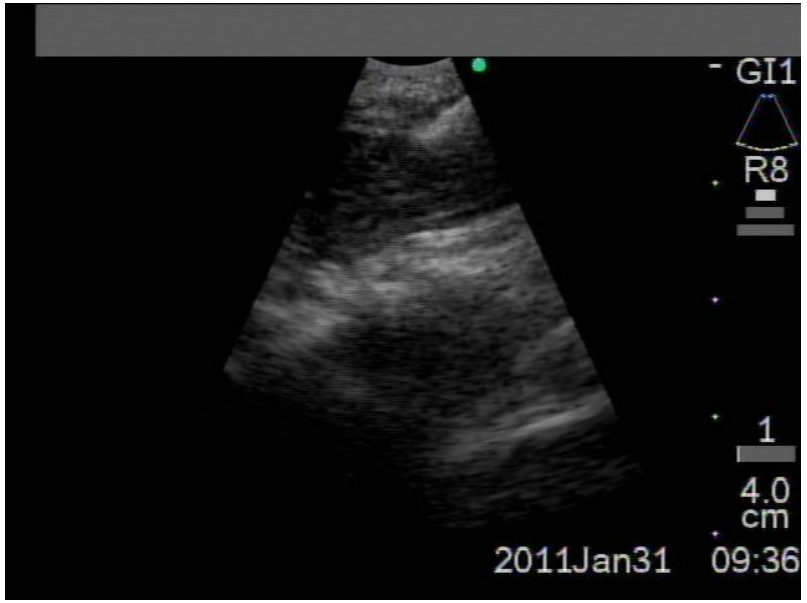
Afatinib 코호트 연구 경험을 통한 제언

고신대학교 복음병원

장 태원

박 00, Female, 56세

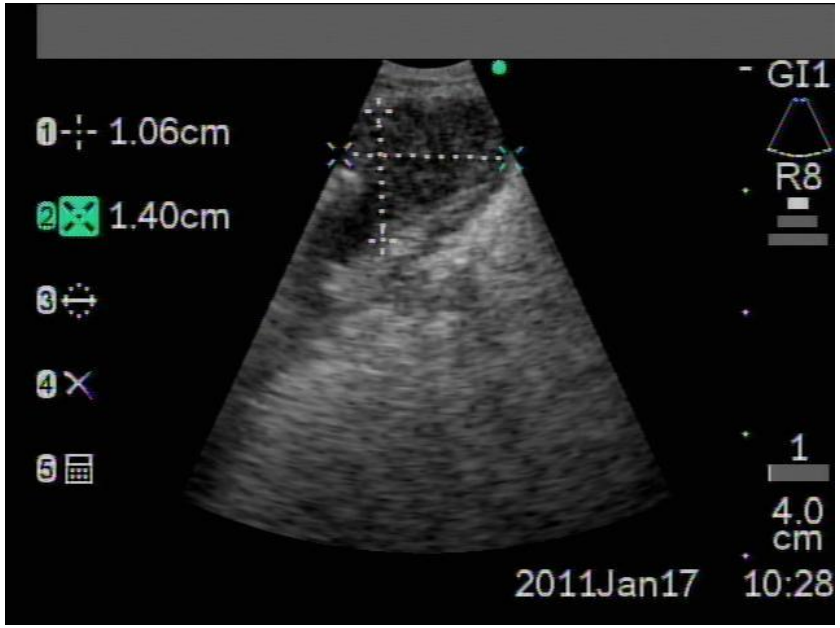
- 2011년 1월 28일
- Lung cancer, adenocarcinoma, stage IVb, C6 vertebrae bone metastasis, ? brain metametasis
- LUX LUNG 6 clinical trial
- EGFR19 del
- Afatinib group
- BSA 1.5 m^2



GIOTRIF® (afatinib) tablets

권 00, Female, 67세

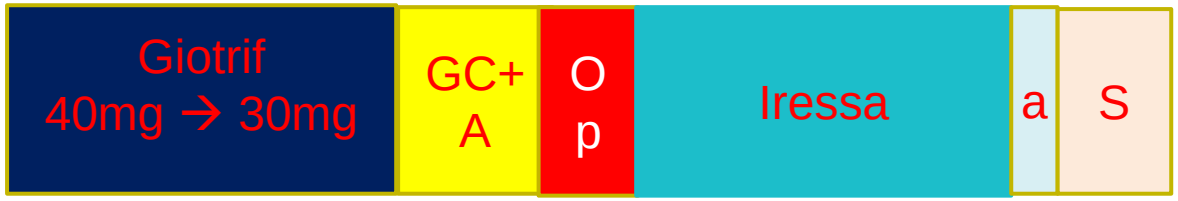
- 2011년 1월 4일
- Lung cancer, adenocarcinoma, stage Ivb, bone, adrenal gland, retroperocadium
- LUX LUNG 6 clinical trial
- L858R
- Afatinib group
- BSA 1.45 m^2



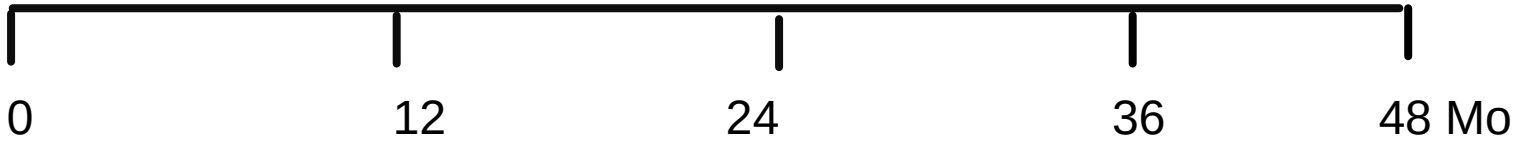
GIOTRIF® (afatinib) tablets

Comparison of two patients

56세, 19del, female, BSA 1.5, 40 month

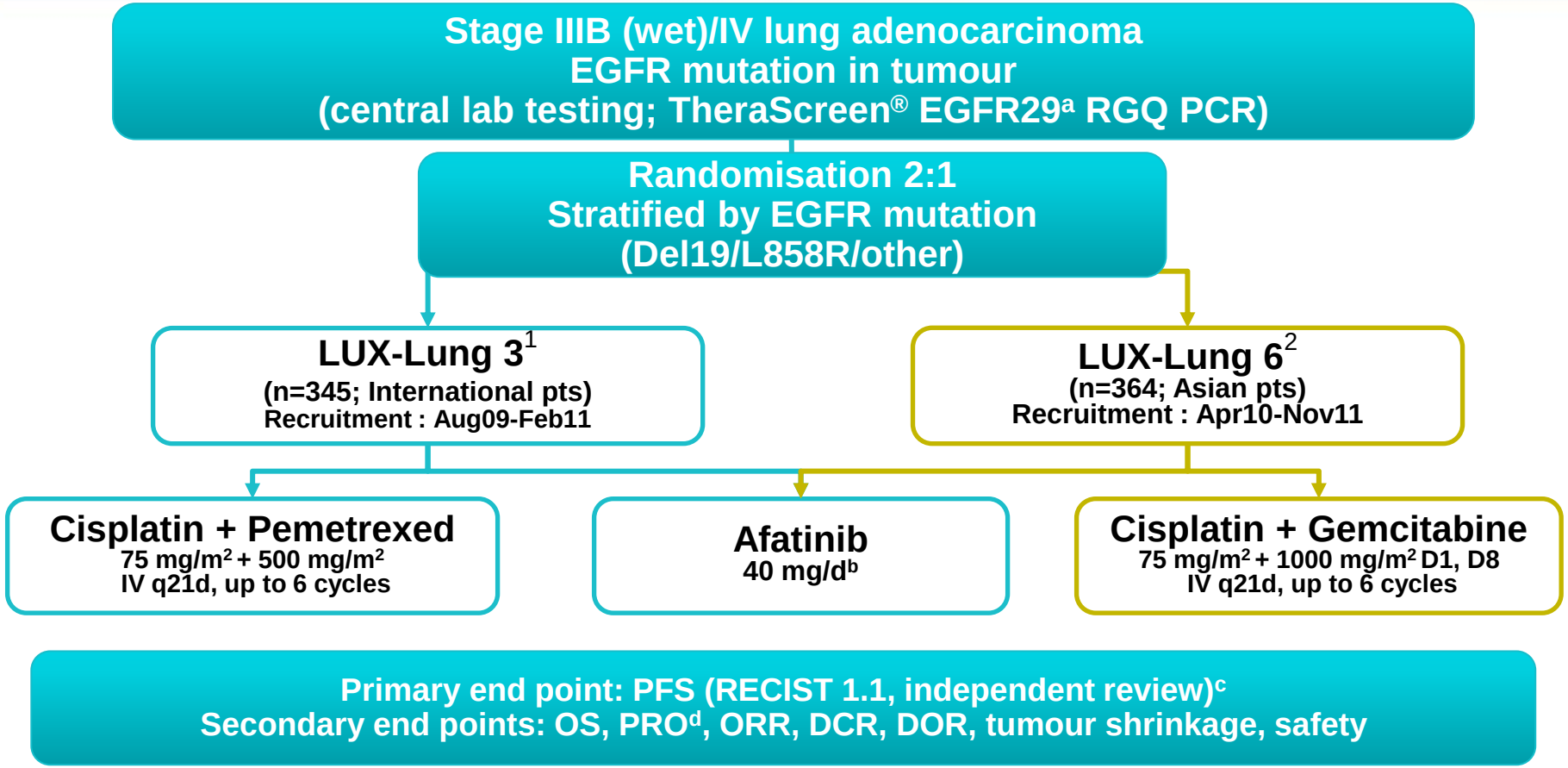


67세, L858R, female, BSA 1.45, 23 month



GIOTRIF® (afatinib) tablets

LUX-Lung 3 and LUX-Lung 6 Study Design



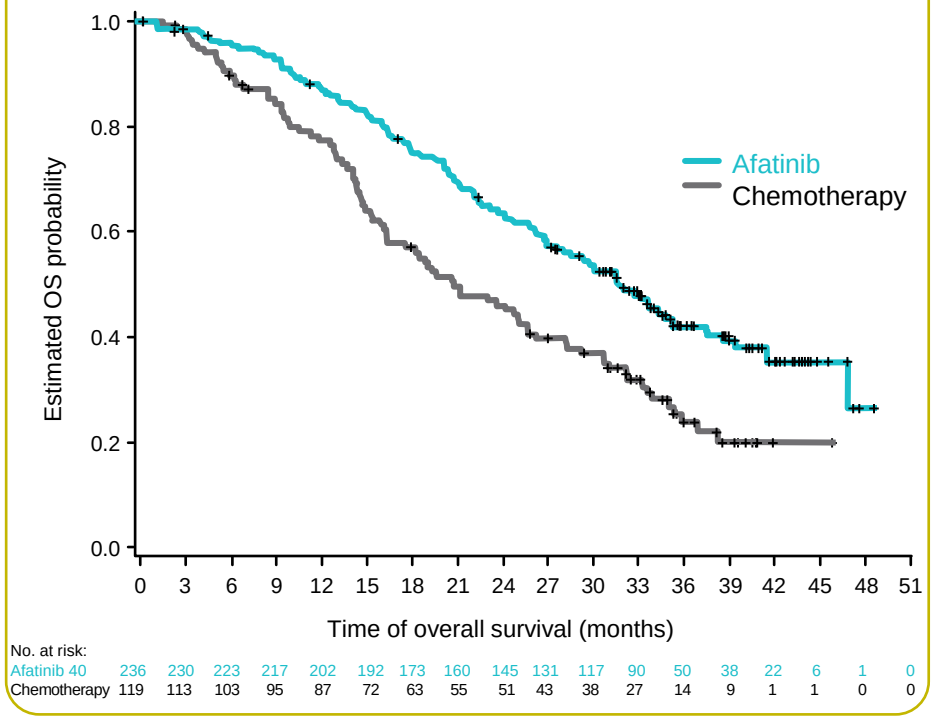
[a]EGFR29: 19 deletions in exon 19, 3 insertions in exon 20, L858R, L861Q, T790M, G719S, G719A and G719C (or G719X), S768I.
[b]Dose escalated to 50 mg if limited AE observed in cycle 1. Dose reduced by 10-mg decrements in case of related G3 or prolonged G2 AE.
[c]Tumour assessments: q6 weeks until week 48 and q12 weeks thereafter until progression/start of new therapy.
[d]Patient-reported outcomes: EQ-5D, EORTC QLQ-C30 and LC 13 at randomisation and q3 weeks until progression or new anticancer therapy.
Note: 24 patients in LUX-Lung 3 and 28 patients in LUX-Lung 6 were still on treatment as of December 2013.
RGQ = rotor-gene Q; PCR = polymerase chain reaction; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours; ORR = objective response rate; DCR = disease control rate; DOR = duration of response; OS = overall survival.

1. Sequist et al. *J Clin Oncol*. 2013;31:3327; 2. Wu et al. *Lancet Oncol*. 2014;15:213.

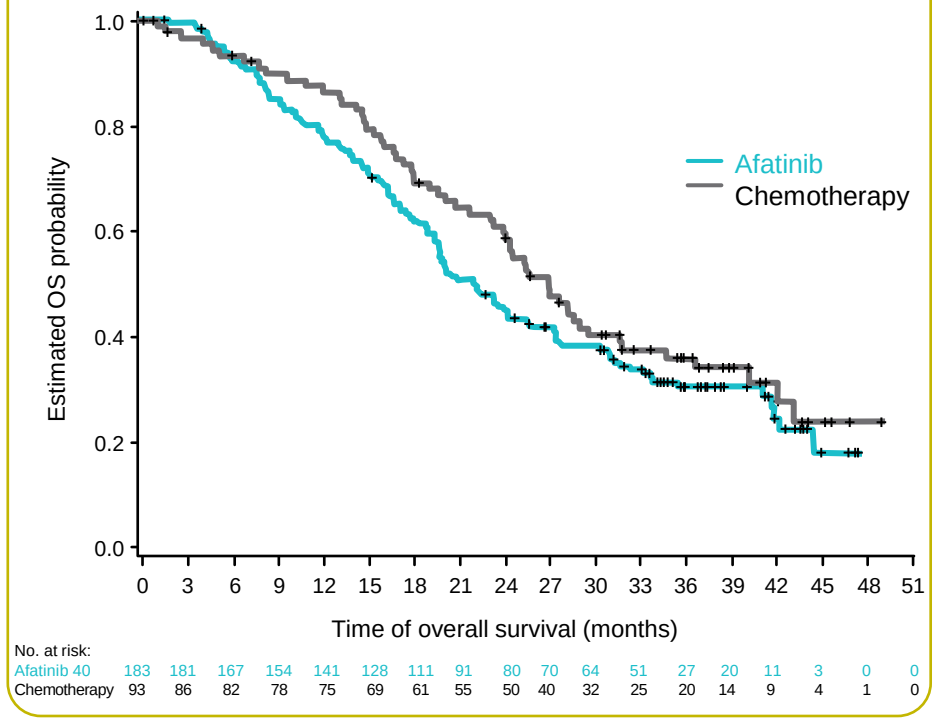
GIOTRIF® (afatinib) tablets

Exploratory Combined OS Analysis: Del19 and L858R Subgroups

Del19



L858R



	Del19		L858R	
	Afatinib (n=236)	Chemo (n=119)	Afatinib (n=183)	Chemo (n=93)
Median, months	**31.7**	**20.7**	**22.1**	**26.9**
HR (95% CI), ***P*-value**	**0.59** (0.45-0.77), ***P*=0.0001**		**1.25** (0.92-1.71), ***P*=0.1600**	

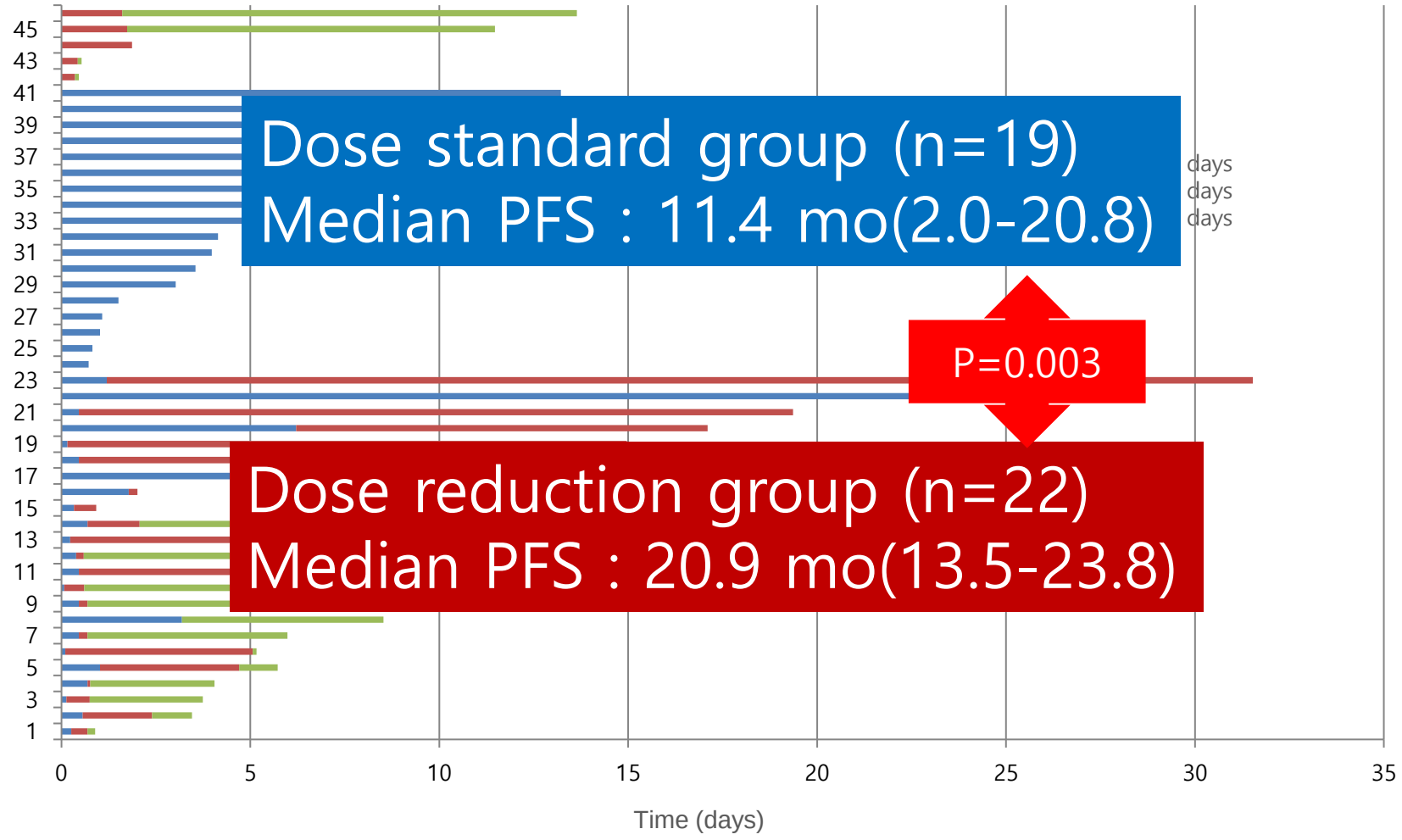
Presented by Yang et al. ASCO 2014. Abstract 8004.

GIOTRIF® (afatinib) tablets

Real World Experience with Afatinib in KMC

- Patients with EGFRm+ NSCLC who started first-line afatinib treatment between Jan 2015 and Sep 2017.
- Forty six patients were available for analysis among all 62 patients (1^{st} to 8^{th} line chemotherapy)
- At the time of data analysis in 22 September 2017, twenty-four of patients (52 %) were still on afatinib

Treatment Duration and Afatinib Dose Level



RWE PLUS AdBoard Meeting

Pulmonologists LUng Cancer Study

Venue: Lotte Hotel World, Jamsil, Seoul

Time: 08:00 – 12:00, 22 Nov 2018

Chaired by Prof Taewon Jang & Dr Luke Lin

BI ROPU SEASK MA Oncology

Real-World Evidence PLUS AdBoard Meeting
Pulmonologists LUng Cancer Study
A g e n d a

From	To	Topic	Presenter
08:00	08:35	Welcome, introduction, meeting objectives	Prof Taewon Jang
08:35	08:55	Asian afatinib real world evidence (RWE) and realGiDo/GioTaq data	Dr Luke Lin
08:55	09:20	Multi-center RWE generation on treatment with EGFR TKIs	Prof Taewon Jang
09:20	09:50	Electronic Case Report Form (eCRF)	Prof Chang-min Choi
09:50	10:10	Status of afatinib RWE cohort from multi-center setting	Prof Sung Yong Lee
10:10	10:30	Coffee break	All
10:30	11:15	Society introduction and plan for national RWE • Malaysia (15 min) • Indonesia (15 min) • Thailand (15 min)	Dr Dr Poh Mau Ern Dr Suryanti Dwi Pratiwi Prof Anakapong Phunmanee
11:15	12:15	Discussion	All
12:15	12:30	Closing remarks	Prof Taewon Jang

2nd Real-World Evidence PLUS AdBoard Meeting

Pulmonologists LUng Cancer Study

Venue: Doubletree Hotel, The Intermark, Kuala Lumpur
Time: 09:00 – 15:00, 27th Apr 2019

Chaired by Prof Taewon Jang & Dr Luke Lin

From	To	Topic	Presenter
09:00	09:10	Welcome, introduction, meeting objectives	Prof Taewon Jang
09:10	09:40	Update on collaboration and publication of Asian afatinib real world evidence (RWE)	Dr Luke Lin
09:40	10:12	Overall update on KMLS and EGFR cohort study	Prof Taewon Jang/ Prof Chang-min Choi
10:20	10:50	Update on afatinib RWE cohort from multi-center setting	Prof Sung Yong Lee
10:50	11:10	***Coffee break***	All
11:10	11:40	Update on local EGFR cohort study from Indonesia	Prof Elisna Syahruddin
11:40	12:10	Update on local EGFR cohort study from Malaysia	Prof Soon Hin How
12:10	12:40	Update on local EGFR cohort study from Thailand	Prof Anakapong Phunmanee
12:40	13:40	***Lunch***	All
13:40	14:50	Discussion on challenges and supports	All
14:50	15:00	Closing remarks	Prof Taewon Jang

MEGIC eCRF User Manual

Prof Chang-Min Choi

Asan Medical Center
Seoul, Korea

Test Site http://katrd.crf.kr/

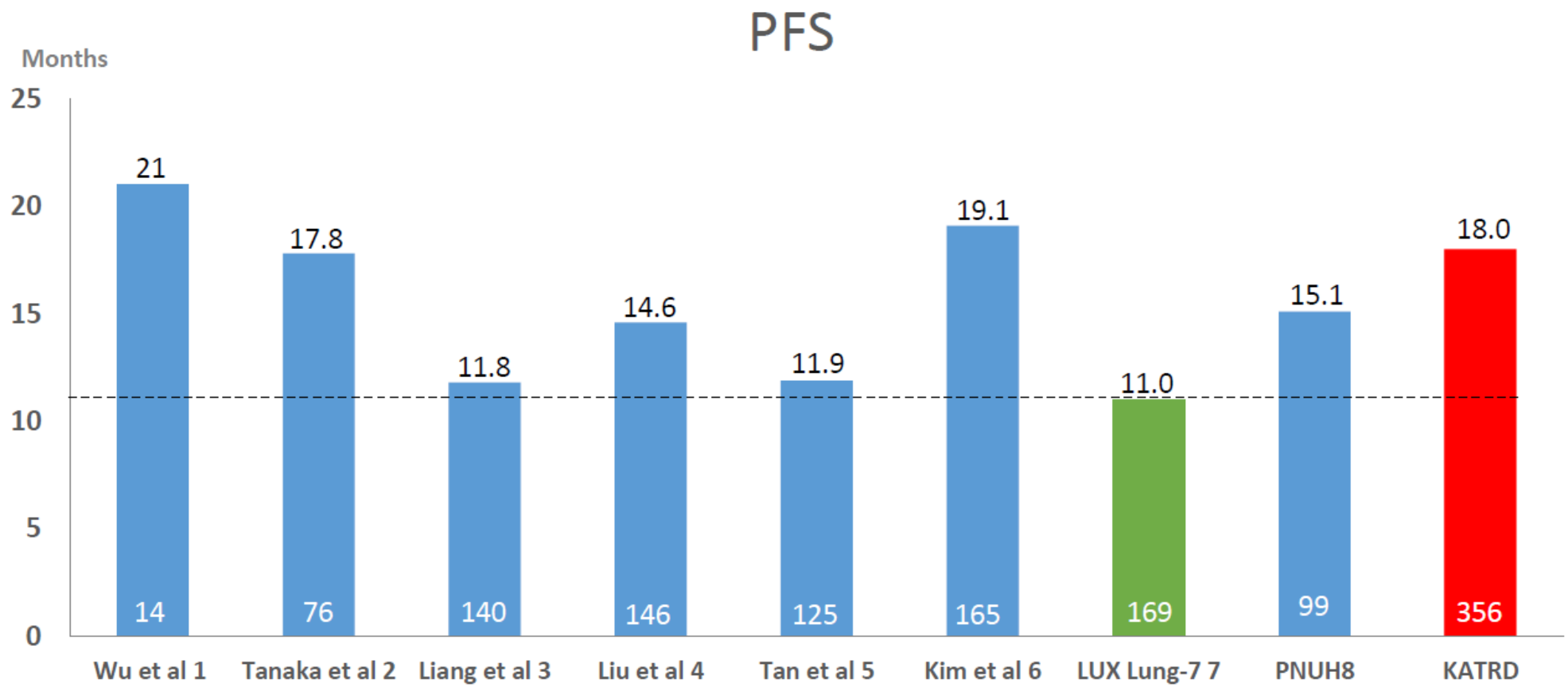
Real World Experience of Afatinib as a First Line Therapy for Advanced EGFR (+) Lung Cancer in KOREA

Sung Yong Lee – MD. PhD.

Korea University Guro Hospital

Comparison of PFS of 1st-line Afatinib Real-world Data

Real-world data show more prolonged PFS



1. Wu SG et al., Oncotarget 2016;7(11):12404-13; 2. Tanaka K et al., JCO 2018(e21173); 3. Liang SK et al., Oncotarget 2017;8(52):90430-90443; 4. Liu CY et al., Oncotarget 2017;8(57):97602-976127; 5. Tan WL et al., CSCO 2017 (poster# B0129); 6. Kim YJ et al., WCLC 2017 (poster# P3.01-023). *Unpublished data from Dr WL Tan, NCC, Singapore. 7. Park Kc et al., Lancer Oncology 2016;17(5):577-89. 8. Yeon SH. Unpublished data.

.


REAL WORLD EVIDENCE PLUS ADVISORY BOARD MEETING
27 APRIL 2019 KUALA LUMPUR

Original Article

Real-world experience of afatinib as first-line therapy for advanced *EGFR* mutation-positive non-small cell lung cancer in Korea

Sung Yong Lee[1#], Chang-Min Choi[2#], Yoon Soo Chang[3], Kye Young Lee[4], Seung Joon Kim[5], Sei Hoon Yang[6], Jeong Seon Ryu[7], Jeong Eun Lee[8], Shin Yup Lee[9], Ji Young Park[10], Young-Chul Kim[11], In-Jae Oh[11], Chi Young Jung[12], Sang Hoon Lee[13], Seong Hoon Yoon[14], Juwhan Choi[1], Tae Won Jang[15]

[1]Korea University Guro Hospital, Seoul, South Korea; [2]Ulsan University Asan Medical Center, Seoul, South Korea; [3]Yonsei University Gangnam Severance Hospital, Seoul, South Korea; [4]Konkuk University Medical Center, Seoul, South Korea; [5]Catholic University Seoul St. Mary's Hospital, Seoul, South Korea; [6]Wonkwang University Hospital, Iksan, South Korea; [7]Inha University Hospital, Incheon, South Korea; [8]Chungnam National University, Daejeon, South Korea; [9]Kyungpook National University Chilgok Hospital, Daegu, South Korea; [10]Hallym University Sacred Heart Hospital, Anyang, South Korea; [11]Chonnam National University Medical School and Hwasun Hospital, Hwasun, South Korea; [12]Daegu Catholic University Medical Center, Daegu, South Korea; [13]Yonsei University Severance Hospital, Seoul, South Korea; [14]Pusan National University Yangsan Hospital, Yangsan, South Korea; [15]Kosin University Gospel Hospital, Busan, South Korea

Contributions: (I) Conception and design: YS Chang, JS Ryu, SY Lee, JY Park, CY Jung, SH Lee, SH Yoon, J Choi, TW Jang; (II) Administrative support: CM Choi, KY Lee, J Choi, TW Jang; (III) Provision of study materials or patients: CM Choi, YS Chang, KY Lee, YC Kim, CY Jung, SH Yoon, TW Jang; (IV) Collection and assembly of data: CM Choi, KY Lee, JS Ryu, JY Park, J Choi, TW Jang; (V) Data analysis and interpretation: SY Lee, CM Choi, KY Lee, SJ Kim, SH Yang, JS Ryu, JE Lee, SY Lee, JY Park, IJ Oh, CY Jung, SH Lee, SH Yoon, J Choi, TW Jang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Tae Won Jang, MD, PhD. Department of Internal Medicine, Kosin University Gospel Hospital, Busan, South Korea. Email: jangtw22@hanmail.net.

Transl Lung Cancer Res 2021;10(12):4353-4367

Afatinib Followed by Osimertinib: A Real-World Study (GioTag)

REAL-WORLD STUDY ON SEQUENTIAL THERAPY IN PATIENTS WITH *EGFR* MUTATION–POSITIVE ADVANCED NSCLC

STUDY OBJECTIVES

Primary objective

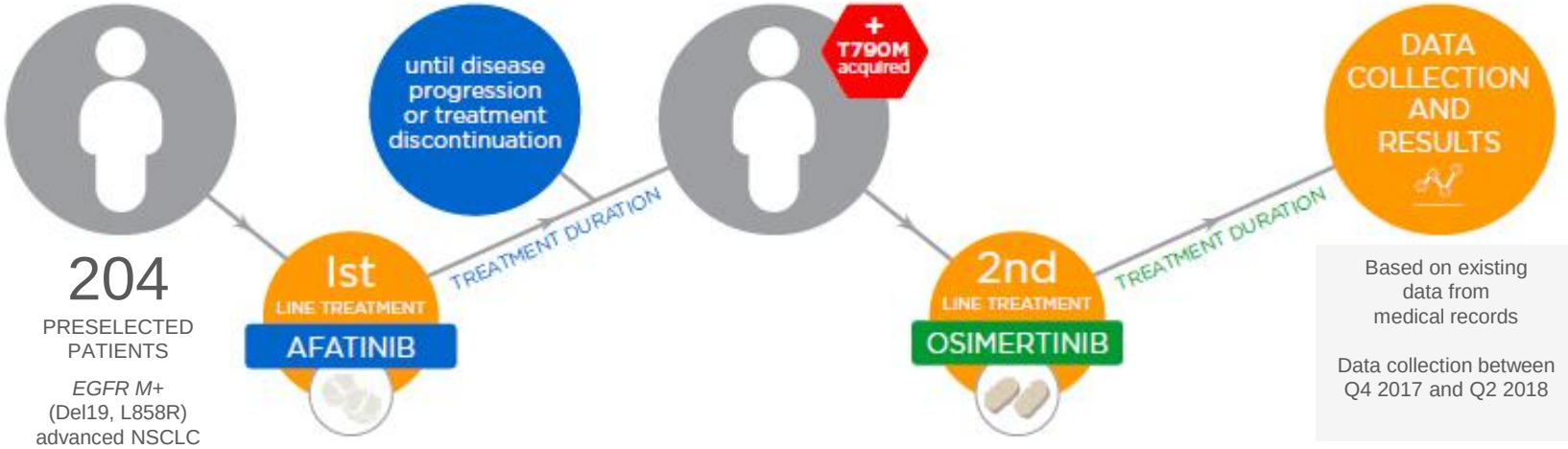
A retrospective review to determine the time on treatment[a] of afatinib as first-line therapy in *EFGR* mutation–positive (M+) followed by osimertinib for T790M resistance–mutation patients in a real-world setting

Secondary objective

To collect data on the acquired resistance mechanism to osimertinib

204 PATIENTS FROM 10 COUNTRIES

Austria
Canada
Israel
Italy
Japan
Singapore
Slovenia
Spain
Taiwan
USA



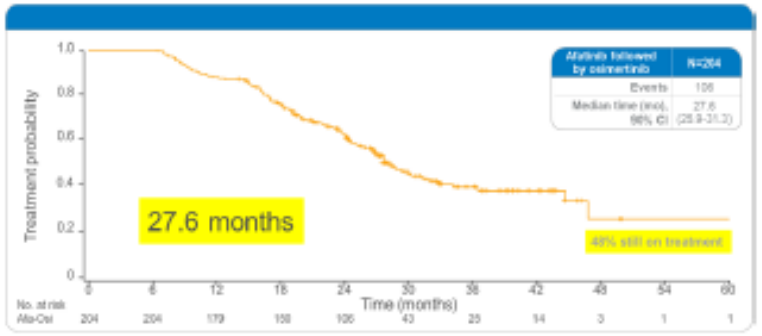
[a] Time on treatment defined from the start of first-line treatment until the end of second-line treatment or death date by any cause.

[b] Randomised controlled trials (RCTs) are designed to assess the efficacy and safety of study drugs under well-defined conditions and in selected patient populations. In contrast, real-world studies include everyd ay patients with characteristics which might preclude their participation in a RCT. Real-world studies are complementary to RCTs, and explore patient outcomes in populations more representative of clinical prac tice than perspective clinical trials. Real-world studies are essential for capturing clinically relevant data at the point of care, and providing clinically meaningful insights which can be applied to patient care. https:/ /clinicaltrials.gov/ct2/show/NCT03370770. Accessed October 9, 2018; Hochmair M et al. Future Oncol. 2018 Oct 19; doi:10.2217/fon-2018-0711.

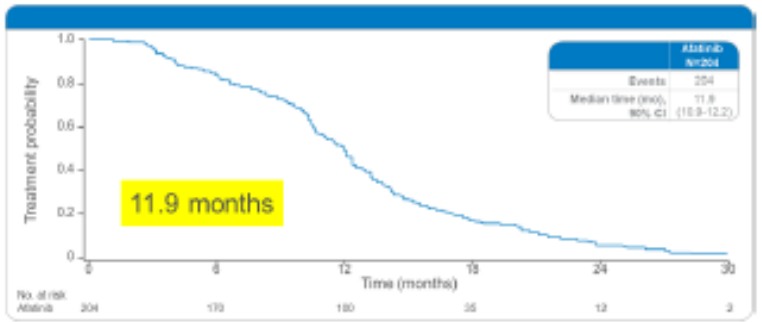
GioTag: 204 Patients from 10 Countries (including SG & TW)

Sequence outcomes in all patients

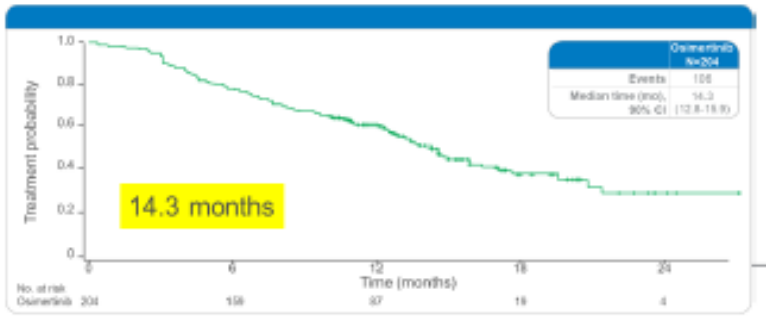
Overall TOT for Afatinib-Osimertinib



TOT with 1st-line Afatinib

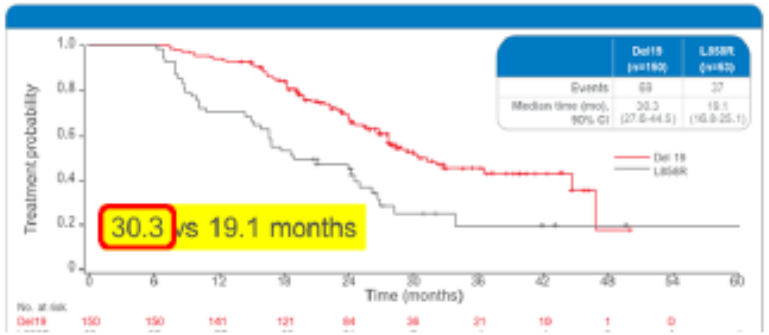


TOT with 2nd-line Osimertinib

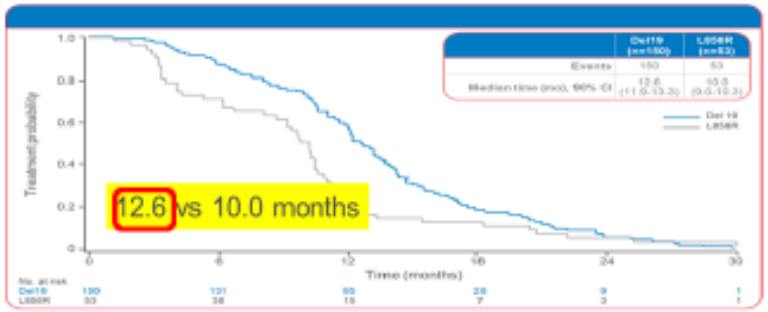


Sequence outcomes by EGFR mutation

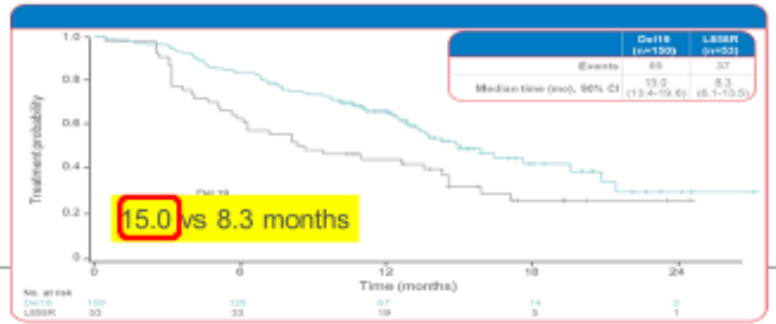
Overall TOT for Afatinib-Osimertinib



TOT with 1st-line Afatinib

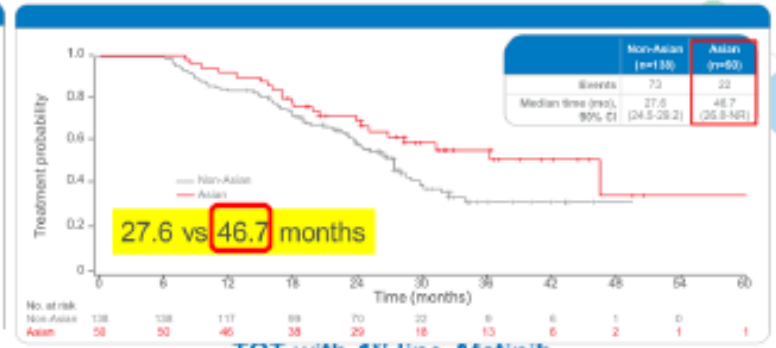


TOT with 2nd-line Osimertinib

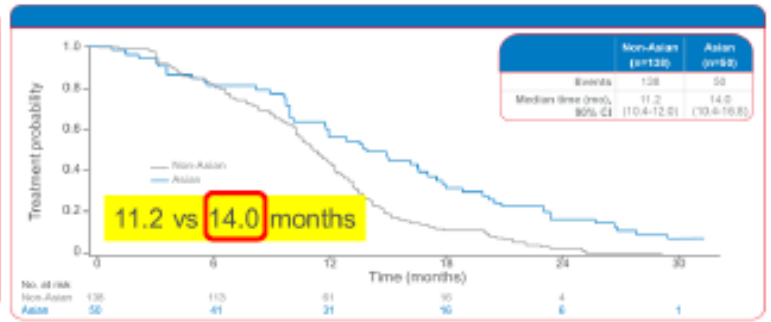


Sequence outcomes by ethnicity

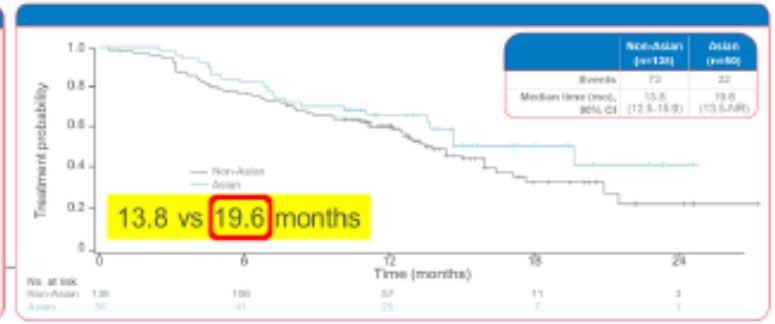
Overall TOT for Afatinib-Osimertinib



TOT with 1st-line Afatinib



TOT with 2nd-line Osimertinib



Hochmair MJ et al. Future Oncol. 2018;14(27):2861-2874.

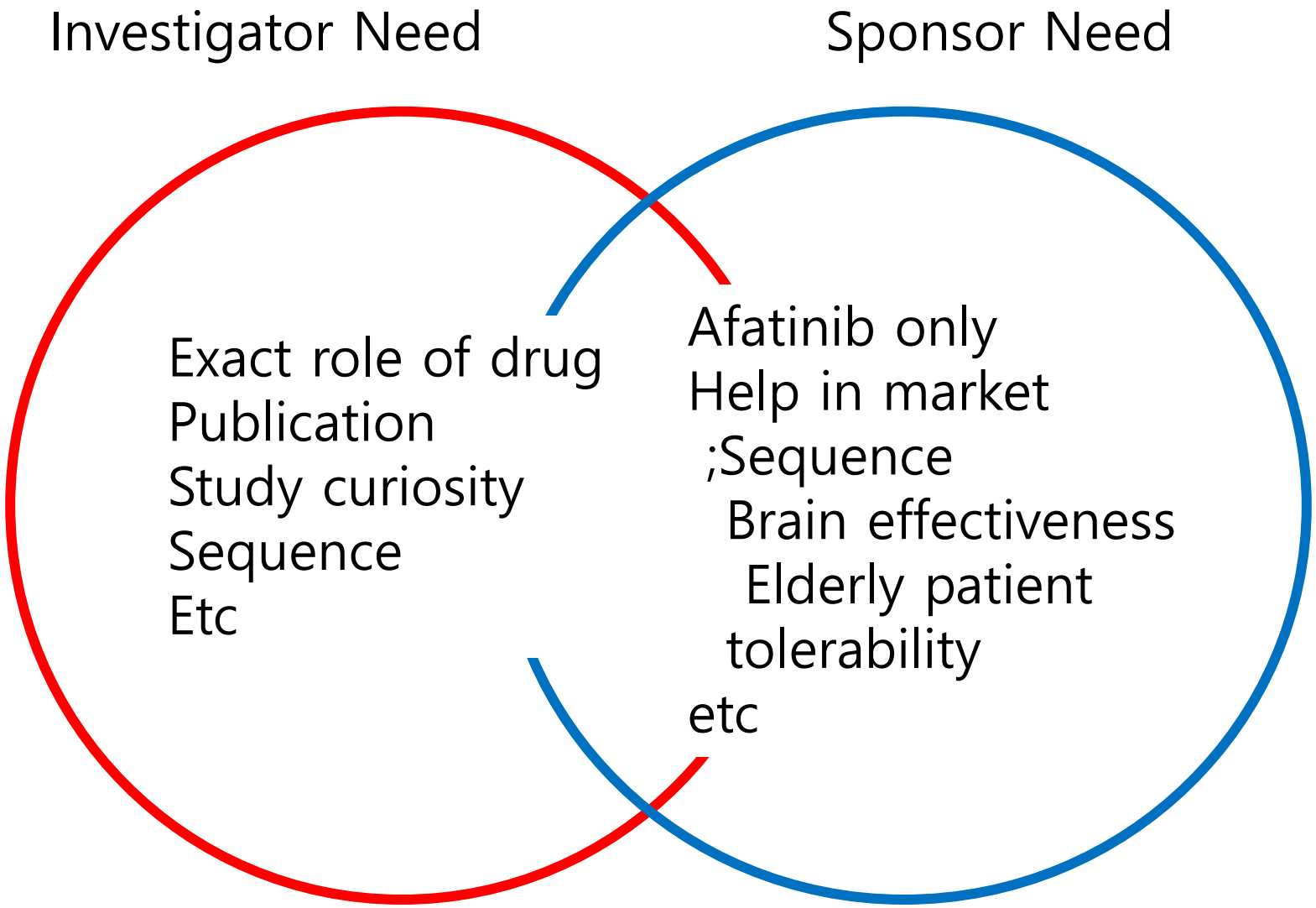
CI = confidence interval;.

Baseline Characteristics

		Start of afatinib N (%)
	Female	110 (53.9)
Median (range)	Age (years)	60.0 (30 – 86)
	Weight (kg); BMI (kg/m²)	70.2 (37 -116); 25.3 (15.0 – 45.2)
Ethnicity	Caucasian	120 (58.8)
	African-American	18 (8.8)
	Asian	50 (24.5)
	Stage IV	197 (96.6)
	Brain mets	21 (10.3)
ECOG	0	43 (21.2)
	1	110 (54.2)
	2/3	31 (15.3)
EGFR	T790M	0 (0.0)
	Del19	150 (73.5)
	L858R	53 (26.0)
	Del19 + L858R	1 (0.5)

Hochmair M et al. *Future Oncol.* 2018 Oct 19; doi:10.2217/fon-2018-0711.

Win-Win Strategy



CLINICAL STUDY PROTOCOL

EudraCT No.:	
Protocol No.:	1200.0319
Investigational Product:	Afatinib (Giotrif®)
Title:	RESET: Real-world sequential trial of frontline afatinib followed by osimertinib in patients with advanced non-small cell lung cancer habouring EGFR common mutations in South Korea
Brief Lay Title:	Retrospective cohort study of frontline afatinib followed by osimertinib
Sponsor Investigator:	Prof Tae Won Jang Kosin University Gospel Hospital 262 Gamchunro Suhgu Busan 49267, South Korea +82-51-990-6637
Sponsor:	Kosin University Gospel Hospital 262 Gamchunro Suhgu Busan 49267, South Korea +82-51-990-6637 +82-51-248-5686
Version, and Date of Protocol:	1.2 22 May 2019 **Page 1 of 24**

No. of patients: ≥100 eligible patients treated with frontline afatinib followed by osimertinib

Main criteria for inclusion:•

- Patients treated with first-line afatinib for EGFR common mutation-positive Stage IIIB/IV NSCLC
- Patients treated with second-line osimertinib for acquired T790M mutation for at least 10 months prior to data entry
- Age ≥18 years

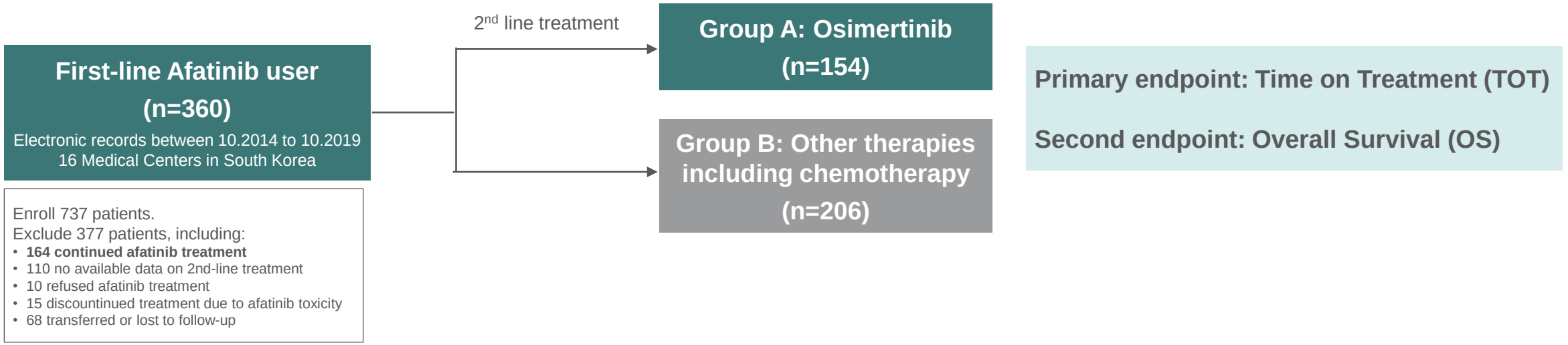
Criteria for efficacy

- Time on treatments (TOT-1 & TOT-2), overall response rates (ORR-1 & ORR-2), disease control rate (DCR-1 & DCR-2), and overall survival (OS)
- Osimertinib's resistance biomarker data (if available) and PD-L1 expression data from biopsy samples (if available) will be also collected

Protocol 변경대비표(V1.4 → V1.5)

구분	변경 전	변경 후	변경 사유
전체페이지 -Header	RESET_Protocol_V1.4_20200407	RESET_Protocol_V1.5_20200723	계획서 개정에 따른 버전 변경
1 페이지 계획서 표지	Protocol version: 1.4 Version Date: 2020-04-07	Protocol version: 1.5 Version Date: 2020-07-23	계획서 개정에 따른 버전 변경
5 페이지	1) 연구의 기간 데이터 수집: IRB 승인일 ~ 2020 년 5 월 20 일 데이터 정리: 2020 년 5 월 21 일 ~ 2020 년 5 월 31 일 예상 데이터 분석 및 결과 도출: 2020 년 6 월 ~ 2020 년 6 월 예상 연구 결과 보고: 2020 년 7 월 총 연구기간: IRB 승인일 ~ 2020 년 7 월 31 일	1) 연구의 기간 데이터 수집: IRB 승인일 ~ 2020 년 5 월 20 일 데이터 정리: 2020 년 5 월 21 일 ~ 2020 년 5 월 31 일 예상 데이터 분석 및 결과 도출: 2020 년 6 월 ~ 2020 년 12 월 예상 연구 결과 보고: 2021 년 1 월 총 연구기간: IRB 승인일 ~ 2021 년 1 월 31 일	연구의 예정기간을 정확히 기재함

RESET: Real-world Experience of SEquential Treatment of afatinib and osimertinib in Korea



Inclusion Criteria:

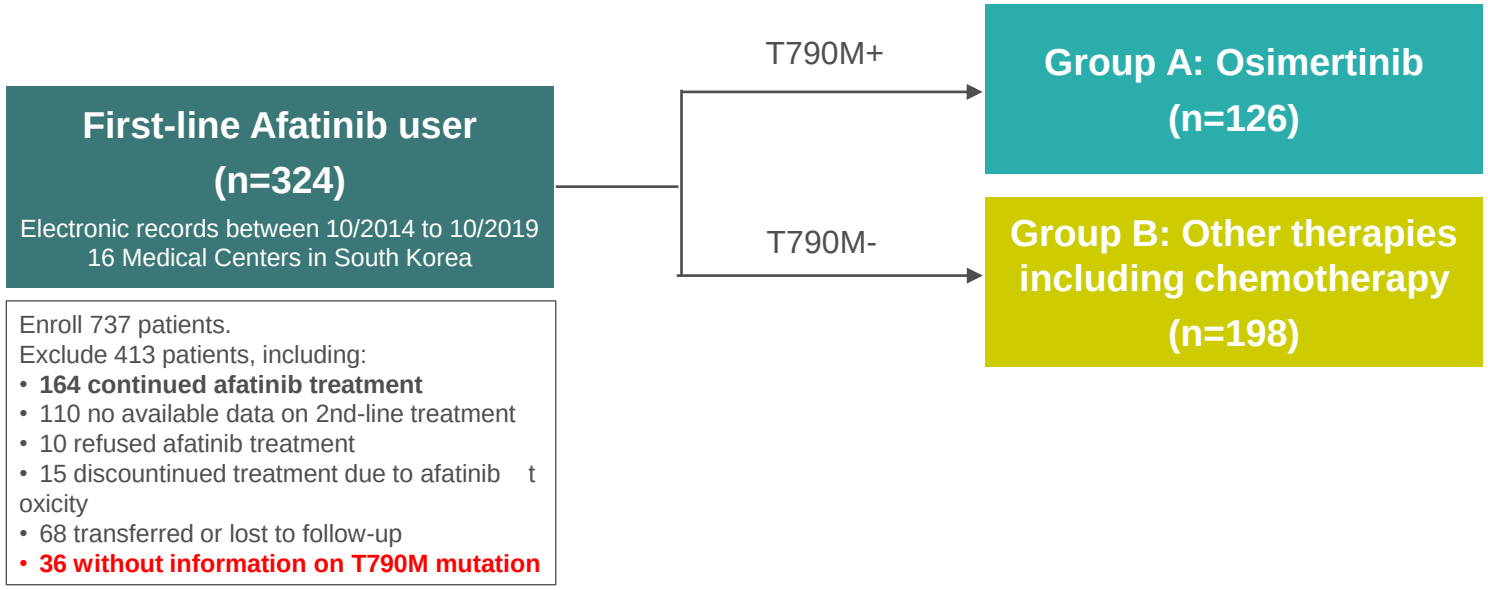
1. age ≥ 19 years with EGFR mutated TKI-naïve advanced-stage NSCLC that was newly diagnosed pathologically
2. Treated first-line with afatinib and second-line with either osimertinib or other treatments.

Exclusion Criteria:

1. Patients who were not treated with afatinib as first line therapy or osimertinib as second-line therapy were excluded.
2. Patients who were initially treated with chemoradiotherapy were also excluded.

19 February 2021, PREPRINT (Version 1) available at Research Square [https://doi.org/10.21203/rs.3.rs-215079/v1]

RESET: Real-world Experience of SEquential Treatment of afatinib and osimertinib in Korea



Primary endpoint: Time on Treatment (TOT)

Second endpoint: Overall Survival (OS)

Inclusion Criteria:

1. age ≥ 19 years with EGFR mutated TKI-naïve advanced-stage NSCLC that was newly diagnosed pathologically
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Cancer Medicine. 2021;10:5809–5822.

RESEARCH ARTICLE

Cancer Medicine Open Access WILEY

Sequential treatment of afatinib and osimertinib or other regimens in patients with advanced non-small-cell lung cancer harboring EGFR mutations: Results from a real-world study in South Korea

Taeyun Kim[1] | Tae Won Jang[2] | Chang Min Choi[3] | Mi-Hyun Kim[4] | Sung Yong Lee[5] | Cheol-Kyu Park[6] | Yoon Soo Chang[7] | Kye Young Lee[8] | Seung Joon Kim[9] | Sei Hoon Yang[10] | Jeong Seon Ryu[11] | Jeong Eun Lee[12] | Shin Yup Lee[13] | Chan Kwon Park[14] | Sang Hoon Lee[15] | Seung Hun Jang[16] | Seong Hoon Yoon[17]

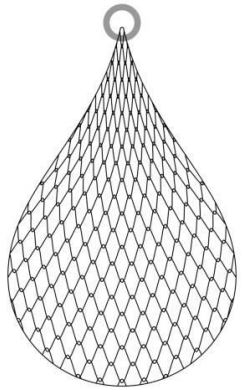
Cancer Medicine. 2021;10:5809–5822.

Study Difficulties

- Covid19: 18 center→ 16 center
- Center variation
  - 2-130명 (703명)→ 충분히 더 많은 수가 있다
  - 연구비 배분
  - Management ?
- Time delay
- Data quality
- Deficiency of Details

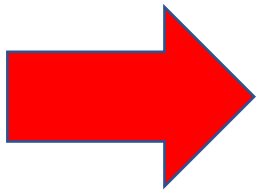
1st author 의 의견

- 전반적으로 data QC 이 후향적 다기관이라는 특징으로 어려울 것으로 생각을 했다.
- CRF에 fill up 된 data의 변수가 몹시 많았던 부분이 오히려 전체적인 데이터 quality 를 떨어트리는 영향도 있지 않았을까 생각이 들어, 광범위하게 그물을 던지는 것보다 원하는 주제에 대해 필요한 변수를 간결하게 선정하고 닻을 내리면 어떨까 하는 생각을 했다.



후향적 다기관 연구로서의 데이터 quality

- ECOG PS : PS >2 : 4.5%
- Smoking hx: pack-yr
- Definition : PFS, TOT, TTF
- 약제의 ORR, DCR
- PDL1 expression: 시간차이와 병원별 차이 보정 실패, data 부재



Prospective Cohort

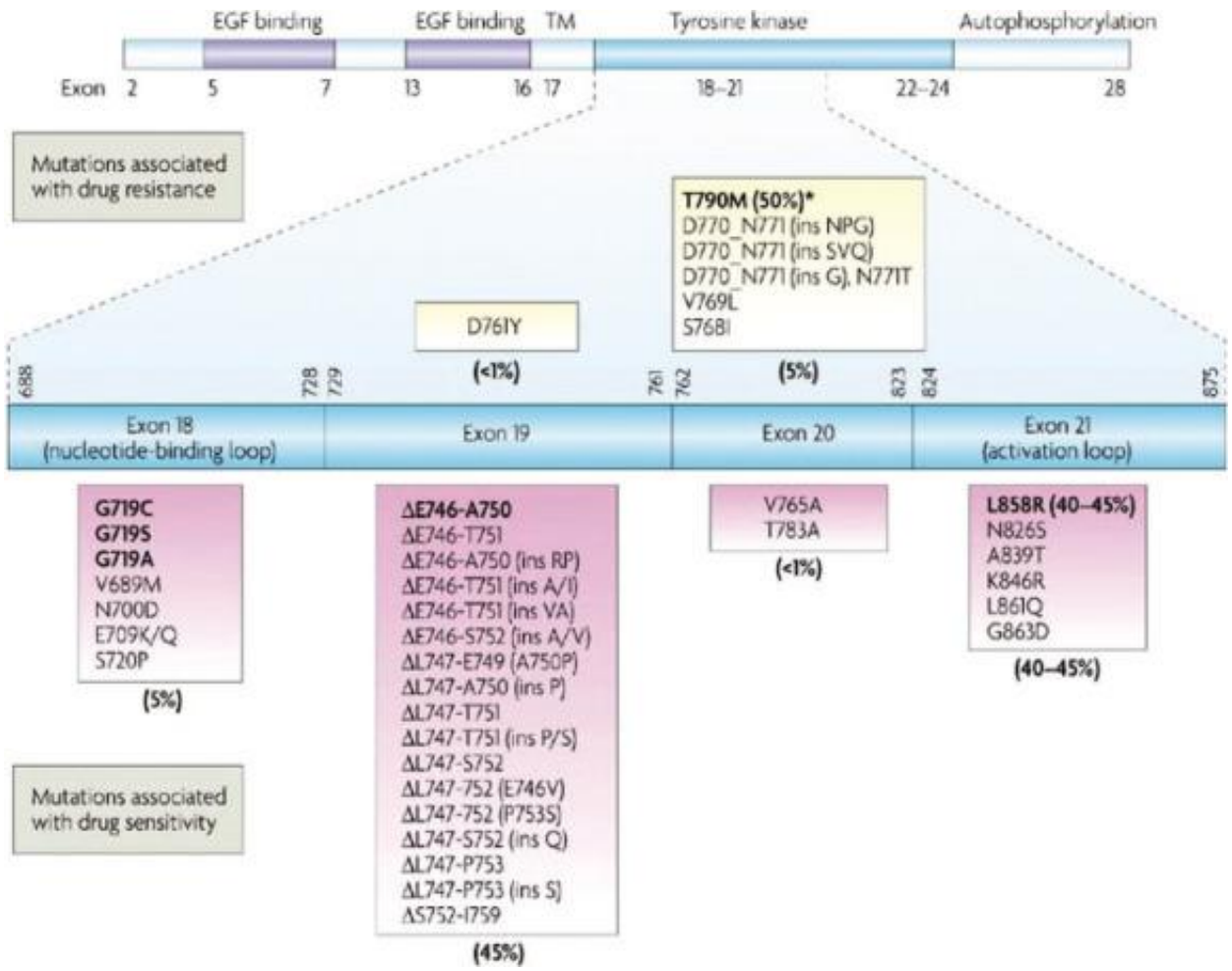
EGFR mutation (e-CRF)

1: Del 19
2: L858R
3: Exon 18
4: Exon 19 (Del 19 제외)
5: Exon 20
6: Exon 21 (L858R 제외)
7: G719X
8: E20Ins
9: T790M
10: S768I
11: C797S
12: L861Q
13: Other

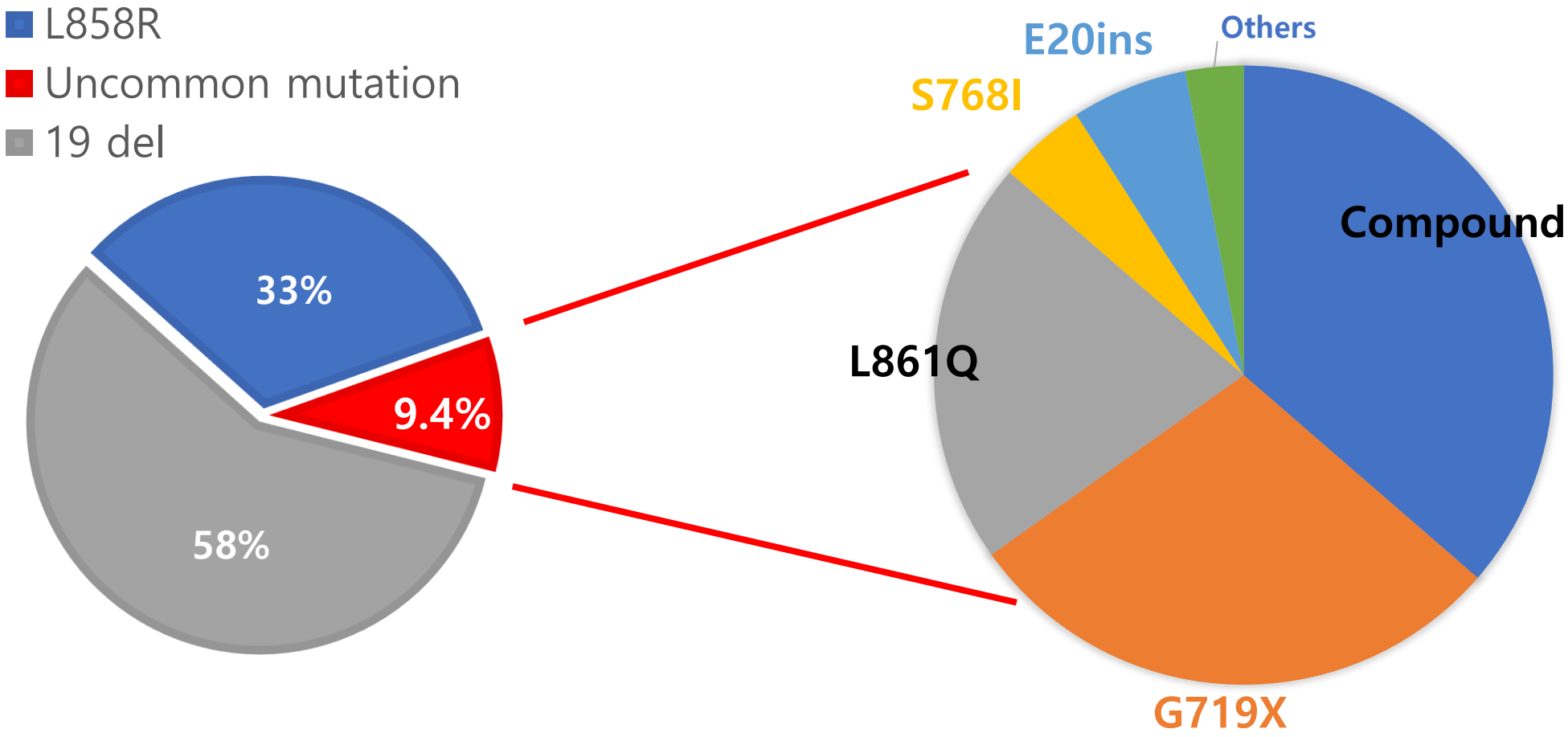
EGFR mutation 해석

- 19 del variants
- L858R and L861Q
- G719X(C,S,A)
- Compound mutation

  → Code problem



Mutation Types



Uncommon Mutation Category

Mono Mutation Type	No
G719X	19
L861Q	14
S768I	3
E20ins	4
T790M	1
c.2317-2319dupCAC	1

Compound mutation Type	No
G719X+S768I	11
G719X+L861Q	4
T790M+Others	6
19del, 20ins	1
19Del, L858R	1
19del, L861Q	1

Real-world study of first line afatinib in patients of advanced stage non-small cell lung cancer with uncommon EGFR mutations in South Korea

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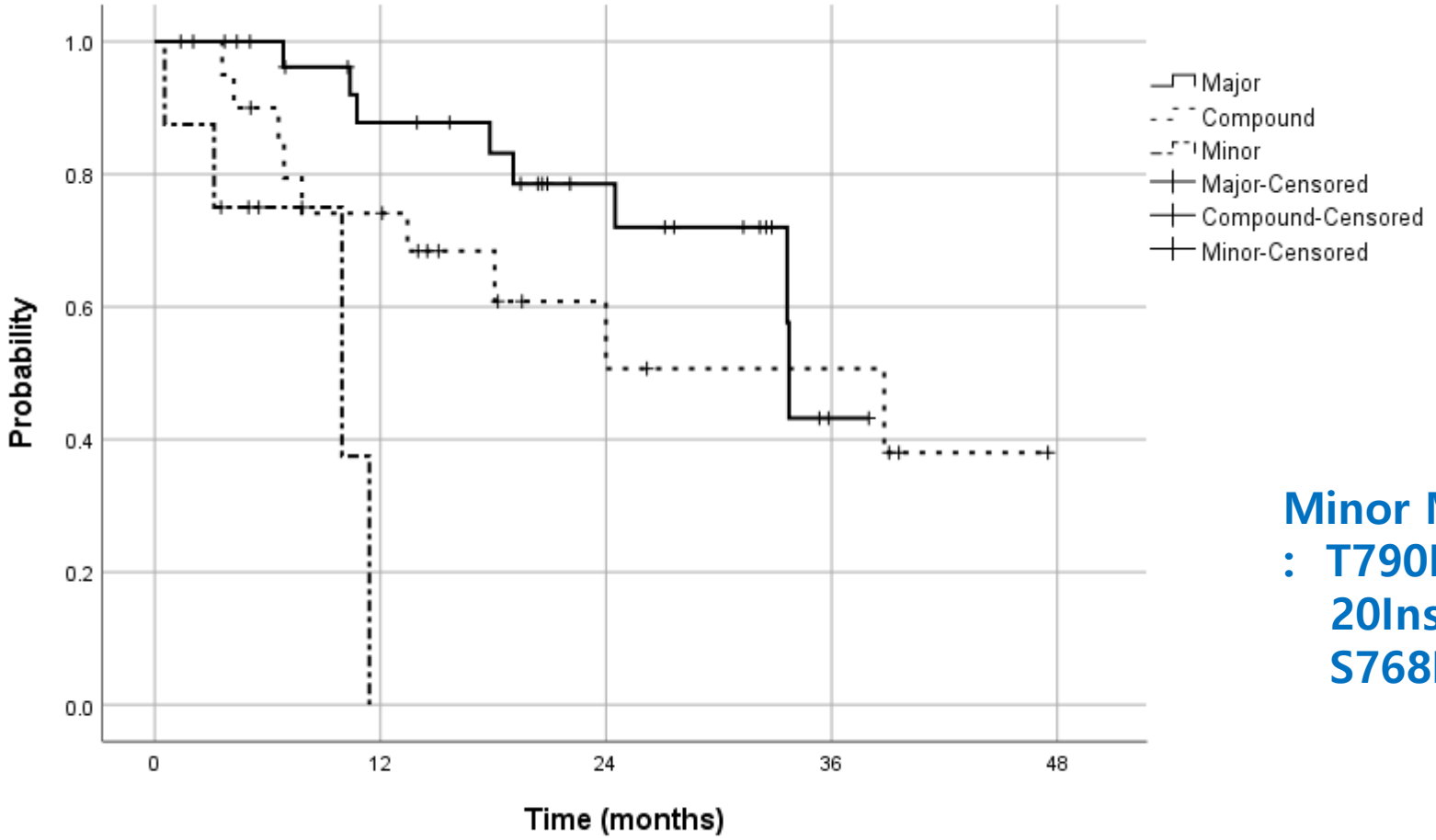

major
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Minor Mutation
: T790M
20Ins
S768I

MH Kim : Anticancer Research accepted

Metastasis data: 8 metastatic sites

Adrenal gland,

Brain,

Bone,

Lung,

Liver,

Pericardium,

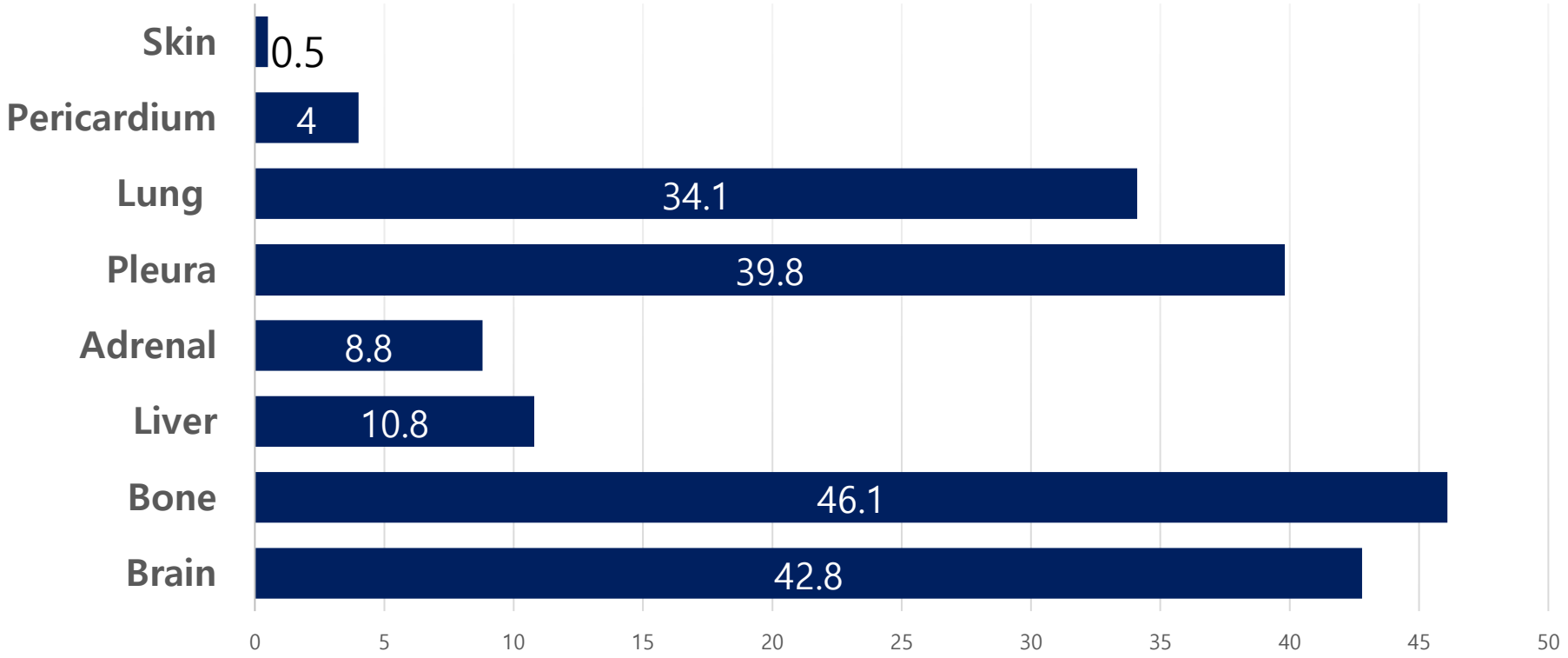
Pleura,

Skin

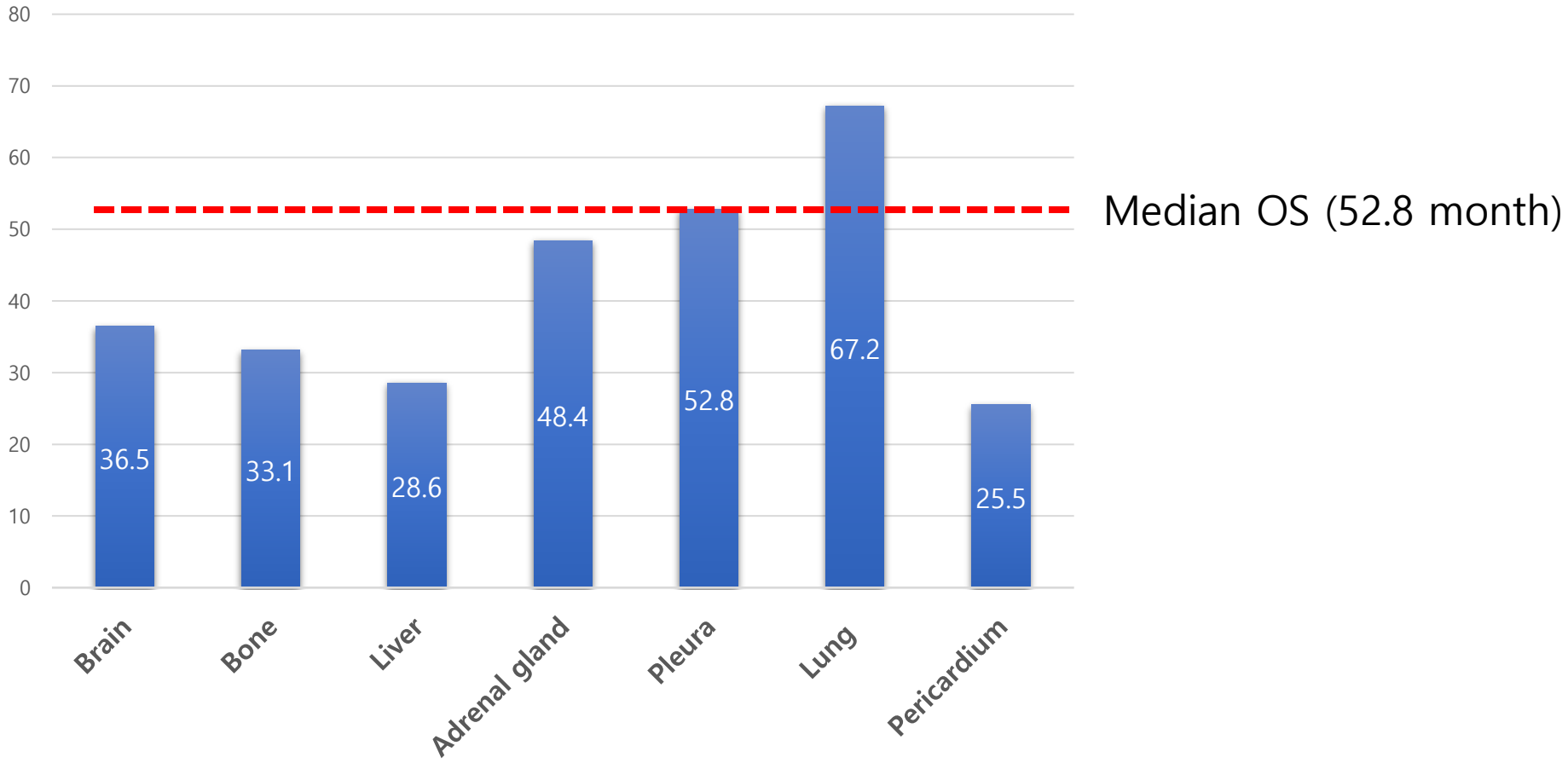
Patients Characteristics

Men/Woman	337/314 (total 651)
Age, year old	63.6 (31-95)
Smoking	
Never	417 (64.8%)
Former	172 (26.7%)
Current	55 (8.5%)
ECOG PS	
0 and 1	552 (92.2%)
≥2	47 (7.8%)
Pathologic diagnosis	
Adenocarcinoma	644 (98.9%)
Others	7 (1.1%)
EGFR Mutation	
19 del	365(56.1%)
L858R	217(33.3%)
Others	69 (10.6%)

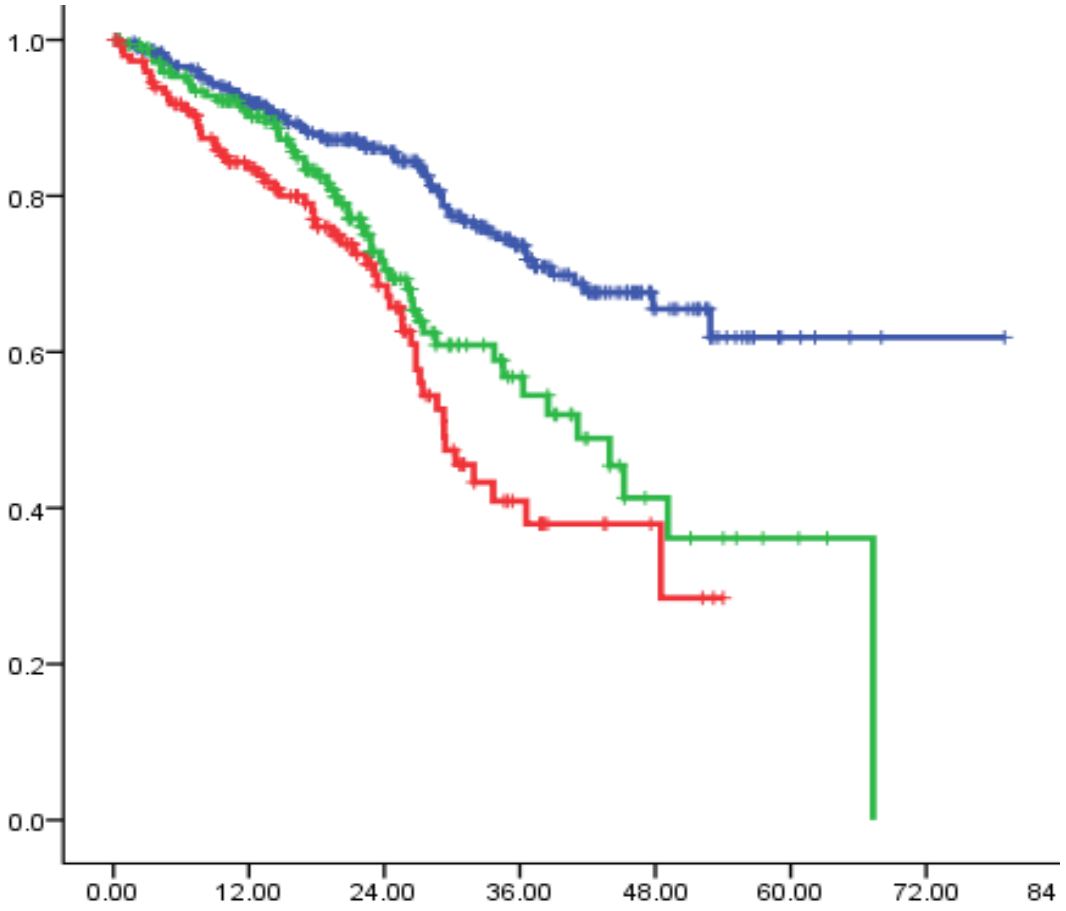
Metastatic prevalence (%) of metastatic organs



Median overall survival of site-specific metastases



Kaplan-Meier OS Curve



Organ Number	Median OS (mo)
1	Not Reached
2	41.1
>3	29.2

P<0.001

Brain metastasis

진단시점 뇌전이 여부
YES = 1
NO = 2
99 = 99

진단 후 폐암 치료 중 뇌전이 발생 여부
1= YES
2= NO
3= Recurrence
99= UK

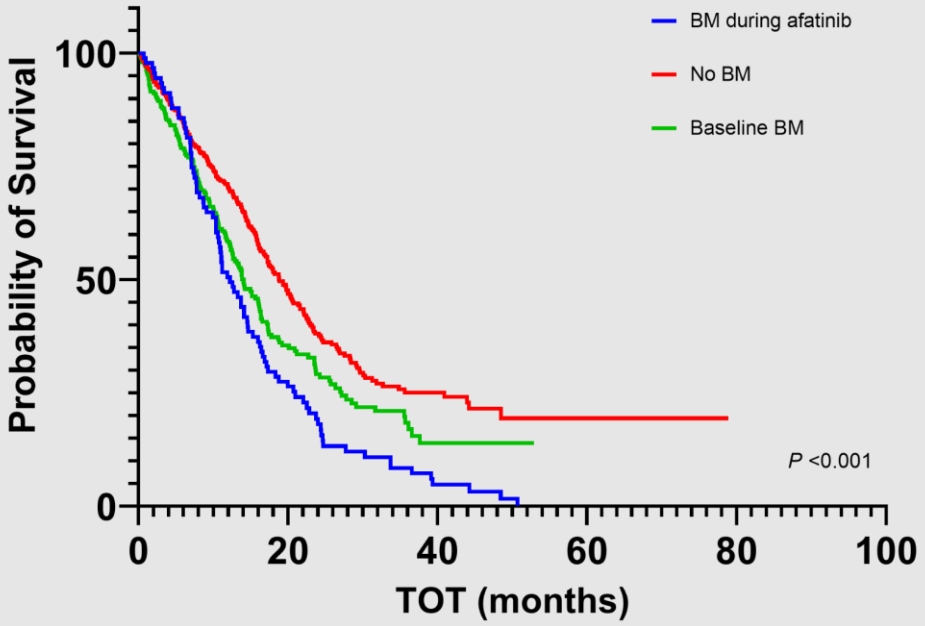
치료 중 뇌전이 발생 날짜

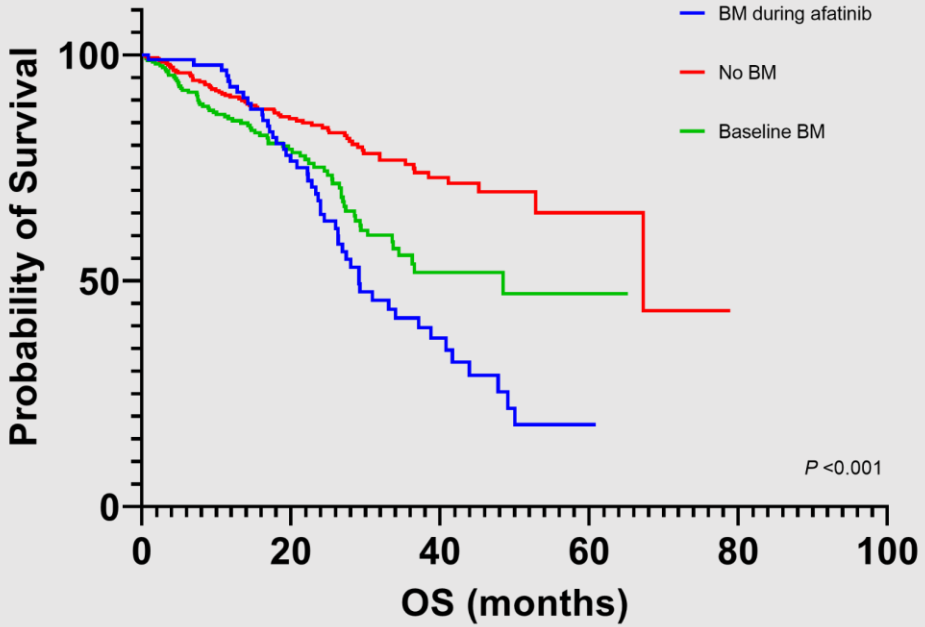
진단시점 뇌전이 유형
1: Single metastasis
2: Multiple metastasis
3: Leptomeningeal seeding
4: Single metastasis + Leptomeningeal seeding
5: Multiple metastasis + Leptomeningeal seeding

치료 중 발생한 뇌전이유형
1: Single metastasis
2: Multiple metastasis
3: Leptomeningeal seeding
4: Single metastasis + Leptomeningeal seeding
5: Multiple metastasis + Leptomeningeal seeding

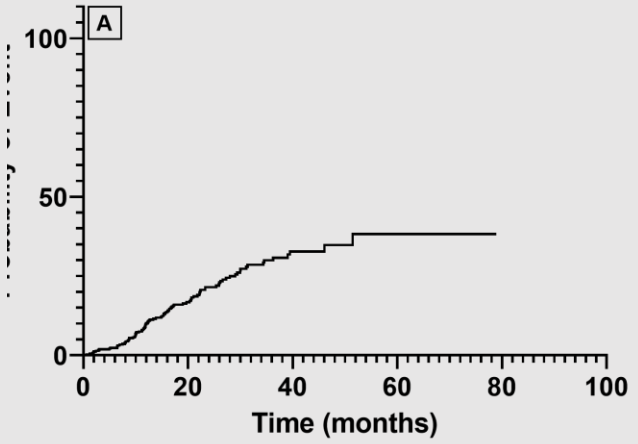
Brain metastasis

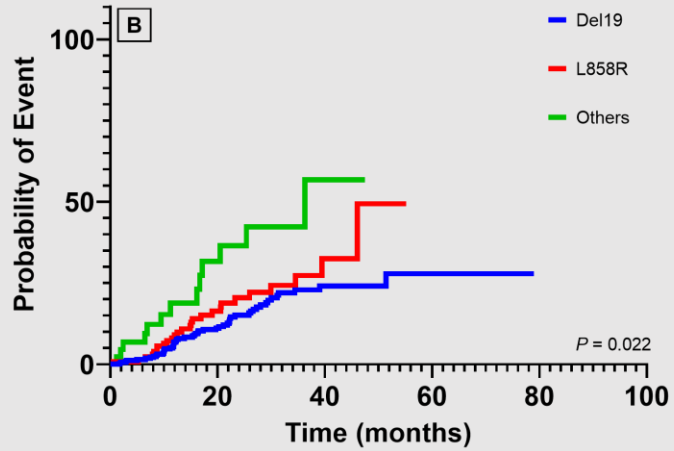
- 부정확한 정보: 검정 과정
- 5 개 variables가 필요?
- Brain meta treatment methods: missing
- Follow up MRI data: brain PFS missing (brain meta 환자의 치료 약제 효과 분석 실패)

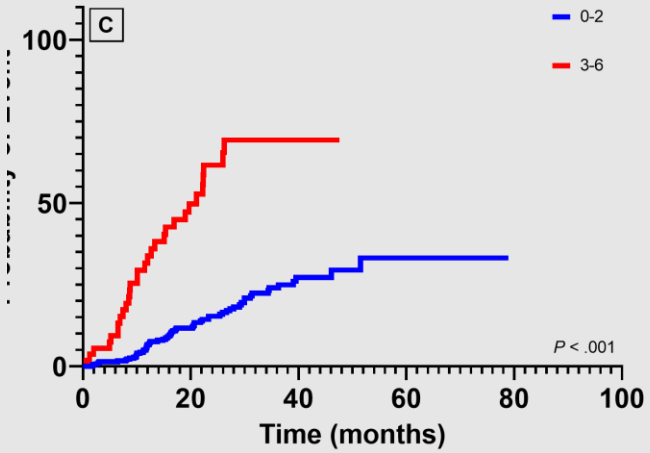


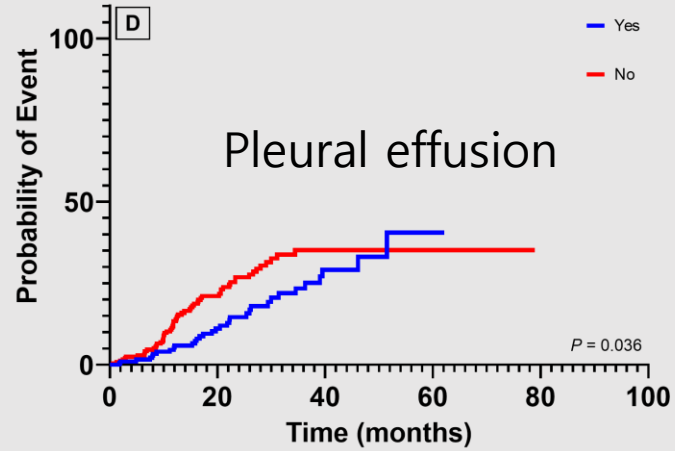


rst line afatinib in patients with





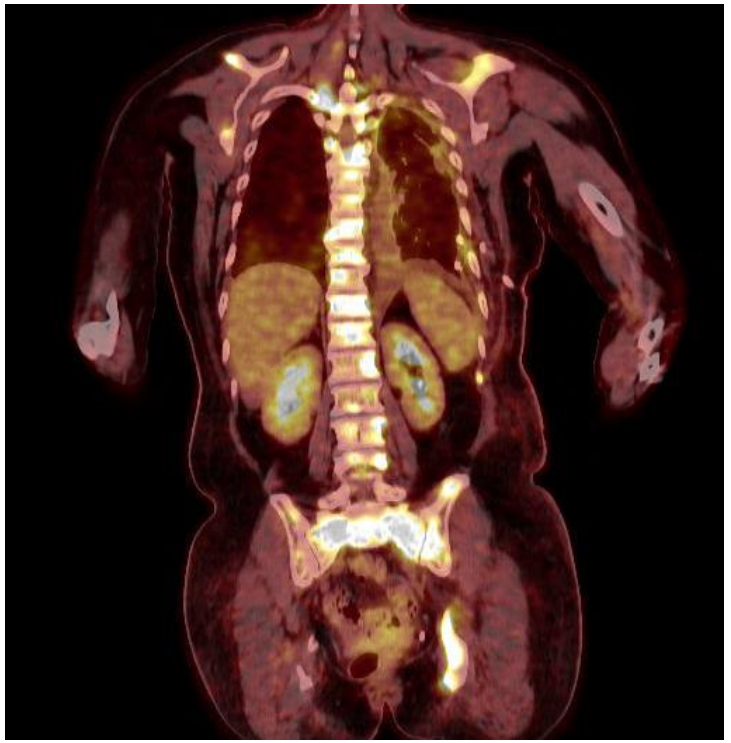




Pleural effusion

Bone metastasis: 아쉬운 data

- Additional bone treatment methods: RT or Surgery
- Site : Weight bearing site
- Single or multiple
- Response 여부, main site와 일치율
- Skeletal Related Events
- QoL, 입원 빈도 등



59/F 19 del

Second Regimen 약제의 종류

1종류 =1
2종류 =2
3종류 =3
그외 = 4

Second regimen 약제의 종류

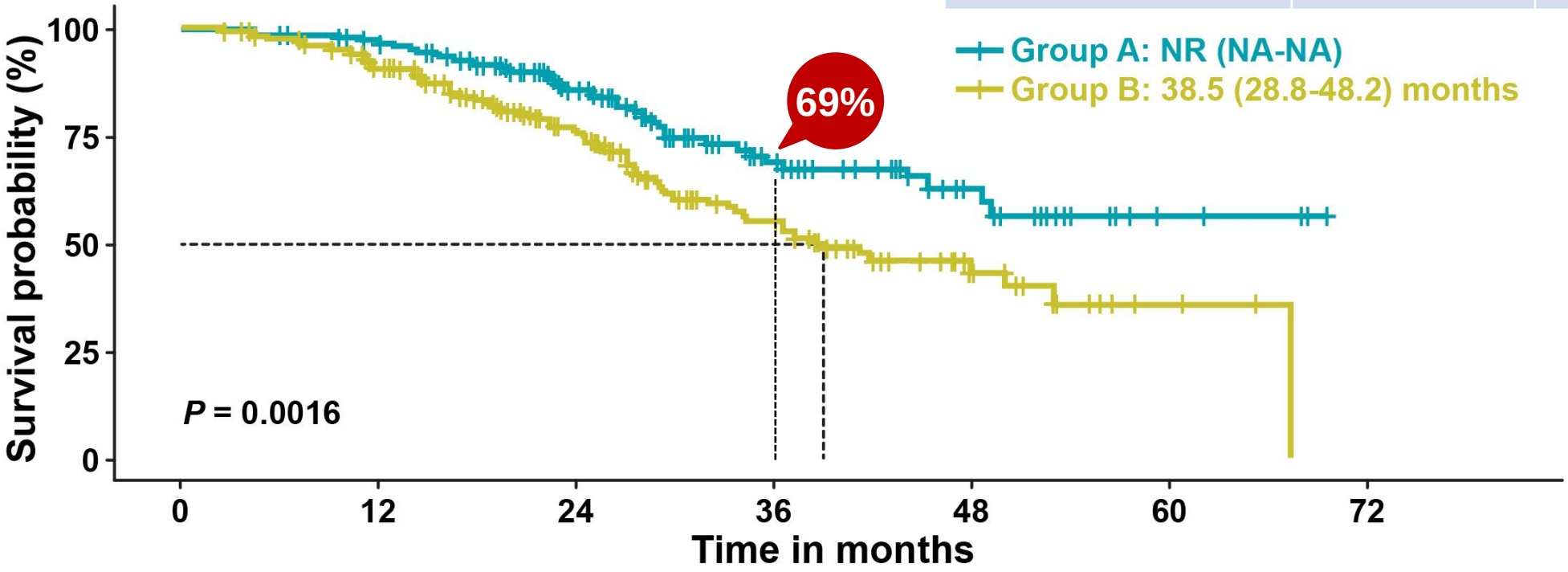
1: Cisplatin
2: Carboplatin
3: Pemetrexed
4: G
5: Paclitaxel
6: Docetaxel
7: Vinorelbine
8: Etoposide
9: Topotecan
10: Belotecan
11: Irinotecan
12: Gefitinib
15: Poziotinib
16: Crizotinib
17: Alectinib
18: Ceritinib
19: Olmutinib
20: Osimertinib
21: Rociletinib
24: Nivolumab
25: Pembrolizumab
26: Atezolizumab
27: Intrathecal_MTX
28: Other

의미있는 data의 추출이 불가능

악마는 디테일에 있다:
The devil is in the details

First-line Afatinib Demonstrated Promising Overall Survival Benefits

	Group A (Afa-Osi)	Group B (Afa-Others)
Median OS (mon)	**NR**	**38.5**
2-year survival rate(%)	**86.0%**	75.9%
3-year survival rate(%)	**69.3%**	55.3%



Cancer Med. 2021; 00: 1–14. https://doi.org/10.1002/cam4.4127

RESET Final Data Cut : 2022년 4월 30일

뭉쳐야 찬다

PULVENGERS

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