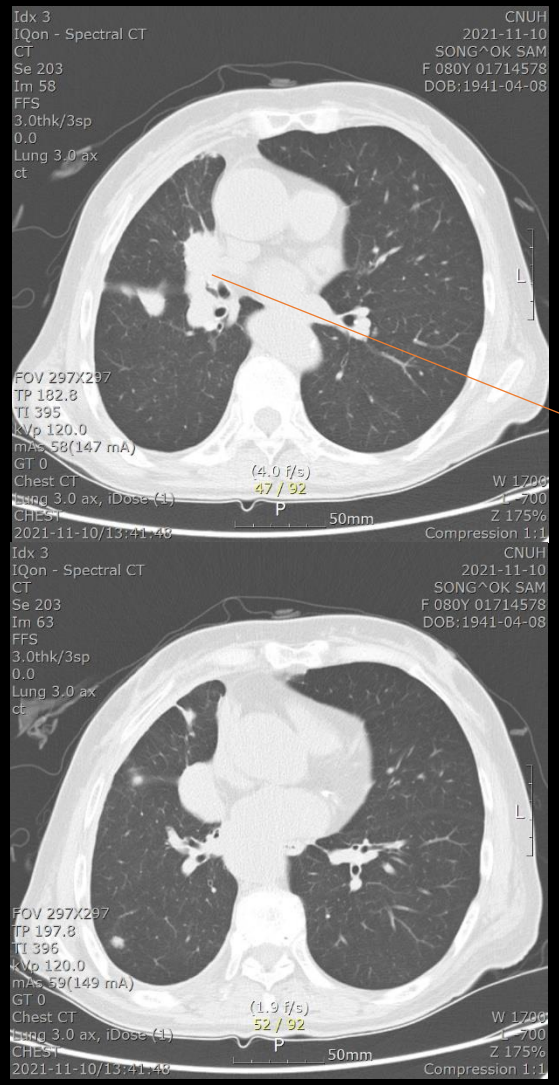




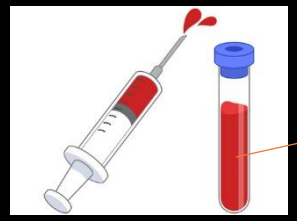
2021.1.21

Cis-pemetrexed #4,
pemetrexed maintenance #10

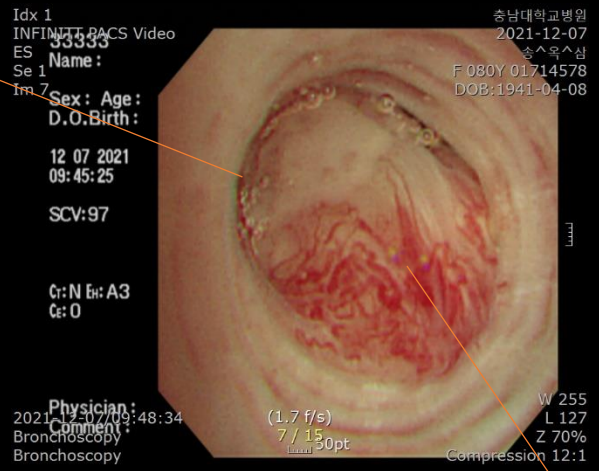
Case #3 78/F, Lung cancer (adeno, RML, T2N3M1b, pleura, brain)



2021.11.10



EGFR(cell free DNA) ; Exon 21 L858R



RML TBLB ; Exon 21 L858R
Exon 20 T790M

Date	Site	Biopsy tool	Result
2019.1	RML	PCNB	Exon 21 L858R
2020.5	RLL	PCNB	Malignancy (-)
	Plasma		Not detected
2021.11	RML	TBLB	Exon 21 L858R Exon 20 T790M
	Plasma		Exon 21 L858R

Spatiotemporal heterogeneity

Rebiopsy

1) **Site** – progression pattern
2) **Timing** – progression time
3) **Repeat** – multiple sites, consider during the subsequent treatment

Contents

1. Rebiopsy

1) Spatiotemporal heterogeneity
2) Clinical factors predicting detection of T790M mutation
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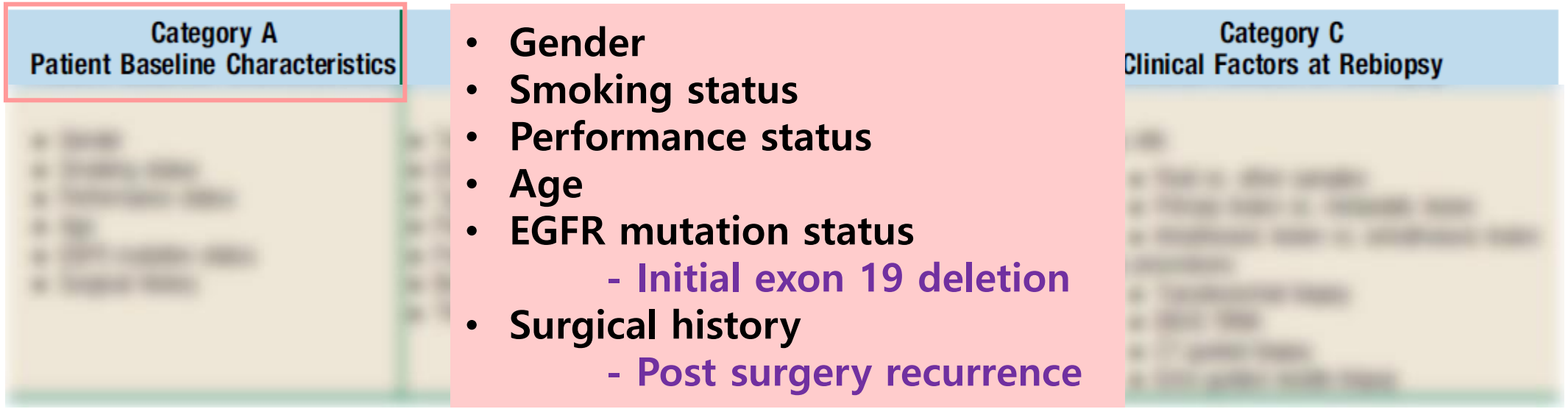
Clinical factors for analysis of T790M Frequency

Category A Patient Baseline Characteristics	Category B Clinical Factors Before Rebiopsy	Category C Clinical Factors at Rebiopsy
• Gender • Smoking status • Performance status • Age • EGFR mutation status • Surgical history	• Total duration of EGFR-TKI treatment before rebiopsy • EGFR-TKI treatment history immediately before rebiopsy • Type of EGFR-TKI administered before rebiopsy • Period of continuation of initial EGFR-TKI treatment beyond PD • Progression-free survival on initial EGFR-TKI treatment • Best response to initial EGFR-TKI treatment • TKI-free interval	Rebiopsy site • Fluid vs. other samples • Primary lesion vs. metastatic lesion • Intrathoracic lesion vs. extrathoracic lesion Rebiopsy procedures • Transbronchial biopsy • EBUS-TBNA • CT-guided biopsy • Echo-guided needle biopsy

Kawamura, Takahisa, et al. *Clinical lung cancer* 19.2 (2018): e247-e252.

Clinical factors for analysis of T790M Frequency



- Gender
- Smoking status
- Performance status
- Age
- EGFR mutation status
  - Initial exon 19 deletion
- Surgical history
  - Post surgery recurrence

Kawamura, Takahisa, et al. *Clinical lung cancer* 19.2 (2018): e247-e252.

Chai, Chee-Shee, et al. *Cancer management and research* 12 (2020): 5439.

Zhou, Jia, et al. *Future Oncology* 17.19 (2021): 2475-2488.

Gao, Wen, et al. *OncoTargets and therapy* 12 (2019): 9495.

Ninomaru, Taira, et al. *Thoracic Cancer* 12.6 (2021): 746-751.

Clinical factors for analysis of T790M Frequency

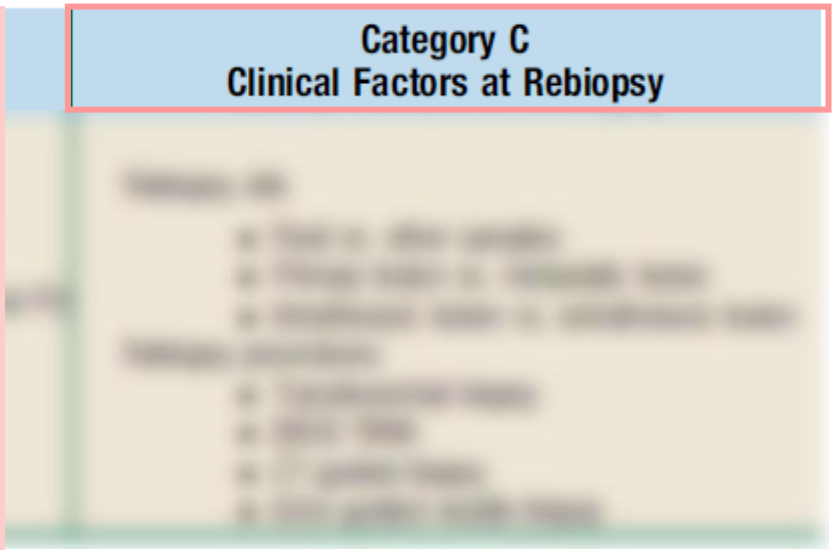
Category A Patient Baseline Characteristics	Category B Clinical Factors Before Rebiopsy	Category C Clinical Factors at Rebiopsy

- Treatment duration of EGFR-TKI before rebiopsy
  - longer duration
- PFS on initial EGFR-TKI treatment
  - longer PFS
- Best response to initial EGFR-TKI treatment
  - PR
- Type of EGFR-TKI administered before rebiopsy
- Period of continuation of initial EGFR-TKI treatment beyond PD
- TKI-free interval
- Progression pattern (primary/metastatic lesion, new metastasis)

Mountzios, Giannis, et al. *Cancers* 13.13 (2021): 3172.
Chai, Chee-Shee, et al. *Cancer management and research* 12 (2020): 5439.
Kawamura, Takahisa, et al. *Clinical lung cancer* 19.2 (2018): e247-e252.
Zhou, Jia, et al. *Future Oncology* 17.19 (2021): 2475-2488.

Clinical factors for analysis of T790M Frequency

- Rebiopsy sample
  - tissue > cytology > plasma
- Rebiopsy site
  - Primary lesion vs. metastatic lesion
  - Intrathoracic lesion vs. extrathoracic lesion
- Rebiopsy procedures
  - TBLB, EBUS-GS-TBLB
  - EBUS-TBNA
  - CT-guided TTNB, sono-guided TTNB
  - Surgery



Kawamura, Takahisa, et al. *Clinical lung cancer* 19.2 (2018): e247-e252.

Rebiopsy methods & T790M mutation

	T790M-positive (n = 55)	T790M-negative (n = 70)	*P* Value
Rebiopsy site			.27
Primary	44	50	
Metastatic	11	20	
Rebiopsy site	Samples other than fluid: n = 69		.55
Intrathoracic	27	24	
Extrathoracic	11	7	
Method (tissue)	n = 69		.19
Transbronchial biopsy	19	18	
EBUS-TBNA	5	0	
CT-guided biopsy	11	9	
Echo-guided needle biopsy	3	4	

Characteristic	T790M-positive	T790M-negative	P value
Specimen of rebiopsy			0.002
- Tissues	73	50	
- Cells	54	63	
- Liquid	26	51	
Cell			0.843
- BALF	20	24	
- Pleural effusion	28	30	
- Pericardial effusion	6	9	
Methods of re-biopsy			0.496
- Ordinary bronchoscope	14	7	
- EBUS-TBNA	10	8	
- EBUS-TBLB	20	16	
- Percutaneous lung biopsy	24	11	
- Liver biopsy	3	5	
- Bone biopsy	2	3	

Kawamura, Takahisa, et al. *Clinical lung cancer* 19.2 (2018): e247-e252.
Zhou, Jia, et al. *Future Oncology* 17.19 (2021): 2475-2488.

Bronchoscopy vs. PCNB

Table 3 – Diagnostic rate and EGFR mutation detection rate by bronchoscopy and CTNB.

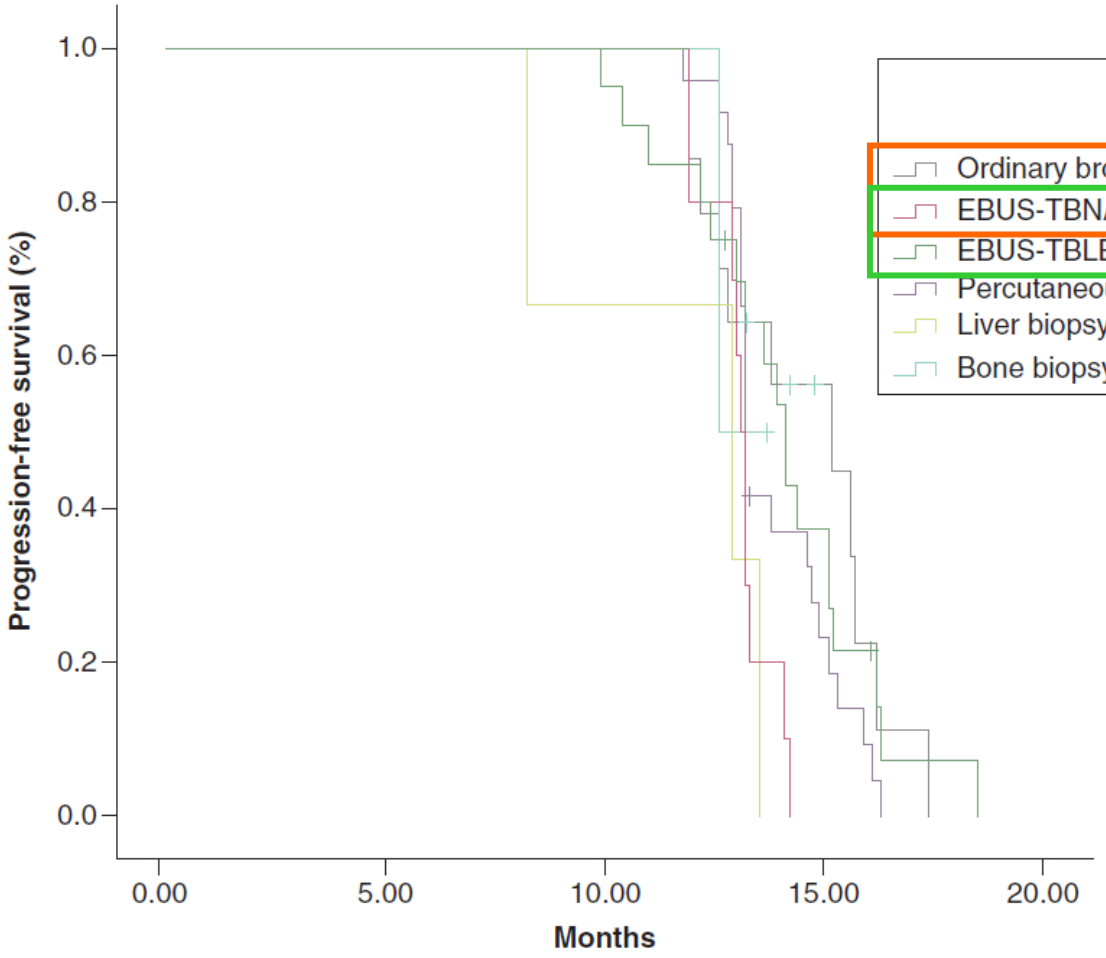
	Bronchoscopy (n = 29)	CTNB (n = 19)	p
Diagnostic positive	22 (75.9%)	19 (100%)	0.03
Histology positive	14 (48.3%)	18 (94.7%)	
Only cytology positive	8 (27.6%)	1 (5.3%)	
	Bronchoscopy (n = 29)	CTNB (n = 18)	
Primary EGFR mutation detection	26 (89.7%)	18 (100%)	0.28
EGFR T790M detection	10 (34.5%)	13 (72.2%)	0.02

CTNB, computed tomography-guided needle biopsy; EGFR, epidermal growth factor receptor.

Peripheral vs. Central lesion ?

Kano, Hirohisa, et al. *Respiratory Investigation* 59.2 (2021): 240-246.

PFS of patients rebiopsied by different methods

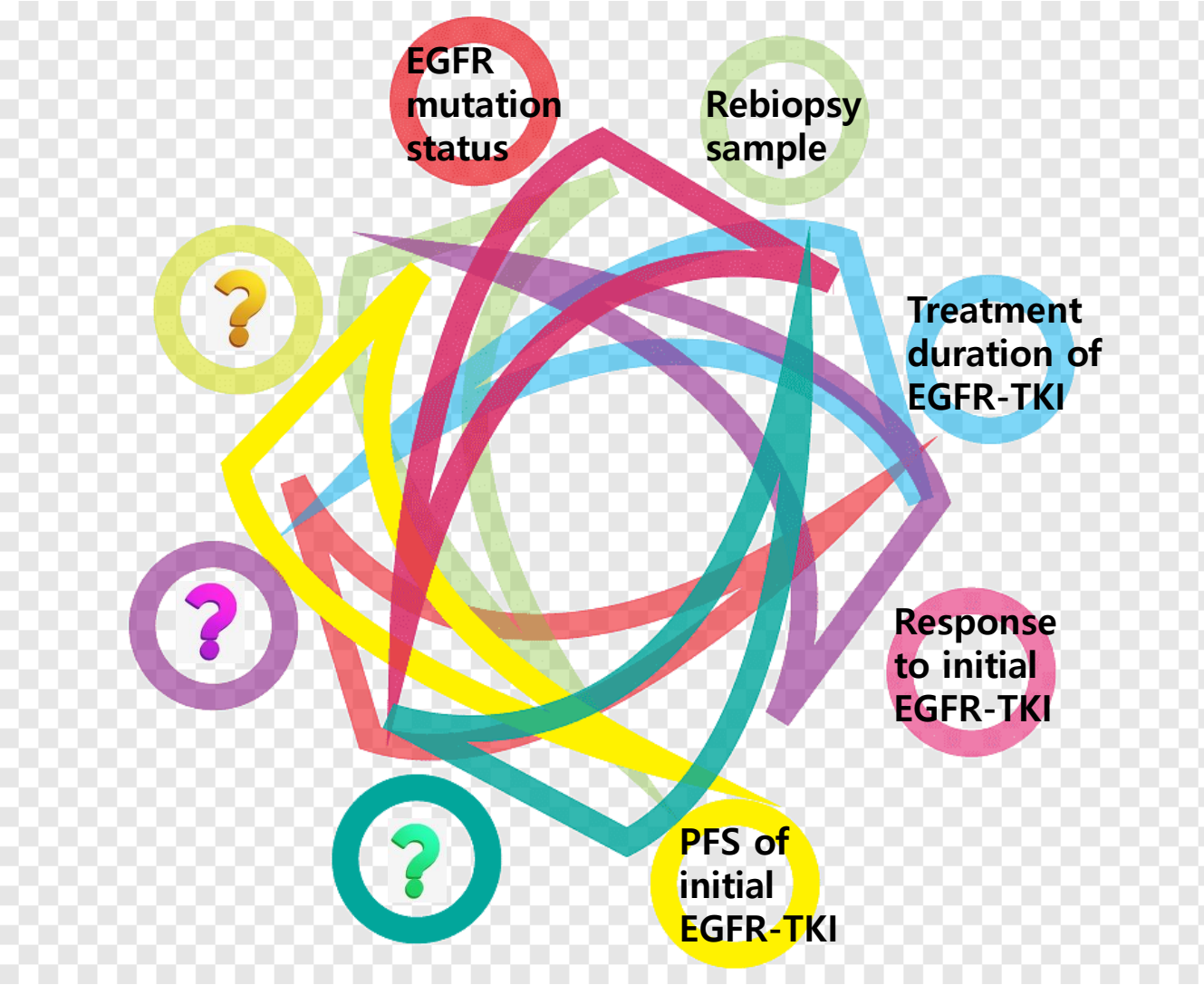


	Median PFS in months (95% CI)
Ordinary bronchoscope	15.20 (11.60 to 18.80)
EBUS-TBNA	13.1 (12.89 to 13.31)
EBUS-TBLB	14.1 (13.41 to 14.79)
Percutaneous lung biopsy	13.2 (13.12 to 13.28)
Liver biopsy	12.9 (5.38 to 20.42)
Bone biopsy	12.6

False-positive or false-negative possibility of T790M mutation in tissue rebiopsy through EBUS-TBNA ?

Zhou, Jia, et al. *Future Oncology* 17.19 (2021): 2475-2488.

Clinical factors for analysis of T790M Frequency



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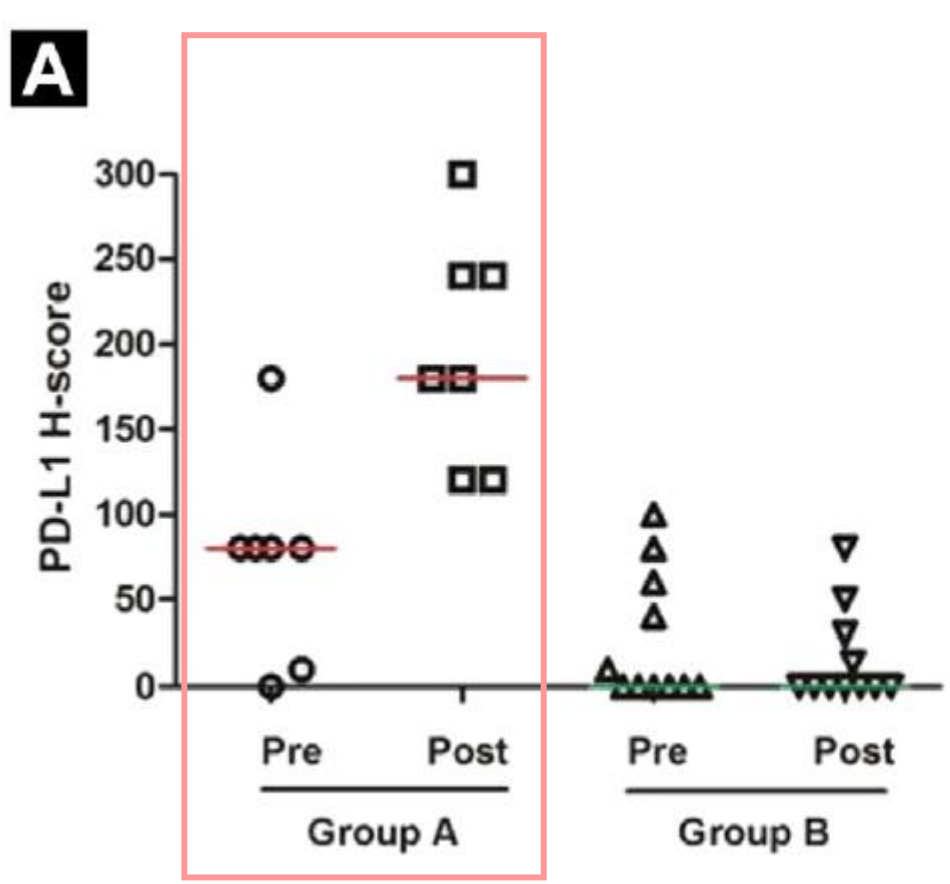
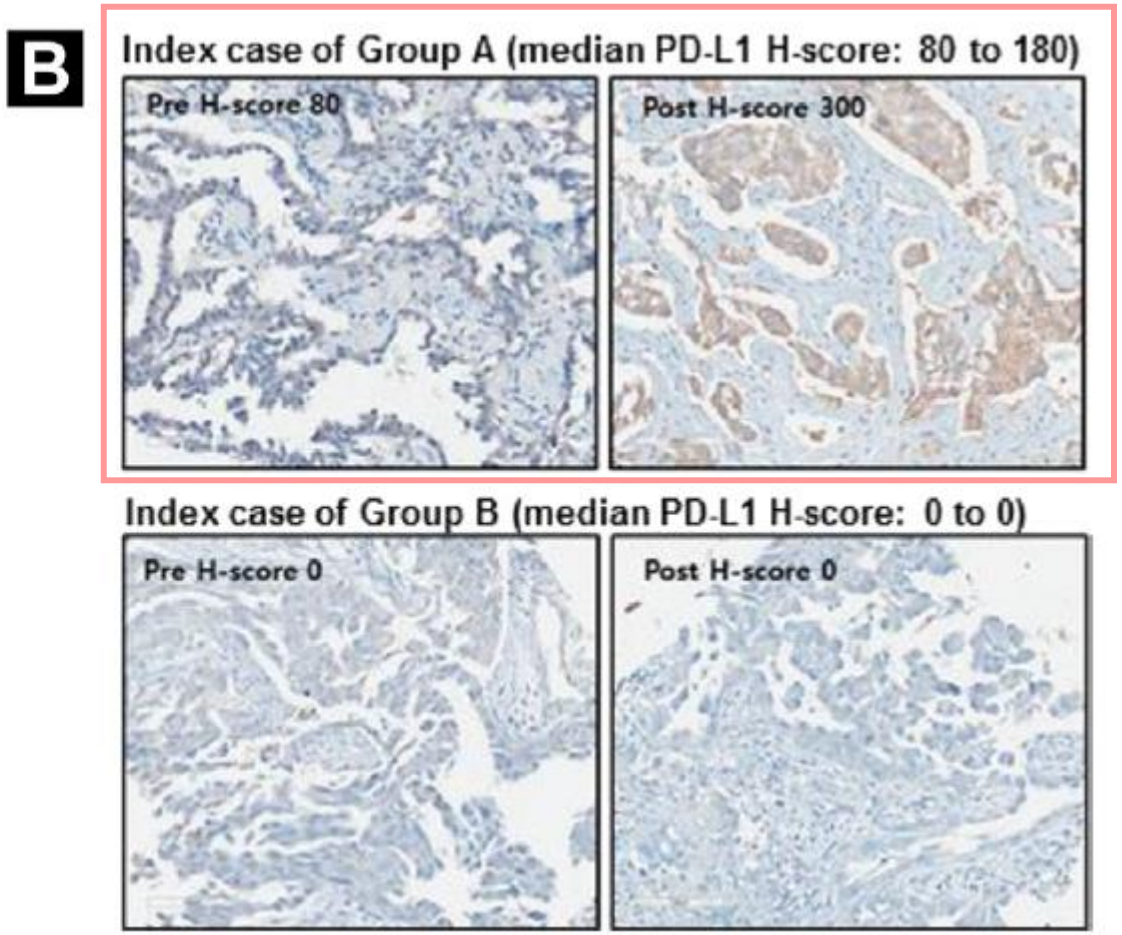
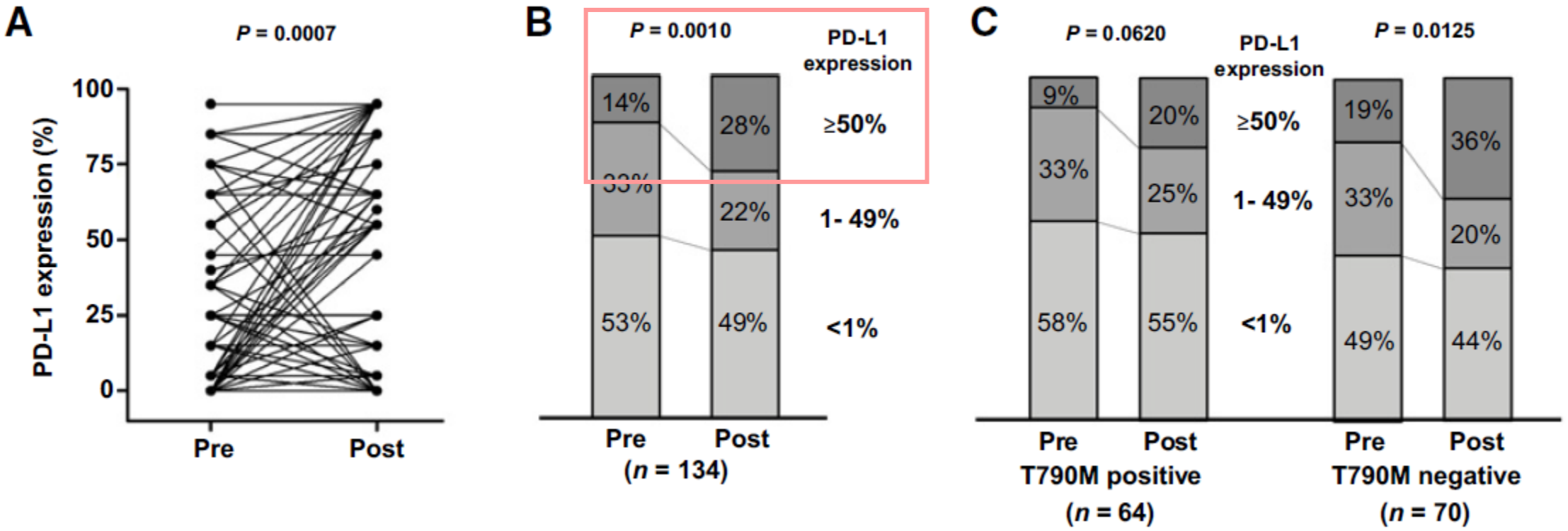
Change in PD-L1 expression after acquiring resistance to gefitinib





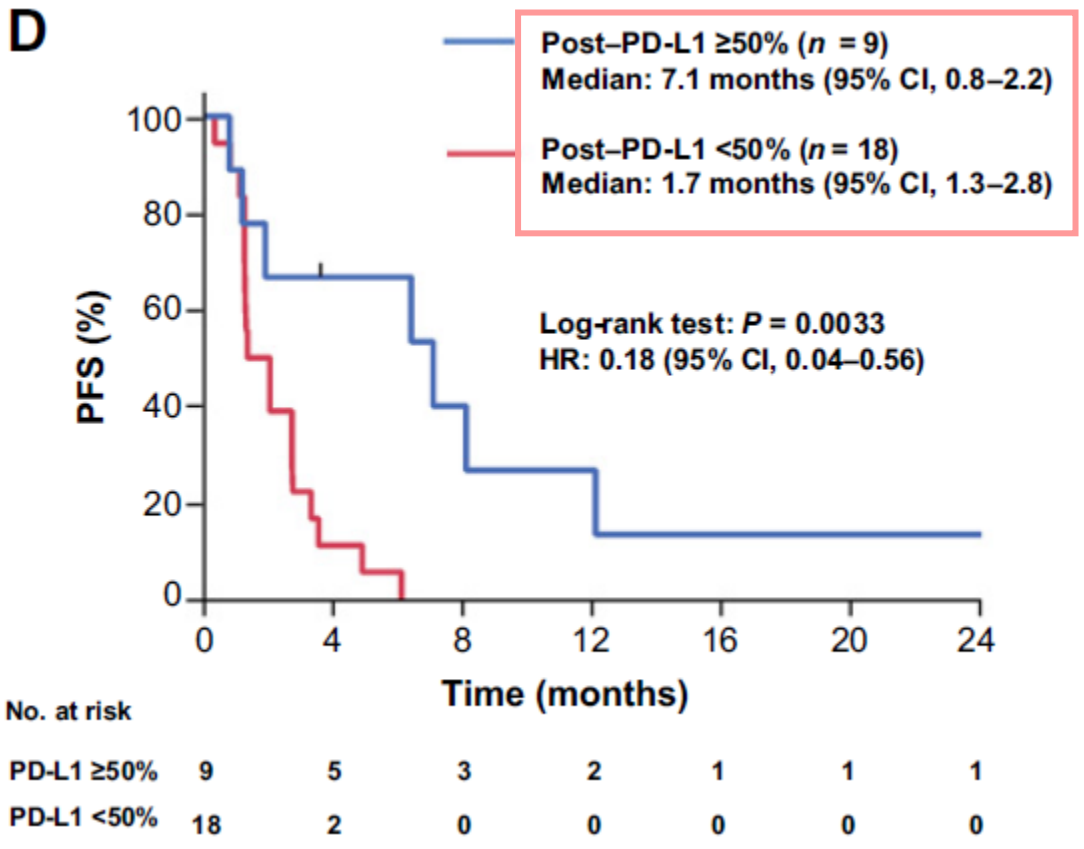
Han, Jae Joon, et al. *Clinical lung cancer* 17.4 (2016): 263-270.

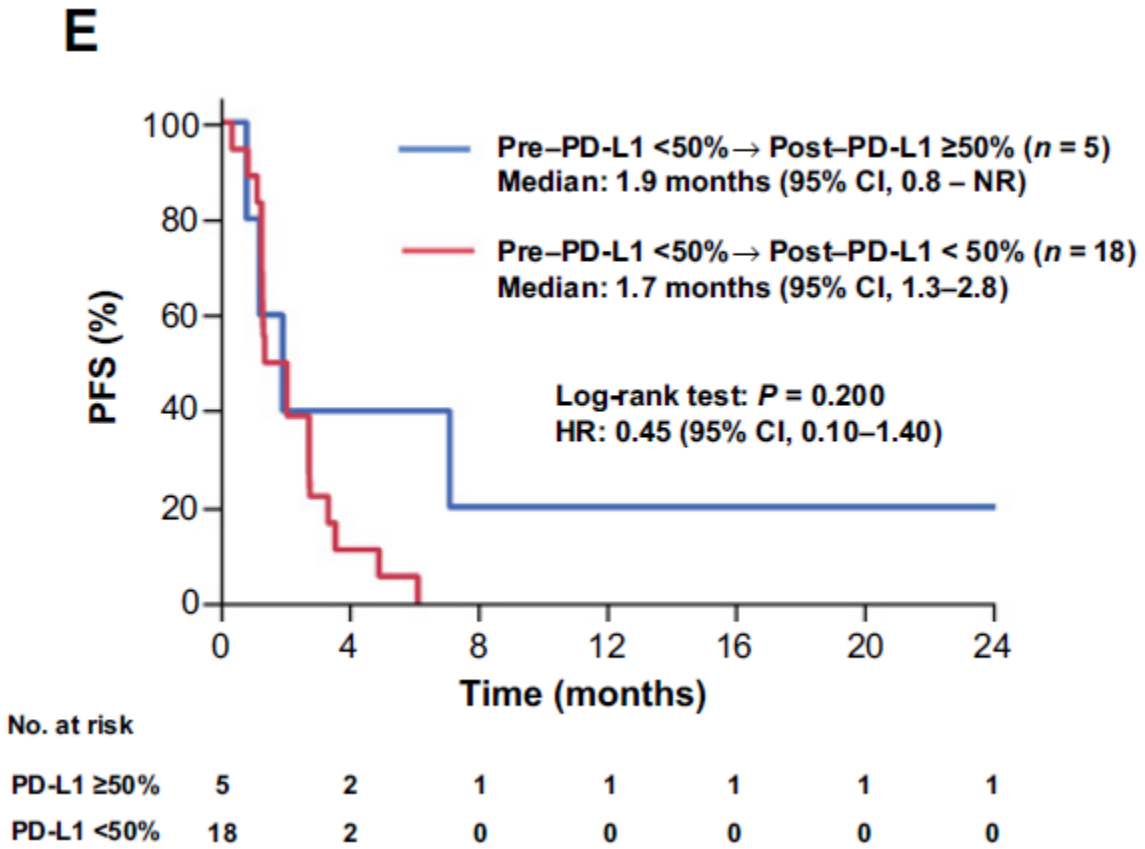
Post PD-L1 change after EGFR-TKI treatment



Isomoto, Kohsuke, et al. *Clinical Cancer Research* 26.8 (2020): 2037-2046.

Post PD-L1 expression correlates with ICI efficacy





Isomoto, Kohsuke, et al. *Clinical Cancer Research* 26.8 (2020): 2037-2046.

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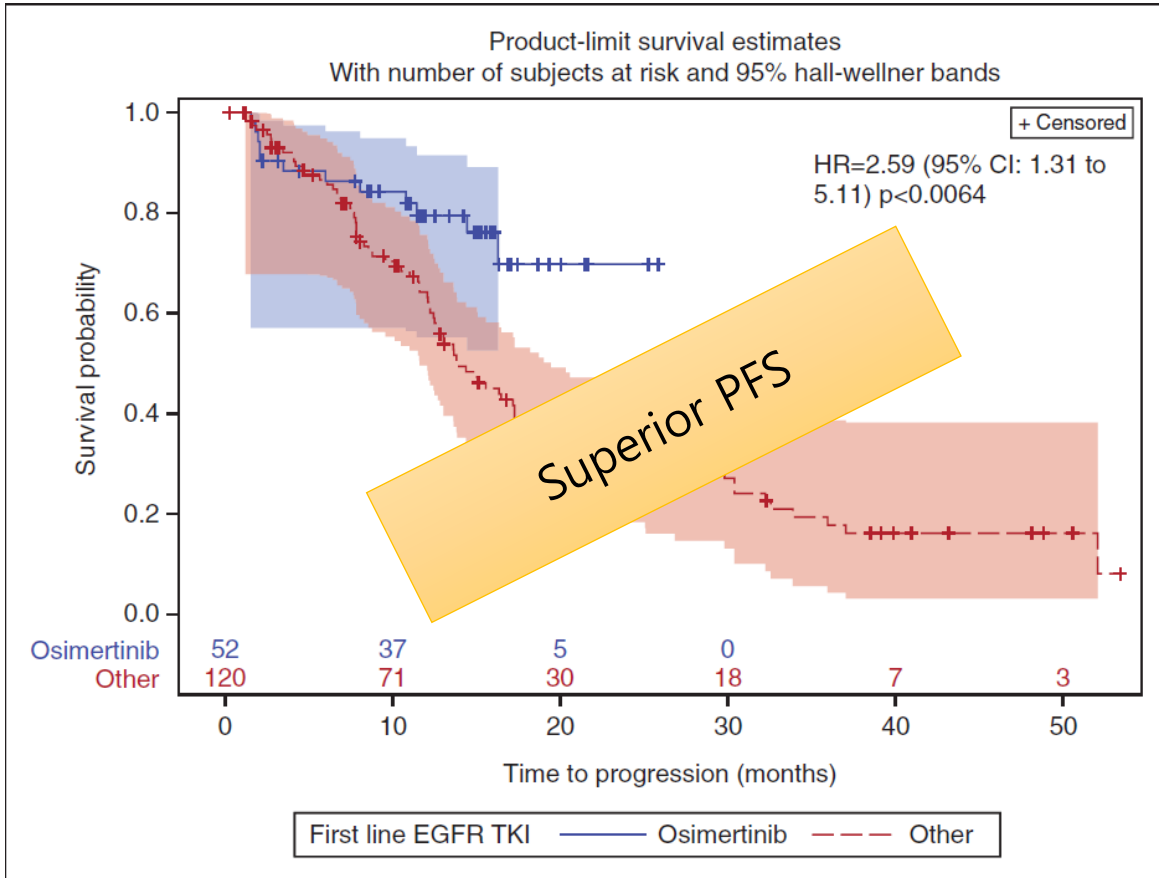
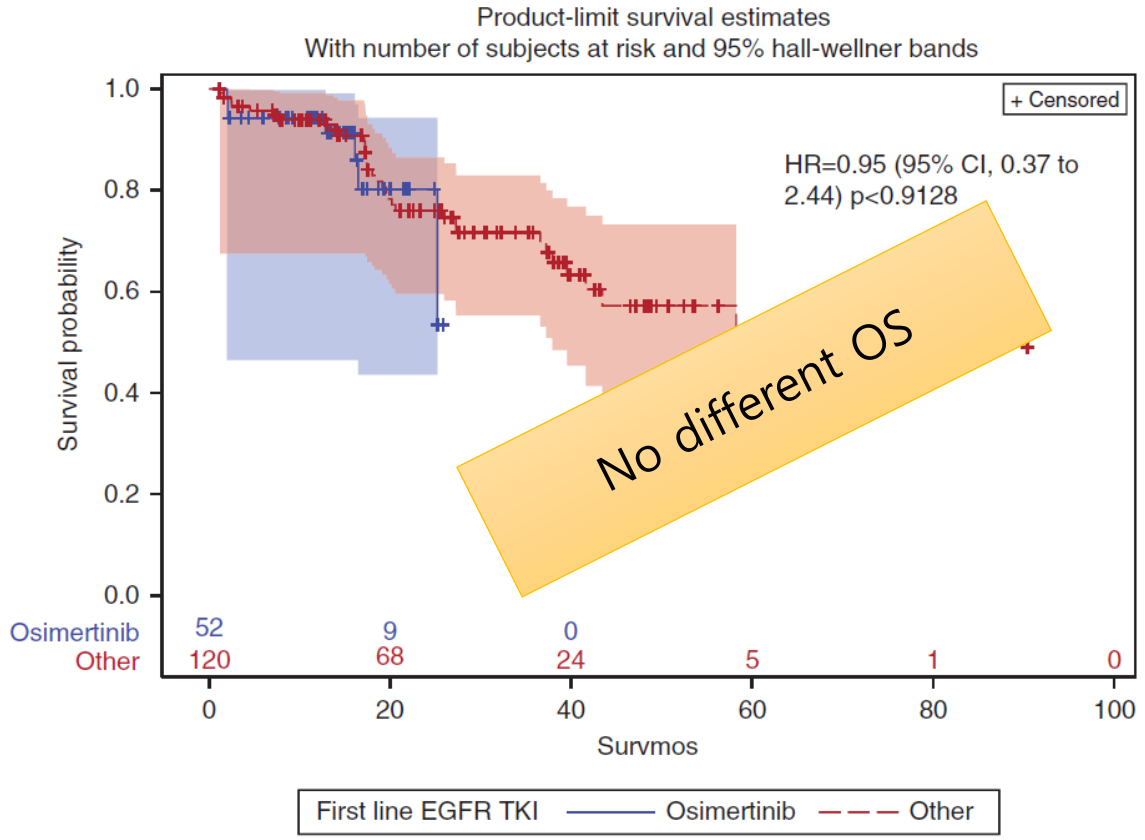
First-line Afatinib vs. Osimertinib

A real world analysis of first line treatment of advanced EGFR mutated non-small cell lung cancer: A multi-center, retrospective study

Two large academic medical centers, USA
172 patients





Lee, Chung-Shien, et al. *Journal of Oncology Pharmacy Practice* (2021): 10781552211020798.

First-line Afatinib vs. Osimertinib

Japan RWE (CJLSG1903): Multicenter observational cohort study

First-line Afatinib or Osimertinib patients

(n=550)

Clinical data between May 2016 and October 2019 from 15 institutions in Japan

→ **Afatinib group (n=225)**

→ **Osimertinib group (n=329)**

<u>Primary endpoint</u>:
Time to discontinuation of any EGFR-TKI (TD-TKI)

<u>Second endpoint</u>:
Overall Survival (OS)

A multicenter cohort study of osimertinib compared with afatinib as first-line treatment for EGFR-mutated non-small-cell lung cancer from practical dataset: CJLSG1903

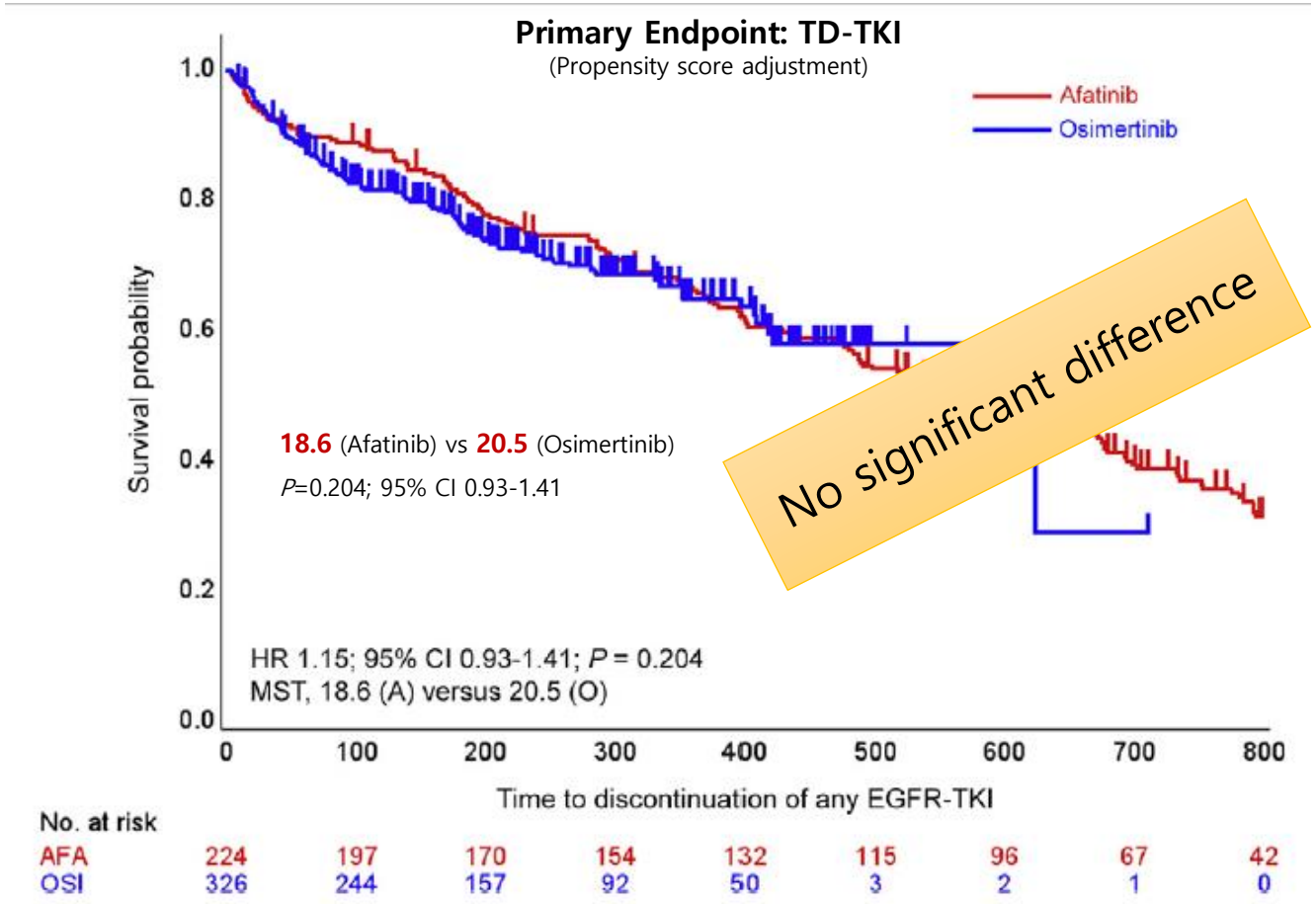
Table 1. Demographics[a]

	Afatinib group (*N* = 224)	Osimertinib group (*N* = 326)	*P* value
Age (years), mean	68.82	70.14	0.152
Sex			
Male/Female	105/119	133/193	0.162
Smoking status			
Never/former or current/unknown	111/107/6	185/137/4	0.153
Clinical stage (8th edition TNM stage classification)			
1-2/3/4/R	5/25/152/42	10/24/228/64	0.469
Histologic subtype[b]			
ADC	215	313	1
SCC	5	7	1
Other	5	6	0.765
EGFR mutation[b]			
Ex19del	114	163	0.862
L858R	74	155	0.001
Uncommon	39	9	<0.001
ECOG PS			
0/1/2 or more/ Unknown	67/124/30/3	114/159/47/6	0.328
Pleural effusion			
Yes	65	114	0.165
Brain metastasis			
Yes	75	85	0.07
PD-L1			
<1/1-49/50≤/ Unknown	53/56/41/74	102/79/55/90	0.233

Ito, K., et al. *ESMO open* 6.3 (2021): 100115.

First-line Afatinib vs. Osimertinib

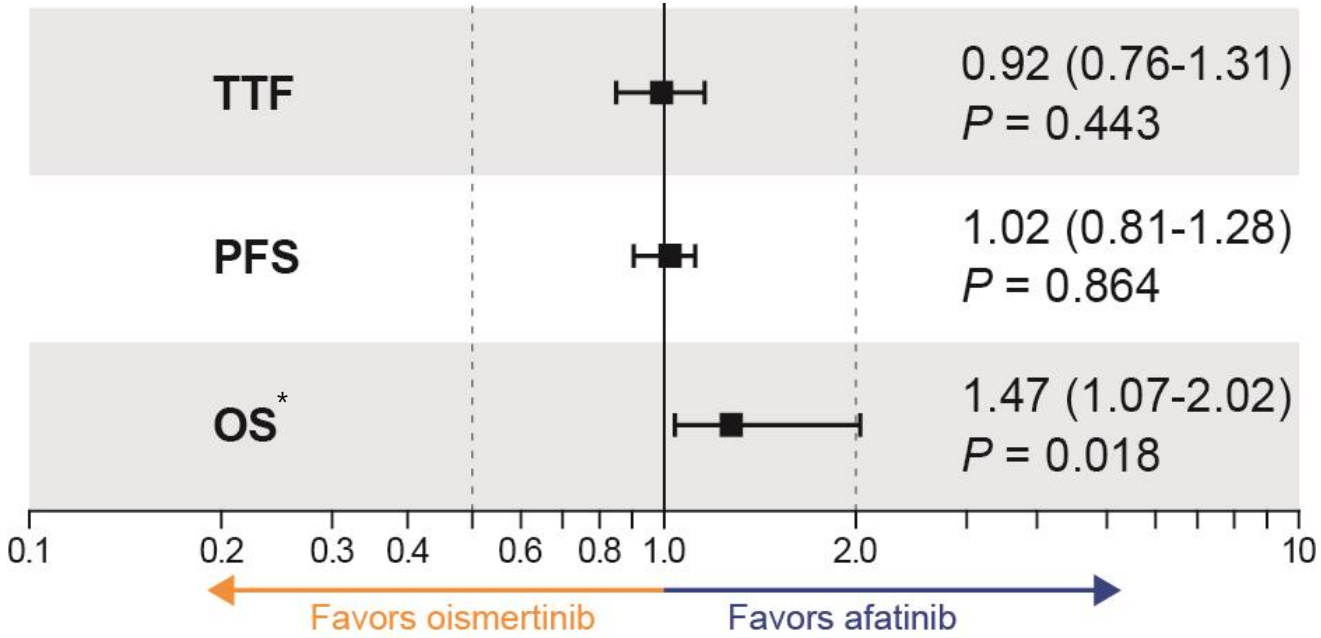
Japan RWE (CJLSG1903): Multicenter observational cohort study



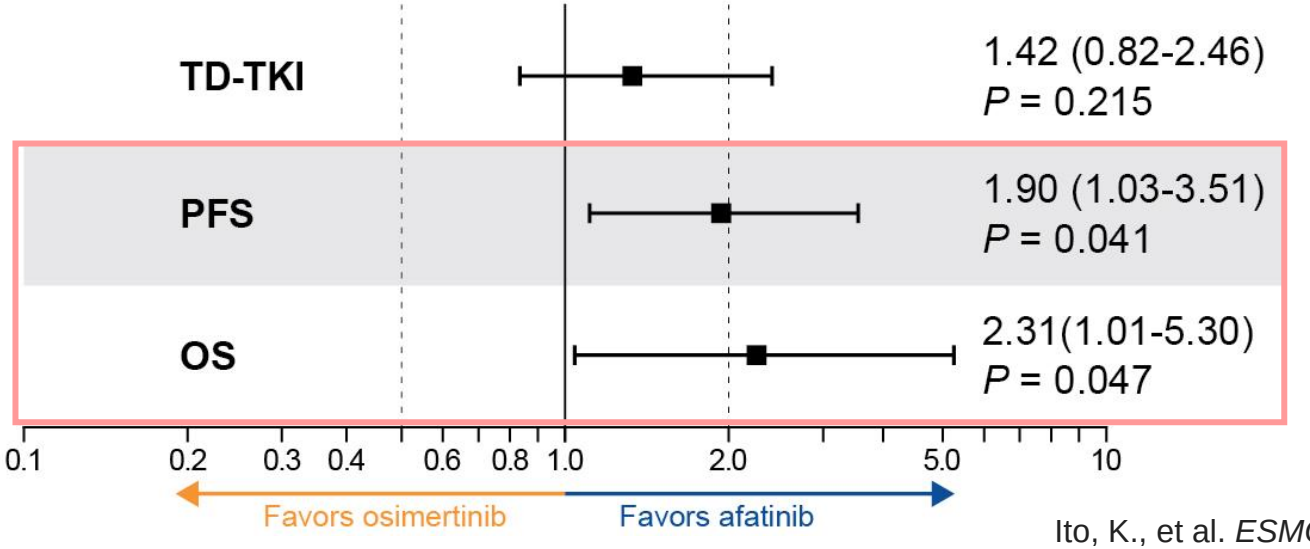
Ito, K., et al. *ESMO open* 6.3 (2021): 100115.

Total patients

MST 36.2 (A) vs. 25.1 (O)



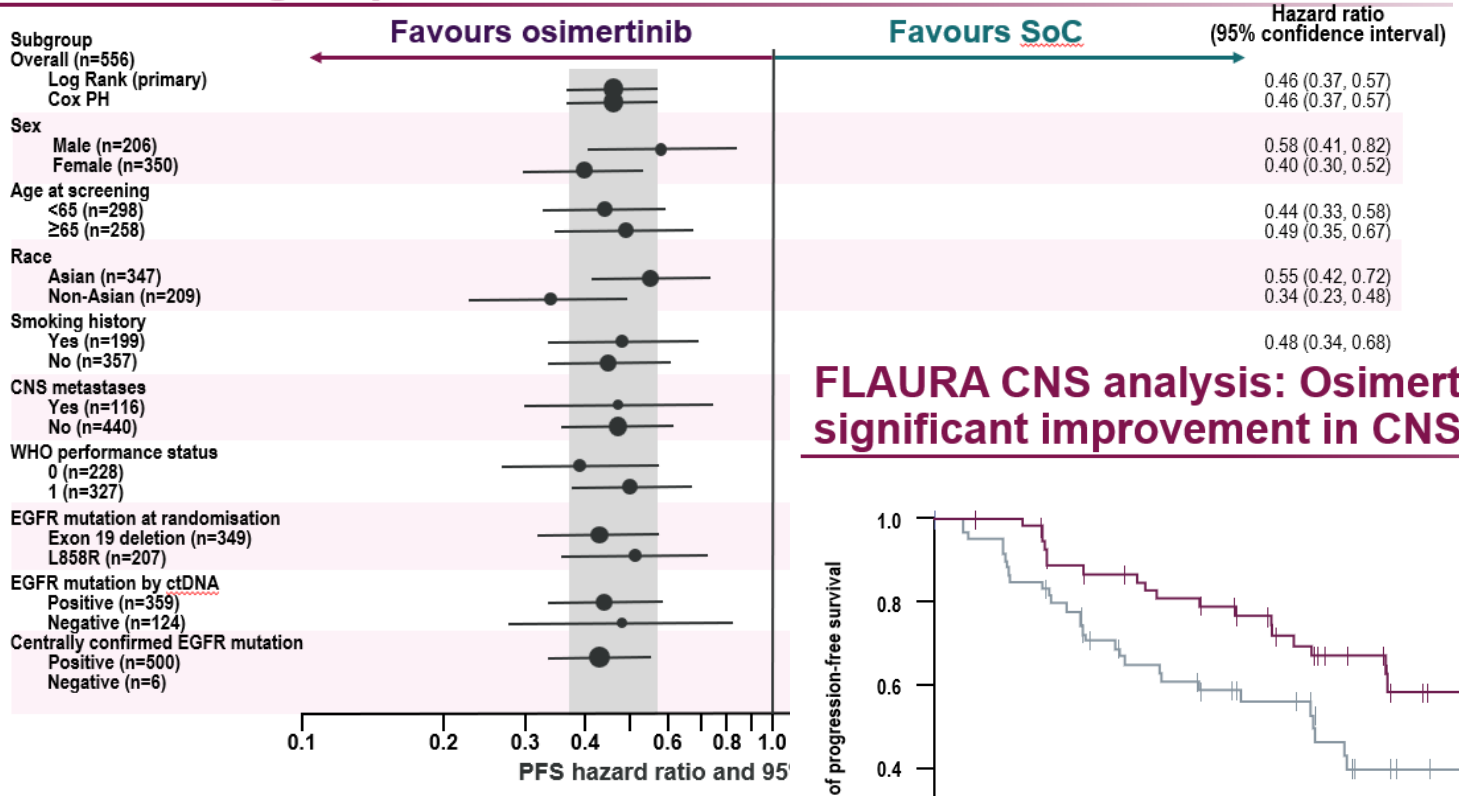
L858R without brain mets



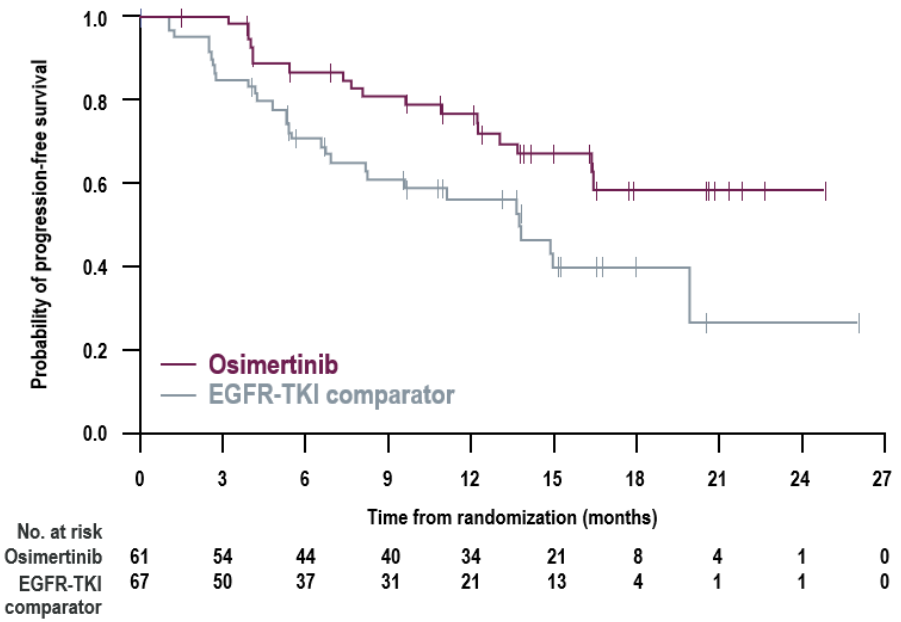
Ito, K., et al. *ESMO open* 6.3 (2021): 100115.

First-line Osimertinib vs. Other EGFR-TKI

PFS across subgroups



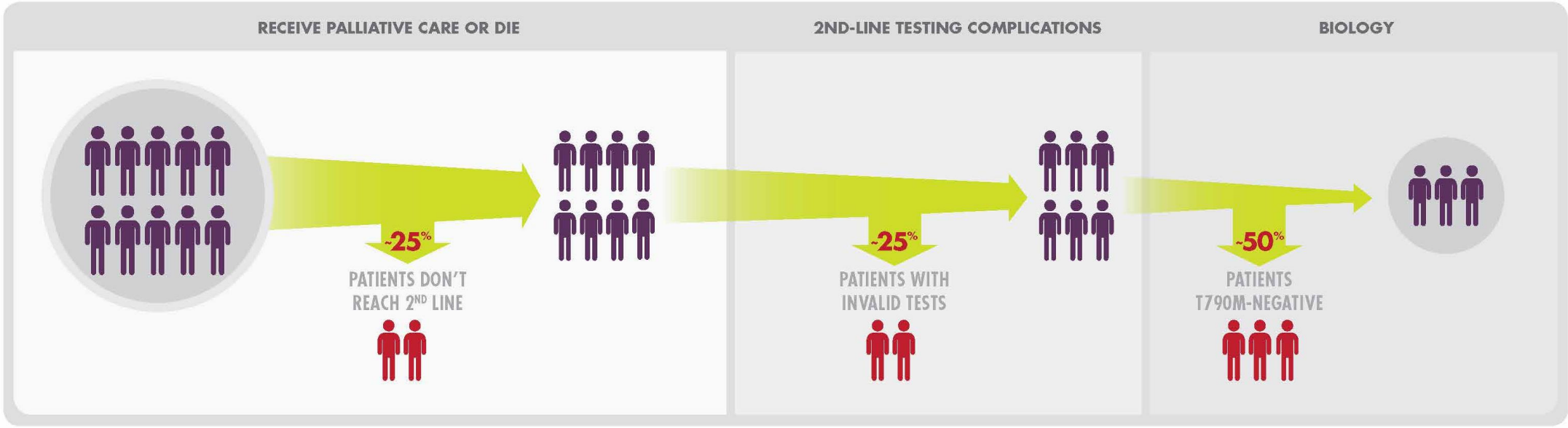
FLAURA CNS analysis: Osimertinib demonstrated a nominally statistically significant improvement in CNS PFS vs EGFR-TKI comparator (CNS FAS)



	Osimertinib (n=61)	EGFR-TKI comparator (n=67)
Median CNS PFS, months (95% CI)	NR (16.5, NC)	13.9 (8.3, NC)
HR* (95% CI); *P*-value	0.48 (0.26, 0.86); *P*=0.014	
Median follow up, months	12.4	7.0

- CNS PFS was nominally statistically significant
  - CNS PFS analysis was third in the hierarchical statistical testing strategy and, as OS did not reach formal statistical significance at this data cut-off, CNS PFS could not be formally tested for statistical significance
  - Interim OS analysis: HR 0.63 (95% CI: 0.45, 0.88); p=0.0068 (NS, p-value of <0.0015 required for statistical significance at 25% maturity)

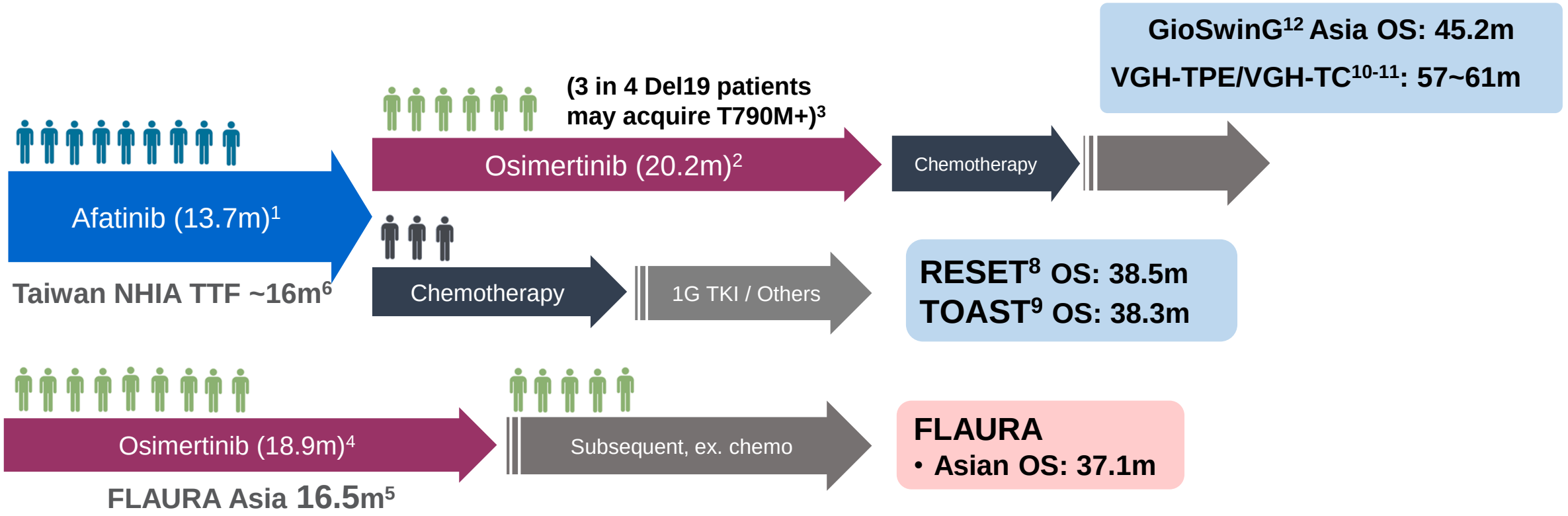
First-line Osimertinib vs. Other EGFR-TKI



Only ~1/3 of all EGFRm patients treated with 1G/2G EGFR-TKI are able to receive osimertinib

1. Lee CK et al. *J Natl Cancer Inst.* 2017;109(6):1-9. 2. Paz-Ares L et al. *Ann Oncol.* 2017;28:270-277. 3. Arcila ME et al. *Clin Cancer Res.* 2011;17(5): 1169-1180. 4. Sun JM et al. *Lung Cancer.*2013;82:294-298. 5. Li W et al. *Lung Cancer.* 2014;84:295-300 6. Pereira, Isabel, et al. *Cureus* 12.12 (2020).

Treatment Sequence in EGFR-Mutant NSCLC in Asian



1. Hochmair M et al. Future Oncol. 2018 Oct. 19; doi:10.2217/fon-2018-0711; 2. Sequist LV et al, ESMO 2017, #1349P; 3. 2019 Journal of Thoracic Oncology, Volume 14, Issue 10, S835 - S836; 4. N Engl J Med 2018; 378:113-125; 5. Yi-Long, Wu, et al. 2019 ESMO Asia; 6. Int J Cancer . 2020 Aug 15;147(4):1107-1116. doi: 10.1002/ijc.32841;.7. Future Oncol. (2020) 16(34), 2799–2808; 8. Cancer Med. 2021 Sep;10(17):5809-5822.; 9. Jung et al. 2021 ASCO. Abstract 9053; 10. Target Oncol. 2020 Aug;15(4):503-512; 11. Sci Rep . 2021 Jun 8;11(1):12084. doi: 10.1038/s41598-021-91657-7. 12. 2021 TSPCCM poster

Optimal sequence of EGFR-TKI therapy

- EGFR mutation type
- Brain metastasis
- Reimbursement

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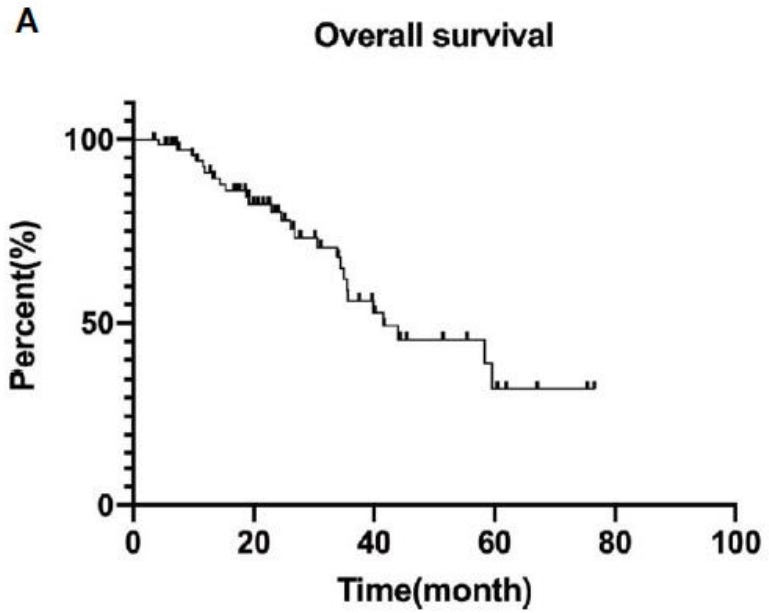
A Multicenter Retrospective Study on the Prognosis of Stage III Unresectable Mutant Non-Small Cell Lung Cancer With Tyrosine Kinase Inhibitors Therapy

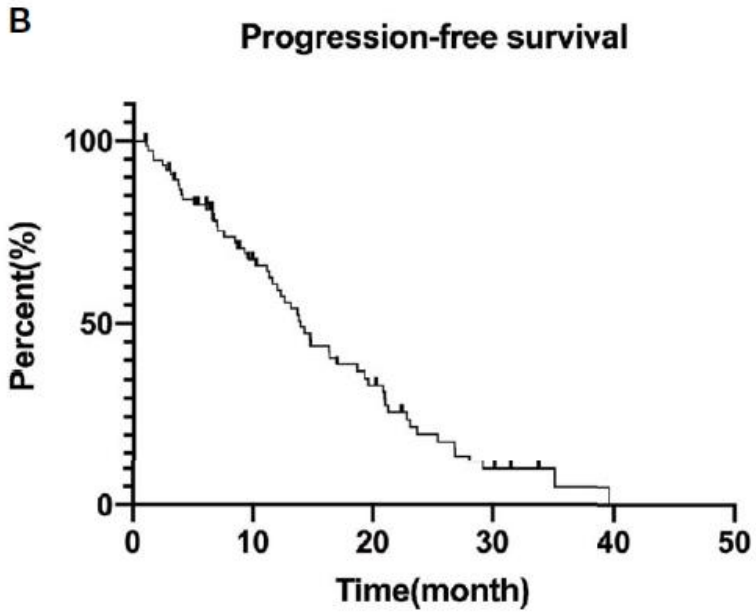
Ranpu Wu[1†], Shaorong Yu[2†], Jinjun Ye[2†], Yimin Wang[3], Zhiting Zhao[2], Hongbing Liu[1,3] and Yong Song[1,3*]*

- 81 patients from the Jinling Hospital and the Jiangsu Cancer Hospital (China)
- Stage III unresectable mutant NSCLC applied targeted therapy
- Retrospective study

First-line treatment	
TKI	63 (77.8)
TKI + chemotherapy	9 (11.1)
TKI + radiotherapy	6 (7.4)
TKI + immunotherapy	2 (2.5)
TKI+ chemoradiotherapy	1 (1.2)



Median OS :
41.47 months (95% CI 20.11–62.83)

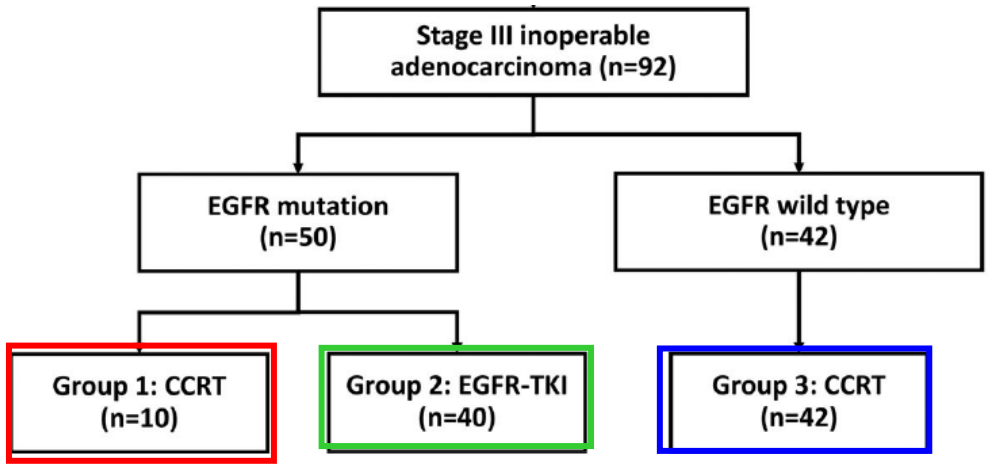


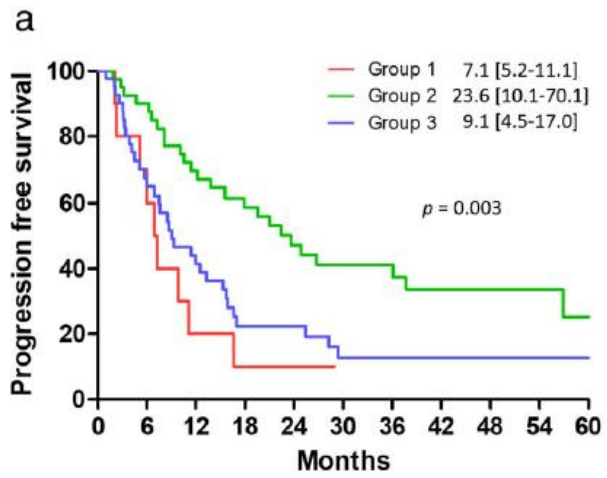
Median PFS :
13.87 months (95% CI 11.66–16.08)

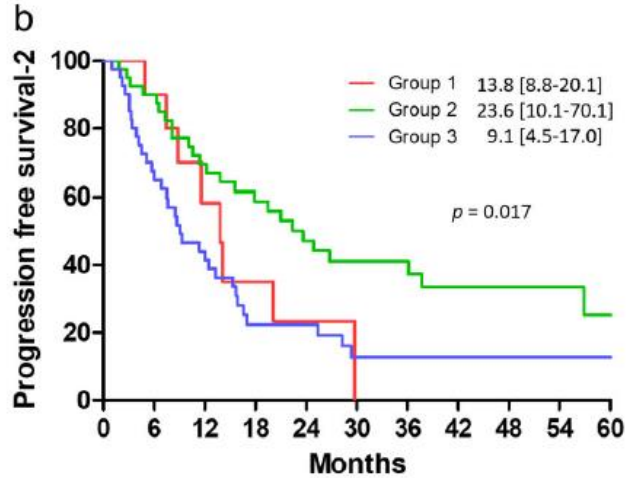
TKIs are a viable option for mutant stage III unresectable NSCLC patients

Wu, Ranpu, et al. *Frontiers in Oncology* (2021): 2624.

Improved survival in patients with unresectable stage III *EGFR*-mutant adenocarcinoma with upfront EGFR-tyrosine kinase inhibitors



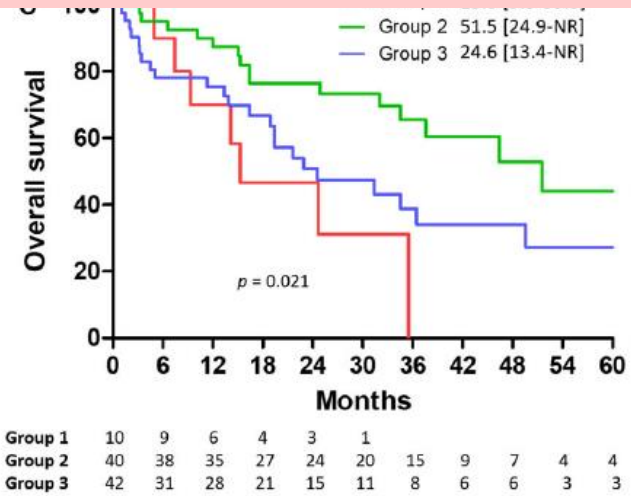




EGFR-TKIs is a better choice for patients with unresectable stage III EGFR-mutant adenocarcinoma

- Single-center, retrospective study
- Treatment was chosen according to physician preference

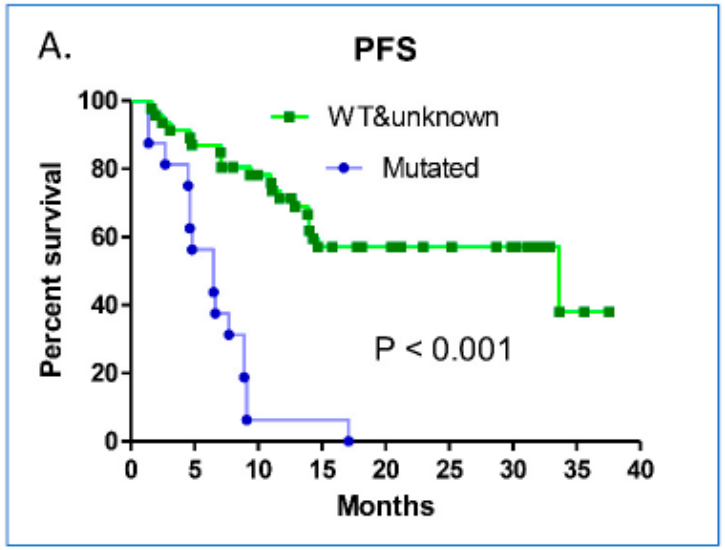
	CCRT (n=10)	EGFR-TKI (n=40)	*P* value
PFS (months)	7.1	23.6	0.003
PFS-2 (months)	13.8	23.6	0.017
OS (months)	15.3	51.5	0.021

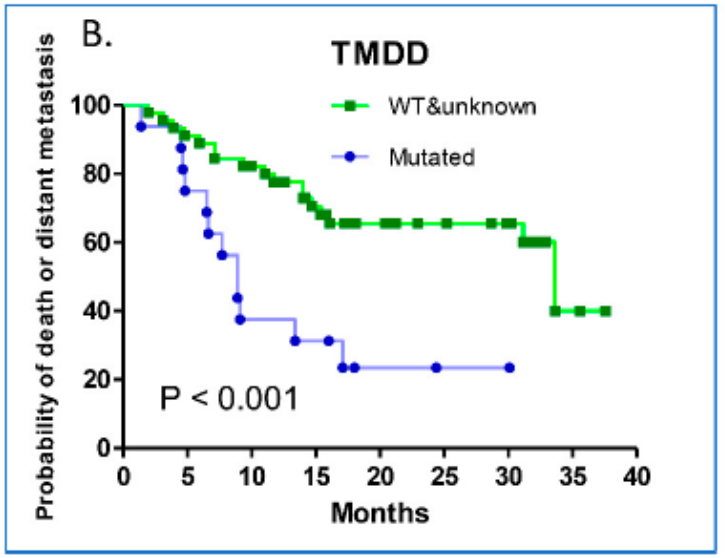


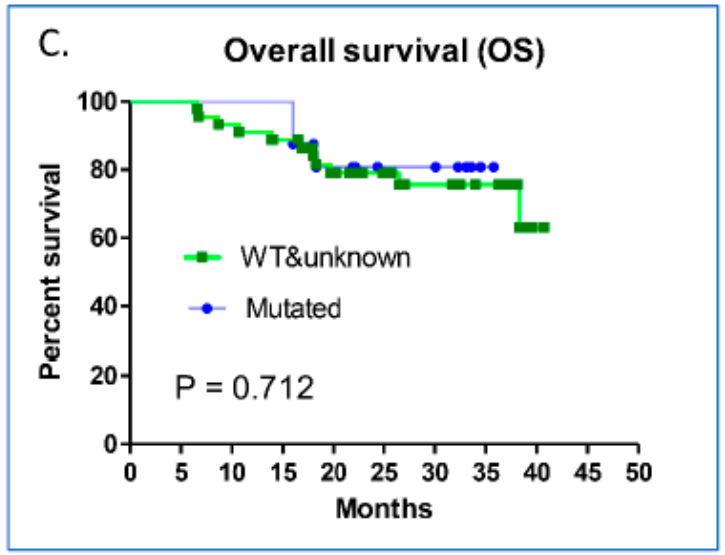
Wang, Sheng-Yuan, et al. *Thoracic cancer* (2022).

Article

Durvalumab as Consolidation Therapy in Post-Concurrent Chemoradiation (CCRT) in Unresectable Stage III Non-Small Cell Lung Cancer Patients: A Multicenter Observational Study





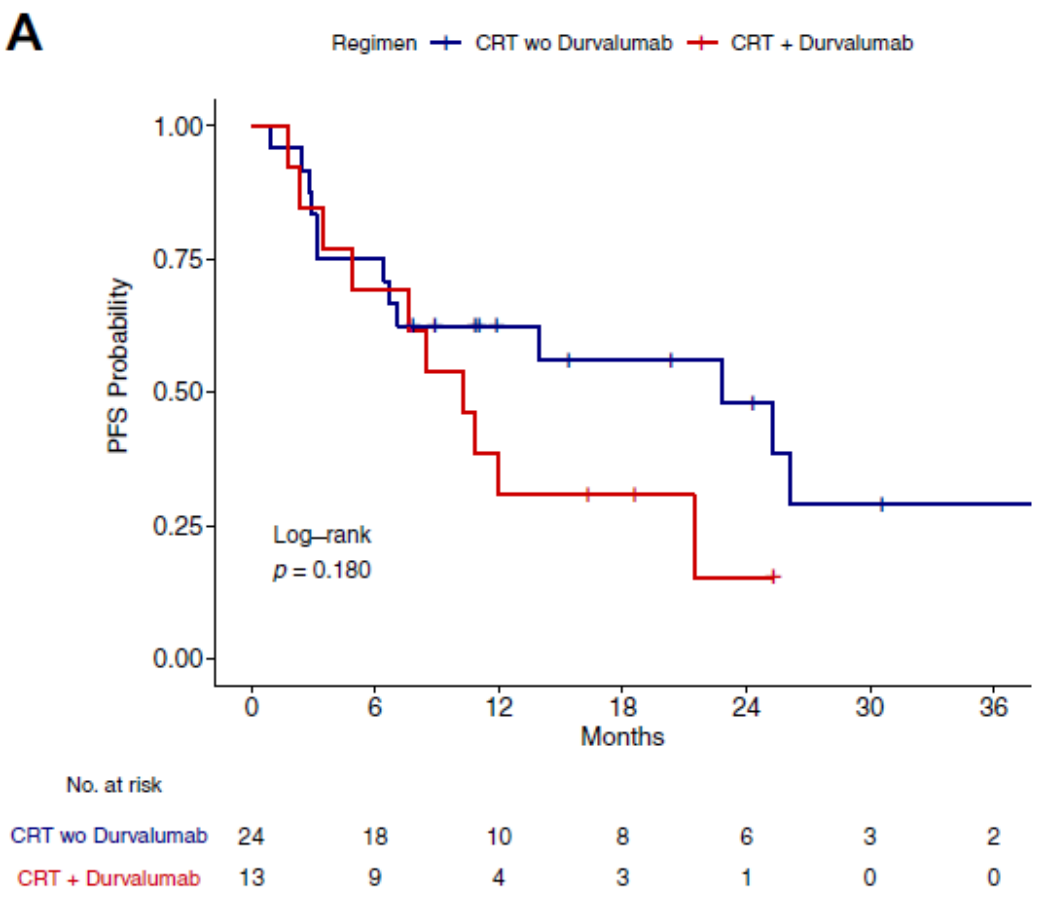


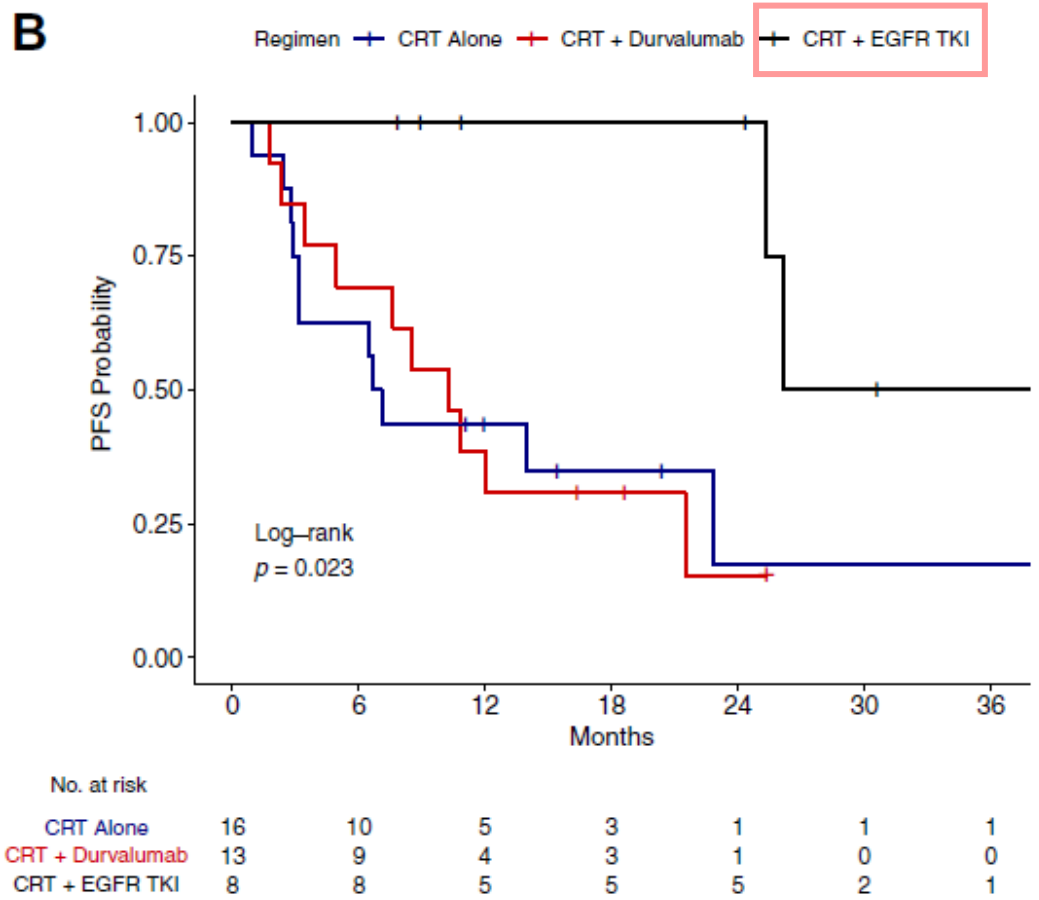
EGFR mutation is an unfavorable factor for consolidation durvalumab.

Wang, Chin-Chou, et al. *Vaccines* 9.10 (2021): 1122.

Durvalumab for Stage III *EGFR*-Mutated NSCLC After Definitive Chemoradiotherapy

No benefit with consolidation durvalumab





Aredo, Jacqueline V., et al. *Journal of Thoracic Oncology* 16.6 (2021): 1030-1041.

IASLC

Durvalumab for Stage III *EGFR*-Mutated NSCLC After Definitive Chemoradiotherapy

Table 2. Characteristics of Patients Who Developed Severe irAEs While Receiving Durvalumab (n = 6)

Patient No.	*EGFR* Mutation	Coalterations	PD-L1 Expression (% TPS)	Cycle(s) of Durvalumab	Time From First Cycle of Durvalumab to irAE Onset, d	irAE	CTCAE G...	Required Hospitalization?	Required High-Dose Steroids?	PFS From CRT Completion, mo
1	L858R	TP53^{mut}, APC^{mut}	0	9	120	Pneu...		Yes	Yes	21.5
2	Exon 20 insertion	CTNNB1^{mut}, U2AF1^{mut}	0	1	2		3	Yes	Yes	12.0
3	L858R	TP53^{mut}, ATM^{mut}, EGFR amp	20	6[a]	161	...eumonitis	2	Yes	No[b]	7.6
4	L858R	SMAD4^{mut}	1	5		Myocarditis	3	Yes	Yes	16.3 (censored)
5	Exon 19 deletion	TP53^{mut}	100	14	201	Hepatitis	2	Yes	Yes	8.5
6	Exon 19 deletion	Not tested	60	2	~20[c]	Colitis	3	Yes	Yes	10.3

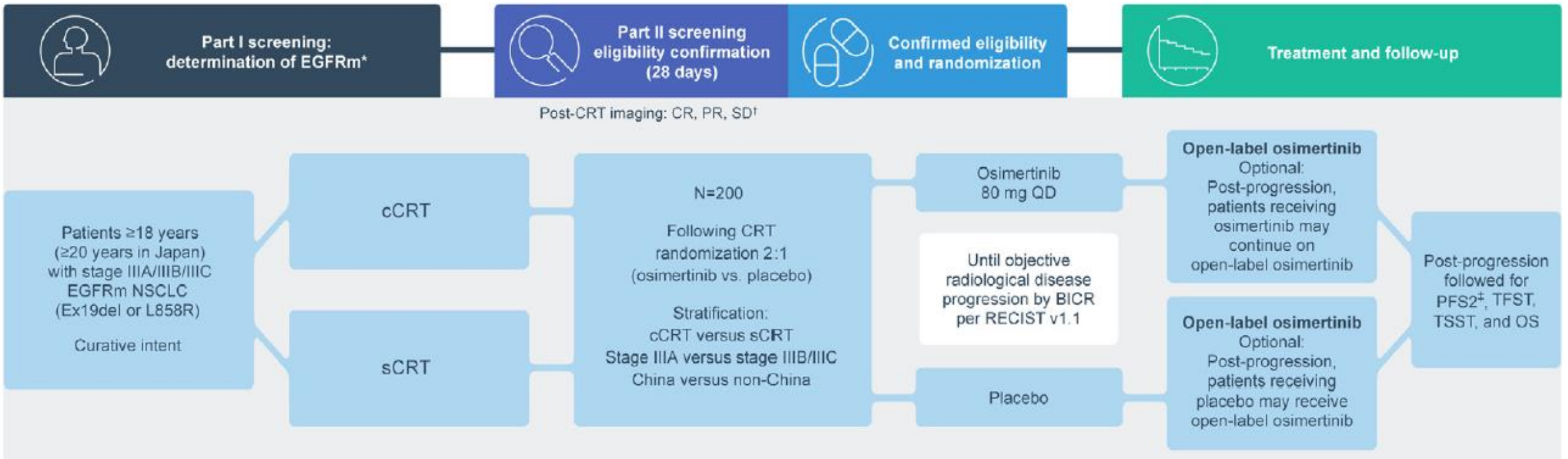
High frequency of irAEs

Aredo, Jacqueline V., et al. *Journal of Thoracic Oncology* 16.6 (2021): 1030-1041.

Current Trial Report

Osimertinib Maintenance After Definitive Chemoradiation in Patients With Unresectable EGFR Mutation Positive Stage III Non–small-cell Lung Cancer: LAURA Trial in Progress

Actual Study Start Date : July 19, 2018
Estimated Primary Completion Date : January 31, 2023
Estimated Study Completion Date : June 29, 2026



Contents

1. Rebiopsy

1) Spatiotemporal heterogeneity
2) Clinical factors predicting detection of T790M mutation
3) Post PD-L1 change after EGFR-TKI treatment

2. Sequential therapy

1) Optimal sequence of EGFR-TKI therapy
2) Treatment options for patients with unresectable stage III EGFR-mutant NSCLC
3) Immunotherapy in EGFR-mutant NSCLC patients

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2022
Non-Small Cell Lung Cancer

NCCN Guidelines Index
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Discussion

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b,c]

ADENOCARCINOMA, LARGE CELL, NSCLC NOS (PS 0–1)

No contraindications to PD-1 or PD-L1 inhibitors[d]

Preferred
- Pembrolizumab/carboplatin/pemetrexed (category 1)[1,2,e]
- Pembrolizumab/cisplatin/pemetrexed (category 1)[2,e]

Other Recommended
- Atezolizumab/carboplatin/paclitaxel/bevacizumab[e] (category
- Atezolizumab/carboplatin/albumin-bound paclitaxel[4,e]
- Nivolumab/ipilimumab[5,d]
- Nivolumab/ipilimumab/pemetrexed/(carboplatin or cisplatin (category 1)[6,e]

Contraindications to PD-1 or PD-L1 inhibitors[d]

Useful in Certain Circumstances
- Bevacizumab[e]/carboplatin/paclitaxel (category 1)[7,g,h,i]
- Bevacizumab[e]/carboplatin/pemetrexed[7,8,g,h,i]
- Bevacizumab[e]/cisplatin/pemetrexed[9,g,h,i]
- Carboplatin/albumin-bound paclitaxel (category 1)[10]

ADENOCARCINOMA, LARGE CELL, NSCLC NOS (PS 2)

Preferred
- Carboplatin/pemetrexed[16]

Other Recommended
- Carboplatin/albumin-bound paclitaxel[23,24]
- Carboplatin/docetaxel[11]
- Carboplatin/etoposide[12,13]
- Carboplatin/gemcitabine[14]
- Carboplatin/paclitaxel[15]
- Docetaxel
- Gemcitabine
- Gemcitabine
- Gemcitabine
- Paclitaxel
- Pemetrexed

ADENOCARCINOMA, LARGE CELL, NSCLC NOS (PS 3–4)

Best supportive care See NCCN Guidelines for Palliative Care

[a] Albumin-bound paclitaxel may be substituted for either paclitaxel or docetaxel in patients who have experienced hypersensitivity reactions after receiving paclitaxel or docetaxel despite premedication, or for patients where the standard premedications (ie, dexamethasone, H2 blockers, H1 blockers) are contraindicated.
[b] Carboplatin-based regimens are often used for patients with comorbidities or those who cannot tolerate cisplatin.
[c] If first-line systemic therapy completed before treatment for an actionable mutation, and disease has progressed, see Subsequent Therapy NSCL-K 4 of 5.

[d] Contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or current use of immunosuppressive agents, or presence of an oncogene (ie, *EGFR exon 19* deletion *or L858R*, *ALK* rearrangements), which would predict lack of benefit.
[e] If progression on PD-1/PD-L1 inhibitor, using a PD-1/PD-L1 inhibitor is not recommended
[f] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[g] Bevacizumab should be given until progression.
[h] Any regimen with a high risk of thrombocytopenia and the potential risk of bleeding should be used with caution in combination with bevacizumab.
[i] Criteria for treatment with bevacizumab: non-squamous NSCLC, and no recent history of hemoptysis. Bevacizumab should not be given as a single agent, unless as maintenance if initially used with chemotherapy.

Maintenance Therapy NSCL-K 3 of 5
Subsequent Therapy NSCL-K 4 of 5
References
Continued

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

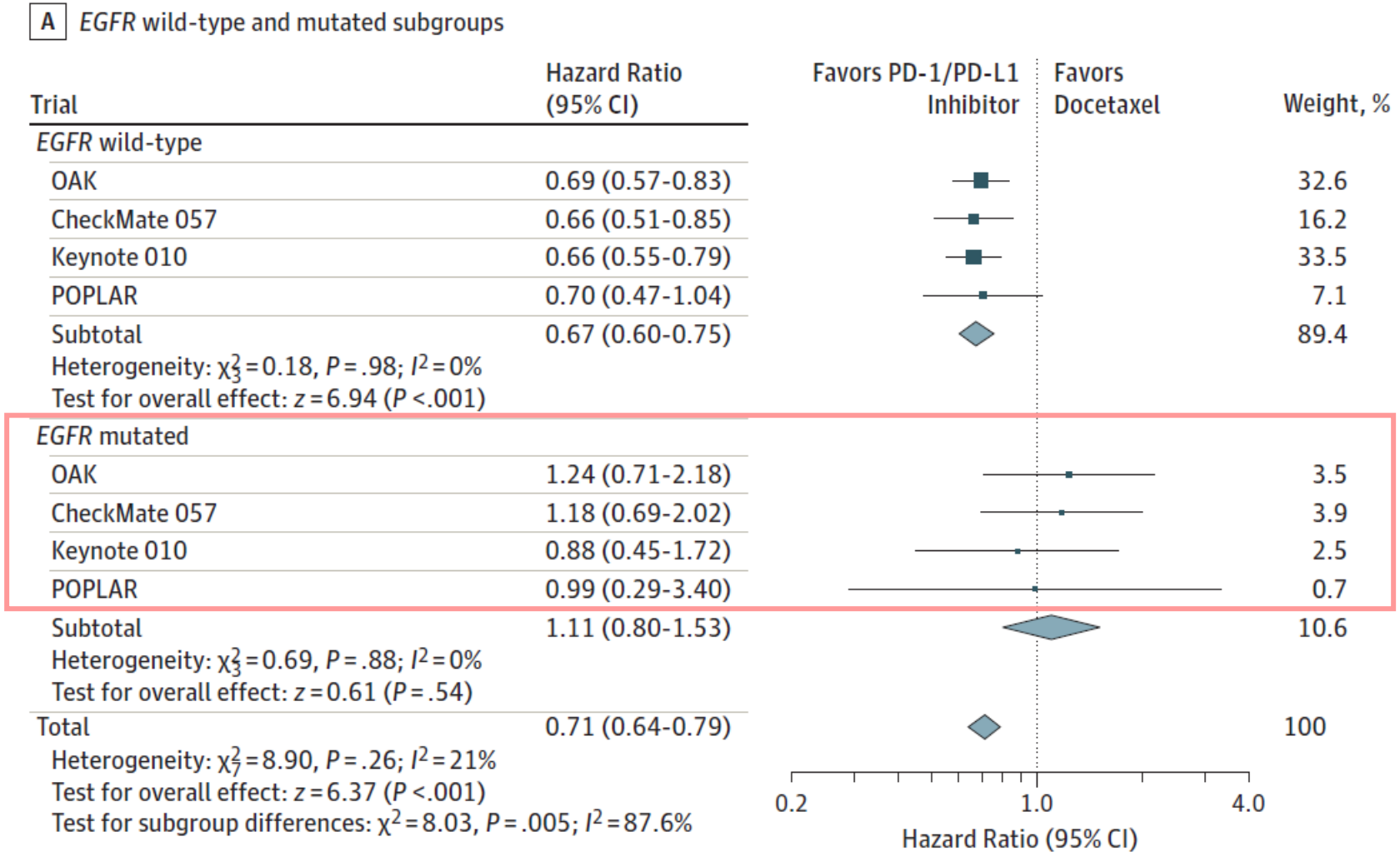
Contraindications for treatment with PD-1/PD-L1 inhibitors

- Active or previously documented autoimmune disease
- Current use of immunosuppressive agents
- **Presence of an oncogene (eg. EGFR exon 19 deletion or L858R, ALK rearrangements)**

JAMA Oncology | Original Investigation

Clinical and Molecular Characteristics Associated With Survival Among Patients Treated With Checkpoint Inhibitors for Advanced Non–Small Cell Lung Carcinoma

A Systematic Review and Meta-analysis



Lee, Chee Khoon, et al. *JAMA oncology* 4.2 (2018): 210-216.

Immune checkpoint inhibitors for patients with advanced lung cancer and oncogenic driver alterations: results from the IMMUNOTARGET registry

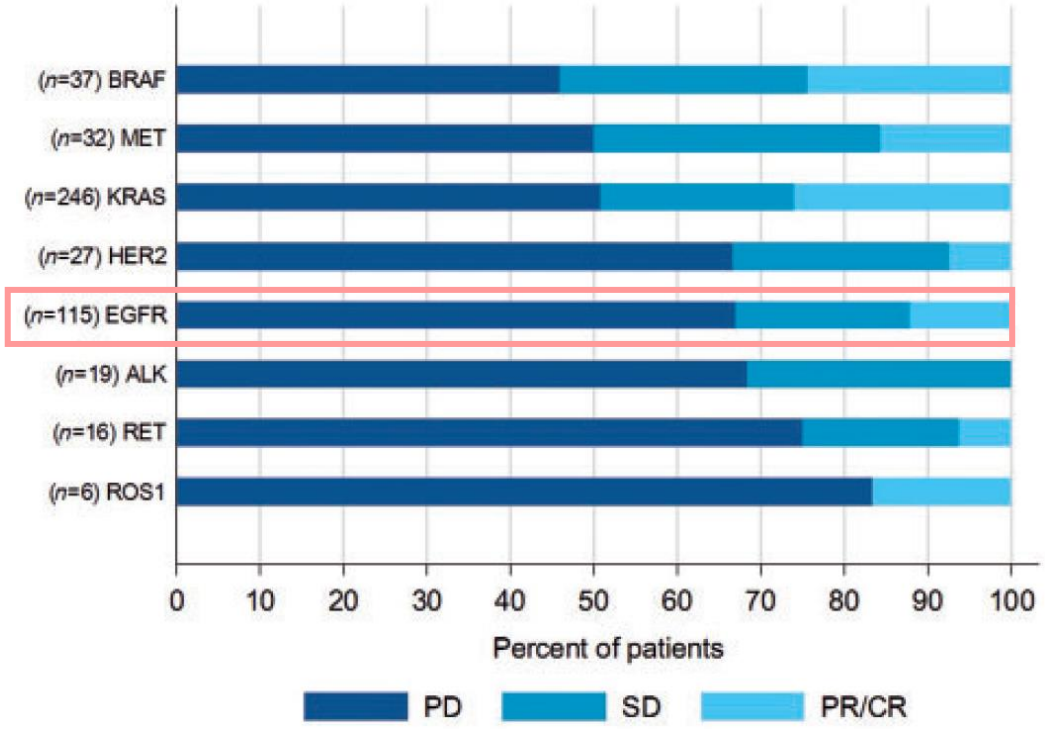


Table 2. PFS according to primary oncogenic driver from initiation of ICI

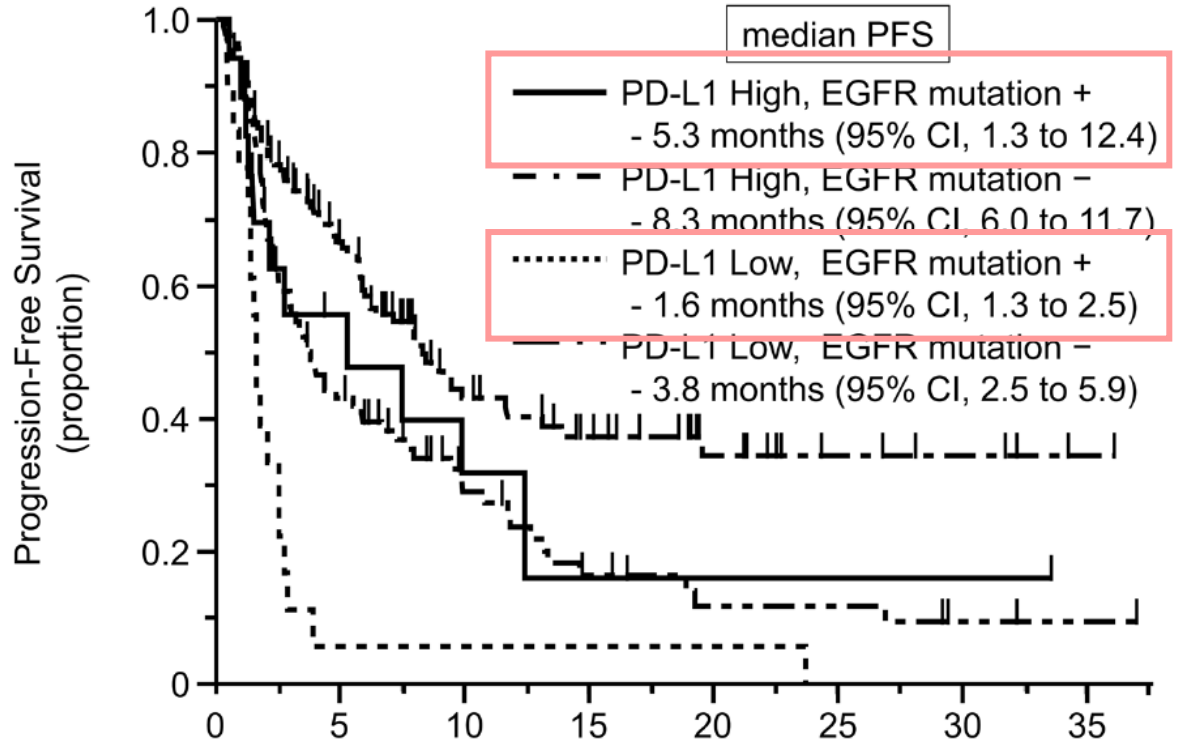
	EVT/*N*	Median PFS [95% CI] (months)	6-month PFS [95% CI]	12-month PFS [95% CI]
KRAS	208/271	3.2 [2.7; 4.5]	37.9 [32.1; 49.8]	25.6 [20.2; 31.3]
EGFR	117/125	2.1 [1.8; 2.7]	18.4 [12.1; 25.6]	6.4 [2.7; 12.1]
BRAF	34/43	3.1 [1.8; 4.6]	32.1 [18.3; 46.6]	18.0 [7.2; 32.7]
HER2	23/29	2.5 [1.8; 3.5]	22.7 [8.9; 40.2]	13.6 [3.6; 30.1]
MET	26/36	3.4 [1.7; 6.2]	36.5 [20.7; 52.4]	23.4 [10.6; 39.0]
ALK	21/23	2.5 [1.5; 3.7]	11.8 [2.2; 30.2]	5.9 [0.4; 23.0]
ROS1	–	–	–	–
RET	15/16	2.1 [1.3; 4.7]	14.1 [2.3; 35.9]	7.0 [0.4; 27.1]

EVT, event; *N*, number.

ORR: 12.1%, median PFS 2.1 months

Mazieres, J., et al. *Annals of Oncology* 30.8 (2019): 1321-1328.

Efficacy of anti-PD-1 antibodies in NSCLC patients with an *EGFR* mutation and high PD-L1 expression



No. at risk								
PD-L1 High,EGFR+	17	7	4	2	1	1	1	0
PD-L1 High,EGFR−	136	74	32	22	12	7	4	1
PD-L1 Low, EGFR+	18	1	1	1	1	0	0	0
PD-L1 Low, EGFR−	92	37	17	8	5	5	2	1

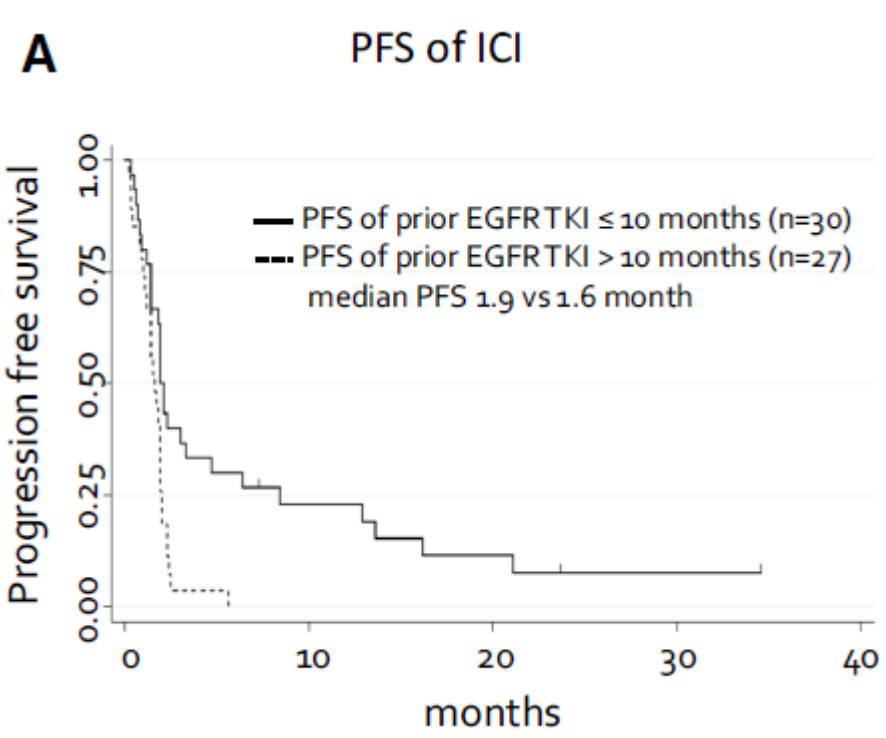
Patients with EGFR-mutated NSCLC and higher PD-L1 expression received a greater benefit of treatment with PD-1 inhibitors in terms of ORR and PFS than patients with low PD-L1 expression.

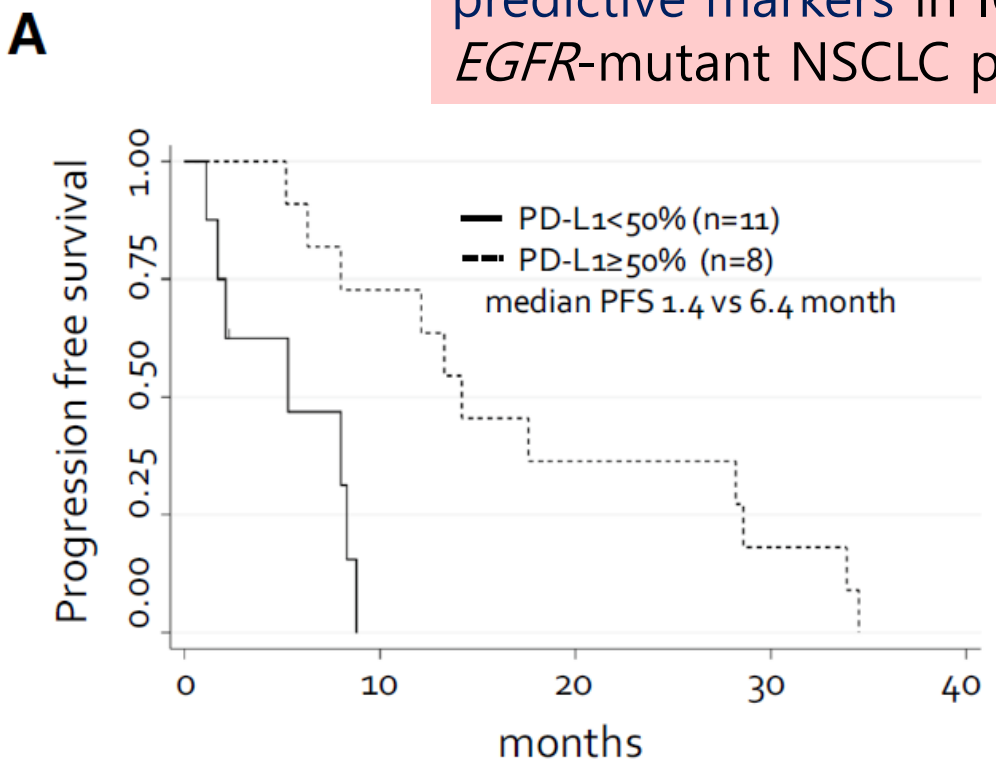
Masuda, Ken, et al. *Journal of Cancer Research and Clinical Oncology* 147.1 (2021): 245-251.

Characteristics of patients with *EGFR*-mutant non-small-cell lung cancer who benefited from immune checkpoint inhibitors

multi-institutional, retrospective, cohort study

The duration of the response to prior EGFR-TKIs and PD-L1 expression could be predictive markers in ICI therapy for *EGFR*-mutant NSCLC patients



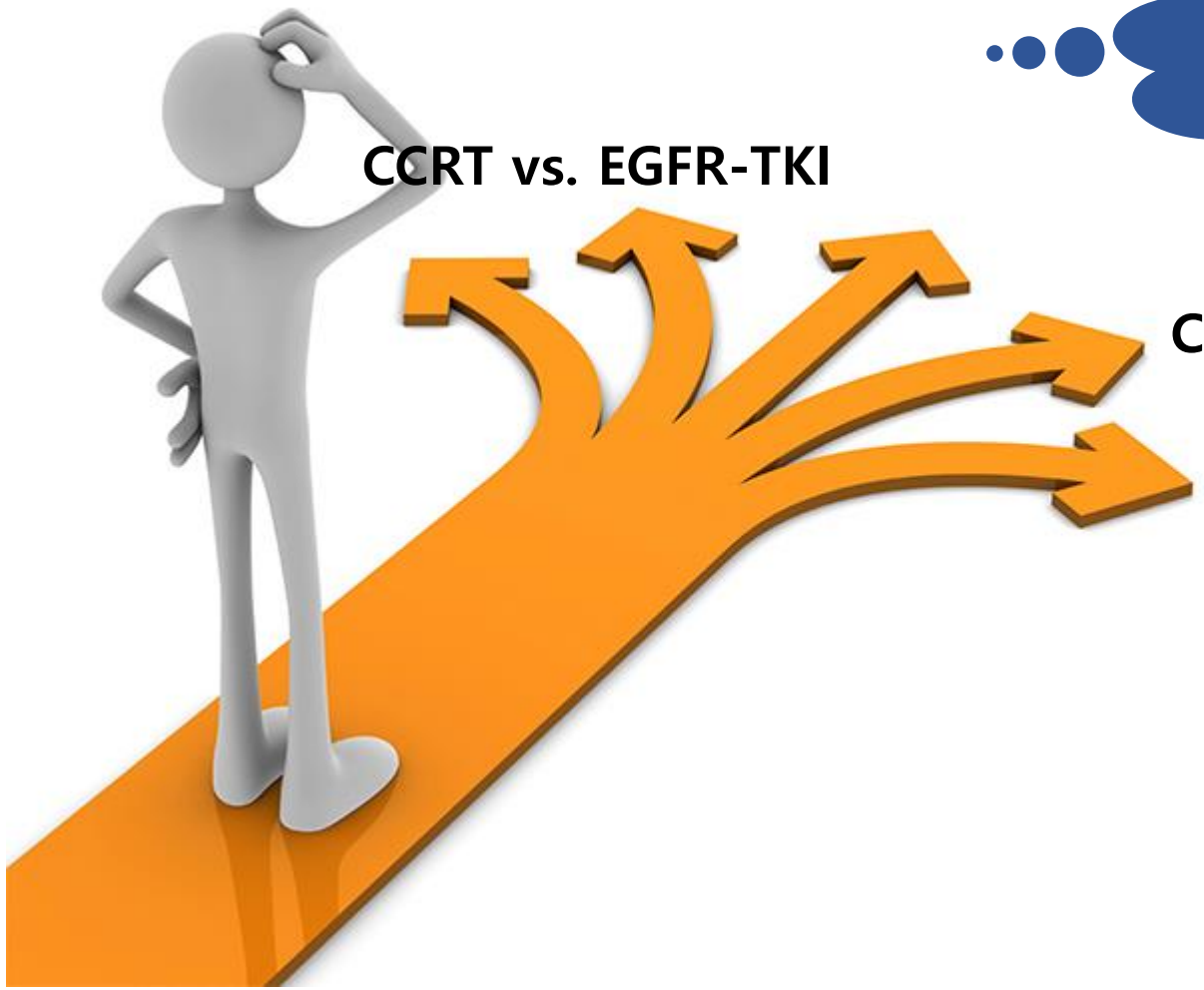


Ichihara, Eiki, et al. *Cancer Immunology, Immunotherapy* 70.1 (2021): 101-106.

Treatment options for EGFR-mutant NSCLC patients

- RT field
- General condition
- Age

CCRT vs. EGFR-TKI



Cytotoxic chemotherapy
vs.
Immunotherapy

- PD-L1 expression
- EGFR-TKI efficacy

Thank you
for your attention