Year in Review: Therapeutic Targets Beyond EGFR for Non-Small Cell Lung Cancer

A CME/MOC-Accredited Live Webinar

Thursday, May 15, 2025
5:00 PM – 6:00 PM ET

Faculty

Jessica J Lin, MD
Joel W Neal, MD, PhD

Moderator

Neil Love, MD

RTP Year in Review 2025

Faculty

Jessica J Lin, MD
Attending Physician
Massachusetts General Hospital
Associate Professor of Medicine
Harvard Medical School
Boston, Massachusetts

Joel W Neal, MD, PhD
Professor of Medicine, Division of Oncology
Stanford University School of Medicine
Medical Director, Cancer Clinical Trials Office
Stanford Cancer Institute
Medical Director, Informatics Technology
Stanford Medicine Cancer Center
Stanford, California

MODERATOR
Neil Love, MD
Research To Practice
Miami, Florida

Commercial Support

This activity is supported by educational grants from AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, and Nuvalent.

Dr Love — Disclosures

Dr Love is president and CEO of Research To Practice. Research To Practice receives funds in the form of educational grants to develop CME activities from the following companies: Aadi Bioscience, AbbVie Inc, ADC Therapeutics, Alexion Pharmaceuticals, Amgen Inc, Array BioPharma Inc, a subsidiary of Pfizer Inc, Arvinas, Astellas, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, Black Diamond Therapeutics Inc, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Bristol Myers Squibb, Clovis Oncology, Coherus BioSciences, CTI BioPharma, a Sobi Company, Daiichi Sankyo Inc, Eisai Inc, Elevation Oncology Inc, Exact Sciences Corporation, Exelixis Inc, Genentech, a member of the Roche Group, Genmab US Inc, Geron Corporation, Gilead Sciences Inc, GSK, Hologic Inc, ImmunoGen Inc, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc, Karyopharm Therapeutics, Kite, A Gilead Company, Kura Oncology, Legend Biotech, Lilly, MEI Pharma Inc, Merck, Mersana Therapeutics Inc, Mirati Therapeutics Inc, Mural Oncology Inc, Natera Inc, Novartis, Novartis Pharmaceuticals Corporation on behalf of Advanced Accelerator Applications, Novocure Inc, Nuvalent, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, Rigel Pharmaceuticals Inc, R-Pharm US, Sanofi, Seagen Inc, Servier Pharmaceuticals LLC, SpringWorks Therapeutics Inc, Stemline Therapeutics Inc, Syndax Pharmaceuticals, Taiho Oncology Inc, Takeda Pharmaceuticals USA Inc, TerSera Therapeutics LLC, and Tesaro, A GSK Company.

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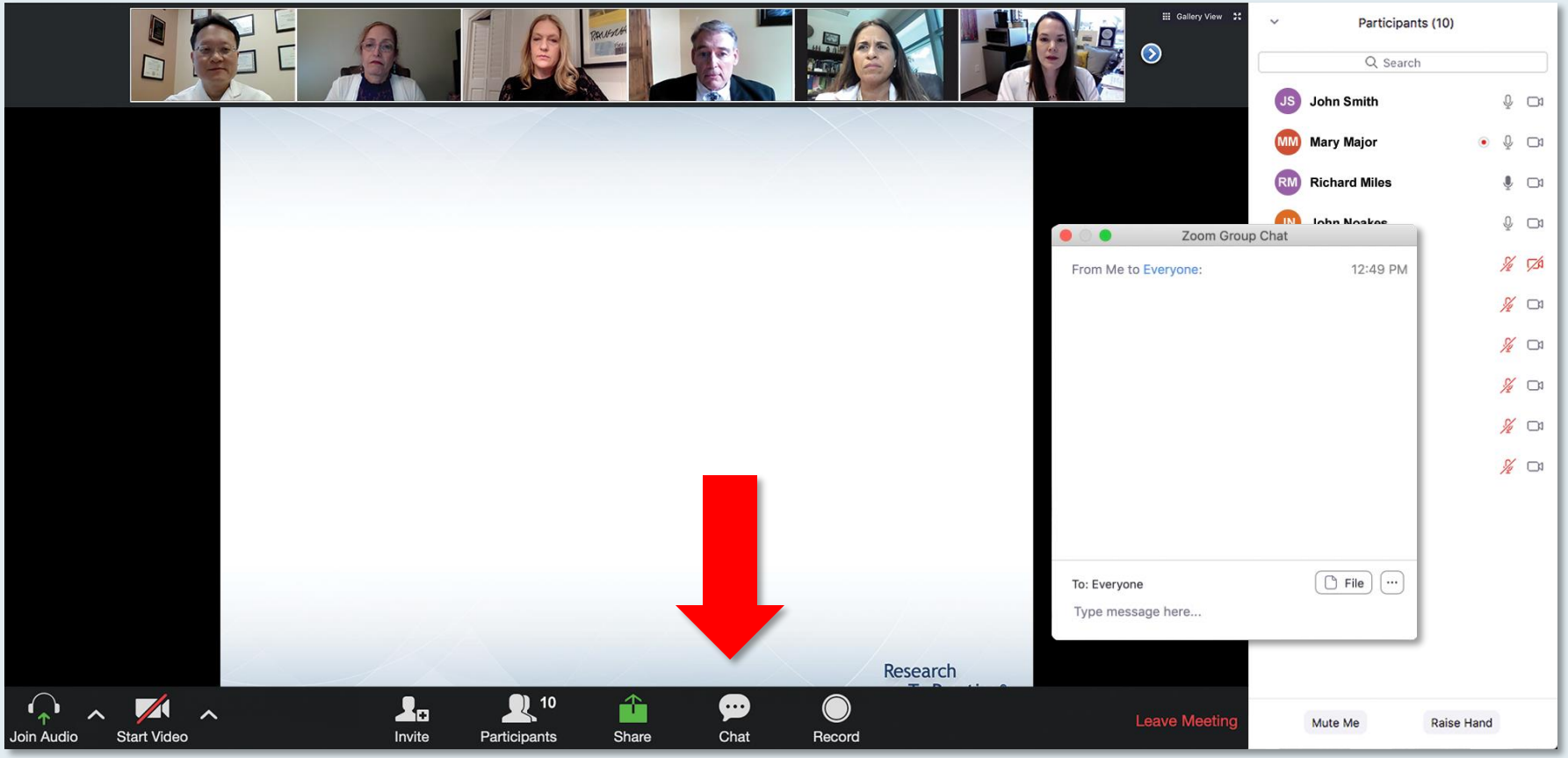

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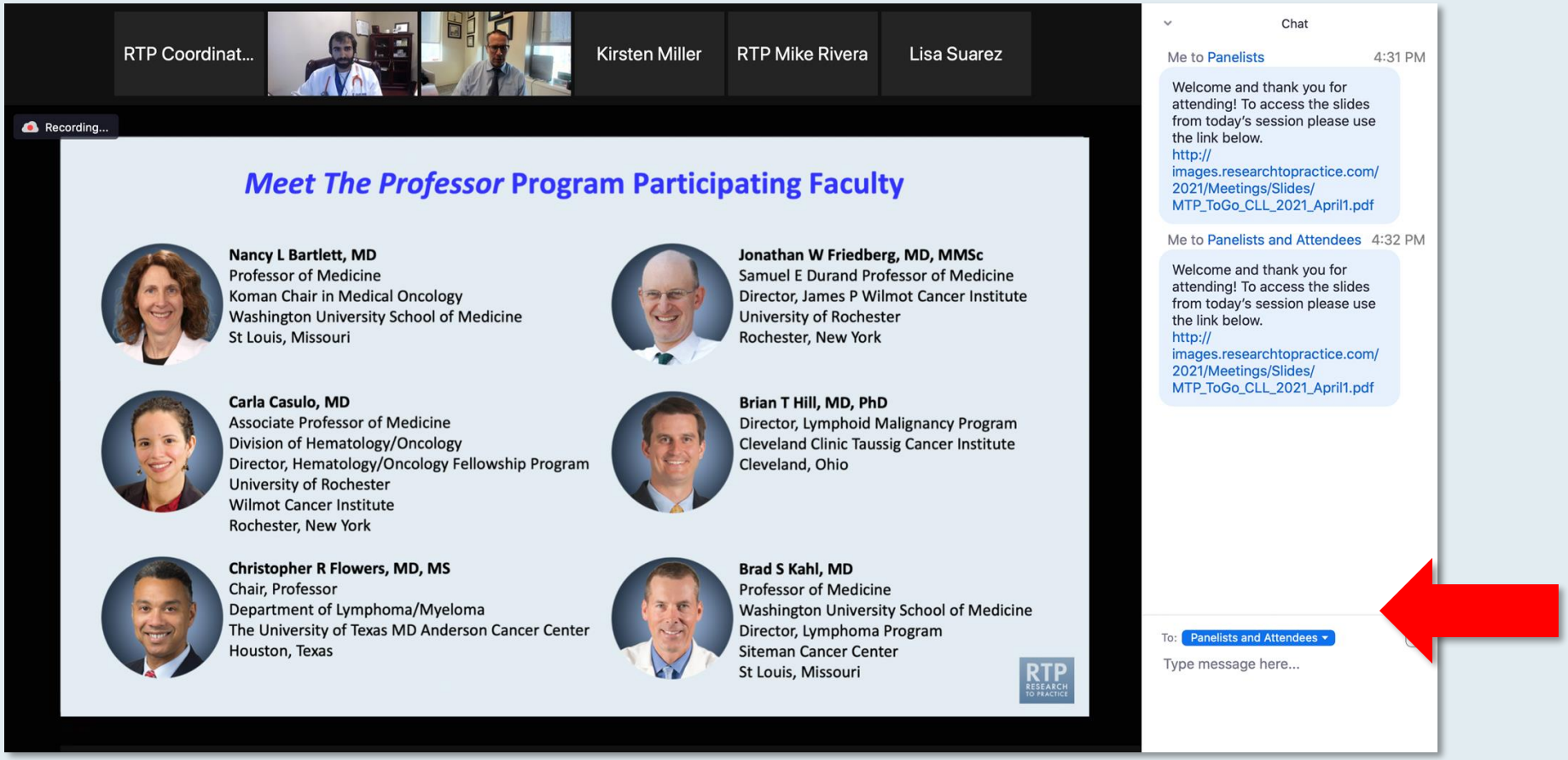

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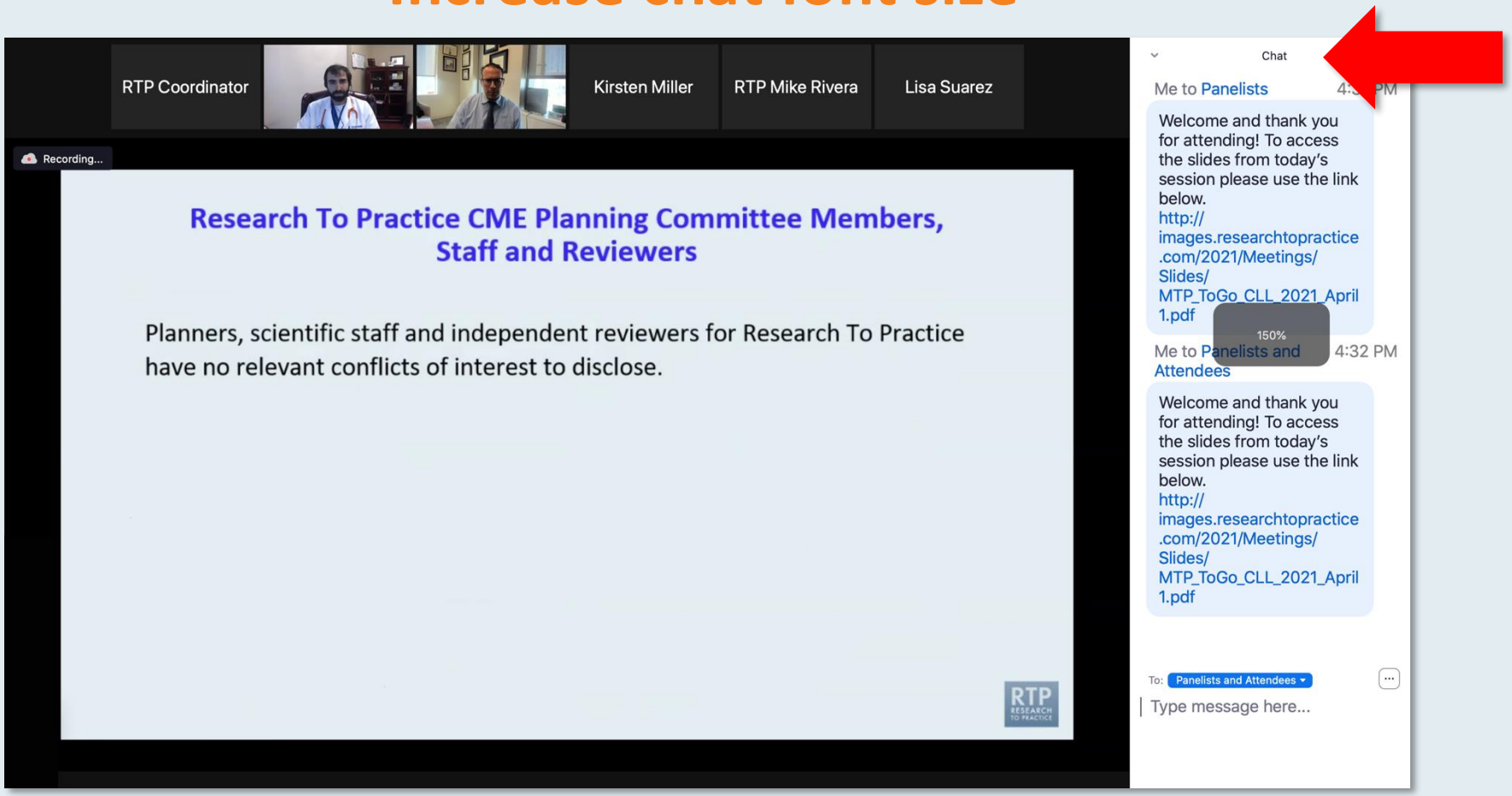

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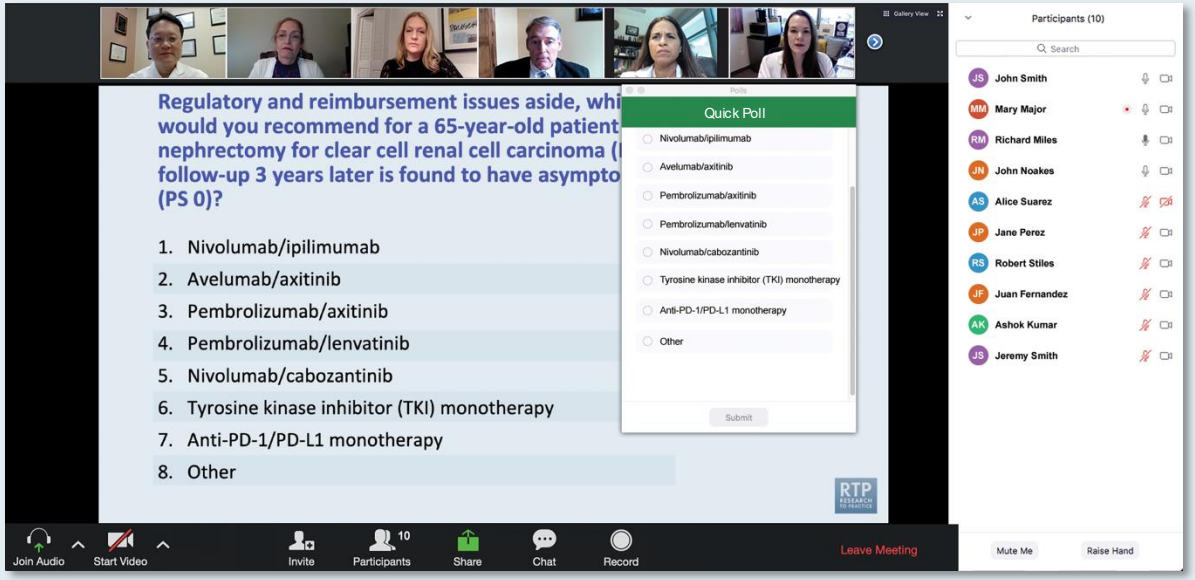

ONCOLOGY TODAY

WITH DR NEIL LOVE

First-Line Therapy for Metastatic Non-Small Cell Lung Cancer and an ALK Rearrangement — An Interview with Dr Justin F Gainor

DR JUSTIN F GAINOR

MASSACHUSETTS GENERAL HOSPITAL

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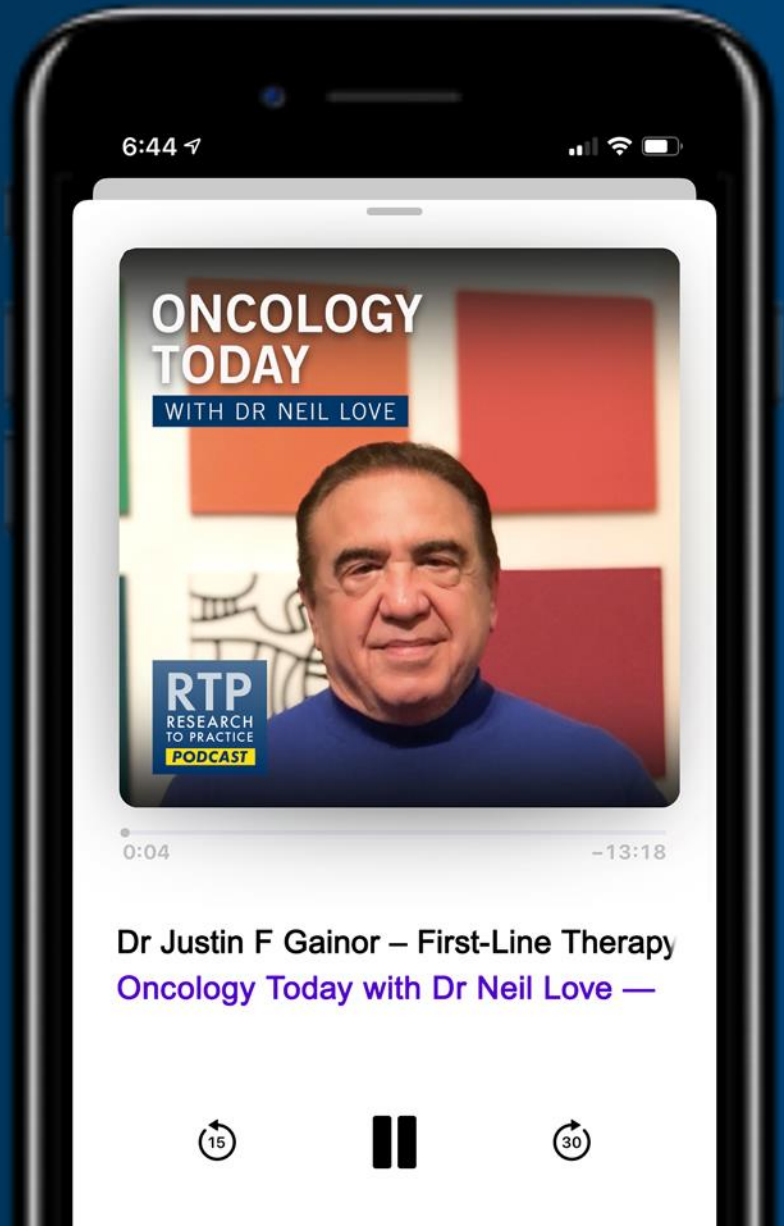

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Neil Love, MD

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11:15 AM – 12:45 PM CT (12:15 PM – 1:45 PM ET)

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Colorectal Cancer

6:30 PM – 8:30 PM CT (7:30 PM – 9:30 PM ET)

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Andrea Cercek, MD
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Pashtoon Kasi, MD, MS
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Metastatic Breast Cancer

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Rashmi Chugh, MD

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Year in Review: Targeted Therapies Beyond EGFR for Non-Small Cell Lung Cancer (NSCLC)

INTRODUCTION: AGAs (Actionable Genomic Alterations)

MODULE 1: ALK

MODULE 2: ROS1

MODULE 3: HER2

MODULE 4: RET

MODULE 5: NTRK

MODULE 6: MET

MODULE 7: BRAF

MODULE 8: KRAS G12C

MODULE 9: NRG1

MODULE 10: Novel Targeted Strategies

RTP Year in Review 2025

Thank you for joining us!

Please take a moment to complete the survey currently up on Zoom.
Your feedback is very important to us.

Information on how to obtain CME, ABIM MOC and ABS credit will be provided in the Zoom chat room.
Attendees will also receive an email in 1 to 3 business days with these instructions.

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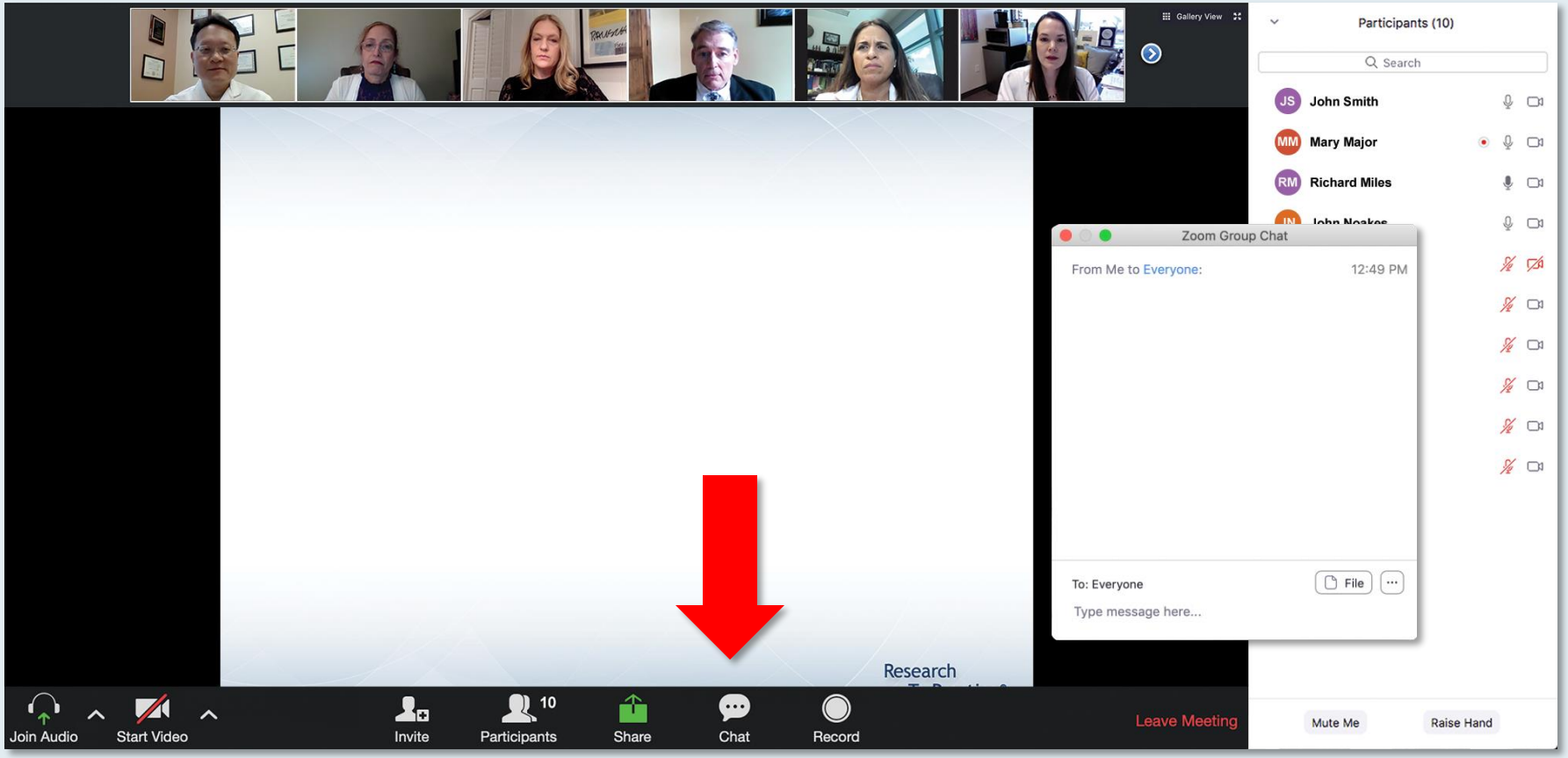

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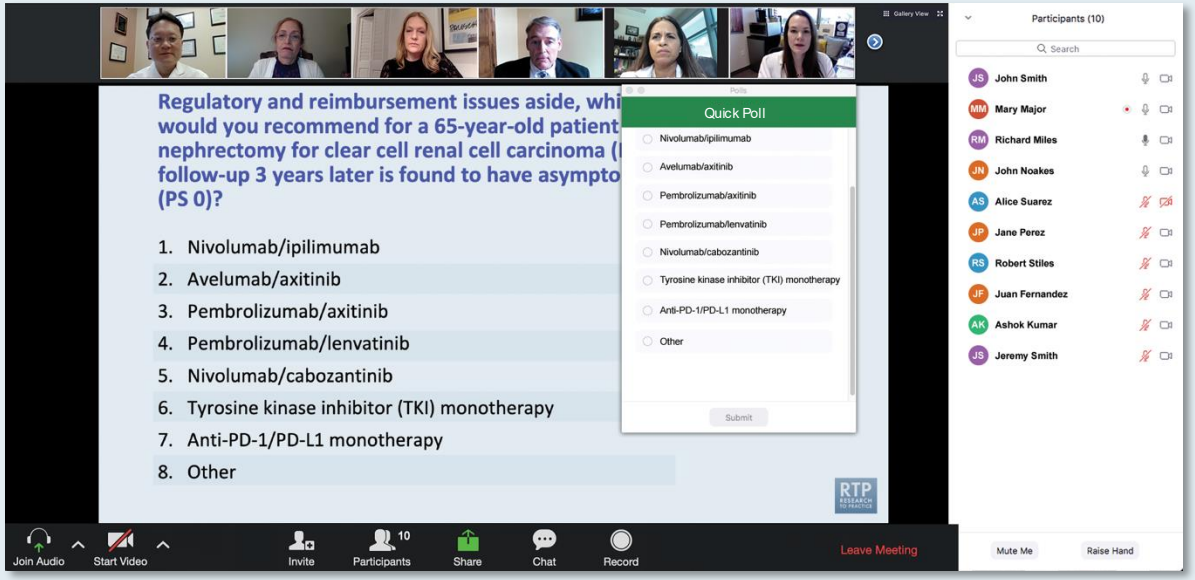

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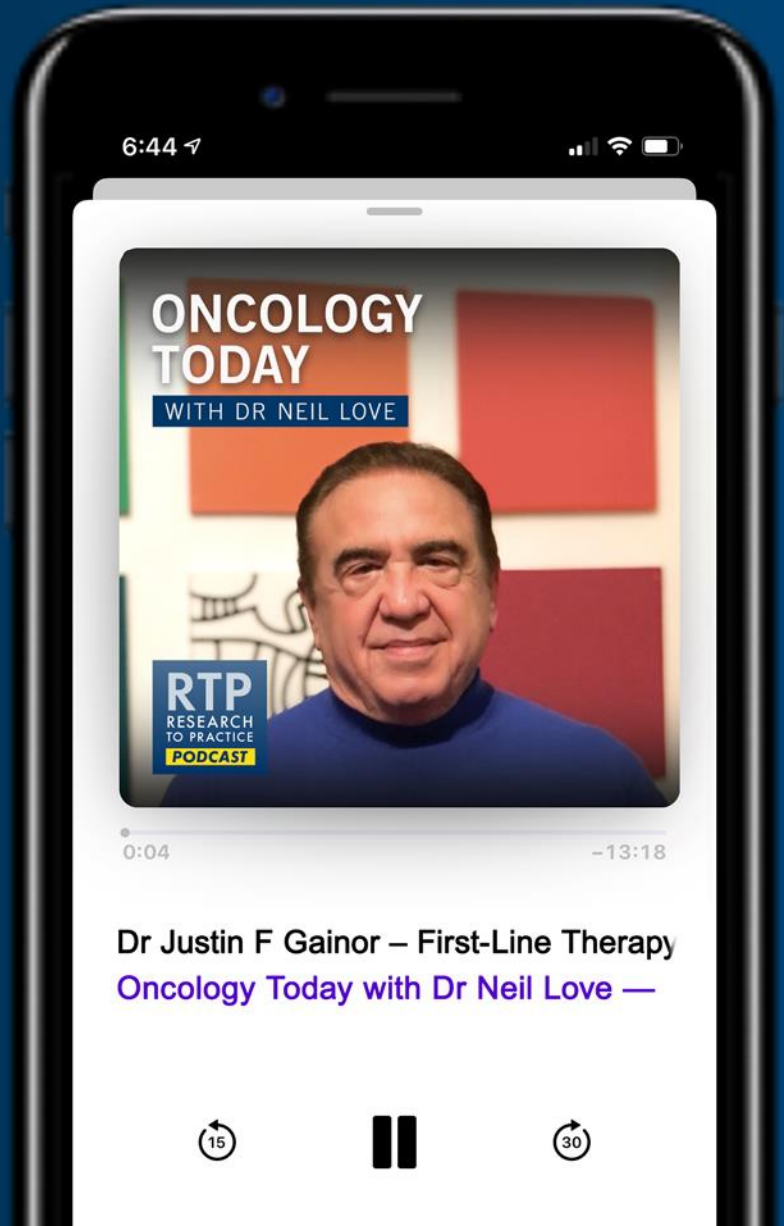

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Year in Review – Targeted Lung Cancer Edition

Therapeutic Approaches Targeting ALK, ROS1, RET, TRK, NRG1

Jessica J. Lin, MD
Massachusetts General Hospital | Harvard Medical School
Boston, MA, USA

Mass General Brigham

HARVARD MEDICAL SCHOOL

Lung Cancer Year In Review: Targeting HER2, MET, BRAF and KRAS

Joel Neal, MD, PhD
Professor of Medicine/Oncology
Stanford University

STANFORD CANCER INSTITUTE
Stanford University Medical Center
A NATIONAL CANCER INSTITUTE-DESIGNATED CANCER CENTER

Key Datasets

Jessica J Lin, MD

- Wu YL et al. **Alectinib** in Resected **ALK-Positive** Non-Small-Cell Lung Cancer. *N Engl J Med* 2024;390(14):1265-76.
- Horinouchi H et al. **ALINA** Safety Results; **Adjuvant Alectinib** vs Chemotherapy in Patients with **Resected ALK+ Non-Small Cell Lung Cancer** (NSCLC). WCLC 2024;Abstract OA13.04.
- Solomon BJ et al. **Lorlatinib** versus Crizotinib in Patients with Advanced **ALK-Positive** Non-Small Cell Lung Cancer: **5-Year Outcomes** from the **Phase III CROWN Study**. *J Clin Oncol* 2024;42(29):3400-9.
- Bauer T et al. **Kinetics and Management of Adverse Events** Associated with **Lorlatinib** after 5 Years of Follow-Up in the **CROWN** Study. WCLC 2024;Abstract MA06.08.
- Hill L et al. Predictors of **Long-Term Ensartinib Response** from the **eXalt3 Trial**. WCLC 2024;Abstract MA06.09.
- Drilon AE at al. **Phase I/II ALKOVE-1** Study of **NVL-655** in **ALK-Positive (ALK+) Solid Tumours**. ESMO 2024;Abstract 1253O.
- Drilon AE et al. **Repotrectinib** in Tyrosine Kinase Inhibitor (TKI)-Naïve Patients (pts) with **Advanced ROS1 Fusion-Positive (ROS1+) NSCLC** in the **Phase 1/2 TRIDENT-1 Trial**: Clinical Update, Treatment Beyond Progression and Subsequent Therapies. ASCO 2024;Abstract 8522.

Key Datasets

Jessica J Lin, MD (continued)

- Besse B et al. **Phase I/II ARROS-1** Study of **Zidesamtinib (NVL-520)** in **ROS1 Fusion-Positive** Solid Tumours. ESMO 2024;Abstract 1256MO.
- Liu G et al. Efficacy and Safety of **Taletrectinib** in Patients with **ROS1+ Non-Small Cell Lung Cancer**: The Global **TRUST-II Study**. WCLC 2024;Abstract MA06.03.
- Pérol M et al. CNS Protective Effect of **Selpercatinib** in First-Line **RET Fusion-Positive** Advanced Non-Small Cell Lung Cancer. *J Clin Oncol* 2024;42(21):2500-5.
- Lin JJ et al. Updated Efficacy, Safety, and Biomarker Analysis in Patients with **TRK Fusion Lung Cancer** Treated with **Larotrectinib**. WCLC 2024;Abstract MA06.12.
- Schram AM et al. Efficacy of **Zenocutuzumab** in **NRG1 Fusion-Positive Cancer**. *N Engl J Med* 2025;392(6):566-76.

Key Datasets

Joel W Neal, MD, PhD

- Janne PA et al. **Trastuzumab Deruxtecan (T-DXd)** in Patients with **HER2-Mutant** Metastatic Non-Small Cell Lung Cancer (mNSCLC): **Final Analysis Results of DESTINY-Lung02**. ASCO 2024;Abstract 8543.
- Smit EF et al. **Trastuzumab Deruxtecan** in Patients with Metastatic Non-Small-Cell Lung Cancer **(DESTINY-Lung01)**: Primary Results of the **HER2-Overexpressing Cohorts** from a Single-Arm, Phase 2 Trial. *Lancet Oncol* 2024;25(4):439-54.
- Planchard D et al. **Trastuzumab Deruxtecan Monotherapy** in Pretreated **HER2-Overexpressing** Nonsquamous Non-Small Cell Lung Cancer: **DESTINY-Lung03 Part 1**. WCLC 2024;Abstract OA16.05.
- Ruiter G et al. Primary Phase Ib Analysis of **Beamion LUNG-1: Zongertinib (BI 1810631)** in Patients with **HER2 Mutation-Positive NSCLC**. WCLC 2024;Abstract PL04.04.
- Le X et al. Safety and Efficacy of **BAY 2927088** In Patients with **HER2-Mutant NSCLC**: Expansion Cohort from the **Phase I/II SOHO-01 Study**. WCLC 2024;Abstract PL04.03.
- Wolf J et al. **Capmatinib** in **MET Exon 14-Mutated** Non-Small-Cell Lung Cancer: **Final Results** from the Open-Label, **Phase 2 GEOMETRY mono-1 Trial**. *Lancet Oncol* 2024;25(10):1357-70.

Key Datasets

Joel W Neal, MD, PhD (continued)

- Camidge DR et al. **Telisotuzumab Vedotin** Monotherapy in Patients with Previously Treated **c-Met Protein-Overexpressing** Advanced Nonsquamous EGFR-Wildtype Non-Small Cell Lung Cancer in the **Phase II LUMINOSITY Trial**. *J Clin Oncol* 2024;42(25):3000-11.
- Riley GJ et al. Updated Efficacy and Safety from the **Phase II PHAROS Study** of **Encorafenib plus Binimetinib** in Patients with **BRAF V600E-Mutant Metastatic NSCLC** (mNSCLC). ESMO 2024;Abstract LBA56.
- Waterhouse DM et al. **Patient-Reported Outcomes** in **CodeBreaK 200**: **Sotorasib** versus Docetaxel for Previously Treated Advanced NSCLC with **KRAS G12C Mutation**. *Lung Cancer* 2024;196:107921.
- Mok TSK et al. **KRYSTAL-12**: **Phase 3 Study of Adagrasib** versus Docetaxel in Patients with Previously Treated Advanced/Metastatic Non-Small Cell Lung Cancer (NSCLC) Harboring **a KRASG12C Mutation**. ASCO 2024;Abstract LBA8509.
- Sacher A et al. **Divarasib Single-Agent** Long-Term Follow-Up and **Atezolizumab Combination Treatment** in Patients with **KRAS G12C-Positive NSCLC**. WCLC 2024;Abstract OA14.06
- Fujiwara Y et al. Efficacy and Safety of **Olomorasib with Pembrolizumab + Chemotherapy** as **First-Line** Treatment in Patients with **KRAS G12C-Mutant Advanced NSCLC**. WCLC 2024;Abstract OA14.04.

Year in Review: Targeted Therapies Beyond EGFR for Non-Small Cell Lung Cancer (NSCLC)

INTRODUCTION: AGAs (Actionable Genomic Alterations)

MODULE 1: ALK

MODULE 2: ROS1

MODULE 3: HER2

MODULE 4: RET

MODULE 5: NTRK

MODULE 6: MET

MODULE 7: BRAF

MODULE 8: KRAS G12C

MODULE 9: NRG1

MODULE 10: Novel Targeted Strategies

RTP Year in Review 2025

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RTP Year in Review 2025

Disease Subtypes

- Lymphomas
- Breast Cancer
- Lung Cancer

Select AGAs Among Patients with Metastatic NSCLC

- EGFR EXON 19 and 21
- EGFR EXON 20
- ALK
- ROS1
- HER2
- RET
- NTRK
- MET EXON 14
- c-MET
- BRAF
- KRAS G12C
- NRG1

Neil’s Top 20+ Questions

RTP Year in Review 2025

What is an AGA?

RTP Year in Review 2025

Other than HER2, RET, BRAF, KRAS G12C NTRK and NRG1, which actionable genomic alterations would be a reasonable target outside of lung cancer (eg, EGFR and ALK)?

For which of these alterations is first-line targeted treatment a reasonable consideration? What about checkpoint inhibition?

Why is the PFS for lorlatinib so long compared to other ALK inhibitors and other targeted treatments?

Year in Review: Targeted Therapies Beyond EGFR for Non-Small Cell Lung Cancer (NSCLC)

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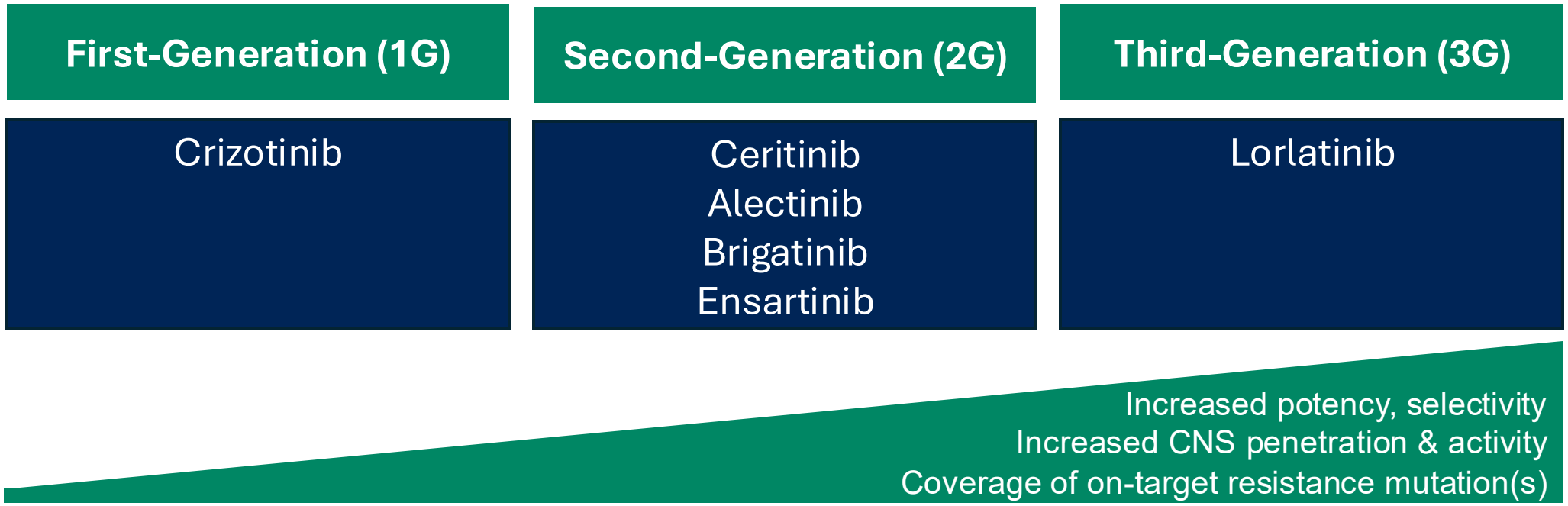
RTP Year in Review 2025

Evolution of First- and Next-Generation ALK Inhibitors for ALK+ NSCLC



Note: Only the FDA-approved ALK inhibitors are shown, with others in development

Courtesy of Jessica J Lin, MD

Lin JJ, ASCO 2024

FDA approves ensartinib for ALK-positive locally advanced or metastatic non-small cell lung cancer

Press Release: December 18, 2024

The Food and Drug Administration approved ensartinib for adult patients with anaplastic lymphoma kinase (ALK)-positive locally advanced or metastatic non-small cell lung cancer (NSCLC) who have not previously received an ALK inhibitor.

Efficacy was evaluated in eXalt3 (NCT02767804), an open-label, randomized, active-controlled, multicenter trial in 290 patients with locally advanced or metastatic ALK-positive NSCLC who had not previously received an ALK-targeted therapy. Patients were randomized 1:1 to receive ensartinib or crizotinib.

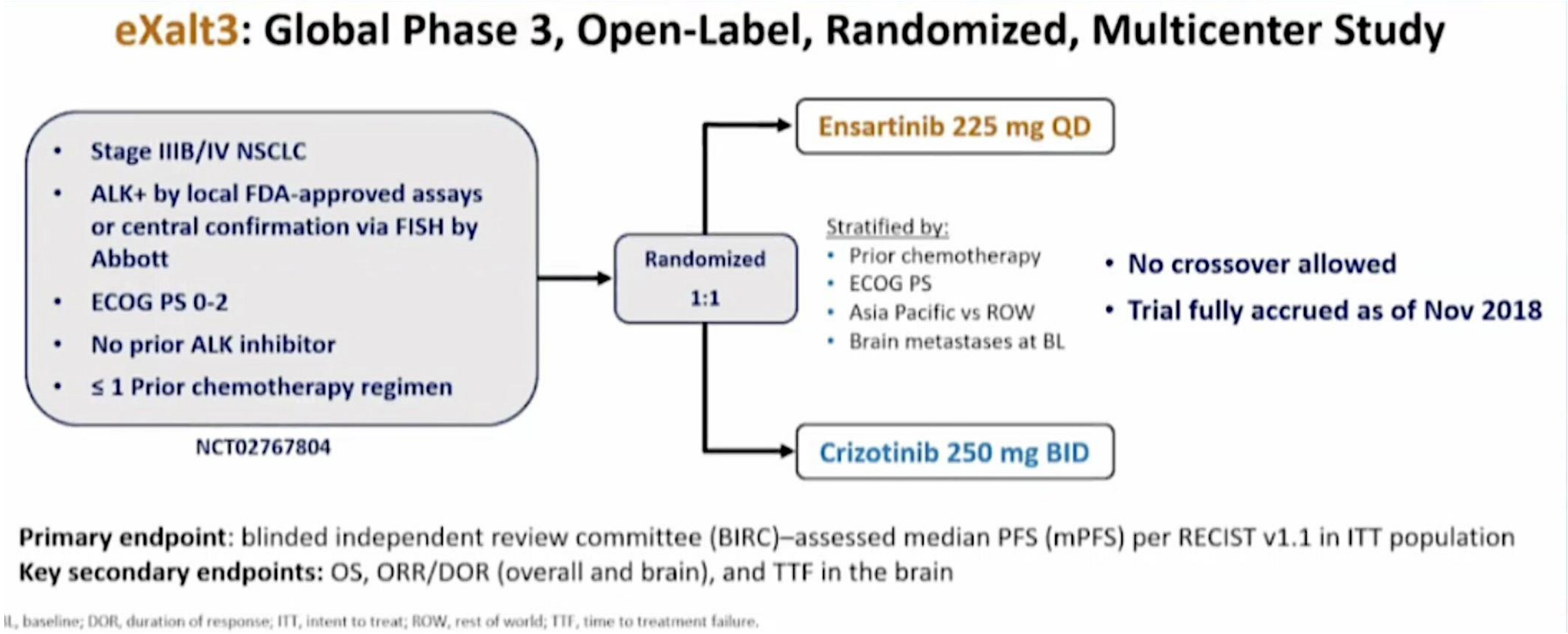
The main efficacy outcome measure was progression-free survival (PFS) as evaluated by blinded independent central review. The key secondary efficacy outcome measure was overall survival (OS). Ensartinib demonstrated a statistically significant PFS improvement compared to crizotinib with a hazard ratio (HR) of 0.56 (95% CI: 0.40, 0.79; p-value 0.0007). The median PFS was 25.8 months (95% CI: 21.8, not estimable) in the ensartinib arm and 12.7 months (95% CI: 9.2, 16.6) in the crizotinib arm. There was no statistically significant difference in OS (HR 0.88 [95% CI: 0.63, 1.23], p-value 0.4570).

The most common adverse reactions (≥20%) were rash, musculoskeletal pain, constipation, cough, pruritis, nausea, edema, pyrexia, and fatigue.

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-ensartinib-alk-positive-locally-advanced-or-metastatic-non-small-cell-lung-cancer

Courtesy of Jessica J Lin, MD

eXalt3 Study Design

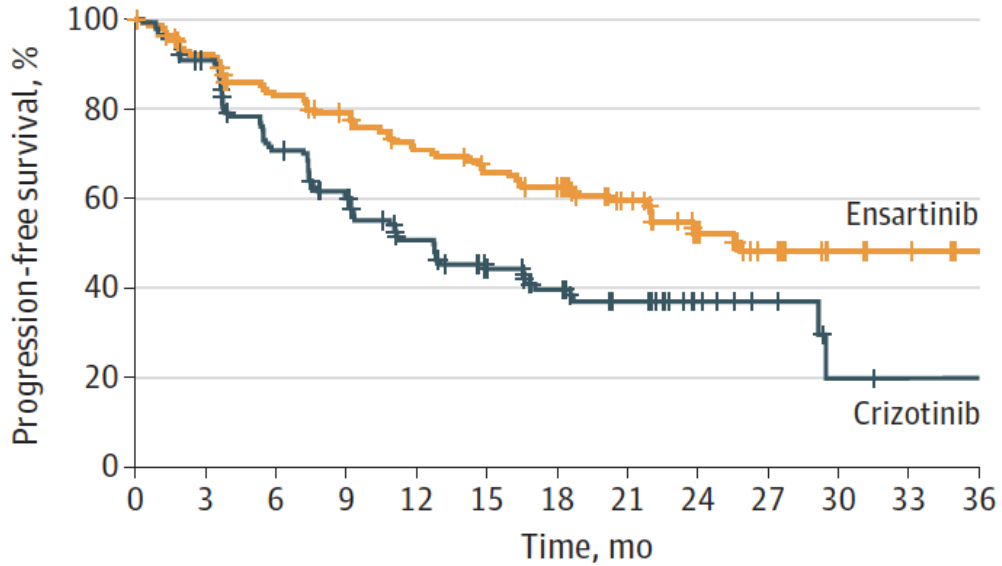


Courtesy of Jessica J Lin, MD

Horn L., WCLC 2020

Ensartinib in Metastatic ALK+ NSCLC: PFS Results, Phase III eXalt3 Trial

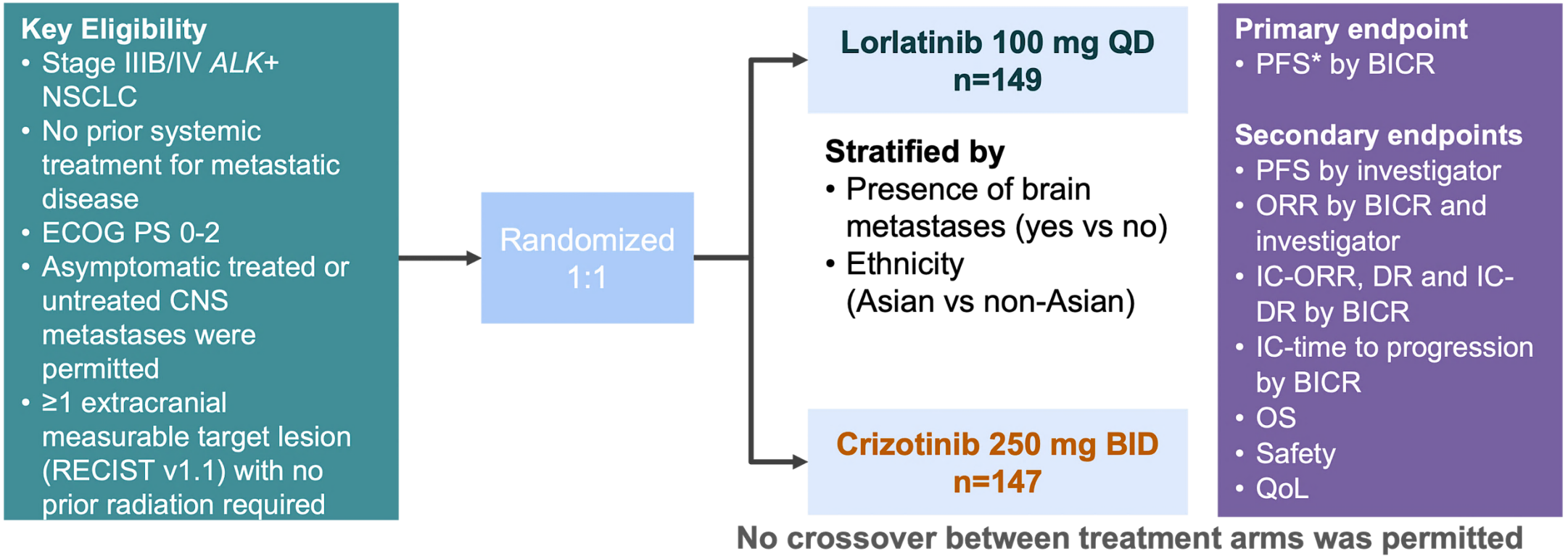
	Ensartinib (n = 143)	Crizotinib (n = 147)
mPFS (95% CI), mo	25.8 (21.8-NR)	12.7 (9.2-16.6)
Hazard ratio (95% CI)	0.51 (0.35-0.72)	
P value (log-rank test)	<.001	



No. at risk													
Ensartinib	143	125	106	98	86	78	72	54	30	21	10	5	1
Crizotinib	147	124	94	75	56	43	32	23	10	6	2	1	1

Courtesy of Jessica J Lin, MD

Lorlatinib in Metastatic ALK+ NSCLC: Phase III CROWN Trial



•*Defined as the time from randomization to RECIST-defined progression or death due to any cause.

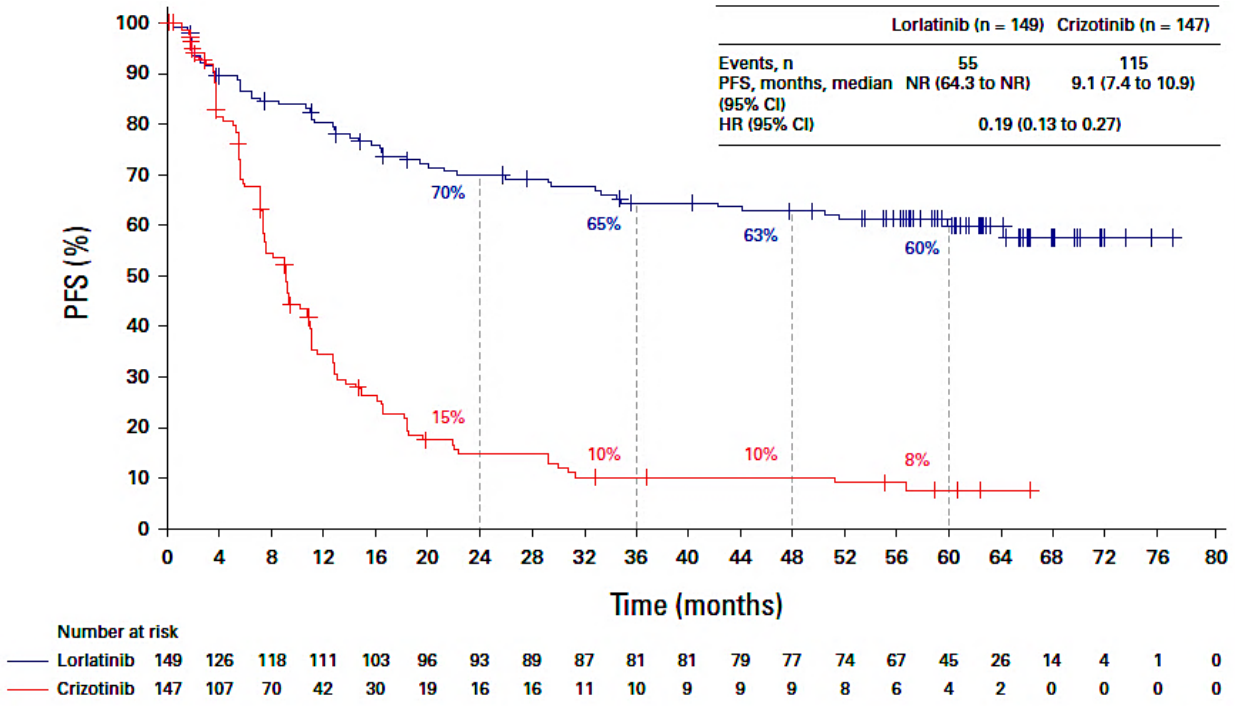
BICR, blinded independent central review; DR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QoL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumors. ClinicalTrials.gov number, NCT03052608

Courtesy of Jessica J Lin, MD

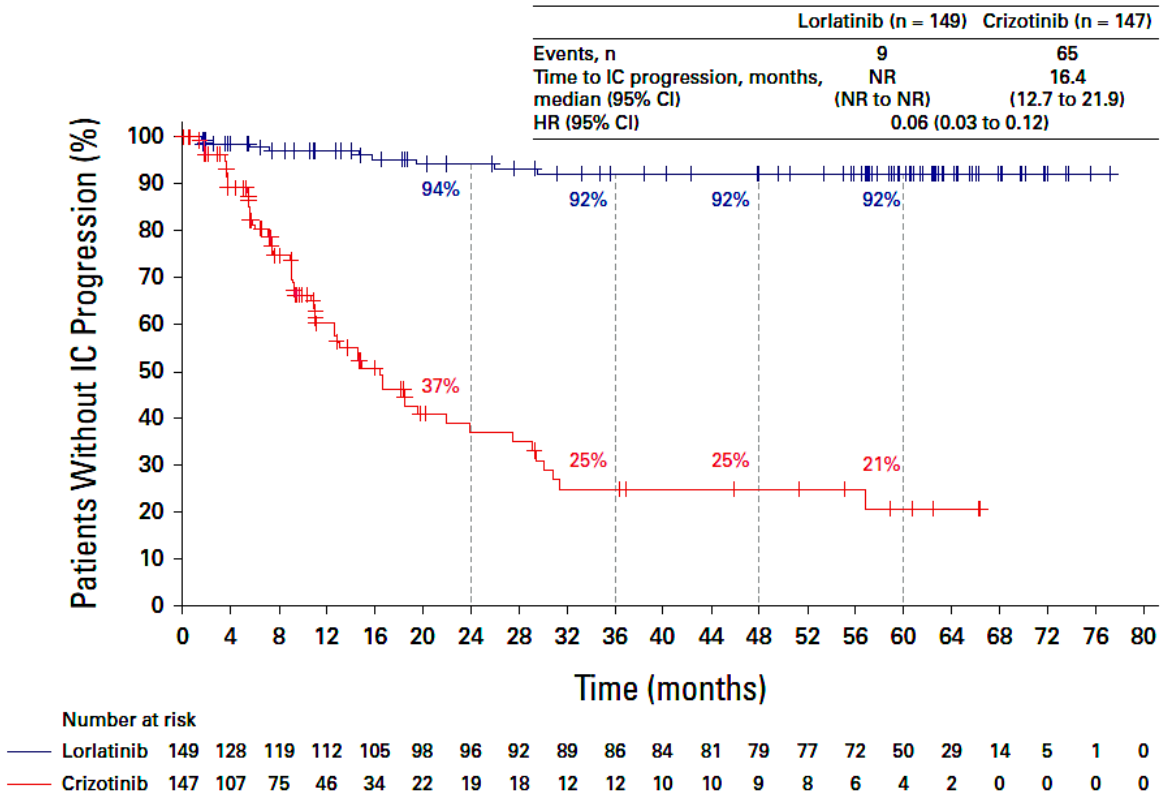
Solomon B et al., ESMO 2020

Lorlatinib in Metastatic ALK+ NSCLC: CROWN Trial 5-Year Outcomes Update

PFS (investigator assessment)



Time to intracranial progression (investigator assessment)

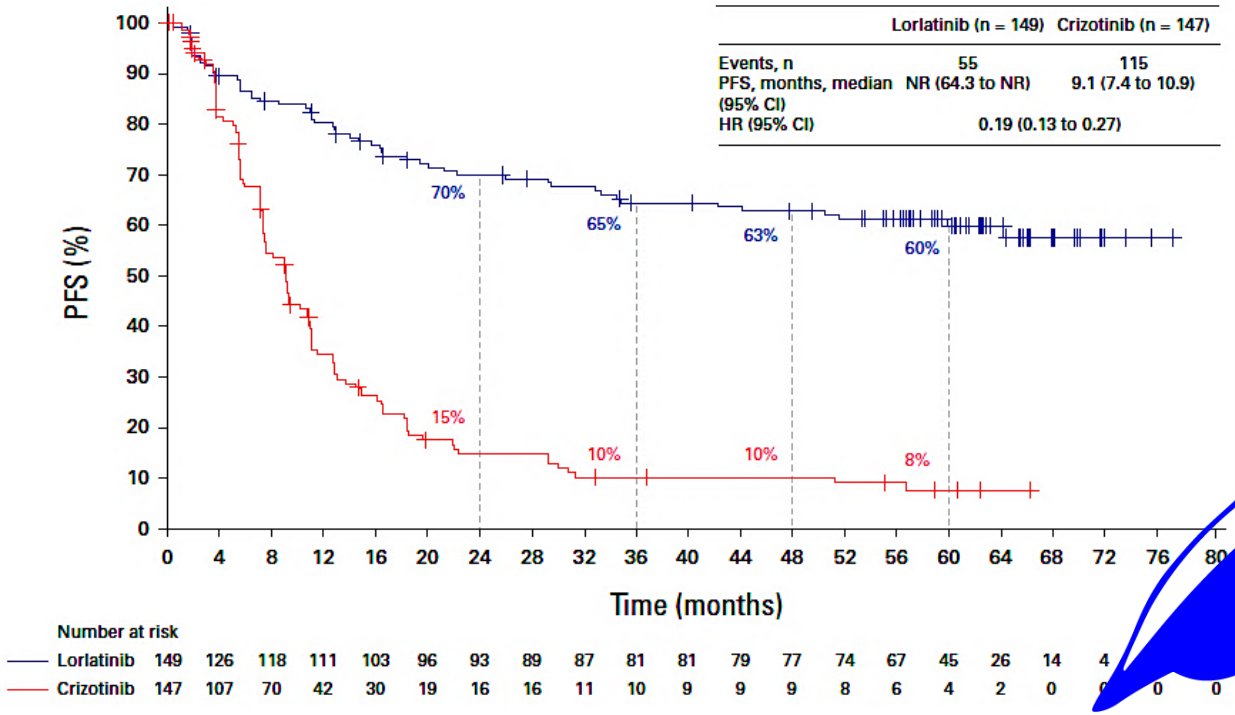


Courtesy of Jessica J Lin, MD

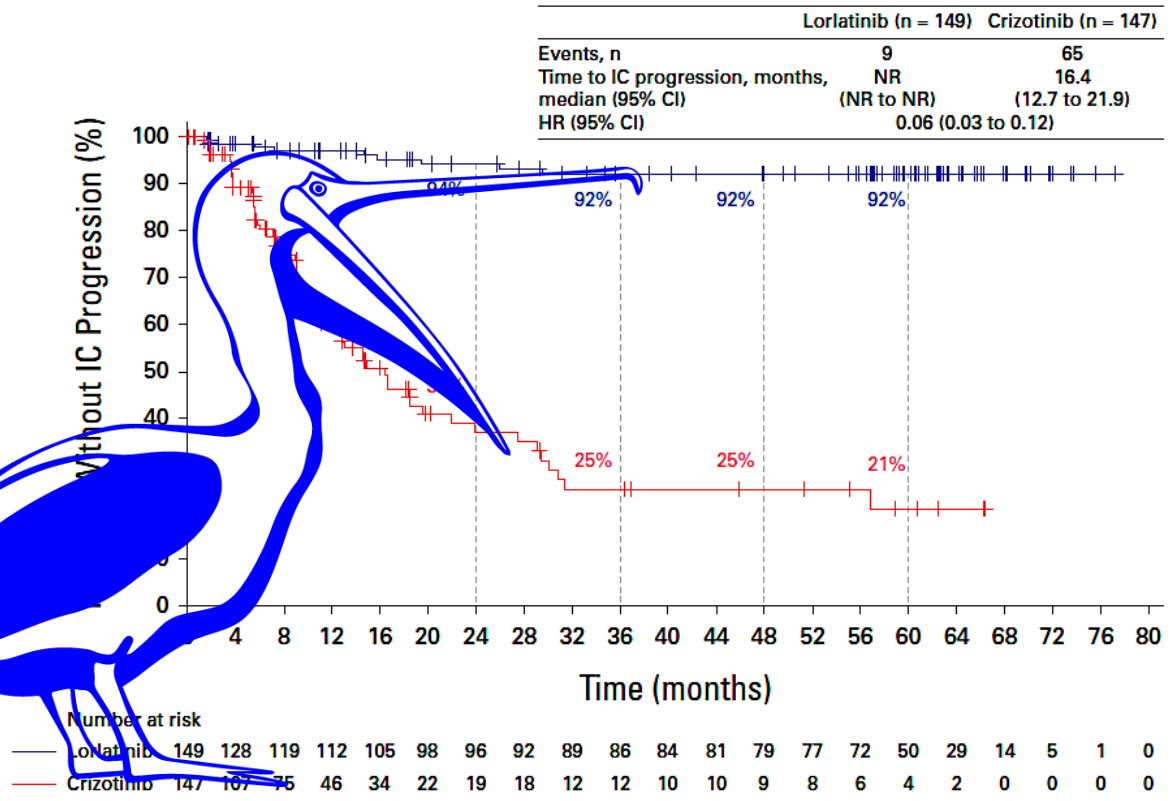
Solomon B et al., J Clin Oncol 2024;42(29):3400-9

Lorlatinib in Metastatic ALK+ NSCLC: CROWN Trial 5-Year Outcomes Update

PFS (investigator assessment)



Time to intracranial progression (investigator assessment)



Courtesy of Jessica J Lin, MD

Solomon B et al., J Clin Oncol 2024;42(29):3400-9

Lorlatinib in Metastatic ALK+ NSCLC: CROWN Trial 5-Year Safety Update

- With long exposure to lorlatinib, **no new safety signals** emerged, and treatment discontinuation remained low after 5 years of follow-up
- With lorlatinib**, all-cause AEs led to permanent discontinuation in 11% of patients; in 5%, these AEs were treatment related**[1]
  - In patients who did not discontinue, AEs were efficiently managed with active measures including dose modifications
- Dose reduction (in the first 16 weeks) did not affect efficacy of lorlatinib[1]

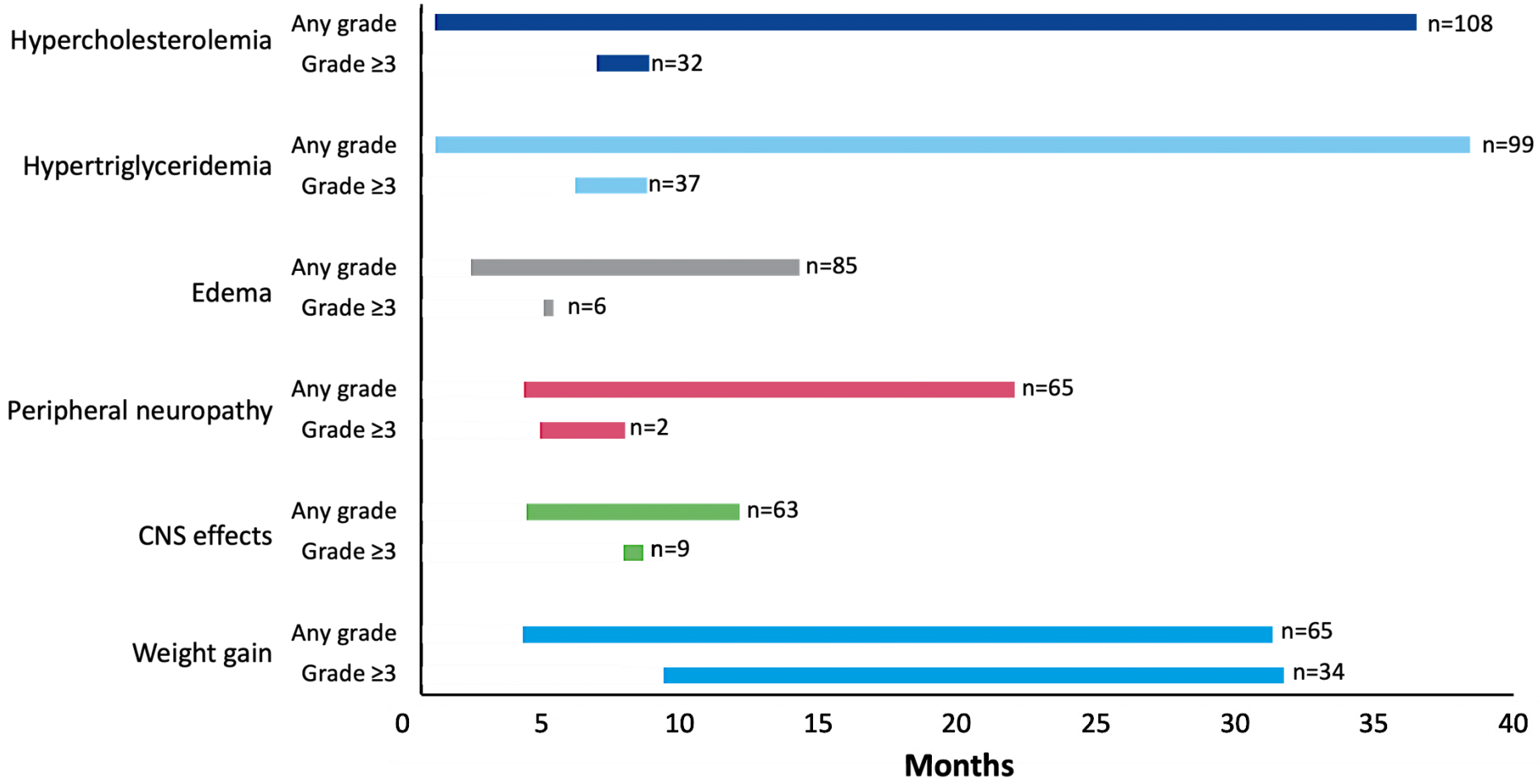
AE, adverse event.

1. Solomon BJ, et al. *J Clin Oncol*. 2024 May 31:JCO2400581.

Courtesy of Jessica J Lin, MD

Solomon B et al., J Clin Oncol 2024;42(29):3400-9
Bauer T et al., WCLC 2024

Lorlatinib in Metastatic ALK+ NSCLC: CROWN Trial 5-Year Safety Update, AE Kinetics

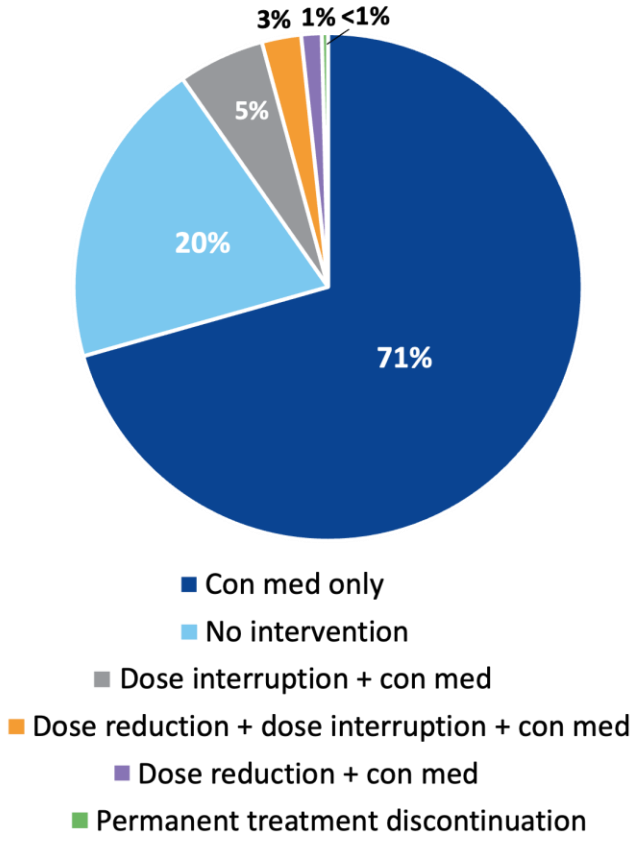


Courtesy of Jessica J Lin, MD

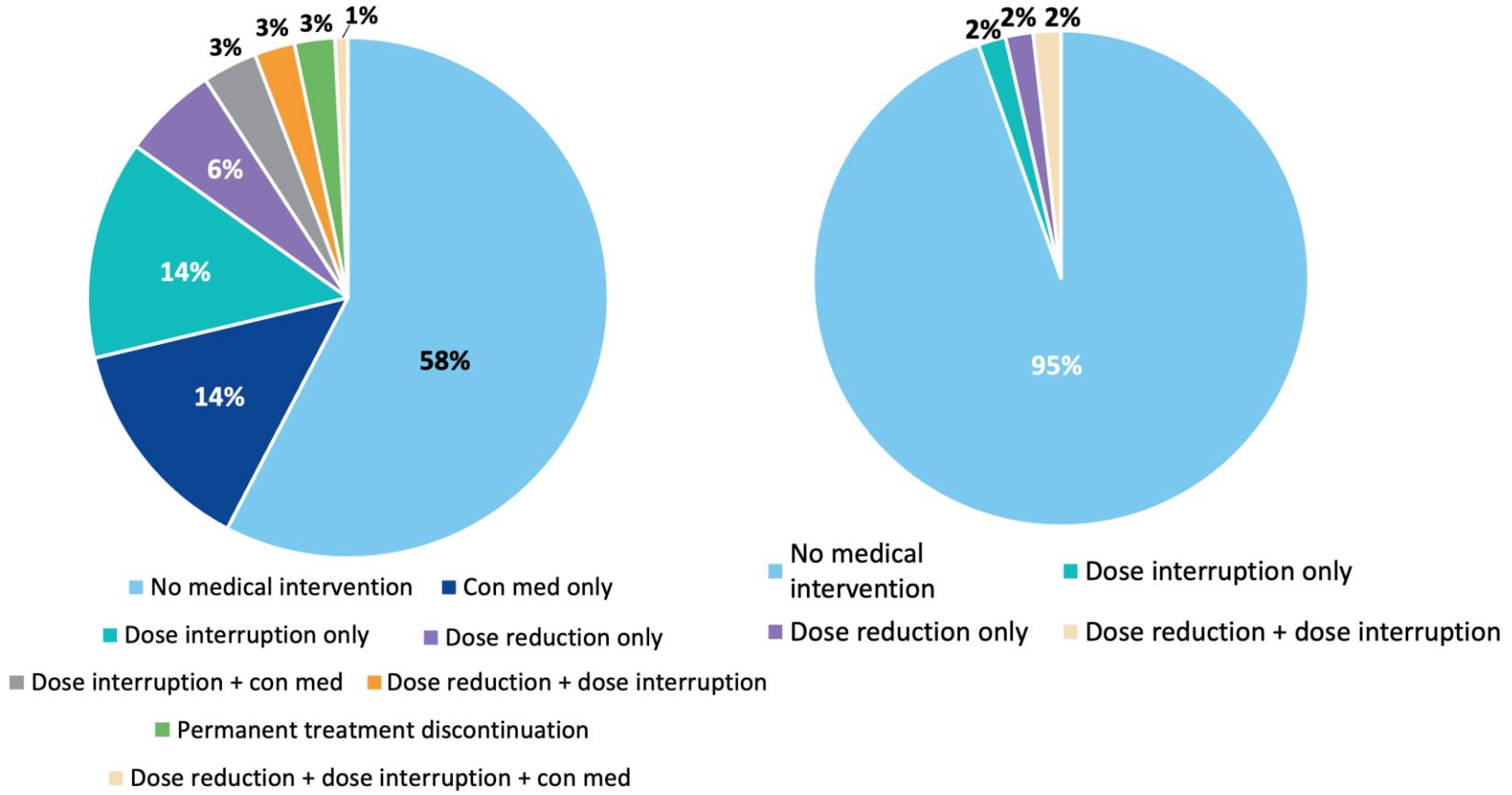
Bauer T et al., WCLC 2024

Lorlatinib in Metastatic ALK+ NSCLC: CROWN Trial 5-Year Safety Update, AE Management

Hyperlipidemia



CNS Adverse Events



Weight gain

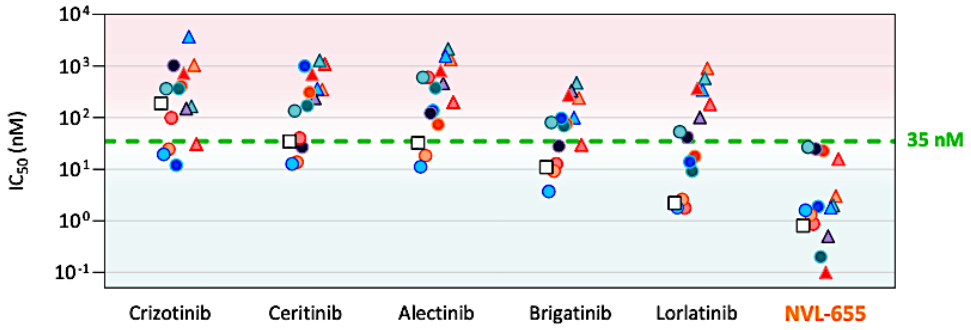
Courtesy of Jessica J Lin, MD

Bauer T et al., WCLC 2024

NVL-655: A Rationally Designed ALK-selective, TRK-sparing TKI

ALK Fusion and ALK Single/Compound Mutation Activity

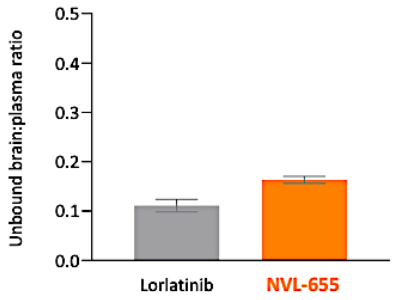
Potent activity (IC_{50} = 0.1 – 30 nM) against ALK-driven cell lines, including ALK single and compound mutants



Cell lines harboring EML4-ALK fusion
3-day cell viability assay

Brain Penetrance

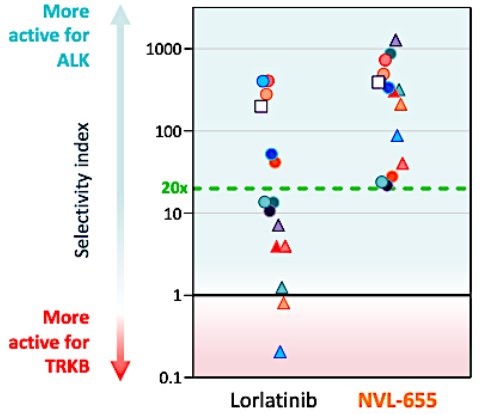
Preclinical pharmacokinetic data similar to lorlatinib



Wistar Han rats
10 mg/kg, single dose PO
1-hour timepoint

Avoidance of TRK Inhibition

Selective inhibition of ALK and ALK mutants over TRK



$$\text{Selectivity index} = \frac{IC_{50}\ (\text{pTRKB})}{IC_{50}\ (\text{Ba/F3 EML4-ALK})}$$

□ No resistance mutations | MGH048-1 (v1)

Single ALK mutations

- T1151M | Ba/F3 (v3)
- I1171N | Ba/F3 (v1)
- F1174L | Ba/F3 (v3)
- V1180L | Ba/F3 (v1)
- L1196M | MGH045-1 (v1)
- L1198F | Ba/F3 (v1)
- G1202R | YU-1077 (v3)
- D1203N | Ba/F3 (v1)

Compound ALK mutations

- G1202R/T1151M | MR448re (v3)
- G1202R/F1174L | Ba/F3 (v3)
- G1202R/L1196M | MGH953-7 (v3)
- G1202R/L1198F | Ba/F3 (v1)
- G1202R/G1269A | Ba/F3 (v1)
- I1171N/L1198F | Ba/F3 (v1)

Lin J.J. et al. (2024). NVL-655 Is a Selective and Brain-Penetrant Inhibitor of Diverse ALK Mutant Oncoproteins, Including Lorlatinib-Resistant Compound Mutations. *Cancer Discovery*. Advance Online Publication.

Cancer Discovery

Head-to-head clinical studies comparing NVL-655 with currently approved or investigational therapies have not been conducted.

IC_{50}, half-maximal inhibitory concentration; **PO**, orally; **v**, EML4 breakpoint variant.

Sources: Lin J.J. et al., Cancer Discovery 2024; Lin J.J. et al., AACR-NCI-EORTC 2023; Lee, J. *et al.* AACR 2023; Fujino, T. *et al.* EORTC-NCI-AACR 2022; Mizuta, H. *et al.* WCLC-IASLC 2022; Tangpeerachaikul, A. *et al.* AACR 2022; Tangpeerachaikul, A. *et al.* AACR-NCI-EORTC 2021; Pelish, H. *et al.* AACR 2021. Data also reflect additional repeat testing and models.

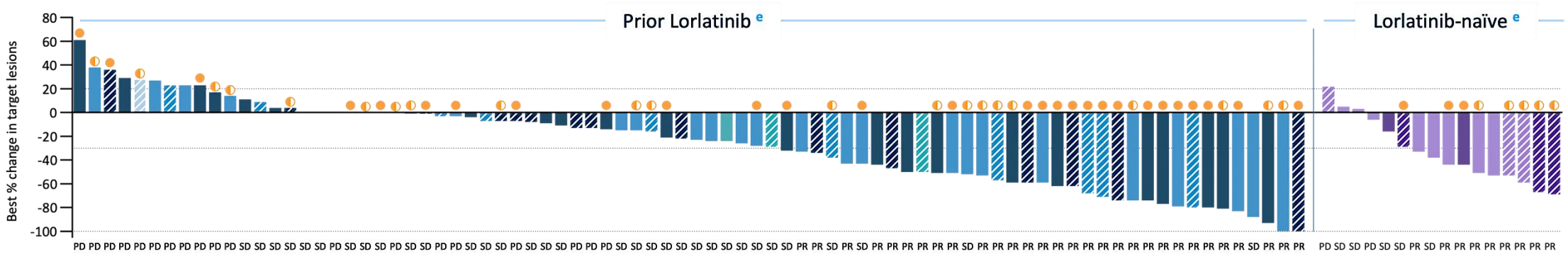
BARCELONA 2024 ESMO congress

Drilon A et al. ESMO 2024;Abstract 1253O.

RTP Year in Review 2025

NVL-655 (Neladalkib) in Metastatic ALK+ NSCLC: Phase I/II ALKOVE-1 Trial

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)



Data cut-off: 15 June 2024. Response-evaluable patients with NSCLC. All responses were confirmed.

NSCLC, non-small cell lung cancer; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1; RP2D, Recommended Phase 2 dose (150 mg QD); SD, stable disease; TKI, tyrosine kinase inhibitor.

[a] Includes all patients with ≥1 identified ALK resistance mutation as per local or central testing of blood (ctDNA) or tissue. Responses observed in patients with ALK I1171N/S, V1180L, L1196Q, L1198F, D1203N, or E1210K mutations, including where multiple mutations co-occur, in addition to those with G1202R.

[b] Includes patients with G1202R single and compound (≥2) mutations.

[c] Cis-allelic configuration has not been confirmed for all patients with compound (≥2) ALK resistance mutations.

[d] ORR = 67% (20/30) for G1202R patients with prior lorlatinib, and ORR= 100% (2/2) for lorlatinib-naïve G1202R patients.

[e] Five response-evaluable patients (4 with no known ALK mutations and 1 with single ALK mutation) not shown due to incomplete or missing post-baseline tumor assessments in the setting of PD or symptomatic deterioration.

KEY: PATIENT DETAILS

Lorlatinib Pre-treated:
- ≥ 3 prior ALK TKI
- 2 prior, 2G + lorlatinib
- 2 prior, 1G + lorlatinib
- 1 prior (lorlatinib only)

Lorlatinib-naïve:
- ≥ 2 prior ALK TKIs
- 1 prior, alectinib

Patient treated at RP2D

- **ALK single resistance mutation**
- **ALK compound (≥2) resistance mutation**

Courtesy of Jessica J Lin, MD

Drilon A et al., ESMO 2024

NVL-655 (Neladalkib) in Metastatic ALK+ NSCLC: Phase I/II ALKOVE-1 Trial

- 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)

Data cut-off: 15 June 2024. Median follow-up for all treated population: 8.0 months (range 0.2, 22.5).
ALT, alanine aminotransferase; AST, aspartate aminotransferase; MTD, maximum tolerated dose; QD, once daily; RP2D, recommended phase 2 dose; TRAE, treatment-related adverse event.
[a] TRAEs resulting in treatment discontinuation were Grade 3-4 ALT/AST elevations (50 mg QD and 100 mg QD) and intolerable Grade 2 constipation (occurred at 100 mg QD following dose increase from 50 mg QD).
[b] TRAEs resulting in dose-reduction in > 1 patient were ALT and/or AST increase (n = 7), dysgeusia (n = 2), peripheral sensory neuropathy (n = 2), and rash maculopapular (n = 2). Reductions by dose level were 200 mg QD (n = 7), 150 mg QD (n = 7), 100 mg QD (n = 4), and 50 mg QD (n = 2).

Courtesy of Jessica J Lin, MD

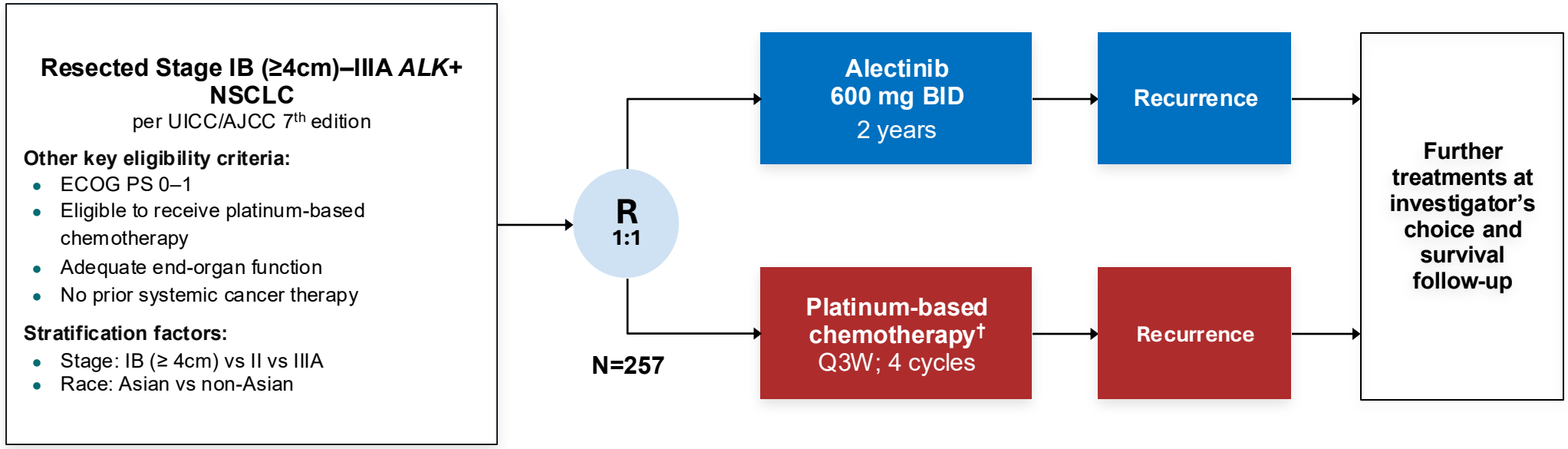
Drilon A et al., ESMO 2024

Treatment of Metastatic ALK+ NSCLC: *My Take*

- Multiple 2nd-/3rd-generation ALK TKIs are FDA-approved (and listed as NCCN category 1) as initial therapy for metastatic ALK+ NSCLC
- The 5-year analyses of CROWN affirm lorlatinib as SOC first-line treatment for metastatic ALK+ NSCLC, with the longest PFS and time to intracranial progression reported to date amongst ALK inhibitors
- 4th-generation ALK TKI NVL-655 is demonstrating encouraging activity and tolerability in a heavily pre-treated patient population
- ***Remaining questions:***
  - How will the prolonged PFS outcomes impact OS outcomes on ALK TKIs in patients?
  - What is the landscape of mechanisms of resistance to first-line lorlatinib therapy and how does this shape subsequent treatments post-lorlatinib?

Courtesy of Jessica J Lin, MD

Bringing ALK-Targeted Therapy to Early-Stage Disease: Phase III ALINA Trial of Alectinib



Primary endpoint

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

Other endpoints

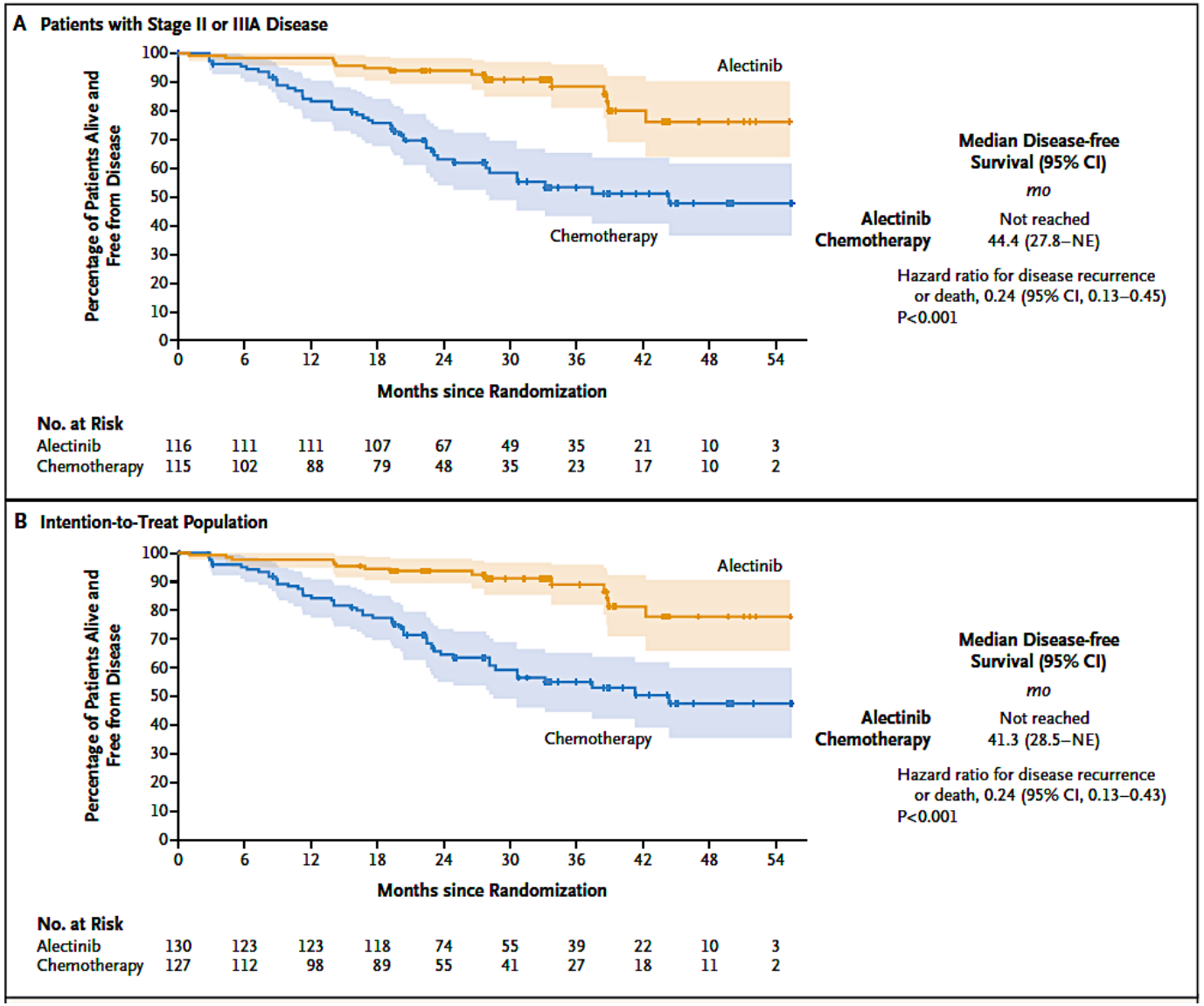
- CNS disease-free survival
- OS
- Safety

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

Courtesy of Jessica J Lin, MD

Solomon B et al., ESMO 2024

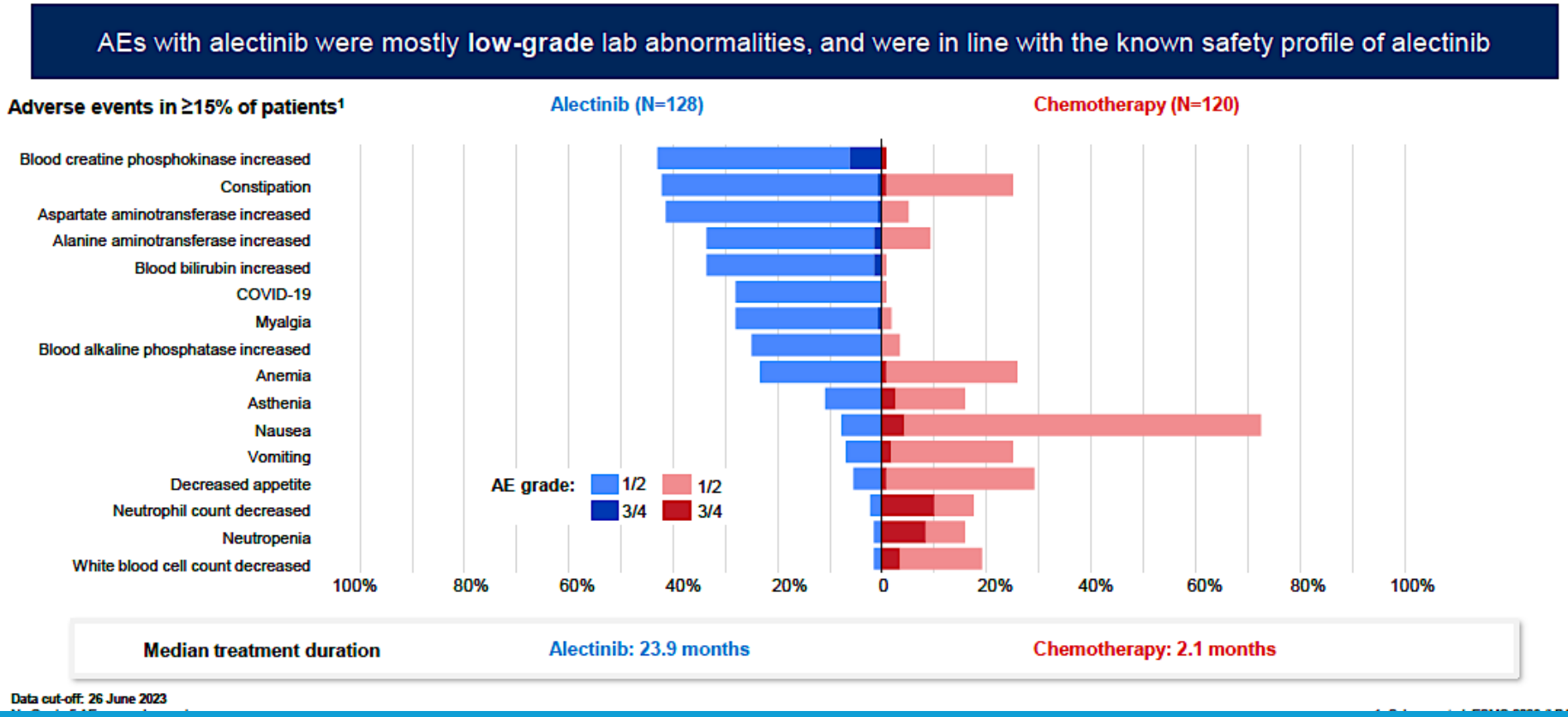
Bringing ALK TKI Alectinib to Early-Stage Disease: ALINA Trial DFS Results



Courtesy of Jessica J Lin, MD

Wu YL et al., N Engl J Med 2024;390(14):1265-76

Safety Data from ALINA



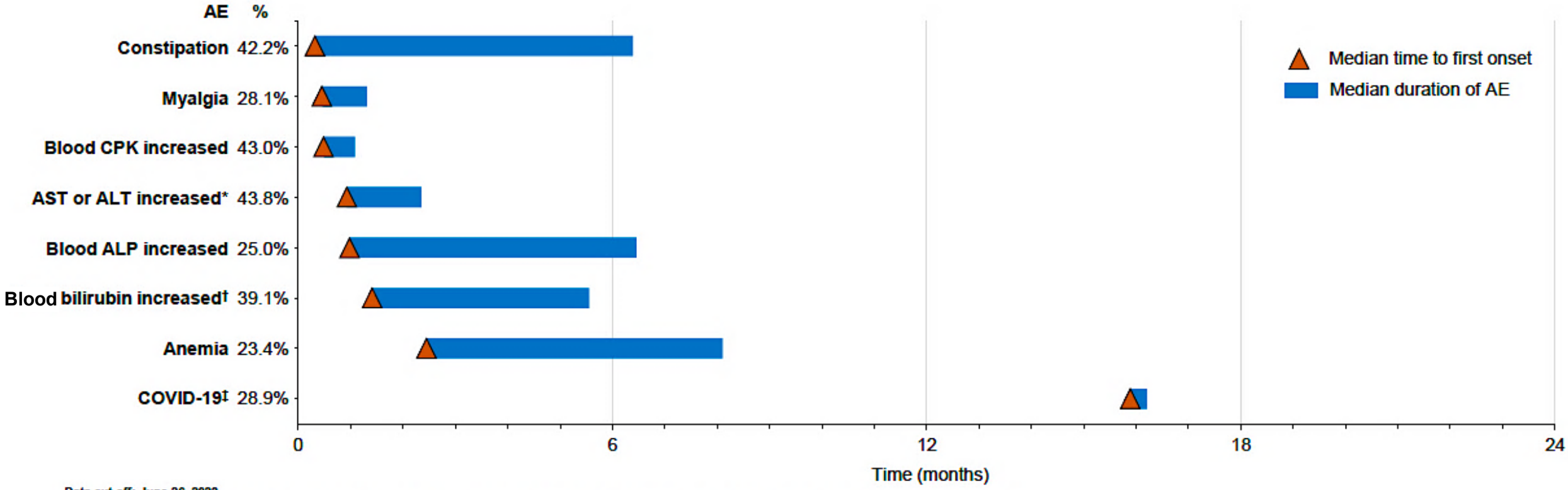
	Alectinib (n=128)	Chemotherapy (n=120)
AEs leading to dose reduction, %	26	10
AEs leading to dose interruption, %	27	18
AEs leading to treatment withdrawal, %	5	13
Median dose intensity, %	99.4	100

Courtesy of Jessica J Lin, MD

Horinuchi H et al., WCLC 2024

Safety Data from ALINA

For the most frequent AEs, the median time to onset occurred mostly during the **first month** of alectinib.
AEs of longer duration were mostly **Grade 1–2** in severity, **manageable** and did not lead to **treatment discontinuation**



Data cut-off: June 26, 2023
Median duration was defined as time from onset to resolution of AEs and summarized using the Kaplan-Meier method; AEs were considered resolved per investigator assessment
*Includes preferred terms aspartate aminotransferase increased and alanine aminotransferase increased; †Includes preferred terms blood bilirubin increased, bilirubin conjugated increased, hyperbilirubinemia, and blood bilirubin unconjugated increased;
‡COVID-19 was not considered to be an adverse drug reaction associated with alectinib treatment
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase

Courtesy of Jessica J Lin, MD

Horinuchi H et al., WCLC 2024

Adjuvant ALK TKI for Resected ALK+ NSCLC: *My Take*

- Adjuvant alectinib is SOC for resected ALK+ NSCLC (FDA- and EMA-approved; NCCN category 1 recommendation)
- Biomarker testing is essential for all stages of NSCLC
- ***Remaining questions:***
  - What is the optimal duration of adjuvant ALK TKI?
  - Who should receive adjuvant chemotherapy prior to (or with) an ALK TKI: all, a subset, or none?
  - Is there a role for ALK-targeted therapy in the neoadjuvant/perioperative setting or after concurrent chemoradiation?

Courtesy of Jessica J Lin, MD

What is the current role of ensartinib?

Is alectinib still being used in first-line treatment, and in what situations is that reasonable?

Which preexisting neurologic or psychiatric conditions should preclude the use of lorlatinib? How do neurologic toxicities of lorlatinib present, and how can these be prevented or ameliorated?

Why do people gain weight on lorlatinib, and how can this be prevented and managed?

Regulatory and reimbursement issues aside, which systemic therapy would you most likely recommend for a patient with PD-L1-negative, ALK-positive metastatic NSCLC who experienced disease progression on first-line lorlatinib?

In the adjuvant setting, what stage disease will lead you to recommend adjuvant alectinib? What about chemotherapy?

What duration of adjuvant therapy is optimal?

Where does dose reduction fit in?

For which of these alterations (other than ALK and EGFR) is targeted treatment a reasonable consideration for localized disease?

For which alterations would you use targeted therapy in the adjuvant setting?

What about postchemoradiation for unresectable locally advanced disease?

For which of these alterations (other than ALK and EGFR) is targeted treatment without radiation therapy a reasonable consideration for a patient with untreated brain metastases?

Year in Review: Targeted Therapies Beyond EGFR for Non-Small Cell Lung Cancer (NSCLC)

INTRODUCTION: AGAs (Actionable Genomic Alterations)

MODULE 1: ALK

MODULE 2: ROS1

MODULE 3: HER2

MODULE 4: RET

MODULE 5: NTRK

MODULE 6: MET

MODULE 7: BRAF

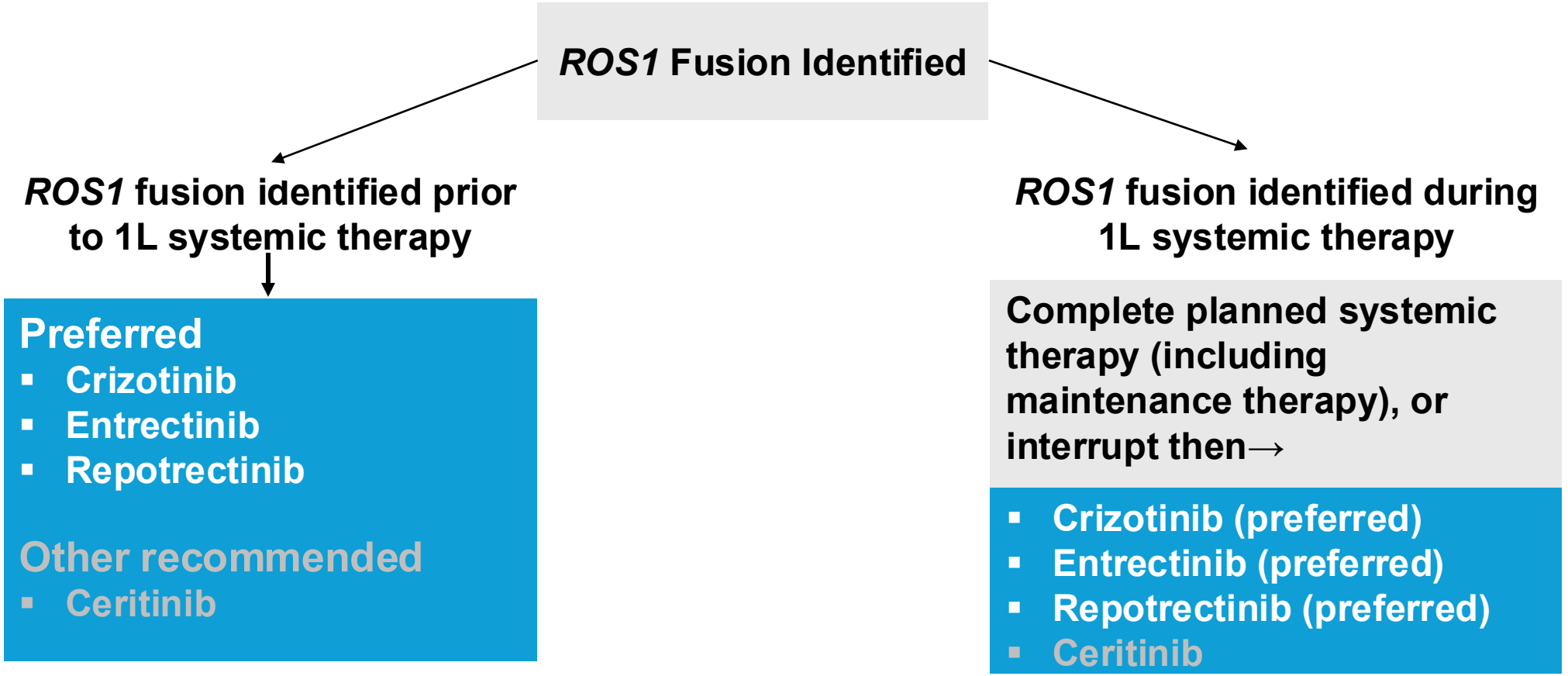
MODULE 8: KRAS G12C

MODULE 9: NRG1

MODULE 10: Novel Targeted Strategies

RTP Year in Review 2025

NCCN Recommendations For the Management of Metastatic ROS1+ NSCLC



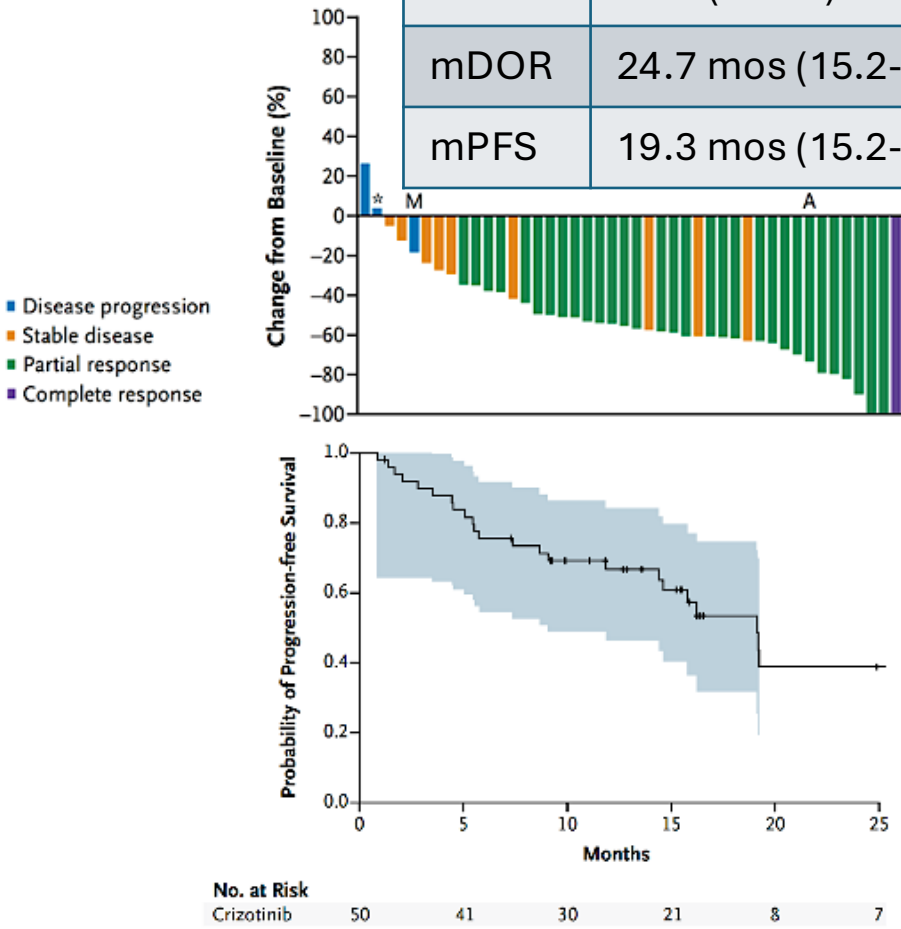
NCCN Guidelines: NSCLC, version 3.2025. nccn.org.

Courtesy of Jessica J Lin, MD

First-Generation ROS1 TKIs Crizotinib and Entrectinib

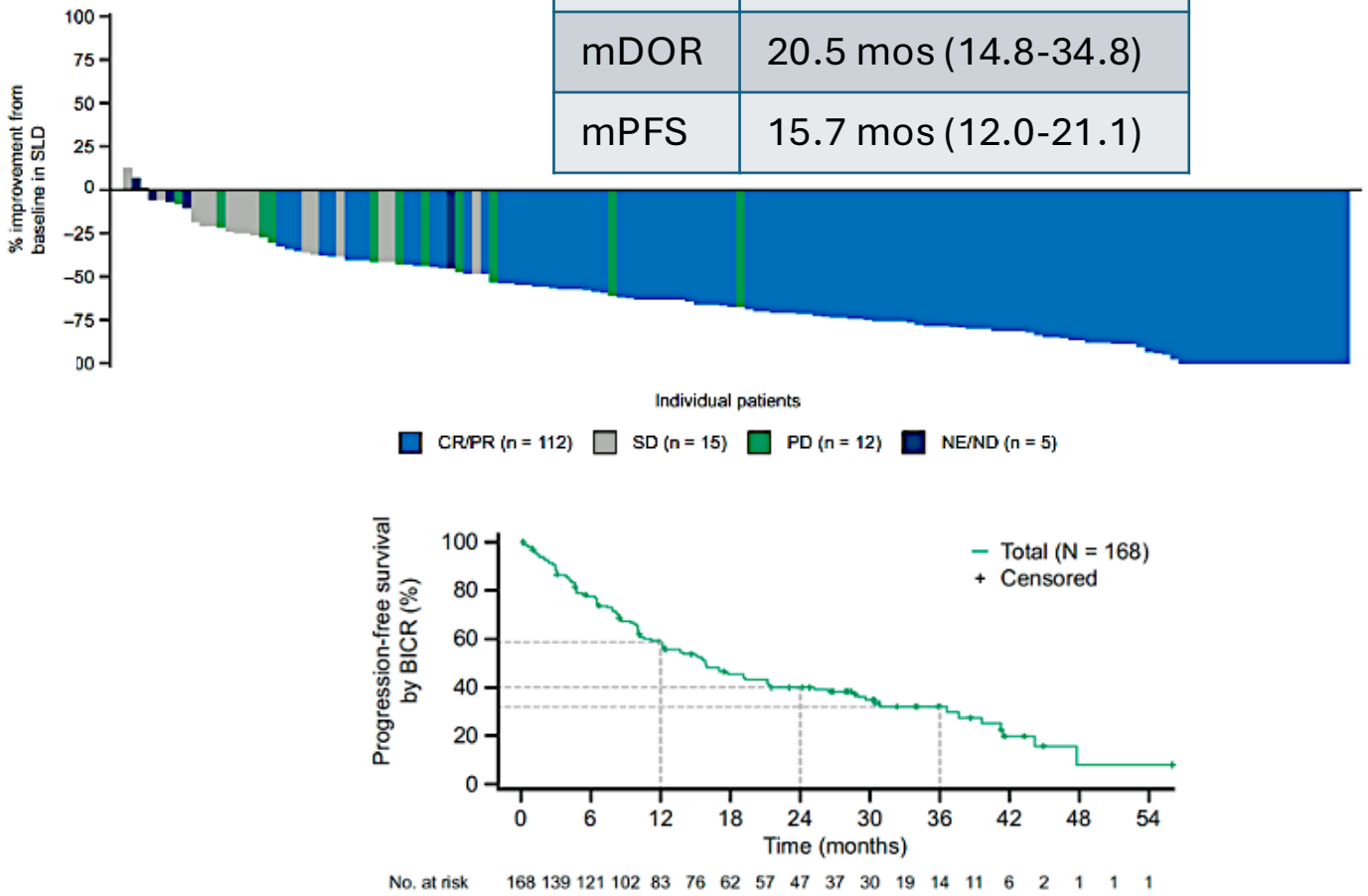
Crizotinib[1,2]

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



Entrectinib[3]

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



1. Shaw AT et al. *N Engl J Med*. 2014;371(21):1963-1971. 2. Shaw AT et al. *Ann Oncol*. 2019;30(7):1121-1126. 3. Drilon A et al. *JTO Clin Res Rep*. 2022;3(6):100332

Courtesy of Jessica J Lin, MD

Repotrectinib in Metastatic ROS1+ NSCLC: Phase I/II TRIDENT-1 Update

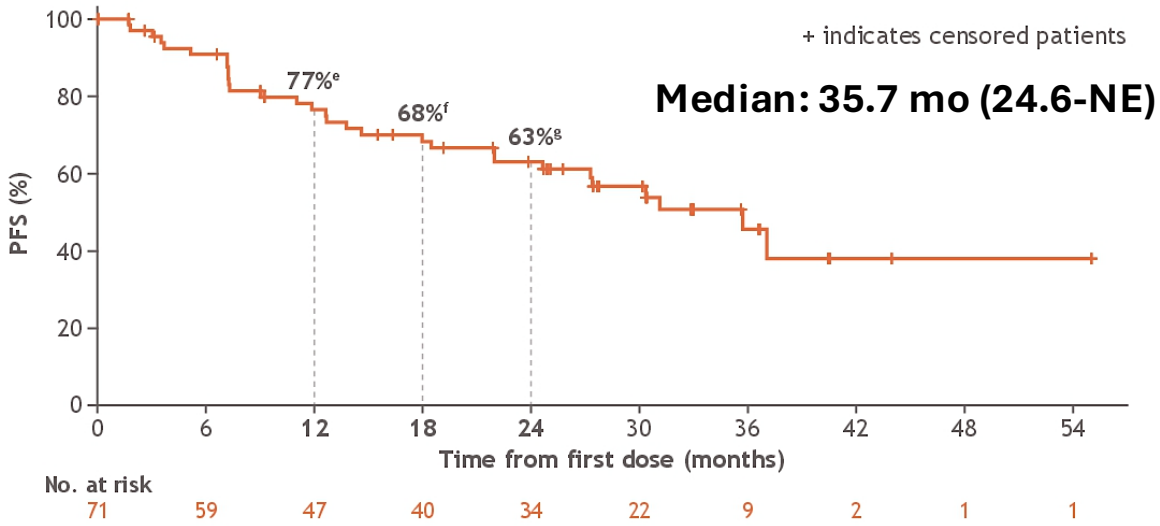
(median follow-up 33.9 mo)

Change in tumor burden per BICR

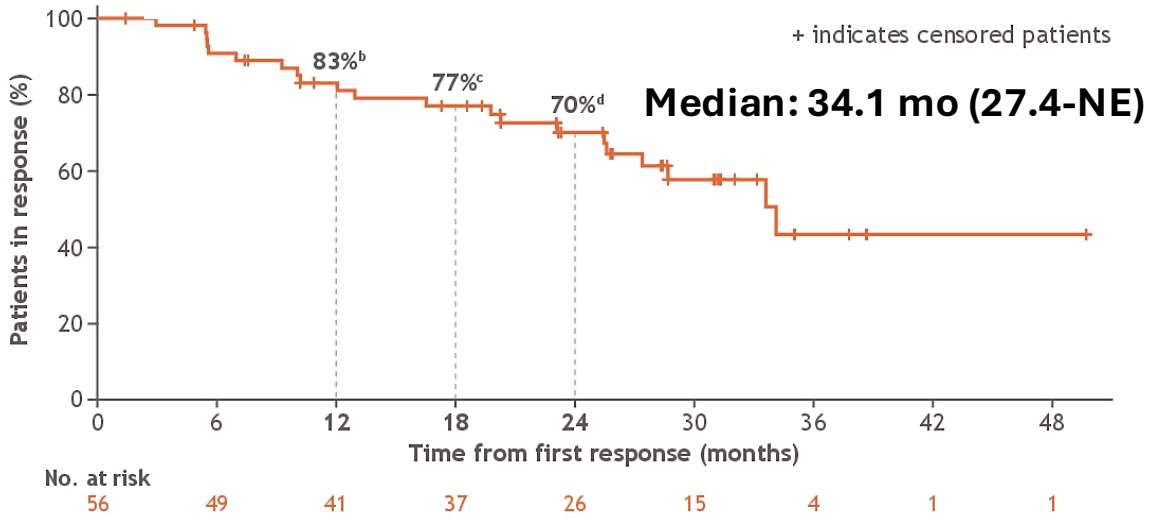
CNS Efficacy

- **IC-ORR 89%** (95% CI, 52-100) (n=9)
- For n=53 without baseline brain metastases, 91% alive and free of IC progression at 12 months; 86% alive and free of IC progression at 24 months

PFS



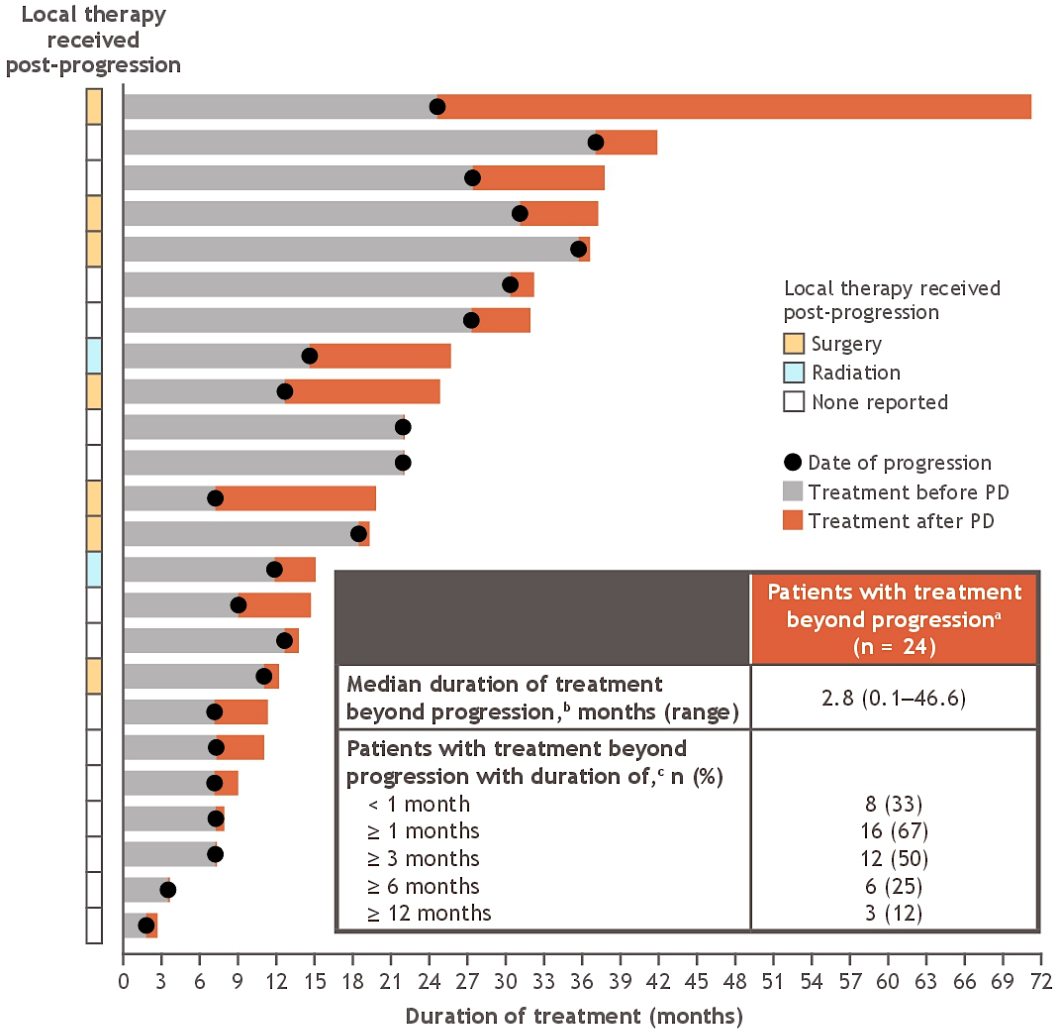
DOR



Courtesy of Jessica J Lin, MD

Drilon A et al., ASCO 2024

Treatment Patterns After First-Line Repotrectinib in TRIDENT-1



	Patients with treatment beyond progression[a] (n = 24)
Median duration of treatment beyond progression,[b] months (range)	2.8 (0.1–46.6)
Patients with treatment beyond progression with duration of,[c] n (%)	
< 1 month	8 (33)
≥ 1 months	16 (67)
≥ 3 months	12 (50)
≥ 6 months	6 (25)
≥ 12 months	3 (12)

[a]Only includes patients who continued treatment beyond first progression. [b]Per BICR, 28 patients had tumor progression. [c]Percentages based on number of patients who continued treatment beyond first progression.

Of 42 patients who discontinued repotrectinib for any reason, 24 received a subsequent therapy

Type of first subsequent therapy reported[a,b]	Patients who discontinued repotrectinib (n = 42)	
	n (%)	Duration of treatment,[c] days (range)
ROS1 TKI — single agent[d]	11 (26)	16–401
ROS1 TKI with chemo[e]	1 (2)	NA
Chemo with/without immunotherapy[f]	10 (24)	1–94
Immunotherapy without chemo[g]	2 (5)	291[h]

[a]Percentages are based on the number of patients who discontinued repotrectinib for any reason. [b]First subsequent therapies were not reported for 18 (43%) ROS1 TKI-naïve patients. [c]Included patients with reported start and end date for subsequent treatment. Does not include 6 patients with missing data. [d]ROS1 TKI single agents included crizotinib (n = 5), entrectinib (n = 3), lorlatinib (n = 2), and NVL-520 (n = 1). [e]Combination of ROS1 TKI and chemo with or without other systemic agents. [f]Chemo with or without other systemic agents, except ROS1 TKI. [g]Immunotherapy alone with or without other systemic agents. [h]Duration of treatment was missing for 1 patient.
NA, not available.

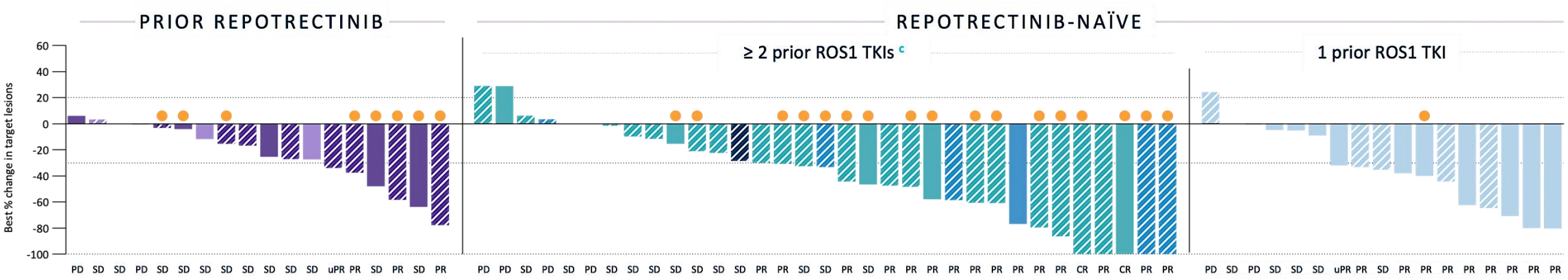
Courtesy of Jessica J Lin, MD

Drilon A et al., ASCO 2024

Zidesamtinib (NVL-520) in ROS1+ NSCLC: Phase I/II ARROS-1 Trial, Preliminary Efficacy

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



Data cut-off: 1 July 2024 . Response-evaluable patients with ROS1+ NSCLC.

CR, complete response; DOR, duration of response; ORR, objective response rate; **PD**, progressive disease; **PR**, partial response; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1; **SD**, stable disease; TKI, tyrosine kinase inhibitor; uPR, unconfirmed partial response.

[a] Includes two ongoing partial responses pending confirmation.

[b] ROS1 mutations as per local or central testing of blood (ctDNA) or tissue. Responses also observed in patients with ROS1 resistance mutations other than G2032R (S1986F, D2033N).

[c] Three response-evaluable patients not shown due to incomplete or missing post-baseline tumor assessments in the setting of symptomatic deterioration.

KEY: PATIENT DETAILS

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

Courtesy of Jessica J Lin, MD

Besse B et al., ESMO 2024

Zidesamtinib (NVL-520) in ROS1+ NSCLC: Phase I/II ARROS-1 Trial, Safety Profile

- 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
All Treated (N = 104)

Preferred Term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Any Grade n (%)
Oedema peripheral	15 (14%)	5 (5%)	-	20 (19%)
ALT increased	11 (11%)	-	-	11 (11%)
AST increased	11 (11%)	-	-	11 (11%)
Weight increased	7 (7%)	3 (3%)	1 (1%)	11 (11%)

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)*

Data cut-off: 1 July 2024. Median follow-up 12.1 months (range, 0.8 – 29.4).
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CNS, central nervous system; MTD, maximum tolerated dose; RP2D, recommended phase 2 dose; QD, once daily; TRAE, treatment-related adverse event.
[a] Only TRAE resulting in dose reduction in >1 patient was oedema peripheral (n=2).

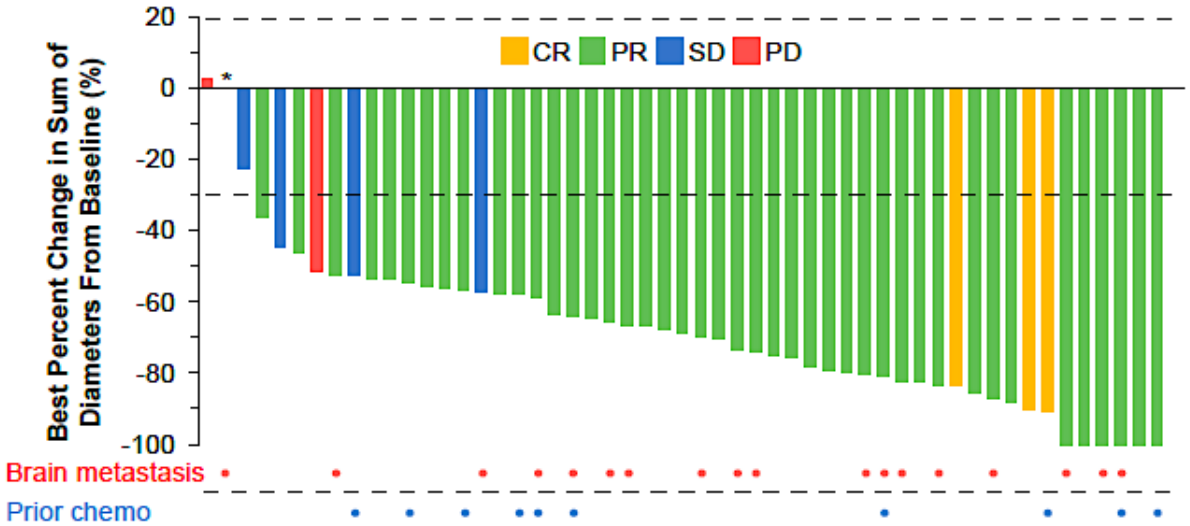
Courtesy of Jessica J Lin, MD

Besse B et al., ESMO 2024

Taletrectinib in Metastatic ROS1+ NSCLC: Global Phase II TRUST-II Trial

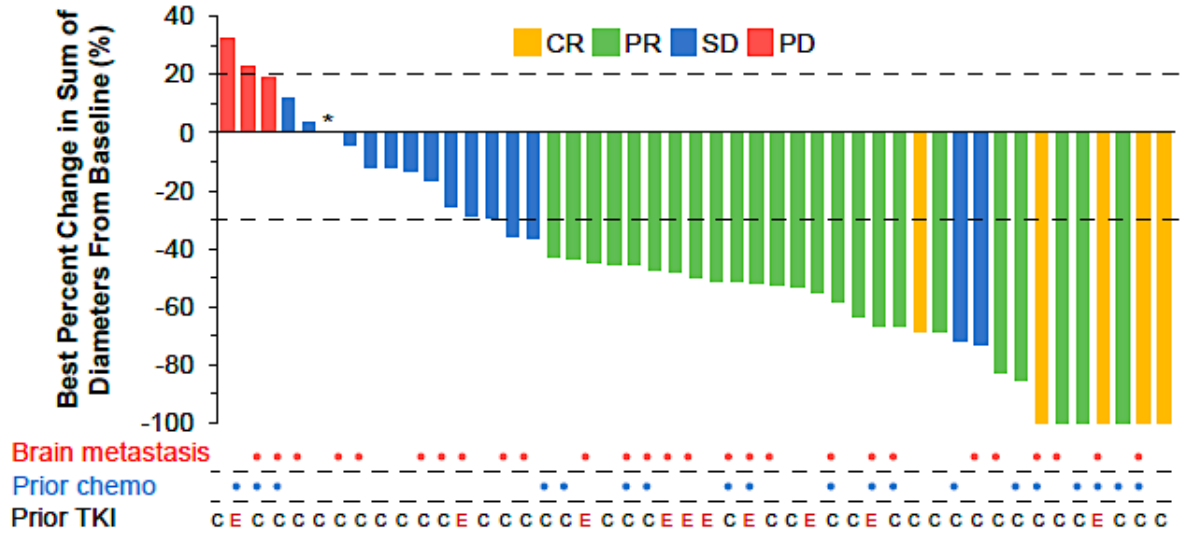
TKI-Naive

	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)



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)



Courtesy of Jessica J Lin, MD

Liu G et al., WCLC 2024

Taletrectinib in Metastatic ROS1+ NSCLC: Safety Data from TRUST-II

TEAEs in ≥15% of Patients (N=159)

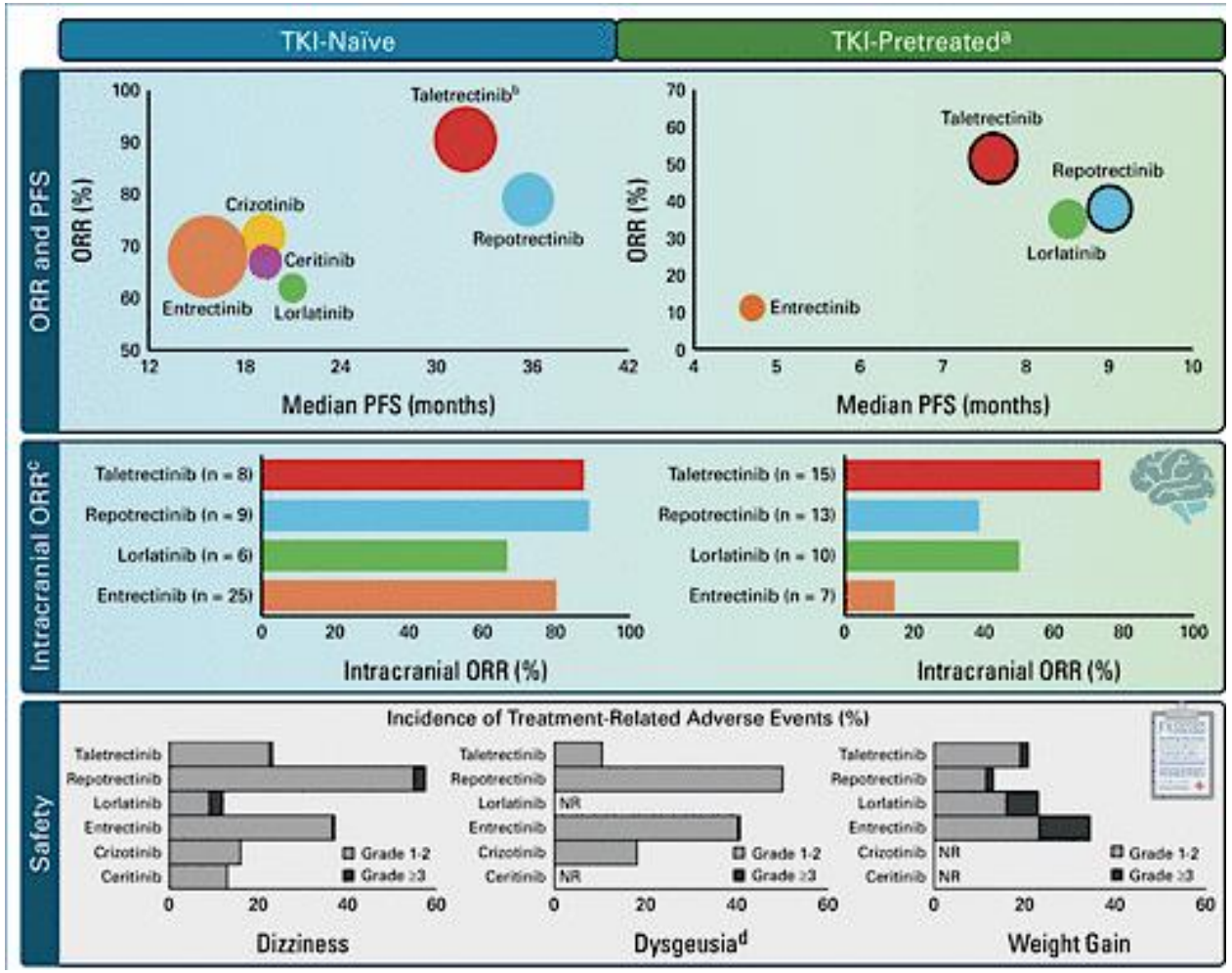
	Any grade, n (%)	Grade ≥3, n (%)
Increased ALT	108 (67.9)	24 (15.1)
Increased AST	107 (67.3)	11 (6.9)
Diarrhea	90 (56.6)	1 (0.6)
Nausea	82 (51.6)	3 (1.9)
Vomiting	53 (33.3)	2 (1.3)
Constipation	40 (25.2)	0 (0)
Anemia	32 (20.1)	7 (4.4)
Dysgeusia	31 (19.5)	0 (0)
Increased blood CPK	29 (18.2)	6 (3.8)
Dizziness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

Liu G et al., WCLC 2024

Courtesy of Jessica J Lin, MD

Treatment of Metastatic ROS1+ NSCLC: *My Take*



- Currently, repotrectinib is the only FDA-approved **next-generation** ROS1 TKI for ROS1+ NSCLC
- The landscape of first- and later-line ROS1 TKIs continues to actively evolve with next-generation agents
- Considerations in **selecting the first-line agent** include systemic and CNS efficacy, tolerability (such as TRK inhibition-mediated side effects), and access to therapy

Waliany S et al., J Clin Oncol 2024;42(22):2622-7

Courtesy of Jessica J Lin, MD

How do you select first-line therapy currently, and how do you indirectly compare approved agents?

How do zidesamtinib and taletrectinib compare to available agents?

Regulatory and reimbursement issues aside, which systemic therapy would you most likely recommend for a patient with ROS1-positive metastatic NSCLC who progressed on first-line repotrectinib?

Year in Review: Targeted Therapies Beyond EGFR for Non-Small Cell Lung Cancer (NSCLC)

INTRODUCTION: AGAs (Actionable Genomic Alterations)

MODULE 1: ALK

MODULE 2: ROS1

MODULE 3: HER2

MODULE 4: RET

MODULE 5: NTRK

MODULE 6: MET

MODULE 7: BRAF

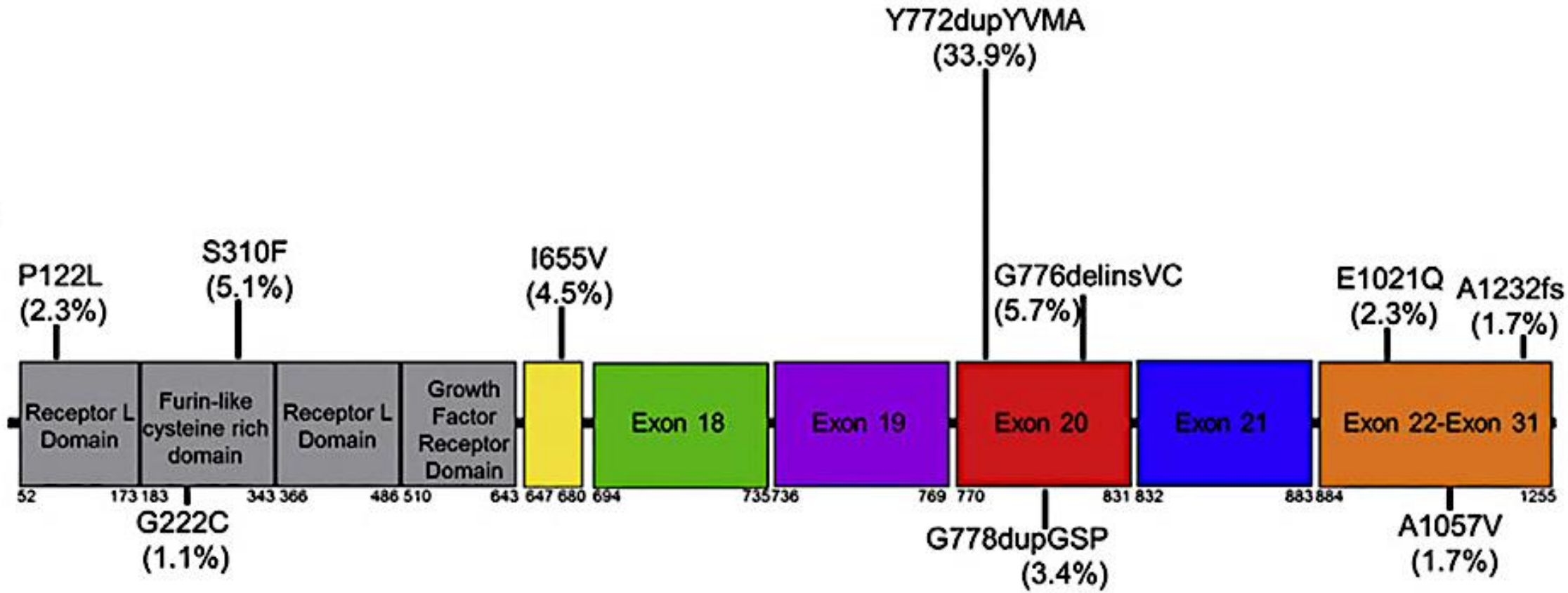
MODULE 8: KRAS G12C

MODULE 9: NRG1

MODULE 10: Novel Targeted Strategies

RTP Year in Review 2025

ERBB2 (HER2) mutations in NSCLC



Courtesy of Joel W Neal, MD, PhD

Robichaux, et al. *Cancer Cell* 2019

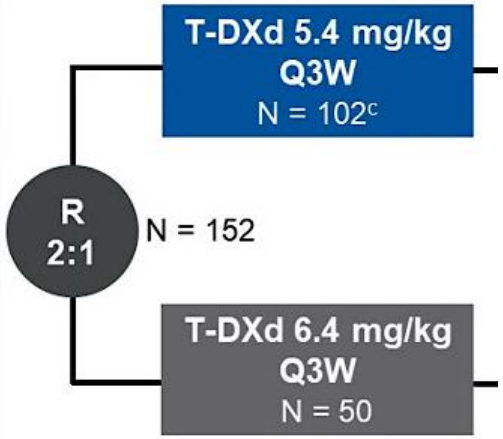
T-DXd for HER2-mutant (DESTINY-Lung02)

Key Eligibility Criteria[a]
- Metastatic *HER2*m[b] NSCLC
- ≥1 prior anticancer therapy (2L+), including platinum-based chemotherapy
- Measurable disease per RECIST v1.1
- ECOG PS of 0 or 1

Stratification Factor:
- Prior anti–PD-(L)1 treatment

Patients and investigators were blinded to the dose level

Study Design



Final analysis data cutoff: August 25, 2023

Efficacy

Efficacy summary	T-DXd 5.4 mg/kg n = 102	T-DXd 6.4 mg/kg n = 50
cORR,[a,b] n (% [95% CI])	51 (50.0 [39.9-60.1])	28 (56.0 [41.3-70.0])
CR | PR	3 (2.9) | 48 (47.1)	4 (8.0) | 24 (48.0)
SD | PD	44 (43.1) | 4 (3.9)	18 (36.0) | 2 (4.0)
Non-evaluable	3 (2.9)	2 (4.0)
DCR,[c] n (% [95% CI])	95 (93.1 [86.4-97.2])	46 (92.0 [80.8-97.8])
DoR,[b] median (95%CI), months	12.6 (6.4 to NE)	12.2 (7.0 to NE)
PFS, median (95% CI), months	10.0 (7.7-15.2)	12.9 (7.2-16.7)
OS, median (95% CI), months	19.0 (14.7 to NE)	17.3 (13.8 to NE)
Follow-up, median (range), months	15.8 (1.1-28.6)	16.5 (0.6-28.7)

Courtesy of Joel W Neal, MD, PhD

Janne ASCO 2024

HER2 immunohistochemistry in LUAD

Ref	N	0	1+	2+	3+	(2+ or 3+)
Hirsch et al, BJC 2002	125	62%	8%	23%	7%	30%
Yoshizawa et al, Lung Cancer 2014	243	42%	42%	13%	3%	16%
Reis et al Lung Cancer 2015 *(stage 3/4)	176	42%	28%	23%	7%	30%
Kim et al PLoS One 2017 (0-3+)	321	77%	31%	7%	1%	8%
Kim et al PLoS One 2017 (H-Score)	321	60%	15%	8%	2%	10%

TABLE A5. Evaluation of HER2 IHC Expression and Comparison of HER2 IHC Scoring Methods

HER2 IHC Scoring Method (n = 87)	IHC 0 or H-Score 0, No. (%)	IHC 1+ or H-Score 1-100, No. (%)	IHC 2+ or H-Score 101-200, No. (%)	IHC 3+ or H-Score 201-300, No. (%)
Breast cancer ASCO/CAP	57 (66)	16 (18)	13 (15)	1 (1)
Gastric cancer ASCO/CAP	43 (49)	16 (18)	26 (30)	2 (2)
H-score	25 (29)	33 (38)	27 (31)	2 (2)

Abbreviations: ASCO/CAP, ASCO/College of American Pathologists; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry.

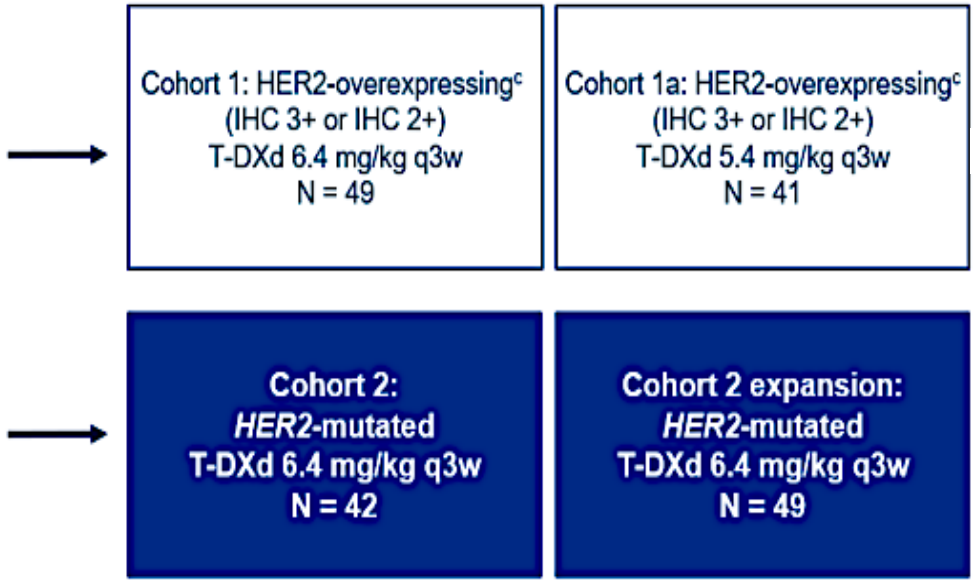
Courtesy of Joel W Neal, MD, PhD

Tan et al, JCO Precision Oncol 2022

T-DXd for HER2-IHC+ (DESTINY-Lung01)

Key eligibility criteria

- Unresectable/metastatic nonsquamous NSCLC
- Relapsed from or is refractory to standard treatment
- Measurable disease by RECIST v1.1
- Asymptomatic CNS metastases at baseline[a]
- ECOG PS of 0 or 1
- Locally reported *HER2* mutation (for Cohort 2)[b]



HER2 status		
IHC 3+	10 (20%)	17 (41%)
IHC 2+	39 (80%)	24 (59%)

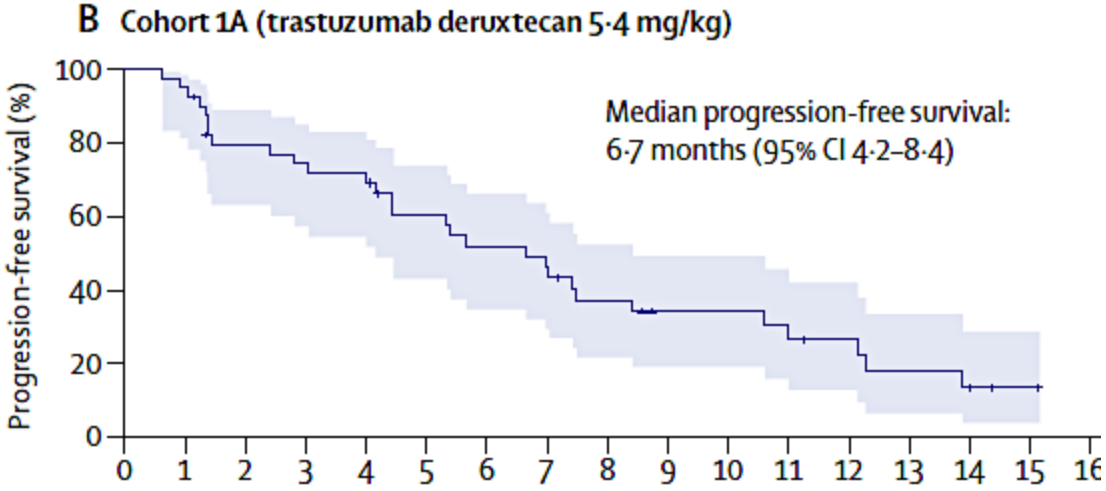
	Cohort 1 (6·4 mg/kg; N=49)	Cohort 1A (5·4 mg/kg; N=41)
Confirmed objective response rate, n (%; 95% CI)	13 (26·5%; 15·0–41·1)	14 (34·1%; 20·1–50·6)
Response outcomes, n (%)		
Complete response	0	2 (5%)
Partial response	13 (27%)	12 (29%)
Stable disease	21 (43%)	18 (44%)
Progressive disease	11 (22%)	4 (10%)
Not evaluable	4 (8%)	5 (12%)
Disease control rate, n (%; 95% CI)	34 (69·4%; 54·6–81·8)	32 (78·0%; 62·4–89·4)
Duration of response, months, median (95% CI)	5·8 (4·3–not evaluable)	6·2 (4·2–9·8)

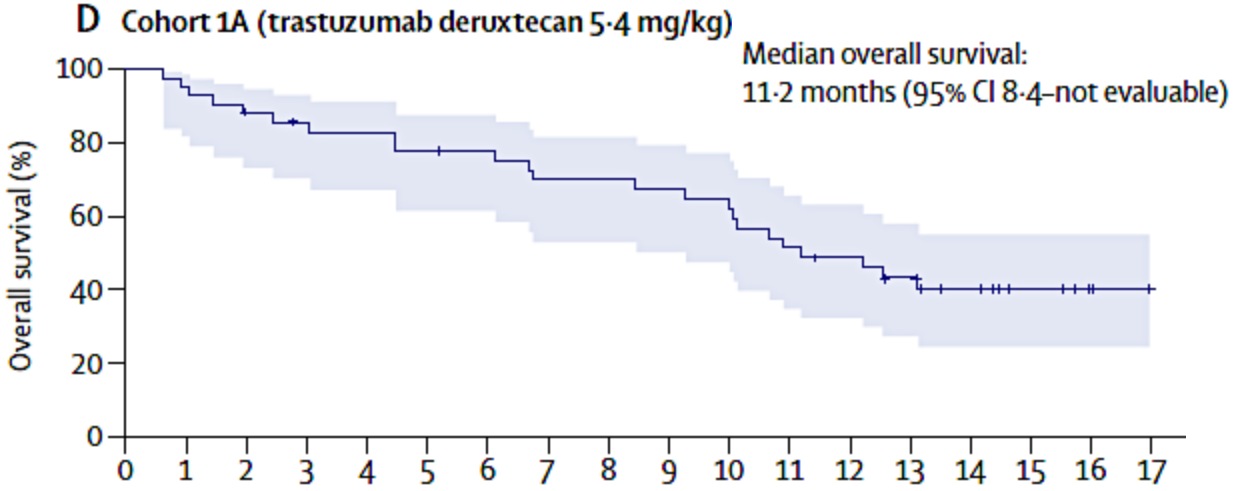
Table 2: **Summary of efficacy by independent central review**

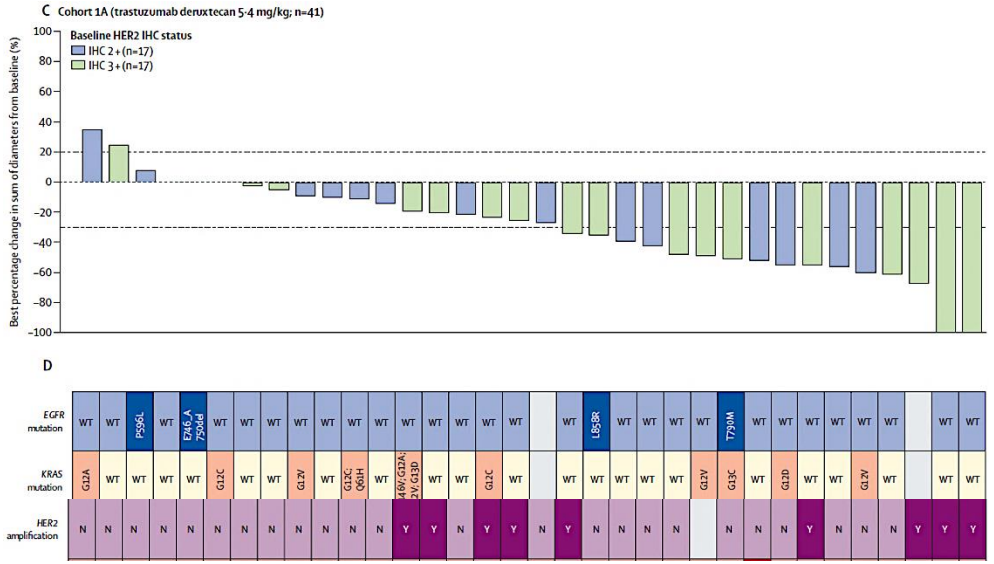
Courtesy of Joel W Neal, MD, PhD

Smit Lancet Oncol 2024

T-DXd for HER2-IHC+ (DESTINY-Lung01)





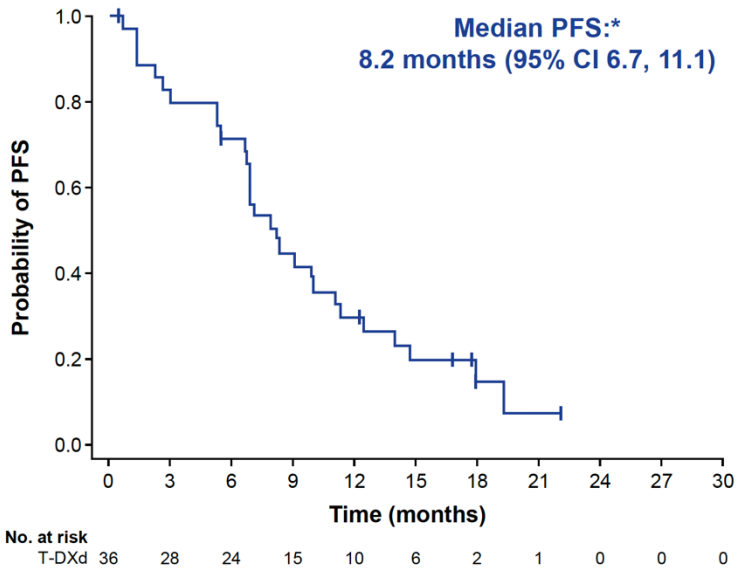


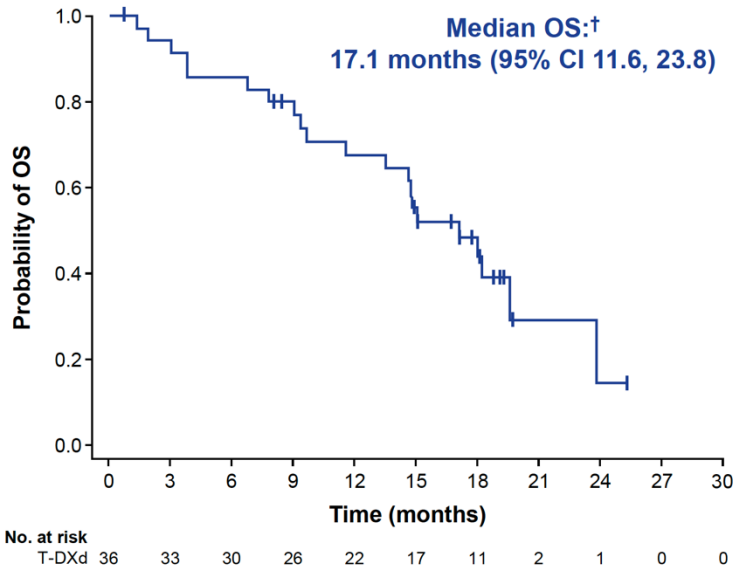
Courtesy of Joel W Neal, MD, PhD

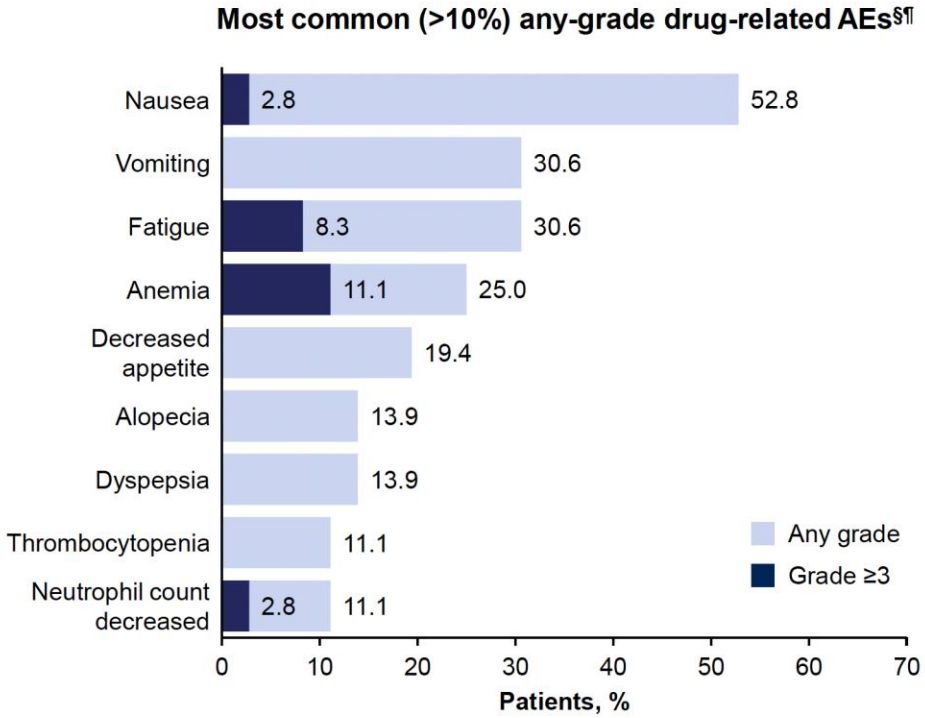
Smit Lancet Oncol 2024

T-DXd for HER2 Overexpression (DESTINY-Lung03)

Survival outcomes: PFS and OS





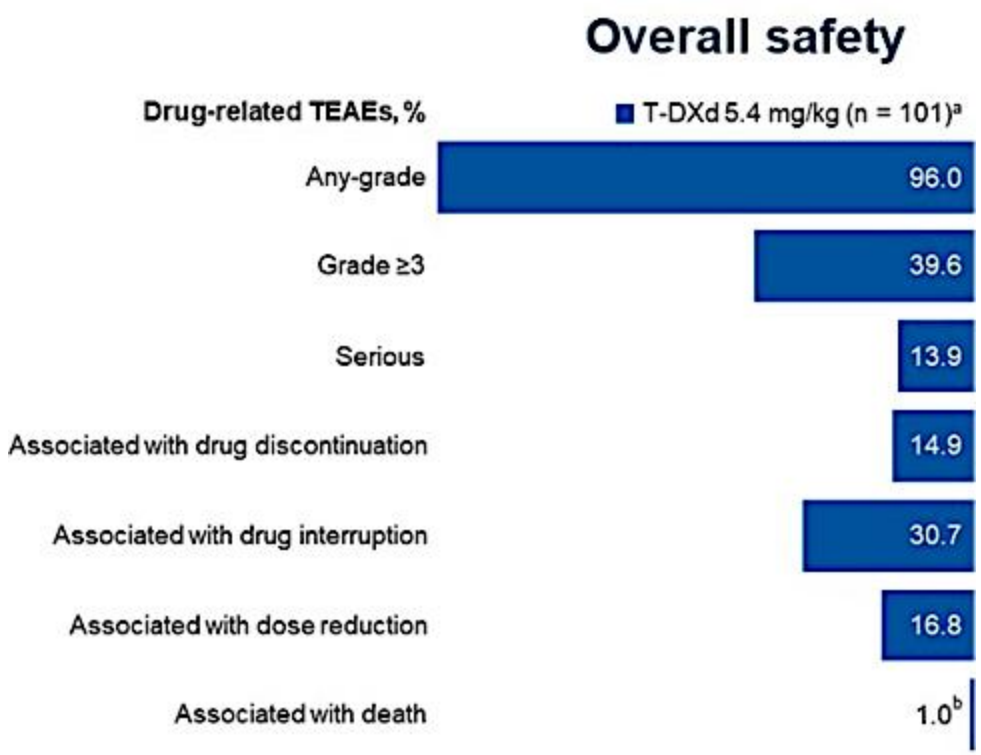


Courtesy of Joel W Neal, MD, PhD

PLANCHARD WCLC 2024

Trastuzumab deruxtecan (T-DXd) - Safety

Nausea	~70%
Fatigue	
Decreased appetite	
Constipation	
Vomiting	
Diarrhoea	
Weight decreased	
Anaemia	
Alopecia	
Dyspnoea	
Dizziness	
Thrombocytopenia	
Hypokalaemia	
Stomatitis	
Cough	
Pneumonitis	~10%



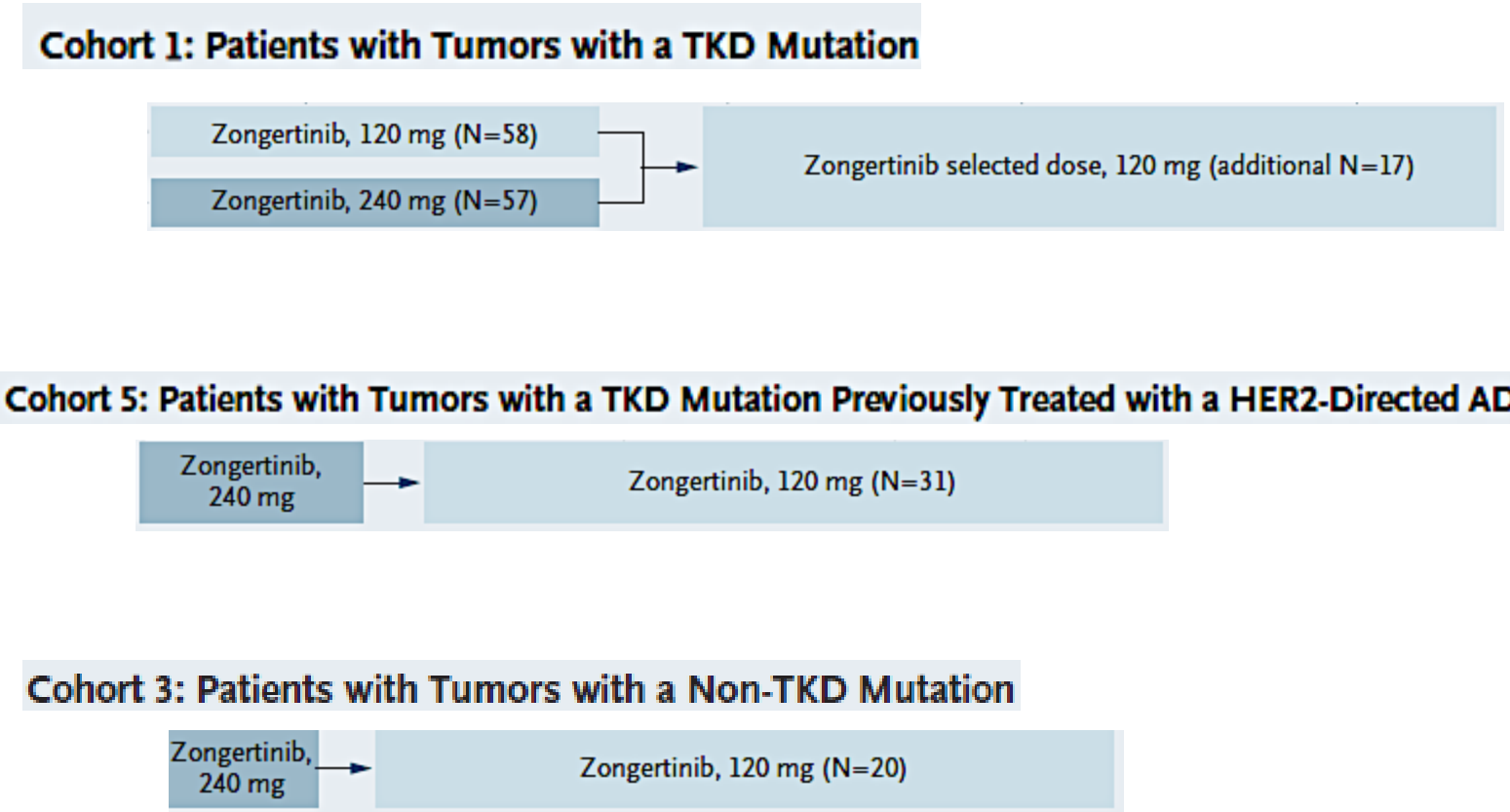
Adjudicated as drug-related ILD/pneumonitis, n (%)	T-DXd 5.4 mg/kg n = 101[a]
Total	15 (14.9)
Grade 1	4 (4.0)
Grade 2	9 (8.9)
Grade 3	1 (1.0)
Grade 4	0
Grade 5	1 (1.0)

Adjudicated drug-related ILD/pneumonitis, n/N (%)	T-DXd 5.4 mg/kg
Time since prior anti–PD-(L)1 therapy[c]	
>3 months	5/44 (11.4)
≤3 months	6/30 (20.0)
No prior therapy	2/27 (14.8)

Courtesy of Joel W Neal, MD, PhD

Janne ASCO 2024 and Smit Lancet Oncol 2024

Zongertinib for HER2-mutant (Beamion LUNG-1)



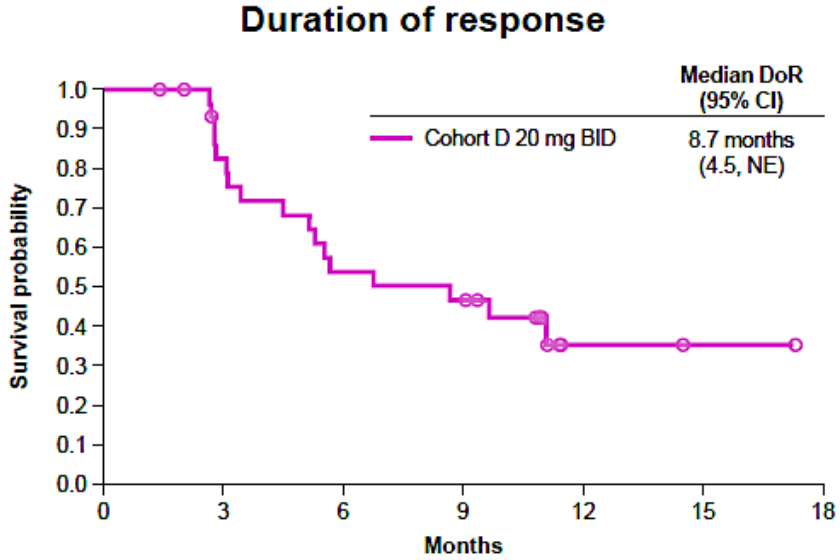
	RR (%)	DCR (%)	DOR (m)	PFS (m)
Cohort 1	71%	96%	14.1m	12.4m
Cohort 5	48%	97%	-	-
Cohort 3	30%	65%	-	-

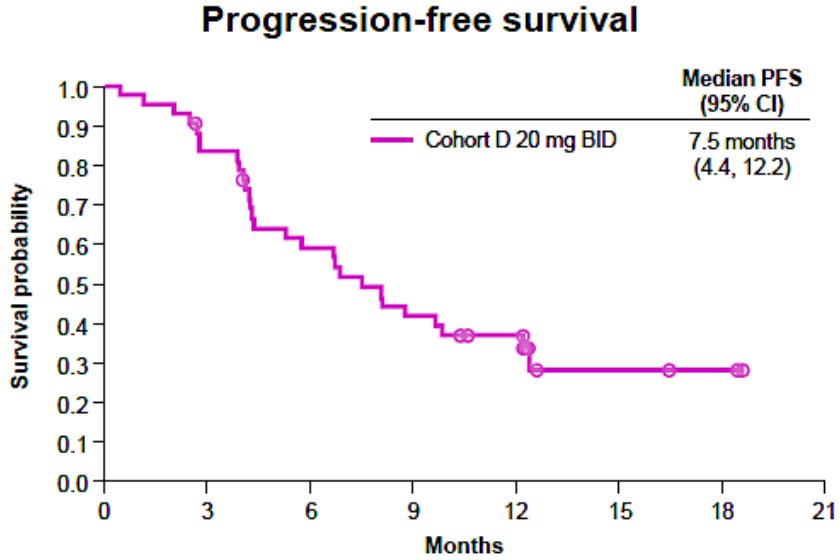
Courtesy of Joel W Neal, MD, PhD

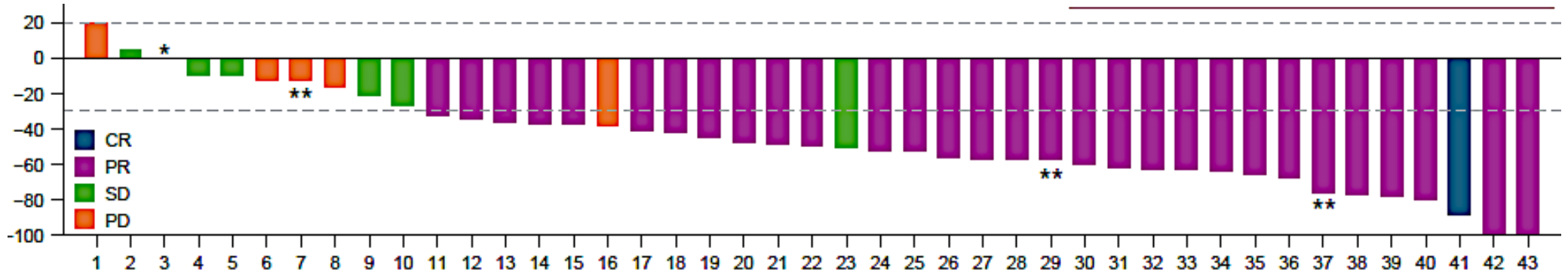
Heymach NEJM 2025

BAY2927088 for HER2-mutant (SOHO-01Cohort D, HER2-mutant, TKI/ADC naïve)

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







Courtesy of Joel W Neal, MD, PhD

Le WCLC 2024

Safety and tolerability of new HER2-TKIs

Zongertinib

Any drug-related adverse event§	
Diarrhea¶	~50%
Rash‖	
Increased aspartate aminotransferase	
Increased alanine aminotransferase	
Nausea	
Dry skin	
Pruritus	
Decreased white-cell count	
Anemia	
Decreased neutrophil count	
Nail disorder	~10%

16% Grade 3
7% dose reduction
3% discontinuation

BAY2927088

Diarrhea	38 (86.4)	~90%
Rash	19 (43.2)	
Paronychia	11 (25.0)	
Nausea	11 (25.0)	
Vomiting	9 (20.5)	
Dermatitis acneiform	8 (18.2)	
Stomatitis	8 (18.2)	
Dry skin	7 (15.9)	
Increased aspartate aminotransferase	6 (13.6)	
Decreased appetite	6 (13.6)	
Increased amylase	5 (11.4)	
Anemia	5 (11.4)	
Increased lipase	5 (11.4)	
Decreased weight	5 (11.4)	
Pruritis	5 (11.4)	~10%

43% Grade 3
32% dose reduction
7% discontinuation

Courtesy of Joel W Neal, MD, PhD

Heymach NEJM 2025 and Le WCLC 2024

ERBB2/HER2 Conclusions:

Clinical Implications:

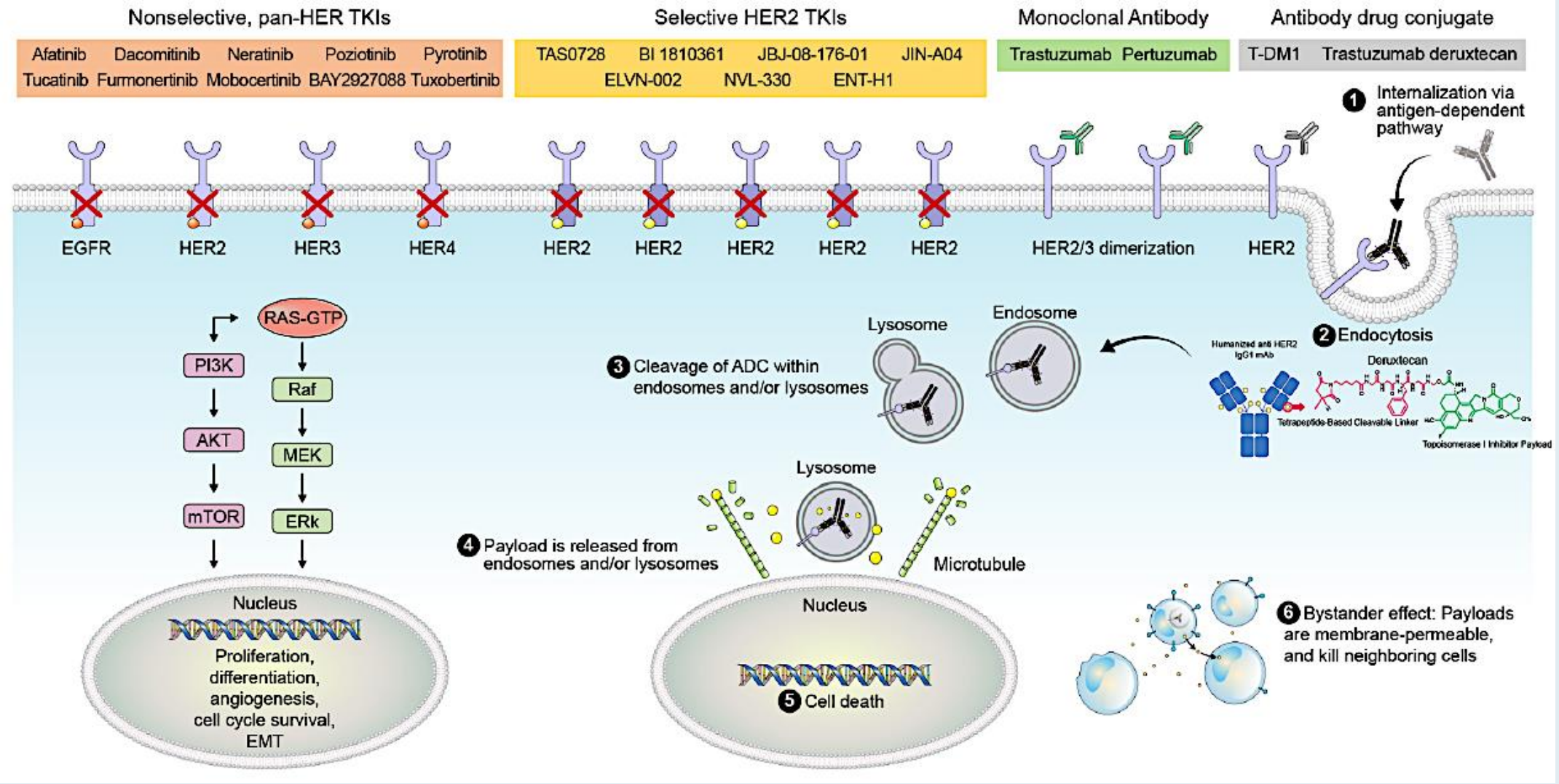
- The ADC T-DXd is FDA-approved for ERBB2/HER2 mutant NSCLC after prior therapy
- T-DXd works pan-tumor for HER2 IHC 2+/3+ (even in EGFR mutant NSCLC)
- The HER2-TKIs are emerging - zongertinib appears most effective and tolerable --- so far

Future Directions:

- Many other emerging HER2 TKIs are in development as well as bispecific antibodies and ADCs

Courtesy of Joel W Neal, MD, PhD

NVL-330: A Novel Selective HER2 Tyrosine Kinase Inhibitor (TKI)



Nützinger J et al. *Lung Cancer* 2023;186:107385.

NVL-330, a Selective HER2 Tyrosine Kinase Inhibitor, in Patients with Advanced or Metastatic HER2-Altered Non-Small Cell Lung Cancer: The Phase 1 HEROEX-1 Study

Le X et al.
ASCO 2025;Abstract TPS8655.

May 31, 2025
Hall A | 1:30 PM – 4:30 PM CT

HEROEX-1: An Ongoing Phase I Study of NVL-330 for Patients with Advanced or Metastatic HER2-Altered NSCLC

Trial Identifier: NCT06521554
Estimated Enrollment: 120

Eligibility

- Histologically or cytologically confirmed locally advanced or metastatic NSCLC
- Phase 1a: Documented oncogenic HER2 mutation such as HER2 exon 20 insertion mutations or single nucleotide variants or HER2 amplification
- Phase 1b: Documented oncogenic HER2 mutation

Phase 1a Dose Escalation
NVL-330 oral daily dosing

→

Phase 1b Dose Expansion
NVL-330 oral daily dosing

Primary outcome measures: Recommended Phase II dose, maximum tolerated dose, treatment-emergent adverse events

Le X et al. ASCO 2025;Abstract TPS8655; www.clinicaltrials.gov. Accessed May 2025.

How do you use trastuzumab deruxtecan (T-DXd) for HER2-mutant disease? HER2-overexpressed disease? What about HER2-low? (IHC1+ or 2+)? HER2-amplified disease?

How do you prevent and manage acute GI toxicities with T-DXd?

How do you screen for interstitial lung disease in patients treated with T-DXd? How do you manage Grade 1 toxicity? Grade 2? Will you rechallenge?

How do you factor in the presence of coexisting cardiopulmonary morbidities (COPD, CAD) in decisions about T-DXd, and how problematic are nonspecific pulmonary densities on imaging?

In the wake of the DESTINY-Breast09 breast cancer trial, what other ongoing trials and strategies that include T-DXd are being investigated?

What are the risks and benefits of HER2-directed tyrosine kinase inhibitors for HER2-mutant disease, and how do available agents compare to newer ones (eg, zongertinib, BAY 2927088, NVL-330)?

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RTP Year in Review 2025

Selpercatinib and Pralsetinib in RET+ 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

Courtesy of Jessica J Lin, MD

Selpercatinib in RET+ NSCLC: CNS Efficacy, Data from the Phase III LIBRETTO-431 Trial

	CNS-Pembro-Mets (N = 42)			
	With Prior CNS Radiotherapy (n = 13)		Without Prior CNS Radiotherapy (n = 29)	
Intracranial Response	Selpercatinib (n = 6)	Control (n = 7)	Selpercatinib (n = 15)	Control (n = 14)
Intracranial BOR, No. (%)				
CR	1 (16.7)	0	8 (53.3)	7 (50.0)
PR	2 (33.3)	3 (42.9)	6 (40.0)	2 (14.3)
SD[a]	2 (33.3)	2 (28.6)	0	3 (21.4)
PD	0	1 (14.3)	0	1 (7.1)
NE	1 (16.7)	1 (14.3)	1 (6.7)	1 (7.1)
Intracranial overall response rate, % (95% CI)	50.0 (11.8 to 88.2)	42.9 (9.9 to 81.6)	93.3 (68.1 to 99.8)	64.3 (35.1 to 87.2)
Median intracranial DOR, months (95% CI)	14.75 (NE to NE)	13.40 (8.74 to NE)	NE (7.62 to NE)	NE (3.45 to NE)
Intracranial DOR rate, % (95% CI)				
At 6 months	100 (100 to 100)	100 (100 to 100)	92.9 (59.1 to 99.0)	87.5 (38.7 to 98.1)
At 12 months	100 (100 to 100)	66.7 (5.4 to 94.5)	77.4 (44.9 to 92.1)	87.5 (38.7 to 98.1)

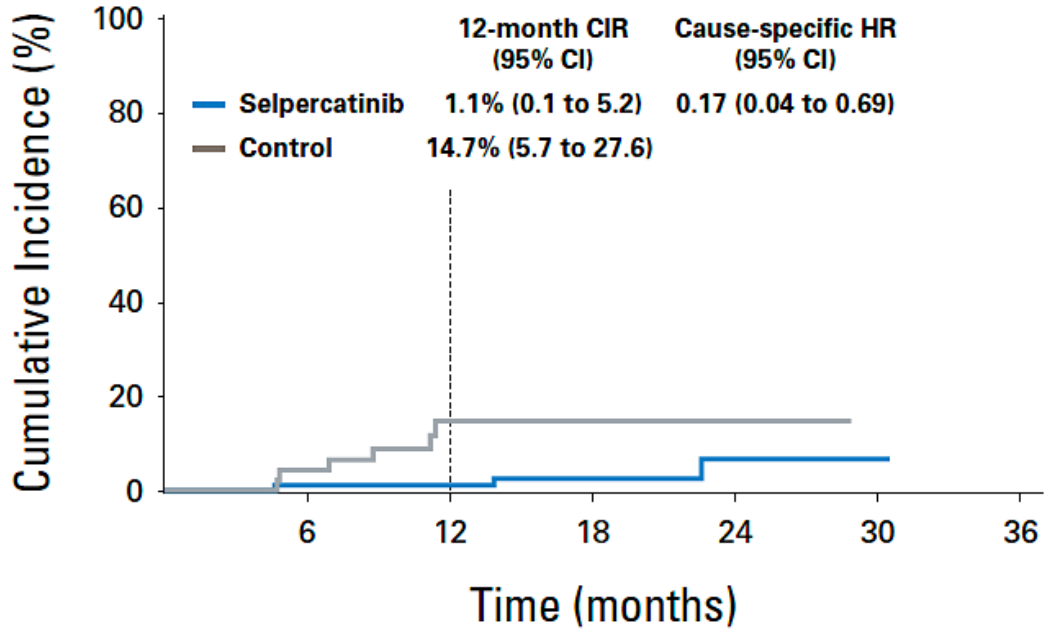
Abbreviations: BOR, best overall response; CNS-pembrolizumab-mets, CNS-pembrolizumab population with baseline brain metastases; CR, complete response; DOR, duration of response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.
[a]Includes non-CR/non-PD in patients with baseline nonmeasurable lesions only.

Courtesy of Jessica J Lin, MD

Pérol M et al., J Clin Oncol 2024;42(21):2500-5

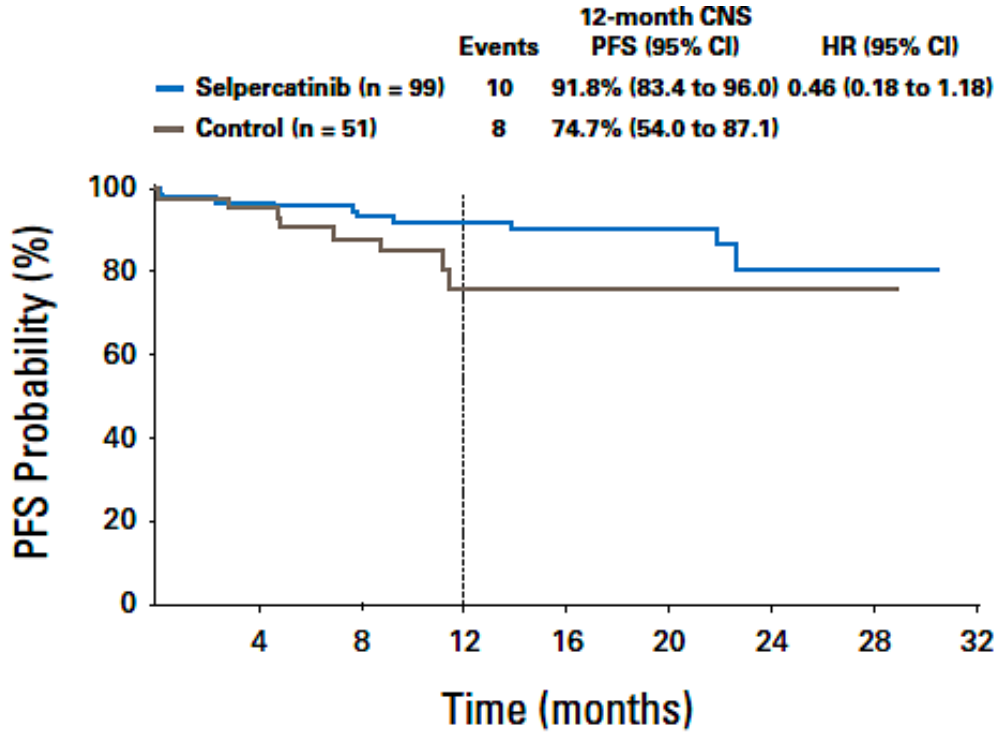
Selpercatinib in RET+ NSCLC: CNS Protective Effect, Data from the Phase III LIBRETTO-431 Trial

Cumulative incidence rate (CIR) of CNS-PD
CNS-pembrolizumab-nonmets population (n=150)



Number of events							
Selpercatinib	0	1	1	2	3	3	3
Control	0	2	6	6	6	6	6

Intracranial PFS
CNS-pembrolizumab-nonmets population



Number at risk									
Selpercatinib	99	86	74	60	44	23	12	2	0
Control	51	39	30	13	11	6	3	1	0

Pérol M et al., J Clin Oncol 2024;42(21):2500-5

Courtesy of Jessica J Lin, MD

Treatment of Metastatic RET+ NSCLC: *My Take*

- Selpercatinib and pralsetinib are FDA-approved, NCCN guideline-recommended first-line therapies for metastatic RET+ NSCLC
- Both RET inhibitors have demonstrated CNS efficacy
- CNS outcome analyses from the LIBRETTO-431 phase III trial further support that a CNS-active TKI like selpercatinib can delay CNS progression and may prevent new brain metastases

Courtesy of Jessica J Lin, MD

How do you select first-line therapy currently, and how do you indirectly compare approved agents?

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RTP Year in Review 2025

Entrectinib in TRK+ NSCLC: Update

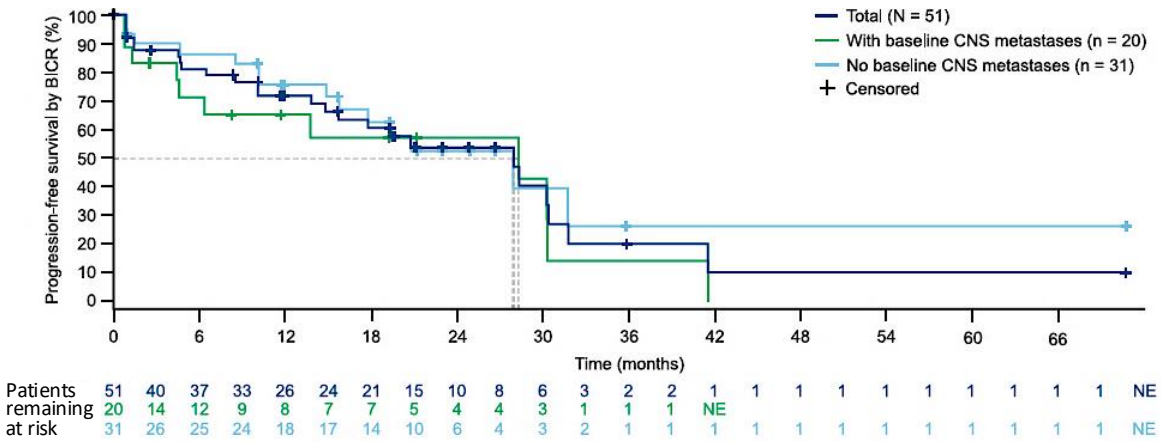
Efficacy parameter	Efficacy-evaluable population (N = 51)	Baseline CNS metastases‡ (n = 20)	No baseline CNS metastases† (n = 31)
Objective response rate*, n (%, 95 % CI)	32 (62.7, 48.1–75.9)	12 (60.0, 36.1–80.9)	20 (64.5, 45.4–80.8)
Best overall response, n (%)			
Complete response	6 (11.8)	2 (10.0)	4 (12.9)
Partial response	26 (51.0)	10 (50.0)	16 (51.6)
Stable disease	5 (9.8)	3 (15.0)	2 (6.5)
Progressive disease	3 (5.9)	2 (10.0)	1 (3.2)
Non-CR/non-PD	3 (5.9)	0	3 (9.7)
Missing or unevaluable†	8 (15.7)	3 (15.0)	5 (16.1)
Duration of confirmed response*	n = 32	n = 12	n = 20
Median, months (95 % CI)	27.3 (19.9–30.9)	29.4 (27.3–NE)	27.1 (18.4–NE)
Patients with event, n (%)	6 (50.0)	9 (45.0)	
12-month event-free rate, % (95 % CI)	15 (46.9) 82.4 (68.2–96.5)	91.7 (76.0–100.0)	78.1 (59.0–97.2)
Progression-free survival*			
Median, months (95 % CI)	28.0 (15.7–30.4)	28.3 (6.5–30.4)	28.0 (15.7–NE)
Patients with event, n (%)	25 (49.0)	11 (55.0)	14 (45.2)
12-month event-free rate, % (95 % CI)	71.6 (58.4–84.7)	65.5 (43.0–87.9)	75.8 (60.1–91.4)
Overall survival			
Median, months (95 % CI)	41.5 (30.9–NE)	41.5 (28.3–NE)	NE (30.9–NE)
Patients with event, n (%)	18 (35.3)	9 (45.0)	9 (29.0)
12-month event-free rate, % (95 % CI)	81.3 (70.3–92.3)	71.6 (50.4–92.8)	86.8 (74.7–98.9)

*As assessed by BICR.
†Missing or unevaluable included patients with on-study scans that could not be evaluated or who discontinued prior to obtaining adequate scans to evaluate or confirm response.
‡CNS disease status determined by the investigator.

N=14 with measurable or nonmeasurable baseline CNS metastases by BICR
IC-ORR 64.3% (35.1-87.2)
IC-DOR 55.7 mo (8.0-NE), IC-PFS 32.7 mo (5.9-NE)

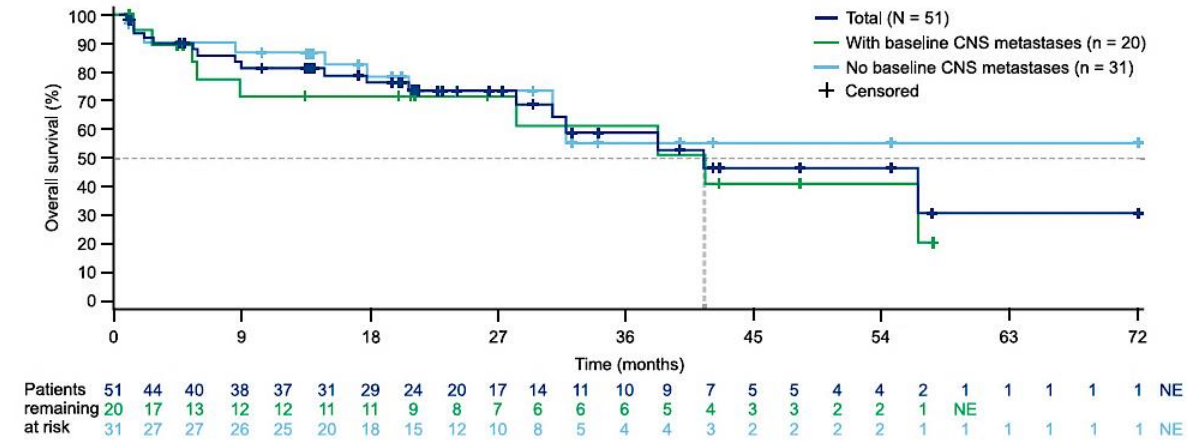
PFS

Median 28.0 mo (15.7-30.4)



OS

Median 41.5 mo (30.9-NE)

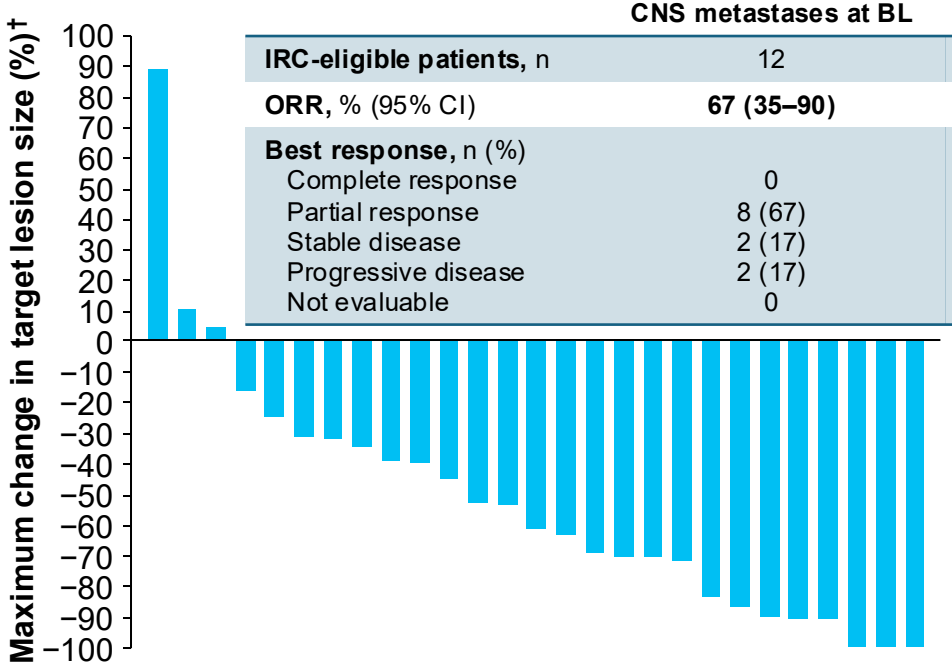


Median survival follow-up time 26.3 mo (21.0-34.1)

Courtesy of Jessica J Lin, MD

Cho BC et al., Lung Cancer 2024 Feb:188:107442

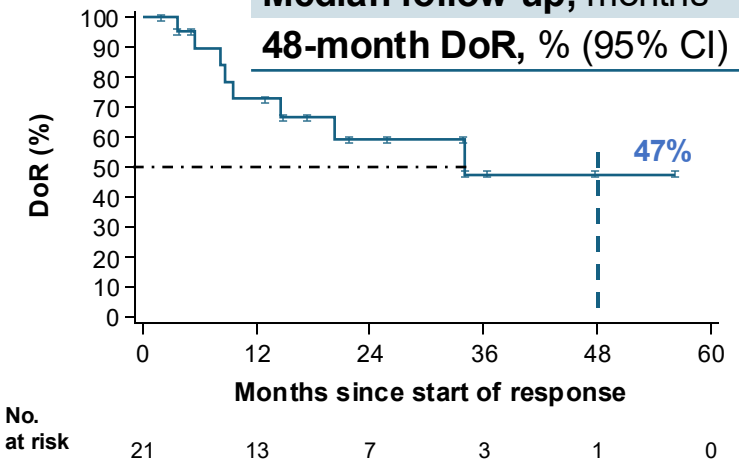
Larotrectinib in TRK+ NSCLC: Update



	Patients with known CNS metastases at BL	Total
IRC-eligible patients, n	12	32
ORR, % (95% CI)	**67 (35–90)**	**66 (47–81)**
Best response, n (%)		
Complete response	0	4 (13)
Partial response	8 (67)	17 (53)
Stable disease	2 (17)	7 (22)
Progressive disease	2 (17)	2 (6)
Not evaluable	0	2 (6)

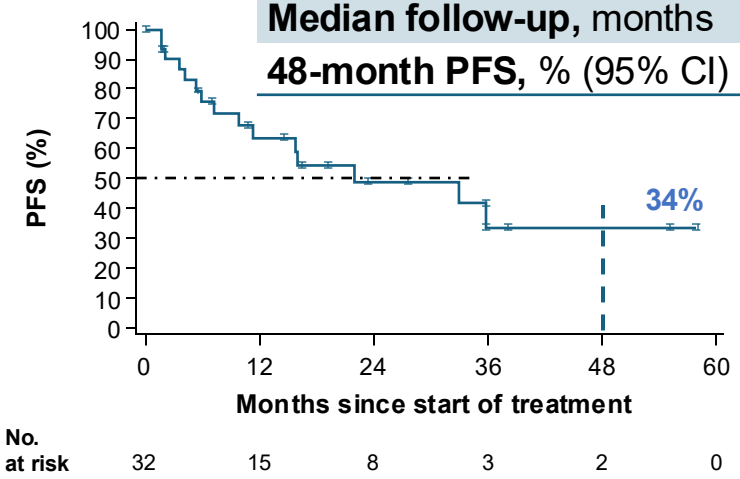
DoR

Median DoR, months (95% CI)	**34 (10–NE)**
Median follow-up, months	26
48-month DoR, % (95% CI)	47 (19–76)



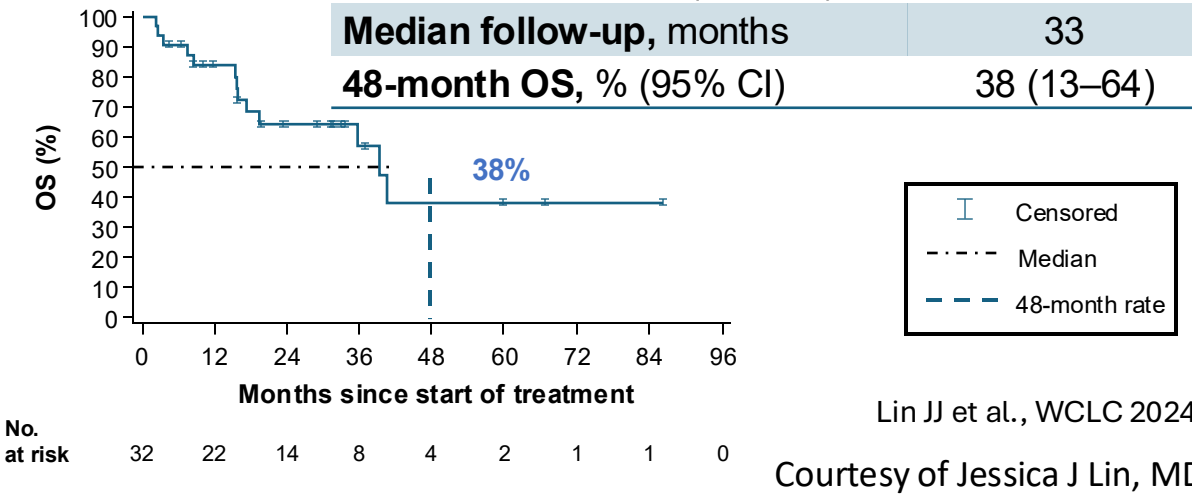
PFS

Median PFS, months (95% CI)	**22 (10–NE)**
Median follow-up, months	28
48-month PFS, % (95% CI)	34 (11–56)



OS

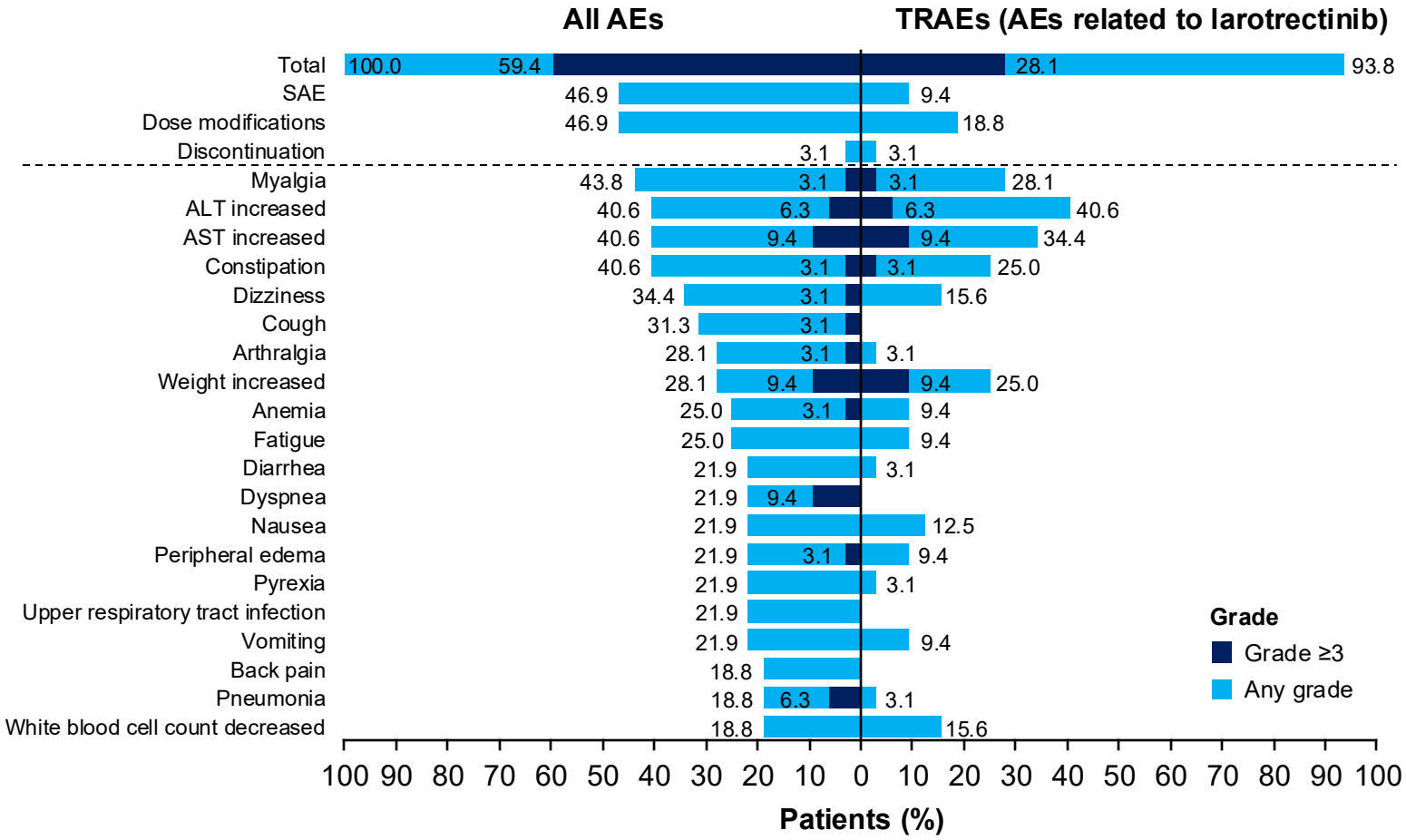
Median OS, months (95% CI)	**39 (17–NE)**
Median follow-up, months	33
48-month OS, % (95% CI)	38 (13–64)



Lin JJ et al., WCLC 2024

Courtesy of Jessica J Lin, MD

Larotrectinib in TRK+ NSCLC: Safety Update



- TRAEs were predominantly Grade 1/2
- Grade 3/4 TRAEs were reported in 9 patients
- One patient discontinued treatment due to TRAEs (increased ALT, AST, and gamma-glutamyl transferase)
- There were no treatment-related deaths

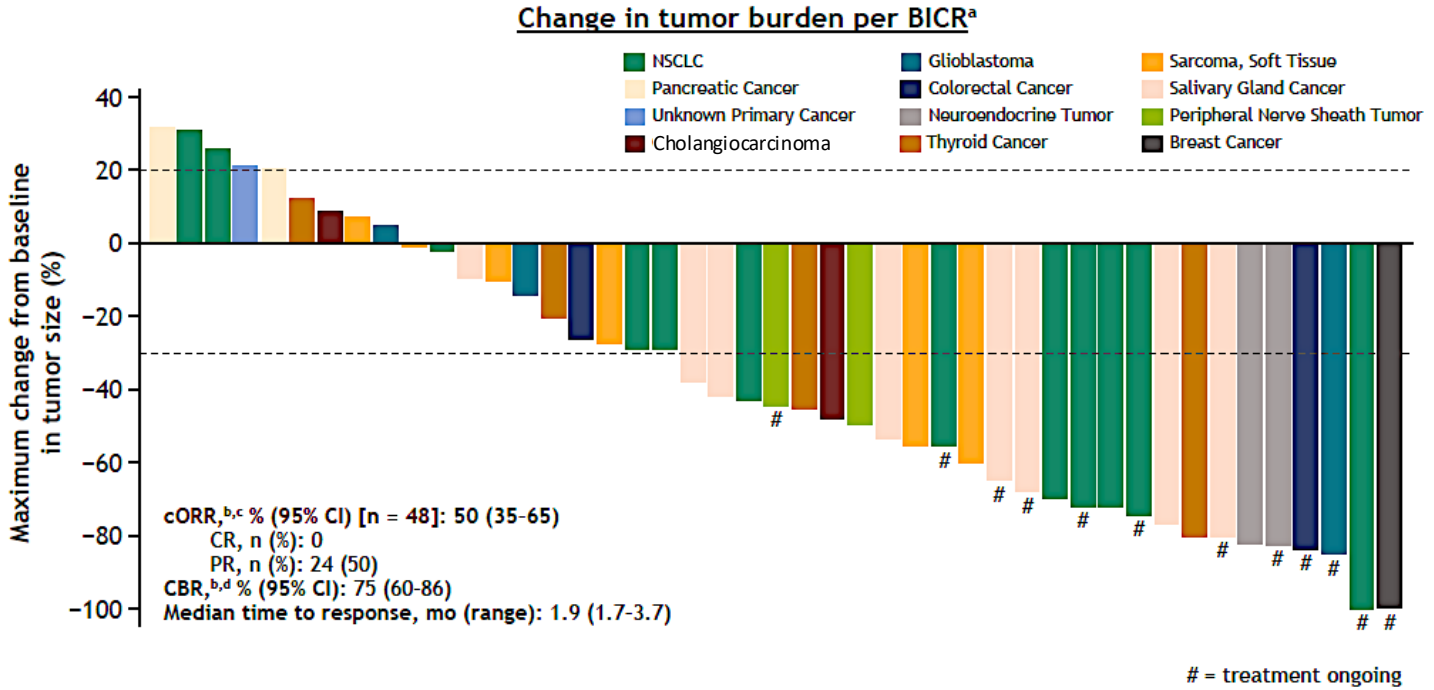
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SAE, serious adverse event; TRAE, treatment-related adverse event.

Courtesy of Jessica J Lin, MD

Lin JJ et al., WCLC 2024

Repotrectinib in TRK+ Solid Tumors: Phase I/II TRIDENT-1 Trial, NTRK1-3 Cohorts

TKI-pretreated patient population (n=48)
cORR 50% (95% CI, 35-65)
Median PFS 7.4 months (3.9-9.7), **Median DOR 9.8 months** (7.4-12.9)
cORR 60% in patients with **solvent front TRK mutation** (n=25; 95% CI 39-79)



6/2024: Received FDA accelerated approval for adult and pediatric patients 12 years or older with advanced *NTRK* fusion+ solid tumors

Courtesy of Jessica J Lin, MD

Solomon B et al. ESMO 2023

Treatment of Metastatic TRK+ NSCLC: *My Take*

- Larotrectinib, entrectinib, and repotrectinib are all FDA-approved, NCCN guideline-recommended first-line therapies for metastatic TRK+ NSCLC
- With longer follow-up, both entrectinib and larotrectinib continue to demonstrate significant clinical activity and favorable tolerability in patients
- Repotrectinib is a next-generation TKI that has shown activity in TKI-naïve and -pretreated patients with TRK+ solid tumors
- Knowledge of TKI-associated toxicities and optimal management strategies are critical for clinicians

Courtesy of Jessica J Lin, MD

How do you select first-line therapy currently, and how do you indirectly compare approved agents?

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RTP Year in Review 2025

FDA Grants Accelerated Approval to Telisotuzumab Vedotin-tllv for NSCLC with High c-Met Protein Overexpression

Press Release: May 14, 2025

"On May 14, 2025, the Food and Drug Administration granted accelerated approval to telisotuzumab vedotin-tllv, a c-Met-directed antibody and microtubule inhibitor conjugate, for adults with locally advanced or metastatic, non-squamous non-small cell lung cancer (NSCLC) with high c-Met protein overexpression [≥50% of tumor cells with strong (3+) staining], as determined by an FDA-approved test, who have received a prior systemic therapy. The FDA also approved a companion diagnostic test to aid in detecting c-Met protein overexpression in patients with non-squamous NSCLC who may be eligible for treatment with telisotuzumab vedotin.

Efficacy was evaluated in the LUMINOSITY study (NCT03539536), a multicenter, open label, multi-cohort trial. The trial included 84 patients with epidermal growth factor receptor (EGFR) wild-type, non-squamous NSCLC with high c-Met protein overexpression who had received prior systemic therapy. The major efficacy outcome measures were confirmed overall response rate (ORR) and duration of response (DOR), determined by blinded independent central review (BICR) according to RECIST 1.1. ORR was 35% (95% CI: 24, 46) and median DOR was 7.2 months (95% CI: 4.2, 12)."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-telisotuzumab-vedotin-tllv-nsclc-high-c-met-protein-overexpression

MET NSCLC Conclusions:

Clinical Implications:

- Capmatinib and tepotinib are approved preferred first line therapies for MET ex14 NSCLC
- Teliso-V may have a role in MET gene amplified NSCLC – under FDA review
- MET protein IHC of uncertain significance

Future Directions:

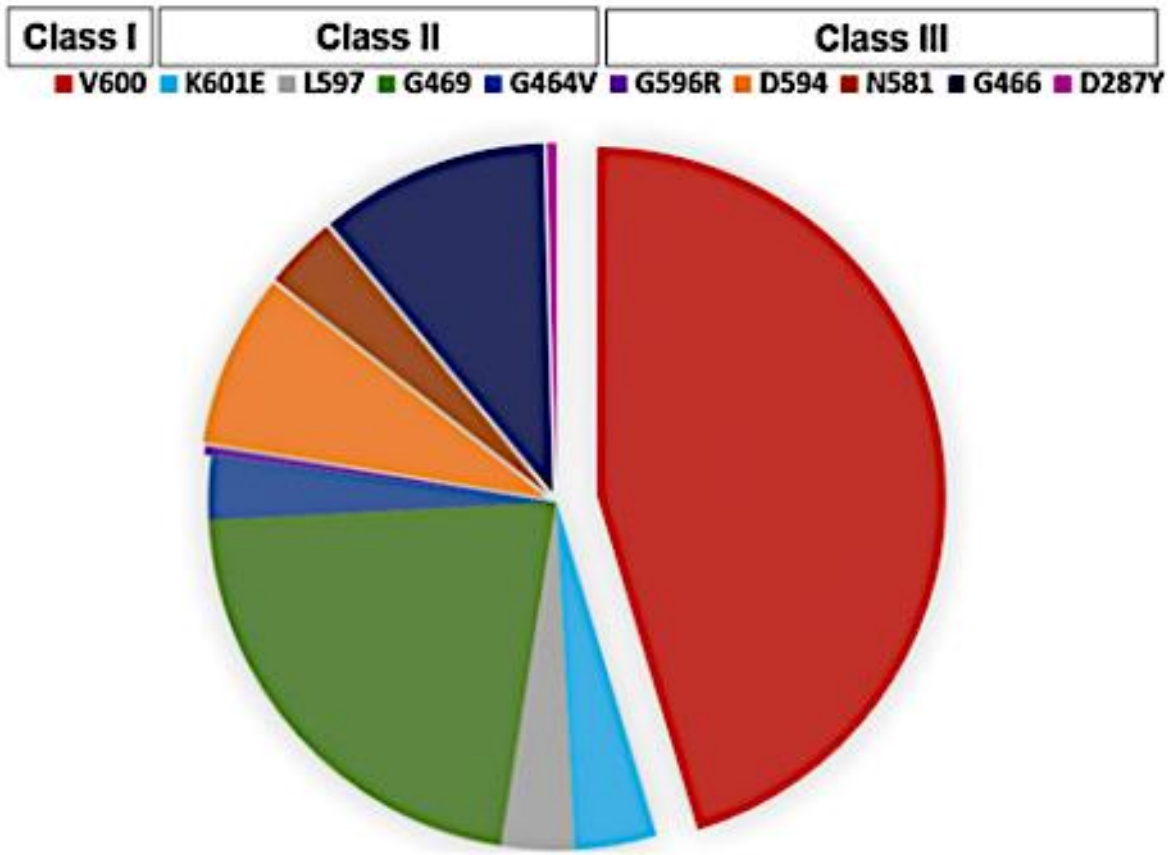
- Many other MET ADC's and TKIs are in development

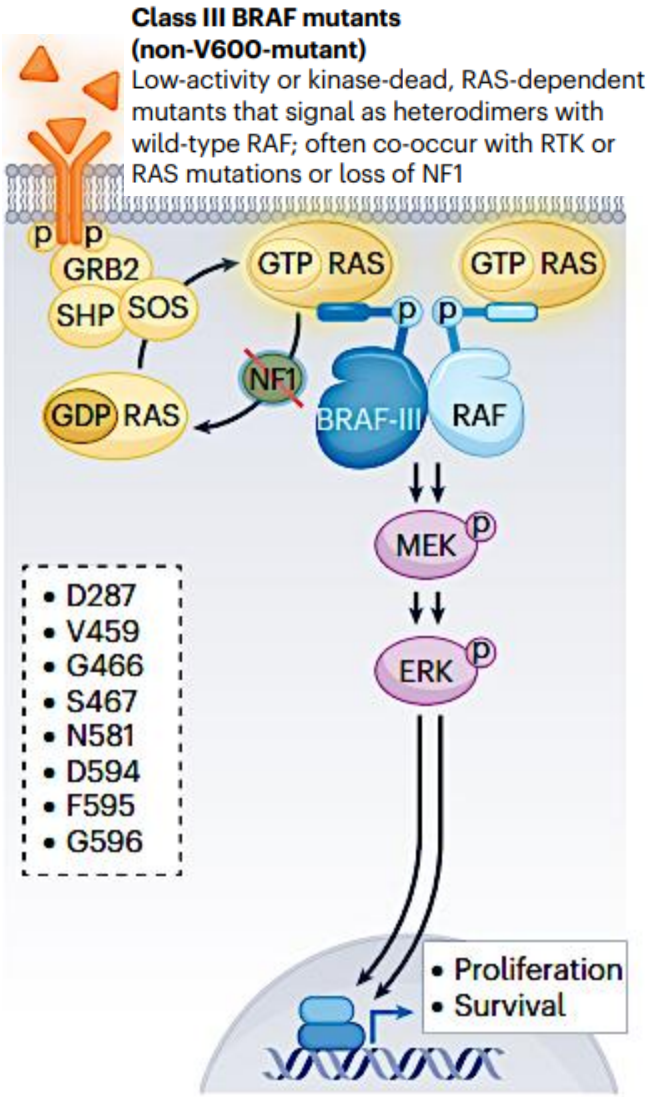
Courtesy of Joel W Neal, MD, PhD

Year in Review: Targeted Therapies Beyond EGFR for Non-Small Cell Lung Cancer (NSCLC)

RTP Year in Review 2025

BRAF V600E mutations in NSCLC

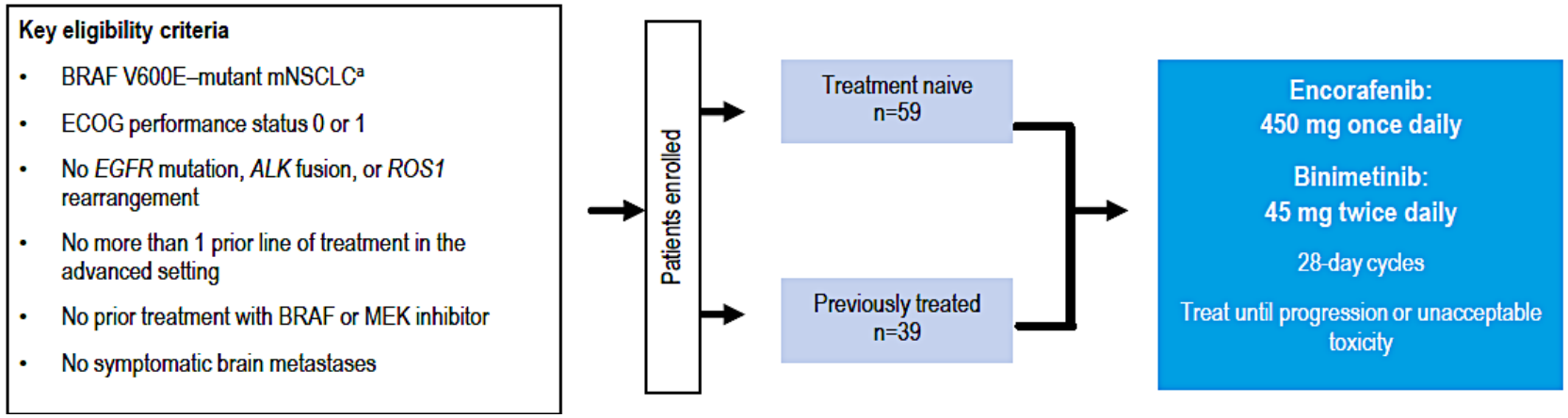




Courtesy of Joel W Neal, MD, PhD

Dagogo-Jack *et al*. CCR. 2018; Hanrahan et al. *Nature Reviews Clinical Oncology*. 2024

Encorafenib and binimetinib for BRAF V600E (PHAROS)



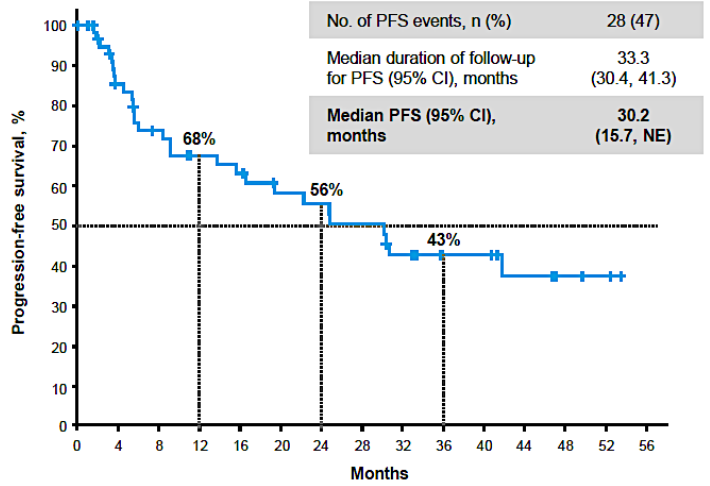
	Current analysis (data cutoff: Apr 1, 2024)	
	Treatment naive	Previously treated
Objective response rate (95% CI), %[a]	**75 (62, 85)**	**46 (30, 63)**
Complete response	9 (15)	4 (10)
Partial response	35 (59)	14 (36)
Stable disease	10 (17)	13 (33)
Progressive disease	2 (3)	3 (8)
Disease control rate at 24 weeks (95% CI), %	64 (51, 76)	44 (28, 60)
Median time to response (range), months	1.9 (1.1-19.1)	1.7 (1.2-7.3)
Median duration of response (95% CI), months	**40.0 (23.1, NE)**	**16.7 (7.4, NE)**

Courtesy of Joel W Neal, MD, PhD

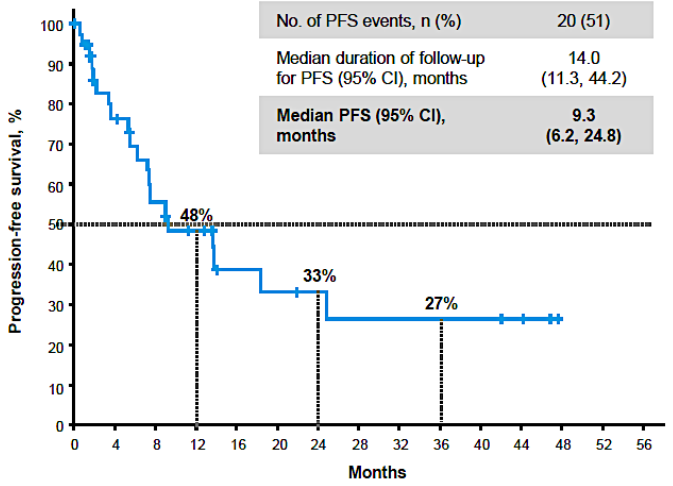
Riley ESMO 2024

Encorafenib and binimetinib for BRAF V600E (PHAROS)

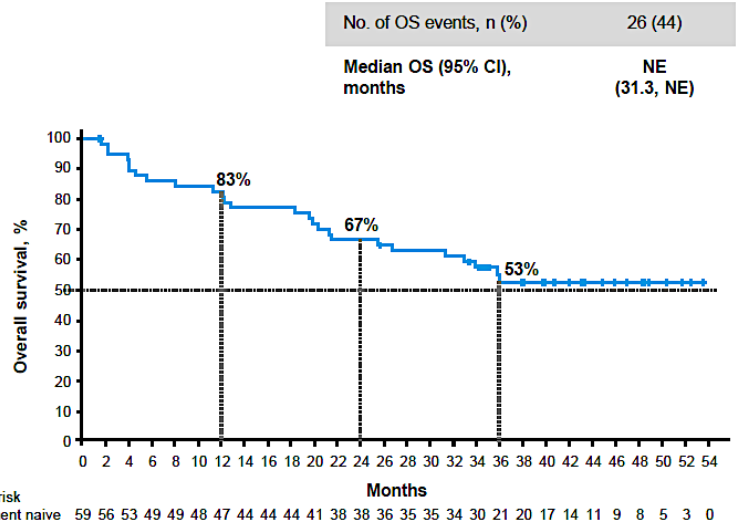
Treatment naive (n=59)



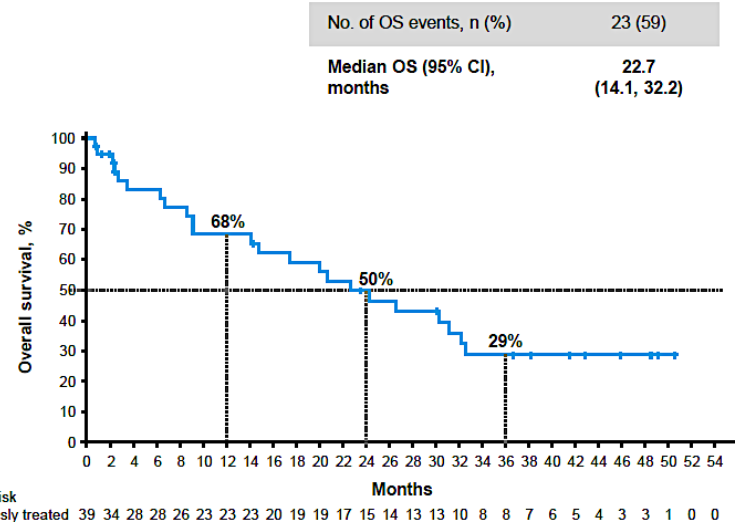
Previously treated (n=39)



Treatment naive (n=59)



Previously treated (n=39)



Nausea ~52%
Diarrhea
Fatigue
Vomiting
Vision blurred
Anemia
Constipation
ALT increased
AST increased
Alopecia
Pruritus
Abdominal pain
CPK increased
Dizziness[a]
Dry skin
Myalgia[a]
Peripheral edema
Rash maculopapular[a]
Asthenia
Rash[a] ~10%

Courtesy of Joel W Neal, MD, PhD

Riley ESMO 2024

BRAF Conclusions:

Clinical Implications:

- Encorafenib and binimetinib is reasonable FDA approved option in BRAF V600E NSCLC (alternative to dabrafenib/trametinib)

Future Directions:

- Type II and Type III BRAF mutations are currently not actionable with approved therapies, but options are in development

Courtesy of Joel W Neal, MD, PhD

How do you find the tolerability/toxicity of encorafenib/binimetinib compared to dabrafenib/trametinib?

Year in Review: Targeted Therapies Beyond EGFR for Non-Small Cell Lung Cancer (NSCLC)

RTP Year in Review 2025

KRAS G12C mutations in NSCLC

Courtesy of Joel W Neal, MD, PhD

Chen, Y., Liu, Qp., Xie, H. et al. Acta Pharmacol Sin (2023).

KRAS Conclusions:

Clinical Implications:

- Adagrasib and sotorasib are FDA approved for KRAS G12C; adagrasib may be modestly more active
- Divarasib and Olomorasib maybe more compatible with immunotherapy for 1L combinations
- Zoldonrasib is a novel KRAS G12D inhibitor with promising efficacy

Future Directions:

- Other Ras-ON inhibitors (for Pan-RAS, G12C, and G12D) are in development

Courtesy of Joel W Neal, MD, PhD

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MODULE 10: Novel Targeted Strategies

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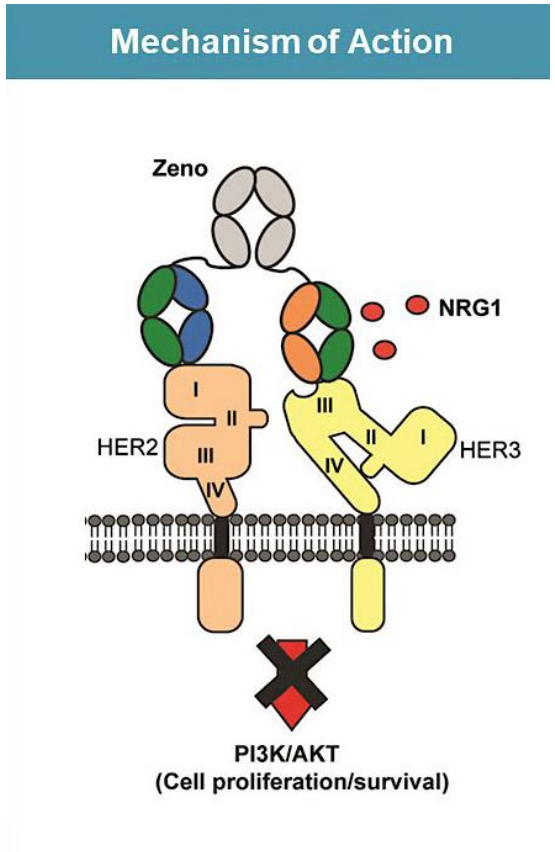
Zenocutuzumab in NRG1+ Cancer: eNRGy Phase II Trial



HER2/HER3 bispecific antibody

Dosing: 750 mg (i.v. infusion every 2 weeks)

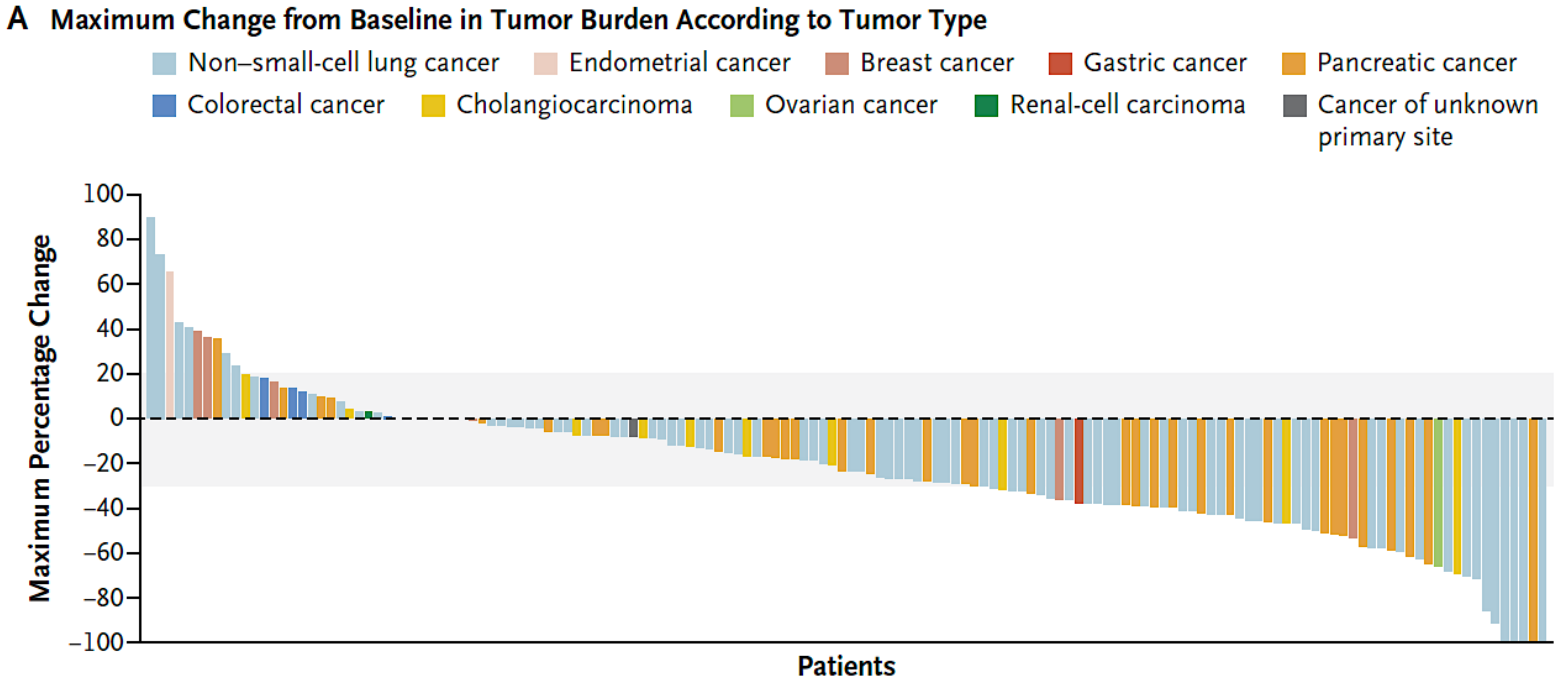


Table 2. Efficacy of Zenocutuzumab in *NRG1* Fusion–Positive Cancer across Multiple Tumor Types.*

Tumor Type	Investigator Assessment			Blinded Independent Central Review		
	Overall Response†		Median Duration of Response (Range)‡	Overall Response†		Median Duration of Response (Range)‡
	no./total no.	*% (95% CI)*	*mo*	*no./total no.*	*% (95% CI)*	*mo*
All *NRG1* fusion–positive tumor types§	47/158	30 (23 to 37)	11.1 (1.7+ to 29.5+)	50/160	31 (24 to 39)	11.5 (1.9+ to 29.5+)
Non–small-cell lung cancer	27/93	29 (20 to 39)	12.7 (1.8+ to 29.5+)	29/94	31 (22 to 41)	13.4 (1.9+ to 29.5+)
Pancreatic cancer	15/36	42 (25 to 59)	7.4 (2.1+ to 20.7)	16/36	44 (28 to 62)	9.1 (1.9+ to 16.6)
Cholangiocarcinoma	2/10	20 (2 to 56)	9.2 (7.4 to 11.1)	2/10	20 (2 to 56)	8.3 (3.7 to 12.9)
Breast cancer	1/7¶	14‖	1.7+	0/8	0	NA
Colorectal cancer	0/6	0	NA	1/6¶	17‖	11.7
Cancer of unknown primary site	0/2	0	NA	0/2	0	NA
Endometrial cancer	0/1	0	NA	0/1	0	NA
Gastric cancer	1/1¶	100‖	1.9+	1/1¶	100‖	1.9+
Ovarian cancer	1/1¶	100‖	12.8	1/1¶	100‖	12.8+
Renal-cell carcinoma	0/1	0	NA	0/1	0	NA

Schram AM et al., N Engl J Med 2025;392(6):566-76; Schram AM et al., ASCO 2022

Courtesy of Jessica J Lin, MD

Zenocutuzumab in NRG1+ Cancer: Safety

- Most common grade 3/4 treatment-related AEs: diarrhea and anemia
- One patient with treatment discontinuation due to drug-related AE (grade 2 pneumonitis)
- AEs resulting in treatment delay: 31% (6% with treatment-related delay)
- AEs resulting in dosing interruption: 10%
- Infusion-related reactions: 14%, all grades 1-2

Table 3. Adverse Events among All the Patients Who Received Zenocutuzumab.*

Event	Regardless of Attribution (N=204)		Treatment-Related (N=204)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Any adverse event	194 (95)	72 (35)	135 (66)	14 (7)
Serious adverse event	49 (24)	33 (16)	4 (2)	2 (1)
Adverse event leading to treatment discontinuation	15 (7)	8 (4)	1 (<1)	0
Adverse event leading to treatment delay	64 (31)	36 (18)	12 (6)	3 (1)
Fatal adverse event	9 (4)	0	0	0
Adverse events occurring in ≥10% of patients				
Diarrhea	60 (29)	4 (2)	37 (18)	3 (1)
Fatigue	42 (21)	5 (2)	24 (12)	0
Nausea	40 (20)	4 (2)	23 (11)	2 (1)
Anemia	34 (17)	10 (5)	9 (4)	3 (1)
Dyspnea†	33 (16)	5 (2)	4 (2)	0
Constipation	28 (14)	0	7 (3)	0
Vomiting	28 (14)	2 (1)	12 (6)	1 (<1)
Abdominal pain‡	26 (13)	4 (2)	3 (1)	1 (<1)
Alanine aminotransferase increased	25 (12)	6 (3)	7 (3)	1 (<1)
Cough§	24 (12)	1 (<1)	3 (1)	0
Hypomagnesemia	23 (11)	4 (2)	5 (2)	0
Covid-19¶	22 (11)	1 (<1)	0	0
Arthralgia	21 (10)	0	7 (3)	0
Aspartate aminotransferase increased	21 (10)	6 (3)	6 (3)	2 (1)
Decreased appetite	20 (10)	2 (1)	5 (2)	1 (<1)

Schram AM et al., N Engl J Med 2025;392(6):566-76

Courtesy of Jessica J Lin, MD

Treatment of Metastatic NRG1+ NSCLC: *My Take*

- Zenocutuzumab represents a new SOC, FDA-approved treatment option for patients with advanced NRG1 fusion+ NSCLC
- The ORR (31%) is more modest relative to other targeted therapies in NSCLC, and therefore, I would reserve zenocutuzumab as later-line therapy

Courtesy of Jessica J Lin, MD

When do you use zenocutuzumab,
and what are the tolerability/toxicity issues?

How, if at all, has the availability of zenocutuzumab impacted your approach to biomarker testing in patients with NSCLCL?

How, if at all, does the association between NRG1 fusions and mucinous adenocarcinoma of the lung influence your approach to biomarker testing and treatment selection in NSCLC?

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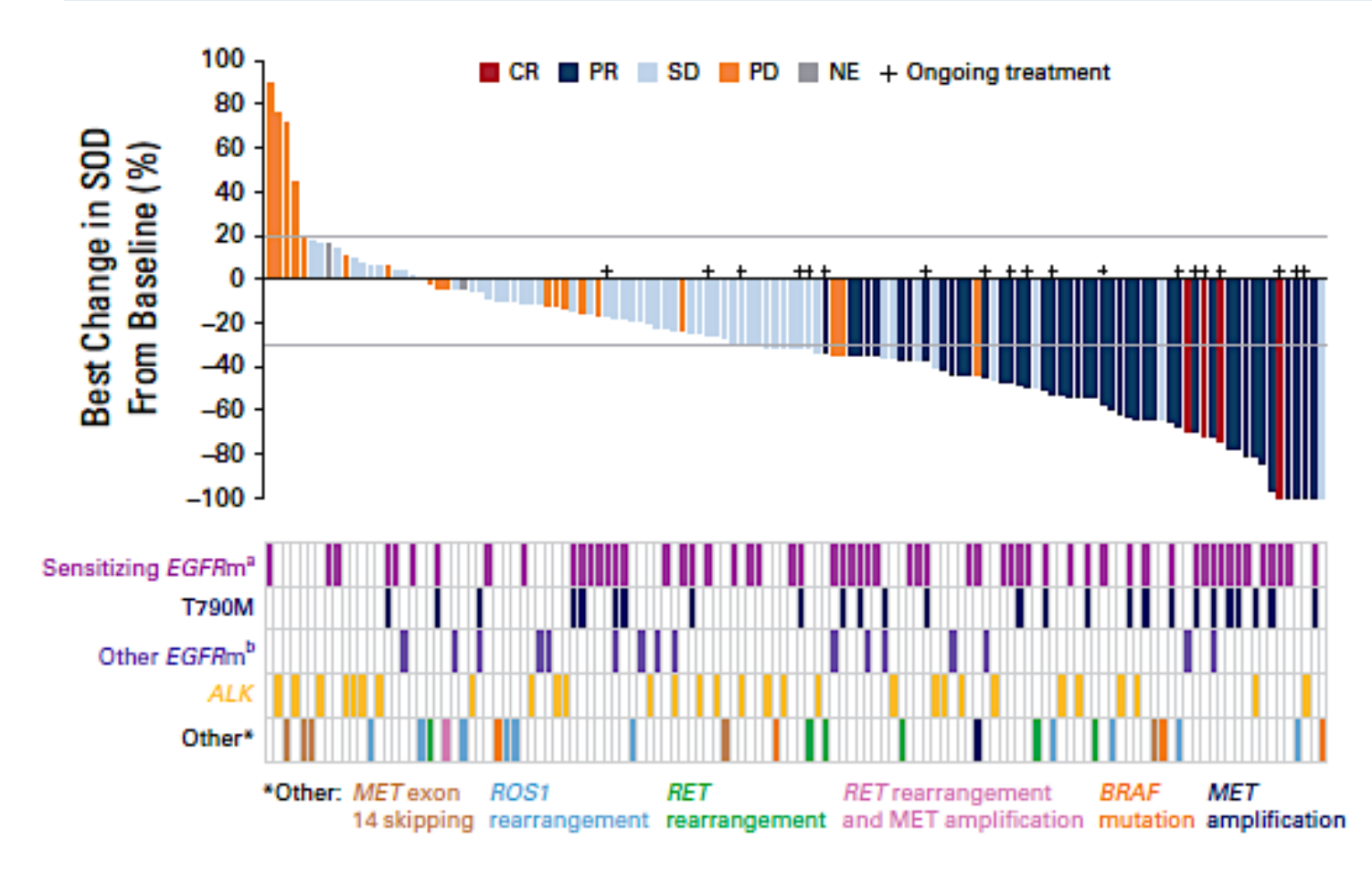
Original Reports | Thoracic Oncology

Datopotamab Deruxtecan in Advanced or Metastatic Non–Small Cell Lung Cancer With Actionable Genomic Alterations: Results From the Phase II TROPION-Lung05 Study

Jacob Sands, MD[1]; Myung-Ju Ahn, MD[2]; Aaron Lisberg, MD[3]; Byoung Chul Cho, MD, PhD[4]; George Blumenschein Jr, MD[5]; Elaine Shum, MD[6]; Elvire Pons Tostivint, MD, PhD[7]; Yasushi Goto, MD, PhD[8]; Kiyotaka Yoh, MD[9]; Rebecca Heist, MD, MPH[10]; Junichi Shimizu, MD, PhD[11]; Jong-Seok Lee, MD, PhD[12]; Paul Baas, MD, PhD[13]; David Planchard, MD, PhD[14,15]; Maurice Pérol, MD[16]; Enriqueta Felip, MD, PhD[17]; Wu-Chou Su, MD[18]; Hong Zebger-Gong, MD, PhD[19]; Lan Lan, PhD[20]; Chelsea Liu, PhD[20]; Paul Howarth, MD[20]; Rachel Chiaverelli, PhD[20]; and Luis Paz-Ares, MD, PhD[21]

J Clin Oncol 2025;43:1254-65.

TROPION-Lung05: Antitumor Activity of Datopotamab Deruxtecan in Metastatic NSCLC with Actionable Genomic Alterations



CR = complete response; PR = partial response; SD = stable disease; PD = disease progression; NE = not estimable

Sands J et al. *J Clin Oncol* 2025;43:1254-65.

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Fang W et al. Ivonescimab plus Chemotherapy in Non-Small Cell Lung Cancer with *EGFR* Variant. *JAMA* 2024 May 31;332(7):561-70.

Fang W et al. HARMONi: Randomized, Double-Blind, Multi-Center, Phase III Clinical Study of Ivonescimab or Placebo Combined with Pemetrexed and Carboplatin in Patients with EGFR-Mutant Locally Advanced or Metastatic Non-Squamous NSCLC Who Have Progression Following EGFR-TKI Treatment. ESMO 2023;Abstract 1504TiP.

Practical Perspectives: Experts Review Actual Cases of Patients with Advanced Gastroesophageal Cancers

A CME/MOC-Accredited Live Webinar

Wednesday, May 21, 2025
5:00 PM – 6:00 PM ET

Faculty

Geoffrey Y Ku, MD
Zev Wainberg, MD, MSc

Moderator

Neil Love, MD

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RESEARCH TO PRACTICE

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Please take a moment to complete the survey currently up on Zoom. Your feedback is very important to us. The survey will remain open for 5 minutes after the meeting ends.

Information on how to obtain CME, ABIM MOC and ABS credit is provided in the Zoom chat room. Attendees will also receive an email in 1 to 3 business days with these instructions.

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