New Treatment Option for NSCLC: 3rd Generation TKI (Lazertinib)

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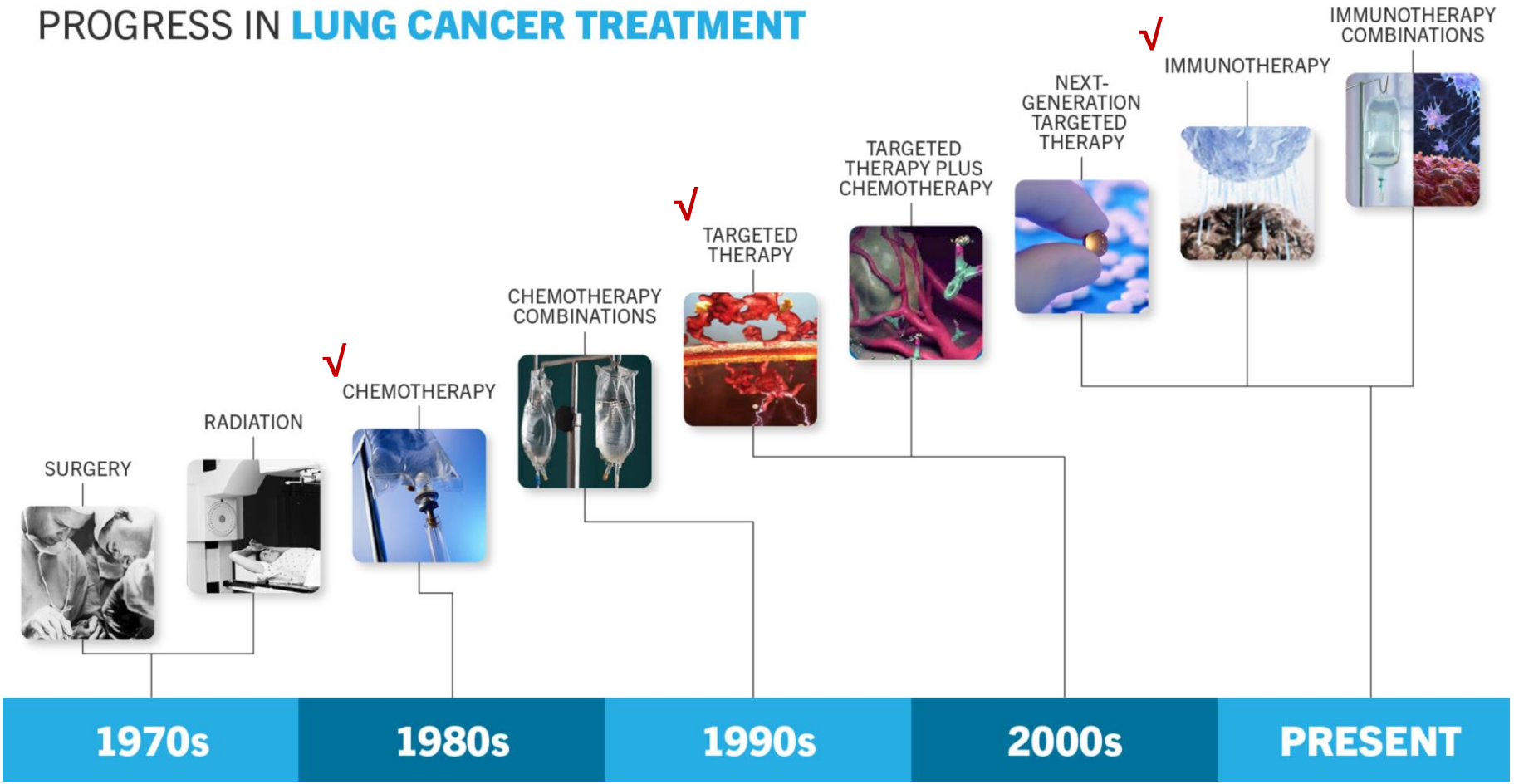
- It may contain therapies currently under clinical development for the purpose of scientific discussion and the company does not recommend any off-label uses.
- Physicians should refer to the approved PI(Product Information) before prescription.



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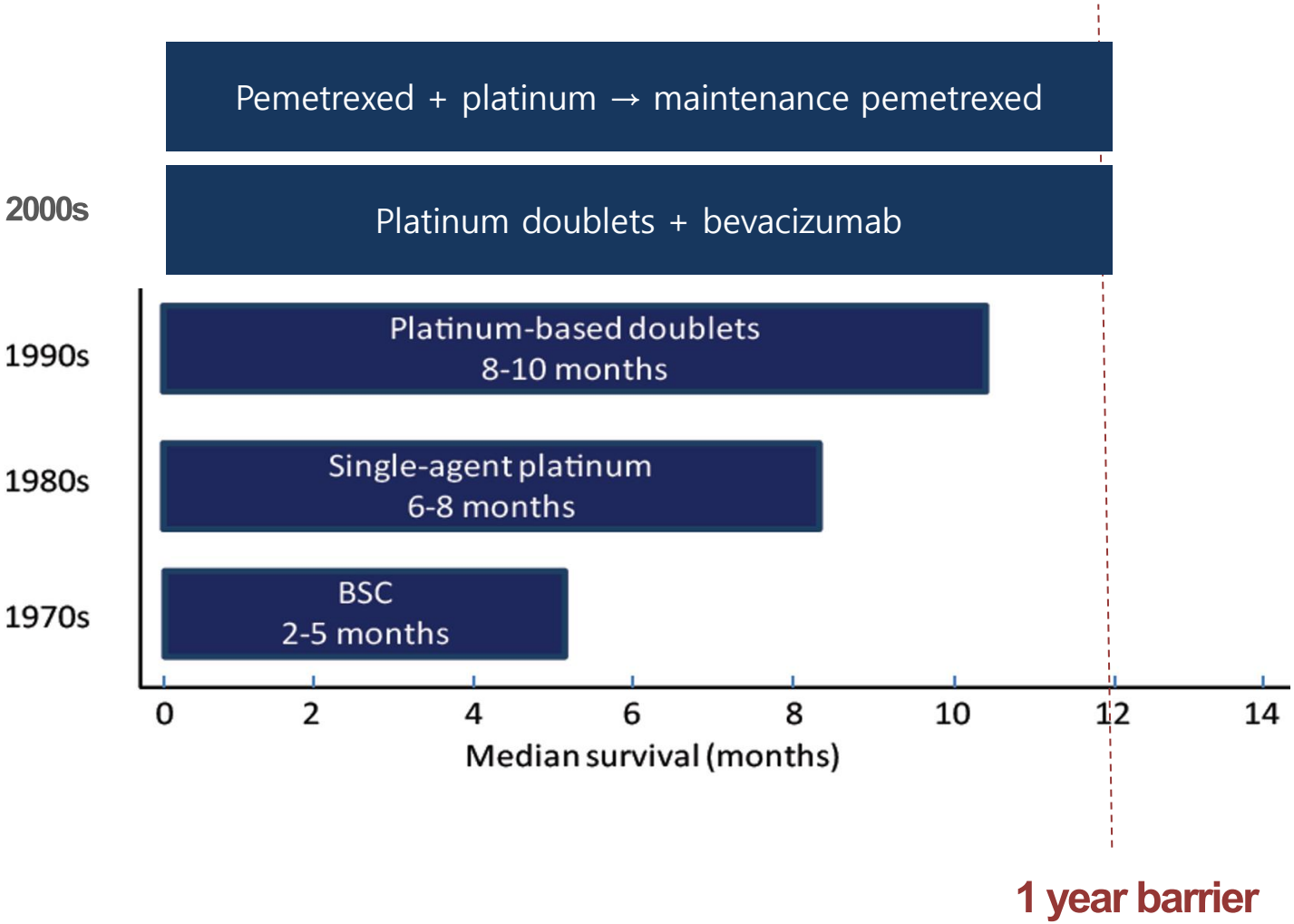

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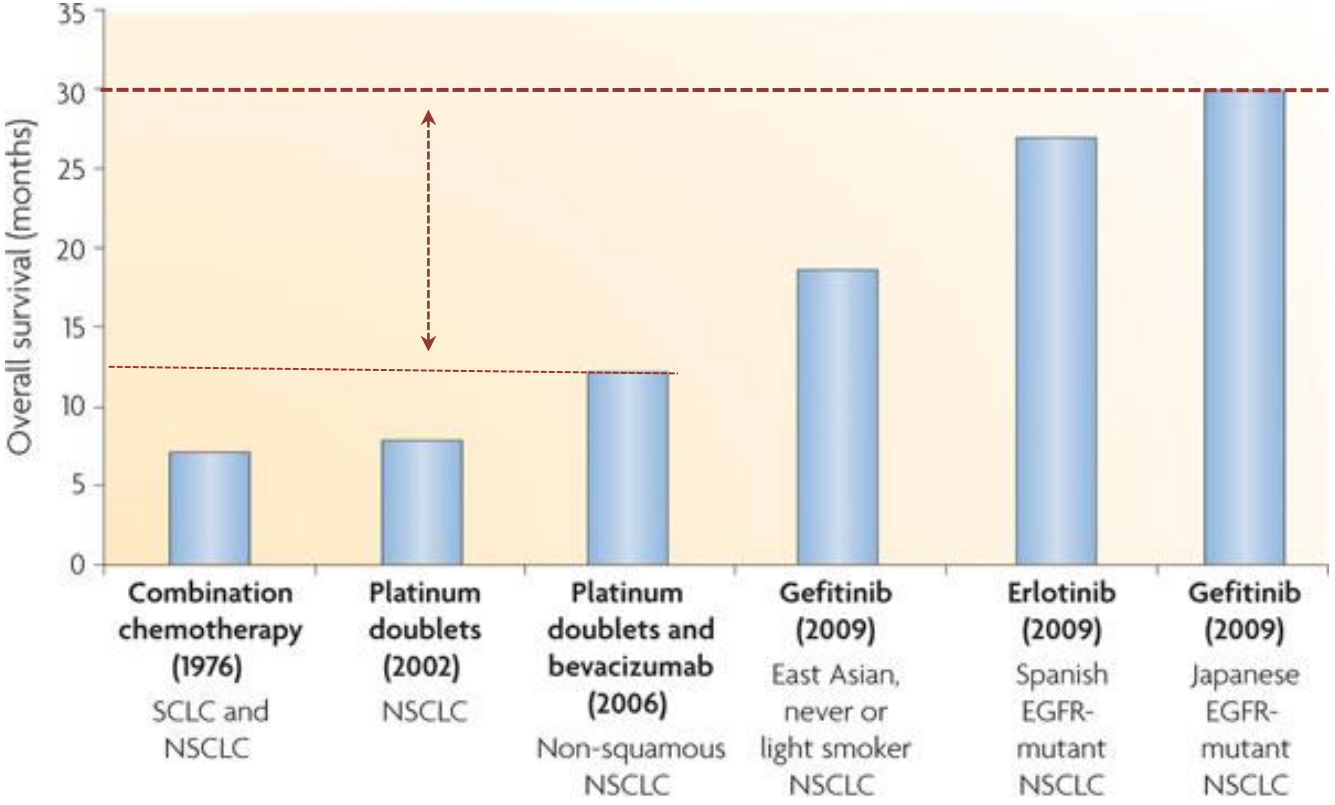
Impact of EGFR-TKIs



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Trends in 5-year survival of lung cancer

단위: % Unit: %

발생기간 Period of diagnosis					
'93-'95	'96-'00	'01-'05	'06-'10	'11-'15	'13-'17
11.6	12.4	15.3	18.0	23.2	25.2
15.8	17.5	20.1	26.0	37.2	41.5

EGFR-TKIs

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1971 - PRESIDENT NIXON DECLARES "WAR ON CANCER"
Launching a $1.6 Billion (US) dollar crusade.

THE LANCET

Lancet 2014; 383: 558–63

The cancer wars 2

Rethinking the war on cancer

Still not winning

adaptive and evasive resistance strategies of cancer under attack

speaker`s own

EGFR sensitizing mutations

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 20, 2004 VOL. 350 NO. 21

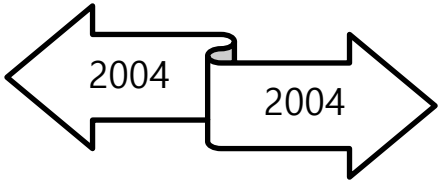
Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non–Small-Cell Lung Cancer to Gefitinib

Thomas J. Lynch, M.D., Daphne W. Bell, Ph.D., Raffaella Sordella, Ph.D., Sarada Gurubhagavatula, M.D., Ross A. Okimoto, B.S., Brian W. Brannigan, B.A., Patricia L. Harris, M.S., Sara M. Haserlat, B.A., Jeffrey G. Supko, Ph.D., Frank G. Haluska, M.D., Ph.D., David N. Louis, M.D., David C. Christiani, M.D., Jeff Settleman, Ph.D., and Daniel A. Haber, M.D., Ph.D.

EGFR Mutations in Lung Cancer: Correlation with Clinical Response to Gefitinib Therapy

J. Guillermo Paez,[1,2*] Pasi A. Jänne,[1,2*] Jeffrey C. Lee,[1,3*] Sean Tracy,[1] Heidi Greulich,[1,2] Stacey Gabriel,[4] Paula Herman,[1] Frederic J. Kaye,[5] Neal Lindeman,[6] Titus J. Boggon,[1,3] Katsuhiko Naoki,[1] Hidefumi Sasaki,[7] Yoshitaka Fujii,[7] Michael J. Eck,[1,3] William R. Sellers,[1,2,4†] Bruce E. Johnson,[1,2†] Matthew Meyerson[1,3,4†]

SCIENCE VOL 304 4 JUNE 2004



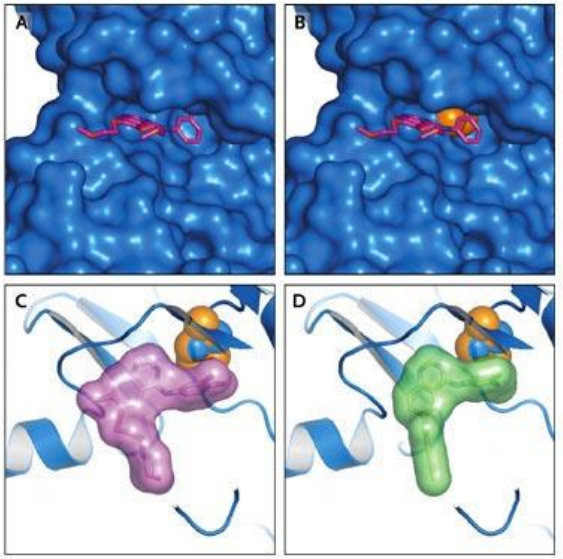
T790M

The NEW ENGLAND JOURNAL of MEDICINE

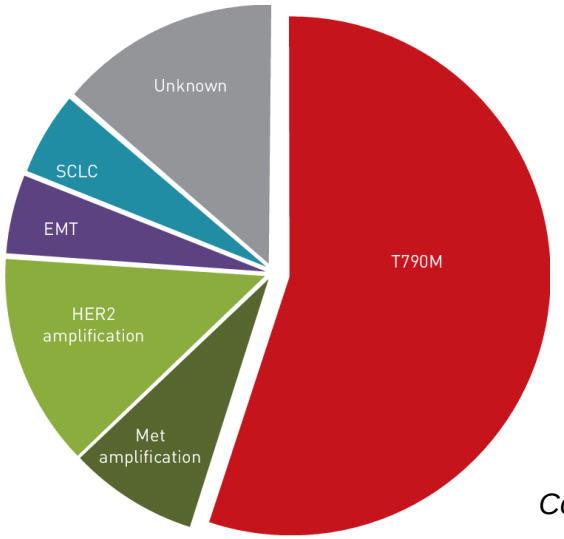
BRIEF REPORT

EGFR Mutation and Resistance of Non–Small-Cell Lung Cancer to Gefitinib

Susumu Kobayashi, M.D., Ph.D., Titus J. Boggon, Ph.D., Tajhal Dayaram, B.A., Pasi A. Jänne, M.D., Ph.D., Olivier Kocher, M.D., Ph.D., Matthew Meyerson, M.D., Ph.D., Bruce E. Johnson, M.D., Michael J. Eck, M.D., Ph.D., Daniel G. Tenen, M.D., and Balázs Halmos, M.D.



Kobayashi S, et al. N Engl J Med 2005



≈50%

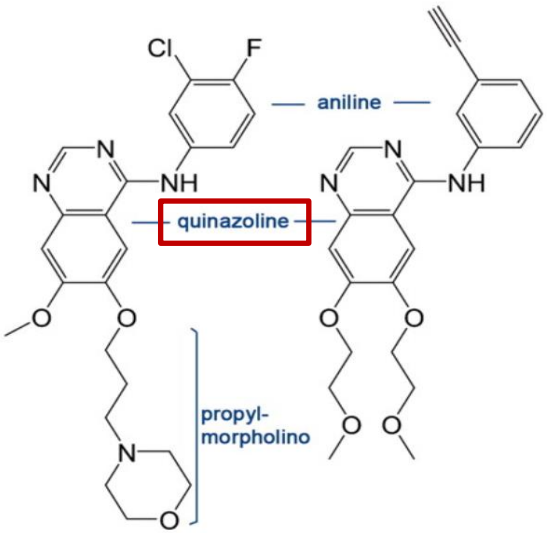
Cortot AB, et al. Eur Respir Rev 2014

nature Vol 462|24/31 December 2009|doi:10.1038/nature08622

LETTERS

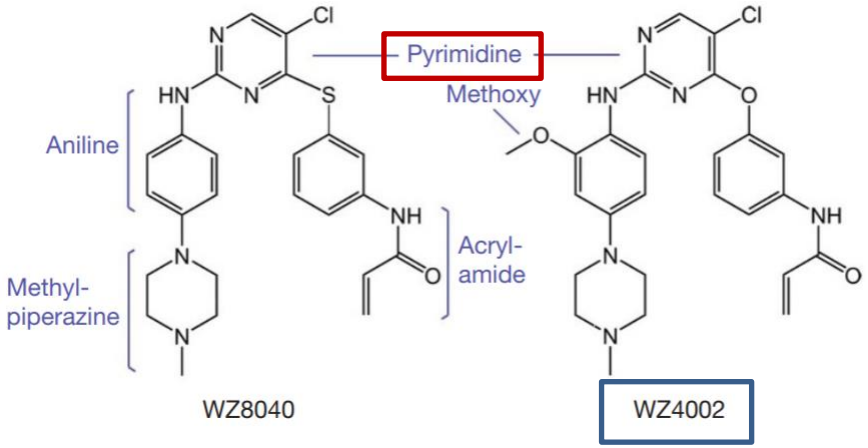
Novel mutant-selective EGFR kinase inhibitors against EGFR T790M

Wenjun Zhou[1,2]*, Dalia Ercan[3,4]*, Liang Chen[3,4]*, Cai-Hong Yun[1,2]*, Danan Li[3,4], Marzia Capelletti[3,4], Alexis B. Cortot[3,4], Lucian Chirieac[5], Roxana E. Iacob[6,7], Robert Padera[5], John R. Engen[6,7], Kwok-Kin Wong[3,4,8,9], Michael J. Eck[1,2], Nathanael S. Gray[1,2] & Pasi A. Jänne[3,4,8]



Gefitinib Erlotinib

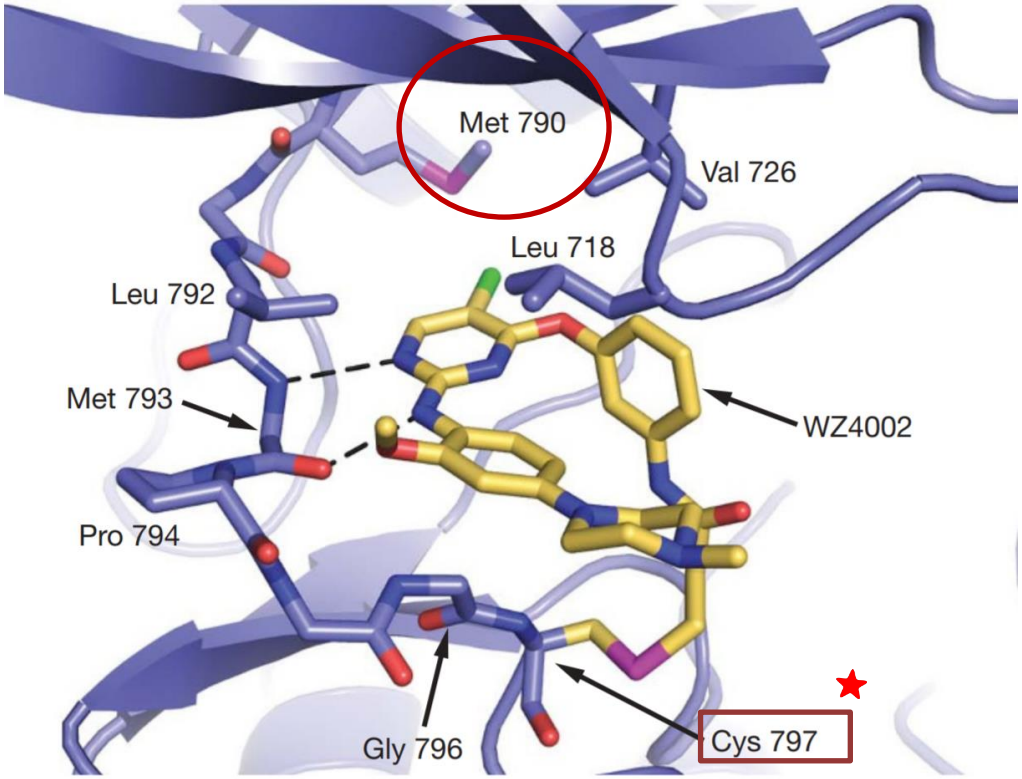
Functional pharmacological screen



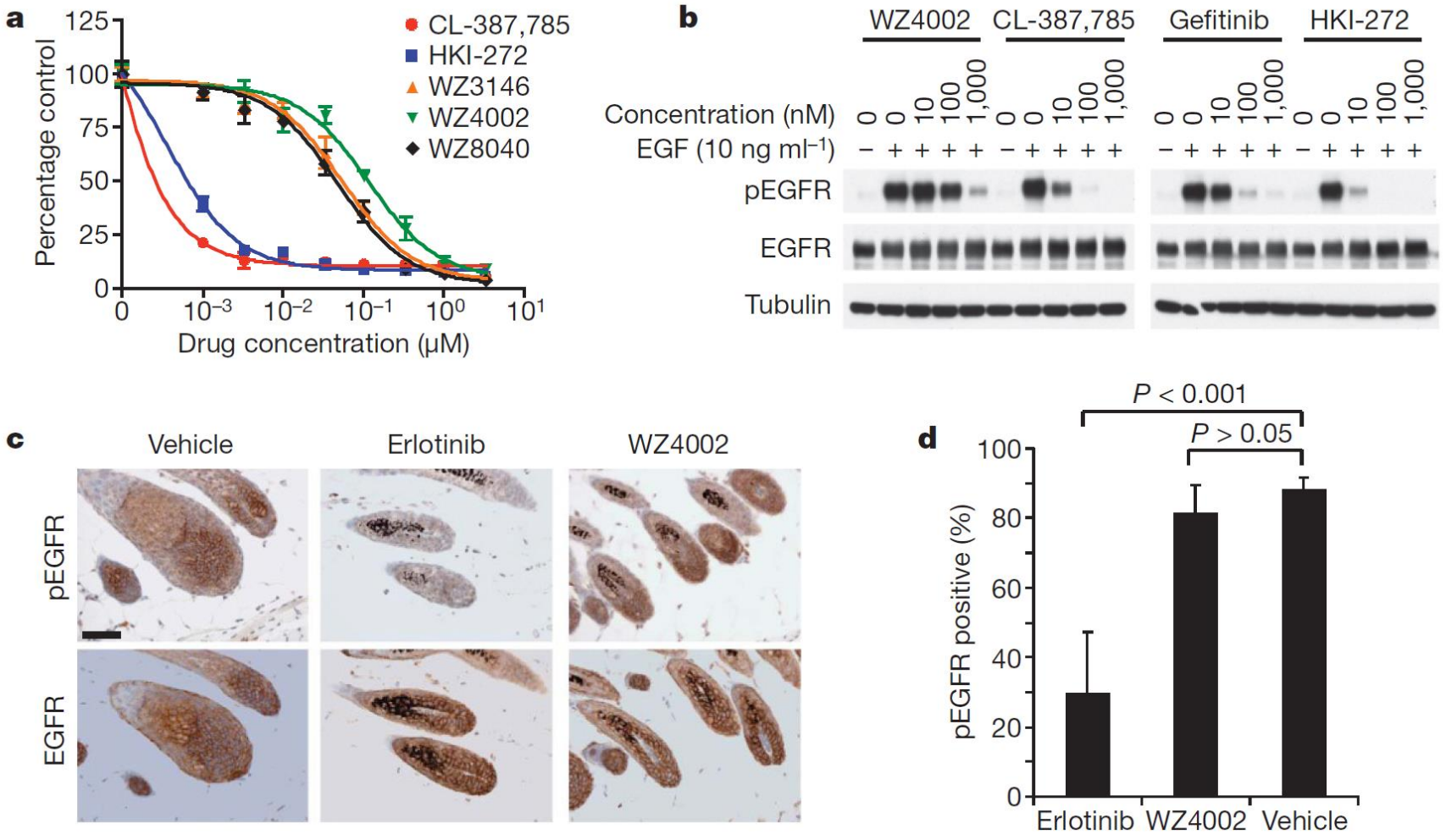
WZ8040 WZ4002

Zhou W, et al. Nature 2009

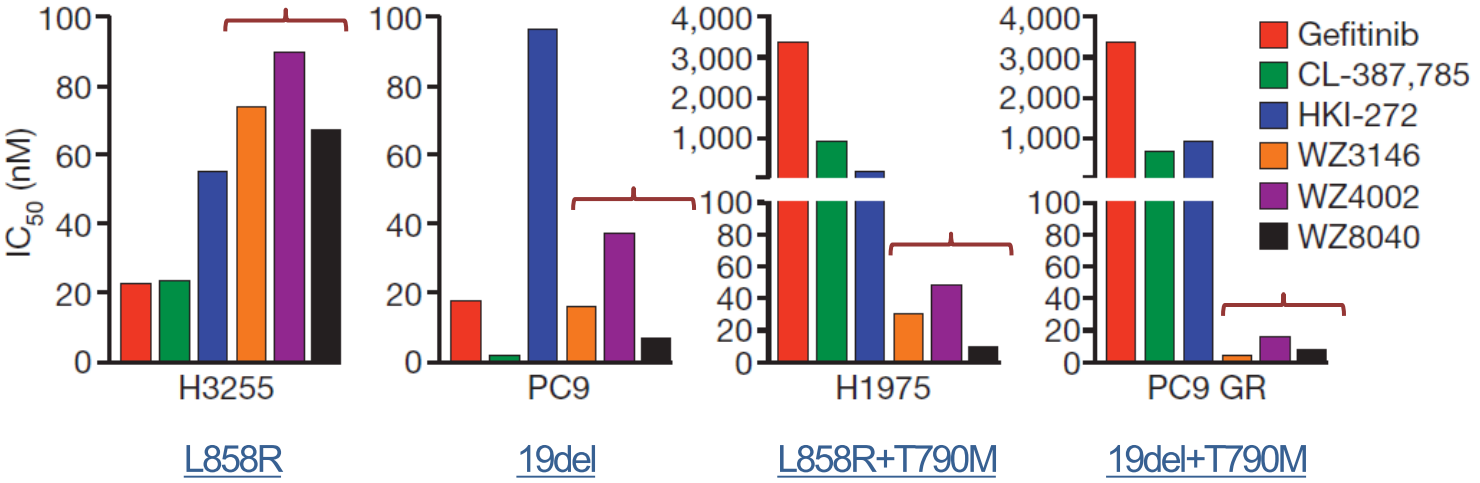
WZ4002



Zhou W, et al. Nature 2009



Zhou W, et al. Nature 2009



Zhou W, et al. Nature 2009

ASCO 50 1964-2014

ASCO American Society of Clinical Oncology
Making a world of difference in cancer care

2016

Response Rate	HM-61713	CO-1686	AZD-9291
T790M +	30%	58%	64%
T790M -	12%	29%	22%
	Olmutinib	Rociletinib	Osimertinib

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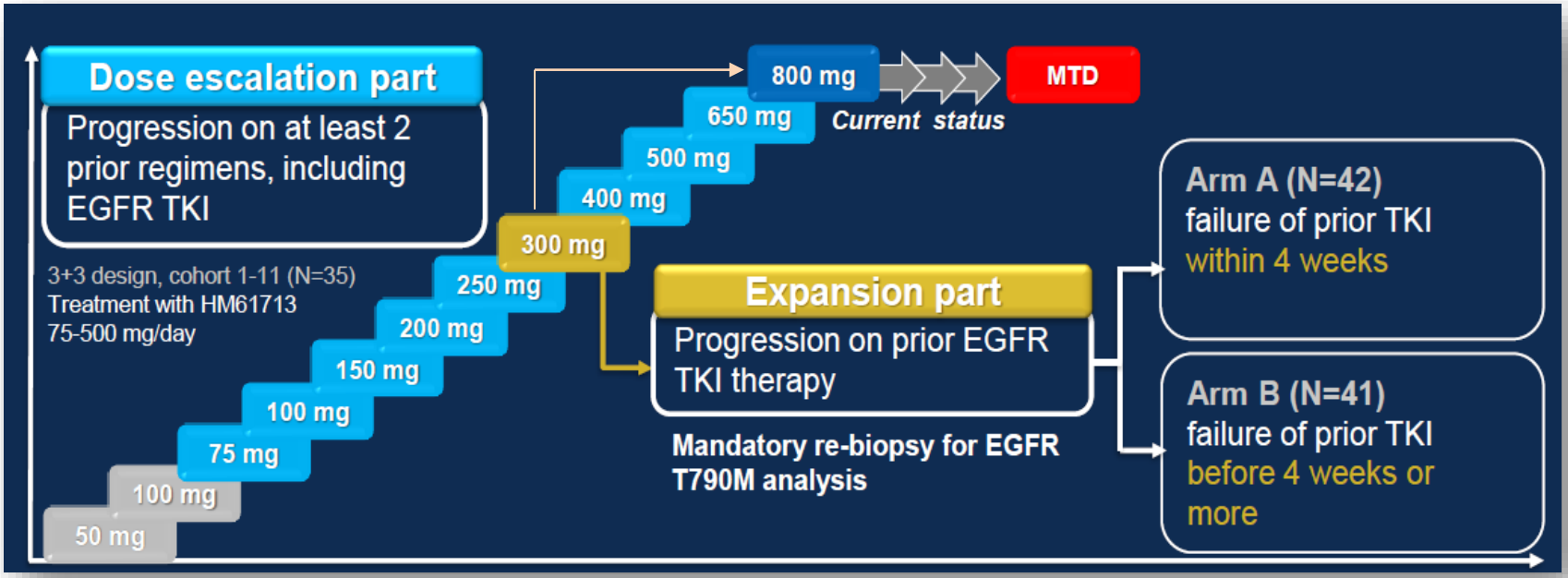

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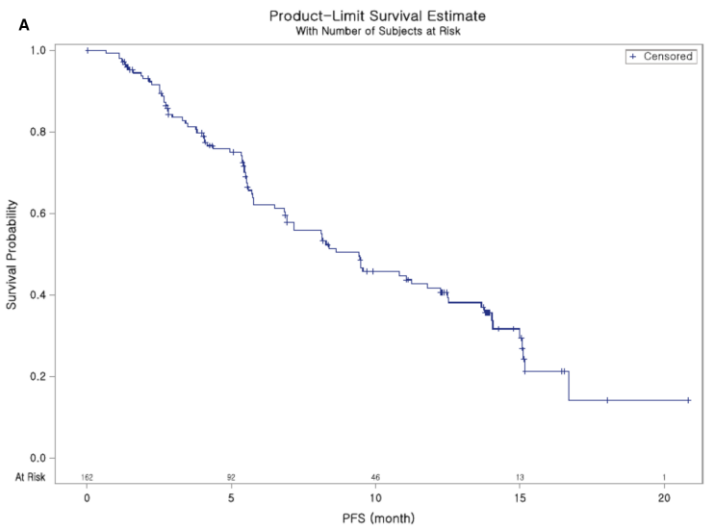
Original Article

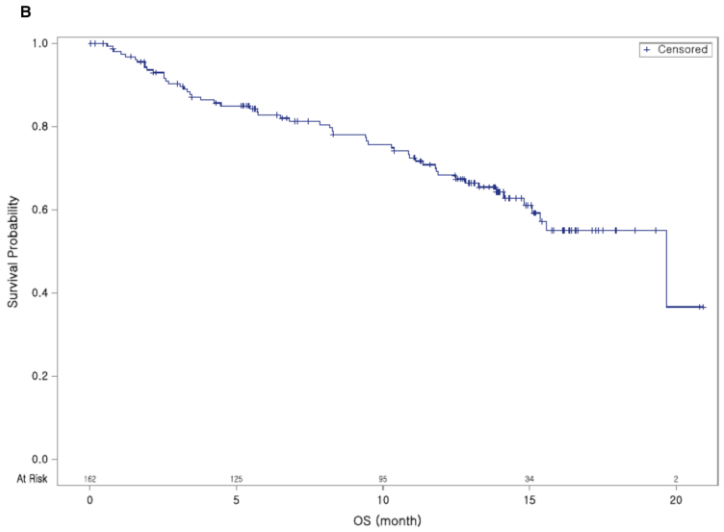
Olmutinib in T790M-Positive Non–Small Cell Lung Cancer After Failure of First-Line Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor Therapy: A Global, Phase 2 Study

Overall Response by Independent Central Review for the Safety Set, n = 162

Parameter	Response Rate, No. (%)	95% CI
Overall response rate (regardless of being confirmed)	84 (51.9)	43.9-59.8
Overall response rate (confirmed)	75 (46.3)	38.4-54.3
Partial response	75 (46.3)	
Stable disease	65 (40.1)	
Disease control rate (confirmed)	140 (86.4)	80.2-91.3
Progressive disease (PD)	8 (4.9)	
Non-CR/Non-PD	2 (1.2)	
Not evaluable	12 (7.4)	

Park K, et al. Cancer 2021





mPFS 9.4

mOS 19.7

Park K, et al. Cancer 2021

Preferred Term	No. of Patients (%)	
	All Patients	Patients With Grade ≥3 Events
All drug-related TEAEs	152 (93.8)	78 (48.2)
Diarrhea	62 (38.3)	5 (3.1)
Nausea	44 (27.2)	1 (0.6)
Hyperkeratosis	43 (26.5)	4 (2.5)
Rash	43 (26.5)	7 (4.3)
Skin exfoliation	38 (23.5)	1 (0.6)
Vomiting	37 (22.8)	3 (1.9)
Palmar-plantar erythrodysesthesia syndrome	35 (21.6)	7 (4.3)
Increased alanine aminotransferase	33 (20.4)	5 (3.1)

Hanmi Pharma Charged for Failure to Report Patient Death in Olmutinib Study

According to reports, one of the patients in the trial treated with Hanmi's lung cancer drug displayed symptoms of Stevens-Johnson syndrome, a life-threatening skin-condition. The patient's condition was not reported to the monitoring agency until his death more than a month later–a violation of Korea's 24-hour reporting rule for severe incidents, the Herald said. But, to make matters worse, Hanmi and the

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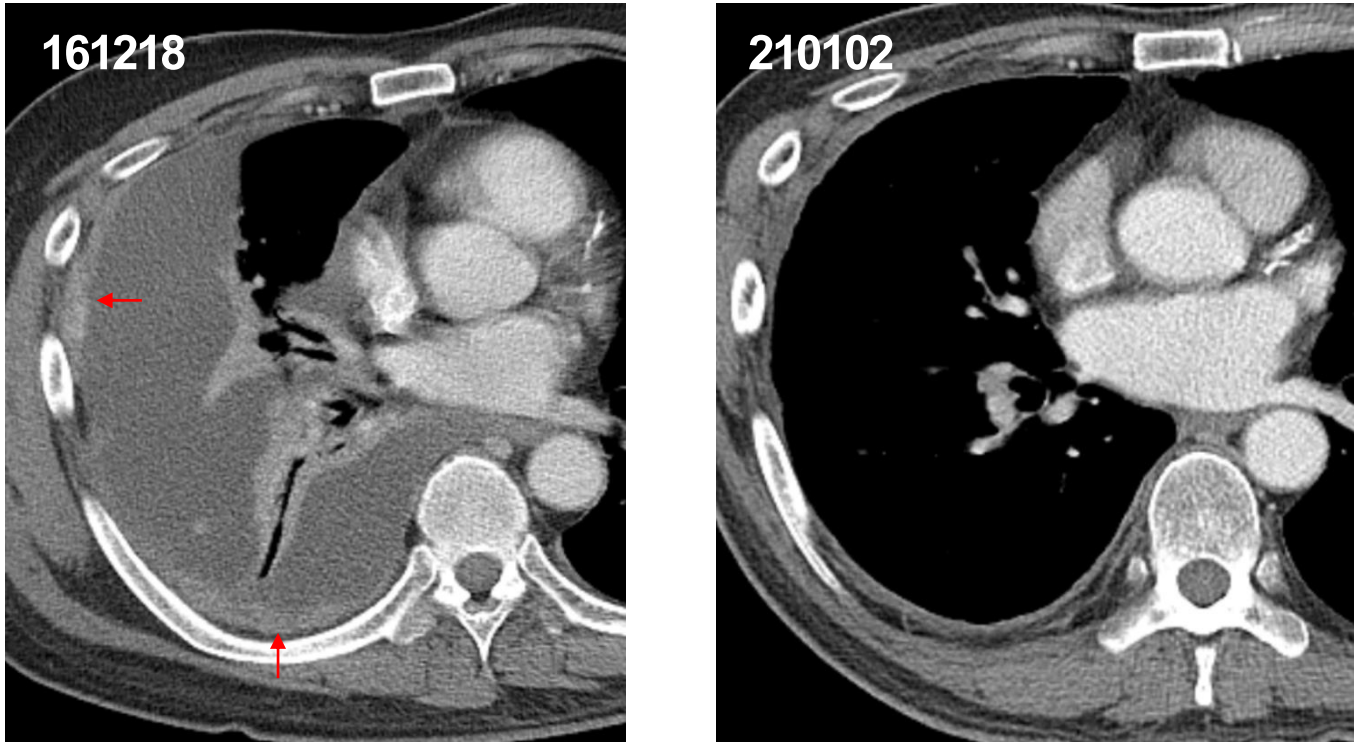
M/65 ACC M/pleura, peritoneum 19del+

- gefitinib (150728 - 161221) T790M+
- olmutinib (170118 - on going)
- WBRT (200408)



olmutinib

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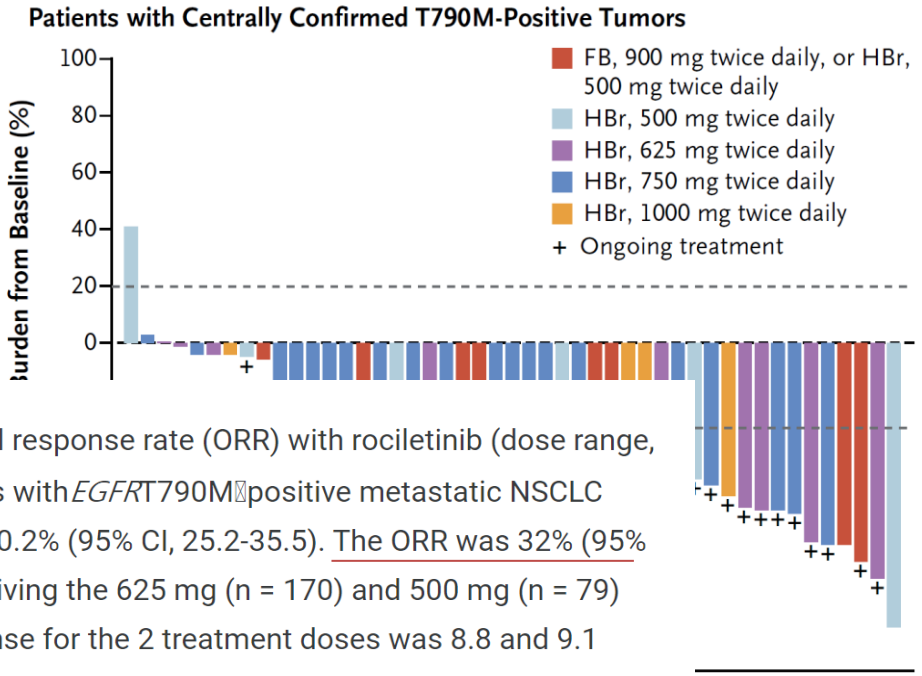
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rociletinib in *EGFR*-Mutated Non–Small-Cell Lung Cancer

Responses were seen in 59 percent of evaluable patients with the T790M mutation (n=46). In this same population, median progression-free survival (PFS) at the time of analysis was 13.1 months;

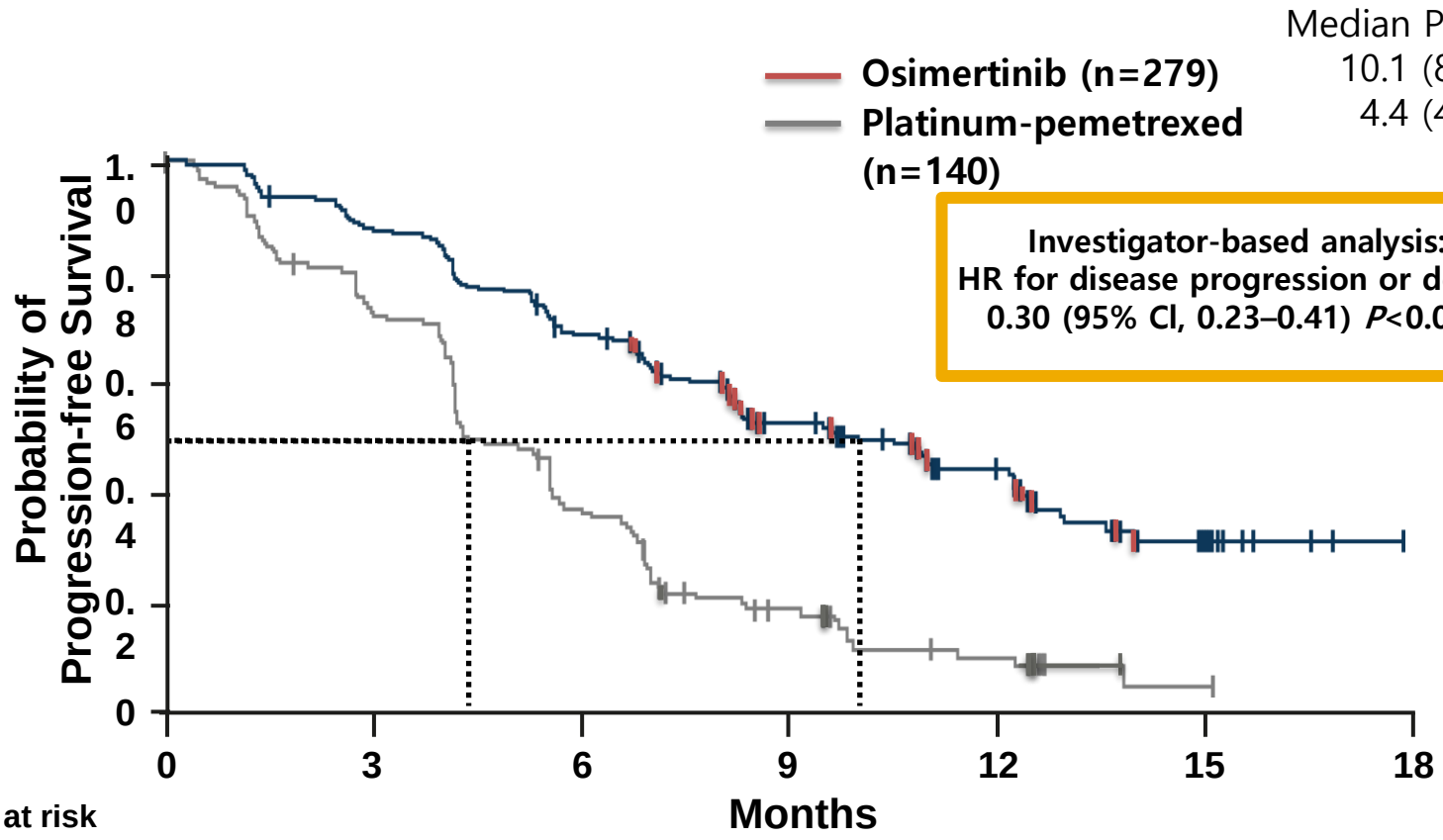


In the pooled TIGER-X/TIGER-2 analysis, the overall response rate (ORR) with rociletinib (dose range, 500 mg to 750 mg twice daily) among 325 patients with *EGFR* T790M positive metastatic NSCLC who progressed on at least 1 EGFR inhibitor was 30.2% (95% CI, 25.2-35.5). The ORR was 32% (95% CI, 25-40) and 23% (95% CI, 14-34) in patients receiving the 625 mg (n = 170) and 500 mg (n = 79) doses, respectively. The median duration of response for the 2 treatment doses was 8.8 and 9.1 months, respectively.

frequent (>10%) grade 3/4 AEs were hyperglycemia and QTc prolongation.

N Engl J Med 2015;372:1700-9.
DOI: 10.1056/NEJMoa1413654

Osimertinib, AURA3 primary endpoint: PFS by investigator assessment



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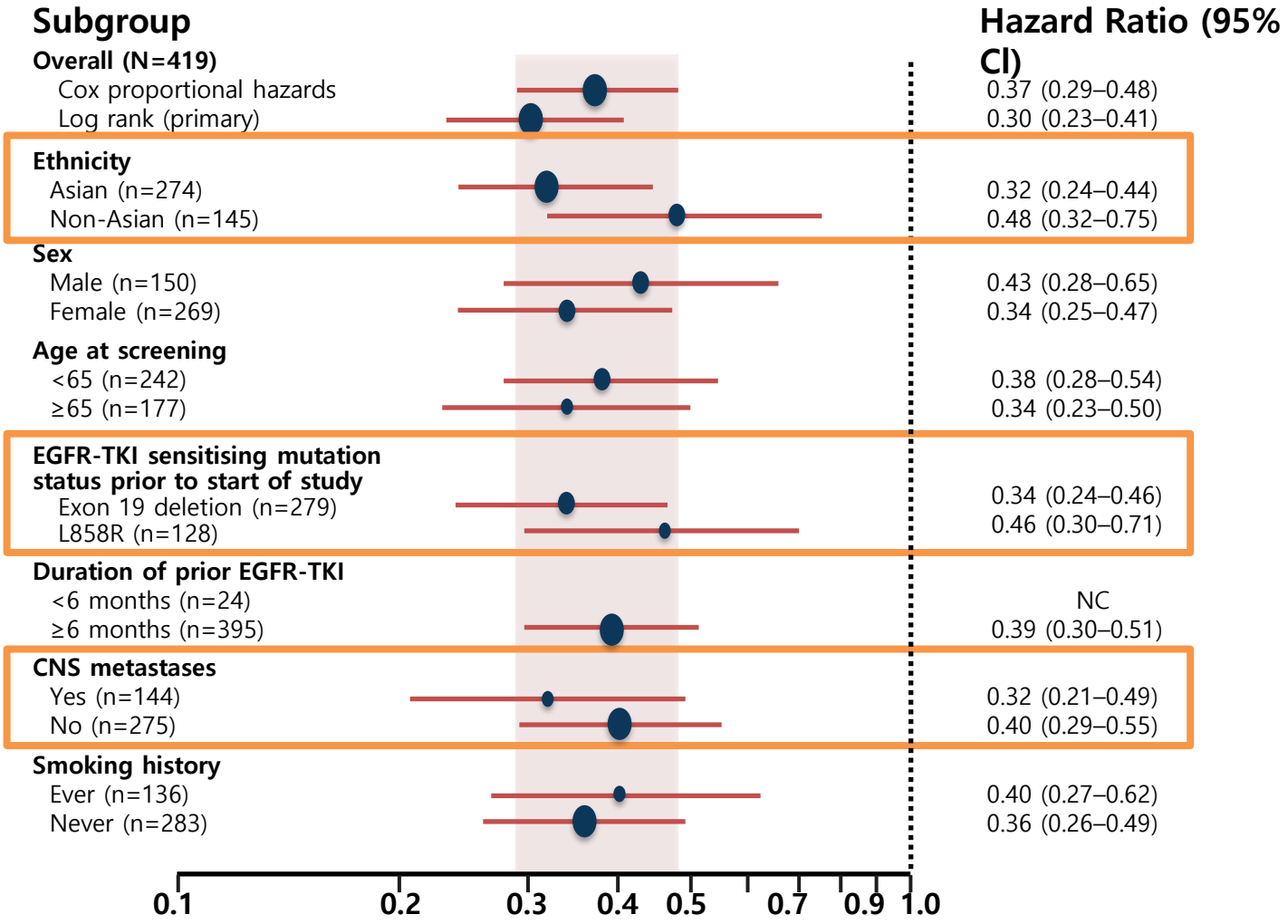
Benefit with osimertinib observed across all subgroups in AURA3



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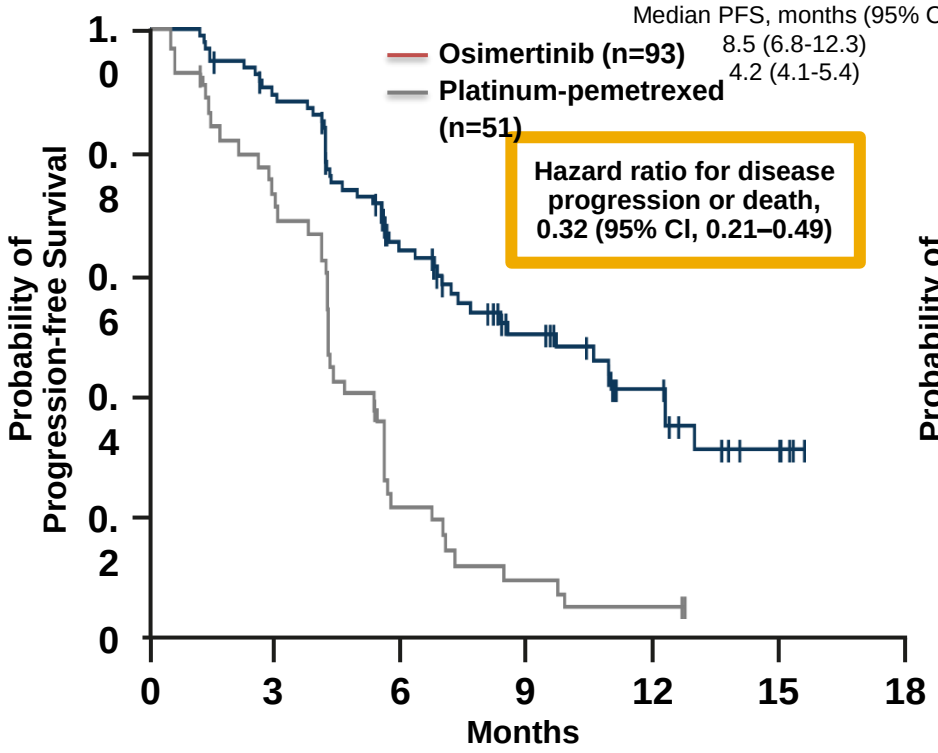
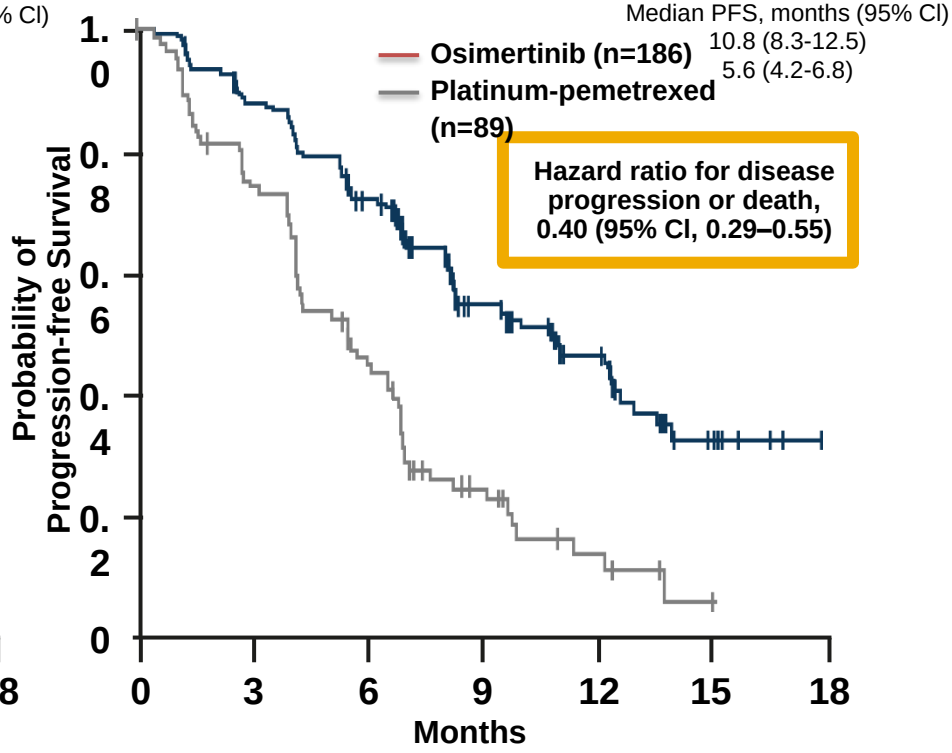
PFS benefit in AURA3 patients with CNS metastases at baseline

With CNS metastases



Without CNS metastases



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Adverse Event	Osimertinib (N = 279)	
	Any Grade	Grade ≥3
Diarrhea	113 (41)	3 (1)
Rash†	94 (34)	2 (1)
Dry skin†	65 (23)	0
Paronychia†	61 (22)	0
Decreased appetite	50 (18)	3 (1)
Cough	46 (16)	0
Nausea	45 (16)	2 (1)
Fatigue	44 (16)	3 (1)
Stomatitis	41 (15)	0
Constipation	39 (14)	0
Pruritus	35 (13)	0
Vomiting	31 (11)	1 (<1)
Back pain	29 (10)	1 (<1)
Thrombocytopenia†	28 (10)	1 (<1)
Nasopharyngitis	28 (10)	0
Headache	28 (10)	0
Dyspnea	24 (9)	3 (1)
Neutropenia†	22 (8)	4 (1)
Leukopenia†	22 (8)	0
Anemia†	21 (8)	2 (1)
Asthenia	20 (7)	3 (1)
Pyrexia	18 (6)	0
Alanine aminotransferase elevation	18 (6)	3 (1)
Aspartate aminotransferase elevation	14 (5)	3 (1)
Malaise	11 (4)	0

2016 AURA3

Adverse Event	Osimertinib (N=279)				
	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
Any adverse event	273 (98)	34 (12)	144 (52)	83 (30)	6 (2)
Rash or acne†	161 (58)	134 (48)	24 (9)	3 (1)	0
Diarrhea	161 (58)	120 (43)	35 (13)	6 (2)	0
Dry skin†	100 (36)	87 (31)	12 (4)	1 (<1)	0
Paronychia†	97 (35)	52 (19)	44 (16)	1 (<1)	0
Stomatitis	80 (29)	65 (23)	13 (5)	1 (<1)	1 (<1)
Decreased appetite	56 (20)	27 (10)	22 (8)	7 (3)	0
Pruritus	48 (17)	40 (14)	7 (3)	1 (<1)	0
Cough	46 (16)	34 (12)	12 (4)	0	0
Constipation	42 (15)	33 (12)	9 (3)	0	0
Nausea	39 (14)	28 (10)	11 (4)	0	0
Fatigue	38 (14)	21 (8)	15 (5)	2 (1)	0
Dyspnea	35 (13)	24 (9)	10 (4)	1 (<1)	0
Anemia	34 (12)	19 (7)	12 (4)	3 (1)	0
Headache	33 (12)	26 (9)	6 (2)	1 (<1)	0
Vomiting	31 (11)	25 (9)	6 (2)	0	0
Upper respiratory tract infection	28 (10)	16 (6)	12 (4)	0	0
Pyrexia	28 (10)	27 (10)	1 (<1)	0	0
Prolonged QT interval on ECG	28 (10)	11 (4)	11 (4)	5 (2)	1 (<1)
Aspartate aminotransferase elevation	26 (9)	18 (6)	6 (2)	2 (1)	0
Alopecia	20 (7)	17 (6)	3 (1)	0	0
Alanine aminotransferase elevation	18 (6)	11 (4)	6 (2)	1 (<1)	0

2017 FLAURA

Journal of Clinical Oncology®
An American Society of Clinical Oncology Journal

LUNG CANCER—NON-SMALL CELL METASTATIC

ECOG-ACRIN 5162: A phase II study of osimertinib 160 mg in NSCLC with EGFR exon 20 insertions.

Results: 21

pts were enrolled between 4/2018 and 7/2019 (median age 65; 15 female, 6 male; median 2 prior therapies); 1 patient did not meet eligibility criteria due to laboratory studies obtained 1 day out of window. As of 1/21/20, 6 pts remain on treatment. Among the 20 eligible pts, the best response was PR in 4 pts and CR in one pt, for a confirmed ORR of 25%; 12 (60%) pts had SD. The median PFS was 9.7 months (95% CI, 4.07, NA), median duration of response (DOR) was 5.7 months (95% CI, 4.73, NA.) Grade > 3 treatment-related adverse events (TRAE) observed in > 1 pt included anemia (n=2), fatigue (n=2), prolonged QT interval (n=2.) One pt had grade 4 respiratory failure, there were no grade 5 TRAEs. One pt discontinued study treatment due to grade 3 anemia.

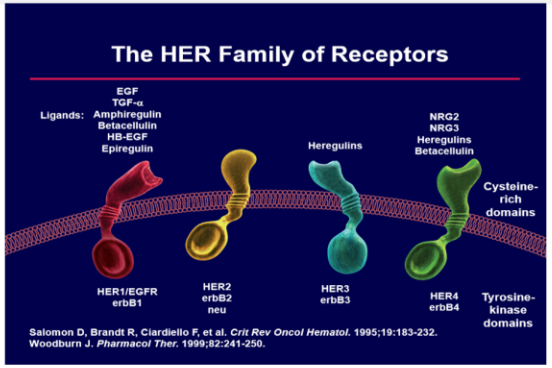
DOI: 10.1200/JCO.2020.38.15_suppl.9513
Journal of Clinical Oncology 38,
no. 15_suppl (May 20, 2020) 9513-9513.

Safety Concern on Cardiac Toxicities

- EGFR (HER1) is one of the receptors in the HER family, and has a high structural similarity to HER2. If a EGFR-TKI inhibit HER2, it can cause cardiac toxicity[1)]
- Some EGFR-TKIs are known to cause QT interval prolongation[2),3)] and left ventricular contractile (LVEF) decline[4)]
- **QT interval prolonged syndrome** can cause Torsade de pontes, which can lead to sudden death[5)]
- **Decreased left ventricular systolic function** may be an indicator of heart failure[6)]

Disproportionality Signal Analysis Calculated by Using the ROR

	ROR (95% CI) for Osimertinib vs database	ROR (95% CI) for Osimertinib vs other TKIs
Cardiac Failure	✱5.4 (4.2-7.1)	✱2.2 (1.5-3.2)
Atrial fibrillation	✱4.0 (2.8-5.8)	✱2.1 (1.3-3.5)
QT prolongation	✱11.2 (7.9-15.8)	✱6.6 (3.4-12.8)
Myocardial Infarction	1.6 (0.9-2.6)	1.2 (0.6-2.3)
Pericardial Effusion	✱8.2 (4.8-14)	1.6 (0.8-3.3)



✱ : significantly different

The reporting odds ratio (ROR) was calculated for osimertinib versus all drugs and osimertinib versus other tyrosine kinase inhibitors (TKIs).
Compared with all other drugs in the U.S. Food and Drug Administration Adverse Events Reporting System database, osimertinib was associated with increased cardiac failure, atrial fibrillation, QT prolongation, and pericardial effusion. RORs for osimertinib versus other TKIs were elevated for cardiac failure, atrial fibrillation, and QT prolongation. CI ¼ confidence interval.

1. Copeland-Halperin et al. Curr Opin Cardiol. 2019 Jul;34(4):451-458; 2. Kloth et al. Br J Cancer. 2015 Mar 17;112(6):1011-6; 3. Anand et al. JACC. 2019; 4. Ewer M et al. J Clin Oncol. 2020
5. Straus et al. Eur Heart J. 2005 Oct;26(19):2007-12; 6. Ejection Fraction. Cleveland Clinic.

LONE SURVIVOR

Osimertinib (tagrisso®)

Dec 21, 2020	Approval	Tagrisso Approved in the US for the Adjuvant Treatment of Patients with Early-Stage EGFR-Mutated Non-Small Cell Lung Cancer
Apr 18, 2018	Approval	FDA Approves Tagrisso (osimertinib) as First-Line Treatment for EGFR-Mutated Non-Small Cell Lung Cancer
Mar 31, 2017	Approval	Tagrisso (osimertinib) Receives FDA Full Approval
Nov 13, 2015	Approval	FDA Approves Tagrisso (osimertinib) for EGFR T790M Mutation-Positive Non-Small Cell Lung Cancer

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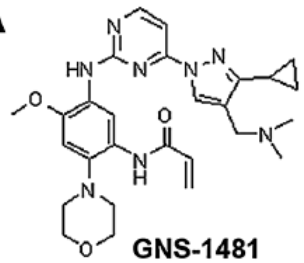
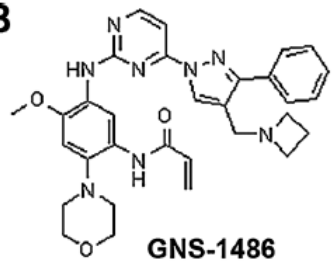
A



GNS-1481

B



GNS-1486

	Kinase	GNS-1481	GNS-1486	AZD9291	CO-1686	Afatinib	Erlotinib
EGFR	Wild type	26.5	121.6	16.7	928.2	0.2	0.6
	Del 19 (E746-A750)	6.6	20.5	8.6	216.5	0.2	0.8
	L858R	25.8	103.6	12.2	742.9	0.3	0.9
	Double Mutant (L858R-T790M)	6.2	8.3	4.5	45.7	18.6	549.3
	T790M	3.4	4.2	2.2	20.5	1.6	395.2
	Double Mutant (Del 19-T790M)	4.2	4.3	3.3	44.1	7.0	715.6
	Wild type/Double Mutant (L858R-T790M)	4.3	14.7	3.7	20.3	0.01	< 0.01

Rho JK, et al. Cancer Res 2017

GNS-1481	% Inhibition	GNS-1486	% Inhibition	AZD9291	% Inhibition
EGFR(T790M,L858R)	101	EGFR(T790M,L858R)	102	EGFR(T790M,L858R)	102
Ret (V804L)	98	Tie2(Y897S)	101	Tie2(Y897S)	101
EGFR(L858R)	96	EGFR(T790M)	97	EGFR(T790M)	100
EGFR(T790M)	95	MLK1	92	EGFR(L858R)	97
EGFR(L861Q)	92	EGFR(L861Q)	88	ErbB4	96
MLK1	92	Ret (V804L)	81	ErbB2	95
Blk	91	EGFR(L858R)	68	EGFR	94
EGFR	87	EGFR	4	EGFR(L861Q)	94
Ret	83			ACK1	89
Txk	83			Mnk2	83

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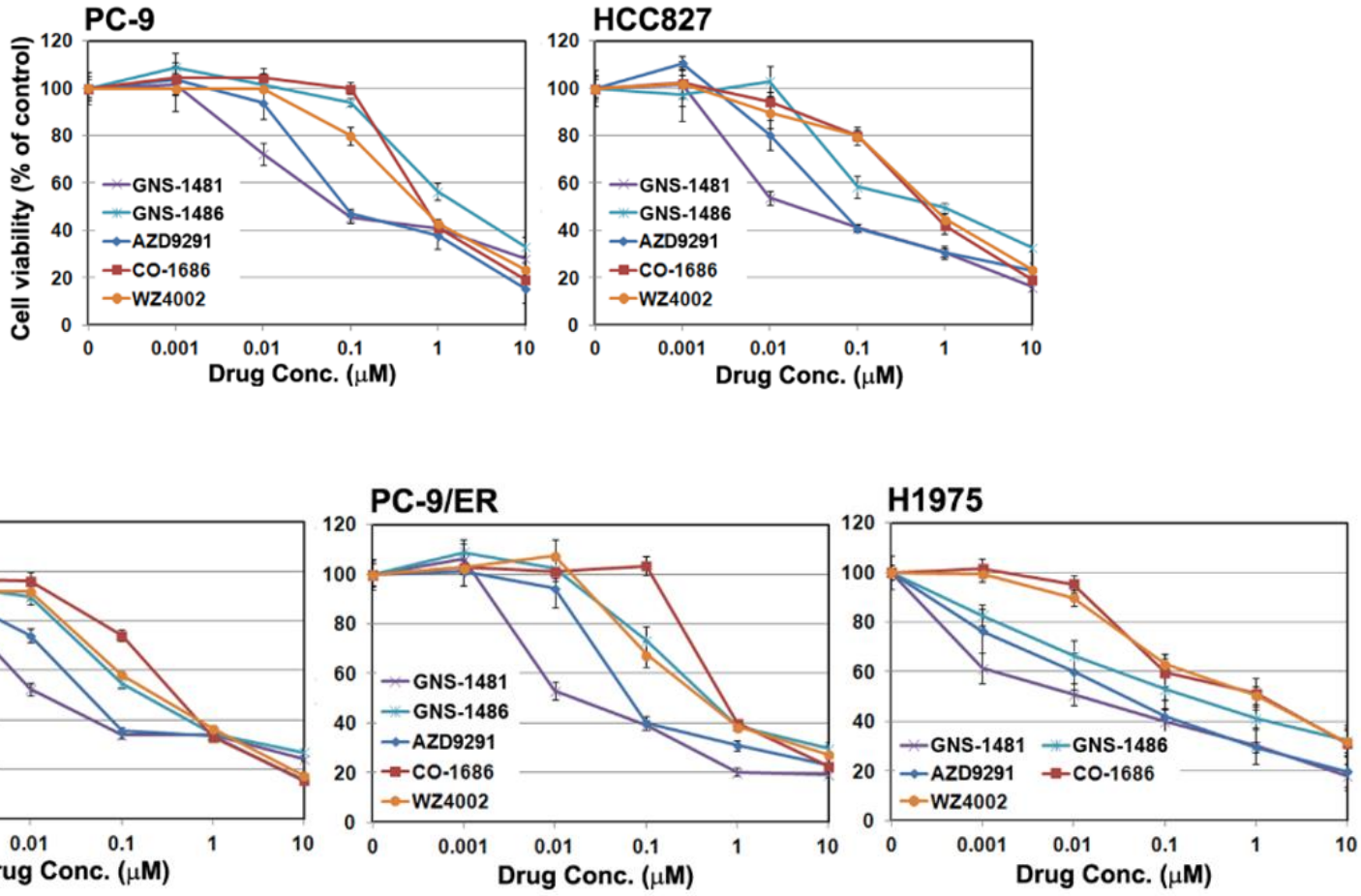

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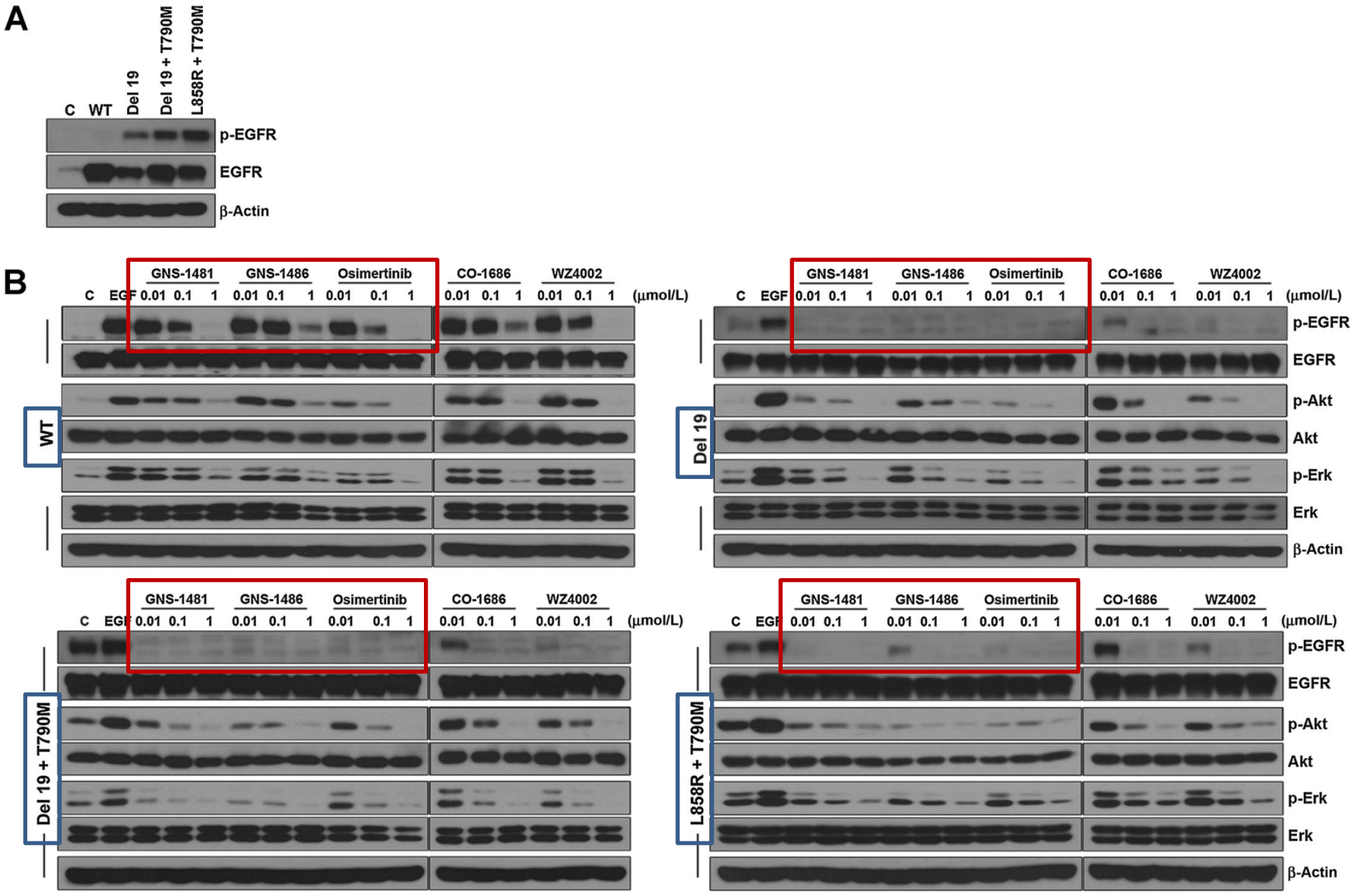

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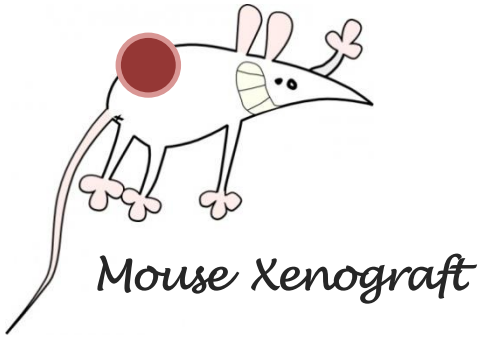

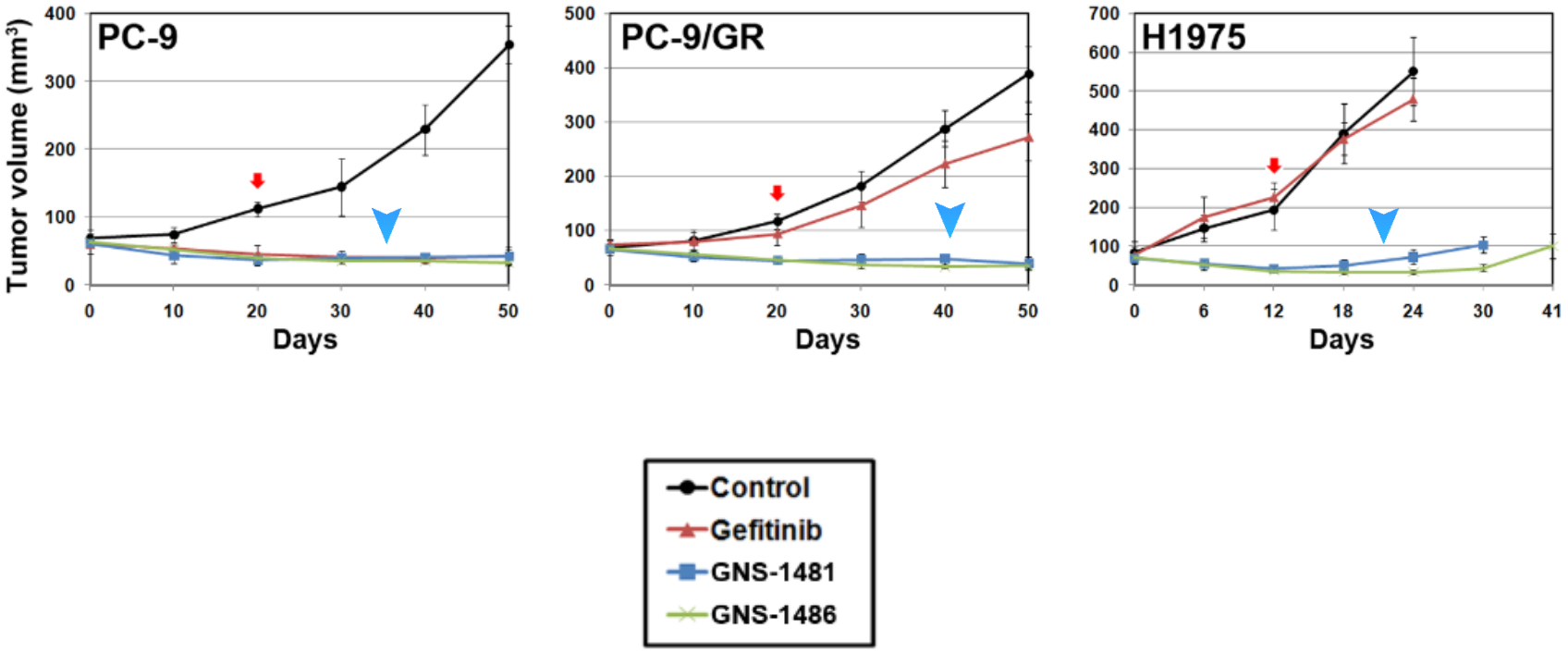

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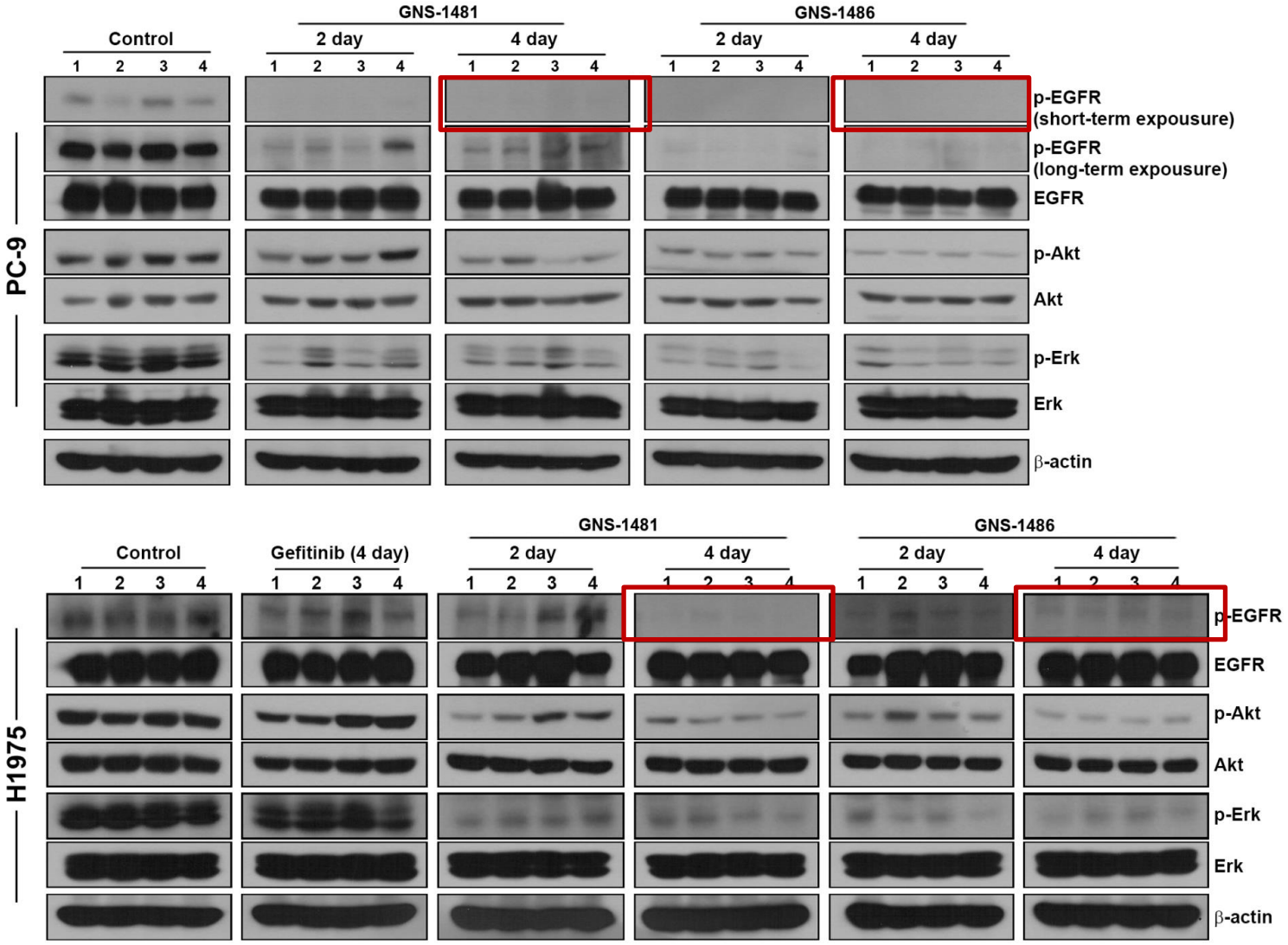
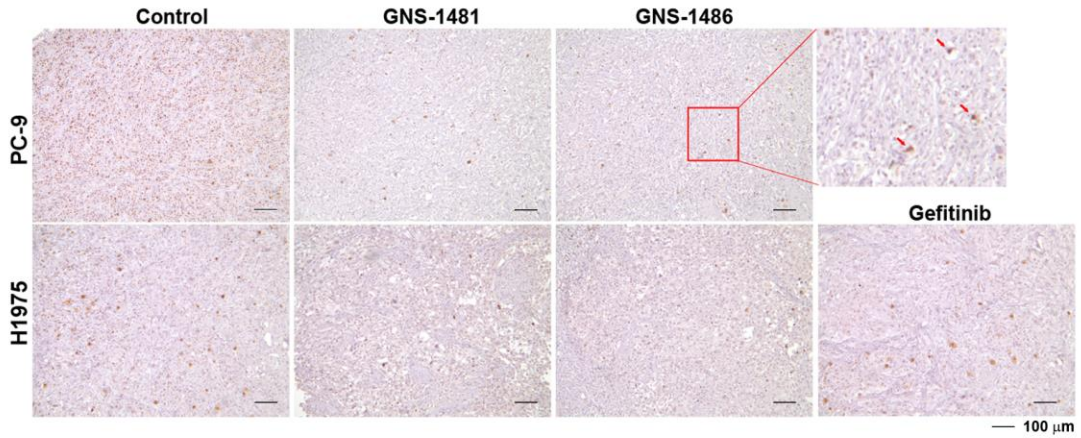
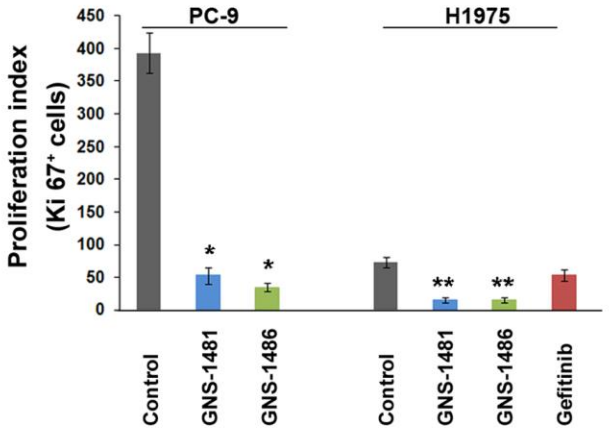
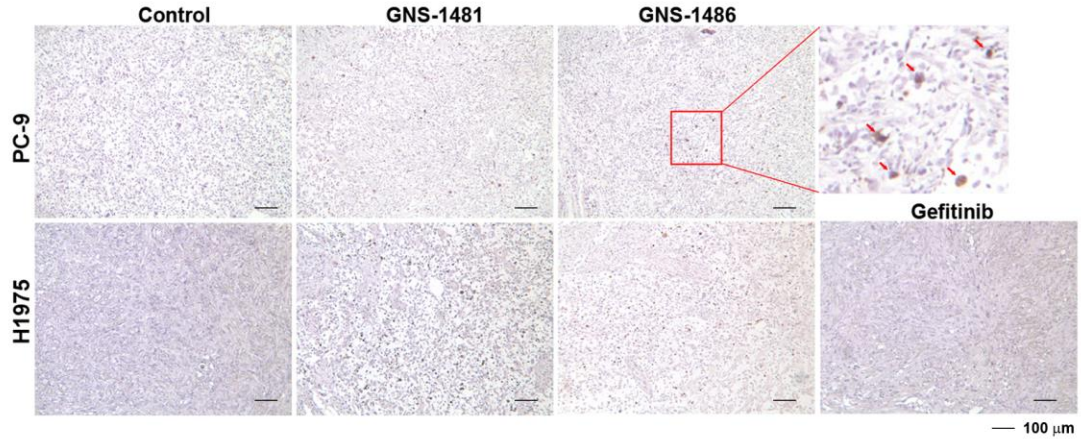
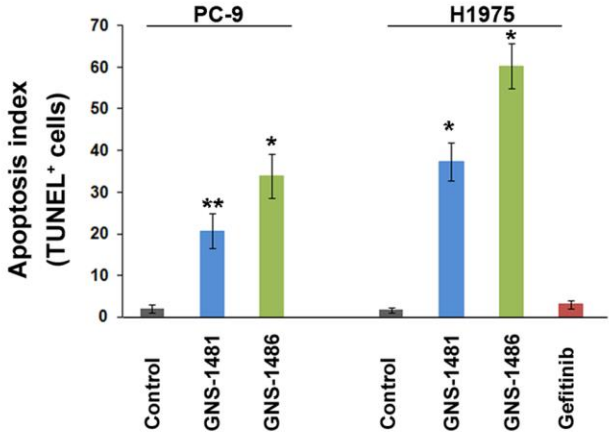


Rho JK, et al. Cancer Res 2017









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BBB penetration of GNS-1481 and GNS-1486 in SD Rat at 10 mg/kg

GNS-1481	Treatment (IV), SD Rat (N=3)		
Time hours (hr)	Plasma Conc. (ng/mL)	Brain Conc. (ng/g)	B/P Ratio
0.5	864 (±120.9)	451 (±53.3)	0.53 (±0.11)
2	646 (±98.3)	3943 (±493)	6.15 (±0.69)

GNS-1486	Treatment (IV), SD Rat (N=3)		
Time hours (hr)	Plasma Conc. (ng/mL)	Brain Conc. (ng/g)	B/P Ratio
0.25	1542.4 (±428.1)	4695.4 (±1240.4)	3.05 (±0.08)
2	493.7 (±116.2)	484.8 (±303.1)	1.07 (±0.85)

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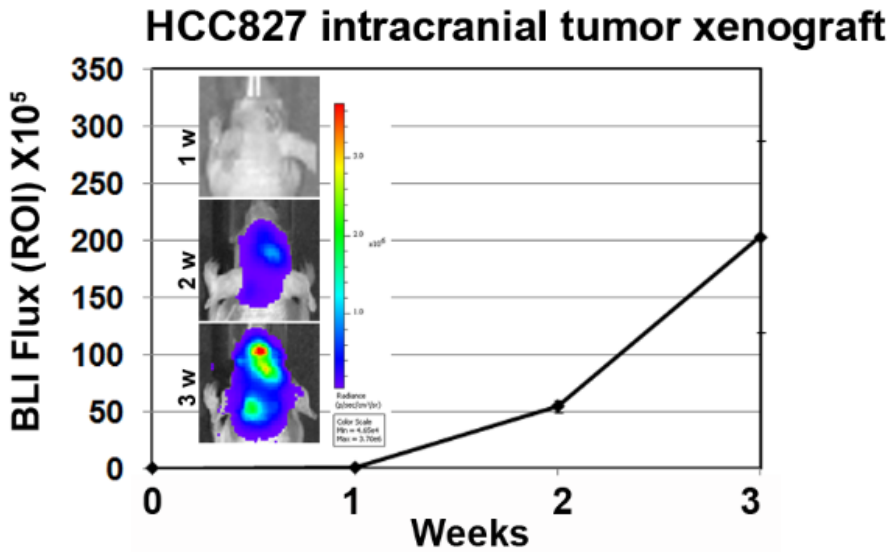

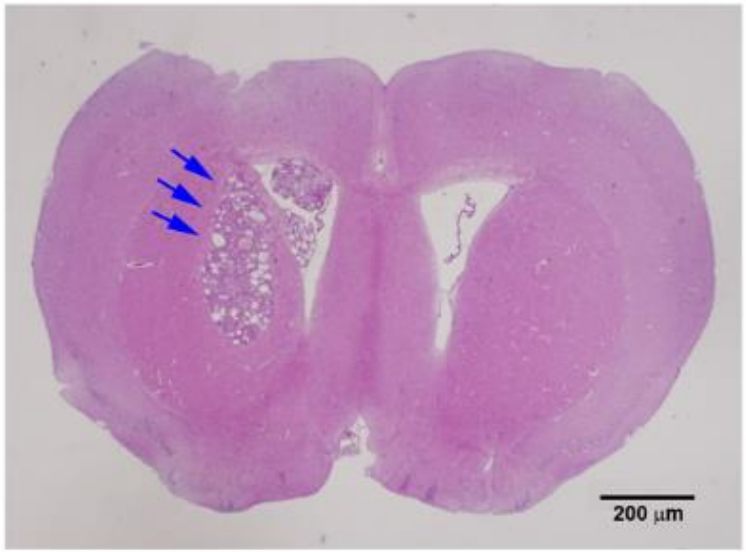

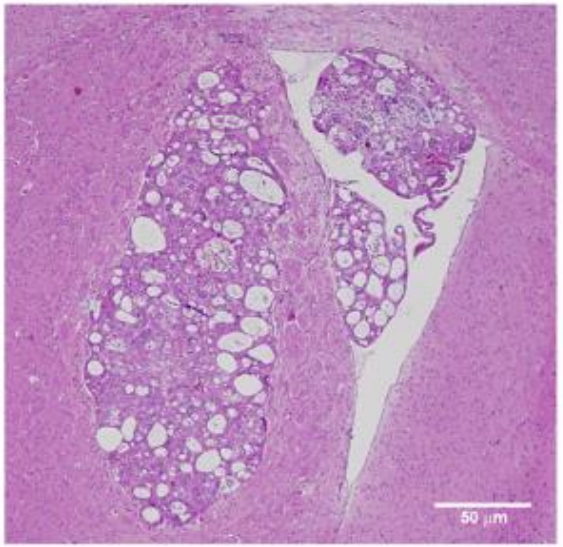

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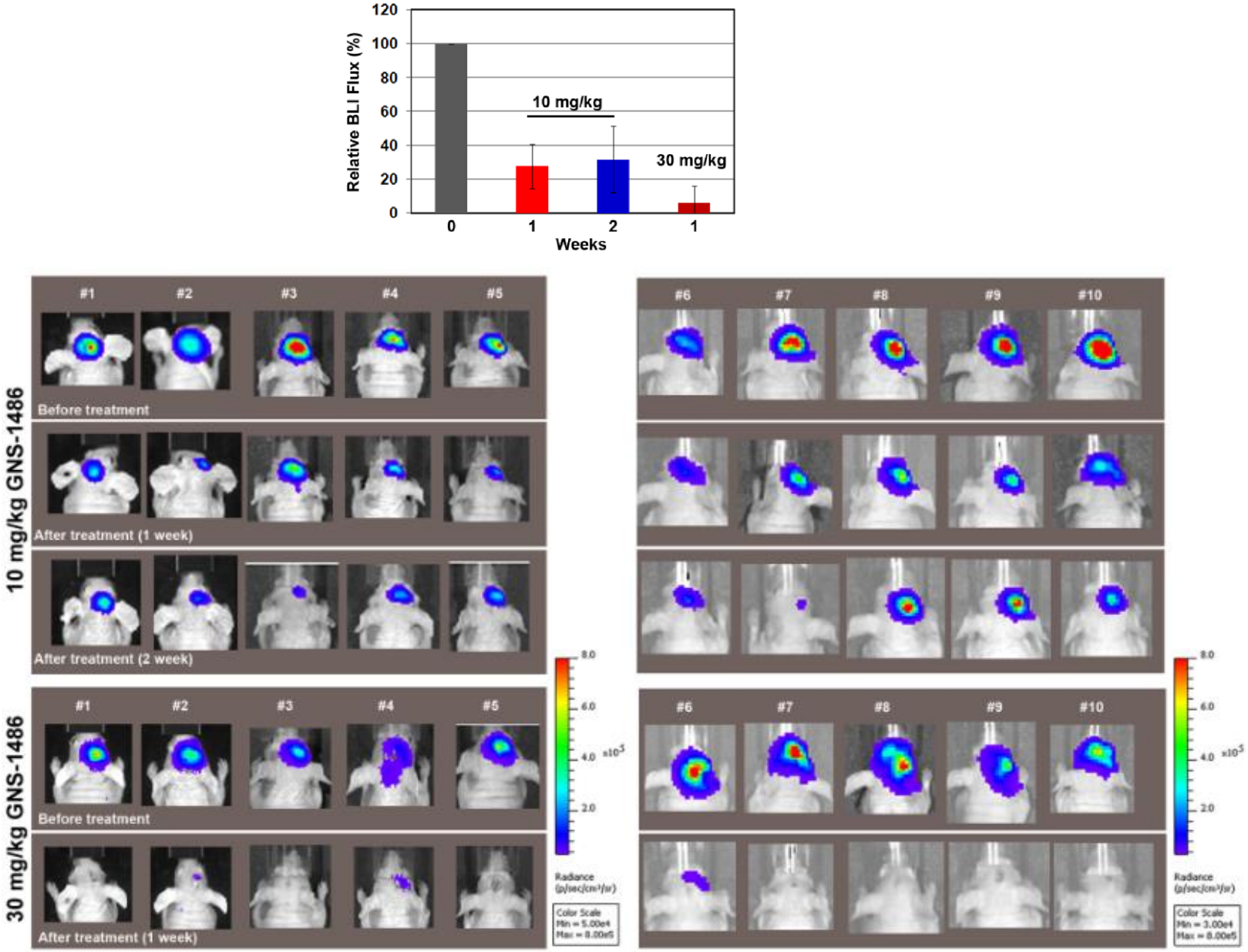

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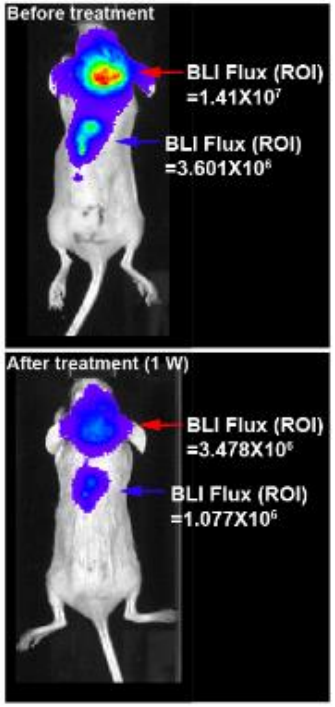
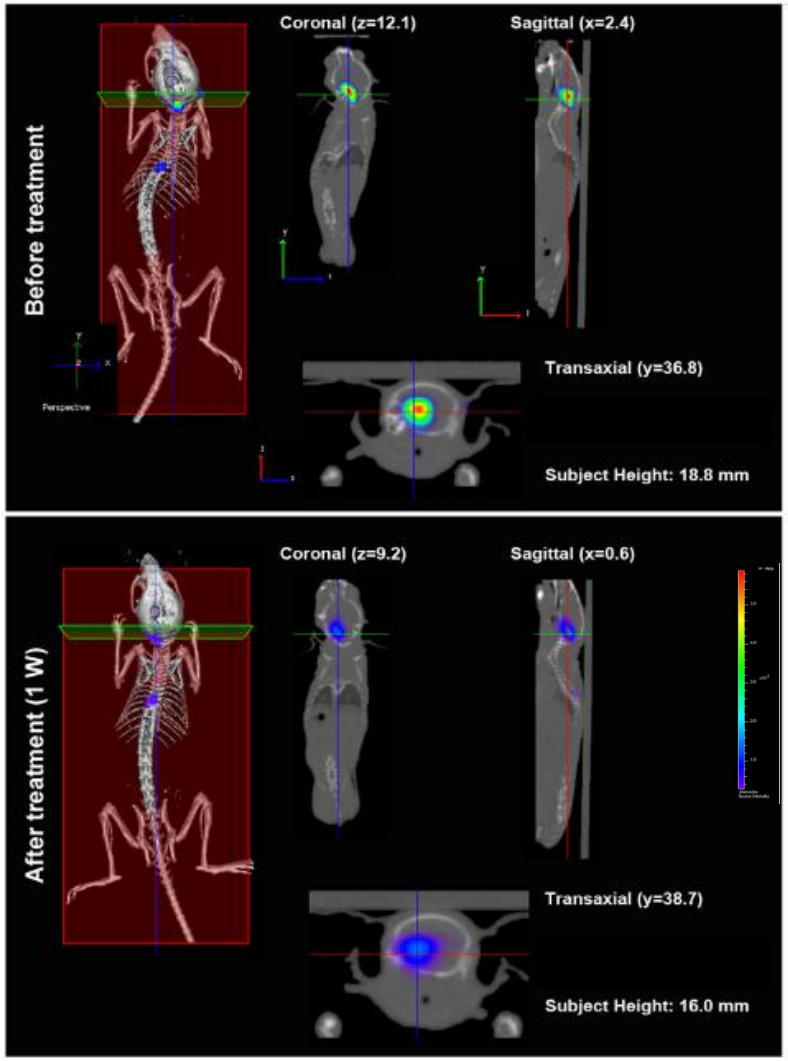
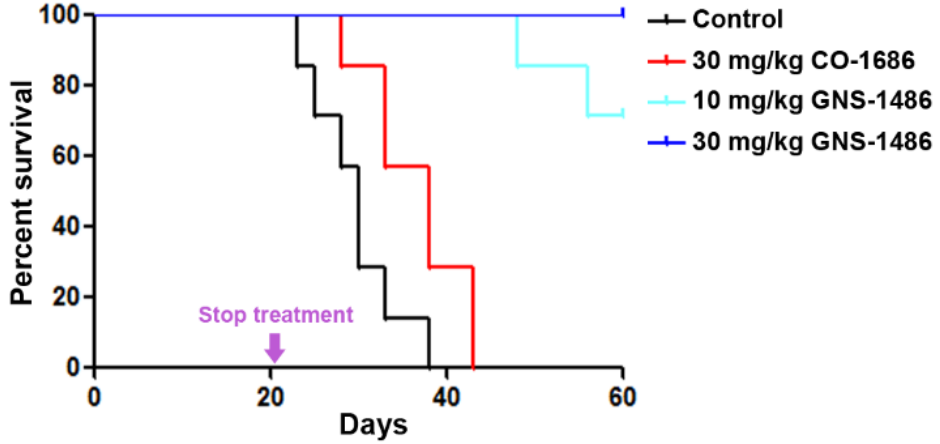
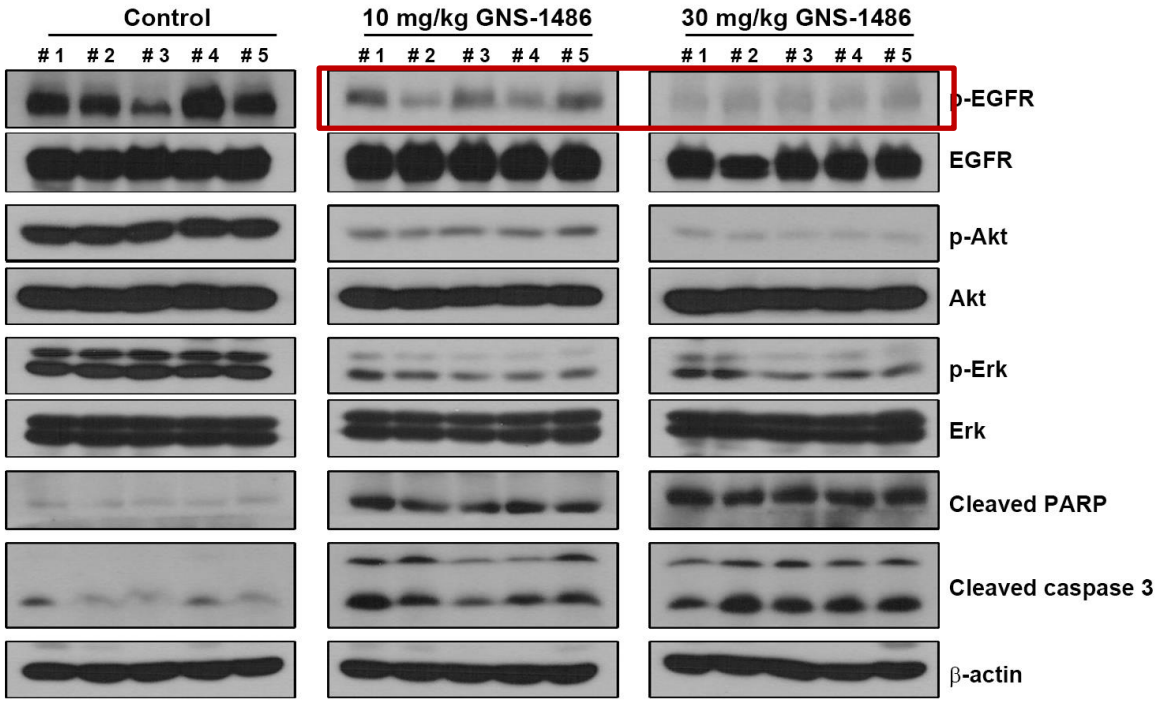




Rho JK, et al. Cancer Res 2017





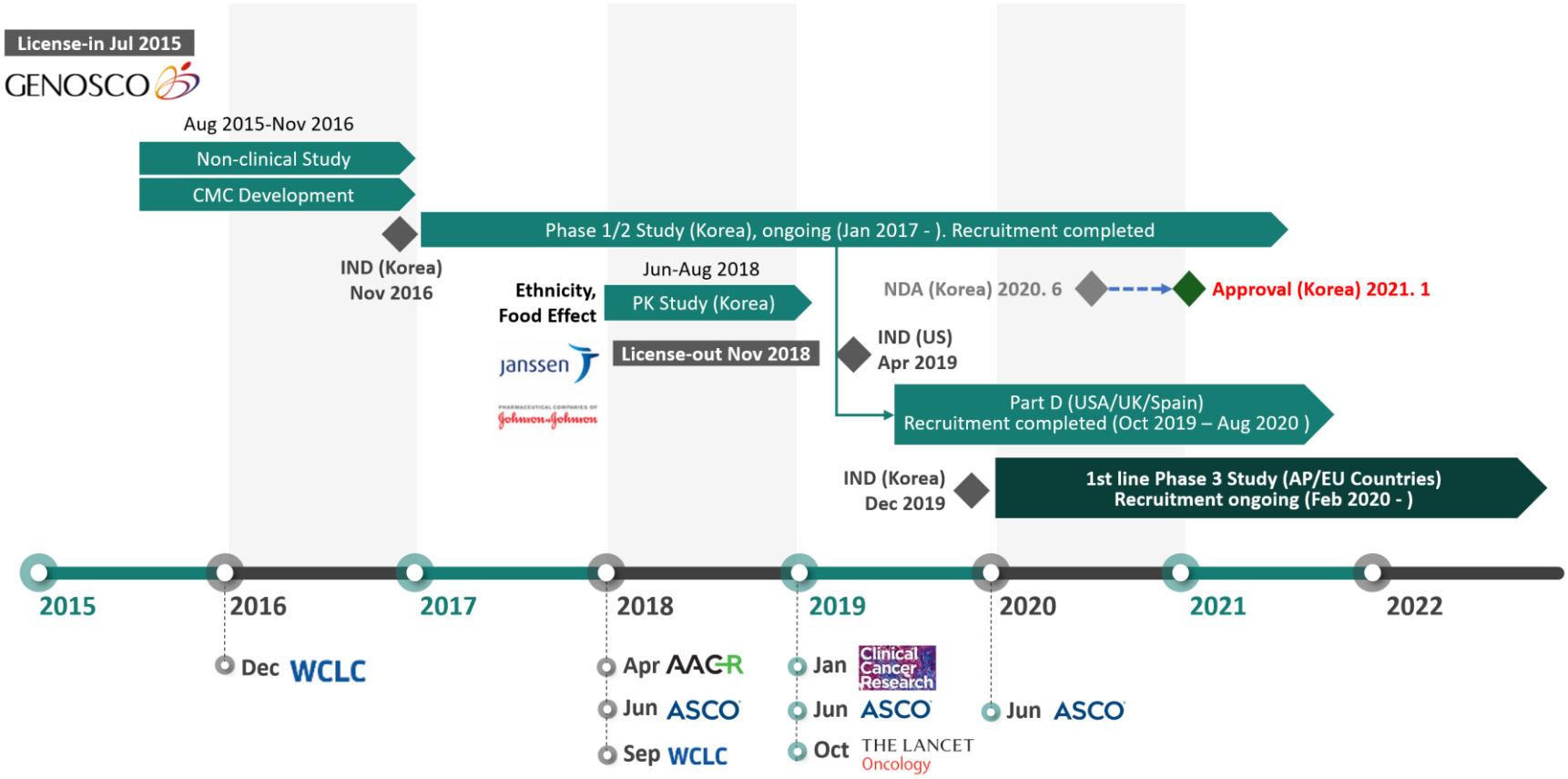
Rho JK, et al. Cancer Res 2017

Therapeutics, Targets, and Chemical Biology

Cancer Research

Superior Efficacy and Selectivity of Novel Small-Molecule Kinase Inhibitors of T790M-Mutant EGFR in Preclinical Models of Lung Cancer

Jin Kyung Rho[1,2,3], In Yong Lee[4], Yun Jung Choi[1,3], Chang-Min Choi[3,5], Jae-Young Hur[1,3], Jong Sung Koh[4], Jaekyoo Lee[4], Byung-Chul Suh[4], Ho-Juhn Song[4], Paresh Salgaonkar[4], Jungmi Lee[4], Jaesang Lee[6], Dong Sik Jung[6], Sang-Yeob Kim[1,2], Dong-Cheol Woo[1,2], In-Jeoung Baek[1,2], Joo-Yong Lee[1,2], Chang Hoon Ha[1,2], Young Hoon Sung[1,2], Jeong Kon Kim[7], Woo Sung Kim[3], Joon Seon Song[8], Cheol Hyeon Kim[9], Trever G. Bivona[10,11], and Jae Cheol Lee[5]



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Translational Cancer Mechanisms and Therapy

Clinical Cancer Research

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

Jiyeon Yun[1], Min Hee Hong[1,2], Seok-Young Kim[1], Chae-Won Park[1], Soyoung Kim[1], Mi Ran Yun[1,3], Han Na Kang[1,3], Kyoung-Ho Pyo[1], Sung Sook Lee[4], Jong Sung Koh[5], Ho-Juhn Song[5], Dong Kyun Kim[6], Young-Sung Lee[6], Se-Woong Oh[6], Soongyu Choi[6], Hye Ryun Kim[1,2], and Byoung Chul Cho[1,2,3]

- **Leclaza® selectively inhibited mutated EGFR rather than wild type EGFR**
- **Major metabolite of Leclaza® was also selective**

Ba/F3_EGFR	IC_{50}, nM		
	YH25448	Osimertinib	Gefitinib
Wild type (Normal)	722.7	519.1	585.3
Del19	3.3	3.5	10.2
L858R	3.9	3.6	71.1
Del19/T790M	4.9	3.4	769.9
L858R/T790M	5.7	4.3	7628.2

* IC_{50}: 50% inhibitory concentration

Clin Cancer Res 2019; 25(8): 2575

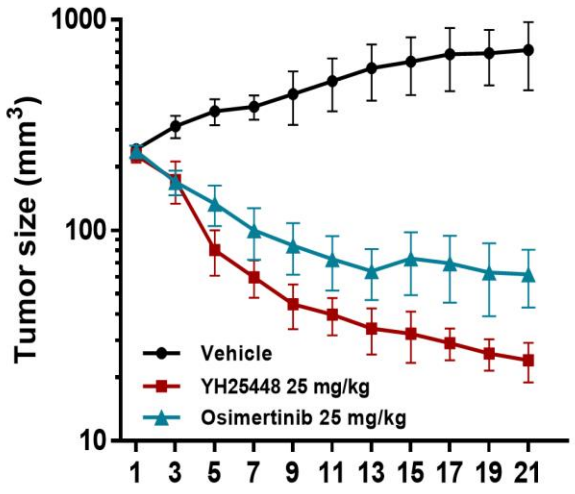
EGFR kinase Genotype	YH25448	[a] YH26334	Osimertinib	[b] AZ5104
EGFR (wild type)	**60**	**91**	**20**	**0.98**
EGFR (G719C)	1.7	4.8	65	4.2
EGFR (G719S)	4.1	9.3	49	3.2
EGFR (E746-A750del)	0.43	1.8	3.7	0.69
EGFR (L747-E749del, A750P)	14	38	3.2	0.53
EGFR (L747-S752del, P753S)	14	16	4.4	0.39
EGFR (L747-T751del, 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

* YH26334: Metabolite of Leclaze®
* AZ5104: Metabolite of osimertinib

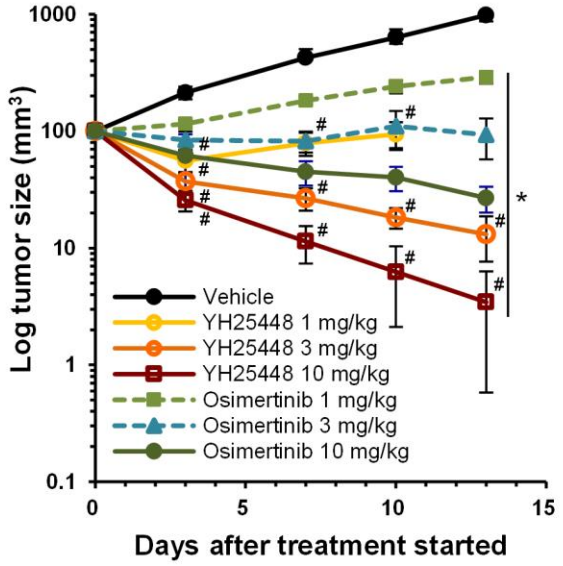
Yun et al. *Clin Cancer Res.* 2019 Apr 15;25(8):2575-2587.

Leclaza® was effective in both single(Del19) and double(L858R/T790M) mutant models

Del19 Mutation



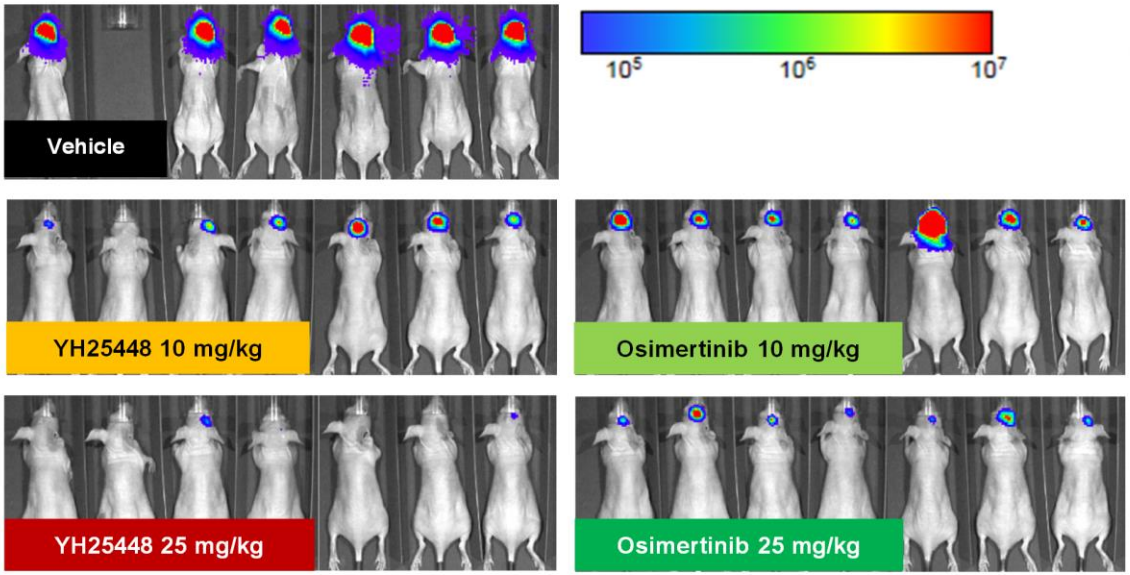
L858R/T790M



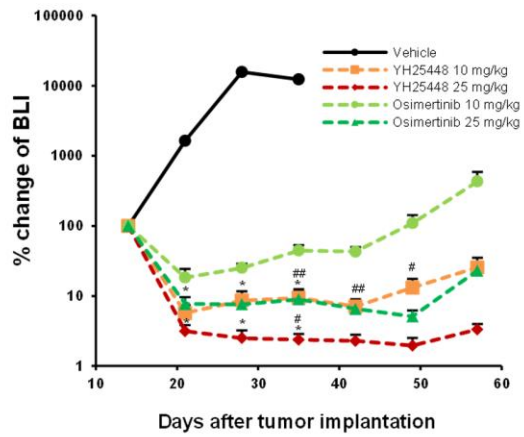
Yun et al. *Clin Cancer Res.* 2019 Apr 15;25(8):2575-2587.

Leclaza® showed great anti-tumor efficacy in brain metastasis animal model

Day 28

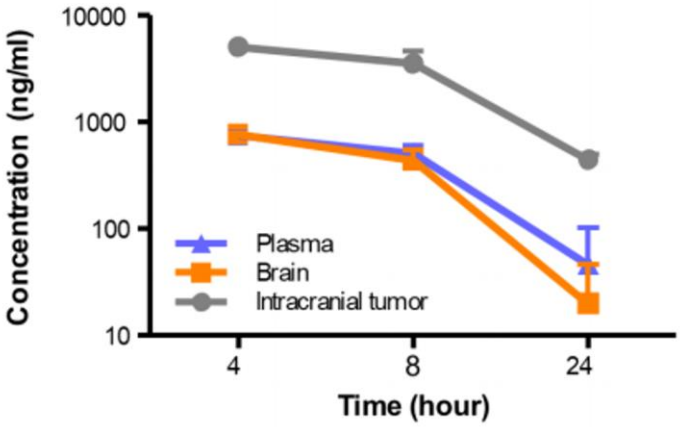


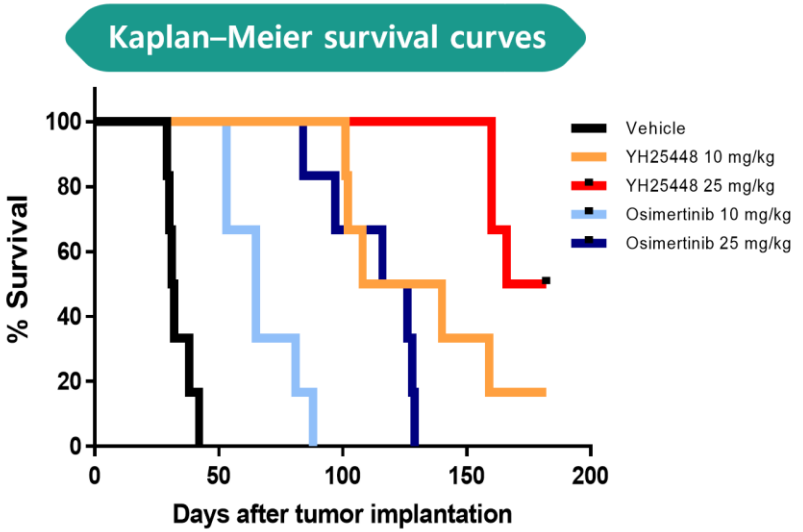
Intracranial tumor size



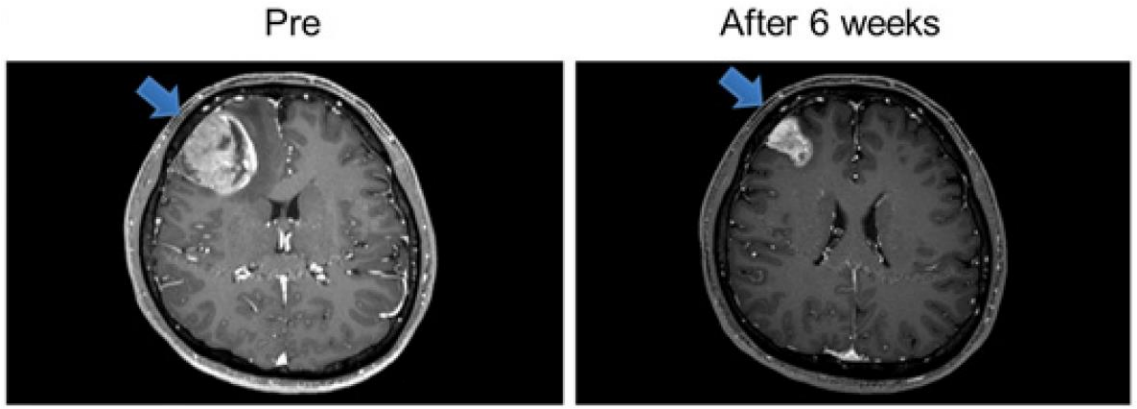
Yun et al. *Clin Cancer Res.* 2019 Apr 15;25(8):2575-2587.

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



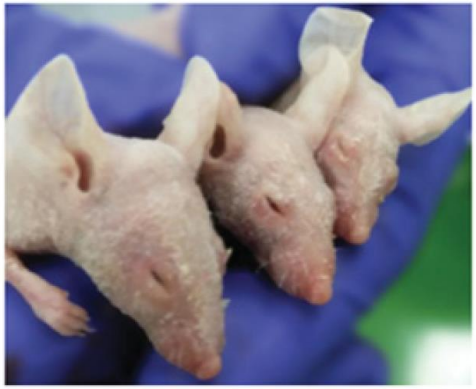


Experiment in H1975(L858R/T790M) –luc brain metastasis model



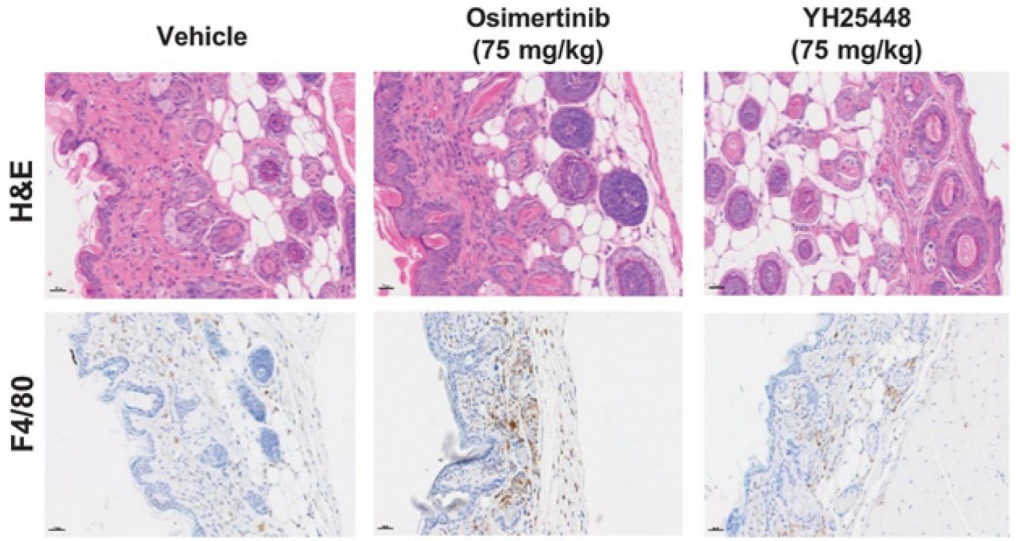
Yun J, et al. Clin Caner Res 2019

YH25448



Osimertinib

Groups	Clinical signs	Severity	Observed regions
Vehicle	-	-	-
YH25448 (50 mg/kg)	-	-	-
YH25448 (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)



Yun J, et al. Clin Caner Res 2019

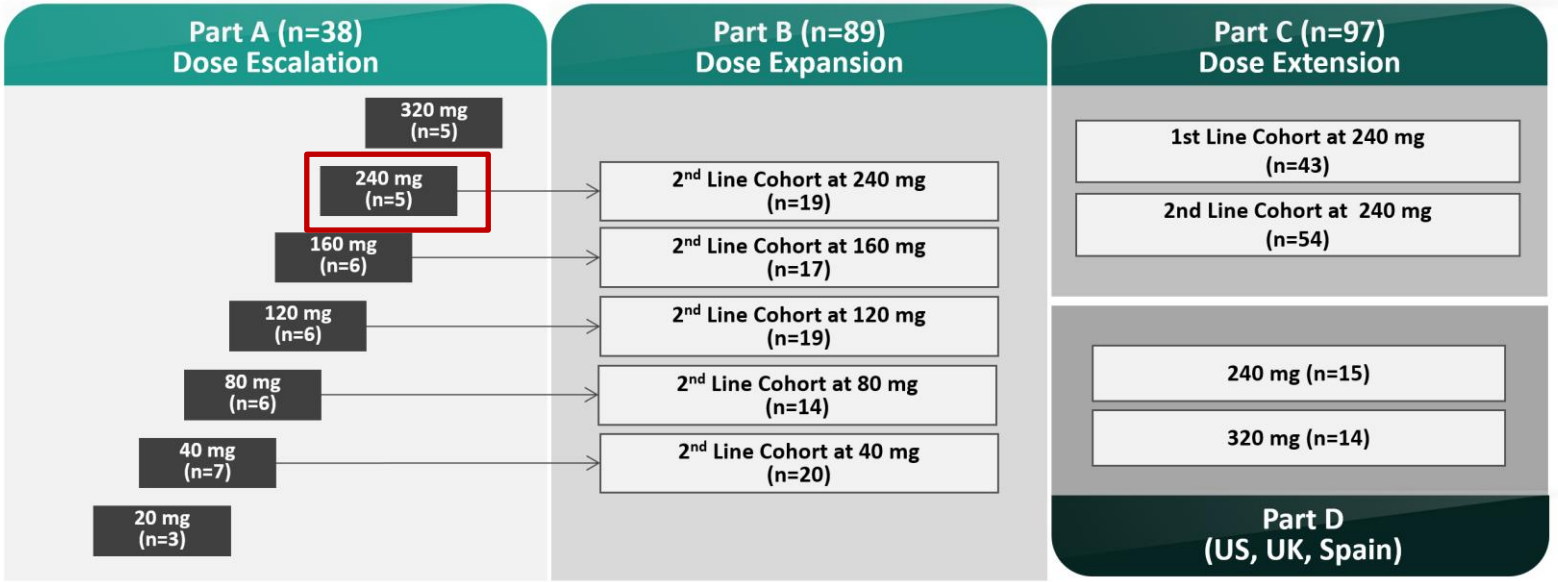
Lazertinib in patients with *EGFR* mutation-positive advanced non-small-cell lung cancer: results from the dose escalation and dose expansion parts of a first-in-human, open-label, multicentre, phase 1–2 study

Lancet Oncol 2019; 20: 1681–90

Study Design of Phase 1/2 Study (No. YH25448-201)

- 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 objective: 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)



YH25448-201 Clinical Study Report Ver2.2 (Date of DCO 30 Sep 2019)

Data on file. Yuhan

Baseline Characteristics

	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, 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	0	13 (48)	10 (50)	12 (38)	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 or Invalid or Not Done	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, 2)	1 (1, 2)	1 (1, 2)	1 (1, 1)	1 (1, 2)
Previous EGFR-TKI therapy[#], 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	2 (8)	0	0	0	3 (2)
Medical history with Cardiac disorder, n(%)	1 (33)	3 (11)	0	4 (16)	1 (4)	1 (1)	0	10 (6)

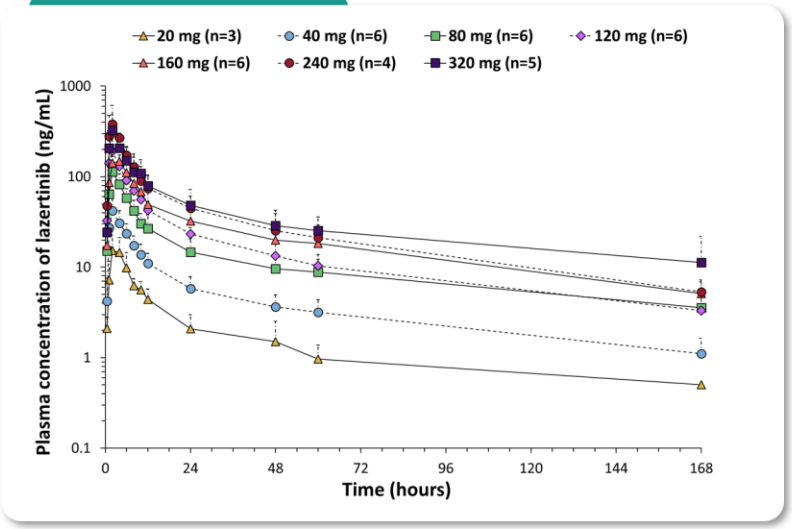
YH25448-201 Clinical Study Report Ver2.2 (Date of DCO 30 Sep 2019)

DCO: 30 Sep 2019

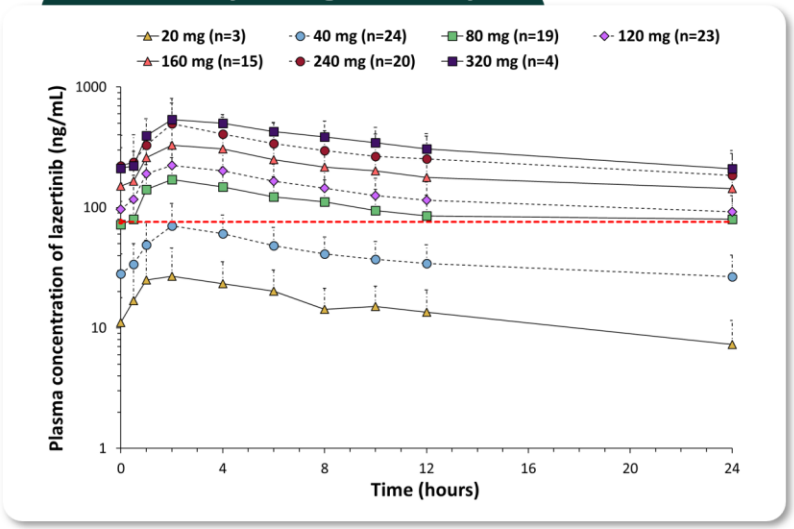
Mean Plasma Concentration Profiles of Leclaza®

- Mean terminal half-life of Leclaza® was approximately 65 hours after single dosing of 240 mg.
- Systemic exposures of Leclaza® 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 Leclaza®.

Single dosing



Once daily dosing for 22 days



Data : arithmetic mean + standard deviation with semi-logarithmic ordinate scale.
Red dashed line : IC_{50} value (75.8 ng/mL) of EGFR phosphorylation in H1975 cell line (corrected by free drug concentration).

YH25448-201 Clinical Study Report Ver2.2 (Date of DCO 30 Sep 2019)

Anti-tumor Response: 2L T790M+ Patients

ICR assessment results – Confirmed response rate

	2L (T790M+)						
	20 mg (n=2)	40 mg (n=26)	80 mg (n=18)	120 mg (n=22)	160 mg (n=18)	240 mg (n=76)	Overall (N=162)
Evaluable patients[a]	**2**	**26**	**18**	**22**	**18**	**76**	**162**
Best overall response[b], **n (%)**							
Complete response	0	1 (4)	0	1 (5)	0	2 (3)	4 (2)
Partial response	1 (50)	14 (54)	10 (56)	13 (59)	12 (67)	42 (55)	92 (57)
Stable disease	1 (50)	9 (35)	7 (39)	7 (32)	1 (6)	24 (32)	49 (30)
Progressive disease	0	1 (4)	1 (6)	1 (5)	4 (22)	6 (8)	13 (8)
Not evaluable	0	1 (4)	0	0	1 (6)	2 (3)	4 (2)
DCR[c], n (%)	2 (100)	24 (92)	17 (94)	21 (95)	13 (72)	68 (89)	145 (90)
ORR[d], n (%)	1 (50)	15 (58)	10 (56)	14 (64)	12 (67)	**44 (58)**	96 (59)
Time to first response[e] (weeks), median (range)	6 (6-6)	5.6 (5.0-77.3)	6.1 (4.3-23.1)	6.0 (5.1-11.9)	5.4 (5.1-11.3)	5.7 (5.1-35.1)	5.7 (4.3-77.3)

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.
b Best overall response is based on investigator's assessment of disease status or lesion measurements using RECIST v1.1.
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 complete response (CR) or partial response (PR).
e Time to first response is measured from the first multiple dose date (cycle 1 day 1) until the date of the first documented response (complete response or partial response, whichever occurs first).
DCO: 30 Sep 2019

YH25448-201 Clinical Study Report Ver2.2 (Date of DCO 30 Sep 2019)

Anti-tumor Response: 2L T790M+ Patients

ICR assessment results – Time to event

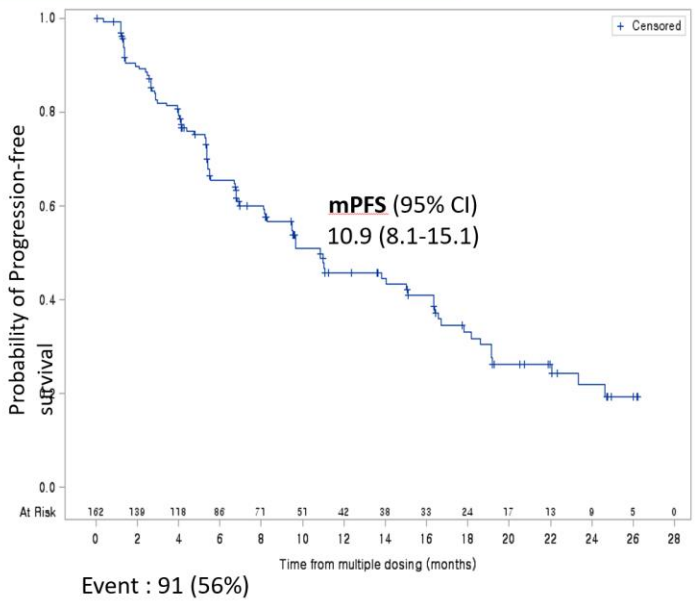
	2L (T790M+)						
	20 mg (n=2)	40 mg (n=26)	80 mg (n=18)	120 mg (n=22)	160 mg (n=18)	240 mg (n=76)	Overall (N=162)
Evaluable patients[a]	**2**	**26**	**18**	**22**	**18**	**76**	**162**
Duration of follow-up (months), median (IQR)†	7.5 (6.9-8.1)	24.9 (9.6-26.0)	24.8 (24.7-26.0)	22.0 (9.5-22.3)	20.7 (20.7-21.9)	9.5 (5.5-15.1)	16.4 (7.0-24.7)
Number of event, n (%)	2 (100)	16 (62)	11 (61)	12 (55)	15 (83)	35 (46)	91 (56)
Number of censored, n (%)	0	10 (38)	7 (39)	10 (45)	3 (17)	41 (54)	71 (44)
Censored before DCO	0	7 (27)	3 (17)	6 (27)	1 (6)	10 (13)	27 (17)
Censored at DCO	0	3 (12)	4 (22)	4 (18)	2 (11)	31 (41)	44 (27)
DoR[b] (months), median (95% CI)#	9.7	15.2 (3.5-NR)	8.6 (2.8-NR)	15.2 (5.7-22.1)	16.6 (6.9-17.9)	13.8 (9.6-NR)	15.2 (9.7-17.6)
PFS[c] (months), median (95% CI)#	6.9 (2.7-11.0)	6.9 (5.3-24.6)	6.7 (2.7-NR)	15.1 (8.3-23.3)	14.0 (1.4-19.2)	**11.0 (5.6-16.4)**	10.9 (8.1-15.1)

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.
b Duration of objective response is measured from the date of the first documented response until objective tumor progression or death, whichever occurs first.
c 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 and IQR are calculated using reverse Kaplan-Meier estimate; # Median and 95% CI are calculated using Kaplan-Meier estimate.
DCO: 30 Sep 2019

Progression-free Survival: 2L T790M+ Patients

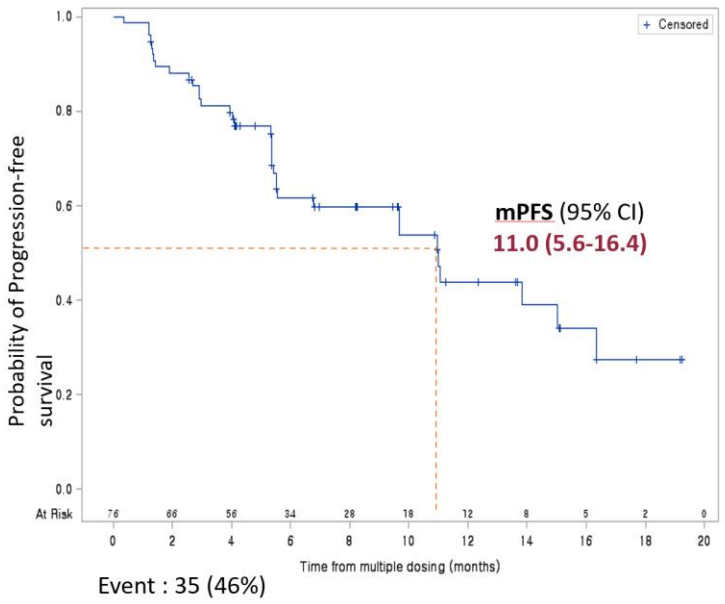
ICR assessment results

2L T790M+, Overall (n=162)



Event : 91 (56%)

2L T790M+, 240 mg (n=76)



Event : 35 (46%)

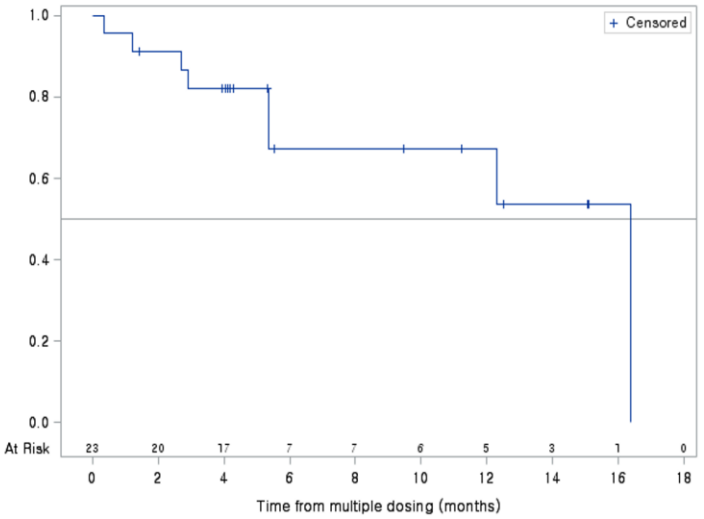
DCO: 30 Sep 2019

Intracranial Efficacy Results

T790M+ patients	Leclaza® 20~240 mg (N=162)		Leclaza® 240 mg (N=76)	
Assessment by	Independent	Investigator	Independent	Investigator
Patients with evaluable brain lesion	55	81	23	39
Duration of follow-up (month), median (IQR)	10.9 (4.2-20.5)	8.4 (5.3-16.4)	5.5 (4.2-12.5)	6.8 (4.2-10.9)
Intracranial PFS (months), median (95% CI)	**NR** (14.0-NR)	**NR** (16.7-NR)	**16.4** (5.4-16.4)	**NR**
Patients with measurable brain lesion	18	19	7	9
Intracranial ORR, n(%)	9 (50)	12 (63)	5 (71)	7 (78)

PFS = Progression-free survival; CI = Confidence Interval; NR = Not reached; ORR = objective response rate;
DCO: 30 Sep 2019

ICR review (240 mg)



YH25448-201 Clinical Study Report Ver2.2 (Date of DCO 30 Sep 2019)

Data on file. Yuhan

Overall Safety Results

Patients with TEAEs, n (%)	Leclaza® 20-320 mg (N=181)	Leclaza® 240 mg (N=78)
TEAEs	171 (94)	75 (96)
Drug related TEAEs	141 (78)	68 (87)
Serious TEAEs	37 (20)	14 (18)
Drug related serious TEAEs	6 (3)	3 (4)
TEAEs with grade ≥ 3	45 (25)	22 (28)
Drug related TEAEs with grade ≥ 3	9 (5)	6 (8)
TEAEs leading to Death	3 (2)	3 (4)
TEAEs leading to Dose reduction	15 (8)	10 (13)
TEAEs leading to Dose interruption	31 (17)	14 (18)
TEAEs leading to Treatment discontinuation	7 (4)	4 (5)

†Grouped term: Folliculitis, Rash, Rash erythematous, Rash macular, Rash maculo-papular, Rash popular, Erythema, Dermatitis acneiform.
Drug related TEAEs are events with relationship certain, probable/likely, possible, unassessable/unclassifiable, or missing.
DCO: 30 Sep 2019

TEAEs Occurring ≥ 10% of All Patients

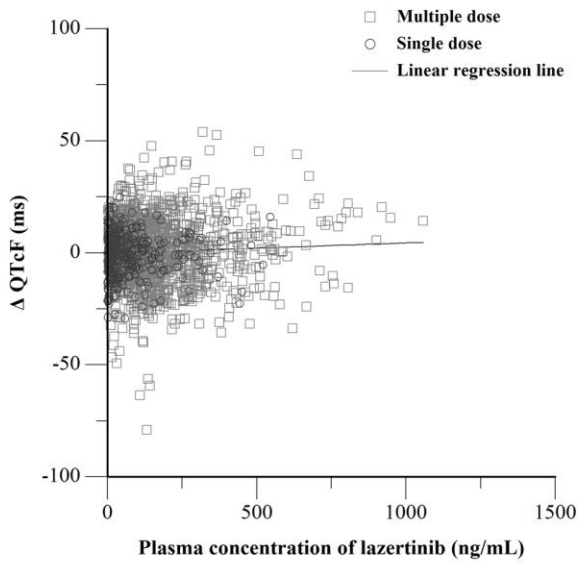
Patients with TEAEs, n (%)	20 mg (n=3)	40 mg (n=27)	80 mg (n=20)	120 mg (n=25)	160 mg (n=23)	240 mg (n=78) All grade	240 mg (n=78) Grade ≥3	320 mg (n=5)	Overall (N=181) All grade	Overall (N=181) Grade ≥3
Rash	0	6 (22)	2 (10)	8 (32)	7 (30)	27 (35)	1 (1)	2 (40)	52 (29)	1 (1)
Pruritus	0	5 (19)	4 (20)	6 (24)	8 (35)	26 (33)	0	1 (20)	50 (28)	0
Constipation	1 (33)	5 (19)	7 (35)	6 (24)	6 (26)	13 (17)	0	2 (40)	40 (22)	0
Paraesthesia	1 (33)	3 (11)	2 (10)	5 (20)	2 (9)	25 (32)	0	0	38 (21)	0
Decreased appetite	1 (33)	4 (15)	3 (15)	2 (8)	6 (26)	16 (21)	0	2 (40)	34 (19)	0
Diarrhoea	0	4 (15)	2 (10)	4 (16)	5 (22)	17 (22)	1 (1)	1 (20)	33 (18)	1 (1)
Headache	1 (33)	3 (11)	2 (10)	4 (16)	1 (4)	19 (24)	0	0	30 (17)	0
Nausea	1 (33)	3 (11)	2 (10)	4 (16)	3 (13)	12 (15)	0	1 (20)	26 (14)	2 (1)
Muscle spasms	0	1 (4)	2 (10)	1 (4)	1 (4)	20 (26)	0	0	25 (14)	0
Cough	2 (67)	2 (7)	3 (15)	3 (12)	1 (4)	12 (15)	0	1 (20)	24 (13)	0
Paronychia	1 (33)	1 (4)	1 (5)	4 (16)	3 (13)	13 (17)	1 (1)	0	23 (13)	1 (1)
Fatigue	1 (33)	2 (7)	2 (10)	3 (12)	2 (9)	12 (15)	0	0	22 (12)	0
Vomiting	1 (33)	1 (4)	1 (5)	5 (20)	4 (17)	8 (10)	1 (1)	0	20 (11)	2 (1)

TEAE: Treatment-Emergent Adverse Event
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).
Percentages are based on the total number of patients in the safety analysis population within relevant dose level.
Patients with two or more adverse events with the same AE term is counted only once for that AE term.

DCO: 30 Sep 2019

Relationship between Concentration and △QTcF

- Mean ΔQTcF at Cmax,ss of 240 mg was 2.2 ms with the upper bound of 3.6 ms (95% one-sided CI).
- Leclaza® has no clinically relevant effect on QTc interval.



Predicted ΔQTcF at $C_{max,ss}$ 517.15 ng/mL of 240 mg

	Mean	Upper bound of the 95% one-sided CI
ΔQTcF	2.2 ms	3.6 ms

Dose levels of Leclaza® : 20-320 mg
Number of patients: 178 for 2nd line
DCO: 30 Sep 2019

ICH E14 Clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs:
A negative "thorough QT/QTc study" is one in which the upper bound of the 95% one-sided confidence interval for the largest time-matched mean effect of the drug on the QTc interval excludes 10 ms. This definition is chosen to provide reasonable assurance that the mean effect of the study drug on the QT/QTc interval is not greater than around 5 ms.

YH25448-201 Clinical Study Report Ver2.2 (Date of DCO 30 Sep 2019)

Data on file. Yuhan

Conclusions

- Leclaza® 240 mg showed the promising antitumor efficacy by ICR assessment.
  - The confirmed ORR and median PFS were 58% and 11.0 months in the T790M+ patients.
  - The confirmed intracranial ORR and iPFS were 71% and 16.4 months in the T790M+ patients.
- Leclaza® showed a tolerable safety profile.
  - No DLT was observed up to Leclaza® 320 mg.
  - Any drug related TEAEs of CTCAE grade ≥ 3 were observed in 5% of patients.
  - There was no clear evidence of a dose-dependent increase in the incidence of TEAEs.
- In conclusion, Leclaza® was demonstrated promising antitumor activity with a tolerable safety profile in EGFR T790M+ NSCLC patients.
- Ingestion of food and ethnicity did not affect systemic exposure of Leclaza® in Phase 1 study.
- Phase 3 studies for 1L Leclaza® monotherapy and combination with amivantamab are underway.

Label of Leclaza®

렉라자®정 80mg

성분명	▪ **레이저티닙메실산염일수화물**
성상	▪ 노란색의 원형 필름코팅정
효능·효과	▪ 이전에 **EGFR-TKI로 치료받은 적이 있는 EGFR T790M 변이 양성** 국소 진행성 또는 전이성 비소세포폐암 환자의 치료
용법/용량	▪ 이 약의 권장 용량은 1일 1회 240mg(80mg, 3정)이며 매일 일정한 시간에 식사와 관계없이 경구 복용한다. 질병의 진행 또는 수용할 수 없는 독성이 나타날 때까지 복용을 지속한다. ▪ 용량 감소가 필요한 경우, 이 약의 용량은 1일 1회 160mg(80mg, 2정)로 감량되어야 한다.

렉라자정 허가사항. 식품의약품안전처 의약품통합정보시스템.

thank you!