Year in Review: Clinical Investigator Perspectives on the Most Relevant New Data Sets and Advances in Oncology

Targeted Therapy for Non-Small Cell Lung Cancer

Wednesday, January 11, 2023
5:00 PM – 6:00 PM ET

Faculty

Zofia Piotrowska, MD, MHS
Gregory J Riely, MD, PhD

Moderator

Neil Love, MD

RTP Year in Review 2023

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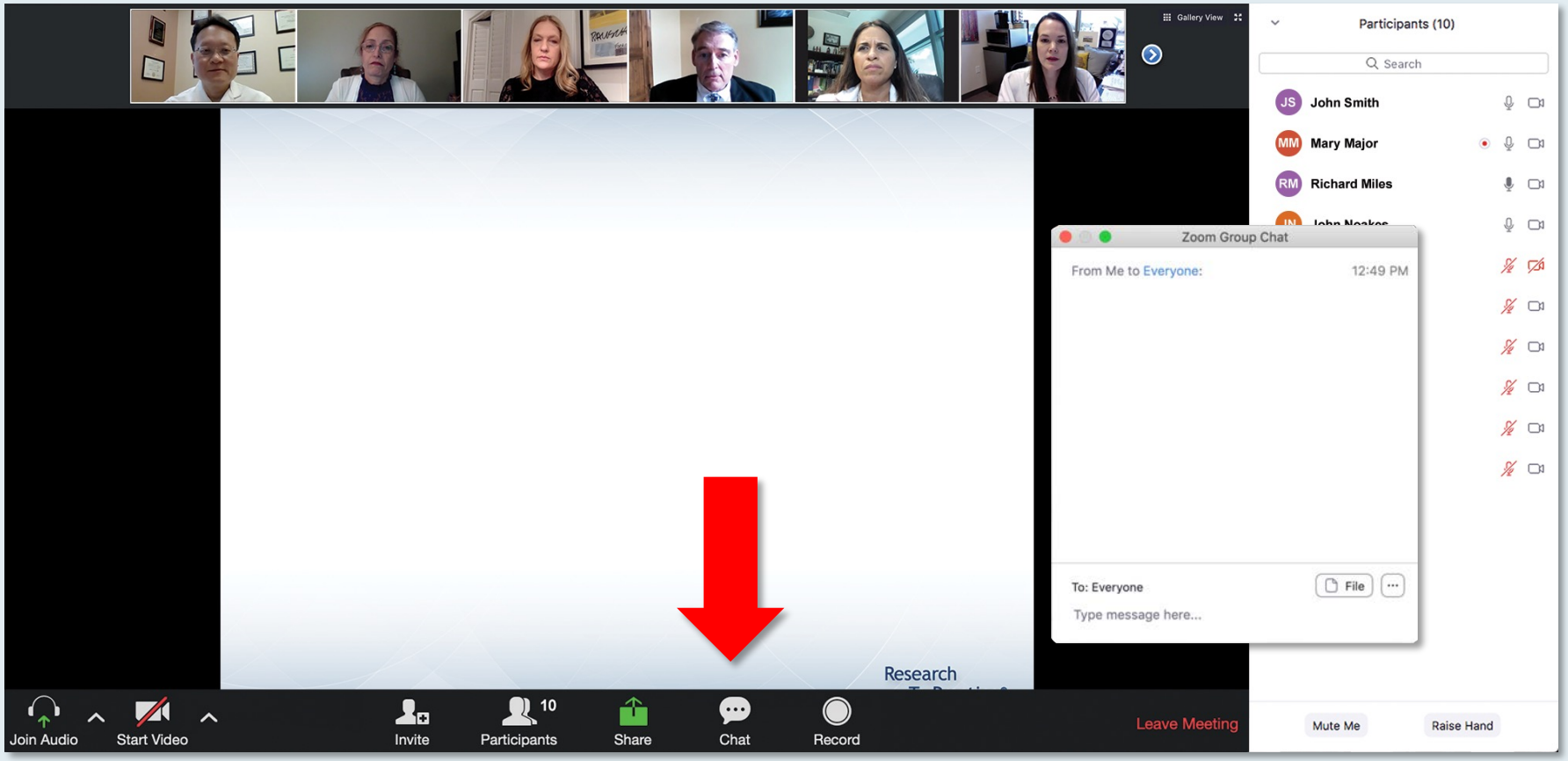
Zofia Piotrowska, MD, MHS
Assistant Professor of Medicine
Harvard Medical School
Massachusetts General Hospital
Boston, Massachusetts

Gregory J Riely, MD, PhD
Attending
Memorial Sloan Kettering Cancer Center
New York, New York

MODERATOR
Neil Love, MD
Research To Practice
Miami, Florida

RTP Year in Review 2023

We Encourage Clinicians in Practice to Submit Questions



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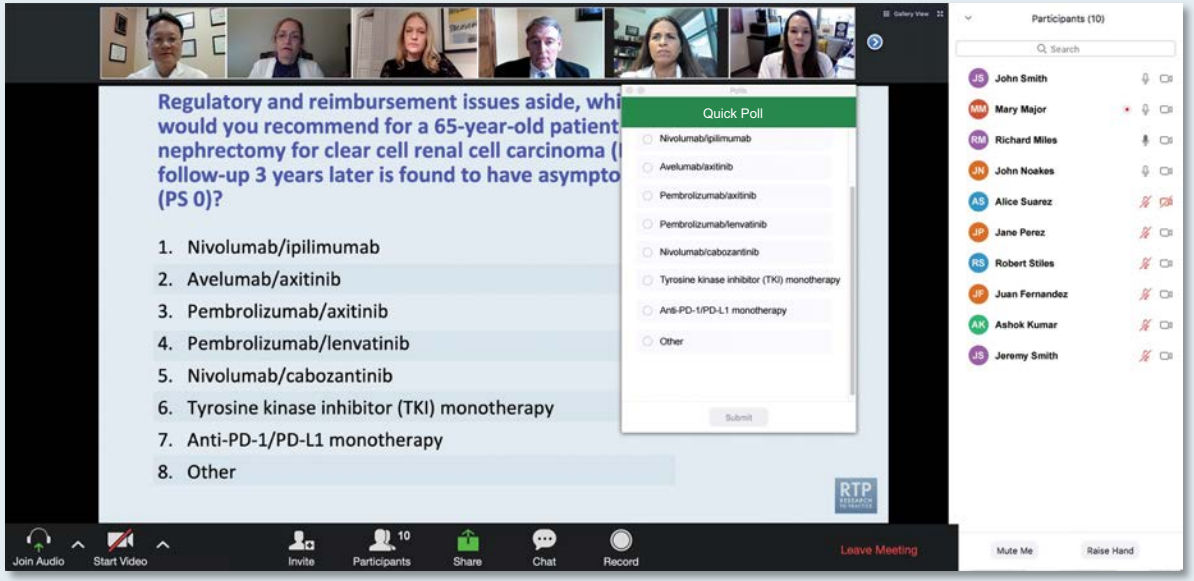

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Dr Love — Disclosures

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Dr Riely — Disclosures

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Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 5 business days.

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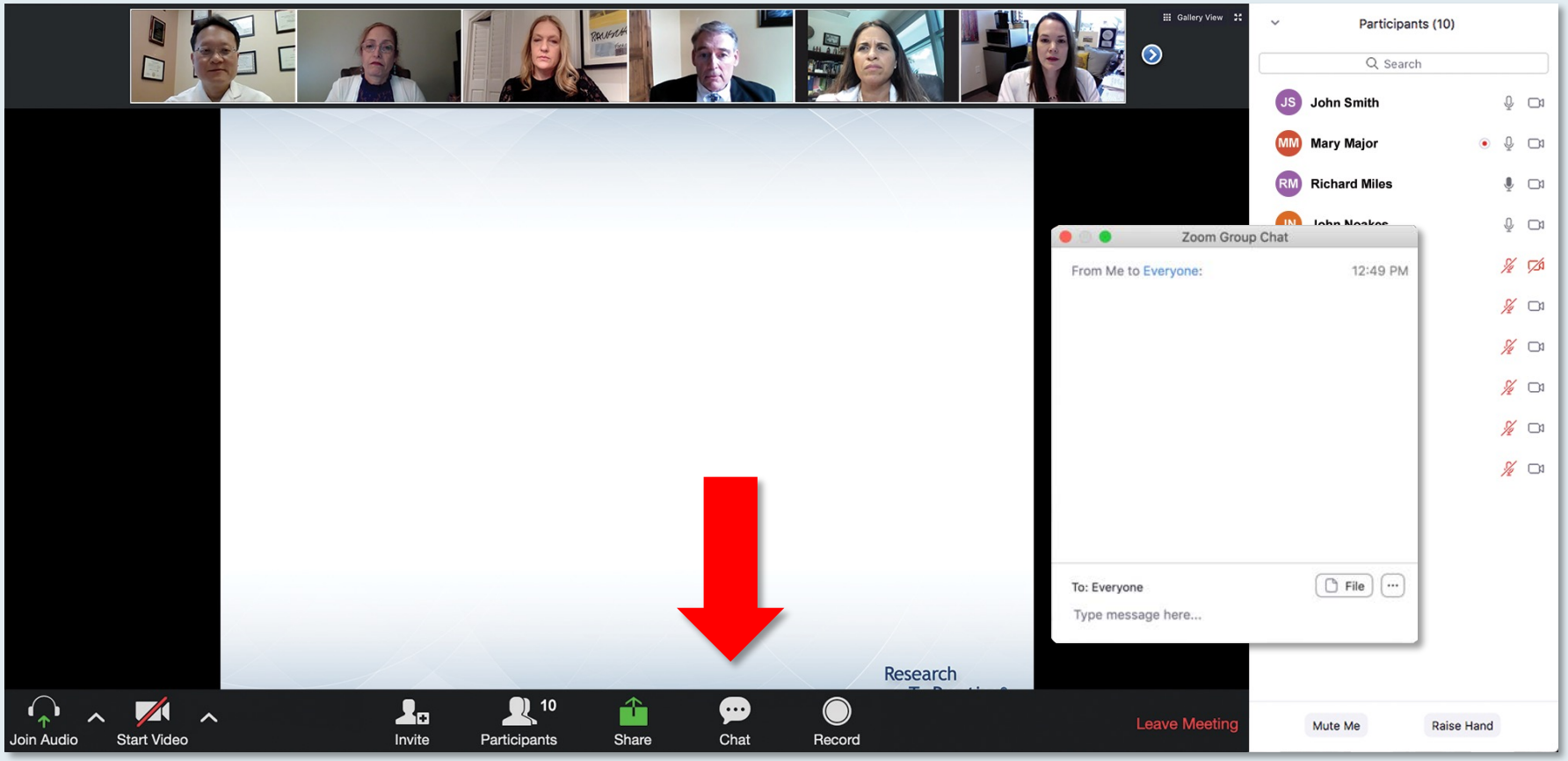

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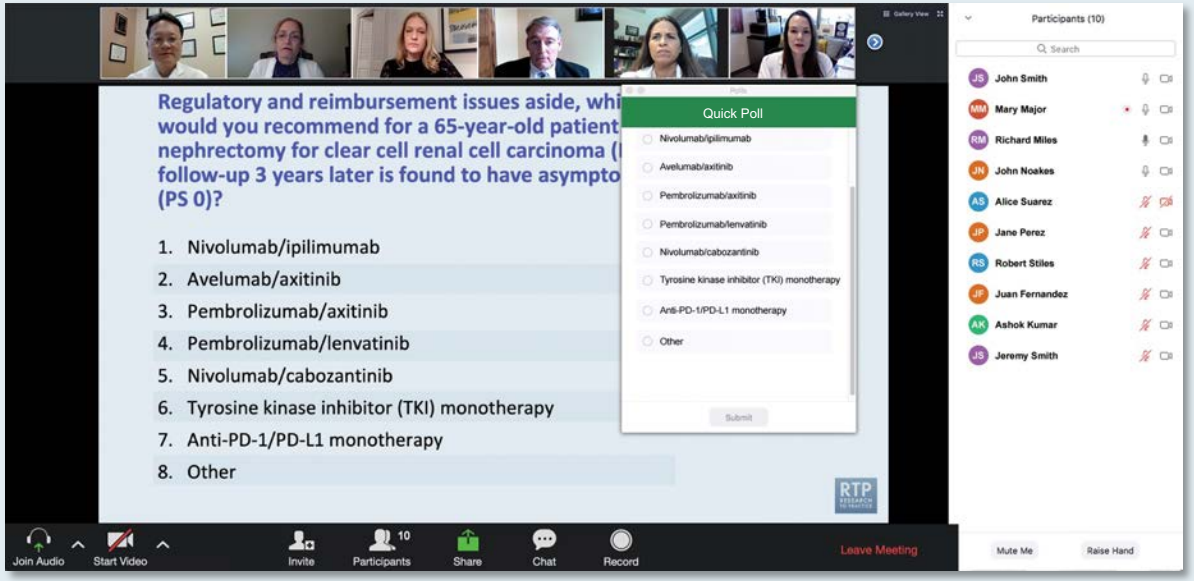

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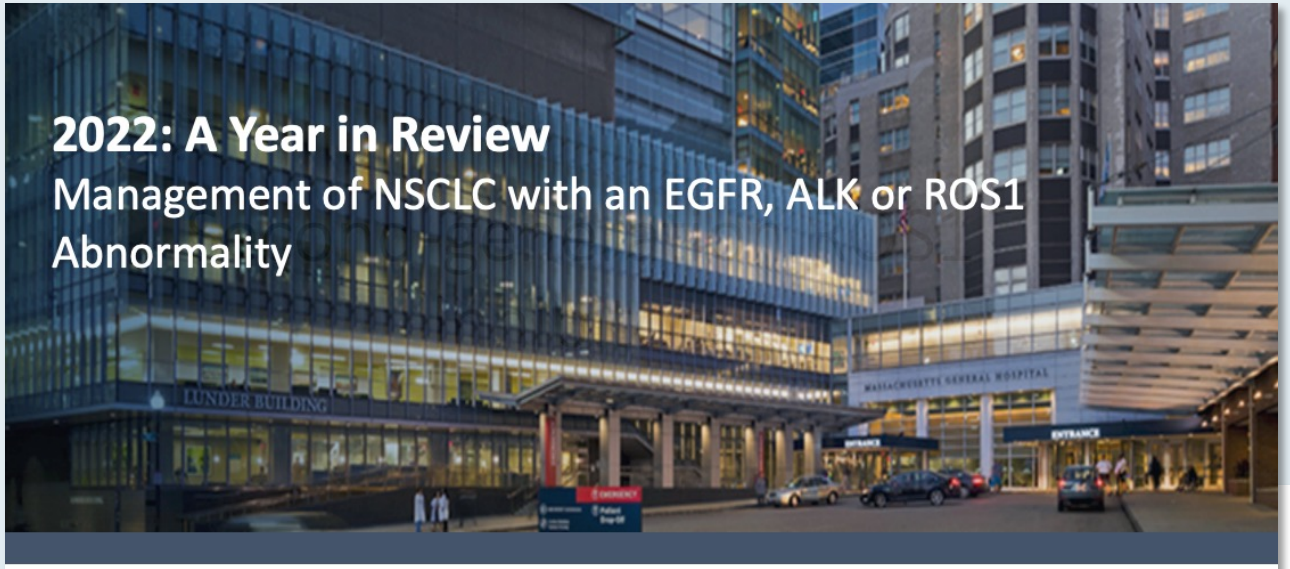

2022: A Year in Review
Management of NSCLC with an EGFR, ALK or ROS1 Abnormality

Zosia Piotrowska, MD, MHS
Assistant Professor of Medicine
Harvard Medical School | Massachusetts General Hospital

Therapeutic Approaches for Patients with Other Actionable Genomic Alterations

Gregory J Riely, MD, PhD
Attending
Memorial Sloan Kettering Cancer Center
New York, New York

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Key Data Sets

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- Piotrowska Z et al. ELIOS: A multicentre, molecular profiling study of patients with epidermal growth factor receptor-mutated advanced NSCLC treated with first-line osimertinib. ESMO 2022;Abstract LBA53.
- Jänne PA et al. Efficacy and safety of patritumab deruxtecan (HER3-DXd) in EGFR inhibitor-resistant, EGFR-mutated non-small cell lung cancer. *Cancer Discov* 2022;12(1):74-89.
- Shu CA et al. Amivantamab and lazertinib in patients with EGFR-mutant non-small cell lung cancer after progression on osimertinib and platinum-based chemotherapy: Updated results from CHRYSALIS-2. ASCO 2022;Abstract 9006.
- Park K et al. Amivantamab in EGFR exon 20 insertion-mutated non-small-cell lung cancer progressing on platinum chemotherapy: Initial results from the CHRYSALIS Phase I study. *J Clin Oncol* 2021;39(30):3391-402.

Key Data Sets

Zofia Piotrowska, MD, MHS (continued)

- Ramalingam SR et al. Phase I/II study of mobocertinib in EGFR exon 20 insertion + metastatic NSCLC: Updated results from platinum-pretreated patients. ESMO 2022;Abstract 988P.
- Hotta K et al. Final overall survival analysis from the Phase III J-ALEX study of alectinib versus crizotinib in ALK inhibitor-naïve Japanese patients with ALK-positive non-small-cell lung cancer. *ESMO Open* 2022;7(4):100527.
- Camidge DR et al. Brigatinib versus crizotinib in ALK inhibitor-naïve advanced ALK-positive NSCLC: Final results of Phase 3 ALTA-1L trial. *J Thorac Oncol* 2021;16(12):2091-108.
- Solomon BJ et al. Post hoc analysis of lorlatinib intracranial efficacy and safety in patients with ALK-positive advanced non-small-cell lung cancer from the Phase III CROWN study. *J Clin Oncol* 2022;40(31):3593-602.
- Fan Y et al. Entrectinib in patients with ROS1 fusion-positive NSCLC: Updated efficacy and safety analysis. WCLC 2022;Abstract MA13.04.

Key Data Sets

Gregory J Riely, MD, PhD

- Li BT et al. Trastuzumab deruxtecan in HER2-mutant non-small-cell lung cancer. *N Engl J Med* 2022;386(3):241-51.
- Goto K et al. Trastuzumab deruxtecan in patients with HER2-mutant metastatic non-small cell lung cancer: Interim results from the Phase II DESTINY-Lung02 trial. ESMO 2022;Abstract LBA55.
- Smit EF et al. Trastuzumab deruxtecan in patients with HER2-overexpressing metastatic non-small cell lung cancer: Results from the DESTINY-Lung01 trial. ESMO 2022;Abstract 975P.
- Johnson ML et al. Sotorasib versus docetaxel for previously treated non-small cell lung cancer with KRAS G12C mutation: CodeBreaK 200 Phase III study. ESMO 2022;Abstract LBA10.
- Jänne PA et al. Adagrasib in non-small-cell lung cancer harboring a $KRAS^{G12C}$ mutation. *N Engl J Med* 2022;387(2):120-31.
- Drilon A et al. Selpercatinib in patients with RET fusion-positive non-small-cell lung cancer: Updated safety and efficacy from the registrational LIBRETTO-001 Phase I/II trial. *J Clin Oncol* 2022;[Online ahead of print].

Key Data Sets

Gregory J Riely, MD, PhD (continued)

- Minchom A et al. Patient-reported outcomes with selpercatinib among patients with RET fusion-positive non-small cell lung cancer in the Phase I/II LIBRETTO-001 trial. *Oncologist* 2022;27(1):22-9.
- Griesinger F et al. Safety and efficacy of pralsetinib in RET fusion-positive non-small-cell lung cancer including as first-line therapy: Update from the ARROW trial. *Ann Oncol* 2022;33(11):1168-78.
- Thomas M et al. Tepotinib in patients with MET exon 14 skipping NSCLC: Primary analysis of the confirmatory VISION cohort C. WCLC 2022;Abstract OA03.05.
- Krebs M et al. Amivantamab in patients with NSCLC with MET exon 14 skipping mutation: Updated results from the CHRYSALIS study. ASCO 2022;Abstract 9008.
- Carrizosa D et al. CRESTONE: Initial efficacy and safety of seribantumab in solid tumors harboring NRG1 fusions. ASCO 2022;Abstract 3006.

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What Is Targeted Therapy?

- First line versus later line?
- Brain metastases?
- Immune checkpoint inhibitors?
- Adjuvant treatment; Stage III unresectable disease

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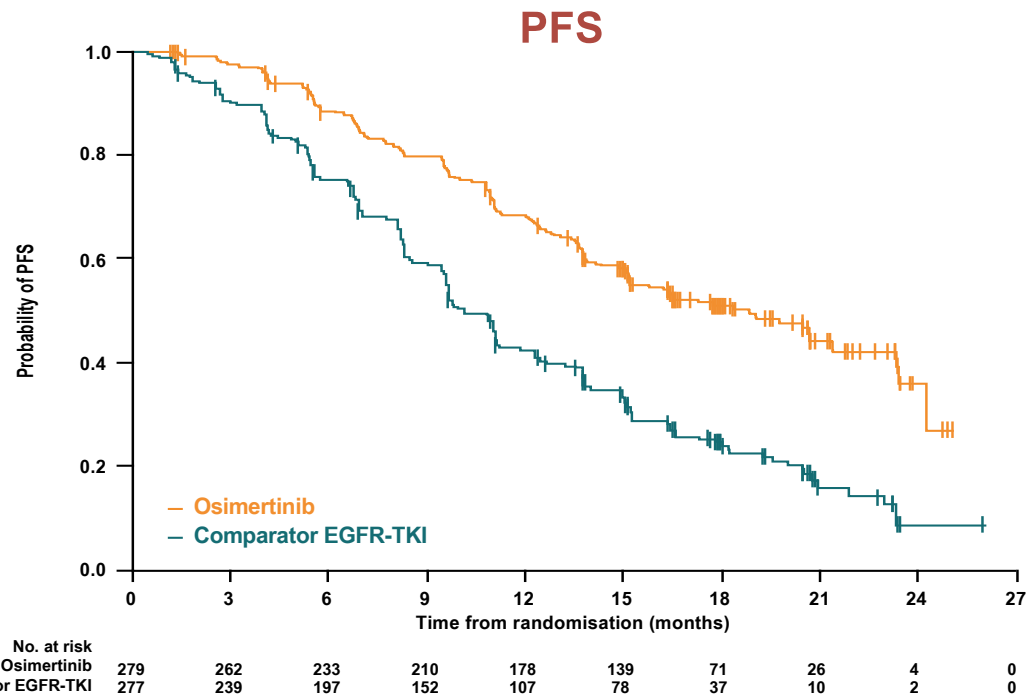
Background: Common EGFR Mutations

- For common, sensitizing EGFR mutations (Exon 19 deletion and L858R), osimertinib (3rd gen EGFR TKI) remains the standard of care.
  - mPFS 1L Osi: 18.9 months; mOS 39 mos
- Treatment options for patients who progress on first-line osimertinib are needed.
- In 2021, osimertinib became the first TKI approved in the adjuvant setting based on improved DFS seen in the ADAURA trial (3 yrs of adjuvant osimertinib vs. placebo)

	Median PFS, mos	HR (95% CI)
Osimertinib	18.9 (15.2, 21.4)	**0.46 (0.37, 0.57); p<0.001**
Comparator EGFR-TKI	10.2 (9.6, 11.1)	



Ramalingam S et al. ESMO 2017. Abstract 4738.
Soria J-C et al. *N Engl J Med.* 2017;378-113-125.

Courtesy of Zofia Piotrowska, MD, MHS

EGFR: Early Stage Disease

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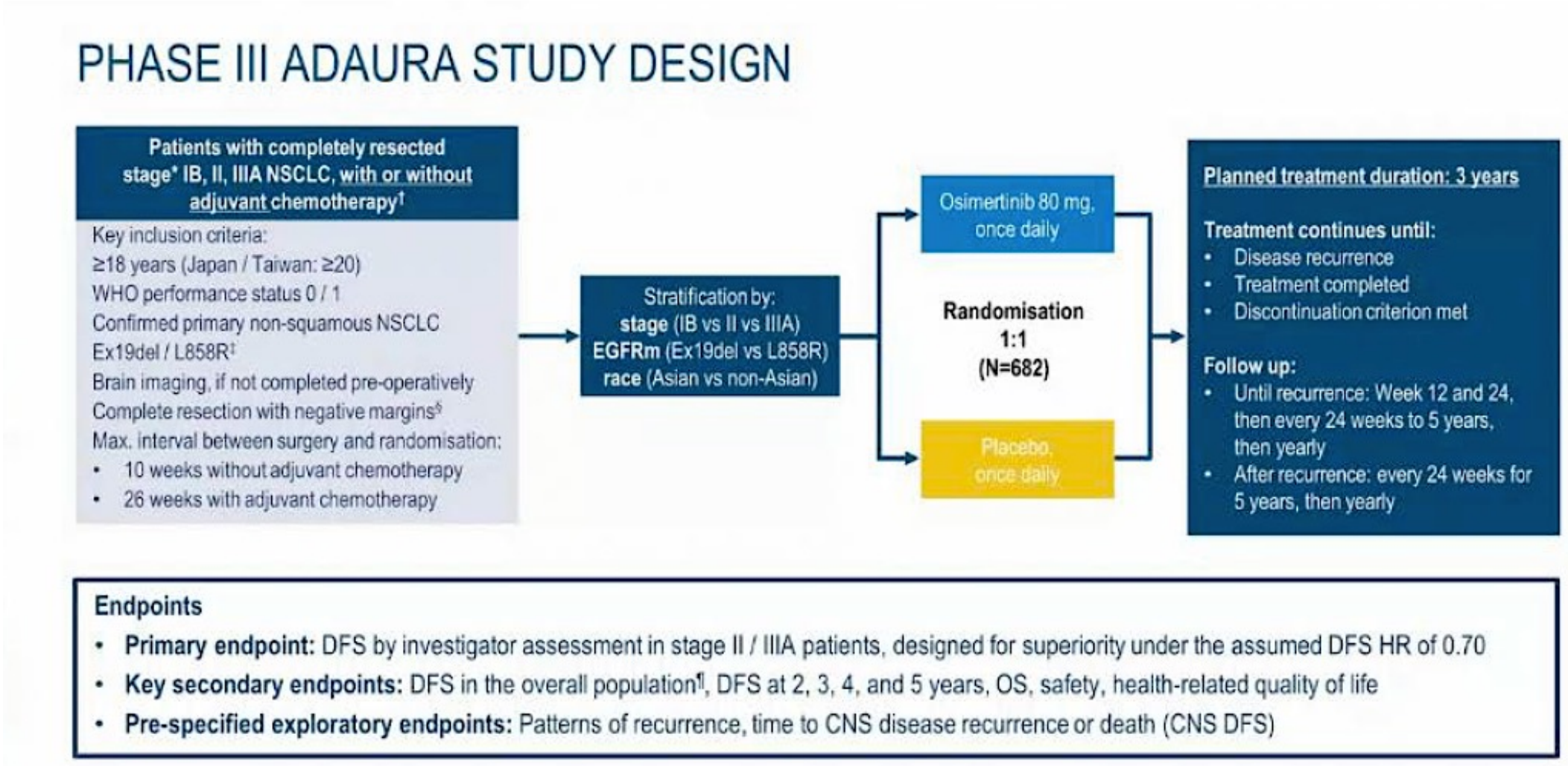
Updated results from ADAURA



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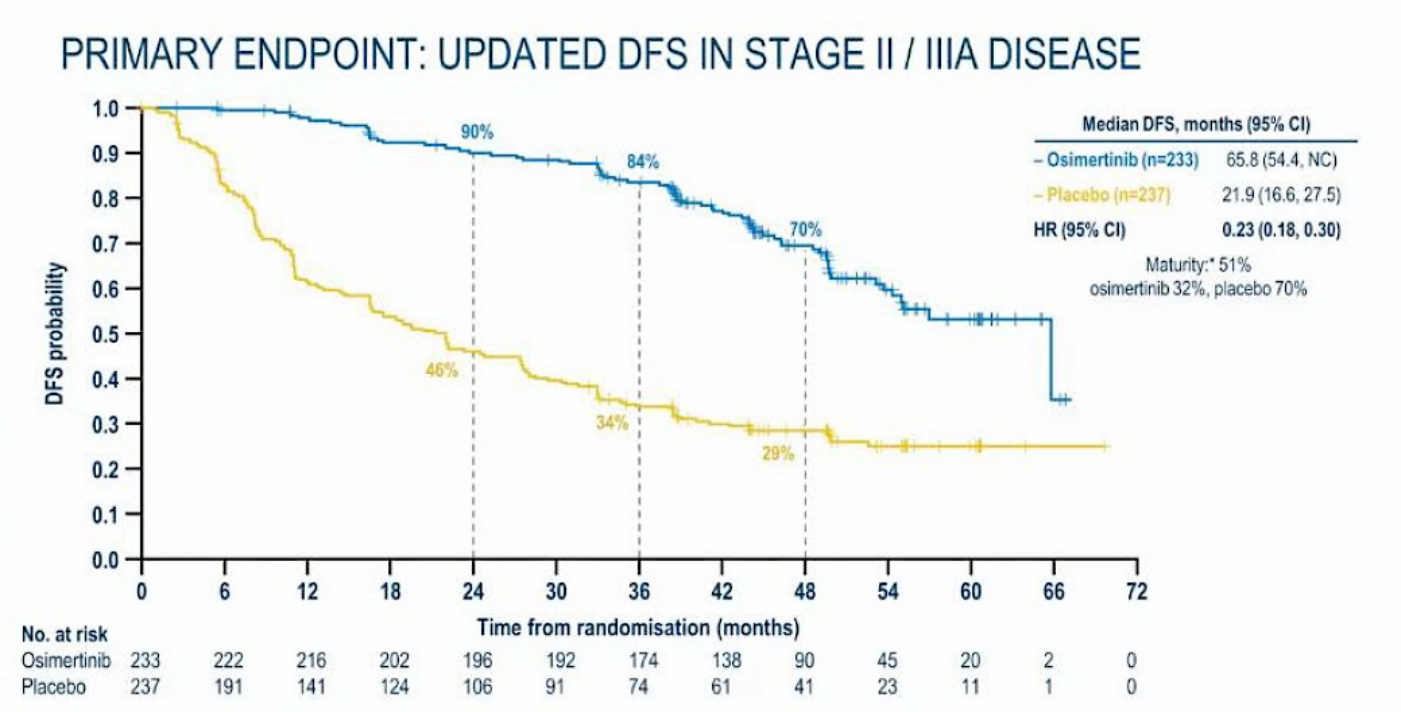


Updated DFS by Stage (AJCC 8th Edition)

	Stage IB	Stage II	Stage IIIA
4 year DFS rate, % (95% CI)			
– Osimertinib	80 (69, 87)	75 (65, 83)	66 (55, 75)
– Placebo	60 (49, 69)	43 (34, 52)	16 (10, 24)
Overall HR (95% CI)	0.44 (0.25, 0.76)	0.33 (0.21, 0.50)	0.22 (0.15, 0.31)

MASSACHUSETTS GENERAL HOSPITAL CANCER CENTER

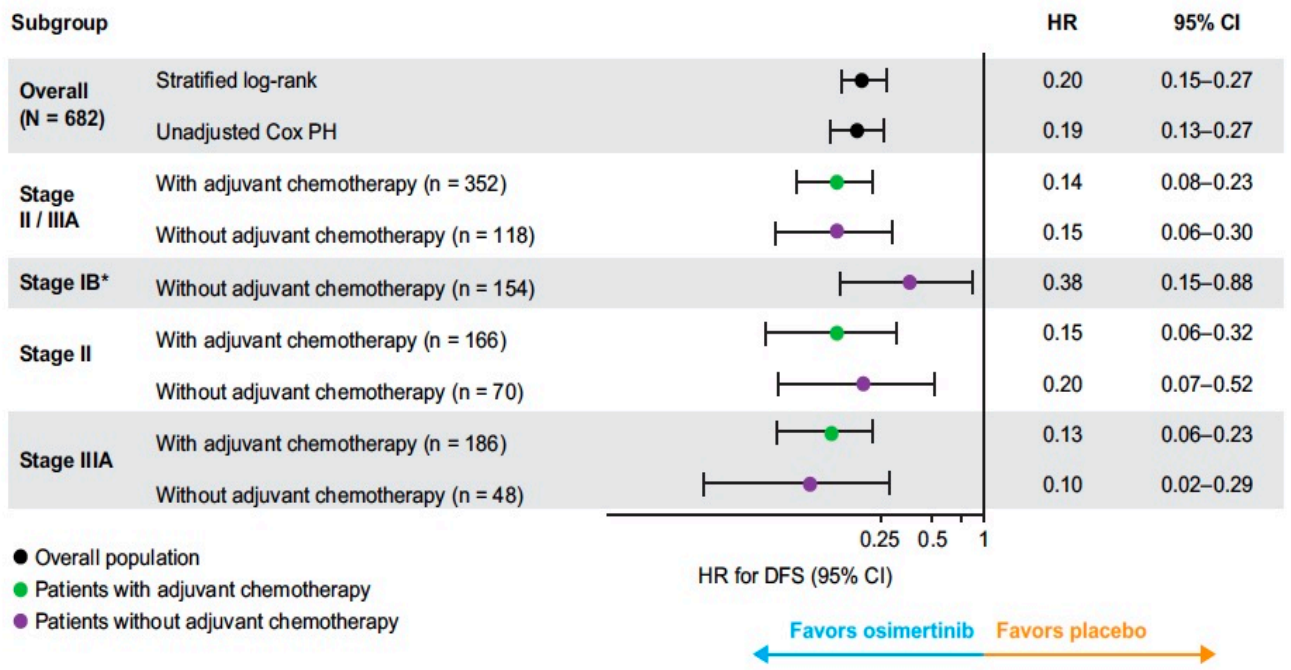
Tsuboi M et al, ESMO 2022.

Courtesy of Zofia Piotrowska, MD, MHS

Postoperative chemo use and outcomes from ADAURA

Table 1. Postoperative (Adjuvant) Chemotherapy Use in ADAURA

Characteristics	Patients, n	Received Adjuvant Chemotherapy, %
Stage IB	216	26[a]
Stage II	231	71[a]
Stage IIIA	235	80[a]
Aged <70 y	509	66
Aged ≥70 y	173	42
WHO PS 0	434	60
WHO PS 1	248	60
Enrolled in Asia[b]	414	65
Enrolled outside of Asia[c]	268	53
Adjuvant chemotherapy	Patients, n[d]	Total, %
Number of patients who received adjuvant chemotherapy	410	60
Adjuvant platinum chemotherapy agents[e]		
Carboplatin	139[f]	20
Cisplatin	275[f]	40
Secondary chemotherapy agents[e]		
Vinorelbine/vinorelbine tartrate	92[f]/101[f]	13/15
Pemetrexed	82[f]	12



Wu YL, *J Thorac Oncol* 2022;17(3):423-33.

Courtesy of Zofia Piotrowska, MD, MHS

Updated results from ADAURA

Clinical Implications:

- The updated results of ADAURA continue to show a sustained improvement in DFS with 3 years of adjuvant osimertinib.
- Adjuvant osimertinib is approved as adjuvant therapy after resection for patients with NSCLC harboring del19 and L858R mutation.
- DFS benefit appears to be maintained regardless of prior chemotherapy use, thus osimertinib can be considered in both chemo-eligible and chemo-ineligible patients.

Future Directions:

- OS Results from ADAURA are eagerly awaited.
- There is a hint that curves may start to come together after 3 years of TKI therapy, a phenomenon that has also been observed in earlier TKI studies-- future studies will be required to determine the optimal duration of adjuvant TKIs.

Courtesy of Zofia Piotrowska, MD, MHS

EGFR: Osimertinib Resistance Mechanisms and Novel Agents

- Piotrowska Z et al. ELIOS: A multicentre, molecular profiling study of patients with epidermal growth factor receptor-mutated advanced NSCLC treated with first-line osimertinib. ESMO 2022;Abstract LBA53.
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Courtesy of Zofia Piotrowska, MD, MHS

ELIOS

Clinical Implications:

- Tissue biopsies are hard to obtain, even in a prospective clinical trial!
- MET Amplification (17%) and EGFR C797S (15%) were the most common resistance mechanisms seen and may be targetable.
- Histologic transformation was not assessed (but occurs in up to 15% of pts in other studies).
- Important to try to get tissue biopsies after first-line osimertinib if possible.

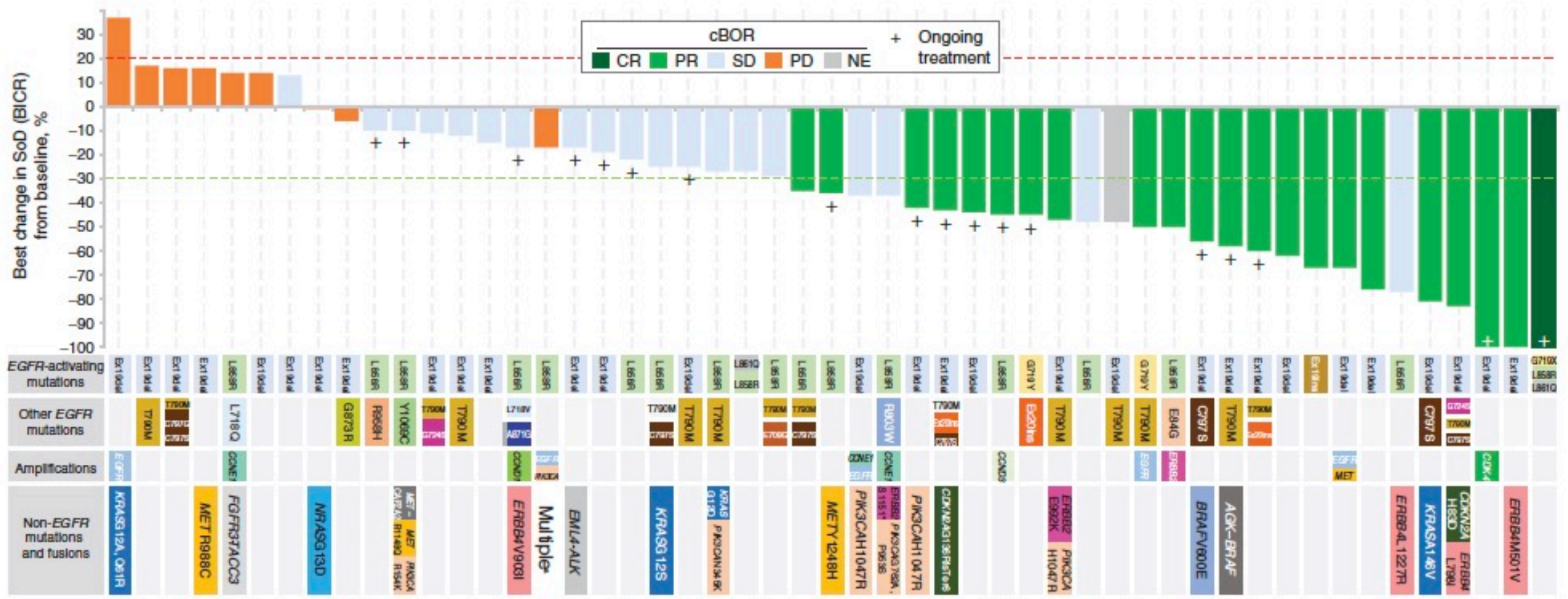
Future Directions:

- Can we develop non-invasive methods for comprehensive evaluation of resistance mechanisms?

Courtesy of Zofia Piotrowska, MD, MHS

Patritumab Deruxtecan
(HER3-DXd; HER3 Antibody-Drug Conjugate)

	All (n=57)	Prior PBC + Osi (n=44)
Confirmed ORR (BICR)	39%	39%
mDOR, mo (range)	6.9 (3.1-NE)	7.0 (3.1-NE)
mPFS, mo (range)	8.2 (4.4-8.3)	8.2 (4.0-NE)



Janne P et al. *Cancer Discovery*, 2022

Courtesy of Zofia Piotrowska, MD, MHS

Patritumab Deruxtecan- Adverse Events

Grade ≥ 3 TEAEs in ≥ 5% pts	5.6 mg/kg (n=57)
Thrombocytopenia	17 (30)
Neutropenia	11 (19)
Fatigue	8 (14)
Anemia	5 (9)
Dyspnea	5 (9)
Febrile neutropenia	5 (9)
Hypoxia	4 (7)
Leukopenia	4 (7)
Hypokalemia	3 (5)
Lymphopenia	3 (5)

TEAEs	5.6 mg/kg (n=57)
TEAEs associated with treatment discontinuation	6 (11)
TEAEs associated with dose reduction	12 (21)
TEAEs associated with dose interruption	21 (37)
TEAEs associated with death * None treatment-related.	4 (7)

Adjudicated treatment-related ILD: 7%

Janne P et al. *Cancer Discovery*, 2022

Courtesy of Zofia Piotrowska, MD, MHS

Patritumab Deruxtecan

Clinical Implications:

- Patritumab deruxtecan is active in TKI- and chemo-resistant EGFR-mutant NSCLC, including patients with various resistance mechanisms (ORR 39%, mPFS 8.2 months)
- Patritumab is not yet approved (has breakthrough therapy designation), but clinical trials are ongoing including osimertinib combinations in the first and second-line setting.

Future Directions:

- Can we find biomarkers of Patritumab response?

Courtesy of Zofia Piotrowska, MD, MHS

Amivantamab + Lazertinib

Clinical Implications:

- Ami/Lazer is another active combination in TKI-resistant EGFR-mutant NSCLC, with activity across various resistance mechanisms.
- Amivantamab/Lazertinib is not yet approved as a combination in EGFR TKI resistance, but trials are ongoing.

Future Directions:

- Again- biomarkers to select patients for treatment are needed!

Courtesy of Zofia Piotrowska, MD, MHS

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MODULE 8: KRAS G12C mutations

EGFR Exon 20 Insertions

- Ramalingam SS et al. Phase I/II study of **mobocertinib in EGFR exon 20 insertion**+ metastatic NSCLC: Updated results from platinum-pretreated patients. ESMO 2022; Abstract 988P.
- Park K et al. **Amivantamab in EGFR exon 20 insertion**-mutated NSCLC progressing on platinum chemotherapy: Initial results from the CHRYSALIS Phase I study. J Clin Oncol 2021;39(30):3391-402.
- Yu HA et al. Phase (Ph) 1/2a study of **CLN-081 in patients (pts) with NSCLC with EGFR exon 20 insertion mutations** (Ins20). ASCO 2022; Abstract 9007.
- Bazhenova L et al. **Sunvozertinib in NSCLC Patients with EGFR Exon20 Insertion** Mutations. 2022 North America Conference on Lung Cancer.

Courtesy of Zofia Piotrowska, MD, MHS

Mobocertinib: Updated Results from the PPP Cohort

Clinical Implications:

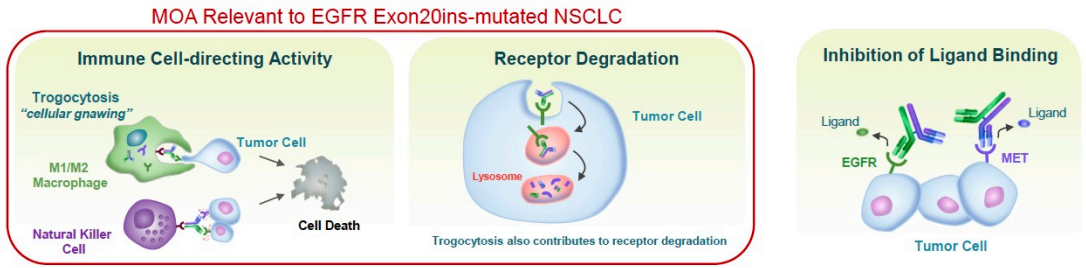
- Efficacy of mobocertinib appears consistent with earlier reports and continues to support the use of osimertinib post-chemotherapy.
- Rates of diarrhea remain high, with > 90% pts experiencing diarrhea.
- Selection between mobocertinib and amivantamab should be made on a case-by-case basis, with the goal of most patients accessing both therapies during their disease course.

Future Directions:

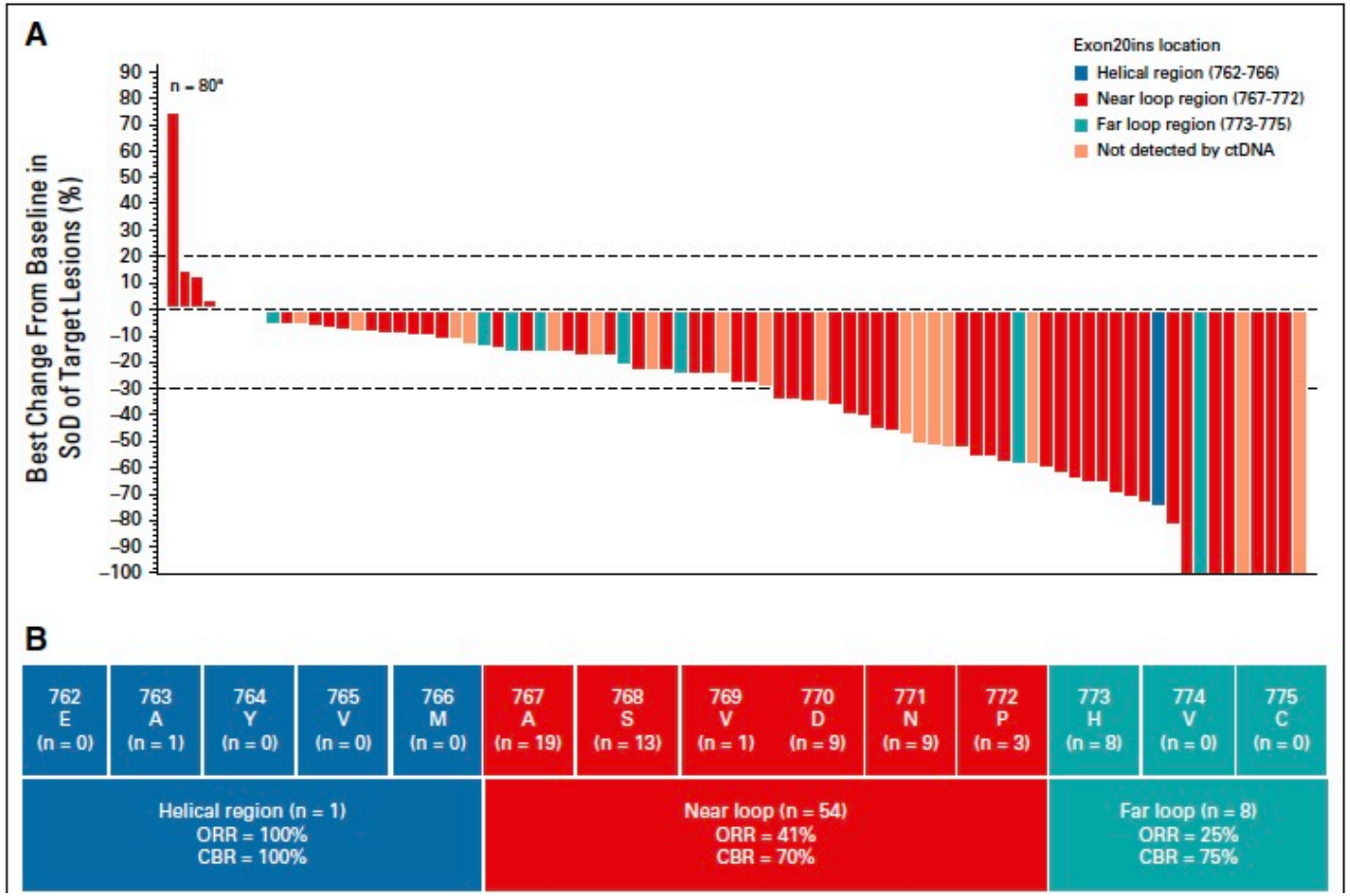
- Will mobocertinib move to the first-line setting?
- Will novel agents improve efficacy, safety and CNS penetration?

Courtesy of Zofia Piotrowska, MD, MHS

Amivantamab



	Post-Platinum EGFR Ins20 N=81
UXX".OI /	: 6+ "
s JUX .OI /	774"s ut zny
s VLY .OI /	>49"s ut zny



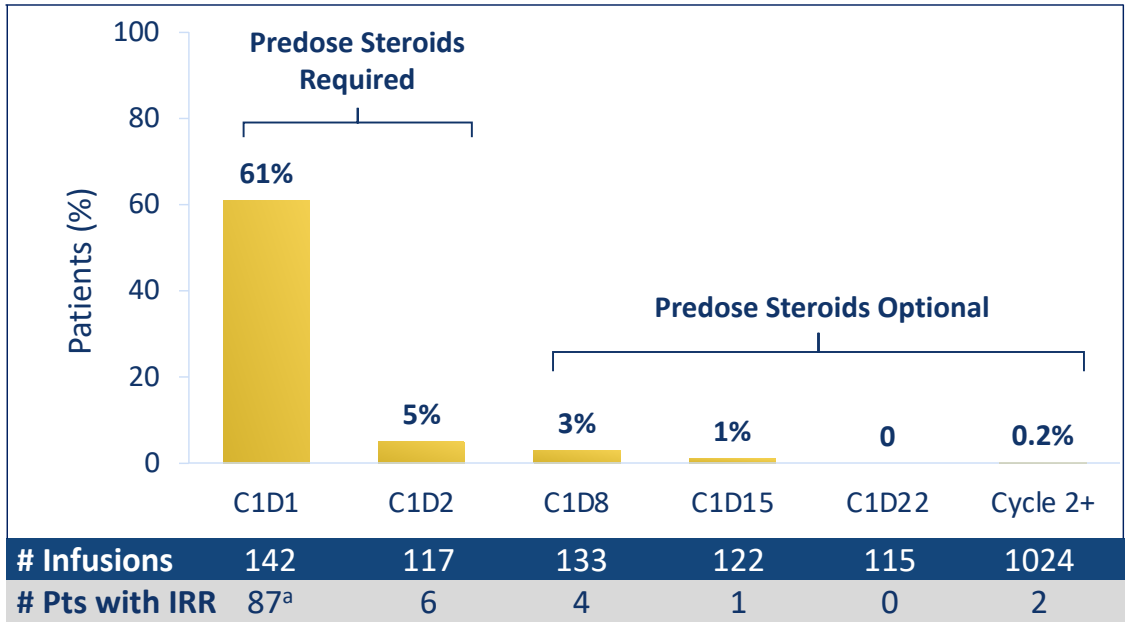
Park K et al. *J Clin Oncol.* 2021;39:3391-3402.
Sabari, J, WCLC 2020

Courtesy of Zofia Piotrowska, MD, MHS

Amivantamab Safety

Adverse Event	Total	Grade 1	Grade 2	Grade ≥ 3
Rash	86%	38%	45%	4%
Infusion-related reaction	66%	8%	55%	3%
Paronychia	45%	25%	19%	1%
Hypoalbuminemia	27%	5%	19%	3%
Constipation	24%	16%	8%	0%
Nausea	19%	15%	4%	0%
Dyspnea	19%	11%	7%	2%
Stomatitis	21%	10%	11%	0%
Peripheral edema	18%	18%	1%	0%
Pruritus	17%	10%	7%	0%
Fatigue	18%	13%	4%	2%
Cough	14%	10%	4%	0%
Dry skin	16%	16%	0%	0%
Incr ALT	15%	13%	1%	1%

Dose reduction: 13% | Dose discontinuation: 10%



- IRR Severity: 98% Gr 1-2; 2% Gr 3
- Chills, SOB, nausea, flushing
- Primarily limited to first infusion
- Improves with split dosing (C1D1, C1D2)

Park K et al. *J Clin Oncol.* 2021;39:3391-3402.
Sabari, J, WCLC 2020

Courtesy of Zofia Piotrowska, MD, MHS

Amivantamab

Clinical Implications:

- Amivantamab is an active therapy for patients with EGFR exon 20 insertions (ORR 40%, mPFS 8.3 months).
- Key toxicities include skin rash and IRRs.
- Selection between mobocertinib and amivantamab should be made on a case-by-case basis, with the goal of most patients accessing both therapies during their disease course.

Future Directions:

- Amivantamab being tested first-line in combination with chemotherapy (PAPILLON)
- More active, better tolerated and more CNS penetrant therapies are needed

Courtesy of Zofia Piotrowska, MD, MHS

EGFR Exon 20: Novel Agents

Clinical Implications:

- Still in clinical trials, but novel EGFR TKIs like Sunvozertinib and CLN-081 appear to have improved efficacy and safety profiles over currently-approved options.

Future Directions:

- New drugs predicted to have CNS penetration (BLU-451, ORIC-114) are now entering the clinic.

Courtesy of Zofia Piotrowska, MD, MHS

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Background: ALK + ROS1 alterations in NSCLC

- ALK-positive NSCLC:
  - In the US, crizotinib, ceritinib, alectinib, brigatinib and lorlatinib are all approved for front-line use in ALK-positive NSCLC.
  - Randomized, phase 3 trials of second-generation (alectinib, brigatinib) and recently, third-generation (lorlatinib) ALK inhibitors have all shown superiority to crizotinib in the front line setting.

- ROS1-positive NSCLC:
  - In the United States, crizotinib and entrectinib are both approved in ROS1+ NSCLC

Shaw. *NEJM*. 2014;371:1963. Shaw. *Ann Oncol*. 2019;30:1121.

Courtesy of Zofia Piotrowska, MD, MHS

ALK+ NSCLC

- Hotta K, et al. **Final overall survival analysis from the Phase III J-ALEX study** of alectinib versus crizotinib in ALK inhibitor-naïve Japanese patients with ALK-positive non-small-cell lung cancer. ESMO Open 2022;7(4):100527.
- Camidge DR et al. Brigatinib versus crizotinib in ALK inhibitor-naïve advanced ALK-positive NSCLC: **Final results of Phase III ALTA-1L trial**. J Thorac Oncol 2021;16(12):2091-108.
- Solomon BJ et al. Efficacy and safety of first-line lorlatinib versus crizotinib in patients with advanced, ALK-positive non-small-cell lung cancer: **Updated analysis of data from the phase 3, randomised, open-label CROWN study**. *Lancet Respir Med* 2022, Published Online December 16, 2022.
- Solomon BJ et al. Post hoc analysis of **lorlatinib intracranial efficacy and safety in patients with ALK-positive advanced non-small-cell lung cancer from the Phase III CROWN** study. J Clin Oncol 2022;40(31):3593-602.

Courtesy of Zofia Piotrowska, MD, MHS

J-ALEX and ALTA-1L Updated Analyses

Clinical Implications:

- With > 5 yrs follow up, no OS difference between first-line Alectinib and Crizotinib in J-ALEX. Not surprising that there was no difference in OS between the two treatment arms, given the widespread availability of alectinib and other next-generation ALK inhibitors and high rates of crossover.
- In the final data from ALTA-1L, brigatinib maintained clear PFS advantage over crizotinib (HR 0.48), but also did not show OS difference.
- Alectinib and brigatinib (both 2nd gen ALK TKIs) remain good first-line treatment options, though the selection of second vs. third-generation ALK inhibitors as first-line therapy remains an area of active debate given the impressive results of the CROWN study (first-line lorlatinib).

Future Directions:

- Will we ever have a 2nd vs. 3rd gen ALK TKI first-line study?

Courtesy of Zofia Piotrowska, MD, MHS

CROWN Trial

Clinical Implications:

- Continued follow-up of the CROWN study and CNS-specific analyses continue to show impressive results with first-line lorlatinib, with 64% pts progression-free at 3 years. These results compare favorably with second-generation ALK TKIs in cross-trial comparisons.
- Intracranial response rates are substantially higher with lorlatinib, which also significantly delays time to intracranial progression.
- CNS Adverse events occurred in 35% pts overall, but dose modification (interruption or reduction) did not adversely impact PFS.
- Lorlatinib is now a preferred first-line TKI for newly diagnosed ALK+ NSCLC, and is my preferred agent for patients with baseline brain mets.

Future Directions:

- Better understanding of Resistance Mechanisms, high-risk subgroups

Courtesy of Zofia Piotrowska, MD, MHS

ROS1+ NSCLC

- Fan Y, et al. **Entrectinib in patients with ROS1 fusion-positive NSCLC**: Updated efficacy and safety analysis. WCLC 2022; Abstract MA13.04.
- Drilon A, et al. **NVL-520 is a selective, TRK-sparing, and brain-penetrant inhibitor of ROS1** fusions and secondary resistance mutations. Cancer Discovery 2022.

Courtesy of Zofia Piotrowska, MD, MHS

Entrectinib in patients with ROS1 fusion-positive NSCLC

Clinical Implications:

- Entrectinib's efficacy is maintained in this analysis and entrectinib remains a standard of care of patients with ROS1+ NSCLC.
- High intracranial response rates make it my preferred first-line ROS1 TKI for patients with baseline brain metastases.

Future Directions:

- Phase III trial of entrectinib vs. crizotinib in ROS1+ NSCLC is ongoing.

Courtesy of Zofia Piotrowska, MD, MHS

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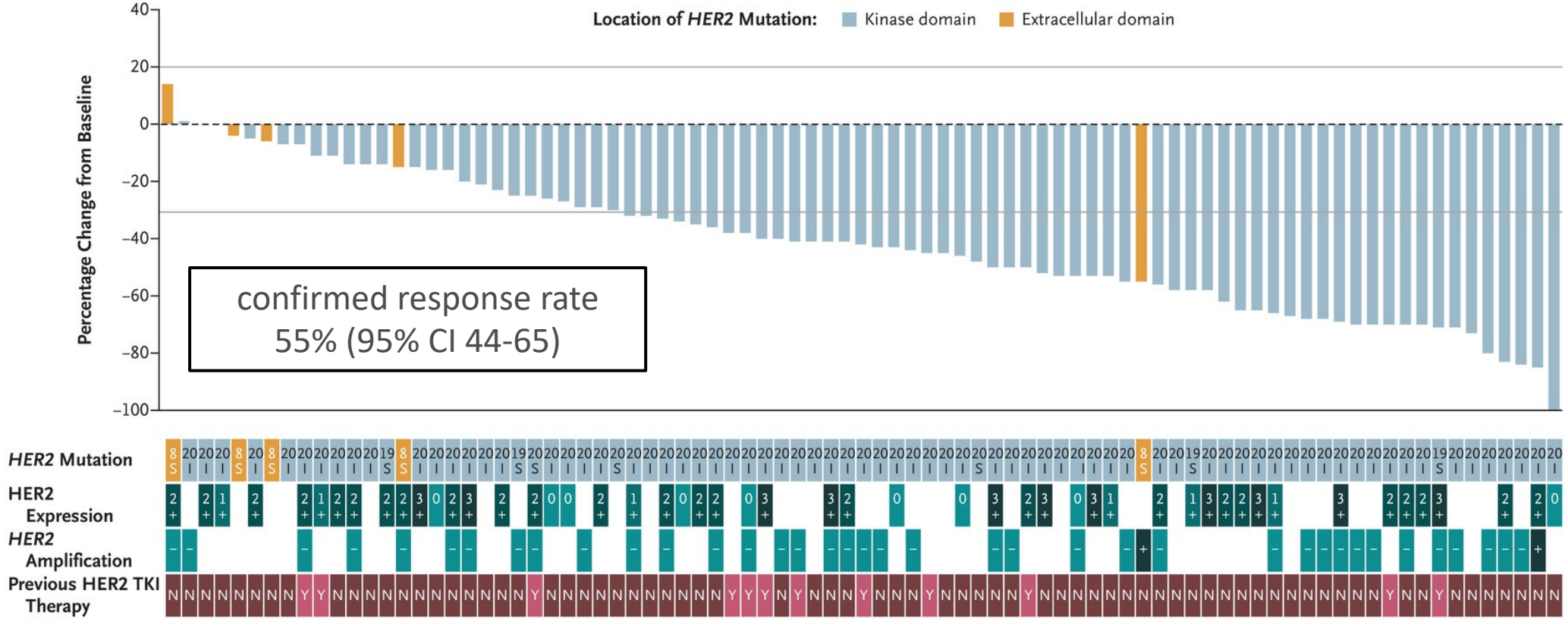
Trastuzumab deruxtecan in patients with HER2 (ERBB2) mutant NSCLC



Li BT et al. Trastuzumab deruxtecan in HER2-mutant non-small-cell lung cancer. N Engl J Med 2022;386(3):241-51.

Courtesy of Gregory J Riely, MD, PhD

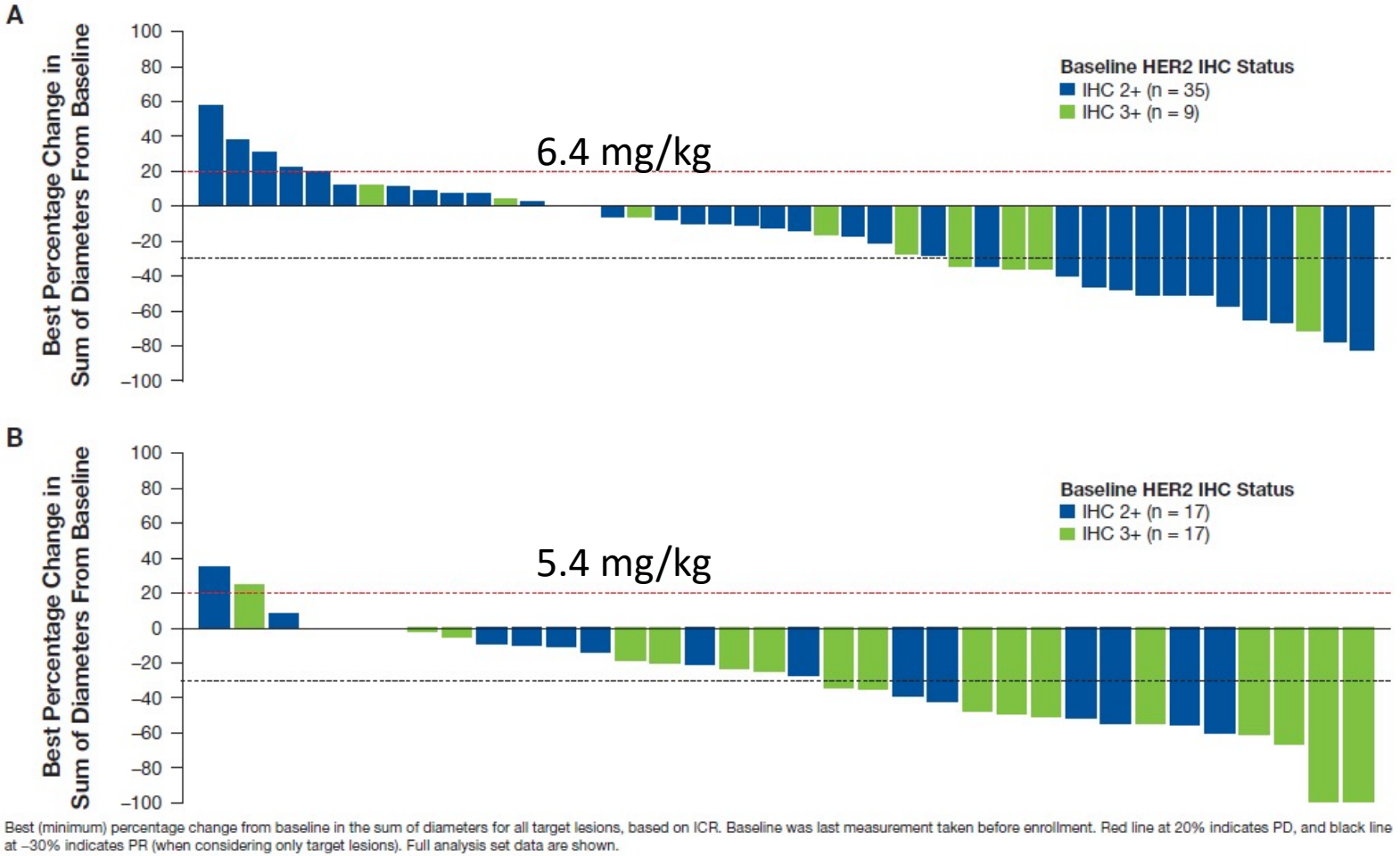
Trastuzumab deruxtecan in patients with HER2 (ERBB2) mutant NSCLC

- Identifying HER2 mutations in patients with NSCLC leads to a targeted therapy option
- In the setting of patients with previously-treated HER2 mutant NSCLC, trastuzumab deruxtecan has reasonable efficacy as evaluated by response rate and progression-free survival

Li BT et al. Trastuzumab deruxtecan in HER2-mutant non-small-cell lung cancer. N Engl J Med 2022;386(3):241-51.

Courtesy of Gregory J Riely, MD, PhD

How effective is trastuzumab deruxtecan in patients with HER2 overexpression?



Best (minimum) percentage change from baseline in the sum of diameters for all target lesions, based on ICR. Baseline was last measurement taken before enrollment. Red line at 20% indicates PD, and black line at −30% indicates PR (when considering only target lesions). Full analysis set data are shown.

Response Rate
27%

mDOR
5.8 months

Response Rate
34%

mDOR
6.2 months

Smit EF et al. Trastuzumab deruxtecan in patients with HER2-overexpressing metastatic non-small cell lung cancer: Results from the DESTINY-Lung01 trial. ESMO 2022;Abstract 975P.

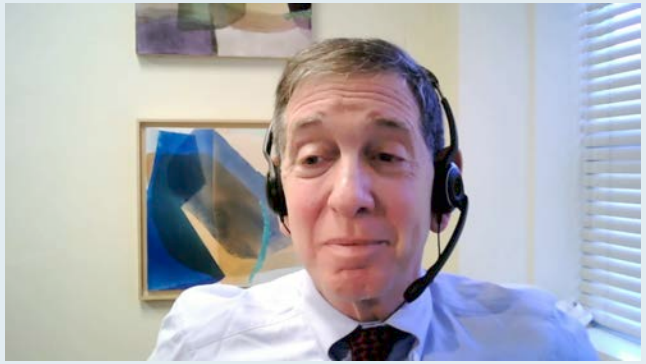
Courtesy of Gregory J Riely, MD, PhD

How effective is trastuzumab deruxtecan in patients with HER2 overexpression?

- Trastuzumab deruxtecan has efficacy in patients with HER2 over-expression (HER2 2+ or HER2 3+)

Smit EF et al. Trastuzumab deruxtecan in patients with HER2-overexpressing metastatic non-small cell lung cancer: Results from the DESTINY-Lung01 trial. ESMO 2022;Abstract 975P.

Courtesy of Gregory J Riely, MD, PhD



Dr Alan Astrow
(Brooklyn, New York)

Case Presentation: 91-year-old woman with "mild" dementia and ER/PR-negative, HER2 IHC 1+ IDC with symptomatic chest wall recurrence s/p neoadjuvant paclitaxel/trastuzumab and lumpectomy

Case Presentation: 90-year-old woman with ER/PR-positive, HER2-low (IHC 1+) mBC and PD on multiple lines of endocrine and chemotherapy receives T-DXd

RTP
RESEARCH
TO PRACTICE

Trastuzumab Deruxtecan (T-DXd)

Disease	Indication	Initial dose (q3wk)	First dose reduction	Second dose reduction	Further dose reduction
Breast	• Unresectable or metastatic disease • Prior anti-HER2 regimen in metastatic or (neo)adjuvant setting w/ recurrence during or w/in 6 months of completing therapy	5.4 mg/kg	4.4 mg/kg	3.2 mg/kg	Discontinue
	• Unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) • Prior chemotherapy in the metastatic setting or developed disease recurrence during or w/in 6 months of completing adjuvant chemotherapy	5.4 mg/kg	4.4 mg/kg	3.2 mg/kg	Discontinue
Lung*	• Unresectable or metastatic NSCLC whose tumors have activating HER2 mutations • Received a prior systemic therapy	5.4 mg/kg	4.4 mg/kg	3.2 mg/kg	Discontinue
Gastric	• Locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma • Received a prior trastuzumab-based regimen	6.4 mg/kg	5.4 mg/kg	4.4 mg/kg	Discontinue

Premedication: T-DXd is moderately emetogenic, which includes delayed nausea and/or vomiting. Administer prophylactic antiemetic medications per local institutional guidelines for prevention of chemotherapy-induced nausea and vomiting.

* This indication is approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Trastuzumab deruxtecan package insert.

What's the right dose of trastuzumab deruxtecan?

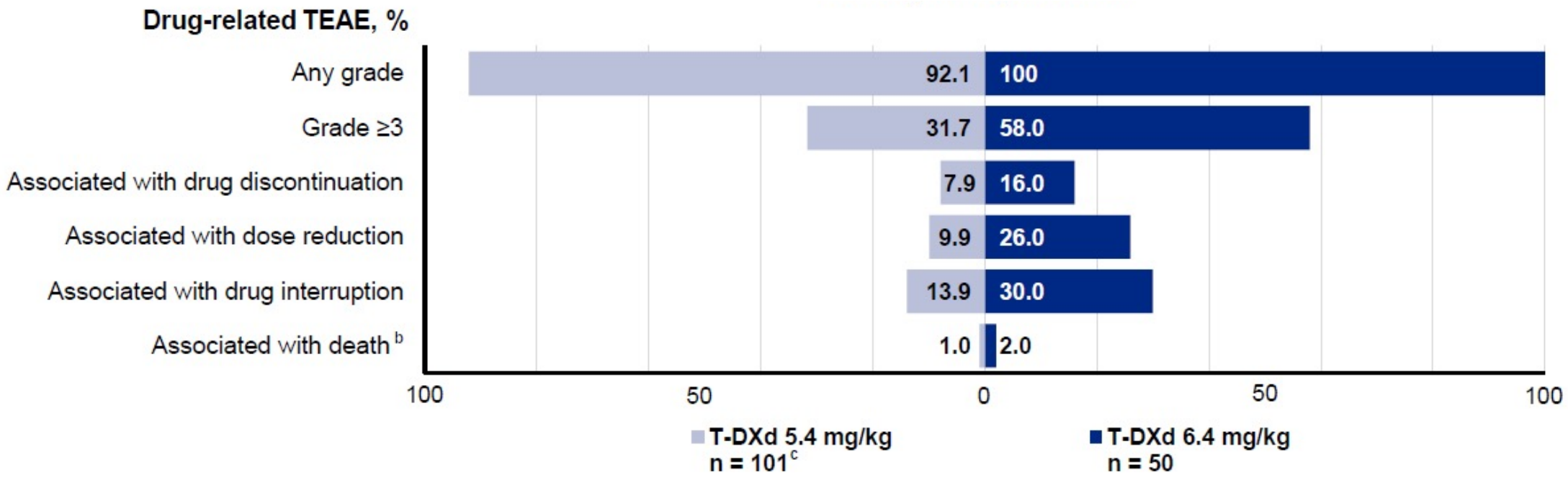
Response by BICR

Response Assessment by BICR	Prespecified early cohort	
	T-DXd 5.4 mg/kg n = 52	T-DXd 6.4 mg/kg n = 28
Confirmed ORR,[a] n (%) [95% CI]	28 (53.8) [39.5, 67.8]	12 (42.9) [24.5, 62.8]
Best overall response, n (%)		
CR	1 (1.9)	1 (3.6)
PR	27 (51.9)	11 (39.3)
SD	19 (36.5)	14 (50.0)
PD	2 (3.8)	1 (3.6)
Not evaluable[b]	3 (5.8)	1 (3.6)
DCR,[c] n (%) [95% CI]	47 (90.4) [79.0, 96.8]	26 (92.9) [76.5, 99.1]
Median DoR, months [95% CI]	NE [4.2, NE]	5.9 [2.8, NE]

Goto K et al. Trastuzumab deruxtecan in patients with HER2-mutant metastatic non-small cell lung cancer: Interim results from the Phase II DESTINY-Lung02 trial. ESMO 2022;Abstract LBA55.

Courtesy of Gregory J Riely, MD, PhD

What's the right dose of trastuzumab deruxtecan?



Median treatment duration, months (range)	3.7 (0.7-11.8)	3.3 (0.7-12.6)
Median follow-up, months (range)	3.8 (0-11.7)	3.9 (0.5-12.1)

Goto K et al. Trastuzumab deruxtecan in patients with HER2-mutant metastatic non-small cell lung cancer: Interim results from the Phase II DESTINY-Lung02 trial. ESMO 2022;Abstract LBA55.

Courtesy of Gregory J Riely, MD, PhD

What's the right dose of trastuzumab deruxtecan?

- Both 5.4 mg/kg and 6.4 mg/kg have efficacy in patients with previously treated HER2 mutant NSCLC
- There was no clear increase in efficacy with the higher dose.
- There was a lower incidence of ILD and other adverse events with the 5.4 mg/kg dose
- "The totality of the evidence and a compelling positive benefit-risk balance supported the FDA's approval of T-DXd 5.4 mg/kg as the first HER2-targeted treatment for patients with previously treated HER2m NSCLC and support the establishment of T-DXd as a new SoC in this population"

Goto K et al. Trastuzumab deruxtecan in patients with HER2-mutant metastatic non-small cell lung cancer: Interim results from the Phase II DESTINY-Lung02 trial. ESMO 2022;Abstract LBA55.

Courtesy of Gregory J Riely, MD, PhD

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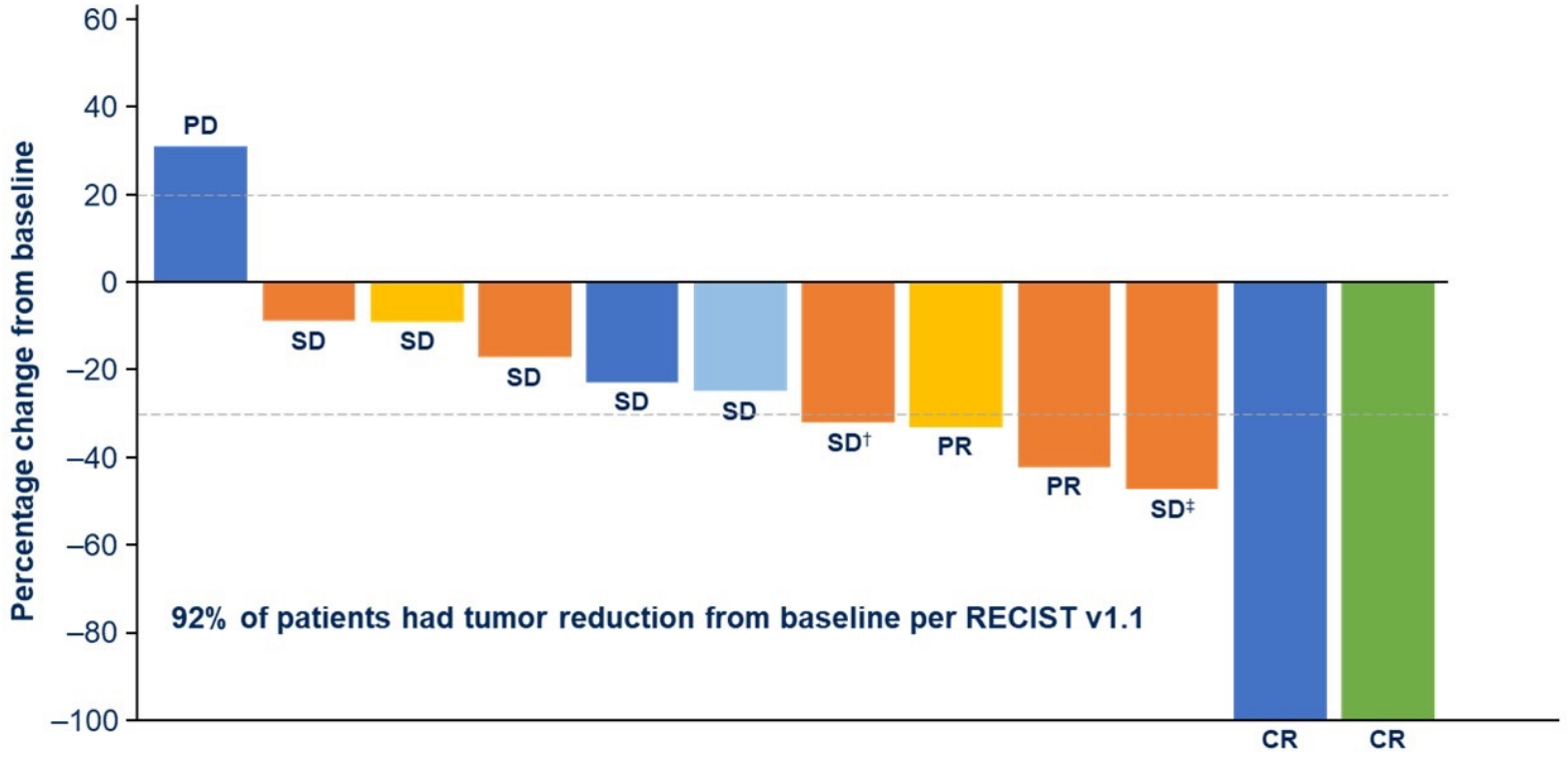
Seribantumab, an anti-HER3 antibody, has efficacy in patients with NRG1 fusions



Confirmed INV-ORR	
Overall	33% (4/12)
NSCLC	36% (4/11)

NRG1 fusion partner:
- SLC3A2
- CD74
- SDC4
- ATP1B1
- ITGB1

Carrizosa D et al. CRESTONE: Initial efficacy and safety of seribantumab in solid tumors harboring NRG1 fusions. ASCO 2022;Abstract 3006.

Courtesy of Gregory J Riely, MD, PhD

Seribantumab, an anti-HER3 antibody, has efficacy in patients with NRG1 fusions

- NRG1 fusions are a rare molecular entity that occur in a range of tumor types. These gene fusions lead to overactivation of the HER3 pathway.

- Seribantumab, an anti-HER3 antibody, has clear efficacy in patients with NRG1 fusions with different tumor types (including lung and pancreas) and different fusion partners.

Carrizosa D et al. CRESTONE: Initial efficacy and safety of seribantumab in solid tumors harboring NRG1 fusions. ASCO 2022;Abstract 3006.

Courtesy of Gregory J Riely, MD, PhD

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Selpercatinib in RET fusion-positive NSCLC

TABLE 2. Efficacy

Response	Treatment-Naive (n = 69)	Previous Platinum Chemotherapy (n = 247)
Objective response by IRC, % (95% CI)	84 (73 to 92)	61 (55 to 67)
Best response, No. (%)		
CR	4 (6)	18 (7)
Partial response	54 (78)	133 (54)
Stable disease	6 (9)	81 (33)
Progressive disease	3 (4)	7 (3)
NE	2 (3)	8 (3)
DoR		
Median (95% CI), months	20.2 (13.0 to NE)	28.6 (20.4 to NE)
PFS		
Disease progression, No. (%)	29 (42.0)	89 (36.0)
Median (95% CI), months	22.0 (13.8 to NE)	24.9 (19.3 to NE)

Modified from Drilon A et al. Selpercatinib in patients with RET fusion-positive non-small-cell lung cancer: Updated safety and efficacy from the registrational LIBRETTO-001 Phase I/II trial. J Clin Oncol 2022;[Online ahead of print].

Courtesy of Gregory J Riely, MD, PhD

Selpercatinib in RET fusion-positive NSCLC

- Further data to support efficacy of selpercatinib in RET fusion positive NSCLC

- Higher response rate in the first-line setting, but other measures of efficacy (PFS, DoR, and OS) are similar

Drilon A et al. Selpercatinib in patients with RET fusion-positive non-small-cell lung cancer: Updated safety and efficacy from the registrational LIBRETTO-001 Phase I/II trial. J Clin Oncol 2022;[Online ahead of print].

Courtesy of Gregory J Riely, MD, PhD

Quality of Life for Selpercatinib in RET fusion-positive NSCLC

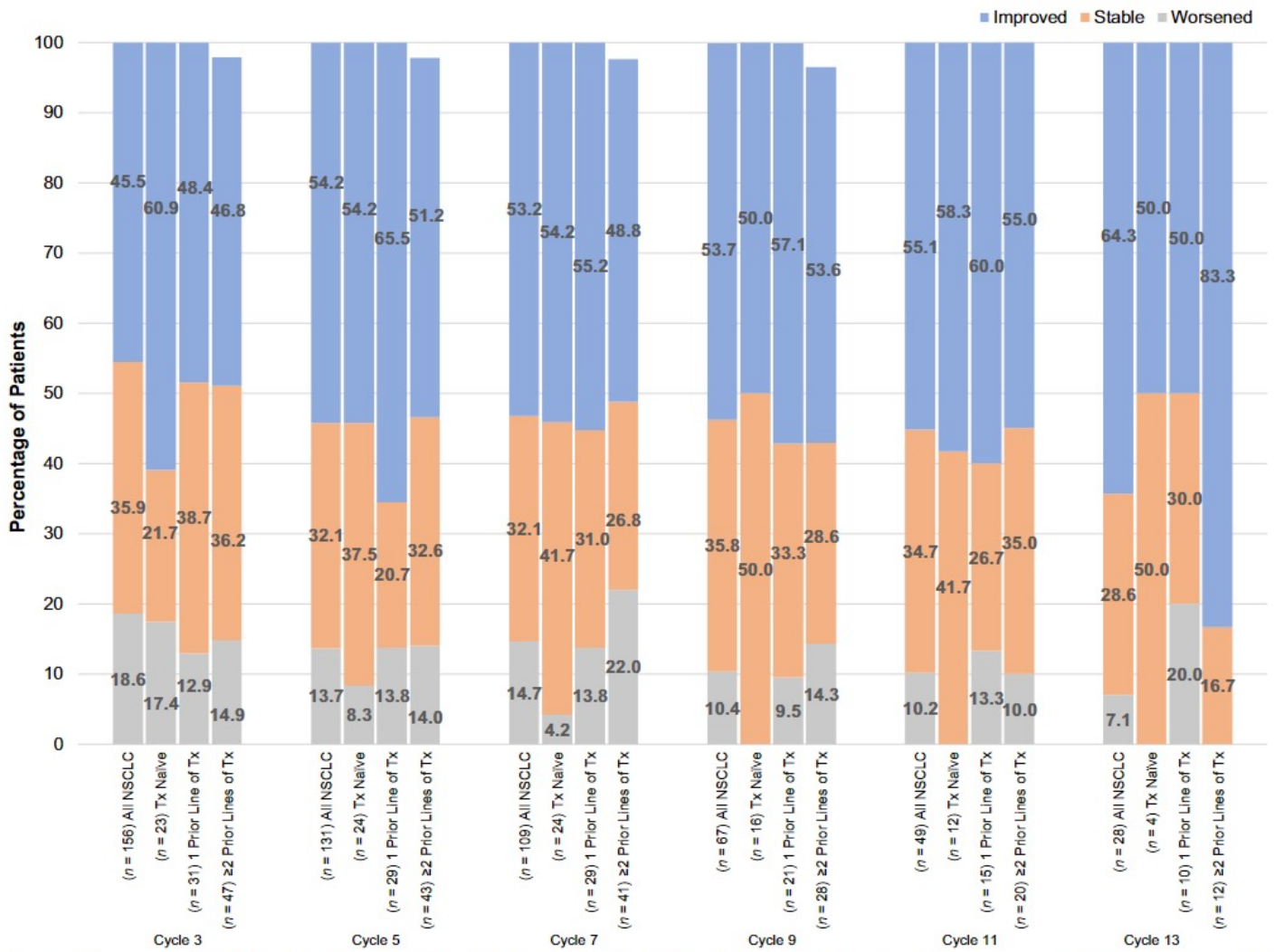


Figure 1. Change in global health status/quality of life from baseline by cycle of study treatment as measured by the Quality of Life Questionnaire (QLQ-C30) in patients with *RET* fusion–positive NSCLC. For each respective cycle, the percentage of patients whose status improved (blue bar), remained stable (orange bar), or worsened (gray bar) from baseline was calculated using the number of patients with both baseline and corresponding postbaseline assessment as the denominator.
Abbreviations: NSCLC, non-small cell lung cancer; Tx, treatment.

Minchom A et al. Patient-reported outcomes with selpercatinib among patients with RET fusion-positive non-small cell lung cancer in the Phase I/II LIBRETTO-001 trial. Oncologist 2022;27(1):22-9.

Courtesy of Gregory J Riely, MD, PhD

Quality of Life for Selpercatinib in RET fusion-positive NSCLC

- In addition to objective evidence of disease regression, selpercatinib treatment clearly improves quality of life across a range of categories.

- Selpercatinib continues to improve quality of life over many cycles of therapy

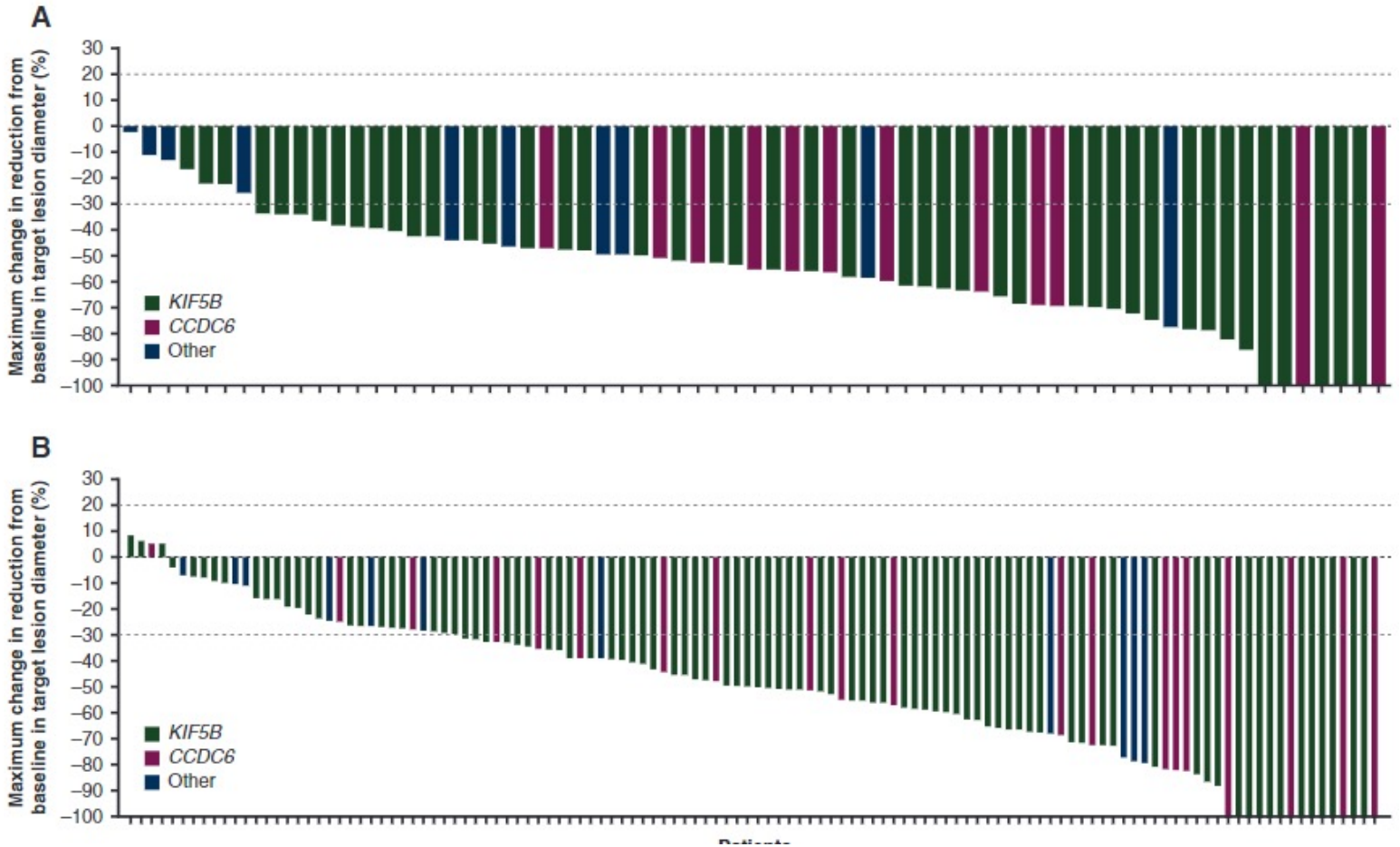
Minchom A et al. Patient-reported outcomes with selpercatinib among patients with RET fusion-positive non-small cell lung cancer in the Phase I/II LIBRETTO-001 trial. Oncologist 2022;27(1):22-9.

Courtesy of Gregory J Riely, MD, PhD

Pralsetinib for treatment of patients with RET fusion-positive NSCLC

First-line
RR- 72%

Prior platinum
RR- 59%



Griesinger F et al. Safety and efficacy of pralsetinib in RET fusion-positive non-small-cell lung cancer including as first-line therapy: Update from the ARROW trial. Ann Oncol 2022;33(11):1168-1178

Courtesy of Gregory J Riely, MD, PhD

Pralsetinib for treatment of patients with RET fusion-positive NSCLC

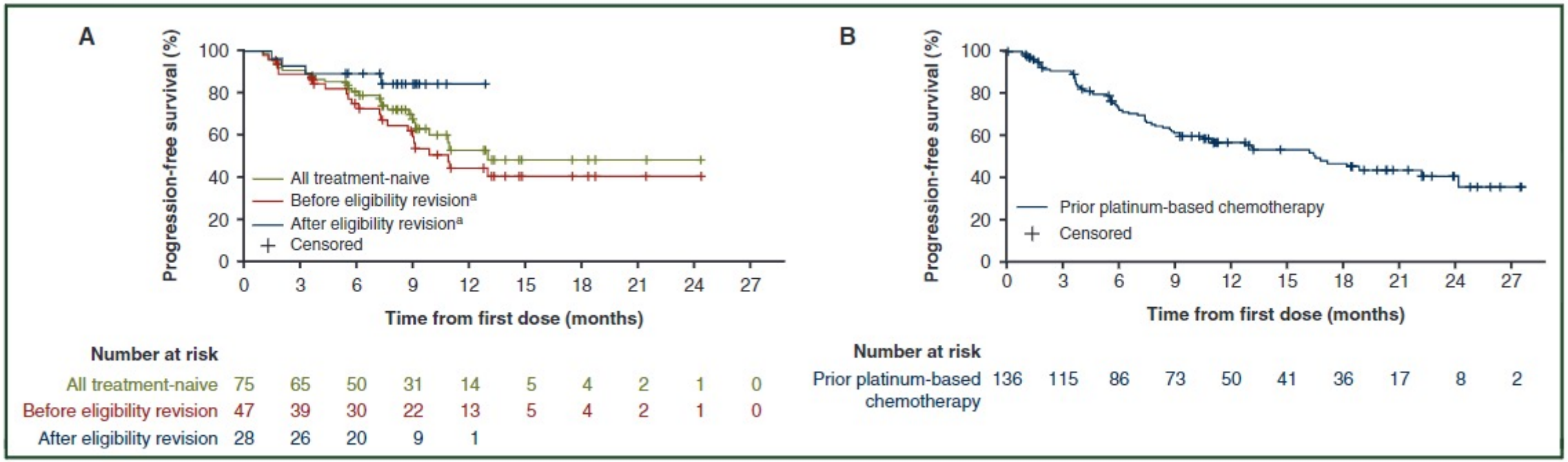


Figure 3. Progression-free survival in patients with *RET* fusion–positive NSCLC. Progression-free survival in (A) treatment-naive patients and (B) patients with prior platinum-based chemotherapy.

[a]Protocol amendment July 2019; this amendment expanded inclusion criteria to allow recruitment of treatment-naive patients eligible for standard platinum-based therapy who had previously not been permitted.

NSCLC, non-small-cell lung cancer.

Griesinger F et al. Safety and efficacy of pralsetinib in RET fusion-positive non-small-cell lung cancer including as first-line therapy: Update from the ARROW trial. Ann Oncol 2022;33(11):1168-1178

Courtesy of Gregory J Riely, MD, PhD

Pralsetinib for treatment of patients with RET fusion-positive NSCLC

- Continued evidence of efficacy for pralsetinib in patients with RET fusion-positive NSCLC

- Higher response rate observed in first-line therapy suggests upfront testing for patients with NSCLC is critical to identify best therapy up front.

Griesinger F et al. Safety and efficacy of pralsetinib in RET fusion-positive non-small-cell lung cancer including as first-line therapy: Update from the ARROW trial. Ann Oncol 2022;33(11):1168-1178

Courtesy of Gregory J Riely, MD, PhD

Agenda

INTRODUCTION: What is targeted therapy?

MODULE 1: EGFR activating mutations

MODULE 2: EGFR exon 20 insertion mutations

MODULE 3: ALK and ROS1 rearrangements

MODULE 4: HER2 mutations

MODULE 5: NRG1 fusions

MODULE 6: RET fusions

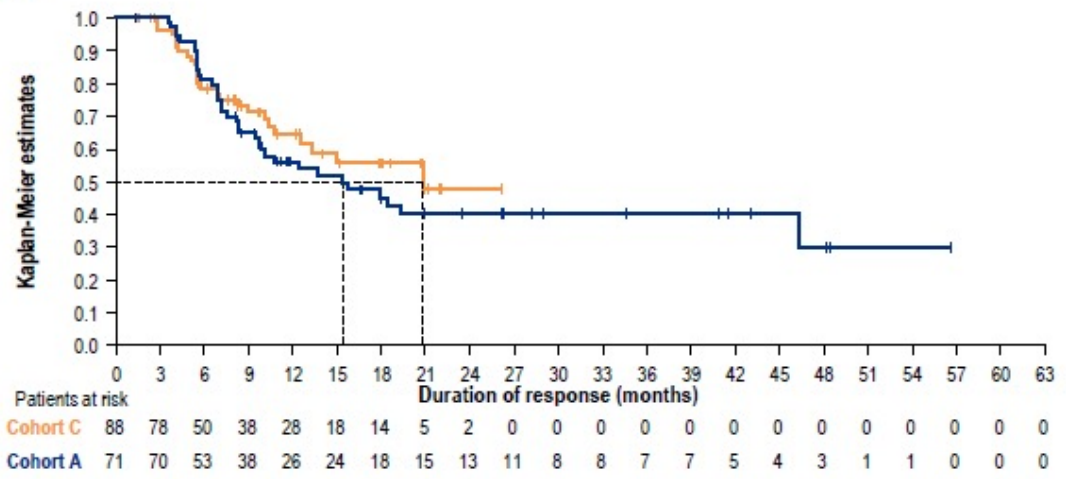
MODULE 7: MET exon 14 mutations

MODULE 8: KRAS G12C mutations

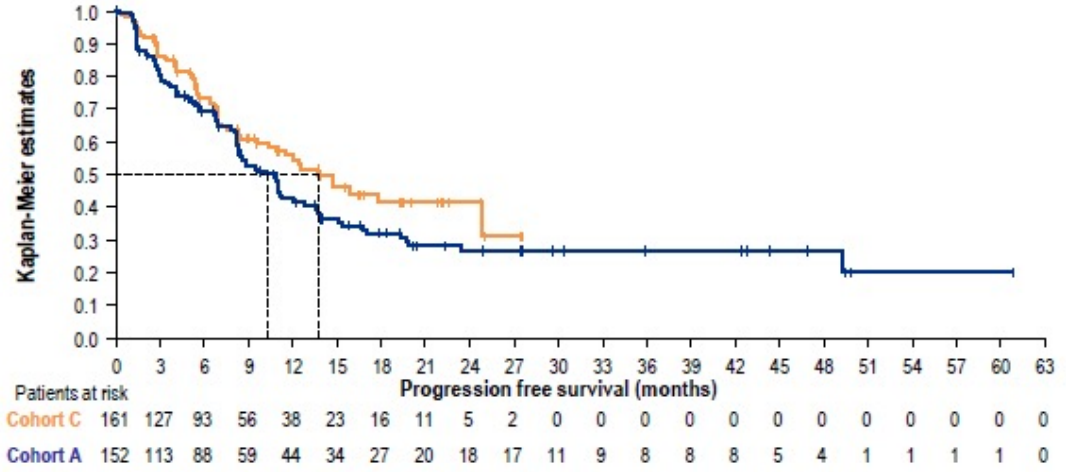
Tepotinib for MET exon 14 NSCLC

	Cohort C (N=161)
ORR, % (95% CI)	54.7 (46.6, 62.5)
DCR, % (95% CI)	80.1 (73.1, 86.0)
mDOR, months (95% CI)	20.8 (12.6, ne)
mPFS, months (95% CI)	13.8 (10.4, ne)
mOS, months (95% CI)	18.8 (14.4, 25.5)

DOR



PFS



Thomas M et al. Tepotinib in patients with MET exon 14 skipping NSCLC: Primary analysis of the confirmatory VISION cohort C. WCLC 2022;Abstract OA03.05.

Courtesy of Gregory J Riely, MD, PhD

Tepotinib for MET exon 14 NSCLC

	1L* (T+ and/or L+)	2L+ (T+ and/or L+)
	Cohort C (n=95)	Cohort C (n=66)
ORR, % (95% CI)	60.0 (49.4, 69.9)	47.0 (34.6, 59.7)
Median DOR, months (95% CI)	ne (13.4, ne)	12.6 (5.1, ne)
Median PFS, months (95% CI)	15.9 (10.4, ne)	12.1 (6.9, ne)
Median OS, months (95% CI)	21.1 (12.7, ne)	18.8 (13.5, ne)

*1L enrollment began approximately 8 months later than 2L+.
1L, first line; 2L+, second-or-later line; CI, confidence interval; DOR, duration of response; L+, *MET*ex14 sk
T+, *MET*ex14 skipping detected in tissue biopsy.

Thomas M et al. Tepotinib in patients with MET exon 14 skipping NSCLC: Primary analysis of the confirmatory VISION cohort C. WCLC 2022;Abstract OA03.05.

Courtesy of Gregory J Riely, MD, PhD

Tepotinib for MET exon 14 NSCLC

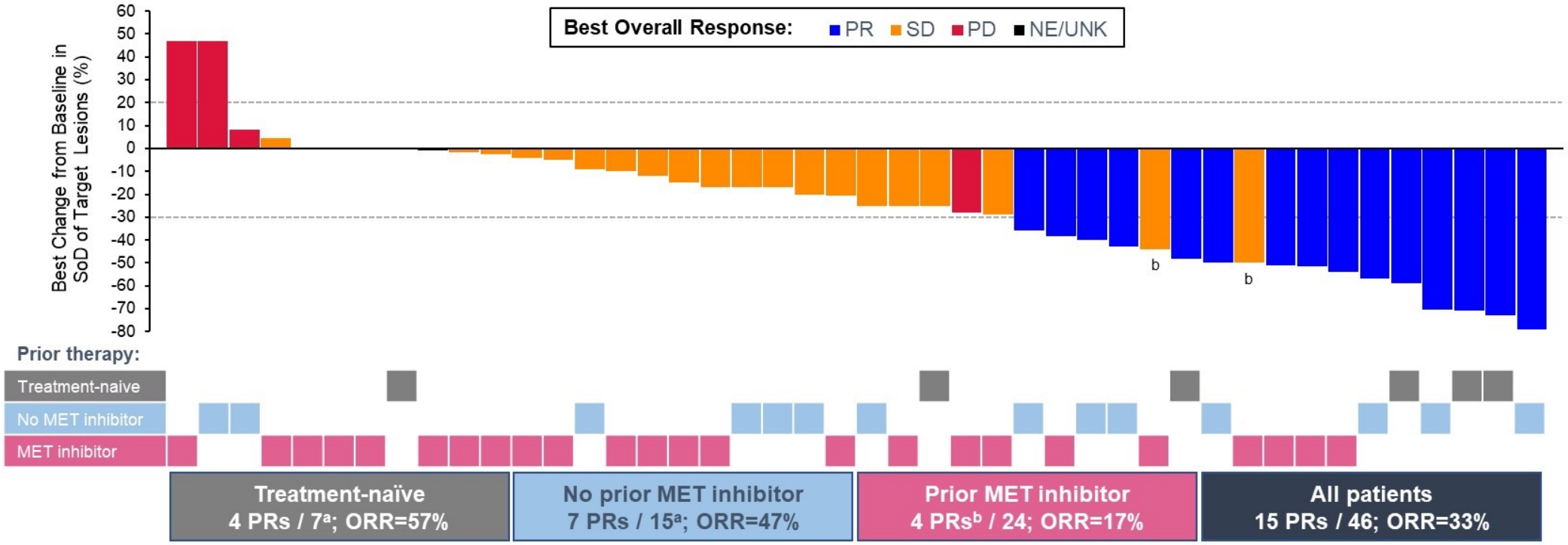
- Additional efficacy data for tepotinib in patients with MET exon 14 positive NSCLC

- Once again see that efficacy data support superiority of first-line use of tepotinib compared with later line therapy in patients with MET exon 14 positive NSCLC

Thomas M et al. Tepotinib in patients with MET exon 14 skipping NSCLC: Primary analysis of the confirmatory VISION cohort C. WCLC 2022;Abstract OA03.05.

Courtesy of Gregory J Riely, MD, PhD

Amivantamab in patients with MET exon 14 NSCLC



[a]Two patients discontinued prior to completing their secondpostbaseline disease assessment (1 in treatment naïve group and 1 in no prior MET inhibitor group). [b]Two additional patients had a best timepoint response of PR but did not confirm. NE/UNK, not evaluable/unknown; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; SoD, sum of diameters; TKI, tyrosine kinase inhibitor.

Krebs M et al. Amivantamab in patients with NSCLC with MET exon 14 skipping mutation: Updated results from the CHRYSALIS study. ASCO 2022;Abstract 9008.

Courtesy of Gregory J Riely, MD, PhD

Amivantamab in patients with MET exon 14 NSCLC

- In addition to capmatinib and tepotinib, the FDA-approved options for patients with MET exon 14 NSCLC, amivantamab has some efficacy and we look forward to additional data exploring its place in this group of patients.
- Very modest efficacy after prior MET-directed therapy.

Krebs M et al. Amivantamab in patients with NSCLC with MET exon 14 skipping mutation: Updated results from the CHRYSALIS study. ASCO 2022;Abstract 9008.

Courtesy of Gregory J Riely, MD, PhD

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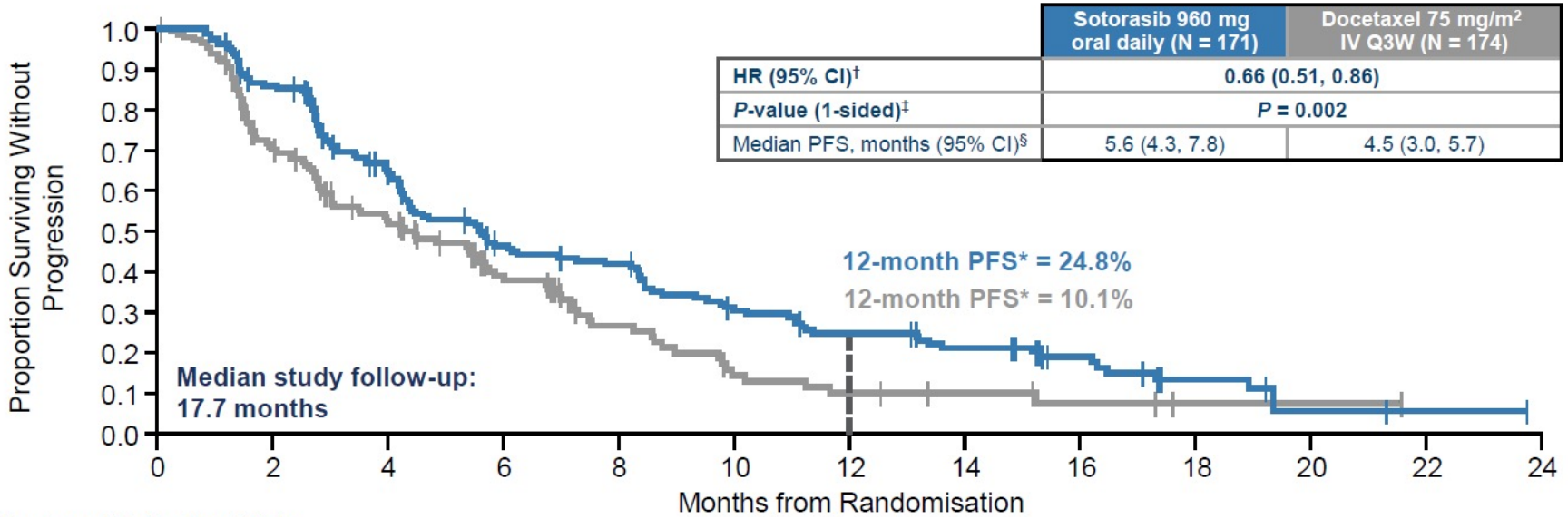
Comparing targeted therapy to chemotherapy in patients with KRAS G12C mutant NSCLC

Improved PFS



	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)

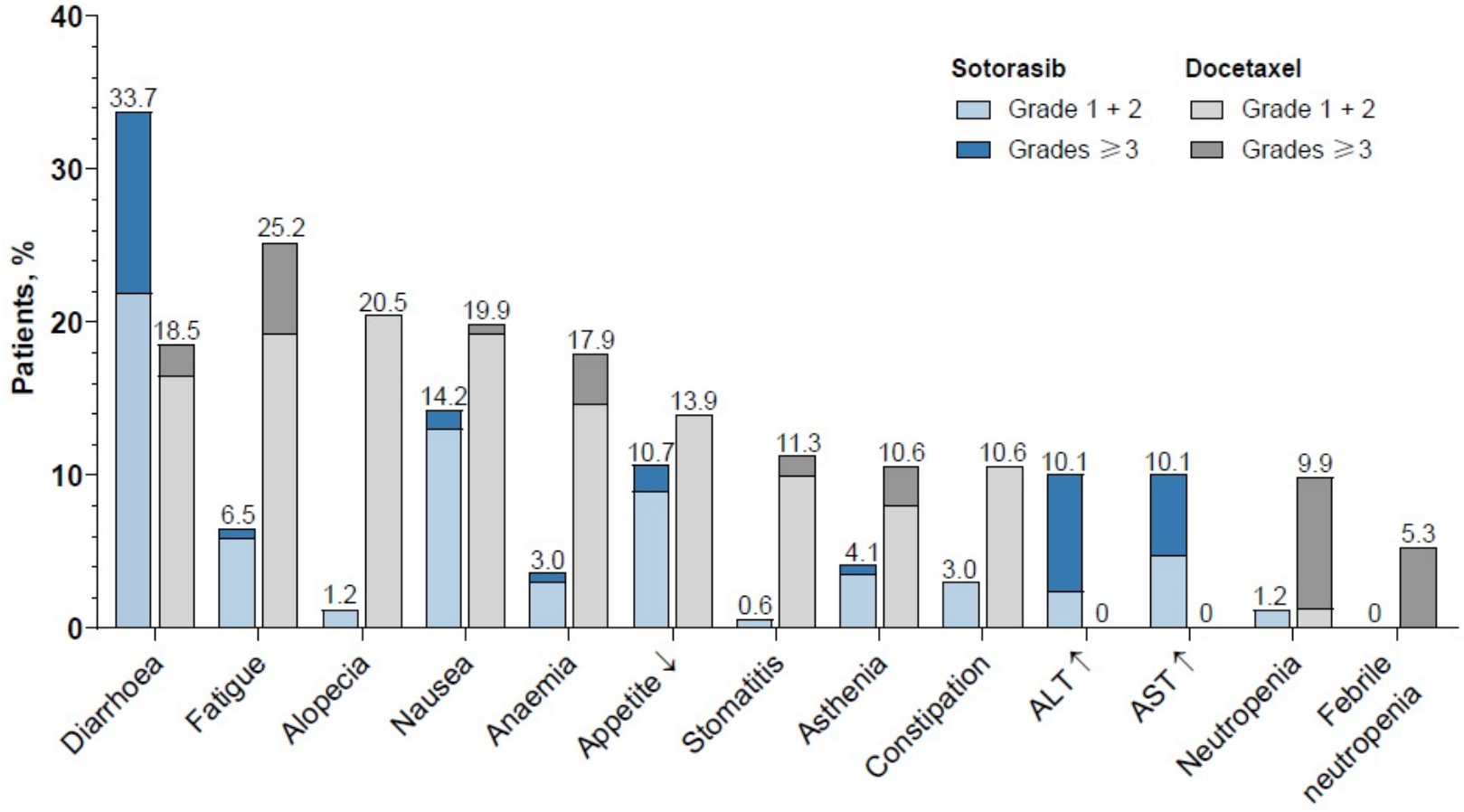
No difference in OS

	Sotorasib 960 mg oral daily (N = 171)	Docetaxel 75 mg/m² IV Q3W (N = 174)
Deaths, n (%)	109 (63.7)	94 (54.0)
HR (95% CI)†	1.01 (0.77, 1.33)	
P-value (1-sided)‡	*P* = 0.53	
Median OS, months (95% CI)§	10.6 (8.9, 14.0)	11.3 (9.0, 14.9)

Johnson ML et al. Sotorasib versus docetaxel for previously treated non-small cell lung cancer with KRAS G12C mutation: CodeBreaK 200 Phase III study. ESMO 2022;Abstract LBA10.

Courtesy of Gregory J Riely, MD, PhD

Comparing targeted therapy to chemotherapy in patients with KRAS G12C mutant NSCLC



Johnson ML et al. Sotorasib versus docetaxel for previously treated non-small cell lung cancer with KRAS G12C mutation: CodeBreaK 200 Phase III study. ESMO 2022;Abstract LBA10.

Courtesy of Gregory J Riely, MD, PhD

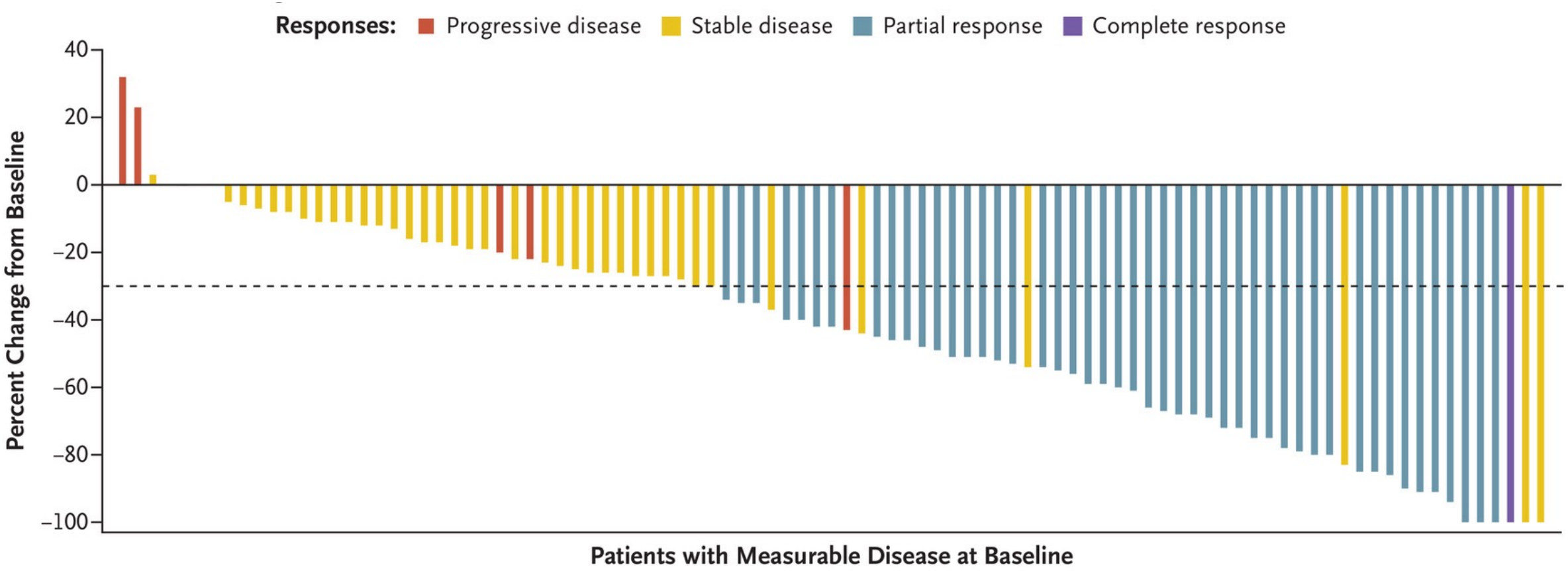
Comparing targeted therapy to chemotherapy in patients with KRAS G12C mutant NSCLC

- Sotorasib is superior to docetaxel based on response rate and primary endpoint of progression free survival
- Absence of an improvement in overall survival from use of sotorasib compared with docetaxel suggests benefits may be fleeting
- Toxicity of sotorasib is superior to docetaxel

Johnson ML et al. Sotorasib versus docetaxel for previously treated non-small cell lung cancer with KRAS G12C mutation: CodeBreaK 200 Phase III study. ESMO 2022;Abstract LBA10.

Courtesy of Gregory J Riely, MD, PhD

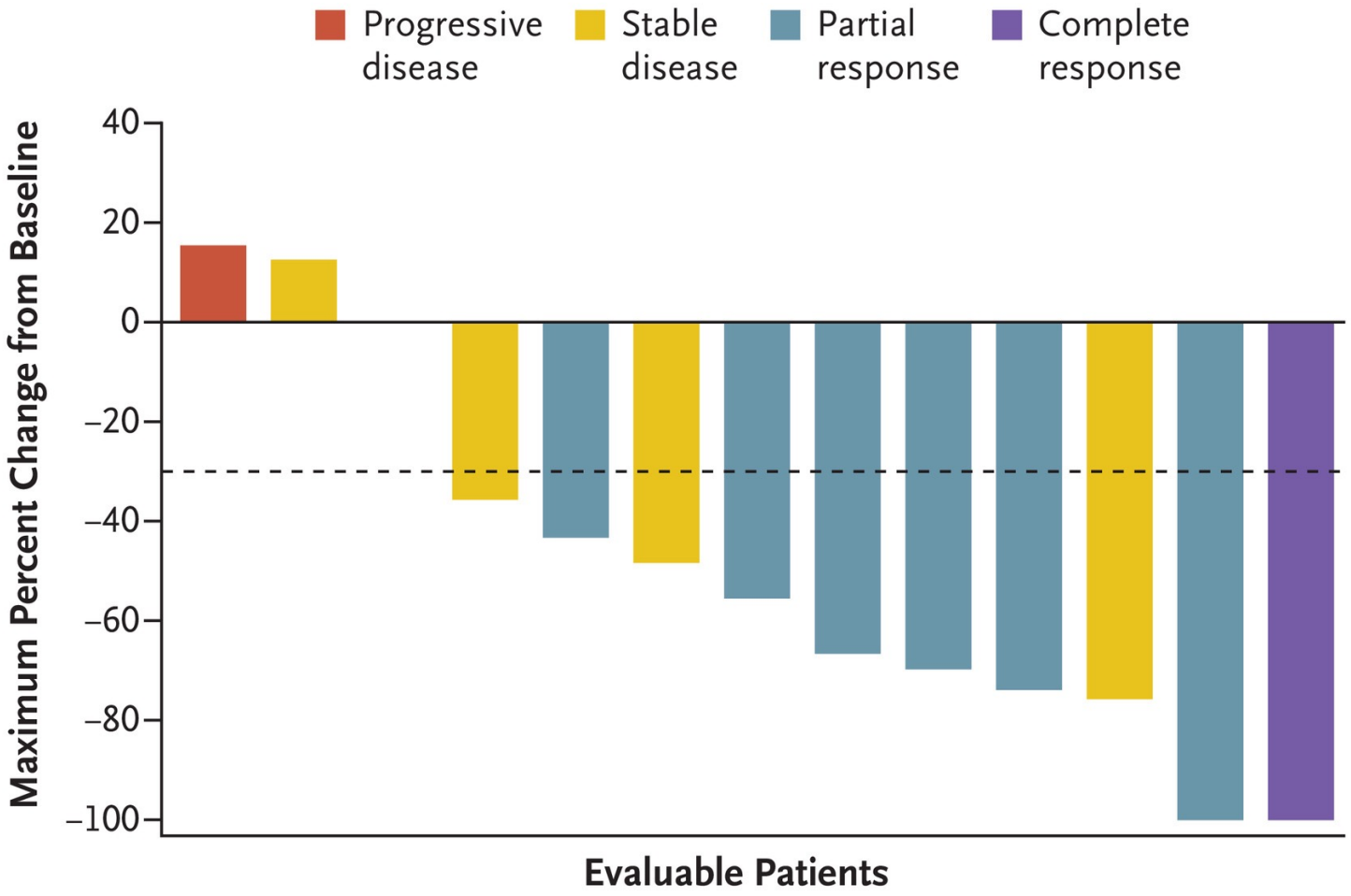
Adagrasib for the treatment of KRAS G12C mutant NSCLC



Jänne PA et al. Adagrasib in non-small-cell lung cancer harboring a KRASG12C mutation. N Engl J Med 2022;387(2):120-31.

Courtesy of Gregory J Riely, MD, PhD

Adagrasib for the treatment of KRAS G12C mutant NSCLC CNS Efficacy



Jänne PA et al. Adagrasib in non-small-cell lung cancer harboring a KRASG12C mutation. N Engl J Med 2022;387(2):120-31.

Courtesy of Gregory J Riely, MD, PhD

Adagrasib for the treatment of KRAS G12C mutant NSCLC

- Adagrasib is a newly approved drug targeting treatment of NSCLC in patients with KRAS G12C mutations
- From single-arm study, similar efficacy to that reported for sotorasib
- Provocative data to suggest CNS efficacy for adagrasib in patients with KRAS G12C mutant NSCLC

Jänne PA et al. Adagrasib in non-small-cell lung cancer harboring a KRASG12C mutation. N Engl J Med 2022;387(2):120-31.

Courtesy of Gregory J Riely, MD, PhD

Adagrasib + Pembrolizumab in KRAS G12C mut NSCLC

- Adagrasib can be safely combined with pembrolizumab in KRAS G12C mutant NSCLC.
- This is contrasted with the excess toxicities observed when sotorasib is given with pembrolizumab.

- There is no clear efficacy advantage to giving this combination, but further study is ongoing.

Jänne et al, Preliminary safety and efficacy of adagrasib with pembrolizumab in patients with advanced non-small cell lung cancer (NSCLC) harboring a $KRAS^{G12C}$ mutation, ESMO IO 12/7/22

Courtesy of Gregory J Riely, MD, PhD

Cases from the Community: Investigators Discuss Available Research Guiding the Care of Patients with Gastrointestinal Cancers

A 3-Part CME Symposium Series Held in Conjunction with the 2023 ASCO Gastrointestinal Cancers Symposium

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7:15 PM – 9:15 PM PT
(10:15 PM – 12:15 AM ET)

Gastroesophageal Cancers

Thursday, January 19, 2023

6:15 PM – 7:45 PM PT
(9:15 PM – 10:45 PM ET)

Hepatobiliary Cancers

Friday, January 20, 2023

6:00 PM – 7:30 PM PT
(9:00 PM – 10:30 PM ET)

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