Current landscape of targeted therapy in advanced *ALK*-positive NSCLC

25-JUL-2020 @ Taichung

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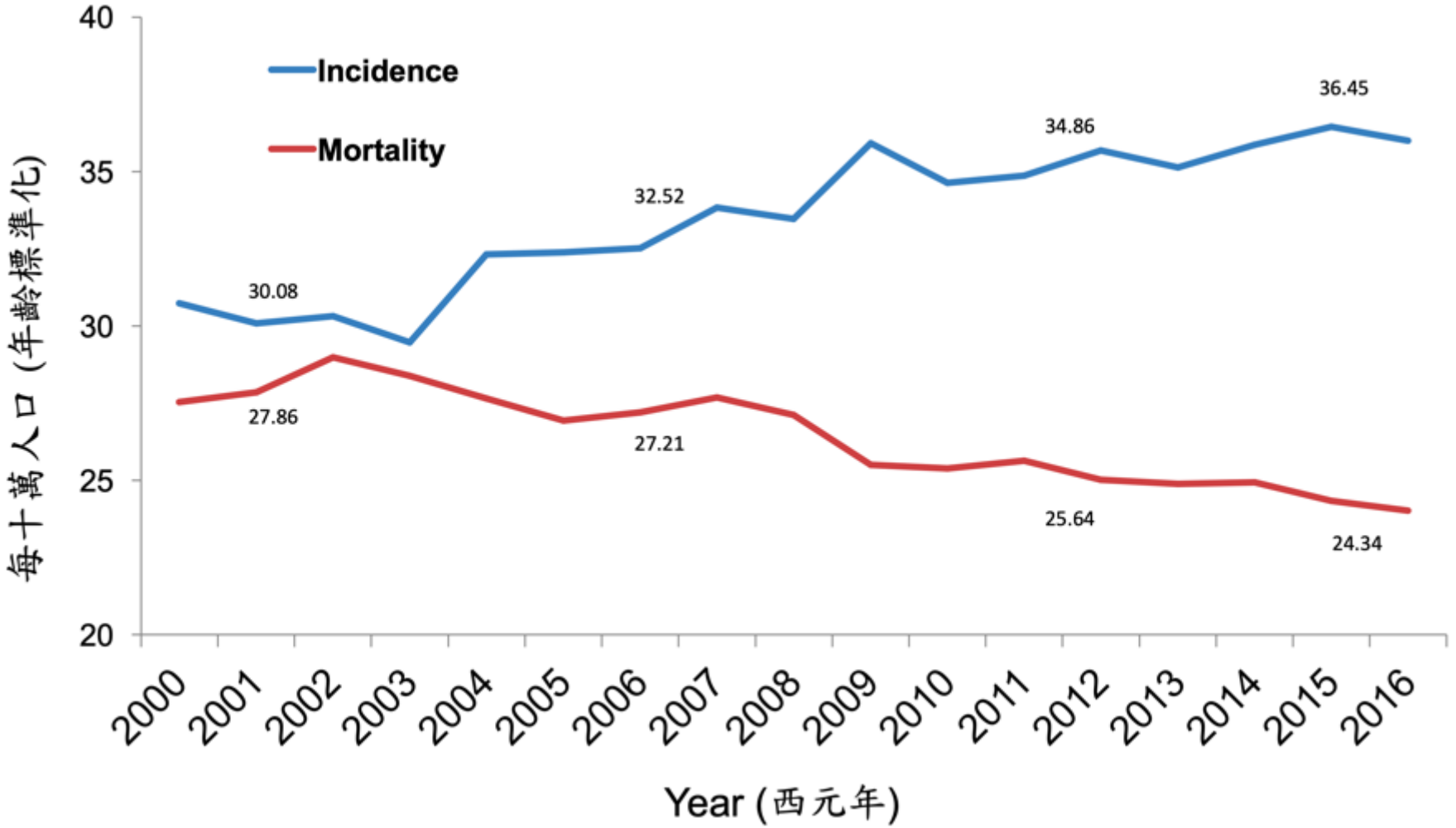
Trend of lung cancer incidence and mortality in Taiwan

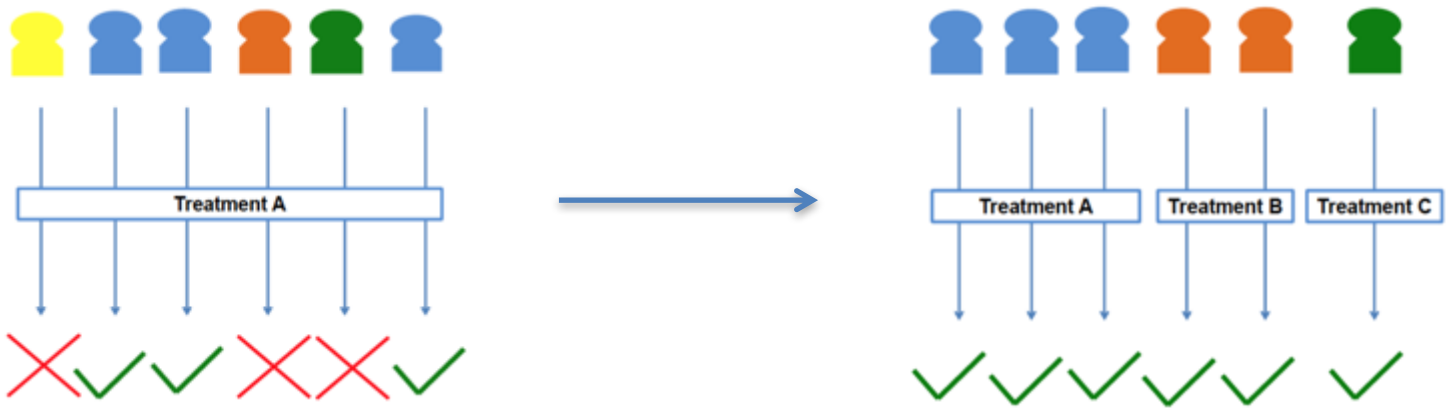


資料來源: 國健署

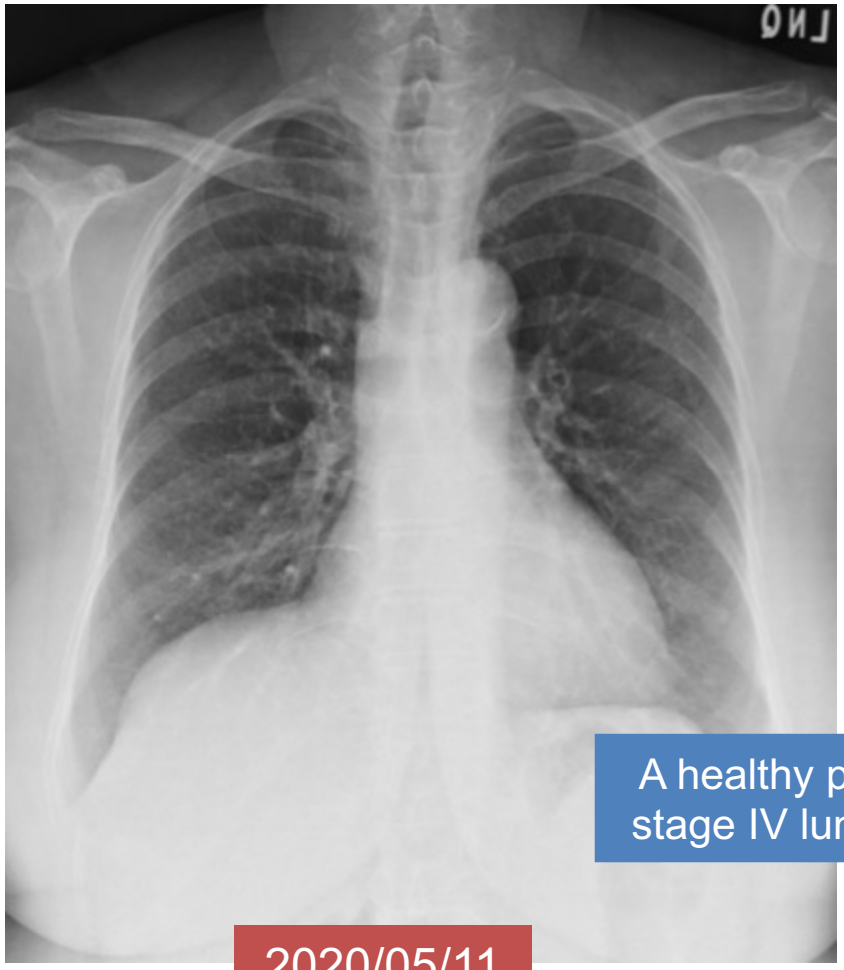
The Outcome of Lung Cancer is Improving

Why ?

Successful patient sorting; personalized therapy

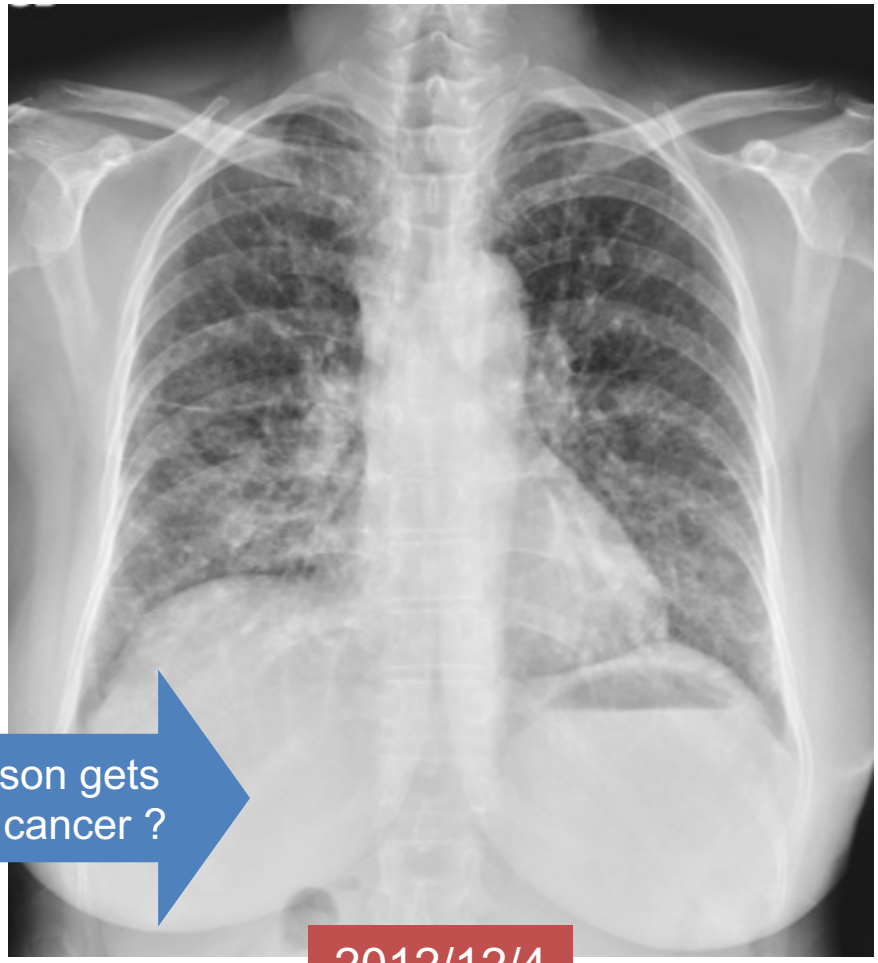


Is there any finding associated with lung cancer in CXR of this 57y/o, non-smoking lady ?



A healthy person gets stage IV lung cancer ?

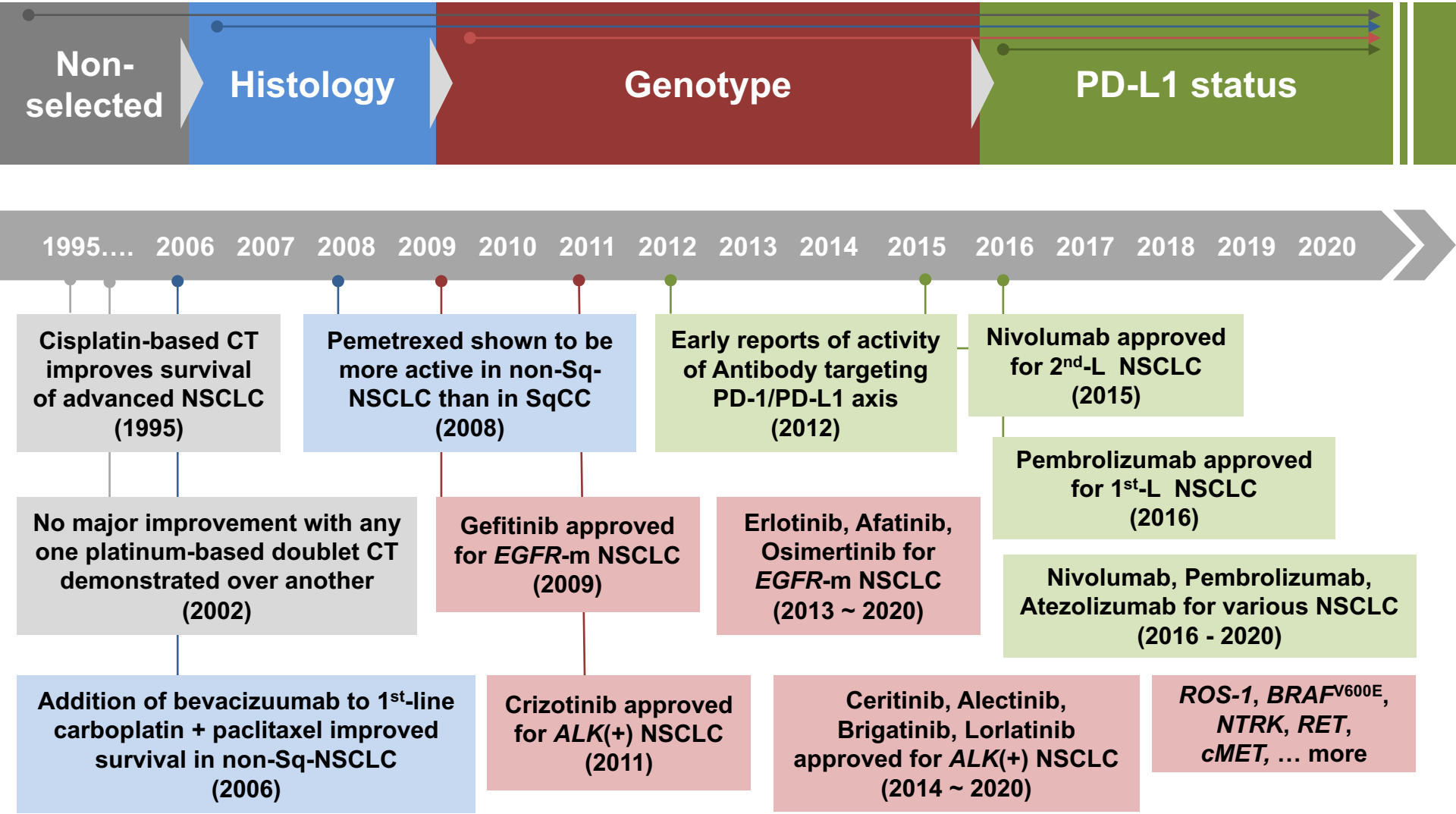
2020/05/11



2012/12/4

What happen to this patient ?

The way toward personalized therapy

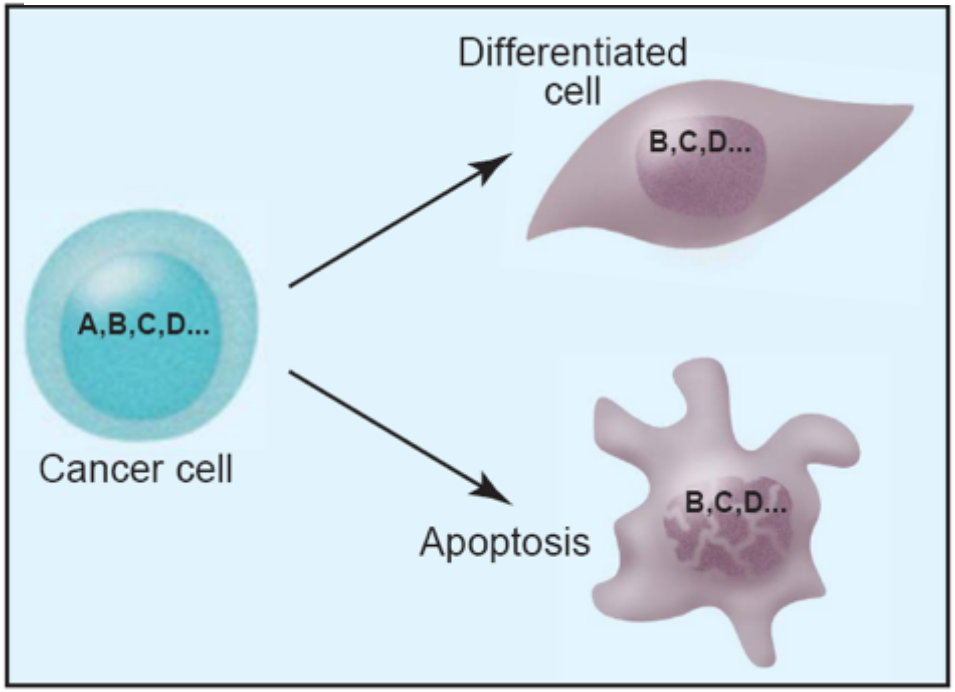


What is targeted therapy?

Driver mutation and oncogene addiction

Science
AAAS

Addiction to Oncogenes--the Achilles Heal of Cancer
I. Bernard Weinstein
Science **297**, 63 (2002);
DOI: 10.1126/science.1073096

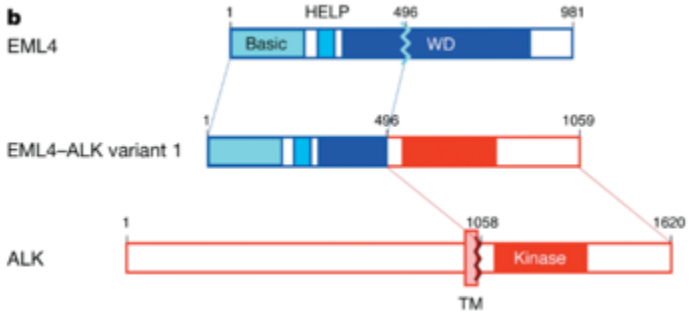


Inactivation of ***a single critical oncogene*** (A) can induce cancer cells to differentiate into cells with normal phenotype or to undergo apoptosis.

In 2007: *EML4-ALK* fusion was identified as an oncogenic mutation in lung cancer

Identification of the transforming *EML4–ALK* fusion gene in non-small-cell lung cancer

Manabu Soda[1,2], Young Lim Choi[1], Munehiro Enomoto[1,2], Shuji Takada[1], Yoshihiro Yamashita[1], Shunpei Ishikawa[5], Shin-ichiro Fujiwara[1], Hideki Watanabe[1], Kentaro Kurashina[1], Hisashi Hatanaka[1], Masashi Bando[2], Shoji Ohno[2], Yuichi Ishikawa[6], Hiroyuki Aburatani[5,7], Toshiro Niki[3], Yasunori Sohara[4], Yukihiko Sugiyama[2] & Hiroyuki Mano[1,7]

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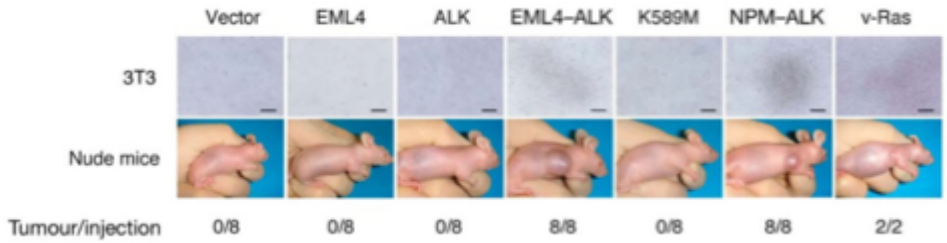
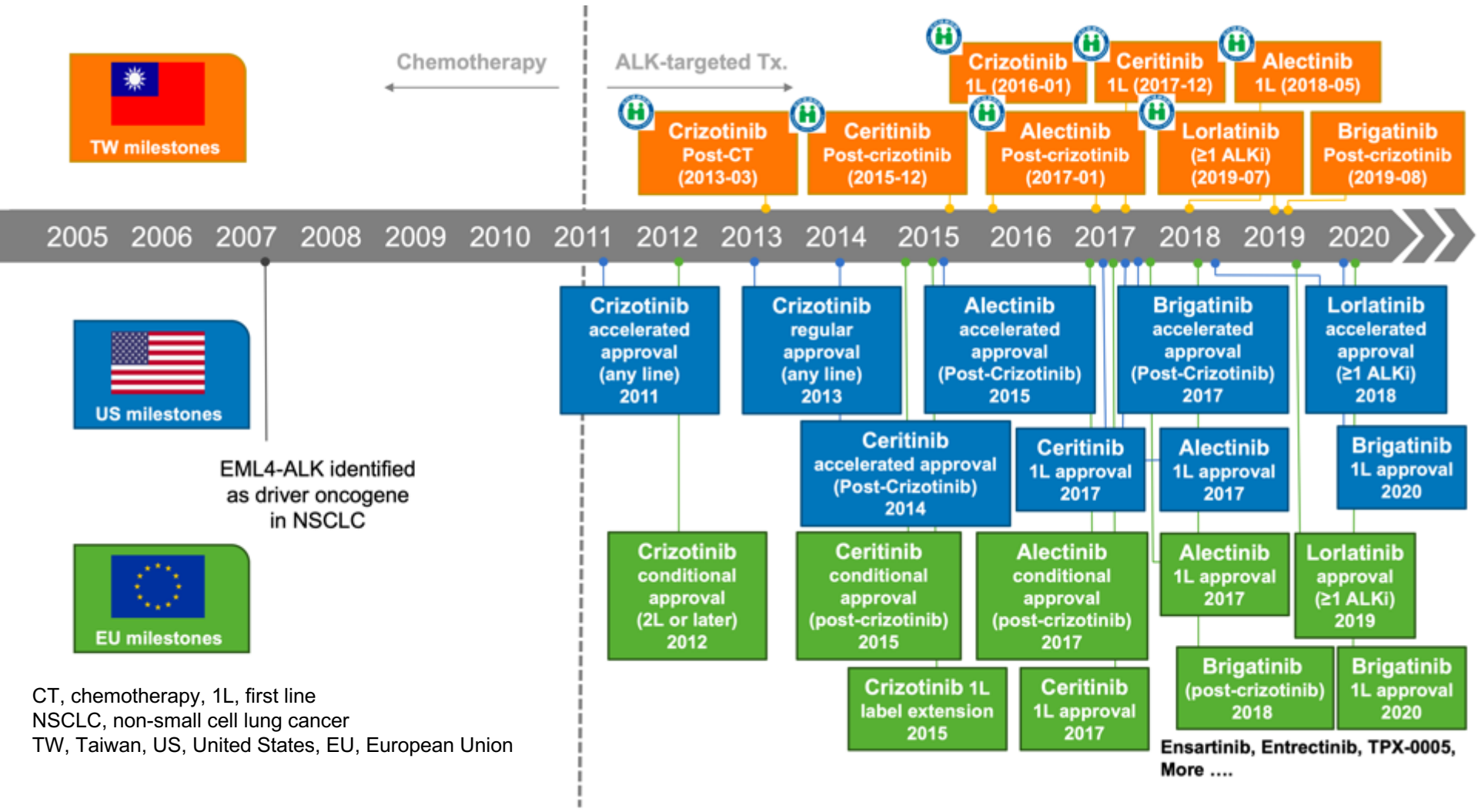


A 62y/o man with adenocarcinoma
Retroviral cDNA expression library

Soda M et al. Nature 2007; 448:561-6.

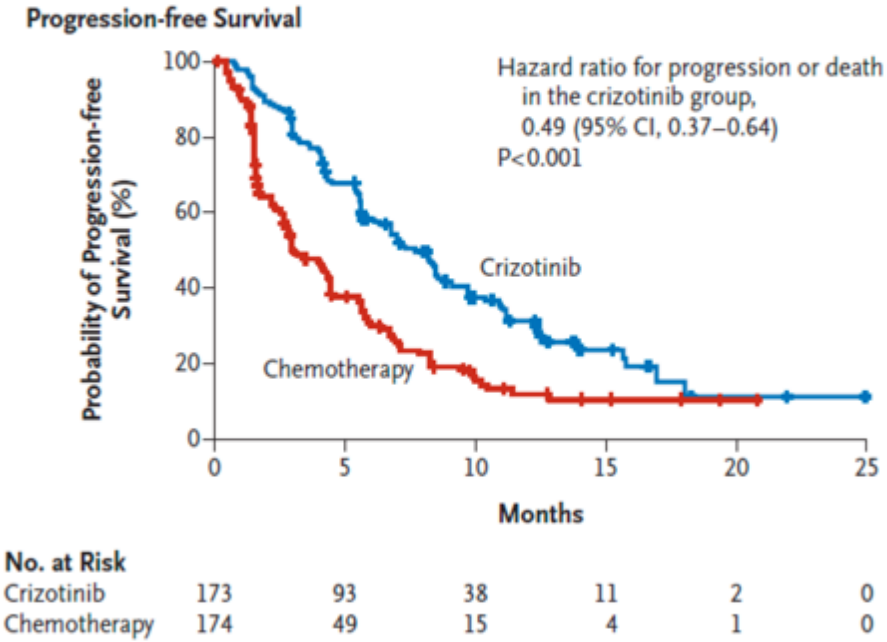
Overview of ALK inhibitor(s) development



CT, chemotherapy, 1L, first line
NSCLC, non-small cell lung cancer
TW, Taiwan, US, United States, EU, European Union

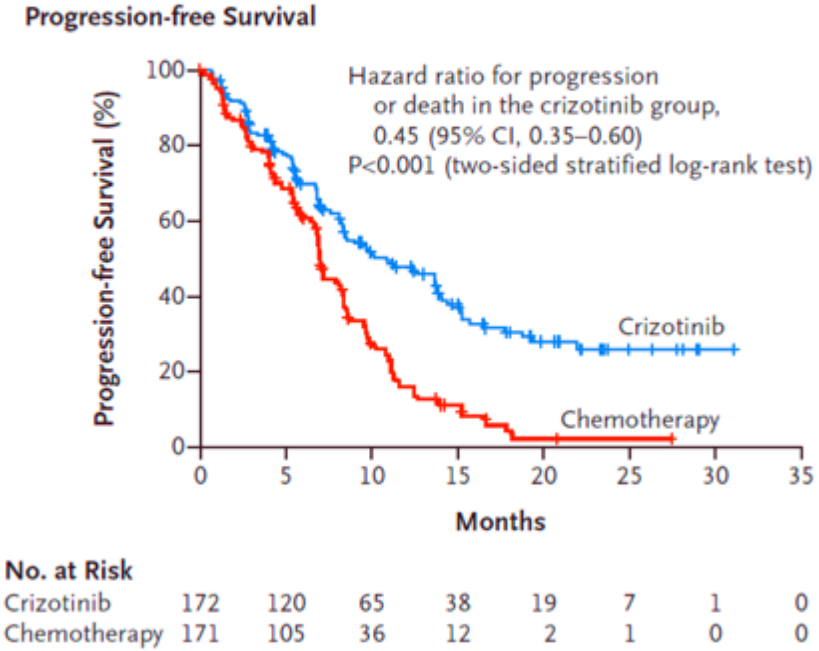
Crizotinib: the 1st-G ALK inhibitor

PROFILE 1007
2nd line vs. CT (single)



ORR 65% vs. 20%

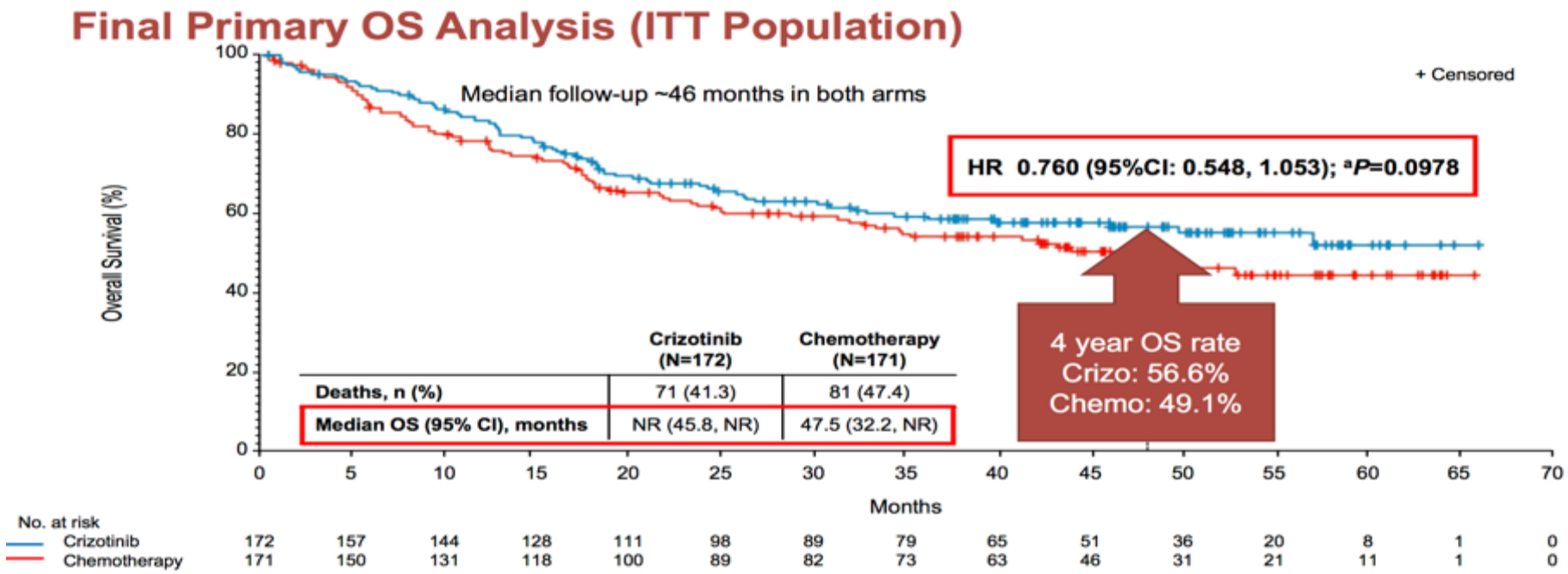
PROFILE 1014
1st line vs. CT (platinum)



ORR 74% vs. 45%

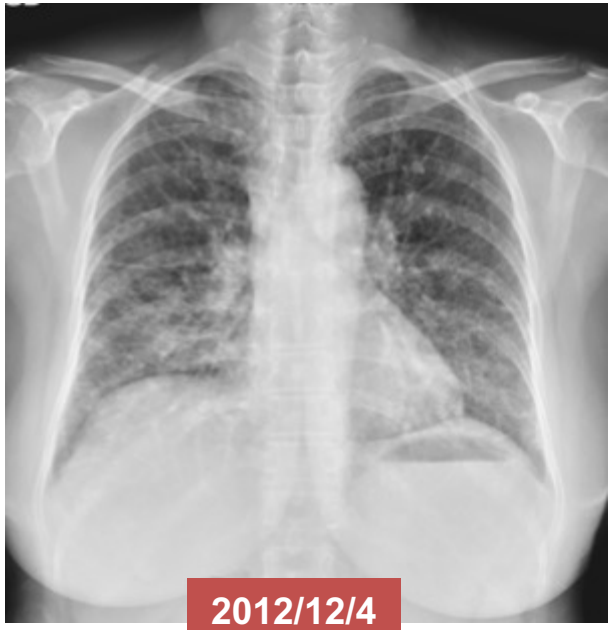
Shaw AT et al. N Engl J Med 2013; 368:2385-94.; Solomon BJ et al. N Engl J Med 2014; 371:2167-77.

Promising outcome in *ALK*(+) NSCLC

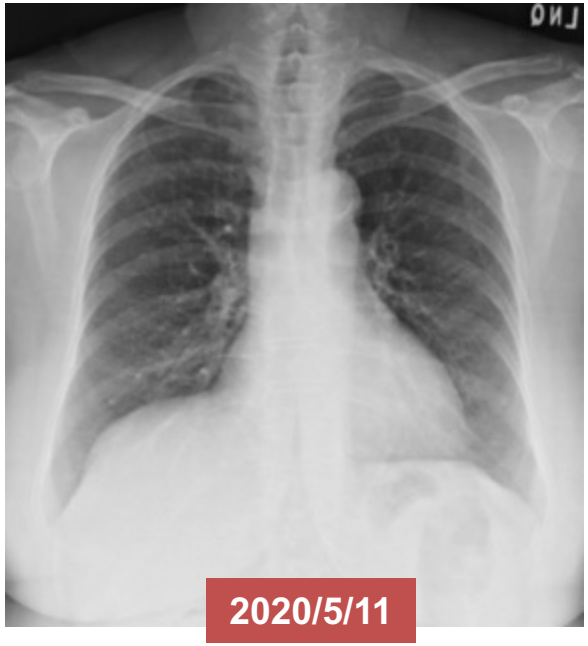


Tony Mok et al. ESMO 2017.

What happen to our patient ?



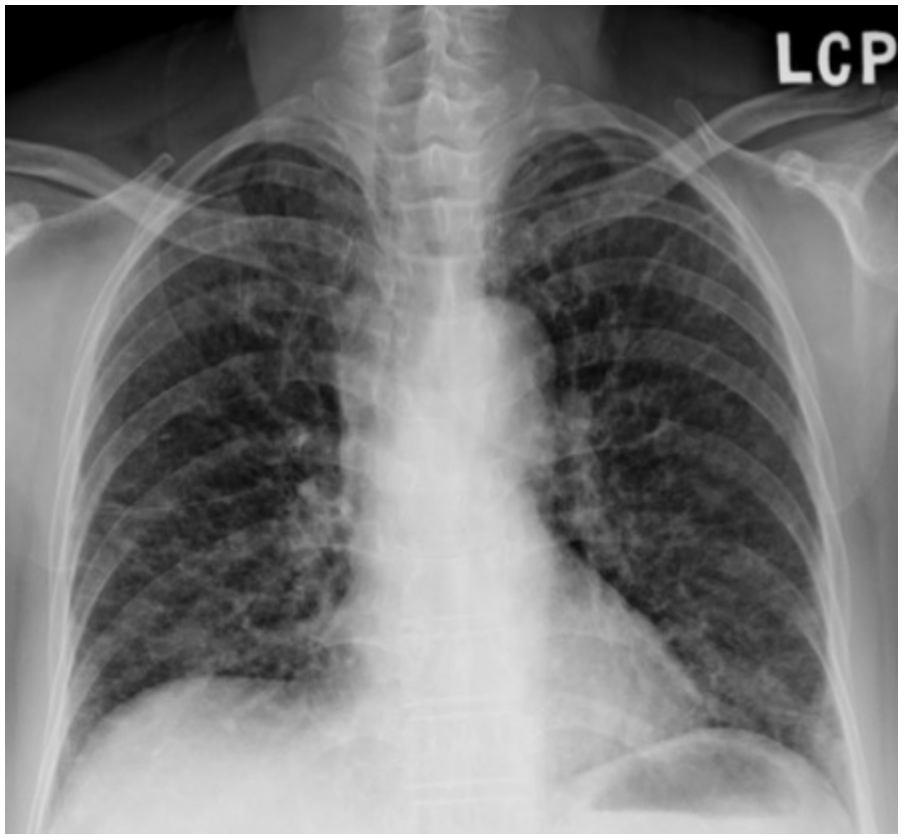
2012/12/4

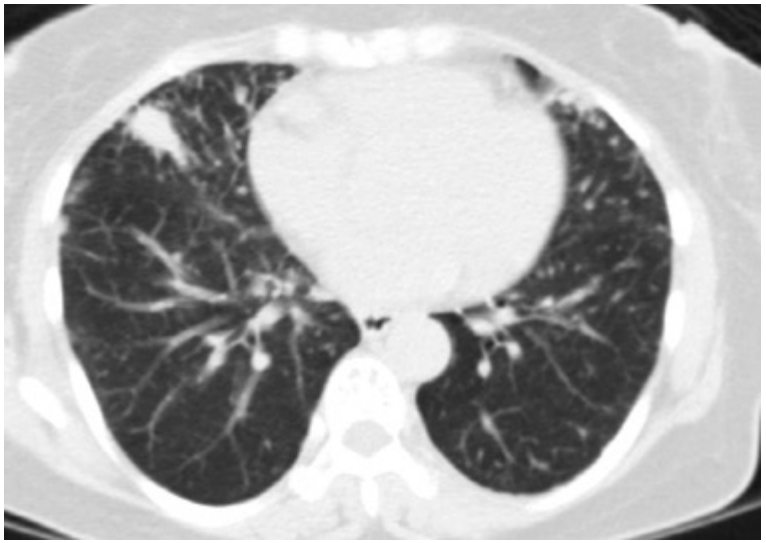


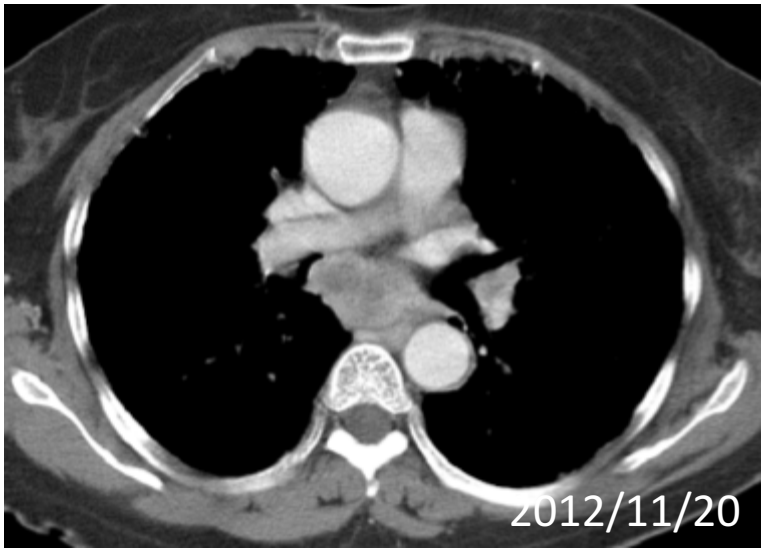
2020/5/11

Chan, 57y/o lady, non-smoker, DOE and BWL for 3 months

(Abnormal LDCT at other hospital)



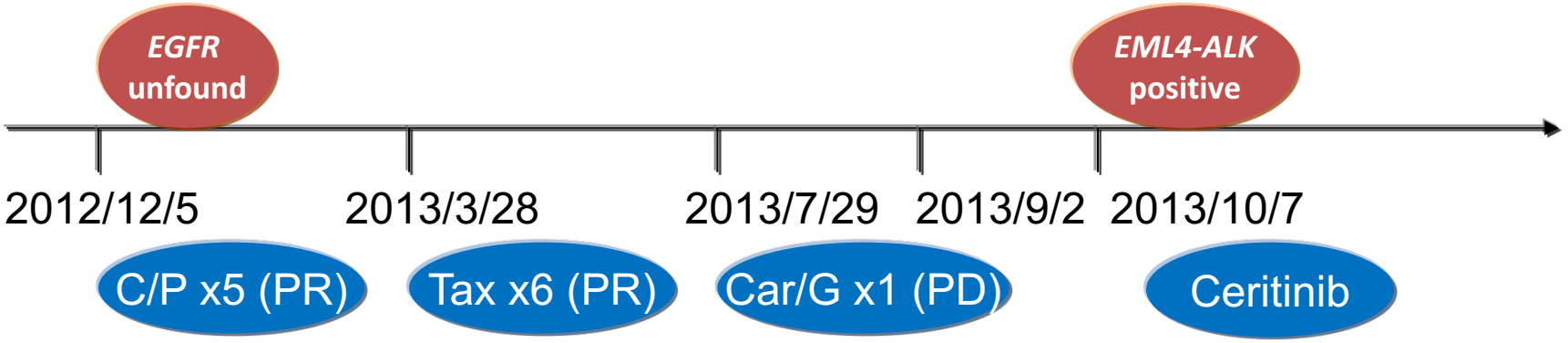


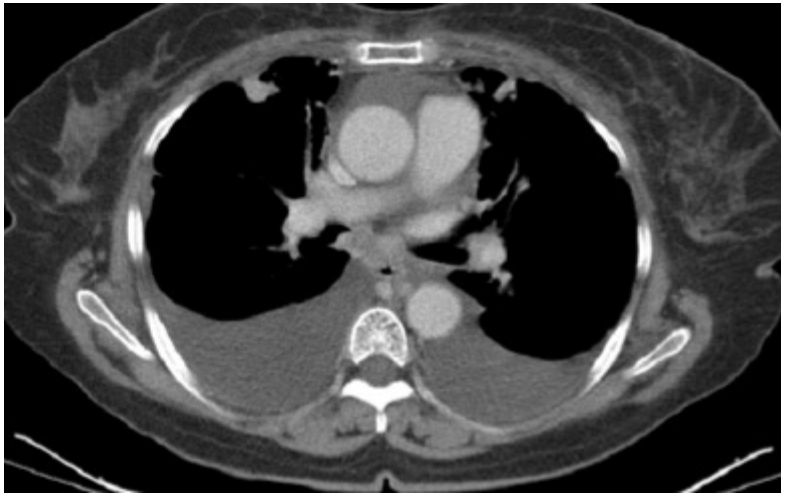


Lung cancer, RML, ADC, cT4N3M1b, stage IV, lung, neck/retroperitoneal LN and bone METs, ECOG PS=1.

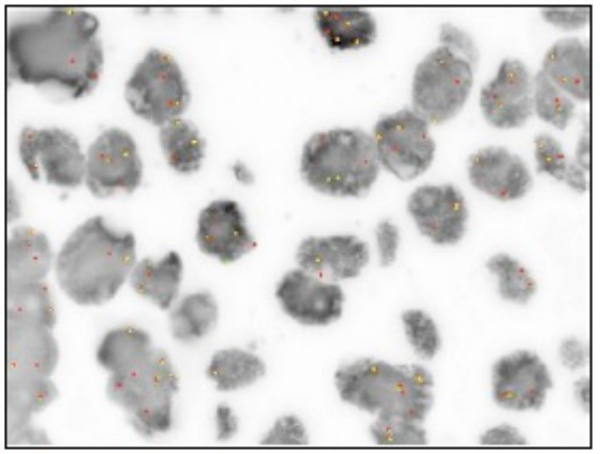
Ms. Chan 56 year-old lady

Never smoker



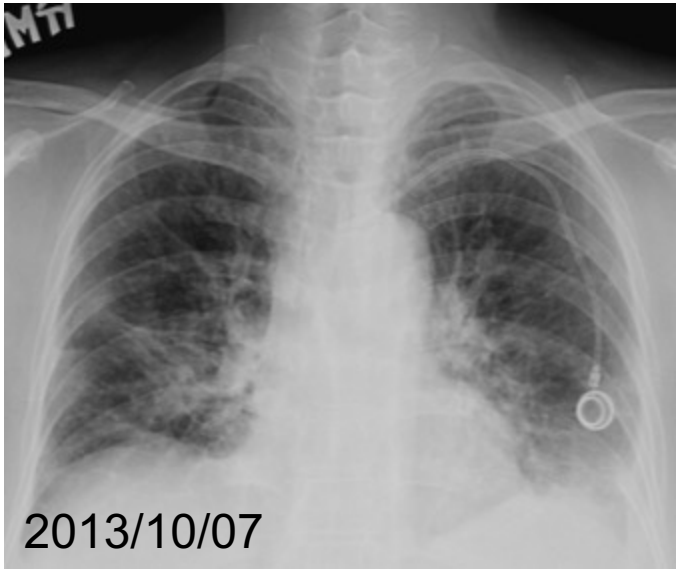


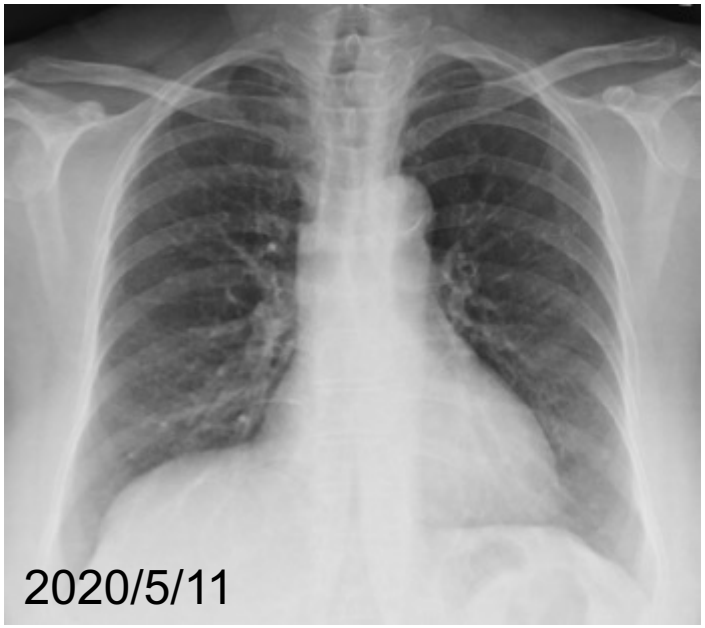
2013/10/2

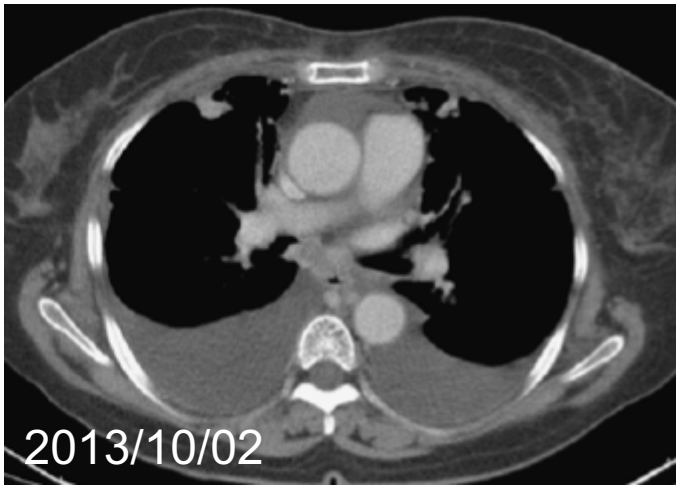


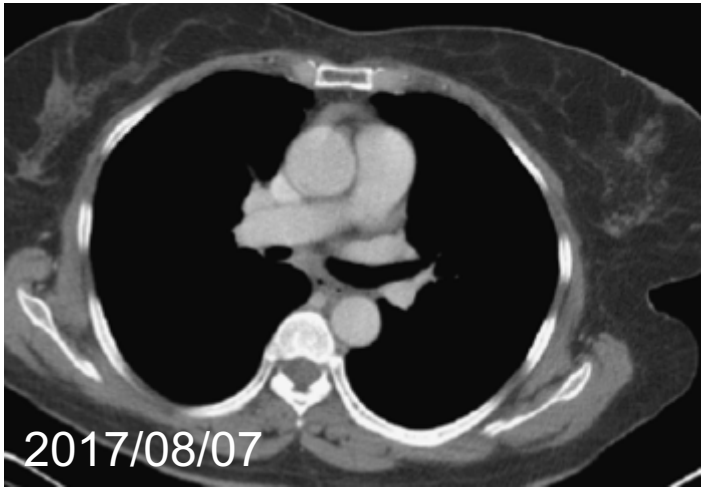
ALK FISH: Positive ALK

Previous neck LN





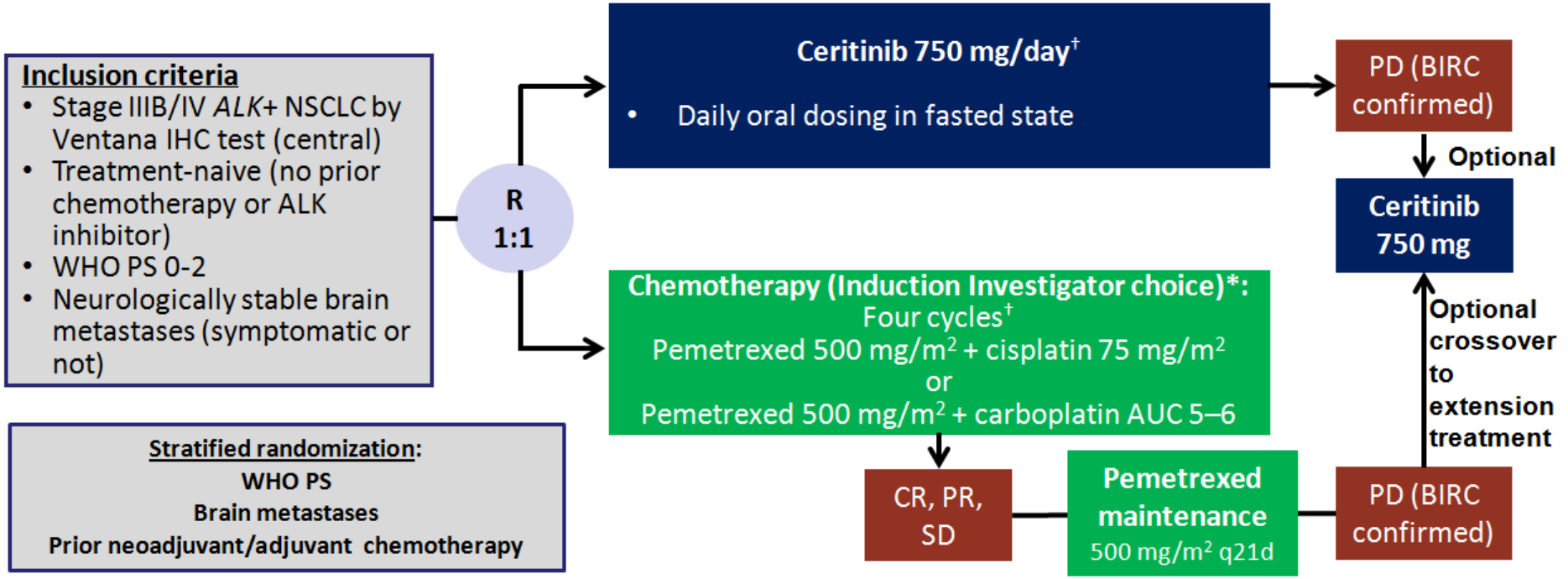




ALK: strong positive (report date 103/8/28)

2nd-G ALKi (Ceritinib) therapy since 2013/10/07 (**PFS ~ 7 yrs**)

Ceritinib: ASCEND-4 study

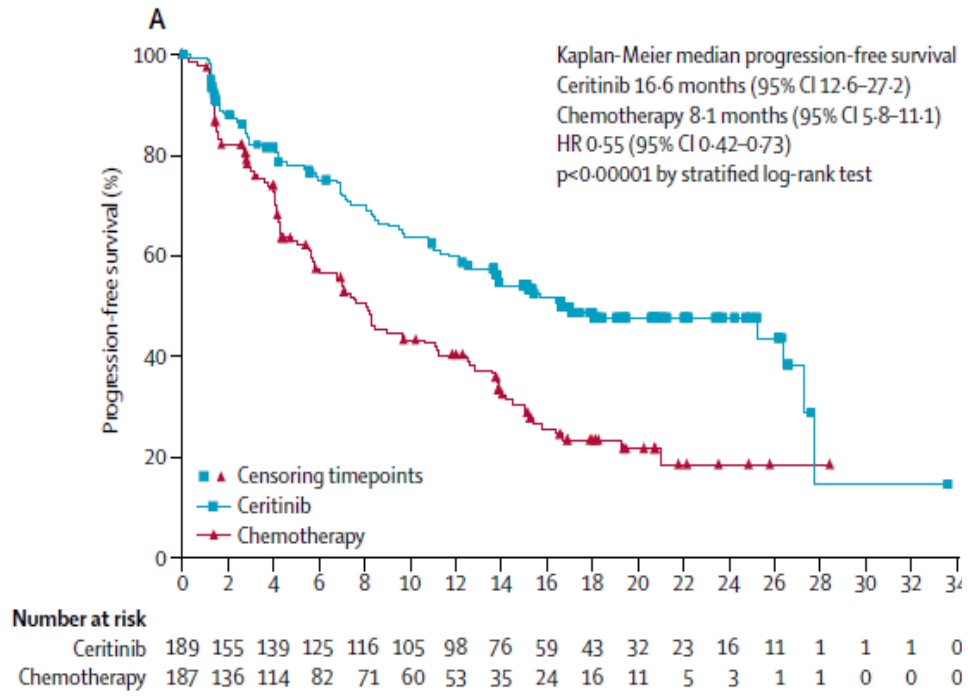


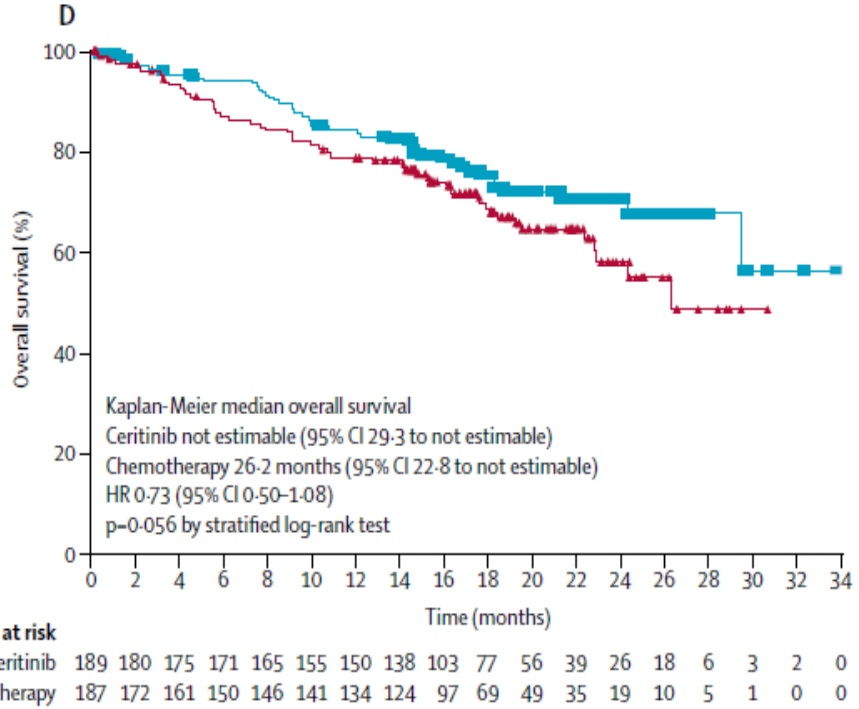
***At the time when ASCEND-4 was designed and initiated, pemetrexed-platinum chemotherapy followed by pemetrexed maintenance was the standard of care in patients with non-squamous advanced NSCLC**

†One cycle = 21 days

BIRC, Blinded Independent Review Committee; CR, complete response; IHC, immunohistochemistry; PD, progressive disease; PR; partial response; PS, performance status; SD, stable disease; WHO, World Health Organization;

Efficacy of Ceritinib in 1st-line





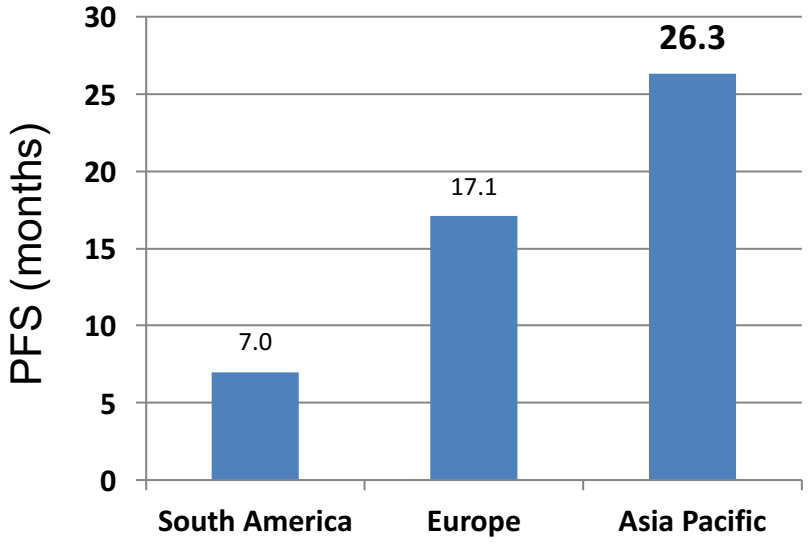
ORR: 72.5% vs. 26.7%
Time to response: 6.1 vs. 13.4 weeks
Duration of response: 23.9 vs. 11. 1 months

***Data by BIRC (blinded independent review committee)**

Lancet 2017;389: 917-29.

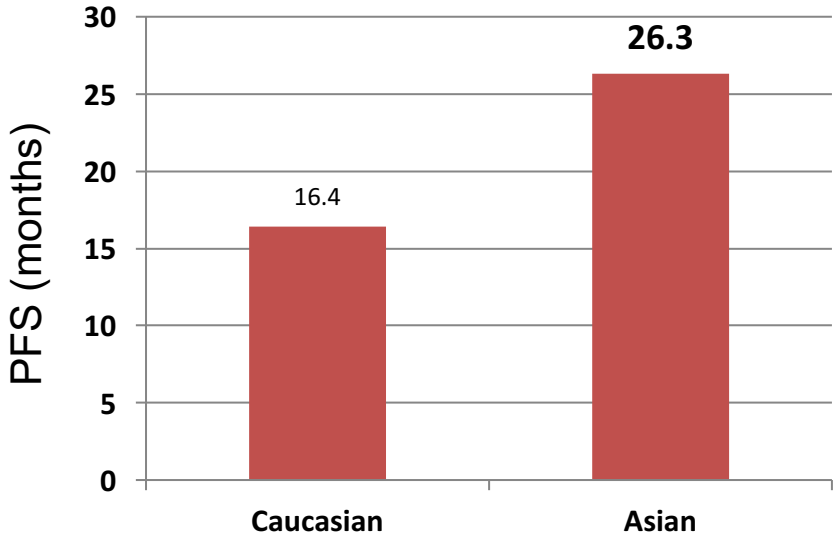
Ceritinib works better among Asians ?

Geographic region



	South America	Europe	Asia Pacific
HR	0.65 (0.17-2.54)	0.54 (0.37-0.80)	0.60 (0.38-0.96)

Race



	Caucasian	Asian
	0.44 (0.30-0.66)	0.66 (0.41-1.06)

Lancet 2017;389: 917-29.

Ceritinib in 1st-line: AE

	Ceritinib (n=189)		Chemotherapy (n=175)	
	All grades	Grade 3 or 4	All grades	Grade 3 or 4
Any adverse event	189 (100%)	148 (78%)	170 (97%)	108 (62%)
Diarrhoea	160 (85%)	10 (5%)	19 (11%)	2 (1%)
Nausea	130 (69%)	5 (3%)	97 (55%)	9 (5%)
Vomiting	125 (66%)	10 (5%)	63 (36%)	10 (6%)
Alanine aminotransferase increased	114 (60%)	58 (31%)	38 (22%)	5 (3%)
Aspartate aminotransferase increased	100 (53%)	32 (17%)	34 (19%)	3 (2%)
Gamma-glutamyltransferase increased	70 (37%)	54 (29%)	18 (10%)	3 (2%)
Decreased appetite	64 (34%)	2 (1%)	55 (31%)	2 (1%)
Blood alkaline phosphatase increased	55 (29%)	14 (7%)	8 (5%)	1 (1%)
Fatigue	55 (29%)	8 (4%)	52 (30%)	5 (3%)
Abdominal pain	47 (25%)	4 (2%)	13 (7%)	0
Cough	46 (24%)	0	28 (16%)	0
Weight decreased	45 (24%)	7 (4%)	26 (15%)	1 (1%)
Blood creatinine increased	42 (22%)	4 (2%)	17 (10%)	0
Upper abdominal pain	39 (21%)	3 (2%)	10 (6%)	0
Non-cardiac chest pain	38 (20%)	2 (1%)	17 (10%)	1 (1%)
Back pain	36 (19%)	3 (2%)	32 (18%)	4 (2%)
Constipation	36 (19%)	0	38 (22%)	0
Pyrexia	34 (18%)	0	24 (14%)	2 (1%)
Asthenia	33 (17·5)	5 (3%)	36 (21%)	6 (3%)
Headache	31 (16%)	0	21 (12%)	2 (1%)
Dyspnoea	29 (15%)	4 (2%)	35 (20%)	11 (6%)
Anaemia	28 (15%)	4 (2%)	62 (35%)	13 (7%)
Neutropenia	9 (5%)	1 (1%)	38 (22%)	19 (11%)
White blood cell count decreased	7 (4%)	0	31 (18%)	7 (4%)

Most common AE:
- Ceritinib: **diarrhea, N/V, LFT↑**
- C/T: N/V, anemia

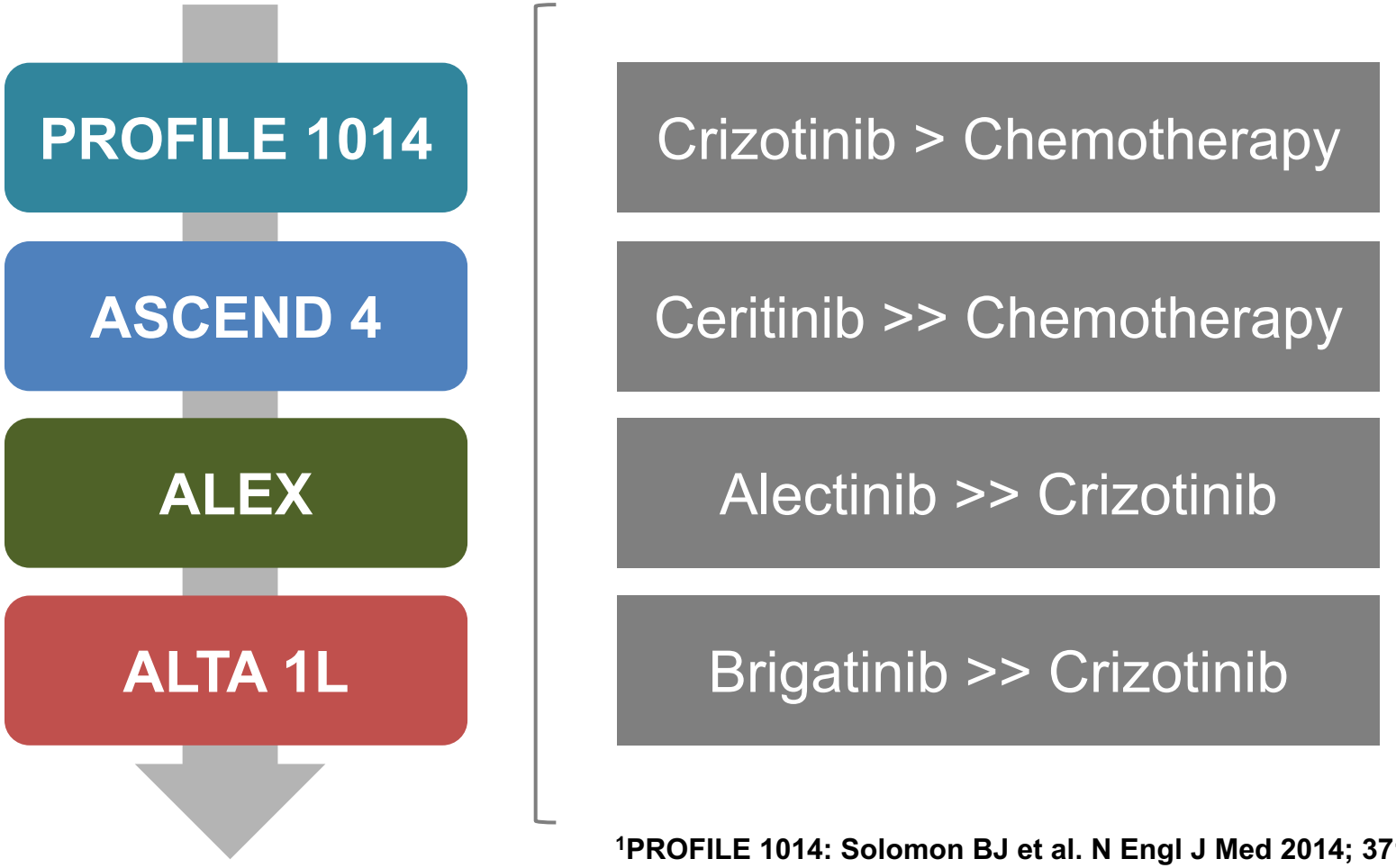
Discontinuation due to study drug related AE:
- Ceritinib: **5.3%**
- C/T: 11.4%

AE-related dose adjustment
- Ceritinib: **80%**
- C/T: 45%

"ASCEND-8":
- Similar PK between low fat diet and fasting, but GI AEs↓

Soria J-C et al. Lancet 2017;389: 917-29.
Gilberto de Castro Jr et al. WCLC 2016.

Phase III Clinical Trials



[1]PROFILE 1014: Solomon BJ et al. N Engl J Med 2014; 371:2167-77.
[2]ASCEND-4: Soria JC et al. Lancet Oncol 2017; 389:917-29.
[3]ALEX: Peters S et al. N Engl J Med 2017; 377:829-38.
[4]ALTA 1L: Camidge DR et al. WCLC 2018.

ALKi(s) as the 1st line Tx. for *ALK*+ NSCLC

Patient characteristics

Study	ALKi	Asians (%)	Smoker (%)	ADC (%)	CNS (+) (%)	PS = 2 (%)	1⁰ endpoint
PROFILE 1014[1]	Crizotinib	45	38	94	26	6	IRC PFS
ASCEND-4[2]	Ceritinib	40	43	95	31	7	IRC PFS
ASCEND-8[3#]	Ceritinib[#]	40	36	99	33	8	PK (plasma)
ALEX[4]	Alectinib	46	35	94	38	7	**INV PFS**
ALTA 1L[5]	Brigatinib	43	39	92	29	4	IRC PFS

ADC, adenocarcinoma; PS, ECOG performance status.
All were phase III RCT, except ASCEND-8 study.
[*]Patient No. of target ALKi.
[#]Ceritinib 450mg fed (efficacy analysis set): **57.5%** ongoing without event/death
NSCLC, non-small cell lung cancer; NR, not reached.
IRC: independent review committee; INV: investigator assessed.

[1]PROFILE 1014: Solomon BJ et al. N Engl J Med 2014; 371:2167-77.
[2]ASCEND-4: Soria JC et al. Lancet Oncol 2017; 389:917-29.
[3]ASCEND-8: Cho BC et al. ESMO 2018 (LBA59).
[4]ALEX: Peters S et al. N Engl J Med 2017; 377:829-38.
[5]ALTA 1L: Camidge DR et al. WCLC 2018 & ESMO 2019.

ALKi(s) as the 1st line Tx. for *ALK*+ NSCLC

Overall efficacy

Study	No.*	ALKi	Comparator	ORR (%)	PFS (m)&	DOR (m)	OS (m)
PROFILE 1014[1]	172	Crizotinib	Platinum-CT	74%	10.9 (8.3-13.9)	11.3 (8.1-13.8)	NR
ASCEND-4[2]	189	**Ceritinib**	Platinum-CT	73%	16.6 (12.6-27.2)	23.9 (16.6-NR)	NR
ASCEND-8[3]	73	**Ceritinib#**	Ceritinib	78%	NR (11.8-NR)	NR (11.2-NR)	NR
ALEX[4]	152	**Alectinib**	Crizotinib	83%	25.7 (19.9-NR)	NR	NR
ALTA 1L[5]	137	**Brigatinib**	Crizotinib	71%	24.0 (18.5-NR)	NR	NR

All were phase III RCT, except ASCEND-8 study.
*Patient No. of target ALKi.
#Ceritinib 450mg fed (efficacy analysis set): **57.5%** ongoing without event/death
&**BIRC evaluated**.
NSCLC, non-small cell lung cancer; NR, not reached.

[1]PROFILE 1014: Solomon BJ et al. N Engl J Med 2014; 371:2167-77.
[2]ASCEND-4: Soria JC et al. Lancet Oncol 2017; 389:917-29.
[3]ASCEND-8: Cho BC et al. ESMO 2018 (LBA59).
[4]ALEX: Peters S et al. N Engl J Med 2017; 377:829-38.
[5]ALTA 1L: Camidge DR et al. WCLC 2018 & ESMO 2019.

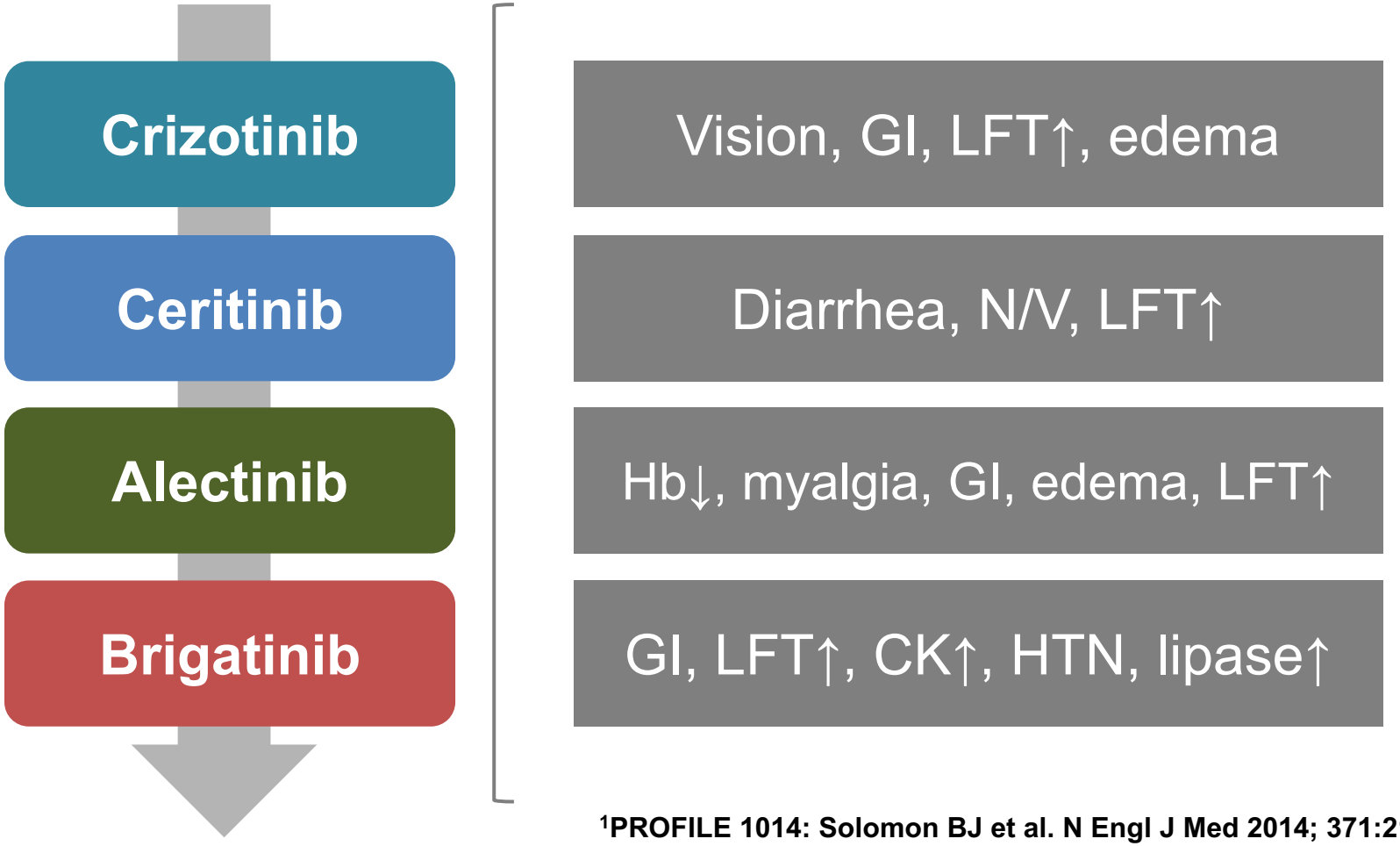
AE-related outcomes

	Crizotinib[1]	Ceritinib[2]		Alectinib[1]	Brigatinib[3]
	250mg bid	750mg fasted	450mg fed	600mg bid	90→180mg qd
Gr. 3 or more AEs	50%	62%	65%	41%	61%
Dose interruption	25%	70%	45%	19%	-
Dose reduction	21%	40%	18%	16%	29%
Discontinuation	13%	7%	**7%**	11%	12%

[1]**ALEX study (phase III), Shaw A et al. ASCO 2017.**
[2]**ASCEND-8: Cho BC et al. ESMO 2018 (LBA59).**
[3]**ALTA-1L (phase III), Camidge DR et al. N Engl J Med 2018.**

Most common AEs of ALKi(s)

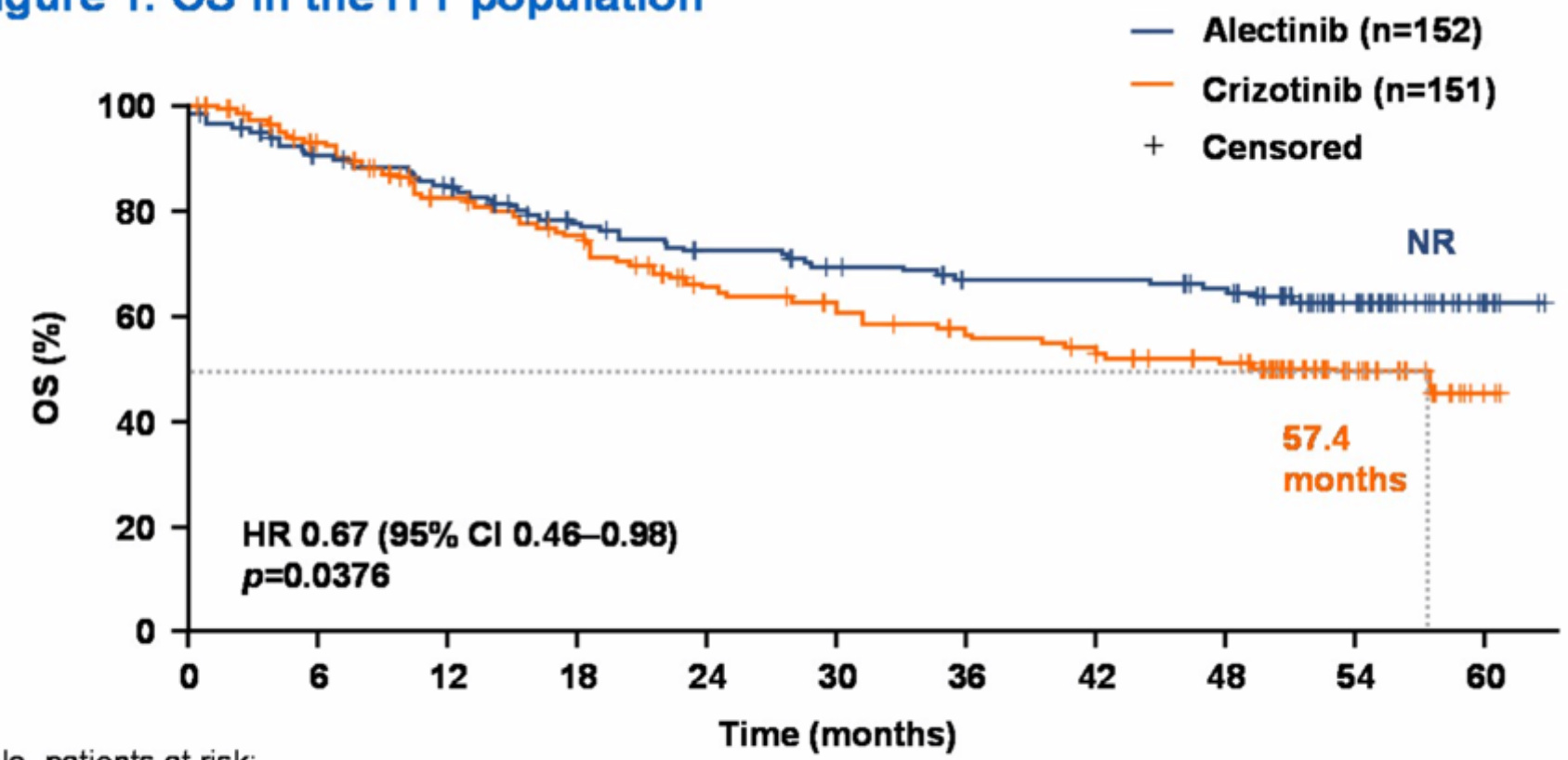
The AEs were different between ALKi(s)



[1]PROFILE 1014: Solomon BJ et al. N Engl J Med 2014; 371:2167-77.
[2]ASCEND-4: Soria JC et al. Lancet Oncol 2017; 389:917-29.
[3]ALEX: Peters S et al. N Engl J Med 2017; 377:829-38.
[4]ALTA 1L: Camidge DR et al. WCLC 2018.

ALEX: updated OS data

Figure 1. OS in the ITT population



No. patients at risk:

Alectinib	152	142	131	127	120	111	103	98	94	94	88	87	81	81	81	80	77	62	46	23	8
Crizotinib	151	141	128	116	104	100	93	84	73	71	67	63	60	59	55	51	48	35	18	12	3

5-year OS rate: 62.5% vs. 45.5%

Peters S et al. ASCO 2020 #9518.

Undoubtedly, the standard front line therapy is *ALK* inhibitor(s)

NCCN GUIDELINES

Preferred
Alectinib[pp] (category 1)
Other Recommended
Brigatinib[pp] (category 1)
or
Ceritinib[pp] (category 1)
Useful in Certain Circumstances
Crizotinib[pp] (category 1)

ESMO
GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

European Society for Medical Oncology

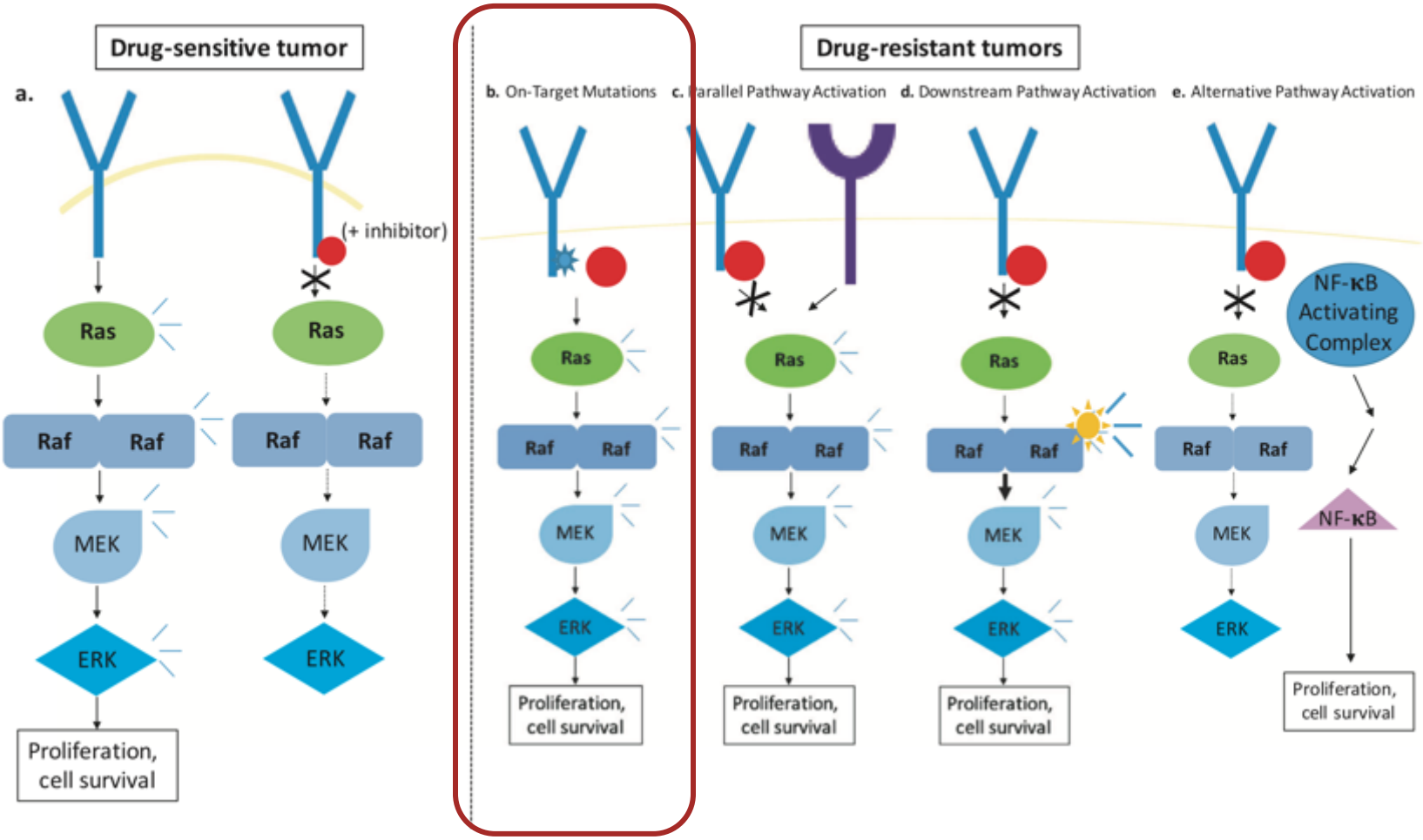
In patients with CNS involvement, front-line use of ALK TKIs is effective, and alectinib [III, A] or ceritinib [IV, B] are recommended, ….

Second line treatment

1. Crizotinib → 2nd-line choice ?
2. 2nd-G ALKi → 2nd-line choice ?

Acquired resistance inevitably occurs

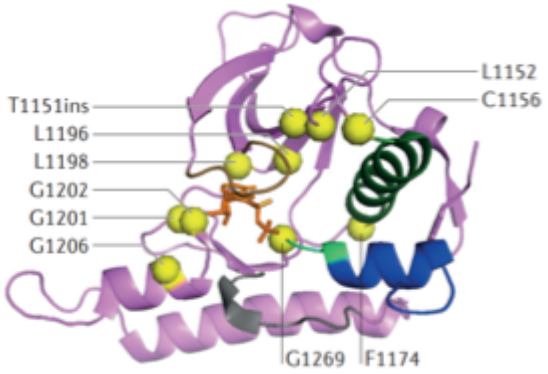
on- and off-target



Dana S. Neel et al. npj Precision Oncology; 2017.

Secondary *ALK* mut(s) mediate ALKi resistance

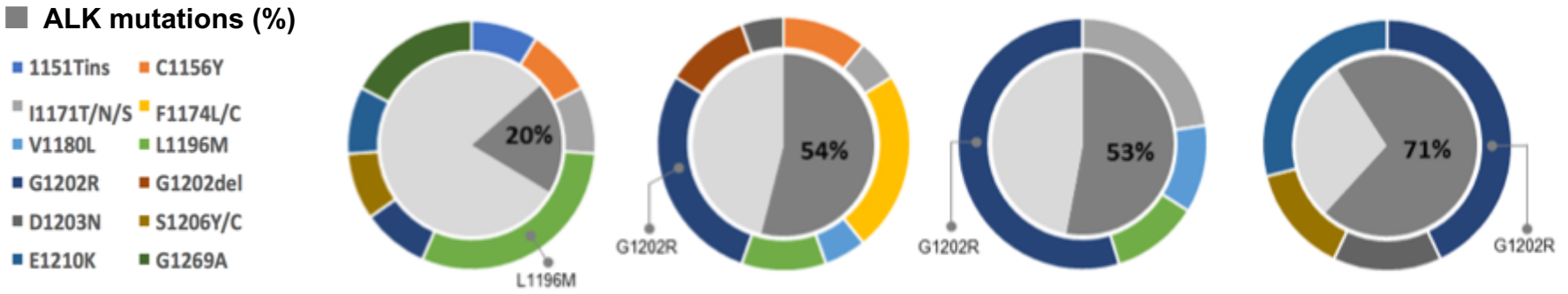
Cellular ALK Phosphorylation Mean IC_{50} (nM)					
Mutation status	**Crizotinib**	**Ceritinib**	**Alectinib**	**Brigatinib**	**Lorlatinib**
Parental Ba/F3	763.9	885.7	890.1	2774.0	11293.8
EML4-ALK v1	38.6	4.9	11.4	10.7	2.3
C1156Y	61.9	5.3	11.6	4.5	4.6
I1171N	130.1	8.2	397.7	26.1	49.0
I1171S	94.1	3.8	117.0	17.8	30.4
I1171T	51.4	1.7	33.6	6.1	11.5
F1174C	115.0	38.0	27.0	18.0	8.0
L1196M	339.0	9.3	117.6	26.5	34.0
L1198F	0.4	196.2	42.3	13.9	14.8
G1202R	381.6	124.4	706.6	129.5	49.9
G1202del	58.4	50.1	58.8	95.8	5.2
D1203N	116.3	35.3	27.9	34.6	11.1
E1210K	42.8	5.8	31.6	24.0	1.7
G1269A	117.0	0.4	25.0	ND	10.0



- IC_{50} ≤ 50nm
- IC_{50} >50 ~ <200nm
- IC_{50} ≥ 200nm

Gainor JF et al. Cancer Discov 2016; 6:1118-33.
Johnson TW et al. J Med Chem 2014; 57:4720-44.
Hallberg B et al. Nat Rev Cancer 2013; 13:685-700.

Resistance of 2nd-G ALK TKI

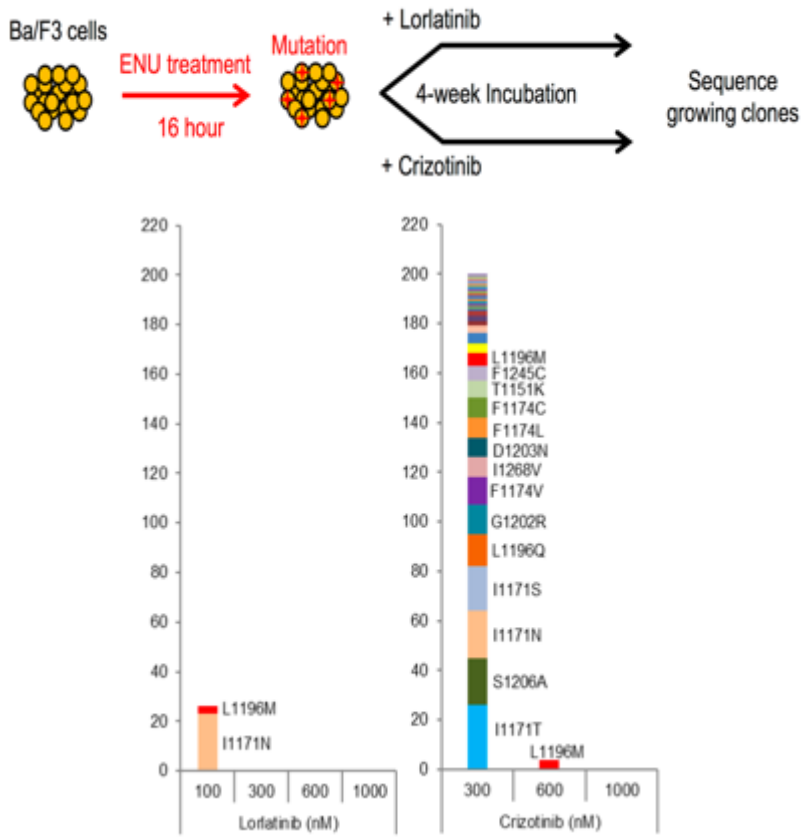


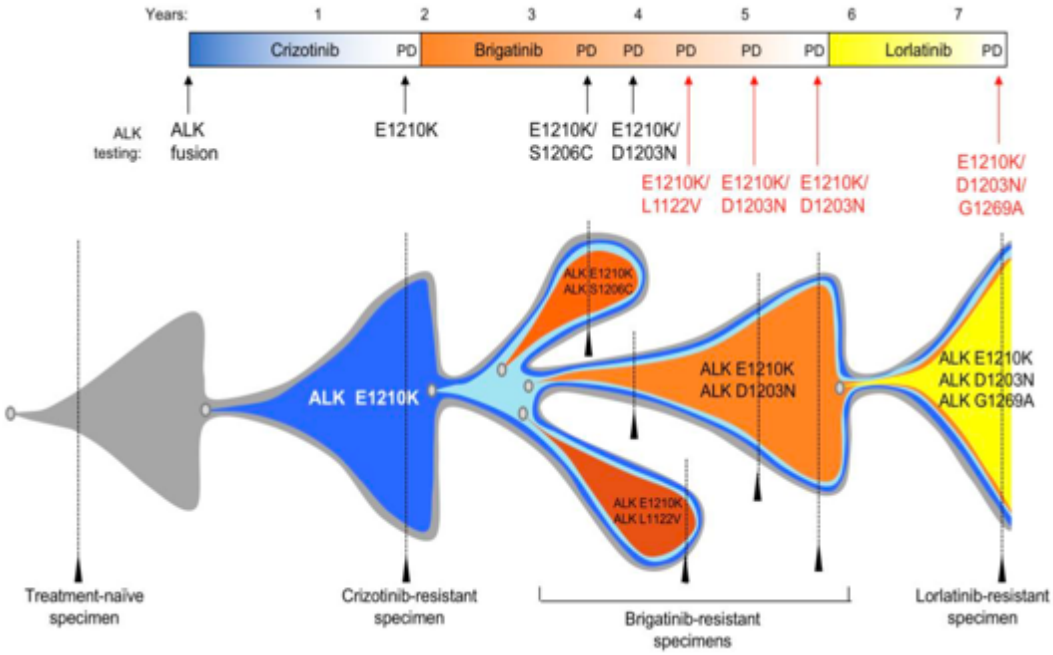
Prior ALKi, n (%)	Crizotinib (n=51*)	Ceritinib (n=23*)	Alectinib (n = 17)	Brigatinib (n = 6*)
Crizotinib	51 (100)	**21 (91)**	**17 (100)**	**5 (83)**
Ceritinib	1 (2)	23 (100)	3 (18)	-
Alectinib	-	3 (13)	17 (100)	-
Brigatinib	-	-	-	6 (100)

*4 of crizotinib, 1 of ceritinib and 1 of brigatinib with 2 separate biopsies.

Gainor JF et al. Cancer Discov 2016; 6:1118-32.

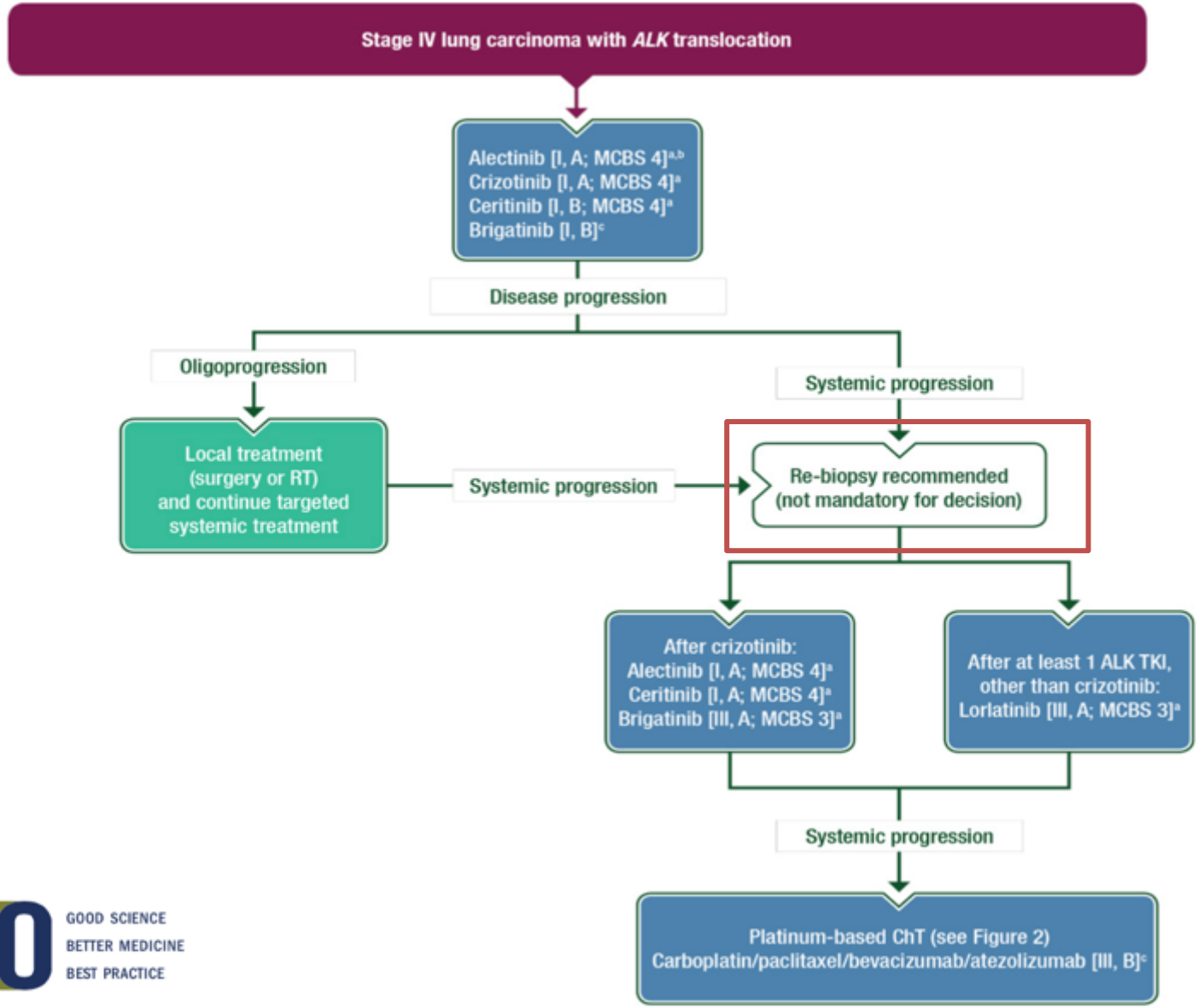
Sequential ALKi can select for lorlatinib-resistant compound ALK mutations





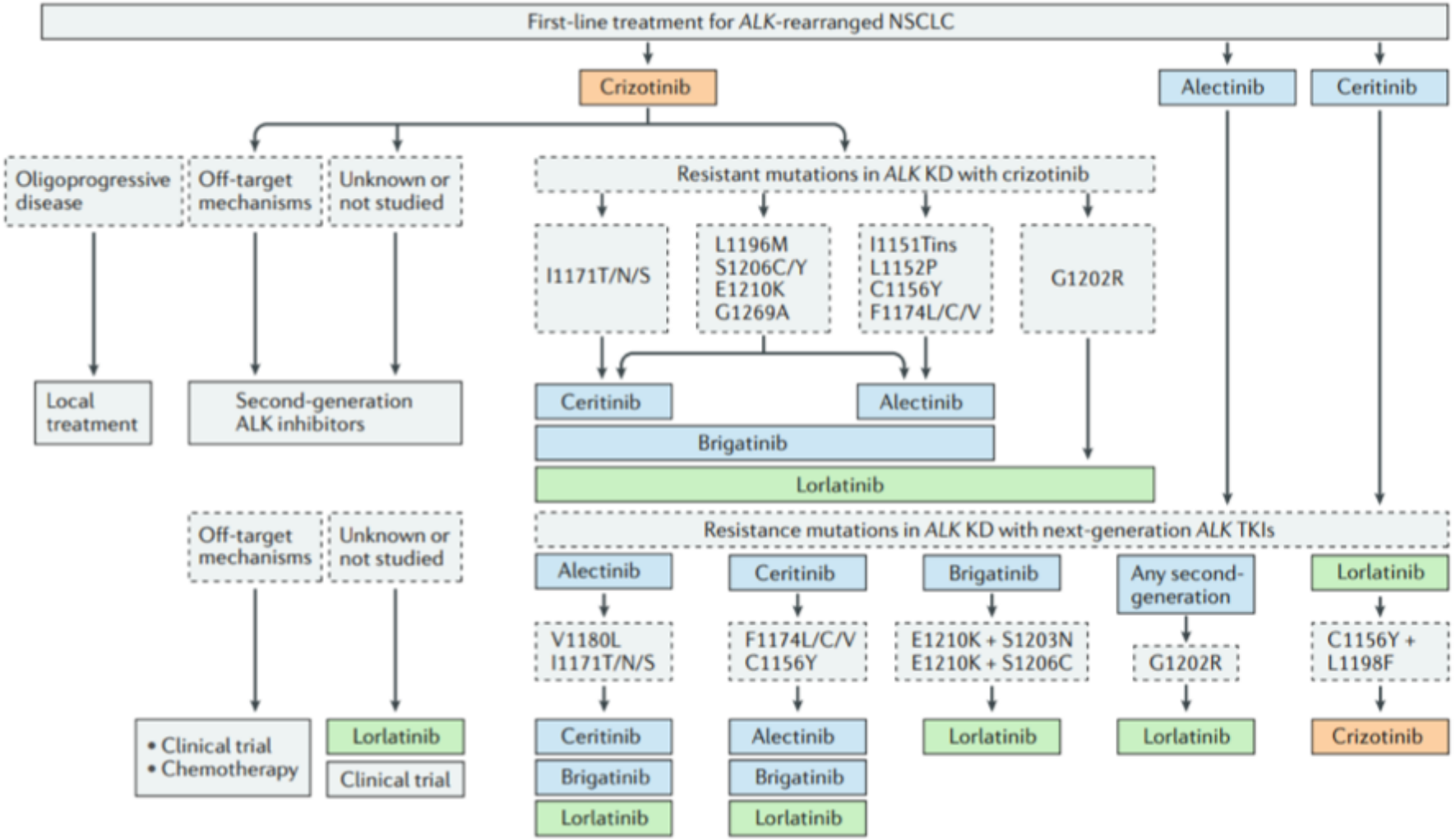
Yoda S et al. Cancer Discov 2018.

ESMO guideline: mNSCLC



ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Biomarker integration in patient management



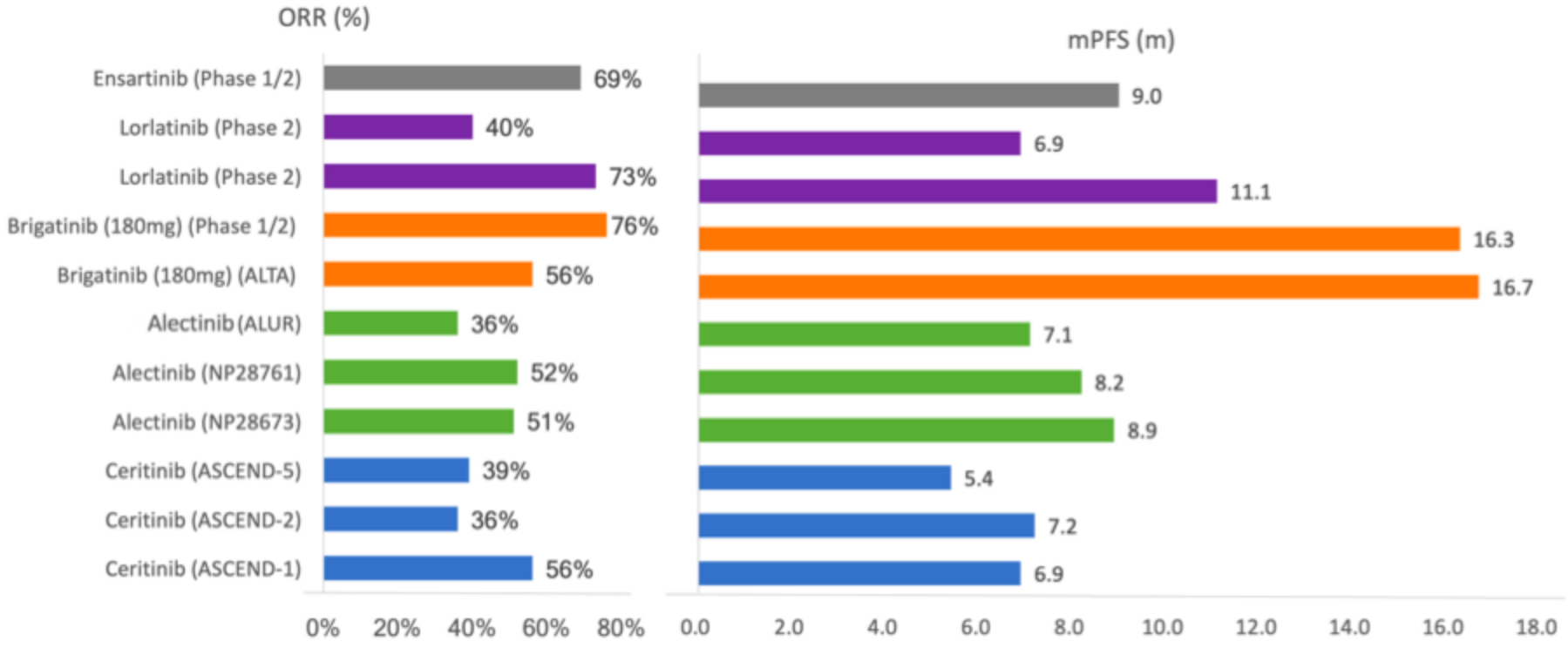
Recondo G et al. Nat Rev Clin Oncol 2018; 15:694-708.

Second line treatment

1. **Crizotinib → 2nd-line choice ?**
2. 2nd-G ALKi → 2nd-line choice ?

ALKi(s) systemic efficacy post-crizotinib

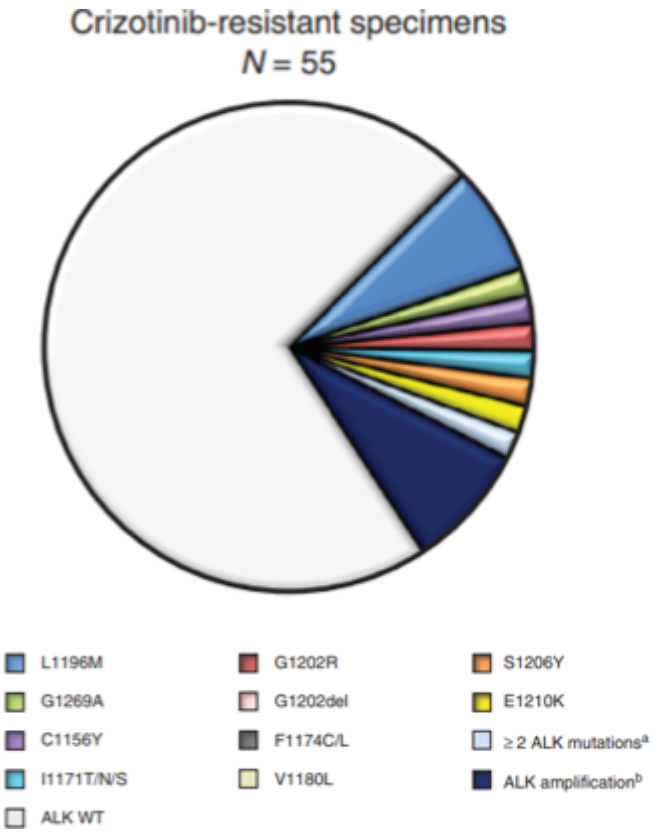
PFS remarkably consistent across trials from same drug but differs by drug, despite similar ORR.
Differ in control of CNS? Differ in suppression of acquired resistance not dominant at baseline? Including non-ALK mechanisms?

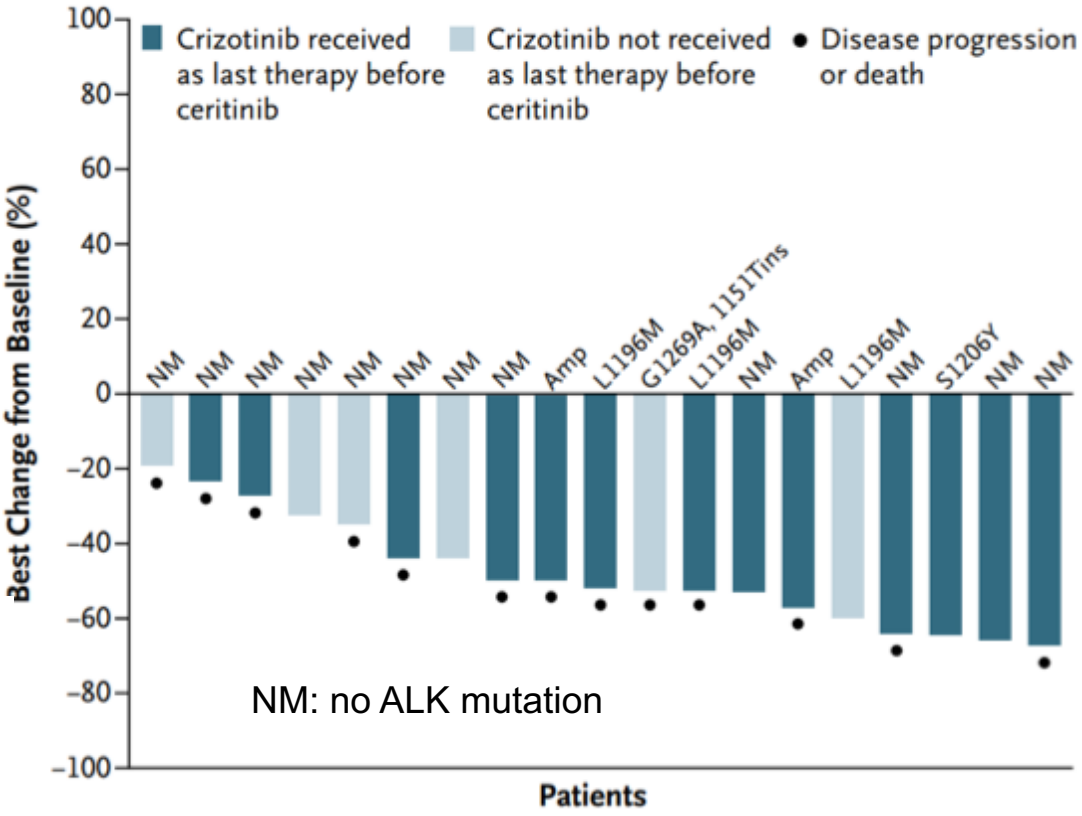


Hom L et al. Clin Cancer Res 2018; 24:2771-9; Besse B et al. J Clin Oncol 2018; 36(15 suppl; abstr 9032); Huber RM et al. J Clin Oncol 2018; 36(15suppl; abstr 9061); Bazhenova L. et al. Ann Oncol 2017; 28 (suppl_5):v460-96; Baresi F et al. Ann Oncol 2016; 27(suppl 6 (suppl 6, abstr 1263P); Camidge DR et al. J Thorac Oncol 2017; 12:S378 (MA07.02); Novello S et al. Ann Oncol 2017; 28(suppl 5); abstr 12990_PR); Kim DW et al. Lancet Oncol 2016; 17:452-63; Crino L et al. J Clin Oncol 2016; 34:2866-73; Shaw AT et al. Lancet Oncol 2017; 7:874-86.

Post-crizotinib: Is rebiopsy needed?

Ceritinib Data





Only 20% with 2nd ALK-m

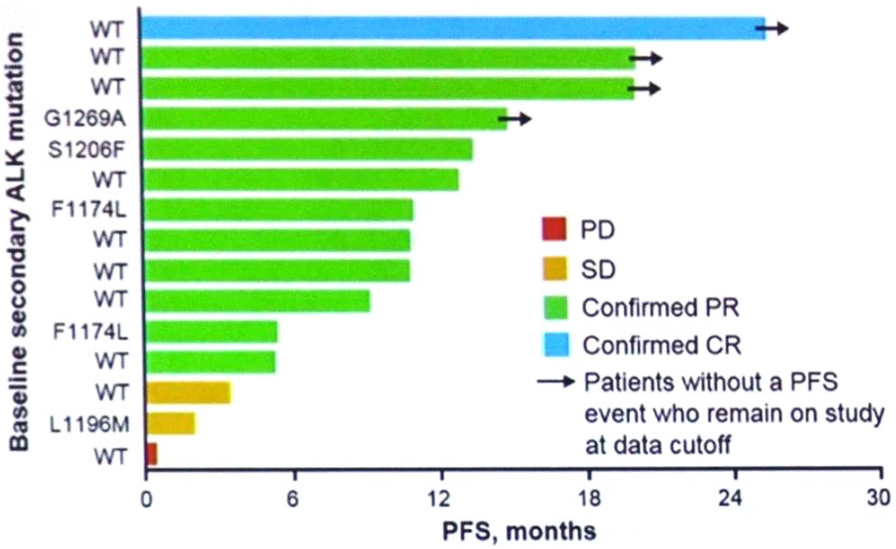
Gainor JF et al. Cancer Discov 2016; 6:1118-32.
Shaw AT et al. N Engl J Med 2014; 370:1189-97.

Post-crizotinib: Is rebiopsy needed?

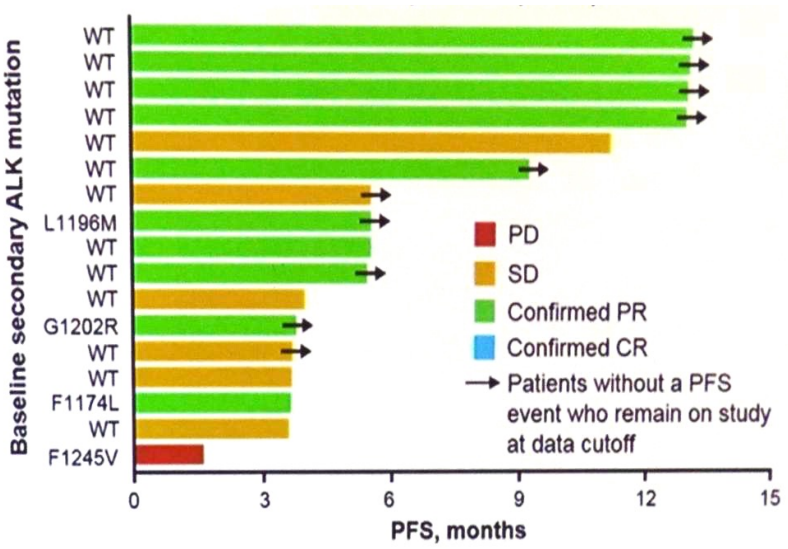
Brigatinib Data

Tumor response and PFS by baseline mutational status

Phase 1/2



Pivotal phase 2



78% (7/9) and **65%** (15/23) of patients **with** and **without** secondary ALK mutations, respectively, responded to the brigatinib treatment.

Gettinger SN et al. ASCO 2016; abstr. 9060.

Most Crizotinib-resistant tumors remain *ALK* dependent and response to more potent ALK-i(s)

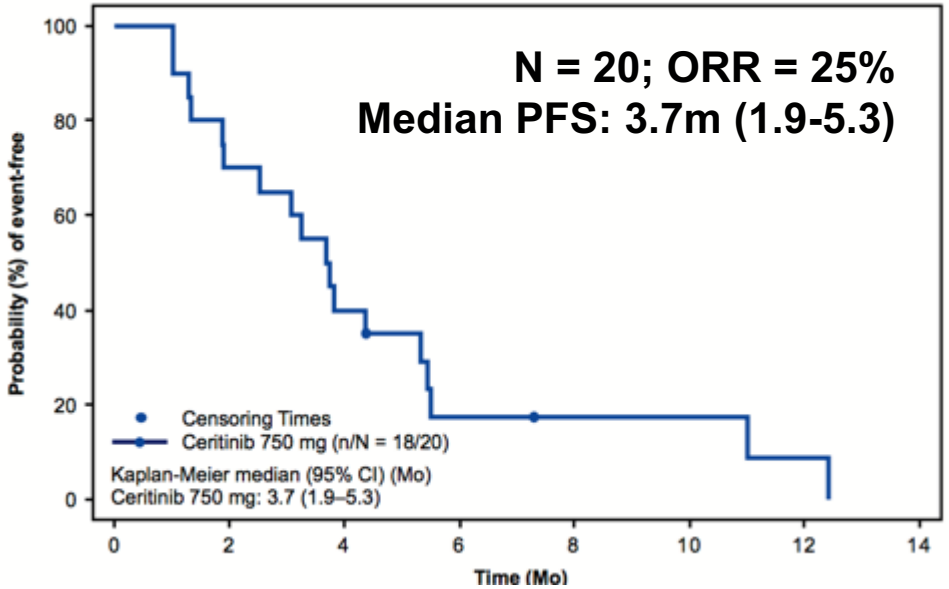
Rebiopsy after crizotinib: may **NOT** require (It could be an individualized decision)

Second line treatment

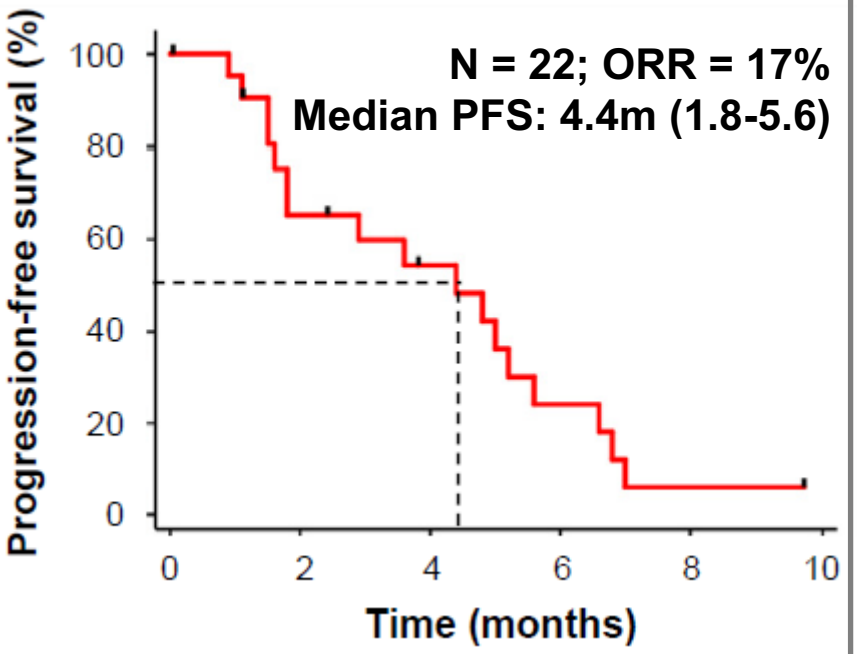
1. Crizotinib → 2nd-line choice ?
2. **2nd-G ALKi → 2nd-line choice ?**

Efficacy of 2nd-G ALKi → 2nd-G ALKi

ASCEND-9 (Phase-II, Japan)
Ceritinib after Alectinib



Retrospective multicenter
Brigatinib after Alectinib

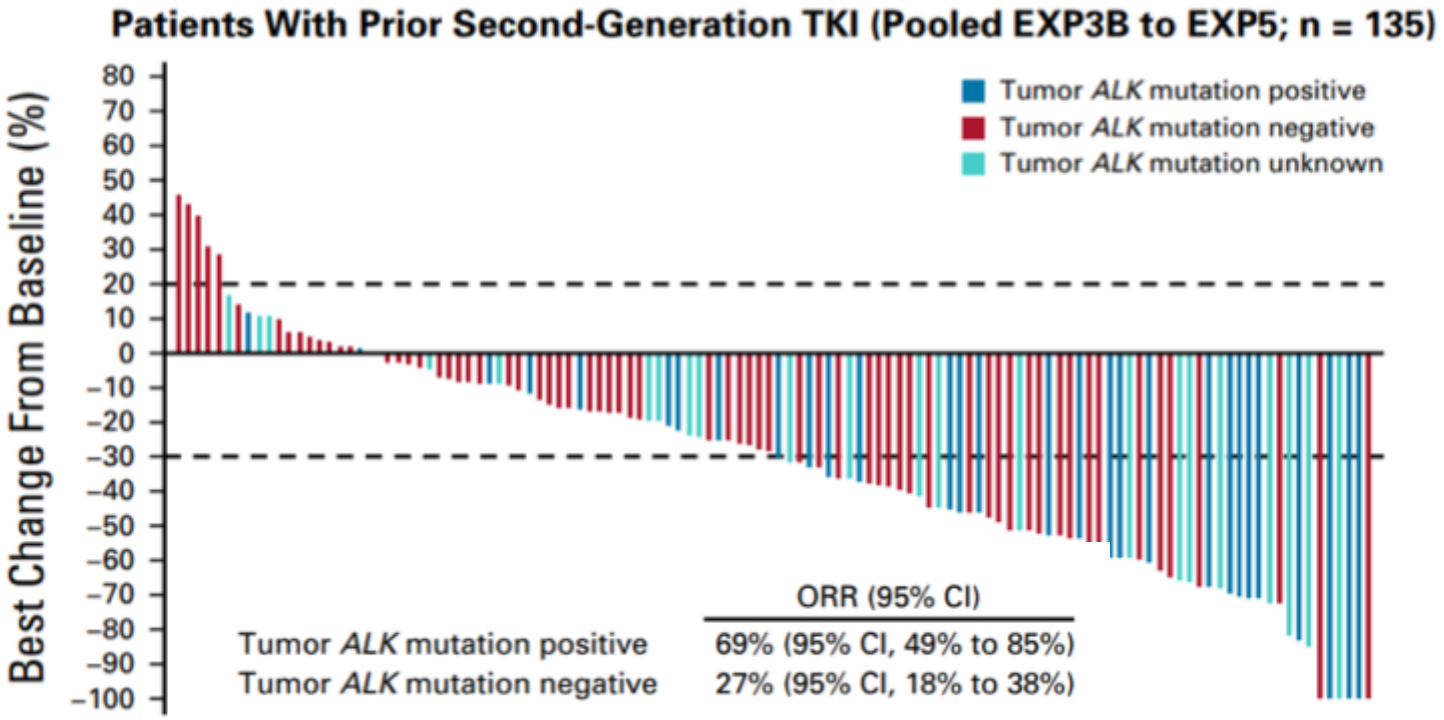


Hida T et al. Cancer Sci 2018; 109:2863-72; Lin JJ et al. J Throac Oncol 2018; 13:1530-8.

2nd-G ALKi → Lorlatinib (3rd-G)

Phase 1/2 study of lorlatinib: study design and patient populations
EXP3B: ORR 42%, PFS 5.5months (95% CI 2.9-9.0)
EXP5 : ORR 48%, PFS 6.9months (95% CI 5.4-9.5)

Role of rebiopsy ???

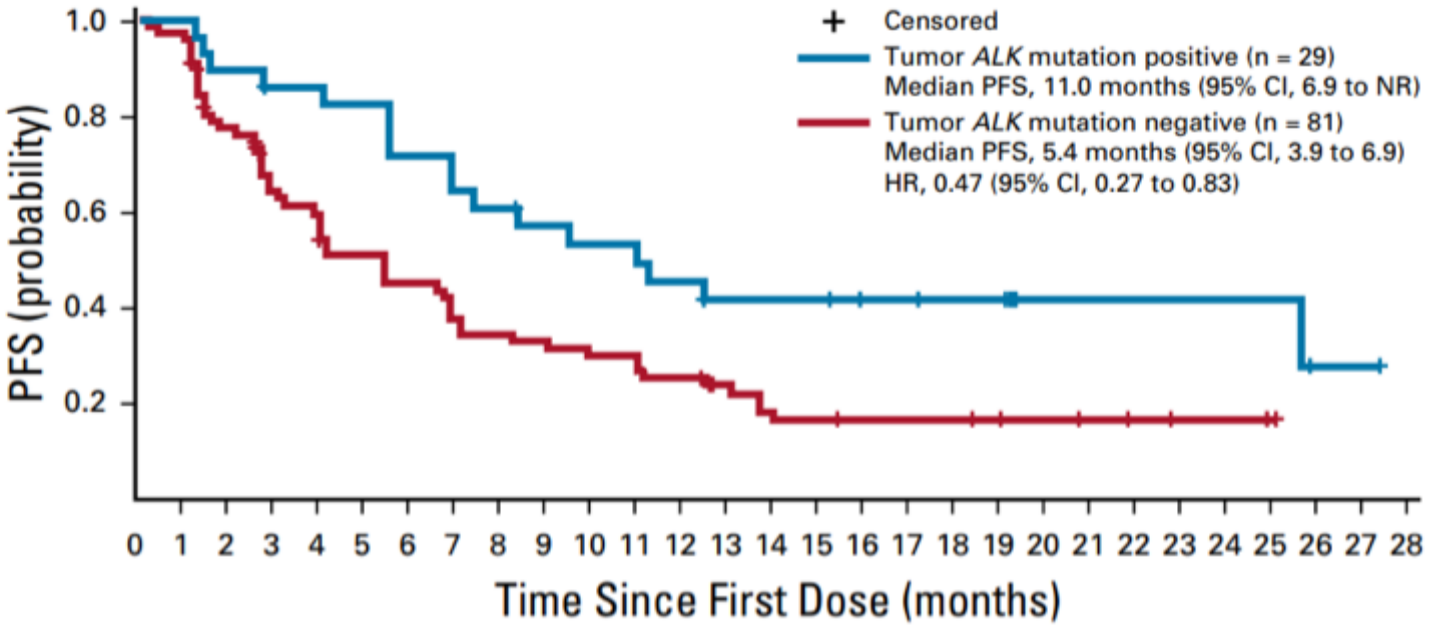


Shaw AT, AACR 2018 & J Clin Oncol 2019; 37:1370-9.

2nd-G ALKi → Lorlatinib (3rd-G)

Phase 1/2 study of lorlatinib: study design and patient populations

Biomarker Can Help

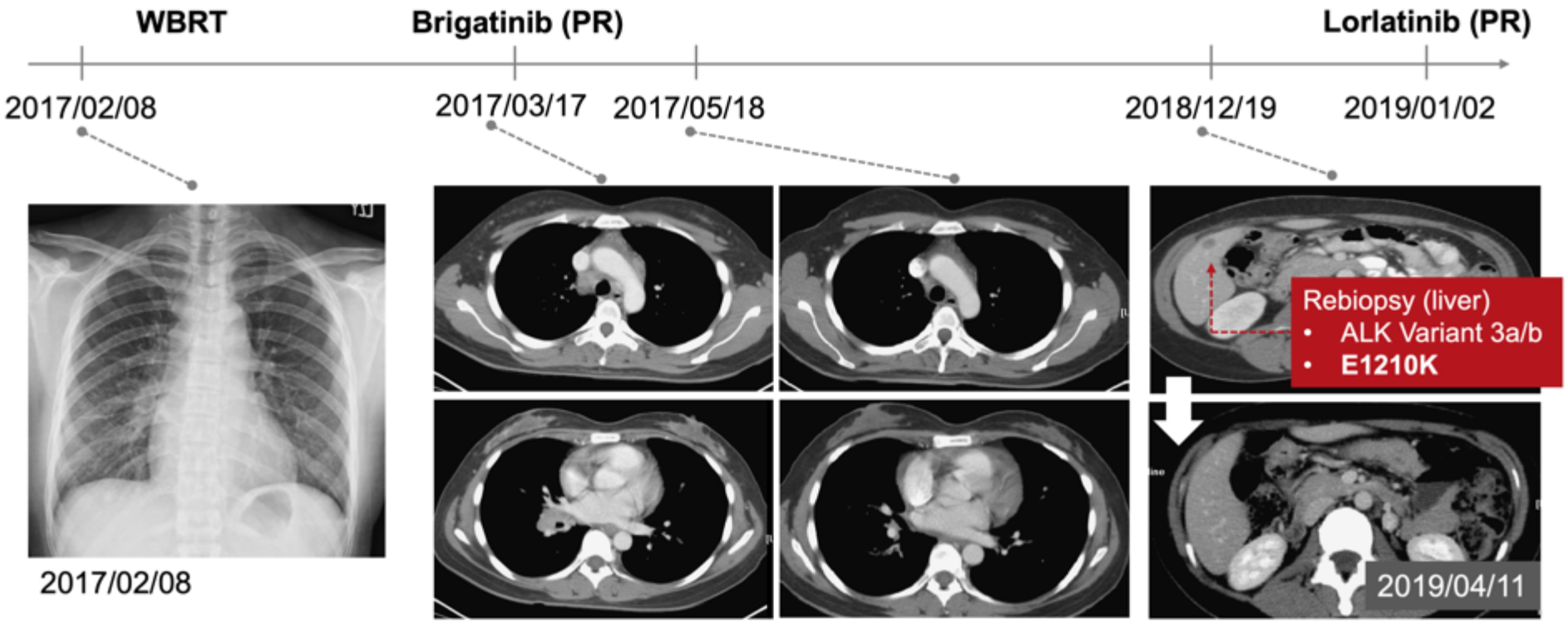


No. at risk																													
Tumor *ALK* mutation positive	29	29	26	24	24	23	20	18	17	15	14	14	12	10	10	10	8	8	7	7	3	3	3	3	3	3	1	1	0
Tumor *ALK* mutation negative	81	76	56	44	37	34	30	25	23	22	20	20	17	13	9	9	8	8	8	7	6	4	3	2	2	1	0	0	0

Shaw AT et al. J Clin Oncol 2019; 37:1370-9.

Ms. Gee, never smoker, cough and bilateral neck LAPs
Lung cancer, RLL, adenocarcinoma, cT3N3M1c, stage IVB with lung, bone, brain, and liver metastasis, ECOG PS=1

EGFR: unfound; ***ALK*: strong positive (by IHC)**

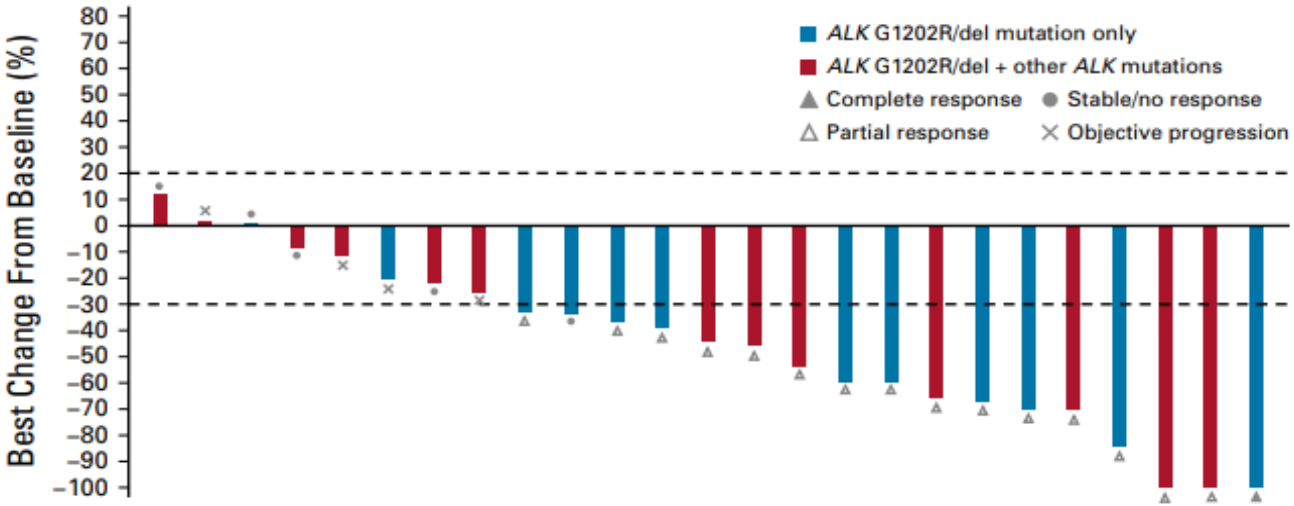


Rebiopsy can guide the treatment

A

ALK Mutation	No.	ORR (95% CI), %	Median DOR, Months (95% CI)	Median PFS, Months (95% CI)
G1202R/del	28	57 (37 to 76)	7 (6.1 to 24.4)	8.2 (5.6 to 25.6)
F1174X	12	42 (15 to 72)	NR (5.7 to NR)	7.4 (2.8 to NR)
L1196M	12	67 (35 to 90)	NR (5.2 to NR)	NR (2.8 to NR)
G1269A	9	89 (52 to 100)	NR (5.6 to NR)	NR (8.2 to NR)
I1171X	8	75 (35 to 97)	4.2 (2.8 to 4.2)	5.5 (4.1 to 6.9)

B



EXP2-5; Tissue or Plasma.

Shaw AT et al. J Clin Oncol 2019; 37:1370-9.

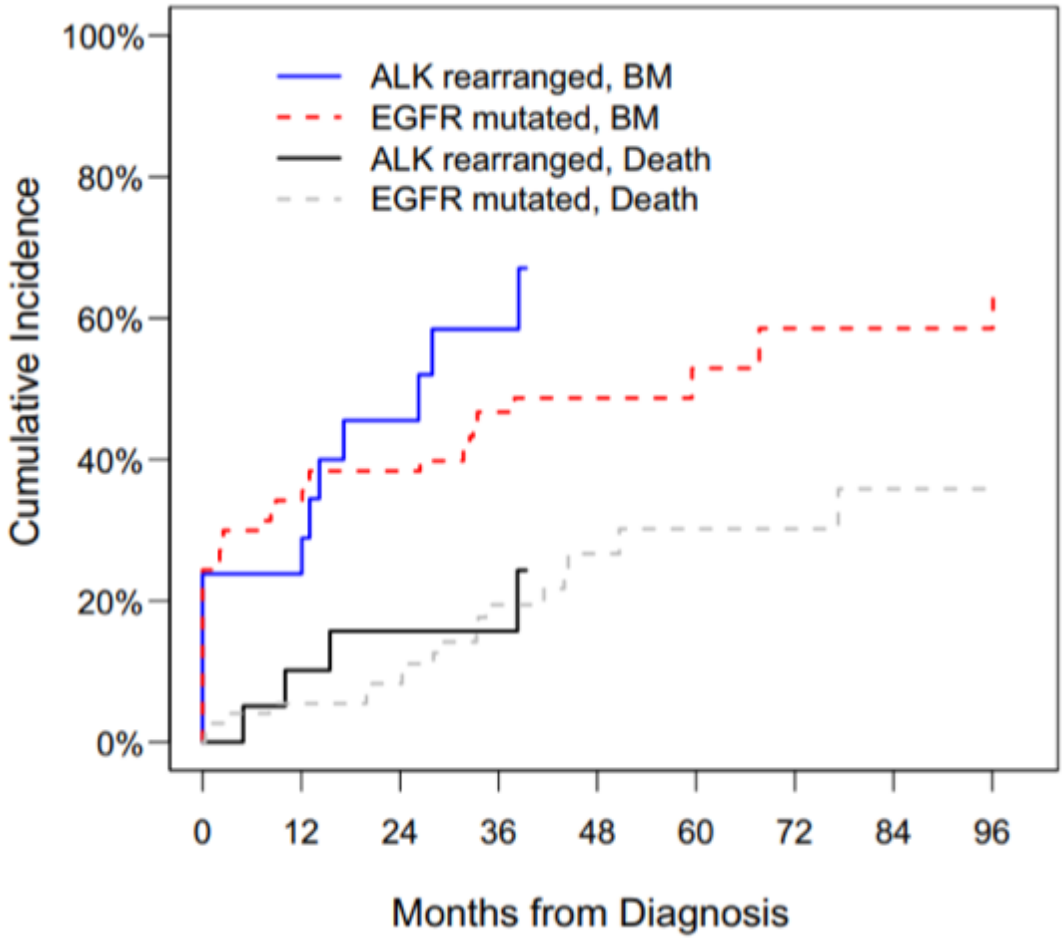
After progression to 2nd-G ALKi, the efficacy of lorlatinib is better than another 2nd-G ALKi

Mutation status in rebiopsy can be used to differentiate the outcome of subsequent lorlatinib therapy

(**Not** mandatory for NHI reimbursement)

Brain metastasis in *ALK*-Pt

Cumulative risk of BM in *ALK*(+) NSCLC



58.4% at 3rd Year

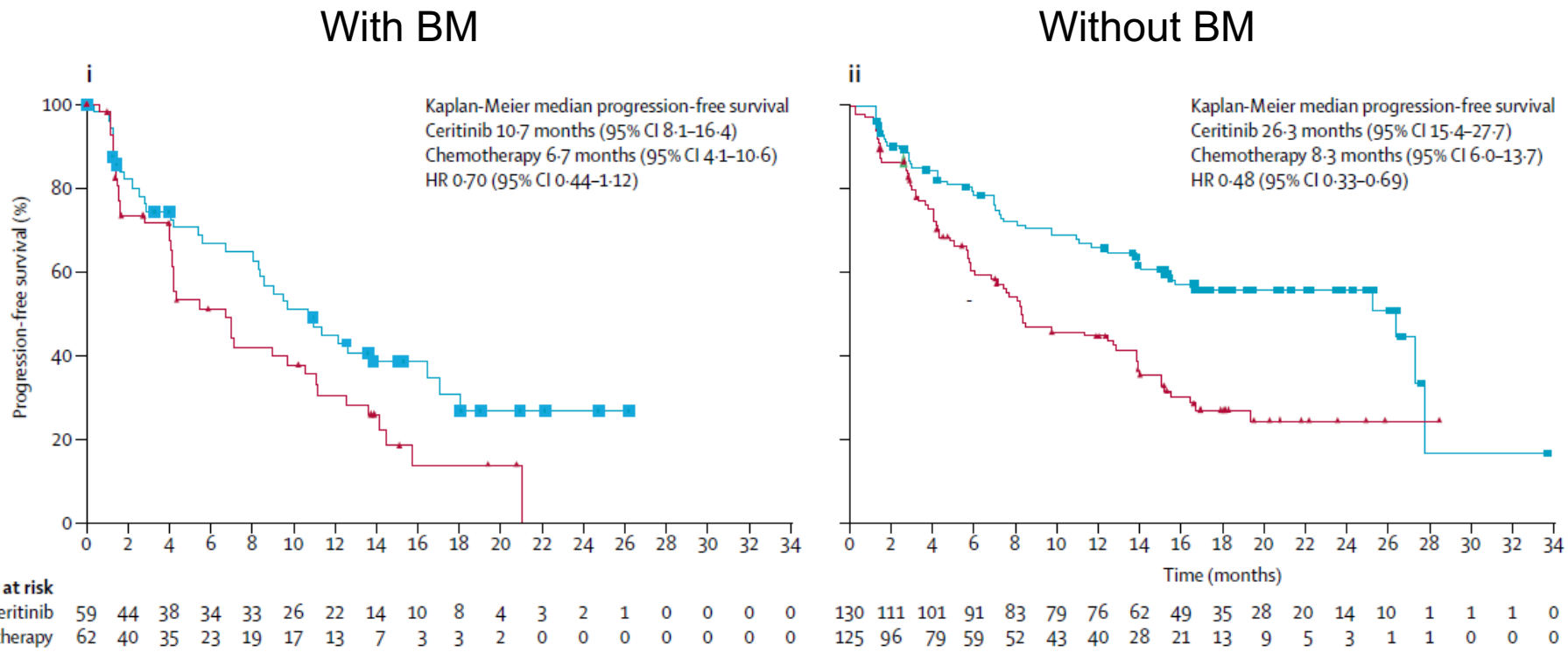
45.5% at 2nd Year

23.8% at 1st Year

*Retrospective: *EGFR* (n = 86); *ALK* (n = 23)

Rangachari D et al. Lung Cancer 2015; 88:108-111.

Ceritinib in 1st-line: BM or not



***Data by BIRC (blinded independent review committee)**

ORR: 72.7% for all patients; 69.2% for patients without previous R/T.

Lancet 2017;389: 917-29.

The Newer is better: also in CNS Efficacy*

	Crizotinib[1]	Ceritinib[2]	Alectinib[1]	Brigatinib[3]
Study	ALEX (n = 22)	ASCEND-4 (n = 22)	ALEX (n = 21)	ALTA 1L (n = 18)
CNS response	11 (50.0%)	16 (72.7%)	17 (81.0%)	14 (77.7)
CNS CR	1 (4.5%)	2 (9.1%)	8 (38.1%)	2 (11.1)
CNS DOR, m(s)	5.5 (2.1-17.3)	16.6 (8.1-NR)	17.3 (14.8-NR)	NR (11.0-NR)#

*With **measurable** baseline brain metastases.

[1]ALEX study (phase III), Shaw A et al. ASCO 2017 and Peters S et al. NEJM 2017.
[2]ASECND-4 (phase III), Gilberto de Castro Jr et al. WCLC 2016 and Soria JC et al. Lancet 2017.
[3]ALTA 1L, Camidge DR et al. WCLC 2018 (#PFS for any brain METs patients was reported not DOR).

CR, complete response; NR, not-reached; NA, not-applicable.

Lorlatinib: CSF penetration

Supplementary Table S7. Lorlatinib concentration in CSF

Patient	CSF concentration unbound* (ng/mL)	Plasma concentration unbound* (ng/mL)	CSF/plasma unbound*
1†	2·6	4·3	0·61
2‡	101	155	0·65
3‡	82	106	0·77
4‡	125	131	0·96

*Unbound refers to drug not bound to plasma proteins.
†Patient 1 originally received a dose of 150 mg, which was de-escalated first to 100 mg QD and then to 75 mg QD. This patient had held lorlatinib for 8 days before CSF sampling.
‡Patients 2–4 were receiving lorlatinib at 100 mg QD at the time of lumbar puncture.
CSF=cerebrospinal fluid; QD=once daily.

Paired blood and CSF samples in four patients:

CSF/plasma (unbound) concentrations of lorlatinib was **0·75**

(0·03 ratio reported with crizotinib)

Shw A et al. Lancet Oncol 2017; 18:1590-9.

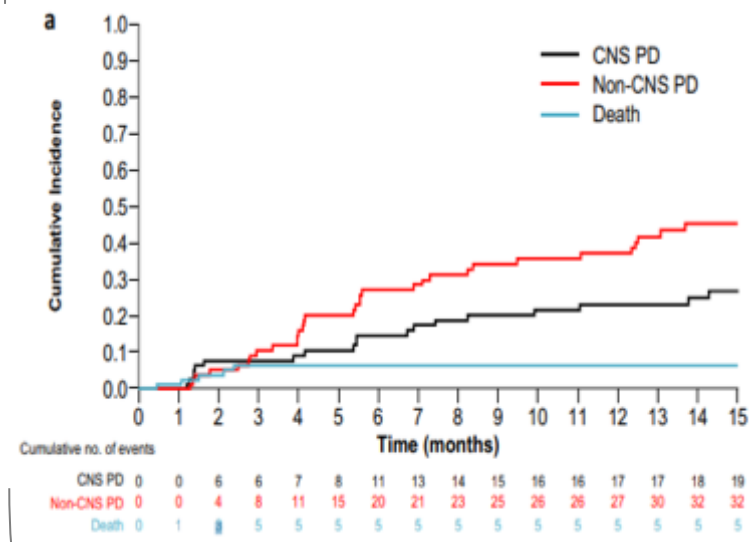
Lorlatinib: intracranial activity

<Intracranial ORR>

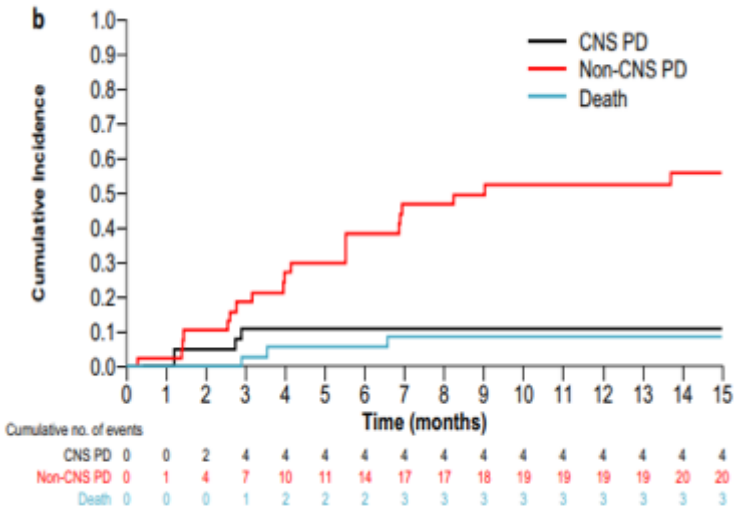
- EXP2-3A (prior crizotinib): 87.5 % (67.6-97.3)
- EXP3B-5 (at least one prior 2nd-G ALKi): 54.4% (40.7-67.6)

EXP3B-5

With baseline CNS metastasis



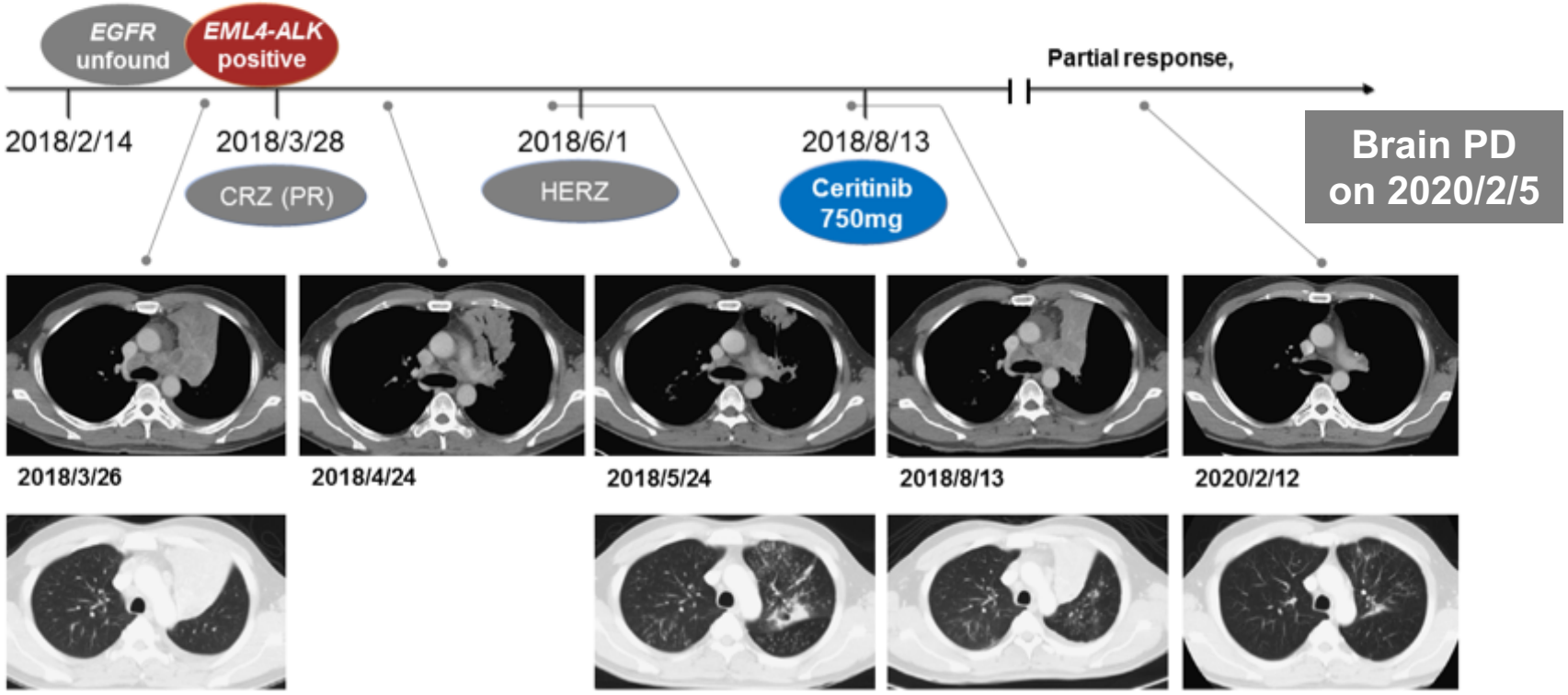
Without baseline CNS metastasis

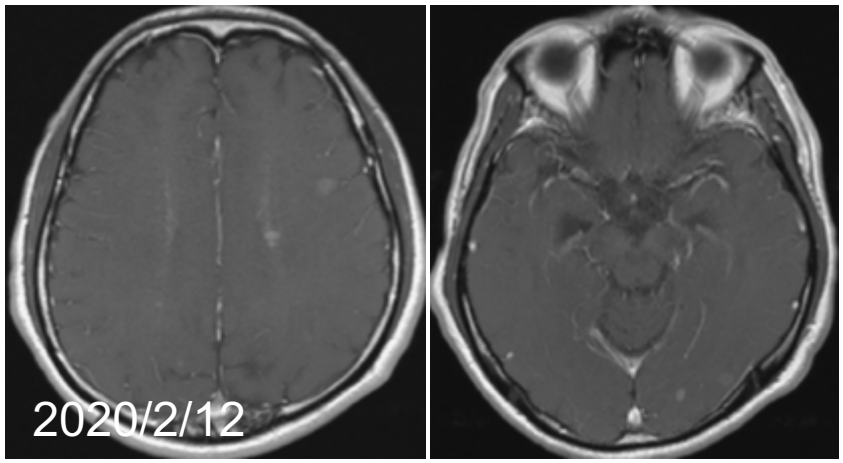


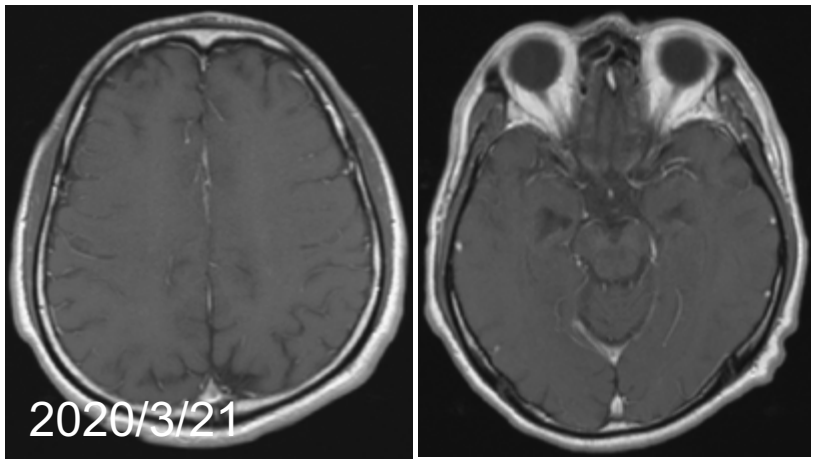
Bauer T et al. Targeted Oncology 2020:15:55-65.

Mr. Chang 50 year-old man, never smoker

Lung cancer, LUL, ADC, cT4N3M1a, stage IV, lung to lung METs, ECOG PS=1.

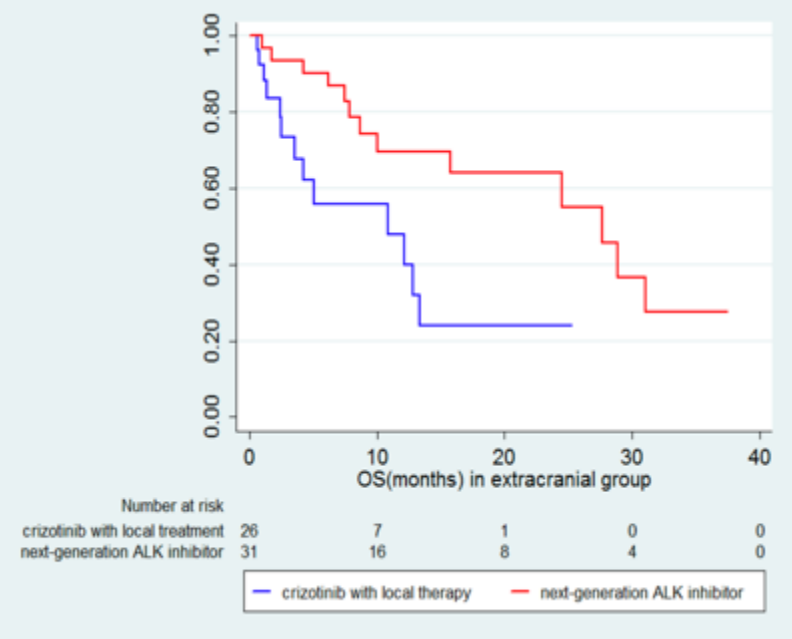




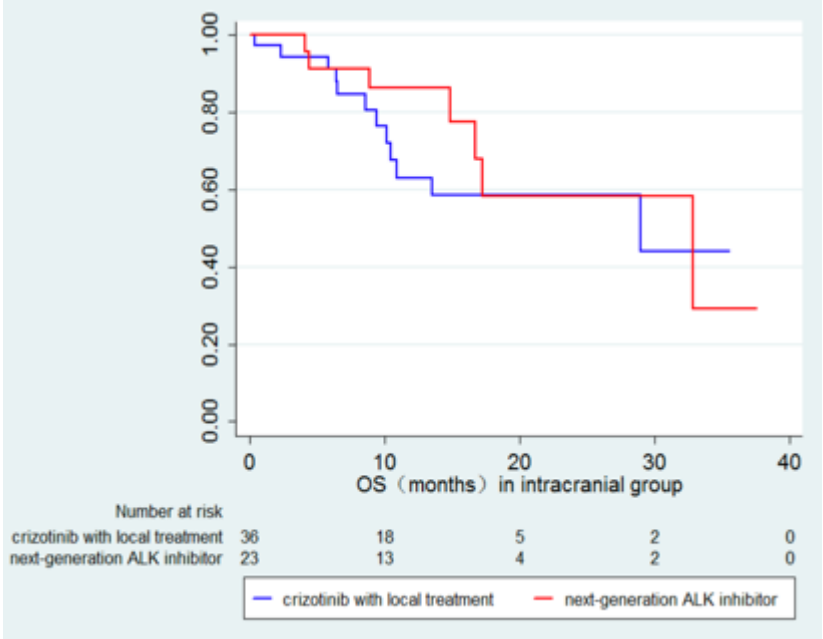


Lorlatinib since 2020/2/12

Oligo-PD after Crizotinib: Tx. beyond PD plus local therapy or Next-G ALKi ?



Extracranial (n = 57)



Intracranial (n = 59)

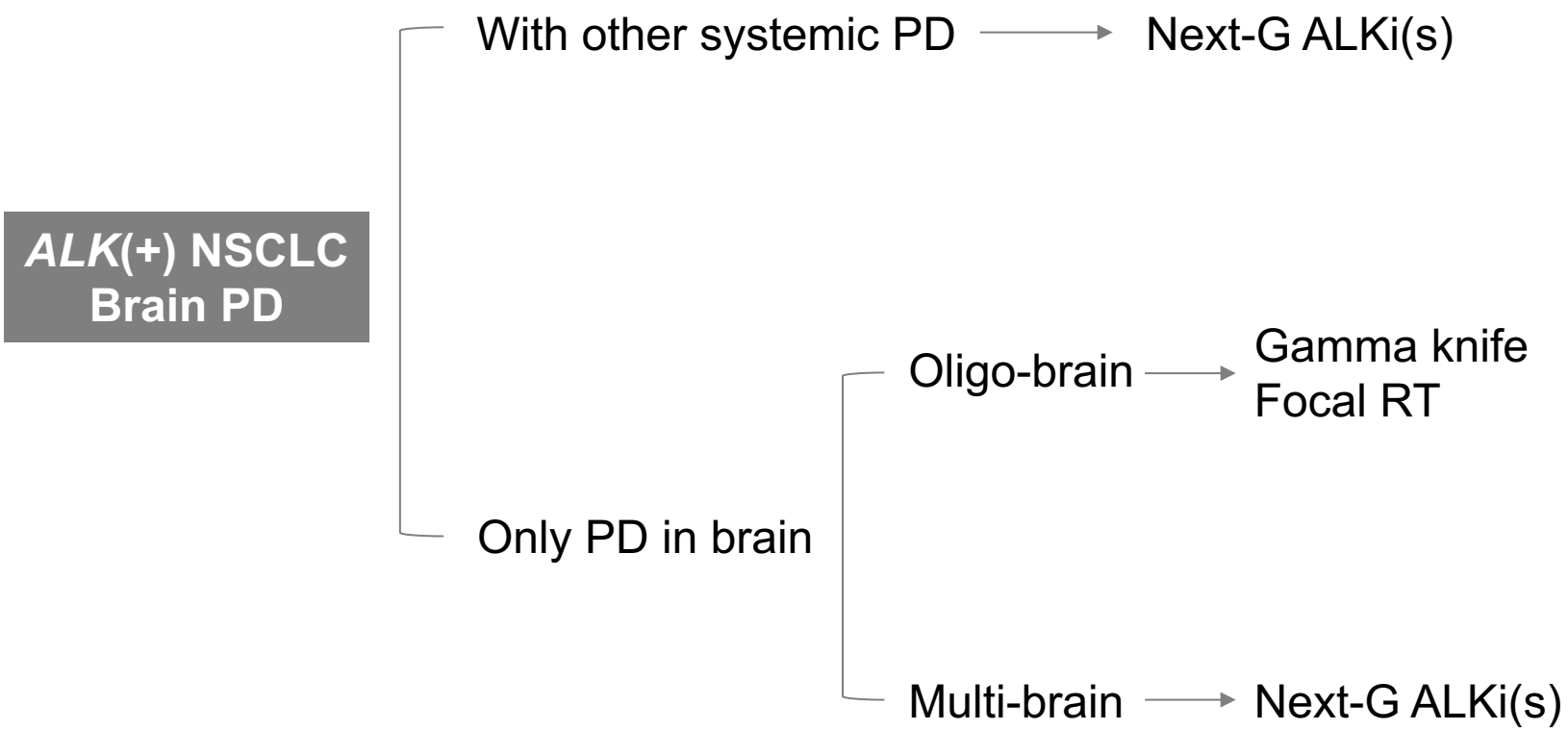
Similar survival but QoL ???

N = 116 Chinese advanced ALK+ NSCLC

Xu H et al. WCLC 2018 (P1.01-101).

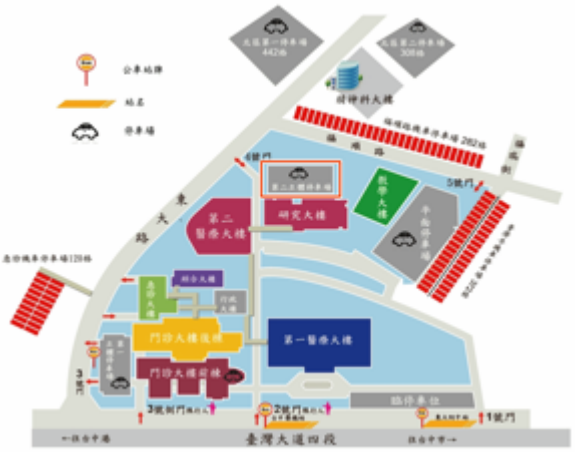
ALK (+)NSCLC with brain PD

Both NCCN & ESMO guidelines suggest local therapy for limited brain PD



Brief conclusions

- Although it is not common, the outcome of treatment is promising in *ALK*(+) NSCLC patients.
- Because of the better efficacy, the second-generation *ALK* inhibitors have emerged as the new standard of front-line treatment.
- Next-generation *ALK* inhibitor(s) could benefit patients in the second line setting. Rebiopsy can be considered in patients who progress from second-generation *ALK* inhibitor(s).
- Brain metastasis remains an important issue in *ALK*(+) patients. The next-generation *ALK* inhibitor(s) have a higher intracranial activity.



Thanks for your attention!

25-JUL-2020 @ Taichung

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Faculty of Medicine, School of Medicine, National Yang-Ming University
Institute of Biomedical Sciences, National Chung Hsing University