2026 ASCO® ANNUAL MEETING

ALKOVE-1: Efficacy and safety of neladalkib in patients with advanced *ALK*+ NSCLC

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Key Takeaways

Neladalkib, an investigational, brain-penetrant, ALK-selective inhibitor, demonstrated meaningful clinical responses in TKI-pretreated patients and encouraging preliminary activity in TKI-naïve patients with advanced *ALK*+ NSCLC

Neladalkib demonstrated clinical activity in patients with CNS disease, including those with prior lorlatinib, and patients with *ALK* G1202R single or compound resistance mutations

Neladalkib was generally well-tolerated with low rates of dose modifications, consistent with its ALK-selective, TRK-sparing design

Encouraging efficacy and safety data from the ALKOVE-1 study support investigation in the front-line setting in the ongoing phase 3 ALKAZAR trial

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Background

- *ALK* fusions are identified in ~3-5% of NSCLC cases.[1-3] Among these patients, brain metastases are present at diagnosis in ~30–40% [4,5]
- Prior generations of ALK TKIs for advanced *ALK*+ NSCLC include 1G TKI crizotinib, 2G TKIs ceritinib, alectinib, brigatinib, and ensartinib, and 3G lorlatinib
- None of these simultaneously address treatment-emergent drug-resistant *ALK* single and compound mutations and brain metastases, while avoiding TRK-related neurologic adverse events [6-8]
- Neladalkib is an investigational ALK TKI designed with the aim to overcome limitations observed with currently available ALK inhibitors [8]
- Here, we report the first analyses of Phase 2 data in TKI-pretreated patients and preliminary data in TKI-naïve patients with advanced *ALK*+ NSCLC from the Phase 1/2 ALKOVE-1 study

NELADALKIB DESIGN GOALS

ALK Activity

+

ALK Single and Compound Mutant Activity

+

Brain Penetrance

+

Avoiding TRK

ALKOVE-1 NCT05384626

CNS, central nervous system; **G**, generation; **NSCLC**, non-small cell lung cancer; **TKI**, tyrosine kinase inhibitor; **TRK**, tropomyosin-related kinase.

1. Koivunen JP et al. *Clin Cancer Res.* 2008; 14:4275-83. **2**. Wong DW et al. *Cancer.* 2009; 115:1723-33. **3**. Owen D, et al. *JAMA Netw Open*. 2024; 7(11):e2442970. **4.** Gainor J et al. *JCO Precis Oncol*. 2017; PO.17.00063. **5**. Uprety D et al. *Lung Cancer.* 2025; 201:108436. **6**. Poie D, et al. *Cancer Drug Resist.* 2024; 7:20. **7**. Cooper A et al. *Nat Rev Clin Oncol.* 2022; 19(8):499-514. **8**. Lin J, et al. *Cancer Discov.* 2024; 4(12):2367-2386..

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ALKOVE-1: A Global First-in-Human Phase 1/2 Clinical Trial of Neladalkib in Advanced *ALK*-Positive NSCLC and Other Solid Tumors (NCT05384626)

PHASE 1

Neladalkib dose escalation (15 – 200 mg QD) in patients with advanced *ALK*+ solid tumors

PHASE 2: Neladalkib 150 mg QD (RP2D)

PATIENT POPULATION	PRIOR ALK TKI	PRIOR LINES CHEMO/I-O	PHASE 2 ENDPOINTS
***ALK*+ NSCLC**	**1 prior 2G** *(ceritinib, alectinib, or brigatinib)*	0-2	• **Primary:** ORR by BICR • **Secondary:** Additional efficacy measures (DOR, TTR, PFS, OS), intracranial activity, overall safety and tolerability, confirmation of PK profile
	2-3 prior, any generation *(crizotinib, ceritinib, alectinib, brigatinib, or lorlatinib [a])*	0-2	
	1 prior 3G *(lorlatinib)*	≤ 1	
	None (TKI-naïve)	≤ 1	
	Any *(not eligible for other cohorts)*	Any	
Other *ALK*+ Solid Tumors	**≥ 1 prior ALK TKI or systemic therapy** (or for whom no satisfactory standard therapy exists)	Any	

Neladalkib is an investigational product and has not been approved by the FDA or any other health authority.

BICR, blinded independent central review; **chemo**, chemotherapy; **DOR**, duration of response; **G**, generation; **I-O**, immunotherapy; **NSCLC**, non-small cell lung cancer; **ORR**, objective response rate; **OS**, overall survival; **PFS**, progression-free survival; **PK**, pharmacokinetic; **QD**, once daily; **RP2D**, recommended phase 2 dose; **TKI**, tyrosine kinase inhibitor; **TRK**, tropomyosin-related kinase; **TTR**, time to response.

[a] Excludes patients who received lorlatinib as the 1st prior ALK TKI.

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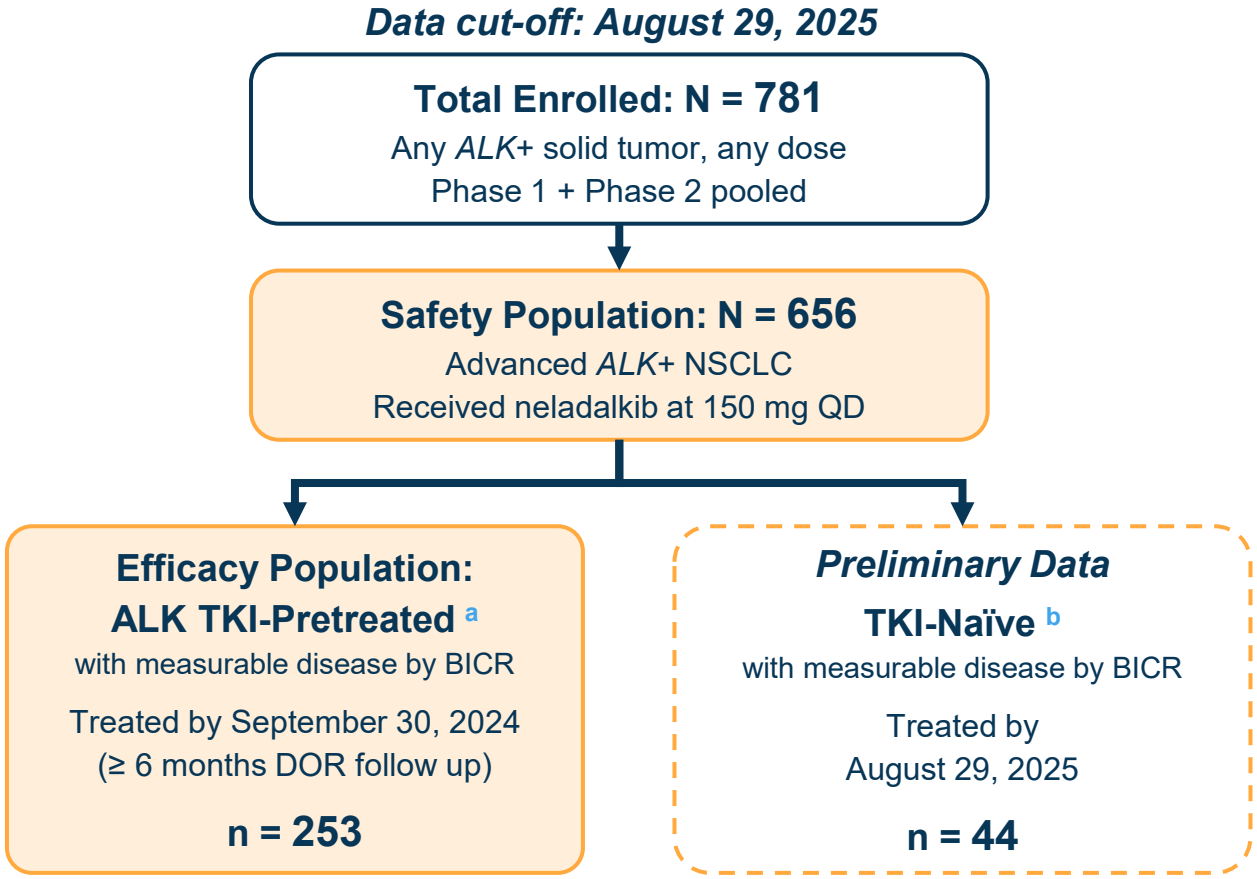
ALKOVE-1: Pivotal TKI-Pretreated Patient Population



BICR, blinded independent central review; **DOR**, duration of response; **NSCLC**, non-small cell lung cancer; **QD**, once daily; **TKI**, tyrosine kinase inhibitor.

[a] Includes 25 patients with other oncogenic driver(s) in addition to ALK: MET amplification (n = 9), KRAS G12C (n = 4*), MET mutation (n = 4), BRAF mutation (n = 4*), RET fusion (n = 2), ERBB2 mutation (n = 1), NTRK fusion (n = 1), FGFR3 fusion (n = 1). [*One patient had both KRAS G12C and BRAF mutations.] [b] No patients with other oncogenic driver(s) in addition to ALK.

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ALKOVE-1: Patient Population

Patient Characteristic	ALK TKI-Pretreated [a] Efficacy Population N = 253
Age, median (range)	56 (24 – 83)
Female	145 (57%)
No history of smoking	167 (66%)
Geographic region	
Asia Pacific	50 (20%)
Europe	101 (40%)
North America	102 (40%)
ECOG PS	
0	90 (36%)
1	163 (64%)
Baseline CNS metastases [b]	101 (40%)
Secondary *ALK* mutation [c]	91 (36%)
G1202R mutation [d]	47 (19%)
≥2 *ALK* mutations [e]	43 (17%)

Treatment History		ALK TKI-Pretreated [a] Efficacy Population N = 253
Prior anticancer therapy, median (range)		3 (1 – 11)
Chemotherapy		128 (51%)
Prior ALK TKIs [f]		
1G	crizotinib	67 (26%)
2G	any 2G	240 (95%)
	alectinib	220 (87%)
	brigatinib	55 (22%)
	ceritinib	27 (11%)
	ensartinib	3 (1%)
3G	lorlatinib	190 (75%)
Lorlatinib-naïve [g, h]		**63 (25%)**
	≥1 prior 2G	**63/63 (100%)**
	1 ALK TKI (alectinib)	**44/63 (70%)**
	≥ 2 ALK TKIs	**17/63 (27%)**
Lorlatinib-experienced		**190 (75%)**
	≥2 ALK TKIs, including 2G and lorlatinib	**177/190 (93%)**
	≥3 ALK TKIs, including 2G and lorlatinib	**69/190 (36%)**

CNS, central nervous system; **G**, generation; **PS**, performance score; **TKI**, tyrosine kinase inhibitor. [a] Includes 25 patients with other oncogenic driver(s) in addition to ALK. [b] Includes patients with treated or untreated, measurable or non-measurable CNS lesions by BICR. [c] *ALK* mutations as per local or central testing of blood (ctDNA) or tissue. [d] Patients may have had other mutations in addition to *ALK* G1202R. [e] Includes 15 patients with confirmed compound mutations (cis-allelic configuration). [f] One patient received an investigational TKI. [g] No patients received crizotinib as the only prior ALK TKI. [h] 46 patients received 1 prior ALK TKI only (alectinib, n = 44; brigatinib, n = 2).

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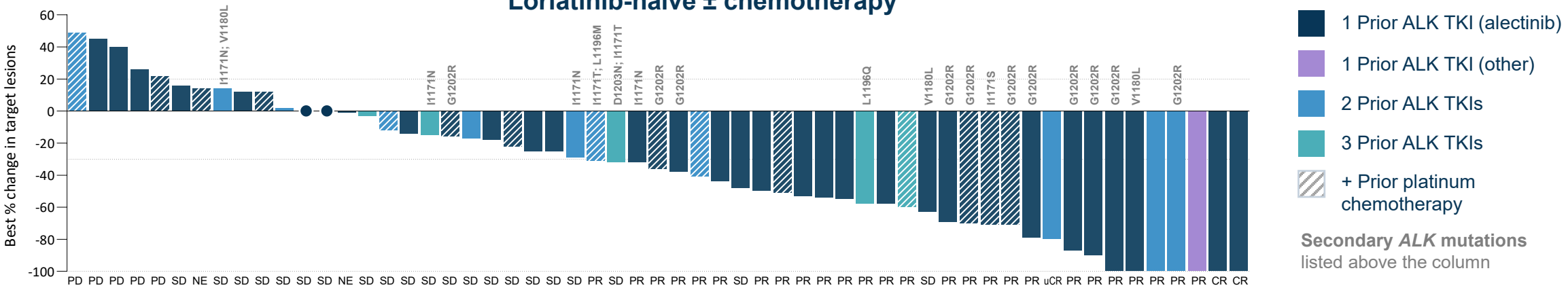
ALKOVE-1: Objective Response in ALK TKI-Pretreated Patients

Advanced *ALK*+ NSCLC RECIST v1.1 by BICR	**Any prior ALK TKI** [a] (1–5 prior ALK TKIs ± chemotherapy) **N = 253**	**Lorlatinib-naive** (1–3 prior ALK TKIs ± chemotherapy) **N = 63**	**Lorlatinib-experienced** (1–5 prior ALK TKIs ± chemotherapy) **N = 190**
ORR, % (n/N) [95% CI]	**31%** (79/253) [b] [26, 37]	**46%** (29/63) [33, 59]	**26%** (50/190) [b] [20, 33]
CR, % (n/N)	2% (6/253) [c]	5% (3/63) [d]	2% (3/190) [d]

[a] Median duration of follow-up of 11.3 months. [b] Includes 2 single-timepoint PR pending confirmation for ongoing patients. [c] Includes 2 single-timepoint CR pending confirmation in ongoing patients with prior confirmed PR. [d] Includes 1 single-timepoint CR pending confirmation in ongoing patient with prior confirmed PR.

- **Prior alectinib only ± chemotherapy:** ORR = **48%** (21/44, 5% CR)
- **≥ 2 prior ALK TKIs ± chemotherapy:** ORR = **28%** (56/198) [b]

Lorlatinib-naïve ± chemotherapy



BICR, blinded independent central review; **CI**, confidence interval; **CR**, complete response; **NE**, not evaluable; **ORR**, objective response rate; **PD**, progressive disease; **PR**, partial response; **SD**, stable disease; **TKI**, tyrosine kinase inhibitor.

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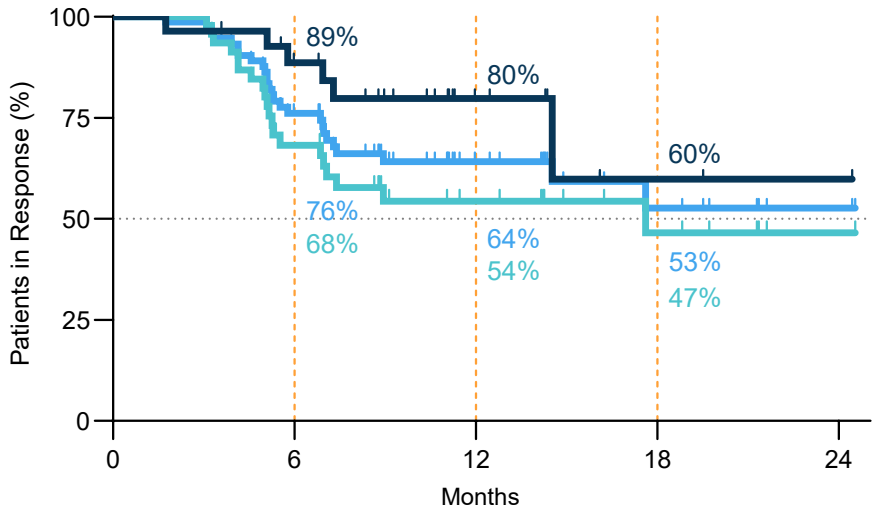
ALKOVE-1: Duration of Response

TKI-Pretreated Advanced *ALK*+ NSCLC Kaplan-Meier Estimate	Any prior ALK TKI (1–5 prior ALK TKI ± chemotherapy) **N = 77**	Lorlatinib-naive (1–3 prior ALK TKI ± chemotherapy) **N = 29**	Lorlatinib-experienced (1–5 prior ALK TKI ± chemotherapy) **N = 48**
DOR ≥ 6 months [95% CI]	**76%** [64, 84]	**89%** [69, 96]	**68%** [52, 80]
DOR ≥ 12 months [95% CI]	**64%** [51, 75]	**80%** [58, 91]	**54%** [38, 68]
DOR ≥ 18 months [95% CI]	**53%** [34, 68]	**60%** [19, 85]	**47%** [27, 64]
Median DOR [95% CI]	**NR** [14.5, NE]	**NR** [14.5, NE]	**17.6** [6.9, NE] [a]

[a] Emerging median continues to mature.

- **Prior alectinib only ± chemotherapy:** median DOR = NR (95% CI: NE, NE).
- **≥ 2 prior ALK TKIs ± chemotherapy**: Emerging median DOR of 17.6 months (95% CI: 7.1, NE) continues to mature.

Kaplan-Meier Plot of DOR
ALK TKI-Pretreated



At Risk					
Any prior	77	48	20	8	2
Lorlatinib-naïve	29	21	7	2	1
Lorlatinib-experienced	48	27	13	6	1

CI, confidence interval; **DOR**, duration of response; **NE**, not estimable; **NR**, not reached; **TKI**, tyrosine kinase inhibitor.

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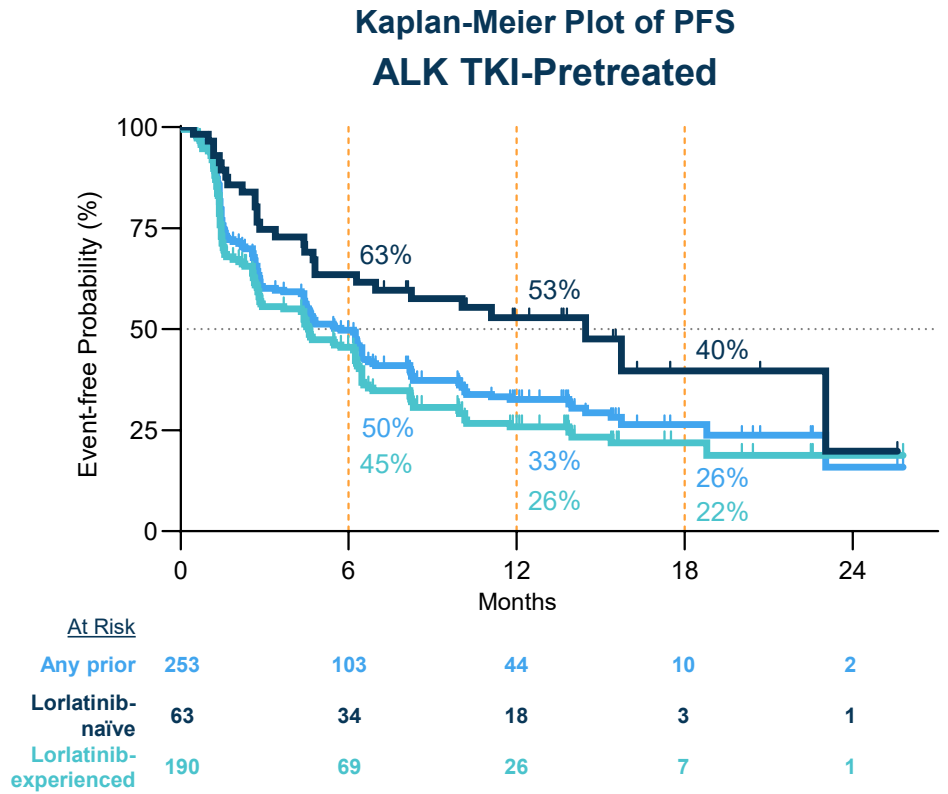
ALKOVE-1: Progression-Free Survival

TKI-Pretreated Advanced *ALK*+ NSCLC Kaplan-Meier Estimate	Any prior ALK TKI (1–5 prior ALK TKI ± chemotherapy) **N = 253**	Lorlatinib-naive (1–3 prior ALK TKI ± chemotherapy) **N = 63**	Lorlatinib-experienced (1–5 prior ALK TKI ± chemotherapy) **N = 190**
PFS ≥ 6 months [95% CI]	**50%** [43, 56]	**63%** [49, 75]	**45%** [38, 53]
PFS ≥ 12 months [95% CI]	**33%** [26, 39]	**53%** [38, 65]	**26%** [19, 33]
PFS ≥ 18 months [95% CI]	**26%** [20, 34]	**40%** [21, 58]	**22%** [15, 30]
Median PFS [95% CI]	**5.7** [4.4. 6.5]	**14.5** [4.8, NE] [a]	**4.6** [2.8, 6.2]

[a] Emerging median continues to mature.



CI, confidence interval; **NE**, not estimable; **PFS**, progression-free survival; **TKI**, tyrosine kinase inhibitor.

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ALKOVE-1: CNS Activity

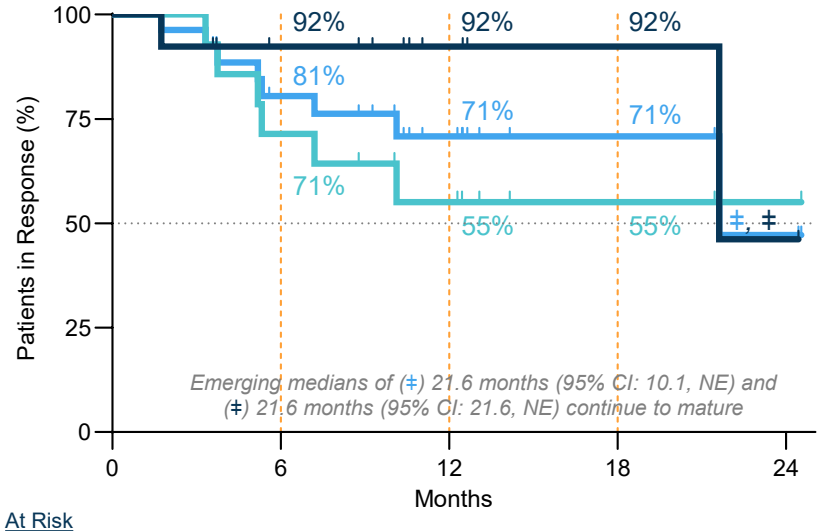
TKI-Pretreated CNS Response-Evaluable [a] RECIST 1.1, BICR [95% CI]	Any prior ALK TKI ± chemotherapy N = 92	Lorlatinib-naive ± chemotherapy N = 24	Lorlatinib-experienced ± chemotherapy N = 68
IC-ORR, % (n/N)	**32%** (29/92) [b] [22, 42]	**63%** (15/24) [b] [41, 81]	**21%** (14/68) [12, 32]
IC-CR, % (n/N)	13% (12/92) [c]	21% (5/24) [c]	10% (7/68)
IC-DOR ≥ 6 months [d]	**81%** [59, 91]	**92%** [57, 99]	**71%** [41, 88]
IC-DOR ≥ 12 months [d]	**71%** [48, 85]	**92%** [57, 99]	**55%** [26, 77]
IC-DOR ≥ 18 months [d]	**71%** [48, 85]	**92%** [57, 99]	**55%** [26, 77]

[a] Includes patients with measurable (≥5mm) CNS lesions by BICR at baseline and no brain radiation within 2 months before first dose of neladalkib. [b] Includes 2 single-timepoint IC-PR pending confirmation in ongoing patients. [c] Includes 1 single-timepoint IC-CR pending confirmation in ongoing patient with prior confirmed IC-PR. [d] Analyses of DOR based on Kaplan-Meier estimates.

- **CNS response-evaluable after prior alectinib only ± chemotherapy:** IC-ORR = **60%** (9/15; 1 IC-uPR); no intracranial progressors among confirmed intracranial responders.
- **CNS response-evaluable after ≥ 2 prior ALK TKIs ± chemotherapy:** IC-ORR = **25%** (19/75; 1 IC-uPR); IC-DOR at 6 months = **78**% (95% CI: 51, 91) and at 12 and 18 months = **66**% (95% CI: 39, 83).

Kaplan-Meier Plot of IC-DOR

TKI-Pretreated CNS Response-Evaluable



At Risk					
Any prior	27	19	10	4	2
Lorlatinib-naïve	13	9	4	2	1
Lorlatinib-experienced	14	10	6	2	1

BICR, blinded independent central review; **CI**, confidence interval; **CNS**, central nervous system; **CR**, complete response; **DOR**, duration of response; **IC**, intracranial; **NE**, not estimable; **NR**, not reached; **ORR**, objective response rate; **TKI**, tyrosine kinase inhibitor; **uPR**, unconfirmed partial response.

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ALKOVE-1: *ALK* G1202R Resistance Mutation

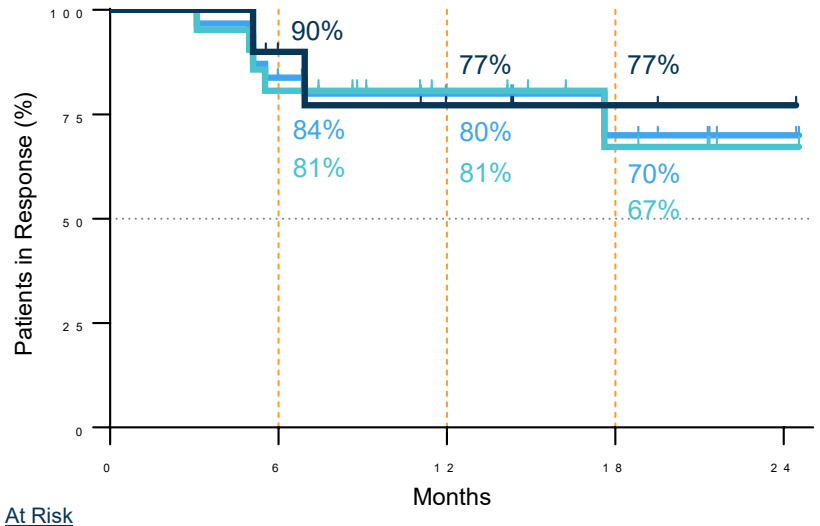
TKI-Pretreated with *ALK* G1202R mutation RECIST 1.1, BICR [95% CI]	Any prior ALK TKI ± chemotherapy [a] N = 47	Lorlatinib-naive ± chemotherapy N = 12	Lorlatinib-experienced ± chemotherapy N = 35
ORR, % (n/N)	**68%** (32/47) [b] [53, 81]	**83%** (10/12) [52, 98]	**63%** (22/35) [b] [45, 79]
DOR ≥ 6 months [c]	**84%** [65, 93]	**90%** [47, 99]	**81%** [56, 92]
DOR ≥ 12 months [c]	**80%** [61, 91]	**77%** [34, 94]	**81%** [56, 92]
DOR ≥ 18 months [c]	**70%** [42, 86]	**77%** [34, 94]	**67%** [32, 87]

[a] Patients may have had other mutations in addition to *ALK* G1202R. [b] Includes 1 single-timepoint PR pending confirmation for ongoing patient. [c] Analysis of DOR based on Kaplan-Meier estimates.

- ***ALK* G1202R after prior alectinib only ± chemotherapy**: ORR = **82**% (9/11); DOR at 12 and 18 months = **74**% (95% CI: 29, 93).
- ***ALK* G1202R after ≥ 2 prior ALK TKIs ± chemotherapy**: ORR = **64**% (23/36, 1 uPR); DOR at 12 months = **82**% (95% CI: 58, 93) and DOR at 18 months = **70**% (95% CI: 37, 88).

Kaplan-Meier Plot of DOR

TKI-Pretreated with *ALK* G1202R Mutation



At Risk					
Any prior	31	23	13	7	2
Lorlatinib-naïve	10	7	4	2	1
Lorlatinib-experienced	21	16	9	5	1

Responses also observed in patients with:

- **≥2 *ALK* mutations after ≥2 prior ALK TKIs ± chemotherapy**: ORR = **58**% (25*/43; includes 1 uPR), mDOR = NR (range, 2.2+ to 24.5+ months), DOR at 12 months = **69**% (95% CI: 45, 84)
- ***ALK* mutations other than G1202R**, including C1156Y, I1171N, I1171T, F1174C, F1174L, V1180L, L1196M, L1198F, D1203N, E1210K, and G1269A

* Among the 25 patients with response, 9 had confirmed compound mutations (cis-allelic configuration).

BICR, blinded independent central review; **CI**, confidence interval; **DOR**, duration of response; **NE**, not estimable; **NR**, not reached; **ORR**, objective response rate; **TKI**, tyrosine kinase inhibitor; **uPR**, unconfirmed partial response.

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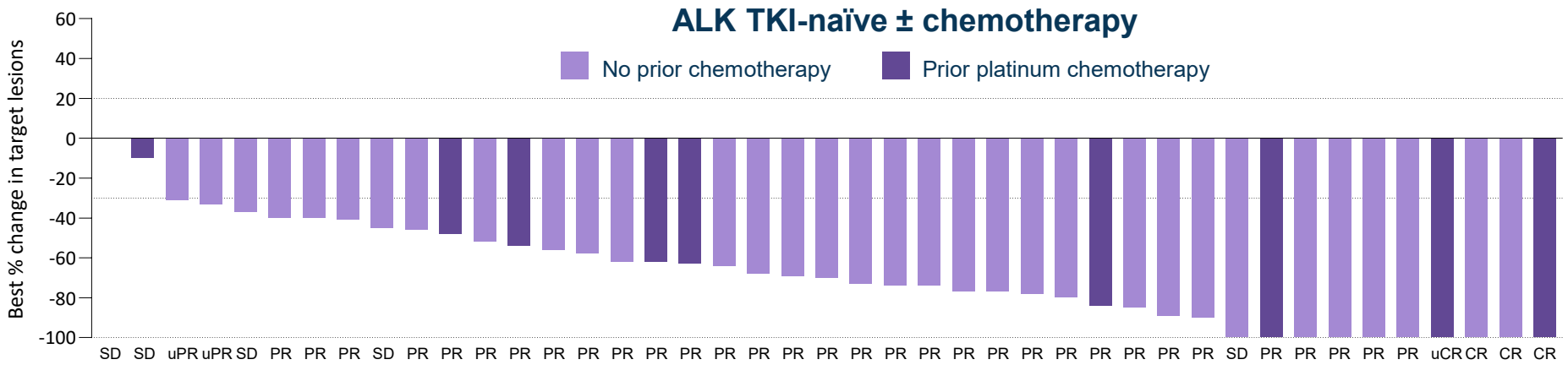
ALKOVE-1 Preliminary Data: TKI-Naïve Patients with Advanced *ALK*+ NSCLC

ALK TKI-naïve, BICR	Response-evaluable N = 44
ORR, % (n/N)	**86%** (38/44) [a]
CR, % (n/N)	9% (4/44) [b]
% DOR ≥ 12 months [95% CI] [c]	**91%** [70, 98]
DOR range	1.7+ to 14.8+ months

[a] Includes 2 single-timepoint PR pending confirmation for ongoing patients. [b] Includes 1 single-timepoint CR pending confirmation in ongoing patient with prior confirmed PR. [c] Analyses of DOR based on Kaplan-Meier estimates.

ALK TKI-naïve, BICR	CNS Response-evaluable N = 9
IC-ORR, % (n/N)	**78%** (7/9)
IC-CR, % (n/N)	44% (4/9) [d]
IC-DOR	**No CNS progression events among intracranial responders**
IC-DOR range	3.1+ to 7.0+ months

[d] Includes 1 single-timepoint IC-CR pending confirmation in ongoing patient with prior confirmed IC-PR.



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ALKOVE-1: Safety in Advanced *ALK*+ NSCLC

Dose reduction due to TEAE: 17%

- Most common (≥1% of patients):
  ALT increased (10%), AST increased (8%) [a]

Discontinuation due to TEAE: 5%

- Most common (≥1% of patients):
  ALT increased (2%), AST increased (1%)

Most common TEAE were transaminase elevations

- Most were asymptomatic lab abnormalities, and observed to be low-grade, transient, and reversible with dose interruptions or reductions
- Preliminary data suggest increased incidence in less heavily pre-treated patients
- Enhanced monitoring and prompt dose interventions implemented in the protocol for the Phase 3 ALKAZAR trial

Overall safety profile consistent with avoiding TRK-related neurotoxicities

All Treatment-Emergent Adverse Events (TEAEs) in ≥ 15% of TKI-Naïve or TKI-Pretreated Patients with Advanced *ALK*+ NSCLC Receiving Neladalkib 150 mg QD (N = 656)

Preferred Term	Any Grade	Grade ≥3
ALT increased	47%	20%
AST increased	44%	16%
Constipation	28%	0.2%
Dysgeusia	23%	0
Peripheral edema	18%	0.3%
Cough	16%	0.5%
Nausea	16%	0.8%

Data pooled for patients in the Phase 1 or Phase 2 portion of ALKOVE-1 with a data cut-off of August 29, 2025. Patients received at least 1 dose of neladalkib at RP2D of 150 mg QD with median duration of exposure of 6.0 months (range: 0.1, 28.4). **ALT**, alanine aminotransferase; **AST**, aspartate aminotransferase; **NSCLC**, non-small cell lung cancer; **RP2D**, recommended phase 2 dose; **QD**, once-daily; **TEAE**, treatment emergent adverse event; **TKI**, tyrosine kinase inhibitor.

[a] Not mutually exclusive: Dose reduction due to any transaminase elevation observed in 11% of patients.

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ALKOVE-1: Summary

In these data from the ALKOVE-1 study of TKI-pretreated patients with advanced *ALK*+ NSCLC, neladalkib demonstrated a clinical profile consistent with its design goals:

- **Meaningful clinical responses for TKI-pretreated patients** (range 1–5 prior ALK TKI) across both lorlatinib-naive (ORR = 46%; median DOR not reached, DOR ≥12 months for 80%) and lorlatinib-experienced patients (ORR = 26%; median DOR of 17.6 months)
- **Intracranial activity,** including in patients who previously received lorlatinib, a population where no other TKI has shown activity (lorlatinib-naïve: IC-ORR = 63%; DOR ≥12 months for 92%; lorlatinib-experienced: IC-ORR = 21%; DOR ≥12 months for 55%)
- **Activity in patients with *ALK* G1202R single or compound resistance mutations** (lorlatinib-naïve: ORR = 83%, DOR ≥12 months for 77%; lorlatinib-experienced: ORR = 63%; DOR ≥12 months for 81%)
- **Generally well-tolerated** with low rates of dose reduction (17%) and treatment discontinuation (5%) due to TEAEs, consistent with its ALK-selective, TRK-sparing design

Encouraging efficacy and safety data support investigation in the front-line setting in the ongoing phase 3 ALKAZAR trial (NCT06765109)

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Dr. Ross Camidge	University of Colorado Denver, USA
Dr. Rosario Campelo	[C.H.U.A.C.] Hospital Universitario da Coruña, Spain
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Dr. Byung Chul Cho	Severance Hospital, Yonsei University College of Medicine, Korea
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Dr. Quincy Chu	Cross Cancer Institute, Canada
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ALKOVE-1 Lay Summary

What did this research tell us?

- The phase 1/2 ALKOVE-1 trial evaluated the efficacy and safety of neladalkib, an investigational ALK-inhibitor designed with the goal of overcoming limitations of currently available ALK inhibitors, in participants with advanced *ALK*+ NSCLC and other solid tumors
- Meaningful clinical responses were observed for participants with *ALK*+ NSCLC who had previously received 1–5 prior ALK TKIs. This included activity in the brain, including in participants who had previously received lorlatinib, a population where no other TKI has shown activity, and activity in participants with 1 or more *ALK* drug-resistance mutations
- Encouraging preliminary activity was observed in a cohort of the study evaluating neladalkib in individuals with advanced *ALK*+ NSCLC and no prior treatment with any ALK inhibitor

Who does this research impact?

- Participants with advanced *ALK*+ NSCLC who had prior treatment with an ALK inhibitor, including those with tumors that have spread to the brain and those with 1 or more *ALK* drug-resistance mutations
- Participants with advanced *ALK*+ NSCLC and no prior treatment with an ALK inhibitor, including those with tumors that have spread to the brain

What does this mean for patients right now?

- These findings support neladalkib as a potential new treatment option (pending FDA review) for individuals with advanced ALK+ NSCLC who had previously received treatment with an ALK inhibitor. A New Drug Application has been submitted to the FDA for this patient population.
- ALKAZAR, a global, phase 3, randomized, controlled trial of neladalkib versus alectinib (NCT06765109), is currently enrolling individuals with advanced *ALK*+ NSCLC and no prior treatment with an ALK inhibitor

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