SEVERANCE

Newly Approved Targeted Agents

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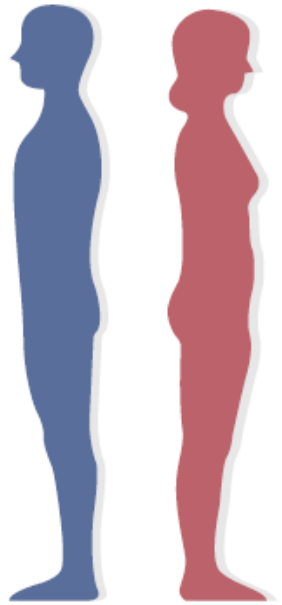
Contents

- Epidemiology
- EGFR (Afatinib, Amivatamab, Movocertinib, Lazertinib)
- ALK (Lorlatinib)
- KRAS (Sotorasib)
- TKI in SqCC

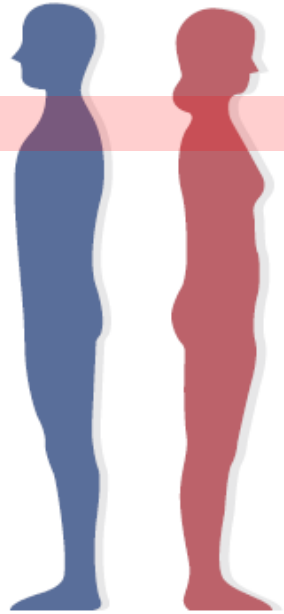
Prediction of Cancer Incidence and Mortality in Korea, 2021

	Men 135,577 (%)	Women 124,422 (%)	
Lung	15.6	21.6	Breast
Stomach	13.2	18.7	Thyroid
Colon and rectum	12.6	8.9	Colon and rectum
Prostate	12.4	8.8	Lung
Liver	8.1	7.1	Stomach
Thyroid	5.9	3.4	Pancreas
Pancreas	3.4	3.1	Gallbladder
Gallbladder	3.3	3.0	Liver
Kidney	3.2	2.8	Corpus uteri
Bladder	3.0	2.5	Cervix uteri
All sites	**100.0**	**100.0**	**All sites**



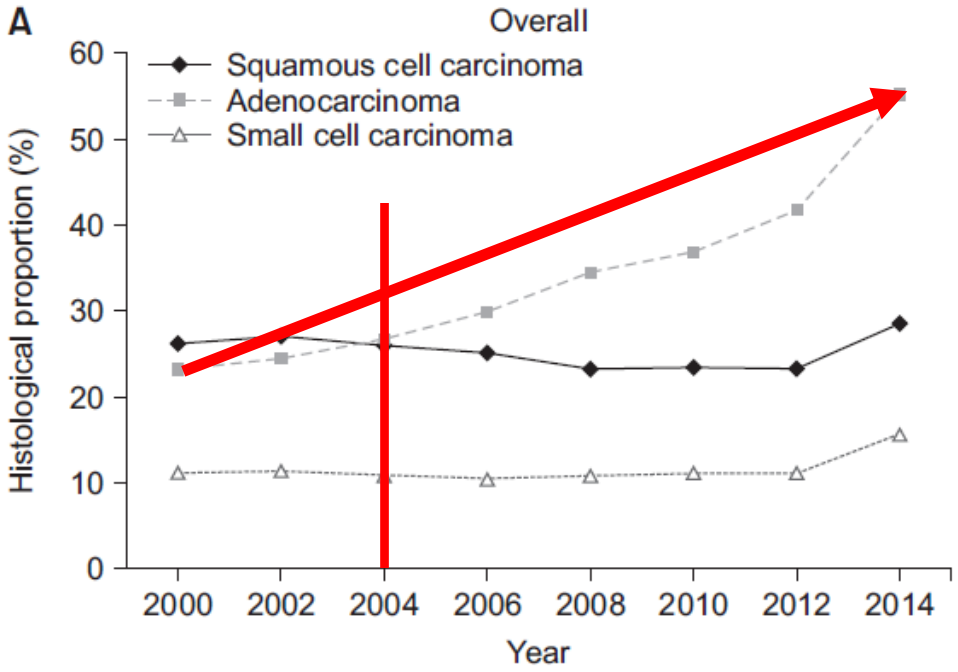
32,149 cases

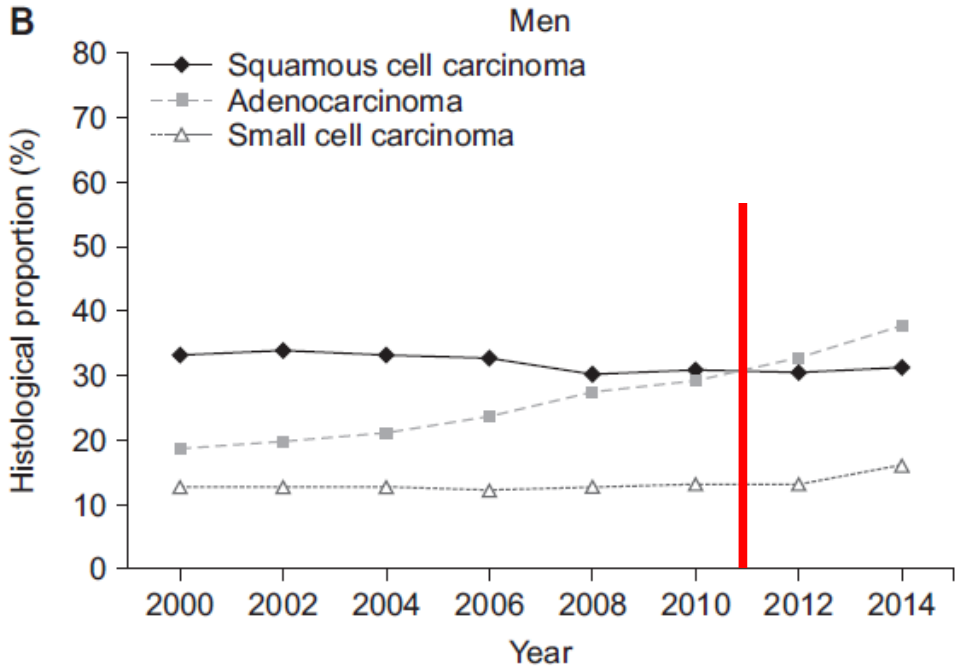
	Men 49,630 (%)	Women 31,937 (%)	
Lung	27.4	14.9	Lung
Liver	14.2	12.4	Colon and rectum
Colon and rectum	9.9	10.6	Pancreas
Stomach	7.7	8.8	Liver
Pancreas	7.3	8.8	Breast
Gallbladder	5.8	7.8	Gallbladder
Prostate	4.3	6.2	Stomach
Non-Hodgkin lymphoma	2.6	4.2	Ovary
Leukemia	2.5	3.0	Non-Hodgkin lymphoma
Bladder	2.3	2.7	Leukemia
All sites	**100.0**	**100.0**	**All sites**

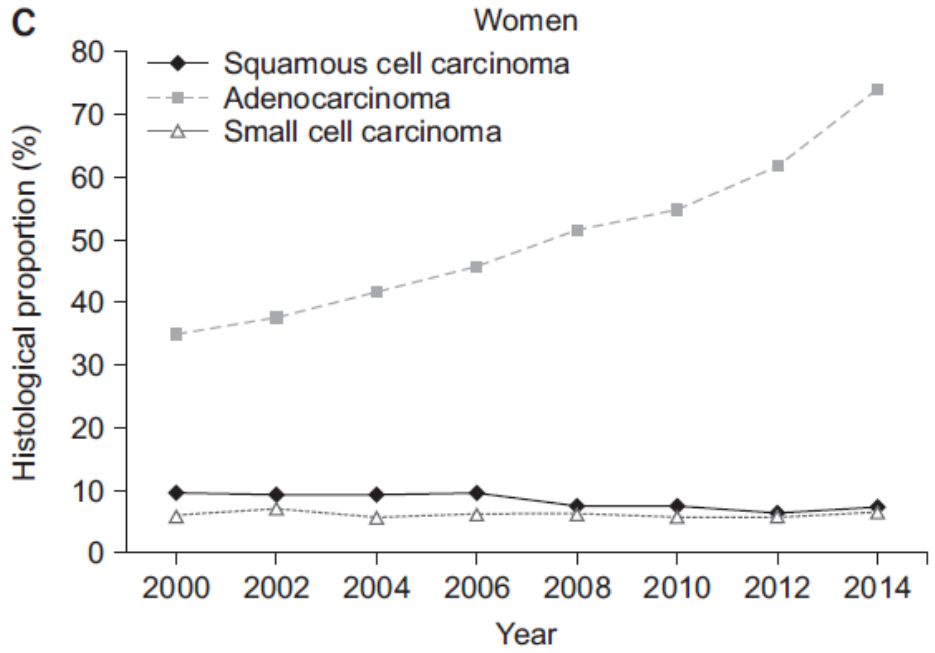


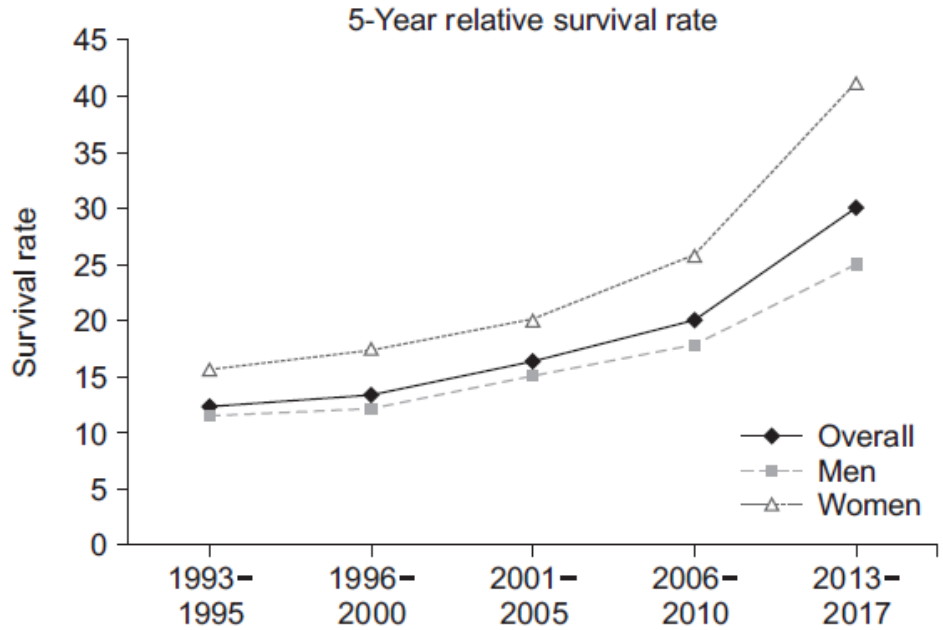
18,379 cases

Cancer Res Treat. 2021;53(2):316-322

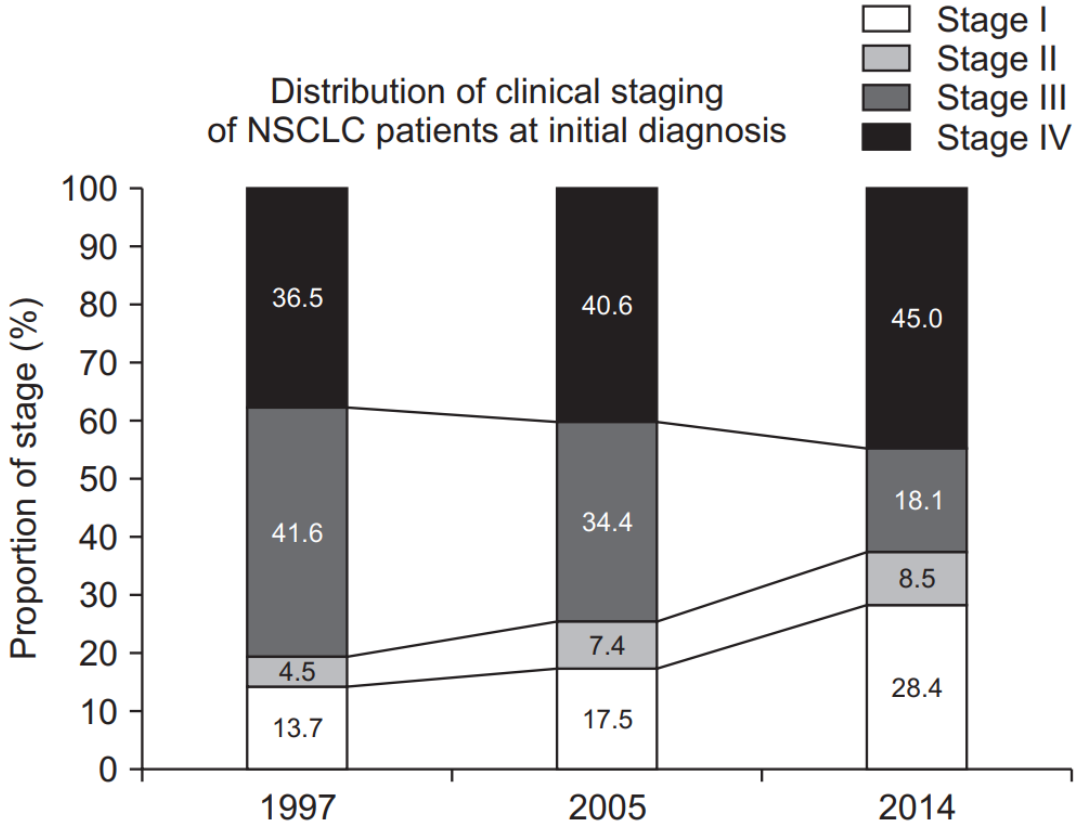


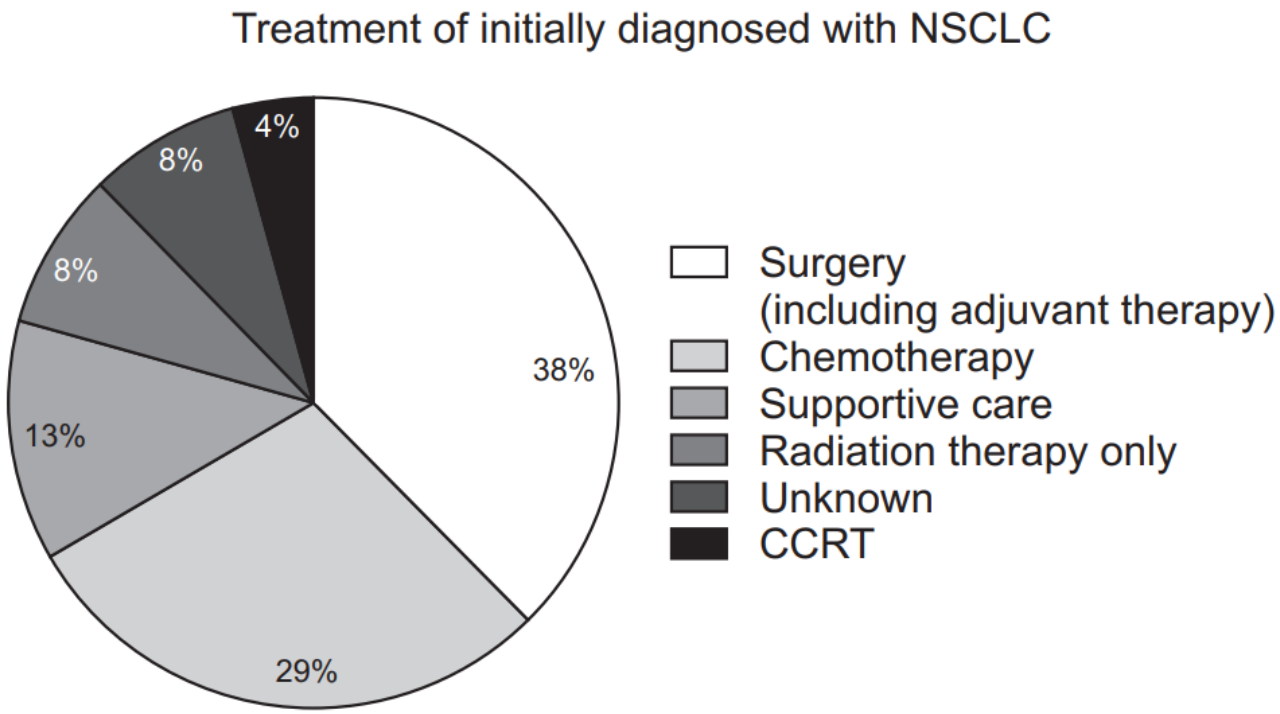






Tuberc Respir Dis 2021;84:89-95



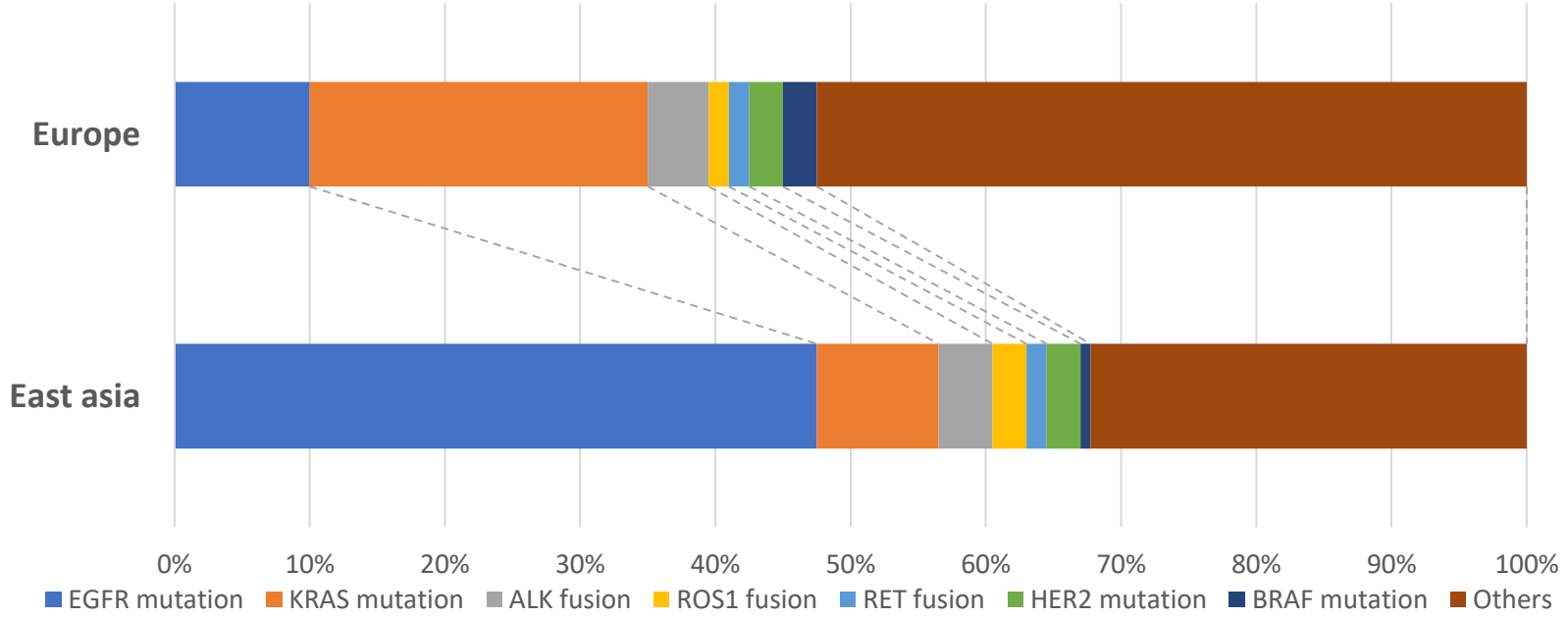


- EGFR mutation ~50 % in adenocarcinoma

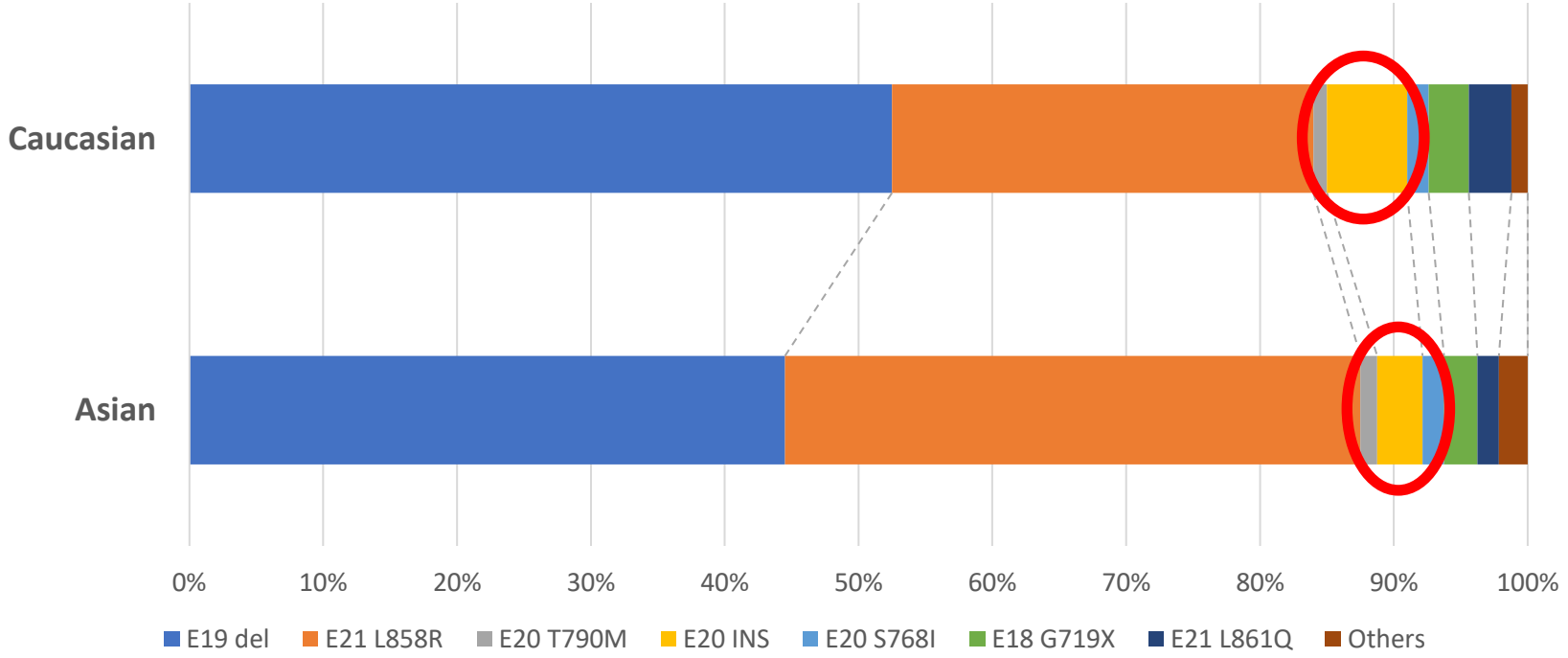
- ALK mutation ~ 5% in NSCLC

Tuberc Respir Dis 2021;84:89-95

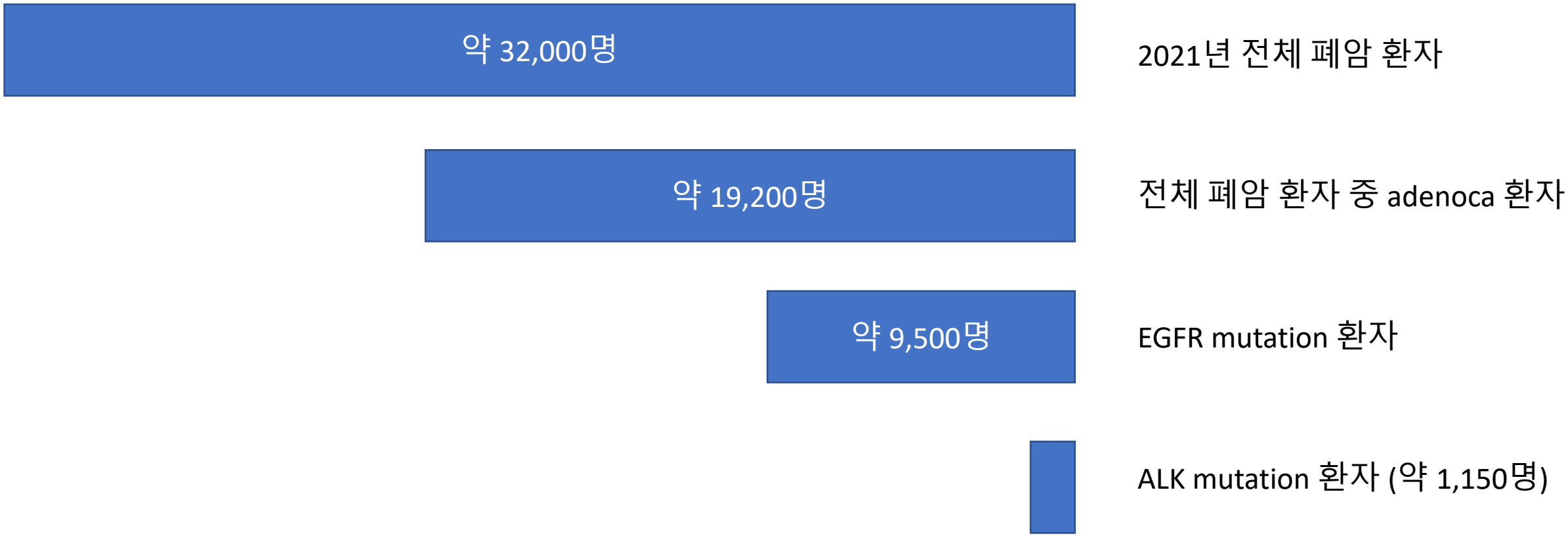
East asia (China, Korea, Japan), Europe, gene mutation prevalance



Asian, Caucasian, EGFR mutation prevalance



폐암 환자의 분포 (Korea)



EGFR

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2021
Non-Small Cell Lung Cancer

NCCN Guidelines Index
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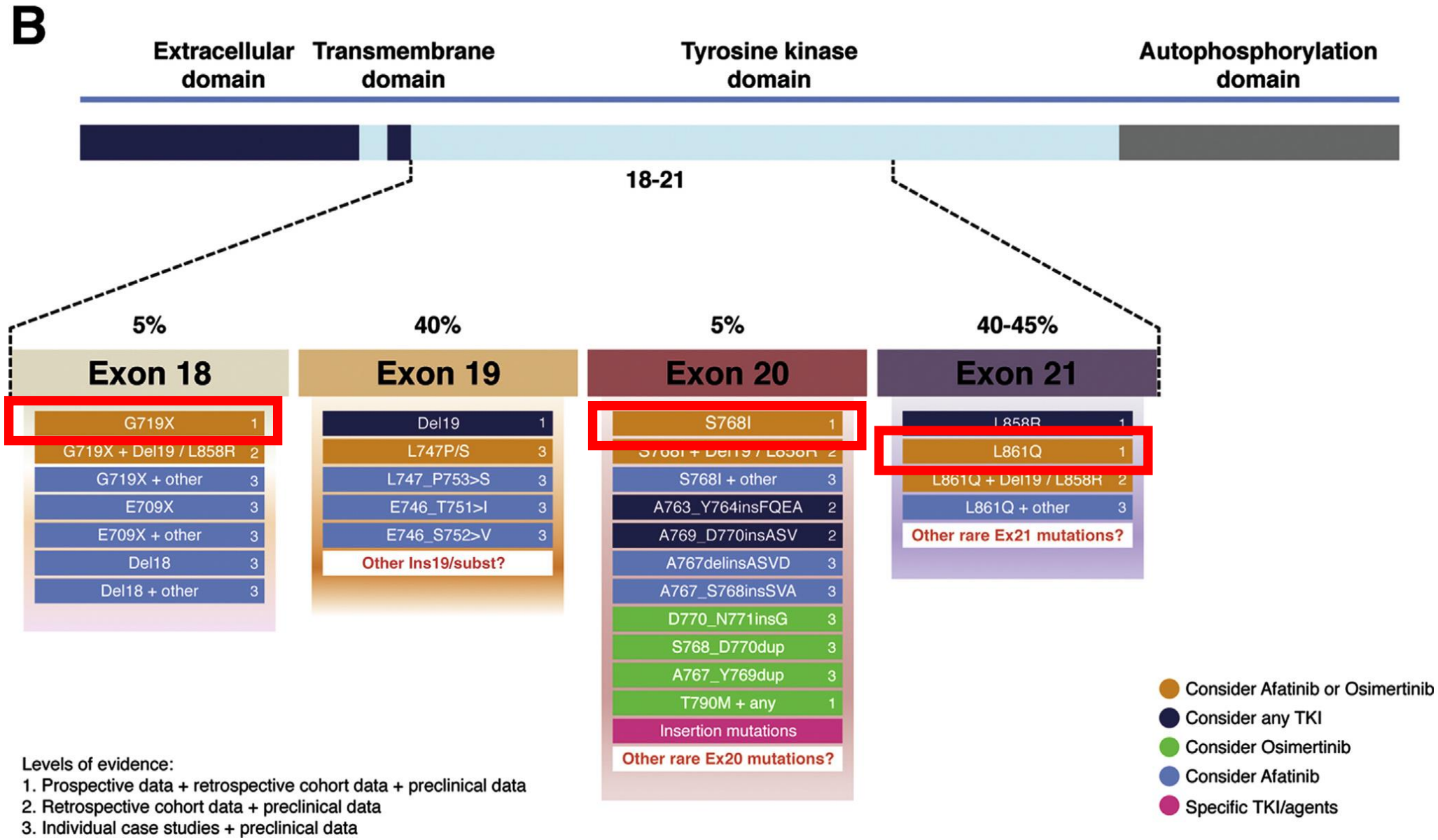
TESTING RESULTS[kk,ll]

Sensitizing *EGFR* mutation positive	NSCL-20
ALK rearrangement positive	NSCL-23
ROS1 rearrangement positive	NSCL-26
BRAF V600E mutation positive	NSCL-27
NTRK1/2/3 gene fusion positive	NSCL-28
METex14 skipping mutation positive	NSCL-29
RET rearrangement positive	NSCL-30
PD-L1 ≥50% and negative for actionable molecular markers above	NSCL-31
PD-L1 ≥1%–49% and negative for actionable molecular markers above	NSCL-32
PD-L1 <1% and negative for actionable molecular markers above	NSCL-33

TESTING RESULTS[ll,mm]

EGFR exon 19 deletion or *L858R* mutation positive	NSCL-20
EGFR S768I, L861Q, and/or *G719X* mutation positive	NSCL-23
EGFR exon 20 insertion mutation positive	NSCL-24
KRAS G12C mutation positive	NSCL-25
ALK rearrangement positive	NSCL-26
ROS1 rearrangement positive	NSCL-29
BRAF V600E mutation positive	NSCL-31
NTRK1/2/3 gene fusion positive	NSCL-32
METex14 skipping mutation positive	NSCL-33
RET rearrangement positive	NSCL-34
PD-L1 ≥50% and negative for actionable molecular biomarkers above	NSCL-35
PD-L1 ≥1%–49% and negative for actionable molecular biomarkers above	NSCL-36
PD-L1 <1% and negative for actionable molecular biomarkers above	NSCL-37



Journal of Thoracic Oncology Vol. 16 No. 5: 764-773

EGFR

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2022
Non-Small Cell Lung Cancer

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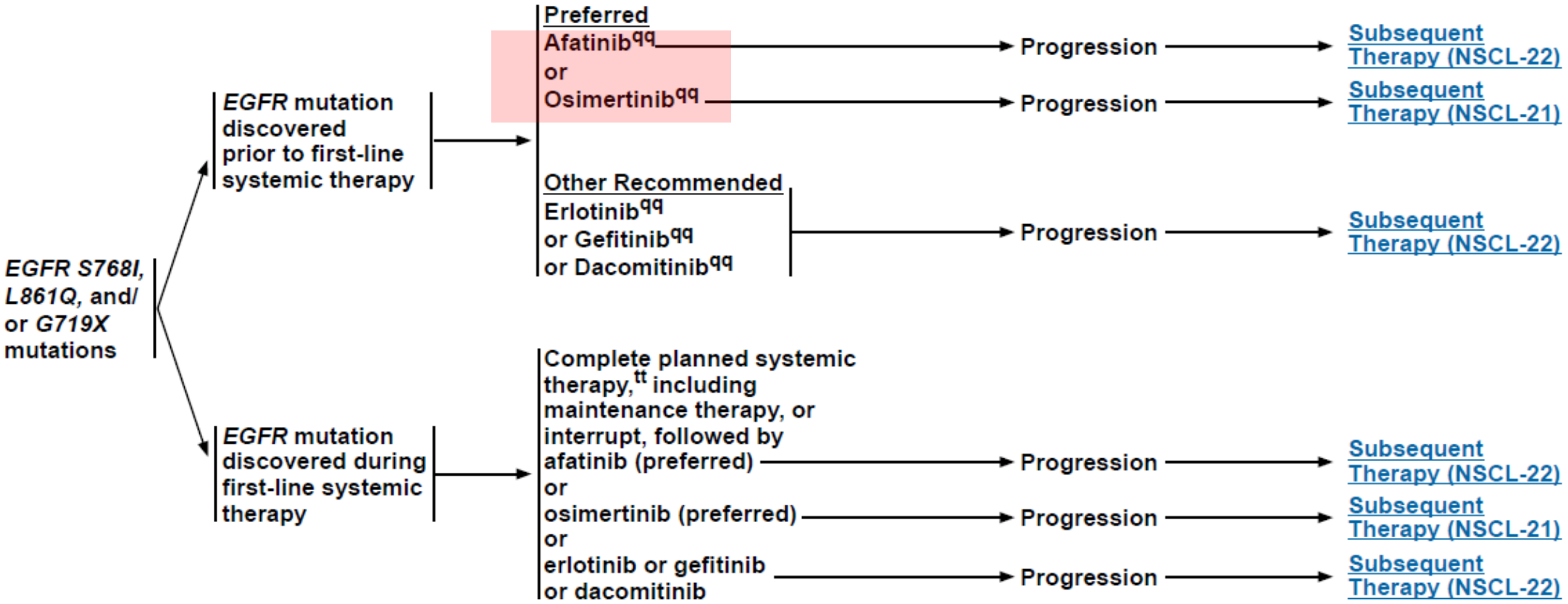
***EGFR S768I, L861Q,* and/or *G719X* MUTATIONS[mm]**

FIRST-LINE THERAPY[pp]



Summary of the EGFR TKI Clinical Data

	G719X				L861Q				S768I				
Study Details	n	ORR, %	Median PFS, mo	Median OS, mo	n	ORR, %	Median PFS, mo	Median OS, mo	n	ORR, %	Median PFS, mo	Median OS, mo	References
First-generation TKI													
Gefitinib/erlotinib													
NEJ002	7	14	–	–	3	33	–	–	–	–	–	–	Watanabe et al. (2014)[31]
Retrospective study, Republic of China	78	37		–	57	40	–	–	7	33	–	–	Chiu et al. (2015)[36]
Retrospective study, Republic of China	15	53	8.1	16.4	15[a]	60[a]	6.0[a]	15.2[a]	4	75	–	–	Wu et al. (2011)[37]
Retrospective study,[b] People's Republic of China	22	23	7.6	–	5	0	5.7	–	11	27	8.0	–	Zhang et al. (2017)[38]
Retrospective study,[b] People's Republic of China	14	43	6.0	19.8	15	47	8.9	22.0	–	–	–	–	Xu et al. (2016)[39]
Retrospective study, People's Republic of China	19	37	-	-	16	31	-	-	2	0	-	-	Chen et al. (2017)[58]
Retrospective study, People's Republic of China	16	50	11.6	25.2	-	-	-	-	-	-	-	-	Tu et al. (2017)[34]
Retrospective study, People's Republic of China	3	33	-	-	-	-	-	-	1	0	6	6.5	Peng et al. (2014)[57]
Retrospective study, United States	-	-	-	-	-	-	-	-	4	25	-	-	Sievers et al. (2016)[59]
Retrospective study, United States	3	100	-	-	-	-	-	-	-	-	-	-	Kobayashi et al. (2013)[55]
Retrospective study, Korea	4	33	-	-	4	50	-	-	-	-	-	-	Keam et al. (2014)[60]
Retrospective study, Korea	7[c]	14	1.3	6.3	-	-	-	-	-	-	-	-	Baek et al. (2015)[56]
BE-POSITIVE, retrospective study, Italy	6	0	8.4	17.0	5	40	5.2	14.5	-	-	-	-	Pilotto et al. (2018)[61]
Retrospective study, France	18[d]	7	3.0	22.0	-	-	-	-	-	-	-	-	Beau-Faller et al. (2014)[62]
Retrospective study, East Asia	2	100	-	-	-	-	-	-	-	-	-	-	Cheng et al. (2015)[63]
Retrospective study, Italy	42[e]	31	8.3	-	-	-	-	-	-	-	-	-	Passaro et al. (2019)[54]
Second-generation TKI													
Afatinib													
LUX-Lung 2,3,6, combined post-hoc analysis	18	78	13.8	26.9	16	56	8.2	17.1	8	100	14.7	NE	Yang et al. (2015)[29]
Afatinib uncommon mutations database	55	63	14.7	-	47	60	10.0	-	8	63	15.6	-	Yang et al. (2020)[28]
Third-generation TKI													
Osimertinib													
KCSG-LU15-09 phase II study, Korea	19	53	8.2	NR	9	78	15.2	NR	8	38	12.3	NR	Cho et al. (2020)[30]

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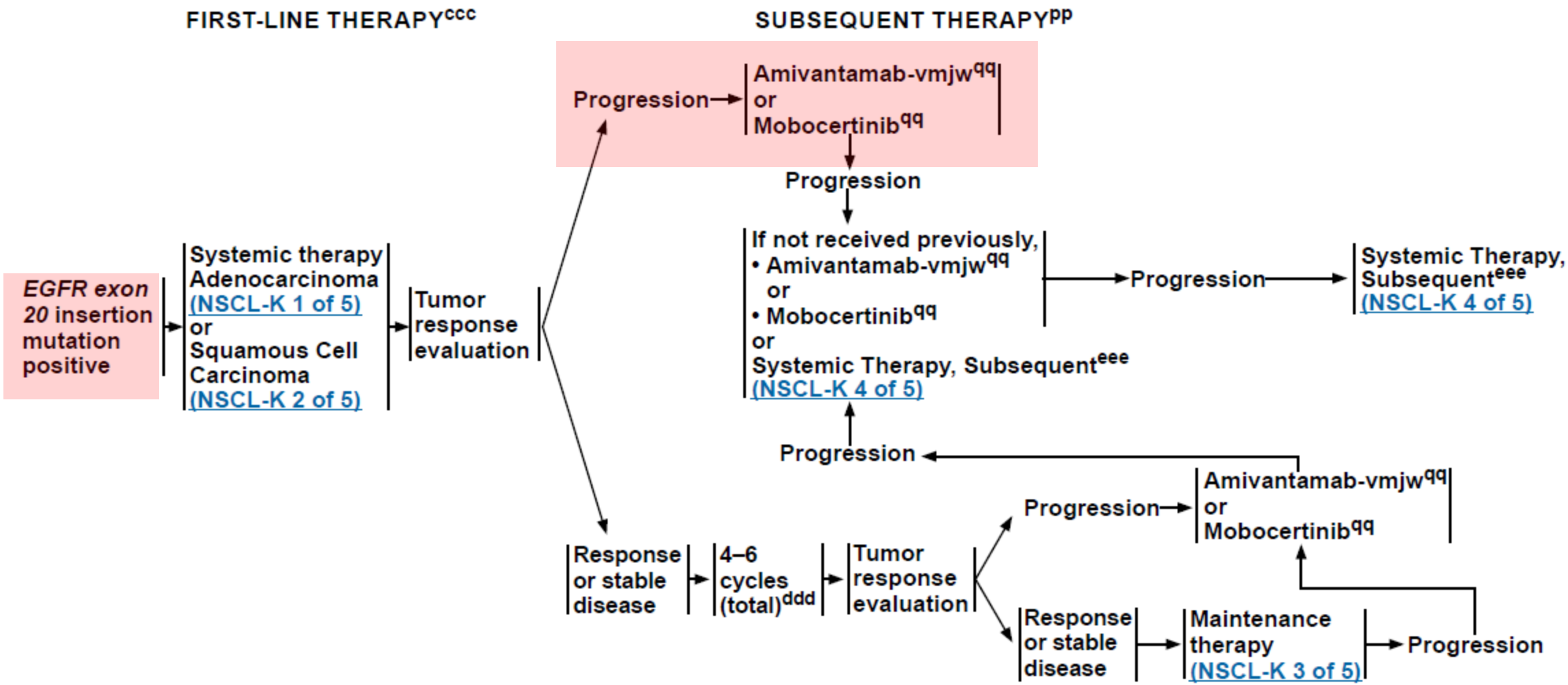
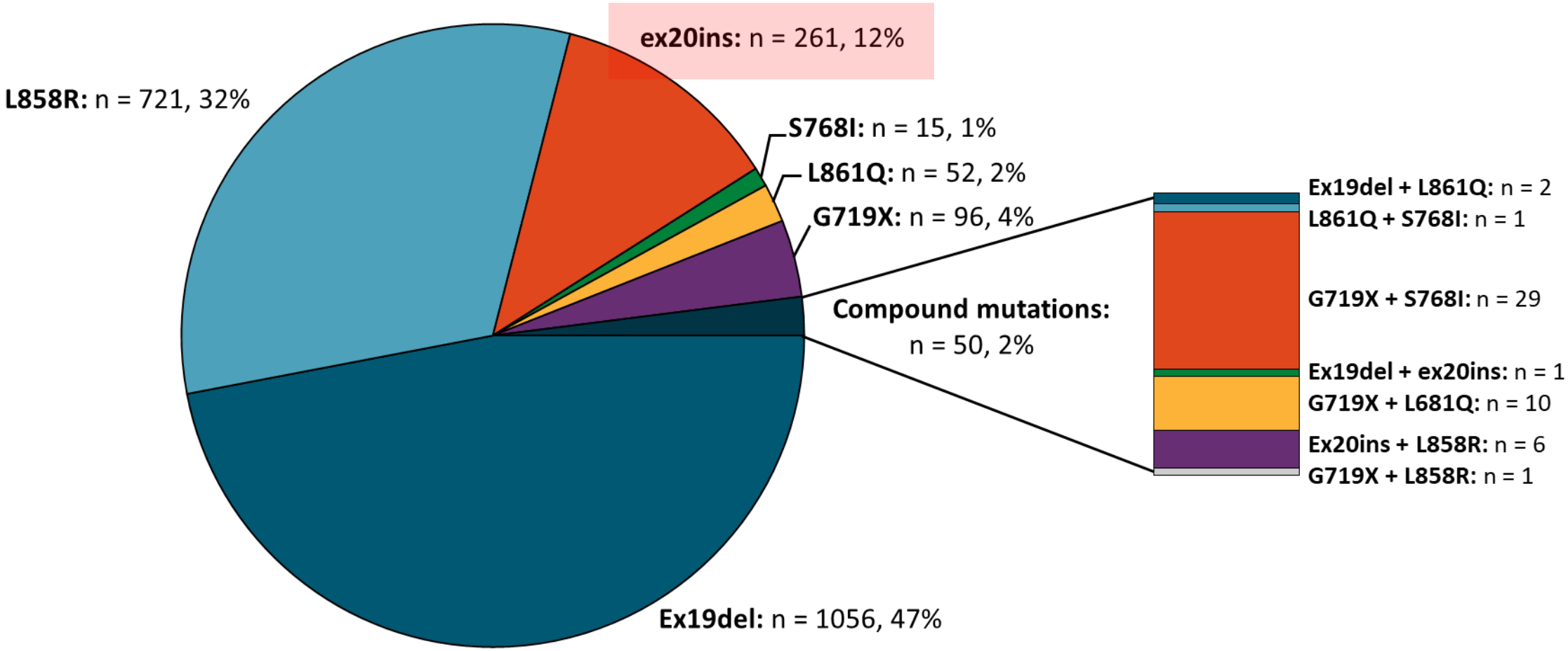
EGFR EXON 20 INSERTION MUTATION POSITIVE[mm]



Frequency and Distribution of *EGFR* Mutations in NSCLC



Thorac Oncol. 2018 October ; 13(10): 1560–1568

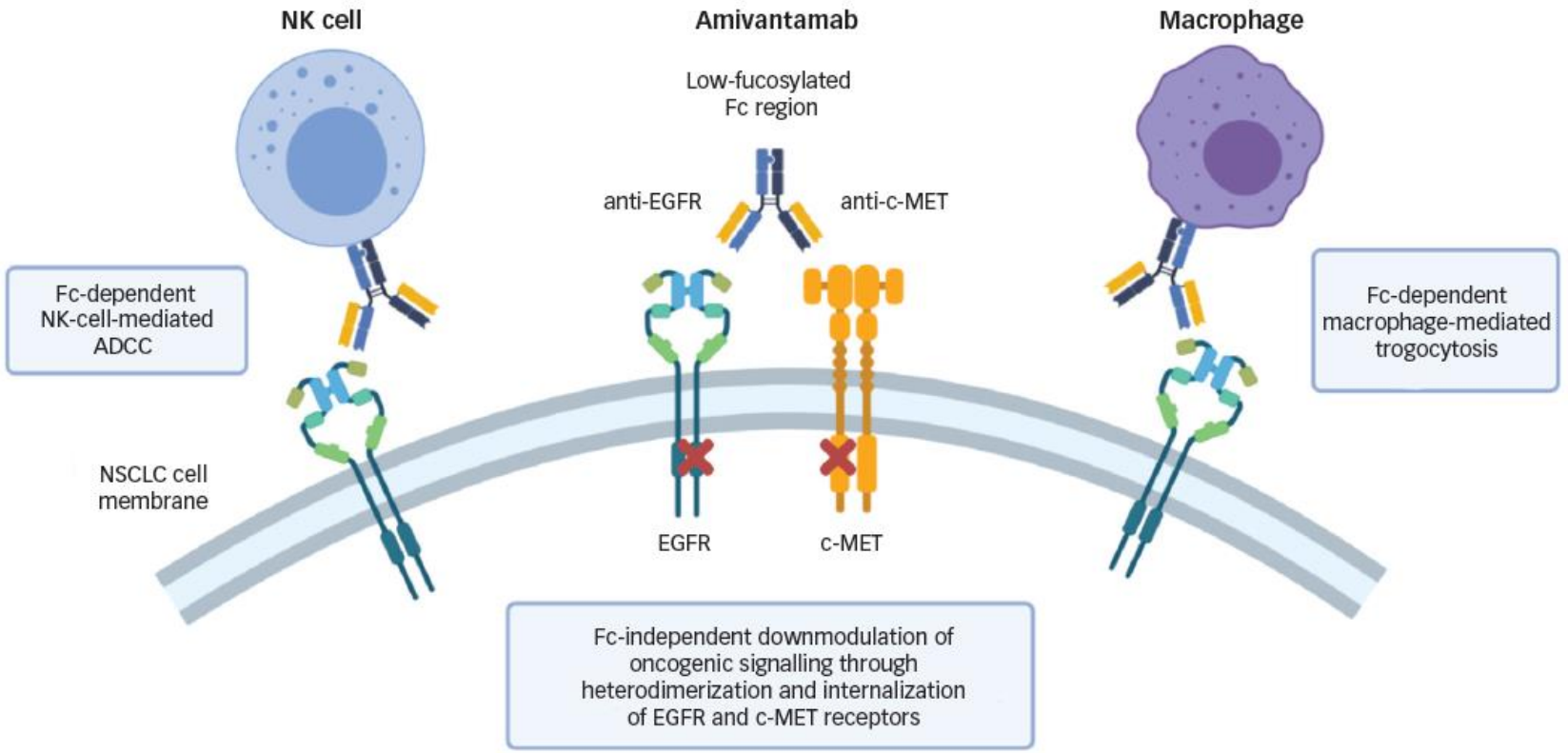
Comparison of Molecular, Pathologic and Clinical Characteristics

	EGFR-WT NSCLC	EGFR-mutant NSCLC (E19del and L858R – T790M neg)	EGFR ex20ins NSCLC	p-value (EGFR-WT vs. EGFR ex20ins)	p-value (EGFR-mutant E19del and L858R vs. ex20ins)	p-value (EGFR-WT vs. EGFR-mutant E19del and L858R – T790M neg)
Total Cases (N)	**12,551**	**1,318**	**260**			
Median Age, years (range)	65 (6-99)	65 (25-95)	63 (14-90)	**0.0007**	0.02	0.07
Sex, F/M (%F)	6,246/6,304 (50%)	888/430 (67%)	161/99 (62%)	**<0.0001**	0.089	**<0.0001**
Histologic Subtype						
Adenocarcinoma	8,572 (68%)	1,149 (87%)	235 (90%)	**<0.0001**	0.15	**<0.0001**
Squamous/Adeno squamous	1,835 (15%)	50 (3.8%)	0			
NSCLC-NOS	2,027 (16%)	115 (8.7%)	23 (8.8%)			
Sarcomatoid	117 (0.9%)	4 (0.3%)	2 (0.8%)			
Frequency of Co-Occurring Genomic Alterations						
Concurrent *EGFR* Copy Number Gain	355 (2.8%)	311 (24%)	57 (22%)	**<0.0001**	0.63	**<0.0001**
Concurrent *TP53* alteration	7,748 (62%)	844 (64%)	146 (56%)	0.0773	0.0163	0.107
Concurrent *RB1* alteration	771 (6.1%)	133 (10%)	28 (11%)	**0.0035**	0.7413	**<0.0001**
Concurrent *CDKN2A/2B* alteration	3,222 (26%)	317 (24%)	57 (22%)	0.1939	0.5232	0.2113
TMB (mutations per MB) Median	**8.1**	**3.6**	**3.6**	**<0.0001**	0.31	**<0.0001**
TMB Low (<5)	3,785 (30%)	832 (63%)	179 (69%)	**<0.01**	NS	**<0.01**
TMB Intermediate Low (5-10)	3,470 (28%)	400 (30%)	69 (27%)	**<0.01**	NS	**<0.01**
TMB Intermediate High (10-20)	3,325 (26%)	82 (6.2%)	10 (3.8%)	**<0.01**	NS	**<0.01**
TMB High (>20)	1,971 (16%)	4 (0.3%)	2 (0.8%)	NS	NS	NS

Thorac Oncol. 2018 October ; 13(10): 1560–1568

- EGFR Exon20ins mutations are molecularly heterogeneous, with > 100 variants identified by NGS
- Low response rate (0 – 9%)
- Reduced median OS 16.0 month vs 39 month (EGFR TKI sensitive Dz)

- fully human bispecific IgG1 antibody targeting both anti-EGFR/c-MET bispecific antibody
- US FDA in March 2020



original reports

Amivantamab in EGFR Exon 20 Insertion–Mutated Non–Small-Cell Lung Cancer Progressing on Platinum Chemotherapy: Initial Results From the CHRYSALIS Phase I Study

Keunchil Park, MD, PhD[1]; Eric B. Haura, MD[2]; Natasha B. Leighl, MD[3]; Paul Mitchell, MD[4]; Catherine A. Shu, MD[5]; Nicolas Girard, MD, PhD[6]; Santiago Viteri, MD[7]; Ji-Youn Han, MD, PhD[8]; Sang-We Kim, MD, PhD[9]; Chee Khoon Lee, MD[10]; Joshua K. Sabari, MD[11]; Alexander I. Spira, MD, PhD[12]; Tsung-Ying Yang, MD, PhD[13]; Dong-Wan Kim, MD, PhD[14]; Ki Hyeong Lee, MD, PhD[15]; Rachel E. Sanborn, MD[16]; José Trigo, MD[17]; Koichi Goto, MD, PhD[18]; Jong-Seok Lee, MD, PhD[19]; James Chih-Hsin Yang, MD, PhD[20]; Ramaswamy Govindan, MD[21]; Joshua M. Bauml, MD[22]; Pilar Garrido, MD, PhD[23]; Matthew G. Krebs, MD, PhD[24]; Karen L. Reckamp, MD[25]; John Xie, PhD[26]; Joshua C. Curtin, PhD[26]; Nahor Haddish-Berhane, PhD[26]; Amy Roshak, BS[26]; Dawn Millington, MS[26]; Patricia Lorenzini, MS[26]; Meena Thayu, MD[26]; Roland E. Knoblauch, MD, PhD[26]; and Byoung Chul Cho, MD, PhD[27]

- 1,050 mg amivantamab (1,400 mg, > 80 kg), once weekly for the first 4 wks and then once every 2 wks
- n= 81, median age; 62 years, median previous lines of therapy = 2
- ORR 40% (95% CI, 29 to 51); 3 – CR
- median DOR 11.1 months (95% CI, 6.9 to not reached).
- median PFS 8.3 months (95% CI, 6.5 to 10.9).
- most common AE - rash in 98 patients (86%)

J Clin Oncol 39:3391-3402. © 2021

Ongoing trials for amivantamab in NSCLC

Trial	Phase	Study treatment	Patient population	Current status
CHRYSALIS Part 2[35]	Ib/II	Amivantamab or amivantamab plus lazertinib	Pre-treated NSCLC with *EGFR* ex20ins mutation, classical *EGFR* mutation with secondary TKI resistance, or METex14 skipping	Recruiting, estimated completion January 2024
CHRYSALIS-2[58]	I/Ib	Amivantamab plus lazertinib	Pre-treated NSCLC with *EGFR* ex19del or L858R mutation post-osimertinib, or pre-treated NSCLC with *EGFR* ex20ins or other uncommon *EGFR* mutations	Recruiting, estimated completion October 2024
PAPILLON[56]	III	Amivantamab plus carboplatin-pemetrexed versus carboplatin-pemetrexed	Treatment-naïve NSCLC with *EGFR* ex20ins	Recruiting, estimated completion November 2024
MARIPOSA[59]	III	Amivantamab plus lazertinib versus osimertinib	Treatment-naïve NSCLC with *EGFR* ex19del or L858R mutation	Recruiting, estimated completion March 2026

touchREVIEWS in Oncology & Haematology. 2021;17(1):42–7

Preliminary efficacy of current investigational therapies for *EGFR* ex20ins NSCLC

Drug	CNS penetration	Overall response rate	Median duration of response	Grade ≥3 adverse events
Amivantamab	No	40%	11.1 months	38%
Mobocertinib	No	28%	17.5 months	46%
Osimertinib 160 mg	Possibly	25%	5.7 months	29%
Poziotinib	No	15%	7.4 months	63%

touchREVIEWS in Oncology & Haematology. 2021;17(1):42–7

Research

JAMA Oncology | Original Investigation

Treatment Outcomes and Safety of Mobocertinib in Platinum-Pretreated Patients With *EGFR* Exon 20 Insertion–Positive Metastatic Non–Small Cell Lung Cancer

A Phase 1/2 Open-label Nonrandomized Clinical Trial

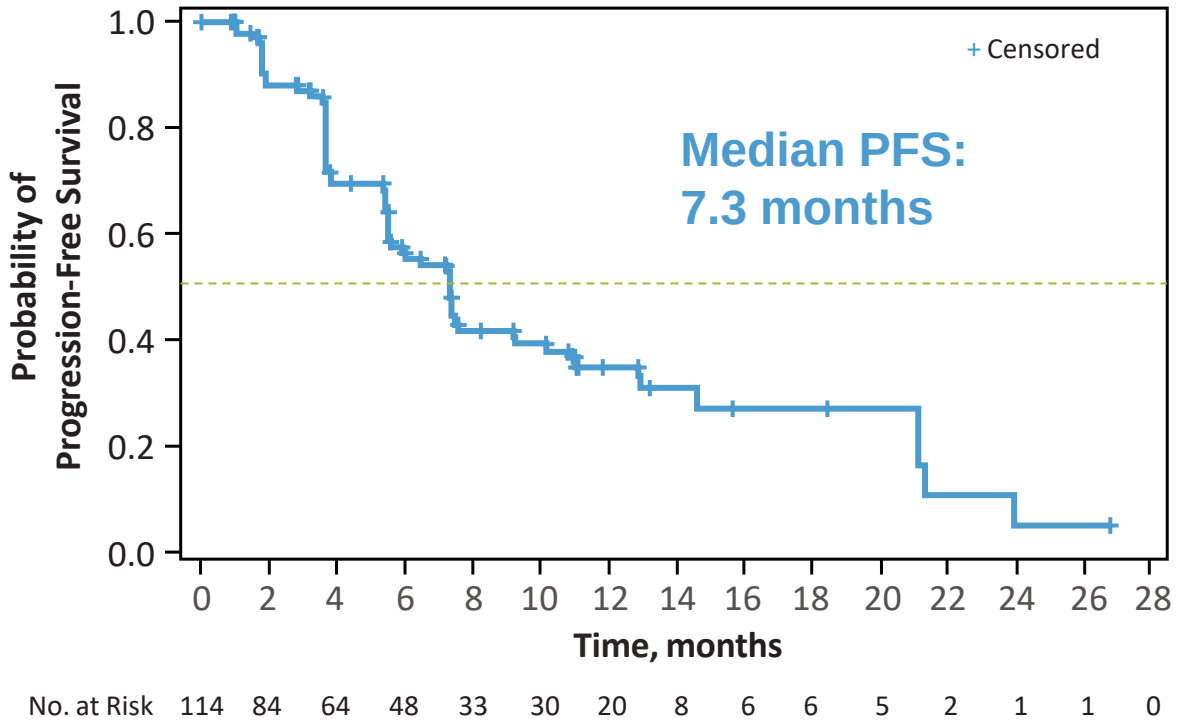
Caicun Zhou, PhD, MD; Suresh S. Ramalingam, MD; Tae Min Kim, MD, PhD; Sang-We Kim, MD; James Chih-Hsin Yang, MD; Gregory J. Riely, MD; Tarek Mekhail, MD; Danny Nguyen, MD; Maria R. Garcia Campelo, MD; Enriqueta Felip, MD; Sylvie Vincent, PhD; Shu Jin, MS; Celina Griffin, PharmD; Veronica Bunn, PhD; Jianchang Lin, PhD; Huamao M. Lin, PhD; Minal Mehta, MBBS; Pasi A. Jänne, MD, PhD

- Tx outcome and safety of mobocertinib in pts with previously treated EGFRex20ins-positive mNSCLC
- open-label, phase 1/2 nonrandomized clinical trial
- between June 2016 and November 2020
- Platinum-pretreated patients (PPP) cohort (n=114), EXCLAIM (n = 86)
- Mobocertinib 160mg once daily

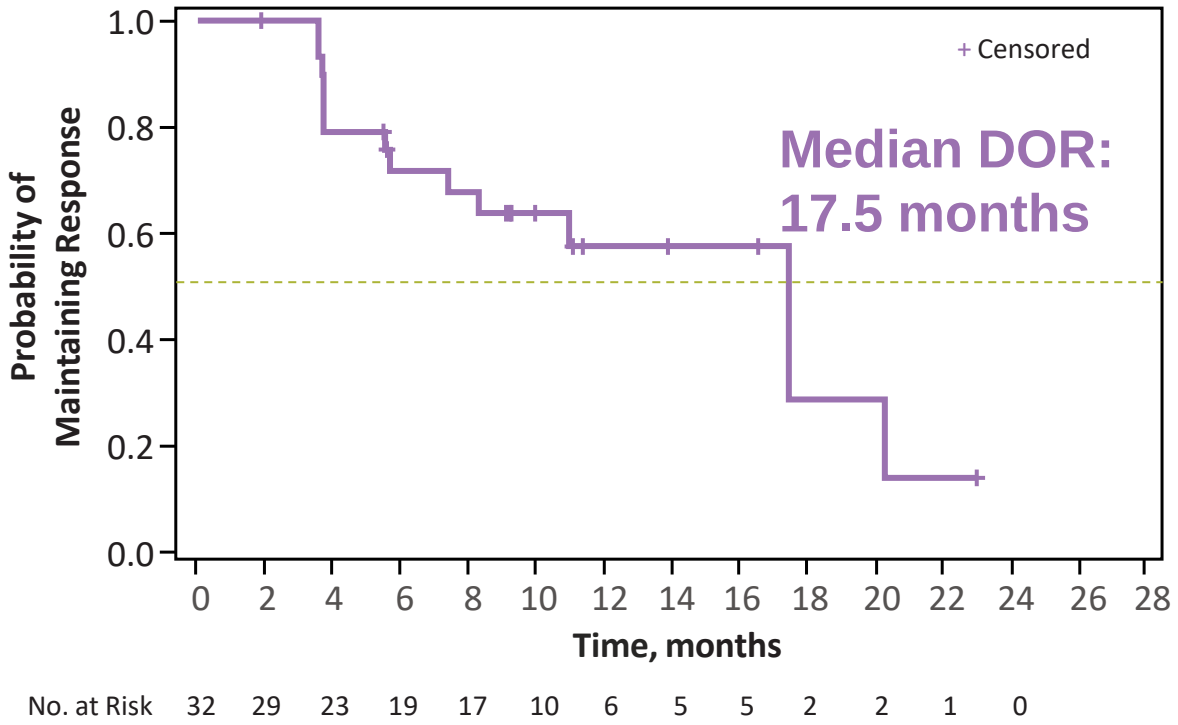
JAMA Oncol . 2021 Dec 1;7(12):e214761

Mobocertinib

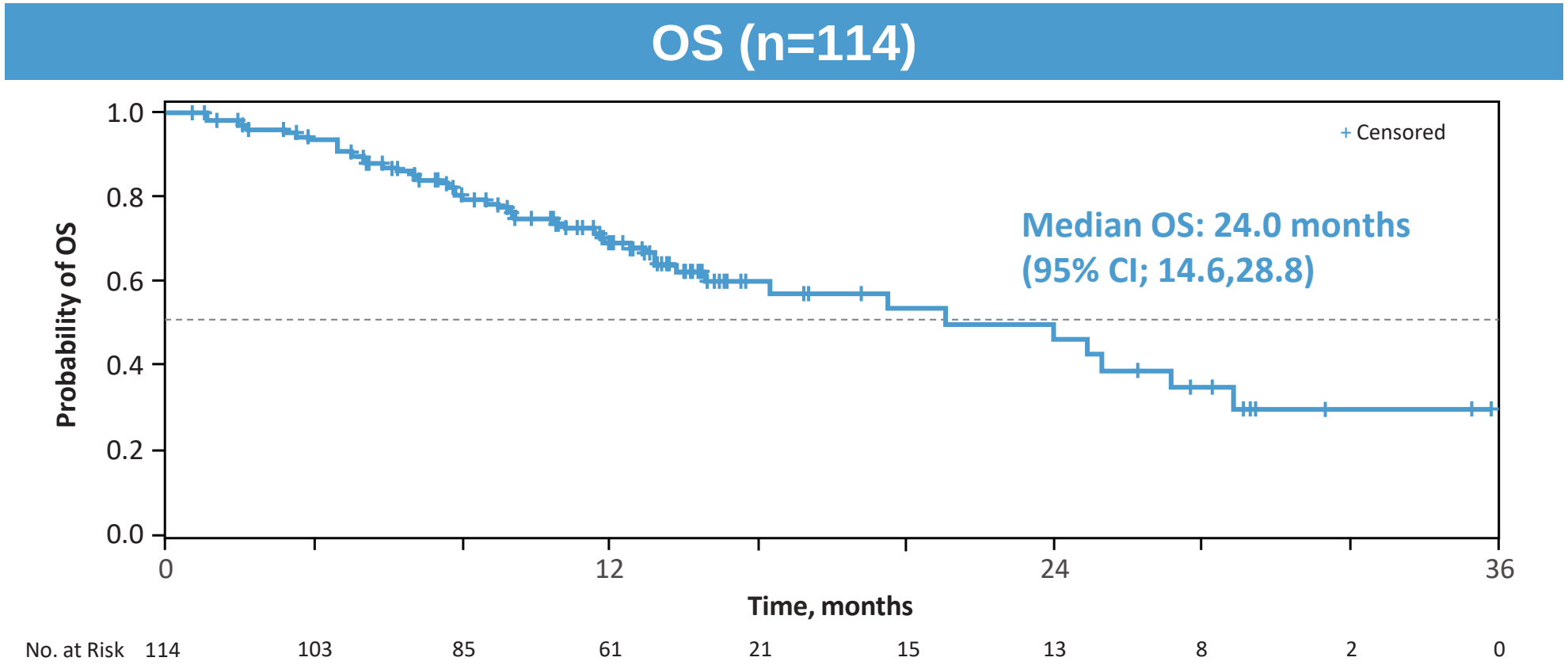
PFS (n=114)



DOR in Confirmed Responders (n=32)



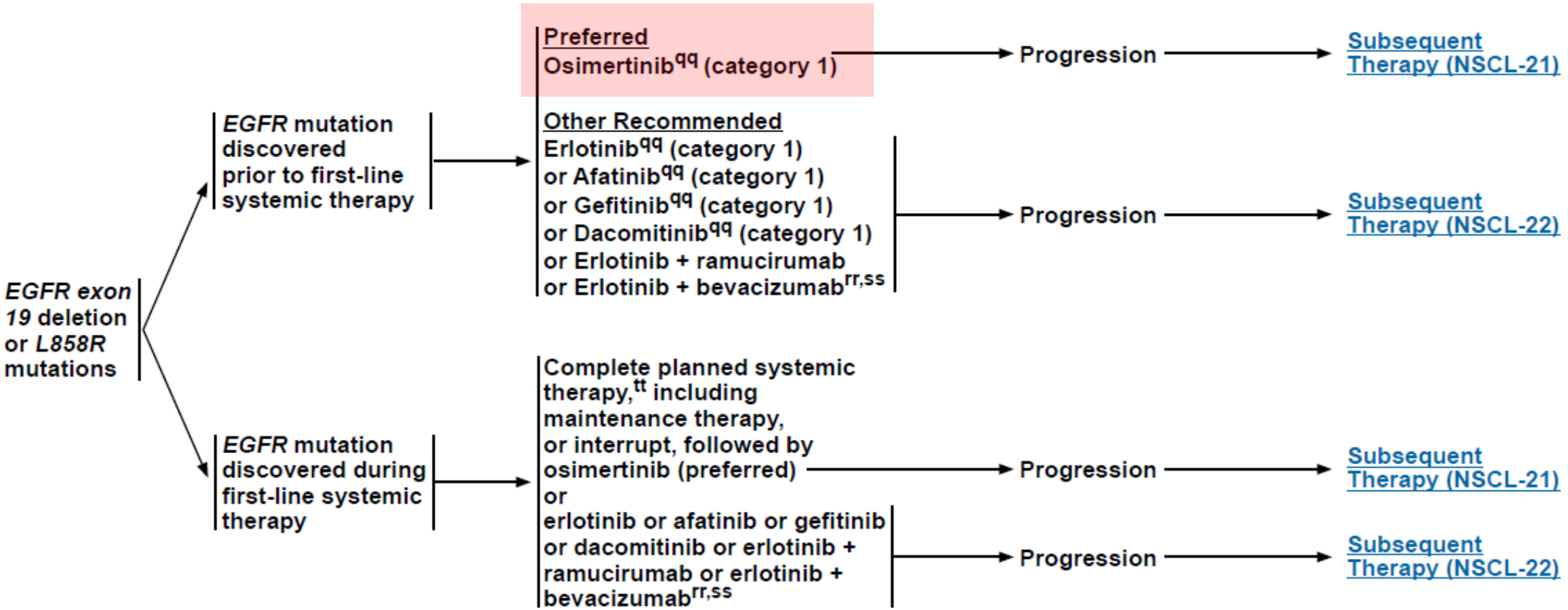
Mobocertinib



	Amivantamab (Phase 1, NCT02609776)	Mobocertinib (Phase 1/2, NCT02716116)
ORR	40%	28%
DCR	74%	78%
mDOR	11.1 months	17.5 months
mPFS	8.3 months	7.3 months
OS	22.8 months	24.0 months
Adverse events	Rash (86%), infusion-related reaction (66%), paronychia (45%)	Diarrhea (91%), Rash (45%), Paronychia (38%)

EGFR EXON 19 DELETION OR *L858R* MUTATIONS[mm]

FIRST-LINE THERAPY[pp]



Lazertinib in patients with *EGFR* mutation-positive advanced non-small-cell lung cancer: results from the dose escalation and dose expansion parts of a first-in-human, open-label, multicentre, phase 1–2 study

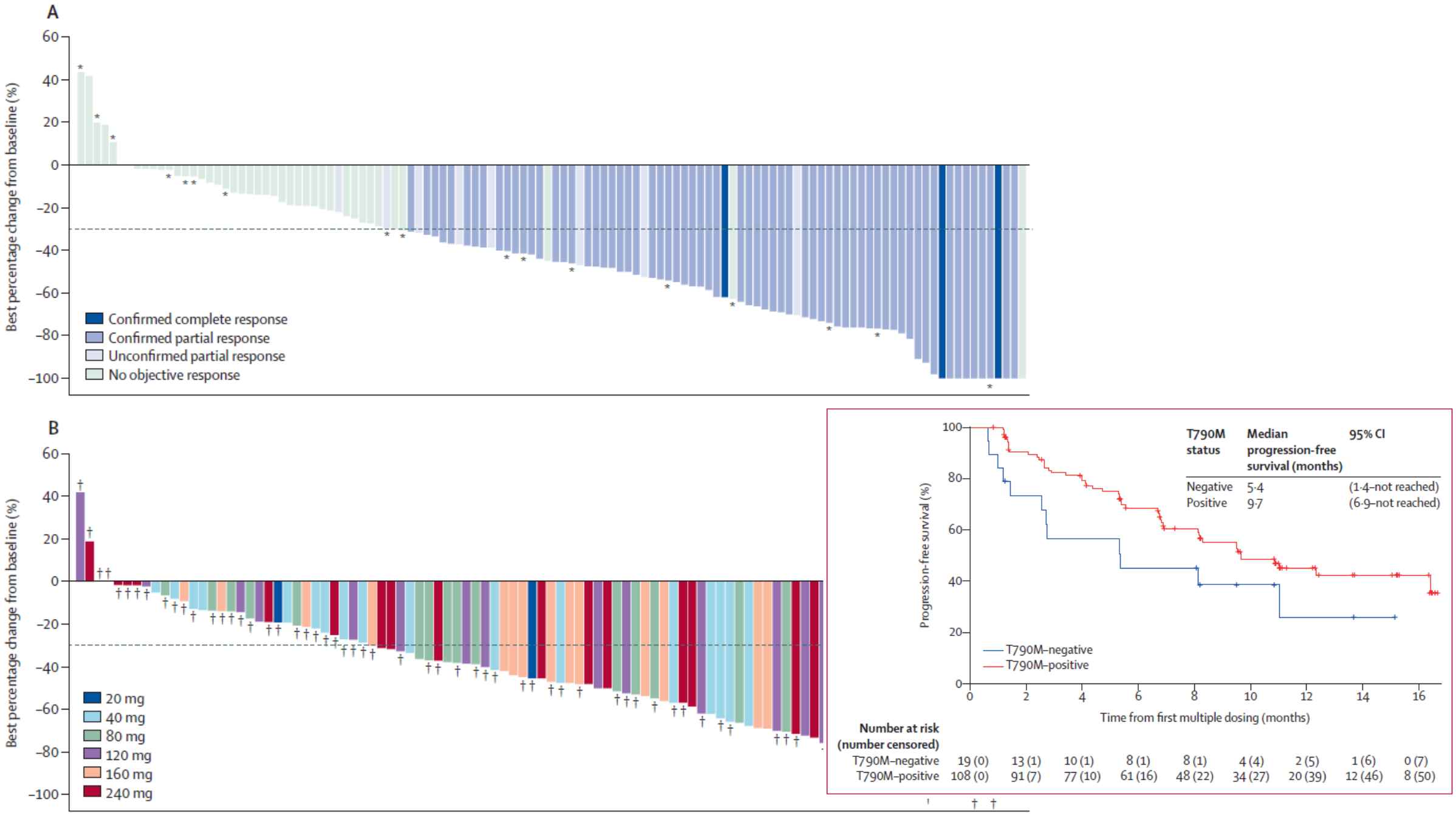
Myung-Ju Ahn, Ji-Youn Han, Ki Hyeong Lee, Sang-We Kim, Dong-Wan Kim, Yun-Gyoo Lee, Eun Kyung Cho, Joo-Hang Kim, Gyeong-Won Lee, Jong-Seok Lee, Young Joo Min, Jin-Soo Kim, Sung Sook Lee, Hye Ryun Kim, Min Hee Hong, Jin Seok Ahn, Jong-Mu Sun, Heung Tae Kim, Dae Ho Lee, Sohee Kim, Byoung Chul Cho

- An oral EGFR-TKI being developed by Yuhan and Janssen Biotech for the treatment of NSCLC
- Received its first approval on 18 January 2021 in the Republic of Korea
- Approved for the treatment of patients with *EGFR* T790M mutation-positive locally advanced or metastatic NSCLC who have previously received EGFR-TKI therapy

Feb 15, 2017, and May 28, 2018, 127 patients

Lancet Oncol 2019; 20: 1681–90

Drugs (2021) 81:1107–1113


A
Best percentage change from baseline (%)
60
40
20
0
−20
−40
−60
−80
−100
Confirmed complete response
Confirmed partial response
Unconfirmed partial response
No objective response
B
Best percentage change from baseline (%)
20 mg
40 mg
80 mg
120 mg
160 mg
240 mg
Progression-free survival (%)
100
80
60
40
20
0
T790M status
Median progression-free survival (months)
95% CI
Negative 5·4 (1·4–not reached)
Positive 9·7 (6·9–not reached)
T790M–negative
T790M–positive
0 2 4 6 8 10 12 14 16
Time from first multiple dosing (months)
Number at risk (number censored)
T790M–negative 19 (0) 13 (1) 10 (1) 8 (1) 8 (1) 4 (4) 2 (5) 1 (6) 0 (7)
T790M–positive 108 (0) 91 (7) 77 (10) 61 (16) 48 (22) 34 (27) 20 (39) 12 (46) 8 (50)

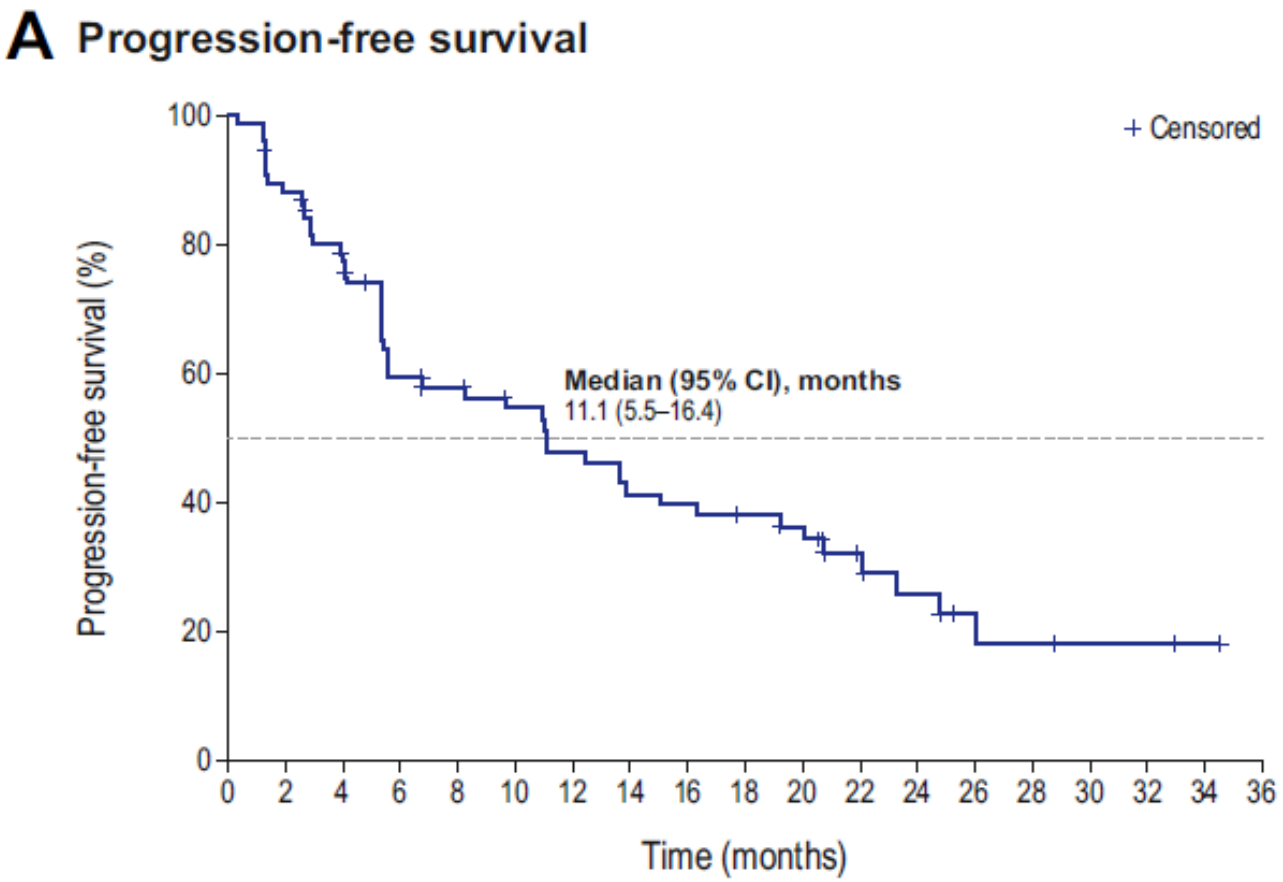
A Phase 1/2 Study of Lazertinib 240 mg in Patients With Advanced *EGFR* T790M-Positive NSCLC After Previous EGFR Tyrosine Kinase Inhibitors

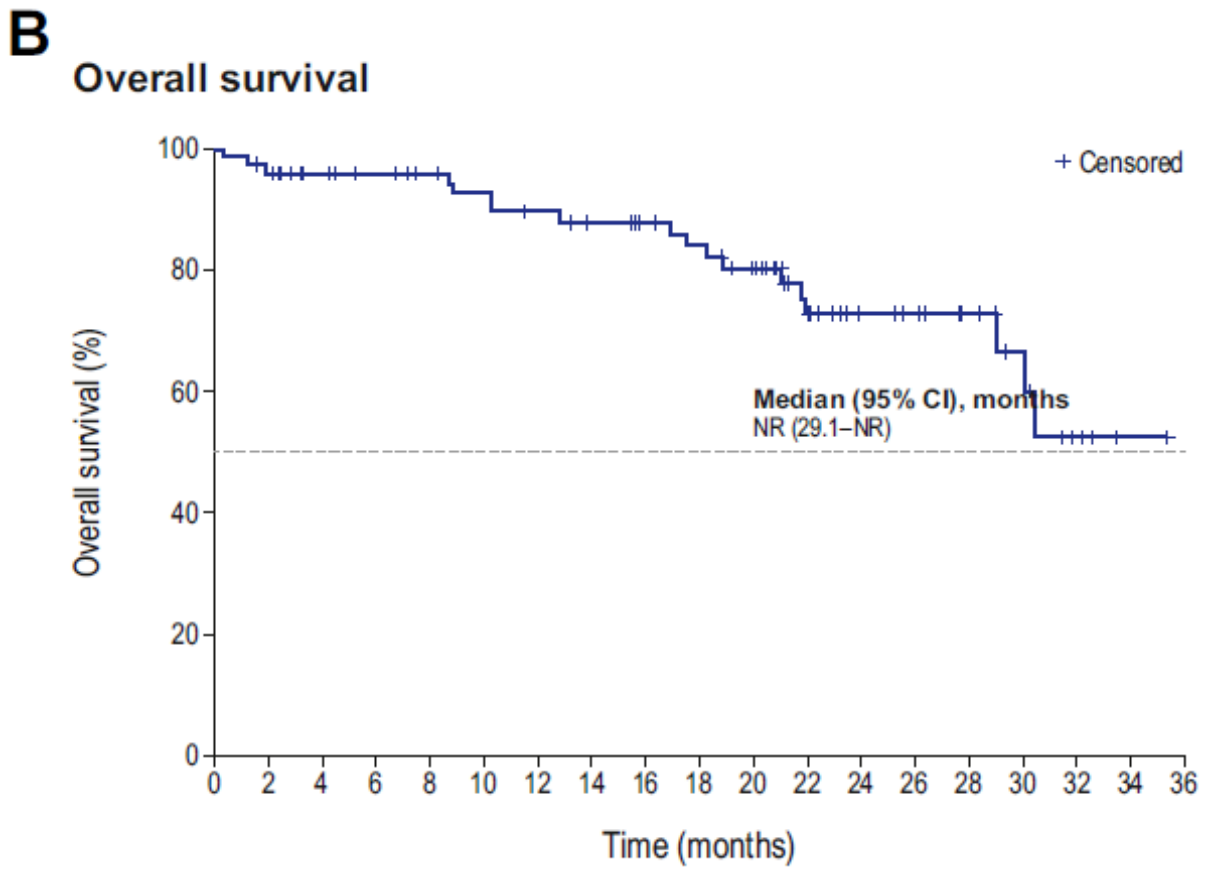
Byoung Chul Cho, MD, PhD,[a] Ji-Youn Han, MD, PhD,[b] Sang-We Kim, MD, PhD,[c] Ki Hyeong Lee, MD, PhD,[d] Eun Kyung Cho, MD, PhD,[e] Yun-Gyoo Lee, MD, PhD,[f] Dong-Wan Kim, MD, PhD,[g] Joo-Hang Kim, MD, PhD,[h] Gyeong-Won Lee, MD, PhD,[i] Jong-Seok Lee, MD, PhD,[j] Byoung Yong Shim, MD, PhD,[k] Jin-Soo Kim, MD, PhD,[l] Sang Hoon Chun, MD, PhD,[m] Sung Sook Lee, MD, PhD,[n] Hye Ryun Kim, MD, PhD,[a] Min Hee Hong, MD,[a] Jin Seok Ahn, MD, PhD,[o] Jong-Mu Sun, MD, PhD,[o] Youngjoo Lee, MD, PhD,[b] Dae Ho Lee, MD, PhD,[c] Ji Ah Kang, MS,[p] NaMi Lee, MS,[p] Mi-Jung Kwon, PhD,[p] Carin Espenschied, MS,[q] Arielle Yablonovitch, PhD,[q] Myung-Ju Ahn, MD, PhD[o,*]

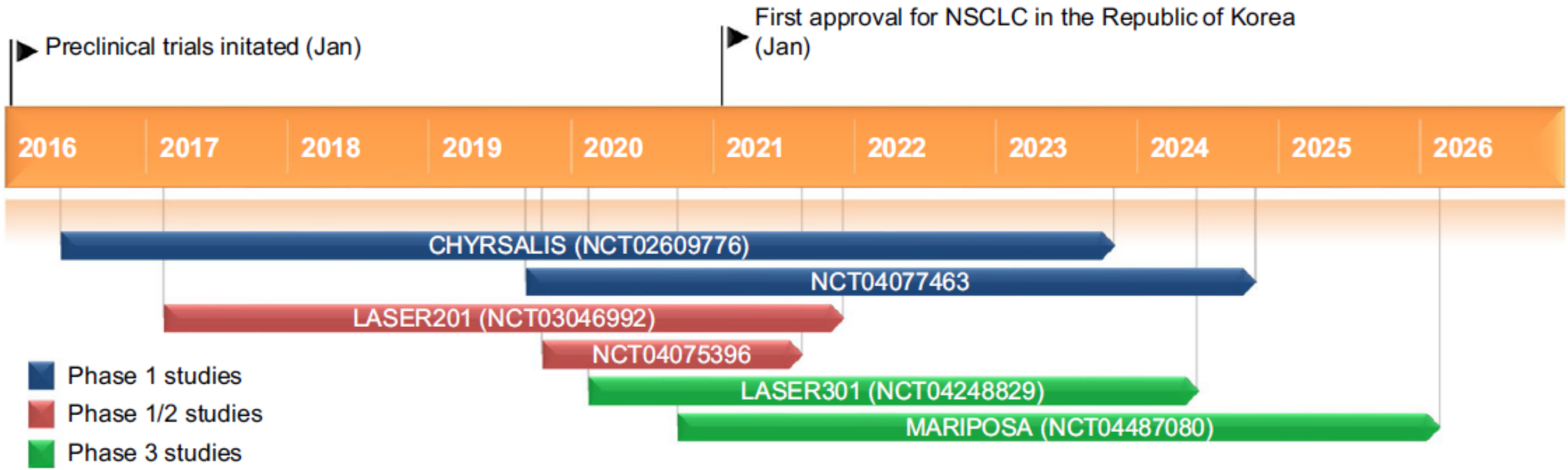
- 78 patients received lazertinib 240 mg at 17 centers

J Thorac Oncol. 2022 Apr;17(4):558-567

Lazertinib


A
Progression-free survival
+ Censored
Progression-free survival (%)
100
80
60
40
20
0
Median (95% CI), months
11.1 (5.5–16.4)
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36
Time (months)


B
Overall survival
+ Censored
Overall survival (%)
100
80
60
40
20
0
Median (95% CI), months
NR (29.1–NR)
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36
Time (months)


Preclinical trials initated (Jan)
First approval for NSCLC in the Republic of Korea (Jan)
2016
2017
2018
2019
2020
2021
2022
2023
2024
2025
2026
CHYRSALIS (NCT02609776)
NCT04077463
LASER201 (NCT03046992)
NCT04075396
LASER301 (NCT04248829)
MARIPOSA (NCT04487080)
Phase 1 studies
Phase 1/2 studies
Phase 3 studies

Lazertinib IIT : Ongoing studies

순번	임상시험제목	실시기관	승인일
1	무증상 혹은 경미한 증상의 **뇌 전이를 동반**한 EGFR 돌연변이 양성 전이성 비소세포폐암 환자를 대상으로 lazertinib(YH25448) 투여 후 항암 작용을 평가하기 위한 공개, 단일 중재군, 다기관, 임상2상, 연구자 주도 임상시험	서울대학교병원/분당서울대병원/길병원/서울성모병원/세브란스병원/고려대학교병원	2021-01-21
2	**연수막 전이**를 동반한 EGFR 돌연변이 양성 비소세포폐암에서 lazertinib과 pemetrexed 2상 임상시험 (LAZARUS)	삼성서울병원/ 세브란스병원/ 분당서울대학교병원/ 국립암센터/ 계명대학교동산병원/ 길병원/ 서울대학교병원	2021-04-05
3	**폐세척액에서** 검출된 T790M 유전자 돌연변이를 갖는 비소세포폐암 환자에서 LAZERTINIB의 유효성을 평가하는 다기관, 단일군 2상 임상시험	건국대학교병원/ 고대구로병원/ 서울아산병원/ 화순전남대학교병원	2021-07-20
4	**희귀 (uncommon) EGFR 돌연변이를** 포함하는 비소세포폐암(NSCLC) 환자를 대상으로 레이저티닙(Lazertinib)의 효과를 평가하기 위한 다기관, 단일군, 제2상 연구	길 병원/ 울산대병원/ 강남세브란스/ 세브란스병원/ 삼성서울병원	2021-09-29
5	동시적 소수전이성 EGFR 돌연변이 비소세포폐암 환자를 대상으로 1 차 선택 lazertinib 과 **국소절제 방사선요법**의 안전성과 유효성을 평가하기 위한 다기관, 두 치료군, 제 II 상 임상시험 (ABLATE)	인천성모병원/ 세브란스병원/경상국립대병원/강남세브란스/ 길병원/ 해운대백병원/ 서울아산병원	2021-10-22
6	뇌전이가 있는 치료받지 않은 EGFR 돌연변이 양성 비소세포폐암 환자에서 레이저티닙의 유효성을 평가하는 단일군, 단일기관, 2상 임상시험	서울아산병원	2021-11-10
7	무증상 혹은 경미한 증상의 뇌 전이를 동반한 **osimertinib에 실패**한 EGFR 돌연변이 양성 전이성 비소세포폐암 환자를 대상으로 lazertinib(YH25448)과 pemetrexed/carboplatin 병용요법에 대한 공개, 단일 중재군, 다기관, 임상2상, 연구자 주도 임상시험	고려대학교의과대학부속병원/ 서울성모병원	2021-12-08
8	**기관지폐포세척액 액상생검으로 검출**된 절제 가능한 EGFR 유전자변이 양성 폐선암 환자에게 레이저티닙 선행항암요법 효과에 관한 전향적 단일기관 단일군 2상 임상 연구	건국대학교병원	2021-12-29
9	**근치적 백금기반 항암화학방사선요법 이후** 질병이 진행되지 않은 상피세포성장인자 수용체(EGFR) 돌연변이 양성의 절제불가능한 국소 진행성 비소세포폐암 (3기) 환자를 대상으로 레이저티닙(Lazertinib) 관해공고요법의 유효성과 안전성을 평가하기 위한 공개, 단일군, 다기관, 제2상 임상시험	화순전남대병원/ 한양대병원/ 충남대병원/ 서울아산병원/ 세브란스병원/ 고신대복음병원/ 계명대동산병원/ 경희대병원/건국대병원/ 고대구로병원	2022-03-04

1. 의약품안전나라 의약품통합정보시스템

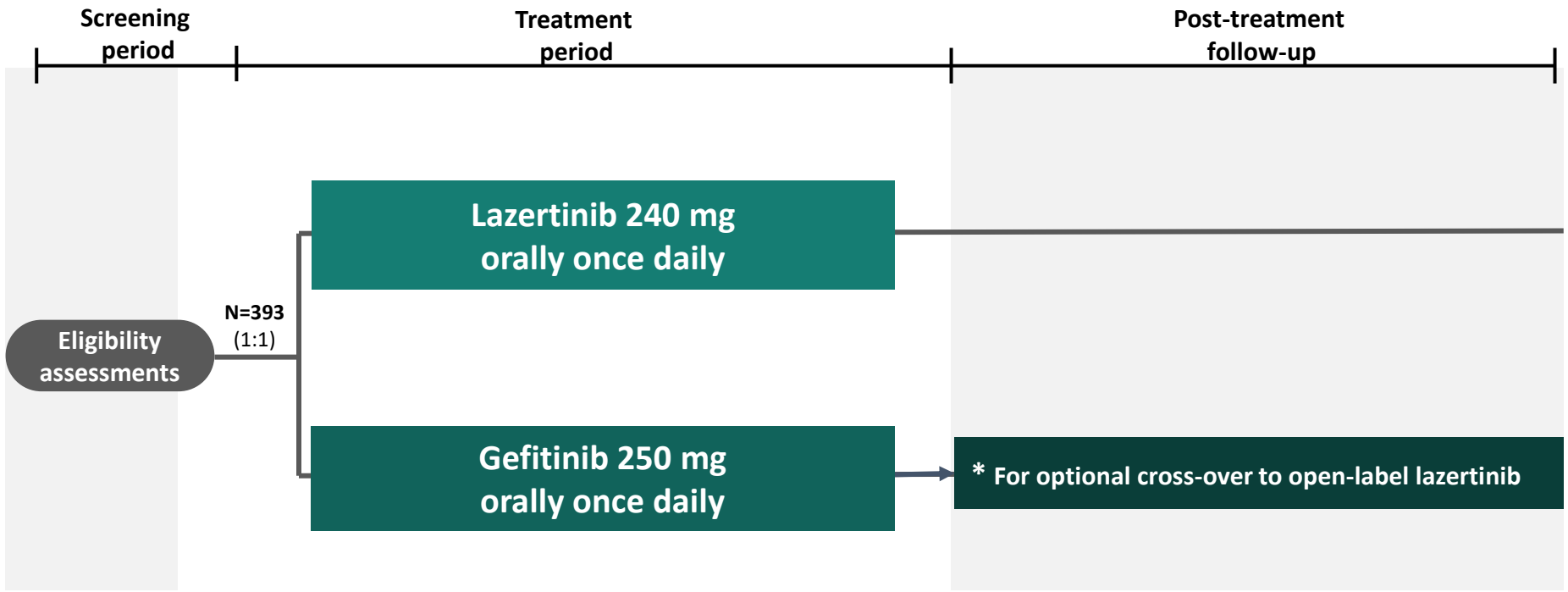
LASER301 Study Design

Study title

A Phase III, Randomized, Double-blind Study to Assess the Efficacy and Safety of Lazertinib versus Gefitinib as the **First-line Treatment** in Patients with Epidermal Growth Factor Receptor Sensitizing Mutation Positive, Locally Advanced or Metastatic Non-Small Cell Lung Cancer

Outcomes

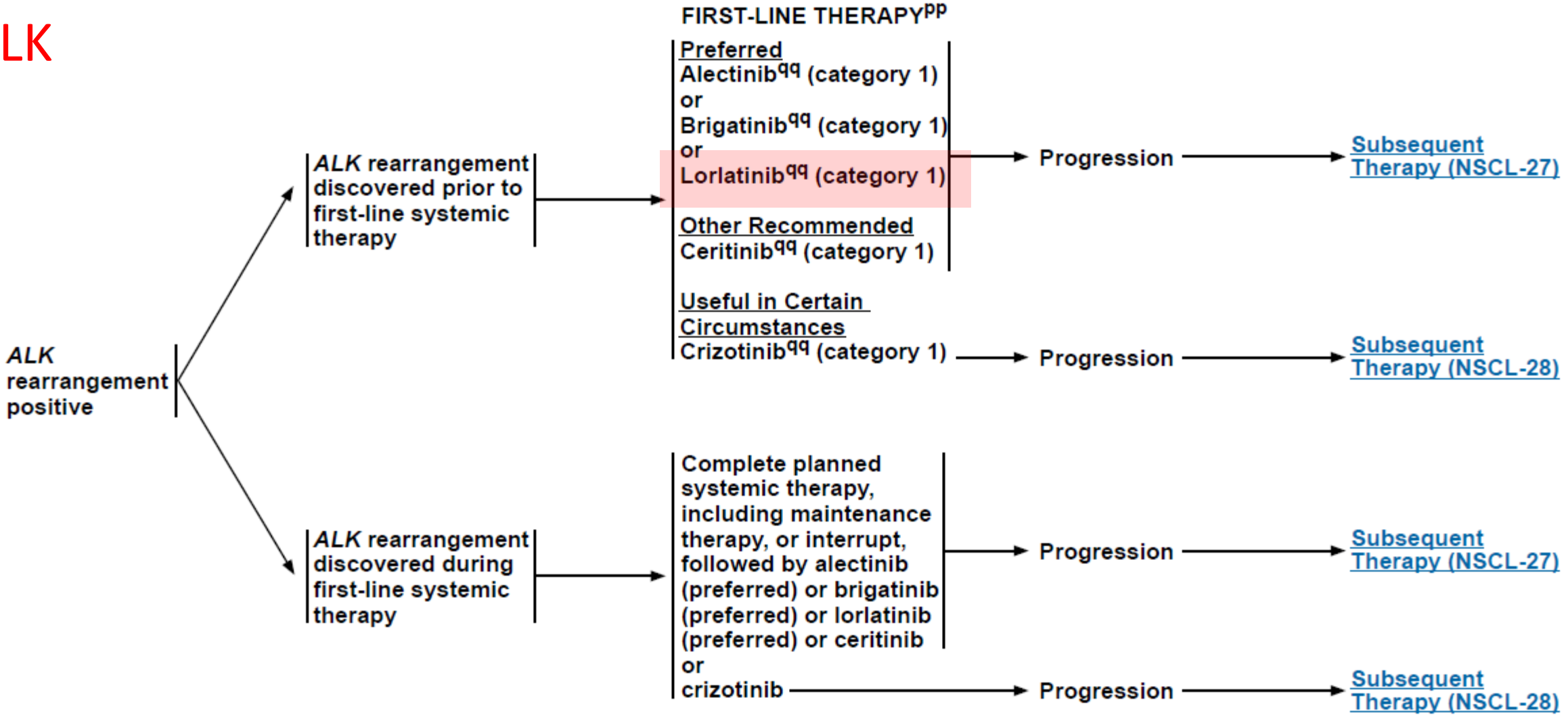
- **Primary:** Progression-Free Survival **(PFS)** according to RECIST v1.1 **by Investigator assessment**
- **Secondary:** ORR, DoR, DCR, Depth of Response, Time to Response, OS, Plasma & CSF concentration, EORTC-QLQ-C30, EORTC QLQ-LC13, EQ-5D-5L



1. NCT04248829, clinicaltrials.gov

	Osimertinib (phase 1/2, NCT01802632)	Lazertinib (phase 1/2, NCT03046992)
ORR	62%	55.3%
DCR	90%	89.5%
mPFS	10.1 months	11.1 months
OS	26.8 months	Not reached
Adverse events	Diarrhea (43%), Rash (40%), Paronychia (31%)	Rash (37.2%), Pruritus (34.6%) Paresthesia (33.3%)

ALK


ALK REARRANGEMENT POSITIVE[mm]
FIRST-LINE THERAPY[pp]
ALK rearrangement positive
ALK rearrangement discovered prior to first-line systemic therapy
ALK rearrangement discovered during first-line systemic therapy
Preferred
Alectinib[qq] (category 1)
or
Brigatinib[qq] (category 1)
or
Lorlatinib[qq] (category 1)
Other Recommended
Ceritinib[qq] (category 1)
Useful in Certain Circumstances
Crizotinib[qq] (category 1)
Complete planned systemic therapy, including maintenance therapy, or interrupt, followed by alectinib (preferred) or brigatinib (preferred) or lorlatinib (preferred) or ceritinib
or
crizotinib
Progression
Subsequent Therapy (NSCL-27)
Progression
Subsequent Therapy (NSCL-28)
Progression
Subsequent Therapy (NSCL-27)
Progression
Subsequent Therapy (NSCL-28)

Trialr	CROWN		ALTA-1L		ALEX		J-ALEX		ALESIA	
Author	Shaw et al.		Camidge et al.		Camidge et al.		Nakagawa et al.		Zhou et al.	
Year	2020		2020		2019		2019		2019	
Design	Phase III, open-label, RCT		Phase III, open-label, RCT		Phase III, open-label, RCT		Phase III, open-label, RCT		Phase III, open-label, RCT	
Intervention	Lorlatinib 100 mg QD	Crizotinib 250 mg BID	Brigatinib 90 mg QD for 7 days, then 180 mg QD	Crizotinib 250 mg BID	Alectinib 600 mg BID	Crizotinib 250 mg BID	Alectinib 300 mg BID	Crizotinib 250 mg BID	Alectinib 600 mg BID	Crizotinib 250 mg BID
Sample size	149	147	137	138	152	151	103	104	125	62
Outcome										
PFS (months, median)	NE	9.3	24.0	11.0	34.8	10.9	34.1	10.2	NE	10.7
PFS (HR, 95% CI)	0.28 (0.19–0.41)		0.49 (0.35–0.69)		0.43 (0.32–0.58)		0.37 (0.26–0.52)		0.37(0.22–0.61)	
ORR	113/149	85/147	101/137	85/138	126/152	114/151	76/83	71/90	114/125 *	48/62 *
ORR (%)	76%	58%	74%	62%	82.9%	75.5%	92%	79%	91%	77%
Safety AE ≥ grade3	72%	56%	73%	61%	45%	51%	26%	52%	29%	48%
					Patient characteristics					
Age (median)	59.1	55.6	58.0	60.0	56.3	53.8	61.0	59.5	51.0	49.0
Male (%)	44%	38%	50%	41%	45%	42%	40%	39%	51%	55%
Baseline brain metastasis (%)	26%	27%	29%	30%	42%	38%	14%	28%	35%	37%

Cancers 2021, 13, 1966.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

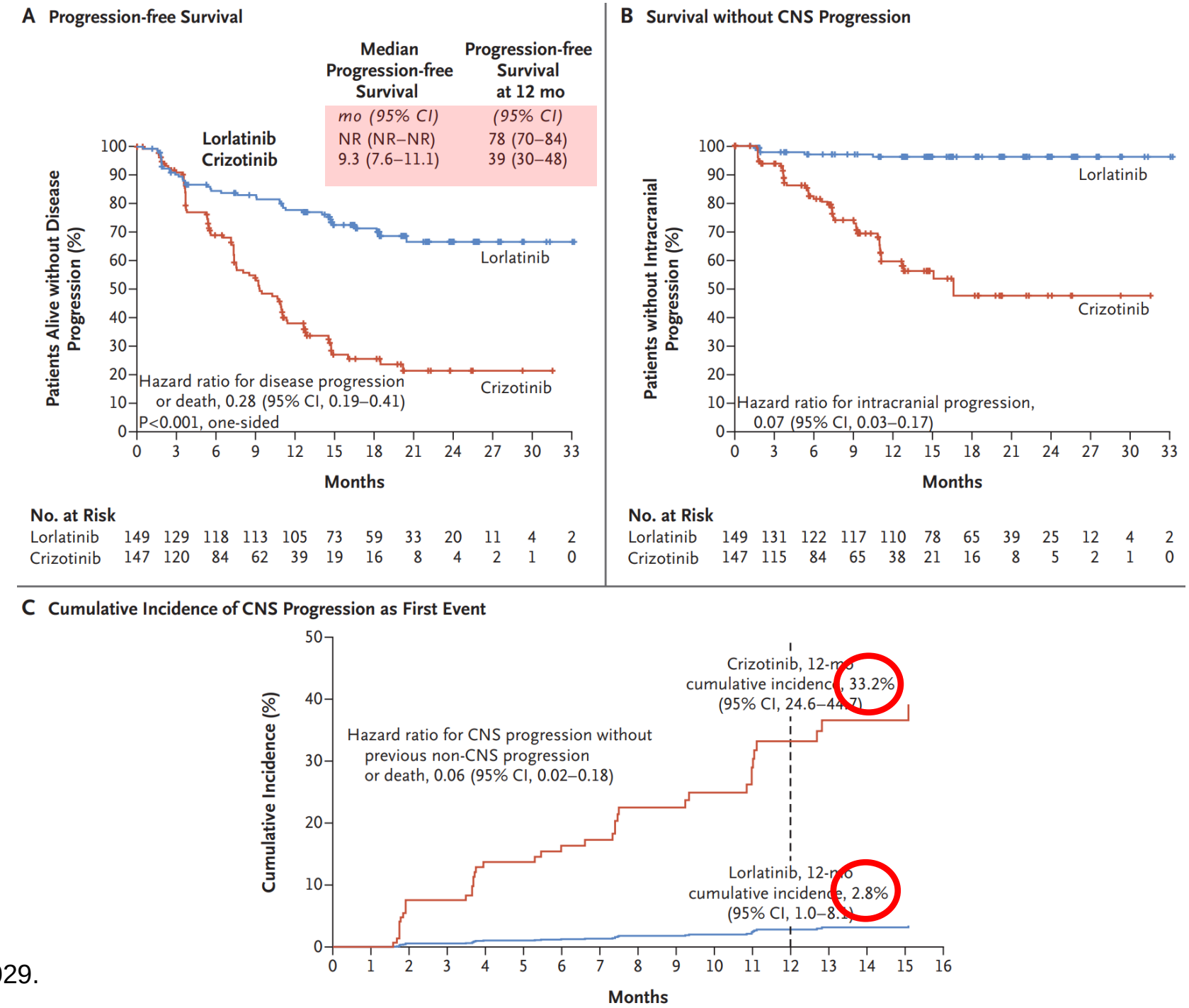
First-Line Lorlatinib or Crizotinib in Advanced *ALK*-Positive Lung Cancer

Alice T. Shaw, M.D., Ph.D., Todd M. Bauer, M.D., Filippo de Marinis, M.D., Ph.D., Enriqueta Felip, M.D., Ph.D., Yasushi Goto, M.D., Ph.D., Geoffrey Liu, M.D., Julien Mazieres, M.D., Ph.D., Dong-Wan Kim, M.D., Ph.D., Tony Mok, M.D., Anna Polli, B.Sc., Holger Thurm, M.D., Anna M. Calella, Ph.D., Gerson Peltz, M.D., M.P.H., and Benjamin J. Solomon, M.B., B.S., Ph.D., for the CROWN Trial Investigators*

- Global, randomized, phase 3 trial
- 296 ALK positive pt
- 1st end point – PFS, 2nd end point – ORR, intracranial response

N Engl J Med. 2020 Nov 19;383(21):2018-2029.

Lorlatinib



N Engl J Med. 2020 Nov 19;383(21):2018-2029.

IASLC

Lorlatinib Should Not be Considered as the Preferred First-Line Option in Patients With Advanced ALK Rearranged NSCLC

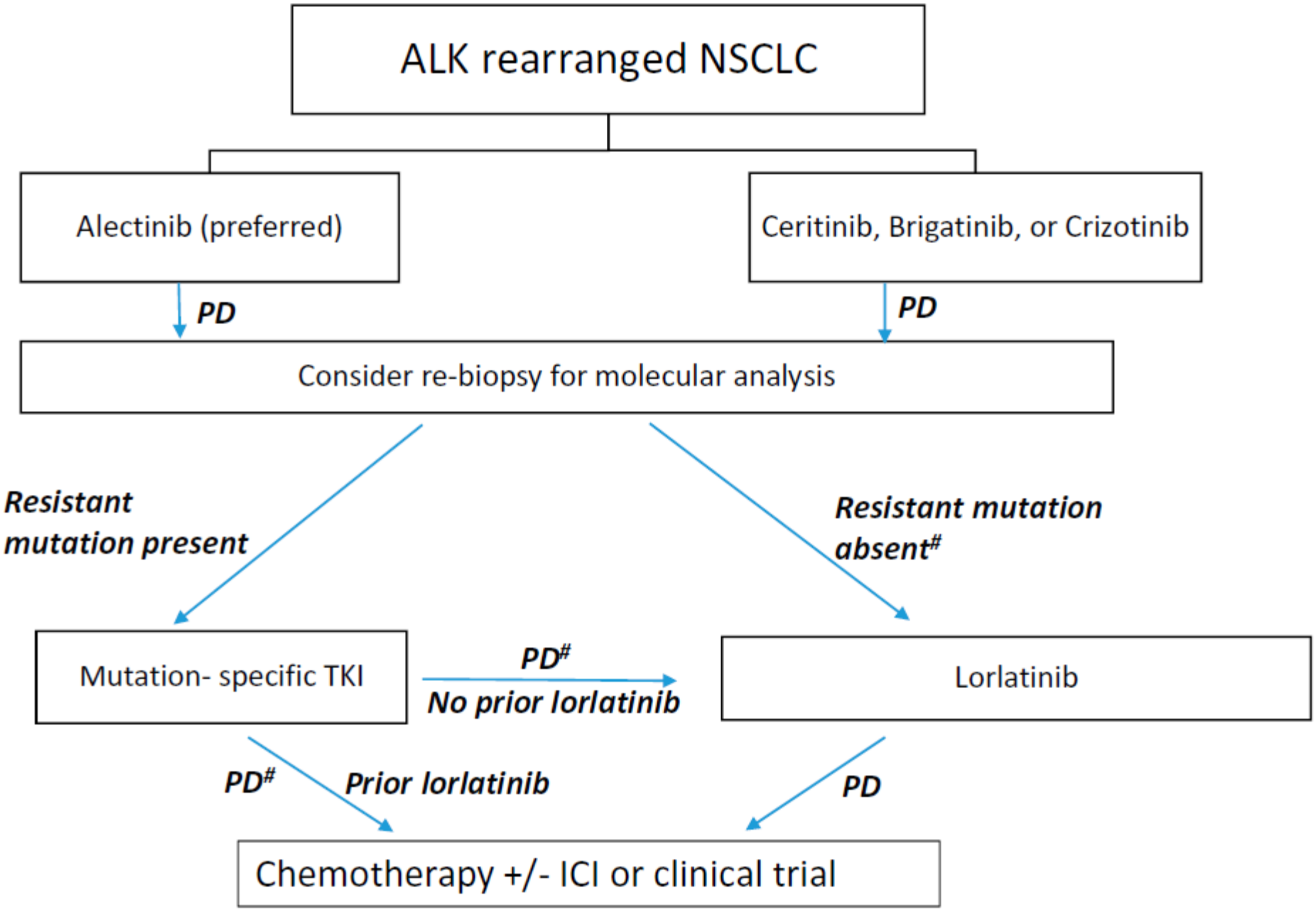
David Ross Camidge, MD, PhD*

ALK+ NSCLC Is a Forgiving Disease

If we start with alectinib, for example, we have several active next-line ALK inhibitor options to consider, reflecting the persistence of ALK dominance in a significant proportion of these patients

Toxicity Matters : hypertriglyceridemia, weight gain,
a total of 54% of patients had at least one of the following: (1) seizures; (2) hallucinations; (3) changes in cognitive function; (4) mood alterations (including suicidal ideation); (5) speech-alterations; (6) mental status changes; or (7) sleep-related adverse effects

Camidge DR. J Thorac Oncol. 2021



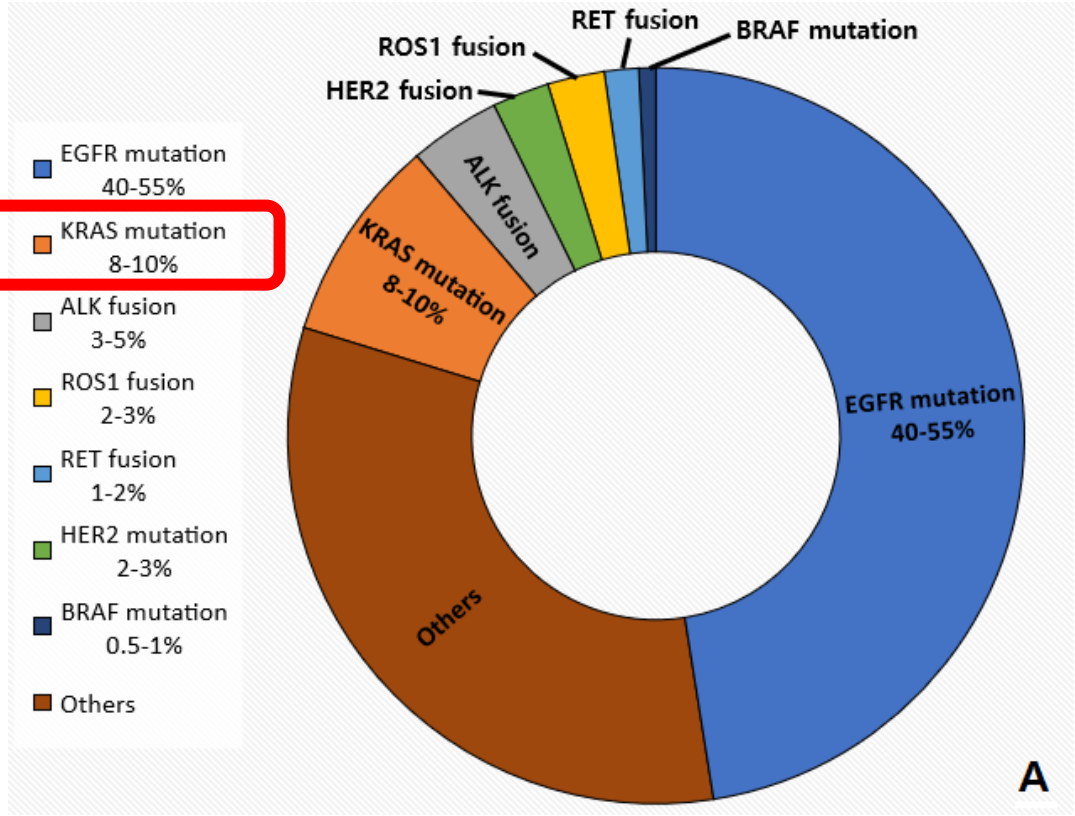
Cancer Management and Research 2020:12 6615–6628

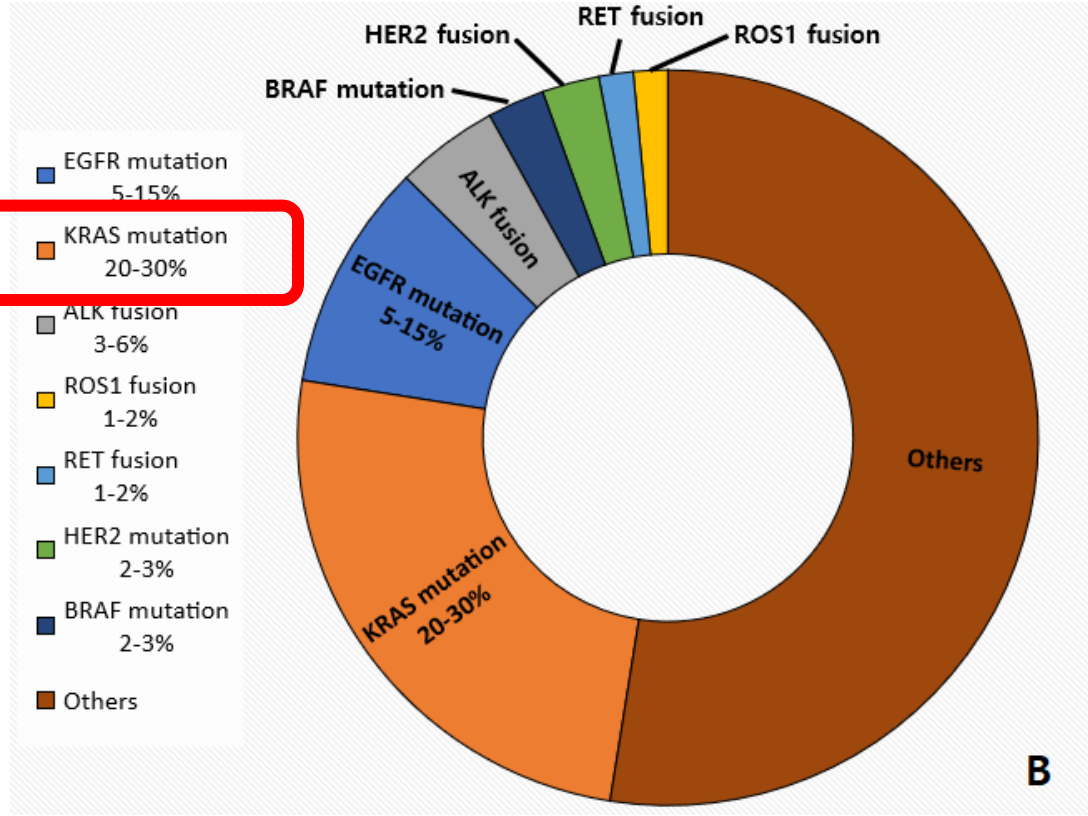
	Lorlatinib (phase 1/2, NCT01970865)		
	TKI-naive	Previously received crizotinib	Previously received 2nd ALK TKI
ORR	76%	69.5%	39.6%
DCR	89%	86.5%	81.3%
PFS			6.6 month
OS			20.7 month

Ann Oncol. 2021 May;32(5):620-630.

Lancet Oncol . 2018 Dec;19(12):1654-1667.

KRAS


EGFR mutation 40-55%
KRAS mutation 8-10%
ALK fusion 3-5%
ROS1 fusion 2-3%
RET fusion 1-2%
HER2 mutation 2-3%
BRAF mutation 0.5-1%
Others
EGFR mutation 40-55%
KRAS mutation 8-10%
Others
A


EGFR mutation 5-15%
KRAS mutation 20-30%
ALK fusion 3-6%
ROS1 fusion 1-2%
RET fusion 1-2%
HER2 mutation 2-3%
BRAF mutation 2-3%
Others
EGFR mutation 5-15%
KRAS mutation 20-30%
Others
B

KRAS

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2021
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

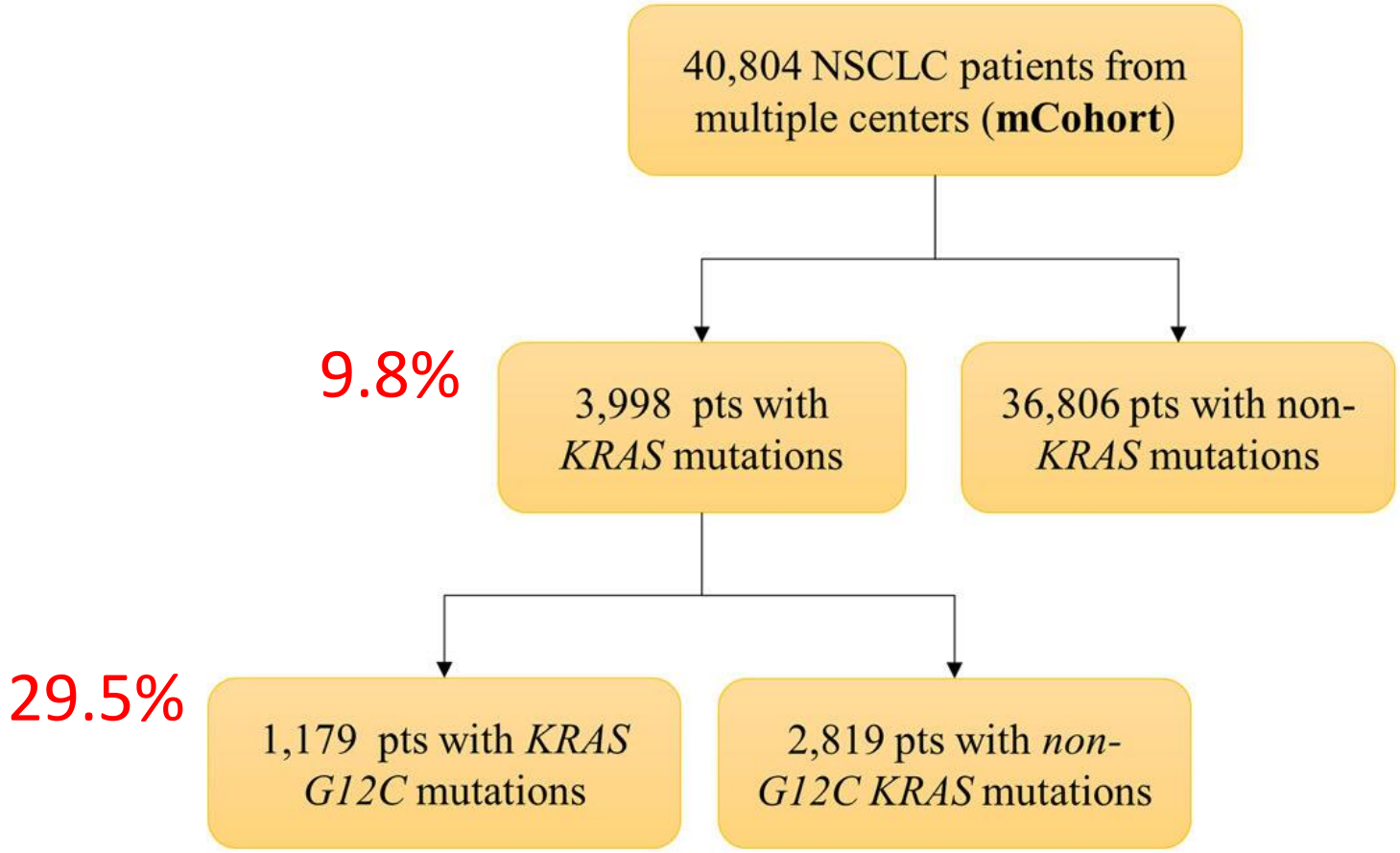
TESTING RESULTS[kk,ll]

Sensitizing *EGFR* mutation positive	NSCL-20
ALK rearrangement positive	NSCL-23
ROS1 rearrangement positive	NSCL-26
BRAF V600E mutation positive	NSCL-27
NTRK1/2/3 gene fusion positive	NSCL-28
METex14 skipping mutation positive	NSCL-29
RET rearrangement positive	NSCL-30
PD-L1 ≥50% and negative for actionable molecular markers above	NSCL-31
PD-L1 ≥1%–49% and negative for actionable molecular markers above	NSCL-32
PD-L1 <1% and negative for actionable molecular markers above	NSCL-33

TESTING RESULTS[ll,mm]

EGFR exon 19 deletion or *L858R* mutation positive	NSCL-20
EGFR S768I, L861Q, and/or *G719X* mutation positive	NSCL-23
EGFR exon 20 insertion mutation positive	NSCL-24
KRAS G12C mutation positive	NSCL-25
ALK rearrangement positive	NSCL-26
ROS1 rearrangement positive	NSCL-29
BRAF V600E mutation positive	NSCL-31
NTRK1/2/3 gene fusion positive	NSCL-32
METex14 skipping mutation positive	NSCL-33
RET rearrangement positive	NSCL-34
PD-L1 ≥50% and negative for actionable molecular biomarkers above	NSCL-35
PD-L1 ≥1%–49% and negative for actionable molecular biomarkers above	NSCL-36
PD-L1 <1% and negative for actionable molecular biomarkers above	NSCL-37

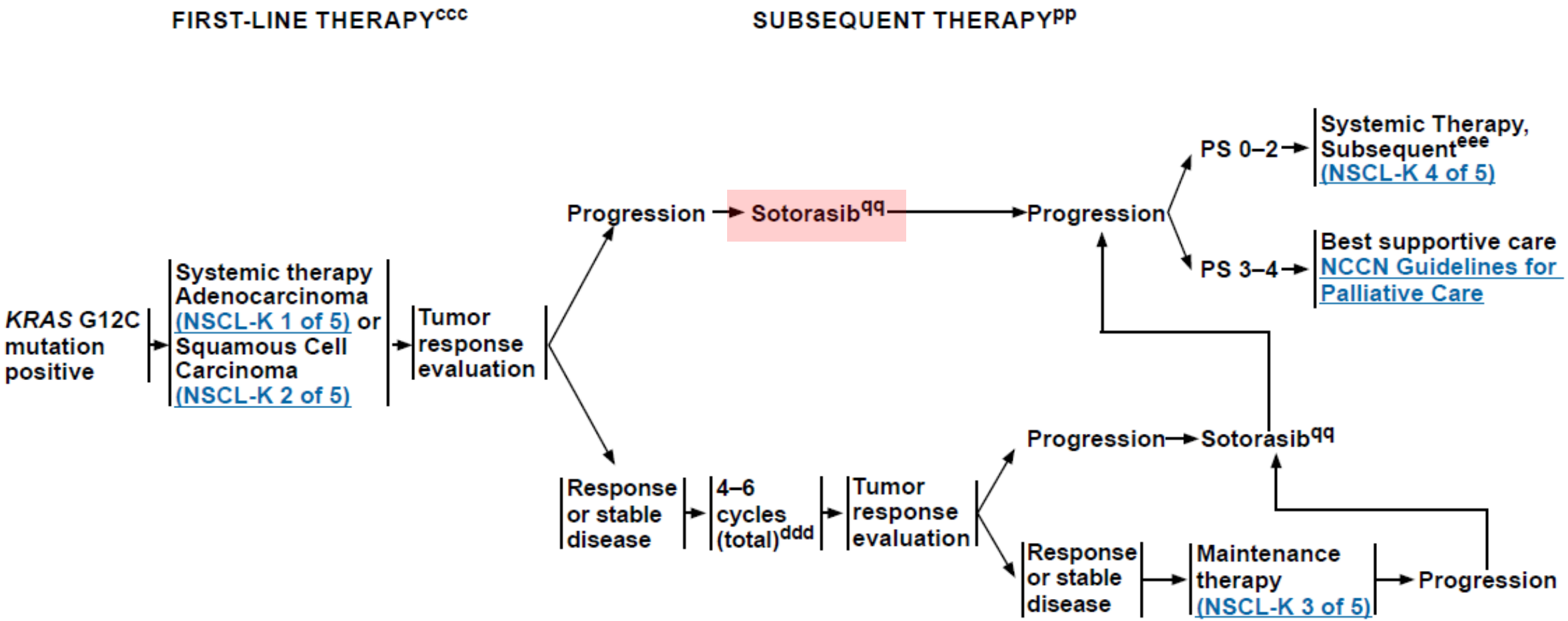
Chinese data



1179/40804 = 2.9%

Liu et al. Biomarker Research (2020) 8:22

KRAS G12C MUTATION POSITIVE[mm]



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 24, 2021 VOL. 384 NO. 25

Sotorasib for Lung Cancers with *KRAS* p.G12C Mutation

F. Skoulidis, B.T. Li, G.K. Dy, T.J. Price, G.S. Falchook, J. Wolf, A. Italiano, M. Schuler, H. Borghaei, F. Barlesi, T. Kato, A. Curioni-Fontecedro, A. Sacher, A. Spira, S.S. Ramalingam, T. Takahashi, B. Besse, A. Anderson, A. Ang, Q. Tran, O. Mather, H. Henary, G. Ngarmchamnanrith, G. Friberg, V. Velcheti, and R. Govindan

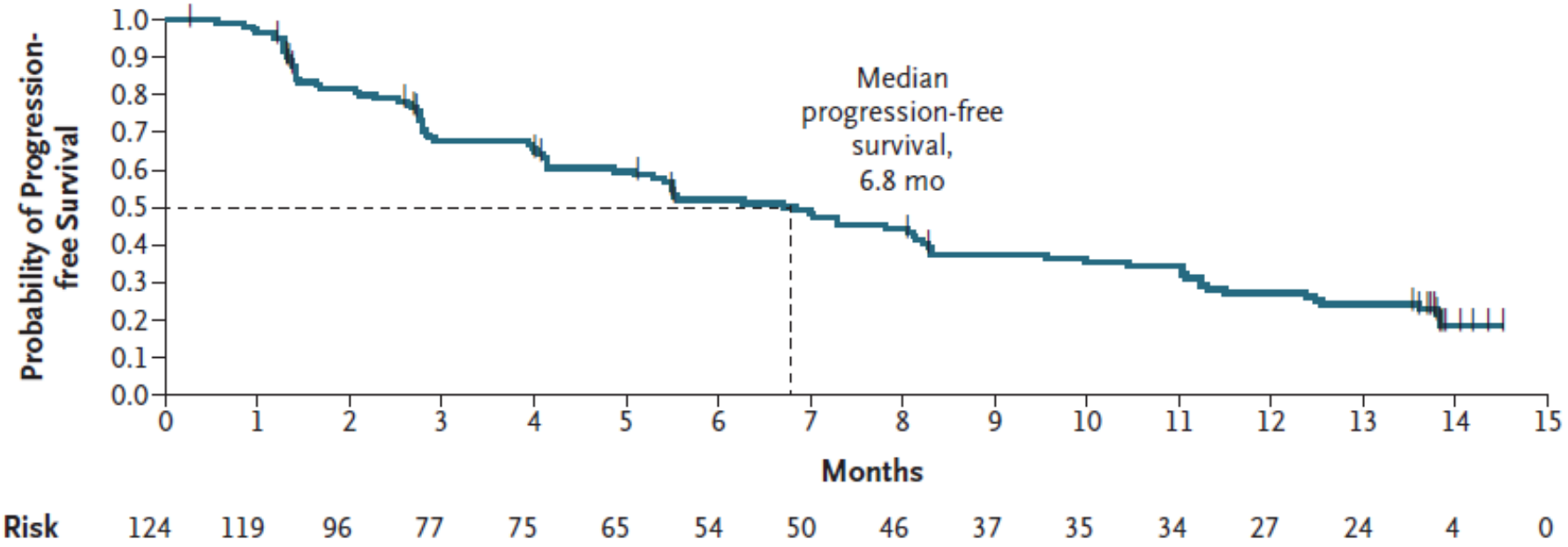
- single-group, phase 2 trial, administered orally at a dose of 960 mg once daily
- *N=112, KRAS* p.G12C–mutated advanced NSCLC previously treated with standard therapies
- Primary end point - objective response (complete or partial response)
- secondary end points included DOR, disease control (defined as complete response, partial response, or stable disease), PFS, OS, and safety

N Engl J Med 2021; 384:2371-2381

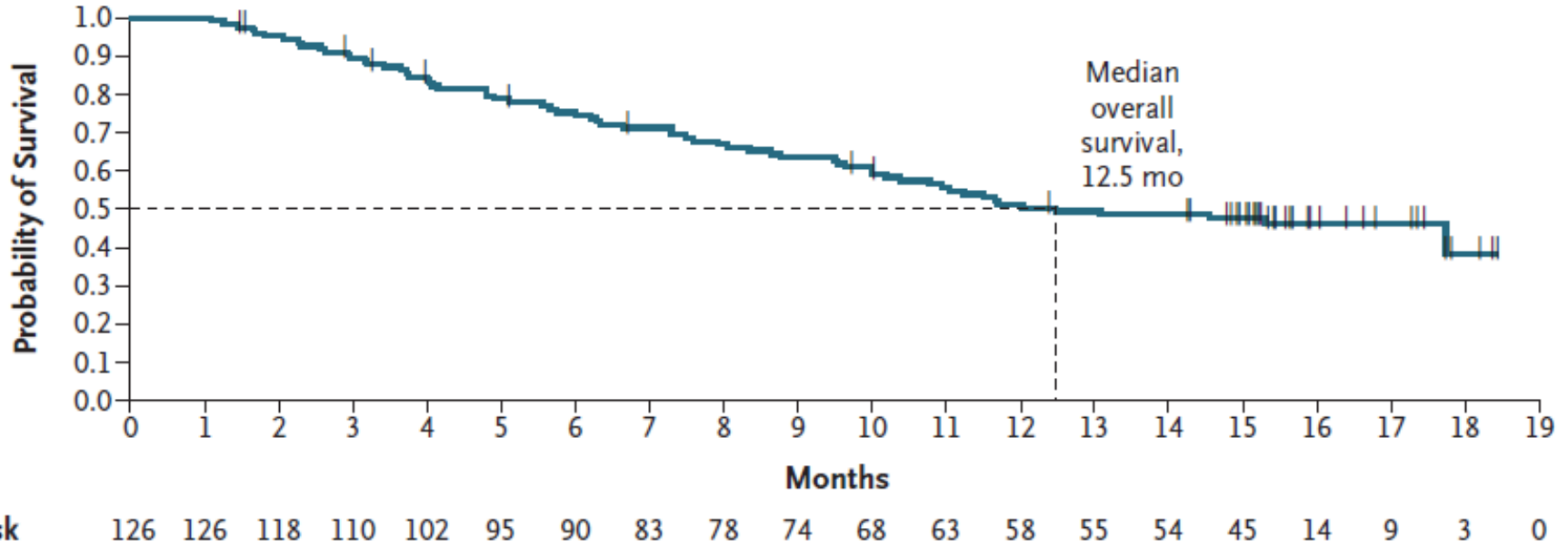
Tumor Response to Sotorasib Therapy According to Independent Central Review

Variable	Patients (N = 124)
Objective response — % (95% CI)†	37.1 (28.6–46.2)
Disease control — % (95% CI)‡	80.6 (72.6–87.2)
Best response — no. (%)	
Complete response	4 (3.2)
Partial response	42 (33.9)
Stable disease	54 (43.5)
Progressive disease	20 (16.1)
Could not be evaluated	2 (1.6)
Missing scan	2 (1.6)
Median duration of objective response (95% CI) — mo§	11.1 (6.9–NE)
Kaplan–Meier estimate of objective response (95% CI) — %	
At 3 mo	90.5 (76.7–96.3)
At 6 mo	70.8 (54.3–82.2)
At 9 mo	57.3 (40.4–71.0)

Progression-free Survival
6.8 month



Overall Survival
12.5 month



Safety

Event	All Patients (N=126)				
	Any Grade	Grade 1 or 2	Grade 3	Grade 4	Fatal
	number of patients (percent)				
Adverse event	125 (99.2)	48 (38.1)	53 (42.1)	4 (3.2)	20 (15.9)
Treatment-related adverse event	88 (69.8)	62 (49.2)	25 (19.8)	1 (0.8)	0
Treatment-related adverse event leading to dose modification	28 (22.2)	8 (6.3)	20 (15.9)	0	0
Treatment-related adverse event leading to discontinuation of therapy	9 (7.1)	4 (3.2)	4 (3.2)	1 (0.8)	0
Treatment-related adverse event of any grade occurring in >5% of the patients or that was grade ≥3					

G3이상: Diarrhea (4%), ALT 상승 (6.3%), AST 상승 (5.6%)

TKI in SqCC

BRIEF REPORT

Efficacy of Targeted Inhibitors in Metastatic Lung Squamous Cell Carcinoma With *EGFR* or *ALK* Alterations

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- EGFR group (n=8), median age = 58yr
- ALK (n=6), median age = 50yr

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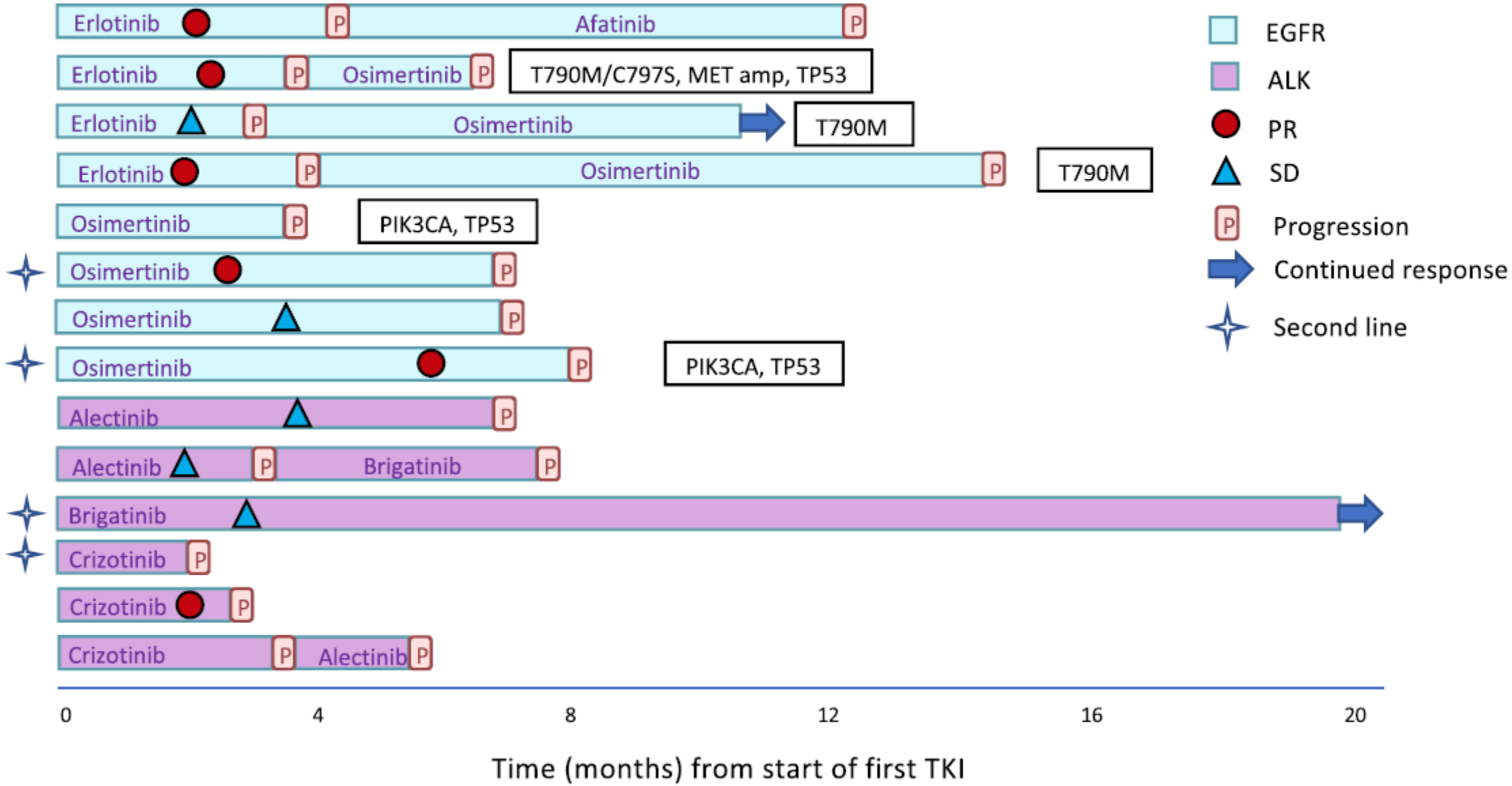
	IHC				Molecular testing		ALK
case #	CK5/6/7	P40/P63	TTF-1	Napsin A	NGS (50-146 gene panel)- Tissue	NGS (70-74 gene panel)- Blood	RNA seq (tissue or blood) or FISH
1	positive	positive	negative	NA	EGFR: p.Leu747_Ser752 delinsGln	PDGFRA:p.D173N	NA
2	NA	positive	negative	NA	EGFR:p.E746_A750del; TP53:p.E224D	EGFR:p.E746_A750del; TP53:p.E224D; ROS1:p.R1948H	negative
3	positive	positive	negative	negative	EGFR:p.L858R	negative	NA
4	positive	positive	negative	negative	EGFR:p.E746_A750del; TP53:p.V143M	NA	negative
5	positive	positive	negative	negative	NA	EGFR:p.E746_A750del; TP53:p.M246T; PIK3CA:p.H1047L	NA
6	NA	positive	NA	NA	NA	EGFR:p.A750_I759delinsPN; TP53:p.C242fs; PIK3CA:p.L755V; MYC:p.R349T	NA
7	NA	positive	NA	NA	EGFR:p.E746_A750del; TP53:p.P190L; NOTCH1:p.N253K	EGFR:p.E746_A750del; TP53:p.P190L	negative
8	NA	positive	negative	NA	EGFR:p.E746_A750del; TP53:p.L137_V143delinsP; STK11:p.Q220[a]; PIK3CA:p.H1047R	NA	negative
9	positive	positive	negative	negative	NA	negative	EML4-ALK fusion
10	NA	positive/positive	negative	NA	TP53:p.Q192[a]	TP53:p.Q192[a]	EML4-ALK fusion
11	positive	positive	negative	NA	negative	NA	EML4-ALK fusion
12	NA	NA	NA	NA	TP53:p.G154V; TSC1:p.R1097H	NA	FISH posituve
13	NA	NA	NA	NA	SMAD4:p.G419W	NA	FISH posituve
14	NA	positive	NA	NA	NA	NA	FISH posituve

Characteristics	EGFR Mutation (n = 8)	EML4-ALK Fusion (n = 6)
Median age (range), y	58.0 (45-83)	50.0 (33-58)
Sex		
Male	1	2
Female	7	4
Smoking history		
Former	2	0
Never	6	6
Brain metastasis		
Yes	1	0
No	7	6
Bone metastasis		
Yes	5	3
No	3	3
Specimen		
Tissue	4	4
ctDNA	2	1
Tissue and ctDNA	2	1
Best response to first TKI		
PR	5	1
SD	2	3
PD	1	2
Median PFS (range), mo	4.9 (3.8-7.5)	2.9 (1.8-32.1)
Median OS (range), mo	16.9 (8.6-27.4)	8.3 (3.2-32.1)


Erlotinib
P
Afatinib
P
Erlotinib
P
Osimertinib
P
T790M/C797S, MET amp, TP53
Erlotinib
P
Osimertinib
T790M
Erlotinib
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Osimertinib
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T790M
Osimertinib
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PIK3CA, TP53
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PIK3CA, TP53
Alectinib
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Alectinib
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Brigatinib
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Brigatinib
Crizotinib
P
Crizotinib
P
Crizotinib
P
Alectinib
P
EGFR
ALK
PR
SD
P
Progression
Continued response
Second line
0
4
8
12
16
20
Time (months) from start of first TKI

Summary

- Lung cancer – 32,000 case in 2021, adenoca ↑
- Uncommon EGFR
  - L861Q - Osimertinib
  - G719X, S768I – Afatinib
- Ex20 ins – Amivantamab (IV), Mobocertinib (oral)
- Lazertinib – cardiac toxicity ↓, paresthesia ↑
- Lorlatinib – 1st line vs 2nd line use
- KRAS – G12C NSLCL 2.9%, sotorasib, mPFS 6.8 months
- TKI in SqCC – never smoker, female, clinical benefit but unsatisfied

Severance

With the Love of God, Free Humankind from Disease and Suffering

Thank you