Shifting Paradigms in ALK+ NSCLC

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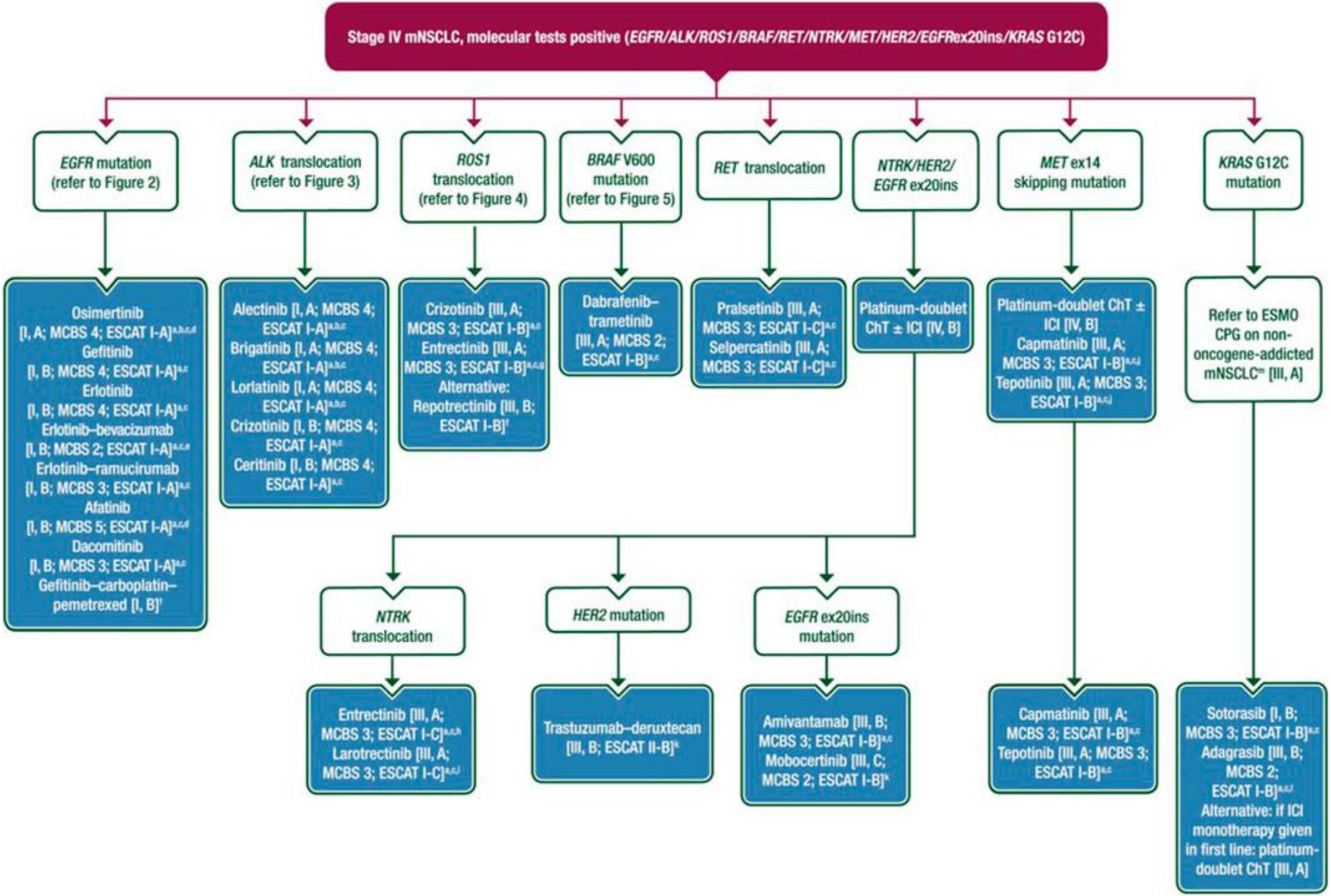
DISCLOSURE SLIDE

I have provided lectures for the following organizations, from whom I have received honoraria:

ACT Genomics, Amgen, AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Chugai, CStone, Eli Lilly, Lotus, Merck Sharp and Dohme, Novartis, Orient EuroPharma, Pfizer, Roche, Takeda

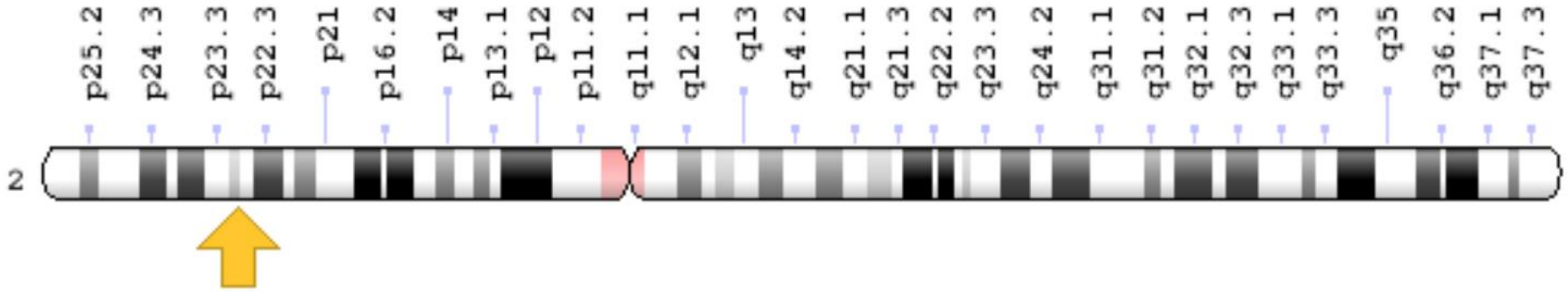
I declare no conflict of interest associated to current topics.

Introduction of ALK mutation in NSCLC


Stage IV mNSCLC, molecular tests positive (EGFR/ALK/ROS1/BRAF/RET/NTRK/MET/HER2/EGFRex20ins/KRAS G12C)
EGFR mutation (refer to Figure 2)
ALK translocation (refer to Figure 3)
ROS1 translocation (refer to Figure 4)
BRAF V600 mutation (refer to Figure 5)
RET translocation
NTRK/HER2/ EGFR ex20ins
MET ex14 skipping mutation
KRAS G12C mutation
Osimertinib [I, A; MCBS 4; ESCAT I-A][a,b,c,d]
Gefitinib [I, B; MCBS 4; ESCAT I-A][a,c]
Erlotinib [I, B; MCBS 4; ESCAT I-A][a,c]
Erlotinib–bevacizumab [I, B; MCBS 2; ESCAT I-A][a,c,e]
Erlotinib–ramucirumab [I, B; MCBS 3; ESCAT I-A][a,c]
Afatinib [I, B; MCBS 5; ESCAT I-A][a,c,d]
Dacomitinib [I, B; MCBS 3; ESCAT I-A][a,c]
Gefitinib–carboplatin–pemetrexed [I, B][f]
Alectinib [I, A; MCBS 4; ESCAT I-A][a,b,c]
Brigatinib [I, A; MCBS 4; ESCAT I-A][a,b,c]
Lorlatinib [I, A; MCBS 4; ESCAT I-A][a,b,c]
Crizotinib [I, B; MCBS 4; ESCAT I-A][a,c]
Ceritinib [I, B; MCBS 4; ESCAT I-A][a,c]
Crizotinib [III, A; MCBS 3; ESCAT I-B][a,c]
Entrectinib [III, A; MCBS 3; ESCAT I-B][a,c,g]
Alternative: Repotrectinib [III, B; ESCAT I-B][f]
Dabrafenib–trametinib [III, A; MCBS 2; ESCAT I-B][a,c]
Pralsetinib [III, A; MCBS 3; ESCAT I-C][a,c]
Selpercatinib [III, A; MCBS 3; ESCAT I-C][a,c]
Platinum-doublet ChT ± ICI [IV, B]
Platinum-doublet ChT ± ICI [IV, B]
Capmatinib [III, A; MCBS 3; ESCAT I-B][a,c,j]
Tepotinib [III, A; MCBS 3; ESCAT I-B][a,c,j]
Refer to ESMO CPG on non-oncogene-addicted mNSCLC[m] [III, A]
NTRK translocation
HER2 mutation
EGFR ex20ins mutation
Entrectinib [III, A; MCBS 3; ESCAT I-C][a,c,h]
Larotrectinib [III, A; MCBS 3; ESCAT I-C][a,c,j]
Trastuzumab–deruxtecan [III, B; ESCAT II-B][k]
Amivantamab [III, B; MCBS 3; ESCAT I-B][a,c]
Mobocertinib [III, C; MCBS 2; ESCAT I-B][k]
Capmatinib [III, A; MCBS 3; ESCAT I-B][a,c]
Tepotinib [III, A; MCBS 3; ESCAT I-B][a,c]
Sotorasib [I, B; MCBS 3; ESCAT I-B][a,c]
Adagrasib [III, B; MCBS 2; ESCAT I-B][a,c,j]
Alternative: if ICI monotherapy given in first line: platinum-doublet ChT [III, A]

Cytogenetic Location: 2p23.2-p23.1, which is the short (p) arm of chromosome 2 between positions 23.2 and 23.1

Molecular Location: base pairs 29,190,992 to 29,921,589 on chromosome 2 (Homo sapiens Updated Annotation Release 109.20191205, GRCh38.p13) (NCBI)



ALK

leading to proliferation and survival of the cancer cells

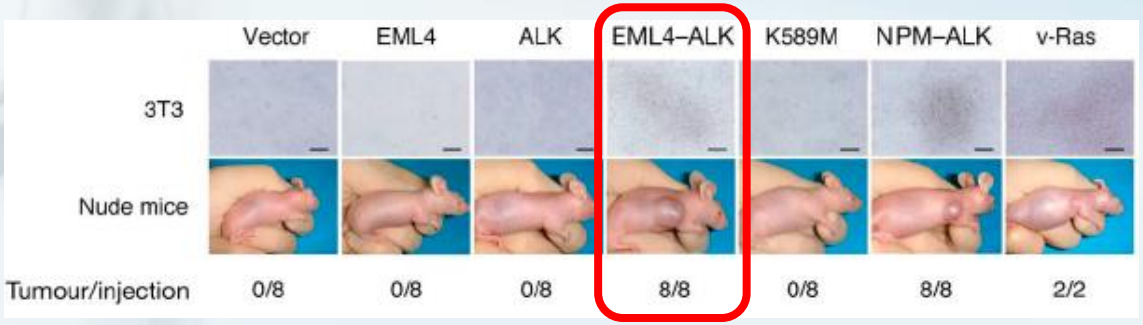
Credit: Genome Decoration Page/NCBI

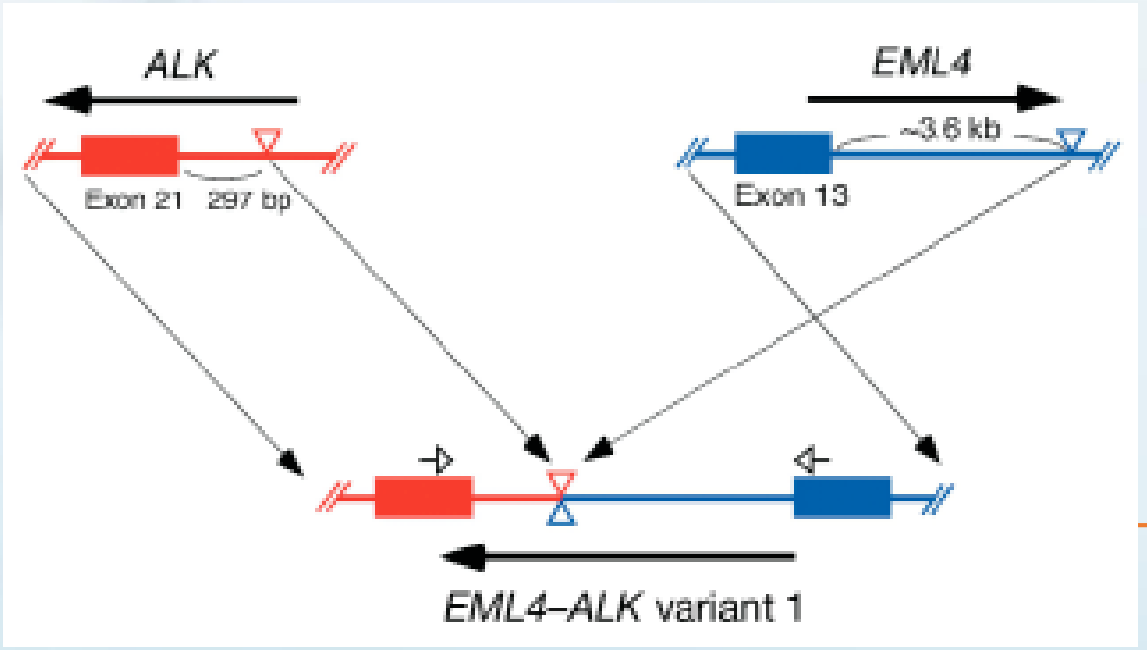
nature

Vol 448|2 August 2007

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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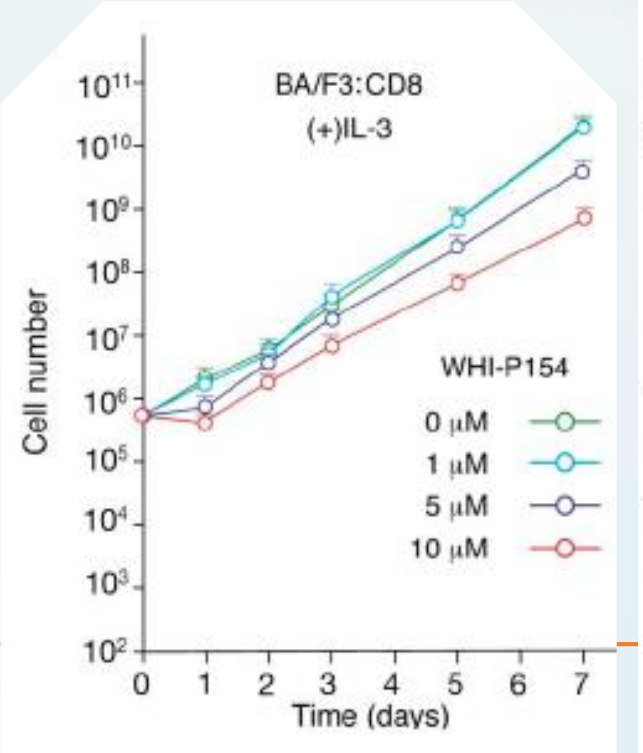
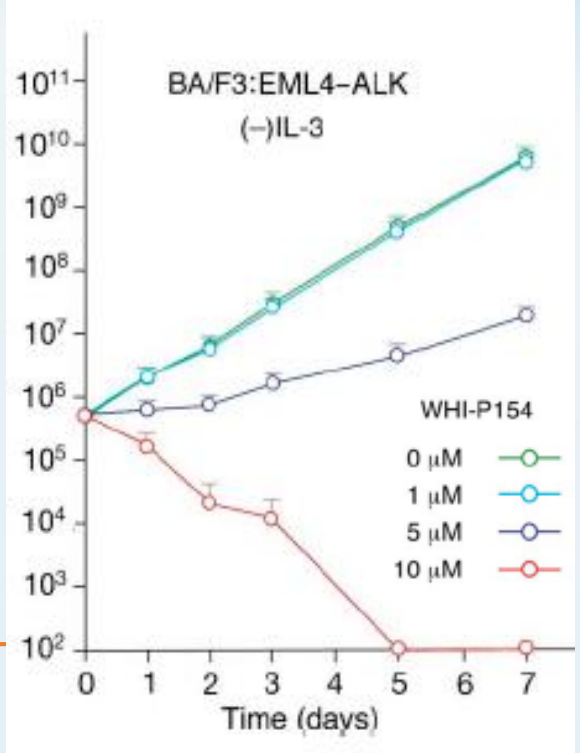
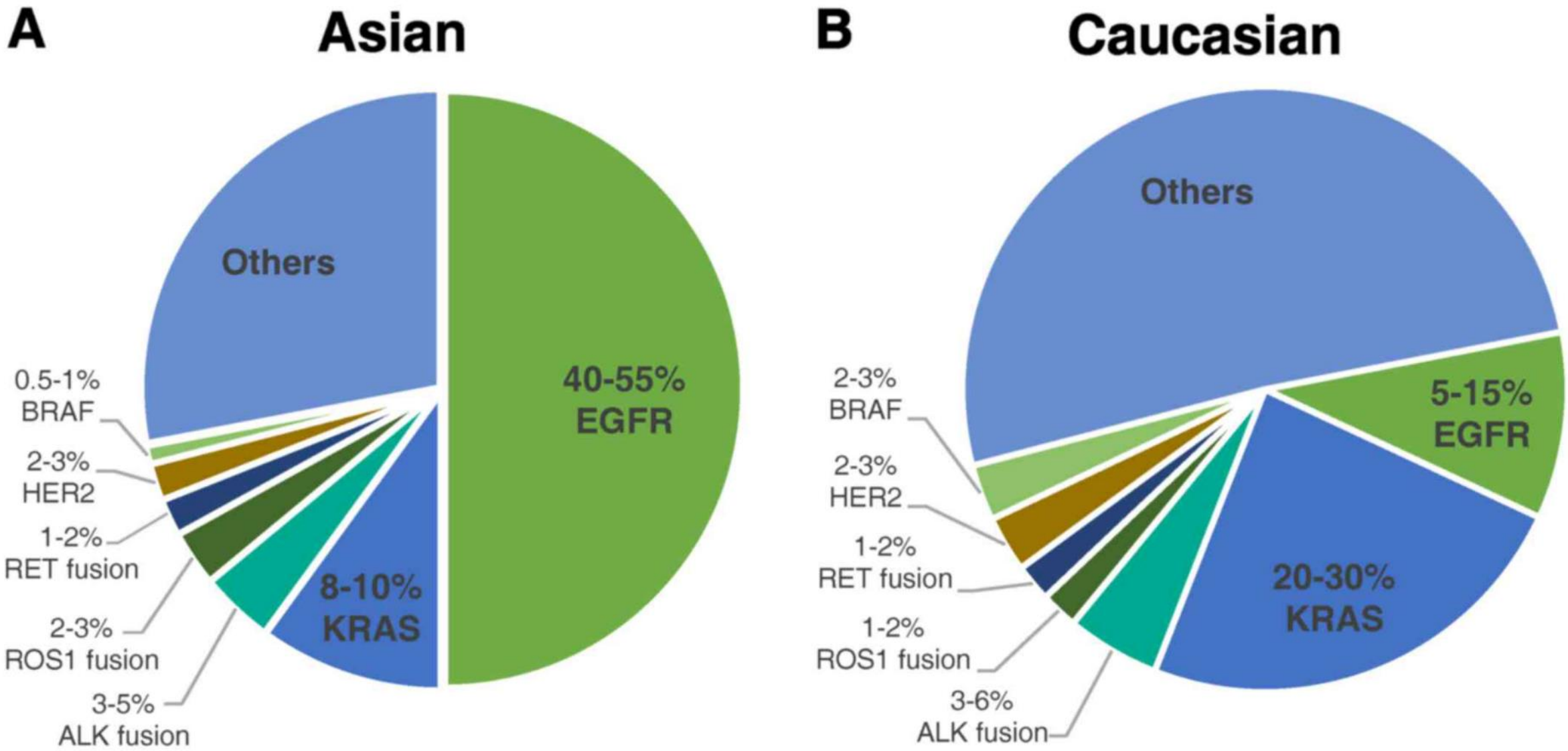




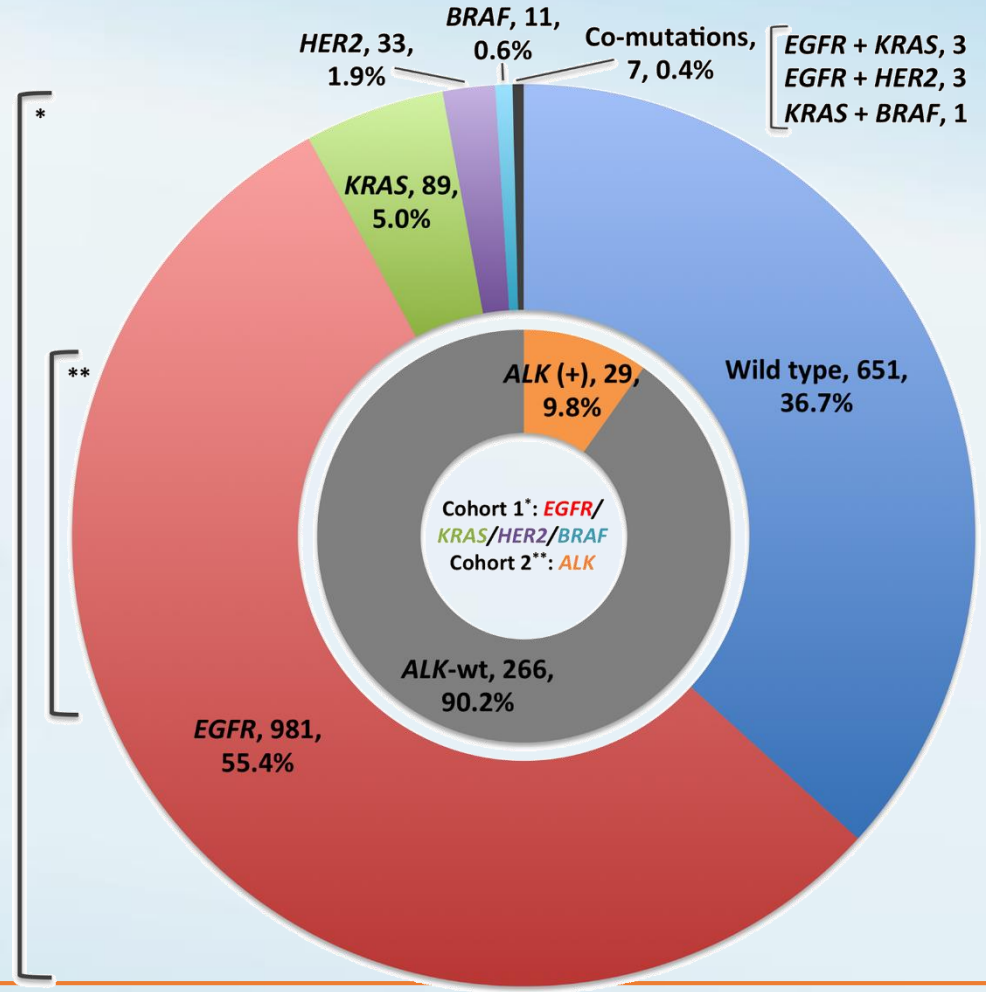
ALK-rearranged in NSCLC

- 3-7% in NSCLC
- Majorly adenocarcinoma histology
- Younger patients (median 5x years old?)
- Never or light smokers
- Several variants
- Detection methods
  - FISH
  - IHC (Ventana method)
  - Next generation sequencing (NGS)



https://doi.org/10.3892/or.2017.5409

Driver gene mutation of adenocarcinoma of lung in Taiwan



Mutations	%
EGFR	55.4
KRAS	5.0
HER2	1.9
BRAF	0.6
ALK*	9.8

* EML-ALK translocation by Ventana method in EGFR wild type patients

*Cohort 1 (n=1772 lung adenocarcinoma): testing of *EGFR/KRAS/HER2/BRAF*.
**Cohort 2 (n=295 *EGFR*-wt lung adenocarcinoma): testing of *ALK*.

https://doi.org/10.1371/journal.pone.0120852

NGS experience

VGH Oncomide NGS, NSCLC Case: 119 2019-11 ~ 2021-03
Tissue:110, cell block:7, cfTNA:2

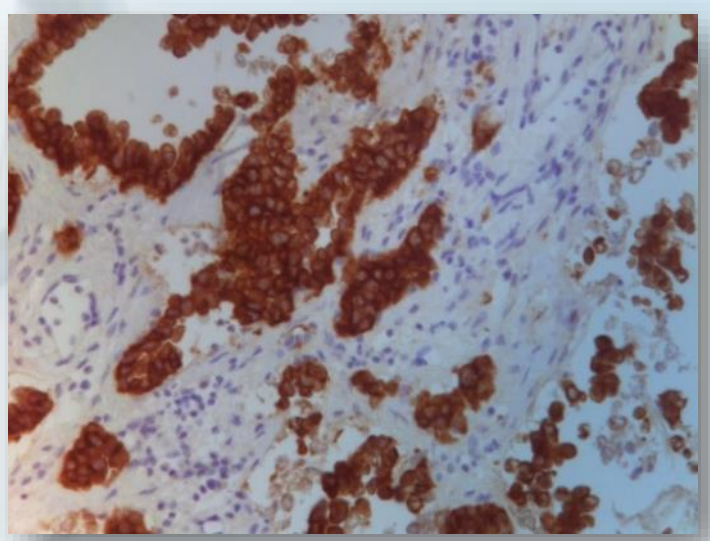
Mutation	ALK EML4	BRAF V600E	EGFR 19/21/OT	ERBB2 exon20i	KRAS
	3%	2%	44% 40/31/25%	22%	9%
	MET exon14s	NTRK 1/2/3	RET KIF5B	ROS1 CD74	NULL
	3%	0%	3%	2%	20%

G12C: 1/11
G12x: 9/11
Amplification: 2

Neutrally exclusive, except amplification

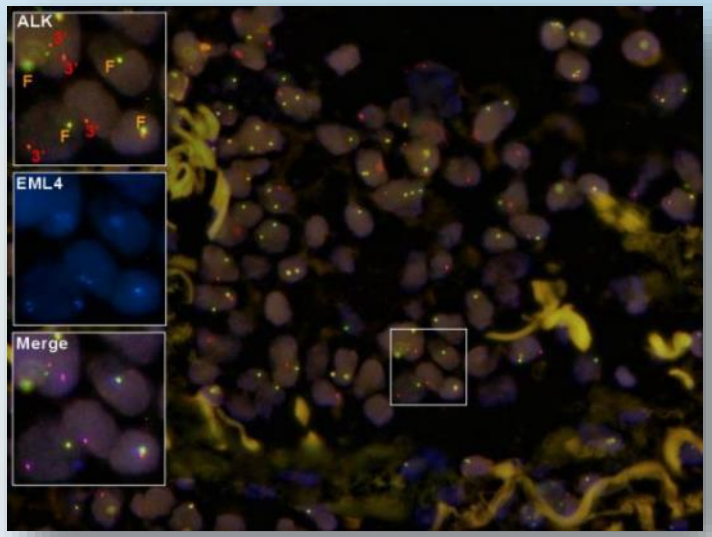
Diagnostics of ALK translocations

IHC



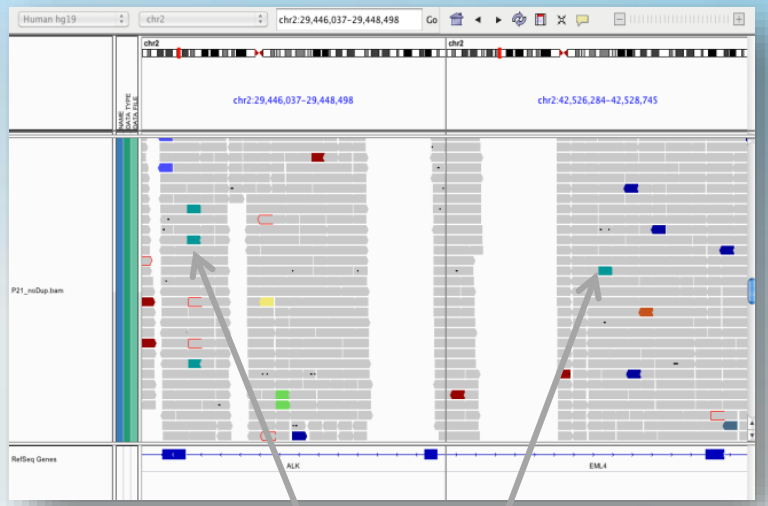
D5F3 (VENTANA)

FISH



Break apart:
Orange:red/green fusion normal
Red: ALK 3´break

NGS



ALK
Reads marked in ALK to pair with region of EML4

EML4
Reads marked in EML4 to pair with region in ALK

AmoyDx® EML4-ALK Fusion Gene Detection Kit

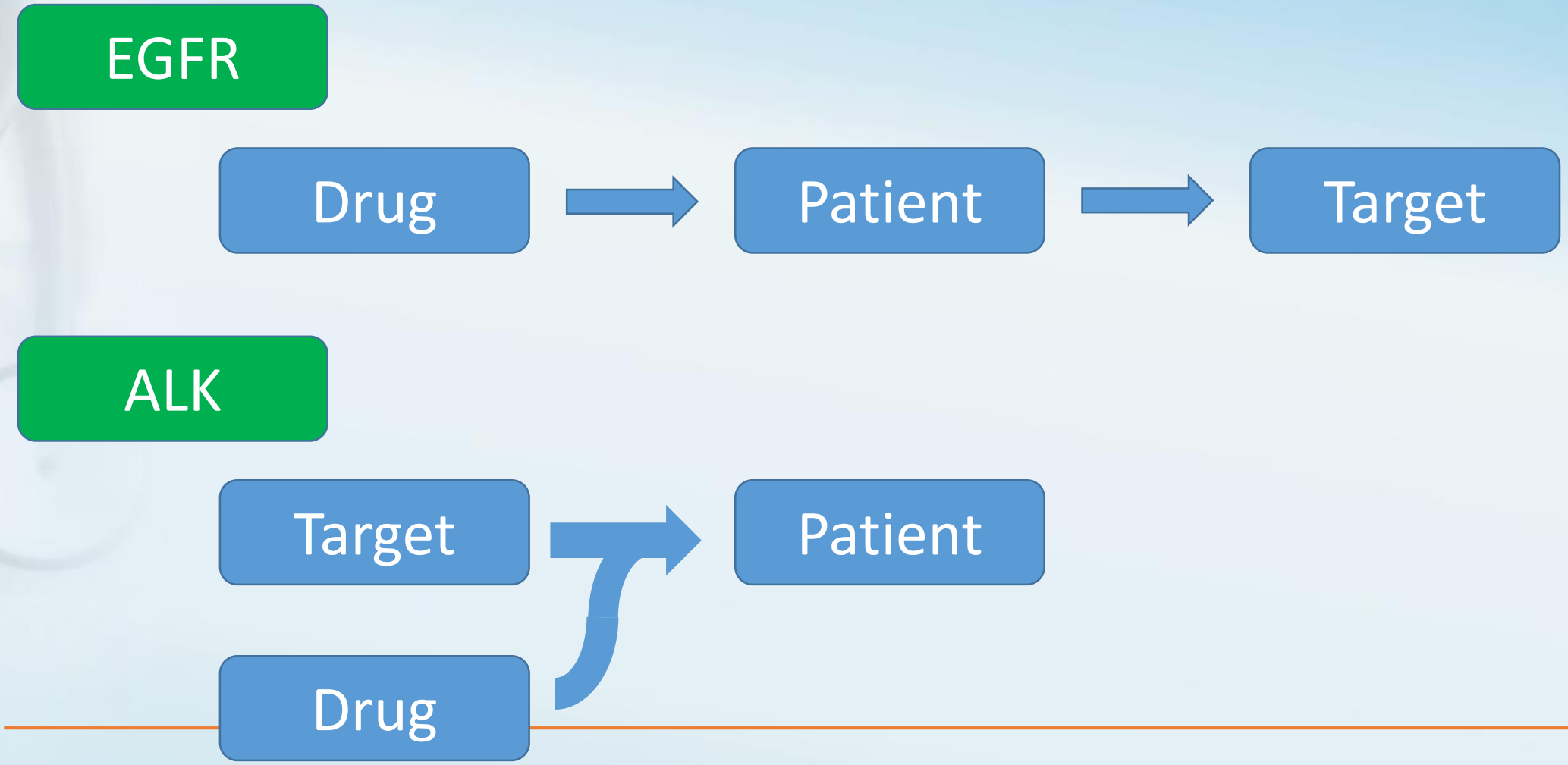
Technology	Tumor	Certificate
PCR	Non-small cell lung cancer	CE IVD RUO

AmoyDx® EML4-ALK Fusion Gene Detection Kit is a **real-time PCR assay**. The kit facilitates the qualitative detection of **up to 21 EML4-ALK fusions** in human **RNA** extracted from FFPE of NSCLC.

Images courtesy of A. Scheel and R. Büttner, Cologne.
https://www.amoydiagnostics.com/products/amoydx-eml4-alk-fusion-gene-detection-kit

History of ALK translocation/fusion in NSCLC

EGFR TKI v.s. ALK TKI



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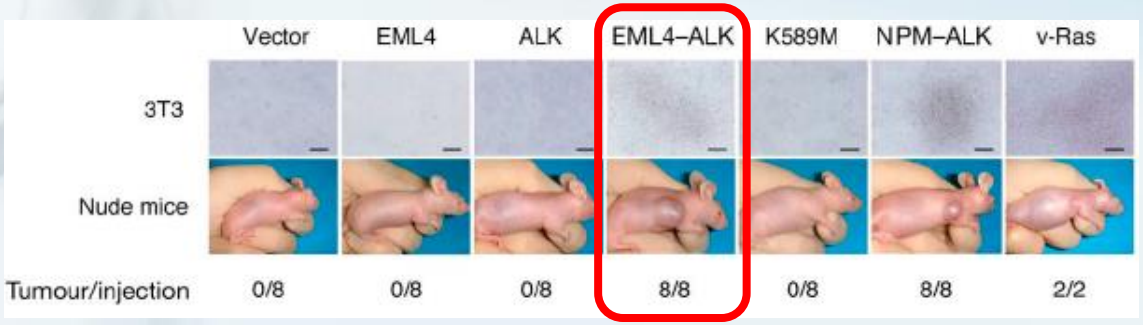

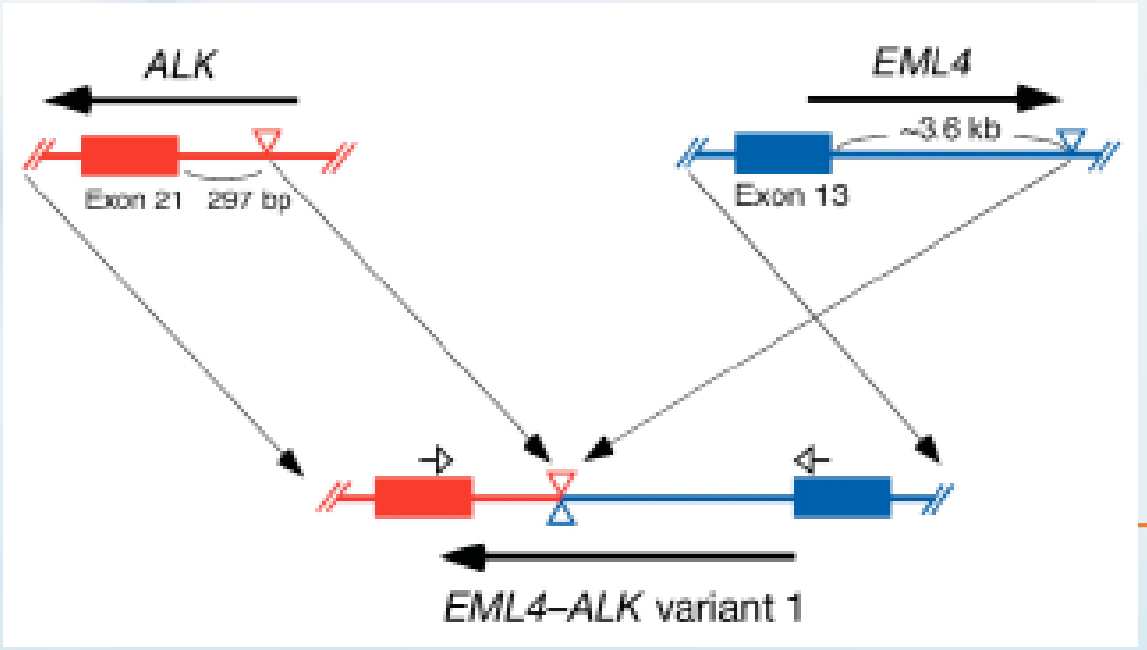


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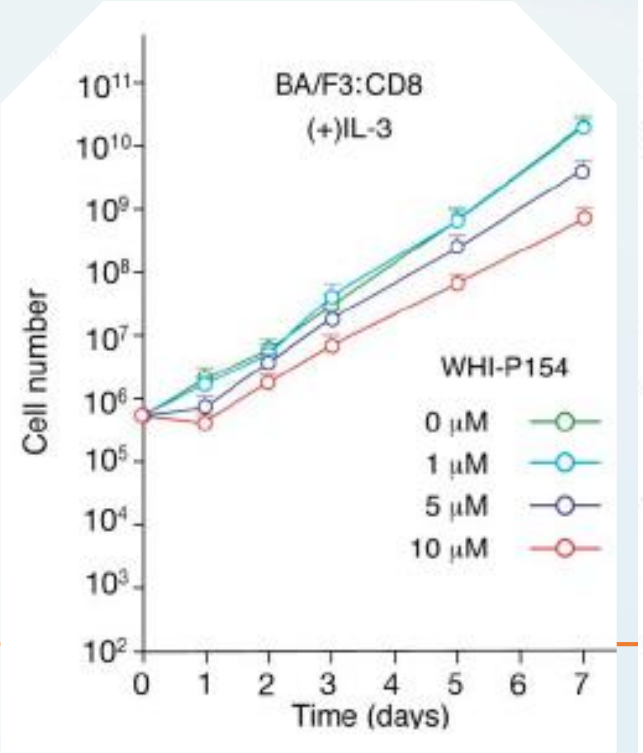
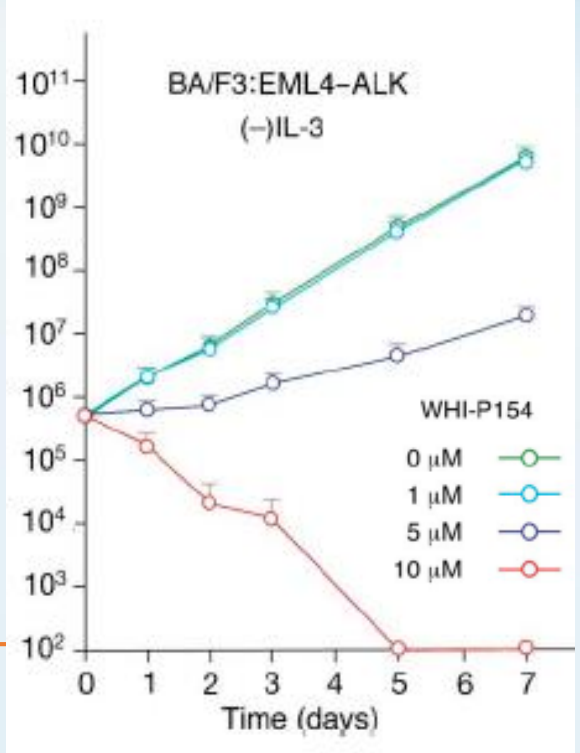
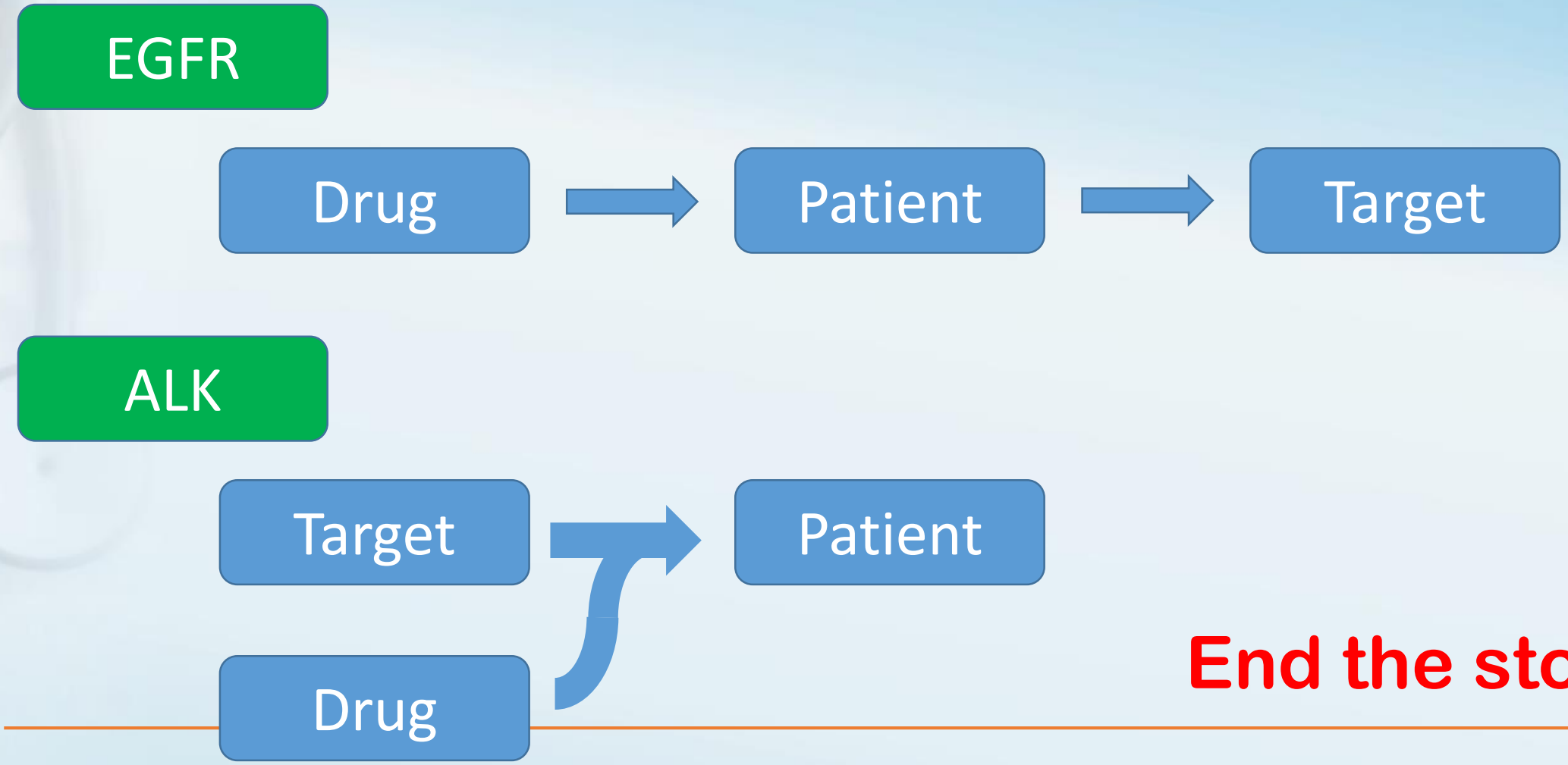




EGFR TKI v.s. ALK TKI



End the story?

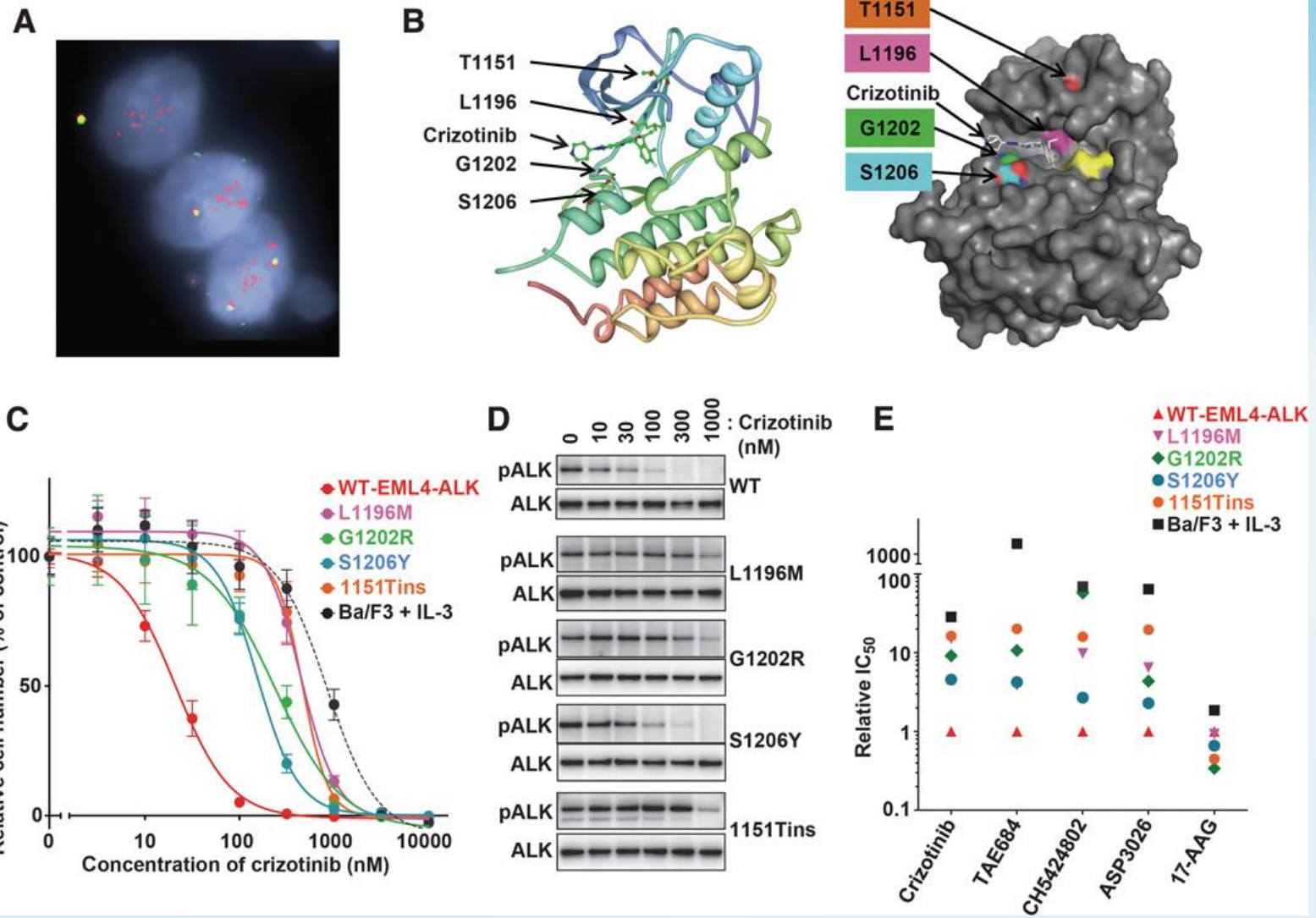
Mechanisms of Acquired Crizotinib Resistance in ALK-Rearranged Lung Cancers

2012

Ryohei Katayama[1,2,*], Alice T. Shaw[1,2,3,*], Tahsin M. Khan[1,3], Mari Mino-Kenudson[2,4], Benjamin J. Solomon[5], Balazs Halm…

+ See all authors and affiliations

Science Translational Medicine 08 Feb 2012:
Vol. 4, Issue 120, pp. 120ra17
DOI: 10.1126/scitranslmed.3003316



Different ALK TKIs have Different Activity Against ALK Resistance Mutations

- 1. Secondary mutations in the ALK kinase domain can induce resistance to first- and second-gen ALK TKIs
- 2. Each ALK inhibitor has a different sensitivity/resistance profile
- 3. ALK G1202R confers resistance to first- and second-gen ALK TKIs

	Cellular ALK Phosphorylation Mean IC50 (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
EML4-ALK C1156Y	61.9	5.3	11.6	4.5	4.6
EML4-ALK I1171N	130.1	8.2	397.7	26.1	49.0
EML4-ALK I1171S	94.1	3.8	177.0	17.8	30.4
EML4-ALK I1171T	51.4	1.7	33.6[a]	6.1	11.5
EML4-ALK F1174C	115.0	38.0[a]	27.0	18.0	8.0
EML4-ALK L1196M	339.0	9.3	117.6	26.5	34.0
EML4-ALK L1198F	0.4	196.2	42.3	13.9	14.8
EML4-ALK G1202R	381.6	124.4	706.6	129.5	49.9
EML4-ALK G1202del	58.4	50.1	58.8	95.8	5.2
EML4-ALK D1203N	116.3	35.3	27.9	34.6	11.1
EML4-ALK E1210K	42.8	5.8	31.6	24.0	1.7
EML4-ALK G1269A	117.0	0.4	25.0	ND	10.0
EML4-ALK D1203N+F1174C	338.8	237.8	75.1	123.4	69.8
EML4-ALK D1203N+E1210K	153.0	97.8	82.8	136.0	26.6

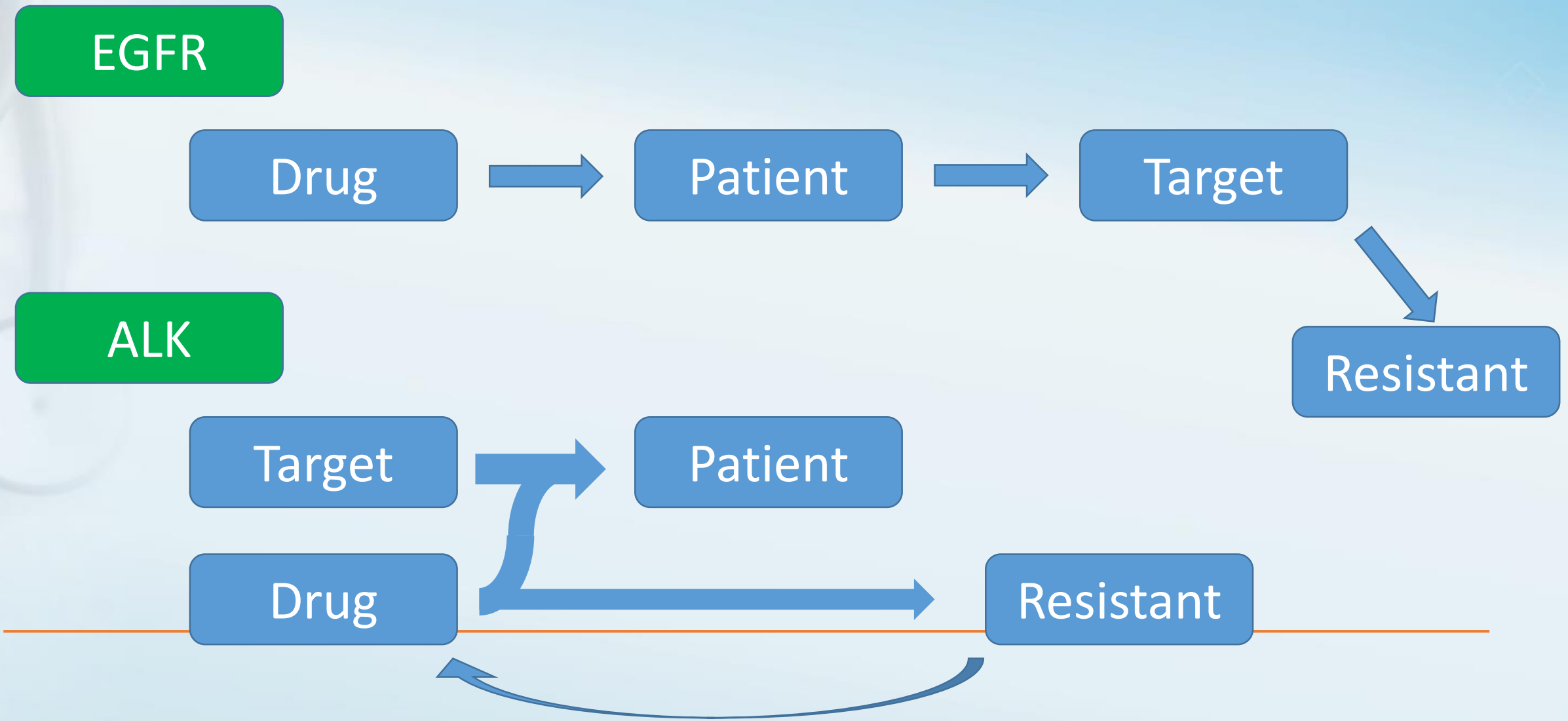
IC50 ≤ 50 nM

IC50 > 50 <200 nM

IC50 ≥ 200 nM

Gainor JF et al. Cancer Discovery 2016;6:1118

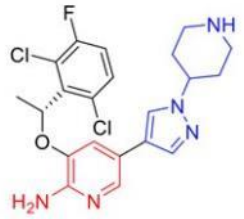
EGFR TKI v.s. ALK TKI



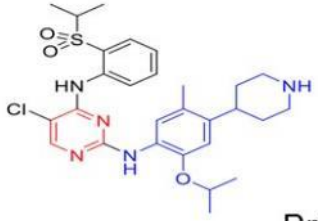
Generations of ALK TKI

First-Generation | **Second-Generation** | **Third-Generation**

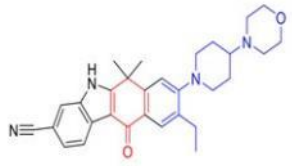
Crizotinib



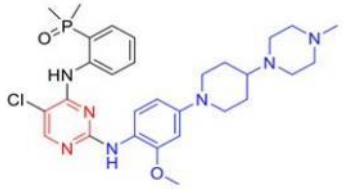
Ceritinib



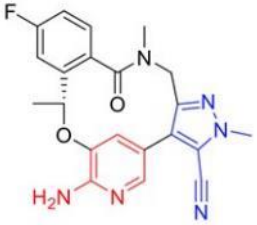
Alectinib



Brigatinib



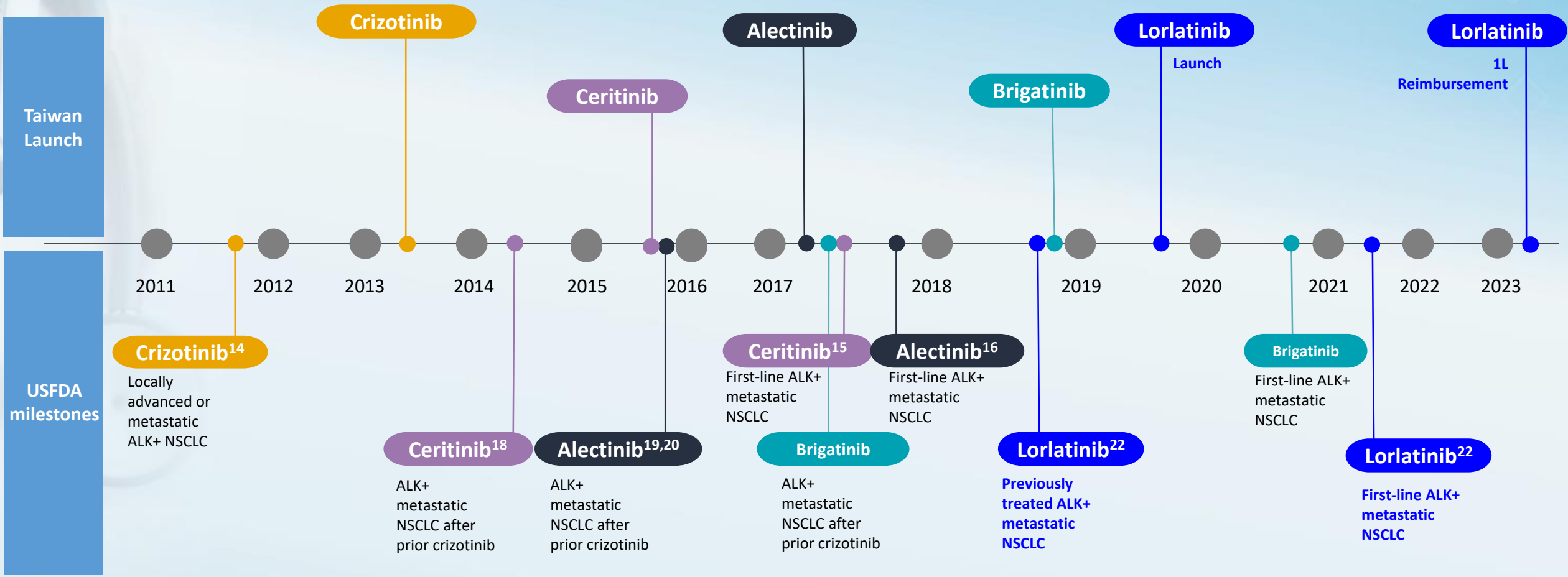
Lorlatinib



Gate gene mutation
(L1196M)
Brain penetration

Brain penetration
Overcome G1202R

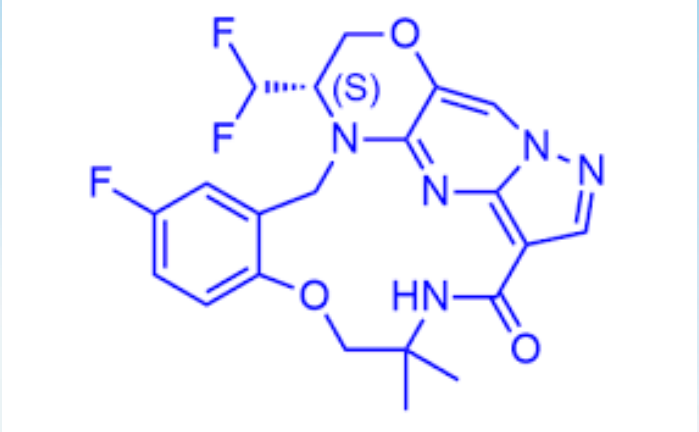
Development of ALK inhibitors within 10 years

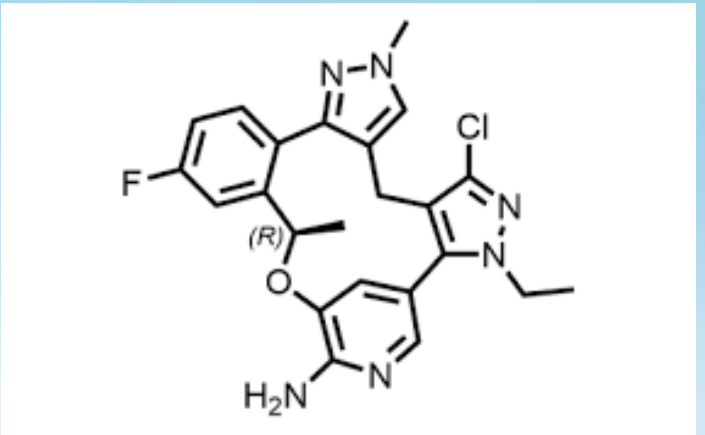


ALK, anaplastic lymphoma kinase; EMA, European Medicines Agency; NSCLC, non-small cell lung cancer; USFDA, United States Food and Drug Administration.

14. Crizotinib FDA package insert (version date: 2011.08.26). **15.** Cceritinib FDA package insert (version date: 2017.05.26). **16.** Aalectinib FDA package insert (version date: 2017.11.06). **17.** Brigatinib FDA package insert (version date: 2020.05.22). **18.** Ceritinib FDA package insert (version date: 2014.04.29). **19.** Alectinib FDA approved date 2015.12.11. **20.** Alectinib FDA package insert (version date: 2016.11.04). **21.** Brigatinib FDA package insert (version date: 2017.04.28). **22.** Lorlatinib FDA package insert (version date: 2018.11.02). **23.** Gristina V, et al. Pharmaceuticals (Basel). 2020;13(12):474. **24.** Yun MR, et al. Clin Cancer Res. 2020;26(13):3287-3295.

4th G ALK TKI





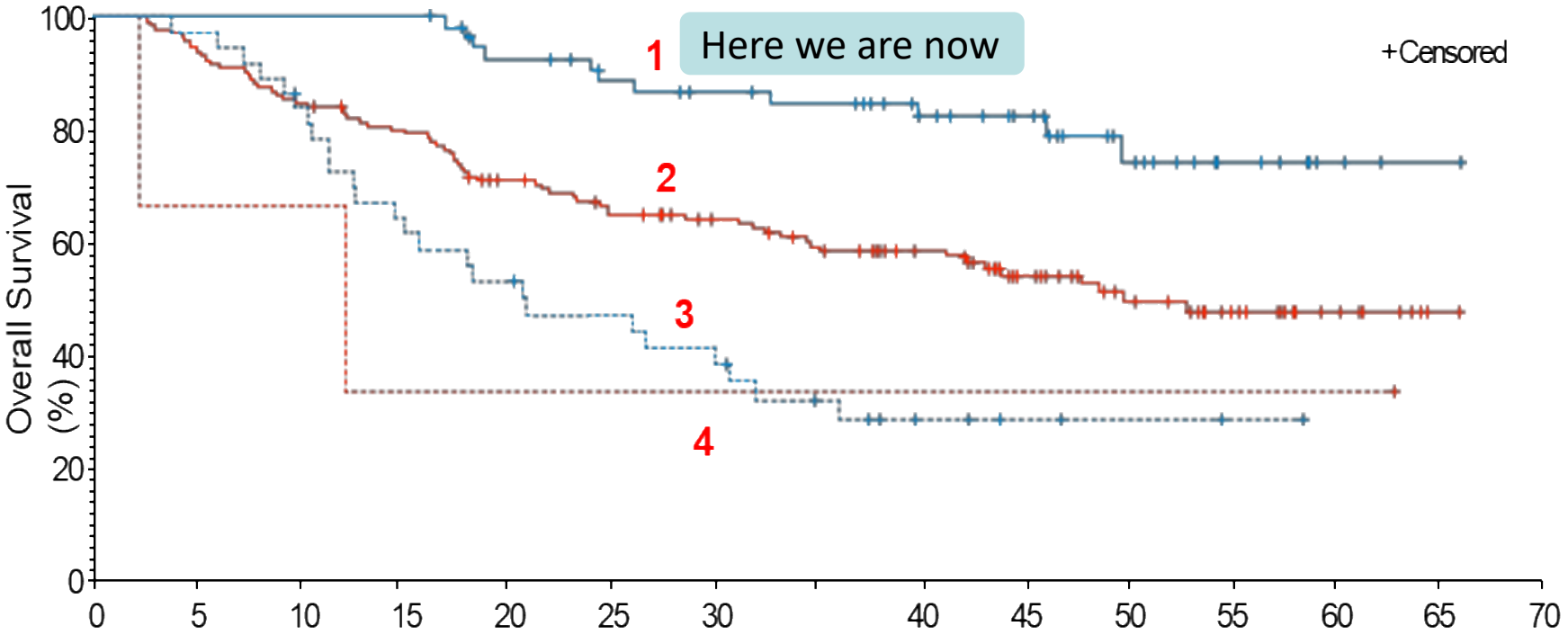
Feature	Crizotinib	2nd gen*	Lorlatinib	TPX-0131	NVL-655 TPP
ALK activity	Yes	Yes	Yes	Yes	Yes
G1202R activity	No	No	Yes	Yes	Yes
G1202R/L1196M activity	No	No	No	Yes	Yes
CNS activity	Not in label	Yes	Yes	Likely[10]	Yes
Sparing TRKB	Limited CNS penetrance	Yes	Limited at dose developed for ALK G1202R**	No	Yes

Transl Lung Cancer Res . 2023 Mar 31;12(3):615-628.
https://nuvalent.com/wp-content/uploads/2023/04/AACR-2023-NVL-655-poster-vSUBMITTED.pdf

Treatment of ALK mutation the 2nd generation ALK-TKI

Best OS by sequential treatment of ALK-TKIs

Updated OS result in PROFLIE1014



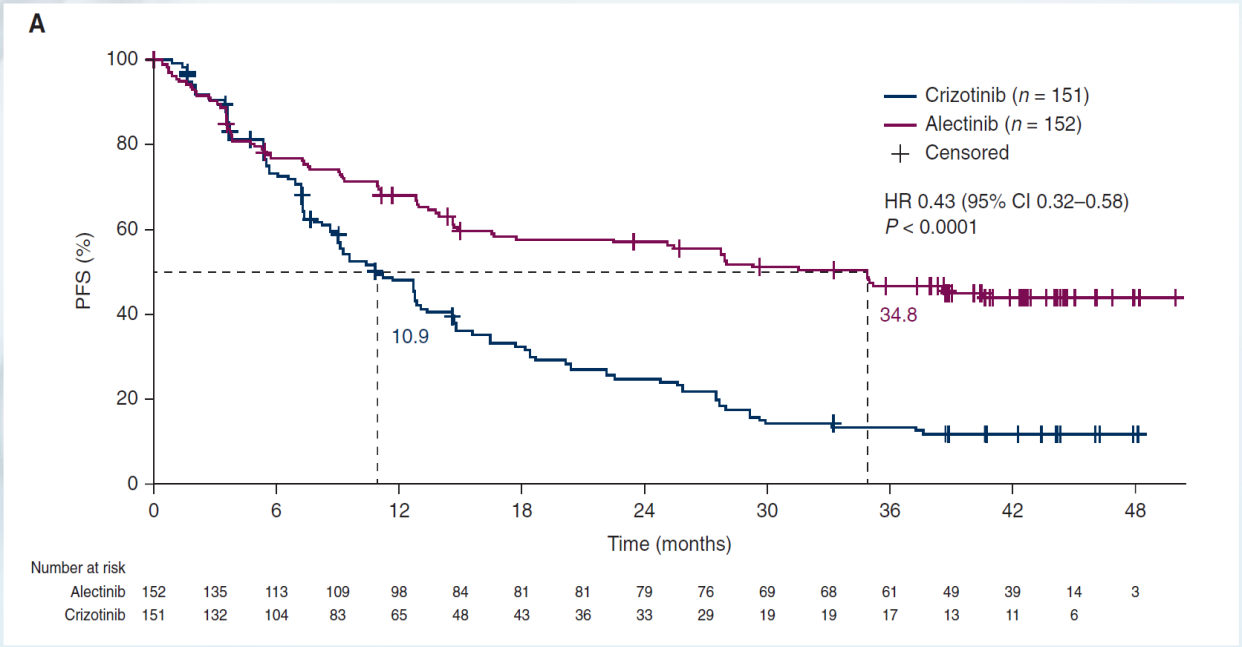
1. Crizotinib→Any other ALK TKI
2. Crizotinib→subsequent therapy other than ALK TKI
3. Chemotherapy→ALK TKI
4. Chemotherapy→subsequent therapy other than ALK TKI

(Abstract LBA50, ESMO 2017)

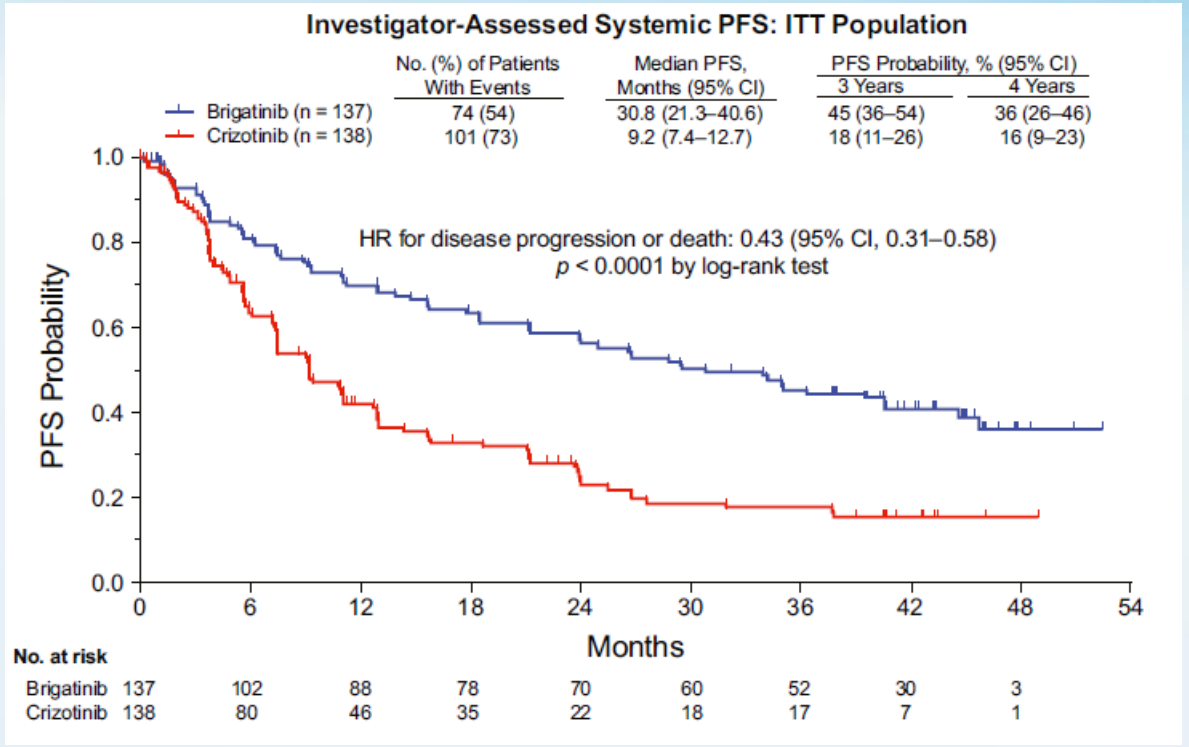
Second-generation TKIs: PFS in ALEX vs ALTA1

ALEX

34.8 months



30.8 months

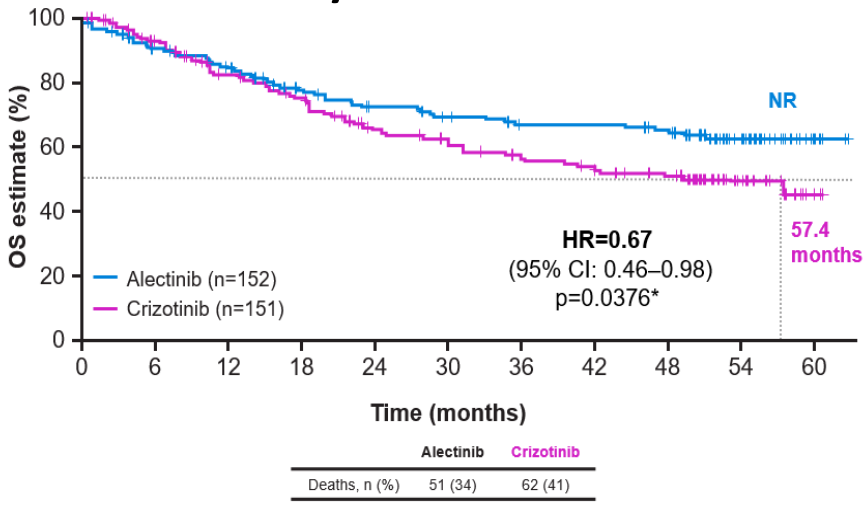


Mok T and Peters S, et al. *Ann Oncol* 2020;31:1056-1064;
J Thorac Oncol. 2021 Dec;16(12):2091-2108

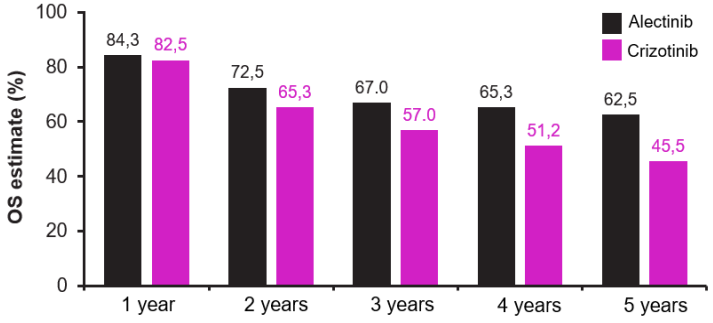
Cross-trial comparisons have significant limitations. This information is presented in order to generate discussion, not to make comparisons between study results.

Overall survival:
ALEX and ALTA-1L

5y OS: 62.5%

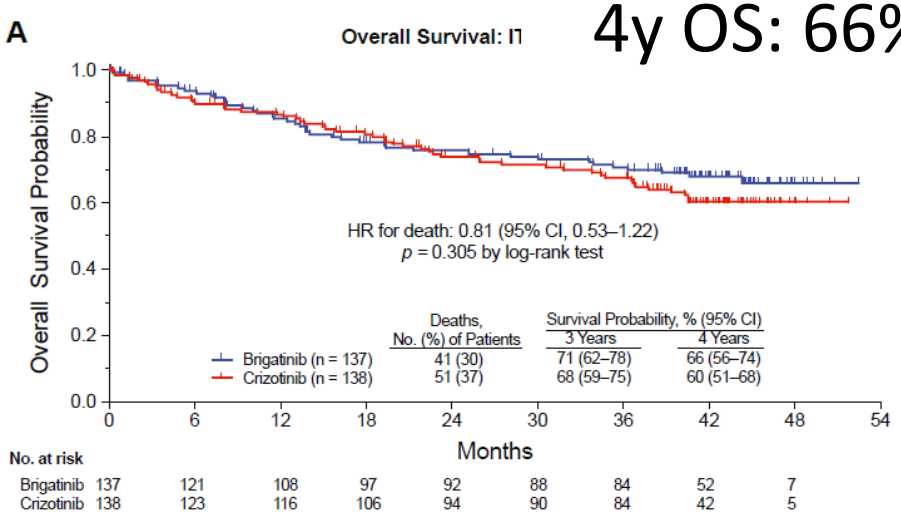


	Alectinib	Crizotinib
Deaths, n (%)	51 (34)	62 (41)



5-year survival rates:
Alectinib: 62.5%
(95% CI: 54.3–70.8)
Crizotinib: 45.5%
(95% CI: 33.6–57.4)

4y OS: 66%



Treatment	Deaths, no. pts (%)	3-year OS, % (95% CI)	4-year OS, % (95% CI)
Brigatinib (n=137)	41 (30)	71% (67–78)	66% (56–74)
Crizotinib (n=138)	51 (37)	68% (59–75)	60% (51–68)

Cross-trial comparisons have significant limitations. This information is presented in order to generate discussion, not to make comparisons between study results.

Mok T and Peters S, et al. *Ann Oncol* 2020;31:1056-1064.
J Thorac Oncol. 2021 Dec;16(12):2091-2108

Penetrate the blood-brain barrier

Physicochemical and pharmacological characteristics of selected molecularly targeted agents for leptomeningeal metastasis from NSCLC[2]

	Target	MW	Substrate for efflux transport	IC_{50}* (main target)	CSF level	CSF:IC_{50}	Penetration (CSF/ plasma or CSF/blood)
Crizotinib	ALK, MET, ROS1	450	Yes	4.5 nM	0.617 ng/mL (0.14 nM)	0.03	0.26%
Ceritinib	ALK, ROS1	558	Yes	0.15 nM			15%
Alectinib	ALK, RET	483	No	1.9 nM	2.69 nM	1.4	63% to 94%
Brigatinib	ALK, ROS1, EGFR	529	Yes	0.62 nM			
Lorlatinib	ALK, ROS1	406	Yes, but low tendency	< 0.07 nM	2.64 - 125 ng/mL (6.5 - 308 nM)	> 92.7	31% to 96%

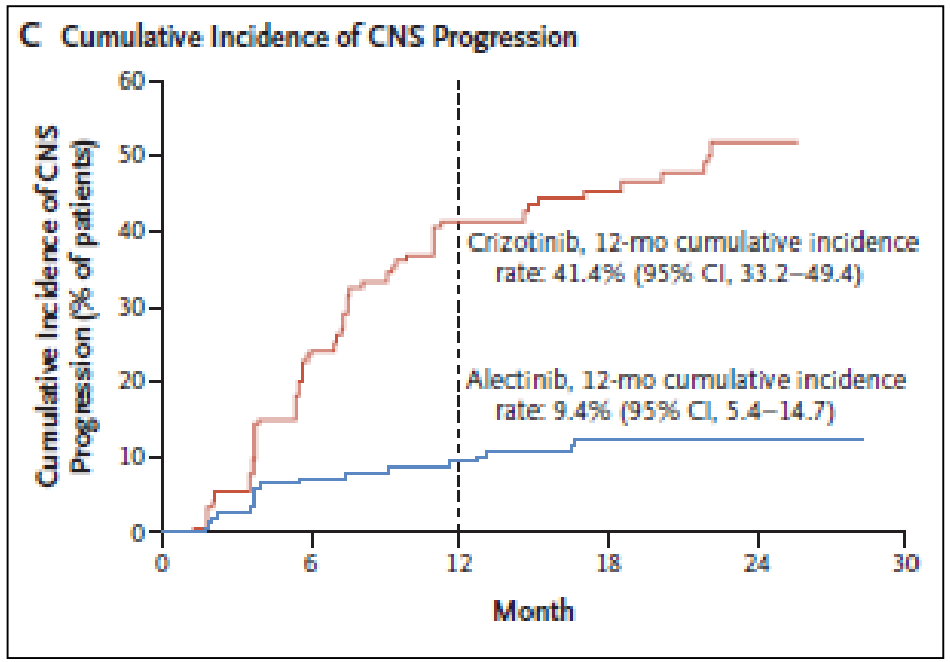
ALK, anaplastic lymphoma kinase; CSF, cerebrospinal fluid; EGFR, epidermal growth factor receptor; IC_{50}, half maximal inhibitory concentrations; MET, mesenchymal-epithelial transition; MW, molecular weight; ND, no data; NSCLC, non-small cell lung cancer; RET, rearranged during transfection; ROS1, c-ros oncogene 1 receptor tyrosine kinase.

1. Costa DB, et al. J Clin Oncol. 2011;29(15):e443-e445. **2.** Cheng H, Perez-Soler R. Lancet Oncol. 2018;19(1):e43-e55.

CNS efficacy
ALEX vs ALTA1

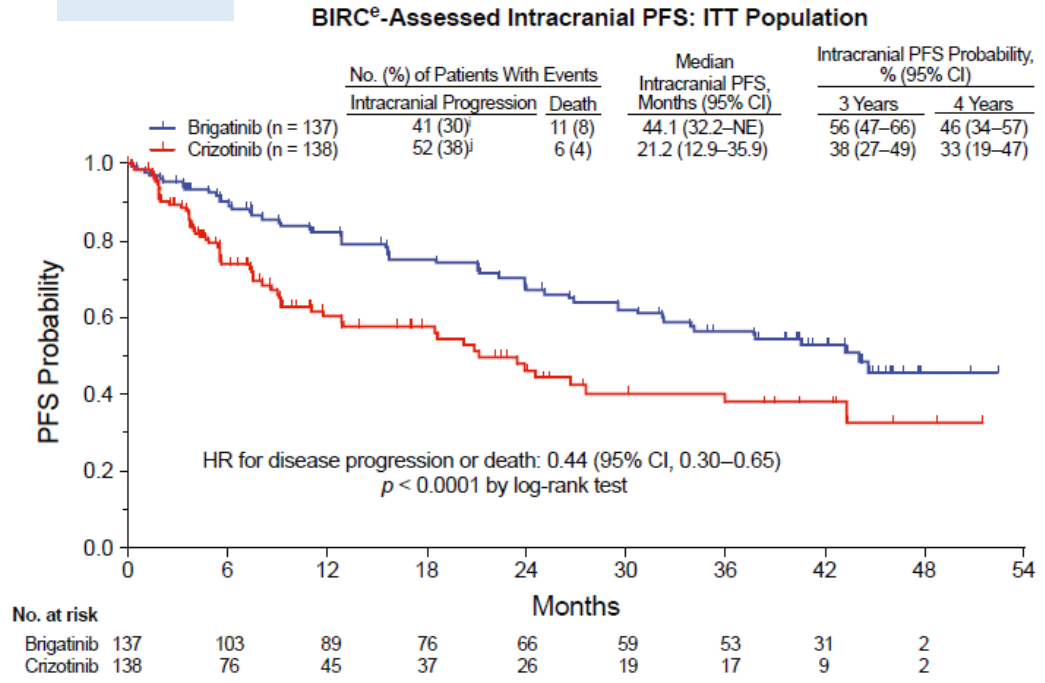
1y CNS PD rate: 9.4%

ALEX



4y CNS PD rate: 54%

ALTA-1



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J Thorac Oncol. 2021 Dec;16(12):2091-2108

Emergent evidence of Lorlatinib, a 3rd generation ALK-TKI

Lorlatinib vs Crizotinib in Treatment-Naive Patients With Advanced *ALK*+ Non-Small Cell Lung Cancer: 5-Year Progression-Free Survival and Safety From the CROWN Study

Benjamin J. Solomon,[1] Geoffrey Liu,[2] Enriqueta Felip,[3] Tony S. K. Mok,[4] Ross A. Soo,[5] Julien Mazieres,[6] Alice T. Shaw,[7] Filippo de Marinis,[8] Yasushi Goto,[9] Yi-Long Wu,[10] Dong-Wan Kim,[11] Jean-François Martini,[12] Rossella Messina,[13] Jolanda Paolini,[13] Anna Polli,[13] Despina Thomaidou,[14] Francesca Toffalorio,[13] Todd M. Bauer[15]

[1]Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [2]Princess Margaret Cancer Centre, Toronto, ON, Canada; [3]Vall d' Hebron University Hospital and Vall d' Hebron Institute of Oncology, Barcelona, Spain; [4]State Key Laboratory of Translational Oncology, Chinese University of Hong Kong, Hong Kong; [5]National University Cancer Institute, Singapore; [6]Toulouse University Hospital and Centre de Recherche Cancérologie Toulouse CRCT, INSERM, France; [7]Massachusetts General Hospital Cancer Center, Boston, MA, USA; [8]European Institute of Oncology, IRCCS, Milan, Italy; [9]National Cancer Center Hospital, Tokyo, Japan; [10]Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital and Guangdong Academy of Medical Sciences, Guangdong, China; [11]Seoul National University College of Medicine and Seoul National University Hospital, Seoul, South Korea; [12]Pfizer, La Jolla, CA, USA; [13]Pfizer, Milan, Italy; [14]Pfizer, Athens, Greece; [15]Greco-Hainsworth Centers for Research/Tennessee Oncology, Nashville, TN, USA

Benjamin J. Solomon, MBBS, PhD
Peter MacCallum Cancer Centre, Melbourne, VIC, Australia

Solomon BJ, et al. *J Clin Oncol* 2024;00:1–10 (JCO.24.00581).

Current post hoc analyses at 5 years

Endpoint evaluation by BICR stopped after the 3-year analysis

Key eligibility criteria

- Stage IIIB/IV *ALK*+ NSCLC
- No prior systemic treatment for metastatic disease
- ECOG PS 0-2
- Asymptomatic treated or untreated CNS metastases were permitted
- ≥1 extracranial measurable target lesion (RECIST 1.1) with no prior radiation required

Randomized 1:1 N=296

Lorlatinib 100 mg once daily n=149

Crizotinib 250 mg twice daily n=147

Stratified by:

- Presence of brain metastases (yes vs no)
- Ethnicity (Asian vs non-Asian)

No crossover between treatment arms was permitted

Current analyses

Data cutoff: October 31, 2023

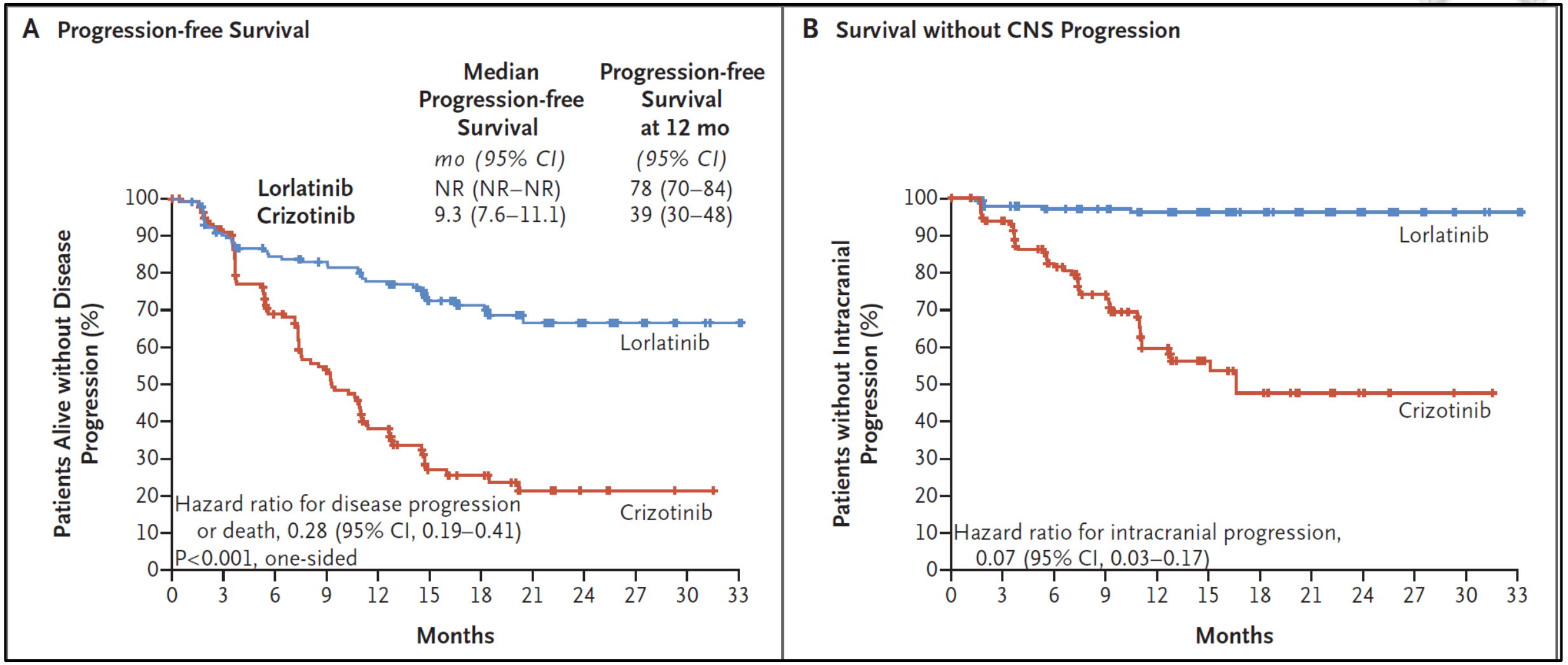
- **Investigator Assessed**
  - PFS[a]
  - ORR and IC ORR
  - DOR and IC DOR
  - IC TTP
- Safety
- Biomarker analyses

- The median duration of follow-up for PFS was 60.2 months (95% CI, 57.4-61.6) in the lorlatinib arm and 55.1 months (95% CI, 36.8-62.5) in the crizotinib arm

CNS, central nervous system; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; IC, intracranial; ORR, objective response rate; NSCLC, non-small cell lung cancer; PFS, progression-free survival; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumors; TTP, time to tumor progression.

[a] Defined as the time from randomization to RECIST-defined progression or death due to any cause.

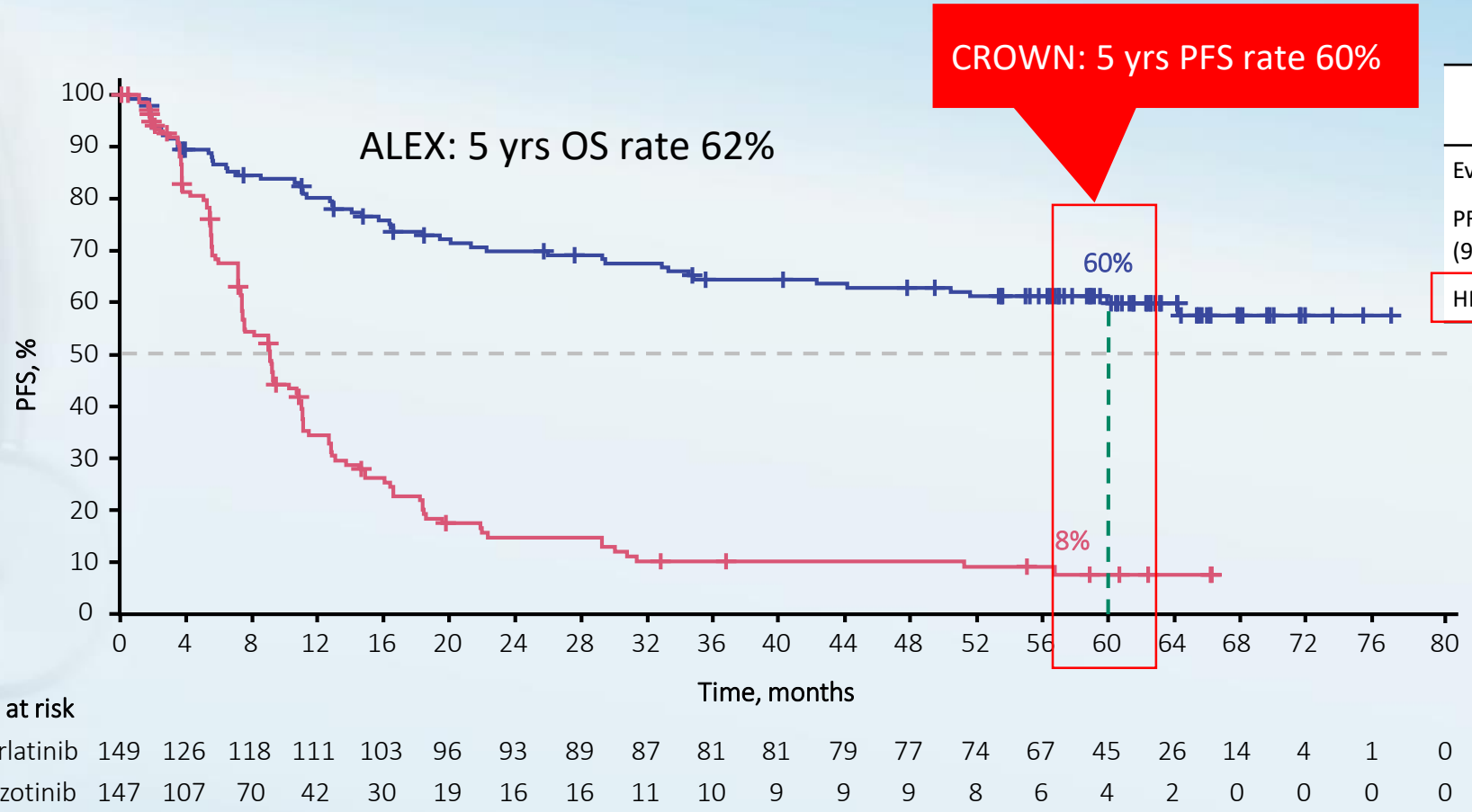
Solomon BJ, et al. *J Clin Oncol* 2024;00:1–10 (JCO.24.00581).



Interim analysis, median follow-up: 18.3 months in the lorlatinib group

Alice T. Shaw, et al. N Engl J Med 2020;383:2018-29.

CROWN study after 60.2 months of median follow-up



	Lorlatinib (n=149)	Crizotinib (n=147)
Events, n	55	115
PFS, median (95% CI), months	NR (64.3-NR)	9.1 (7.4-10.9)
HR (95% CI)	**0.19 (0.13-0.27)**	

At the time of this analysis, the required number of OS events for a protocol-specified second interim analysis **has not been reached**. OS follow up is ongoing

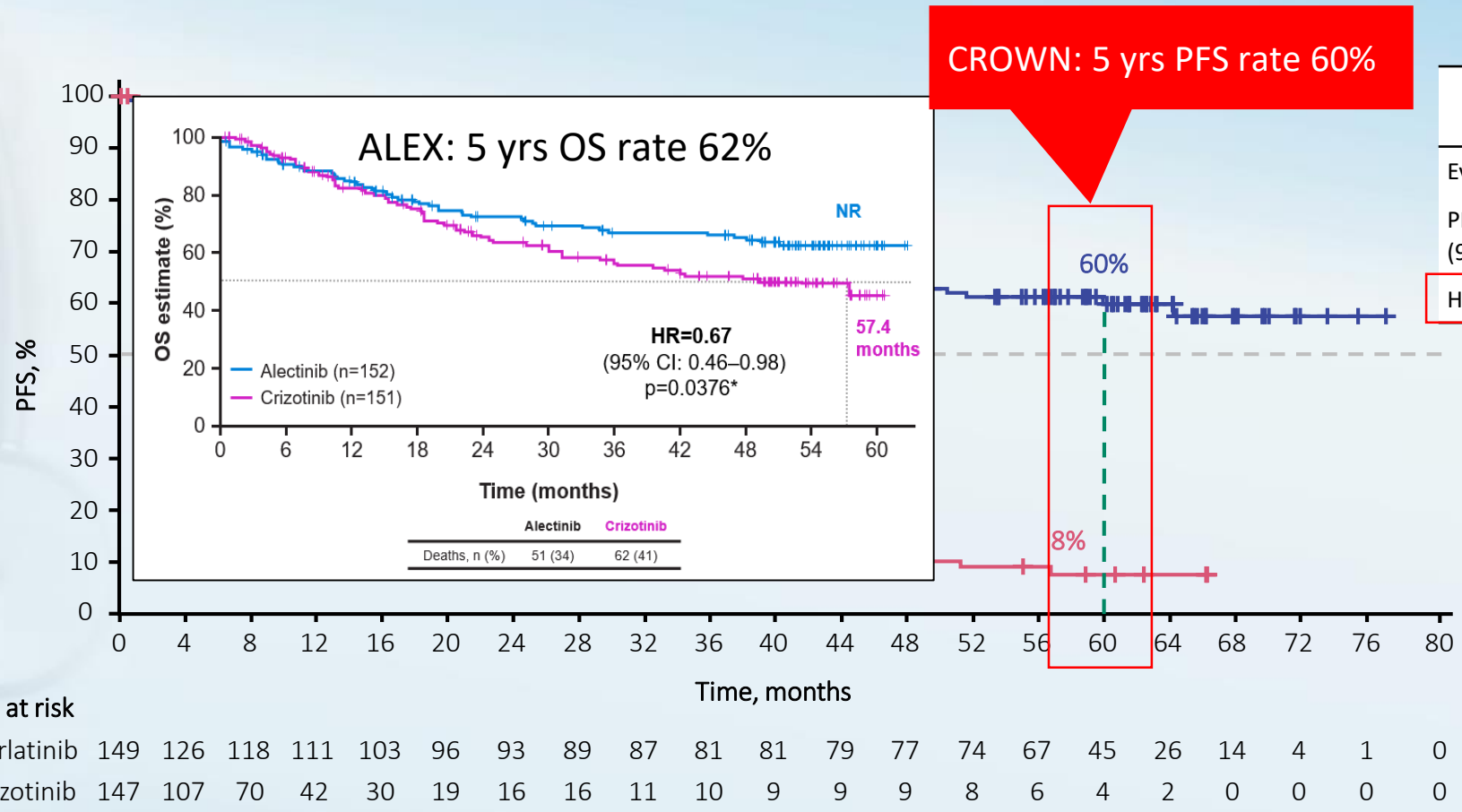
HR, hazard ratio; ITT, intention to treat; NR, not reached; OS, overall survival; PFS, progression-free survival.

Cross-trial comparisons have significant limitations. This information is presented in order to generate discussion, not to make comparisons between study results.

Mok T and Peters S, et al. *Ann Oncol* 2020;31:1056-1064;

Solomon BJ, et al. *J Clin Oncol* 2024;00:1–10 (JCO.24.00581).

CROWN study after 60.2 months of median follow-up



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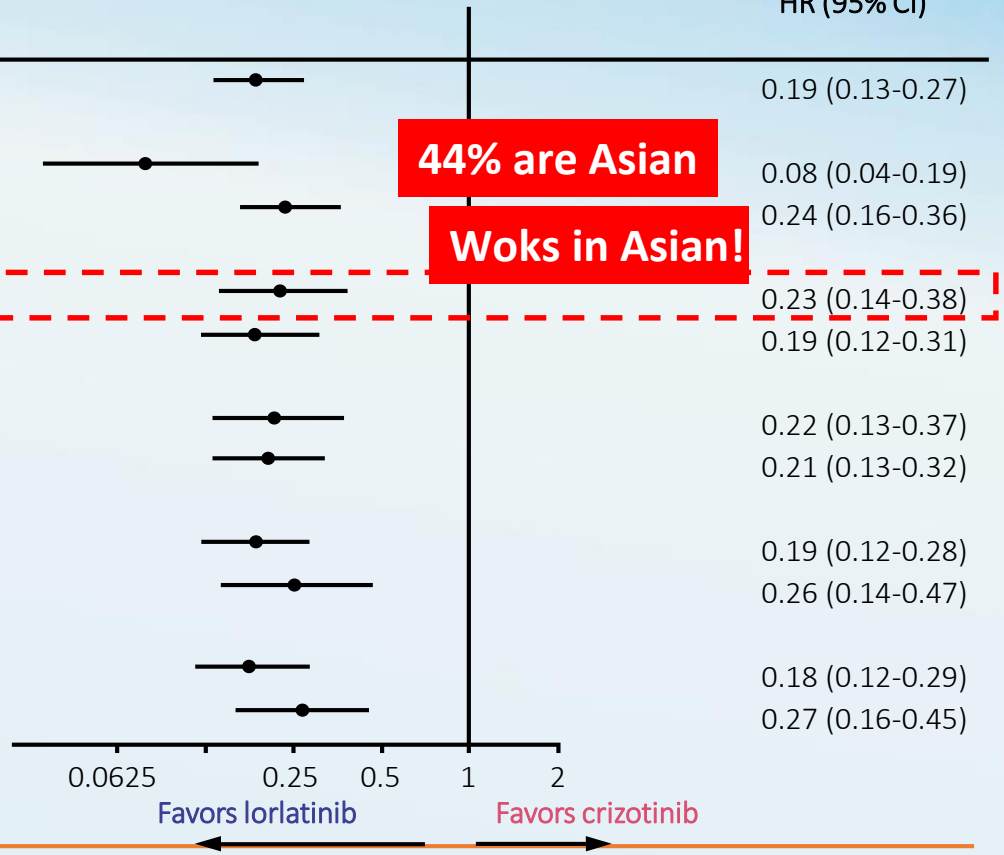
Mok T and Peters S, et al. *Ann Oncol* 2020;31:1056-1064;

Solomon BJ, et al. *J Clin Oncol* 2024;00:1–10 (JCO.24.00581).

PFS benefit with lorlatinib was observed across patient subgroups

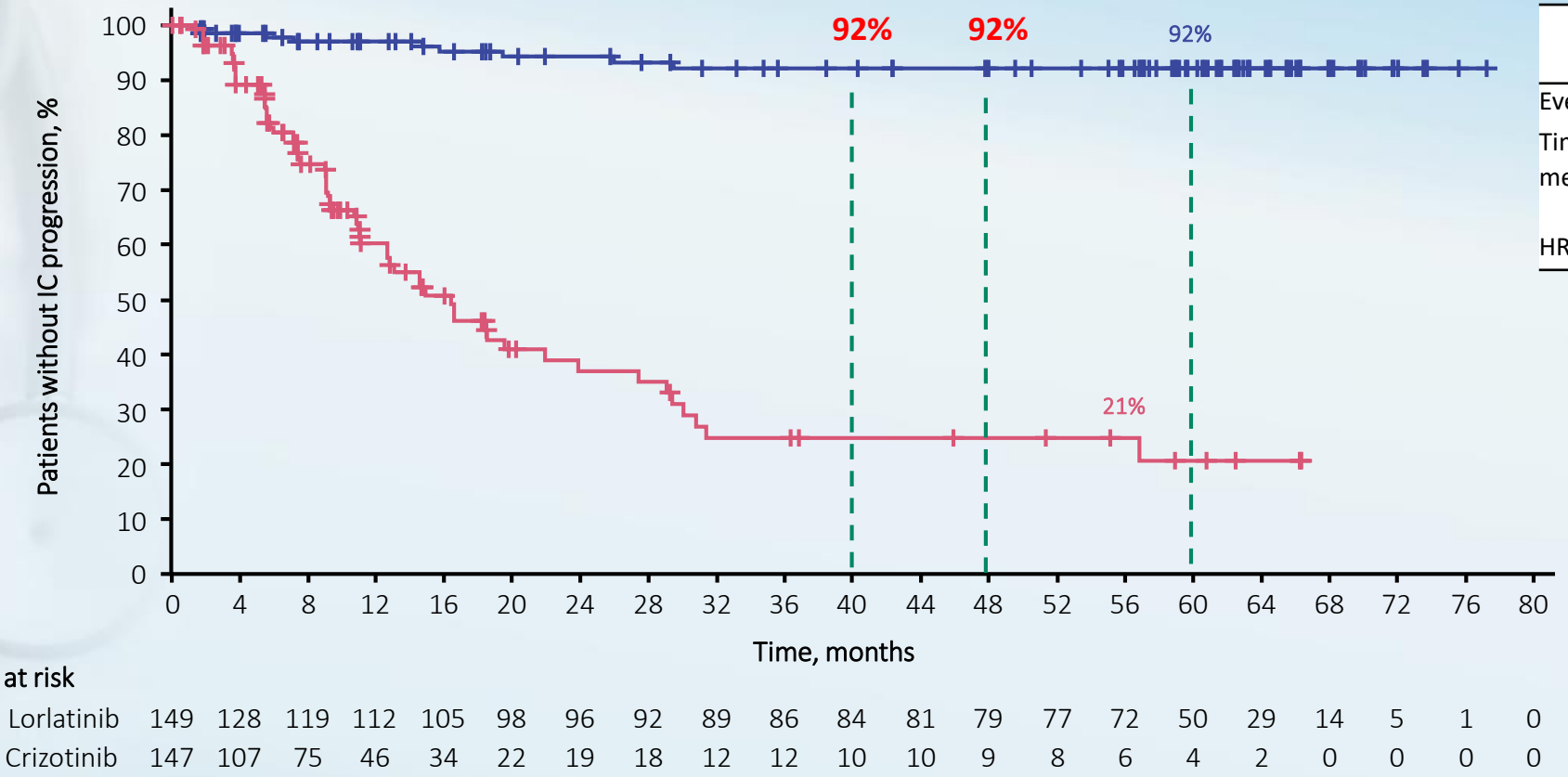
Subgroup	Patients, n (%)		Events, n		HR (95% CI)
	Lorlatinib	Crizotinib	Lorlatinib	Crizotinib	
All patients (stratified)	149 (100)	147 (100)	55	115	0.19 (0.13-0.27)
Presence of brain metastases					
Yes	35 (23)	38 (26)	16	34	0.08 (0.04-0.19)
No	114 (77)	109 (74)	39	81	0.24 (0.16-0.36)
Ethnic origin					
Asian	66 (44)	65 (44)	25	50	0.23 (0.14-0.38)
Non-Asian	83 (56)	82 (56)	30	65	0.19 (0.12-0.31)
Sex					
Male	65 (44)	56 (38)	24	48	0.22 (0.13-0.37)
Female	84 (56)	91 (62)	31	67	0.21 (0.13-0.32)
Age					
<65 years	96 (64)	110 (75)	33	88	0.19 (0.12-0.28)
≥65 years	53 (36)	37 (25)	22	27	0.26 (0.14-0.47)
Smoking status					
Never	81 (54)	94 (64)	30	75	0.18 (0.12-0.29)
Current/former	68 (46)	52 (35)	25	39	0.27 (0.16-0.45)



PFS, progression-free survival.

Solomon BJ, et al. *J Clin Oncol* 2024;00:1–10 (JCO.24.00581).

Time to CNS progression (overall patients)



	Lorlatinib (n=149)	Crizotinib (n=147)
Events, n	9	65
Time to IC progression, median (95% CI), months	NR (NR-NR)	16.4 (12.7-21.9)
HR (95% CI)	0.06 (0.03-0.12)	

Tumor assessments, including brain MRI, have been performed **every 8 weeks in all patients** throughout the study

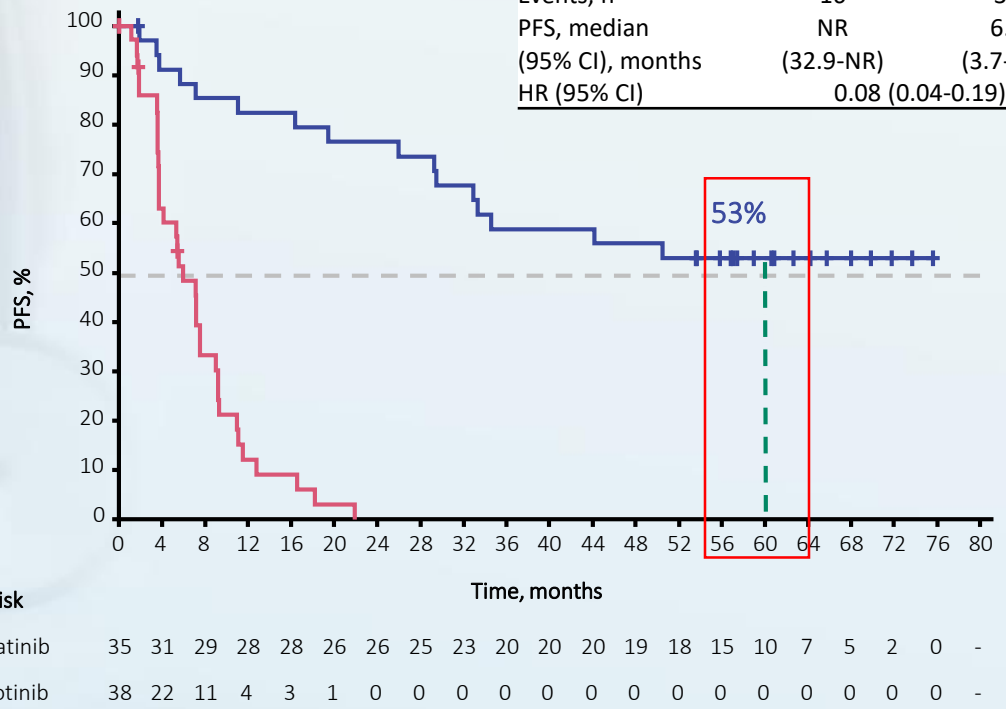
HR, hazard ratio; IC, intracranial; ITT, intention to treat; NR, not reached. MRI, magnetic resonance imaging

Solomon BJ, et al. *J Clin Oncol* 2024;00:1–10 (JCO.24.00581).

PFS benefit in the presence or absence of brain metastases at baseline

With Baseline Brain Metastases

	Lorlatinib (n=35)	Crizotinib (n=38)
Events, n	16	34
PFS, median	NR	6.0
(95% CI), months	(32.9-NR)	(3.7-7.6)
HR (95% CI)	0.08 (0.04-0.19)	

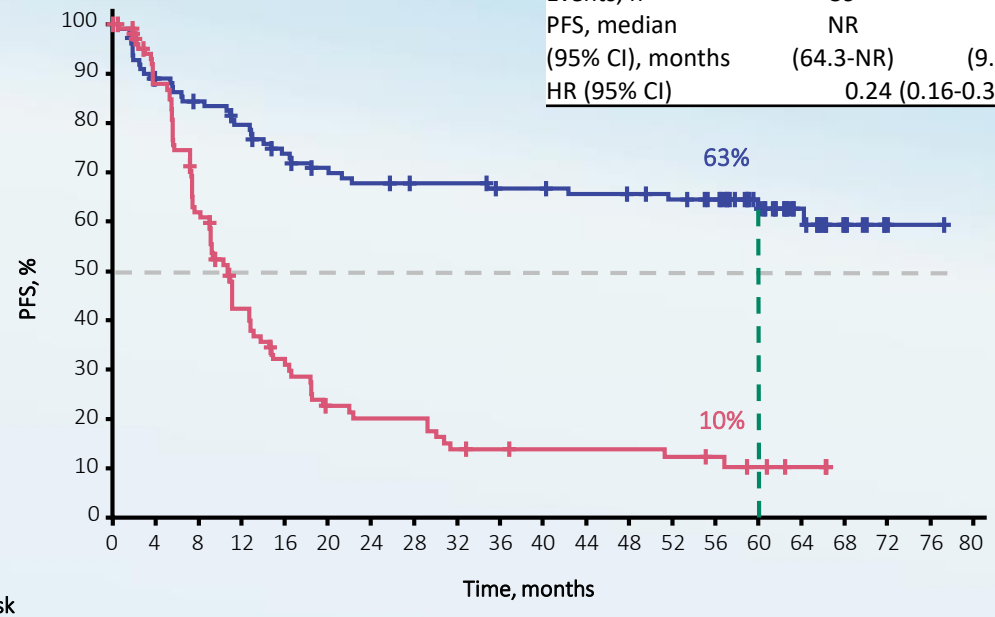


No. at risk

Lorlatinib	35	31	29	28	28	26	26	25	23	20	20	20	19	18	15	10	7	5	2	0	-
Crizotinib	38	22	11	4	3	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-

Without Baseline Brain Metastases

	Lorlatinib (n=114)	Crizotinib (n=109)
Events, n	39	81
PFS, median	NR	10.8
(95% CI), months	(64.3-NR)	(9.0-12.8)
HR (95% CI)	0.24 (0.16-0.36)	



No. at risk

Lorlatinib	114	95	89	83	75	70	67	64	64	61	61	59	58	56	52	35	19	9	2	1	0
Crizotinib	109	85	59	38	27	18	16	16	11	10	9	9	9	8	6	4	2	0	0	0	0

HR, hazard ratio; NR, not reached; PFS, progression-free survival.

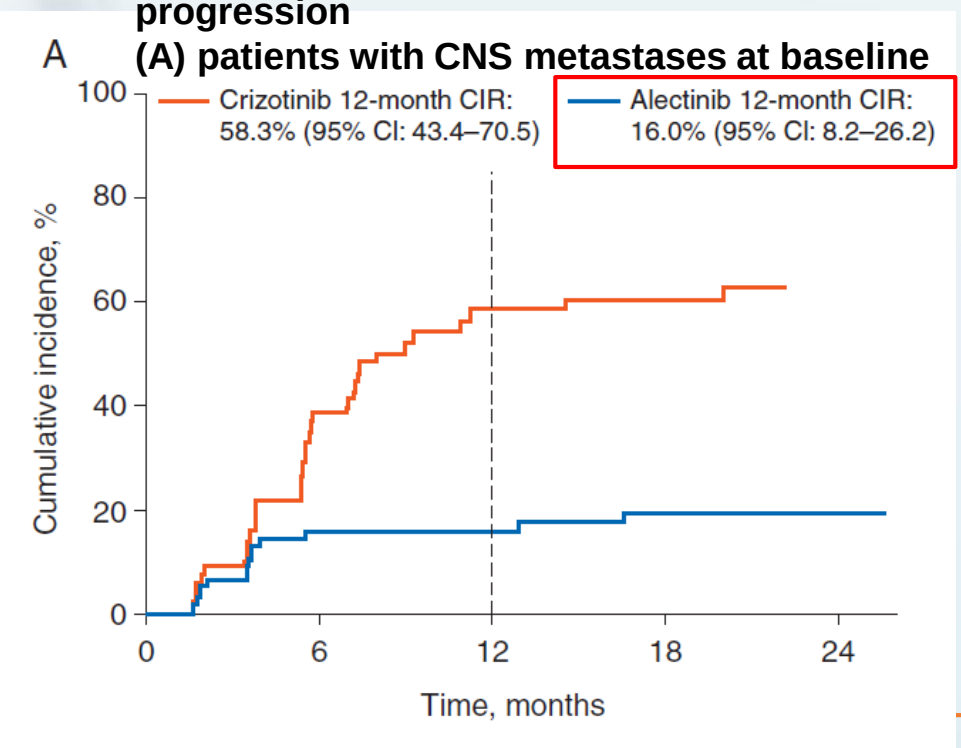
Solomon BJ, et al. *J Clin Oncol* 2024;00:1–10 (JCO.24.00581).

What about patients with CNS at baseline ? CNS PD Rate

ALEX Study – CNS PD rate

在原本有腦轉移的病人中, 1年顱內累積惡化率16%

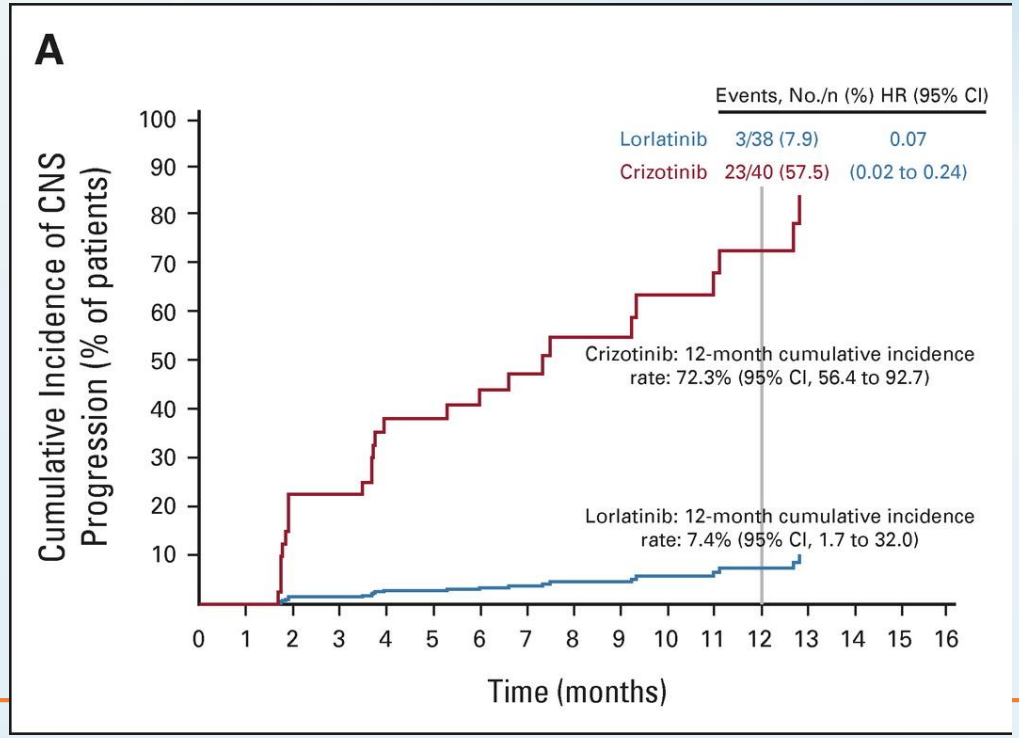
Cumulative incidence rate (CIR) of CNS progression
(A) patients with CNS metastases at baseline



Annals of Oncology 29: 2214–2222, 2018

CROWN Study – CNS PD rate

在原本有腦轉移的病人中, 1年顱內累積惡化率7.4%



Solomon BJ, et al. *J Clin Oncol* 2024;00:1–10 (JCO.24.00581).

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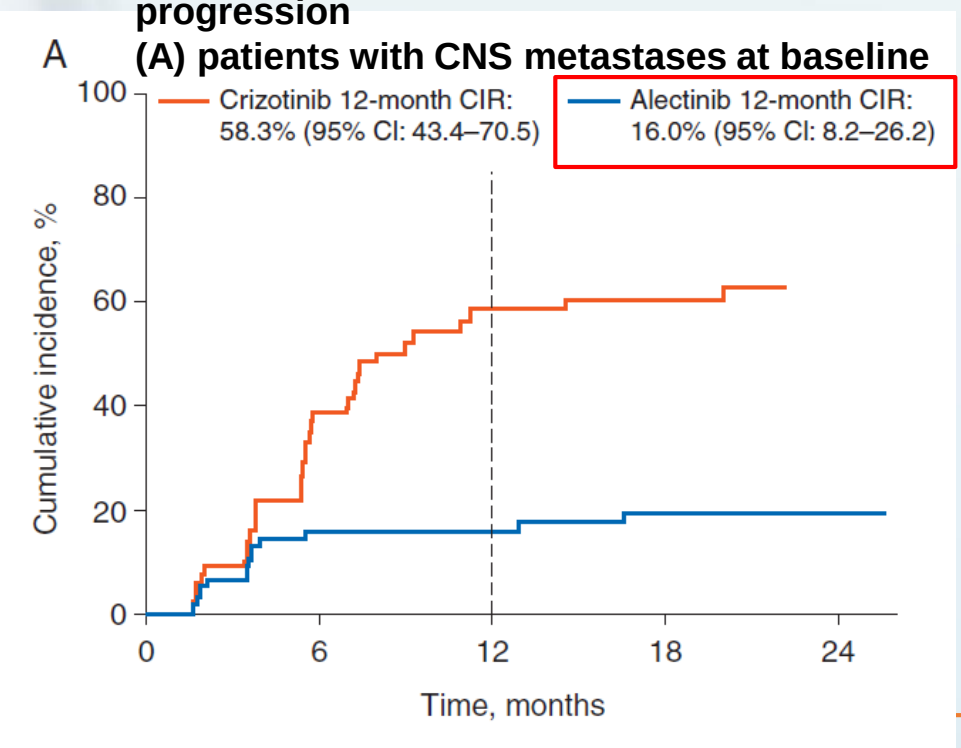
What about patients with CNS at baseline ? CNS PD Rate

ALEX Study – CNS PD rate

在原本有腦轉移的病人中, 1年顱內累積惡化率16%

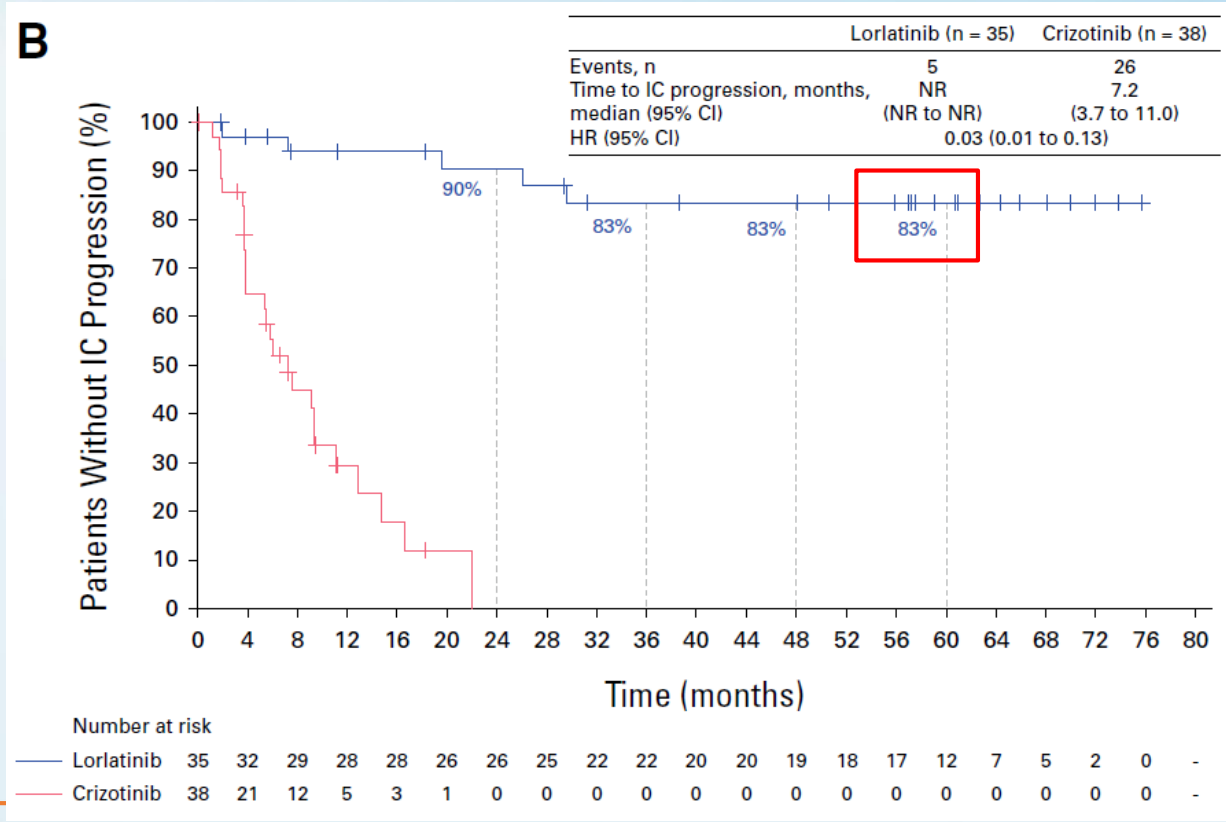
Cumulative incidence rate (CIR) of CNS progression
(A) patients with CNS metastases at baseline



Annals of Oncology 29: 2214–2222, 2018

CROWN Study – CNS PD rate

在原本有腦轉移的病人中, 5年顱內累積惡化率17%



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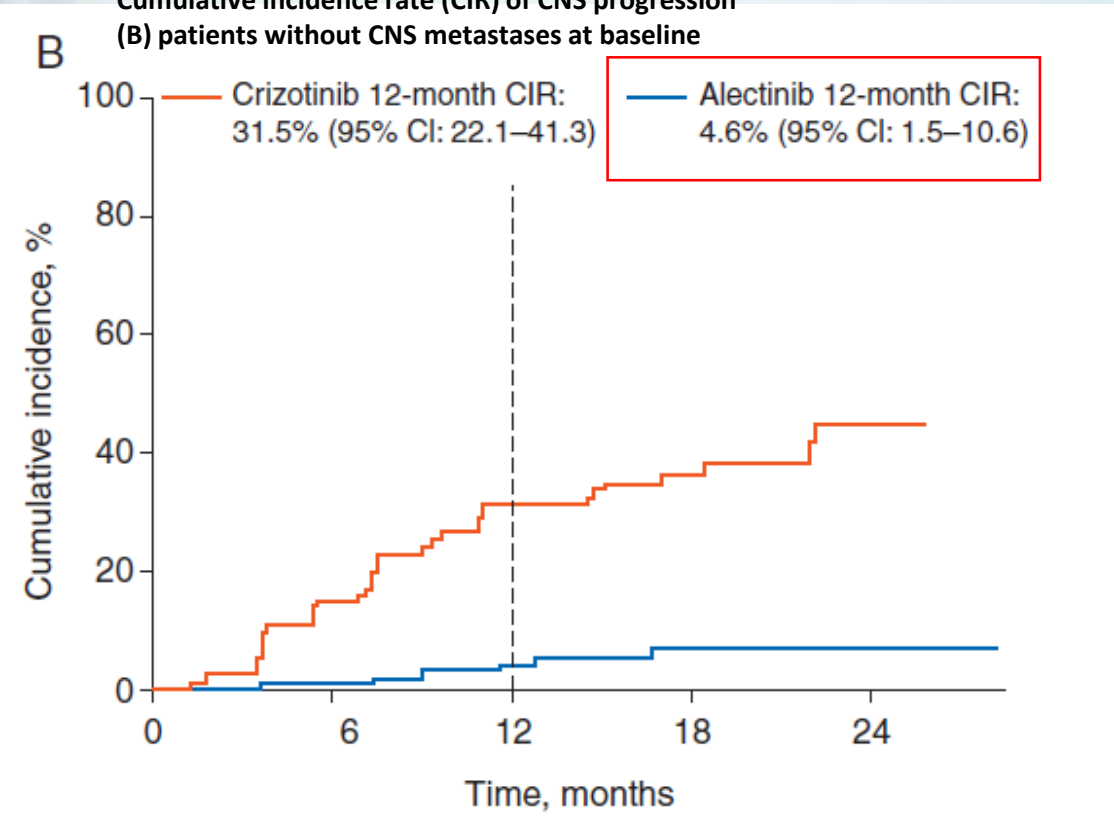
Time to IC progression was longer with lorlatinib in absence of baseline brain metastases

ALEX Study – CNS PD rate

在原本無腦轉移的病人中, 1年顱內累積惡化率4.6%

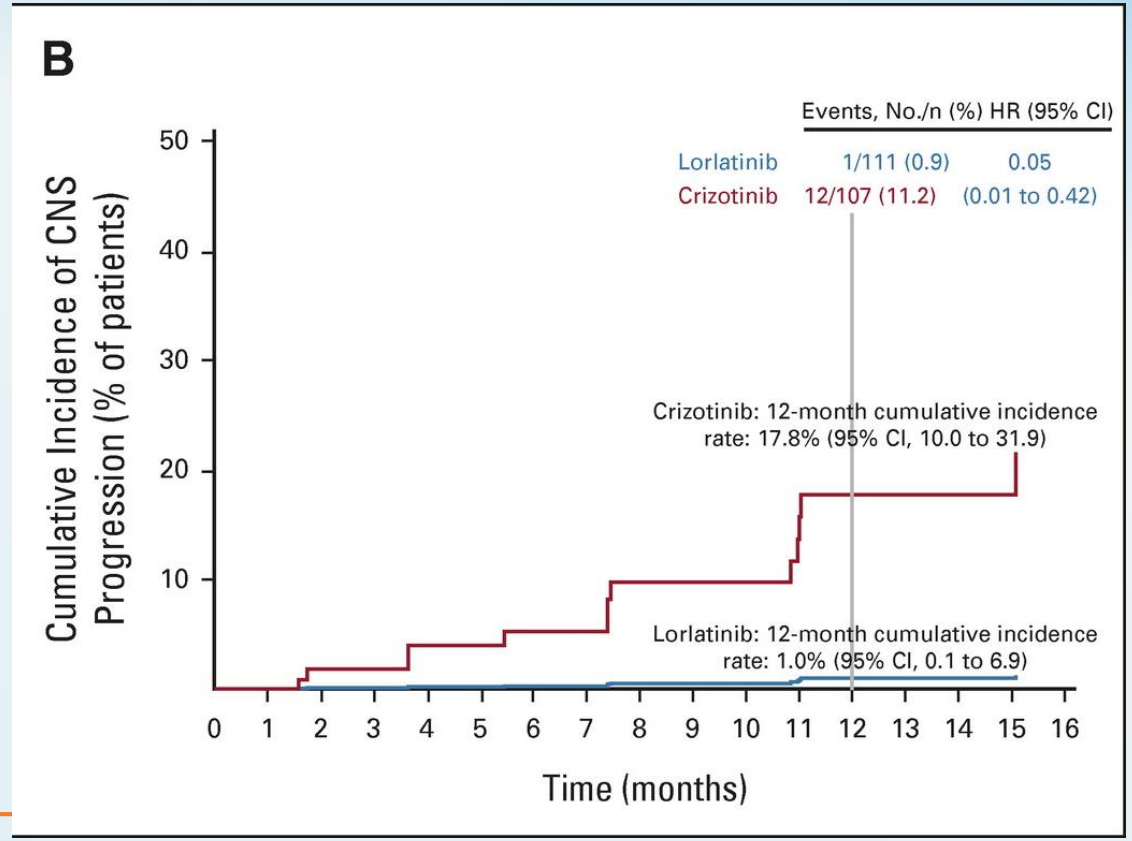
Cumulative incidence rate (CIR) of CNS progression
(B) patients without CNS metastases at baseline



Annals of Oncology 29: 2214–2222, 2018

CROWN Study – CNS PD rate (Non-BM)

在原本無腦轉移的病人中, 1年顱內累積惡化率1.0%



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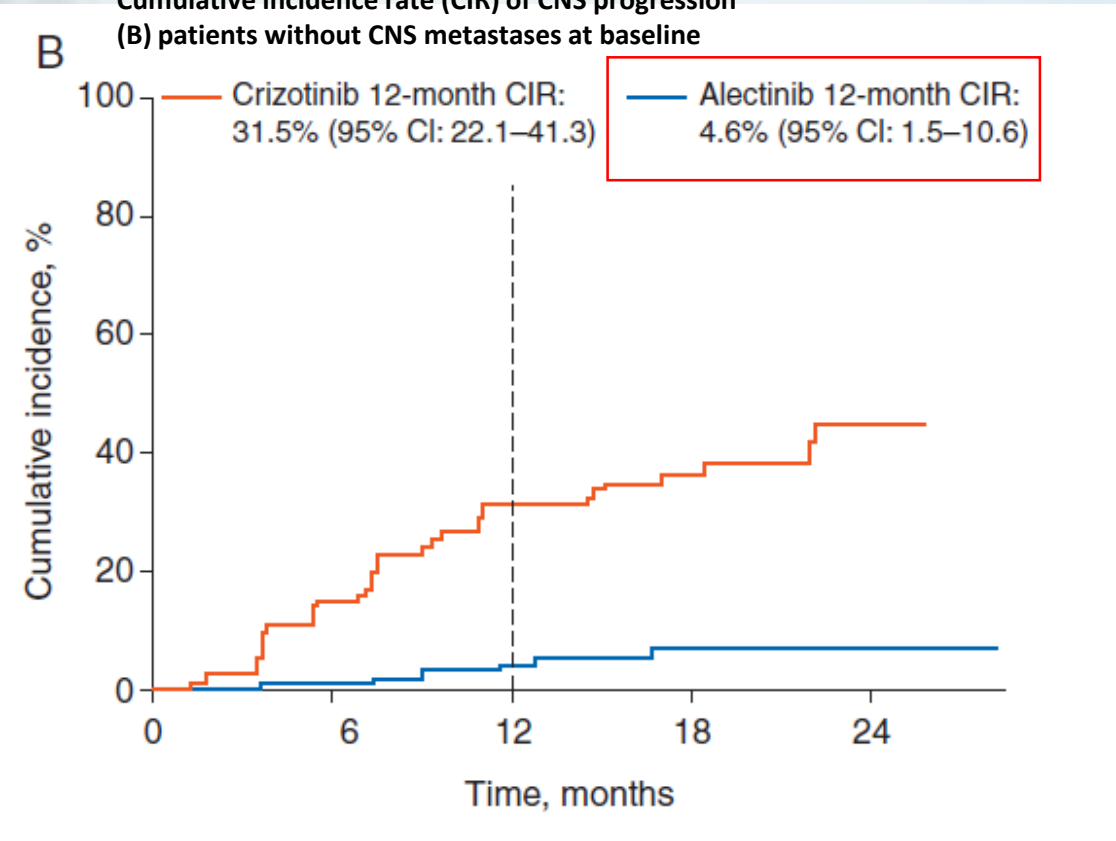
Time to IC progression was longer with lorlatinib in absence of baseline brain metastases

ALEX Study – CNS PD rate

在原本無腦轉移的病人中, 1年顱內累積惡化率4.6%

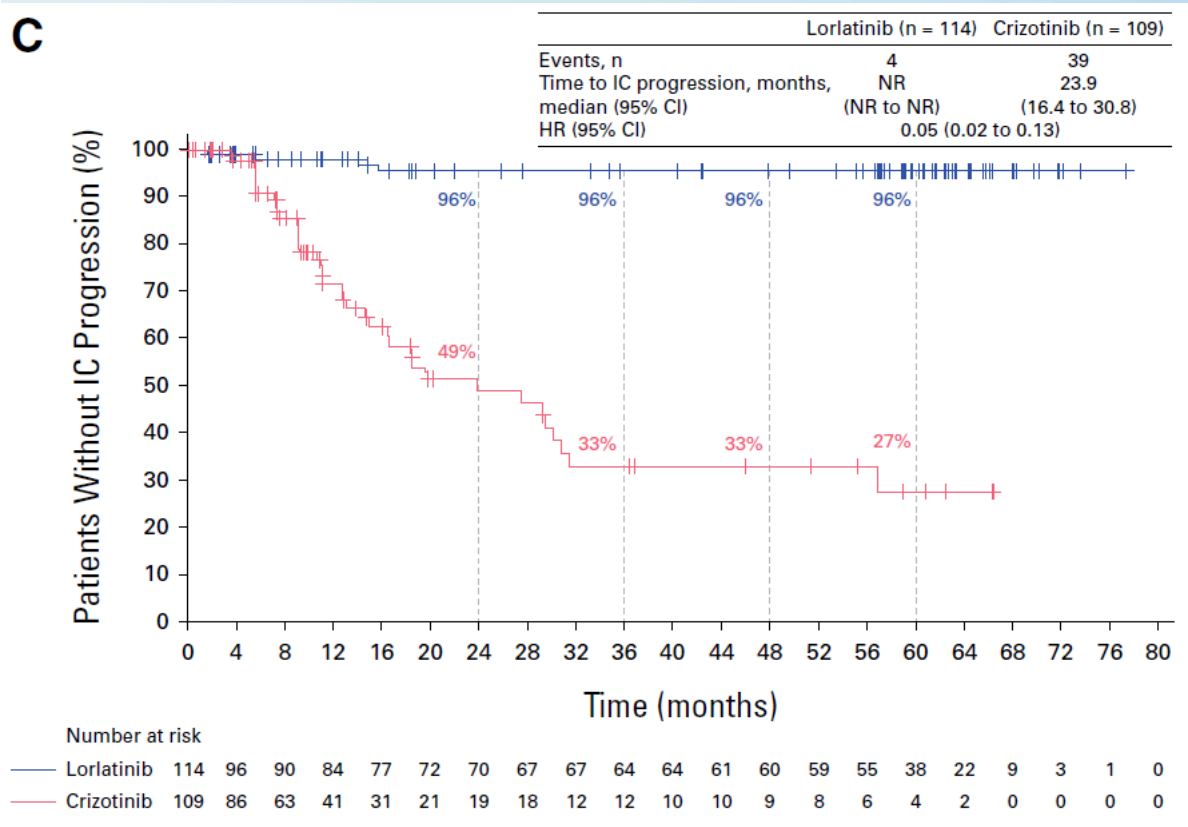
Cumulative incidence rate (CIR) of CNS progression
(B) patients without CNS metastases at baseline



Annals of Oncology 29: 2214–2222, 2018

CROWN Study – CNS PD rate (Non-BM)

在原本無腦轉移的病人中, 5年顱內累積惡化率4%



Solomon BJ, et al. *J Clin Oncol* 2024;00:1–10 (JCO.24.00581).

Cross-trial comparisons have significant limitations. This information is presented in order to generate discussion, not to make comparisons between study results.

Discussion in CROWN Study

	G-ALEX	ALTA-1L	eXalt3	CROWN
Study drug (control:crizotinib)	alectinib	brigatinib	ensartinib	lorlatinib
Response rate	82.9% (75.5%)	71% (60%)	75% (67%)	76% (58%)
mPFS (mo)	25.7 (10.4)	24	25.8	NS (9.3)
mPFS Hazard ratio	0.50	0.49	0.51	0.28
Survival at 12 mo	68.4% (48.7%)	67% (43%)	-	78% (39%)
Intracranial response rate	38%	28%	27%	82%
AE > Gr 3	45% (c:51%)	73% (c:61%)	-	72% (c:56%)
Median follow up (mo)	18.6	11.0	23.8	18.3
Publication	NEJM 2017	NEJM 2018	Abstract	NEJM 2020

Alice T. Shaw, et al. N Engl J Med 2020;383:2018-29.

Comparison of ALK inhibitor clinical trials

Trail	PROFILE 1014	ASCEND-4	G-ALEX	ALTA-1L	CROWN
ALK inhibitor	**Crizotinib** 250mg BID (n=172)	**Ceritinib** 750mg QD (n=189)	**Alectinib** 600mg BID (n=152)	**Brigatinib** 250mg BID (n=137)	**Lorlatinib** 100mg BID (n=149)
Control	Platinum-based chemotherapy (n=171)	Platinum-based chemotherapy (n=187)	Crizotinib (n=151)	Crizotinib (n=138)	Crizotonib (n= 147)
Response rate (%)	**74** vs **45**	**72.5** vs **26.7**	**82.9** vs **75.5**	**71** vs **60**	**76** vs **58**
Median PFS (months)	**10.9** vs **7.0** (HR 0.45)	**16.6** vs **8.1** (HR 0.55)	**34.8** vs **10.9** (HR 0.43)	**NR** vs **9.8** (HR 0.49)	**NR** vs **9.3** (HR 0.28)
Median OS (months)	**NR** vs **47.5** (HR 0.76, 95% CI 0.548–1.05; p=0.0978)	**NR** vs **26.2** (HR 0.73, 95% CI 0.5–1.08; p=0.056)	**NR** vs **57.4** (HR 0.67, 95% CI 0.46–0.98; p=0.0376)	–	–
PFS in pts with CNS meta (months)	**9.0** vs **4.0** (**HR 0.40**, 95% CI 0.23 – 0.69)	**10.7** vs **6.7** (**HR 0.70**, 95% CI 0.44–1.12)	**25.4** vs **7.4** (**HR 0.37**, 95% CI 0.25–0.58)	**24** vs **5.6** (**HR 0.31**, 95% CI 0.17–0.56)	–
PFS in pts w/o CNS meta (months)	**11.1** vs **7.2** (**HR 0.51**, 95% CI 0.38 – 0.69)	**26.3** vs **8.3** (**HR 0.48**, 95% CI 0.33–0.69)	**38.6** vs **14.8** (**HR 0.46**, 95% CI 0.33–0.80)	**32.3** vs **NR** (**HR 0.78**, 95% CI 0.41–1.48)	–
mF/u	**45.7 mo**	-	**48.2 mo**	**11.0 mo**	**60.2 mo**

ALK-TKI (Lorlatinib)
side/adverse effects and management

Toxicity Profiles of ALK TKIs

	Crizotinib[1]	Ceritinib[a,2]	Alectinib[3]	Brigatinib[b,4]
Common AEs: All grades	Vision disorder 71% ↑ALT 79% ↑AST 66% Diarrhea 61% Nausea 56% Edema 49% Vomiting 46% Constipation 43% Upper respiratory infection 32% ↓Appetite 30% Fatigue 29% Neuropathy 21% Dizziness 18%	Diarrhea 85% Nausea 69% Vomiting 67% Fatigue 45% Abdominal pain 40% ↓Appetite 34% Weight loss 24%	Anemia 62% Constipation 34% Fatigue 26% Myalgia 23% Edema 22%	Nausea 40% Diarrhea 38% Fatigue 36% Cough 34% Headache 27%
Grade 3-4 AEs / laboratory abnormalities (≥3%)	Neutropenia 11% Lymphopenia 7% Hypophosphatemia 10% ↑ALT 15% ↑AST 8%	Fatigue 7% Vomiting 5% Diarrhea 4.8% Anemia 4.2% Abdominal pain 3.7% Weight loss 3.7% ↑GGT 49% ↑ALT 34% ↑AST 21% ↑ALP 12% Hyperglycemia 10% ↑Amylase 8% ↑Lipase 6% ↑Creatinine 4.2% ↓Phosphate 3.7%	Anemia 7% ↑ALT 6% ↑AST 6% Hyperbilirubinemia 5% ↑Creatinine 4.1%	↑CPK 12% Hypertension 6.4% Pneumonia 5.5%[c] ↑Lipase 5.5% Lymphopenia 4.5% Hyperglycemia 3.6% ↓Phosphorous 3.6%

Indirect comparison for illustration only; clinical significance is not implied. Cross-trial comparisons are potentially confounded by differences in trial design and study population.

[a]Values reported for 750 mg fasted; [b]180 mg once daily with a 7-day lead in at 90 mg; [c]Includes one grade 5 event.

1. Xalkori (crizotinib) [package insert]. New York, NY: Pfizer Inc; 2018. 2. Zykadia (ceritinib) [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2017. 3. Alecensa (alectinib) [package insert]. South San Francisco, CA: Genentech USA, Inc; 2017. 4. Alunbrig (brigatinib) [package insert]. Cambridge, MA: Takeda Pharmaceutical Company Limited, USA; 2018.

Safety profile of ALK TKIs

Trail	PROFILE 1014	ASCEND-4	ALEX	ALTA 1L	CROWN
ALK inhibitor	**Crizotinib** 250mg BID (n=172)	**Ceritinib** 750mg QD (n=189)	**Alectinib** 600mg BID (n=152)	**Brigatinib** 250mg BID (n=137)	**Lorlatinib** 100mg BID (n=149)
Comparator	Platinum-based chemotherapy (n=171)	Platinum-based chemotherapy (n=187)	Crizotinib (n=151)	Crizotinib (n=138)	Crizotonib (n= 147)
median duration Of treatment (months)	10.9 vs 4.1	15.3 vs 6.2	28.1 vs 10.8	9.2 vs 7.4	NE vs 9.6
Grade ≥3 AEs	**47%** vs 55% (**liver function** abnormalities)	**78%** vs 62% (**GI toxicity** & liver function abnormalities)	**41%** vs 50% (**liver function** abnormalities)	**61%** vs 55% (**muscle pain**, hypertension)	**72%** vs 56% (**lipid abnormalities**)
AE leading to permanent treatment discontinuation	**12%** vs 14%	**5%** vs 11%	**14.5%** vs 14.6%	**12%** vs 9%	**7%** vs 9%
AE leading to temporally dose interruption or dose reduction	–	80% vs 45%	Dose reduction: 20.4% vs 19.9% Dose interruption: 26.3% vs 26.5%	29% vs 21%	49% vs 47%

Lorlatinib side effects

Hyperlipidemia

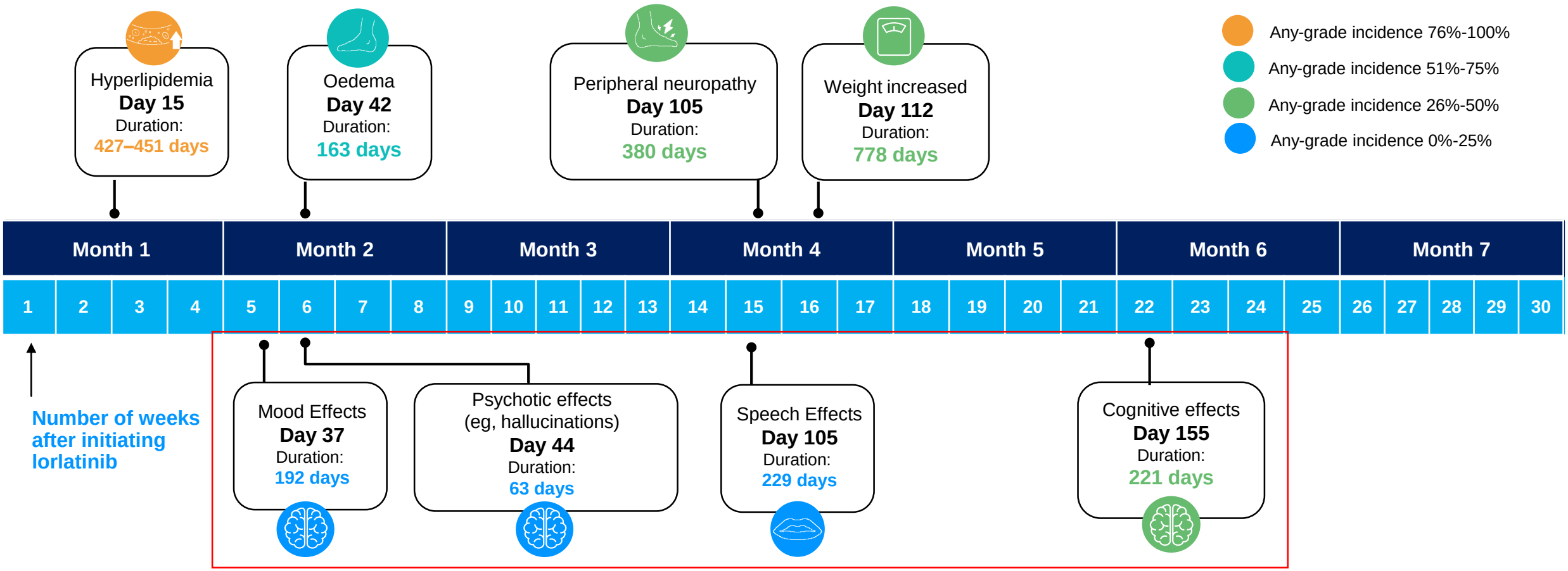
Oedema

Peripheral neuropathy

Weight gain

CNS side effects

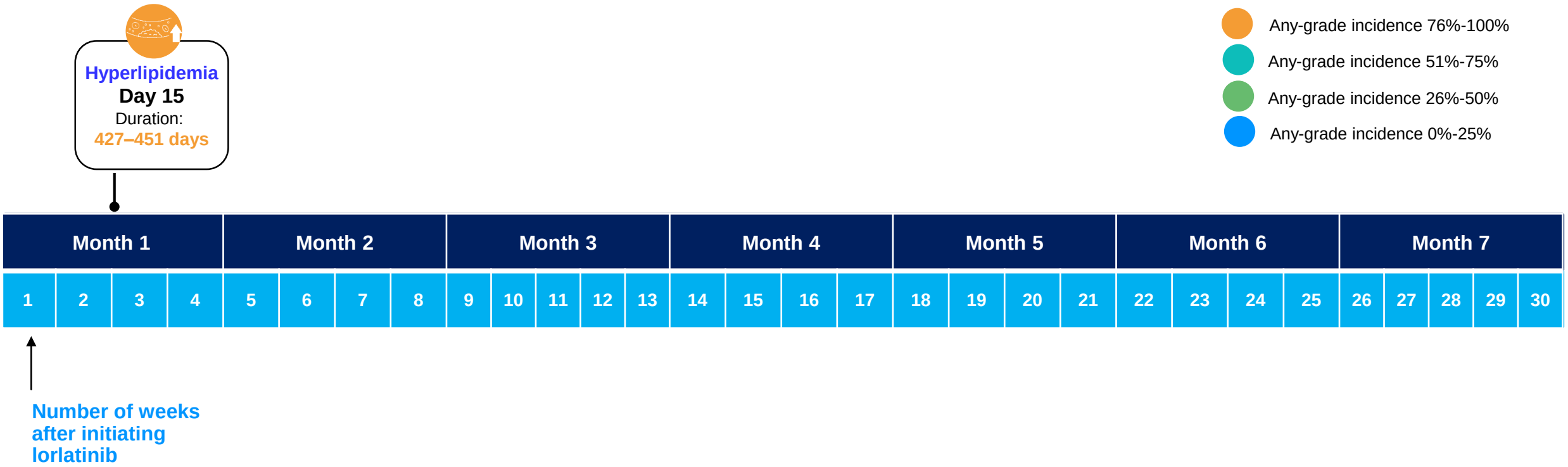
Median time to onset (range) and duration of select adverse reactions with lorlatinib[1]*



*The values listed here represent median time to first occurrence for each AE. There is a distribution in which some may occur earlier or later than these median values.

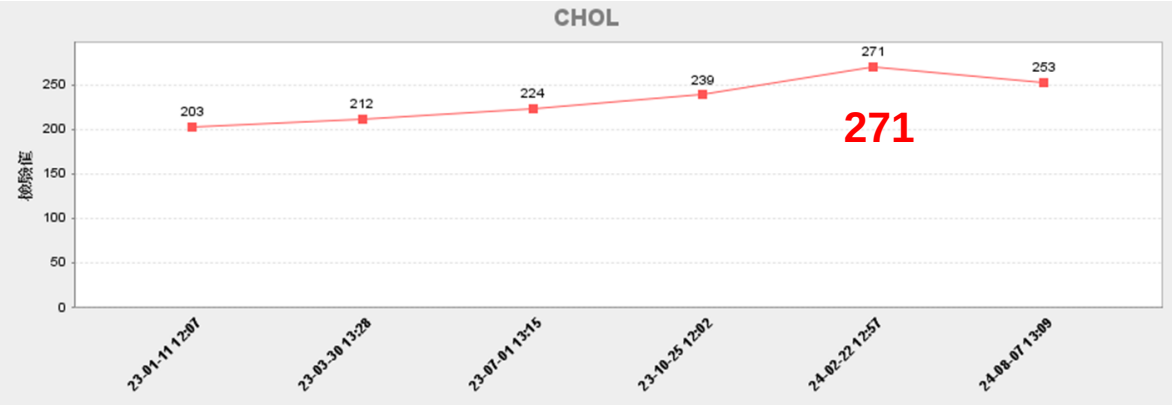
1. Liu G, et al. *Lung Cancer*. 2024;191:107535.

Median time to onset (range) and duration of select adverse reactions with lorlatinib[1]*



*The values listed here represent median time to first occurrence for each AE. There is a distribution in which some may occur earlier or later than these median values.

1. Liu G, et al. *Lung Cancer*. 2024;191:107535.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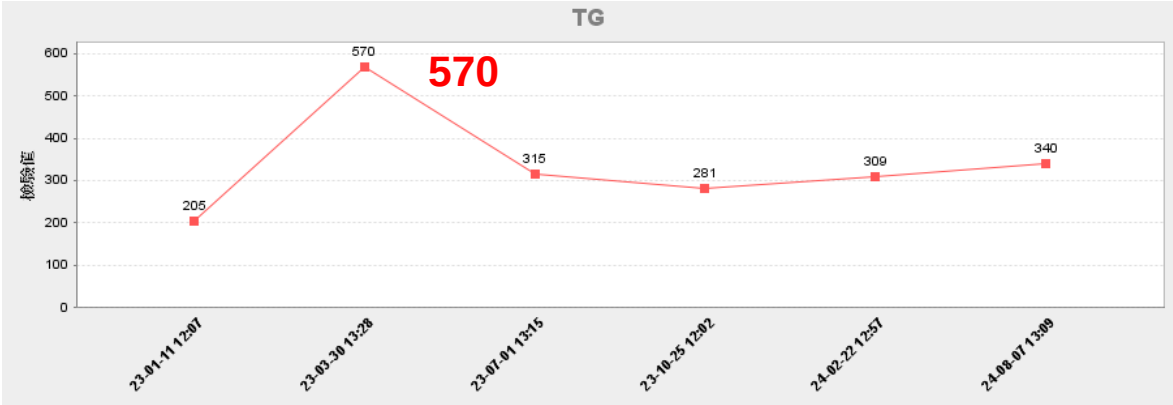
224
239
271
253
271
23-01-11 12:07
23-03-30 13:28
23-07-01 13:15
23-10-25 12:02
24-02-22 12:57
24-08-07 13:09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309
340
570
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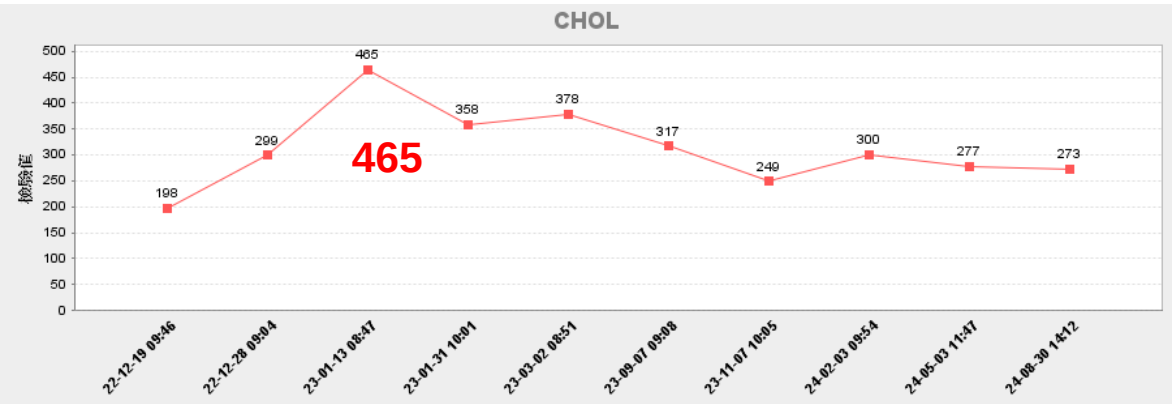
23-03-30 13:28
23-07-01 13:15
23-10-25 12:02
24-02-22 12:57
24-08-07 13:09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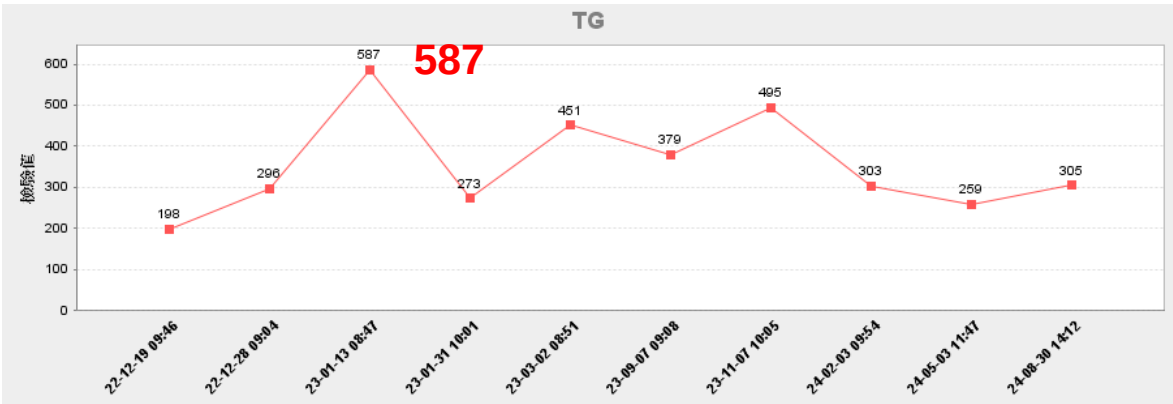
TG
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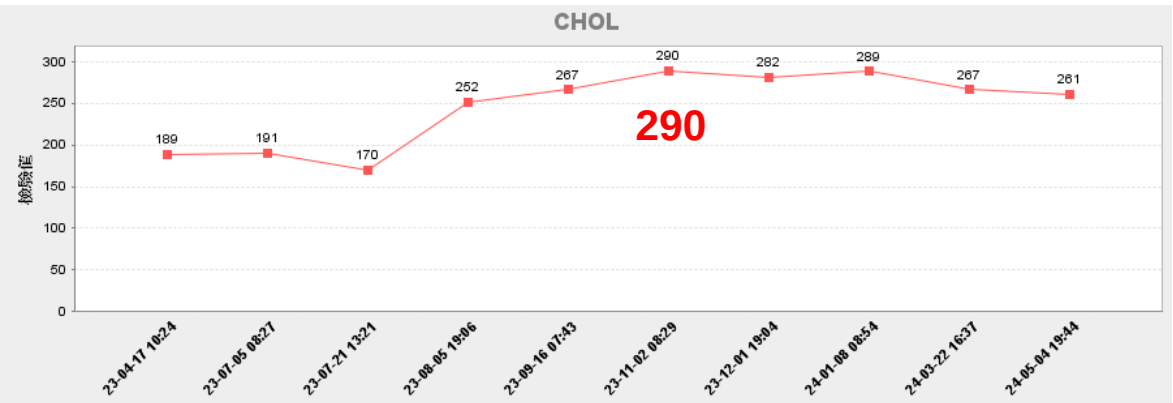
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23-08-05 19:06
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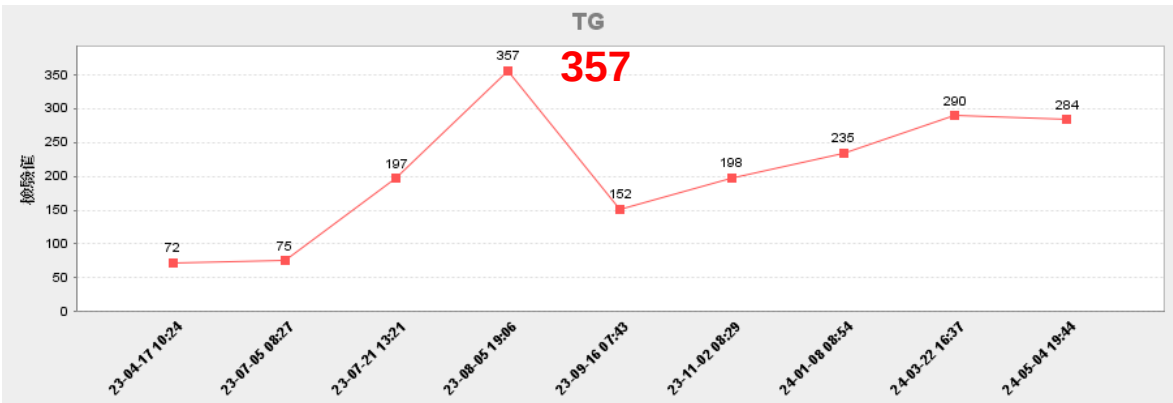
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檢驗值
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198
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290
284
357
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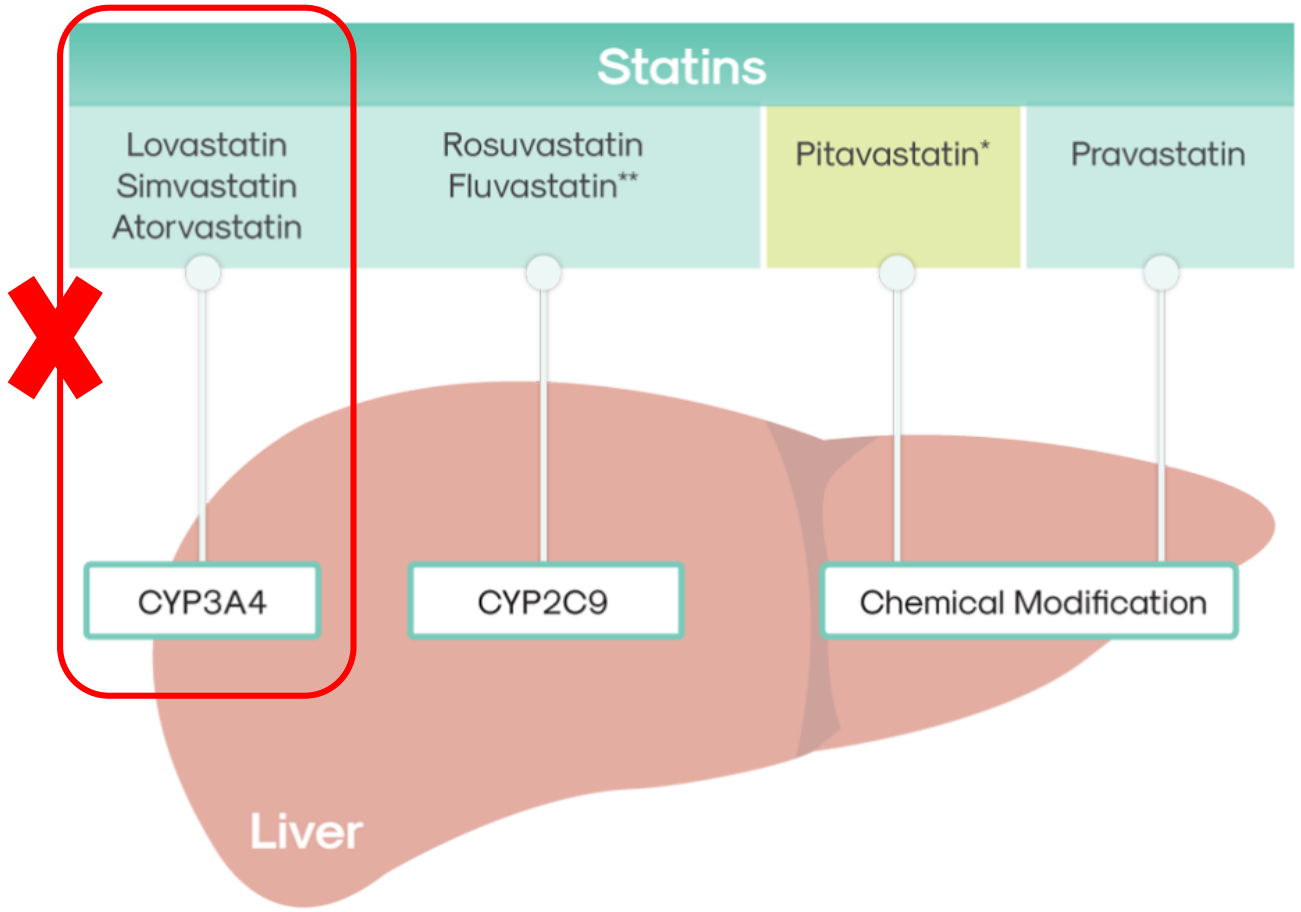
23-07-05 08:27
23-07-21 13:21
23-08-05 19:06
23-09-16 07:43
23-11-02 08:29
24-01-08 08:54
24-03-22 16:37
24-05-04 18:44

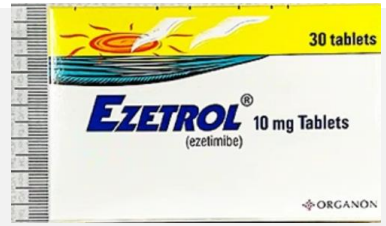
Avoid statin with CYP3A4 pathway because Lorlatinib is both a substrate and inducer of the CYP3A enzyme system



* Pitavastatin is marginally metabolized by CYP2C9 and to a lesser extent by CYP2C8.
** CYP2C9 isoenzyme is primarily involved in the metabolism of fluvastatin (approximately 75%), while CYP2C8 and CYP3A4 isoenzymes are involved to a much less extent, i.e., approximately 5% and approximately 20%, respectively.

https://www.zypitamag.com/metabolism-and-processing

針對血脂相關副作用的處置建議

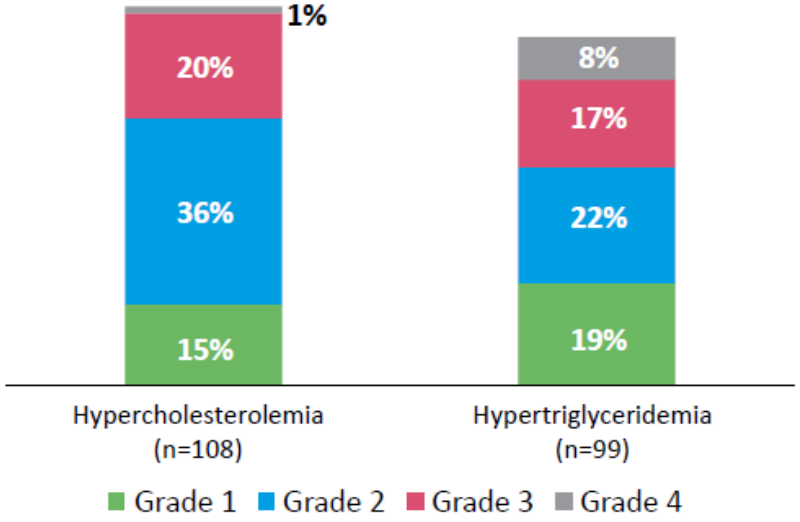
準備	監測 (於第一個月)		定期評估直到情況 穩定/改善
測量血脂 如升高則加入降血脂藥物 **藥物治療** 選擇下列任一藥物: • Pitavastatin (1 mg QD, max 4mg) • Pravastatin (10-40 mg OD, max 40mg) • Rosuvastatin (5 mg QD, max 20mg)	**正常血脂濃度**	▶ 於每次回診時監測血脂濃度	 如果血脂持續未被控制，增加降血脂藥物劑量或加入第二種降血脂藥物 • TG 仍高: 加入Fenofibrate 200mg QD • TC 仍高: 加入Ezetimibe 10mg QD 如已達到降血脂藥的最大劑量，則降低 25 mg Lorlatinib 的治療劑量 ▼
	血脂濃度升高 Total cholesterol (TC) 300-500 mg/dL or triglycerides (TG) 500-1,000 mg/dL	▶ 開始、增加或改變降血脂藥物治療	
	血脂濃度高至危及生命 Total cholesterol (TC) >500 mg/dL or triglycerides (TG) >1,000 mg/dL	⏸ → ▶ 暫停 Lorlatinib 並給予降血脂藥物治療直到 TC恢復至 <400 mg/dL且 TG <500 mg/dL 後，再重新給予 Lorlatinib	

⏸ 暫停: lorlatinib 劑量中斷　▶ 持續: 維持 lorlatinib 劑量　▼ 降低: lorlatinib 劑量降低 (每次降低25mg)

J Clin Oncol . 2024 May 31:JCO2400581. Online ahead of print.

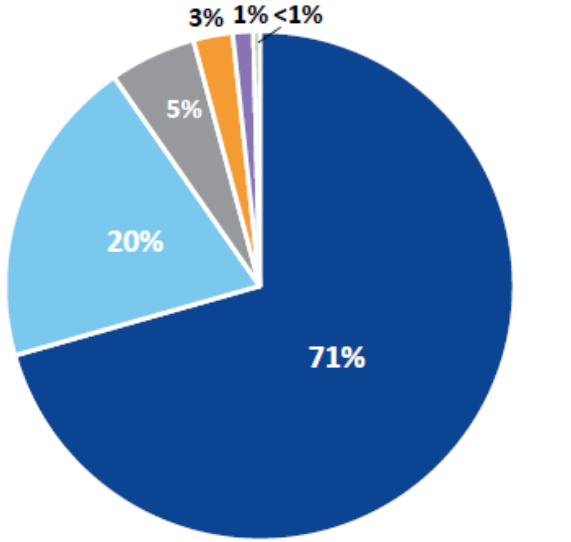
Most Hyperlipidemia Events were Managed Medically

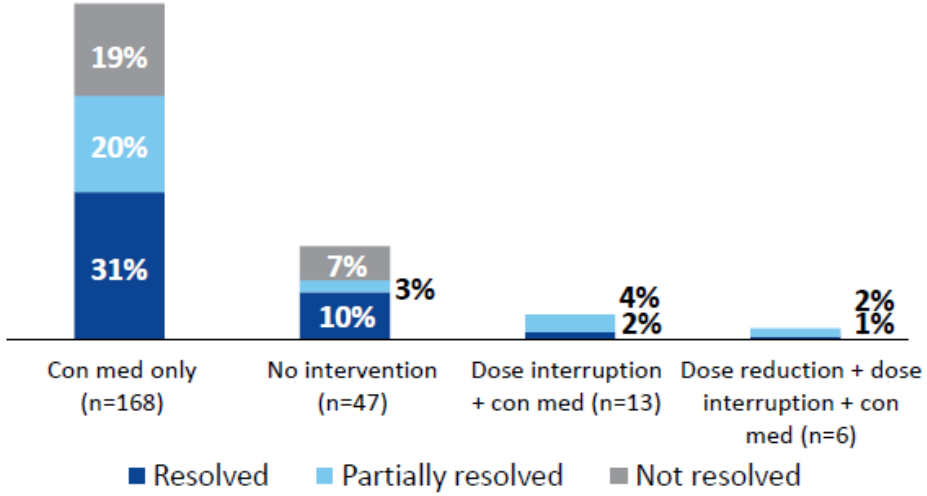
Lorlatinib (N=149)



- Hypercholesterolemia and hypertriglyceridemia were observed in the majority of patients treated with lorlatinib

Total hyperlipidemia events (n=238)



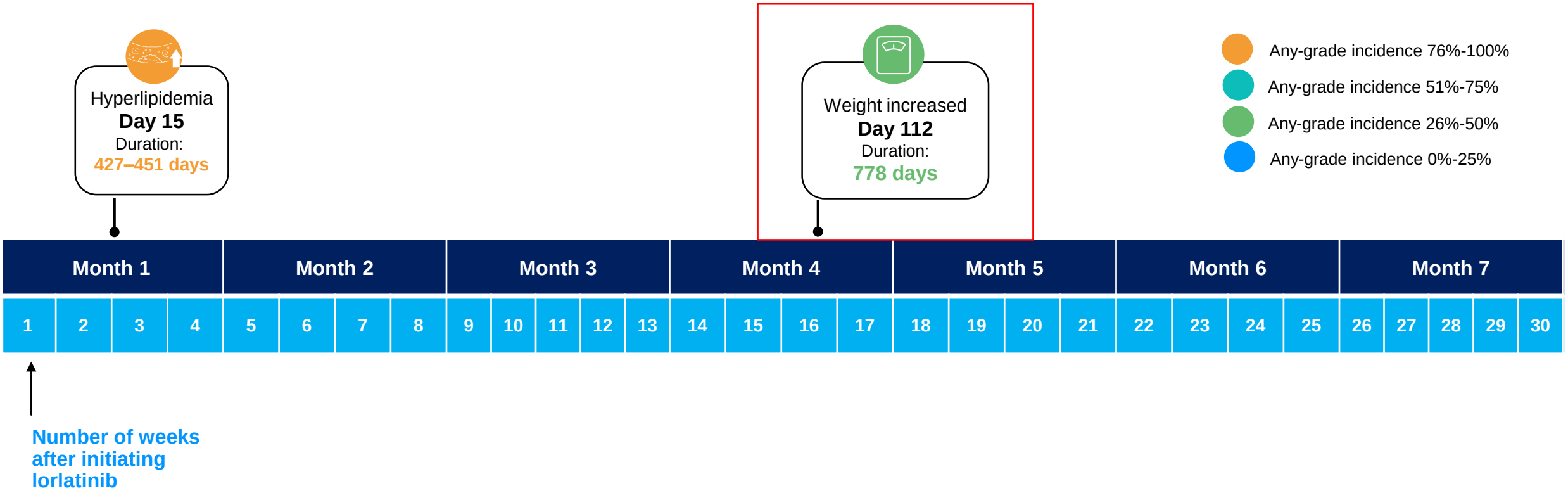


- Most of the hyperlipidemia events were managed and controlled with lipid-lowering agents[1]
- Pitavastatin, pravastatin, or rosuvastatin should initially be considered based on their low involvement with CYP3A4[2]
- 45% of hyperlipidemia events resolved
- 1 event led to permanent treatment discontinuation

con, concurrent; med, medication.

1. Liu G, et al. *Lung Cancer*. 2024;191:107535. 2. Neuvonen PJ, et al. *Clin Pharmacol Ther*. 2006;80:565–581.

Median time to onset (range) and duration of select adverse reactions with lorlatinib[1]*



*The values listed here represent median time to first occurrence for each AE. There is a distribution in which some may occur earlier or later than these median values.

1. Liu G, et al. *Lung Cancer*. 2024;191:107535.

針對**體重增加**的副作用處置建議

副作用	副作用對於日常生活的影響程度?[1]			定期評估直到情況穩定/改善
	不影響日常生活 (Normal)	輕至中度影響日常生活 (Grade 1-2)	重度影響日常生活 (Garde 3-4)	
體重增加 Weight gain	生活方式改變(包含飲食管理及運動)、副作用監測			如果情況惡化,  如果情況穩定或改善, 

 暫停: lorlatinib 劑量中斷  持續: 維持 lorlatinib 劑量  降低: lorlatinib 劑量降低 (每次降低25mg)

1隨著嚴重性的增加，從左到右增加管理。例如，對於嚴重困擾的水腫，請考慮改變生活方式、治療介入、劑量中斷和減少劑量。請注意，所有不良反應均主觀;如果患者經歷中度令人困擾的不良反應，導致功能衰弱或功能有害，則在與患者和醫護人員討論後，也可以被解釋為嚴重令人困擾。

2 中樞神經系統毒性往往令人煩惱，且不太可能對緩解治療產生反應，嚴重令人困擾可能等同於任何中樞神經系統功能損害。因此，建議及早降低藥物劑量並結合暫時性治療。且不建議在症狀緩解後增加劑量。

Liu G, et al. Lung Cancer. 2024;191:107535.

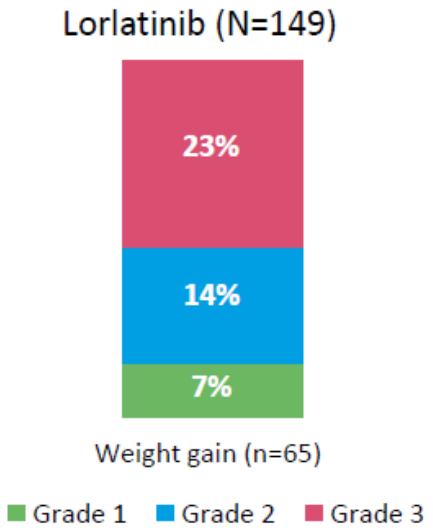
CTCAE Grade Definition of Weight Gain

CTCAE Grade Definitions

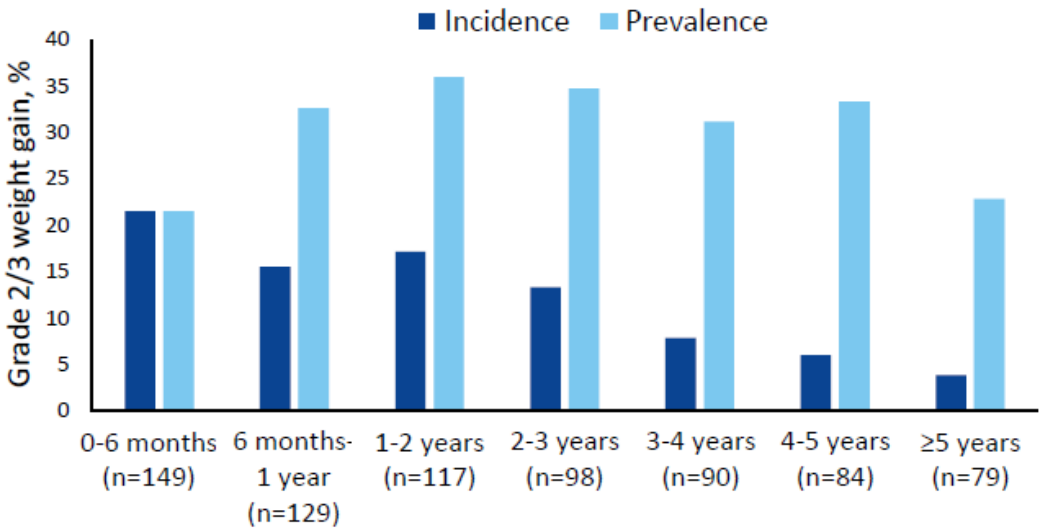
AE	Grade 1	Grade 2	Grade 3	Grade 4
Weight gain	5% to 10% from baseline	10% to 20% from baseline	≥20% from baseline	N/A

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events.
Common Terminology Criteria for Adverse Events (CTCAE). V4.0.

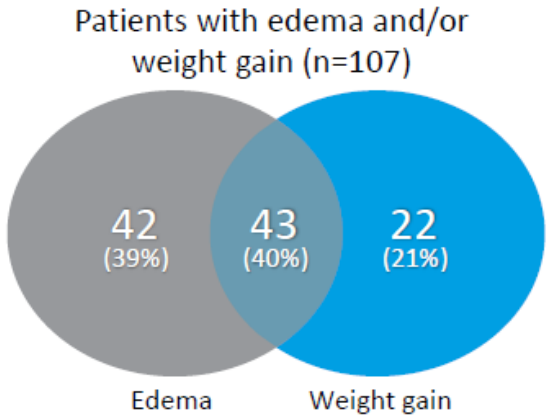
Weight Gain Occurred in 44% of Patients



	Grade 2/3 weight gain (n=55)	No grade 2/3 weight gain (n=94)
Baseline body weight, median (range), kg	64 (43-88)	64 (32-105)

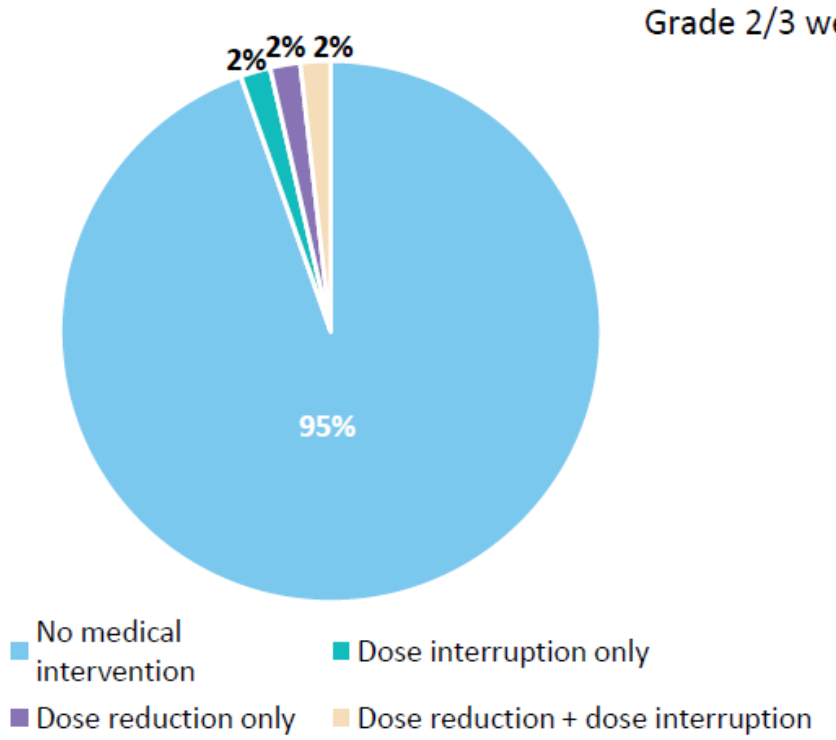


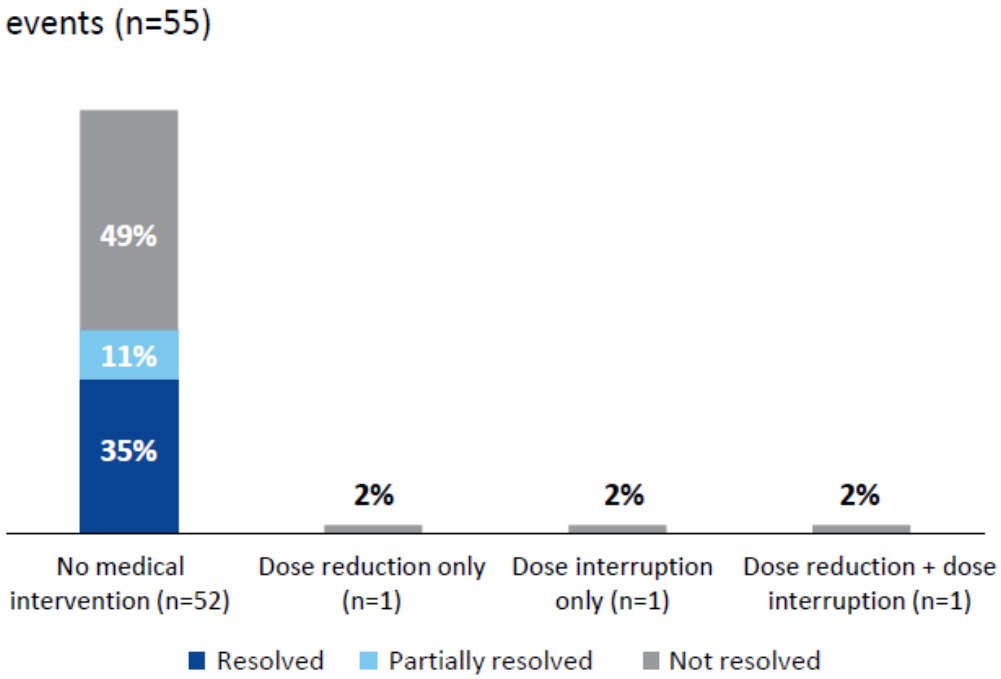
- Baseline body weight did not influence subsequent weight gain
- Incidence and prevalence of weight gain did not increase over time
- Weight gain and edema seem to correlate only in a fraction of patients, suggesting different pathogenic mechanisms



AE, adverse event.

Most Weight Gain Events Were Managed With Lifestyle Modifications

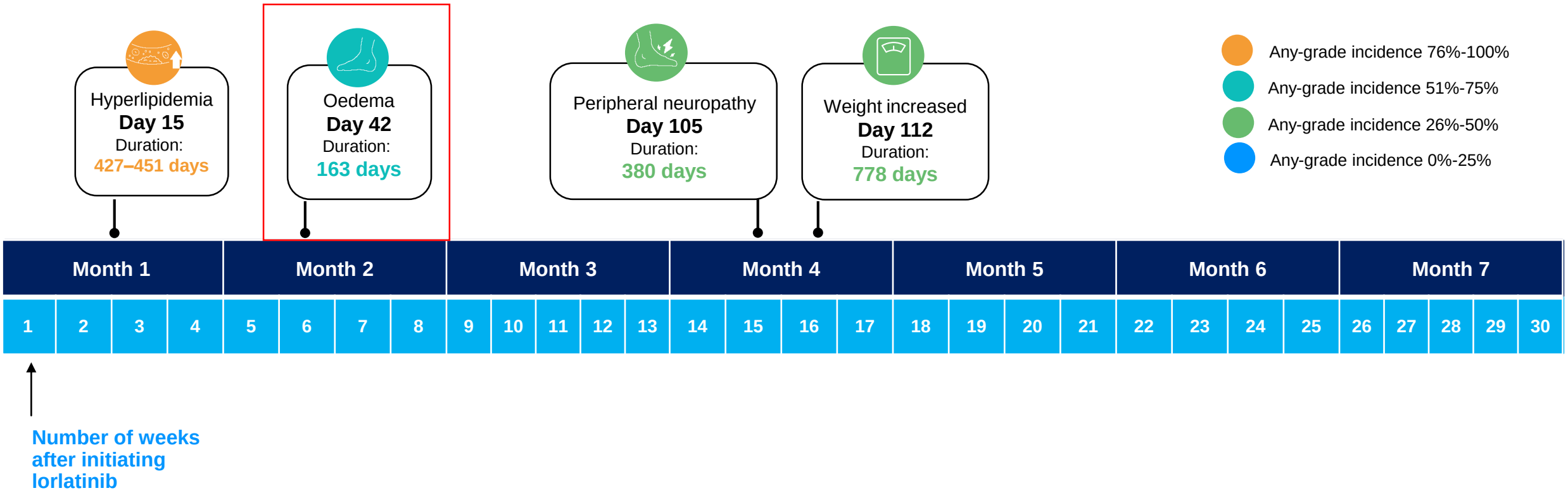




- Weight gain was primarily managed with lifestyle modifications[1]
- 35% of all weight gain events resolved with no medical intervention

1. Liu G, et al. *Lung Cancer*. 2024;191:107535.

Median time to onset (range) and duration of select adverse reactions with lorlatinib[1]*



*The values listed here represent median time to first occurrence for each AE. There is a distribution in which some may occur earlier or later than these median values.

1. Liu G, et al. *Lung Cancer*. 2024;191:107535.

Incidence and management outcome in CROWN Phase 1/2 study and Phase 3 after 5 years follow up

CROWN (5-year expanded safety analysis):

1.8 Months

Median time to onset, any-grade AEs[1]

4.4 Months

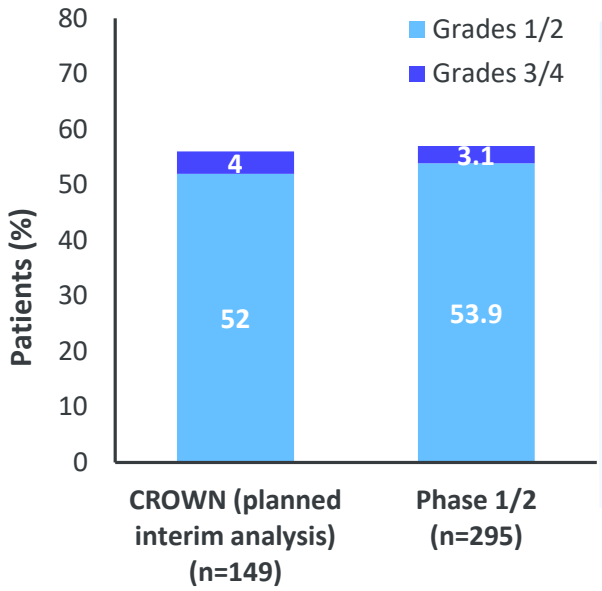
Median time to onset, grade ≥3 AEs[1]

Phase 1/2:

42 Days

Median time to onset
(range, 1–232)[2]

Incidence of Edema in Clinical Trials[3]



Edema included edema, edema peripheral, eyelid edema, face edema, generalized edema, localized edema, periorbital edema, peripheral swelling, and swelling[3]

5%[3] of patients required **dose reductions of lorlatinib** due to edema (CROWN)

6%[3] of patients required **dose reductions of lorlatinib** due to edema (Phase 1/2)

5%[3] of patients required **dose interruption of lorlatinib** due to edema (CROWN)

7%[3] of patients required **dose interruption of lorlatinib** due to edema (Phase 1/2)

1. Bauer TM, et al. Presented at: WCLC Annual Meeting; September 7-10th, 2024 San Diego, CA. 2. Bauer TM, et al. *Oncologist*. 2019;24:1103-1110. 3. Lorbrena®. Prescribing Information. New York, NY: Pfizer, Inc. 2023.

CTCAE Grade Definition of edema

CTCAE Grade Definitions

AE	Grade 1	Grade 2	Grade 3	Grade 4
Edema	Localized to dependent areas, no disability or functional impairment	Moderate localized edema and intervention indicated; limiting instrumental ADL	Severe localized edema and intervention indicated; limiting self-care ADL	N/A

Grade information for edema varies based on specific edema type. See NCI CTCAE version 4.0.

ADL, activities of daily living; AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; NCI, National Cancer Institute.
Common Terminology Criteria for Adverse Events (CTCAE). V4.0.

Monitor edema at each visit after initiation of lorlatinib[1]

If Grade 1/2

Continue lorlatinib at the same dose or at a reduced dose[2]

If Grade 3/4

Withhold lorlatinib[2]

After symptoms resolve to Grade ≤2 or baseline[2]

Resume lorlatinib at a reduced dose[2,*]

Therapy for Edema[2]

Low-Grade edema

- Compression stockings
- Leg elevations
- Lifestyle modifications (exercise, limiting dietary salt)
- Diuretics (usually furosemide)

Edema refractory to furosemide monotherapy

- Add spironolactone

Pfizer does not have any recommendations regarding the management of edema in patients receiving lorlatinib. Clinical judgment based on the medical history and the clinical status of a specific patient should dictate the appropriate actions to be taken.

*If not considered a safety risk for the patient.

1. Reed M, et al. *Adv Ther*. 2020;37:3019-3030. 2. Bauer TM, et al. *Oncologist*. 2019;24:1103-1110.

針對水腫的副作用處置建議

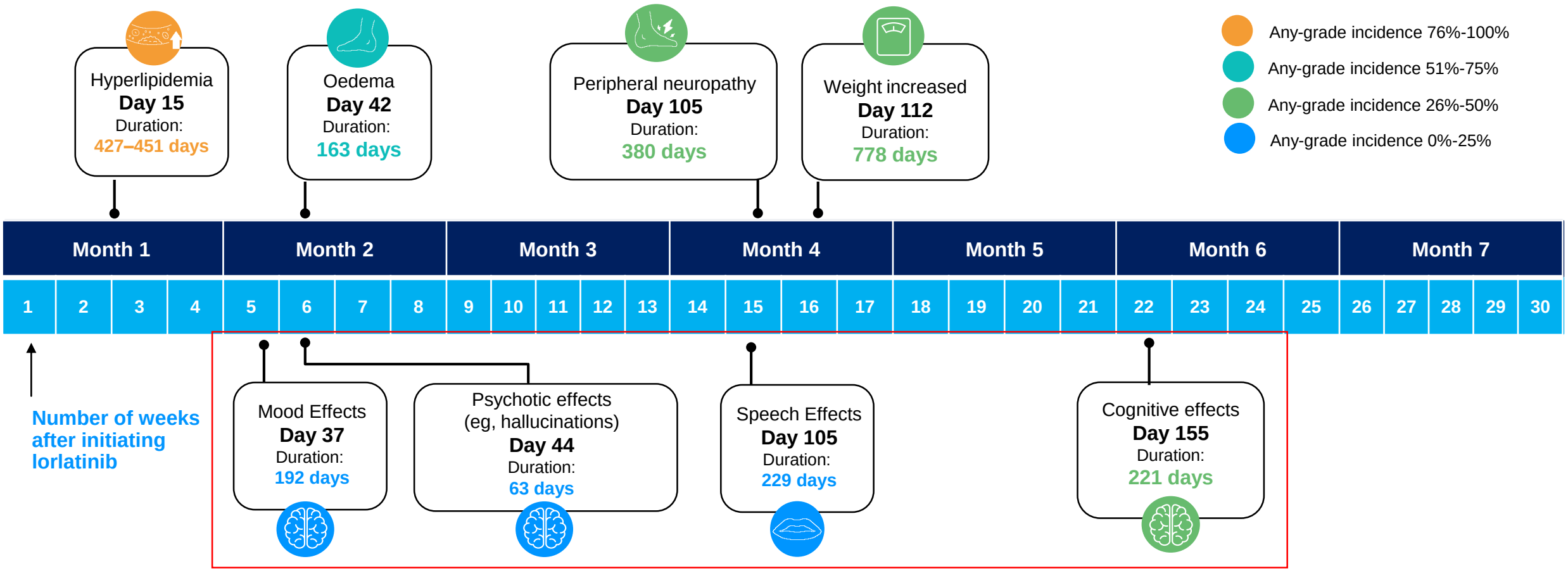
副作用	副作用對於日常生活的影響程度?[1]			定期評估直到情況穩定/改善
	不影響日常生活 (Normal)	輕至中度影響日常生活 (Grade 1-2)	重度影響日常生活 (Garde 3-4)	
體重增加 Weight gain	生活方式改變(包含飲食管理及運動)、副作用監測			如果情況惡化, ▼ 如果情況穩定或改善, ▶
水腫 Oedema	生活方式改變與部分治療		⏸ → ▼	

⏸ 暫停: lorlatinib 劑量中斷　▶ 持續: 維持 lorlatinib 劑量　▼ 降低: lorlatinib 劑量降低 (每次降低25mg)

1隨著嚴重性的增加，從左到右增加管理。例如，對於嚴重困擾的水腫，請考慮改變生活方式、治療介入、劑量中斷和減少劑量。請注意，所有不良反應均主觀;如果患者經歷中度令人困擾的不良反應，導致功能衰弱或功能有害，則在與患者和醫護人員討論後，也可以被解釋為嚴重令人困擾。
2 中樞神經系統毒性往往令人煩惱，且不太可能對緩解治療產生反應，嚴重令人困擾可能等同於任何中樞神經系統功能損害。因此，建議及早降低藥物劑量並結合暫時性治療。且不建議在症狀緩解後增加劑量。

Liu G, et al. Lung Cancer. 2024;191:107535.

Median time to onset (range) and duration of select adverse reactions with lorlatinib[1]*



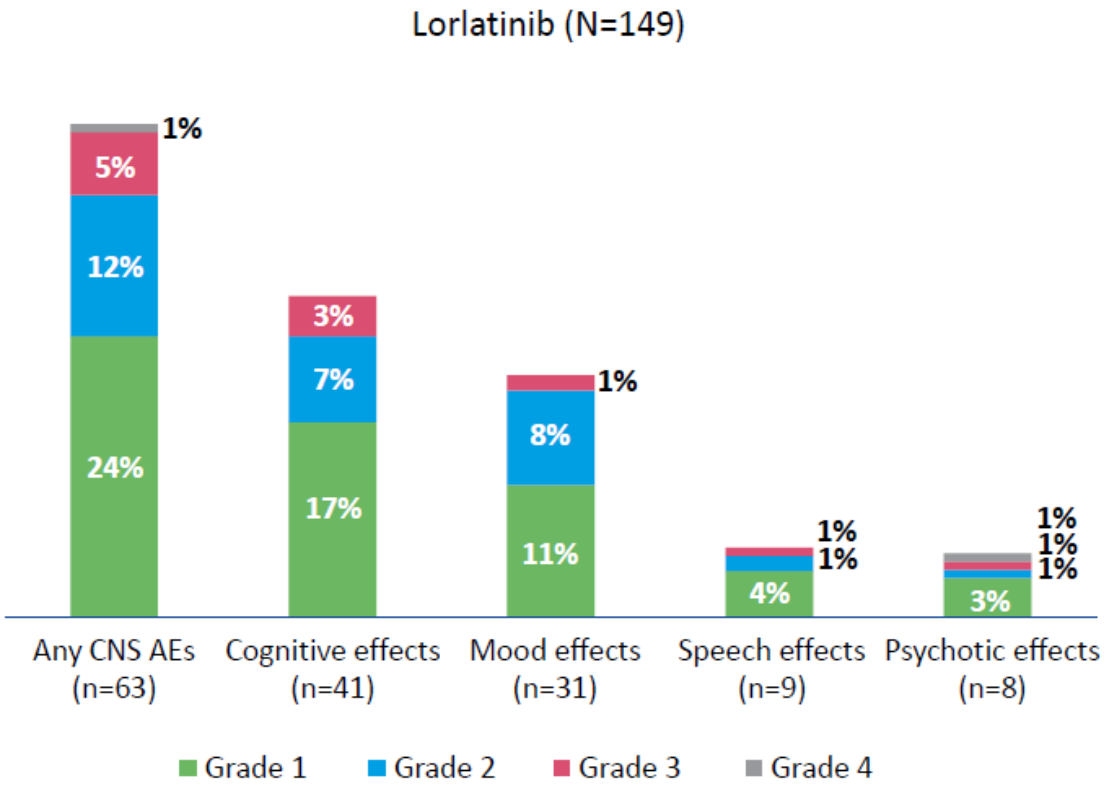
*The values listed here represent median time to first occurrence for each AE. There is a distribution in which some may occur earlier or later than these median values.

1. Liu G, et al. *Lung Cancer*. 2024;191:107535.

CTCAE Grade Definition of CNS effect

AE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
CNS effects	Mild disturbances without influence on daily activities of life	Moderate disruption affecting daily activities of life	Serious disorders, no hospitalization required	Harm to self or others and/or hospitalization is required	Death
Cognitive effects					
Delirium	Mild acute confusional state	Moderate and acute confusional state; limiting instrumental ADL	Severe and acute confusional state; limiting self-care ADL; hospitalization indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Cognitive disturbances	Mild cognitive disability; not interfering with work/school/life performance; specialized educational services/devices not indicated	Moderate cognitive disability; interfering with work/school/life performance but capable of independent living; specialized resources on part-time basis indicated	Severe cognitive disability; significant impairment of work/school/life performance	–	–
Confusion	Mild disorientation	Moderate disorientation; limiting instrumental ADL	Severe disorientation; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Concentration impairment	Mild inattention or decreased level of concentration	Moderate impairment in attention or decreased level of concentration; limiting instrumental ADL	Severe impairment in attention or decreased level of concentration; limiting self-care ADL	–	–
Memory impairment	Mild memory impairment	Moderate memory impairment; limiting instrumental ADL	Severe memory impairment; limiting self-care ADL	–	–
Amnesia	Mild; transient memory loss	Moderate; short-term memory loss; limiting instrumental ADL	Severe; long-term memory loss; limiting self-care ADL	–	–
Mood effects					
Anxiety	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; hospitalization not indicated	Life-threatening; hospitalization indicated	Death
Depression	Mild depressive symptoms	Moderate depressive symptoms; limiting instrumental ADL	Severe depressive symptoms; limiting self-care ADL; hospitalization not indicated	Life-threatening consequences; threats of harm to self or others; hospitalization indicated	Death
Irritability	Mild; easily consolable	Moderate; limiting instrumental ADL; increased attention indicated	Severe abnormal or excessive response; limiting self-care ADL; inconsolable	–	–
Speech effects					
Dysarthria	Mild slurred speech	Moderate impairment of articulation or slurred speech	Severe impairment of articulation or slurred speech	–	–
Psychotic effects					
Delusion	–	Moderate delusional symptoms	Severe delusional symptoms; hospitalization not indicated	Life-threatening consequences; threats of harm to self or others	Death
Hallucinations	Mild hallucinations (e.g., perceptual disorders)	Moderate hallucinations	Severe hallucinations; hospitalization not indicated	Life-threatening consequences; threats of harm to self or others; hospitalization indicated	Death

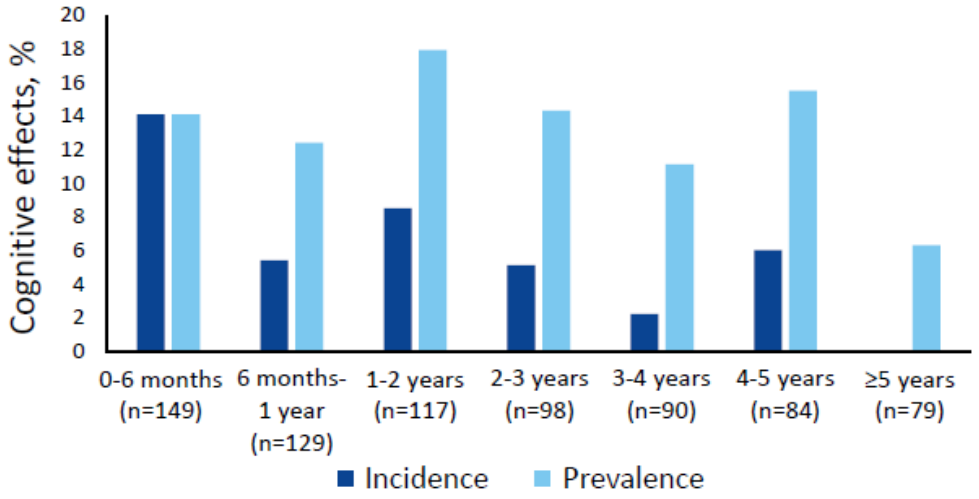
Most CNS AEs Were of Grade 1/2 Severity

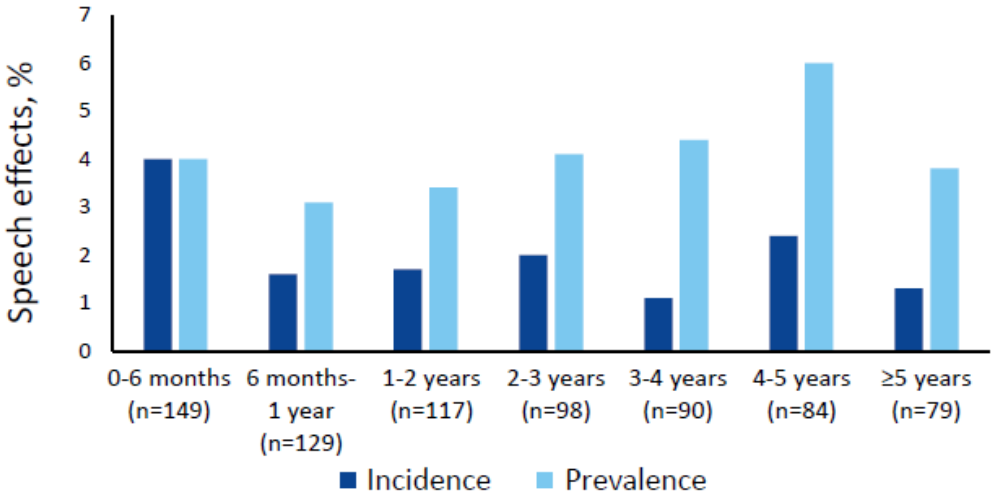


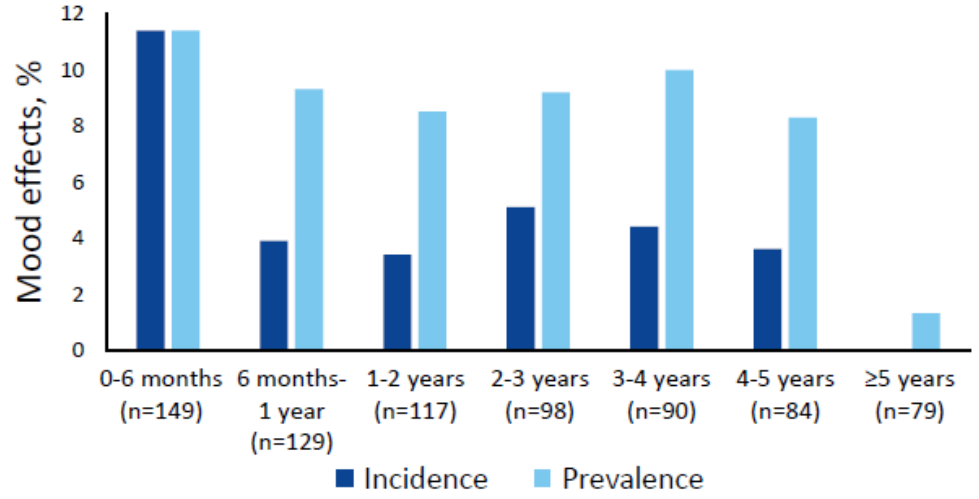
- All-causality CNS AEs occurred in 42% of patients, the majority of which (86%) were of grade 1/2 severity[1]
- As previously reported, CNS AEs occurred in 67% of patients who had prior brain radiotherapy (n=9) and 41% of patients without prior brain radiotherapy (n=140)[1]

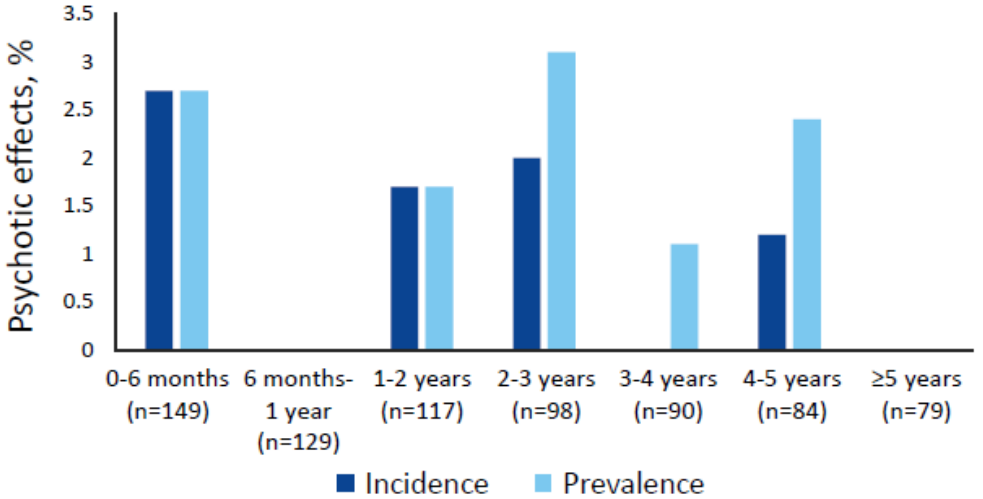
1. Solomon BJ, et al. *J Clin Oncol*. 2024:JCO2400581.

Incidence and Prevalence of CNS AEs did not Increase Over Time

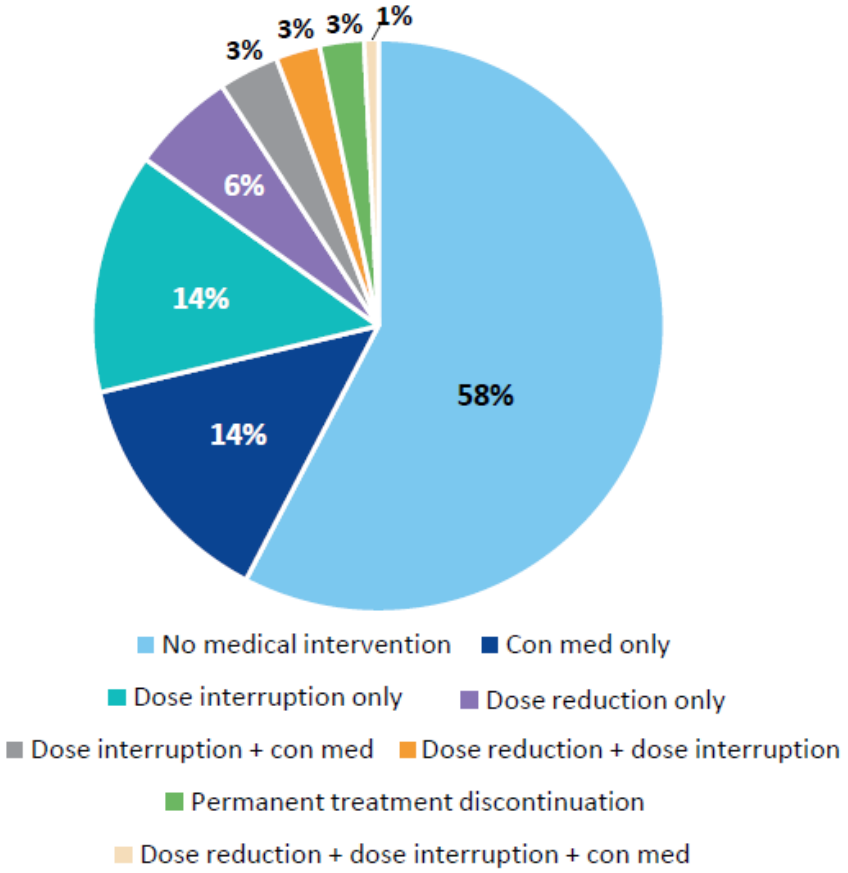


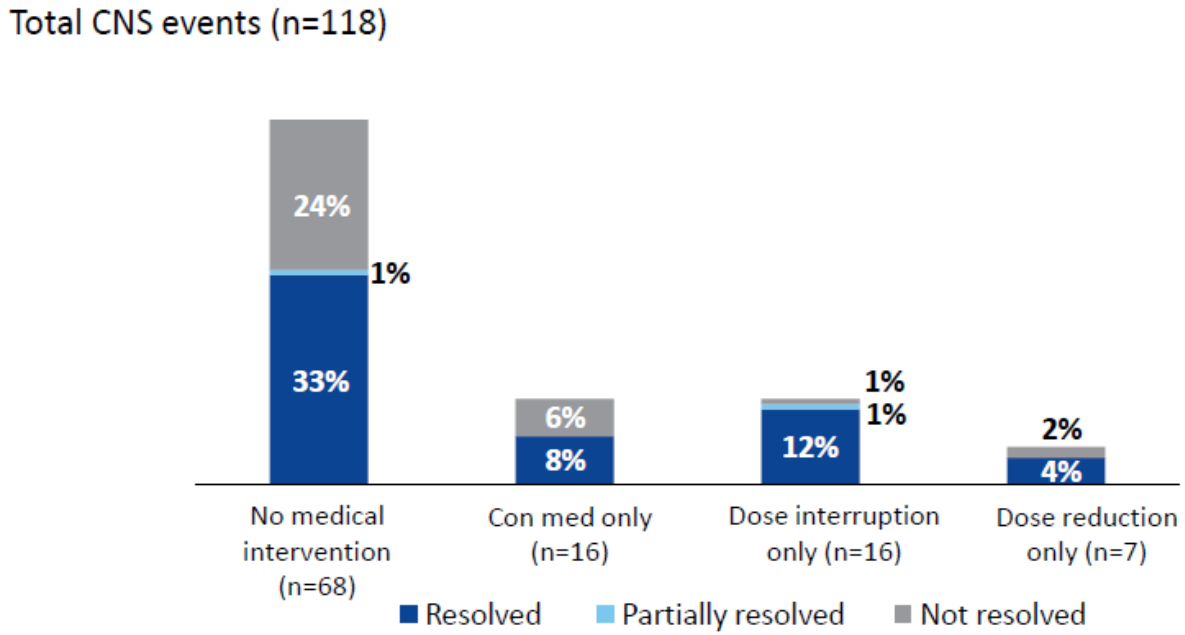






Most CNS AEs did not Require Medical Intervention





- More than half of the CNS AEs did not require any pharmacological intervention; management strategies to minimize the impact of CNS effects are useful[1]
- 60% of CNS AEs resolved, either with management strategies, dose interruption, or concurrent medication
- 3% of events led to permanent treatment discontinuation

con, concurrent; med, medication.

1. Liu G, et al. *Lung Cancer*. 2024;191:107535.

腦轉移、曾經做過腦部放療有較高風險會發展CNS副作用

ORIGINAL ARTICLE

IASLC

Factors Associated With Developing Neurocognitive Adverse Events in Patients Receiving Lorlatinib After Progression on Other Targeted Therapies

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Available online - XXX

Associated with developing cognitive effects :

- **Brain metastases (p=0.008)**
- **Brain radiation (p =0.033)**
- **Psychiatric illness (p =0.008)**
- **Psychiatric medications (p =0.001)**
- **Antiepileptics (p =0.001)**
- **Stimulants (p =0.026)**

J Thorac Oncol. 2023 Jan;18(1):67-78.

針對**CNS相關**的副作用處置建議

<table>
<tr><th rowspan="2">副作用</th><th colspan="3">副作用對於日常生活的影響程度?[1]</th><th rowspan="2">定期評估直到情況
穩定/改善</th></tr>
<tr><th>不影響日常生活
(Normal)</th><th>輕至中度影響日常生活
(Grade 1-2)</th><th>重度影響日常生活
(Garde 3-4)</th></tr>
<tr><td>體重增加 Weight gain</td><td colspan="3">生活方式改變(包含飲食管理及運動)、副作用監測</td><td rowspan="4">如果情況惡化,
▼
如果情況穩定或改善,
▶</td></tr>
<tr><td>水腫 Oedema</td><td colspan="2">生活方式改變與部分治療</td><td rowspan="3">⏸ → ▼</td></tr>
<tr><td>周邊神經病變
Peripheral neuropathy</td><td rowspan="2">副作用監測</td><td rowspan="2">⏸ → ▶ OR ▼
⏸ → ▼</td></tr>
<tr><td>中樞神經系統影響 CNS [2]
(mood, cognition, speech,
irritability, psychosis)</td></tr>
</table>

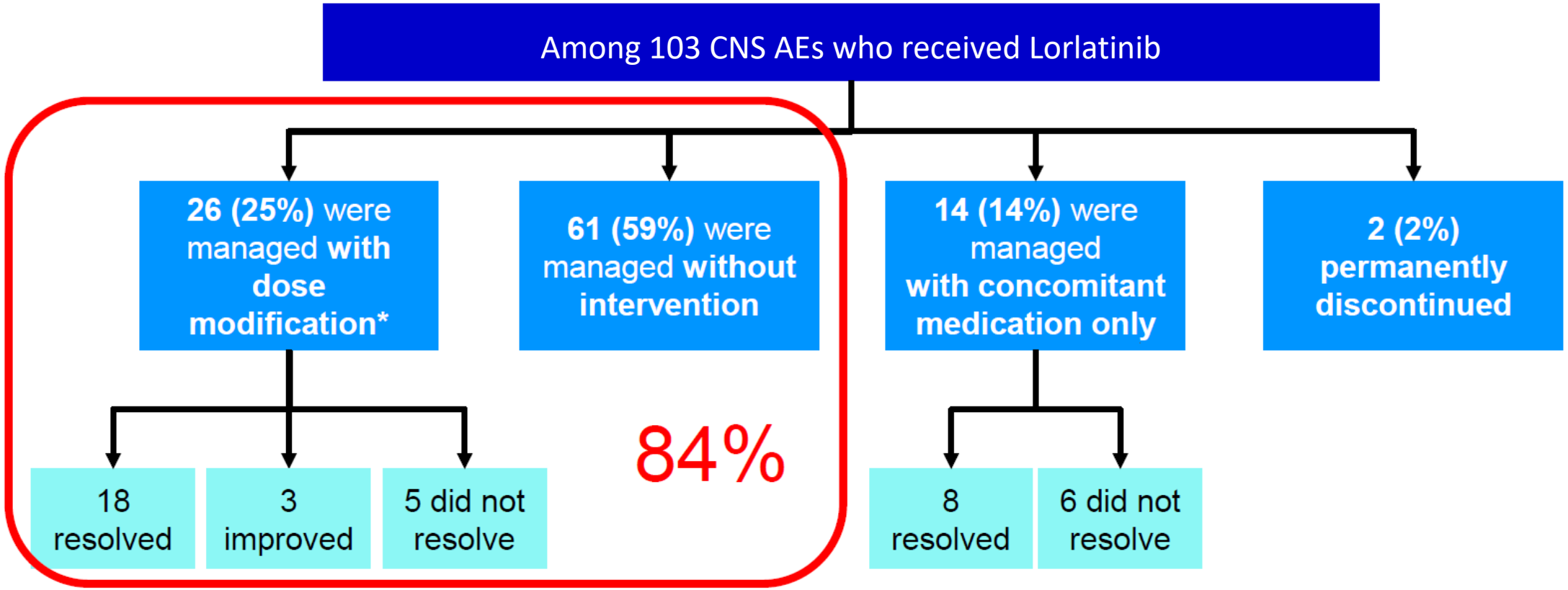
⏸ 暫停: lorlatinib 劑量中斷　▶ 持續: 維持 lorlatinib 劑量　▼ 降低: lorlatinib 劑量降低 (每次降低25mg)

1隨著嚴重性的增加，從左到右增加管理。例如，對於嚴重困擾的水腫，請考慮改變生活方式、治療介入、劑量中斷和減少劑量。請注意，所有不良反應均主觀;如果患者經歷中度令人困擾的不良反應，導致功能衰弱或功能有害，則在與患者和醫護人員討論後，也可以被解釋為嚴重令人困擾。

2 中樞神經系統毒性往往令人煩惱，且不太可能對緩解治療產生反應，嚴重令人困擾可能等同於任何中樞神經系統功能損害。因此，建議及早降低藥物劑量並結合暫時性治療。且不建議在症狀緩解後增加劑量。

Liu G, et al. Lung Cancer. 2024;191:107535.

8成以上的副作用都能以暫緩/降低劑量方式緩解



*Dose modification = reduction and/or interruption, +/- concomitant medication.
AE, adverse event; CNS, central nervous system.
Solomon BJ, et al. *Lancet Respir Med* 2023;11(4):354–66.

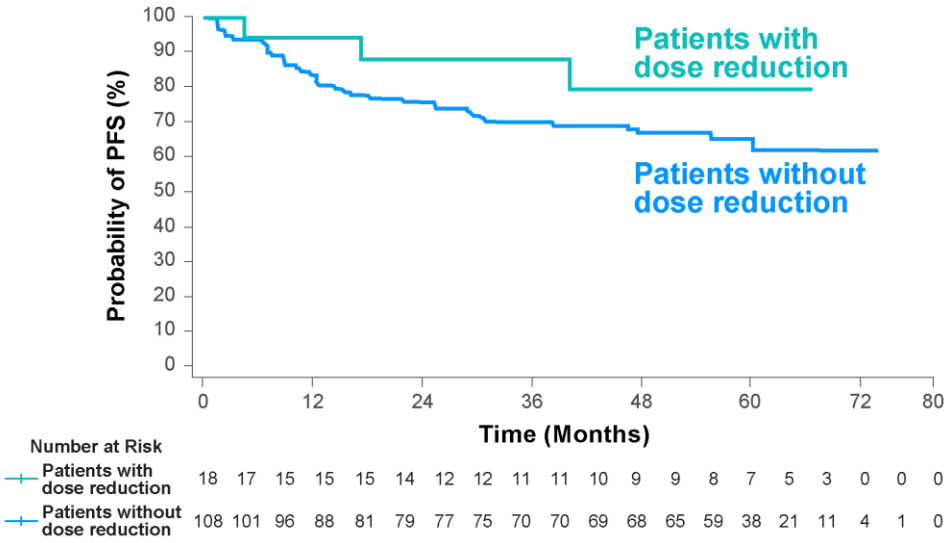
Solomon BJ, et al.,Lancet Respir Med 2023; 11 (4): 354-66

前16周若因為AE需要調降劑量,不影響Lorlatinib的療效

PFS and intracranial progression outcomes in patients who had first lorlatinib dose reduction within 16 weeks (INV-assessed)[1*]

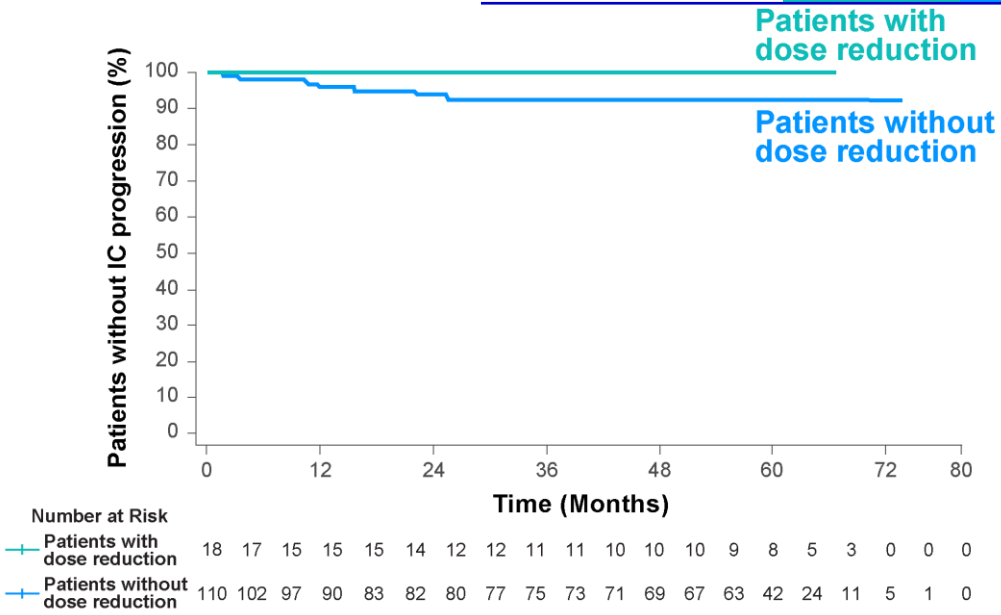
Time to systemic progression: ITT population[1]

Median PFS, months	NR	NR
Events, n	3	37
(95% CI)	(NR to NR)	(NR to NR)



Time to intracranial progression: ITT population[1]

Median PFS, months	NR	NR
Events, n	0	7
(95% CI)	(NR to NR)	(NR to NR)



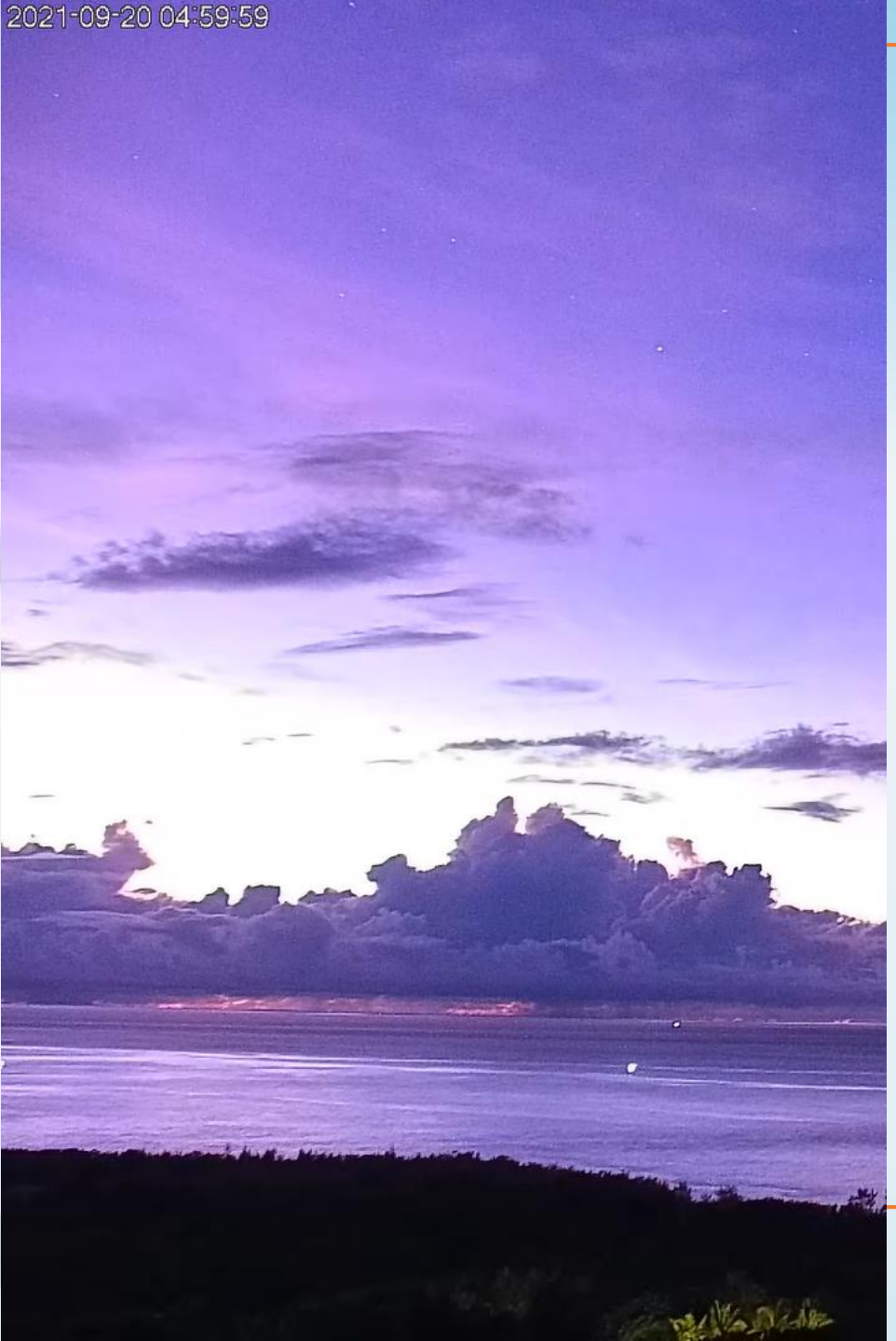
Data cutoff: 31 October 2023.[1]

*LIMITATIONS: The results of this unplanned investigator-assessed analysis are descriptive. No formal hypothesis testing was performed given that the PFS endpoint was previously met in the CROWN trial primary analysis; results are presented descriptively.[1]

Based on data from 60-month follow-up of 149 patients who received lorlatinib 100 mg once daily in the Phase 3 CROWN trial.

HR=hazard ratio; ITT=intention to treat; NE=not evaluable; PFS=progression-free survival.

1. Solomon BJ, et al. *J Clin Oncol.* 2024 in press. doi:10.1200/JCO.24.00581.



Conclusion

1) ALK mutation is a druggable mutation of NSCLC
2) Most ALK-TKI are effective and durable treatment for ALK mutation in NSCLC
3) Lorlatinib have the best PFS in published phase III clinical trial
4) The side/adverse effects of Lorlatinib were manageable

臺北榮民總醫院 胸腔部

胸腔內科	陳育民主任、羅永鴻主任、邱昭華、蕭慈慧、江起陸、黃煦晴、曾彥寒、沈佳儀
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核醫	林可瀚、胡蓮欣

其他	臨床藥師、營養師、個管師、社工師 安寧照護師
戰力	歷屆總醫師、研究醫師、護理師群

Thanks For Your Attention

趙 恒 勝 (Heng-sheng Chao)
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