ALK in Front Line Therapy: Second or Third Generation TKI Inhibitors. What Can Help Us to Choose the Best Therapeutic Agent?

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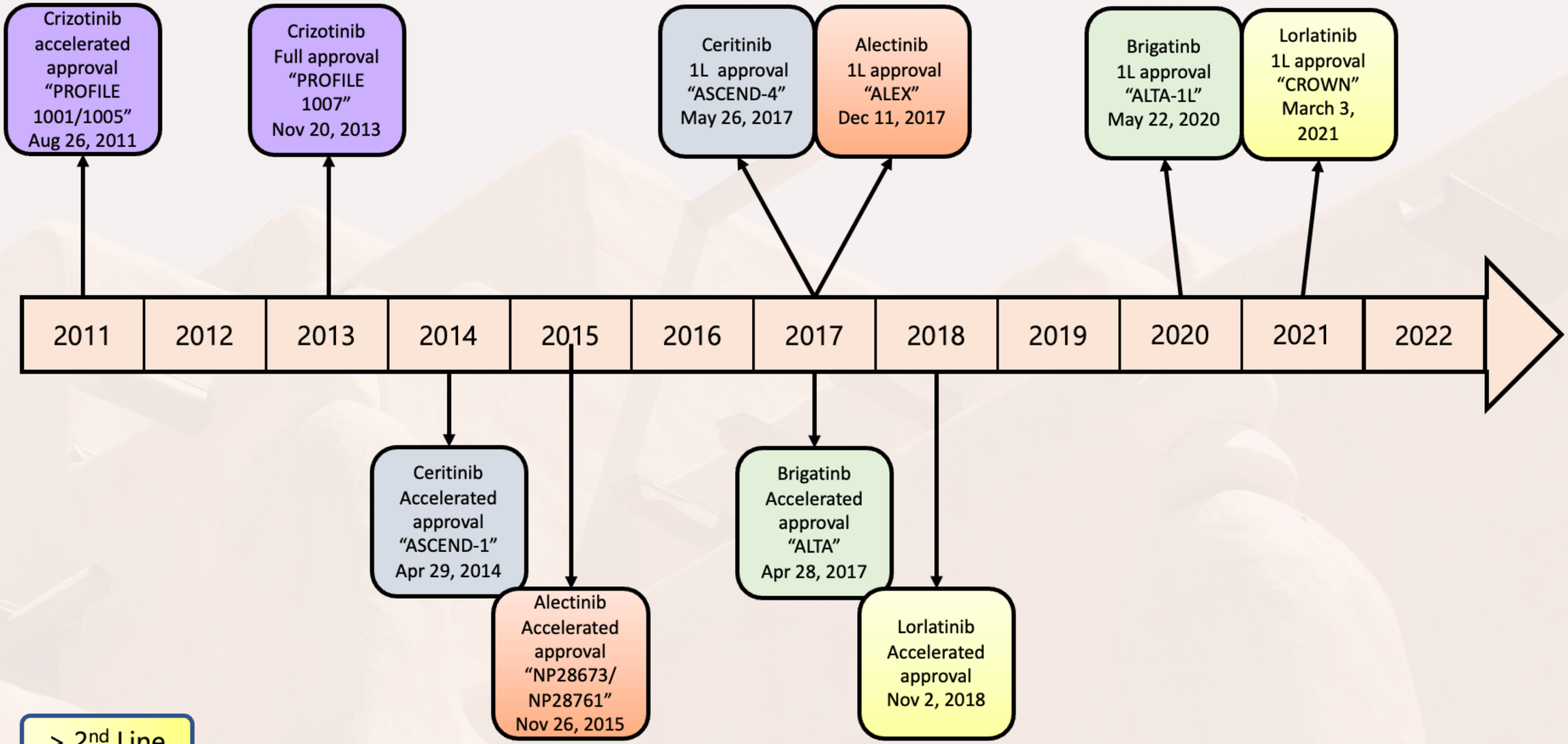
- Background
- Pre-clinical potency
- Clinical efficacy
- Tolerability
- Special situation (CNS)

1st Line (1L)



≥ 2nd Line

All 6 approved ALK TKIs heatmaps

EML4-ALK Variant

A 1

	Crizotinib	Ceritinib	Ensartinib	Alectinib	Brigatinib	Lorlatinib
WT	23.30 16.23 to 33.46	12.47 7.813 to 19.92	1.281 1.073 to 1.530	1.377 1.044 to 1.818	0.959 0.794 to 1.158	0.267 0.212 to 0.337
G1123S	27.17 16.75 to 44.09	661.6 271.7 to 1611	0.983 0.711 to 1.358	1.559 1.167 to 2.082	11.14 7.082 to 17.53	2.855 2.238 to 3.642
L1152R	361.3 205.5 to 635.1	167.3 145.2 to 968.4	34.75 23.42 to 51.56	3.501 3.110 to 3.943	0.798 0.640 to 0.995	7.402 8.190 to 20.24
C1156Y	306.0 100.6 to 931.3	199.7 54.09 to 737.4	27.27 9.057 to 82.12	13.61 5.461 to 33.91	7.659 3.999 to 14.67	8.938 4.206 to 18.99
I1171T	471.9 190.3 to 1171	165.1 59.20 to 460.4	69.25 339.21 to 122.3	379.8 126.4 to 1141	25.85 10.58 to 63.14	52.53 23.42 to 117.8
F1174C	294.4 72.52 to 1195	205.1 69.89 to 601.6	58.55 24.82 to 138.1	19.22 9.222 to 40.05	29.10 12.31 to 68.78	9.786 5.047 to 18.98
F1174V	57.91 33.13 to 100.7	51.28 24.74 to 106.3	6.992 5.689 to 8.593	1.988 1.700 to 2.325	5.165 4.110 to 6.491	2.100 1.732 to 2.545
V1180L	114.5 44.44 to 295.0	11.87 7.962 to 17.70	4.436 3.401 to 5.786	1902 1186 to 3051	1.563 1.233 to 1.983	1.650 1.394 to 1.953
L1196M	637.1 246.7 to 1645	133.8 59.24 to 302.4	59.53 31.25 to 113.4	58.74 23.75 to 145.3	20.09 8.841 to 45.65	56.52 30.07 to 106.2
L1198F	27.97 14.30 to 54.73	1722 587.6 to 5045	0.323 0.199 to .524	201.9 125.2 to 325.5	48.53 29.15 to 80.80	56.61 26.51 to 120.9
G1202del	179.9 59.72 to 541.6	319.1 165.9 to 614.0	138.9 68.17 to 283.0	963 614.7 to 1509	25.02 14.85 to 42.15	11.15 5.858 to 21.21
G1202R	289.5 197.4 to 424.4	252.4 147.7 to 413.3	316.0 212.4 to 470.2	1918 1151 to 3197	30.92 233.47 to 40.72	31.18 26.41 to 36.81
S1206Y	177.5 65.38 to 482.0	53.14 25.64 to 110.1	31.45 21.92 to 45.14	7.216 3.878 to 13.43	17.56 8.543 to 36.10	4.704 2.795 to 7.918
E1210K	4027 887.6 to 20981	345.6 147.4 to 809.1	3010 1015 to 9077	5065 2991 to 8557	299.2 144.7 to 622	38.04 10.67 to 139.3
F1245C	197.6 68.43 to 571.3	216.3 87.17 to 536.6	22.03 11.88 to 40.85	13.62 6.995 to 26.53	26.00 12.48 to 54.18	7.357 4.538 to 11.93
G1269A	699.3 176.9 to 2765	67.13 29.22 to 154.3	221.8 97.82 to 503.1	58.66 42.83 to 80.35	11.41 5.492 to 23.72	76.39 31.93 to 182.7

1000nM
800nM
600nM
400nM
200nM

EML4-ALK Variant 3

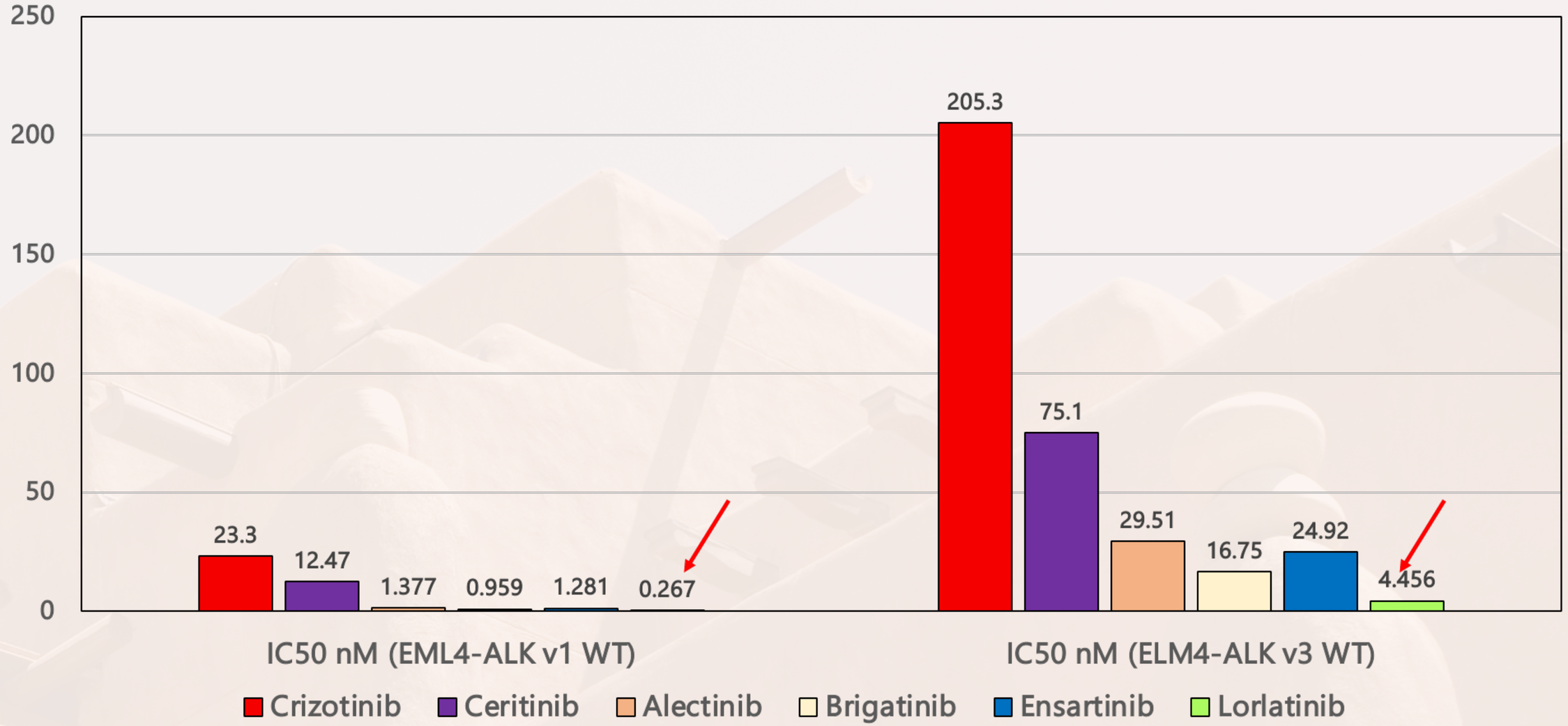
B

	Crizotinib	Ceritinib	Ensartinib	Alectinib	Brigatinib	Lorlatinib
WT	205.3 70.5 to 597.9	75.1 29.72 to 189.8	24.92 9.450 to 65.70	29.51 15.53 to 56.05	16.75 10.10 to 27.77	4.456 2.376 to 8.357
G1123S	54.50 23.65 to 125.6	651.2 179.3 to 2365	1.309 0.701 to 2.446	3.000 1.424 to 6.319	25.79 9.503 to 69.99	3.557 2.111 to 5.992
L1152R	124.3 66.44 to 232.6	165.7 533.61 to 511.9	14.80 7.863 to 27.86	3.300 2.502 to 4.354	0.190 0.126 to 0.287	4.246 2.228 to 8.091
C1156Y	110.4 69.28 to 176.1	58.66 38.68 to 88.98	10.92 7.338 to 16.25	5.266 3.842 to 7.218	2.263 3.842 to 7.218	2.313 1.570 to 3.407
I1171T	152.8 79.26 to 294.5	17.60 13.11 to 23.62	13.84 6.726 to 28.50	24.78 14.50 to 42.36	3.135 2.297 to 4.278	7.450 4.528 to 12.26
F1174C	257.7 85.86 to 773.5	248.5 110.2 to 560.4	64.79 23.95 to 175.3	286.2 123.0 to 665.8	28.06 13.40 to 58.75	13.11 6.494 to 26.48
F1174V	238.8 170.4 to 1003	157.4 60.73 to 408.0	33.28 22.67 to 48.86	38.43 21.25 to 69.52	31.92 20.08 to 50.75	8.258 5.731 to 11.90
V1180L	98.12 43.35 to 222.6	18.63 7.693 to 45.10	9.423 5.058 to 17.56	2166 601.8 to 7798	3.523 1.950 to 6.365	2.653 1.569 to 4.484
L1196M	924.5 415.4 to 2057	205.9 58.74 to 721.6	81.31 37.03 to 178.6	929.6 422.2 to 2047	26.66 11.10 to 64.04	69.81 28.04 to 173.8
L1198F	46.52 17.84 to 121.3	2072 382.2 to 11228	3.807 2.080 to 6.966	1205 494.7 to 2933	157.0 59.32 to 415.5	59.47 313.53 to 112.2
G1202del	322.0 125.6 to 765.0	586.7 173.2 to 1988	474.7 169.0 to 1333	>10000 N/A	104.6 337.6 to 290.8	26.19 12.51 to 54.86
G1202R	440.5 175.7 to 1105	405.6 189.5 to 868.1	315.9 194.1 to 514.1	>10000 N/A	83.82 50.43 to 139.3	35.72 20.46 to 62.36
D1203N	332.0 170.1 to 648.2	329.2 172.0 to 630.1	21.10 11.73 to 37.98	142.7 46.29 to 439.7	33.42 20.19 to 55.30	19.73 12.16 to 32.01
S1206C	308.1 152.9 to 620.9	222.2 91.30 to 541.0	42.49 20.41 to 88.46	30.94 14.02 to 68.29	81.80 27.80 to 240.6	6.129 3.167 to 11.86
S1206Y	175.7 60.74 to 508.3	90.05 24.02 to 337.6	48.24 23.47 to 99.14	9.804 6.057 to 15.87	16.29 8.313 to 31.94	3.238 3.042 to 5.134
E1210K	482.6 170.5 to 1366	178.2 83.58 to 380.1	527.6 198.5 to 1402	759.3 255.7 to 2255	162.9 58.92 to 450.3	7.565 3.780 to 15.14
F1245C	289.9 119.2 to 704.8	208.0 63.52 to 680.9	52.90 23.83 to 117.5	65.55 27.22 to 157.9	46.16 21.58 to 98.70	14.82 6.461 to 34.00
G1269A	511.4 169.3 to 1544	52.65 23.98 to 115.6	123.1 65.00 to 268.6	100.4 45.83 to 220.0	10.02 5.337 to 18.82	42.70 20.85 to 87.42

1000nM
800nM
600nM
400nM
200nM

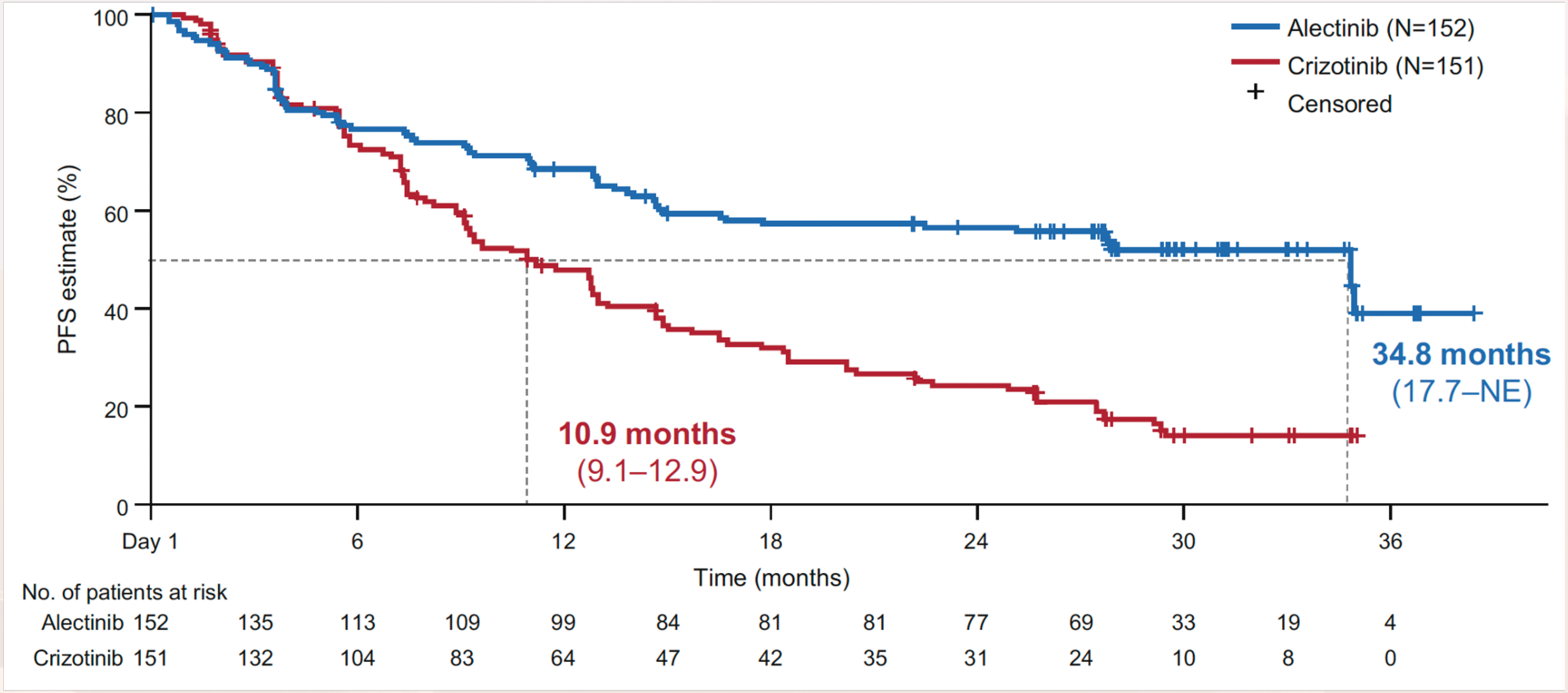
Horn et al. J Thorac Oncol. 2019;14:1901-1911. Work of Dr. Christine Lovly

Comparison of IC_{50} among ALK TKIs in the back ground of EML4-ALK variant 1 and variant 3



Ou, Lee, Nagasaka Crit Rev Oncol Hematol. 2023 Jul;187:104019)

ALEX most recent update (2019)



J Thorac Oncol 2019; 7: 1233-1243

SINGAPORE 2022 ESMO ASIA

Alectinib vs crizotinib in Asian patients with treatment-naïve advanced *ALK*+ non-small cell lung cancer: 5-year update from the Phase 3 ALESIA study

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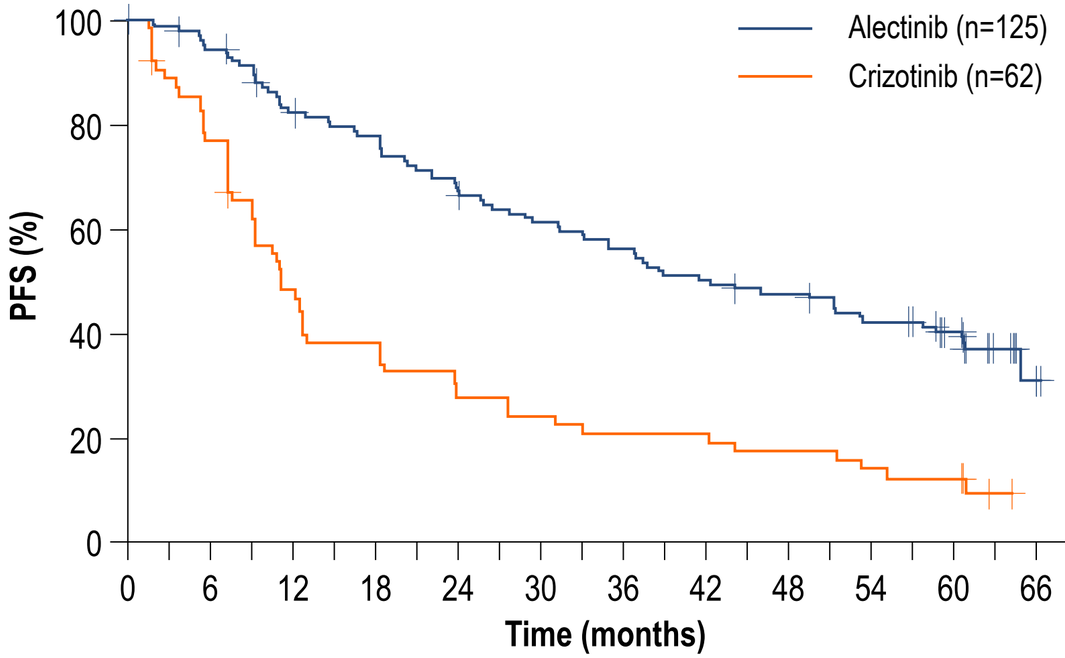
Zhou C,[1] Lu Y,[2] Kim S-W,[3] Baisamut (Reungwetwattana) T,[4] Zhou J,[5] Zhang Y,[6] He J,[7] Yang J-J,[8] Cheng Y,[9] Lee S-H,[10] Chang J,[11] Fang J,[12] Liu Z,[13] Bu L,[14] Qian L,[14] Xu T,[14] Archer V,[15] Hilton M,[16] Zhou M,[14] Zhang L[17]

[1]Shanghai Pulmonary Hospital, Tongji University, Shanghai, China; [2]West China Hospital, Sichuan University, Chengdu, China; [3]Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; [4]Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; [5]The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; [6]Zhejiang Cancer Hospital, Hangzhou, China; [7]The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China; [8]Guangdong Lung Cancer Institute, Guangdong General Hospital, Guangzhou, China; [9]Jilin Cancer Hospital, Changchun, China; [10]Sungkyunkwan University School of Medicine, Seoul, South Korea; [11]Cancer Hospital and Shenzhen Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Shenzhen, China; [12]Beijing Cancer Hospital, Beijing, China; [13]Beijing Chest Hospital, Capital Medical University, Beijing, China; [14]Roche Pharma Development, Shanghai, China; [15]Roche Products Ltd, Welwyn Garden City, UK; [16]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [17]Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, China

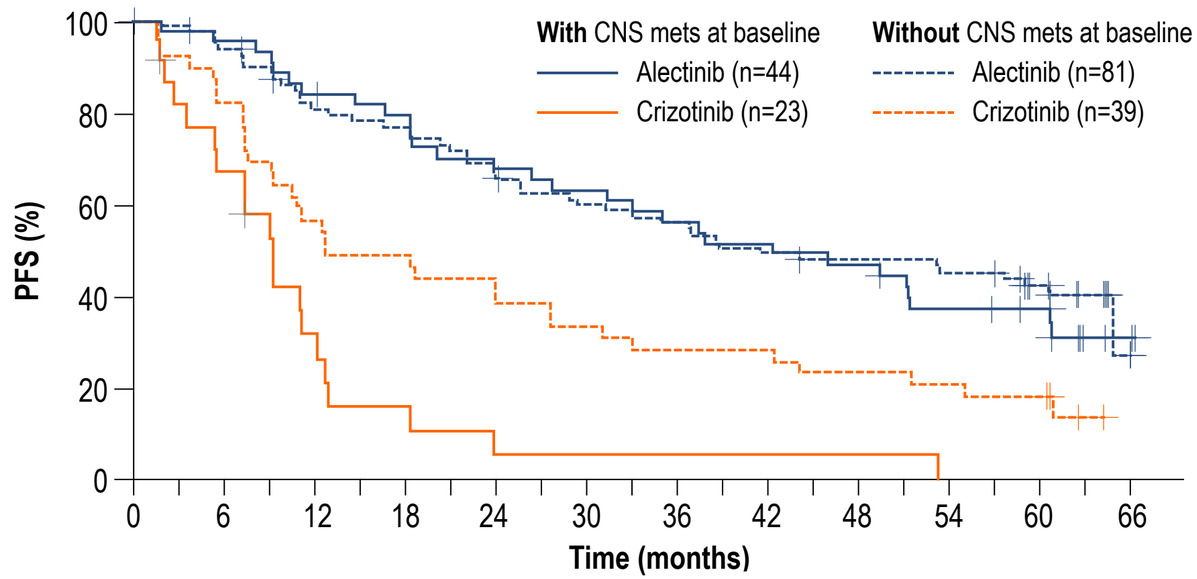
Updated analyses from ALESIA demonstrate durable PFS benefit for alectinib versus crizotinib, irrespective of CNS involvement at baseline

Updated PFS: ITT population



	Alectinib n=125	Crizotinib n=62
Median PFS, months (95% CI)	**41.6** (33.1–58.9)	**11.1** (9.1–18.4)
HR (95% CI)	**0.33** (0.23–0.49)	

PFS according to CNS status at baseline



	With CNS mets at baseline	
	Alectinib n=44	Crizotinib n=23
Median PFS, months (95% CI)	**42.3** (27.8–60.7)	**9.2** (5.5–12.2)
HR (95% CI)	**0.17** (0.09–0.33)	**0.45** (0.29–0.71)

Data cut-off 16 May 2022. CI, confidence interval; CNS, central nervous system; HR, hazard ratio; ITT, intent-to-treat; mets, metastases; PFS, progression-free survival

Efficacy and safety of first-line lorlatinib versus crizotinib in patients with advanced, *ALK*-positive non-small-cell lung cancer: updated analysis of data from the phase 3, randomised, open-label CROWN study

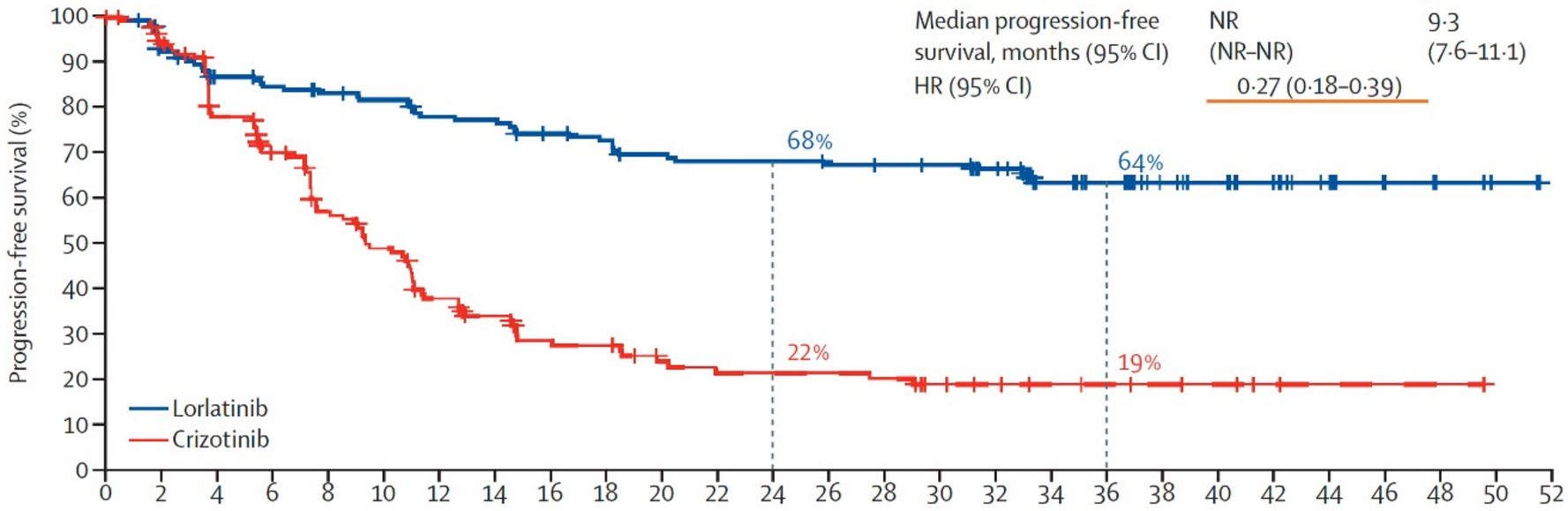
Benjamin J Solomon, Todd M Bauer, Tony S K Mok, Geoffrey Liu, Julien Mazieres, Filippo de Marinis, Yasushi Goto, Dong-Wan Kim, Yi-Long Wu, Jacek Jassem, Froylán López López, Ross A Soo, Alice T Shaw, Anna Polli, Rossella Messina, Laura Iadeluca, Francesca Toffalorio, Enriqueta Felip

Summary

Background After a median follow-up of 18·3 months, the third-generation anaplastic lymphoma kinase (ALK) *Lancet Respir Med 2022*

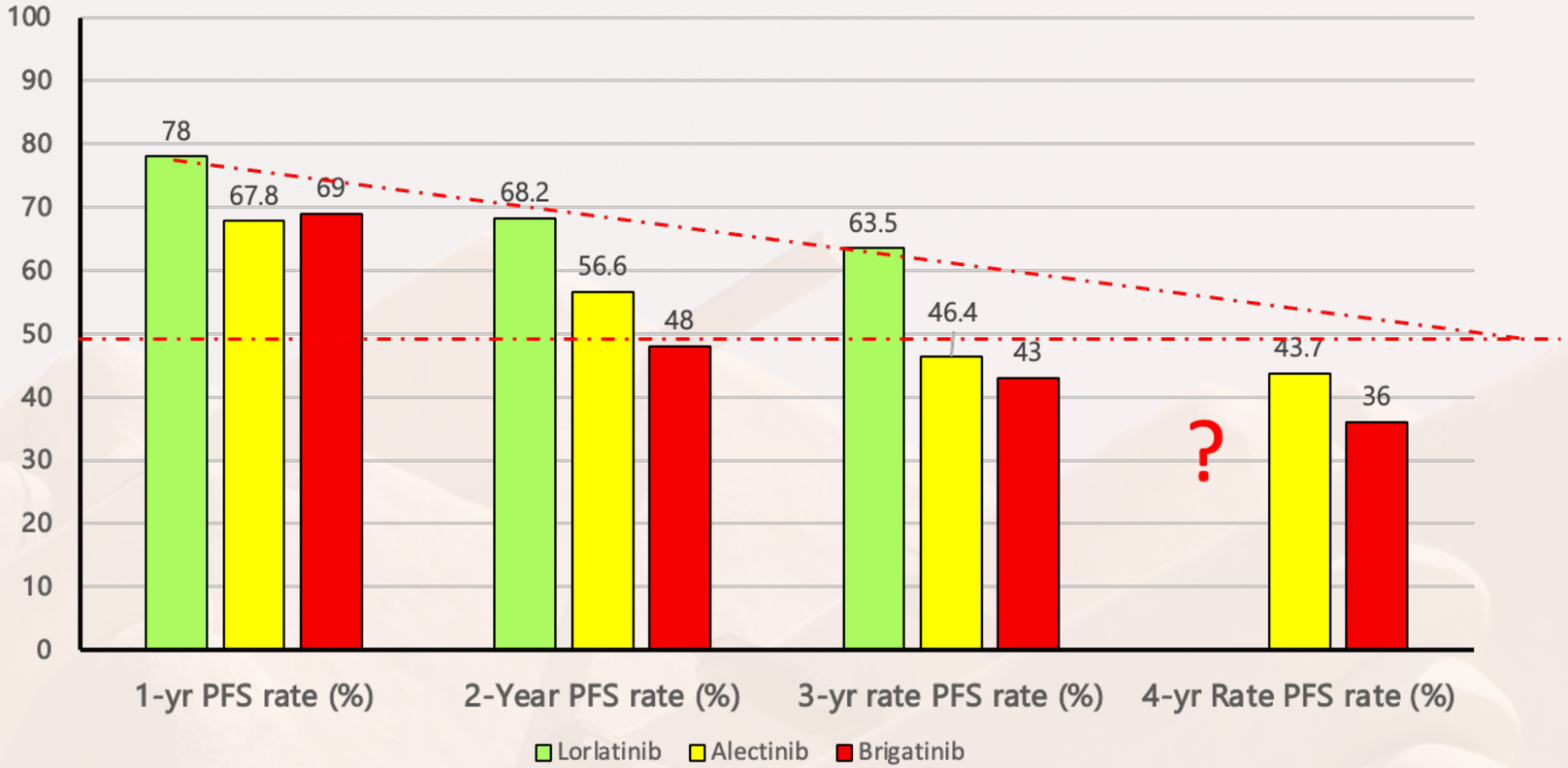
Solomon et al, Lancet Respir Med. 2023 Apr;11(4):354-366.

	Lorlatinib (n=149)	Crizotinib (n=147)
Events	49	92
Number censored	100	55
Median progression-free survival, months (95% CI)	NR (NR–NR)	9·3 (7·6–11·1)
HR (95% CI)	0·27 (0·18–0·39)	



Number at risk (number censored)

Lorlatinib	149 (0)	133 (5)	122 (8)	118 (9)	114 (11)	111 (12)	105 (13)	104 (13)	98 (15)	95 (16)	90 (17)	88 (17)	88 (17)	86 (18)	85 (19)	83 (21)	72 (31)	55 (45)	50 (50)	34 (66)	31 (69)	23 (77)	15 (85)	7 (93)	4 (96)	2 (98)	0 (100)
Crizotinib	147 (0)	126 (13)	100 (18)	85 (23)	64 (29)	54 (30)	40 (32)	33 (35)	26 (37)	25 (37)	19 (40)	17 (40)	17 (40)	17 (40)	16 (40)	11 (44)	9 (46)	7 (48)	6 (49)	5 (50)	4 (51)	2 (53)	1 (54)	1 (54)	1 (54)	0 (55)	0 ..

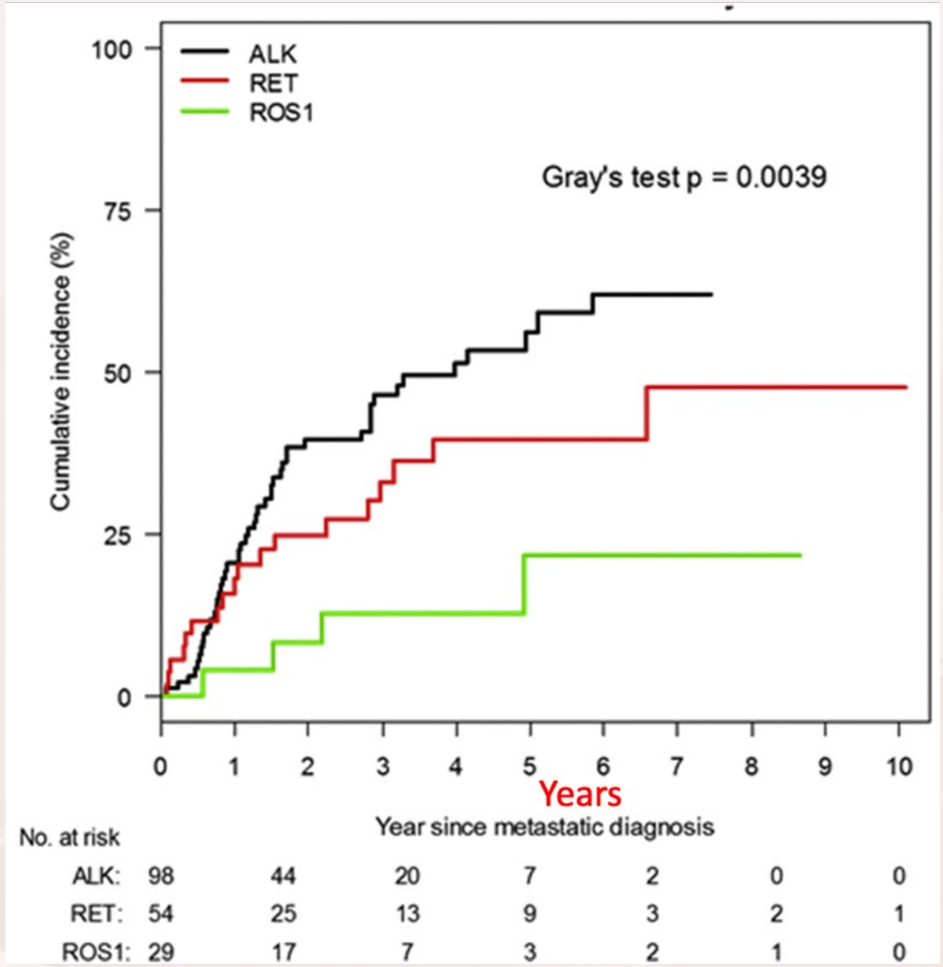


	Lorlatinib	Alectinib	Brigatinib
1-yr PFS (%)	78	67.8	69
2-yr PFS (%)	68	56.6	48
3-yr PFS (%)	64	46.4	43
4-yr PFS (%)	NA	43.7	36

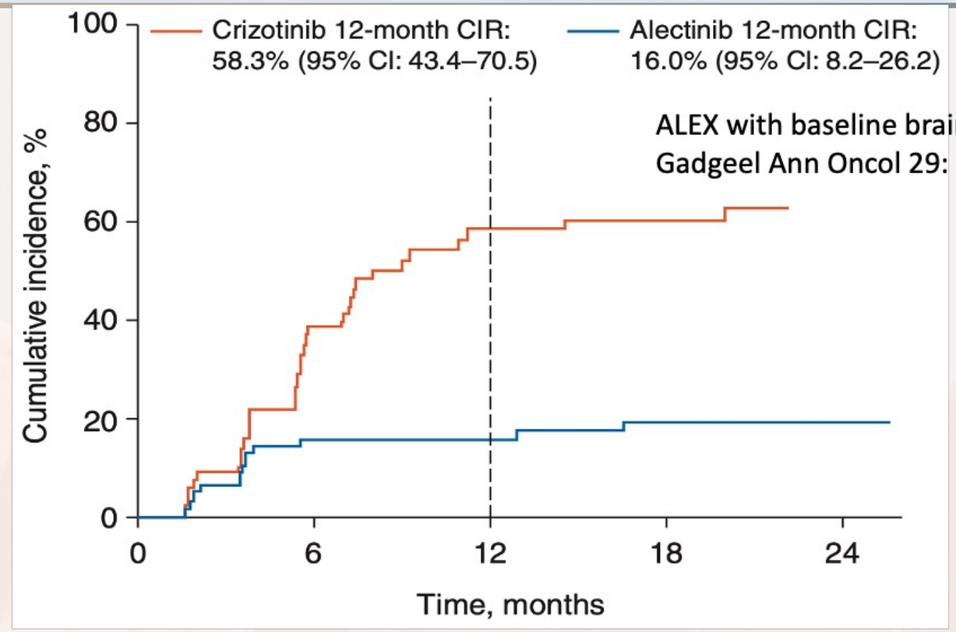
Ou et al Critical Review Oncology Hematology 2023; 187: 104019

Peters NEJM 2017; Camidge JTO 2019; Camidge JCO 2020; Camidge JTO 2021; Solomon Lancet Res Med 2023

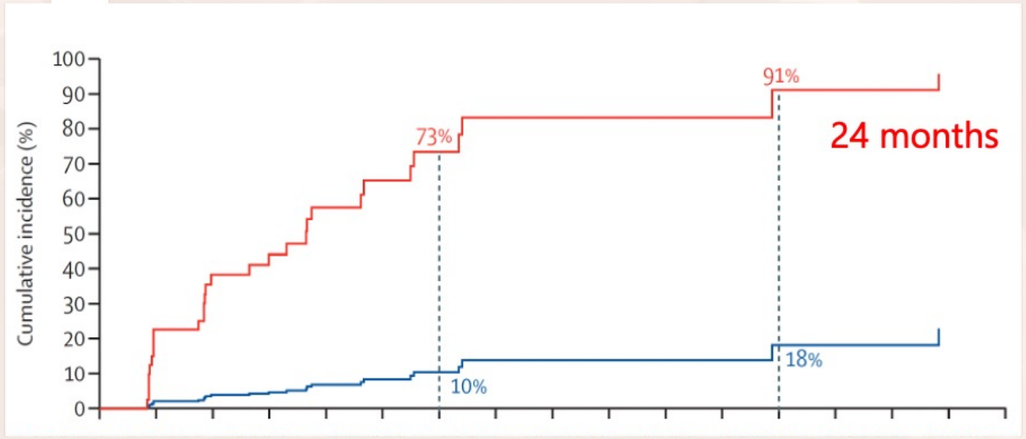
ALEX and CROWN
With baseline CNS mets
Cumulative incidence of CNS mets



Drilon, Lin et al, J Thorac Oncol 2018; 13: 1595-1601

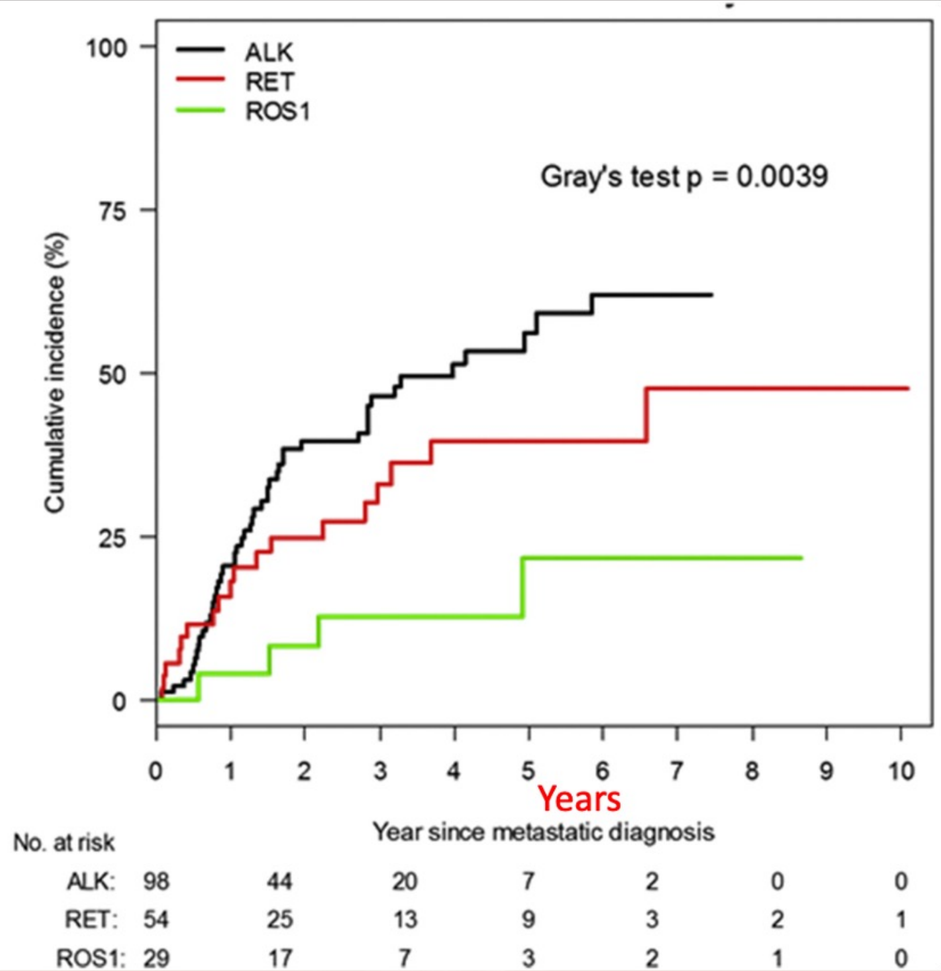


Cumulative Incidence of CNS progression in CROWN with baseline bran mets

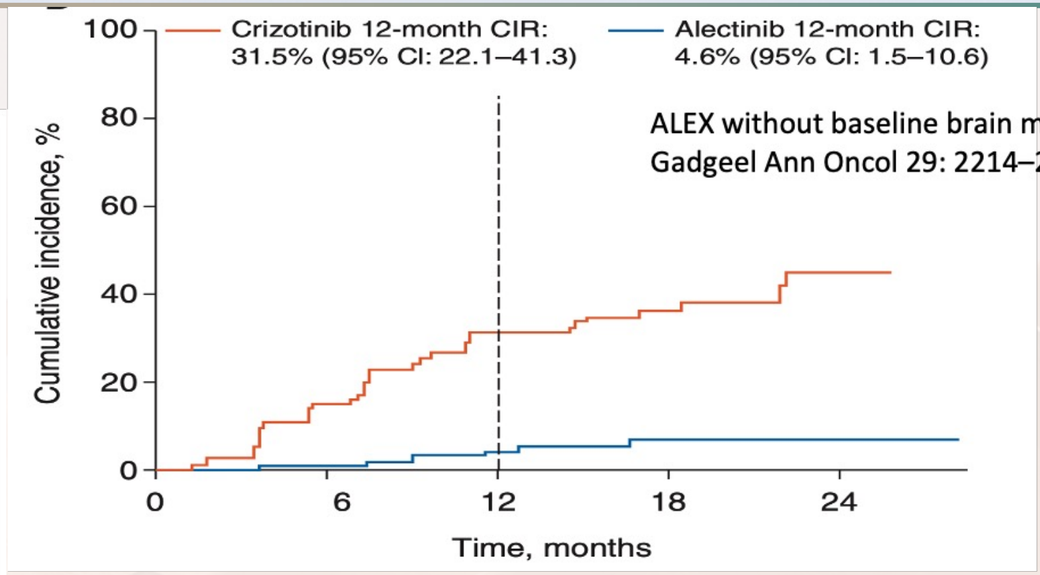


Solomon et al, Lancet Respir Med 2023 Apr;11(4):354-366

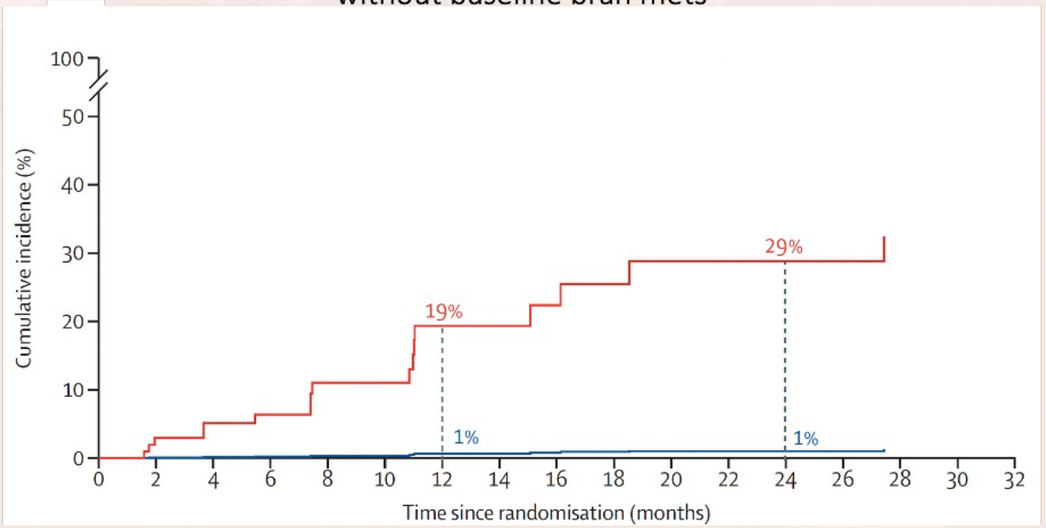
ALEX and CROWN
Without baseline CNS mets
Cumulative incidence of CNS mets



Drilon, Lin et al, J Thorac Oncol 2018; 13: 1595-1601



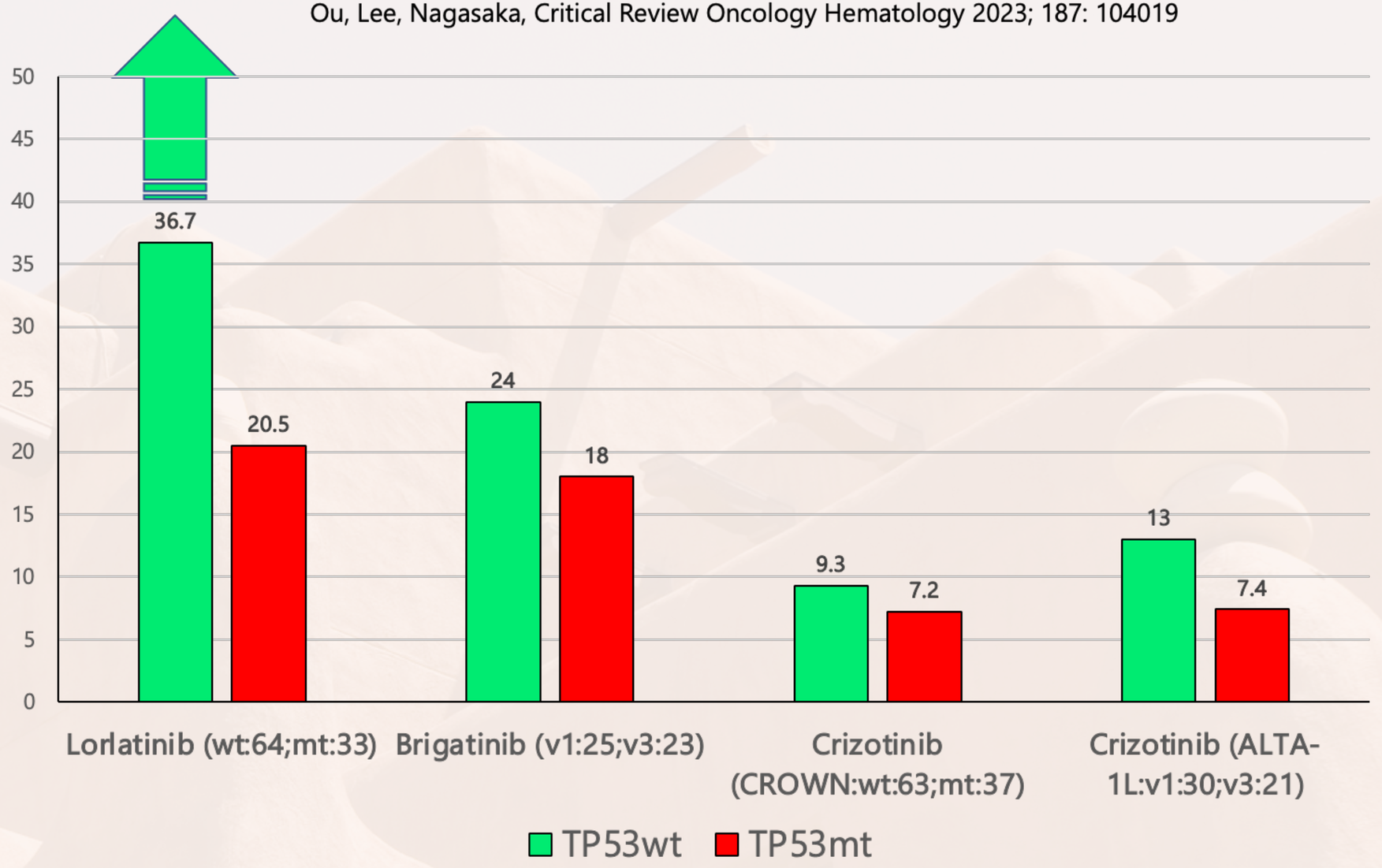
Cumulative Incidence of CNS progression in CROWN without baseline bran mets



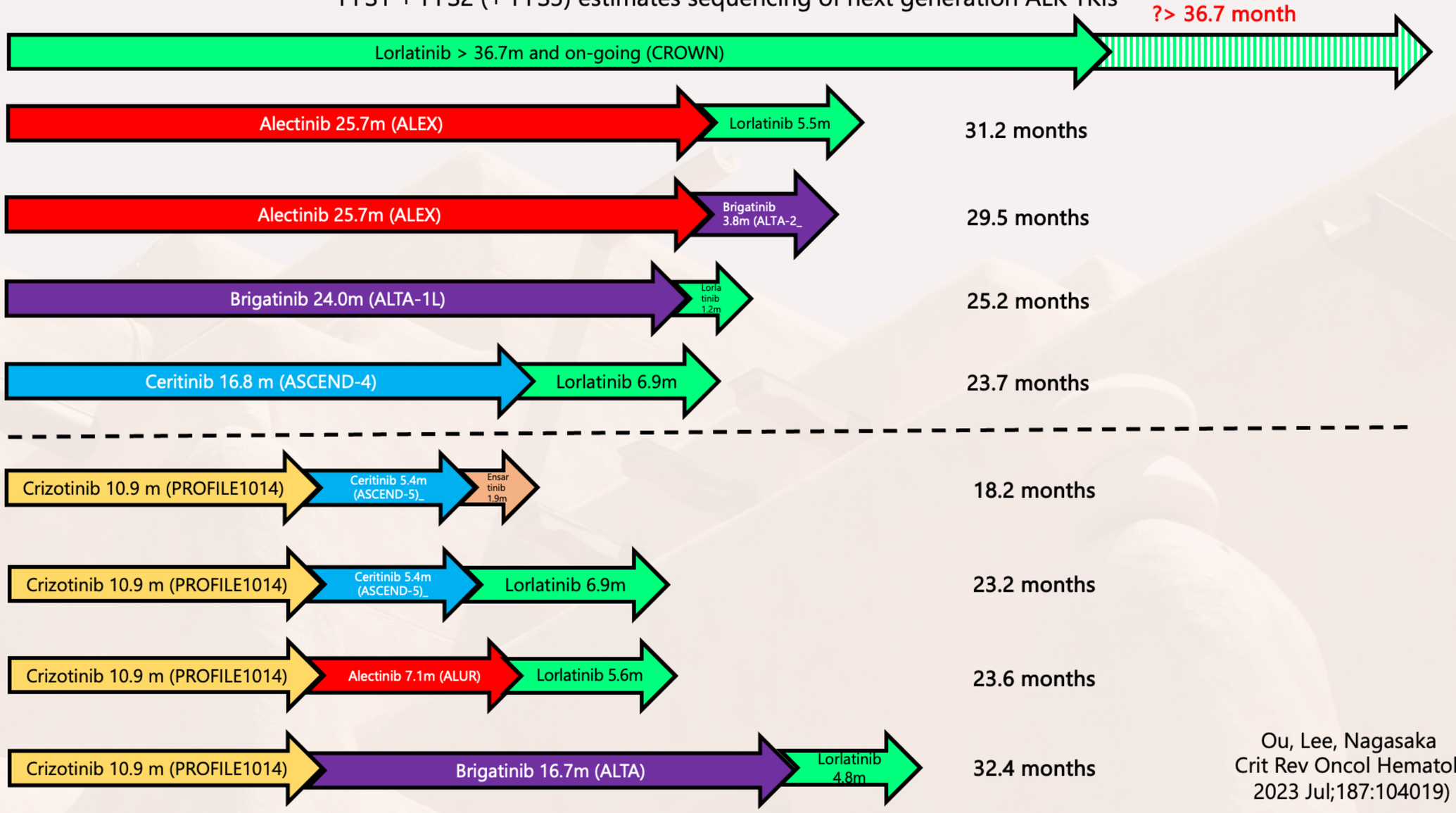
Solomon et al, Lancet Respir Med 2023 Apr;11(4):354-366

PFS by *TP53* mutation status detected by ctDNA (CROWN, ALTA-1L)

Ou, Lee, Nagasaka, Critical Review Oncology Hematology 2023; 187: 104019



PFS1 + PFS2 (+ PFS3) estimates sequencing of next generation ALK TKIs



Ou, Lee, Nagasaka
Crit Rev Oncol Hematol.
2023 Jul;187:104019)

Thank you

PFS by EML4-ALK v1 versus v3 detected by ctDNA (CROWN, ALEX, ALTAl-1L)

Ou, Lee, Nagasaka, Critical Review Oncology Hematology 2023; 187: 104019