I TREAT PATIENTS WITH GENE FUSIONS

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DECLARATION OF INTERESTS

Consulting, advisory role or lectures: AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Daiichi Sankyo, Eli Lilly, Merck, Novartis, Pfizer, prIME Oncology, Peer CME, Roche, Janssen, Abbvie

Honoraria: AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Eli Lilly, Merck, Novartis, Pfizer, prIME Oncology, Peer CME, Roche, Janssen, Abbvie

Clinical trials research as principal or co-investigator (Institutional financial interests): AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, Merck, Novartis, Pfizer, Roche, Medimmun, Sanofi-Aventis, Taiho Pharma, Novocure, Daiichi Sankyo, Janssen, Abbvie

Travel, Accommodations, Expenses: AstraZeneca, Roche, Novartis, prIME Oncology, Pfizer

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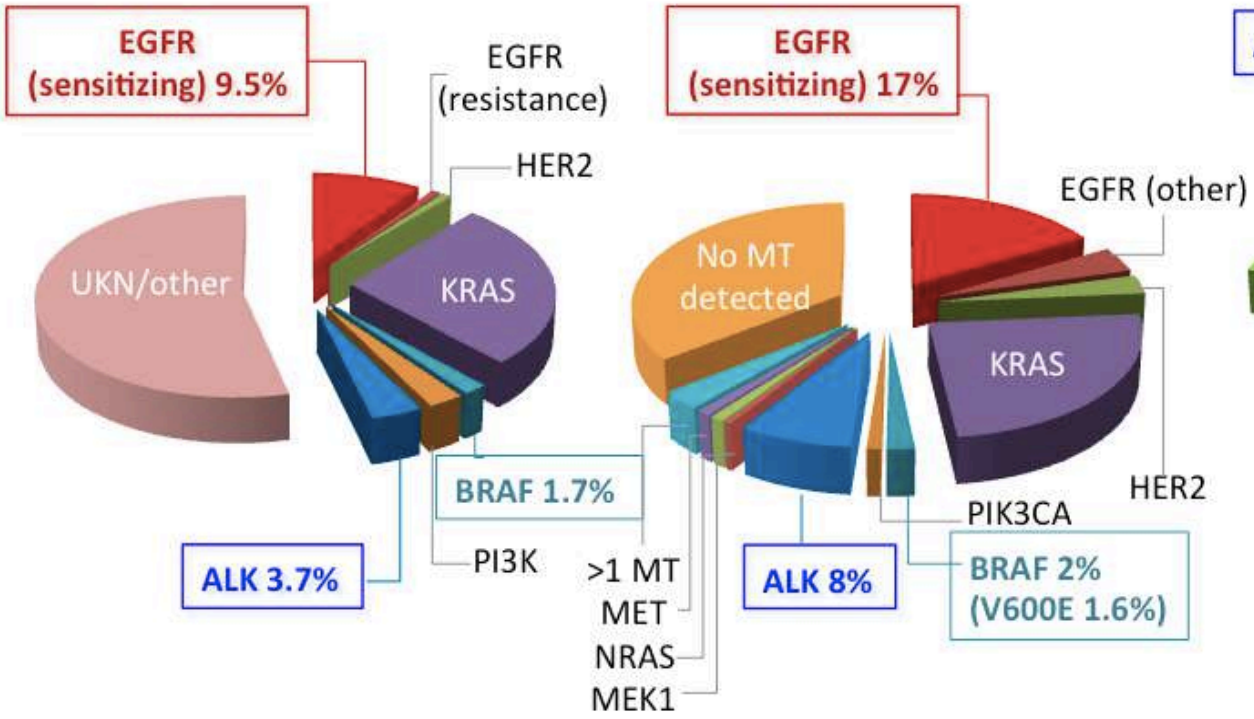
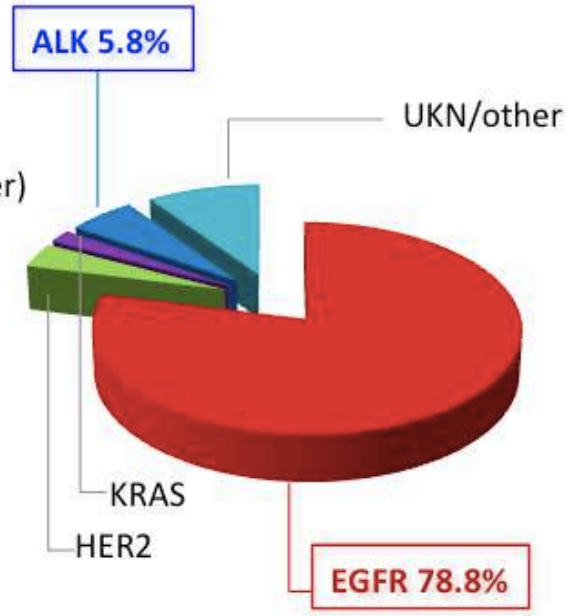
ALK rearrangement NSCLC

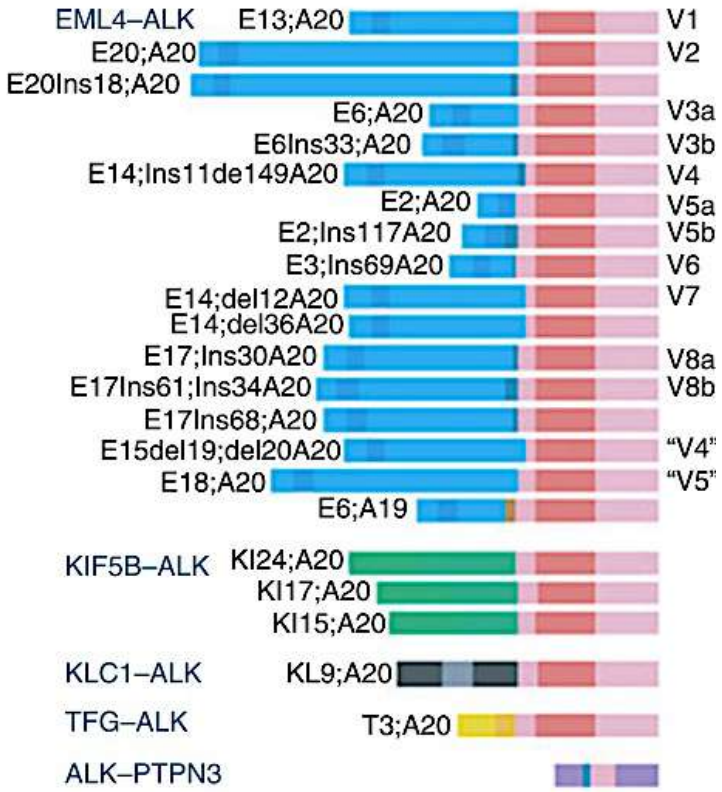
Europe (n=9,911), France[1]
All histology



US (n=733), LCMC[2]
Adenocarcinoma

East Asia (n=52)[3]
Adenocarcinoma, never smokers





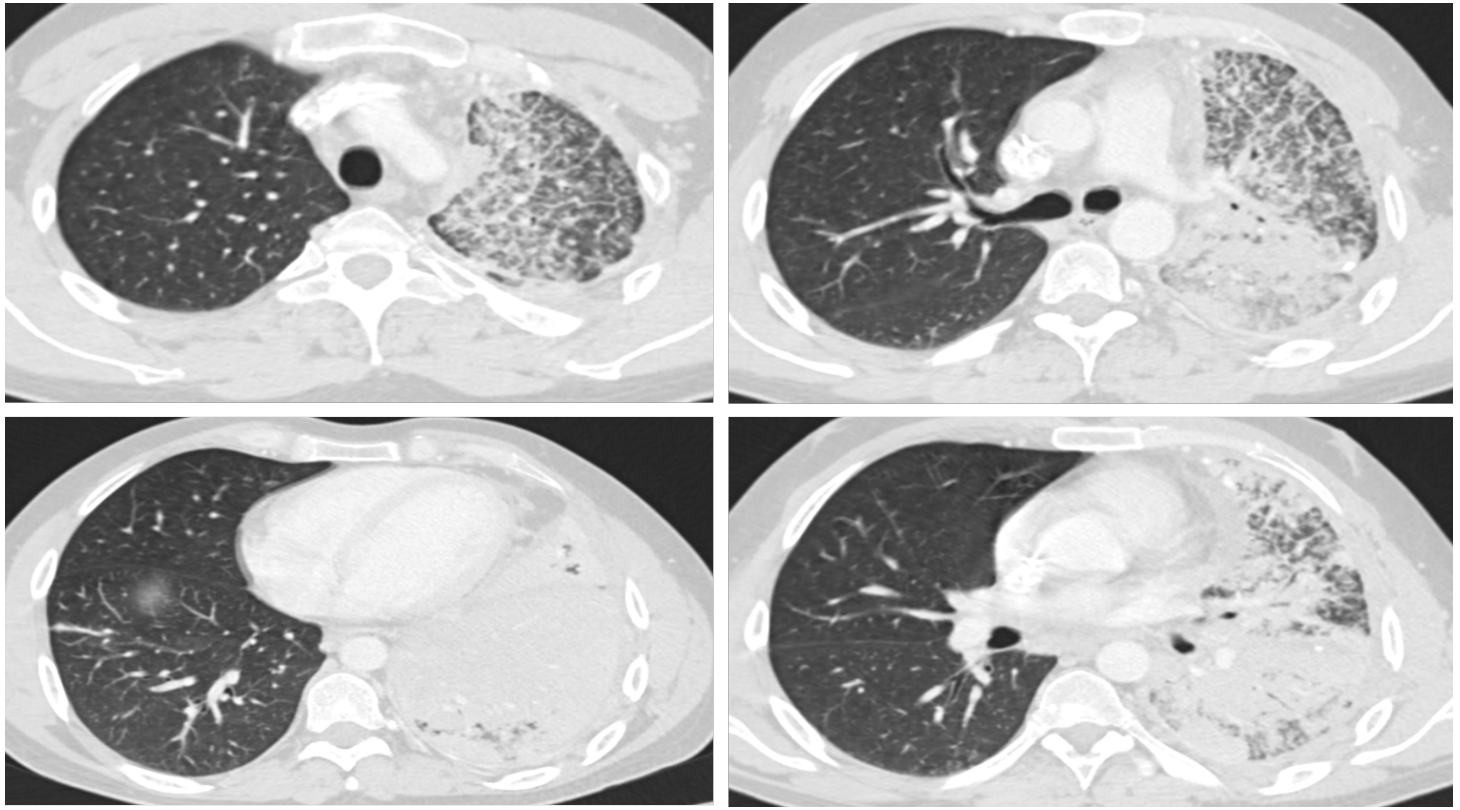
Incidence : 4 – 8%

Barlesi ASCO 2013, Johnson ASCO 2013, Sun JCO 2010

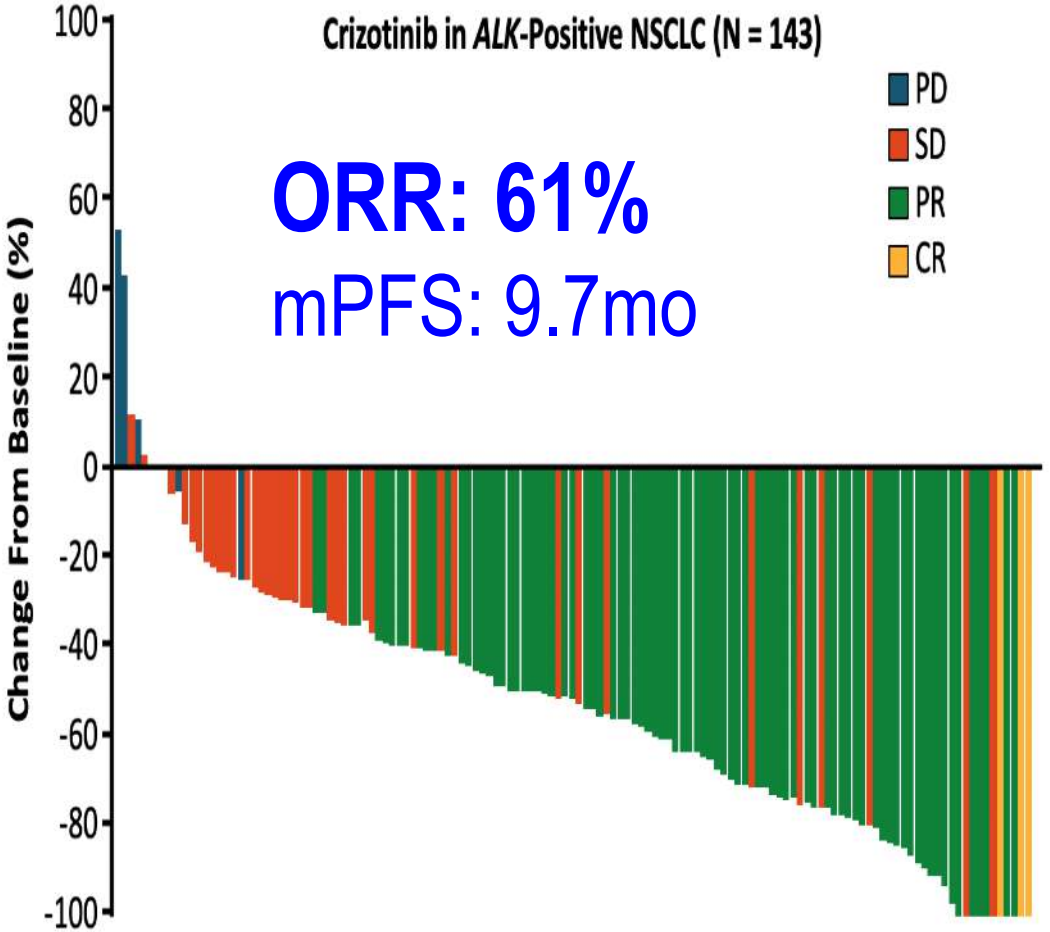
I start with 1st generation ALK TKI

1G

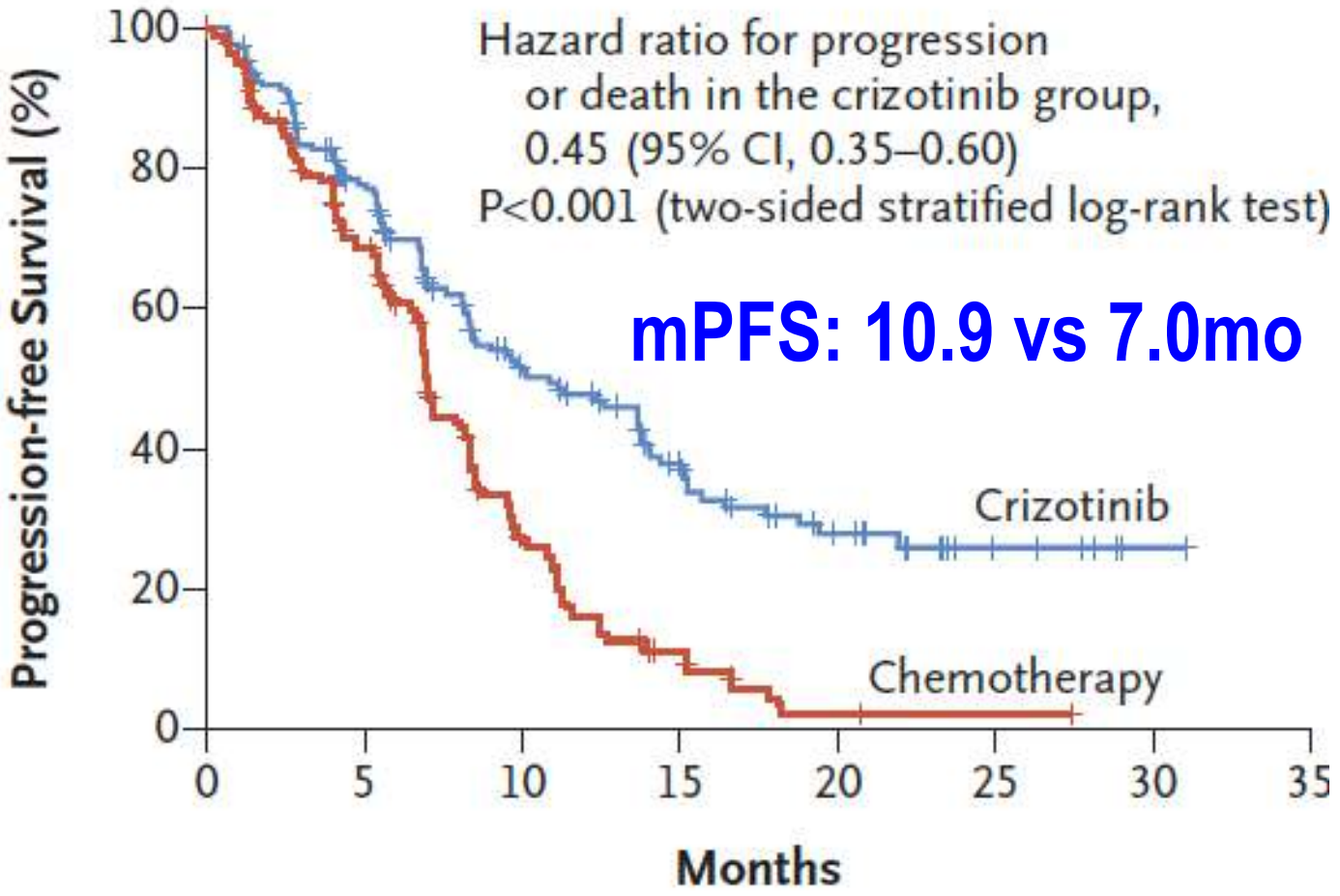
Crizotinib



I start with 1st generation ALK TKI

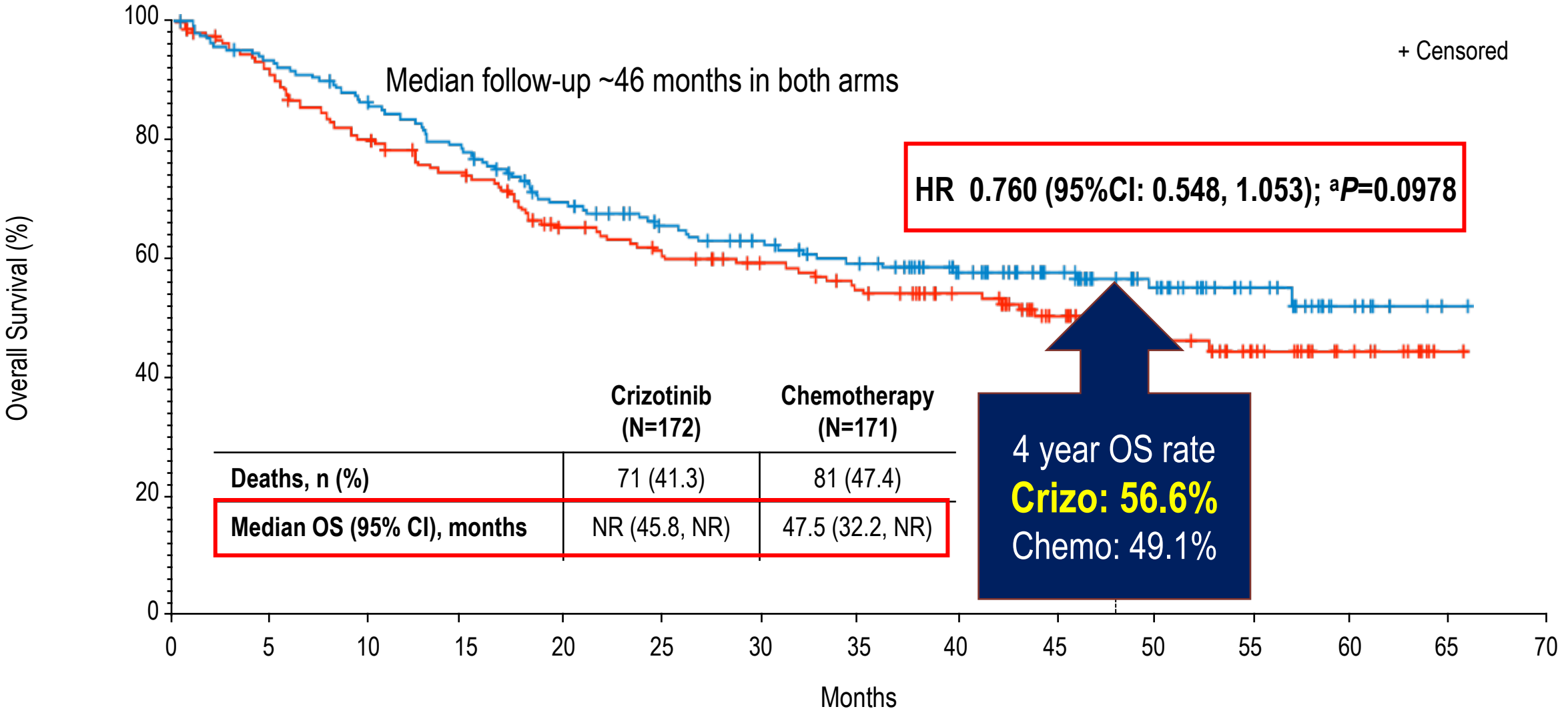


Camidge Lancet Oncology 2012



Solomon, Mok et al. NEJM 2014

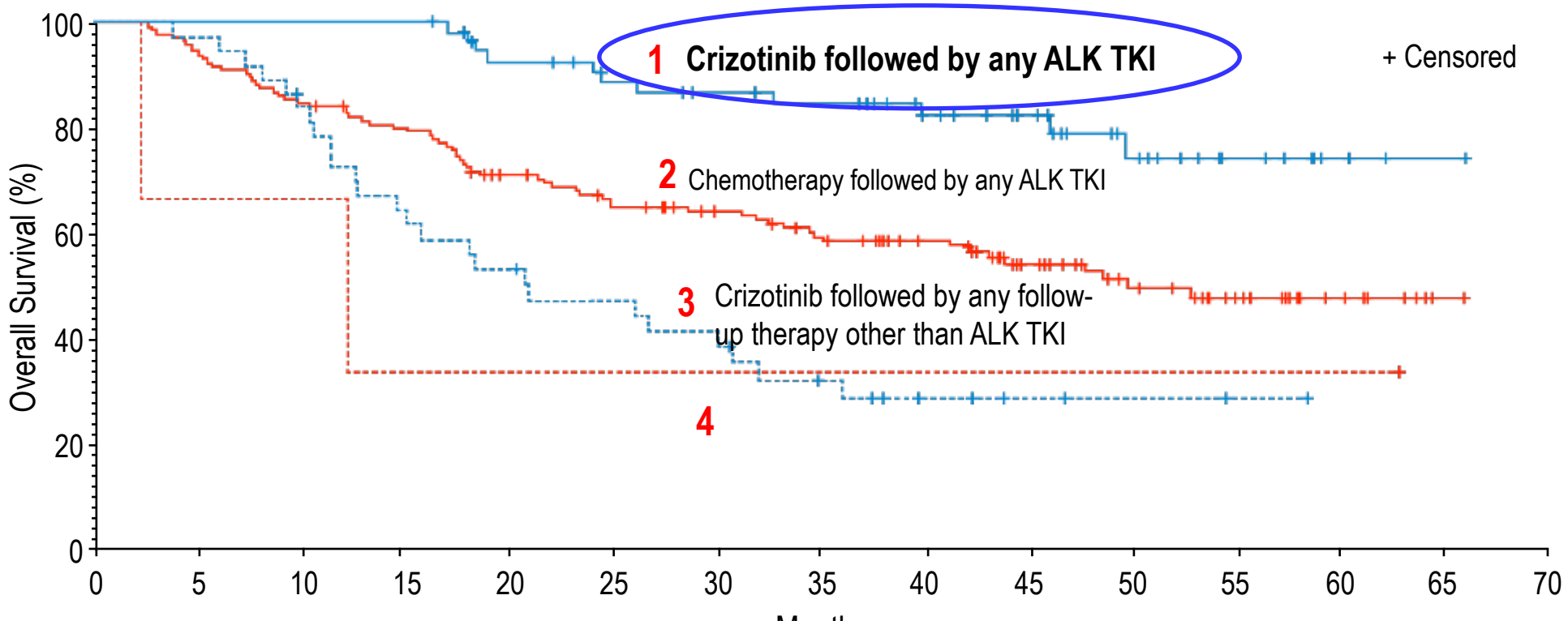
PROFILE 1014: Final Primary OS Analysis (ITT Population)



T.Mok et al, ASCO 2017, B.J Solomon et al, JCO 2018

Impact of Subsequent Therapy on OS: ALK TKI versus treatment other than ALK TKI

3y-OS: 82%



No. at risk														
Crizotinib followed by any ALK TKI	57	57	57	57	50	45	42	40	33	25	16	8	3	1	0
Crizotinib followed by any follow-up therapy other than ALK TKI	37	36	30	22	19	16	13	9	5	3	2	1	0	0	0
Chemotherapy followed by any ALK TKI	145	136	123	113	97	86	79	70	60	43	30	20	10	1	0
Chemotherapy followed by any follow-up therapy other than ALK TKI	3	2	2	1	1	1	1	1	1	1	1	1	1	0	0

T.Mok et al, ASCO 2017, B.J Solomon et al, JCO 2018

2nd generation ALK-TKI in crizotinib-refractory NSCLC

Design/Assessment	Ceritinib Phase 1/2	Alectinib Phase 2	Brigatinib Phase 2
Median PFS	6.9M (5.6-8.7)	8.9M (5.6-11.3)	15.6M (11.1-NR)
ORR	**56%** (49-64)	**50%** (41-59)	**55%** (44-66)
IC ORR	**36%**	**57%**	**67%**
Duration of Response	8.3M	11.2M	14.8M

Kim et al Lancet Oncology 2016; Shaw et al. Lancet Oncology 2016; Kim DW et al, JCO 2017

3nd generation ALK-TKI in crizotinib-refractory NSCLC

LORLATINIB: Pooled Efficacy (EXP2–3A)

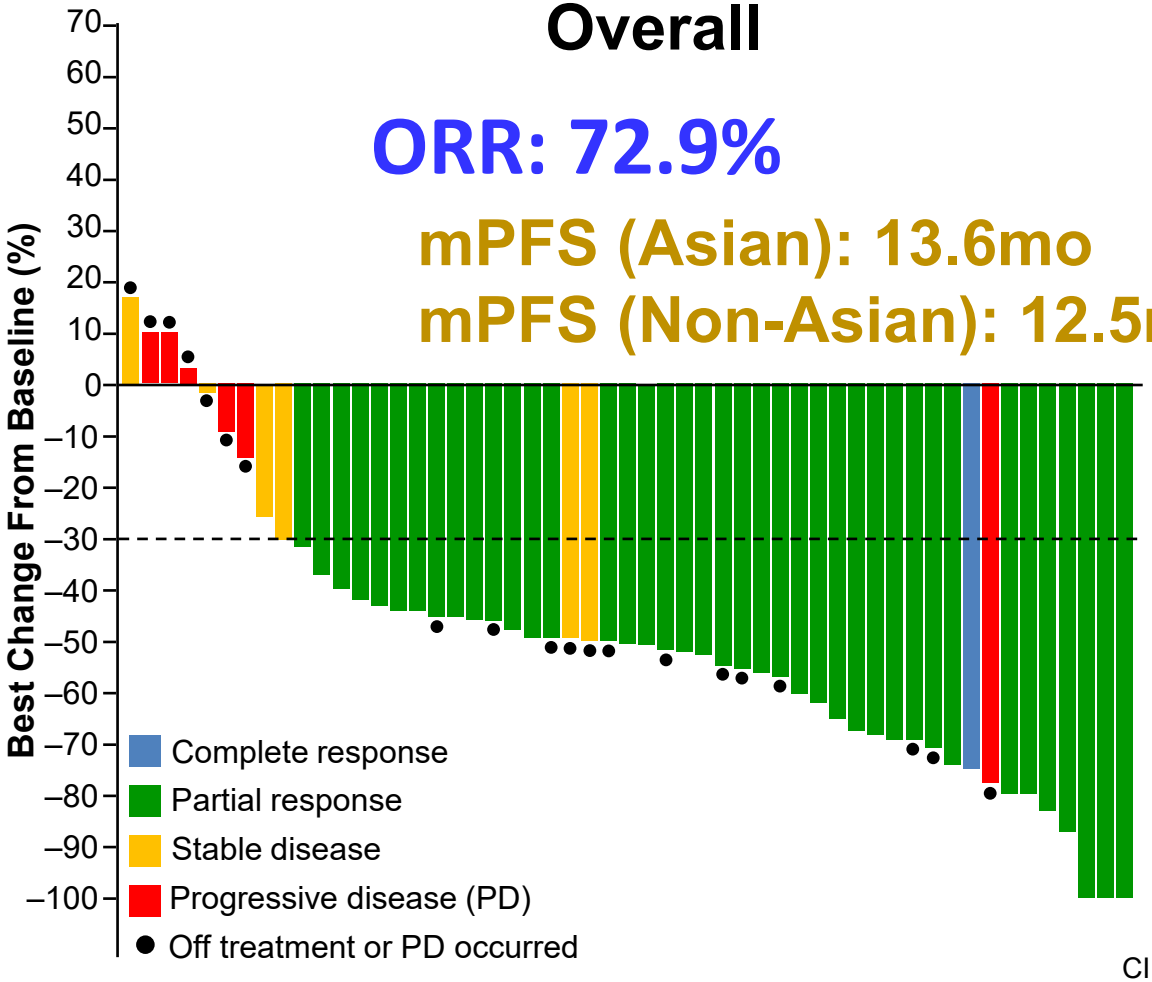
(ALK+, Crizotinib Only)

Overall

ORR: 72.9%

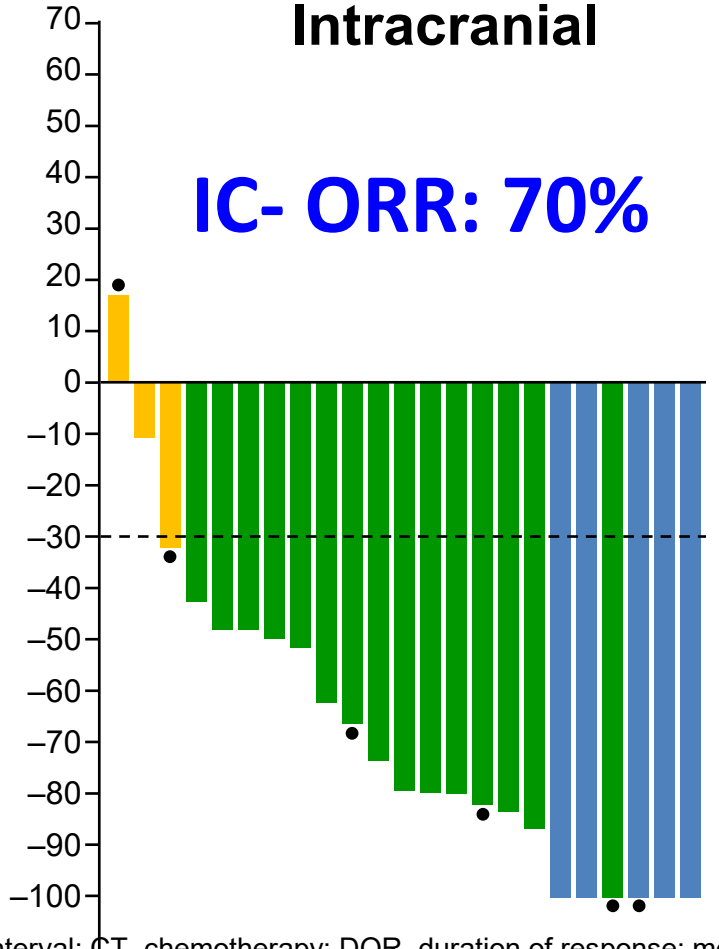
mPFS (Asian): 13.6mo

mPFS (Non-Asian): 12.5mo



Intracranial

IC- ORR: 70%



CI, confidence interval; CT, chemotherapy; DOR, duration of response; mo, months; NR, not reached.

[a] Patients with at least one on-study target lesion assessment as per independent central review were included. If any procedure was different and not interchangeable from the procedure at screening, the percent change from baseline could not be calculated and is not displayed.
[b] Complete response was defined as the disappearance of all target lesions; when nodal disease was included in target lesions, reversion to normal node size (<10 mm) prevented the percent change from baseline from reaching –100%. Some patients with a total change from baseline of –100% are shown as partial responses due to the inclusion of non-target lesions in the summary.

Updated Efficacy and Safety: B.Besse et al, ASCO 2019

Benjamin J. Solomon et al, WCLC 2017; lancet onco 2018

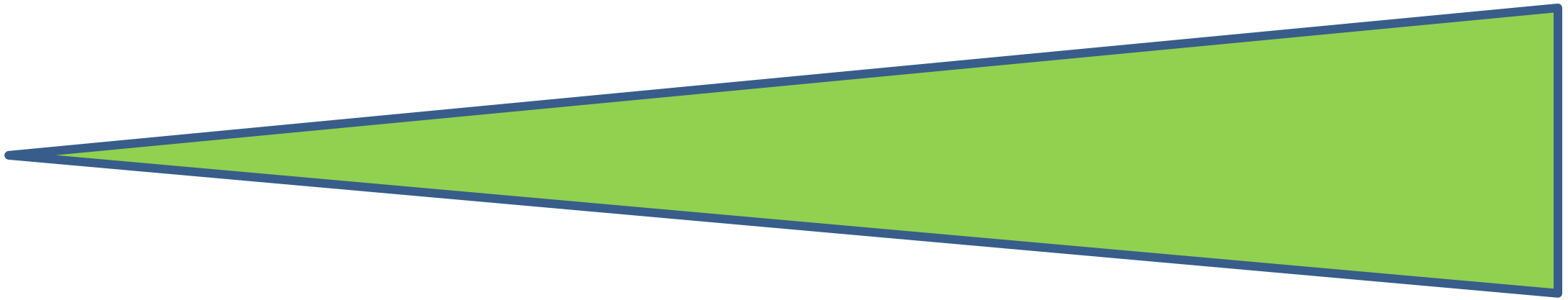
I start with 2nd generation ALK TKI

1G

Crizotinib

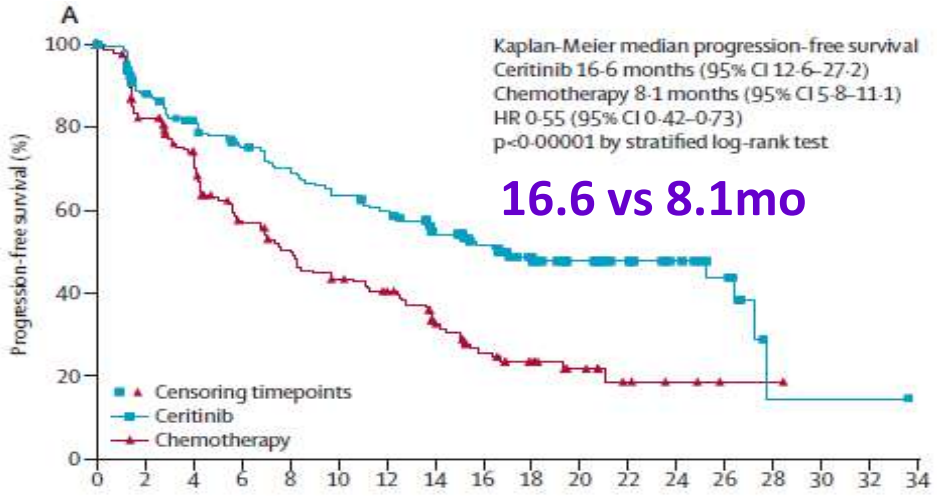
2G

Ceritinib
Alectinib
Brigatinib
Ensartinib



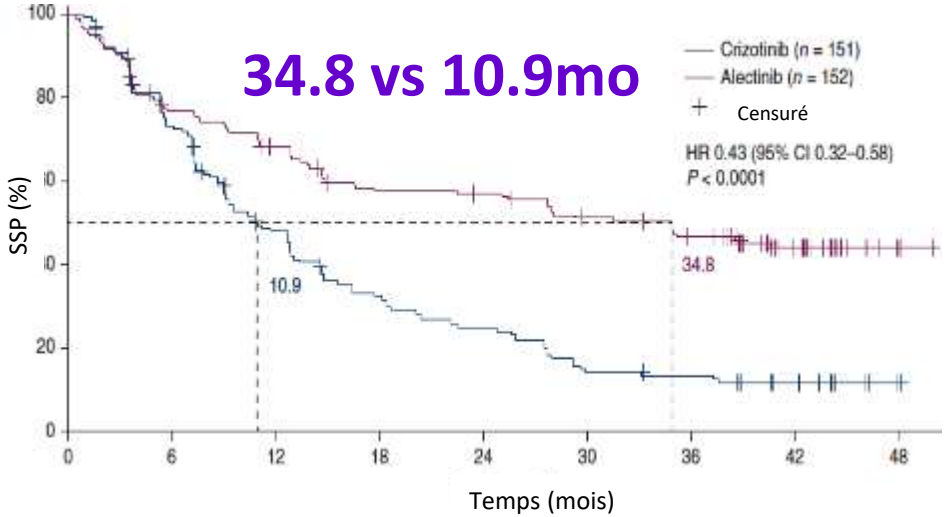
I start with 2nd generation ALK TKI

Ceritinib
ASCEND-4
HR 0.55



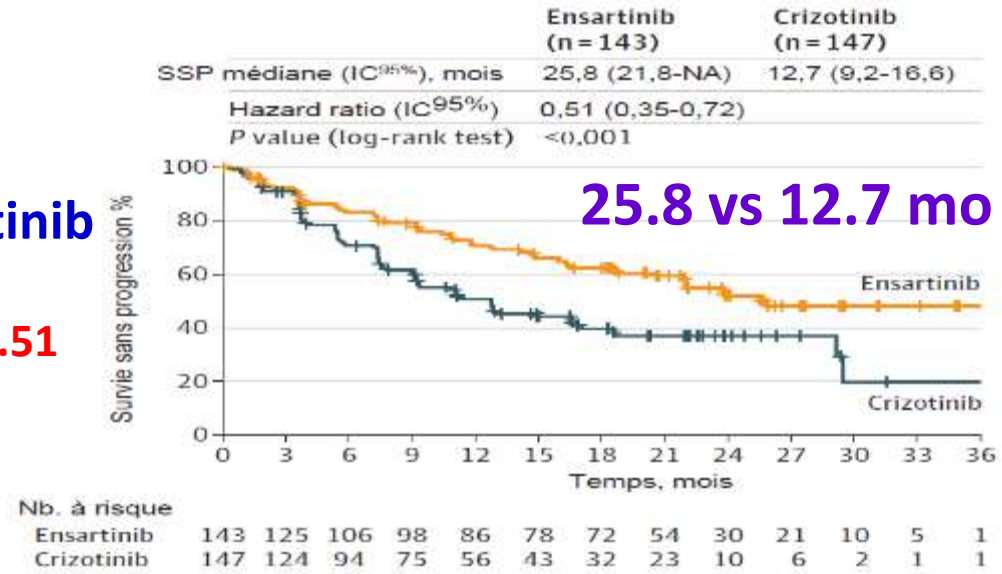
Soria JC, et al. Lancet 2017

Alectinib
ALEX
HR 0.43



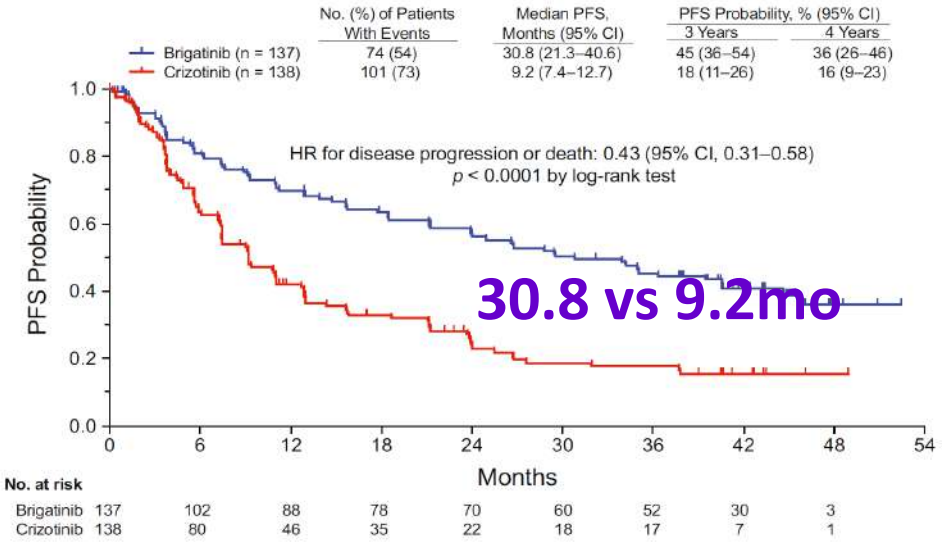
Mok et al. Annals of Oncology 2020

Ensartinib
eXalt3
HR 0.51



Horn L. et al. JAMA Oncol. 2021

Brigatinib
ALTA-1L
HR 0.43



Camidge R et al, JTO 2021

This made 2nd generation TKI Standard of Care

INSPIRE: Phase III, Iruplinalkib

INSPIRE: Phase Ⅲ, Open-Label, Randomized, Multicenter Study

Key Eligibility Criteria

- Stage ⅢB/IV NSCLC
- ALK positive centrally confirmed by FISH (Abbott Molecular), or by local NMPA-approved tests
- ECOG PS 0-1
- ALK TKI-naïve
- Previously treated with ≤1 chemotherapy regimen

Randomized 1:1 (N=292)

Iruplinalkib 180 mg qd with 7-day lead-in at 60 mg qd

Crizotinib 250 mg bid

Stratification factors:

- Previous chemotherapy regimens (0/1)
- Baseline CNS metastases (present/no)
- Previous radiotherapy to CNS metastases (yes/no)

Treatment until PD, intolerable toxicity, and other reasons for discontinuation

Primary endpoint

- IRC-assessed PFS per RECIST v1.1

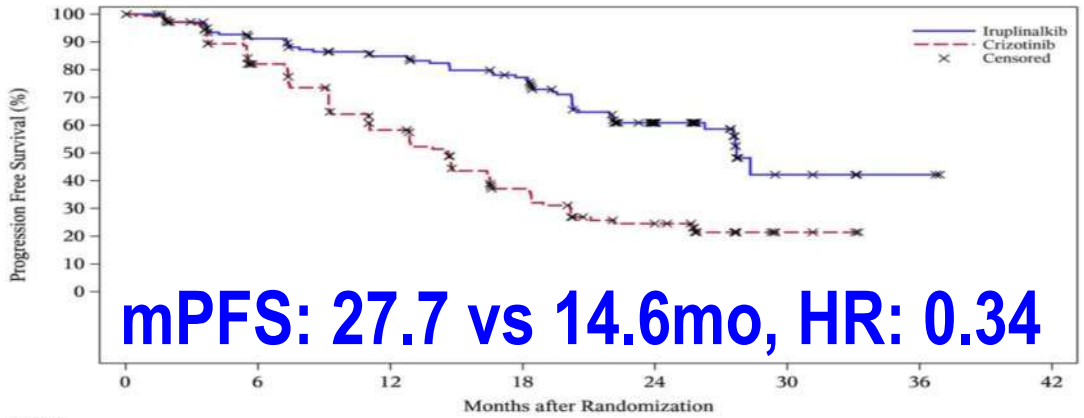
Key secondary endpoints

- Investigator-assessed PFS
- ORR and DoR (IRC and investigator)
- Intracranial ORR (IRC and investigator)
- OS
- Safety

Trial fully accrued in 2 December 2020
Data cutoff date: 13 November 2022
This study is registered with Center for Drug Evaluation of NMPA (CTR20191231) and Clinicaltrials.gov (NCT04632758).

Abbreviations: NSCLC, non-small cell lung cancer; NMPA, National Medical Products Administration; ECOG, Eastern Cooperative Oncology Group; IRC, independent review committee; CNS, central nervous system; PFS, progression-free survival; ORR, objective response rate; DoR, duration of response; OS, overall survival; PD, progressive disease.

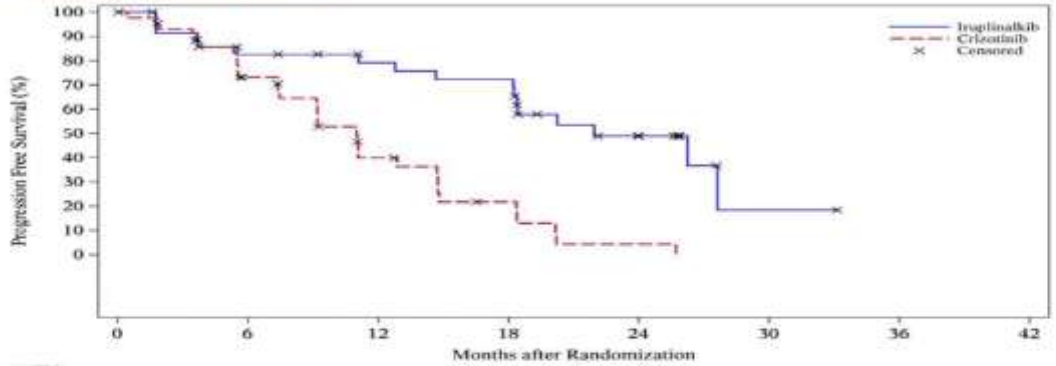
Primary Endpoint: IRC-Assessed PFS (ITT)



mPFS: 27.7 vs 14.6mo, HR: 0.34

At Risk								
Iruplinalkib	143	118	103	90	43	6	2	0
Crizotinib	149	107	70	37	19	3	0	

IRC-assessed PFS in patients with baseline CNS metastases (ITT)



At Risk								
Iruplinalkib	37	27	23	21	9	1	0	
Crizotinib	44	27	12	5	1	0		

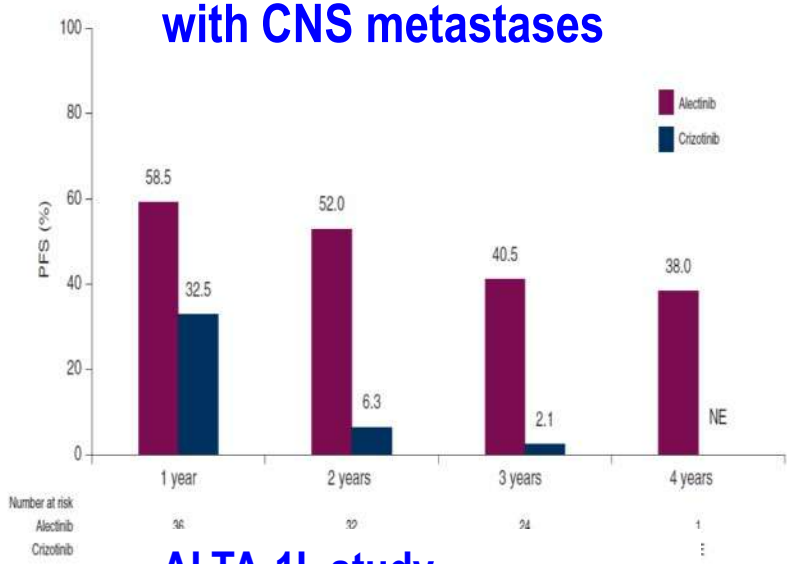
	Iruplinalkib (N=37)	Crizotinib (N=44)
Median PFS (95% CI), mo	21.95 (18.23-NE)	11.01 (7.46-14.72)
Hazard ratio (95% CI)	0.242 (0.119-0.493)	
P value (log-rank test)	<0.0001	

Runxiang Yang et al, WCLC 2023

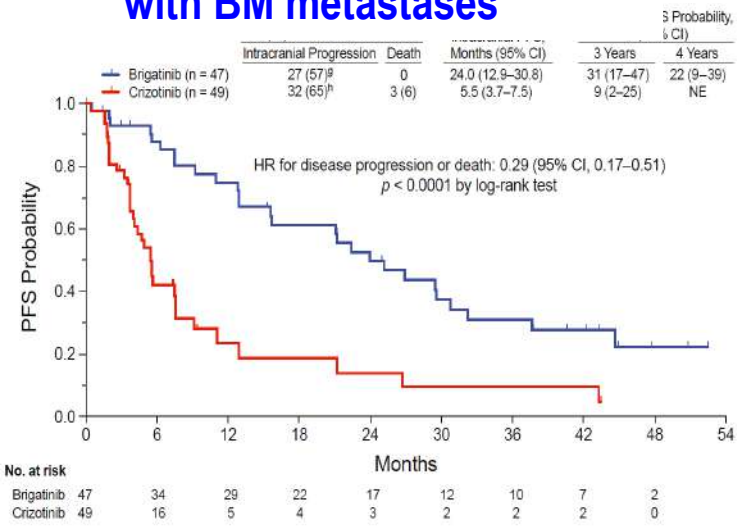
Second-Generation ALK inhibitors given in frontline vs crizotinib

	Alectinib ALEX	Brigatinib ALTA-1L
BM, %	40	29
Prior Brain RT	38	13
Previous chemoT	0	27
HR for PFS, investigators	0.43	0.43
HR for PFS, BIRC	0.50	0.48
Pts with BM at baseline, HR for PFS	**0.37**	**0.25**
Pts without BM at baseline, HR for PFS	**0.46**	**0.65**
IC response rate, mesurable lesions, %	81	78
IC complete response rate, %	45	45
Cumulative incidence of CNS progression as first event at 12 mo	9.4	9

ALEX study with CNS metastases



ALTA-1L study with BM metastases



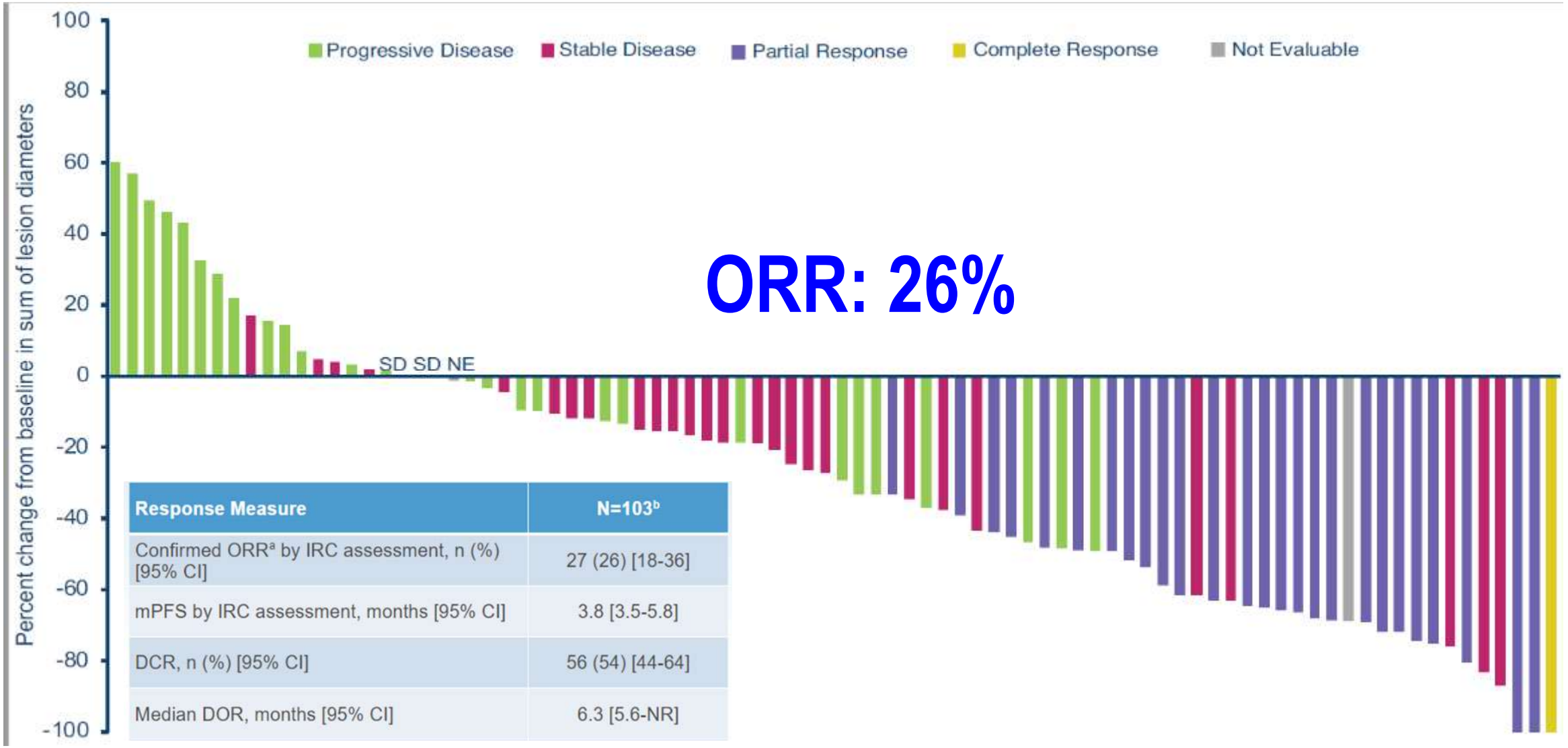
T. Mok et al, annals of oncology 2020

Camidge R et al, JTO 2021

Maurice Perol and Aurelie Swalduz, JCO 2022

Which 2nd line after alectinib/ceritinib: Brigatinib?

Efficacy of Brigatinib in patients who progressed on alectinib or ceritinib: ALTA-2 Study



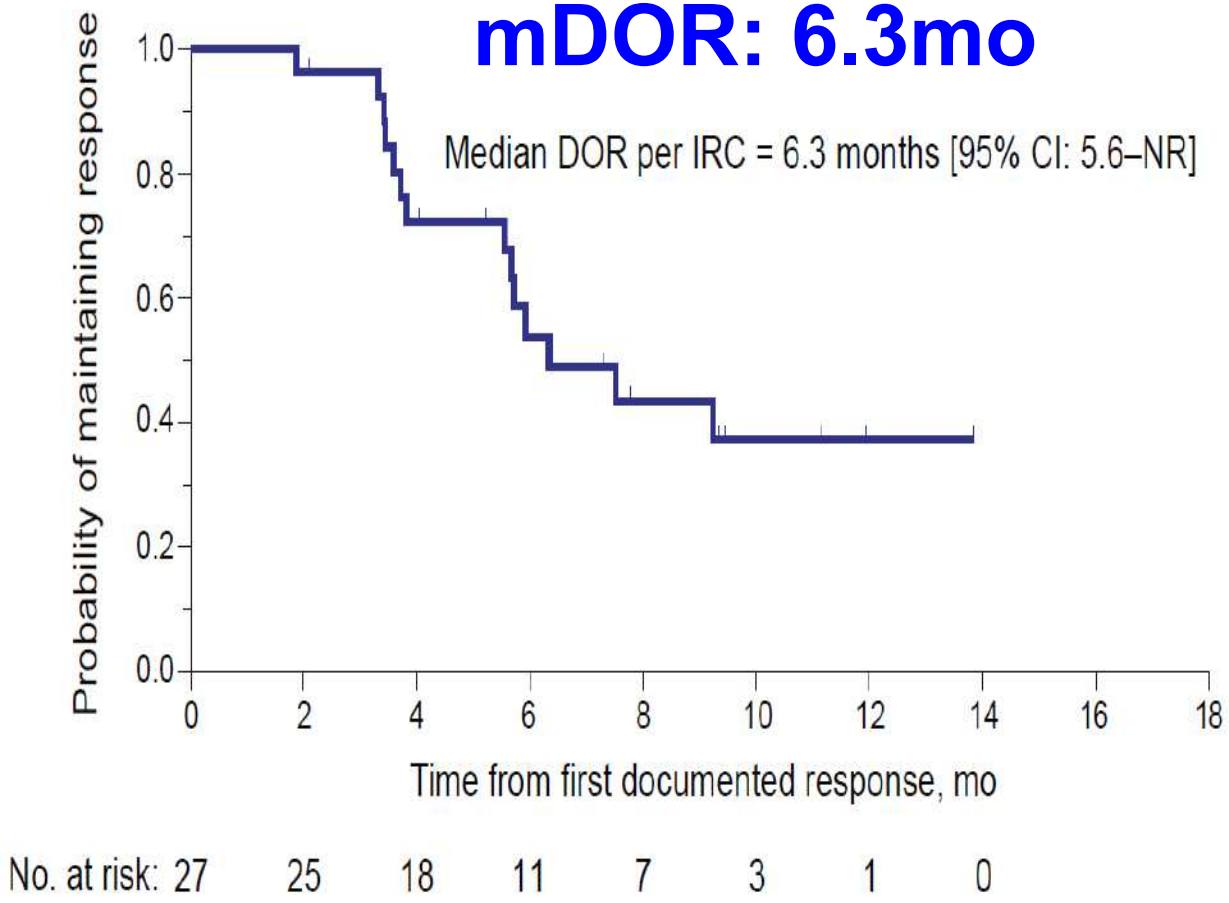
ORR: 26%

Response Measure	N=103[b]
Confirmed ORR[a] by IRC assessment, n (%) [95% CI]	27 (26) [18-36]
mPFS by IRC assessment, months [95% CI]	3.8 [3.5-5.8]
DCR, n (%) [95% CI]	56 (54) [44-64]
Median DOR, months [95% CI]	6.3 [5.6-NR]

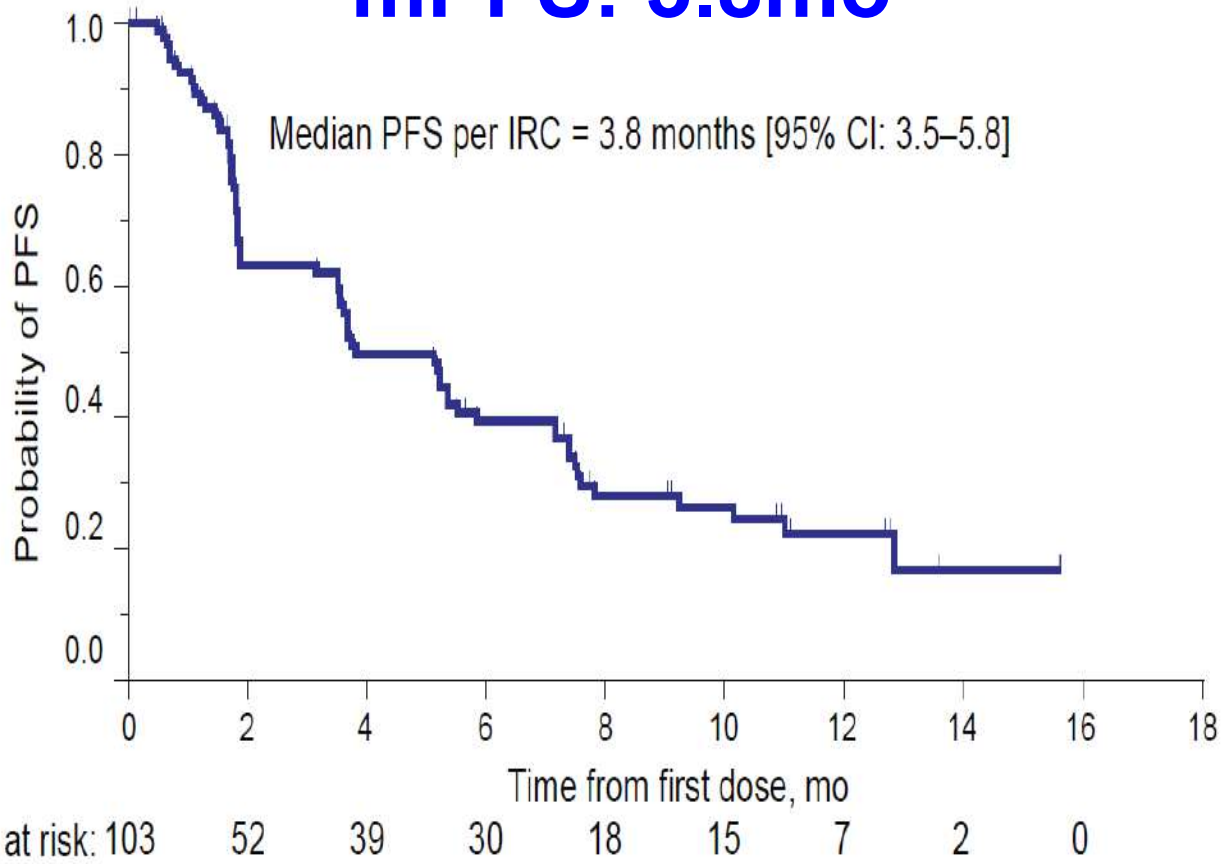
Ou S.HI, et al. Journal of Thoracic Oncology (2022)

Efficacy results in overall population

mDOR: 6.3mo



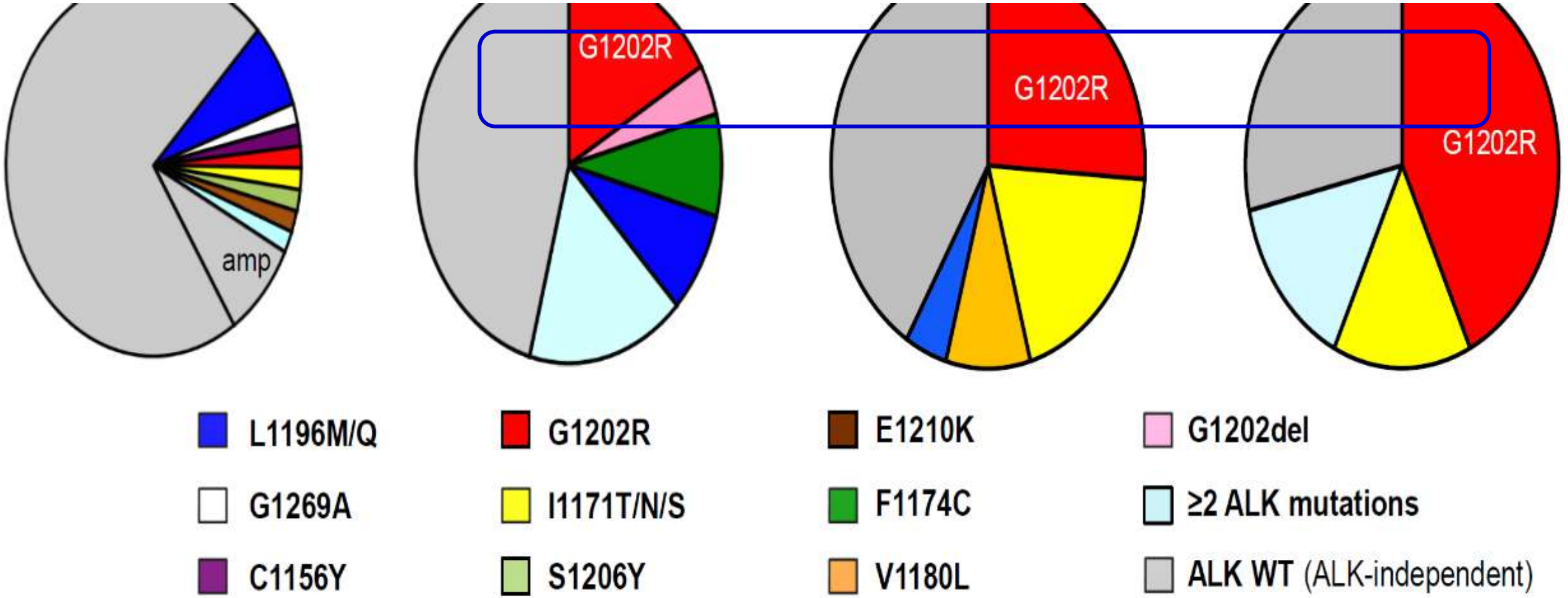
mPFS: 3.8mo



Brigatinib: limited activity post-ceritinib or post-alectinib therapy

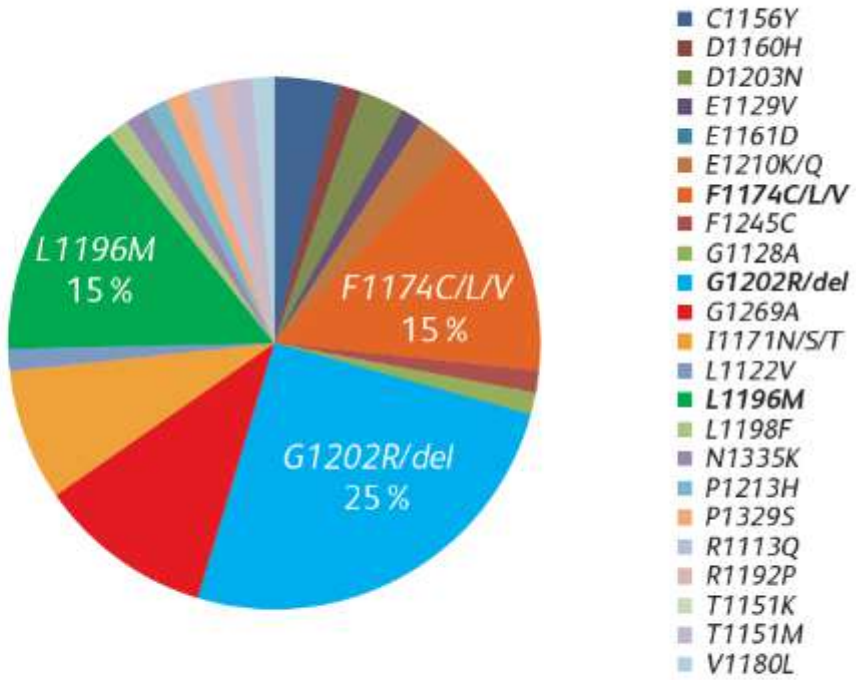
Ou S.HI, et al. Journal of Thoracic Oncology (2022)

Disctinct profiles of ALK resistance mutations after failure of a second generation ALK TKI

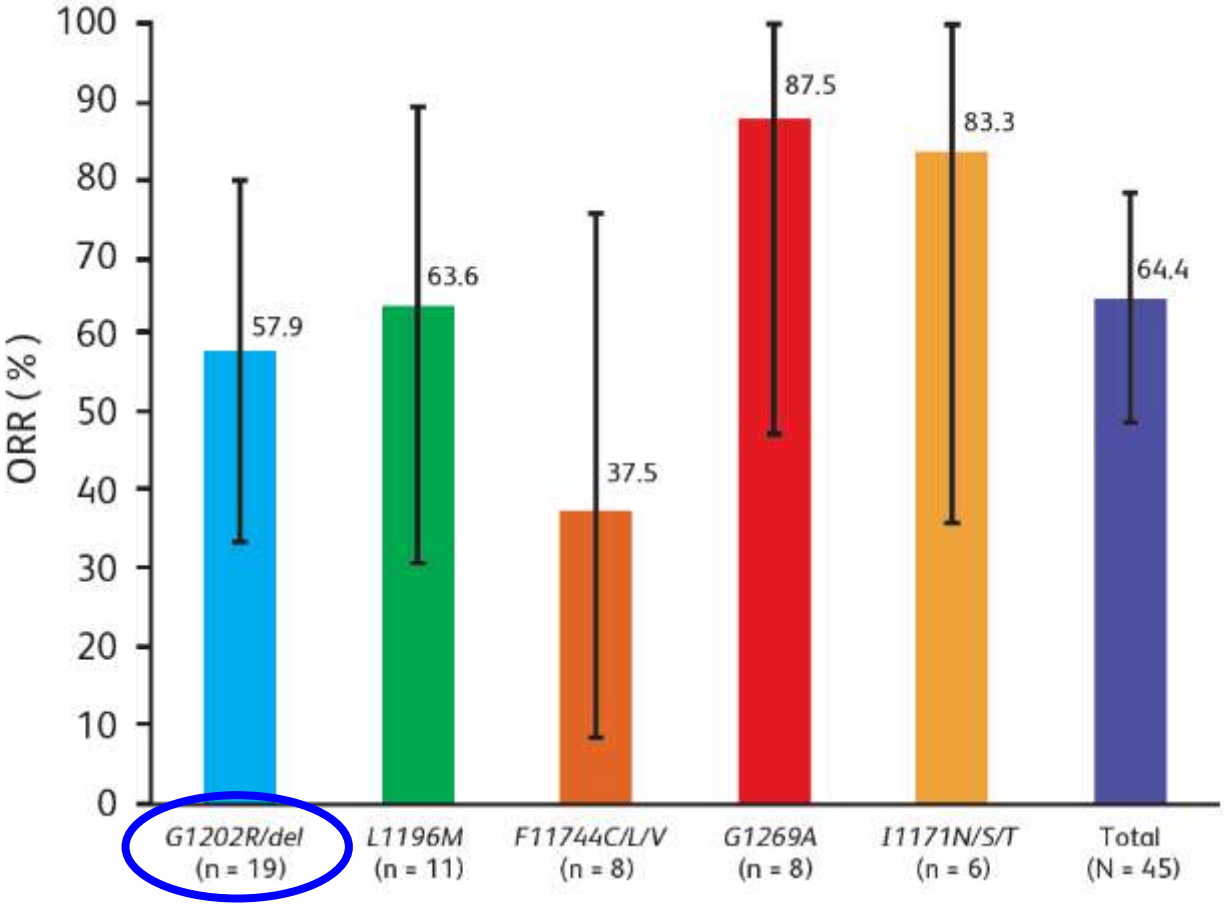


updated from Gainor et al., Cancer Discov 6: 1118-33, 2016

Lorlatinib-ORR in previously treated patients with ALK+ NSCLC harboring the most frequent ALK mutations in cfDNA (EXP2–5)



ALK Kinase Domain Mutations Detected in cfDNA of Previously Treated Patients With ALK+ NSCLC (EXP2–5)



Updated Efficacy and Safety: B.Besse et al, ASCO 2019

Lorlatinib in patients with at least one prior 2nd-generation ALK TKI (EXP3B-5) phase 1/2 study

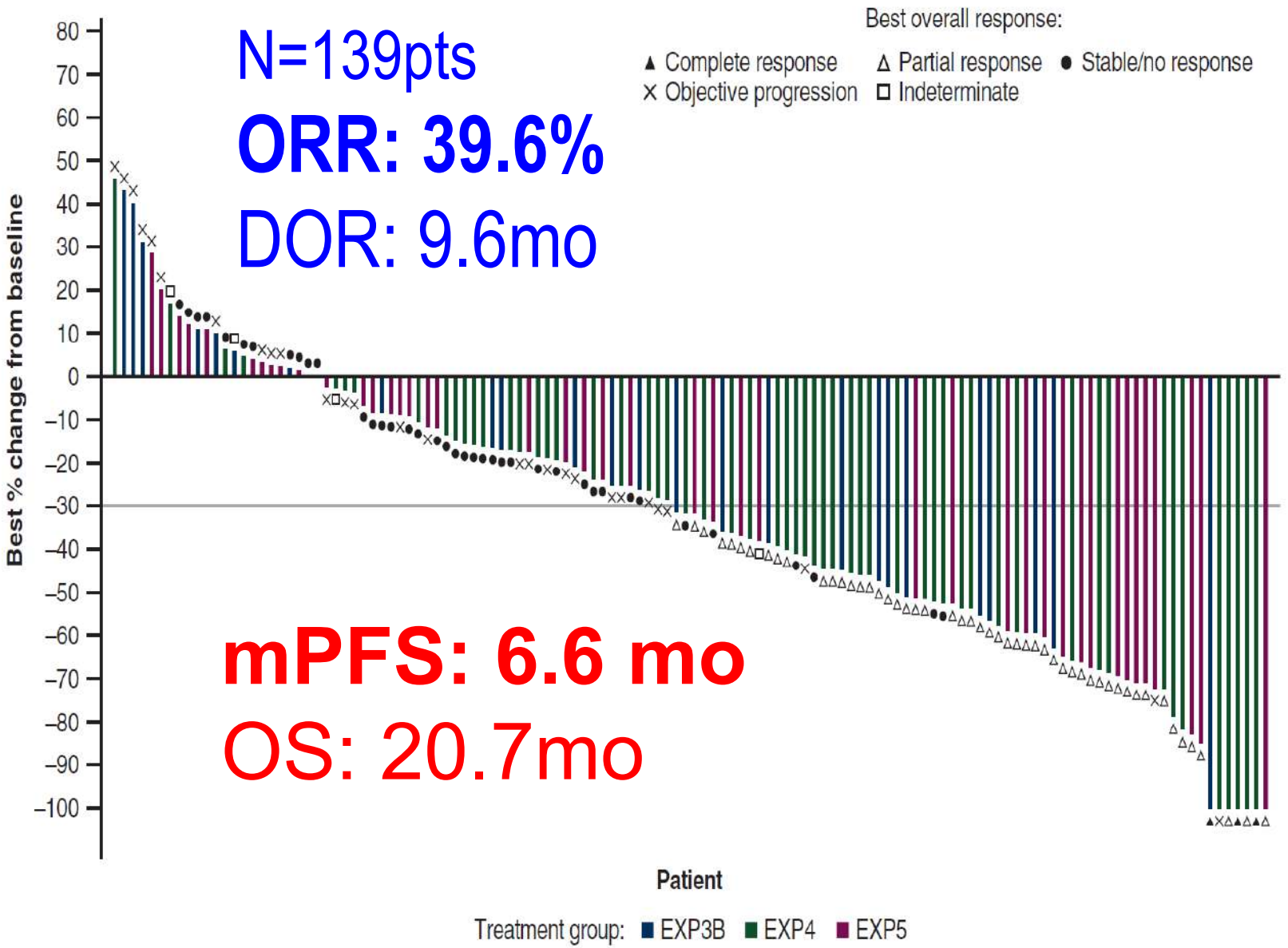
N=139pts

ORR: 39.6%

DOR: 9.6mo

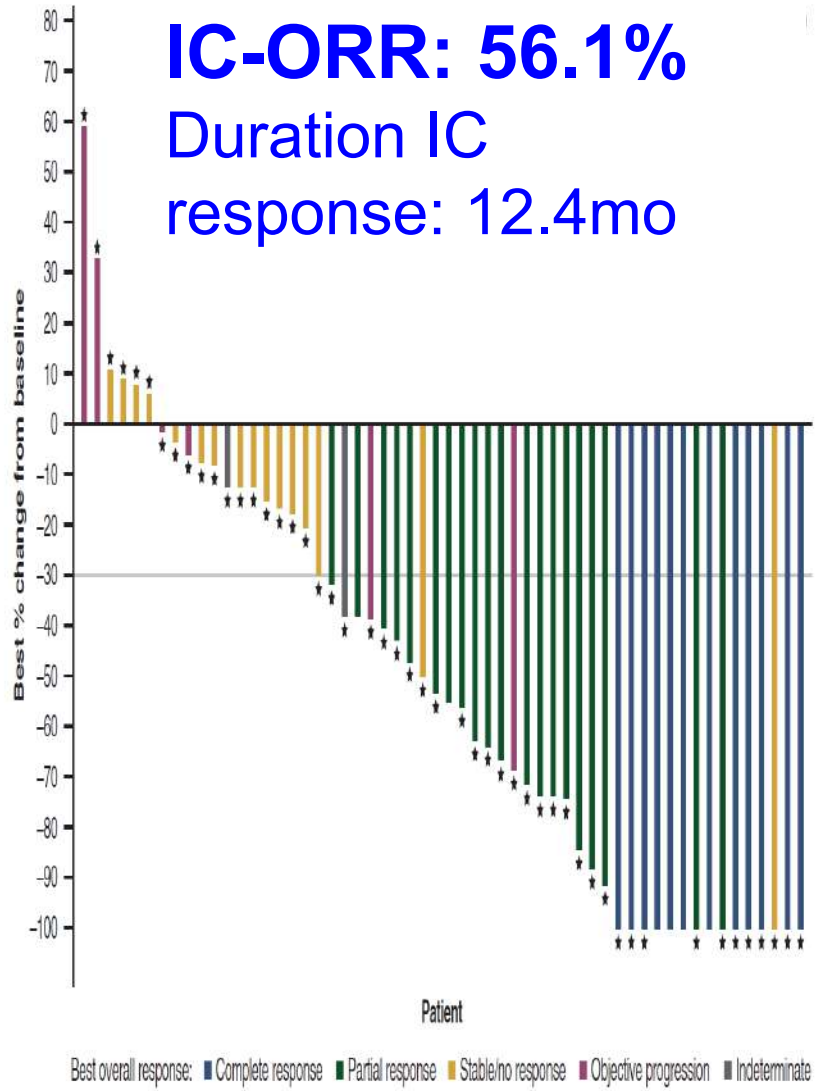
mPFS: 6.6 mo

OS: 20.7mo



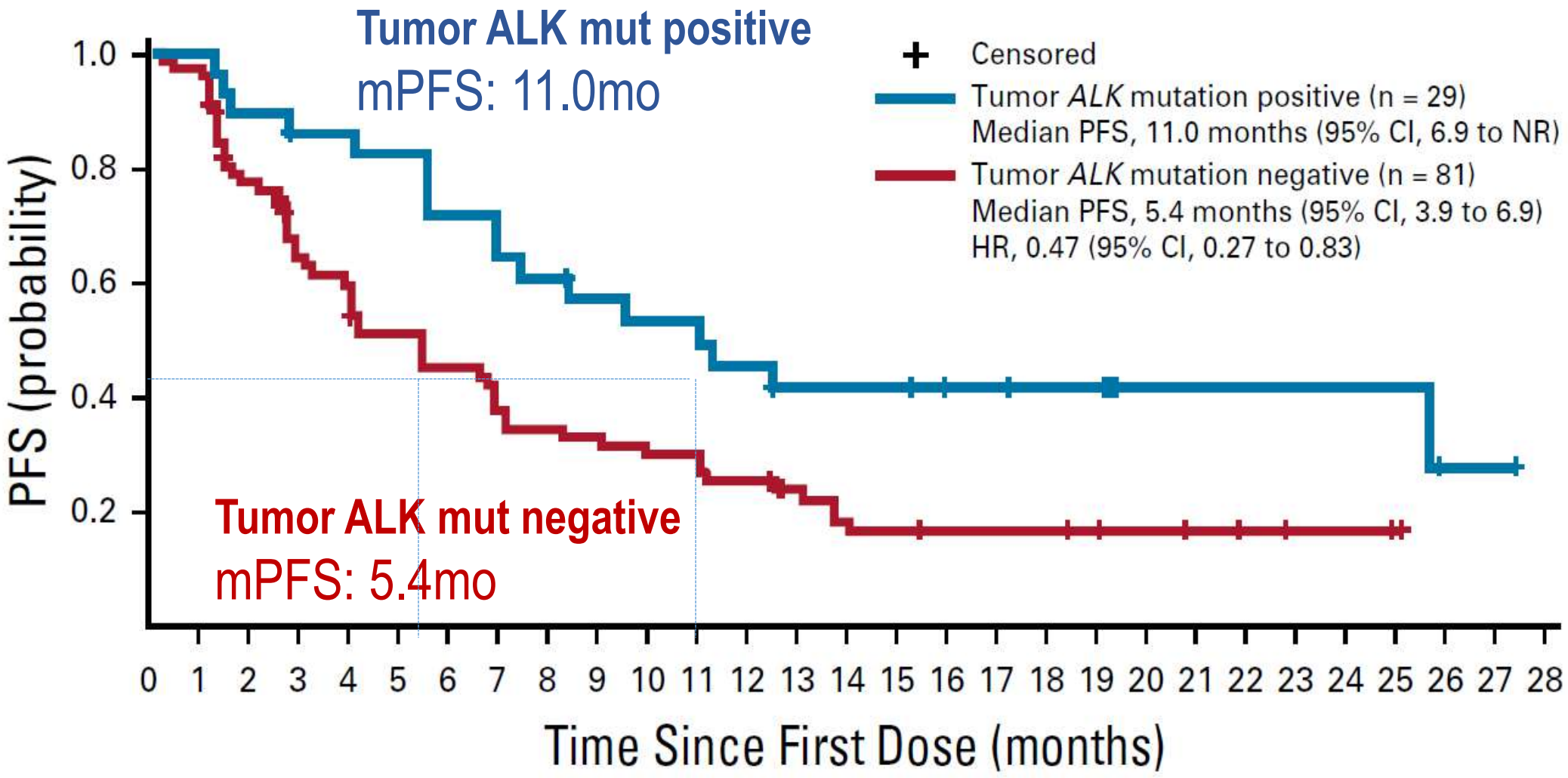
IC-ORR: 56.1%

Duration IC response: 12.4mo



E.Felip et al, annals onco 2021

ALK resistance mutations in tumor tissue predict response to lorlatinib after a 2nd generation ALK TKI



Shaw et al, JCO 2019

The 3nd Generation ALK/ROS1 TKI Lorlatinib has become a standard therapy after 2nd Generation TKIs

crizotinib

ceritinib
alectinib
brigatinib

lorlatinib

ceritinib
alectinib
brigatinib

lorlatinib

I start with 3nd generation ALK TKI

1G

Crizotinib

2G

Ceritinib
Alectinib
Brigatinib
Ensartinib

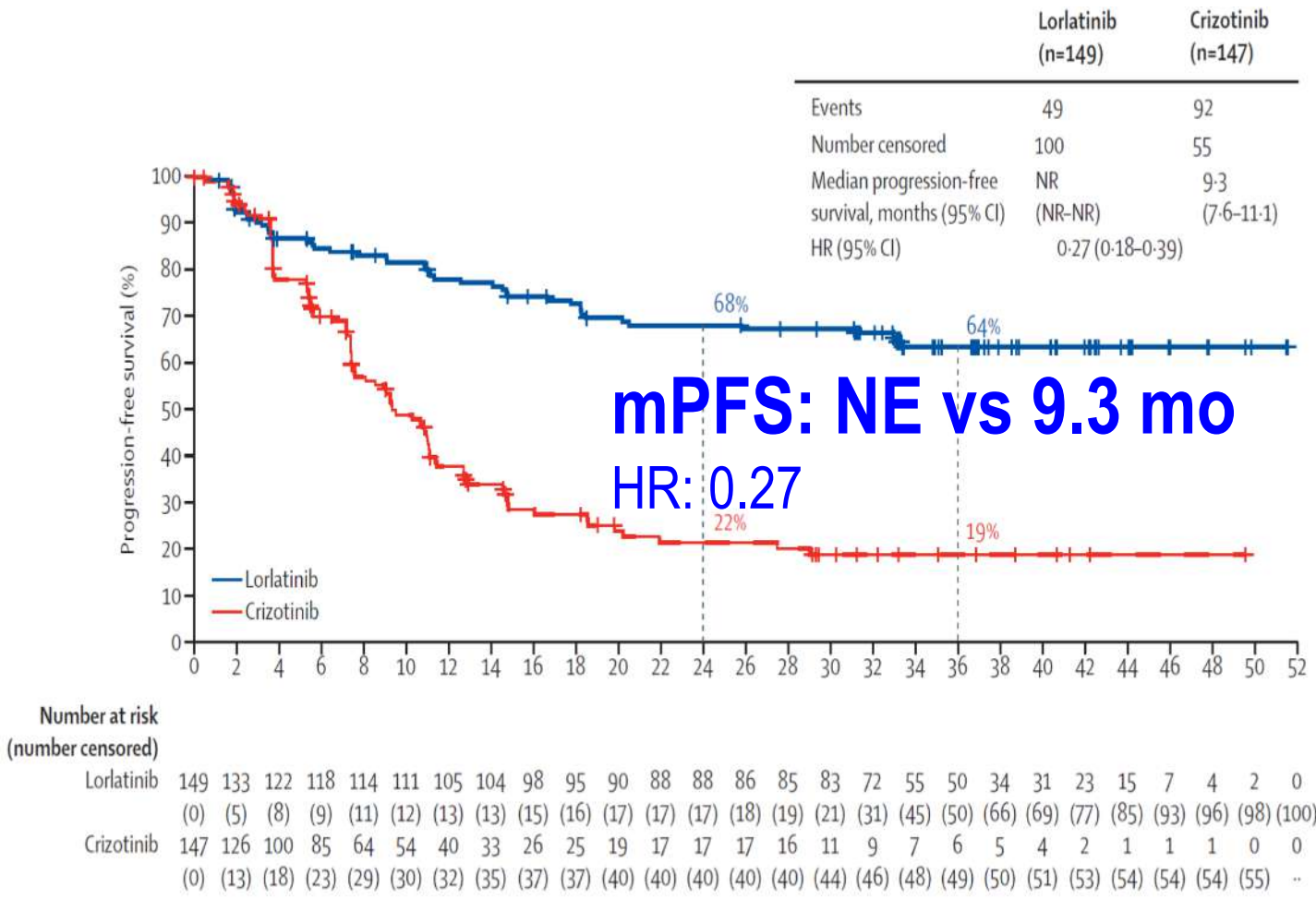
3G

Lorlatinib

Increased potency against ALK
Increased CNS penetration and activity
Broader coverage of ALK resistance mutations

I start with 3rd generation ALK TKI (CROWN Study)

Crizotinib | **Ceritinib** | **Alectinib** | **Brigatinib** | **Ensartinib** | **Lorlatinib**



	Lorlatinib (n=149)	Crizotinib (n=147)
Patients with event, n (%)	49	92
Median PFS, months (95% CI)	NE (NE–NE)	9.3 (7.6-11.1)
HR (95% CI) 1-sided P value*	**0.27** (0.18-0.39) <0.001	

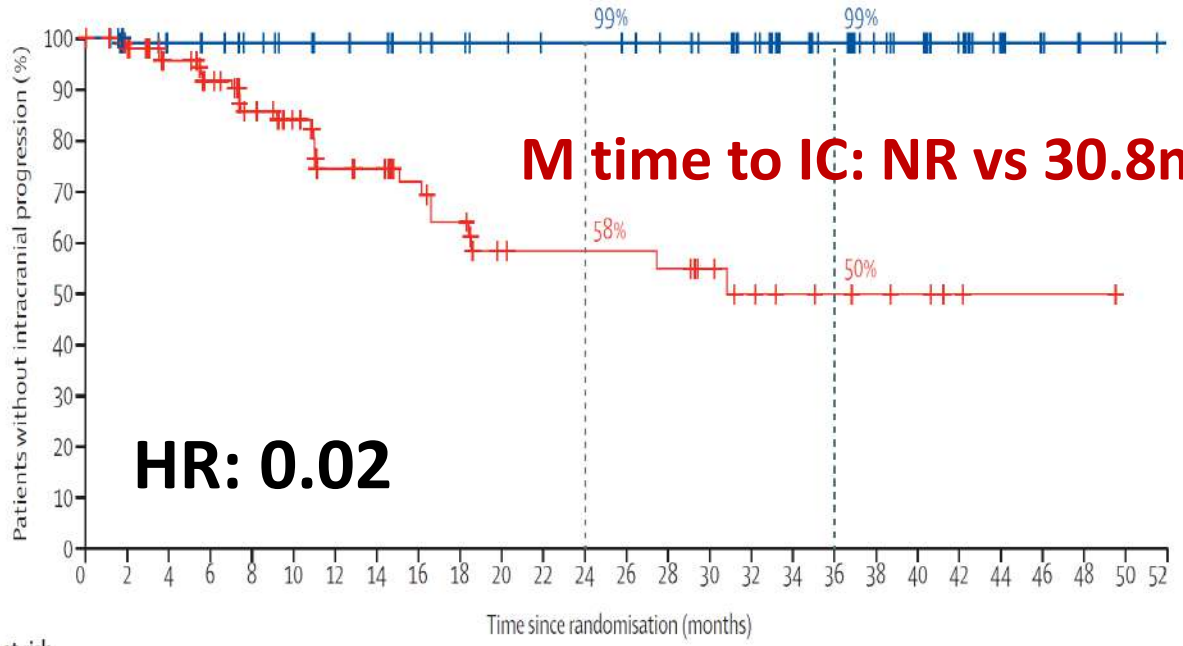
*By stratified log-rank test.

BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; NE, not estimable; PFS, progression-free survival

Benjamin J Solomon et al, Lancet Respir Med 2022

I start with 3rd generation ALK TKI (BM)

IC time to progression in patients without baseline BM



M time to IC: NR vs 30.8mo

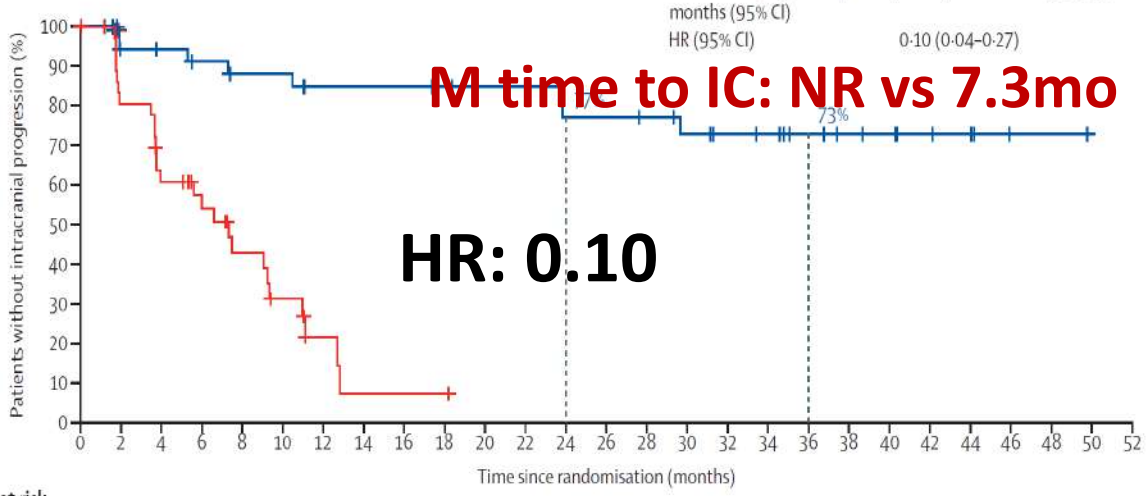
HR: 0.02

Number at risk (number censored)

Lorlatinib	112	99	96	93	90	87	85	84	81	79	76	74	74	73	71	69	61	49	44	31	27	20	13	7	3	1	0
	(0)	(12)	(15)	(18)	(21)	(24)	(26)	(27)	(30)	(32)	(35)	(37)	(37)	(38)	(40)	(42)	(50)	(62)	(67)	(80)	(84)	(91)	(98)	(104)	(108)	(110)	(111)
Crizotinib	108	89	76	67	54	47	36	34	28	24	18	17	17	17	16	12	9	7	6	5	4	2	1	1	1	0	0
	(0)	(17)	(28)	(34)	(43)	(49)	(55)	(57)	(62)	(63)	(67)	(68)	(68)	(68)	(68)	(72)	(74)	(76)	(77)	(78)	(79)	(81)	(82)	(82)	(82)	(83)	..

IC time to progression in patients with baseline BM

Events	8	26
Number censored	29	13
Median time to intracranial progression, months (95% CI)	NR (NR-NR)	7·3 (3·7-9·3)
HR (95% CI)	0·10 (0·04-0·27)	



M time to IC: NR vs 7.3mo

HR: 0.10

Number at risk (number censored)

Lorlatinib	37	32	31	29	27	27	24	24	24	23	22	22	20	20	19	17	14	13	10	8	7	5	4	1	1	0	0
	(0)	(3)	(4)	(5)	(6)	(6)	(8)	(8)	(8)	(9)	(10)	(10)	(10)	(10)	(11)	(12)	(15)	(16)	(19)	(21)	(22)	(24)	(25)	(28)	(28)	(29)	..
Crizotinib	39	29	21	16	11	7	3	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	(0)	(3)	(4)	(7)	(9)	(10)	(12)	(12)	(12)	(12)	(13)	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..

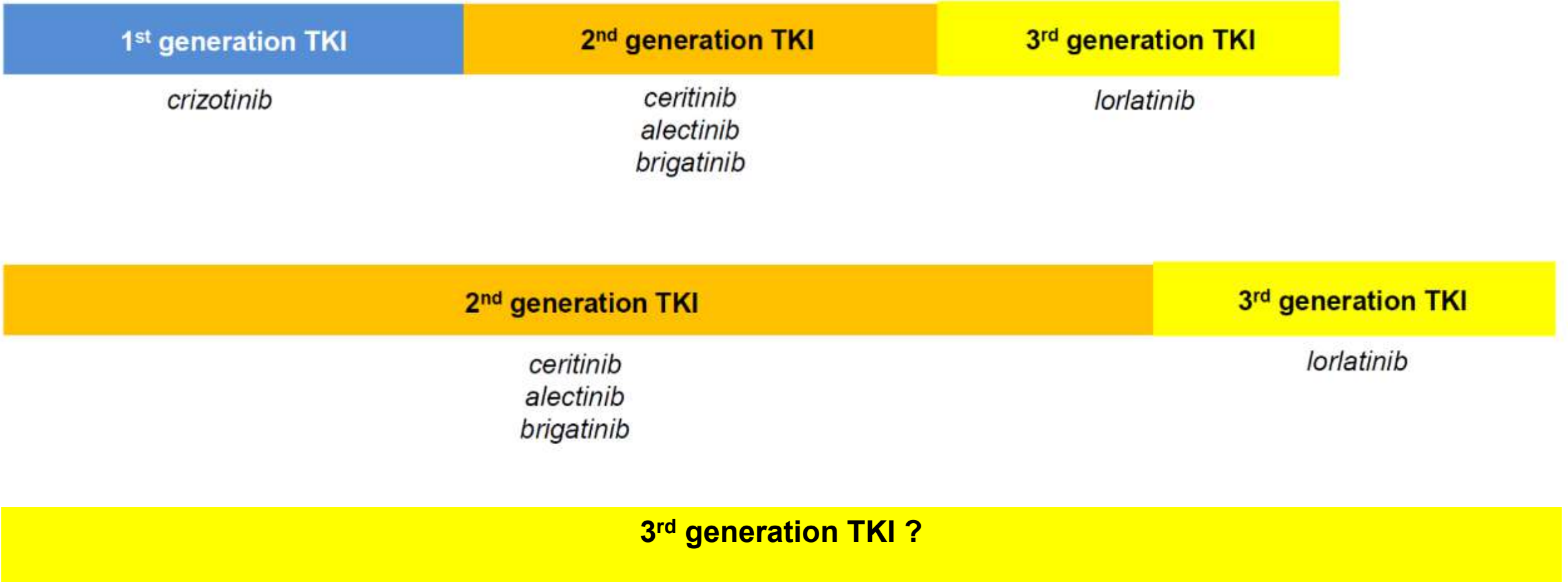
Benjamin J Solomon et al, Lancet Respir Med 2022

Main Results in Terms of Efficacy of Available Second- and Third-Generation ALK Inhibitors Given in Frontline Versus Crizotinib

	Alectinib ALEX	Brigatinib ALTA-1L	Lorlatinib CROWN
BM, %	40	29	26
Prior Brain RT	38	13	6
Previous chemoT	0	27	0
HR for PFS, investigators	0.43	0.43	0.19
HR for PFS, BIRC	0.50	0.48	0.27
Pts with BM at baseline, HR for PFS	**0.37**	**0.25**	**0.21**
Pts without BM at baseline, HR for PFS	**0.46**	**0.65**	**0.29**
IC response rate, mesurable lesions, %	81	78	82
IC complete response rate, %	45	45	60
Cumulative incidence of CNS progression as first event at 12 mo	9.4	9	2.8

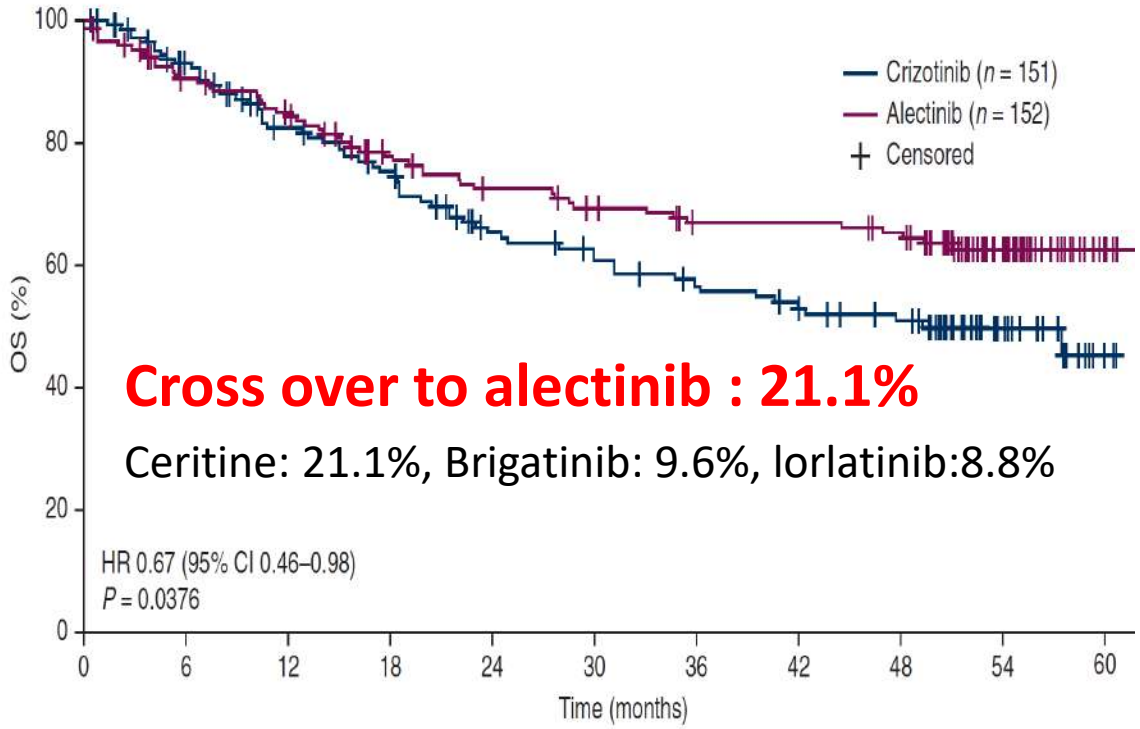
Maurice Perol and Aurelie Swalduz, JCO 2022

Best sequence?



Overall survival (ALEX study)

ALEX



Cross over to alectinib : 21.1%

Ceritine: 21.1%, Brigatinib: 9.6%, lorlatinib:8.8%

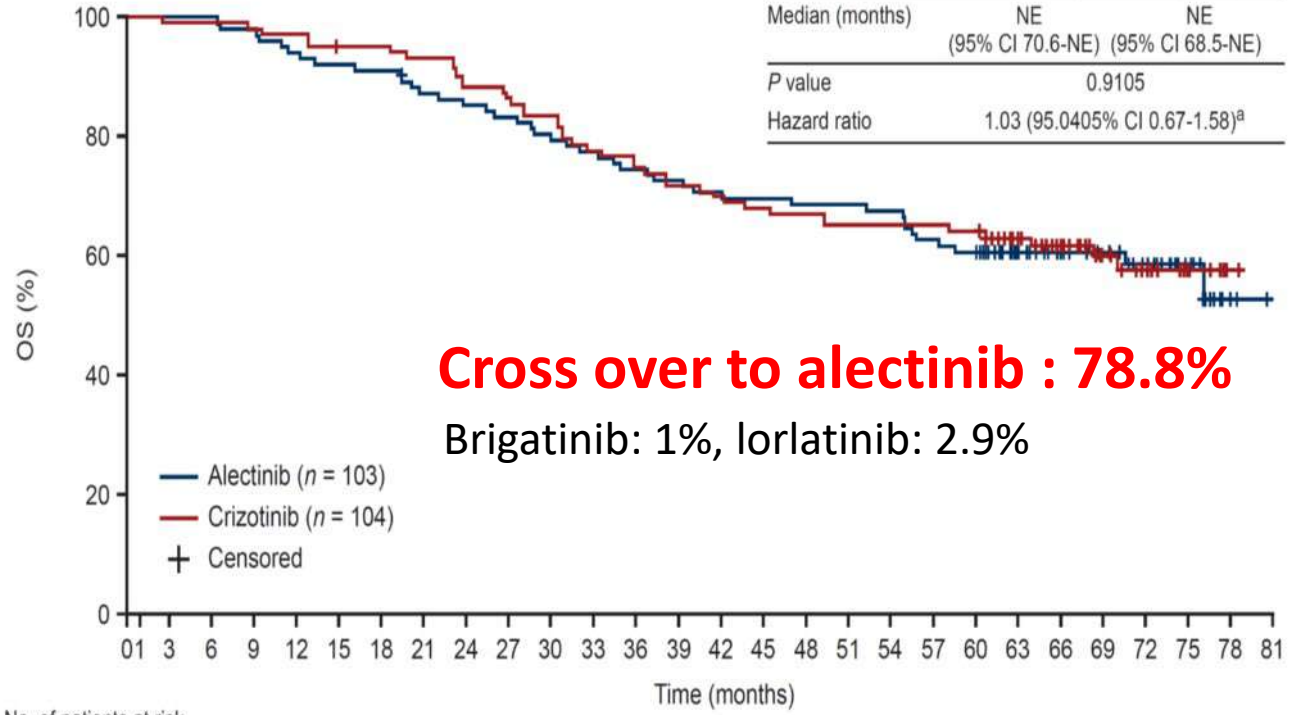
Number at risk

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

T. Mok et al, annals of oncology 2020

J-ALEX

	Alectinib n = 103	Crizotinib n = 104
Patient with event	42 (40.8%)	41 (39.4%)
Patient without event	61 (59.2%)	63 (60.6%)
Median (months)	NE (95% CI 70.6-NE)	NE (95% CI 68.5-NE)
P value	0.9105	
Hazard ratio	1.03 (95.0405% CI 0.67-1.58)[a]	



Cross over to alectinib : 78.8%

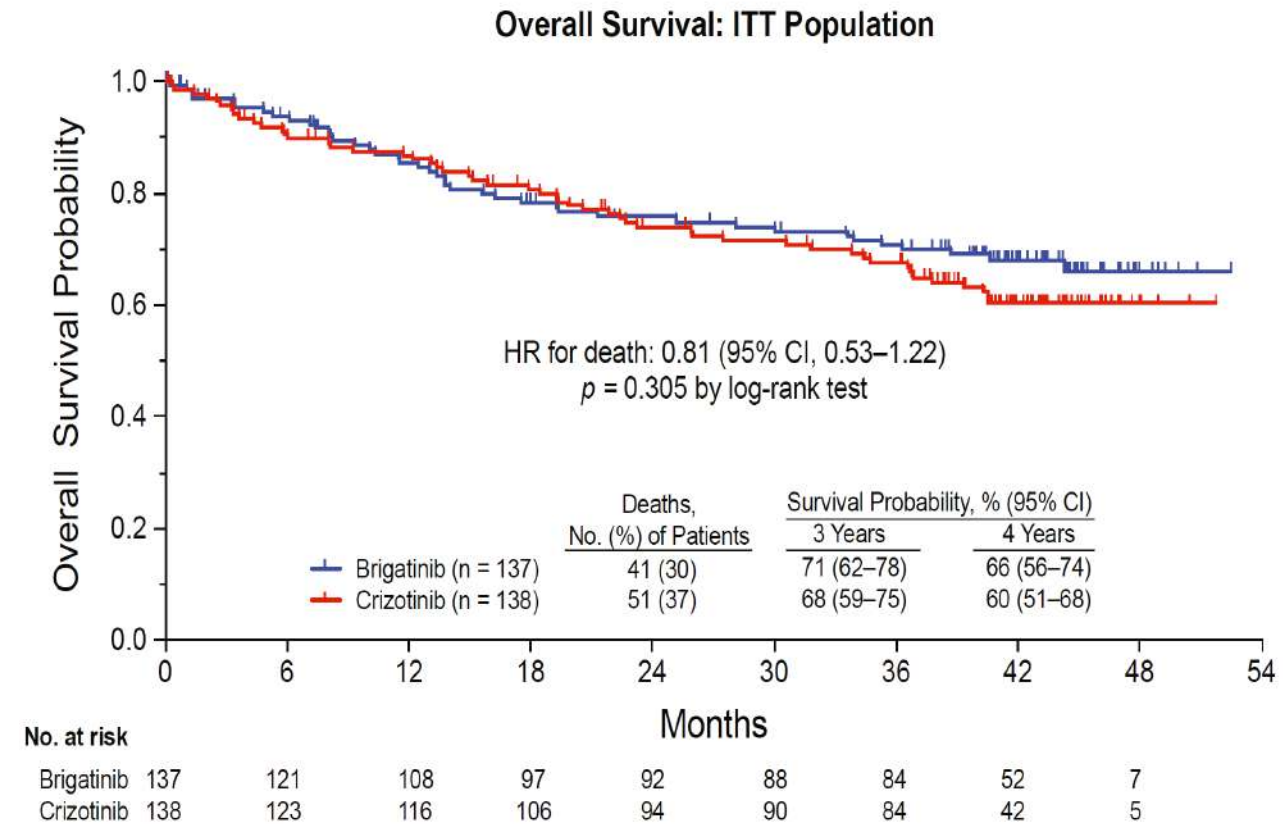
Brigatinib: 1%, lorlatinib: 2.9%

No. of patients at risk

Crizotinib	104	103	103	102	101	98	98	96	91	88	86	80	77	74	72	70	69	67	67	67	66	54	42	27	20	10	2						
Alectinib	103	103	103	101	97	95	94	89	87	85	82	79	76	74	72	71	70	70	69	64	62	48	40	31	23	13	3						

K. Hotta et al, ESMO open 2022

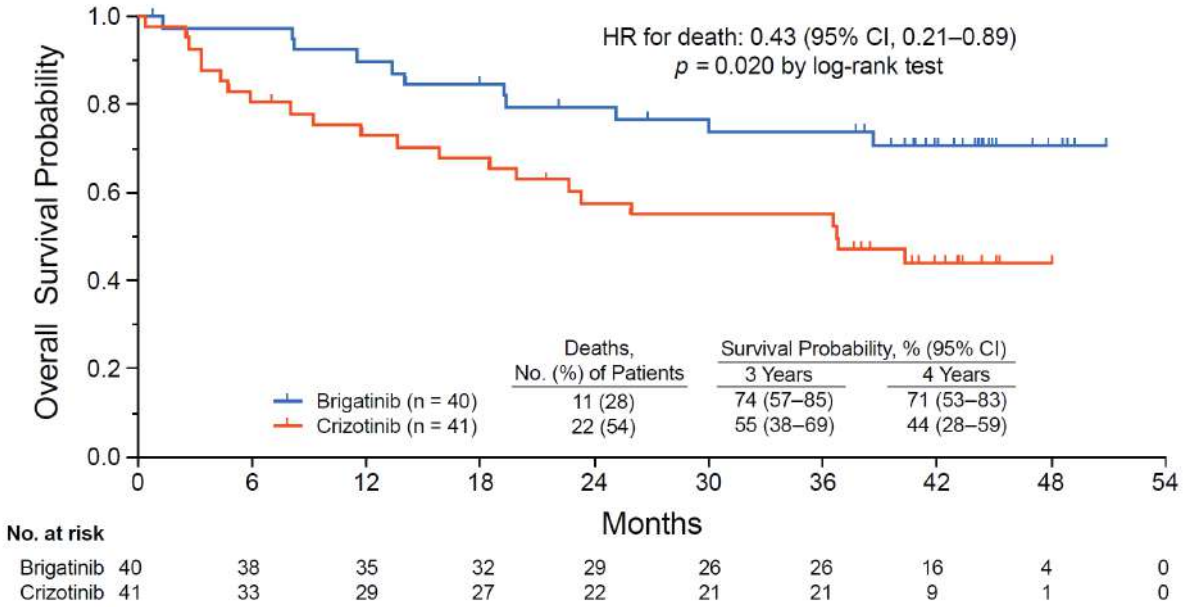
Overall survival (ALTA-1L study)



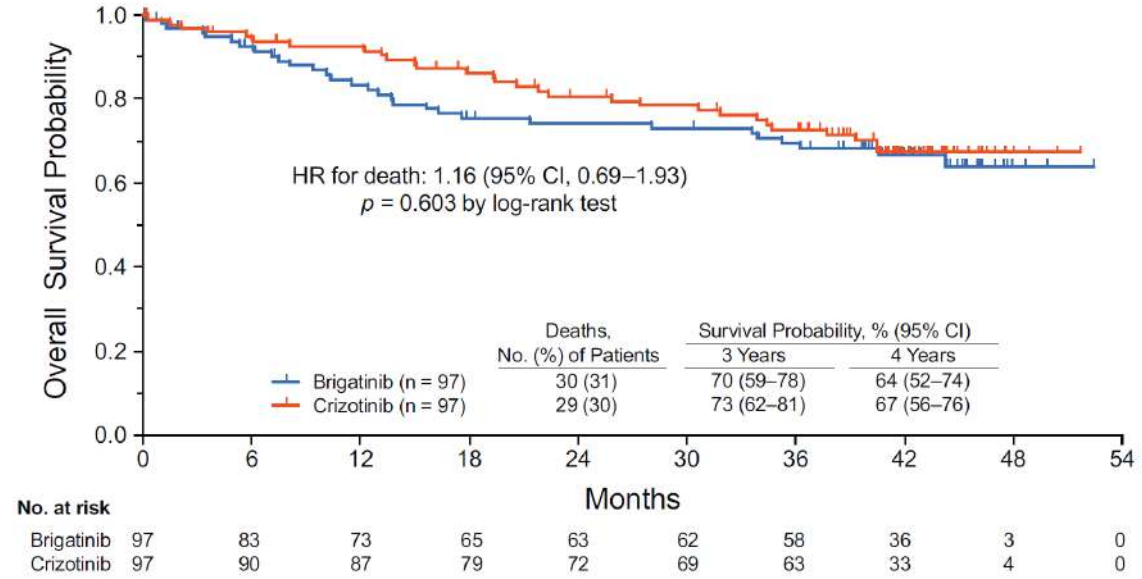
Cross over to ALK TKI : 93%

alectinib : 68%, crizotinib 5%, ceritinib 3%, brigatinib 21%

with brain metastases at baseline



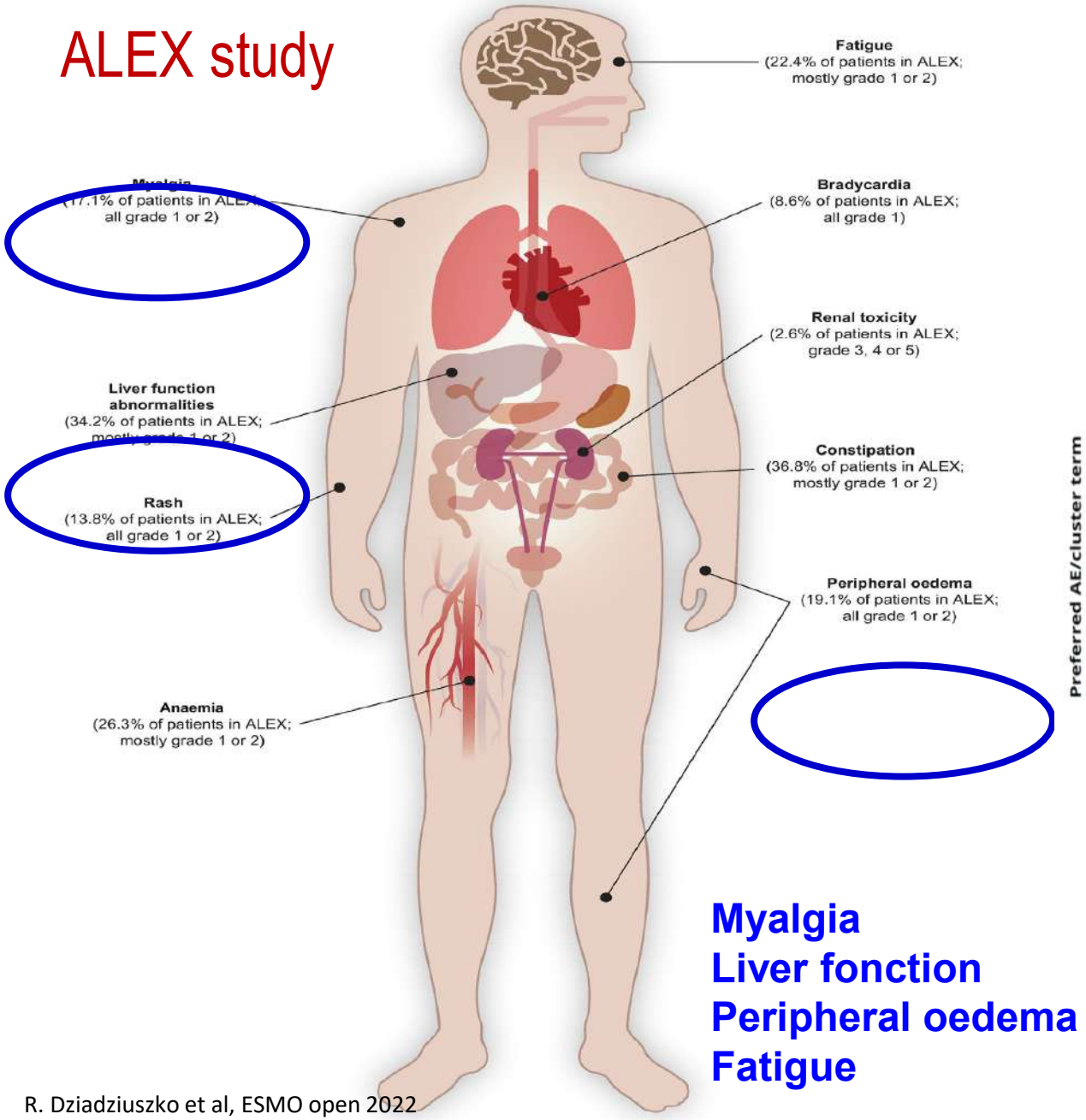
without brain metastases at baseline



Camidge R et al, JTO 2021

Safety profile of Lorlatinib

ALEX study

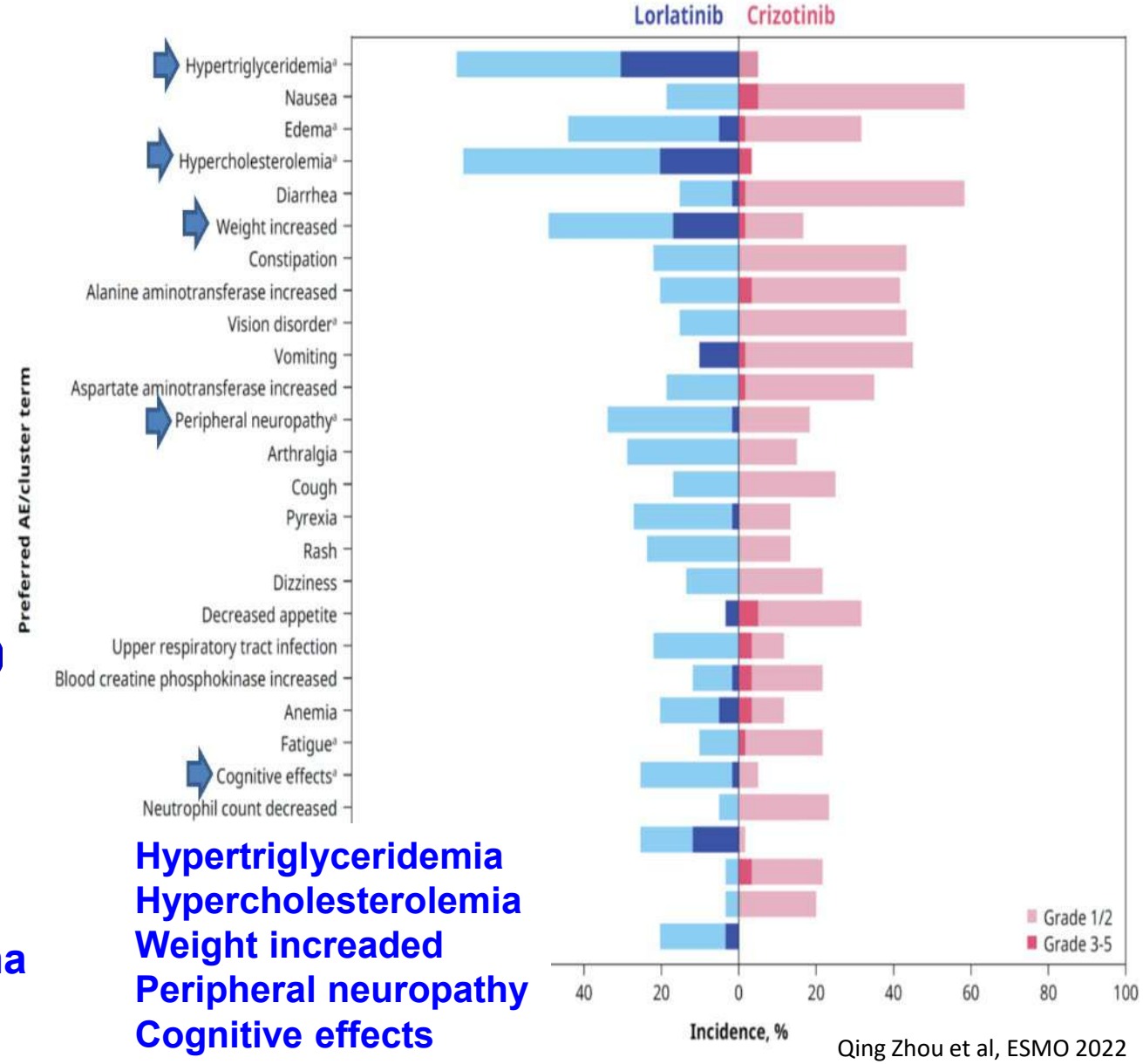


Myalgia
Liver fonction
Peripheral oedema
Fatigue

R. Dziadziuszko et al, ESMO open 2022

CROWN study

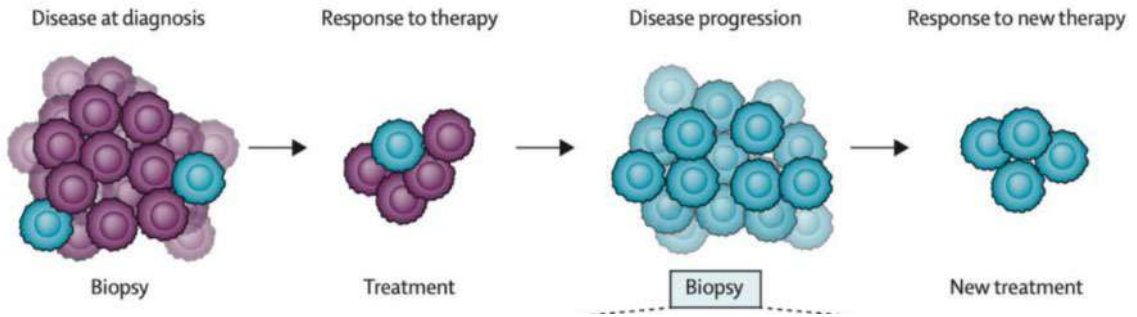
Asian patients

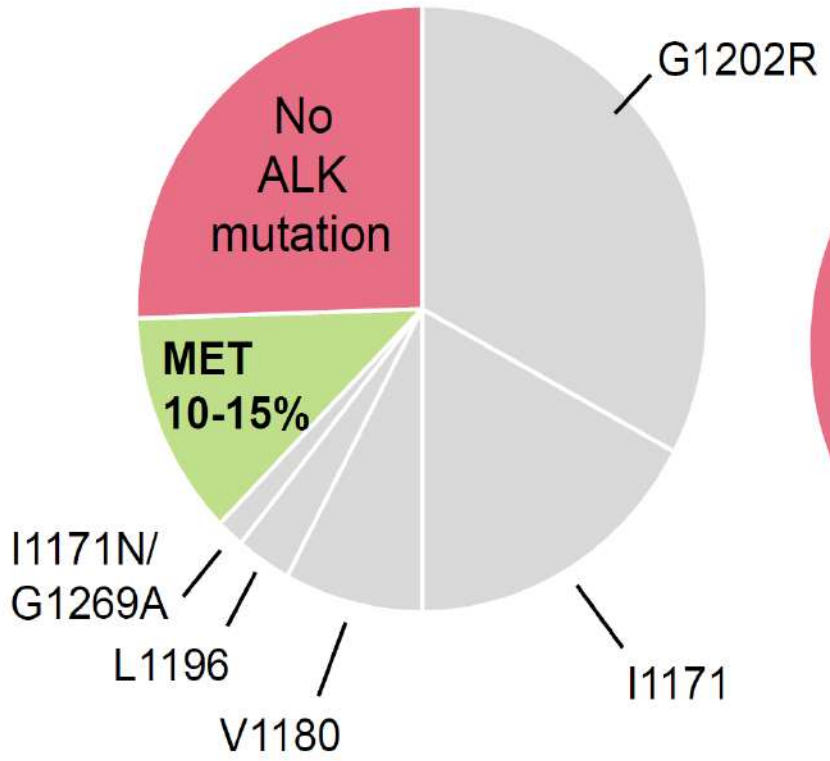


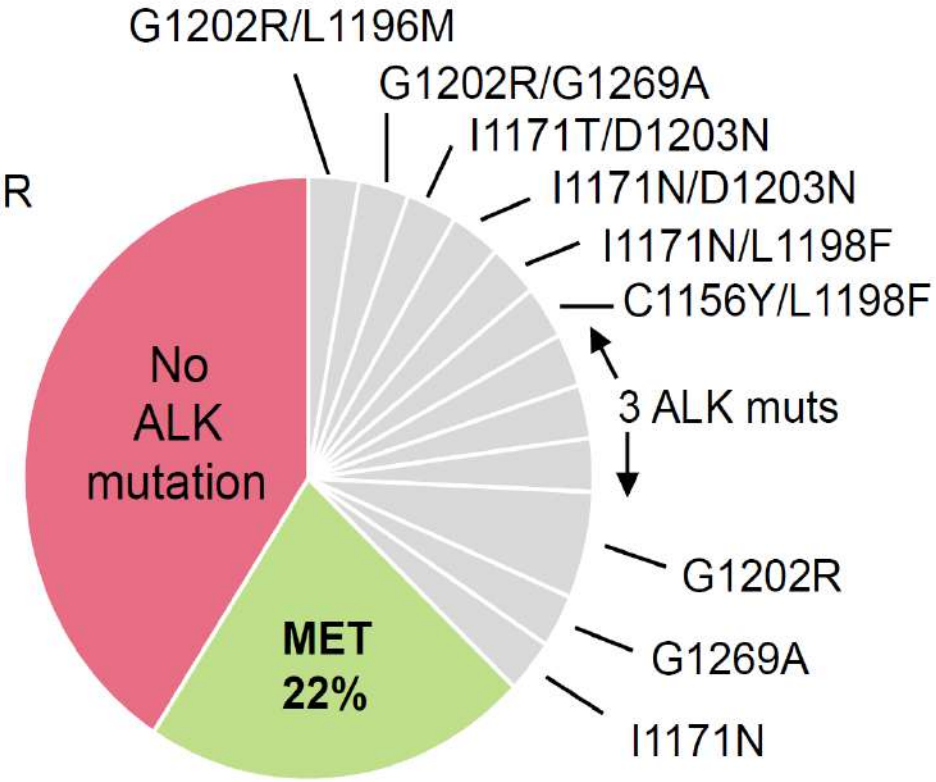
Hypertriglyceridemia
Hypercholesterolemia
Weight increaded
Peripheral neuropathy
Cognitive effects

Qing Zhou et al, ESMO 2022

How does resistance to targeted therapy develop ?





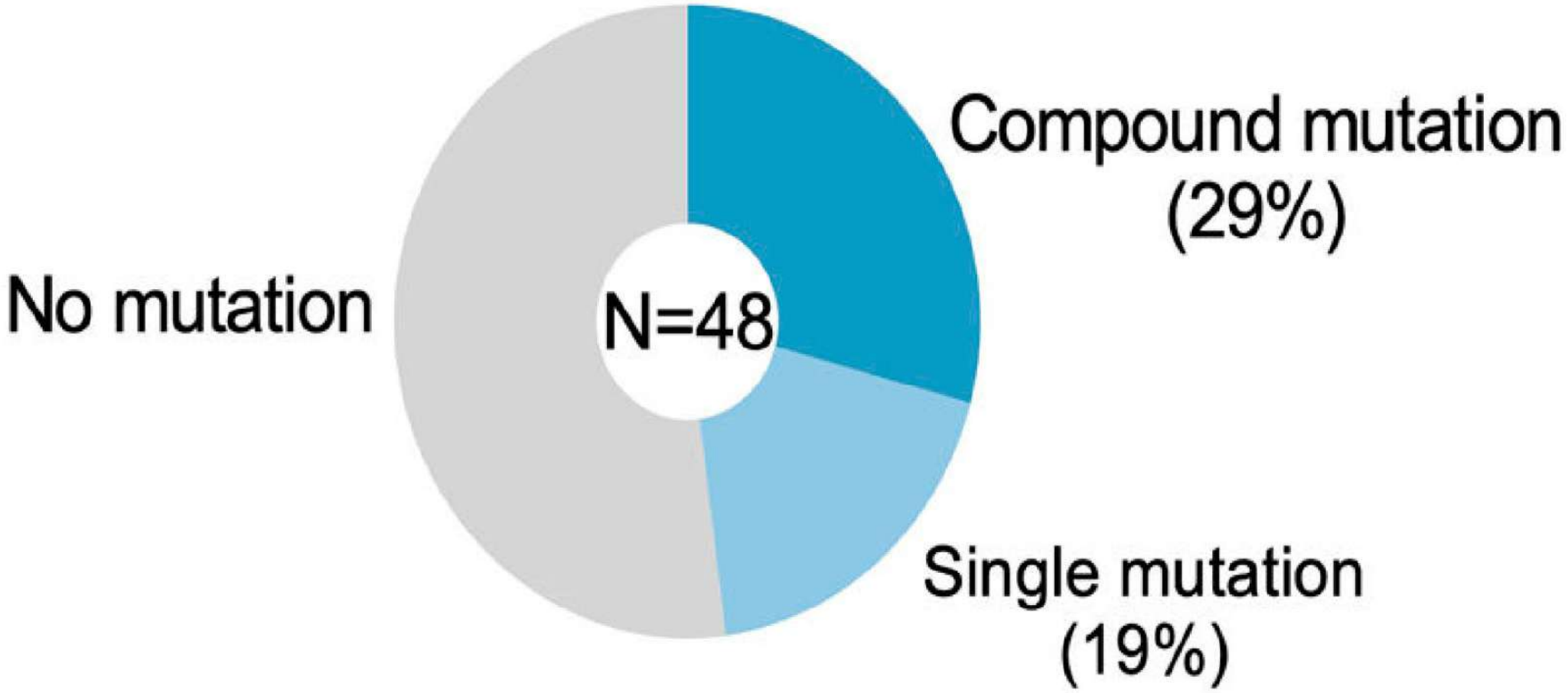


2G TKI **Lorlatinib**

Dagogo-Jack I et al, CCR 2020

Frequencies of compound, single, vs no ALK mutation detected in lorlatinib-resistant tissue biopsies

Post-Lorlatinib tissue biopsies



Aya Shiba-Ishii et al, Nat cancer 2022

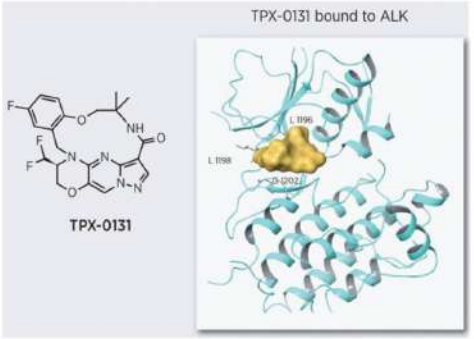
Overcoming ALK-Dependent resistance to lorlatinib: Novel 4th-Generation ALK TKIs

Overcoming ALK-Dependent Resistance to Lorlatinib: Novel 4th-Generation ALK TKIs

TPX-0131 (NCT04849273)

Ba/F3 EML4-ALK		TPX-0131	Crizotinib[a]	Alectinib[a]	Brigatinib[a]	Ceritinib[a]	Lorlatinib[a]
L1196M/L1198F	N=3	<0.2	252	2250	253	1410	1310
L1198F/C1156Y	N=3	<0.2	19.3	776	102	1310	140
G1202R/C1156Y	N=3	0.2	745	2420	810	1300	521
G1202R/L1196M	N=3	0.7	808	>10000	1100	1260	4780
G1202R/L1198F	N=3	<0.2	188	3000	2040	2010	1710
G1202R/G1269A	N=3	9.9	705	7200	164	303	636
G1202R/G1269A/L1204V	N=3	14.9	634	6740	176	345	673
G1202R/G1269A/L1198F	N=3	0.2	596	>10000	907	1670	6330

[a] Proxy reagents purchased from commercial sources



Cui JJ et al., AACR 2020; Brion WM et al., Mol Cancer Ther 2021

NVL-655 (NCT05384626)

	Cell with ALK fusion	NUV-655	Crizotinib	Ceritinib	Alectinib	Brigatinib	Lorlatinib
No kinase domain mutations	NCI-H2228 (EML4-ALK v3)	0.70	90	55	13	13	< 1.1
	NCI-H3122 (EML4-ALK v1)	2.0	180	48	22	22	3.5
	Wild-type	1.6	270	90	25	42	4.2
G1202R+ mutations	G1202R	< 0.73	950	570	1600	400	120
	G1202R/L1196M	7.0	1500	1400	2200	820	3900
	G1202R/G1269A	3.0	1100	350	1300	240	970
	G1202R/L1198F	2.0	170	1300	2200	470	720

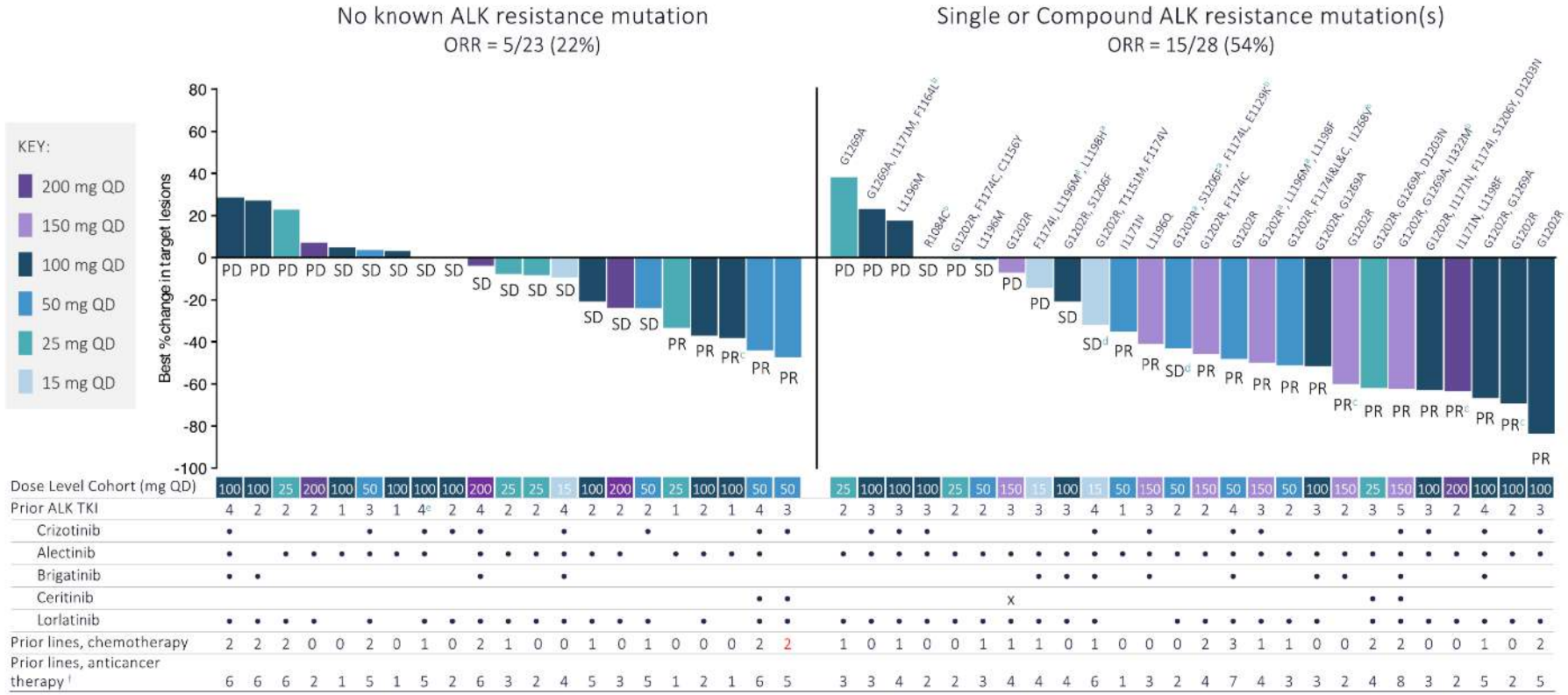
Pelish HE et al., AACR 2021

Slide courtesy of Jessica Lin, MD

4G ALK TKI NVL-655: Preliminary Efficacy and Safety

ALKOVE-1 global phase I/II study

- Coverage of **single and compound *ALK* mutations** demonstrated clinically
- Activity in heavily pre-treated patients including those with and without compound *ALK* resistance mutations [**ORR 56% (9/16) with compound mutations**], those who have received **prior lorlatinib [ORR 40% (10/25)]**, and those with history of **brain metastases [ORR 52% (15/29)]**



Lin JJ et al., AACR-NCI-EORTC 2023

TROPION-Lung05: Datopotamab deruxtecan : previously treated NSCLC with AGA

Screening

Key Inclusion Criteria

- Stage IIIB, IIIC or IV NSCLC
- Presence of ≥1 actionable genomic alteration (*EGFR*, *ALK*, *ROS1*, *NTRK*, *BRAF*, *MET* exon 14 skipping, or *RET*)
- ECOG PS = 0 or 1
- ≥1 line of targeted therapy
- 1 to 2 prior cytotoxic agent-containing therapies in the metastatic setting
- Radiographic disease progression after targeted therapy

Treatment

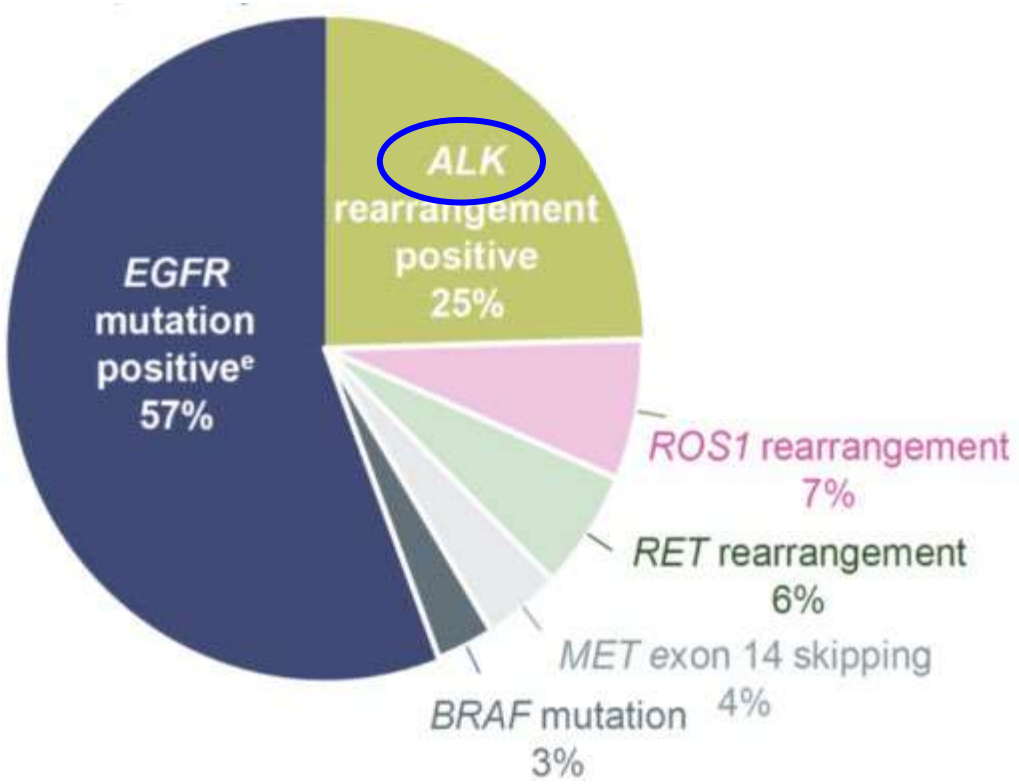
Dato-DXd
6 mg/kg
Q3W

Endpoints[a]

Primary: ORR by BICR

Secondary:

- By BICR and investigator: DOR, DCR, CBR, PFS, TTR
- By investigator: ORR
- OS, safety, PK, immunogenicity



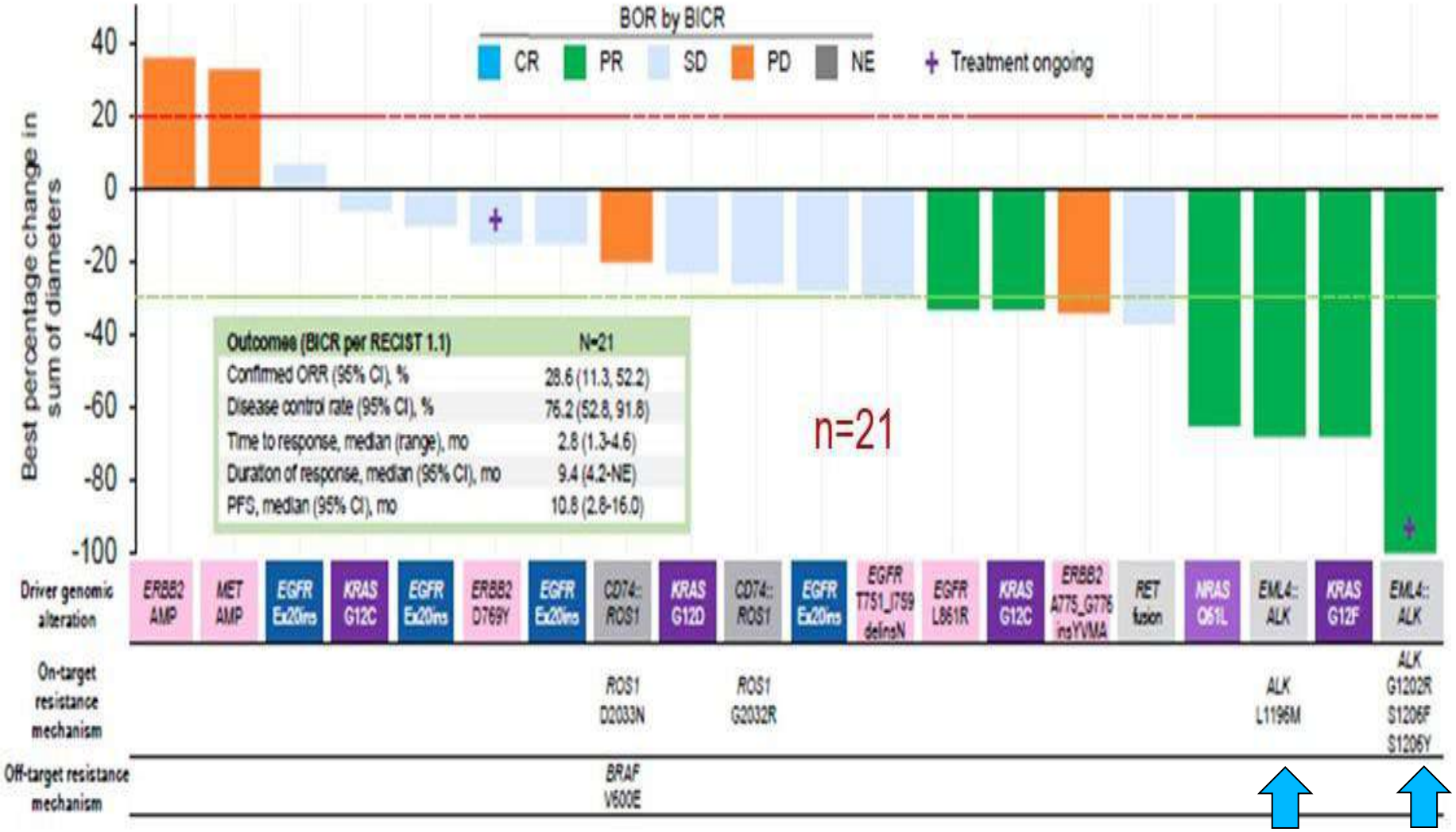
Response per BICR	All treated (N=137)	Patients with *EGFR* mutations (N=78)	Patients with *ALK* rearrangement (N=34)
ORR confirmed, n (%) [95% CI][a]	49 (35.8) [27.8,44.4]	34 (43.6) [32.4,55.3]	8 (23.5) [10.7,41.2]
Median DOR, months[b] [95% CI]	7.0 [4.2,9.8]	7.0 [4.2,10.2]	7.0 [2.8,8.4]
DCR confirmed, n (%) [95% CI][a]	108 (78.8) [71.0,85.3]	64 (82.1) [71.7,89.8]	25 (73.5) [55.6,87.1]
Median PFS, months[b] [95% CI]	5.4 [4.7,7.0]	5.8 [5.4,8.3]	4.3 [2.6,6.9]

23.5%

L.Paz-Ares et al, ESMO2023

Efficacy of HER3-DXd (Patritumab deruxtecan) in NSCLC without EGFR-activating mutations (dose expension cohort 2)

MET, RET, ROS1, EGFR Ex20ins, KRAS, ALK, NRAS



Driver Alteration Identified

ORR: 28.6%

DCR: 76.2%

Median DOR: 9.4 months

mPFS: 10.8mo

Conor E.Steuer et al, ASCO 2022

ALINA: efficacy and safety of adjuvant alectinib versus chemotherapy in pts with early-stage ALK+ NSCLC

IB-IIIA

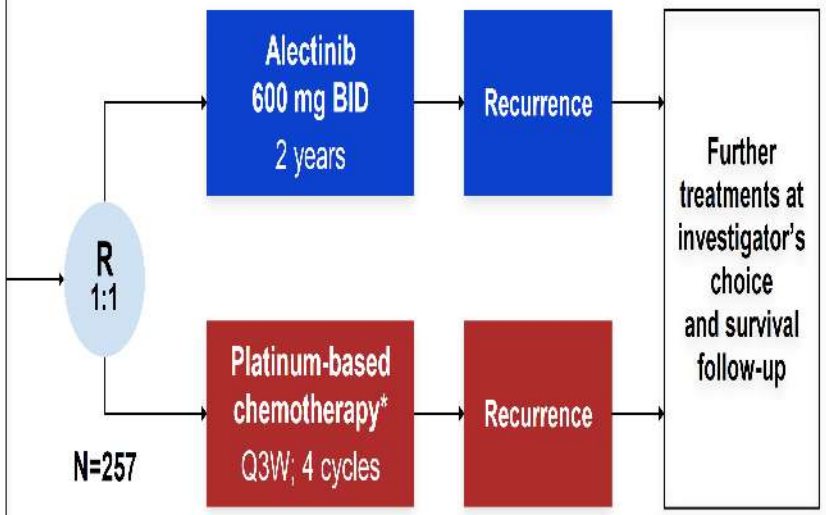
Resected Stage IB (≥4cm)–IIIA *ALK*+ NSCLC

Other key eligibility criteria:

- ECOG PS 0–1
- Eligible to receive platinum-based chemotherapy
- Adequate end-organ function
- No prior systemic cancer therapy or ALK TKIs

Stratification factors:

- Disease stage per UICC/AJCC 7th edition: IB (≥ 4cm) vs II vs IIIA
- Race: Asian vs non-Asian



- *Disease assessments (including brain MRI)‡ were conducted: at baseline, every 12 weeks for year 1–2, every 24 weeks for year 3–5, then annually*

Primary endpoint

- **DFS per investigator,§ tested hierarchically:**
  - **Stage II–IIIA → ITT (Stage IB–IIIA)**

Other endpoints

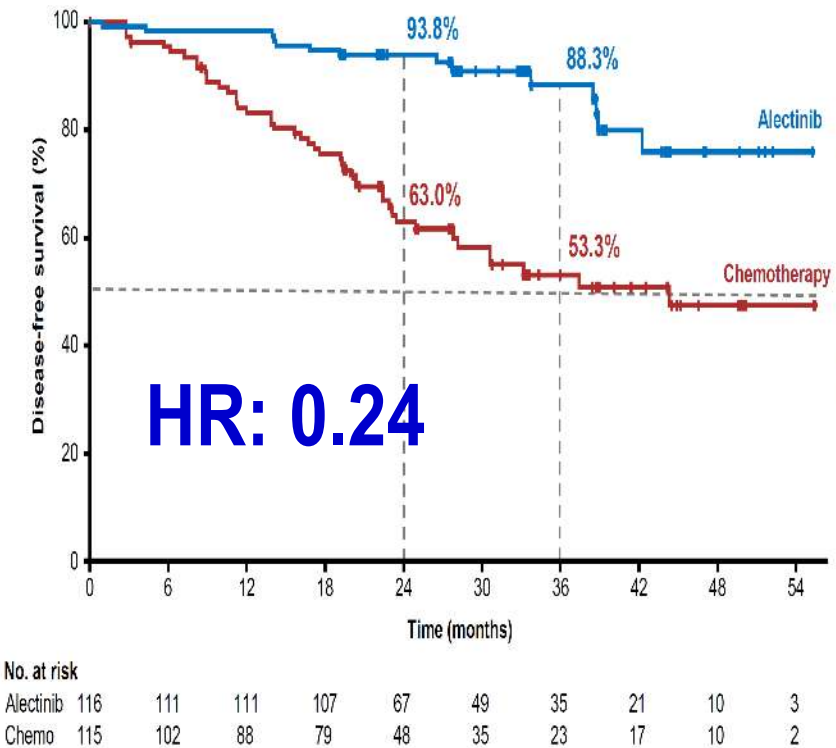
- CNS disease-free survival
- OS
- Safety

Here, we report data from the pre-specified interim analysis of DFS

Characteristic	Alectinib (n=130)	Chemotherapy (n=127)
Median age <65 / ≥65 years, %	54 years 79 / 21	57 years 73 / 27
Sex: female / male, %	58 / 42	46 / 54
Smoking status: never / former / current, %	65 / 32 / 4	55 / 43 / 2
Race: Asian / non-Asian, %	55 / 45	56 / 44
ECOG PS: 0 / 1, %	55 / 45	51 / 49
Stage at diagnosis*: IB / II / IIIA, %	11 / 36 / 53	9 / 35 / 55
Nodal status: N0 / N1 / N2, %	16 / 35 / 49	14 / 34 / 52
Histology: squamous / non-squamous, %	5 / 95	2 / 98
Surgical procedure: Lobectomy / Other‡, %	97 / 3	92 / 8

B.J. Solomon et al, ESMO 2023

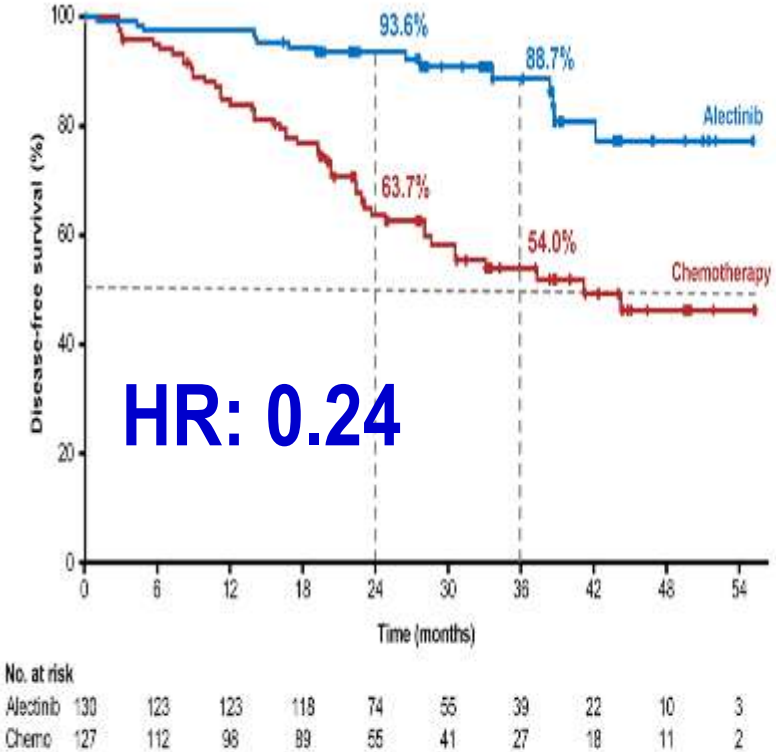
Disease-free survival: stage II–IIIA*



	Alectinib (N=116)	Chemotherapy (N=115)
Patients with event Death Recurrence	14 (12%) 0 14	45 (39%) 1 44
Median DFS, months (95% CI)	Not reached	44.4 (27.8, NE)
DFS HR (95% CI)	**0.24** (0.13, 0.45) p†<0.0001	

Median survival follow up: alectinib, 27.9 months; chemotherapy, 27.8 months

Disease-free survival: ITT (stage IB–IIIA)*



	Alectinib (N=130)	Chemotherapy (N=127)
Patients with event Death Recurrence	15 (12%) 0 15	50 (39%) 1 49
Median DFS, months (95% CI)	Not reached	41.3 (28.5, NE)
DFS HR (95% CI)	**0.24** (0.13, 0.43) p*<0.0001	

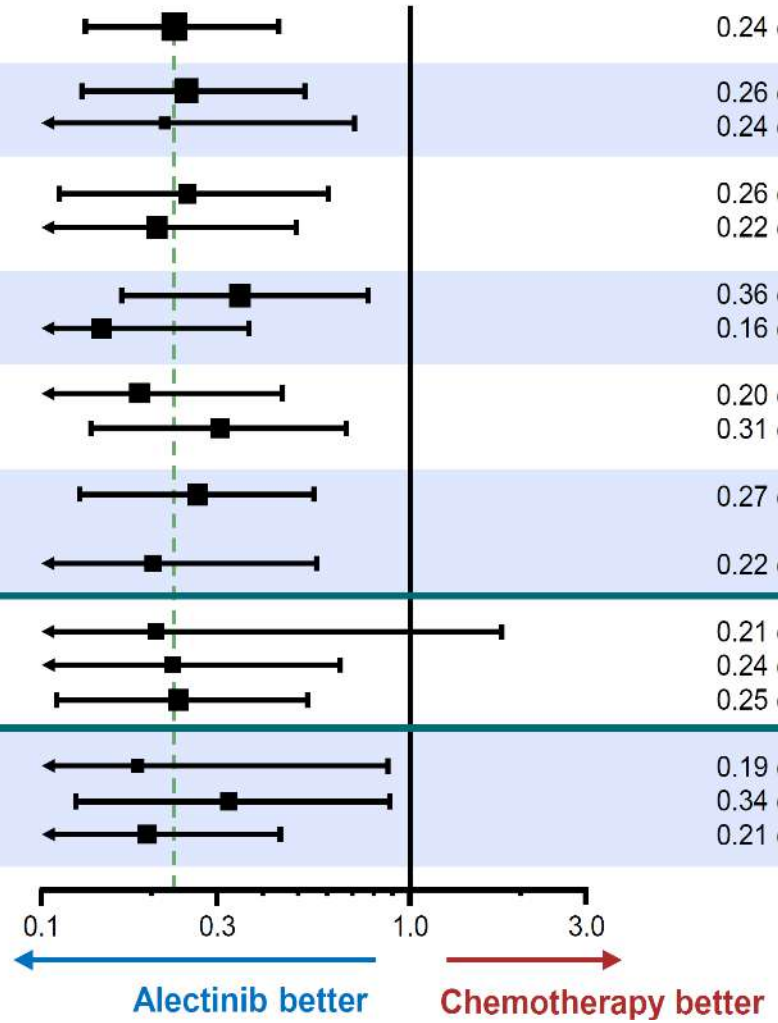
At the data cutoff date, **OS data were immature** with only 6 (2.3%) OS events reported‡

Median survival follow up: alectinib, 27.8 months; chemotherapy, 28.4 months

B.J. Solomon et al, ESMO 2023

Disease-free survival subgroup analysis (ITT)

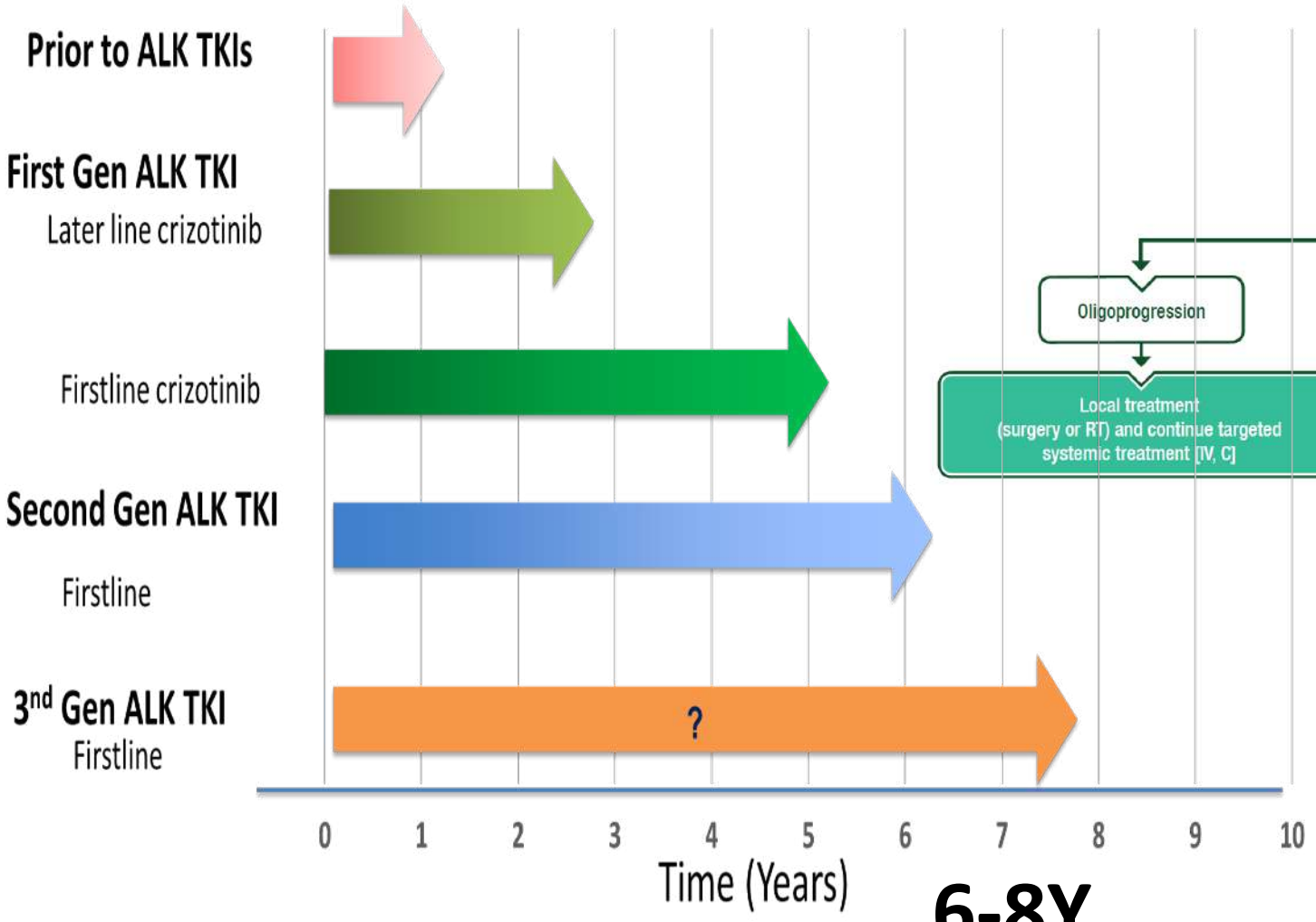
Subgroup		No. of events / patients	DFS HR (95% CI)
All patients		65 / 257	0.24 (0.14–0.43)
Age	<65	43 / 196	0.26 (0.13–0.52)
	≥65	22 / 61	0.24 (0.08–0.71)
Sex	Male	35 / 123	0.26 (0.11–0.60)
	Female	30 / 134	0.22 (0.10–0.50)
Race	Asian	31 / 143	0.36 (0.17–0.79)
	Non-Asian	34 / 114	0.16 (0.06–0.38)
ECOG PS at baseline	0	32 / 137	0.20 (0.09–0.46)
	1	33 / 120	0.31 (0.14–0.69)
Tobacco use history	Never	37 / 154	0.27 (0.13–0.55)
	Current	0 / 8	NE
	Previous	28 / 95	0.22 (0.08–0.57)
Stage*	Stage IB	6 / 26	0.21 (0.02–1.84)
	Stage II	22 / 92	0.24 (0.09–0.65)
	Stage IIIA	37 / 139	0.25 (0.12–0.53)
Regional lymph node status	N0	11 / 39	0.19 (0.04–0.88)
	N1	20 / 88	0.34 (0.13–0.89)
	N2	34 / 130	0.21 (0.09–0.47)



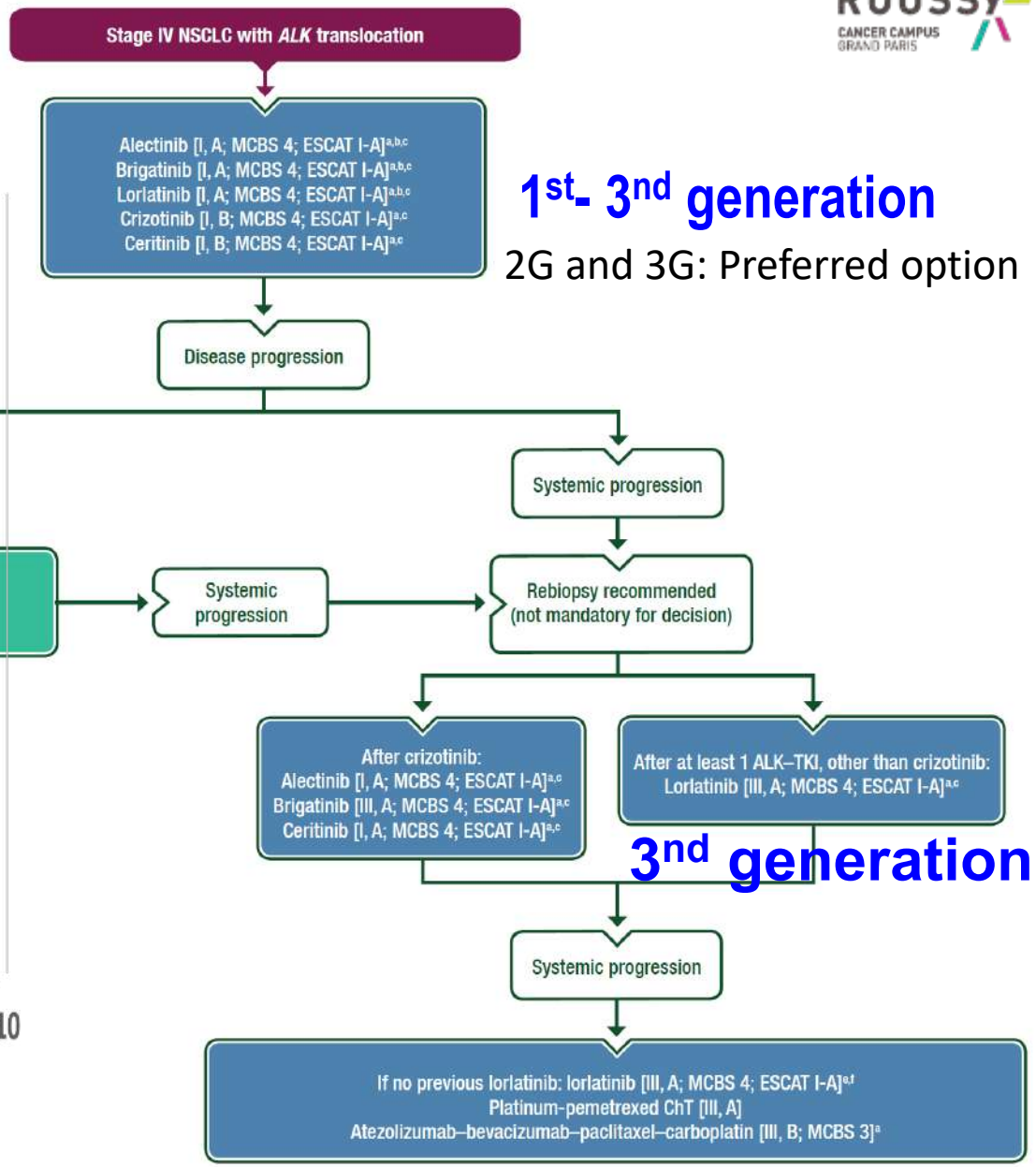
Adjuvant alectinib represents an important new treatment strategy for patients with resected, stage IB–IIIA, *ALK*+ NSCLC

B.J. Solomon et al, ESMO 2023

ESMO Guidelines



6-8Y....

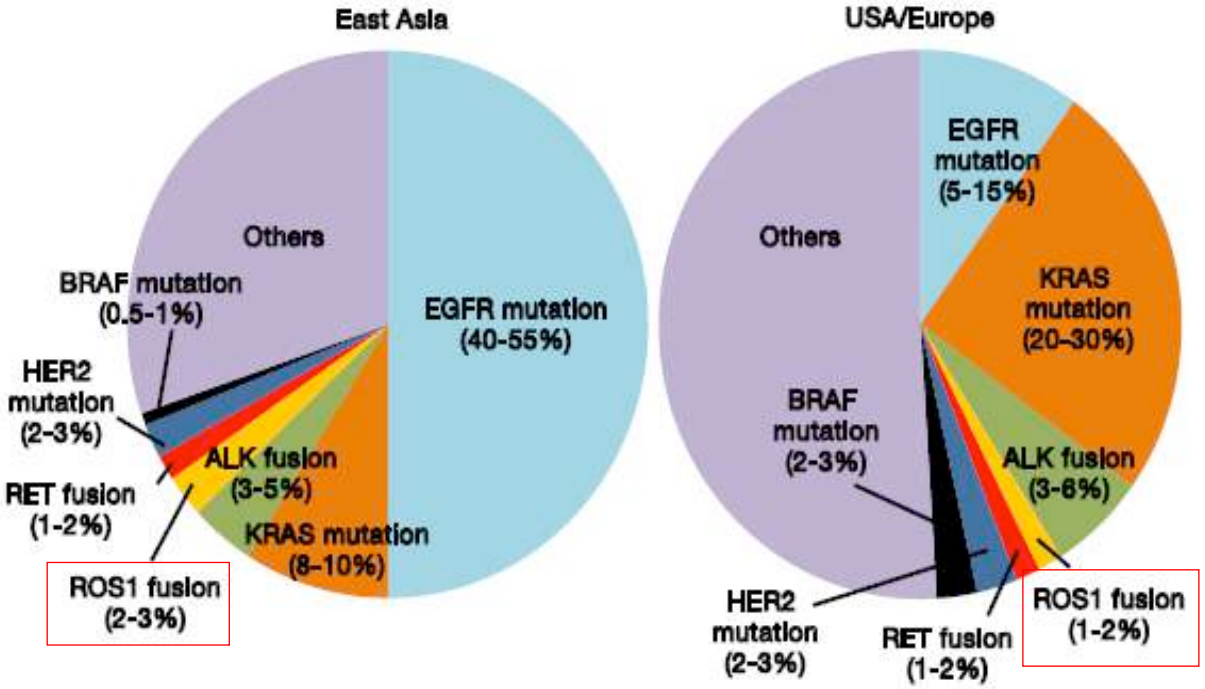


1st- 3nd generation

2G and 3G: Preferred option

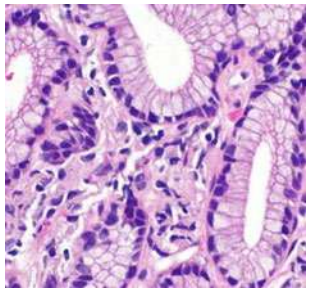
3nd generation

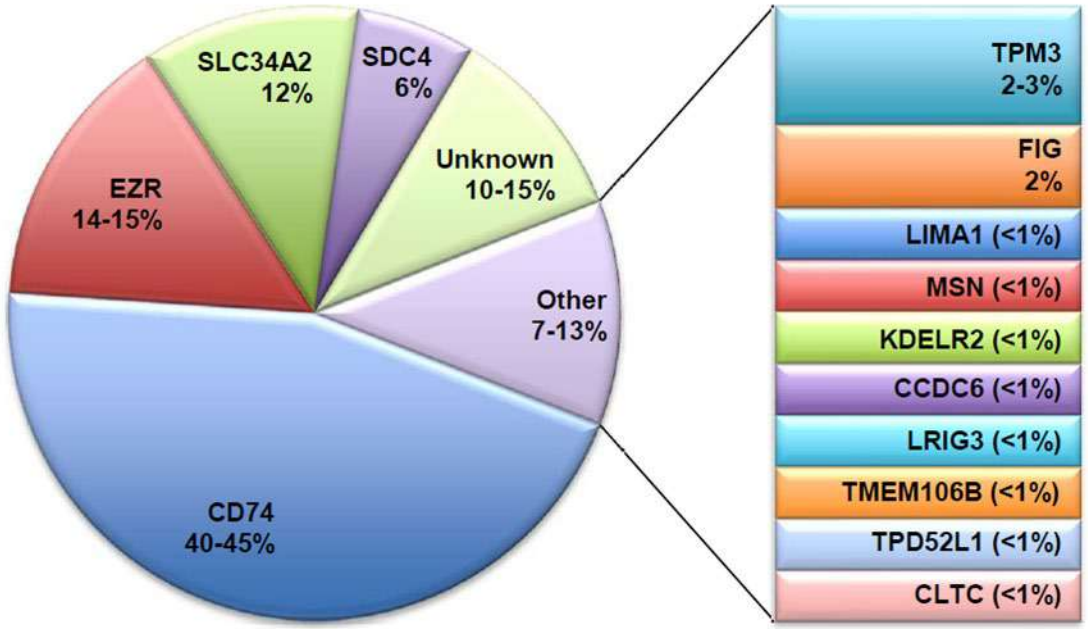
Patients with ROS1+ NSCLC



Incidence : 0.9 – 2%

ROS1 rearrangements are associated with:





Jessica J. Lin et al, JTO2017

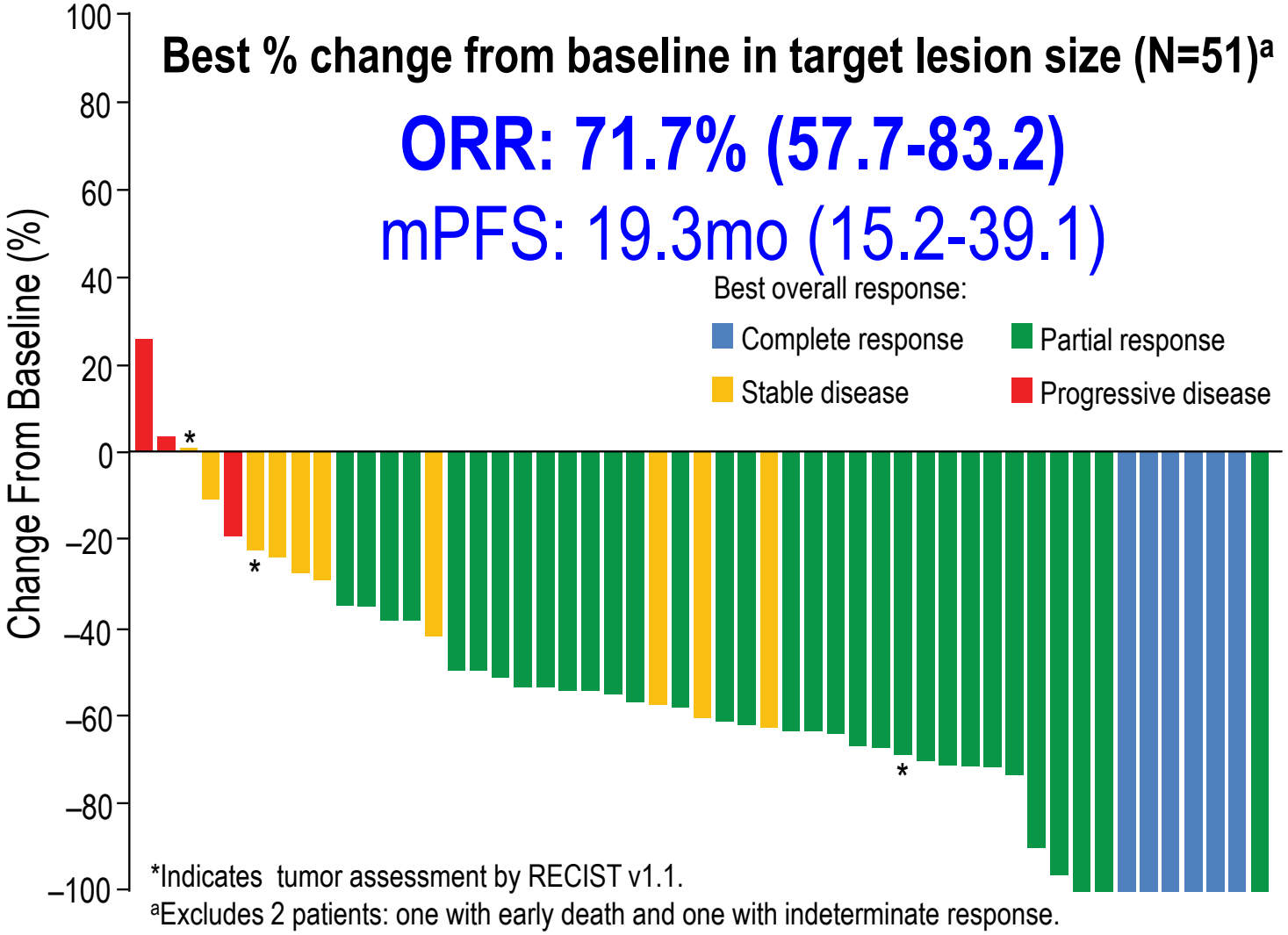
Davies CCR 2012, Park JTO 2018, Lin JTO2017, Kron Ann Oncol 2018, Aisner CCR 2018, Aggarwal JCO Precis Oncol 2018

1st, 2nd and 3rd Generation ALK and ROS1 inhibitors

Inhibitor	Generation	Other Targets	Approval
Crizotinib	1st	ALK, MET, ROS1	1L ALK or 1L+ ROS1
Ceritinib	2nd	ALK, ROS1, IGFR-1	1L-2L ALK
Alectinib	2nd	ALK, RET, LTK	1L-2L ALK
Brigatinib	2nd	ALK,ROS1, Mutant EGFR	1L-2L ALK
Entrectinib	2nd	ALK, ROS1, TRK	1L+ ROS1
Lorlatinib	3rd	ALK, ROS1	2L/3L ALK, ROS1
Repotrectinib	3rd	TRK, ROS1	1L-2L ROS1
Taletrectinib	3rd	ROS1	1L-2L ROS1
NVL-520	3rd	ROS1	2L ROS1

PROFILE 1001: CRIZOTINIB - ROS1 EXPANSION COHORT (N=53)

TKI naive patients



	ROS1-rearranged NSCLC (N=53)	Shaw et al. 2014 (N=50)
BOR, n (%)		
CR	6 (11.3)	3 (6)
PR	32 (60.4)	33 (66)
SD	10 (18.9)	9 (18)
PD	3 (5.7)	3 (6)
NE[a]	2 (3.8)	2 (4)
ORR, %	71.7	72
95% CI	57.7–83.2	58–84
Median TTR, wks	7.9	7.9
Range	4.3–103.6	4.3–32.0
Median DOR[b], mos	24.7	17.6
95% CI	15.2–45.3	14.5–NR

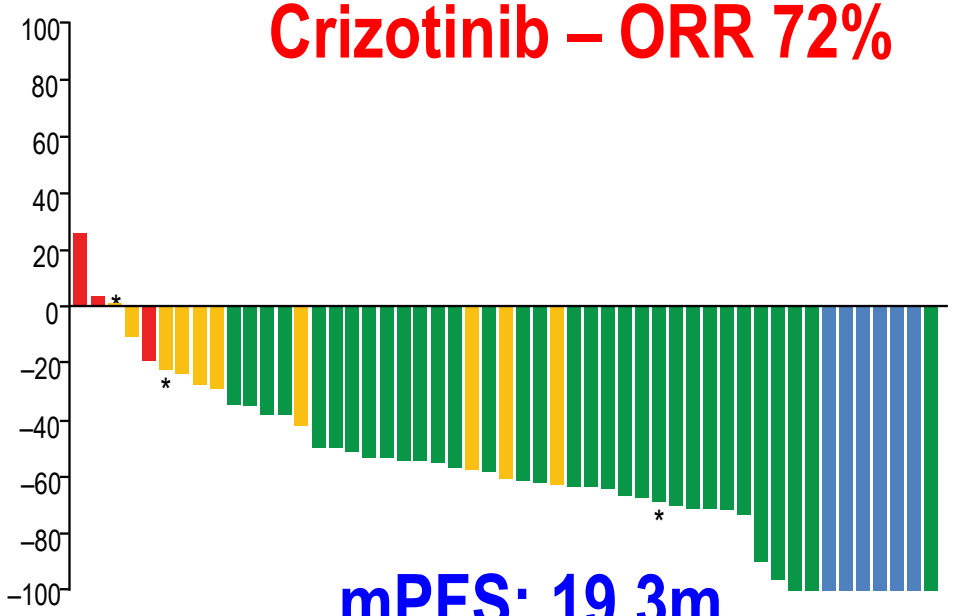
[a]Responses could not be evaluated in 2 patients because of early death or indeterminate response.
[b]Estimated using the Kaplan-Meier method.

BOR, best overall response; CI, confidence interval; CR, complete response; DOR, duration of response; mos, months; NE, not evaluable; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; TTR, time to response; wks, weeks.

Shaw.A et al, ELCC 2019 and annals onco 2019

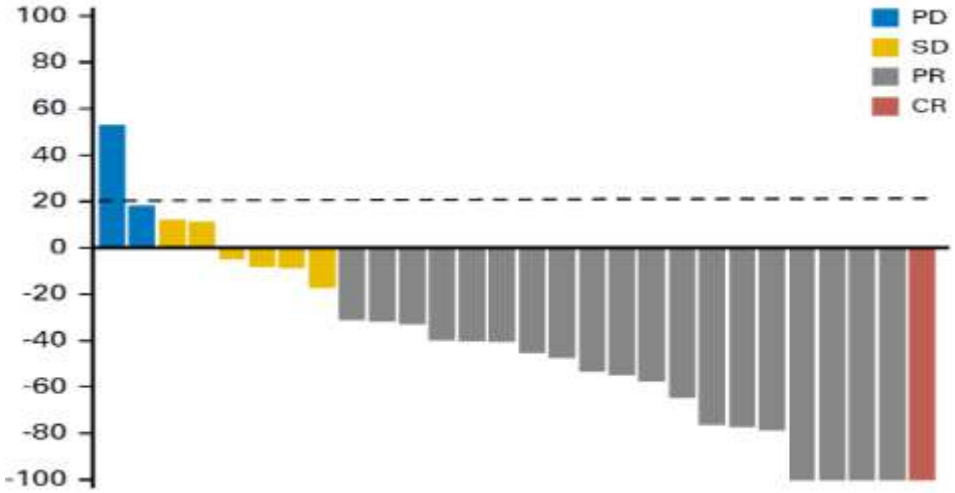
ROS1 inhibitors in TKI naive patients

Crizotinib – ORR 72%



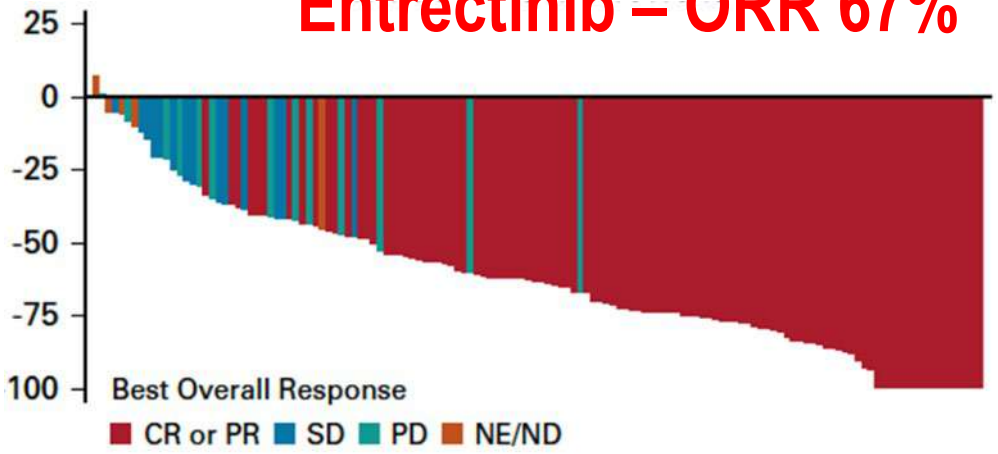
mPFS: 19.3m

Ceritinib – ORR 62%



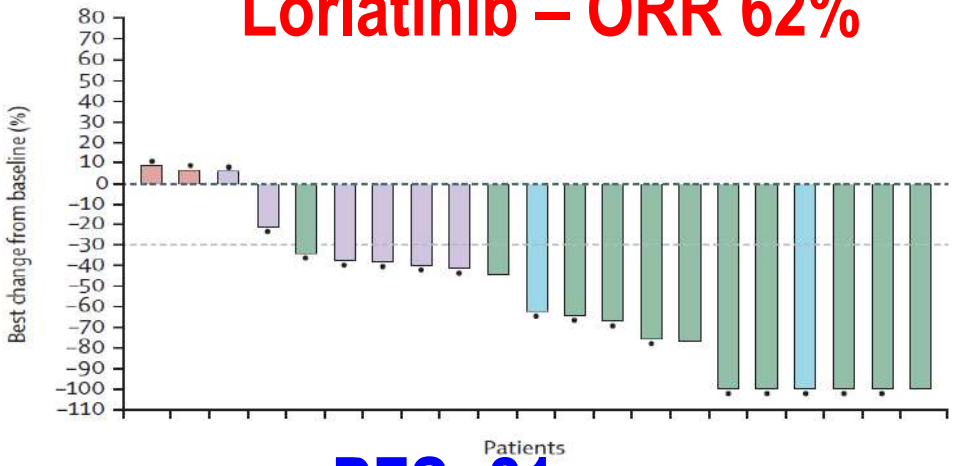
mPFS: 19.3m

Entrectinib – ORR 67%



mPFS = 15.7 mo

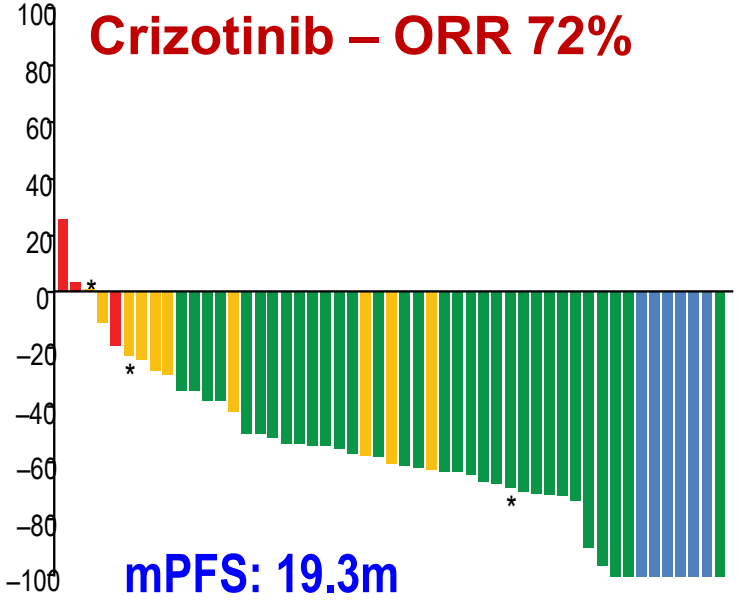
Lorlatinib – ORR 62%



mPFS: 21mo

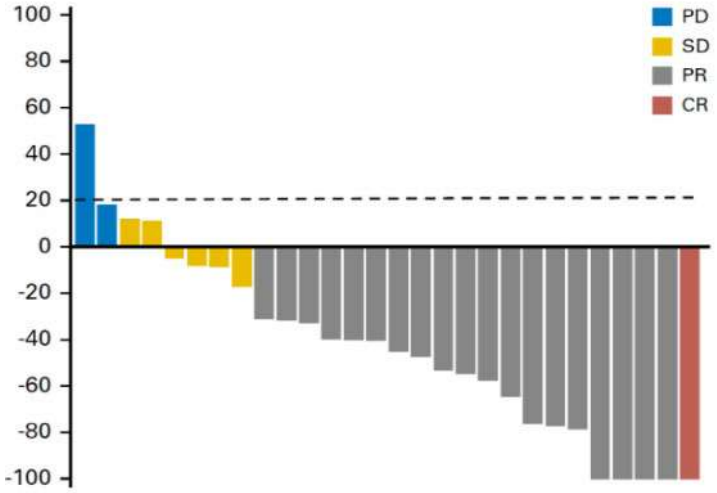
ROS1 inhibitors in TKI naive patients

Crizotinib – ORR 72%



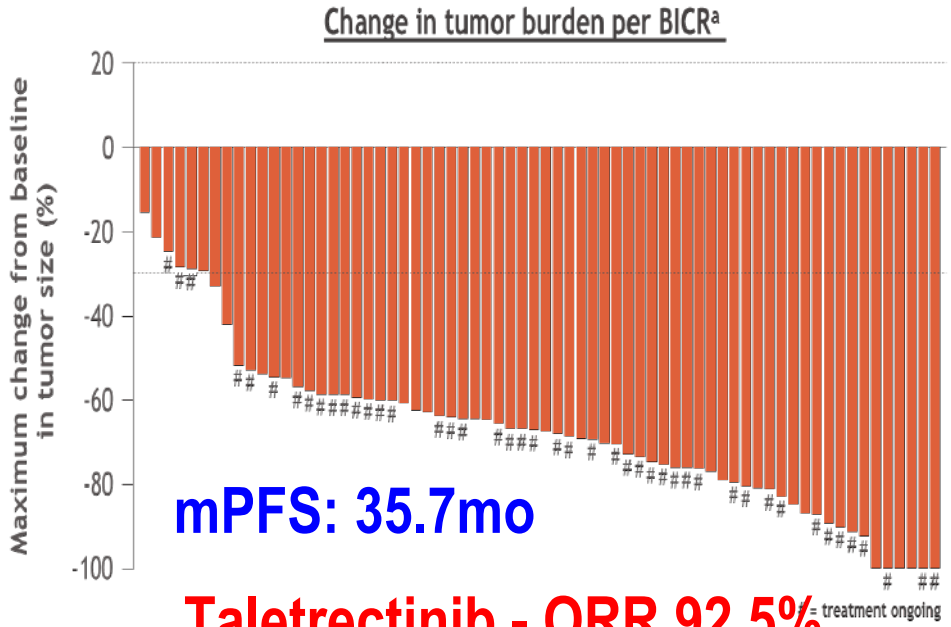
mPFS: 19.3m

Ceritinib – ORR 62%



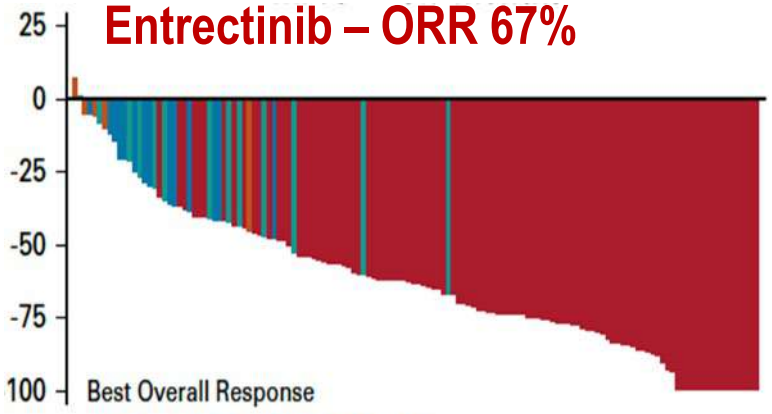
mPFS: 19.3m

Repotrectinib – ORR 79%



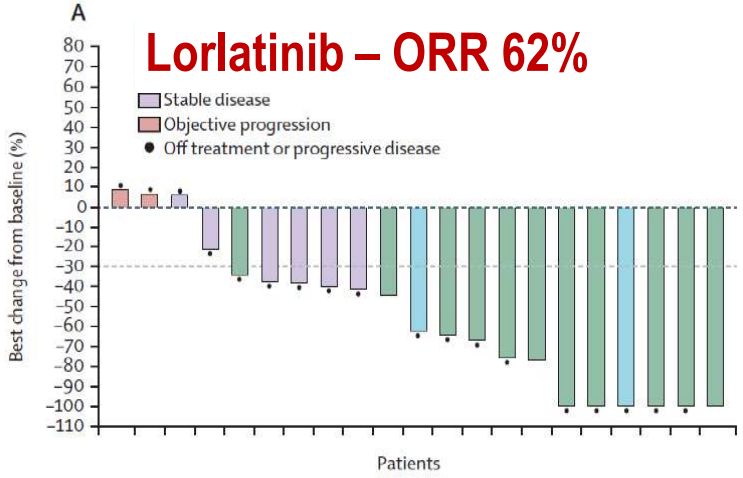
mPFS: 35.7mo

Entrectinib – ORR 67%



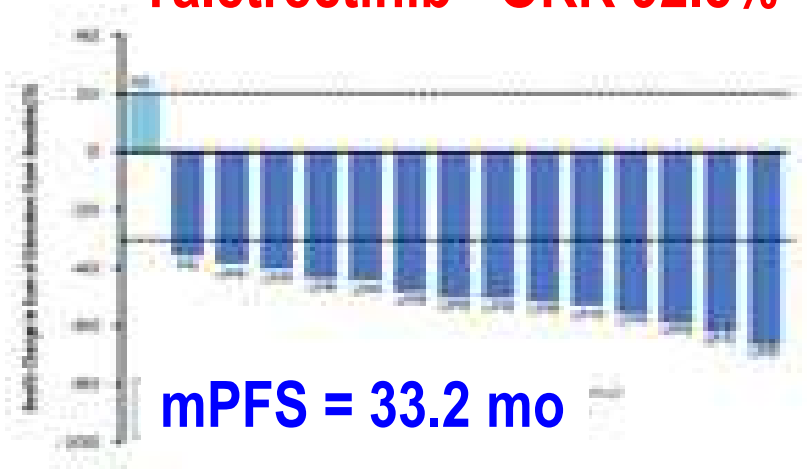
mPFS = 15.7 mo

Lorlatinib – ORR 62%



mPFS: 21mo

Taletrectinib - ORR 92.5%



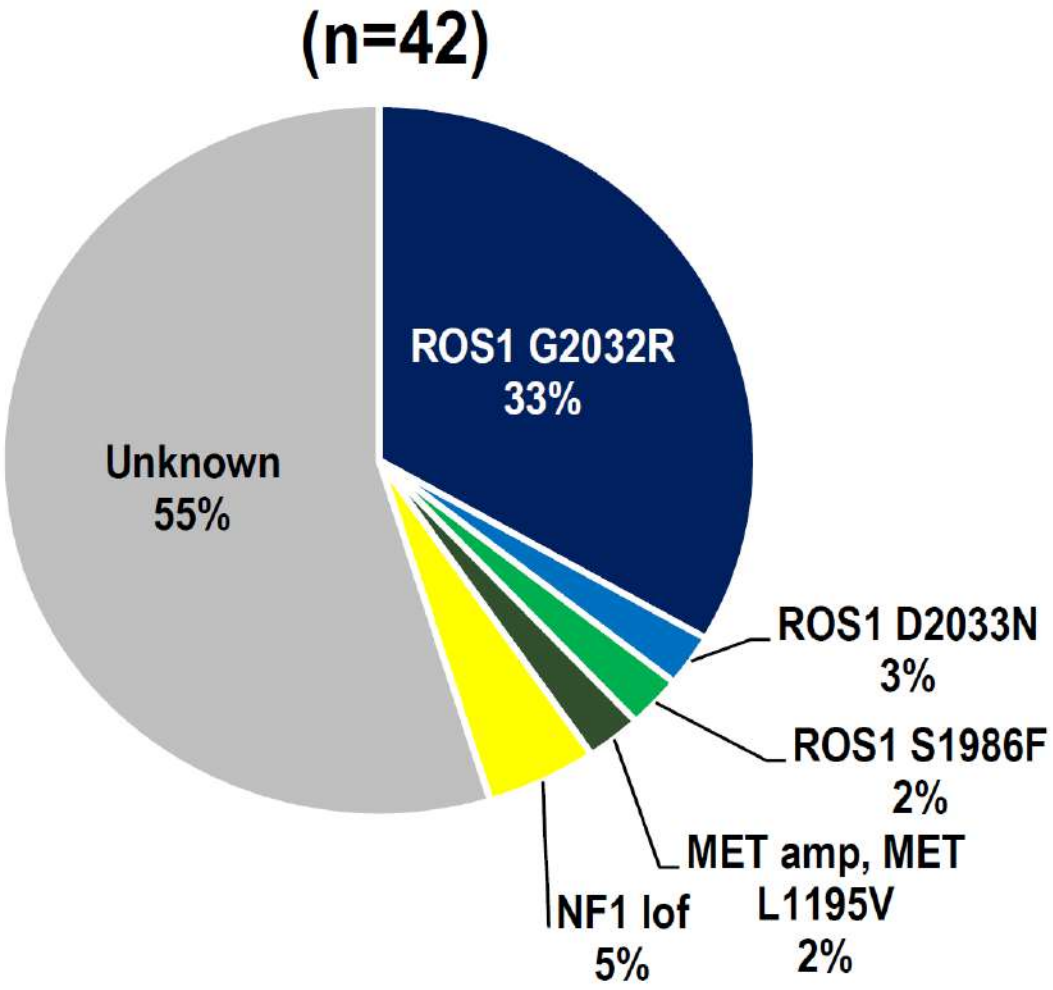
mPFS = 33.2 mo

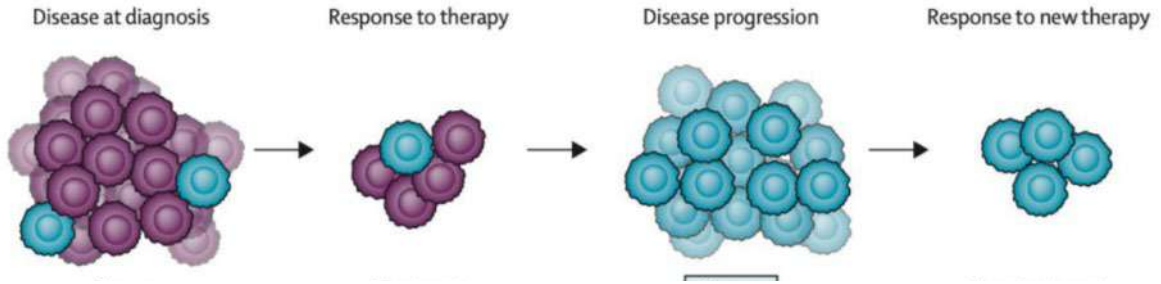
Summary of ROS1 TKIs in TKI-naive ROS1+ NSCLC

	Crizotinib (Profile 1001)	Entrectinib (ALKA, STARTRK-1, STARTRK-2)	Ceritinib (Korean phase 2)	Lorlatinib (Phase ½)	Taletrectinib (TRUST chinese phase 2)	Repotretinib (TRIDENT-1, Phase ½)	NVL-520 (ARROS-1)
N	53	168	20	21	67	71	
ORR	**72%**	**68%**	**67%**	**62%**	**92.5%**	**79%**	
mPFS	**19.3mo**	**15.7mo**	**19.3mo**	**21mo**	**33.2mo**	**35.7mo**	
CNS activity	N/A	(25/48) **52%** pts with mesurable or nonmeasurable IC disease	(2/5) **40%** pts with mesurable or nonmeasurable IC disease	(7/11) **64%** pts with mesurable or nonmeasurable IC disease	(11/12) **92%** pts with mesurable IC disease	(8/9) **89%** pts with mesurable IC disease	~100-fold increased potency for ROS1 and ROS1 G2032R over TRK
Reference	Shaw et al, annal oncol 2019	Dirlon et la, JTO CRR 2022	Lim et al, JCO 2017	Shaw et al, lancet oncol 2019	Li W et al, ASCO 2022	Cho et al, ENA 2022 Cho et al, WCLC23	A Drilon et al, cancer discovey 2023

On-Target resistance to ROS1 TKIs

Crizotinib-resistant biopsies

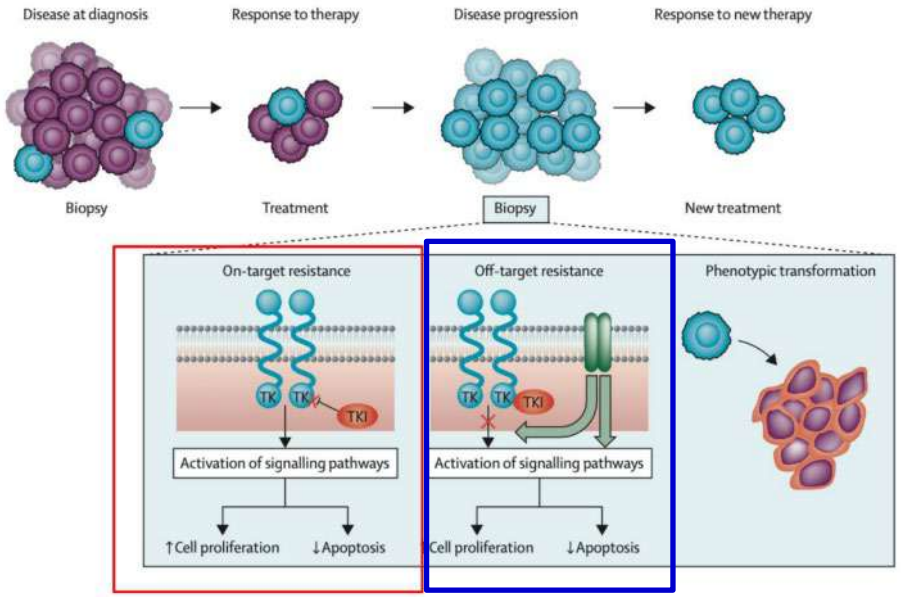




- **Up to 40% of crizotinib-resistant patient biopsies** harbor on-target, *ROS1* resistance mutations
- The most common *ROS1* resistance mutation after crizotinib is ***ROS1* G2032R**
  - Solvent front mutation (analogous to *ALK* G1202R) refractory to several TKIs
  - **Detected in ~1/3** of resistant biopsies

Lin JJ et al., Clin Cancer Res 2021;27:2899-909

Post-lorlatinib resistance…



32 post-lorlatinib biopsies

ROS1 mutations identified in 46%
ROS1 G2032R: most commonly occurring mutation in approximately one third of cases

Additional ROS1 mutation
L2086F(3.6%)
G2032R/L2086F (3.6%)
G2032R/S1986F/L2086F (3.6%)
and S1986F/L2000V (3.6%)

Also identified
MET amplification (4%)
KRAS G12C (4%)
KRAS amplification (4%)
NRAS mutation (4%)
and MAP2K1 mutation (4%)

J.J.Lin et al, CCR 2021

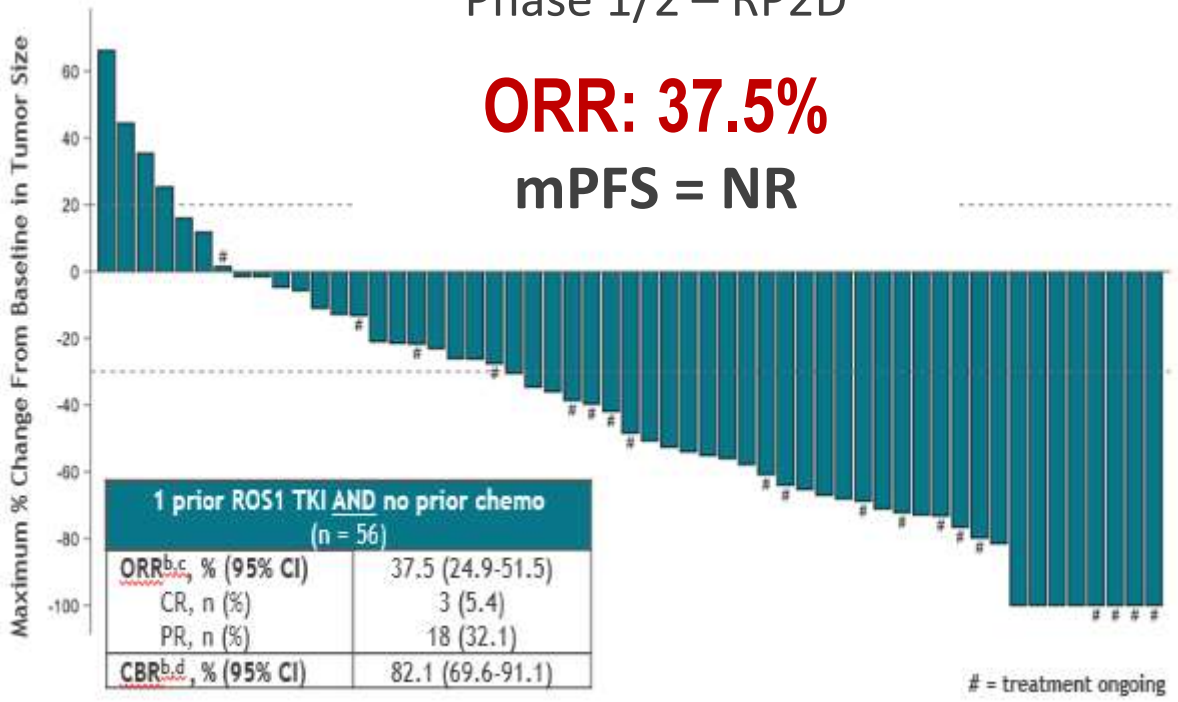
ROS1 inhibitors in TKI pre-treated patients

Repotrectinib - n=56

Phase 1/2 – RP2D

ORR: 37.5%

mPFS = NR



1 prior ROS1 TKI AND no prior chemo (n = 56)	
ORR[b,c], % (95% CI)	37.5 (24.9-51.5)
CR, n (%)	3 (5.4)
PR, n (%)	18 (32.1)
CBR[b,d], % (95% CI)	82.1 (69.6-91.1)

Byoung Chul Cho et al, ENA 2022

RP2D : recommended phase 2 dose

ROS1 G2032R resistance mutation

Repotrectinib

N=17, ORR: 58.8%

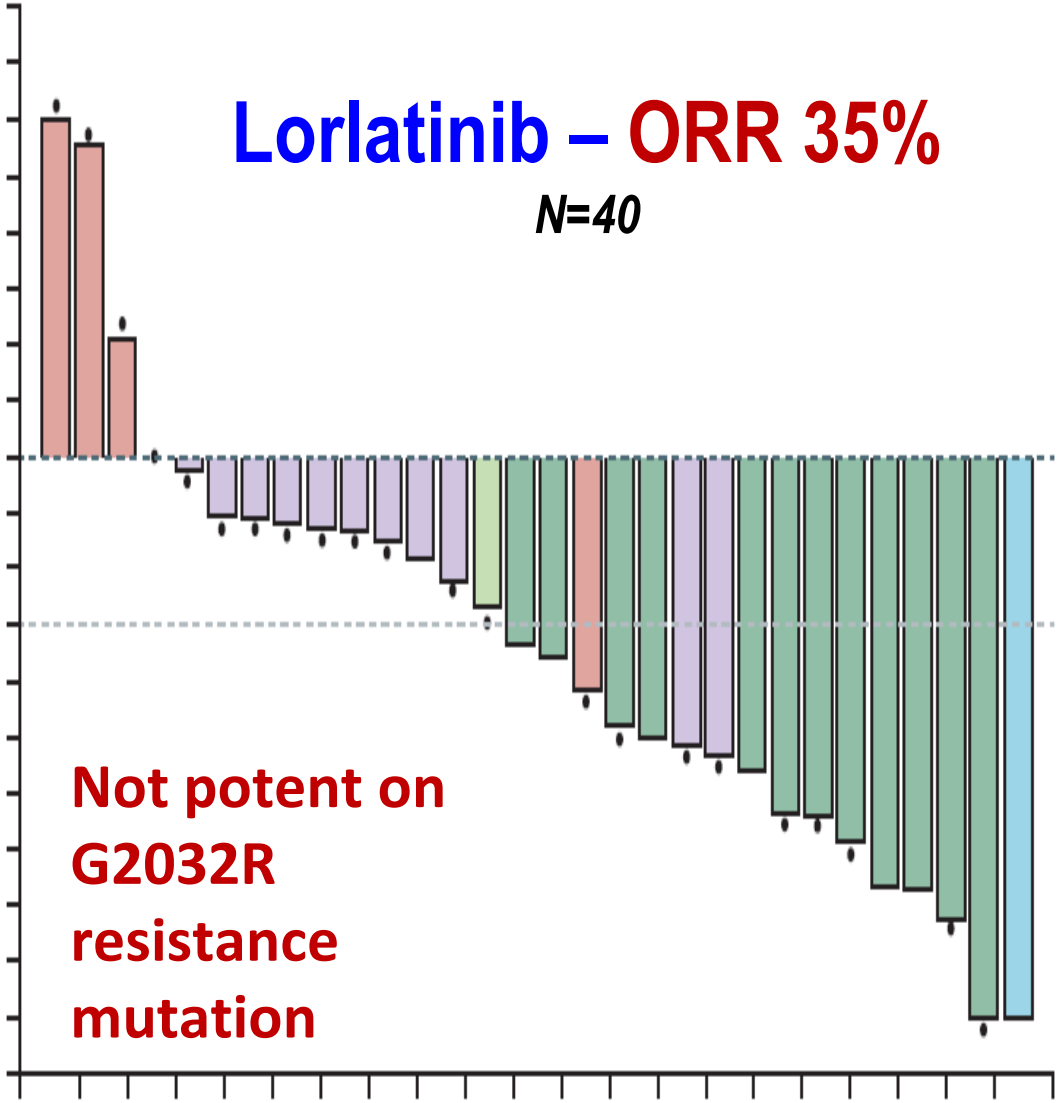
Patients with *ROS1 G2032R* resistance mutation (n = 17)	
ORR[c,d], % (95% CI)	58.8 (32.9-81.6)
CR, n (%)	1 (5.9)
PR, n (%)	9 (52.9)
CBR[c,e], % (95% CI)	70.6 (44.0-89.7)
DOR ≥ 6 months, % (95% CI)	70.0 (41.6-98.4)

Byoung Chul Cho et al, ENA 2022

ROS1 inhibitors in TKI pre-treated patients

Lorlatinib – ORR 35%

N=40



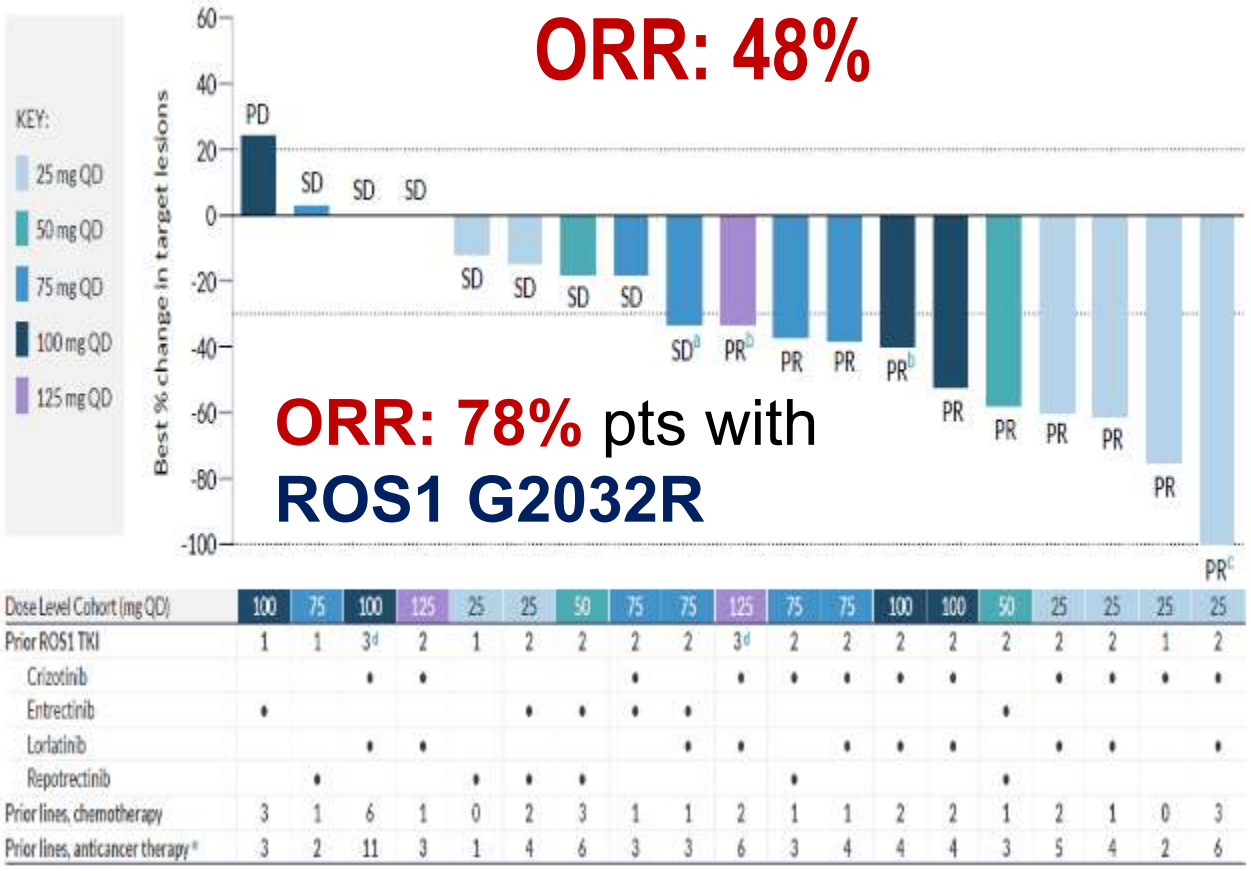
Not potent on G2032R resistance mutation

Shaw Lancet Oncol 2019

NVL-520 - n=21

Phase 1 – dose escalation

ORR: 48%



ORR: 78% pts with **ROS1 G2032R**

Dose Level Cohort (mg QD)	100	75	100	125	25	25	50	75	75	125	75	75	100	100	50	25	25	25	25
Prior ROS1 TKI	1	1	3[d]	2	1	2	2	2	2	3[d]	2	2	2	2	2	2	2	1	2
Crizotinib			•	•				•		•	•	•	•	•		•	•	•	•
Entrectinib	•					•	•	•	•						•				
Lorlatinib			•	•					•	•		•	•	•		•	•		•
Repotrectinib		•			•	•	•				•				•				
Prior lines, chemotherapy	3	1	6	1	0	2	3	1	1	2	1	1	2	2	1	2	1	0	3
Prior lines, anticancer therapy*	3	2	11	3	1	4	6	3	3	6	3	4	4	4	3	5	4	2	6

Drillon ENA 2022

ROS1 TKIs in crizotinib/TKI-pretreated; Next-generation ROS1 TKIs

	Lorlatinib (Phase 1/2)	Repotrectinib (TRIDENT-1 Phase 1/2)	Taletrectinib (TRUST Chinese Phase 2)	NVL-520 (Phase 1)
N	40	56	38	21
ORR	**35%** (prior crizotinib)	**38%** (only 1 prior ROS1 TKI and no prior chemo)	**50%** (prior crizotinib)	**48%** 53%(9/17) with≥2prior ROS1TKI, ≥1 chemo
mPFS	**8.5mo**	**9.0**	**9.8**	**NA**
CNS activity	(12/24) **50%** pts with baseline measurable or nonmesurable CNS metastases	(5/12) **42%** pts with baseline mesurable CNS metastases	(11/12) **92%** pts with baseline mesurable CNS metastases	(8/11) **73%** pts with baseline CNS metastases
Clinical ROS1 G2032R activity	Response in 0/6 (**0%**) pts with baseline **ROS1 G2032R** in plasma	Response in 10/17 (**59%**) pts with baseline **ROS1 G2032R**	Response in 4/5 (**80%**) pts with baseline **ROS1 G2032R**	(7/9) **78%** pts with baseline **ROS1 G2032R**
Most common treatment-related or trtt-emergent AEs	Hypercholesterolemia, hypertriglyceridemias, edema, peripheral neuropathy, cognitive effects, weight increaded, dizziness, mood effects, lipase increased	Dizziness, dysgeusia, constipation, paresthesia, dsypnea, anemia, fatigue, nausea, muscular weakness, ataxia	Diarrhea, nausea, vomiting, ALT increase, AST increase, anemia, neutrophil count decrease	Fatigue, nausea, ALT and AST increased, oedema, myalgia
Reference	Shaw et al, lancet oncol 2019	Cho et al, AACR-NCI-EORTC 2022, Cho et al WCLC23	Li W et al, ASCO 2022; Li W et al, ELCC23	Drillon et al, ENA 2022

Advanced ROS1+ NSCLC
Current 2L treatment Paradigm

Entrectinib
Crizotinib

→ **Next-gen ROS1 TKI**

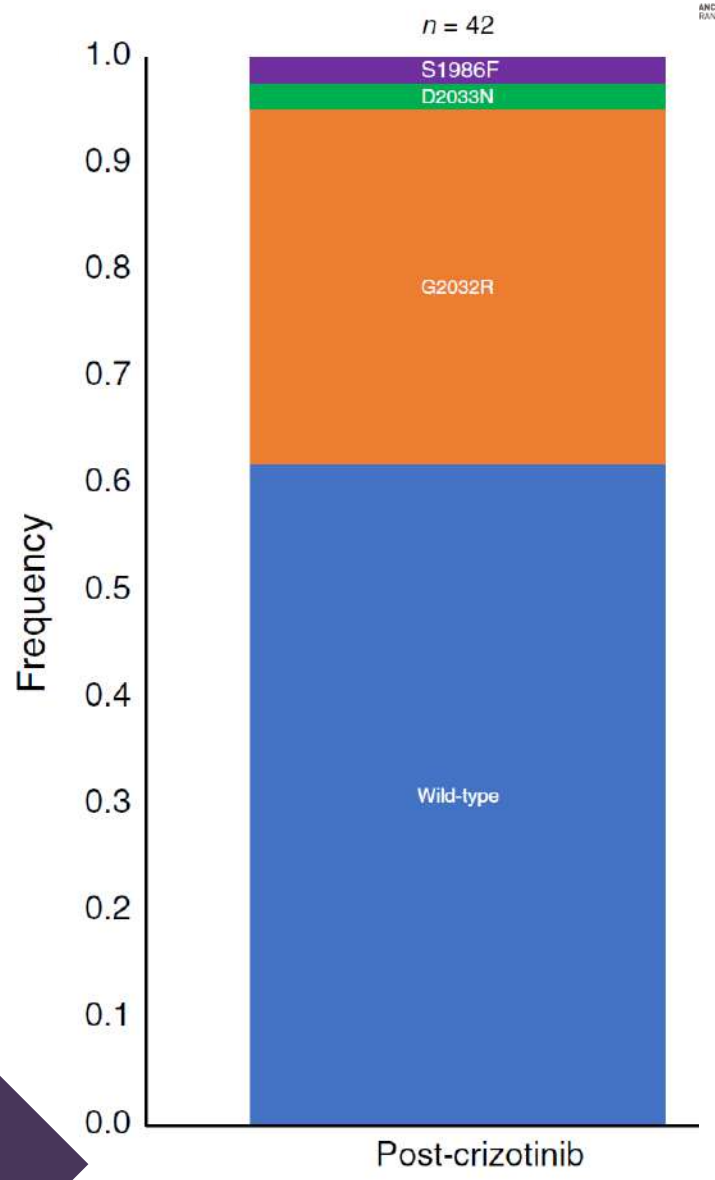
Entrectinib
Crizotinib

→ **Chemotherapy**
Clinical trial

Entrectinib:Preferred over crizotinib in patients with BM
(ESMO Guidelines)

Next-gen ROS1 TKI (Reprotrectinib…) ?

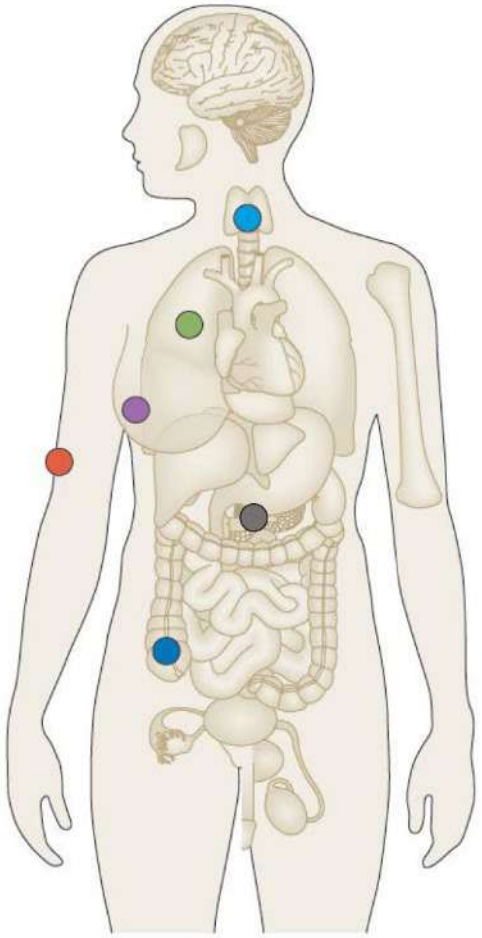
15 Nov2023, FDA approved repotrectinib (AUGTYRO) for the treatment of pts ROS1-positive NSCLC
Not EMA approved



Lin JJ et al, CCR 2021

Clinical features of RET-rearranged NSCLC

***RET* fusions**



Non-small cell lung cancer (2%)

Papillary and other thyroid cancers (10–20%)

Pancreatic cancer (<1%)

Salivary gland cancer (<1%)

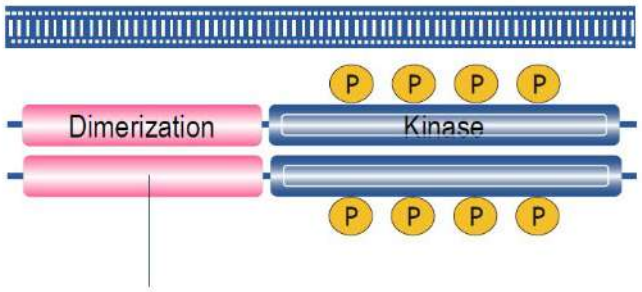
Spitz tumors (<1%)

Colorectal cancer (<1%)

Ovarian cancer (<1%)

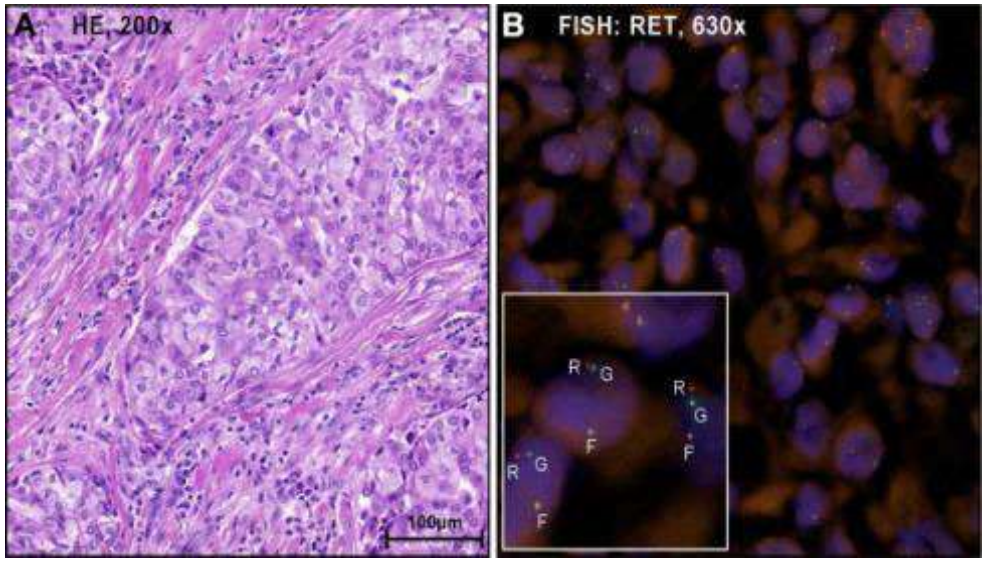
Myeloproliferative disorders (<1%)

Many others (<1%)



KIF5B (most common in lung cancer)

CCDC6* or *NCOA4 (most common in thyroid c



- **1-2% of NSCLC**
- Median age 61
- More frequent in adenocarcinoma
- Predominance of non-smokers

Drilon Nature Reviews Clinical Oncology 2018; Gautschi JCO 2018; Michels et al. JTO 2015

Multi-kinase RET Inhibitors

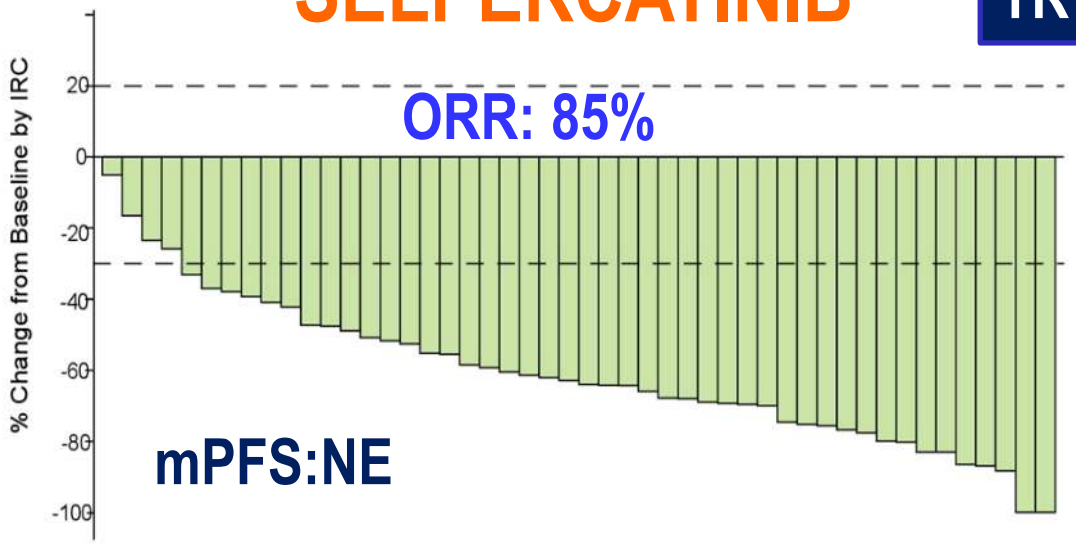
multi-kinase RET inhibitors	study type (n)	ORR(%)	mPFS (months)	mOS (months)	dose-reduction rate (%)	drug discontinuation rate (%)
Cabozantinib	Phase II trial (26)[1]	28	5.5	9.9	73	8
Vandetanib	Phase II trial (17)[2]	18	4.5	11.6	23	NA
	Phase II trial (19)[3]	47	4.7	11.1	53	21
Lenvatinib	Phase II trial (25)[4]	16	7.3	NE	64	20
Sunitinib	Retrospective series (9)[5]	22	2.2	6.8	NA	NA
Alectinib	Retrospective series (4)[6]	25	NA	NA	0	25
	Phase I/II trial (25)[7]	19	NA	NA	31	NA
RXDX-105	Phase I trial (22)[8]	27	NA	NA	NA	NA
	Phase I/Ib trial (31)[9]	4	3.4	19	NA	NA

Within the ranges of **16%-53%** and **2.3-7.3** months for ORR and mPFS, respectively.

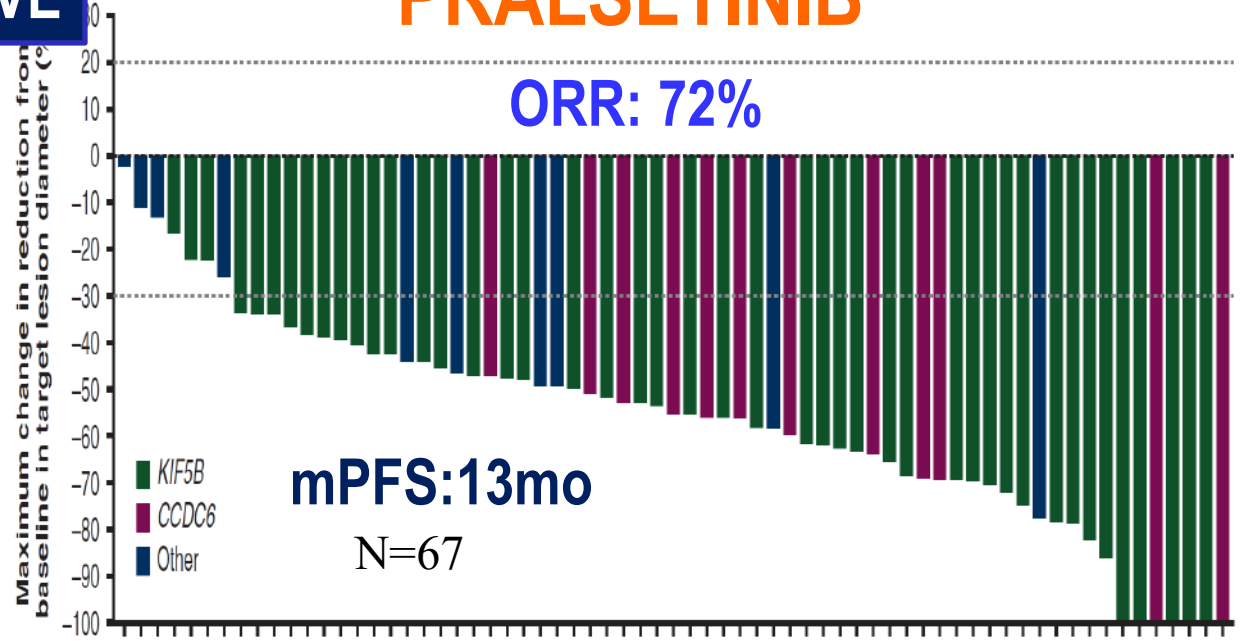
RET: LIBRETTO and ARROW Trials

SELPERCATINIB

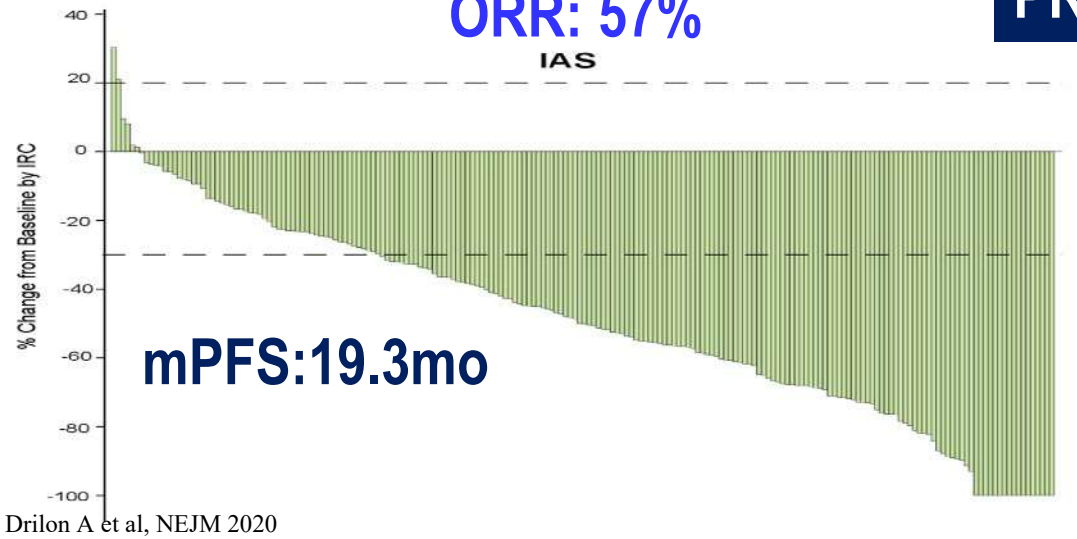
TRT-NAIVE

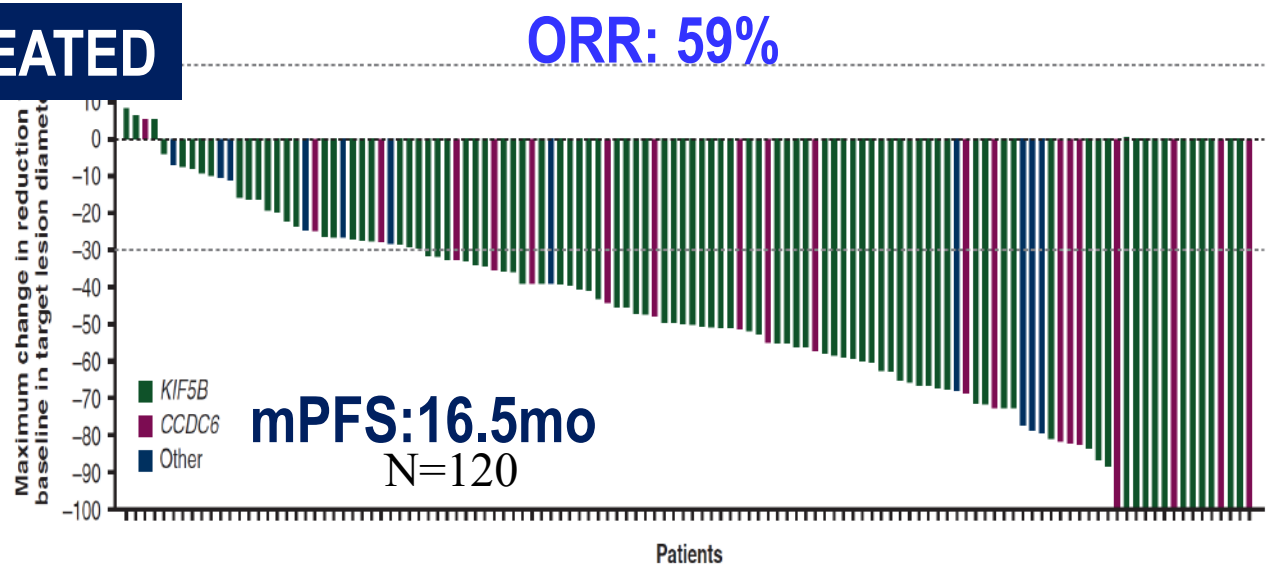


PRALSETINIB



PRETREATED



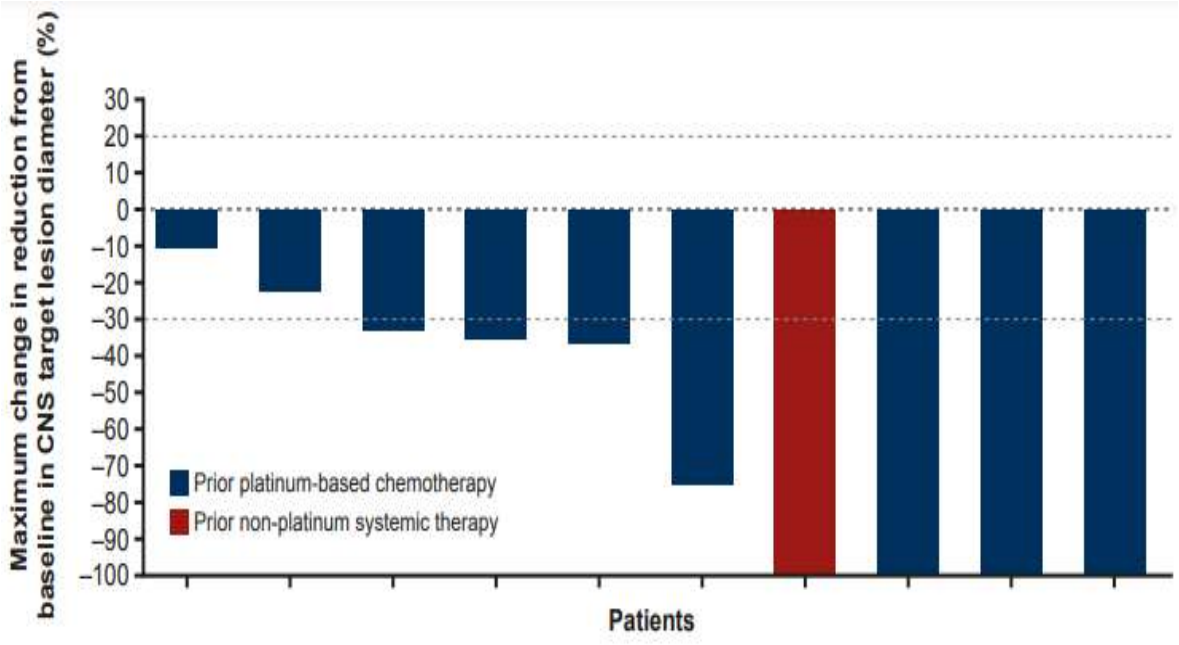


Drilon A et al, NEJM 2020

F.Griesinger et al, annals of onco 2022

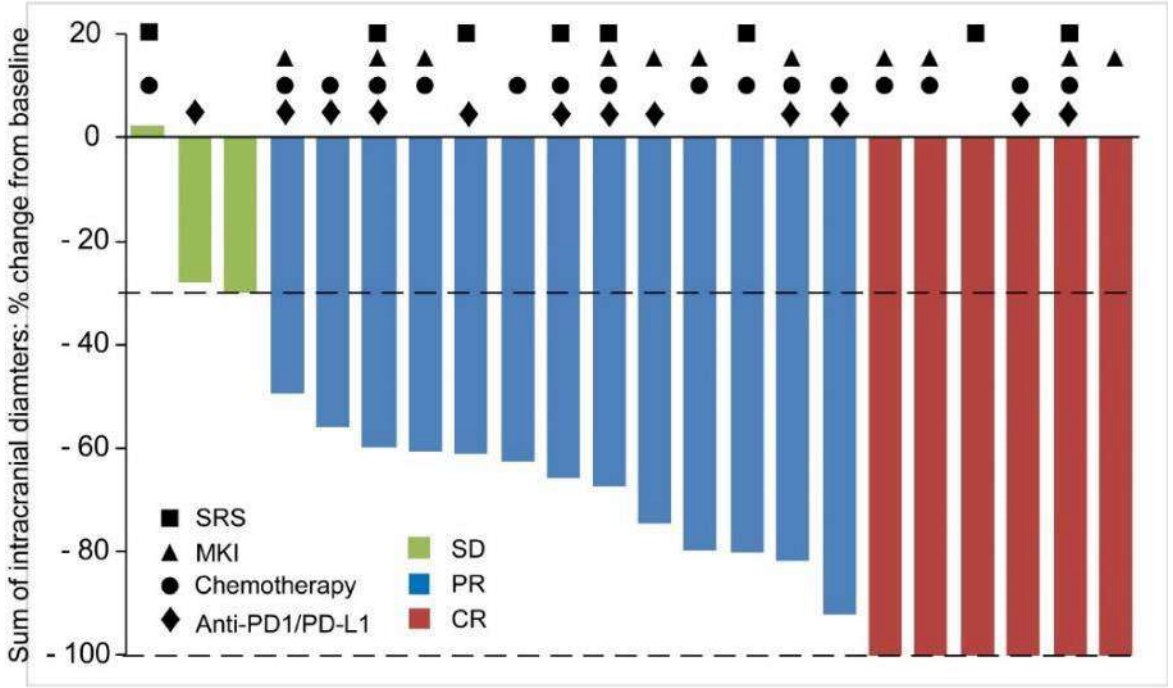
Specific RET inhibitors – intracranial activity

Pralsetinib



Intracranial ORR: 70%
N=10

Selpercatinib



Intracranial ORR: 82%
N=23

LIBRETTO-431 phase 3 open-label study design

Key Eligibility Criteria

- Stage IIIB-IIIC[1], IV non-squamous NSCLC
- No prior systemic therapy for metastatic disease
- *RET* fusion identified via NGS or PCR
- ECOG PS 0-2
- Symptomatic CNS metastases excluded

Stratification factors:

- Geography (East Asian vs. non-East Asian)
- Brain metastases (present vs. abse
- Investigator's choice of treatment w pembrolizumab

BM:20%

R 2:1[3]

Selpercatinib (160 mg BID)
N= 159

Carboplatin (AUC 5) or **Cisplatin** (75 mg/m^2)
+ **Pemetrexed** (500 mg/m^2)
+/- **Pembrolizumab** (200 mg)
N= 102

Optional Crossover → **Selpercatinib** (Upon BICR confirmed PD)

Gated Primary Endpoints: PFS by blinded independent central review (BICR) in ITT-Pembrolizumab[4] and ITT population

Secondary Endpoints:

- **Efficacy** ([OS, ORR, DOR], CNS [ORR, DOR, time t
- **Safety**
- **Patient Reported Outcomes** (NSCLC-SAQ [tertiary endpoint EORTC QLQ-C30])

Pembro:81%

[1] Not suitable for radical surgery or radiation therapy
[2] Investigator assessed
[3] The initial randomization ratio was 1:1, but amended to 2:1
[4] ITT-Pembrolizumab are patients stratified with investigator intent to receive chemotherapy with pembrolizumab and per protocol had to be at least 80% of the ITT population
[5] Baseline and longitudinal intracranial scans were required for all patients following an amendment. Prior to the amendment, longitudinal intracranial scans were required if patients had known CNS metastases at baseline

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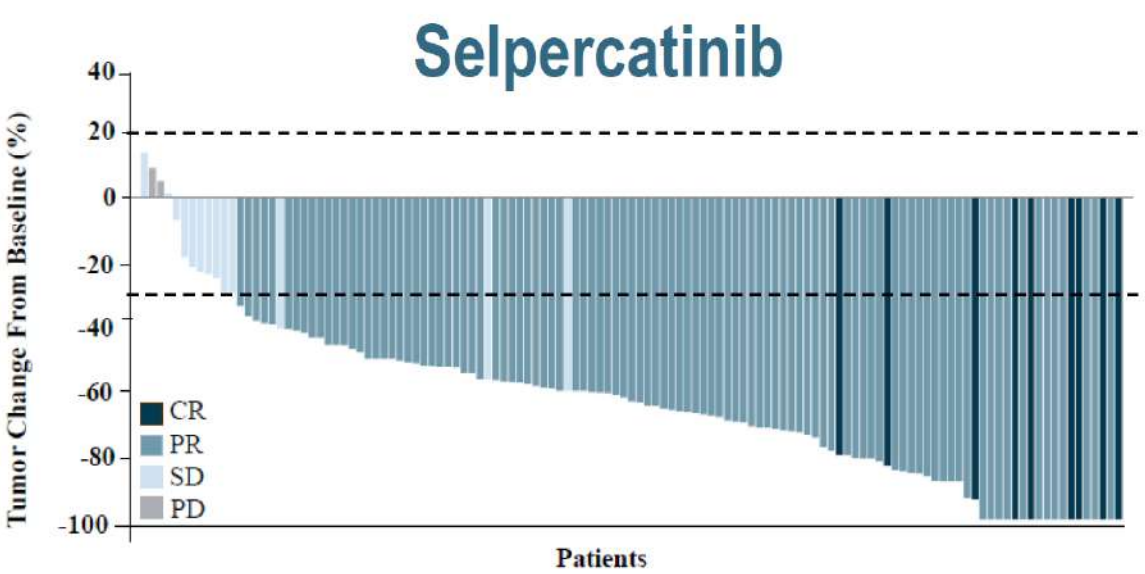
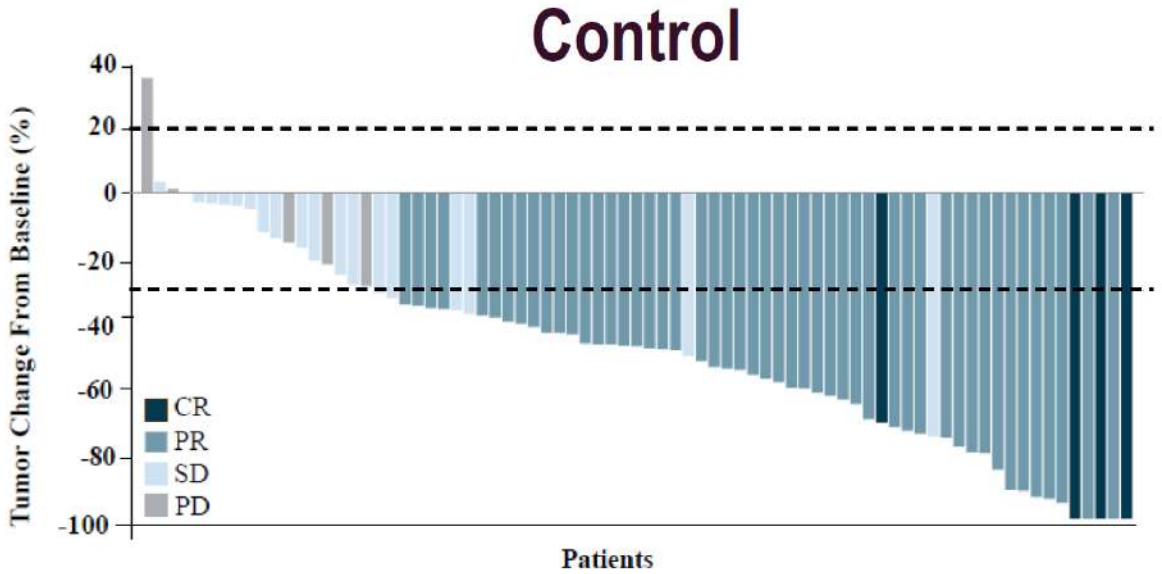
LIBRETTO-431 - Systemic ORR





ORR: 83.7%

	Selpercatinib N= 129	Control N= 83
ORR, % (95% CI)	83.7 (76.2, 89.6)	65.1 (53.8, 75.2)
CR	7.0 (3.2, 12.8)	6.0 (2.0, 13.5)
PR	76.7 (68.5, 83.7)	59.0 (47.7, 69.7)
SD	10.9 (6.1, 17.5)	24.1 (15.4, 34.7)
PD	1.6 (0.2, 5.5)	6.0 (2.0, 13.5)
NE	3.9 (1.3, 8.8)	4.8 (1.3, 11.9)

ORR: 65.1%

IC-ORR (n=17 and 12pts): 82.4 vs 58.3%

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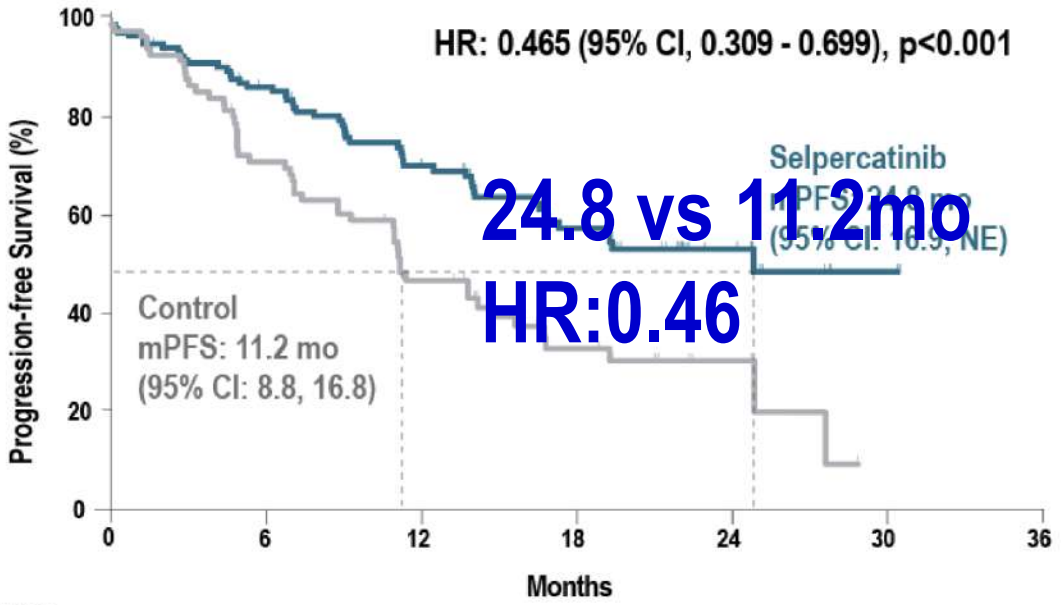
Progression-free survival (PFS) assessed by BICR

ITT-Pembrolizumab Population

(Median follow-up of ~19 mo)



24.8 vs 11.2mo

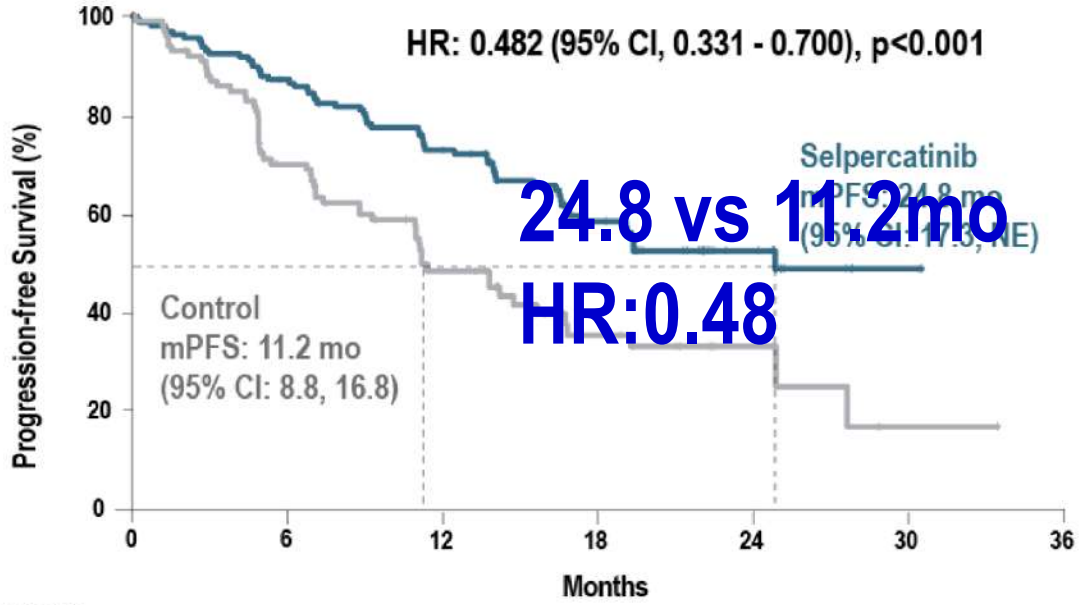
HR:0.46

No. at Risk

Selpercatinib	129	105	72	44	16	2	0
Control	83	55	29	15	6	0	0

ITT Population

(Median follow-up of ~18 mo)



24.8 vs 11.2mo

HR:0.48

No. at Risk

Selpercatinib	159	130	90	52	18	3	0
Control	102	63	33	16	7	1	0

The primary endpoints were met, as selpercatinib resulted in a statistically significant improvement in PFS in both pre-specified populations

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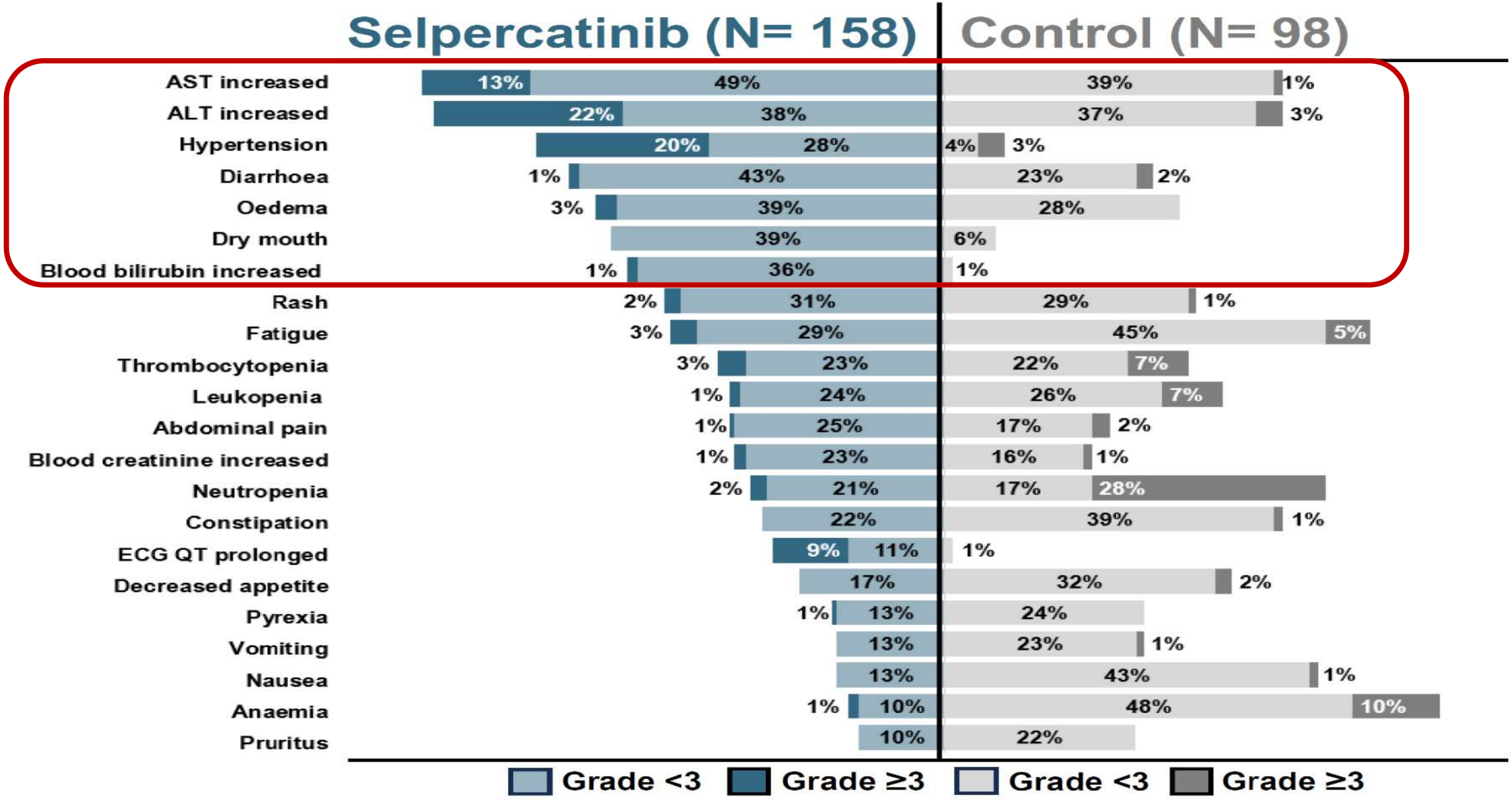
Safety


Selpercatinib (N= 158)
Control (N= 98)
AST increased 13% 49% 39% 1%
ALT increased 22% 38% 37% 3%
Hypertension 20% 28% 4% 3%
Diarrhoea 1% 43% 23% 2%
Oedema 3% 39% 28%
Dry mouth 39% 6%
Blood bilirubin increased 1% 36% 1%
Rash 2% 31% 29% 1%
Fatigue 3% 29% 45% 5%
Thrombocytopenia 3% 23% 22% 7%
Leukopenia 1% 24% 26% 7%
Abdominal pain 1% 25% 17% 2%
Blood creatinine increased 1% 23% 16% 1%
Neutropenia 2% 21% 17% 28%
Constipation 22% 39% 1%
ECG QT prolonged 9% 11% 1%
Decreased appetite 17% 32% 2%
Pyrexia 1% 13% 24%
Vomiting 13% 23% 1%
Nausea 13% 43% 1%
Anaemia 1% 10% 48% 10%
Pruritus 10% 22%
Grade <3
Grade ≥3
Grade <3
Grade ≥3

Selpercatinib should be considered a first-line standard of care in *RET* fusion-positive advanced NSCLC. These results reinforce the importance of genomic testing to identify *RET* fusions at the time of diagnosis to inform initial therapy

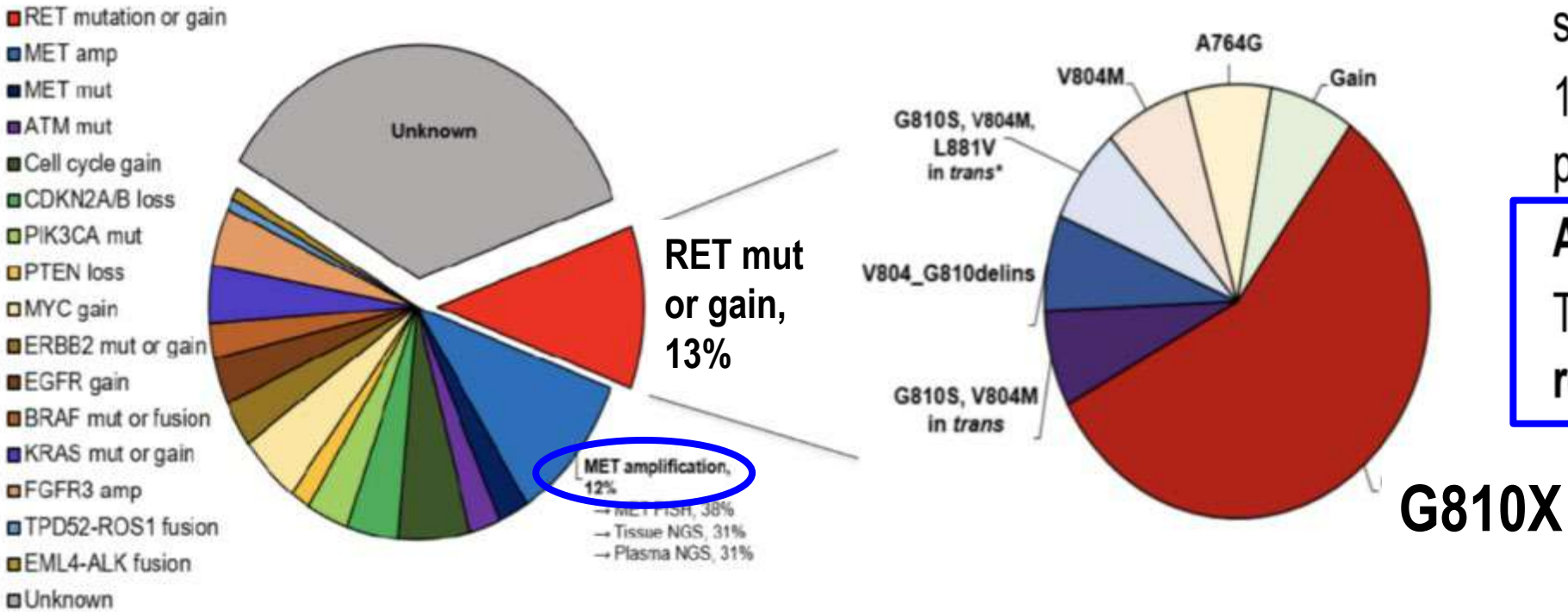
Next gen RET inhibitors

Several ongoing trials + pre-clinical data on new molecules

Drug	Company	Status	Activity
LOXO-260	LOXO-Lilly	Phase I	Active against solvent front and gatekeeper mutations
SY-5007	Shouyao Holdings	Phase I completed (ASCO 2023): ORR 62%, DCR 94% Phase II ongoing	Selective RET inhibitor
TPX-0046	Turning Point Therapeutics	Phase I/II	RET/SRC inhibitor, active against solvent front mutations
TY-1091	TYK Medicines	Phase I/II	Active against solvent front and gatekeeper mutations
TAS0953/HM06	Helsinn Healthcare	Phase I/I	Active against solvent front and gatekeeper mutations

RET: Resistance to selective RET inhibitors

Global RETgistry consortium



Retrospective multi-institutional study

105 biopsies from 89 patients progressing on selective RET TKI

Acquired *RET* mutations in 13%

The **most common *RET* resistance mutation is G810X**

- **Solvent front mutation** analogous to ALK G1202R and ROS1 G2032R
- **Detected in 10%**

AJ.Cooper et al, ASCO 2023

Addressing On-Target resistance to RET TKIs

Next-generation RET TKIs

Compound	*RET* Substitution Coverage			VEGFR2	Other Non-RET Kinases	CNS?	Status
	V804X Gatekeeper	G810X Solvent Front	Other *RET* Mutation				
TPX-0046[1]	Less potent	✓	Y806N (hinge)	-	TRKA-C, SRC, FGFR1-2, FLT3, JAK2	?	Phase I/II (NCT04161391)
LOXO-260[2]	✓	✓	G810S+V804M	-	TRKC (40x selectivity)	?	Phase I/II (NCT05241834)
Vepafestinib[3,4] **(TAS0953/HM06)**	✓	✓	Y806C/N	-		✓	Phase I/II (NCT04683250)
EP0031[5] **(A400/KL590586)**	✓	✓		-	JAK1/2 (10-22x selectivity)	✓	Phase I/II (NCT05443126)
APS03118[6]	✓	✓	Y806H	-		✓	Phase I/II (NCT05653869)

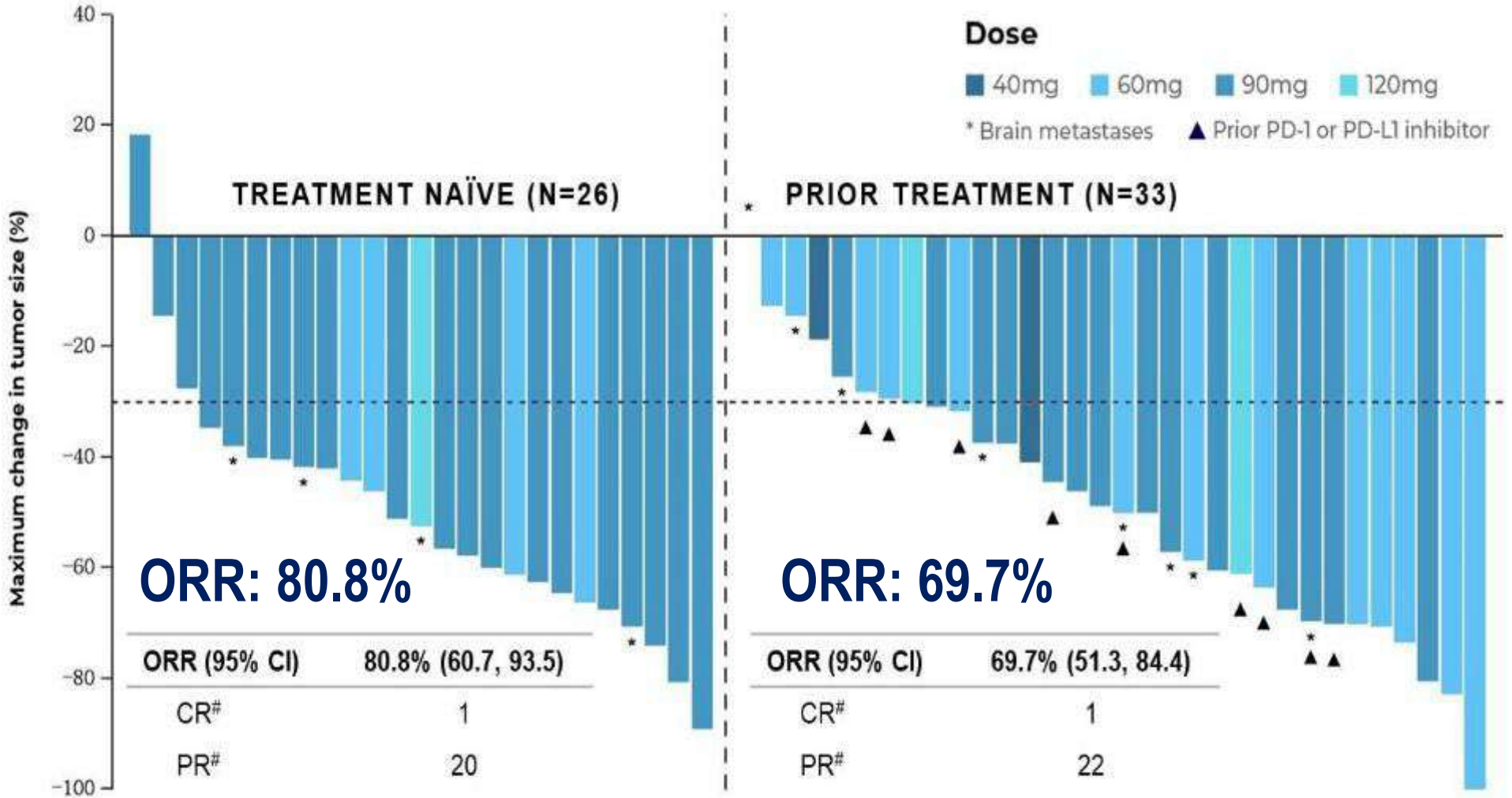
Data based on publicly-available preclinical data; grey = unknown

[1]Drilon A et al., ESMO 2019; [2]Kolakowski GR et al., AACR 2021; [3]Miyazaki I et al., AACR-NCI-EORTC 2021
[4]Odintsov I et al., AACR-NCI-EORTC 2021; [5]Zhou Q et al., ASCO 2023; [6]Drilon A et al., AACR 2022

KL590586 (A400/EP0031) activity

CHANGE IN TUMOR SIZE FOR PATIENTS WITH NSCLC ADMINISTERED KL590586 40-120MG QD

 # All responses are confirmed on two consecutive assessments as per RECIST 1.1.



ORR: 80.8%

ORR (95% CI)	80.8% (60.7, 93.5)
CR#	1
PR#	20
SD	4
DCR (95% CI)	96.2% (80.4, 99.9)

ORR: 69.7%

ORR (95% CI)	69.7% (51.3, 84.4)
CR#	1
PR#	22
SD	9
DCR (95% CI)	97.0% (84.2, 99.9)

a cut-off date: 20 Apr 2023.

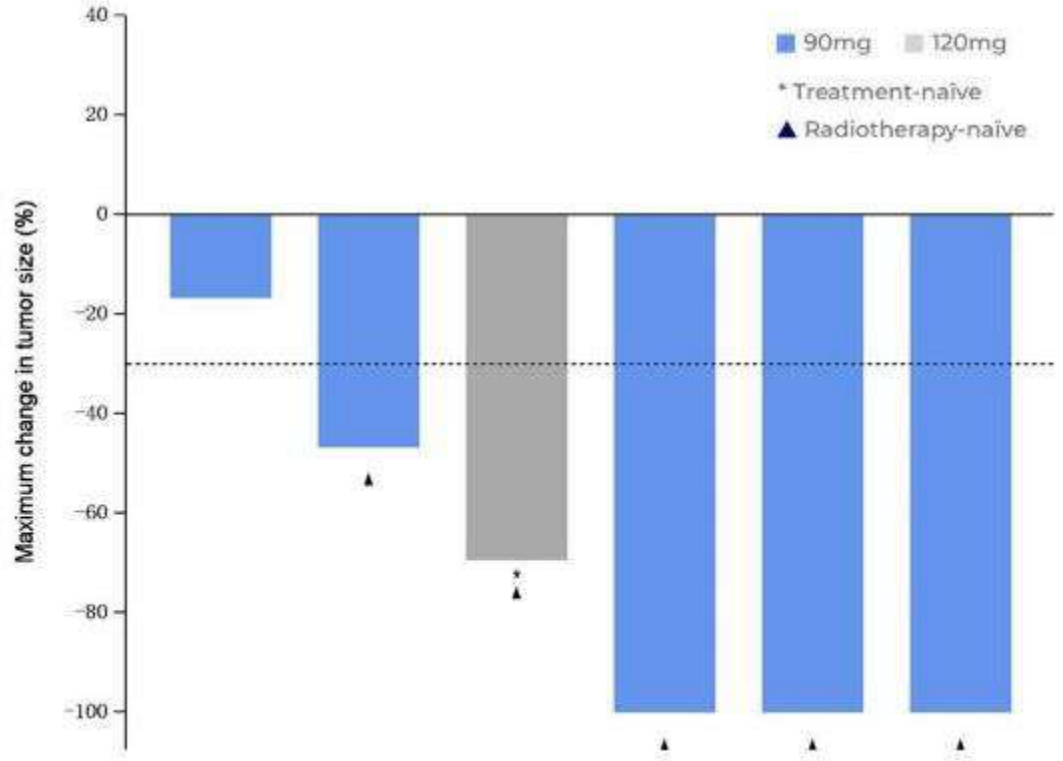
Qing Zhou et al, ASCO 2023

Brain activity - KL590586 (A400/EP0031)

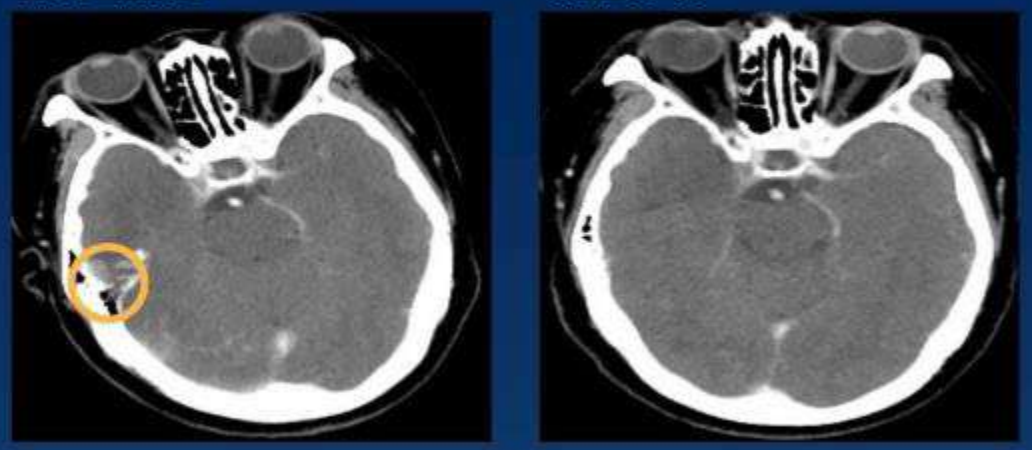
against intracranial metastases

INTRACRANIAL RESPONSE IN NSCLC

- 5/6 patients with intracranial target lesions at baseline had intracranial responses
- 100% shrinkage observed in 3 patients



Data cut-off date: 20 Apr 2023



FEMALE, 60 YEARS, WITH NSCLC, 4 PRIOR TREATMENT REGIMENS

- Progressed after sintilimab (PD-1), with brain, bone and pleural metastases
- KL590586, 90mg QD
- Deep PR (70% shrinkage of target lesions)
- 100% shrinkage of brain lesions
- Response continues after 7 months

Qing Zhou et al, ASCO 2023

ONGOING ADJUVANT TKI TRIALS IN *ALK*+, *RET*+

Alectinib

ALINA (NCT03456076), ph III

- Resected stage IB (≥ 4 cm)–IIIA*
- *ALK*+ NSCLC
- ECOG PS 0-1

N=225

R 1:1

Alectinib 600 mg BID, 2 years

Stratify by:
- Stage IB vs. II vs. IIIA
- Race (Asian vs. non-Asian)

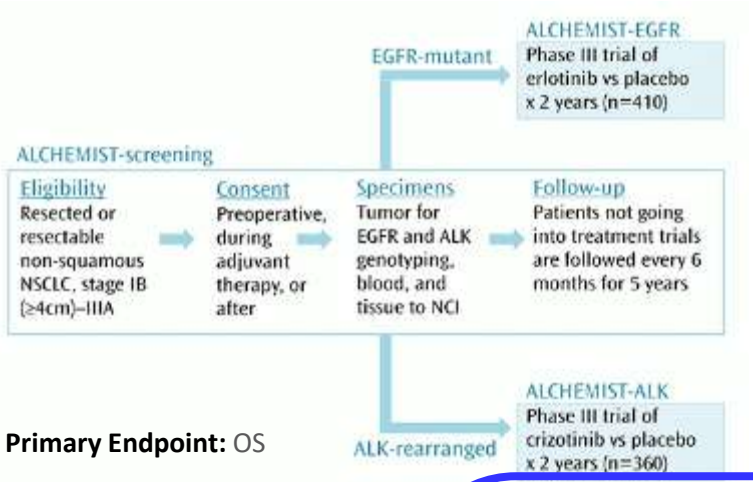
Platinum-based CT, 4 cycles

Primary Endpoint: DFS

*IIIA N2 post-operative RT not allowed

Crizotinib

ALCHEMIST (NCT02194738), ph III



Primary Endpoint: OS

Ensartinib

Heberi University (NCT05241028), ph II

- Resected stage IB (≥ 4 cm)–IIIA
- *ALK*+ NSCLC
- ECOG PS 0-1

N=80

Ensartinib 225 mg PO, 3 years

Primary Endpoint: 3-year DFS

Ensartinib

Sichuan University (NCT05186506), ph II

- Resected stage II-IIIA
- *ALK*+ NSCLC
- ECOG PS 0-1

N=152

R 1:1

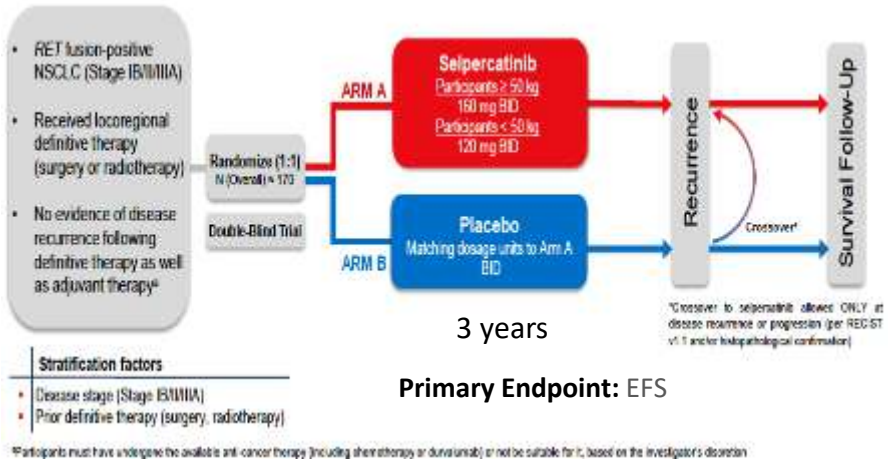
Ensartinib 225 mg, PO 2 years

Platinum-based CT 4 cycles

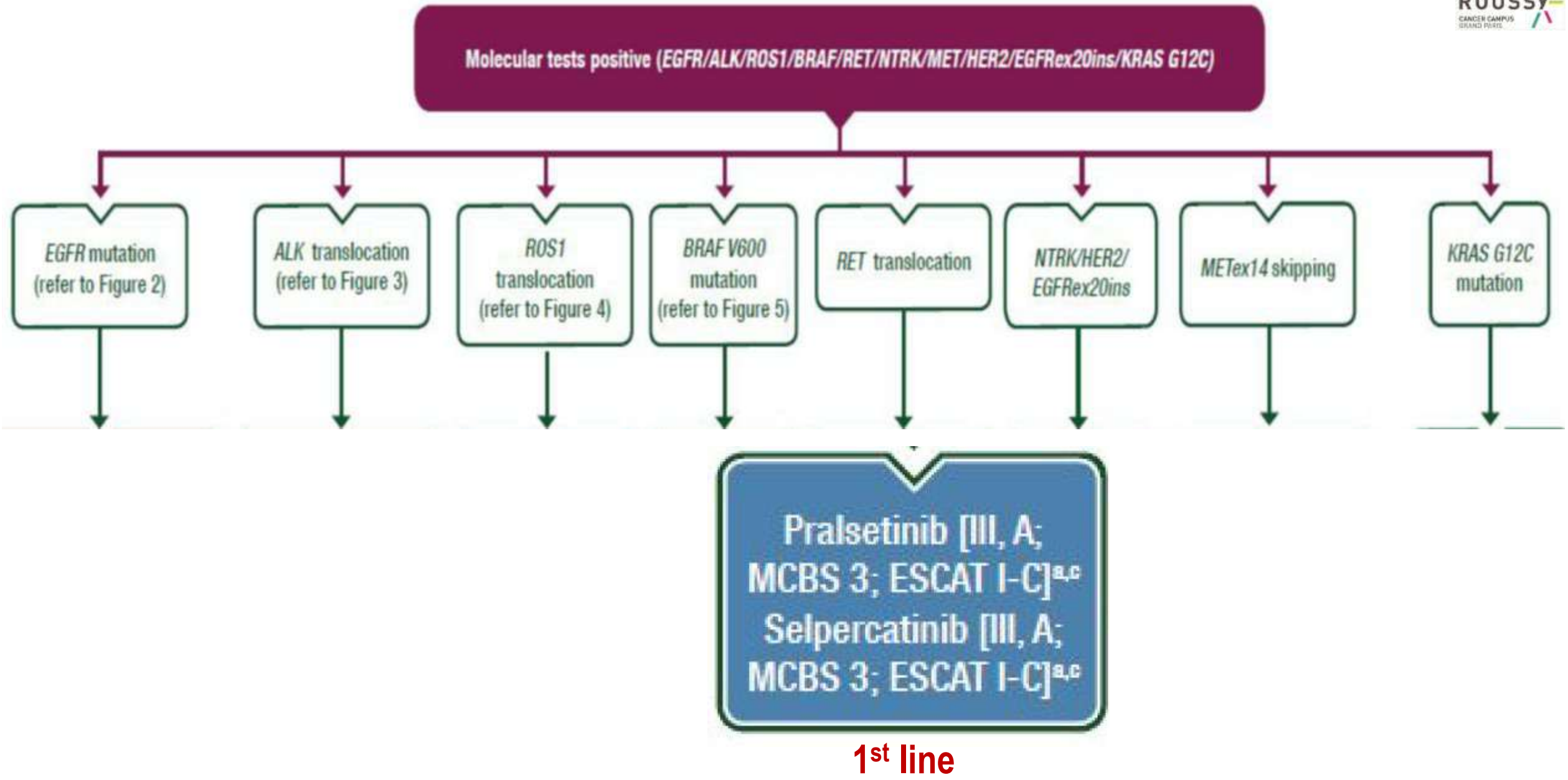
Primary Endpoint: DFS

Selpercatinib

LIBRETTO-432 (NCT04819100), ph III



Primary Endpoint: EFS

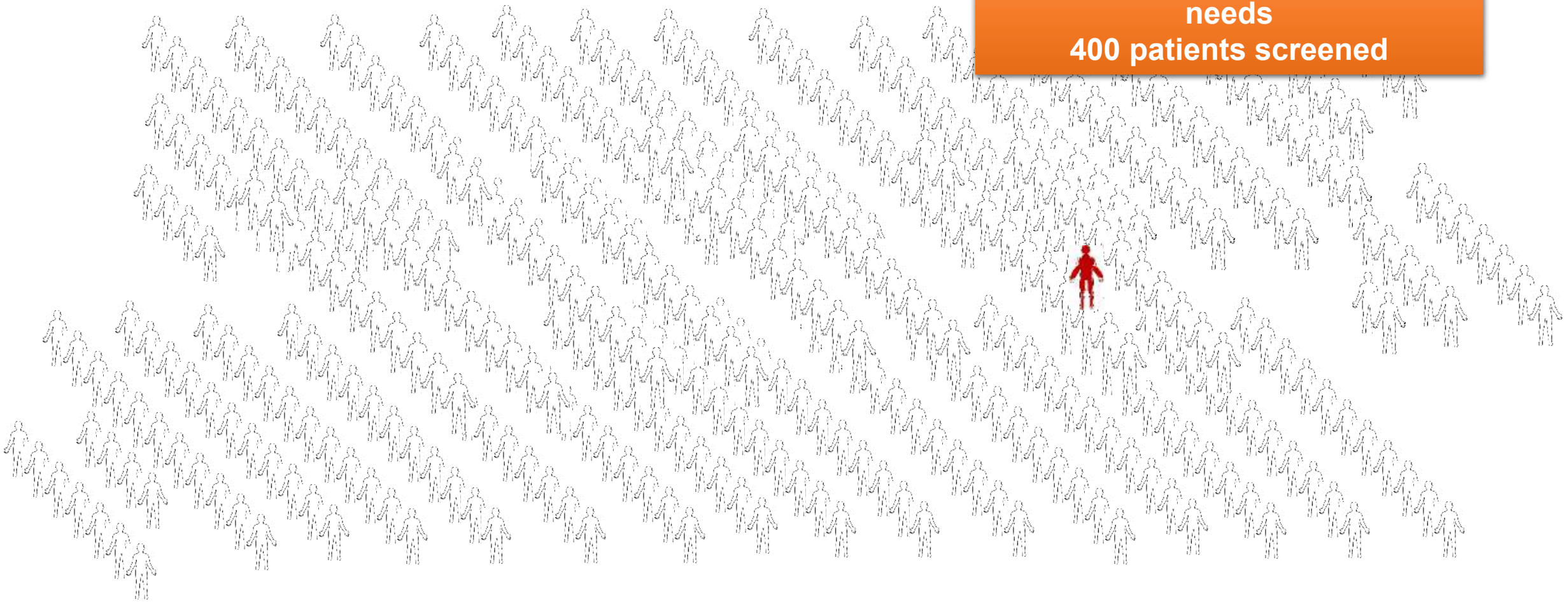


1st line

L. E. Hendriks, K. Kerr, J. Menis, T. S. Mok, U. Nestle, A. Passaro, S. Peters, D. Planchard, E.F Smit, B. J. Solomon, G. Veronesi & M. Reck, Annals of onco 2023

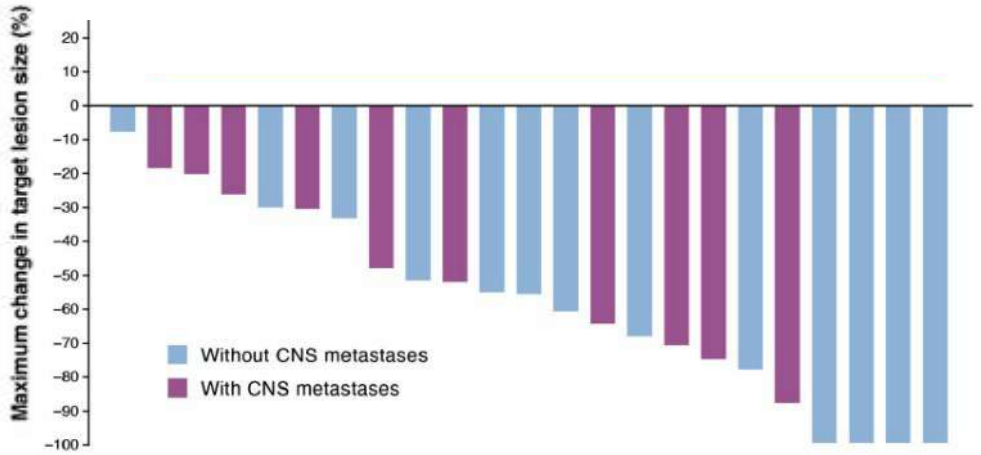
NTRK is a VERY rare fusion

1 NTRK fusion
needs
400 patients screened



Larotrectinib and Entrectinib in NTRK+ NSCLC

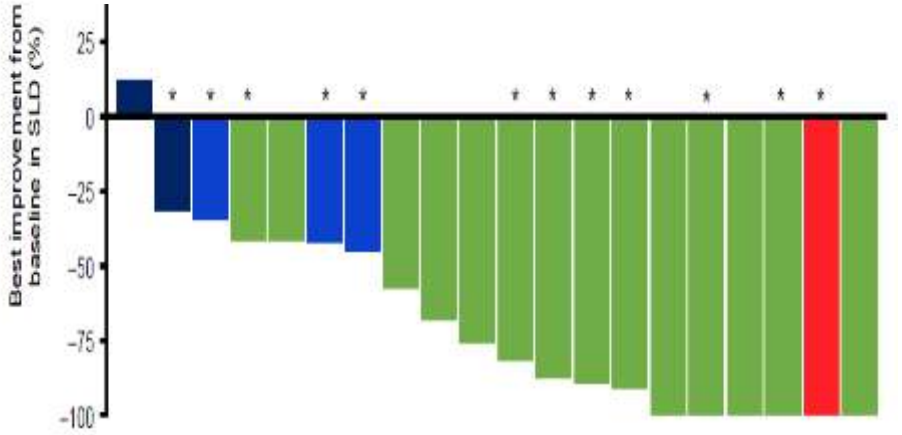
Larotrectinib (n=26)



ORR, % (95%, CI)	83% (61-95)
Median PFS, mo (95% CI)	**NR** (9.9–NR)
Median DoR, mo (95% CI)	**NR** (9.5–NR)
Median OS, mo (95% CI)	**40.7** (19.4-NE)

ORR: 83%

Entrectinib (n=22)

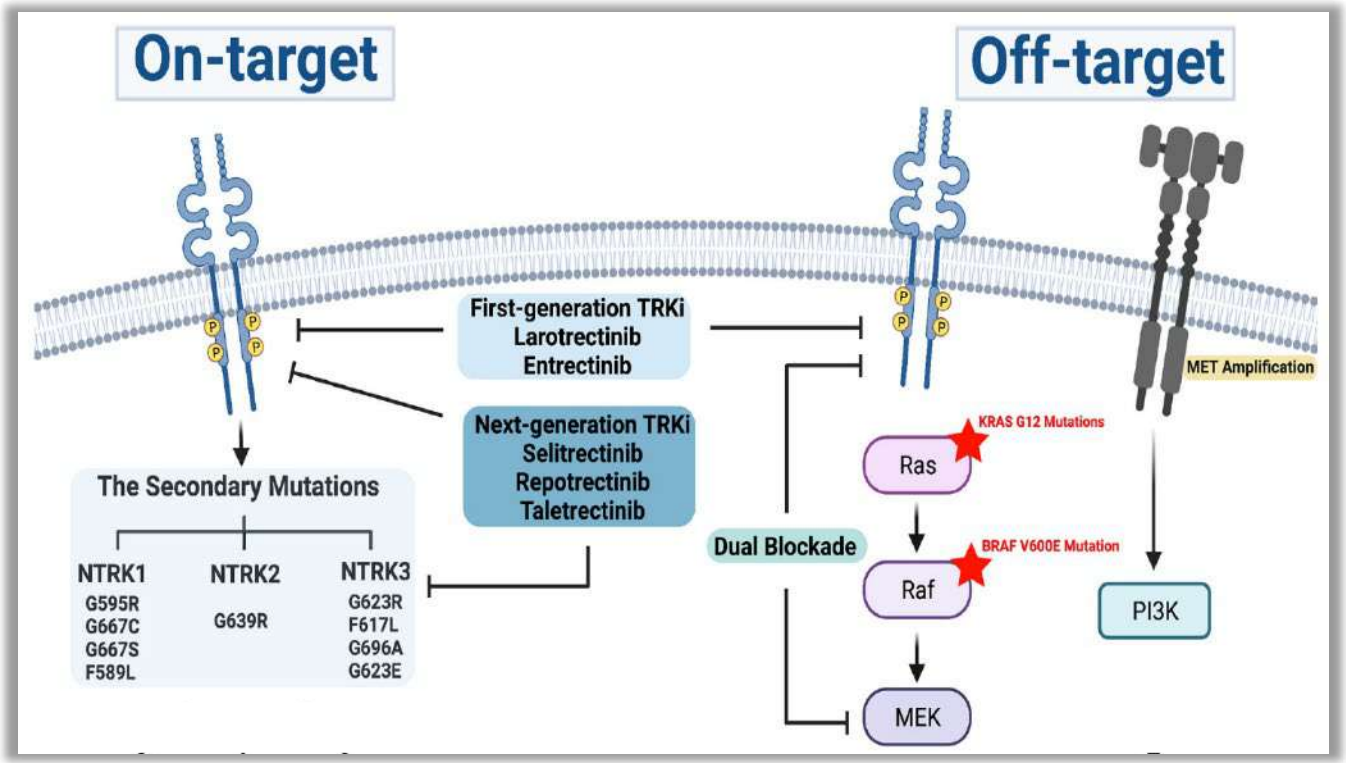


ORR, % (95%, CI)	63.6% (40.7-82.8)
Median PFS, mo (95% CI)	**14.9** (6.5–30.4)
Median DoR, mo (95% CI)	**19.9** (10.4-29.4)
Median OS, mo (95% CI)	**NE** (20.8-NE)

ORR: 63.6%

Drilon ASCO 2022, Cho ELCC 2022

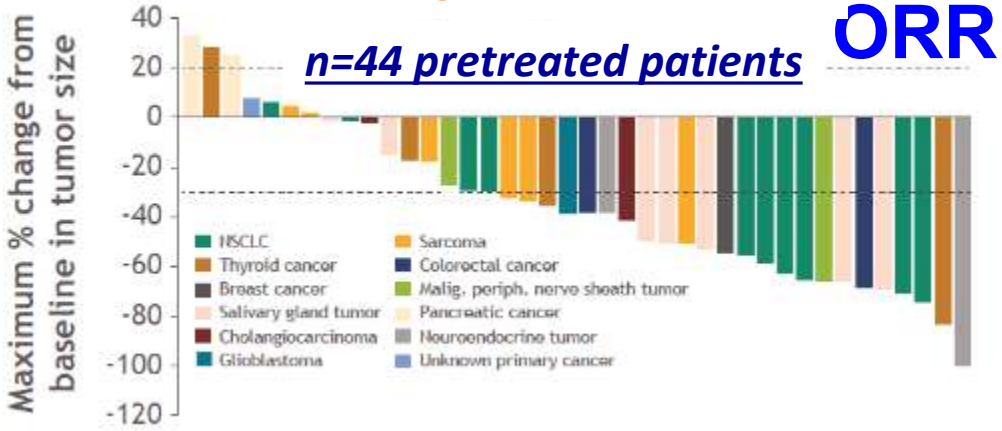
Resistance to 1st generation inhibitors



Repotrectinib

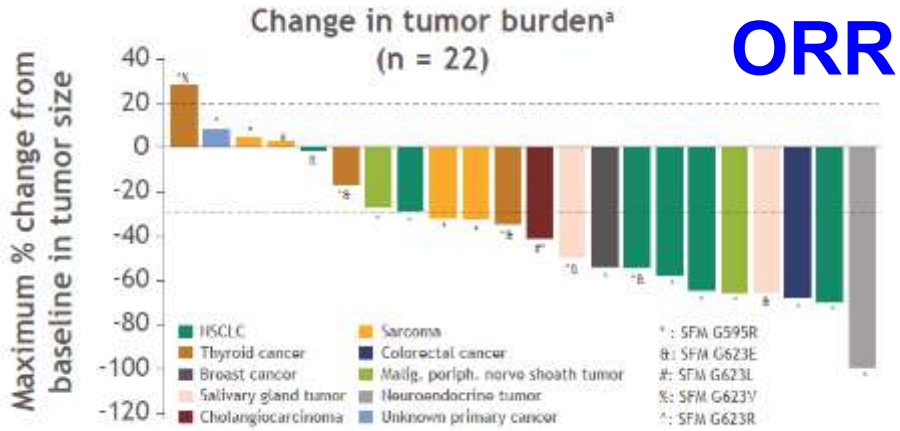
n=44 pretreated patients

ORR: 43%



n=22 Pretreated with NTRK Resistance Mutations

ORR 50%

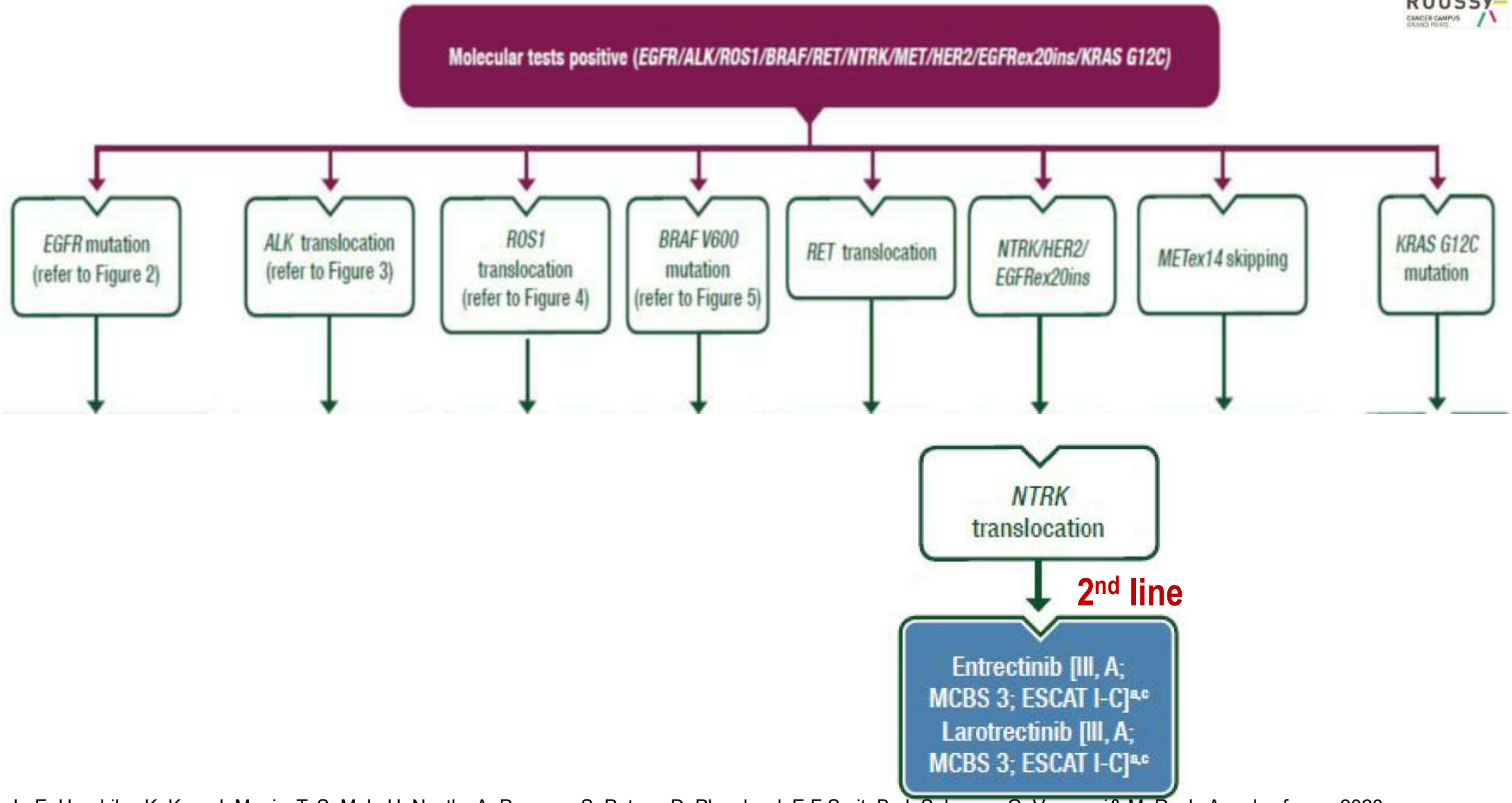


Liu Front Oncol 2021, Besse ENA 2022

NTRK+ NSCLC

	EMA and FDA approved		Second Generation inhibitors			
	Larotrectinib	Entrectinib	Taletrectinib (DS-6051b/AB-106)	Repotrectinib (TPX-0005)	Selitrectinib (LOXO-195)	ICP-723
Targets	TRK A/B/C	TRK A/B/C, ROS1, ALK	TRK A/B/C, ROS1	TRK A/B/C, ROS1, ALK	TRK A/B/C	TRK A/B/C, ROS1
IC50 against TRK in vitro, nmol/L	9.8-25	0.1-1.7	3-20	<0.2	<5	Not reported
CNS penetration (Brain to plasma ratio in mice)	0.03-0.23	0.6-1	Not reported	0.028-0.057	0.017-0.025	Not reported
ORR %	74%	61%	Not reported	43%	9/20 patients with NTRK mutation	4/6 (dose escalation)
PFS, mo	29.4	13.8	Not reported	Not reported	Not reported	Not reported
Sensitivity to NTRK secondary mutation	No	No	Yes	Yes	Yes	Yes

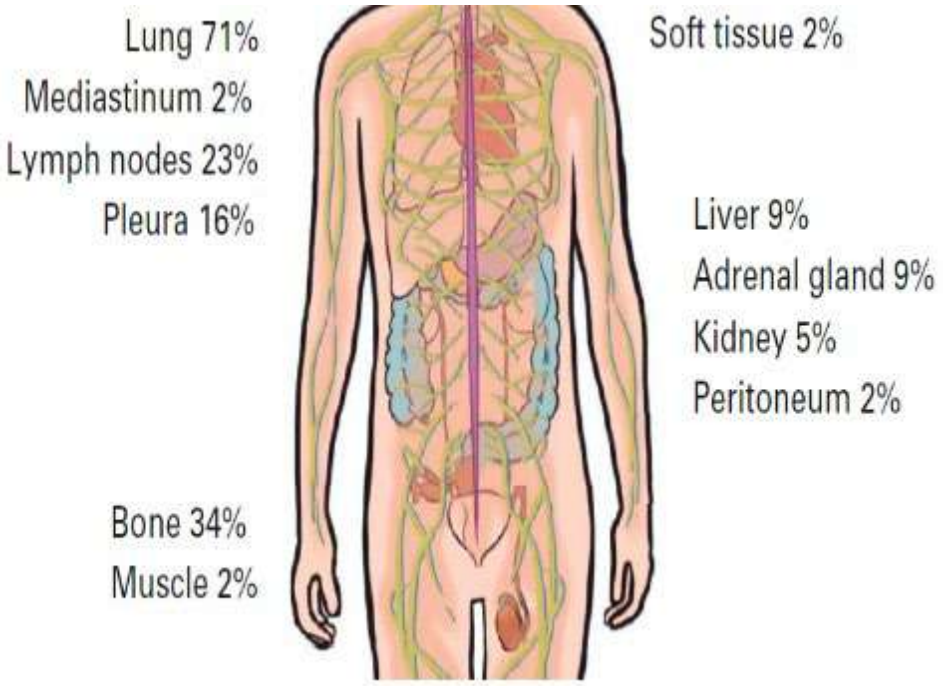
Haratake Clin Lung Cancer 2021, Drilon ASCO 2022, Wei ASCO 2022, Besse ENA 2022



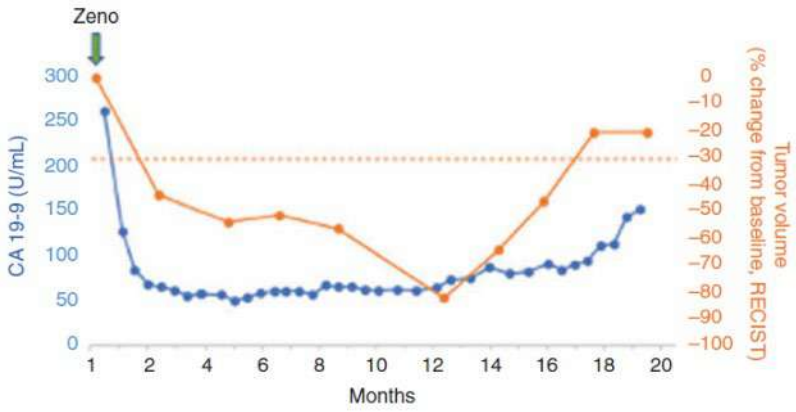
L. E. Hendriks, K. Kerr, J. Menis, T. S. Mok, U. Nestle, A. Passaro, S. Peters, D. Planchard, E.F Smit, B. J. Solomon, G. Veronesi& M. Reck, Annals of onco 2023

NRG1

- NRG1 = ligand or HER3
- 0.3% of NSCLC
- 57% never smoker
- 94% adenocarcinoma
  - invasive mucinous 57%



Response	Platinum-Doublet–Based Chemotherapy	Taxane-Based Chemotherapy	Targeted Therapy With Afatinib
Response rate, %	13	14	25
CR, % (n/N)	0 (0/15)	0 (0/7)	0 (0/20)
PR, % (n/N)	13 (2/15)	14 (1/7)	25 (5/20)
SD, % (n/N)	47 (7/15)	14 (1/7)	15 (3/20)
PD, % (n/N)	40 (6/15)	71 (5/7)	60 (12/20)
Median PFS (95% CI), range	5.8 months (2.2 to 9.8), 0.7-12.1	4.0 months (0.8 to 5.3), 0.8-5.5	2.8 months (1.9 to 4.3), 0.3-25.3

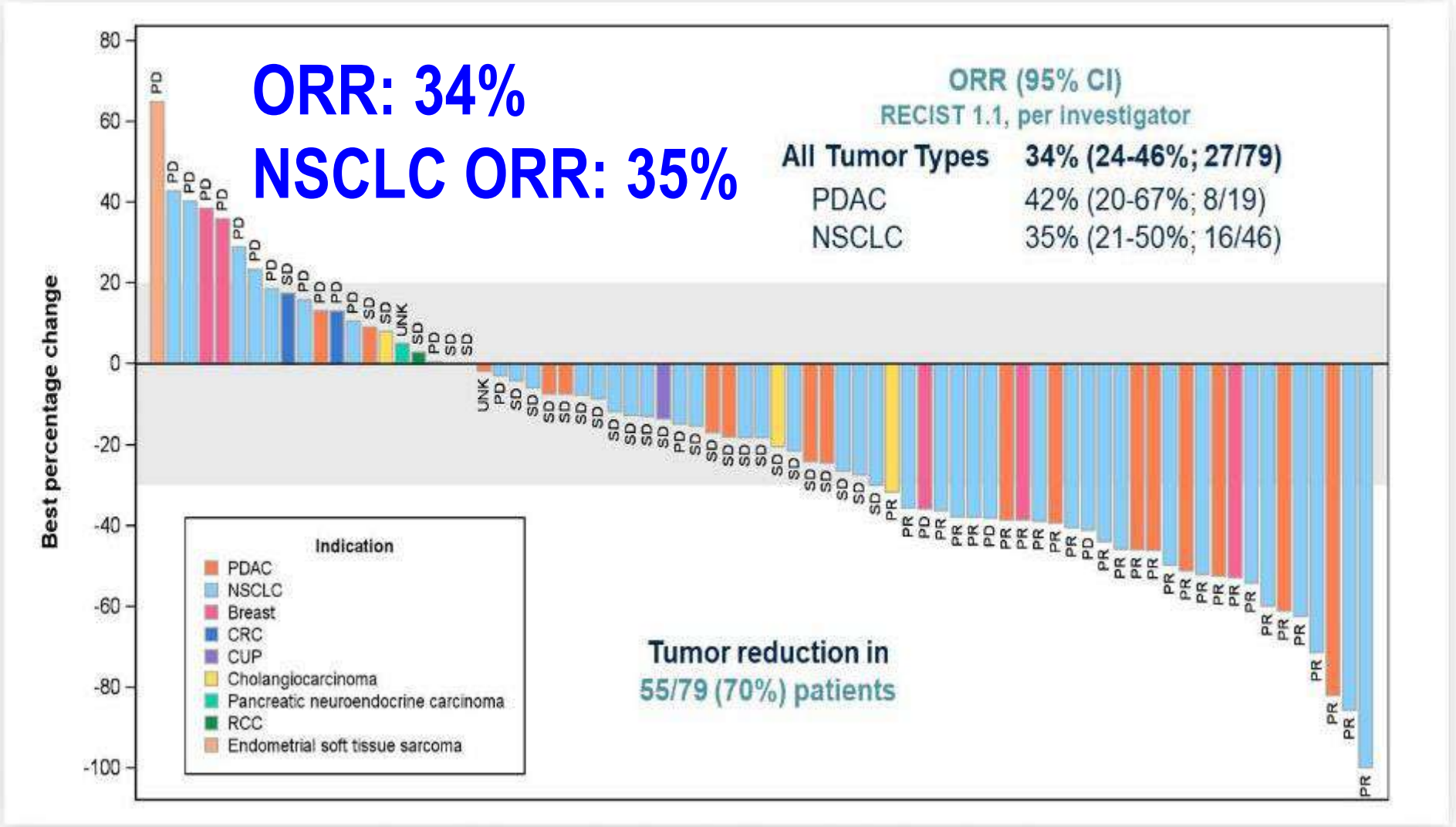


Zenocutuzumab
HER2xHER3 bispecific antibody

Drillon JCO 2021, Jonna S CCR 2019, Schram Cancer Disc 2022

Zenocutuzumab activity in NRG1+ cancer

HER2xHER3 bispecific antibody



Note. 4 patients are not included in the waterfall plot, 3 due to absence of post-baseline assessment (early progression) and 1 had incomplete assessment of target lesions at first post-baseline assessment

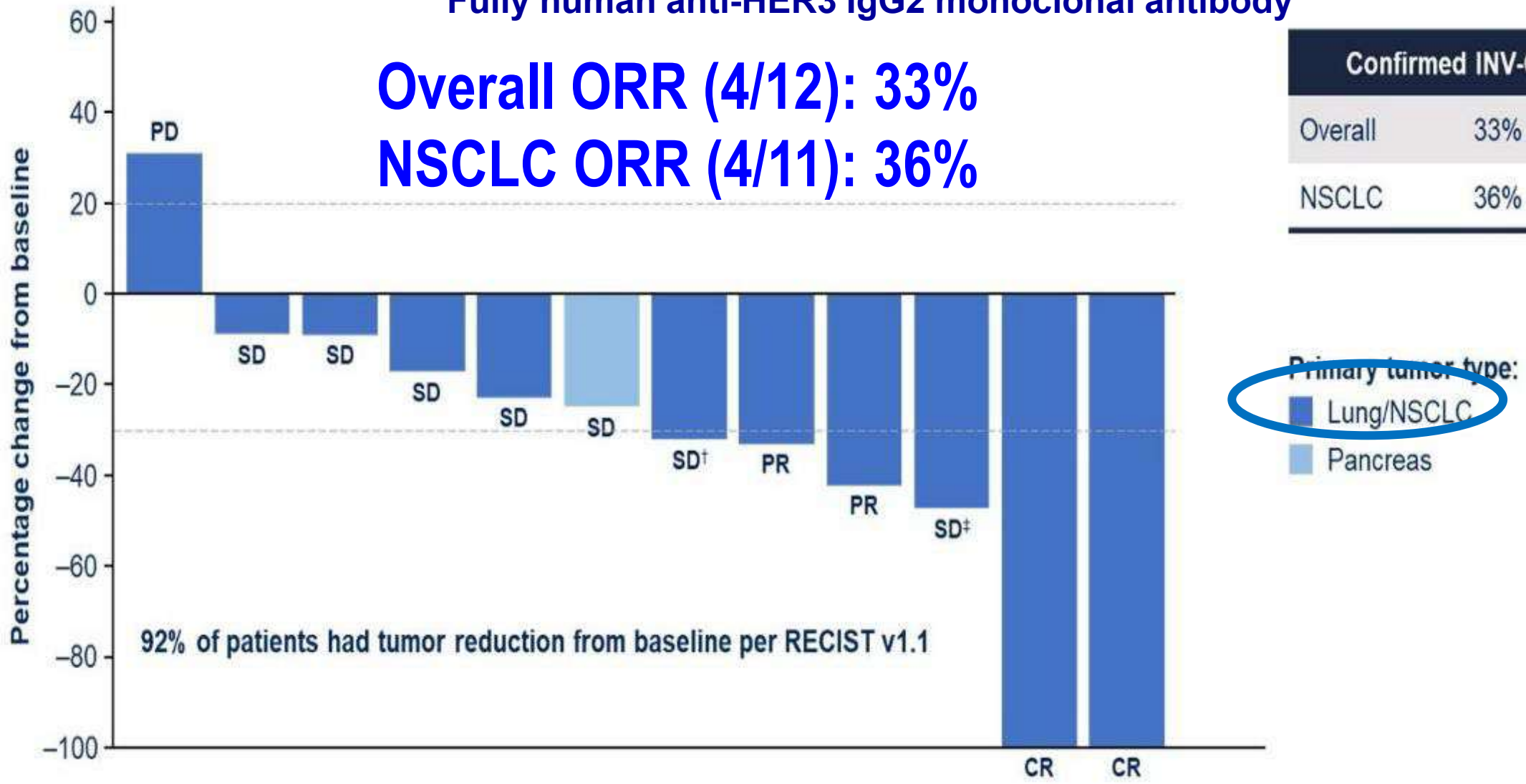
Daniel R.Carrizosa et al, ASCO 2022

Seribantumab in solid tumors with NRG1 fusions
(CRESTON, phase 2 study)

Fully human anti-HER3 IgG2 monoclonal antibody

Overall ORR (4/12): 33%
NSCLC ORR (4/11): 36%

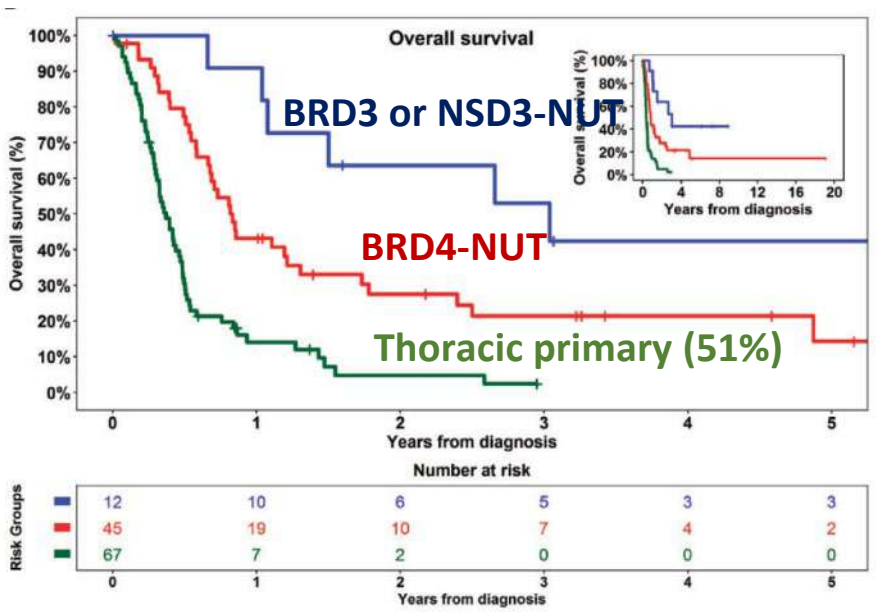
Confirmed INV-ORR	
Overall	33% (4/12)
NSCLC	36% (4/11)

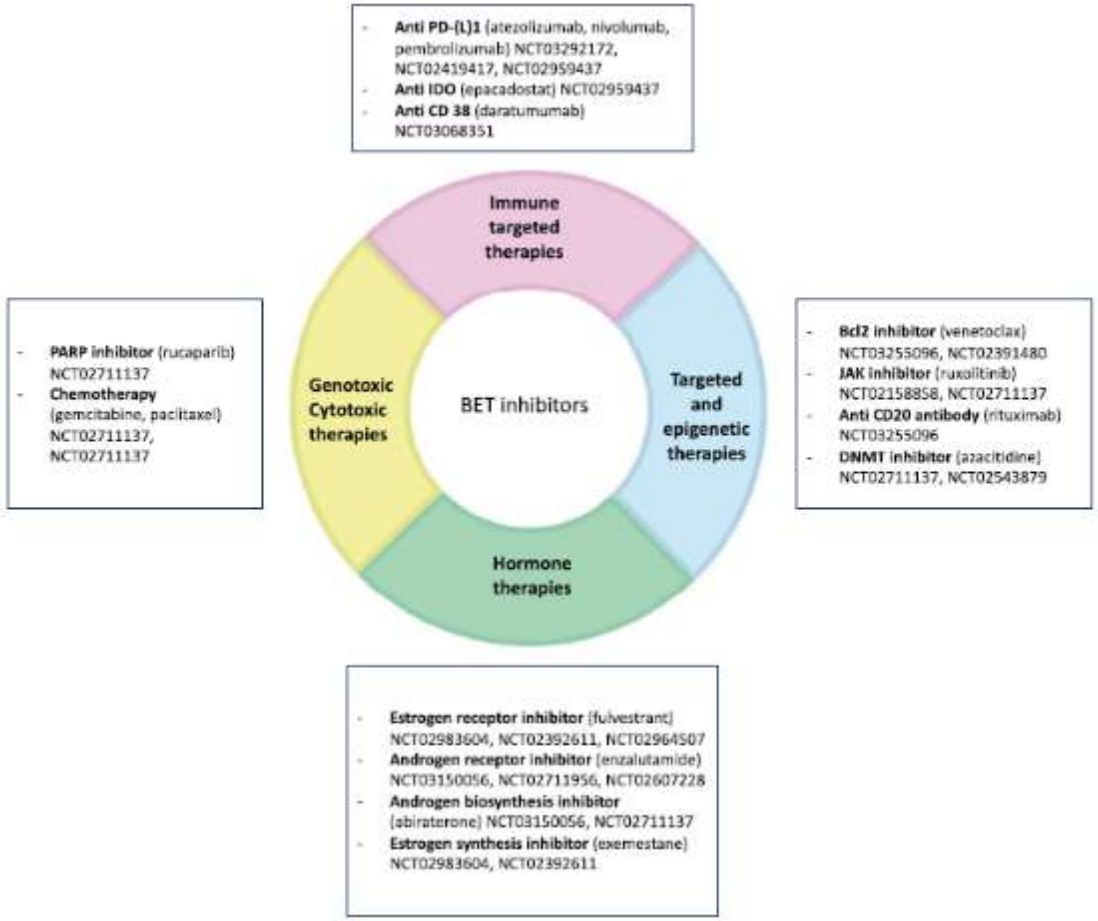


Daniel R.Carrizosa et al, ASCO 2022

NUT MIDLINE CARCINOMA

- NUT : fusion >90% with BRD4 or BRD3
- IHC NUT positive
- Children and adults, median age 23.6 mo
- Very very rare
- Median OS : 6.5 months





Research programs: Pr B.Besse (Gustave Roussy)

Bauer CCR 2012, Chau JNCI cancer spectrum 2019, Martin-Romano JNCI cancer spectrum 2019

Fusions in NSCLC

- **<u>Fusions restricted to NSCLC :</u>**
- ALK : 3nd generations ALK inhibitors, optimal sequence?
- ROS1 : 2nd generation ROS1 inhibitors are effective!
- RET : 1st generation RET inhibitors are standard of care

- **<u>Fusions in solid tumors, including NSCLC :</u>**
- NTRK: access to TRK inhibitors is a major issue
- NGR1: HER2/3 inhibitors should be offered
- NUT: join research programs!

GREAT ADVANCES HAVE BEEN MADE IN LUNG CANCER THERAPY FOR BRAF, MET AND HER2…

Personalised therapy in advanced-stage NSCLC

Diagnostic workup

1. Multidisciplinary discussion to determine optimal procedure for tissue procedure
2. Biopsy
3. Morphology
4. Review of patient and tumour data

Molecular profiling

Integrated NGS-based assay to detect mutations, amplifications, and translocations

Patient selection / Treatment

EGFR	ALK	ROS1	BRAF	MET	RET	NTRK1/2/3	HER2	KRAS^{G12C}	NRG1
Gefitinib, erlotinib, afatinib, dacomitiinb osimertinib	Crizotinib ❶ Alectinib ❶ Ceritinib ❶ Brigatinib ❶ Lorlatinib ❶v TPX-0131 NVL-655	Crizotinib ❶ Entrectinib ❶ Ceritinib Lorlatinib Repotrectinib Taletrectinib NVL-520	Dabrafenib ❶ + trametinib Vemurafenib Encorafenib +Binimetinib	Crizotinib Cabozantinib Capmatinib ❶ Tepotinib ❶ Savolitinib Merestinib Glesatinib Amivantamab	Cabozantinib Vandetanib Sunitinib Lenvetanib Alectinib Ponatinib Selpercatinib ❶ Pralsetinib ❶ TPX-0046 LOXO-26° TAS0953 EP0031 APS03118	Entrectinib ❶ Larotrectinib ❶ Selitrectinib Repotrectinib Taletrectinib ICP-723	Neratinib+/- Temsirolimus Afatinib Dacomatinib Poziotinib Pyrotinib TAK-788 Trastuzumab TDM-1 Trastuzumab-Deruxtecan ❶ Zongertinib BAY292088	Sotorasib ❶ Adagrasib JNJ746 → NRG1 → Afatinib Seribantumab Zenocutuzumab	Zenocutuzumab Seribantumab

❶ EMA approved

Therapy switch/combination based on re-biopsies or liquid therapy

THANK YOU !

Benjamin BESSE
Thierry LE CHEVALIER
Fabrice BARLESI
Jordi REMON
Charles NALTET
Anas GAZZAH
Pernelle LAVAUD
Pamela ABDAYEM
Mihaela ALDEA
Maxime FRELAUT
Cécile LE PECHOUX
Angéla BOTTICELLA
Antonin LEVY

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