Updates in Cancer Therapies: An ASCO | ESMO Review

Updates on Targeting ALK, ROS1, and RET in NSCLC

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TARGETED THERAPY

ALK FUSION+ LUNG CANCER

ALK: Multiple Globally Approved ALK-Targeted TKIs

1G

Crizotinib

2G

Ceritinib
Alectinib
Brigatinib
Ensartinib

3G

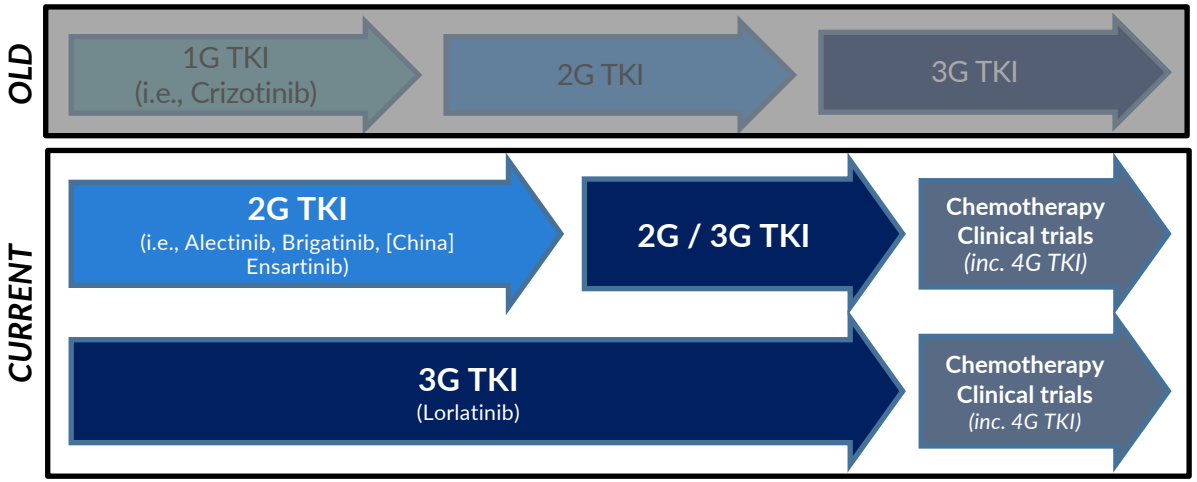
Lorlatinib

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

Schneider JL et al. *Nat Cancer*. 2023;4(3):330-343
Cooper AJ et al. *Nat Rev Clin Oncol*. 2022;19(11):744

ALK: Evolving 1L Targeted Therapy Landscape

Current standard 1L therapy for advanced ALK+ NSCLC: *Next-generation (2G or 3G) ALK TKI*



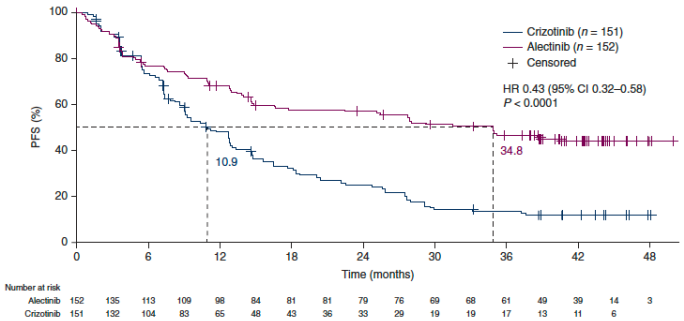
NOT drawn to scale or to reflect relative median PFS on each treatment option

- **2G ALK TKIs** have clearly supplanted crizotinib as preferred 1L agent
- Is it time for a **3G ALK TKI** to supplant 2G ALK TKIs as preferred initial therapy?

Schneider JL et al. *Nat Cancer*. 2023;4(3):330-343
Cooper AJ et al. *Nat Rev Clin Oncol*. 2022;19(11):744

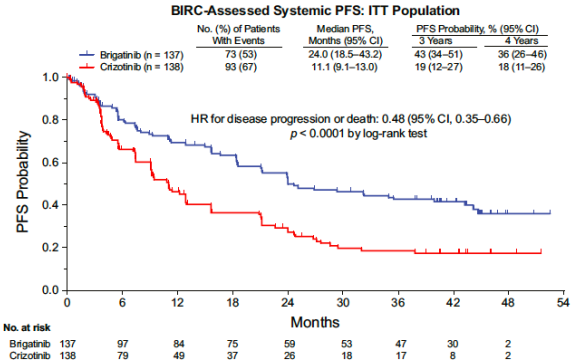
Cross-Trial Comparisons of PFS Data for Selected 3 Next-Generation ALK TKIs in the 1L Setting

Global ALEX[1,2]
1L Alectinib vs Crizotinib



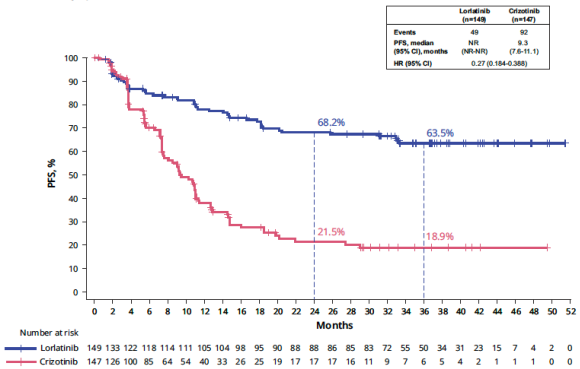
Median PFS per BIRC: 25.7 months
3-year PFS rate per investigator: 46.4%
5-year OS rate: 62.5%

ALTA-1L[3,4]
1L Brigatinib vs Crizotinib



Median PFS per BIRC: 24.0 months
3-year PFS rate per BIRC: 43%
4-year OS rate: 66%

CROWN[5,6]
1L Lorlatinib vs Crizotinib

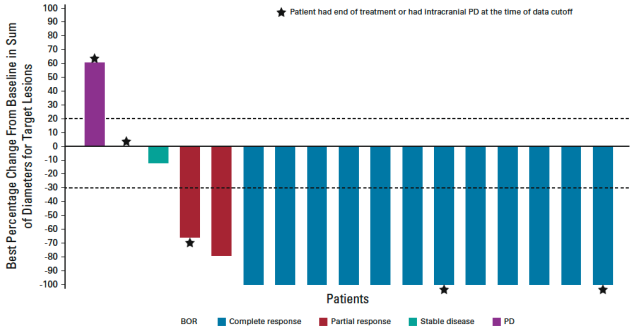


Median PFS per BIRC: NR at 3-year follow-up analysis
3-year PFS rate per BIRC: 63.5%

1. Peters S et al. *N Engl J Med*. 2017;377(9):829-838. 2. Mok T et al. *Ann Oncol*. 2020;31(8):1056-1064. 3. Camidge DR et al. *N Engl J Med*. 2018;379(21):2027-2039. 4. Camidge DR et al. *J Thorac Oncol*. 2021;16(12):2091-2108. 5. Shaw AT et al. *N Engl J Med*. 2020;383(21):2018-2029. 6. Solomon BJ et al. *Lancet Respir Med*. 2022;11(4):354-366.

ALK: Optimizing the CNS Efficacy & CNS Protective Effect of 1L Therapy

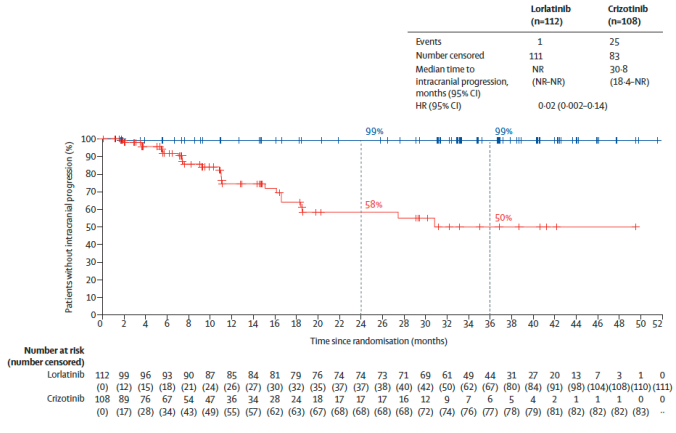
Intracranial responses in patients with baseline measurable brain metastases on 1L lorlatinib[1]



Measurable CNS lesions	Confirmed IC-ORR	Confirmed IC-CR rate	Median IC-DOR
Lorlatinib (CROWN)[1]	**83% (15/18)**	**72% (13/18)**	**NR (NR-NR)**
Alectinib (ALEX)[2]	81% (17/21)	38% (8/21)	17.3 mos (14.8-NE)
Brigatinib (ALTA-1L)[3]	78% (14/18)	28% (5/18)	27.9 mos (5.7-NE)
Ensartinib (eXalt3)[4]	64% (7/11)	27% (3/11)	Not reported

Time to intracranial progression by BICR per modified RECIST v1.1[1]

Patients without baseline brain metastases



HR 0.02 (0.002-0.14)
1 event of intracranial progression in 112 patients without baseline brain met treated with 1L lorlatinib after 3 years
3-year IC-PFS rate of 99% (95% CI, 94-100)

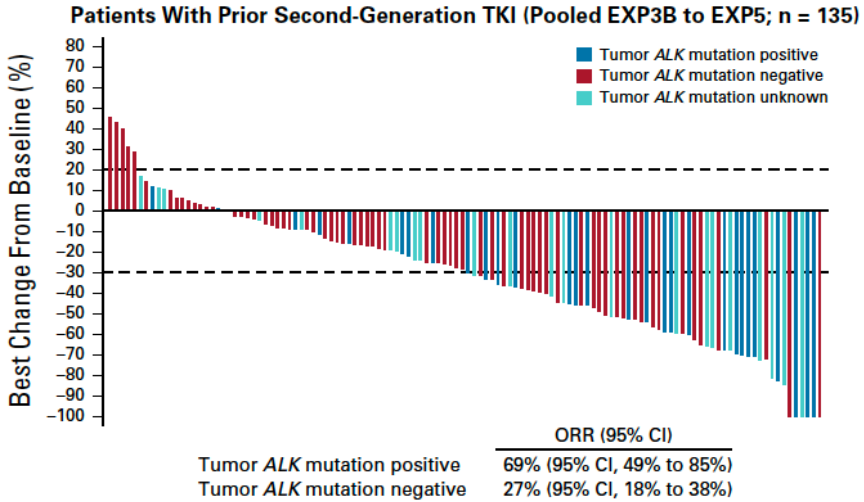
1. Solomon BJ et al. *Lancet Respir Med*. 2022;11(4):354-366. 2. Peters S et al. *N Engl J Med*. 2017;377(9):829-838.
3. Camidge DR et al. *N Engl J Med*. 2018;379(21):2027-2039. 4. Horn L et al. *JAMA Oncol*. 2021;7(11):1617-1625.

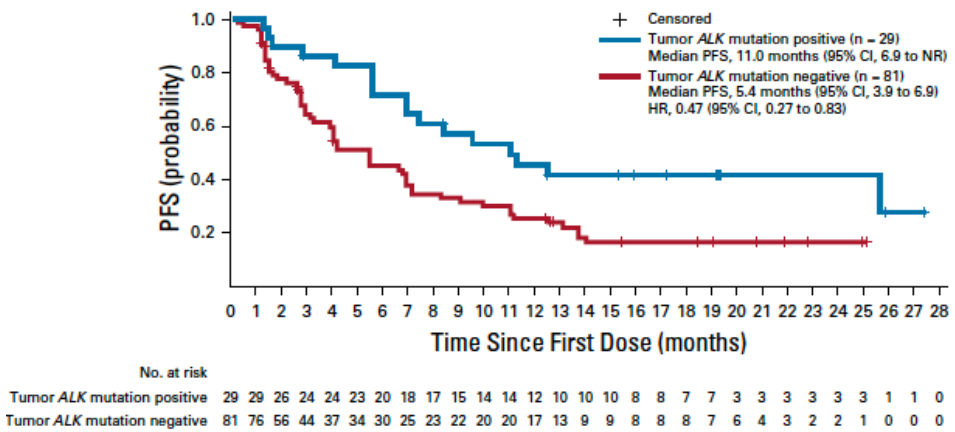
Efficacy of Lorlatinib (3G ALK TKI) After 2G ALK TKIs

Phase II study efficacy data

ORR s/p 2G ALK TKI(s) (n=139): **39.6%** (31.4-48.2)
Median DOR: 9.6 months (95% CI, 5.6-16.7)
Median PFS: 6.6 months (95% CI, 5.4-7.4)
IC-ORR: 56.1% (42.4-69.3)

Lorlatinib is recommended as a subsequent treatment option after progression on prior ALK TKIs in the NCCN Guidelines

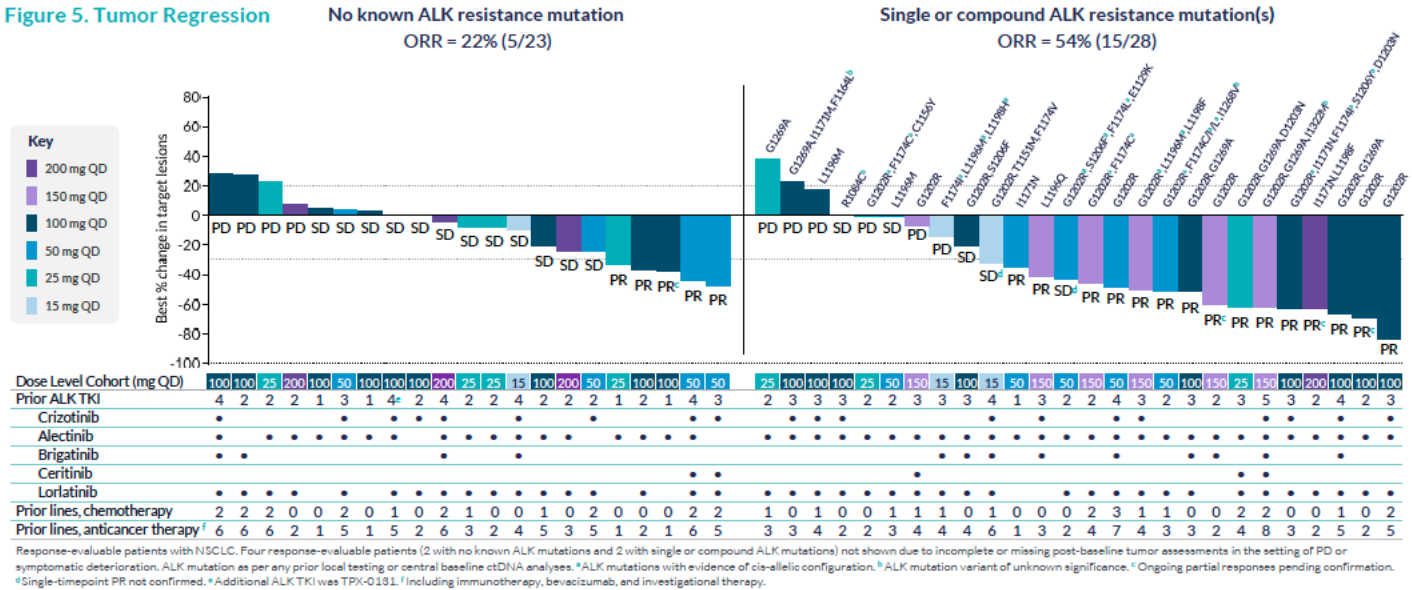




Felip E et al., Ann Oncol 2021;32(5)620-30
NCCN Guidelines Version 4.2023. Accessed 10/31/23
Shaw AT et al. *J Clin Oncol* 2019;37(16):1370-9

NVL-655, ALK-Selective & CNS-Penetrant 4th-Generation ALK TKI: Preliminary Efficacy from Phase I Study (ALKOVE-1)

- 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)]**



Response-evaluable patients with NSCLC. Four response-evaluable patients (2 with no known ALK mutations and 2 with single or compound ALK mutations) not shown due to incomplete or missing post-baseline tumor assessments in the setting of PD or symptomatic deterioration. ALK mutation as per any prior local testing or central baseline ctDNA analyses. [a] ALK mutations with evidence of cis-allelic configuration. [b] ALK mutation variant of unknown significance. [c] Ongoing partial responses pending confirmation. [d] Single-timepoint PR not confirmed. [e] Additional ALK TKI was TPX-0131. [f] Including immunotherapy, bevacizumab, and investigational therapy.

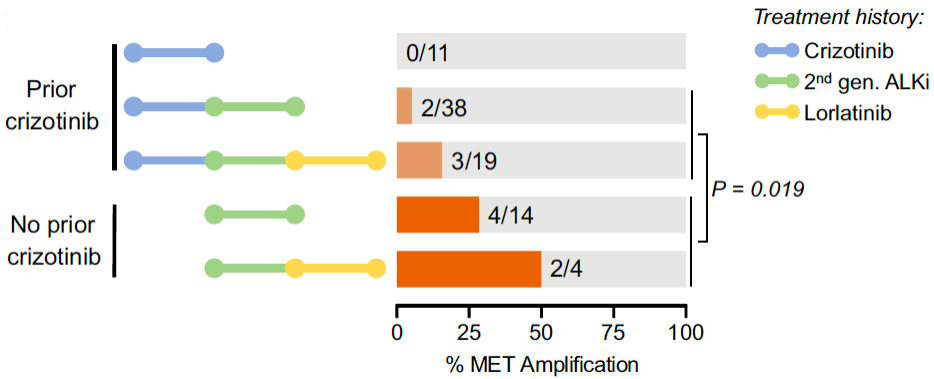
Lin JJ et al. AACR-NCI-EORTC 2023

ALK: Addressing Resistance with Combinations
Example of ALKi + METi Targeting *MET* Amplification

MET amplification identified in[1]:

12% of patients progressing on 2G ALK TKI

22% of patients progressing on 3G ALK TKI (lorlatinib)



Case series[2], n=12

ALK/MET co-targeting strategies, ORR 42% (5/12)

Patient	ALK/MET Therapy	Best Response Time on Treatment	Pre-ALK/MET Targeted Therapy Biopsy Findings
1	Crizotinib 250 mg BID	PD <1 month	**MET/CEP7 ≥ 25**, *TP53* R273C, *TP53* Q192*, *SETD2* V2280fs*89
2	Crizotinib 250 mg BID	PR (-38%) 3.5 months	**MET/CEP7 ≥ 25**, *TSC2* D1612N, *TP53* A161T
3	Lorlatinib 75 mg QD#+ Crizotinib 250 mg BID	PR (-30%) 3 months	**MET/CEP7 5.7**, *ATM* S378G, *MDM4* splice region variant, *ARID1A* D1193N, *PIK3CA* E453K
4	Lorlatinib 50 mg QD+ Crizotinib 250 mg BID	PD <1 month	**MET/CEP7 2.4**, *NF1* G2379R, *TP53* V274G, *MYC* gain
5	Lorlatinib 50 mg QD# + Crizotinib 250 mg BID	PR (-60%) 11 months**	**MET/CEP7 ≥ 25**, *APC* Y1642_V1644del
6	Lorlatinib 50 mg QD+ Crizotinib 250 mg BID	PD <1 month	**MET/CEP7 5.5**, *TP53* R273C
7	Lorlatinib 50 mg QD + Crizotinib 250 mg BID	PR (-51%) 6 months	***MET* amplification (2.5)**, *TP53* E346*, *MYC* amplification (3.8) by plasma
8	Lorlatinib 50 mg QD + Crizotinib 250 mg BID	PD <1 month	***MET* amplification (5.4)**, *TP53* C135F (4.6), *BRCA2* D3188fs (2.4), *APC* M314T (0.6), *STK11* A43V (0.3)
9	Alectinib 600 mg BID#+ Capmatinib 400 mg BID	SD (Non-CR/Non-PD) 9 months	**MET/CEP7 ≥ 25**, *SMARCA4* P47T, *EGFR* P596L
10	Alectinib 600 mg BID + Capmatinib 400 mg BID#	SD (-8%) 10 months	**MET/CEP7 ≥ 25**, *TP53* E180*, *APC* E1156K
11	Alectinib 600 mg BID + Capmatinib 300 mg BID	PR (-70%) 7 months	**MET/CEP7 7.7**, *TP53* N131Y, *SMARCA4* D1183N
12	Alectinib 600 mg BID+ Crizotinib 200 mg BID	SD (-26%) 6 months	***MET* amplification** by NGS, *TP53* E285K

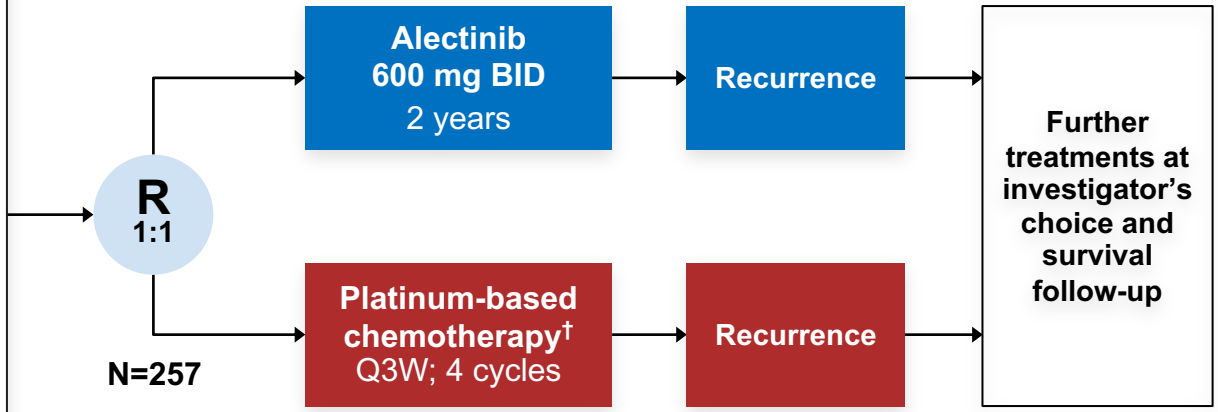
1. Dagogo-Jack I et al. *Clin Cancer Res*. 2020;26(11):2535-2545
2. Dagogo-Jack I et al. *JTO Clin Res Rep*. 2023;8(4):100534

Assessing ALK TKIs in Earlier-Stage ALK+ NSCLC
Adjuvant ALK TKI Alectinib: ALINA Study Design

Resected Stage IB (≥4cm)–IIIA *ALK*+ NSCLC
per UICC/AJCC 7th edition

Other key eligibility criteria:
- ECOG PS 0–1
- Eligible to receive platinum-based chemotherapy
- Adequate end-organ function
- No prior systemic cancer therapy

Stratification factors:
- Stage: IB (≥ 4cm) vs II vs IIIA
- Race: Asian vs non-Asian



Primary endpoint
- DFS per investigator,‡ tested hierarchically:
  - Stage II–IIIA → ITT (Stage IB–IIIA)

Other endpoints
- CNS disease-free survival
- OS
- Safety

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

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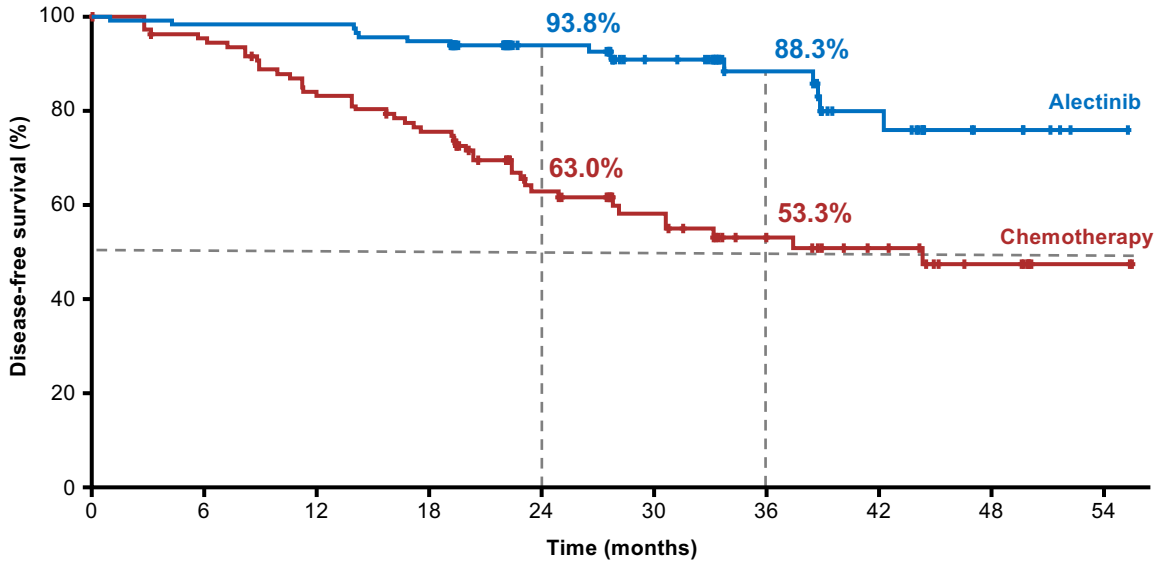
Solomon BJ et al., ESMO 2023

Data cut-off: 26 June 2023; CNS, central nervous system; DFS, disease-free survival; ITT, intention to treat
*Superiority trial; †Cisplatin + pemetrexed, cisplatin + vinorelbine or cisplatin + gemcitabine; cisplatin could be switched to carboplatin in case of intolerability; ‡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; §Assessment by CT scan where MRI not available; NCT03456076

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

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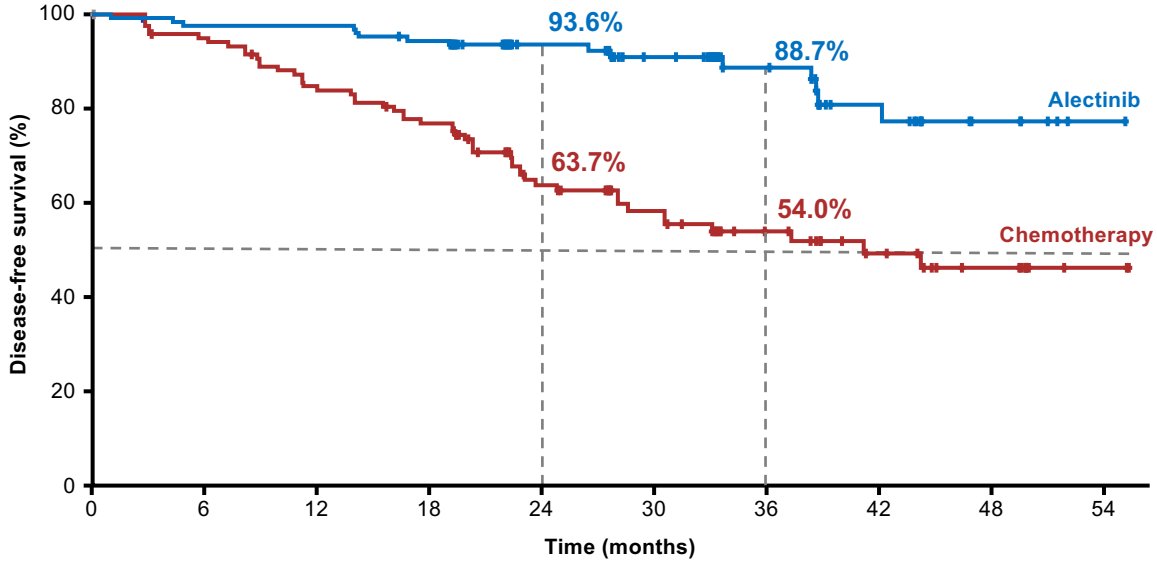
Solomon BJ et al., ESMO 2023

Data cut-off: 26 June 2023; Time from last patient in to data cut off was ~18 months

*Per UICC/AJCC 7th edition; †Stratified log rank; 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: 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

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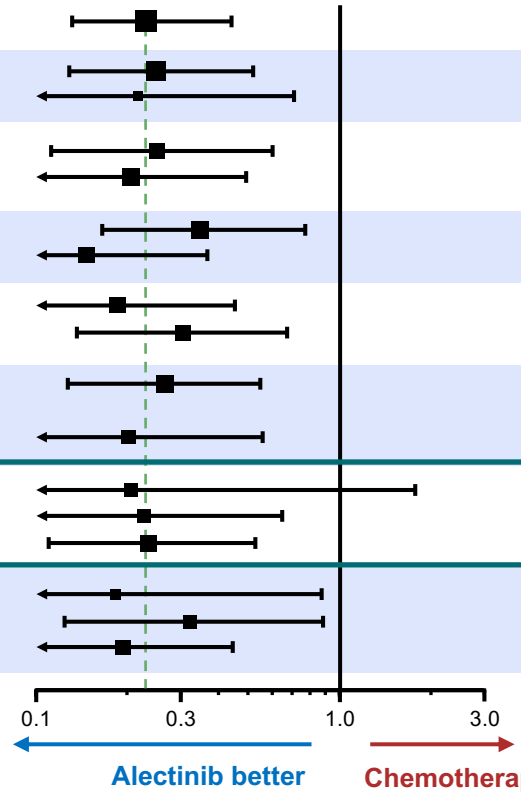
Solomon BJ et al., ESMO 2023

Data cut-off: 26 June 2023; Time from last patient in to data cut off was ~18 months

*Per UICC/AJCC 7th edition; †Stratified log rank; ‡2 events in the alectinib arm, 4 events in the chemo arm; one additional patient in the chemo arm 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)

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)



Data cut-off: 26 June 2023

Arrows indicate lower bound of the CI<0.1; *Per UICC/AJCC 7th edition

Post-recurrence subsequent therapy

Number of patients with disease recurrence, n (%)	Alectinib (n=15)	Chemotherapy (n=49)
Patients with any subsequent therapy	13 (87)	43 (88)
Systemic therapy	13 (87)	38 (78)
ALK TKI	7 (47)	37 (76)
Alectinib	4 (27)	29 (59)
Brigatinib	4 (27)	4 (8)
Crizotinib	0	4 (8)
Lorlatinib	0	2 (4)
Ceritinib	0	1 (2)
Chemotherapy	6 (40)	2 (4)
Immunotherapy	1 (7)	1 (2)
Other anti-cancer therapy	1 (7)	1 (2)
Radiotherapy	5 (33)	9 (18)
Surgery	1 (7)	3 (6)

Data cut-off: 26 June 2023

Includes any subsequent therapy reported on or after date of earliest contributing event to disease recurrence; Patients may have received more than one subsequent anticancer therapy

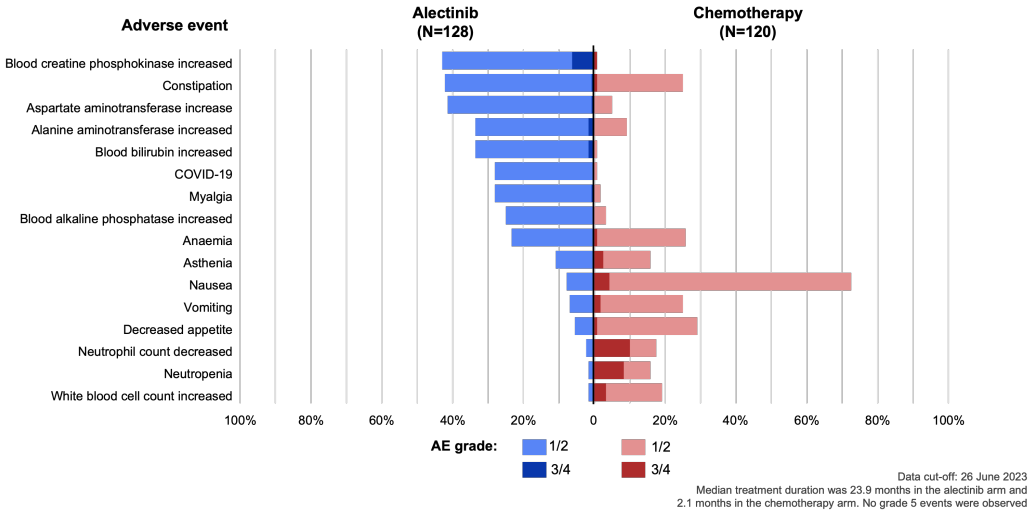
Solomon BJ et al., ESMO 2023

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%** in the alectinib arm ongoing treatment

AEs occurring in ≥15% of patients



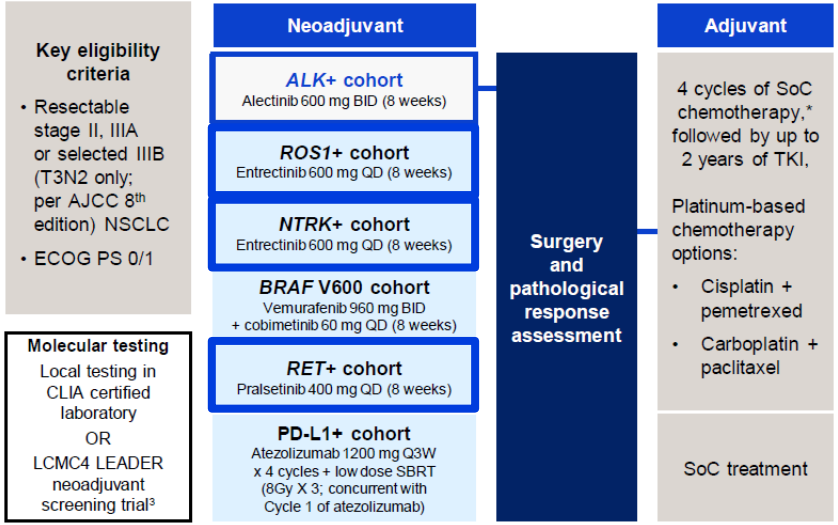
Data cut-off: 26 June 2023
Median treatment duration was 23.9 months in the alectinib arm and 2.1 months in the chemotherapy arm. No grade 5 events were observed

Solomon BJ et al., ESMO 2023

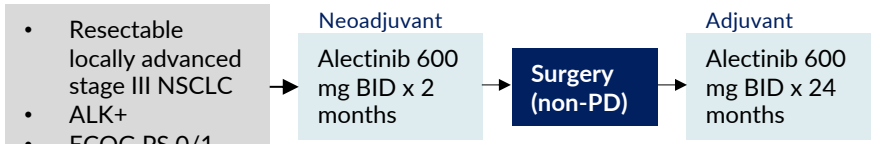
Data cut-off: 26 June 2023
Multiple occurrences of the same AE in one individual are counted only once in each category

Assessing ALK TKIs in Earlier-Stage ALK+ NSCLC: Neoadjuvant ALK TKI Trials

NAUTIKA1 (NCT04302025)[1,2]



ALNEO (GOIRC-01-2020; NCT05015010)[3,4]



Primary Endpoint: MPR

[1]Lee JM et al., WCLC 2022; [2]Clinicaltrials.gov, https://classic.clinicaltrials.gov/ct2/show/NCT04302025 (accessed 16 Jul 2023)
[3]Leonetti A et al., Clin Lung Cancer 2021;22(5):473-7; [4]Clinicaltrials.gov, https://classic.clinicaltrials.gov/ct2/show/NCT05015010 (accessed 16 Jul 2023)

Assessing ALK TKIs in Earlier-Stage ALK+ NSCLC: Neoadjuvant ALK TKI Trials: *Emerging Data*

	Study	Stage	Size	Neoadjuvant	Adjuvant	Imaging Response	Surgery Rate	R0 Resection Rate	MPR Rate	PCR Rate
ALK	**NeoALK**[1] (Chinese Retrospective RWD)	IIIA-IIIB	40 Alectinib, 21 Crizotinib, 19	Alectinib or crizotinib	Local RT / TKI	Alectinib: 71% (15/21) Crizotinib: 74% (14/19)	Alectinib: 81% (17/21) Crizotinib: 68% (13/19)	100% (30/30)	**Alectinib: 65%** (11/17) **Crizotinib: 46%** (6/13)	**Alectinib: 35%** (6/17) **Crizotinib: 15%** (2/13)
	ALNEO[2] (Phase 2)	III	33	Alectinib x 8 weeks	Alectinib x 2 years	TBD	TBD	TBD	TBD	TBD
	NAUTIKA1[3] (Phase 2)	II-IIIB	25	Alectinib x 8 weeks	Chemo -> Alectinib x 2 years	44% (4/9)	100% (9/9)	89% (8/9)	67% (6/9)	33% (3/9)
EGFR	**NEOS**[4] (Phase 2b)	IIA-IIIB	40	Osimertinib x 6 weeks	Chemo -> Osi x 3 years	68% (27/40)	80% (32/40)	94% (30/32)	**11% (3/28)**	**4% (1/28)**
	NCT03433469[5] (Phase 2)	I-IIIA	27	Osimertinib x 1-2 months	?	48%	89% (24/27)	100% (24/24)	**15% (4/27)**	**0% (0/27)**
	NeoADAURA[6] (Phase 3)	II-IIIB	351	Osimertinib x 9 weeks vs Chemo +/- Osi x 3 cycles	Investigator's choice SOC, Osi x 3 years	TBD	TBD	TBD	TBD	TBD

[1]Zhang C et al., AATS 2023; [2]Leonetti A et al., Clin Lung Cancer 2021;22(5):473-7; [3]Lee JM et al., WCLC 2023
[4]Lv C et al., Lung Cancer 2023;178:151-6; [5]Aredo JV et al., ASCO 2023; [6]Tsuboi M et al., Future Oncol 2021;17(31):4045-55

TARGETED THERAPY

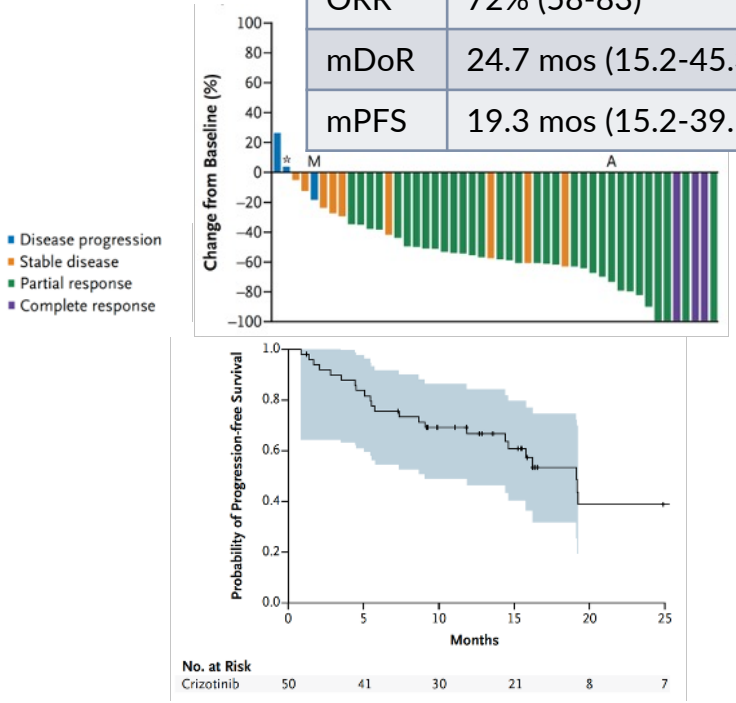
ROS1 FUSION+ LUNG CANCER

Standard 1L ROS1 TKIs…as of early Nov 2023

Crizotinib and Entrectinib: Systemic Efficacy

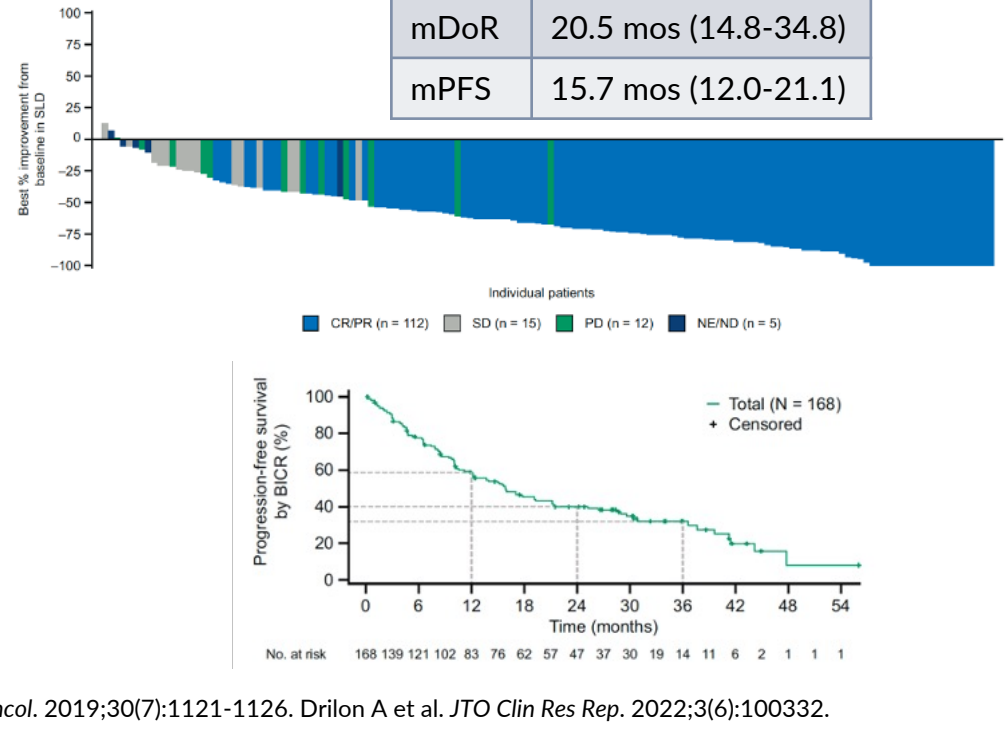
Crizotinib

ORR	72% (58-83)
mDoR	24.7 mos (15.2-45.3)
mPFS	19.3 mos (15.2-39.1)



Entrectinib

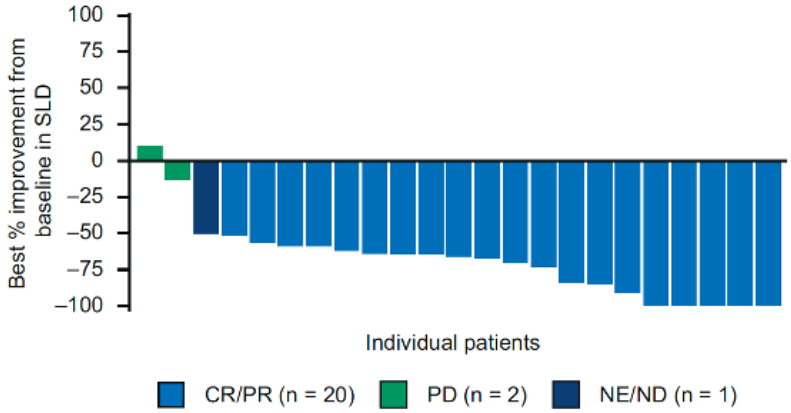
ORR	68% (60-75)
mDoR	20.5 mos (14.8-34.8)
mPFS	15.7 mos (12.0-21.1)



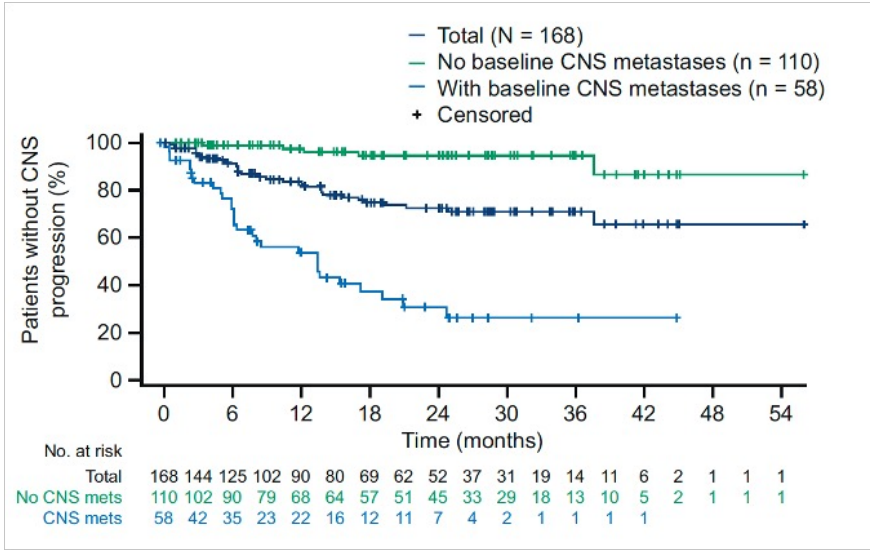
Shaw AT et al. *N Engl J Med*. 2014;371(21):1963-1971. Shaw AT et al. *Ann Oncol*. 2019;30(7):1121-1126. Drilon A et al. *JTO Clin Res Rep*. 2022;3(6):100332.

Entrectinib: CNS Efficacy

Best intracranial responses, patients with baseline measurable CNS metastases



Time to CNS progression



- **Intracranial ORR**: 80% (59.3-93.2) among 25 patients with measurable baseline CNS metastases
- **Median intracranial PFS**: 8.4 months (6.4-13.8)
- **Time to CNS progression**: not estimable overall; 13.6 months (6.7-19.3) in patients with baseline CNS metastases

Drilon A et al. *JTO Clin Res Rep*. 2022;3(6):100332.

ROS1: Advances in Optimizing 1L Targeted Therapy

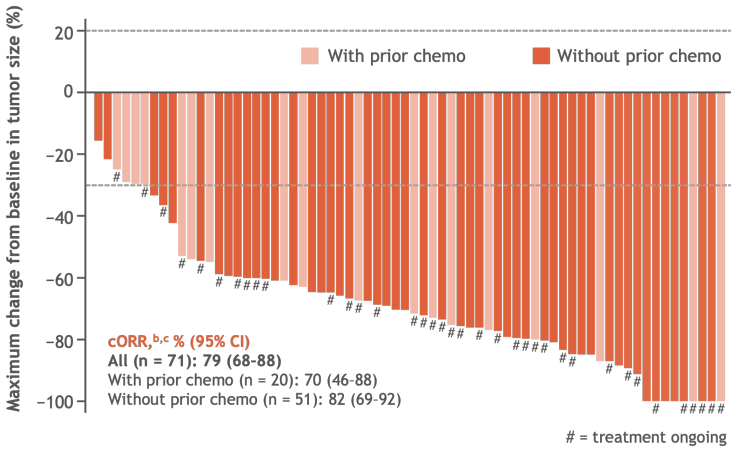
	Crizotinib* (PROFILE 1001)	Entrectinib* (ALKA-372-001, STARTRK-1, STARTRK-2)	Ceritinib (Korean Phase 2)	Brigatinib (BAROSSA phase II)	Lorlatinib (Phase 1/2)	Unecritinib (Chinese phase 2)	Taletrectinib# (TRUST-I Chinese Phase 1/2)	Repotrectinib* (TRIDENT-1 Phase 1/2)
N	53	168	20	28	21	111 (59% 1L)	67 (phase II)	71
ORR	**72%**	**68%**	**67%**	**67.9%**	**62%**	**78.4%**	**93%**	**79%**
Median PFS	**19.3 months**	**15.7 months**	**19.3 months**	**Not mature**	**21.0 months**	**15.6 months**	**33.2 months** (pooled)	**35.7 months**
CNS activity	N/A	25/48 (52%) patients with measurable or nonmeasurable intracranial disease	2/5 (40%) patients with measurable or nonmeasurable intracranial disease	N/A	7/11 (64%) patients with measurable or nonmeasurable intracranial disease	N/A	11/12 (92%) patients with baseline measurable CNS metastases	8/9 (89%) patients with measurable intracranial disease
Ref	Shaw AT et al. *Ann Oncol*. 2019.	Drilon A et al. *JTO Clin Res Rep*. 2022.	Lim SM et al. *J Clin Oncol*. 2017.	Toyozawa R et al. ESMO 2022.	Shaw AT et al. *Lancet Oncol*. 2019.	Lu S et al. ELCC 2022.	Li W et al. ELCC 2023.	Cho B et al. WCLC 2023.

***Received FDA approval** **#Received FDA breakthrough therapy designation**

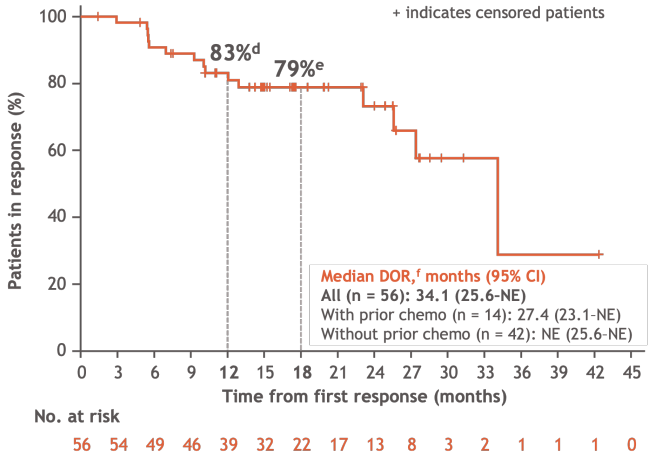
Repotrectinib in TKI-Naïve *ROS1* Fusion+ NSCLC (TRIDENT-1)

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).

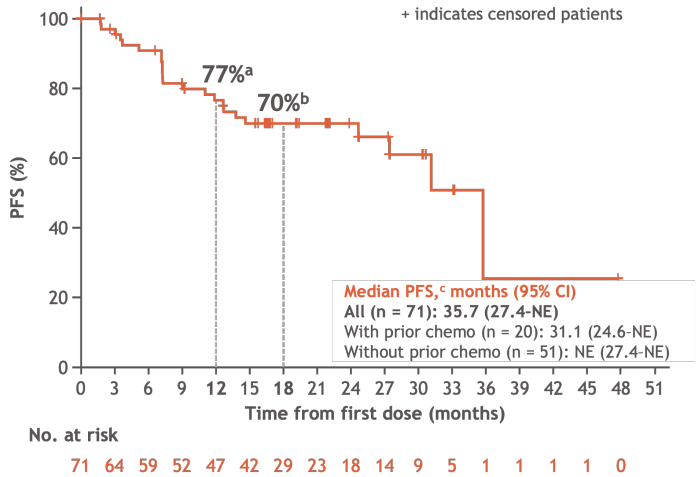
[a]Three patients did not have post-baseline tumor size measurement. [b]By RECIST v1.1. [c]10% (n = 7) and 69% (n = 49) of patients had CR and PR, respectively. [d]95% CI, 73-93. [e]95% CI, 68-90. [f]Number of events = 15; number of patients censored (%) = 41 (73). [g]12- and 18-month DOR rates (95%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

Cho BC et al., WCLC 2023

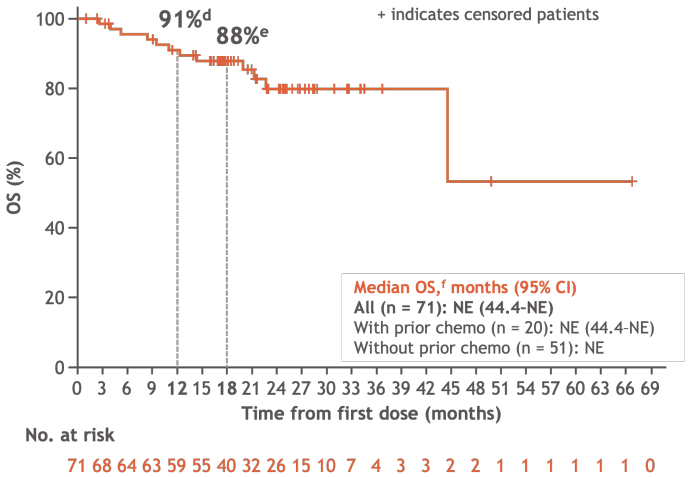
Repotrectinib in TKI-Naïve *ROS1* Fusion+ NSCLC (TRIDENT-1)

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]

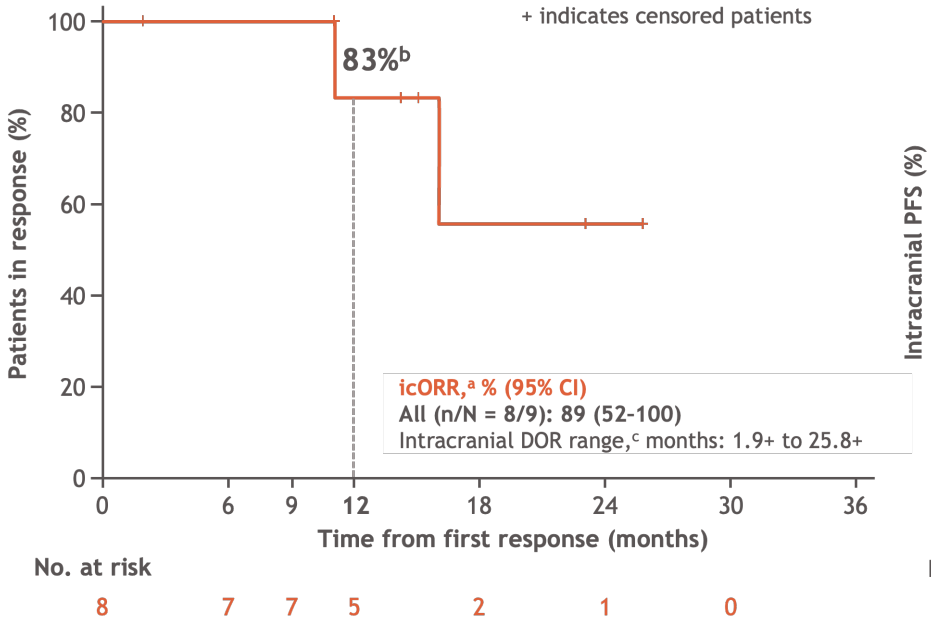
Median follow-up: 24.0 months (range, 14.2-66.6).

[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.

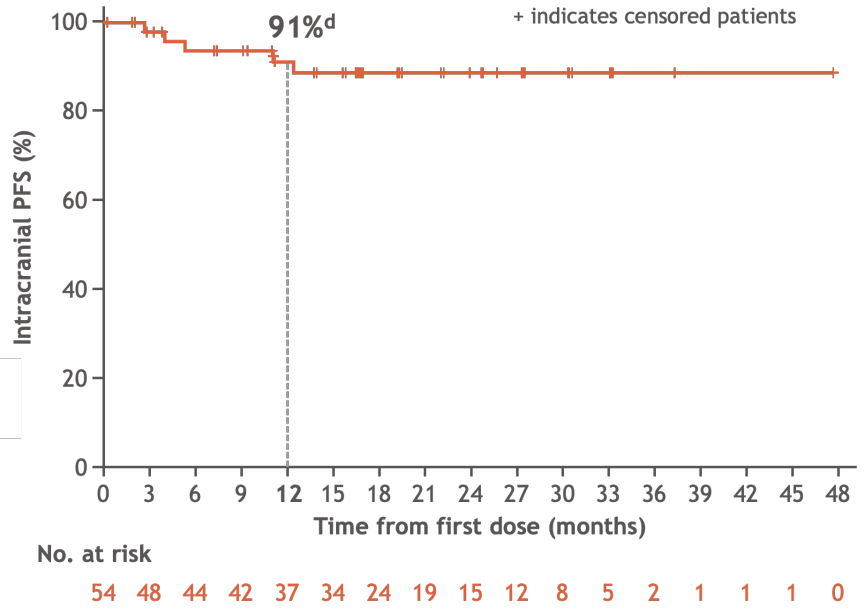
Cho BC et al., WCLC 2023

Repotrectinib in TKI-Naïve *ROS1* Fusion+ NSCLC (TRIDENT-1): Intracranial Efficacy

Intracranial DOR in patients with measurable baseline brain metastasis



Intracranial PFS in patients without baseline brain metastasis



Cho BC et al., WCLC 2023

ROS1: Emerging Data on the Efficacy of Next-Gen ROS1 TKIs in the 1L Setting

FDA Approves Repotrectinib for Locally Advanced or Metastatic ROS1+ NSCLC

November 15, 2023
Kristi Rosa

News Article

The FDA has approved repotrectinib (Augtyro) for the treatment of adult patients with locally advanced or metastatic ROS1-positive non–small cell lung cancer.

FDA

The FDA has approved repotrectinib for the treatment of adult patients with locally advanced or metastatic *ROS1*-positive non–small cell lung cancer.[1,2]

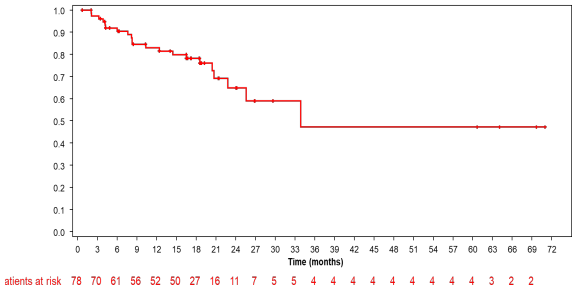
The regulatory decision is based on findings from the phase 1/2 TRIDENT-1 study (NCT03093116). In TKI-naive patients (n = 71), repotrectinib elicited a confirmed objective response rate (ORR) of 79% (95% CI, 68%-88%), which included a complete response (CR) rate of 6% and a partial response (PR) rate of 73%. The median duration of response (DOR) was 34.1 months (95% CI, 25.6-not evaluable [NE]). Seventy percent of patients experienced a response that lasted for at least 12 months.

In those who were pretreated with 1 prior ROS1 TKI and who did not receive prior chemotherapy or immunotherapy (n = 56), the confirmed ORR was 38% (95% CI, 25%-52%), which was comprised of a 5% CR rate and a 32% PR rate. In this group, the median DOR was 14.8 months (95% CI, 7.6-NE) with 48% of patients experiencing a response that persisted for 12 months or longer.

Taletrectinib (phase 1+2 pooled data, China TRUST)[2]

Median PFS 33.2 months (22.1-NR)
18-month DOR rate 81.3%
Median follow-up 18.0 months

PFS



IC-ORR*

	Efficacy (N=12)
IC-ORR, % (n/N) [95% CI]	91.7 (11/12) [61.5% – 99.8%]
IC-DCR, % (n/N) [95% CI]	100 (12/12) [73.5% – 100.0%]

**includes both TKI-naïve and -pretreated*

1. Cho BC et al. WCLC 2023. Abstract 3255.
2. Li W et al. ELCC 2023. Abstract 14MO.

ROS1: Advances in Addressing Resistance with Next-Generation TKIs

	Lorlatinib (Phase 1/2)	Repotrectinib (TRIDENT-1 Phase 1/2)	Taletrectinib (TRUST-II Global Phase 2[1])	NVL-520 (ARROS-1 Phase 1)
Patients	N=40	N=56	N=21	N=21
ORR	**35%** **(prior crizotinib)**	**38%** **(only 1 prior ROS1 TKI and no prior chemo)*** *FDA breakthrough therapy designation	**57.1%** **(1 prior ROS1 TKI and ≤1 prior chemo)*** *FDA breakthrough therapy designation	**48%** • **53% (9/17) with ≥2 prior ROS1 TKI, ≥1 chemo** • **50% (9/18) with prior lorlatinib or repotrectinib**
Median PFS	**8.5 months**	**9.0 months**	**11.7 months**	**Not reported**
CNS activity	12/24 (50%) with measurable or nonmeasurable CNS disease	5/13 (38%) with measurable CNS metastases	5/8 (62.5%) with measurable CNS metastases	CNS responses reported
Clinical ROS1 G2032R activity	Response in 0/6 **(0%)** patients with a baseline ROS1 G2032R in plasma	Responses in 10/17 **(59%)** patients with a baseline ROS1 G2032R	Responses in 4/5 **(80%)** patients with a baseline ROS1 G2032R[2]	Responses in 7/9 **(78%)** patients with a baseline ROS1 G2032R
Most common TRAEs or TEAEs (all grades)	Hypercholesterolemia, hypertriglyceridemia, edema, peripheral neuropathy, cognitive/mood effects, weight increased	Dizziness, dysgeusia, constipation, paresthesia, dyspnea, anemia, fatigue, nausea, muscular weakness, ataxia	Diarrhea, nausea, vomiting, ALT increase, AST increase, anemia, neutrophil count decrease	No DLTs or treatment-related SAEs or dizziness reported
Reference	Shaw AT et al. *Lancet Oncol*. 2019.	Cho BC et al. WCLC 2023.	1. Pérol M et al. ESMO 2023 2. Li W et al. ELCC 2023.	Drilon A et al. EORTC-NCI-AACR 2022.

TARGETED THERAPY

RET FUSION+ LUNG CANCER

Selective RET TKIs (Selpercatinib and Pralsetinib) in *RET* Fusion+ NSCLC

	Platinum-Pretreated		Treatment-Naïve	
	Selpercatinib (LIBRETTO-001)	**Pralsetinib** (ARROW)	**Selpercatinib** (LIBRETTO-001)	**Pralsetinib** (ARROW)
Patients	N=247	N=136	N=69	N=75
ORR (95% CI)	61% (55-67)	59% (50-67)	84% (73-92)	72% (60-82)
Median PFS (95% CI)	24.9 months (19.3-NE)	16.5 months (10.5-24.1)	22.0 months (13.8 months-NE)	13.0 months (9.1-NR)
Median duration follow-up	24.7 months	18.4 months (13.2-19.8)	21.9 months	9.2 months (8.6-11.0)
Median DOR (95% CI)	28.6 months (20.4-NE)	22.3 months (15.1-NR)	20.2 months (13.0-NE)	NR (9.0 months-NR)
Median duration follow-up	21.2 months	16.7 months (12.9-18.5)	20.3 months	7.4 months (6.4-9.5)
Intracranial ORR (95% CI)	85% (65-96) (n=26 – pretreated + treatment-naïve)	70% (35-93) (n=10; 1/10 received prior non-platinum therapy)		
Reference	Drilon A et al. *J Clin Oncol*. 2022.	Griesinger F et al. *Ann Oncol*. 2022.	Drilon A et al. *J Clin Oncol*. 2023.	Griesinger F et al. *Ann Oncol*. 2022.

LIBRETTO-431: 1L Selpercatinib Superior to Platinum/Pemetrexed +/- Pembrolizumab

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:

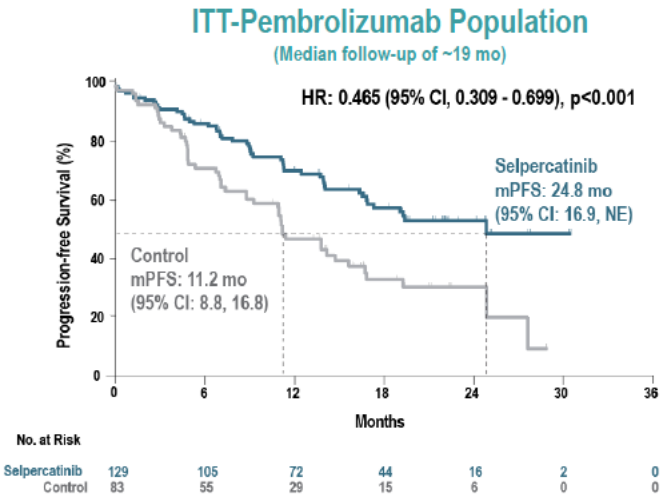
- Geography (East Asian vs. non-East Asian)
- Brain metastases (present vs. absent/unknown)[2]
- Investigator's choice of treatment with pembrolizumab

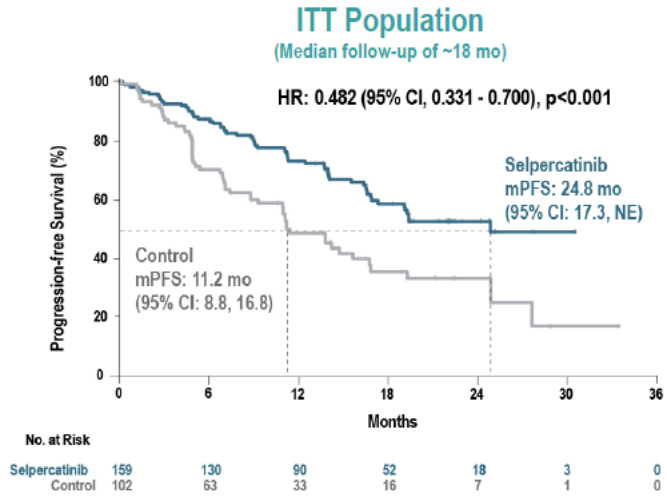
R 2:1[3]

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)





Loong HF et al., ESMO 2023

RET: Resistance to Selective RET Inhibitors

Global RETgistry consortium, initial data

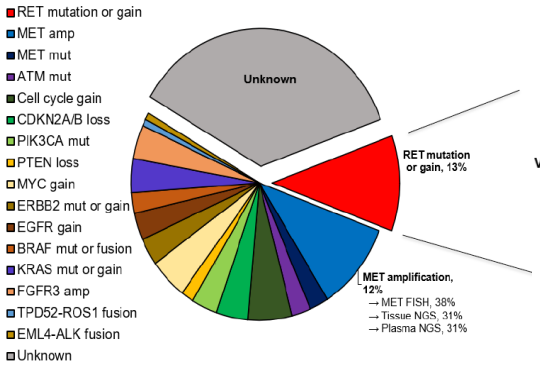


Fig. 2. Putative on- and off-target resistance mechanisms detected in post-RET TKI biopsies. The diagnostic method used for *MET* amplification detection is listed.

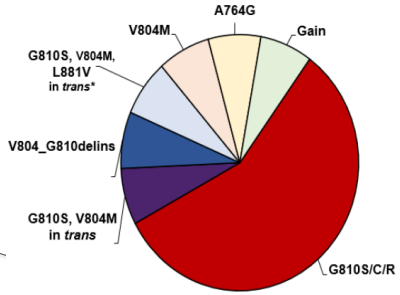


Fig. 3. On-target (*RET*) resistance alterations detected in post-RET TKI biopsies. *G810 and V804M mutations known to be in *trans*.

- 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%**

Cooper AJ et al., ASCO 2023

RET: Advances in Addressing Resistance with 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)

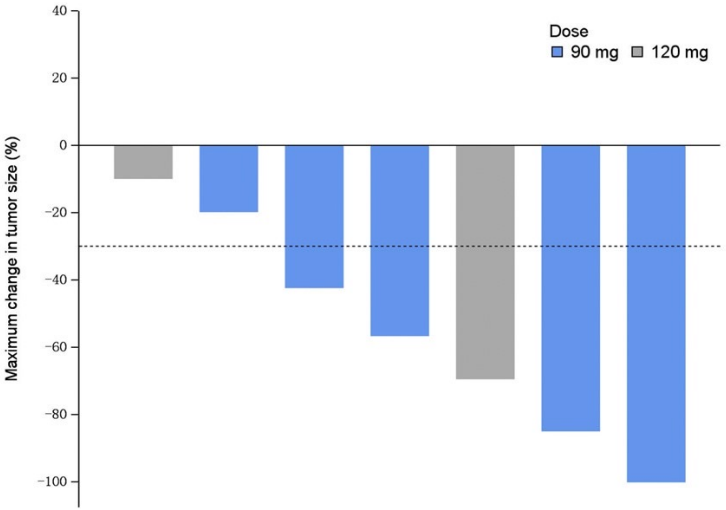
Data based on publicly-available preclinical data; grey = unknown

1. Drilon A et al. ESMO 2019. Abstract 4307. 2. Kolakowski GR et al. AACR 2021. Poster 1464. 3. Miyazaki I et al. AACR-NCI-EORTC 2021. Abstract P06-02. 4. Odintsov I et al. AACR-NCI-EORTC 2021. Abstract P233. 5. Zhou Q et al. ASCO 2023. Abstract 3007. 6. Drilon A et al. AACR 2022. Abstract 5363.

RET: Early Efficacy Data of EP0031, Next-Generation Selective RET TKI From China Phase I Study

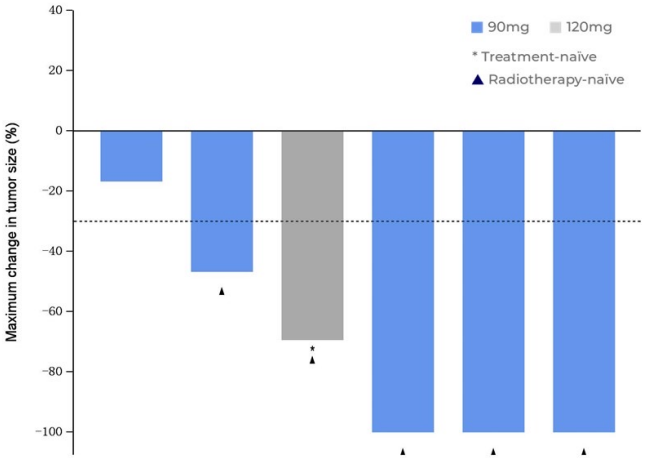
(KL400-I/II-01, NCT05265091)

TARGET LESION RESPONSE IN NSCLC PATIENTS WITH PRIOR 1ST GEN SRI TREATMENT



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.

Zhou Q et al., ASCO 2023

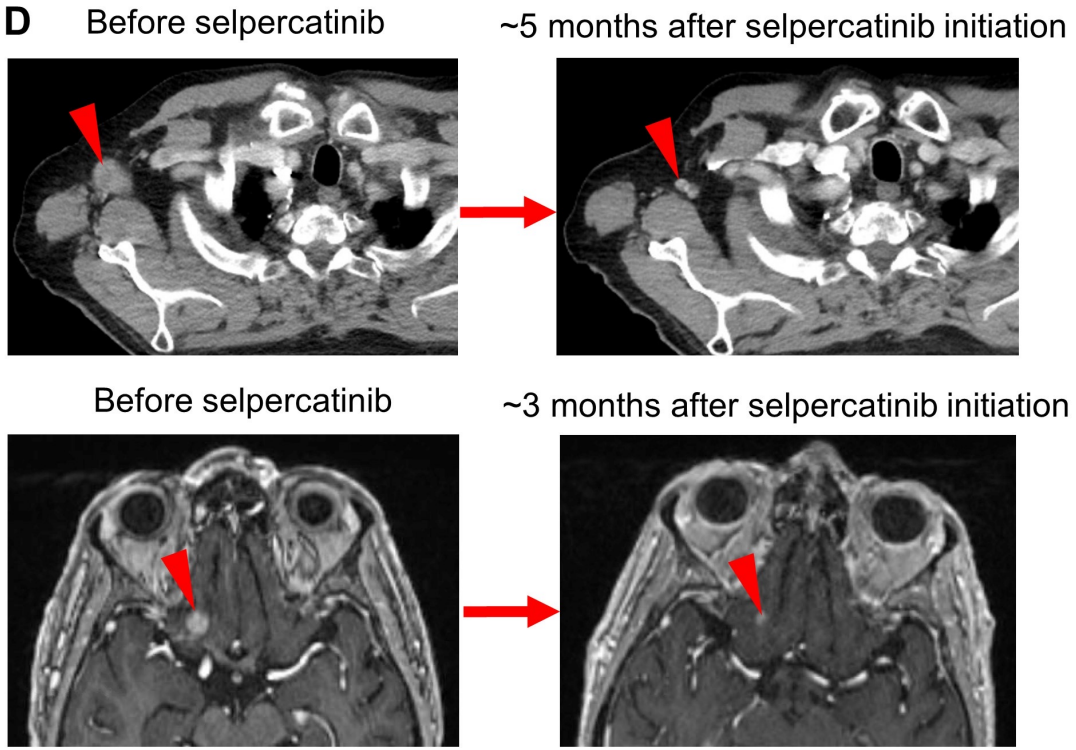
Response of *RET*-Amplified NSCLC to Selpercatinib

Case: response to selpercatinib in *RET*-amplified NSCLC

CASE SCENARIO:
- 69-year-old man with stage III NSCLC (favor adenocarcinoma) treated with chemoradiation + durvalumab, with metastatic disease recurrence in the right axillary lymph node and CNS (frontal lobe lesion)
- SRS to brain metastasis deferred given lesion's proximity to optic nerve.

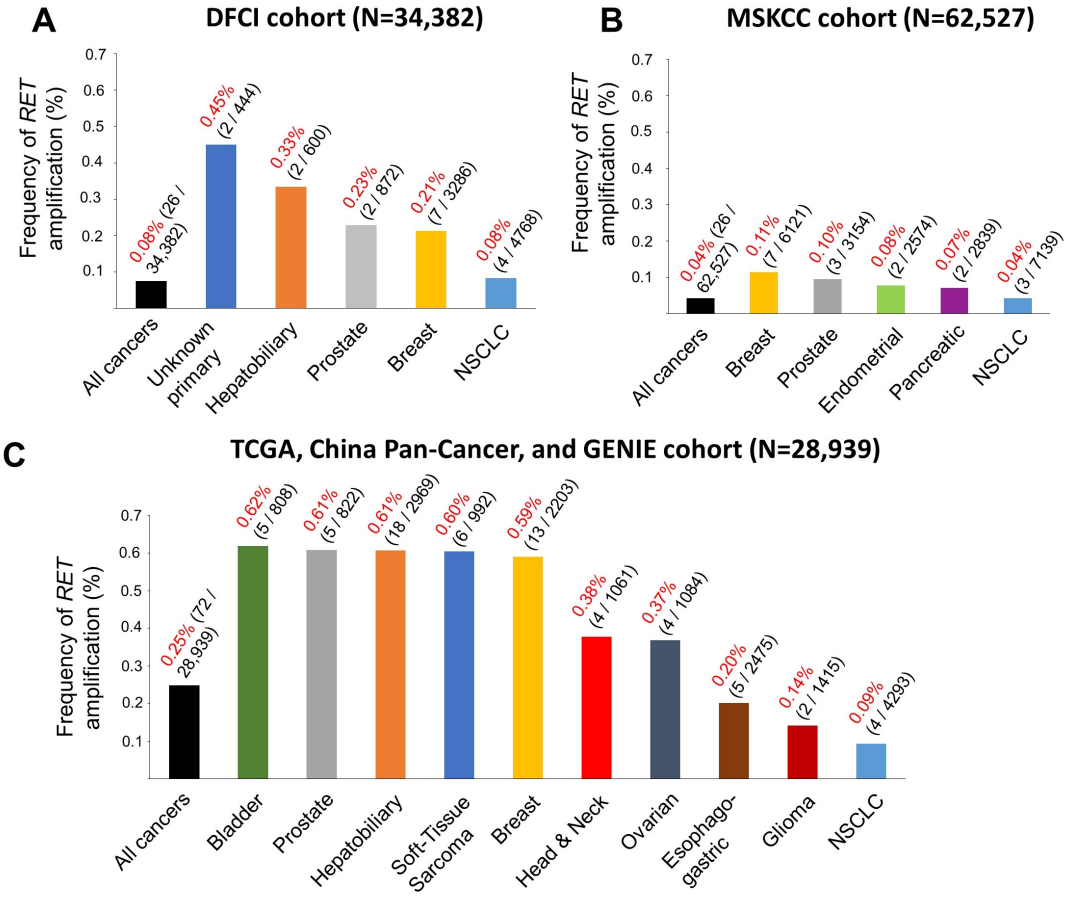
GENOMICS:
- Focal *RET* amplification (22 and 28 copies on initial and recurrent biopsy specimens, respectively) without *RET* fusion or other drivers.

TREATMENT OUTCOMES:
- Initiated on selpercatinib 160 mg BID.
- Experienced a systemic and intracranial response (complete response in right axillary lymph node, -53% reduction in brain lesion). Response ongoing at ~5 months.
- Treatment has been well-tolerated.



Gandhi MM et al., ASCO 2023

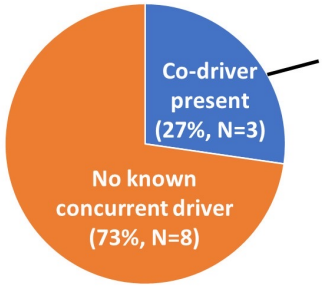
RET Amplification Across Cancers



- **Frequency 0.04-0.25% among all cancers** and 0.04-0.09% in NSCLC
- **Occurs without a concurrent driver in a subset of NSCLC**

D

Concurrent Driver Alterations (among N=11 *RET*-amplified NSCLC cases)



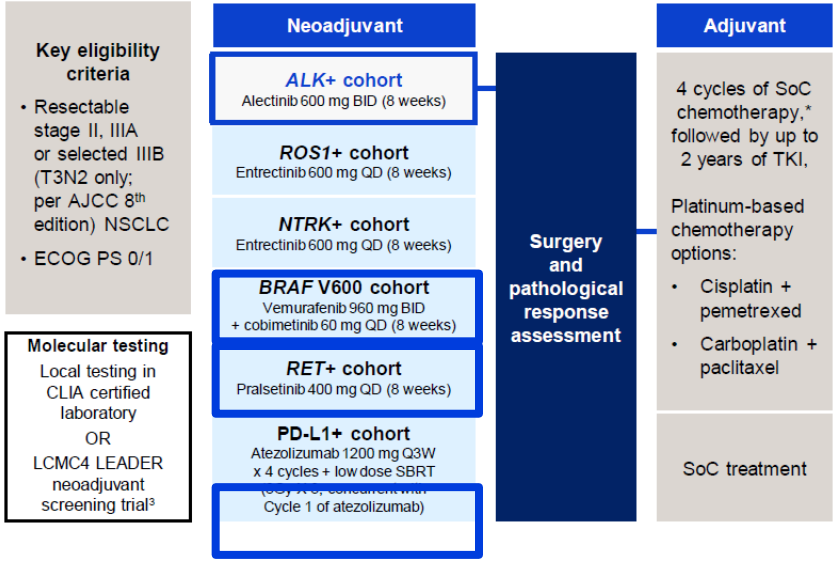
Type of Co-Driver

- *KRAS* G12C
- *MET* amplification
- *EGFR* exon 20 insertion

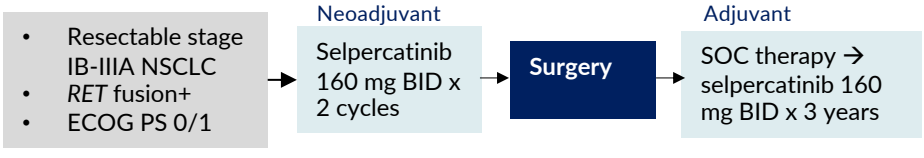
Gandhi MM et al., ASCO 2023

Assessing RET TKIs in Earlier-Stage *RET* Fusion-Driven NSCLC: Adjuvant and Neoadjuvant RET TKI Trials

NAUTIKA1 (NCT04302025)[1,2]

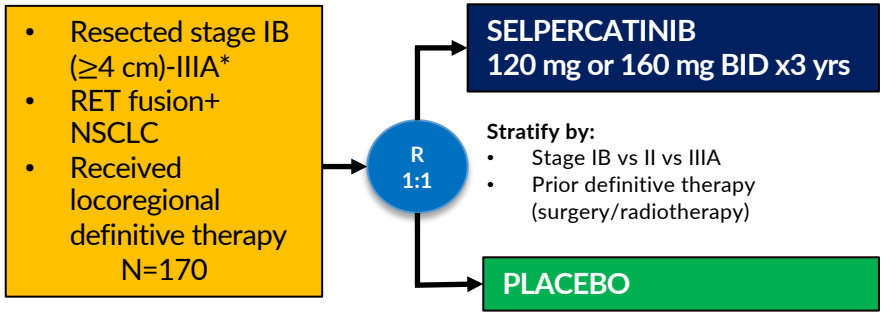


LIBRETTO-001, cohort 7 (NCT03157128)[3,4]



Primary Endpoint: MPR

LIBRETTO-432 (NCT04819100)[5]



Primary Endpoint: EFS

[1]Lee JM et al., WCLC 2022; [2]Clinicaltrials.gov, https://classic.clinicaltrials.gov/ct2/show/NCT04302025 (accessed 16 Jul 2023)
[3]Rajaram R et al., ASCO 2022; [4]Clinicaltrials.gov, https://classic.clinicaltrials.gov/ct2/show/NCT03157128 (accessed 16 Jul 2023)
[5]Clinicaltrials.gov, https://classic.clinicaltrials.gov/ct2/show/NCT04819100 (accessed 16 Jul 2023)

IO in *ALK/ROS1/RET* Fusion+ NSCLC: Minimal Benefit from ICI Monotherapy

Driver	n	RR	PFS	OS	Impact (+/-) on PFS of				Comments
					PDL1	Smoking	Nb line	Subtype	
Total		19%	2.8	13.3					Outcome consistent with registration trials for ICI
KRAS	271	26%	3.2	13.5	+	X	X	X	Clear benefit across all subgroups
EGFR	125	12%	2.1	10	+	X	X	+/-(1)	Could be considered in PDL1 + after TKIs exhaustion
BRAF	43	24%	3.1	13.6	NA	+	X	X	Could be considered in smokers
MET	36	16%	3.4	18.4	NA	X	NA	X	Could be considered after conventionnal treatment
HER2	29	7%	2.5	20.3	NA	+	X	NA	
ALK	23	0	2.5	17	NA	-	X	NA	Poor outcome. New biomarker needed.
RET	16	6%	2.1	21.3					
ROS1	7	17%	-	-					

+ : positive impact on PFS
X : non-significant impact on PFS
- : negative impact on PFS

Mazieres J et al. *Ann Oncol*. 2019;30(8):1321-1328.

Limited Evidence Regarding Role for Chemo + Anti-PD(L)1 +/- Anti-VEGF – Borrowing Data Mostly from EGFRmut NSCLC

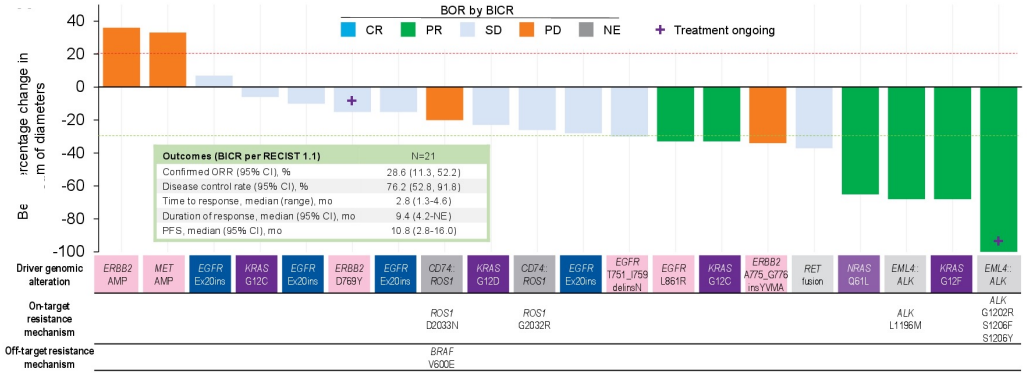
Trial	Treatment	Genotype	N	ORR	PFS	OS
KEYNOTE-789[1]	**Pembrolizumab** + platinum/pem vs platinum/pem	EGFR	245 vs 247	29.0% vs 27.1%	**HR 0.80 (0.65-0.97)** **5.6 mo vs 5.5 mo**	**HR 0.84 (0.69-1.02)** **15.9 mo vs 14.7 mo**
CheckMate-722[2]	**Nivolumab** + platinum/pem vs platinum/pem	EGFR	144 vs 150	31% vs 27%	**HR 0.75 (0.56-1.00)** **5.6 mo vs 5.4 mo**	**HR 0.82 (0.61-1.10)** **19.4 mo vs 15.9 mo**
ORIENT-31[3]	**Sintilimab** + **IBI305** + cis/pem (arm A) vs **sintilimab** + cis/pem (arm B) vs cis/pem (arm C)	EGFR	158 vs 158 vs 160	48.1% vs 34.8% vs 29.4%	**Arm A vs C: HR 0.51** (0.39-0.67) **Arm B vs C: HR 0.72** (0.55-0.94) **7.2 mo vs 5.5 mo vs 4.3 mo**	**Arm A vs C: HR 0.98** (0.72-1.34) **Arm B vs C: HR 0.97** (0.71-1.32) **21.1 mo vs 20.5 mo vs 19.2 mo**
IMpower150[4,5]	**Atezolizumab** + **bev** + carbo/pac vs **atezolizumab** + carbo/pac vs **bev** + carbo/pac	EGFR subgroup	34 vs 45 vs 44	70.6% vs 35.6% vs 41.9%	**ABCP vs BCP HR 0.61** (0.36-1.03) **ACP vs BCP HR 1.14** (0.73-1.78) **10.2 mo vs 6.9 mo vs 6.9 mo**	**ABCP vs BCP HR 0.91** (0.53-1.59) **ACP vs BCP HR 1.16** (0.71-1.89) **26.1 mo vs 21.4 mo vs 20.3 mo**
IMpower151[6]	**Atezolizumab** + **bev** + carbo + pem/pac vs **bev** + carbo + pem/pac	EGFR/ALK subgroup	81 vs 82	-----	**HR 0.86 (0.61, 1.21)** **8.5 mo vs 8.3 mo**	-----
ATTLAS, KCSG-LU19-04[7]	**Atezolizumab** + **bev** + carbo/pac vs PT/pem	EGFR/ALK	154 vs 74	**69.5% vs 41.9%**	**HR 0.62 (0.45-0.86)** **8.48 mo vs 5.62 mo**	**HR 1.01 (0.69-1.46)** **20.63 mo vs 20.27 mo**

[1]Yang J et al., ASCO 2023; [2]Mok T et al., ESMO Asia 2022; [3]Lu S et al., Lancet Respir Med 2023;11(7):624-36; [4]Reck M et al., Lancet Respir Med 2019;7(5):387-401; [5]Nogami N et al., J Thorac Oncol 2022;17(2):309-23; [6]Zhou C et al., WCLC 2023; [7]Ahn MJ et al., ESMO 2023

Exploring resistance mechanism-agnostic approach

ADCs in TKI-Resistant Fusion-Driven NSCLC

Activity of patritumab deruxtecan in NSCLC with non-classical EGFRmut AGAs[1]



Activity of datopotamab deruxtecan in NSCLC with AGAs[2] including EGFR and ALK

Response per BICR	All treated patients (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 (95% CI), months	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, (95% CI), months[b]	5.4 (4.7-7.0)	5.8 (5.4-8.3)	4.3 (2.6-6.9)

- **Patritumab deruxtecan** (**anti-HER3 ADC**)[1] & **datopotamab deruxtecan** (**anti-TROP2 ADC**)[2] have shown signals of activity in patients with fusion-driven NSCLC (small n's)
- In early data, clinical activity of ADCs across AGA subsets appears **irrespective of** the spectrum of known or unknown **resistance mechanisms**[1-3]

[1]Steuer C et al., ASCO 2022; [2]Paz Ares L et al., ESMO 2023
[3]HA et al., WCLC 2023; doi: 10.1200/JCO.23.01476

Highlights from ASCO, WCLC, ESMO 2023 on *ALK/ROS1/RET* Fusion-Driven NSCLC

- ✓ Adjuvant alectinib represents a new standard treatment strategy for patients with surgically resected, stage IB-IIIA, ALK+ NSCLC
- ✓ Across fusion-driven lung cancers, targeted therapy represents the standard-of-care 1L treatment in the advanced/metastatic setting
- ✓ Next-generation TKIs can be accessed through clinical trials after disease relapse on 1L targeted therapies and have shown promising results across *ALK*, *ROS1*, *RET* fusion+ NSCLC
- ✓ Anti-PD(L)1 immune checkpoint inhibitors are generally not effective in fusion-driven lung cancers, and we have not seen conclusive data to support the chemo + anti-PD(L)1 + anti-angiogenic strategy post-TKIs
- ✓ ADCs have shown encouraging activity in TKI-refractory, fusion-driven lung cancers