2022 동계 분자폐암연구회
임상연구 워크샵

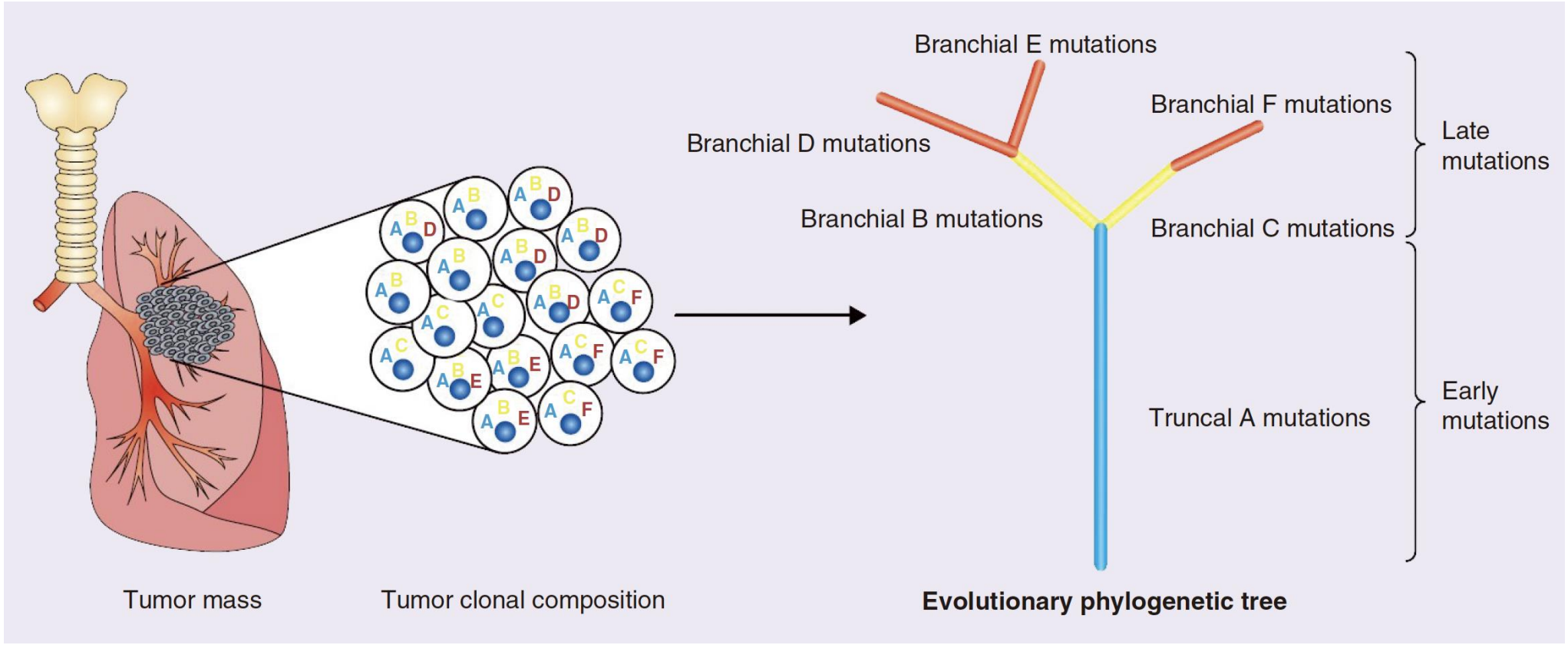
연세의대 김은영

Biology and Prognostic Biomarkers

Introduction

- Treatment response is not uniform for each patient in EGFR-mutant lung cancer.

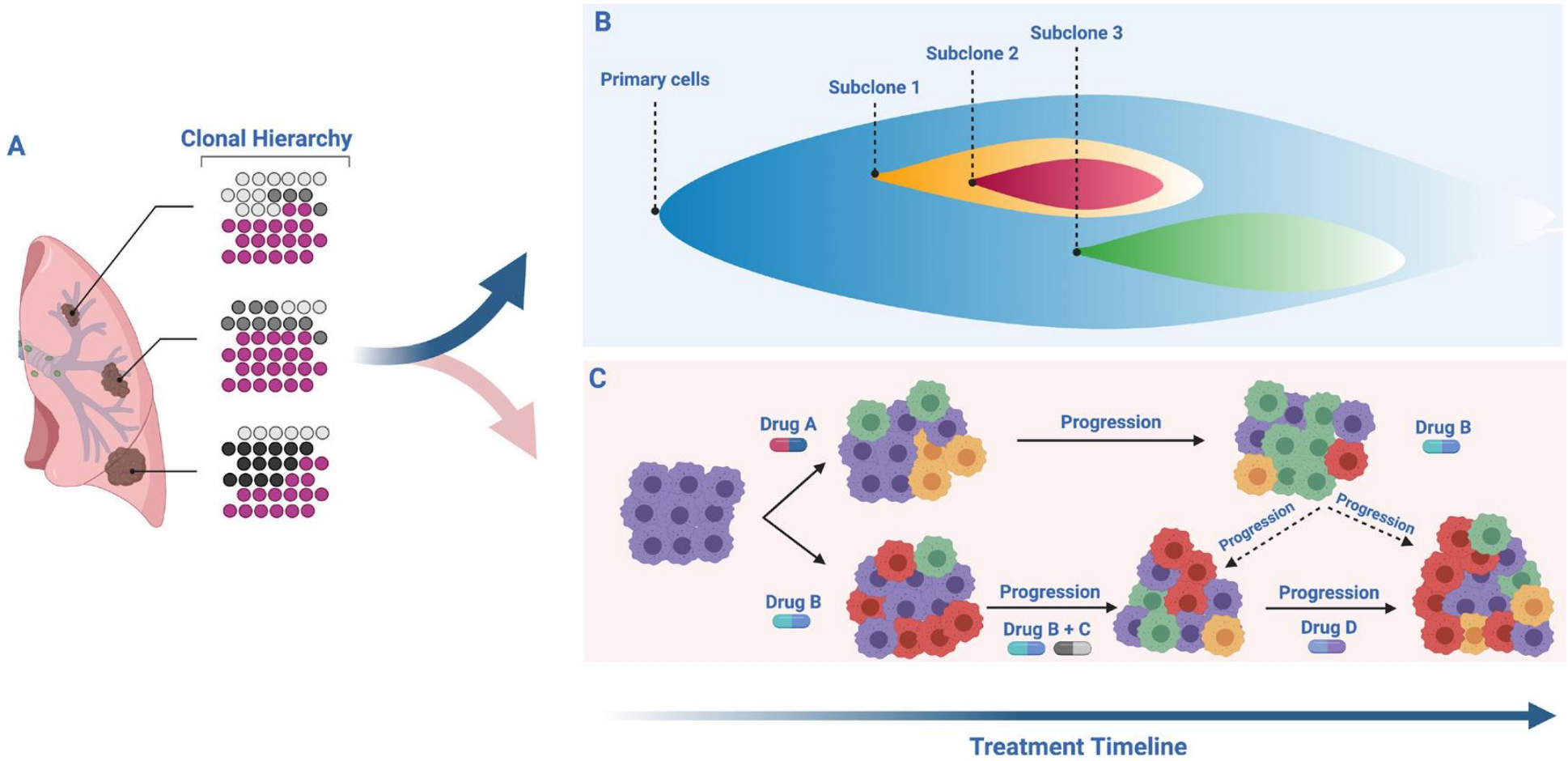
- Ununiform treatment responses suggest that a treatment strategy based on *molecularly defined subgrouping* through in-depth analysis of molecular heterogeneity is needed in clinics.



✓ These genetic diversification, clonal expansion, and selection are highly variable, forming various biological entities of tumors and eventually leading to treatment failure.

Kohsaka, Shinji, et al. Future Oncology 15.6 (2019): 637-652. Passaro, Antonio, et al. ESMO open 5.5 (2020): e000919.

Clonal evolution through epidermal growth factor receptor-targeted therapy



✓ Genetic diversification, clonal expansion and selection are highly variable patterns of genetic diversity, resulting in different biological entities, also a prerequisite for Darwinian selection and therapeutic failure.

Passaro, Antonio, et al. ESMO open 5.5 (2020): e000919.

Commentary

Co-mutations in EGFR driven non-small cell lung cancer

Rafael Rosell [a,*], Niki Karachaliou [b]

[a] Germans Trias i Pujol Research Institute and Hospital, Badalona, Spain
[b] Merck KgaA, Darmstadt, Germany

- ✓ The selected 71 of 423 patients with EGFR mutations treated with first-generation EGFR TKIs were selected based on the differences in PFS.

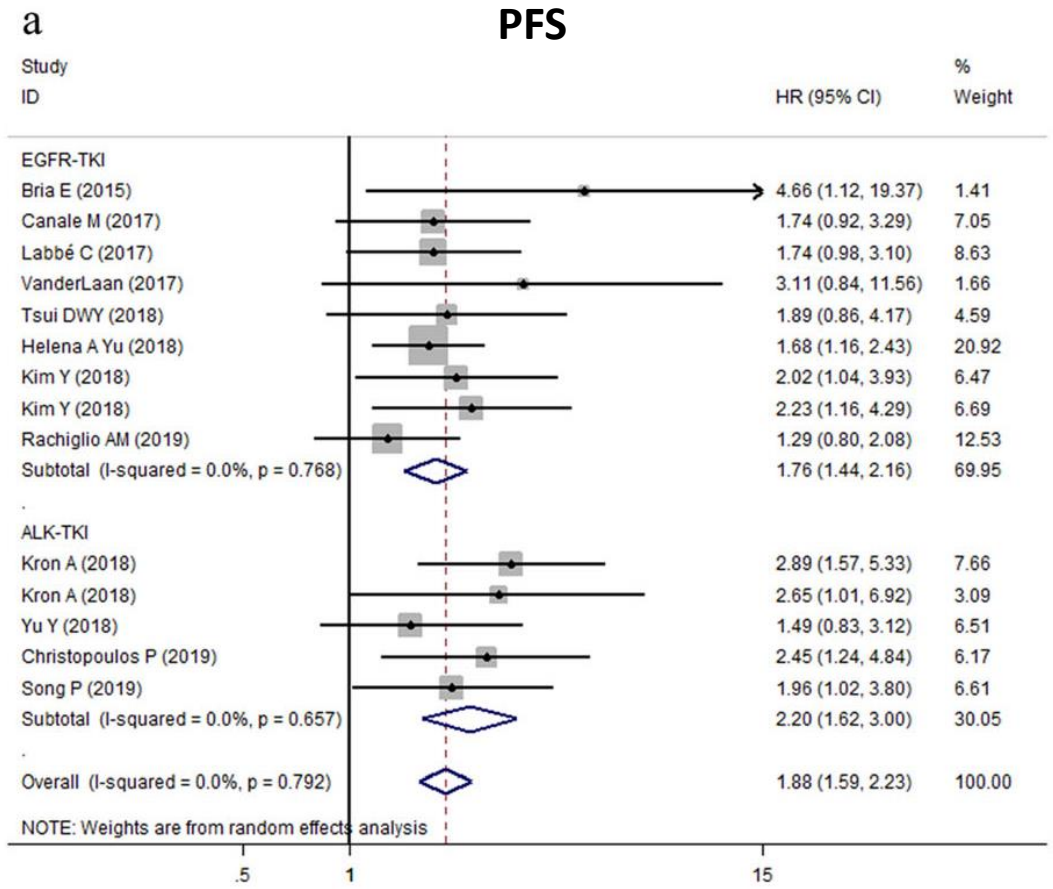
EGFR-TKI response is expected to be closely linked to tumor heterogeneity caused by *compound EGFR mutations*, *other genetic alterations*, and *differences in the immune environment*.

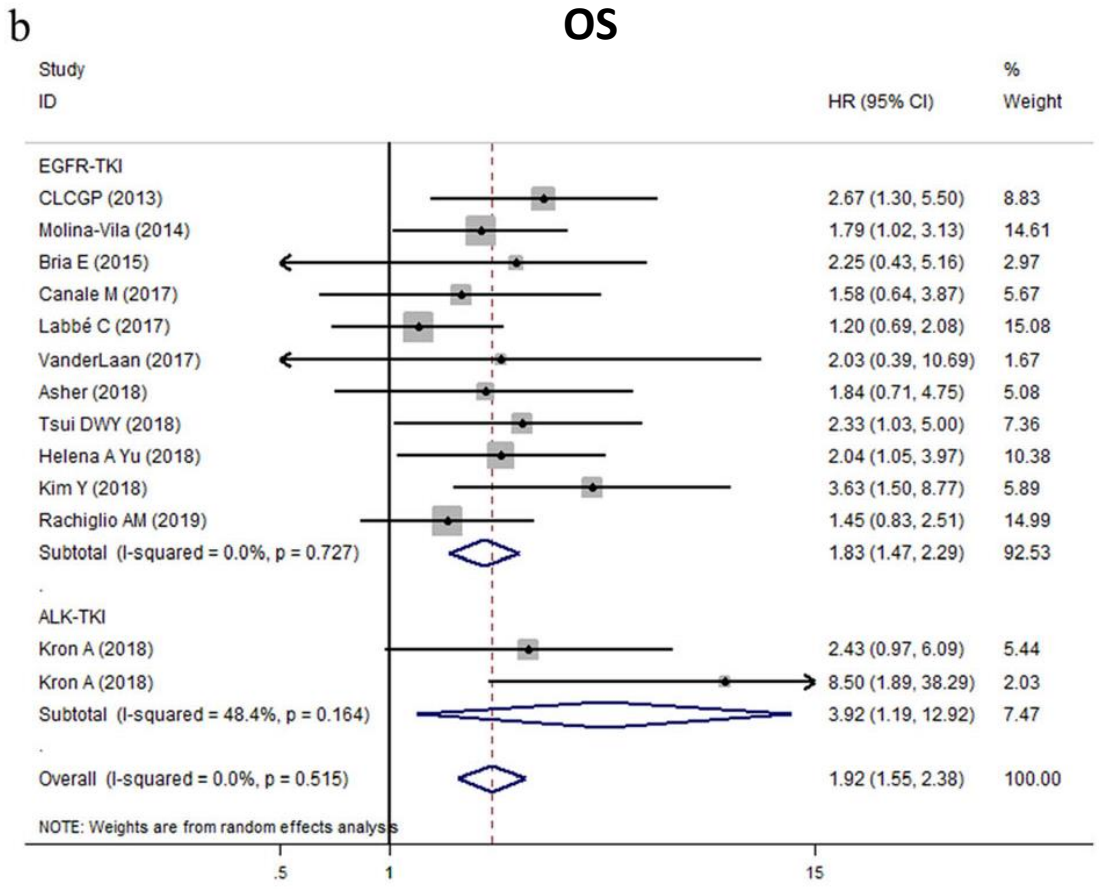
PFS > 24 mo, n = 41

PFS < 6 mo, n = 30

	Long PFS group		Short PFS group		P
	No.	Percent (%)	No.	Percent (%)	
21L858R	25	61%	18	60%	1·000
19 Del	17	41%	13	43%	1·000
Del746–750	14	82%	7	54%	0·121
Complex EGFR mutations	9	22%	13	43%	0·071
T790M mutation	4	10%	8	27%	0·106
Co-occurring driver gene mutation	4	10%	10	33%	0·018
Number of mutations	7.63 ± 0.50		8·43 ± 0·65		0·314
EGFR pathway related mutations	1.51 ± 0.19		1·37 ± 0·18		0·652
Non EGFR pathway mutations	4.83 ± 0.41		5·57 ± 0·59		0·337
TP 53 mutations	22	54%	20	67%	0·332
TP53 missense mutation	11	27%	14	47%	0·131
RB1 mutations	5	12%	5	16%	0·733
PIK3CA missense mutation	0	–	3	10%	0·071
MAP2K2	6	15%	0	–	0·036
EGFR amplification	6	15%	7	23%	0·371
BIM polymorphism	4	10%	4	13%	0·714

Chen, Minjiang, et al. EBioMedicine 42 (2019): 304-310.

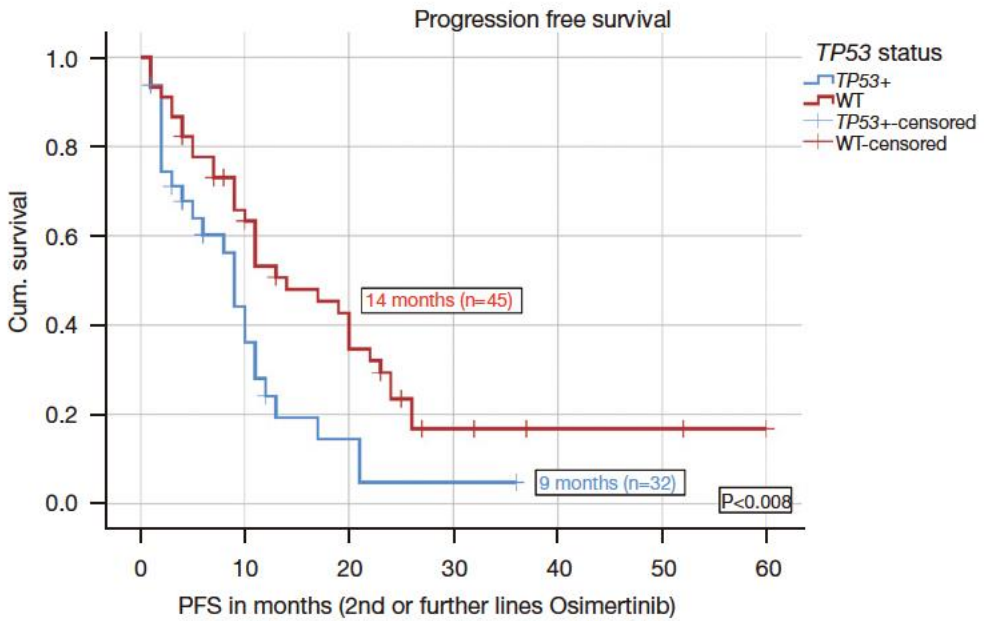


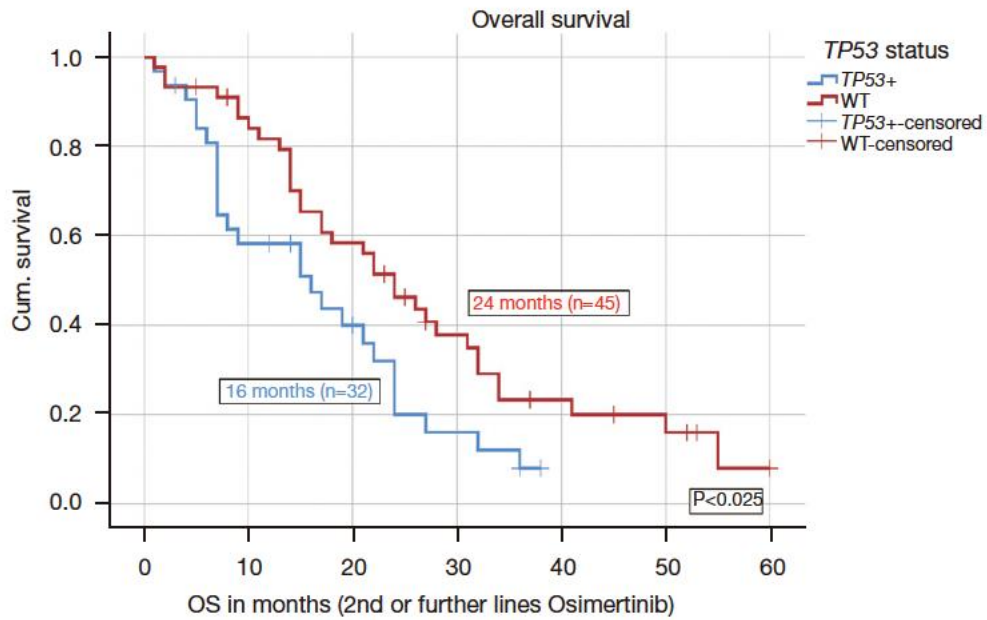


- ✓ 15 studies with 1,342 EGFR mutant patients
- ✓ *TP53 mutations was a negative prognostic factor* and associated with poorer outcomes of patients with EGFR-TKIs.
  PFS: HR = 1.88, 95%CI: 1.59–2.23, p < 0.001, I2 = 0.0%, P =0.792
  OS: HR = 1.92, 95%CI: 1.55–2.38, p < 0.001, I2 = 0.0%, P = 0.515

- ✓ TP53 mutations might be involved in primary resistance to EGFR-TKIs.

Qin, Kang, et al. BMC cancer 20.1 (2020): 1-16.



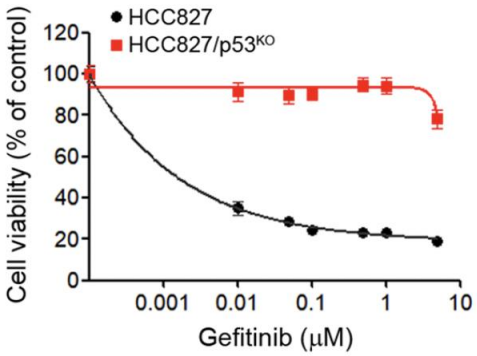


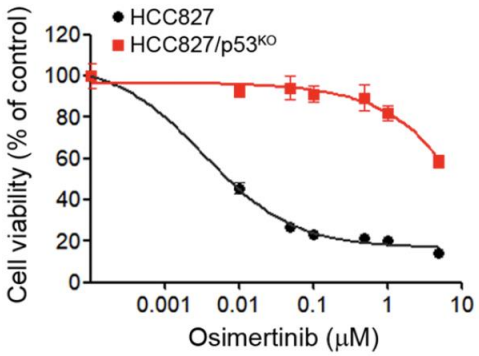
- ✓ PFS and OS of Osimertinib in 2nd/further lines depending on TP53 status.
- ✓ *TP53 mutation* was a statistically significant independent *negative predictive factor* for PFS and OS in 2nd/further lines osimertinib treatment.

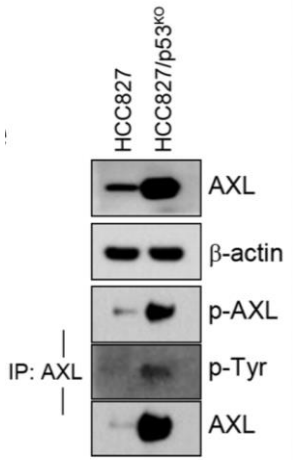
Transl Lung Cancer Res 2022;11(1):4-13

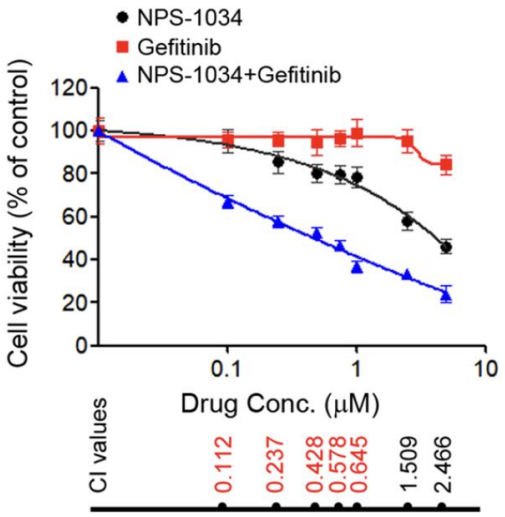
Contribution of p53 in sensitivity to EGFR tyrosine kinase inhibitors in non-small cell lung cancer

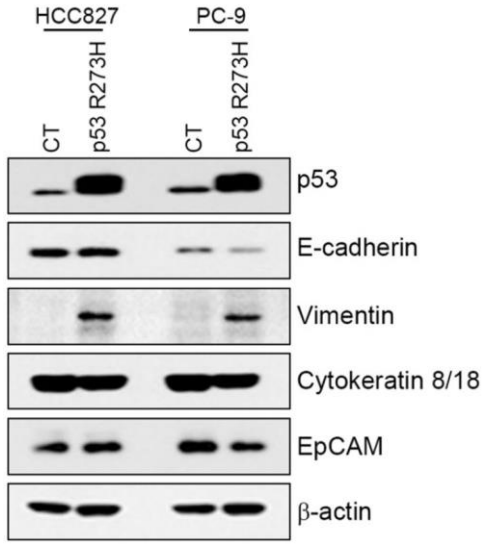
Sangyong Jung[1,6], Dong Ha Kim[2,6], Yun Jung Choi[2], Seon Ye Kim[2], Hyojeong Park[1], Hyeonjeong Lee[1], Chang-Min Choi[3], Young Hoon Sung[4], Jae Cheol Lee[5]✉ & Jin Kyung Rho[4]✉

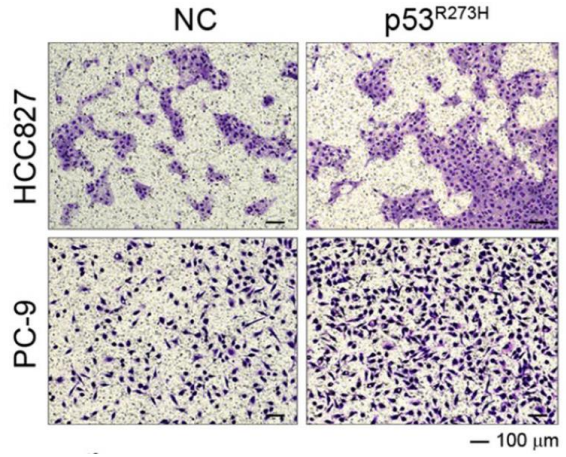


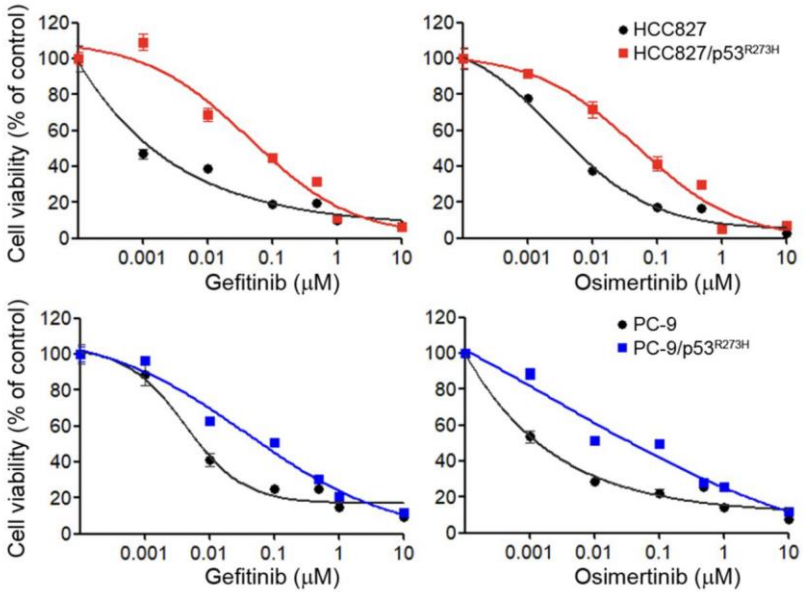












Jung, Sangyong, et al. Scientific reports 11.1 (2021): 1-10.

Summary 1

- TP53 mutation can affect both primary and acquired resistance to EGFR-TKIs.

- Co-occurring driver mutation such as BRAF, HER2, and MET,
  as well as other genetic alterations such as TP53 and PIK3CA,
  should be considered in efforts to improve the therapeutic efficacy of EGFR-TKIs
  for NSCLC.

EGFR mutation subtype and compound EGFR mutation

compound EGFR mutation

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Compound EGFR mutations are defined as **double or multiple independent mutations of the EGFR tyrosine kinase domain (TKD)**, in which an EGFR-TKI-sensitizing or other mutation is identified together with a mutation of unclarified clinical significance. Jan 19, 2016

https://www.ncbi.nlm.nih.gov › articles › PMC4848002

Compound EGFR mutation is frequently detected with ... - NCBI

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People also ask

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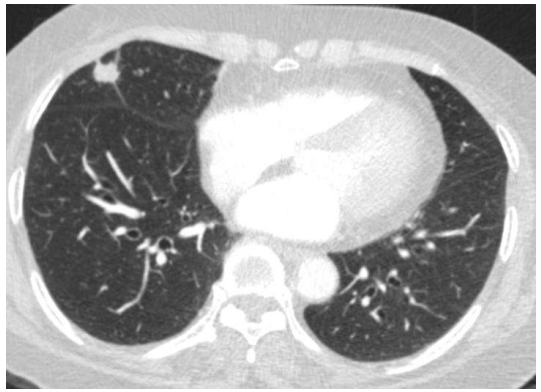
Can EGFR mutation be cured?

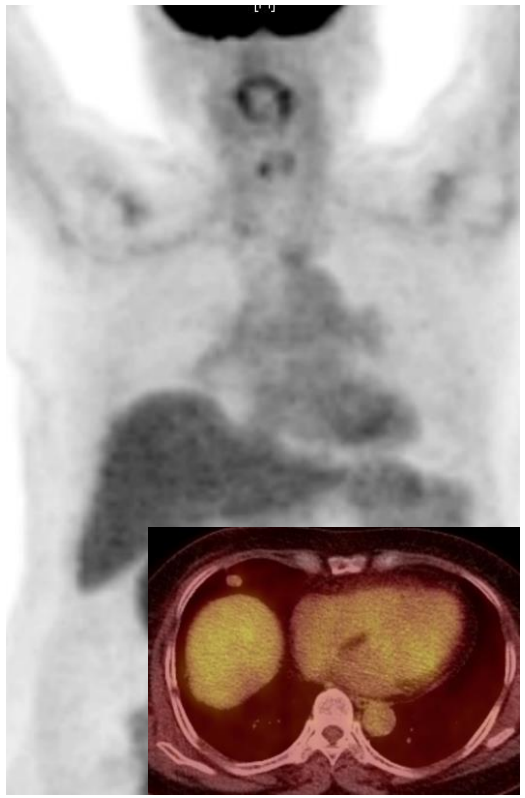
What are EGFR mutations?

What causes EGFR to mutate?

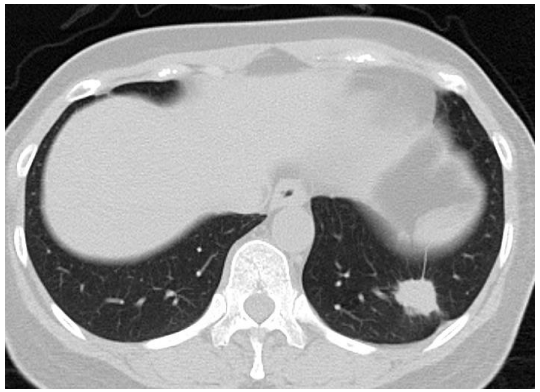
Feedback

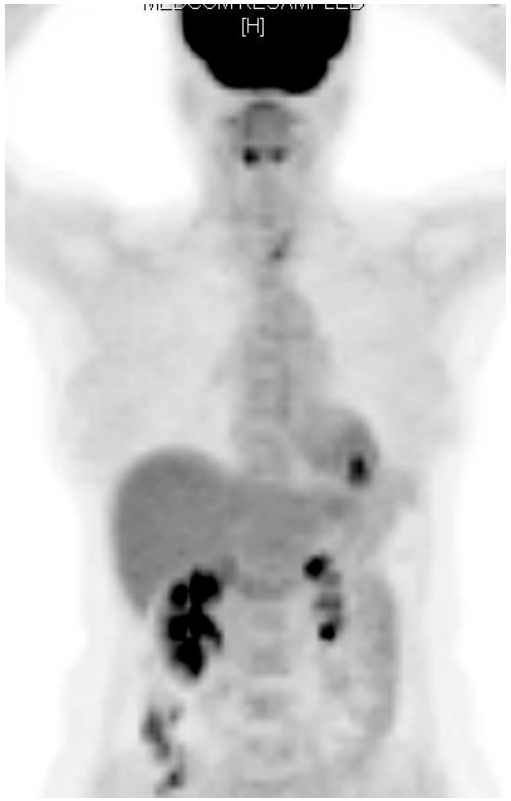
F/73, never smoker,
1.6cm adenoca,
cT1bN0M0



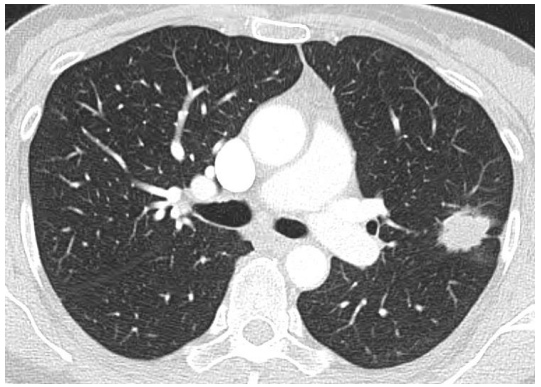


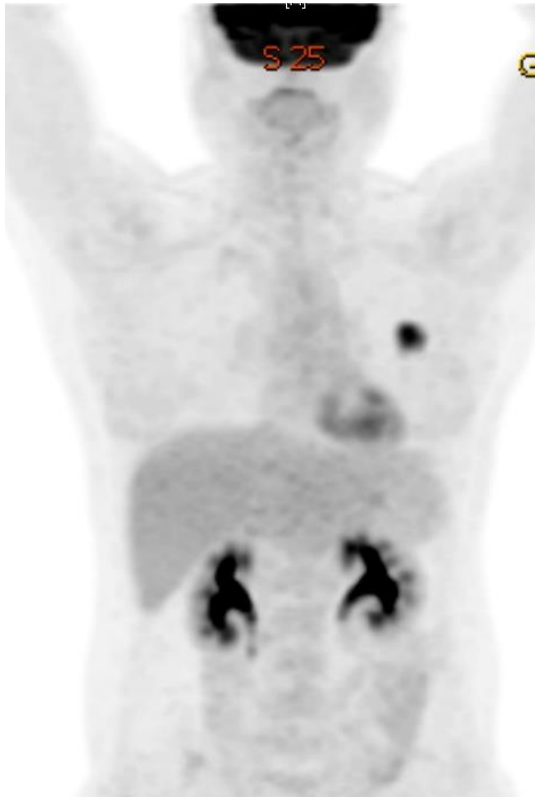
F/51, never smoker,
2.2cm adenoca,
cT1bN0M0



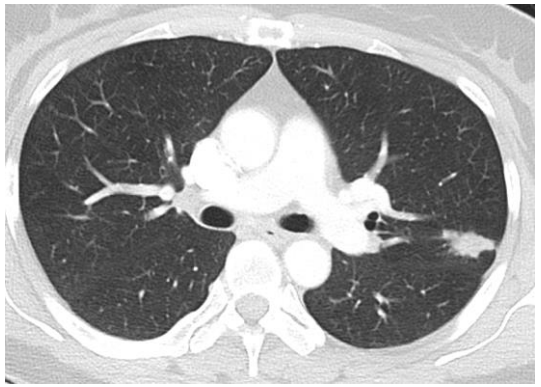


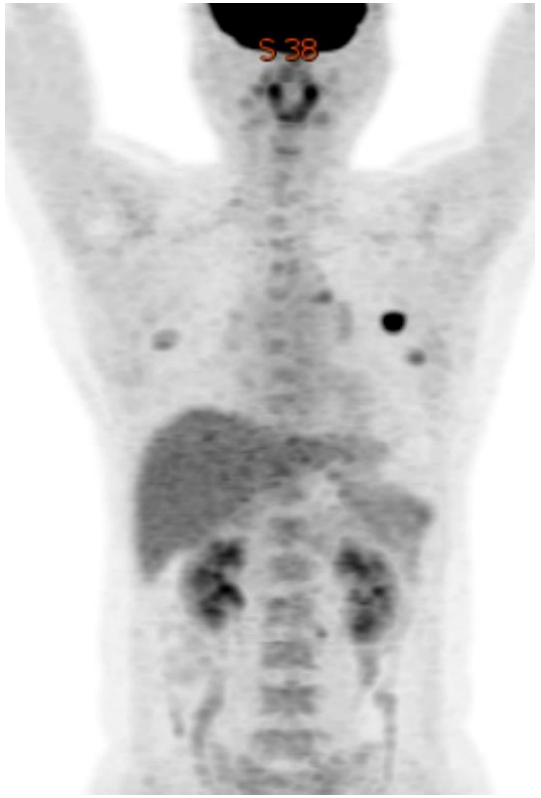
F/53, never smoker,
2.5cm adenoca,
cT1cN0M0



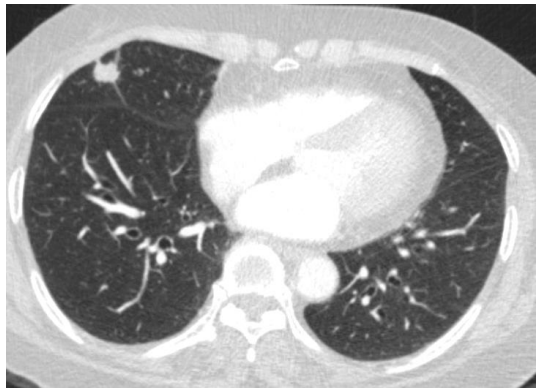


F/52, never smoker,
2.1cm adenoca,
cT1bN0M0





F/73, never smoker,
cT1bN0M0



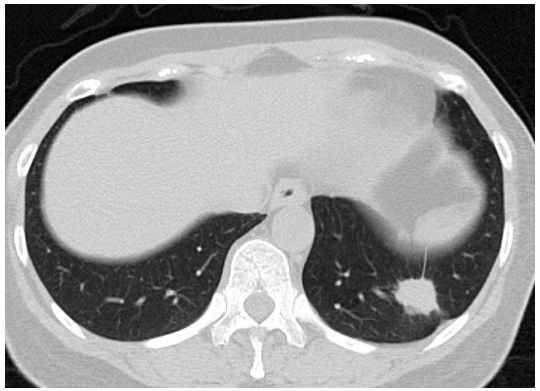
adenocarcinoma,
acinar predominant

pT2a/pN0M0 (PL1)

NGS brief summary:

EGFR exon 19 deletion
mutation
(p.T751_I759delinsN)

F/51, never smoker,
cT1bN0M0



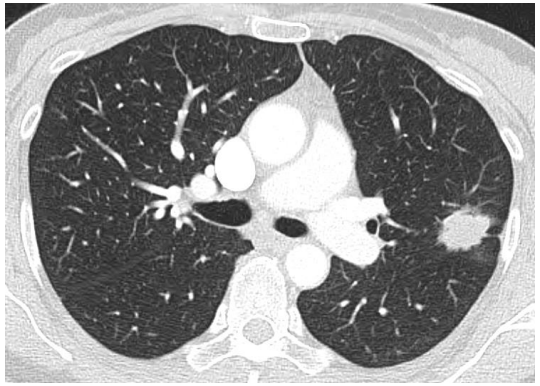
adenocarcinoma,
papillary predominant

pT1c/pN2a1M0

NGS brief summary:

EGFR Inframe deletion
p.E746_A750del 46.3%
TP53 Missense
mutation p.M246V 43.8%

F/53, never smoker,
cT1cN0M0



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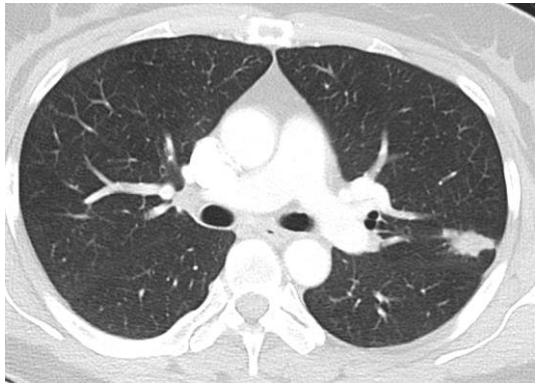
acinar predominant

pT2aN0M0 (PL1)

NGS brief summary:

EGFR Missense mutation
p.G719S 29.69 %
EGFR Missense mutation
p.R776H 29.68 %
TP53 Frameshift deletion
p.R156Pfs*23 41.78 %
BRAF Missense
mutation p.V600E 1.37 %

F/52, never smoker,
cT1bN0M0



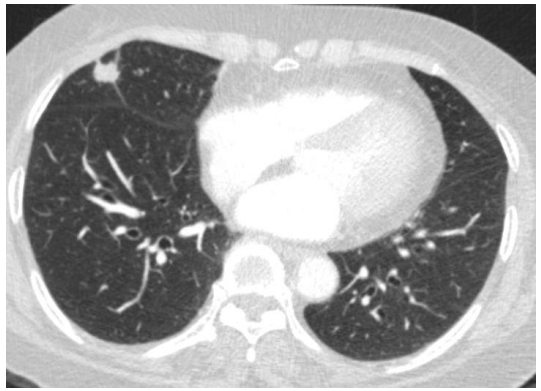
adenocarcinoma,
papillary predominant

pT2a/pN2a2M0

NGS brief summary:

EGFR mutation exon 19
deletion (p.E746_A750del)
TP53 mutation (p.H179R)
AKT2 copy number gain
FGFR3 copy number gain

F/73, never smoker,
cT1bN0M0



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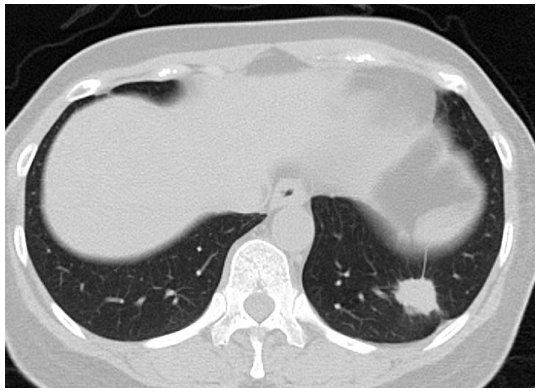

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papillary predominant

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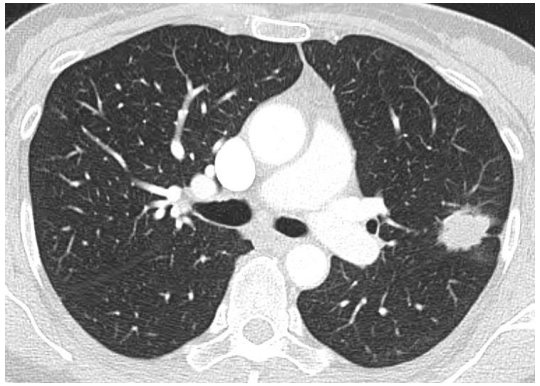

adenocarcinoma,
acinar predominant

pT2aN0M0 (PL1)

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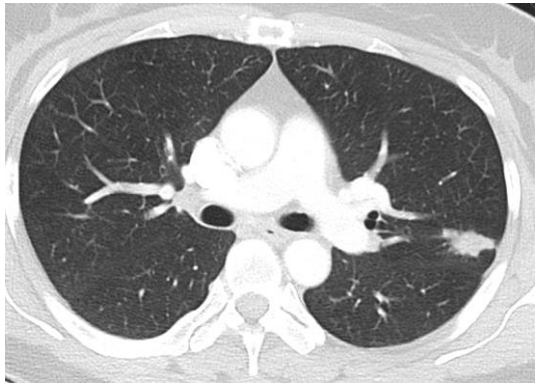


adenocarcinoma,
papillary predominant

pT2a/pN2a2M0

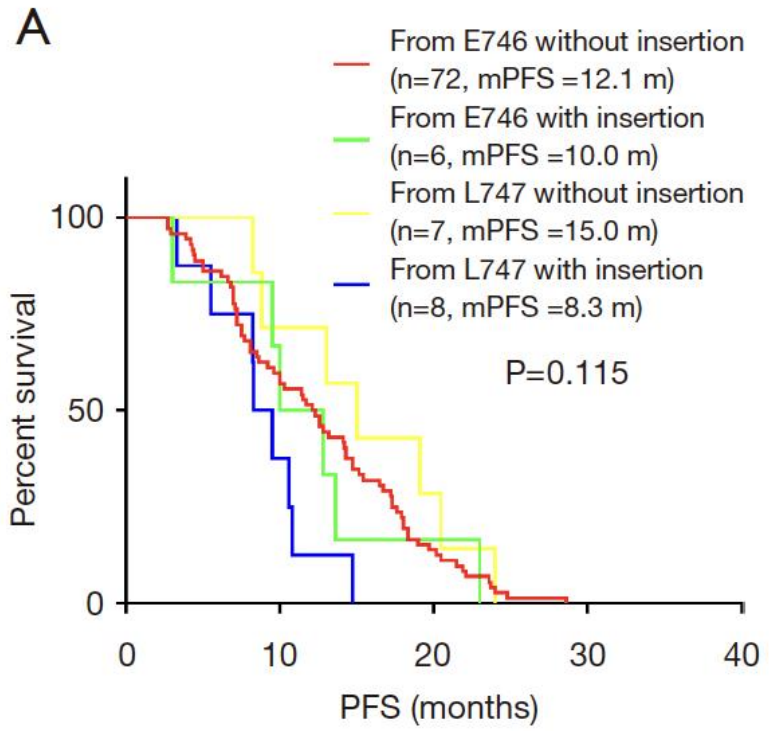
NGS brief summary:

EGFR mutation exon 19
deletion (p.E746_A750del)
TP53 mutation (p.H179R)
AKT2 copy number gain
FGFR3 copy number gain

EGFR exon 19del subtypes in NSCLC patients

	No.	Subtypes	N (%) (total =181)
E746	1	delE746_A750	130 (71.8)
	2	delE746_T751insA	3 (1.7)
	3	delE746_T751insI	1 (0.6)
	4	delE746_S752insI	1 (0.6)
	5	delE746_S752insV	8 (4.4)
L747	6	delL747_E749	1 (0.6)
	7	delL747_A750insP	7 (3.9)
	8	delL747_T751insP	2 (1.1)
	9	delL747_S752	1 (0.6)
	10	delL747_P753insQ	1 (0.6)
	11	delL747_T751	14 (7.7)
	12	delL747_P753insS	11 (6.1)
	13	delL747_A755insSRD	1 (0.6)

PFS in EGFR 19del with first-line EGFR-TKIs



12.1 mo

10.0 mo

15.0 mo

8.3 mo

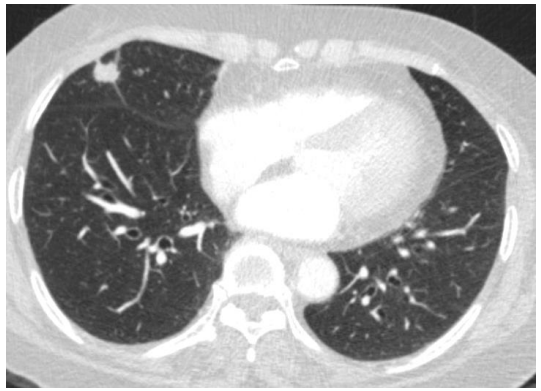
Zhao, Chao, et al. Translational Lung Cancer Research 9.4 (2020): 1149.

Clinicopathological features of EGFR 19del variants

Items	delE746_A750, n (%)	Others, n (%)	P value	Deletion starting from E746, n (%)	Deletion starting from L747, n (%)	P value
Sex			0.003			0.013
Female	80 (61.5)	19 (37.3)		85 (59.4)	14 (36.8)	
Male	50 (38.5)	32 (62.7)		58 (40.6)	24 (63.2)	
Smoking status			0.002			0.014
Never	101 (77.7)	28 (54.9)		108 (75.5)	21 (55.3)	
Light/smoker	29 (22.3)	23 (45.1)		35 (24.5)	17 (44.7)	
T790M*			0.001			0.006
Yes	32 (65.3)	2 (15.4)		33 (63.5)	1 (10.0)	
No	17 (34.7)	11 (84.6)		19 (36.5)	9 (90.0)	

Zhao, Chao, et al. Translational Lung Cancer Research 9.4 (2020): 1149.

F/73, never smoker,
cT1bN0M0



adenocarcinoma,
acinar predominant

pT2a/pN0M0 (PL1)

NGS brief summary:

EGFR exon 19 deletion mutation (p.T751_I759delinsN)

Article

A Nationwide Study on the Impact of Routine Testing for *EGFR* Mutations in Advanced NSCLC Reveals Distinct Survival Patterns Based on *EGFR* Mutation Subclasses

Bart Koopman [1], Betzabel N. Cajiao Garcia [1], Chantal C. H. J. Kuijpers [2], Ronald A. M. Damhuis [3], Anthonie J. van der Wekken [4], Harry J. M. Groen [4], Ed Schuuring [1], Stefan M. Willems [1] and Léon C. van Kempen [1,*]

- ✓ Netherlands Cancer Registry (NCR), 2013-2017
- ✓ EGFR test performed via PCR, NGS and other methods
- ✓ EGFR mutation detected in 925 out of of 7,908 (11.7 %)

Variant(s)
R108K
C595F
Q701K
L703F
R705S
E709_T710delinsD
E709A/G719A
E709A/G719R
E709A/G719S
E709D
E709K/G719S
I715fs*
G719_S720delinsAF
G719A
G719A/D761Y
G719A + Exon 20 insertion, NOS
G719A/L861Q
G719A/R776H
G719A/S768I
G719A/V769M
G719C
G719C/S768I
G719S
G719S/L747S

Variant(s)
G719S/L861Q
G719S/S768I
G719X, NOS
G719X, NOS/S768I
G724A/S768I
G724S/S768I
c.2184 + 19G > A
L730fs*1
I740_K745dup
A743S
I744_P753delinsSNISG
E746_A750del
E746_A750del/G873E
E746_A750del/K754Q
E746_A750del/P848L
E746_A750del/V765M
E746_A750delinsEP
E746_A750delinsIP
E746_A750dup
E746_K754delinsVSR
E746_L747delinsIP
E746_P753delinsANKE
E746_P753delinsIS
E746_P753delinsVS
[illegible]

Variant(s)
E746_S752delinsI
E746_S752delinsV
E746_T751del
E746_T751delinsA
E746_T751delinsAA
E746_T751delinsI
E746_T751delinsK
E746_T751delinsL
E746_T751delinsP
E746_T751delinsS
E746_T751delinsVP
L747_A750delinsP
L747_A750delinsP/V845L
L747_A755delinsSKD
L747_E749del
L747_K754delinsATSPE
L747_K754delinsG
L747_K754delinsQPN
L747_P753delinsQ
L747_P753delinsS
L747_S752del
L747_S752del/K754R
L747_S752del/L777Q
L747_S752delinsQ
L747_T751del
L747_T751del/S768I

Variant(s)
L747_T751delinsP
L747P
E749_A755delinsD
A750_E758delinsP
T751_I759delinsN
S752_I759del
P753L
K757R
A763S
A763_Y764insFQEA
V765M
A767_V769dup
A767T
S768_D770dup
S768_V769delinsIL
S768I
S768I/L861Q
S768I/V774M
V769L
V769M
D770_H773dup
D770_N771insG
D770_N771insGF
D770_N771insSVA
D770_N771insT
D770_N771insY

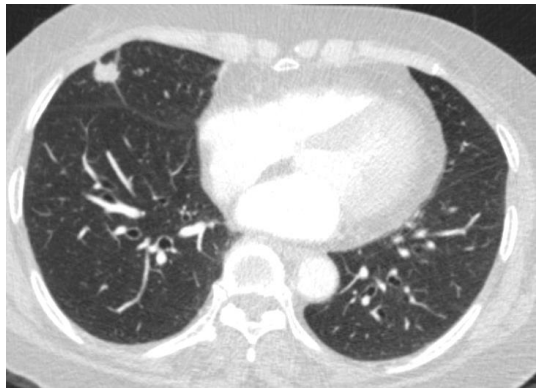
Variant(s)
D770_P772dup
D770delinsEQPP
D770delinsGY
D770Y
N771_H773dup
N771_P772insH
N771_P772insR
N771delinsGF
N771delinsGY
N771delinsKG
N771delinsTH
N771L
P772_C775dup
P772_H773dup
P772_H773insANP
H773_V774dup
H773_V774insAH
H773delinsYNPY
H773dup
V774delinsHC
V774M
V774M/L861R
C775F
R776H
R776L
G779F
G779S

Variant(s)
C781F
Q787E
T790M
G796C
L799M
D830Y
L832T
L833V/H835L
R836L
R836R
A840T
P848L
L858_K860delinsRTI
L858R
L858R/A871E
L858R/A871G
L858R/E709G
L858R/L718M
L858R/L747V
L858R/R776H
L858R/S768I
L858R/V834L
A859T
L861Q
L861R
1 (0.11%)

Variant(s)	
G863D	
A864T	
A864V	
E866K	
EGFR variant, NOS	
Exon 18 variant, NOS + Exon 20 variant, NOS	
Exon 19 deletion, NOS	
Exon 19 variant, NOS	
Exon 20 insertion, NOS	
Exon 20 SNV (silent)	
Exon 21 variant, NOS	
[a] Amount of tumors repo frequency; DOI, digital ob cancer; SNP, single nucleo	
1 (0.11%)	
1 (0.11%)	
1 (0.11%)	
1 (0.11%)	
1 (0.11%)	
2 (0.22%)	
4 (0.43%)	
1 (0.11%)	
1 (0.11%)	
19 (2.05%)	
3 (0.32%)	
No evidence	

Variant(s)	*n* (%) [a]	Rationale	Prediction	LoE	Group
L747_T751delinsP	6 (0.65%)	Net loss of amino acids on exon 19 (deletion)	sensitive	IA	exon 19 deletion
L747P	4 (0.43%)	Clinical sensitivity to EGFR-TKI reported [70]	sensitive	IID	uncommon, actionable
E749_A755delinsD	1 (0.11%)	Net loss of amino acids on exon 19 (deletion)	sensitive	IA	exon 19 deletion
A750_E758delinsP	1 (0.11%)	Net loss of amino acids on exon 19 (deletion)	sensitive	IA	exon 19 deletion
T751_I759delinsN	1 (0.11%)	Net loss of amino acids on exon 19 (deletion)	sensitive	IA	exon 19 deletion
S752_I759del	4 (0.43%)	Net loss of amino acids on exon 19 (deletion)	sensitive	IA	exon 19 deletion
P753L	1 (0.11%)	No evidence on pathogenicity or actionability	no benefit	III	not actionable/unknown
K757R	1 (0.11%)	No evidence on pathogenicity or actionability	no benefit	III	not actionable/unknown
A763S	2 (0.22%)	No evidence on pathogenicity or actionability	no benefit	III	not actionable/unknown
A763_Y764insFQEA	1 (0.11%)	Net gain of amino acids on exon 20 (insertion)	no benefit	IIC	exon 20 insertion
V765M	2 (0.22%)	Only reported in combination with other variants, no evidence on individual variant	no benefit	III	not actionable/unknown
A767_V769dup	16 (1.73%)	Net gain of amino acids on exon 20 (insertion)	no benefit	IIC	exon 20 insertion
A767T	1 (0.11%)	No evidence on pathogenicity or actionability	no benefit	III	not actionable/unknown
S768_D770dup	9 (0.97%)	Net gain of amino acids on exon 20 (insertion)	no benefit	IIC	exon 20 insertion
S768_V769delinsIL	4 (0.43%)	Considered comparable to S768I	sensitive	IIC	uncommon, actionable
S768I	5 (0.54%)	Clinical sensitivity to EGFR-TKI reported [49]	sensitive	IIC	uncommon, actionable
S768I/L861Q	2 (0.22%)	Clinical sensitivity to EGFR-TKI reported [65]	sensitive	IIC	uncommon, actionable
S768I/V774M	2 (0.22%)	Considered comparable to S768I	sensitive	IIC	uncommon, actionable
V769L	2 (0.22%)	Only reported in combination with other variants, no evidence on individual variant	no benefit	III	not actionable/unknown
V769M	2 (0.22%)	Possible germline variant [71], no evidence sensitivity to EGFR-TKI	no benefit	III	not actionable/unknown
D770_H773dup	1 (0.11%)	Net gain of amino acids on exon 20 (insertion)	no benefit	IIC	exon 20 insertion
D770_N771insG	3 (0.32%)	Net gain of amino acids on exon 20 (insertion)	no benefit	IIC	exon 20 insertion
D770_N771insGF	1 (0.11%)	Net gain of amino acids on exon 20 (insertion)	no benefit	IIC	exon 20 insertion
D770_N771insSVA	2 (0.22%)	Net gain of amino acids on exon 20 (insertion)	no benefit	IIC	exon 20 insertion
D770_N771insT	1 (0.11%)	Net gain of amino acids on exon 20 (insertion)	no benefit	IIC	exon 20 insertion
D770_N771insY	1 (0.11%)	Net gain of amino acids on exon 20 (insertion)	no benefit	IIC	exon 20 insertion

F/73, never smoker,
cT1bN0M0



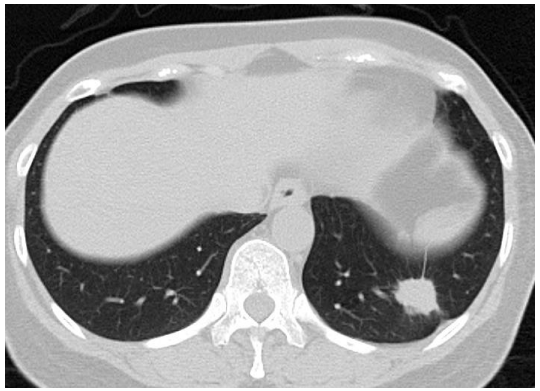
adenocarcinoma,
acinar predominant

pT2a/pN0M0 (PL1)

NGS brief summary:

EGFR exon 19 deletion
mutation
(p.T751_I759delinsN)

F/51, never smoker,
cT1bN0M0



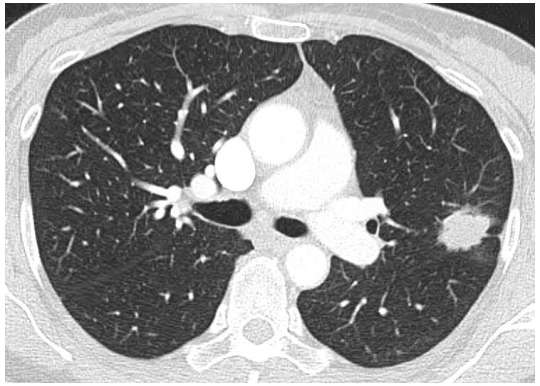
adenocarcinoma,
papillary predominant

pT1c/pN2a1M0

NGS brief summary:

EGFR Inframe deletion
p.E746_A750del 46.3%
TP53 Missense
mutation p.M246V 43.8%

F/53, never smoker,
cT1cN0M0



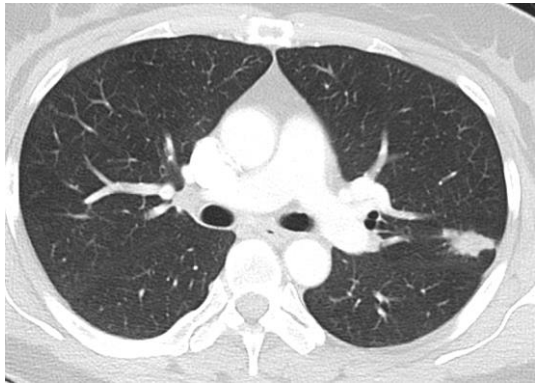
adenocarcinoma,
acinar predominant

pT2aN0M0 (PL1)

NGS brief summary:

EGFR Missense mutation
p.G719S 29.69 %
EGFR Missense mutation
p.R776H 29.68 %
TP53 Frameshift deletion
p.R156Pfs*23 41.78 %
BRAF Missense
mutation p.V600E 1.37 %

F/52, never smoker,
cT1bN0M0



adenocarcinoma,
papillary predominant

pT2a/pN2a2M0

NGS brief summary:

EGFR mutation exon 19
deletion (p.E746_A750del)
TP53 mutation (p.H179R)
AKT2 copy number gain
FGFR3 copy number gain

Table 4. Rationale for classification of expected first- and second-generation EGFR-TKI sensitivity for *EGFR* variants reported in the Dutch population in 2013, 2015 and 2017.

Variant(s)	*n* (%) [a]	Rationale	Prediction	LoE	Group
R108K	1 (0.11%)	Known gain of function in brain tumors [59], but actionability unknown in NSCLC	no benefit	III	not actionable/unknown
C595F	1 (0.11%)	No evidence on pathogenicity or actionability	no benefit	III	not actionable/unknown
Q701K	1 (0.11%)	No evidence on pathogenicity or actionability	no benefit	III	not actionable/unknown
L703F	1 (0.11%)	No evidence on pathogenicity or actionability	no benefit	III	not actionable/unknown
R705S	1 (0.11%)	No evidence on pathogenicity or actionability	no benefit	III	not actionable/unknown
E709_T710delinsD	3 (0.32%)	Clinical sensitivity to EGFR-TKI reported [60,61]	sensitive	IID	uncommon, actionable
E709A/G719A	4 (0.43%)	Clinical sensitivity to EGFR-TKI reported [21]	sensitive	IIC	uncommon, actionable
E709A/G719R	1 (0.11%)	Considered comparable to E709A/G719A	sensitive	IIC	uncommon, actionable
E709A/G719S	1 (0.11%)	Considered comparable to E709A/G719A	sensitive	IIC	uncommon, actionable
E709D	1 (0.11%)	No evidence on pathogenicity or actionability. Similar amino acid properties between Glu (E) and Asp (D), thus no effect expected	no benefit	III	not actionable/unknown
E709K/G719S	1 (0.11%)	Clinical sensitivity to EGFR-TKI reported [62]	sensitive	IIC	uncommon, actionable
I715fs*	1 (0.11%)	No evidence on pathogenicity or actionability	no benefit	III	not actionable/unknown
G719_S720delinsAF	1 (0.11%)	Considered comparable to G719A	sensitive	IID	uncommon, actionable
G719A	18 (1.95%)	Clinical sensitivity to EGFR-TKI reported [63]	sensitive	IIC	uncommon, actionable
G719A/D761Y	1 (0.11%)	Considered comparable to G719A	sensitive	IIC	uncommon, actionable
G719A + Exon 20 insertion, NOS	1 (0.11%)	No EGFR-TKI sensitivity expected due to exon 20 insertion, grouped accordingly	no benefit	IIC	exon 20 insertion
G719A/L861Q	3 (0.32%)	Clinical sensitivity to EGFR-TKI reported [64]	sensitive	IIC	uncommon, actionable
G719A/R776H	1 (0.11%)	Considered comparable to G719A	sensitive	IIC	uncommon, actionable
G719A/S768I	5 (0.54%)	Clinical sensitivity to EGFR-TKI reported [65]	sensitive	IIC	uncommon, actionable
G719A/V769M	1 (0.11%)	Considered comparable to G719A	sensitive	IIC	uncommon, actionable
G719C	2 (0.22%)	Clinical sensitivity to EGFR-TKI reported [66]	sensitive	IIC	uncommon, actionable
G719C/S768I	6 (0.65%)	Clinical sensitivity to EGFR-TKI reported [67]	sensitive	IIC	uncommon, actionable
G719S	1 (0.11%)	Clinical sensitivity to EGFR-TKI reported [66]	sensitive	IIC	uncommon, actionable
G719S/L747S	1 (0.11%)	Considered comparable to G719S	sensitive	IIC	uncommon, actionable

Article

Structure-based classification predicts drug response in *EGFR*-mutant NSCLC

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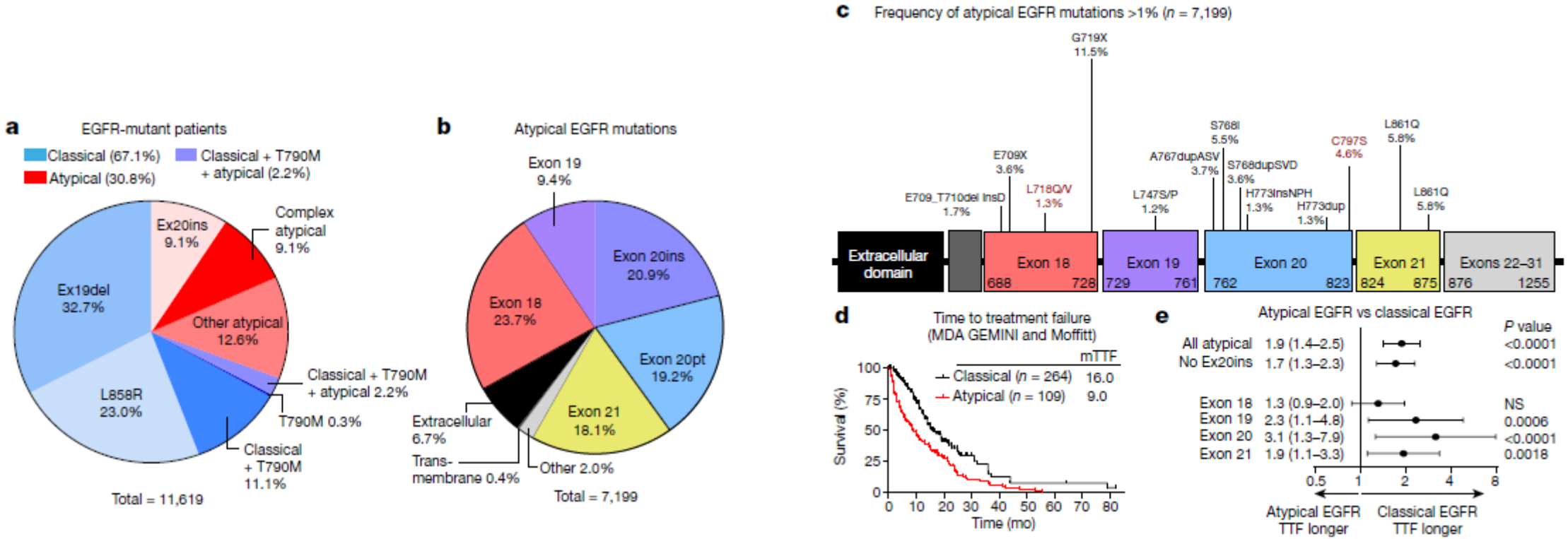
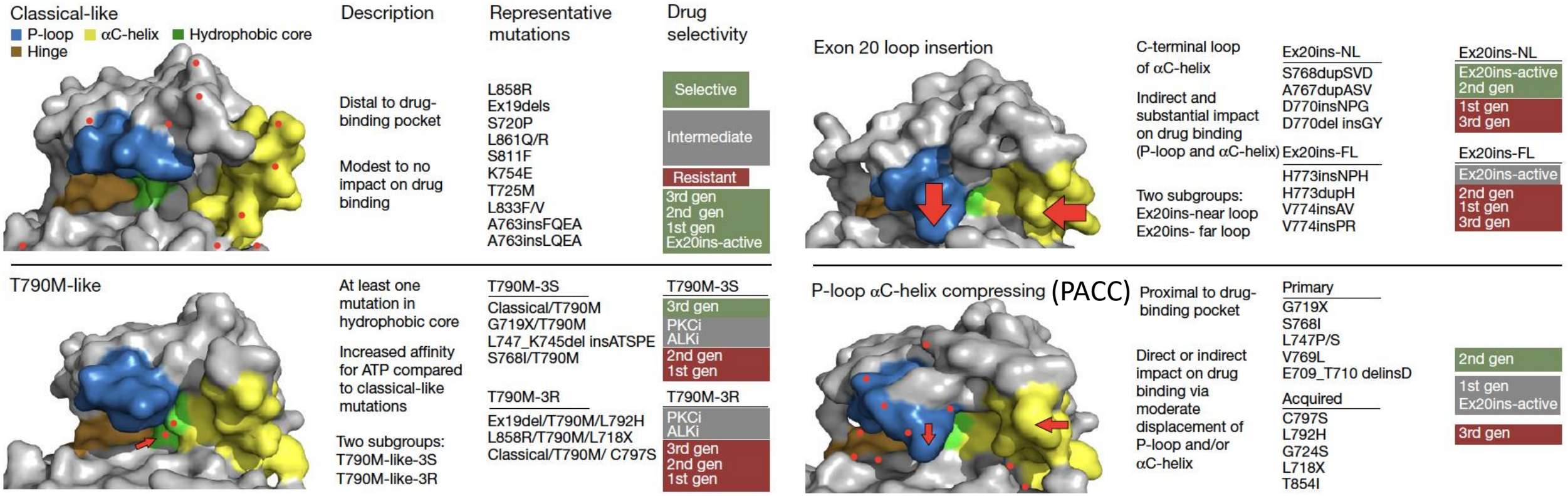
Open access

Jacqulyne P. Robichaux[1], Xiuning Le[1], R. S. K. Vijayan[2], J. Kevin Hicks[3], Simon Heeke[1], Yasir Y. Elamin[1], Heather Y. Lin[4], Hibiki Udagawa[1], Ferdinandos Skoulidis[1], Hai Tran[1], Susan Varghese[1], Junqin He[1], Fahao Zhang[1], Monique B. Nilsson[1], Lemei Hu[1], Alissa Poteete[1], Waree Rinsurongkawong[5], Xiaoshan Zhang[6], Chenghui Ren[6], Xiaoke Liu[1,7], Lingzhi Hong[1], Jianjun Zhang[1], Lixia Diao[8], Russell Madison[9], Alexa B. Schrock[9], Jennifer Saam[10], Victoria Raymond[10], Bingliang Fang[6], Jing Wang[8], Min Jin Ha[4], Jason B. Cross[2], Jhanelle E. Gray[11] & John V. Heymach[1]✉



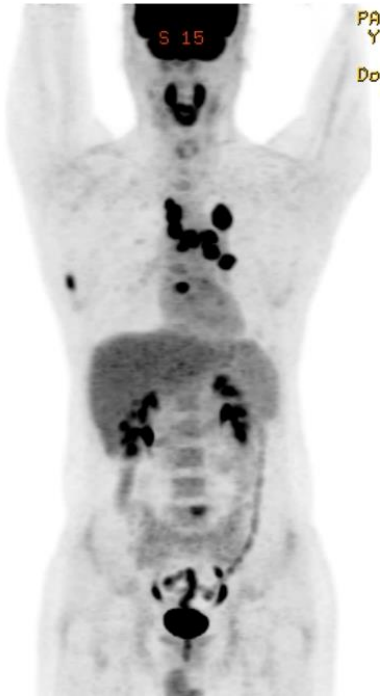


- ✓ Drug selectivity was tested in a panel of 76 cell lines expressing EGFR mutations spanning exons 18–21 against 18 EGFR inhibitors representing 1st (non-covalent), 2nd (covalent) and 3rd (covalent, T790M targeting) generation and Ex20ins-active TKIs.

- ✓ Mutations within an exon are heterogenous and that an exon-based classification is unlikely to be optimal for guiding treatment decisions.

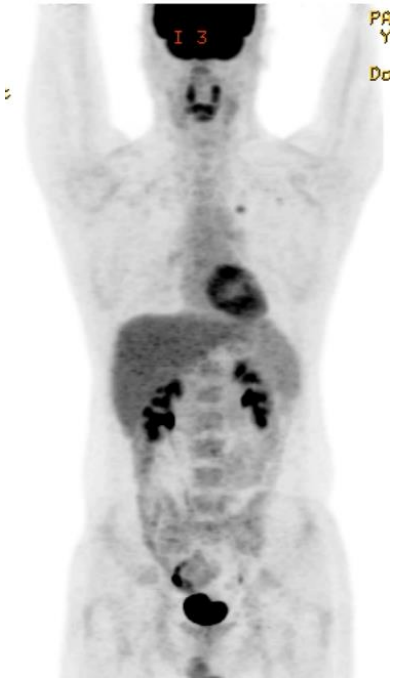
Robichaux, Jacqulyne P., et al. Nature 597.7878 (2021): 732-737.

M/32, current smoker, 10 PY
cT2aN3M1c, bone, brain



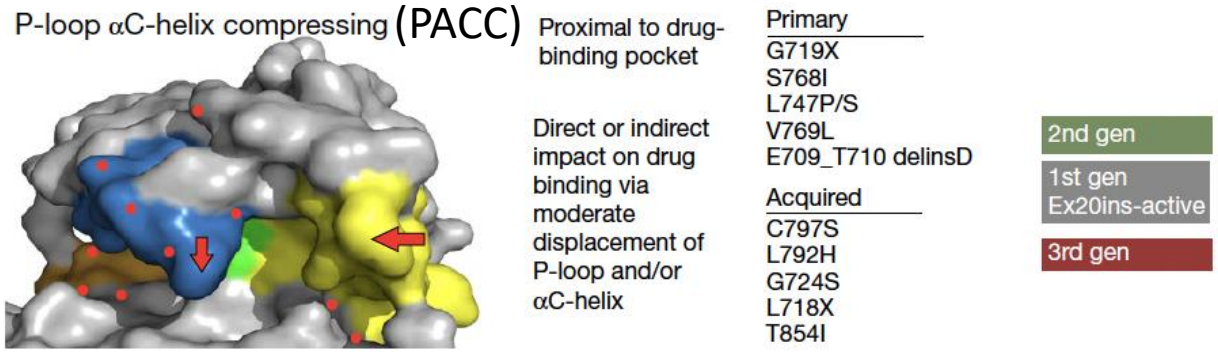
NGS brief summary:
EGFR Missense mutation
p.L858R 19.47%
EGFR Missense mutation
p.L747S 21.48%
TP53 Missense mutation
p.Y234C 20.05%

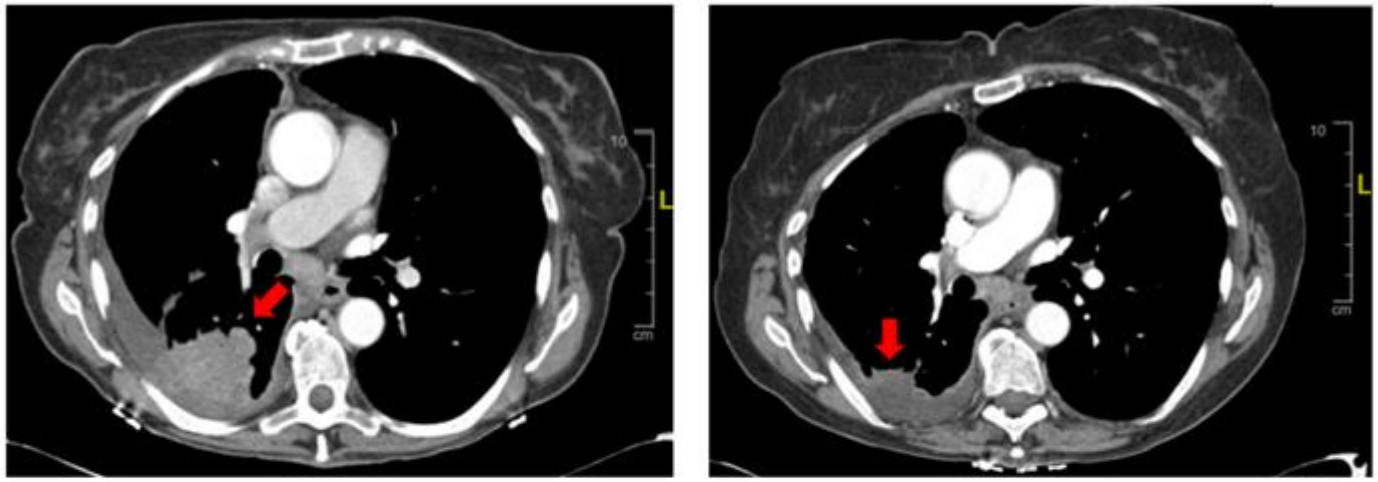
Afatinib 40mg, PR, 12mo

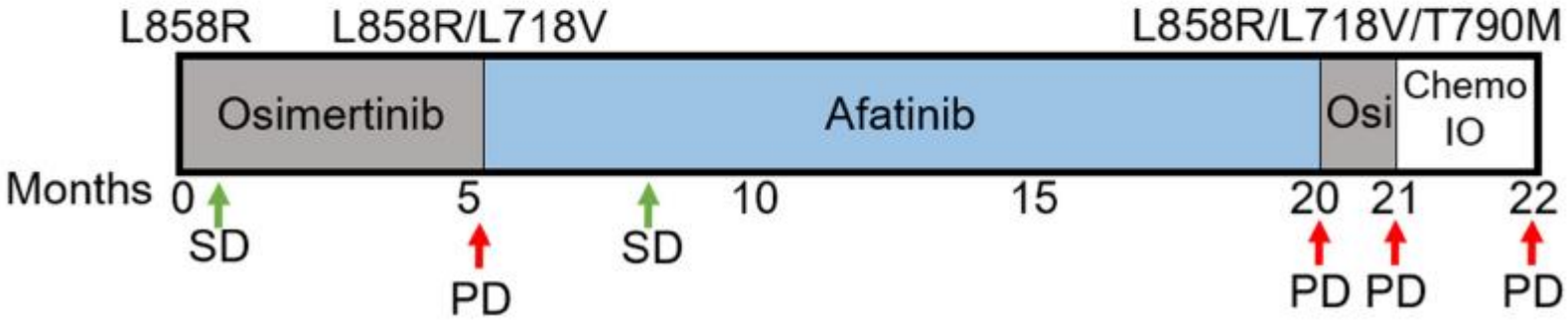


2020.07

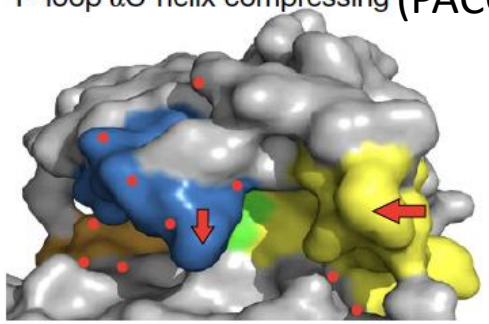
2021.07







P-loop αC-helix compressing (PACC)



Proximal to drug-binding pocket

Direct or indirect impact on drug binding via moderate displacement of P-loop and/or αC-helix

Primary
G719X
S768I
L747P/S
V769L
E709_T710 delinsD

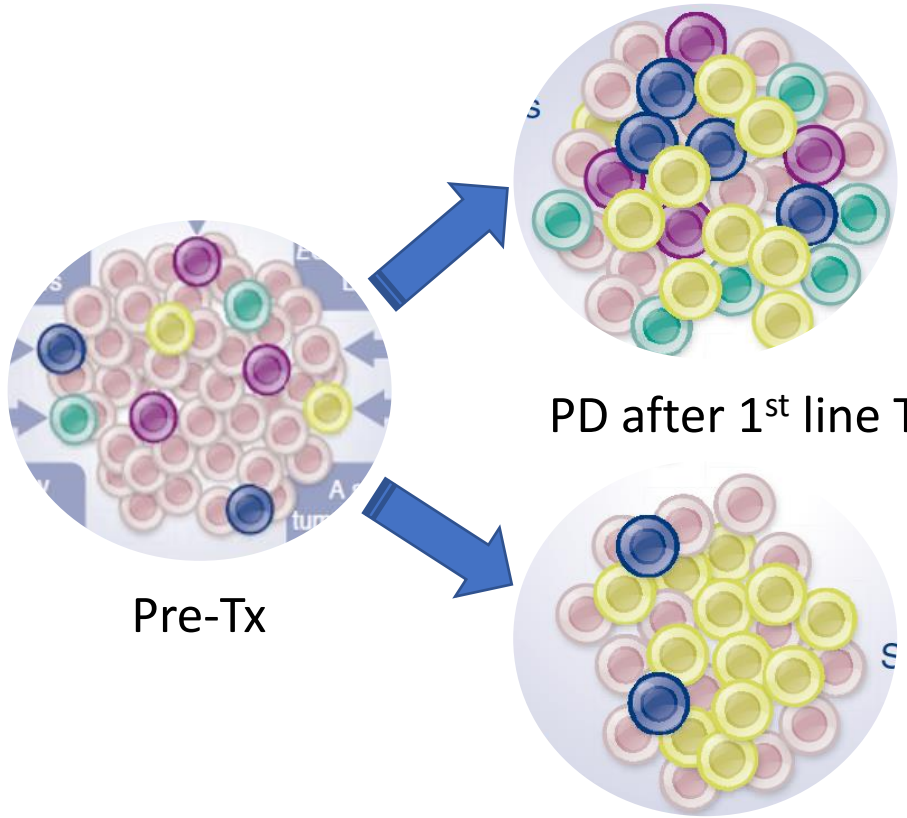
Acquired
C797S
L792H
G724S
L718X
T854I

2nd gen
1st gen Ex20ins-active
3rd gen

Robichaux, Jacqulyne P., et al. Nature 597.7878 (2021): 732-737.

Summary 2

- The *diversity and higher* than previously appreciated prevalence of atypical EGFR mutations shown here highlights the necessity of comprehensive next-generation sequencing (NGS) for patients with NSCLC.



Transl Lung Cancer Res. 2020 Oct; 9(5): 1952–1962.
doi: 10.21037/tlcr-20-915

Low T790M relative allele frequency indicates concurrent resistance mechanisms and poor responsiveness to osimertinib

Ye Wang,[1,2,#] Yanqi He,[1,#] Panwen Tian,[1,2] Weiya Wang,[3] Ke Wang,[1,2] Shannon Chuai,[4] Yalun Li,[1] Shuang Zhao,[1] Yu Wang,[5] and Weimin Li[1]

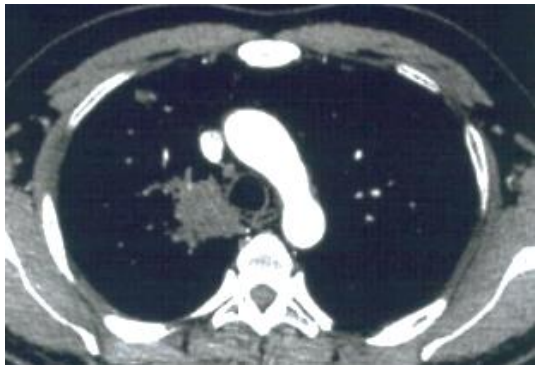
- ✓ T790M relative allele frequency (RAF) in plasma, = the ratio of T790M to EGFR-sensitizing mutation AF.
- ✓ Low T790M RAF (<20%) had significantly lower ORRs (0 vs. 68.8%, P=0.03) and DCRs (60% vs. 100%, P=0.048) in response to osimertinib compared to patients with high T790M RAF.
- ✓ T790M RAF less than 20% were more likely to harbor concurrent resistance mechanisms, such as MET or ERBB2 amplification, and small cell lung cancer transformation.

Kohsaka, Shinji, et al. Future Oncology 15.6 (2019): 637-652. Wang, Ye, et al. Translational Lung Cancer Research 9.5 (2020): 1952.

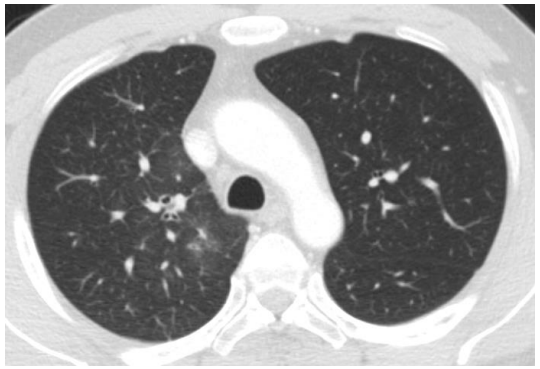
- The clonal nature of tumor evolution underpins the difficulty of long-term treatment of tumors.

- Any treatment modality, be it traditional chemotherapeutics or targeted therapies, may impose strong selective pressure on tumor cells allowing resistant cells to survive which, under the right circumstances, may develop into a tumor which is resistant to treatment and, *in terms of molecular characteristics, different to the original malignancy*.

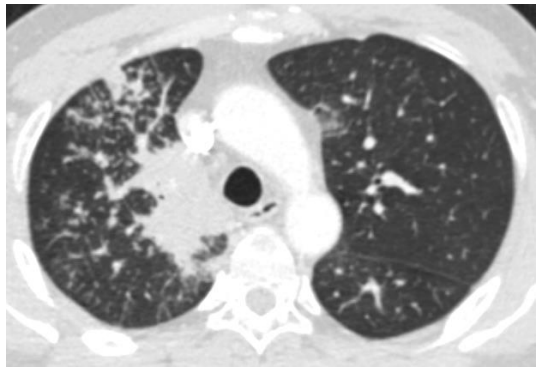
M/43, ex-smoker, 0.3P*10Y, cT4N3M1c, bone, brain



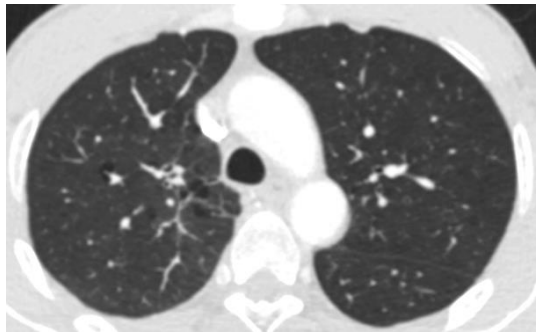
At Diagnosis,
Adenoca, EGFR E19 del



1st line afatinib 40mg, PR, 1mo



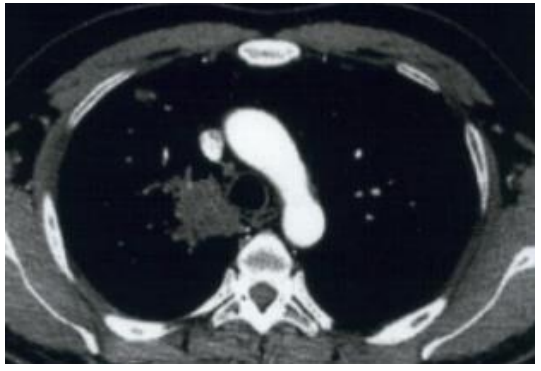
Afatinib 40mg, PD, 10mo,
EGFR E19 del, T790M,
PD L1 22C3 5%, SP263 0%



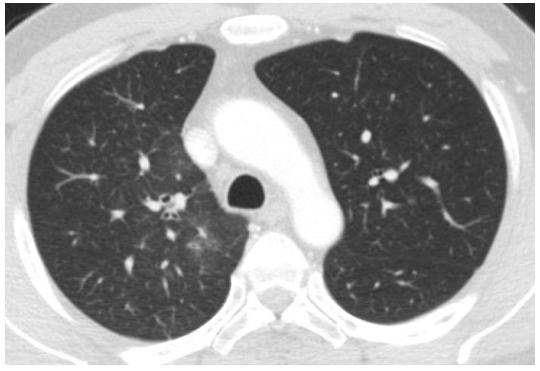
2nd line Osimertinib, 17mo

2nd line Osimertinib, PD, 22mo
3rd line Amivantamab, variable response,
4th line Pemetrexed/Carboplatin,
5th line Docetaxel …

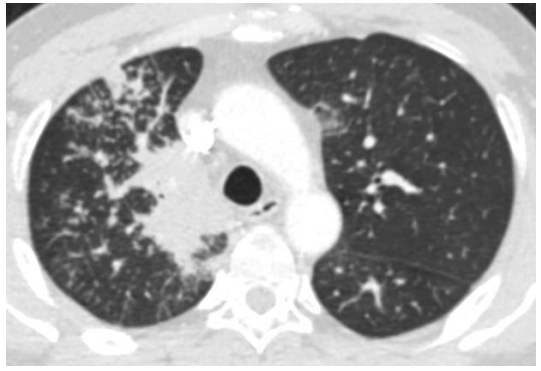
M/43, ex-smoker, 0.3P*10Y, cT4N3M1c, bone, brain



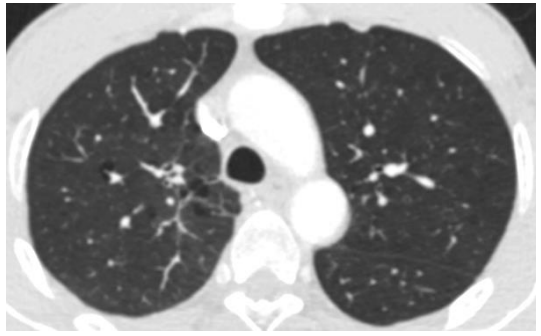
At Diagnosis,
Adenoca, EGFR E19 del



1st line afatinib 40mg, PR, 1mo



Afatinib 40mg, PD, 10mo,
EGFR E19 del, T790M,
PD L1 22C3 5%, SP263 0%



2nd line Osimertinib, 17mo

2nd line Osimertinib, PD, 22mo
3rd line Amivantamab, variable response,
4th line Pemetrexed/Carboplatin,
5th line Docetaxel …

Liver biopsy at **36 mo** after diagnosis
: Metastatic adenocarcinoma, poorly differentiated

NGS brief summary:
EGFR Inframe deletion p.E746_A750del 23.41%
EGFR Missense mutation p.T790M 29.02%
PIK3CA Missense mutation p.E545K 55.94%
TP53 Missense mutation p.R273C 85.54%
APC Frameshift mutation p.D849Ifs*12 82.3%
PTCH1 Frameshift mutation p.S1203Afs*52 51.51%
MPL Missense mutation p.R102C 44.83%
NCOR1 Nonsense mutation p.R672* 41.63%
NCOR1 Nonsense mutation p.R672* 41.63%
FBXW7 Missense mutation p.R441Q 41.26%
ARID1A Frameshift mutation p.D1850Tfs*33 40.81%
PTEN Frameshift mutation p.N323Kfs*2 27.88%
BBC3 Frameshift mutation p.R243Qfs*7 18.07%
ARID5B Frameshift mutation p.K967Nfs*15 3.31%
ARID1B Nonsense mutation p.Q1400* 1.45%
FGFR1 copy number gain (Fold change: 2.267)
MYC copy number gain (Fold change: 2.148)
TMB: High (22/Mb)
MSI: High (32.23%)

Summary 3

- Clonal evolution plays a key role in acquired resistance of tumors to treatment.
- Understand the clonal architecture of tumors prior to initiation of, and during, therapy through NGS and liquid biopsy would be highly advantageous.

Summary 4

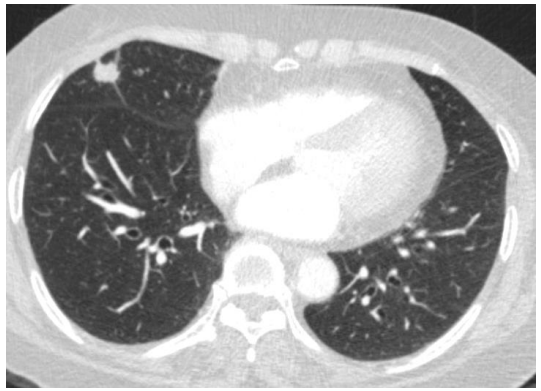
- EGFR mutation-lung cancers are genetically *heterogeneous* and undergo *clonal evolution.*

- Two sources of heterogeneity in EGFR-mutant lung cancers are: co-occurring genetic alterations and different EGFR mutations within a single tumor.

- The detailed *genomic profiling* of tumor and *tracking the clonal evolution* could be the way to individualize the further targeted treatment in EGFR-mutant lung cancer.

- Characterizing the tumor and immune microenvironment during tumor evolution could be the way forward for the qualitative leap.

F/73, never smoker,
cT1bN0M0



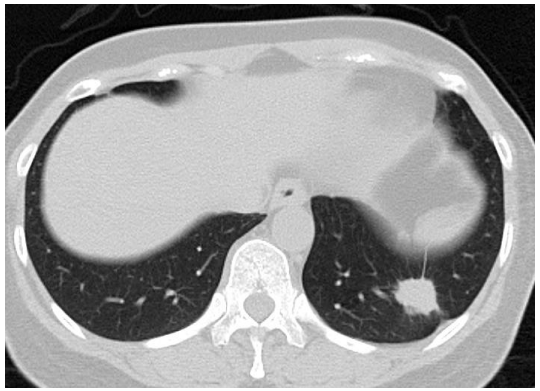
pT2a/pN0M0 (PL1)

NGS brief summary:

EGFR exon 19 deletion mutation (p.T751_I759delinsN)

24개월 후 recur

F/51, never smoker,
cT1bN0M0



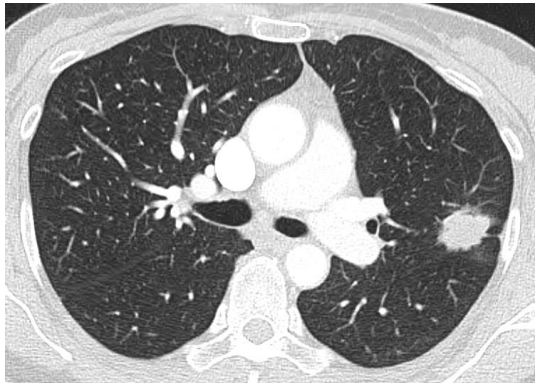
pT1c/pN2a1M0

NGS brief summary:

EGFR Inframe deletion p.E746_A750del 46.3%
TP53 Missense mutation p.M246V 43.8%,

Adjuvant gefitinib 24mo, NED

F/53, never smoker,
cT1cN0M0



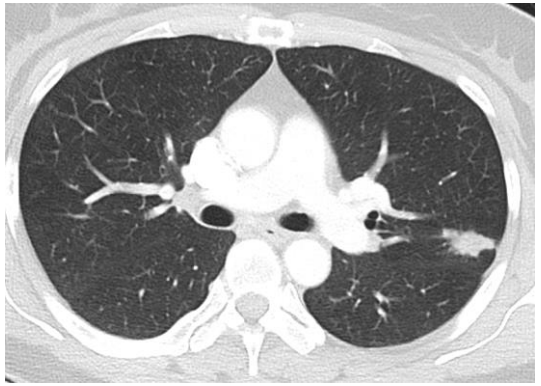
pT2aN0M0 (PL1)

NGS brief summary:

EGFR Missense mutation p.G719S 29.69 %
EGFR Missense mutation p.R776H 29.68 %
TP53 Frameshift deletion p.R156Pfs*23 41.78 %
BRAF Missense mutation p.V600E 1.37 %

14개월 후 recur,
1st line afatinib 40mg, PD, 20mo

F/52, never smoker,
cT1bN0M0



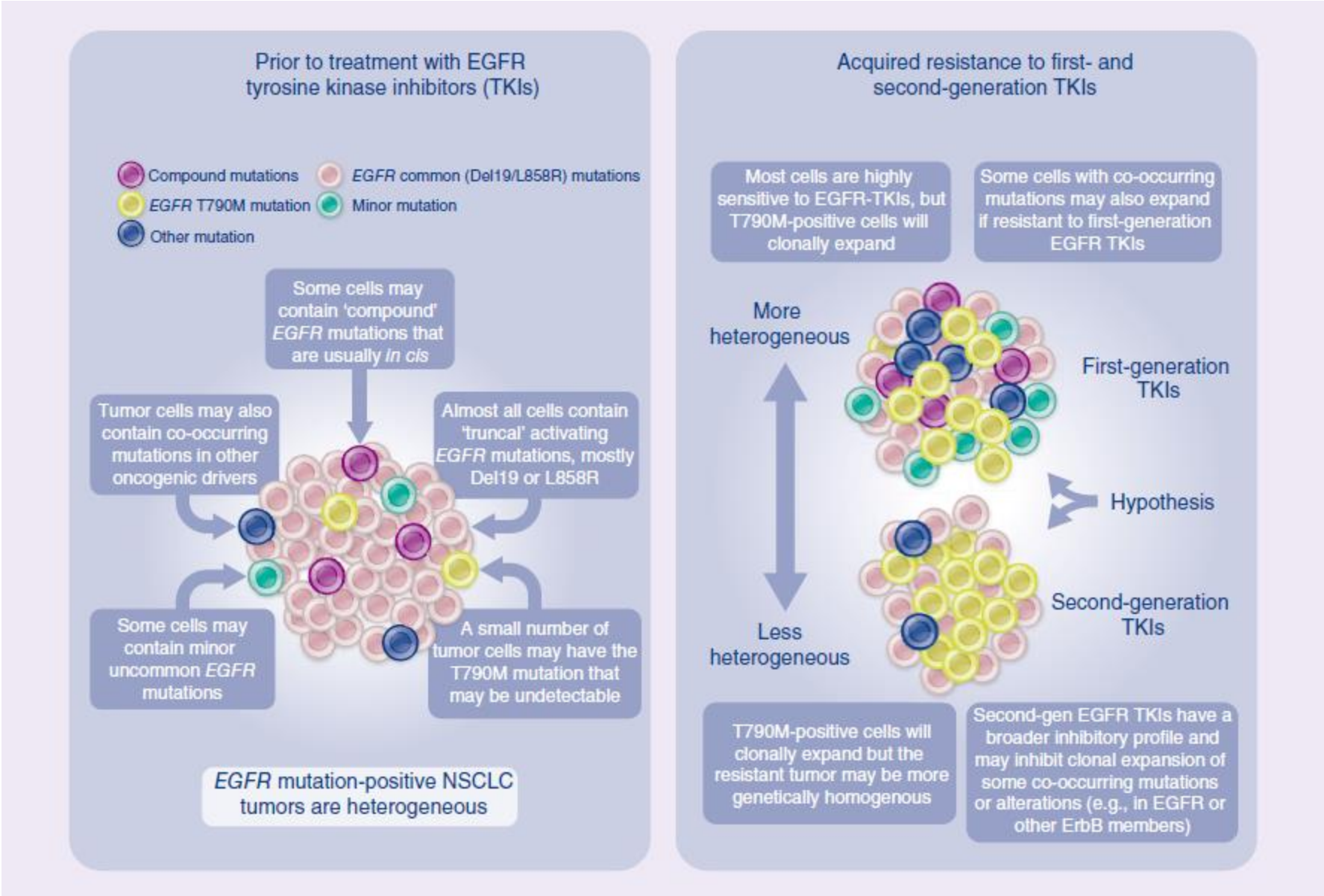
pT2a/pN2a2M0

NGS brief summary:

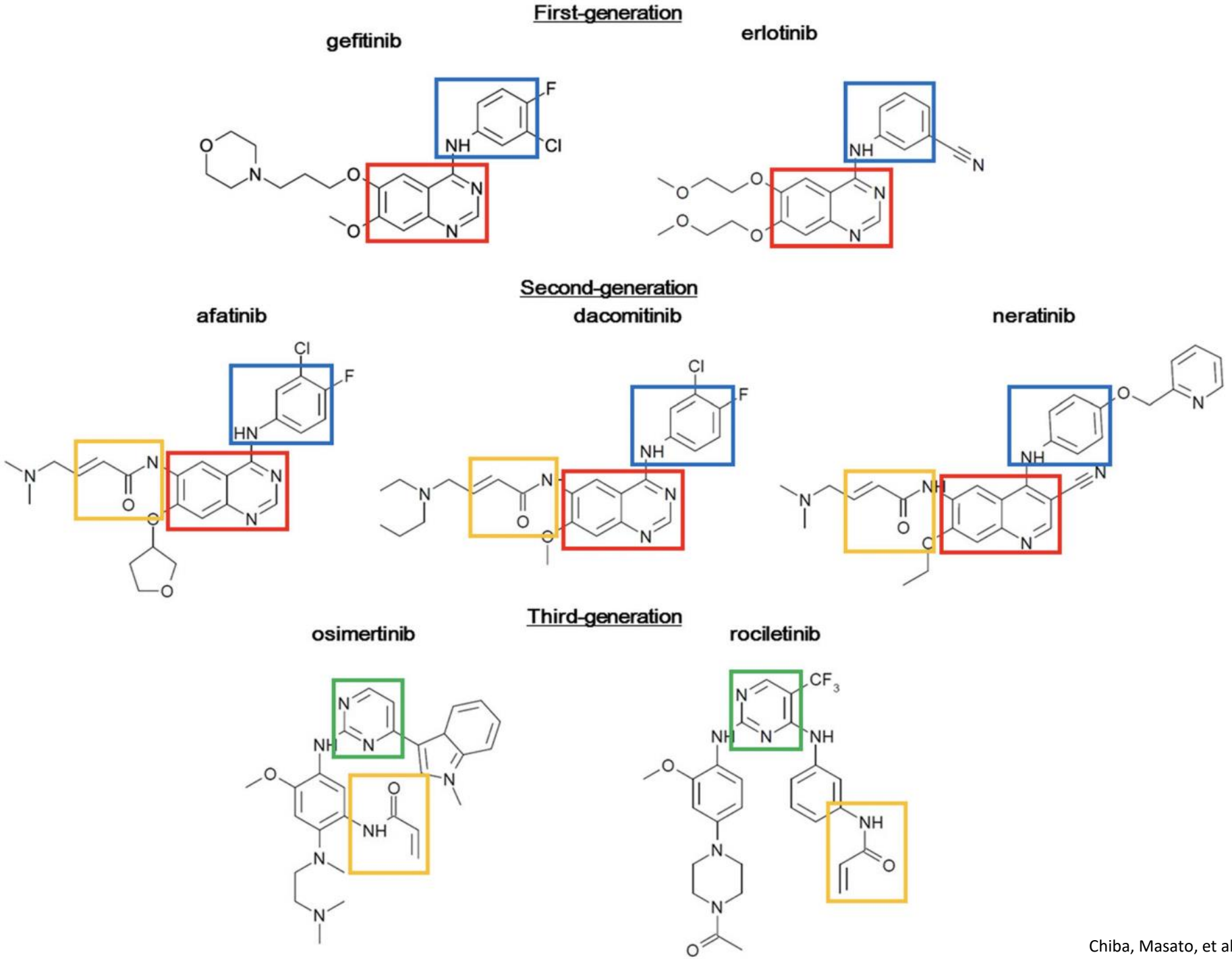
EGFR mutation exon 19 deletion (p.E746_A750del)
TP53 mutation (p.H179R)
AKT2 copy number gain
FGFR3 copy number gain

Adjuvant NP,
11개월 후 recur,
On gefitinib, PR, 26mo

Thank you for your attention!



Kohsaka, Shinji, et al. Future Oncology 15.6 (2019): 637-652.

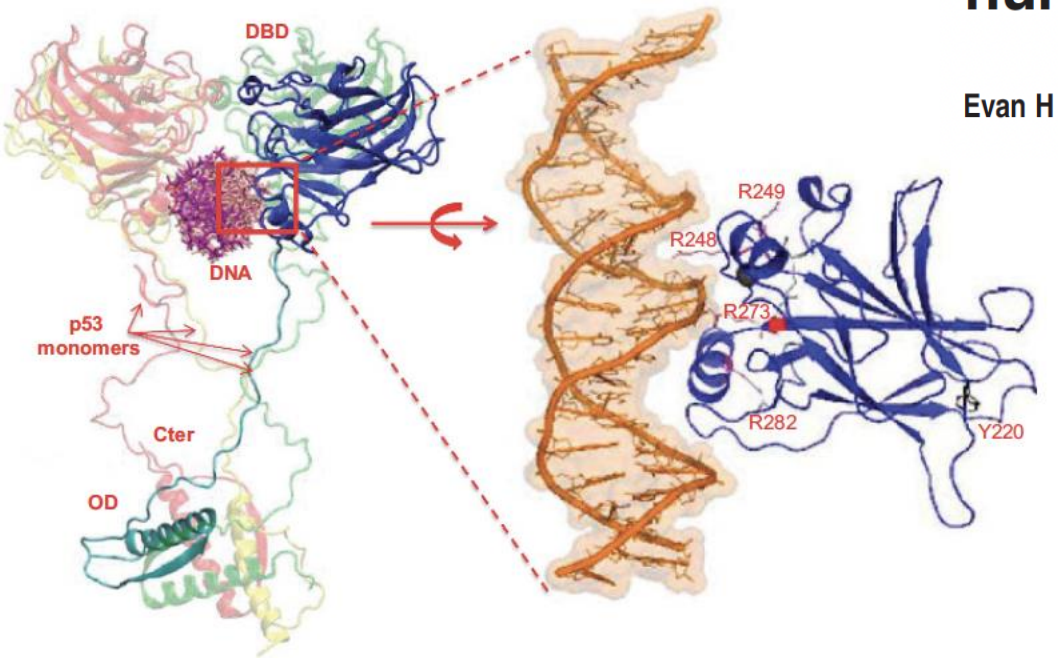


Chiba, Masato, et al. BMC cancer 17.1 (2017): 1-10.

Review

Why are there hotspot mutations in the *TP53* gene in human cancers?

Evan H Baugh[1], Hua Ke[2], Arnold J Levine*[,3], Richard A Bonneau[1,4] and Chang S Chan[2]



Most p53 mutations are at the DNA binding interface: why?

Graphical Abstract

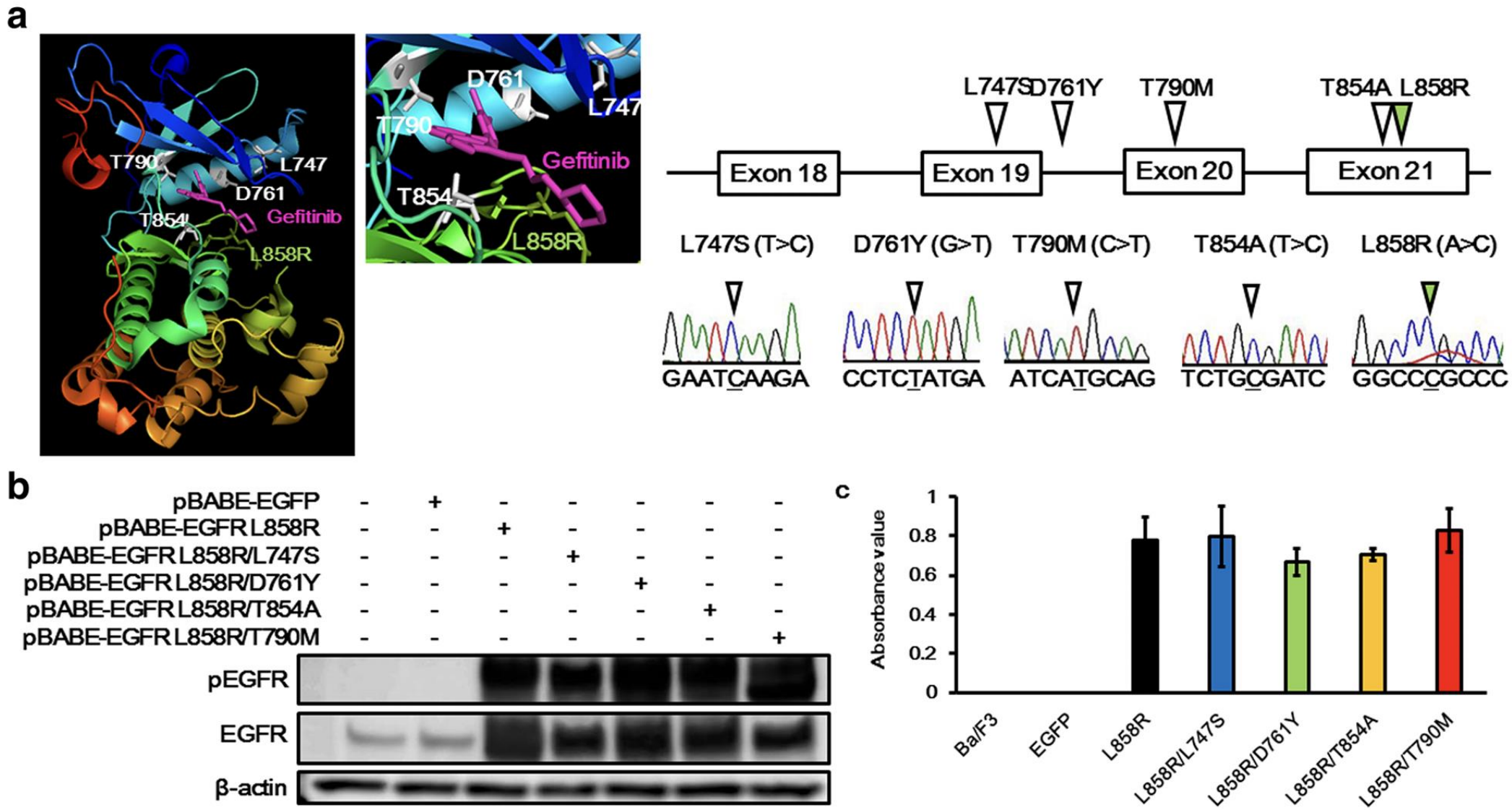
Facts

- TP53 missense mutations are the most common mutation in human cancers.
- Although missense TP53 mutations occur at ~190 codons in the gene, eight of these mutations make up ~28% of all p53 mutations.

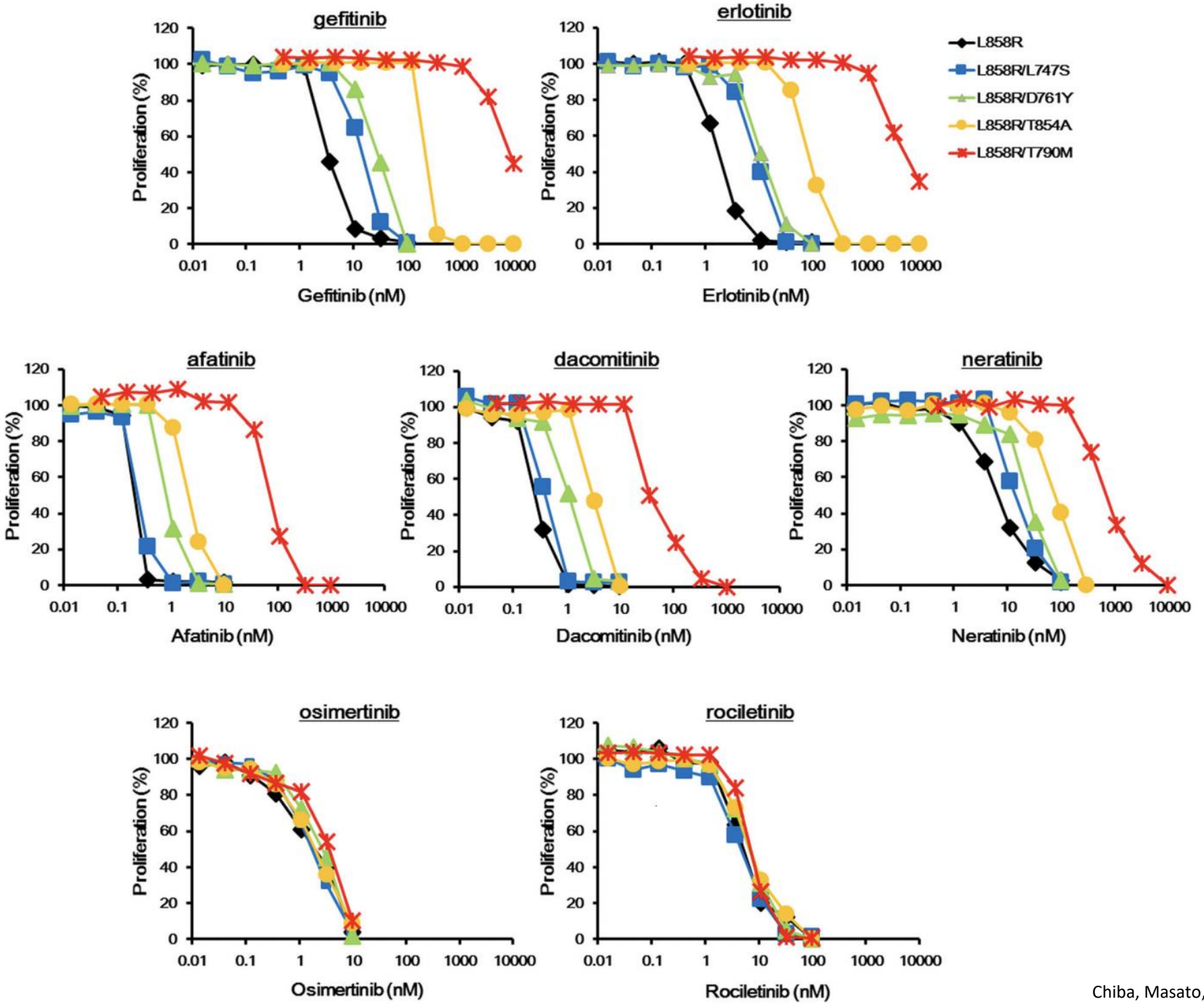
Mutant	Cases	%	VIPUR	Mutant	Cases	%	VIPUR
R175H	1215	5.6	0.742	*R280T*	108	0.5	0.907
R248Q	949	4.37	0.135	P151S	104	0.48	0.492
R273H	856	3.95	0.655	C141Y	103	0.47	0.953
R248W	765	3.53	0.185	C176Y	103	0.47	0.979
R273C	717	3.31	0.947	R158L	103	0.47	.0942
R282W	613	2.83	0.656	H193R	101	0.47	0.508
G245S	457	2.11	0.407	E286K	99	0.46	0.699
R249S	442	2.04	0.302	C135Y	94	0.43	0.962
Subtotal	6014	27.74		P278S	94	0.43	0.75

Open Questions

- Some or possibly all p53 missense mutant proteins demonstrate an ability to gain new functions. Do these gain-of-function mutations that favor a cancer phenotype contribute to the selection of some hotspot mutations?
- What properties of this gain of function are selected for in a cancerous cell?
- What is the mechanism that produces a gain-of-function phenotype?



Chiba, Masato, et al. BMC cancer 17.1 (2017): 1-10.



Chiba, Masato, et al. BMC cancer 17.1 (2017): 1-10.

- Biology

- 동반 변이

- TME

- Prognostic biomarkers

- 동반 변이 in targeted therapies

- IO related biomarkers (PD-L1, TMB are not efficacious)

- Potential subpopulations in ICI Tx

- Multi-organ metastasis, intratumor heterogeneity, tumor NGS

- Poor Px factors: smoker, male, old age, multi-organ metastasis 환자에서 co-mutation, PD-L1, TMB 분석
- Shorter TKI-PFS 의 underlying mechanism, baseline TME, 치료 후 변이 변화 분석, TME 변화 분석
- KRAS 에서처럼, co-occurring genomic alterations에 따라 distinct biology, immune profiles를 가진 define major subsets 구분이 필요하다.
- 결국, after TKI, sequential IO or TKI + IO in subpopulations 의 전략?
- Or 2세대 약제 + 3세대 약제 (lazertinib coverage 확인)

- Real world cohort 를 분석하는 이유:
  responder에서 OS를 더 늘릴 수 있는 방법을 찾고,
  Poor responder를 찾아내고 이들을 위한 another plan을 세우기 위해
- Real-world 2nd line 3rd gen EGFR-TKI 성적 비교

: Global/western/china/japan/Korea

- 1st line TKI 의 SD 비율 vs. 2nd line TKI 의 SD 비율 비교
- 그 이유를 co-mutation 으로 설명? TME 변화?
- Palliative surgery 후 tumor mutation and TME 변화 확인
- 대책:

1) Combination Tx
2) ICI Tx 로부터 benefit 이 있을 수 있는 subpopulation은?

Cancer Res Treat. 2020;52(4):1120-1134 https://doi.org/10.4143/crt.2020.307

Original Article Open Access

Genetic Alterations in Preinvasive Lung Synchronous Lesions

Gene	Amino acid change	Clinical significance (CliniVar ID)	P1								P5				P8			
			AAH1	AAH2	AAH3	AIS	MIA1	MIA2	ADC1	ADC2	AAH	AIS	MIA	ADC	AAH	AIS	MIA	AD
EGFR	p.G719D		-	-	-	-	-	-	-	9	-	-	-	-	-	-	-	-
	p.G719C	Pathogenic (45225)	-	-	-	-	-	-	-	-	-	17	-	-	-	-	-	-
	p.L858R	Drug response (16609)	-	-	-	-	-	-	-	-	20	0.5[a)]	15	30	-	-	-	-
TP53	c.240_240delinsT		-	-	-	-	13	-	-	-	-	-	-	-	-	-	-	-
	p.Q60X (stopgain)		-	-	-	-	-	-	42	43	-	-	-	-	-	-	-	-
KRAS	p.Q61H	Pathogenic/likely pathogenic (177881)	-	-	-	-	-	-	-	-	-	-	-	-	7	-	-	-
	p.G13C	Pathogenic (45123)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	8
	p.G12V	Pathogenic (12583)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	15	-
BRAF	p.G466V	Pathogenic/likely pathogenic (13967)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	15
	p.G464R	Pathogenic (279992)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	16	-
SETD2	p.P2124Q		-	-	-	-	-	-	-	-	-	-	-	-	-	4	-	-
	p.R441Q		-	5	-	-	-	-	-	-	-	-	-	-	-	-	-	-
CTNNB1	p.D115V		-	-	-	-	12	11	-	-	-	-	-	-	-	-	-	-
NF1	p.N1388K		-	-	-	-	-	-	-	-	5	-	-	-	-	-	-	-
RBM10	p.Y505X		-	-	-	-	-	-	-	-	-	-	8	-	-	-	-	-
	c.2337_2337delins-G		-	-	-	-	27	13	-	-	-	-	-	-	-	-	-	-
	p.G780V		-	-	-	-	28	14	-	-	-	-	-	-	-	-	-	-
RBM23	p.A355A		-	-	-	-	-	-	-	-	20	19	22	-	-	17	15	19
SMARCA4	p.E1133E		-	-	-	12	-	-	-	-	-	-	-	-	-	-	-	-
U2AF1	p.S34F	Likely pathogenic (376025)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	46

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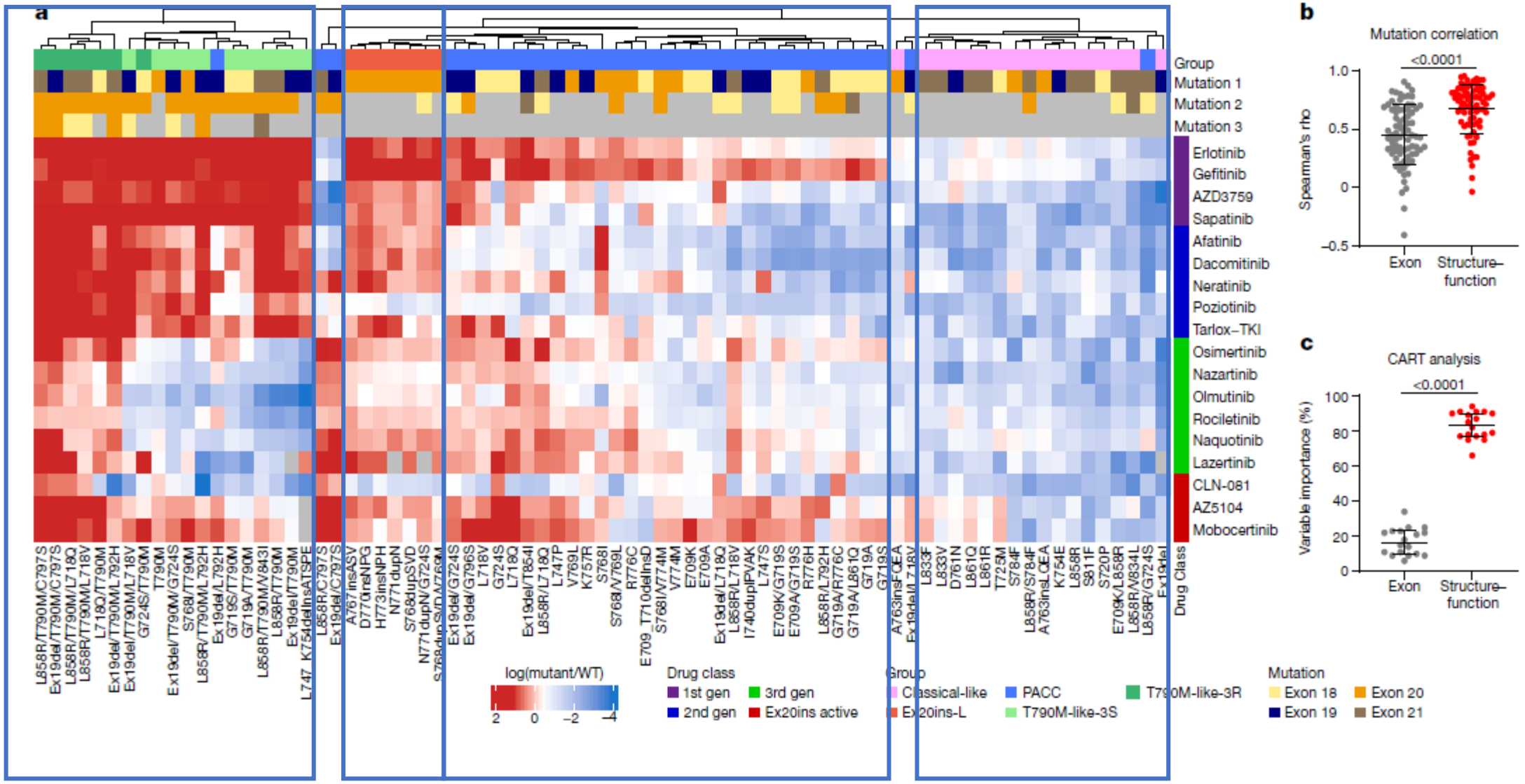

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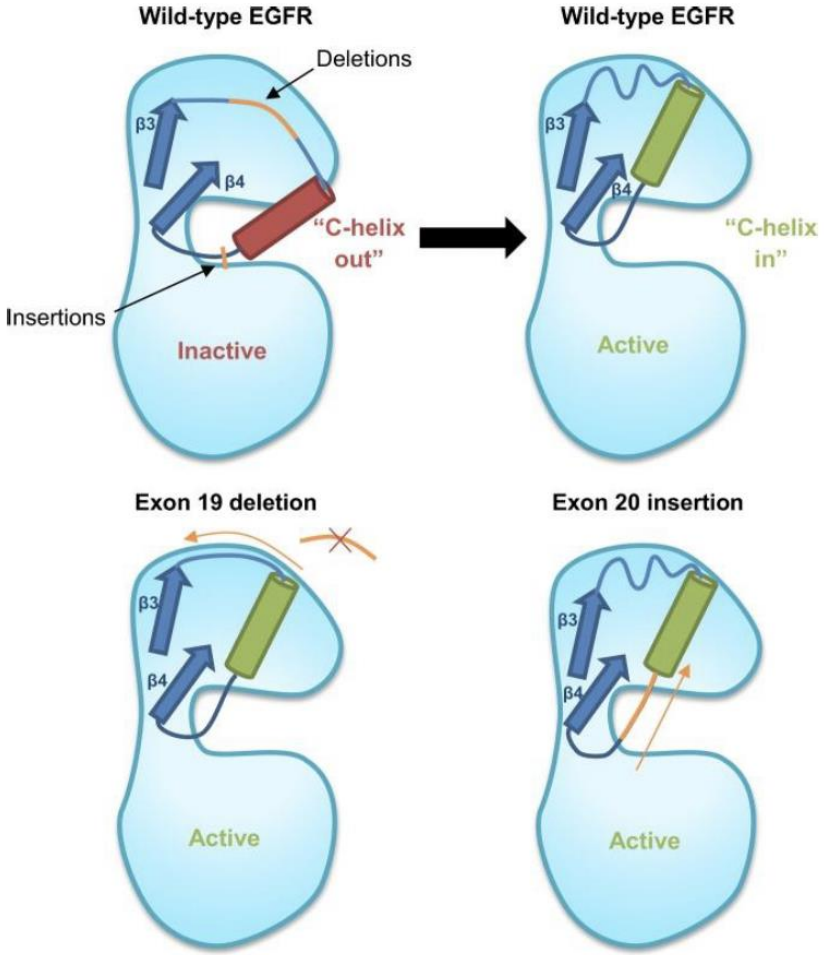
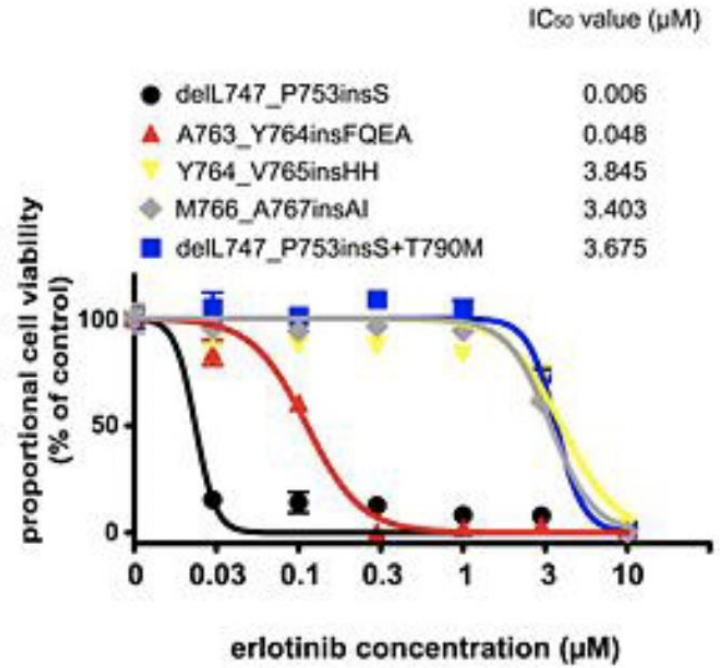


- Currently approved TKIs have limited activity in the frontline setting:
  - 1st gen: Erlotinib/gefitinib (RR, 8% to 27%; median PFS, <3 months)
  - 2nd gen: Afatinib (RR, 8.7%; median PFS, 2.7 months)
  - 3rd gen: Osimertinib 80 mg (RR, 5%; median PFS, 3.6 months)



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