Targeted Therapies and Resistance, New Agents are Coming

PRIMO- February 7, 2025

Misako Nagasaka, MD PhD

Associate Clinical Professor
University of California Irvine School of Medicine
Division of Hematology and Oncology

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Actionable driver mutation	Approved drugs
EGFR del19/L858R	Gefitinib, Erlotinib, Erlotlinib/Ramcirumab, Afatinib, Daco, Osimertinib
EGFR del19/L858R + T790M	Osi, Osi-chemo (2/16/24), Ami-Laz (8/19/24), Ami-chemo (9/19/24)
EGFR uncommon mutations (G719X, S768I, L861Q)	Afatinib
EGFR exon20 insertion	Amivantamab-vmjm (5/21/2021), Ami-Chemo (3/1/24), ~~Mobocertinib (September 15, 2021)~~
ALK	Crizotinib, Ceritinib, Alectinib, Brigatinib, Lorlatinib, adjuvant Alectinib (4/18/24)
ROS1	Crizotinib, Entrectinib, Repotrectinib (November 15, 2023)
RET	Selpercatinib (May 8, 2020), Pralsetinib (September 4, 2020)
NTRK	Larotrectinib (November 26, 2018), Entrectinib (August 15, 2019), Repotrectinib (7/13/24)
BRAF V600E	Dabra + Trametinib (6/22/2017), Encorafenib + binimetinib (10/11/23)
MET ex14 splice site mutation	Capmatinib (May 6, 2020), Tepotinib (February 3, 2021)
KRAS G12C	Sotorasib (May 28, 2021), Adagrasib (December 12, 2022)
HER2 mutation	Fam-trastuzumab deruxtecan-nxki /T-DXd (August 11, 2022)
NRG1 fusion	Zenocutuzumab (12/ 4/24)

Slide courtesy of Dr Ignatius Ou

Table of contents

ALK

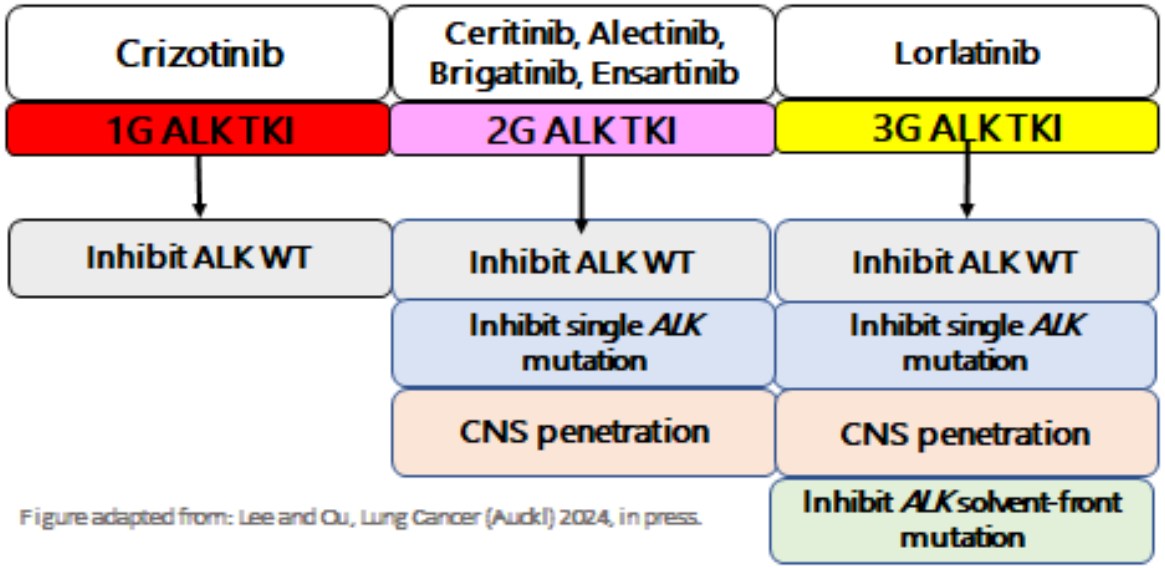


Figure adapted from: Lee and Ou, Lung Cancer (Auckl) 2024, in press.

- ALK fusions are oncogenic drivers in 3-5% of NSCLC and various cancers[1]
- ~30-40% of patients with ALK+ NSCLC present with CNS metastases[2]
- ~50% of patients develop single mutations (e.g., G1202R, I1171X, F1174X) after progression on 1G and 2G ALK TKIs[3,4]

[1] Kwak, E. *et al*. N Engl J Med. 2010; [2] Gainor, J. *et al*. JCO Precis Oncol. 2017;
[3] Dagogo-Jack, I. *et al*. Clin Cancer Res. 2019; [4] Gainor, J. *et al*. Cancer Discov. 2016;

ALK

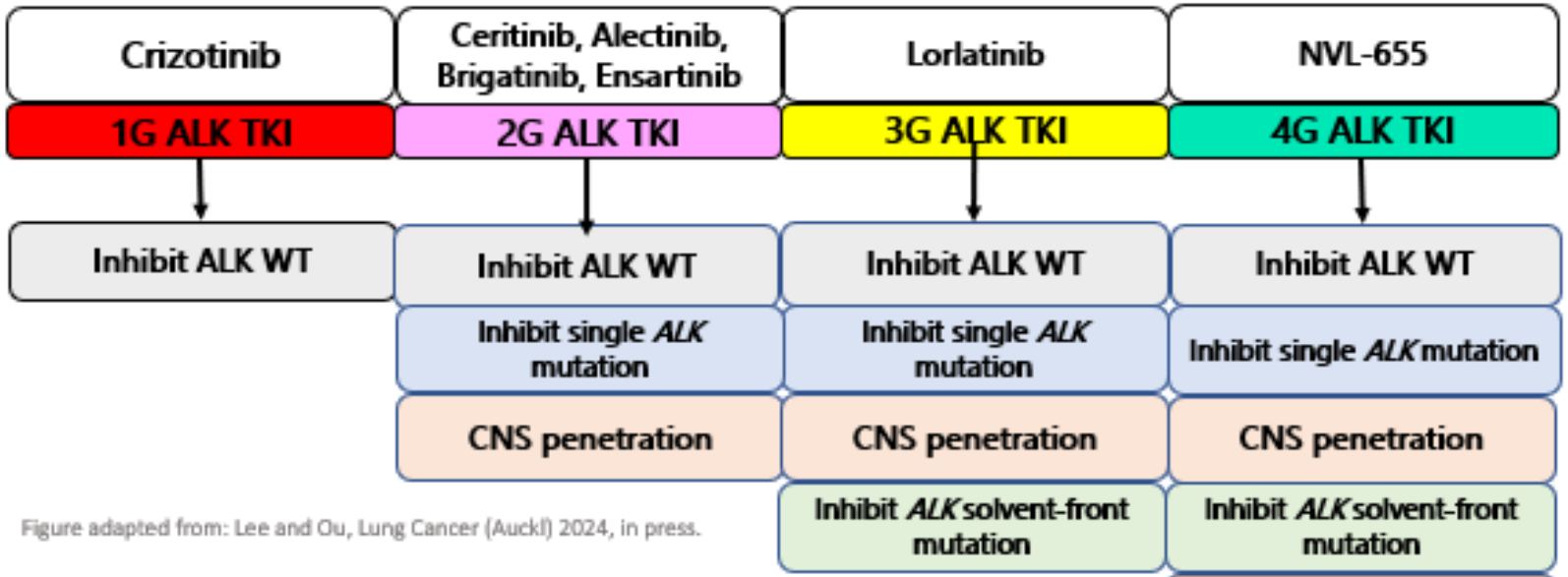


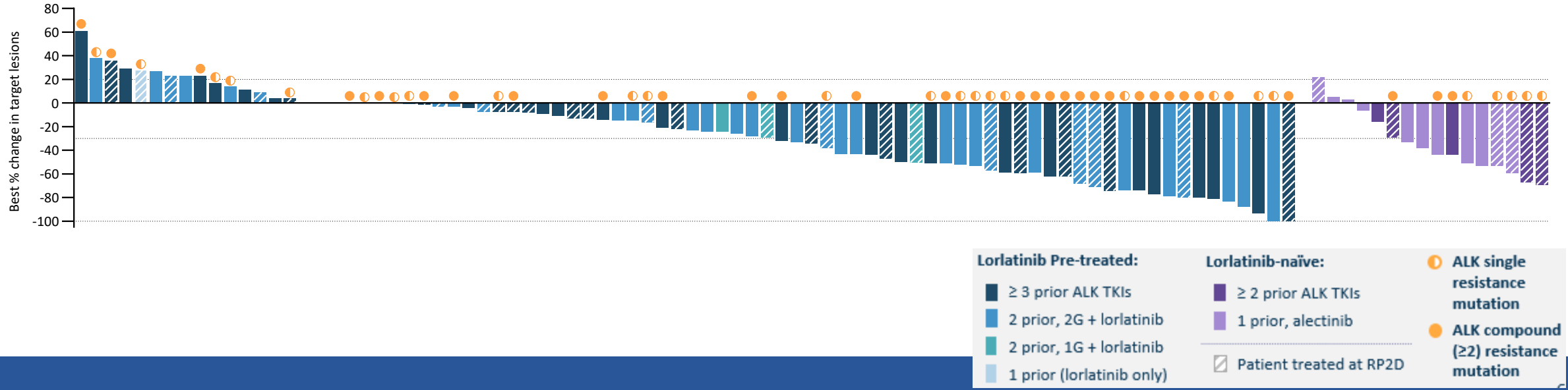
Figure adapted from: Lee and Ou, Lung Cancer (Auckl) 2024, in press.

- ~25 – 50% of patients develop compound mutations (e.g., G1202R/L1196M) after progression on sequential 2G to 3G TKIs[1,2]
- TRK inhibition in the brain is linked to neurologic adverse events and dose-limiting toxicities[3,4]

[1] Dagogo-Jack, I. *et al.* Clin Cancer Res. 2019; [2] Shiba-Ishii *et al.*, Nature Cancer 2022;
[3] Cocco, E. *et al.* Nat Rev Clin Oncol. 2018; [4] Shaw, A. *et al.* N Engl J Med. 2020.

NVL-655

RECIST 1.1 ORR, % (n/N) *All patients ± chemotherapy*	NSCLC Response-Evaluable (Any Prior ALK TKI, range 1 – 5)			Prior Lorlatinib (≥2 ALK TKIs)			Lorlatinib-naive (≥1 2G ± 1G)	
	All	Any ALK mutation [a]	G1202R [b]	All	Any ALK mutation	Compound ALK mutation [c]	All	Any ALK mutation
All Doses	**38%** (39/103)	**52%** (30/58)	**69%** (22/32) [d]	**35%** (30/85)	**47%** (23/49)	**54%** (15/28)	**53%** (9/17)	**88%** (7/8)
RP2D	**38%** (15/39)	**55%** (12/22)	**71%** (10/14)	**35%** (11/31)	**50%** (8/16)	**64%** (7/11)	**57%** (4/7)	**80%** (4/5)



Alex Drilon, et al. Phase 1/ 2 ALKOVE-1 study of NVL-655 in ALK-positive (ALK+) solid tumors, ESMO 2024

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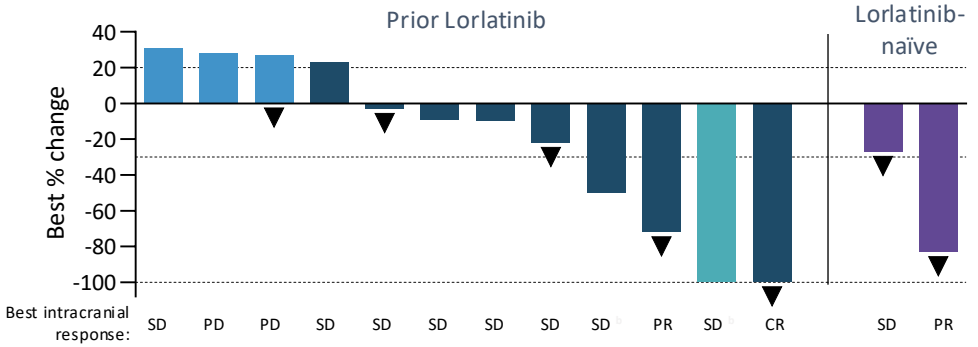
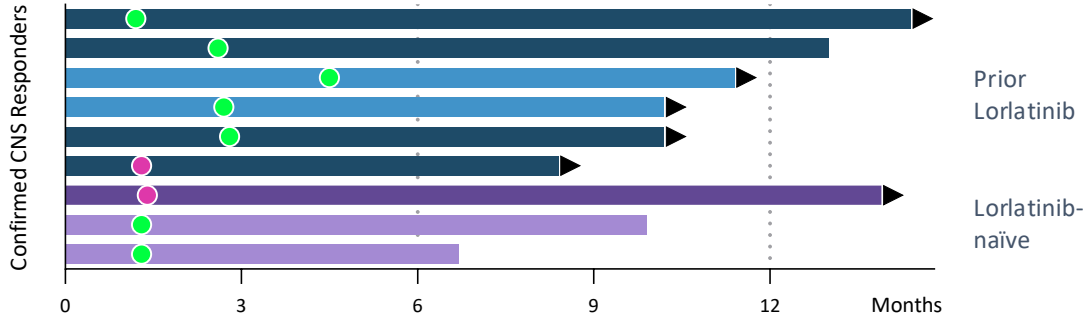
NVL-655

- **IC-ORR** (patients with measurable CNS lesions):
  - **Lorlatinib-naïve**: 50% (1/2)
  - **Prior lorlatinib:** 15% (2/13)
    - 31% (4/13) including 2 CNS uPRs not confirmed due to discontinuation of treatment in absence of CNS progression
- **No CNS progression among confirmed CNS responders, including in patients who previously received the brain-penetrant TKI lorlatinib** (measurable or unmeasurable CNS lesions)
    - Treatment duration: 6.7 - 14.4+ months

CNS Tumor Shrinkage
(Patients with Measurable CNS Lesions [a])



Duration of Treatment for all Confirmed CNS Responders
(Patients with Measurable or Unmeasurable CNS Lesions)



NVL-655

- Discontinuation due to TRAE: 2% (3/133) [a]
- Dose reduction due to TRAE: 15% (20/133) [b]
- Preliminary overall safety profile consistent with avoiding TRK-related neurotoxicities

Treatment-Related Adverse Events (TRAEs) in ≥ 10% of Patients
All Treated (N = 133)

Preferred Term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)
ALT increased	21 (16%)	6 (5%)	17 (13%)	1 (1%)	45 (34%)
AST increased	21 (16%)	7 (5%)	12 (9%)	-	40 (30%)
Constipation	15 (11%)	6 (5%)	-	-	21 (16%)
Dysgeusia	15 (11%)	2 (2%)	-	-	17 (13%)
Nausea	15 (11%)	1 (1%)	-	-	16 (12%)

RP2D selected as 150 mg QD

MTD not reached through 200 mg QD

No clear dose-toxicity relationship through 150 mg QD dose level

150 mg QD maintained steady state plasma levels at or above the target efficacy thresholds

(ALK fusions + ALK single/compound mutations in periphery and in the CNS)

ALK

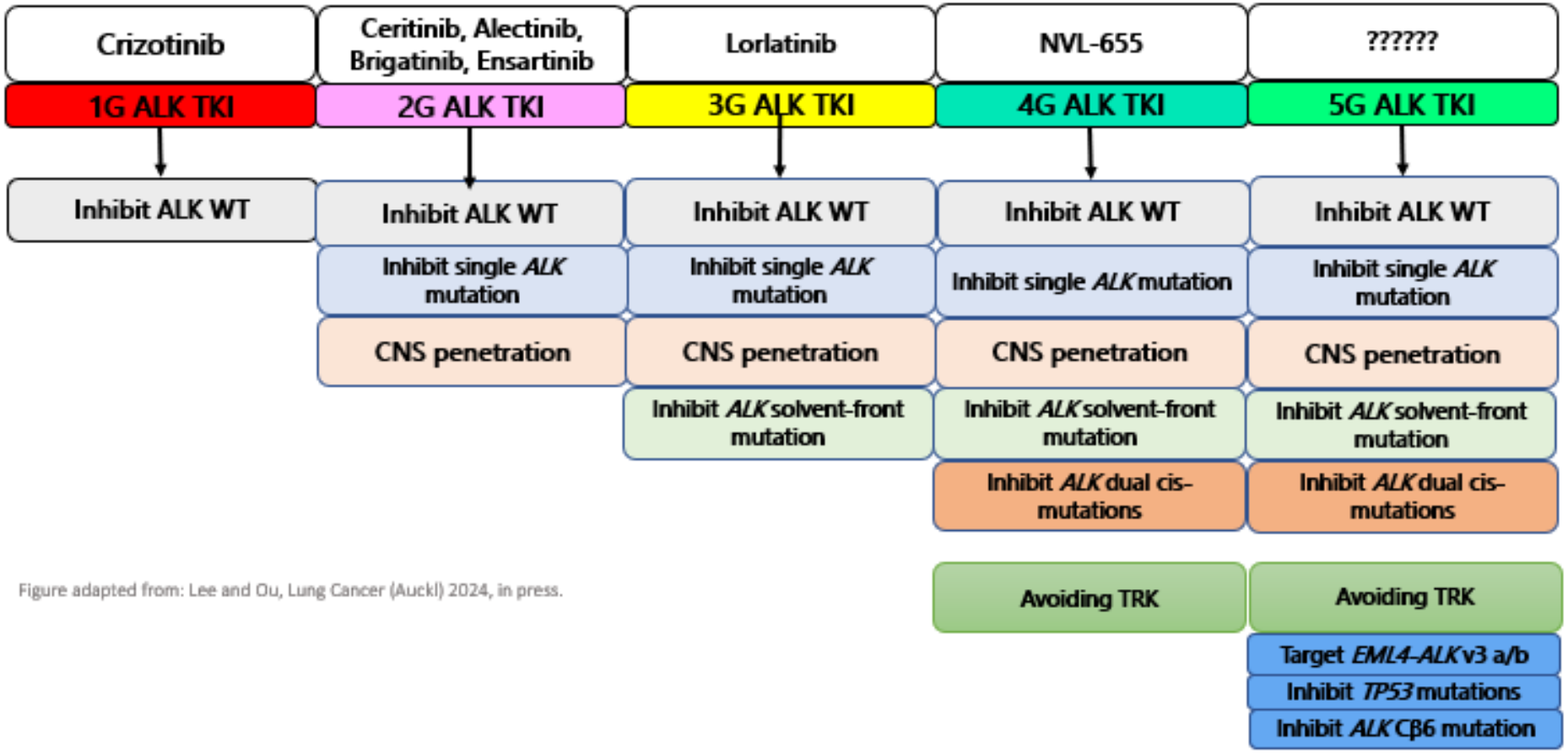
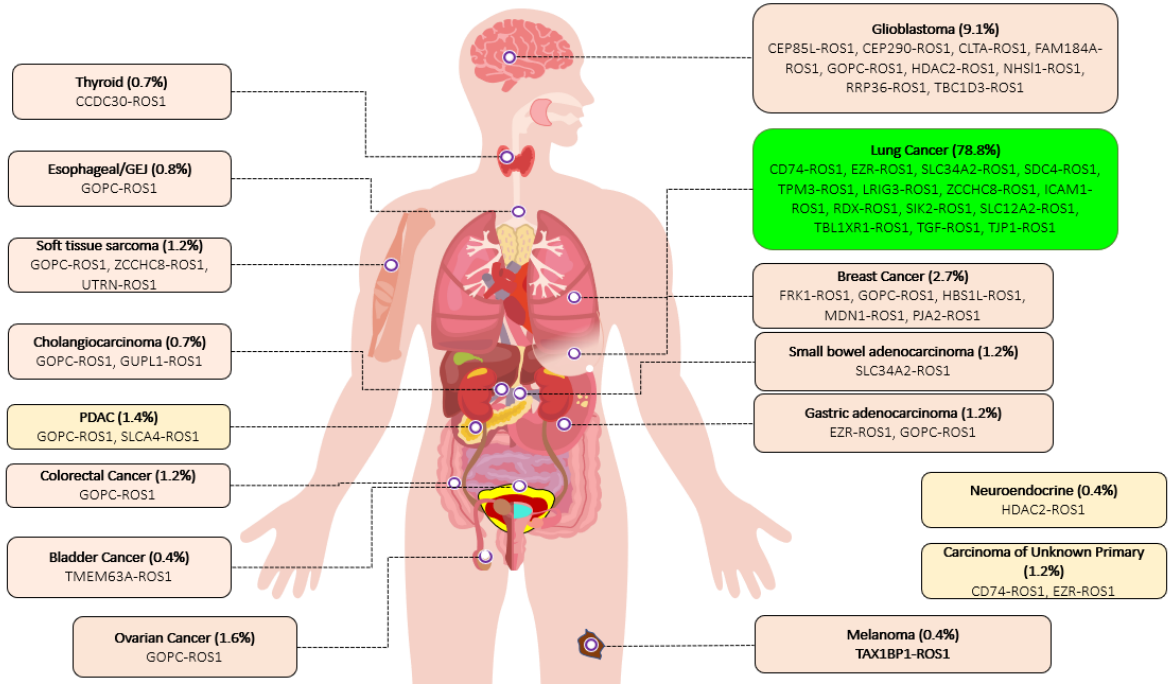


Figure adapted from: Lee and Ou, Lung Cancer (Auckl) 2024, in press.

ROS1

- *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]



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. Nagasaka M, et al. *BMC Cancer* 2023; 23(1):1000.

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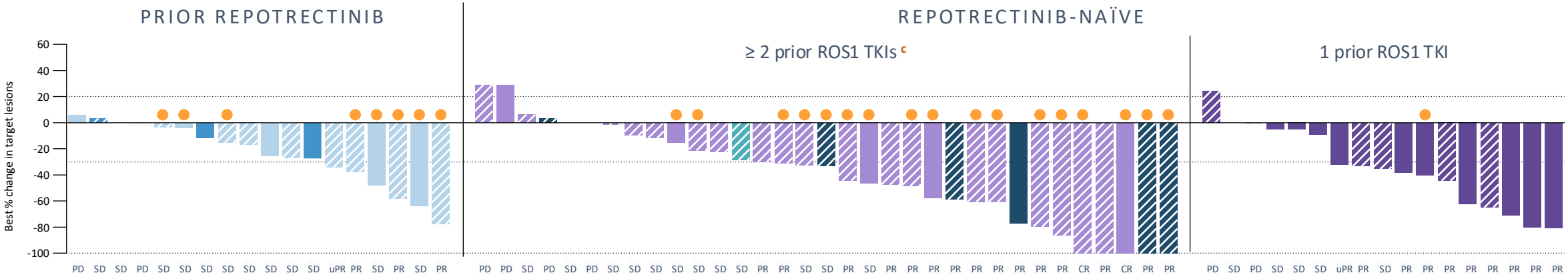
NVL-520 (zidesamtinib)

Prior Repotrectinib: ≥ 2 prior ROS1 TKIs; 1 prior ROS1 TKI
Repotrectinib-naive: 4 prior ROS1 TKIs; 3 prior ROS1 TKIs; 2 prior ROS1 TKIs; 1 prior ROS1 TKI
+ chemotherapy
ROS1 G2032R mutation

All NSCLC Response Evaluable Patients *± chemotherapy*	Any Prior ROS1 TKI (range 1-4)		≥ 2 prior ROS1 TKIs			ROS1 G2032R Resistance Mutation [b]		1 prior ROS1 TKI (crizotinib)
	All	Repotrectinib-naive	All	Prior Lorlatinib	Repotrectinib-naive	Prior Repotrectinib	Repotrectinib-naive	
RECIST 1.1 ORR % (n/n) [a]	**44%** (31/71)	**51%** (27/53)	**41%** (21/51)	**44%** (17/39)	**47%** (17/36)	**38%** (3/8)	**72%** (13/18)	**73%** (8/11)
CR*	2	2	2	2	2	-	2	-

* 2 confirmed CRs ongoing with DOR 19.3+ and 26.3+ months. 5 additional CRs observed among patients without measurable disease (2 prior ROS1 TKIs [n=2], 1 prior ROS1 TKI (crizotinib [n=1], entrectinib [n=2]), all ongoing with DOR 3.6+, 3.7+, 13.8+, 13.9+, and 18.5+ months.



B Besse, et al. Phase 1/ 2 ARROS-1 study in zidesamtinib (NVL-520) in ROS1 fusion-positive solid tumors, ESMO 2024

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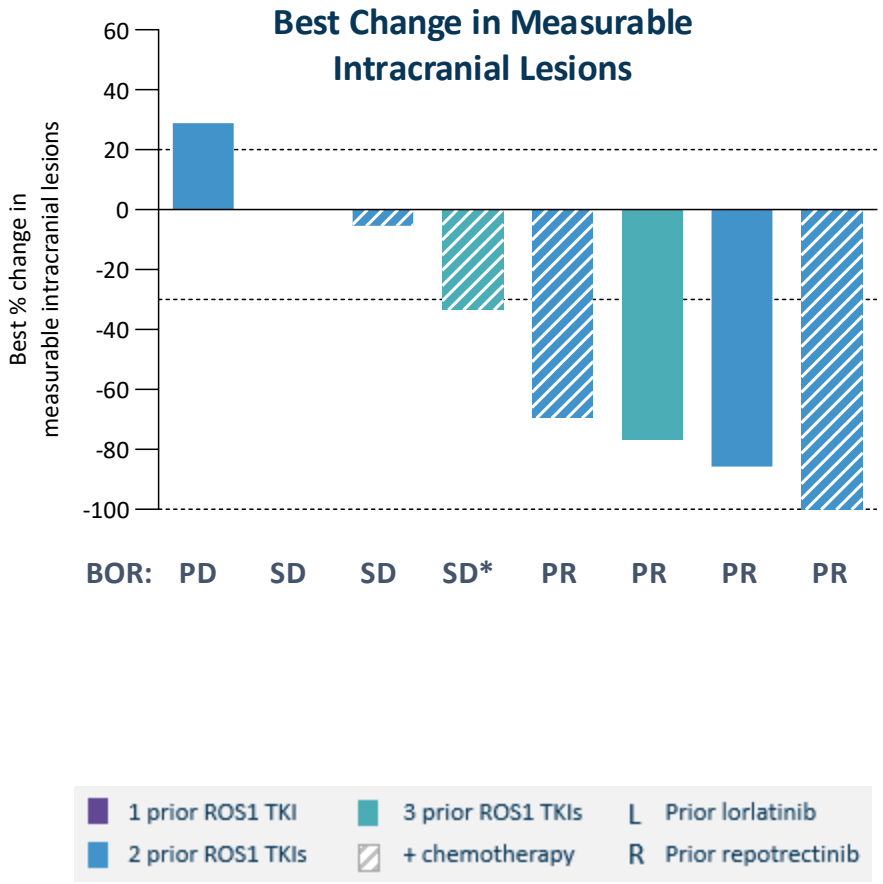
NVL-520 (zidesamtinib)

Among IC-response evaluable patients with measurable intracranial lesions (≥ 10 mm) at baseline:

- IC-ORR: **50%** (4/8)
  - Nearly all (7/8) patients previously received ≥ 2 ROS1 TKIs, including the brain-penetrant ROS1 TKIs lorlatinib and/or repotrectinib
- mDOR: **NR**
  - All IC responses are censored without IC-progression, with IC DORs of 21.0+, 17.4+, 5.6+, and 1.9+ months



B Besse, et al. Phase 1/ 2 ARROS-1 study in zidesamtinib (NVL-520) in ROS1 fusion-positive solid tumors, ESMO 2024

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NVL-520 (zidesamtinib)

- No TRAEs leading to discontinuation
- Dose reduction due to TRAE: 8% (8/104) [a]
- Preliminary overall safety profile consistent with avoiding TRK-related neurotoxicities

Treatment-Related Adverse Events (TRAEs) in ≥ 10% of Patients [b]
All Treated (N = 104)

Preferred Term	Any Grade n (%)	Grade ≥3 n (%)
Oedema peripheral	20 (19%)	-
ALT increased	11 (11%)	-
AST increased	11 (11%)	-
Weight increased	11 (11%)	1 (1%)

RP2D selected as 100 mg QD

MTD not reached through 150 mg QD

No clinically significant exposure-response relationships for safety and efficacy were observed

100 mg QD maintained steady state plasma levels at or above the target efficacy thresholds
(ROS1 fusions + ROS1 mutations in periphery and in the CNS)

B Besse, et al. Phase 1/ 2 ARROS-1 study in zidesamtinib (NVL-520) in ROS1 fusion-positive solid tumors, ESMO 2024

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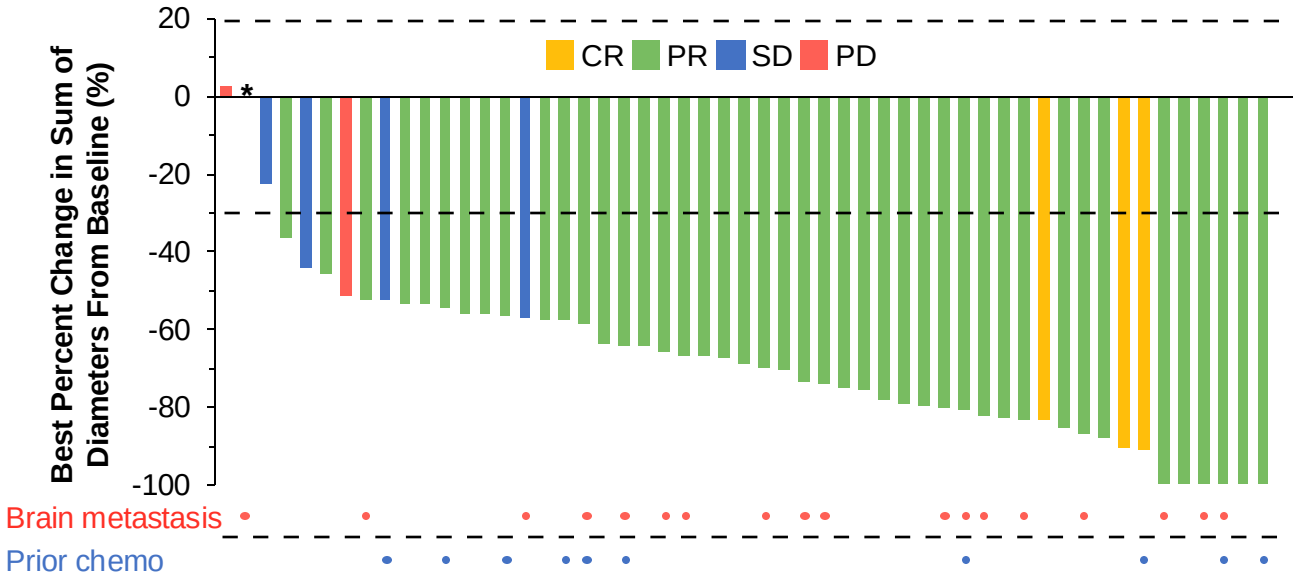
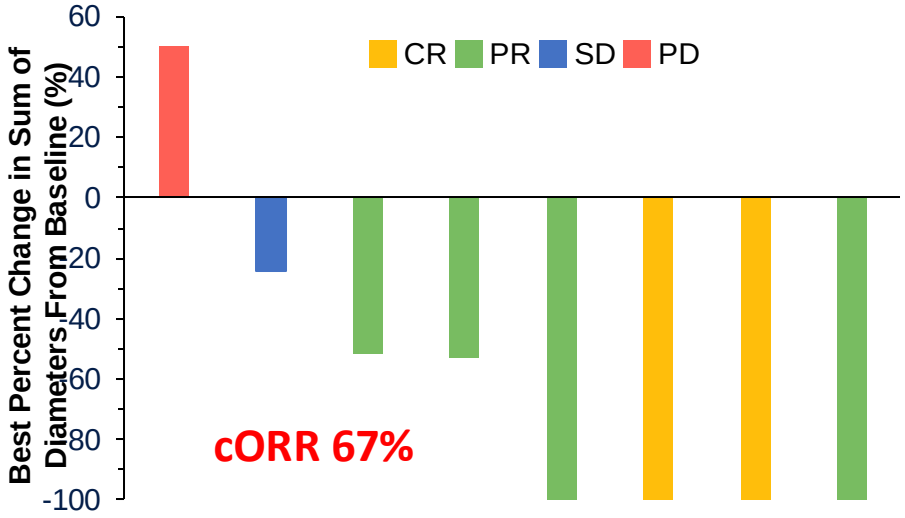
Taletrectinib

TKI-naive

Response Rate	TKI Naive (n=54)
cORR, % (95% CI)	85.2 (72.88, 93.38)
Asia ORR (n=33)	87.9 (71.80, 96.60)
Non-Asia ORR (n=21)	81.0 (58.09, 94.55)

Measurable baseline brain metastases	TKI Naive (n=9)
IC-ORR, % (95% CI)	**66.7 (29.93, 92.51)**
CR, n (%)	2 (22.2)
PR, n (%)	4 (44.4)



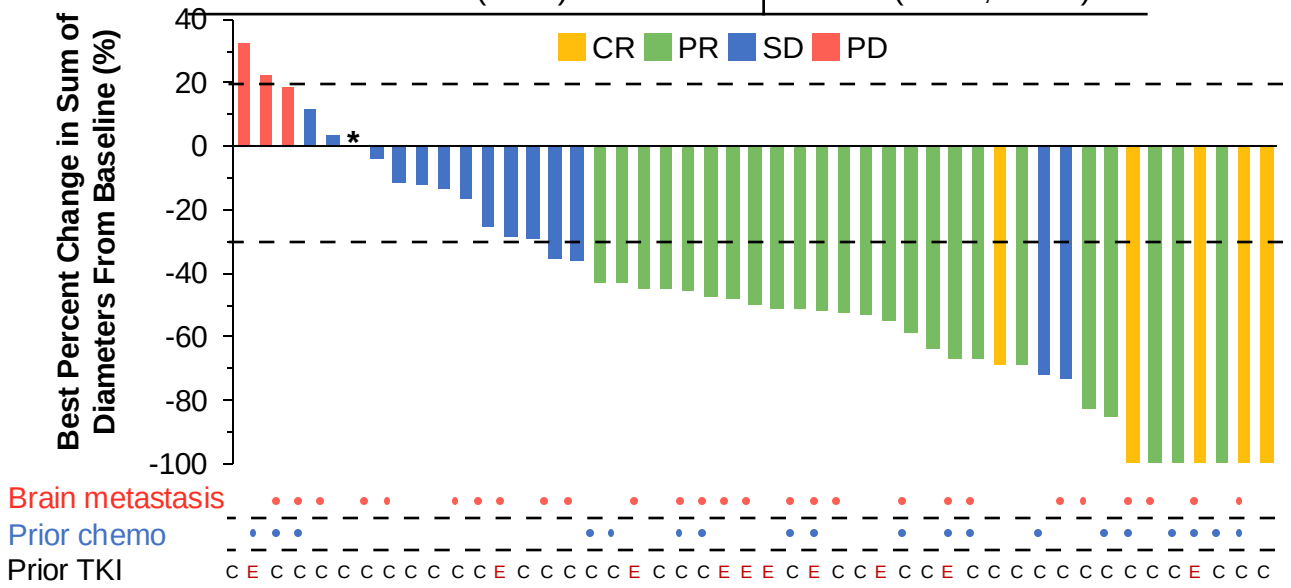


Median follow-up: 15.8 mo (range: 3.6–29.8)

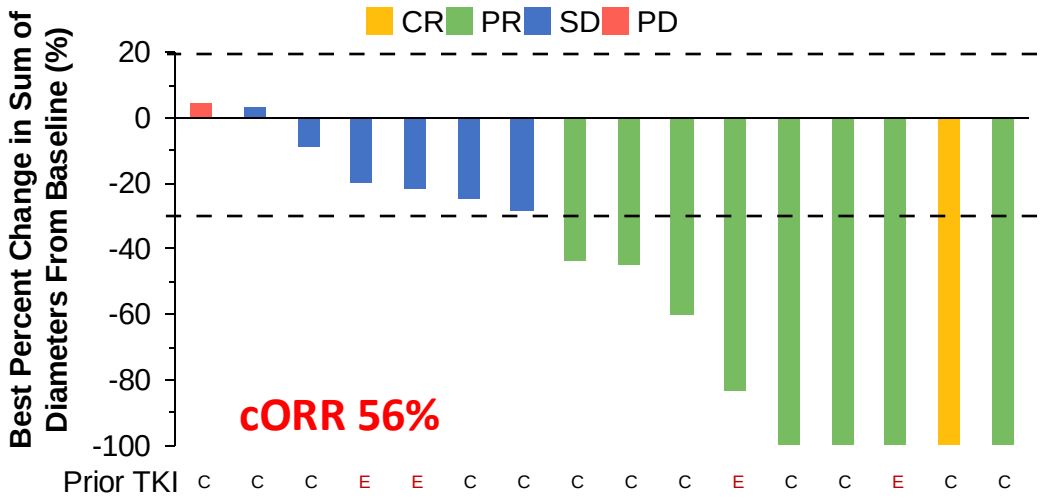
Taletrectinib

TKI-pretreated

	TKI Pretreated (n=47)
cORR, % (95% CI)	61.7 (46.38, 75.49)
Asia ORR (n=21)	57.1 (34.02, 78.18)
Non-Asia ORR (n=26)	65.4 (44.33, 82.79)



Measurable baseline brain metastases	TKI Pretreated (n=16)
IC-ORR, % (95% CI)	**56.3 (29.88, 80.25)**
CR, n (%)	1 (6.3)
PR, n (%)	8 (50.0)



Median follow-up: 15.7 mo (range: 3.9–29.8)

Geoffrey Liu, et al | Efficacy and safety of taletrectinib in patients with ROS1+ Non-Small Cell Lung Cancer: The global TRUST-II study; WCLC 2024

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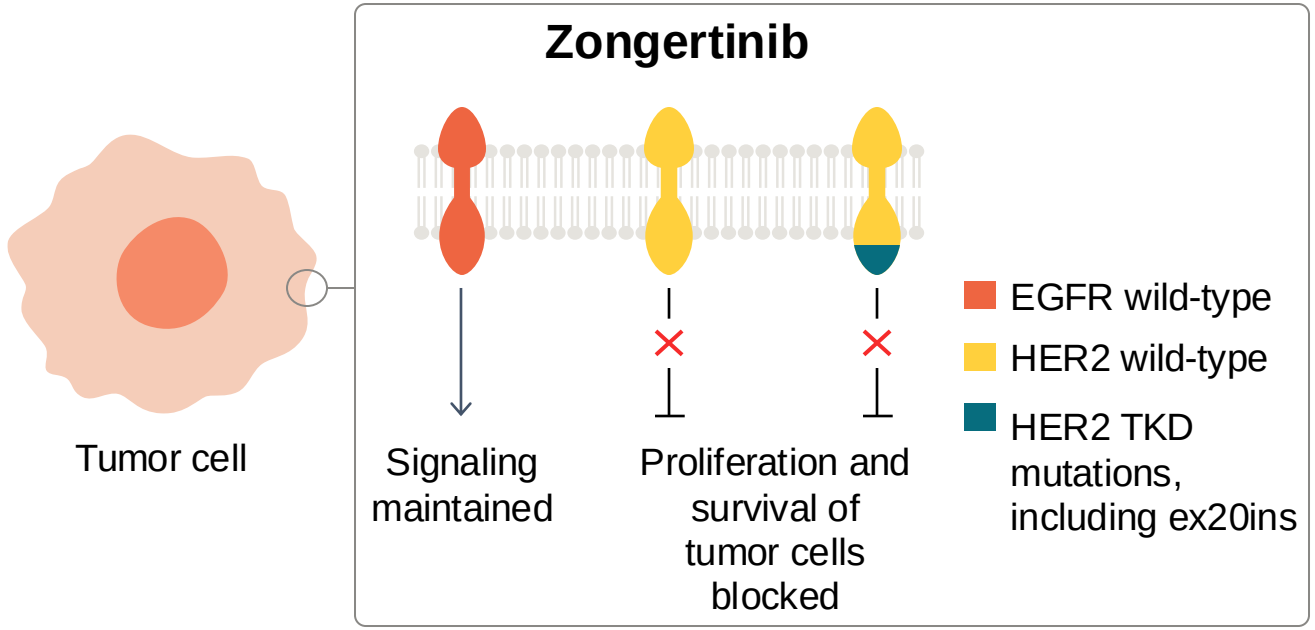
Taletrectinib

	Any grade, n (%)	Grade ≥3, n (%)
Increased ALT	108 (67.9)	24 (15.1)
Increased AST	107 (67.3)	11 (6.9)
Diarrhea	90 (56.6)	1 (0.6)
Nausea	82 (51.6)	3 (1.9)
Vomiting	53 (33.3)	2 (1.3)
Constipation	40 (25.2)	0 (0)
Anemia	32 (20.1)	7 (4.4)
Dysgeusia	31 (19.5)	0 (0)
Increased blood CPK	29 (18.2)	6 (3.8)
Dizziness	27 (17.0)	0 (0)
Prolonged QT	24 (15.1)	5 (3.1)

- Median exposure of taletrectinib was 8.4 months (range: 0.1–28.9)
- **37.1%** of patients had a TEAE leading to a dose reduction
  - The most common events leading to dose reduction were **elevated liver enzymes** (16.4%)
- 7.5% of patients had a TEAE leading to treatment discontinuation; **1.3% were treatment-related**
- Rates of neurologic TEAEs were low (dysgeusia: 19.5%; dizziness: 17.0%); none were grade ≥3
- No treatment-related AE led to death

HER2

HER2 mutations occur in approximately 2–4% of NSCLC cases, and are associated with a poor prognosis and higher incidence of brain metastases[1,2]



1. Baraibar I, et al. Crit Rev Oncol Hematol 2020;148:102906; 2. Li BT, et al. N Engl J Med 2022;386:241–51
EGFR, epidermal growth factor receptor; ex20ins, exon 20 insertions; HER2, human epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer; TKD, tyrosine kinase domain; TKI, tyrosine kinase inhibitor

Zongertinib

The primary endpoint, confirmed response by BICR, was met for all treated patients at 120 mg (n = 75) in Phase Ib Cohort 1

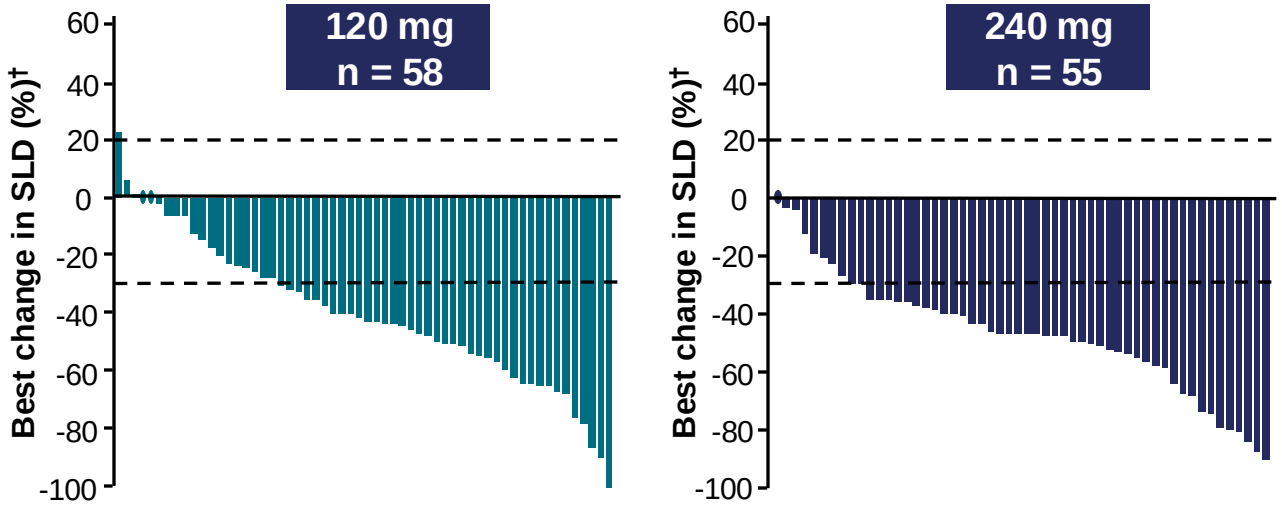
- ORR by central review for 120 mg (n = 75): 66.7% (97.5% CI 53.8–77.5), p<0.0001*
- Ongoing patients could still achieve response

Tumor shrinkage of any magnitude was observed in 94% of patients (124/132), per investigator assessment†

DoR and PFS data are currently immature, two-thirds of patients remained on treatment at data cut-off

Table below represents patient recruitment when 1:1 randomization occurred for both doses to allow for proper comparison

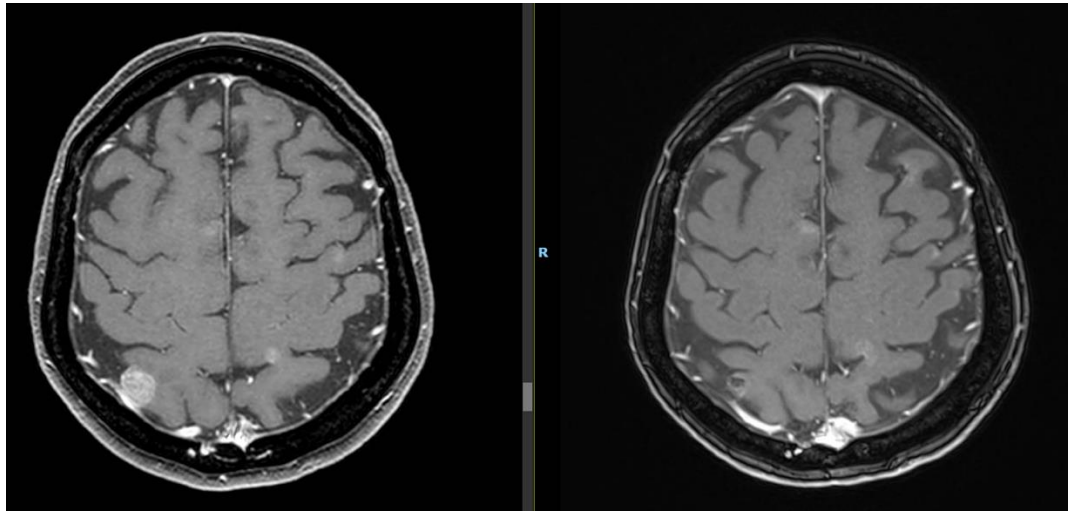
Confirmed Best Overall Response by Central Review, n (%)	120 mg n = 58	240 mg n = 55
ORR	42 (72.4)	43 (78.2)
CR	1 (1.7)	2 (3.6)
PR	41 (70.7)	41 (74.5)
DCR	55 (94.8)	55 (100.0)
SD	13 (22.4)	12 (21.8)
PD	3 (5.2)	0
NE	0	0



Zongertinib

These data show encouraging preliminary intracranial activity with zongertinib

Confirmed BOR (RANO-BM) by BICR	120 mg n = 27	240 mg n = 25
ORR, n (%) 95% CI	**9 (33)** 19–52	**10 (40)** 23–59
CR, n (%)	4 (15)	5 (20)
PR, n (%)	5 (19)	5 (20)
DCR, n (%) 95% CI	**20 (74)** 55–87	**23 (92)** 75–98
SD, n (%)	11 (41)	13 (52)
PD, n (%)	2 (7)	1 (4)
NE, n (%)	5 (19)	1 (4)



Baseline **Best response after 6 weeks**

- 63-year-old female
- Diagnosed in 2022 with Stage IV NSCLC *HER2* Y772_A775dup
- PD after 6 months of carboplatin–pemetrexed–pembrolizumab
- Received second-line treatment with zongertinib 240 mg
- Duration of response in brain (RANO-BM): 6 months (since discontinued treatment due to PD)

Zongertinib

Majority of TRAEs were mild and manageable

Most cases of diarrhea and rash were mild

- Diarrhea: 43% grade 1, 11% grade 2
- Rash: 19% grade 1, 8% grade 2

No fatal TRAEs occurred

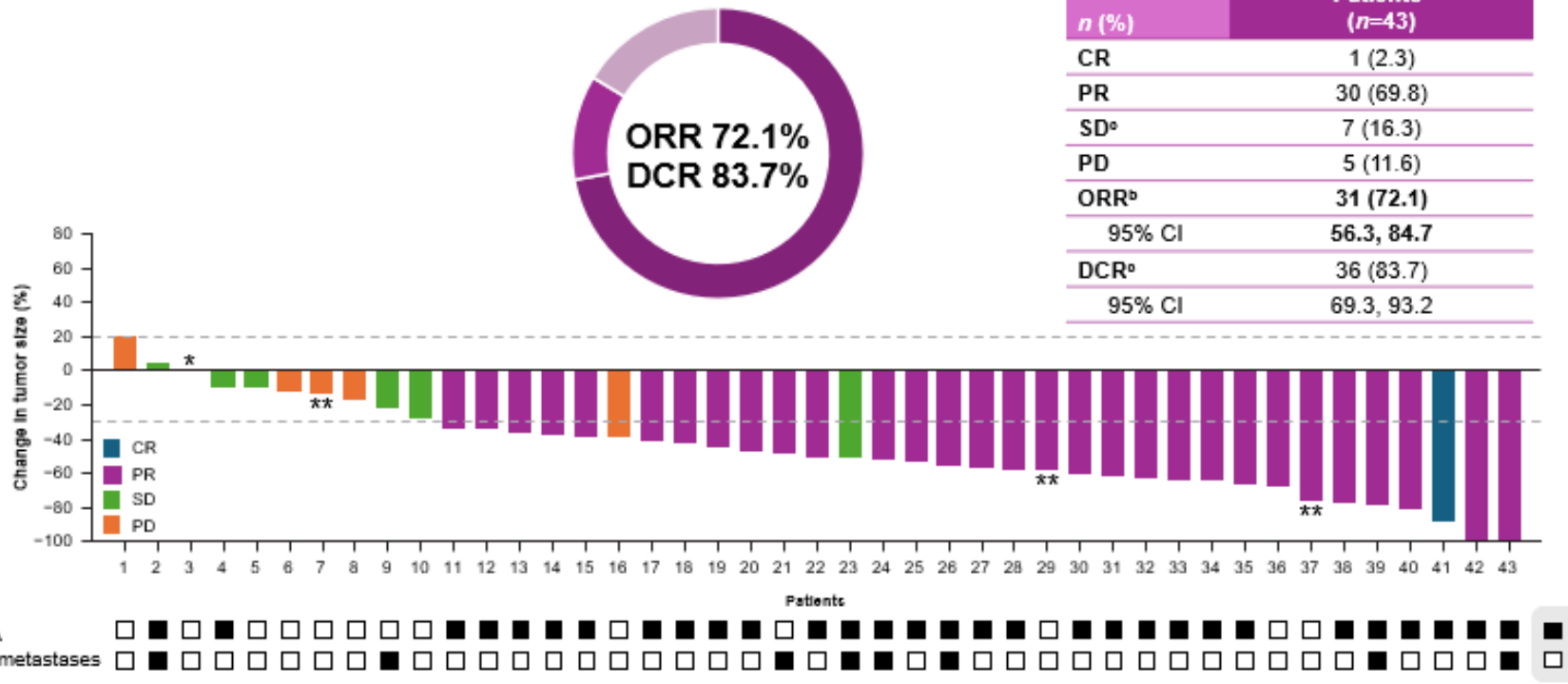
AEs leading to **dose reduction** occurred in 14 (11%) patients

Only 4 patients (3%) had AEs leading to **treatment discontinuation**

TRAEs, n (%)	120 mg n = 75		240 mg n = 57	
	All	Grade ≥3	All	Grade ≥3
Any TRAE*	69 (92)	13 (17)	57 (100)	11 (19)
Diarrhea	36 (48)	1 (1)	37 (65)	1 (2)
Rash†	18 (24)	0	17 (30)	0
ALT increased	14 (19)	6 (8)	16 (28)	6 (11)
AST increased	16 (21)	4 (5)	14 (25)	4 (7)
Anemia	8 (11)	0	10 (18)	0
Nausea	10 (13)	0	4 (7)	0
Neutrophil count decreased	7 (9)	1 (1)	7 (12)	3 (5)
Pruritus	6 (8)	0	8 (14)	0
Serious TRAE	3 (4)	3 (4)	7 (12)	5 (9)

BAY 2927088

SOHO-01 Cohort D: ORR per investigator by RECIST v1.1



n (%)	Patients[a] (*n*=43)
CR	1 (2.3)
PR	30 (69.8)
SD[c]	7 (16.3)
PD	5 (11.6)
ORR[b]	**31 (72.1)**
95% CI	**56.3, 84.7**
DCR[c]	36 (83.7)
95% CI	69.3, 93.2

[a]All evaluable patients; [b]Patients with confirmed CR or PR; [c]Patients with confirmed CR or confirmed PR or SD for ≥12 weeks; *0%, SD; ***HER2* point mutations
CI, confidence interval; CR, complete response; DCR, disease control rate; NR, no response; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease

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n (%)	All grades (*N*=44)	Grade ≥3 (*N*=44)
Any TRAE	42 (95.5)	19 (43.2)
Most common TRAEs occurring in ≥10% of patients		
Diarrhea	38 (86.4)	11 (25.0)
Rash	19 (43.2)	0
Paronychia	11 (25.0)	0
Nausea	11 (25.0)	1 (2.3)
Vomiting	9 (20.5)	2 (4.5)
Dermatitis acneiform	8 (18.2)	0
Stomatitis	8 (18.2)	1 (2.3)
Dry skin	7 (15.9)	0
Increased aspartate aminotransferase	6 (13.6)	1 (2.3)
Decreased appetite	6 (13.6)	2 (4.5)
Increased amylase	5 (11.4)	0
Anemia	5 (11.4)	0
Increased lipase	5 (11.4)	0
Decreased weight	5 (11.4)	0
Pruritis	5 (11.4)	1 (2.3)

- Diarrhea was the most common TRAE, experienced by 38 patients (86.4%); principally grade 1 or 2
- 3 patients (6.8%) had TRAEs leading to treatment discontinuation
  - Included corneal epithelial microcysts (*n*=1), reduced visual acuity (*n*=1), abnormal hepatic function (*n*=1), and dyspnea (*n*=1)
- 14 patients (31.8%) had dose reductions due to TRAEs[a]
- 5 patients (11.4%) had serious TRAEs
  - Included diarrhea (*n*=1), duodenitis (*n*=1), vomiting (*n*=1), and abnormal hepatic function (*n*=2)
- There were no grade 4 TRAEs and one grade 5 event (dyspnea); no reports of ILD/pneumonitis

[a]≥2 patients: diarrhea (*n*=6), hepatic function abnormal (*n*=2), ALT increase (*n*=2), decreased appetite (*n*=2)
ILD, interstitial lung disease; TRAE, treatment-related adverse event

Thank you

Acknowledgements: Dr. Ignatius Ou

Email: nagasakm@hs.uci.edu

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