Targeted agents in lung cancer

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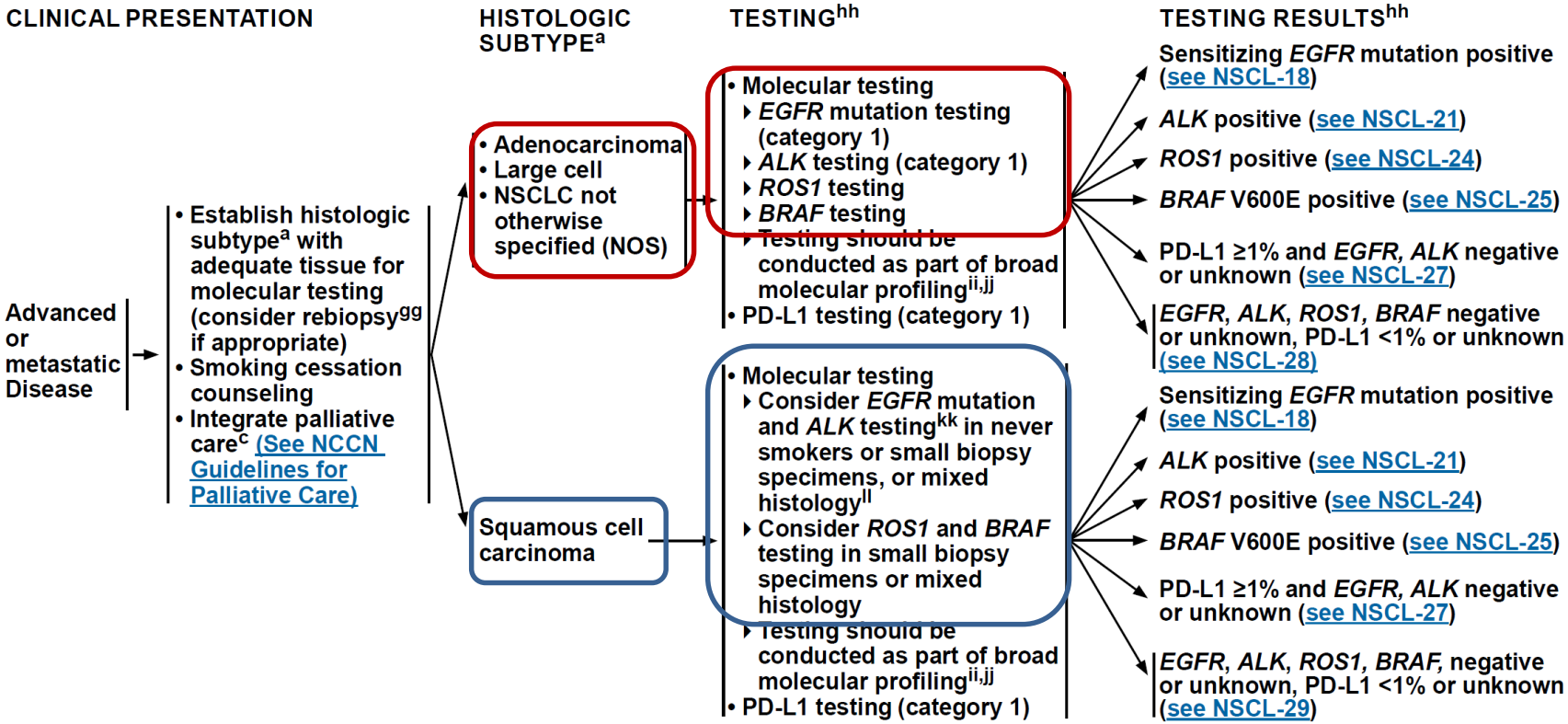
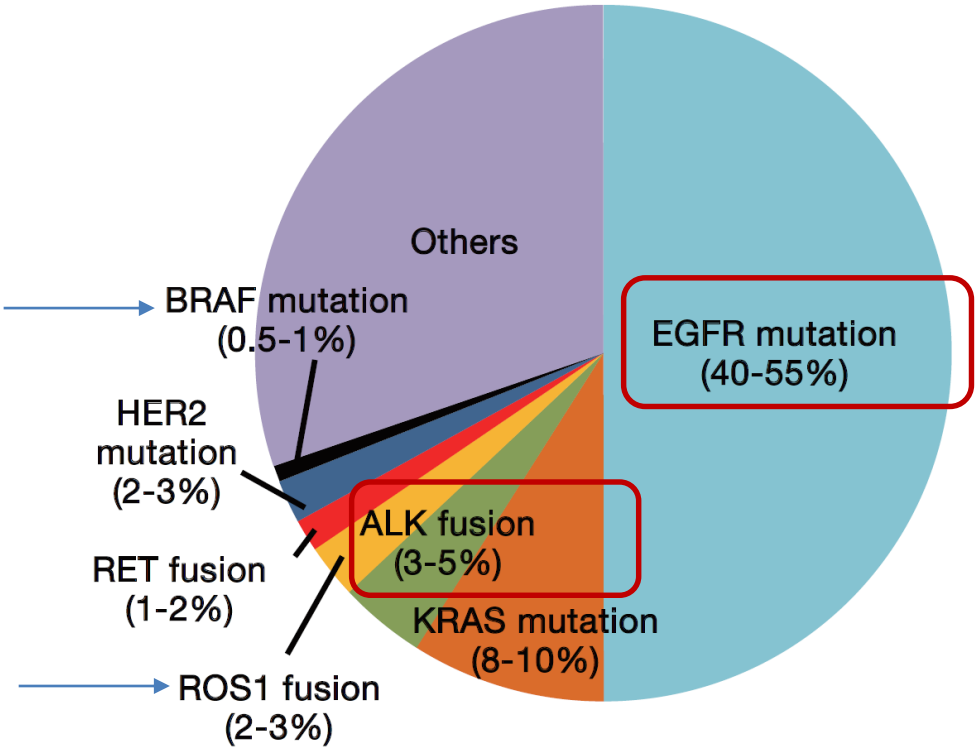
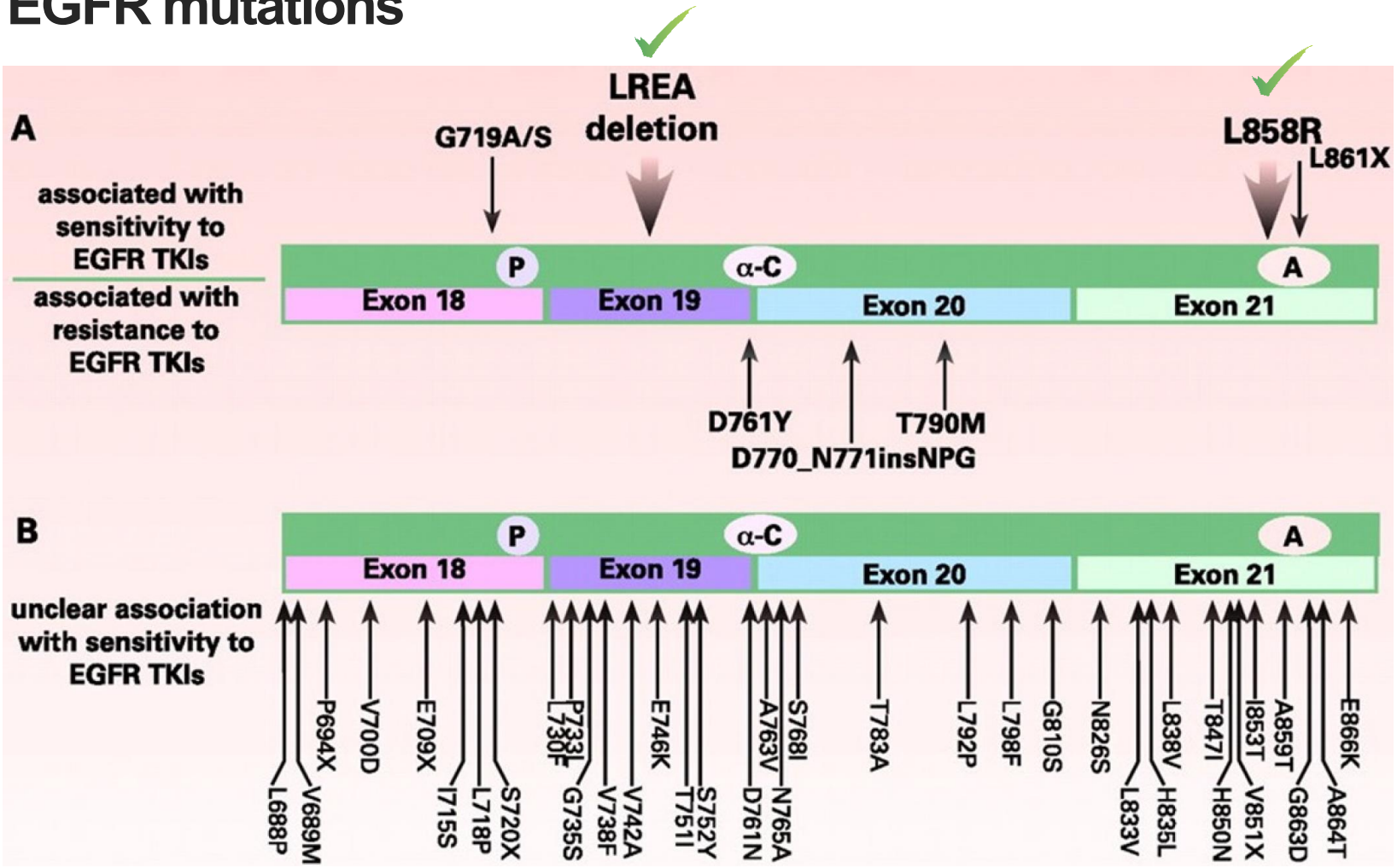
NCCN Guidelines Version 4.2019
Non-Small Cell Lung Cancer





Transl Lung Cancer Res 2015;4(2):156-164

EGFR mutations



Ahmed *et al. J Unexplored Med Data* 2017;2:39-47

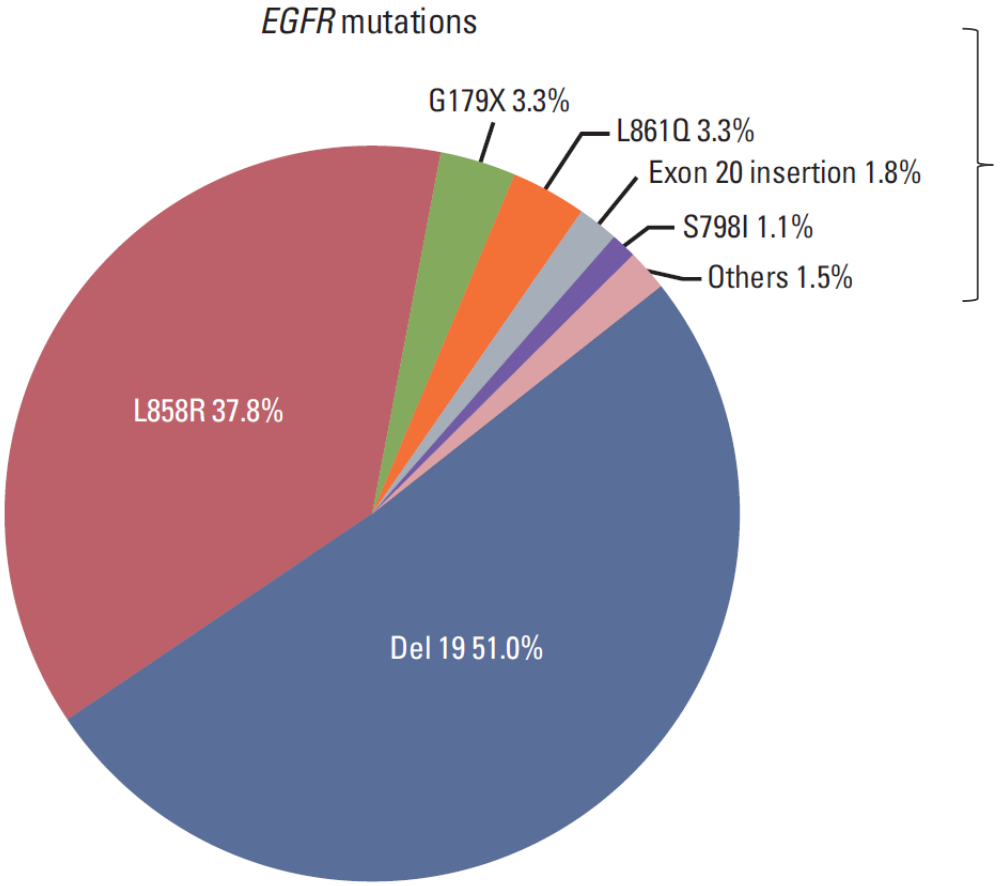


Fig. 1. Distribution of epidermal growth factor receptor (*EGFR*) mutations in advanced non-small cell lung cancer patients (n=1,479).

Cancer Res Treat. 2019;51(2):623-631

EGFR mutation by PNA clamping (real-time PCR)

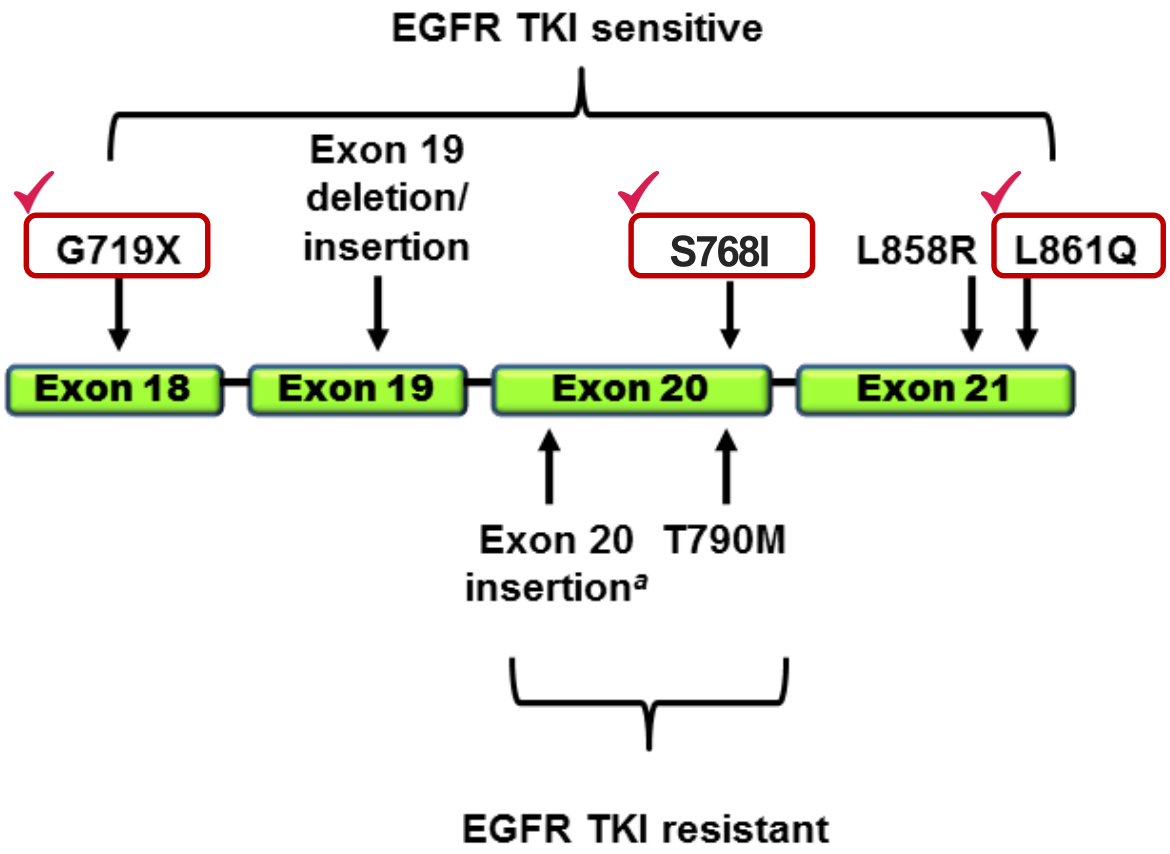
EGFR 19 V742S

EGFR 20 ins

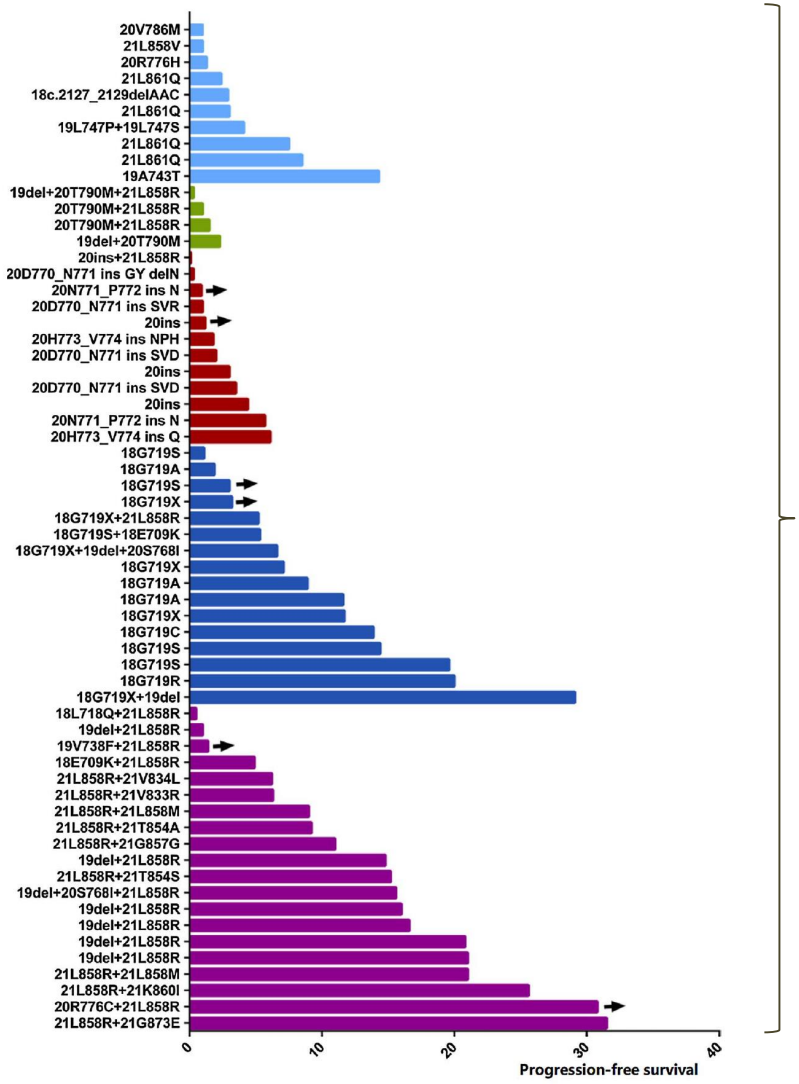
EGFR T790M + L858R

Uncommon mutations in epidermal growth factor receptor and response to first and second generation tyrosine kinase inhibitors: A case series and literature review

Mutations	N	TKI	BOR	RR	DCR
Exon 18					
G719any[a]	142	108 (E, G)	38 PR, 34 SD, 34 PD, 2 NA	35.2%	66.7%
E709-T710 deletions	6	4 (E, G)	1 SD, 3 PD	0.0%	25.0%
E709any[b]	5	3 (E, G)	2 SD, 1 PD	0.0%	66.7%
S720any	5	3 (E)	1 SD, 2 PD	0.0%	33.3%
Other point mutations[c]	23	17 (A, E, G)	2 PR, 4 SD, 10 PD, 1 NA	11.8%	35.3%
Exon 19					
V742any	3	3 (E, G)	2 PR, 1 SD	66.7%	100.0%
E746any	3	0	NA	NA	NA
Other point mutations	12	12 (A, E, G)	1 PR, 4 SD, 4 PD, 3 NA	8.3%	41.7%
Multiple codon insertions	4	1 (E)	1 PR	100.0%	100.0%
Exon 20					
S768I	20	15 (A, G, E)	4 PR, 6 SD, 5 PD	26.7%	66.7%
Multiple codon insertions from A767	17	9 (E, G)	5 SD, 4 PD	0.0%	55.6%
Multiple codon insertions from D770	9	4 (E, G)	1 PR, 1 SD, 2 PD	25.0%	50.0%
Multiple codon insertions from H773	8	4 (E, G)	2 SD, 2 PD	0.0%	50.0%
S768I + other exon 20 mutations	7	5 (E, G)	1 PR, 3 SD, 1 PD	20.0%	80.0%
De novo T790M	7	6 (E)	1 PR, 1 SD, 3 PD, 1 NA	16.7%	33.3%
Multiple codon insertions from S768	5	5 (E)	1 SD, 3 PD, 1 NA	0.0%	20.0%
V774any	4	4 (E, G)	1 PR, 3 PD	25.0%	25.0%
Multiple codon insertions from P772	3	2 (E, G)	2 PD	0.0%	0.0%
Other point mutations[d]	18	10 (E, G)	3 PR, 1 SD, 4 PD, 2 NA	30.0%	40.0%
Other single codon insertions	17	5 (E, G)	2 PR, 2 SD, 1 PD	40.0%	80.0%
Other multiple codon insertions	11	6 (A, E, G)	2 PR, 3 SD, 1 PD	33.3%	83.3%
Exon 21					
L861any[e]	79	70 (E, G)	27 PR, 24 SD, 19 PD	38.6%	72.9%
L858R + other exon 21 mutations	15	12 (E, G)	6 PR, 3 SD, 3 PD	50.0%	75.0%
V851any[f]	3	2 (E, G)	1 SD, 1 PD	0.0%	50.0%
H835any[g]	3	1 (E)	1 PR	100.0%	100.0%
A859any[h]	3	3 (E)	1 PR, 1 PD, 1 NA	33.3%	33.3%
V843any	3	2 (E)	2 PD	0.0%	0.0%
T854any[i]	3	3 (E, G)	1 SD, 2 PD	0.0%	33.3%
Other point mutations[j]	23	18 (E, G)	3 PR, 8 SD, 6 PD, 1 NA	16.7%	61.1%


EGFR TKI sensitive
Exon 19 deletion/ insertion
G719X
S768I
L858R
L861Q
Exon 18
Exon 19
Exon 20
Exon 21
Exon 20 insertion[a]
T790M
EGFR TKI resistant

What if other uncommon mutations?

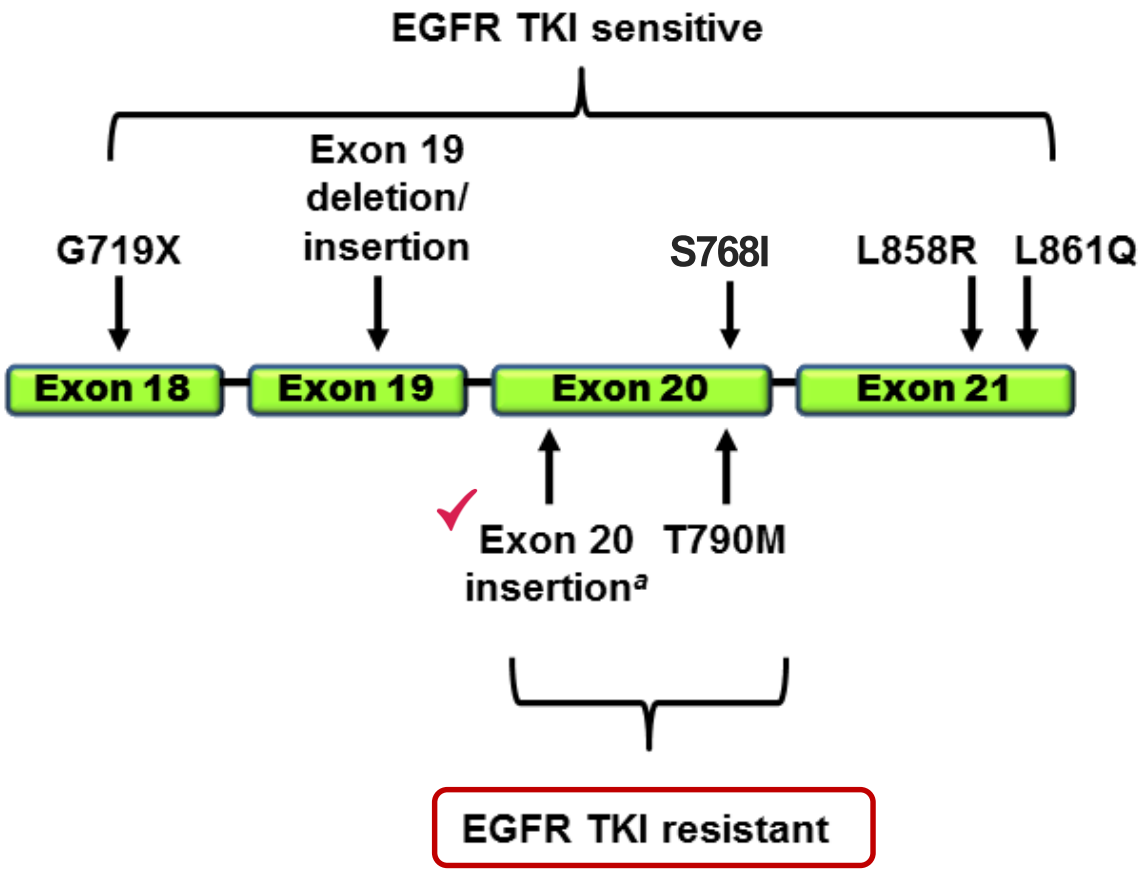


Heterogeneous

Too small to prove

Worth a try !

Lung Cancer 114 (2017) 96–102


EGFR TKI sensitive
Exon 19 deletion/ insertion
G719X
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L861Q
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Exon 19
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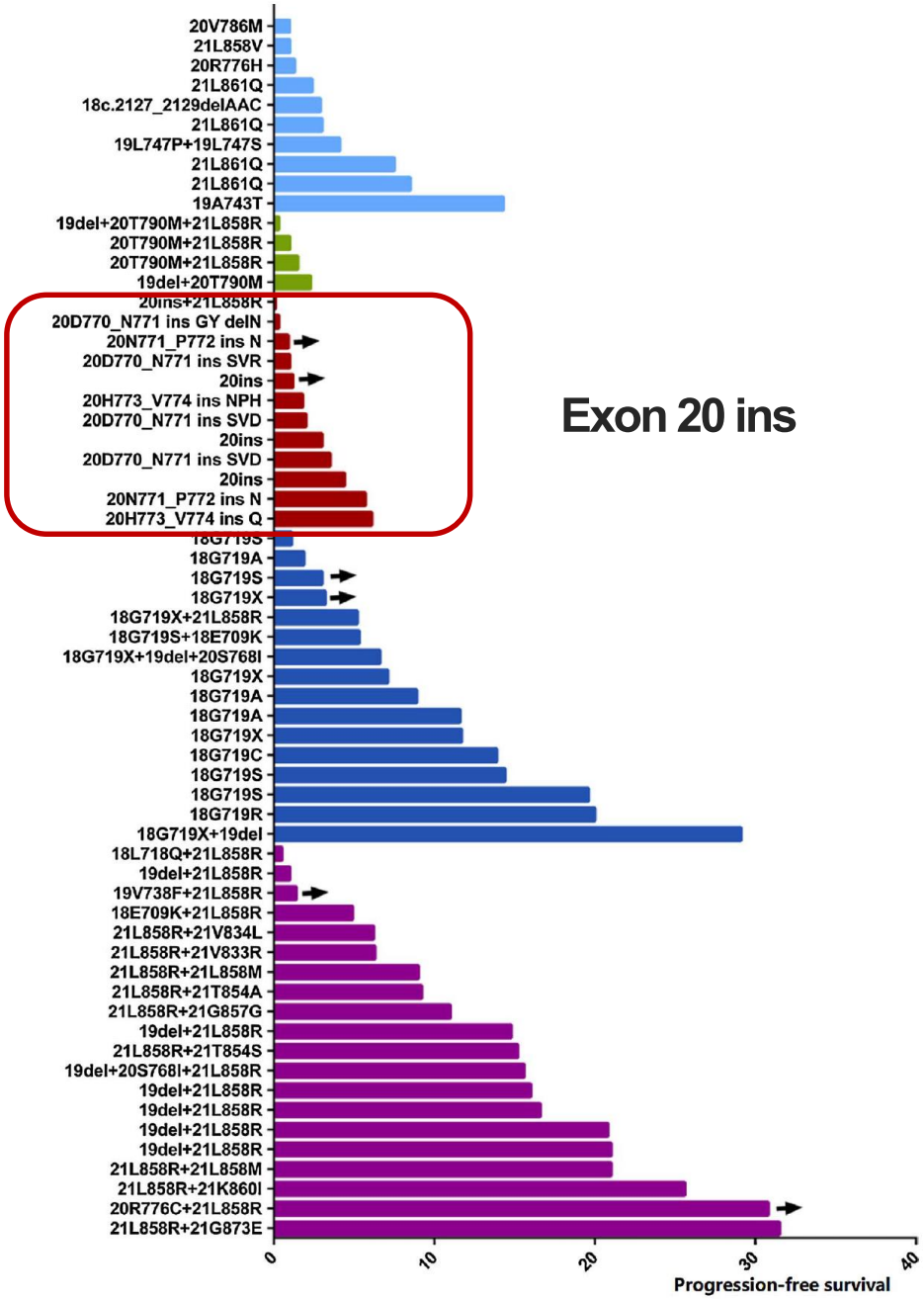
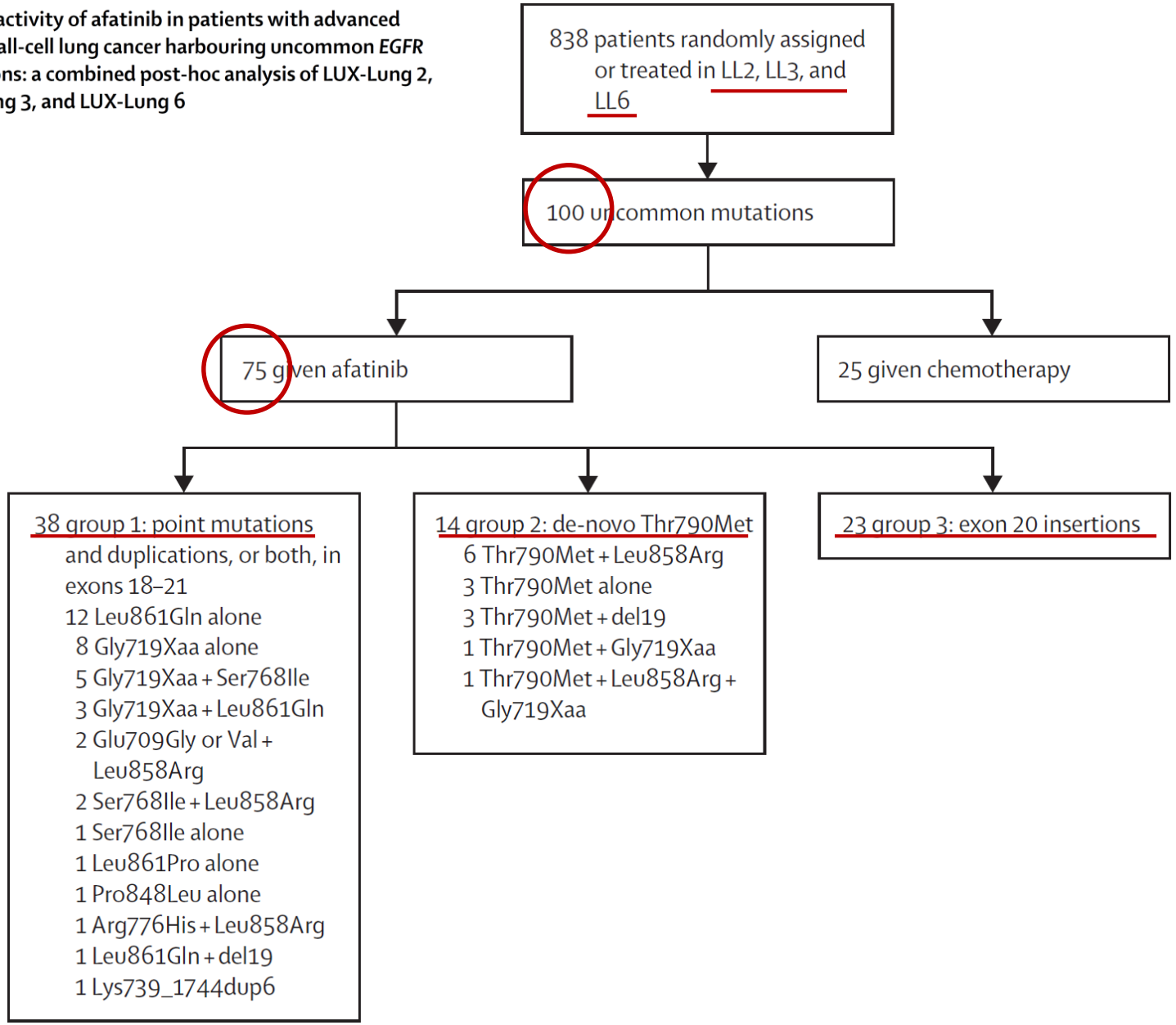
Exon 21
Exon 20 insertion[a]
T790M
EGFR TKI resistant

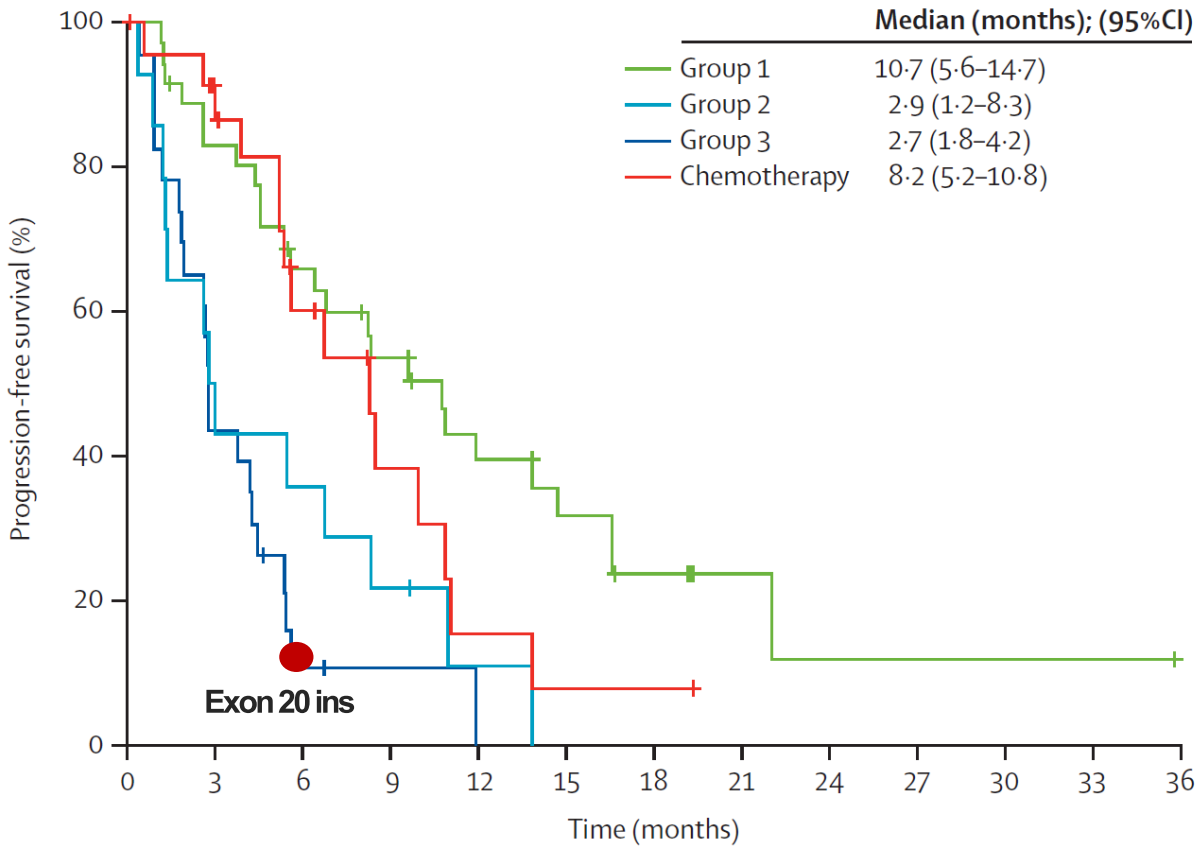


Exon 20 ins

Lung Cancer 114 (2017) 96–102

Clinical activity of afatinib in patients with advanced non-small-cell lung cancer harbouring uncommon *EGFR* mutations: a combined post-hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6





Number at risk

Group 1	38	29	22	17	11	8	5	2	1	1	1	1	0
Group 2	14	6	5	3	1	0	0	0	0	0	0	0	0
Group 3	23	10	2	1	0	0	0	0	0	0	0	0	0
Chemotherapy	25	18	10	5	2	1	1	0	0	0	0	0	0

Table 4. Clinical information and treatment outcomes of six patients who received EGFR TKIs

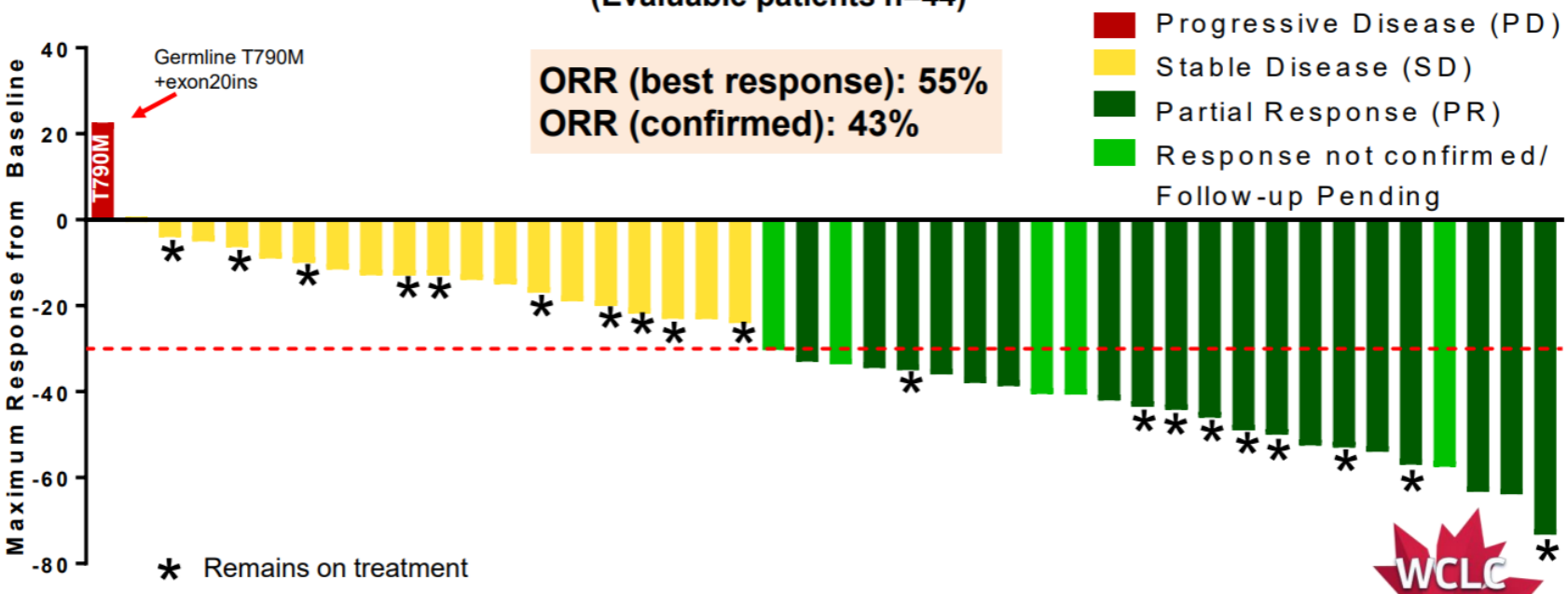
Sex	Age (yr)	Exon 20 type	ECOG	Smoking history	Initial stage	TKI type	EGFR TKI response	PFS
F	44	Insertion	1	Never-smoker	IV	Erlotinib	PD	0.7
M	65	Insertion	2	Never-smoker	IV	Afatinib	PD	0.9
M	60	Insertion	1	Current smoker 30PY	IV	Erlotinib	PD	2.6
M	48	Insertion	0	Ex-smoker 20PY	IV	Erlotinib	SD	11.4
M	62	Insertion+L858R	1	Ex-smoker 10PY	IIB	Afatinib	PR	1.9
F	43	Insertion+G719S	1	Never-smoker	IV	Osimertinib	PR	2.8

Table 5. Published studies evaluating clinical response to EGFR TKIs in NSCLC patients with exon 20 insertion

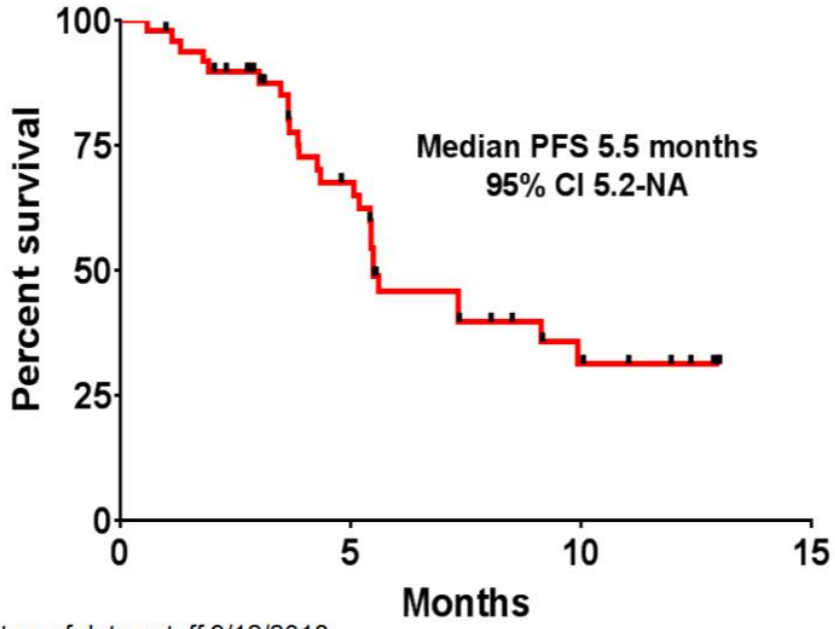
Study	Type of *EGFR* Exon 20 mutation	Patients treated with EGFR TKIs	ORR to TKI (%)	PFS to TKI	OS
Tu et al. [18]	Insertion 20	12	0	3.0 (1.3-4.7)	12.5 (0-25.5)
Lund-Iversen et al. [13]	Insertion 20	3	0	-	-
Arcila et al. [15]	Insertion 20	5	40	2.5	> 48 mo
Naidoo et al. [12]	Insertion 20	11	27	-	-
Yasuda et al. [17]	Insertion 20	19	11	-	-
Kuiper et al. [19]	Insertion 20	16	0	2.9 (2.3-3.6)	9.7
Current study	Insertion 20	4	25	2.6 (0.7-11.4)	29.4 (9.3-49.6)

Poziotinib efficacy in EGFR Exon 20 mutant NSCLC

(Evaluable patients n=44)



Progression Free Survival (ITT population)



*19 patients remain on treatment as of data cutoff 9/12/2018

M/67 ACC M/brain, lung EGFR 20 ins

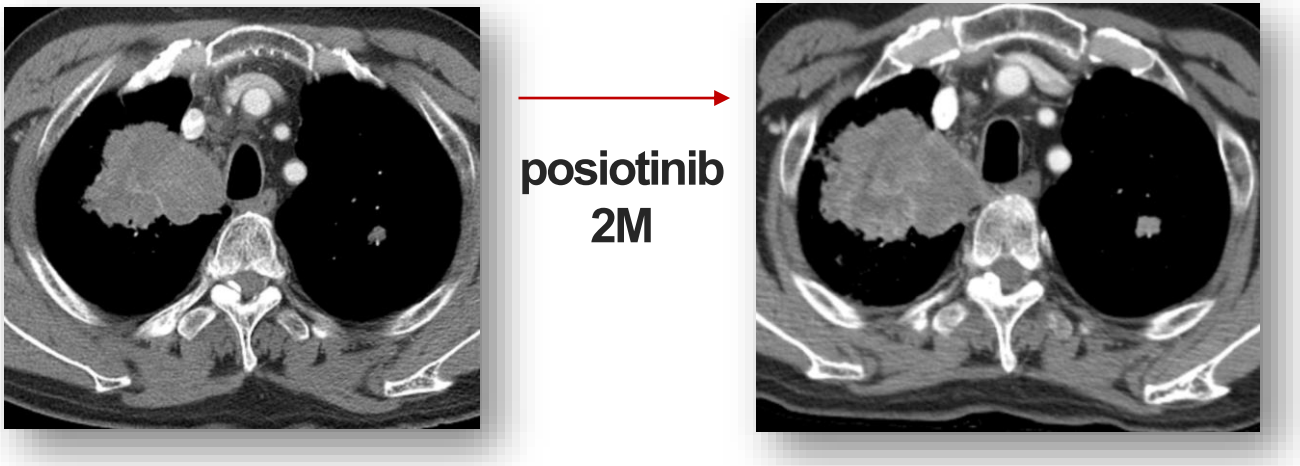
1L pemetrexed #4 after PP#4 (PR)

2L erlotinib (PD)

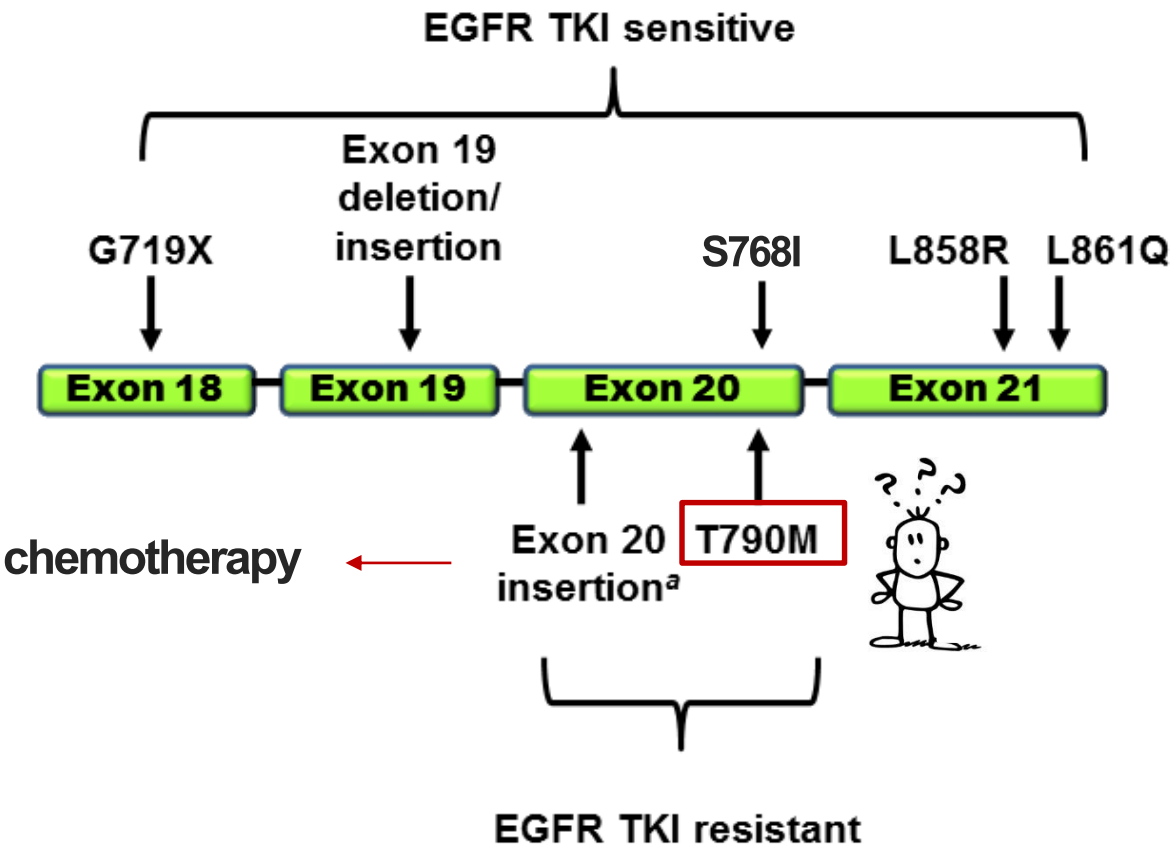
3L GC #4 (PR)

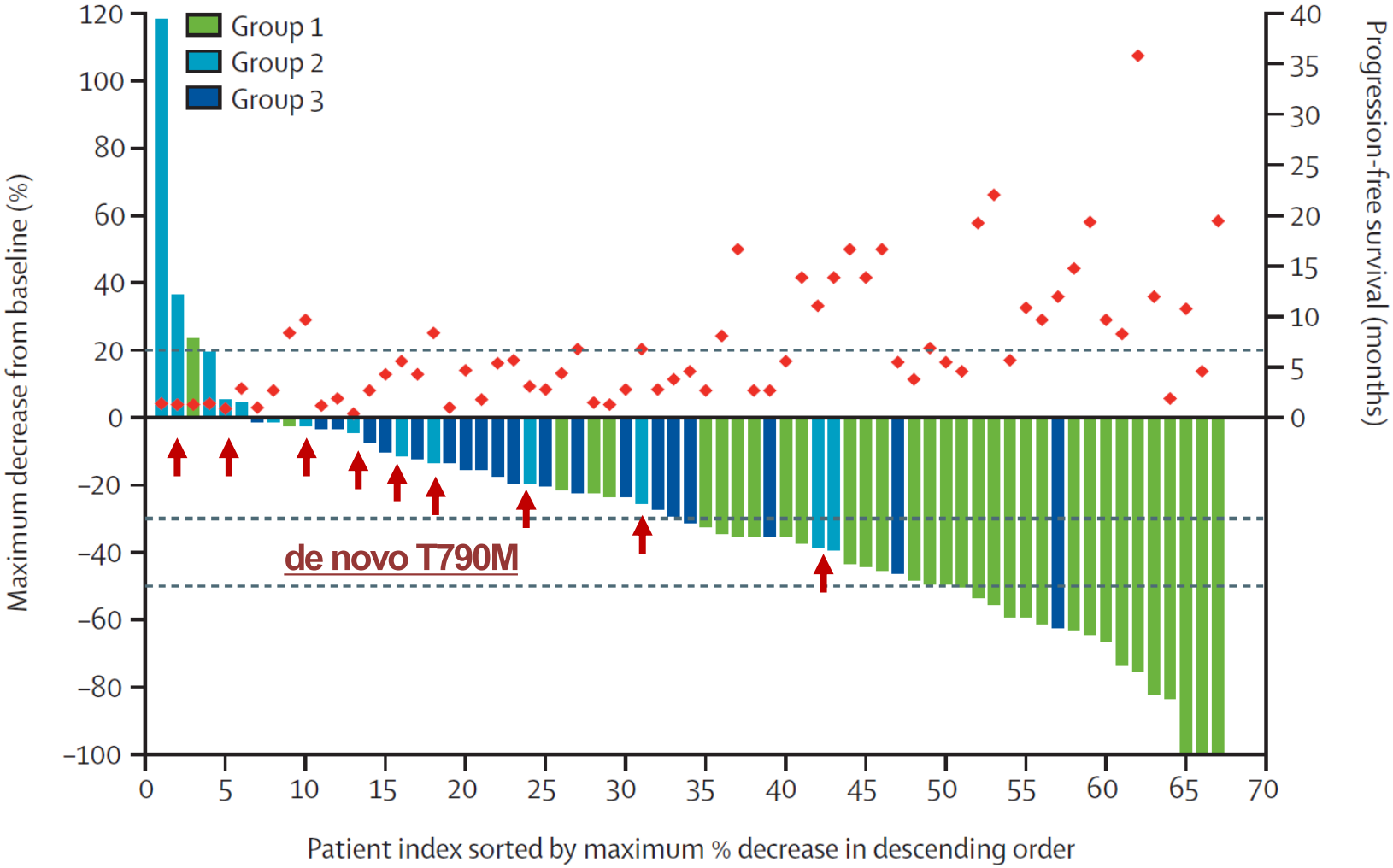
4L docetaxel (PD)

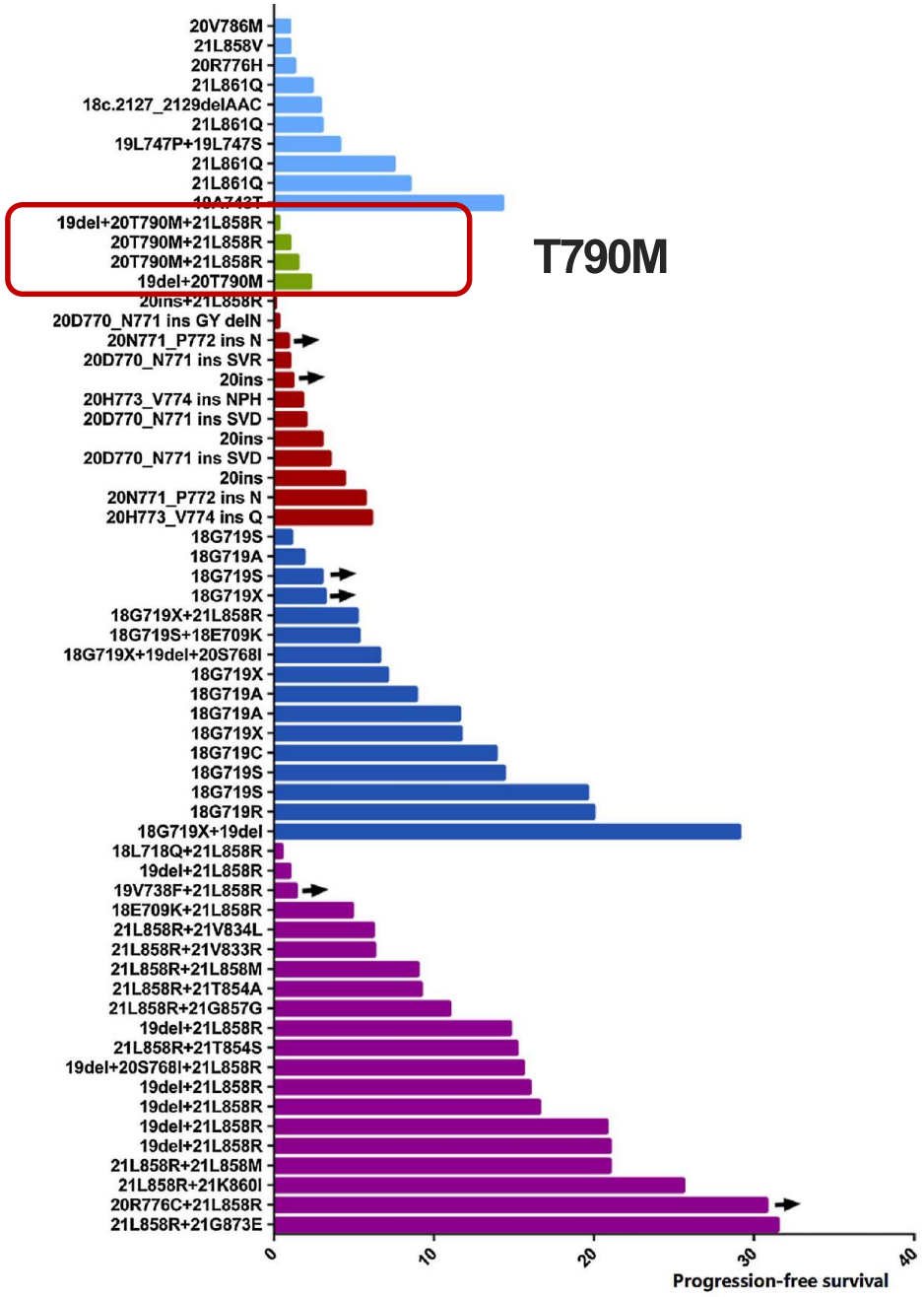
5L poziotinib



AE; skin rash, stomatitis, dyspepsia (all Gr 2)


EGFR TKI sensitive
Exon 19 deletion/ insertion
G719X
S768I
L858R
L861Q
Exon 18
Exon 19
Exon 20
Exon 21
chemotherapy
Exon 20 insertion[a]
T790M
EGFR TKI resistant


Group 1
Group 2
Group 3
de novo T790M
Maximum decrease from baseline (%)
Progression-free survival (months)
Patient index sorted by maximum % decrease in descending order
120
100
80
60
40
20
0
−20
−40
−60
−80
−100
40
35
30
25
20
15
10
5
0
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70



T790M

Lung Cancer 114 (2017) 96–102

Pretreatment EGFR T790M Mutation and BRCA1 mRNA Expression in Erlotinib-Treated Advanced Non–Small-Cell Lung Cancer Patients with EGFR Mutations

	All patients	T790M present	T790M absent	
	***n* = 129** ***n* (%)**	***n* = 45** ***n* (%)**	***n* = 84** ***n* (%)**	***P***
Age, median (range)	67 (22–86)	68 (22–80)	65.5 (35–86)	0.31
Sex				0.31
Male	36 (27.9)	10 (22.2)	26 (31)	
Female	93 (72.1)	35 (77.8)	58 (69)	
Bone metastases				0.03
No	99 (76.7)	29 (64.4)	70 (83.3)	
Yes	30 (23.3)	16 (35.6)	14 (16.7)	
Brain metastases				0.99
No	116 (89.9)	41 (91.1)	75 (89.3)	
Yes	13 (10.1)	4 (8.9)	9 (10.7)	
Erlotinib therapy				0.58
First-line	65 (50.4)	21 (46.7)	44 (52.4)	
Second-line	64 (49.6)	24 (53.3)	40 (47.6)	
Type of EGFR mutation				0.05
del 19	81 (62.8)	23 (51.1)	58(69)	
L858R	48 (37.2)	22 (48.9)	26(31)	
Response				0.39
Complete or partial response	80 (68.9)	28 (63.6)	52 (72.3)	

Pretreatment Epidermal Growth Factor Receptor (*EGFR*) T790M Mutation Predicts Shorter EGFR Tyrosine Kinase Inhibitor Response Duration in Patients With Non–Small-Cell Lung Cancer

		Responders to TKI (PR)		
		No.	%	*P*†
EGFR-activating mutations¶	56	37	66.1	
With T790M	23	13	56.5	.257
Without T790M	33	24	72.7	

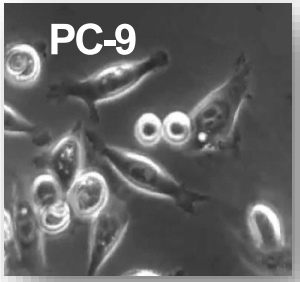
J Clin Oncol 30:433-440.

T790M

Not categorical (binary) variable

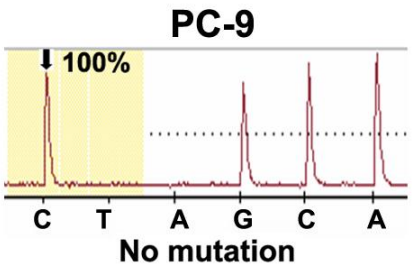
Continuous variable

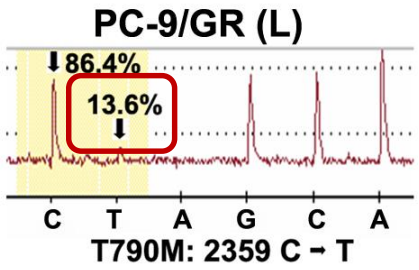
6 months

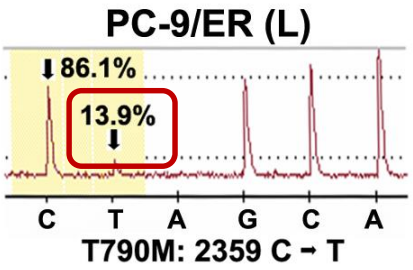


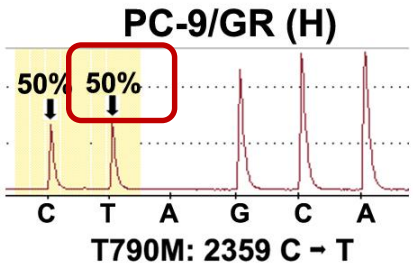
Gefitinib	PC-9/GR/L	PC-9/GR/H
Erlotinib	PC-9/ER/L	PC-9/ER/H

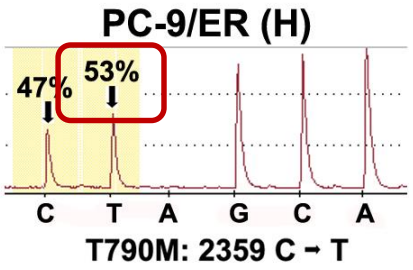
>12 months

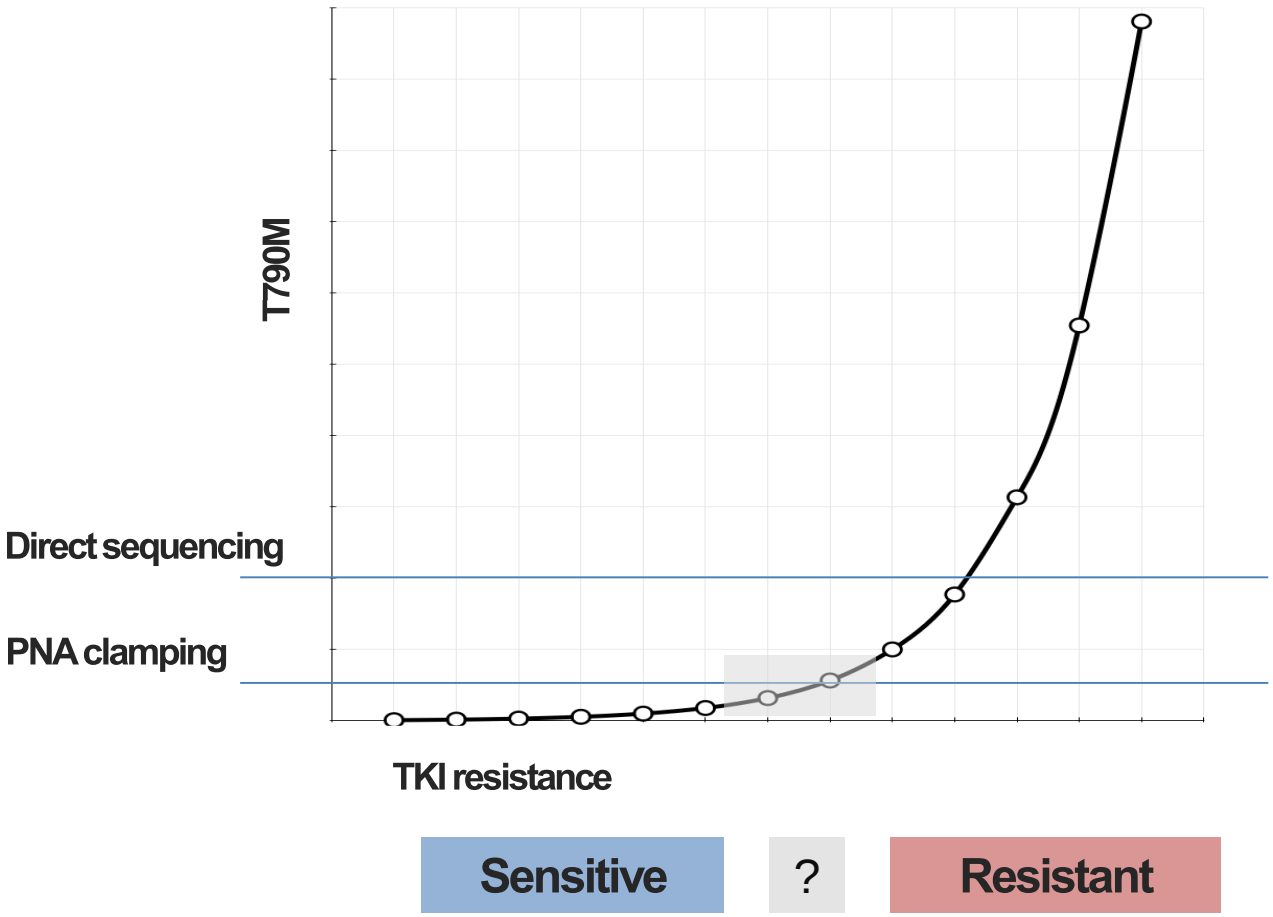











T790M
Direct sequencing
PNA clamping
TKI resistance
Sensitive
?
Resistant

de novo T790M in Korea

1st or 2nd generation EGFR-TKI

3rd generation EGFR-TKI

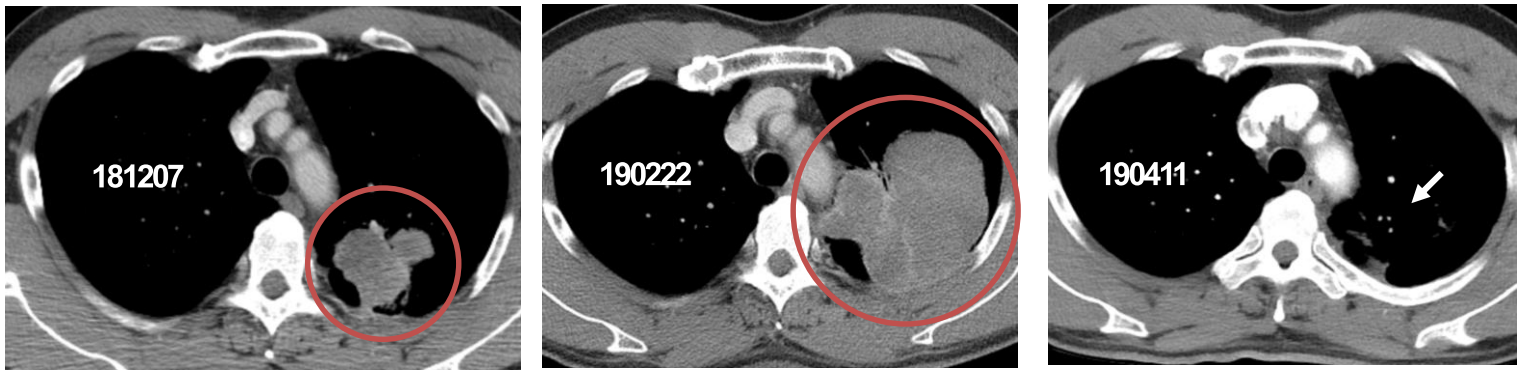
M/49 ACC M/pleura 19del + T790M PD-L1-

1L pemetrexed #2 after PP#4 (외부병원)

Rebiopsy done 19del + T790M

2L gefitinib

3L osimertinib

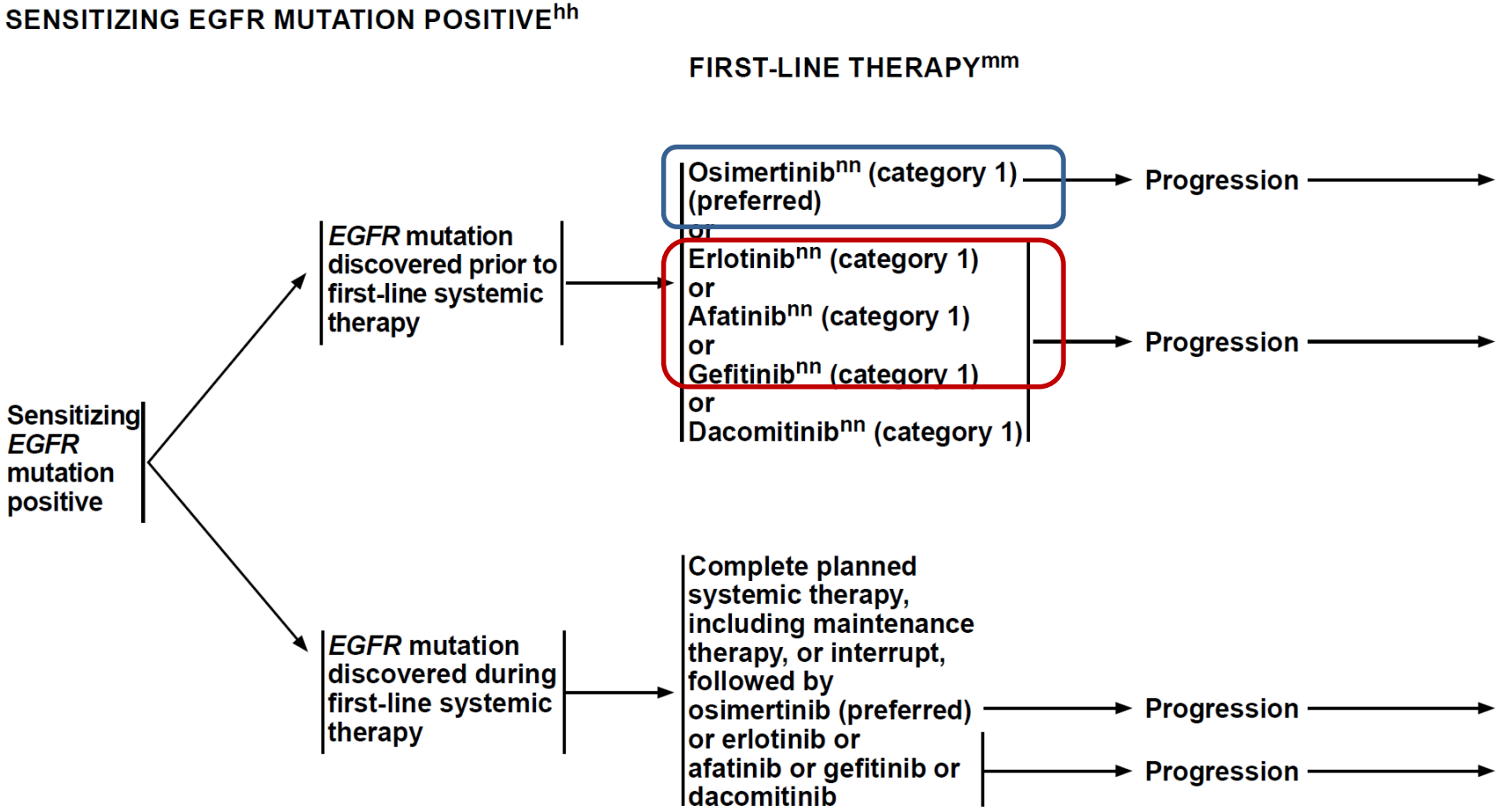


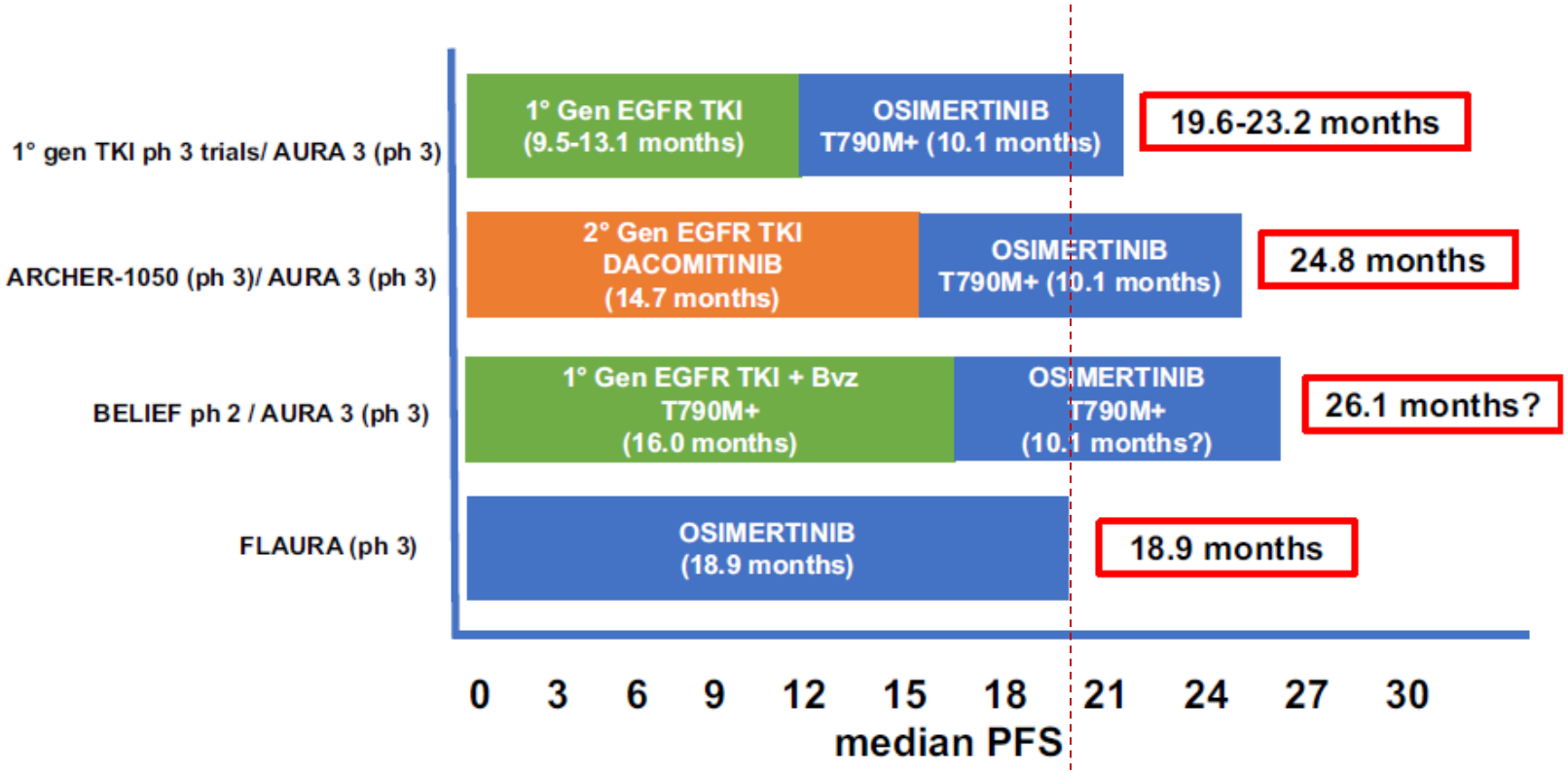
gefitinib

190124

osimertinib

190222


SENSITIZING EGFR MUTATION POSITIVE[hh]
FIRST-LINE THERAPY[mm]
Sensitizing EGFR mutation positive
EGFR mutation discovered prior to first-line systemic therapy
EGFR mutation discovered during first-line systemic therapy
Osimertinib[nn] (category 1) (preferred)
or
Erlotinib[nn] (category 1)
or
Afatinib[nn] (category 1)
or
Gefitinib[nn] (category 1)
or
Dacomitinib[nn] (category 1)
Complete planned systemic therapy, including maintenance therapy, or interrupt, followed by osimertinib (preferred) or erlotinib or afatinib or gefitinib or dacomitinib
Progression
Progression
Progression
Progression


1° gen TKI ph 3 trials/ AURA 3 (ph 3)
1° Gen EGFR TKI (9.5-13.1 months)
OSIMERTINIB T790M+ (10.1 months)
19.6-23.2 months
ARCHER-1050 (ph 3)/ AURA 3 (ph 3)
2° Gen EGFR TKI DACOMITINIB (14.7 months)
OSIMERTINIB T790M+ (10.1 months)
24.8 months
BELIEF ph 2 / AURA 3 (ph 3)
1° Gen EGFR TKI + Bvz T790M+ (16.0 months)
OSIMERTINIB T790M+ (10.1 months?)
26.1 months?
FLAURA (ph 3)
OSIMERTINIB (18.9 months)
18.9 months
0 3 6 9 12 15 18 21 24 27 30
median PFS

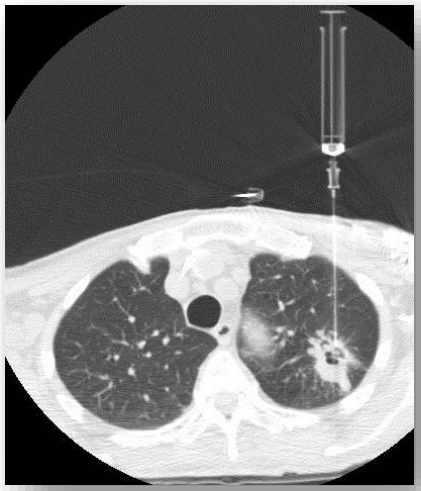
re-biopsy


Problems

Resistance by T790M ≈ 50 ~ 60 %

Re-biopsy Success Rate ≈ 60 ~ 80 %

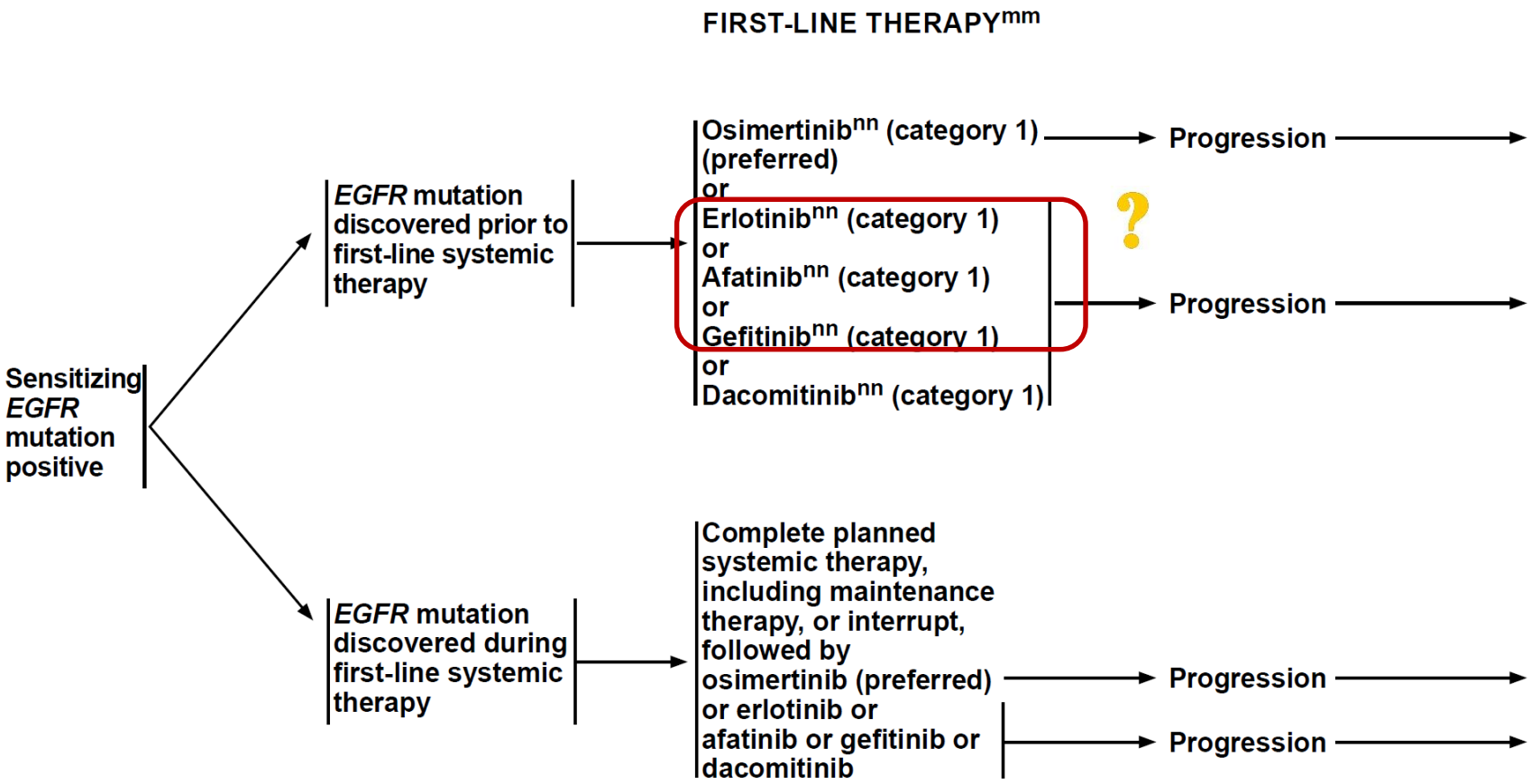
Eligible for osimertinib ≈ 30 ~ 40% of resistance



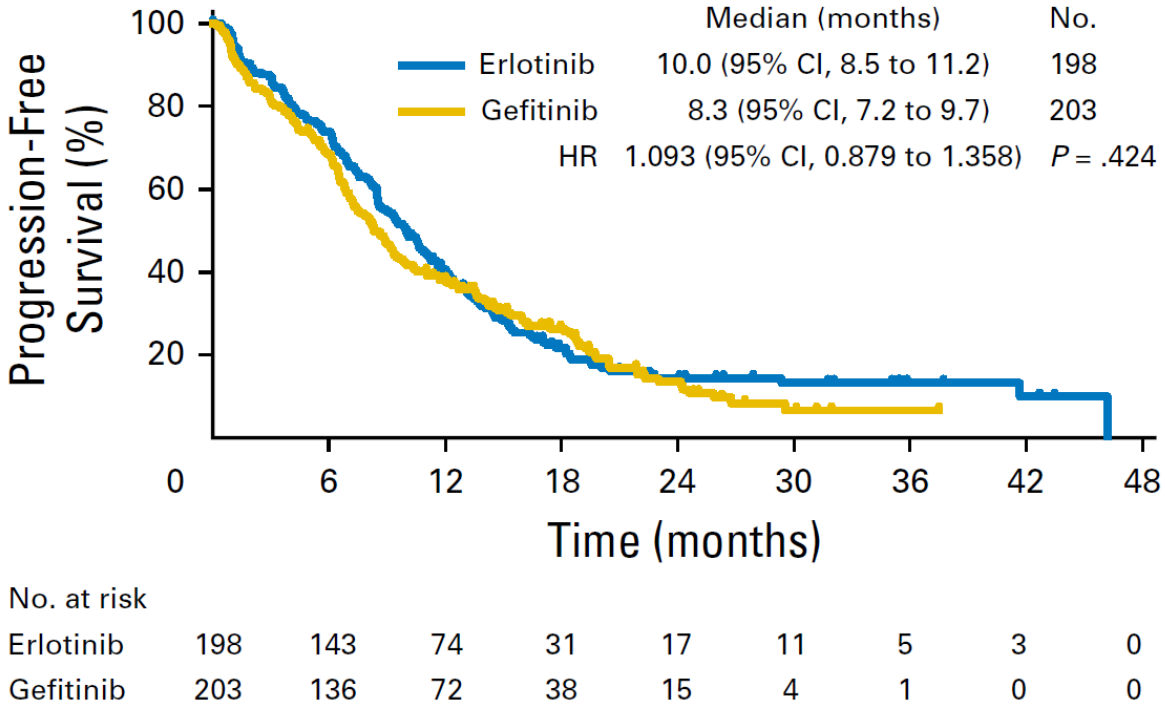
↓

1st line osimertinib >> others

SENSITIZING EGFR MUTATION POSITIVE[hh]

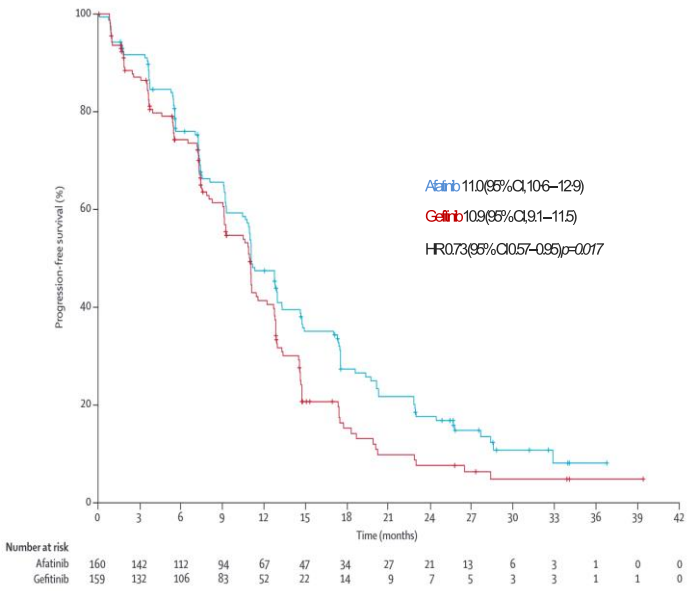


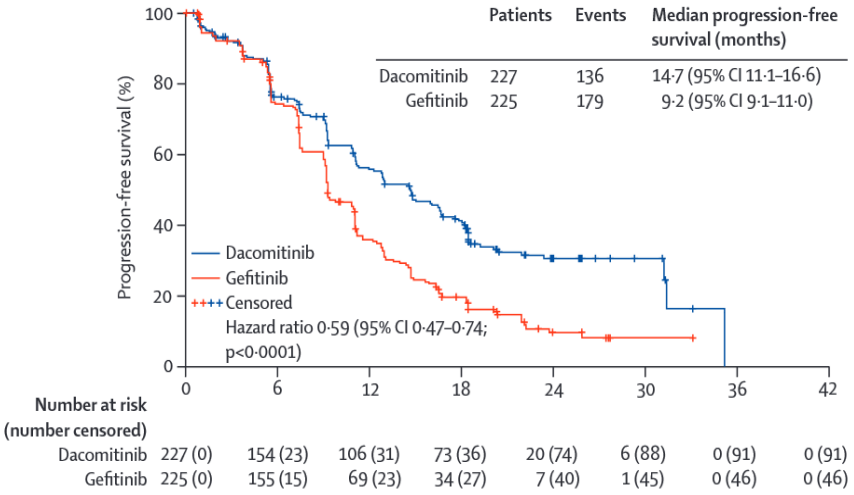
Randomized Phase III Study Comparing Gefitinib With Erlotinib in Patients With Previously Treated Advanced Lung Adenocarcinoma: WJOG 5108L



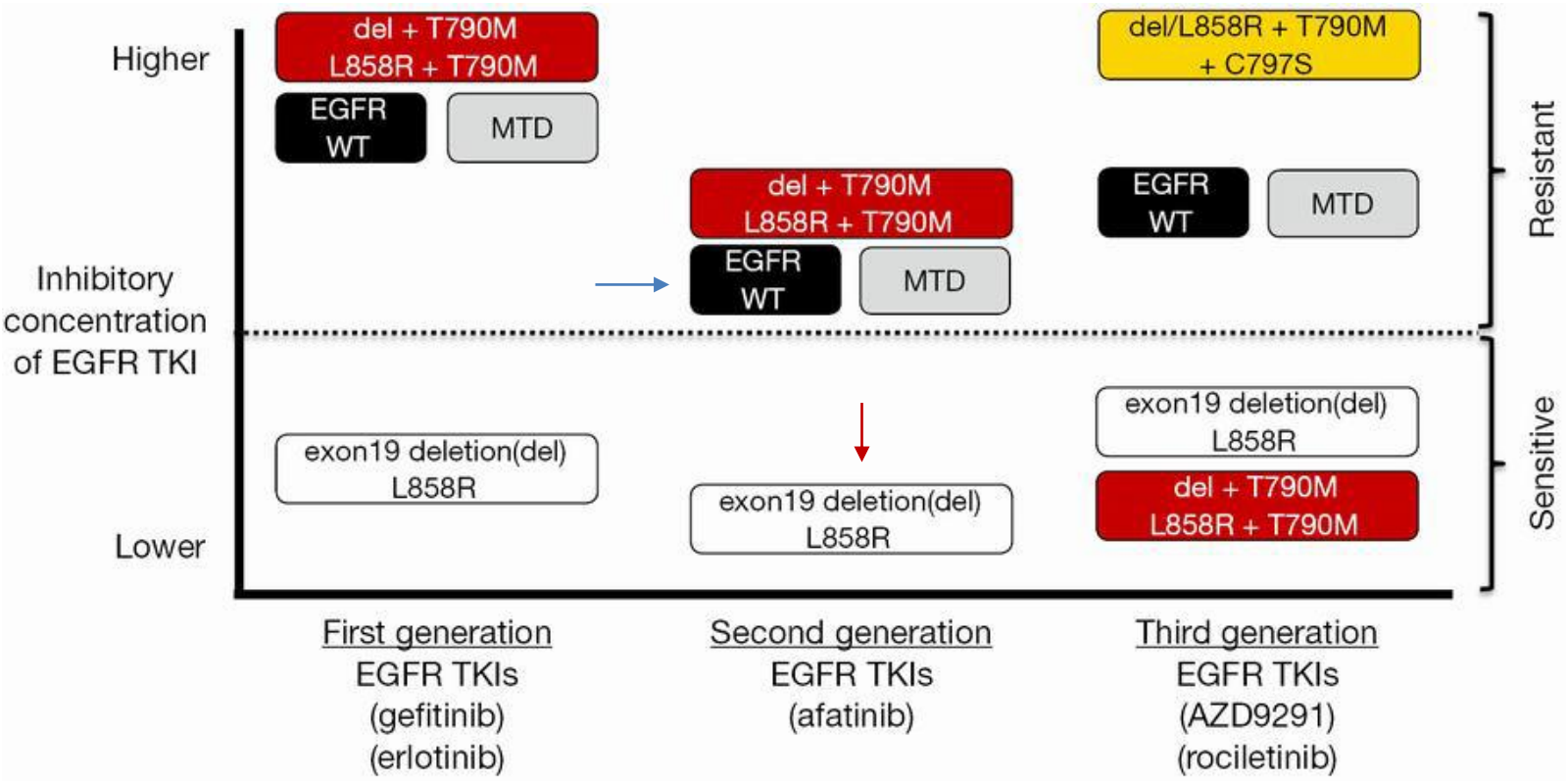
J Clin Oncol 34:3248-3257.

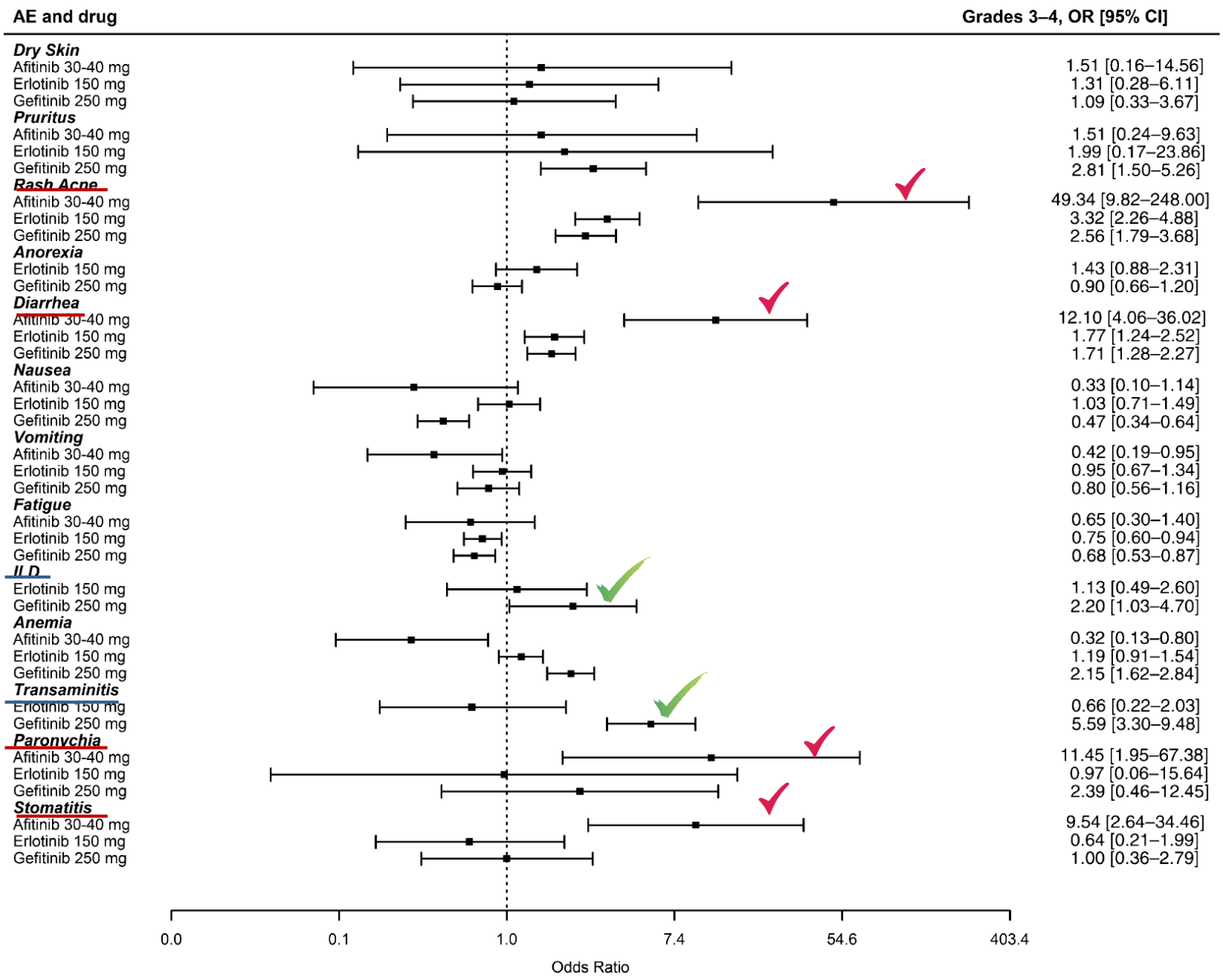
Regimen	Trials	Median PFS (Months)
Gefitinib	WJTOG3405, NEJ002, LUX-Lung 7, ARCHER 1050	9.2–10.9
Erlotinib	EURTAC, OPTIMAL, NEJ026	10.4–13.3
Afatinib	LUX-Lung 3, LUX-Lung 6, LUX-Lung 7	11.0–11.1
Dacomitinib	ARCHER 1050	14.7
Erlotinib + Bevacizumab	NEJ026	16.9
Osimertinib (second line)	AURA3	10.1
Osimertinib (first line)	FLAURA	18.9





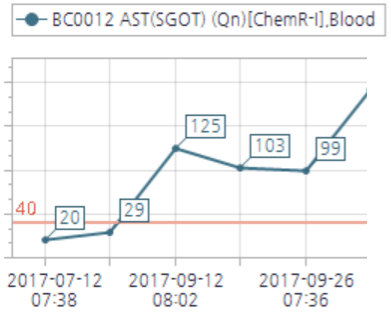
Int. J. Mol. Sci. **2019**, *20*, 146; doi:10.3390/ijms20010146


Higher
Inhibitory concentration of EGFR TKI
Lower
del + T790M L858R + T790M
EGFR WT
MTD
exon19 deletion(del) L858R
del + T790M L858R + T790M
EGFR WT
MTD
exon19 deletion(del) L858R
del/L858R + T790M + C797S
EGFR WT
MTD
exon19 deletion(del) L858R
del + T790M L858R + T790M
Resistant
Sensitive
First generation EGFR TKIs (gefitinib) (erlotinib)
Second generation EGFR TKIs (afatinib)
Third generation EGFR TKIs (AZD9291) (rociletinib)



The Oncologist 2015;20:400–410

F/54 ACC 19del



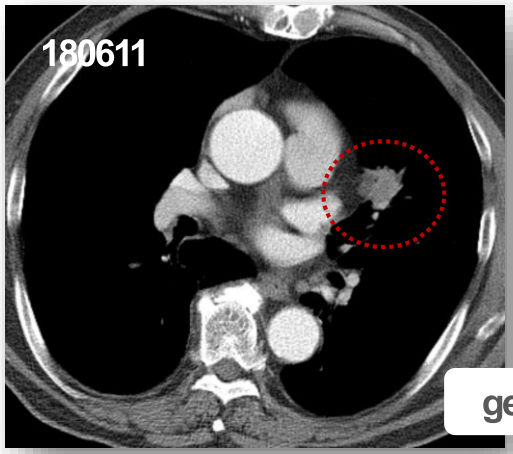
↑ gefitinib

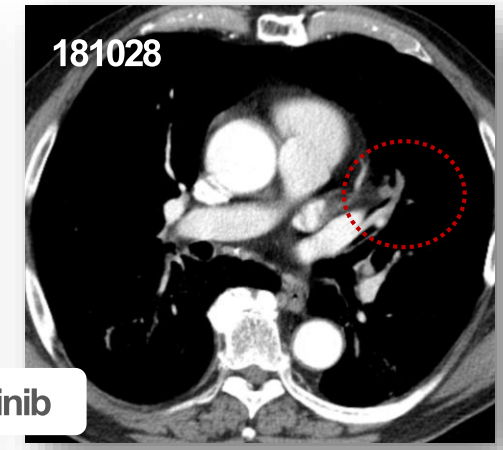
Pneumonitis in advanced non-small-cell lung cancer patients treated with EGFR tyrosine kinase inhibitor: Meta-analysis of 153 cohorts with 15,713 patients

Meta-analysis of incidence and risk factors of EGFR-TKI pneumonitis in NSCLC

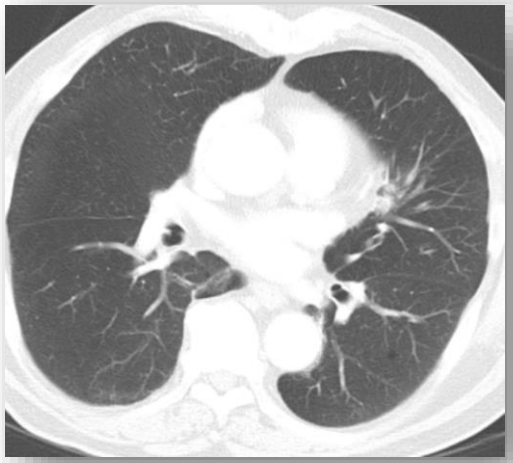
Subgroup		All-grade pneumonitis		High-grade pneumonitis		Grade 5 pneumonitis	
		No. of studies	Incidence (%) (95% CI)	No. of studies	Incidence (%) (95% CI)	No. of studies	Incidence (%) (95% CI)
Overall		111[b]	1.12 (0.79-1.58)[a]	108[b]	0.61 (0.40-0.93)	130[b]	0.20 (0.11-0.38)
EGFR-TKI	Erlotinib	54	0.80 (0.42-1.50)[a]	60	0.46 (0.24-0.86)	72	0.21 (0.10-0.43)
	Afatinib	8	1.00 (0.37-2.69)	7	0.61 (0.20-1.88)	8	0.14 (0.02-0.98)
	Gefitinib	49	1.53 (1.02-2.28)[a]	41	0.95 (0.52-1.72)	50	0.28 (0.10-0.76)[a]

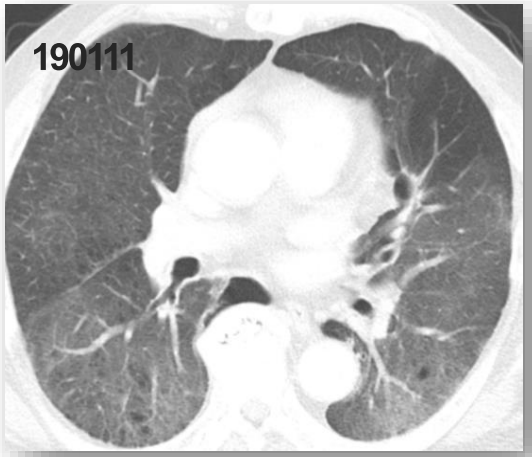
M/71 ACC 19del





gefitinib



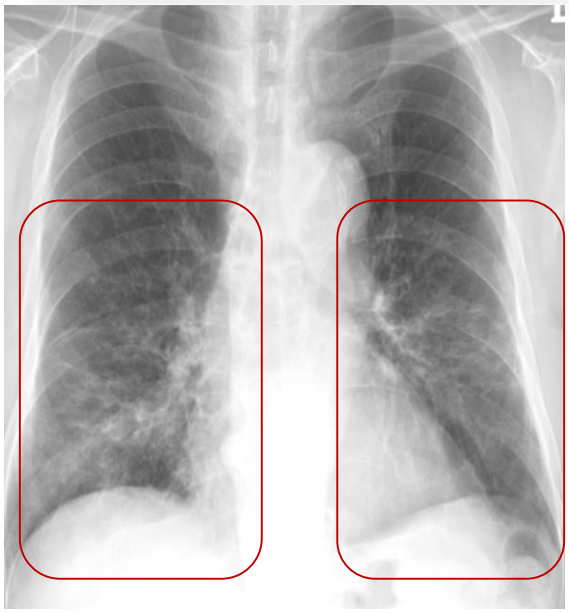


gefitinib hold
Pd 30mg bid → tapering over 6 wks

0033369925

181220 restart

WHAT TO DO ?

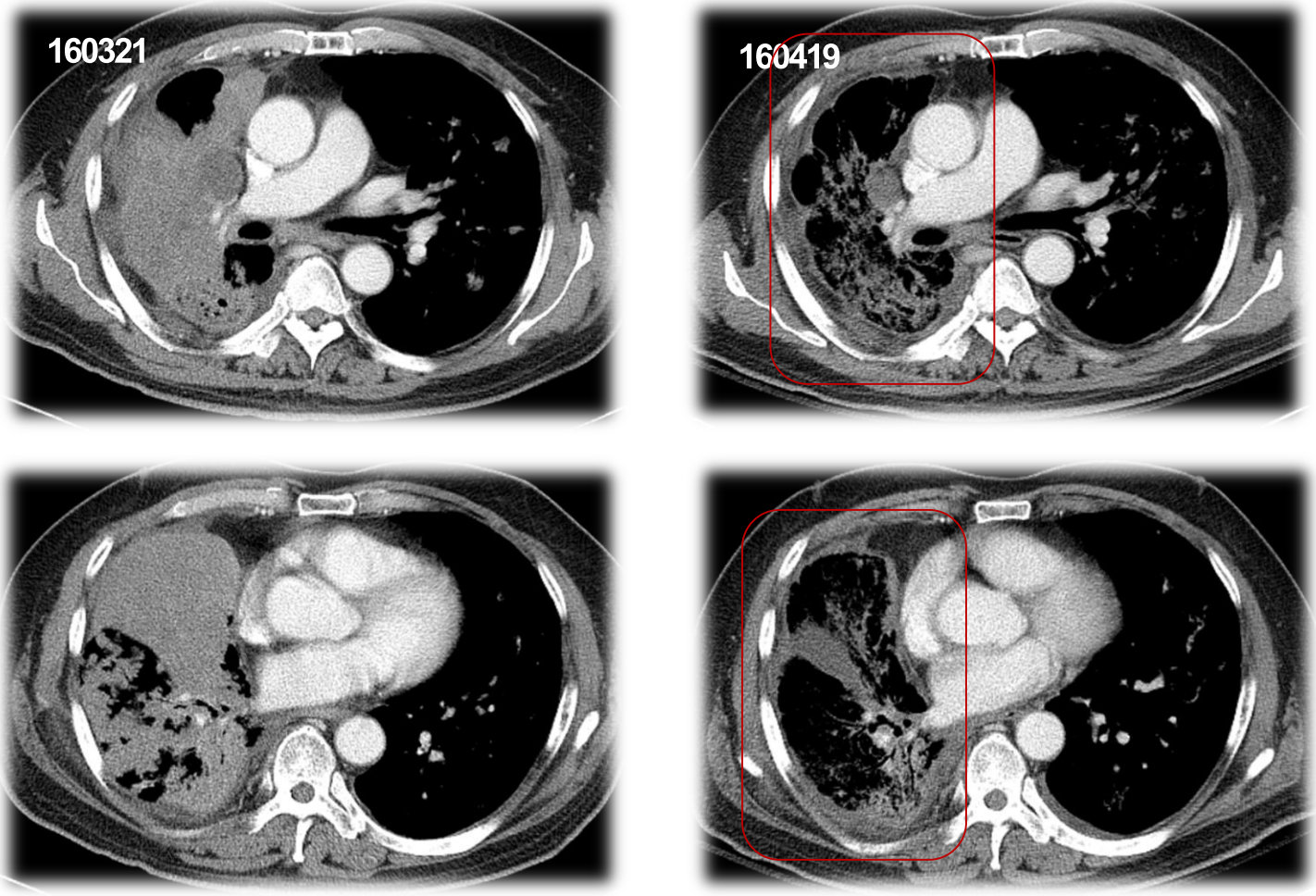


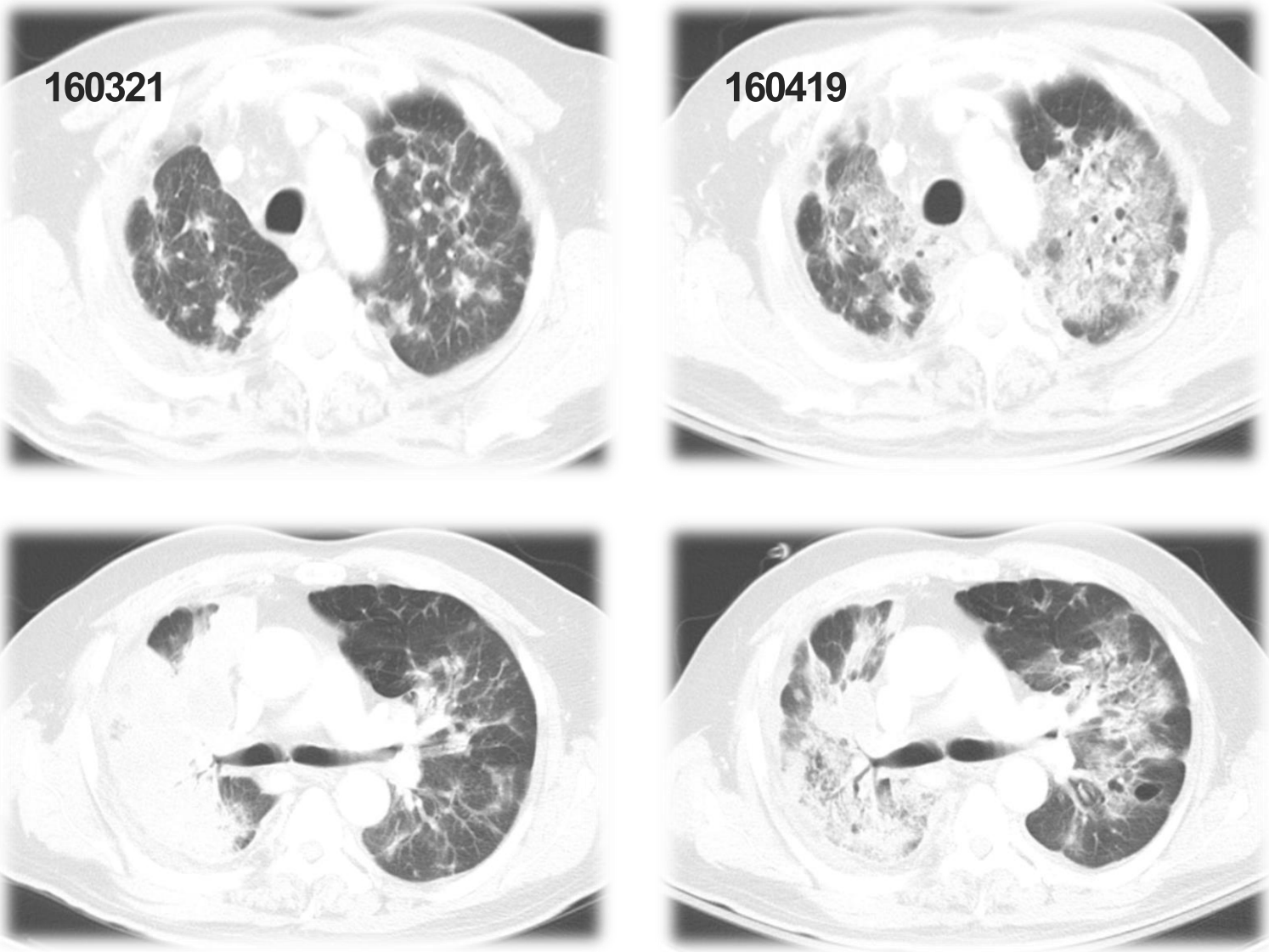

190508


190622

M/75 ACC 19del

gefitinib

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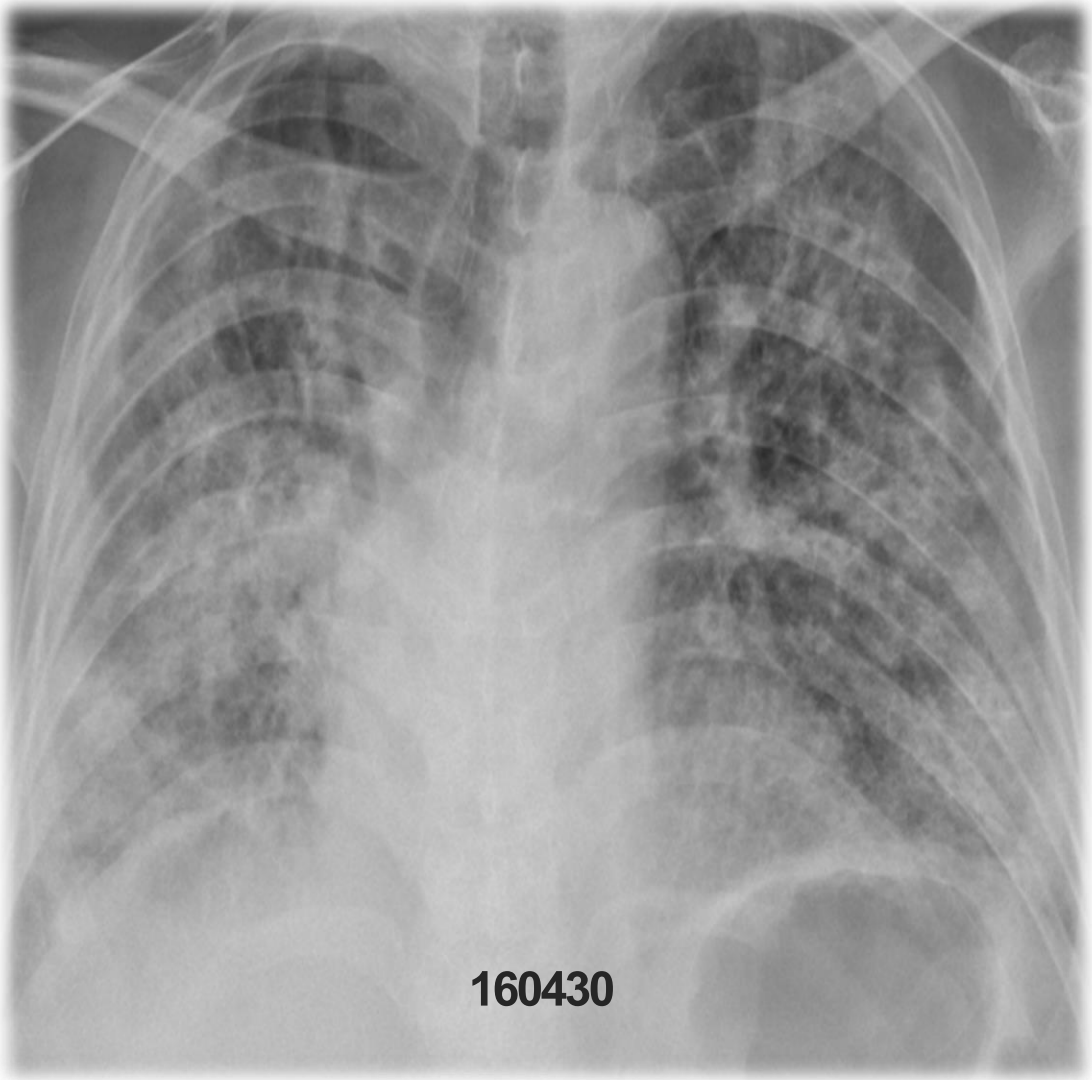
160419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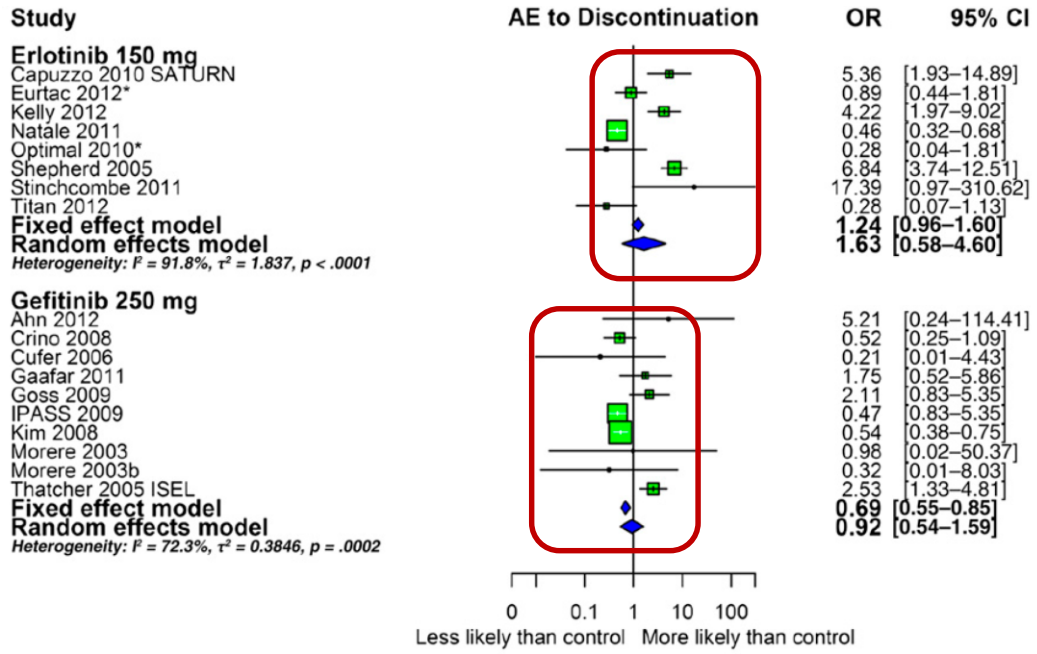
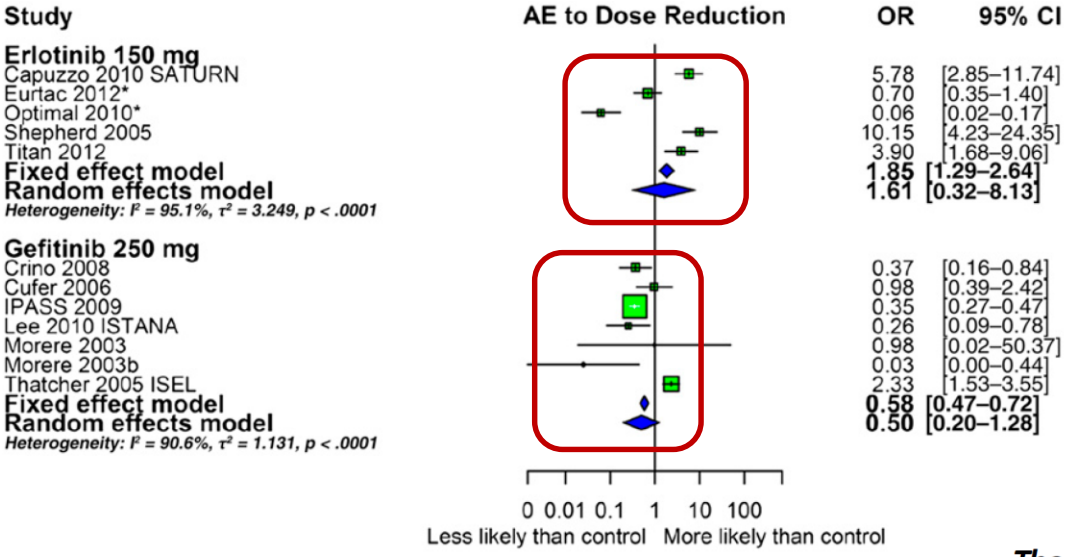
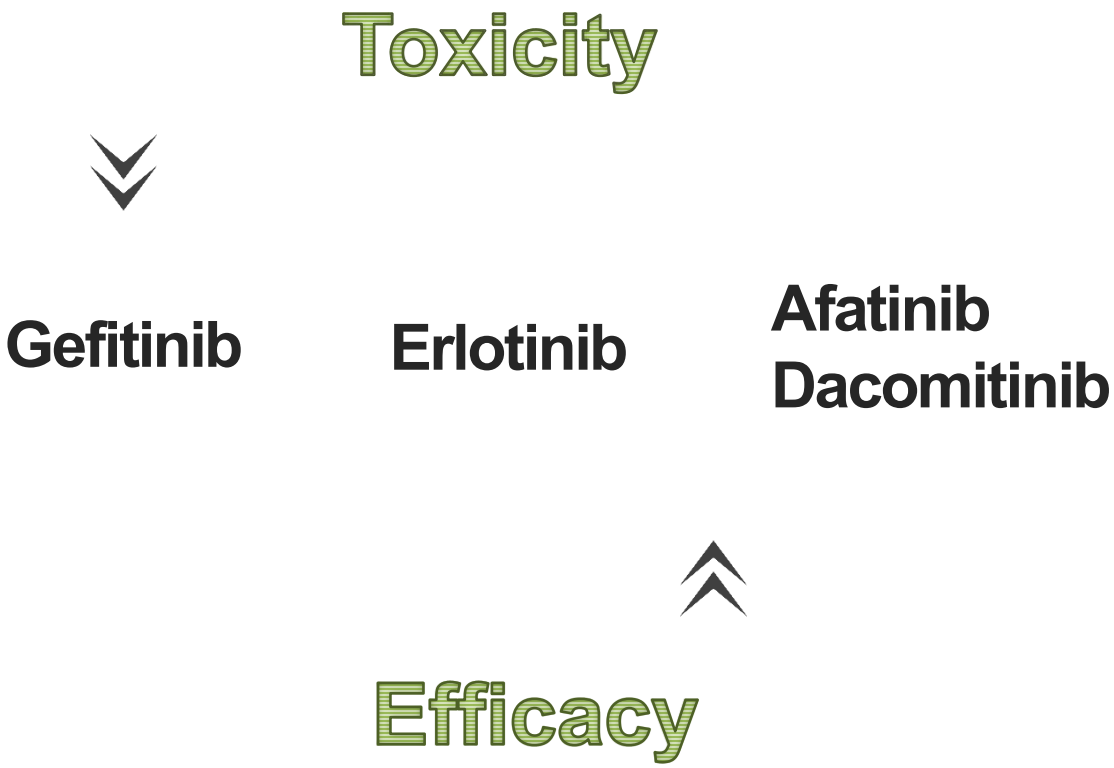
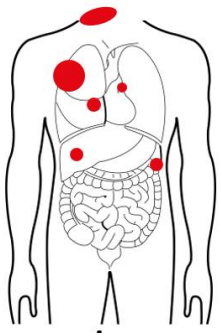




The Oncologist 2015;20:400–410

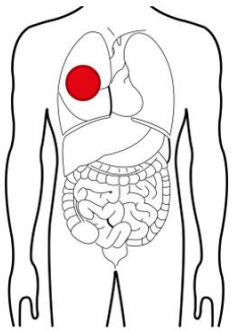

Toxicity
Gefitinib
Erlotinib
Afatinib
Dacomitinib
Efficacy

Systemic-PD



- **Low volume and asymptomatic:** Keep the same treatment beyond progression
- **More significant and symptomatic:** Change to a TKI with different activity

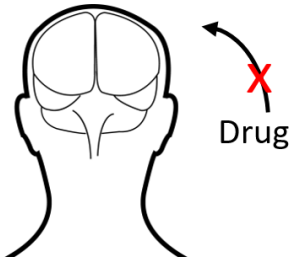
Oligo-PD



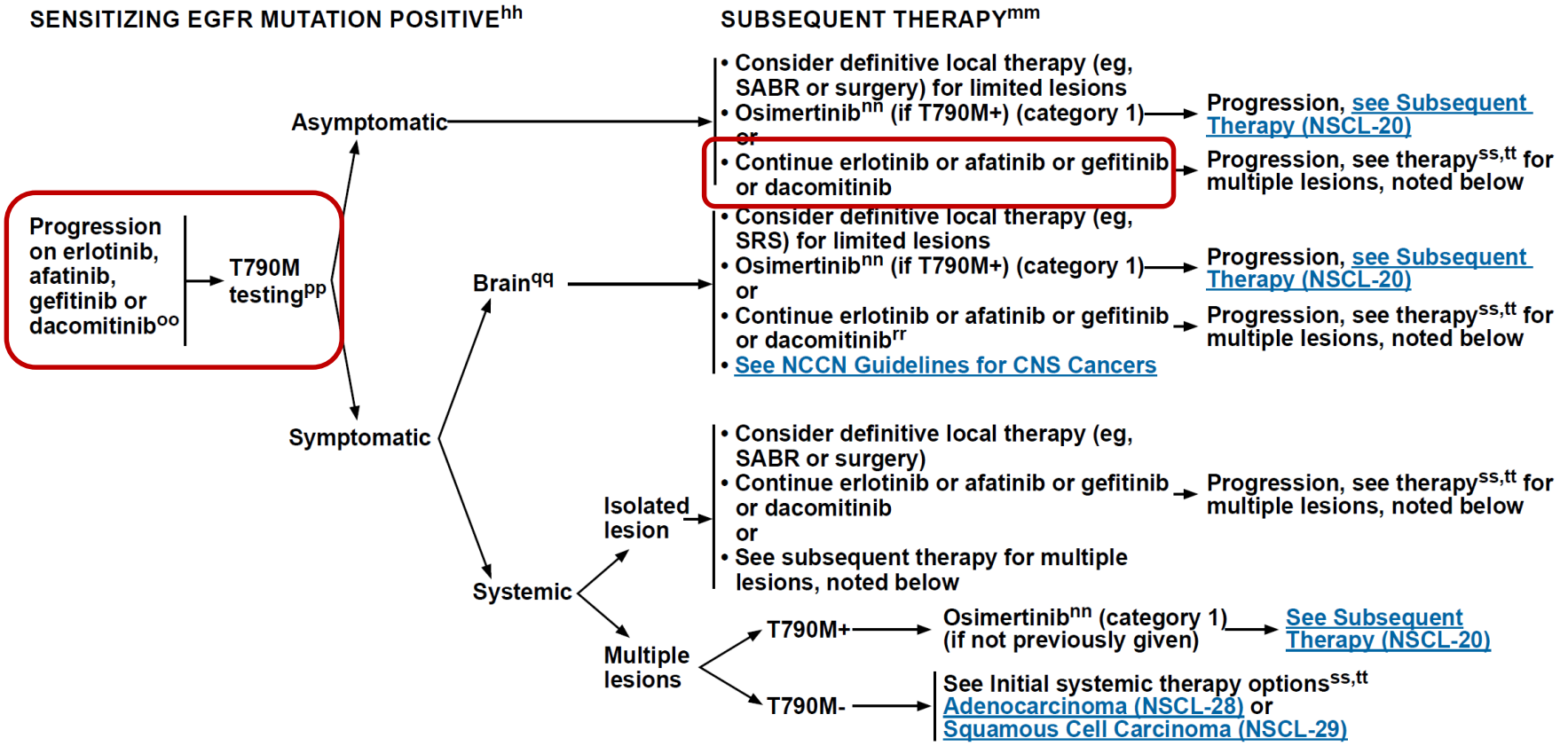
Aggressive local therapy plus continuation of the same therapy[2]

CNS-PD

Inadequate CNS penetration?

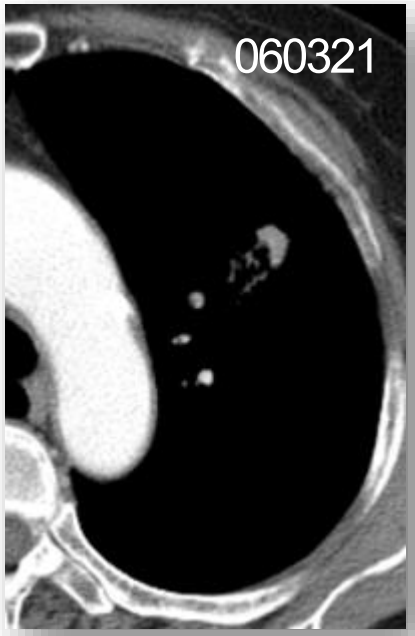


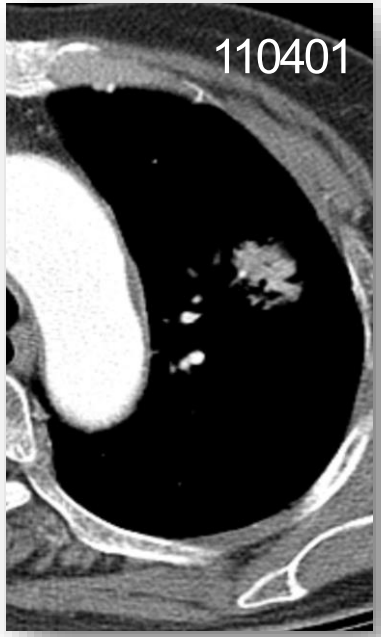
Switch to TKI with better CNS penetration[3,4] with or without local ablation therapy


SENSITIZING EGFR MUTATION POSITIVE[hh]
SUBSEQUENT THERAPY[mm]
Progression on erlotinib, afatinib, gefitinib or dacomitinib[oo]
T790M testing[pp]
Asymptomatic
• Consider definitive local therapy (eg, SABR or surgery) for limited lesions
• Osimertinib[nn] (if T790M+) (category 1)
or
• Continue erlotinib or afatinib or gefitinib or dacomitinib
Progression, see Subsequent Therapy (NSCL-20)
Progression, see therapy[ss,tt] for multiple lesions, noted below
Symptomatic
Brain[qq]
• Consider definitive local therapy (eg, SRS) for limited lesions
• Osimertinib[nn] (if T790M+) (category 1)
or
• Continue erlotinib or afatinib or gefitinib or dacomitinib[rr]
• See NCCN Guidelines for CNS Cancers
Progression, see Subsequent Therapy (NSCL-20)
Progression, see therapy[ss,tt] for multiple lesions, noted below
Systemic
Isolated lesion
• Consider definitive local therapy (eg, SABR or surgery)
• Continue erlotinib or afatinib or gefitinib or dacomitinib
or
• See subsequent therapy for multiple lesions, noted below
Progression, see therapy[ss,tt] for multiple lesions, noted below
Multiple lesions
T790M+
Osimertinib[nn] (category 1) (if not previously given)
See Subsequent Therapy (NSCL-20)
T790M-
See Initial systemic therapy options[ss,tt] Adenocarcinoma (NSCL-28) or Squamous Cell Carcinoma (NSCL-29)

F/84 ACC 19del

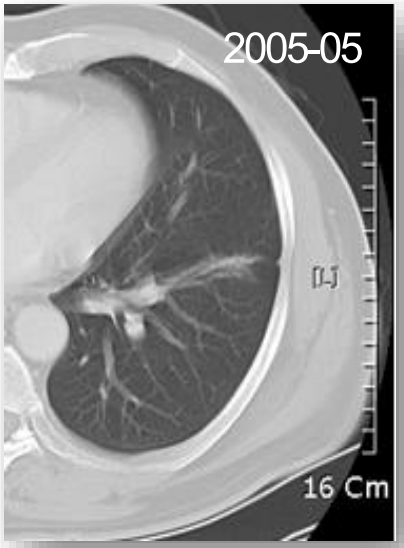
EGFR-TKI since 2006



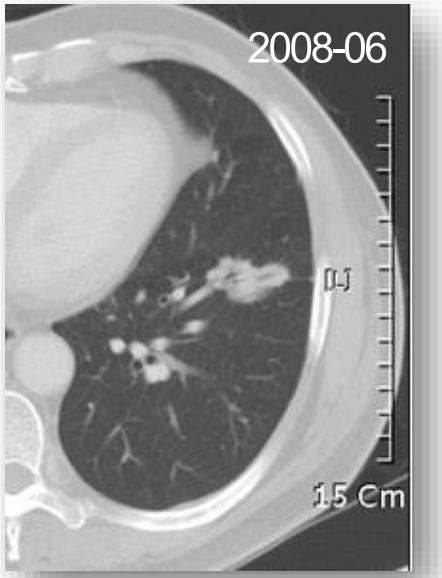


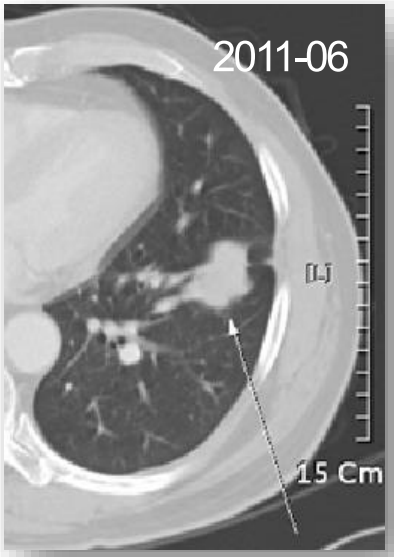
0021818493

M/60 ACC 19del

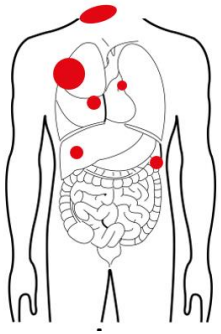


EGFR-TKI since 2004





Systemic-PD



Low volume and asymptomatic:
Keep the same treatment beyond progression

More significant and symptomatic:
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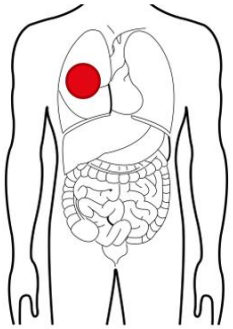
Oligo-PD

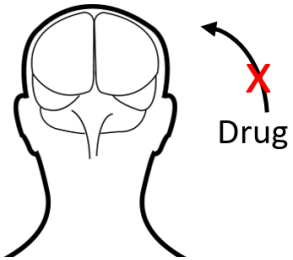


Aggressive local therapy plus continuation of the same therapy[2]

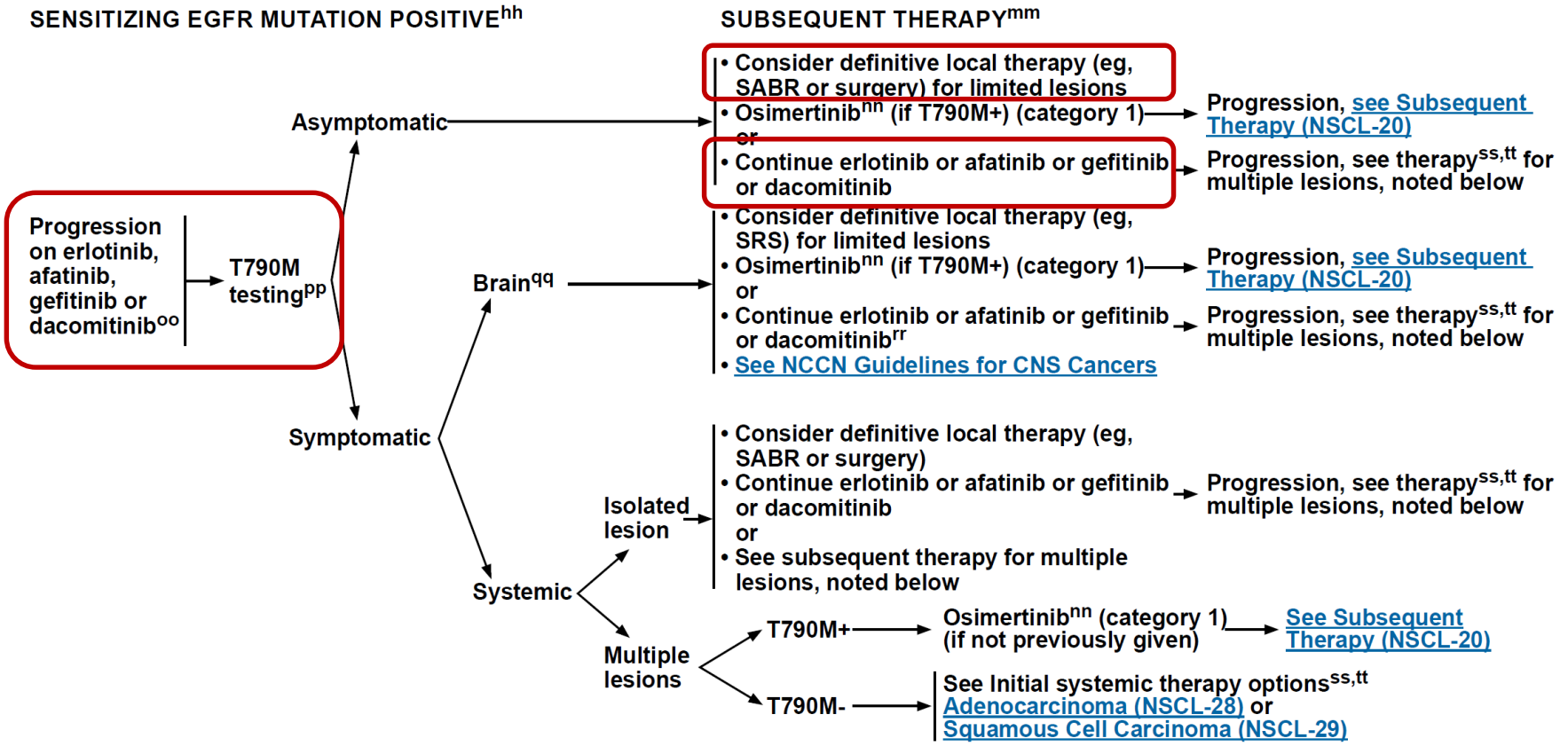
Tumor Heterogeneity

CNS-PD

Inadequate CNS penetration?



Switch to TKI with better CNS penetration[3,4] with or without local ablation therapy


SENSITIZING EGFR MUTATION POSITIVE[hh]
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T790M testing[pp]
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Isolated lesion
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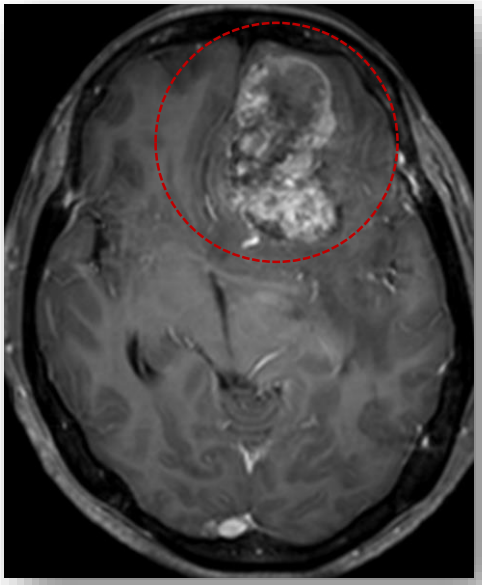
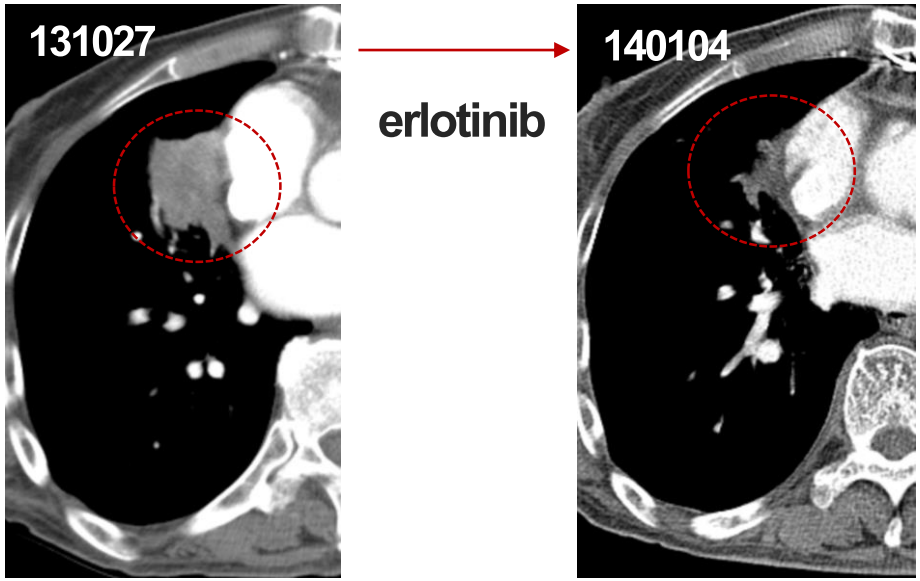
T790M+
Osimertinib[nn] (category 1) (if not previously given)
See Subsequent Therapy (NSCL-20)
T790M-
See Initial systemic therapy options[ss,tt] Adenocarcinoma (NSCL-28) or Squamous Cell Carcinoma (NSCL-29)

F/70 ACC M/brain L858R

Brain tumor resection (131024)
1L erlotinib (131115 ~ 160302)
Recurred brain mets; Cyberknife (140130)
2L pemetrexed #2; PD
Rebiopsy; T790M+
3L osimertinib (160531 ~)





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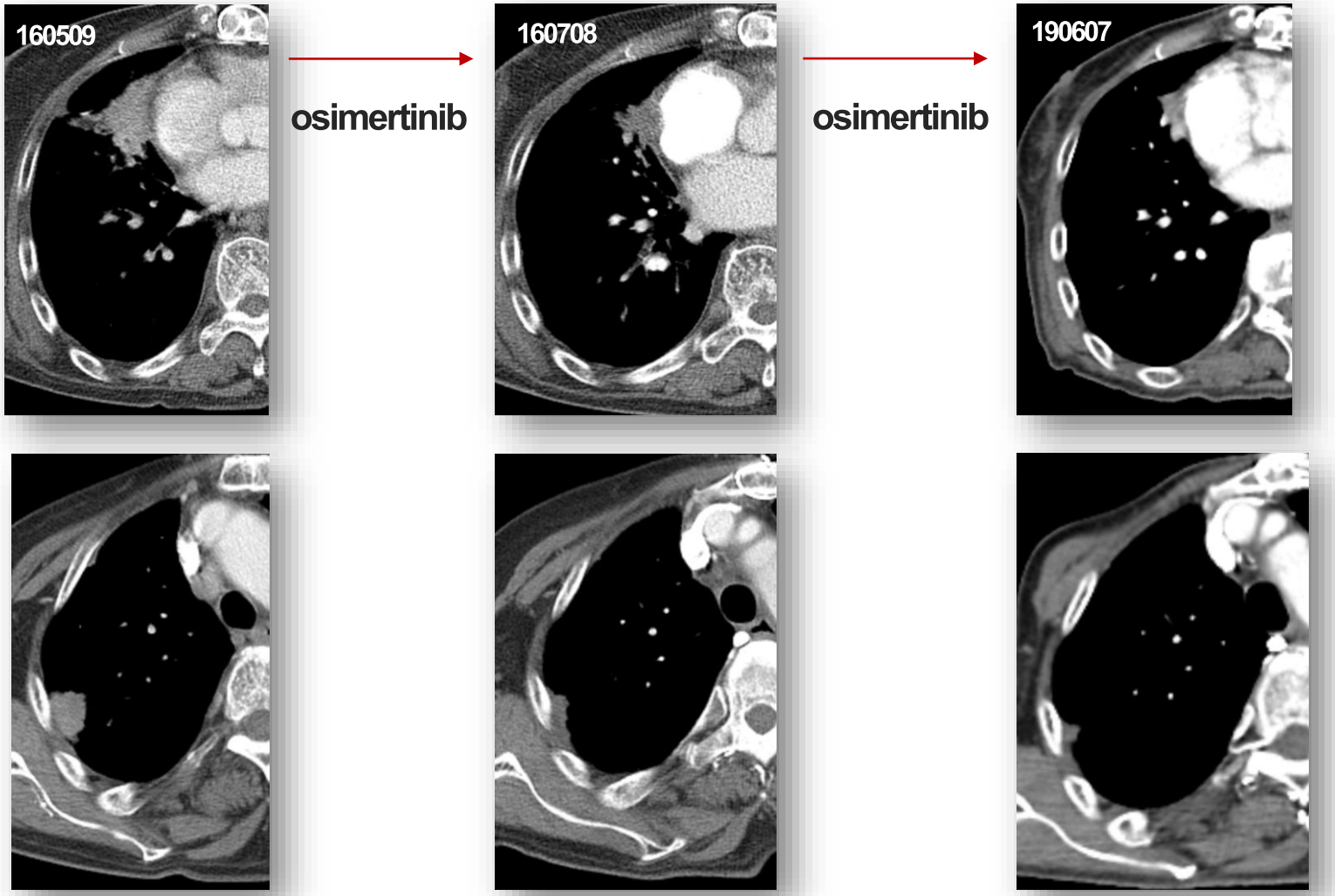
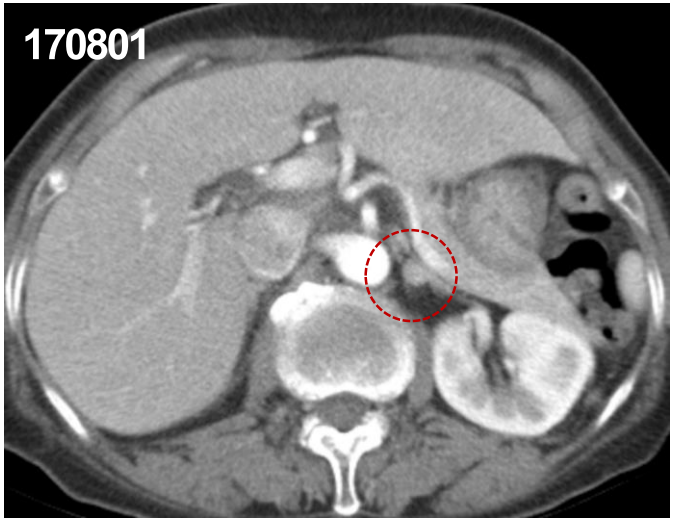

160509
osimertinib
160708
osimertinib
190607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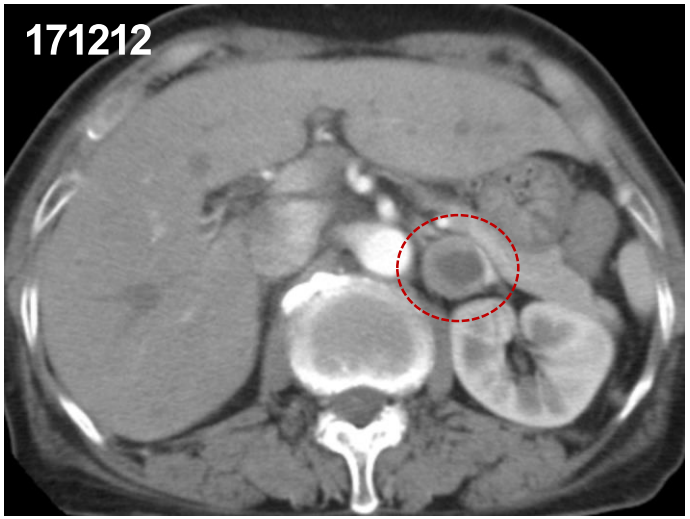
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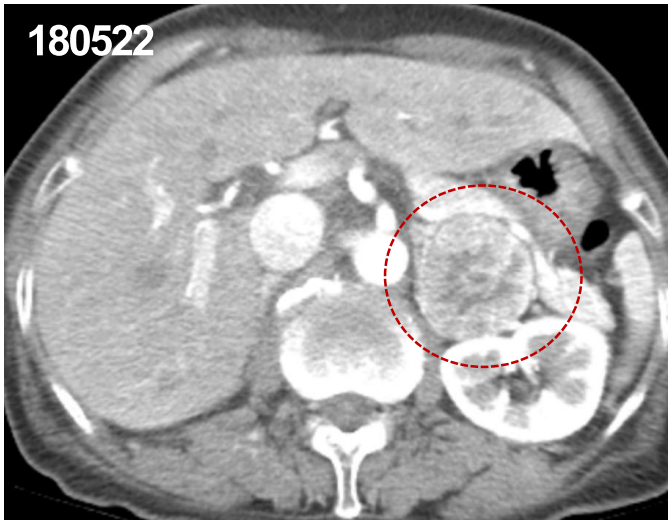
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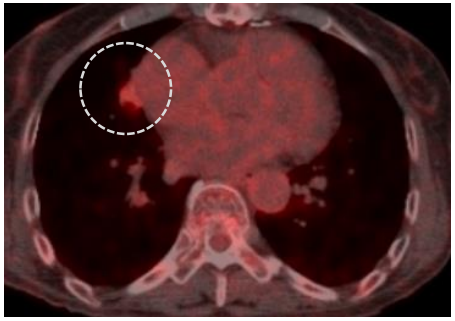
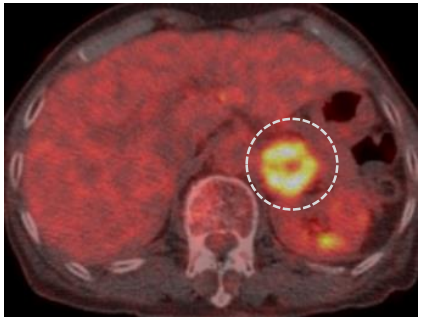
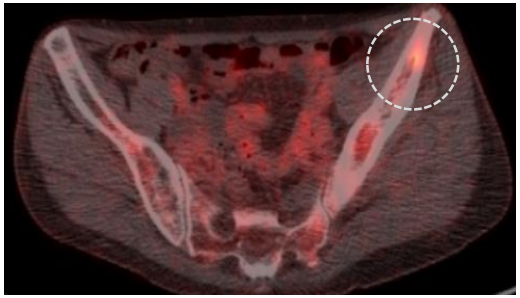






180523 lt adrenal gland resection

stable till now with osimertinib

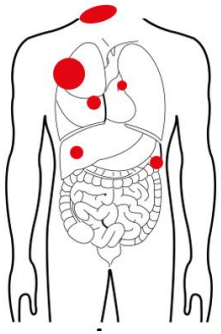
180523 L858R+ T790M-

160321 L858R+ T790M+

131114 L858R+ T790M-

Tumor Heterogeneity

Systemic-PD



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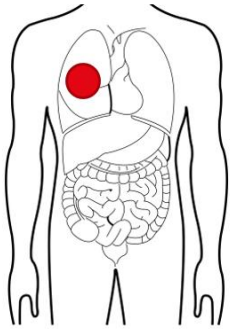
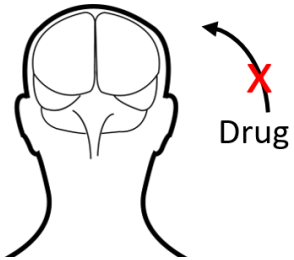
Oligo-PD



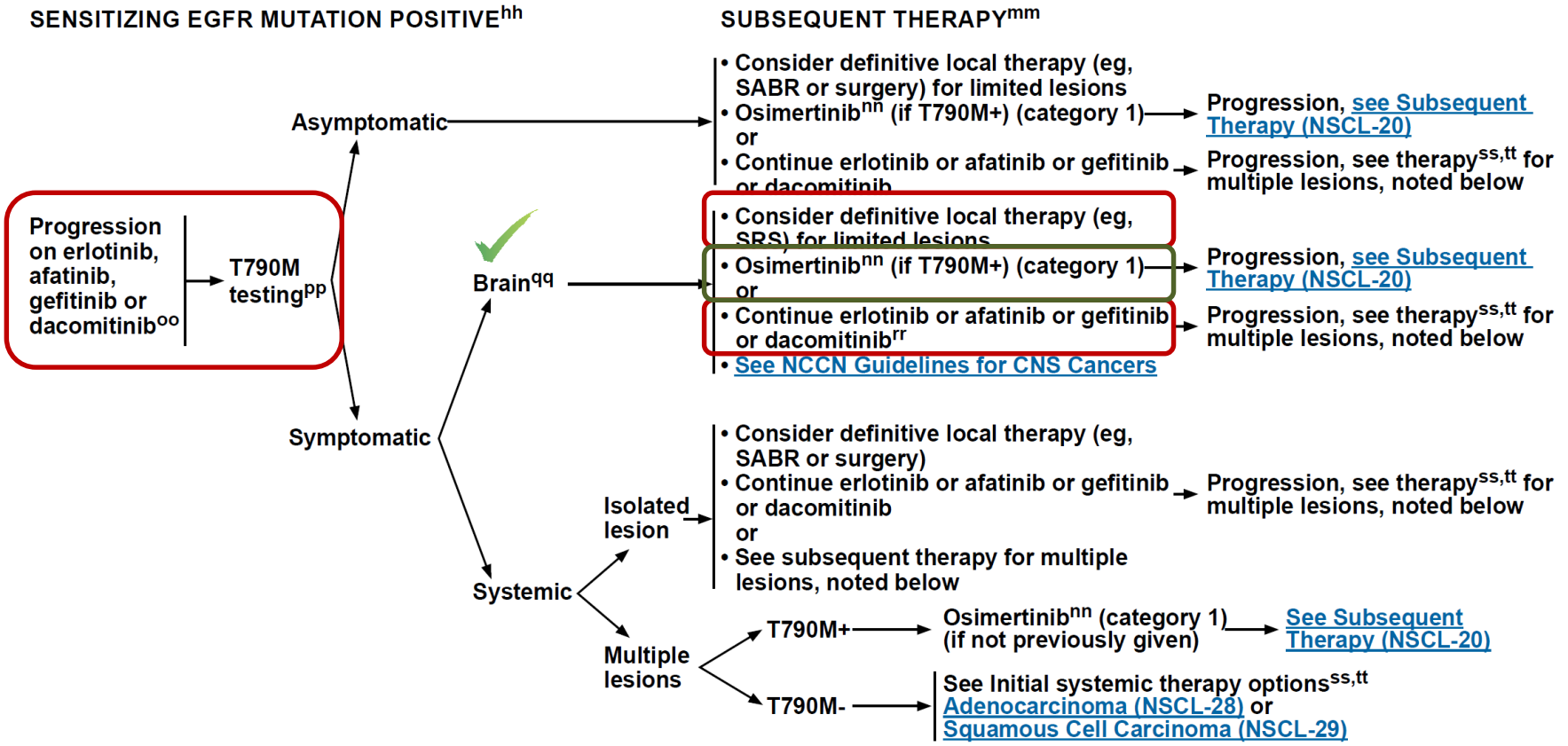
Aggressive local therapy plus continuation of the same therapy[2]

CNS-PD

Inadequate CNS penetration?



Switch to TKI with better CNS penetration[3,4] with or without local ablation therapy


SENSITIZING EGFR MUTATION POSITIVE[hh]
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Progression on erlotinib, afatinib, gefitinib or dacomitinib[oo]
T790M testing[pp]
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Isolated lesion
Multiple lesions
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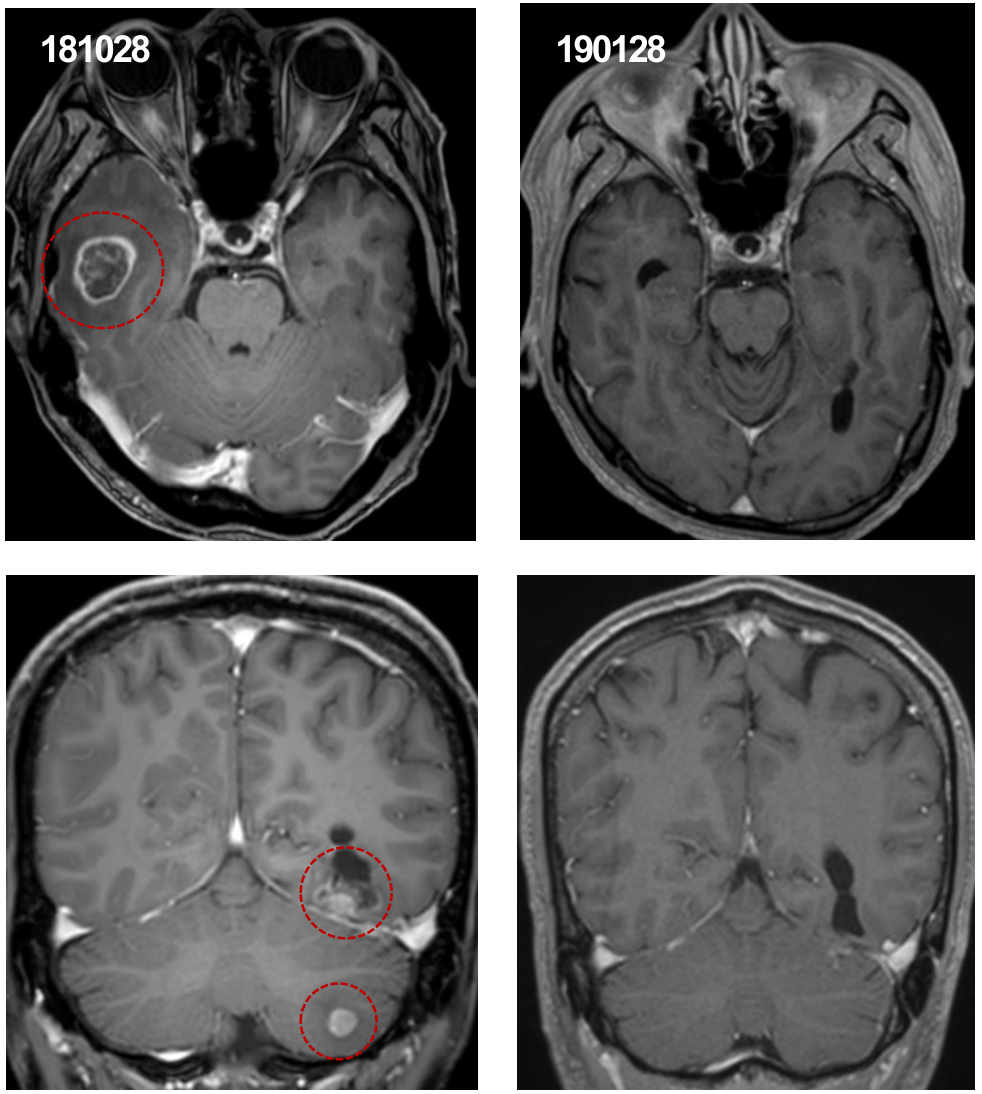
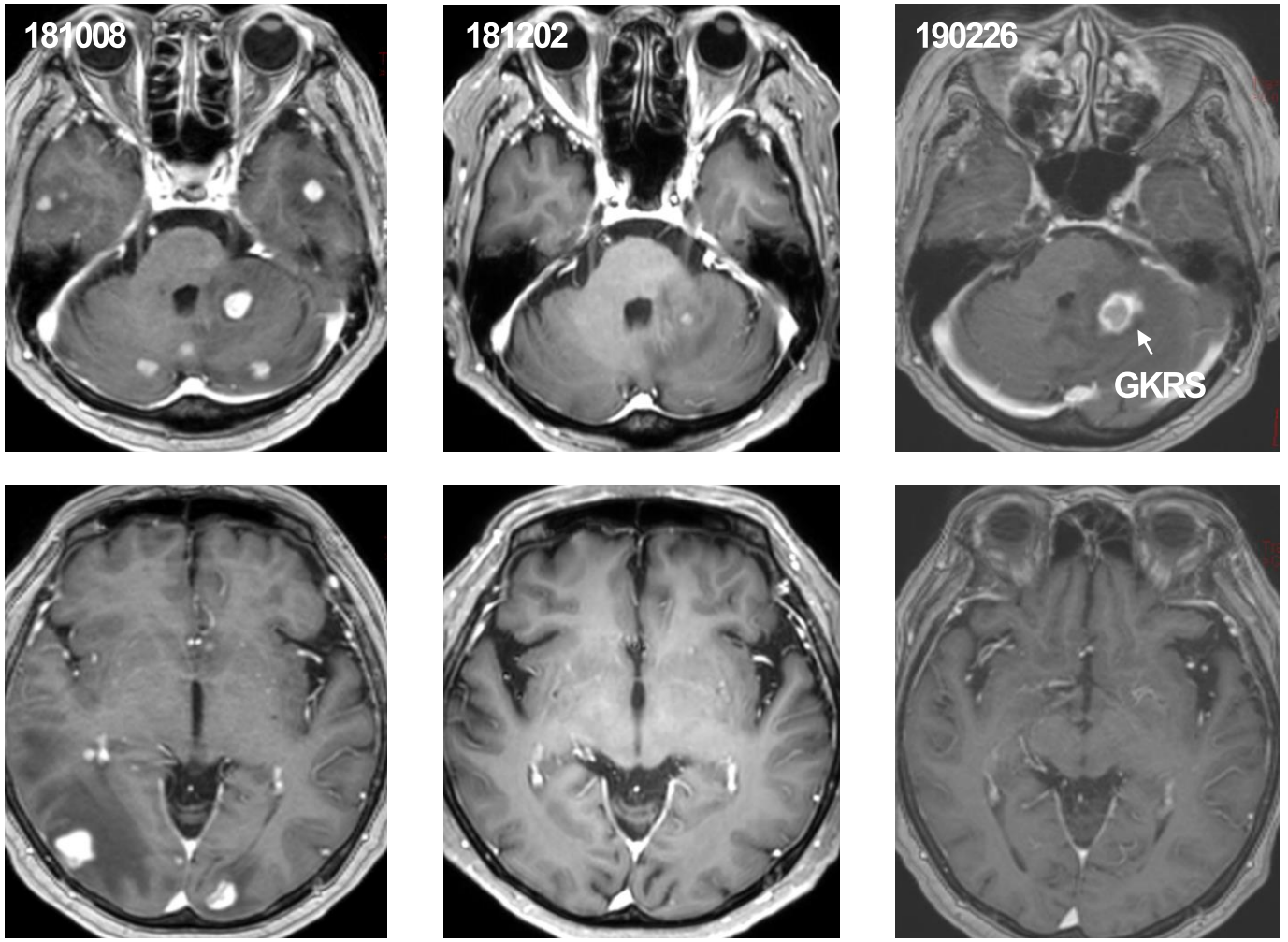
See Subsequent Therapy (NSCL-20)
See Initial systemic therapy options[ss,tt]
Adenocarcinoma (NSCL-28) or
Squamous Cell Carcinoma (NSCL-29)

M/52 ACC 19del
s/p gefitinib
PD with new brain mets
T790M+
Osimertinib 181128 ~



0051608666

F/73 19del s/p gefitinib PD with new brain mets
T790M+ osimertinib 181010 ~



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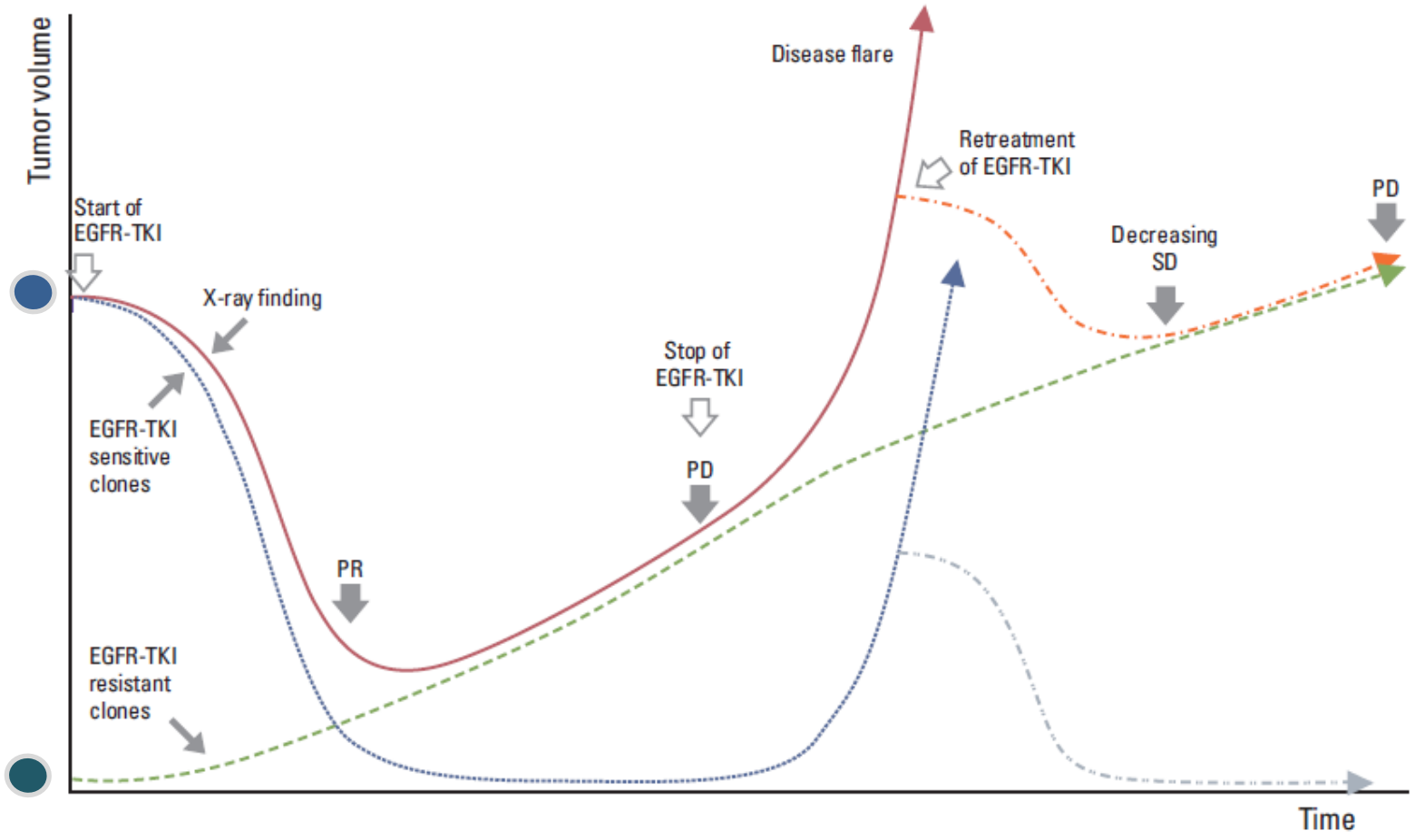
Retreatment



Treatment of Non-small Cell Lung Carcinoma after Failure of Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor

Table 1. Studies of erlotinib retreatment after gefitinib failure

Reference	No.	CR/PR/SD	PD	PFS (mo)
Lee et al. [26]	23	2	21	6.2
Cho et al. [25]	21	6	15	2
Viswanathan et al. [27]	5	0	5	<2
Costa et al. [28]	18	4	14	2
Sim et al. [29]	16	4	12	1.7
Wong et al. [30]	21	12	9	3.7
Zhou et al. [31]	21	6	15	1.8
Vasile et al. [32]	8	5	3	5.9

Table 2. Response to retreatment with the same drug after EGFR-TKI failure

Reference	No.	Drug	CR/PR/SD	PD	PFS (mo)
Asahina et al. [36]	16	Gefitinib	7	9	2.5
Oh et al. [35]	20	Gefitinib	15	5	3.4
Yokouchi et al. [34]	9	Gefitinib	8	1	6.2
Becker et al. [33]	14	Erlotinib	12	2	6.5

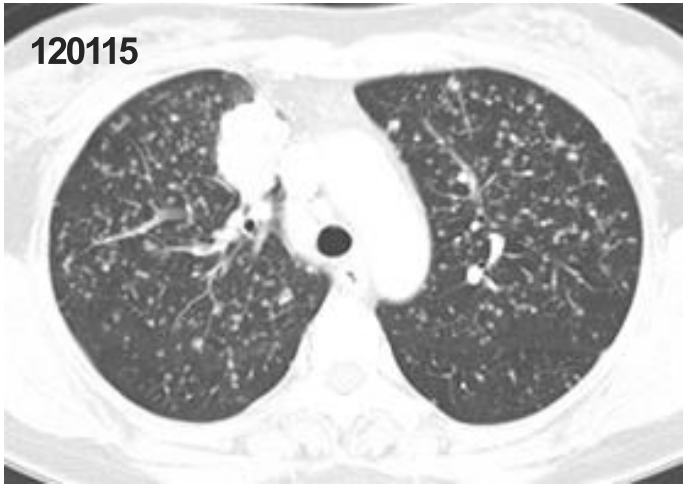
F/48 ACC M/lung 19del

1L erlotinib (090310 ~ 100204)

Rebiopsy; T790M+

2L Pemetrexed #24 (100225 ~120115)

3L afatinib (120120 ~ 130808)



afatinib

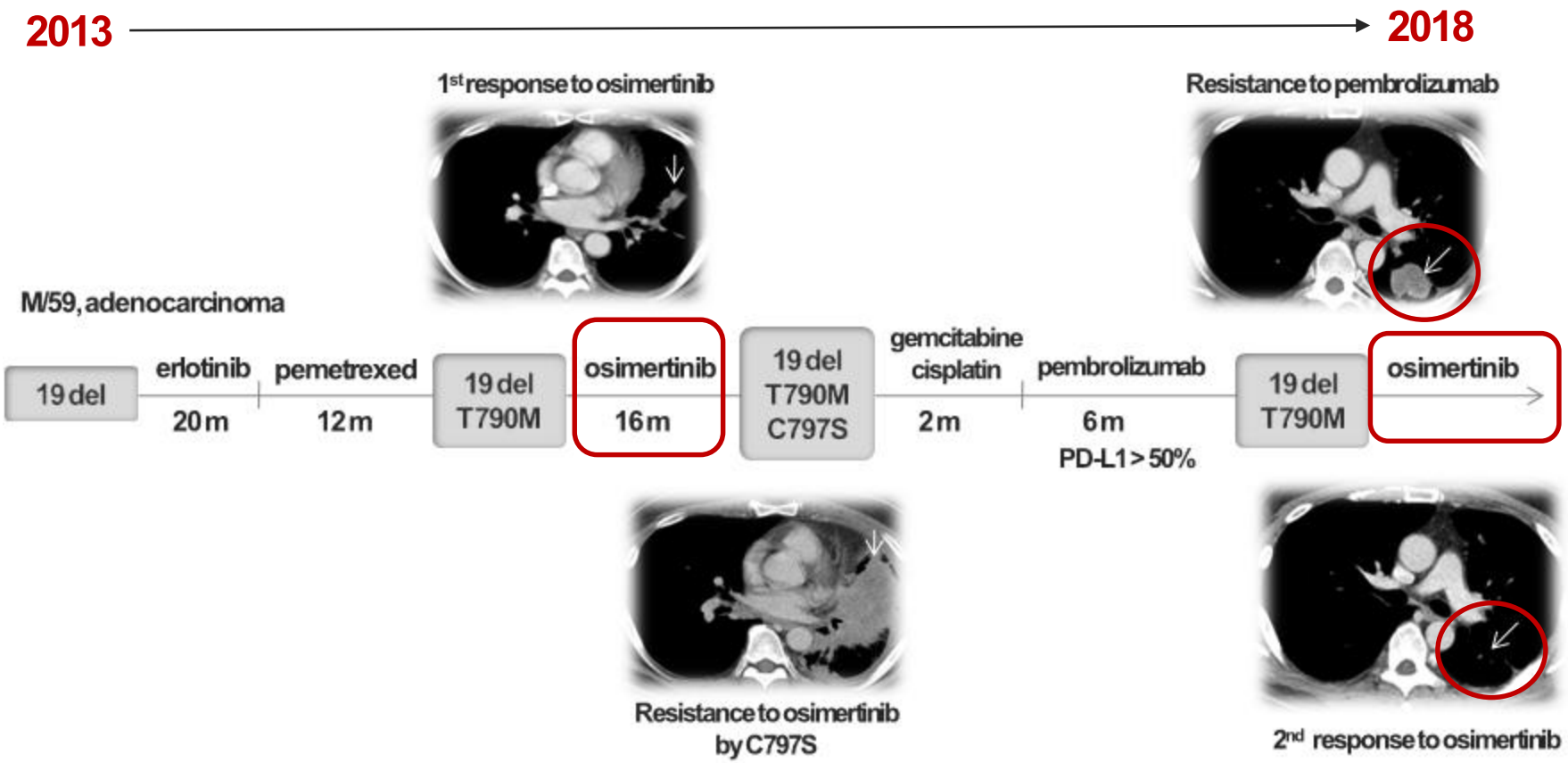
F/58 ACC M/pleura 19del

1L gefitinib (170109 ~ 190131)

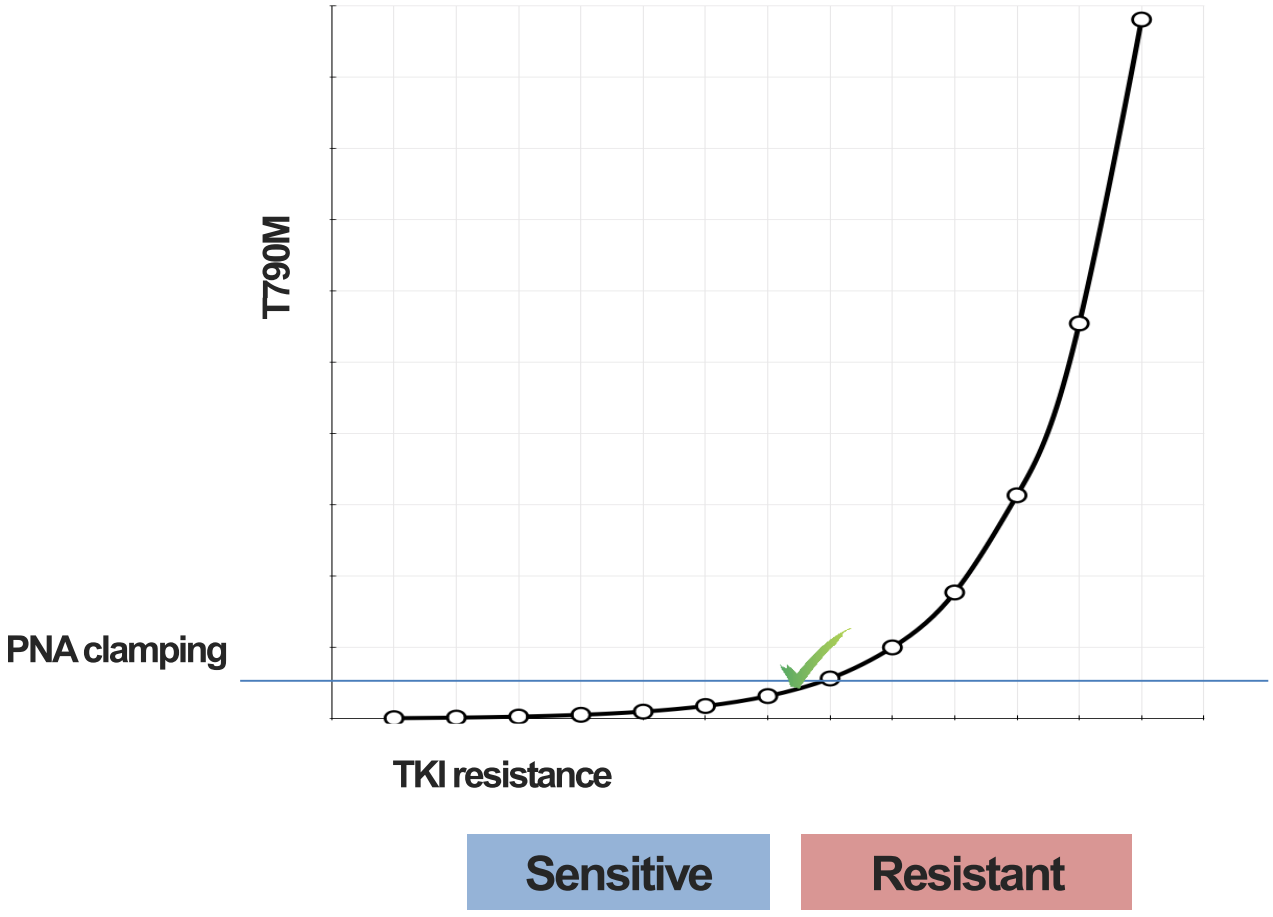
Rebiopsy; T790M-

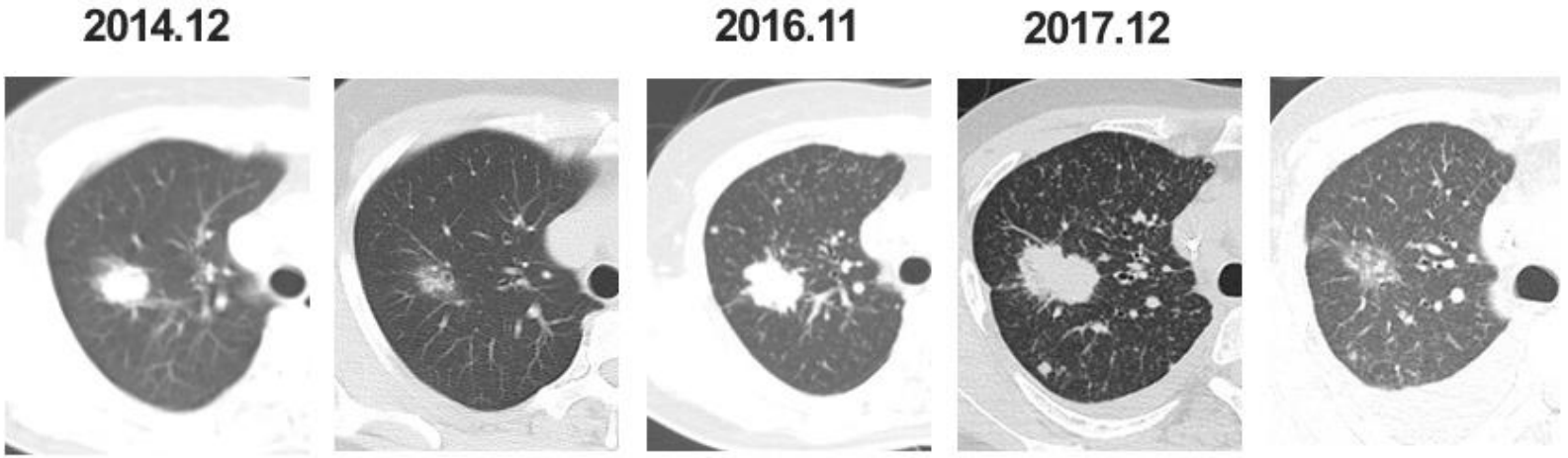
Cytotoxic chemo refused

2L afatinib (190416 ~)


2013
2018
1st response to osimertinib
Resistance to pembrolizumab
M/59, adenocarcinoma
19 del
erlotinib
20 m
pemetrexed
12 m
19 del
T790M
osimertinib
16 m
19 del
T790M
C797S
gemcitabine
cisplatin
2 m
pembrolizumab
6 m
PD-L1 > 50%
19 del
T790M
osimertinib
Resistance to osimertinib
by C797S
2nd response to osimertinib

Rebiopsy in initial T790M-negative – repeat or not ?





Dr. Lee SH's case

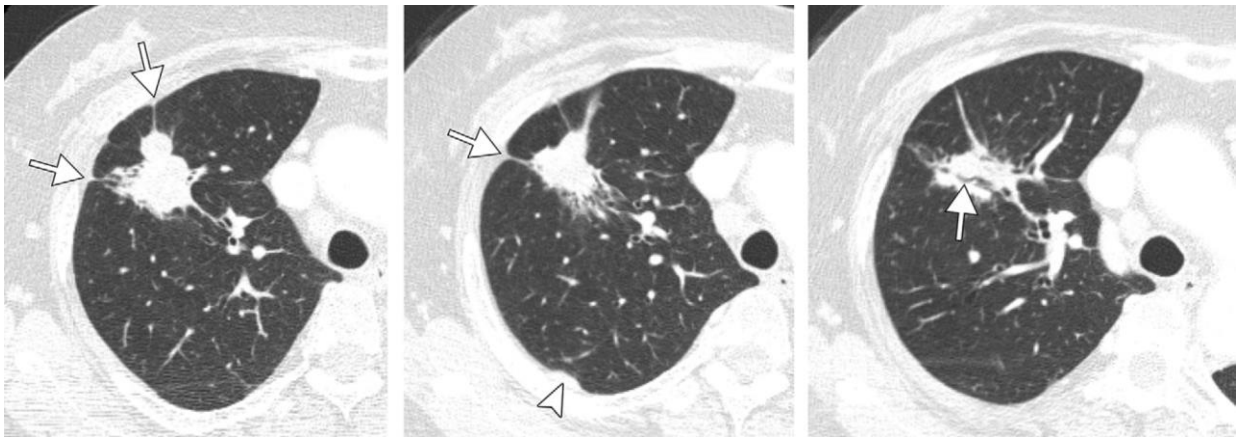
Non–Small Cell Lung Cancer with Resistance to EGFR-TKI Therapy: CT Characteristics of T790M Mutation–positive Cancer

Hyun Jung Koo, MD, PhD • Mi Young Kim, MD, PhD • Sojung Park, MD • Han Na Lee, MD • Hwa Jung Kim, MD, PhD • Jae Cheol Lee, MD, PhD • Sang-We Kim, MD, PhD • Dae Ho Lee, MD, PhD • Chang-Min Choi, MD, PhD

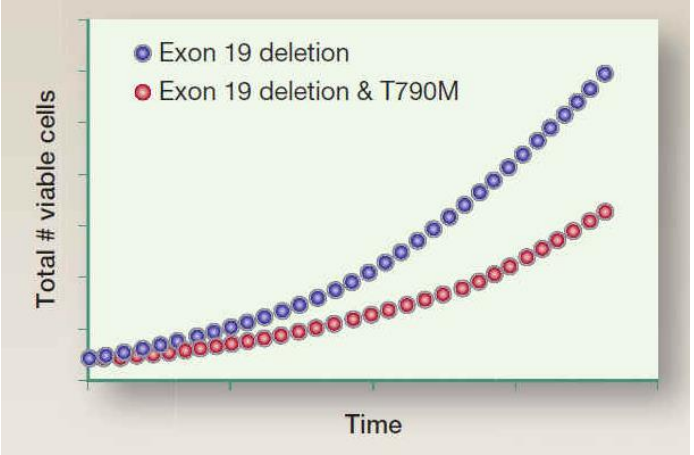
Radiology 2018; 289:227–237

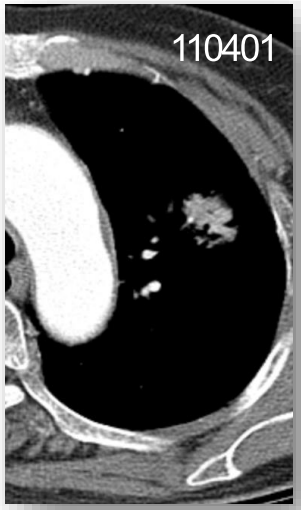
Summary

CT characteristics such as peripheral tumor location with vascular convergence, the presence of a pleural tag, and air bronchogram of lung lesions at the time of rebiopsy were significantly associated with positivity for the T790M mutation in patients with non–small cell lung cancer after first-line epidermal growth factor receptor–tyrosine kinase inhibitor therapy failure.



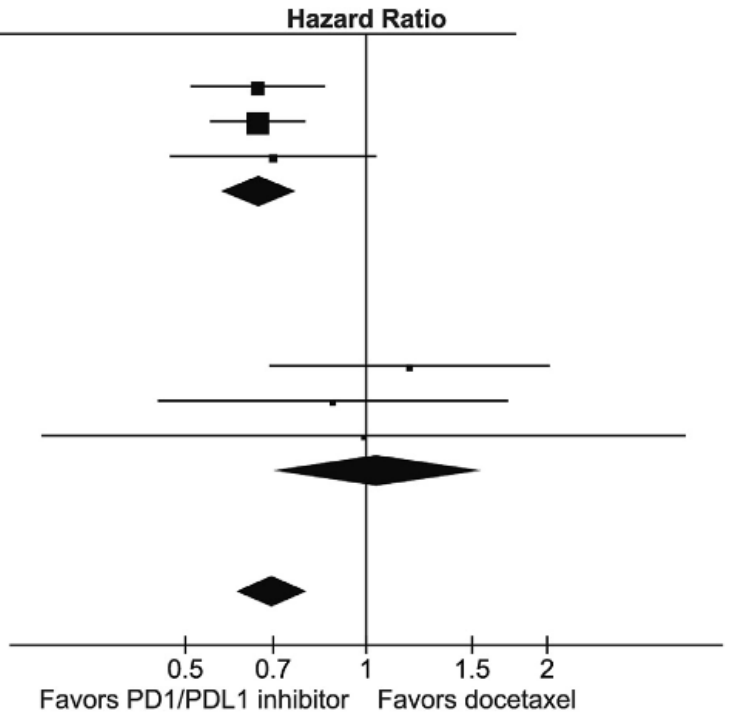
Indolent growth





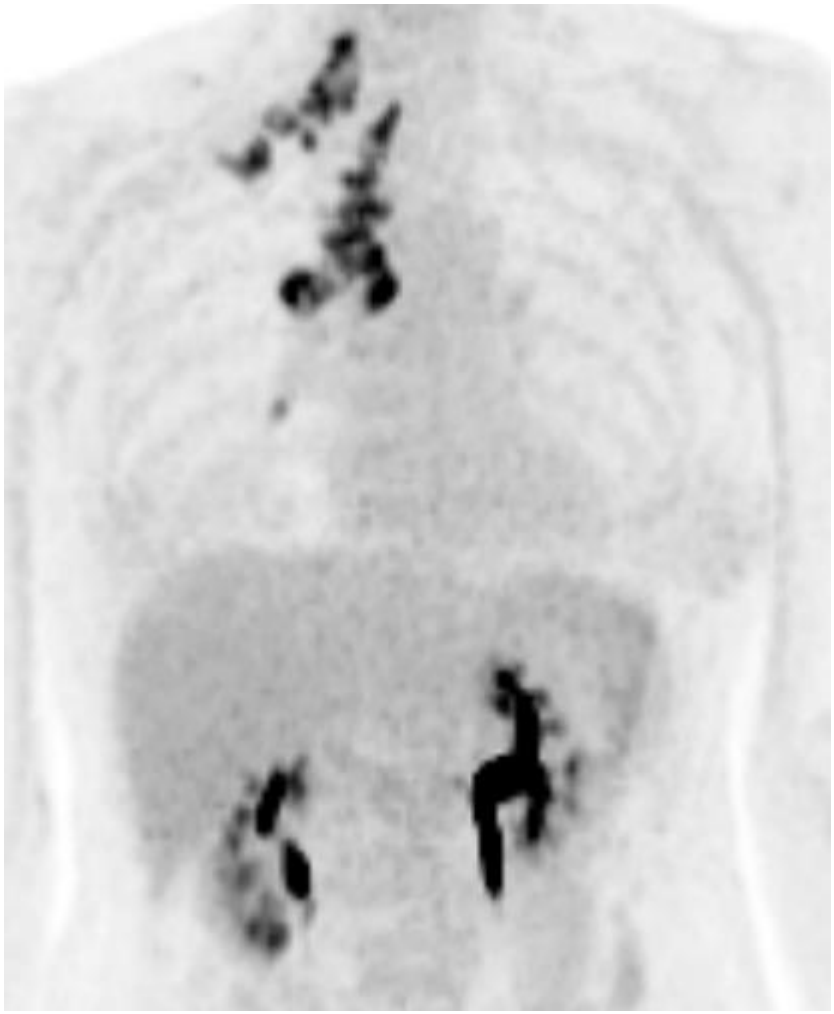
Immunotherapy?

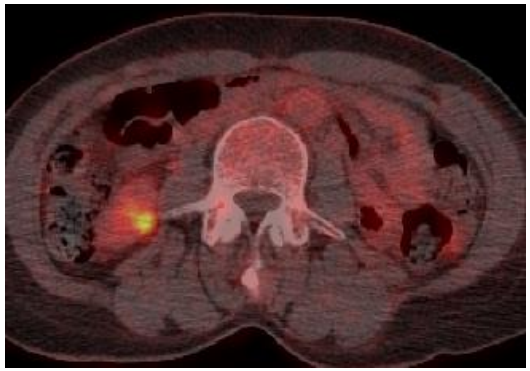
Study	Weight	Hazard Ratio [95% CI]
EGFR wild-type		
Checkmate 057	26.0%	0.66 [0.51, 0.86]
Keynote 010	52.0%	0.66 [0.55, 0.80]
POPLAR	11.0%	0.70 [0.47, 1.04]
Subtotal (95% CI)	**89.0%**	**0.66 [0.58, 0.76]**
EGFR mutant		
Checkmate 057	6.0%	1.18 [0.69, 2.00]
Keynote 010	3.8%	0.88 [0.45, 1.70]
POPLAR	1.1%	0.99 [0.29, 3.40]
Subtotal (95% CI)	**11.0%**	**1.05 [0.70, 1.55]**
Total (95% CI)	**100.0%**	**0.70 [0.61, 0.80]**



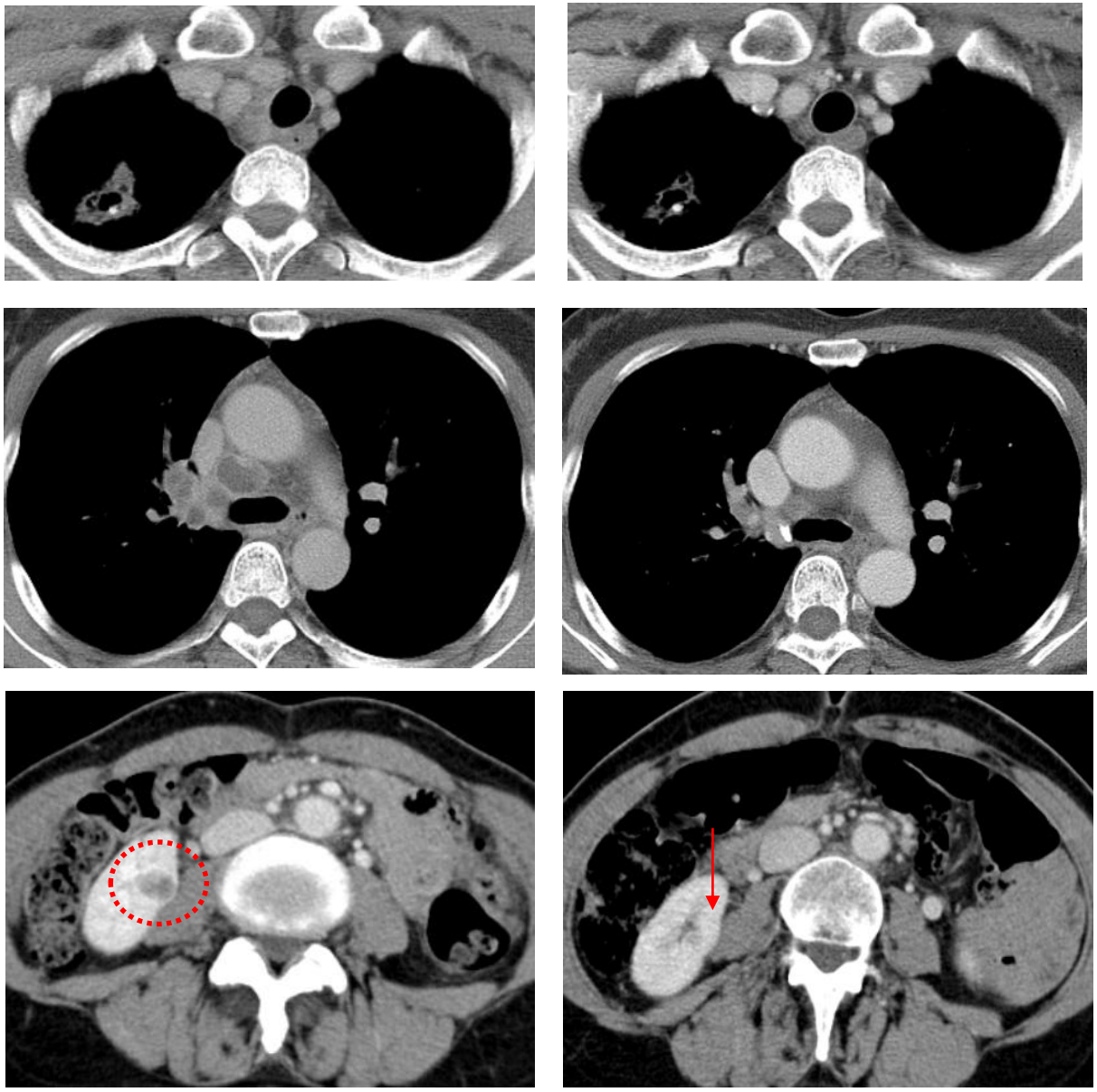
Journal of Thoracic Oncology Vol. 12 No. 2: 403-407

F/50, adeno, M/cervical LNs, kidney, 19del

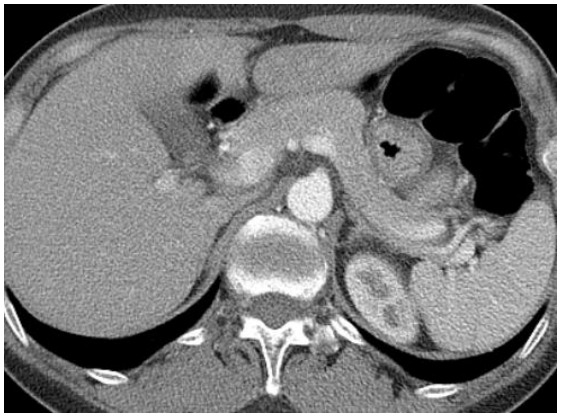




170402 → Gefitinib → 170608

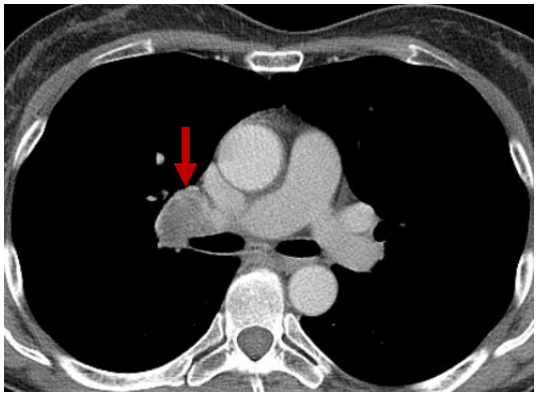


170608



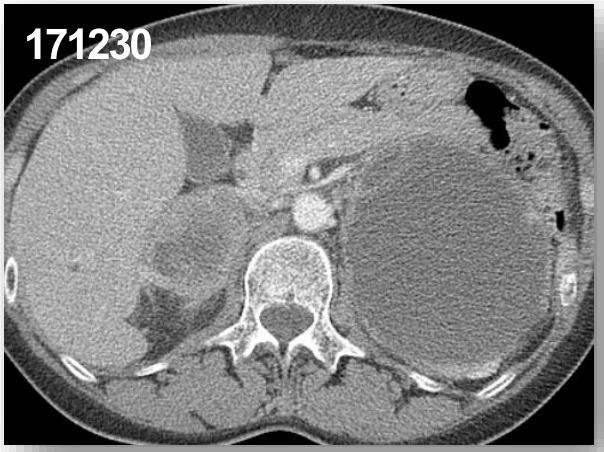
171011

GP#2 171230

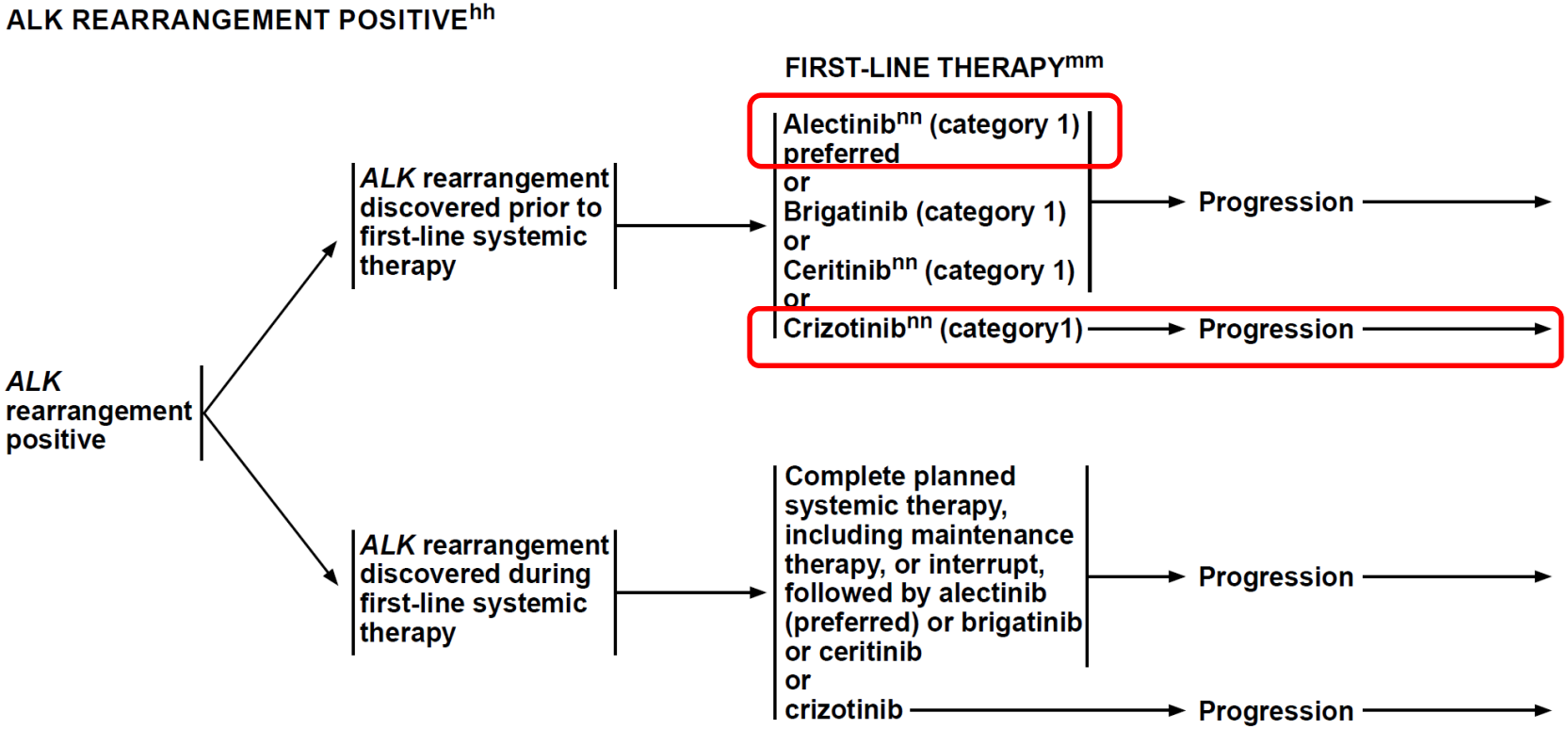


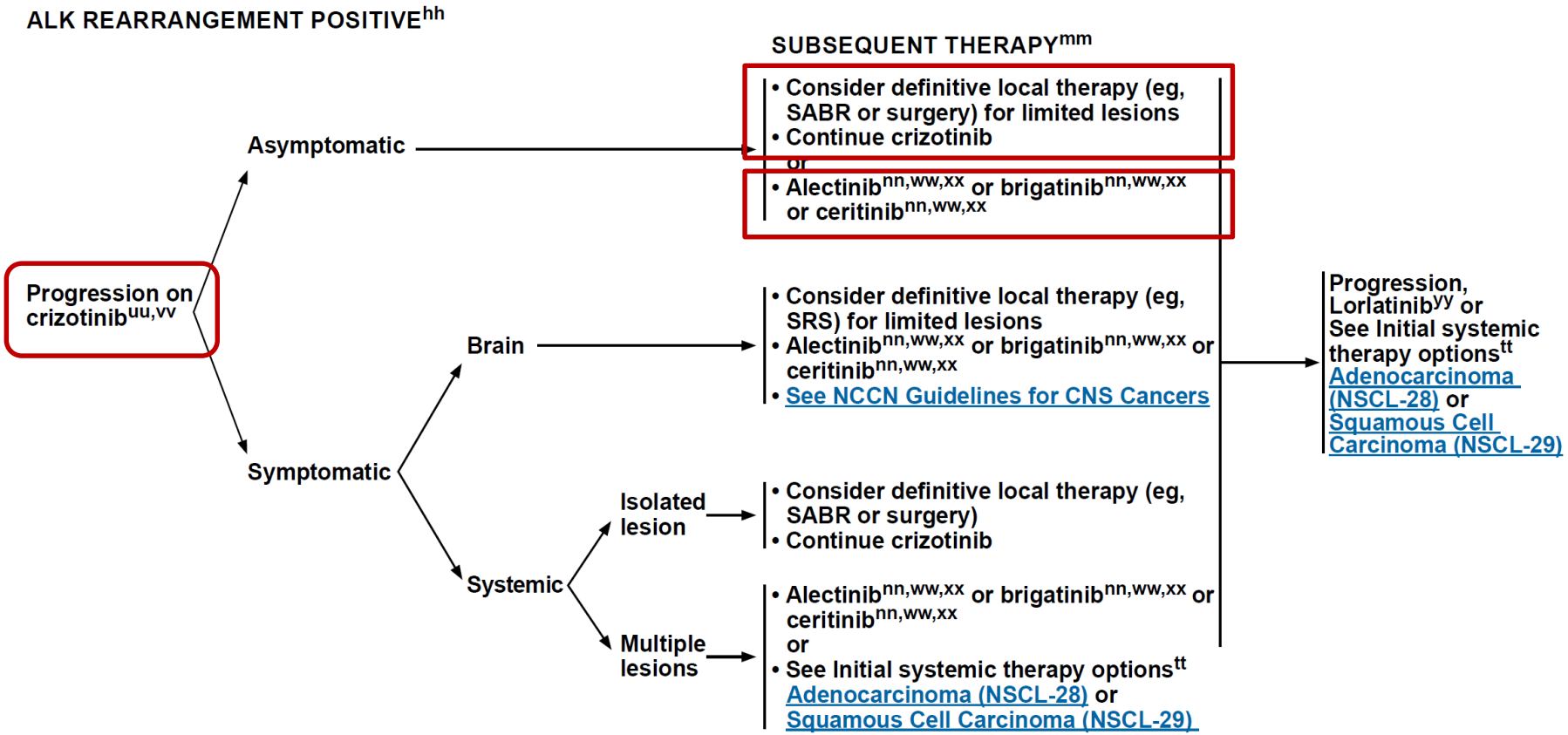
PD-L1 22C3, SP263 strong + >90%

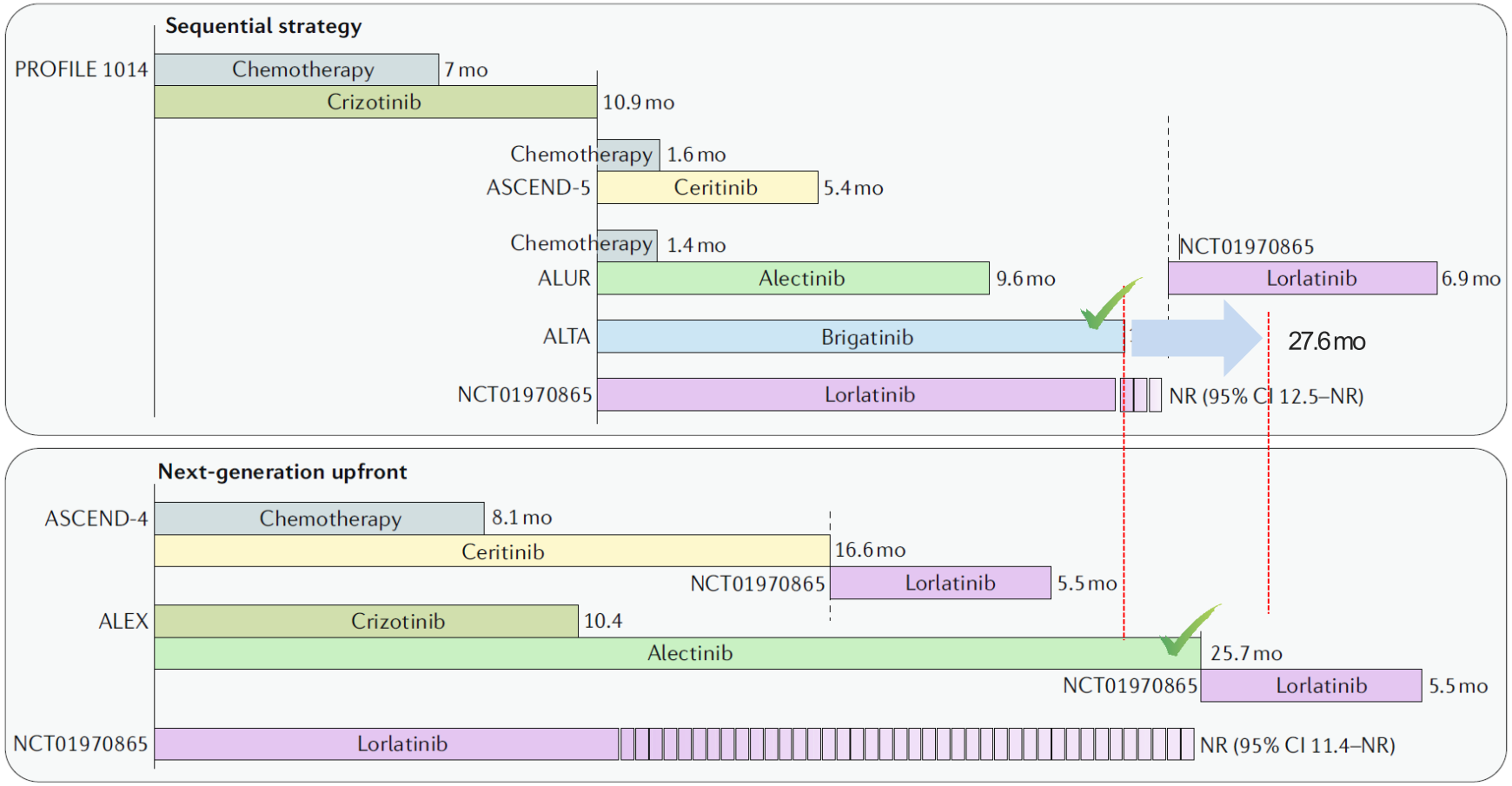
Pembrolizumab

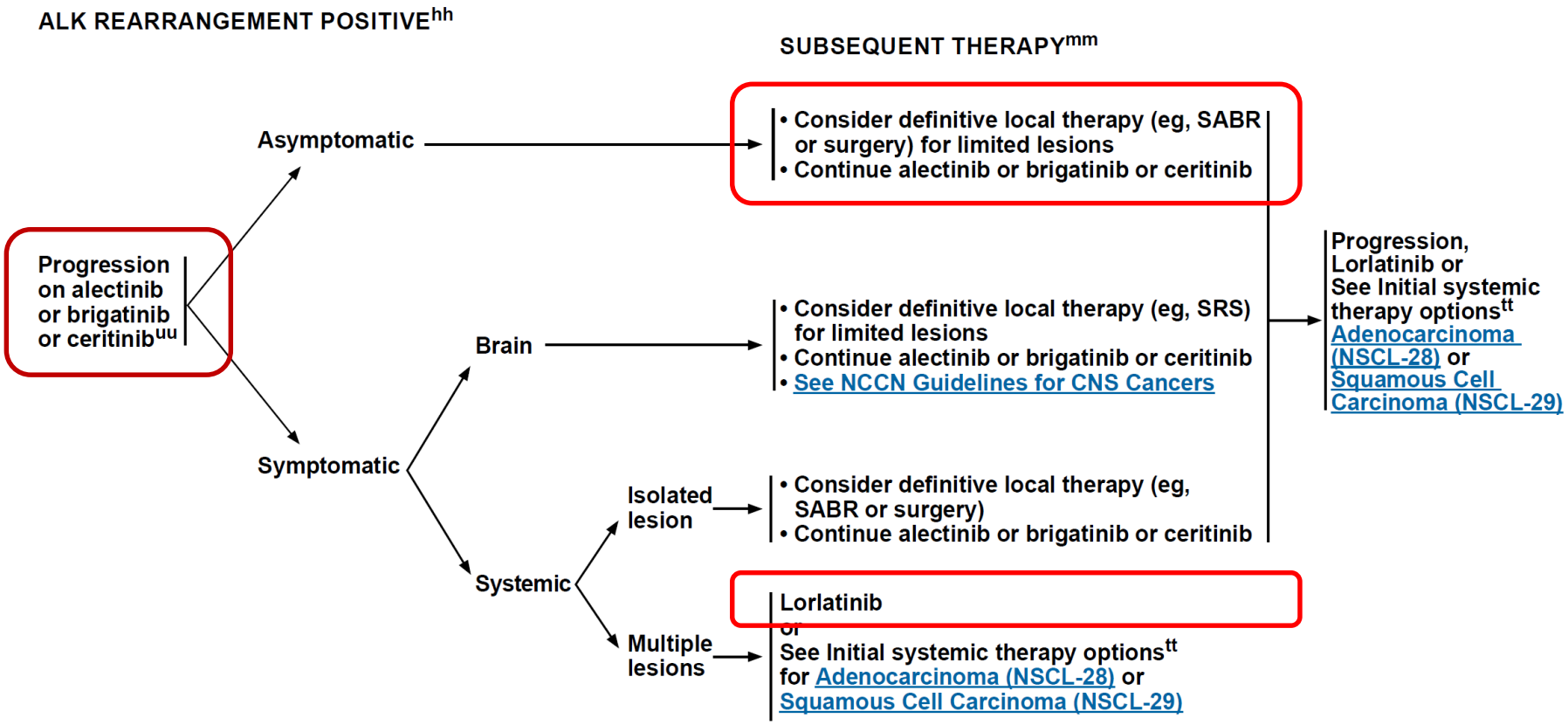


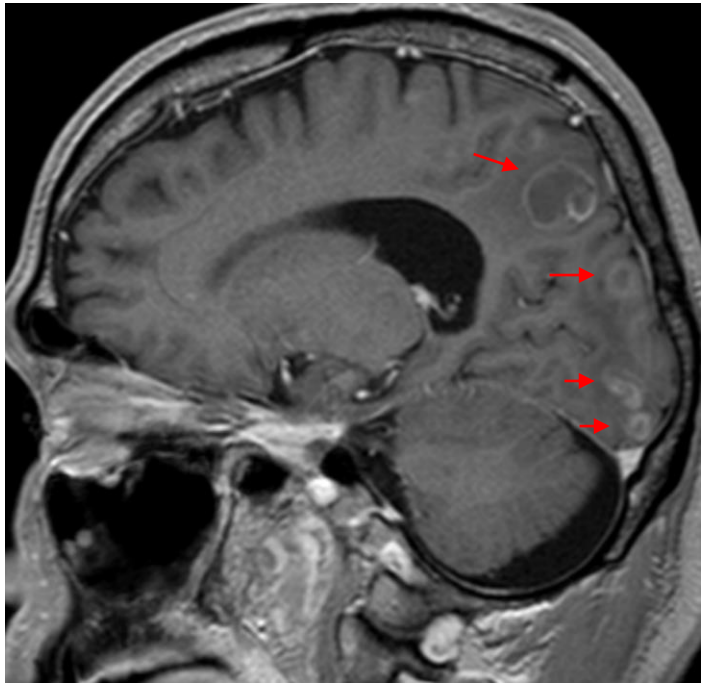
Tumor Heterogeneity

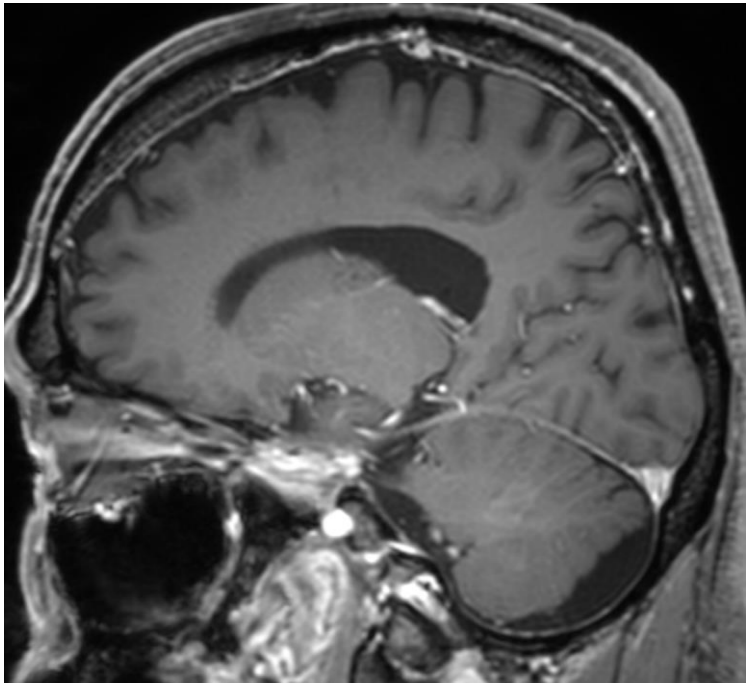

ALK REARRANGEMENT POSITIVE[hh]
FIRST-LINE THERAPY[mm]
ALK rearrangement positive
ALK rearrangement discovered prior to first-line systemic therapy
Alectinib[nn] (category 1) preferred
or
Brigatinib (category 1)
or
Ceritinib[nn] (category 1)
or
Crizotinib[nn] (category1)
Progression
Progression
Progression
ALK rearrangement discovered during first-line systemic therapy
Complete planned systemic therapy, including maintenance therapy, or interrupt, followed by alectinib (preferred) or brigatinib or ceritinib
or
crizotinib
Progression
Progression


ALK REARRANGEMENT POSITIVE[hh]
SUBSEQUENT THERAPY[mm]
Asymptomatic
• Consider definitive local therapy (eg, SABR or surgery) for limited lesions
• Continue crizotinib
or
• Alectinib[nn,ww,xx] or brigatinib[nn,ww,xx] or ceritinib[nn,ww,xx]
Progression on crizotinib[uu,vv]
Brain
• Consider definitive local therapy (eg, SRS) for limited lesions
• Alectinib[nn,ww,xx] or brigatinib[nn,ww,xx] or ceritinib[nn,ww,xx]
• See NCCN Guidelines for CNS Cancers
Symptomatic
Isolated lesion
• Consider definitive local therapy (eg, SABR or surgery)
• Continue crizotinib
Systemic
Multiple lesions
• Alectinib[nn,ww,xx] or brigatinib[nn,ww,xx] or ceritinib[nn,ww,xx]
or
• See Initial systemic therapy options[tt] Adenocarcinoma (NSCL-28) or Squamous Cell Carcinoma (NSCL-29)
Progression, Lorlatinib[yy] or See Initial systemic therapy options[tt] Adenocarcinoma (NSCL-28) or Squamous Cell Carcinoma (NSCL-29)


Sequential strategy
PROFILE 1014
Chemotherapy
7 mo
Crizotinib
10.9 mo
Chemotherapy
1.6 mo
ASCEND-5
Ceritinib
5.4 mo
Chemotherapy
1.4 mo
ALUR
Alectinib
9.6 mo
NCT01970865
Lorlatinib
6.9 mo
ALTA
Brigatinib
27.6 mo
NCT01970865
Lorlatinib
NR (95% CI 12.5–NR)
Next-generation upfront
ASCEND-4
Chemotherapy
8.1 mo
Ceritinib
16.6 mo
NCT01970865
Lorlatinib
5.5 mo
ALEX
Crizotinib
10.4
Alectinib
25.7 mo
NCT01970865
Lorlatinib
5.5 mo
NCT01970865
Lorlatinib
NR (95% CI 11.4–NR)


ALK REARRANGEMENT POSITIVE[hh]
SUBSEQUENT THERAPY[mm]
Progression on alectinib or brigatinib or ceritinib[uu]
Asymptomatic
• Consider definitive local therapy (eg, SABR or surgery) for limited lesions
• Continue alectinib or brigatinib or ceritinib
Symptomatic
Brain
• Consider definitive local therapy (eg, SRS) for limited lesions
• Continue alectinib or brigatinib or ceritinib
• See NCCN Guidelines for CNS Cancers
Systemic
Isolated lesion
• Consider definitive local therapy (eg, SABR or surgery)
• Continue alectinib or brigatinib or ceritinib
Multiple lesions
Lorlatinib
or
See Initial systemic therapy options[tt] for Adenocarcinoma (NSCL-28) or Squamous Cell Carcinoma (NSCL-29)
Progression, Lorlatinib or See Initial systemic therapy options[tt] Adenocarcinoma (NSCL-28) or Squamous Cell Carcinoma (NSCL-29)





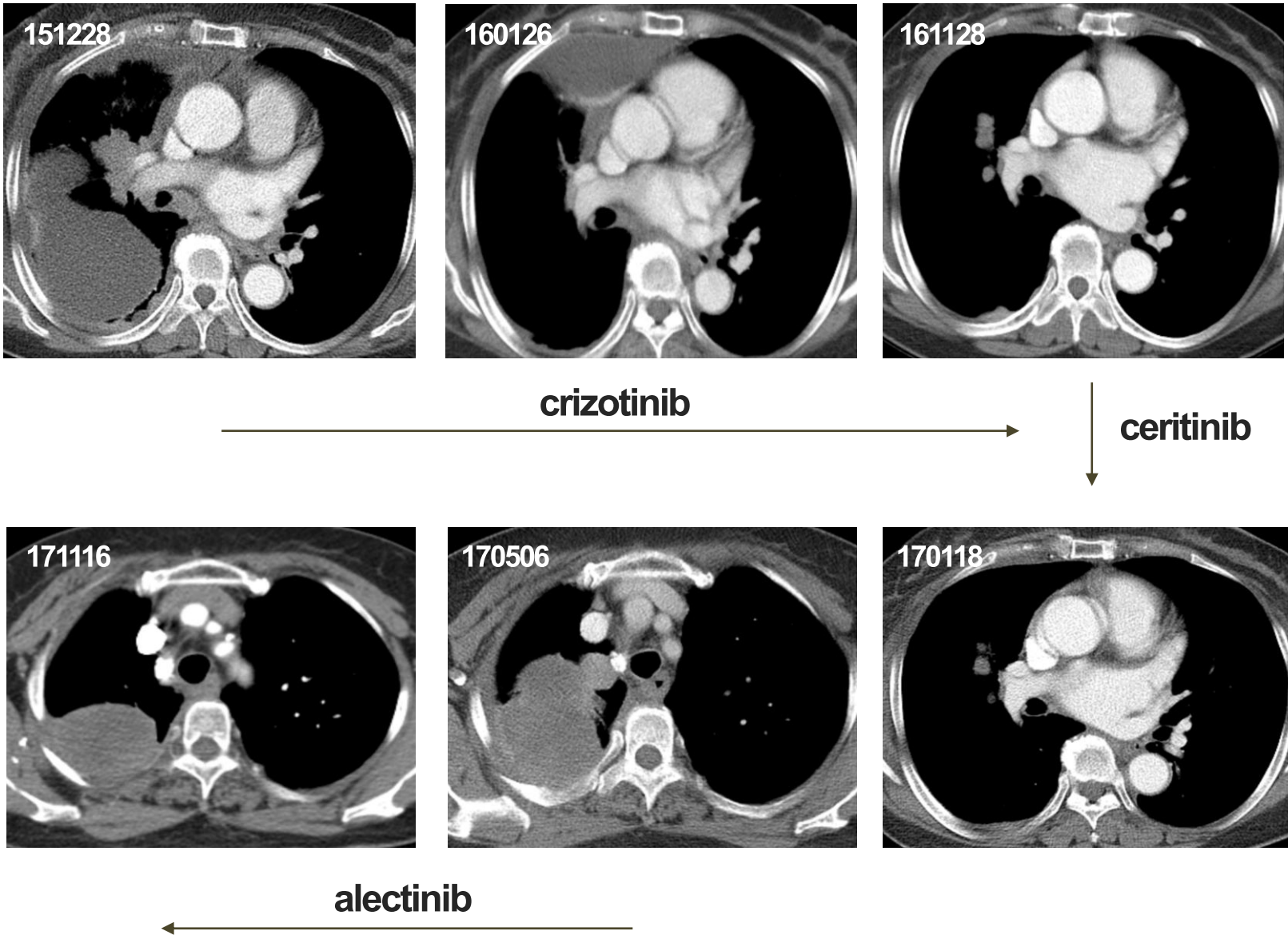
alectinib

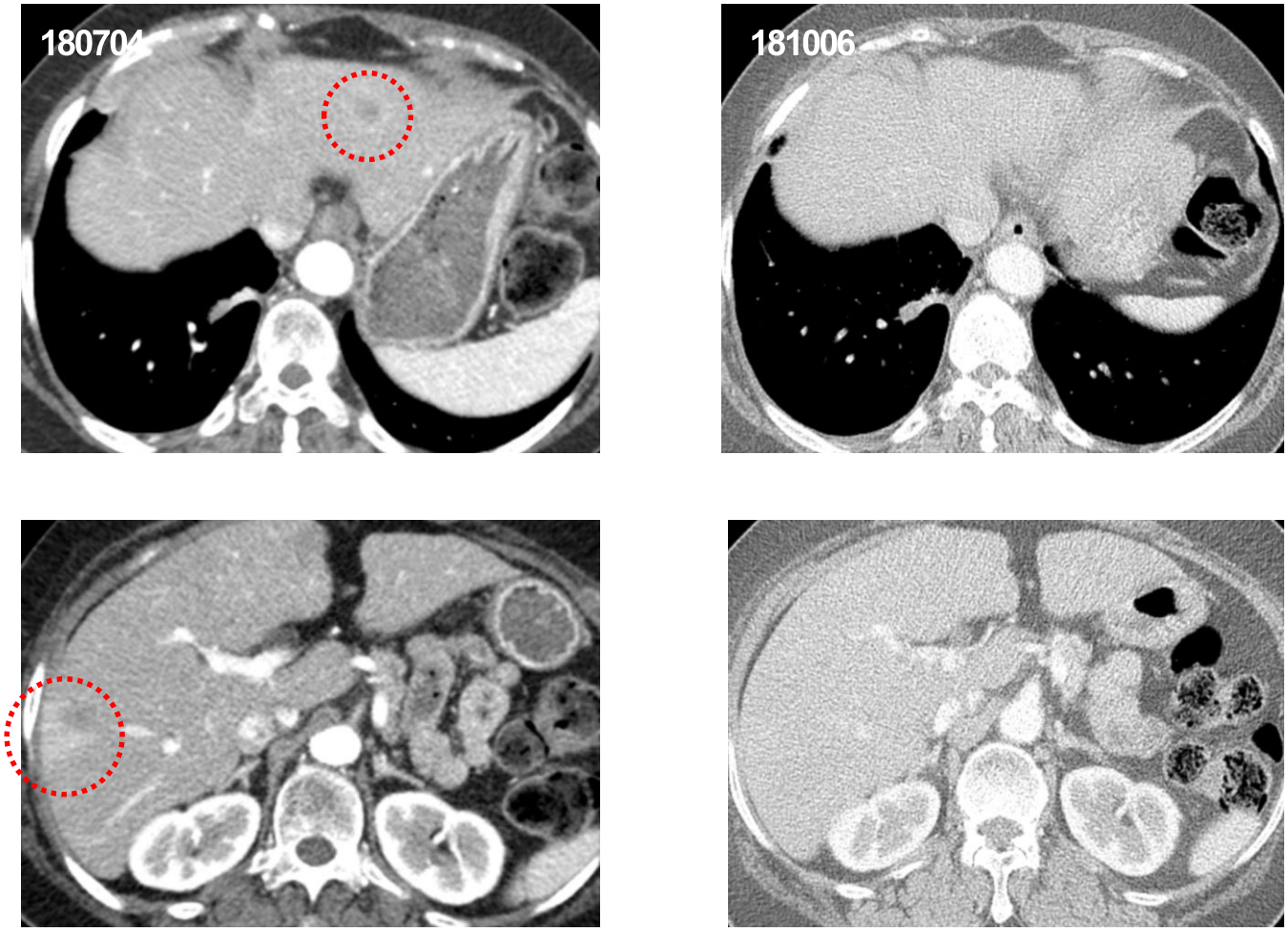
0052773246

F/73 ACC M/pleura, brain ALK+

1L PP#1 (151208)
2L crizotinib (151229-161130)
3L ceritinib (161130-170508)
4L alectinib (170830-180710)
5L loratinib (180816~)

0050043204


151228
160126
161128
crizotinib
ceritinib
171116
170506
170118
alectinib

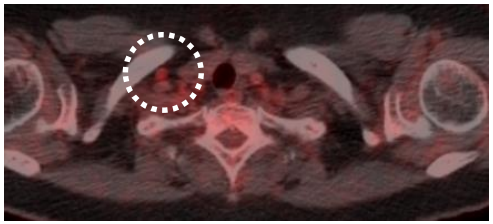

180704
181006
loratinib

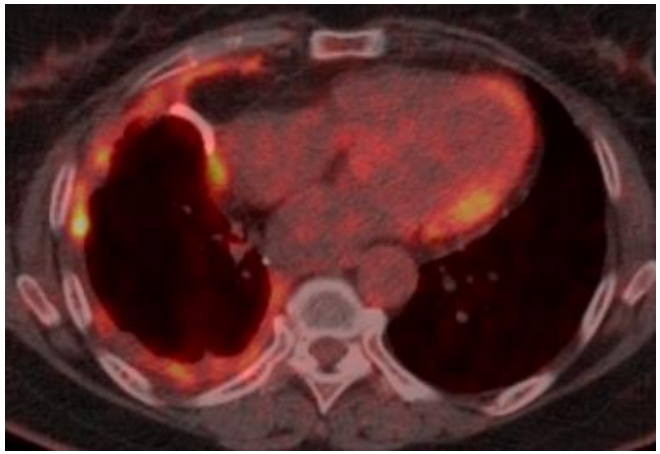
F/60 ACC M/lung ALK+

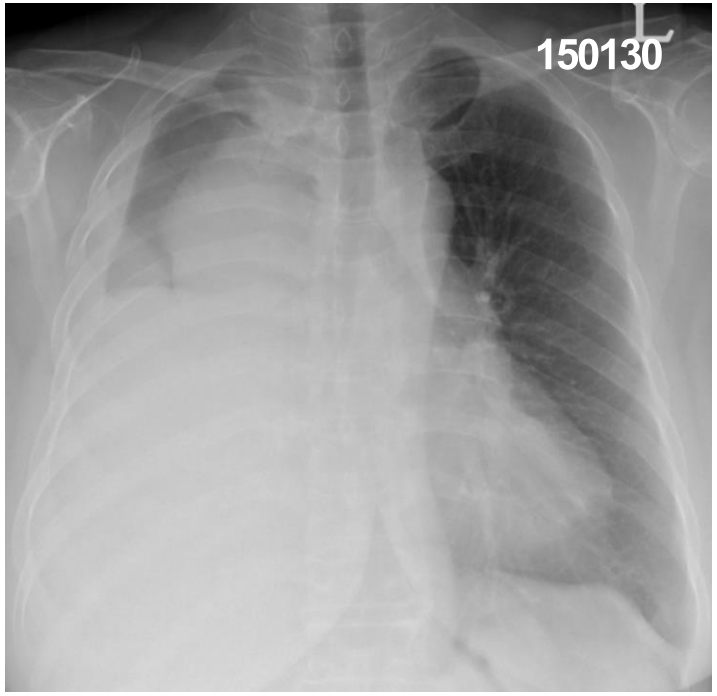
s/p RLLobectomy, VATS (120116) + adj.TP #4

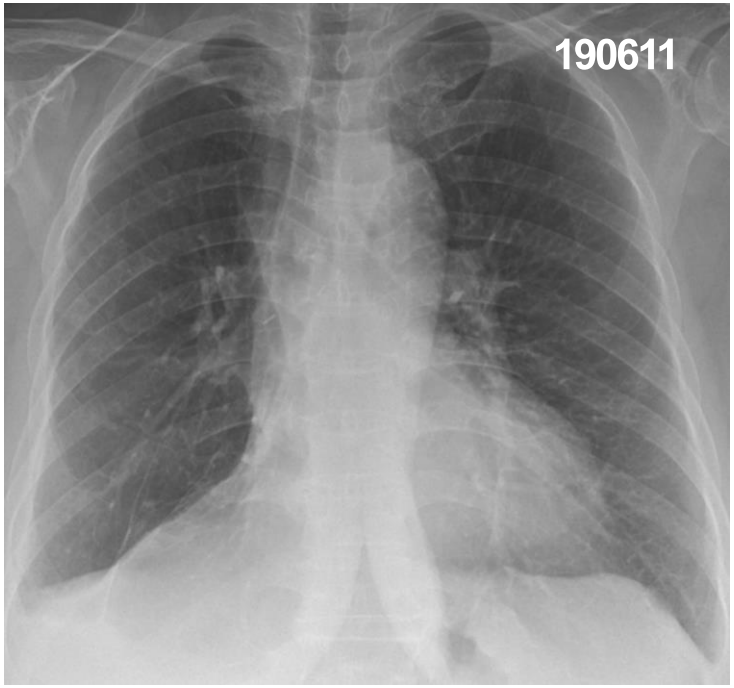
Recur to pleura, rt SCN

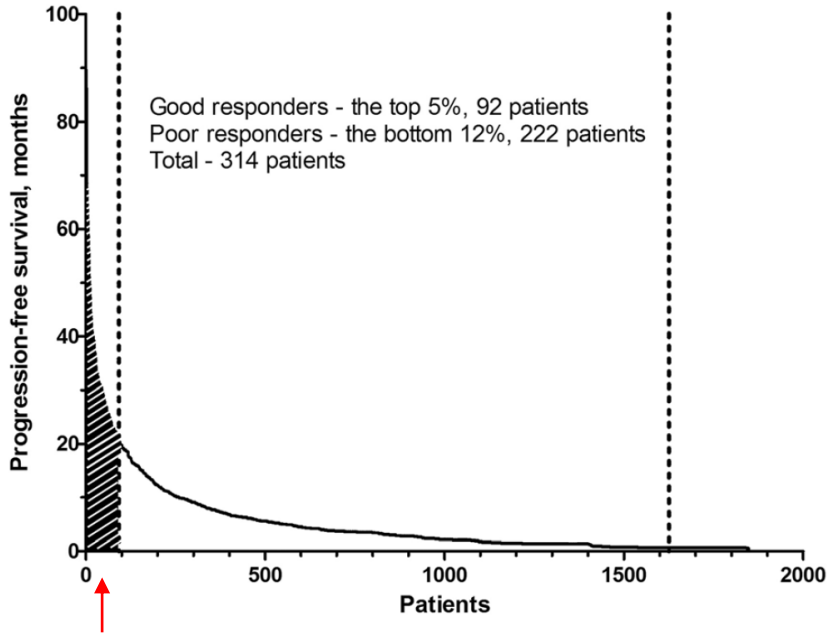
Pemetrexed #58 after PP#4 since150217 ⟶ ongoing



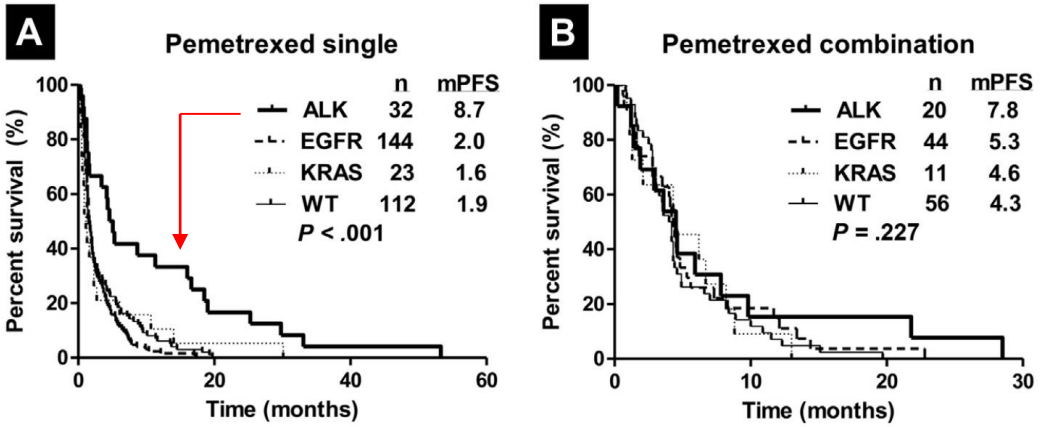



150130


190611



BMC Cancer. 2016 Jul 7;16:417



Clin Lung Cancer. 2015 Nov;16(6):e203-12

thank you!