2024 동계 분자폐암연구회 임상연구 워크숍

Exploratory Lung Cancer Research to solve unmet needs in clinical practice

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Contents

- 현재 폐암 치료 문제점을 인식→ 해결 과정
- Retrospective study, NGS 연구, Liquid biopsy
- IIT, translational research

연구의 원동력

- **내부적 요인**

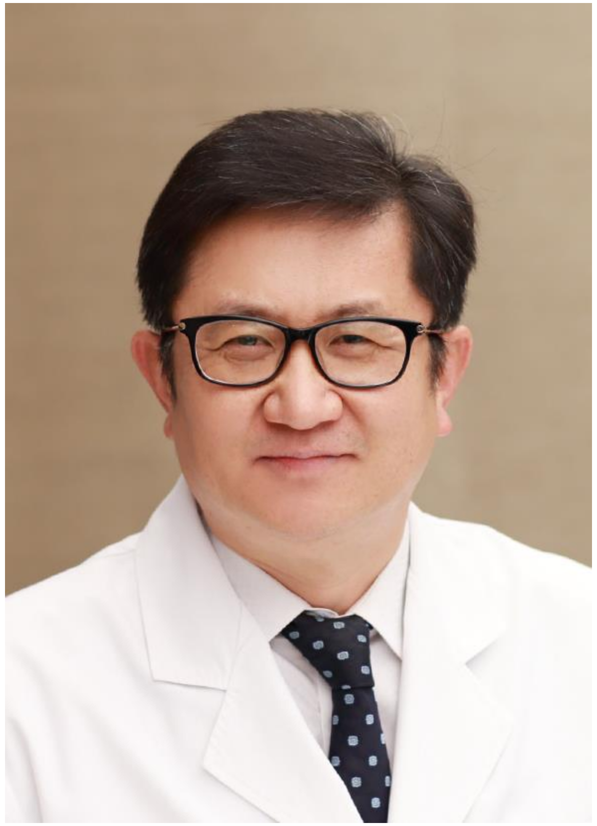
- **현재 치료의 문제점은 무엇인가?**

- **어떻게 해야, 무엇을 알아야 환자 예후를 개선시킬 수 있을까?**

- **Fundamental Questions**

연구의 원동력

- 외부적 요인
  - 연구를 좋아하고 아이디어가 풍부한 Mentor
  - 의견 제시와 Discussion 을 통해 연구 진행
  - 동의와 보완, 실행



Q:EGFR-TKI 효과는 왜 개인차가 있을까?

Hypothesis : 흡연량과 PFS 상관 관계

Kim *et al. BMC Cancer* (2018) 18:768
https://doi.org/10.1186/s12885-018-4691-0

BMC Cancer

RESEARCH ARTICLE **Open Access**

CrossMark

Cumulative smoking dose affects the clinical outcomes of EGFR-mutated lung adenocarcinoma patients treated with EGFR-TKIs: a retrospective study

In Ae Kim[1,2], Jong Sik Lee[1], Hee Joung Kim[1,2], Wan Seop Kim[1,3] and Kye Young Lee[1,2*]

연구 Idea

- Retrospectively analyzed 142 patients with EGFR-mutation positive advanced lung adenocarcinoma, treated with EGFR-TKIs(2005-2016)
- Aimed to investigate the effect of cumulative smoking dose on clinical outcomes (PFS, OS, Response rate)
  - Never smokers, light smokers (≤10 PYs)
  - moderate smokers (11–30 PYs)
  - heavy smokers (> 30 PYs)

■ 의견
회의적: 이미 흡연 논문은 많이 나와 있어 publish 가 어려울 거다.
긍정적: 몇 명 들여다 보니 흡연량에 따라 정말 PFS 가 차이가 보인다.

PFS

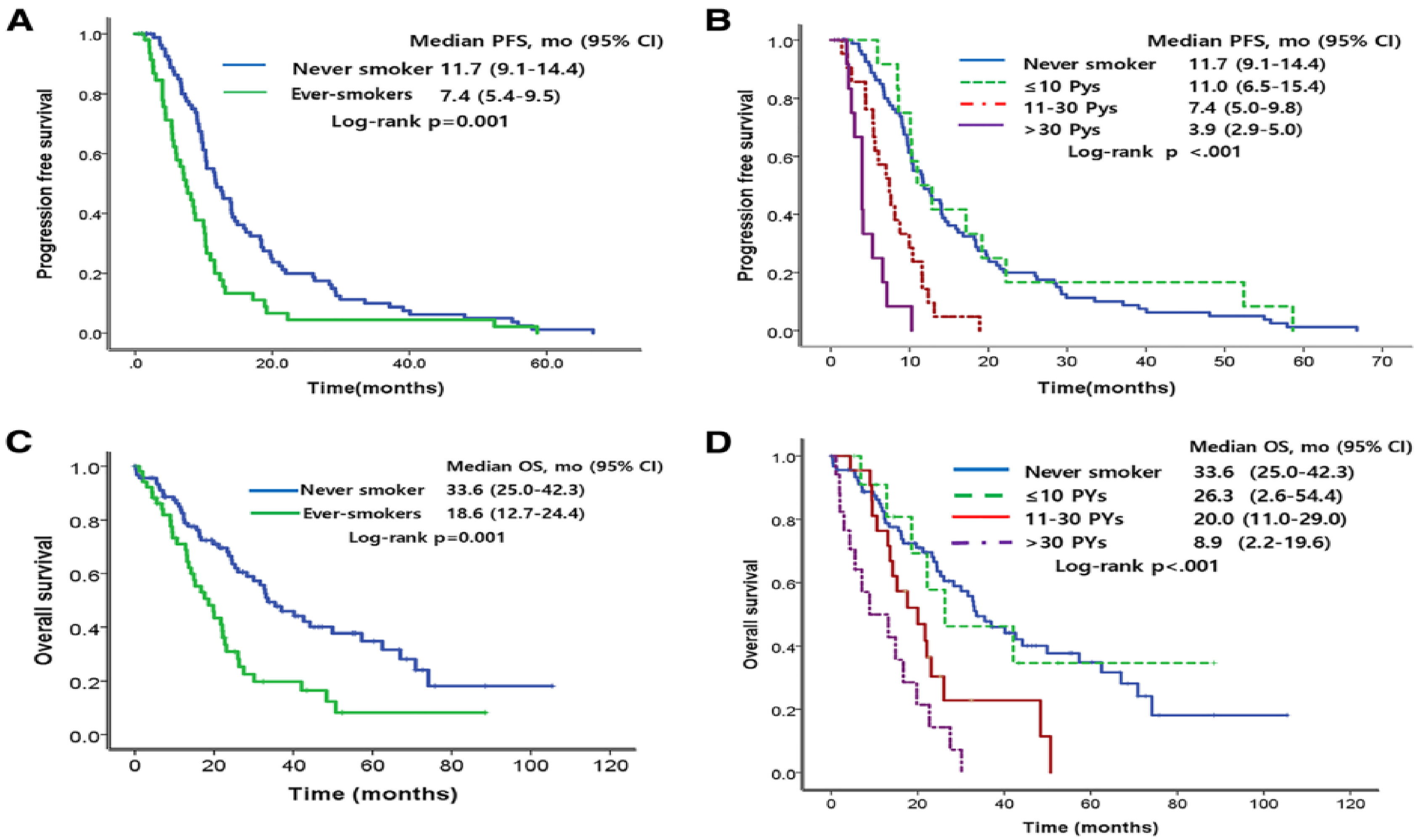


Fig. 1 Comparisons of PFS and OS according to cumulative smoking dose in patients receiving EGFR-TKIs. Comparison of PFS by (**a**) smoking history, and (**b**) cumulative smoking dose. Comparison of OS by (**c**) smoking history and (**d**) cumulative smoking dose

Response rate

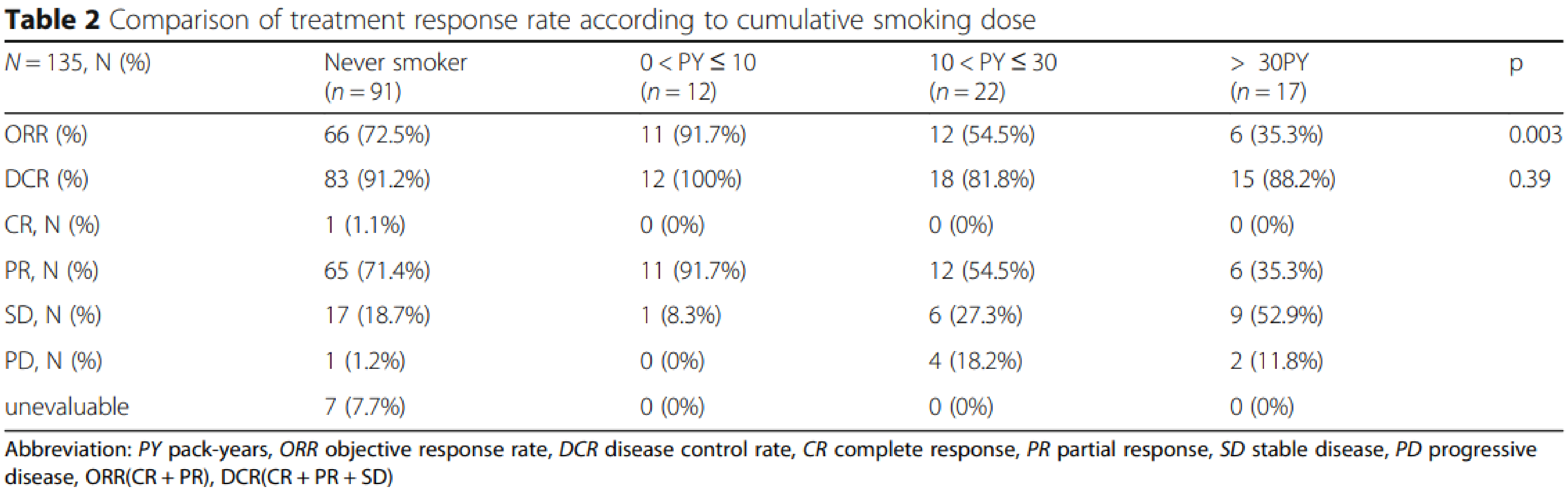


Table 2 Comparison of treatment response rate according to cumulative smoking dose

N = 135, N (%)	Never smoker (*n* = 91)	0 < PY ≤ 10 (*n* = 12)	10 < PY ≤ 30 (*n* = 22)	> 30PY (*n* = 17)	p
ORR (%)	66 (72.5%)	11 (91.7%)	12 (54.5%)	6 (35.3%)	0.003
DCR (%)	83 (91.2%)	12 (100%)	18 (81.8%)	15 (88.2%)	0.39
CR, N (%)	1 (1.1%)	0 (0%)	0 (0%)	0 (0%)	
PR, N (%)	65 (71.4%)	11 (91.7%)	12 (54.5%)	6 (35.3%)	
SD, N (%)	17 (18.7%)	1 (8.3%)	6 (27.3%)	9 (52.9%)	
PD, N (%)	1 (1.2%)	0 (0%)	4 (18.2%)	2 (11.8%)	
unevaluable	7 (7.7%)	0 (0%)	0 (0%)	0 (0%)	

Abbreviation: *PY* pack-years, *ORR* objective response rate, *DCR* disease control rate, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, ORR(CR + PR), DCR(CR + PR + SD)

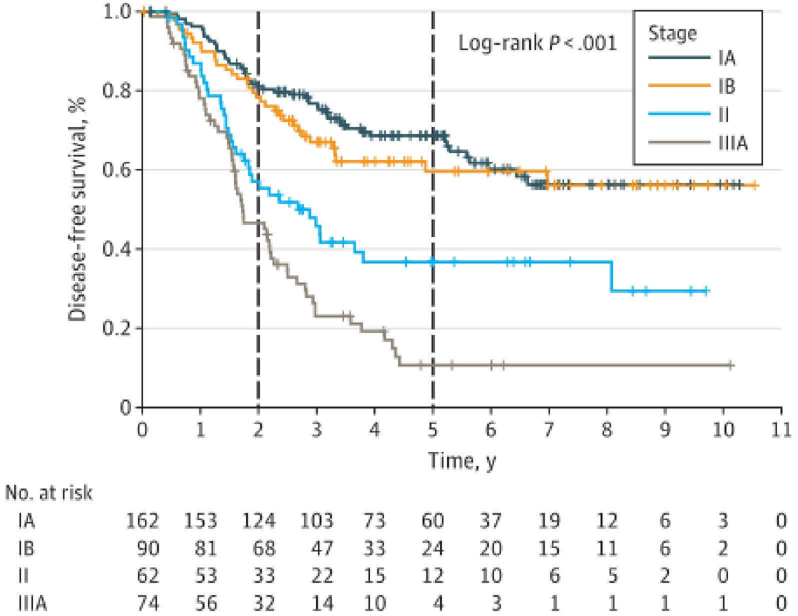
- Retrospective study : 아이디어, 시간과 노력, 그리고 통계 만 있으면 된다.
- 이미 출판된 주제라도 잘 분석하고 정리, 해석하면 된다.

Q: 근치적 절제한 1기 폐암이 왜 재발할까?

- 초기 폐암 Lobectomy & LND 까지 했는데 왜 재발할까?

- Stage I 의 재발율 30-40%
  - Micrometastasis ?
  - Recurrent EGFR mutated lung cancer 의 경우 EGFR-TKI 효과가 있다
  - 연구 가설: Resected tumor 의 genetic alteration 이 재발과 연관이 있지 않을까?

Figure 2. Two- and 5-Year Disease-Free Survival by Stage for Epidermal Growth Factor Receptor (EGFR)-Positive Non-Small Cell Lung Cancer Cohort Demonstrating Long-term Survival for a Subset of Patients



No. at risk

	0	1	2	3	4	5	6	7	8	9	10	11
IA	162	153	124	103	73	60	37	19	12	6	3	0
IB	90	81	68	47	33	24	20	15	11	6	2	0
II	62	53	33	22	15	12	10	6	5	2	0	0
IIIA	74	56	32	14	10	4	3	1	1	1	1	0

Saw et al. JAMA Network Open. 2021

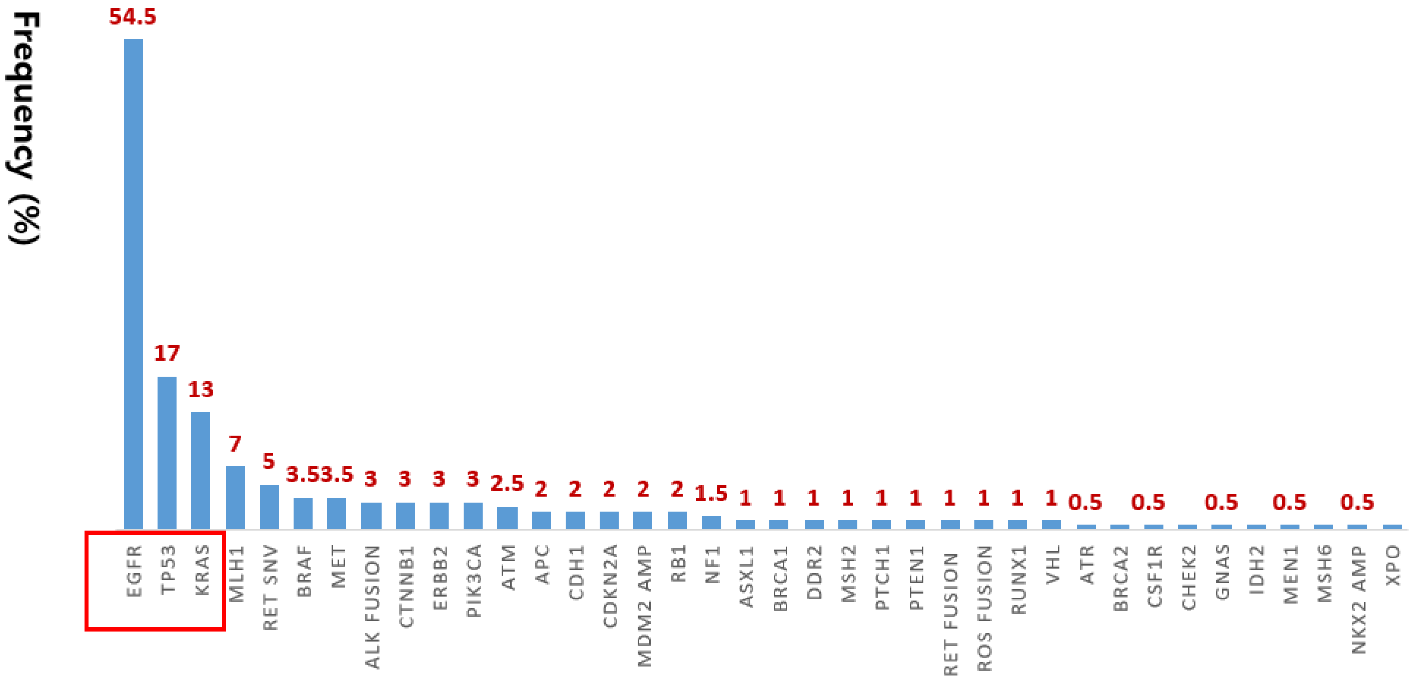
2018-2019 년

- 본원 2005-2017 총 400 명의 폐암 수술 조직의 NGS 데이터
- The Post-Genome Technology Development Program.(병리과 김완섭 교수님)

- 230 명 I-II기 lung adenocarcinoma
- 207 cancer related gene panel (Ilumina based-NGS)
- Lobectomy한 1기 환자도 재발을 한다.
  → 원인을 알면 예방할 수 있지 않을까?

- To evaluate the prognostic effect of genetic alteration, we compared the DFS (disease-free survival) according to frequent genetic alteration using the Kaplan-Meier method.

The frequency of genetic alterations in whole patients



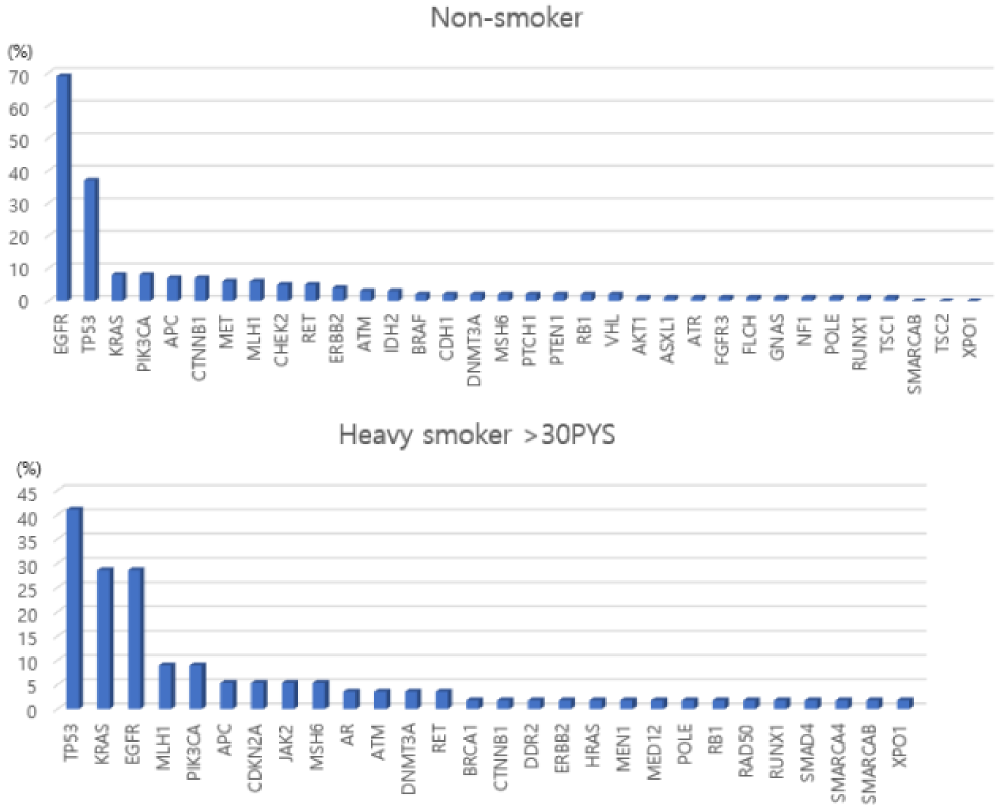


Figure 3. Comparison of genetic alteration according to smoking dose

Sex

Table 5. Comparison of genetic alteration according to sex

pathogen	Female (94)	%	Male (108)	%	*P-value*
APC	6	6.4	4	3.7	0.38
ATM	3	3.2	3	2.8	0.86
BRAF	2	2.1	1	0.9	0.48
CDH1	2	2.1	0	0.0	0.12
CDKN2A	0	0.0	4	3.7	0.05
CHEK2	5	5.3	1	0.9	0.06
CTNNB1	7	7.4	3	2.8	0.12
DNMT3A	1	1.1	4	3.7	0.22
EGFR	64	68.1	51	47.2	**0.00**
IDH2	3	3.2	1	0.9	0.24
JAK2	0	0.0	3	2.8	0.10
KRAS	7	7.4	20	18.5	**0.02**
MET	6	6.4	4	3.7	0.38
MLH1	5	5.3	13	12.0	0.09
MSH6	2	2.1	4	3.7	0.51
NF1	0	0.0	2	1.9	0.18
PIK3CA	6	6.4	15	13.9	0.08
POLE	2	2.1	1	0.9	0.48
PTCH1	2	2.1	0	0.0	0.12
PTEN1	2	2.1	2	1.9	0.88
RB1	3	3.2	1	0.9	0.24
RET	4	4.3	6	5.6	0.67
RUNX1	1	1.1	1	0.9	0.92
TP53	31	33.0	45	41.7	0.20
VHL	2	2.1	0	0.0	0.12

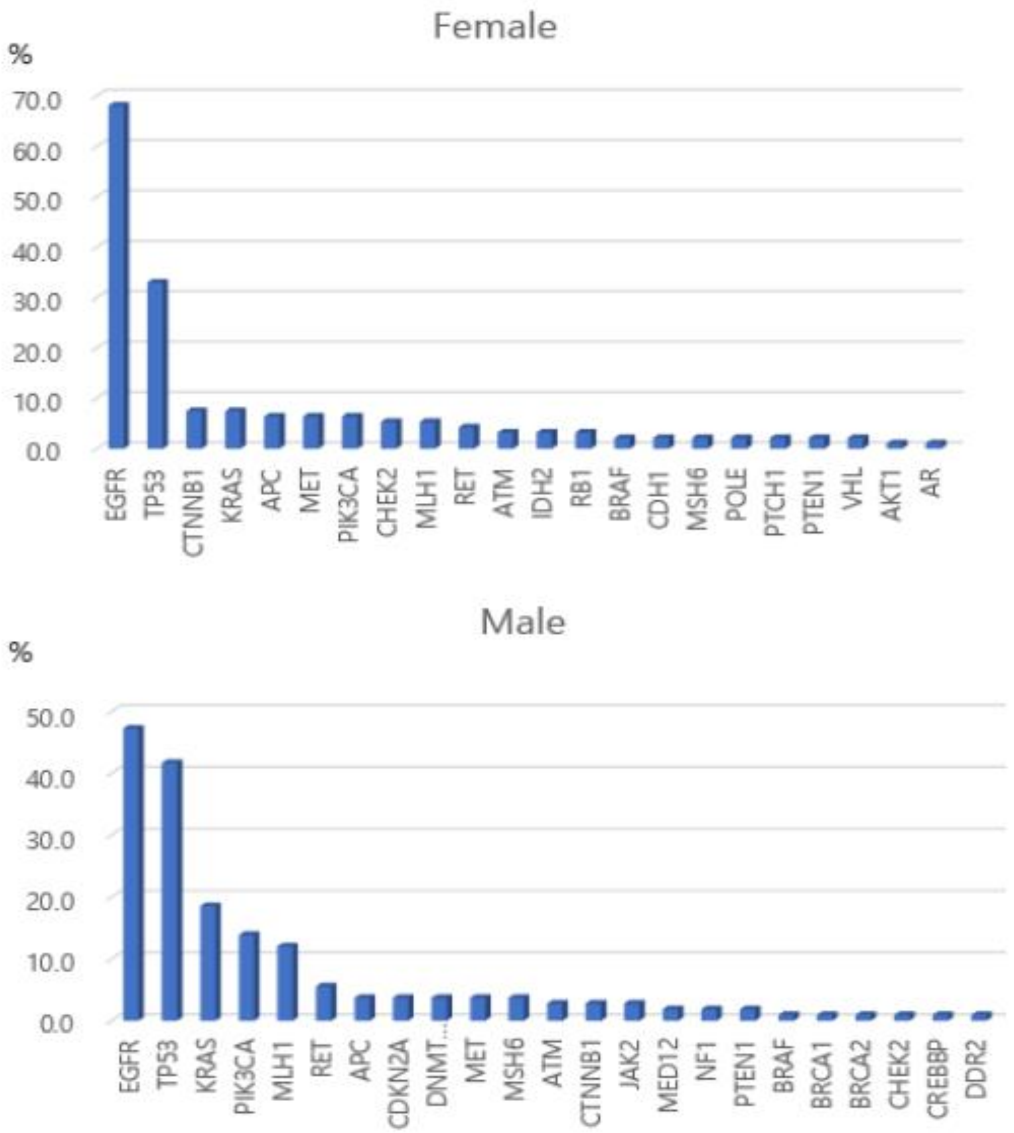


Figure 2. Comparison of genetic alteration according to sex

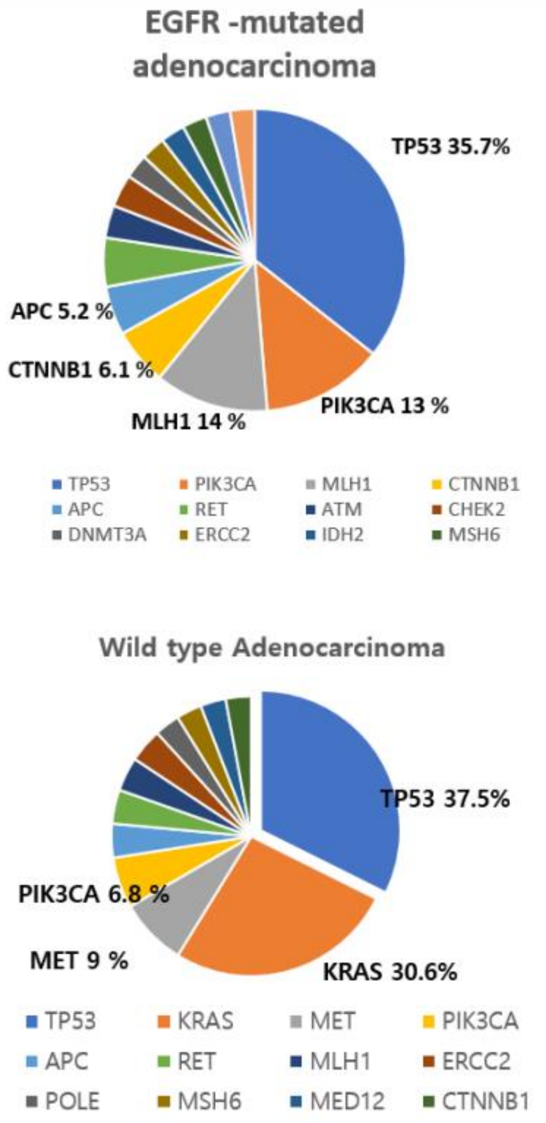


Figure 4. Composition of co-occurring mutation in adenocarcinoma

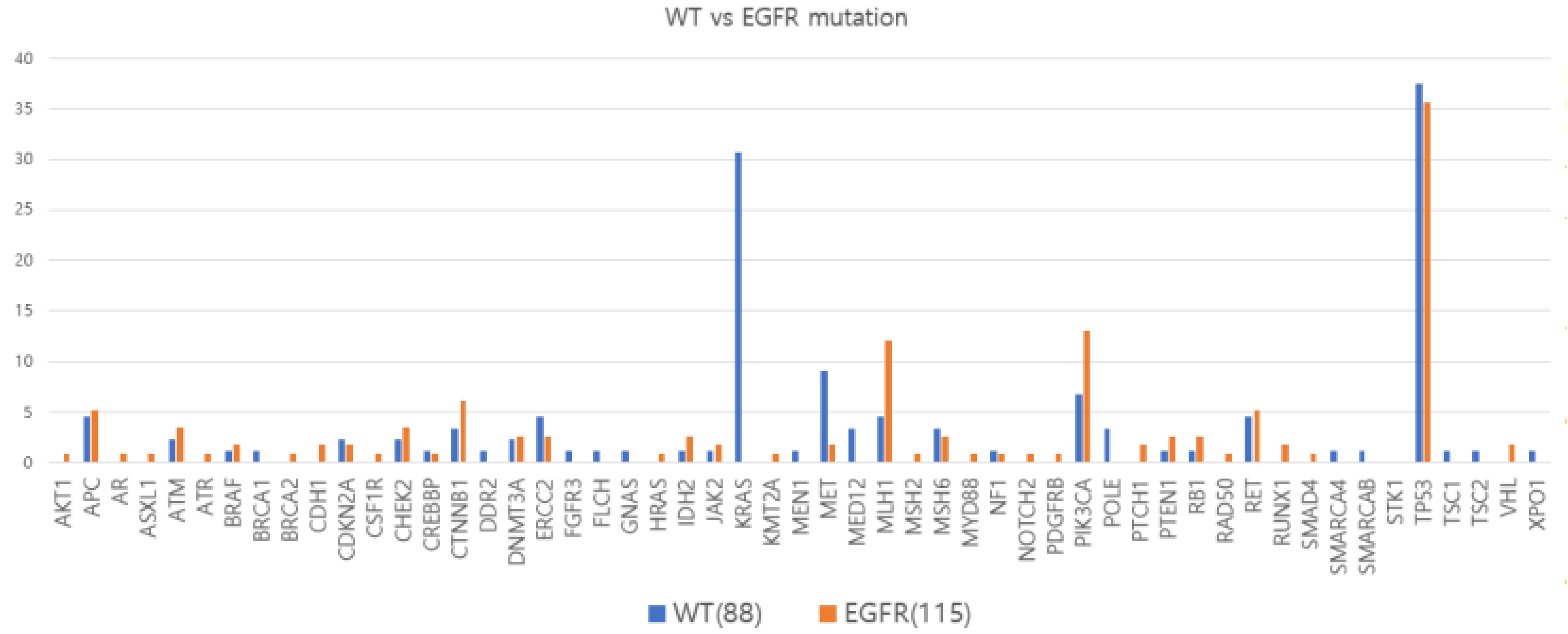


Table8. The type of EGFR mutation

EGFR mutation	N =115	%
19 Deletion	47	40.8
21 L858R or L861Q	51	44.3
19 del or L858 R + other EGFR mutation	7	6.0
Exon 18 mutation	2	1.7
Exon 20 mutation	9	7.8

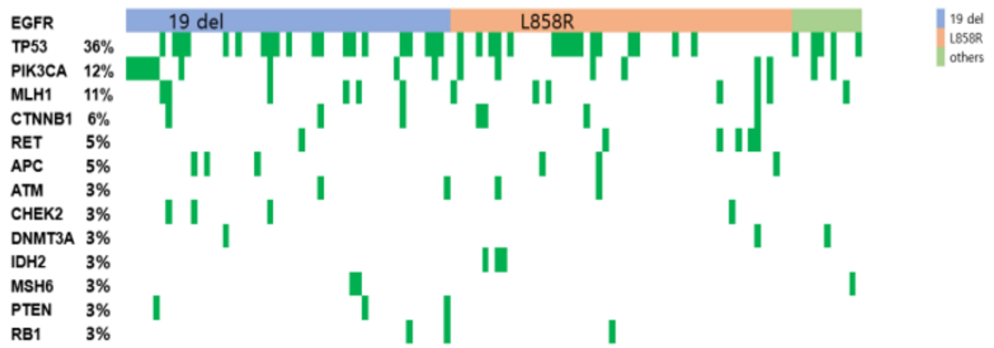
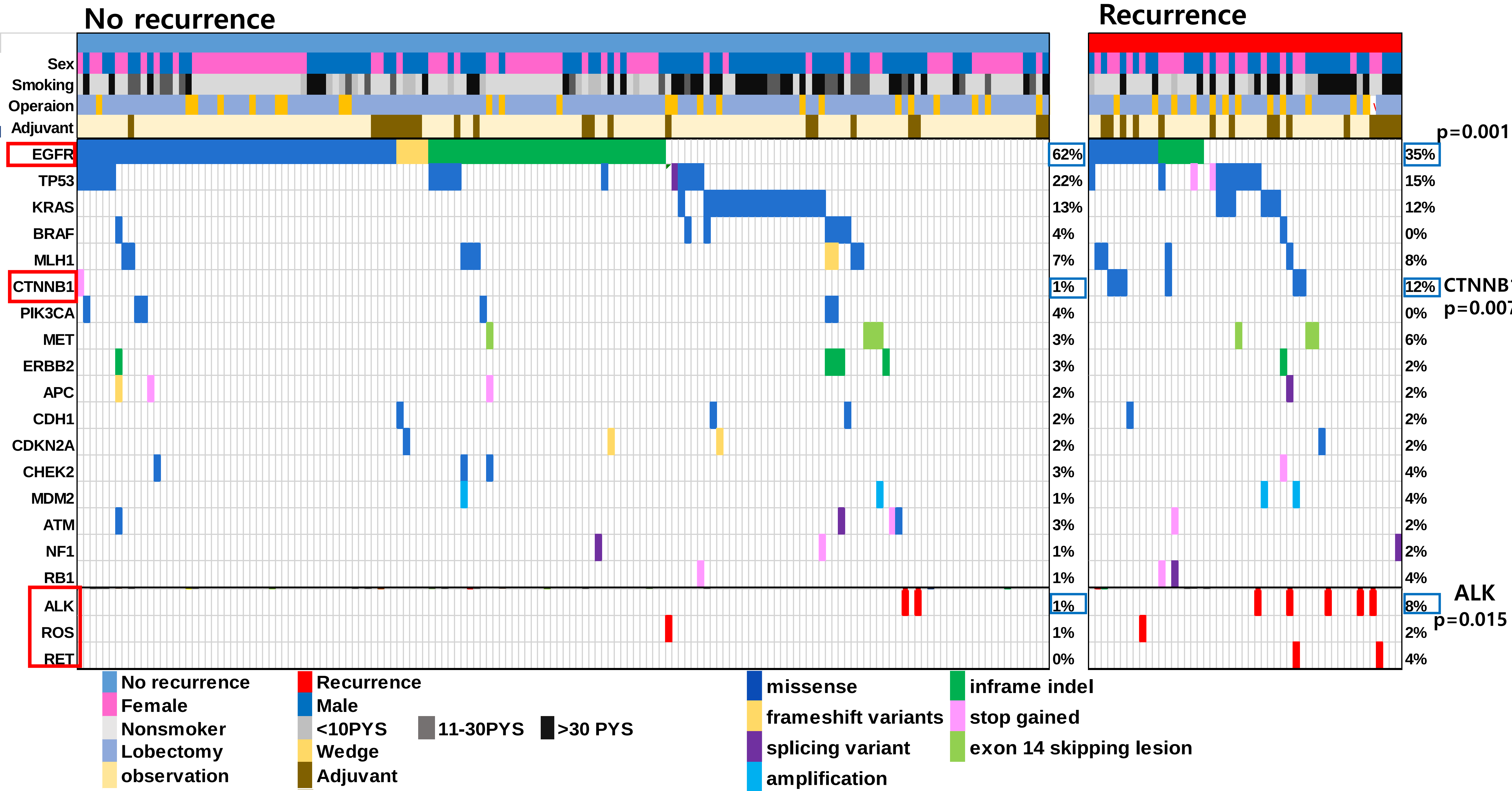
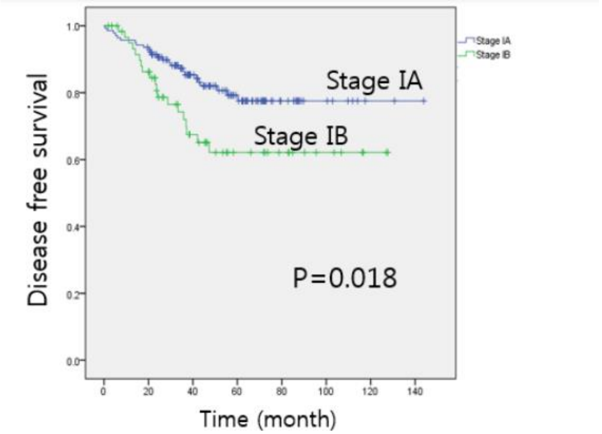


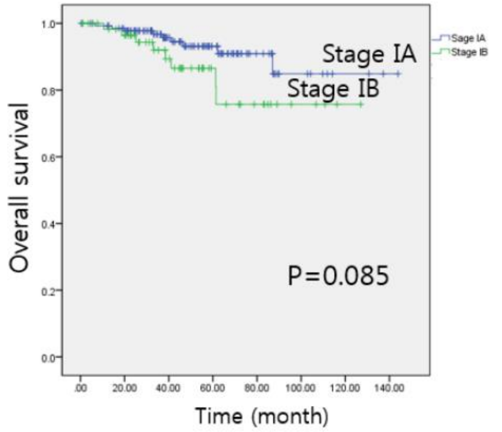
Figure 6. Co- occurring mutation in EGFR mutated adenocarcinoma (115 cases)

Genetic landscape of Stage I pulmonary adenocarcinoma



Disease-free survival





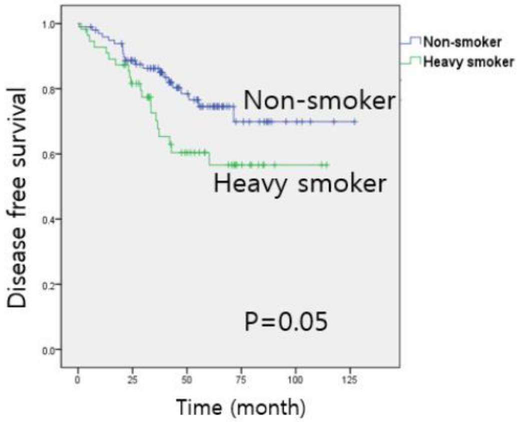


Figure 10. DFS classified by smoking dose (heavy smoker >30PYs)

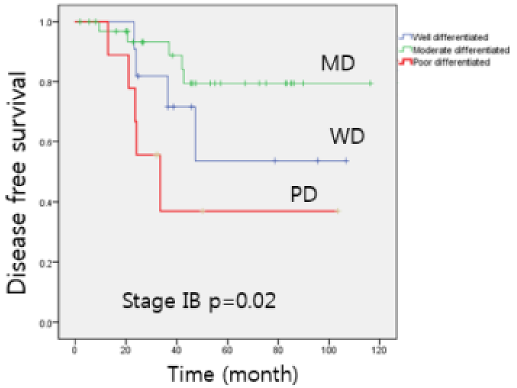


Figure 11. Comparison DFS according to tumor differentiation

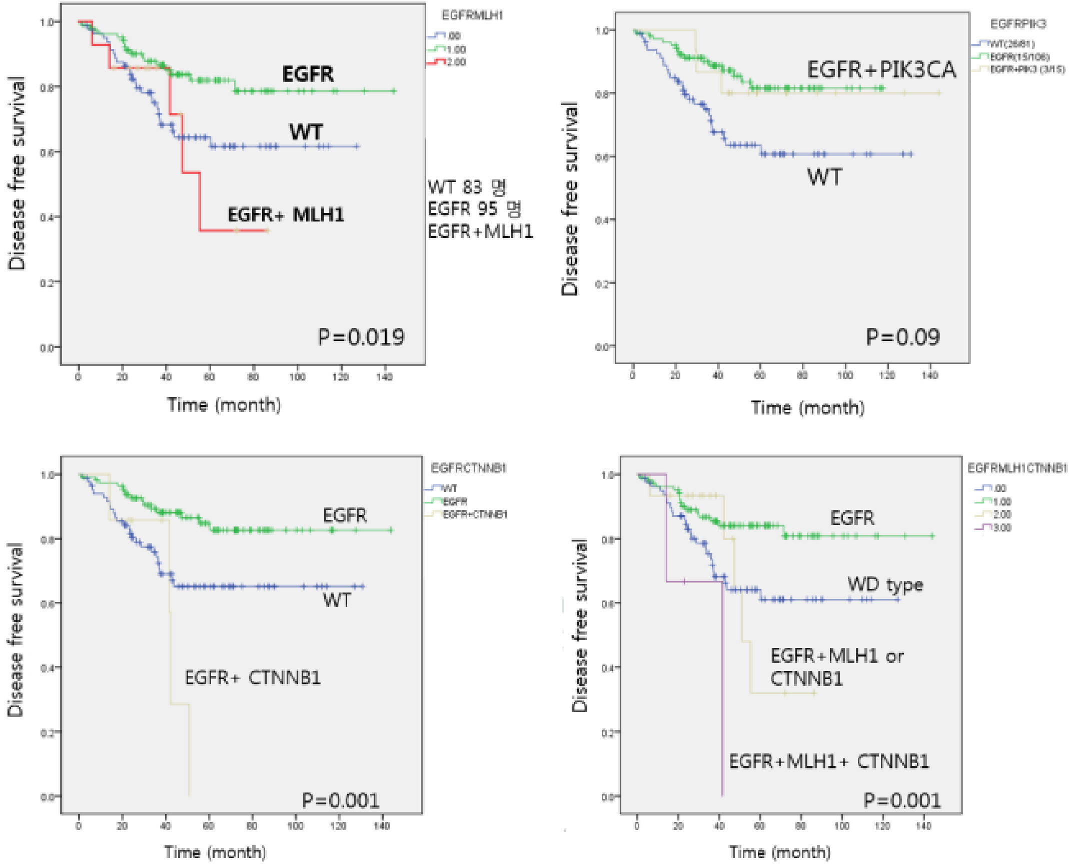
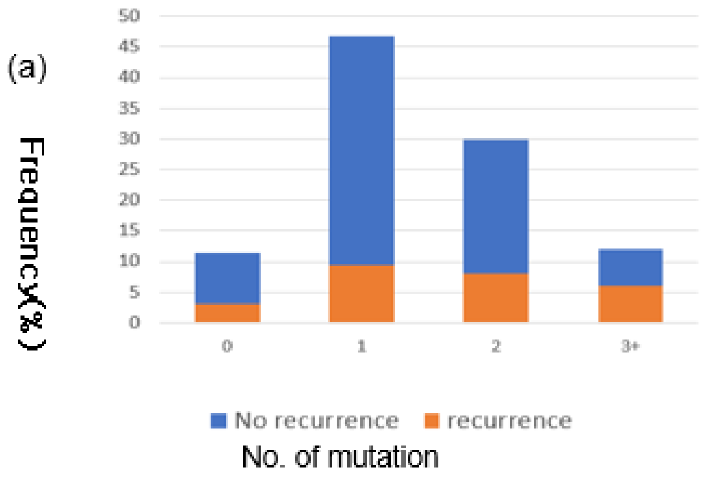
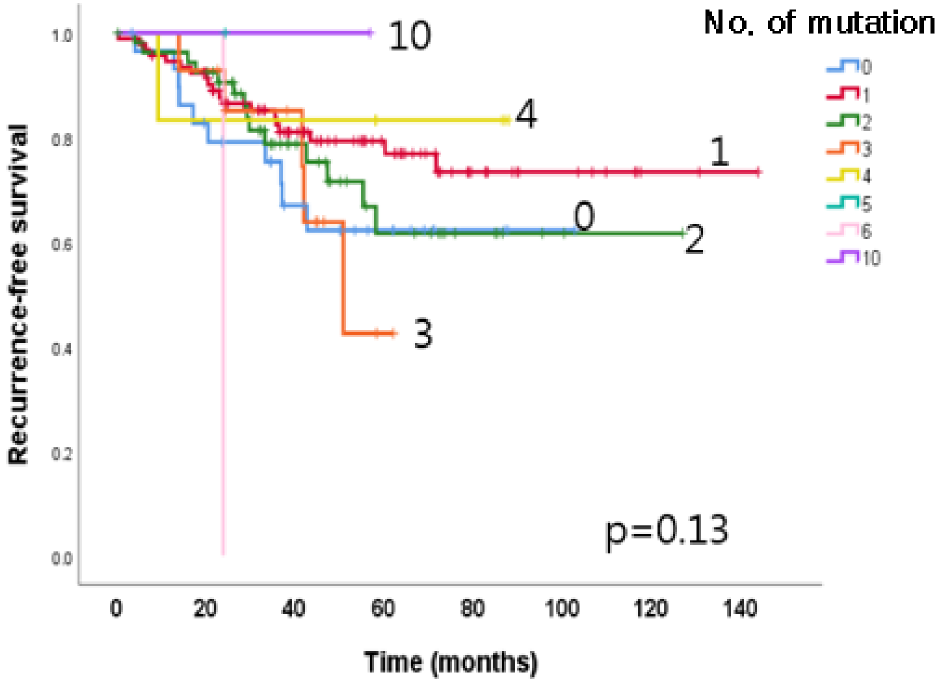


Figure 16. Disease free survival according to multiple gene combinations

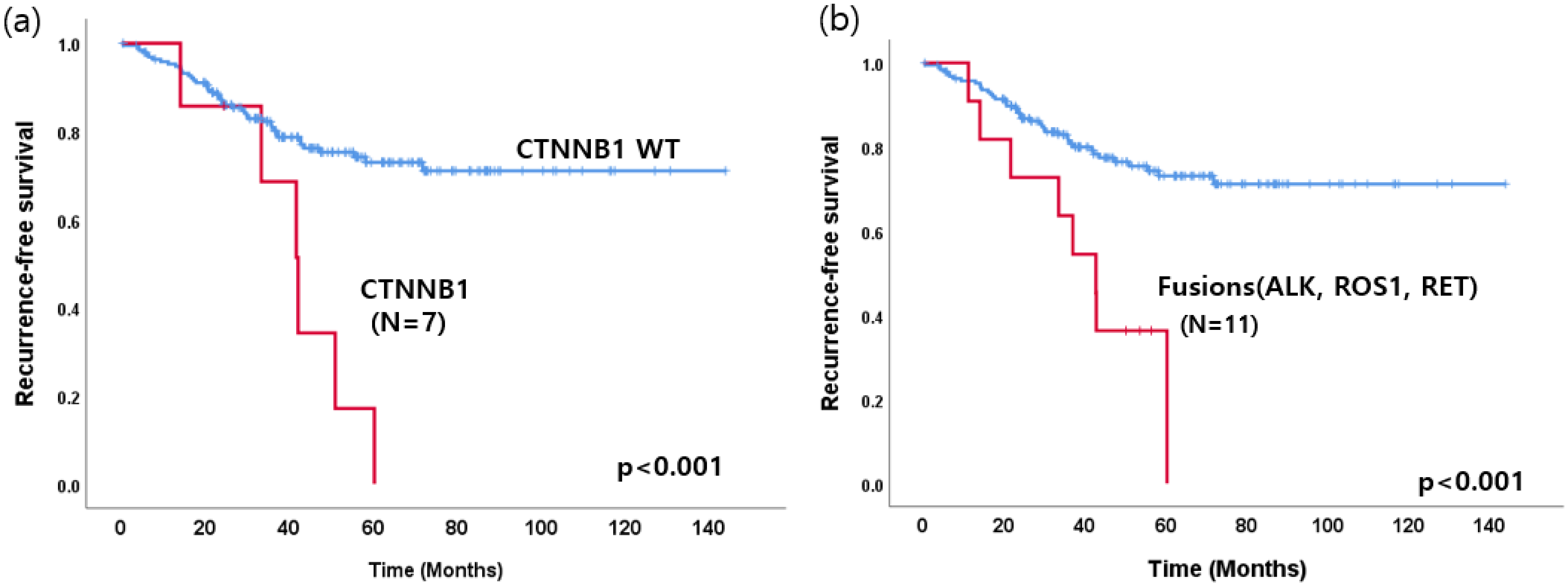
The association with the number of genetic alteration and recurrence



No. of mutation	No. of patients (%)	No. of recurrence	Recurrence rate	p-value
0	23 (11.4)	6	26.1	0.13
1	94 (46.8)	19	20.2	
2	60 (29.8)	16	26.7	
3+	24 (12.0)	8	33.3	

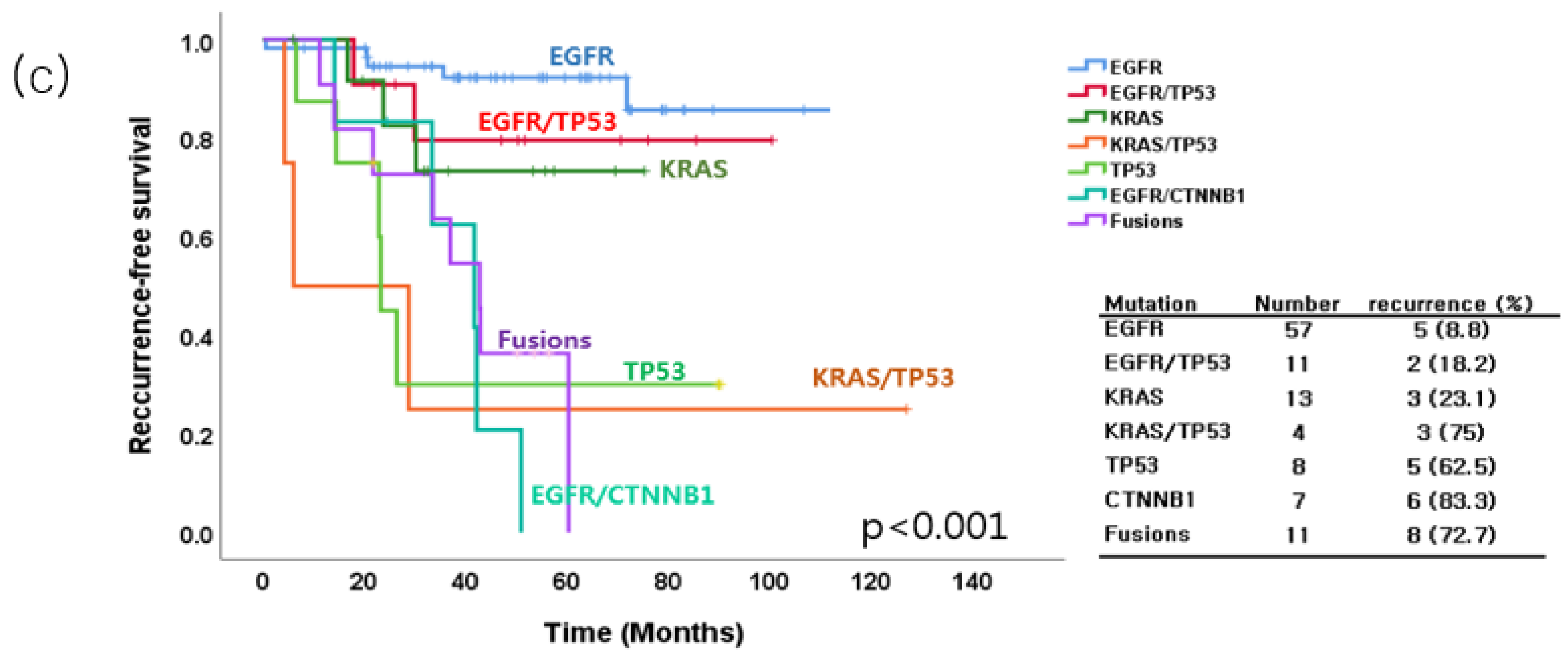


Recurrence-free survival according to (a) CTNNB1 (b) fusion genes(ALK, ROS1 and RET)



β-Catenin is a component of cell–cell adhesion structures and regulates the cell proliferation, differentiation, cancer signaling and metastasis.

Recurrence-free survival according to various type co-mutations



Mutation	Number	recurrence (%)
EGFR	57	5 (8.8)
EGFR/TP53	11	2 (18.2)
KRAS	13	3 (23.1)
KRAS/TP53	4	3 (75)
TP53	8	5 (62.5)
CTNNB1	7	6 (83.3)
Fusions	11	8 (72.7)

- ➢ EGFR is favorable prognostic factor for recurrence, but EGFR/CTNNB1 combination mutation showed shorter RFS.

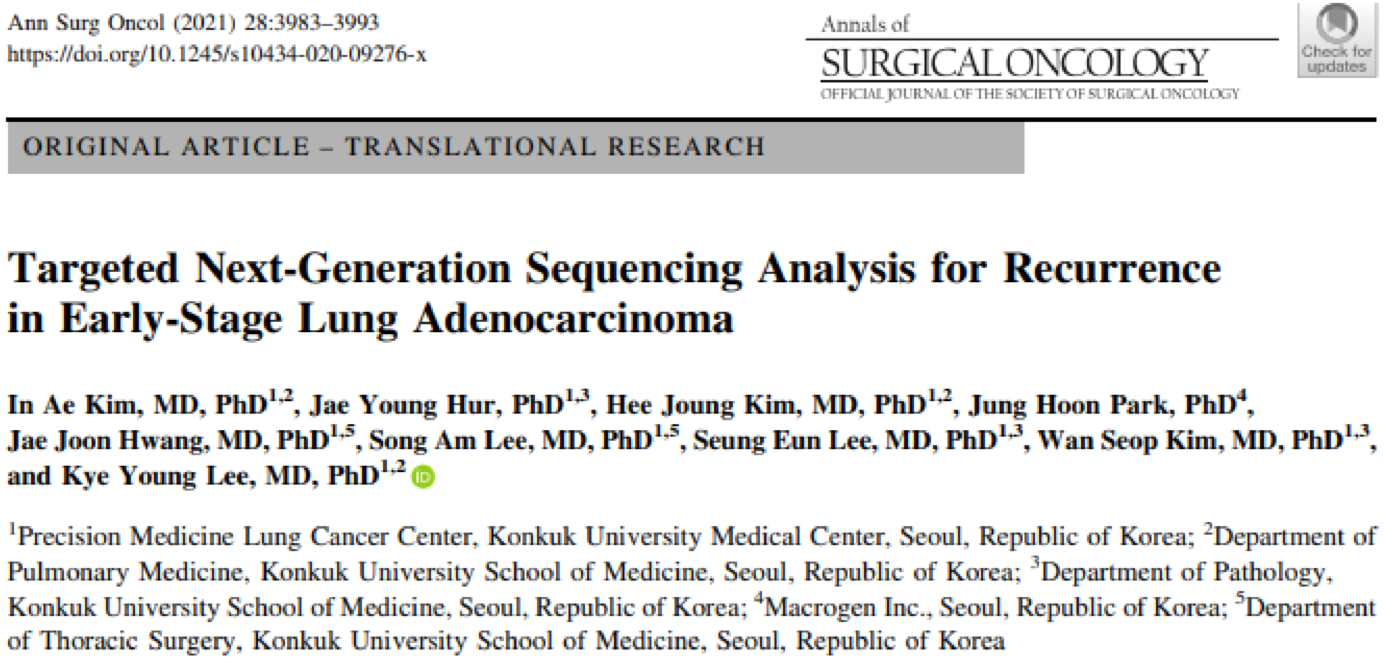
Univariate and multivariate models for RFS according to genetic alterations

		Univariate			**Multivariate**		
Category	**Variables**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Age	≥60 vs <60	0.85	0.47-1.54	0.59	1	0.54-1.84	0.99
Sex	Male vs female	1.18	0.65-2.15	0.74	1.07	0.41-2.85	0.88
Smoking history	smoker vs non-smoker	1.24	0.68-2.26	0.47	1.3	0.51-3.34	0.58
Pathologic Stage	IB vs IA(1+2+3)	2.26	1.23-3.94	**0.004**	**2.07**	**0.98-4.36**	**0.05**
Grade of differentation	WD or MD vs PD	**2.48**	**1.13-5.40**	**0.022**	**2.93**	**1.24-6.90**	**0.014**
Surgical procedure	Wedge or lobectomy	1.4	0.71-2.78	0.32	1.8	0.85-2.94	0.13
Pathologic invasion	VPI vs none	**2.78**	**1.56-4.96**	**0.001**	**2.63**	**1.44-7.81**	**0.002**
Adjuvant chemotherapy	Adjuvant chemothrapy	**2.27**	**1.25-4.11**	**0.007**	**2.17**	**1.14-4.13**	**0.017**
EGFR mutation	All EGFR vs wild	**0.41**	**0.22-0.76**	**0.001**	**0.43**	**0.23-0.82**	**0.011**
	EGFR/TP53 vs EGFR	**4.9**	**1.49-16.1**	**0.009**	**5.55**	**1.34-23.1**	**0.018**
CTNNB1	CTNNB1 vs wild	**3.76**	**1.55-9.07**	**0.001**	4.89	**1.98-12.1**	**0.001**
	EGFR/CTNNB1 vs EGFR	**14.2**	**3.5-57.64**	**<0.001**	**61.4**	**5.6-669**	**0.001**
TP53 mutation	TP53 vs wild	**1.66**	0.85-3.26	0.13	1.78	**0.90-3.53**	0.096
	TP53 only vs EGFR only	**7.05**	**1.65-29.9**	**0.008**	111.7	**4.7-2644**	**0.003**
KRAS mutation	KRAS vs wild	1.05	0.45-2.47	0.91	0.97	0.39-2.38	0.95
	KRAS only vs EGFR only	2.47	0.47-12.8	0.28	2.78	0.56-13.8	0.21
	KRAS/TP53 vs EGFR only	**12.2**	**2.8-52.3**	**0.001**	**11.8**	**1.83-75.4**	**0.009**
MET 14 skipping	MET exon 14 skipping vs Wild	1.52	0.46-4.88	0.49	1.73	0.51-5.80	0.37
Fusion Genes	ALK, ROS1, RET vs wild	**3.78**	**1.76-8.10**	**0.001**	3.25	**1.35-7.80**	**0.008**

CI, confidence intervals; HR, hazard ratio; EGFR, epidermal growth factor receptor;VPI, viceral-pleural invasion

The CTNNB1 mutation and fusion genes were associated recurrence and EGFR mutation was a favorable predictive factor for recurrence in the multivariate analysis adjusted by age, sex, smoking history, stage, and surgical procedures.

2021



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Annals of
SURGICAL ONCOLOGY
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ORIGINAL ARTICLE – TRANSLATIONAL RESEARCH

Targeted Next-Generation Sequencing Analysis for Recurrence in Early-Stage Lung Adenocarcinoma

In Ae Kim, MD, PhD[1,2], Jae Young Hur, PhD[1,3], Hee Joung Kim, MD, PhD[1,2], Jung Hoon Park, PhD[4], Jae Joon Hwang, MD, PhD[1,5], Song Am Lee, MD, PhD[1,5], Seung Eun Lee, MD, PhD[1,3], Wan Seop Kim, MD, PhD[1,3], and Kye Young Lee, MD, PhD[1,2]

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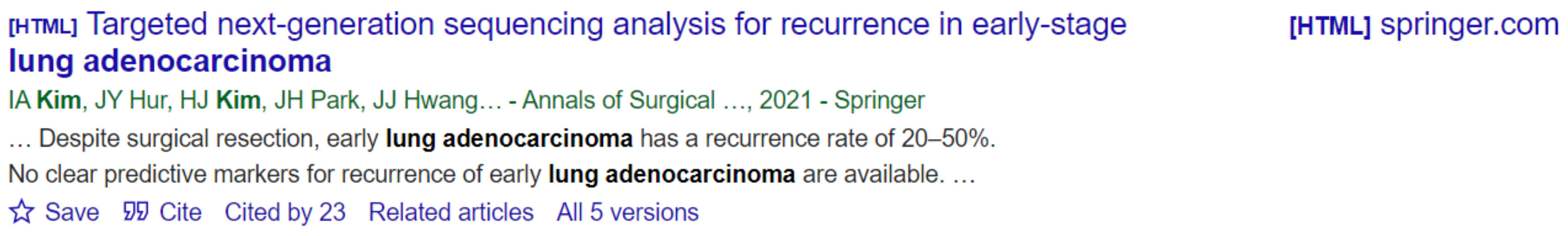

[HTML] Targeted next-generation sequencing analysis for recurrence in early-stage **lung adenocarcinoma**

[HTML] springer.com

IA **Kim**, JY Hur, HJ **Kim**, JH Park, JJ Hwang… - Annals of Surgical …, 2021 - Springer

… Despite surgical resection, early **lung adenocarcinoma** has a recurrence rate of 20–50%. No clear predictive markers for recurrence of early **lung adenocarcinoma** are available. …

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Prognosis of recurrence after complete resection in early-stage lung adenocarcinoma based on molecular alterations: a systematic review and meta-analysis

Chu Zhou, Zhongying Jing, Wei Liu, Zihuan Ma, Siyao Liu & Yueyu Fang ✉

Scientific Reports **13**, Article number: 18710 (2023) | Cite this article

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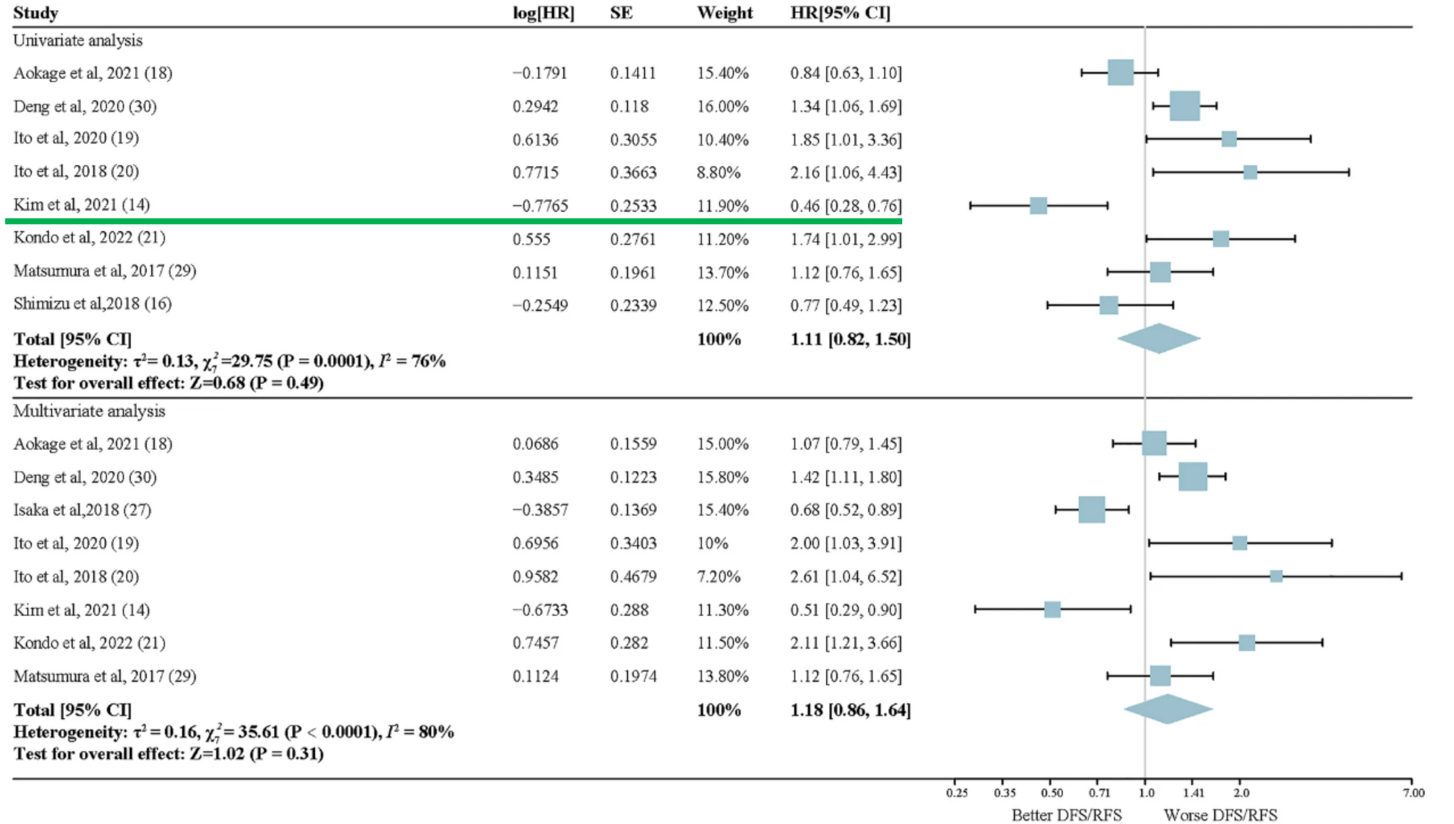


Study	**log[HR]**	**SE**	**Weight**	**HR[95% CI]**
Univariate analysis				
Aokage et al, 2021 (18)	−0.1791	0.1411	15.40%	0.84 [0.63, 1.10]
Deng et al, 2020 (30)	0.2942	0.118	16.00%	1.34 [1.06, 1.69]
Ito et al, 2020 (19)	0.6136	0.3055	10.40%	1.85 [1.01, 3.36]
Ito et al, 2018 (20)	0.7715	0.3663	8.80%	2.16 [1.06, 4.43]
Kim et al, 2021 (14)	−0.7765	0.2533	11.90%	0.46 [0.28, 0.76]
Kondo et al, 2022 (21)	0.555	0.2761	11.20%	1.74 [1.01, 2.99]
Matsumura et al, 2017 (29)	0.1151	0.1961	13.70%	1.12 [0.76, 1.65]
Shimizu et al,2018 (16)	−0.2549	0.2339	12.50%	0.77 [0.49, 1.23]
Total [95% CI]			**100%**	**1.11 [0.82, 1.50]**
Multivariate analysis				
Aokage et al, 2021 (18)	0.0686	0.1559	15.00%	1.07 [0.79, 1.45]
Deng et al, 2020 (30)	0.3485	0.1223	15.80%	1.42 [1.11, 1.80]
Isaka et al,2018 (27)	−0.3857	0.1369	15.40%	0.68 [0.52, 0.89]
Ito et al, 2020 (19)	0.6956	0.3403	10%	2.00 [1.03, 3.91]
Ito et al, 2018 (20)	0.9582	0.4679	7.20%	2.61 [1.04, 6.52]
Kim et al, 2021 (14)	−0.6733	0.288	11.30%	0.51 [0.29, 0.90]
Kondo et al, 2022 (21)	0.7457	0.282	11.50%	2.11 [1.21, 3.66]
Matsumura et al, 2017 (29)	0.1124	0.1974	13.80%	1.12 [0.76, 1.65]
Total [95% CI]			**100%**	**1.18 [0.86, 1.64]**

Univariate analysis:
Heterogeneity: $\tau^2 = 0.13$, $\chi^2_7 = 29.75$ ($P = 0.0001$), $I^2 = 76\%$
Test for overall effect: $Z = 0.68$ ($P = 0.49$)

Multivariate analysis:
Heterogeneity: $\tau^2 = 0.16$, $\chi^2_7 = 35.61$ ($P < 0.0001$), $I^2 = 80\%$
Test for overall effect: $Z = 1.02$ ($P = 0.31$)

TABLE 3 Individual characteristics of patients with CTNNB1 mutations or fusion genes

Case	Age	Sex	Site	Surgery	Stage	Adjuvant	EGFR mutation	Concurrent alterations	Recurrence	RFS (mon)	Recurrence site	CTNNB1 exon ID	CTNNB1 DNA change	VAF (%)	Characterization	Protein
CTNNB1																
1	71	F	RLL	Lobec.	1A2	N	21L858R	TP53, VHL	N	24.4	NA	4/15	c.283C > T	5.26	Stop gained	p.R95*
2	49	F	LUL	Lobec.	1A2	N	21L858R	T790M	R	50.9	LLL effusion	3/15	c.134C > T	29.8	Missense	p.S45F
3	68	M	RUL	Lobec.	1Bs[a]	Y	21L858R	JAK2,RUNX1	R	42.1	brain	3/15	c.122C > T	2.11	Missense	p.T41I
4	65	F	LUL	Lobec.	1A3	Y	21L858R	RET	R	41.7	multi.lung nodules	3/15	c.98C > G	3.32	Missense	p.S33C
5	64	F	RLL	Lobec.	1A3	N	19 Del	MLH1	R	14.0	Brain	3/15	c.121A > G	12.7	Missense	p.T41A
6	75	F	LUL	Lobec.	1Bv[b]	N	WT	No	R	33.3	multi.lung nodules	3/15	c.110C > T	12.1	Missense	p.S37F
7	76	F	RLL	Lobec.	1A2	N	WT	KIF5B-RET	R	60.3	RUL	3/15	c.100G > A	14.2	Missense	p.G34R
8	61	M	RML	Lobec.	IIB	Y	19 Del	TP53	R	8.5	Lt adrenal	3/15	c.98C > G	22.7	Missense	p.S33C
9	76	M	RUL	Lobec.	IIB	N	WT	PIK3CA,TP53, SMAD4	R	2.7	multi.lung nodules	9/15	c.1271T > G	6.5	Missense	p.L424R

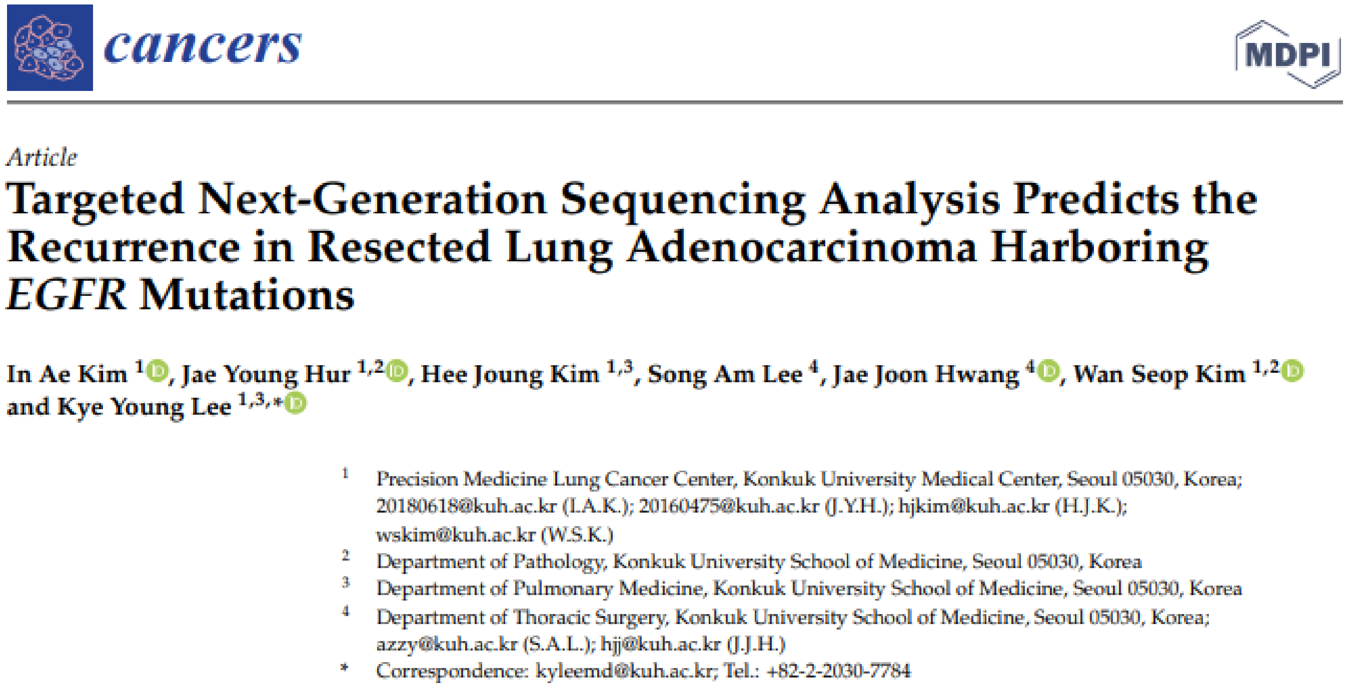
Case	Age	Sex	Site	Surgery	Stage	Adjuvant	Fusion mutation	Concurrent alterations	Recurrence	RFS	Recurrence site	Validation methods of fusions
1	71	M	LLL	Lobec.	1Bv	Y	ALK	APC, MLH1	R	42.7	RML	FISH
2	47	M	RLL	Lobec.	1A2	N	ALK	None	R	33.5	Multiple	IHC
3	30	M	RML	Lobec.	1A3	N	ALK	None	R	42.8	Brain	FISH
4	64	F	LLL	Wedge	1A3	Y	ALK	None	R	14.0	4R LN	FISH
5	64	M	RLL	Lobec.	1Bv	Y	ALK	None	N	53.5	None	FISH
6	82	M	LUL	Lobec.	1A2	N	ALK	None	N	50.1	None	IHC
7	81	M	LUL	Lobec.	1Bv	N	ALK	None	R	11.1	Brain, lung	IHC
8	71	F	RLL	Lobec.	1A3	N	ROS1	21L858R	R	21.6	Brain	FISH
9	60	M	RUL	Wedge.	1A2	Y	ROS1	None	N	56.4	None	RT-PCR
10	53	F	LUL	Lobec.	IIB	Y	ROS1	None	R	30.5	Lung	RT-PCR
11	76	F	RLL	Lobec.	1A2	N	RET	CTNNB1	R	60.3	RUL, multiple bone	FISH
12	59	F	RLL	Lobec.	1Bs	v	RET	None	R	37.0	4R LN	FISH

Adjuvant Adjuvant chemotherapy, *mon* Months, *FISH* Fluorescent in situ hybridization, *F* Female, *Lobec* Lobectomy, *IHC* Immunohistochemistry, *Multi.* Multiple, *M* Male, *LN* Lymph node, *LUL* Left upper lobe, *LLL* Left lower love, *R* Recurrence, *N* No recurrence, *RUL* Right upper lobe, *RML* Right middle lobe, *RLL* Right lower lobe, RFS Recurrence-free survival, *19 Del* 19 Deletion, *NA* Not available, *WT* Wild type, *VAF* Variant allele frequency, *Wedge*. Wedge resection

[a] 1Bs means the tumor size is 3–4 cm

[b] 1Bv means the tumor invades viceral-pleura

2021



cancers MDPI

Article

Targeted Next-Generation Sequencing Analysis Predicts the Recurrence in Resected Lung Adenocarcinoma Harboring *EGFR* Mutations

In Ae Kim [1], Jae Young Hur [1,2], Hee Joung Kim [1,3], Song Am Lee [4], Jae Joon Hwang [4], Wan Seop Kim [1,2] and Kye Young Lee [1,3,*]

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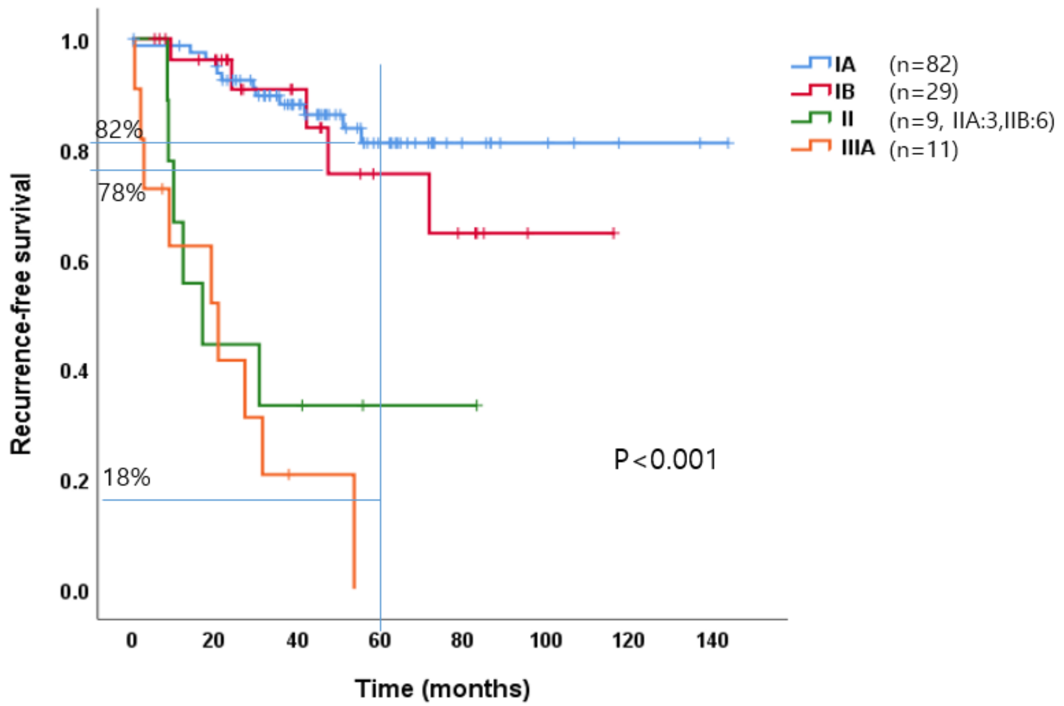
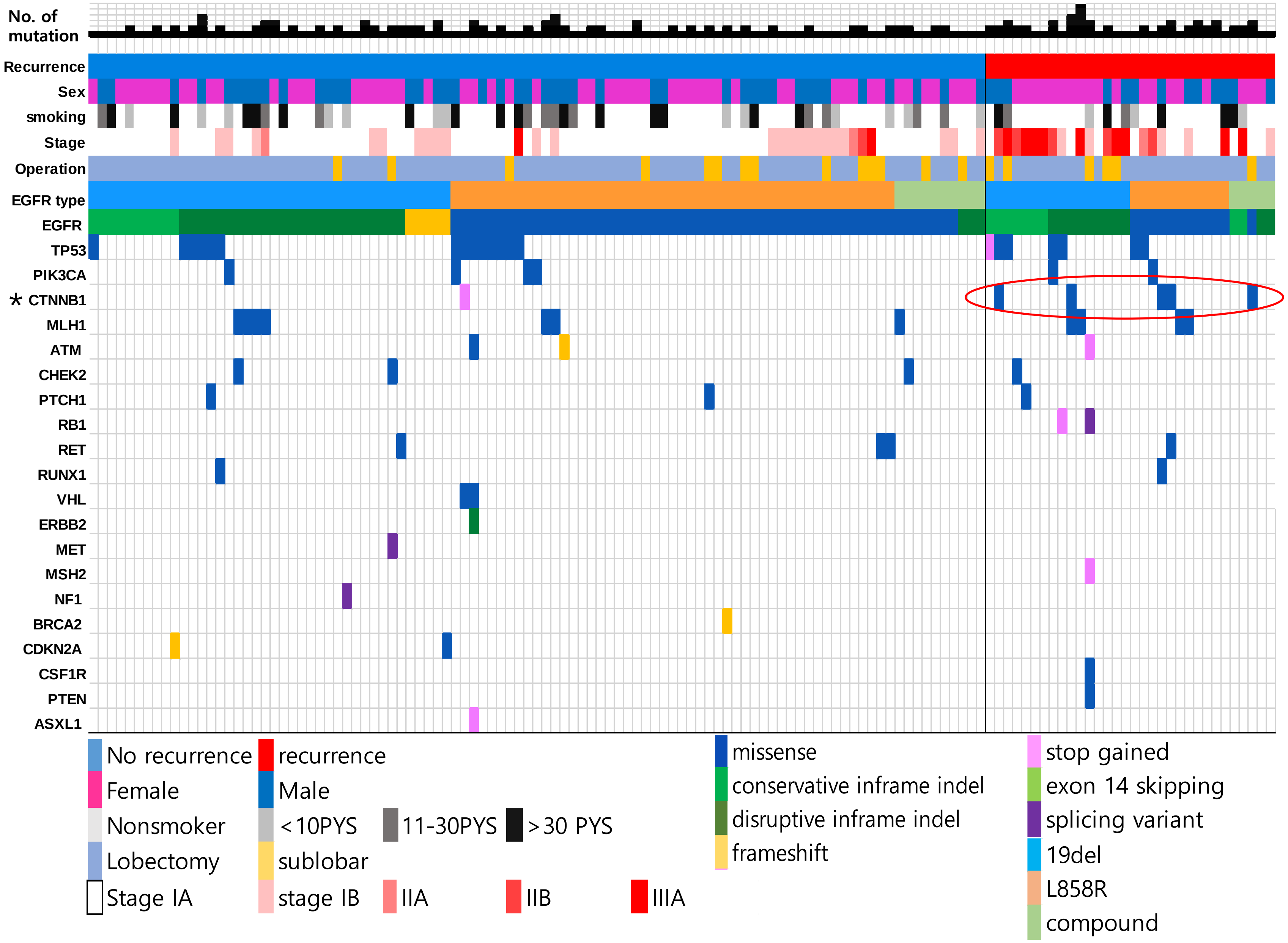
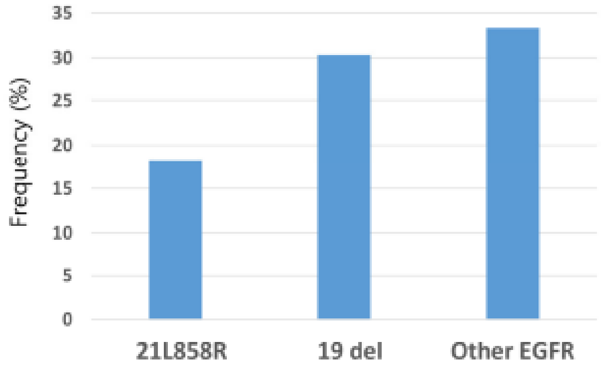
RFS according to pathologic stage in resected EGFR-mutated lung adenocarcinoma



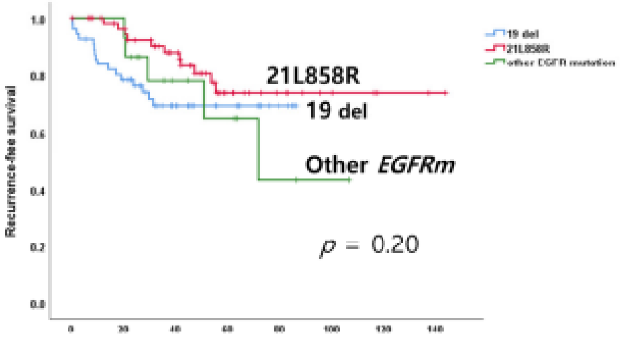
Genetic landscape of resected EGFR–mutated lung adenocarcinoma



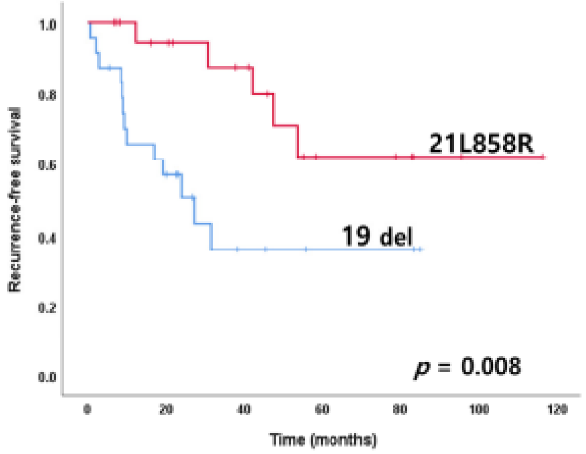


(a)

(a) Recurrence rate according to EGFR mutation subtypes

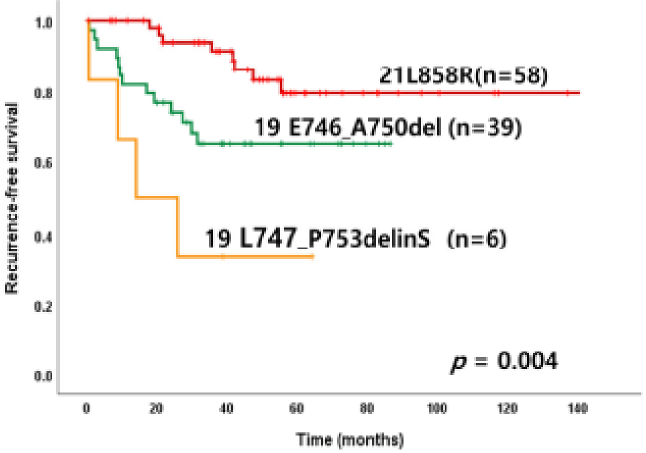


(b) RFS according to EGFR mutation types in all stage



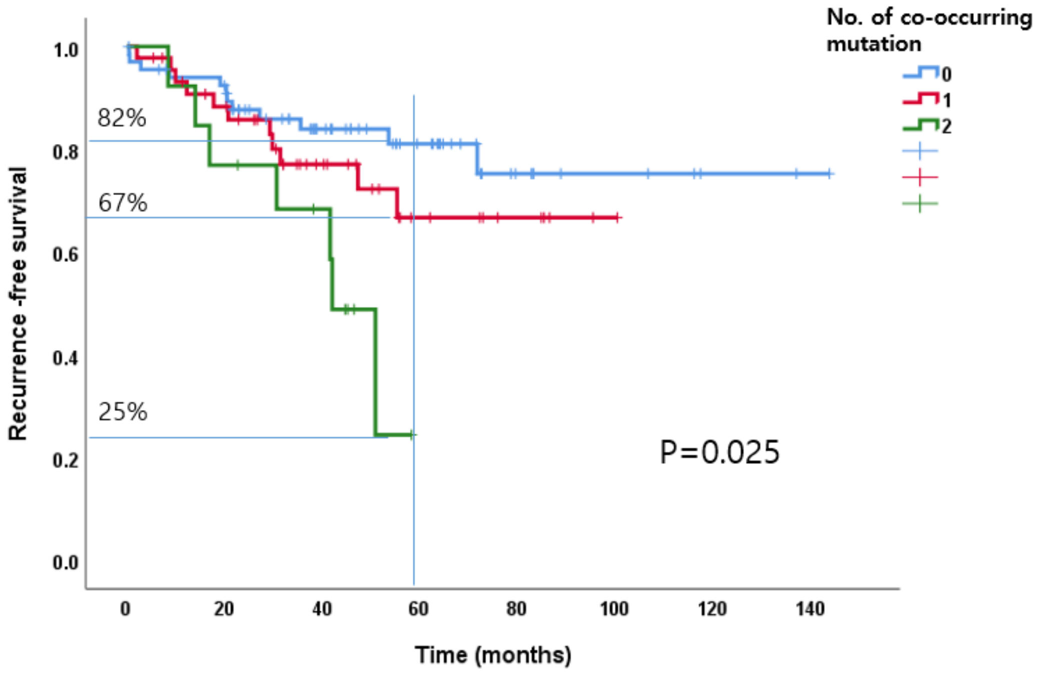
(c)

(c) RFS according to EGFR mutation subtype in stage IB-IIIA



(d)

(d) RFS according to EGFR 19 del subtypes



RFS was proportionally decreased according to the number of accompanying co-mutations. (p=0.025)

Prognostic factors for recurrence by multivariate analysis in resected EGFR-mutated lung adenocarcinoma

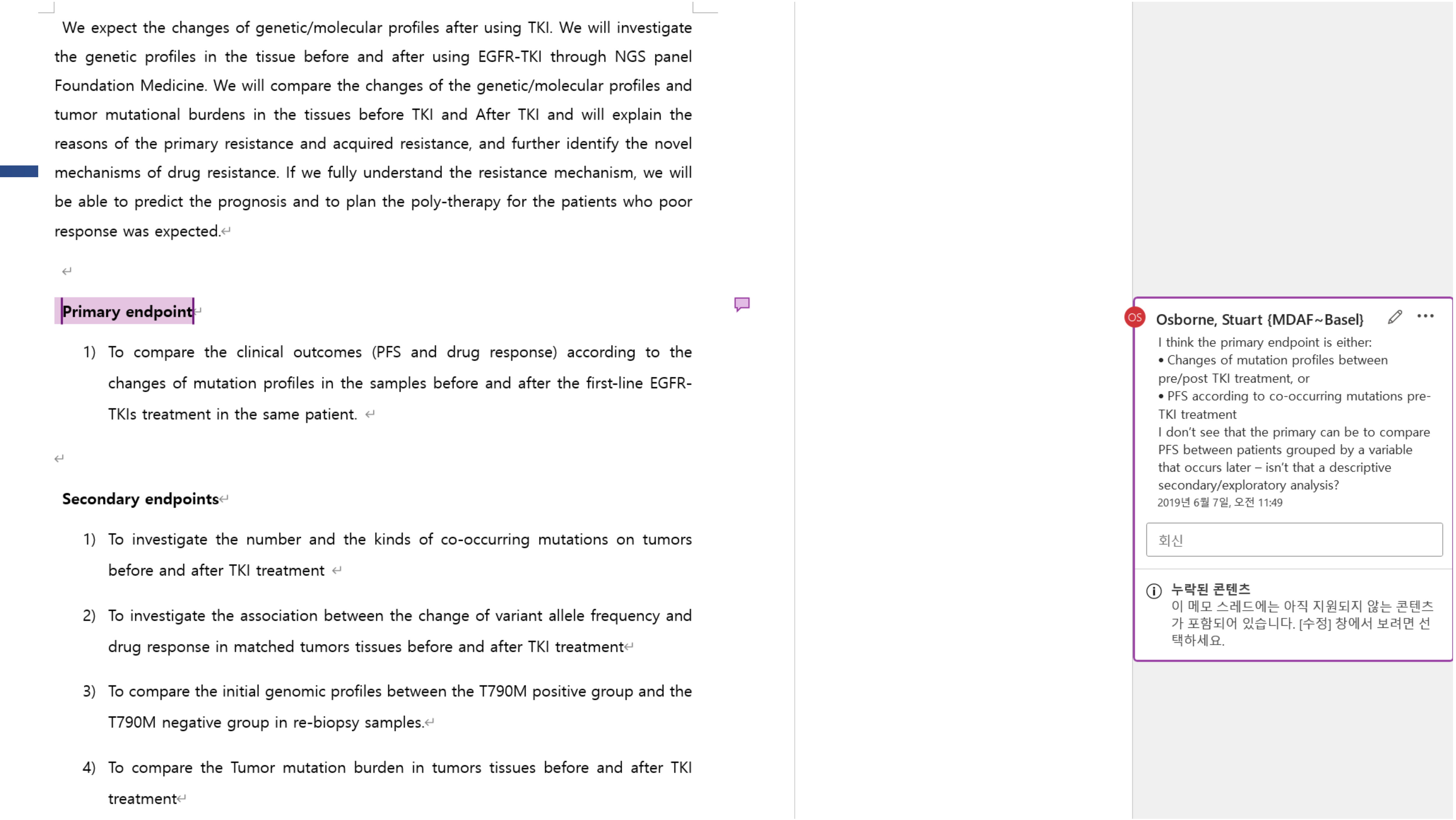
		Univariate analysis			Multivariate analysis		
Category	Variables	HR	95% CI	p-value	HR	95% CI	p-value
Age	≥65 vs <65	0.37	0.16-0.82	0.009	0.38	0.15-0.97	0.04
Sex	Male vs female	0.93	0.46-1.89	0.85	0.75	0.24-2.28	0.61
Smoking history	Ever-smoker vs non-smoker	1.04	0.49-2.17	0.91	1.15	0.36-3.59	0.8
Pathologic Stage	II-III vs I	9.23	4.45-18.7	<0.001	8.02	3.73-17.2	<0.001
Extension of surgery	sublobar resection or lobectomy	1.32	0.54-3.21	0.53	1.44	0.74-2.80	0.27
Pathologic invasion	VPI vs none	4.52	2.23-9.18	<0.001	8.02	3.73-17.2	<0.001
Adjuvant chemotherapy	Adjuvant chemothrapy	4.78	2.36-9.67	<0.001	2.21	1.14-4.24	0.017
No. of co-mutation	1 vs 0	1.51	0.66-3.4	0.32	1.76	0.72-4.3	0.213
	2 vs 0	3.84	1.47-10.1	0.006	5.57	1.57-19.6	0.008
EGFR mutation	19 del vs 21L858R	1.88	0.87-4.07	0.1	1.82	0.76-4.32	0.17
	p746_A 750del vs 21L858R	2.19	1.04-4.60	0.03	1.7	0.75-3.83	0.2
	pL747_P753delinS vs 21L858R	6.76	1.93-23.7	0.003	7.55	1.91-29.8	0.004
	pL747_P753delinS vs p746_A 750del	2.52	0.71-8.88	0.15	1.69	0.75-3.83	0.2
CTNNB1	CTNNB1/EGFR vs EGFR	5.19	1.97-13.6	0.001	8.65	3.0-24.9	<0.001
TP53 mutation	TP53/EGFR vs EGFR(All stage)	1.89	0.71-5.05	0.2	2.14	0.84-5.43	0.1
	TP53/EGFR vs EGFR(IB-IIIA)	3.48	1.21-10.0	0.02	3.06	1.01-11.7	0.05

CI, confidence intervals; HR, hazard ratio; EGFR, epidermal growth factor receptor;VPI, viceral-pleural invasion, PD: poor differentiation, MD; moderate defferentiation, WD; well differentiation

P values were calculated using multivariate Cox proportional hazard models, adjusted for age, sex, smoking status, stage.

Q:EGFR-TKI 효과차는 Co-mutation 차이?

- 2019년도 synopsis 를 Roche에 제출
- 문헌 search – co-mutations with EGFR mutation. (MSKCC)
- Add : ① Multicenter
  ② TKI 치료 전후를 비교→ resistance 원인 규명
- Foundation medicine 협업
- Multicenter- EGFR mutation NGS Research
  - 2019년도 연구 시작
  - Multicenter- 아산, CMC, 고대 구로, 고신대, 한림대



We expect the changes of genetic/molecular profiles after using TKI. We will investigate the genetic profiles in the tissue before and after using EGFR-TKI through NGS panel Foundation Medicine. We will compare the changes of the genetic/molecular profiles and tumor mutational burdens in the tissues before TKI and After TKI and will explain the reasons of the primary resistance and acquired resistance, and further identify the novel mechanisms of drug resistance. If we fully understand the resistance mechanism, we will be able to predict the prognosis and to plan the poly-therapy for the patients who poor response was expected.

Primary endpoint

1) To compare the clinical outcomes (PFS and drug response) according to the changes of mutation profiles in the samples before and after the first-line EGFR-TKIs treatment in the same patient.

Secondary endpoints

1) To investigate the number and the kinds of co-occurring mutations on tumors before and after TKI treatment
2) To investigate the association between the change of variant allele frequency and drug response in matched tumors tissues before and after TKI treatment
3) To compare the initial genomic profiles between the T790M positive group and the T790M negative group in re-biopsy samples.
4) To compare the Tumor mutation burden in tumors tissues before and after TKI treatment

Osborne, Stuart {MDAF~Basel}

I think the primary endpoint is either:
- Changes of mutation profiles between pre/post TKI treatment, or
- PFS according to co-occurring mutations pre-TKI treatment

I don't see that the primary can be to compare PFS between patients grouped by a variable that occurs later – isn't that a descriptive secondary/exploratory analysis?

2019년 6월 7일, 오전 11:49

누락된 콘텐츠

이 메모 스레드에는 아직 지원되지 않는 콘텐츠가 포함되어 있습니다. [수정] 창에서 보려면 선택하세요.

Next-generation sequencing analysis to investigate the clinical impact of concomitant genetic alterations in the patients with advanced EGFR-mutated lung adenocarcinoma: A multicenter study.

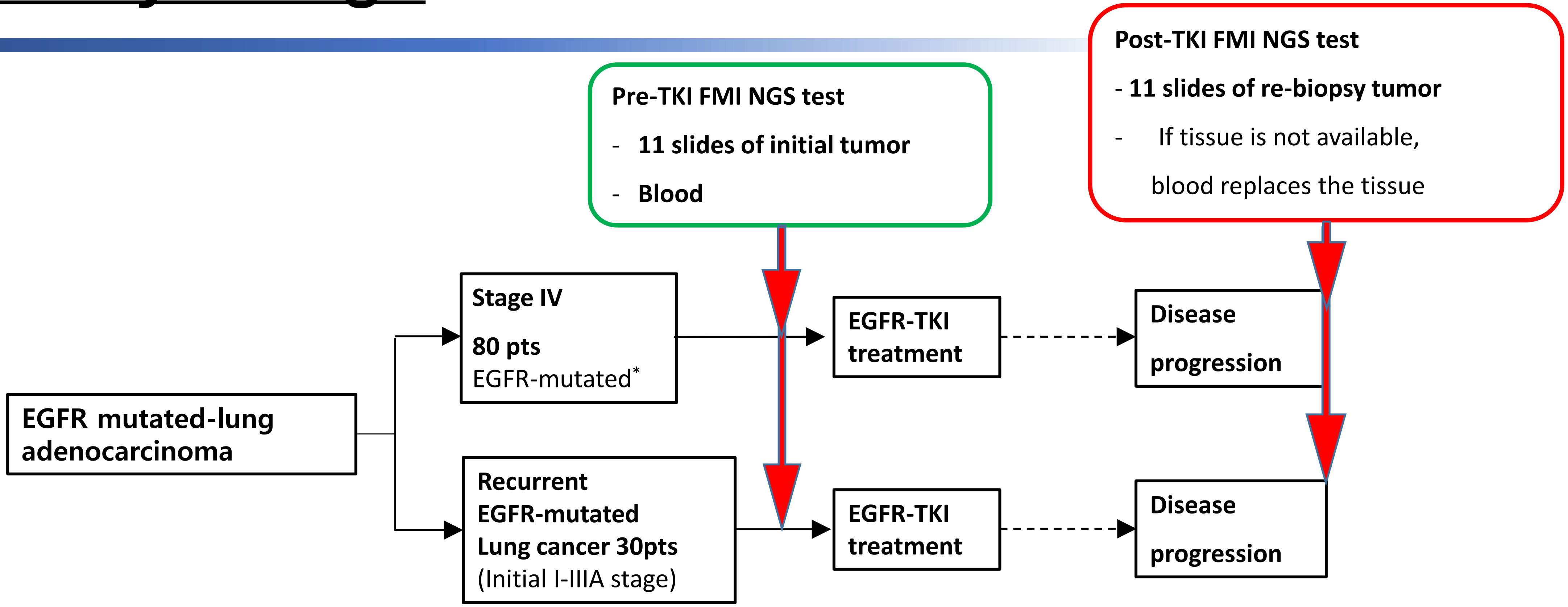
- **Background**
  - The response rate of patients treated by EGFR-TKIS is high, but they have progression after around 12 months.
  - clinical courses of advanced EGFR-mutated lung adenocarcinoma are quite various
  - It might be related with acquired resistances or primary resistances
    - T790M (50%), downstream or bypath signal pathway (RAS/ERK pathway or PI3K/AKT/mTOR pathway), MET or ERBB2 amplification

- **Inclusion criteria**

Newly diagnosed EGFR-mutated stage IV lung adenocarcinoma patients

+ adequate tissue for NGS analysis.(10 slides) + naïve EGFR-TKIs

Study Design :



Pre-TKI FMI NGS test

- **11 slides of initial tumor**
- **Blood**

Post-TKI FMI NGS test

- 11 slides of re-biopsy tumor

- If tissue is not available,

  blood replaces the tissue

EGFR mutated-lung adenocarcinoma

Stage IV

80 pts
EGFR-mutated*

Recurrent EGFR-mutated Lung cancer 30pts
(Initial I-IIIA stage)

EGFR-TKI treatment

Disease progression

EGFR-TKI treatment

Disease progression

Study Design

- Comprehensive NGS analysis (SNV, Indel, Copy number variation and fusion) on paired biopsy samples of before and after treatment with EGFR-TKI will be performed

- We plan to combine the retrospective and prospective studies to reduce the research period,

  ① **Retrospective study**- patients with archival tissue of pre/post TKI

  ② **Combination with retrospective and prospective study –** patients with archival tissue with pre-TKI on the time of enrollment, the post-TKI tissue after progression are analyzed later. The biopsy site would not be available after progression, we will get the blood instead

  ③ **Prospective study**- If the fresh tissue with pre-TKI is sent the FMI at the time of enrollment, blood is collected simultaneously at base line. Then NGS of available tissue of post TKI will be performed after the disease progress prospectively. If the biopsy site would not be available after progression, we will get the blood instead. (around 40-50 cases).

  ④ patients who occurred recurrence after surgical resection in the early stage of EGFR-mutated adenocarcinoma

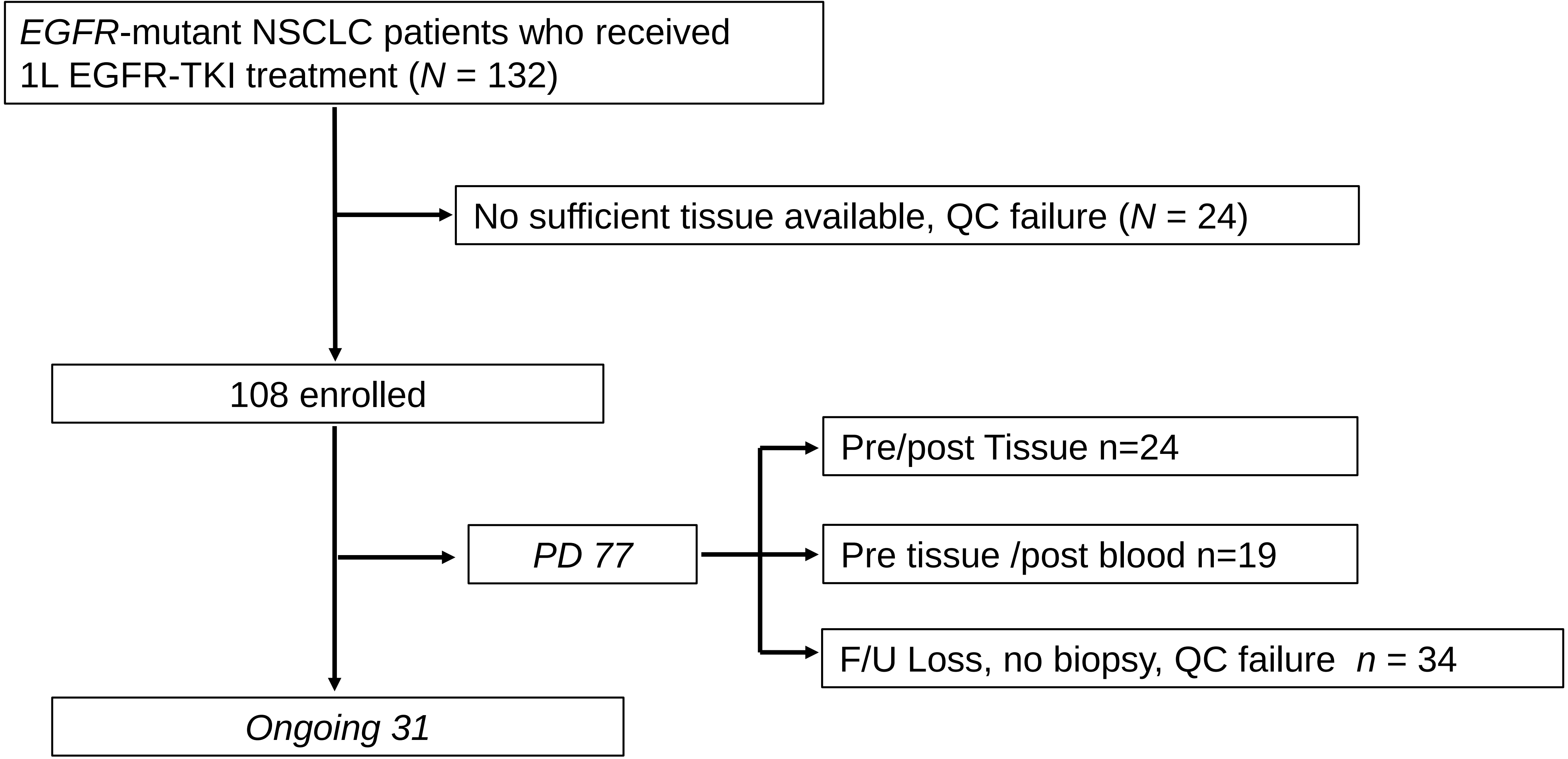
Outcomes

- Change of mutation profiles between pre/post TKI treatment
- PFS according to the co-occurring mutations with pre-TKI treatment
- The number and the kinds of co-occurring mutations on tumors before and after TKI treatment
- Tumor mutation burden in tumors tissues before and after TKI treatment
- The association between the change of variant allele frequency and drug response in matched tumors tissues before and after TKI treatment
- To compare the initial genomic profiles between the T790M positive group and the T790M negative group in re-biopsy samples

Enrollment

Center		cases
Central	Konkuk University Medical Center	35 cases
Local	Asan Medical Center	10 cases
	Guro Hospital, Korea University Medical Center	8 cases
	Catholic University of Korea, Seoul St. Mary's Hospita	10 cases
	Kosin University Gospel Hospital	4 cases
	Hallym University Sacred Heart Hospital	2 case
	Catholic University of Korea, Yeouido ST. Mary's Hospital	1 case

Study flow



EGFR-mutant NSCLC patients who received 1L EGFR-TKI treatment (*N* = 132)

No sufficient tissue available, QC failure (*N* = 24)

108 enrolled

PD 77

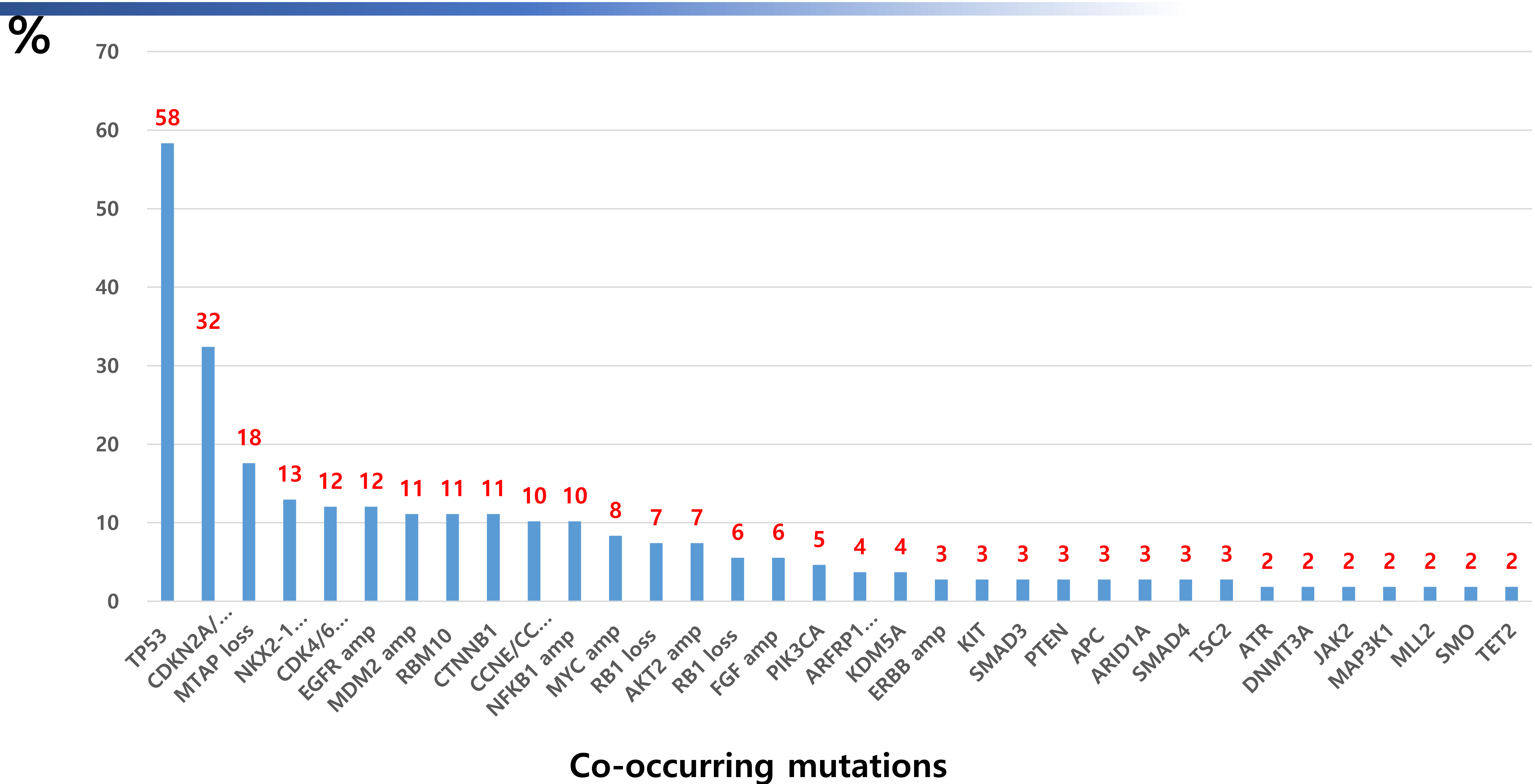
Pre/post Tissue n=24

Pre tissue /post blood n=19

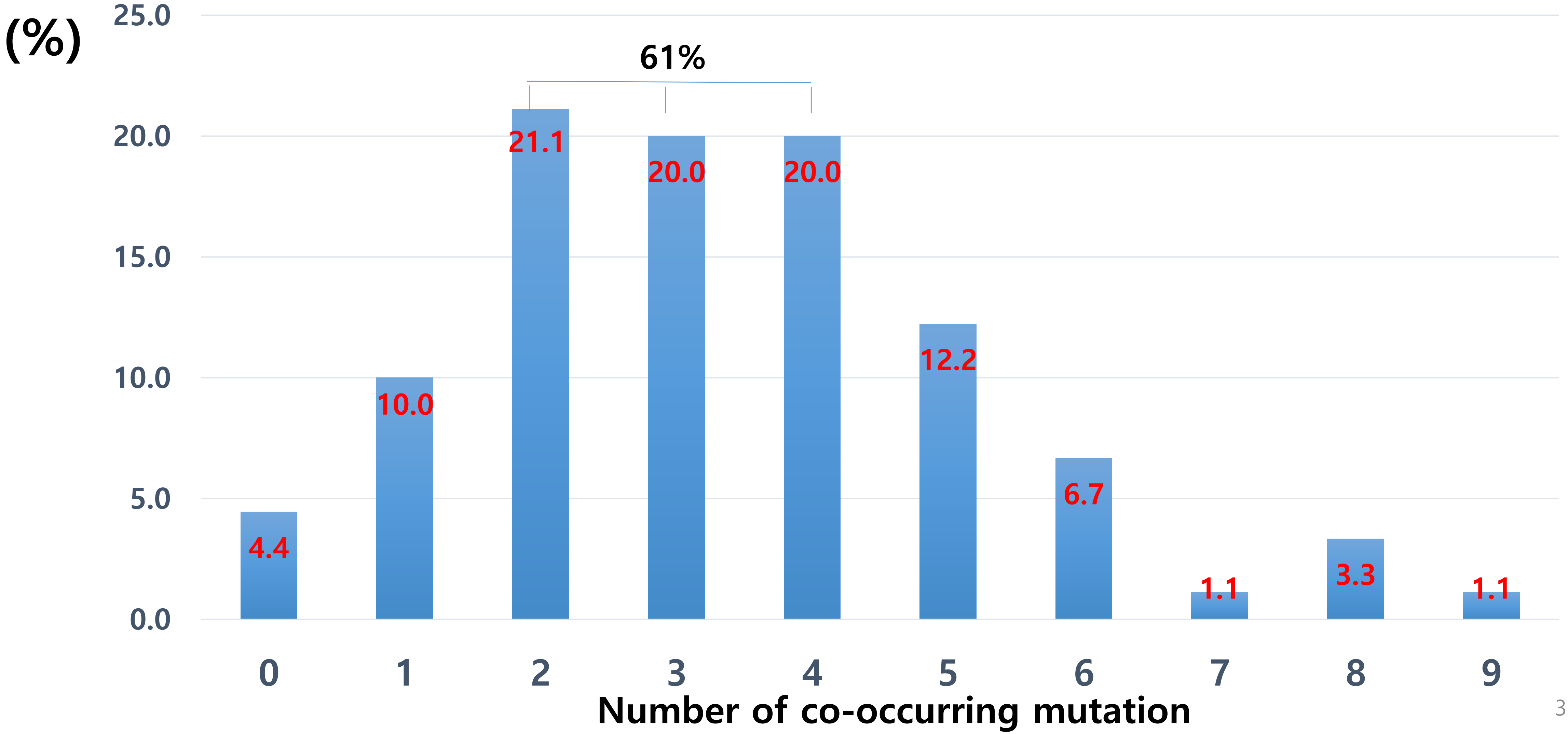
F/U Loss, no biopsy, QC failure *n* = 34

Ongoing 31

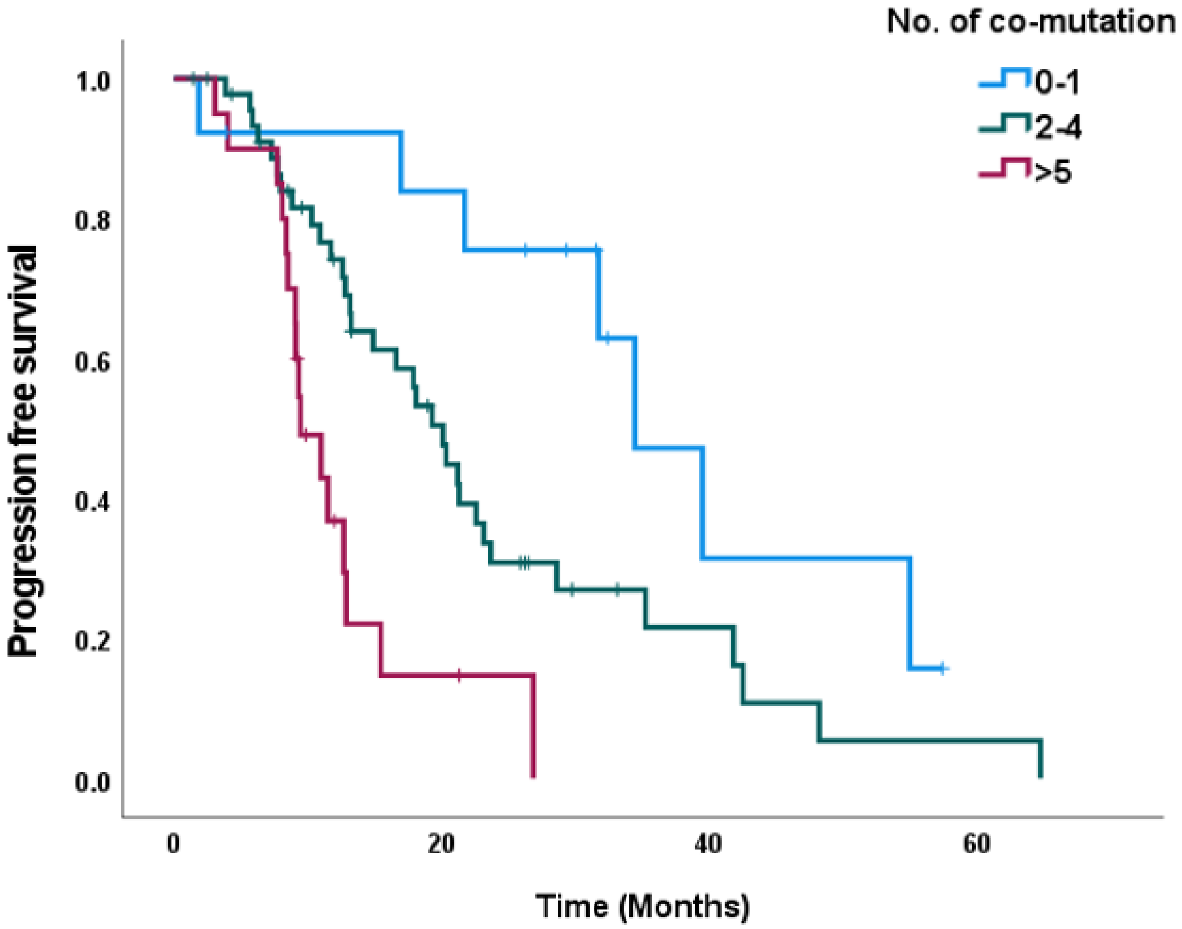
Frequency of mutations



Number of co-mutations



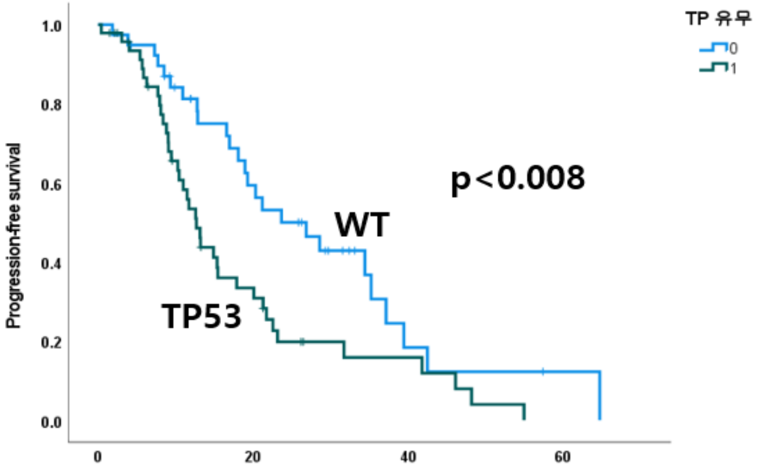
Progression-free-survival according to No of co-mutations



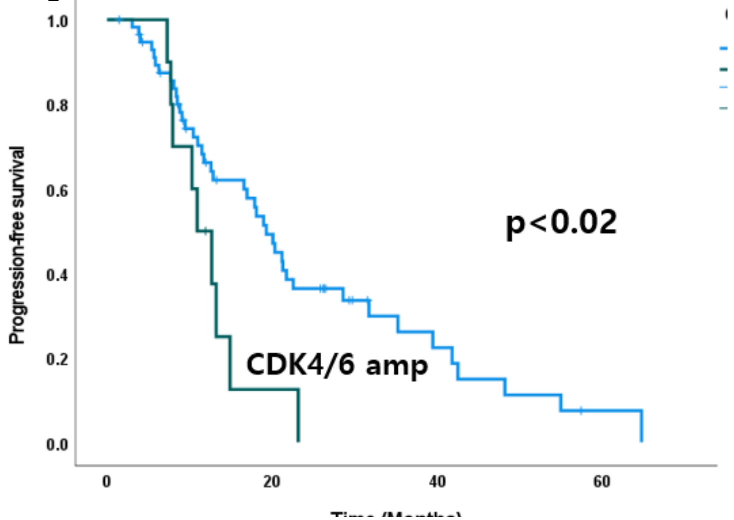
No of mutation	mPFS	P value
0~1	34.4 (25.7-43.0)	p<0.001
2~4	20.0 (16.6-23.5)	
≥5	9.4 (6.9-11.9)	

Progression-free-survival according to genetic alteration

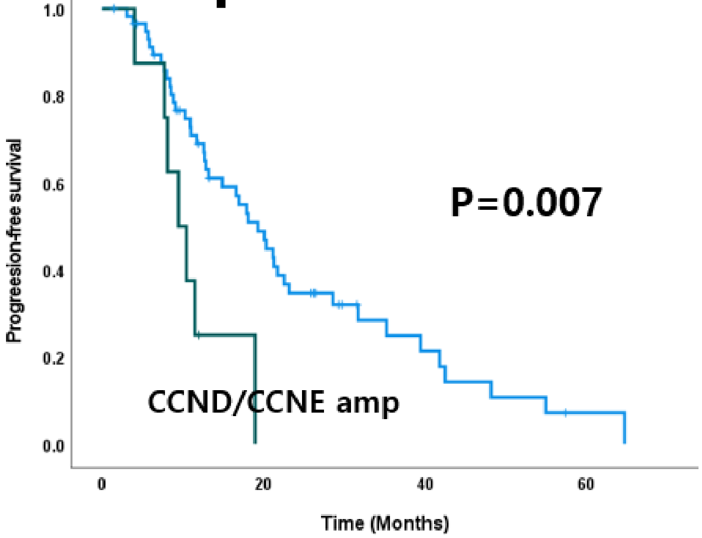
(a) *TP53*



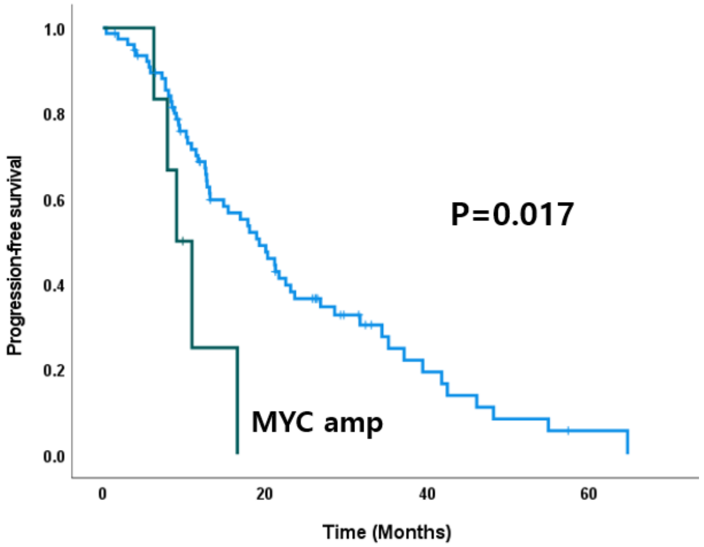
(b) CDK4/6 amp



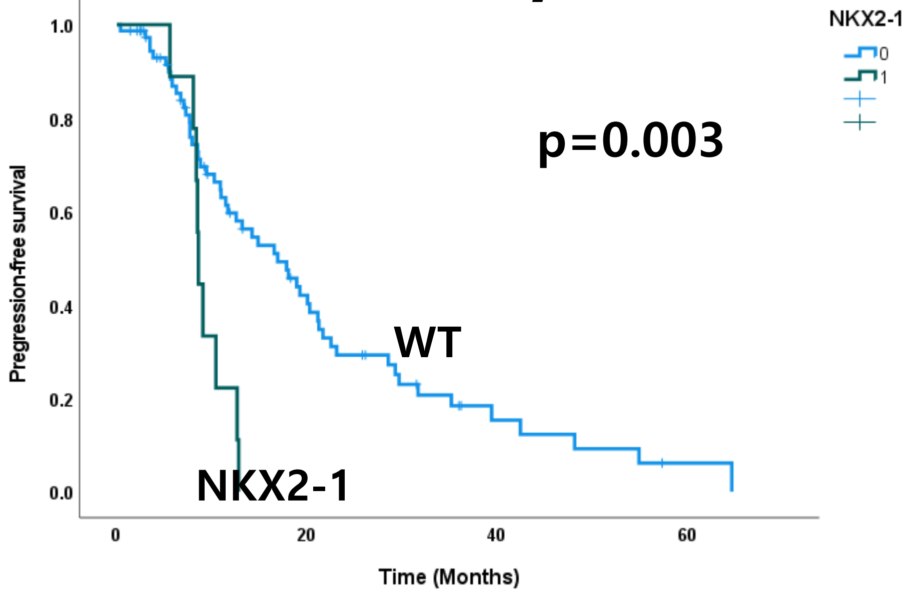
(c) *CCND/CCNE1* amp



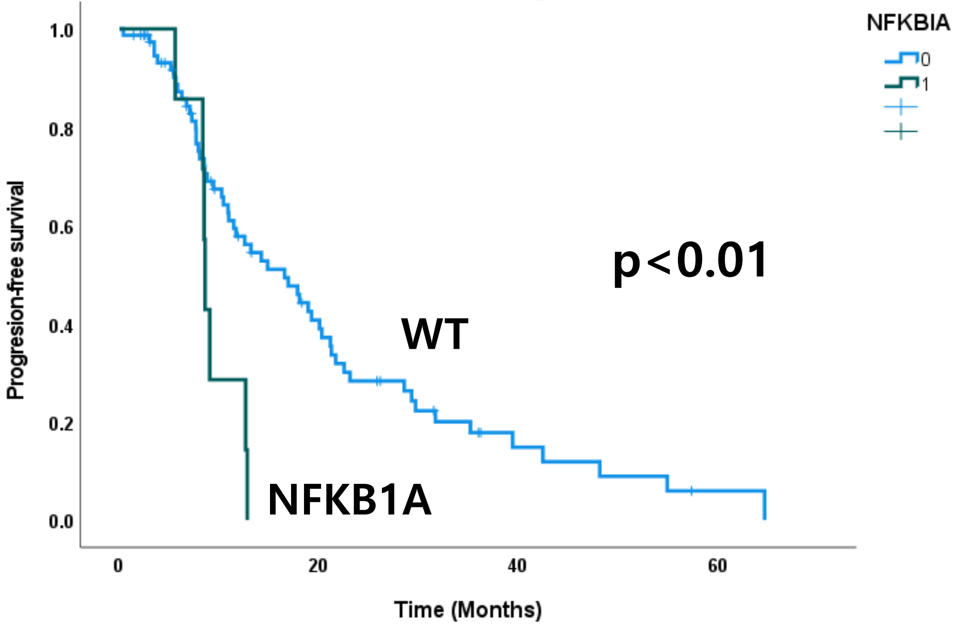
(d) *Myc* amp



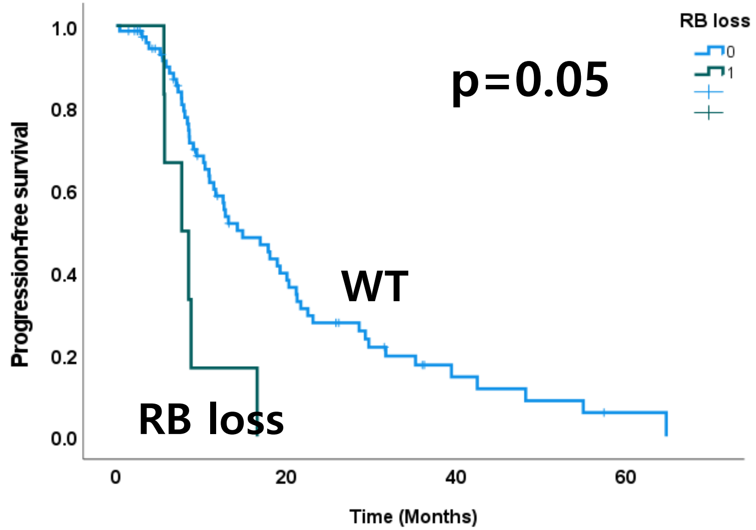
(E) *NKX2-1 amp*



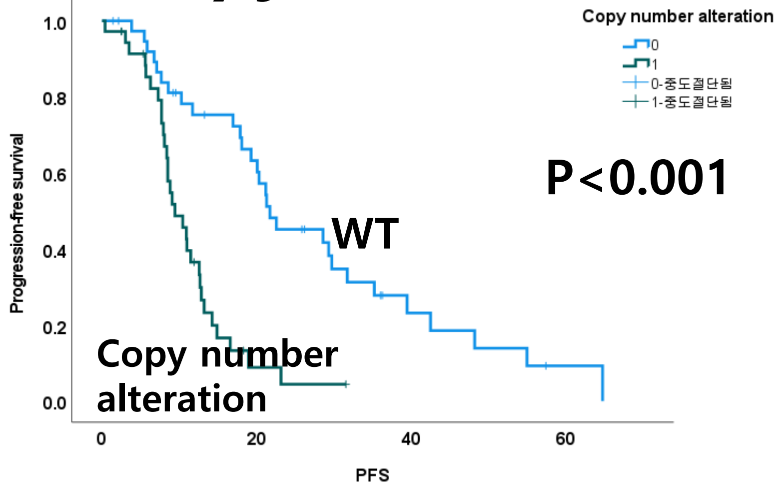
(F) *NFKBIA amp*



(G) *RB loss*



(H) *Copy number alteration*



Univariate and multivariate models for PFS according to genetic alterations

		Univariate			**Multivariate**		
Category	**Variables**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Age	≥65 vs <65	0.95	0.60-1.50	0.84	1	0.54-1.84	0.99
Sex	Male vs female	0.64	0.39-1.03	0.06	1.07	0.41-2.85	0.88
Smoking history	smoker vs non-smoker	0.66	0.39-1.10	0.11	1.3	0.51-3.34	0.58
No. of mutation	2-4 vs 0~1	**3.45**	**2.06-5.79**	**<0.001**	**2.95**	**1.20-7.25**	**0.018**
***TP53* mutation**	TP53 vs wild	**2.08**	**1.29-3.35**	**0.002**	**1.97**	**1.20-3.22**	**0.007**
***CDK4/CDK6* amp**	CDK4/CDK6 amp vs wild	**1.81**	0.81-2.93	0.02	1.61	0.83-3.13	0.16
***CCND/CCNE1* amp.**	CCND/CCNE1 amp vs wild	**2.74**	**1.32-5.69**	**0.007**	**2.52**	**1.18-5.37**	**0.017**
***Myc* amp**	Myc amp vs wild	**2.54**	**1.08-6.12**	**0.03**	**2.86**	**1.18-6.92**	**0.02**
***RB* loss**	RB loss vs wild	3.5	1.44-8.46	0.005	**3.66**	**1.49-8.97**	**0.004**
***NKX2-1* amp**	NKX2-1 amp vs wild	3.05	1.41-6.55	0.004	**2.71**	**1.22-6.04**	**0.014**
***NFKBIA* amp**	NFKBIA amp vs wild	2.84	1.23-6.54	0.014	**2.57**	**1.09-6.05**	**0.03**
Copy number amp.	Copy no. amp. vs wild	2.28	1.40-3.72	0.001	**2.37**	**1.43-3.94**	**0.001**

CI, confidence intervals; HR, hazard ratio; EGFR, epidermal growth factor receptor

The No. of mutation, *TP53* mutation, *CCND/CCNE1* amp, Myc amp, RB loss, NKX2-1 and NFKBIA amp were associated short PFS in the multivariate analysis adjusted by age, sex, smoking history, mutation type and EGFR-TKI regimen.

Baseline mutations affect the emergence of acquired T790M mutation.

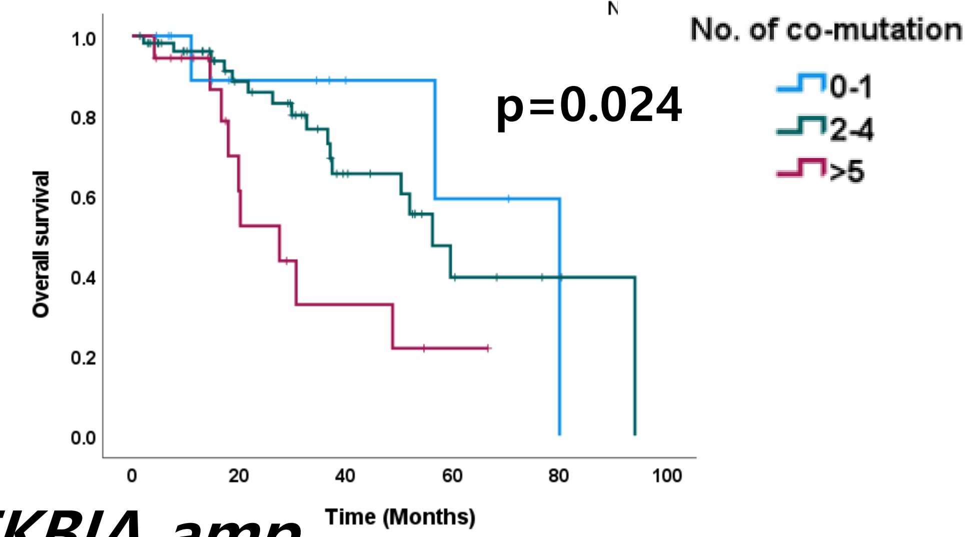
		T790M (+) (%)	**T790M (-) (%)**	***P-value***
	PD =77	30 (38.9)	47 (61.1)	
EGFR type	19del	**21(50)**	21 (50)	0.105
	L858R	10 (31.3)	22 (68.8)	
TP53	TP53	21 (43.8)	27 (56.3)	0.49
	WT	10 (35.7)	18 (64.3)	
CDKN2A/B loss	*CDKN2A/B loss*	**14 (51.9)**	13 (48.1)	0.13
	WT	16 (34.0)	31 (66.0)	
CDK4/6 amp	*CDK4/6 amp*	**6 (60)**	4 (40)	0.18
	WT	25 (38.)	41 (62)	
CCND/CCNE1 amp	*CCND/CCNE1 amp*	2 (22.2)	7 (77.8)	0.23
	WT	28 (43.1)	37 (56.9)	
CCGA*	CCGA	20 (46.5)	23 (53.5)	0.24
	WT	11 (33.3)	22 (66.7)	
CCGA/TP53	*CCGA/TP53*	13 (52.0)	12 (48.0)	0.16
	WT	18 (35.3)	33 (64.7)	
CCGA/TP53/19del	*CCGA/TP53/19del*	9 (75)	3 (25)	**0.009**
	WT	22 (34.4)	42 (65.6)	

***Cell cycle gene alteration(CCGA) defined as CDKN2A/B loss and CDK4/6 amp.**

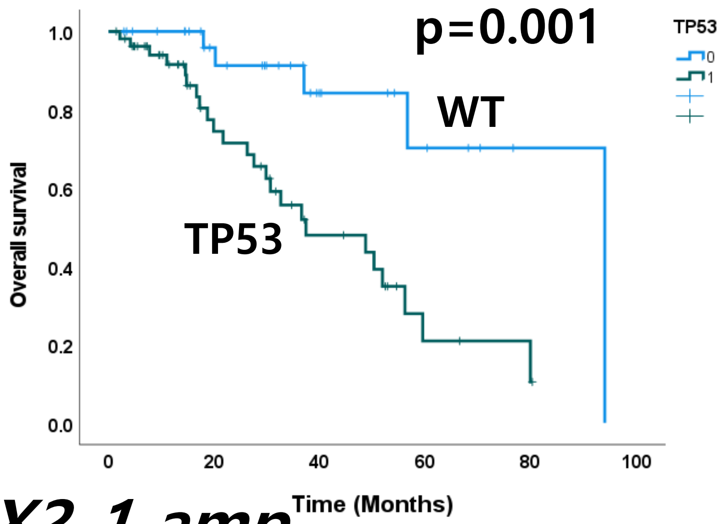
We found the 19del+CDKN2A/B loss+CDK4/6 mutation combination Induced the T790M emergence.

Overall survival according to genetic alteration

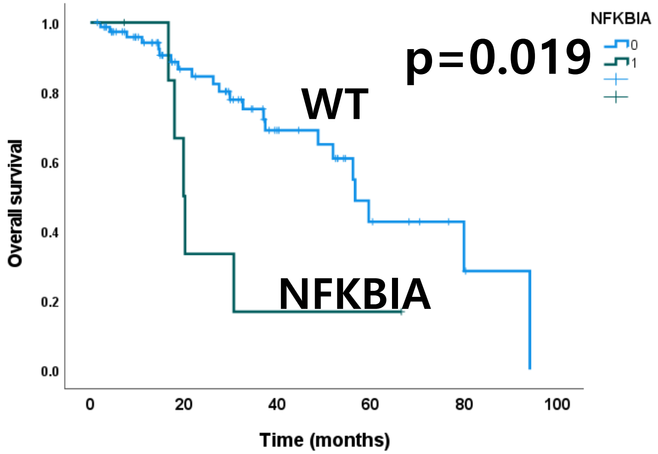
(a) No. of co-mutation



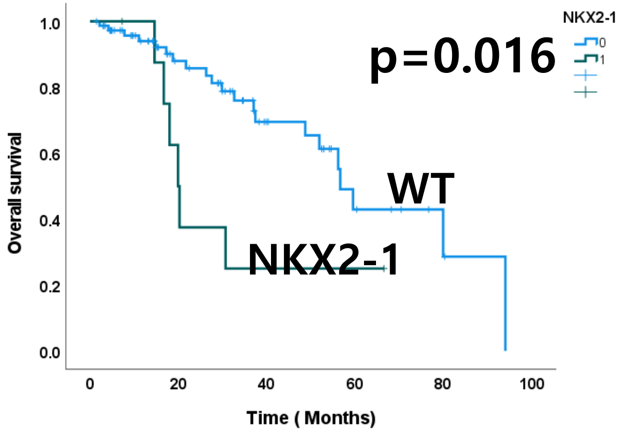
(b) *TP53*



(c) *NFKBIA amp*



(d) *NKX2-1 amp*



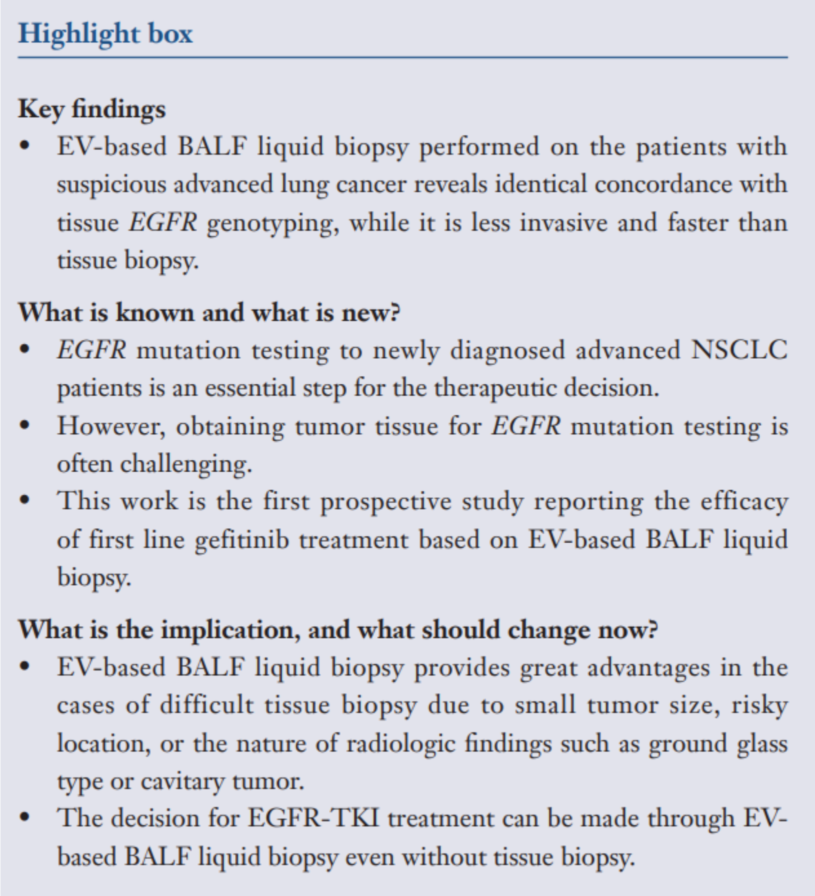
Liquid biopsy

Q:조직 검사 없이 진단하고 치료할 수는 없을까?

- 침습적 조직 검사 대신 BALF-Liquid biopsy
  - Plasma cfDNA

- BALF – Exosome 을 ultracentrifuge 로 추출

- Exosome에서 EGFR mutation DNA 추출- Panamutyper 로 PCR



Highlight box

Key findings

- EV-based BALF liquid biopsy performed on the patients with suspicious advanced lung cancer reveals identical concordance with tissue *EGFR* genotyping, while it is less invasive and faster than tissue biopsy.

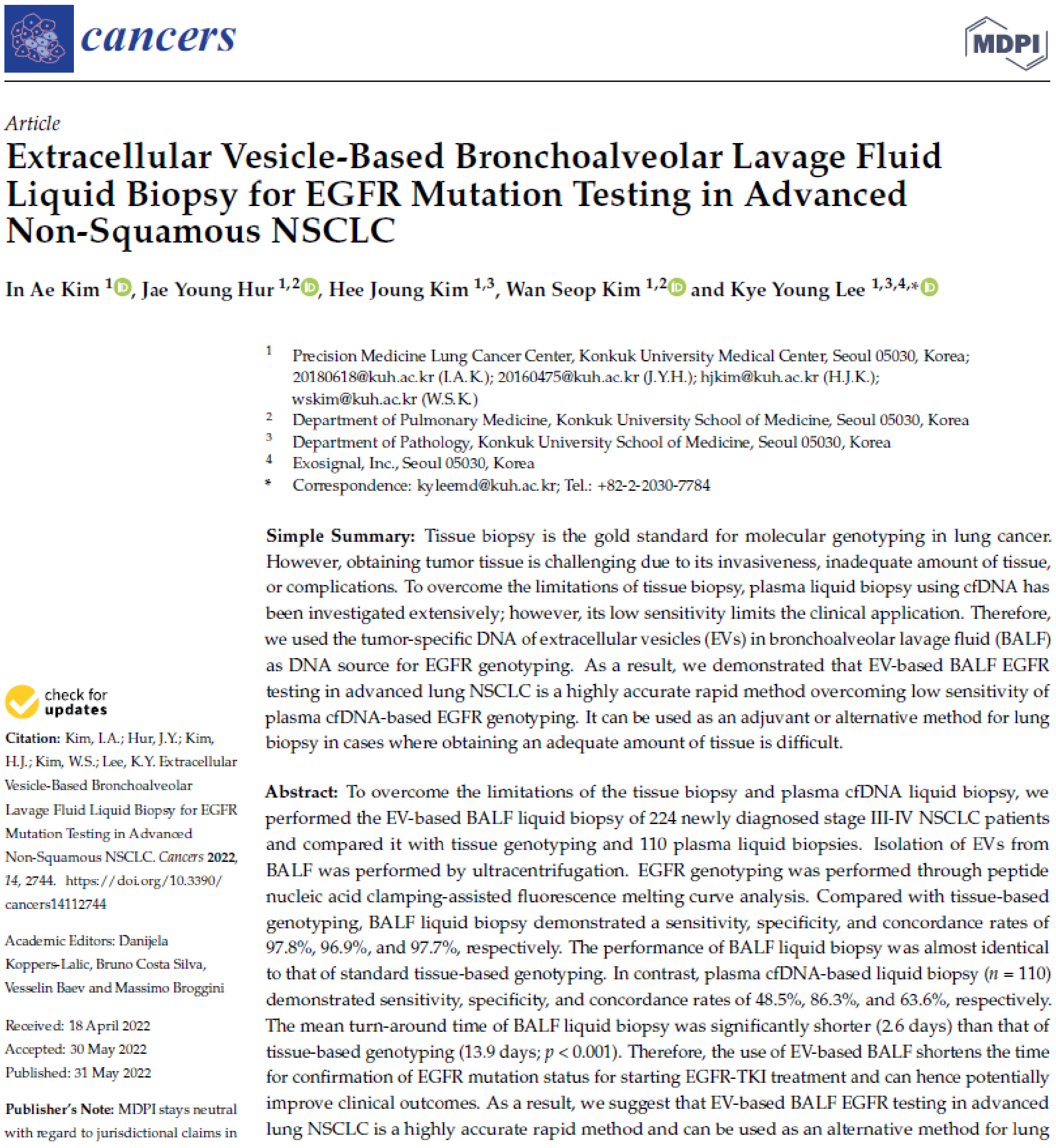
What is known and what is new?

- *EGFR* mutation testing to newly diagnosed advanced NSCLC patients is an essential step for the therapeutic decision.
- However, obtaining tumor tissue for *EGFR* mutation testing is often challenging.
- This work is the first prospective study reporting the efficacy of first line gefitinib treatment based on EV-based BALF liquid biopsy.

What is the implication, and what should change now?

- EV-based BALF liquid biopsy provides great advantages in the cases of difficult tissue biopsy due to small tumor size, risky location, or the nature of radiologic findings such as ground glass type or cavitary tumor.
- The decision for EGFR-TKI treatment can be made through EV-based BALF liquid biopsy even without tissue biopsy.

Diagnosis



cancers

MDPI

Article

Extracellular Vesicle-Based Bronchoalveolar Lavage Fluid Liquid Biopsy for EGFR Mutation Testing in Advanced Non-Squamous NSCLC

In Ae Kim [1], Jae Young Hur [1,2], Hee Joung Kim [1,3], Wan Seop Kim [1,2] and Kye Young Lee [1,3,4,*]

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[2] Department of Pulmonary Medicine, Konkuk University School of Medicine, Seoul 05030, Korea
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Simple Summary: Tissue biopsy is the gold standard for molecular genotyping in lung cancer. However, obtaining tumor tissue is challenging due to its invasiveness, inadequate amount of tissue, or complications. To overcome the limitations of tissue biopsy, plasma liquid biopsy using cfDNA has been investigated extensively; however, its low sensitivity limits the clinical application. Therefore, we used the tumor-specific DNA of extracellular vesicles (EVs) in bronchoalveolar lavage fluid (BALF) as DNA source for EGFR genotyping. As a result, we demonstrated that EV-based BALF EGFR testing in advanced lung NSCLC is a highly accurate rapid method overcoming low sensitivity of plasma cfDNA-based EGFR genotyping. It can be used as an adjuvant or alternative method for lung biopsy in cases where obtaining an adequate amount of tissue is difficult.

Abstract: To overcome the limitations of the tissue biopsy and plasma cfDNA liquid biopsy, we performed the EV-based BALF liquid biopsy of 224 newly diagnosed stage III-IV NSCLC patients and compared it with tissue genotyping and 110 plasma liquid biopsies. Isolation of EVs from BALF was performed by ultracentrifugation. EGFR genotyping was performed through peptide nucleic acid clamping-assisted fluorescence melting curve analysis. Compared with tissue-based genotyping, BALF liquid biopsy demonstrated a sensitivity, specificity, and concordance rates of 97.8%, 96.9%, and 97.7%, respectively. The performance of BALF liquid biopsy was almost identical to that of standard tissue-based genotyping. In contrast, plasma cfDNA-based liquid biopsy ($n = 110$) demonstrated sensitivity, specificity, and concordance rates of 48.5%, 86.3%, and 63.6%, respectively. The mean turn-around time of BALF liquid biopsy was significantly shorter (2.6 days) than that of tissue-based genotyping (13.9 days; $p < 0.001$). Therefore, the use of EV-based BALF shortens the time for confirmation of EGFR mutation status for starting EGFR-TKI treatment and can hence potentially improve clinical outcomes. As a result, we suggest that EV-based BALF EGFR testing in advanced lung NSCLC is a highly accurate rapid method and can be used as an alternative method for lung

check for updates

Citation: Kim, I.A.; Hur, J.Y.; Kim, H.J.; Kim, W.S.; Lee, K.Y. Extracellular Vesicle-Based Bronchoalveolar Lavage Fluid Liquid Biopsy for EGFR Mutation Testing in Advanced Non-Squamous NSCLC. *Cancers* **2022**, *14*, 2744. https://doi.org/10.3390/cancers14112744

Academic Editors: Danijela Koppers-Lalic, Bruno Costa Silva, Vesselin Baev and Massimo Broggini

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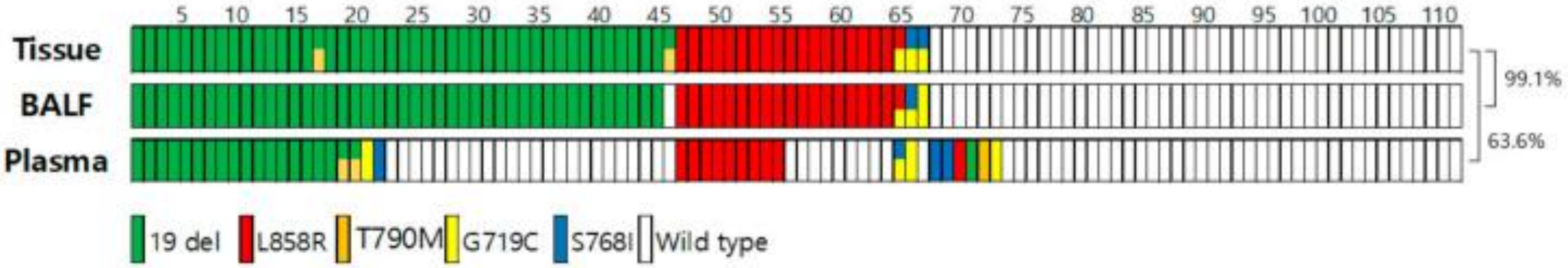
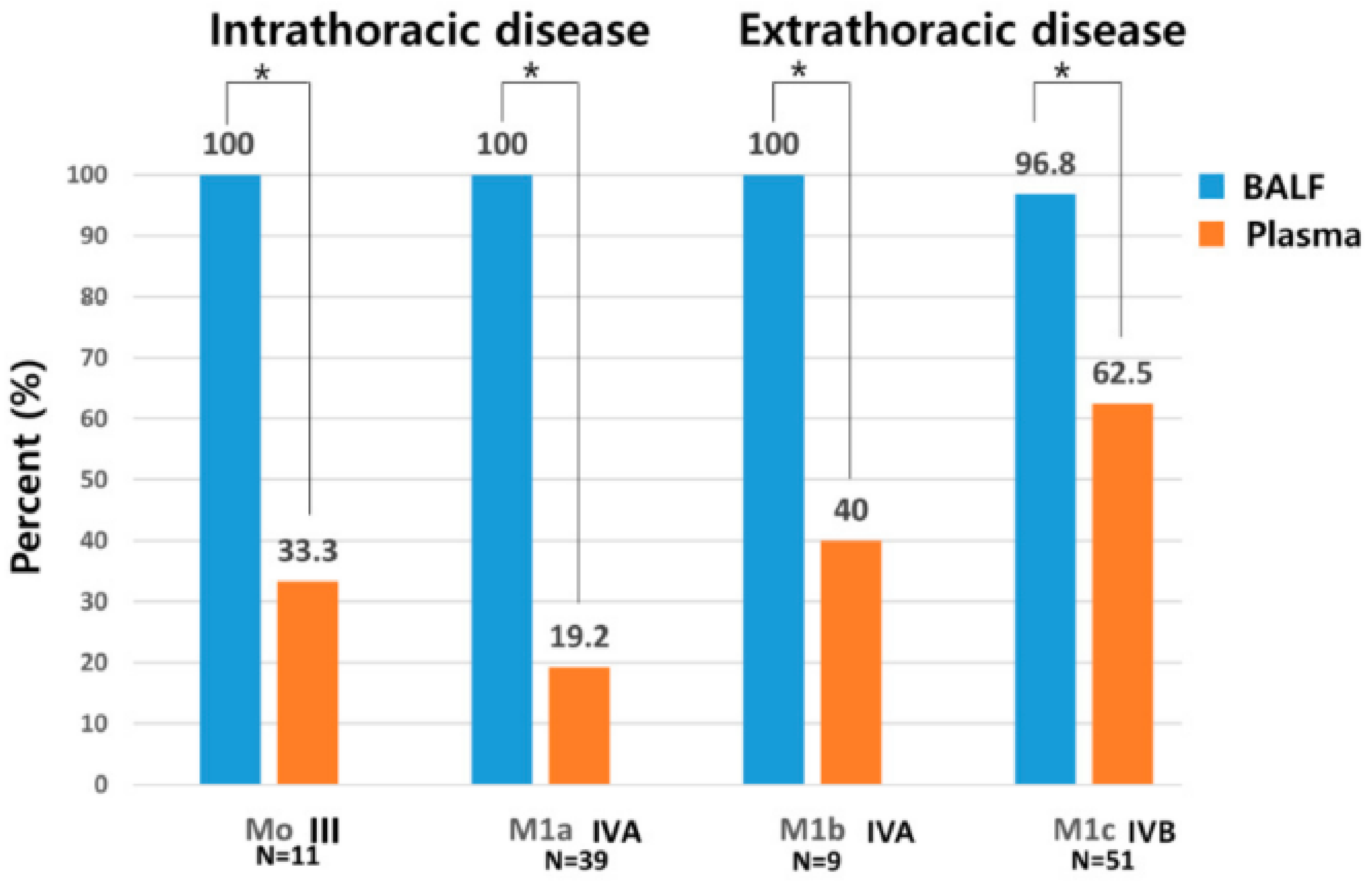
Accepted: 30 May 2022
Published: 31 May 2022

Diagnosis using BALF-liquid bx

EGFR genotype	Tissue	BALF (n=224)		Tissue	plasma (n=110)	
		Mutant type	Wild type		Mutant type	Wild type
Mutant type	93	91	2	66	32	34
Wild type	131	3	128	44	6	38
Sensitivity	**97.8%**(91/93) (95% CI, 92.4-99.7)			**48.5%** (32/66) (95% CI, 36.6-61.1)		
Specificity	**96.9 %** (128/131) (95% CI, 93.5-99.5)			**86.3%** (41/49) (95% CI, 72.6-94.8)		
PPV	**96.8%**(91/94)			**84.2%** (32/38)		
NPV	**98.4%** (128/130)			**52.7%** (38/72)		
Concordance rate	**97.7%** (91+128)/224			**63.6%** (32+38)/110		



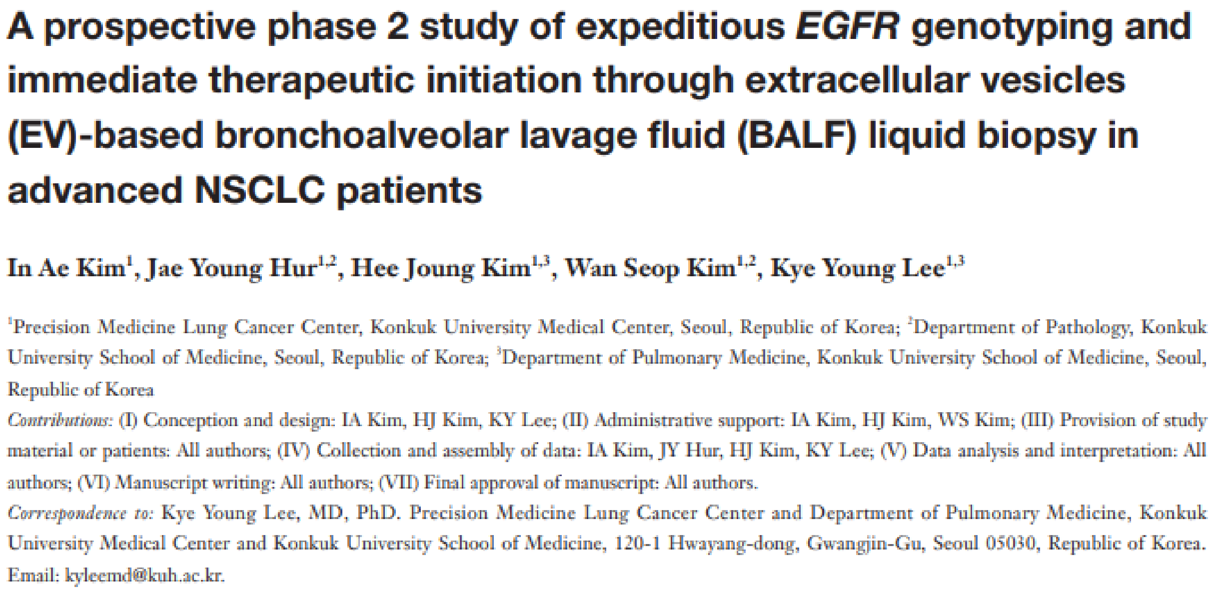
Diagnosis using BALF-liquid bx



* indicates statistic significant difference.

BAL 기술을 이용하여 폐암원발 부위에서 암유전자를 채취하니 혈액의 cfDNA 를 이용한 것보다 민감도가 높아진다

Treatment using BALF-liquid bx



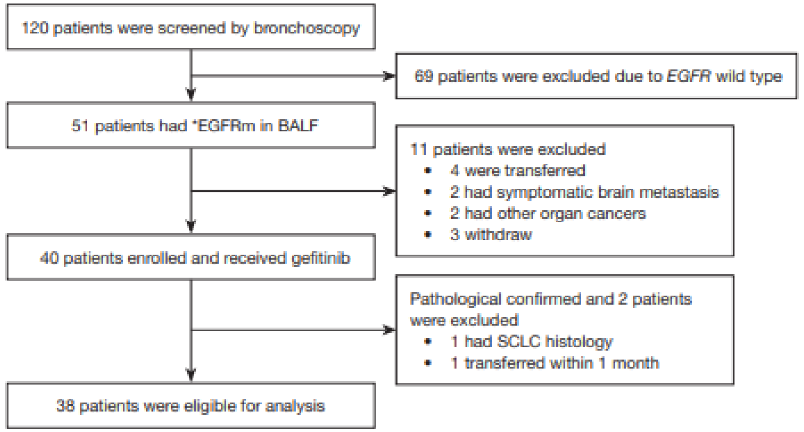
A prospective phase 2 study of expeditious *EGFR* genotyping and immediate therapeutic initiation through extracellular vesicles (EV)-based bronchoalveolar lavage fluid (BALF) liquid biopsy in advanced NSCLC patients

In Ae Kim[1], Jae Young Hur[1,2], Hee Joung Kim[1,3], Wan Seop Kim[1,2], Kye Young Lee[1,3]

[1]Precision Medicine Lung Cancer Center, Konkuk University Medical Center, Seoul, Republic of Korea; [2]Department of Pathology, Konkuk University School of Medicine, Seoul, Republic of Korea; [3]Department of Pulmonary Medicine, Konkuk University School of Medicine, Seoul, Republic of Korea

Contributions: (I) Conception and design: IA Kim, HJ Kim, KY Lee; (II) Administrative support: IA Kim, HJ Kim, WS Kim; (III) Provision of study material or patients: All authors; (IV) Collection and assembly of data: IA Kim, JY Hur, HJ Kim, KY Lee; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Kye Young Lee, MD, PhD. Precision Medicine Lung Cancer Center and Department of Pulmonary Medicine, Konkuk University Medical Center and Konkuk University School of Medicine, 120-1 Hwayang-dong, Gwangjin-Gu, Seoul 05030, Republic of Korea. Email: kyleemd@kuh.ac.kr.



120 patients were screened by bronchoscopy

69 patients were excluded due to *EGFR* wild type

51 patients had *EGFRm in BALF

11 patients were excluded
- 4 were transferred
- 2 had symptomatic brain metastasis
- 2 had other organ cancers
- 3 withdraw

40 patients enrolled and received gefitinib

Pathological confirmed and 2 patients were excluded
- 1 had SCLC histology
- 1 transferred within 1 month

38 patients were eligible for analysis

**EGFR* mutation (EGFRm) had 21L858R, E19Del, L861Q, G719X or rare mutation combination.

Figure 1 The study flow diagram of rapid diagnosis and EGFR-TKI initiation by EV-based BALF liquid biopsy in advanced NSCLC patients. EV, extracellular vesicle; BALF, bronchoalveolar lavage fluid; EGFR, epidermal growth factor receptor; SCLC, small cell lung cancer; TKI, tyrosine kinase inhibitor; NSCLC, non-small cell lung cancer.

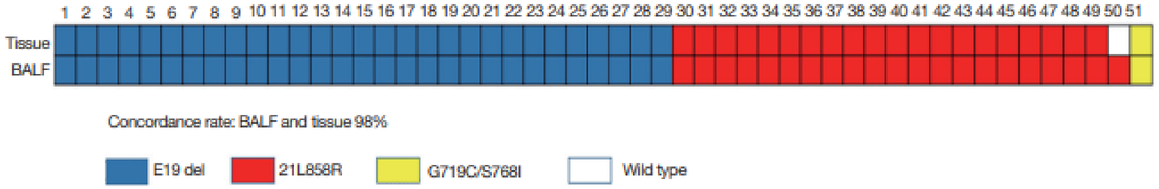


Figure 2 Concordance rate of EV-based BALF liquid biopsy for *EGFR* genotyping to tissue genotyping and plasma liquid biopsy (n=51). EV, extracellular vesicle; BALF, bronchoalveolar lavage fluid; EGFR, epidermal growth factor receptor.

총 120명 스크리닝 하여 BALF EGFR mutation 이 나온 40명의 환자에게 조직 검사 전 gefitinib 투여하면서 치료 반응 관찰
(최종 조직 검사로 EGFR 확인)

Transl Lung Cancer Res 2023;12(7):1425-1435

Treatment using BALF-liquid bx

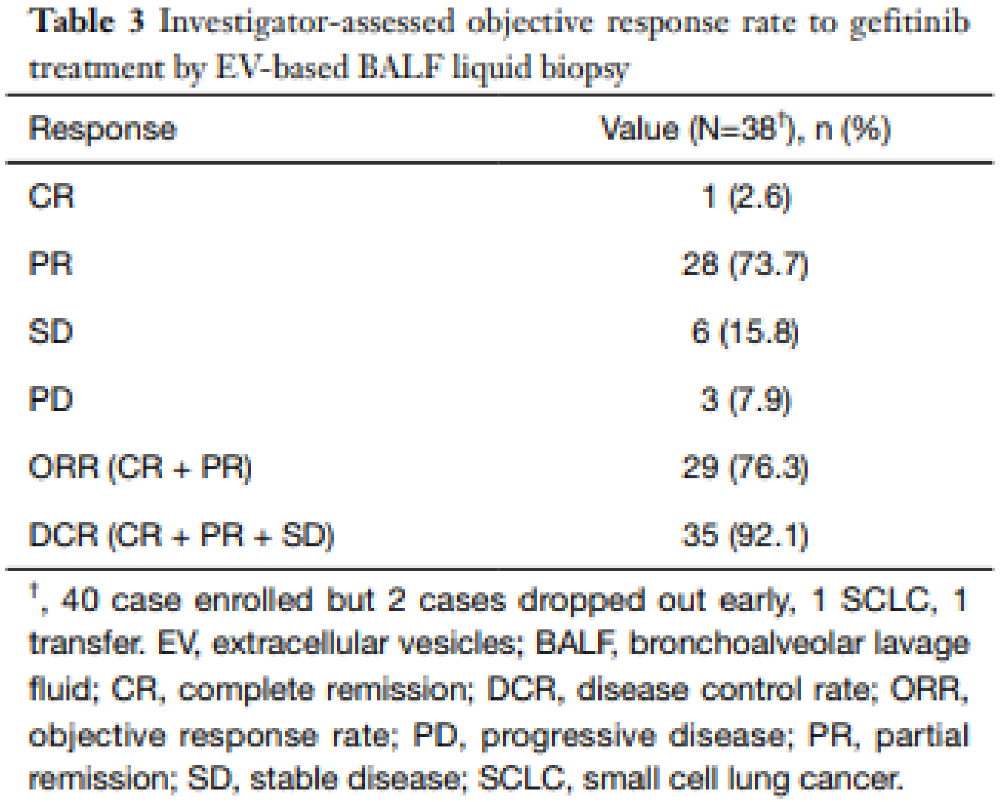


Table 3 Investigator-assessed objective response rate to gefitinib treatment by EV-based BALF liquid biopsy

Response	Value (N=38†), n (%)
CR	1 (2.6)
PR	28 (73.7)
SD	6 (15.8)
PD	3 (7.9)
ORR (CR + PR)	29 (76.3)
DCR (CR + PR + SD)	35 (92.1)

†, 40 case enrolled but 2 cases dropped out early, 1 SCLC, 1 transfer. EV, extracellular vesicles; BALF, bronchoalveolar lavage fluid; CR, complete remission; DCR, disease control rate; ORR, objective response rate; PD, progressive disease; PR, partial remission; SD, stable disease; SCLC, small cell lung cancer.

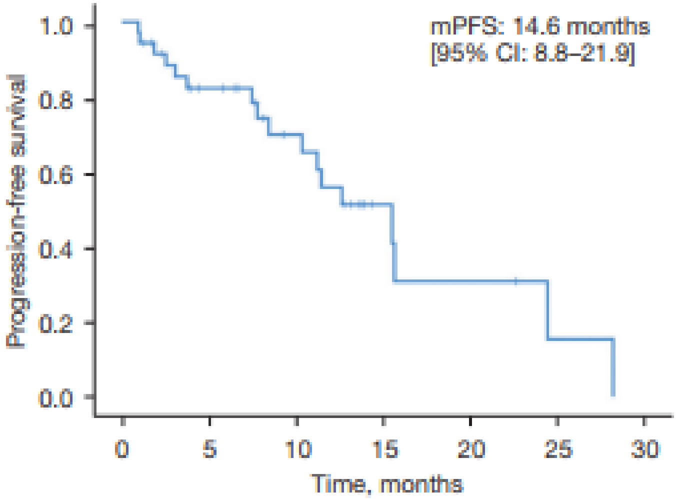
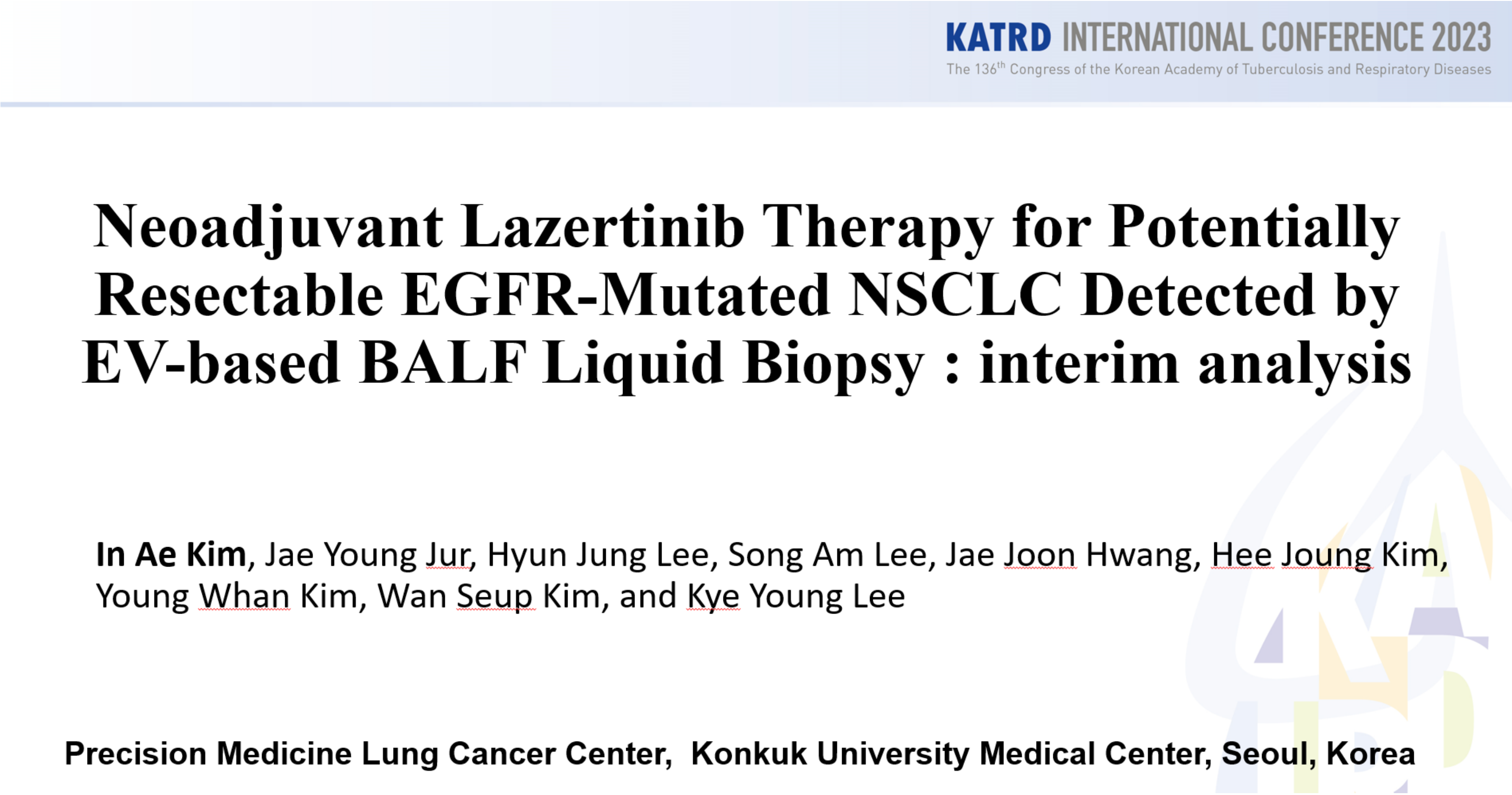


Figure 3 Kaplan-Meier curve of PFS in patients treated by gefitinib based on BALF liquid biopsy (n=38). CI, confidence interval; mPFS, median progression-free survival; PFS, progression-free survival; BALF, bronchoalveolar lavage fluid.

Q: 수술전 TKI 로 치료하고 수술 하면 재발이 줄지 않을까?

- Neoadjuvant EGFR-TKI treatment



KATRD INTERNATIONAL CONFERENCE 2023

The 136th Congress of the Korean Academy of Tuberculosis and Respiratory Diseases

Neoadjuvant Lazertinib Therapy for Potentially Resectable EGFR-Mutated NSCLC Detected by EV-based BALF Liquid Biopsy : interim analysis

In Ae Kim, Jae Young Jur, Hyun Jung Lee, Song Am Lee, Jae Joon Hwang, Hee Joung Kim,
Young Whan Kim, Wan Seup Kim, and Kye Young Lee

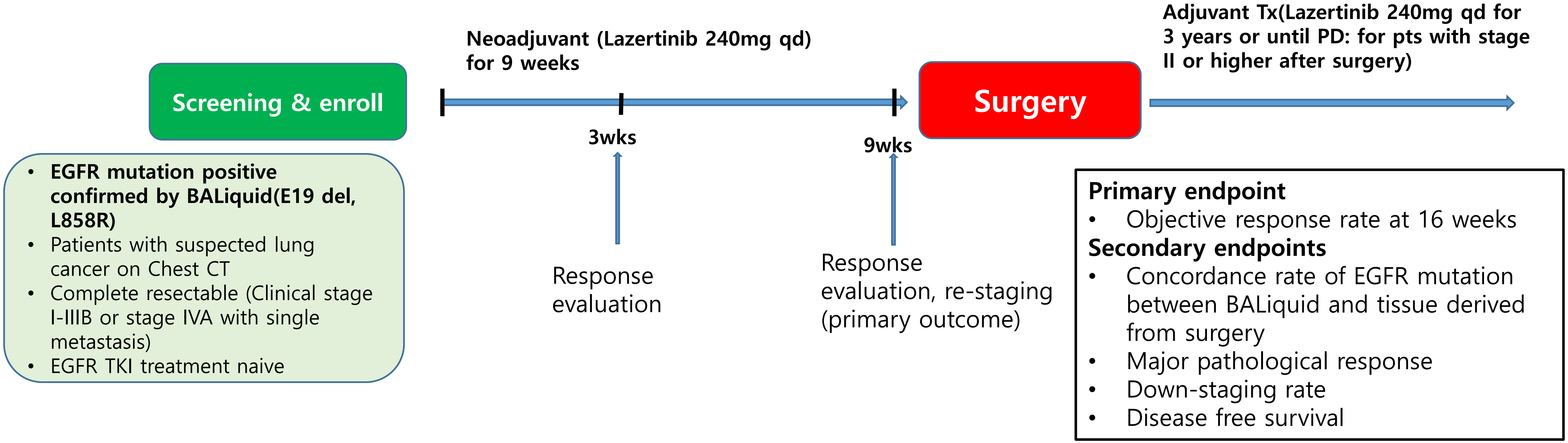
Precision Medicine Lung Cancer Center, Konkuk University Medical Center, Seoul, Korea

Funding

- 연구비 지원 : 유한양행- lazertinib
- IIT – 연구비 save.
- CRO – 비용이 많이 소요. 그러나 편하다.

Study design

Prospective, open-label, double-arm, phase 2 clinical trial



Screening & enroll

- **EGFR mutation positive confirmed by BALiquid(E19 del, L858R)**
- Patients with suspected lung cancer on Chest CT
- Complete resectable (Clinical stage I-IIIB or stage IVA with single metastasis)
- EGFR TKI treatment naive

Neoadjuvant (Lazertinib 240mg qd) for 9 weeks

3wks

Response evaluation

9wks

Response evaluation, re-staging (primary outcome)

Surgery

Adjuvant Tx(Lazertinib 240mg qd for 3 years or until PD: for pts with stage II or higher after surgery)

Primary endpoint

- Objective response rate at 16 weeks

Secondary endpoints

- Concordance rate of EGFR mutation between BALiquid and tissue derived from surgery
- Major pathological response
- Down-staging rate
- Disease free survival

전자민원/보고

전자민원안내 및 신청

민원인이 가정과 사무실에서 편리하게 인터넷, eCTD 민원서식기 등을 이용하여 행정서비스를 이용하실 수 있습니다.
민원신청처리, 진행상황을 SMS, e-mail 등으로 신속하게 알려드립니다.

전자민원 처리절차

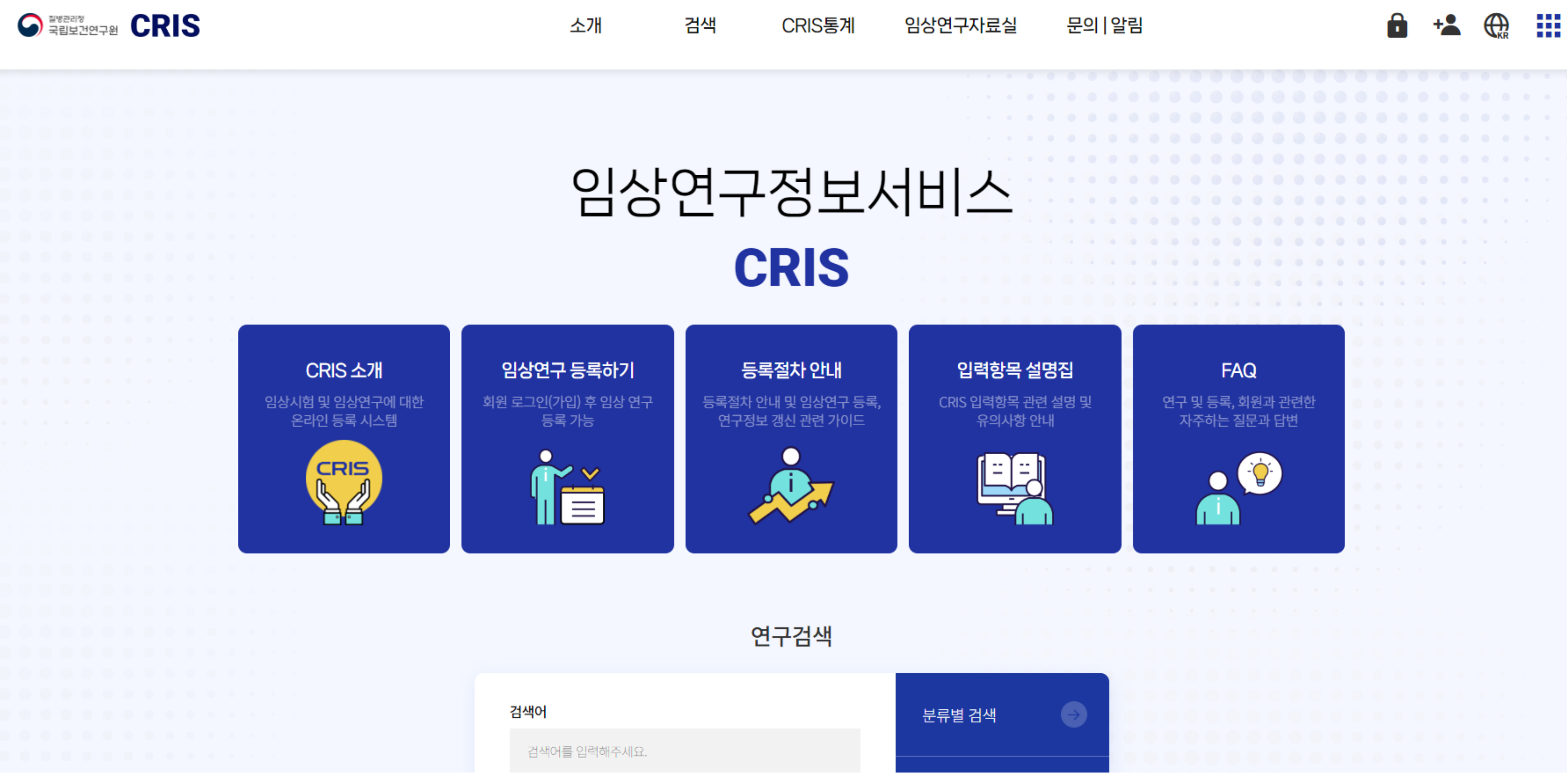
1 민원신청
2 수수료 납부
3 진행상황 확인
4 면허세 납부
5 허가, 신고증 출력

민원/보고 사무 찾기

전자민원/보고를
온라인으로 이용해보세요.

로그인 하시면 나의 민원
진행상황을 확인하실 수 있습니다.

CRIS, Clinical Trial 에 임상연구 등록



CRIS 소개
임상시험 및 임상연구에 대한 온라인 등록 시스템

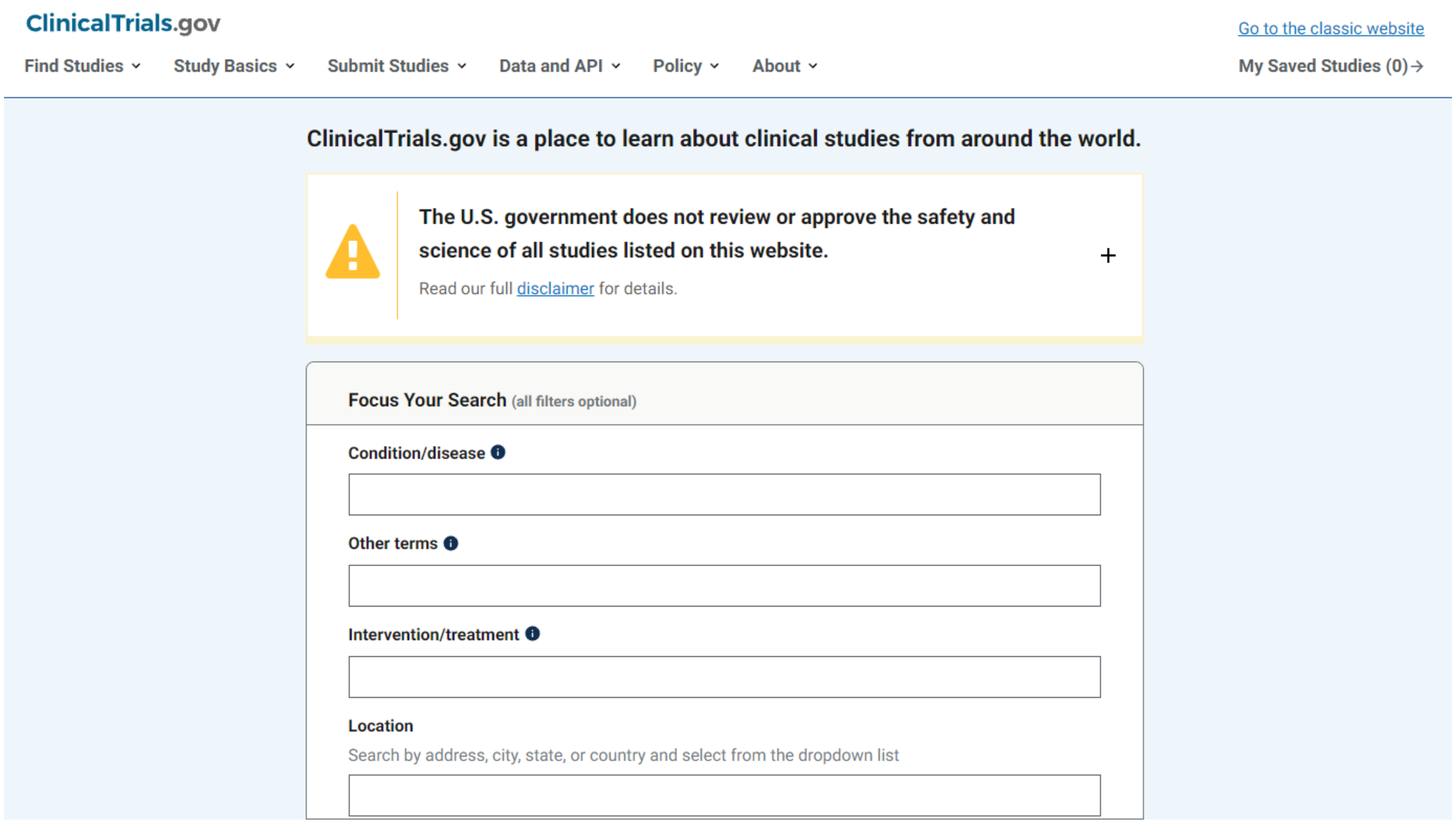
임상연구 등록하기
회원 로그인(가입) 후 임상 연구 등록 가능

등록절차 안내
등록절차 안내 및 임상연구 등록, 연구정보 갱신 관련 가이드

입력항목 설명집
CRIS 입력항목 관련 설명 및 유의사항 안내

FAQ
연구 및 등록, 회원과 관련한 자주하는 질문과 답변

ClinicalTrial.gov



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Other terms

Intervention/treatment

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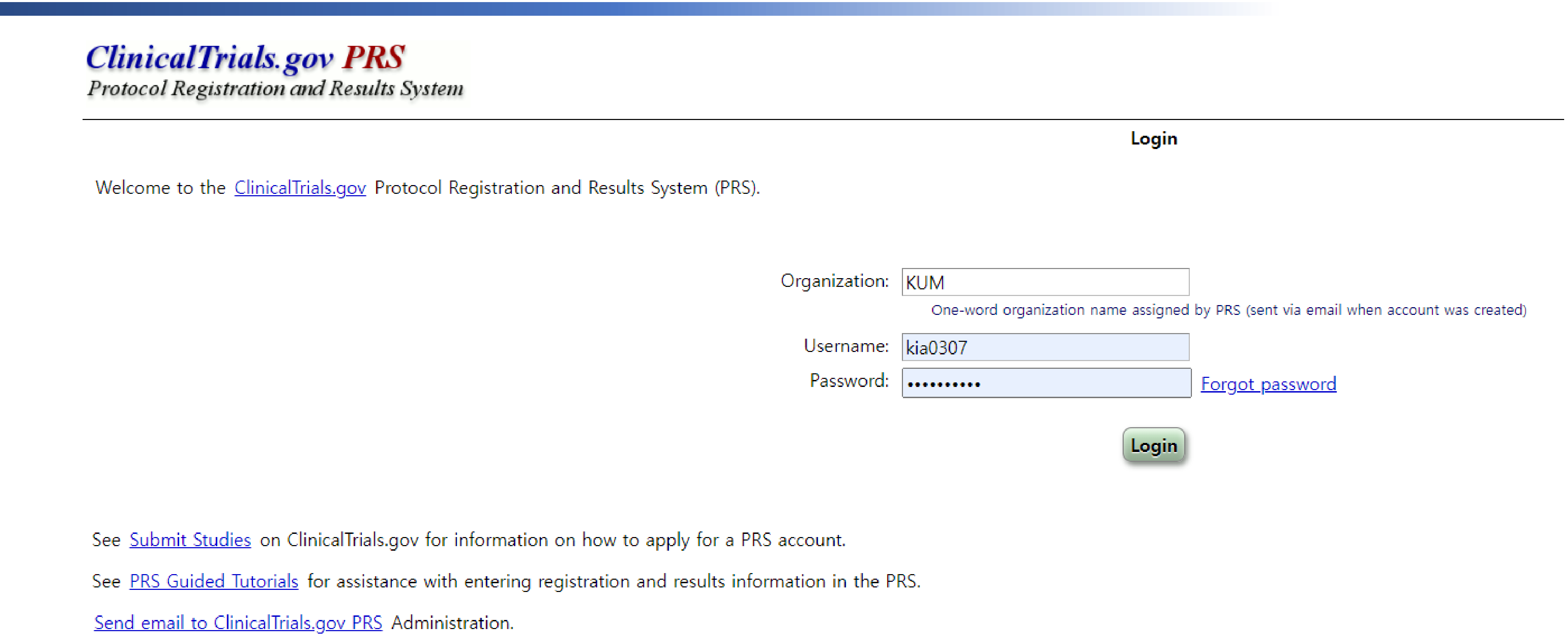

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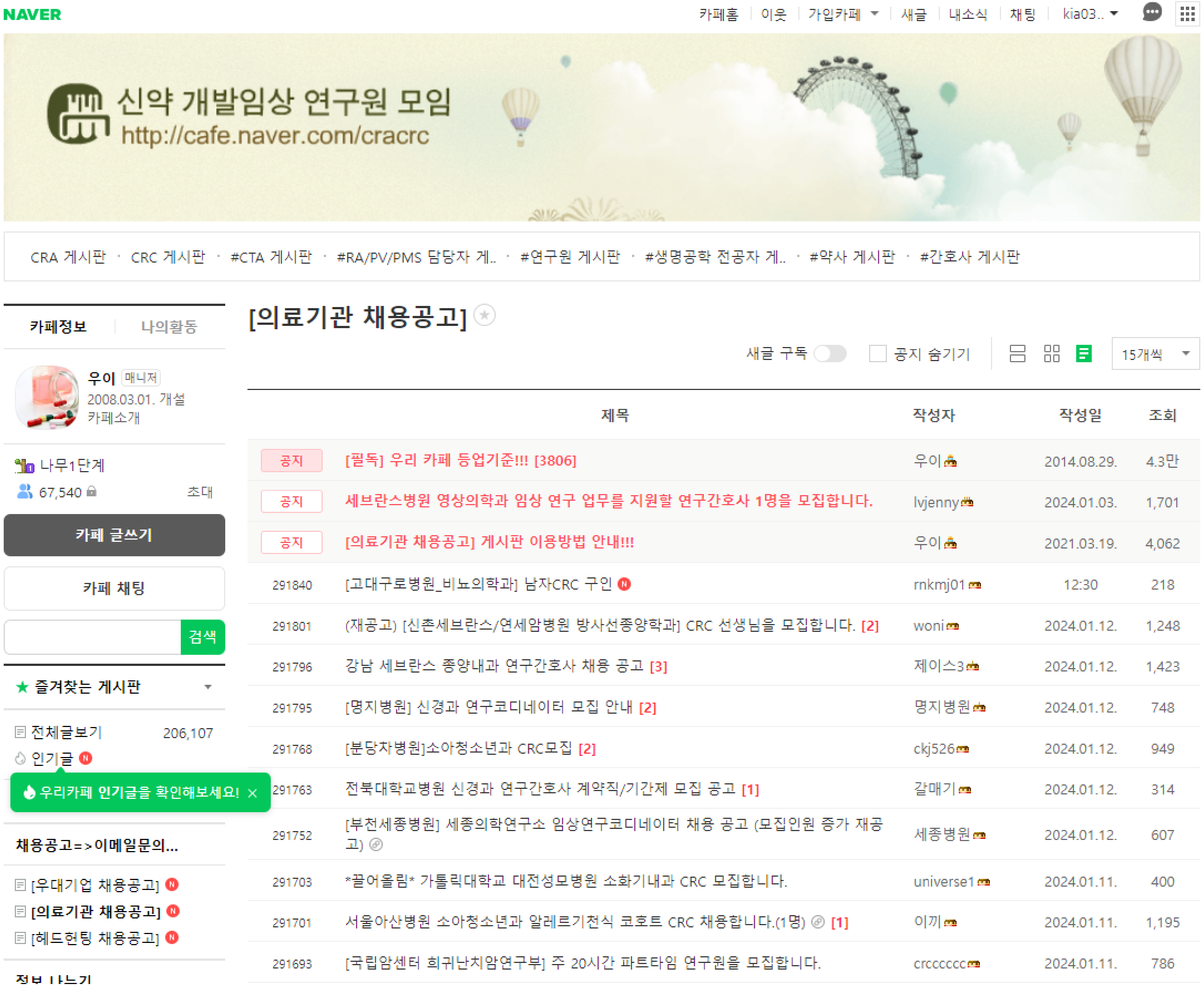


[의료기관 채용공고]

	제목	작성자	작성일	조회
공지	[필독] 우리 카페 등업기준!!! [3806]	우이	2014.08.29.	4.3만
공지	세브란스병원 영상의학과 임상 연구 업무를 지원할 연구간호사 1명을 모집합니다.	lvjenny	2024.01.03.	1,701
공지	[의료기관 채용공고] 게시판 이용방법 안내!!!	우이	2021.03.19.	4,062
291840	[고대구로병원_비뇨의학과] 남자CRC 구인	rnkmj01	12:30	218
291801	(재공고) [신촌세브란스/연세암병원 방사선종양학과] CRC 선생님을 모집합니다. [2]	woni	2024.01.12.	1,248
291796	강남 세브란스 종양내과 연구간호사 채용 공고 [3]	제이스3	2024.01.12.	1,423
291795	[명지병원] 신경과 연구코디네이터 모집 안내 [2]	명지병원	2024.01.12.	748
291768	[분당차병원]소아청소년과 CRC모집 [2]	ckj526	2024.01.12.	949
291763	전북대학교병원 신경과 연구간호사 계약직/기간제 모집 공고 [1]	갈매기	2024.01.12.	314
291752	[부천세종병원] 세종의학연구소 임상연구코디네이터 채용 공고 (모집인원 증가 재공고)	세종병원	2024.01.12.	607
291703	*끌어올림* 가톨릭대학교 대전성모병원 소화기내과 CRC 모집합니다.	universe1	2024.01.11.	400
291701	서울아산병원 소아청소년과 알레르기천식 코호트 CRC 채용합니다.(1명) [1]	이끼	2024.01.11.	1,195
291693	[국립암센터 희귀난치암연구부] 주 20시간 파트타임 연구원을 모집합니다.	crcccccc	2024.01.11.	786

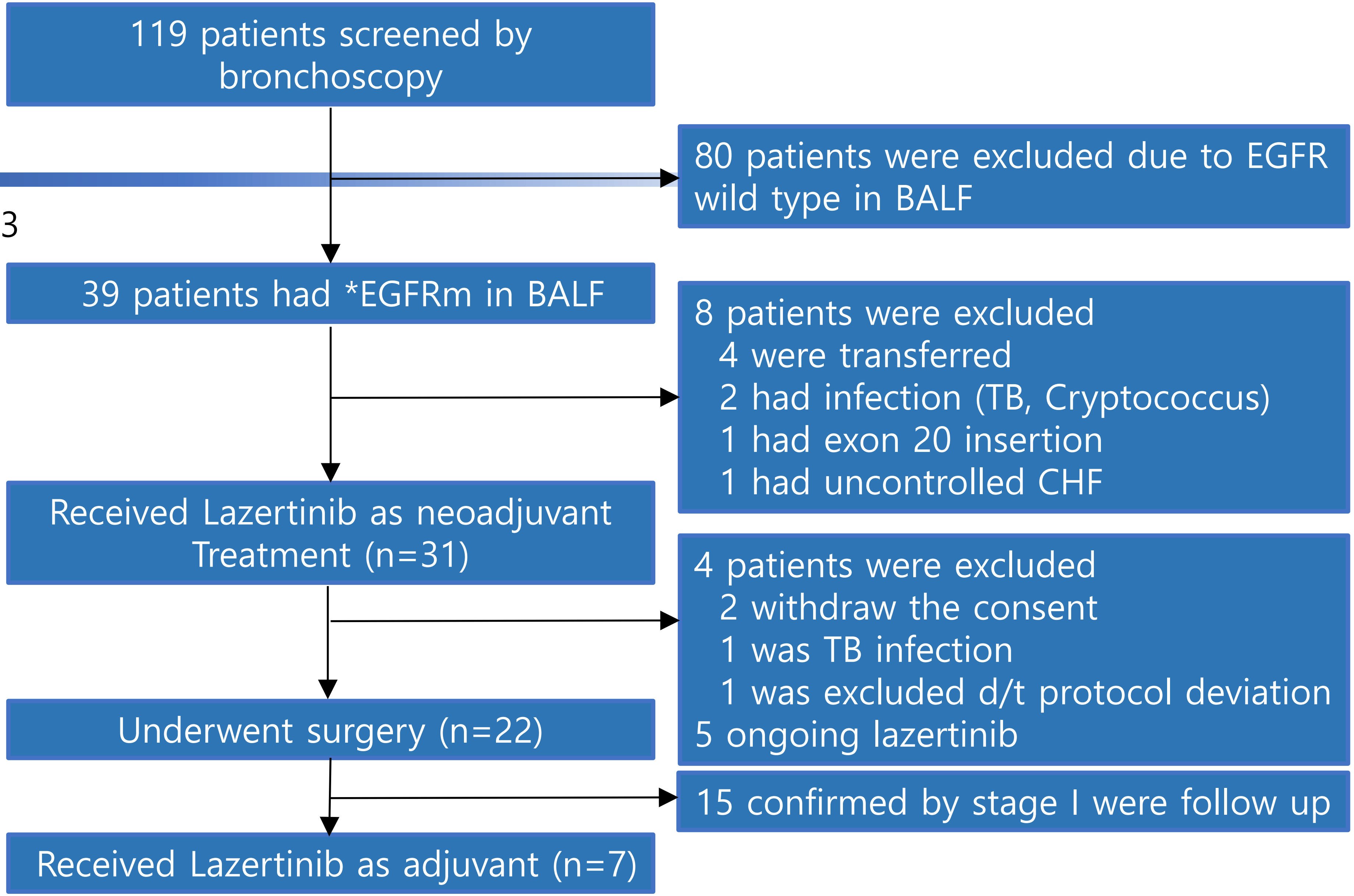
임상연구 요양급여 적용 결정 신청 및 조회

1. 기관(병원)의 요양급여용 인증서를 발급(기관마다 발급되는 기간에 차이가 있습니다.)
2. 요양기관업무포털 https://biz.hira.or.kr 접속
3. 각 기관(병원)의 요양급여용 인증서를 사용하여 로그인

4. 기관의 요양기관 번호 입력

Study Flow

From May 2022 to Oct 2023



119 patients screened by bronchoscopy

80 patients were excluded due to EGFR wild type in BALF

39 patients had *EGFRm in BALF

8 patients were excluded
- 4 were transferred
- 2 had infection (TB, Cryptococcus)
- 1 had exon 20 insertion
- 1 had uncontrolled CHF

Received Lazertinib as neoadjuvant Treatment (n=31)

4 patients were excluded
- 2 withdraw the consent
- 1 was TB infection
- 1 was excluded d/t protocol deviation

5 ongoing lazertinib

Underwent surgery (n=22)

15 confirmed by stage I were follow up

Received Lazertinib as adjuvant (n=7)

*Sensitive EGFR mutation(EGFRm) had 21L858R or E19Del or rare mutation combination.
Abbreviation: BALF, bronchoalveolar lavage; SCLC, small cell lung cancer.

Objective response rate

Response	N =22, N (%)
Partial response	12 (54.5%)
Stable disease	10 (45.5%)
ORR (CR+PR)	12/22 (54.5%)
DCR (CR+PR+SD)	22/22 (100%)

Concordance rate of EGFR mutation in tissue and BALF

EGFR genotype	Tissue	BALF (n=66)	
		Mutant type	Wild type
Mutant type	31	22	9
Wild type	35	0	35
Sensitivity	**70.9 %** (22/31)		
Specificity	**100 %** (35/35)		
PPV	**100 %** (22/22)		
NPV	**77.7 %** (35/44)		
Concordance rate	**86.3 %** (22+35)/66		

Down-staging rate

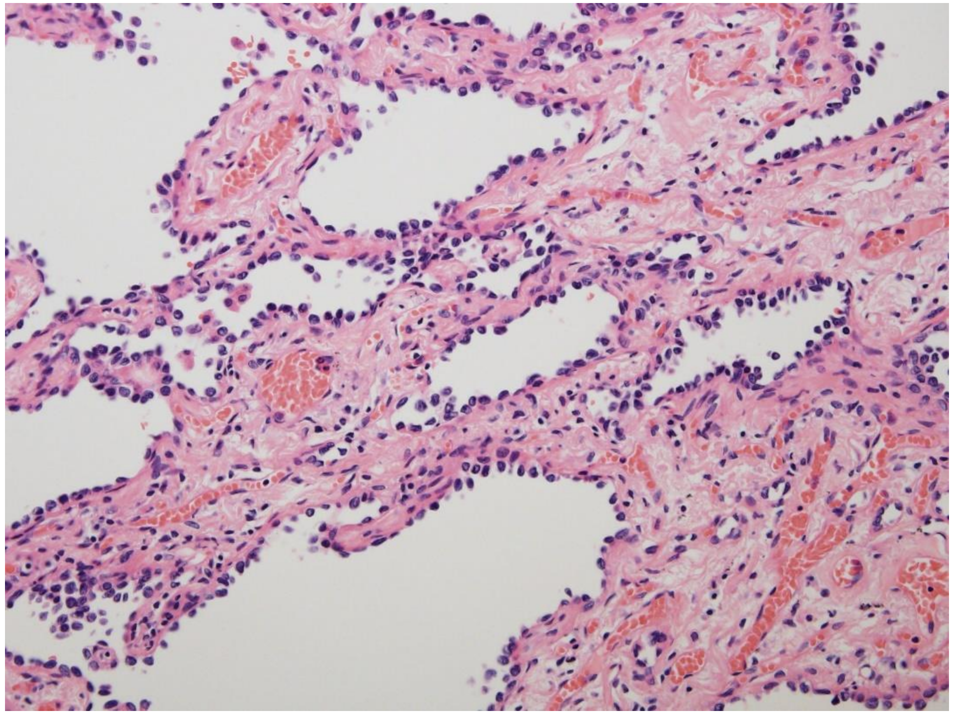
Clinical stage	Pre tissue (N)	Down stage (N)	%
I	14	4	28.5%
II	2	1	50%
III	4	3	75%
IVA	2	1	50%
Total	22	9	**41%**

	Clinical stage	Pathological stage	Down stage
I	1A2	1A1	(T↓)
	1A3	1A1	(T↓)
	IB	1A2	(T↓)
	IB	1A3	(T↓)
II	IIA	1A1	(T↓)
III	IIIB	IIB	(N↓)
	IIIB	IIA	(T↓) (N↓)
	IIIB	1A3	(T↓)(N↓)
IV	IVA	1A3	(T↓)(N↓)

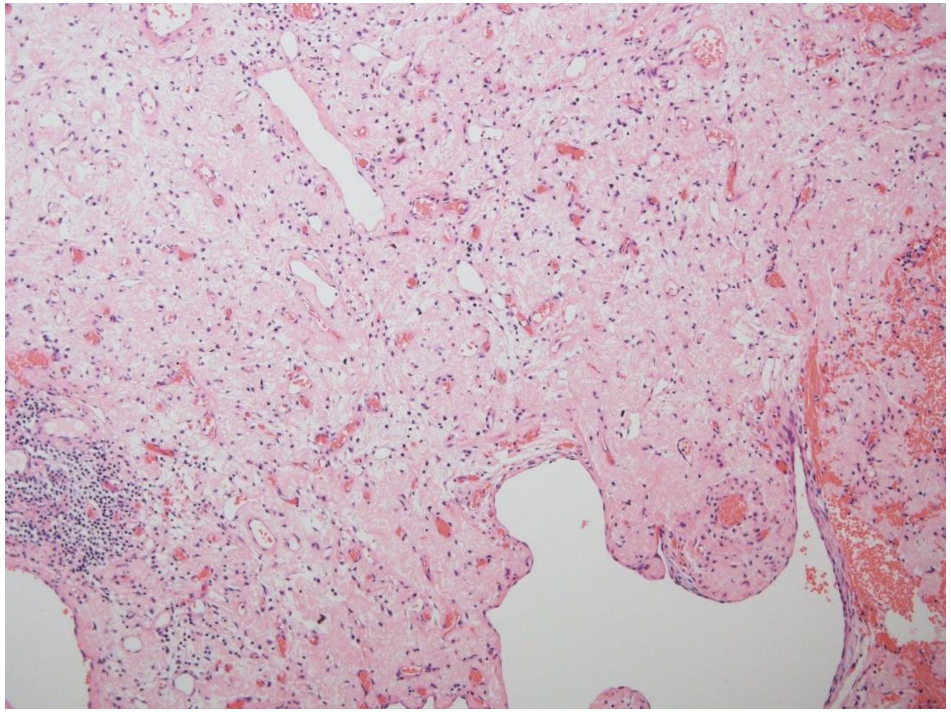
Major pathologic response

4 of 22 (18.2 %), **pCR=0%**

MPR case



Most commonly observed from, tumor cells shrink so gap between cancer cells widen. Cytoplasm is barely visible and the nucleus is pyknotic. Stroma is generally fibrotic and has rare inflammatory cells.



Tumor cell disappeared. In stroma, hemorrhage and lymphocyte infiltration were observed. No Necrosis.

후속 연구

- Neoadjuvant EGFR-TKI 로 치료된 tumor MPR 대체 biomarker 연구 – Cell death assay

- 초기 폐암 진단과 감별 위한 BALF methylation 연구 (시선바이오)

- BALF microRNA 연구

- **2024.04.19 (금):**KUMC lung cancer conference(정보, 토론의 장)

2024 KUMC Precision Medicine Lung Cancer Conference

April 19th (Friday), 2024

건국대학교병원 지하3층 대강당

1:00 – 1:10 Opening

Session 1. Updates in lung cancer biology 좌장 울산의대 이재철

1:10 – 1:40 A minimal sufficient condition for the development of lung cancer
충북의대 배석철

1:40 – 2:10 Pyroptosis: implicating the pathogenesis of recurrent NSCLC
건국대학교신순영

2:10 – 2:40 Autophagy in EGFR-TKI resistance 원자력병원 김철현

Coffee break

Session 2. Early lung cancer diagnosis 좌장 고려의대 이승룡

3:00 – 3:30 Peripheral lung nodule 한림의대 장승훈

3:30 – 4:00 Lung biopsy in peripheral lung nodule 충남의대 박동일

4:00 – 4:30 Management of lung nodule guided by exosome-based liquid biopsy
건국의대 이계영

Coffee break

Session 3. Exosome research in lung cancer 좌장 건국의대 김완섭

4:45 – 5:15 Exosomal proteomics 씨젠의료재단 백제현

5:15 – 5:45 Identification of exosomal microRNA panel as diagnostic and prognostic biomarker for small cell lung cancer 울산의대 노진경

Conclusion

- 현재 치료의 문제점을 인식하고 해결 방안을 모색
  - Fundamental Question 을 해결하는 연구

- 가이드라인을 따라가는 것도 좋지만 개선할 수 있는 연구

- 아이디어를 실천할 수 있는 열정

- 경청해 주셔서 감사합니다.