Meet The Professor
Non-Small Cell Lung Cancer with an Actionable Target Beyond EGFR

Melissa Johnson, MD
Director, Lung Cancer Research Program
Associate Director of Drug Development for the
Drug Development Unit in Nashville
Sarah Cannon Research Institute
Nashville, Tennessee

Commercial Support

This activity is supported by educational grants from Amgen Inc, AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Elevation Oncology Inc, Genentech, a member of the Roche Group, Novartis, and Turning Point Therapeutics Inc.

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Dr Love — Disclosures

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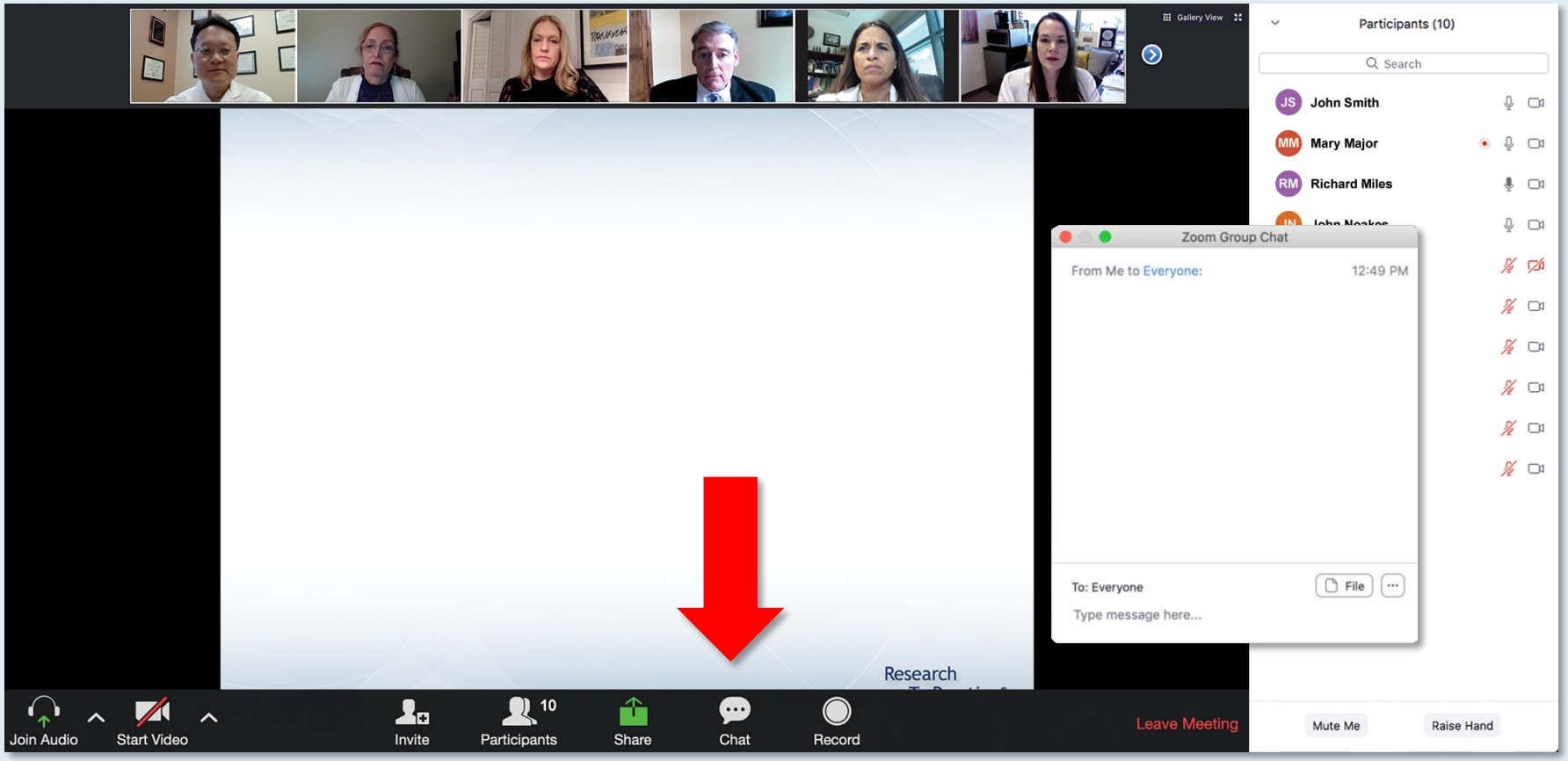

Feel free to submit questions now before the program begins and throughout the program.

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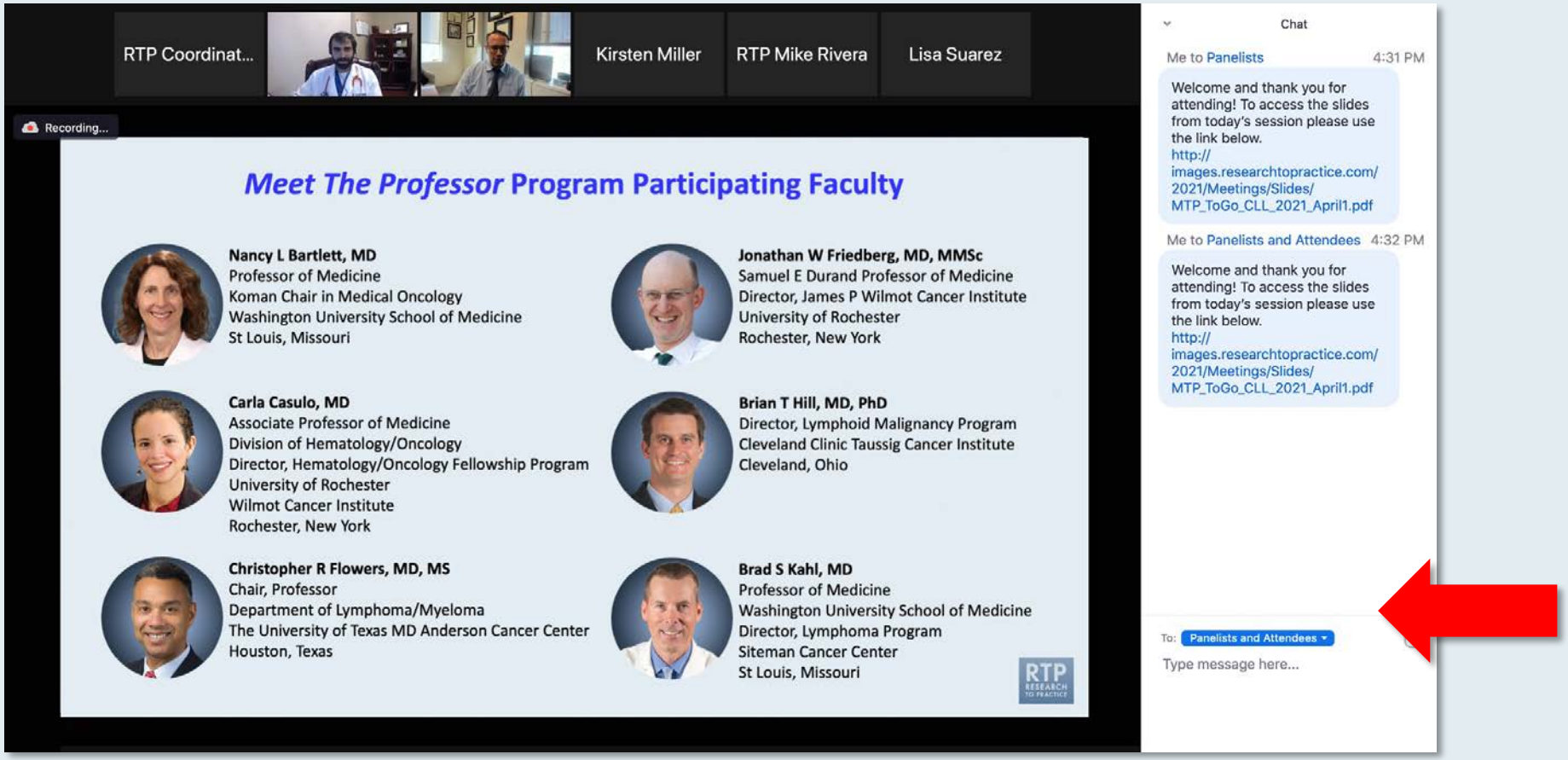

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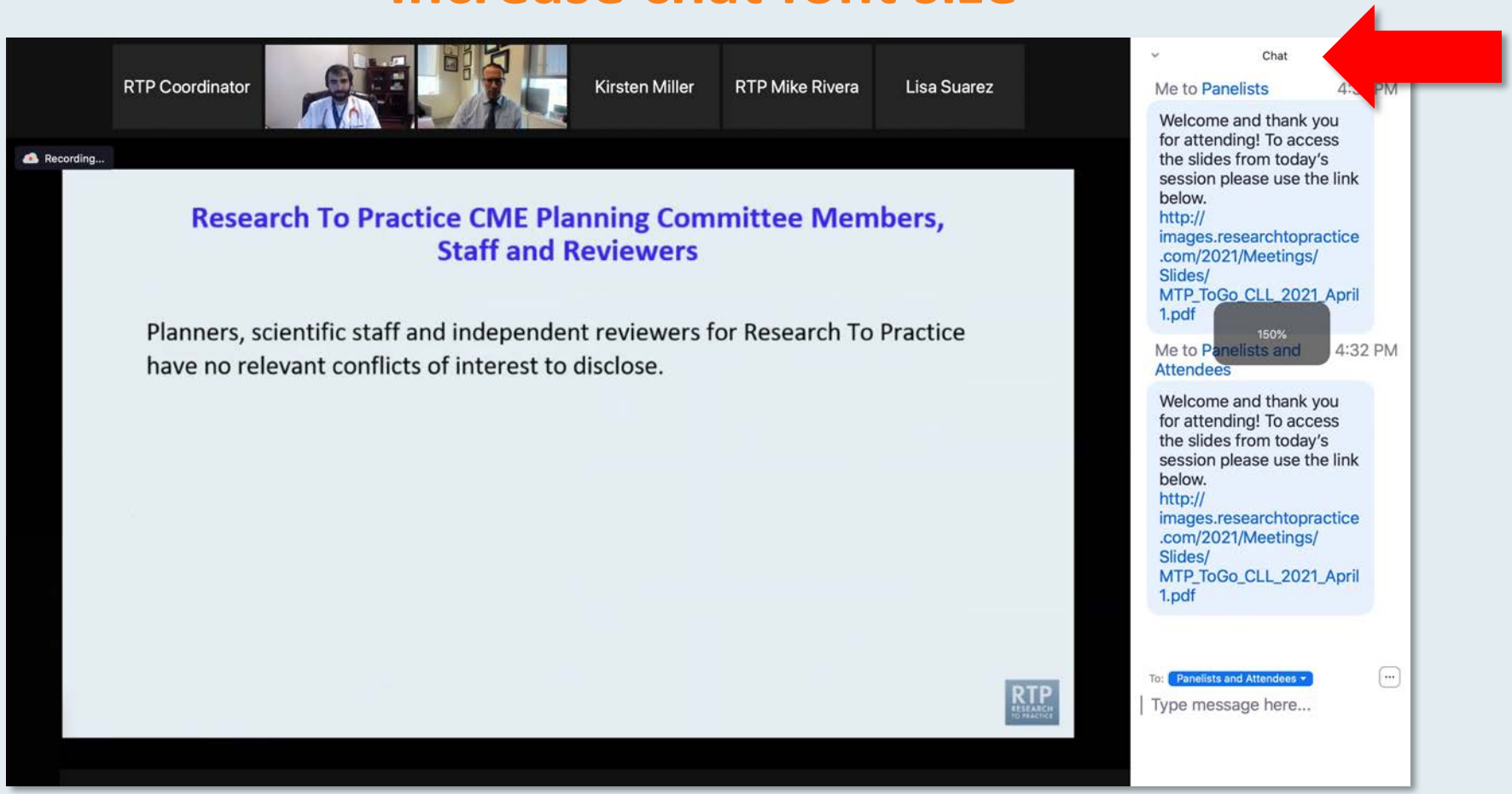

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ONCOLOGY TODAY

WITH DR NEIL LOVE

NSCLC with EGFR Exon 20 Insertion Mutations

DR GREGORY RIELY
MEMORIAL SLOAN KETTERING CANCER CENTER

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Meet The Professor

Optimizing the Management of Ovarian Cancer

Tuesday, June 21, 2022
5:00 PM – 6:00 PM ET

Faculty

Shannon N Westin, MD, MPH

Moderator

Neil Love, MD

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Meet The Professor

Optimizing the Management of Gastroesophageal Cancers

Wednesday, June 22, 2022
5:00 PM – 6:00 PM ET

Faculty

Manish A Shah, MD

Moderator

Neil Love, MD

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PARP Inhibition in the Management of Prostate Cancer — Where We Are and Where We're Headed

Thursday, June 23, 2022
5:00 PM – 6:00 PM ET

Faculty

Johann S de Bono, MB ChB, MSc, PhD, FMedSci
Fred Saad, MD

Moderator

Neil Love, MD

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Meet The Professor

Optimizing the Management of Chronic Myeloid Leukemia

Tuesday, June 28, 2022
5:00 PM – 6:00 PM ET

Faculty

Jorge E Cortes, MD

Moderator

Neil Love, MD

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Meet The Professor

Current and Future Management of Non-Small Cell Lung Cancer with an EGFR Mutation

Thursday, June 30, 2022
5:00 PM – 6:00 PM ET

Faculty

Joel W Neal, MD, PhD

Moderator

Neil Love, MD

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Meet The Professor

Optimizing the Management of Ovarian Cancer

Wednesday, July 6, 2022
5:00 PM – 6:00 PM ET

Faculty

Ursula Matulonis, MD

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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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Sarah Cannon Research Institute
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Massachusetts General Hospital
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Nashville, Tennessee

MODERATOR
Neil Love, MD
Research To Practice

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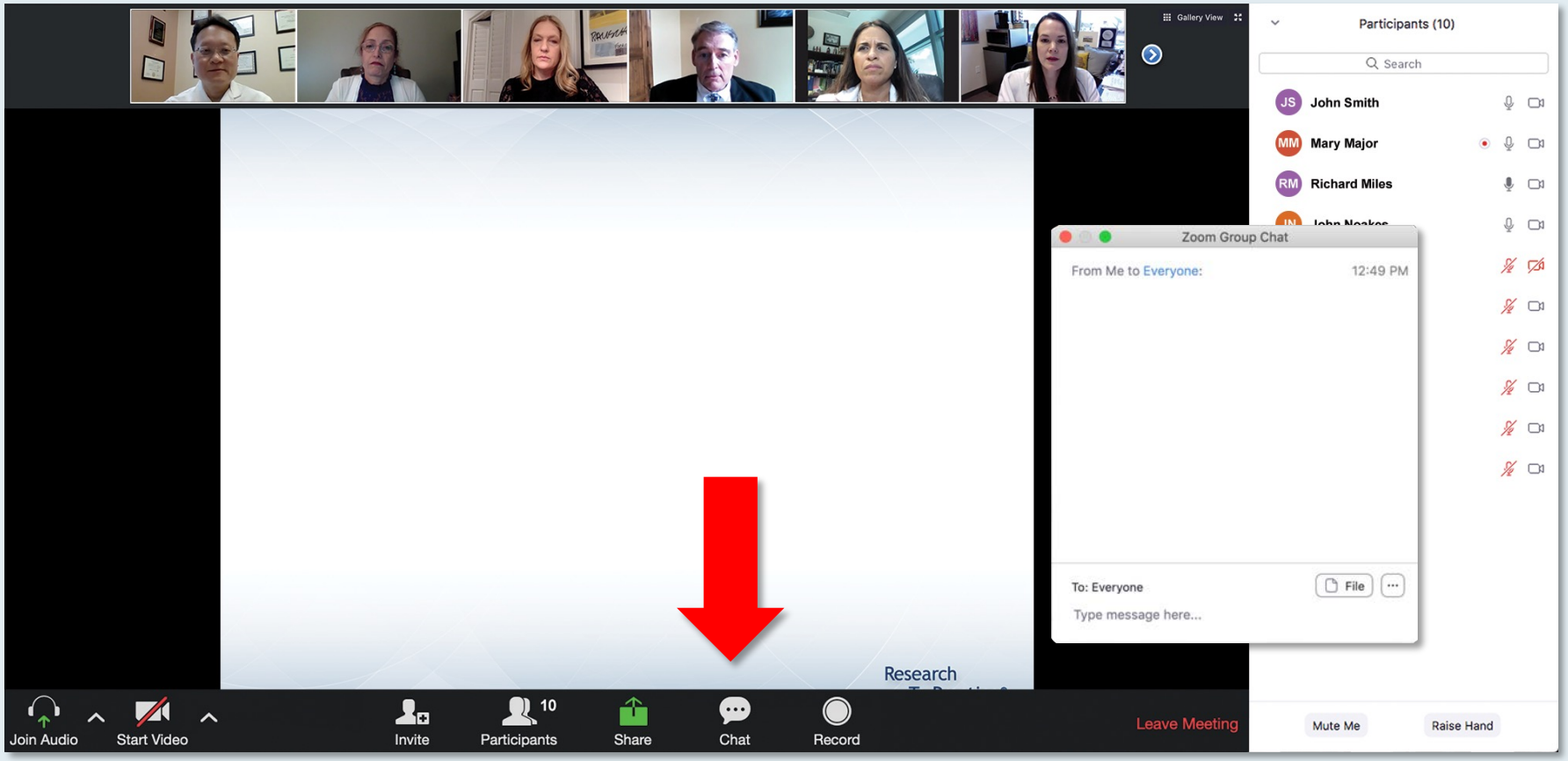

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Meet The Professor with Dr Johnson

Introduction: KRAS in Lung Cancer

MODULE 1: Case Presentations

MODULE 2: Faculty Survey

MODULE 3: MET Exon 14 and HER2 Mutations

MODULE 4: Journal Club with Dr Johnson

MODULE 5: Appendix of Key Publications

Meet The Professor with Dr Johnson

Introduction: KRAS in Lung Cancer

MODULE 1: Case Presentations

MODULE 2: Faculty Survey

MODULE 3: MET Exon 14 and HER2 Mutations

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MODULE 5: Appendix of Key Publications

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Durvalumab ± Tremelimumab + Chemotherapy as First-Line Treatment for mNSCLC: Results from the Phase 3 POSEIDON Study

Melissa L Johnson,[1] Byoung Chul Cho,[2] Alexander Luft,[3] Jorge Alatorre-Alexander,[4] Sarayut Lucien Geater,[5] Konstantin Laktionov,[6] Aleksandr Vasiliev,[7] Dmytro Trukhin,[8] Sang-We Kim,[9] Grygorii Ursol,[10] Maen Hussein,[11] Farah Louise Lim,[12] Cheng-Ta Yang,[13] Luiz Henrique Araujo,[14] Haruhiro Saito,[15] Niels Reinmuth,[16] Xiaojin Shi,[17] Lynne Poole,[18] Solange Peters,[19] Edward B Garon,[20] Tony Mok[21]

[1]Sarah Cannon Research Institute, Tennessee Oncology, PLLCC, Nashville, TN, USA; [2]Yonsei Cancer Center, Seoul, Korea; [3]Leningrad Regional Clinical Hospital, St Petersburg, Russia; [4]Health Pharma Professional Research, Mexico City, Mexico; [5]Prince of Songkla University, Songkhla, Thailand; [6]Federal State Budgetary Institution "N.N. Blokhin National Medical Research Center of Oncology" of the Ministry of Health of the Russian Federation (N.N. Blokhin NMRCO), Moscow, Russia; [7]"Private Health Institution "Clinical Hospital" RZD-Medicine", St Petersburg, Russia; [8]Odessa Regional Oncological Dispensary, Odessa, Ukraine; [9]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [10]Acinus, Kropyvnytskyi, Ukraine; [11]Florida Cancer Specialists – Sarah Cannon Research Institute, Leesburg, FL, USA; [12]Queen Mary University of London, London, United Kingdom; [13]Chang Gung Memorial Hospital, Taoyuan City, Taiwan; [14]Instituto Nacional de Cancer-INCA, Rio de Janeiro, Brazil; [15]Kanagawa Cancer Center, Yokohama, Japan; [16]Asklepios Lung Clinic, Munich-Gauting, Germany; [17]AstraZeneca, Gaithersburg, MD, USA; [18]AstraZeneca, Cambridge, UK; [19]Centre Hospitalier Universitaire Vaudois, Lausanne University, Lausanne, Switzerland; [20]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [21]Chinese University of Hong Kong, Hong Kong, China

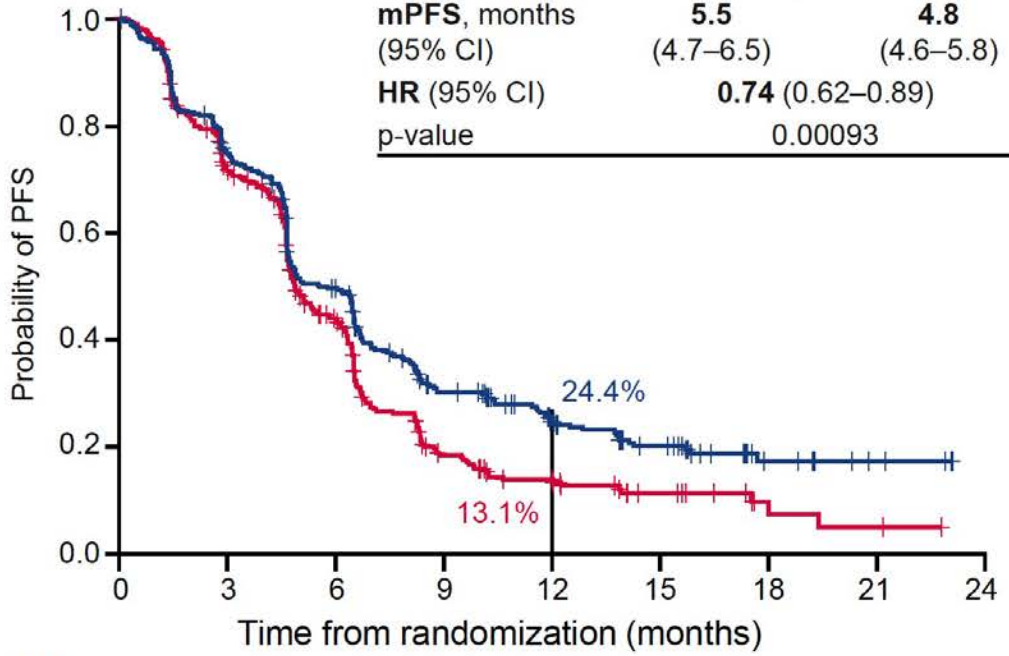
IASLC 2021 World Conference on Lung Cancer
SEPTEMBER 8 - 14, 2021 I WORLDWIDE VIRTUAL EVENT

Abstract PL02.01

POSEIDON: Progression-Free and Overall Survival with Durvalumab and Chemotherapy versus Chemotherapy Alone

PFS

	D+CT	CT
Events, n/N (%)	253/338 (74.9)	258/337 (76.6)
mPFS, months (95% CI)	**5.5** (4.7–6.5)	**4.8** (4.6–5.8)
HR (95% CI)	**0.74** (0.62–0.89)	
p-value	0.00093	



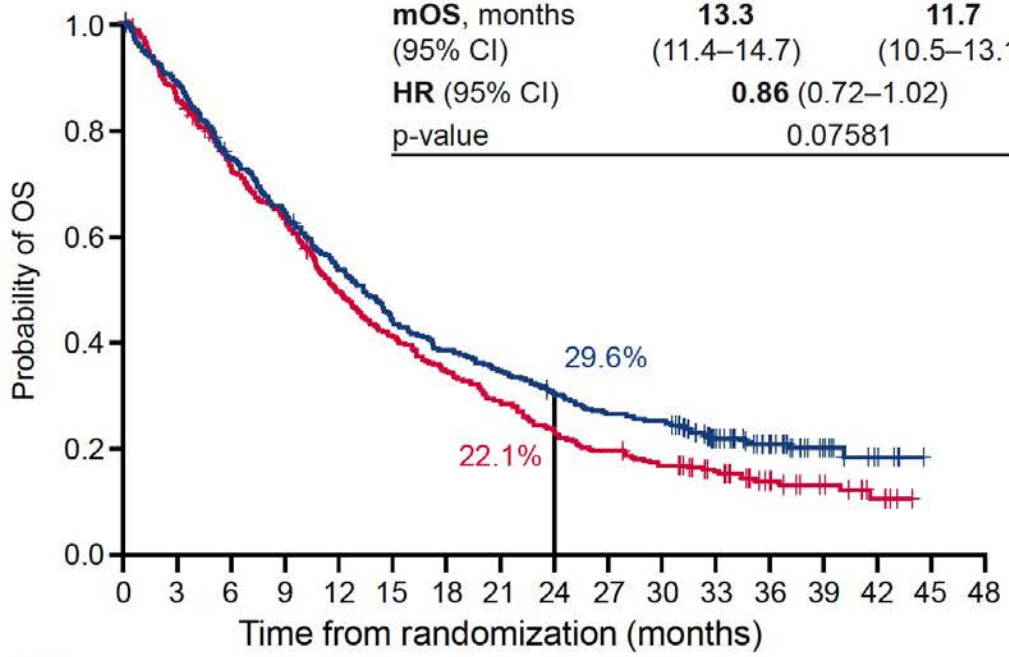
No. at risk

D+CT	338	246	158	88	53	35	11	4	0
CT	337	219	121	43	23	12	3	2	0

- Median follow-up in censored patients at DCO: 10.3 months (range 0–23.1)

OS

	D+CT	CT
Events, n/N (%)	264/338 (78.1)	285/337 (84.6)
mOS, months (95% CI)	**13.3** (11.4–14.7)	**11.7** (10.5–13.1)
HR (95% CI)	**0.86** (0.72–1.02)	
p-value	0.07581	



No. at risk

D+CT	338	296	247	212	176	142	126	112	97	85	81	51	33	15	5	0	0
CT	337	284	236	204	160	132	111	91	72	62	52	38	21	13	6	0	0

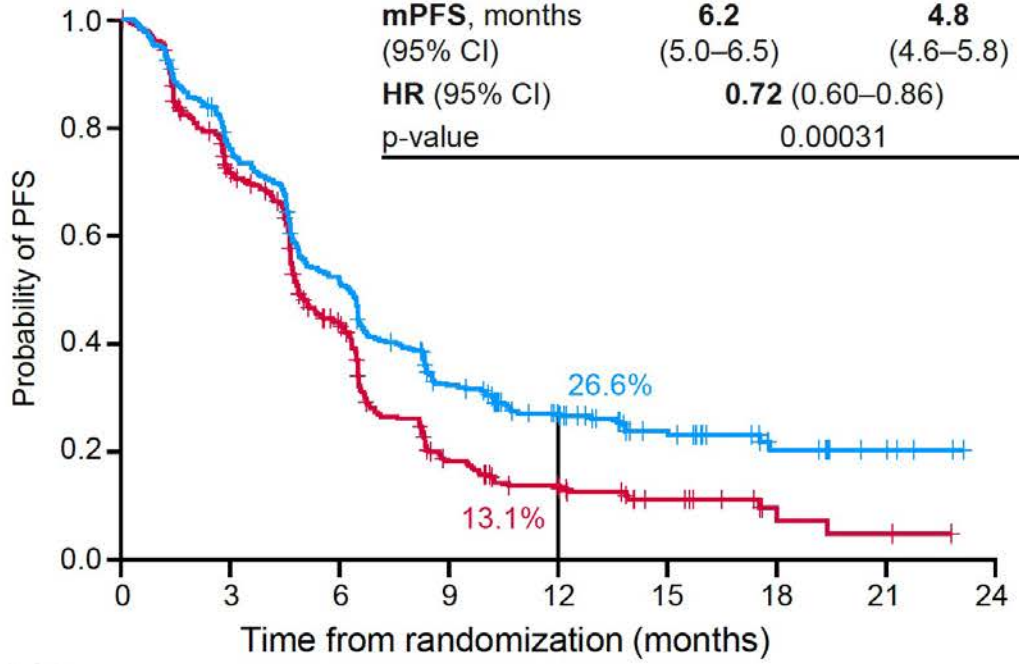
- Median follow-up in censored patients at DCO: 34.9 months (range 0–44.5)

Johnson ML et al. WCLC 2021;Abstract PL02.01.

POSEIDON: Progression-Free and Overall Survival with Durvalumab/ Tremelimumab/Chemotherapy versus Chemotherapy Alone

PFS

	D+T+CT	CT
Events, n/N (%)	238/338 (70.4)	258/337 (76.6)
mPFS, months (95% CI)	**6.2** (5.0–6.5)	**4.8** (4.6–5.8)
HR (95% CI)	**0.72** (0.60–0.86)	
p-value	0.00031	

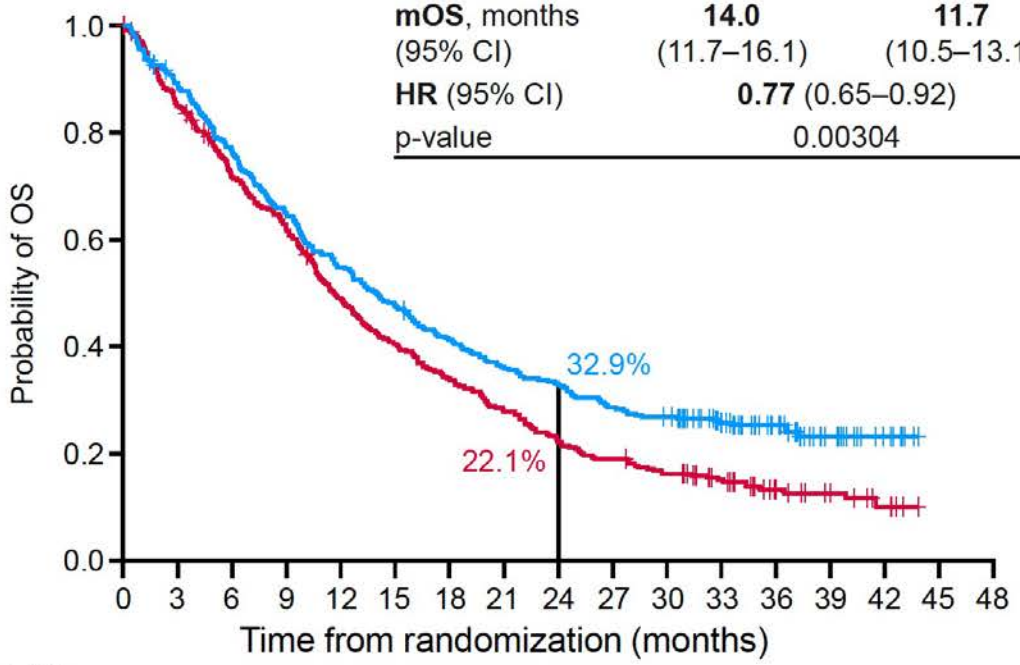


No. at risk									
D+T+CT	338	243	161	94	56	32	13	5	0
CT	337	219	121	43	23	12	3	2	0

- Median follow-up in censored patients at DCO: 10.3 months (range 0–23.1)

OS

	D+T+CT	CT
Events, n/N (%)	251/338 (74.3)	285/337 (84.6)
mOS, months (95% CI)	**14.0** (11.7–16.1)	**11.7** (10.5–13.1)
HR (95% CI)	**0.77** (0.65–0.92)	
p-value	0.00304	

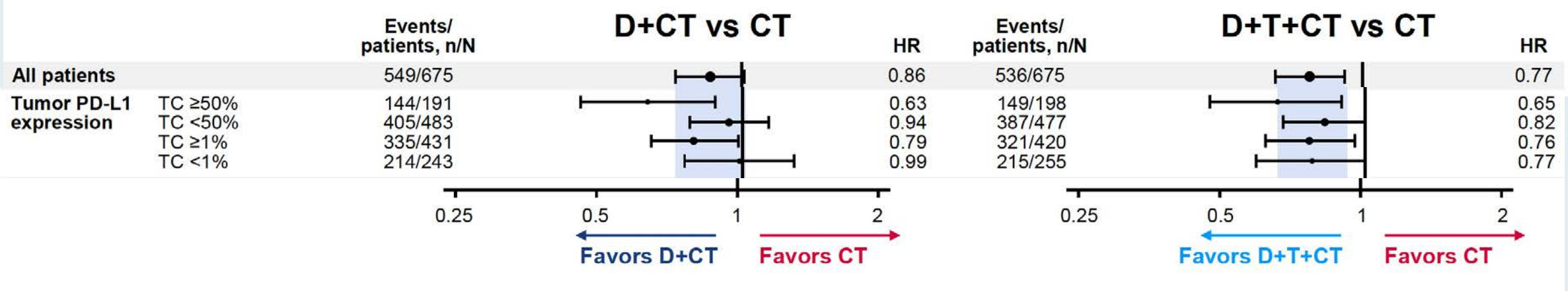


No. at risk																		
D+T+CT	338	298	256	217	183	159	137	120	109	95	88	64	41	20	9	0	0
CT	337	284	236	204	160	132	111	91	72	62	52	38	21	13	6	0	0

- Median follow-up in censored patients at DCO: 34.9 months (range 0–44.5)

Johnson ML et al. WCLC 2021;Abstract PL02.01.

POSEIDON: Overall Survival Subgroup Analysis by Tumor PD-L1 Expression



Johnson ML et al. WCLC 2021;Abstract PL02.01.

POSEIDON Conclusions

- In POSEIDON, PFS was significantly improved with first-line durvalumab + CT vs CT in patients with mNSCLC, with a positive trend for OS that did not reach statistical significance
  - PFS HR 0.74 (95% CI 0.62–0.89; p=0.00093)
  - OS HR 0.86 (95% CI 0.72–1.02; p=0.07581)
- First-line durvalumab + tremelimumab + CT demonstrated statistically significant and clinically meaningful improvements in both PFS and OS vs CT in patients with mNSCLC
  - PFS HR 0.72 (95% CI 0.60–0.86; p=0.00031)
  - OS HR 0.77 (95% CI 0.65–0.92; p=0.00304)
  - OS and PFS benefit were more prominent among patients with non-squamous (than squamous) histology
- Overall, the safety profile was similar across all three arms, with no new safety signals identified. Adding tremelimumab to durvalumab + CT did not lead to a meaningful increase in treatment discontinuation
  - TRAE discontinuation rate 15.5% and 14.1% with D+T+CT and D+CT, respectively
- **Durvalumab + tremelimumab + CT represents a potential new first-line treatment option for mNSCLC**

Johnson ML et al. WCLC 2021;Abstract PL02.01.

Regulatory and reimbursement issues aside, what would be your preferred first-line therapy for a 65-year-old asymptomatic patient with metastatic nonsquamous NSCLC (PD-L1 TPS 50%) and a KRAS G12C mutation?

 Dr Baik	Carboplatin/ pemetrexed/ pembrolizumab	 Dr Gainor	Pembrolizumab
 Dr Camidge	Carboplatin/ pemetrexed/ pembrolizumab	 Dr Johnson	Pembrolizumab
 Dr Drilon	Pembrolizumab	 Dr Spira	Carboplatin/ pemetrexed/ pembrolizumab

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Regulatory and reimbursement issues aside, in which line of therapy would you generally offer targeted treatment to a patient with metastatic nonsquamous NSCLC (PD-L1 TPS 50%) and a KRAS G12C mutation, and which targeted therapy would you generally offer?

 Dr Baik	Second line Sotorasib	 Dr Gainor	Second line Sotorasib
 Dr Camidge	Second line Sotorasib	 Dr Johnson	Second line Sotorasib
 Dr Drilon	Second line Sotorasib	 Dr Spira	Second line Sotorasib

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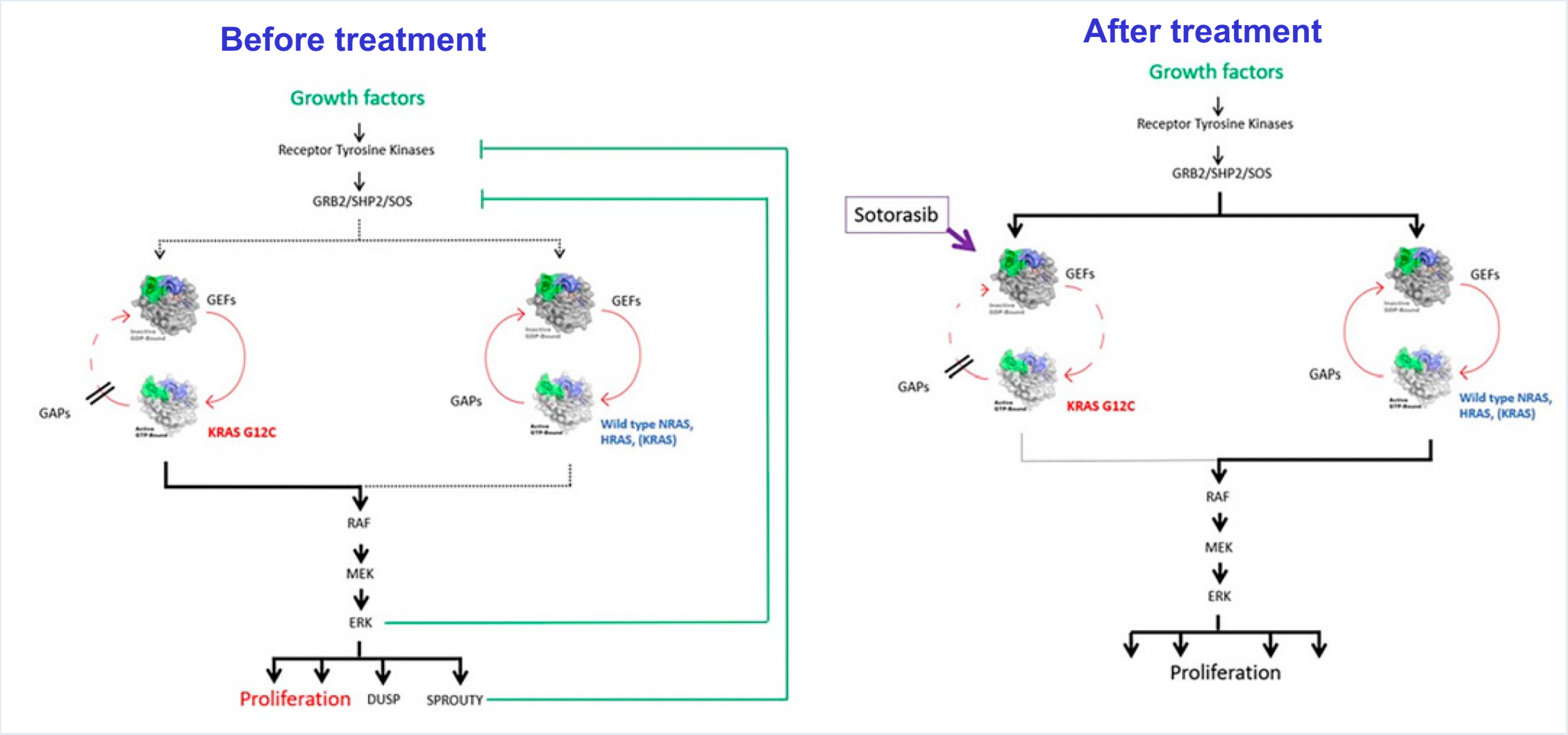
ASCO 2022 Education Book

DEVELOPMENTAL THERAPEUTICS—MOLECULARLY TARGETED AGENTS AND TUMOR BIOLOGY

More to the RAS Story: KRAS^{G12C} Inhibition, Resistance Mechanisms, and Moving Beyond KRAS^{G12C}

Caressa D. Lietman, PhD[1]; Melissa L. Johnson, MD[2]; Frank McCormick, PhD, FRS[3]; and Colin R. Lindsay, MBChB, PhD[4]

Signaling Pathways from KRAS G12C and the Effect of Sotorasib



Lietman CD et al. ASCO 2022 Education Book.

AACR American Association for Cancer Research ANNUAL MEETING 2022 New Orleans

Long-term Outcomes With Sotorasib in Pre-treated *KRAS* p.G12C Mutated NSCLC: 2-year Analysis of CodeBreaK 100

Presenter: Grace K. Dy[1], MD

[1]Roswell Park Comprehensive Cancer Center

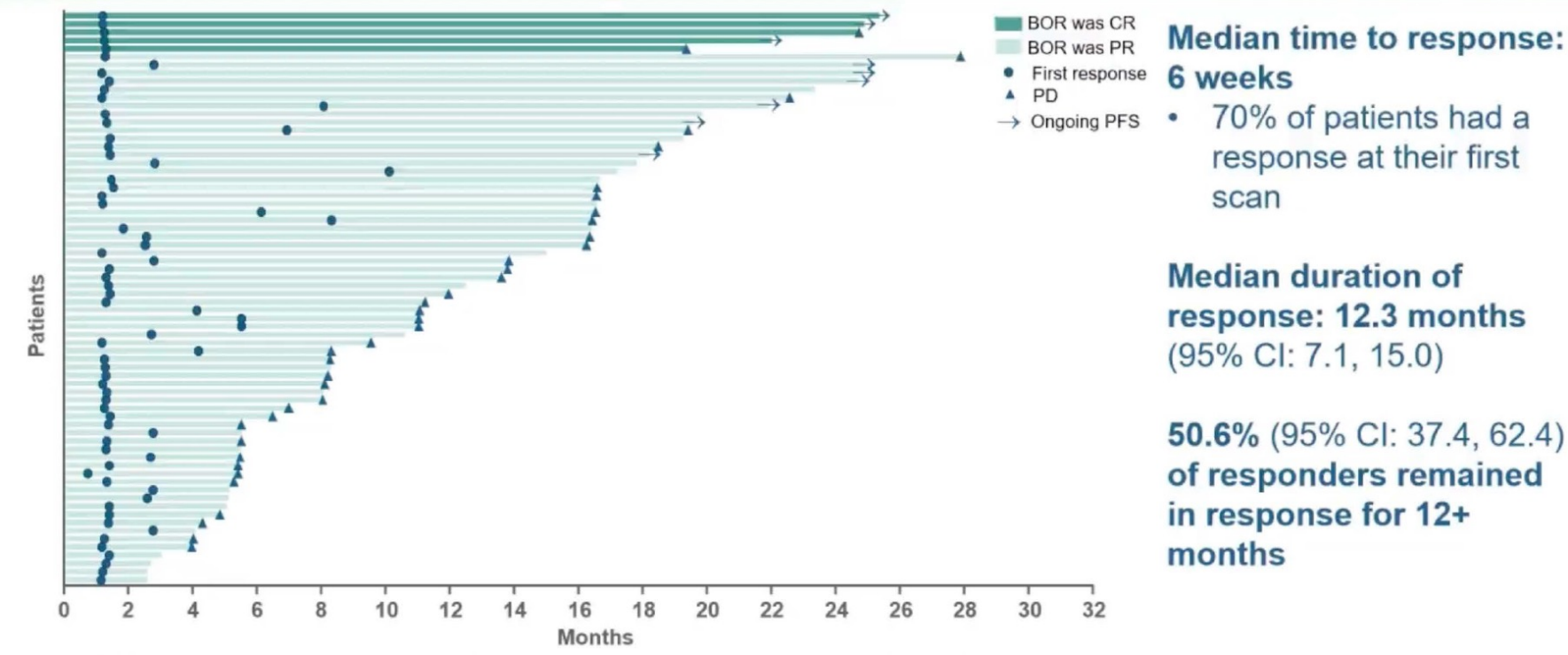
On behalf of: Ramaswamy Govindan[2], Vamsidhar Velcheti[3], Gerald S. Falchook[4], Antoine Italiano[5], Juergen Wolf[6], Adrian G. Sacher[7], Toshiaki Takahashi[8], Suresh S. Ramalingam[9], Christophe Dooms[10], Dong-Wan Kim[11], Alfredo Addeo[12], Jayesh Desai[13], Martin Schuler[14], Pascale Tomasini[15], Qui Tran[16], Simon Jones[16], Agnes Ang[16], Abraham Anderson[16], Antreas Hindoyan[16], David S. Hong[17], Bob T. Li[18]

[2]Washington University in St Louis, [3]New York University Langone, [4]Sarah Cannon Research Institute, [5]Institut Bergonie, [6]Universitatsklinikum Koln, [7]Princess Margaret Cancer Centre, [8]Shizuoka Cancer Center [9]Winship Cancer Institute, [10]Universitair Ziekenhuis Leuven [11]Seoul National University Hospital, [12]Hopitaux Universitaires de Geneve, [13]Peter MacCallum Cancer Centre, [14]Universitätsklinikum Essen, [15]Hopital de la Timone, [16]Amgen Inc., [17]MD Anderson Cancer Center, [18]Memorial Sloan Kettering Cancer Center

Abstract CT008

RTP RESEARCH TO PRACTICE

CodeBreaK 100: 2-Year Update with Sotorasib for Previously Treated Metastatic NSCLC with KRAS p.G12C Mutation



Median time to response: 6 weeks

- 70% of patients had a response at their first scan

Median duration of response: 12.3 months (95% CI: 7.1, 15.0)

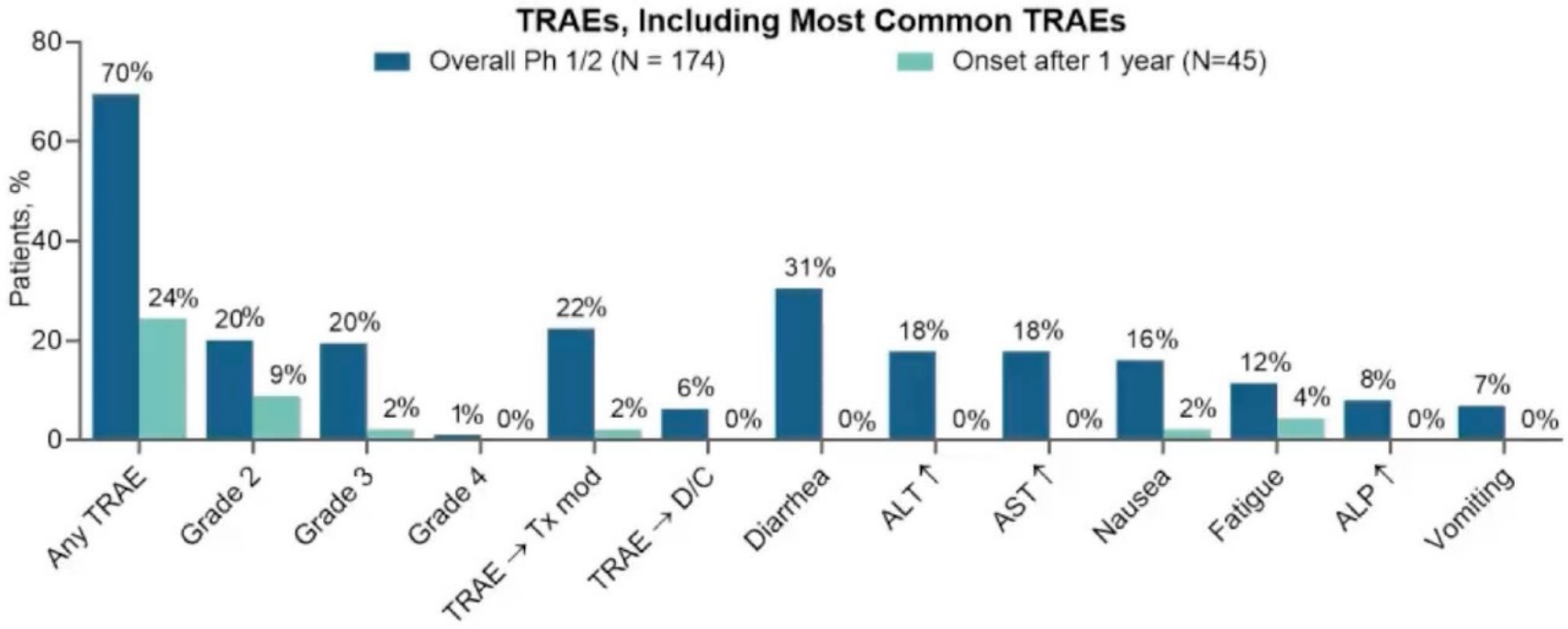
50.6% (95% CI: 37.4, 62.4) **of responders remained in response for 12+ months**

Efficacy Update (N = 172)
ORR: 40.7%
DCR: 83.7%
Median PFS: 6.3 mo
Median OS: 12.5 mo
1-year OS rate: 50.8%

Dy GK et al. AACR 2022;Abstract CT008.

RTP RESEARCH TO PRACTICE

CodeBreaK 100: Treatment-Related Adverse Events



Grade 3 or 4 TRAEs occurred in 21% of patients

- One patient with new onset Grade 3 TRAE after 1 year (hemolytic anemia)

No fatal TRAEs occurred

- No TRAE leading to discontinuation after 1 year

Well-tolerated in the long-term: late-onset TRAEs were mild and manageable

Dy GK et al. AACR 2022;Abstract CT008.

RTP RESEARCH TO PRACTICE

Oncologist 2022;[Online ahead of print].

Clinical Trial Results

OXFORD

Phase I Study of JNJ-74699157 in Patients with Advanced Solid Tumors Harboring the *KRAS G12C* Mutation

Judy Wang[1,‡], Patricia Martin-Romano[2], Philippe Cassier[3], Melissa Johnson[4], Eric Haura[5], Laurie Lenox[6], Yue Guo[6], Nibedita Bandyopadhyay[7], Michael Russell[6], Elizabeth Shearin[6], Josh Lauring[6], LaetitiaDahan [*,8]

JC JOURNAL CLUB

RTP RESEARCH TO PRACTICE

The NEW ENGLAND JOURNAL of MEDICINE

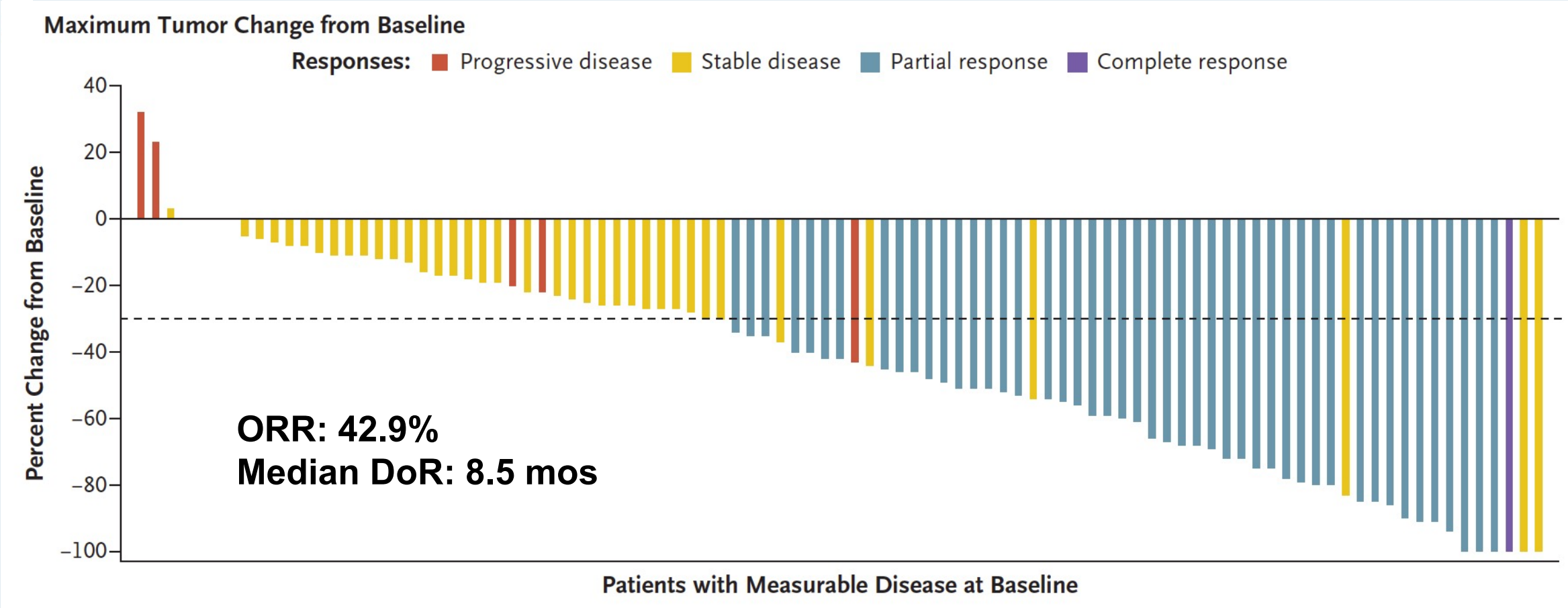
ORIGINAL ARTICLE

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.

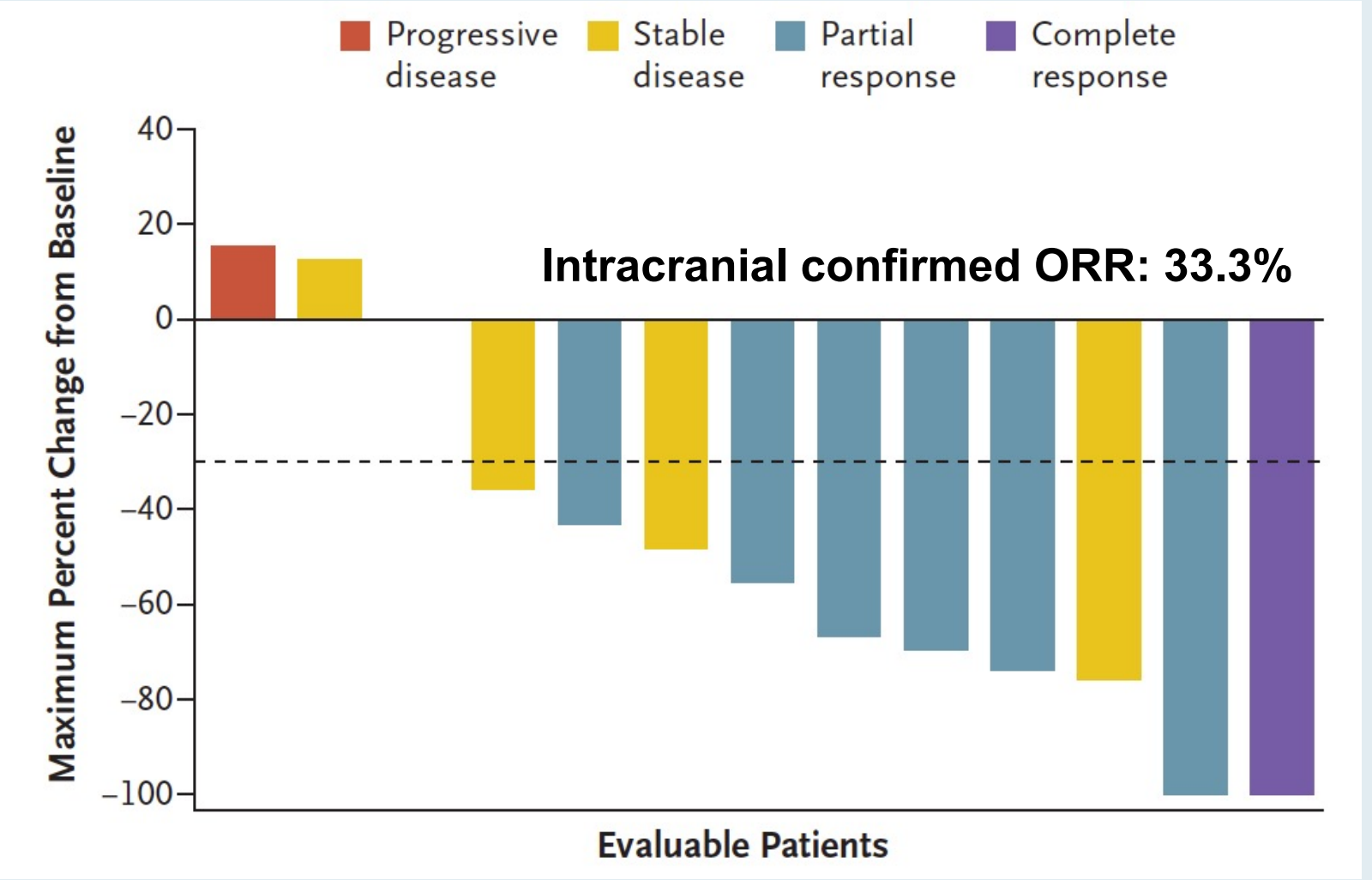
***N Engl J Med* 2022;[Online ahead of print].**

KRYSTAL-1: Response in a Phase II Study of Adagrasib for Advanced or Metastatic NSCLC Harboring a KRAS G12C Mutation



Jänne PA et al. *N Engl J Med* 2022;[Online ahead of print].

KRYSTAL-1: Intracranial Responses with Adagrasib for Advanced or Metastatic NSCLC Harboring a KRAS G12C Mutation



Jänne PA et al. *N Engl J Med* 2022;[Online ahead of print].

KRYSTAL-1: Select Treatment-Related Adverse Events with Adagrasib for Advanced or Metastatic NSCLC Harboring a KRAS G12C Mutation

Adverse event (N = 116)	Any grade	Grade ≥3
Diarrhea	70.7%	0.9%
Nausea	69.8%	4.3%
Fatigue	59.5%	6.9%
Vomiting	56.9%	0.9%
Blood creatinine increased	34.5%	0.9%
ALT increased	28.4%	5.2%
AST increased	26.7%	5.2%

Jänne PA et al. *N Engl J Med* 2022;[Online ahead of print].

Meet The Professor with Dr Johnson

Introduction: KRAS in Lung Cancer

MODULE 1: Case Presentations

- Dr Chen: A 60-year-old woman with adenocarcinoma of the lung and a ROS1 fusion, with bone, brain and leptomeningeal metastases
- Dr Niu: A 58-year-old man with Stage IVa lung cancer and malignant pleural effusion and a BRAF V600E mutation – PD-L1 60%
- Dr Morganstein: A 64-year-old woman with adenocarcinoma of the lung, a solitary brain metastasis and an ALK fusion
- Dr Mushtaq: A 50-year-old woman with metastatic adenocarcinoma of the lung and a RET mutation – PD-L1 TPS 40%
- Dr Niu: A 72-year-old woman with Stage IV lung adenocarcinoma and malignant pleural effusion and NRG1 fusion
- Dr Ibrahim: A 69-year-old man with metastatic squamous cell carcinoma of the lung and an ALK translocation
- Dr Ibrahim: A 67-year-old man with metastatic squamous cell carcinoma of the lung and an IDH1 mutation

MODULE 2: Faculty Survey

MODULE 3: MET Exon 14 and HER2 Mutations

MODULE 4: Journal Club with Dr Johnson

MODULE 5: Appendix of Key Publications

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Case Presentation: A 60-year-old woman with adenocarcinoma of the lung and a ROS1 fusion, with bone, brain and leptomeningeal metastases

Dr Gigi Chen (Pleasant Hill, California)

Regulatory and reimbursement issues aside, what would be your preferred first-line therapy for a 65-year-old asymptomatic patient with metastatic nonsquamous NSCLC (PD-L1 TPS 50%) and a ROS1 rearrangement?

 Dr Baik	Entrectinib	 Dr Gainor	Crizotinib
 Dr Camidge	Entrectinib	 Dr Johnson	Entrectinib
 Dr Drilon	Entrectinib	 Dr Spira	Entrectinib

RTP RESEARCH TO PRACTICE

AACR-NCI-EORTC Virtual International Conference on
MOLECULAR TARGETS AND CANCER THERAPEUTICS
October 7-10, 2021

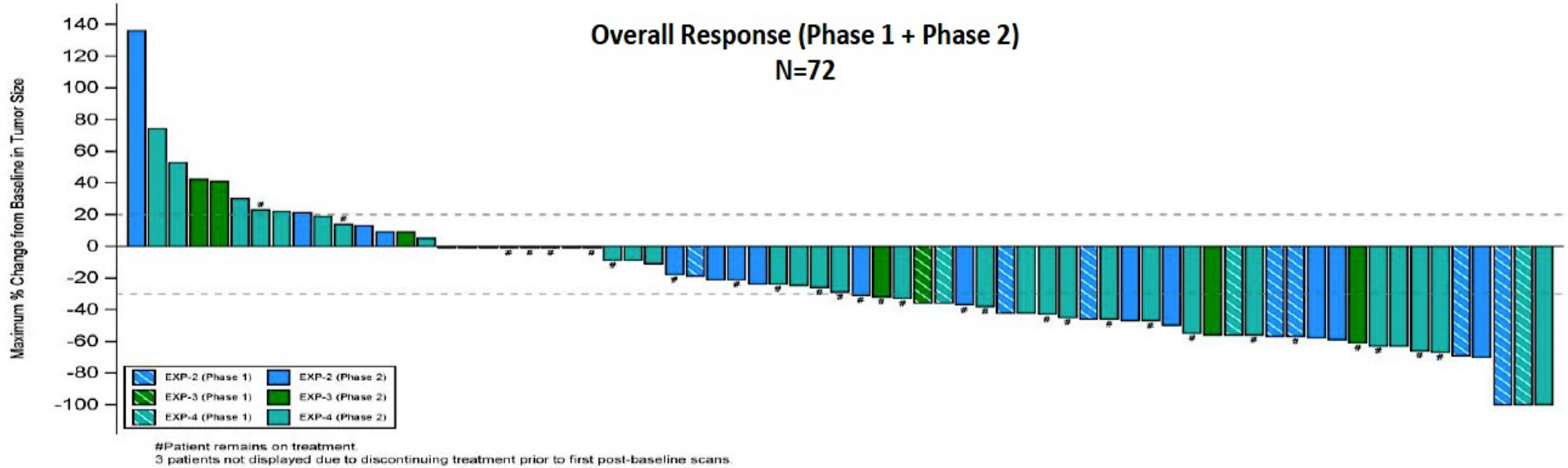
Poster #: P224

Update from the Phase 2 registrational trial of repotrectinib in TKI-pretreated patients with *ROS1+* advanced non-small cell lung cancer and with *NTRK+* advanced solid tumors (TRIDENT-1)

Jessica J. Lin,[1] Byoung Chul Cho,[2] Christoph Springfeld,[3] D. Ross Camidge,[4] Benjamin Solomon,[5] Christina Baik,[6] Vamsidhar Velcheti,[7] Young-Chul Kim,[8] Victor Moreno,[9] Anthonie J. van der Wekken,[10] Enriqueta Felip,[11] Dipesh Uprety,[12] Denise Trone,[13] Shanna Stopatschinskaja,[13] Alexander Drilon[14]

[1]Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; [2]Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea; [3]Heidelberg University Hospital, National Center for Tumor Diseases, Department of Medical Oncology, Heidelberg, Germany; [4]University of Colorado Denver, Anschutz Medical Campus, Aurora, CO, USA; [5]Peter MacCallum Cancer Center, Melbourne, Australia; [6]University of Washington School of Medicine, Seattle Cancer Care Alliance, Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [7]NYU Perlmutter Cancer Center, New York, NY, USA; [8]Chonnam National University Medical School, and CNU Hwasun Hospital, Hwasun-gun, Republic of Korea; [9]Fundación Jiménez Díaz - START Madrid, Madrid, Spain; [10]University of Groningen, University Medical Centre Groningen, Groningen, Netherlands; [11]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [12]Karmanos Cancer Institute, Detroit, MI, USA; [13]Turning Point Therapeutics Inc, San Diego, CA, USA; [14]Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, New York, NY, USA.

TRIDENT-1: Preliminary Efficacy in Patients with TKI-Pretreated Advanced NSCLC with ROS1 Fusions



	EXP-2		EXP-3		EXP-4	
	Phase 2 (N=16)	Phase 1 + 2 (N=23)	Phase 2 (N=9)	Phase 1 + 2 (N=10)	Phase 2 (N=36)	Phase 1 + 2 (N=39)
Confirmed ORR (cORR) (95% CI)	**31%** (11 – 59)	**39%** (20 – 61)	**33%** (7 – 70)	**30%** (7 – 65)	**31%*** (16 – 48)	**33%*** (19 – 50)
Duration of Response (range in months)	1.8+ – 9.2 n=5	1.8+ – 11.1 n=9	1.9+ – 12.9+ n=3	1.9+ – 12.9+ n=3	1.7+ – 15.0+ n=11	0.8+ – 15.0+ n=13

Lin JJ et al. AACR 2021;Abstract 224.

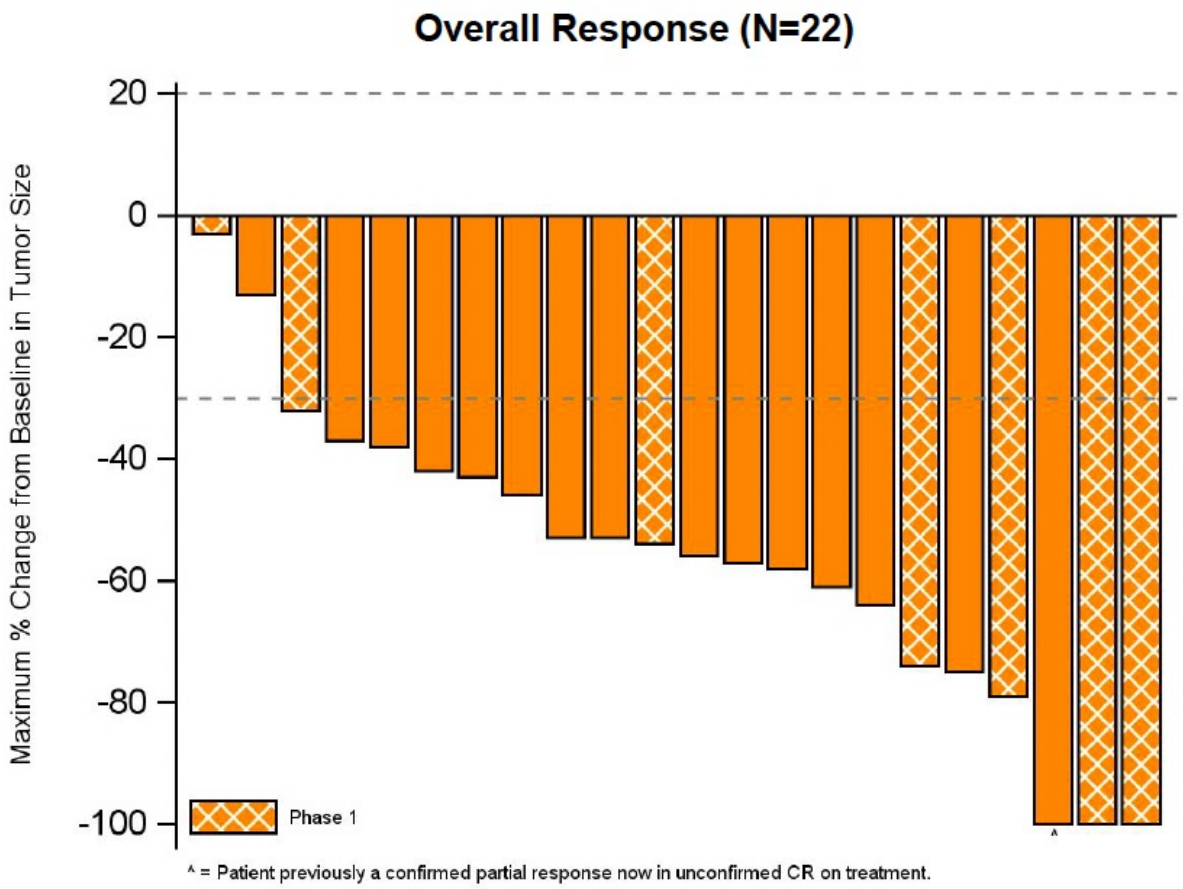
Abstract 3255

Phase 1/2 TRIDENT-1 Study of Repotrectinib in Patients with *ROS1*+ or *NTRK*+ Advanced Solid Tumors

Byoung Chul Cho,[1] Robert C. Doebele,[2] Jessica J. Lin,[3] Misako Nagasaka,[4] Christina Baik,[5] Anthonie J. van der Wekken,[6] Vamsidhar Velcheti,[7] Ki Hyeong Lee,[8] Stephen V. Liu,[9] Benjamin Solomon,[10] Steven Kao,[11] Matthew G. Krebs,[12] Viola Zhu,[13] Shanna Stopatschinskaja,[14] D. Ross Camidge,[15] Alexander Drilon[16]

[1]Yonsei Cancer Center, Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea; [2]University of Colorado Anschutz Medical Campus, Aurora, CO, USA; [3]Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; [4]Karmanos Cancer Institute, Wayne State University, Detroit, MI, USA; [5]Seattle Cancer Care Alliance, Fred Hutchinson Cancer Research Center, University of Washington School of Medicine, Seattle, WA, USA; [6]University of Groningen and University Medical Centre Groningen, Groningen, Netherlands; [7]Perlmutter Cancer Center, NYU Langone Health, New York, NY, USA; [8]Chungbuk National University Hospital, Cheongju, Republic of Korea; [9]Georgetown Lombardi Comprehensive Cancer Center, Georgetown University, Washington D.C., USA; [10]Peter MacCallum Cancer Center, Melbourne, Australia; [11]The Chris O'Brien Lifehouse, Camperdown, Australia; [12]Division of Cancer Sciences, The University of Manchester and the Christie NHS Foundation Trust, Manchester, UK; [13]Chao Family Comprehensive Cancer Center, University of California Irvine School of Medicine, Orange, CA, USA; [14]Turning Point Therapeutics Inc., San Diego, CA, USA; [15]Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, New York, NY, USA

TRIDENT-1: Clinical Activity in TKI-Naïve Advanced NSCLC with ROS1 Fusions



	Phase 2 N=15	Phase 1+2 N=22
Confirmed ORR, % (95% CI)	93% (68–100)	91% (71–99)

N=22 patients with baseline and at least two post baseline scans

- *N=15 Phase 2 patients*
- *N=7 Phase 1 patients treated at or above the Phase 2 recommended dose*

As of 31 December 2020, the 16th patient in Phase 2 has an unconfirmed PR and is on treatment awaiting a second post-baseline confirmatory scan.

Cho BC et al. WCLC 2020;Abstract 3255.

Case Presentation: A 58-year-old man with Stage IVa lung cancer and malignant pleural effusion and a BRAF V600E mutation – PD-L1 60%

Dr Jason Niu (Gilbert, Arizona)

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Case Presentation: A 58-year-old man with Stage IVa lung cancer and malignant pleural effusion and a BRAF V600E mutation – PD-L1 60% (continued)

Dr Jason Niu (Gilbert, Arizona)

Regulatory and reimbursement issues aside, what would be your preferred first-line therapy for a 65-year-old asymptomatic patient with metastatic nonsquamous NSCLC (PD-L1 TPS 50%) and a BRAF V600E mutation?

 Dr Baik	Dabrafenib/trametinib*	 Dr Gainor	Dabrafenib/trametinib
 Dr Camidge	Dabrafenib/trametinib	 Dr Johnson	Dabrafenib/trametinib
 Dr Drilon	Dabrafenib/trametinib	 Dr Spira	Dabrafenib/trametinib

* If the patient is a nonsmoker or if the patient has a high disease burden and needs a fast tumor response

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Case Presentation: A 64-year-old woman with adenocarcinoma of the lung, a solitary brain metastasis and an ALK fusion

Dr Neil Morganstein (Summit, New Jersey)

RTP
RESEARCH
TO PRACTICE

Regulatory and reimbursement issues aside, what would be your preferred first-line therapy for a 65-year-old asymptomatic patient with metastatic nonsquamous NSCLC (PD-L1 TPS 50%) and an ALK rearrangement?

 Dr Baik	Alectinib	 Dr Gainor	Lorlatinib
 Dr Camidge	Alectinib	 Dr Johnson	Alectinib
 Dr Drilon	Alectinib	 Dr Spira	Alectinib

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In general, what would be your preferred second-line therapy for a patient with metastatic nonsquamous NSCLC with an ALK rearrangement and a TPS of 50% who experiences disease progression on alectinib?

 Dr Baik	Lorlatinib	 Dr Gainor	Lorlatinib
 Dr Camidge	Lorlatinib or Brigatinib (if no 2nd driver mutation)	 Dr Johnson	Lorlatinib
 Dr Drilon	Lorlatinib	 Dr Spira	Brigatinib

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For a patient with metastatic nonsquamous NSCLC with an ALK rearrangement and a PD-L1 TPS of 50% who receives first-line alectinib with response followed by disease progression, would you recommend repeat mutation testing?

 Dr Baik	Yes, tissue biopsy	 Dr Gainor	Yes, liquid and tissue biopsy
 Dr Camidge	Yes, liquid and tissue biopsy	 Dr Johnson	Yes, liquid biopsy
 Dr Drilon	Yes, liquid and tissue biopsy	 Dr Spira	Yes, liquid and tissue biopsy

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Regulatory and reimbursement issues aside, would you generally offer targeted treatment in the adjuvant setting for a patient with high-risk (eg, Stage IIB) NSCLC (PD-L1 TPS 50%) who has undergone resection and is found to have an ALK rearrangement?

 Dr Baik	No	 Dr Gainor	No
 Dr Camidge	No	 Dr Johnson	No
 Dr Drilon	Yes, alectinib for 3 years	 Dr Spira	Yes, alectinib for 1 year

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Case Presentation: A 50-year-old woman with metastatic adenocarcinoma of the lung and a RET mutation – PD-L1 TPS (tumor proportion score) 40%

Dr Rao Mushtaq (Thornton, Colorado)

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Regulatory and reimbursement issues aside, what would be your preferred first-line therapy for a 65-year-old asymptomatic patient with metastatic nonsquamous NSCLC (PD-L1 TPS 50%) and a RET fusion?

 Dr Baik	Pralsetinib	 Dr Gainor	Pralsetinib
 Dr Camidge	Selpercatinib	 Dr Johnson	Selpercatinib
 Dr Drilon	Selpercatinib	 Dr Spira	Selpercatinib

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LIBRETTO-432: A Placebo-Controlled Phase 3 Study of Adjuvant Selpercatinib in Stage IB-IIIA RET Fusion-Positive NSCLC

Goldman J et al.

IASLC 2021;Abstract P01.01.

Lancet Oncol 2021;22(7):959-69.

Pralsetinib for *RET* fusion-positive non-small-cell lung cancer (ARROW): a multi-cohort, open-label, phase 1/2 study

Justin F Gainor, Giuseppe Curigliano, Dong-Wan Kim, Dae Ho Lee, Benjamin Besse, Christina S Baik, Robert C Doebele, Philippe A Cassier, Gilberto Lopes, Daniel S W Tan, Elena Garralda, Luis G Paz-Ares, Byoung Chul Cho, Shirish M Gadgeel, Michael Thomas, Stephen V Liu, Matthew H Taylor, Aaron S Mansfield, Viola W Zhu, Corinne Clifford, Hui Zhang, Michael Palmer, Jennifer Green, Christopher D Turner, Vivek Subbiah

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 27, 2020 VOL. 383 NO. 9

Efficacy of Selpercatinib in *RET* Fusion–Positive Non–Small-Cell Lung Cancer

A. Drilon, G.R. Oxnard, D.S.W. Tan, H.H.F. Loong, M. Johnson, J. Gainor, C.E. McCoach, O. Gautschi, B. Besse, B.C. Cho, N. Peled, J. Weiss, Y.-J. Kim, Y. Ohe, M. Nishio, K. Park, J. Patel, T. Seto, T. Sakamoto, E. Rosen, M.H. Shah, F. Barlesi, P.A. Cassier, L. Bazhenova, F. De Braud, E. Garralda, V. Velcheti, M. Satouchi, K. Ohashi, N.A. Pennell, K.L. Reckamp, G.K. Dy, J. Wolf, B. Solomon, G. Falchook, K. Ebata, M. Nguyen, B. Nair, E.Y. Zhu, L. Yang, X. Huang, E. Olek, S.M. Rothenberg, K. Goto, and V. Subbiah

Pivotal Studies of Selpercatinib and Pralsetinib for Advanced NSCLC with RET Fusion

	Selpercatinib[1]	Pralesetinib[2]
Pivotal study	LIBRETTO-001 Phase I/II (N = 105)	ARROW Phase I/II (N = 233)
FDA approval	May 8, 2020	September 4, 2020
Setting	Previous platinum-based chemotherapy and previously untreated	Previous platinum-based chemotherapy and previously untreated
ORR	64%	Prior platinum-based chemo: 61% Treatment-naïve: 70%
Median duration of response	17.5 months	Not reached
Common Grade ≥3 adverse events	Hypertension (14%) Increased ALT (12%) and AST (10%) Hyponatremia (6%) Lymphopenia (6%)	Neutropenia (18%) Hypertension (11%) Anemia (10%) Decreased WBC (6%)

[1] Drilon A et al. *N Engl J Med* 2020;383(9):813-24. [2] Gainor JF et al. *Lancet Oncol* 2021;22(7):959-69.

Case Presentation: A 72-year-old woman with Stage IV lung adenocarcinoma and malignant pleural effusion and NRG1 fusion

Dr Jason Niu (Gilbert, Arizona)

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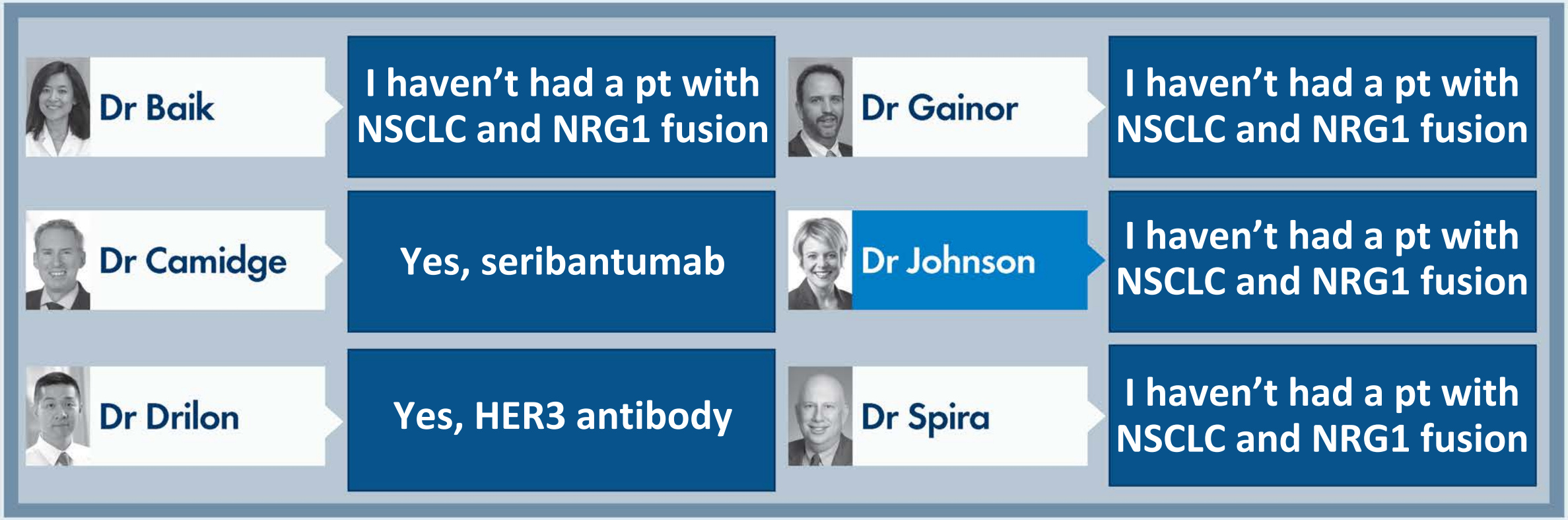
Regulatory and reimbursement issues aside, what would be your preferred first-line therapy for a 65-year-old asymptomatic patient with metastatic NSCLC (PD-L1 TPS 50%) and an NRG1 fusion?

 Dr Baik	Carboplatin/ pemetrexed/ pembrolizumab*	 Dr Gainor	Carboplatin/ pemetrexed/ pembrolizumab
 Dr Camidge	Carboplatin/ pemetrexed/ pembrolizumab	 Dr Johnson	Pembrolizumab
 Dr Drilon	Carboplatin/ pemetrexed/ pembrolizumab	 Dr Spira	Carboplatin/ pemetrexed/ pembrolizumab

* If patient does not have smoking history; pembrolizumab alone if patient has a smoking history

RTP RESEARCH TO PRACTICE

Have any of your patients with advanced NSCLC and an NRG1 fusion responded to targeted therapy?



RTP RESEARCH TO PRACTICE

2022 ASCO® ANNUAL MEETING

Abstract 3006

CRESTONE: Initial Efficacy and Safety of Seribantumab in Solid Tumors Harboring NRG1 Fusions

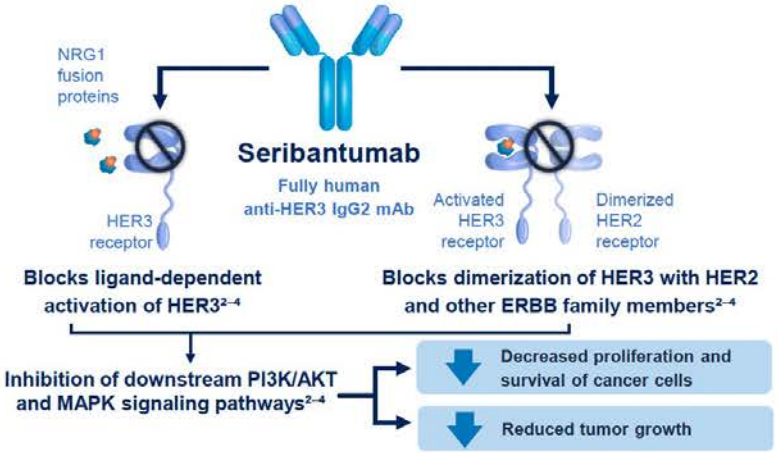
Daniel R. Carrizosa,[1] Mark E. Burkard,[2] Yasir Y. Elamin,[3] Jayesh Desai,[4] Shirish M. Gadgeel,[5] Jessica J. Lin,[6] Saiama N. Waqar,[7] David R. Spigel,[8] Young Kwang Chae,[9] Parneet K. Cheema,[10] Eric B. Haura,[11] Stephen V. Liu,[12] Danny Nguyen,[13] Karen L. Reckamp,[14] Frank Yung-Chin Tsai,[15] Valerie M. Jansen,[16] Alexander Drilon,[17] Sai-Hong Ignatius Ou,[18] D Ross Camidge,[19] Tejas Patil[19]

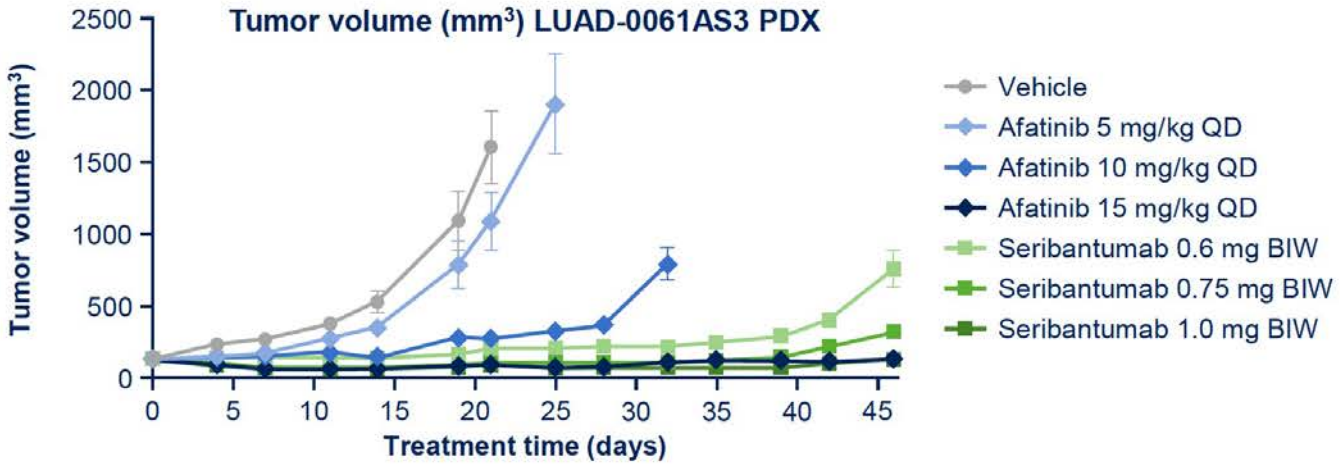
[1]Levine Cancer Institute/Atrium Health, Charlotte, NC; [2]University of Wisconsin Carbone Cancer Center, Madison, WI; [3]The University of Texas MD Anderson Cancer Center, Houston, TX; [4]Peter MacCallum Cancer Centre, Melbourne, Australia; [5]Henry Ford Cancer Institute/Henry Ford Health System, Detroit, MI; [6]Massachusetts General Hospital, Boston, MA; [7]Washington University School of Medicine, St. Louis, MO; [8]Sarah Cannon Research Institute, Nashville, TN; [9]Northwestern University, Chicago, IL; [10]William Osler Health System, Calgary, Canada; [11]H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; [12]Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC; [13]City of Hope, Huntington Beach and Irvine, CA; [14]Cedars-Sinai Medical Center, Los Angeles, CA; [15]HonorHealth, Scottsdale, AZ; [16]Elevation Oncology, Inc. New York, NY; [17]Memorial Sloan Kettering Cancer Center, New York, NY; [18]Chao Family Comprehensive Cancer Center, University of CA-Irvine, Orange, CA; [19]University of Colorado Cancer Center, Aurora, CO

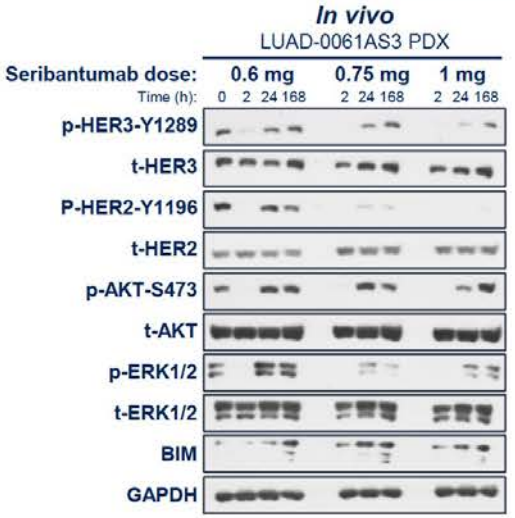
RTP RESEARCH TO PRACTICE

Seribantumab Inhibits NRG1 Fusion Tumor Growth

- Seribantumab is a fully human anti-HER3 IgG2 monoclonal antibody[1,2]
  - Competes with NRG1 to bind to HER3[2,4]
  - Prevents dimerization and phosphorylation of HER3 with other HER family members[2–4]
  - Inhibits downstream PI3K/AKT and MAPK/ERK pathways to inhibit tumor cell growth and proliferation[2–4]
- Seribantumab inhibited tumor growth and induced tumor regression in preclinical models at clinically achievable concentrations[4]





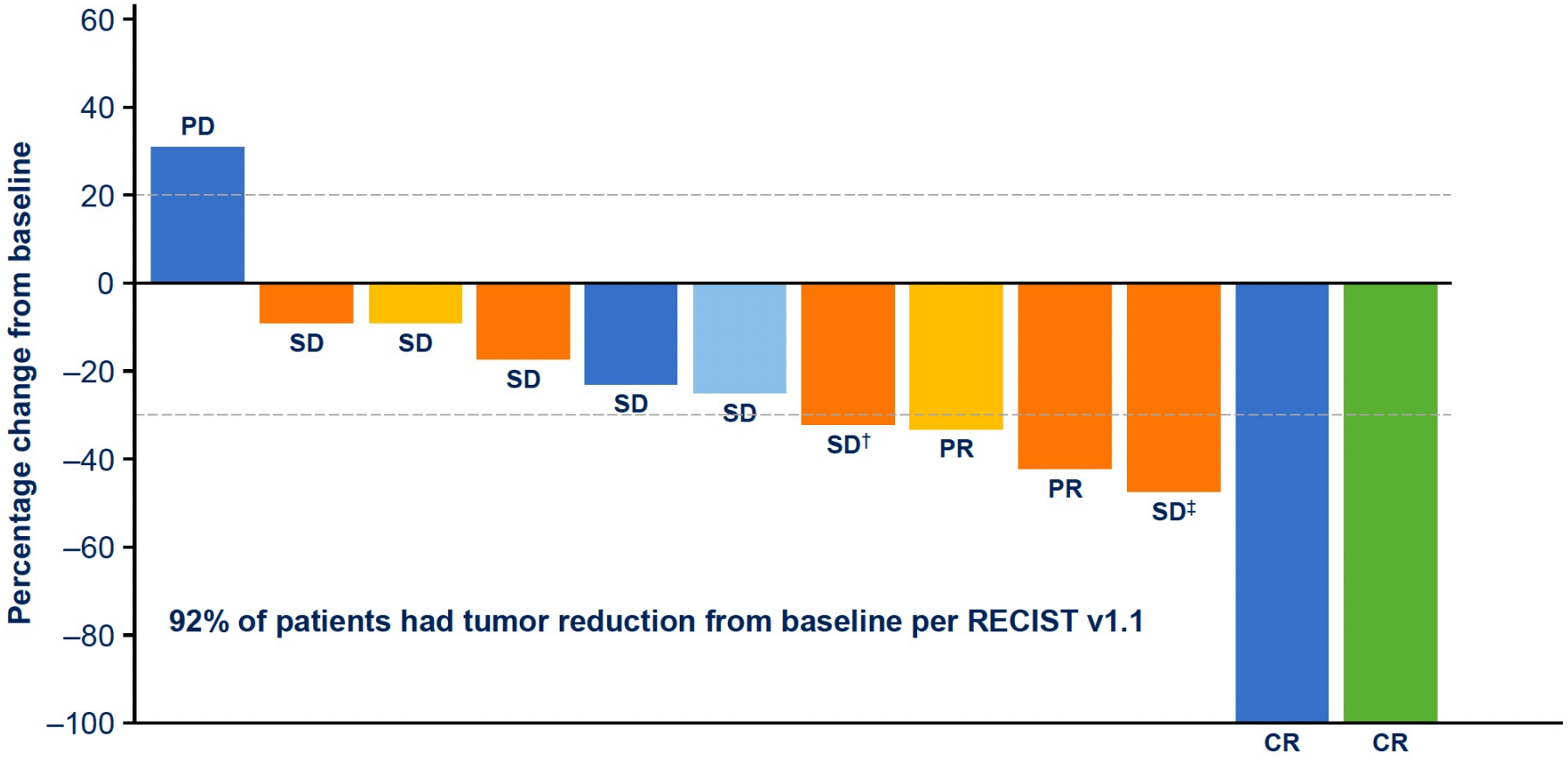


Seribantumab is under investigation in a clinical trial and has not been approved by the FDA for any indication
LUAD, lung adenocarcinoma; PDX, patient-derived xenograft

Sources: 1. Schoeberl B et al. *Sci Signal*. 2009;77:1–14; 2. Schoeberl B et al. *Cancer Res*. 2010;70:2485–2494; 3. Schoeberl B et al. *NPJ Syst Biol Appl*. 2017;3:16034; 4. Odinstov I et al. *Clin Cancer Res*. 2021;27:3154–3166.

Bendell JC et al. Gastrointestinal Cancers Symposium 2021;Abstract TPS449.

CRESTONE: Efficacy of Seribantumab for Tumors Harboring NRG1 Fusions Regardless of Fusion Partner



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

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

Carrizosa DR et al. ASCO 2022;Abstract 3006.

CRESTONE: Safety Summary of Seribantumab Monotherapy

Adverse events reported in ≥15% of patients

	Treatment-emergent AEs (N=35); n (%)				Treatment-related AEs (N = 35); n (%)			
Preferred Term	**Any Grade**	**Grade 1**	**Grade 2**	**Grade ≥ 3†**	**Any Grade**	**Grade 1**	**Grade 2**	**Grade ≥ 3‡**
Patients with ≥1 AE	35 (100)	8 (23)	10 (29)	17 (49)	30 (86)	17 (49)	11 (31)	2 (6)
Diarrhea	17 (49)	11 (31)	4 (11)	2 (6)	14 (40)	10 (29)	3 (9)	1 (3)
Fatigue	14 (40)	7 (20)	7 (20)	0	10 (29)	5 (14)	5 (14)	0
Rash§	11 (31)	9 (26)	2 (6)	0	9 (26)	7 (20)	2 (6)	0
Hypokalemia	10 (29)	6 (17)	3 (9)	1 (3)	3 (9)	3 (9)	0	0
Nausea	10 (29)	7 (20)	1 (3)	2 (6)	6 (17)	5 (14)	1 (3)	0
Abdominal pain‖	8 (23)	4 (11)	2 (6)	2 (6)	3 (9)	1 (3)	2 (6)	0
Decreased appetite	8 (23)	4 (11)	3 (9)	0	3 (9)	1 (3)	2 (6)	0
Headache	8 (23)	7 (20)	1 (3)	0	1 (3)	1 (3)	0	0
Hypomagnesemia	8 (23)	6 (17)	1 (3)	0	2 (6)	2 (6)	0	0
Cough	7 (20)	5 (14)	2 (6)	0	1 (3)	1 (3)	0	0
Anemia^	6 (17)	4 (11)	1 (3)	1 (3)	1 (3)	1 (3)	0	0
Dysuria	6 (17)	6 (17)	0	0	0	0	0	0

- Safety profile of 35 patients with tumors harboring NRG1 fusions who received at least 1 dose of seribantumab in the CRESTONE study
  - One DLT (Grade 2 fatigue resulting in dose reduction by the Investigator in the safety run-in)
  - 27 (77%) patients received the optimized RP2D of seribantumab 3g QW
- Majority (80%) of TRAEs were Grade 1 or 2
- Two (6%) patients received dose reductions for AEs per the Investigator
  - One patient for Grade 1 ALT increase
  - One patient for Grade 2 fatigue
- No patients discontinued seribantumab for AEs

DLT = dose-limiting toxicity; RP2D = recommended Phase II dose

Carrizosa DR et al. ASCO 2022;Abstract 3006.

Dr Sulfi Ibrahim
Richmond, Indiana

Case Presentation: A 69-year-old man with metastatic squamous cell carcinoma of the lung and an ALK translocation

Case Presentation: A 67-year-old man with metastatic squamous cell carcinoma of the lung and an IDH1 mutation

RTP
RESEARCH
TO PRACTICE

Meet The Professor with Dr Gainor

Introduction: KRAS in Lung Cancer

MODULE 1: Case Presentations

MODULE 2: Faculty Survey

- **MET exon 14 and HER2**
- Stage IIIB NSCLC

MODULE 3: MET Exon 14 and HER2 Mutations

MODULE 4: Journal Club with Dr Johnson

MODULE 5: Appendix of Key Publications

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Regulatory and reimbursement issues aside, what would be your preferred first-line therapy for a 65-year-old asymptomatic patient with metastatic nonsquamous NSCLC (PD-L1 TPS 50%) and a MET exon 14 skipping mutation?

 Dr Baik	Capmatinib*	 Dr Gainor	Capmatinib
 Dr Camidge	Capmatinib	 Dr Johnson	Tepotinib
 Dr Drilon	Capmatinib	 Dr Spira	Capmatinib

* If the patient is a nonsmoker

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, what would be your preferred first-line therapy for a 65-year-old asymptomatic patient with metastatic nonsquamous NSCLC (PD-L1 TPS 50%) and an NTRK fusion?

 Dr Baik	Larotrectinib	 Dr Gainor	Larotrectinib
 Dr Camidge	Entrectinib	 Dr Johnson	Larotrectinib
 Dr Drilon	Larotrectinib	 Dr Spira	Larotrectinib

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, what would be your preferred first-line therapy for a 65-year-old asymptomatic patient with metastatic nonsquamous NSCLC (PD-L1 TPS 50%) and a HER2 mutation?

T-DXd = trastuzumab deruxtecan

Regulatory and reimbursement issues aside, in which line of therapy would you generally offer targeted treatment to a patient with metastatic nonsquamous NSCLC (PD-L1 TPS 50%) and a HER2 mutation, and which targeted therapy would you generally offer?

 Dr Baik	Second line T-DXd	 Dr Gainor	Second line T-DXd
 Dr Camidge	Second line T-DXd	 Dr Johnson	Second line T-DXd
 Dr Drilon	First line T-DXd	 Dr Spira	First line T-DXd

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, what would be your preferred first-line therapy for a 65-year-old asymptomatic patient with metastatic nonsquamous NSCLC (PD-L1 TPS 50%) and HER2 overexpression?

 Dr Baik	Pembrolizumab	 Dr Gainor	Carboplatin/ pemetrexted/ pembrolizumab
 Dr Camidge	Carboplatin/ pemetrexed/ pembrolizumab	 Dr Johnson	Pembrolizumab
 Dr Drilon	Pembrolizumab	 Dr Spira	Carboplatin/ pemetrexted/ pembrolizumab

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, in which line of therapy would you generally offer targeted treatment to a patient with metastatic nonsquamous NSCLC (PD-L1 TPS 50%) and HER2 overexpression, and which targeted therapy would you generally offer?

 Dr Baik	Third line T-DXd	 Dr Gainor	No targeted therapy
 Dr Camidge	Third line Likely T-DXd	 Dr Johnson	Second line T-DXd
 Dr Drilon	Third line T-DXd	 Dr Spira	Third line T-Dxd

RTP RESEARCH TO PRACTICE

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Regulatory and reimbursement issues aside, would you generally offer targeted therapy as consolidation treatment to a patient with unresectable Stage IIIB NSCLC (PD-L1 TPS 50%) who has undergone definitive chemoradiation therapy and is found to have a ROS1 rearrangement?

 Dr Baik	No	 Dr Gainor	No
 Dr Camidge	No	 Dr Johnson	No
 Dr Drilon	Yes, entrectinib/crizotinib for 3 years	 Dr Spira	No

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, would you generally offer targeted therapy as consolidation treatment to a patient with unresectable Stage IIIB NSCLC (PD-L1 TPS 50%) who has undergone definitive chemoradiation therapy and is found to have a BRAF V600E mutation?

 Dr Baik	No	 Dr Gainor	No
 Dr Camidge	No	 Dr Johnson	No
 Dr Drilon	Yes, dabrafenib/trametinib for 3 years	 Dr Spira	No

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, would you generally offer targeted therapy as consolidation treatment to a patient with unresectable Stage IIIB NSCLC (PD-L1 TPS 50%) who has undergone definitive chemoradiation therapy and is found to have a RET fusion?

 Dr Baik	Yes, pralsetinib for 2 years	 Dr Gainor	No
 Dr Camidge	No	 Dr Johnson	No
 Dr Drilon	Yes, selpercatinib for 3 years	 Dr Spira	No

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, would you generally offer targeted therapy as consolidation treatment to a patient with unresectable Stage IIIB NSCLC (PD-L1 TPS 50%) who has undergone definitive chemoradiation therapy and is found to have a MET exon 14 skipping mutation?

 Dr Baik	No	 Dr Gainor	No
 Dr Camidge	No	 Dr Johnson	No
 Dr Drilon	Yes, crizotinib/capmatinib for 3 years	 Dr Spira	No

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, would you generally offer targeted therapy as consolidation treatment to a patient with unresectable Stage IIIB NSCLC (PD-L1 TPS 50%) who has undergone definitive chemoradiation therapy and is found to have a KRAS G12C mutation?

 Dr Baik	No	 Dr Gainor	No
 Dr Camidge	No	 Dr Johnson	No
 Dr Drilon	Yes, sotorasib for 3 years	 Dr Spira	No

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, would you generally offer targeted therapy as consolidation treatment to a patient with unresectable Stage IIIB NSCLC (PD-L1 TPS 50%) who has undergone definitive chemoradiation therapy and is found to have a HER2 mutation?

 Dr Baik	No	 Dr Gainor	No
 Dr Camidge	No	 Dr Johnson	No
 Dr Drilon	No	 Dr Spira	No

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, would you generally offer targeted therapy as consolidation treatment to a patient with unresectable Stage IIIB NSCLC (PD-L1 TPS 50%) who has undergone definitive chemoradiation therapy and is found to have HER2 overexpression?

 Dr Baik	No	 Dr Gainor	No
 Dr Camidge	No	 Dr Johnson	No
 Dr Drilon	No	 Dr Spira	No

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, would you generally offer targeted therapy as consolidation treatment to a patient with unresectable Stage IIIB NSCLC (PD-L1 TPS 50%) who has undergone definitive chemoradiation therapy and is found to have an NTRK fusion?

 Dr Baik	Yes, larotrectinib for 2 years	 Dr Gainor	No
 Dr Camidge	No	 Dr Johnson	No
 Dr Drilon	Yes, larotrectinib for 3 years	 Dr Spira	No

RTP RESEARCH TO PRACTICE

Meet The Professor with Dr Johnson

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MET Exon 14 Skipping

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Tepotinib and Capmatinib Receive FDA Approval for the Treatment of Advanced NSCLC with MET Exon 14 Skipping Mutations

Tepotinib Press Release – February 3, 2021

The FDA granted accelerated approval to tepotinib for adult patients with metastatic NSCLC harboring mesenchymal-epithelial transition (MET) exon 14 skipping alterations. Efficacy was demonstrated in the VISION trial (NCT02864992), a multicenter, non-randomized, open-label, multicohort study enrolling 152 patients with advanced or metastatic NSCLC with MET exon 14 skipping alterations. Patients received tepotinib 450 mg orally once daily until disease progression or unacceptable toxicity.

Capmatinib Press Release – May 6, 2020

The FDA granted accelerated approval to for adult patients with metastatic NSCLC whose tumors have a mutation that leads to mesenchymal-epithelial transition (MET) exon 14 skipping. Efficacy was demonstrated in the GEOMETRY mono-1 trial (NCT02414139), a multicenter, non-randomized, open-label, multicohort study enrolling 97 patients with metastatic NSCLC with confirmed MET exon 14 skipping. Patients received capmatinib 400 mg orally twice daily until disease progression or unacceptable toxicity.

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-tepotinib-metastatic-non-small-cell-lung-cancer. https://wayback.archive-it.org/7993/20201222063225/https://www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-capmatinib-metastatic-non-small-cell-lung-cancer

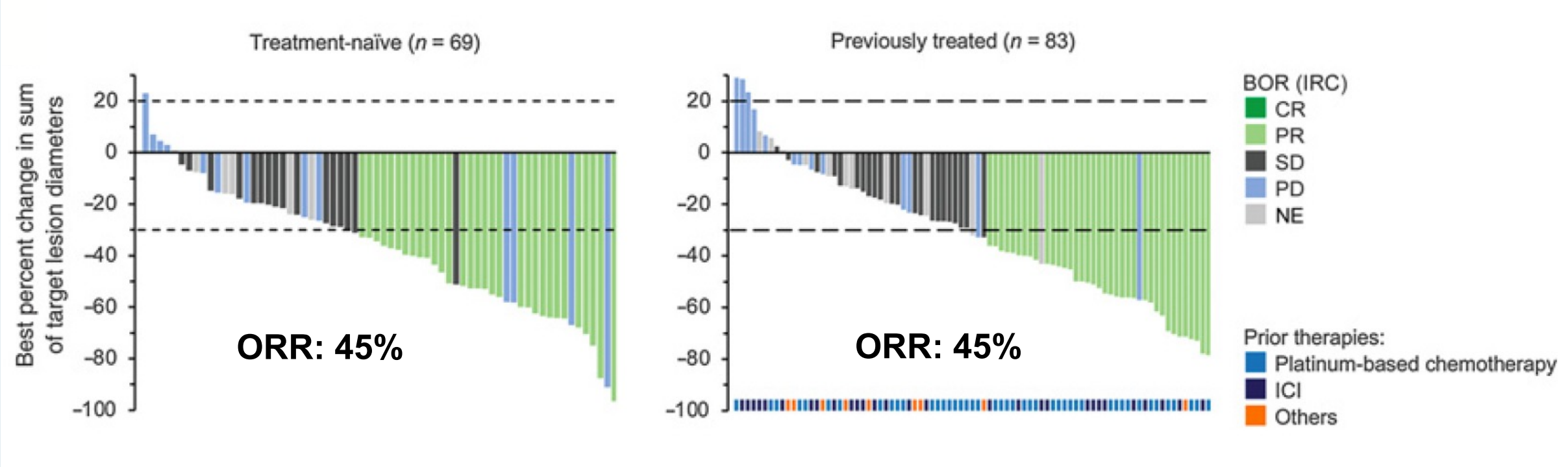
CLINICAL CANCER RESEARCH | CLINICAL TRIALS: TARGETED THERAPY

Tepotinib Efficacy and Safety in Patients with *MET* Exon 14 Skipping NSCLC: Outcomes in Patient Subgroups from the VISION Study with Relevance for Clinical Practice

Xiuning Le[1], Hiroshi Sakai[2], Enriqueta Felip[3], Remi Veillon[4], Marina Chiara Garassino[5,6], Jo Raskin[7], Alexis B. Cortot[8], Santiago Viteri[9], Julien Mazieres[10], Egbert F. Smit[11], Michael Thomas[12], Wade T. Iams[13], Byoung Chul Cho[14], Hye Ryun Kim[14], James Chih-Hsin Yang[15], Yuh-Min Chen[16], Jyoti D. Patel[17], Christine M. Bestvina[18], Keunchil Park[19], Frank Griesinger[20], Melissa Johnson[21], Maya Gottfried[22], Christian Britschgi[23], John Heymach[1], Elif Sikoglu[24], Karin Berghoff[25], Karl-Maria Schumacher[26], Rolf Bruns[27], Gordon Otto[26], and Paul K. Paik[28,29]

***Clin Cancer Res* 2022;28(6):1117-26.**

VISION: Tepotinib for Advanced NSCLC with MET Exon 14 Skipping Mutations



Le X et al. *Clin Cancer Res* 2022;28(6):1117-26.

VISION: Treatment-Related Adverse Events with Tepotinib

Adverse events	Cohorts A + C (N = 255)	
	Any grade	Grade 3/4
Peripheral edema	54%	8%
Nausea	20%	<1%
Diarrhea	20%	<1%
Blood creatinine increase	18%	<1%
Hypoalbuminemia	15%	2%
ALT increase	9%	2%
Decreased appetite	8%	<1%
Amylase increase	8%	2%

6 confirmed ILD-like events were reported

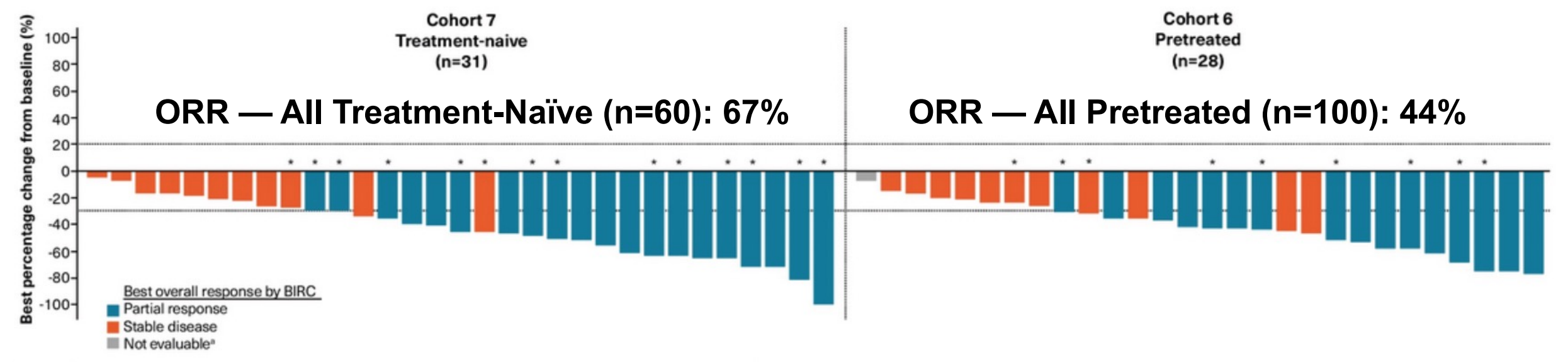
Le X et al. *Clin Cancer Res* 2022;28(6):1117-26.

Capmatinib in *MET* Exon 14-Mutated, Advanced NSCLC: Updated Results from the GEOMETRY mono-1 Study

Wolf J et al.

ASCO 2021;Abstract 9020.

GEOMETRY mono-1: Overall Response Rates (Cohorts 7 and 6)



Wolf J et al. ASCO 2021;Abstract 9020.

RTP RESEARCH TO PRACTICE

2022 ASCO® ANNUAL MEETING

Abstract 9008

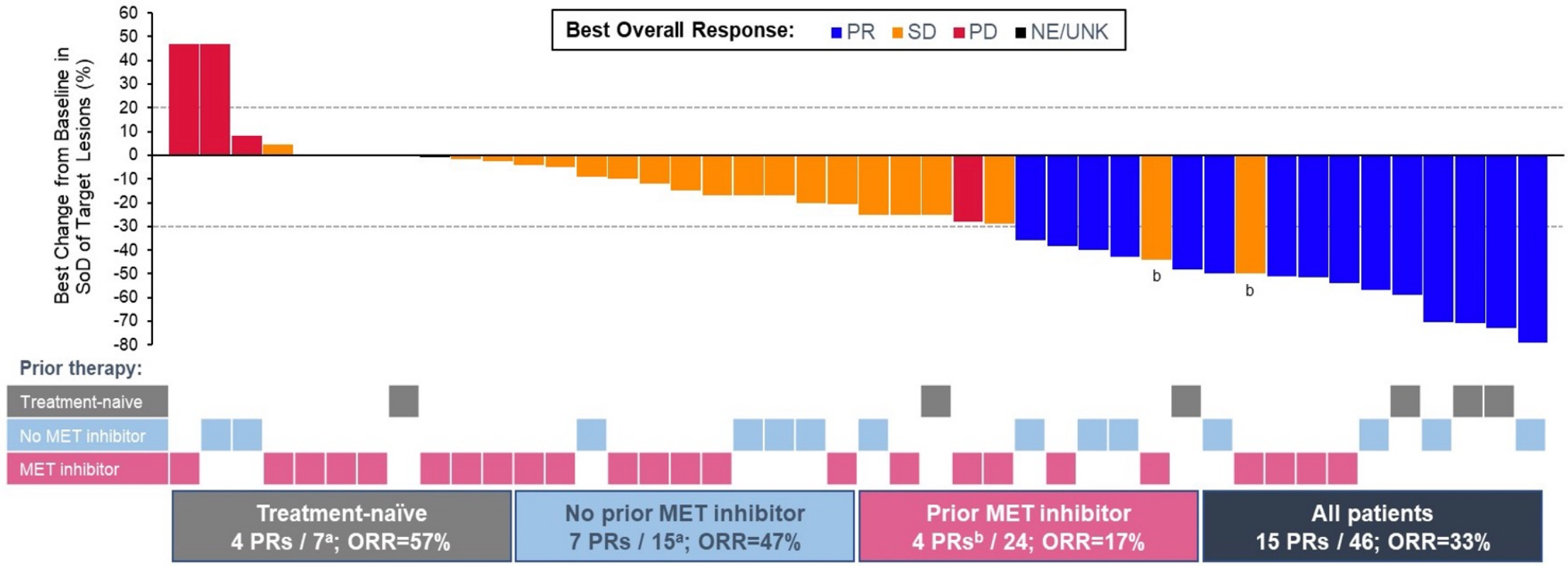
Amivantamab in NSCLC patients with MET exon 14 skipping mutation: Updated results from the CHRYSALIS study

Matthew G. Krebs,[1] Alexander I. Spira,[2] Byoung Chul Cho,[3] Benjamin Besse,[4] Jonathan W. Goldman,[5] Pasi A. Jänne,[6] Zhiyong Ma,[7] Aaron S. Mansfield,[8] Anna Minchom,[9] Sai-Hong Ignatius Ou,[10] Ravi Salgia,[11] Zhijie Wang,[12] Casilda Llacer Perez,[13] Grace Gao,[14] Joshua C. Curtin,[14] Amy Roshak,[14] Robert W. Schnepp,[14] Meena Thayu,[14] Roland E. Knoblauch,[14] Chee Khoon Lee[15]

[1]Division of Cancer Sciences, The University of Manchester and The Christie NHS Foundation Trust, Manchester, UK; [2]Virginia Cancer Specialists Research Institute, US Oncology Research, Fairfax VA; [3]Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea; [4]Institut Gustave Roussy, Villejuif, France; [5]David Geffen School of Medicine at UCLA, Los Angeles, CA; [6]Dana Farber Cancer Institute, Boston, MA; [7]Henan Cancer Hospital, Zhengzhou, China; [8]Mayo Clinic, Rochester, MN; [9]Drug Development Unit, Royal Marsden/Institute of Cancer Research, Sutton, UK; [10]University of California Irvine, Orange, CA; [11]City of Hope, Duarte, CA; [12]Cancer Hospital Chinese Academy of Medical Sciences, Beijing, China; [13]Medical Oncology Intercenter Unit, Regional and Virgen de la Victoria University Hospitals, IBIMA, Málaga, Spain; [14]Janssen R&D, Spring House, PA; [15]St George Hospital, Kogarah, Australia

CHRYSALIS: Antitumor Activity of Amivantamab

- A total of 46 patients were efficacy evaluable



Krebs MG et al. ASCO 2022;Abstract 9008.

RTP RESEARCH TO PRACTICE

HER2 Mutation

N Engl J Med 2022;386(3):241-51.

The NEW ENGLAND JOURNAL of MEDICINE

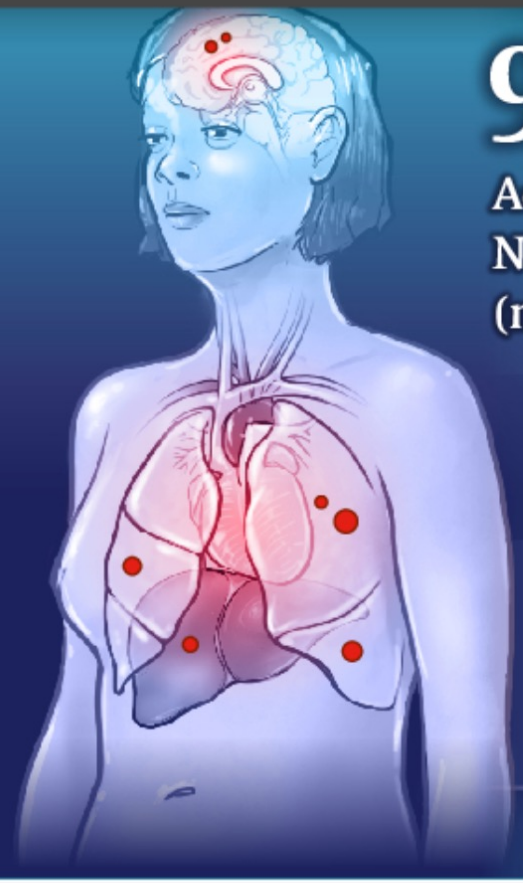
ORIGINAL ARTICLE

Trastuzumab Deruxtecan in *HER2*-Mutant Non–Small-Cell Lung Cancer

Bob T. Li, M.D., Ph.D., M.P.H., Egbert F. Smit, M.D., Ph.D., Yasushi Goto, M.D., Ph.D., Kazuhiko Nakagawa, M.D., Hibiki Udagawa, M.D., Julien Mazières, M.D., Misako Nagasaka, M.D., Ph.D., Lyudmila Bazhenova, M.D., Andreas N. Saltos, M.D., Enriqueta Felip, M.D., Ph.D., Jose M. Pacheco, M.D., Maurice Pérol, M.D., Luis Paz-Ares, M.D., Kapil Saxena, M.D., Ryota Shiga, B.Sc., Yingkai Cheng, M.D., Ph.D., Suddhasatta Acharyya, Ph.D., Patrik Vitazka, M.D., Ph.D., Javad Shahidi, M.D., David Planchard, M.D., Ph.D., and Pasi A. Jänne, M.D., Ph.D., for the DESTINY-Lung01 Trial Investigators*

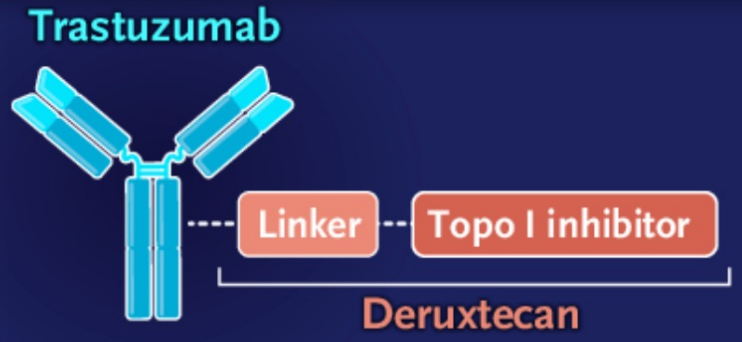
DESTINY-Lung01 Study

MULTICENTER, INTERNATIONAL, PHASE 2 STUDY



91

Adults with metastatic *HER2*-mutant NSCLC refractory to standard treatment (median follow-up, 13 mo)



Confirmed objective response (assessed by independent central review)	55% (95% CI, 44–65)
Duration of response	9.3 mo
Progression-free survival	8.2 mo
Overall survival	17.8 mo

Grade 3 or higher drug-related adverse events occurred in 46% of patients.

Trastuzumab deruxtecan showed durable anticancer activity.

Li BT et al. *N Engl J Med* 2022;386(3):241-51.

DESTINY-Lung01: Summary of Adverse Events and AEs of Clinical Interest

Event	N = 91
Discontinued due to AEs	25%
Dose reduction due to AEs	34%
Dose interruption due to AEs	32%
Drug-related interstitial lung disease (ILD)	26% (N = 24)
Grade 1	3 pts
Grade 2	15 pts
Grade 3	4 pts
Grade 5	2 pts
Median time to onset of ILD	141 days
Median duration of ILD	43 days

Li BT et al. *N Engl J Med* 2022;386(3):241-51.

Meet The Professor with Dr Johnson

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TROPION-PanTumor01: Updated Results From the NSCLC Cohort of the Phase 1 Study of Datopotamab Deruxtecan in Solid Tumors

Edward B. Garon, MD, MS

David Geffen School of Medicine at UCLA
Los Angeles, CA, USA

Edward B. Garon,[1] Melissa Johnson,[2] Aaron E. Lisberg,[1] Alexander Spira,[3] Noboru Yamamoto,[4] Rebecca S. Heist,[5] Jacob M. Sands,[6] Kiyotaka Yoh,[7] Funda Meric-Bernstam,[8] Satoru Kitazono,[9] Jonathan Greenberg,[10] Fumiaki Kobayashi,[11] Ferdinand Guevara,[10] Yui Kawasaki,[11] Toshio Shimizu[4]

[1]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [2]Sarah Cannon Research Institute, Tennessee Oncology, PLLC, OneOncology, Nashville, TN, USA; [3]Virginia Cancer Specialists and US Oncology Research, Fairfax, VA, USA; [4]National Cancer Center Hospital, Tokyo, Japan; [5]Massachusetts General Hospital, Boston, MA, USA; [6]Dana-Farber Cancer Institute, Boston, MA, USA; [7]National Cancer Center Hospital East, Chiba, Japan; [8]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [9]The Cancer Institute Hospital of JFCR, Tokyo, Japan; [10]Daiichi Sankyo, Inc, Basking Ridge, NJ, USA; [11]Daiichi Sankyo Co, Ltd, Tokyo, Japan

IASLC 2021 World Conference on Lung Cancer
SEPTEMBER 8 - 14, 2021 | WORLDWIDE VIRTUAL EVENT

Abstract MA03.02

A Phase 2 Study of Datopotamab Deruxtecan (Dato-DXd) in Advanced NSCLC With Actionable Genomic Alterations (TROPION-Lung05)

Melissa L. Johnson,[1] Alexander Spira,[2] Kiyotaka Yoh,[3] Rebecca S. Heist,[4] Aaron E. Lisberg,[5] Jonathan Greenberg,[6] Penny Phillips,[6] Lan Lan,[6] Wen Gu,[6] Yong Zhang,[6] Jacob M. Sands[7]

[1]Sarah Cannon Research Institute, Nashville, TN, USA; [2]Virginia Cancer Specialists, Fairfax, VA, USA; [3]National Cancer Center Hospital East, Kashiwa, Japan; [4]Mass General Cancer Center, Boston, MA, USA; [5]UCLA Jonsson Comprehensive Cancer Center, Santa Monica, CA, USA; [6]Daiichi Sankyo, Inc, Basking Ridge, NJ, USA; [7]Dana-Farber Cancer Institute, Boston, MA, USA

IASLC 2021 World Conference on Lung Cancer
SEPTEMBER 8 - 14, 2021 I WORLDWIDE VIRTUAL EVENT

Abstract P47.05

2021 ESMO congress

Efficacy of Datopotamab Deruxtecan (Dato-DXd) in Patients With Advanced/Metastatic Non-Small Cell Lung Cancer (NSCLC) and Actionable Genomic Alterations (AGAs): Preliminary Results From the Phase 1 TROPION-PanTumor01 Study

Edward B. Garon,[1] Melissa L. Johnson,[2] Aaron E. Lisberg,[1] Alexander Spira,[3] Noboru Yamamoto,[4] Rebecca S. Heist,[5] Jacob M. Sands,[6] Kiyotaka Yoh,[7] Funda Meric-Bernstam,[8] Satoru Kitazono,[9] Jonathan Greenberg,[10] Fumiaki Kobayashi,[11] Yui Kawasaki,[11] Lori Jukofsky,[10] Kota Nakamura,[10] Toshio Shimizu[4]

[1]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [2]Sarah Cannon Research Institute, Tennessee Oncology, PLLC/OneOncology, Nashville, TN, USA; [3]Virginia Cancer Specialists, Fairfax, VA, USA; [4]Department of Experimental Therapeutics, National Cancer Center Hospital, Tokyo, Japan; [5]Massachusetts General Hospital, Boston, MA, USA; [6]Dana-Farber Cancer Institute, Boston, MA, USA; [7]National Cancer Center Hospital East, Chiba, Japan; [8]The University of Texas, MD Anderson Cancer Center, Houston, TX, USA; [9]The Cancer Institute Hospital of JFCR, Tokyo, Japan; [10]Daiichi Sankyo, Inc, Basking Ridge, NJ, USA; [11]Daiichi Sankyo Co, Ltd, Tokyo, Japan

Abstract LBA49

JC JOURNAL CLUB RTP RESEARCH TO PRACTICE

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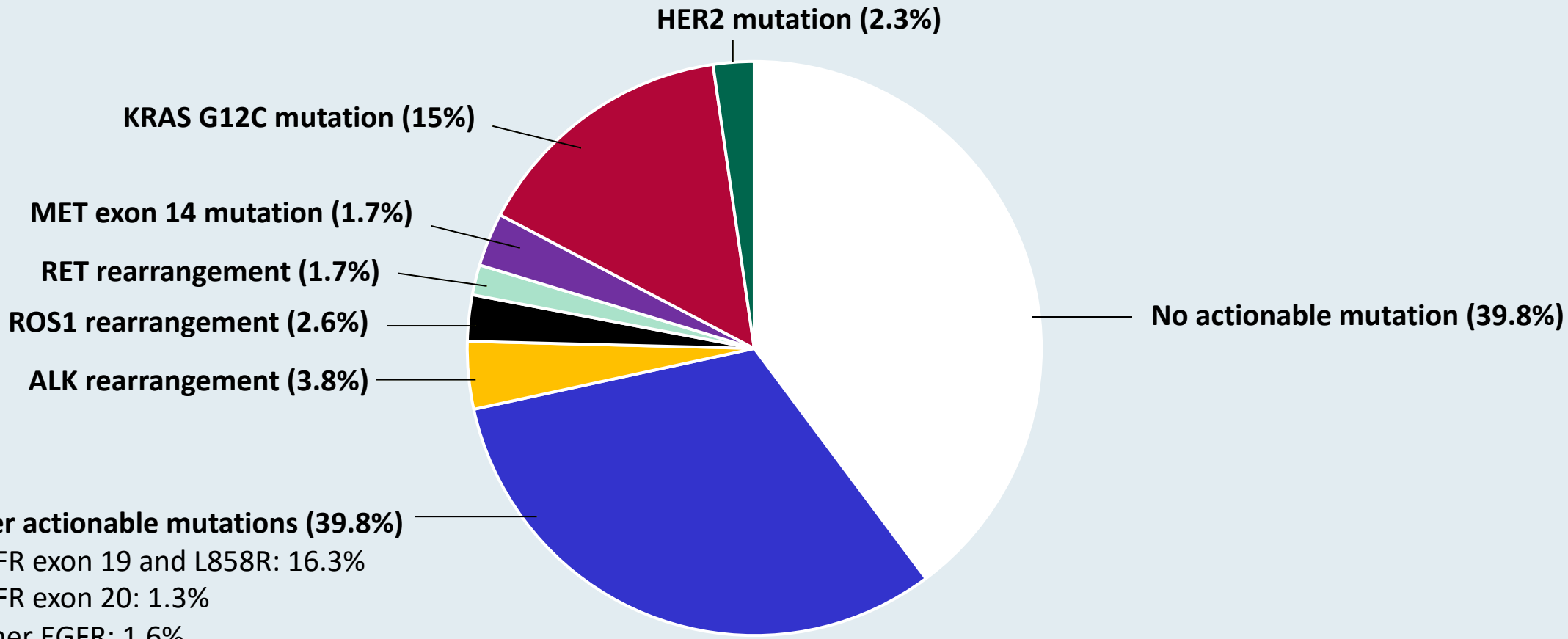
Frequency of Targetable Oncogenic Driver Molecular Alterations in Adenocarcinoma of the Lung

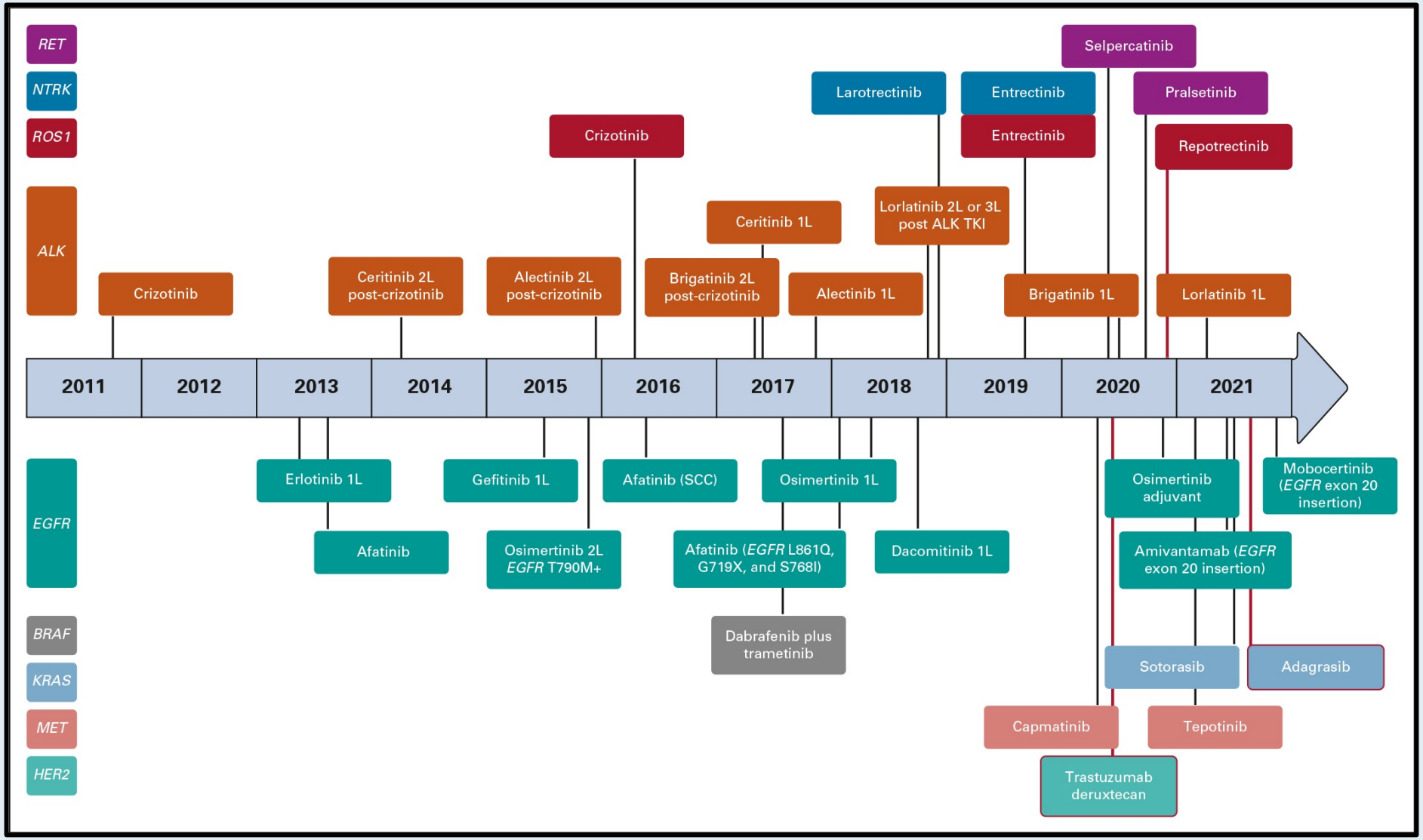


Other actionable mutations (39.8%)
--EGFR exon 19 and L858R: 16.3%
--EGFR exon 20: 1.3%
--Other EGFR: 1.6%
--Other KRAS: 10.3%
--BRAF V600E: 2.1%
--NTRK rearrangement: 0.23%

Derived from Tan AC et al. *J Clin Oncol* 2022;40(6):611-25.

RTP RESEARCH TO PRACTICE

Timeline of Select FDA-Approved Targeted Therapies for Oncogene-Driven NSCLC

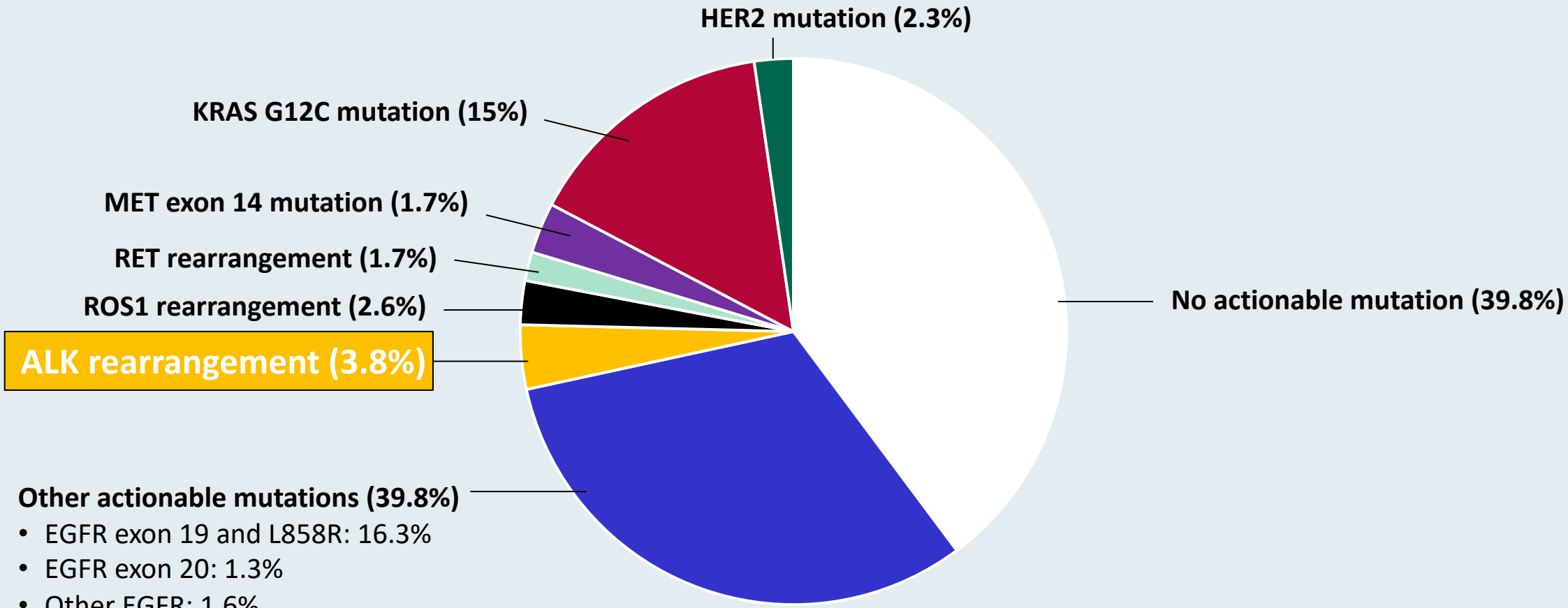


Tan AC et al. *J Clin Oncol* 2022;40(6):611-25.

Note: Red line indicates breakthrough therapy designation

RTP RESEARCH TO PRACTICE

Frequency of Targetable Oncogenic Driver Molecular Alterations in Adenocarcinoma of the Lung



- EGFR exon 19 and L858R: 16.3%
- EGFR exon 20: 1.3%
- Other EGFR: 1.6%
- Other KRAS: 10.3%
- BRAF V600E: 2.1%
- NTRK rearrangement: 0.23%

Derived from Tan AC et al. *J Clin Oncol* 2022;40(6):611-25.

RTP RESEARCH TO PRACTICE

Key Randomized Trials in Treatment-Naïve Advanced ALK-Rearranged NSCLC

Study	Intervention	Comparator	ORR	CNS ORR
PROFILE 1014	Crizotinib	Platinum/pemetrexed	74% vs 45%	—
PROFILE 1029	Crizotinib	Platinum/pemetrexed	88% vs 46%	—
ASCEND-4	Ceritinib	Platinum/pemetrexed	73% vs 27%	73% vs 27%
ALEX	Alectinib	Crizotinib	83% vs 76%	81% vs 50%
J-ALEX	Alectinib	Crizotinib	92% vs 79%	—
ALESIA	Alectinib	Crizotinib	91% vs 77%	—
ALTA-1L	Brigatinib	Crizotinib	71% vs 60%	78% vs 26%
CROWN	Lorlatinib	Crizotinib	76% vs 58%	82% vs 23%
eXalt3	Ensartinib	Crizotinib	75% vs 67%	64% vs 21%

Tan AC et al. *J Clin Oncol* 2022;40(6):611-25; Soria JC et al. *Lancet* 2017;389(10072):917-29; Peters S et al. *N Engl J Med* 2017;377(9):829-38; Camidge DR et al. *J Thorac Oncol* 2021;16(12):2091-108; Shaw AT et al. *N Engl J Med* 2020;383(21):2018-29; Horn L et al. *JAMA Oncol* 2021;7(11):1617-25; Popat S et al. ESMO 2021;Abstract 1195P.

Key Randomized Trials in Treatment-Naïve Advanced ALK-Rearranged NSCLC (Continued)

Study	Intervention	Comparator	Median PFS	PFS Hazard ratio	OS Hazard ratio
PROFILE 1014	Crizotinib	Platinum/pemetrexed	11 vs 7 mo	0.45	0.76
PROFILE 1029	Crizotinib	Platinum/pemetrexed	11 vs 7 mo	0.40	0.90
ASCEND-4	Ceritinib	Platinum/pemetrexed	17 vs 8 mo	0.55	0.73
ALEX	Alectinib	Crizotinib	35 vs 11 mo	0.50	0.67
J-ALEX	Alectinib	Crizotinib	34 vs 10 mo	0.37	0.80
ALESIA	Alectinib	Crizotinib	NR v 11 mo	0.37	0.28
ALTA-1L	Brigatinib	Crizotinib	24 vs 11 mo	0.49	0.92
CROWN	Lorlatinib	Crizotinib	NR vs 9 mo	0.28	0.72
eXalt3	Ensartinib	Crizotinib	26 vs 13 mo	0.52	0.88

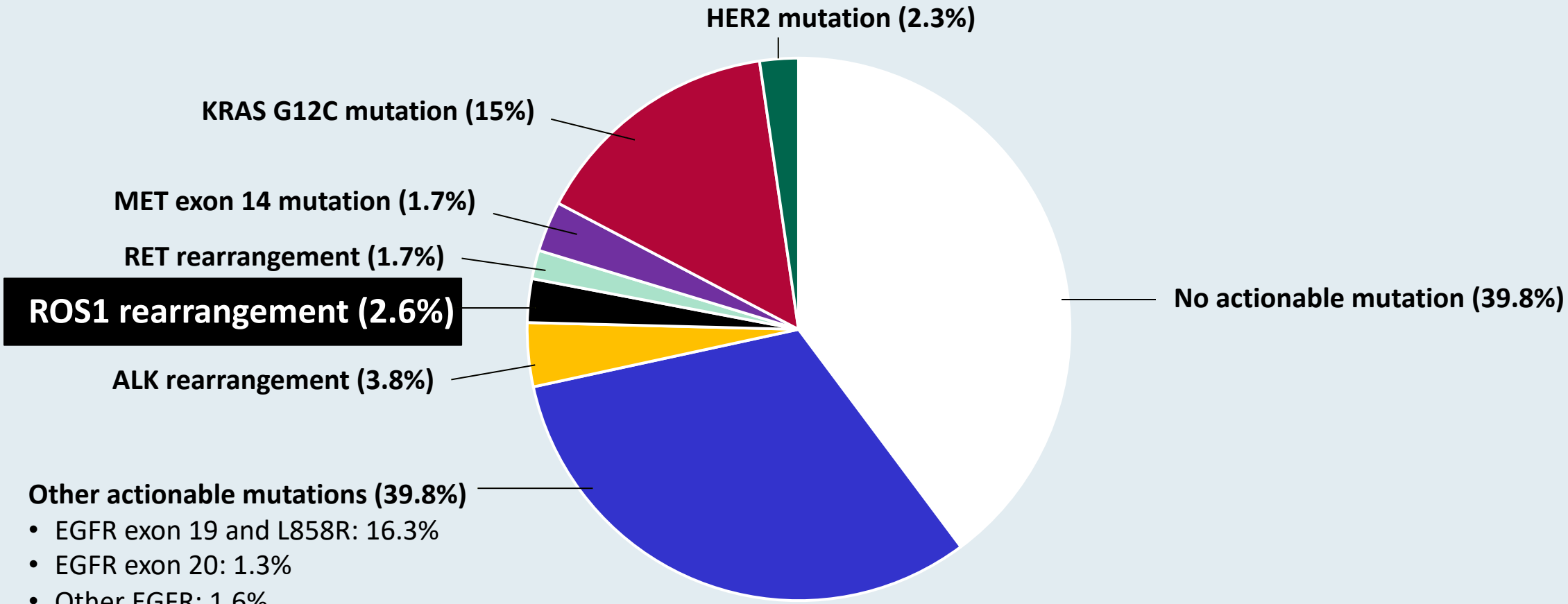
Tan AC et al. *J Clin Oncol* 2022;40(6):611-25; Soria JC et al. *Lancet* 2017;389(10072):917-29; Peters S et al. *N Engl J Med* 2017;377(9):829-38; Camidge DR et al. *J Thorac Oncol* 2021;16(12):2091-108; Shaw AT et al. *N Engl J Med* 2020;383(21):2018-29; Horn L et al. *JAMA Oncol* 2021;7(11):1617-25; Popat S et al. ESMO 2021;Abstract 1195P.

Common and Unique Adverse Effects of ALK TKIs

ALK TKI	Most common adverse effects
Crizotinib	Vision disorders, nausea, diarrhea, vomiting, edema, constipation, elevated transaminases, fatigue, decreased appetite, upper respiratory infection, dizziness and neuropathy
Ceritinib	Diarrhea, nausea, vomiting, fatigue, abdominal pain, decreased appetite and weight loss
Alectinib	Constipation, fatigue, edema, myalgia and anemia
Brigatinib	Diarrhea, fatigue, nausea, rash, cough, myalgia, headache, hypertension, vomiting and dyspnea
Lorlatinib	Hypercholesterolemia, hypertriglyceridemia, edema, peripheral neuropathy, weight gain, cognitive effects, fatigue, dyspnea, arthralgia and diarrhea
Ensartinib	Rash, nausea, pruritus and vomiting

Crizotinib PI, rev 1/2021; Ceritinib PI, rev 3/2019; Alectinib PI, rev 1/2021; Brigatinib PI, rev 5/2020; Lorlatinib PI, rev 3/2021
Xia B et al. *Transl Lung Cancer Res* 2020;9(6):2521-253; Gristina V et al. *Pharmaceuticals* 2020;13(12):474.

Frequency of Targetable Oncogenic Driver Molecular Alterations in Adenocarcinoma of the Lung



Other actionable mutations (39.8%)

- EGFR exon 19 and L858R: 16.3%
- EGFR exon 20: 1.3%
- Other EGFR: 1.6%
- Other KRAS: 10.3%
- BRAF V600E: 2.1%
- NTRK rearrangement: 0.23%

Derived from Tan AC et al. *J Clin Oncol* 2022;40(6):611-25.

RTP RESEARCH TO PRACTICE

Key Trials of ROS1 TKIs for TKI-Naïve NSCLC with ROS1 Fusions

ROS1 TKI	Study	Phase	ORR	Median DoR	Median PFS	Intracranial ORR
Crizotinib	PROFILE 1001	Ib	38/53 (72%)	25 mo	19 mo	—
	OxOnc	II	91/127 (72%)	20 mo	16 mo	—
	EUCROSS	II	21/30 (70%)	19 mo	20 mo	—
	AcSe	II	35/36 (69%)	—	6 mo	—
	METROS	II	17/26 (65%)	21 mo	23 mo	33%
Entrectinib	Drilon et al	I/II	41/53 (77%)	25 mo	19 mo	55%
Ceritinib	Lim et al	II	20/30 (67%)	21 mo	19 mo	29%
Brigatinib	Gettinger et al	I	1/1 (100%)	—	—	—
Lorlatinib	Shaw et al	I/II	13/21 (62%)	25 mo	21 mo	64%
Repotrectinib	Cho et al	I/II	10/11 (91%)	—	—	100%
Taletrectinib	Fujiwara et al	I	6/9 (67%)	—	—	—

Drilon A et al. *Nat Rev Clin Oncol* 2021;18(1):35-55.

Key Trials of ROS1 TKIs for TKI-Pretreated NSCLC with ROS1 Fusions

ROS1 TKI	Study	Phase	ORR
Entrectinib (after crizotinib)	Drilon et al	I/II	0/6 (0%)
Ceritinib (after crizotinib)	Lim et al	II	0/2 (0%)
Brigatinib (after crizotinib)	Gettinger et al	I	0/2 (0%)
Lorlatinib	Shaw et al	I/II	After crizotinib: 14/40 (35%) After ≥2 prior TKIs: 0/6 (0%)
Repotrectinib	Drilon et al	I/II	After 1 prior TKI: 7/18 (39%) After ≥2 prior TKIs: 2/7 (29%)
Taletrectinib (after crizotinib)	Fujiwara et al	I	1/3 (33%)

Drilon A et al. *Nat Rev Clin Oncol* 2021;18(1):35-55.

original reports

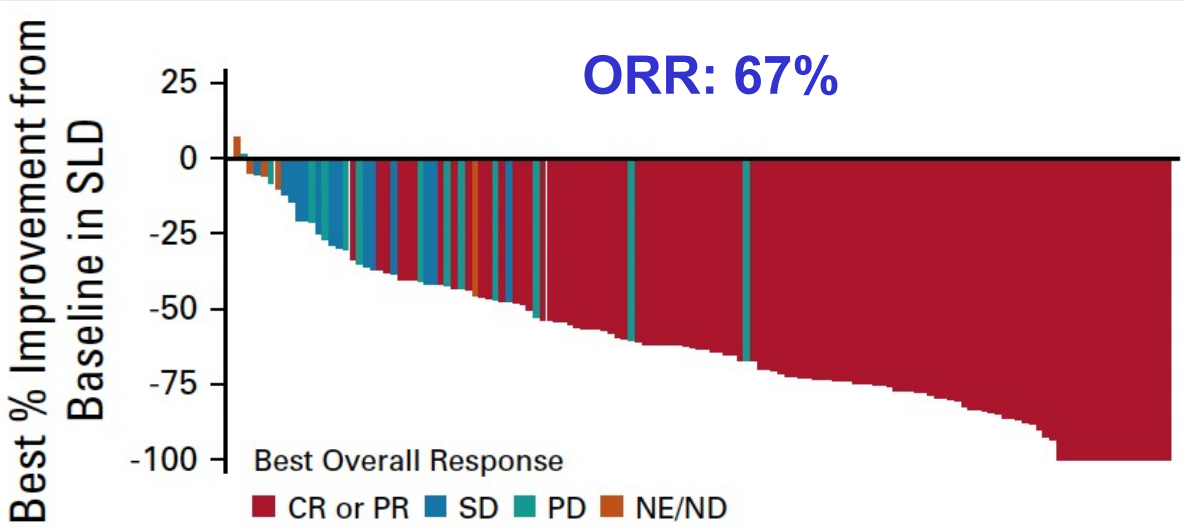
Updated Integrated Analysis of the Efficacy and Safety of Entrectinib in Locally Advanced or Metastatic *ROS1* Fusion–Positive Non–Small-Cell Lung Cancer

Rafal Dziadziuszko, MD, PhD[1]; Matthew G. Krebs, MD, PhD[2]; Filippo De Braud, MD[3,4]; Salvatore Siena, MD[3,5]; Alexander Drilon, MD[6]; Robert C. Doebele, MD, PhD[7]; Manish R. Patel, DO[8]; Byoung Chul Cho, MD, PhD[9]; Stephen V. Liu, MD[10]; Myung-Ju Ahn, MD, PhD[11]; Chao-Hua Chiu, MD[12]; Anna F. Farago, MD, PhD[13]; Chia-Chi Lin, MD[14]; Christos S. Karapetis, MBBS, MMedSc[15]; Yu-Chung Li, MD[16]; Bann-mo Day, PhD[17]; David Chen, PharmD[17]; Timothy R. Wilson, PhD[17]; and Fabrice Barlesi, MD, PhD[18,19]

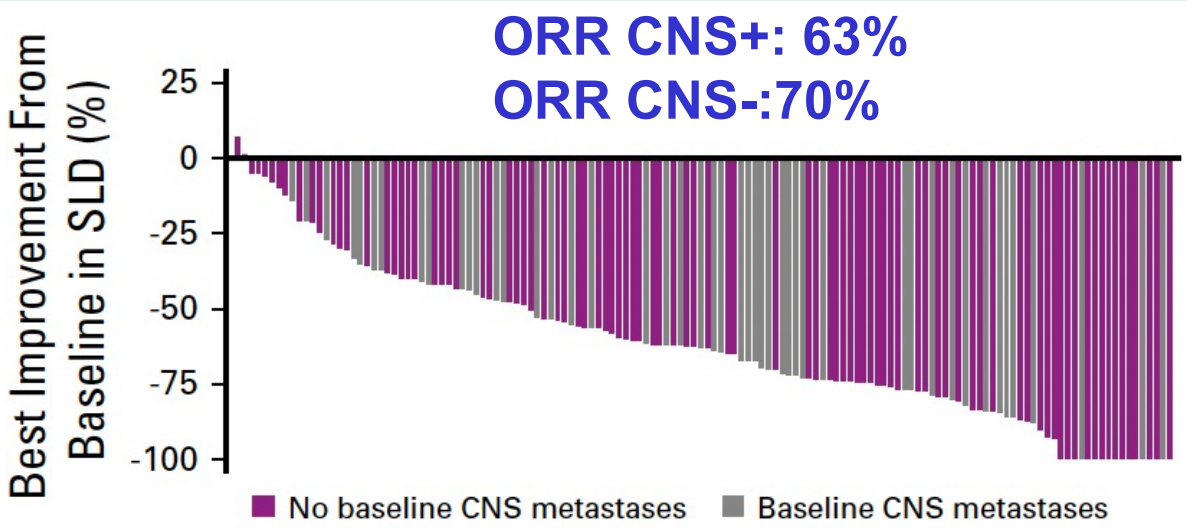
J Clin Oncol 2021;39(11):1253-63.

Integrated Analysis of ALKA-372-001, STARTRK-1, STARTRK-2, and STARTRK-NG

Efficacy Evaluable Population (N = 161)



Patients with (n = 56) and without (n = 105) CNS Metastases at Baseline



ORR = objective response rate

Dziadziuszko R et al. *J Clin Oncol* 2021;39(11):1253-63.

Entrectinib Duration of Response and Survival Analyses

Efficacy	NSCLC with ROS1 fusions		
	Efficacy evaluable (N = 161)	Baseline CNS metastases (n = 56)	No baseline CNS metastases (n = 105)
Median DoR	15.7 mo	14.9 mo	24.6 mo
12-month DoR	63%	62%	63%
Median PFS	15.7 mo	11.8 mo	19.0 mo
12-month PFS	55%	47%	60%
Median OS	NE	28.3 mo	NE
12-month OS	81%	75%	84%

Dziadziuszko R et al. *J Clin Oncol* 2021;39(11):1253-63.

Select Treatment-Related Adverse Events

Adverse events	NSCLC with ROS1 fusions safety evaluable population (N = 210)	
	Any grade	Grade ≥3
Dysgeusia	43%	<1%
Dizziness	35%	<1%
Constipation	31%	0
Fatigue	30%	<1%
Diarrhea	27%	3%
Weight increase	29%	8%
AST increase	12%	2%
ALT increase	11%	3%

Dziadziuszko R et al. *J Clin Oncol* 2021;39(11):1253-63.

2022 ASCO® ANNUAL MEETING

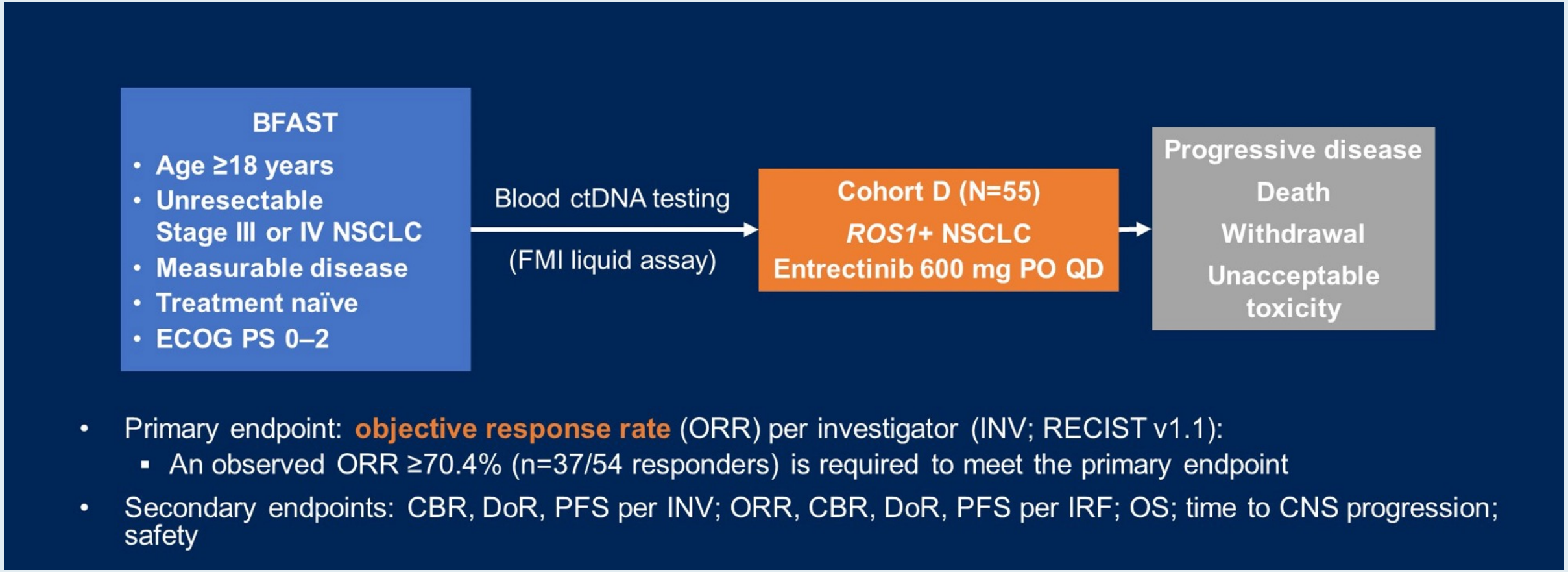
Abstract LBA9023

EFFICACY AND SAFETY OF ENTRECTINIB IN PATIENTS WITH *ROS1*-POSITIVE (*ROS1*+) ADVANCED/METASTATIC NSCLC FOR THE BLOOD FIRST ASSAY SCREENING TRIAL (BFAST)

Solange Peters,[1] Shirish M. Gadgeel,[2] Tony Mok,[3] Ernest Nadal,[4] Saadettin Kilickap,[5] Maurice Pérol,[6] Jacques Cadranel,[7] Shunichi Sugawara,[8] Chao-Hua Chiu,[9] Mor Moskovitz,[10] Chong-Jen Yu,[11] Tomohiro Tanaka,[12] Rhea Nersesian,[13] Sarah M. Shagan,[13] Margaret Maclennan,[14] Michael Mathisen,[13] Vijay Bhagawati-Prasad,[15] Venice Archer,[15] Rafal Dziadziuszko[16]

[1]Lausanne University Hospital, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland; [2]Henry Ford Cancer Institute/Henry Ford Health System, Detroit, Michigan; [3]State Laboratory of Translational Oncology, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong, Hong Kong SAR; [4]Thoracic Oncology Unit, Department of Medical Oncology, Catalan Institute of Oncology (ICO), L'Hospitalet de Llobregat, Barcelona, Spain; [5]Istinye University Faculty of Medicine, Department of Medical Oncology, Instanbul, Turkey; [6]Department of Medical Oncology, Centre Léon Bérard, Lyon, France; [7]Department of Pneumology and Thoracic Oncology, APHP, Hôpital Tenon and GRC04 Theranoscan Sorbonne Université, Paris, France; [8]Department of Pulmonary Medicine, Sendai Kousei Hospital, Sendai, Japan; [9]Department of Chest Medicine, Taipei Veterans General Hospital, Taipei, Taiwan; [10]Thoracic Cancer Service, Rambam Health Care Campus, Haifa, Israel; [11]Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan; [12]Chugai Pharmaceutical Co. Ltd, Tokyo, Japan; [13]Genentech Inc., South San Francisco, California; [14]Syneos Health, Edinburgh, UK; [15]Roche Products Ltd, Welwyn Garden City, UK; [16]Department of Oncology and Radiotherapy and Early Clinical Trials Unit, Medical University of Gdansk, Gdansk, Poland

BFAST Study Design



- Primary endpoint: **objective response rate** (ORR) per investigator (INV; RECIST v1.1):
  - An observed ORR ≥70.4% (n=37/54 responders) is required to meet the primary endpoint
- Secondary endpoints: CBR, DoR, PFS per INV; ORR, CBR, DoR, PFS per IRF; OS; time to CNS progression; safety

Peters S et al. ASCO 2022;Abstract LBA9023.

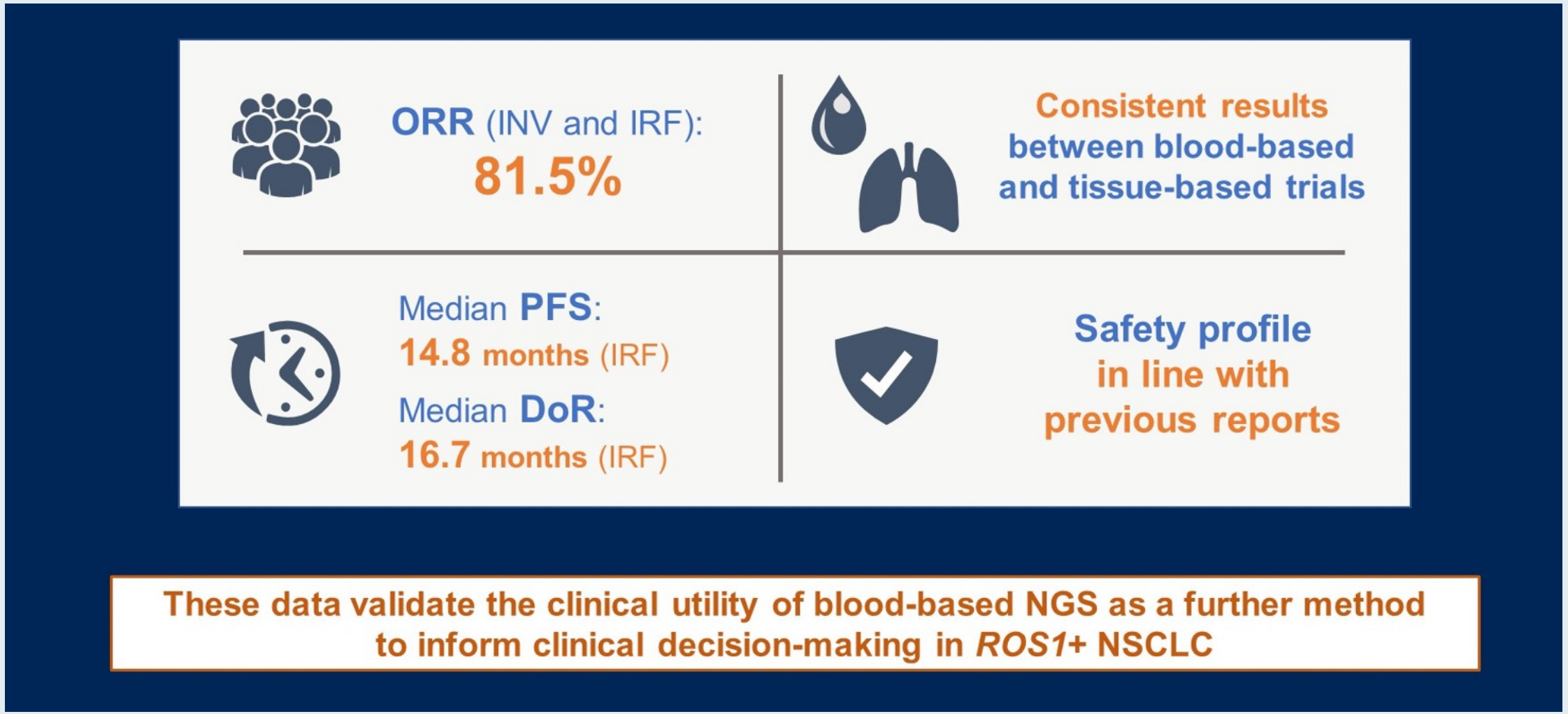
BFAST: Entrectinib Efficacy Consistent with Tissue-Based Trials

- **BFAST met its primary endpoint in the *ROS1*+ NSCLC arm**
  - Confirmed ORR: 81.5% per INV and IRF
- **Responses were durable** in this cohort:
  - Median PFS per INV: 12.9 months
  - Median DoR per INV: 13.0 months
  - Median time to CNS PD was not reached
- OS data were immature, with only 20 events reported
- **No new safety signals** were identified

BFAST *ROS1*+ NSCLC arm (N=54)		
	INV assessment	**IRF assessment**
ORR, n (%) [95% CI]	**44 (81.5)** [68.6–90.8]	**44 (81.5)** [68.6–90.8]
Complete response (CR)	2 (3.7)	3 (5.6)
Partial response (PR)	42 (77.8)	41 (75.9)
CBR*, n (%) [95% CI]	47 (87.0) [75.1–94.6]	44 (81.5) [68.6–90.8]
Median PFS, months (95% CI)	**12.9** (8.7–18.5)	**14.8** (7.2–24.0)
12-month event-free rate, %	50.7	52.4
Median DoR, months (95% CI)	**13.0** (6.3–18.4)	**16.7** (5.6–24.0)
12-month event-free rate, %	53.2	57.3
Median time to CNS PD, months (95% CI)	**NE** (NE)	**NE** (NE)
12-month event-free rate, %	83.5	86.4
OS	*Immature*	
Patients with event, n (%)	20 (36)	

Peters S et al. ASCO 2022;Abstract LBA9023.

BFAST Summary



Peters S et al. ASCO 2022;Abstract LBA9023.

Repotrectinib Granted FDA Breakthrough Therapy Designation for Metastatic NSCLC with ROS1 Fusions

Press Release – December 8, 2020

"…repotrectinib has been granted breakthrough therapy designation by the Food and Drug Administration (FDA) for the treatment of patients with ROS1-positive metastatic non-small cell lung cancer (NSCLC) who have not been treated with a ROS1 tyrosine kinase inhibitor (TKI-naïve).

The breakthrough therapy designation for repotrectinib was supported by the initial data from TKI-naïve ROS1-positive NSCLC patients enrolled in the Phase 1 and Phase 2 portions of the TRIDENT-1 study, which is currently evaluating patients in multiple potentially registrational cohorts."

https://www.biospace.com/article/releases/turning-point-therapeutics-granted-fda-breakthrough-therapy-designation-for-repotrectinib-treatment-in-patients-with-ros1-positive-metastatic-non-small-cell-lung-cancer-/

RTP RESEARCH TO PRACTICE

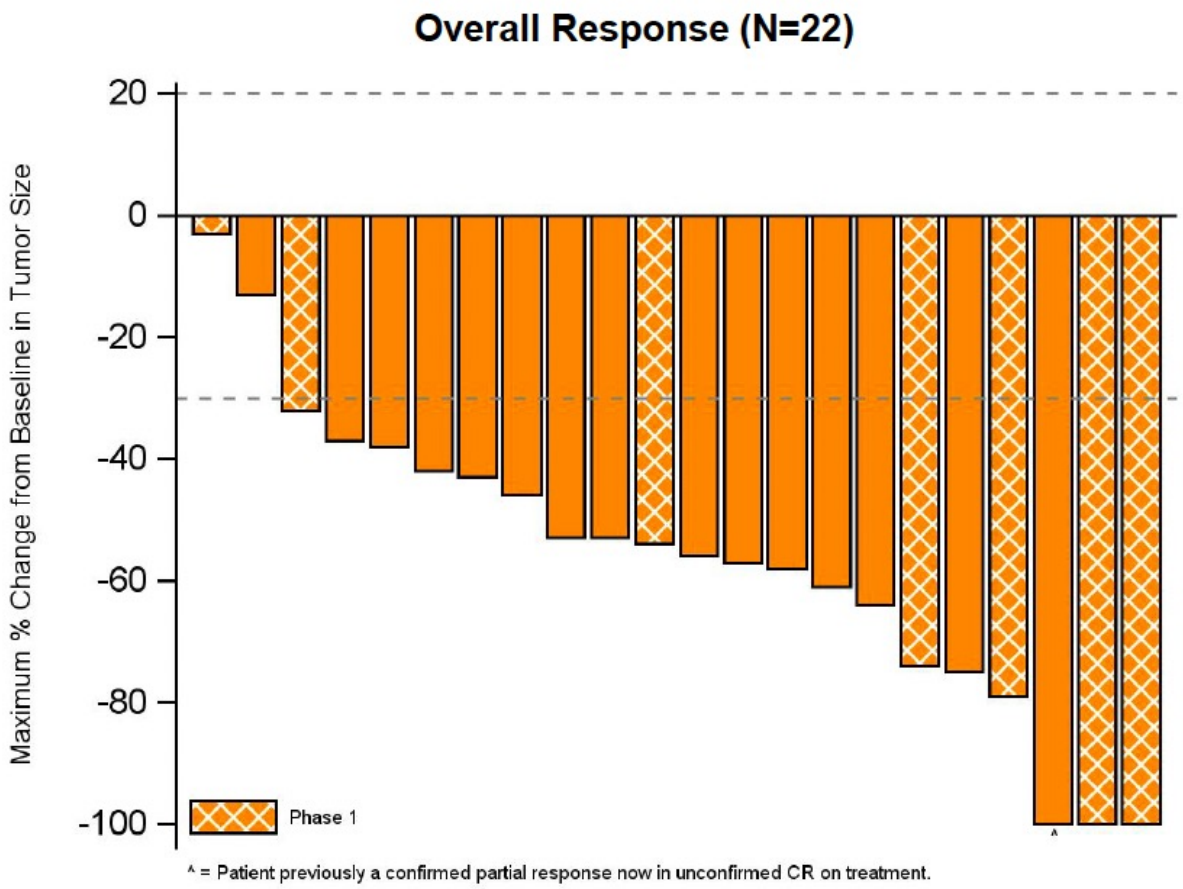
Abstract 3255

Phase 1/2 TRIDENT-1 Study of Repotrectinib in Patients with *ROS1*+ or *NTRK*+ Advanced Solid Tumors

Byoung Chul Cho,[1] Robert C. Doebele,[2] Jessica J. Lin,[3] Misako Nagasaka,[4] Christina Baik,[5] Anthonie J. van der Wekken,[6] Vamsidhar Velcheti,[7] Ki Hyeong Lee,[8] Stephen V. Liu,[9] Benjamin Solomon,[10] Steven Kao,[11] Matthew G. Krebs,[12] Viola Zhu,[13] Shanna Stopatschinskaja,[14] D. Ross Camidge,[15] Alexander Drilon[16]

[1]Yonsei Cancer Center, Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea; [2]University of Colorado Anschutz Medical Campus, Aurora, CO, USA; [3]Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; [4]Karmanos Cancer Institute, Wayne State University, Detroit, MI, USA; [5]Seattle Cancer Care Alliance, Fred Hutchinson Cancer Research Center, University of Washington School of Medicine, Seattle, WA, USA; [6]University of Groningen and University Medical Centre Groningen, Groningen, Netherlands; [7]Perlmutter Cancer Center, NYU Langone Health, New York, NY, USA; [8]Chungbuk National University Hospital, Cheongju, Republic of Korea; [9]Georgetown Lombardi Comprehensive Cancer Center, Georgetown University, Washington D.C., USA; [10]Peter MacCallum Cancer Center, Melbourne, Australia; [11]The Chris O'Brien Lifehouse, Camperdown, Australia; [12]Division of Cancer Sciences, The University of Manchester and the Christie NHS Foundation Trust, Manchester, UK; [13]Chao Family Comprehensive Cancer Center, University of California Irvine School of Medicine, Orange, CA, USA; [14]Turning Point Therapeutics Inc., San Diego, CA, USA; [15]Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, New York, NY, USA

TRIDENT-1: Clinical Activity in TKI-Naïve Advanced NSCLC with ROS1 Fusions



	Phase 2 N=15	Phase 1+2 N=22
Confirmed ORR, % (95% CI)	93% (68–100)	91% (71–99)

N=22 patients with baseline and at least two post baseline scans

- *N=15 Phase 2 patients*
- *N=7 Phase 1 patients treated at or above the Phase 2 recommended dose*

As of 31 December 2020, the 16th patient in Phase 2 has an unconfirmed PR and is on treatment awaiting a second post-baseline confirmatory scan.

Cho BC et al. WCLC 2020;Abstract 3255.

AACR-NCI-EORTC Virtual International Conference on
MOLECULAR TARGETS AND CANCER THERAPEUTICS
October 7-10, 2021

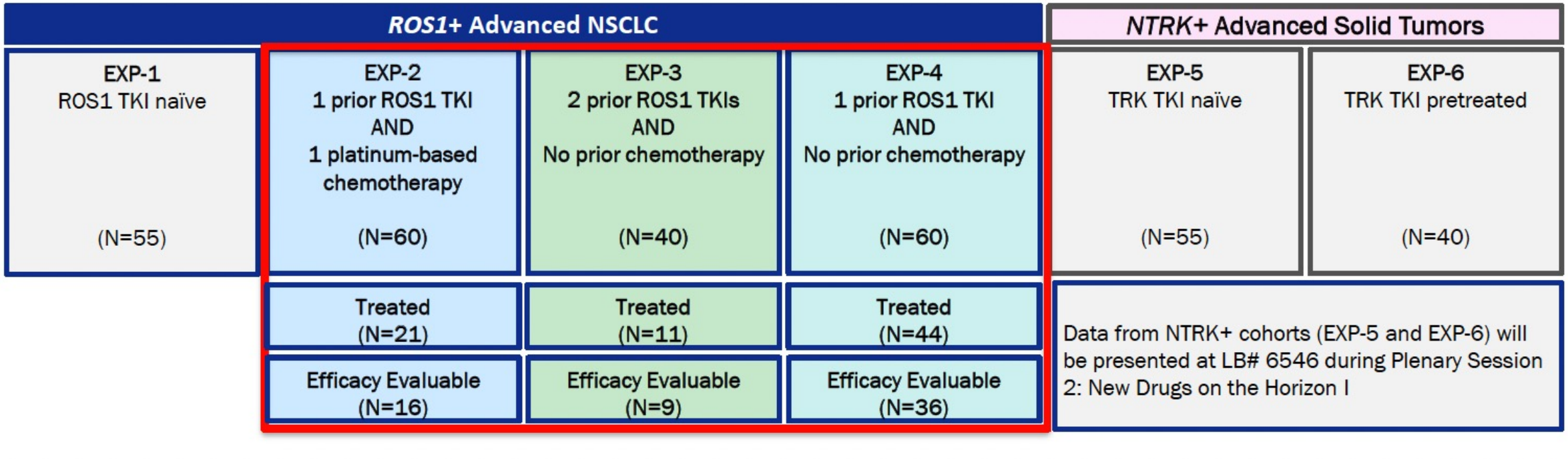
Poster #: P224

Update from the Phase 2 registrational trial of repotrectinib in TKI-pretreated patients with *ROS1+* advanced non-small cell lung cancer and with *NTRK+* advanced solid tumors (TRIDENT-1)

Jessica J. Lin,[1] Byoung Chul Cho,[2] Christoph Springfeld,[3] D. Ross Camidge,[4] Benjamin Solomon,[5] Christina Baik,[6] Vamsidhar Velcheti,[7] Young-Chul Kim,[8] Victor Moreno,[9] Anthonie J. van der Wekken,[10] Enriqueta Felip,[11] Dipesh Uprety,[12] Denise Trone,[13] Shanna Stopatschinskaja,[13] Alexander Drilon[14]

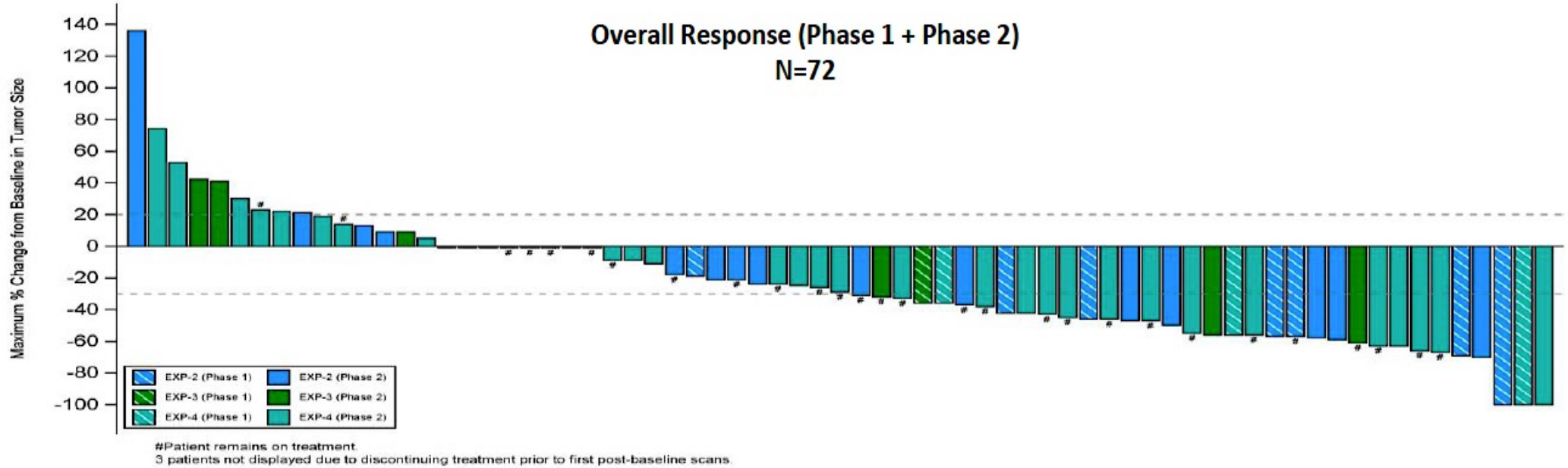
[1]Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; [2]Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea; [3]Heidelberg University Hospital, National Center for Tumor Diseases, Department of Medical Oncology, Heidelberg, Germany; [4]University of Colorado Denver, Anschutz Medical Campus, Aurora, CO, USA; [5]Peter MacCallum Cancer Center, Melbourne, Australia; [6]University of Washington School of Medicine, Seattle Cancer Care Alliance, Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [7]NYU Perlmutter Cancer Center, New York, NY, USA; [8]Chonnam National University Medical School, and CNU Hwasun Hospital, Hwasun-gun, Republic of Korea; [9]Fundación Jiménez Díaz - START Madrid, Madrid, Spain; [10]University of Groningen, University Medical Centre Groningen, Groningen, Netherlands; [11]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [12]Karmanos Cancer Institute, Detroit, MI, USA; [13]Turning Point Therapeutics Inc, San Diego, CA, USA; [14]Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, New York, NY, USA.

TRIDENT-1: A Phase II Study Design



Lin JJ et al. AACR 2021;Abstract 224.

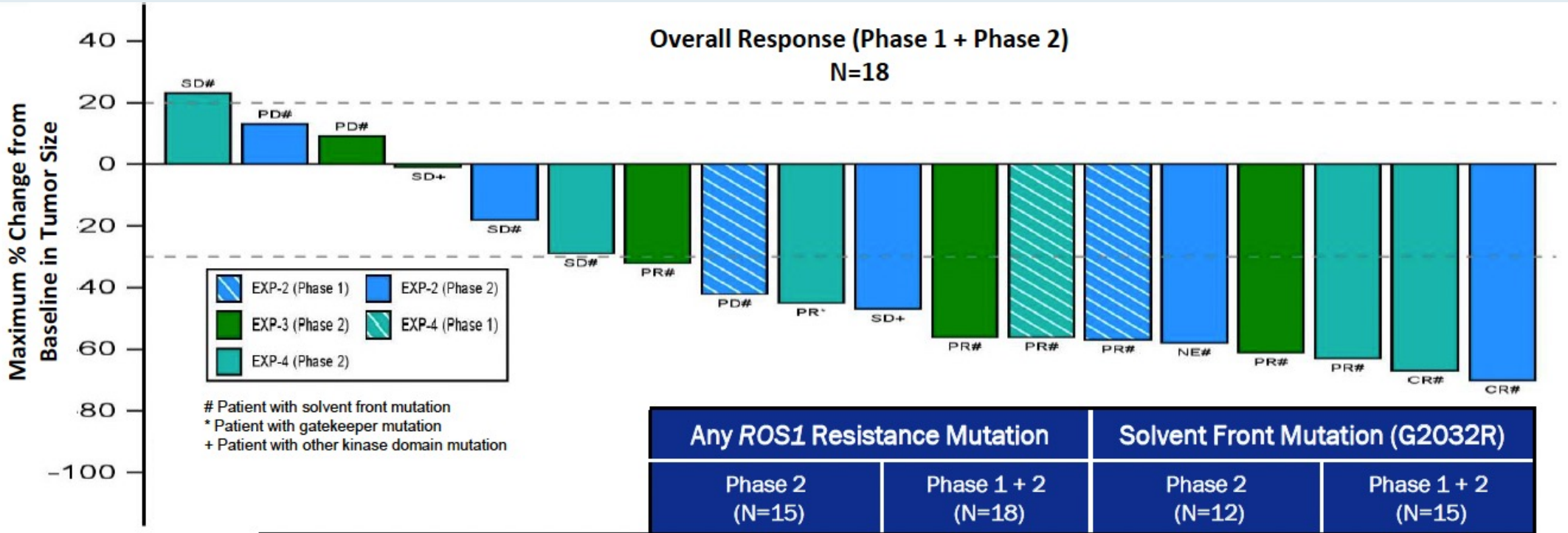
TRIDENT-1: Preliminary Efficacy in Patients with TKI-Pretreated Advanced NSCLC with ROS1 Fusions



	EXP-2		EXP-3		EXP-4	
	Phase 2 (N=16)	Phase 1 + 2 (N=23)	Phase 2 (N=9)	Phase 1 + 2 (N=10)	Phase 2 (N=36)	Phase 1 + 2 (N=39)
Confirmed ORR (cORR) (95% CI)	**31%** (11 – 59)	**39%** (20 – 61)	**33%** (7 – 70)	**30%** (7 – 65)	**31%*** (16 – 48)	**33%*** (19 – 50)
Duration of Response (range in months)	1.8+ – 9.2 n=5	1.8+ – 11.1 n=9	1.9+ – 12.9+ n=3	1.9+ – 12.9+ n=3	1.7+ – 15.0+ n=11	0.8+ – 15.0+ n=13

Lin JJ et al. AACR 2021;Abstract 224.

TRIDENT-1: Preliminary Efficacy in Patients with TKI-Pretreated Advanced NSCLC with ROS1 Fusions and Baseline ROS1 Resistance Mutations



	Any *ROS1* Resistance Mutation		Solvent Front Mutation (G2032R)	
	Phase 2 (N=15)	Phase 1 + 2 (N=18)	Phase 2 (N=12)	Phase 1 + 2 (N=15)
Confirmed ORR (cORR) (95% CI) CR PR	47% (21 – 73) 2 (13%) 5 (33%)	50% (26 – 74) 2 (11%) 7 (39%)	50% (21 – 79) 2 (17%) 4 (33%)	53% (27 – 79) 2 (13%) 6 (40%)
Duration of Response (range in months)	*1.9+ - 15.0+* n=7	*1.9+ - 15.0+* n=9	*1.9+ - 15.0+* n=6	*1.9+ - 15.0+* n=8

Lin JJ et al. AACR 2021;Abstract 224.

TRIDENT-1: Treatment-Emergent Adverse Events (N = 301)

Adverse event	Any grade	Grade 3/4
Dizziness	60%	2%
Dysgeusia	44%	<1%
Constipation	34%	<1%
Paraesthesia	29%	1%
Dyspnea	28%	6%
Anemia	27%	8%
Fatigue	24%	2%
Nausea	21%	1%
	Rate	
Drug discontinuation due to TEAEs	11%	
Drug dose reduction due to TEAEs	17%	

Lin JJ et al. AACR 2021;Abstract 224.

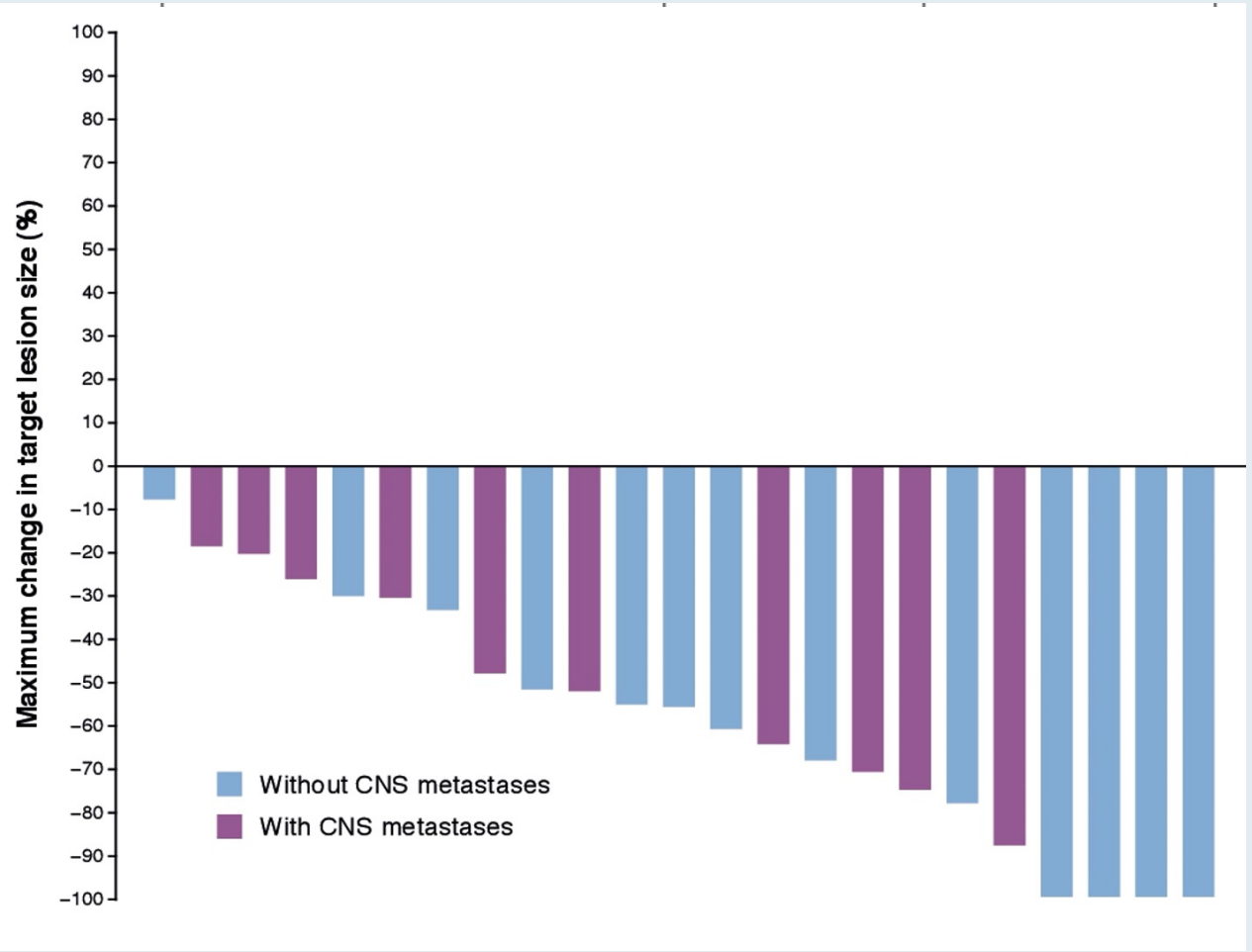
Updated Efficacy and Safety of Larotrectinib in Patients with Tropomyosin Receptor Kinase (TRK) Fusion Lung Cancer

Peters S et al.

ASCO 2022;Abstract LBA9024.

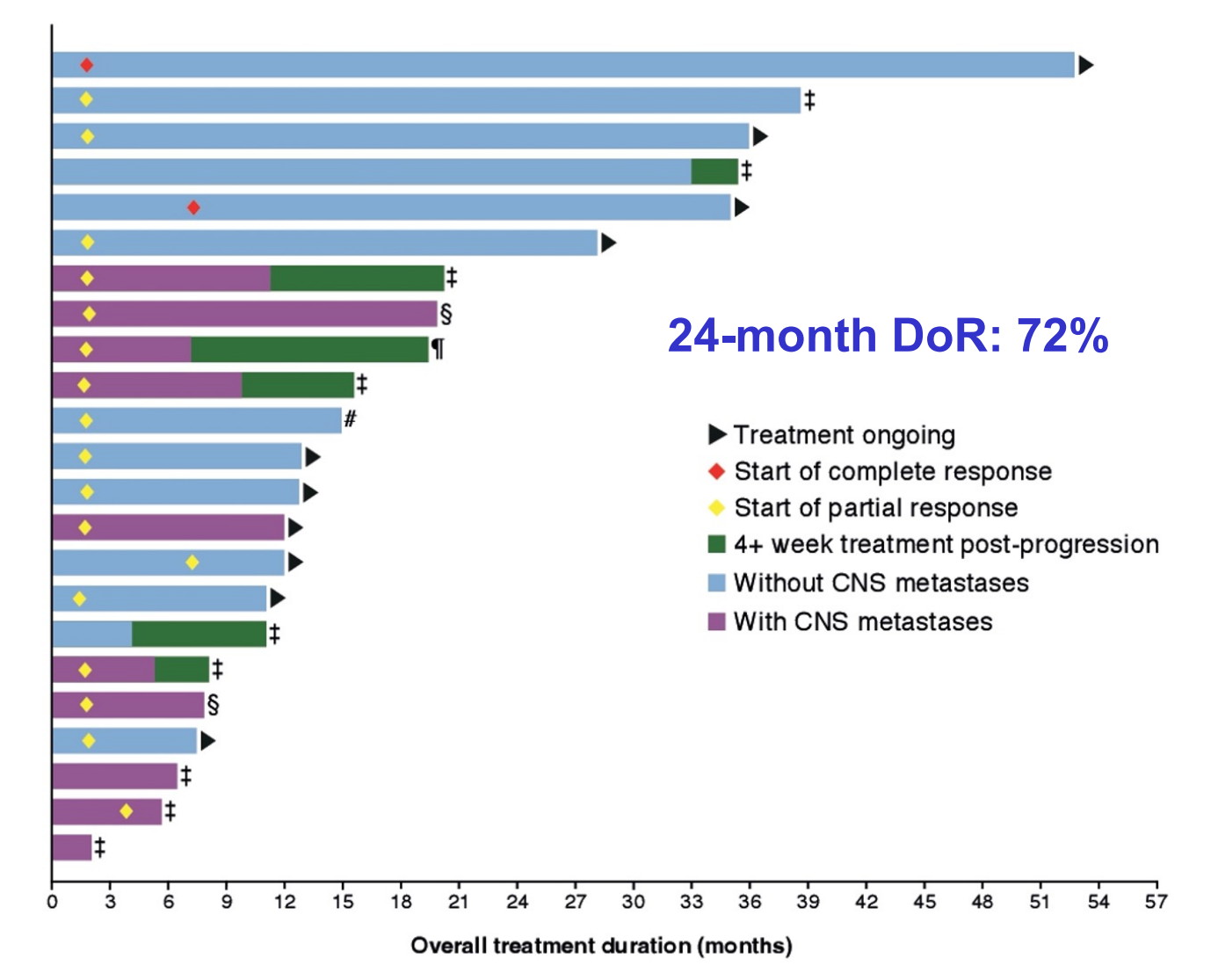
Response to Larotrectinib

	All patients (N=26)	Patients with CNS metastases (n=12)
Evaluable patients, n	23	10
ORR, % (95% CI)	83 (61–95)	80 (44–97)
Best overall response, n (%)		
Complete response	2 (9)	0
Partial response	17 (74)	8 (80)
Stable disease	4 (17)	2 (20)
Progressive disease	0	0



Peters S et al. ASCO 2022;Abstract LBA9024.

Larotrectinib Duration of Response

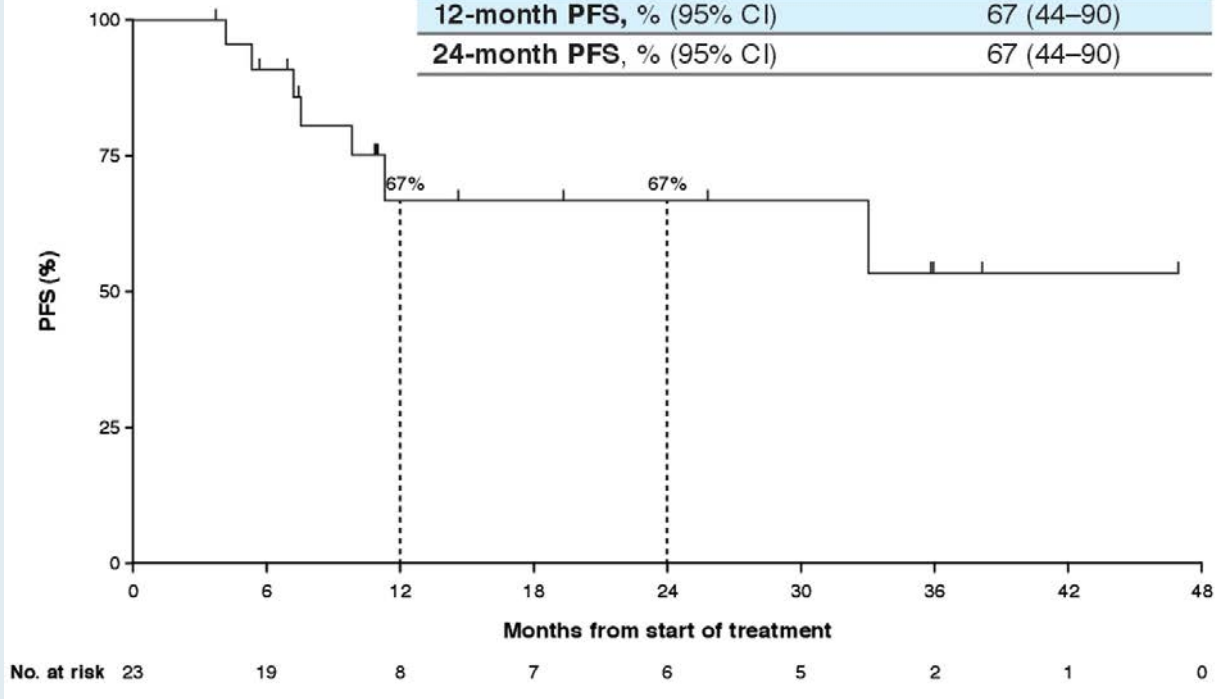


Peters S et al. ASCO 2022;Abstract LBA9024.

Survival Analyses with Larotrectinib

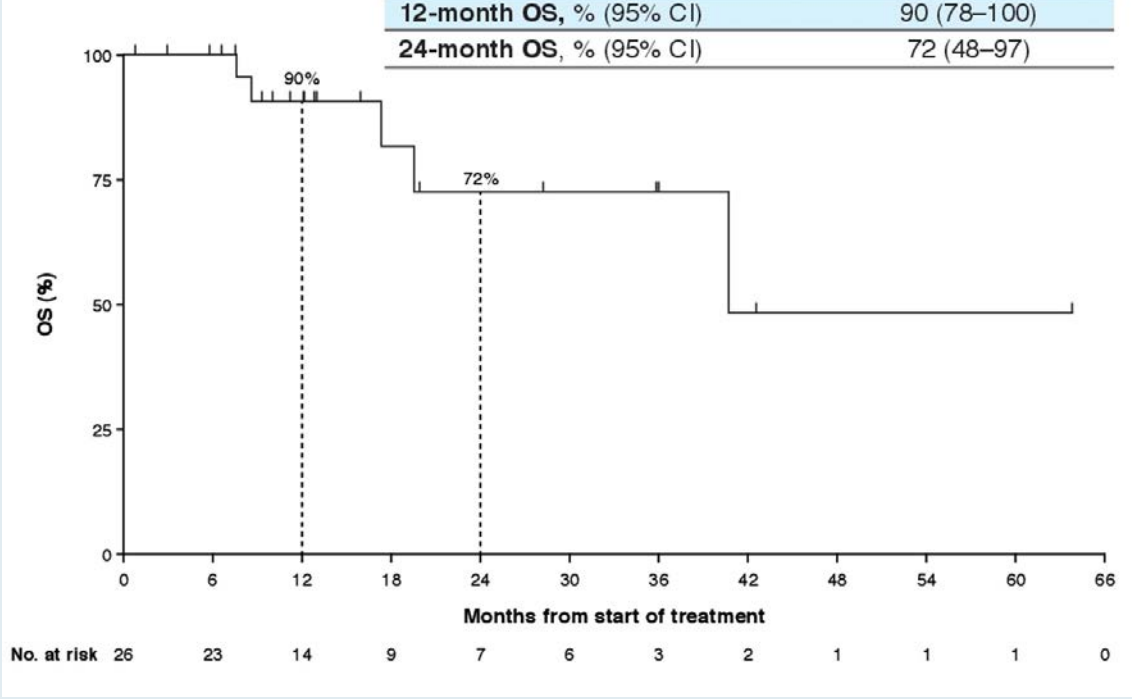
PFS

Median PFS, months (95% CI)	Not reached (9.9–NE)
Median follow-up, months	14.6
12-month PFS, % (95% CI)	67 (44–90)
24-month PFS, % (95% CI)	67 (44–90)



OS

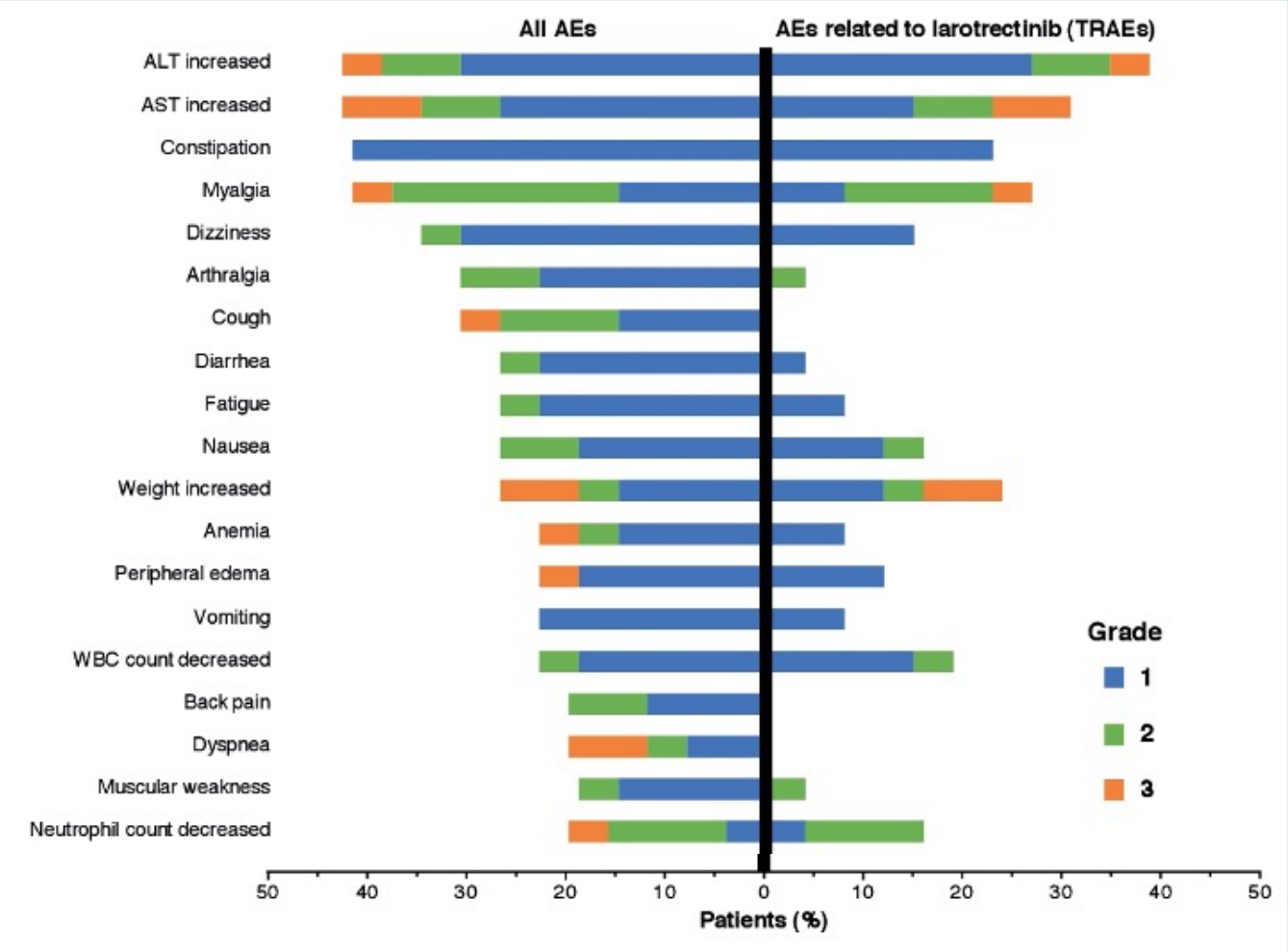
Median OS, months (95% CI)	40.7 (19.4–NE)
Median follow-up, months	12.9
12-month OS, % (95% CI)	90 (78–100)
24-month OS, % (95% CI)	72 (48–97)



Peters S et al. ASCO 2022;Abstract LBA9024.

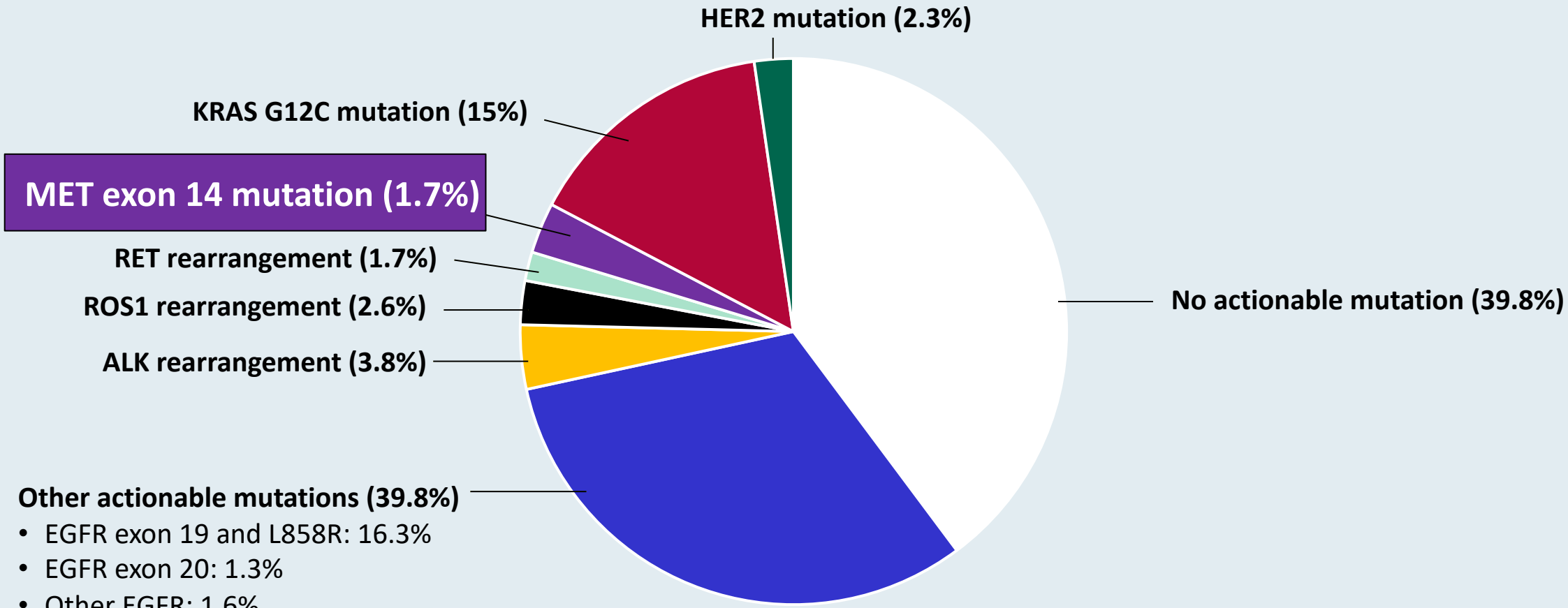
RTP RESEARCH TO PRACTICE

Safety Profile with Larotrectinib



Peters S et al. ASCO 2022;Abstract LBA9024.

Frequency of Targetable Oncogenic Driver Molecular Alterations in Adenocarcinoma of the Lung



- EGFR exon 19 and L858R: 16.3%
- EGFR exon 20: 1.3%
- Other EGFR: 1.6%
- Other KRAS: 10.3%
- BRAF V600E: 2.1%
- NTRK rearrangement: 0.23%

Derived from Tan AC et al. *J Clin Oncol* 2022;40(6):611-25.

RTP RESEARCH TO PRACTICE

2022 ASCO® ANNUAL MEETING

Abstract 9008

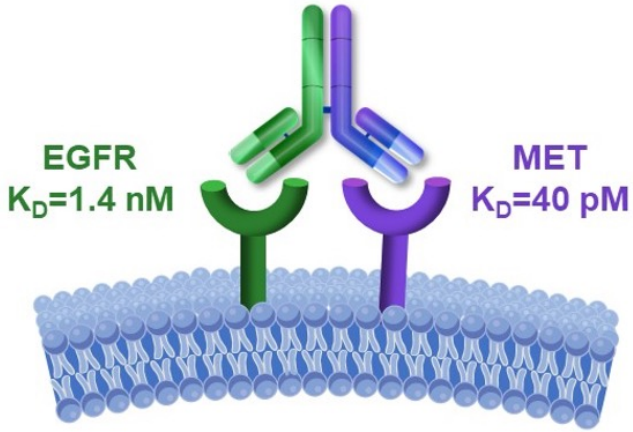
Amivantamab in NSCLC patients with MET exon 14 skipping mutation: Updated results from the CHRYSALIS study

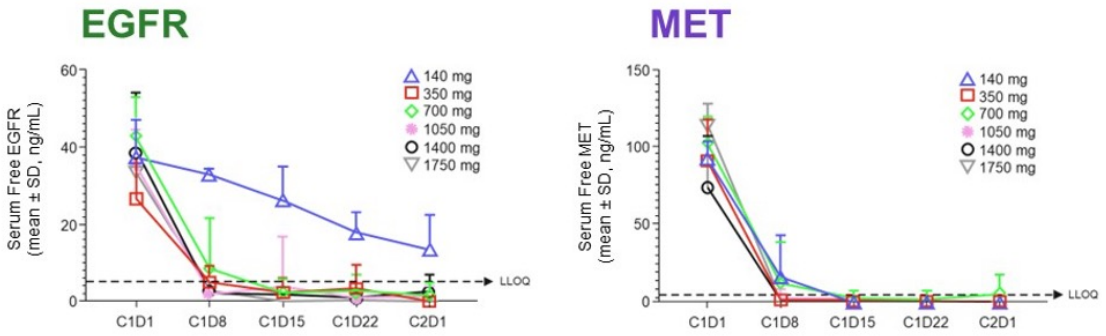
Matthew G. Krebs,[1] Alexander I. Spira,[2] Byoung Chul Cho,[3] Benjamin Besse,[4] Jonathan W. Goldman,[5] Pasi A. Jänne,[6] Zhiyong Ma,[7] Aaron S. Mansfield,[8] Anna Minchom,[9] Sai-Hong Ignatius Ou,[10] Ravi Salgia,[11] Zhijie Wang,[12] Casilda Llacer Perez,[13] Grace Gao,[14] Joshua C. Curtin,[14] Amy Roshak,[14] Robert W. Schnepp,[14] Meena Thayu,[14] Roland E. Knoblauch,[14] Chee Khoon Lee[15]

[1]Division of Cancer Sciences, The University of Manchester and The Christie NHS Foundation Trust, Manchester, UK; [2]Virginia Cancer Specialists Research Institute, US Oncology Research, Fairfax VA; [3]Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea; [4]Institut Gustave Roussy, Villejuif, France; [5]David Geffen School of Medicine at UCLA, Los Angeles, CA; [6]Dana Farber Cancer Institute, Boston, MA; [7]Henan Cancer Hospital, Zhengzhou, China; [8]Mayo Clinic, Rochester, MN; [9]Drug Development Unit, Royal Marsden/Institute of Cancer Research, Sutton, UK; [10]University of California Irvine, Orange, CA; [11]City of Hope, Duarte, CA; [12]Cancer Hospital Chinese Academy of Medical Sciences, Beijing, China; [13]Medical Oncology Intercenter Unit, Regional and Virgen de la Victoria University Hospitals, IBIMA, Málaga, Spain; [14]Janssen R&D, Spring House, PA; [15]St George Hospital, Kogarah, Australia

Amivantamab: EGFR-MET Bispecific Antibody

- Demonstrated monotherapy activity in EGFR ex20ins NSCLC following progression on platinum-based chemotherapy (ORR, 40%; DOR, 11.1 months)[1]
- Demonstrated activity in TKI-resistant EGFRm NSCLC with MET amplification[2,3]
- Has higher affinity for MET (40 pM) than EGFR (1.4 nM)
- Depletion of free soluble target proteins, suggesting total body target engagement, occurs at ≥140 mg for sMET and ≥350 mg for sEGFR
- Evaluation in primary MET-driven tumors is ongoing





C, cycle; D, day; DOR, duration of response; EGFR, epidermal growth factor receptor; EGFRm, EGFR-mutated; ex20ins, exon 20 insertion mutations; K_D, dissociation constant; LLOQ, lower limit of quantification; NSCLC, non-small cell lung cancer; ORR, overall response rate; SD, standard deviation; sEGFR, soluble EGFR; sMET, soluble MET; TKI, tyrosine kinase inhibitor.

1. Park K, et al. *J Clin Oncol*. 2021;39(30):3391-3402. 2. Haura EB, et al. Presented at: ASCO; May 31-June 4, 2019. 9009 (oral). 3. Bauml J, et al. Presented at: ASCO; June 4-8, 2021. 9006 (oral).

Krebs MG et al. ASCO 2022;Abstract 9008.

CHRYSALIS Phase I Study Design

Part 1: Dose Escalation

140–1750 mg

Objective: Establish RP2D

RP2D

Amivantamab
1050 mg (<80 kg)
1400 mg (≥80 kg)

Intravenous dosing
C1 QW, C2+ Q2W

Part 2: Dose Expansion

MET-2 Cohort: *METex14* n=55[a]
(up to 100 planned)

Objective: Safety and efficacy at the RP2D

Eligibility

- Metastatic or unresectable/advanced NSCLC
- Failed or ineligible for standard of care therapy

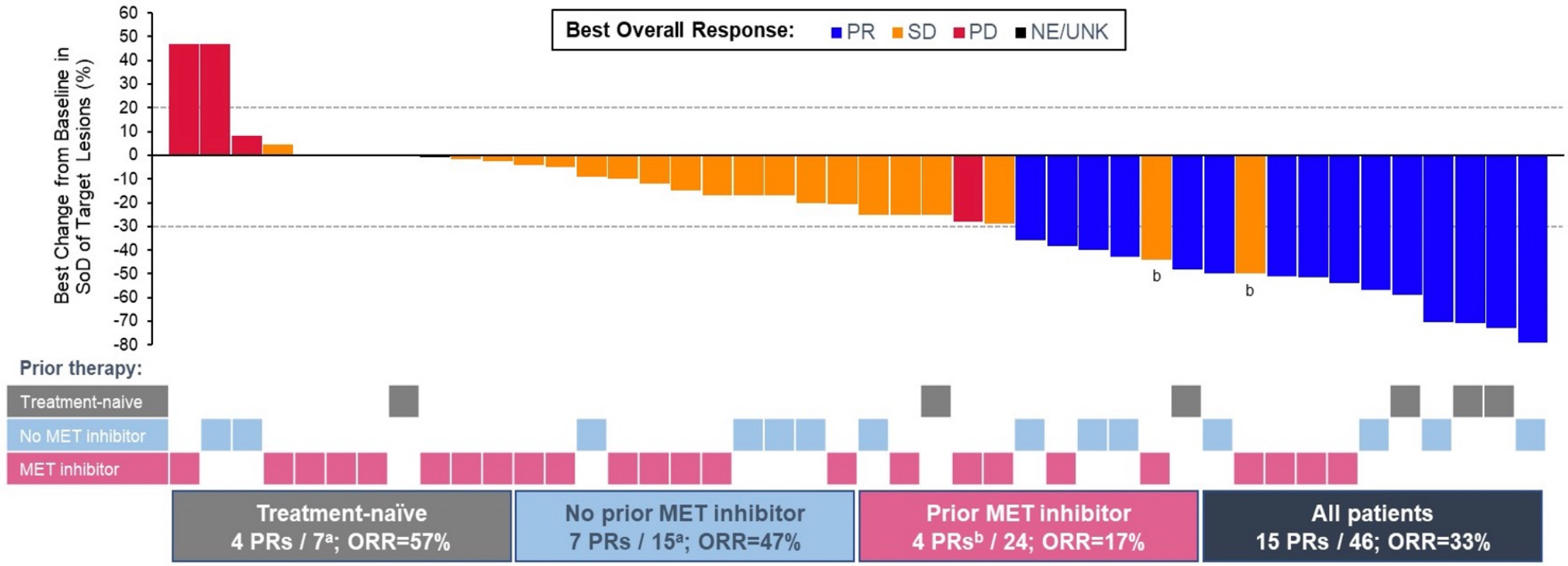
Eligibility for METex14 Cohort

- Measurable disease
- Primary METex14 mutation by NGS of tumor or ctDNA

Krebs MG et al. ASCO 2022;Abstract 9008.

CHRYSALIS: Antitumor Activity of Amivantamab

- A total of 46 patients were efficacy evaluable



Krebs MG et al. ASCO 2022;Abstract 9008.

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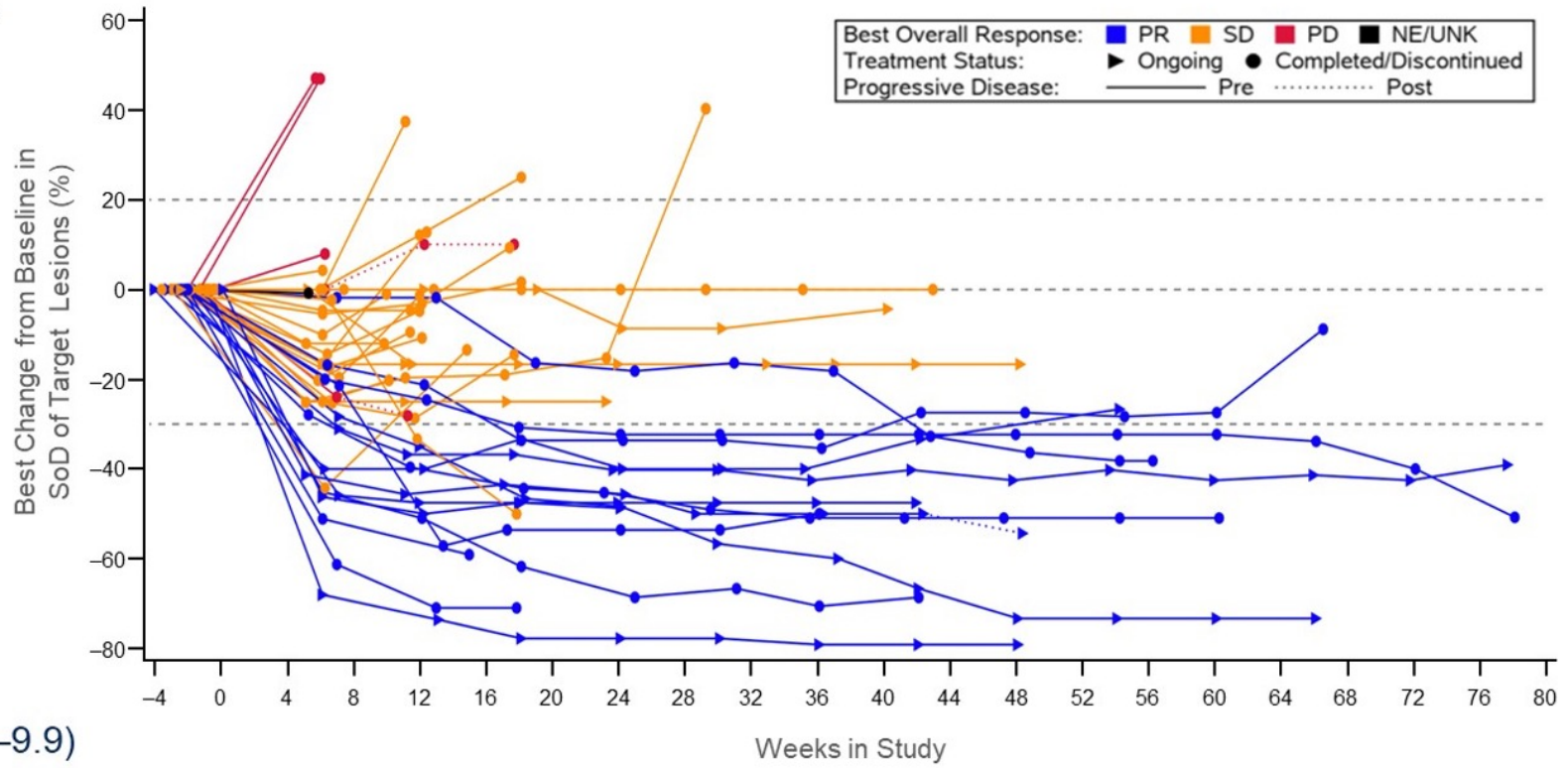
CHRYSALIS: Durability of Response to Amivantamab

- Median duration of response is not estimable
  - 11/15 patients who responded are ongoing
  - 10 patients (67% of responders) with response duration ≥6 months
- Clinical benefit rate=59%[a]
  - Treatment-naïve: 71%
  - No prior MET: 53%
  - Prior MET: 58%
- Median PFS=6.7 mo (95% CI 2.9–15.3)
  - Treatment-naïve: NE (95% CI 2.6–NE)
  - No prior MET: 8.3 mo (95% CI 1.5–15.3)
  - Prior MET: 4.2 mo (95% CI 2.9–NE)
- Median time to response=1.6 mo (range, 1.2–9.9)



Krebs MG et al. ASCO 2022;Abstract 9008.

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CHRYSALIS: Safety Profile

TEAE (≥15%) by Preferred Term, n (%)	RP2D (n=425) Median follow-up 11.8 months		METex14 Subset (n=55) Median follow up 5.1 months	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Infusion related reaction	283 (67)	11 (3)	38 (69)	3 (5)
Rash	155 (36)	8 (2)	17 (31)	1 (2)
Dermatitis acneiform	155 (36)	4 (1)	22 (40)	0
Paronychia	193 (45)	7 (2)	21 (38)	0
Fatigue	93 (22)	8 (2)	17 (31)	2 (4)
Hypoalbuminemia	135 (32)	10 (2)	15 (27)	1 (2)
Stomatitis	91 (21)	2 (0.5)	15 (27)	0
Decreased appetite	76 (18)	2 (0.5)	12 (22)	0
Dyspnea	96 (23)	21 (5)	12 (22)	4 (7)
Peripheral edema	104 (24)	4 (1)	11 (20)	0
Pruritus	79 (19)	0	12 (22)	0
Nausea	104 (24)	2 (0.5)	11 (20)	0
Constipation	105 (25)	0	10 (18)	0
Hypomagnesemia	41 (10)	0	9 (16)	0
Aspartate aminotransferase increased	64 (15)	5 (1)	9 (16)	1 (2)
Alanine aminotransferase increased	72 (17)	10 (2)	8 (15)	1 (2)
Cough	78 (18)	0	3 (5)	0

- Treatment modifications due to toxicity (n=425): interruptions in 21%, reductions in 12%, and discontinuations in 5% of patients
  - Rates of pneumonitis/ILD was 4%
  - Cumulative grouped rash-related AEs[a] occurred in 322 (76%) patients, with 16 grade ≥3 (4%)
- Safety profile for METex14 subset is consistent with the larger CHRYSALIS safety population, with majority of events grade 1-2
- No new safety signals found

Krebs MG et al. ASCO 2022;Abstract 9008.

Tepotinib and Capmatinib Receive FDA Approval for the Treatment of Advanced NSCLC with MET Exon 14 Skipping Mutations

Tepotinib Press Release – February 3, 2021

The FDA granted accelerated approval to tepotinib for adult patients with metastatic NSCLC harboring mesenchymal-epithelial transition (MET) exon 14 skipping alterations. Efficacy was demonstrated in the VISION trial (NCT02864992), a multicenter, non-randomized, open-label, multicohort study enrolling 152 patients with advanced or metastatic NSCLC with MET exon 14 skipping alterations. Patients received tepotinib 450 mg orally once daily until disease progression or unacceptable toxicity.

Capmatinib Press Release – May 6, 2020

The FDA granted accelerated approval to for adult patients with metastatic NSCLC whose tumors have a mutation that leads to mesenchymal-epithelial transition (MET) exon 14 skipping. Efficacy was demonstrated in the GEOMETRY mono-1 trial (NCT02414139), a multicenter, non-randomized, open-label, multicohort study enrolling 97 patients with metastatic NSCLC with confirmed MET exon 14 skipping. Patients received capmatinib 400 mg orally twice daily until disease progression or unacceptable toxicity.

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-tepotinib-metastatic-non-small-cell-lung-cancer. https://wayback.archive-it.org/7993/20201222063225/https://www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-capmatinib-metastatic-non-small-cell-lung-cancer

RTP RESEARCH TO PRACTICE

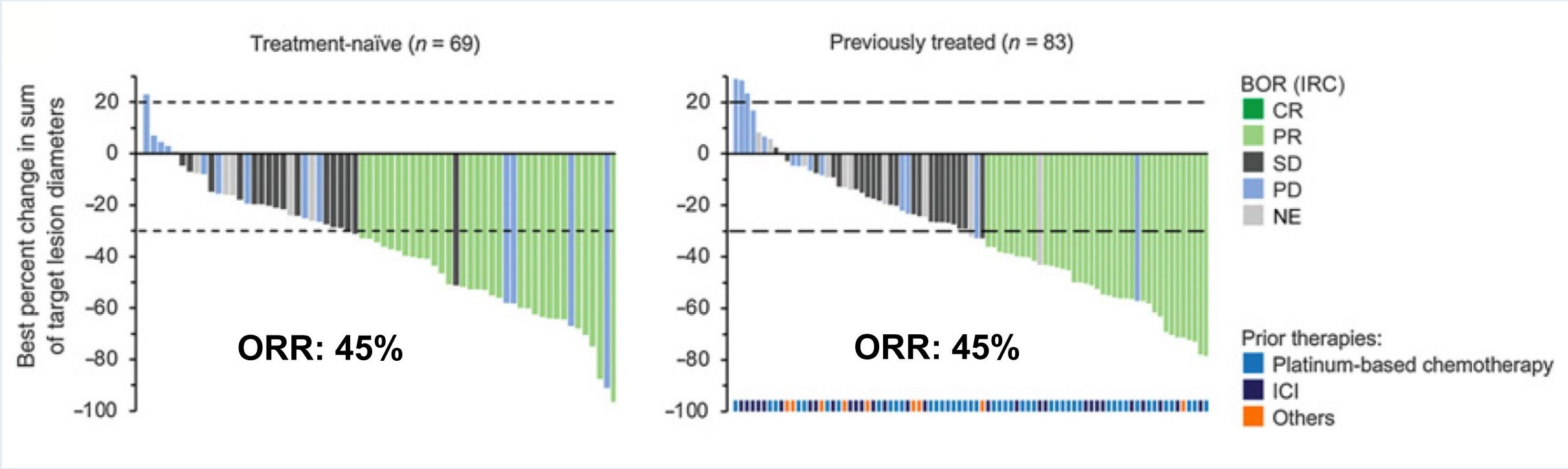
CLINICAL CANCER RESEARCH | CLINICAL TRIALS: TARGETED THERAPY

Tepotinib Efficacy and Safety in Patients with *MET* Exon 14 Skipping NSCLC: Outcomes in Patient Subgroups from the VISION Study with Relevance for Clinical Practice

Xiuning Le[1], Hiroshi Sakai[2], Enriqueta Felip[3], Remi Veillon[4], Marina Chiara Garassino[5,6], Jo Raskin[7], Alexis B. Cortot[8], Santiago Viteri[9], Julien Mazieres[10], Egbert F. Smit[11], Michael Thomas[12], Wade T. Iams[13], Byoung Chul Cho[14], Hye Ryun Kim[14], James Chih-Hsin Yang[15], Yuh-Min Chen[16], Jyoti D. Patel[17], Christine M. Bestvina[18], Keunchil Park[19], Frank Griesinger[20], Melissa Johnson[21], Maya Gottfried[22], Christian Britschgi[23], John Heymach[1], Elif Sikoglu[24], Karin Berghoff[25], Karl-Maria Schumacher[26], Rolf Bruns[27], Gordon Otto[26], and Paul K. Paik[28,29]

***Clin Cancer Res* 2022;28(6):1117-26.**

VISION: Tepotinib in Advanced NSCLC with MET Exon 14 Skipping Mutations



Le X et al. *Clin Cancer Res* 2022;28(6):1117-26.

VISION: Treatment-Related Adverse Events with Tepotinib

Adverse events	Cohorts A + C (N = 255)	
	Any grade	Grade 3/4
Peripheral edema	54%	8%
Nausea	20%	<1%
Diarrhea	20%	<1%
Blood creatinine increase	18%	<1%
Hypoalbuminemia	15%	2%
ALT increase	9%	2%
Decreased appetite	8%	<1%
Amylase increase	8%	2%

6 confirmed ILD-like events were reported

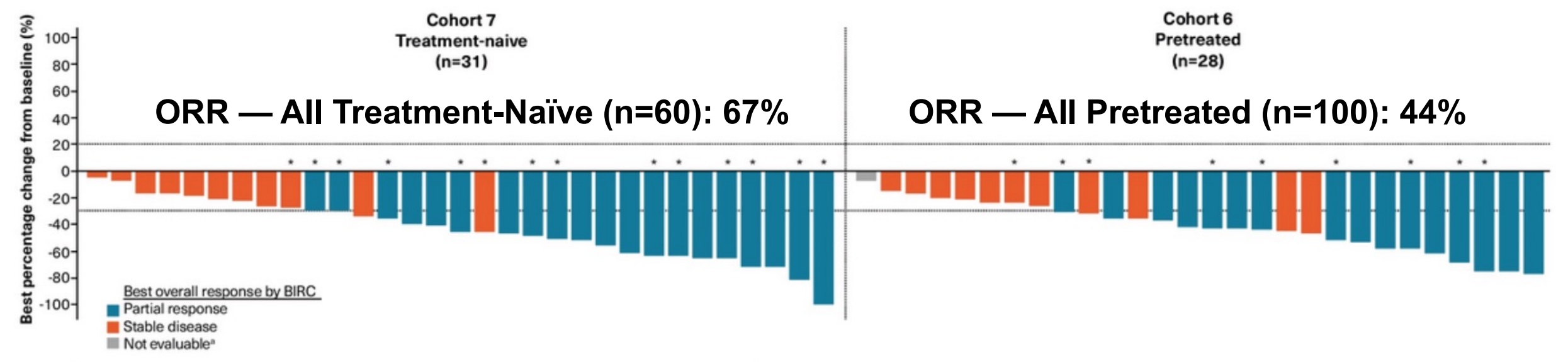
Le X et al. *Clin Cancer Res* 2022;28(6):1117-26.

Capmatinib in *MET* Exon 14-Mutated, Advanced NSCLC: Updated Results from the GEOMETRY mono-1 Study

Wolf J et al.

ASCO 2021;Abstract 9020.

GEOMETRY mono-1: Overall Response Rates (Cohorts 7 and 6)



Wolf J et al. ASCO 2021;Abstract 9020.

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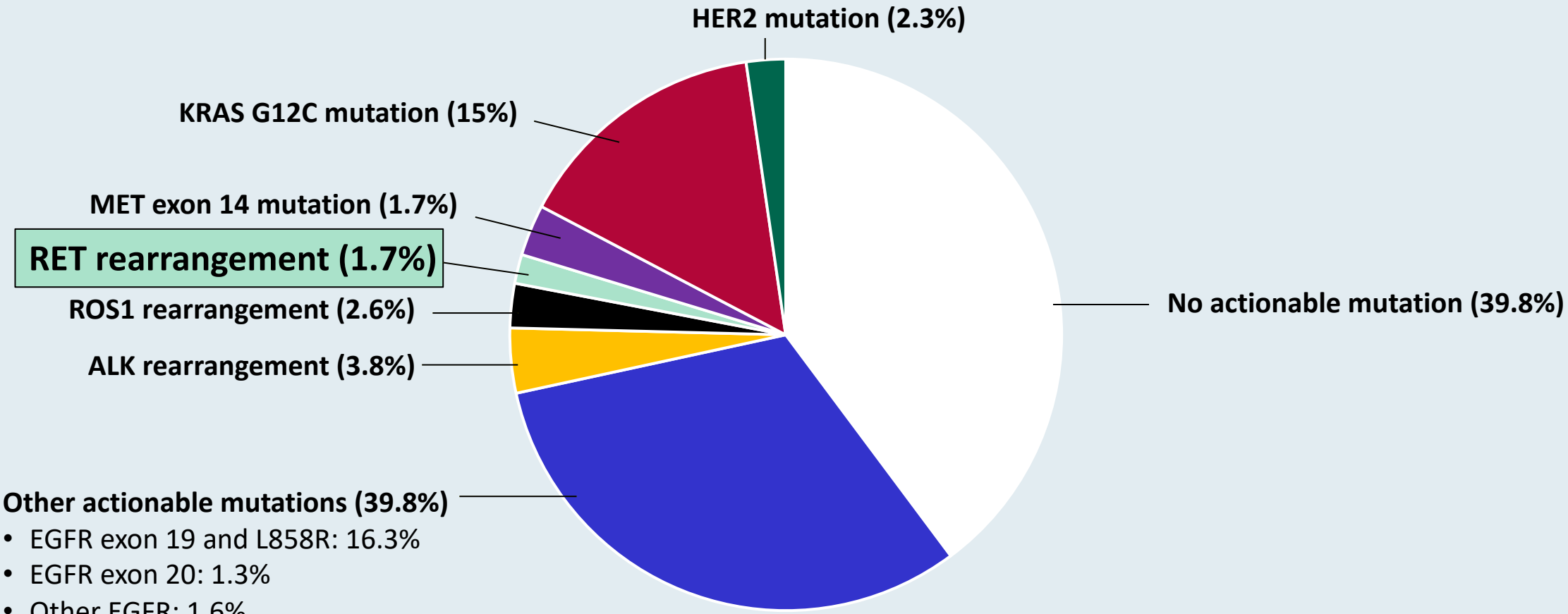
GEOMETRY mono-1: Most Common Adverse Events (Cohorts 7 and 6)

Adverse event	Cohort 7 — Treatment naïve N = 32		Cohort 6 — Second line N = 31	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Peripheral edema	72%	13%	71%	13%
Nausea	44%	0	32%	3%
Vomiting	15%	3%	26%	0
Increase blood creatinine	31%	0	29%	0
Dyspnea	6%	3%	10%	0
Fatigue	19%	0	29%	0
Decreased appetite	16%	3%	16%	0

Wolf J et al. ASCO 2021;Abstract 9020.

Frequency of Targetable Oncogenic Driver Molecular Alterations in Adenocarcinoma of the Lung



- EGFR exon 19 and L858R: 16.3%
- EGFR exon 20: 1.3%
- Other EGFR: 1.6%
- Other KRAS: 10.3%
- BRAF V600E: 2.1%
- NTRK rearrangement: 0.23%

Derived from Tan AC et al. *J Clin Oncol* 2022;40:611-625.

RTP RESEARCH TO PRACTICE

Lancet Oncol 2021;22(7):959-69.

Pralsetinib for *RET* fusion-positive non-small-cell lung cancer (ARROW): a multi-cohort, open-label, phase 1/2 study

Justin F Gainor, Giuseppe Curigliano, Dong-Wan Kim, Dae Ho Lee, Benjamin Besse, Christina S Baik, Robert C Doebele, Philippe A Cassier, Gilberto Lopes, Daniel S W Tan, Elena Garralda, Luis G Paz-Ares, Byoung Chul Cho, Shirish M Gadgeel, Michael Thomas, Stephen V Liu, Matthew H Taylor, Aaron S Mansfield, Viola W Zhu, Corinne Clifford, Hui Zhang, Michael Palmer, Jennifer Green, Christopher D Turner, Vivek Subbiah

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 27, 2020 VOL. 383 NO. 9

Efficacy of Selpercatinib in *RET* Fusion–Positive Non–Small-Cell Lung Cancer

A. Drilon, G.R. Oxnard, D.S.W. Tan, H.H.F. Loong, M. Johnson, J. Gainor, C.E. McCoach, O. Gautschi, B. Besse, B.C. Cho, N. Peled, J. Weiss, Y.-J. Kim, Y. Ohe, M. Nishio, K. Park, J. Patel, T. Seto, T. Sakamoto, E. Rosen, M.H. Shah, F. Barlesi, P.A. Cassier, L. Bazhenova, F. De Braud, E. Garralda, V. Velcheti, M. Satouchi, K. Ohashi, N.A. Pennell, K.L. Reckamp, G.K. Dy, J. Wolf, B. Solomon, G. Falchook, K. Ebata, M. Nguyen, B. Nair, E.Y. Zhu, L. Yang, X. Huang, E. Olek, S.M. Rothenberg, K. Goto, and V. Subbiah

Pivotal Studies of Selpercatinib and Pralsetinib for Advanced NSCLC with RET Fusion

	Selpercatinib[1]	Pralesetinib[2]
Pivotal study	LIBRETTO-001 Phase I/II (N = 105)	ARROW Phase I/II (N = 233)
FDA approval	May 8, 2020	September 4, 2020
Setting	Previous platinum-based chemotherapy and previously untreated	Previous platinum-based chemotherapy and previously untreated
ORR	64%	Prior platinum-based chemo: 61% Treatment-naïve: 70%
Median duration of response	17.5 months	Not reached
Common Grade ≥3 adverse events	Hypertension (14%) Increased ALT (12%) and AST (10%) Hyponatremia (6%) Lymphopenia (6%)	Neutropenia (18%) Hypertension (11%) Anemia (10%) Decreased WBC (6%)

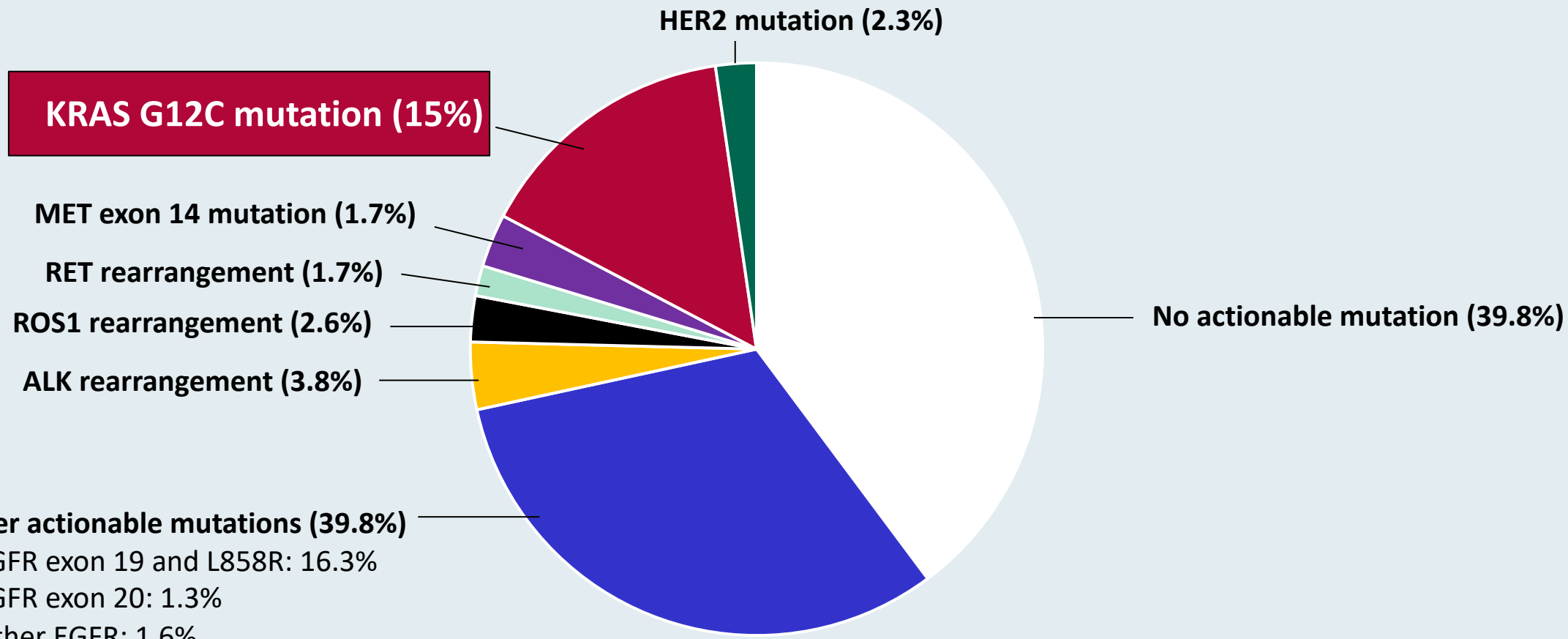
[1] Drilon A et al. *N Engl J Med* 2020;383(9):813-24. [2] Gainor JF et al. *Lancet Oncol* 2021;22(7):959-69.

Ongoing Phase III Trials of Selpercatinib or Pralsetinib for NSCLC with RET Fusion

Trial identifier	Setting	Treatment arms
LIBRETTO-431 (NCT04194944)	Untreated Stage IIIB-IIIC or Stage IV non-squamous NSCLC that is not suitable for radical surgery or radiation therapy	• Selpercatinib • Pemetrexed and platinum with or without pembrolizumab
LIBRETTO-432 (NCT04819100)	Stage IB, II or IIIA NSCLC after definitive locoregional therapy	• Selpercatinib • Placebo
AcceleRET-Lung (NCT04222972)	Locally advanced or metastatic NSCLC that has not been treated with systemic anticancer therapy for metastatic disease	• Pralsetinib • Platinum-based chemotherapy (with or without pembrolizumab)
NCT05170204	Unresectable Stage III NSCLC	<u>Cohort A3</u> • Pralsetinib • Durvalumab

www.clinicaltrials.gov. Accessed March 2022.

Frequency of Targetable Oncogenic Driver Molecular Alterations in Adenocarcinoma of the Lung



Other actionable mutations (39.8%)

- EGFR exon 19 and L858R: 16.3%
- EGFR exon 20: 1.3%
- Other EGFR: 1.6%
- Other KRAS: 10.3%
- BRAF V600E: 2.1%
- NTRK rearrangement: 0.23%

Derived from Tan AC et al. *J Clin Oncol* 2022;40(6):611-25.

RTP RESEARCH TO PRACTICE

FDA Grants Accelerated Approval to Sotorasib for NSCLC with KRAS G12C Mutation

Press Release – May 28, 2021

"The Food and Drug Administration granted accelerated approval to sotorasib, a RAS GTPase family inhibitor, for adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC), as determined by an FDA-approved test, who have received at least one prior systemic therapy.

FDA also approved the QIAGEN therascreen® KRAS RGQ PCR kit (tissue) and the Guardant360® CDx (plasma) as companion diagnostics for sotorasib. If no mutation is detected in a plasma specimen, the tumor tissue should be tested.

Approval was based on CodeBreaK 100, a multicenter, single-arm, open label clinical trial (NCT03600883) which included patients with locally advanced or metastatic NSCLC with KRAS G12C mutations. Efficacy was evaluated in 124 patients whose disease had progressed on or after at least one prior systemic therapy. Patients received sotorasib 960 mg orally daily until disease progression or unacceptable toxicity."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-sotorasib-kras-g12c-mutated-nsclc

RTP RESEARCH TO PRACTICE

AACR American Association for Cancer Research ANNUAL MEETING 2022 New Orleans

Long-term Outcomes With Sotorasib in Pre-treated *KRAS* p.G12C Mutated NSCLC: 2-year Analysis of CodeBreaK 100

Presenter: Grace K. Dy[1], MD

[1]Roswell Park Comprehensive Cancer Center

On behalf of: Ramaswamy Govindan[2], Vamsidhar Velcheti[3], Gerald S. Falchook[4], Antoine Italiano[5], Juergen Wolf[6], Adrian G. Sacher[7], Toshiaki Takahashi[8], Suresh S. Ramalingam[9], Christophe Dooms[10], Dong-Wan Kim[11], Alfredo Addeo[12], Jayesh Desai[13], Martin Schuler[14], Pascale Tomasini[15], Qui Tran[16], Simon Jones[16], Agnes Ang[16], Abraham Anderson[16], Antreas Hindoyan[16], David S. Hong[17], Bob T. Li[18]

[2]Washington University in St Louis, [3]New York University Langone, [4]Sarah Cannon Research Institute, [5]Institut Bergonie, [6]Universitatsklinikum Koln, [7]Princess Margaret Cancer Centre, [8]Shizuoka Cancer Center [9]Winship Cancer Institute, [10]Universitair Ziekenhuis Leuven [11]Seoul National University Hospital, [12]Hopitaux Universitaires de Geneve, [13]Peter MacCallum Cancer Centre, [14]Universitätsklinikum Essen, [15]Hopital de la Timone, [16]Amgen Inc., [17]MD Anderson Cancer Center, [18]Memorial Sloan Kettering Cancer Center

Abstract CT008

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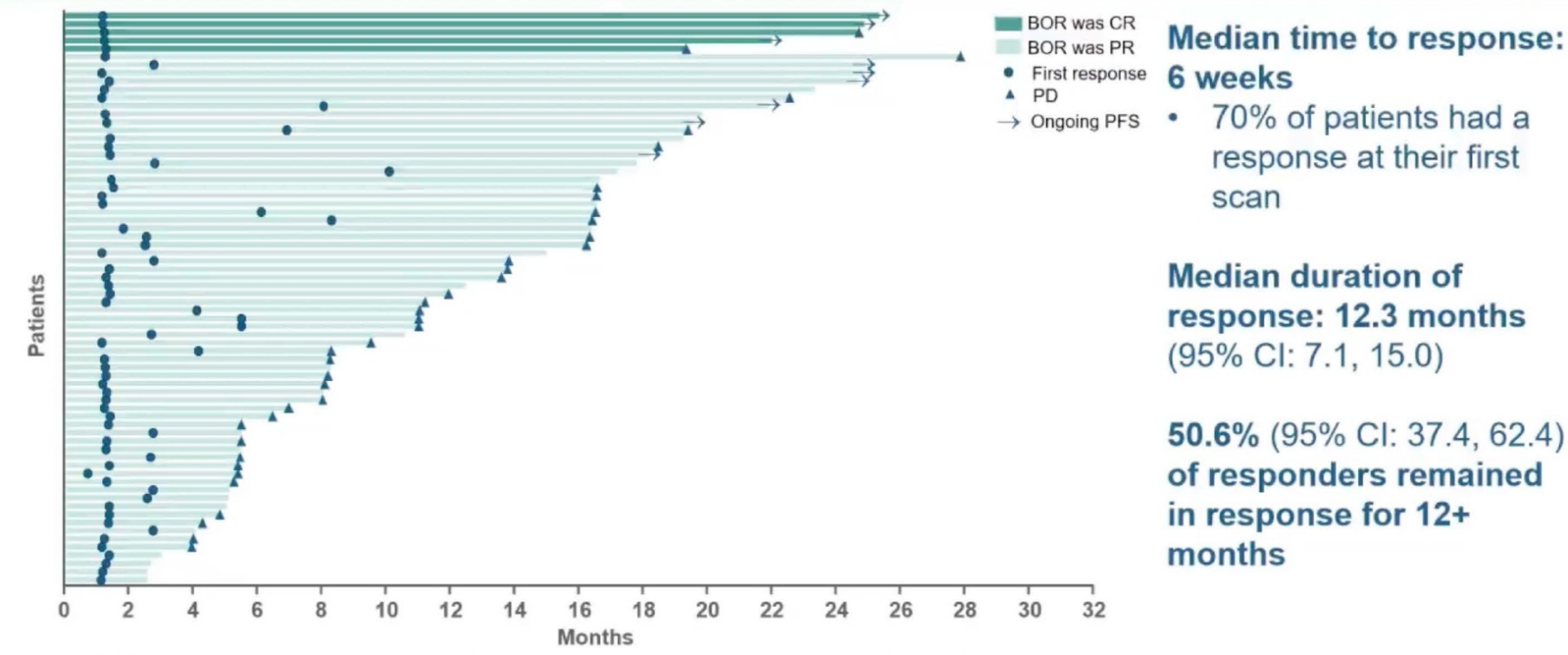
CodeBreaK 100: 2-Year Update with Sotorasib for Previously Treated Metastatic NSCLC with KRAS p.G12C Mutation



Median time to response: 6 weeks

- 70% of patients had a response at their first scan

Median duration of response: 12.3 months (95% CI: 7.1, 15.0)

50.6% (95% CI: 37.4, 62.4) **of responders remained in response for 12+ months**

Efficacy Update (N = 172)
ORR: 40.7%
DCR: 83.7%
Median PFS: 6.3 mo
Median OS: 12.5 mo
1-year OS rate: 50.8%

Dy GK et al. AACR 2022;Abstract CT008.

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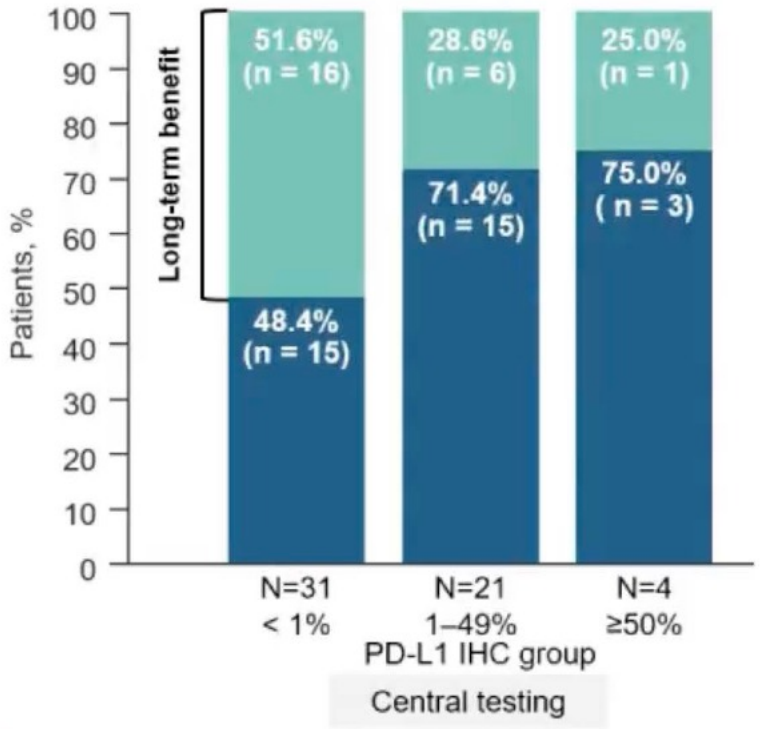
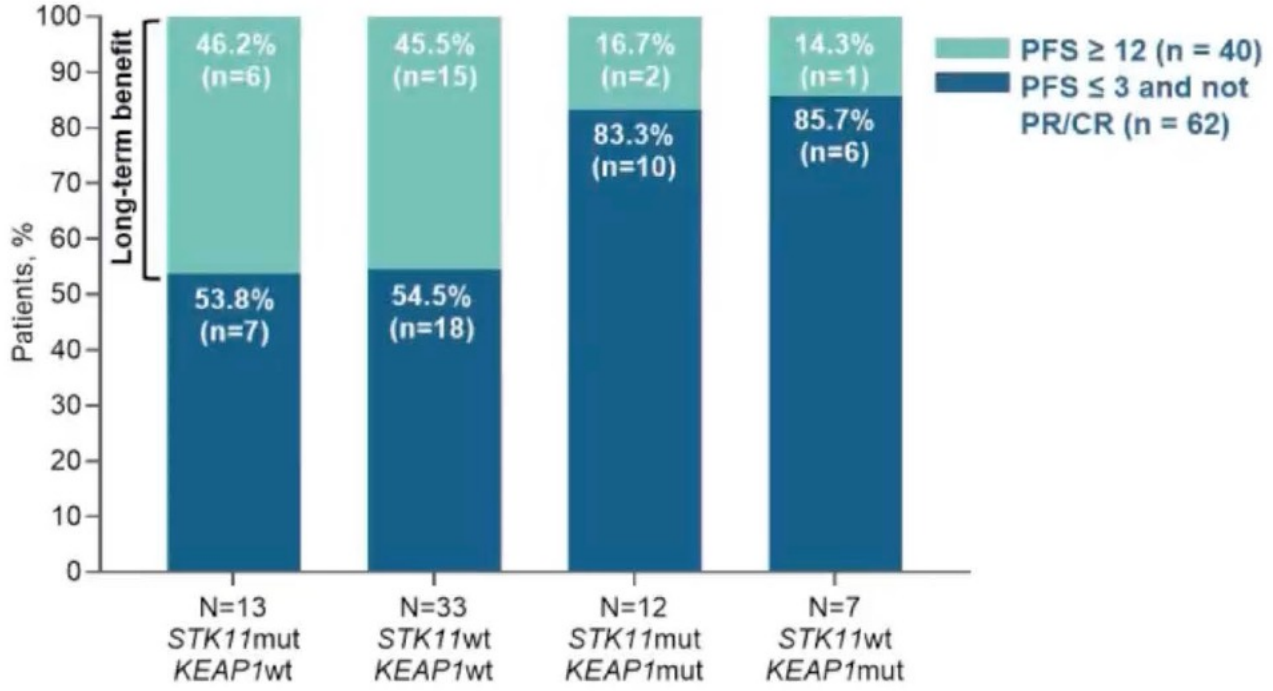
CodeBreaK 100: Exploratory Biomarker Analyses





Prolonged clinical benefit was observed across PD-L1 expression, including tumors with low PD-L1 expression and *STK11* co-mutations

Dy GK et al. AACR 2022;Abstract CT008.

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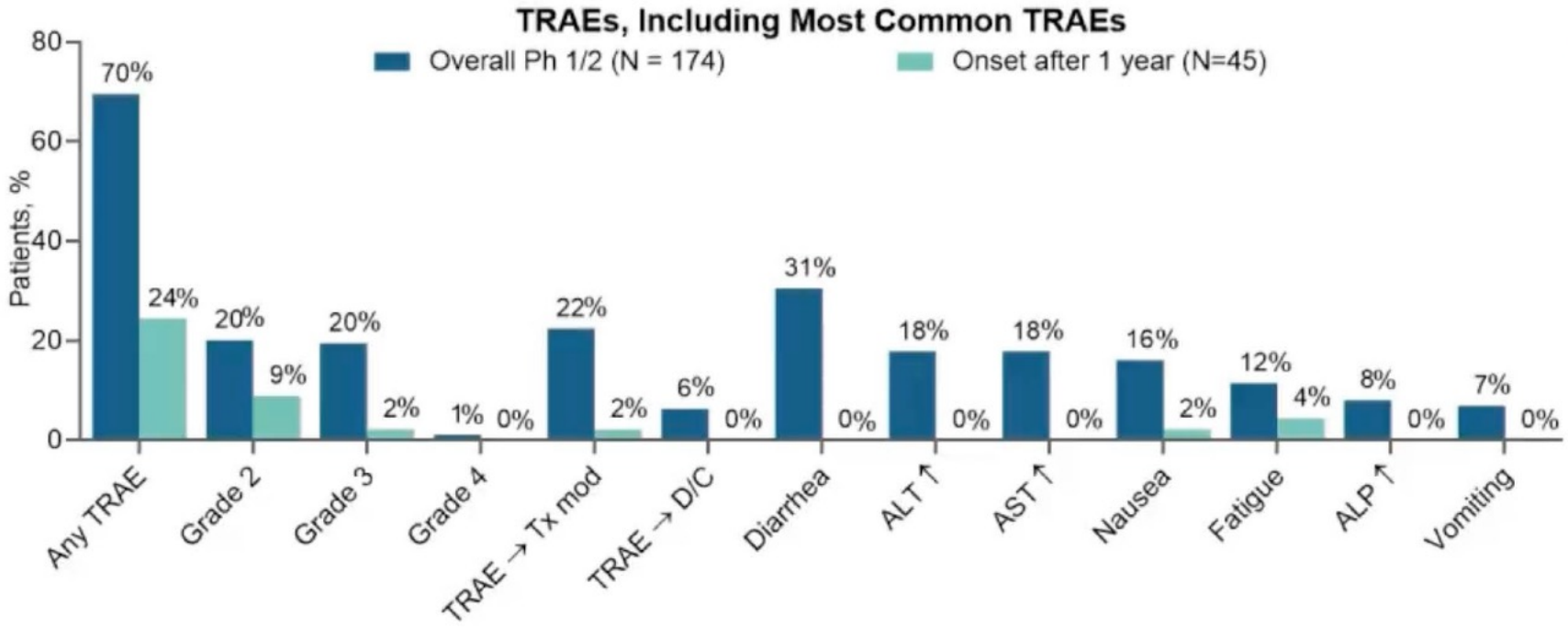
CodeBreaK 100: Treatment-Related Adverse Events



Grade 3 or 4 TRAEs occurred in 21% of patients

- One patient with new onset Grade 3 TRAE after 1 year (hemolytic anemia)

No fatal TRAEs occurred

- No TRAE leading to discontinuation after 1 year

Well-tolerated in the long-term: late-onset TRAEs were mild and manageable

Dy GK et al. AACR 2022;Abstract CT008.

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The NEW ENGLAND JOURNAL of MEDICINE

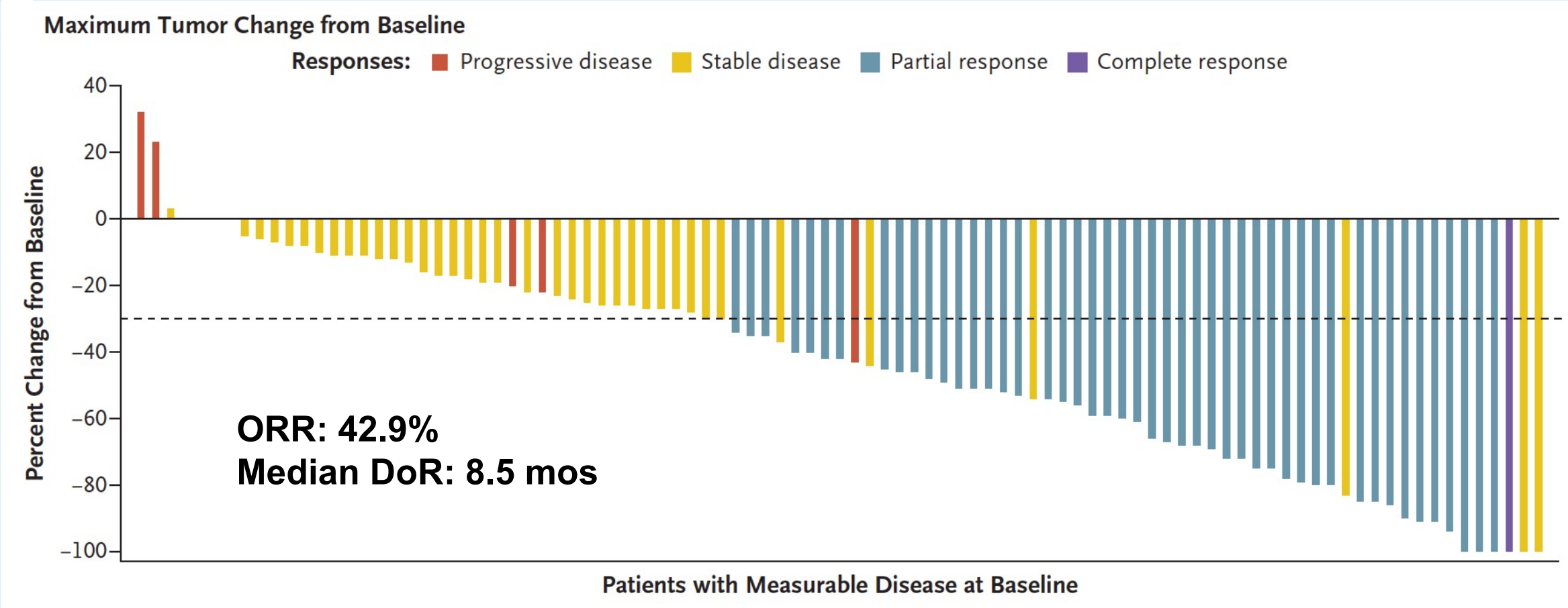
ORIGINAL ARTICLE

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.

***N Engl J Med* 2022;[Online ahead of print].**

KRYSTAL-1: Response in a Phase II Study of Adagrasib for Advanced or Metastatic NSCLC Harboring a KRAS G12C Mutation



Jänne PA et al. *N Engl J Med* 2022;[Online ahead of print].

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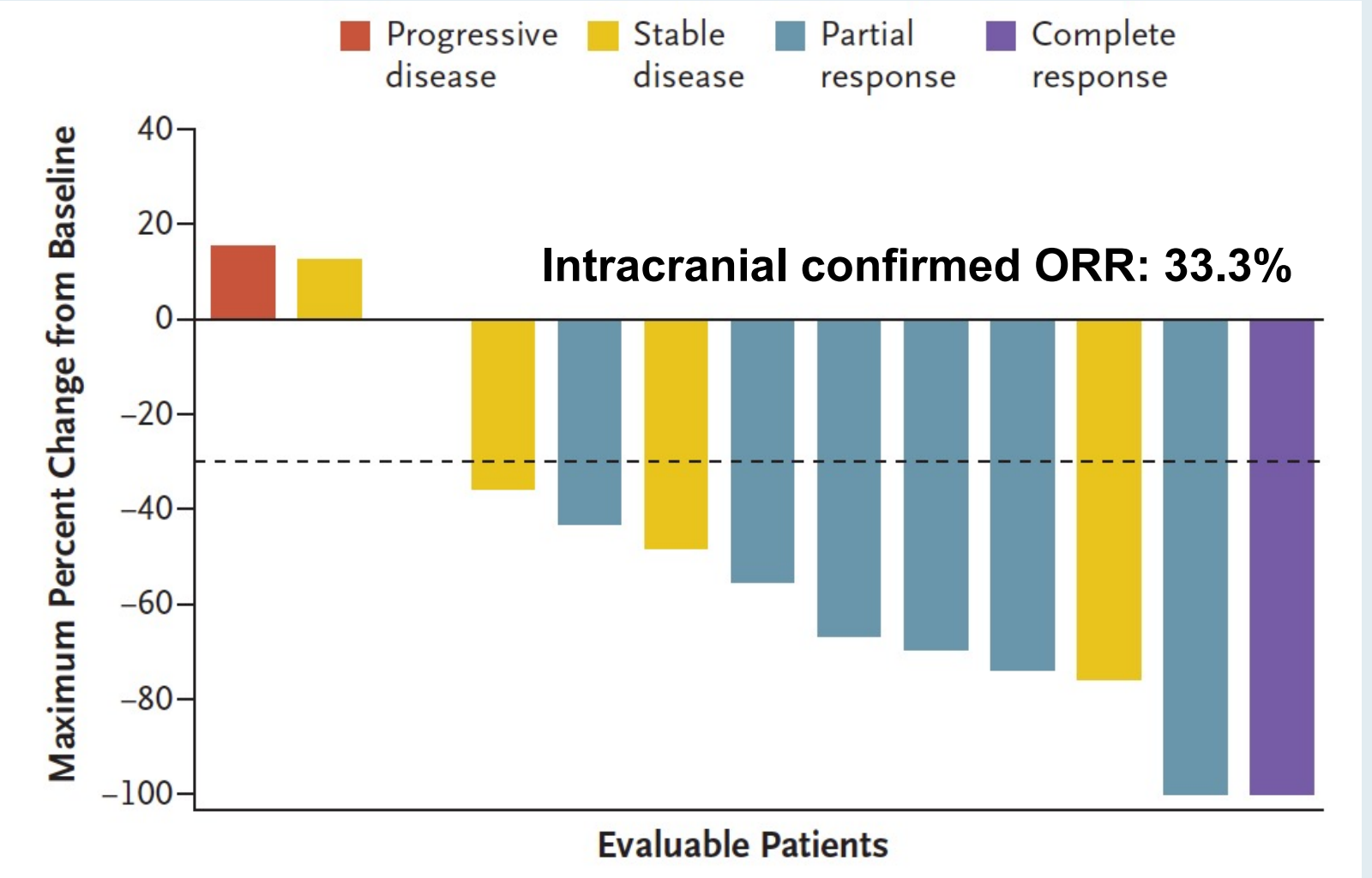
KRYSTAL-1: Intracranial Responses with Adagrasib for Advanced or Metastatic NSCLC Harboring a KRAS G12C Mutation



Jänne PA et al. *N Engl J Med* 2022;[Online ahead of print].

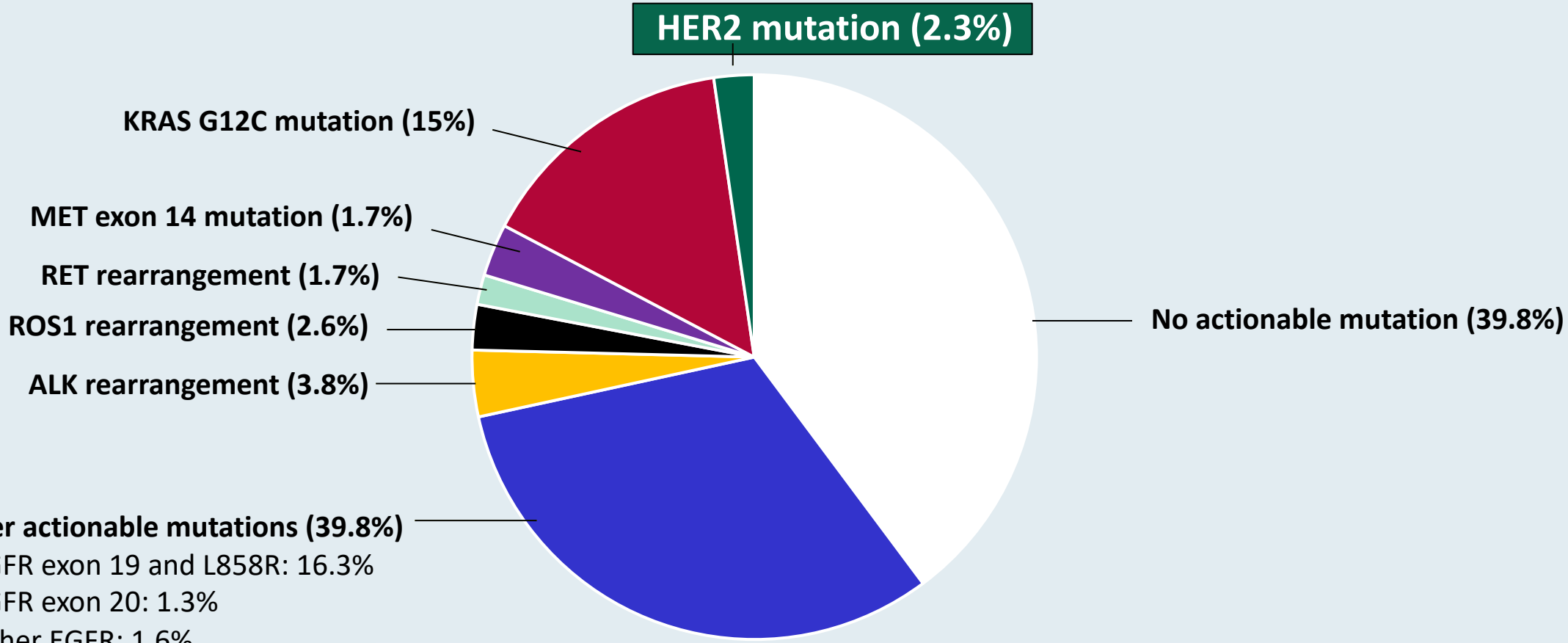
RTP RESEARCH TO PRACTICE

KRYSTAL-1: Select Treatment-Related Adverse Events with Adagrasib for Advanced or Metastatic NSCLC Harboring a KRAS G12C Mutation

Adverse event (N = 116)	Any grade	Grade ≥3
Diarrhea	70.7%	0.9%
Nausea	69.8%	4.3%
Fatigue	59.5%	6.9%
Vomiting	56.9%	0.9%
Blood creatinine increased	34.5%	0.9%
ALT increased	28.4%	5.2%
AST increased	26.7%	5.2%

Jänne PA et al. *N Engl J Med* 2022;[Online ahead of print].

Frequency of Targetable Oncogenic Driver Molecular Alterations in Adenocarcinoma of the Lung



- EGFR exon 19 and L858R: 16.3%
- EGFR exon 20: 1.3%
- Other EGFR: 1.6%
- Other KRAS: 10.3%
- BRAF V600E: 2.1%
- NTRK rearrangement: 0.23%

Derived from Tan AC et al. *J Clin Oncol* 2022;40:611-25.

RTP RESEARCH TO PRACTICE

N Engl J Med 2022;386(3):241-51.

The NEW ENGLAND JOURNAL of MEDICINE

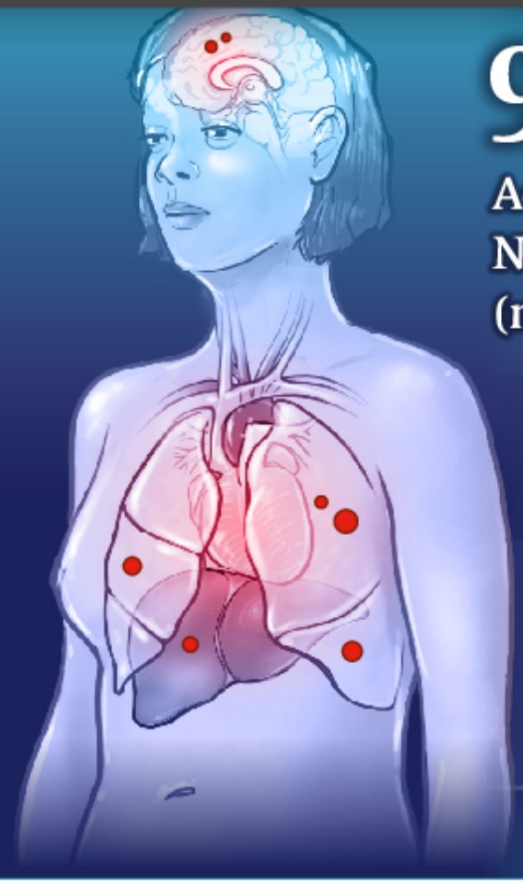
ORIGINAL ARTICLE

Trastuzumab Deruxtecan in *HER2*-Mutant Non–Small-Cell Lung Cancer

Bob T. Li, M.D., Ph.D., M.P.H., Egbert F. Smit, M.D., Ph.D., Yasushi Goto, M.D., Ph.D., Kazuhiko Nakagawa, M.D., Hibiki Udagawa, M.D., Julien Mazières, M.D., Misako Nagasaka, M.D., Ph.D., Lyudmila Bazhenova, M.D., Andreas N. Saltos, M.D., Enriqueta Felip, M.D., Ph.D., Jose M. Pacheco, M.D., Maurice Pérol, M.D., Luis Paz-Ares, M.D., Kapil Saxena, M.D., Ryota Shiga, B.Sc., Yingkai Cheng, M.D., Ph.D., Suddhasatta Acharyya, Ph.D., Patrik Vitazka, M.D., Ph.D., Javad Shahidi, M.D., David Planchard, M.D., Ph.D., and Pasi A. Jänne, M.D., Ph.D., for the DESTINY-Lung01 Trial Investigators*

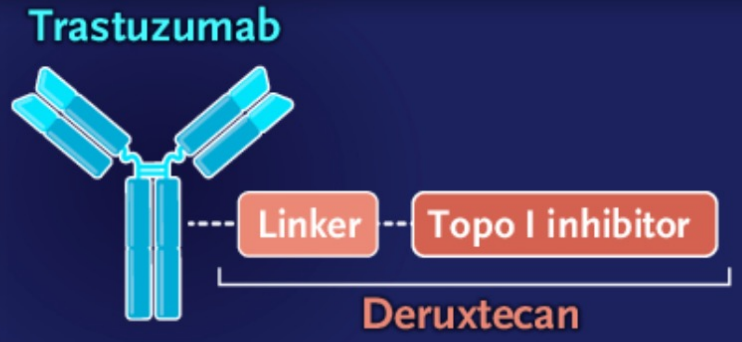
DESTINY-Lung01 Study

MULTICENTER, INTERNATIONAL, PHASE 2 STUDY



91

Adults with metastatic *HER2*-mutant NSCLC refractory to standard treatment (median follow-up, 13 mo)



Confirmed objective response (assessed by independent central review)	55% (95% CI, 44–65)
Duration of response	9.3 mo
Progression-free survival	8.2 mo
Overall survival	17.8 mo

Grade 3 or higher drug-related adverse events occurred in 46% of patients.

Trastuzumab deruxtecan showed durable anticancer activity.

Li BT et al. *N Engl J Med* 2022;386(3):241-51.

DESTINY-Lung01: Summary of Adverse Events and AEs of Clinical Interest

Event	N = 91
Discontinued due to AEs	25%
Dose reduction due to AEs	34%
Dose interruption due to AEs	32%
Drug-related interstitial lung disease (ILD)	26% (N = 24)
Grade 1	3 pts
Grade 2	15 pts
Grade 3	4 pts
Grade 5	2 pts
Median time to onset of ILD	141 days
Median duration of ILD	43 days

Li BT et al. *N Engl J Med* 2022;386(3):241-51.

DESTINY-Lung01: Common Adverse Events (N = 91)

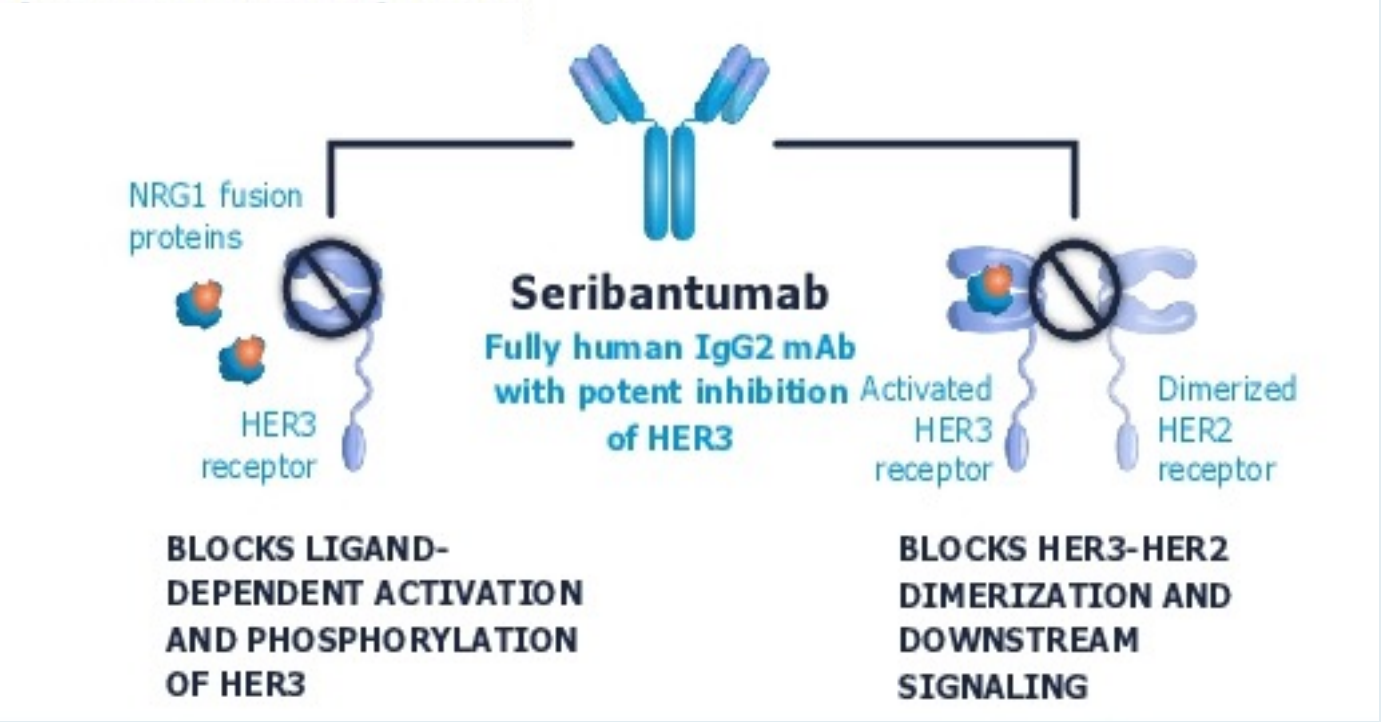
Event	Any grade	Grade ≥3
Nausea	73%	9%
Fatigue	53%	7%
Alopecia	46%	0
Vomiting	40%	3%
Neutropenia	35%	18%
Anemia	33%	10%
Diarrhea	32%	3%
Decreased appetite	30%	0
Leukopenia	23%	4%
Constipation	22%	0

Li BT et al. *N Engl J Med* 2022;386(3):241-51.

Other Potential Oncogenic Driver Molecular Alterations in Adenocarcinoma of the Lung

Neuregulin-1 (NRG1) Gene Fusions and Seribantumab Mechanism of Action

- NRG1 gene fusions are rare oncogenic drivers found in 0.2% of solid tumors, including lung, colorectal, breast and ovarian
- NRG1 fusion proteins predominantly retain an active EGF-like domain, which drives tumorigenesis and proliferation through aberrant HER3 activation
- Seribantumab is a fully human monoclonal antibody against HER3



Bendell JC et al. Gastrointestinal Cancers Symposium 2021;Abstract TPS449.

Investigational New Drugs (2021) 39:1604–1612
https://doi.org/10.1007/s10637-021-01145-y

PHASE I STUDIES

Phase 1 dose escalation study of seribantumab (MM-121), an anti-HER3 monoclonal antibody, in patients with advanced solid tumors

Crystal S. Denlinger[1] · Vicki L. Keedy[2] · Victor Moyo[3] · Gavin MacBeath[3] · Geoffrey I. Shapiro[4]

Best Overall Response with and Recommended Phase II Dose of Seribantumab for Advanced Solid Tumors

Best response	Dose escalation (n = 25)	Dose expansion (n = 18)
Overall response	0	0
Complete response	0	0
Partial response	0	0
Stable disease	6 (24%)	7 (39%)
Progressive disease	11 (44%)	8 (44%)

- Most adverse events were transient and mild to moderate (Grade 1 or 2) in severity
- The maximum tolerated dose was not reached in the dose escalation portion, and the 40 mg/kg loading dose followed by 20 mg/kg weekly maintenance dose was considered well tolerated and chosen for the dose expansion portion of the study

Denlinger CS et al. *Invest New Drugs* 2021;39(6):1604-12.

2022 ASCO® ANNUAL MEETING

Abstract 3006

CRESTONE: Initial Efficacy and Safety of Seribantumab in Solid Tumors Harboring NRG1 Fusions

Daniel R. Carrizosa,[1] Mark E. Burkard,[2] Yasir Y. Elamin,[3] Jayesh Desai,[4] Shirish M. Gadgeel,[5] Jessica J. Lin,[6] Saiama N. Waqar,[7] David R. Spigel,[8] Young Kwang Chae,[9] Parneet K. Cheema,[10] Eric B. Haura,[11] Stephen V. Liu,[12] Danny Nguyen,[13] Karen L. Reckamp,[14] Frank Yung-Chin Tsai,[15] Valerie M. Jansen,[16] Alexander Drilon,[17] Sai-Hong Ignatius Ou,[18] D Ross Camidge,[19] Tejas Patil[19]

[1]Levine Cancer Institute/Atrium Health, Charlotte, NC; [2]University of Wisconsin Carbone Cancer Center, Madison, WI; [3]The University of Texas MD Anderson Cancer Center, Houston, TX; [4]Peter MacCallum Cancer Centre, Melbourne, Australia; [5]Henry Ford Cancer Institute/Henry Ford Health System, Detroit, MI; [6]Massachusetts General Hospital, Boston, MA; [7]Washington University School of Medicine, St. Louis, MO; [8]Sarah Cannon Research Institute, Nashville, TN; [9]Northwestern University, Chicago, IL; [10]William Osler Health System, Calgary, Canada; [11]H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; [12]Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC; [13]City of Hope, Huntington Beach and Irvine, CA; [14]Cedars-Sinai Medical Center, Los Angeles, CA; [15]HonorHealth, Scottsdale, AZ; [16]Elevation Oncology, Inc. New York, NY; [17]Memorial Sloan Kettering Cancer Center, New York, NY; [18]Chao Family Comprehensive Cancer Center, University of CA-Irvine, Orange, CA; [19]University of Colorado Cancer Center, Aurora, CO

RTP RESEARCH TO PRACTICE

CRESTONE: An Ongoing Phase II Study of Seribantumab in Patients with Advanced Solid Tumors with NRG1 Fusions

Trial identifier: NCT04383210 (open)

Advanced solid tumor with an NRG1 gene fusion

Disease progression on or unresponsive to at least 1 prior standard therapy appropriate for tumor type and stage of disease

No further available curative therapy options

No prior pan-ERBB or any ERBB/HER2/HER3-directed therapy (Cohort 1 only)

Primary endpoint: Objective response rate

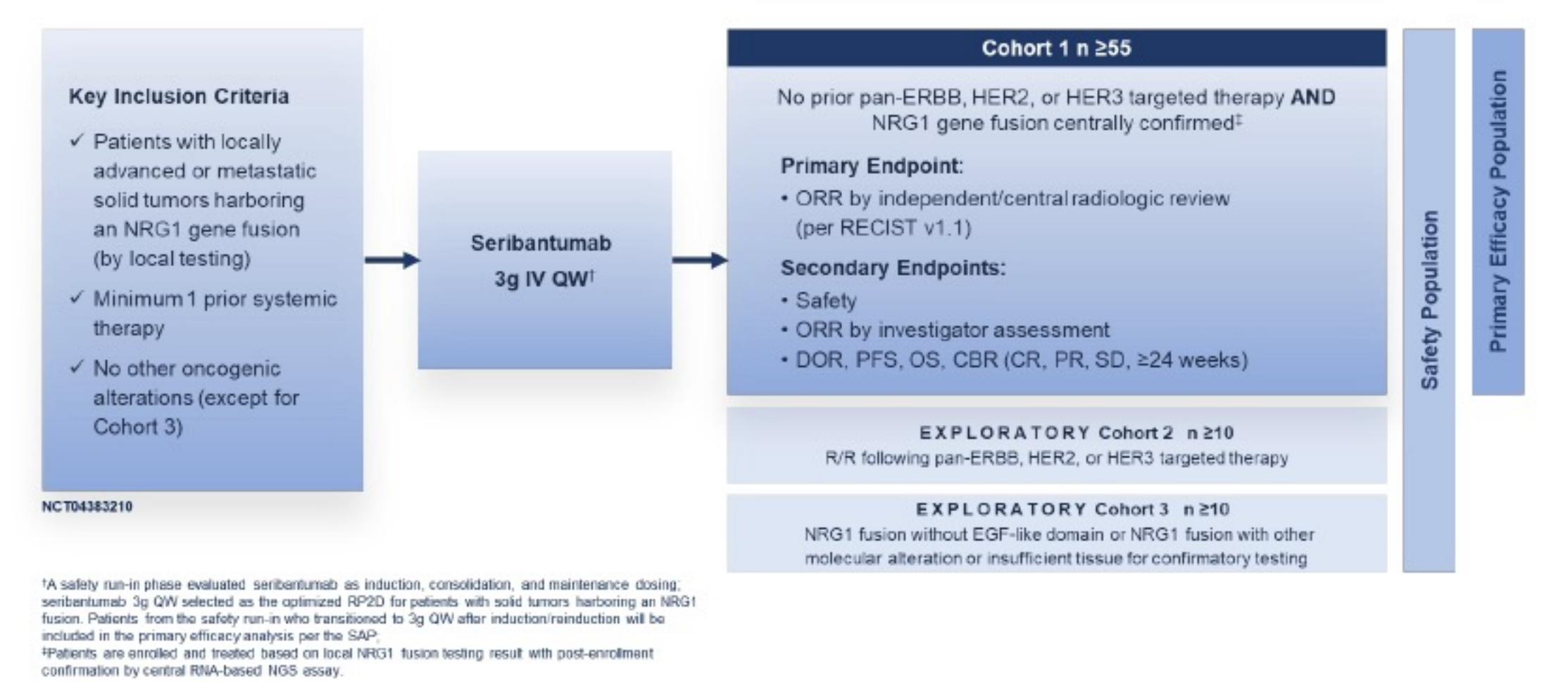
Seribantumab
1-h IV infusion at various doses once weekly, every 2 weeks and every 3 weeks, during the induction, consolidation and maintenance dosing phases, respectively

Patient Cohorts:
Cohort 1: A minimum of 55 adults with advanced solid tumors harboring NRG1 gene fusions who have received prior standard treatment, excluding prior ERBB-directed therapy
Cohort 2: Up to 10 adults with advanced solid tumors harboring NRG1 gene fusions who have received prior standard treatment, including prior ERBB-directed therapy
Cohort 3: Up to 10 adults with advanced solid tumors harboring NRG1 gene fusions lacking an EGF-like domain who have received prior standard treatment, which may have included prior ERBB-directed therapy

www.clinicaltrials.gov. Accessed April 2022.

RTP RESEARCH TO PRACTICE

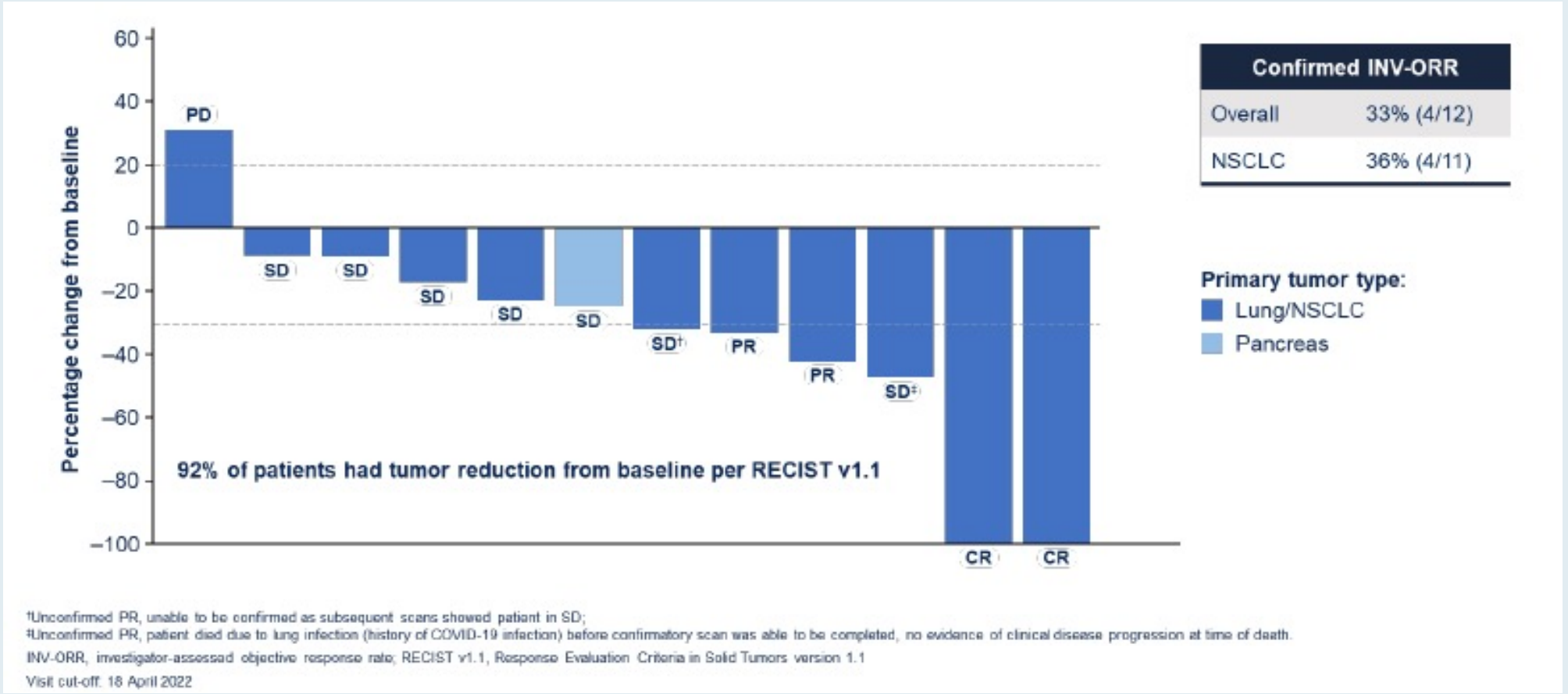
CRESTONE: A Phase II Study of Seribantumab for Patients with Advanced Solid Tumors Harboring NRG1 Fusions



QW = once weekly; ORR = objective response rate; DOR = duration of response; PFS = progression-free survival; OS = overall survival; CBR = clinical benefit rate; CR = complete response; PR = partial response; SD = stable disease

Carrizosa DR et al. ASCO 2022;Abstract 3006.

CRESTONE: Efficacy of Seribantumab for Patients with Advanced Solid Tumors Harboring NRG1 Fusions



PD = progressive disease; SD = stable disease; PR = partial response; CR = complete response

- Median DoR has not been reached

Carrizosa DR et al. ASCO 2022;Abstract 3006.

CRESTONE: Select Treatment-Related Adverse Events with Seribantumab in Patients with Advanced Solid Tumors Harboring NRG1 Fusions

Treatment-related adverse event (N = 35)	Any grade	Grade ≥3
Patients with ≥1 AE	30 (86%)	2 (6%)
Diarrhea	14 (40%)	1 (3%)
Fatigue	10 (29%)	0
Rash	9 (26%)	0
Hypokalemia	3 (9%)	0

Carrizosa DR et al. ASCO 2022;Abstract 3006.

Meet The Professor

Optimizing the Management of Ovarian Cancer

Tuesday, June 21, 2022
5:00 PM – 6:00 PM ET

Faculty

Shannon N Westin, MD, MPH

Moderator

Neil Love, MD

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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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