The Implications of Recent Datasets for the Current and Future Management of Non-Small Cell Lung Cancer with Actionable Targets Beyond EGFR

A CME/MOC-Accredited Live Webinar in Conjunction with the IASLC 2024 World Conference on Lung Cancer

Wednesday, September 11, 2024

5:00 PM – 6:00 PM ET

Faculty

Ibiayi Dagogo-Jack, MD

Corey J Langer, MD

Moderator

Neil Love, MD

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Faculty

Ibiayi Dagogo-Jack, MD
Assistant Professor of Medicine
Harvard Medical School
Massachusetts General Hospital
Boston, Massachusetts

MODERATOR
Neil Love, MD
Research To Practice
Miami, Florida

Corey J Langer, MD
Director of Thoracic Oncology
Abramson Cancer Center
Professor of Medicine
Perelman School of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania

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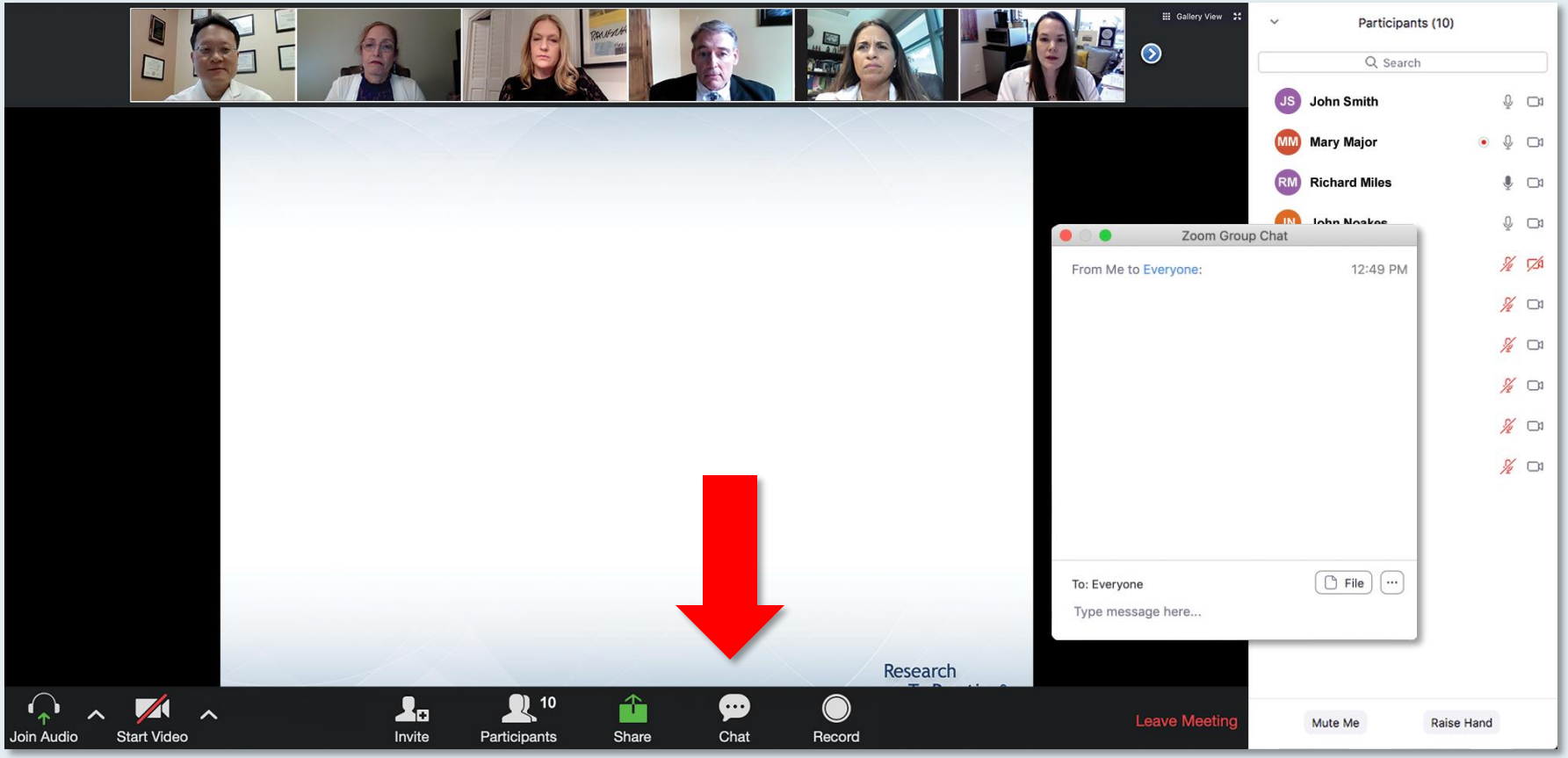

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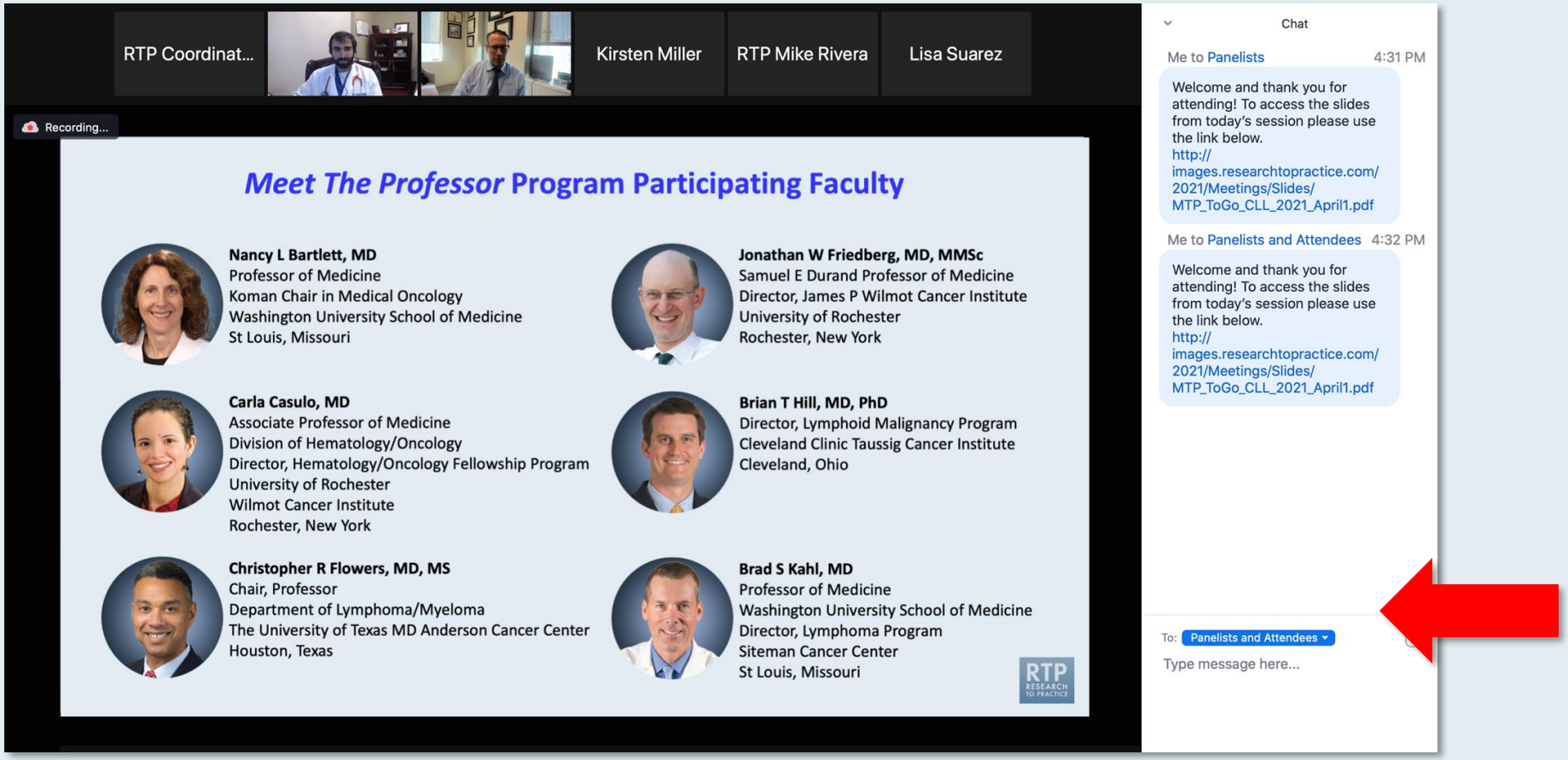

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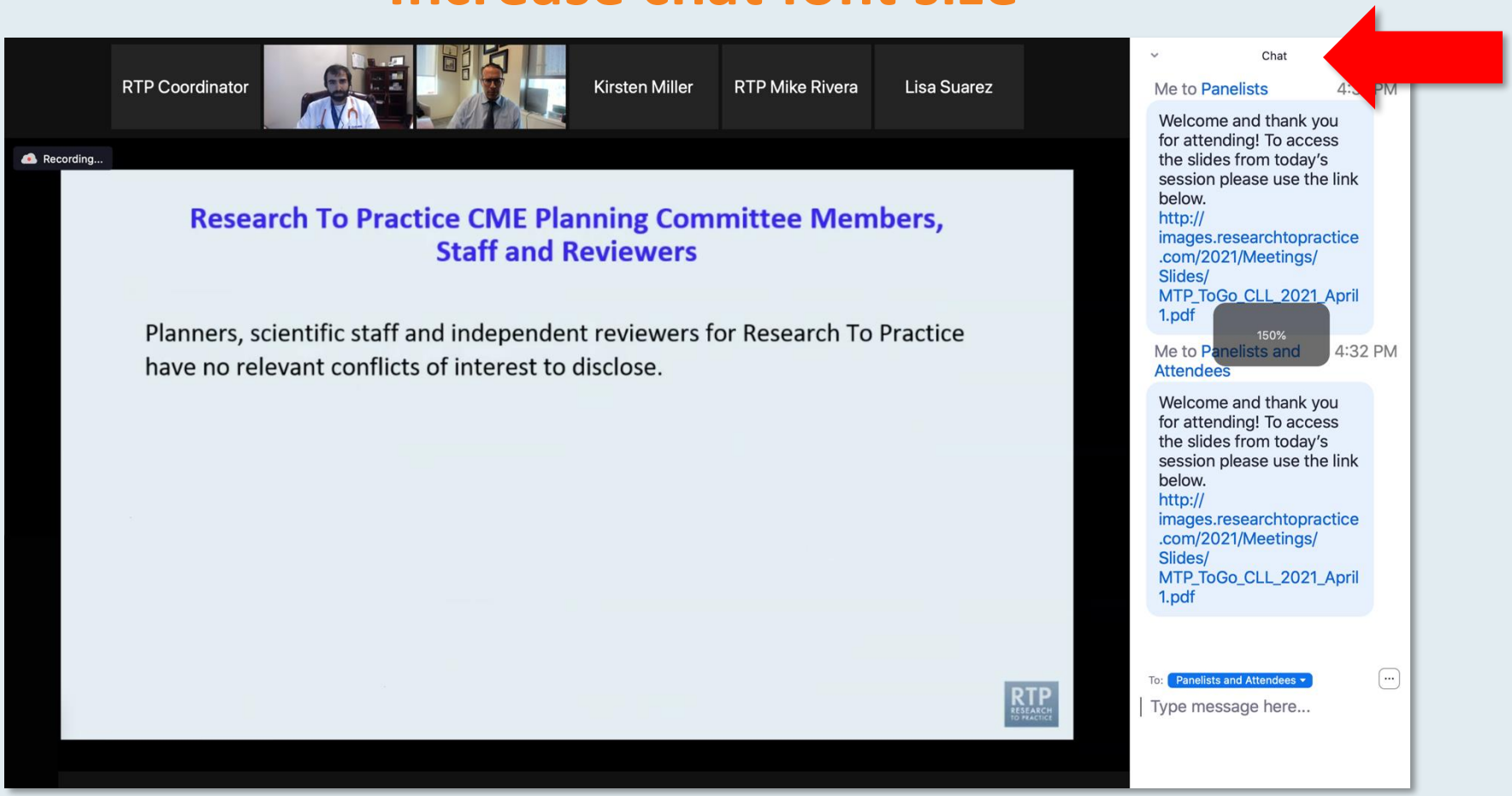

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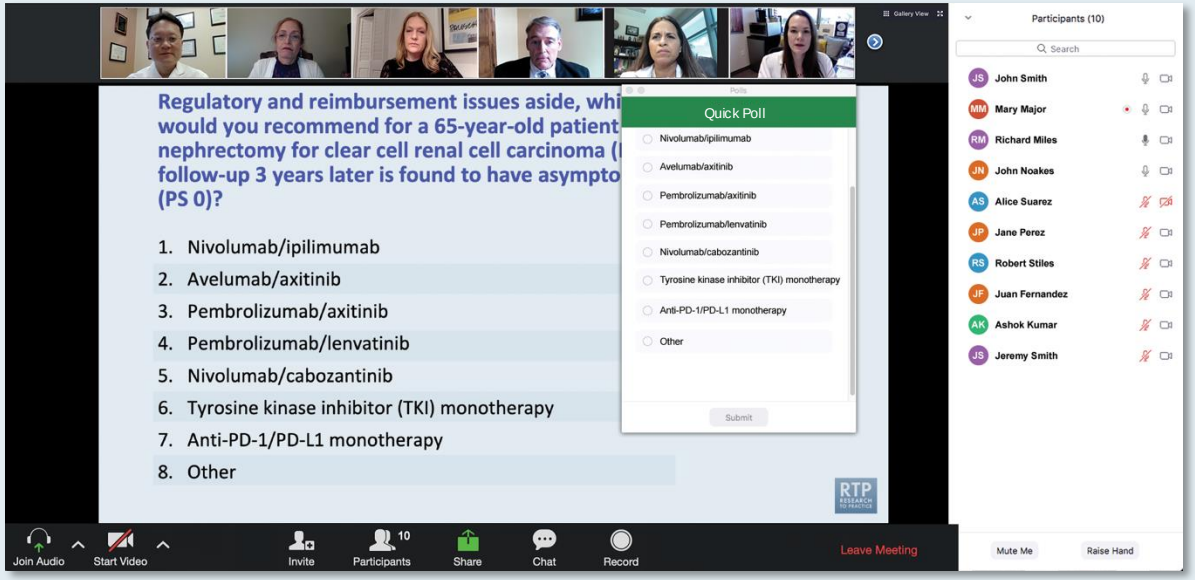

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DR MELISSA JOHNSON
SARAH CANNON RESEARCH INSTITUTE

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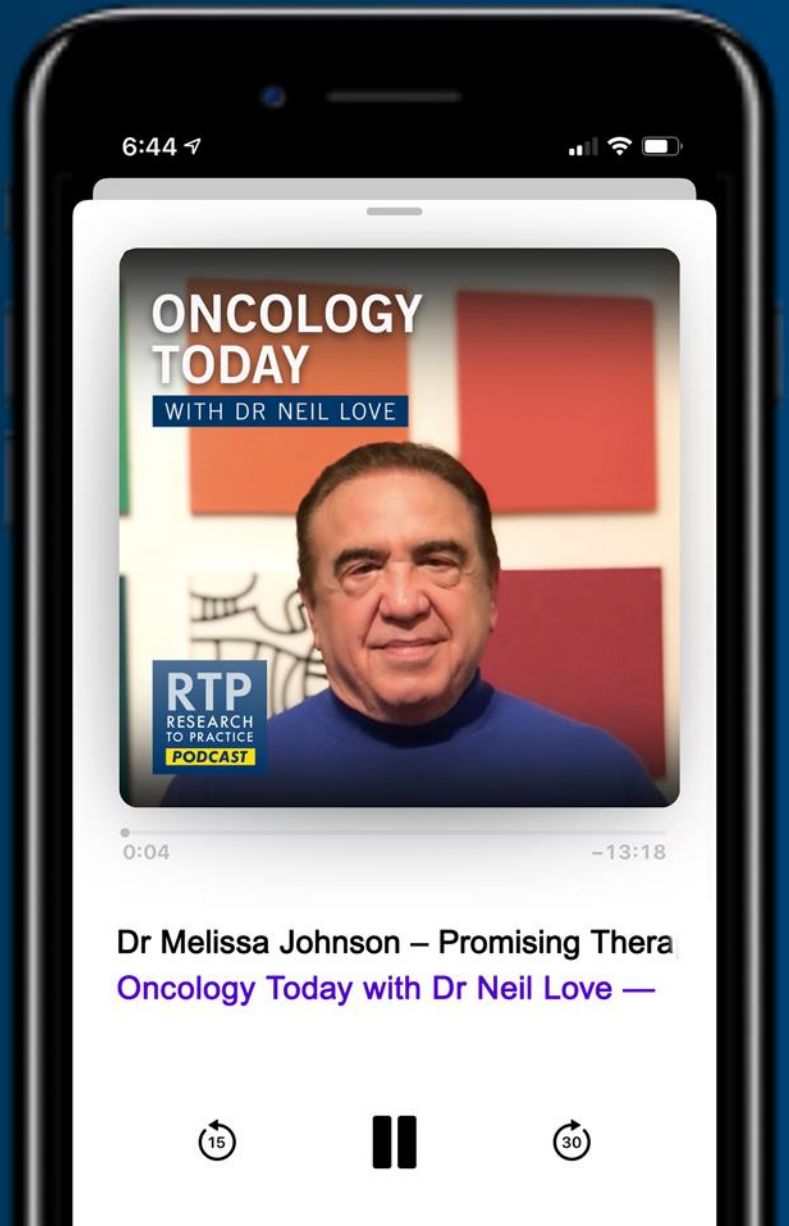

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RESEARCH TO PRACTICE

Practical Perspectives: Optimizing Diagnosis and Treatment for Patients with Desmoid Tumors

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Mrinal Gounder, MD

Moderator

Neil Love, MD

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Practical Perspectives: Optimizing the Role of BTK Inhibitors in the Management of Mantle Cell Lymphoma

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Michael Wang, MD

Moderator

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Data + Perspectives: Clinical Investigators Explore the Application of Recent Datasets in Current Oncology Care

A Multitumor Hybrid Symposium in Partnership with Florida Cancer Specialists & Research Institute

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Lung Cancer

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Additional faculty to be announced.

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Moderated by Neil Love, MD

Thank you for joining us!

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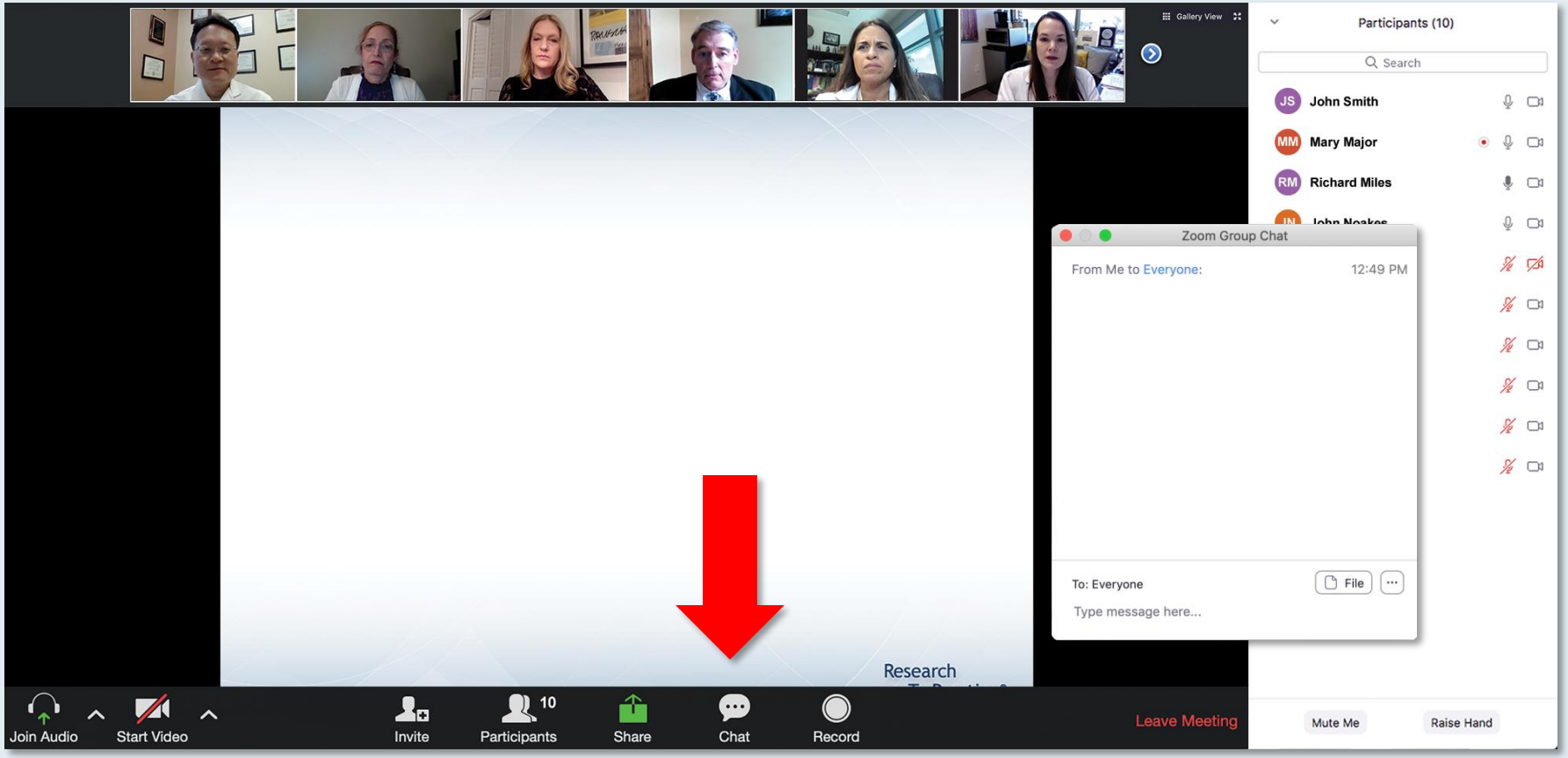

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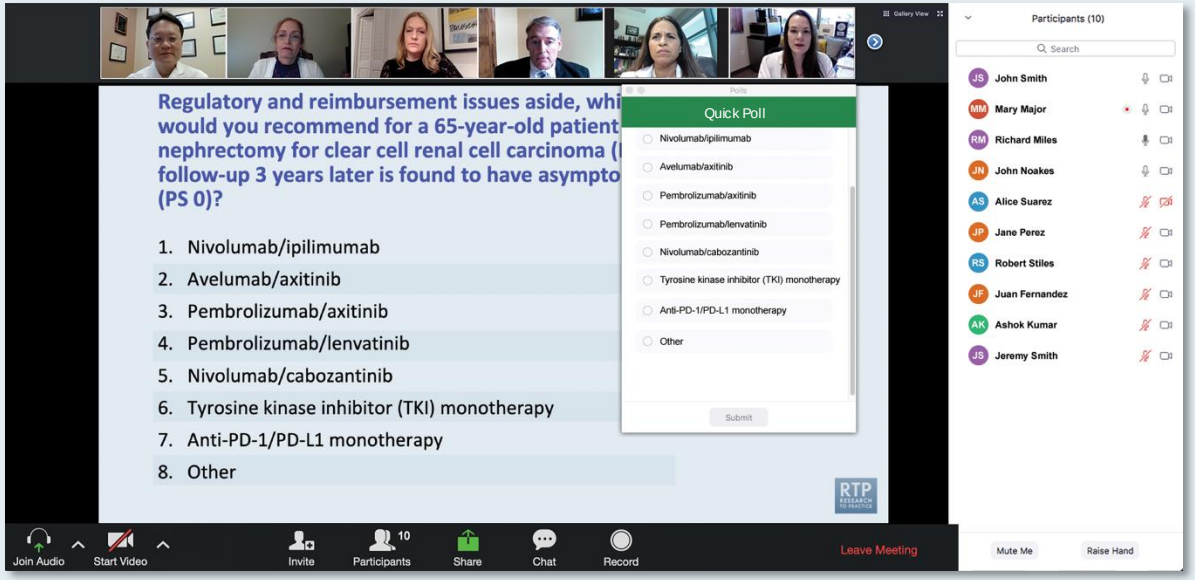

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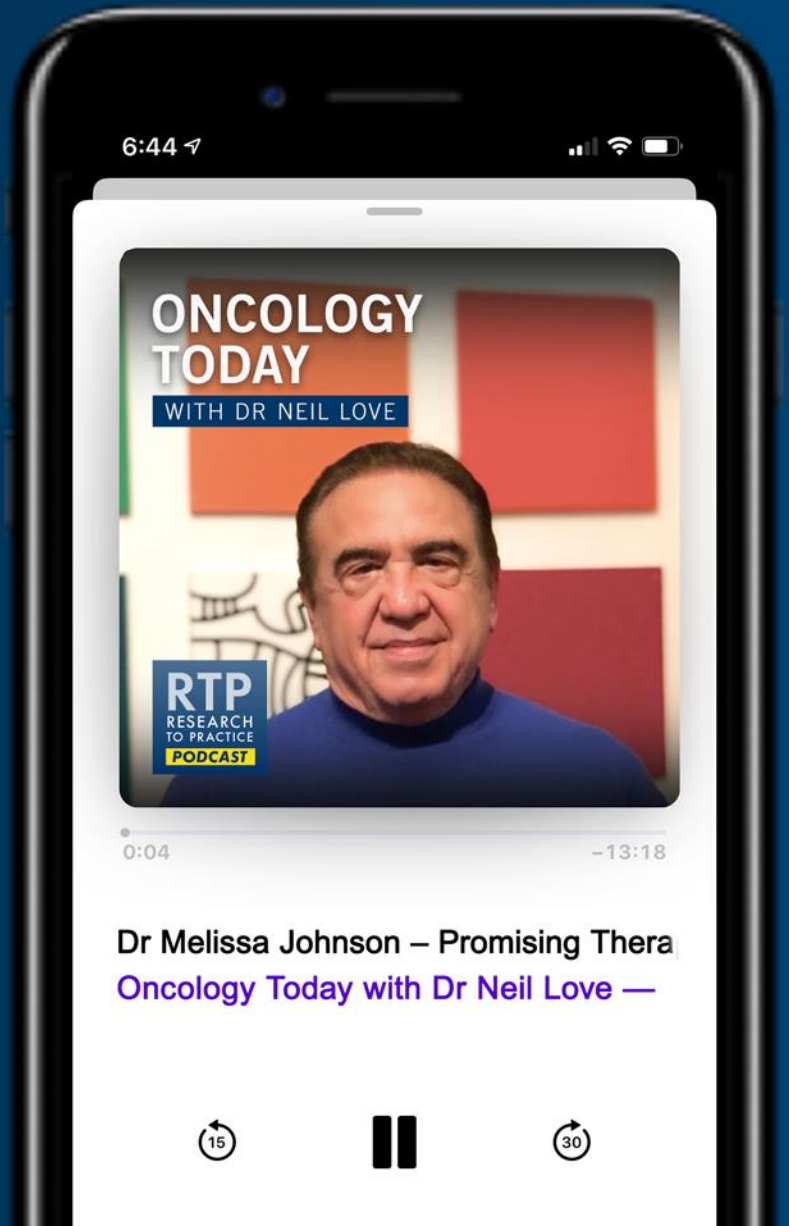

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RESEARCH TO PRACTICE

Agenda

Introduction: A Model for Targeted Treatment in Non-Small Cell Lung Cancer (NSCLC)

Module 1: NSCLC with ALK, ROS1 and NTRK Rearrangements — Dr Langer

Module 2: Current and Future Treatment of Metastatic NSCLC with RET, MET, HER2 and KRAS Alterations — Dr Dagogo-Jack

Agenda

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General Issues Related to the Management of NSCLC

Where do ROS1-, NTRK-, RET-, MET-, BRAF-, KRAS- and HER2-targeted treatments fit in?

- Adjuvant therapy
- Stage III resectable disease
- First-line treatment of metastatic disease
- Brain metastases (without radiation therapy)
- Role of immunotherapy, if any

Agenda

Introduction: A Model for Targeted Treatment in Non-Small Cell Lung Cancer (NSCLC)

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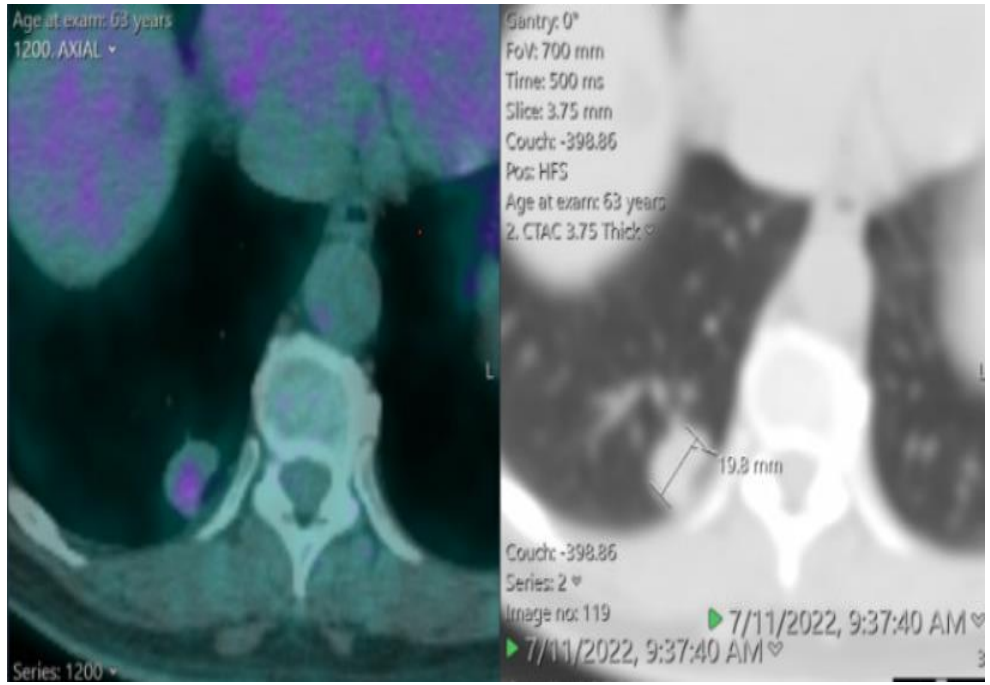
RTP RESEARCH TO PRACTICE

Case Presentation – Dr Langer: ALK (+) Adjuvant

- 57 yo WM never smoker, after a long motorcycle trip across several states, developed pain c/w L renal colic, presented to a local ED in NYS where CT A/P demonstrated a non-obstructing L renal stone and "incidental" 2-3 cm RLL nodule c/w malignancy
- Discharged home w/ pain meds
- Passed the stone spontaneously in < 1 wk
- Subsequently seen by Penn pulmonologist
- PET/CT demonstrated a 2.8 cm RLL nodule w/ SUV 3, no other suspicious uptake.
- **Clinical stage:** Stage IA3 (cT1c, cN0, cM0)
- **07/22/22:** Robotic R upper lobectomy w/ LN dissection. Path c/w moderately differentiated adenocarcinoma w/ + Levels 7, 11, 12, 4 nodes (none seen pre-op on CT or PET)
- **08/03/22:** MRI Brain unremarkable
- **Final pathologic stage:** IIIA - (pT1c, pN2, cM0) - 2.8 cm, 6/18 nodes
- PD-L1: 1%. Fusion panel (+) EML4ALK. NGS otherwise (-)

What's the next step?



Penn Medicine
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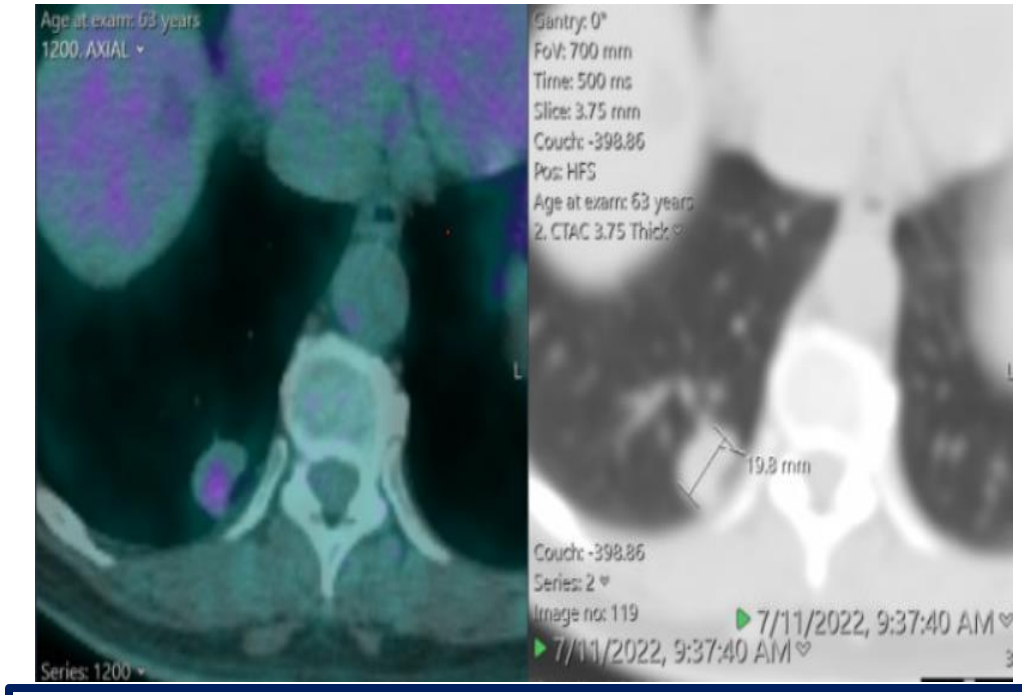

- **Pt received DDP-Pem x 3 cycles with 4th cycle changed to Carbo/Pem b/o cumulative GI toxicity and vertigo**
- **Long discussion re: utility of alectinib (preceded unveiling of ALINA data).**
- **After consultation with various ALK experts, went ahead with full dose: 600 mg BID**

Penn Medicine
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Division of Hematology & Oncology

Contemporary Care for Pts with NSCLC and ALK, ROS1 and NTRK
State-of-the-Art – post ASCO and WCLC 2024

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Abramson Cancer Center
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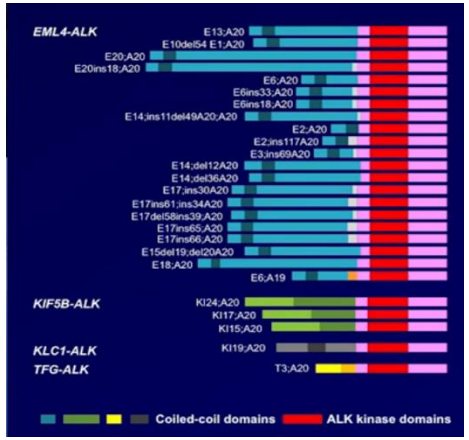
ALK+ NSCLC in brief

1. Incidence of *ALK* rearrangements: 5-7% of all NSCLC*



* Over 50.000 new cases/year worldwide

2. Testing for *ALK* rearrangements is mandatory

COLLEGE of AMERICAN PATHOLOGISTS

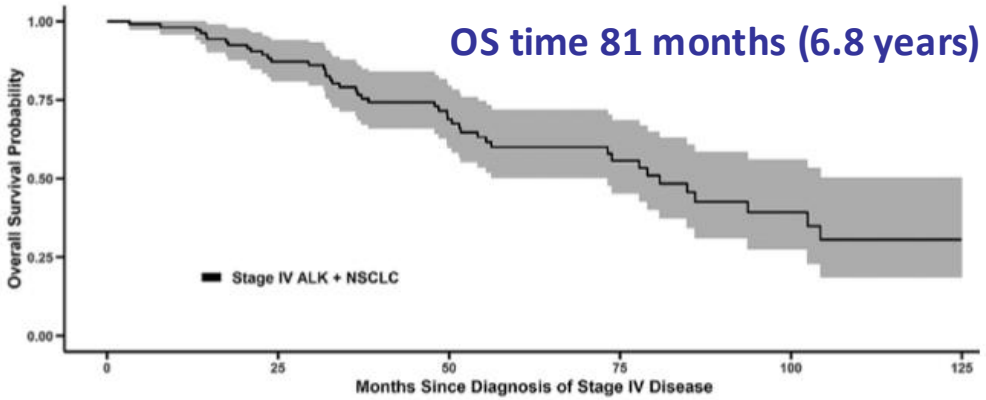
IASLC INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER Conquering Thoracic Cancers Worldwide

AMP ASSOCIATION FOR MOLECULAR PATHOLOGY

Molecular Testing Guideline for Selection of Lung Cancer Patients – Revision
2016 Draft Recommendations

Strong Recommendation: Physicians must use *EGFR* and *ALK* molecular testing for lung adenocarcinoma patients at the time of diagnosis for patients presenting with advanced stage disease or at progression in patients who originally presented with lower stage disease but were not previously tested.

3. ALK-Is are extending survival in *ALK+* NSCLC



Pacheco JM, JTO 2018

4. No role for IT as single agent or in combination with ALK-Is

	EGFR	*ALK*	*ROS1*	*BRAF*	*KRAS*
Targeted therapy	**80%**[a]	**83%**	*77%*	*64%*	*54%*[b]
ICI	**11%**	**4%**	**14%**	**24%**	**57%**[c]
					25%
ICI + targeted therapy	*75%*[d]	*81%*[d]			
Chemotherapy + ICI	***81%***[a]	**NA**			***41%***

Calles A, et al. ASCO EDBK 2020

Penn Medicine Abramson Cancer Center

Is There a BEST First-line Option?

	ALECTINIB (Global ALEX)	BRIGATINIB (ALTA-1L)	ENSARTINIB eXalt3	LORLATINIB (CROWN)
Comparator	Crizotinib	Crizotinib	Crizotinib	Crizotinib
N	ALEC: 152 CRZ: 151	BRIG: 137 CRZ: 138	ENSAR: 143 CRZ: 147	LOR: 149 CRZ: 147
PFS, median	ALEC: 25.7 mos CRZ: 10.4 mos HR 0.50 (0.36-0.70)	BRIG: 24.0 mos CRZ: 11.0 mos HR 0.48 (0.35-0.66)	ENSAR: 25.8 mos CRZ: 12.7 mos HR 0.51 (0.35-0.72)	LOR: NR CRZ: 9.6 HR 0.27 (0.18-0.39)
Median f/u for PFS	ALEC: 18.6 mos CRZ: 17.6 mos	BRIG: 40.4 mos CRZ: 15.2 mos	ENSAR: 23.8 mos CRZ: 20.2 mos	LOR: 36.7 mos CRZ: 29.3 mos
CNS mets at baseline	ALEC: 42% CRZ: 38%	BRIG: 29% CRZ: 30%	ENSAR: 33% CRZ: 39%	LOR: 26% CRZ: 27%
PFS in patients with CNS mets	ALEC: 25.4 mos CRZ: 7.4 mos HR 0.37 (0.23-0.58)	BRIG: 24.0 mos CRZ: 5.6 mos HR 0.25 (0.14-0.46)	ENSAR: 11.8 mos CRZ: 7.5 mos HR 0.55 (0.30-1.01)	LOR: NR CRZ: 11.0 mos HR 0.21 (0.10-0.44)
PFS in pts without CNS mets	ALEC: 38.6 mos CRZ: 14.8mos HR 0.46 (0.31-0.68)	BRIG: 24.0 mos CRZ: 13.0 mos HR 0.62 (0.43-0.91)	ENSAR: NR CRZ: 16.6 mos HR 0.40 (0.23-0.70)	LOR: NR CRZ: 11.0 HR 0.29 (0.19-0.44)
Response rate	ALEC: 83% CRZ: 76%	BRIG: 74% CRZ: 62%	ENSAR: 74% CRZ: 67%	LOR: 77% CRZ: 58%

Peters S, et al. *N Engl J Med*. 2017;377(9):829-838. Mok T, et al. *Ann Oncol*. 2020;31(8):1056-1064. Camidge DR, et al. *N Engl J Med*. 2018;379(21):2027-2039. Camidge DR et al. J Thorac Oncol. 2021;16(12):2091-2108. Horn L, et al. *JAMA Oncol*. 2021;7(11):1617-1625. Solomon BJ, et al. *J Clin Oncol*. 2022;40(31):3593-3602.

NCCN Preferred Regimens 1L in *ALK*+ NSCLC

ALK rearrangement

ALK rearrangement discovered prior to first-line systemic therapy

FIRST-LINE THERAPY
Preferred
Alectinib (category 1)
Brigatinib (category 1)
Lorlatinib (category 1)

Other Recommended
Ceritinib (category 1)

Useful in certain circumstances
Crizotinib (category 1)

ALK rearrangement discovered during first-line systemic therapy

Complete planned systemic therapy, including maintenance therapy, or interrupt, followed by alectinib (preferred) or brigatinib (preferred) or loratinib (preferred) or ceritinib or crizotinib

Current Treatment Paradigm

Second-generation TKI (alectinib or brigatinib) → **Third-gen TKI** → **Chemotherapy or clinical trials**

Third-gen TKI (Lorlatinib) → **Chemotherapy or clinical trials**

NCCN. Accessed September 2024.
https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

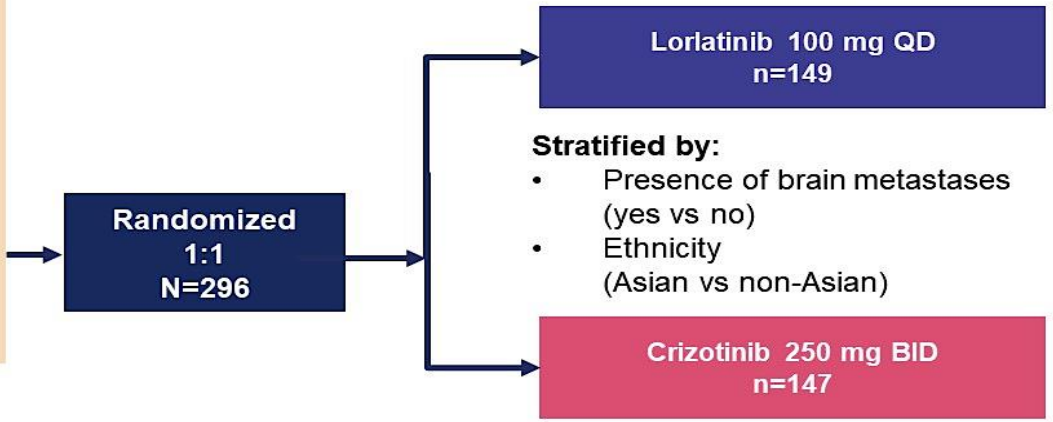
CROWN Trial

Current Post Hoc Analyses at 5 Years

Endpoint evaluation by BICR stopped after the 3-year analysis

Key eligibility criteria

- Stage IIIB/IV *ALK*+ NSCLC
- No prior systemic treatment for metastatic disease
- ECOG PS 0-2
- Asymptomatic treated or untreated CNS metastases were permitted
- ≥1 extracranial measurable target lesion (RECIST 1.1) with no prior radiation required



Current analyses

Data cutoff: October 31, 2023

- PFS[a] by investigator
- ORR and IC ORR by investigator
- DOR and IC DOR by investigator
- IC TTP by investigator
- Safety
- Biomarker analyses

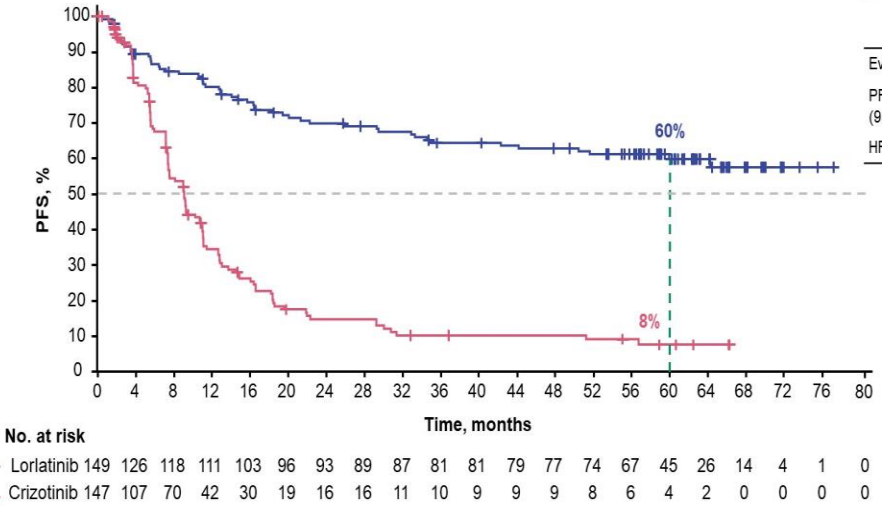
No crossover between treatment arms was permitted

BICR, blinded independent central review; BID, twice daily; CNS, central nervous system; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; IC, intracranial; ORR, objective response rate; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; PFS, progression-free survival; PS, performance status; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; TTP, time to tumor progression.

[a] Defined as the time from randomization to RECIST-defined progression or death due to any cause.

PRESENTED BY: Benjamin J. Solomon (Ben.Solomon@petermac.org)

At 60.2 Months of Median Follow-Up, Median PFS by Investigator Was Still Not Reached With Lorlatinib

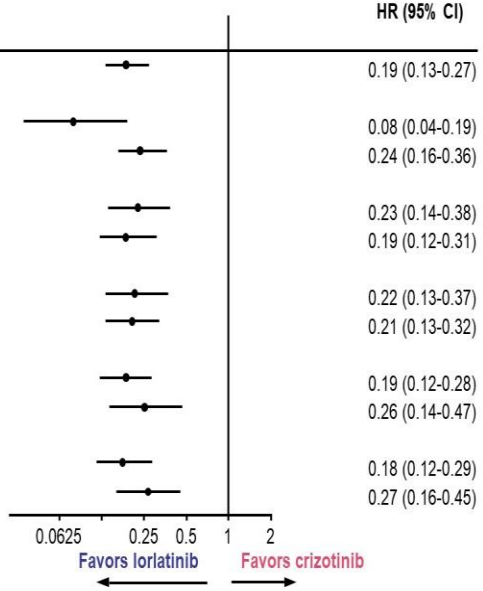


	Lorlatinib (n=149)	Crizotinib (n=147)
Events, n	55	115
PFS, median (95% CI), months	NR (64.3-NR)	9.1 (7.4-10.9)
HR (95% CI)	**0.19 (0.13-0.27)**	

HR, hazard ratio; ITT, intention to treat; NR, not reached; PFS, progression-free survival.

PFS Benefit With Lorlatinib Was Observed Across Patient Subgroups

Subgroup	Patients, n (%) Lorlatinib	Patients, n (%) Crizotinib	Events, n Lorlatinib	Events, n Crizotinib	HR (95% CI)
All patients (stratified)	149 (100)	147 (100)	55	115	0.19 (0.13-0.27)
Presence of brain metastases					
Yes	35 (23)	38 (26)	16	34	0.08 (0.04-0.19)
No	114 (77)	109 (74)	39	81	0.24 (0.16-0.36)
Ethnic origin					
Asian	66 (44)	65 (44)	25	50	0.23 (0.14-0.38)
Non-Asian	83 (56)	82 (56)	30	65	0.19 (0.12-0.31)
Sex					
Male	65 (44)	56 (38)	24	48	0.22 (0.13-0.37)
Female	84 (56)	91 (62)	31	67	0.21 (0.13-0.32)
Age					
<65 years	96 (64)	110 (75)	33	88	0.19 (0.12-0.28)
≥65 years	53 (36)	37 (25)	22	27	0.26 (0.14-0.47)
Smoking status					
Never	81 (54)	94 (64)	30	75	0.18 (0.12-0.29)
Current/former	68 (46)	52 (35)	25	39	0.27 (0.16-0.45)

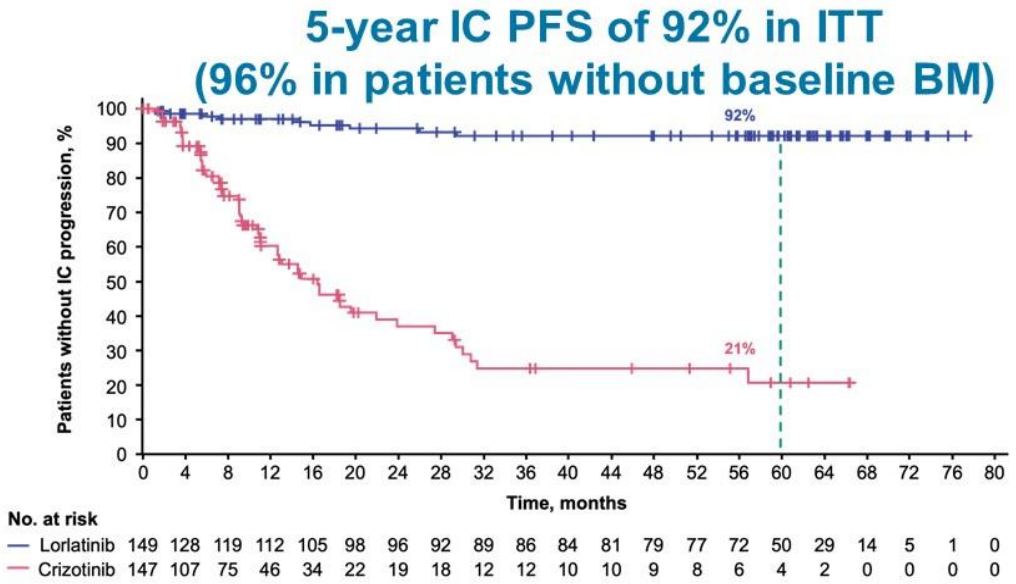


PFS, progression-free survival.

2024 ASCO ANNUAL MEETING #ASCO24 PRESENTED BY: Benjamin J. Solomon (Ben.Solomon@petermac.org) ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

Evaluating CROWN in the Context of ALK Treatment Landscape: CNS Efficacy

- **Brain metastases are common** at initial diagnosis (25-40%) and cumulatively (>70% at 5 years)[1-2]
- Despite CNS activity of 2G ALK TKIs, **CNS relapses** occur
  - **1L Alectinib**: 12-month cumulative incidence rate for CNS progression 9.4%[3]
  - **1L Brigatinib**: 3-year intracranial PFS rate 57%[4]

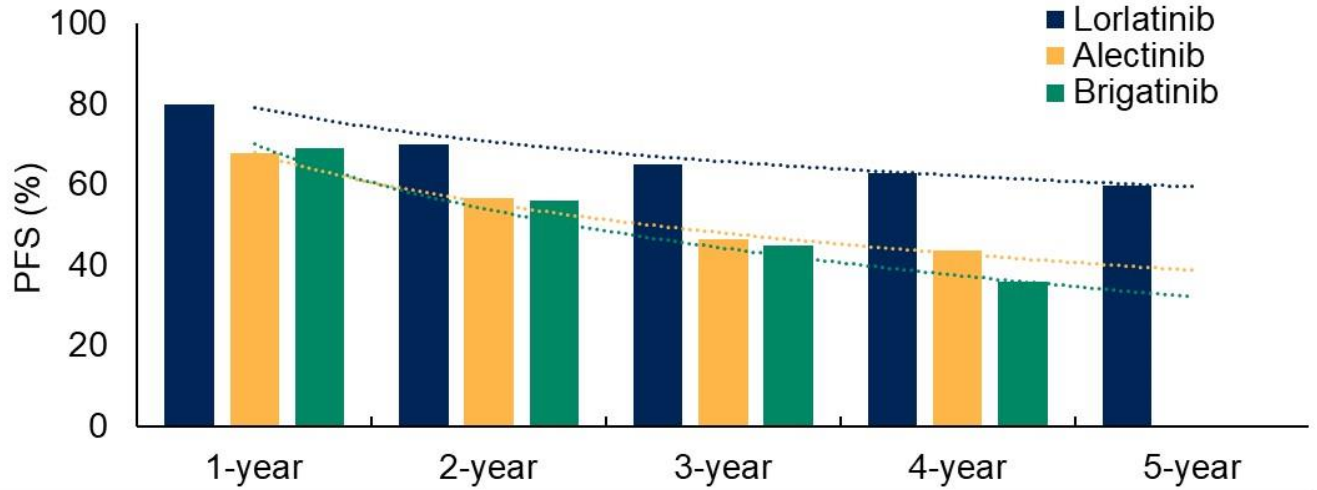


	Lorlatinib (n=149)	Crizotinib (n=147)
Events, n	9	65
Time to IC progression, median (95% CI), months	NR (NR-NR)	16.4 (12.7-21.9)
HR (95% CI)	**0.06 (0.03-0.12)**	

1. Gainor JF et al., JCO Precis Oncol 2017:PO.17.00063; 2. Pacheco JM et al., J Thorac Oncol 2019;14(4):691-700
3. Peters S et al., N Engl J Med 2017;377(9):829-38; 4. Camidge DR et al., J Thorac Oncol 2021;16(12):2091-108

PRESENTED BY: Jessica J. Lin (jjlin1@mgb.org)

Evaluating CROWN in the Context of ALK Treatment Landscape: Systemic Efficacy



	Median PFS	1-year PFS (%)	2-year PFS (%)	3-year PFS (%)	4-year PFS (%)	5-year PFS (%)
Lorlatinib[1-3]	**Not reached at 60.2 mos**	80	70	63	63	60
Alectinib[4]	**34.8 mos**	67.8	56.6	46.4	43.7	N/A
Brigatinib[5-7]	**30.8 mos**	69	56	45	36	N/A

**PFS results per investigator assessment in CROWN, global ALEX (alectinib), and ALTA-1L (brigatinib) trials. N/A, not available; mos, months*

1. Shaw AT et al., N Engl J Med 2020;383:2018-29
2. Solomon BJ et al., Lancet Respir Med 2023;11(4):354-66
3. Solomon BJ et al., ASCO 2024
4. Mok T et al., Ann Oncol 2020;31(8):1056-64
5. Camidge DR et al., N Engl J Med 2018; 379:2027-39
6. Camidge DR et al., J Clin Oncol 2020;38(31):3592-603
7. Camidge DR et al., J Thorac Oncol 2021;16(12):2091-108

PRESENTED BY: Jessica J. Lin (jjlin1@mgb.org)

Evaluating CROWN in the Context of A… Treatment Landscape: Systemic T…

Beware: Cross Trial Comparisons – NOT statistically valid and Toxicity is a major concern

	Med…	…year PFS (%)	3-year PFS (%)	4-year PFS (%)	5-year PFS (%)
Lorlatinib[1-3]	**Not re… at 60.2 mos**	80	70	63	63	60
Alectinib[4]	**34.8 mos**	67.8	56.6	46.4	43.7	N/A
Brigatinib[5-7]	**30.8 mos**	69	56	45	36	N/A

**PFS results per investigator assessment in CROWN, global ALEX (alectinib), and ALTA-1L (brigatinib) trials. N/A, not available; mos, months*

1. Shaw AT et al., N Engl J Med 2020;383:2018-29
2. Solomon BJ et al., Lancet Respir Med 2023;11(4):354-66
3. Solomon BJ et al., ASCO 2024
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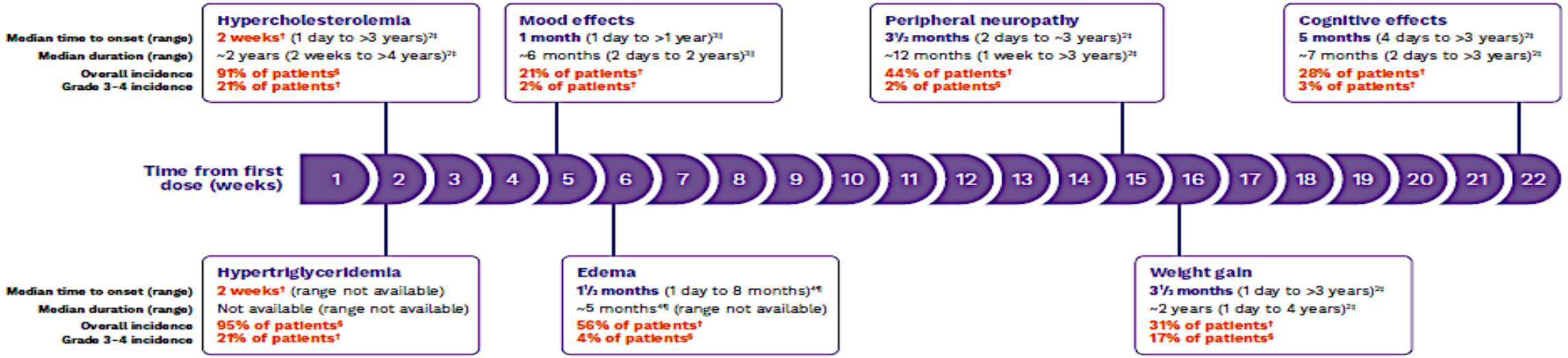
5. Camidge DR et al., N Engl J Med 2018; 379:2027-39
6. Camidge DR et al., J Clin Oncol 2020;38(31):3592-603
7. Camidge DR et al., J Thorac Oncol 2021;16(12):2091-108

PRESENTED BY: Jessica J. Lin (jjlin1@mgb.org)

Timing and Incidence of Most Common Adverse Reactions Based on Data from the CROWN and Phase I/2 Trials

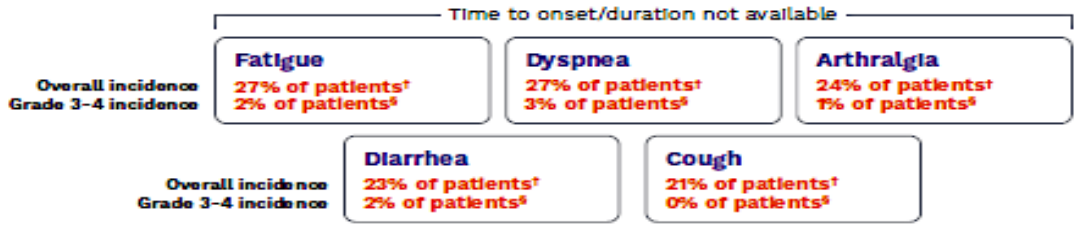


Dose modification and discontinuation rates due to ARs in the CROWN trial

- Among patients receiving lorlatinib, incidence of dose interruption was 49%, incidence of dose reduction was 21%, and the permanent discontinuation rate was 6.7%

INTERPRETING THE TIMELINE

- Data from the USPI are shown in orange; data from peer-reviewed publications reporting on the CROWN and Phase 1/2 trials are shown in black
- "Median time to onset" is the median time from the first dose of lorlatinib to the first occurrence of the AR
- **Mood effects** include agitation, anxiety, depression, euphoria, and irritability
- **Cognitive effects** include memory impairment, confusion, and disorientation



Penn Medicine
Abramson Cancer Center

CROWN: Jessica Lin's Commentary

What will I do next week with a patient with newly diagnosed metastatic ALK+ NSCLC presenting to clinic?

Recognizing that treatment decisions will always need to be individualized to meet each patient's goals and needs, *lorlatinib will be my preferred initial therapy* for most patients

PRESENTED BY: Jessica J. Lin (jjlin1@mgb.org)

CROWN: Langer's Commentary

What will I do next week with a patient
metastatic ALK+ NSCLC pre

Recognizin

- **Langer's Pragmatic Approach:**
- **Lorlatinib** for younger pts, with limited or no co-morbidities, aggressive tumor +/- CNS involvement
- **Alectinib (or brigatinib)** for older pts, limited tumor burden, absence of CNS invasion
- **I'd personally favor a randomized trial with OS as primary endpoint along with Quality-Adjusted Survival**

ica J. Lin (jjlin1@mgb.org)

AACR-NCI-EORTC INTERNATIONAL CONFERENCE ON MOLECULAR TARGETS AND CANCER THERAPEUTICS

Safety and preliminary activity of the selective ALK inhibitor NVL-655 in patients with ALK fusion-positive solid tumors

J.J. Lin[1], M.L. Johnson[2], E. Felip[3], S.H.I Ou[4], B. Besse[5], C.S. Baik[6], J. Mazières[7], Y.Y Elamin[8], J.E. Reuss[9], A. Minchom[10], A. Swalduz[11], N. Pavlakis[12], G. Liu[13], S.M. Gadgeel[14], D.R. Camidge[15], J. Green[16], J. Shen[16], J. Soglia[16], Y. Sun[16], V.W. Zhu[16], A. Drilon[17]

Preclinical NVL-655 activity against ALK

Wild-type ALK Fusions, *in vitro* NSCLC models

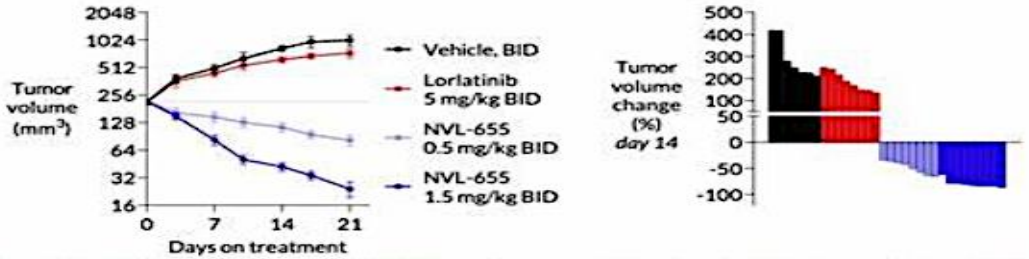
in vitro

IC_{50} cell viability assay (nM)	Nuvalent NVL-655	CRIZOTINIB	CERITINIB	ALECTINIB	BRIGATINIB	LORLATINIB
NCI-H2228 (EML4-ALK v3)	0.70 nM	90 nM	55 nM	13 nM	13 nM	< 1.1 nM
NCI-H3122 (EML4-ALK v1)	2.0 nM	180 nM	48 nM	22 nM	22 nM	3.5 nM
Ba/F3 EML4-ALK v1	1.6 nM	270 nM	90 nM	25 nM	42 nM	4.2 nM

IC_{50}: 0-49 nM; 50 - 499 nM; ≥ 500 nM

IN VIVO ACTIVITY

NVL-655 induced regression in the MGH953-7 patient-derived xenograft (PDX) model without causing significant body weight changes (data not shown). MGH953-7 showed no response to lorlatinib, consistent with treatment history.



▲ Figure 5 NVL-655 induced regression in MGH953-7 subcutaneously implanted in NSG mice. Vehicle was 20% HP-β-CD and was used to formulate NVL-655. Lorlatinib was formulated in water adjusted to pH 3.0 by HCl. All treatments were administered orally and were well-tolerated. Mean ± SEM plotted.

Table 5. Phase 1 Patient Characteristics & Treatment History

Patient Characteristic	All treated N = 93
Age, median (range)	59 (24, 82)
Female	60 (65%)
ECOG PS	
0	38 (41%)
1	55 (59%)
Non-smoker	68 (73%)
Tumor Type	
NSCLC	91 (98%)
Pancreatic adenocarcinoma	1 (1%)
Atypical carcinoid, lung	1 (1%)
History of CNS metastases [a]	54 (58%)
ALK Fusion	93 (100%)
Secondary ALK mutation	43 (46%)
Single ALK mutation	19 (20%)
Compound (i.e., ≥ 2) ALK mutations [b]	24 (26%)
G1202R (single or compound)	22 (24%)

Treatment History	All treated N = 93
Prior lines of anticancer treatment	
1	12 (13%)
2	16 (17%)
≥ 3	65 (70%)
Median (range)	3 (1, 8)
Prior treatments	
1 ALK TKI	14 (15%)
2 ALK TKIs	36 (39%)
≥ 3 ALK TKIs	43 (46%)
Chemotherapy	53 (57%)
ALK TKIs received [c]	
1G (crizotinib)	41 (44%)
2G	88 (95%)
Alectinib	85 (91%)
Brigatinib	21 (23%)
Ceritinib	11 (12%)
3G (lorlatinib)	77 (83%)
Any 2G or lorlatinib	93 (100%)
≥ 2 ALK TKIs, including 2G and lorlatinib	72 (77%)
≥ 3 ALK TKIs, including 2G and lorlatinib	41 (44%)

All data shown as n (%) unless otherwise specified.
[a] Includes patients with untreated CNS lesions.
[b] Cis-allelic configuration not confirmed in all cases.
[c] Categories are not mutually exclusive.

NVL-655: ALKOVE-1 PHASE 1

Preliminary Safety Profile: Favorable and Consistent with ALK-Selective, TRK-Sparing Design of NVL-655

- MTD has not been identified
  - 1 DLT: transient asymptomatic Grade 4 CPK increase (200 mg QD)
- Infrequent TRAEs requiring dose modification:
  - 2 (2%) discontinued due to TRAE [a]
  - 5 (5%) dose-reduced due to TRAE [b]
- Preliminary overall safety profile consistent with avoiding TRK-related neurotoxicities

Treatment-Related Adverse Events (TRAEs) in ≥ 5% of patients

All Treated Patients (N = 93)

	Grade 1 n (%)	Grade 2 n (%)	Grade ≥3 n (%)	Any Grade N (%)
Any TRAE	25 (27%)	14 (15%)	10 (11%)	49 (53%)
ALT increased	8 (9%)	4 (4%)	6 (6%)	18 (19%)
AST increased	11 (12%)	2 (2%)	4 (4%)	17 (18%)
Nausea	8 (9%)	1 (1%)	-	9 (10%)
Dysgeusia	7 (8%)	-	-	7 (8%)
Constipation	3 (3%)	3 (3%)	-	6 (6%)
Fatigue	5 (5%)	-	-	5 (5%)
Peripheral edema	4 (4%)	-	1 (1%)	5 (5%)

Lin JJ et al. AACR-EORTC-NCI International Conference on Molecular Targets and Cancer. October, 2023; Abstract B154.

Preliminary Activity: Tumor Response Across Heavily Pretreated Patient Populations

Patients with ALK+ NSCLC	All NSCLC Response-Evaluable	History of CNS Metastases	With ALK resistance mutation [a]				≥3 prior ALK TKI including 2G & lorlatinib		2G ± 1G, no lorlatinib
			Any	Single	Compound	G1202R [b]	All	+ Chemo	
ORR across all dose levels	**39% (20/51)**	**52% (15/29)**	**54% (15/28)**	**50% (6/12)**	**56% (9/16)**	**71% (12/17)**	**40% (10/25)**	**42% (8/19)**	**71% (5/7)**
Best Response									
PR [c]	20	15	15	6	9	12	10	8	5
SD	17	8	5	2	3	3	7	4	2
PD	11	4	7	3	4	2	6	5	0
NE [d]	3	2	1	1	0	0	2	2	0
ORR at doses ≥ 50 mg QD	**44% (18/41)**	**50% (13/26)**	**61% (14/23)**	**55% (6/11)**	**67% (8/12)**	**79% (11/14)**	**43% (9/21)**	**44% (7/16)**	**67% (4/6)**

Data cut-off: 8 Aug 2023. Response-evaluable patients with ALK+ NSCLC. **1G**, 1st generation ALK TKI (crizotinib); **2G**, 2nd generation ALK TKI (alectinib, brigatinib, or ceritinib); **CNS**, central nervous system; **NE**, not evaluable; **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.

[a] Out of 16 patients harboring presumed compound ALK mutations, 8 have evidence of cis-allelic configuration by central ctDNA analysis.

[b] Includes patients with single G1202R mutation (n=5) and G1202R with compound mutations (n=12; 6 with evidence of cis-allelic configuration).

[c] Includes 4 patients with ongoing partial responses pending confirmation.

[d] Three patients discontinued treatment due to clinical progression without post-baseline radiographic assessment.

Source: Lin JJ. et al., AACR-NCI-EORTC 2023.

MADRID 2023 ESMO congress

ALINA: efficacy and safety of adjuvant alectinib versus chemotherapy in patients with early-stage *ALK*+ NSCLC

Benjamin J. Solomon[1], Jin Seok Ahn[2], Rafal Dziadziuszko[3], Fabrice Barlesi[4], Makoto Nishio[5], Dae Ho Lee[6], Jong-Seok Lee[7], Wenzhao Zhong[8], Hidehito Horinouchi[9], Weimin Mao[10], Maximilian Hochmair[11], Filippo de Marinis[12], Maria Rita Migliorino[13], Igor Bondarenko[14], Tania Ochi Lohmann[15], Tingting Xu[16], Andres Cardona[17], Walter Bordogna[18], Thorsten Ruf[19], Yi-Long Wu[8]

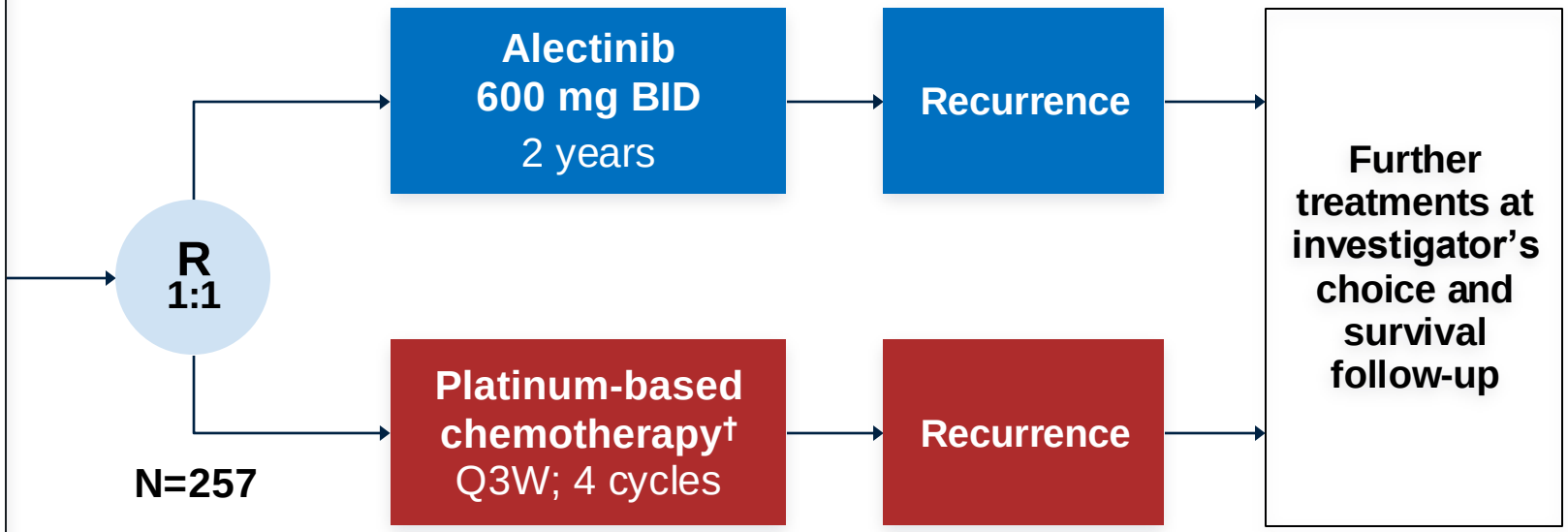
[1]Peter MacCallum Cancer Centre, Melbourne, Australia; [2]Samsung Medical Center, Seoul, Republic of Korea; [3]Medical University of Gdansk, Gdańsk, Poland; [4]International Center for Thoracic Cancers (CICT), France; Paris Saclay University, Faculty of Medicine, France; [5]Cancer Institute Hospital, Japanese Foundation for Cancer Research, Koto, Tokyo, Japan; [6]Asan Medical Center, Seoul, Republic of Korea; [7]Division of Hematology and Medical Oncology, Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Republic of Korea; [8]Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital, Guangdong, China; [9]Department of Thoracic Oncology, National Cancer Center Hospital, Chuo City, Tokyo, Japan; [10]Institute of Basic Medicine and Cancer, Chinese Academy of Sciences, Zhejiang, China; [11]Department of Respiratory & Critical Care Medicine, Karl-Landsteiner-Institute of Lung Research & Pulmonary Oncology, Clinic Floridsdorf; [12]Thoracic Oncology Division, European Institute of Oncology, Via Giuseppe Ripamonti, Milan, Italy; [13]Pneumo-Oncology Unit, San Camillo Forlanini Hospital, Rome, Italy; [14]Dnipropetrovsk Medical Academy, Dnipro, Ukraine; [15]PD Oncology, F. Hoffmann-La Roche Ltd, Basel, Switzerland; [16]Department of Clinical Science, Roche (China) Shanghai, China; [17]Data and Statistical Sciences, F. Hoffmann-La Roche Ltd, Switzerland; [18]Product Development Medical Affairs, F. Hoffmann-La Roche Ltd, Basel, Switzerland; [19]PD Safety Risk Management, F. Hoffmann-La Roche Ltd, Basel, Switzerland

ALINA study design*

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

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

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



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

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

Disease assessments (including brain MRI)§ were conducted: at baseline, every 12 weeks for year 1–2, every 24 weeks for year 3–5, then annually

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Data cut-off: 26 June 2023; CNS, central nervous system; DFS, disease-free survival; ITT, intention to treat
*Superiority trial; †Cisplatin + pemetrexed, cisplatin + vinorelbine or cisplatin + gemcitabine; cisplatin could be switched to carboplatin in case of intolerability; ‡DFS defined as the time from randomisation to the first documented recurrence of disease or new primary NSCLC as determined by the investigator, or death from any cause, whichever occurs first; §Assessment by CT scan where MRI not available; NCT03456076

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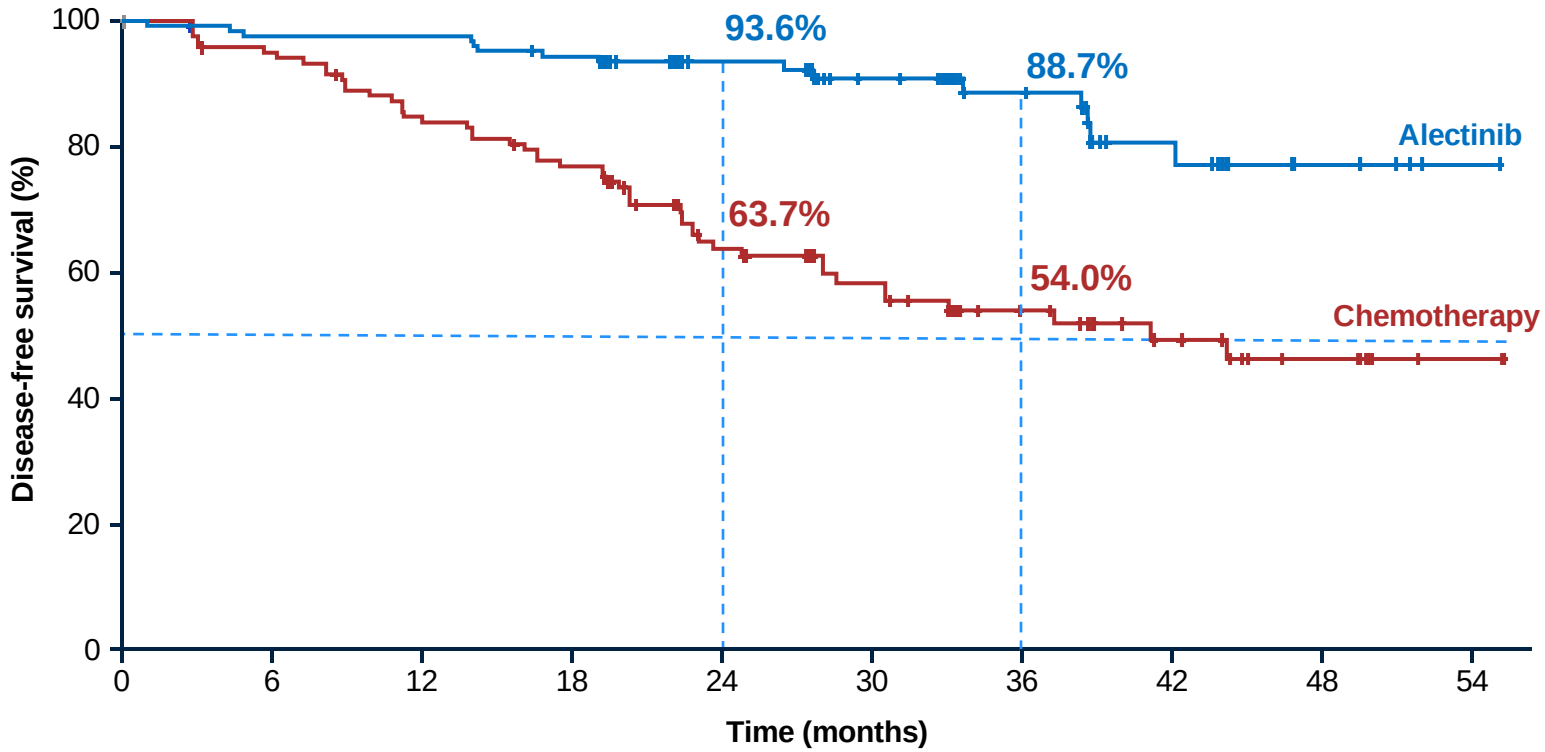
Wu YL et al. N Engl J Med. 2024;390(14):1265-1276.

Disease-free survival: ITT (stage IB–IIIA)*



No. at risk

Alectinib	130	123	123	118	74	55	39	22	10	3
Chemo	127	112	98	89	55	41	27	18	11	2

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

At the data cutoff date, **OS data were immature** with only 6 (2.3%) OS events reported‡

Median survival follow up: alectinib, 27.8 months; chemotherapy, 28.4 months

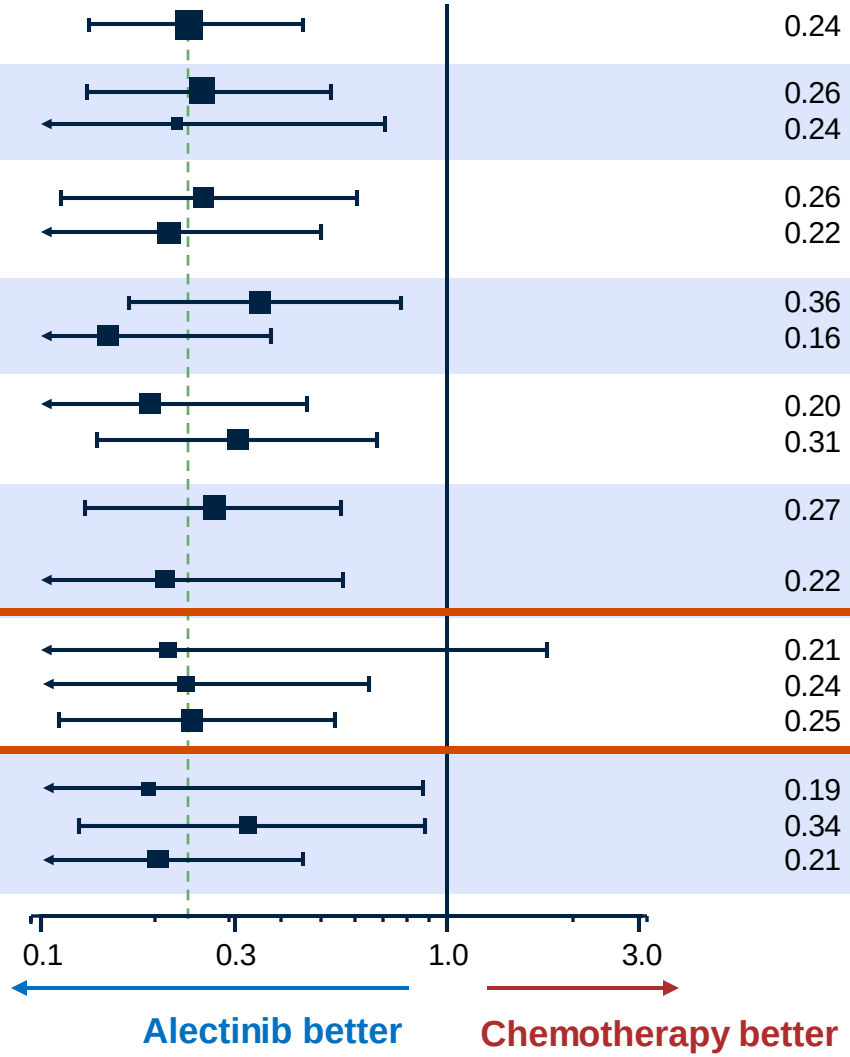
Data cut-off: 26 June 2023; Time from last patient in to data cut off was ~18 months

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

Wu YL et al. N Engl J Med. 2024;390(14):1265-1276.

Disease-free survival subgroup analysis (ITT)

Subgroup		No. of events / patients	DFS HR (95% CI)
All patients		65 / 257	0.24 (0.14–0.43)
Age	<65	43 / 196	0.26 (0.13–0.52)
	≥65	22 / 61	0.24 (0.08–0.71)
Sex	Male	35 / 123	0.26 (0.11–0.60)
	Female	30 / 134	0.22 (0.10–0.50)
Race	Asian	31 / 143	0.36 (0.17–0.79)
	Non-Asian	34 / 114	0.16 (0.06–0.38)
ECOG PS at baseline	0	32 / 137	0.20 (0.09–0.46)
	1	33 / 120	0.31 (0.14–0.69)
Tobacco use history	Never	37 / 154	0.27 (0.13–0.55)
	Current	0 / 8	NE
	Previous	28 / 95	0.22 (0.08–0.57)
Stage*	Stage IB	6 / 26	0.21 (0.02–1.84)
	Stage II	22 / 92	0.24 (0.09–0.65)
	Stage IIIA	37 / 139	0.25 (0.12–0.53)
Regional lymph node status	N0	11 / 39	0.19 (0.04–0.88)
	N1	20 / 88	0.34 (0.13–0.89)
	N2	34 / 130	0.21 (0.09–0.47)



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Data cut-off: 26 June 2023

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

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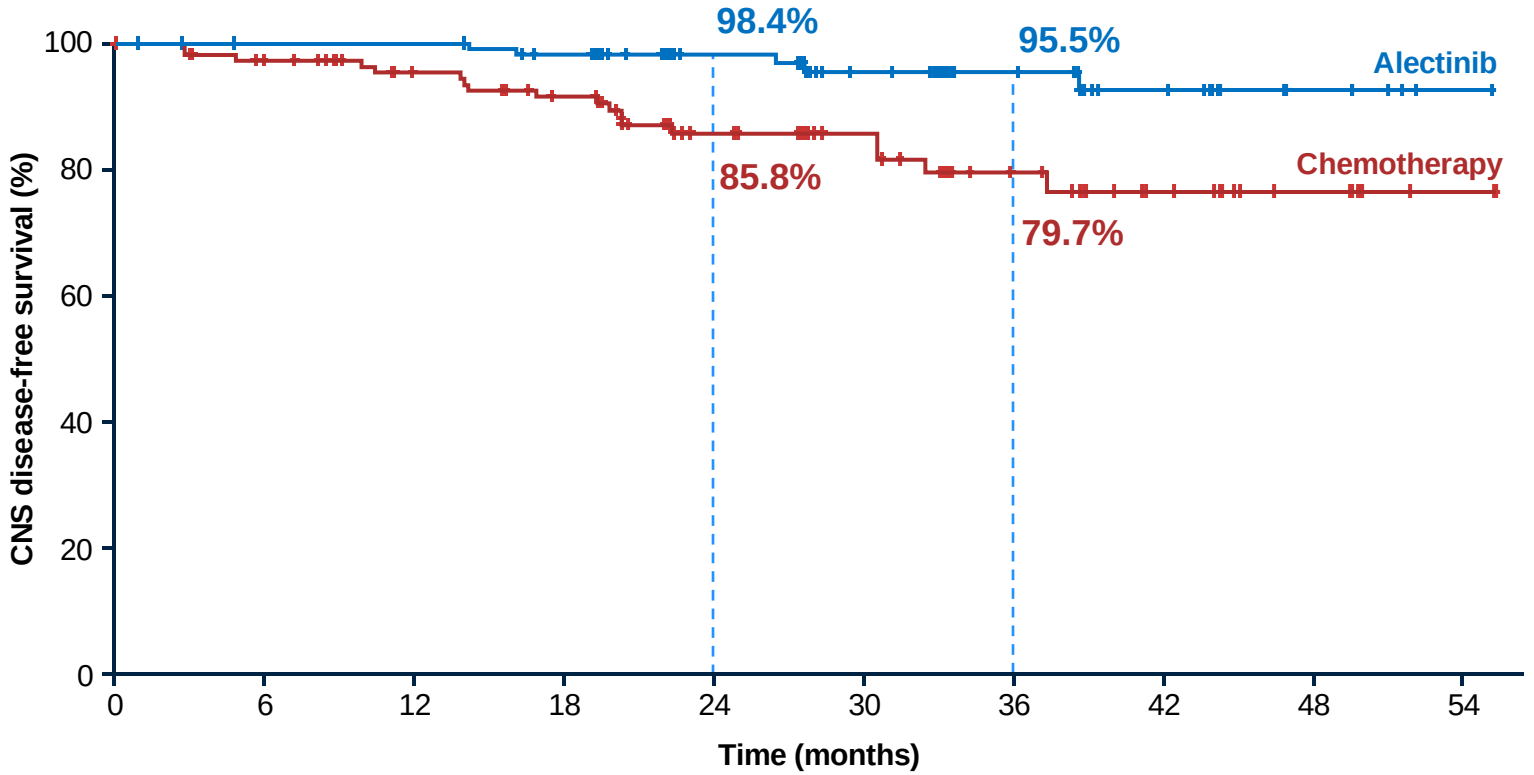
CNS disease-free survival in the ITT population



No. at risk

Alectinib	130	124	124	118	74	55	39	22	10	3
Chemo	127	113	98	90	57	43	27	18	11	2

	Alectinib (N=130)	Chemotherapy (N=127)
Patients with event	5	18
Death	1	4
Brain recurrence	4	14
CNS-DFS HR* (95% CI)	**0.22** (0.08, 0.58)	

Median survival follow up: alectinib, 27.8 months; chemotherapy, 28.4 months

Data cut-off: 26 June 2023

*Stratified analysis with race and stage as stratification factors

CNS-DFS defined as time from randomisation to the first documented recurrence of disease in the CNS or death from any cause

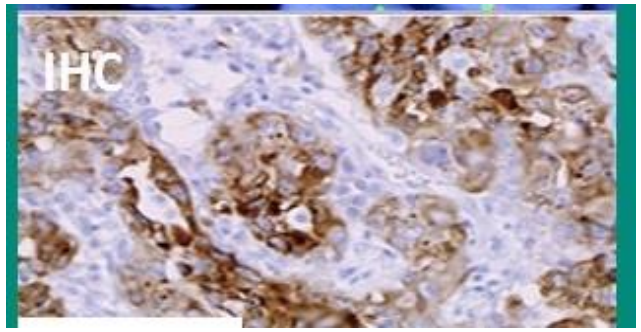
Wu YL et al. N Engl J Med. 2024;390(14):1265-1276.

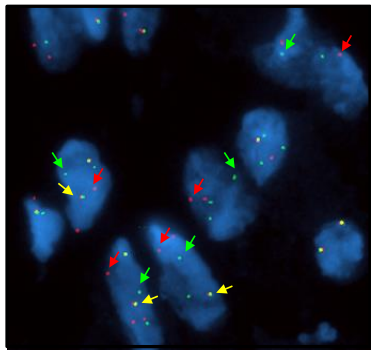
Questions?

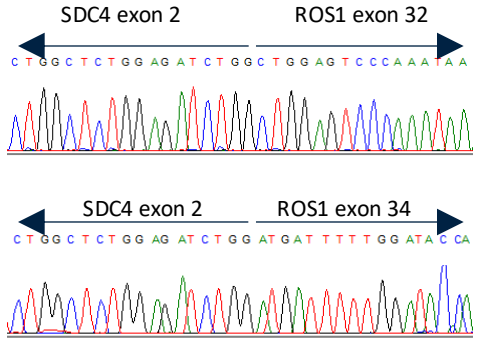
RTP
RESEARCH
TO PRACTICE

ROS1 rearrangements in NSCLC

- Patients with ROS1 rearrangements share many features in common with *ALK+* patients (adenocarcinoma histology, younger age at diagnosis, never or light smokers)
- Rare event occurring in 1-2 % of NSCLC and mutually exclusive with *EGFR, HER2, KRAS, BRAF* mutations and with *ALK* rearrangements
- According to current guidelines, ROS1 testing should be performed on all adenocarcinoma patients irrespective of clinical characteristics (and I'd add all never smokers or remote former smokers regardless of histology)
- Screening test: IHC → positive results confirmed by FISH or other cytogenetic method







- Indicated agents: crizotinib, entrectinib, repotrectinib

Bergethon K, et al. J Clin Oncol 2012; Davies KD, et al. Clin Cancer Res 2012; Kalemkerian GP, et al. JCO 2018

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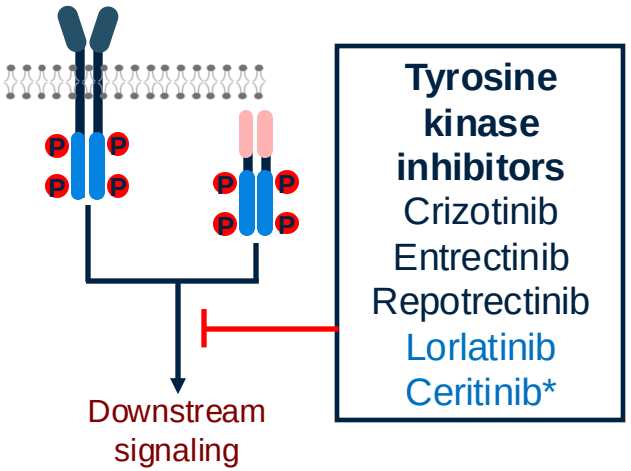
ROS1 Agents with Activity in ROS1 rearrangements[1,2]



Therapy	Trial(s)	Efficacy		CNS Penetration	
		ORR	PFS (mo)	IC-ORR	IC-PFS (mo)
Crizotinib	PROFILE 1001 (NCT00585195)[3,4]	72%†	19.3†	—	—
Entrectinib‡[5]	ALKA STARTRK-1 (NCT02097810) STARTRK-2 (NCT02568267)	77%†	19.0†	55%	13.6§
Repotrectinib	TRIDENT-1 (NCT03093116)[6]	79%	35.7		

Approved therapy MOA: Tyrosine kinase inhibitors; limits downstream signaling

mNSCLC therapy setting:

- First line: crizotinib, entrectinib, and repotrectinib preferred, ceritinib and lorlatinib also yield responses
- Subsequent therapy: depends on extent of progression and prior therapy
- Entrectinib was recommended as first-line or subsequent therapy for patients with CNS metastasis
- **Repotrectinib has displaced both entrectinib and crizotinib as 1st line drug of choice**

*Not approved for this indication. †Assessed by independent review. ‡Pooled analysis.. §Assessed by investigator. Abbreviations: CNS, central nervous system; IC, intracranial; mNSCLC, metastatic non-small cell lung cancer; MOA, mechanism of action; ORR, objective response rate; PFS, progression-free survival; ROS1, proto-oncogene tyrosine-protein kinase. 1. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer V.2.2024. © National Comprehensive Cancer Network, Inc. 2024. All rights reserved. Accessed February 23, 2024. To view the most recent and complete version of the guideline, go online to NCCN.org. 2. Pal P, et al ROS-1. *J Clin Pathol.* 2017;1:1-9. 3. Shaw At, et al. *N Engl J Med*. 2014;371(21):1963-71. 4. Shaw AT, et al. *Ann Oncol.* 2019;30(7):1121-1126. 5. Drilon A, et al. *Lancet Oncol.* 2020;21(2):261-270. 6. Drilon A, et al. *N Engl J Med*. 2024;390(2):118-131.

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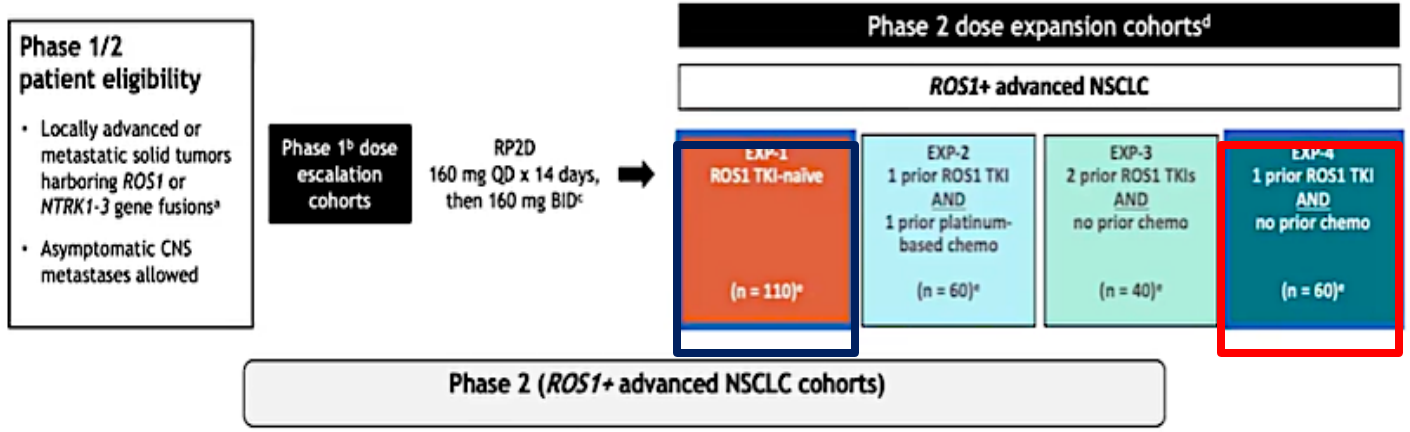
Repotrectinib in ROS1 (+) mNSCLC

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



Primary endpoint

cORR by BICR using RECIST v1.1

Key secondary endpoints

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

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

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

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

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

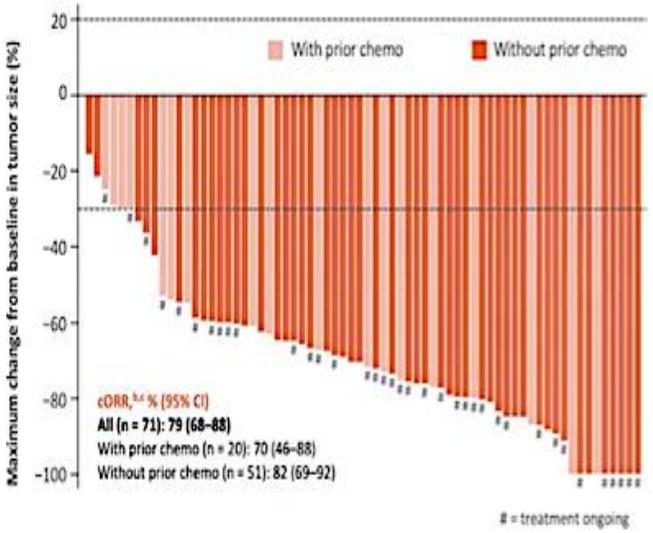
[a]8 (phase 1) + 63 (phase 2). [b]3 + 53. [c]Includes Australia, Canada, and Europe. [d]Identified in tumor tissues by local NGS testing or in plasma ctDNA using the Guardant360 CDx NGS test performed by Guardant Health (or using the GeneseeqLite NGS for patients enrolled in China). [e]In the 1 prior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

Drilon A, Camidge DR, Lin JJ, et al. *N Engl J Med*. 2024;390(2):118-131.

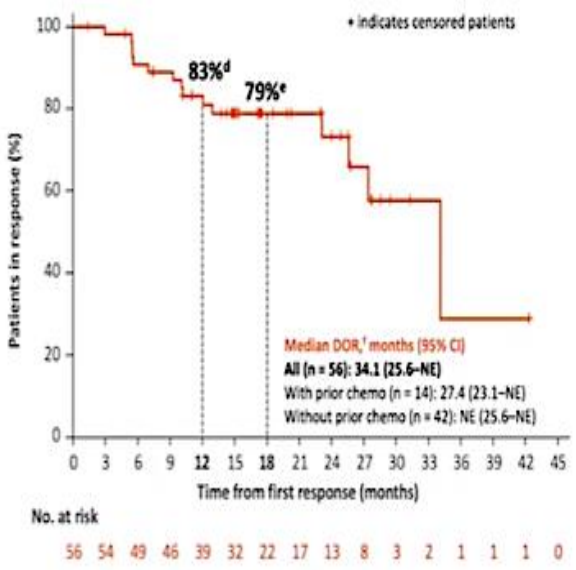
Repotrectinib in Tx-naïve 1L ROS1 (+) mNSCLC

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

Change in tumor burden per BICR[a]



DOR



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

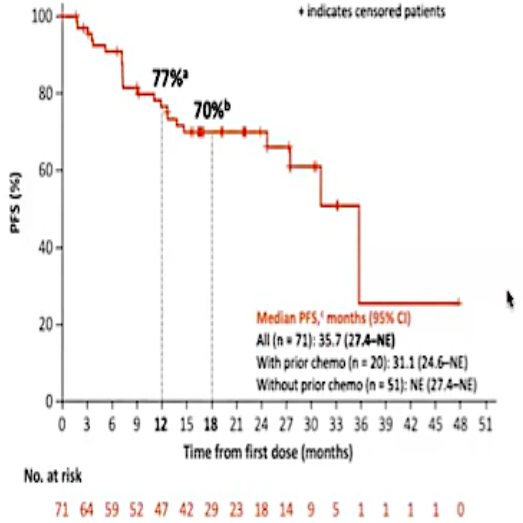
Median follow-up: 24.0 months (range, 14.2–66.6).

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

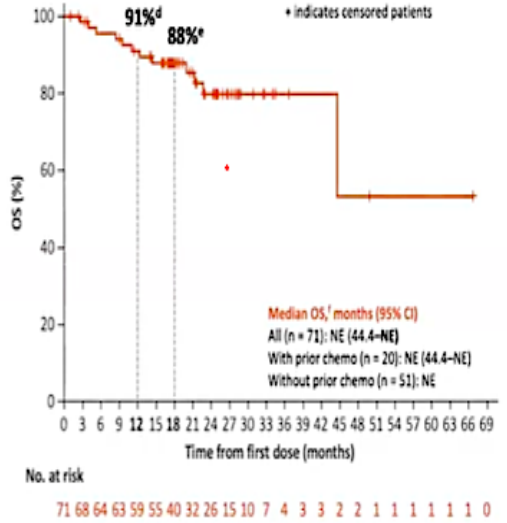
TRIDENT-1 update: Repotrectinib in *ROS1*+ NSCLC

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

PFS



OS



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

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

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

Drilon A, Camidge DR, Lin JJ, et al. *N Engl J Med*. 2024;390(2):118-131.

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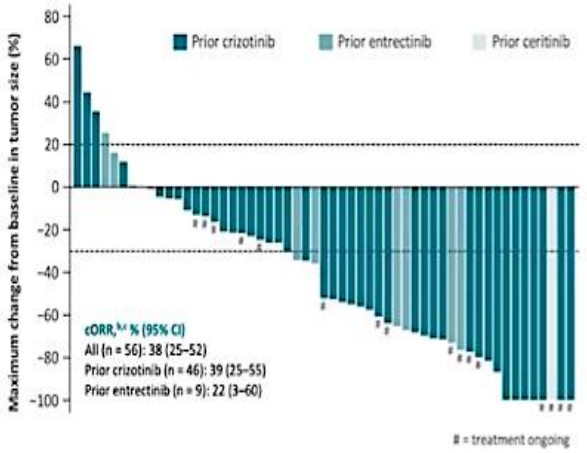
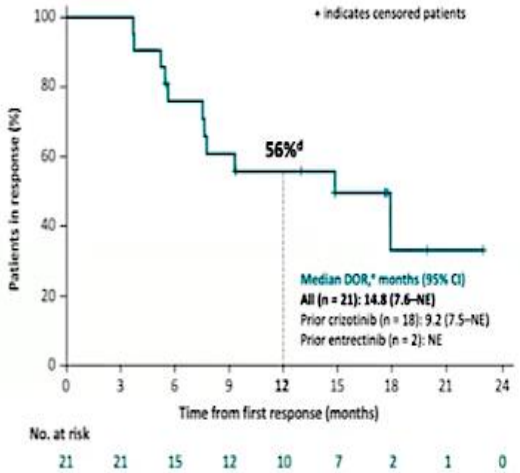
Repotrectinib in 2L ROS1 (+) mNSCLC

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

Change in tumor burden per BICR[a]



DOR



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

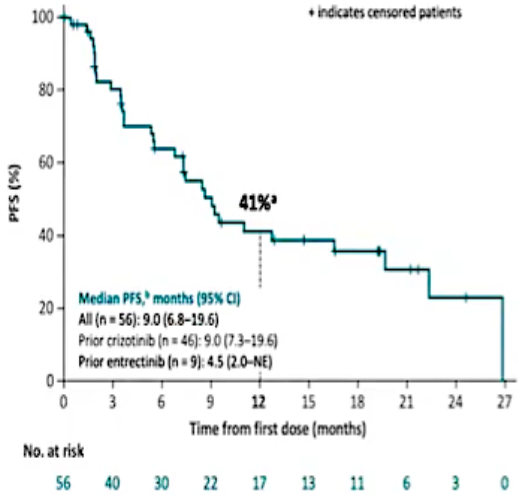
Median follow-up: 21.5 months (range, 14.2–58.6).

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

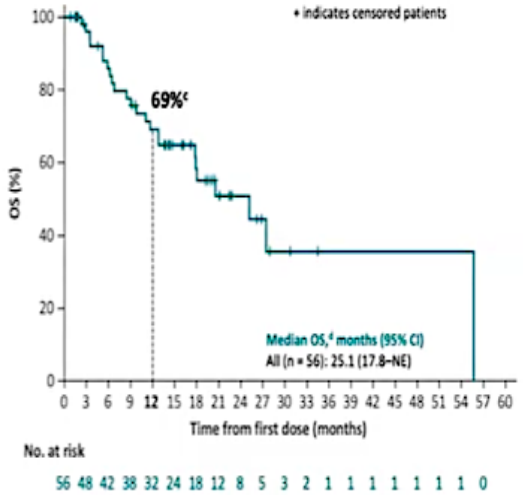
TRIDENT-1 update: Repotrectinib in *ROS1*+ NSCLC

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

PFS



OS



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

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

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

Drilon A, Camidge DR, Lin JJ, et al. *N Engl J Med*. 2024;390(2):118-131.

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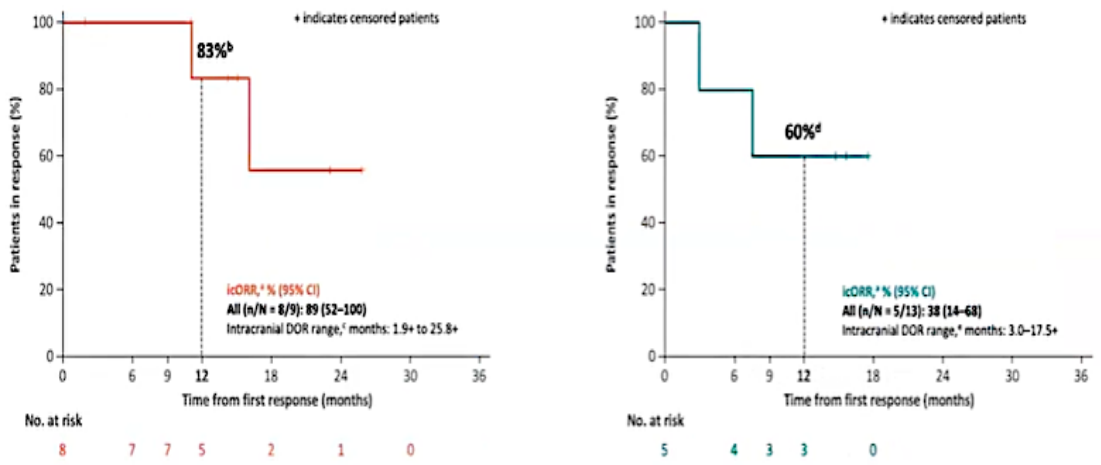
Repotrectinib: CNS Activity

TRIDENT-1 update: Repotrectinib in *ROS1*+ NSCLC

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

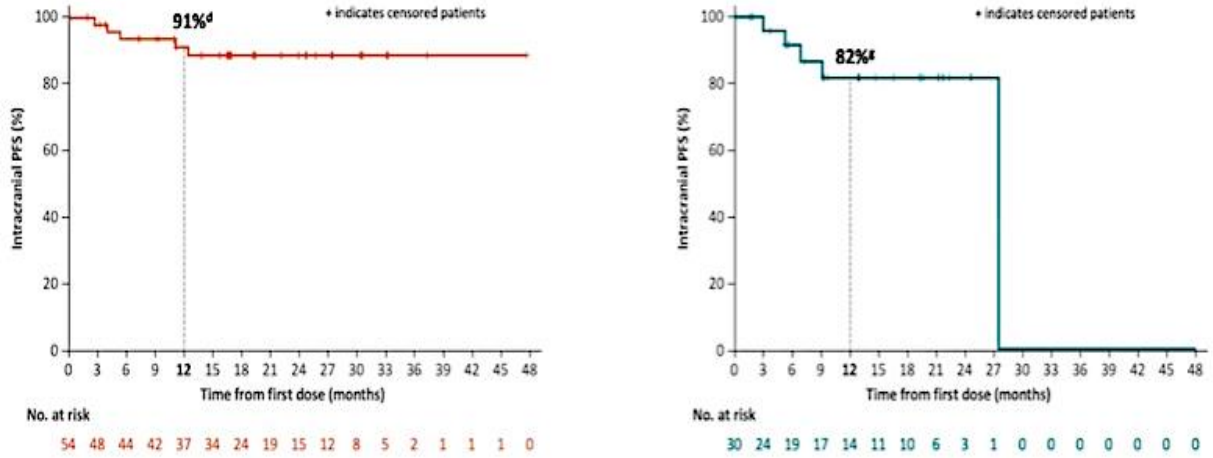


Median follow-up: ROS1 TKI-naïve, 24.0 months (range, 14.2–66.6); 1 prior ROS1 TKI and no prior chemo, 21.5 months (range, 14.2–58.6).

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

TRIDENT-1 update: Repotrectinib in *ROS1*+ NSCLC

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



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

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

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

Drilon A, Camidge DR, Lin JJ, et al. *N Engl J Med*. 2024;390(2):118-131.

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Repotrectinib: Toxicity

Safety summary in patients treated at the RP2D

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

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

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

Safety summary in all treated patients[a]

	All treated patients (N = 444)					
	TEAEs (>20% of patients)			TRAEs		
Adverse events, n (%)	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4[c]
Any AE	442 (99.5)	173 (39.0)	29 (6.5)	416 (93.7)	95 (21.4)	6 (1.4)
Dizziness	272 (61.3)	12 (2.7)	0	150 (56.3)	12 (2.7)	0
Dysgeusia	219 (49.3)	0	0	210 (47.3)	0	0
Constipation	163 (36.7)	1 (0.2)	0	110 (24.8)	0	0
Anemia	153 (34.5)	36 (8.1)	1 (0.2)	98 (22.1)	15 (3.4)	0
Paresthesia	141 (31.8)	3 (0.7)	0	126 (28.4)	3 (0.7)	0
Dyspnea	128 (28.8)[b]	27 (6.1)	6 (1.4)	37 (8.3)	2 (0.5)	0
Fatigue	107 (24.1)	6 (1.4)	0	73 (16.4)	3 (0.7)	0
Nausea	92 (20.7)	3 (0.7)	0	53 (11.9)	0	0
ALT increased	91 (20.5)	7 (1.6)	1 (0.2)	69 (25.5)	5 (1.1)	0

- The most common TEAE was low-grade dizziness (61.3%), which was Grade 1 in 73.2% (199/272) of patients
  - Overall, 19.6% (87/444) of patients reported ataxia; 20 (4.5%) reported ataxia in the absence of dizziness
- Repotrectinib was titrated up to 160 mg BID in 83% of patients
- Dose modifications due to TEAEs: 45% of patients had TEAEs leading to drug interruption, 34% had TEAEs leading to dose reductions, and 9.7% had TEAEs leading to drug discontinuation; no events of dizziness or ataxia led to treatment discontinuation

[a]Safety analysis population includes all Phase 1 and Phase 2 patients across all cohorts who received at least 1 dose of repotrectinib. [b]Grade 5 dyspnea was reported in one patient. [c]Grade 4 TRAEs: not shown 3 patients with transient CPK increase and 1 patient with

Solomon BJ et al. ESMO 2023; Abstract 1372P. Cho BC, Lin JJ, Camidge DR, et al. EORTC-NCI-AACR Molecular Targets and Cancer Therapeutics Symposium 2022; Abstract 2LBA.

TRUST-II (NCT04919811): Phase 2 Trial of Taletrectinib in ROS1+ NSCLC[a]

Key Eligibility Criteria

Inclusion Criteria:

- Locally advanced or metastatic NSCLC
- Age ≥18 years[b]
- ECOG PS 0–1
- Evidence of ROS1 fusion

Cohort 1: ROS1 TKI naive
Taletrectinib 600 mg QD

Cohort 2: 1 Prior ROS1 TKI
Taletrectinib 600 mg QD

Endpoints

Primary:

- IRC-assessed cORR per RECIST v1.1

Secondary:

- DOR
- BOR
- TTR
- Safety[c]
- IC-ORR
- DCR
- PFS

Category	TKI Naive (n=55)[a]	TKI Pretreated (n=50)[a]	Overall (N=159)[c]
Median age, years (range)	57.0 (27–82)	55.0 (27–79)	57.0 (27–83)
Female, n (%)	31 (56.4)	27 (54.0)	89 (56.0)
Never smoker, n (%)	28 (50.9)	30 (60.0)	90 (56.6)
Region, Asia/Non-Asia, n (%)	34 (61.8)/21 (38.2)	22 (44.0)/28 (56.0)	74 (46.5)/85 (53.5)
ECOG PS 0/1, n (%)	22 (40.0)/33 (60.0)	24 (48.0)/26 (52.0)	66 (41.5)/93 (58.5)
Stage IV disease, n (%)	49 (89.1)	49 (98.0)	151 (95.0)
Prior anticancer chemotherapy, n (%)	11 (20.0)	19 (38.0)	64 (40.3)
Brain metastasis, n (%)	19 (34.5)	28 (56.0)	72 (45.3)
Prior crizotinib/entrectinib, n (%)	–	40 (80.0)/10 (20.0)	82 (51.6)/27 (17.0)

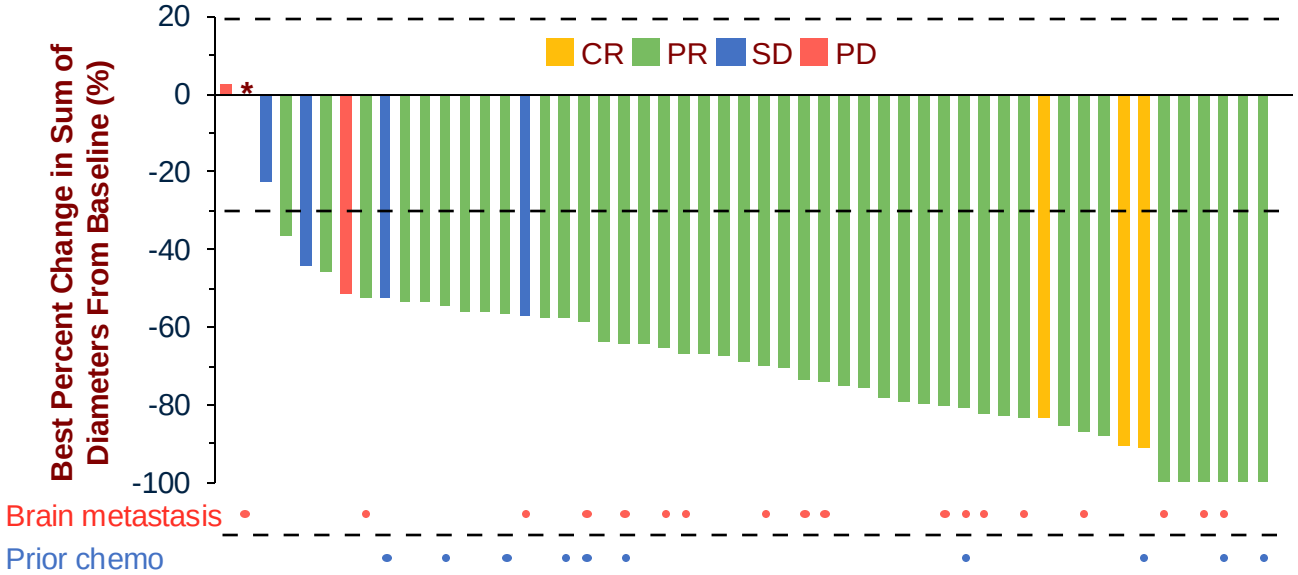
Data cutoff: June 7, 2024. [a]Registrational cohorts are shown. [b]Or ≥20 years, as required by local regulations. [c]Safety population includes all patients who received ≥1 dose of taletrectinib 600 mg. BOR, best overall response; cORR, confirmed objective response rate; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IC, intracranial; IRC, independent review committee; NSCLC, non–small cell lung cancer; PFS, progression-free survival; QD, every day; RECIST, Response Evaluation Criteria in Solid Tumors; TKI, tyrosine kinase inhibitor; TTR, time to response.

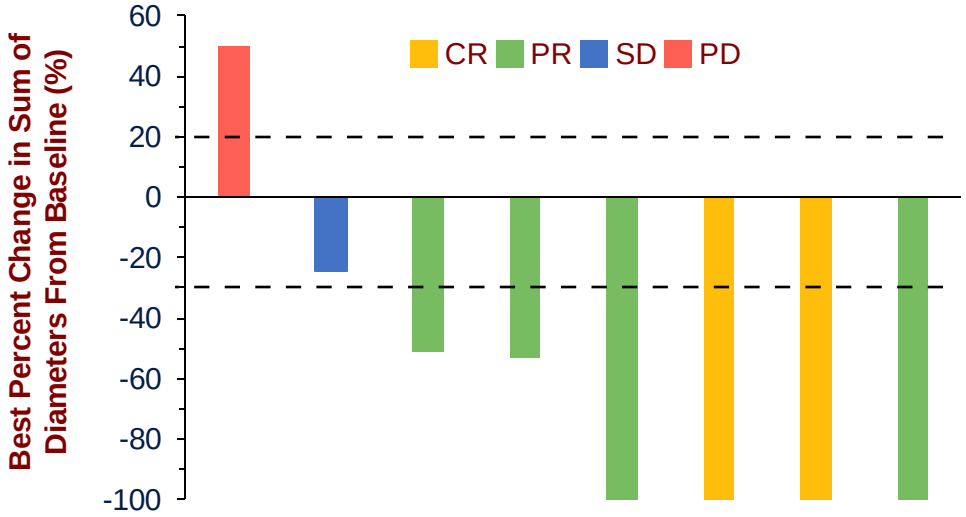
Liu G et al. WCLC 2024; Abstract MA06.03.

Taletrectinib Responses in TKI-Naive ROS1+ NSCLC[a,b]

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

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





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

Data cutoff: June 7, 2024. [a]Response evaluable population (patients with ≥1 measurable lesion at baseline who received ≥1 dose of taletrectinib). [b]Patients with confirmed BOR as not evaluable are not displayed in the waterfall plots. *One patient had a best percent change of 0%. BOR, best overall response; CI, confidence interval; cORR, confirmed objective response rate; CR, complete response; IC, intracranial; DOR, duration of response; NR, not reached; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor.

Liu G et al. WCLC 2024; Abstract MA06.03.

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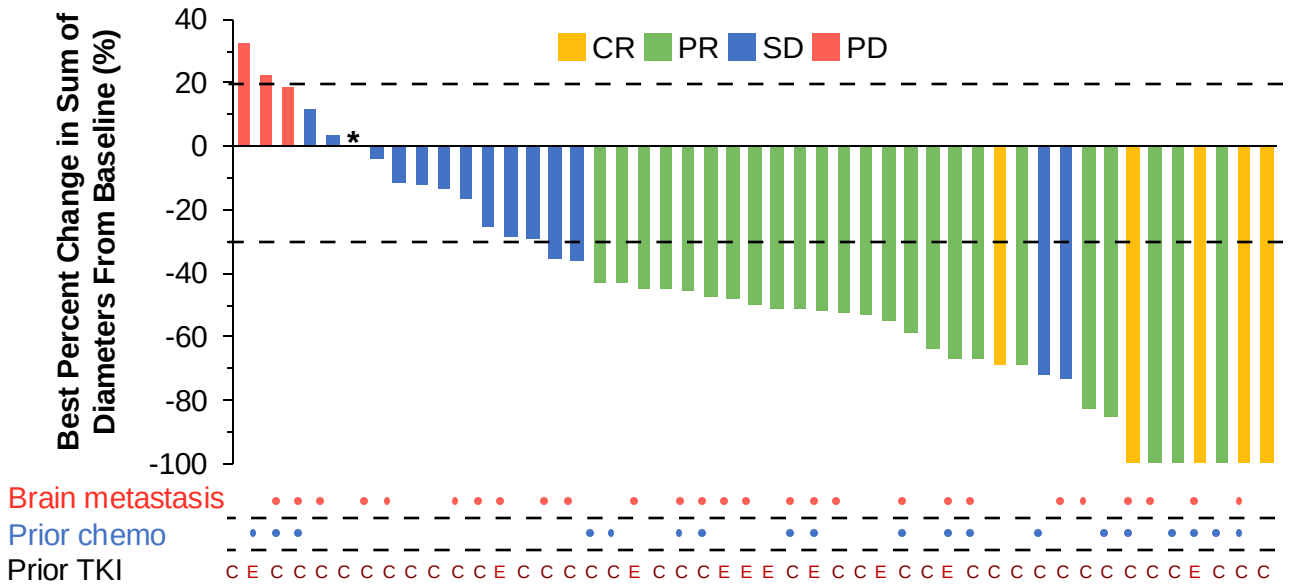
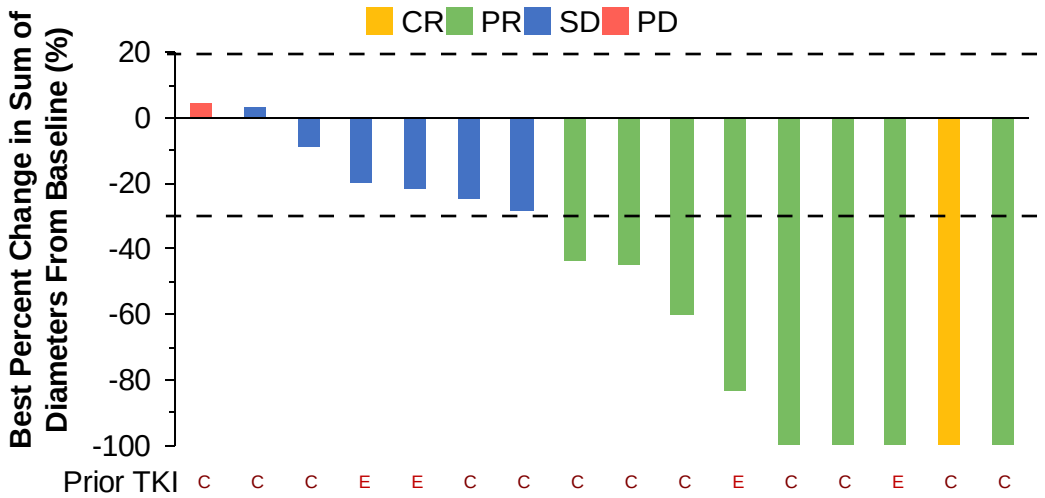
Taletrectinib Responses in TKI-Pretreated ROS1+ NSCLC[a,b]

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

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





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

Data cutoff: June 7, 2024. [a]Response evaluable population (patients with ≥1 measurable lesion at baseline who received ≥1 dose of taletrectinib). [b]Patients with confirmed BOR as not evaluable are not displayed in the waterfall plots. *One patient had a best percent change of 0%. C, crizotinib; CI, confidence interval; cORR, confirmed objective response rate; CR, complete response; E, entrectinib; IC, intracranial; DOR, duration of response; NR, not reached; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor.

Liu G et al. WCLC 2024; Abstract MA06.03.

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Taletrectinib Safety: 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

Data cutoff: June 7, 2024. AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatinine phosphokinase; TEAE, treatment-emergent adverse event.

Liu G et al. WCLC 2024; Abstract MA06.03.

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Zidesamtinib (NVL-520)

Zidesamtinib

Medical need	Crizotinib	Entrectinib	Lorlatinib	Taletrectinib	Repotrectinib	Zidesamtinib
Activity against ROS1 ROS1 fusions are oncogenic drivers in various cancers, including 1 – 3% of NSCLC[3]	Yes	Yes	Yes	Yes	Yes	**Yes**
Brain penetrance CNS metastases are the site of progression in ~50% of patients receiving crizotinib[4]	No	Yes	Yes	Yes	Yes	**Yes**
Activity against resistance mutations ROS1 G2032R develops after progression on crizotinib (~40%), entrectinib, and lorlatinib[5]	No	No	No	Yes	Yes	**Yes**
Avoiding TRK-related neurotoxicities TRK inhibition in CNS is linked to neurologic adverse events and dose-limiting toxicities[6]	Limited brain penetrance	No	No	No	No	**Yes**

▲ **Table 1 | Comparative profile of ROS1 TKIs.** Based on clinical and preclinical observations. Also see Disclaimer.

Disclaimer: As of March 2024, crizotinib, entrectinib, and repotrectinib have been approved by the FDA for the treatment of patients with ROS1+ metastatic NSCLC. Zidesamtinib is being investigated in a Phase 1/2 trial for patients with advanced ROS1+ NSCLC and other solid tumors (ARROS1, NCT05118789). No head-to-head clinical studies have been conducted for approved or investigational therapies versus zidesamtinib. Preclinical experiments are not powered to determine the statistical significance of differences in measurements between any of the inhibitors tested.

Drilon A, Horan JC, Tangpeerachaikul A, et al. *Cancer Discov*. 2023;13(3):598-615. Tangpeerachaikul A et al. AACR 2024; Abstract LB182.

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ARROS-1: A Phase 1/2 Study of NVL-520 in Patients With Advanced NSCLC and Other Solid Tumors Harboring ROS1 Rearrangements

	Cohort	Tumor Type	Treatment Status	Prior ROS1 TKI	Prior Chemo/ Immunotherapy
Potentially registration-directed	2a	ROS1+ NSCLC	ROS1 TKI-naïve	None	Up to 1
	2b	ROS1+ NSCLC	Previously treated with a ROS1 TKI	1	None
	2c			1	1
	2d			2 or more	Up to 1
Exploratory	2e	Any ROS1+ solid tumor	Any Prior Therapy	Any	Any

Key Inclusion Criteria

- Age ≥ 12 years (Patients aged 12 to 17 will only be enrolled in countries and sites where regulations allow)
- Advanced non-small cell lung cancer (NSCLC) or other solid tumor
- Histologically or cytologically confirmed metastatic solid tumor with documented ROS1 rearrangement
- Measurable disease according to RECIST 1.1
- Adequate baseline organ function and bone marrow reserve

Key Exclusion Criteria

- Patient's cancer has a known oncogenic driver alteration other than ROS1
- Major surgery within 4 weeks of study entry
- Actively receiving systemic treatment or direct medical intervention on another therapeutic clinical study

https://clinicaltrials.gov/study/NCT05118789; Manufacturer's website.

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Questions?

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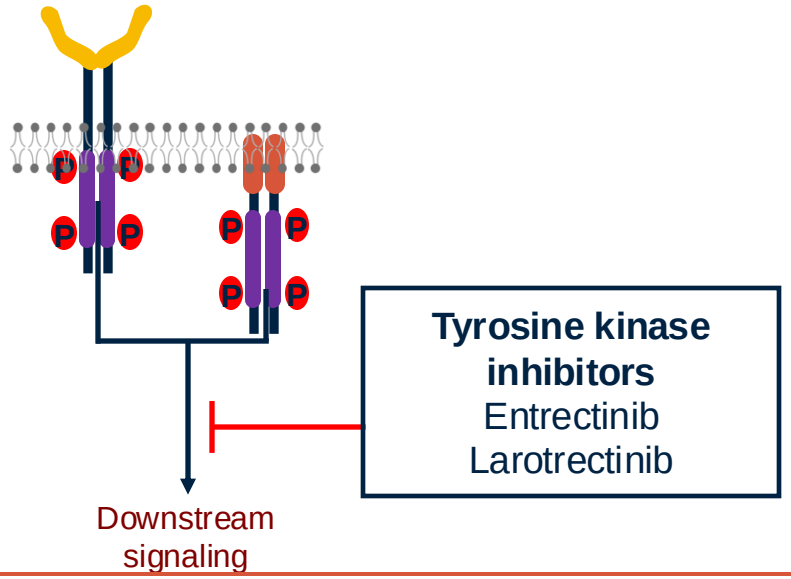
NTRK 1/2/3 Fusions



Protein function: Receptor tyrosine kinase

Actionable driver: 3' sequence of the *NTRK* gene fuses to the 5' sequence of a partner gene, resulting in a TRK fusion protein

Incidence: VERY low, likely < 0.1% of all Non-sq NSCLC

Typical clinical characteristics: difficult to classify due to rarity of fusions and small sample size of previous studies

Approved therapy MOA:

-- Entrectinib – pan-TRK–, ROS1-, and ALK-TKI;

-- Larotrectinib – pan-TRK–TKI; blocks downstream signal

mNSCLC therapy setting:

- First line: larotrectinib and entrectinib preferred
- Subsequent therapy: depends on histology and prior therapy

Therapy	Trial(s)	Efficacy		CNS Penetration	
		ORR	PFS (mo)	IC-ORR	IC-PFS (mo)
Entrectinib*†[3]	ALKA STARTRK-1 (NCT02097810) STARTRK-2 (NCT02568267)	64.5%	20.8	60%	8.9
Larotrectinib*‡[4]	LOXO-TRK-14001 (NCT02122913) NAVIGATE (NCT02576431)	73%	35.4	—	—

*Pooled analysis. †Assessed by independent review. ‡Investigator assessed. Abbreviations: EGFR, epidermal growth factor receptor; mNSCLC, metastatic non-small cell lung cancer; MOA, mechanism of action; ORR, objective response rate; PFS, progression-free survival; TKI, tyrosine kinase inhibitor; TRK, tropomyosin receptor kinase.

1. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer V.2.2024. © National Comprehensive Cancer Network, Inc. 2024. All rights reserved. Accessed February 23, 2024. To view the most recent and complete version of the guideline, go online to NCCN.org. 2. Liu F, et al. *Front Oncol.* 2022;12:864666. 3. Cho BC, et al. *J Clin Oncol.* 2023;41(suppl_16):9047..4. Drilon A, et al. *JCO Precis Oncol.* 2022;6:e2100418.

Repotrectinib in patients with NTRK fusion-positive advanced solid tumors, including NSCLC: Phase 1/ 2 TRIDENT-1 trial

On June 13, 2024, the FDA granted accelerated approval to repotrectinib for adult and pediatric patients 12 years and older with solid tumors that have a neurotrophic tyrosine receptor kinase gene fusion, are locally advanced or metastatic or where surgical resection is likely to result in severe morbidity, and that have progressed following treatment or have no satisfactory alternative therapy.

	TRK TKI-naïve patients with *NTRK*+ NSCLC (n = 21)	TRK TKI-pretreated patients with *NTRK*+ NSCLC (n = 14)
cORR,[a] % (95% CI) CR, n (%) PR, n (%)	62 (38–82) 2 (10) 11 (52)	43 (18–71) 0 6 (43)
CBR,[a] % (95% CI)	86 (64–97)[b]	57 (29–82)[c]
12-mo DOR, % (95% CI)	92 (76–100)	44 (1–88)
12-mo PFS, % (95% CI)	64 (43–86)	23 (0–49)
Median time to response, mo (range)	1.8 (1.6–3.9)	1.9 (1.8–2.0)

[a]By RECIST v1.1. [b]CBR was defined as CR + PR + SD; 24% (n = 5) and 5% (n = 1) of patients, respectively, had SD or PD. [c]CBR was defined as CR + PR + SD; 14% (n = 2) and 21% (n = 3) of patients, respectively, had SD or PD.
CR, complete response; mo, month; PD, progressive disease; PR, partial response; SD, stable disease.

Solomon B et al. ESMO 2023; Abstract 1372P.

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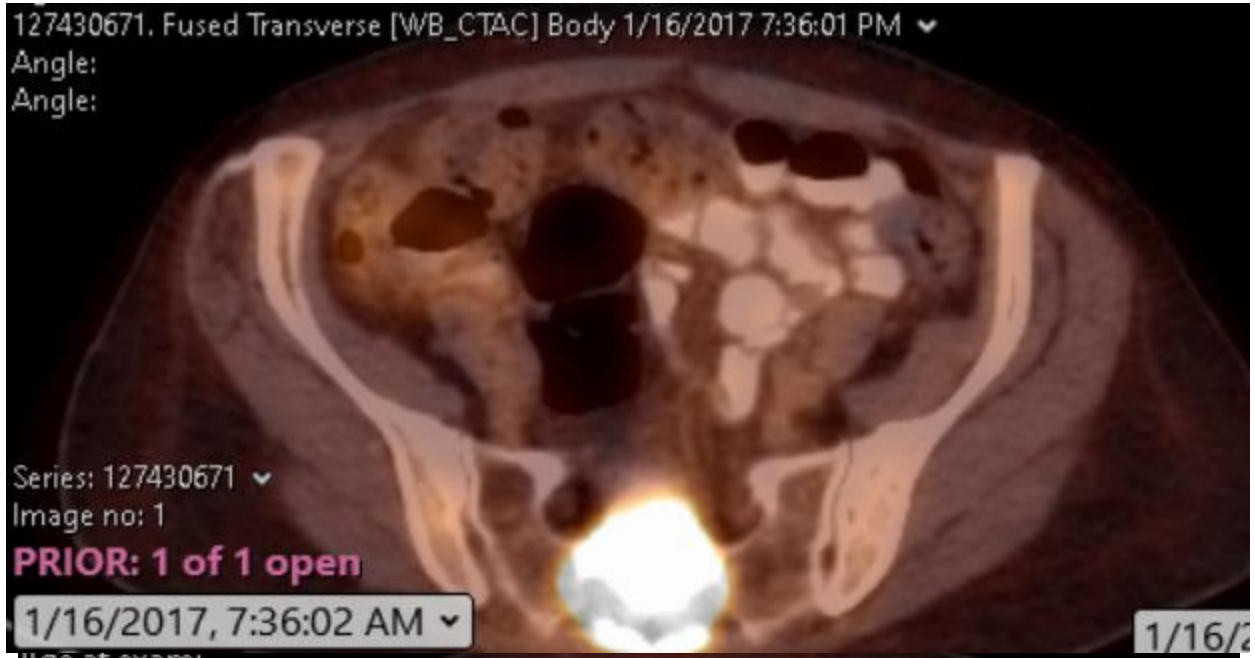
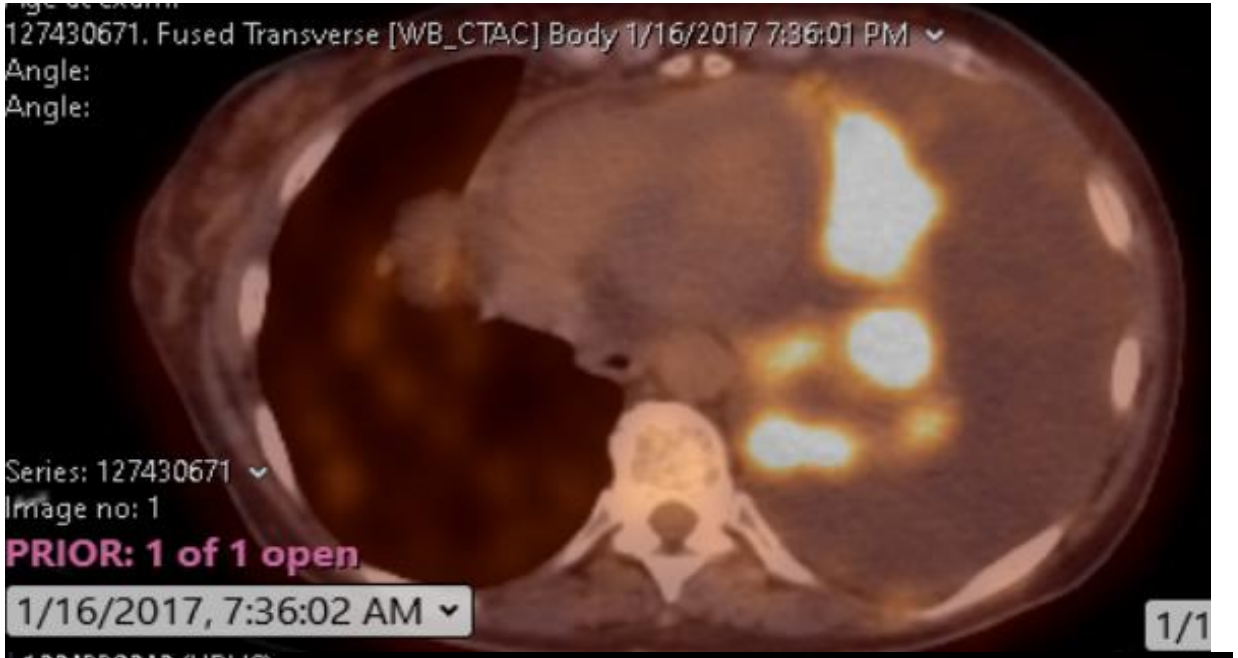
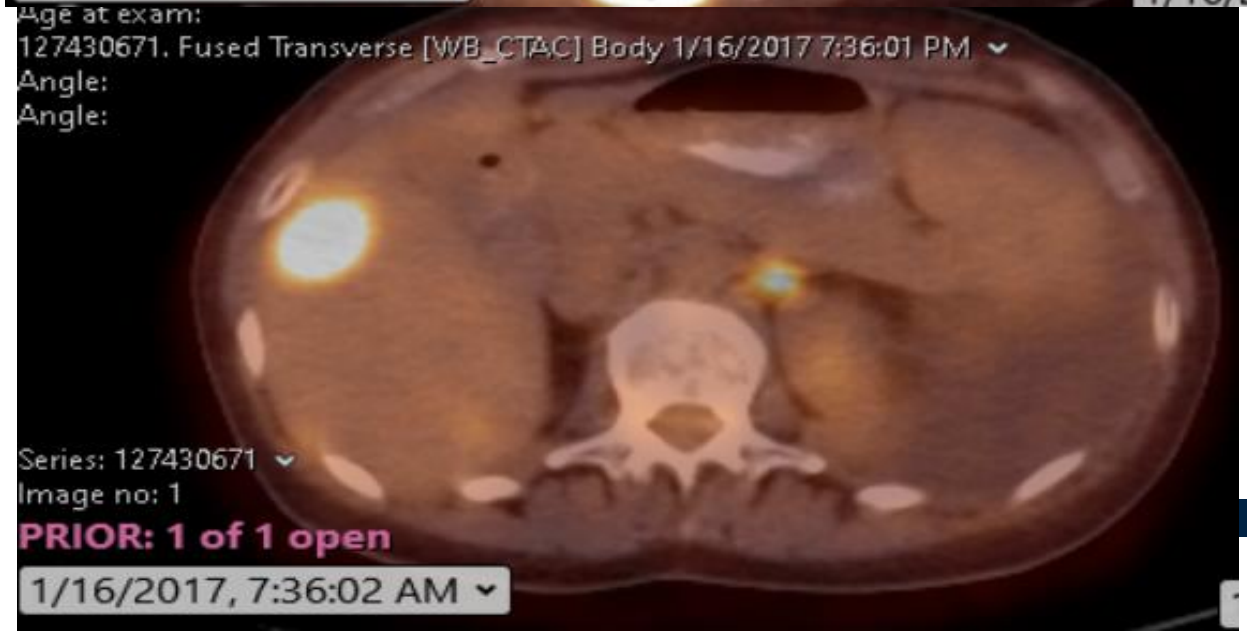
Case Presentation – Dr Langer: 52 yo WF - ROS1 (+) mNSCLC

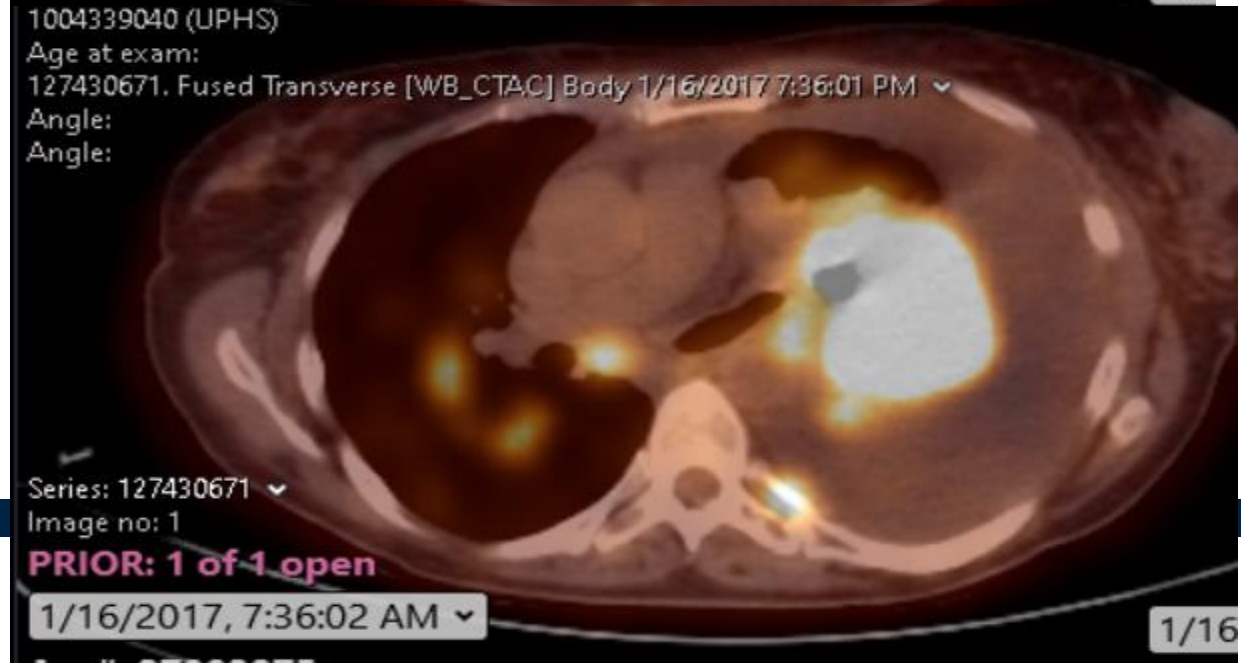
- **HPI (12/27/16):** 52 yo WF never smoker presented to OSH ER in 11/16 with 7 lb weight loss, increasing cough, DOE and LUQ pain --> ribs.
- Sx prompted abdominal US, which showed a small L pl effusion; normal liver, bile duct, GB and pancreas.
- CXR showed multiple pulmonary nodules suspicious for cancer, with large, semi-lucent LUL mass.
- CT demonstrated a solid LUL mass measuring 56 x 46 mm with consolidation in the anterior lingula;
- It also showed a discrete 28 mm mass in the LLL and 20 mm mass in anterior LLL, along with innumerable additional bilateral pulmonary nodules, as well as moderate L pleural effusion.
- Additional findings:
  - 13 x 13 mm infracarinal LN
  - Sclerotic lesions in the mid-sternum and T12
  - 2.4 cm hypodense lesion in the posterior segment of the R hepatic lobe ; < 1 cm lesion in the L hepatic lobe.
- Seen by Pulmonary who recommended a CT guided bx of the LUL, which was performed on 11/09/16
- Pathology proved c/w adenocarcinoma of lung origin.
- Additional testing included EGFR, ALK, ROS1 and PDL1 was initially deemed (-)
- Ultimately, pt was recommended to consider systemic chemo, but has opted for naturopathic approaches
- Over 6 wks on various vitamins and supplements, cough improved, but she continued to lose wt and noted progressive DOE.
- PET imaging ordered

Case Presentation – Dr Langer: 52 yo WF - ROS1 (+) mNSCLC (Continued)



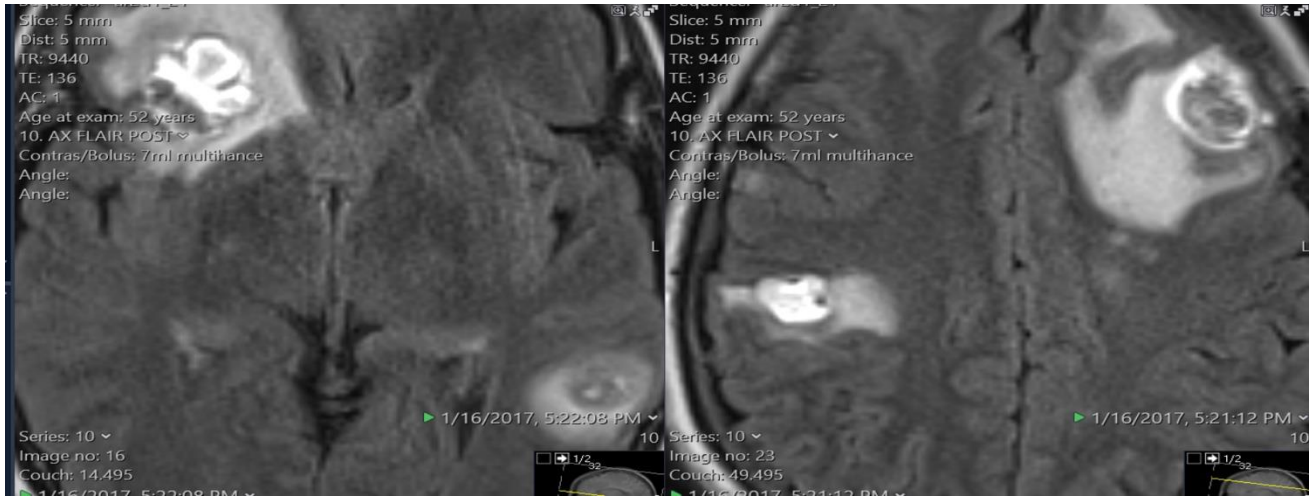






Case Presentation – Dr Langer: 52 yo WF - ROS1 (+) mNSCLC (Continued)

- **MRI: multiple CNS mets, TNTC**
- **Stage:** IV (bone, liver, lung, brain, nodal)
- **Repeated molecular markers:**
  - EGFR (-)
  - KRAS (-)
  - ALK (-)
  - BRAF (-)
  - **ROS1 (+): 16% of 200 nuclei had separation of the 3' ROS1 and 5' ROS1.Interval**



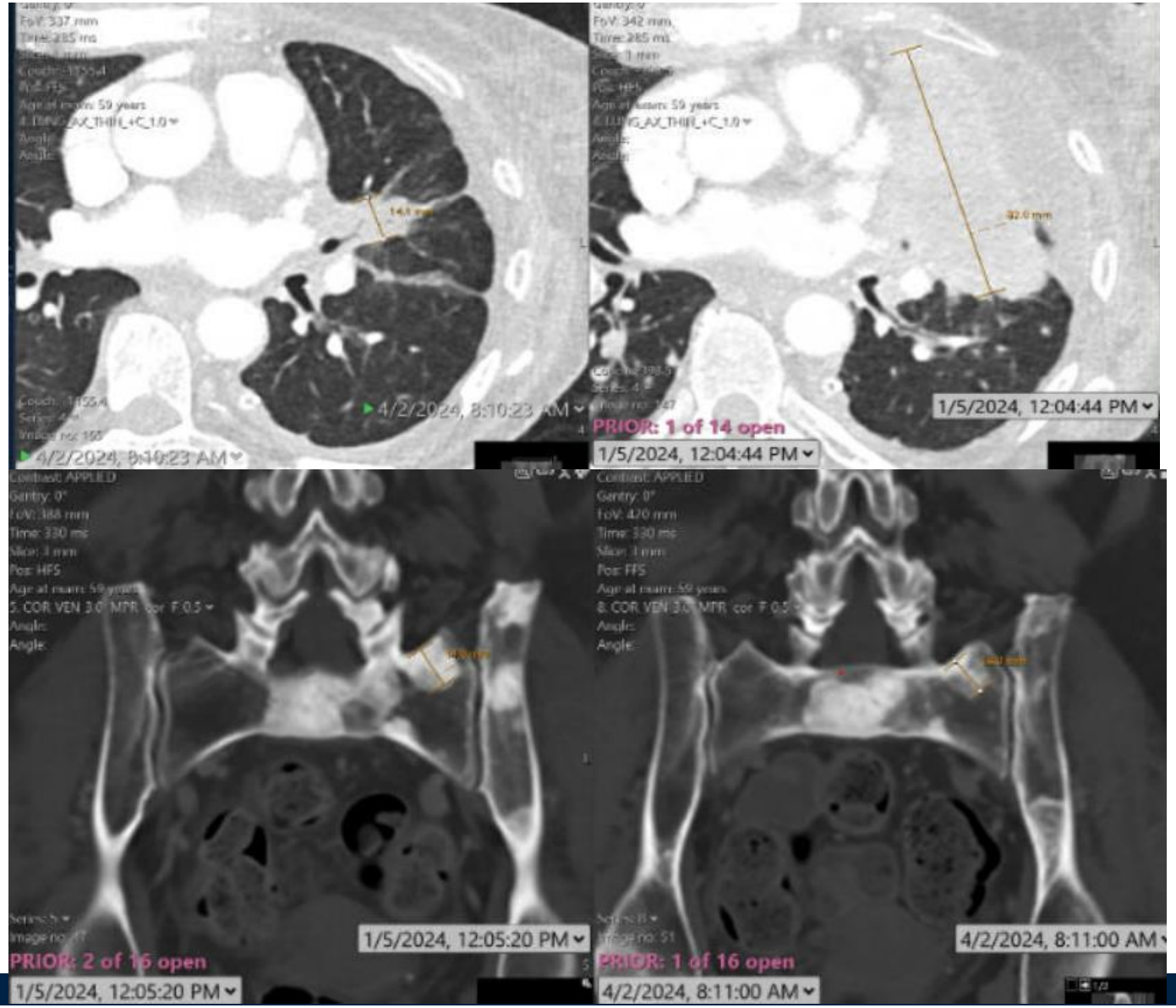
- **01/19/17:** pt was feeling worse with increasing DOE and declining appetite. No neurologic Sx, x for occasional HAs. **Started crizotinib and began WBRT.** Remained on assorted vitamin supplements, but began to question their utility. No other complaints.
- **Interval Hx 02/16/17**: pt returned in follow-up for 2 week toxicity evaluation on crizotinib. S/p WBRT. Her energy and appetite were good with less insomnia. LUQ pain had resolved s/p thoracentesis x 2.
- She noted mild bilateral LE edema, which started after initiating dexamethasone and crizotinib, prompting steroid taper.
- Pt also noted brief visual disturbances (flashing lights), mostly at night. No lightheadedness, only mild DOE.

Case Presentation – Dr Langer: 52 yo WF - ROS1 (+) mNSCLC (Continued): Tx Course (1)

- **01/17:** began Crizotinib, completed WBRT: Major response in all sites
- **SRS 11/09/18** with repeat GK **SRS 01/11/19** to 5 separate Asx'ic sites, all < 10 mm:.
- **05/26/22:** Smoldering PD - LUL and L hilar LN, all other sites resolved/improved
- **09/01/22**: Increasing pace of PD - oligo PD in LUL, new CNS lesions, each 1-3 mm; other sites stable
- **11/22:** GK for 15 lesions. Crizotinib continued
- **03/02/23:** Continued PD - LUL with increasing L pleural effusion; stable bone mets
- **04/10/23 - 04/13/23:** Lorlatinib initiated at 50% dose, but c/b intractable dizziness, fatigue, anxiety and insomnia. Pt paused lorlatinib, then resumed after 4 wks, but dev'd similar Sx at 25% dose
- **06/08/23:** PD - LUL, pleura, pulmonary nodules, bones (sacrum, spine); new onset LBP
- **07/23:** Palliative XRT to sacral bone mets
- **07/23:** Entrectinib started at 1/3 dose; stopped by 09/23, c/b profound fatigue and anorexia
- **07/23 – 01/24**: Off Tx, diminishing PS, new sites of bone pain. Needed L pleurex catheter. Declined chemo

Case Presentation – Dr Langer: 52 yo WF - ROS1 (+) mNSCLC (Continued): Tx Course (1)

- **Palliative XRT to T10**, finished 01/31/24
  01/09/24: Started repotrectinib, after multiple delays:
- **By 1/30/24 -** 50% dose due to toxicity, but felt better by 2/19/24, prompting dose increase to 80mg BID
- **04/02/24 - 07/16/24:** Profound PR
- Has required periodic SRS for growing CNS lesions in interim
- **09/09/24: Current side effects**: grade 1-2 peripheral edema, fatigue, and constipation



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Agenda

Introduction: A Model for Targeted Treatment in Non-Small Cell Lung Cancer (NSCLC)

Module 1: NSCLC with ALK, ROS1 and NTRK Rearrangements — Dr Langer

Module 2: Current and Future Treatment of Metastatic NSCLC with RET, MET, HER2 and KRAS Alterations — Dr Dagogo-Jack

RTP RESEARCH TO PRACTICE

Case Presentation – Dr Dagogo-Jack: Stage IV *RET*-Rearranged NSCLC

- A 69-year-old with a remote 12 pack year smoking history presented with cervical radiculopathy prompting a CXR and neck x-ray which demonstrated a RML opacity.
- CT chest confirmed a 2.7 cm RML nodule without associated lymphadenopathy. Brain MRI and PET did not demonstrate metastases.
- Bronchoscopy/EBUS confirmed a diagnosis of NSCLC without nodal involvement. He subsequently underwent right middle lobe wedge resection with pathology consistent with lung adenocarcinoma—stage IA (pT1cN0M0).
- No adjuvant therapy was advised.
- 1 year later, he developed an enlarging subcutaneous nodule. Biopsy confirmed metastatic lung cancer. Restaging studies, including brain MRI and PET, demonstrated a solitary 1 cm frontal metastasis, findings concerning for suture line recurrence, and multifocal osseous uptake.
- RNA NGS identified a *KIF5B-RET* rearrangement.
- He commenced treatment with Selpercatinib. He tolerated the medication with side effects of hypertension and dry mouth.
- 3 years into treatment, he developed progression of the frontal (CNS) metastasis prompting craniotomy and resection. Molecular testing demonstrated a G810S solvent front mutation.
- He continued on Selpercatinib until 9 months later when he developed symptomatic leptomeningeal disease and transitioned to hospice.

World Lung Targeted Lung Webinar September 2024

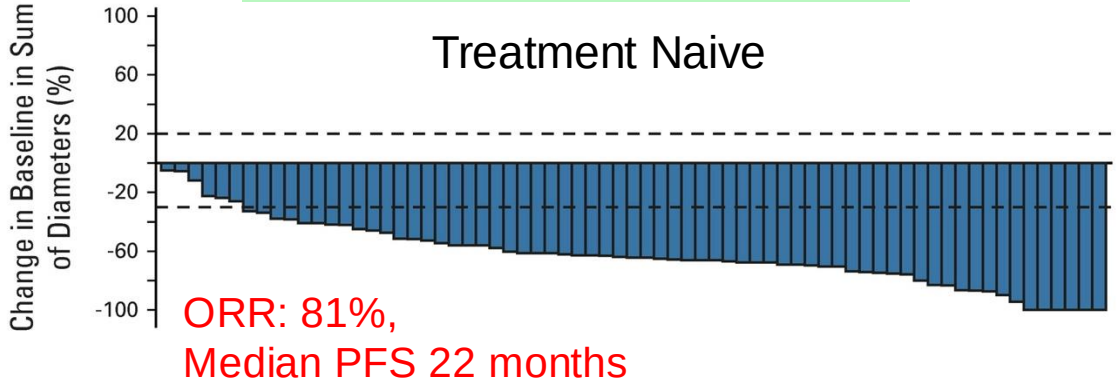
Ibiayi Dagogo-Jack, MD
Assistant Professor of Medicine
Massachusetts General Hospital Cancer Center
Harvard Medical School

RET-Rearranged NSCLC: Current Management

Selpercatinib and Pralsetinib are both FDA-approved for treatment of *RET*-rearranged NSCLC

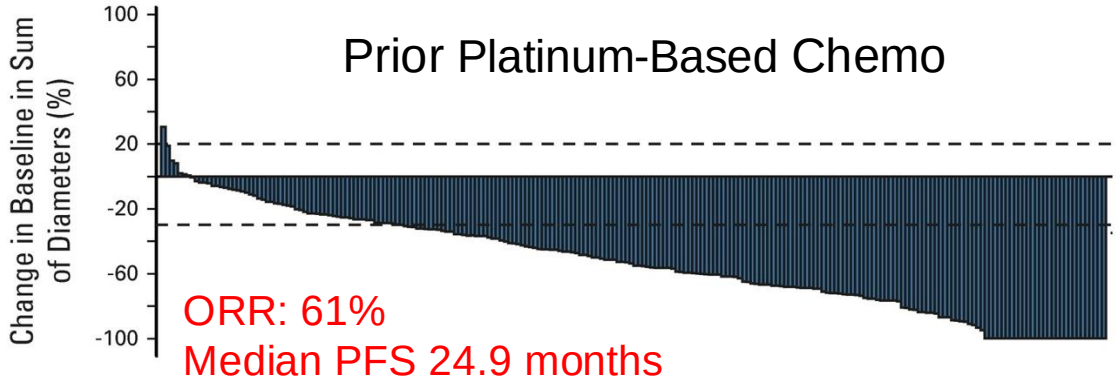
Selpercatinib

Treatment Naive



ORR: 81%,
Median PFS 22 months

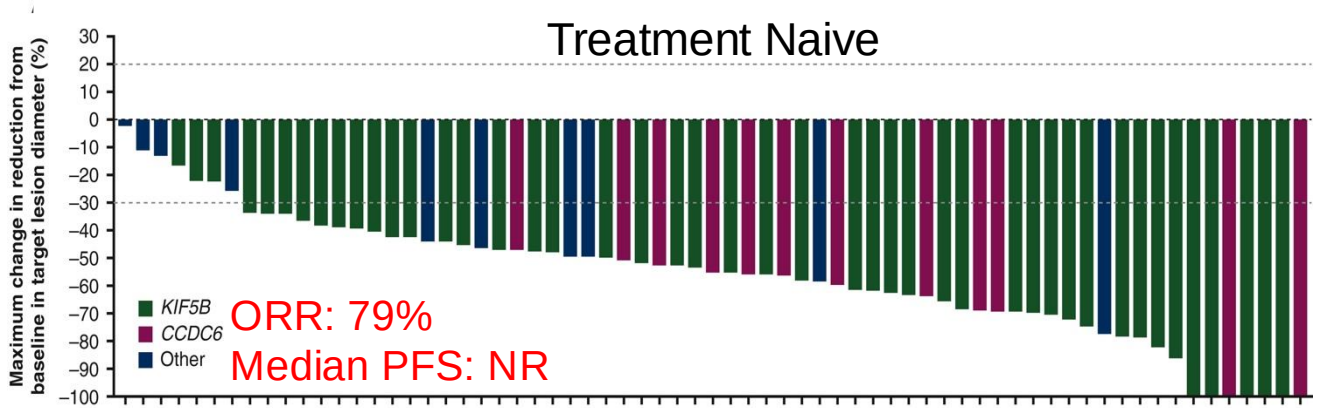
Prior Platinum-Based Chemo



ORR: 61%
Median PFS 24.9 months

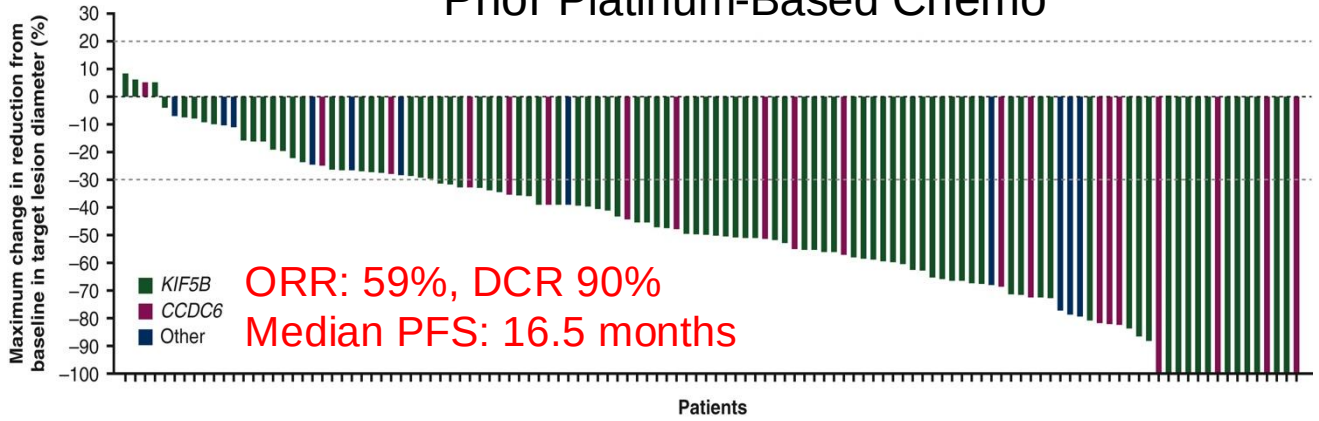
Pralsetinib

Treatment Naive



ORR: 79%
Median PFS: NR

Prior Platinum-Based Chemo

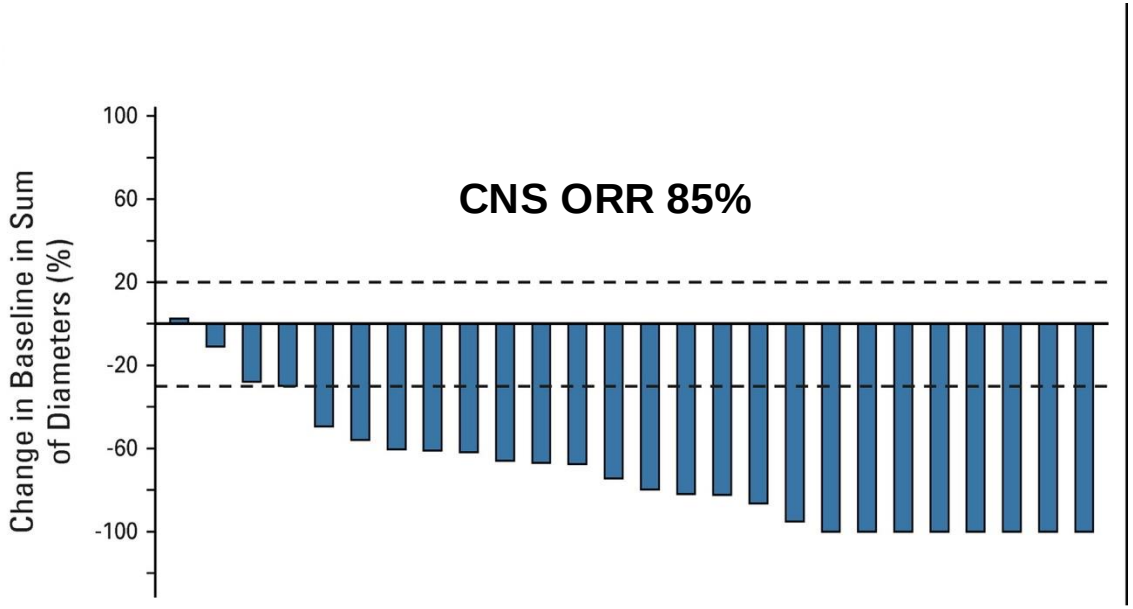


ORR: 59%, DCR 90%
Median PFS: 16.5 months

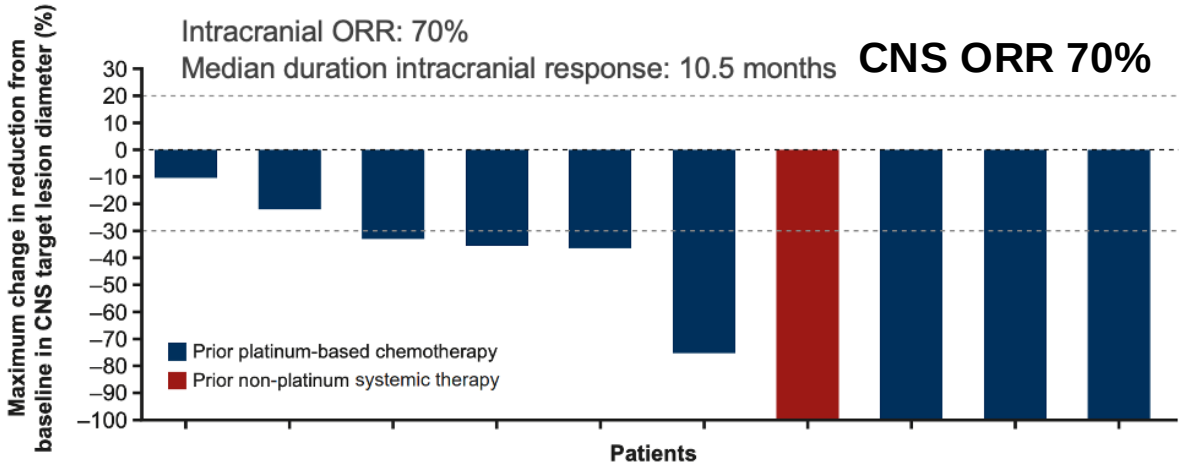
Drilon JCO 2023, Greisinger Annals of Oncology 2022

Intracranial Activity of Selpercatinib and Pralsetinib

Selpercatinib



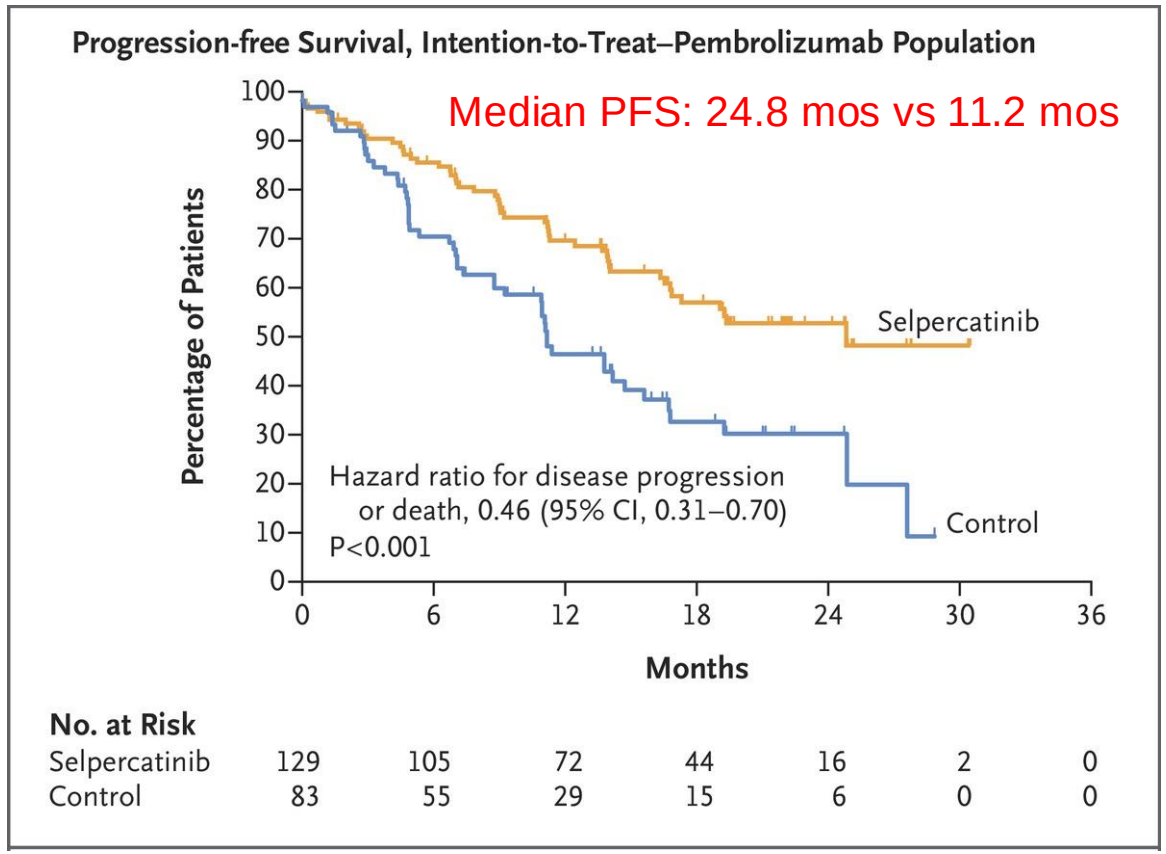
Pralsetinib

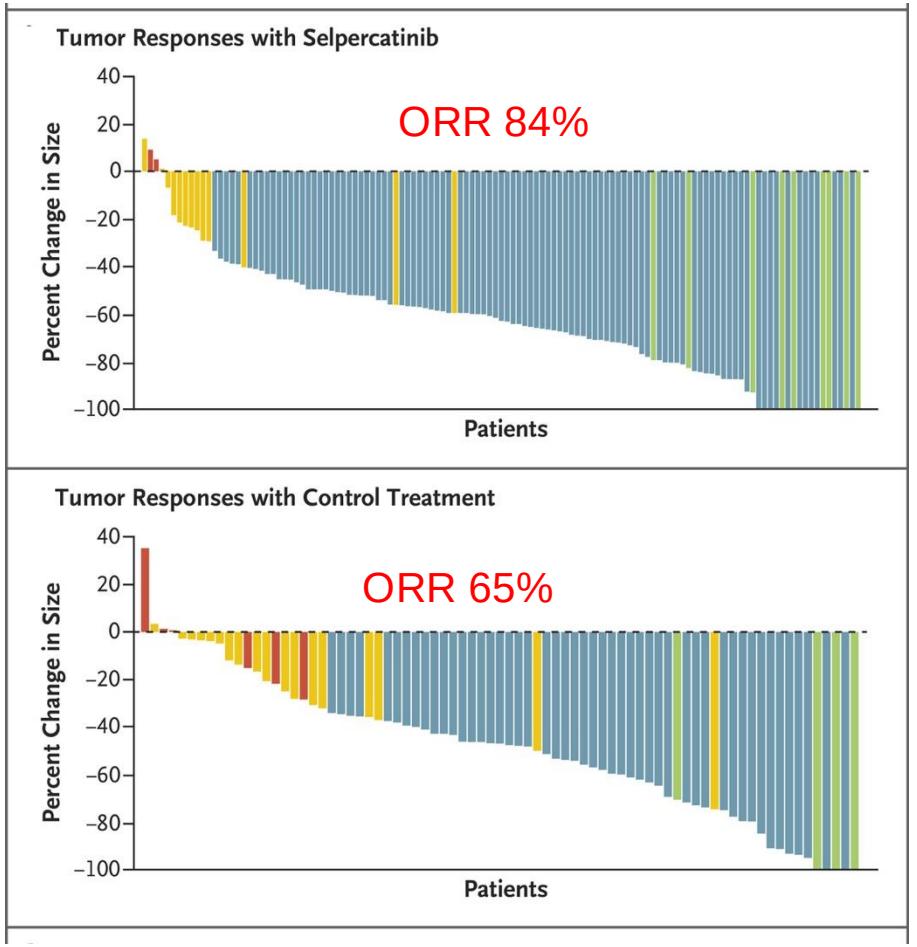


Drilon JCO 2023, Greisinger Annals of Oncology 2022

1st Line Selpercatinib: LIBRETTO-431

- Global randomized phase III study comparing Selpercatinib to chemo +/- immunotherapy in 1st line
- Initially 1:1 randomization, ultimately 2:1 (overall 1.6:1).
- Crossover occurred in 60% of pts in control arm + additional 15% of pts received a RET TKI outside of study





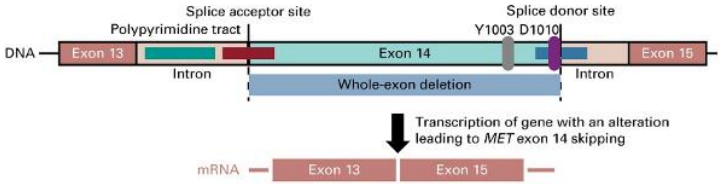
Selpercatinib CNS ORR
82%

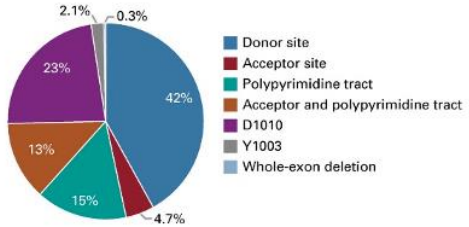
ChemoIO CNS ORR
58%

Zhou NEJM 2023

Diverse MET Alterations in NSCLC

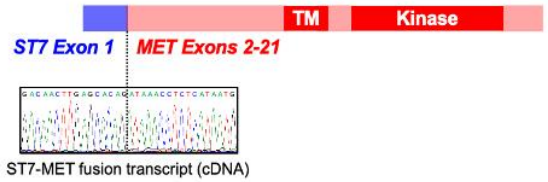
Mutations





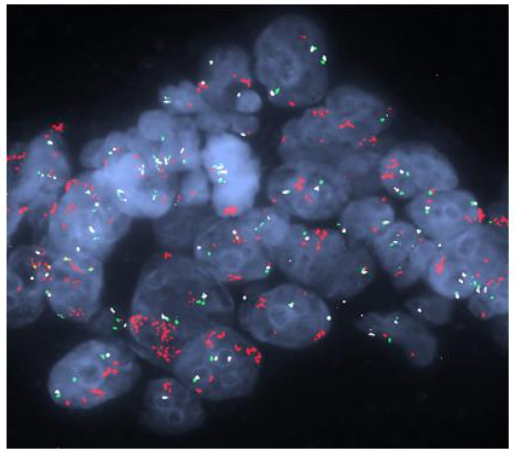
- Present in ~3% of NSCLCs
- Exon 14 skipping mutations are the most common
- Can co-occur with MET amplification

Rearrangements



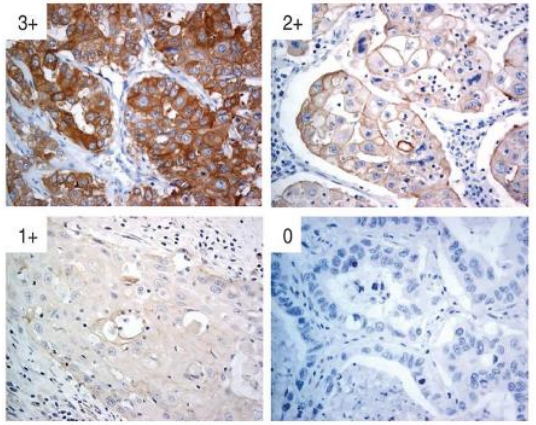
- Very rare, identified in 0.5% of NSCLCs

Amplification



- Seen in 3-5% of NSCLC de novo
- Can overlap with other alterations (e.g., EGFR, ALK, RET, ROS1, KRAS)

Overexpression

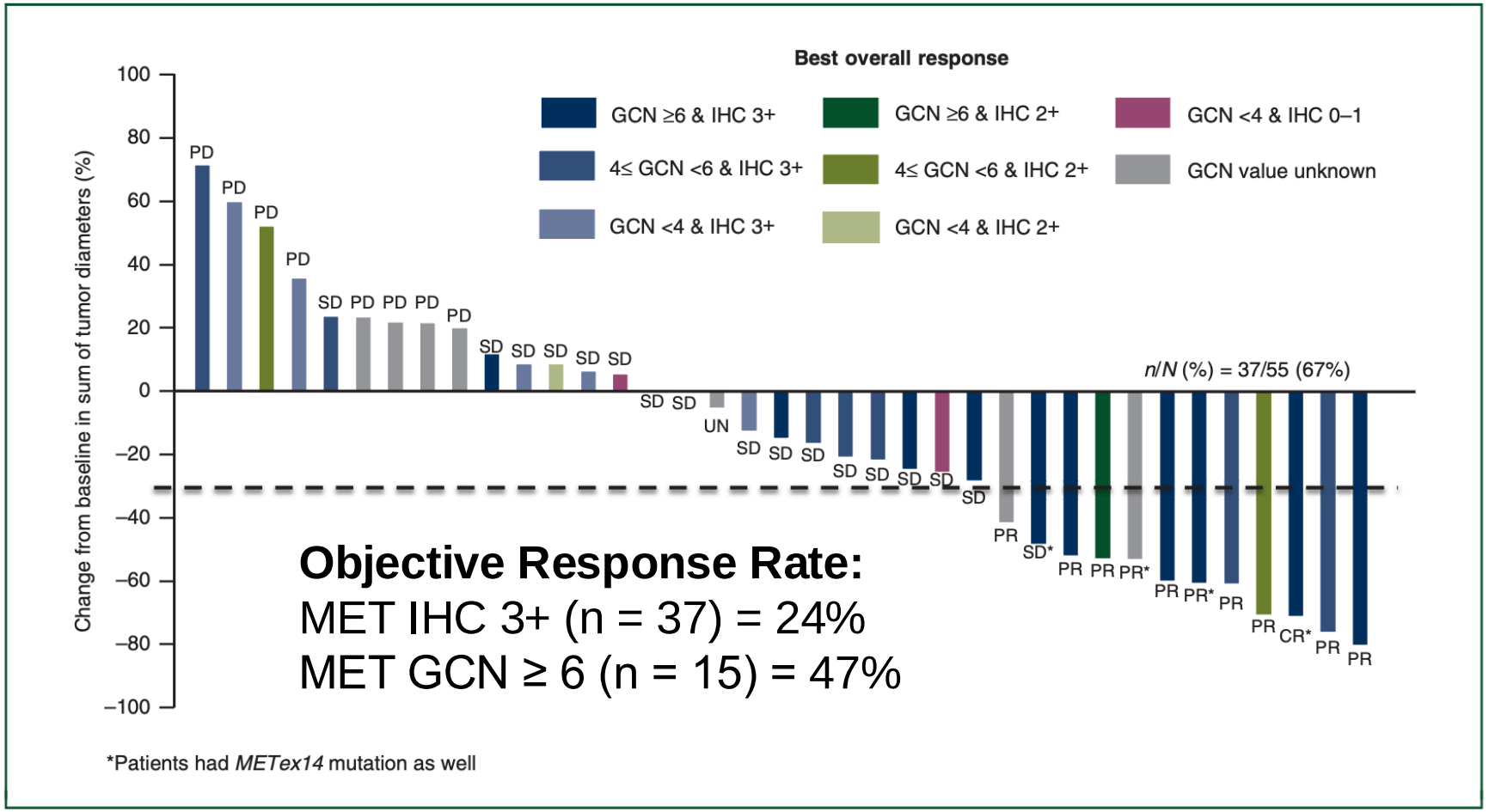


- Most lung cancers express MET
- Overexpression can be seen in 20-50% of NSCLCs
- Can be independent of MET mutations or amplification

Socinski MA JCO Precis Oncology, Zhu Annals of Oncology 2018, Dagogo-Jack Clin Cancer Res 2022

Capmatinib in NSCLC with MET Overexpression

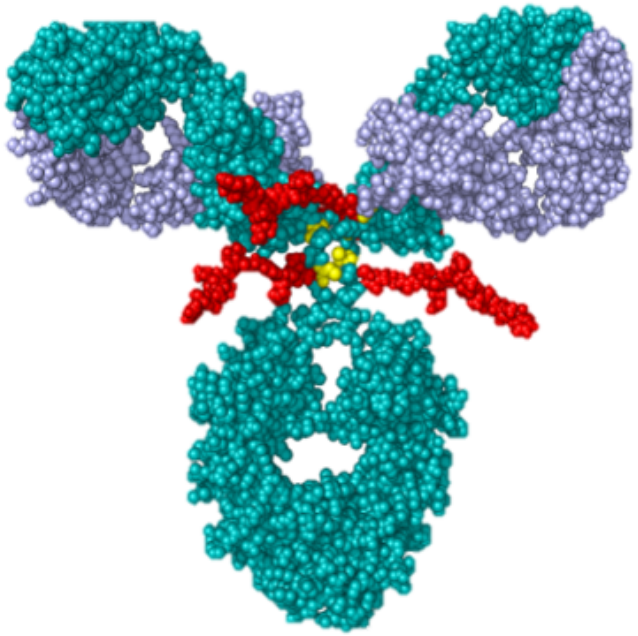
Genomic alterations (*MET* amplification and exon 14 skipping) predict sensitivity to capmatinib better than *MET* overexpression



Schuler Annals Oncology 2020

Telisotuzumab Vedotin (Teliso-V), an anti-cMET ADC

Dosed at 1.9 mg/kg IV Q2Weeks



MMAE: monomethyl auristatin E = microtubule polymerization inhibitor

ABT-700 (anti-c-Met antibody): High affinity humanized antibody that targets a unique epitope of the c-Met receptor[1,2]

MMAE (cytotoxin): MMAE is released following ADC internalization and lysosomal cleavage, resulting in inhibition of microtubule polymerization[1,3]

Mechanism of action (MOA)

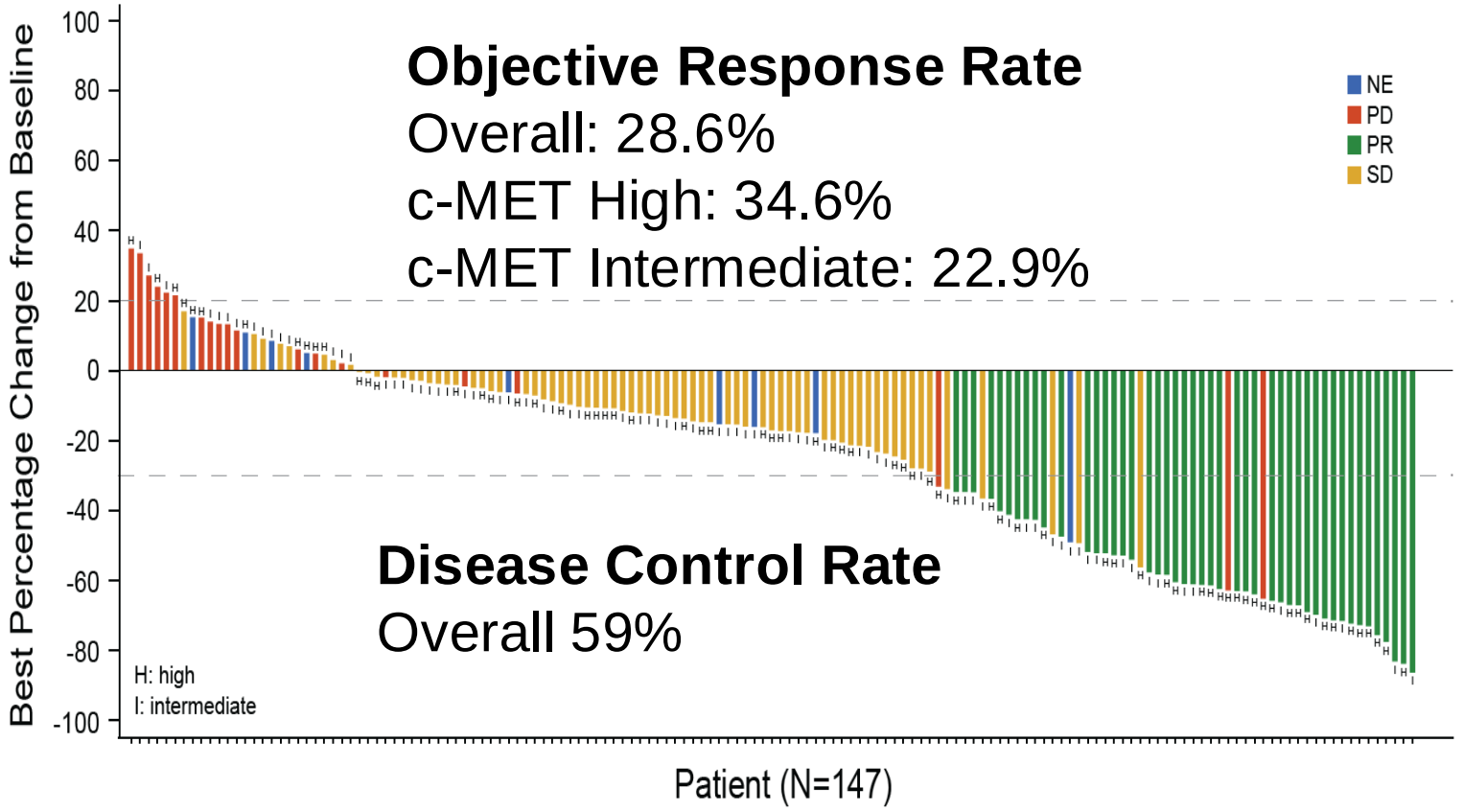
- c-Met protein overexpression predicts anti-tumor activity in pre-clinical models regardless of *MET* pathway addiction[1]
- MOA is targeted delivery of cytotoxin MMAE to the tumor via c-Met binding[1–3]
- MMAE induces cell cycle arrest and subsequent tumor cell apoptosis[2]

LUMINOSITY study: Phase 2 non-randomized multicenter study for patients with c-MET overexpressing metastatic NSCLC after ≤2 lines of therapy
Primary Endpoint: ORR by independent central review per RECIST v1.1

LUMINOSITY Phase 2: Teliso-V in MET Overexpressing EGFR^{wt} Non-Squamous NSCLC

c-MET overexpression definition (Ventana SP44 antibody):

(1) High: ≥50% of tumor cells with 3+ staining (2) Intermediate: 25-49% of tumor cells with 3+ staining



Objective Response Rate

Overall: 28.6%

c-MET High: 34.6%

c-MET Intermediate: 22.9%

Disease Control Rate

Overall 59%

Median PFS:

c-MET High: 5.5 months

c-MET Intermediate: 6.0 months

Median Duration of Response:

c-MET High: 9.0 months

c-MET Intermediate: 7.2 months

Median OS:

c-MET High: 14.6 months

c-MET Intermediate: 14.2 months

Camidge JCO 2024

LUMINOSITY: Safety of Teliso-V in MET Overexpressing EGFR^{wt} Non-Squamous NSCLC

TRAEs Occurring in > 5% of Pts	NSQ *EGFR*^{wt} NSCLC (N = 172)	
	Any Grade	Grade ≥3
Treatment-emergent AE	167 (97.1)	97 (56.4)
TRAE	140 (81.4)	48 (27.9)
Peripheral sensory neuropathy	52 (30.2)	12 (7.0)
Peripheral edema	28 (16.3)	3 (1.7)
Fatigue	24 (14.0)	4 (2.3)
Decreased appetite	20 (11.6)	1 (0.6)
Increased ALT	19 (11.0)	6 (3.5)
Pneumonitis	18 (10.5)	5 (2.9)
Hypoalbuminemia	18 (10.5)	0
Nausea	17 (9.9)	0
Vision blurred	16 (9.3)	2 (1.2)
Increased AST	16 (9.3)	0
Asthenia	13 (7.6)	1 (0.6)
Anemia	10 (5.8)	1 (0.6)
Increased γ-glutamyltransferase	10 (5.8)	1 (0.6)
Keratitis	10 (5.8)	0
Peripheral neuropathy	9 (5.2)	1 (0.6)
Decreased weight	9 (5.2)	0

Payload Toxicity
MET Class Toxicity
Pneumonitis

- **2 patients (1.2%) with grade 5 TRAEs of ILD and respiratory failure**
- **Peripheral neuropathy** was cumulative and was grade ≥3 in 9.3% of pts
- **Drug-related ILD** seen in 9.9% of pts, with 5.2% grade ≥3 and 1.7% grade 5
- **21.5% of patents discontinued treatment due to TRAEs**
  - ILD/Pneumonitis (8.7%)
  - Peripheral neuropathy (10.5%)

Camidge JCO 2024

Questions?

RTP
RESEARCH
TO PRACTICE

Trastuzumab Deruxtecan in HER2-Mutant NSCLC: DESTINY-Lung02

- Trastuzumab deruxtecan is approved for NSCLC with a *HER2* mutation
- Randomized two cohort noncomparative phase 2 to optimize safety (i.e., ILD risk)
- FDA-approved dose is 5.4 mg/kg.

DESTINY-Lung02	Not Powered to Compare the 2 Arms	
Response Assessment	**T-DXd 5.4 mg/kg n = 102**	**T-DXd 6.4 mg/kg n = 50**
Confirmed Objective Response Rate, n (%)	50 (49.0)	28 (56.0)
Best overall response, n (%) Complete Response Partial Response Stable Disease Progressive Disease	 1 (1.0) 49 (48.0) 45 (44.1) 4 (3.9)	 2 (4.0) 26 (52.0) 148 (36.0) 2 (4.0)
Disease Control Rate, n (%)	95 (93.1)	46 (92.0)
Median PFS, Months	9.9	15.4
Median OS, Months	19.5	NR
Interstitial Lung Disease (Prior ICI/No Prior ICI), %	**12.9 (14.9/7.4)**	**28.0 (28.2/27.3)**
Dose Reduction/Drug Discontinuation, %	16.8/13.9	32/20

Should We Use T-DXd in the 1st Line?

- DESTINY-Lung04

Median Onset of ILD

- 88 days

CNS ORR and DOR

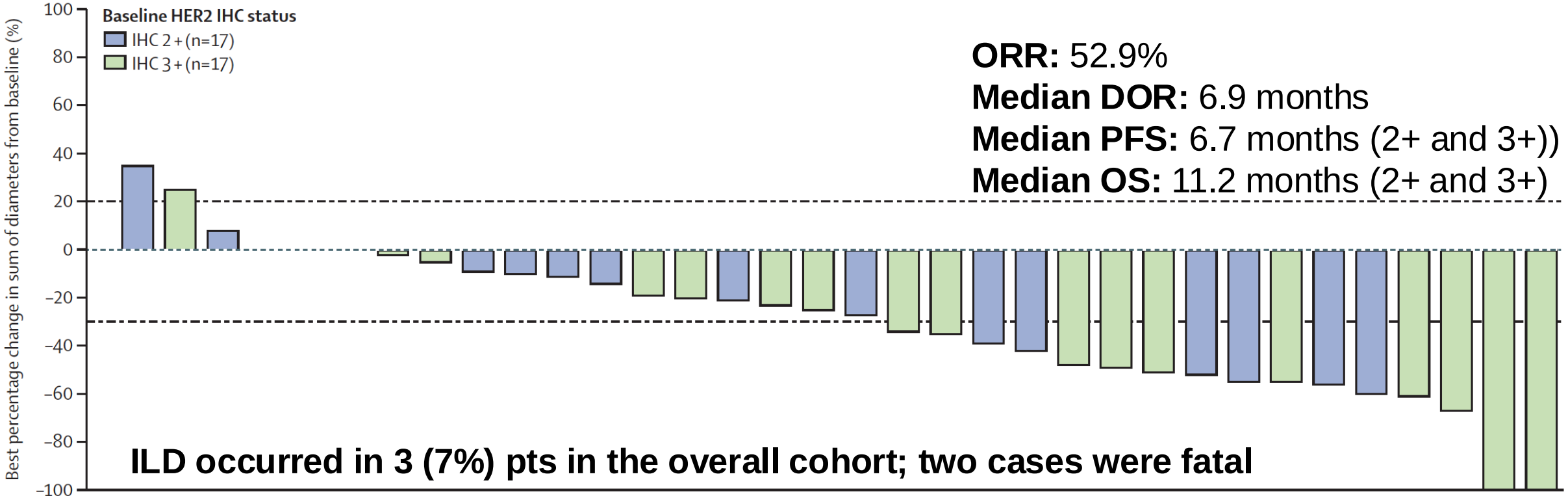
- 50% with 5.4 mg/kg
- 9.5 months with 5.4 mg/kg

Goto JCO 2023

Trastuzumab Deruxtecan in HER2 Expressing NSCLC: DESTINY-Lung01 (5.4 mg/kg)

On April 5, 2024, FDA granted accelerated approval to T-DXd for pts with metastatic HER2-positive (IHC 3+) solid tumors following progression on standard therapy

- HER2 “overexpression” is observed in ~10-23 % of NSCLC
- Approval in lung cancer based on DESTINY-Lung01 where 3+ constituted strong expression in ≥10% of individual cells or in a tumor cell cluster

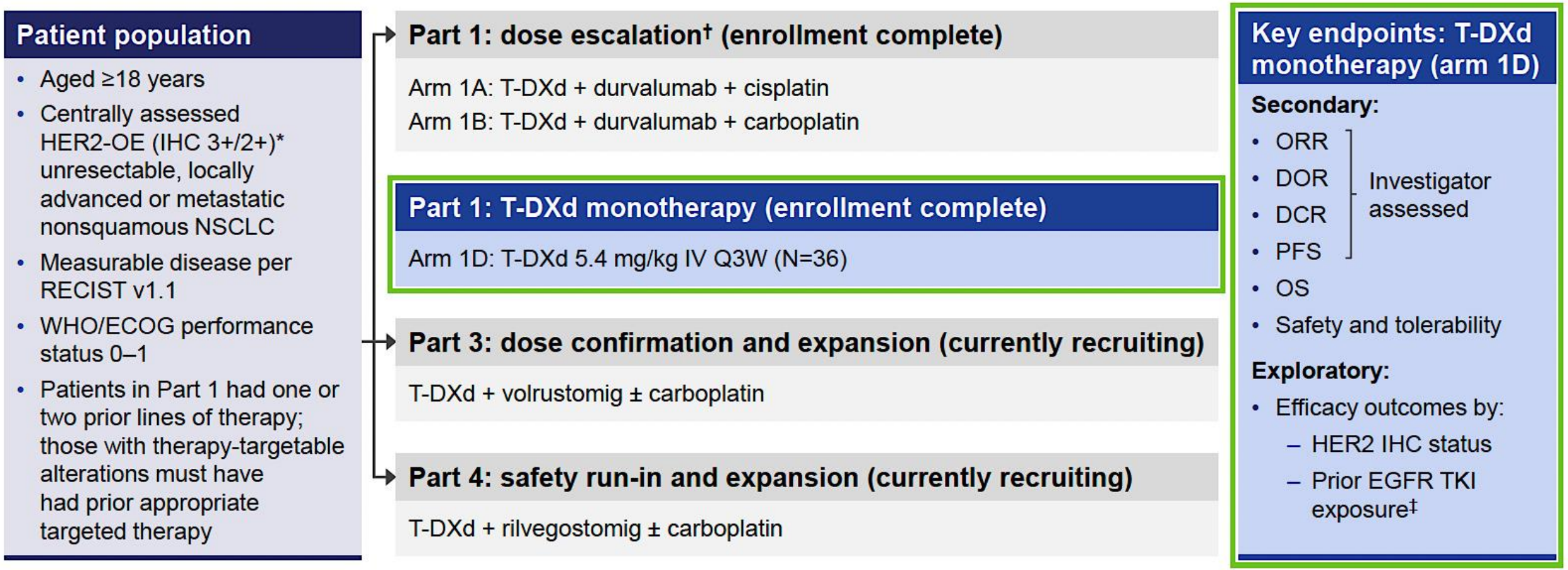


ORR: 52.9%
Median DOR: 6.9 months
Median PFS: 6.7 months (2+ and 3+))
Median OS: 11.2 months (2+ and 3+)

ILD occurred in 3 (7%) pts in the overall cohort; two cases were fatal

Smit Lancet 2024

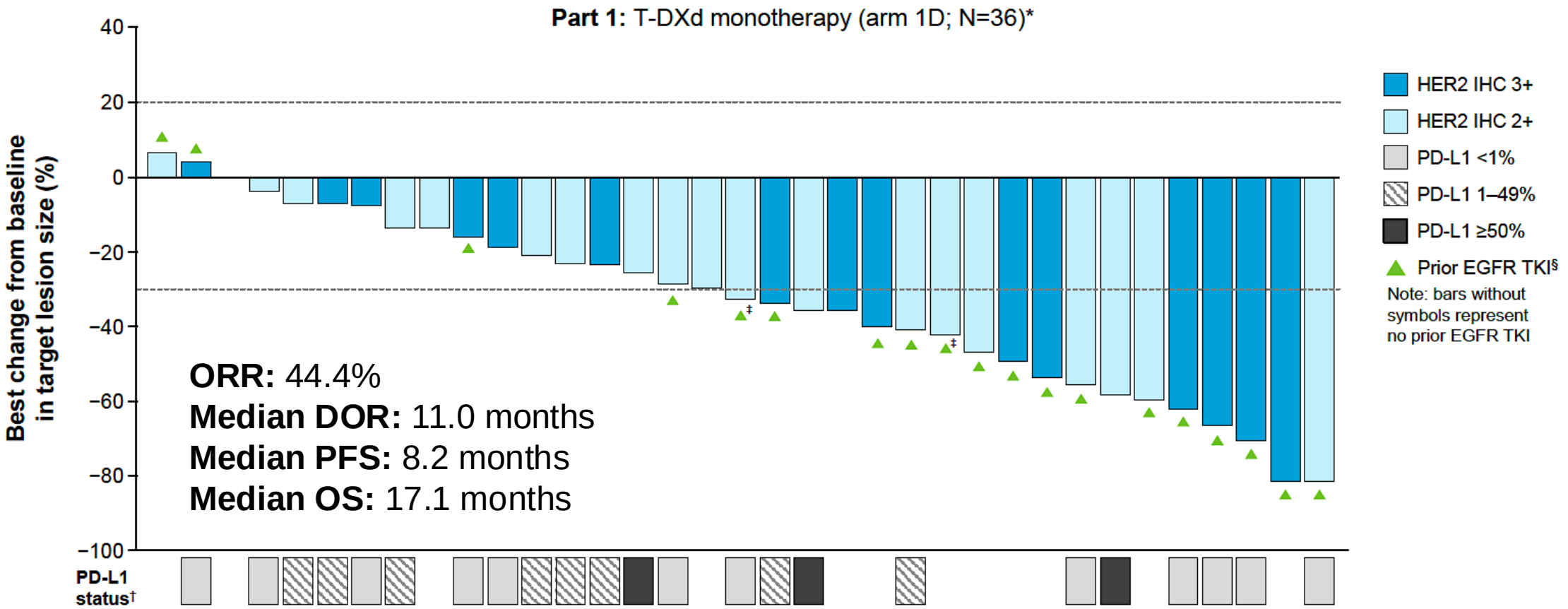
DESTINY-Lung03: Phase IB Dose-Escalation Study of Trastuzumab Deruxtecan for HER2-Overexpressing (HER2-OE) NSCLC



ORR = objective response rate; DOR = duration of response; DCR = disease control rate; PFS = progression-free survival; OS = overall survival; TKI = tyrosine kinase inhibitor

Yang WCLC 2024

Trastuzumab Deruxtecan for HER2-OE NSCLC: DESTINY-Lung03



Results from DESTINY-Lung03 Part 1 confirm the clinical benefit of T-DXd monotherapy (5.4 mg/kg; arm 1D) for pretreated HER2-overexpressing (IHC 3+/2+) metastatic NSCLC, building on DESTINY-Lung01 cohort 1a results

Yang WCLC 2024

WCLC HER2 Tyrosine Kinase Inhibitor Updates

SOHO-01 (BAY 2927088) oral HER2 TKI (n=44 pts)

Presented by Dr. Xuining Le

- ORR 72.1%, DCR 83.7%, median PFS 7.5 months
- Among YVMA mutations (71% of pts): ORR 90%, DCR 97%, PFS 9.9 months
- Safety: 87% with diarrhea; 32% dose reduction; 7% dose discontinuation

BEAMION Lung-01 (Zongertinib), oral HER2 TKI (n=132 pts)

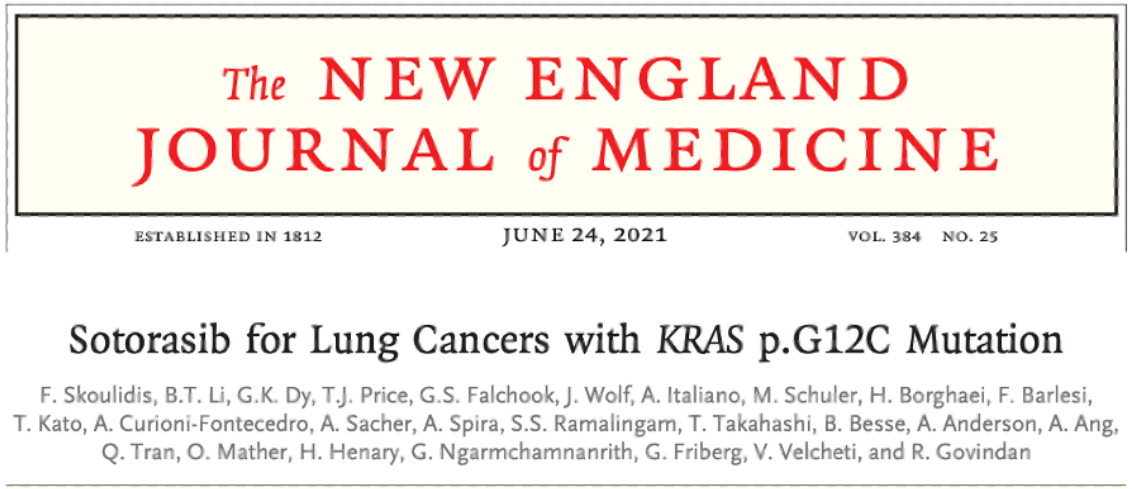
Presented by Dr. Gerrina Ruiter

- ORR 67%, DCR >94% across 2 doses: 120 mg and 240 mg
- CNS ORR 33-40%
- Diarrhea 48%; 3% treatment discontinuation; 11% dose reduction

2 FDA-Approved KRAS G12C Inhibitors

Approved 5/2021

Sotorasib (CodeBreak100)



The NEW ENGLAND JOURNAL of MEDICINE

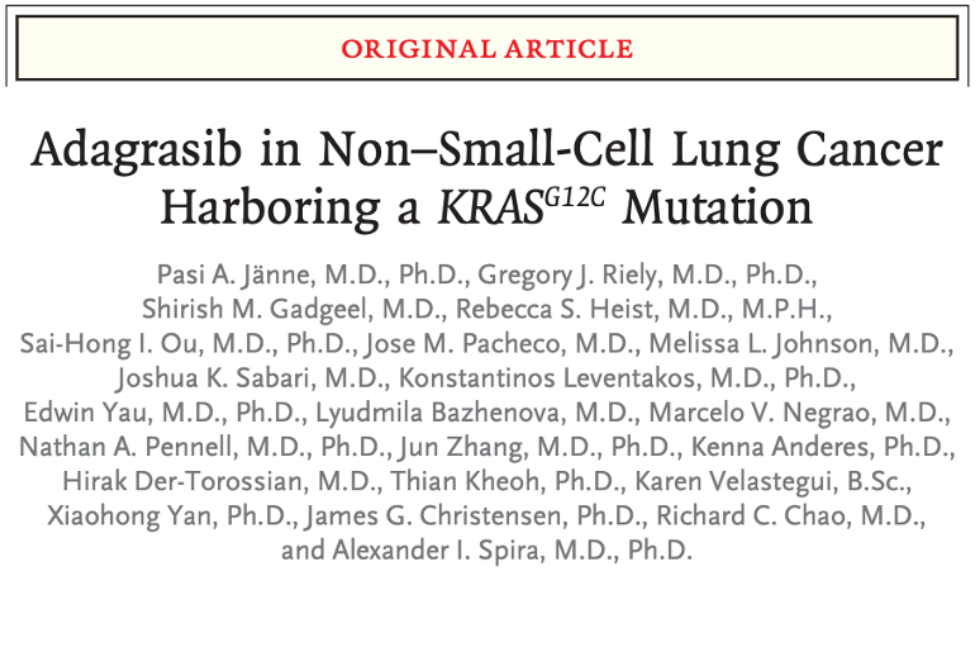
ESTABLISHED IN 1812 JUNE 24, 2021 VOL. 384 NO. 25

Sotorasib for Lung Cancers with *KRAS* p.G12C Mutation

F. Skoulidis, B.T. Li, G.K. Dy, T.J. Price, G.S. Falchook, J. Wolf, A. Italiano, M. Schuler, H. Borghaei, F. Barlesi, T. Kato, A. Curioni-Fontecedro, A. Sacher, A. Spira, S.S. Ramalingam, T. Takahashi, B. Besse, A. Anderson, A. Ang, Q. Tran, O. Mather, H. Henary, G. Ngarmchamnanrith, G. Friberg, V. Velcheti, and R. Govindan

Approved 12/2022

Adagrasib (KRYSTAL)



The NEW ENGLAND JOURNAL of MEDICINE

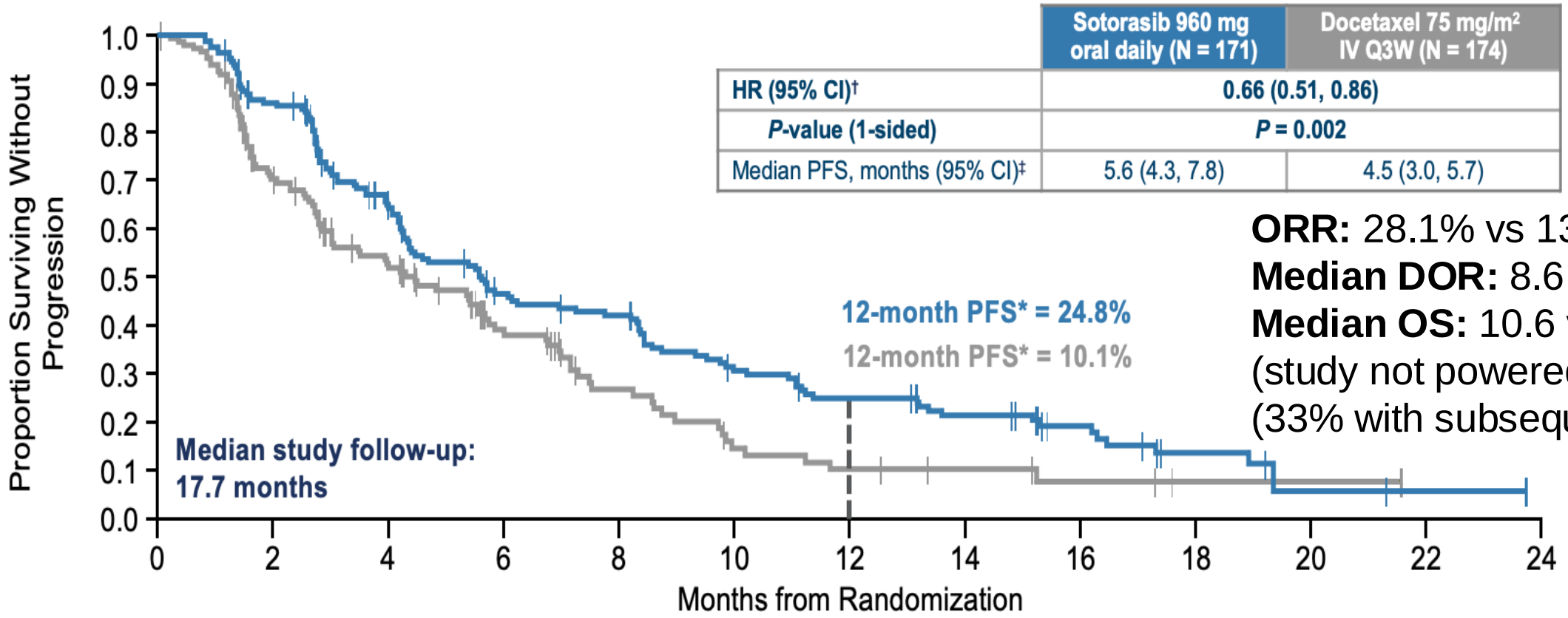
ORIGINAL ARTICLE

Adagrasib in Non–Small-Cell Lung Cancer Harboring a *KRAS*^{G12C} Mutation

Pasi A. Jänne, M.D., Ph.D., Gregory J. Riely, M.D., Ph.D., Shirish M. Gadgeel, M.D., Rebecca S. Heist, M.D., M.P.H., Sai-Hong I. Ou, M.D., Ph.D., Jose M. Pacheco, M.D., Melissa L. Johnson, M.D., Joshua K. Sabari, M.D., Konstantinos Leventakos, M.D., Ph.D., Edwin Yau, M.D., Ph.D., Lyudmila Bazhenova, M.D., Marcelo V. Negrao, M.D., Nathan A. Pennell, M.D., Ph.D., Jun Zhang, M.D., Ph.D., Kenna Anderes, Ph.D., Hirak Der-Torossian, M.D., Thian Kheoh, Ph.D., Karen Velastegui, B.Sc., Xiaohong Yan, Ph.D., James G. Christensen, Ph.D., Richard C. Chao, M.D., and Alexander I. Spira, M.D., Ph.D.

CodeBreak 200: Open-Label Phase 3 Study of Sotorasib vs Docetaxel (1:1 Randomization)

Primary Endpoint: PFS by BICR



	Sotorasib 960 mg oral daily (N = 171)	Docetaxel 75 mg/m² IV Q3W (N = 174)
HR (95% CI)†	0.66 (0.51, 0.86)	
P-value (1-sided)	*P* = 0.002	
Median PFS, months (95% CI)‡	5.6 (4.3, 7.8)	4.5 (3.0, 5.7)

Number of Patients at Risk:

Sotorasib	171	139	93	63	56	38	30	24	14	6	2	1	0
Docetaxel	174	93	62	36	20	10	7	5	3	1	1	0	

ORR: 28.1% vs 13.2%
Median DOR: 8.6 vs 6.8 mo
Median OS: 10.6 vs 11.3 mo
(study not powered for OS)
(33% with subsequent G12Ci)

deLangen Lancet 2024

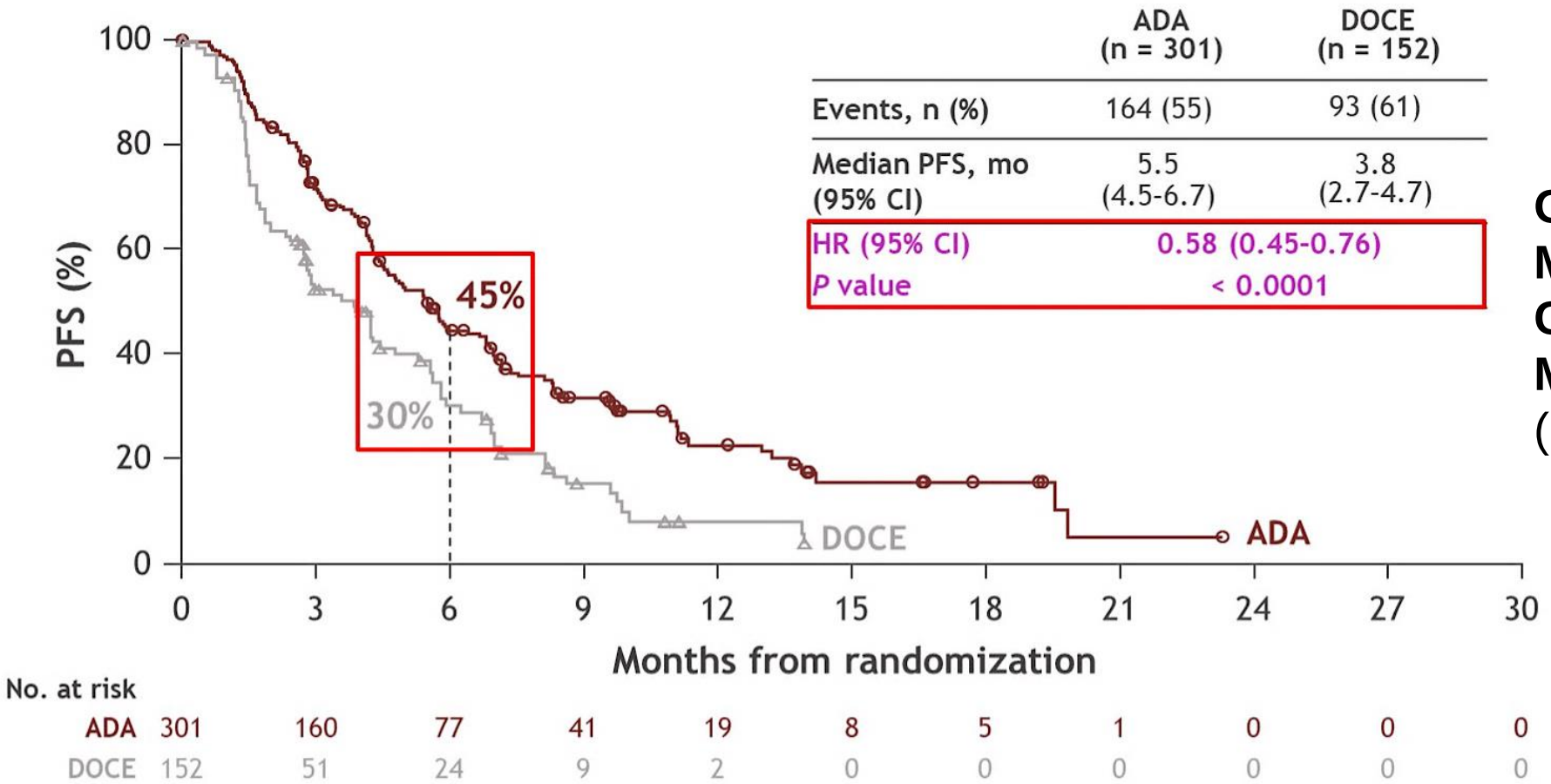
CodeBreak 200: Sotorasib vs Docetaxel Safety Profiles

Adverse Event	Sotorasib All | Grade ≥3	Docetaxel All | Grade ≥3
Diarrhea	34%| 12%	12%| 1%
Fatigue	7%| 1%	25%| 6%
Alopecia	1%| 0%	21%| 0%
Nausea	14%|1%	20%| 1%
Anemia	3%| 1%	18%| 3%
Decreased Appetite	11%|2%	14%| 0%
Stomatitis	1%|0%	11%| 1%
Constipation	3%|0%	11%|0%
Asthenia	4%|1%	11%|3%
AST Increase	10%|8%	0%|0%
ALT Increase	10%|5%	0%|0%
Peripheral Neuropathy	0%|0%	10%|1%
Dose Reduction	15%	27%
Discontinuation	10%	11%

deLangen Lancet 2024

KRYSTAL-12: Open-Label Phase 3 Study of Adagrasib vs Docetaxel (2:1 Randomization)

Primary Endpoint: PFS by BICR; Hierarchical (PFS→ORR→OS); OS immature



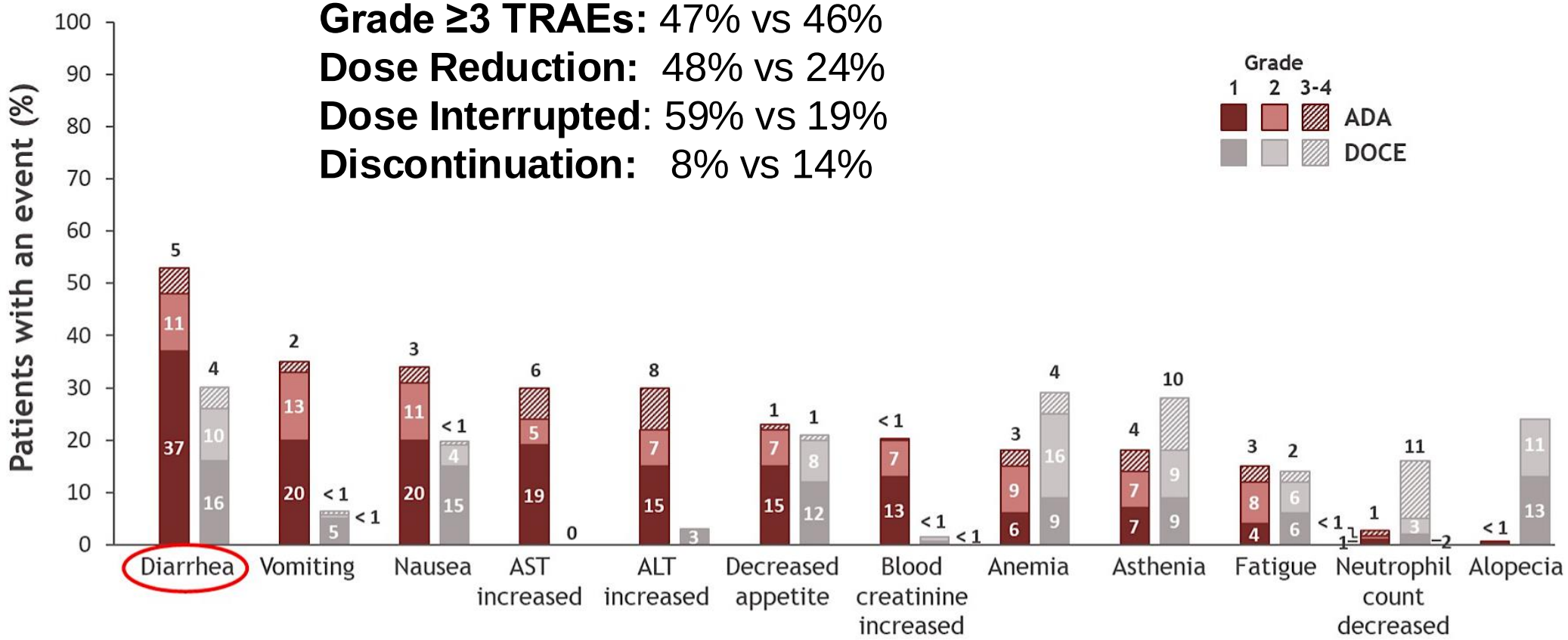
	ADA (n = 301)	DOCE (n = 152)
Events, n (%)	164 (55)	93 (61)
Median PFS, mo (95% CI)	5.5 (4.5-6.7)	3.8 (2.7-4.7)
HR (95% CI)	0.58 (0.45-0.76)	
P value	< 0.0001	

ORR: 32% vs 9%
Median DOR: 8.3 vs 5.4 mo
CNS ORR: 24% vs 11%
Median OS: 10.6 vs 11.3 mo
(29% crossover)

Mok ASCO 2024

KRYSTAL-12: Open-Label Phase 3 Study of Adagrasib vs Docetaxel (Safety Findings)

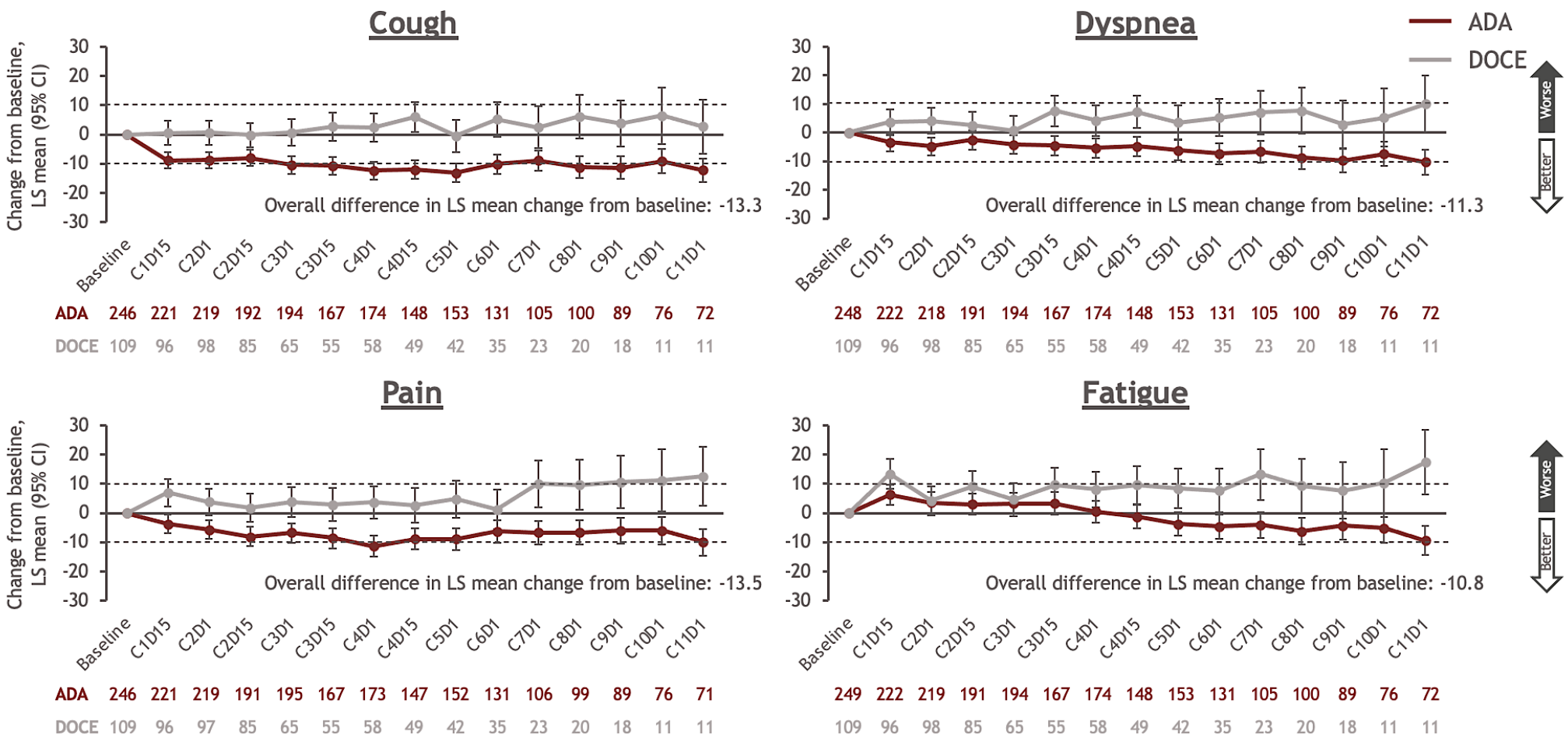
	ADA	DOC
Grade ≥3 TRAEs:	47%	46%
Dose Reduction:	48%	24%
Dose Interrupted:	59%	19%
Discontinuation:	8%	14%



Mok ASCO 2024

KRYSTAL-12: Impact on QOL (>85% Completion Rate)

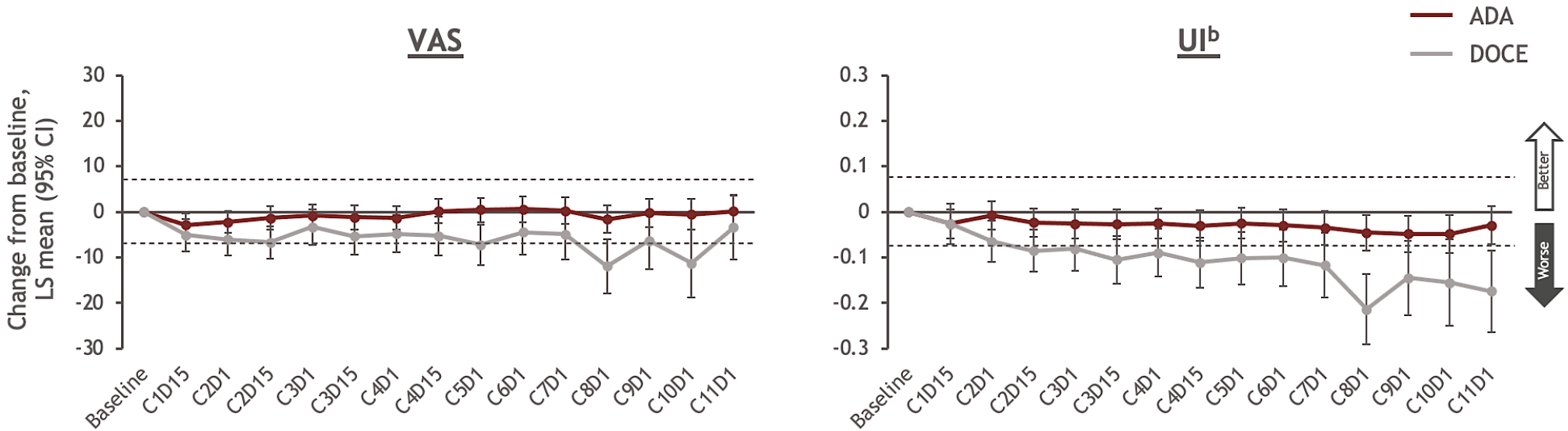
MMRM analysis[a]: Difference in overall LCSS change from baseline



Minimally important difference for improvement/worsening is 10 points for ASBI scores. [a]Model included variables for treatment, time, treatment by time interaction and baseline score, and controlled for region (non-Asia-Pacific vs Asia-Pacific) and prior therapy (sequential vs concurrent chemotherapy and immunotherapy).

KRYSTAL-12: Impact on QOL

MMRM analysis[a]: Difference in overall EQ-5D-5L change from baseline



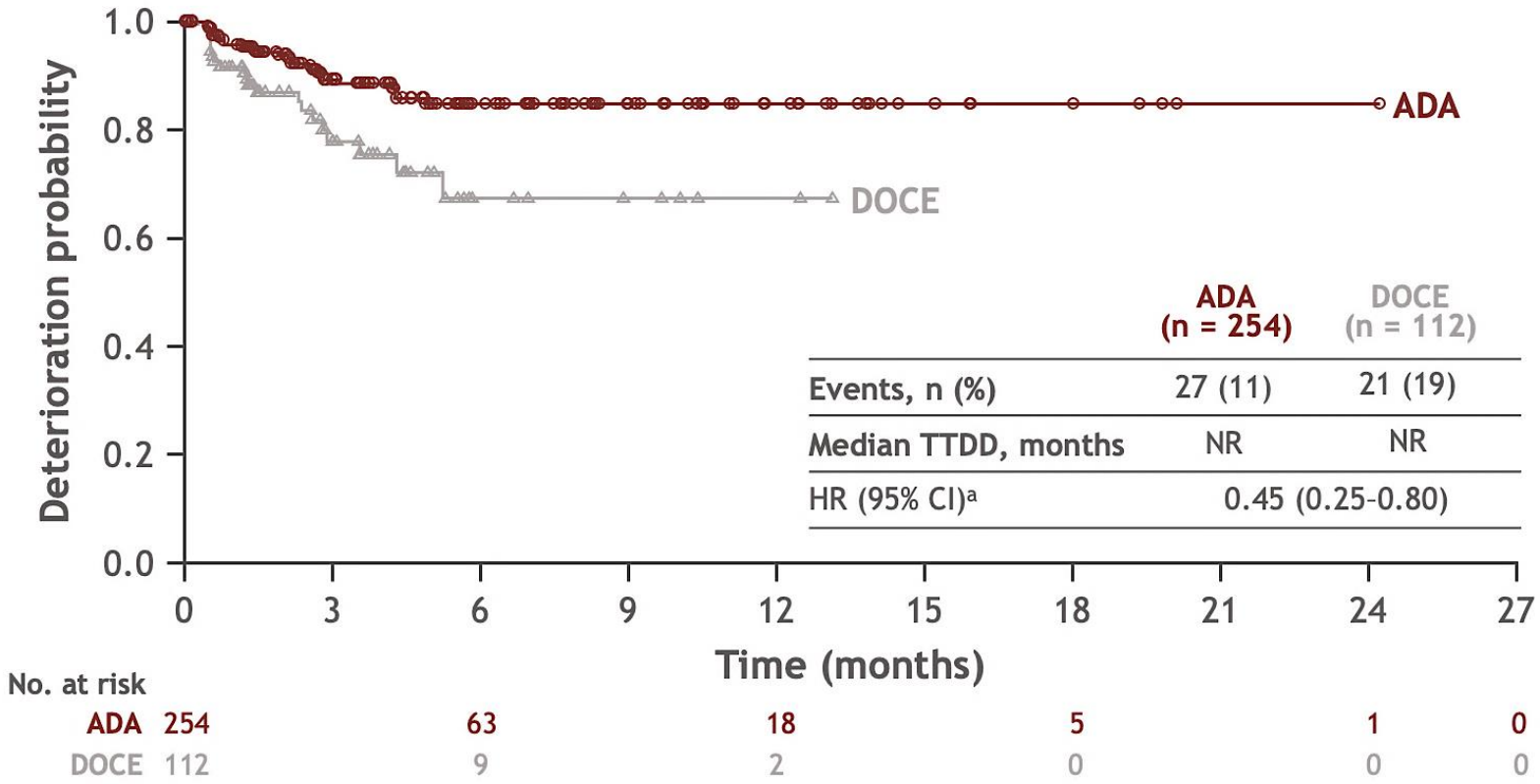
	ADA	DOCE
Overall LS mean change from baseline (95% CI)	-0.7 (-2.7 to 1.3)	-6.1 (-9.2 to -3.1)
Mean difference (95% CI)	5.4 (2.0 to 8.9)	

	ADA	DOCE
Overall LS mean change from baseline (95% CI)	-0.030 (-0.056 to -0.005)	-0.112 (-0.152 to -0.072)
Mean difference (95% CI)	0.082 (0.037 to 0.126)	

In the EQ-5D-5L, higher scores reflect better HRQoL. Minimally important difference for improvement/worsening is 7 points for VAS scores and 0.078 points for UI scores. Positive differences favor ADA.
[a]Model included variables for treatment, time, treatment by time interaction and baseline score, and controlled for region (non-Asia-Pacific vs Asia-Pacific) and prior therapy (sequential vs concurrent chemotherapy and immunotherapy). [b]UK utility scores (Sheffield DSU algorithm).

KRYSTAL-12: Impact on QOL

Time to definitive deterioration (TTDD) in LCSS ASBI



	ADA (n = 254)	DOCE (n = 112)
Events, n (%)	27 (11)	21 (19)
Median TTDD, months	NR	NR
HR (95% CI)[a]	0.45 (0.25-0.80)	

TTDD is defined as the time to first deterioration of ≥10 points compared with baseline score and sustained deterioration of ≥10 points compared with baseline score at all subsequent timepoints. Patients with no definitive deterioration before end of follow-up, radiographic disease progression, or death were censored at the date of their last available PRO assessment in the case of death, or at the time of their first PRO assessment post-progression or initiation of new therapy in the case of these events.

[a]Calculated using the stratified Cox proportional hazards model.

Felip WCLC 2024

Questions?

RTP
RESEARCH
TO PRACTICE

Efficacy of Investigational KRAS G12C Inhibitors

Drug	ORR	DCR	Median PFS
Divarasib (n=44)	59%	—	15.3 months
Olomorasib	35% (all solid tumors) 41% (NSCLC post-G12Ci)	89%	8.1 months
Garsorasib (n=74)	52%	89%	9.1 months
Glecirasib (n=119)	48%	86%	8.2 months
IBI351 (n=116)	49%	91%	9.7 months

Sacher WCLC 2024, Heist ASCO 2024, Li WCLC 2024, Li ASCO 2022, Zhou WCLC 2024

Case Presentation – Dr Dagogo-Jack: Stage IV $KRAS^{G12C}$ NSCLC

- A 52-year-old male with an active smoking history was taken to the emergency room after losing consciousness while driving. Brain MRI demonstrated a 5 cm R frontal mass with extensive edema, as well as several smaller brain metastases. PET + CT chest, abdomen, pelvis revealed a 1.2 cm right middle lobe nodule without lymphadenopathy or abdominopelvic abnormalities.
- He underwent R frontal craniotomy with pathology consistent with a PD-L1 negative metastatic lung adenocarcinoma harboring KRAS G12C in addition to STK11 and KEAP1 mutations.
- Stereotactic radiosurgery was performed on four separate sub-centimeter brain metastases. He also received fractionated radiation to the resection cavity.
- He was subsequently treated with carboplatin + pemetrexed + pembrolizumab.
- After 4 cycles, scans demonstrated progression of CNS disease and an unchanged lung nodule.
- He underwent whole brain radiation therapy.
- Six months later in the setting of further progression in the CNS despite whole brain radiation, he initiated Adagrasib. He required a dose reduction after 6 weeks due to intractable nausea/vomiting.
- Repeat imaging on Adagrasib demonstrated progression of 1 brain metastasis with slight decrease in size of the remaining metastases. He underwent SRS and remained on Adagrasib for 5 months before it was discontinued in setting of poor tolerance and further CNS progression.

The Implications of Recent Datasets for the Current and Future Use of Nontargeted Therapy for Metastatic Non-Small Cell Lung Cancer

A CME/MOC-Accredited Live Webinar in Conjunction with the IASLC 2024 World Conference on Lung Cancer

Thursday, September 12, 2024

5:00 PM – 6:00 PM ET

Faculty

Edward B Garon, MD, MS

Luis Paz-Ares, MD, PhD

Moderator

Neil Love, MD

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Thank you for joining us!

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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