유한양행

Where Today, Where Tomorrow of LECLAZA®?

Yonsei University College of Medicine

Eun Young Kim

렉라자® 정 80mg
(레이저티닙메실산염일수화물)

Conflict of Interest

- ✓ I have no conflicts of interest to declare.

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유한양행

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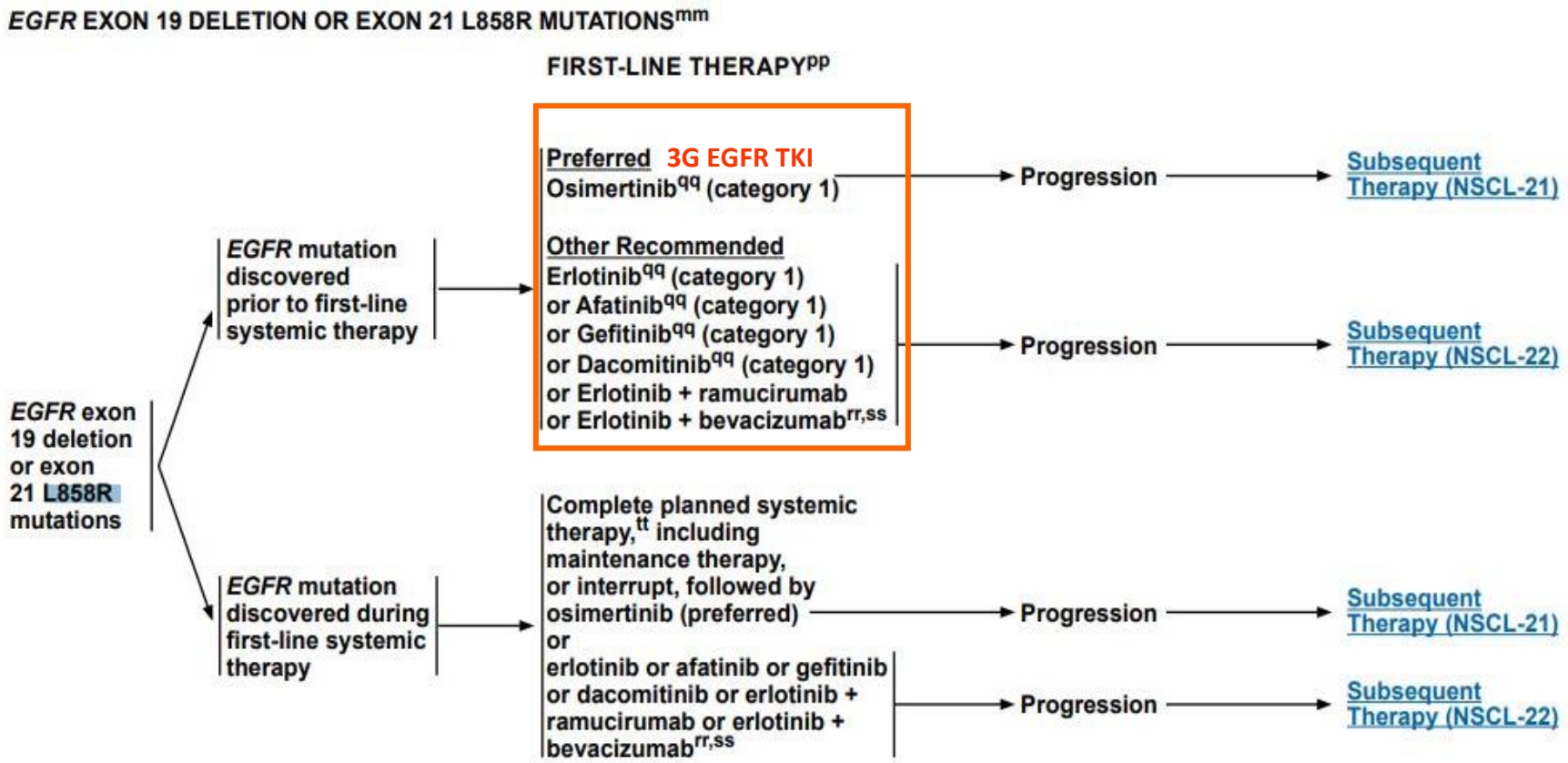
- Dose Modification Strategy in targeted therapy
- Conclusions

Treatment of NSCLC

Current Treatment Guideline for EGFR mutated NSCLC

1st line treatment for patients with EGFR mutated NSCLC

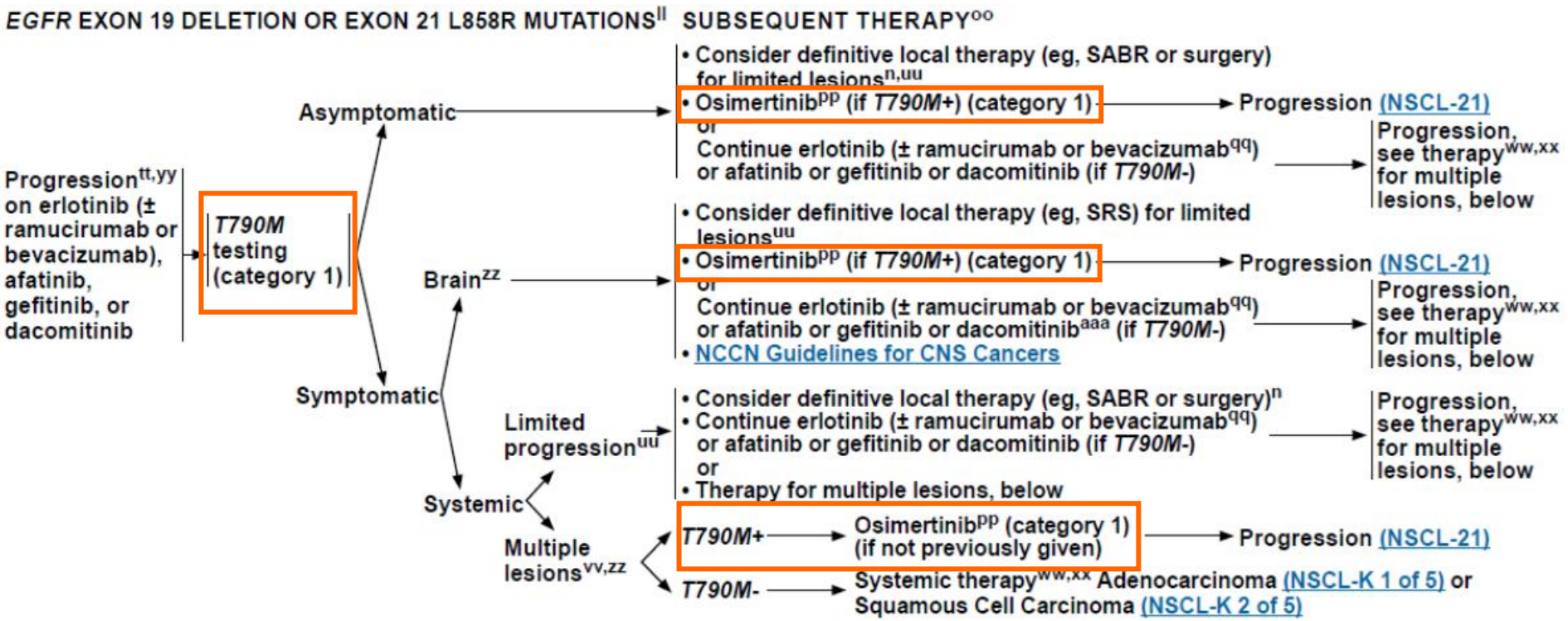


[mm] Principles of Molecular and Biomarker Analysis (NSCL-H).
[pp] Moleculer or Biomarker-Directed Therapy for Advanced or Metastatic Disease (NSCL-J).
[qq] For performance status 0–4.
[rr] Criteria for treatment with bevacizumab: nonsquamous NSCLC, and no recent history of hemoptysis.
[ss] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[tt] If systemic therapy regimen contains an immune checkpoint inhibitor, physicians should be aware of the long half-life of such drugs and data reporting adverse events when using osimertinib in combination with or following checkpoint inhibitors. Schoenfeld AJ, et al. Ann Oncol 2019;30:839-844; Oshima Y, et al. JAMA Oncol 2018;4:1112-1115; Oxnard GR, et al. Ann Oncol 2020;31:507-516.

NCCN Guideline. NSCLC. Version 2. 2023

Current Treatment Guideline for EGFR mutated NSCLC

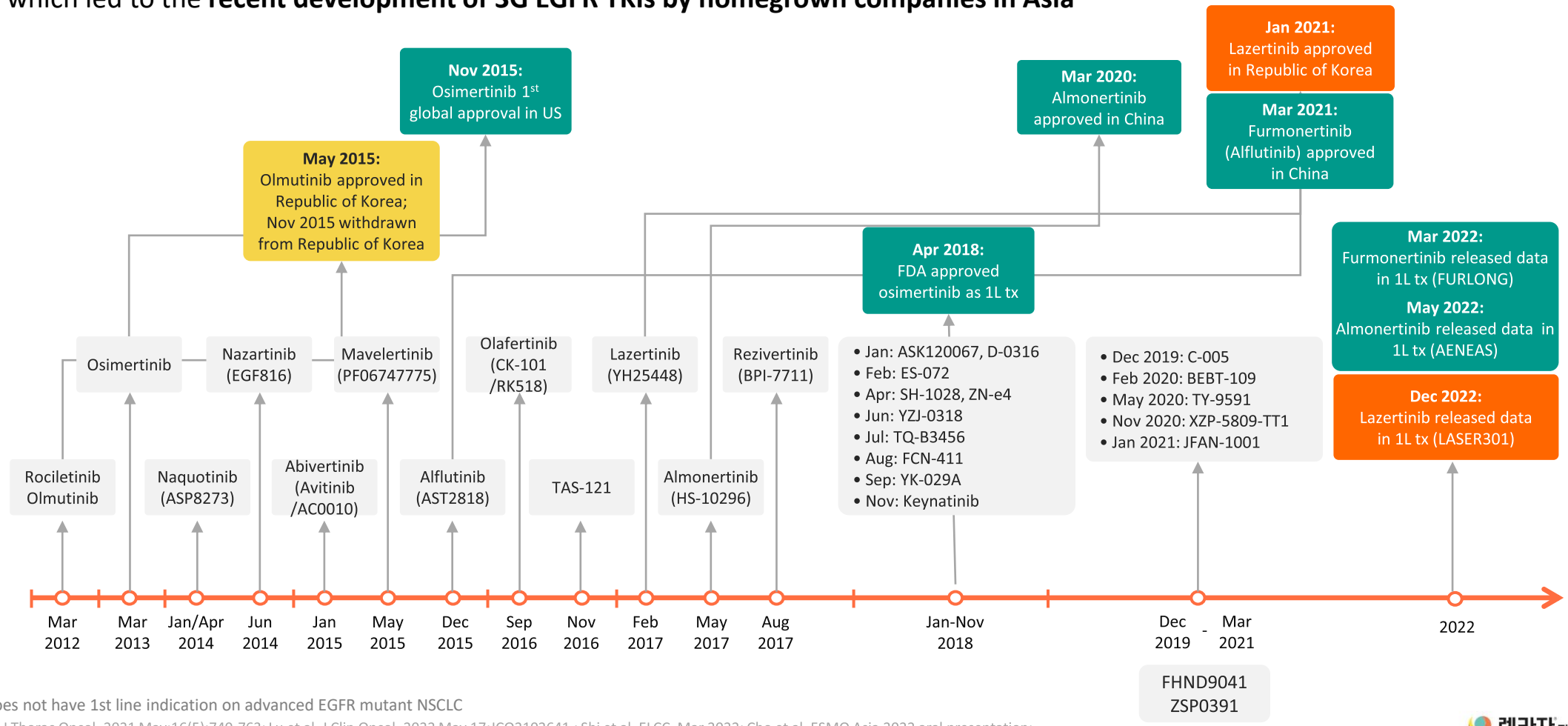
2nd line treatment for patients with EGFR mutated NSCLC



[n] IGTA therapy (eg, cryotherapy, microwave, radiofrequency) may be an option for select patients not receiving SABR or definitive RT.
Principles of Image-Guided Thermal Ablation Therapy (NSCL-D).
[ll] Principles of Molecular and Biomarker Analysis (NSCL-H).
[oo] Molecular or Biomarker-Directed Therapy for Advanced or Metastatic Disease (NSCL-J).
[pp] For performance status 0–4.
[qq] Criteria for treatment with bevacizumab: nonsquamous NSCLC, and no recent history of hemoptysis.
[tt] Beware of flare phenomenon in subset of patients who discontinue TKI. If disease flare occurs, restart TKI.
[uu] Clinical trials have included up to 3 to 5 progressing sites.
[vv] Consider a biopsy at time of progression to rule out SCLC transformation (approximately 6%) and evaluate mechanisms of resistance. NCCN Guidelines for Small Cell Lung Cancer.
[ww] Afatinib + cetuximab may be considered in patients with disease progression on EGFR TKI therapy.
[xx] The data in the second-line setting suggest that PD-1/PD-L1 inhibitor monotherapy is less effective, irrespective of PD-L1 expression, in *EGFR* exon 19 deletion or exon 21 L858R, *ALK*+ NSCLC.
[yy] Plasma or tissue-based testing via broad molecular profiling should be considered at progression, for the T790M mutation and other genomic resistance mechanisms. If plasma-based testing is negative, tissue-based testing with rebiopsy material is strongly recommended. Practitioners may want to consider scheduling the biopsy concurrently with plasma testing referral.
[zz] Consider osimertinib (regardless of T790M status) for progressive CNS disease or leptomeningeal disease. In the BLOOM study, osimertinib was used at 160 mg once daily for patients with leptomeningeal disease.
[aaa] In the randomized phase III trial of dacomitinib, patients with brain metastases were not eligible for enrollment. In the setting of brain metastases, consider other options.

Landscape of 3G EGFR TKI Development

- Until 2022, osimertinib was the only globally approved 3G EGFR TKI to treat EGFR T790M mutation
- The **monopoly of a single 3G EGFR TKI** to treat 50% of patients with NSCLC in Asia had unintended consequences in cost and accessibility, which led to the **recent development of 3G EGFR TKIs by homegrown companies in Asia**

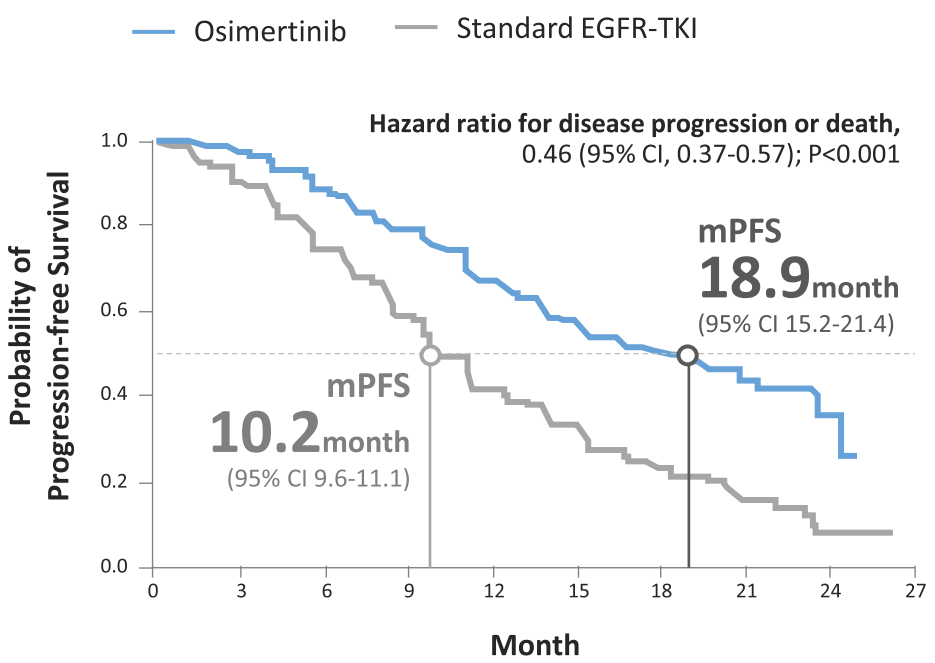


*Lazertinib does not have 1st line indication on advanced EGFR mutant NSCLC

Nagasake et al. J Thorac Oncol. 2021 May;16(5):740-763; Lu et al. J Clin Oncol. 2022 May 17:JCO2102641.; Shi et al. ELCC. Mar 2022; Cho et al. ESMO Asia 2022 oral presentation; https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-osimertinib-first-line-treatment-metastatic-nsclc-most-common-egfr-mutations

Osimertinib in 1st line Treatment (FLAURA)

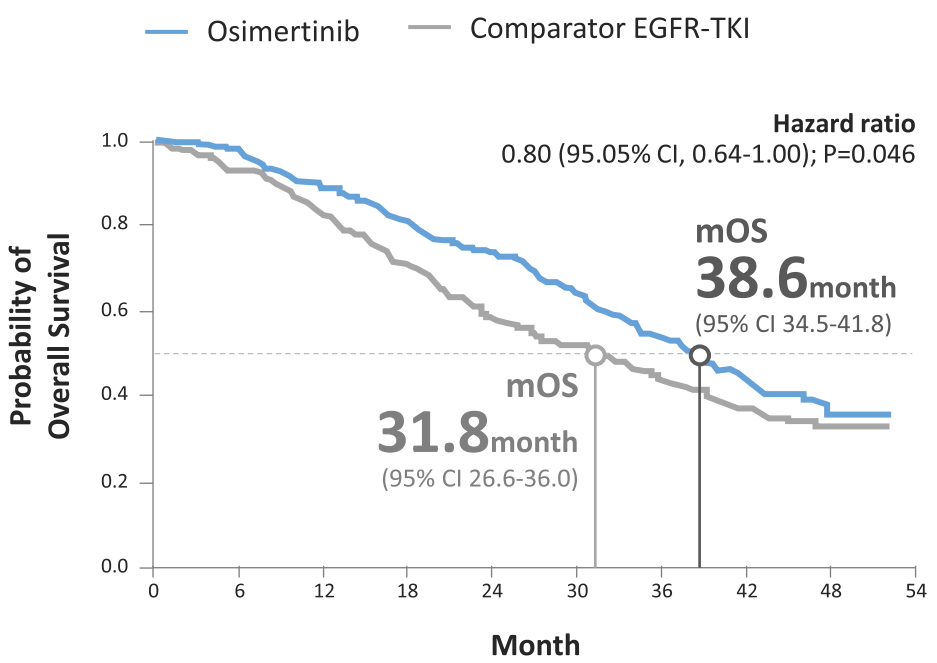
PFS in full analysis set



No.at Risk

Osimertinib	279	262	233	210	178	139	71	26	4	0
Standard EGFR-TKI	277	239	197	152	107	78	37	10	2	0

OS in full analysis set

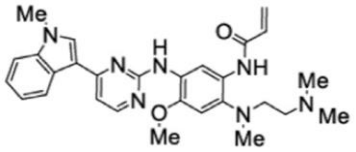
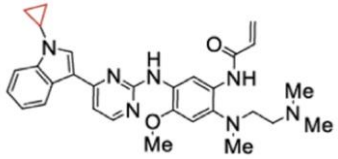
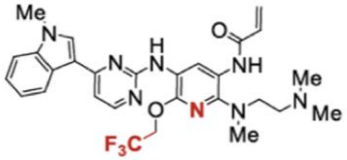
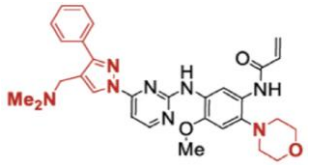
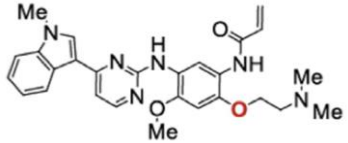


No.at Risk

Osimertinib	279	276	270	254	245	236	217	204	193	180	166	153	138	123	86	50	17	2	0
Comparator EGFR-TKI	277	263	252	239	219	205	182	165	148	138	131	121	110	101	72	40	17	2	0

Soria et al. N Engl J Med. 2018 Jan 11;378(2):113-125; Ramalingam et al. N Engl J Med. 2020 Jan 2;382(1):41-50.

Comparison of 3G EGFR TKI in 1L treatment

		 Osimertinib	 Aumolertinib	 Furmonertinib	 Lazertinib	 Rezivertinib
Dose		80mg	110mg	80mg	240mg	180mg
Marketed		2015 (Global)	2020 (China)	2021 (China)	2021 (Korea)	-
Indication		1st & 2nd Line and Adjuvant	1st and 2nd Line	2nd Line	2nd Line	-
1L Treatment	**Study Design**	[Global] Osimertinib (n=279) SoC (n=277 (G: 183/E: 94))	(China) Aumolertinib (n=214) Gefitinib (n=215)	(China) Furmonertinib (n=178) Gefitinib (n=179)	[Global] Lazertinib (n=196) Gefitinib (n=197)	(China) Rezivertinib (n=43)
	PFS	18.9m vs 10.2m (HR 0.46)	19.3m vs 9.9m (HR 0.46)	20.8m vs 11.1m (HR 0.44)	20.6m vs 9.7m (HR 0.45)	20.7m (by BICR) 22.0m (by investigator)
	Any AE G ≥ 3	34% vs 45%	36% vs 36%	11% vs 18%	41% VS 43%	-
	AE Profile (any grade)	Diarrhea(58%), Rash(58%), Dry Skin(36%), Paronychia(35%), Stomatitis(29%), Decrease appetite(20%), Pruritus(17%), Constipation(15%)	CPK increase(36%), AST increase (30%), ALT increase(29%), Leukopenia(24%), Rash(23%), Plt decrease(22%), UTI(22%), Anemia(20%), Diarrhea(16%)	Elevated ALT(28%), Diarrhea(25%), Elevated AST(25%), Rash(17%), Decreased WBC(15%), Oral ulcer(12%), Decreased neutrophil count(10%), Anaemia(8%), Decreased platelet count(8%), QTc prolongation(6%)	Paresthesia(39%), Rash(36%), Pruritus(27%), Diarrhea(26%), Paronychia(18%), Anemia(18%) Decreased appetite(17%), Stomatitis(16%), Dry Skin(15%), Nausea(15%)	WBC decreased(44%), PLT decreased(40%), ANC decreased(30%), Anemia (26%), ALT increased(19%), Lymphocyte count decreased(14%), AST increased(12%), Leukopenia(9%)

*Lazertinib does not have 1st line indication on advanced EGFR mutant NSCLC

1. Nagasake et al. J Thorac Oncol. 2021 May;16(5):740-763; 2. Soria et al. N Engl J Med. 2018 Jan 11;378(2):113-125; 3. S Lu et al. J Clin Oncol . 2022 Sep 20;40(27):3162-3171; 4. Y Shi et al. Lancet Respir Med . 2022 Nov;10(11):1019-1028.
5. Cho et al. ESMO Asia 2022 oral presentation; 6. Y Shi et al. BMC Med . 2023 Jan 8;21(1):11

Consideration of 3G EGFR TKI as 1L Treatment

- **CNS Metastasis**

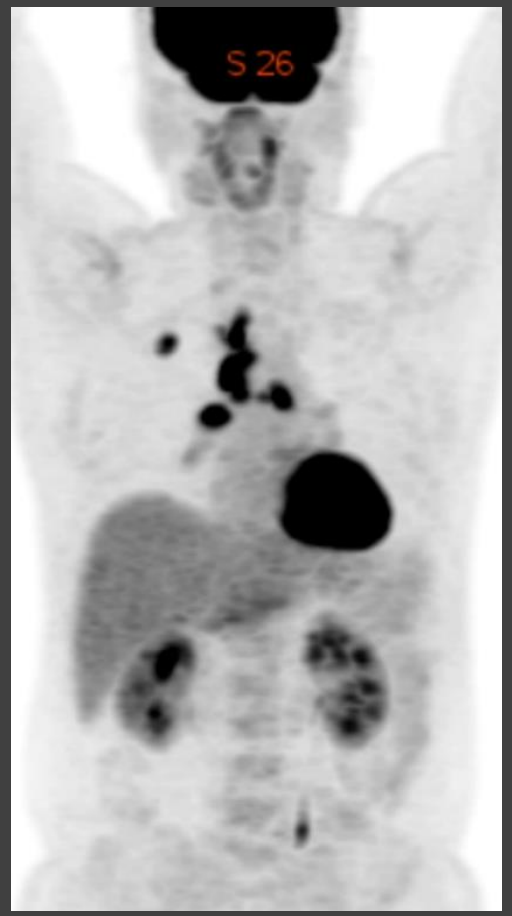
- **Sequential 1/2G TKI vs. Upfront 3G TKI**
  - ✓ 19del/L858R
  - ✓ Brain metastasis
  - ✓ T790M detection rate

- **Re-biopsy strategies**
  - ✓ For T790M detection

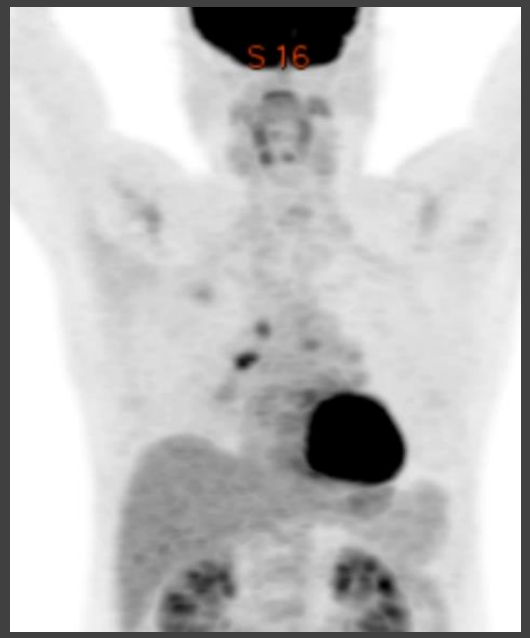
- **Mechanisms of resistance after 3G TKIs**

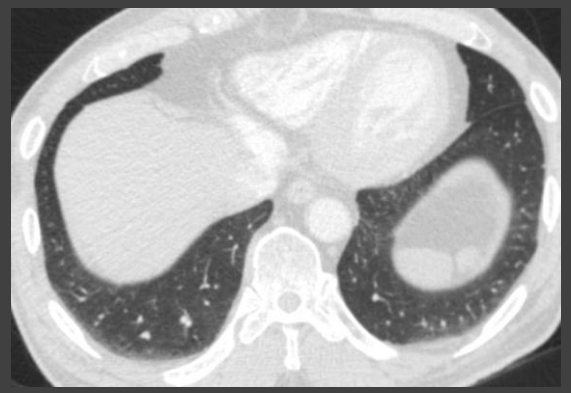
M/63, 43pyrs, current smoker

Lung cancer (adenocarcinoma), cT1bN3M0, stage IIIB, EGFR E19del

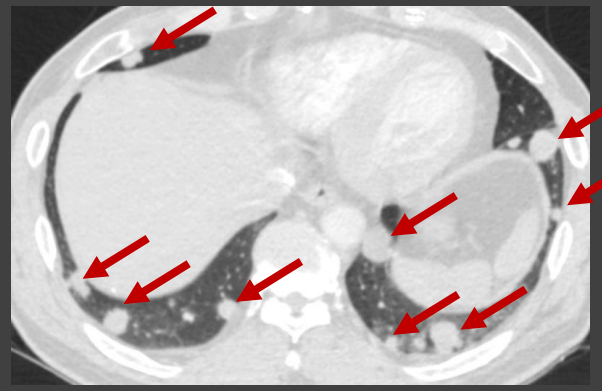


At diagnosis
(2020.03)



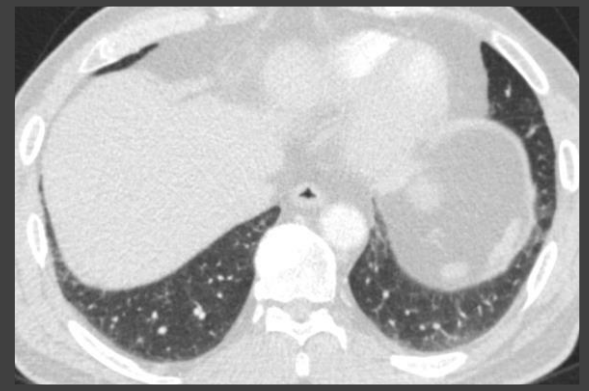


After def CCRTx
(2020.06)



Lung to lung metastasis
(2020.10)

afatinib 40mg 시작



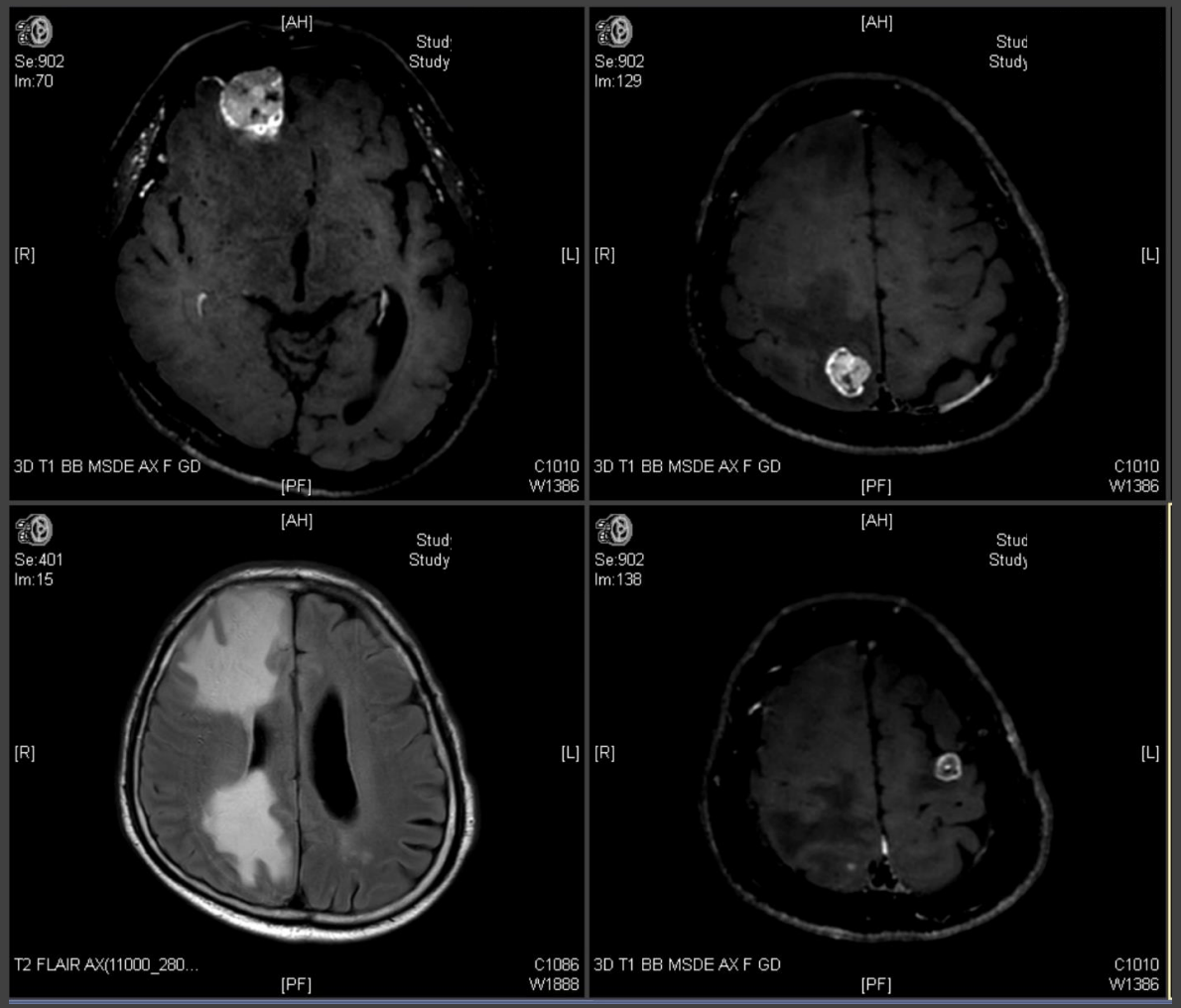
2021.01

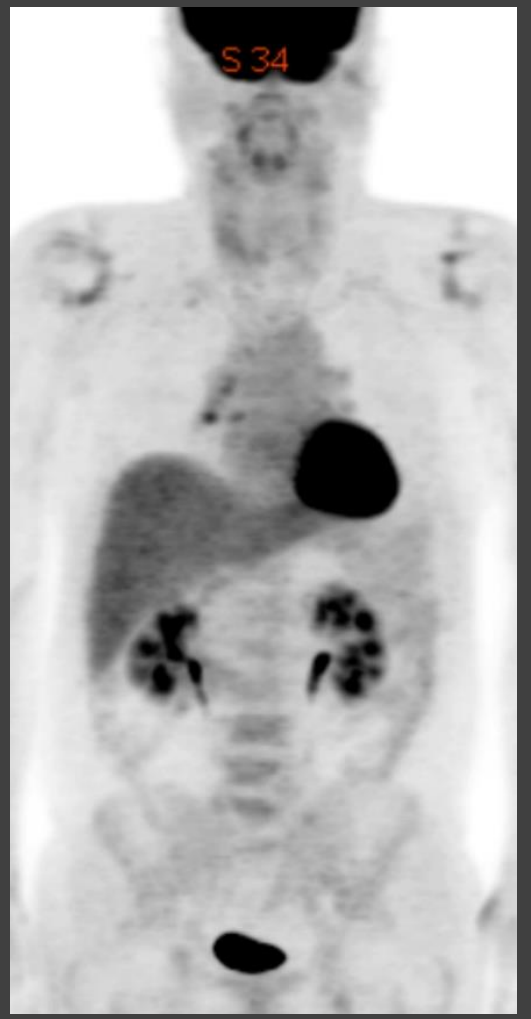
3mo of afatinib 40mg

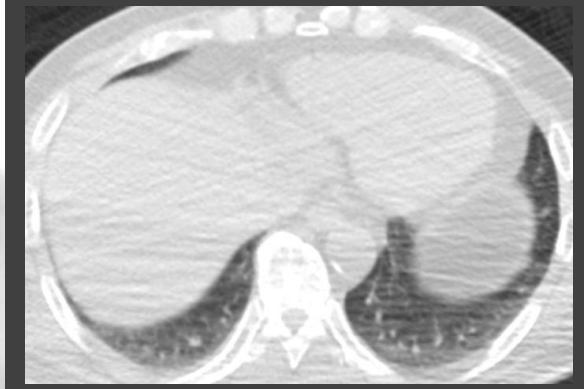
Speaker's own

M/63, 43pyrs, current smoker

Lung cancer (adenocarcinoma), cT1bN3M0, stage IIIB, EGFR E19del
s/p definitive CCRTx (-2020.05), progression (2020.10)
1L afatinib (2020.10-), Lt side weakness, Brain PD at 8 months



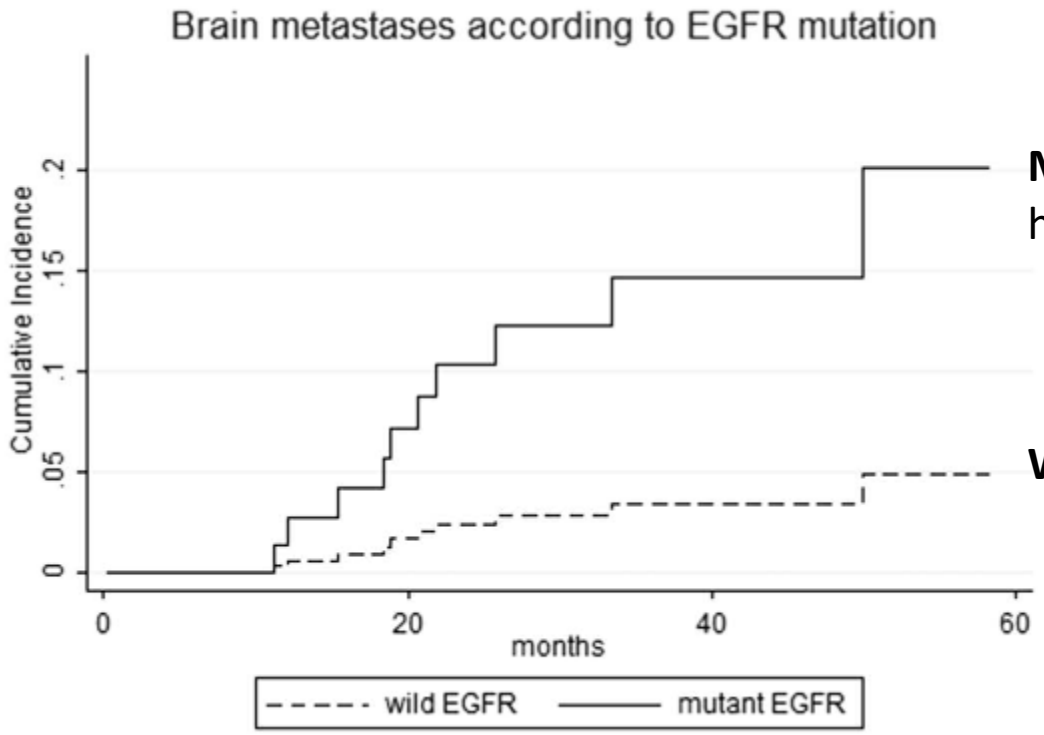




2021.06

8mo of afatinib 40mg

Cumulative risk of recurrence of brain metastasis after curative resection



Mutant EGFR
hazard ratio = 4.49, p = 0.026

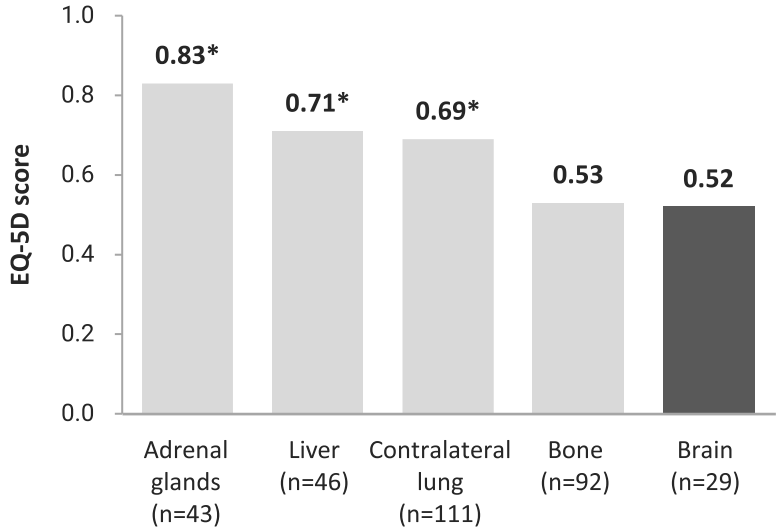
Wild type EGFR

Shin DY, Na II, Kim CH, Park S, Baek H, Yang SH. EGFR mutation and brain metastasis in pulmonary adenocarcinomas. *J Thorac Oncol*. 2014;9(2):195-199

CNS Metastasis

- **The incidence of CNS metastases** in patients with EGFRm+ NSCLC is **24% at first diagnosis and almost doubles over the course of the disease,** despite treatment with EGFR-TKIs, within 5 years
- Treatment for CNS metastases from NSCLC includes surgical resection, stereotactic radiosurgery, and WBRT
  - However, the results of the QoL after treatment for BM (QUARTZ) study indicate that WBRT does not improve survival or QoL, compared with supportive care alone
  - Symptoms with cognitive impairment after chemotherapy (chemo brain) were still present even years after treatment stopped
- Lead to poor prognosis, including neurological death associated with significant economic burden

EQ-5D score for NSCLC patients with one metastatic site



" Health-related utilities or preference scores were significantly lower in patients with brain metastases compared with those with adrenal, liver or lung metastases "

Quality of life was evaluated by EQ-5D
*Significant difference compared with brain metastases

NSCLC, Non small cell lung cancer; **QoL,** Quality of life; **BM,** Brain metastasis; **WBRT**, Whole brain radiotherapy

1. *Lung Cancer* 2015; 80:108-111; 2. *Lancet* 2016; 388:2004-2014; 3. The voice of the patient, Lung Cancer, FDA, 2013; 4. *Advances in Radiation Oncology* 2019; 1-8; 5. *Journal of Medical Economics,* 2011; 1136-1147; 6. *ESMO Open* 2018;3:e000414; 7. Presented at the ISPOR 17th Annual European Congress, Amsterdam, The Netherlands, 8–12 November. Abstract 50998.

Intracranial activity of targeted therapies in NSCLC

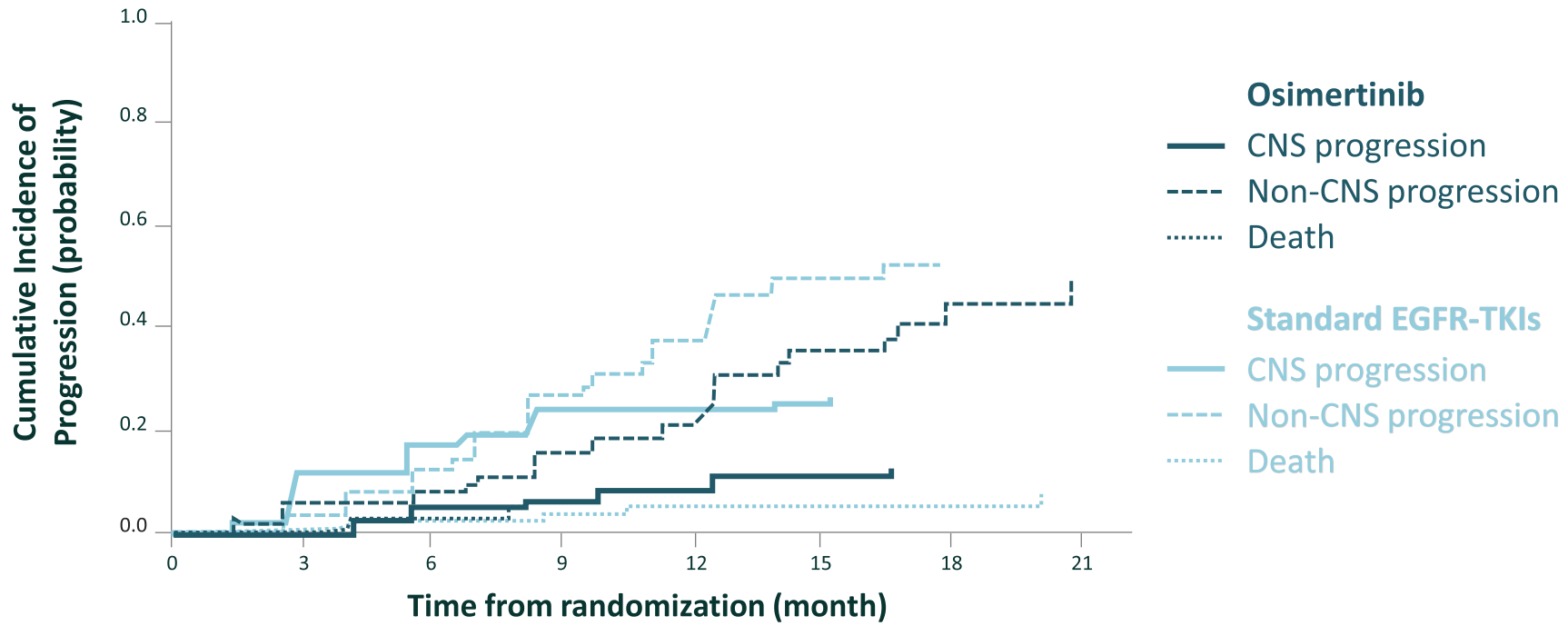
	population	n	Intracranial ORR (%)	Intracranial CR (%)	Median intracranial DoR, mo, (95% CI)	Median intracranial PFS, mo, (95% CI)
Osimertinib[1]	Measurable baseline intracranial metastatic disease	30	**70**	7	8.9 (4.3, NE)	11.7
Lazertinib[2]	Measurable baseline intracranial metastatic disease	7	**86**	14	15.1 (2.8-NR)	26.0 (5.4-NR)
Alectinib[3] (ALK inhibitor)	Measurable baseline intracranial metastatic disease	50	**64**	22	10.8 (7.6-14.1)	9.2 (7.4-15.9)
Praseltinib[4] (RET inhibitor)	Measurable baseline intracranial metastatic disease	10	**70**	30	Not reached	Not reported
Selpercatinib[5] (RET inhibitor)	Measurable baseline CNS disease	26	**85**	27	9.4 (7.4, 15.3)	Not reported

1. Wu YL, et al, *J Clin Oncol*. 2018, 2. Cho, BC, et al. *J Thor Oncol.* 2022. 3. Gadgeal SM, et al, *J Clin Oncol.* 2016,
4. F Griesinger, et al, *Ann oncol.* 2022, 5. Alexander Drilon, et al, *J Clin Oncol*. 2023

Cumulative incidence of CNS Progression (cFAS)

- On the basis of a competing risk analysis, **the estimated probability of observing a CNS progression event** (in the absence of a non-CNS progression event or death) **at 6 months was 5%** (95% CI, 1%-13%) **with Osimertinib versus 18%** (95% CI, 10%-28%) **with standard EGFR-TKIs**
- **At 12 months, it was 8%** (95% CI, 3%-16%) **with Osimertinib versus 24%** (95% CI, 15%-35%) **with standard EGFR-TKIs**

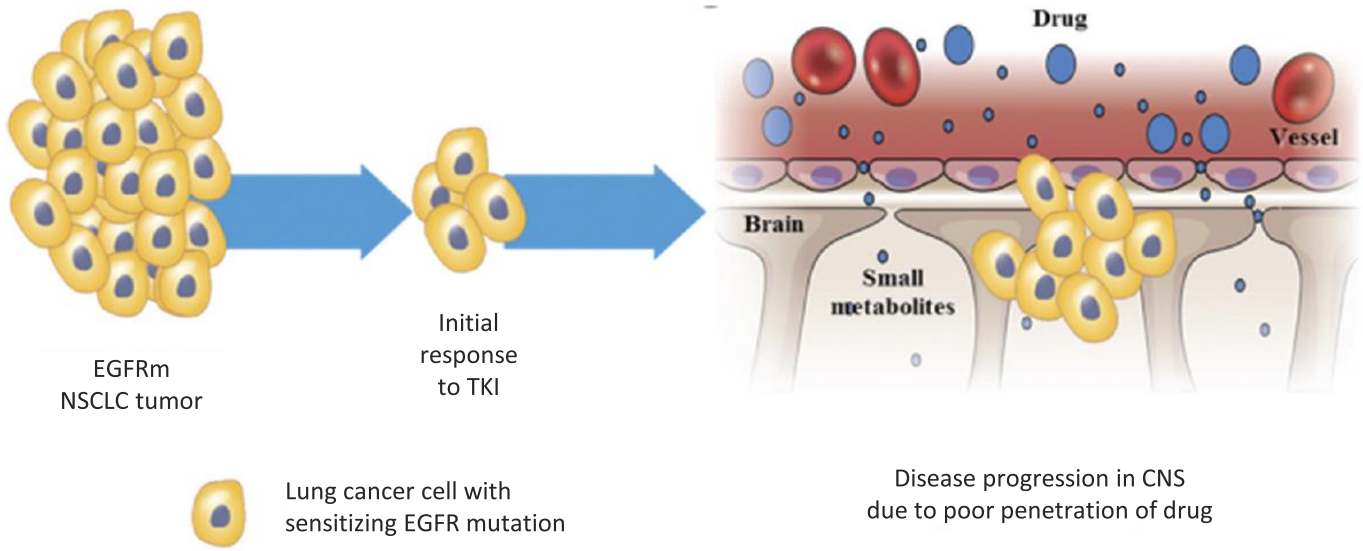
Cumulative incidence of CNS Progression



CNS Failure in EGFR TKI Treatment

- CNS is frequently the initial failure site after clinical benefit from TKIs
- Tumor cells invading the brain become resistant to these therapeutic agents, making the brain as a potential **“sanctuary site”** for metastases. This also reflects insufficient control of cerebral tumor spread and growth by current treatment strategies

Diagrammatic Representation of Brain as a “Sanctuary site”



CNS Penetration of 1st & 2nd G EGFR TKI

EGFR TKI	Dose	CSF/ Plasma ratio	Brain/ plasma ratio (*in vitro*)
Gefitinib	250 mg	1.5-4.5%	0.21
Erlotinib	150 mg	2.5-13.3%	NA
Afatinib	40 mg	2.45-2.91%	NA

1. Shetty & Babu. *Indian J Cancer.* 2019 Nov;56(Supplement):S31-S37; 2. Zao et al. *Clin Lung Cancer.* 2013 Mar;14(2):188-93; 3. Tagashi et al. *Cancer Chemother Pharmacol.* 2011 Oct;68(4):1089-92;
4. Tamiya et al. *Anticancer Res.* 2017 Aug;37(8):4177-4182.

M/63, 43pyrs, current smoker

Lung cancer (adenocarcinoma), cT1bN3M0, stage IIIB, EGFR E19del
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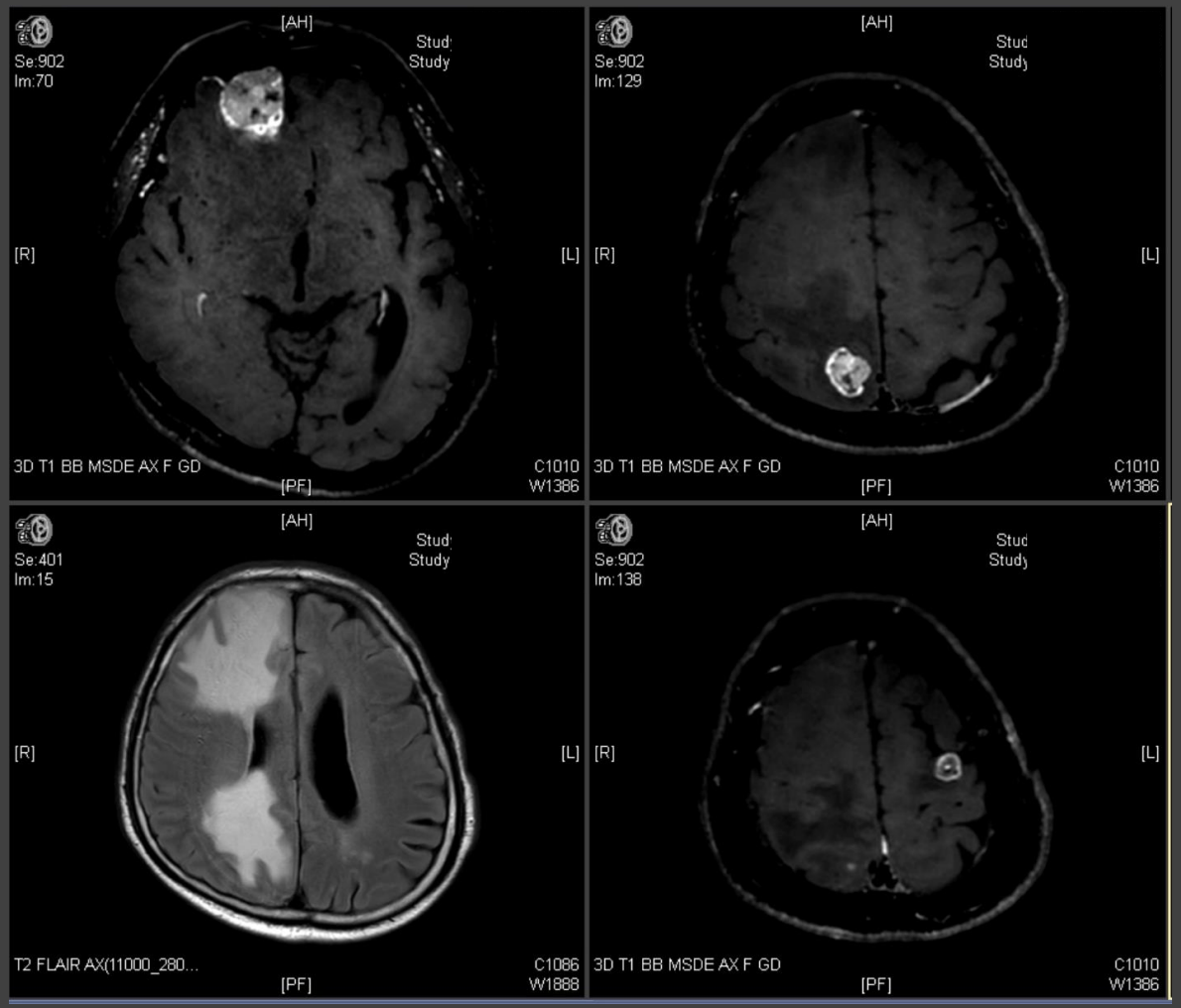
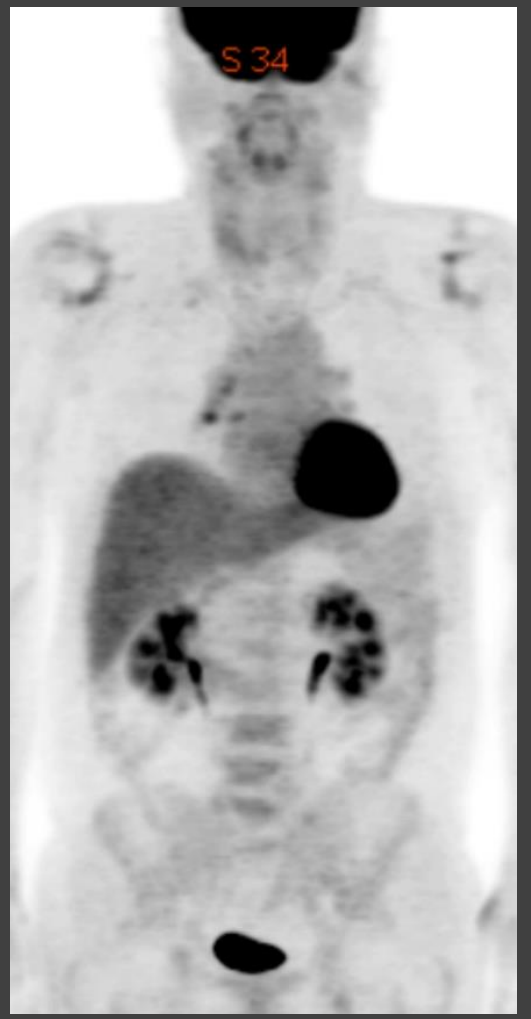
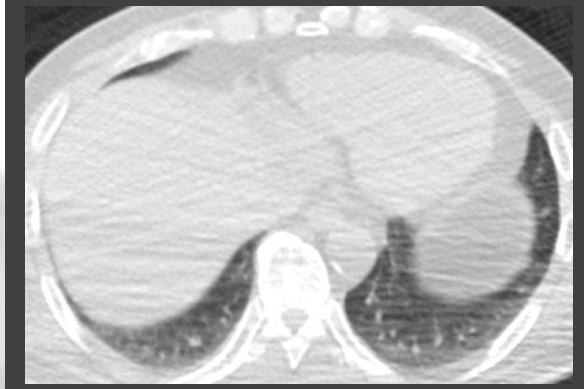






EGFR mutation [plasma cfDNA]	G719X		Not detected
	Ex19Del		Mutant(13.58)
	S768I		Not detected
	T790M		Mutant(8.37)
	Ex20Ins		Not detected
	L858R		Not detected
	L861Q		Not detected

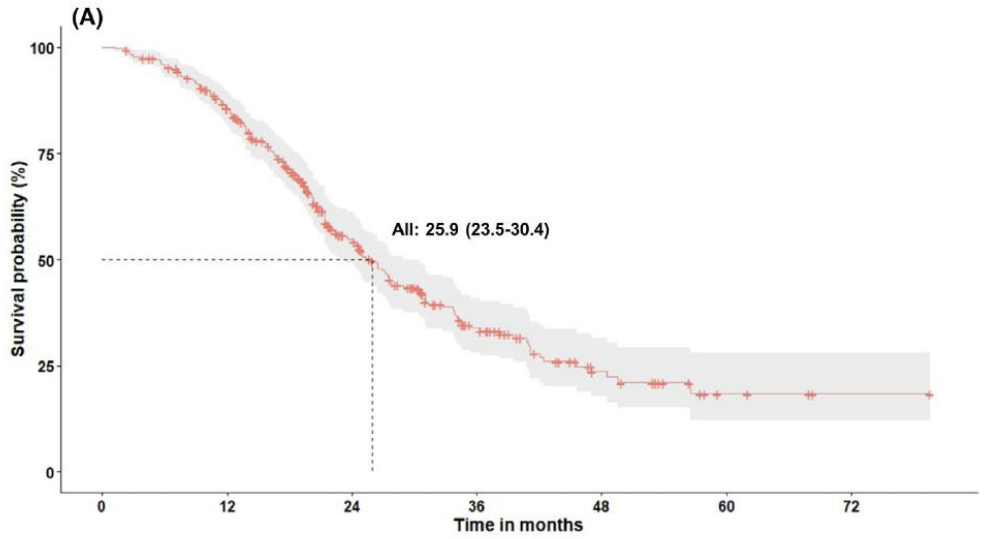
2021.06

8mo of afatinib 40mg

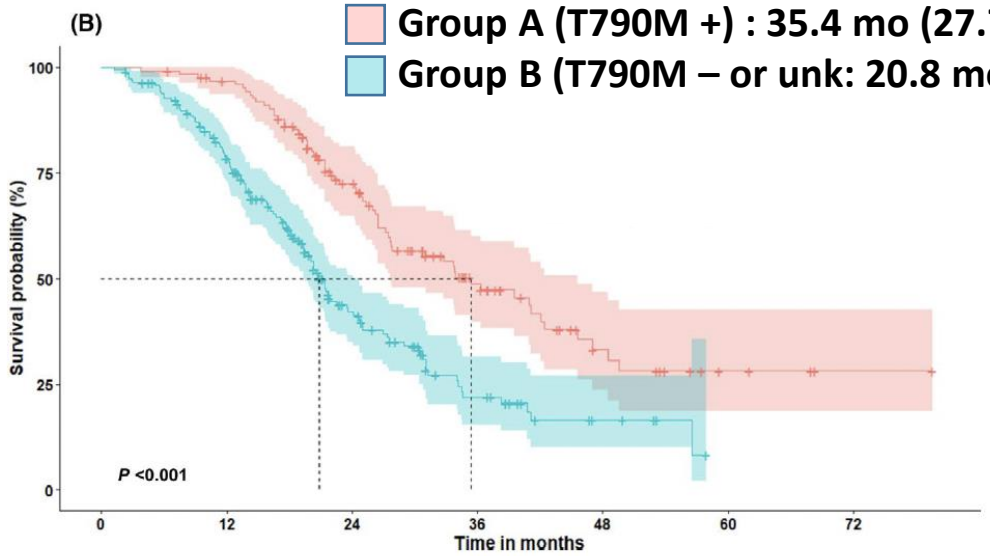
Real-world Experience of sequential treatment of afatinib and osimertinib (RESET)

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] |



Overall time-on-treatment (TOT) in all patients (n=324)



Overall time-on-treatment (TOT) in
Group A: afatinib and then osimertnib (n=126)
Group B: afatinib and then other therapy (n=198)

T790M rates after Afatinib, Gefitinib or Erlotinib

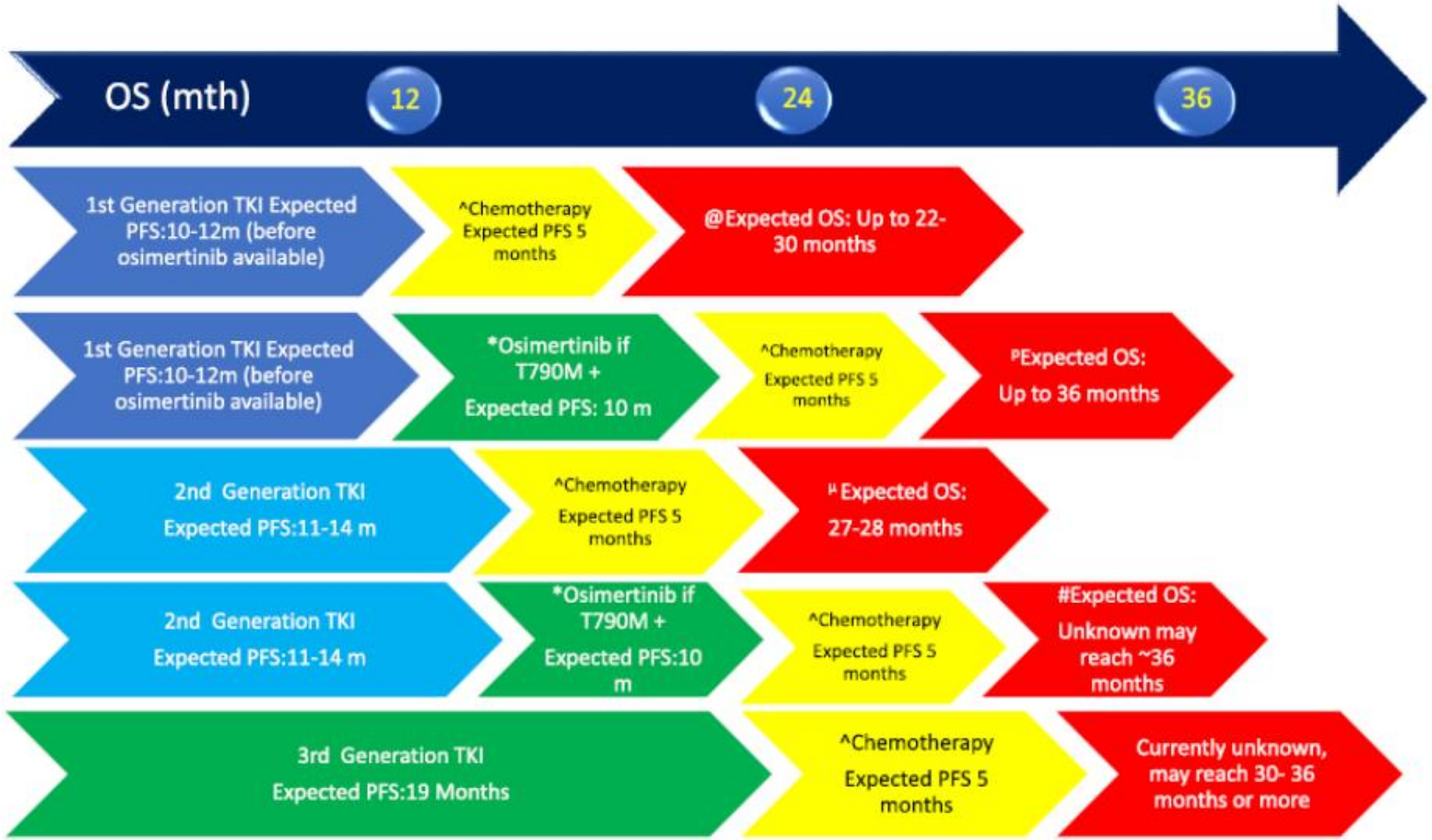
Table 3
Success rates of repeat biopsies, T790 M mutation rates, and histologic Transformation according to EGFR-TKIs.

	Afatinib	Erlotinib	Gefitinib	Total
Number of acquired resistance (A)	116	57	165	338
Number of repeat biopsies (B)	89	48	137	274
Rate of repeat biopsies (B/A)	76.7%	84.2%	83%	81.1%
Number of successful repeat biopsies (C)	86	44	133	263
Rate of successful repeat biopsies (C/A)	74.1%	77.2%	80.5%	77.8%
Number of T790 M mutation (D)	35	25	73	133
Rate of T790 M mutation (D/C)	40.7%	56.8%	54.9%	50.6%
Number of histologic transformations	5	0	1	6
Small cell carcinoma	2	0	1	3
Squamous cell carcinoma	3	0	0	3

30-40% in real-world rebiopsy

K. Lee et al. Lung Cancer 2019;130:87-92

Potential Sequencing of EGFR TKIs and its Estimated OS

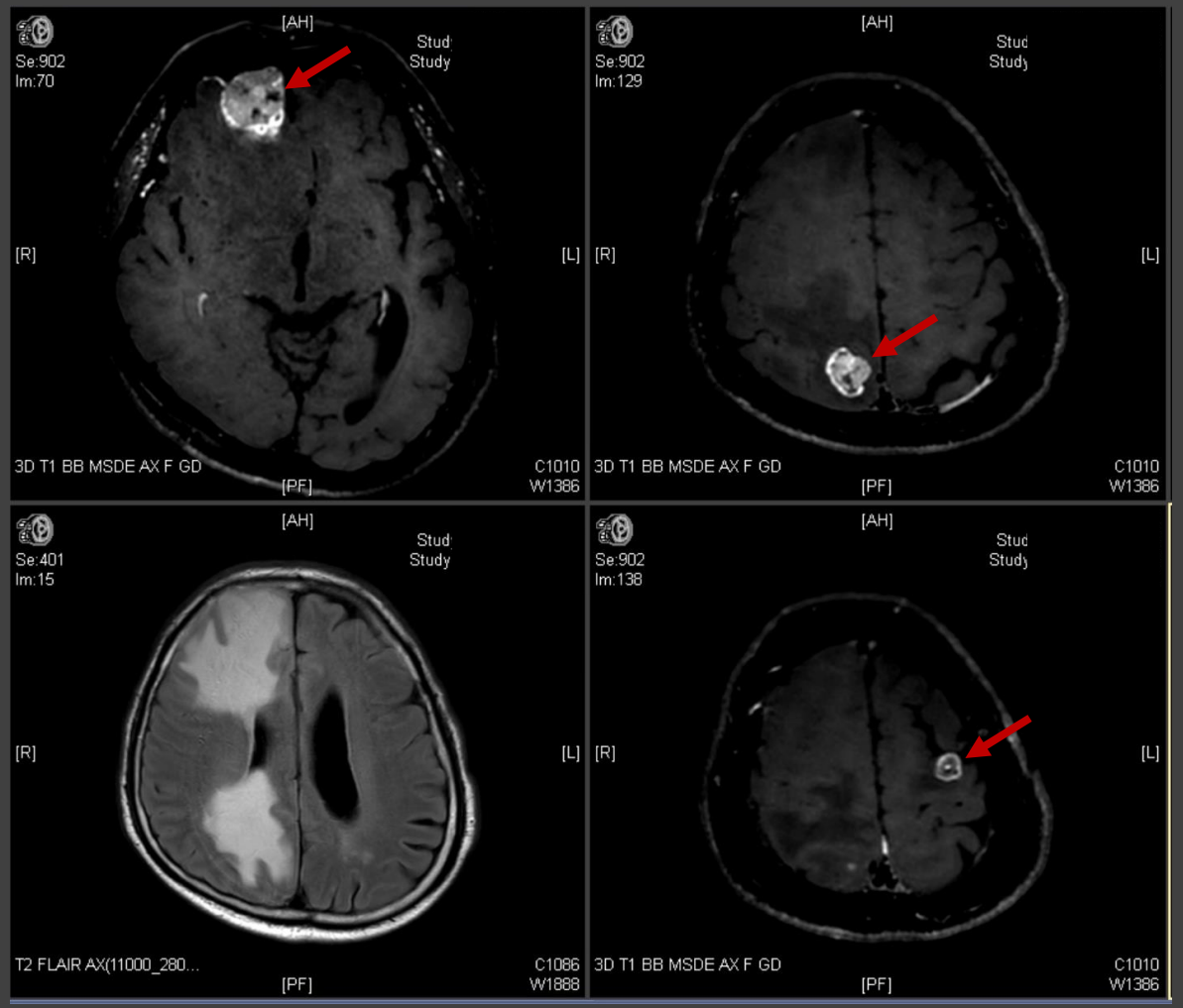


Estimated based on First Line EGFR TKI studies IPASS, WJTOG3405. *Estimated based on Pooled analysis AURA Extension & AURA2 as well as AURA3 Study. P Estimated based on OS reported from the Pooled analysis AURA. Extension & AURA2 Reported OS: 26.8 months + 10–12 months expected PFS from 1st Gen TKI. µ updated OS from Lux Lung 7. #Currently limited data. Only ~ 10% of patients received osimertinib post progression on Afatinib in Lux Lung 7. OS for these 10% patients is not available. ^ Estimated based on AURA3

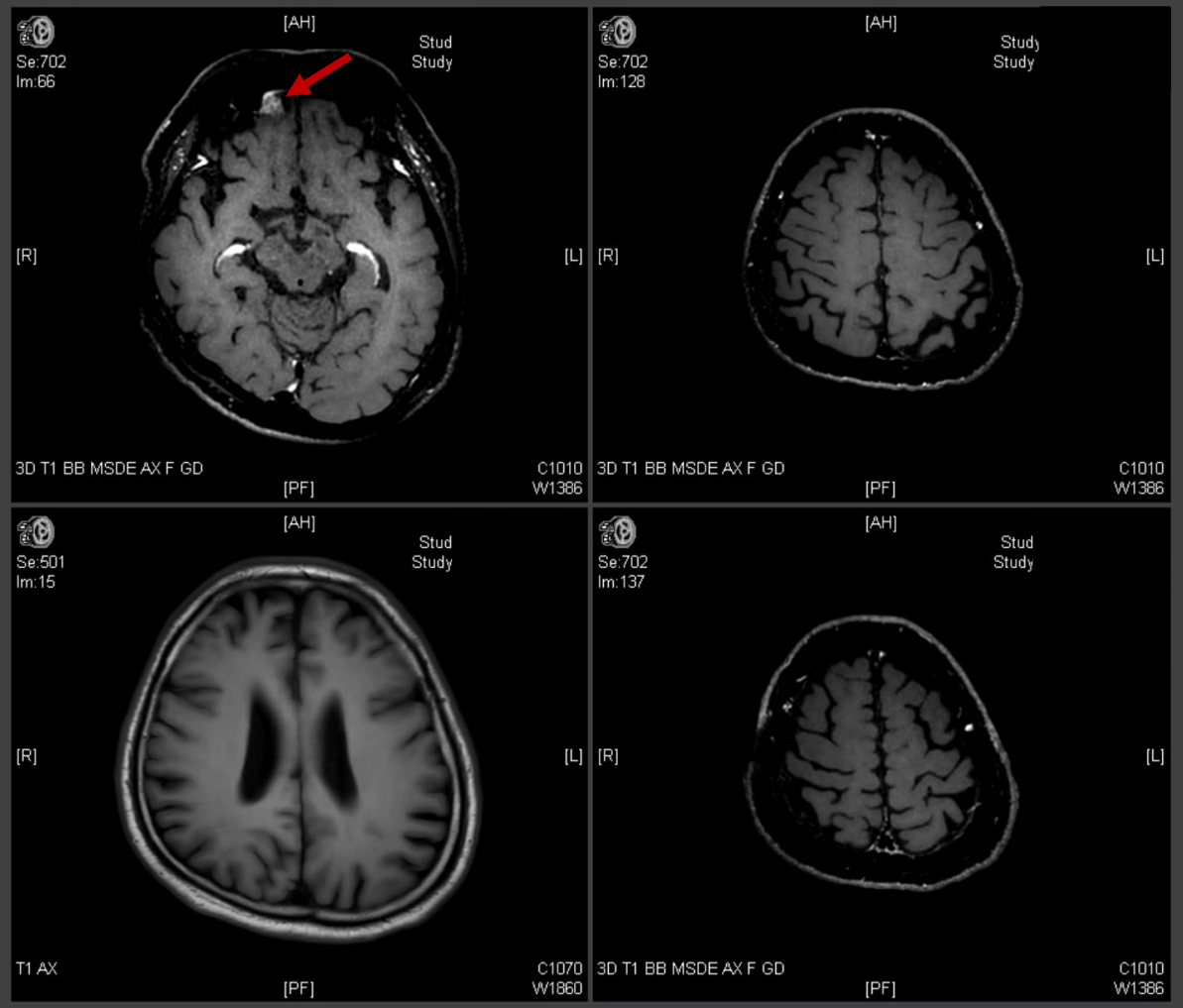
CS Tan et al. Mol Cancer . 2018 Feb 19;17(1):29.

M/63, 43pyrs, current smoker

Lung cancer (adenocarcinoma), cT1bN3M0, stage IIIB, EGFR E19del



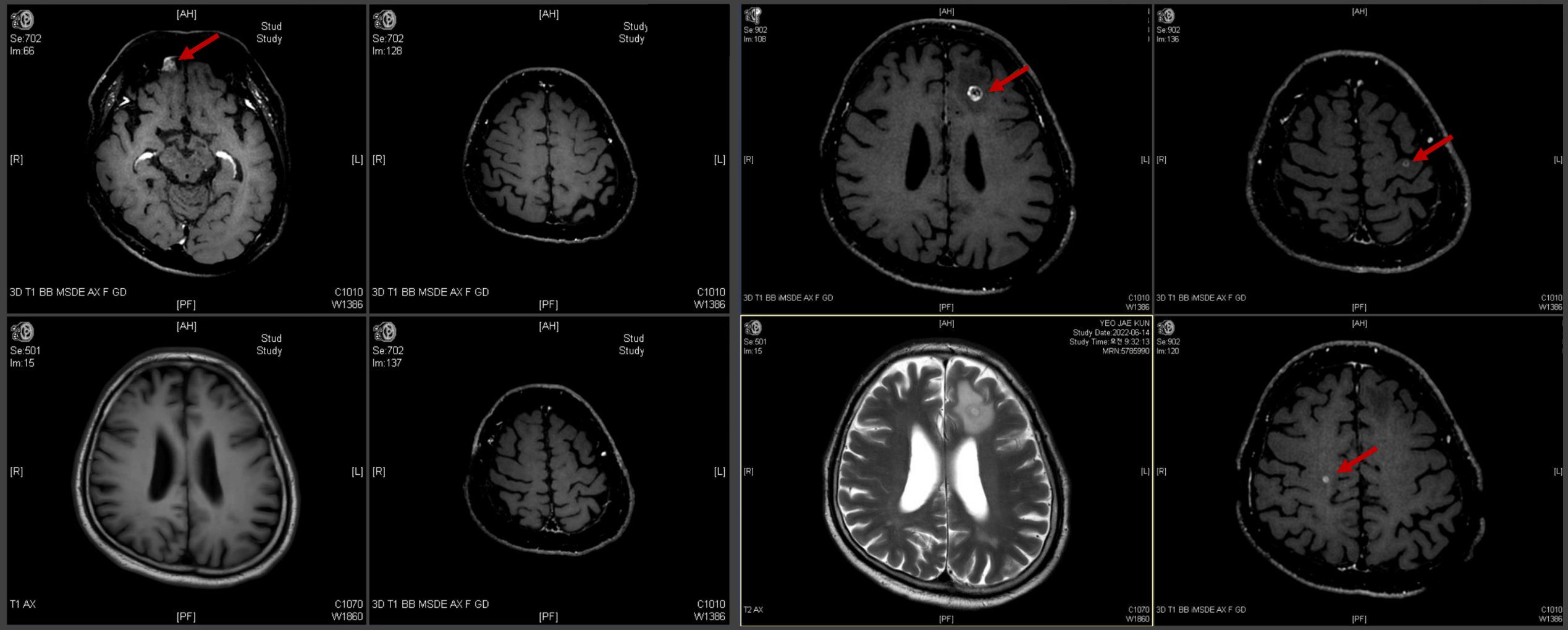
2021.06



2021.09
s/p GKS, 3mo of osimertinib 80mg

M/63, 43pyrs, current smoker

Lung cancer (adenocarcinoma), cT1bN3M0, stage IIIB, EGFR E19del

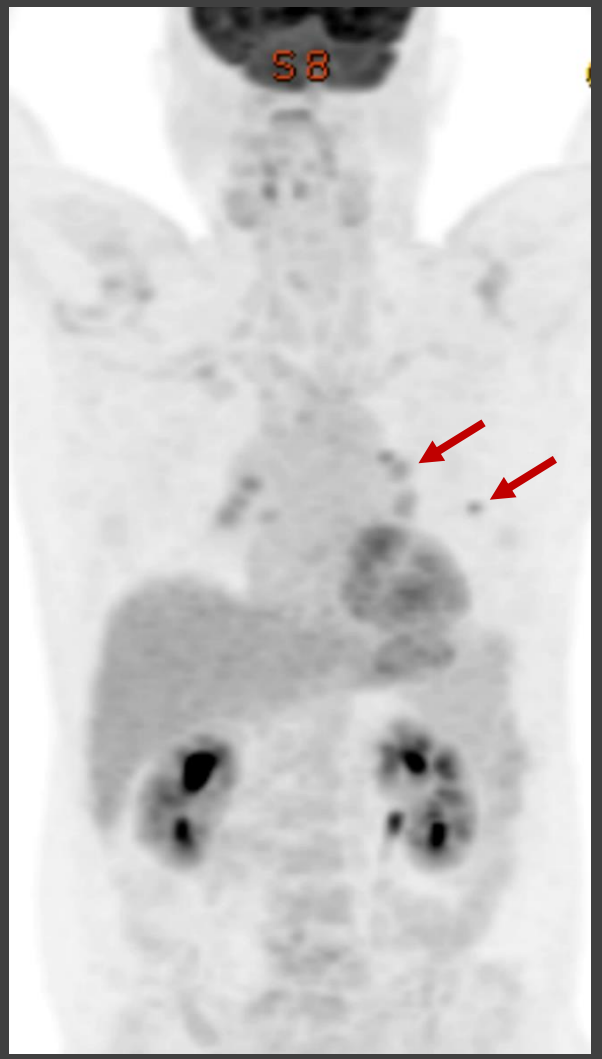


2021.09
s/p GKS, 3mo of osimertinib 80mg

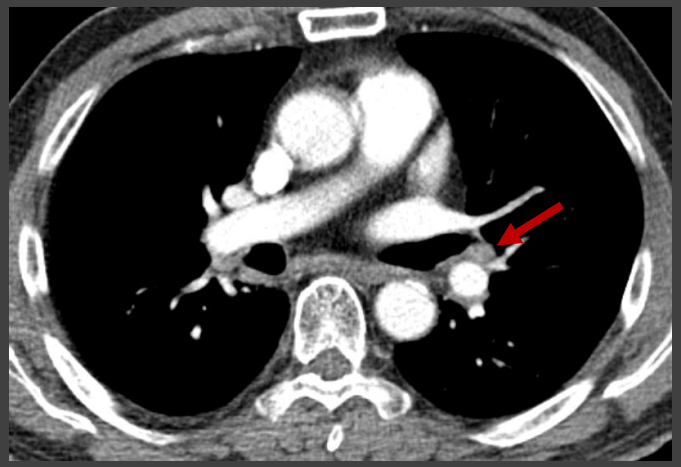
2022.06
12 mo of osimertinib 80mg

M/63, 43pyrs, current smoker

Lung cancer (adenocarcinoma), cT1bN3M0, stage IIIB, EGFR E19del



s/p definitive CCRTx (-2020.05)
1L afatinib (2020.10-)
2L osimertinib (2021.06-)



2022.06
12 mo of osimertinib 80mg

[Name Of Operation]
Lymph nodes, labeled "11L and 11Rs", EBUS-TBNA

[Pathological Diagnosis]
[Final report]
A. Labeled "11L": Malignant tumor, favor small cell carcinoma, see note.
B. Labeled "11Rs": No evidence of malignancy or granuloma

Note)
1. 현재 생검된 조직의 histology 및 immunophenotype은 small cell carcinoma에 합당합니다. 환자의 과거력을 종합해 보았을 때, adenocarcinoma의 transformation to small cell carcinoma 를 고려해 볼 수 있습니다. Clinical correlation 하시기 권유드립니다.

2. The immunohistochemical stain results:
- TTF-1: Negative in tumor cells
- CD56 and synaptophysin: Positive in tumor cells
- CK (AE1/AE3): Positive in tumor cells with perinuclear dot pattern

3. EGFR mutation (Droplet digital PCR): E19del Mutant

Mechanisms of Resistance after 3G TKIs

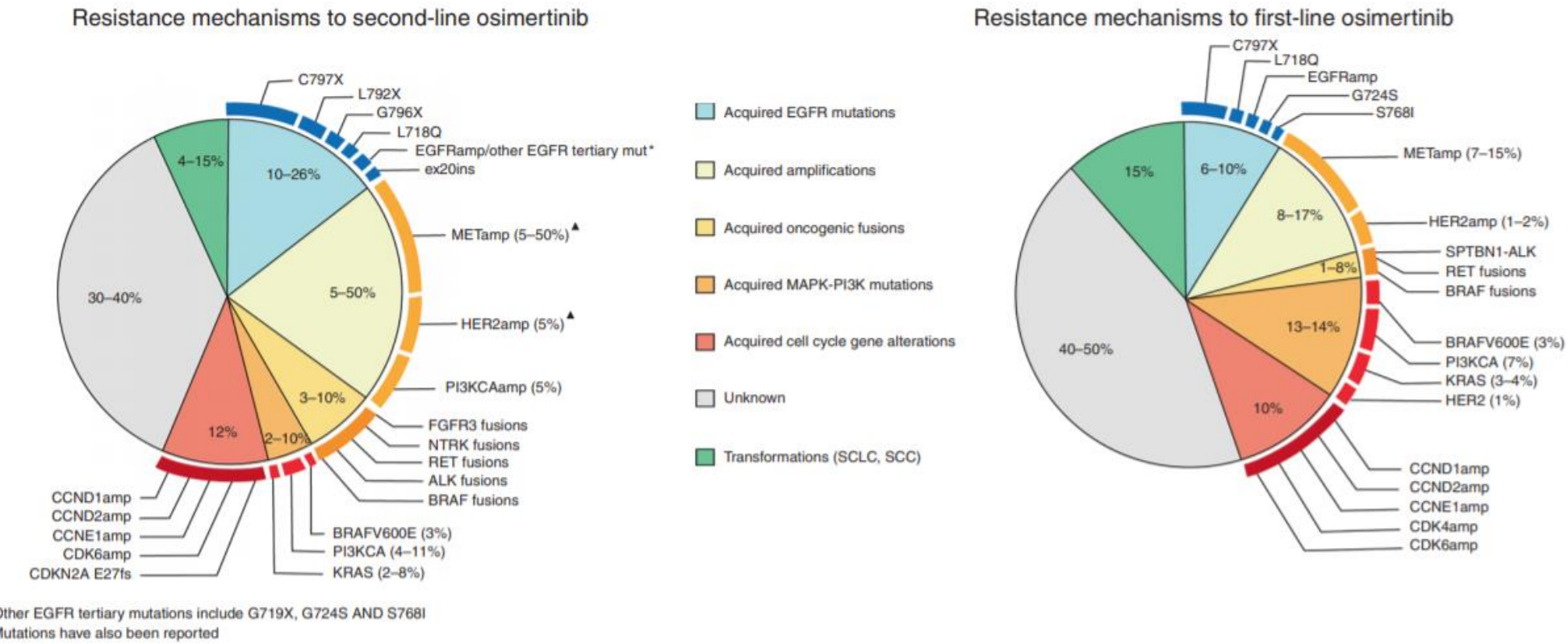


Fig. 1 Resistance mechanisms reported for osimertinib according to the line of treatment. The two pie charts depict resistance mechanisms that have been identified in tissue and/or in plasma after resistance to second-line and first-line osimertinib, respectively. Only studies that enrolled more than 15 patients have been taken into account for the ranges of the percentages. In some cases, different molecular aberrations might co-exist in the same patient

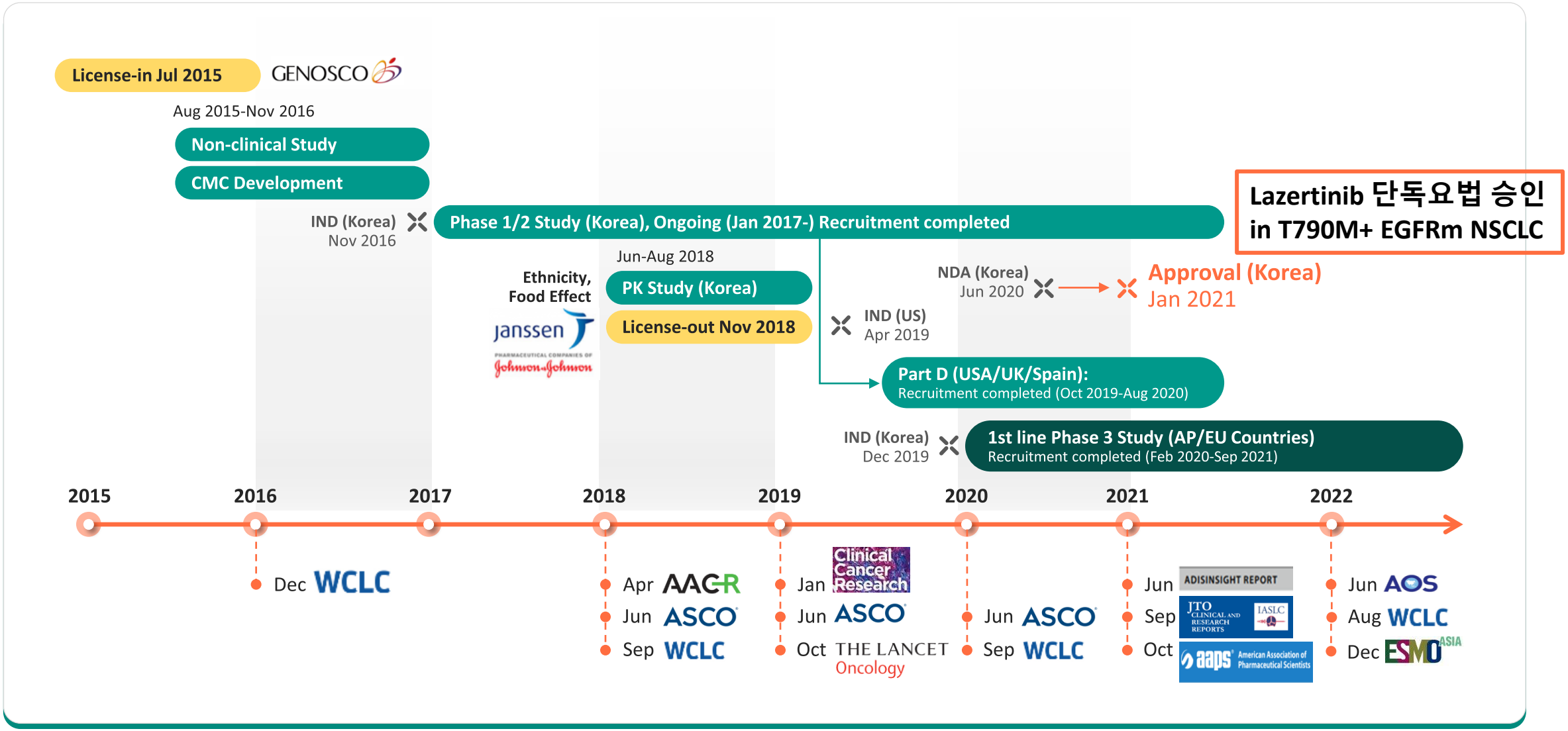
Leonetti et al. Br J Cancer. 2019 Oct;121(9):725-737.

유한양행

Overview of Lazertinib

렉라자® 정 80mg
(레이저티닙메실산염일수화물)

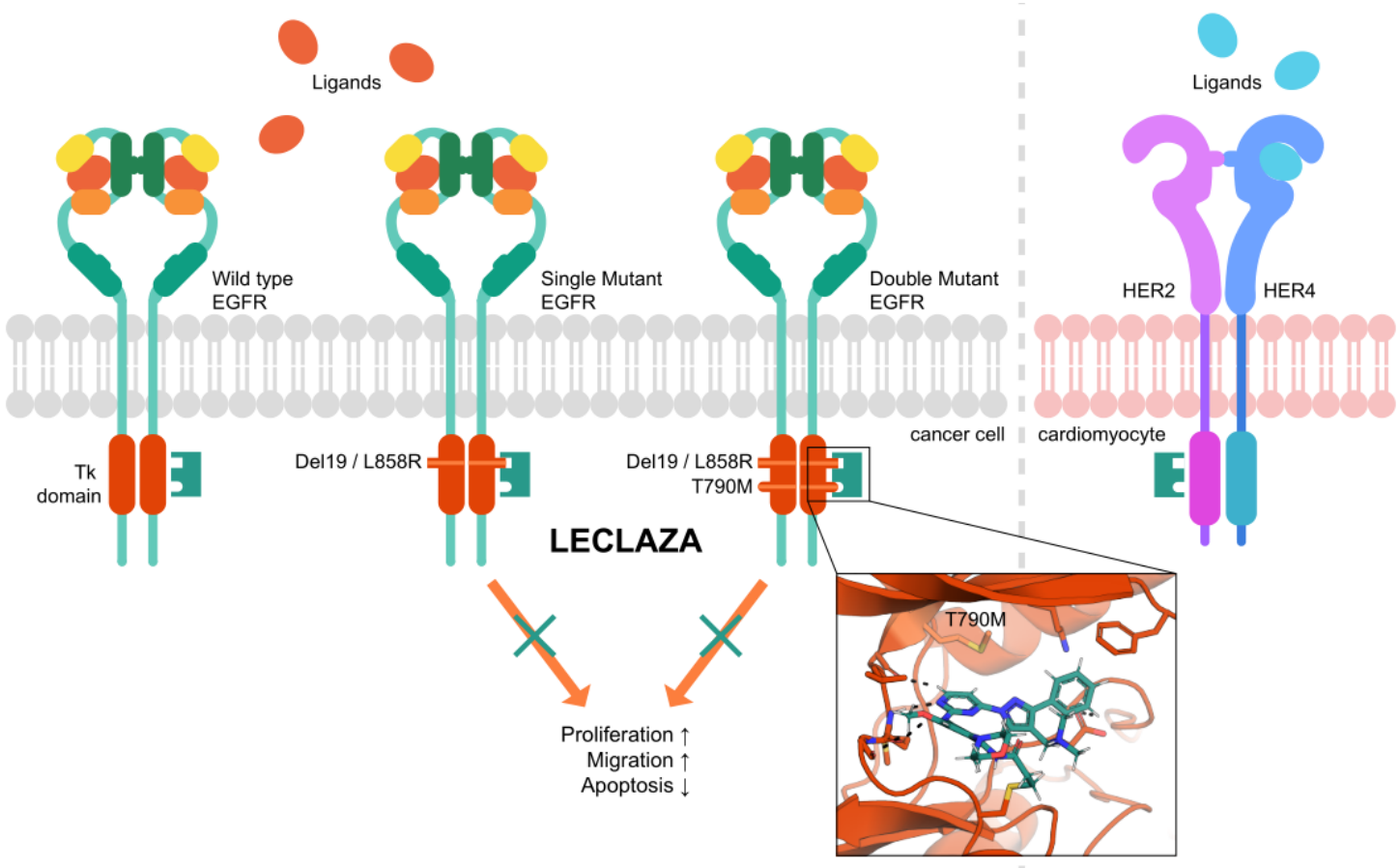
Lazertinib Development Overview



1. Data on file. Yuhan (Apr, 2023)

Lazertinib Mechanism of Action

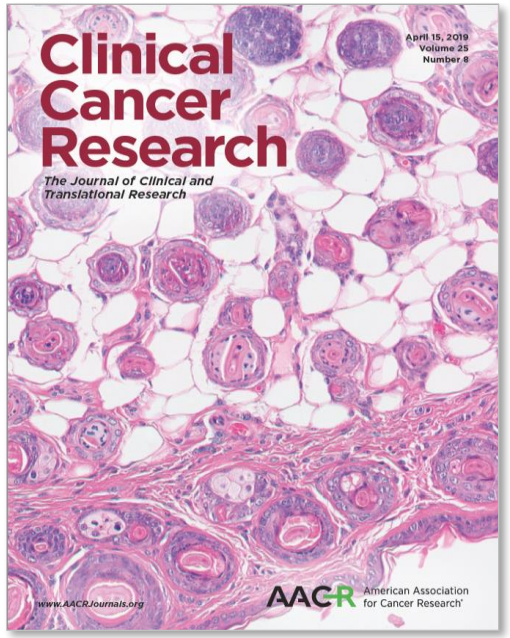
- Lazertinib is an oral, highly potent, irreversible, mutant selective and wild type sparing 3rd generation EGFR-TKI that targets sensitizing EGFR mutations as well as the T790M mutation



EGFR, Epidermal growth factor receptor; **HER,** human epidermal growth factor receptor; **Tk,** Tyrosine kinase

1. Yun JY, et al. *Clin Cancer Res;* 25(8) April 15, 2019

Key Results of Nonclinical Study

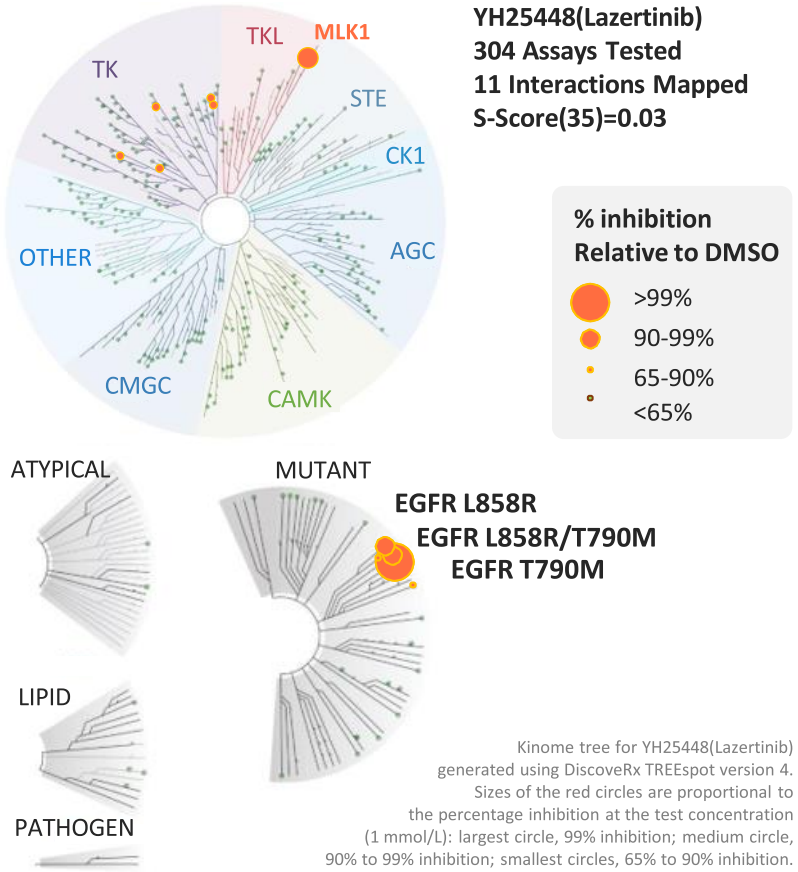


YH25448, an Irreversible EGFR-TKI with Potent Intracranial Activity in EGFR Mutant Non-Small Cell Lung Cancer

Yun J et al. *Clin Cancer Res.* 2019;25(8):2575-2587

Highly Mutant-Selective, Potent Irreversible Inhibitor

- Lazertinib showed a high selectivity and a strong activity against the various mutant EGFRs, it exhibited less activity against WT EGFR, compared with that of osimertinib in preclinical data.



Kinome tree for YH25448(Lazertinib) generated using DiscoveRx TREEspot version 4. Sizes of the red circles are proportional to the percentage inhibition at the test concentration (1 mmol/L): largest circle, 99% inhibition; medium circle, 90% to 99% inhibition; smallest circles, 65% to 90% inhibition.

Osimertinib (17)	% inhibition	Lazertinib® (10)	% inhibition
EGFR(T790M,L858R)(h)	102	EGFR(T790M)(h)	101
EGFR(T790M)(h)	100	EGFR(T790M,L858R)(h)	98
EGFR(L858R)(h)	97	MLK1(h)	97
ErbB4(h)	96	EGFR(L858R)(h)	91
ErbB2(h)	95	EGFR(h)	86
EGFR(h)	94	EGFR(L861Q)(h)	86
EGFR(L861Q)(h)	94	Ret(h)	86
ACK1(h)	89	Fer(h)	85
Mnk2(h)	83	Mer(h)	71
BTK(h)	77	Axl(h)	67
Blk(h)	75		
Flt3(D835Y)(h)	73		
Tec(h) activated	71		
IR(h), activated	70		
LRRK2(h)	69		
TSSK1(h)	66		
FAK(h)	65		

[over 65% inhibition]
Tested cmpd conc.: 1,000 nM

Comparison of YH25448(Lazertinib) and osimertinib selectivity profiles against approximately 320 kinases. The kinases listed were subject to over 65% inhibition by each compound, compared with DMSO.

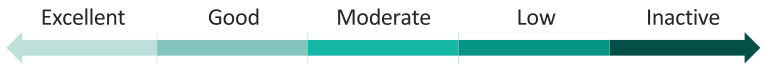
1. Yun J et al. *Clin Cancer Res.* 2019;25(8):2575-2587

Selectivity of Lazertinib

- **Lazertinib selectively inhibited mutated EGFRs rather than wild type EGFR** in preclinical data
- Major metabolite of Lazertinib was also selective

EGFR kinase Genotype	IC_{50}, nM			
	Lazertinib	YH26334[a]	Osimertinib	AZ5104[b]
EGFR (wild type)	60	91	20	0.98
EGFR (G719C)	1.7	4.8	65	4.2
EGFR (G719S)	4.1	9.3	49	3.2
EGFR (E746-A750del)	0.43	1.8	3.7	0.69
EGFR (L747-E749del, A750P)	14	38	3.2	0.53
EGFR (L747-S752del, P753S)	14	16	4.4	0.39
EGFR (L747-T751del, Sins)	8.3	13	4.9	1.1
EGFR (S752-I759del)	96	91	6.4	1.1
EGFR (L861Q)	14	22	5.6	0.54

a: YH26334: Metabolite of Lazertinib
b: AZ5104: Metabolite of osimertinib



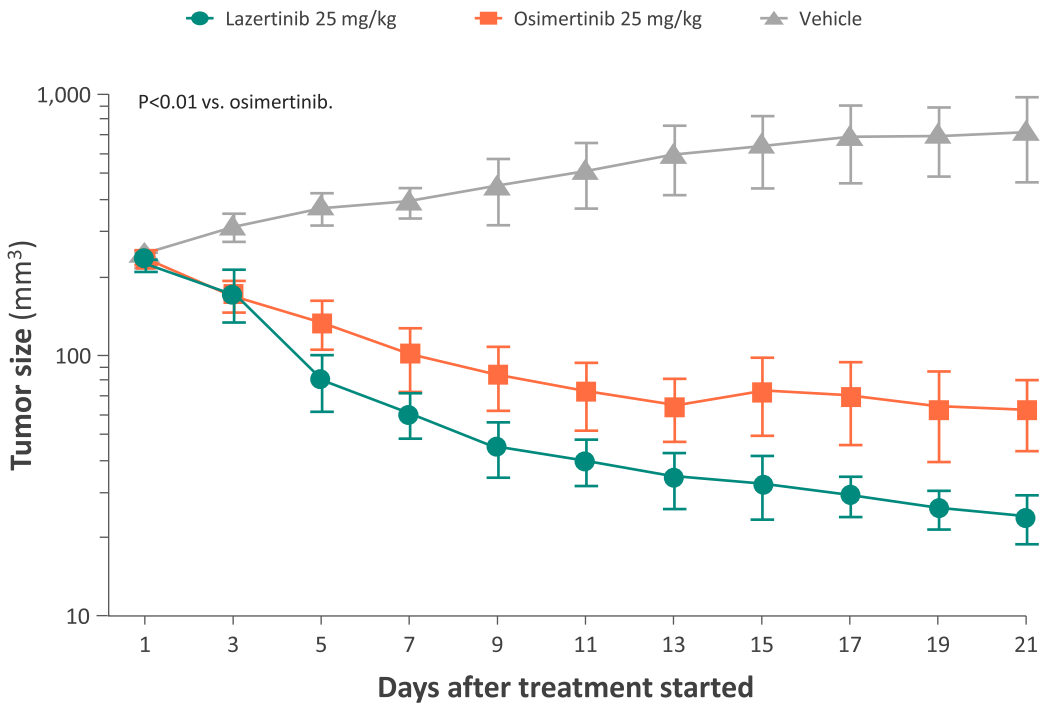
Each value represents the mean SEM calculated from at least two independent experiments.
The active metabolite of Lazertinib (YH26334) is present in humans at levels approximately 3% those of the parent (NCT03046992).
The active metabolite of osimertinib (AZ5104) is present in humans at levels approximately 10% those of the parent.

1. Yun J et al. *Clin Cancer Res.* 2019;25(8):2575-2587; **2.** Gunawan Indrayanto et al. *Profiles of Drug Substances, Excipients and Related Methodology* 2021;46:273-307

Anti-Tumor Efficacy

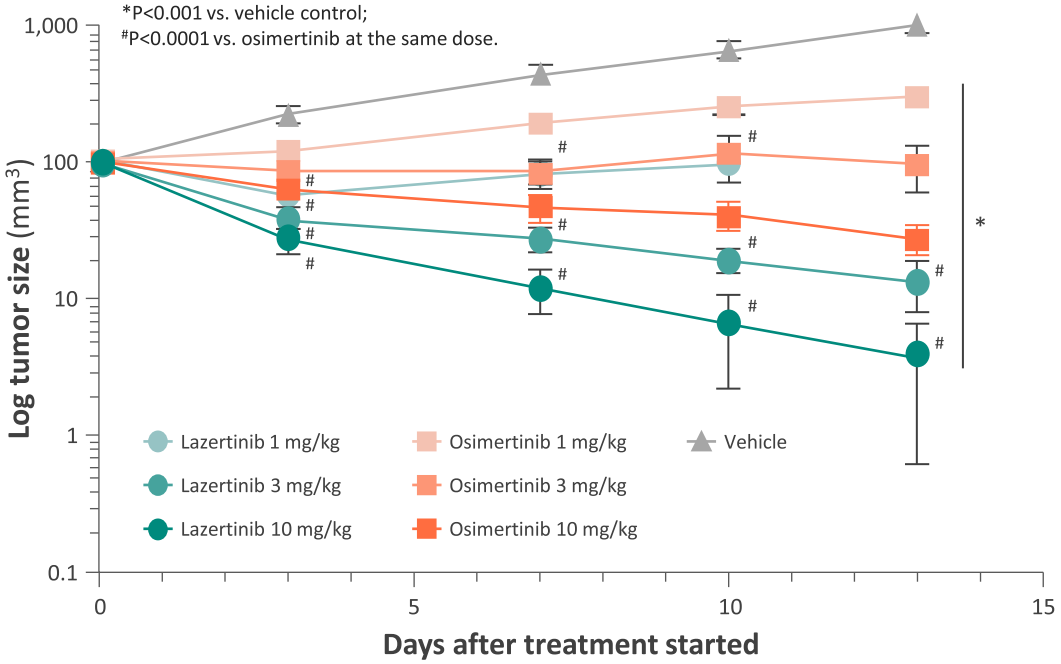
- Lazertinib was effective in both single (Del19) and double (L858R/T790M) mutant animal models

Del19 mutation (preclinical data)



Patient-derived tumors implanted in mice (YHIM-1003; EGFR Del 19; passage 3) were treated with Lazertinib or osimertinib at 25 mg/kg, once daily, when tumors reached 200 mm^3 in volume. Data represent the mean±SEM (n=7/group).

L858R/T790M mutation (preclinical data)



Antitumor effects of Lazertinib in H1975 (L858R/T790M) tumor-bearingmice (n=7/group). Mice were treated with Lazertinib, osimertinib, or vehicle once daily for 2 weeks after the tumor volume reached 100 mm^3. Data represent the mean±SEM (n=7/group).

EFGR, Epidermal Growth Factor Receptor; **NSCLC,** Non Small Cell Lung Cancer; **SEM,** Scanning Electron Microscope.

1. Yun J et al. *Clin Cancer Res.* 2019;25(8):2575-2587

Brain Penetration

Lazertinib is NOT a substrate of BCRP and a WEAK substrate of MDR1 (P-gp)*

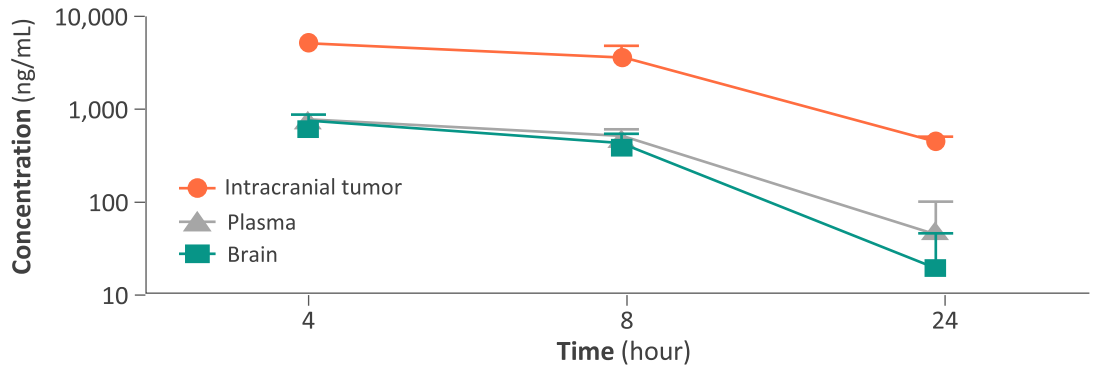
– Less likely affected by efflux transporters

	Net Efflux Ratio (ER)	
Lazertinib	**MDR1** (P-gp)	**BCRP**
0.1 μM	1.08±2.61	-0.34±0.61
1 μM	2.12±0.41	1.01±0.36
10 μM	0.26±0.08	-0.64±0.20

(Transporter assay in MDCK cells highly expressing MDR1 [P-glycoprotein] or BCRP)

Lazertinib had the ability to penetrate BBB

BBB penetration	
Relative exposure ratio (AUC_{last} based)	10 mg/kg
Brain/Plasma	**0.9**
Intracranial tumor/Plasma	**7.0**
Intracranial tumor/Brain	**7.9**



*Plasma, intracranial tumor, and brain tissue samples obtained at 4, 8, and 24 hours post dosing of Lazertinib (10 mg/kg) on day 21 post-dose were analyzed with a validated LC/MS-MS method.

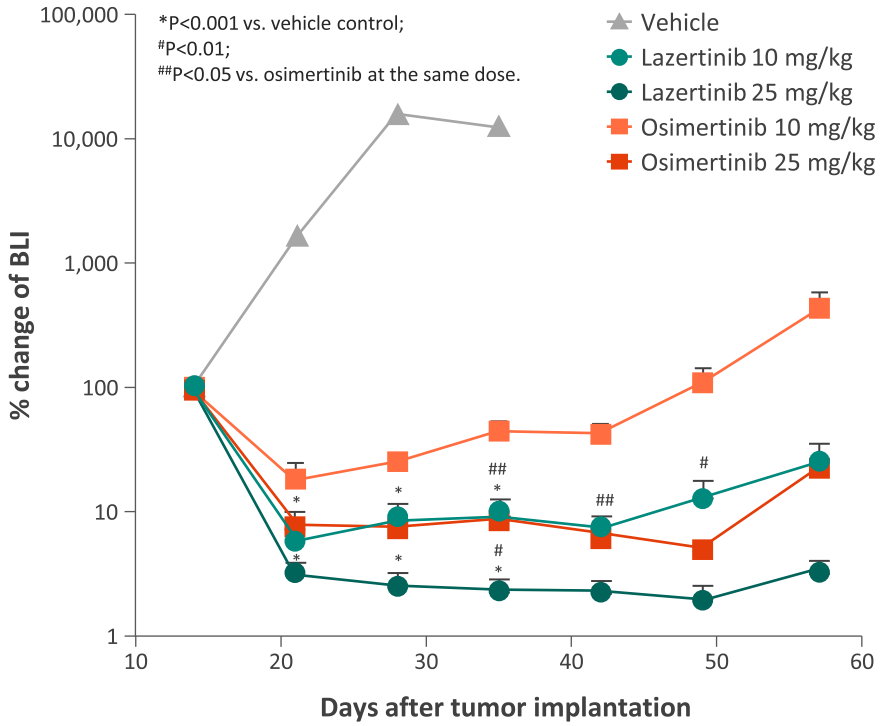
BCRP, breast cancer resistant protein; **ER,** efflux ratio; **MDCK,** Madin-Darby canine kidney cell; **MDR1,** multi-drug resistance protein 1; **P-gp,** P-glycoprotein.

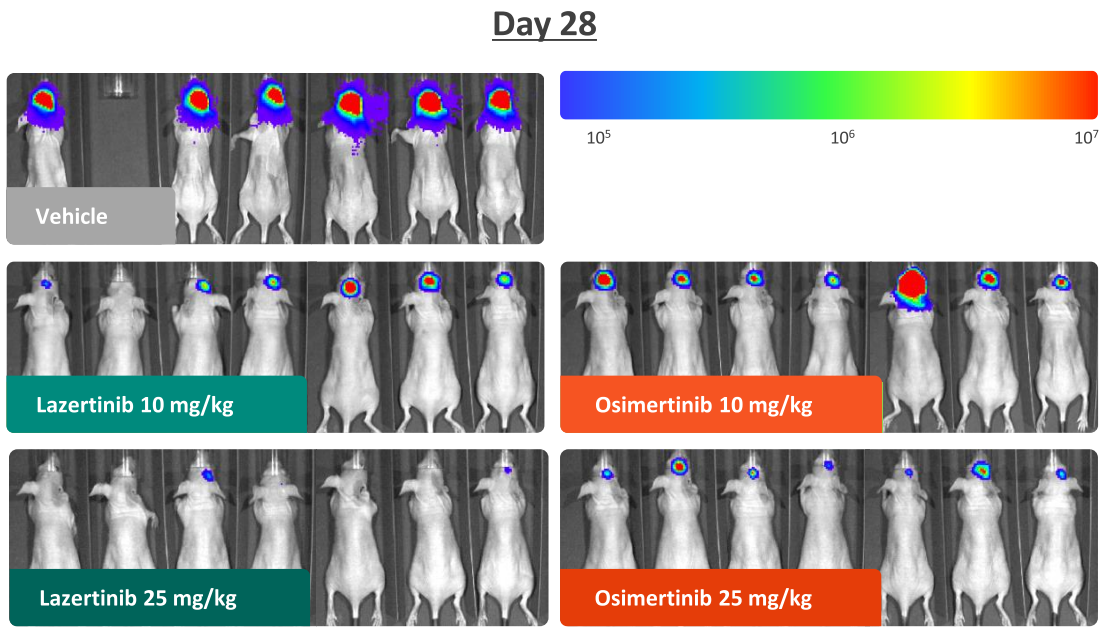
1. Data on file. Yuhan; **2.** CCR 2019; Internal data on file using transporter assay in MDCK cells highly expressing MDR1 or BCR0P; **3.** Yun J et al. *Clin Cancer Res.* 2019;25(8):2575-2587

CNS Activity of Lazertinib

Lazertinib showed **significant anti-tumor efficacy in brain metastasis animal model**

Intracranial tumor growth





An intracranial tumor growth model was established with BALB/c nude mice using H1975-luc cells. Two weeks after H1975 (L858R/T790M)-luc (luciferase-transfected H1975 cells) injection, animals were treated with Lazertinib or osimertinib once daily. BLI(bioluminescent imaging) was used to detect intracranial tumor growth in vivo. Data represent the mean±SEM (n=7/group).

BLI, bioluminescent imaging.

1. Yun JY, et al. *Clin Cancer Res;* 25(8) April 15, 2019

Skin Safety of Lazertinib

- Lazertinib shows **less severe skin toxicity** than osimertinib at high dose in preclinical study

Lazertinib (75 mg/kg) Osimertinib (75 mg/kg)

"Representative photographs of 75 mg/kg Lazertinib or Osimertinib-treated BALB/c nude mice after 12 days of treatment"

Groups	Clinical signs	Severity	Observed regions
Vehicle	-	-	-
Lazertinib (50 mg/kg)	**-**	**-**	**-**
Lazertinib (75 mg/kg)	**Keratosis (2/5)**	**Minimal (2/5)**	**Abdomen (2/5)**
Osimertinib (50 mg/kg)	Keratosis (1/5)	Minimal (1/5)	Left fore-arm (1/5)
Osimertinib (75 mg/kg)	Keratosis (5/5)	Severe (5/5)	Face, neck, abdomen (5/5)

"Skin problems of BALB/c nude mice-treated with vehicle, Lazertinib (50 and 75 mg/kg), or osimertinib (50 and 75 mg/kg)."

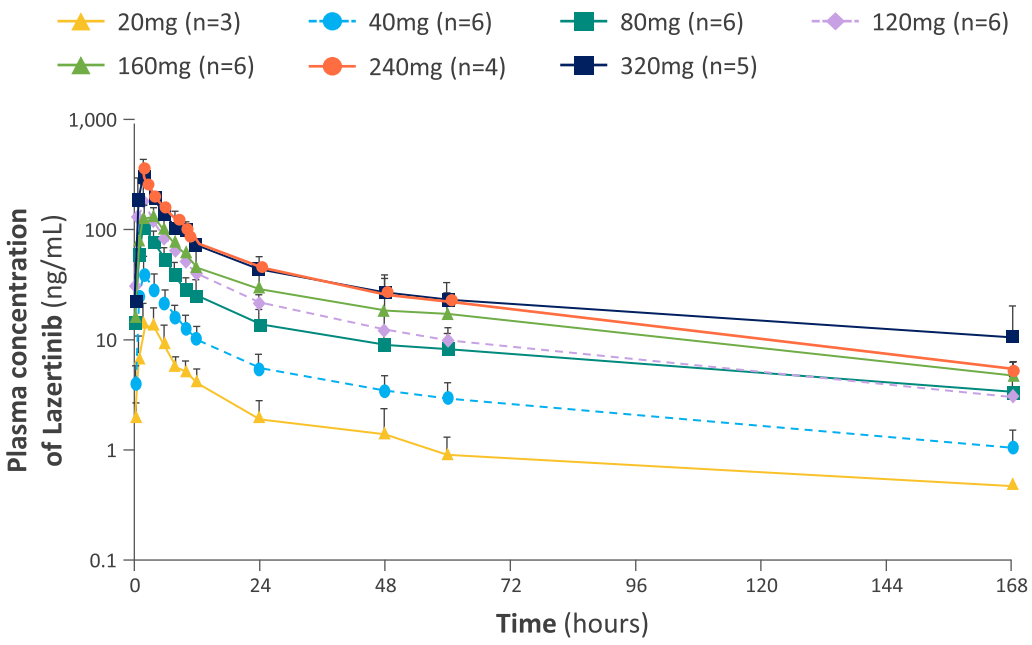
1. Yun JY, et al. *Clin Cancer Res;* 25(8) April 15, 2019

Pharmacokinetic Profiles

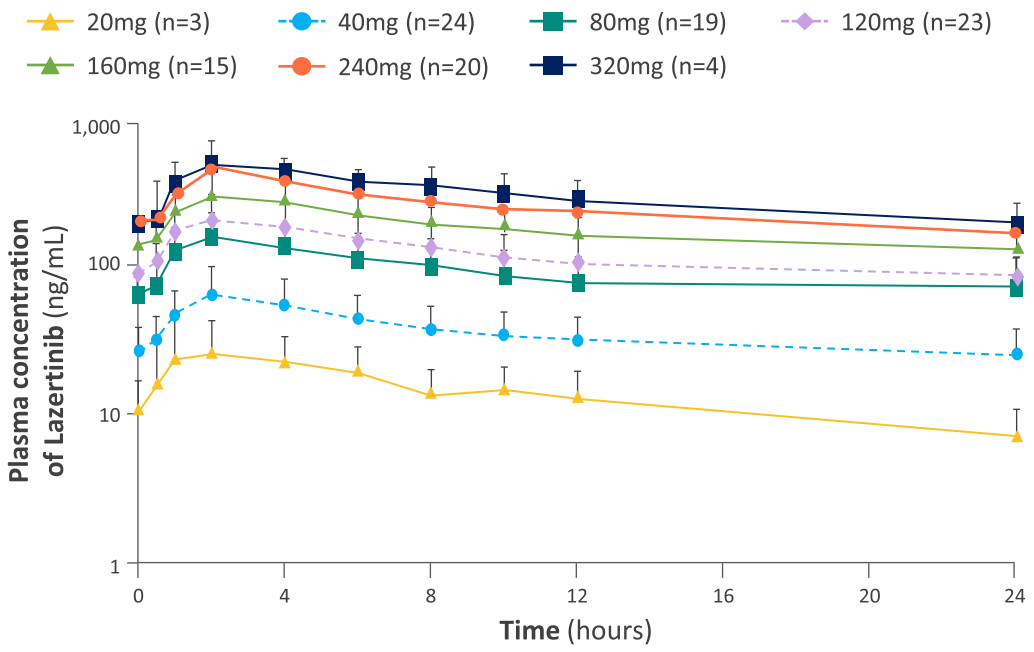
Mean Plasma Concentration Profiles

- Systemic exposures of Lazertinib increased in the near dose-proportional manner over the dose range of 20 to 320 mg
- Systemic exposure of major metabolite YH26334 at steady state was 2 to 4% of that of unchanged Lazertinib

Single dosing



Once daily dosing for 22 days

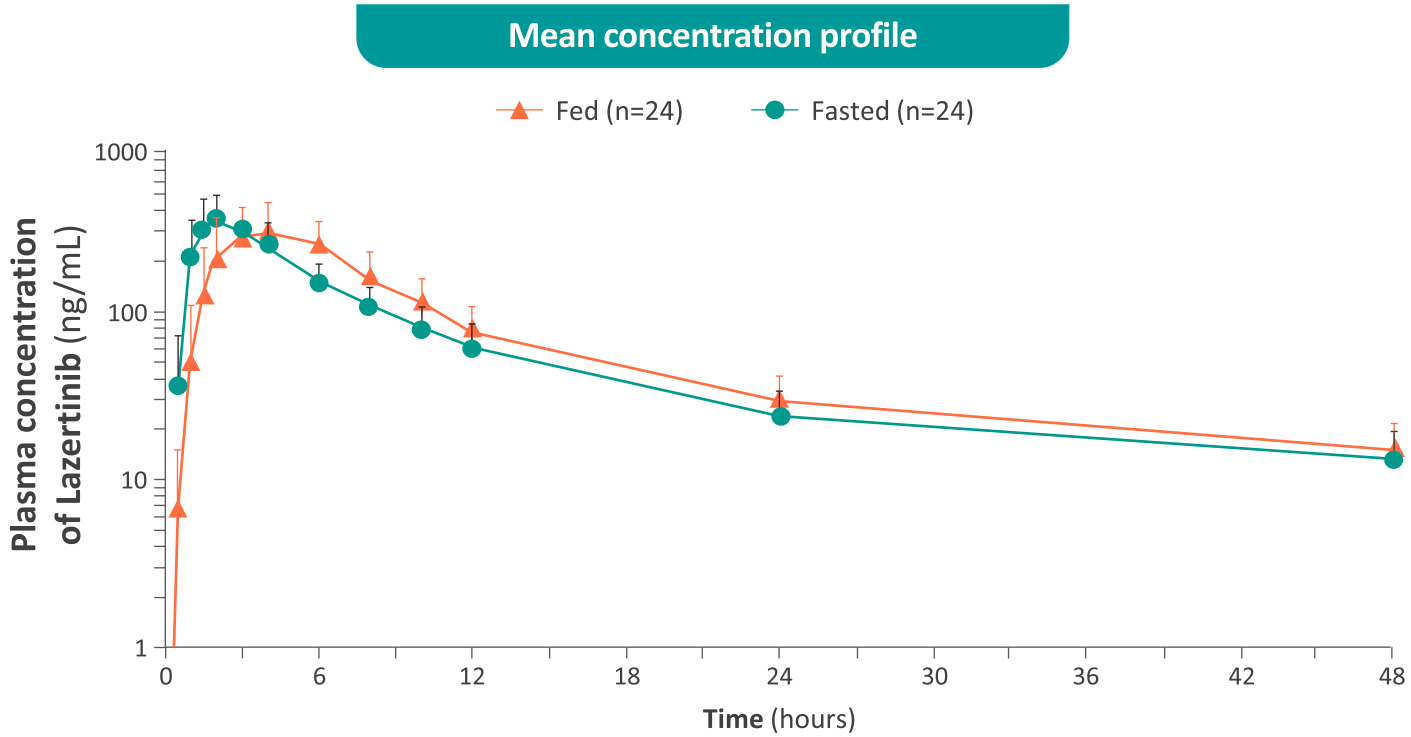


Data : arithmetic mean+standard deviation with semi-logarithmic ordinate scale.

1. Ahn MJ, et al. *Lancet Oncology* 2019;20:1681-1690.

Food Effect Results

- Following administration of Lazertinib 240 mg with food, the systemic exposure of Lazertinib was comparable to that under fasted condition
- No clinically significant difference in systemic exposure.

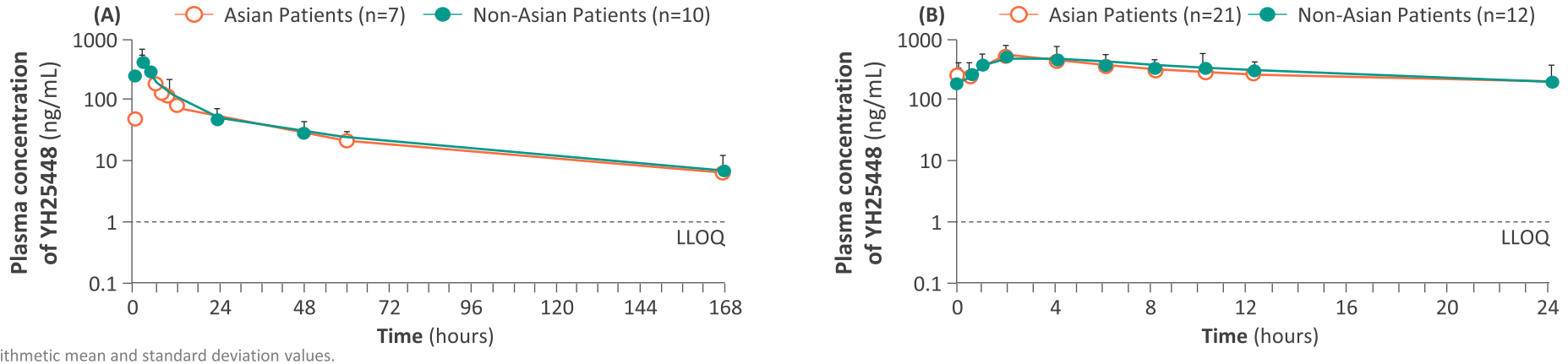


Data : arithmetic mean + standard deviation with semi-logarithmic ordinate scale
Fed: a high-fat, high-calorie meal (containing fat content approximately 50% and 800~1,000 kcal)
1. Lung Cancer, 2023;175:112-120.

PK Profile Comparison in Asian & Non-Asian

- At 240 mg, the systemic exposure of Lazertinib in non-Asian patients (n=12) was similar to that in Asian patients (n=21)

Mean Plasma Concentrations of Lazertinib for Asian and Non-Asian Patients



Data presented as arithmetic mean and standard deviation values.
(A) Single dosing on Day 1, Cycle 0 in Parts A and D; (B) Multiple dosing on Day 1, Cycle 2 in Parts A, B and D.

Comparison of Pharmacokinetic Parameter

Dosing	Pharmacokinetic parameter	Geometric Mean				Geometric Mean Ratio (Non-Asian /Asian Patients)	
		Asian	(n)	Non-Asian	(n)	Point Estimate	90% CI
Single (Day 1)	C_{max} (ng/mL)	421.32	(7)	418.14	(10)	**0.9924**	0.7425-1.3265
	AUC_t (h·ng/mL)	5296.34	(7)	5531.74	(10)	**1.0444**	0.7675-1.4212
Multiple (Day 22)	$C_{max,ss}$ (ng/mL)	480.32	(21)	449.62	(12)	**0.9361**	0.7111-1.2322
	AUC_{ss} (h·ng/mL)	6064.80	(21)	5898.41	(12)	**0.9726**	0.7228-1.3087

C_{max}, Maximum plasma concentration; **AUC_t**, Area under the plasma concentration-time curve from zero to the time of the last quantitative concentration; $C_{max,ss}$, Maximum plasma concentration at steady state; **AUC_{ss}**, Area under the plasma concentration-time curve from zero to the end of the dosing interval.

1. Lung Cancer, 2023;175:112-120.

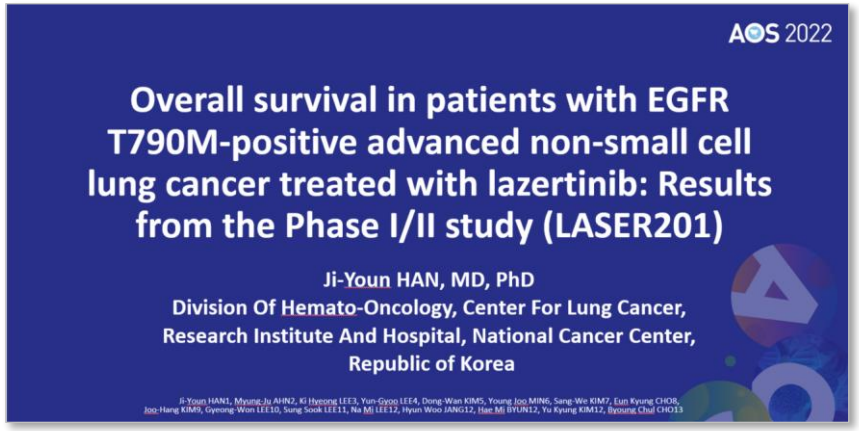
Key Results of Clinical Study


Articles

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

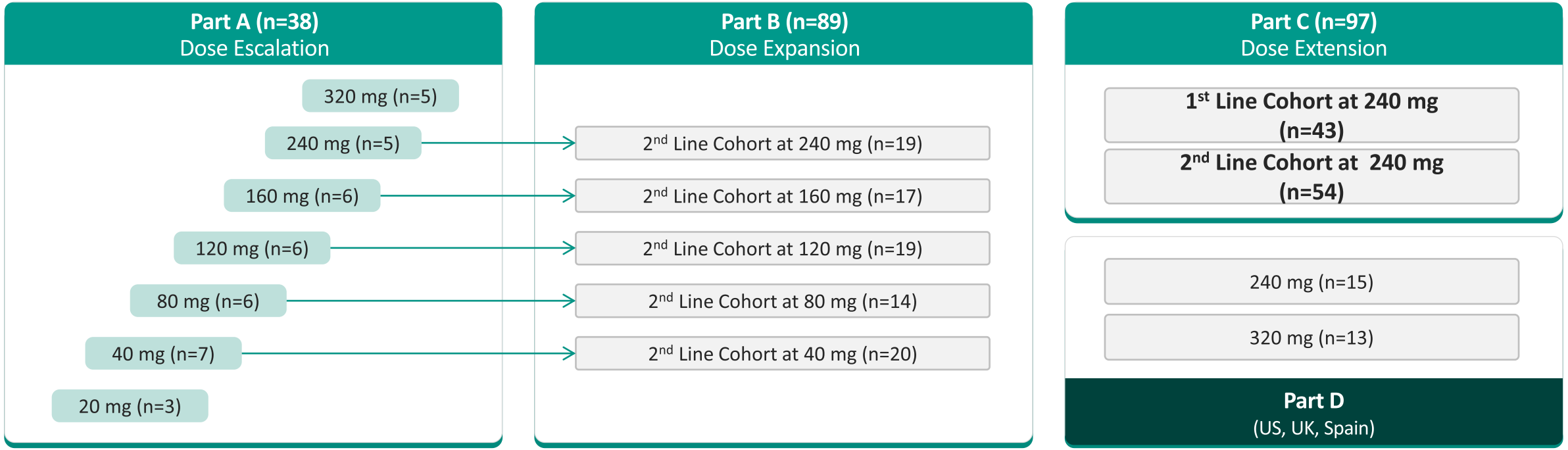
Ahn MJ et al., *Lancet Oncol.* 2019 Dec;20(12):1681-1690



Han et al. *AOS Oral presentation,* 2022

Study Design of LASER201 (Phase 1/2 Study)

- **Open-label, multicenter, phase 1/2 study:** Lazertinib was orally administrated once daily in patients with locally advanced or metastatic NSCLC with acquired resistance to prior EGFR-TKI treatments (NCT03046992)
- **Study Objectives**
  - Primary objectives: To evaluate the safety, tolerability and efficacy of Lazertinib
  - Secondary objectives: To define the MTD, PK, anti-tumor efficacy (ORR, DCR, DoR, PFS or OS)



MTD, Maximum Tolerated Dose; **PK,** Pharmacokinetics; **ORR,** Objective Response Rate; **DCR,** Disease Control Rate; **DoR,** Duration of Response; **PFS,** Progression Free Survival; **OS,** Overall Survival.

1, Ahn MJ et al., *Lancet Oncol.* 2019 Dec;20(12):1681-1690; **2.** Cho, BC et al. Journal of Thoracic Oncology, 2022;17(4):558-567

Baseline Characteristics: 2L Patients T790M +/-

	20 mg (n=3)	40 mg (n=27)	80 mg (n=20)	120 mg (n=25)	160 mg (n=23)	240 mg (n=78)	320 mg (n=5)	Overall (n=181)
Age in years, median (range)	58 (52, 62)	61 (37, 81)	67 (48, 84)	63 (28, 82)	62 (44, 83)	62 (33, 82)	64 (44, 82)	62 (28, 84)
Male, n (%)	2 (67)	9 (33)	7 (35)	9 (36)	11 (48)	40 (51)	0	78 (43)
ECOG performance status, n (%)								
0	2 (67)	9 (33)	6 (30)	8 (32)	2 (9)	20 (26)	1 (20)	48 (27)
1	1 (33)	18 (67)	14 (70)	17 (68)	21 (91)	58 (74)	4 (80)	133 (73)
Adenocarcinoma, n (%)	3 (100)	27 (100)	20 (100)	25 (100)	22 (96)	74 (95)	5 (100)	176 (97)
AJCC stage[a], n (%)								
IIIB	0	0	1 (5)	1 (4)	1 (4)	2 (3)	0	5 (3)
IV	3 (100)	27 (100)	19 (95)	24 (96)	22 (96)	75 (96)	5 (100)	175 (97)
Brain metastasis at baseline[b]	0	13 (48)	10 (50)	12 (48)	12 (52)	40 (51)	2 (40)	89 (49)
EGFR mutation by central testing, n (%)								
Exon19Del	2 (67)	21 (78)	9 (45)	14 (56)	12 (52)	53 (68)	2 (40)	113 (62)
L858R	1 (33)	6 (22)	9 (45)	11 (44)	11 (48)	23 (29)	2 (40)	63 (35)
L861Q	0	0	0	0	0	1 (1)	0	1 (1)
Negative	0	0	2 (10)	0	0	1 (1)	1 (20)	4 (2)
T790M Positive	2 (67)	26 (96)	18 (90)	22 (88)	18 (78)	76 (97)	0	162 (90)
Number of previous EGFR-TKIs, median (range)	1 (1, 1)	1 (1, 2)	1 (1, 2)	1 (1, 3)	1 (1, 2)	1 (1, 3)	1 (1, 2)	1 (1, 3)
Previous EGFR-TKI therapy[c], n (%)								
Gefitinib	1 (33)	19 (70)	12 (60)	16 (64)	16 (70)	40 (51)	4 (80)	108 (60)
Erlotinib	2 (67)	8 (30)	6 (30)	7 (28)	3 (13)	16 (21)	0	42 (23)
Afatinib	0	1 (4)	3 (15)	3 (12)	6 (26)	28 (36)	1 (20)	42 (23)
Other	0	1 (4)	0	1 (4)	0	0	0	2 (1)

DCO : Jan 2021

[a] AJCC: The American Joint Committee on Cancer, 7th edition; [b] Brain metastasis at baseline is based on the brain lesion site by investigator's assessment; [c] Patients may have more than one previous EGFR TKI therapy

1, Ahn MJ et al., *Lancet Oncol* . 2019 Dec;20(12):1681-1690; **2.** Data on file, Yuhan

Anti-tumor Response & PFS: 2L T790M+ Patients

ICR (Independent Central Review) assessment results

	2L (T790M+)	
	240 mg	Overall
Evaluable patients[a], n	**76**	**162**
Best overall response[b], n (%)		
Complete response	1 (1)	3 (2)
Partial response	41 (54)	91 (56)
Stable disease	26 (34)	51 (32)
Progressive disease	6 (8)	13 (8)
Not evaluable	2 (3)	4 (2)
DCR[c], n (%)	68 (89)	145 (90)
ORR[d], n (%)	**42 (55)**	94 (58)
DOR[e] (month), median [95% CI][#]	**17.7 [9.9-NR]**	15.2 [11.0-17.9]
PFS[f] (month), median [95% CI][#]	**11.1 [5.5-16.4]**	11.0 [8.1-15.1]

Investigator assessment results

	2L (T790M+)	
	240 mg	Overall
Evaluable patients[a], n	**76**	**162**
Best overall response[b], n (%)		
Complete response	0	2 (1)
Partial response	55 (72)	108 (67)
Stable disease	17 (22)	41 (25)
Progressive disease	2 (3)	8 (5)
Not evaluable	2 (3)	3 (2)
DCR[c], n (%)	72 (95)	151 (93)
ORR[d], n (%)	**55 (72)**	110 (68)
DOR[e] (month), median [95% CI][#]	**12.6 [9.9-18.2]**	12.6 [11.0-17.9]
PFS[f] (month), median [95% CI][#]	**12.4 [9.6-17.7]**	11.1 [8.2-13.2]

DCO : Jan 2021

NR, Not reached; Percentages are calculated based on number of evaluable patients.

[a] Patients in the safety analysis population who has a baseline RECIST 1.1 assessment whose tumor EGFR mutation status was confirmed via a central testing and T790M positive; [b] Best overall response was derived based upon time point tumor responses during the study; [c] Disease control rate is the proportion of patients who have a best overall response of complete response (CR) or partial response (PR) or stable disease (SD) (SD at ≥ 5 weeks); [d] Objective response rate is the proportion of patients who have a confirmed best overall response of CR or PR; [e] Duration of objective response is measured from the date of the first documented response until objective tumor progression or death, whichever occurs first; [f] Progression free survival is measured from the first multiple dose date (cycle 1 day 1) until objective tumor progression or death, whichever occurs first; [#] Median with 95% CI is calculated from Kaplan-Meier estimate.

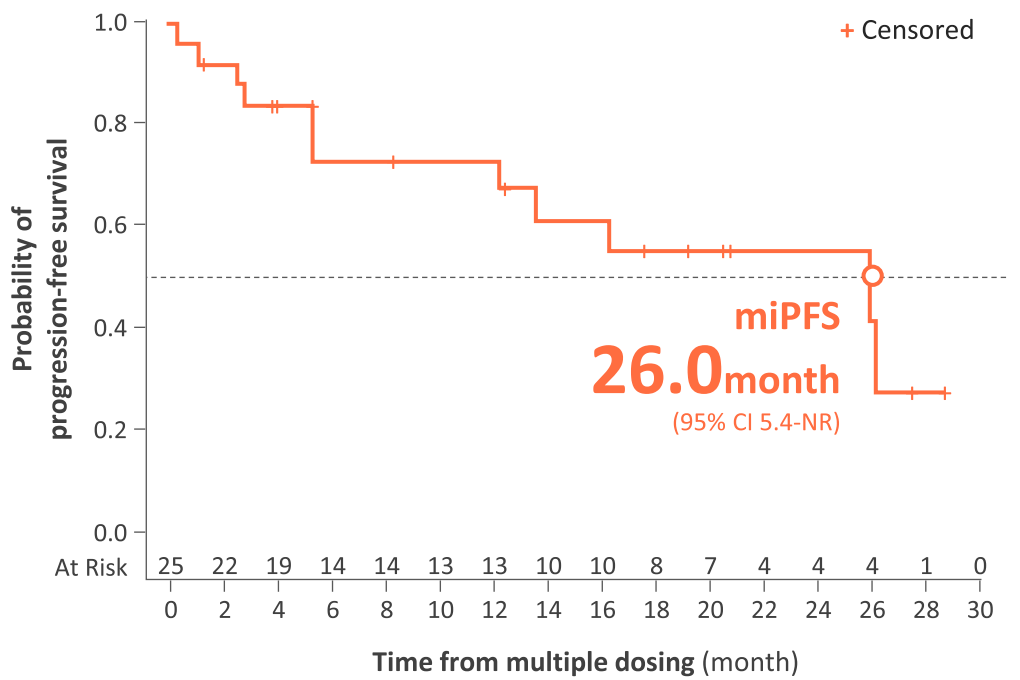
1, Cho, B. C., et al. *Journal of Thoracic Oncology* 17.4 (2022): 558-567 2. Cho et al. KALC. 2021, LASER201 Clinical study report (data cut-off 08Jan2021)

Intracranial Efficacy: 2L T790M+ Patients

ICR assessment results

	2L (T790M+)	
	240 mg	Overall
BM full analysis population, n	**25**	**57**
Intracranial PFS[a] (months), median [95% CI][#]	**26.0 [5.4-NR]**	35.8 [14.0-NR]
BM population evaluable for response, n	**7**	**18**
Intracranial ORR[b], n(%)	6 (86)	10 (56)
Intracranial DCR[c], n (%)	7 (100)	18 (100)
Intracranial DOR[d] (months), median [95% CI][#]	15.1 [2.8-NR]	15.1 [2.8-NR]

Intracranial Progression-Free Survival in BM Patients by ICR (T790M+, 240 mg)



DCO : Jan 2021

NR, Not reached

[a] IPFS is measured from the first multiple dose date (cycle 1 day 1) until objective tumor intracranial progression or death, whichever occurs first. ; [b] OIRR is the proportion of patients who have a confirmed best overall intracranial response of complete response (CR) or partial response (PR); [c] IDCR is the proportion of patients who have a best overall intracranial response of complete response (CR) or partial response (PR) or stable disease (SD) (SD at ≥ 5 weeks) ; [d] Duration of intracranial objective response is measured from the date of the first documented response until objective tumor progression or death, whichever occurs first; [#] Median and 95% CI are calculated using Kaplan-Meier estimate.

1, Cho, B. C., et al. *Journal of Thoracic Oncology* 17.4 (2022): 558-567 2. Cho et al. KALC. 2021, LASER201 Clinical study report (data cut-off 08Jan2021)

Sites of Disease Progression

- Lazertinib showed CNS progression occurred in **7 patients (9.2%);** new CNS lesions were documented **in 2 cases** in LASER201

	2L (T790M+)	
	240 mg	Overall
Evaluable patients[a]	76	162
Any disease progression, n(%)	46 (61)	107 (66)
Number of patients with CNS progression, n(%)	7 (9)	16 (10)
Progression in CNS only	7 (9)	13 (8)
New lesion only	2 (3)	6 (4)
Existing lesions only	5 (7)	7 (4)
New and existing lesions	0	0
Progression in CNS and non-CNS	0	3 (2)
New lesion only	0	0
Existing lesions only	0	3(2)
New and existing lesions	0	0

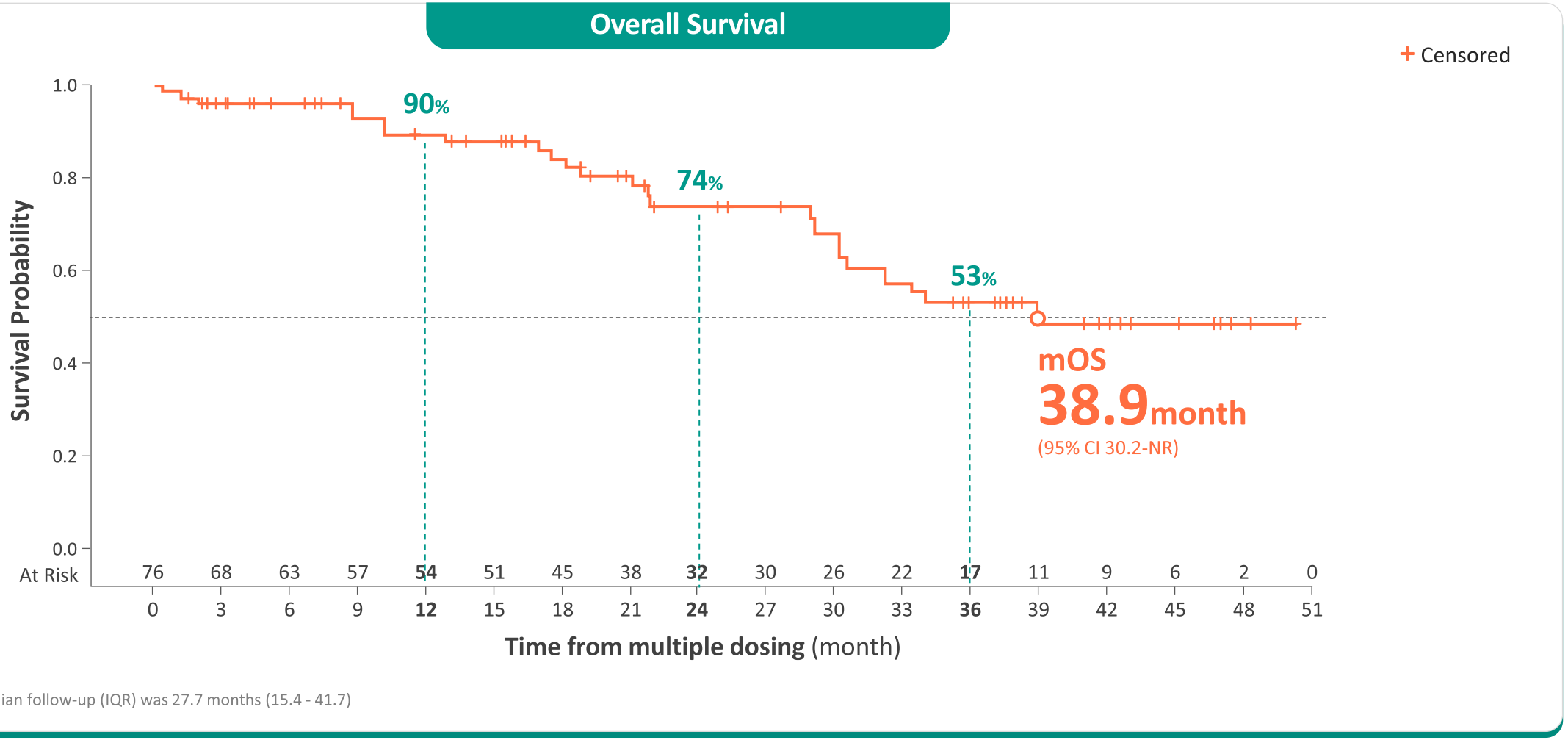
Percentages are calculated based on number of evaluable patients. ICR assessment result.

[a] Patients in the safety analysis population who has a baseline RECIST 1.1 assessment whose tumor EGFR mutation status was confirmed via a central testing.

1. Cho, B. C., et al. Journal of Thoracic Oncology 17.4 (2022): 558-567 2. Data on file, Yuhan , LASER201 CSR, DCO Jan 2021

DCO: 08 Jan 2021

Overall Survival: 2L T790M+ Patients



Duration of median follow-up (IQR) was 27.7 months (15.4 - 41.7)

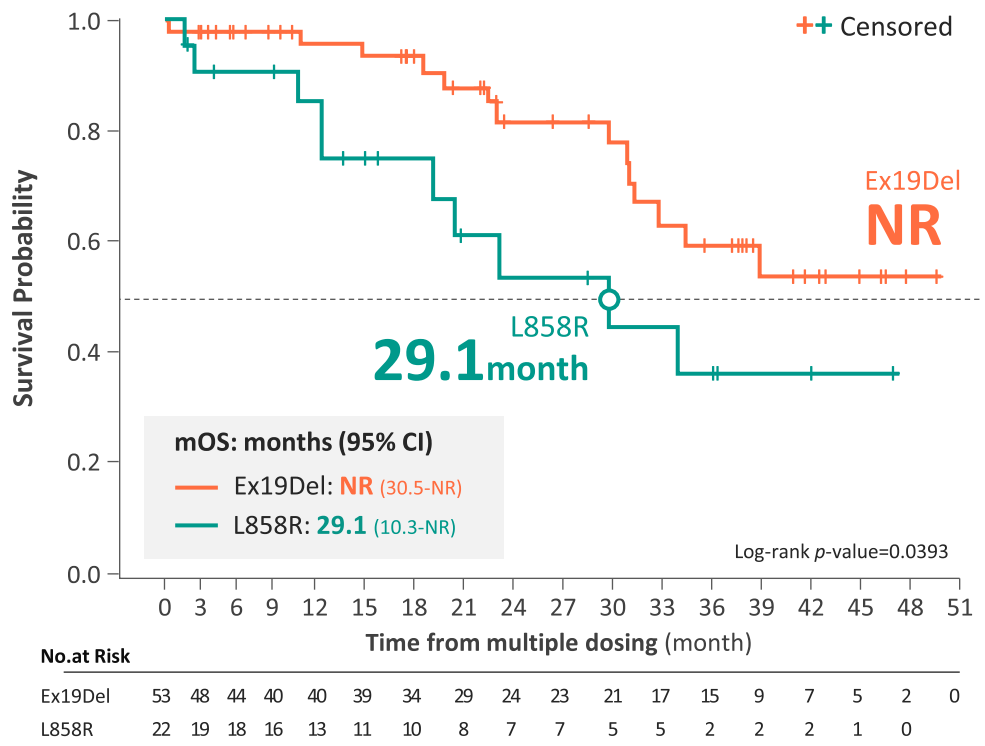
Overall survival is measured from the first multiple dose date (cycle 1 day 1) until death due to any cause or date of last known alive.
Median and 95% CI are calculated using Kaplan-Meier estimate.

1. Han et al. AOS Oral presentation, 2022

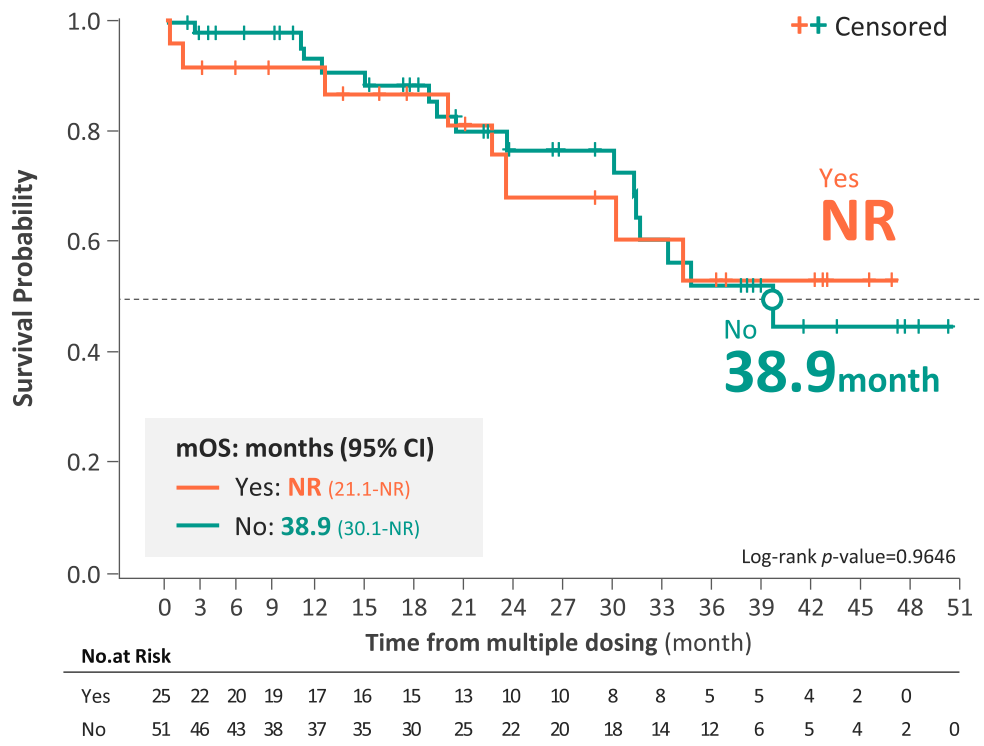
Data cut-off: 8 Apr 2022

OS: Subgroup – Baseline Characteristics

OS by EGFR Mutation Type



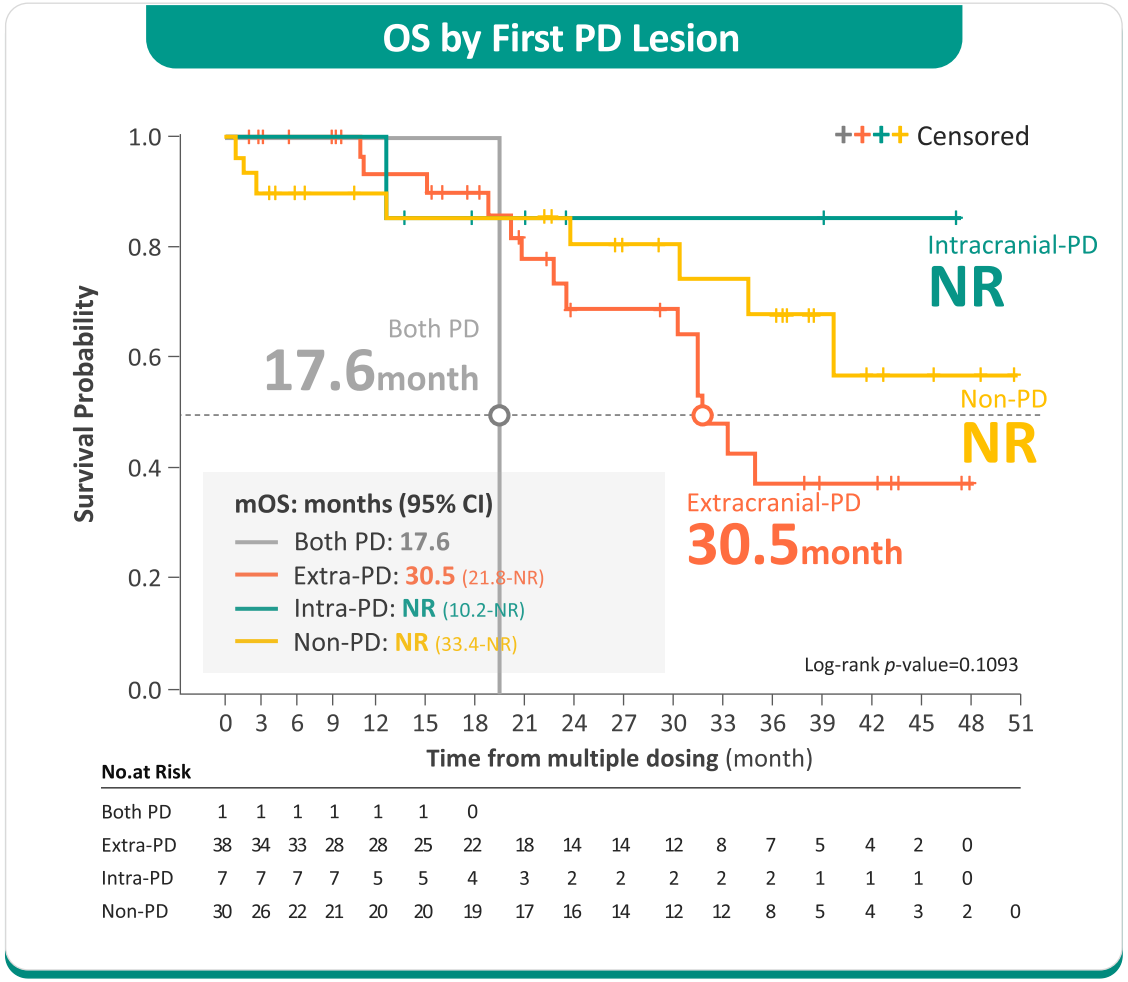
OS by Brain Metastases Status



DCO: 08Apr2022

1. Han et al. *AOS Oral presentation,* 2022

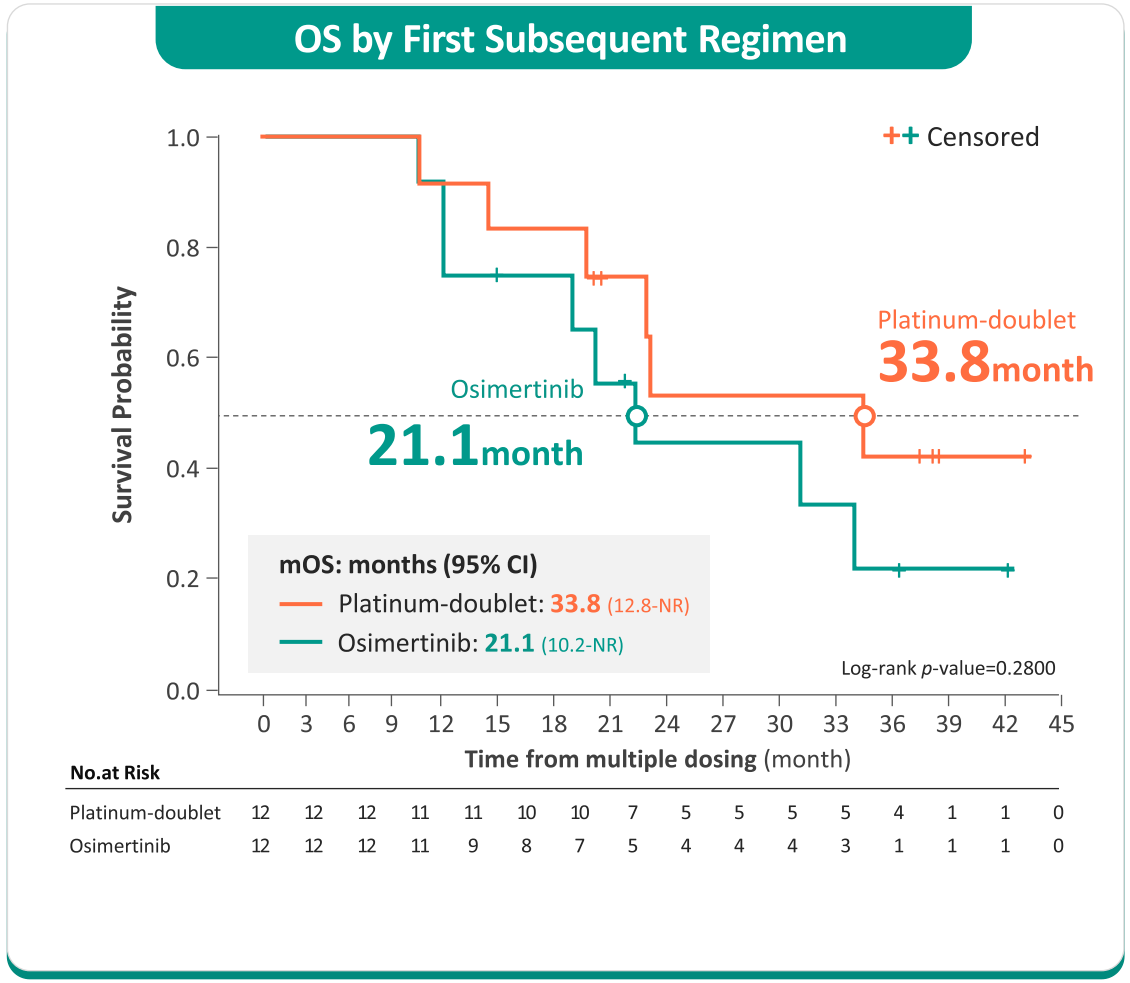
OS: Subgroup – First PD lesion



DCO: 08Apr2022

1. Han et al. *AOS Oral presentation,* 2022

OS: Subgroup – Post-treatment



DCO: 08Apr2022

First subsequent Treatment	N=31
OSIMERTINIB	12
Platinum-Doublet	12
ATEZOLIZUMAB W/BEVACIZUMAB AND CARBOPLATIN AND PACLITAXEL	3
INVESTIGATIONAL DRUG	2
PEMETREXED	1
GEMCITABINE W/VINORELBINE	1

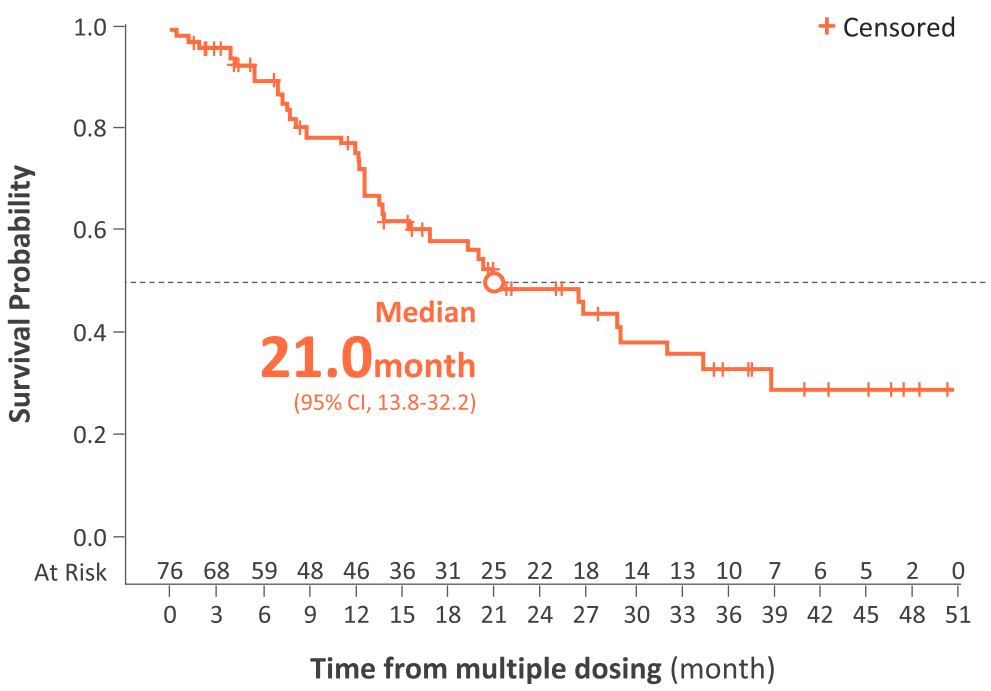
동의철회 29명

2nd subsequent Treatment	N=19
OSIMERTINIB	6
PEMETREXED	3
CARBOPLATIN W/ETOPOSIDE	1
ERLOTINIB W/GEMCITABIN AND VINORELBINE	1
CARBOPLATIN W/IRINOTECAN	1
ERLOTINIB	1
CISPLATIN W/GEMCITABINE	1
CARBOPLATIN W/GEMCITABINE	1
INVESTIGATIONAL DRUG	1
CISPLATIN W/PACLITAXEL	1
CISPLATIN W/PEMETREXED	1
DURVALUMAB W/PROTEIN KINASE INHIBITORS	1

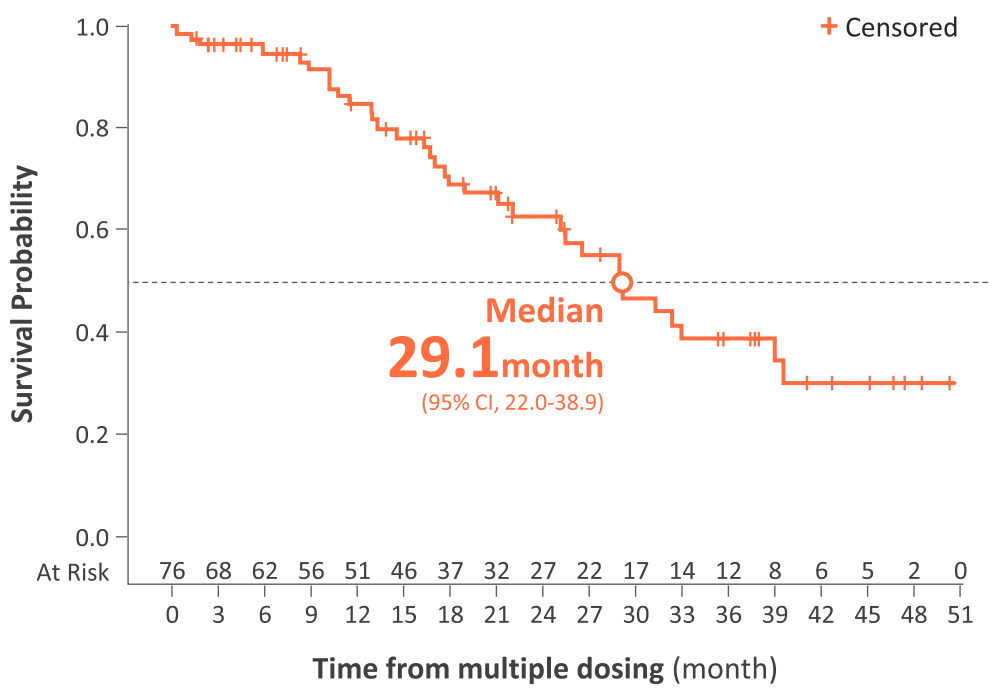
1. Han et al. *AOS Oral presentation,* 2022

Time to Subsequent Therapy or Death

Time to First Subsequent Therapy or Death



Time to Second Subsequent Therapy or Death



DCO: 08Apr2022

1. Han et al. *AOS Oral presentation,* 2022

Overall Treatment-Emergent Adverse Events

Patients with TEAEs, n (%)	240 mg (N=78)
TEAEs	76 (97)
Drug related TEAEs	69 (88)
Serious TEAEs	21 (27)
Drug related serious TEAEs	3 (4)
TEAEs with grade ≥ 3	28 (36)
Drug related TEAEs with grade ≥ 3	11 (14)
TEAEs leading to	
Death	3 (4)
Dose reduction	13 (17)
Drug interruption	17 (22)
Drug withdrawal	6 (8)

DCO: 08 Apr 2022

TEAEs, Treatment-Emergent Adverse Events.
TEAEs are defined as events with onset date on or after the first dose of study medication and prior to 28 day follow-up period (28+7 days after the last dose of study medication).
Adverse events were graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.
Drug related TEAEs are events with relationship certain, probable/likely, possible, unassessable/unclassifiable, or missing.
Overall median duration of therapy was 13.3 months (range 0.3-50.3).

1. Han et al. *AOS Oral presentation*, 2022

Drug-related TEAEs ≥ 10% of All Patients

Preferred Term	240 mg (N=78)
Rash	29 (37)
Paraesthesia	26 (33)
Pruritus	25 (32)
Muscle spasms	21 (27)
Diarrhoea	16 (21)
Paronychia	14 (18)
Decreased appetite	13 (17)
Headache	13 (17)
Fatigue	12 (15)
Nausea	12 (15)
Stomatitis	9 (12)
Aspartate aminotransferase increased	8 (10)
Myalgia	8 (10)
Electrocardiogram QT prolonged	3 (4)
Pneumonitis	1 (1)
Thrombocytopenia	1 (1)

TEAEs, Treatment-Emergent Adverse Events.
TEAEs are defined as events with onset date on or after the first dose of study medication and prior to 28 day follow-up period (28+7 days after the last dose of study medication).
Adverse events were graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.
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Overall median duration of therapy was 13.3 months (range 0.3-50.3).

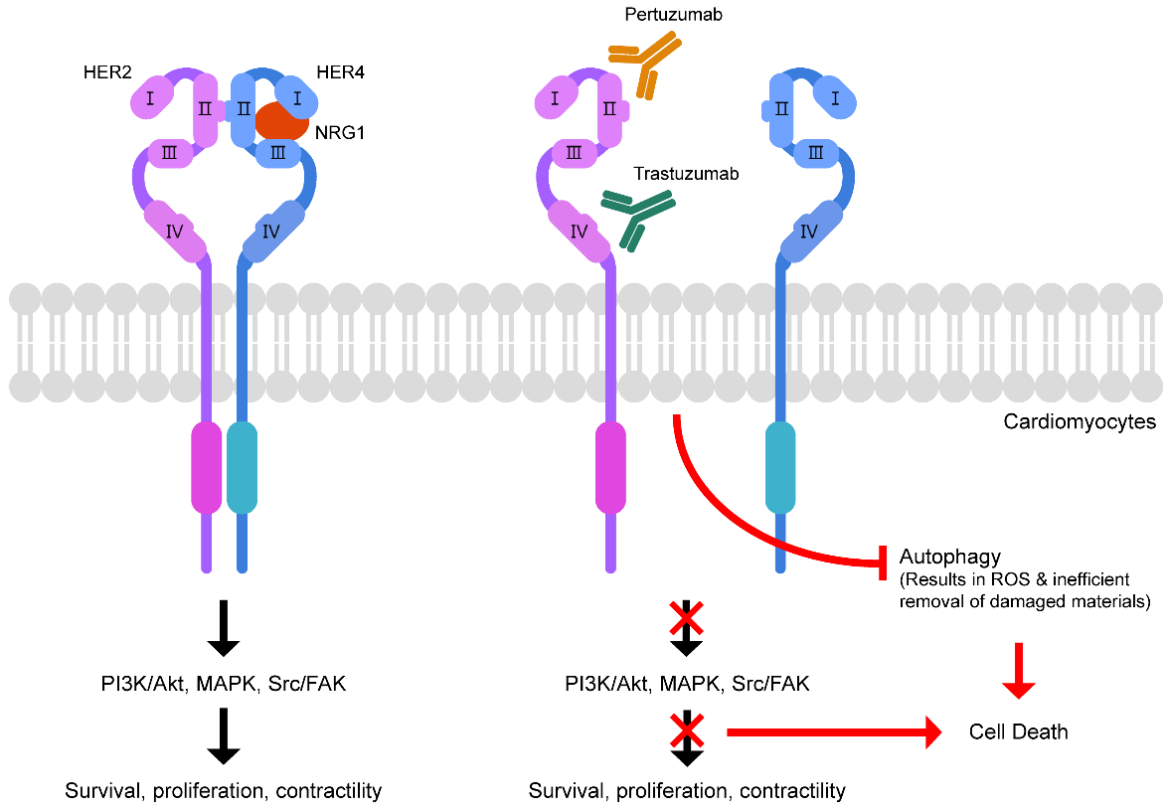
1. Han et al. *AOS Oral presentation*, 2022

DCO: 08 Apr 2022

Cardiac Toxicity of EGFR TKI

- Cardiotoxicity and adverse events such as QTc prolongation and decreased LVEF have been associated with use of various TKIs including nilotinib, lapatinib and osimertinib
- **The underlying mechanism of EGFR TKI-induced cardiotoxicity remains unclear**
- Given the known risk of cardiotoxicity with anti-HER2 agents such as trastuzumab, HER2 inhibition may be related to cardiotoxicity

Mechanism of HER-2 related Cardiotoxicity



Potential mechanisms by which trastuzumab (and pertuzumab) could mediate cardiotoxic effects.00

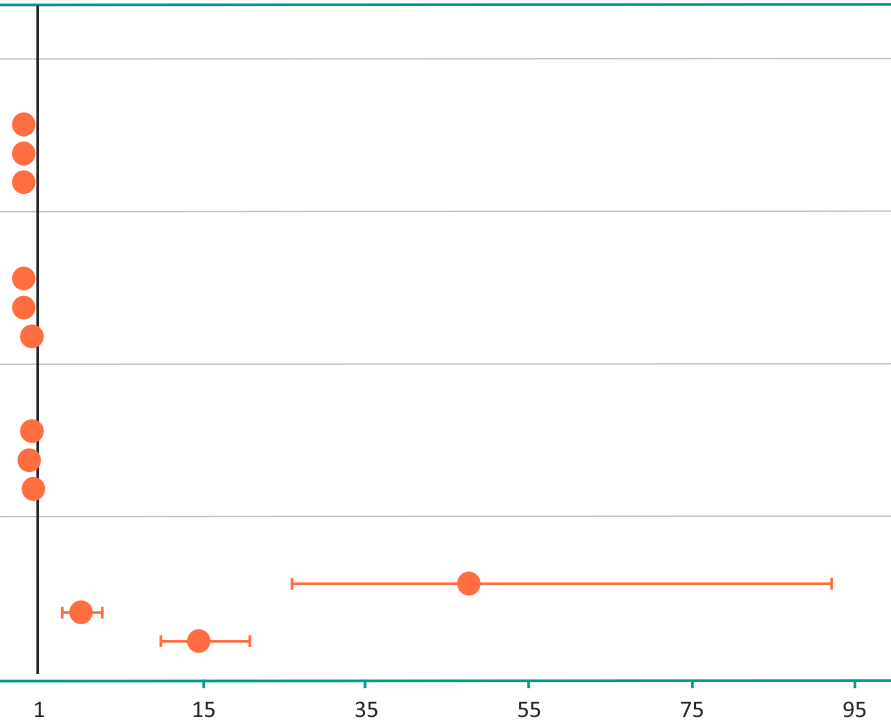
1. Anand et al. *JACC.* 2019; **2.** An et al. *Curr Cancer Drug Targets.* 2019;19(5):400-407; **3.** Jang et al. *JTO Clin Res Rep.* 2021.

Cardiovascular ADRs in EGFR TKI

Assessment of **odds of long QT syndrome** associated with inhibitors of EGFR

ROR (99% CI) of Long QT Syndrome from Each EGFR Inhibitor Relative to Comparator Group

	ADRs (%)	ROR (99% CI)	IC (IC025)
EGFR inhibitors	104 (0.17%)		
Afatinib	1 (0.01%)		
Relative to other EGFR inhibitors		0.06(0.004-0.78)	
Relative to NSCLC targeted therapies		0.03(0.002-0.39)	
Relative to full VigiBase database		0.09(0.007-1.24)	-2.89 (-6.69)
Erlotinib	15 (0.04%)		
Relative to other EGFR inhibitors		0.09(0.04-0.18)	
Relative to NSCLC targeted therapies		0.07(0.03-0.13)	
Relative to full VigiBase database		0.31(0.16-0.60)	-1.67 (-2.49)
Gefitinib	4 (0.05%)		
Relative to other EGFR inhibitors		0.28(0.08-1.04)	
Relative to NSCLC targeted therapies		0.14(0.04-0.50)	
Relative to full VigiBase database		0.43(0.12-1.56)	-1.12 (-2.86)
Osimertinib	84 (1.71%)		
Relative to other EGFR inhibitors		49.19(25.88-93.47)	
Relative to NSCLC targeted therapies		6.13(4.43-8.48)	
Relative to full VigiBase database		14.34(10.79-19.04)	3.71 (3.38)



Investigators extracted all cases of arrhythmia (including conduction disease, QT prolongation, supraventricular tachycardia, ventricular arrhythmias) and heart failure available between database inception in 11/14/1967 and 7/10/2020. WHO pharmacovigilance database VigiBase to compare odds of heart failure, conduction disease, QT prolongation, supraventricular tachycardia (SVT), and ventricular arrhythmias between inhibitors of EGFR (erlotinib, gefitinib, afatinib, osimertinib), BRAF (dabrafenib), MEK (trametinib), and ALK ± ROS1 (alectinib, brigatinib, ceritinib, crizotinib, lorlatinib).

ADR, adverse drug reaction; **CI,** confidence interval; **IC,** information component; **ROR,** reporting OR.

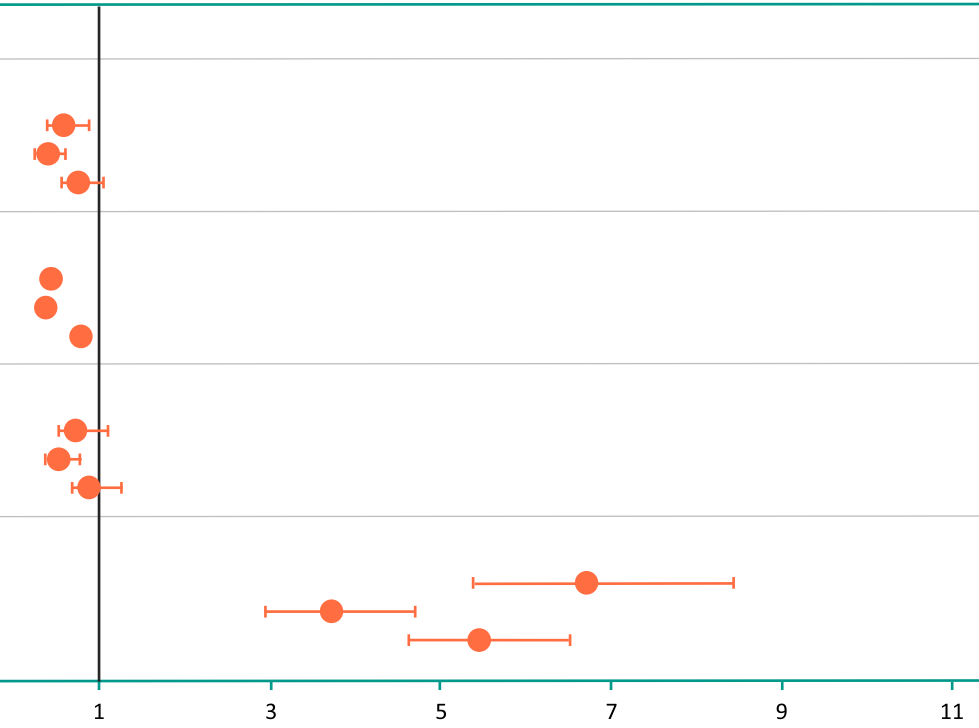
1. Sarah W,et al. *J Thorac Oncol* 2021 Aug 18;S1556-0864(21)02377-7

Cardiovascular ADRs in EGFR TKI

Assessment of **odds of Heart Failure** associated with inhibitors of EGFR

ROR (99% CI) of Heart Failure from Drug Relative to Comparator Group

	ADRs (%)	ROR (99% CI)	IC (IC025)
EGFR inhibitors	494 (0.80%)		
Afatinib	46 (0.53%)		
Relative to other EGFR inhibitors		0.62(0.41-0.92)	
Relative to NSCLC targeted therapies		0.43(0.29-0.63)	
Relative to full VigiBase database		0.75(0.51-1.10)	-0.41 (-0.85)
Erlotinib	221 (0.55%)		
Relative to other EGFR inhibitors		0.43(0.34-0.54)	
Relative to NSCLC targeted therapies		0.35(0.29-0.42)	
Relative to full VigiBase database		0.79(0.66-0.93)	-0.35 (-0.54)
Gefitinib	48 (0.63%)		
Relative to other EGFR inhibitors		0.75(0.51-1.12)	
Relative to NSCLC targeted therapies		0.52(0.35-0.76)	
Relative to full VigiBase database		0.90(0.62-1.30)	-0.16 (-0.59)
Osimertinib	179 (3.36%)		
Relative to other EGFR inhibitors		6.75(5.29-8.62)	
Relative to NSCLC targeted therapies		3.64(2.94-4.50)	
Relative to full VigiBase database		5.37(4.42-6.54)	2.36 (2.14)



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ADR, adverse drug reaction; **CI,** confidence interval; **IC,** information component; **ROR,** reporting OR.

1. Sarah W,et al. *J Thorac Oncol* 2021 Aug 18;S1556-0864(21)02377-7

Cardiac Safety of Lazertinib

No clinically relevant effect on QT interval or LVEF

ORIGINAL ARTICLE

IASLC

Cardiac Safety Assessment of Lazertinib: Findings From Patients With *EGFR* Mutation-Positive Advanced NSCLC and Preclinical Studies

Check for updates

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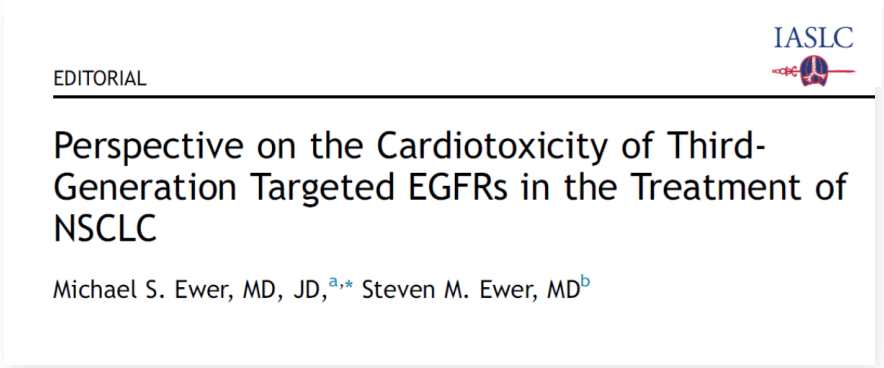
Available online 8 September 2021



EDITORIAL

IASLC

Perspective on the Cardiotoxicity of Third-Generation Targeted EGFRs in the Treatment of NSCLC

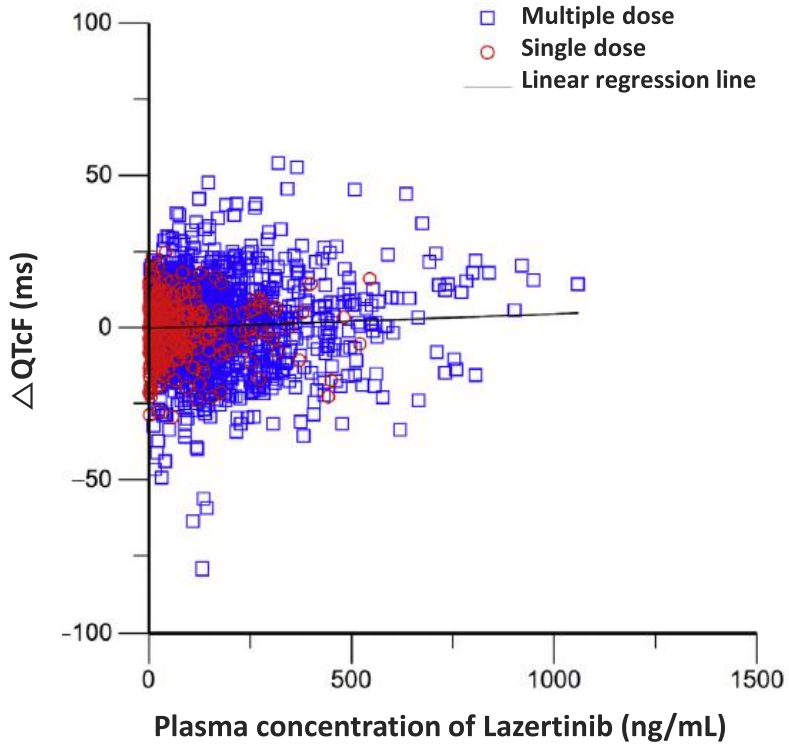
Michael S. Ewer, MD, JD,[a,*] Steven M. Ewer, MD[b]

1. Jang et al. JTO Clin Res Rep. 2021; 2. Ewer MS et al, JTO Clin Res Rep.2021;2(10):100233.

Low Concern for QT Prolongation

- Certain TKIs (e.g., lapatinib, imatinib, osimertinib) inhibit hERG potassium channels and cause a delay in cardiac repolarization, thus leading to QTc prolongation
- **Lazertinib had an IC_{50} of 5.3 µM in the hERG** cellular patch-clamp assay, whereas an earlier study of osimertinib reported an IC_{50} of 0.57 µM in a similar assay
- The IC_{50} value of lazertinib was **630-fold higher than the $C_{max,ss}$** at the therapeutic dose of 240 mg
- The ΔQTcF from baseline at the $C_{max,ss}$ for therapeutic dose was 2.2 ms with an estimated upper bound (two-sided 90% CI) of 3.6 ms, which was within the **category of low concern (upper bound ≤5 ms)**

Plot of QTcF values against time-matched concentration of Lazertinib



1. Jang et al. *JTO Clin Res Rep*. 2021; **2.** Jin et al. *Front Pharmacol.* 2018 May 31;9:577.

No Significant QTcF Interval Changes Observed

Lazertinib has **no clinically relevant effect on QTc interval** in any patients and any dose level.

ECG test (QTcF)

	240 mg	Overall
Patients number	**78**	**181**
Maximum Increase from baseline (ms), n(%)		
≤30	73 (93.6)	162 (89.5)
>30 to ≤60	5 (6.4)	17 (9.4)
>60	0	0 (0)
Maximum post baseline value (ms), n(%)		
≤450	70 (89.7)	157 (86.7)
>450 to ≤480	8 (10.3)	22 (12.2)
>480 to ≤500	0	2 (1.1)
>500	0	0

Percentages were calculated using the number of patients in the safety analysis population for each treatment as the denominator and the number of patients with each event as the numerator.
ECG, Electrocardiogram; **QTc,** QT interval corrected for heart rate.
1. Jang et al. *JTO Clin Res Rep.* 2021.

No Significant LVEF Changes Observed

- **No clinically meaningful decrease of LVEF** was observed
- Cardiac failure-associated AE occurred in one patient (Grade 2 decreased LVEF) and **resolved without any dose modifications**

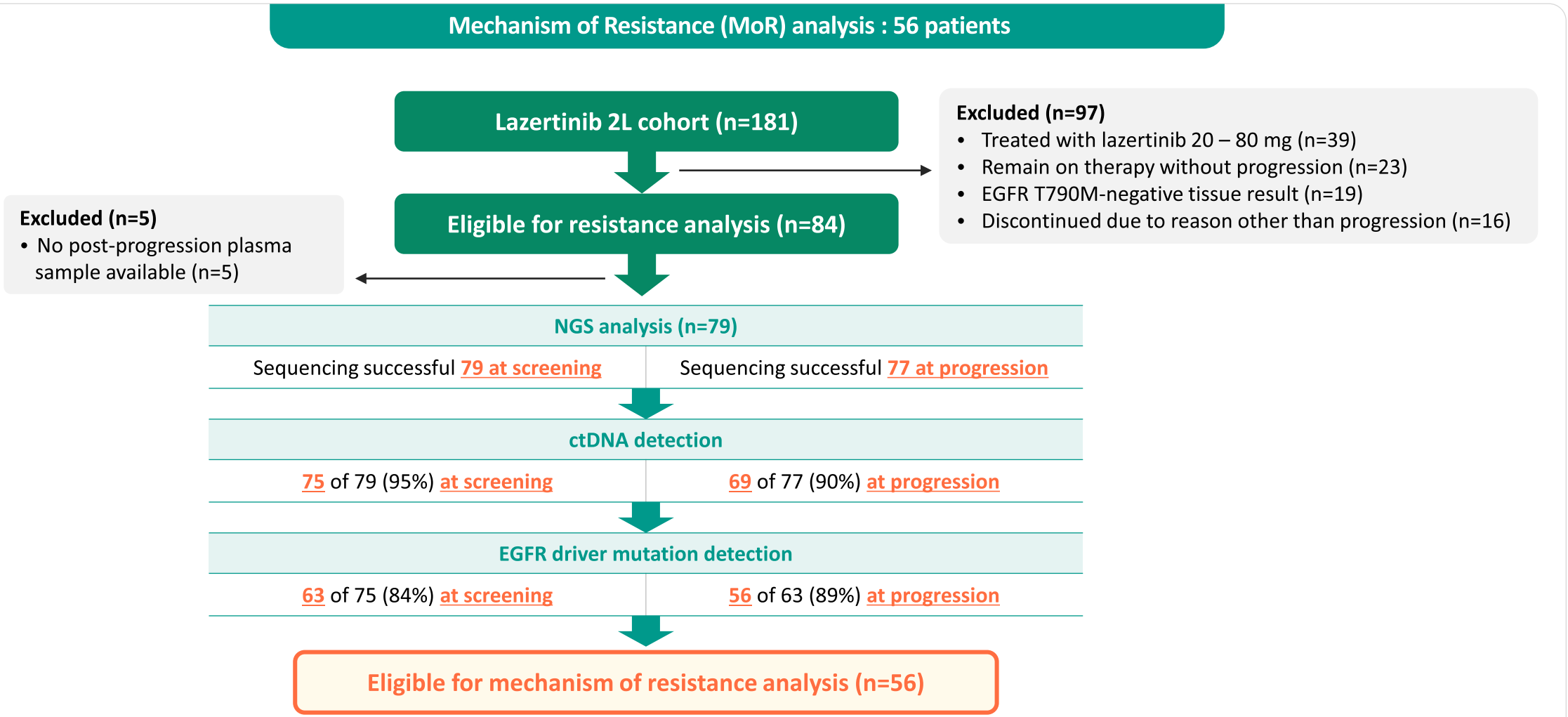
Echocardiography

	240 mg	Overall
Patients number	**78**	**181**
Minimum post baseline value (%), n(%)[a]		
≥50	73 (93.6)	171 (94.5)
≥45 to <50	0	0
<45	0	1 (0.6)
Maximum decrease in LVEF from baseline value (% point), n(%)[a,b]		
<10	61 (78.2)	146 (80.7)
≥10 to <15	9 (11.5)	20 (11.0)
≥15	3 (3.9)	6 (3.3)
LVEF decreases of ≥10%p and absolute value of <50%	**0**	**0**

Note: Percentages were calculated using the number of patients in the safety analysis population for each treatment as the denominator and the number of patients with each event as the numerator.
Percentages were based on the number of patients in the respective dose cohorts. The maximum decrease in LVEF value from baseline was calculated from the baseline LVEF value – the minimum postbaseline LVEF value.
[a] Data were unavailable for nine patients without postbaseline LVEF value.
[b] None of the patients had a decrease in LVEF from baseline greater than 20 percentage points.
AE, adverse event; **LVEF,** left ventricular ejection fraction
1. Jang et al. *JTO Clin Res Rep.* 2021.

Resistance Mechanism

Resistance Mechanisms to Lazertinib



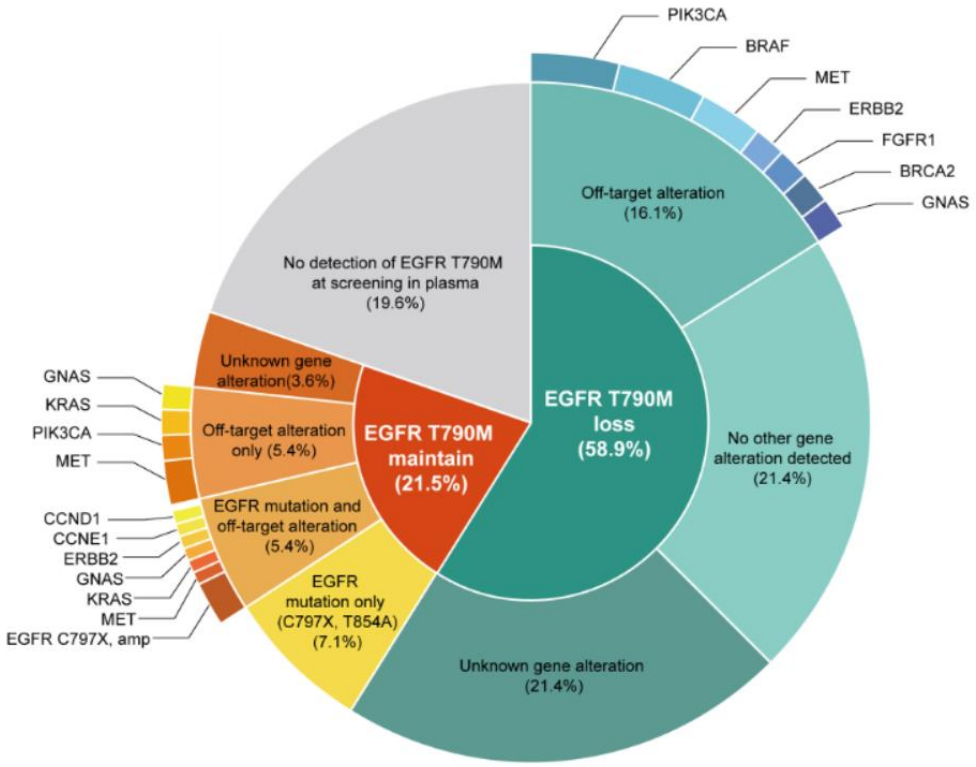
MoR, mechanism of resistance; **NGS,** next generation sequencing; **ctDNA,** circulating tumor DNA

1. Cho et al. *KALC.* 2021, LASER201 Clinical study report (data cut-off 08Jan2021)

Resistance Mechanisms to Lazertinib

- The distribution of acquired resistance mechanisms in 2nd-line treatment was similar with prior studies of 3G EGFR TKI
- The major acquired resistance mechanism was loss of EGFR T790M (58.9%)

Resistance mechanisms identified in plasma after resistance to second-line Lazertinib



Summary (Total n=56)	
EGFR T790M loss	58.9%
Acquired EGFR mutations	16.1%
MET amplification	8.9%
MAPK-PI3K/PKA-cAMP gene alterations	17.9%
PIK3CA alteration	8.9%
Cell cycle gene alterations	8.9%
DNA repair/chromatin	5.4%
HER2 amplification	3.6%

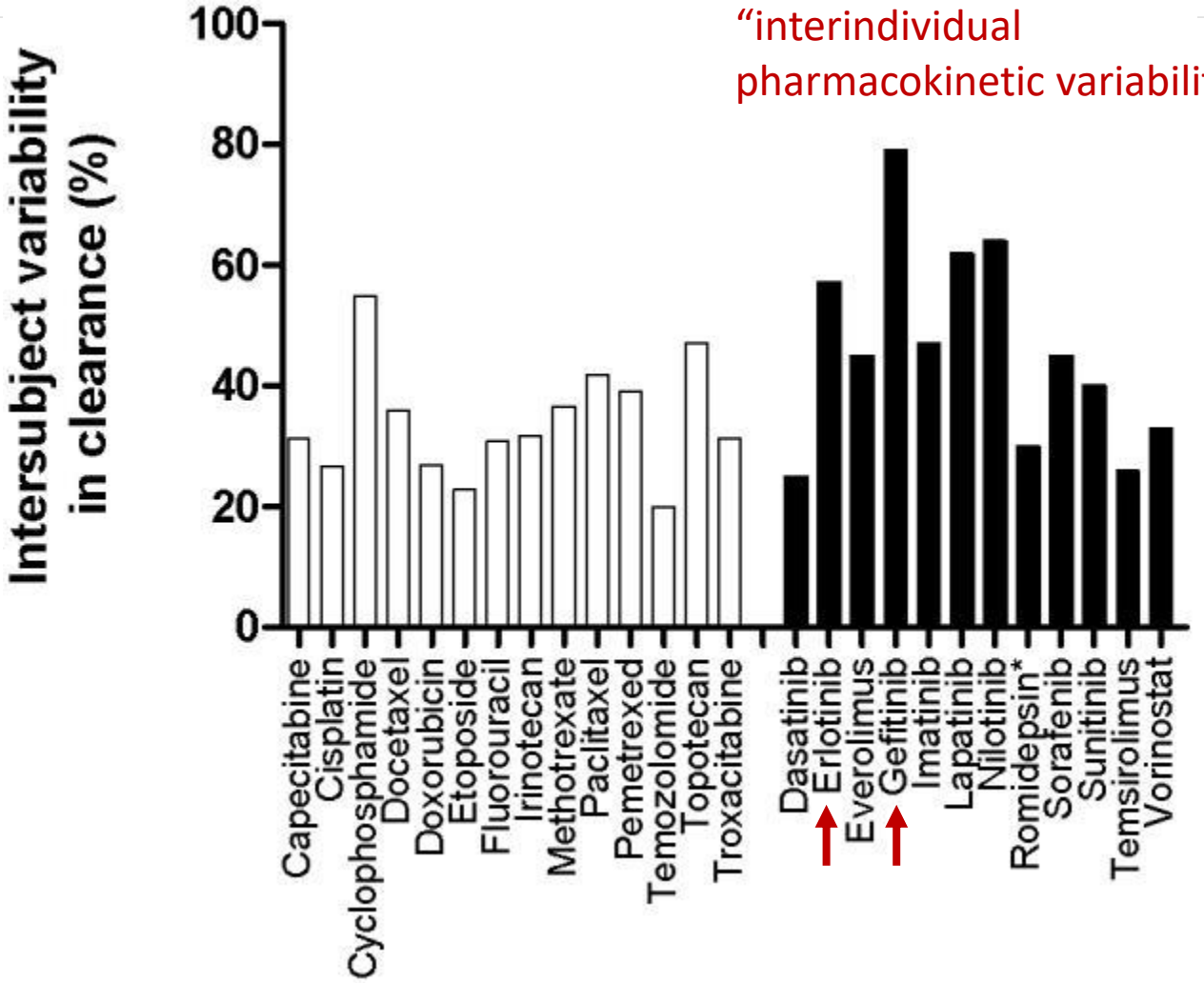
- In some cases, different gene alterations co-existed in the same patient.
- Unknown gene alteration: gene alterations of unknown functional/clinical significance; No other gene alteration detected: no gene alterations were detected in the gene list of Guardant360.
- Acquired EGFR mutations: 2 of 9 patients (3.6% in total) had no detection of EGFR T790M at screening in plasma.

1. Cho et al. *KALC*. 2021, LASER201 Clinical study report (data cut-off 08Jan2021)

렉라자 정 80mg
(레이저티닙메실산염일수화물)

유한양행

Dose Tailored Strategy in targeted therapy



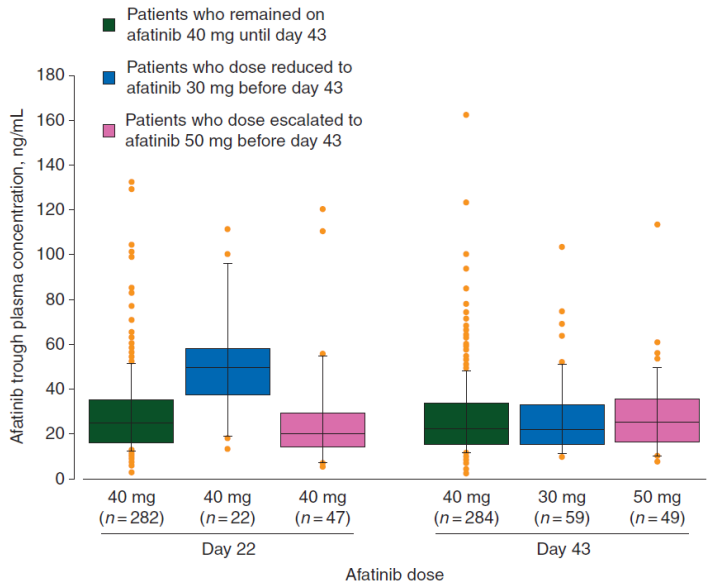
"interindividual pharmacokinetic variability"

Sparreboom A, Verweij J. Advances in cancer therapeutics. Clin Pharmacol Ther. 2009 Feb;85(2):113-7. doi: 10.1038/clpt.2008.259. PMID: 19151631; PMCID: PMC2629589.

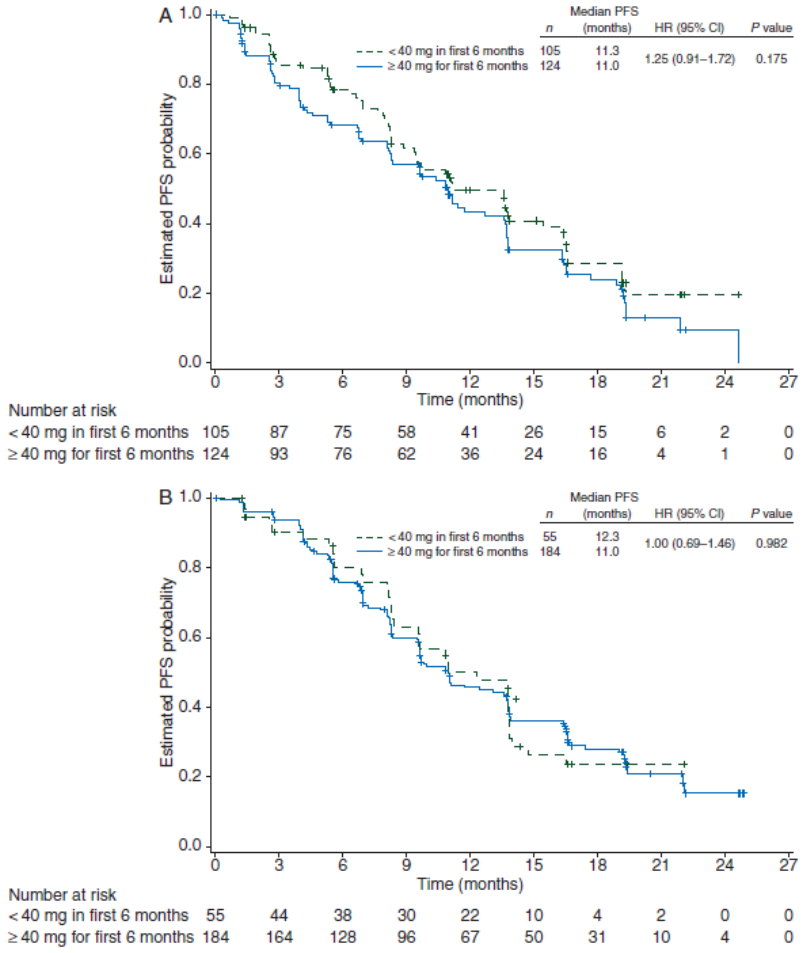
Afatinib Dose Modification in RCT

- Afatinib trough plasma concentrations with the 40 mg dose were higher at day 22. Plasma concentrations were similar between groups on day 43
- **Following dose reduction, treatment-related AE incidence decreased** (105; 86.1%), with fewer patients experiencing grade ≥3 treatment-related AEs (25; 20.5%)
- The median **PFS was similar** in patients who dose reduced during the first 6 months of afatinib treatment and those who did not: **11.3 versus 11.0 months** [HR 1.25 (95% CI 0.91–1.72), P = 0.175]

<Plasma Concentration>



<Efficacy Results>

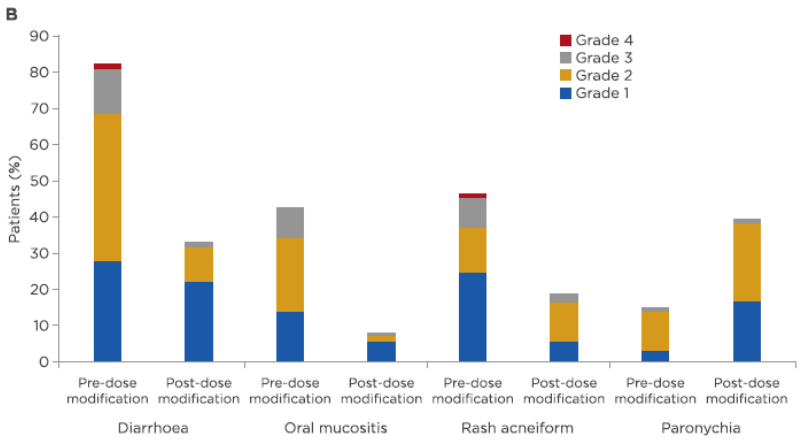


Yang et al. *Ann Oncol.* 2016 Nov;27(11):2103-2110.

Afatinib Dose Modification in RWE

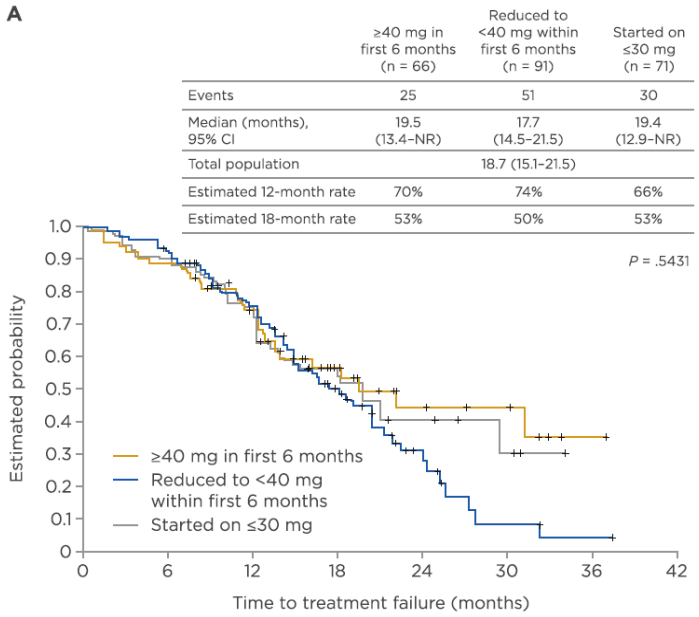
- A total of 71 (31.1%) received a modified starting dose of ≤30 mg
- 228 patients were enrolled from 13 countries. Overall, consistent with the LUX-Lung 3, 6 and 7 trials, **dose reduction lowered the intensity and frequency of AEs** (overall ADR incidence of 98.6% and 71.2% before and after dose reduction)
- Consistent with results from the LUX-Lung clinical studies, **dose adjustment of afatinib did not appear to compromise its clinical activity**

<Safety by Dose Modification>



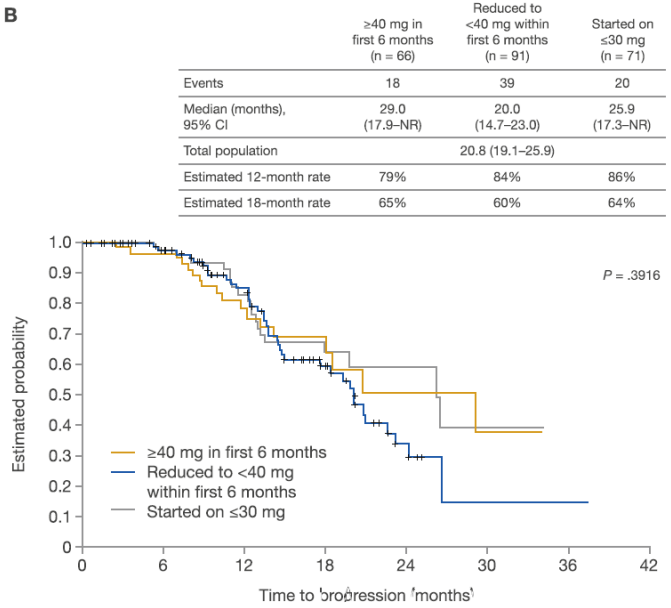
* Common ADRs (> 10% incidence) pre- and post-dose reduction in patients who had a dose reduction within thefirst 6 months after starting on afatinib 40 mg/day (N = 91)

<Time to Treatment Failure>



	≥40 mg in first 6 months (n = 66)	Reduced to <40 mg within first 6 months (n = 91)	Started on ≤30 mg (n = 71)
Events	25	51	30
Median (months), 95% CI	19.5 (13.4–NR)	17.7 (14.5–21.5)	19.4 (12.9–NR)
Total population		18.7 (15.1–21.5)	
Estimated 12-month rate	70%	74%	66%
Estimated 18-month rate	53%	50%	53%

<PFS>

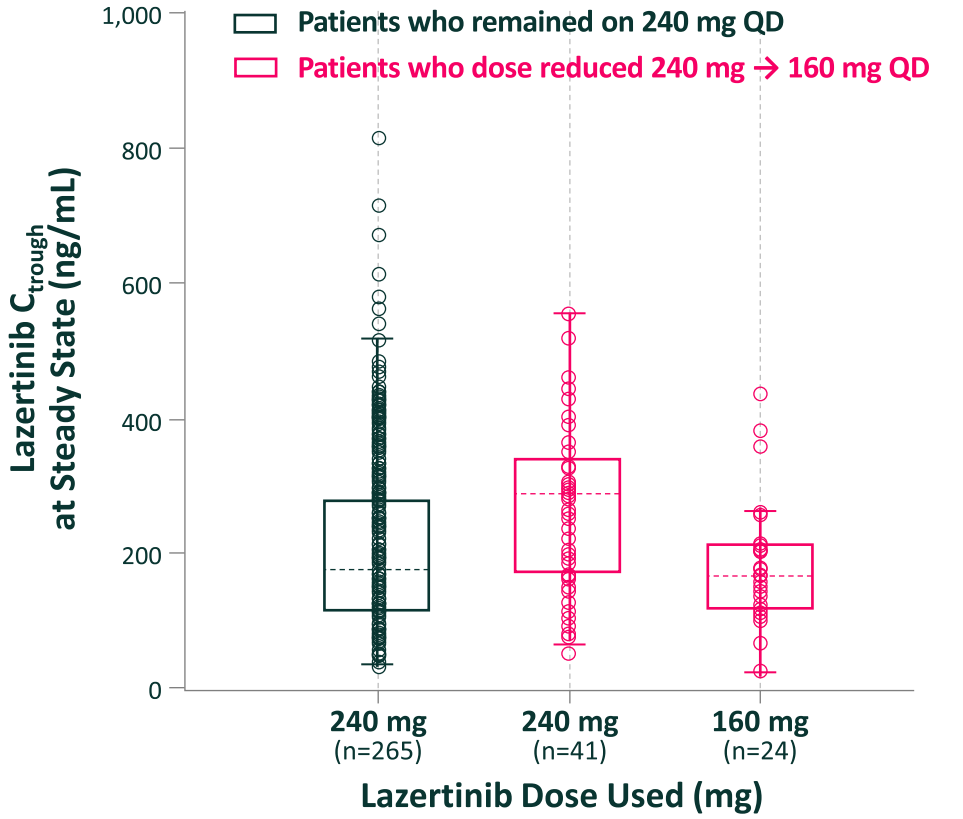


	≥40 mg in first 6 months (n = 66)	Reduced to <40 mg within first 6 months (n = 91)	Started on ≤30 mg (n = 71)
Events	18	39	20
Median (months), 95% CI	29.0 (17.9–NR)	20.0 (14.7–23.0)	25.9 (17.3–NR)
Total population		20.8 (19.1–25.9)	
Estimated 12-month rate	79%	84%	86%
Estimated 18-month rate	65%	60%	64%

Halmos et al. *Lung Cancer.* 2019 Jan;127:103-111.

Dose reduction: Integrated Analysis from data of LASER301 and LASER201

- Comparison of Lazertinib trough concentration at steady state in patients remaining on 240 mg, dose reducing to 160 mg in integrated analysis for LASER301 and LASER201



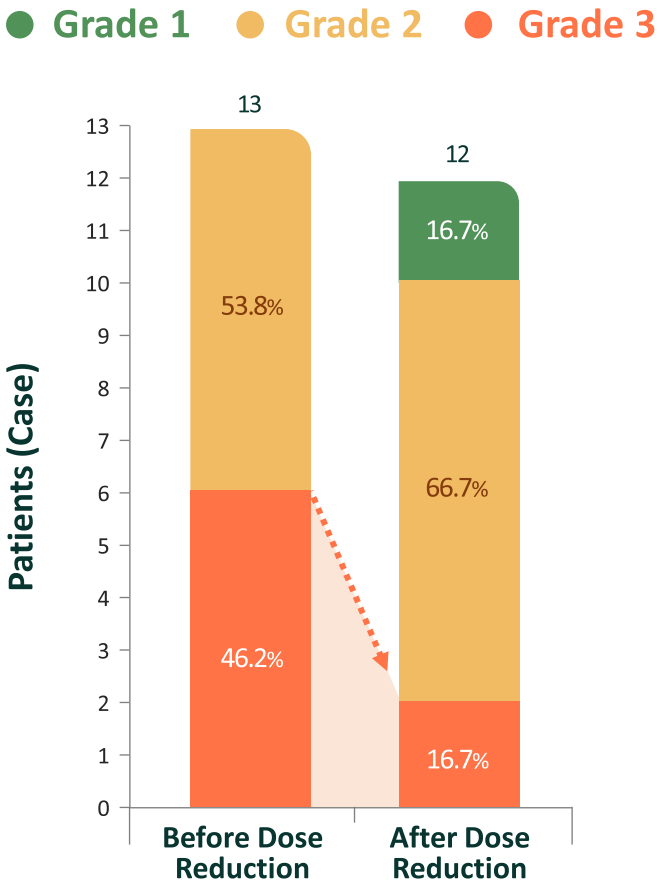
Population	Dose	N	Mean	SD	Min	Median	Max
Patients remaining on 240 mg	240 mg	265	209.9	132.1	39.0	**177.9**	813.0
Patients dose reducing to 160 mg (before)	240 mg	41	276.1	119.7	69.5	**290.6**	556.0
Patients dose reducing to 160 mg (after)	160 mg	24	188.4	97.1	27.6	**168.5**	436.0

(Unit: ng/mL)

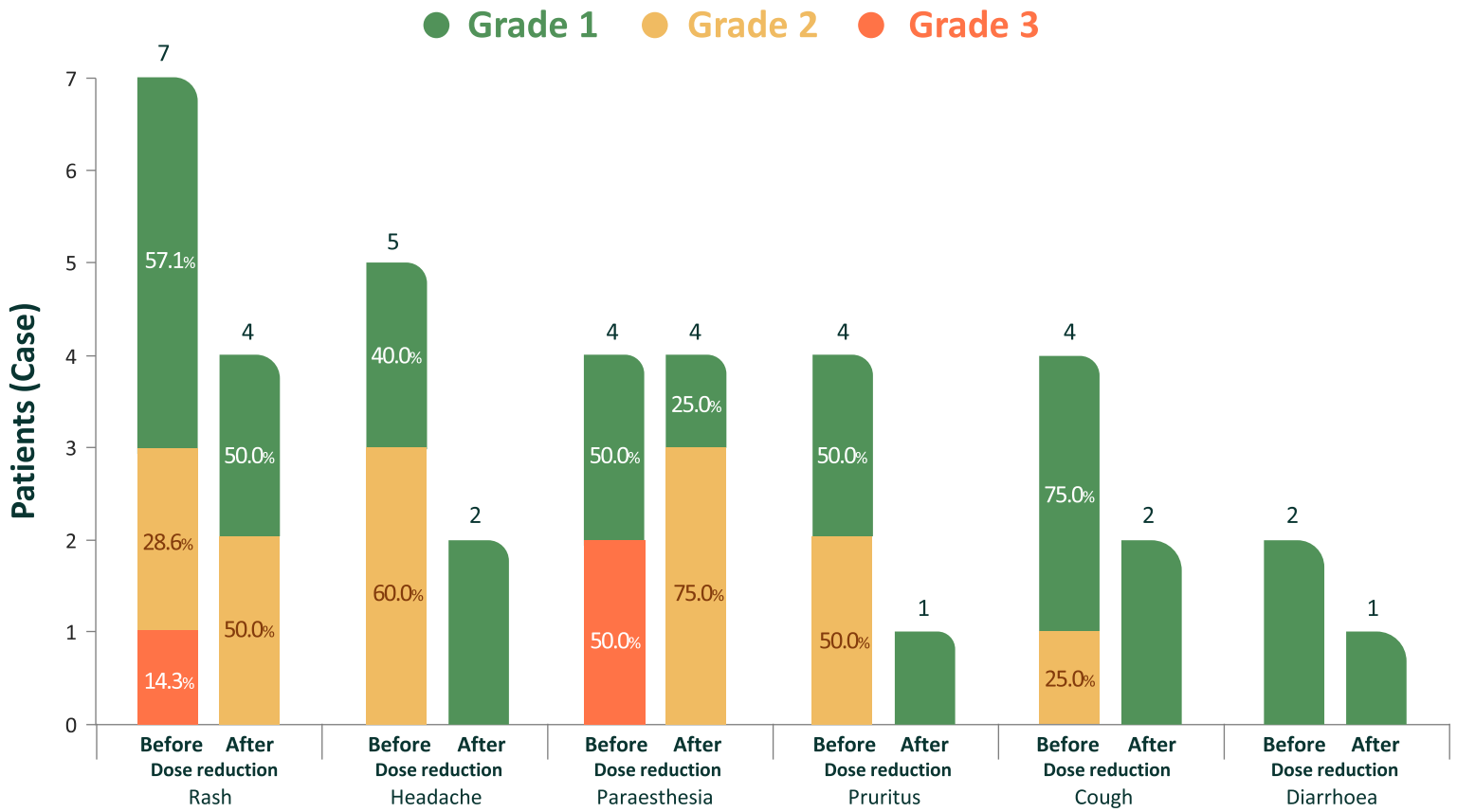
Ref_Data on File, Yuhan

Adverse Events with Dose Reduction in LASER201

Total AE (Patients No., %)



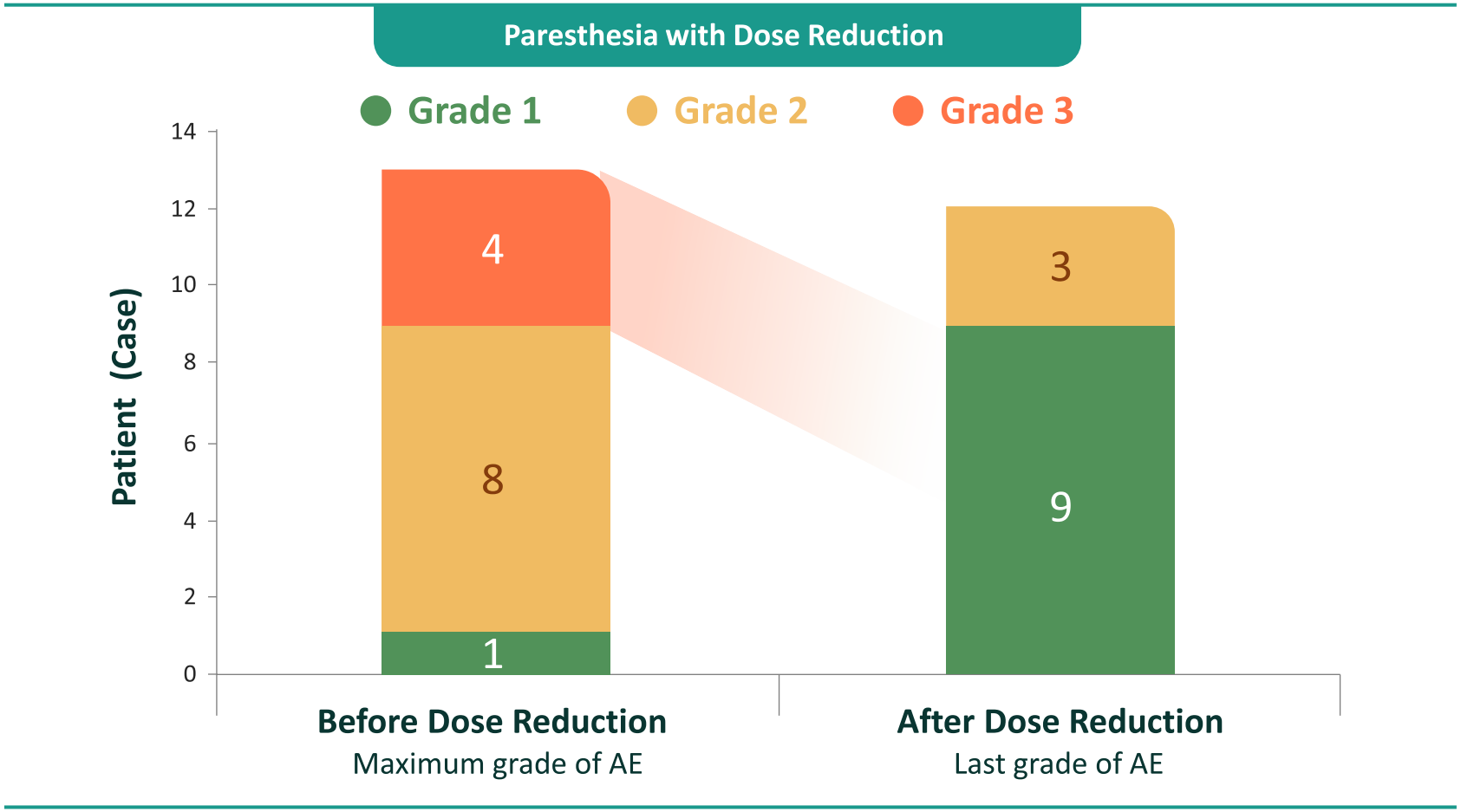
Most common treatment-related AEs before /After Lazertinib dose reduction in patients



Ref_Data on File, Yuhan

Paresthesia with Dose Reduction in LASER301

- 1 patient recovered after dose reduction
- 62% patients (8/13) downgraded after dose reduction

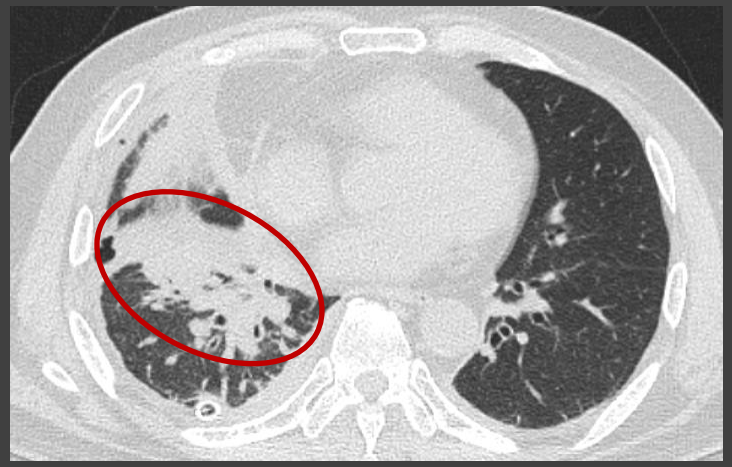


Ref_Data on File, Yuhan

M/65, 42pyrs, ex-smoker

Lung cancer (adenocarcinoma), cT1bN0M1a, stage IV, EGFR E19del
DM, HTN, CKD (eGFR 53)

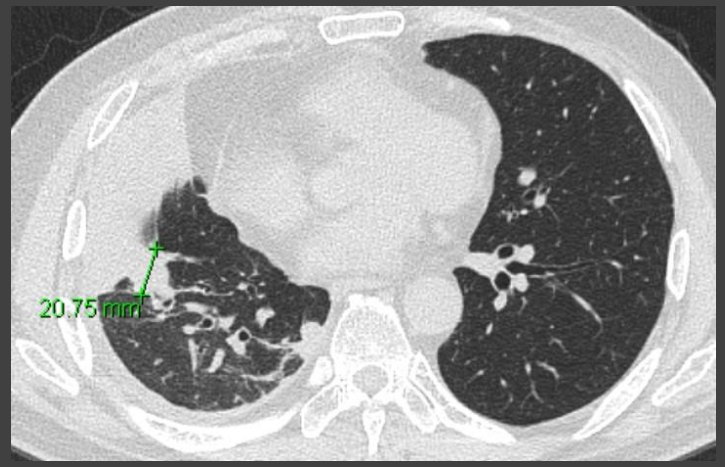
1L gefinitib (2020.06-), PD at 28 months



2022.10

Plasma E19del/T790M -/-

Effusion/tumor tissue EGFR
: E19del/T790M +/+
2L Lazertinib 240mg (2022.10-)

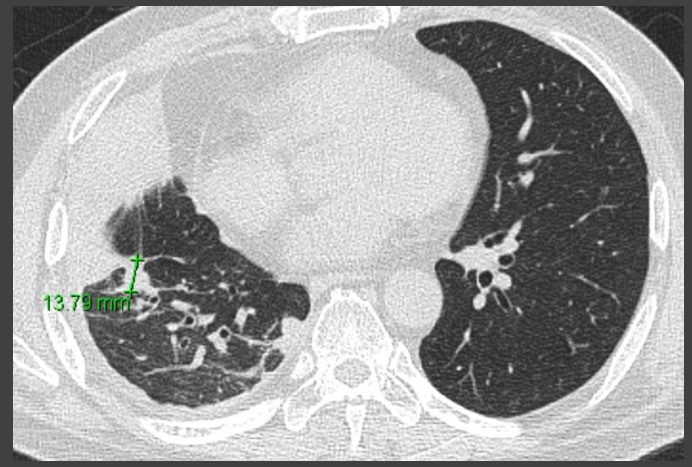


2023.01

On 2L Lazertinib 240mg 3mo

Numbness G2,
muscle cramping G2

Dose reduction to 160mg



2023.03

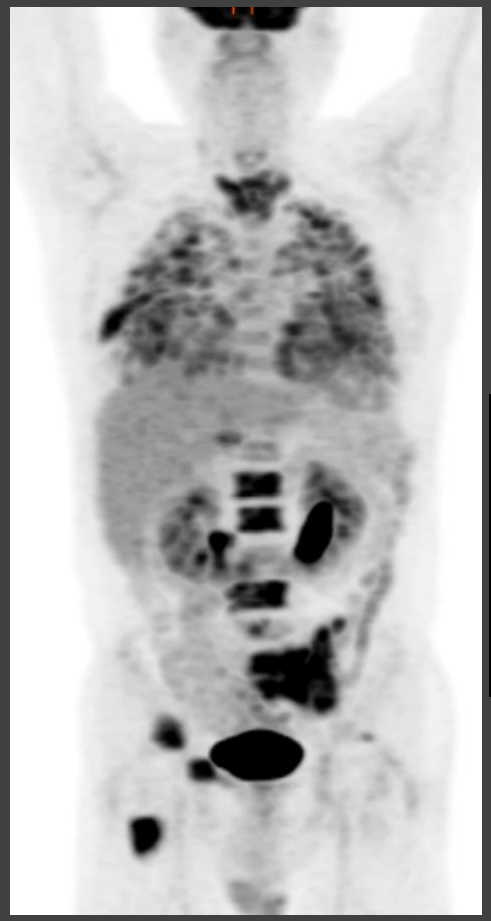
On 2L Lazertinib 160mg

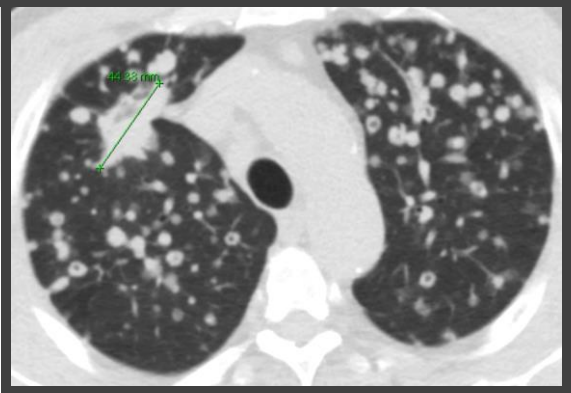
Numbness G1
muscle cramping (-)

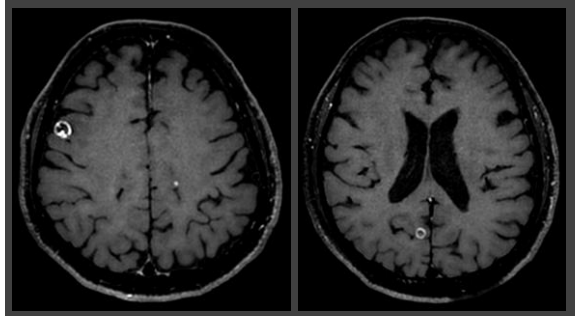
M/69, 15pyrs, ex-smoker

Lung cancer (adenocarcinoma), cT4N2/3M1c, stage IV, EGFR E19del
Lung to lung, bone, brain metastasis

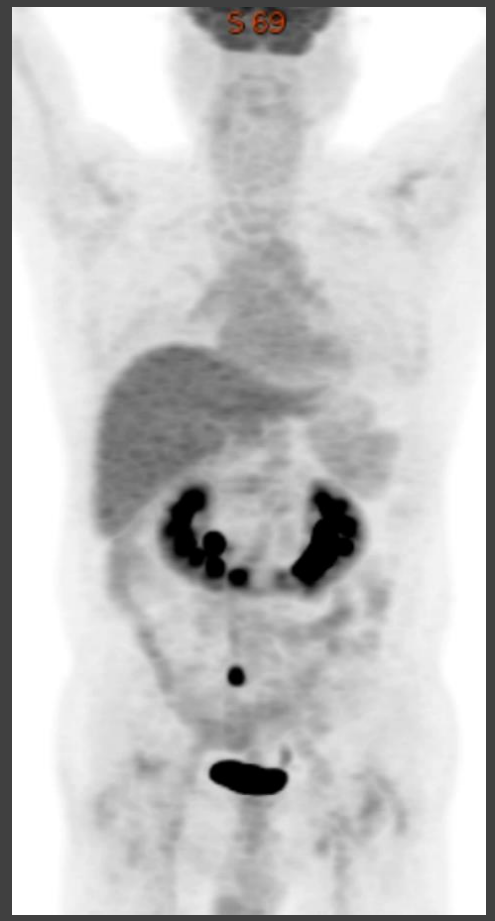
1L afatinib 40mg (2020.08-), Radiation on brain and bones

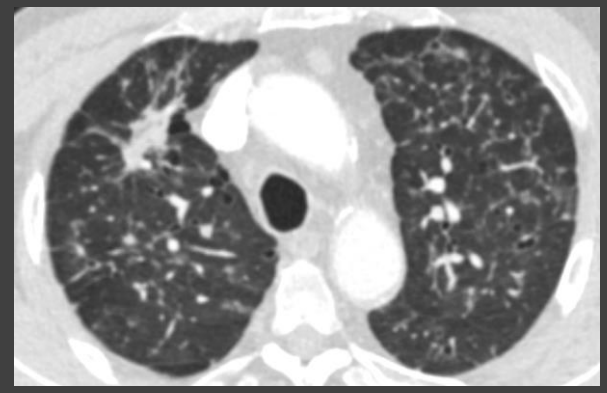


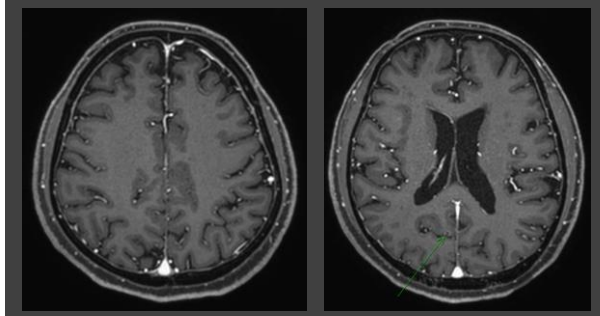




At diagnosis





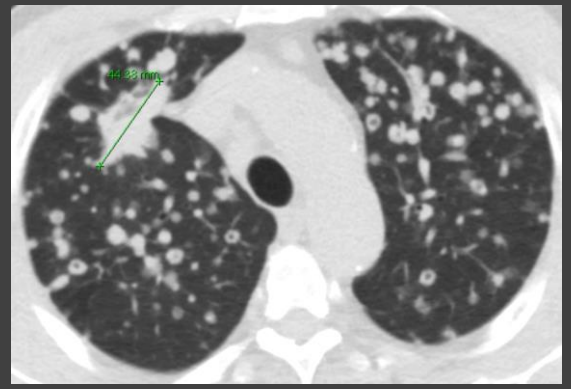


Afatinib 3mo

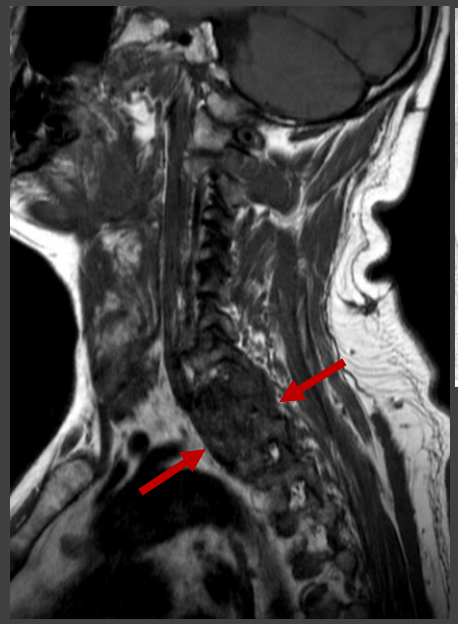
M/69, 15pyrs, ex-smoker

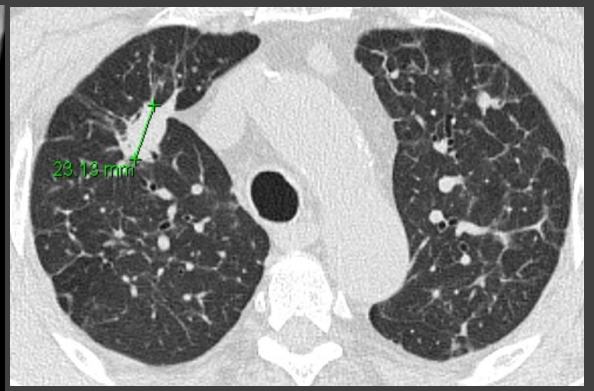
Lung cancer (adenocarcinoma), cT4N2/3M1c, stage IV, EGFR E19del
Lung to lung, bone, brain metastasis

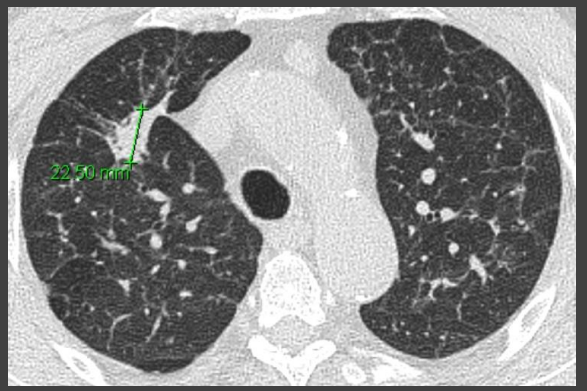
1L afatinib 40mg (2020.08-), PD at 18 months



2020.08







2023.02
stable disease

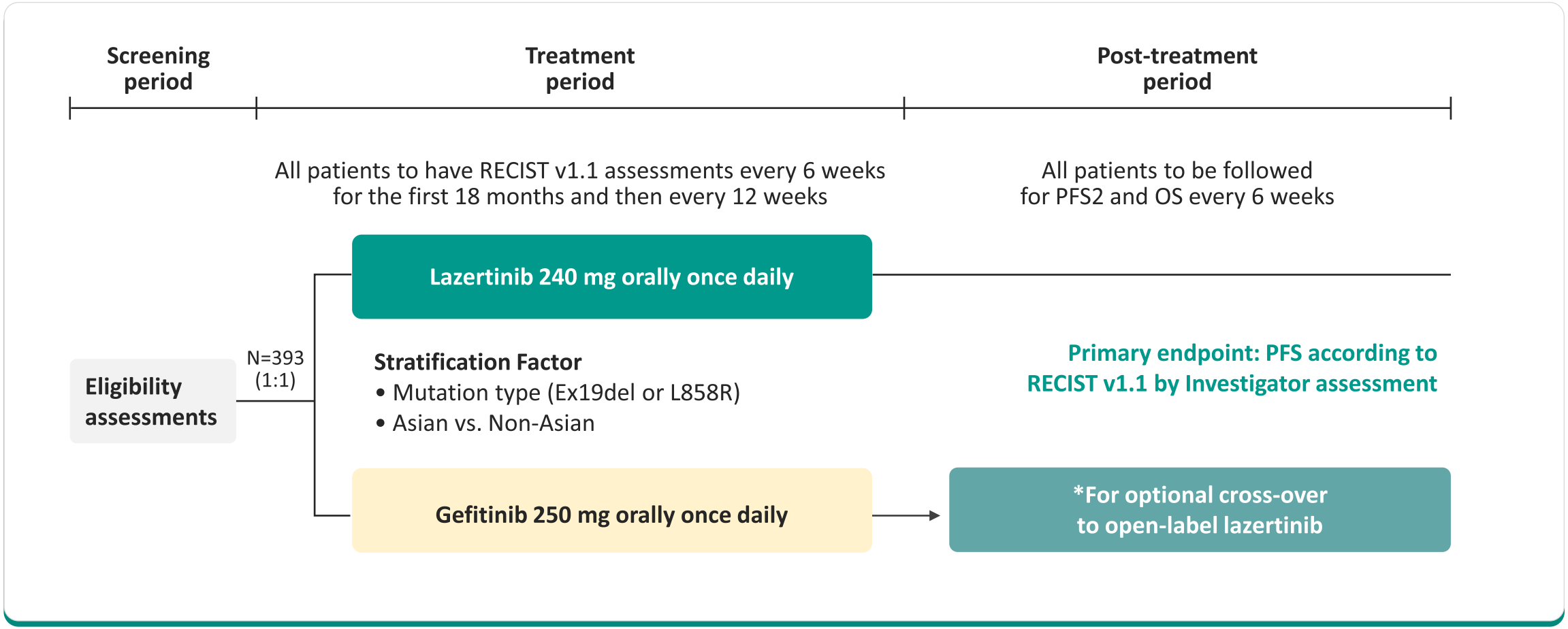
2022.02, T1 spine metastasis

Plasma EGFR E19del/T790M +/+

Lazertinib 240mg (2022.02-)

	2020.08	1L afatinib 40mg
	2022.02	2L lazertinib 240mg
1mo	2022.03	paronychia G1 → 없어짐, “편안하다”
2mo	2022.04	손, 발에 numbness G1
5mo	2022.07	손은 호전, 발의 numbness G1 지속, duloxetine (Cymbalta) 60mg 시작
8mo	2022.10	duloxetine 투여 후 무력감, 변비로 자의 중단
10mo	2022.12	날이 추워지니 발이 더 저리다, lazertinib 감량은 refuse, duloxetine 60mg 재투여
11mo	2023.01	저림은 비슷, 호전도 악화도 없다, 변비 +
13mo	2023.03	저림은 비슷, 손은 괜찮고 발바닥에 이물감이 든다, 넘어질 우려로 lazertinib 감량 권유 → 뇌전이 악화 걱정으로 refuse

Lazertinib Phase 3 (LASER301): Design(1ST Line)(NCT04248829)



* Lazertinib does not have 1st line indication on advanced EGFR mutant NSCLC

*If disease progression assessed by the Investigator according to RECIST v1.1 is confirmed by blinded independent central review(BICR), and T790M mutation positive, it will be given the opportunity of open-label lazertinib treatment to patients who were randomized to the gefitinib.

1. Clinicaltrial gov. NCT04248829

Conclusions

- **Lazertinib 240 mg showed the promising antitumor activities or efficacy for the T790M+ patients.**
  - **The confirmed ORR, median PFS and median DOR were 55%, 11.1 months and 17.7 months**, respectively.
  - **The confirmed intracranial ORR and iPFS were 86% and 26.0 months**, respectively.
  - With a median follow-up duration of 27.7 months, **median OS was 38.9 months.**
    No difference in OS was seen between patients with and without brain metastases.
- **Lazertinib showed a tolerable safety profile.**
  - No DLTs were observed up to Lazertinib 320 mg.
  - The drug-related TEAEs ≥ CTCAE Grade 3 occurred only in 8% of patients.
  - **There was no clinically relevant effect on QT interval or LVEF**.
- **Lazertinib is the one of the treatment option for EGFR mutant positive NSCLC patients.**