ALK: First-line treatment and mechanism of resistance

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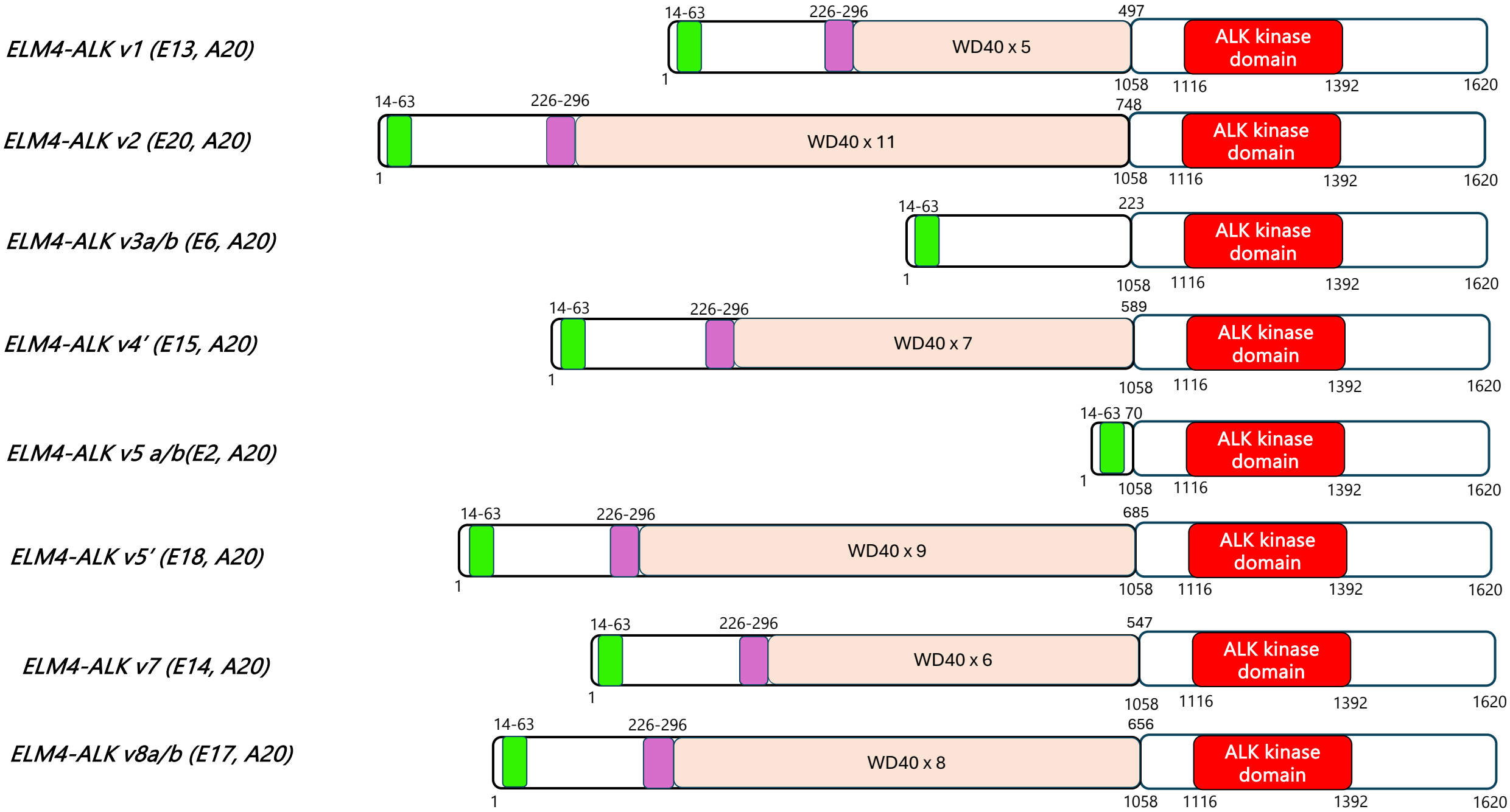
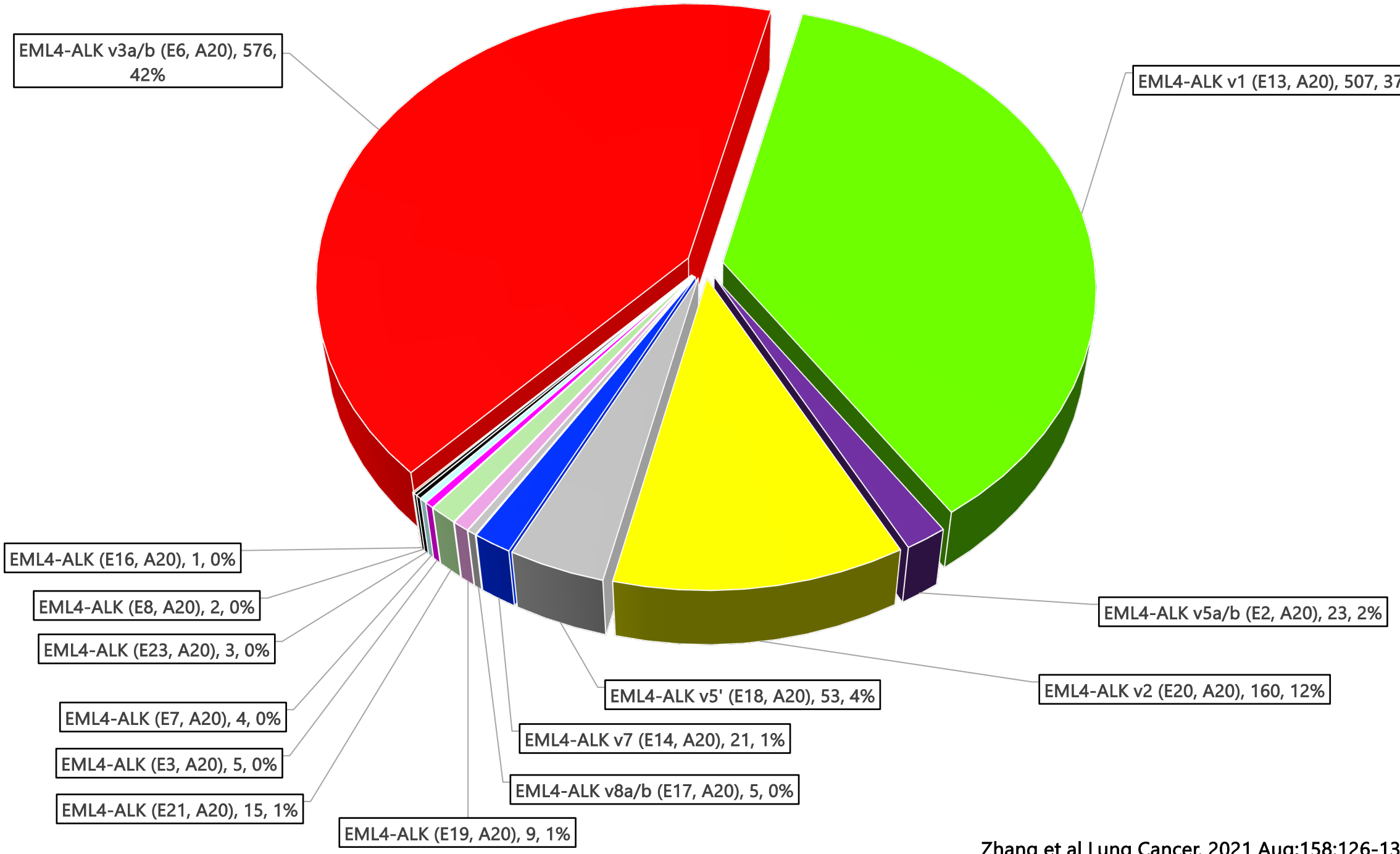
4:05 pm to 4:20 pm July 20, 2024 (Saturday)



Zhang et al Lung Cancer. 2021 Aug;158:126-136.



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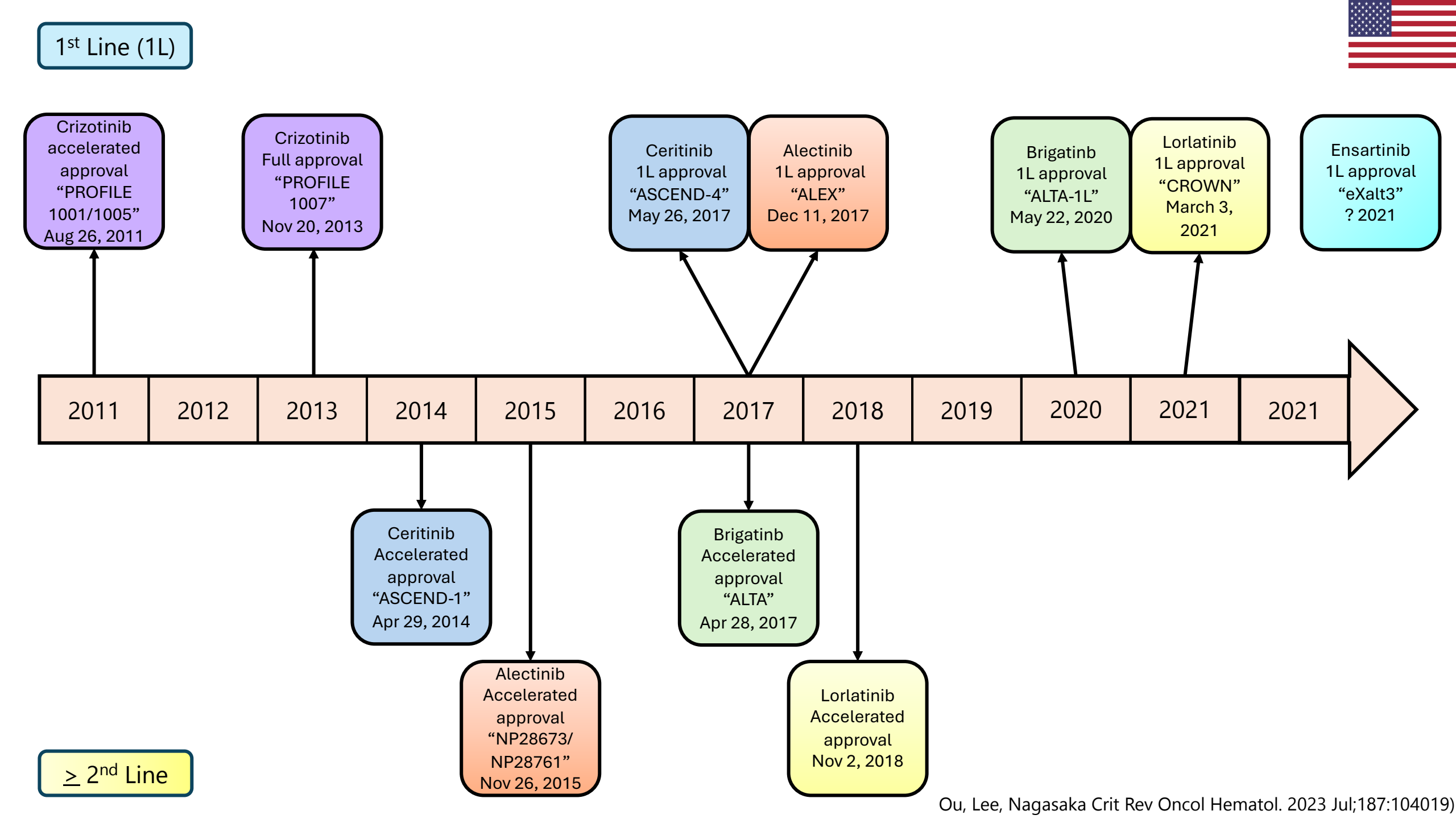
5 pillars of an ideal ALK TKI for *ALK+* NSCLC

- 1. High potency to inhibit wildtype ALK kinase
- 2. Excellent CNS penetration to treat and to delay CNS progression
- 3. Ability to overcome multiple acquired ALK mutations in particular "solvent-front" mutation, *ALK* G1202R, given legacy use of crizotinib and 2nd generation ALK TKIs
- 4. Ability to treat the poor prognostic group of ALK+ NSCLC (*EML4-ALK variant 3* AND/OR *TP53+*)
- 5. Well tolerated as measured by MEAN and MEDIAN relative dose intensity (RDI) over a long duration of treatment



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

Landscape of 1L ALK TKIs approved globally

- 5 ALK TKIs Approved for 1st-line treatment of advanced *ALK+* NSCLC in USA
  - Crizotinib, ceritinib, alectinib, brigatinib, lorlatinib
  - Ensartinib's Prescription Drug User Fee Act (PDUFA) date is December 28, 2024

- 8 ALK TKIs Approved for 1st-line treatment of advanced *ALK+* NSCLC in China
  - Crizotinib, ceritinib, alectinib, brigatinib, ensartinib, lorlatinib
  - Iruplinalkib, envonalkib

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
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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
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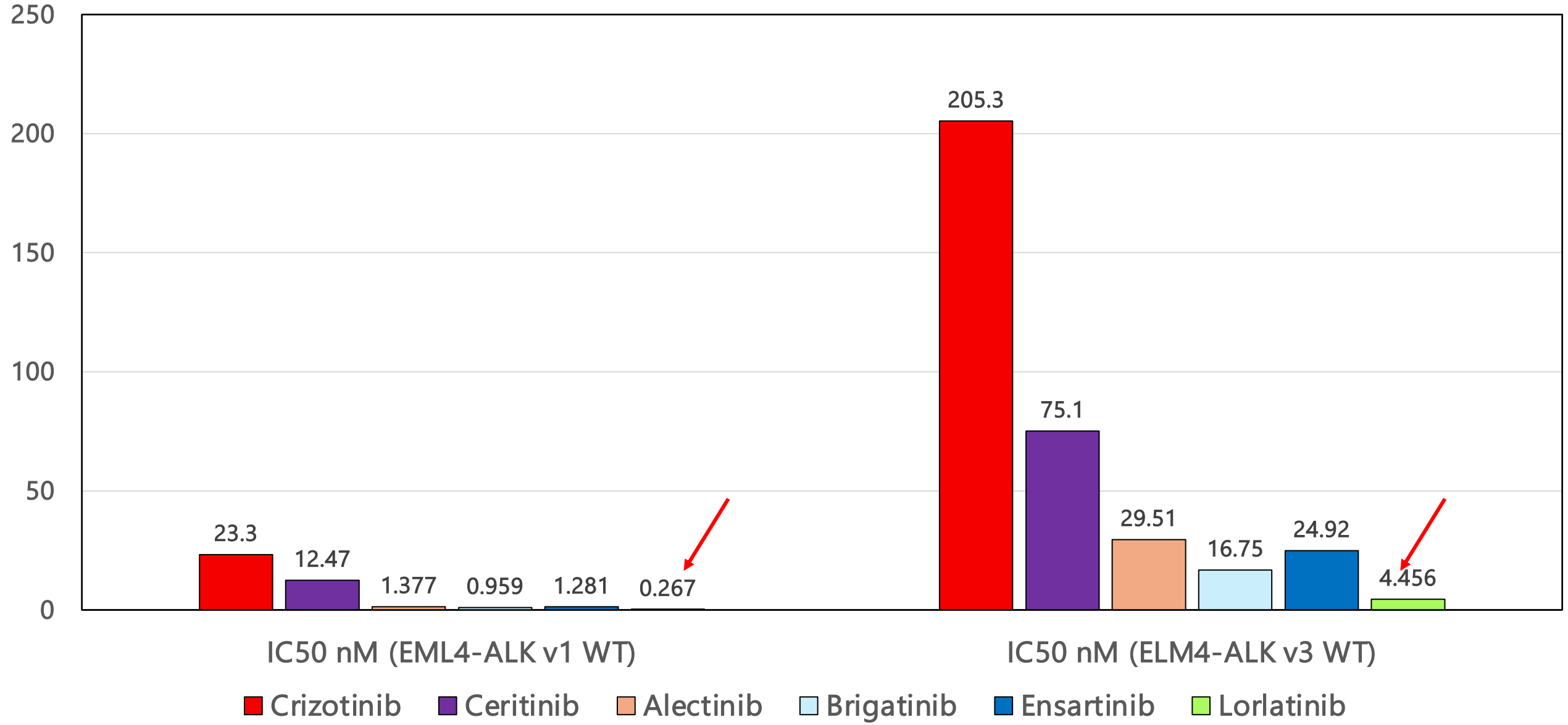
400nM
200nM

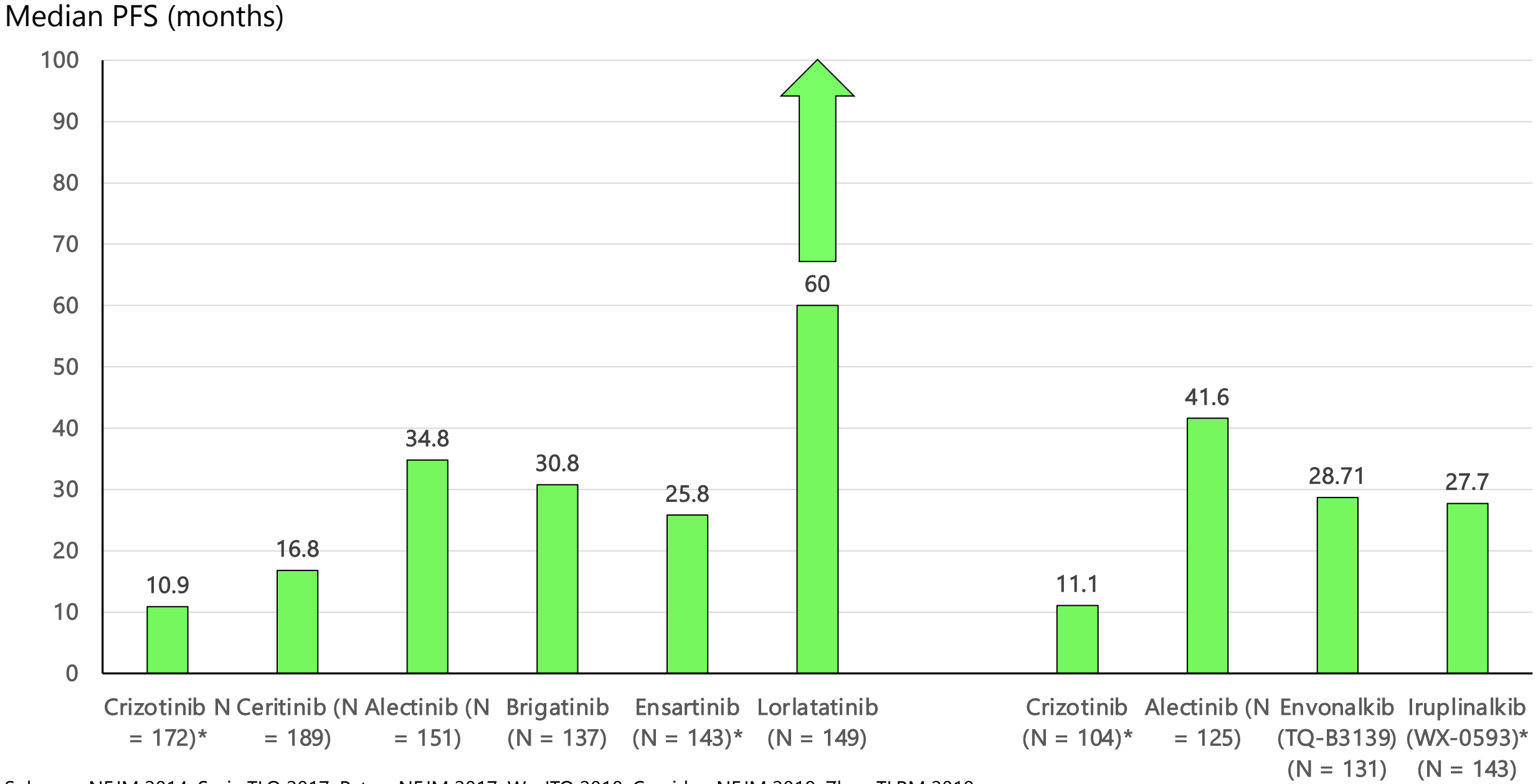
Horn et al, J Thorac Oncol. 2019;14:1901-1911. Work of Dr. Christine Lovy

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



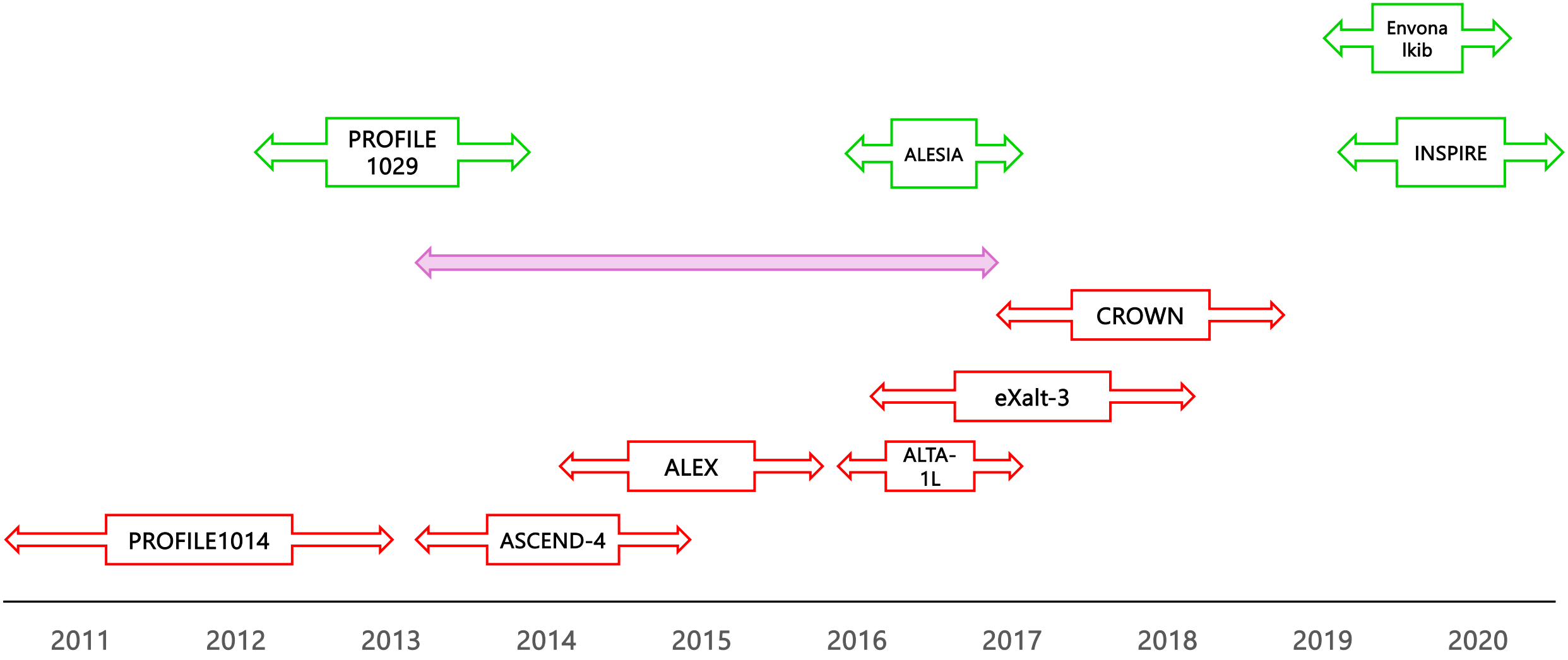
Ou, Lee, Nagasaka Crit Rev Oncol Hematol. 2023 Jul;187:104019)

Median Investigator-assessed median PFS of the comparison arm ALK TKI



Solomon NEJM 2014; Soria TLO 2017; Peters NEJM 2017; Wu JTO 2018; Camidge NEJM 2018; Zhou TLRM 2019; Shaw NEJM 2020; Horn JAMA Oncol 2021; Yang Signal Transduct Target Ther 2023; Yang Shi TJO 2024 ; Solomon JCO 2024

Timeline on the accrual of Phase 3 ALK TKI trials



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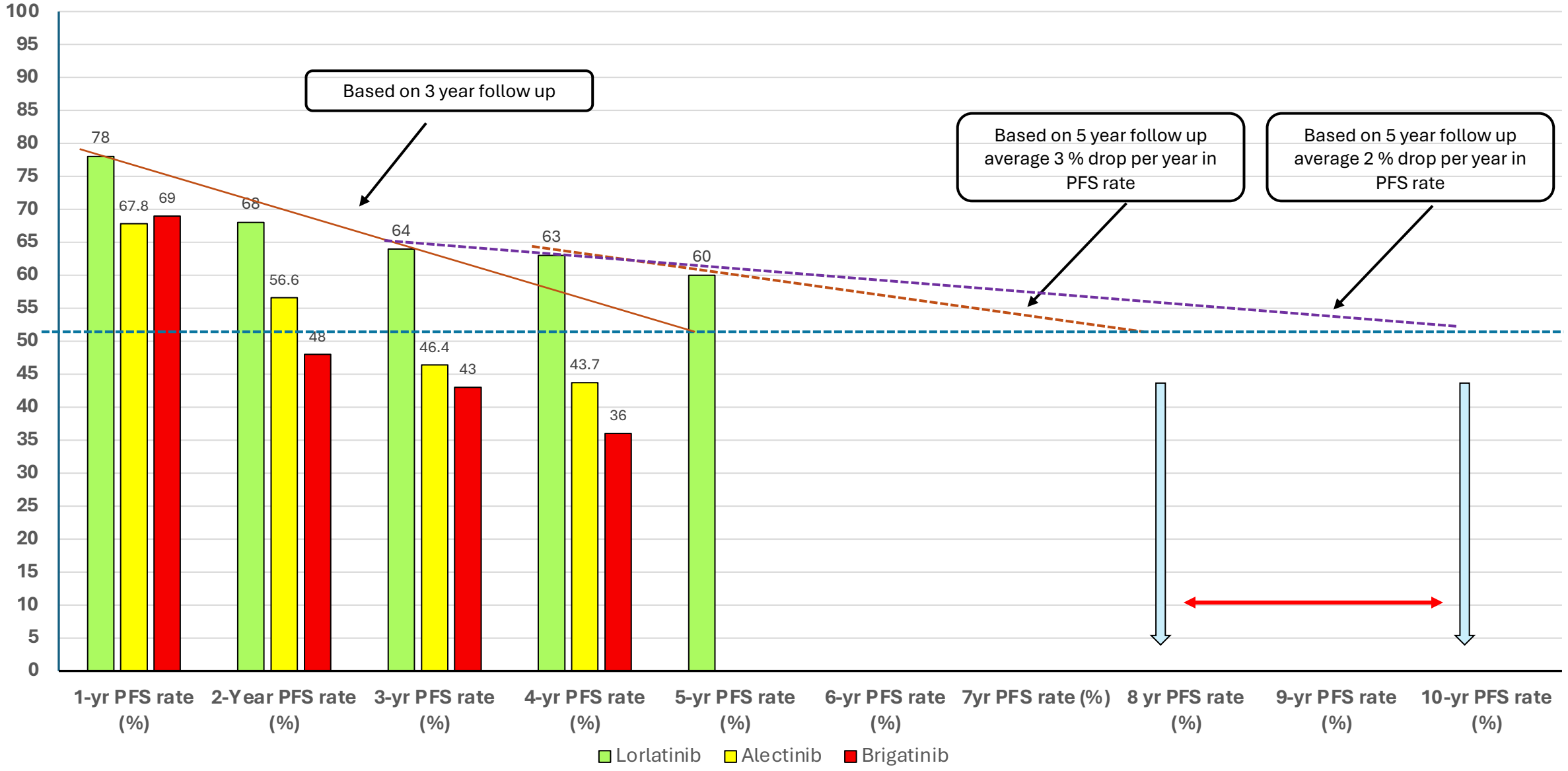
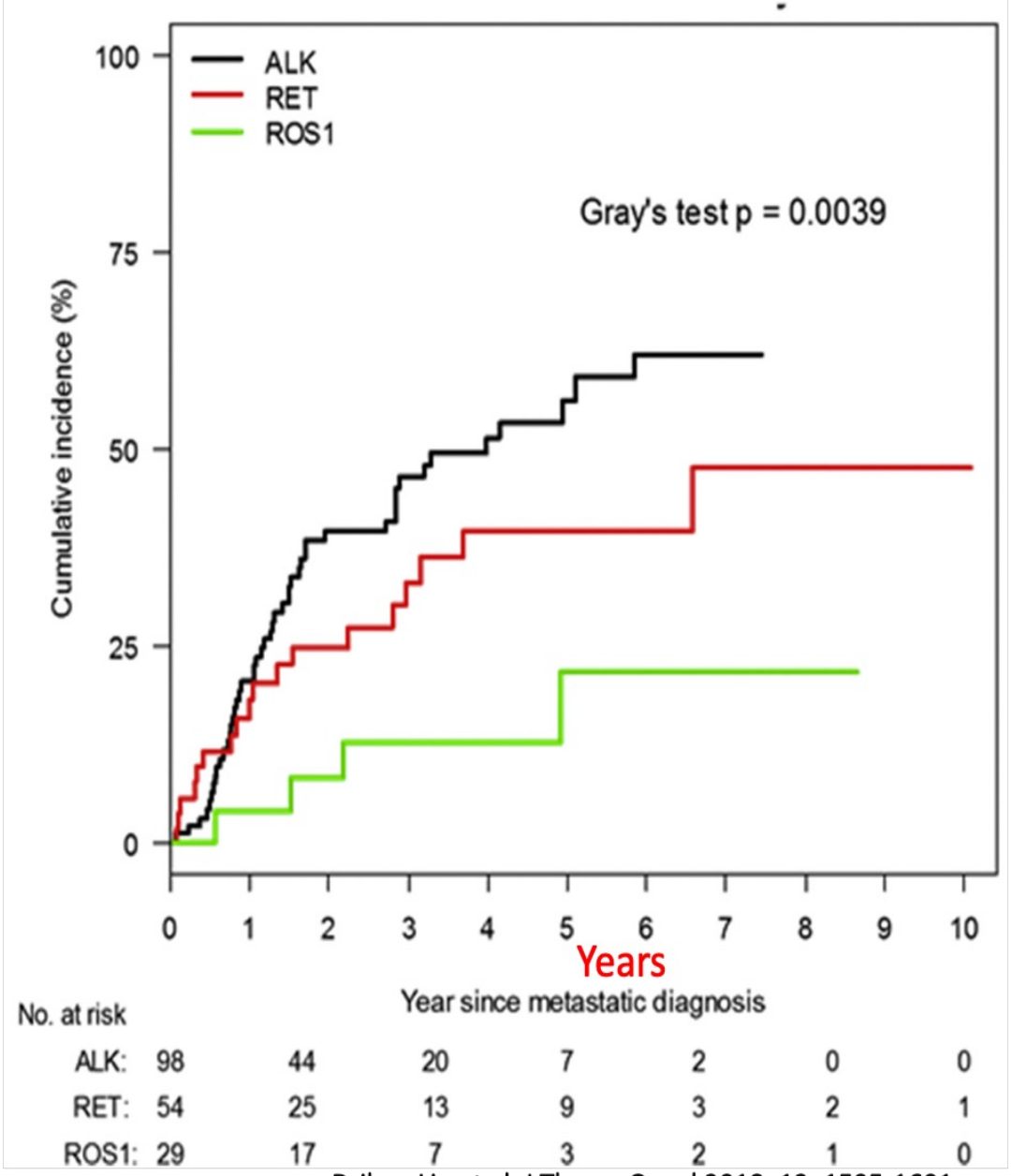
Shaw NEJM 2020; Horn JAMA Oncol 2021; Yang Signal Transduct Target Ther 2023; Yang Shi TJO 2024

Projection of 50% PFS of lorlatinib for CROWN (~ median PFS of lorlatinib)



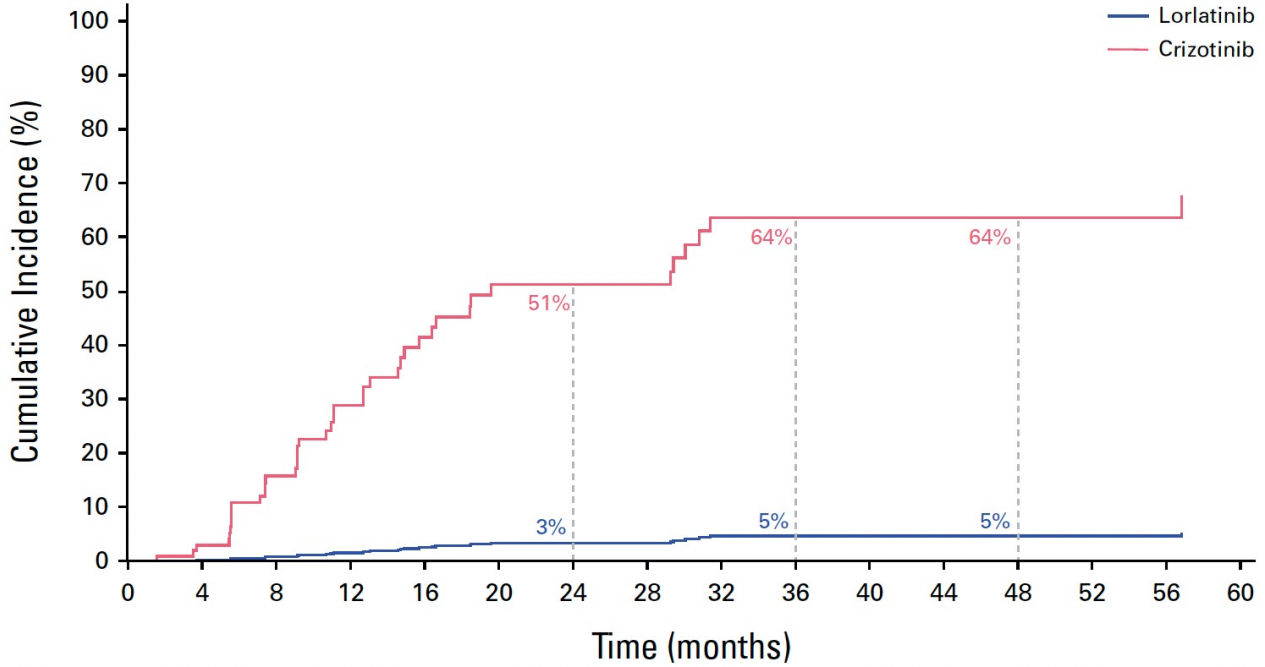
Camidge J Thorac Oncol. 2019 Jul;14(7):1233-1243; Camidge J Thorac Oncol. 2021 Dec;16(12):2091-2108; Solomon Lancet Respir Med. 2023 Apr;11(4):354-366; Solomon JCO 2024

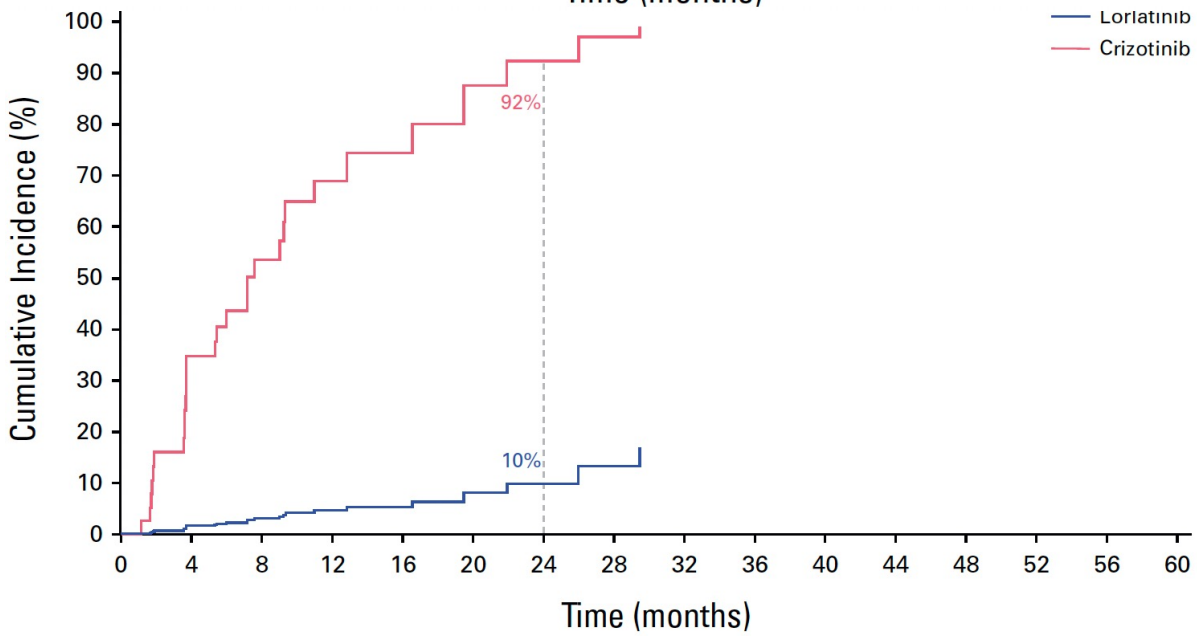
Lorlatinib changed the natural history of advanced ALK+ NSCLC



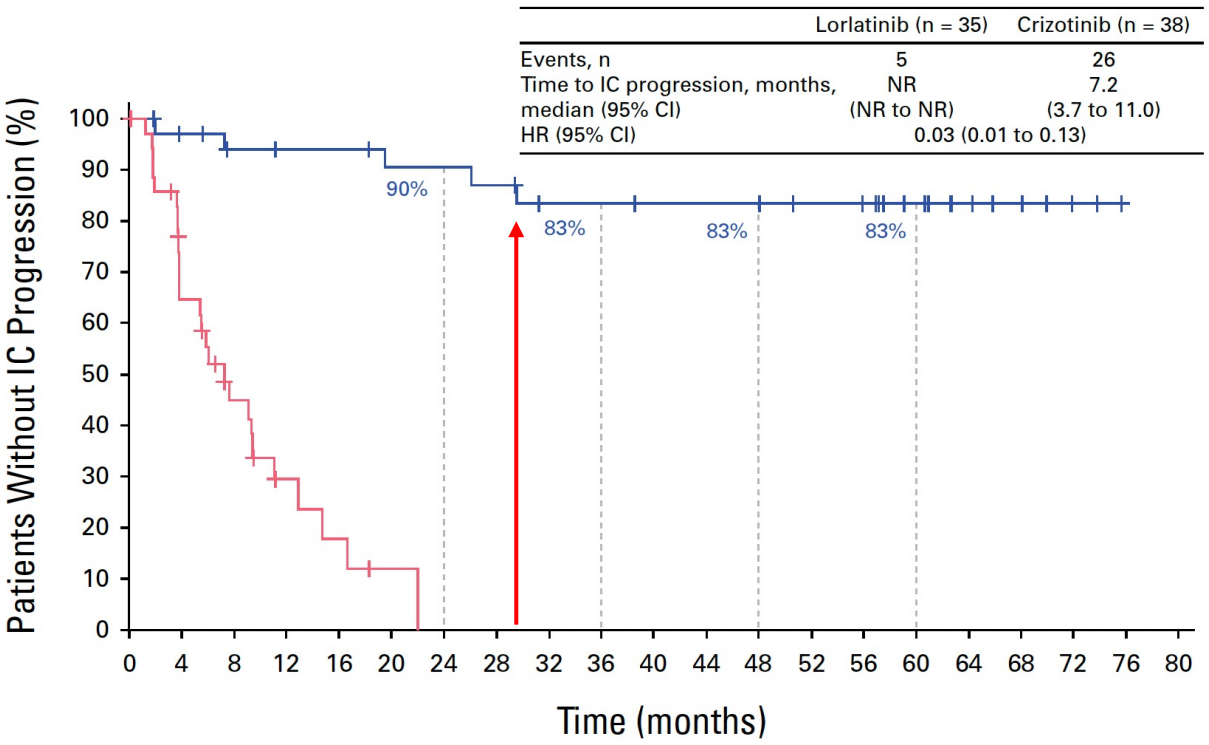
Drilon, Lin et al, J Thorac Oncol 2018; 13: 1595-1601

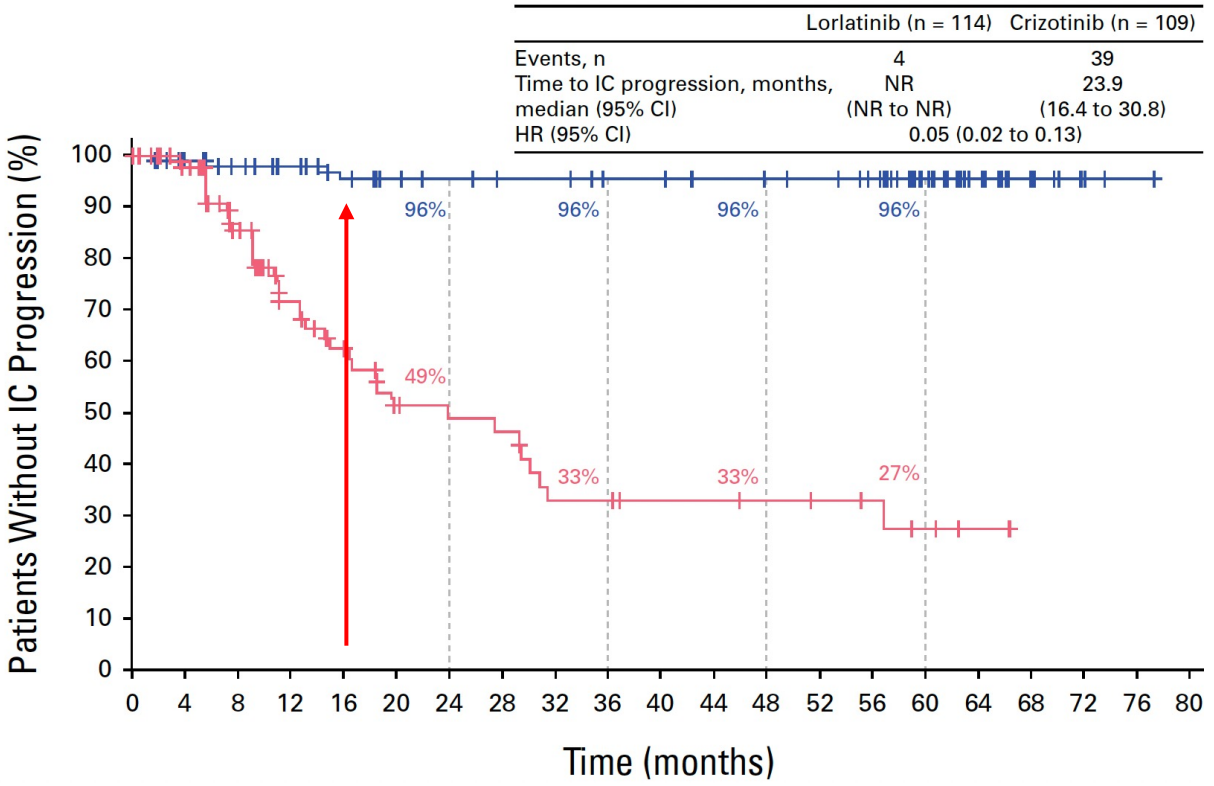
Solomon JCO 2024





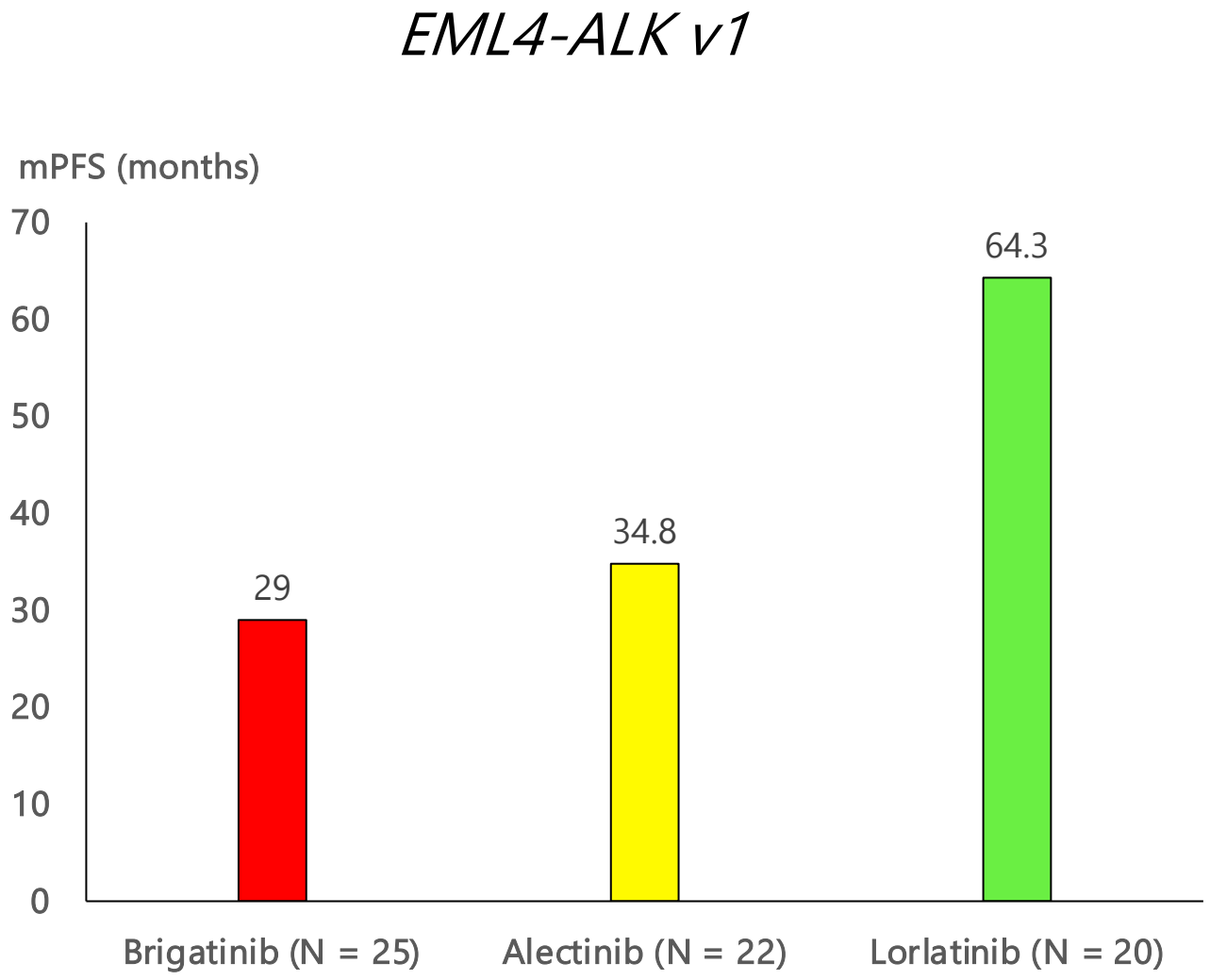
Lorlatinib prevent late relapse in the CNS

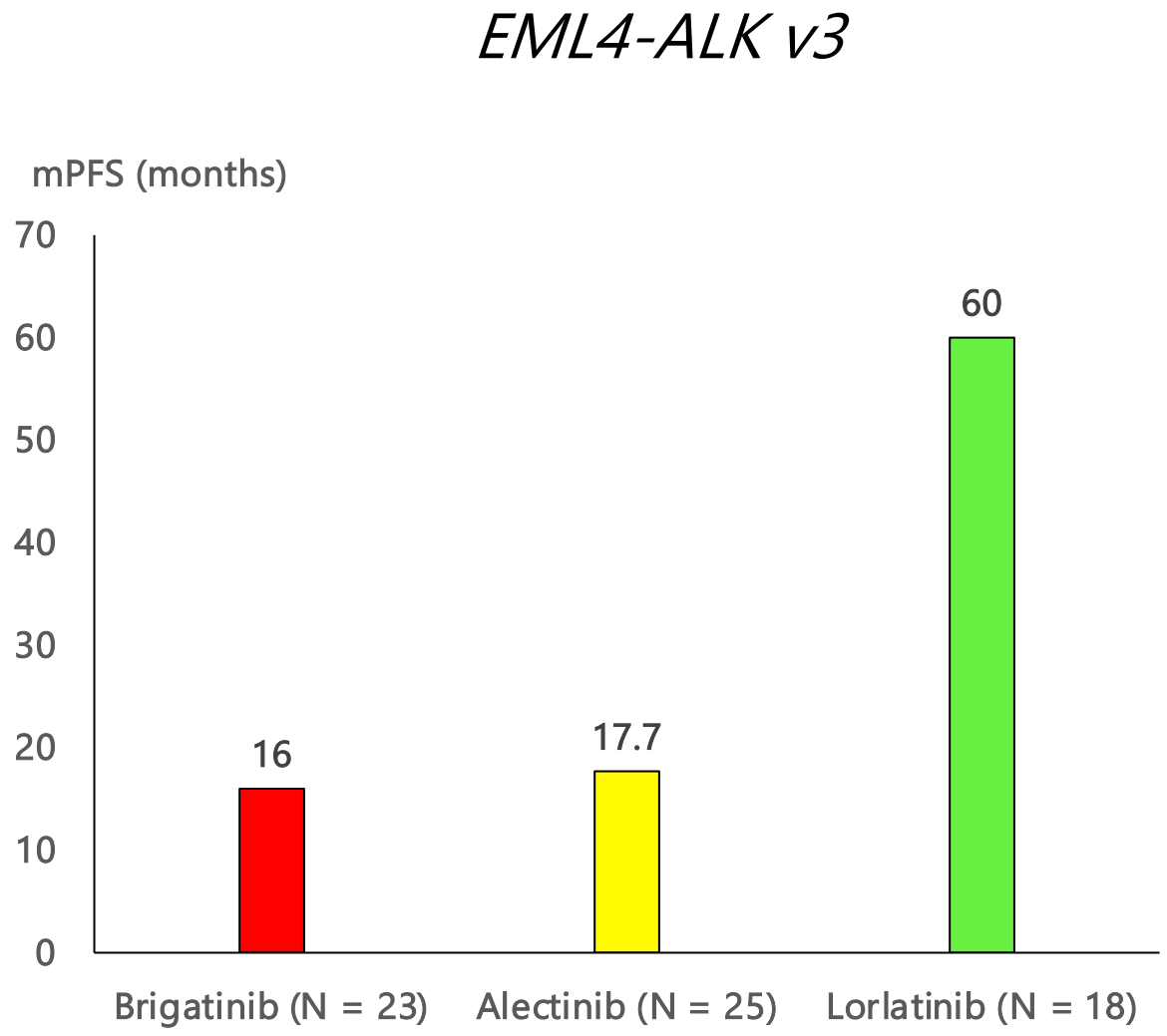




Solomon JCO 2024

Median PFS of EML4-ALK variants (v1 vs, v3) from ctDNA from ALEX, ALTA-1L, and CROWN





Camidge JTO 2019, Camidge JTO 2021, Solomon JCO 2024

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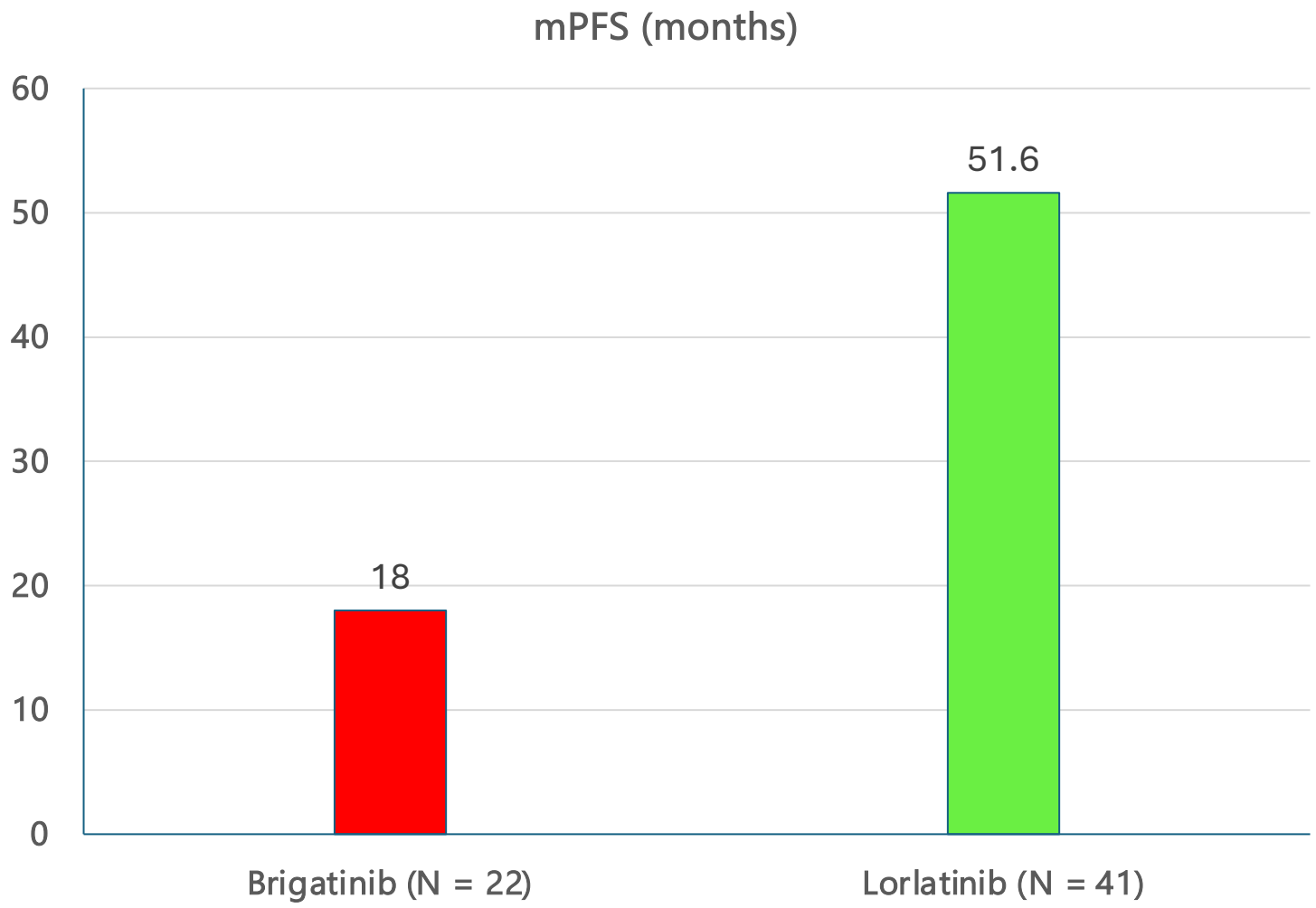

Camidge JTO 2021, Solomon JCO 2024

Mean and Median Relative Dose Intensity (RDI) of ALK TKIs from phase 3 trials

	ASCEND-4	ALEX	CROWN
ALK TKI	Ceritinib	Alectinib	Lorlatinib
N	189	152	149
Median follow up time	19.7 months (all patients)	18.6 months (range: 0.5 – 29.0)	60.2m (95%CI: 57.4 – 61.9)
Median Duration of Treatment	66·4 weeks (IQR 30·0–83·7)	17.9 months (range: 0 – 29)	57.0 months (IQR: 13.9 – 63.3)
Does interruption (%)	80% (interruption + reduction)	22.4%	62%
Dose reduction (%)		16.4%	23%
Dose discontinuation (%)	5.3% (10/189)	13.2%	11%
Relative median dose intensity	78.4% (IQR: 63.2 – 97.5)	100% 27.8 months (range: 0.5–38.7)	99% (IQR: 80 – 100)
Relative mean dose intensity	Not reported	95.6±10.3%**	92%*

*Geoffrey Liu personal communications; soria Lancet 2017; Peters NEJM 2017; Solomon JCO 2024

Mechanism of resistance

Principles of resistance mechanisms

- On-target resistance
  - Sequential use of more potent ALK TKIs (but not starting with the most potent ALK TKI) leads to single and then compound mutations
  - Use of lorlatinib 1L so far no acquired resistance mutation identified
    - Though theoretical Cβ6 (central beta-sheet #6) ALK L1256F could happen but so far no reported cases
- Off-target resistance
  - MET amplification
  - Combination of ALK TKI with a MET TKI has been reported in case report format

All 6 approved ALK TKIs heatmaps

EML4-ALK Variant

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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
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EML4-ALK Variant 3

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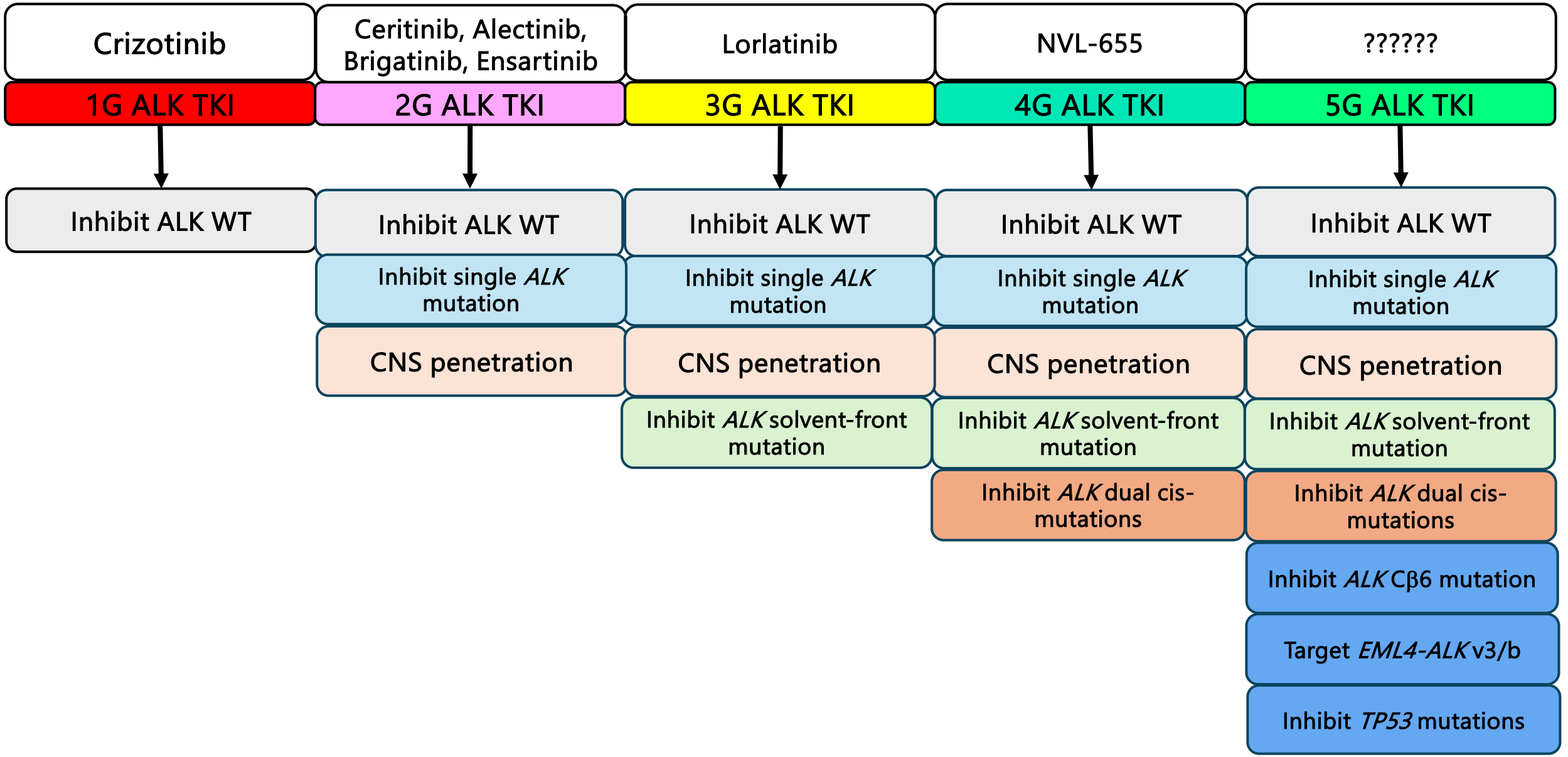
G1202R	440.5 175.7 to 1105	405.6 189.5 to 868.1	315.9 194.1 to 514.1	>10000 N/A	83.82 50.43 to 139.3	35.72 20.46 to 62.36
D1203N	332.0 170.1 to 648.2	329.2 172.0 to 630.1	21.10 11.73 to 37.98	142.7 46.29 to 439.7	33.42 20.19 to 55.30	19.73 12.16 to 32.01
S1206C	308.1 152.9 to 620.9	222.2 91.30 to 541.0	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 Lovy

Functional progression from 1G to 5G ALK TKI



Ou et al, Lung Cancer: Targets and Therapy. 2024 Feb 27:15:19-27

To not have to deal with resistance is not to allow resistance to develop

Resistance mechanisms to lorlatinib in CROWN (N = 31)

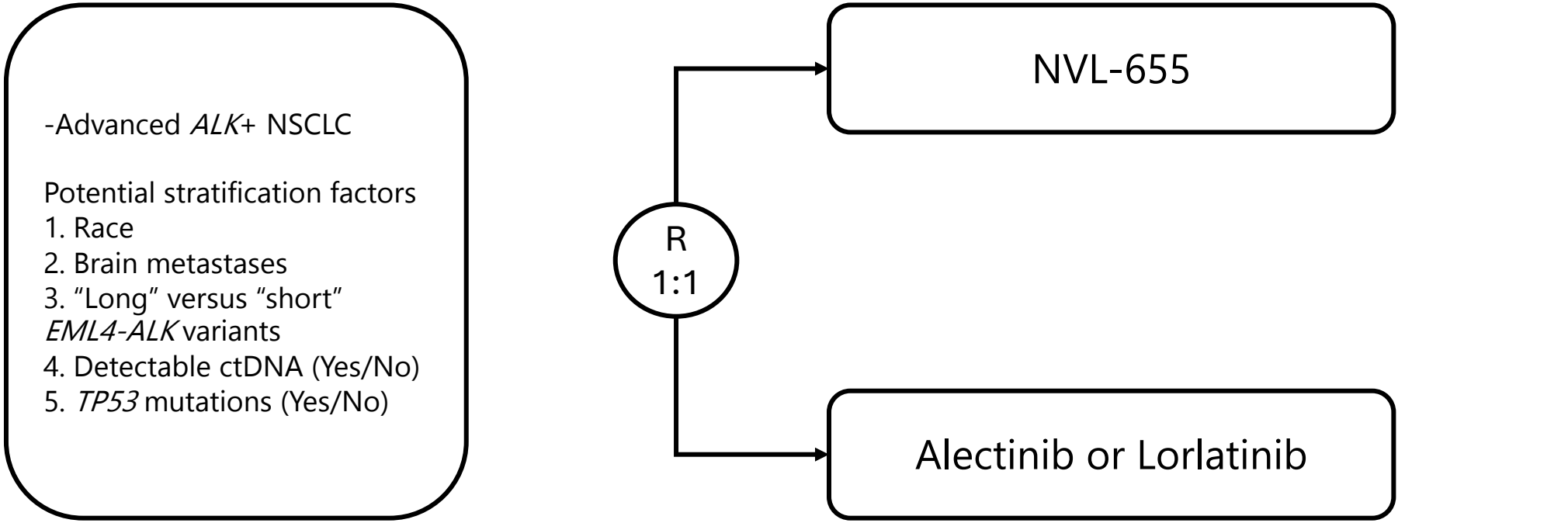
- No acquired resistance mutations detected
- Bypass pathway (Off-target resistance mutations)
  - KRAS G12C, BRAF amplification
  - MET amplification

Solomon JCO 2024

Beyond Lorlatinib

- NVL-655 (4th generation: double mutant positive)
- 5th generation (“holistic” ALK TKI)
- Given the 5-year CROWN update how to move beyond 10 year mPFS?
- Trial Design?
  - PFS as primary endpoint?
- Line of Therapy?
  - Always first-line?

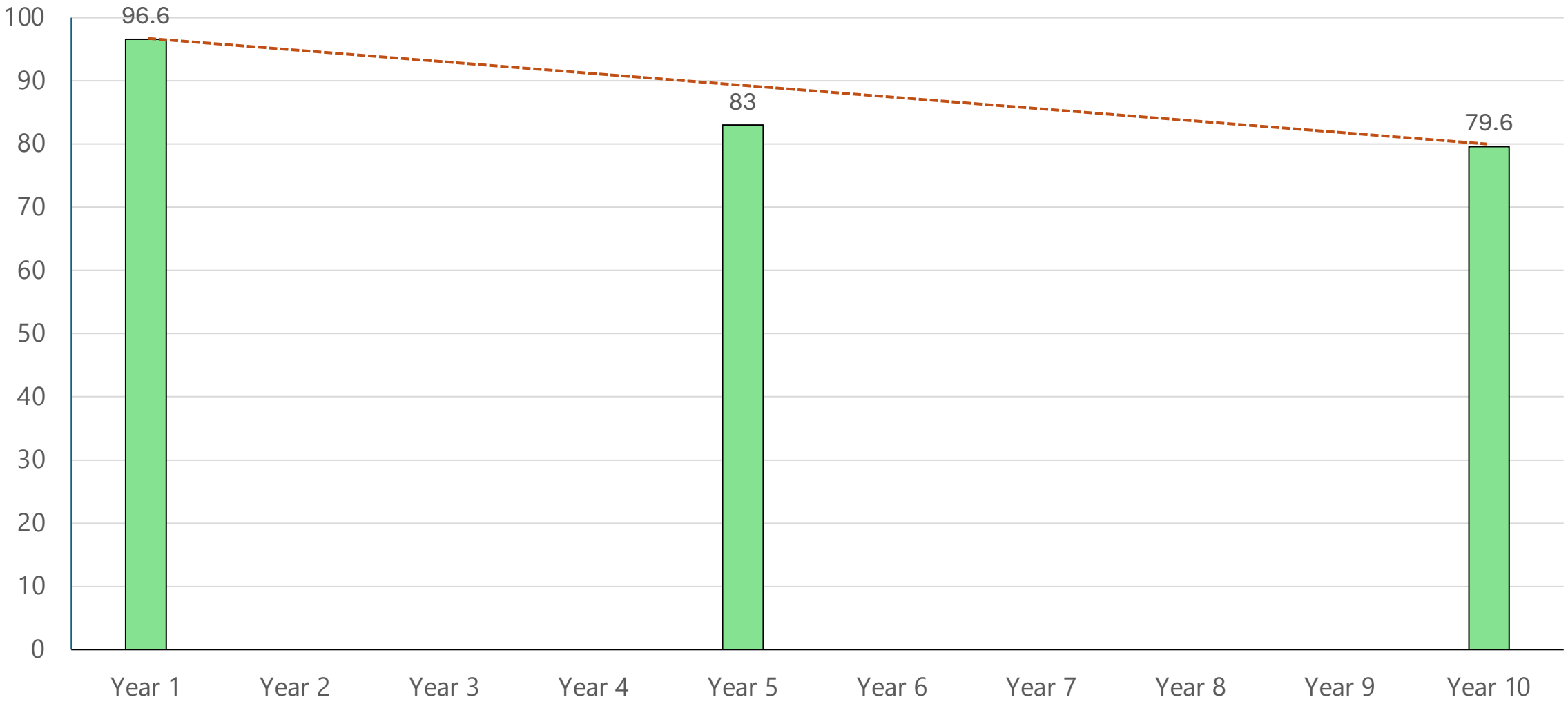
Conceptual first-line randomized phase 3 trial design of 4G ALK TKIs



1^0 endpoint: PFS (BIRC-assessed)
25% improvement in mPFS from 28-34 months to 35-42 months

Ou et al, Transl Oncol. 2021 Nov;14(11):101191.

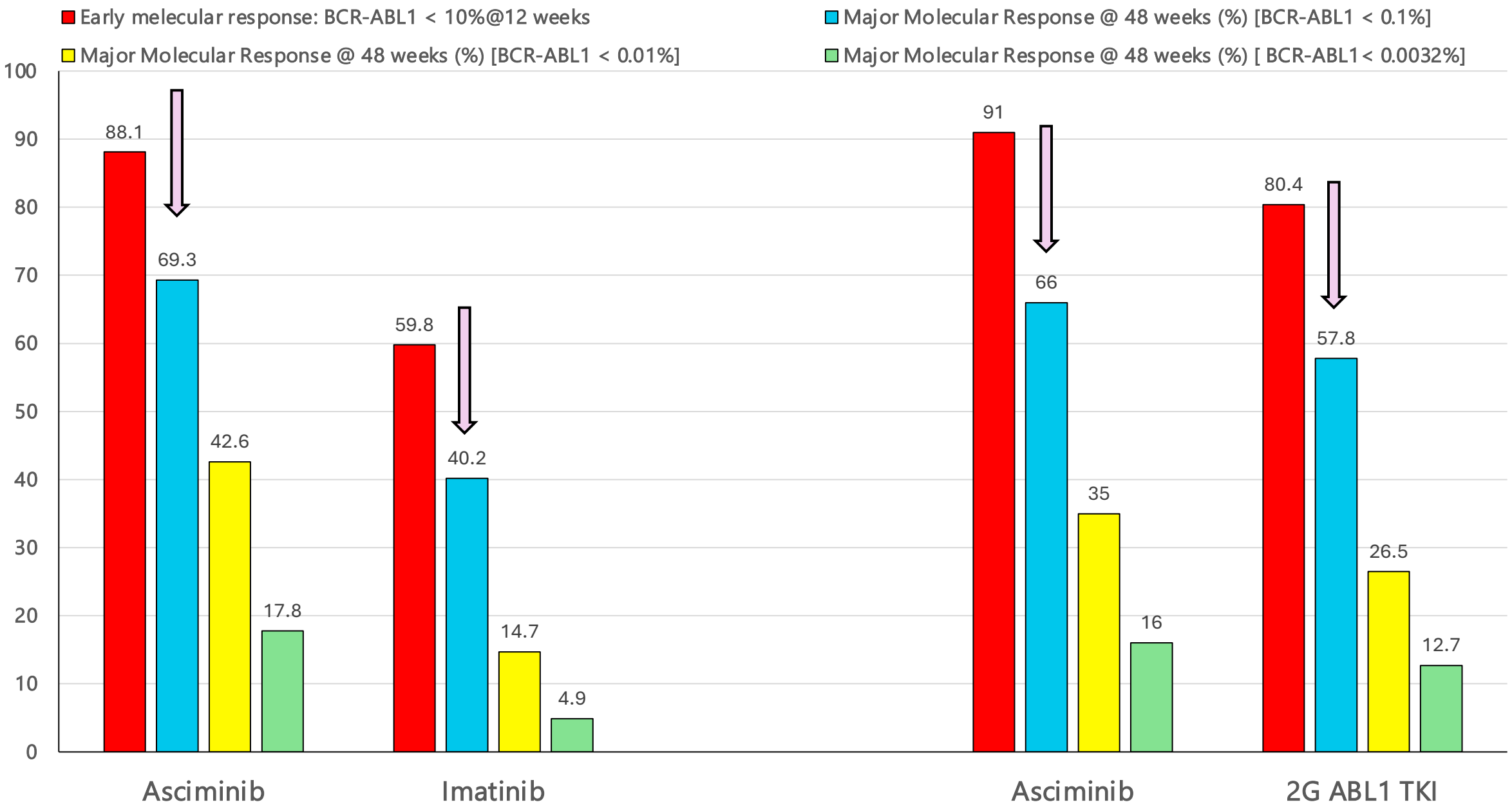
Event-free Survival (EFS) rate of imatinib in chronic CML from the IRIS trial



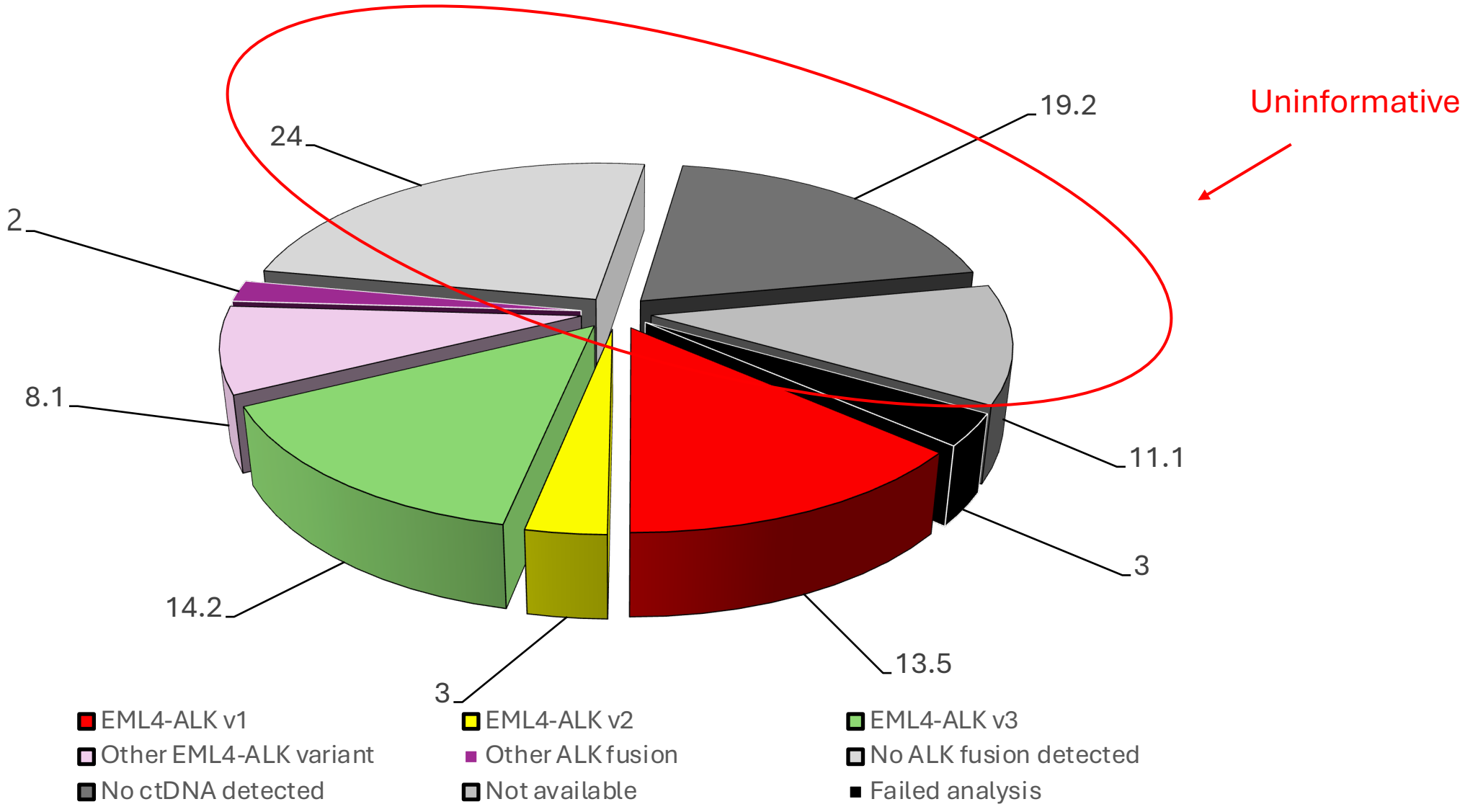
Hochhaus et al, NEJM 2017; 376: 917-927

Comparison of generation of tyrosine inhibitors against BCR-ABL1 in chronic phase CML

Hochhaus, NEJM 2024

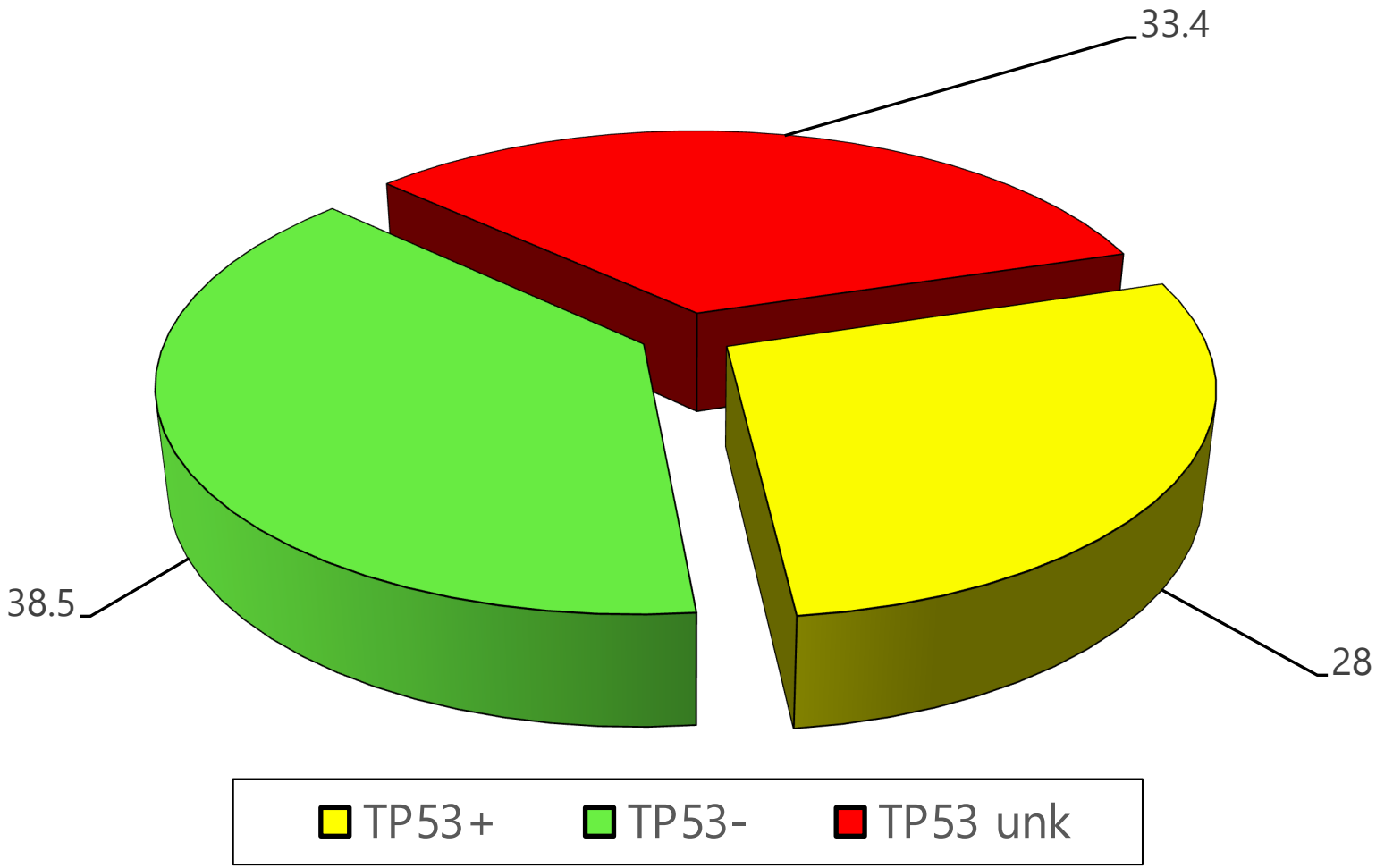


Outcome of plasma genotyping in CROWN



Solomon et al, JCO 2024

Prevalence of TP53 mutation from plasma genotyping in CROWN



Solomon et al, JCO 2024

ALK+ NSCLC versus Chronic phase CML

	ALK+ NSCLC	CML
Discovery timeline	2007-EML4-ALK in NSCLC	1960-Philadelphia chromosome 1973- t(9;22) (q34.1;q11.2) 1986
Chromosomal rearrangement	inv(2)(p21;p23)	t(9;22) (q34.1;q11.2)
Major oncokinase	EML4-ALK variant 1 (E13;A20) EML4-ALK variant 3 (E6; A20)	$P210^{BCR\text{-}ANL1}$ (e13/14;a2)
Minor oncokinase isoforms/variants	EML4-ALK variant 2 (E20;A20) EML4-ALK variant 5 (E2;A20)	$P190^{BCR\text{-}ABL1}$ (e1;a2) $P230^{BCR\text{-}ABL1}$ (e19;a2) e6a2, e8a2, e13a3, e14a3
First-generation kinase inhibitor	Crizotinib	Imatinib
Second-generation kinase inhibitor	Ceritinib, Alectinib, Brigatinib, Ensartinib, Envonalkib, Irupalikb	Dasatinib, Nilotinib, Bosulitinib
Third-generation kinase inhibitor	Lorlatinib	Ponatinib, Asciminib
High risk sub-population	EML4-ALK v3/TP53+	High Sokol score
Efficacy of 1G Inhibitor	5-yr PFS rate of 8%	10-year EFS rate of 79%
Efficacy measurement	PFS	*BCR-ABL1*^{IS} ≤ 0.1% at 48 weeks (Major molecular response)
Biologic relevant surrogate marker	ALK fusion mRNA *EML4-ALK/ALK?*	*BCR-ABL1/ABL1* ≤ 0.1% *BCR-ABL1/ABL1* ≤ 0.01% *BCR-ABL1/ABL1* ≤ 0.0032% *BCR-ABL1/ABL1* ≤ 0.001%

Summary (Personal)

- Lorlatinib should be the first-choice ALK TKI for advanced *ALK+* NSCLC
- It took 3 generations of ALK TKI to reach the efficacy achieved by imatinib in CML
- While there are 2nd and 3rd generation of ABL1 TKIs approved based on surrogate biomarkers, that is so lacking in solid tumor and in ALK+ NSCLC.
- If median PFS is the benchmark for ALK TKI beyond lorlatinib, we may have reached the zenith of ALK TKI treatment for a long while