Approach to NSCLC With Targetable Mutations (EGFR, ALK and ROS-1)

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Gaps and Disparities in Biomarker Testing in NSCLC

MYLUNG Consortium

Test Types	Overall (N = 3,474)	Nonsquamous (n = 2,820)
EGFR	70%	76%
ALK	70%	76%
ROS1	68%	73%
BRAF	55%	59%
PD-L1	83%	83%
Any biomarker	90%	91%
All 5 biomarker tests	46%	49%
NGS	37%	39%

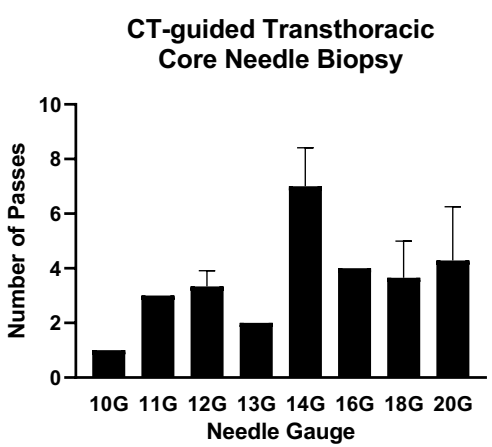
FLATIRON EHR-Derived Data

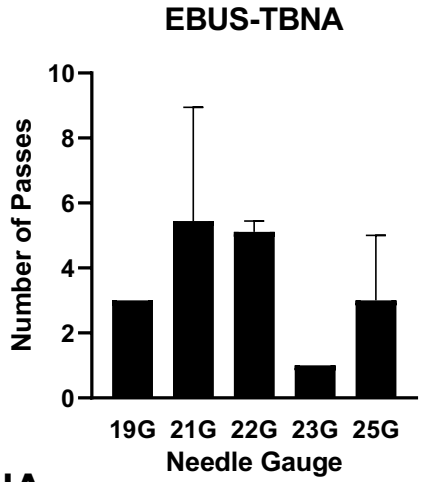
	NSCLC Overall (N = 14,768)	White (n = 9,793)	Black/AA (n = 1,288)	P, White vs Black/AA
All patients with NSCLC				
Ever tested	11,297 (76.5%)	7,477 (76.4%)	948 (73.6%)	.03
Tested prior to 1L therapy		6,064 (61.9%)	784 (60.9%)	.47
Ever NGS tested	7,185 (48.7%)	4,904 (50.1%)	513 (39.8%)	< .0001
NGS tested prior to 1L therapy		3,081 (31.5%)	332 (25.8%)	< .0001
Patients with nonsquamous NSCLC				
Ever tested	8,786 (85.0%)	5,699 (85.0%)	764 (82.9%)	.09
Tested prior to 1L therapy		4,881 (72.8%)	662 (71.8%)	.52
Ever NGS tested	5,494 (53.2%)	3,668 (54.7%)	404 (43.8%)	< .0001
NGS tested prior to 1L therapy		2,452 (36.6%)	274 (29.7%)	< .0001

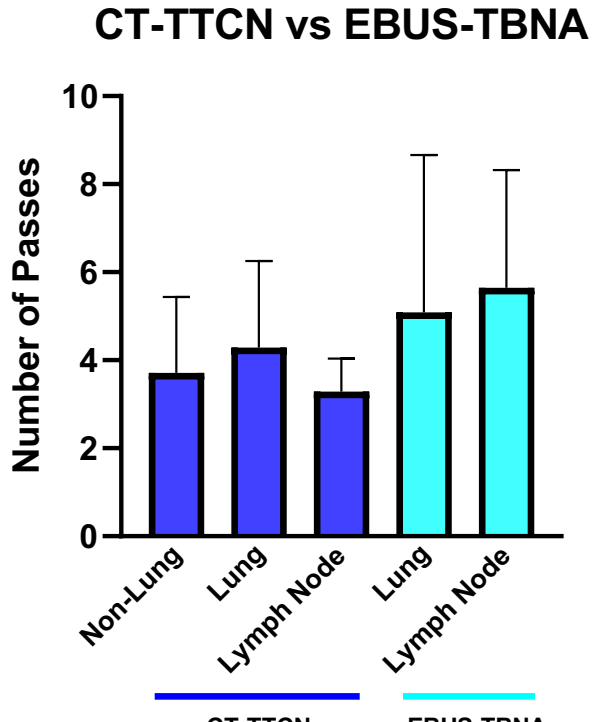
Study Period: April 2018 to March 2020

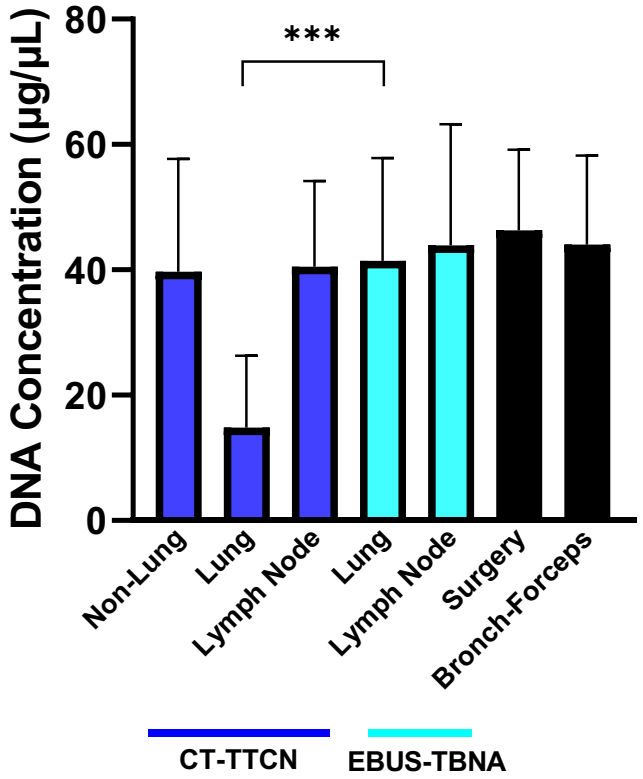
Still missing the mark overall, and there are notable disparities in testing

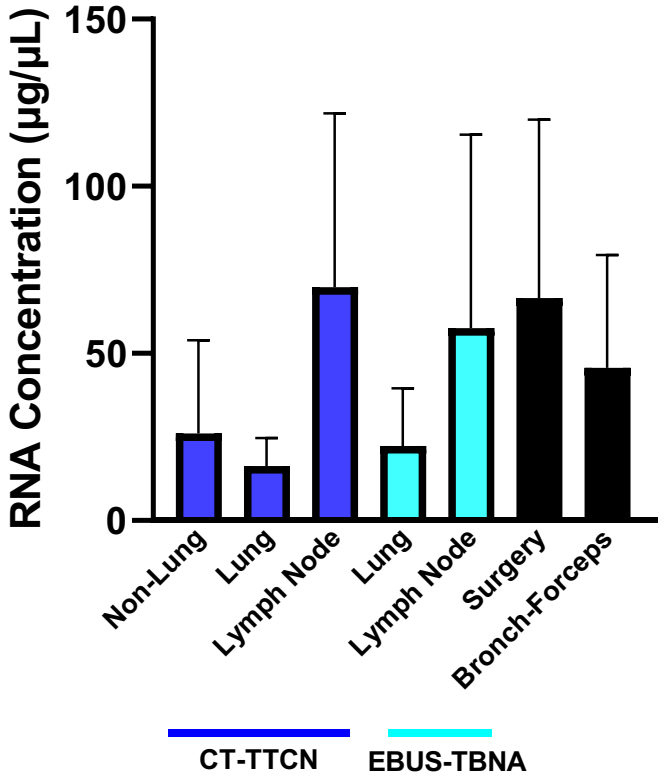
Biopsy Technique and Yield of Nucleic Acids



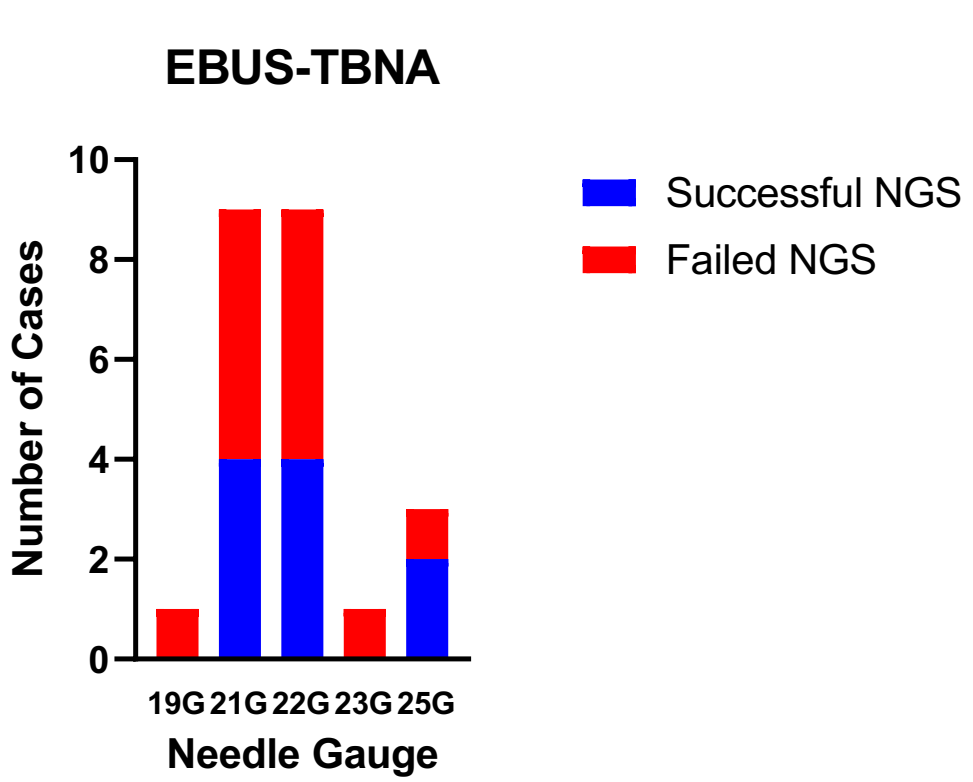


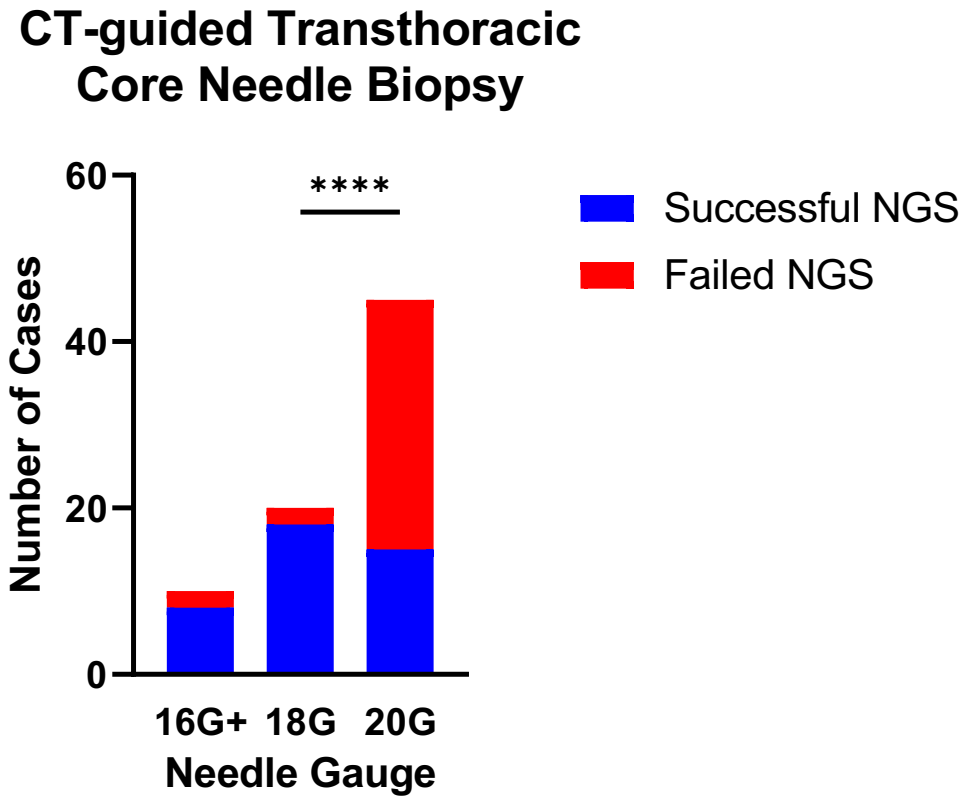






CT-TTCN 18G v 20G Needle Size





Next-Generation Sequencing Success

Biopsy Type		Next-Generation Sequencing Status			
		Complete MI Profile	Limited Tissue	Partial QNS	QNS
CT-TTCN (n=77)	Non-Lung Site (n=25)	19 (76%)	4 (16%)	1 (4%)	1 (4%)
	Lung (n=45)	15 (33.33%)	20 (44.44%)	2 (4.44%)	8 (17.78%)
	Lymph Node (n=7)	7	0	0	0
EBUS-TBNA (n=74)	Lung (n=25)	16 (64%)	8 (32%)	0	1 (4%)
	Lymph Node (n=49)	27 (55.1%)	17 (34.7%)	3 (6.12%)	2 (4.08%)
Surgical Resections (n=107)		105 (98.1%)	1 (0.95%)	1 (0.95%)	0
Bronch-Forceps (n=27)		22 (81.5%)	2 (7.4%)	0	3 (11.1%)
Other (n=12)		5 (41.7%)	4 (33.3%)	0	3 (25%)

Diep et al JIM 2023

EGFR Mutation

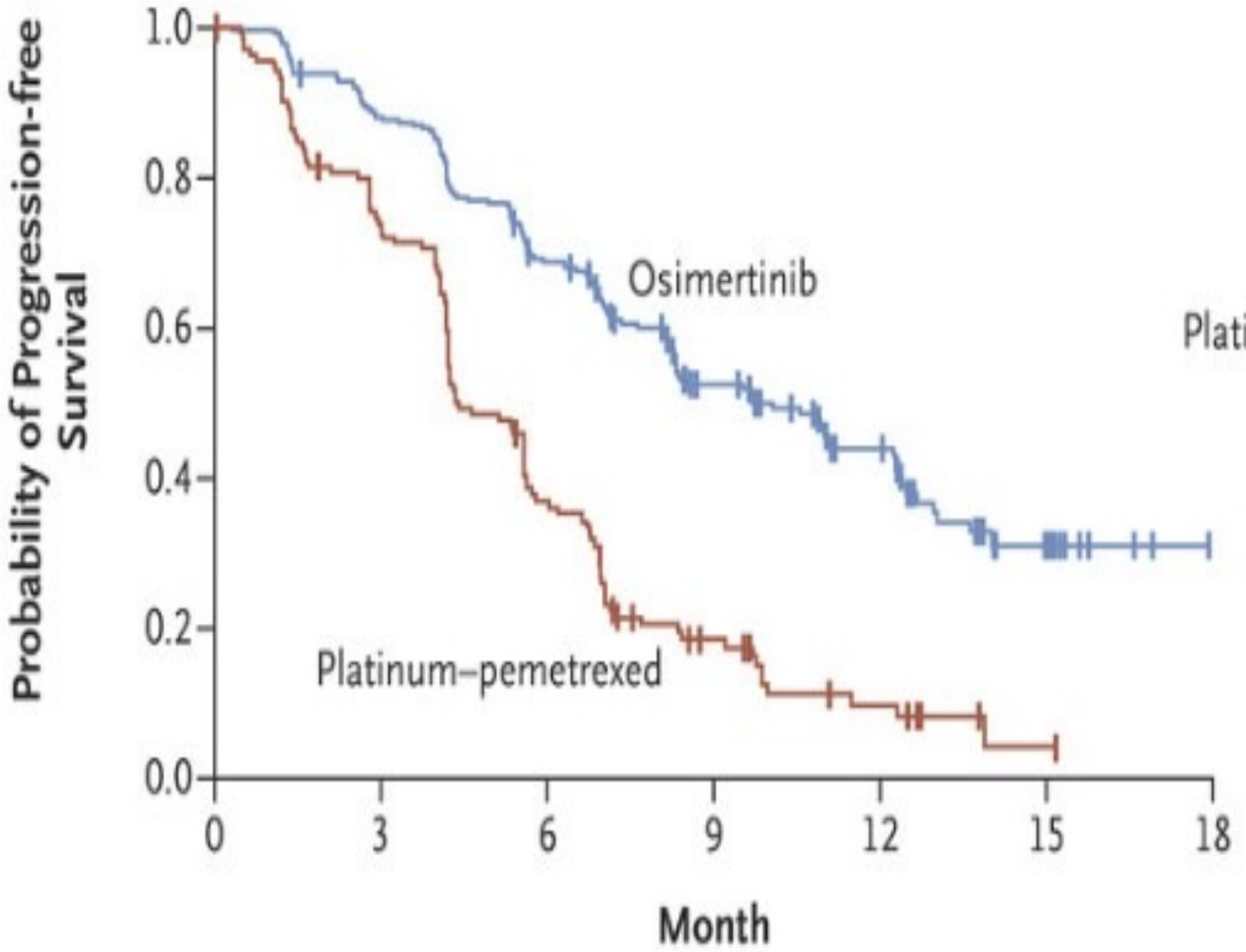
First line EGFR TKI vs. chemotherapy in EGFR mut + NSCLC

	Response (%)		Median PFS (mo)	
Trial	**TKI**	**Chemo**	**TKI**	**Chemo**
IPASS [Gefitinib]	71	47	9.5	6.3
First-SIGNAL [Gefitinib]	84	37	8.4	6.7
WJTOG [Gefitinib]	62	32	9.2	6.3
NEJ002 [Gefitinib]	73	30	10.8	5.4
OPTIMAL [Erlotinib]	83	36	13.7	4.6
EURTAC [Erlotinib]	58	15	9.7	5.2
LUX-Lung 3 [Afatinib]	56	22	11.1	6.9
LUX-Lung 6 [Afatinib]	67	23	11	5.6

EGFR

- Activating mutations in exon 19 (deletions) and exon 21 (L858R) are most common
  - approved agents include gefitinib, erlotinib, dacomitinib, afatinib, and osimertinib
- Exon 20 mutations include T790M and insertion mutations
  - osimertinib approved for T790M
  - Amivantimab and Mobocertinib approved for insertions
- Less common mutations are targetable
  - afatinib approved for S768I, L861Q, and/or G719X

Osimertinib is superior to chemo for Patients with EGFR T790M



	No. of Patients	Median Progression-free Survival
		mo (95% CI)
Osimertinib	279	10.1 (8.3–12.3)
Platinum–pemetrexed	140	4.4 (4.2–5.6)

Hazard ratio for disease progression or death, 0.30 (95% CI, 0.23–0.41)
P<0.001

Mok et al, NEJM 2017; 376:629-640

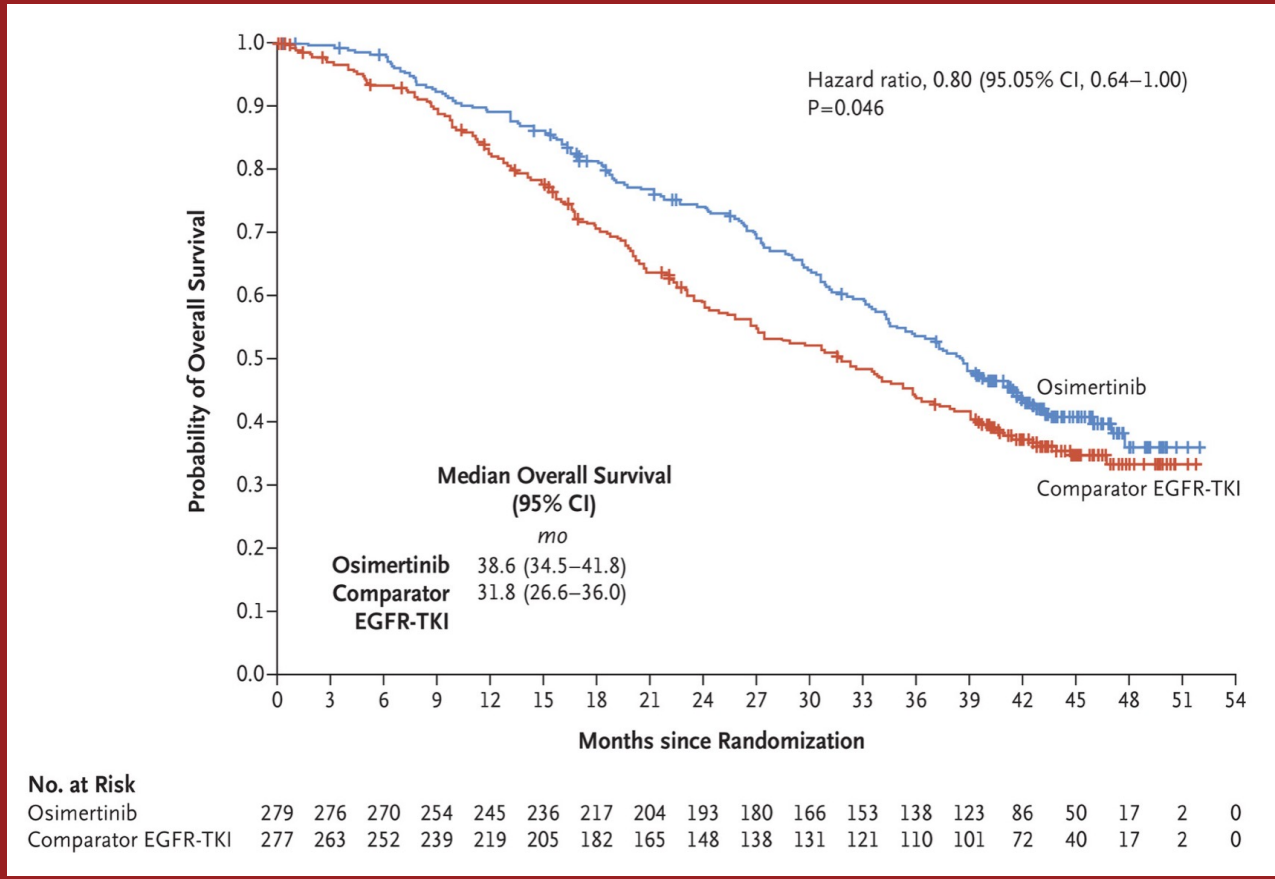
FLAURA: Osimertinib vs Gefitinib or Erlotinib in First- line *EGFR* Mutation + NSCLC

Soria et al, NEJM 2018;378:113-125

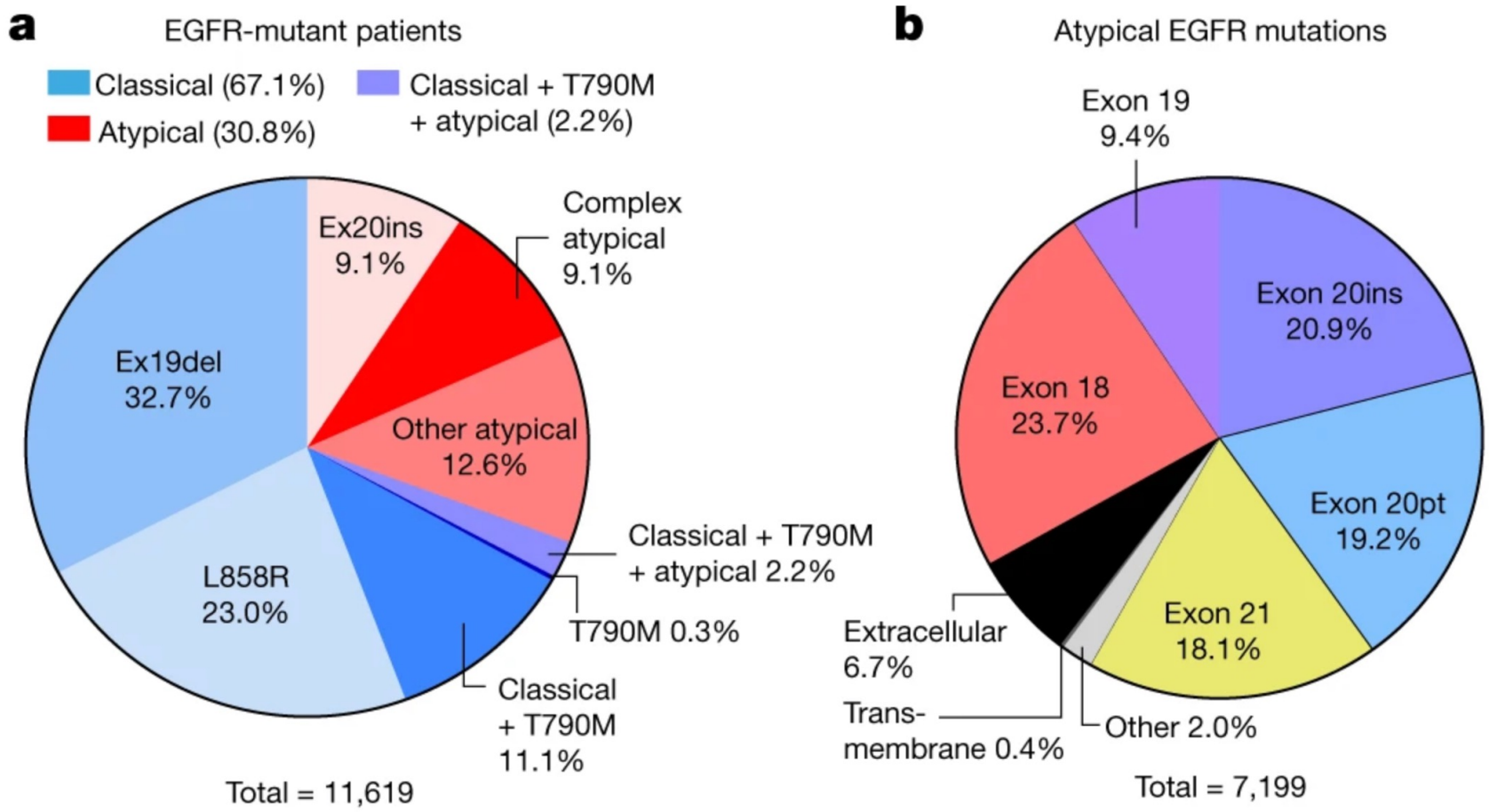
- ***EGFR*** **mutation (exon 19 deletion and/or L858R mutation) (N=650)**

1:1

- **Osimertinib**
- **Gefitinib or Erlotinib**

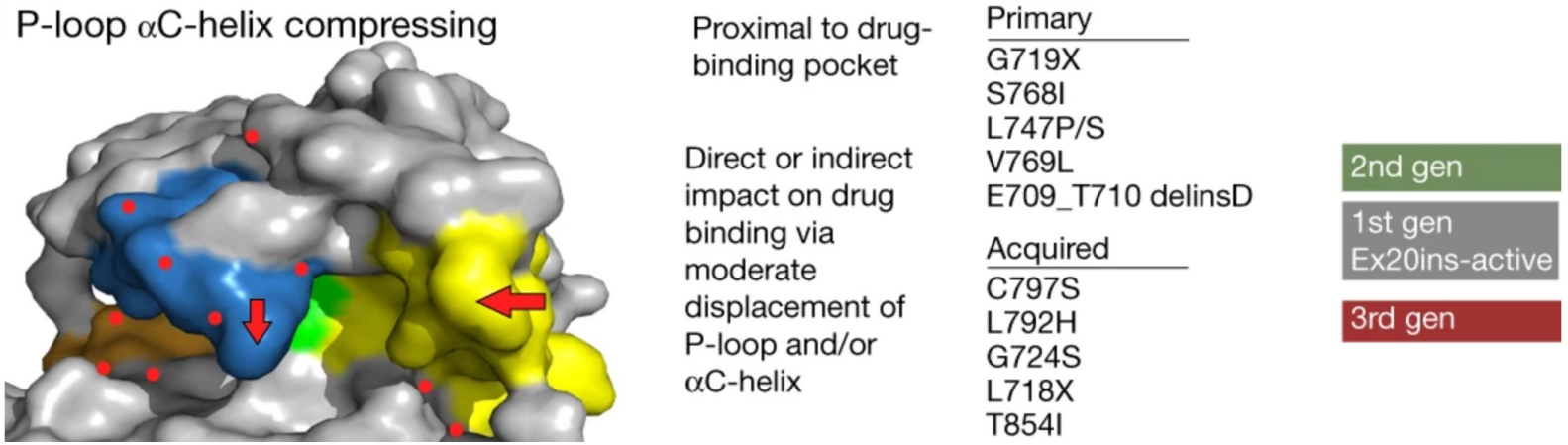


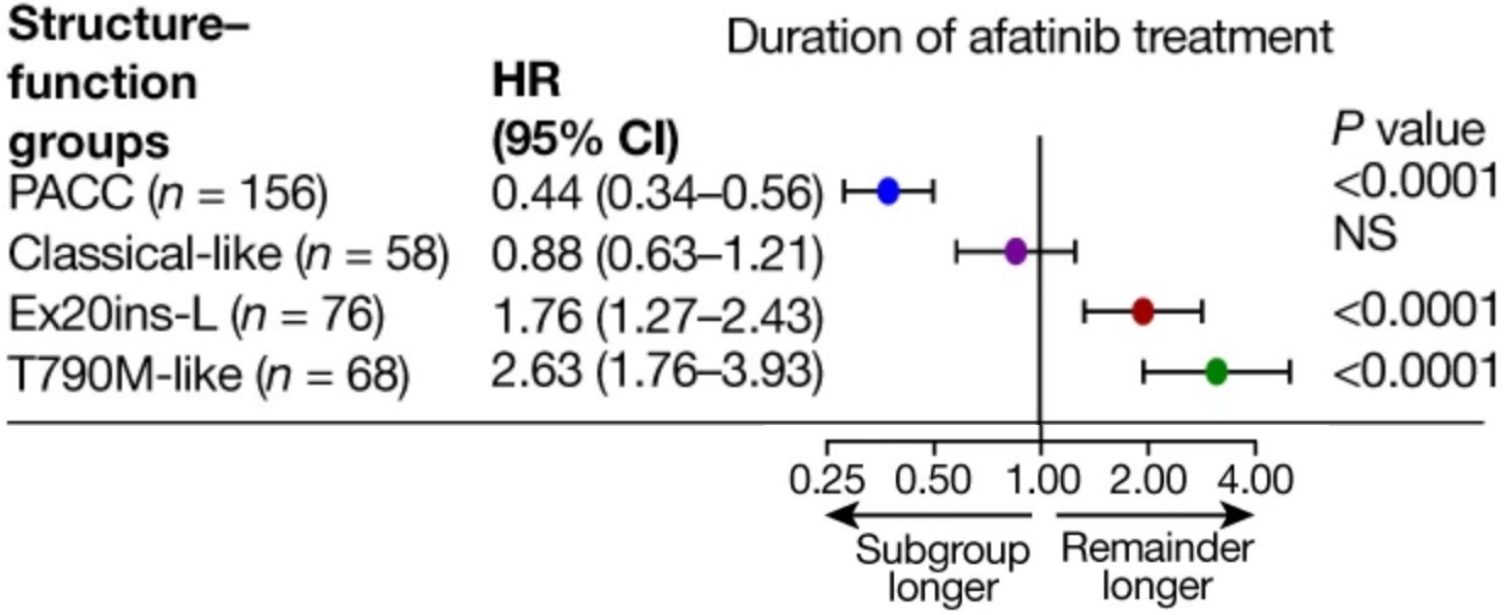
Not all EGFR mutations are alike



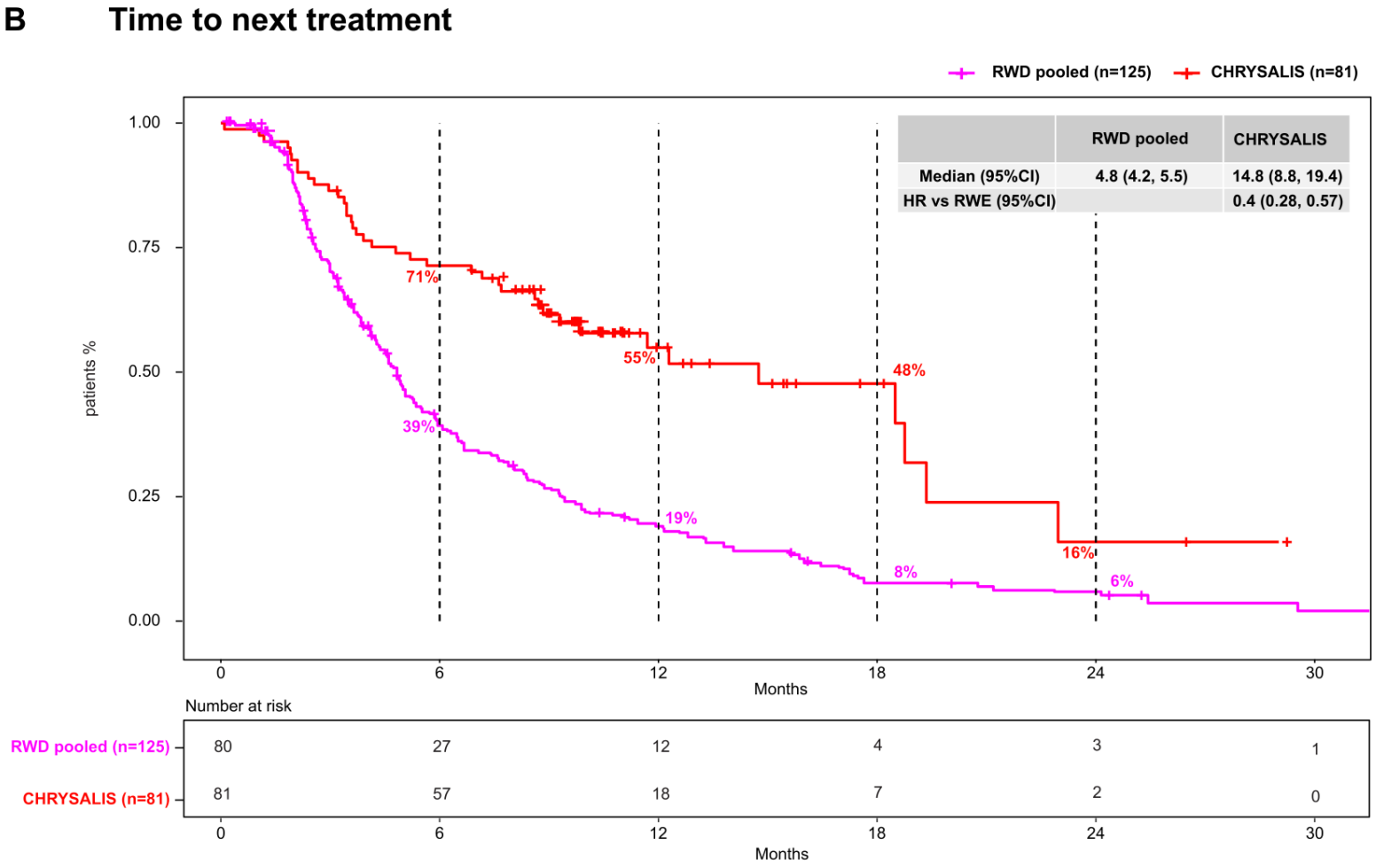
Robichaux et al Nature 2021

When not to use Osimertinib 1st line



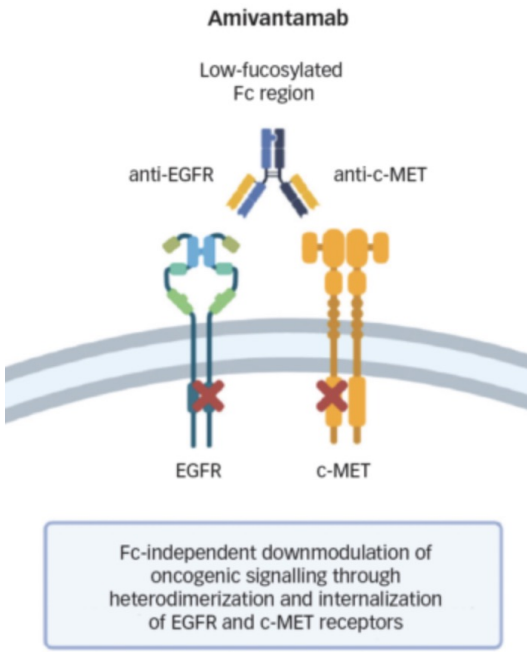


Exon 20 Insertions – Amivantimab RWE



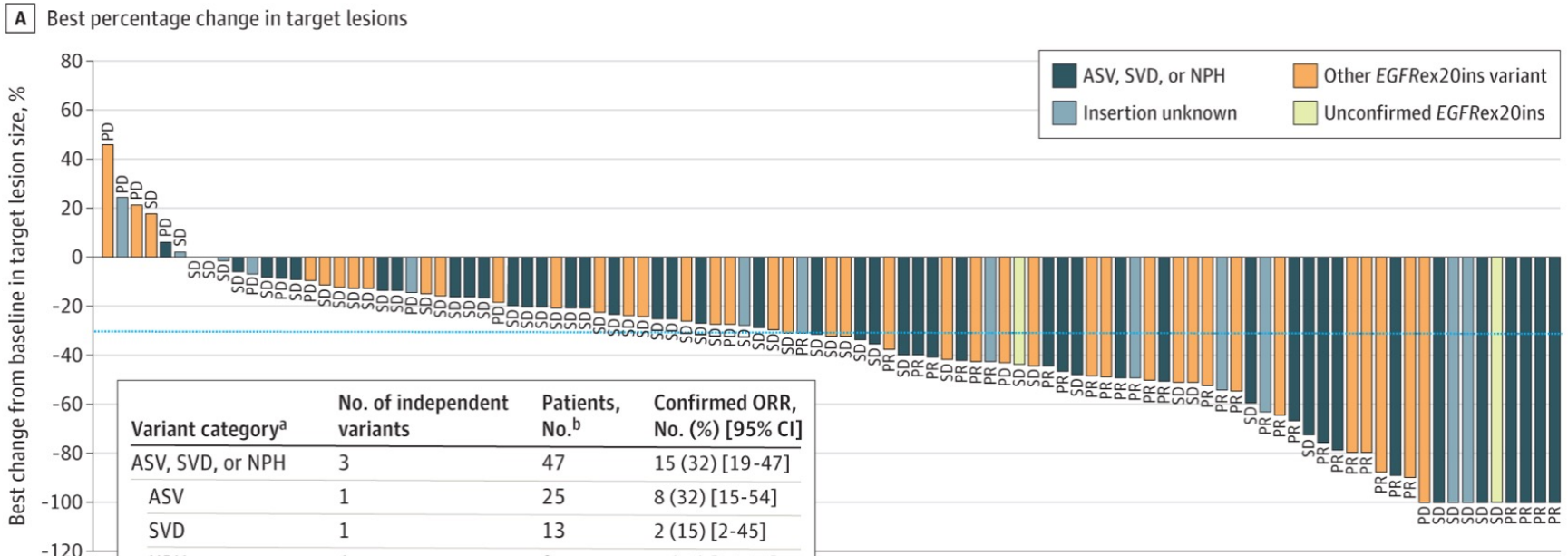
ORR 40%

Median DOR 11.1 mo

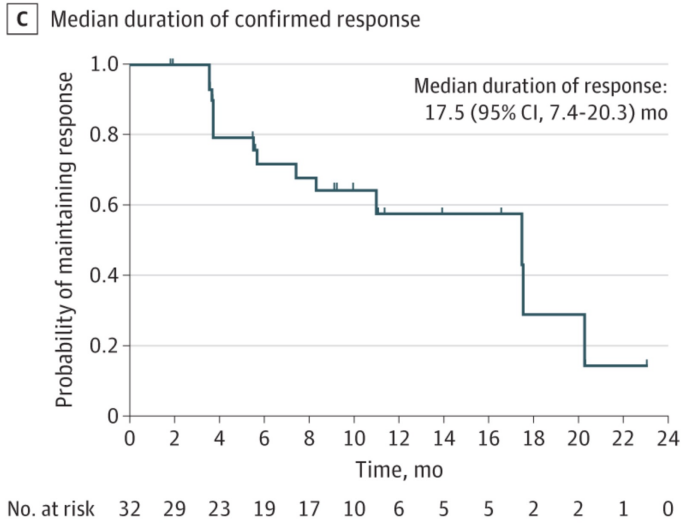


Minchom et al Lung Cancer 168 (2022) 74–82

Exon20 insertions Mobocertinib (TAK-788)



Variant category[a]	No. of independent variants	Patients, No.[b]	Confirmed ORR, No. (%) [95% CI]
ASV, SVD, or NPH	3	47	15 (32) [19-47]
ASV	1	25	8 (32) [15-54]
SVD	1	13	2 (15) [2-45]
NPH	1	9	5 (56) [21-86]
Other *EGFR*ex20ins	29	48	12 (25) [14-40]
Insertion unknown		16	5 (31) [11-59]



Zhou et al Jama Oncol 2021

Key Head-to-Head trials other than FLAURA

- afatinib superior PFS compared to gefitinib
- dacomitinib superior OS compared to gefitinib
- carboplatin + pemetrexed + gefitinib superior OS compared to gefitinib
- erlotinib + ramucirumab (or bevacizumab) superior PFS compared to erlotinib

FUTURE AGENTS

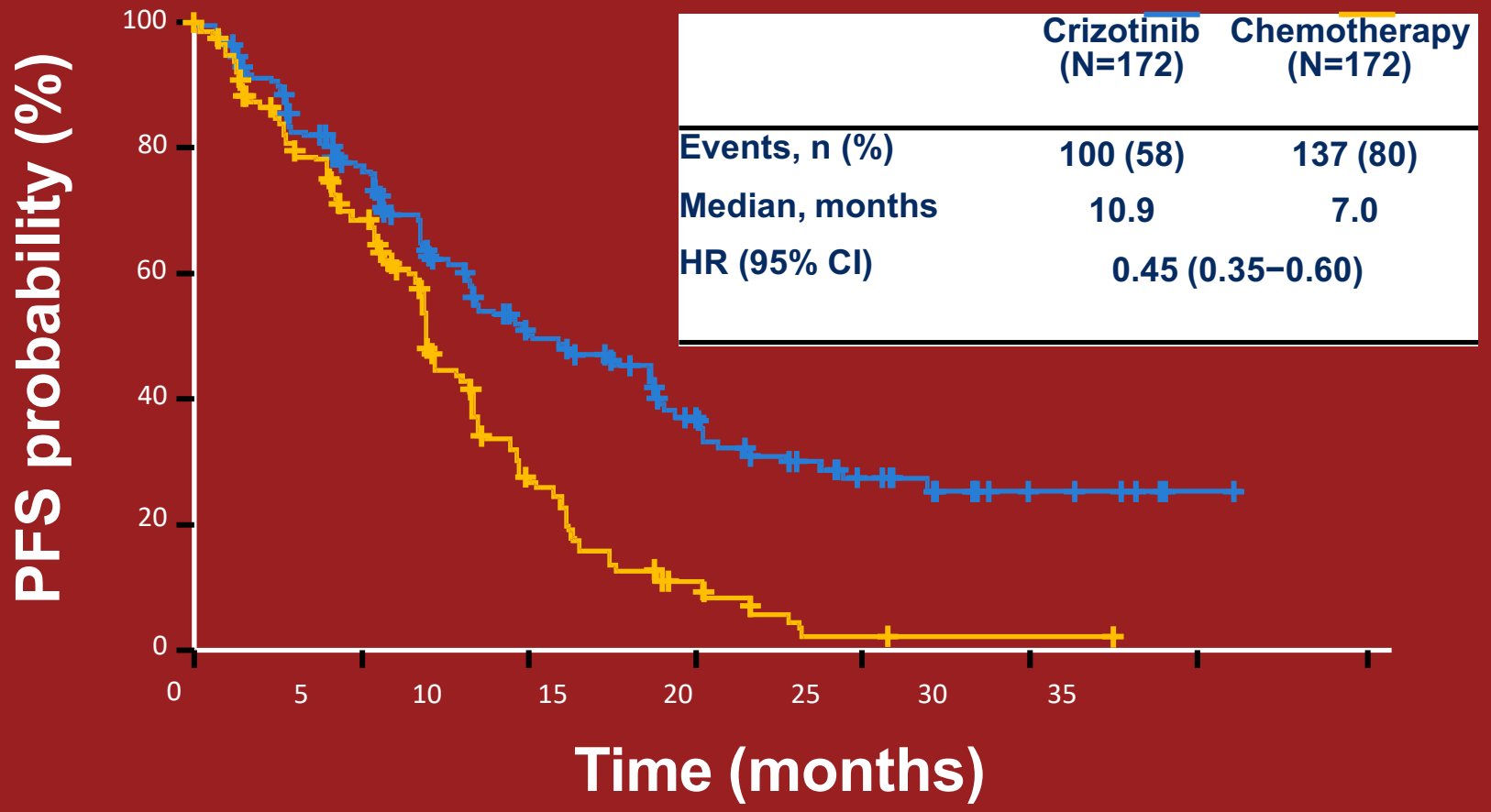
Lazertinib, Almonertinib, furmonertinib, oritinib, Aumolertinib

ALK Fusions

1st line Crizotinib prolongs PFS

Compared to platinum/pemetrexed

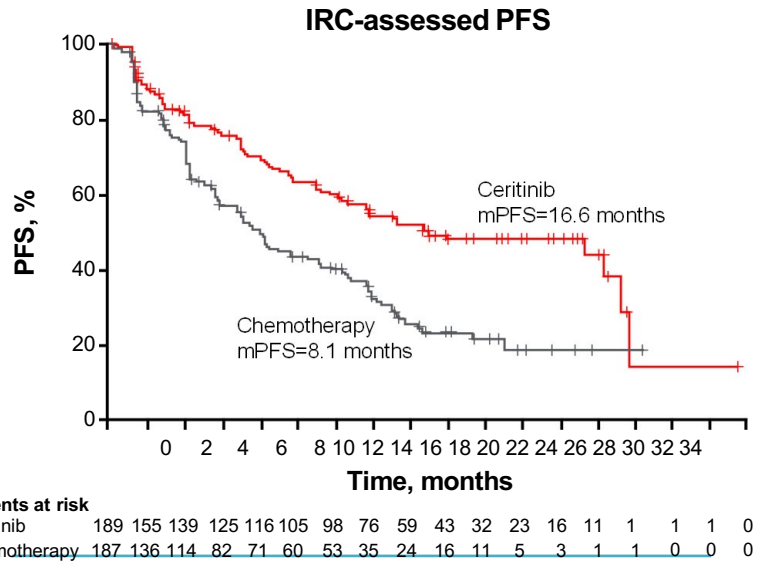
Solomon et al, NEJM 2014;371:2167-77



	Crizotinib (N=172)	Chemotherapy (N=172)
Events, n (%)	100 (58)	137 (80)
Median, months	10.9	7.0
HR (95% CI)	0.45 (0.35−0.60)	

1st line Ceritinib prolongs PFS compared to chemotherapy

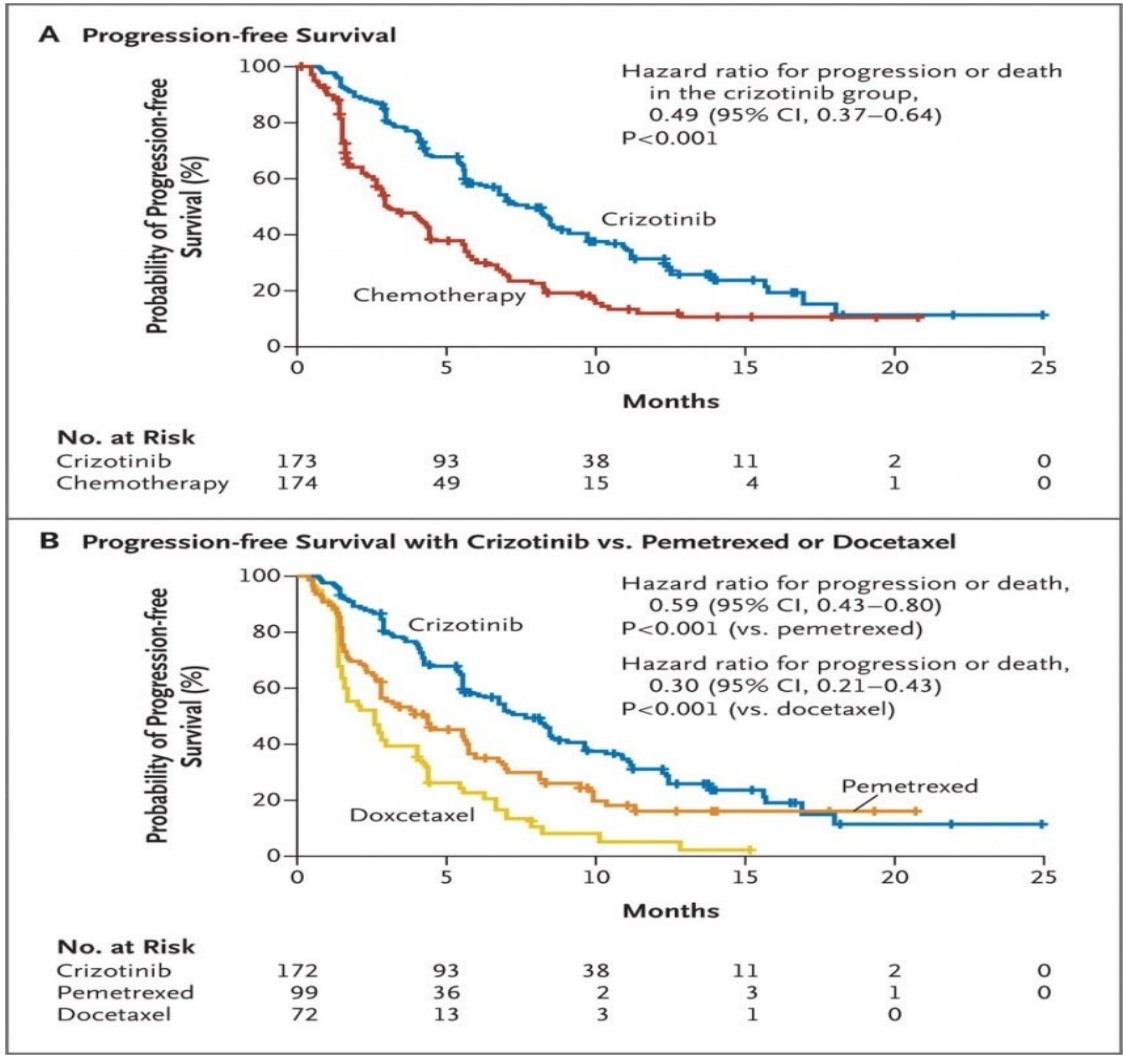
Soria et al, NEJM 2017;389:917-29



	Ceritinib (n=189)	Chemotherapy (n=187)
ORR, % (95% CI)	72.5 (65.5-78.7)	26.7 (20.5-33.7)
Median PFS,[a] months (95% CI)	16.6 (12.6-27.2)	8.1 (5.8-11.1)
HR (95% CI)	0.55 (0.42-0.73) *P*<0.00001[b]	

- Most common AEs with ceritinib vs chemotherapy were diarrhea (85% vs 11%), nausea (69% vs 55%), vomiting (66% vs 36%), increase in ALT (60% vs 31%) and AST (53% vs 17%); 65% of ceritinib patients reported grade 3/4 treatment-related AEs (vs 40% of chemotherapy patients)
- Treatment discontinuation due to treatment-related AEs: 5% with ceritinib and 11% with chemotherapy
- Treatment adjustment or interruption attributable to AEs: 80% with ceritinib and 45% with chemotherapy

2nd line Crizotinib vs. Docetaxel or Pemetrexed in ALK + patients



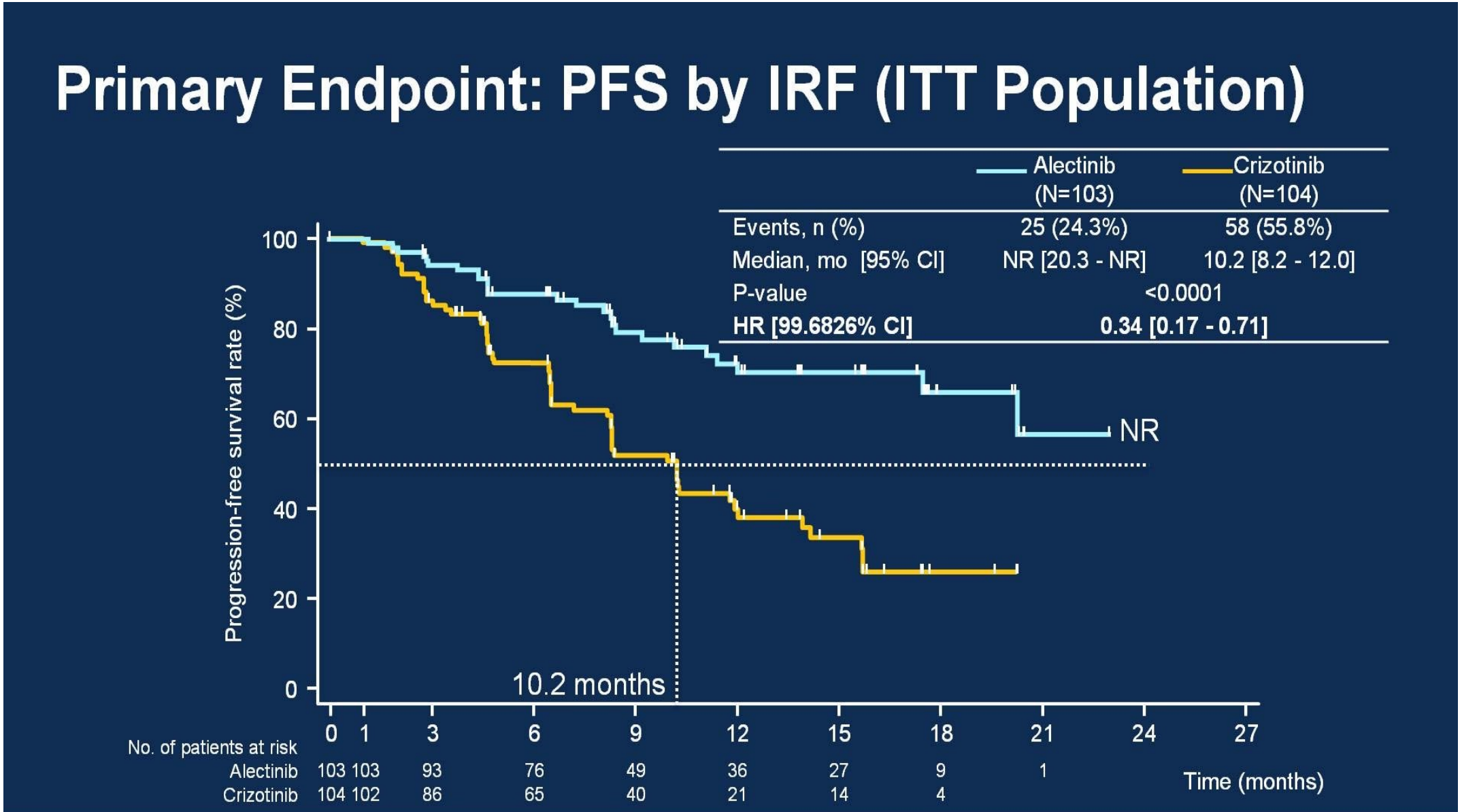
These studies establish the superiority of ALK inhibitor compared to chemotherapy in patients with ALK fusions

Which ALK Inhibitor?

- Can pre-screen patients with ALK IHC and confirm with FISH or PCR
- EML4 is most common fusion partner
- Crizotinib, Ceritinib, Brigatinib, Lorlatinib and Alectinib are FDA approved 1st line

Alectinib vs. Crizotinib 1st line (J-ALEX)

Peters el al NEJM 2017;377:829-38

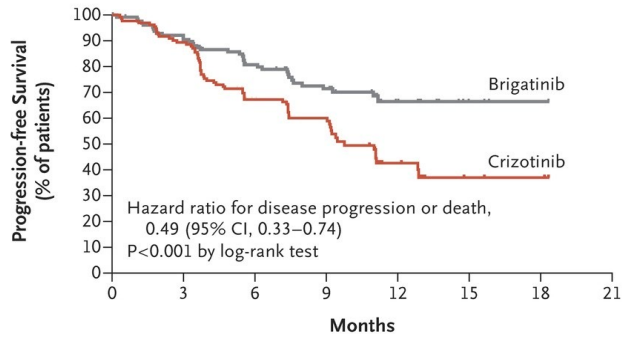


Brigatinib vs. Crizotinib 1st line

Camidge DR et al. N Engl J Med 2018;379:2027-2039

A Progression-free Survival

	Median (95% CI)	At 1 Yr (95% CI)
	mo	%
Brigatinib	NR	67 (56–75)
Crizotinib	9.8 (9.0–12.9)	43 (32–53)

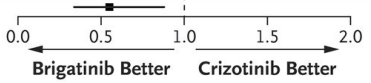


No. at Risk

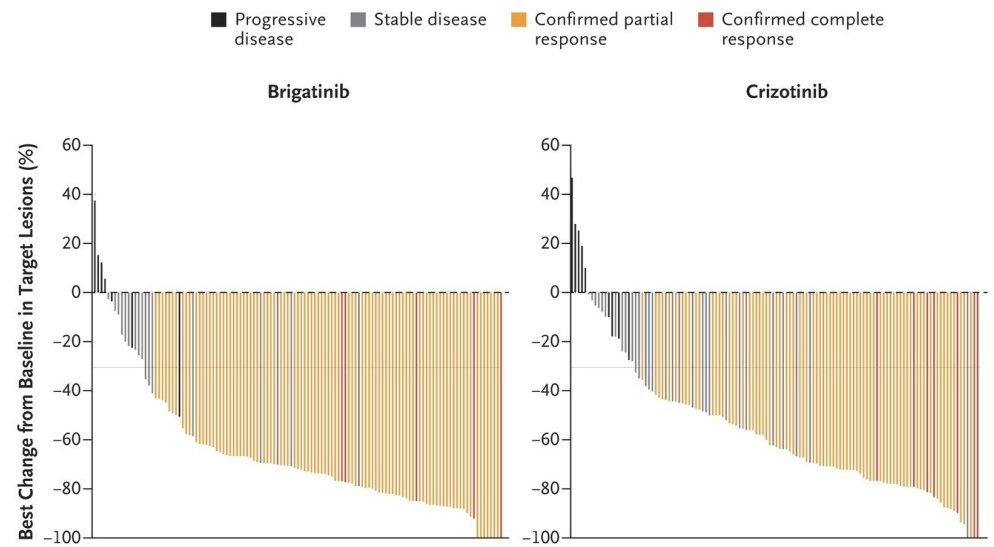
Brigatinib	137	114	90	64	26	3	1
Crizotinib	138	117	75	50	18	3	2

B Subgroup Analysis

Subgroup	No. of Patients		Hazard Ratio for Disease Progression or Death (95% CI)
	Brigatinib	Crizotinib	
Overall	137	138	0.49 (0.33–0.74)
Age			
18–64 yr	93	95	0.44 (0.26–0.74)
≥65 yr	44	43	0.59 (0.30–1.18)
Sex			
Female	69	81	0.44 (0.24–0.84)
Male	68	57	0.49 (0.28–0.85)
Race			
Non-Asian	78	89	0.54 (0.33–0.90)
Asian	59	49	0.41 (0.20–0.86)
History of tobacco use			
Never smoked	84	75	0.47 (0.27–0.84)
Former smoker	49	56	0.51 (0.27–0.97)
ECOG performance-status score			
0	58	60	0.19 (0.06–0.55)
1	73	72	0.60 (0.37–0.98)
Brain metastases at baseline			
Yes	40	41	0.20 (0.09–0.46)
No	97	97	0.72 (0.44–1.18)
Previous chemotherapy			
Yes	36	37	0.35 (0.14–0.85)
No	101	101	0.55 (0.34–0.88)

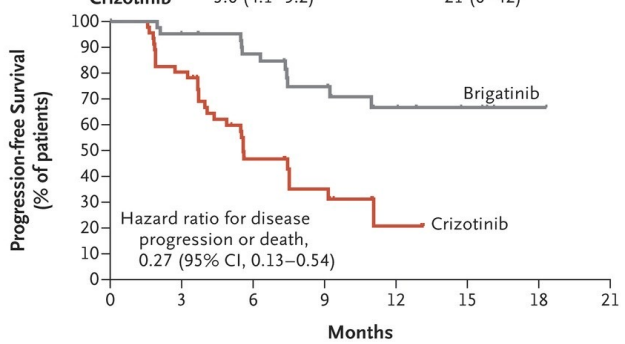


C Best Target-Lesion Responses



D Survival without Intracranial Disease Progression among Patients with Brain Metastases at Baseline

	Median (95% CI)	At 1 Yr (95% CI)
	mo	%
Brigatinib	NR (11–NR)	67 (47–80)
Crizotinib	5.6 (4.1–9.2)	21 (6–42)



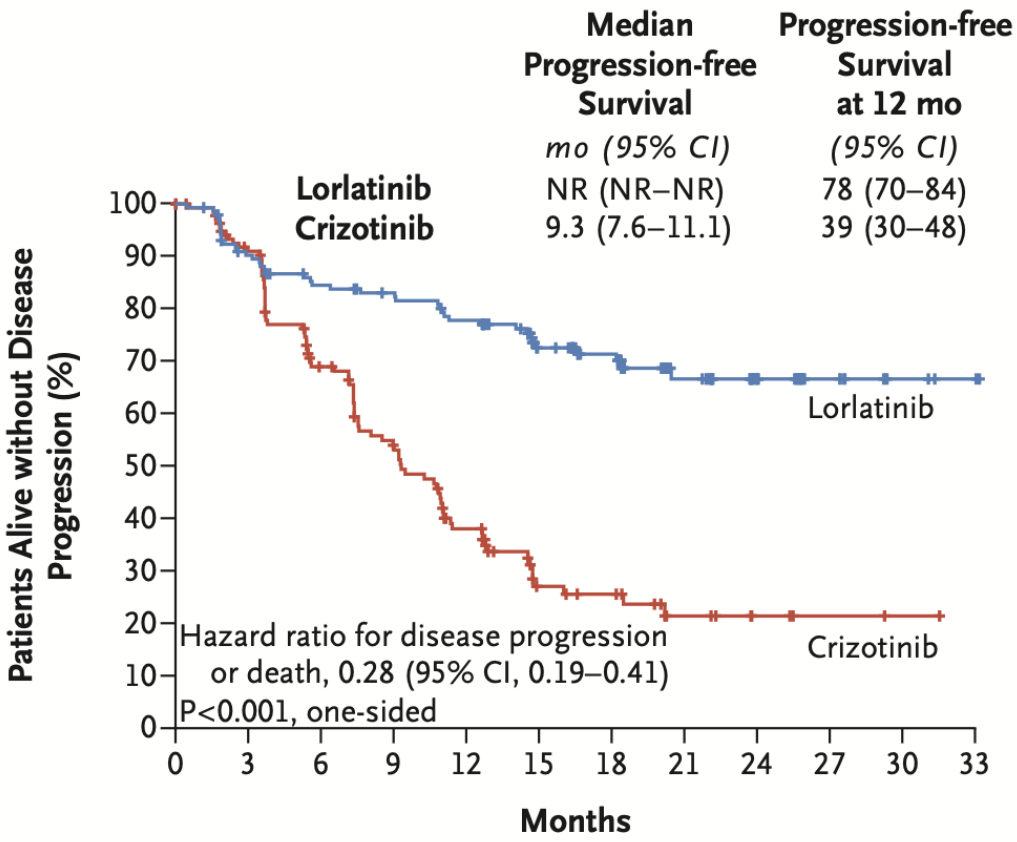
No. at Risk

Brigatinib	43	39	32	22	9	5	1
Crizotinib	47	37	16	9	2	0	0

Lorlatinib in ALK-positive NSCLC

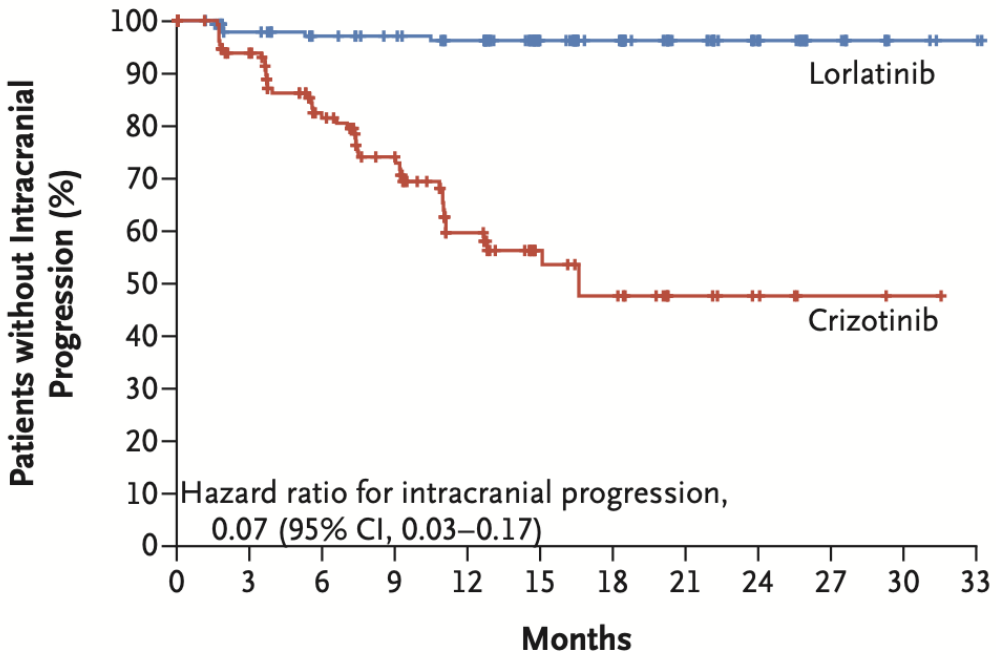
CROWN trial, Efficacy as 1st line therapy

A **Progression-free Survival**



No. at Risk												
Lorlatinib	149	129	118	113	105	73	59	33	20	11	4	2
Crizotinib	147	120	84	62	39	19	16	8	4	2	1	0

B **Survival without CNS Progression**



No. at Risk												
Lorlatinib	149	131	122	117	110	78	65	39	25	12	4	2
Crizotinib	147	115	84	65	38	21	16	8	5	2	1	0

N Engl J Med 2020;383:2018-29.

Table 2 Brigatinib activity against various *ALK* mutations

ALK mutation	Gainor et al, cancer discovery 2016[19]				Zhang et al, AACR 2015 abstract 781[26]		
	ALK phosphorylation mean IC_{50} (nmol/L)						
	Ceritinib	Alectinib	Brigatinib	Lorlatinib	Ceritinib	Alectinib	Brigatinib
EML4–ALK	5	11	11	2	37	25	14
C1156Y	5	12	5	5	195	67	45
I1171N	8	398	26	49	119	724	124
I1171S	4	177	18	30	ND	ND	ND
I1171T	4	34	6	12	ND	ND	ND
F1174C	38	27	18	8	109	31	58
F1174L	ND	ND	ND	ND	117	44	55
F1174V	ND	ND	ND	ND	121	46	64
V1180L	ND	ND	ND	ND	16	597	11
L1196M	9	118	27	34	67	133	41
L1198F	196	42	14	15	697	84	82
L1152R	ND	ND	ND	ND	437	62	11
L1152p	ND	ND	ND	ND	451	48	20
G1202R	124	707	130	50	354	690	184
G1202R del	50	59	96	5	ND	ND	ND
D1203N	35	28	35	11	159	42	79
E1210K	6	32	24	2	80	59	107
G1269A	0	25	ND	10	29	56	9
D1203N + F1174c	238	75	123	70	ND	ND	ND
D1203N + E1210K	98	83	136	27	ND	ND	ND
T1151Tins	ND	ND	ND	ND	283	201	114

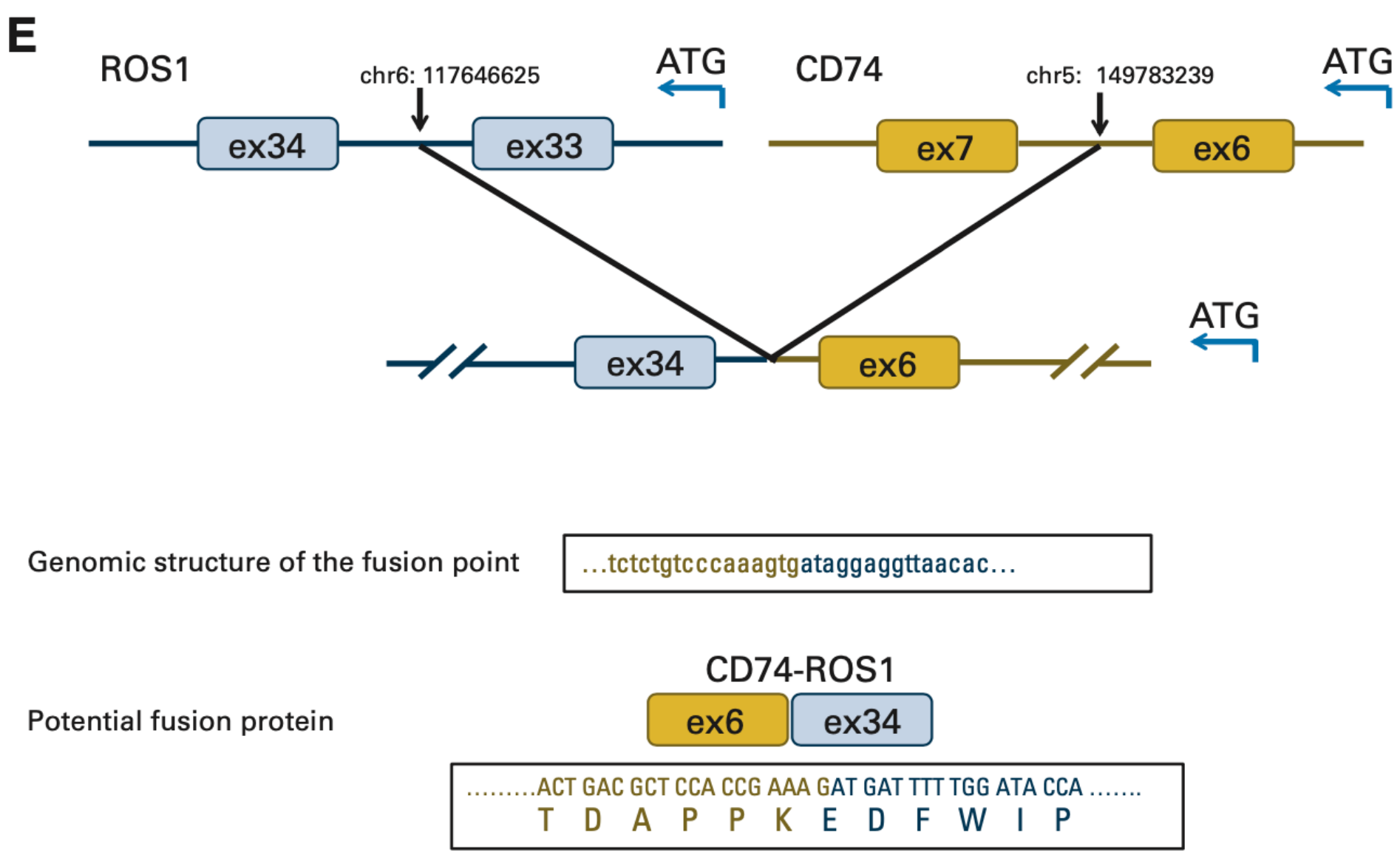
ND = not done	IC_{50} <50	IC_{50} 50–200	IC_{50} >200

Notes: The in vitro activity of brigatinib is shown relative to the *ALK* inhibitors alectinib, ceritinib, and brigatinib. Results from two independent studies are summarized in this table.
Abbreviations: AACR, American Association of Cancer Research; ALK, anaplastic lymphoma kinase.

Summary for ALK inhibitors

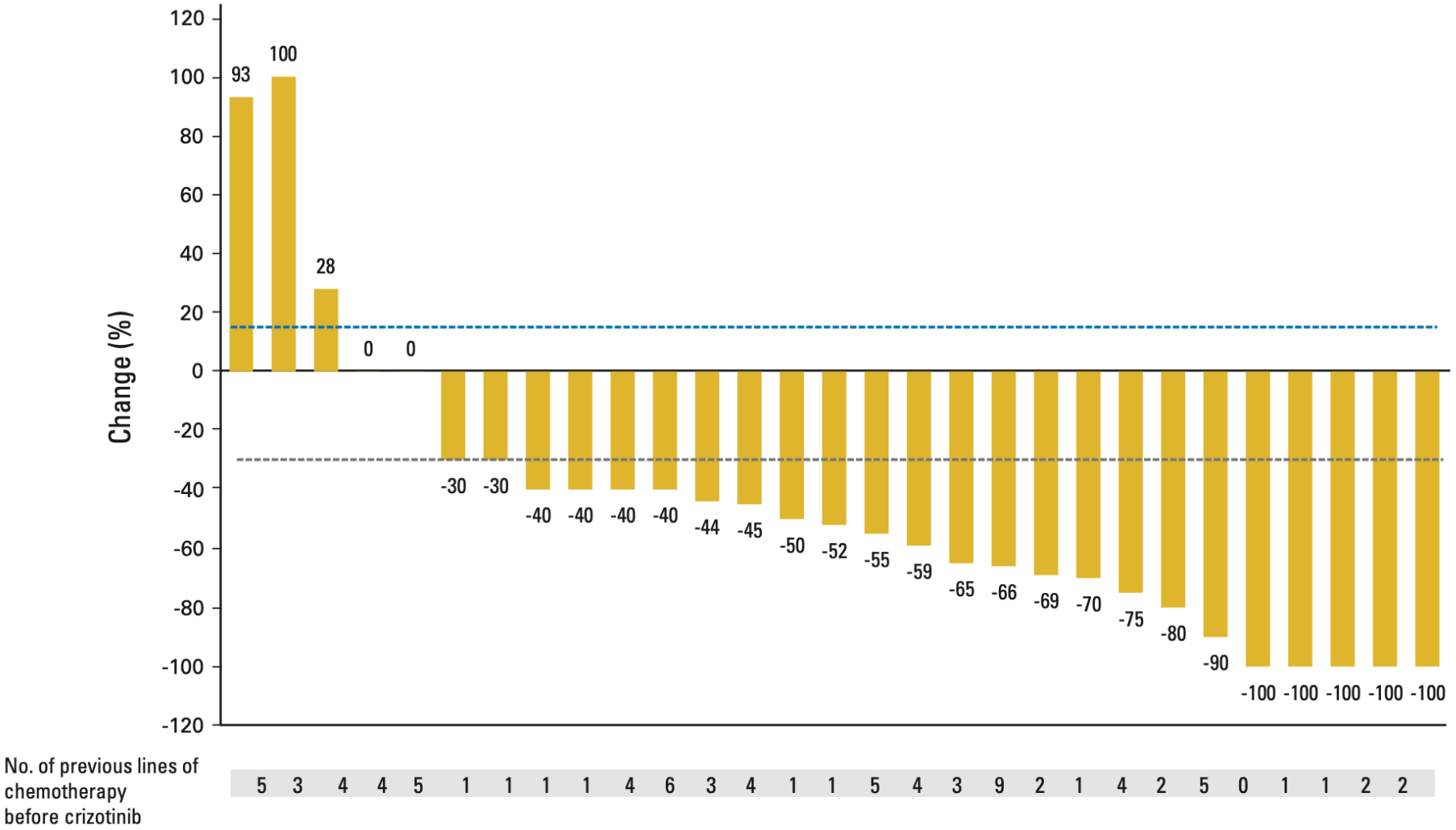
- ALK inhibitors superior to chemo in both 1st and 2nd line setting
- Crizotinib is INFERIOR to Alectinib and Brigatinib, and Lorlatinib
- Lorlatinib has a worse toxicity profile, but better CNS penetration.

ROS-1 Fusion



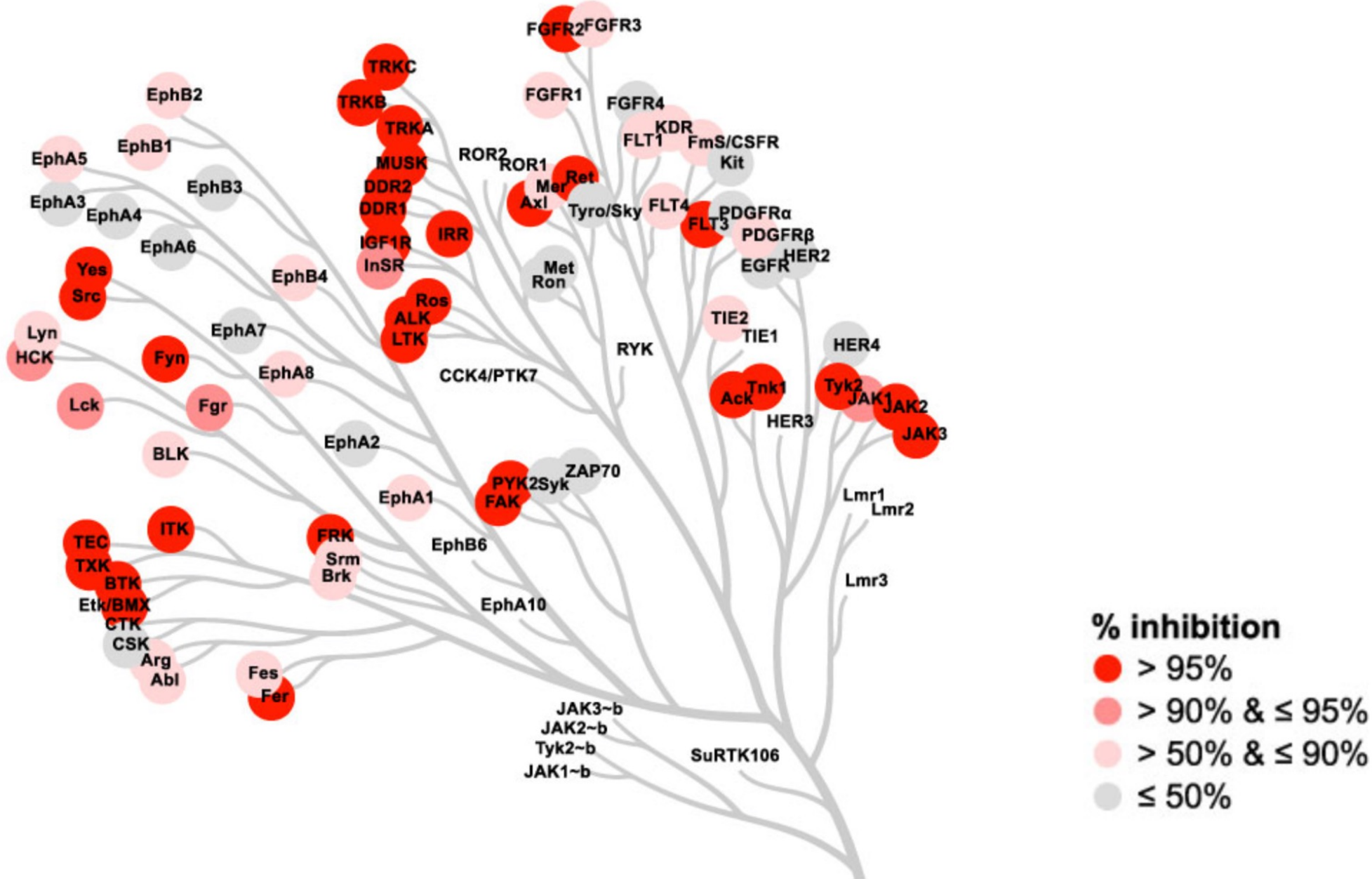
Mazieres et al. J Clin Oncol 33:992-999. 2015

Initial Experience with Crizotinib



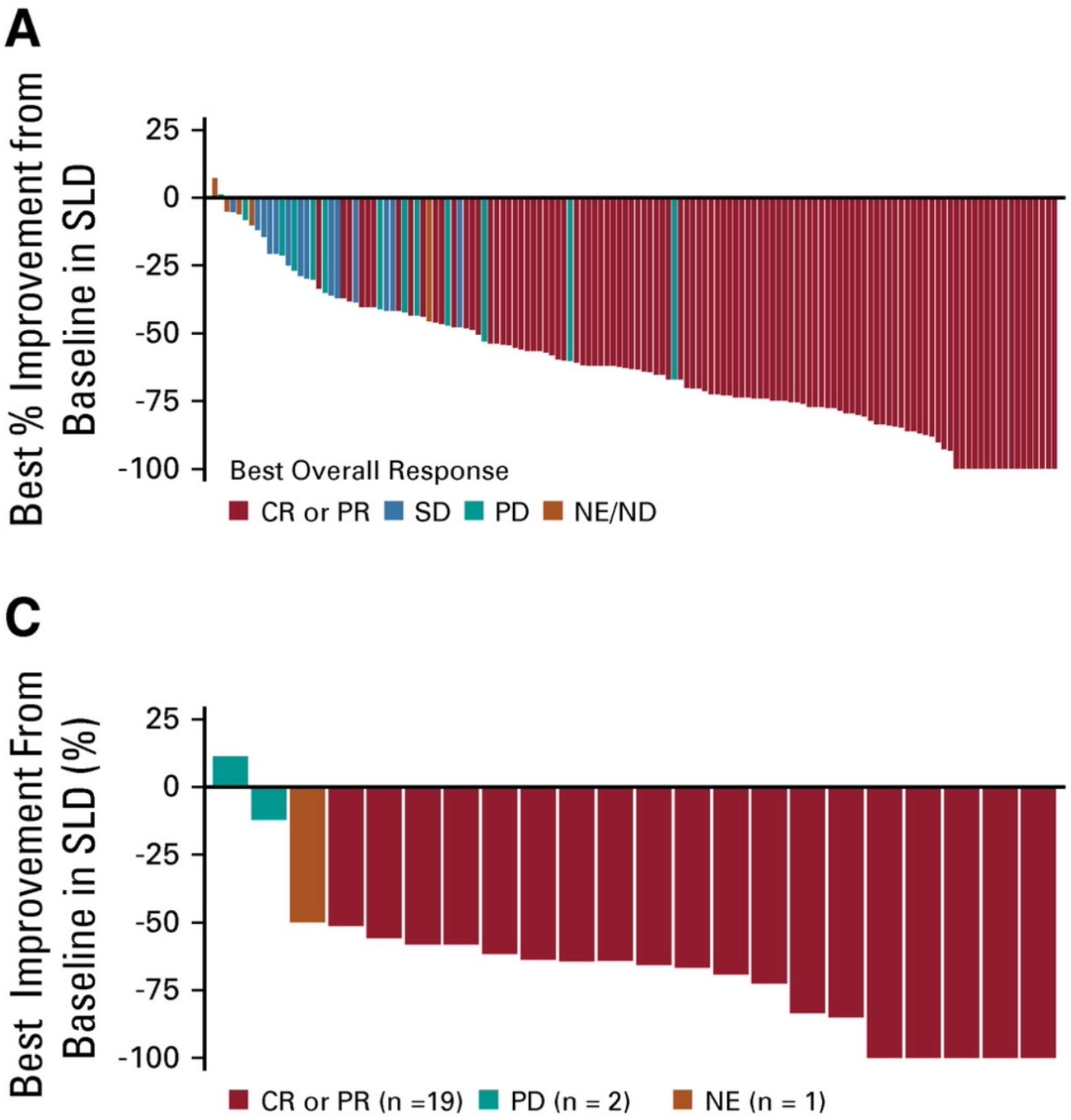
Mazieres et al. J Clin Oncol 33:992-999. 2015

entrectinib



% inhibition

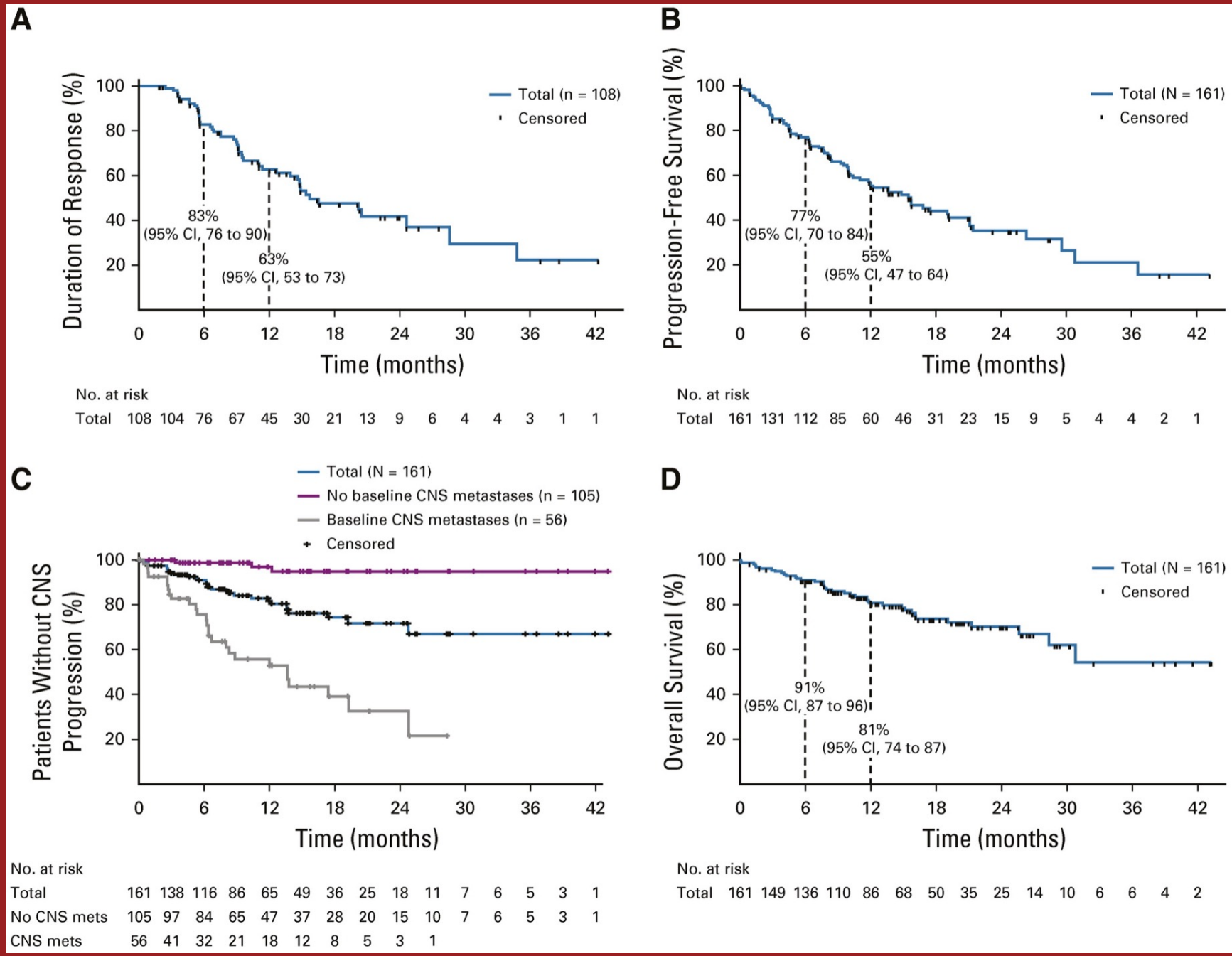
- > 95%
- > 90% & ≤ 95%
- > 50% & ≤ 90%
- ≤ 50%



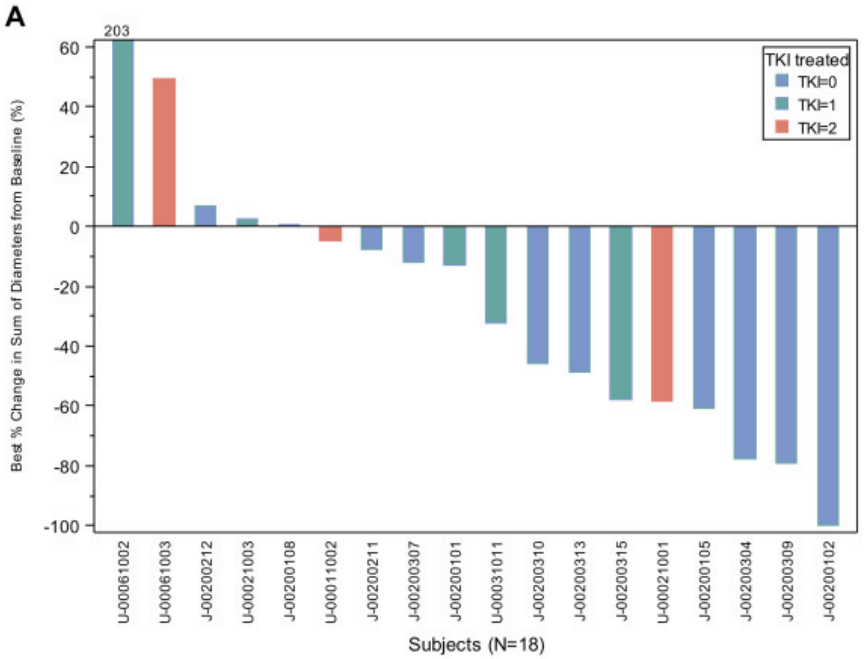
Dziadziuszko et al J Clin Oncol 39, no. 11 (2021) 1253-1263.

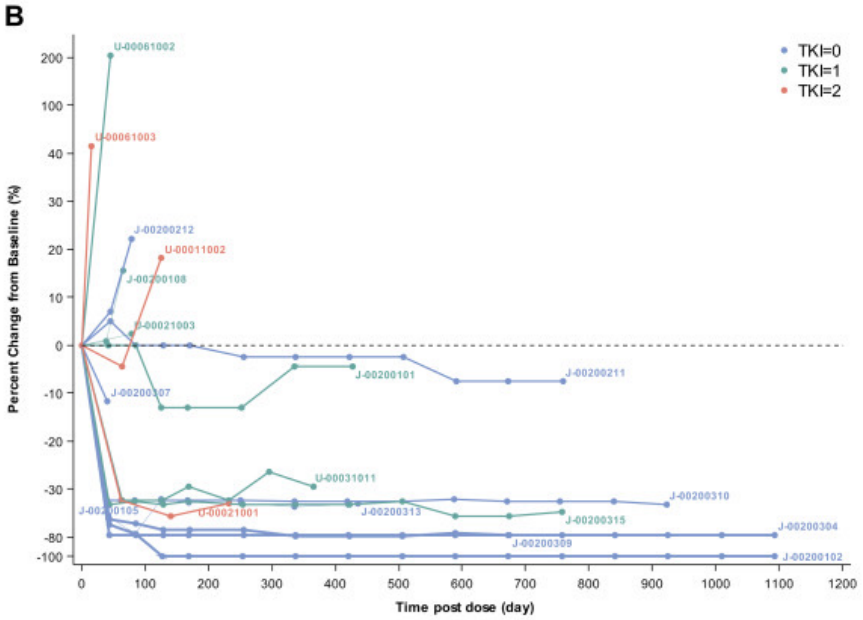
Entrectinib

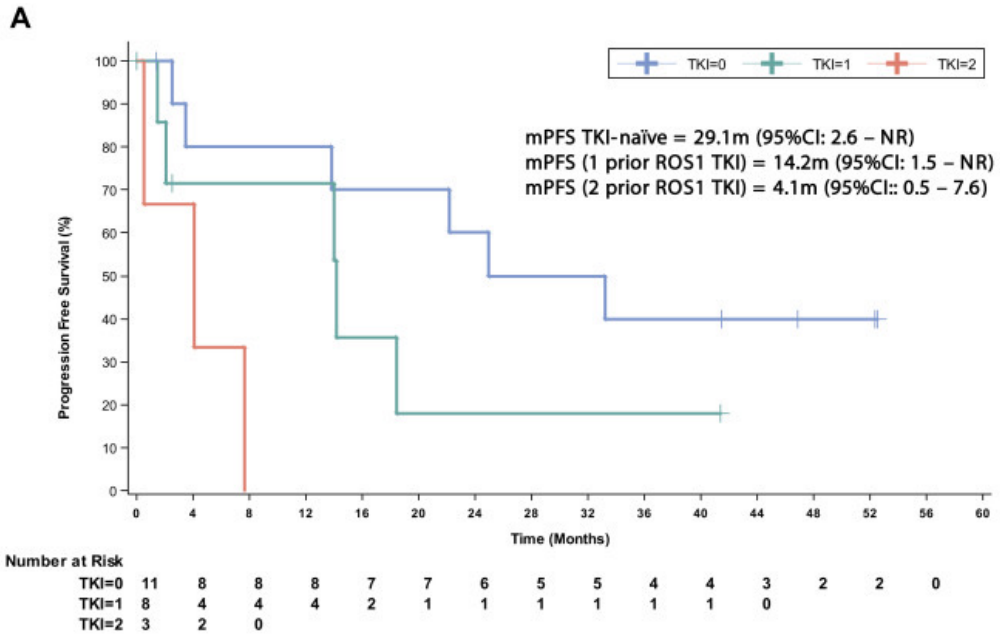
Dziadziuszko et al J Clin Oncol 39, no. 11 (2021) 1253-1263.

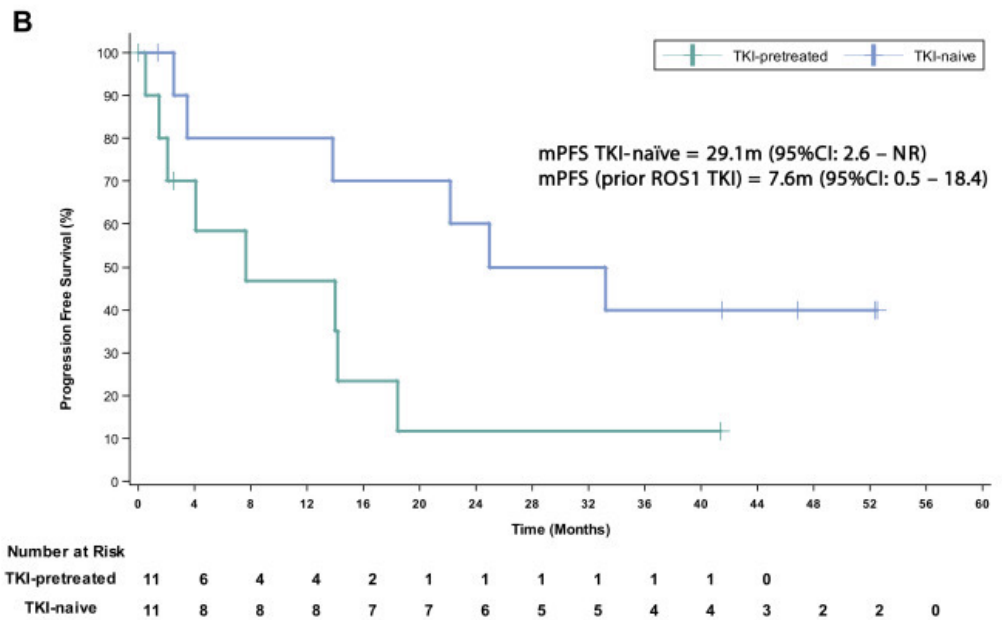


Coming Soon: Taletrectinib









Summary of ROS1 Treatments

- Both Crizotinib and Entrectinib are FDA approved based on response data
- Entrectinib has better CNS penetration
- Newer agents are currently in clinical trials.

Thank You