ALK, RET and ROS-1

Updates to Targeted Therapy in NSCLC

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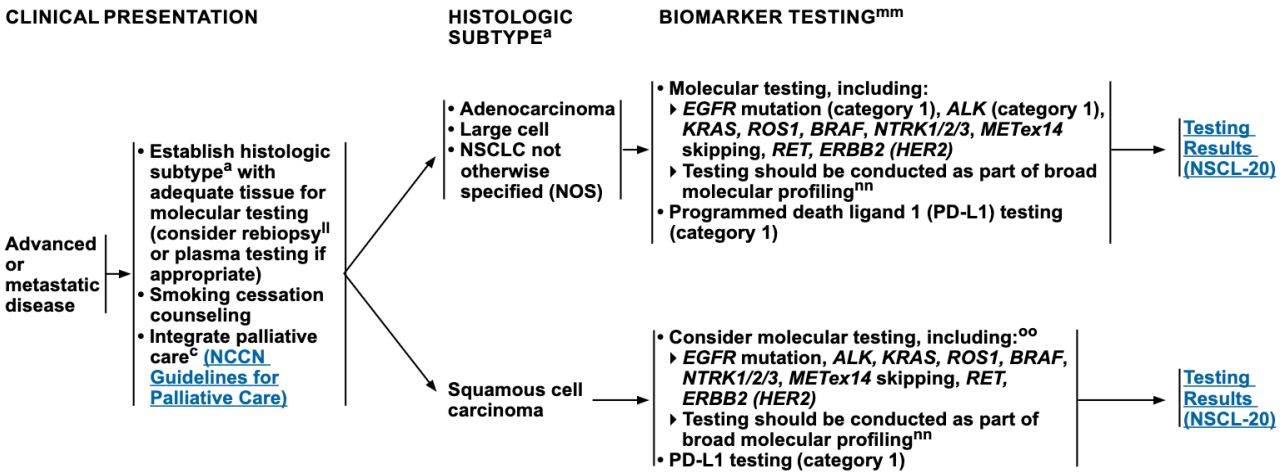
Molecular Testing

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2024
Non-Small Cell Lung Cancer



[a] Principles of Pathologic Review (NSCL-A).

[c] Temel JS, et al. N Engl J Med 2010;363:733-742.

[ll] Complete genotyping for *EGFR*, *KRAS, ALK*, *ROS1*, *BRAF*, *NTRK1/2/3, MET, RET,* and *ERBB2 (HER2)* via biopsy and/or plasma testing. Combinations of tissue and plasma testing, either concurrently or in sequence are acceptable. Concurrent testing can improve time to test results and should be considered in the appropriate clinical situation. Negative results (meaning absence of definitive driver mutation) by one method suggests the use of a complementary method. If a clinically actionable marker is found, it is reasonable to start therapy based on the identified marker. Treatment is guided by available results and, if unknown, these patients are treated as though they do not have driver oncogenes.

[mm] Principles of Molecular and Biomarker Analysis (NSCL-H).

Adjuvant Treatment in ALK+ NSCLC

The ALINA study

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NCCN Guidelines Version 2.2024
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

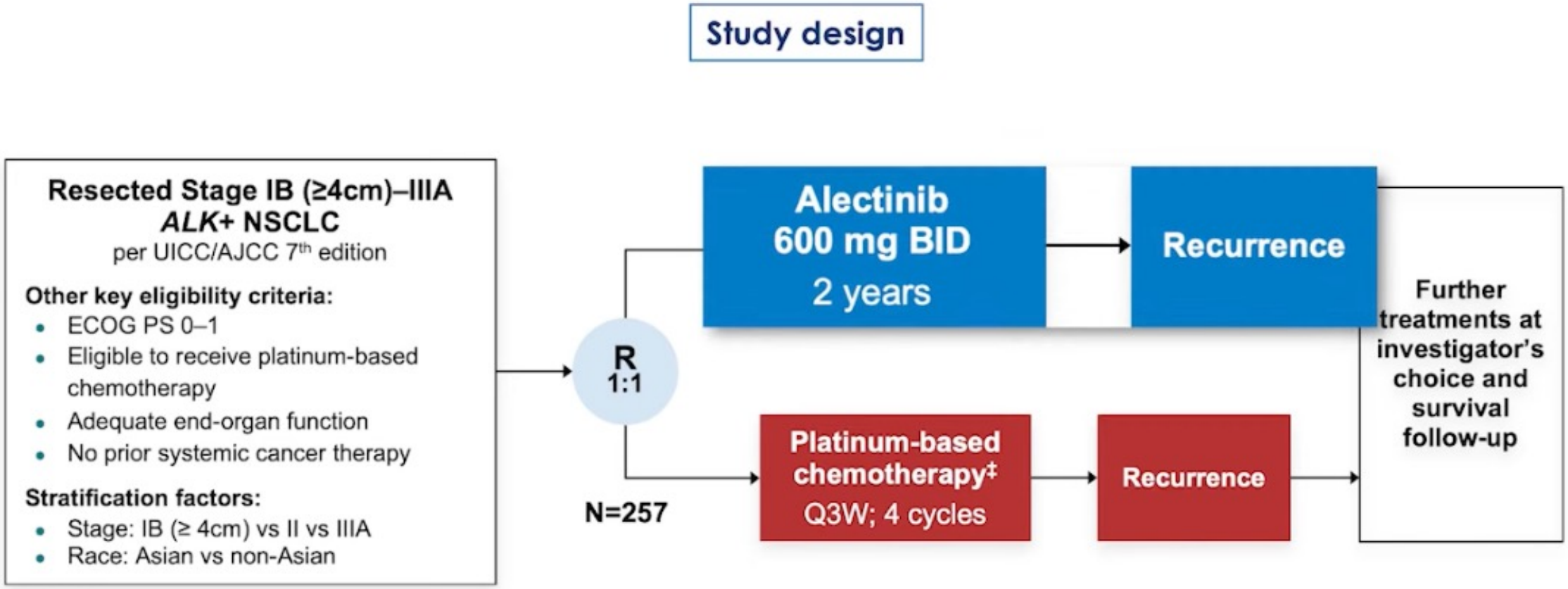
PERIOPERATIVE SYSTEMIC THERAPY

- **Neoadjuvant Systemic Therapy in Patients Who Are Candidates for Immune Checkpoint Inhibitors, see below.**
- **Neoadjuvant Systemic Therapy for Patients Who Are Not Candidates for Immune Checkpoint Inhibitors**
- **Adjuvant Chemotherapy**
- **Systemic Therapy Following Previous Neoadjuvant or Adjuvant Systemic Therapy**

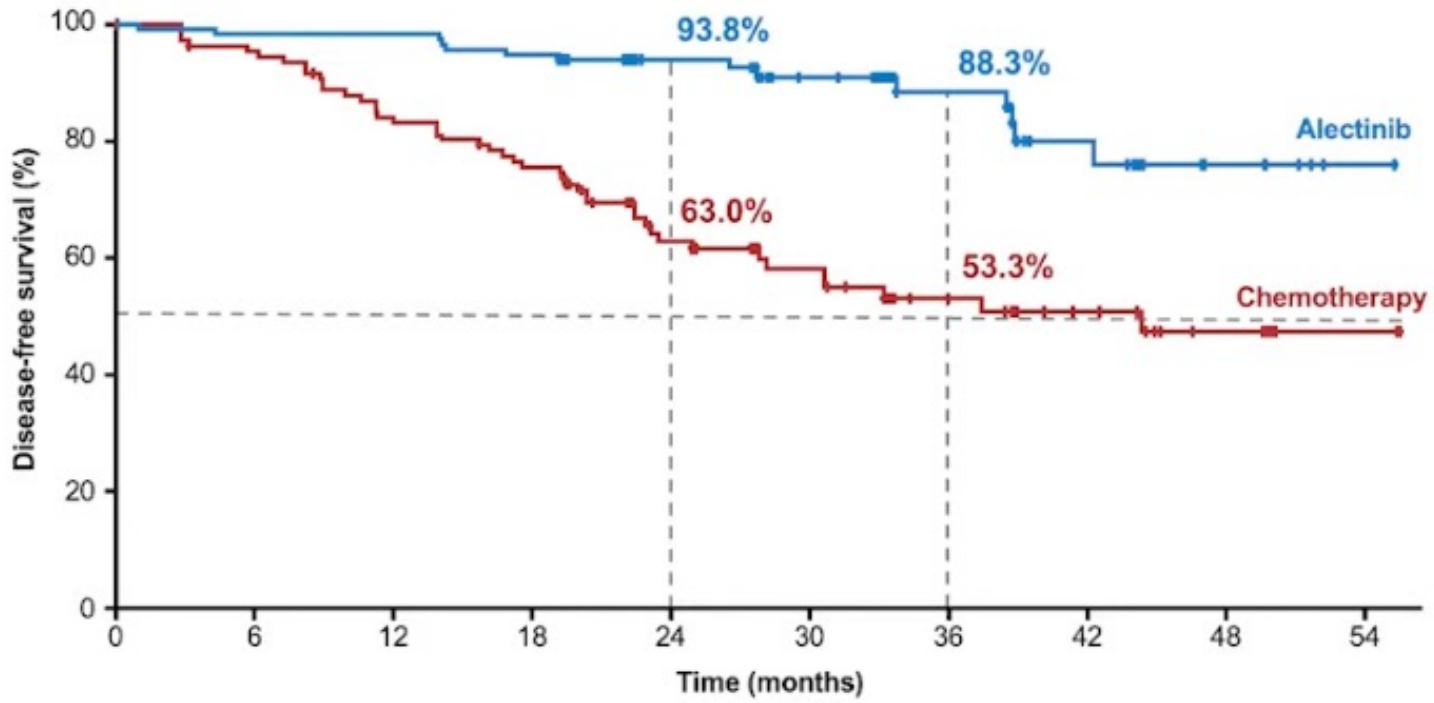
Neoadjuvant Systemic Therapy

- **All patients should be evaluated for preoperative therapy, with strong consideration for nivolumab or pembrolizumab + chemotherapy for those patients with tumors ≥4 cm or node positive and no contraindications to immune checkpoint inhibitors.[a] Otherwise refer to the Neoadjuvant Systemic Therapy for Patients Who Are Not Candidates for Immune Checkpoint Inhibitors.**
- **Test for PD-L1 status, *EGFR* mutations, and *ALK* rearrangements (stages IB–IIIA, IIIB [T3,N2]). PD-L1 status can be incorporated with other clinical factors to determine patients who may benefit from induction chemotherapy and immunotherapy. Principles of Molecular and Biomarker Analysis (NSCL-H).**
- **Clinical trials for neoadjuvant nivolumab + chemotherapy excluded patients harboring *EGFR* mutations and *ALK* rearrangements. Thus, exclusion of these biomarkers, at a minimum, is recommended prior to consideration for neoadjuvant nivolumab + chemotherapy.**
- **After surgical evaluation, patients likely to receive adjuvant chemotherapy may be treated with induction systemic therapy as an alternative.**

Study design



Disease-free survival
Stage II-IIIA



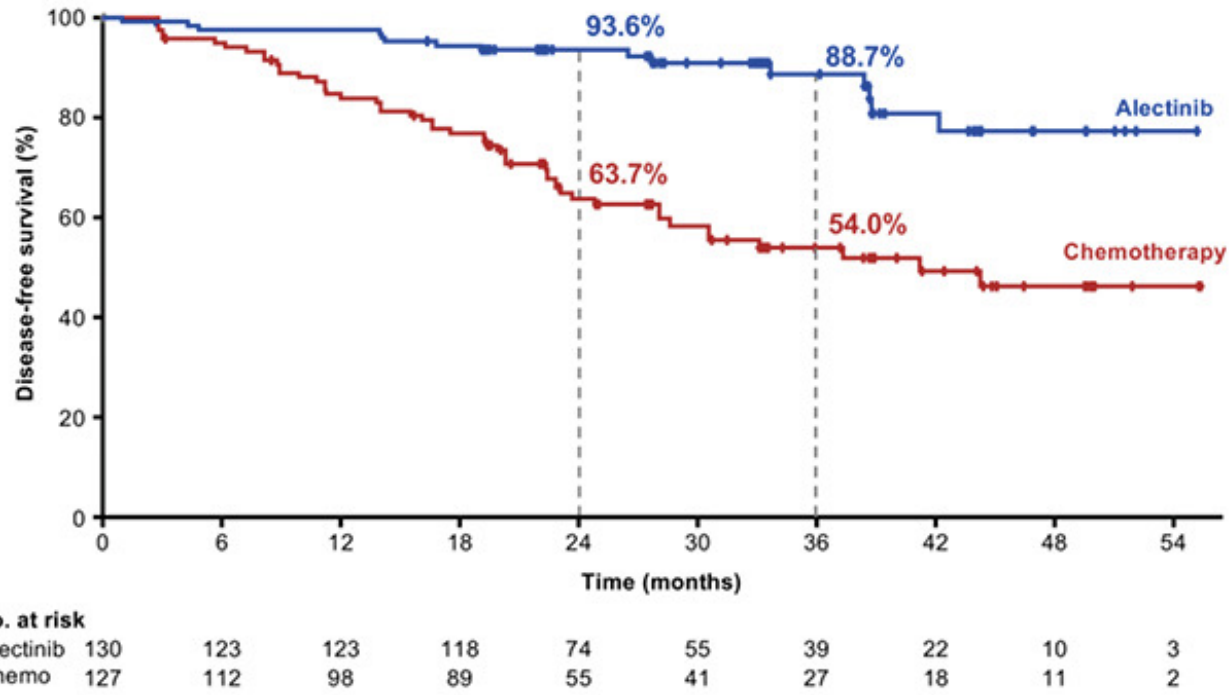
No. at risk

Alectinib	116	111	111	107	67	49	35	21	10	3
Chemo	115	102	88	79	48	35	23	17	10	2

	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)*



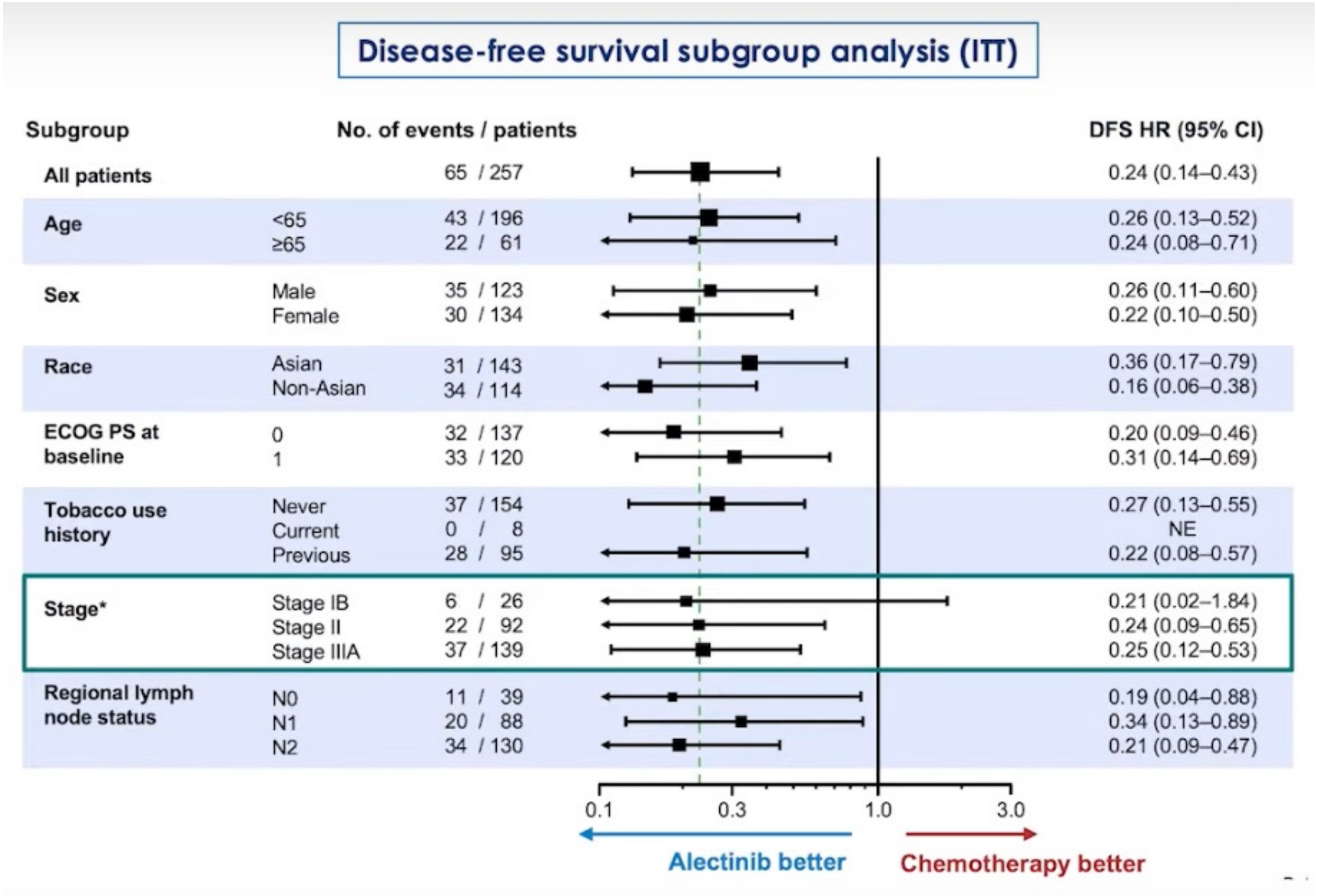
	Alectinib (N=130)	Chemotherapy (N=127)
Patients with event Death Recurrence	15 (12%) 0 15	50 (39%) 1 49
Median DFS, months (95% CI)	Not reached	41.3 (28.5, NE)
DFS HR (95% CI)	**0.24** (0.13, 0.43) p‡<0.0001	

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

Data cut-off: 26 June 2023; *Per UICC/AJCC 7th edition; ‡Stratified log rank; §2 events in the alectinib arm, 4 events in the chemo arm; one patient in chemo died but was censored due to incomplete date of death recorded. DFS defined as the time from randomisation to the first documented recurrence of disease or new primary NSCLC as determined by the investigator, or death from any cause, whichever occurs first.

Disease-free survival subgroup analysis (ITT)

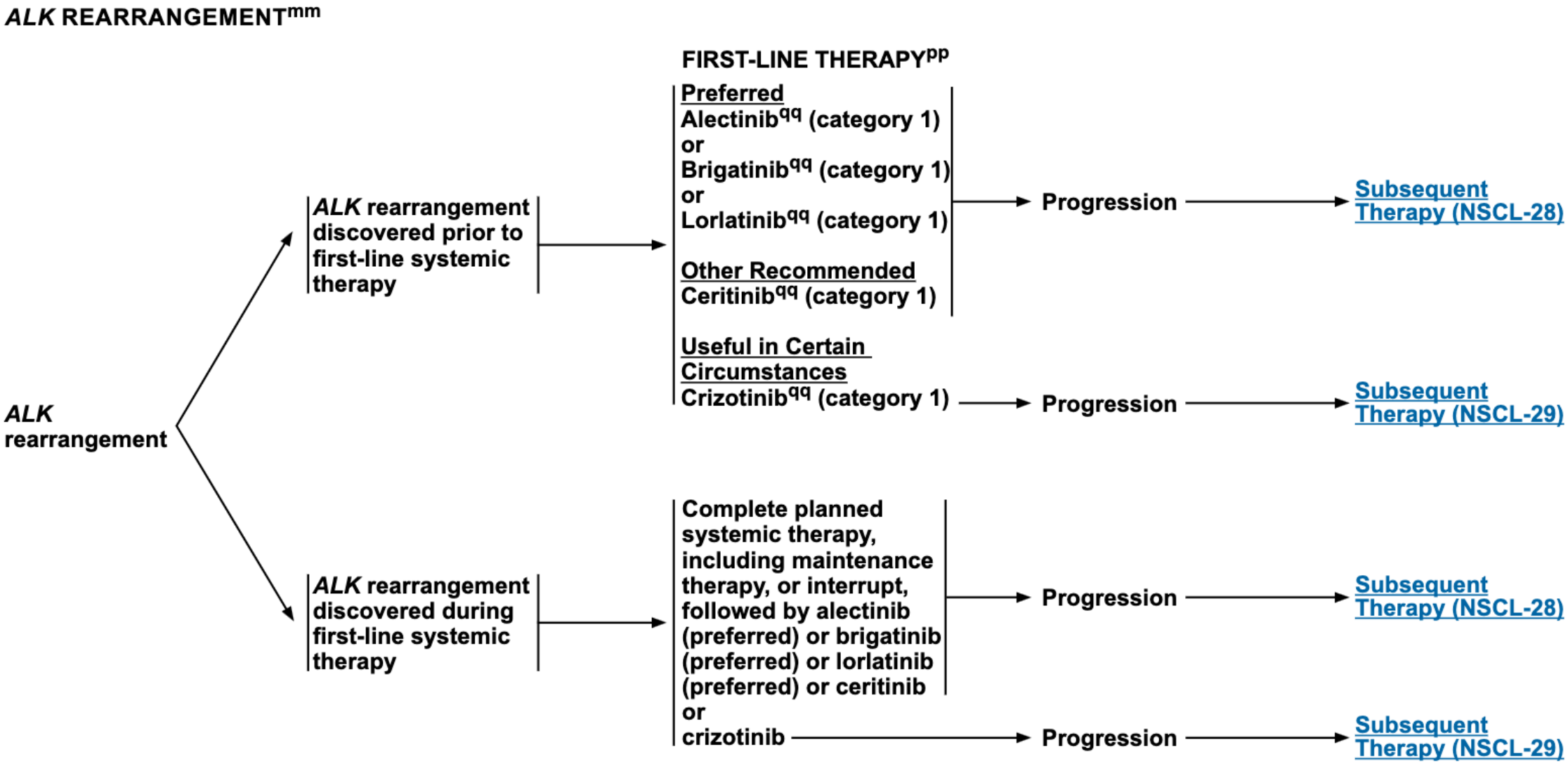


Safety summary

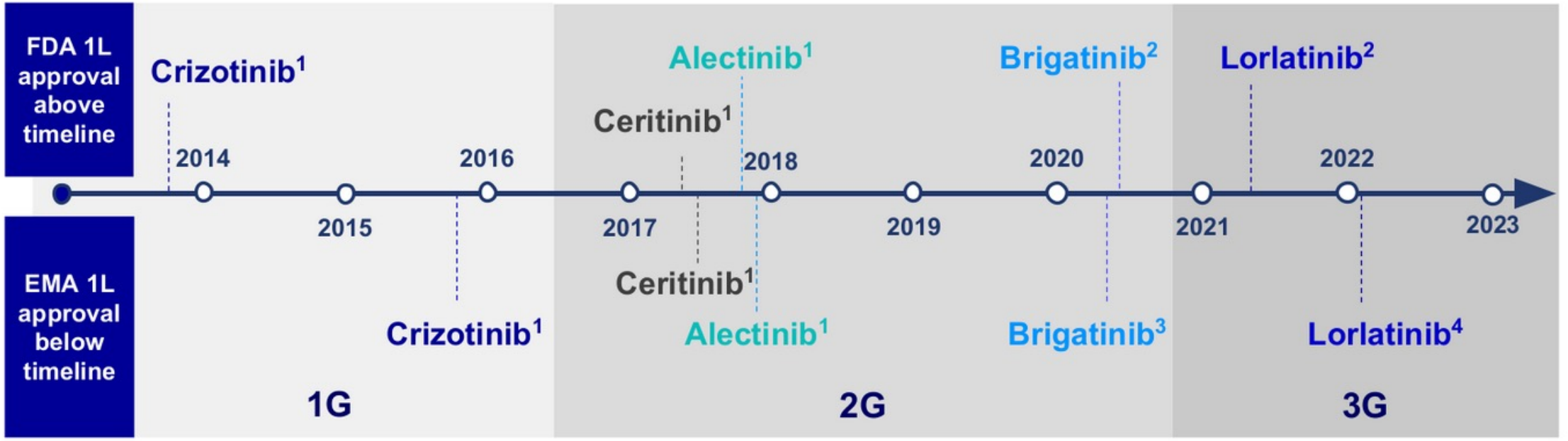
	Alectinib (n=128)	Chemotherapy (n=120)
Median treatment duration	**23.9 months**	**2.1 months**
Patients with any AEs, %	**98**	**93**
Grade 3/4 AEs	30	31
Grade 5 AEs	0	0
Serious AEs	13	8
Treatment-related serious AEs	2	7
AEs leading to dose reduction	26	10
AEs leading to dose interruption	27	18
AEs leading to treatment withdrawal	5	13

- At data cut off, **20.3%** of patients in the alectinib arm were ongoing treatment

Metastatic Treatment in ALK+ NSCLC


ALK REARRANGEMENT[mm]
FIRST-LINE THERAPY[pp]
ALK rearrangement
ALK rearrangement discovered prior to first-line systemic therapy
Preferred
Alectinib[qq] (category 1)
or
Brigatinib[qq] (category 1)
or
Lorlatinib[qq] (category 1)
Other Recommended
Ceritinib[qq] (category 1)
Useful in Certain Circumstances
Crizotinib[qq] (category 1)
Progression
Subsequent Therapy (NSCL-28)
Progression
Subsequent Therapy (NSCL-29)
ALK rearrangement discovered during first-line systemic therapy
Complete planned systemic therapy, including maintenance therapy, or interrupt, followed by alectinib (preferred) or brigatinib (preferred) or lorlatinib (preferred) or ceritinib or crizotinib
Progression
Subsequent Therapy (NSCL-28)
Progression
Subsequent Therapy (NSCL-29)

Current 1L treatment landscape of *ALK*+ NSCLC



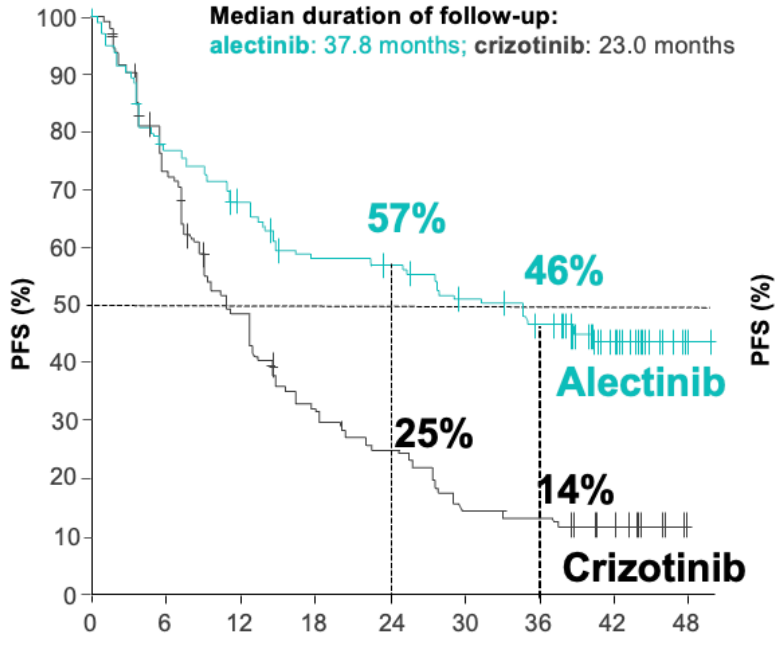
Increasing potency against ALK, better penetration of the BBB, and broader coverage of secondary *ALK* resistance mutations[5,6]

PFS outcomes from ALK TKI clinical trials

	ALEX[1,2]		ALTA-1L[3]		CROWN[4]	
	Alectinib (n=152)	Crizotinib (n=151)	Brigatinib (n=137)	Crizotinib (n=138)	Lorlatinib (n=149)	Crizotinib (n=147)
Median follow-up, months	18.6	17.6	40.4	15.2	36.7	29.3
Median PFS, months – IRC	**25.7**	**10.4**	**24.0**	**11.1**	**NR**	**9.3**
HR (95% CI)	**0.50 (0.36–0.70)**		**0.48 (0.35–0.66)**		**0.27 (0.18–0.39)**	
Median follow-up, months	37.8	23.0	40.4	15.2	36.7	29.3
Median PFS, months – INV	**34.8**	**10.9**	**30.8**	**9.2**	**NR**	**9.1**
HR (95% CI), months	**0.43 (0.32–0.58)**		**0.43 (0.31–0.58)**		**0.19 (0.13–0.27)**	
Treatment beyond progression	Not allowed		Allowed		Allowed	

Kaplan–Meier curves of PFS for alectinib, brigatinib, and lorlatinib

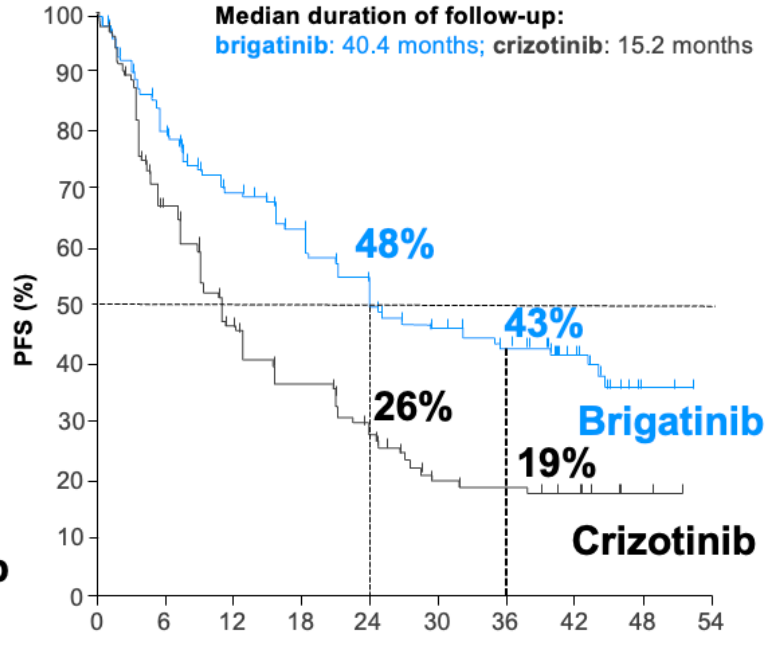
ALEX (alectinib)[1]



No. at risk									
Alectinib	152	113	98	81	79	69	61	39	3
Crizotinib	151	104	65	43	33	19	17	11	NE

Figure adapted from Mok T, et al. 2020.

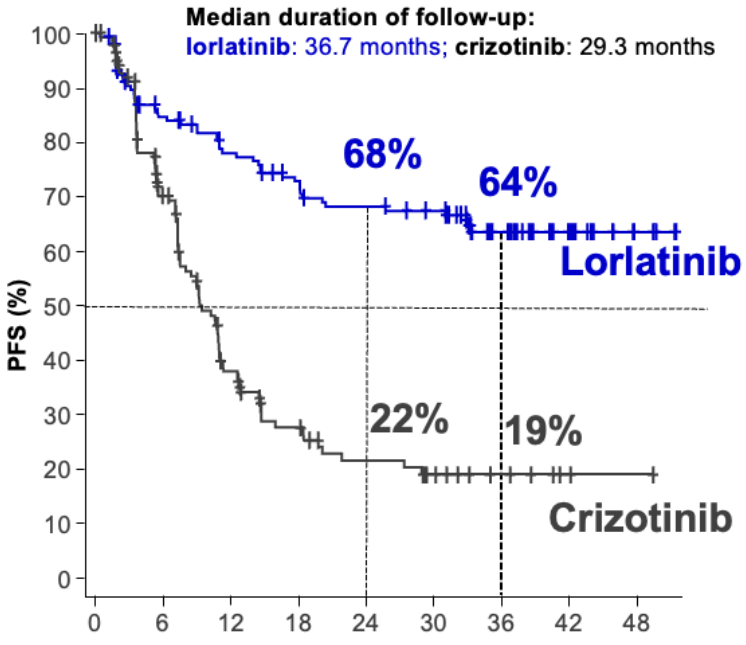
ALTA-1L (brigatinib)[2,3]



No. at risk									
Brigatinib	137	97	84	75	59	53	47	30	2
Crizotinib	138	79	49	37	26	18	17	8	2

Figure adapted from Camidge DR, et al. 2020 & Camidge DR, et al. 2021.

CROWN (lorlatinib)[4]



No. at risk									
Lorlatinib	149	118	105	95	88	83	50	23	4
Crizotinib	147	85	40	25	17	11	6	2	1

Figure adapted from Solomon BJ, et al. 2023.

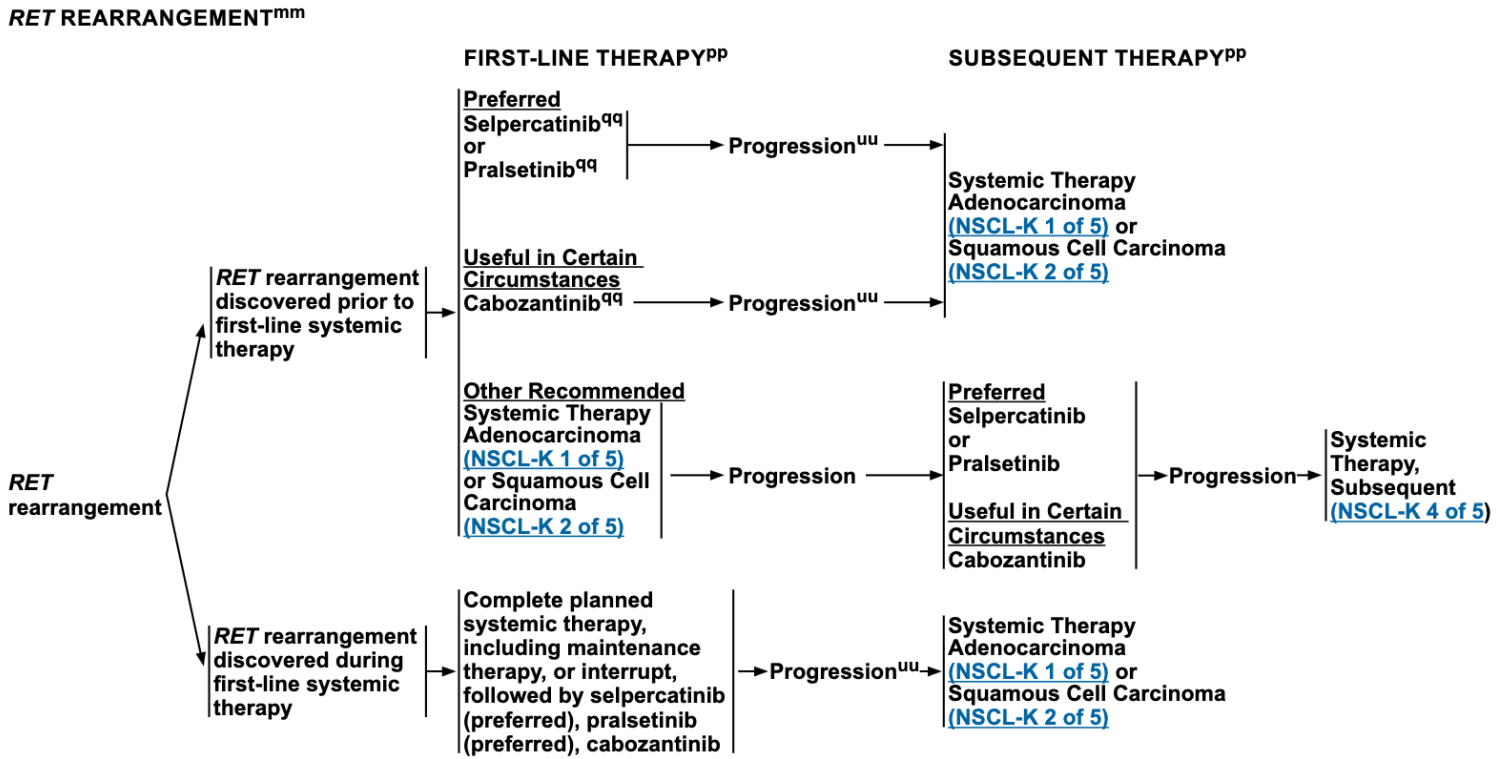
IC efficacy of ALK TKIs in patients with measurable brain metastases at baseline*

Drug	Study	IC-ORR (%)	IC-CR (%)	Brain PD/year (%)
Alectinib	ALEX[1]	81	38	9.4
Brigatinib	ALTA-1L[2,3]	78	28	8.8
Lorlatinib	CROWN[4,5]	83	72	2.8
Crizotinib	Control arm[1–5]	23–50	≤8	≥18.8

Patients experience:

- More brain metastases with other drugs than lorlatinib[1,2,4]
- More symptoms after diagnosis of brain metastases than before[6]

RET Fusion Positive NSCLC



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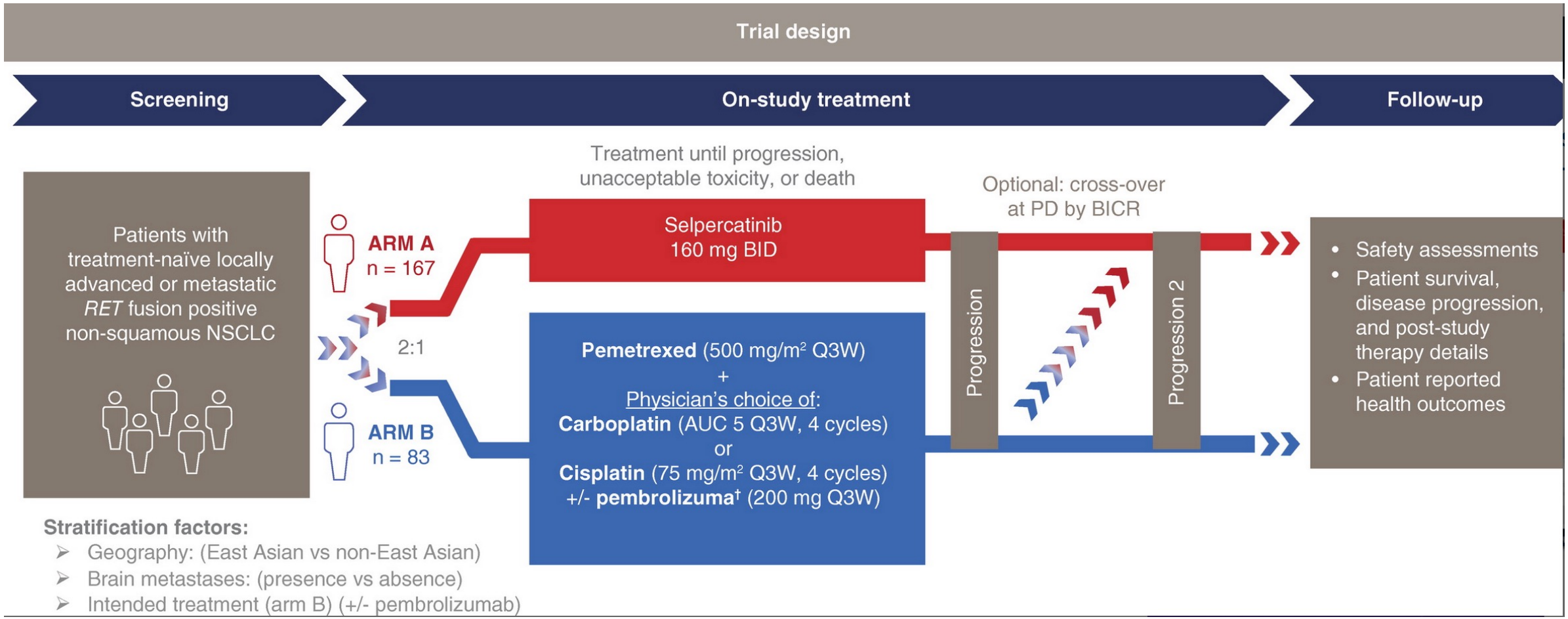
RESEARCH SUMMARY

First-Line Selpercatinib or Chemotherapy and Pembrolizumab in *RET* Fusion–Positive NSCLC

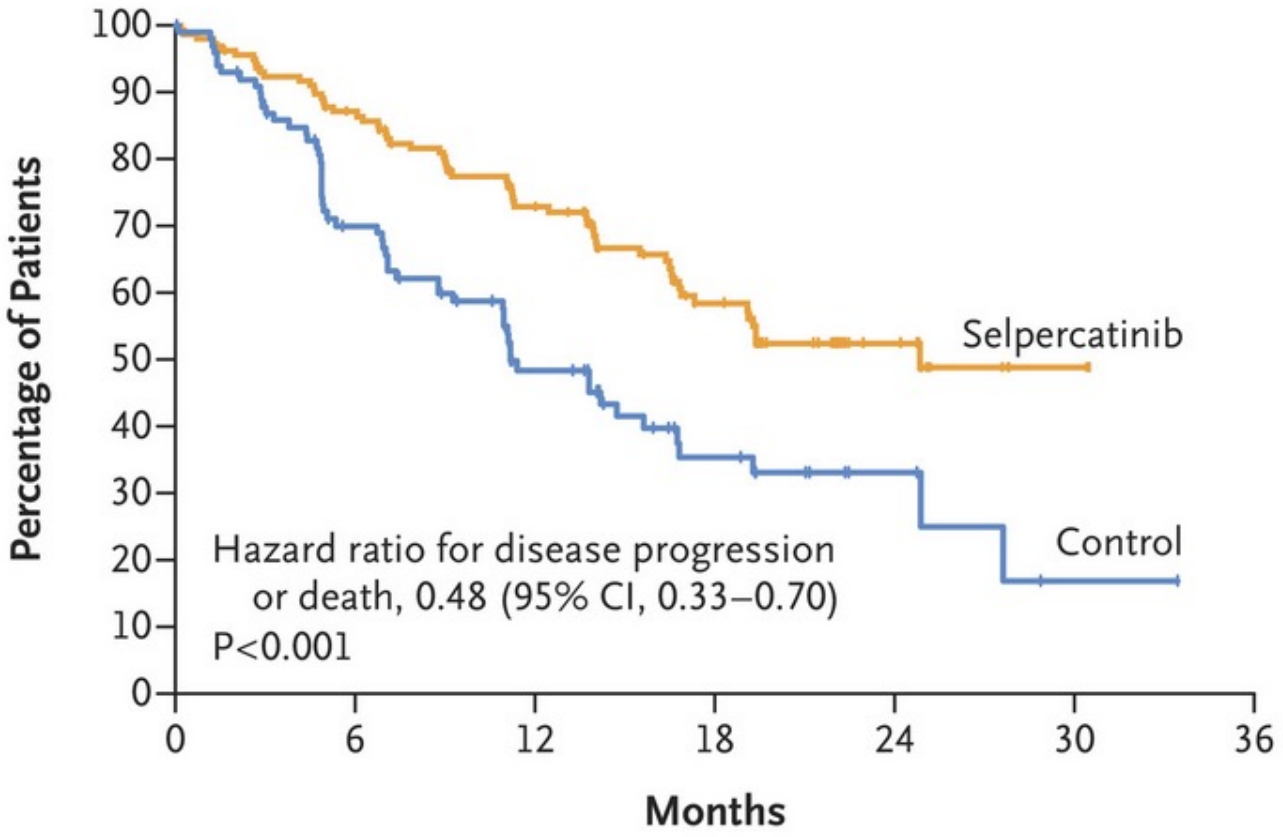
Zhou C et al. DOI: 10.1056/NEJMoa2309457

Review of 1st line use of
Selpercatinib versus Chemotherapy/Pembrolizumab
in
RET fusion positive NSCLC



Libretto-431

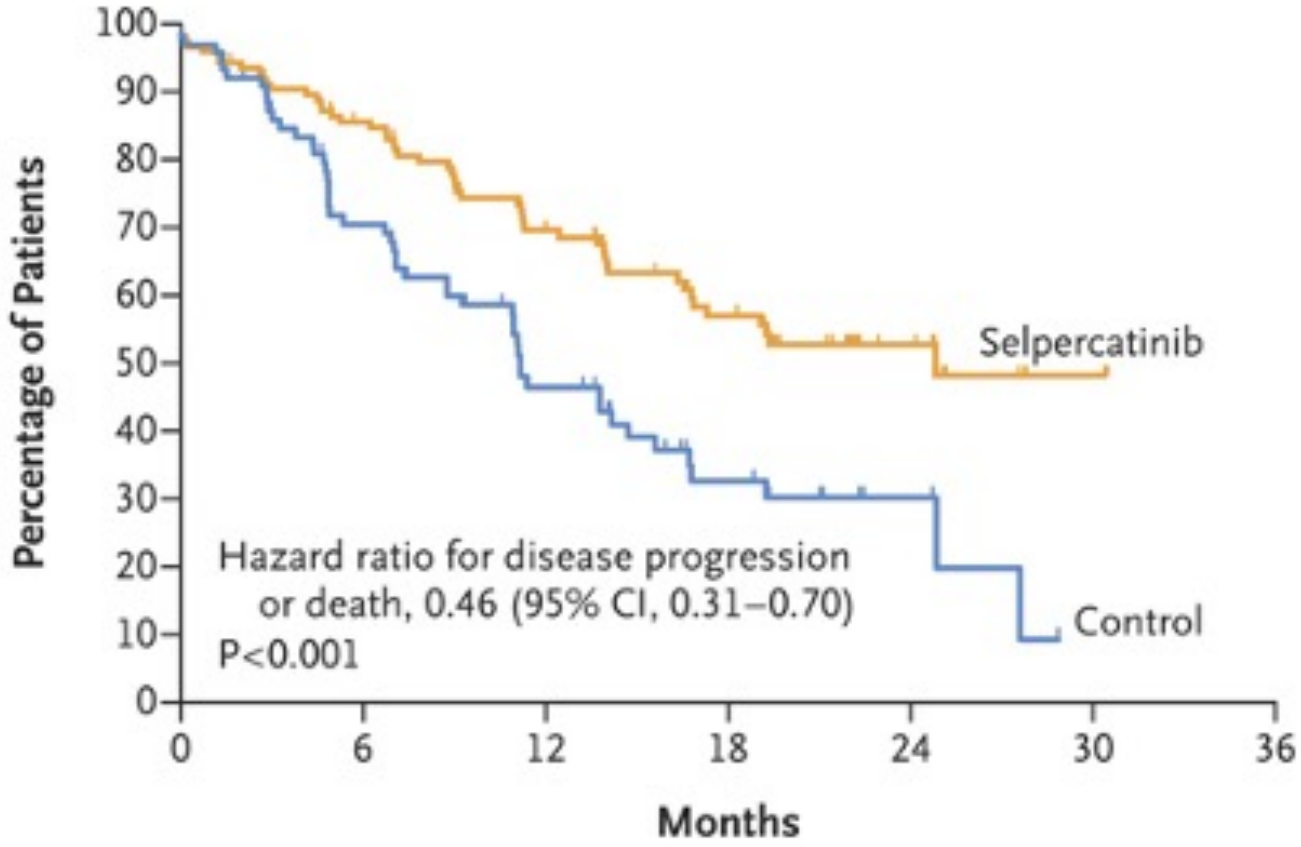
PFS by BICR (Overall ITT)



No. at Risk							
Selpercatinib	159	130	90	52	18	3	0
Control	102	63	33	16	7	1	0

C Zhou et al. N Engl J Med 2023;389:1839-1850.

PFS by BICR (ITT/ pembrolizumab)

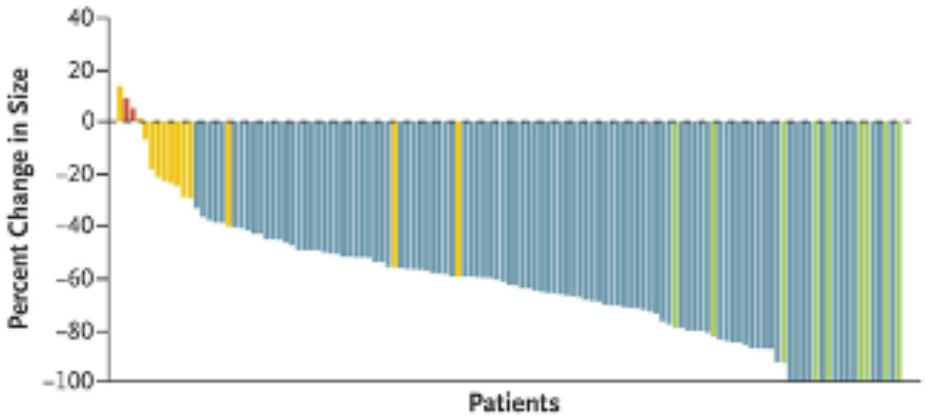


No. at Risk							
Selpercatinib	129	105	72	44	16	2	0
Control	83	55	29	15	6	0	0

C Zhou et al. N Engl J Med 2023;389:1839-1850.

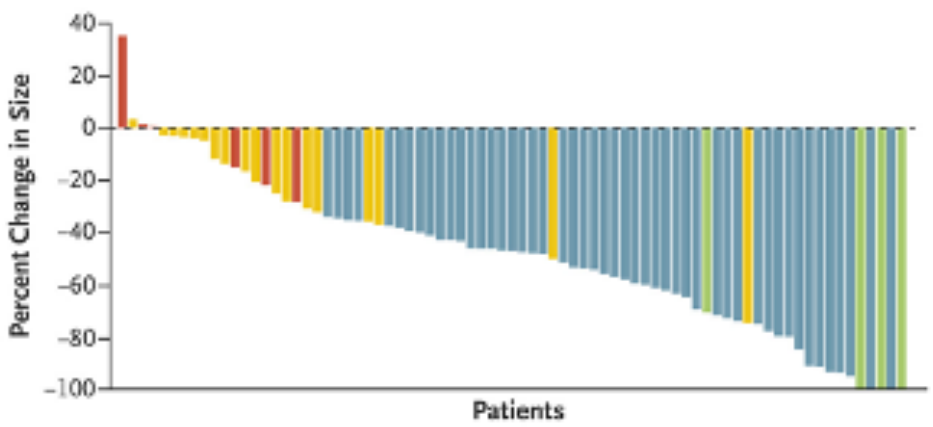
Tumor Response

Selpercatinib



n=123

Control Group

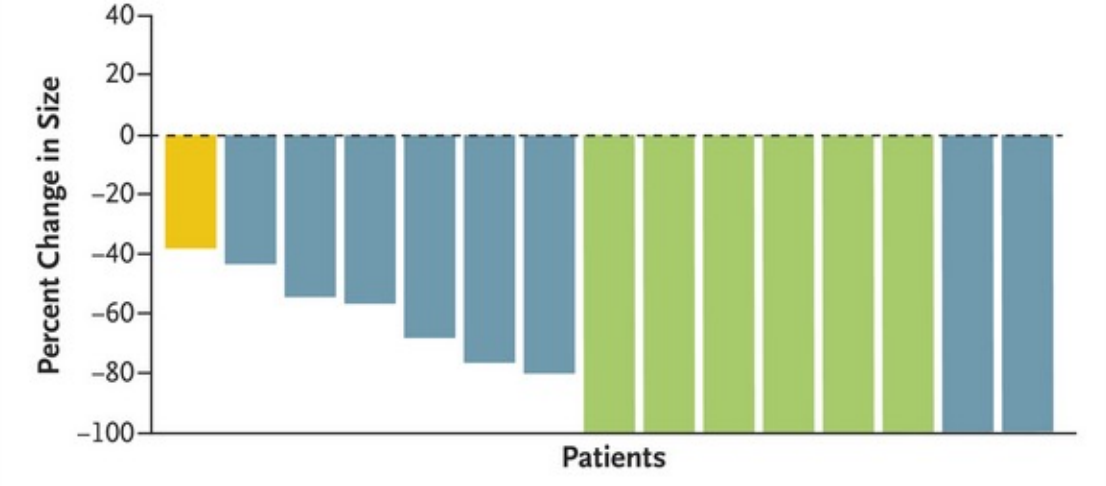


n=77

C Zhou et al. N Engl J Med 2023;389:1839-1850.

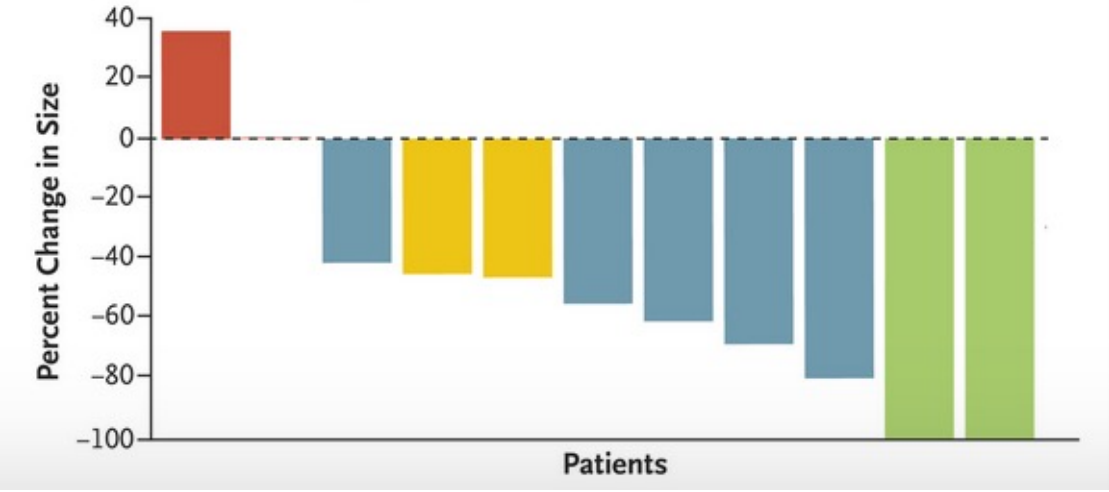
Intracranial Tumor Responses

Selpercatinib



n=15

Control Group



n=11

C Zhou et al. N Engl J Med 2023;389:1839-1850.

No apparent difference in PFS between chemo vs chemo/pembro results

Table 2. Summary of End Points Assessed by Blinded Independent Central Review.*

End Point	Intention-to-Treat–Pembrolizumab Population		Overall Intention-to-Treat Population	
	Selpercatinib (N=129)	Control (N=83)	Selpercatinib (N=159)	Control (N=102)
Progression-free survival — mo				
Median progression-free survival (95% CI)	24.8 (16.9–NE)	11.2 (8.8–16.8)	24.8 (17.3–NE)	11.2 (8.8–16.8)
Median duration of follow-up (95% CI)	19.4 (16.7–19.7)	18.9 (14.2–22.3)	19.4 (16.7–19.6)	16.5 (13.6–21.0)
Objective response (95% CI) — % of patients	84 (76–90)	65 (54–75)	84 (77–89)	63 (53–72)
Best overall response — no. (%)				
Complete response	9 (7)	5 (6)	12 (8)	5 (5)
Partial response	99 (77)	49 (59)	121 (76)	59 (58)
Stable disease	14 (11)	20 (24)	17 (11)	26 (25)
Progressive disease	2 (2)	5 (6)	2 (1)	7 (7)
Not evaluable	5 (4)	4 (5)	7 (4)	5 (5)
Duration of response				
Patients with a response — no.	108	54	133	64
Patients with a response and censored data — no. (%)	74 (69)	25 (46)	43 (32)	31 (48)
Median duration of response (95% CI) — mo	24.2 (17.9–NE)	11.5 (9.7–23.3)	24.2 (17.9–NE)	12.0 (9.7–23.3)
Median duration of follow-up (95% CI) — mo	18.0 (16.5–19.5)	14.6 (11.2–19.8)	17.9 (15.7–18.7)	12.7 (11.1–16.6)

* Percentages may not total 100 because of rounding. Confidence intervals have not been adjusted for multiplicity and cannot be used to infer treatment effects. Efficacy outcomes were assessed with the use of Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, and were confirmed by blinded independent radiologic review. NE denotes not estimable.

PFS (ITT pembrolizumab)

24.8 vs 11.2 mts

PFS (ITT)

24.8 vs. 11.2 mts

C Zhou et al. N Engl J Med 2023;389:1839-1850.

LFT abnormality

Hypertension

QTc Prolongation

Table 3. Adverse Events That Occurred during Treatment (Safety Population).*

Event	Selpercatinib (N=158)		Control (N=98)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Any event	158 (100)	111 (70)	97 (99)	56 (57)
AST increase	97 (61)	20 (13)	39 (40)	1 (1)
ALT increase	95 (60)	35 (22)	39 (40)	3 (3)
Hypertension	76 (48)	32 (20)	7 (7)	3 (3)
Diarrhea	70 (44)	2 (1)	24 (24)	2 (2)
Edema	65 (41)	4 (3)	27 (28)	0
Dry mouth	62 (39)	0	6 (6)	0
Blood bilirubin increase	59 (37)	2 (1)	1 (1)	0
Rash	52 (33)	3 (2)	29 (30)	1 (1)
Fatigue	51 (32)	5 (3)	49 (50)	5 (5)
Thrombocytopenia	42 (27)	5 (3)	28 (29)	7 (7)
Abdominal pain	40 (25)	1 (1)	19 (19)	2 (2)
Leukopenia	40 (25)	2 (1)	32 (33)	7 (7)
Blood creatinine increase	39 (25)	2 (1)	17 (17)	1 (1)
Neutropenia	36 (23)	3 (2)	44 (45)	27 (28)
Constipation	34 (22)	0	39 (40)	1 (1)
QT prolongation on ECG	32 (20)	14 (9)	1 (1)	0
Decreased appetite	27 (17)	0	33 (34)	2 (2)
Pyrexia	21 (13)	1 (1)	23 (23)	0
Nausea	20 (13)	0	43 (44)	1 (1)
Vomiting	20 (13)	0	23 (23)	1 (1)
Anemia	18 (11)	2 (1)	58 (59)	10 (10)
Pruritus	16 (10)	0	22 (22)	0

* Shown are events that occurred during treatment in at least 20% of the patients in either group. The terms used to describe the adverse events are adapted from or composites of *Medical Dictionary for Regulatory Activities*, version 25.0, preferred terms. ALT denotes alanine aminotransferase, AST aspartate aminotransferase, and ECG electrocardiogram.

C Zhou et al. N Engl J Med 2023;389:1839-1850.

IASLC 2023 World Conference on Lung Cancer

Repotrectinib in patients with *ROS1* fusion-positive non-small cell lung cancer: update from the pivotal phase 1/2 TRIDENT-1 trial

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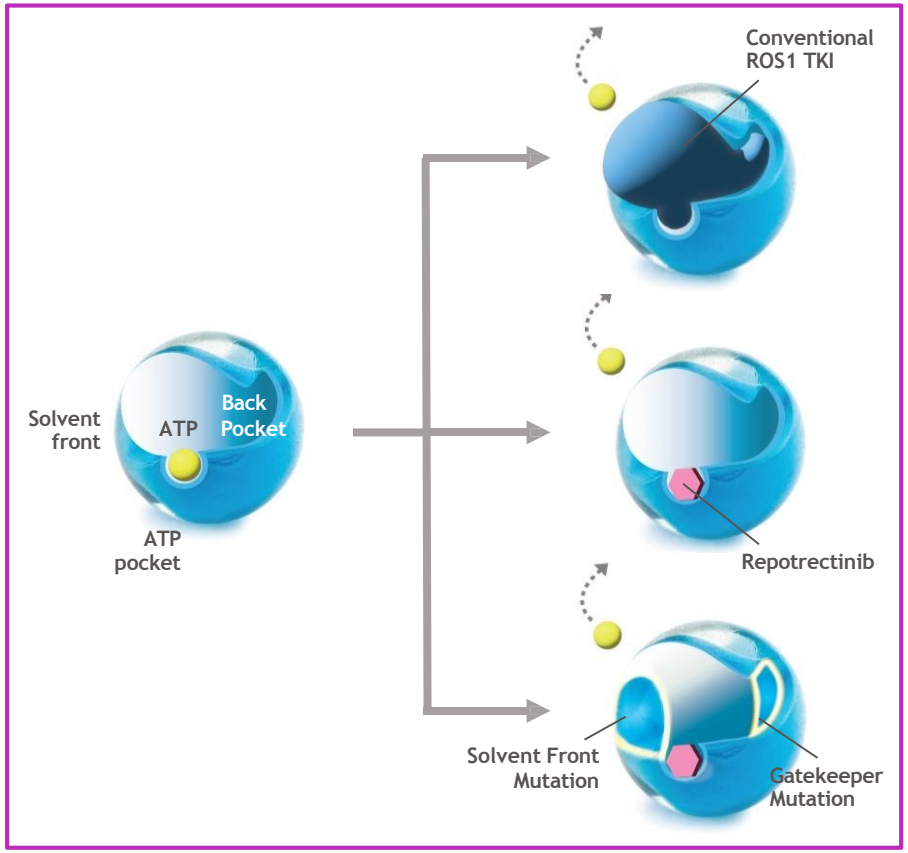
Presentation number OA03.06

Introduction

- *ROS1* oncogenic-driver gene fusions have been identified in up to 2% of NSCLC[1]
  - Standard-of-care ROS1 TKIs, such as crizotinib and entrectinib,[2] result in limited durability of response due to acquired *ROS1* resistance mutations (e.g., G2032R)[3,4]; there is also a need for further improvement in intracranial activity[5,6]
- Repotrectinib is a next-generation ROS1 and TRK TKI with a compact macrocyclic structure designed to improve durability of benefit by[7]:
  - Decreasing the potential for developing *ROS1* resistance mutations
  - Circumventing known *ROS1* resistance mutations
  - Displaying favorable characteristics for enhanced intracranial activity
- In the global, pivotal phase 1/2 TRIDENT-1 trial, repotrectinib demonstrated durable clinical activity in both TKI-naïve and TKI-pretreated patients with *ROS1* fusion-positive (*ROS1*+) advanced NSCLC[8]



- Here, we report a clinical update from the TRIDENT-1 trial (median follow-up: 21.5 to 24 months) in patients with *ROS1*+ NSCLC

1. Bergethon K, et al. *J Clin Oncol* 2012;30:863–870. 2. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer. V.3.2023. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed June 12, 2023. 3. Dziadziuszko R, et al. *Mol Oncol* 2022;16:2000–2014. 4. Lin JJ, et al. *Clin Cancer Res* 2021;27:2899–2909. 5. Landi L, et al. *Clin Cancer Res* 2019;25:7312–7319. 6. Patil T, et al. *J Thorac Oncol* 2018;13:1717–1726. 7. Drilon A, et al. *Cancer Discov* 2018;8:1227–1236. 8. Cho BC, et al. Oral presentation at the EORTC-NCI-AACR (ENA) Symposium; October 26-28, 2022; Barcelona, Spain. Abstract 2LBA.

TRIDENT-1: overview of phase 1/2 trial design

Phase 1/2 patient eligibility

- Locally advanced or metastatic solid tumors harboring *ROS1* or *NTRK1-3* gene fusions[a]
- Asymptomatic CNS metastases allowed

Phase 1[b] dose escalation cohorts

RP2D
160 mg QD x 14 days, then 160 mg BID[c]

Phase 2 dose expansion cohorts[d]

***ROS1*+ advanced NSCLC**

EXP-1	EXP-2	EXP-3	EXP-4
ROS1 TKI-naïve	1 prior ROS1 TKI AND 1 prior platinum-based chemo	2 prior ROS1 TKIs AND no prior chemo	1 prior ROS1 TKI AND no prior chemo
(n = 110)[e]	(n = 60)[e]	(n = 40)[e]	(n = 60)[e]

Phase 2 (*ROS1+* advanced NSCLC cohorts)

Primary endpoint

cORR by BICR using RECIST v1.1

Key secondary endpoints

- DOR,[f] CBR,[f] TTR[f]
- cORR[e] in TKI-pretreated patients harboring *ROS1* G2032R
- PFS,[f] OS
- icORR by mRECIST v1.1 in patients with measurable brain metastases
- Safety, patient-reported outcomes

- Primary efficacy population includes patients pooled from phase 1[g] and 2 who began repotrectinib treatment approximately 14 months prior to data cutoff date of December 19, 2022

Data cutoff date: December 19, 2022.
[a]*ROS1* or *NTRK1-3* gene fusions were identified by tissue-based local testing using NGS, qPCR, or FISH with prospective confirmation by a central diagnostic laboratory. [b]Phase 1 primary endpoints: DLT, MTD, RP2D. [c]Based on tolerability. [d]Trial design includes 2 additional cohorts of patients with *NTRK* fusions (not presented here). [e]N's for expansion cohorts indicate enrollment targets. [f]By RECIST v1.1. [g]Patients from phase 1 received 40 mg QD to 240 mg QD and 200 mg BID.

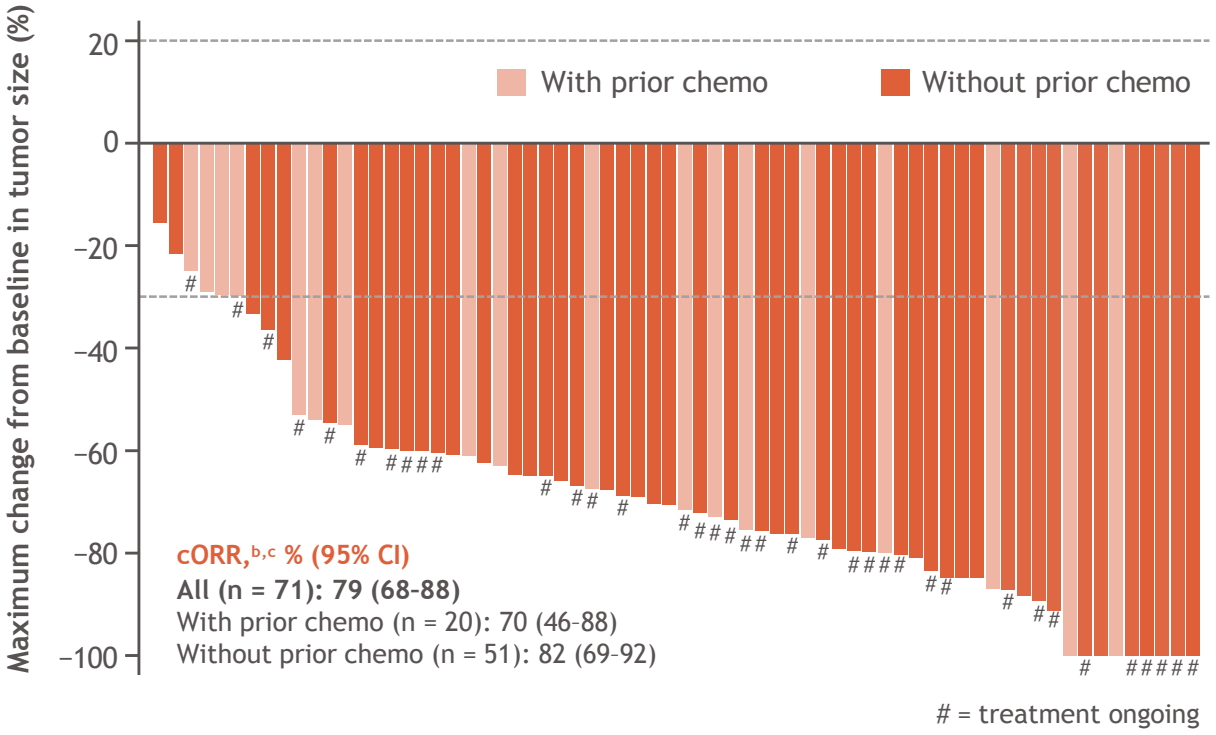
Demographics and baseline characteristics of patients with *ROS1*+ advanced NSCLC

	ROS1 TKI-naïve (n = 71[a])	1 prior ROS1 TKI AND no prior chemo (n = 56[b])
Median age, years (range)	57 (28-80)	57 (33-78)
Region, n (%)		
US	11 (16)	17 (30)
Asia	41 (58)	23 (41)
Other[c]	19 (27)	16 (29)
Female, n (%)	43 (61)	38 (68)
ECOG PS, n (%)		
0	24 (34)	18 (32)
1	47 (66)	38 (68)
Never smoked, n (%)	45 (63)	36 (64)
Brain metastasis per BICR, n (%)	17 (24)	26 (46)
Resistance mutation,[d,e] n (%)		
Solvent front (G2032R)	Not applicable	6 (11)
Lines of prior chemo with/without immunotherapy,[f,g] n (%)		
0	51 (72)	56 (100)
1	17 (24)	0
No. prior systemic anticancer therapy[h], n (%)		
0	51 (72)	0
1	16 (22)	56 (100)
Prior TKI treatment,[i] n (%)		
Crizotinib	Not applicable	46 (82)
Entrectinib		9 (16)

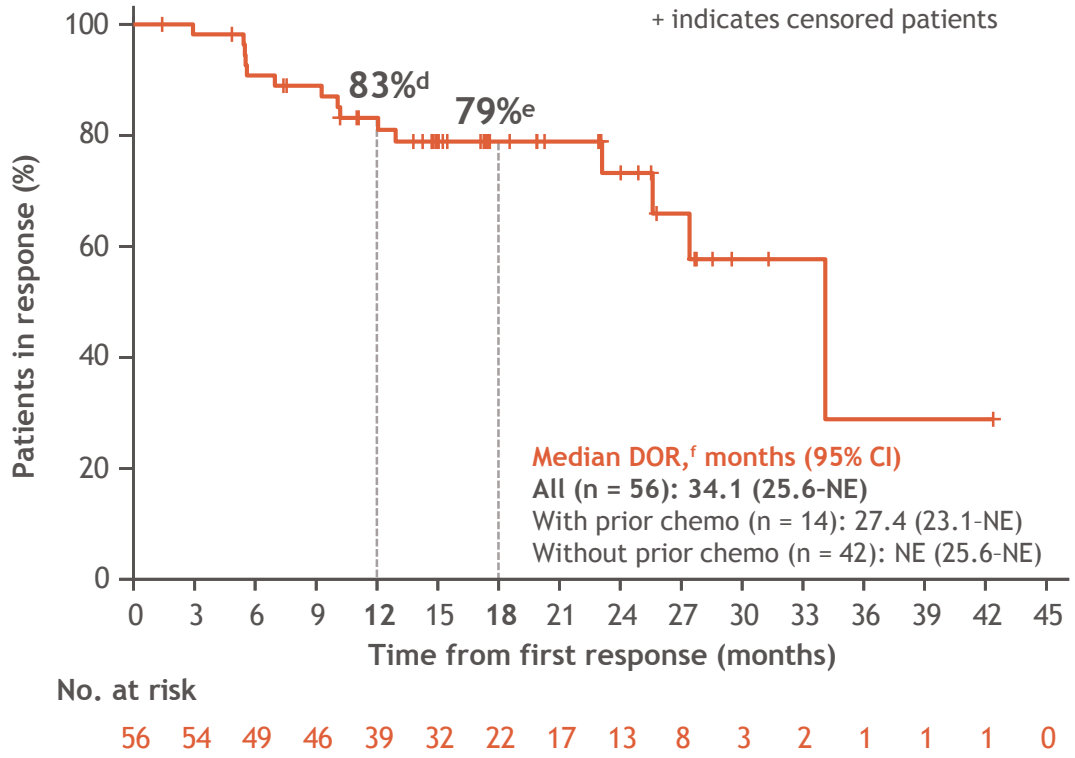
[a]8 (phase 1) + 63 (phase 2). [b]3 + 53. [c]Includes Australia, Canada, and Europe. [d]Identified in tumor tissues by local NGS testing or in plasma ctDNA using the Guardant360 CDx NGS test performed by Guardant Health (or using the GeneseeqLite NGS for patients enrolled in China). [e]In the 1 prior ROS1 TKI and no prior chemo cohort, 1 patient (2%) each had a gatekeeper and other resistance mutation, respectively. [f]In the ROS1 TKI-naïve cohort, 2 patients (3%) received 1 line of prior immunotherapy alone. [g]In the ROS1 TKI-naïve cohort, 2 patients (3%) had 2 lines of prior chemo with/without immunotherapy and 1 patient (1%) had ≥ 3 lines of prior chemo with/without immunotherapy. [h]In the ROS1 TKI-naïve cohort, 2 patients (3%) each had 2 lines and ≥ 3 lines of prior systemic anticancer therapy, respectively. [i]In the 1 prior ROS1 TKI and no prior chemo cohort, 1 patient (2%) was previously treated with ceritinib.

Tumor response per BICR in TKI-naïve patients with *ROS1*+ advanced NSCLC

Change in tumor burden per BICR[a]



DOR



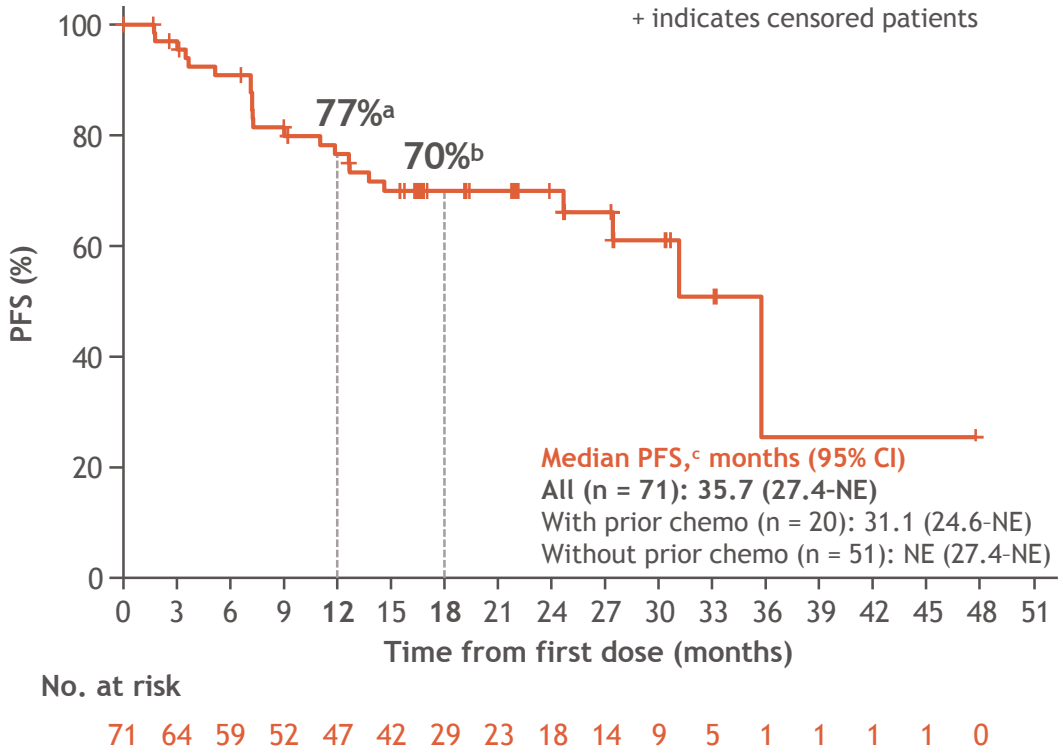
- Of patients in the ROS1 TKI-naïve cohort treated at the RP2D (n = 63), cORR was 78% (95% CI, 66–87) and median DOR was NE (95% CI, 25.6–NE)[g]

Median follow-up: 24.0 months (range, 14.2-66.6).

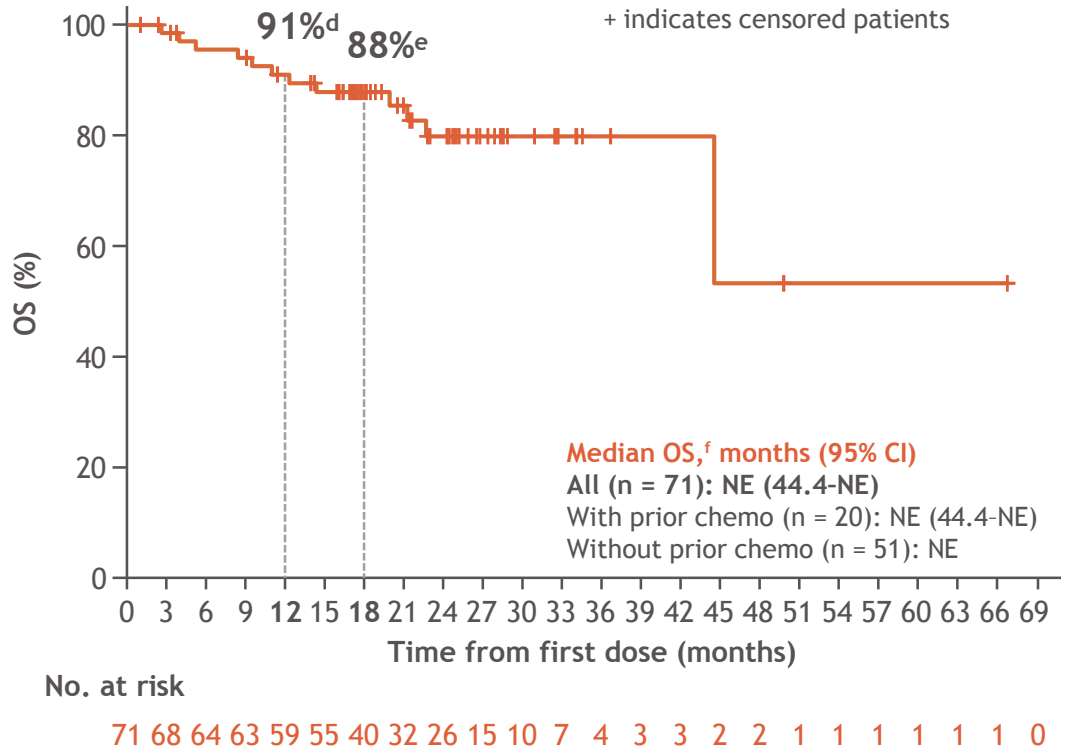
[a]Three patients did not have post-baseline tumor size measurement. [b]By RECIST v1.1. [c]10% (n = 7) and 69% (n = 49) of patients had CR and PR, respectively. [d]95% CI, 73-93. [e]95% CI, 68-90. [f]Number of events = 15; number of patients censored (%) = 41 (73). [g]12- and 18-month DOR rates (95% CI) were 85% (75-95) and 80% (69-92), respectively.

PFS and OS in TKI-naïve patients with *ROS1*+ advanced NSCLC

PFS



OS



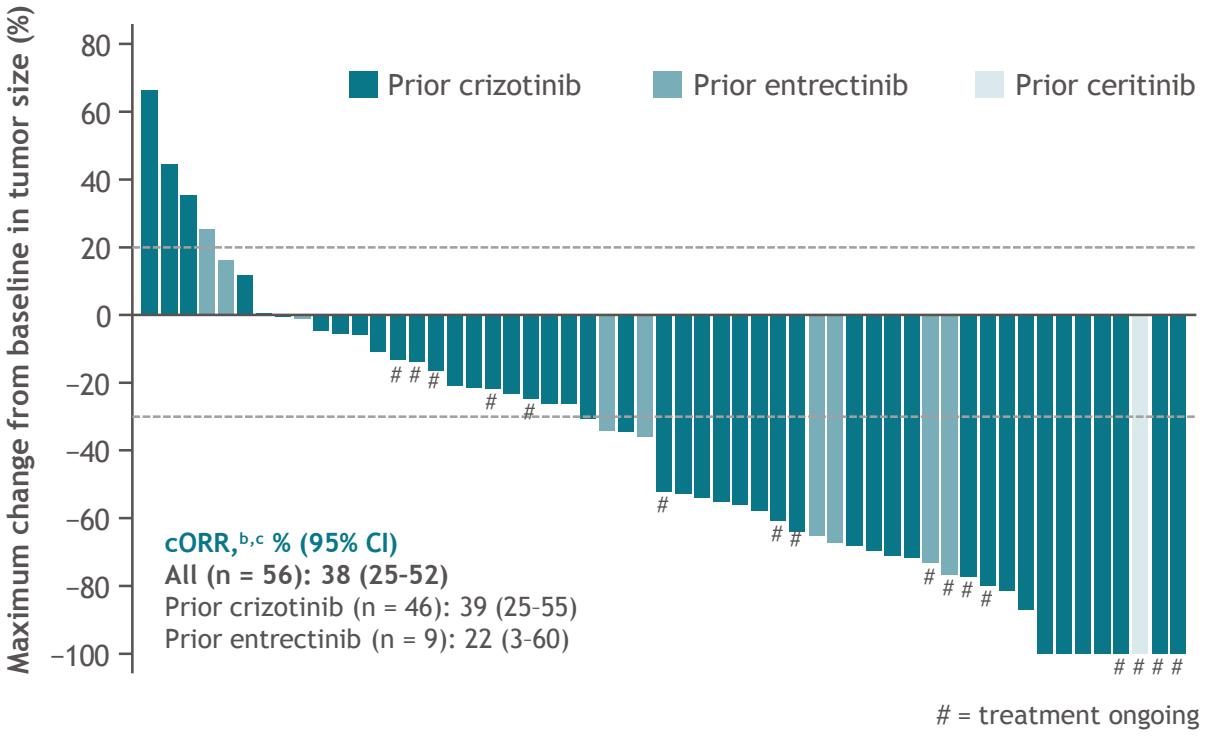
- Of patients in the ROS1 TKI-naïve cohort treated at the RP2D (n = 63), median PFS was NE months (95% CI, 27.4-NE)[g] and median OS was NE[h]

Median follow-up: 24.0 months (range, 14.2-66.6).

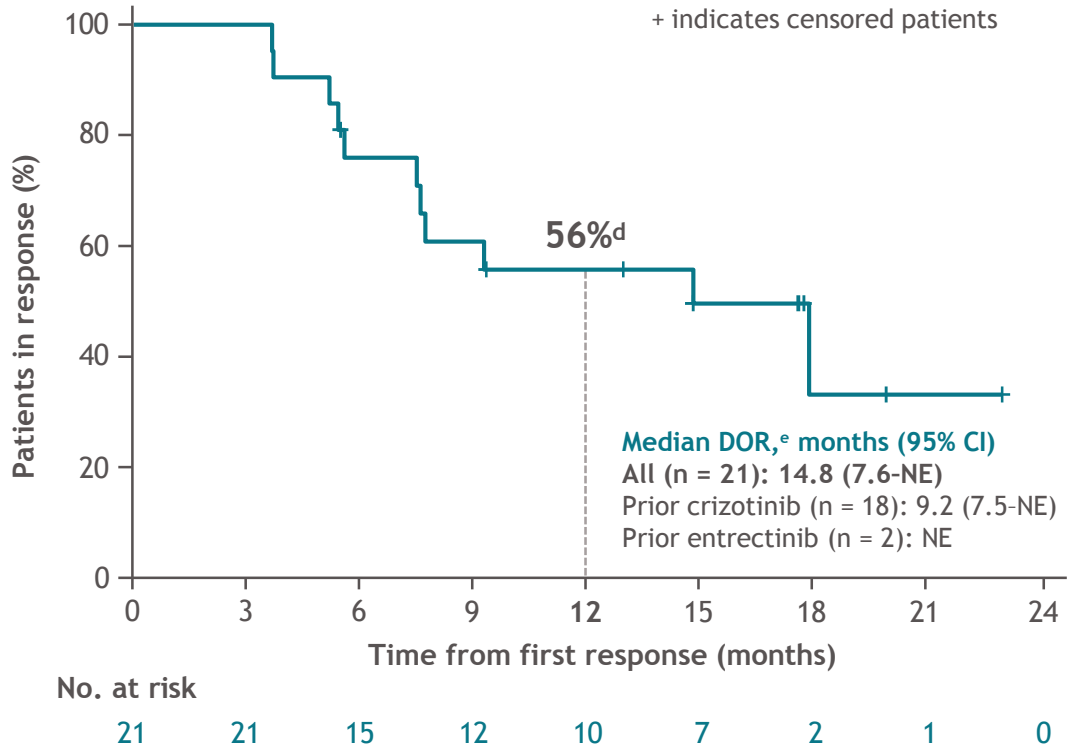
[a]95% CI, 66-87. [b]95% CI, 59-81. [c]Number of events = 23; number of patients censored (%) = 48 (68). [d]95% CI, 84-98. [e]95% CI, 80-96. [f]Number of events = 12; number of patients censored (%) = 59 (83). [g]12- and 18-month PFS rates (95% CI) were 76% (64-87) and 70% (58-82), respectively. [h]12- and 18-month OS rates (95% CI) were 92% (85-99) and 88% (80-96), respectively.

Tumor response per BICR in patients with *ROS1*+ advanced NSCLC pretreated with 1 prior ROS1 TKI and no prior chemo

Change in tumor burden per BICR[a]



DOR



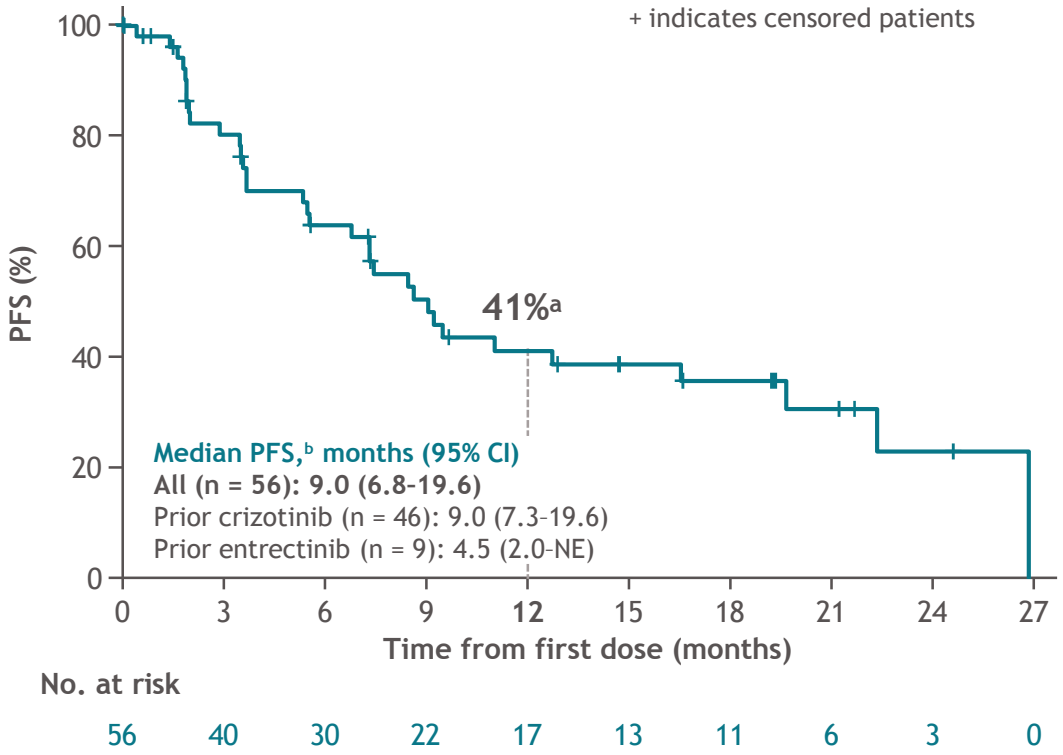
- Of patients in the 1 prior ROS1 TKI and no prior chemo cohort treated at the RP2D (n = 53), cORR was 38% (95% CI, 25–52) and median DOR was 14.8 months (95% CI, 7.5–NE)[f]

Median follow-up: 21.5 months (range, 14.2-58.6).

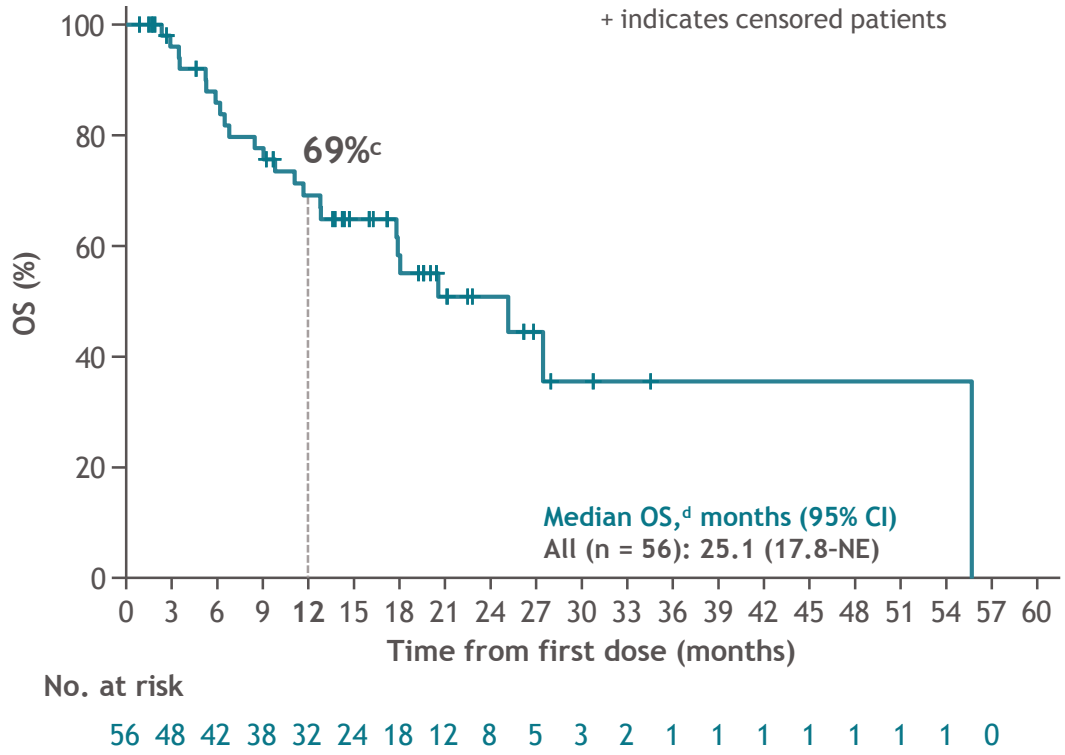
[a]One patient did not have post-baseline tumor size measurement. [b]By RECIST v1.1. [c]5% (n = 3) and 32% (n = 18) of patients had CR and PR, respectively. [d]95% CI, 34-77. [e]Number of events = 11; number of patients censored (%) = 10 (48). [f]12-month DOR rate (95% CI) was 55% (33-77).

PFS and OS in patients with *ROS1*+ advanced NSCLC pretreated with 1 prior ROS1 TKI and no prior chemo

PFS



OS



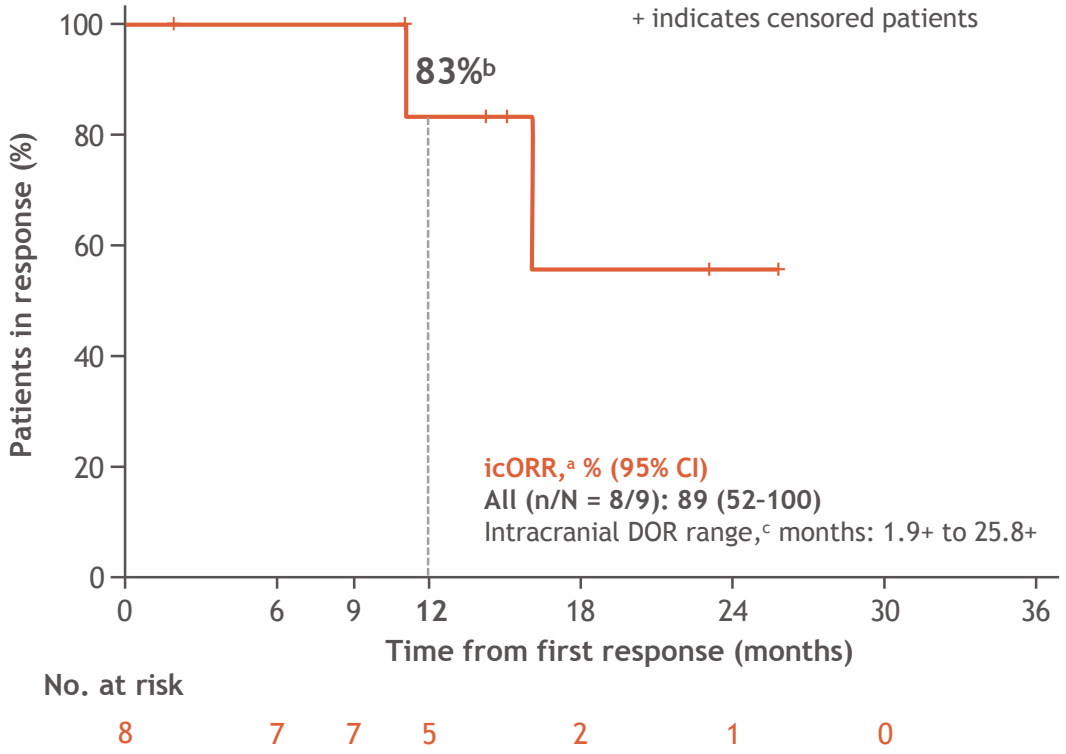
- Of patients in the 1 prior ROS1 TKI and no prior chemo cohort treated at the RP2D (n = 53), median PFS was 9.0 months (95% CI, 6.8–19.6)[e] and median OS was 20.5 months (95% CI, 17.8–NE)[f]

Median follow-up: 21.5 months (range, 14.2-58.6).

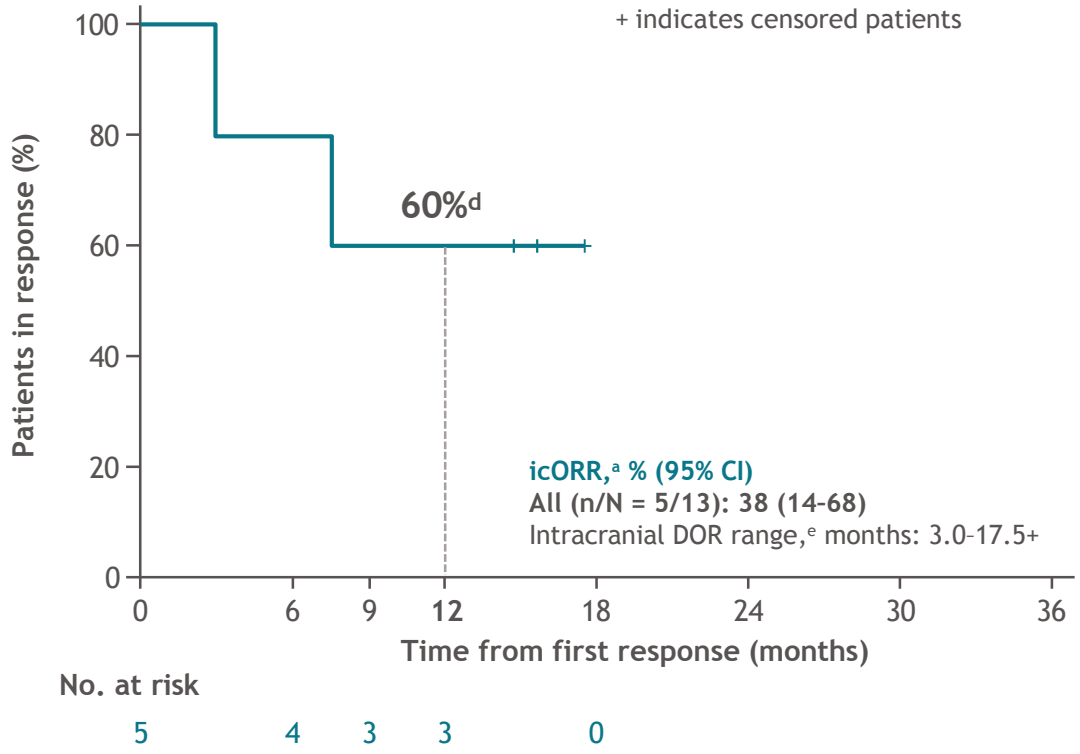
[a]95% CI, 27–56. [b]Number of events = 33; number of patients censored (%) = 23 (41). [c]95% CI, 56–82. [d]Number of events = 24; number of patients censored (%) = 32 (57). [e]12-month PFS rate (95% CI) was 42% (28–57). [f]12-month OS rate (95% CI) was 69% (56-83).

Intracranial DOR[a] in TKI-naïve and TKI-pretreated patients with measurable baseline brain metastasis

ROS1 TKI-naïve



1 prior ROS1 TKI and no prior chemo

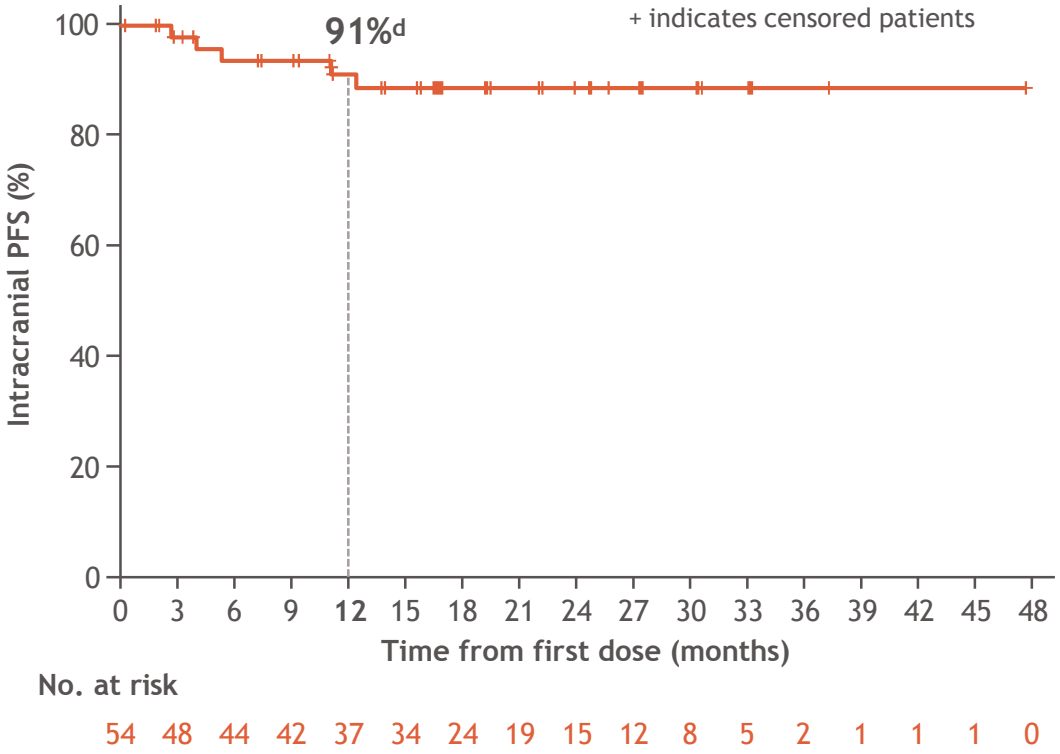


Median follow-up: ROS1 TKI-naïve, 24.0 months (range, 14.2-66.6); 1 prior ROS1 TKI and no prior chemo, 21.5 months (range, 14.2-58.6).

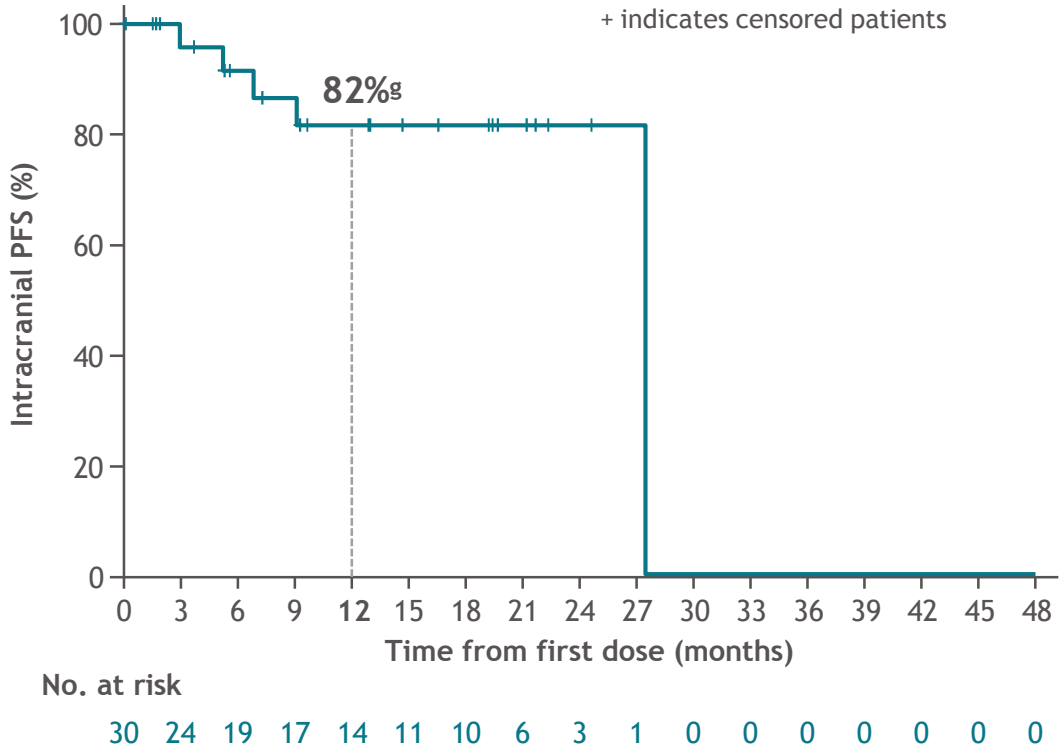
[a]Per BICR. [b]95% CI, 54-100. [c]Number of events = 2. [d]95% CI, 17-100. [e]Number of events = 2.

Intracranial PFS in TKI-naïve and TKI-pretreated patients without baseline brain metastasis[a]

ROS1 TKI-naïve[b,c]



1 prior ROS1 TKI and no prior chemo[e,f]



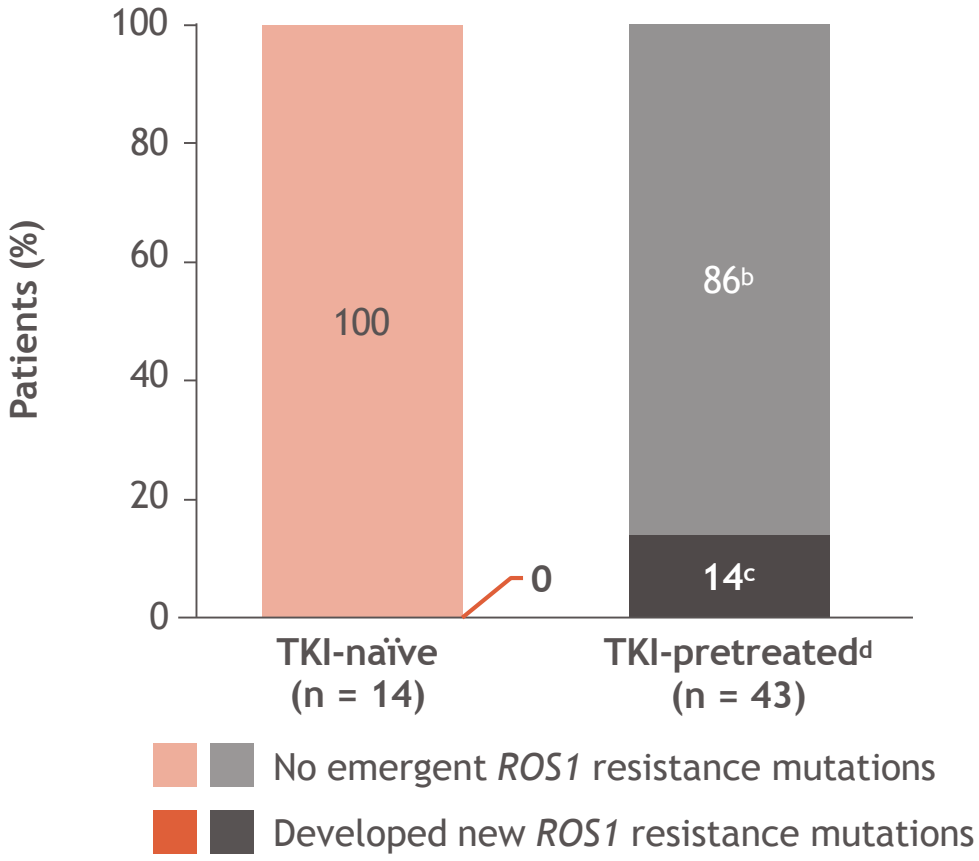
- In an analysis of time to first intracranial progression only,[h] none occurred within 18 months of repotrectinib treatment in both TKI-naïve and TKI-pretreated patients

Median follow-up: ROS1 TKI-naïve, 24.0 months (range, 14.2-66.6); 1 prior ROS1 TKI and no prior chemo, 21.5 months (range, 14.2-58.6).

[a]Exploratory analysis of intracranial PFS based on time of development of new brain lesions as assessed by BICR. [b]Includes patients from phase 1 (n = 6) and phase 2 (n = 48). [c]Number of events = 5. [d]95% CI, 83-100. [e]Includes patients from phase 1 (n = 3) and phase 2 (n = 27). [f]Number of events = 5. [g]95% CI, 65-98. [h]Intracranial PFS censored by non-intracranial progression or death.

Emergence of new *ROS1* resistance mutations at progression and efficacy in TKI-pretreated patients with baseline G2032R resistance mutation

Emergent *ROS1* resistance mutations in patients who progressed on repotrectinib[a]



- No TKI-naïve patients who progressed on repotrectinib developed an on-target resistance mutation
- Among TKI-pretreated patients with baseline G2032R mutation (n = 17)[d]
  - cORR was 59% (95% CI, 33–82)
  - Median DOR was 7.6 months (95% CI, 4.4–17.8)
  - Median PFS was 9.2 months (95% CI, 1.9–12.8)

[a]Among tumor tissue and ctDNA baseline and ctDNA post-progression samples (n = 57), paired plasma samples were evaluated by Guardant360 CDx (or GeneseeqLite NGS for patients enrolled in China) and tumor tissues were tested by local NGS. [b]Of 37 TKI-pretreated patients who did not develop *ROS1* resistance mutations at progression, 8 had pre-existing *ROS1* mutation at baseline. [c]Of 6 TKI-pretreated patients who developed a *ROS1* resistance mutations at progression, 5 *ROS1* G2032R and 1 *ROS1* L2086F were observed. Two of 6 patients had a pre-existing *ROS1* resistance mutation at baseline. [d]Across 3 TKI pre-treated *ROS1*+ NSCLC cohorts.

Subsequent therapy after repotrectinib treatment in TKI-naïve and TKI-pretreated patients with *ROS1*+ advanced NSCLC

	ROS1 TKI-naïve (n = 71)	1 prior ROS1 TKI AND no prior chemo (n = 56)
Patients who discontinued repotrectinib, n (%)	34 (48)	40 (71)
Type of first subsequent therapies reported,[a-c] n (%)		
ROS1 TKI – single agent	6 (18)	10 (25)
ROS1 TKI with chemo[d]	1 (3)	1 (2)
Chemo with/without immunotherapy[e]	8 (24)	12 (30)
Immunotherapy without chemo[f]	2 (6)	0

[a]Percentages are based on number of patients who discontinued repotrectinib. [b]Median time (range) from end of repotrectinib treatment to the start of first subsequent therapy was 9.0 days (2.0–106.0) in the ROS1 TKI-naïve cohort and 8.0 days (1.0–24.0) in the 1 prior ROS1 TKI and no prior chemo cohort. [c]First subsequent therapies were not reported for 17 (50%) ROS1 TKI-naïve patients and for 17 (42%) patients who received 1 prior ROS1 TKI and no prior chemo. [d]Combination of ROS1 TKI and chemotherapy with or without other systemic agents. [e]Chemotherapy with or without other systemic agents, except ROS1 TKI. [f]Immunotherapy alone with or without other systemic agents.

Safety summary in patients treated at the RP2D

	All patients treated at the RP2D[a] (n = 426)		All patients with *ROS1*+ NSCLC treated at the RP2D (n = 320)	
AEs, n (%)	**TEAEs**	**TRAEs**	**TEAEs**	**TRAEs**
All patients with AEs	422 (99)	409 (96)	318 (99)	306 (96)
Leading to dose reduction	163 (38)	149 (35)	112 (35)	100 (31)
Leading to drug interruption	213 (50)	150 (35)	158 (49)	107 (33)
Leading to treatment discontinuation	31 (7)	14 (3)	23 (7)	11 (3)
Serious AEs	147 (34)	38 (9)	106 (33)	24 (8)
Grade ≥ 3 AEs	216 (51)	122 (29)	156 (49)	86 (27)
Fatal AEs	19 (4)	0	13 (4)	0

- The most common TEAE was dizziness, which was reported in 62% of patients (n = 264); grade ≥ 3 treatment-emergent dizziness was reported in 3% of patients (n = 11); no patients discontinued repotrectinib due to treatment-emergent dizziness[b]

[a]Safety analysis population includes patients across all cohorts (including *ROS1*+ and *NTRK*+ cohorts) who received repotrectinib at the RP2D. [b]Median (range) time to onset of any-grade treatment-emergent dizziness was 7.0 (1.0–526.0) days; dose reduction and dose interruption of repotrectinib due to treatment-emergent dizziness was required in 11% (n = 47) and 8% (n = 35) of patients, respectively.

Summary

- Molecular Testing + PD-L1 assessment is SOC for all patients eligible to receive systemic therapy ***independent of stage***
- ALK+ disease has multiple therapeutic options (alectinib, brigatinib, lorlatinib) with lorlatinib demonstrating apparent superior efficacy with unique side effect profile. No head-to-head trials to advise optimal sequence.
- Adjuvant ALK therapy with alectinib as new SOC for stage IB-IIIA.
- RET+ NSCLC with 1st line SOC with selpercatinib.
- ROS1 has new option with repotrectinib, dual ROS1/NTRK inhibitor, with best in class efficacy and NTRK ontarget side effect profile.

Thank you!

The US Oncology Network