Meet The Professor

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

Monday, October 10, 2022
5:00 PM – 6:00 PM ET

Faculty

Pasi A Jänne, MD, PhD

Moderator

Neil Love, MD

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Commercial Support

This activity is supported by educational grants from AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, and Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC.

Dr Love — Disclosures

Dr Love is president and CEO of Research To Practice. Research To Practice receives funds in the form of educational grants to develop CME activities from the following companies: AbbVie Inc, Adaptive Biotechnologies Corporation, ADC Therapeutics, Agios Pharmaceuticals Inc, Alexion Pharmaceuticals, Amgen Inc, Array BioPharma Inc, a subsidiary of Pfizer Inc, Astellas, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, BeyondSpring Pharmaceuticals Inc, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Clovis Oncology, Coherus BioSciences, CTI BioPharma Corp, Daiichi Sankyo Inc, Eisai Inc, Elevation Oncology Inc, EMD Serono Inc, Epizyme Inc, Exact Sciences Corporation, Exelixis Inc, Five Prime Therapeutics Inc, Foundation Medicine, G1 Therapeutics Inc, Genentech, a member of the Roche Group, Genmab, Gilead Sciences Inc, GlaxoSmithKline, Grail Inc, Halozyme Inc, Helsinn Healthcare SA, ImmunoGen Inc, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc, Karyopharm Therapeutics, Kite, A Gilead Company, Kronos Bio Inc, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, MEI Pharma Inc, Merck, Mersana Therapeutics Inc, Mirati Therapeutics Inc, Natera Inc, Novartis, Novartis Pharmaceuticals Corporation on behalf of Advanced Accelerator Applications, Novocure Inc, Oncopeptides, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, Sanofi, Seagen Inc, Servier Pharmaceuticals LLC, Sumitomo Dainippon Pharma Oncology Inc, Taiho Oncology Inc, Takeda Pharmaceuticals USA Inc, TerSera Therapeutics LLC, Tesaro, A GSK Company, TG Therapeutics Inc, Turning Point Therapeutics Inc, Verastem Inc and Zymeworks Inc.

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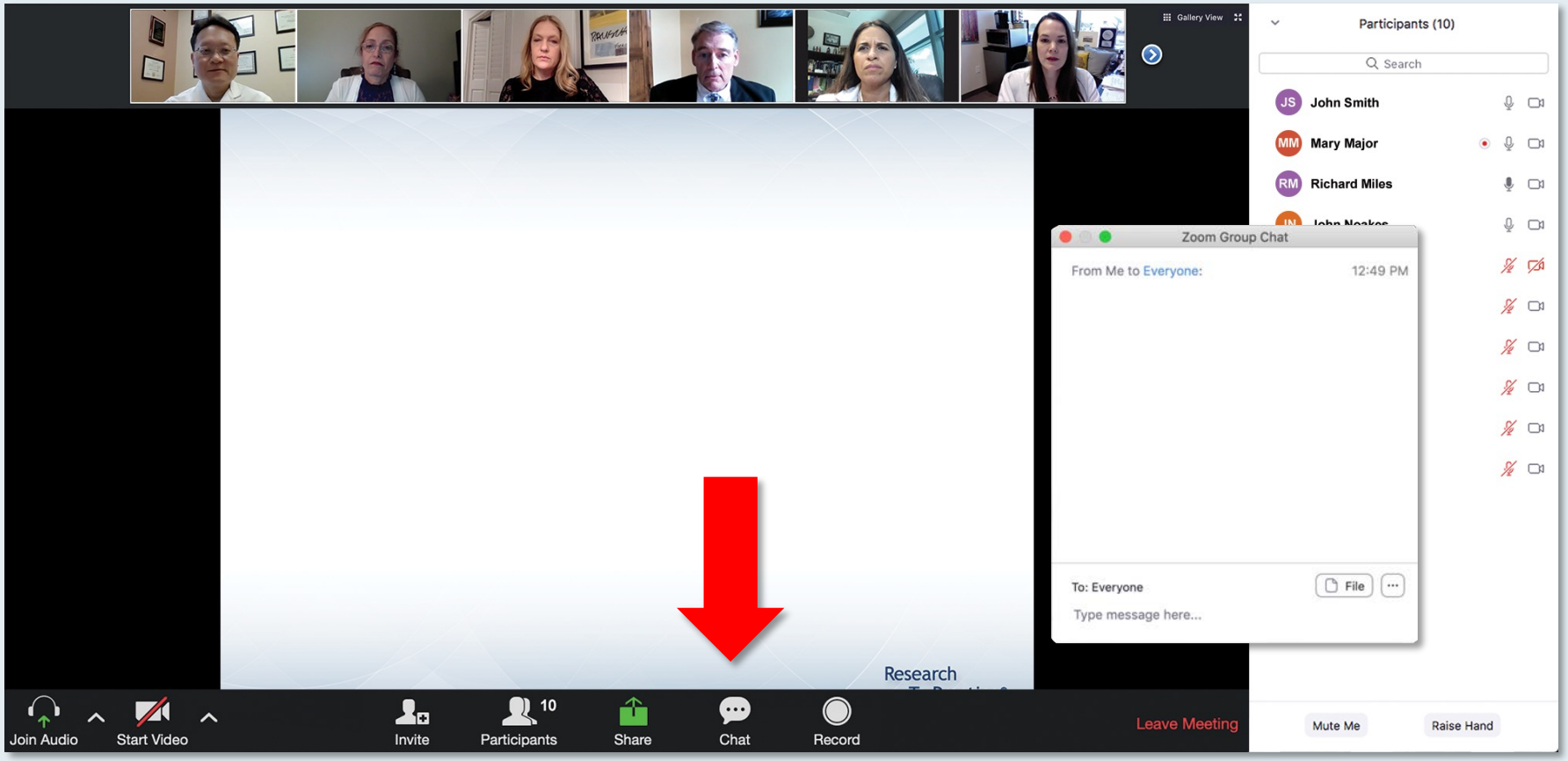
Contracted Research	Astellas, AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim Pharmaceuticals Inc, Daiichi Sankyo Inc, Lilly, Puma Biotechnology Inc, Revolution Medicines, Takeda Pharmaceuticals USA Inc
Nonrelevant Financial Relationship	Labcorp for postmarketing royalties from Dana-Farber Cancer Institute-owned intellectual property on EGFR mutations licensed to Labcorp

We Encourage Clinicians in Practice to Submit Questions



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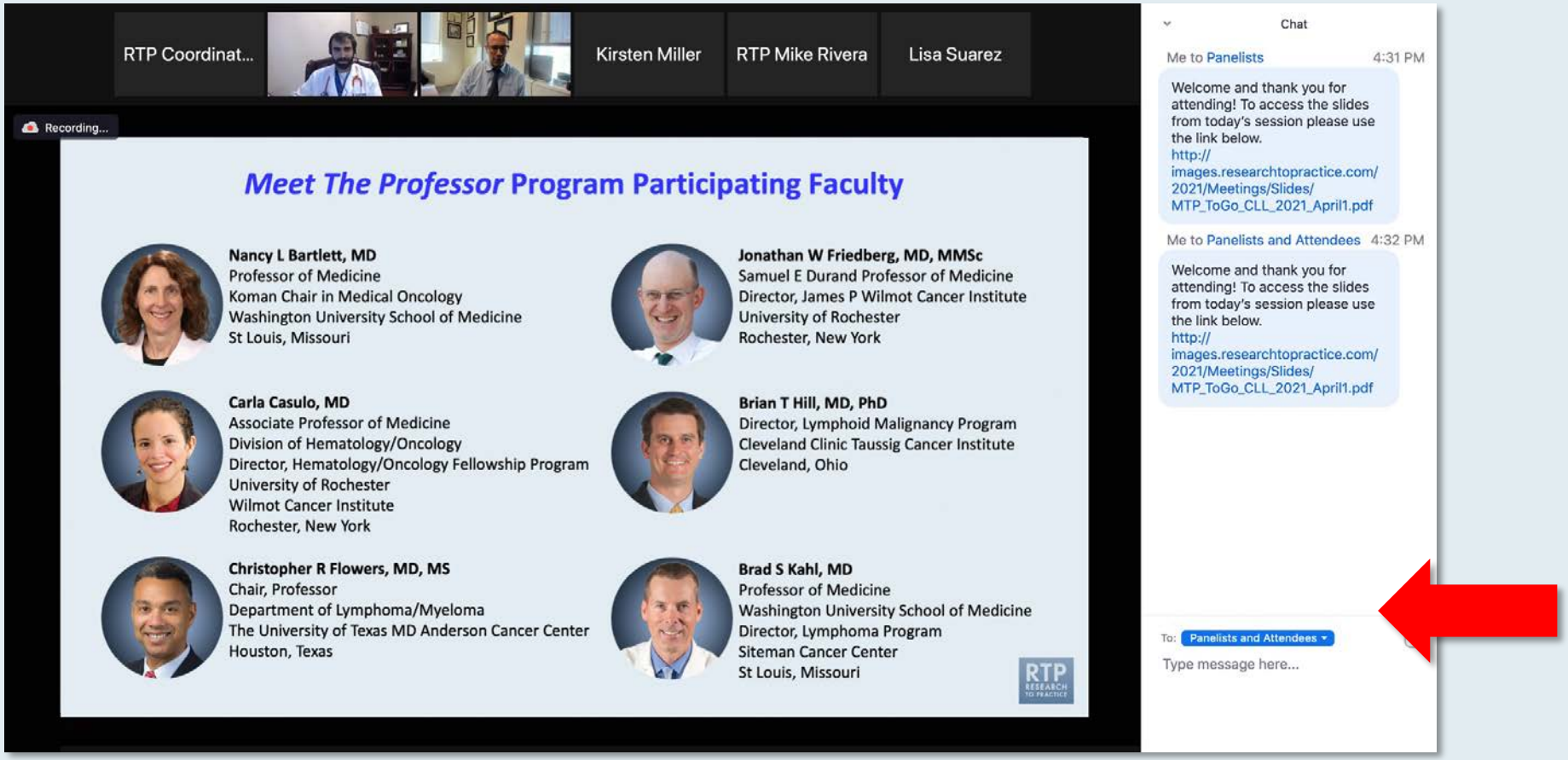
Expand chat submission box



Drag the white line above the submission box up to create more space for your message.

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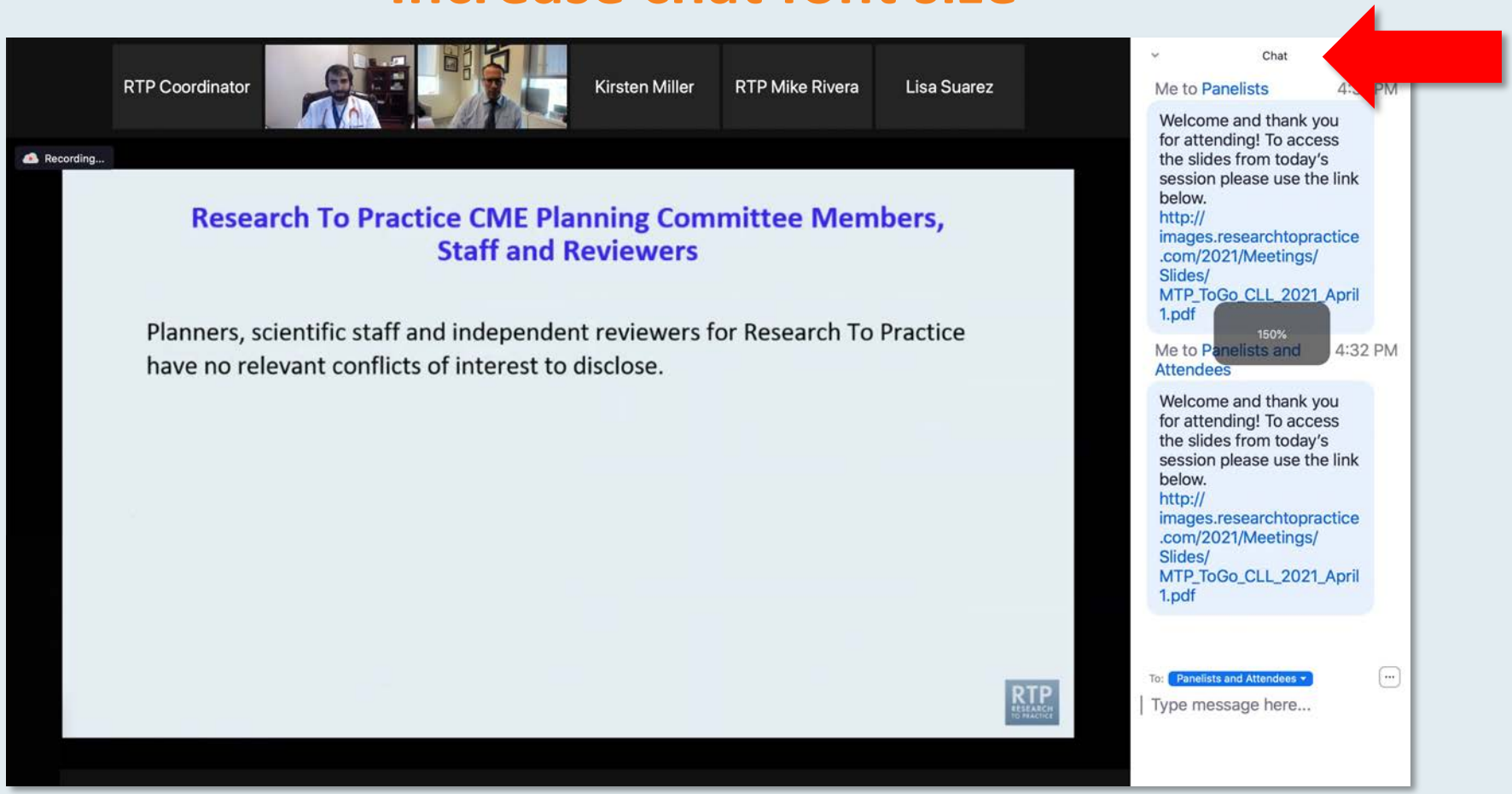

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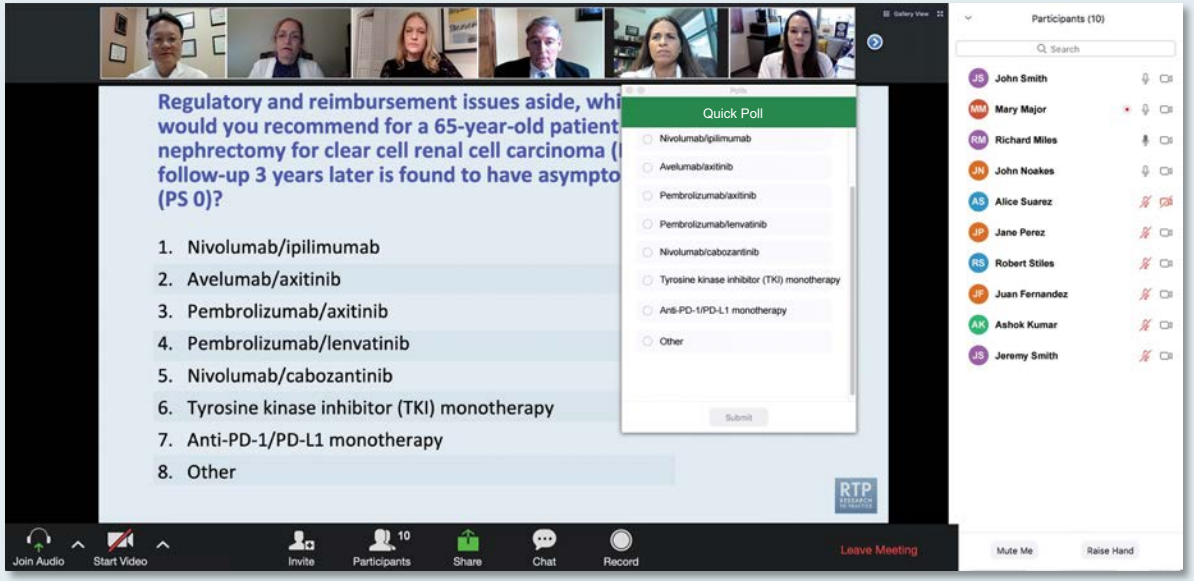
You may do this as many times as you need for readability.

Clinicians in the Audience, Please Complete the Pre- and Postmeeting Surveys



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WITH DR NEIL LOVE

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STANFORD CANCER INSTITUTE

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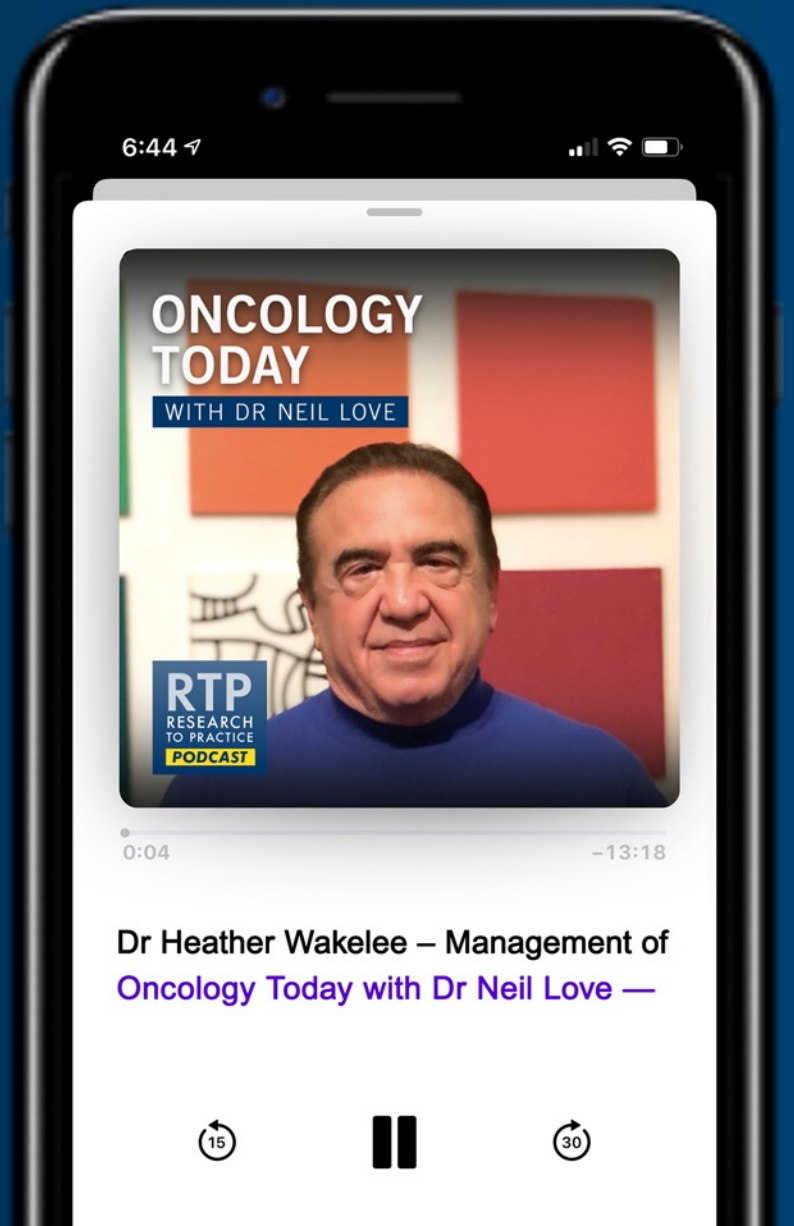

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William G Wierda, MD, PhD

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RTP RESEARCH TO PRACTICE

The Clinical Implications of Key Recent Data Sets in Oncology: A Daylong Multitumor Educational Symposium in Partnership with Florida Cancer Specialists

Saturday, October 22, 2022

7:30 AM – 5:30 PM ET

JW Marriott Orlando | Orlando, Florida

Faculty

Ghassan Abou-Alfa, MD, MBA
Matthew P Goetz, MD
Ian E Krop, MD, PhD
Ann S LaCasce, MD, MMSc
Corey J Langer, MD
Prof Georgina Long, AO, BSc, PhD, MBBS
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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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Joel W Neal, MD, PhD
Associate Professor of Medicine
Division of Oncology, Department of Medicine
Stanford Cancer Institute
Stanford University
Palo Alto, California

David Planchard, MD, PhD
Head of Thoracic Cancer Group
Department of Medical Oncology
Thoracic Group
Gustave Roussy
Villejuif, France

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

Lecia V Sequist, MD, MPH
Director, Center for Innovation in Early Cancer Detection
Massachusetts General Hospital Cancer Center
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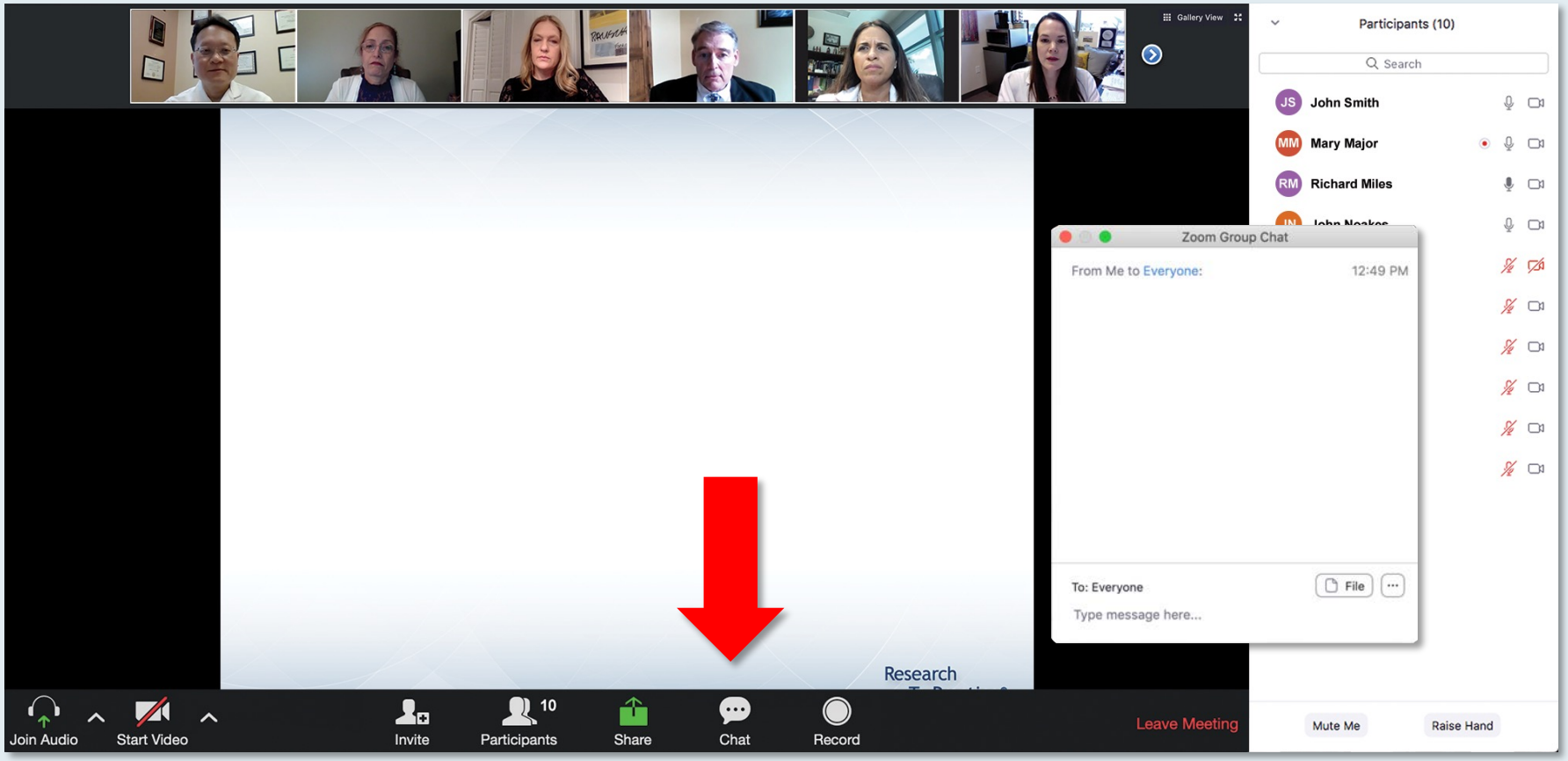

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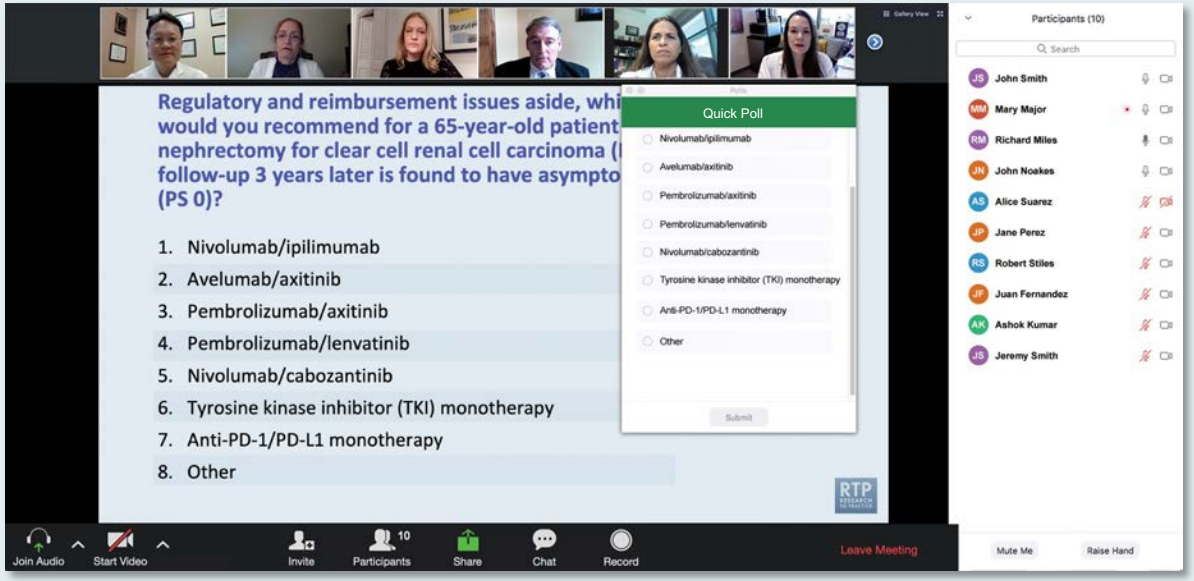

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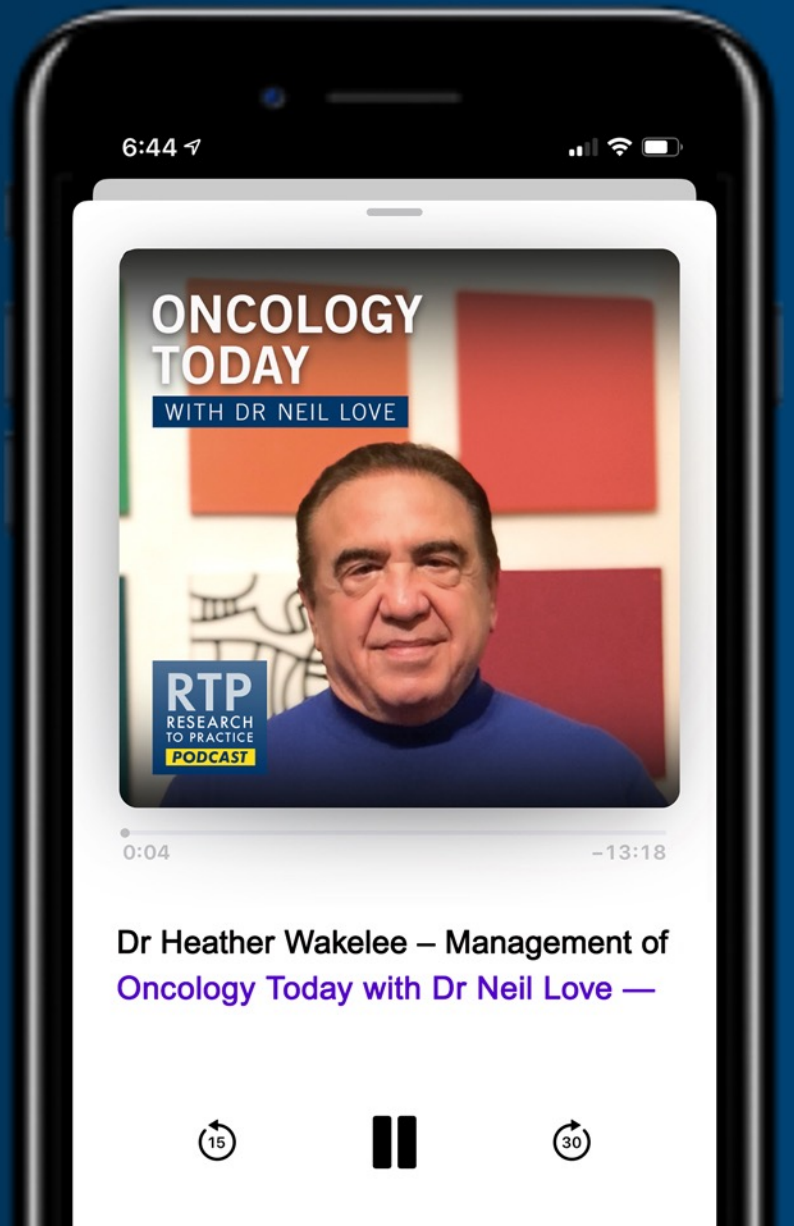

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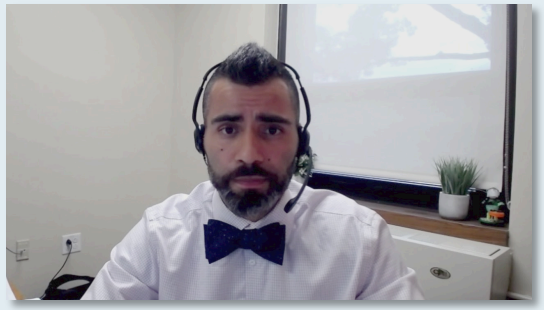
Jennifer L Dallas, MD
Novant Health Cancer Institute
Charlotte, North Carolina

Jiaxin (Jason) Niu, MD, PhD
MD Anderson Cancer Center
Gilbert, Arizona



Rohit Gosain, MD
UPMC Hillman Cancer Center
Jamestown, New York

Namrata I Peswani, MD
UT Southwestern Medical Center
Harold C Simmons Comprehensive Cancer Center Richardson, Texas

Rao Mushtaq, MD
National Jewish Health
Thornton, Colorado

Ferdy Santiago, MD
Florida Cancer Specialists
Naples, Florida

Jarushka Naidoo, MB BCH,
Johns Hopkins University
Baltimore, Maryland

John Yang, MD
Oncologist
Fall River, Massachusetts

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Meet The Professor with Dr Jänne

INTRODUCTION: Journal Club with Dr Jänne – Part 1

MODULE 1: Case Presentations

MODULE 2: Faculty Survey

MODULE 3: Journal Club with Dr Jänne – Part 2

MODULE 4: Appendix of Key Publications

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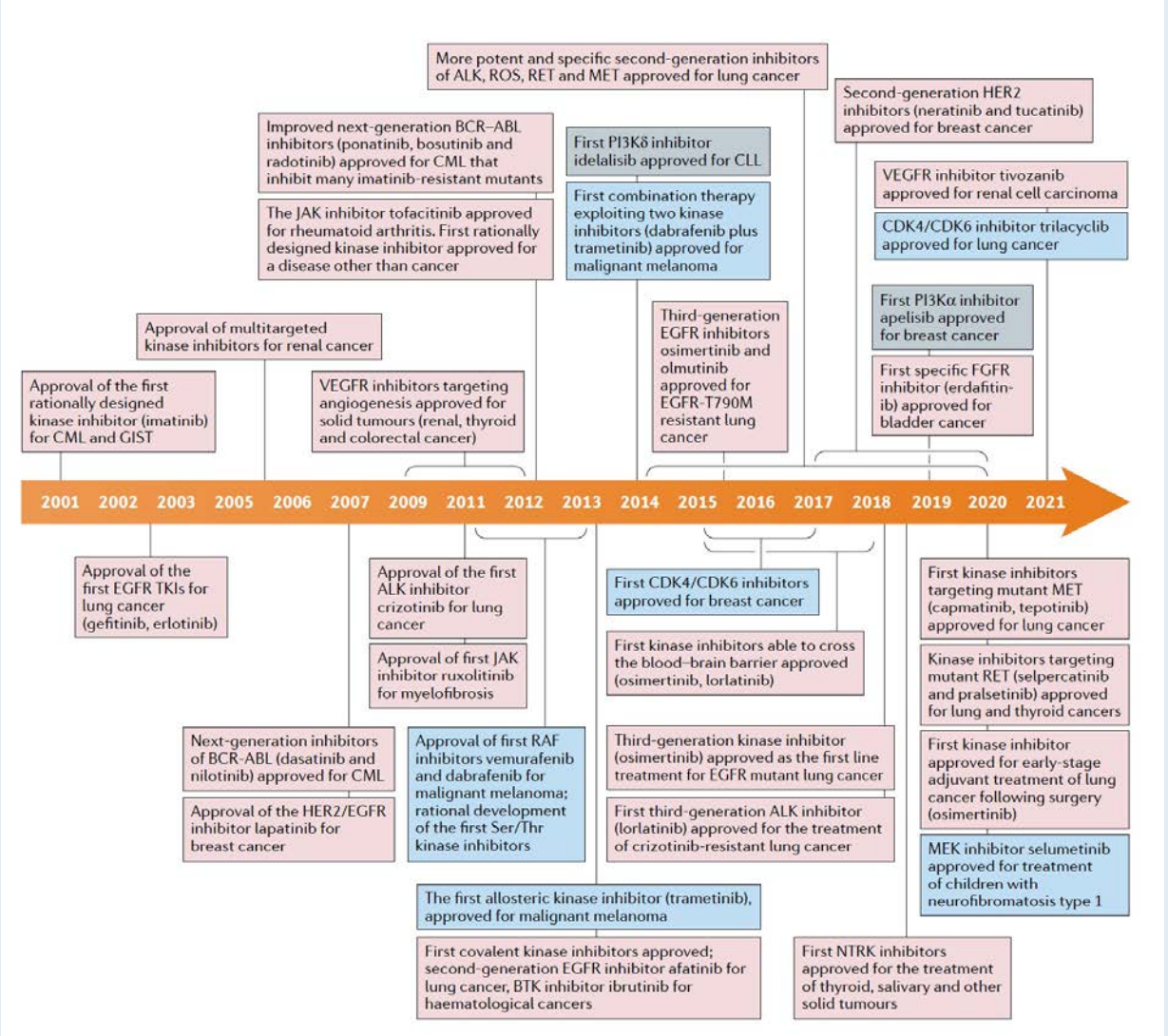
Nat Rev Drug Discov 2021 July;20(7):551-69.

Kinase drug discovery 20 years after imatinib: progress and future directions

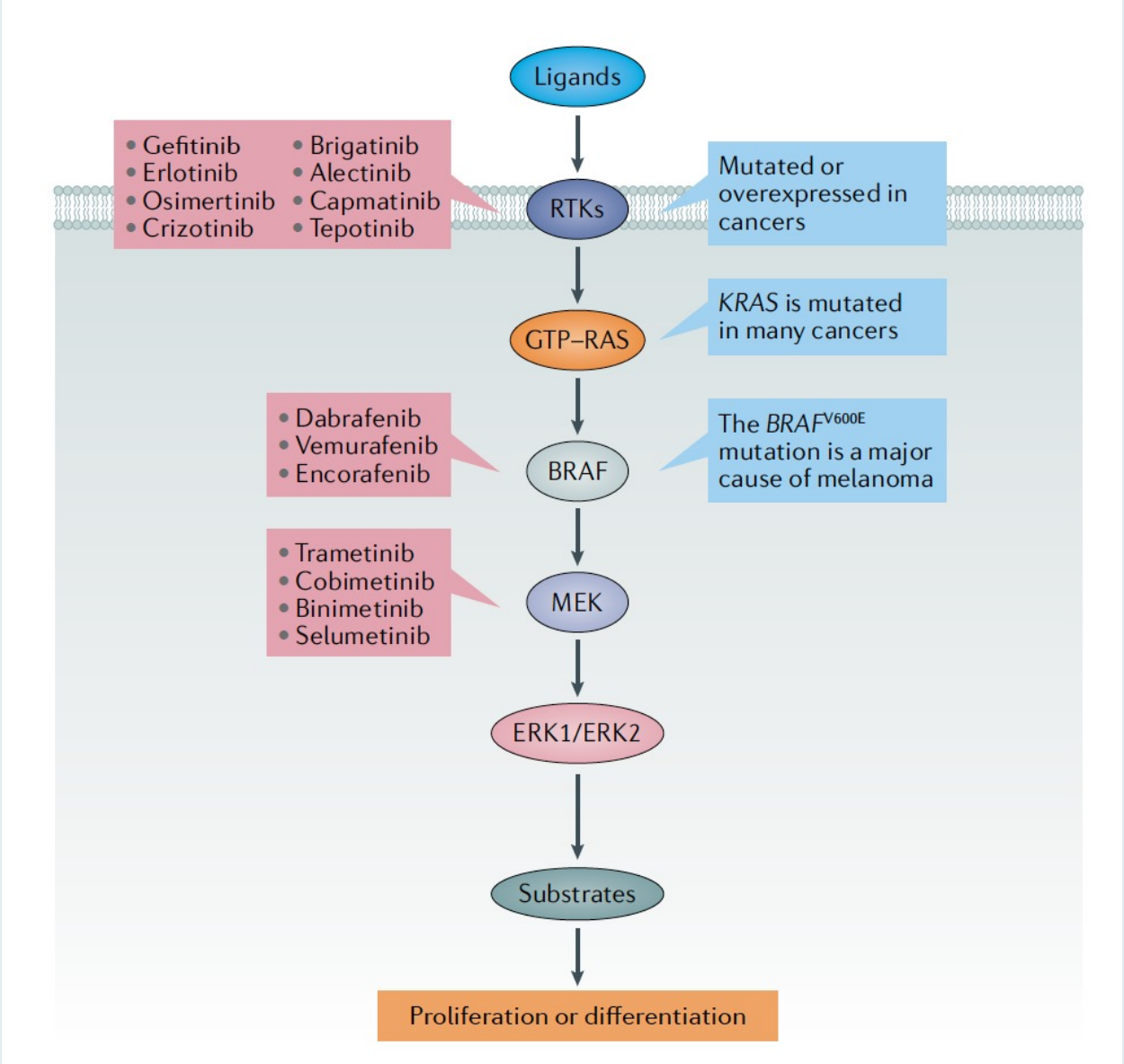
Philip Cohen[1] ✉, *Darren Cross*[2] ✉ *and Pasi A. Jänne*[3] ✉

Timeline Depicting Important Events in the Development and Approval of Kinase Inhibitors Over the 20 Years Following Imatinib's Approval for Treatment of CML in 2001



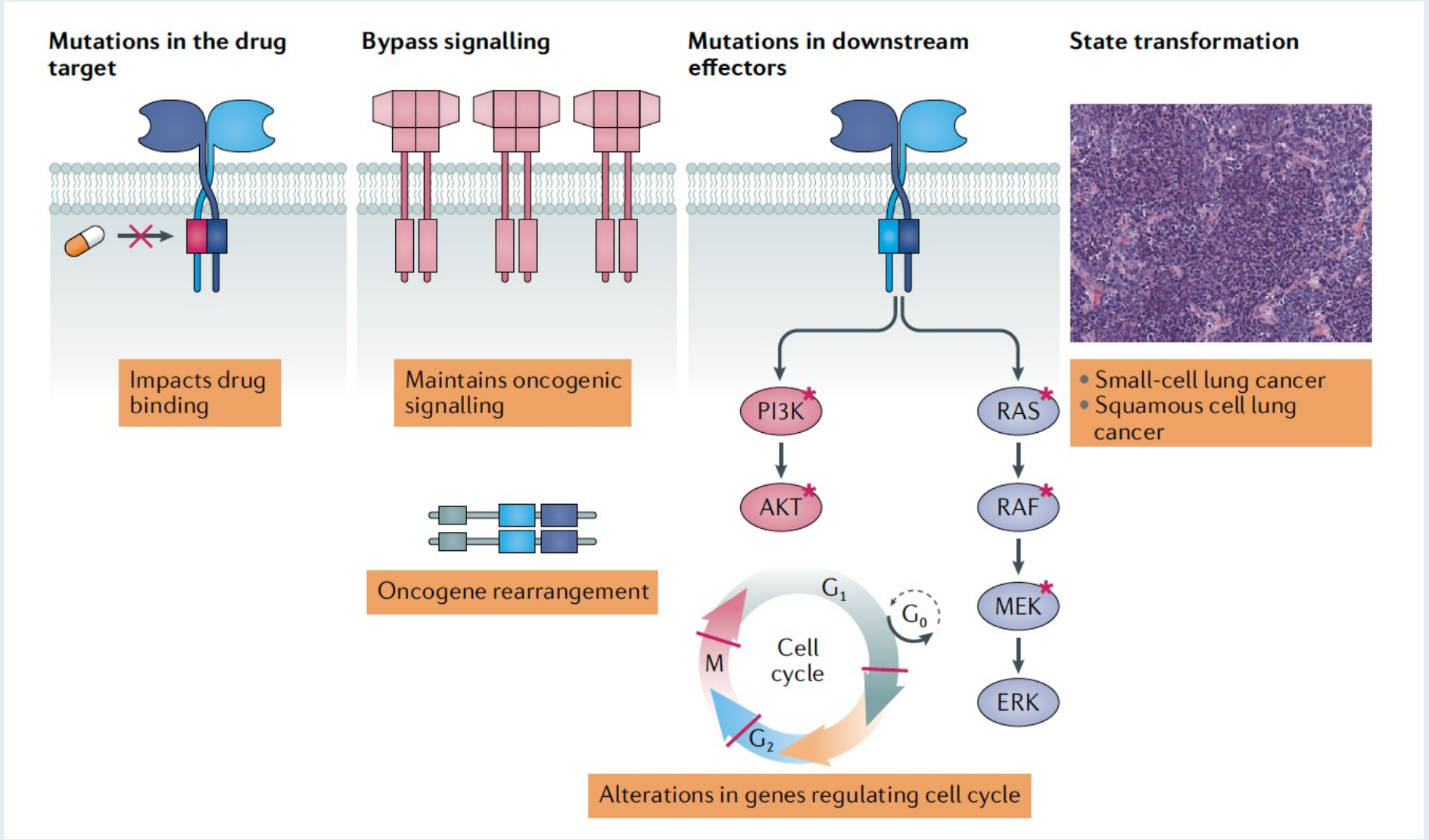
Cohen P et al. *Nat Rev Drug Discov* 2021 July;20(7):551-69.

Mutations in the Classical MAP Kinase Cascade Cause Cancer



Cohen P et al. *Nat Rev Drug Discov* 2021 July;20(7):551-69.

Mechanisms That Can Cause Drug Resistance



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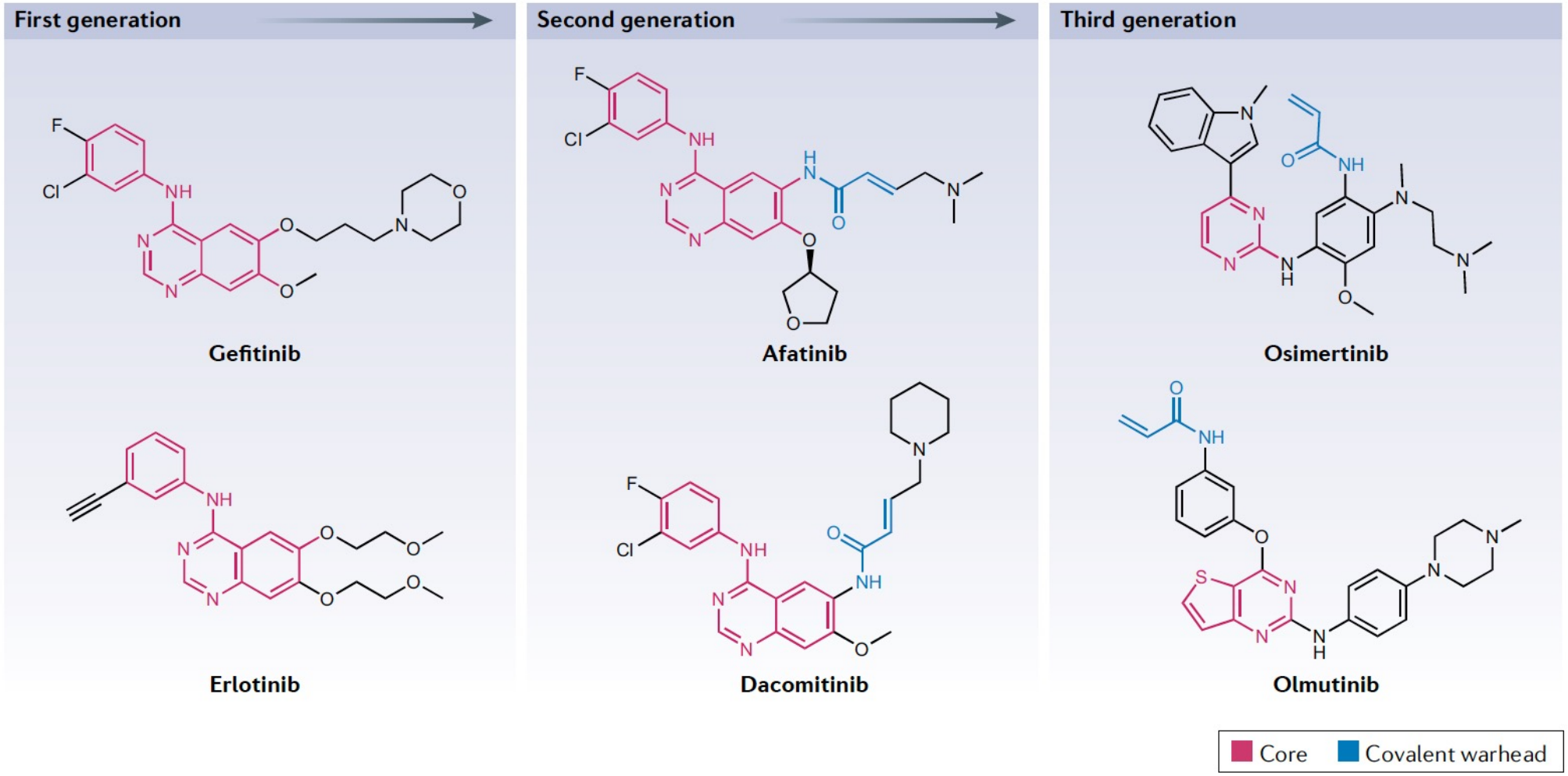
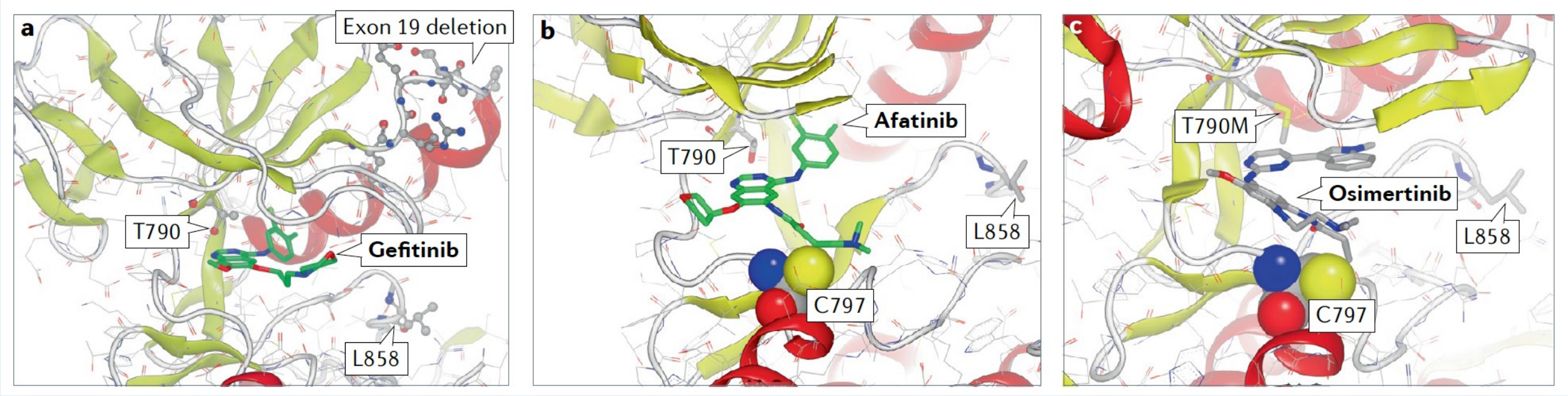
Chemical Structures of First-Generation, Second-Generation and Third-Generation EGFR Inhibitors



Cohen P et al. *Nat Rev Drug Discov* 2021 July;20(7):551-69.

Binding Modes for First-Generation, Second-Generation and Third-Generation EGFR Inhibitors



Cohen P et al. *Nat Rev Drug Discov* 2021 July;20(7):551-69.

nature cancer

Nat Cancer 2021 April;2(4):377-91.

REVIEW ARTICLE

https://doi.org/10.1038/s43018-021-00195-8

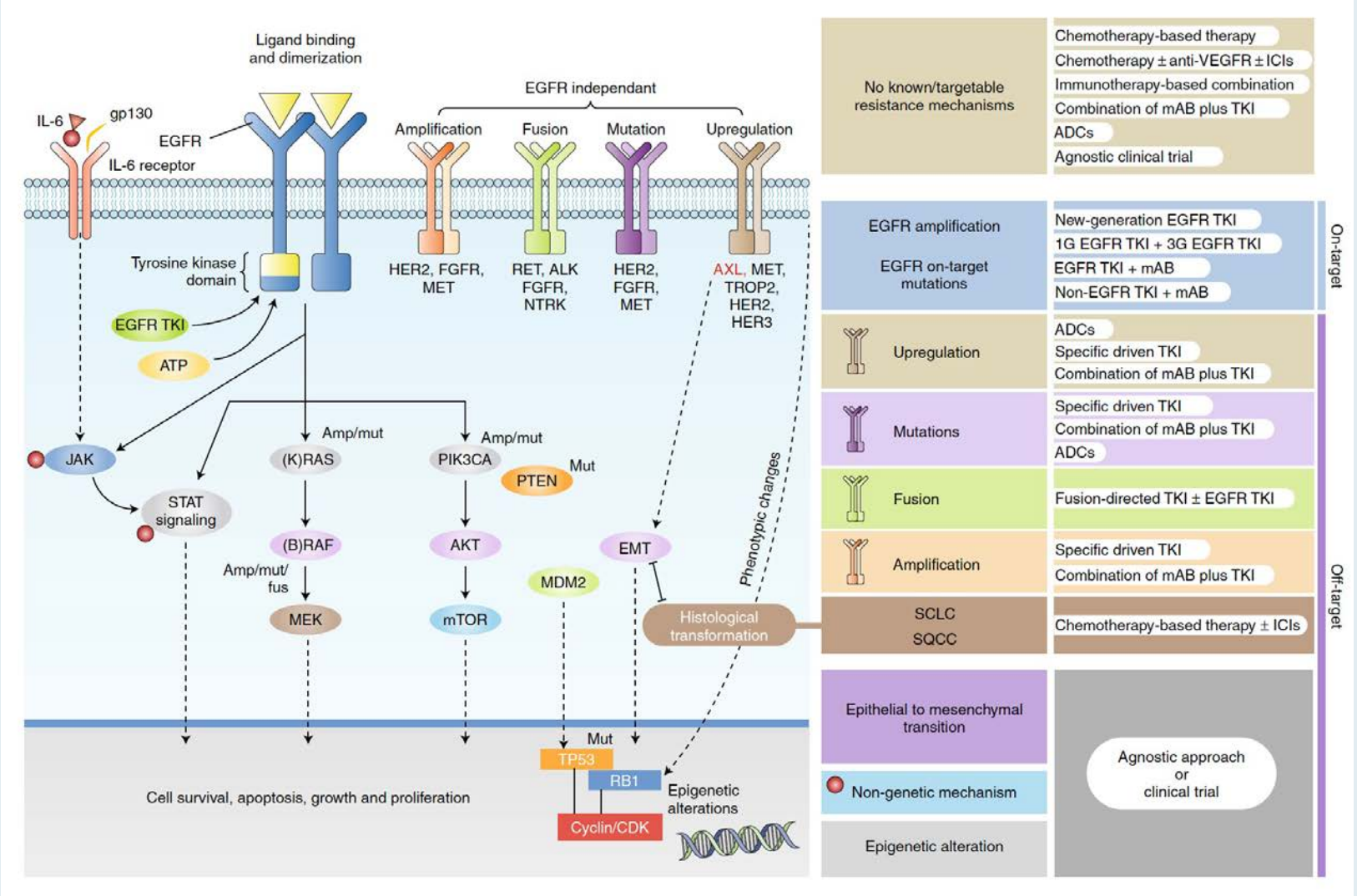
Check for updates

Overcoming therapy resistance in *EGFR*-mutant lung cancer

Antonio Passaro[1]✉, Pasi A. Jänne[2,5], Tony Mok[3,5] and Solange Peters[4,5]

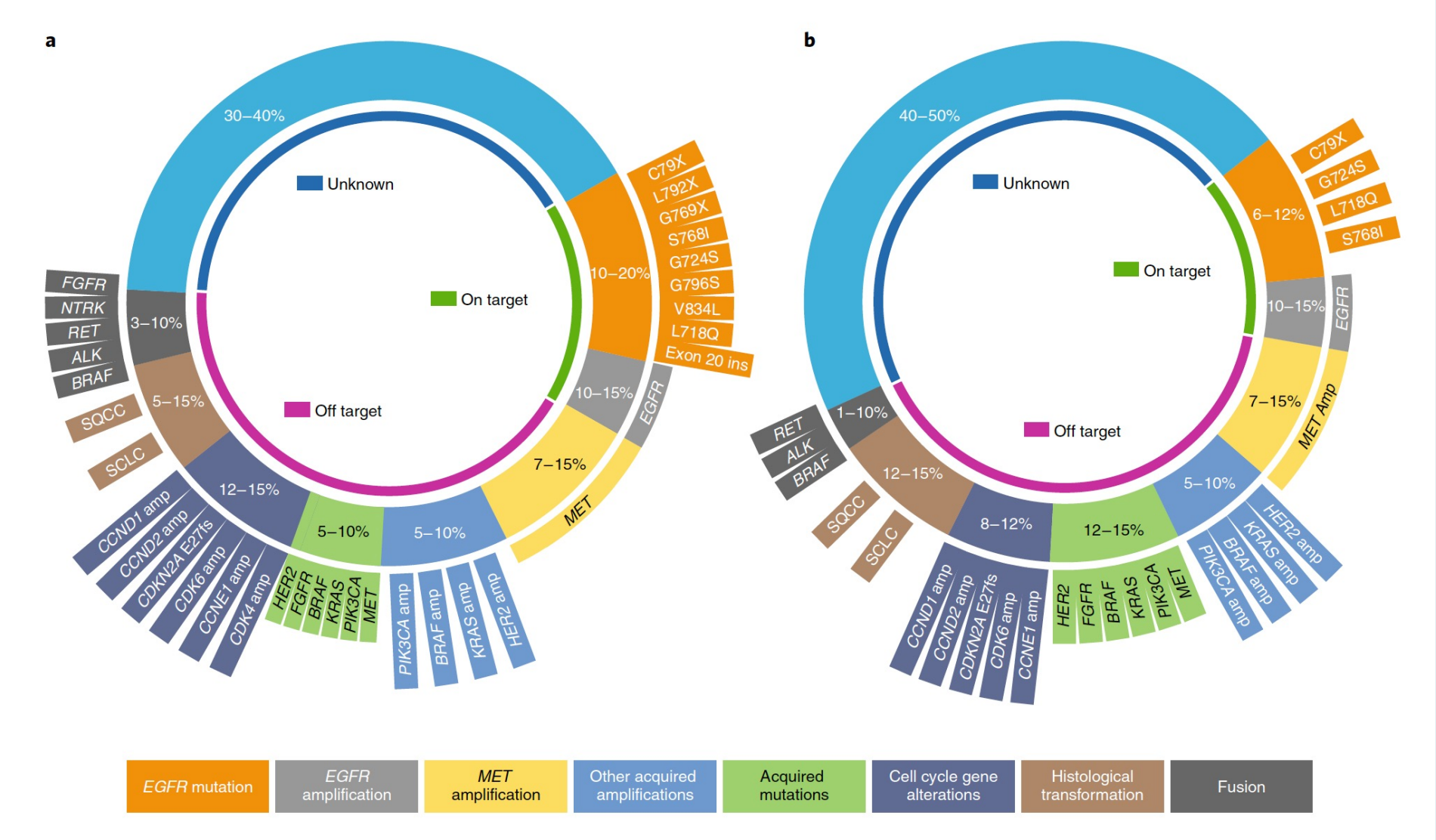
JC JOURNAL CLUB RTP RESEARCH TO PRACTICE

Overview of the EGFR Signal Transduction Pathway Model, with a Focus on the Acquired Resistance Mechanisms and Related Potential Treatment Strategies



Passaro A et al. *Nat Cancer* 2021 April;2(4):377-91 .

Mechanisms of Resistance to Osimertinib



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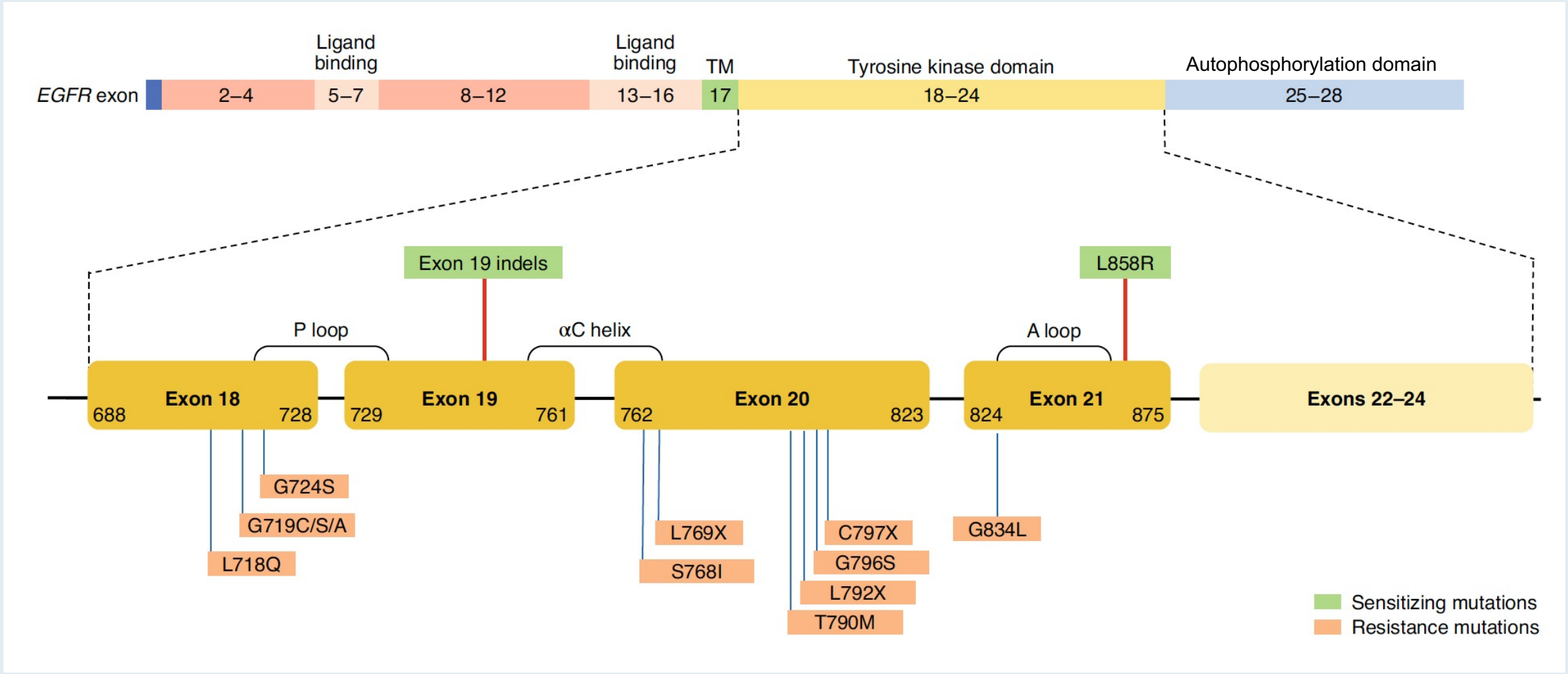
Specific EGFR-Dependent (On-Target) Mutations Acquired After Osimertinib Treatment



Passaro A et al. *Nat Cancer* 2021 April;2(4):377-91 .

Cancer Discov 2021 April;11(4):810-4.

IN FOCUS

The Promising Evolution of Targeted Therapeutic Strategies in Cancer

Solange Peters[1], Tony Mok[2], Antonio Passaro[3], and Pasi Antero Jänne[4]

Meet The Professor with Dr Jänne

MODULE 1: Case Presentations – Part 1

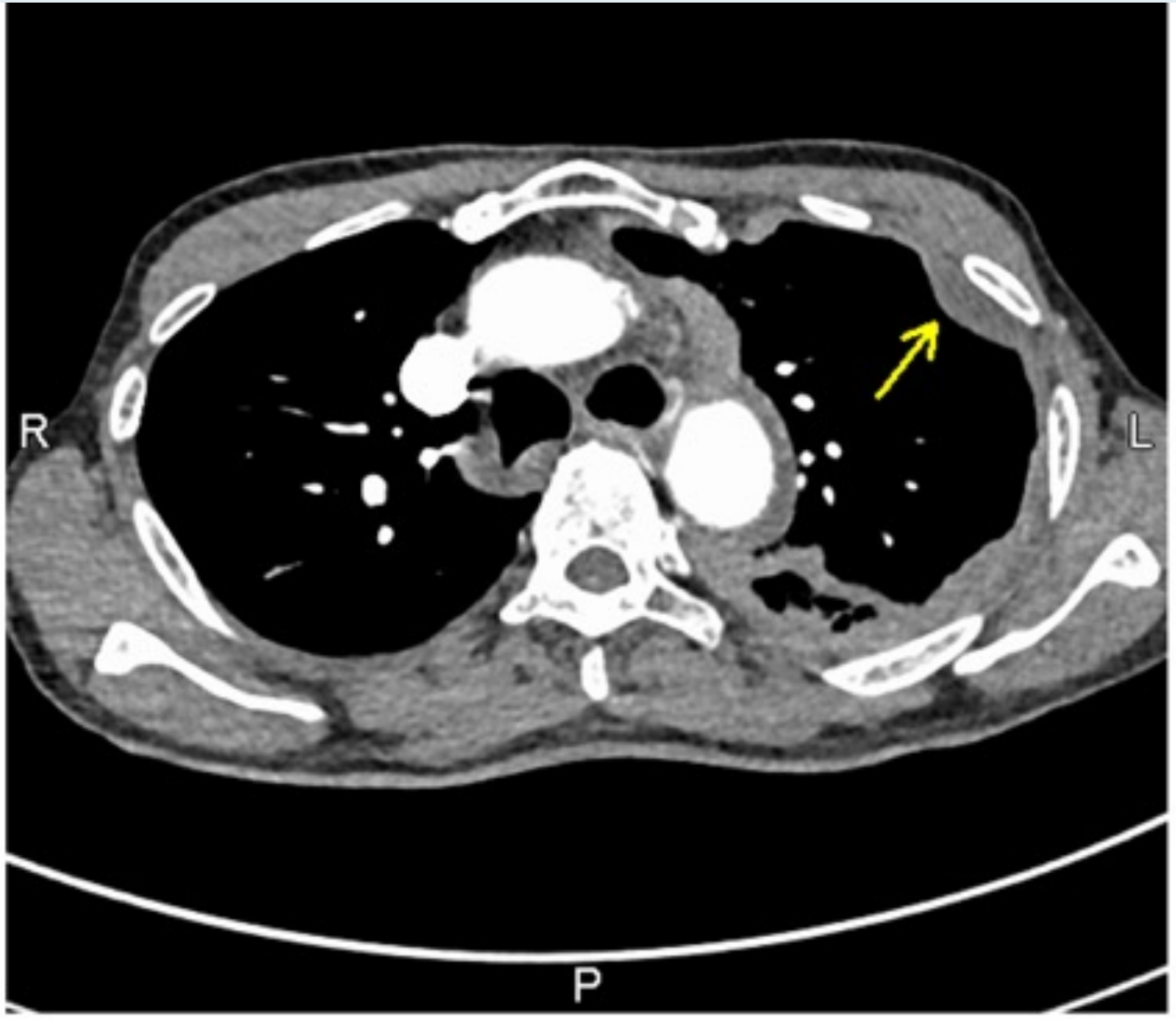
- Dr Dallas: 67-year-old Asian man with adenocarcinoma of the lung and pleural effusion with EGFR amplification – PD-L1 20%
- Dr Gosain: 58-year-old man with metastatic adenocarcinoma of the lung with discordant EGFR testing results and a new mediastinal lesion s/p osimertinib
- Dr Peswani: 48-year-old man with metastatic adenocarcinoma of the lung and a brain metastasis with an EGFR exon 19 mutation and PD s/p SBRT and osimertinib, now with an ALK mutation by RNA testing – PD-L1 0
- Dr Santiago: 53-year-old man with Stage III unresectable adenocarcinoma of the lung who receives chemoRT and consolidation durvalumab, now with EGFR mutation-positive metastatic recurrence
- Dr Naidoo: 70-year-old man with Stage IIIC large cell neuroendocrine carcinoma of the lung and EGFR S768I mutation – PD-L1 1%
- Dr Niu: 81-year-old man with metastatic adenocarcinoma of the lung with an EGFR exon 20 insertion mutation and disease progression on mobocertinib
- Dr Niu: 74-year-old woman with adenocarcinoma of the lung and an EGFR exon 20 insertion mutation with new bone and brain metastases s/p osimertinib

RTP RESEARCH TO PRACTICE

Case Presentation: 67-year-old Asian man with adenocarcinoma of the lung and pleural effusion with EGFR amplification – PD-L1 20%

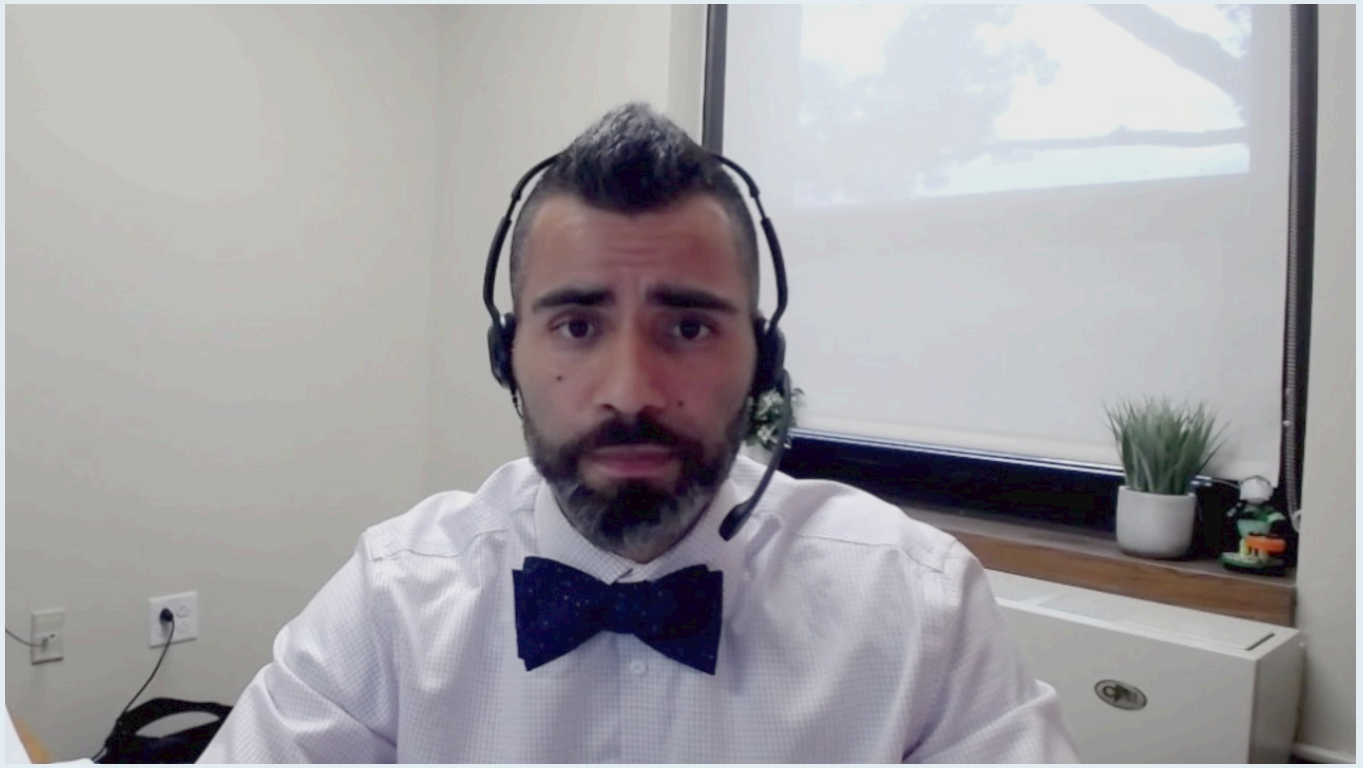
Dr Jennifer Dallas (Charlotte, North Carolina)

RTP
RESEARCH
TO PRACTICE



CT chest with PE protocol shows pleural thickening.

Case Presentation: 58-year-old man with metastatic adenocarcinoma of the lung with discordant EGFR testing results and a new mediastinal lesion s/p osimertinib



Dr Rohit Gosain (Jamestown, New York)

Case Presentation: 48-year-old man with metastatic adenocarcinoma of the lung and a brain metastasis with an EGFR exon 19 mutation and PD s/p SBRT and osimertinib, now with an ALK mutation by RNA testing – PD-L1 0

Dr Namrata Peswani (Richardson, Texas)

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Case Presentation: 53-year-old man with Stage III unresectable adenocarcinoma of the lung who receives chemoRT and consolidation durvalumab, now with EGFR mutation-positive metastatic recurrence

Dr Ferdy Santiago (Naples, Florida)

RTP
RESEARCH
TO PRACTICE

Case Presentation: 70-year-old man with Stage IIIC large cell neuroendocrine carcinoma of the lung and EGFR S768I mutation – PD-L1 1%

Dr Jarushka Naidoo (Baltimore, Maryland)

RTP RESEARCH TO PRACTICE

Case Presentation: 81-year-old man with metastatic adenocarcinoma of the lung with an EGFR exon 20 insertion mutation and disease progression on mobocertinib

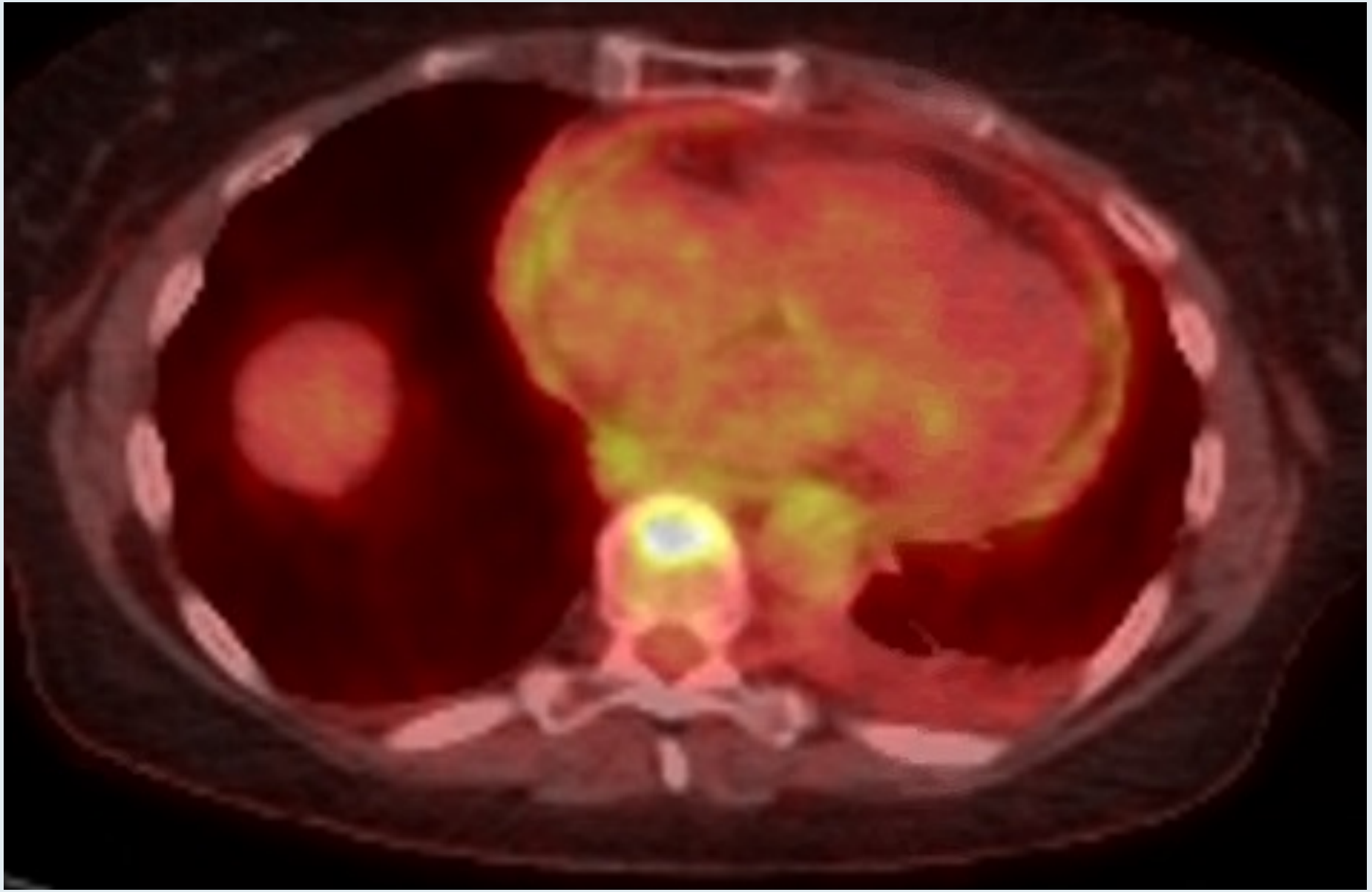
Dr Jason Niu (Gilbert, Arizona)

RTP
RESEARCH
TO PRACTICE

Case Presentation: 74-year-old woman with adenocarcinoma of the lung and an EGFR exon 20 insertion mutation with new bone and brain metastases s/p osimertinib

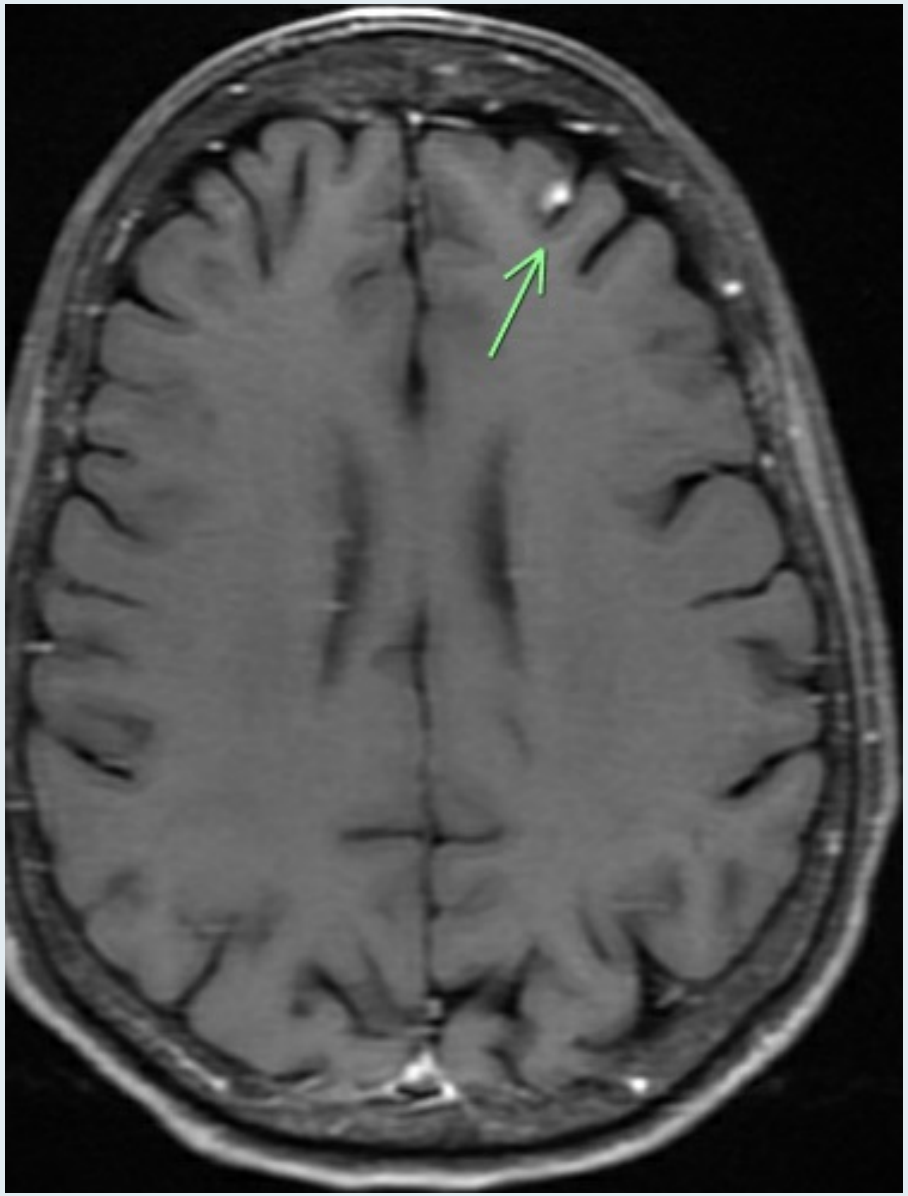
Dr Jason Niu (Gilbert, Arizona)

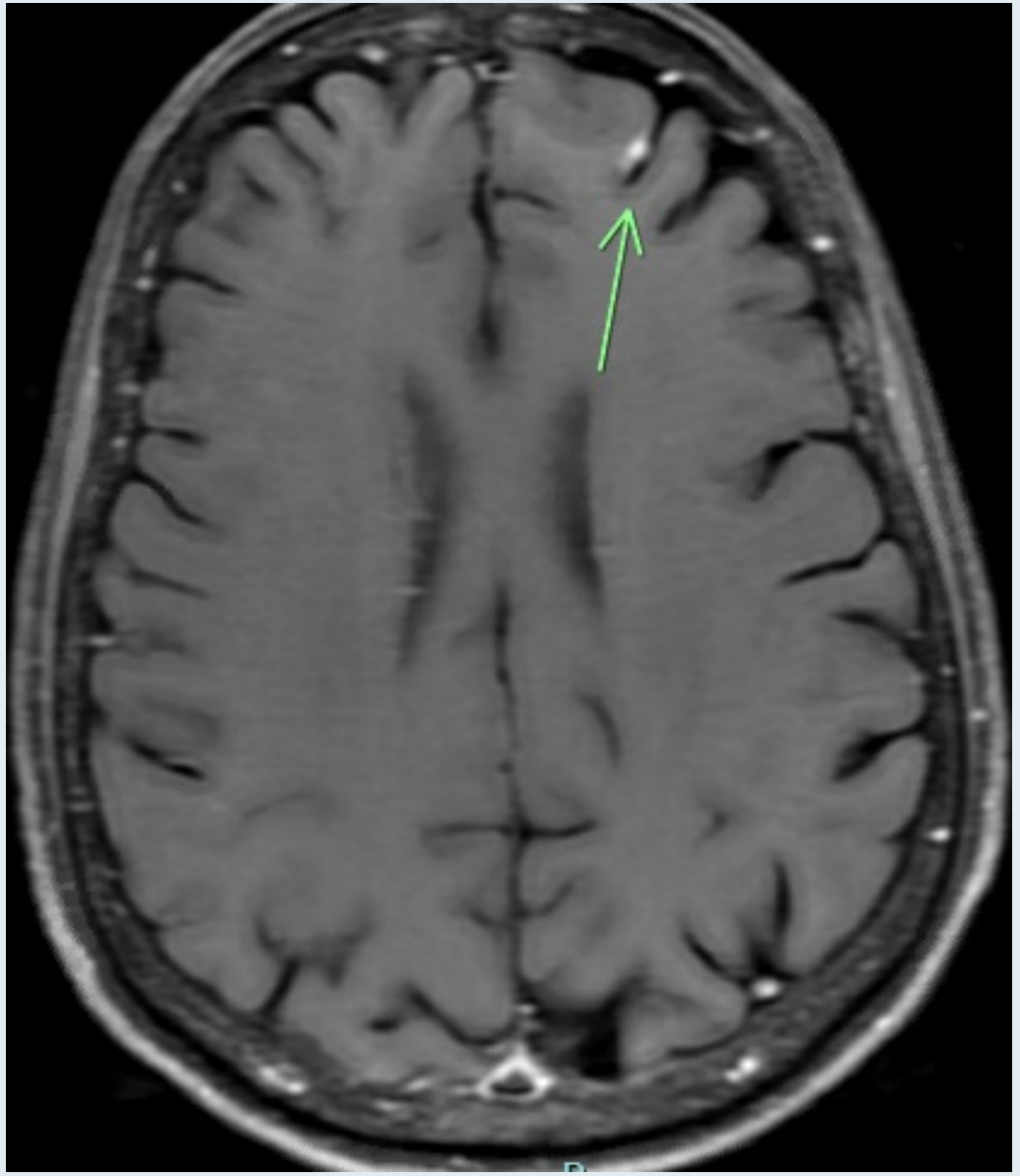
RTP
RESEARCH
TO PRACTICE



3/2021: Left pleural effusion

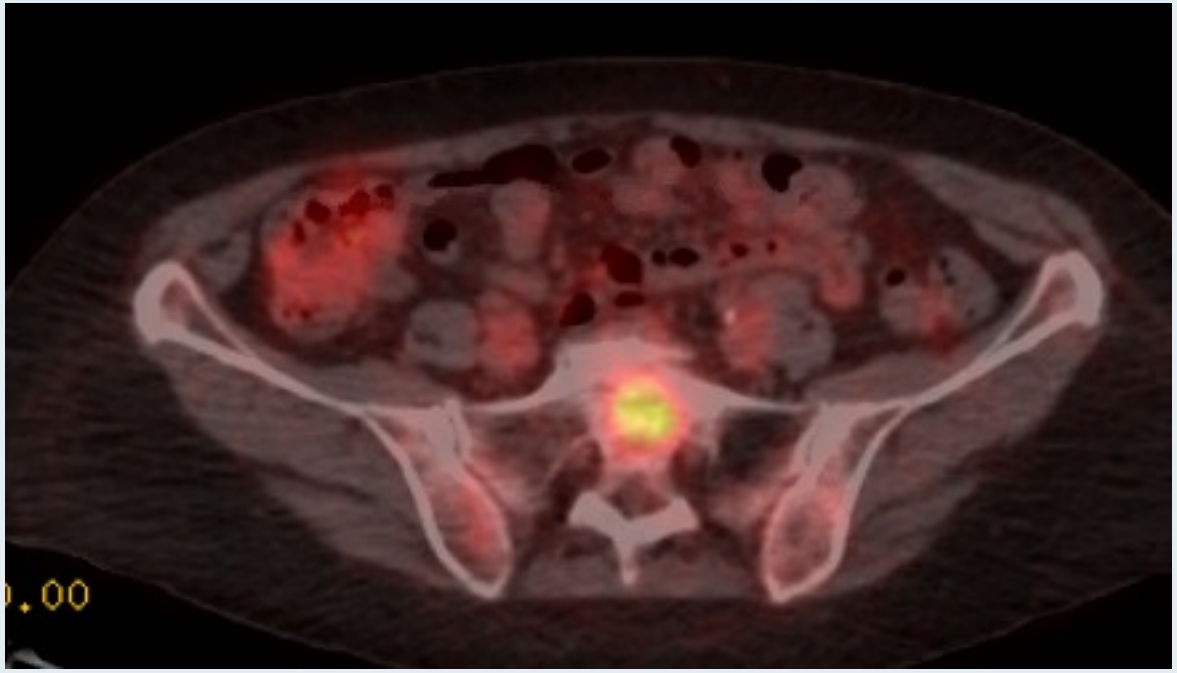
RTP
RESEARCH
TO PRACTICE



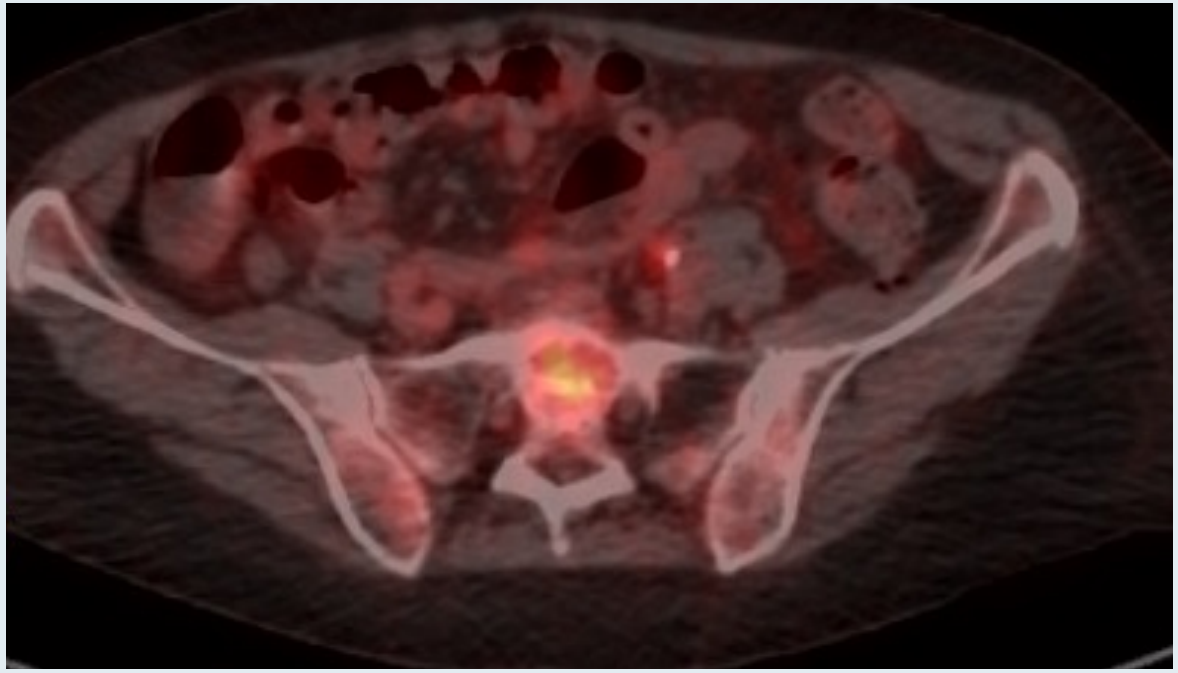


1/2022: Solitary brain metastases

RTP
RESEARCH
TO PRACTICE



1/2022



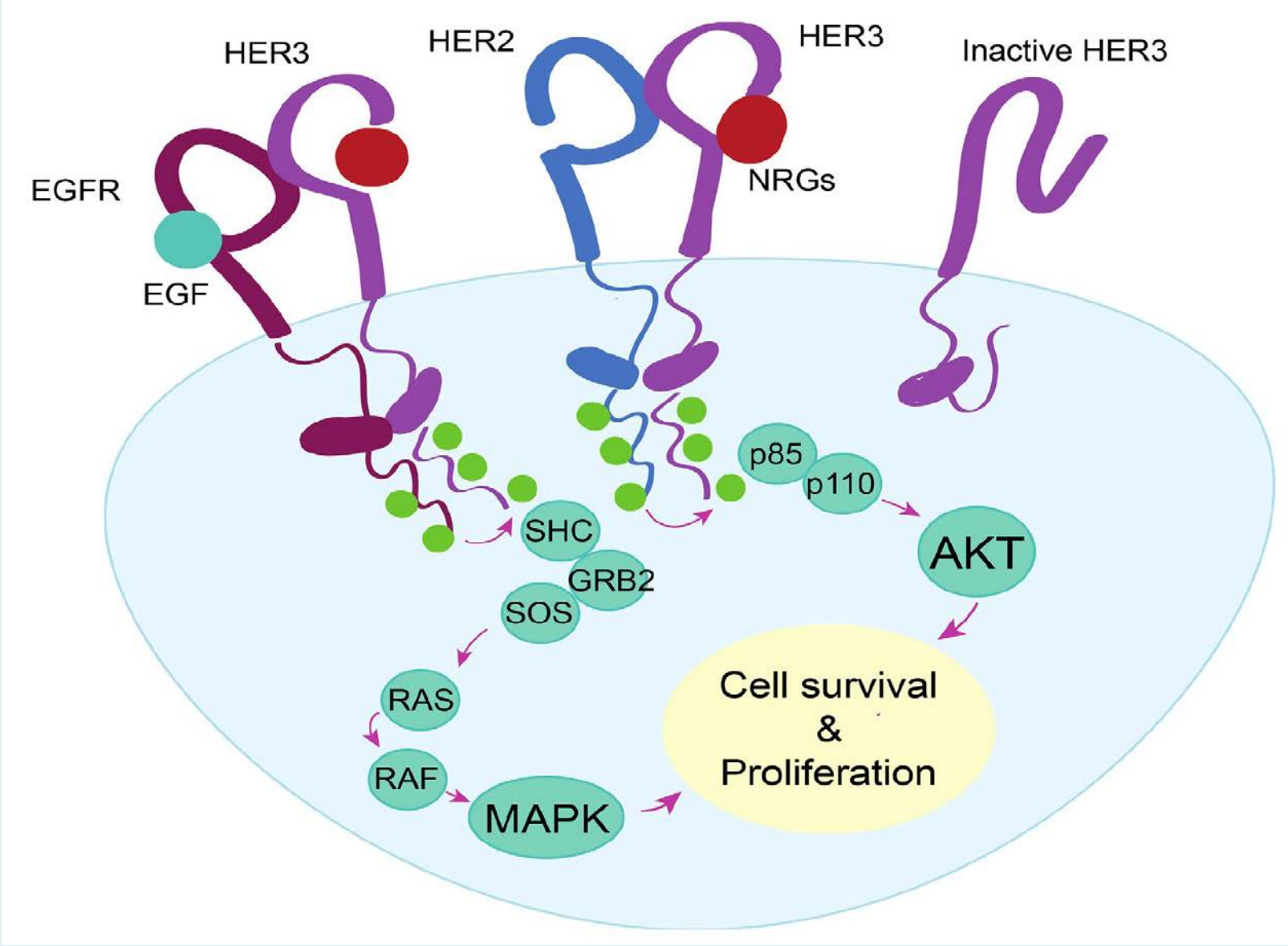
3/2022

Clin Cancer Res. 2021 July 01; 27(13): 3528–3539.

30 years of HER3: From basic biology to therapeutic interventions

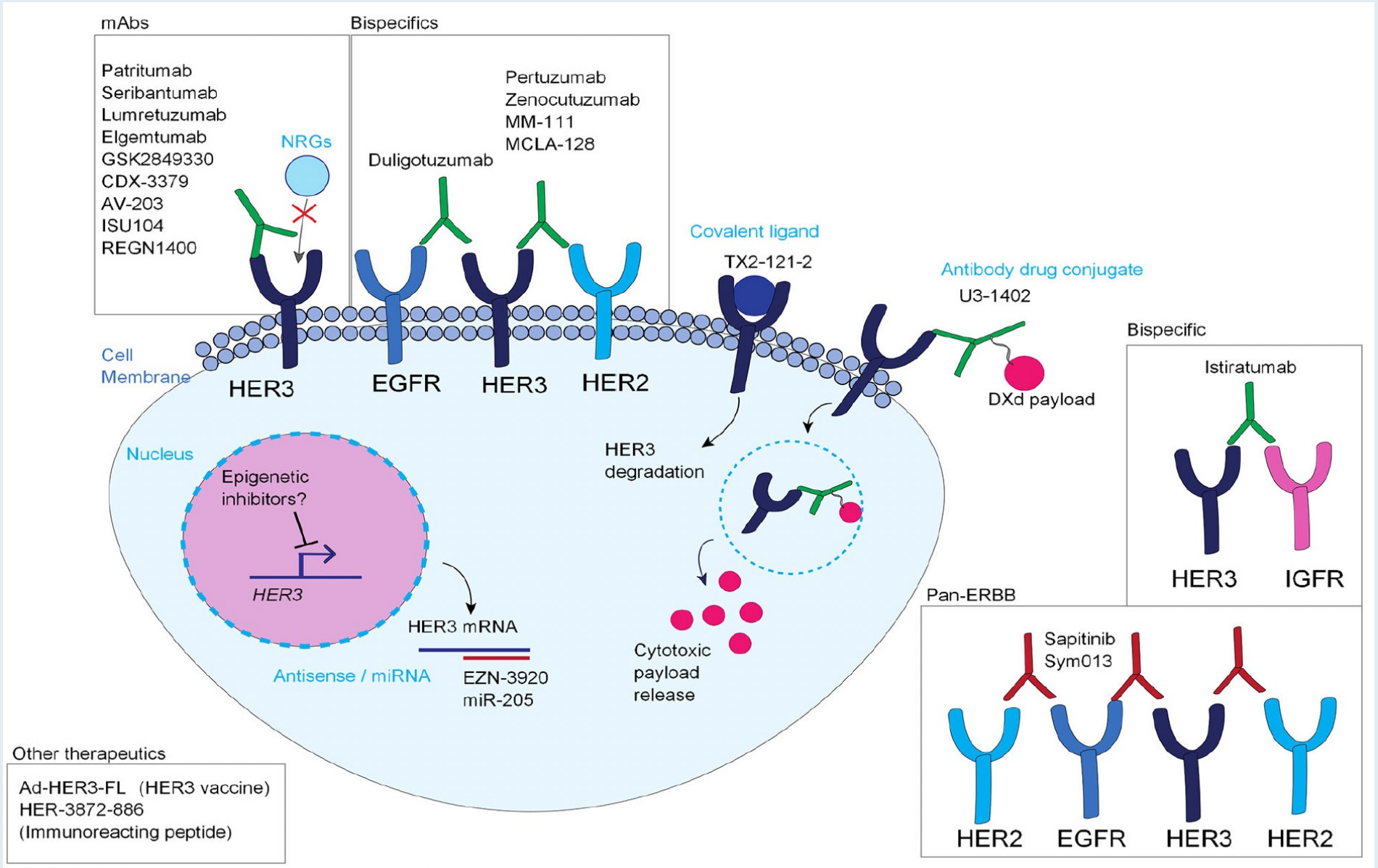
Heidi M. Haikala[1,2], **Pasi A. Jänne**[1,2,*]

HER3 Dimerization and Signaling Cascade



Haikala HM, Jänne PA. *Clin Cancer Res* 2021;27(13):3528-39.

Therapeutic Strategies to Target HER3



Haikala HM, Jänne PA. *Clin Cancer Res* 2021;27(13):3528-39.

Phase 1 Study of Patritumab Deruxtecan (HER3-DXd; U3-1402) in Combination with Osimertinib in Patients with Advanced EGFR-Mutated NSCLC

Janne PA et al.

ASCO 2022;Abstract TPS3161.

Cancer Discov 2022 January;12(1):74-89.

RESEARCH ARTICLE

Efficacy and Safety of Patritumab Deruxtecan (HER3-DXd) in EGFR Inhibitor–Resistant, *EGFR*-Mutated Non–Small Cell Lung Cancer

Pasi A. Jänne[1], Christina Baik[2], Wu-Chou Su[3], Melissa L. Johnson[4], Hidetoshi Hayashi[5], Makoto Nishio[6], Dong-Wan Kim[7], Marianna Koczywas[8], Kathryn A. Gold[9], Conor E. Steuer[10], Haruyasu Murakami[11], James Chih-Hsin Yang[12], Sang-We Kim[13], Michele Vigliotti[14], Rong Shi[14], Zhenhao Qi[14], Yang Qiu[14], Lihui Zhao[14], David Sternberg[14], Channing Yu[14], and Helena A. Yu[15]

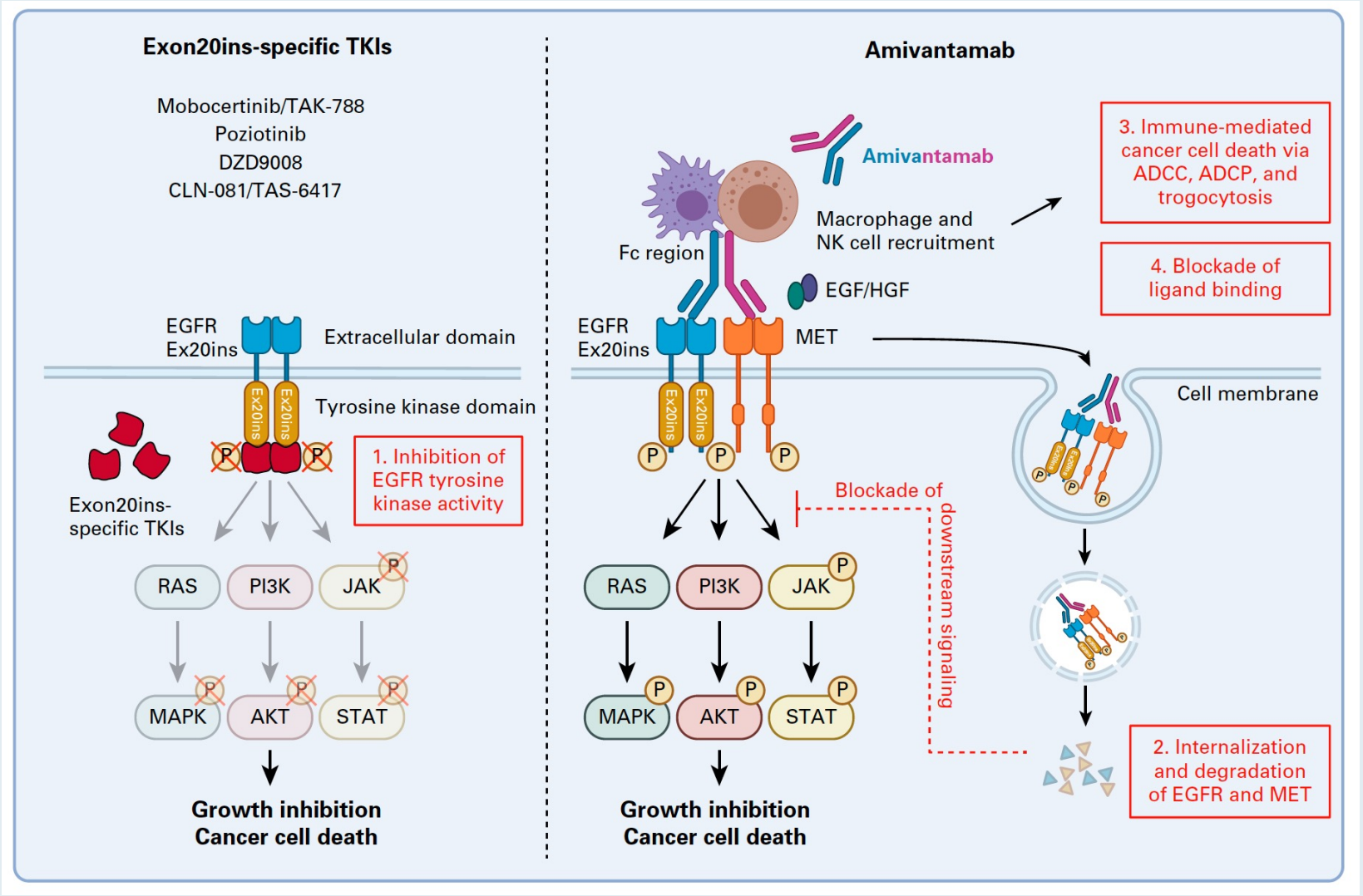
Amivantamab: Treating *EGFR* Exon 20–Mutant Cancers With Bispecific Antibody-Mediated Receptor Degradation

Jens Köhler, MD[1] and Pasi A. Jänne, MD, PhD[1,2,3]

J Clin Oncol 2021 October 20;39(30):3403-6.

JC JOURNAL CLUB RTP RESEARCH TO PRACTICE

The New Generation of TKIs Selective to EGFR Exon 20 Insertion Mutations (EGFR Ex20ins) Inactivates EGFR Downstream Signaling via the RAS-MAPK, PI3K-AKT-mTOR and JAK-STAT Pathways



Kohler J et al. *J Clin Oncol* 2021 October 20;39(30):3403-6.

2022 ASCO® ANNUAL MEETING

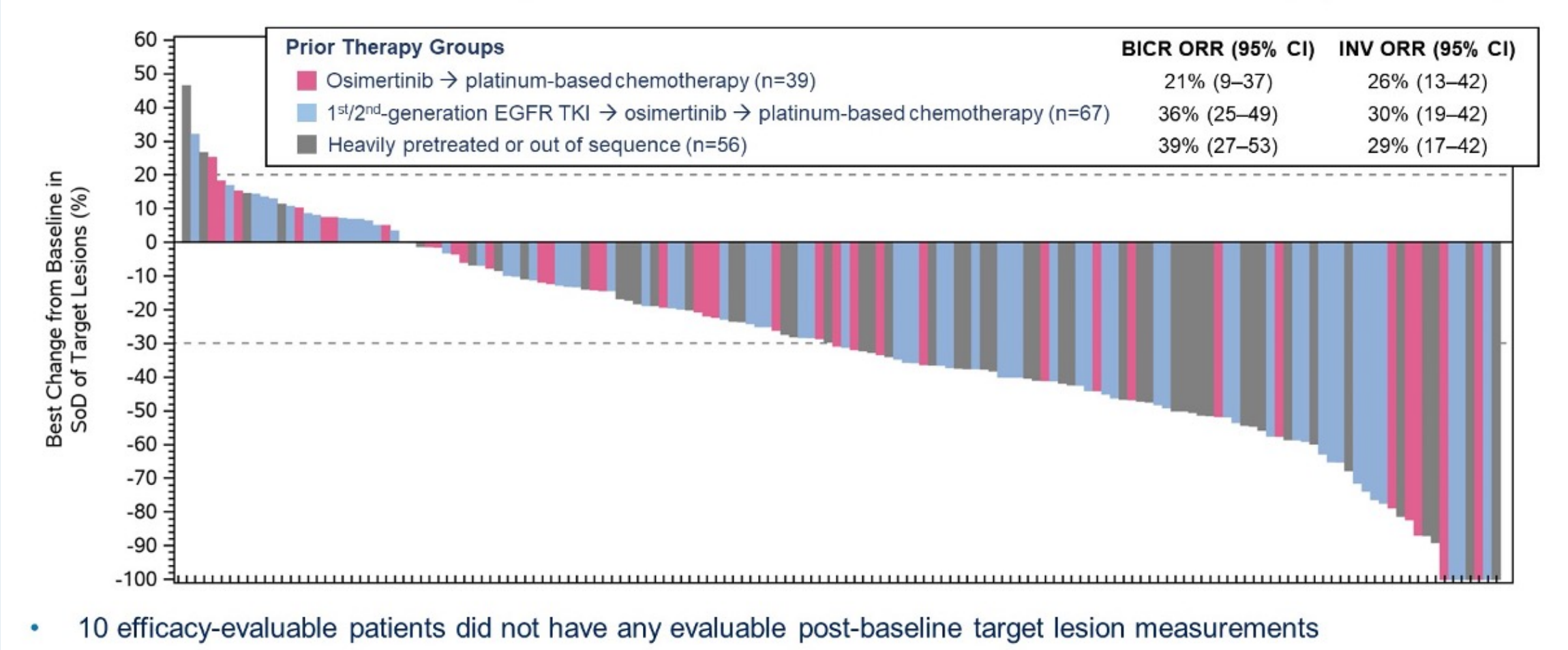
Abstract 9006

Amivantamab and lazertinib in patients with EGFR-mutant non-small cell lung cancer (NSCLC) after progression on osimertinib and platinum-based chemotherapy: Updated results from CHRYSALIS-2

Catherine A. Shu,[1] Koichi Goto,[2] Yuichiro Ohe,[3] Benjamin Besse,[4] Se-Hoon Lee,[5] Yongsheng Wang,[6] Frank Griesinger,[7] James Chih-Hsin Yang,[8] Enriqueta Felip,[9] Rachel E. Sanborn,[10] Reyes Bernabe Caro,[11] Joshua C. Curtin,[12] Jun Chen,[12] Janine Mahoney,[12] Leonardo Trani,[12] Joshua M. Bauml,[12] Meena Thayu,[12] Roland E. Knoblauch,[12] Byoung Chul Cho[13]

[1]Columbia University Medical Center, New York, NY, USA; [2]National Cancer Center Hospital East, Kashiwa, Japan; [3]National Cancer Center Hospital, Tokyo, Japan; [4]Paris-Sacaly University, Institut Gustave Roussy, Villejuif, France; [5]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [6]Institute of Clinical Trial Center and Cancer Center, West China Hospital, Sichuan University, Chengdu, China; [7]Pius-Hospital, University of Oldenburg, Oldenburg, Germany; [8]National Taiwan University Cancer Center, Taipei, Taiwan; [9]Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Spain; [10]Earle A. Chiles Research Institute, Providence Cancer Institute, Portland, OR, USA; [11]Hospital Universitario Virgen Del Rocio, Seville, Spain; [12]Janssen R&D, Spring House, PA, USA; [13]Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea

CHRYSALIS-2: Best Antitumor Response and ORR by Prior Therapy Group



BICR = blinded independent central review; ORR = overall response rate; INV = investigator

Shu CA et al. ASCO 2022;Abstract 9006.

2022 ASCO® ANNUAL MEETING

Abstract 9008

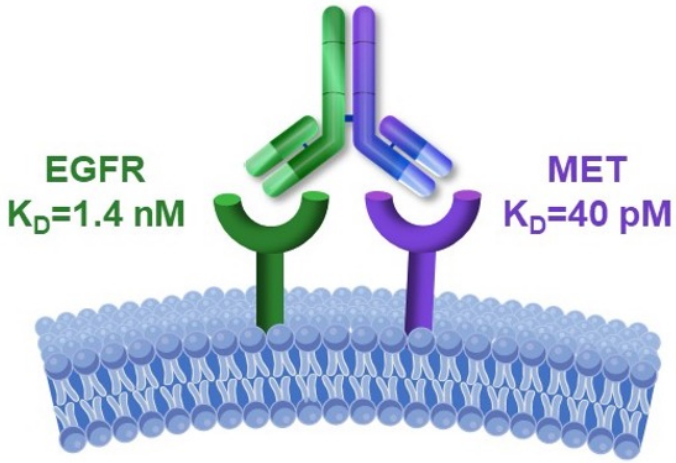
Amivantamab in NSCLC patients with MET exon 14 skipping mutation: Updated results from the CHRYSALIS study

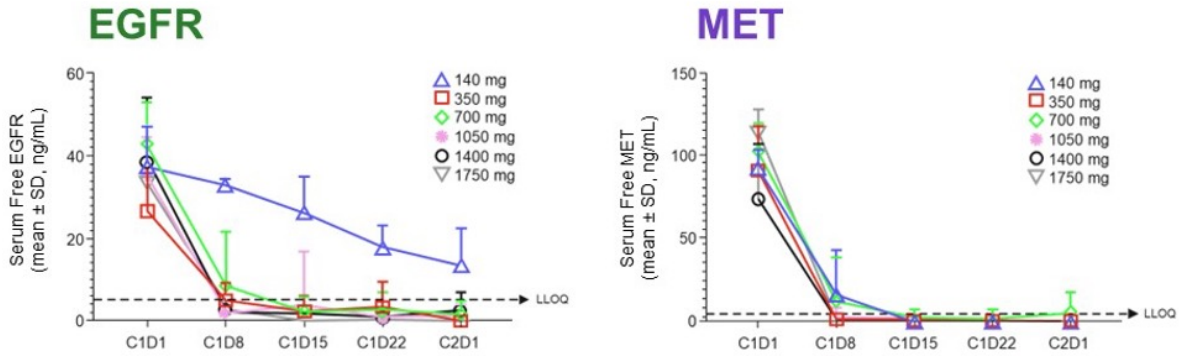
Matthew G. Krebs,[1] Alexander I. Spira,[2] Byoung Chul Cho,[3] Benjamin Besse,[4] Jonathan W. Goldman,[5] Pasi A. Jänne,[6] Zhiyong Ma,[7] Aaron S. Mansfield,[8] Anna Minchom,[9] Sai-Hong Ignatius Ou,[10] Ravi Salgia,[11] Zhijie Wang,[12] Casilda Llacer Perez,[13] Grace Gao,[14] Joshua C. Curtin,[14]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





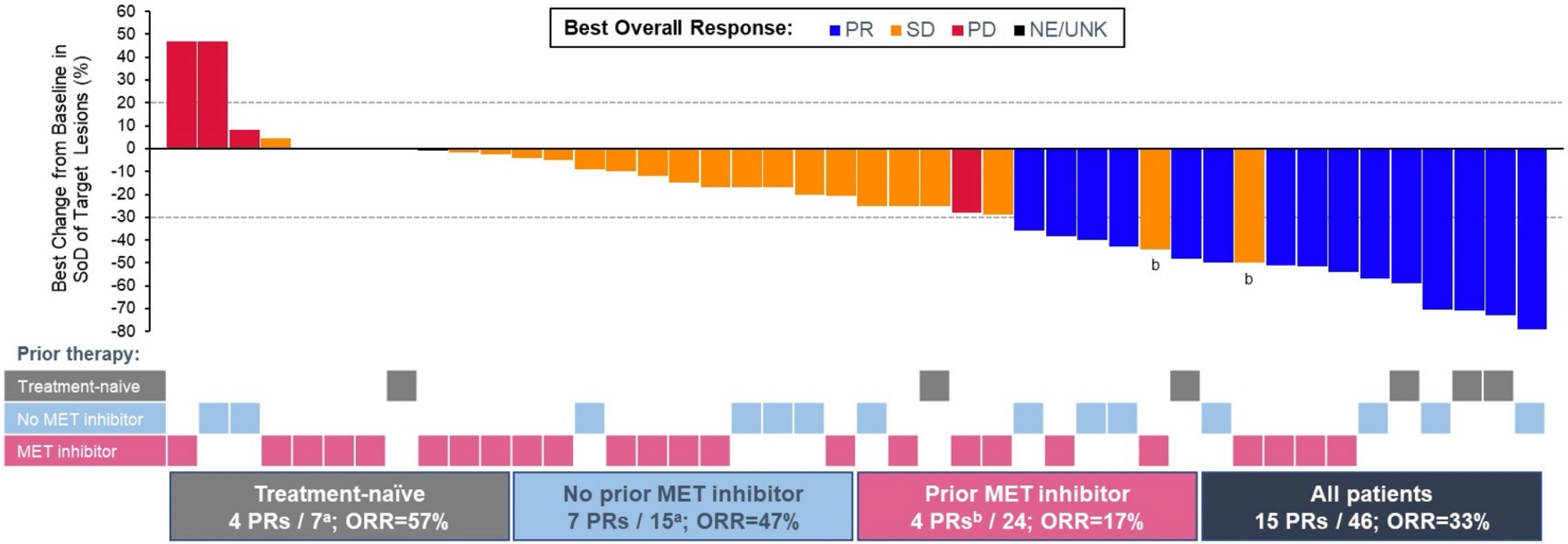
C, cycle; D, day; DOR, duration of response; EGFR, epidermal growth factor receptor; EGFRm, EGFR-mutated; ex20ins, exon 20 insertion mutations; K_D, dissociation constant; LLOQ, lower limit of quantification; NSCLC, non-small cell lung cancer; ORR, overall response rate; SD, standard deviation; sEGFR,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

Antitumor Activity of Amivantamab Monotherapy

- A total of 46 patients were efficacy evaluable

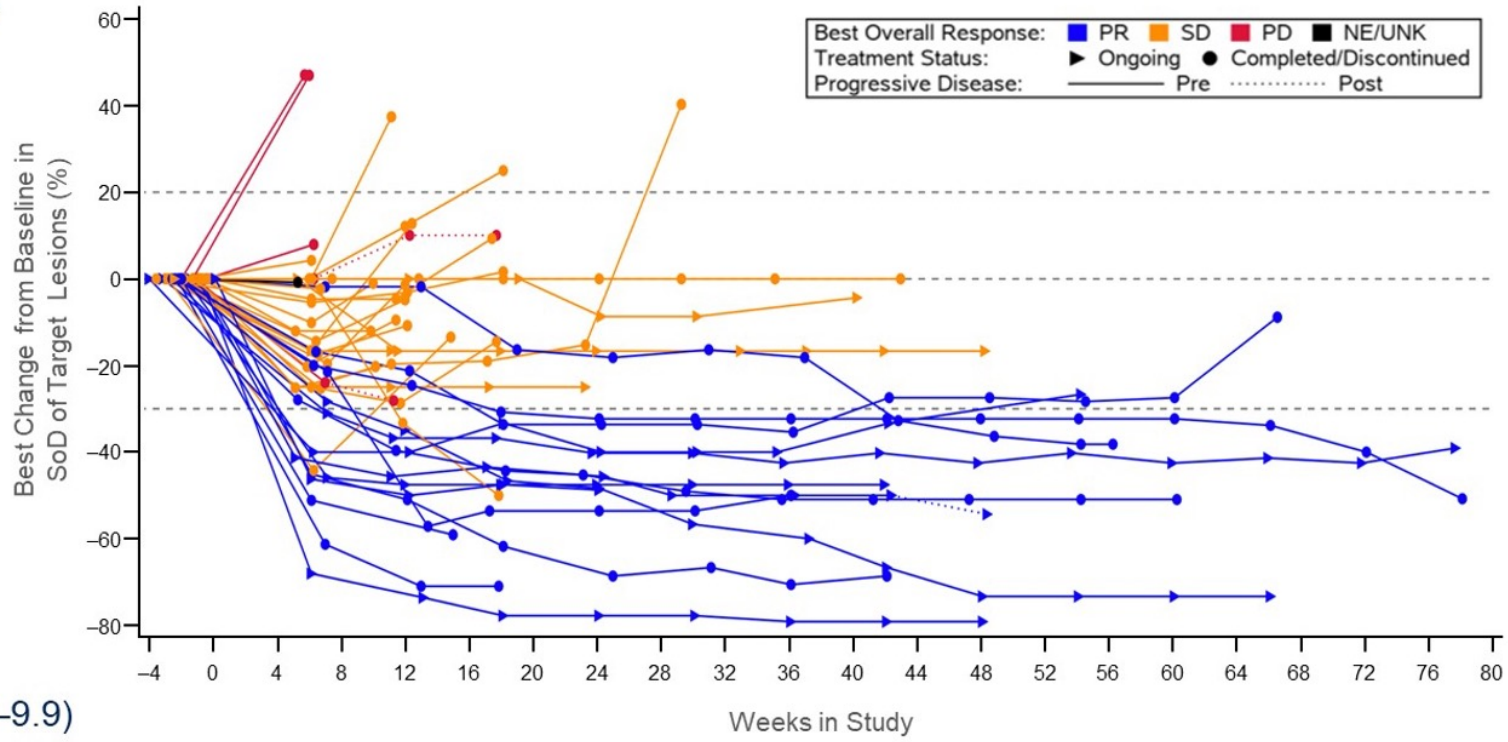


[a]Two patients discontinued prior to completing their secondpostbaseline disease assessment (1 in treatment naïve group and 1 in no prior MET inhibitor group). [b]Two additional patients had a best timepoint response of PR but did not confirm. NE/UNK, not evaluable/unknown; ORR, overall response rate;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

Krebs MG et al. ASCO 2022;Abstract 9008.

Durable Responses to Amivantamab over Time

- 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)



[a]Percentage of patients with confirmed response or SD of ≥11 weeks duration. CI, confidence interval; NE/UNK, not evaluable/unknown; mo, month; PD, progressive disease; PR, partial response; SD, stable disease.

Krebs MG et al. ASCO 2022;Abstract 9008.

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

[a]Rash-related terms include rash, dermatitis acneiform, acne, blister, dermatitis, dermatitis atopic, dermatitis exfoliative generalized, dermatitis infected, eczema asteatotic, erythema, erythema multiforme, folliculitis, hand dermatitis, macule, palmar-plantar erythrodysaesthesia syndrome, perineal rash, perioral dermatitis, pustule, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, skin exfoliation, skin lesion, and toxic epidermal necrolysis; cumulative grouped rash-related AEs occurred 39 (69%; grade ≥3, 2 [4%]) patients for the METex14 subset. AE, adverse event; ILD, interstitial lung disease; METex14, MET exon 14 skipping mutations; RP2D, recommended phase-2 dose; TEAE, treatment-emergent AE.

Krebs MG et al. ASCO 2022;Abstract 9008.

Mobocertinib (TAK-788) in EGFR Exon 20 Insertion (ex20ins) + Metastatic Non-Small Cell Lung Cancer (mNSCLC): Treatment (tx) Beyond Progressive Disease (PD) in Platinum-Pretreated Patients (pts) with and without Intracranial PD

Janne PA et al.

ASCO 2022;Abstract 9099.

Research

JAMA Oncology | Original Investigation

Treatment Outcomes and Safety of Mobocertinib in Platinum-Pretreated Patients With *EGFR* Exon 20 Insertion–Positive Metastatic Non–Small Cell Lung Cancer

A Phase 1/2 Open-label Nonrandomized Clinical Trial

Caicun Zhou, PhD, MD; Suresh S. Ramalingam, MD; Tae Min Kim, MD, PhD; Sang-We Kim, MD; James Chih-Hsin Yang, MD; Gregory J. Riely, MD; Tarek Mekhail, MD; Danny Nguyen, MD; Maria R. Garcia Campelo, MD; Enriqueta Felip, MD; Sylvie Vincent, PhD; Shu Jin, MS; Celina Griffin, PharmD; Veronica Bunn, PhD; Jianchang Lin, PhD; Huamao M. Lin, PhD; Minal Mehta, MBBS; Pasi A. Jänne, MD, PhD

JAMA Oncol 2021;7(12):e214761.

Antitumor Activity of Sunvozertinib in NSCLC Patients with EGFR Exon20 Insertion Mutations after Platinum and Anti-PD(L)1 Treatment Failures

Janne PA et al.

ASCO 2022;Abstract 9015.

Cancer Discov 2022;12(7):1676-89.

RESEARCH ARTICLE

Sunvozertinib, a Selective EGFR Inhibitor for Previously Treated Non–Small Cell Lung Cancer with *EGFR* Exon 20 Insertion Mutations

Mengzhao Wang[1], James Chih-Hsin Yang[2], Paul L. Mitchell[3], Jian Fang[4], D. Ross Camidge[5], Weiqi Nian[6], Chao-Hua Chiu[7], Jianying Zhou[8], Yanqiu Zhao[9], Wu-Chou Su[10], Tsung-Ying Yang[11], Viola W. Zhu[12], Michael Millward[13], Yun Fan[14], Wen-Tsung Huang[15], Ying Cheng[16], Liyan Jiang[17], Daniel Brungs[18], Lyudmila Bazhenova[19], Chee Khoon Lee[20], Bo Gao[21], Yan Xu[1], Wei-Hsun Hsu[22], Li Zheng[23], and Pasi A. Jänne[24]

Sunvozertinib in NSCLC Patients with EGFR Exon20 Insertion Mutations: Effect of Prior Treatment

Yang J C-H et al.

IASLC 2022;Abstract EP08.02-029.

Phase 1 Studies of DZD9008, an Oral Selective EGFR/HER2 Inhibitor in Advanced NSCLC with EGFR Exon20 Insertion Mutations

Janne PA et al.

IASLC 2022;Abstract OA15.02.

In general, in which line of therapy would you most likely use trastuzumab deruxtecan for an asymptomatic patient with low-volume metastatic adenocarcinoma of the lung and a HER2 mutation?

- First line
- Second line
- Third line
- Beyond third line
- I would not use trastuzumab deruxtecan for this patient
- I’m not sure

PARIS 2022 ESMO congress

Abstract LBA55

Trastuzumab Deruxtecan in Patients With *HER2* Mutant Metastatic Non–Small-Cell Lung Cancer: Interim Results From the Phase 2 DESTINY-Lung02 Trial

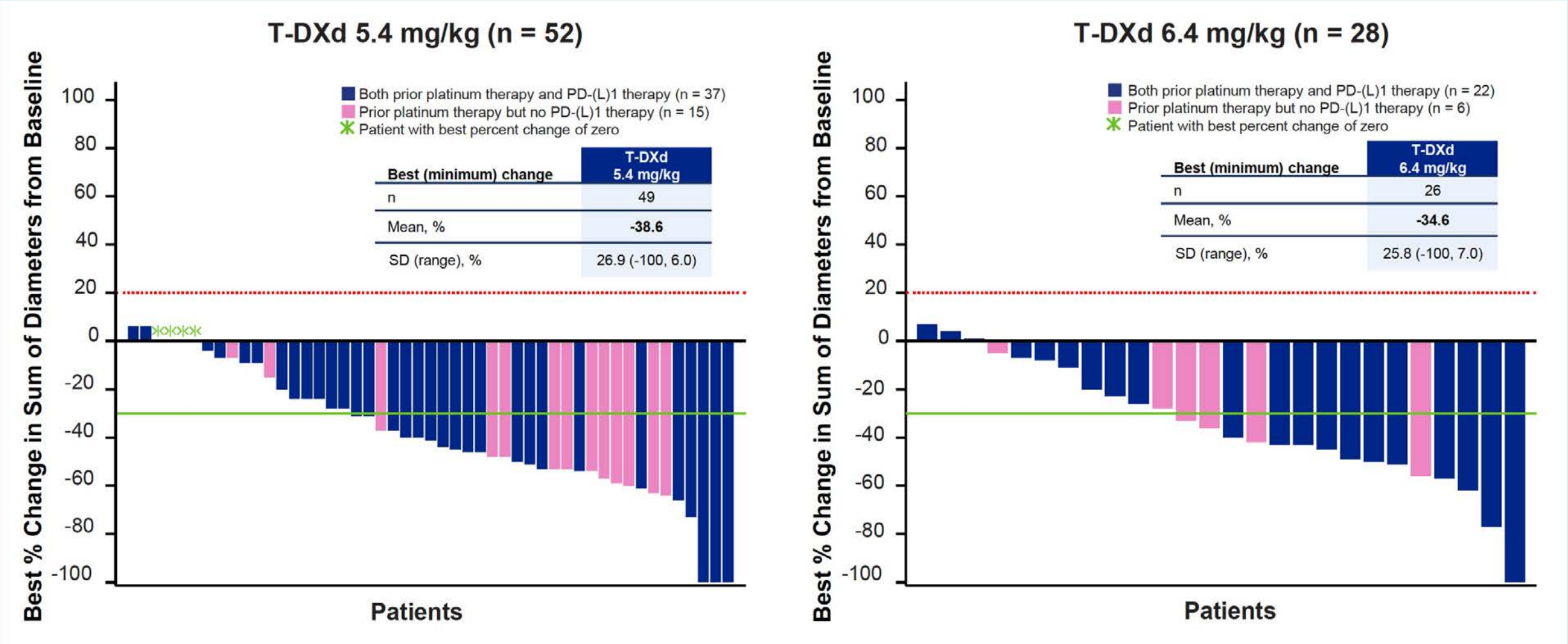
Koichi Goto, MD, PhD,[a] Sang-We Kim, Toshio Kubo, Yasushi Goto, Myung-Ju Ahn, David Planchard, Dong-Wan Kim, James Chih-Hsin Yang, Tsung-Ying Yang, Kaline Pereira, Kapil Saxena, Ryota Shiga, Yingkai Cheng, Mehreteab Aregay, Pasi A. Jänne

On behalf of the DESTINY-Lung02 investigators

[a]National Cancer Center Hospital East, Kashiwa, Japan

RTP RESEARCH TO PRACTICE

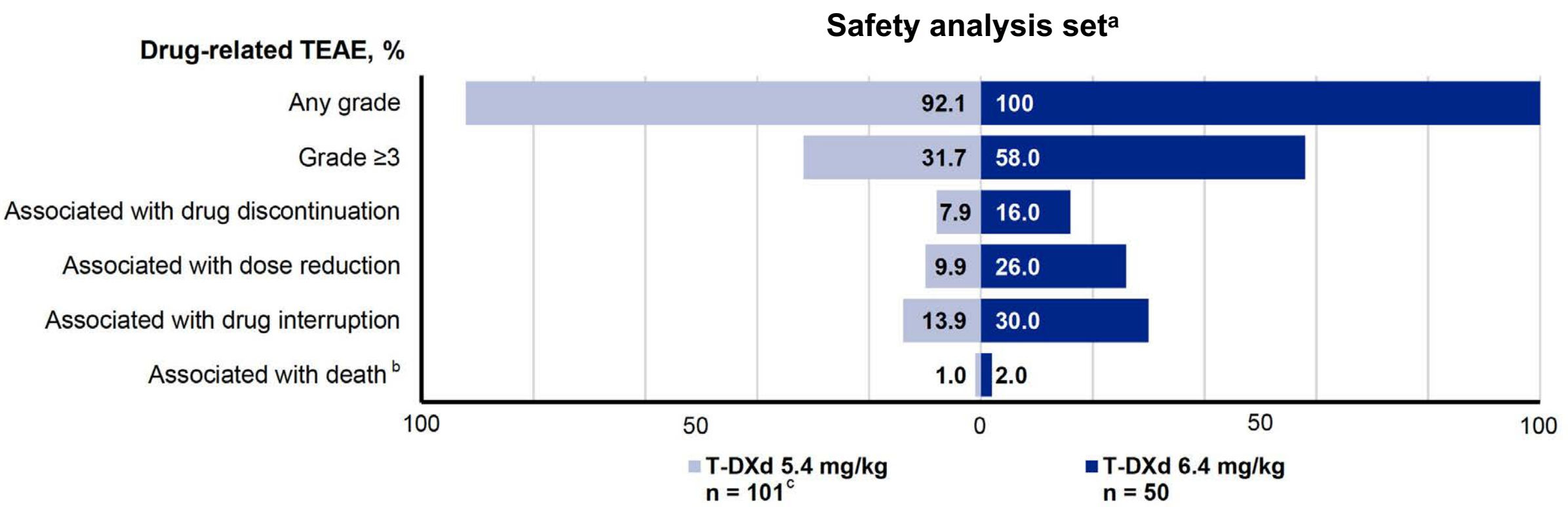
DESTINY-Lung02: Best Percent Change in Tumor Size by BICR



BICR = blinded independent central review

Goto K et al. ESMO 2022;Abstract LBA55.

DESTINY-Lung02: Overall Safety Summary



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

TEAE = treatment-emergent adverse event

Goto K et al. ESMO 2022;Abstract LBA55.

DESTINY-Lung02: Adjudicated Drug-Related Interstitial Lung Disease (ILD)

Adjudicated as drug-related ILD[a]	Safety analysis set[b]	
	T-DXd 5.4 mg/kg n = 101	T-DXd 6.4 mg/kg n = 50
Any grade, n (%)	**6 (5.9)**	**7 (14.0)**
Grade 1	3 (3.0)	1 (2.0)
Grade 2	2 (2.0)	6 (12.0)
Grade 3	1 (1.0)	0
Grade 4	0	0
Grade 5	0	0
Cases resolved, n (%)	3 (50.0)	1 (14.3)
Median time to onset of first adjudicated ILD, days (range)	67.5 (40-207)	41.0 (36-208)

- The rate of adjudicated drug-related ILD was lower in the T-DXd 5.4 mg/kg arm compared with the 6.4 mg/kg arm
- Most cases of adjudicated drug-related ILD were low grade (grade 1/2)

Goto K et al. ESMO 2022;Abstract LBA55.

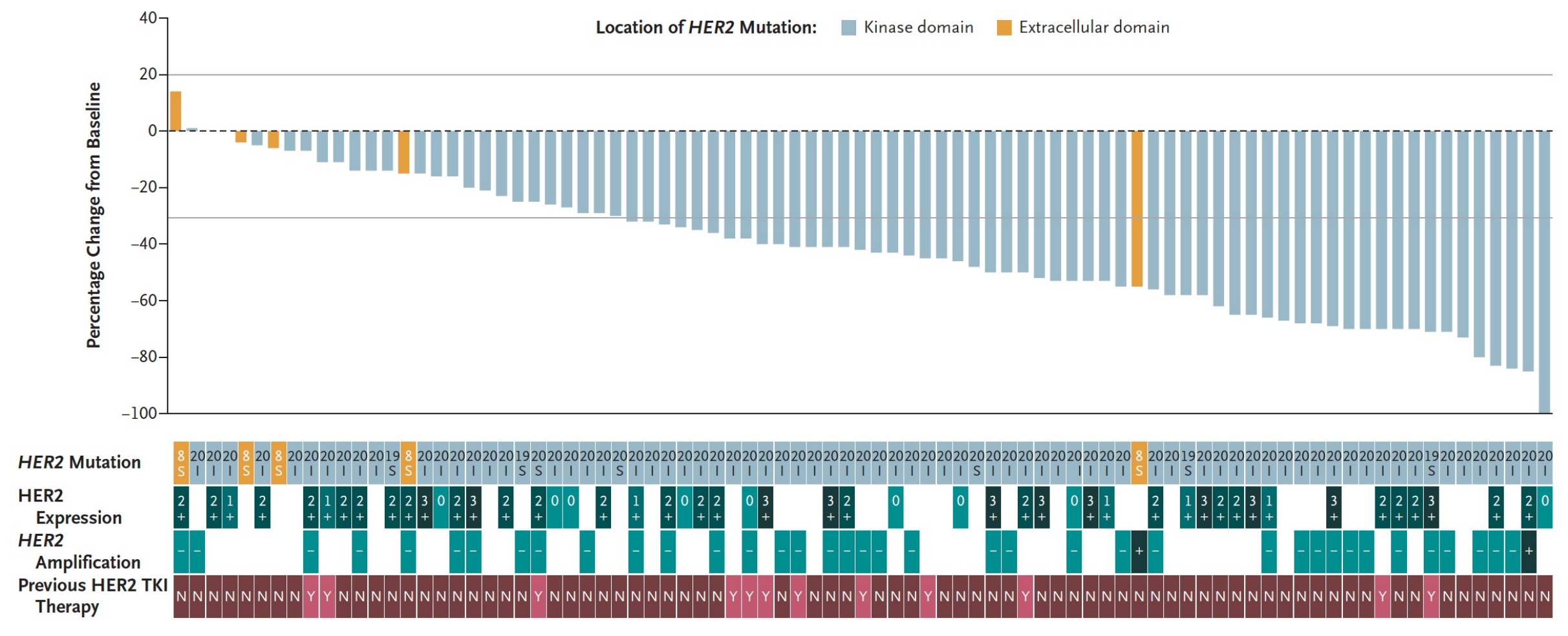
N Engl J Med 2022;386(3):241-51.
The NEW ENGLAND JOURNAL of MEDICINE

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*

Best Percent Change in Sum of Largest Tumor Diameters



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

Trastuzumab Deruxtecan in Patients (pts) with HER2-Overexpressing (HER2-OE) Metastatic Non-Small-Cell Lung Cancer (NSCLC): Results from the DESTINY-Lung01 Trial

Smit EF et al.

ESMO 2022;Abstract 975P.

Cancer Res 2022 April 15;82(8):1633-45.

CANCER RESEARCH | TRANSLATIONAL SCIENCE

A Novel HER2-Selective Kinase Inhibitor Is Effective in HER2 Mutant and Amplified Non–Small Cell Lung Cancer

Jieun Son[1,2,3], Jaebong Jang[4,5], Tyler S. Beyett[4,5], Yoonji Eum[1,2,3], Heidi M. Haikala[1,2,3], Alyssa Verano[4,5], Mika Lin[1,2,3], John M. Hatcher[4,5], Nicholas P. Kwiatkowski[4,5], Pinar Ö. Eser[1,2,3], Michael J. Poitras[6], Stephen Wang[7], Man Xu[7], Prafulla C. Gokhale[6,7], Michael D. Cameron[8], Michael J. Eck[4,5], Nathanael S. Gray[9], and Pasi A. Jänne[1,2,3,7]

Meet The Professor with Dr Jänne

MODULE 1: Case Presentations – Part 2

- Dr Yang: 84-year-old woman with metastatic adenocarcinoma of the lung and EGFR exon 21 mutation, switched to erlotinib due to osimertinib-related toxicities, now with recurrence at the primary site – PD-L1 10%
- Dr Niu: 70-year-old Asian man with metastatic adenocarcinoma of the lung and an EGFR exon 19 deletion and brain metastases who receives SBRT and osimertinib but has biopsy-proven SCLC extracranial PD
- Dr Mushtaq: 70-year-old woman with EGFR mutation-positive metastatic adenocarcinoma of the lung and brain and bone metastases s/p SRS and osimertinib

Case Presentation: 84-year-old woman with metastatic adenocarcinoma of the lung and EGFR exon 21 mutation, switched to erlotinib due to osimertinib-related toxicities, now with recurrence at the primary site – PD-L1 10%

Dr John Yang (Fall River, Massachusetts)

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Case Presentation: 70-year-old Asian man with metastatic adenocarcinoma of the lung and an EGFR exon 19 deletion and brain metastases who receives SBRT and osimertinib but has biopsy-proven SCLC extracranial PD

Dr Jason Niu (Gilbert, Arizona)

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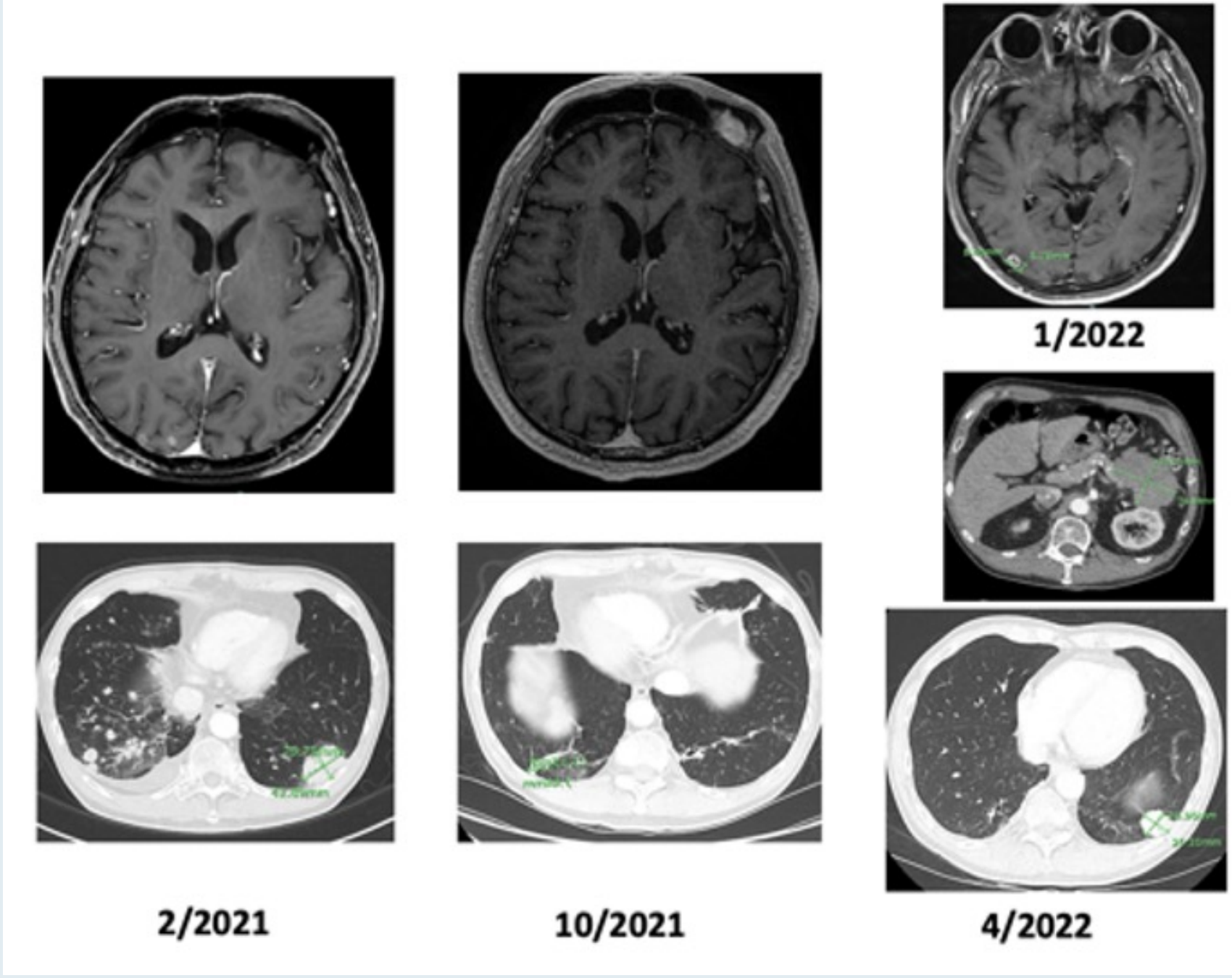
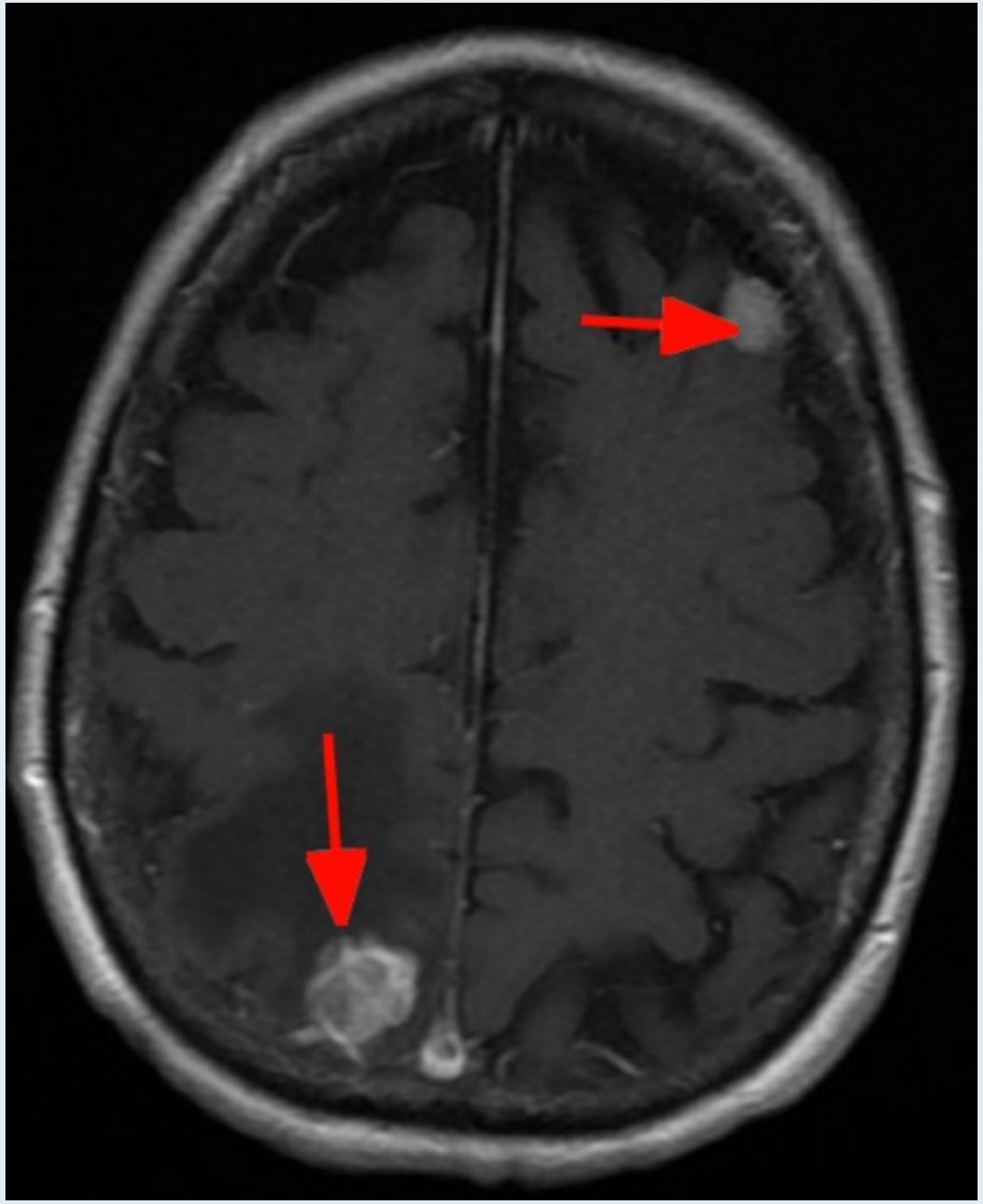
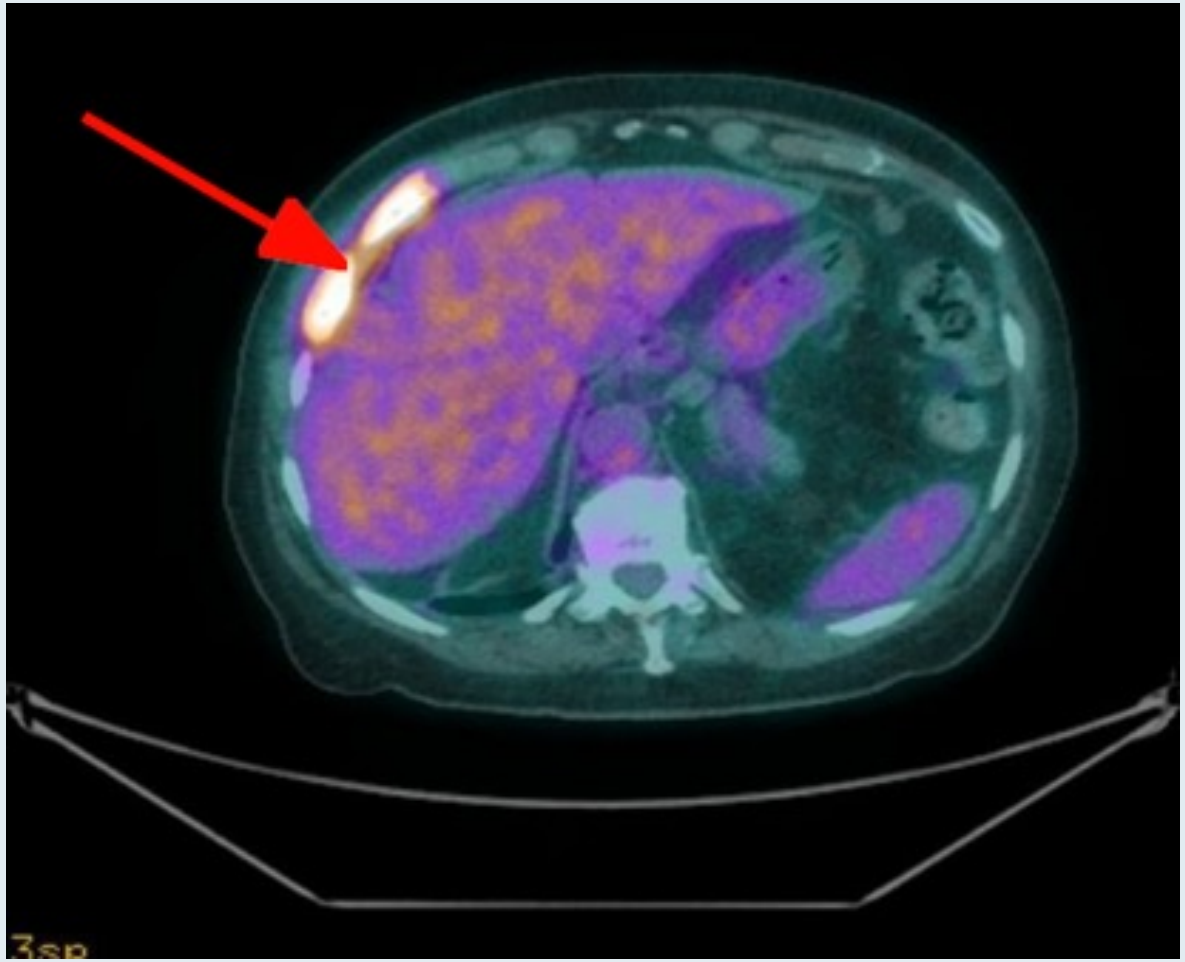


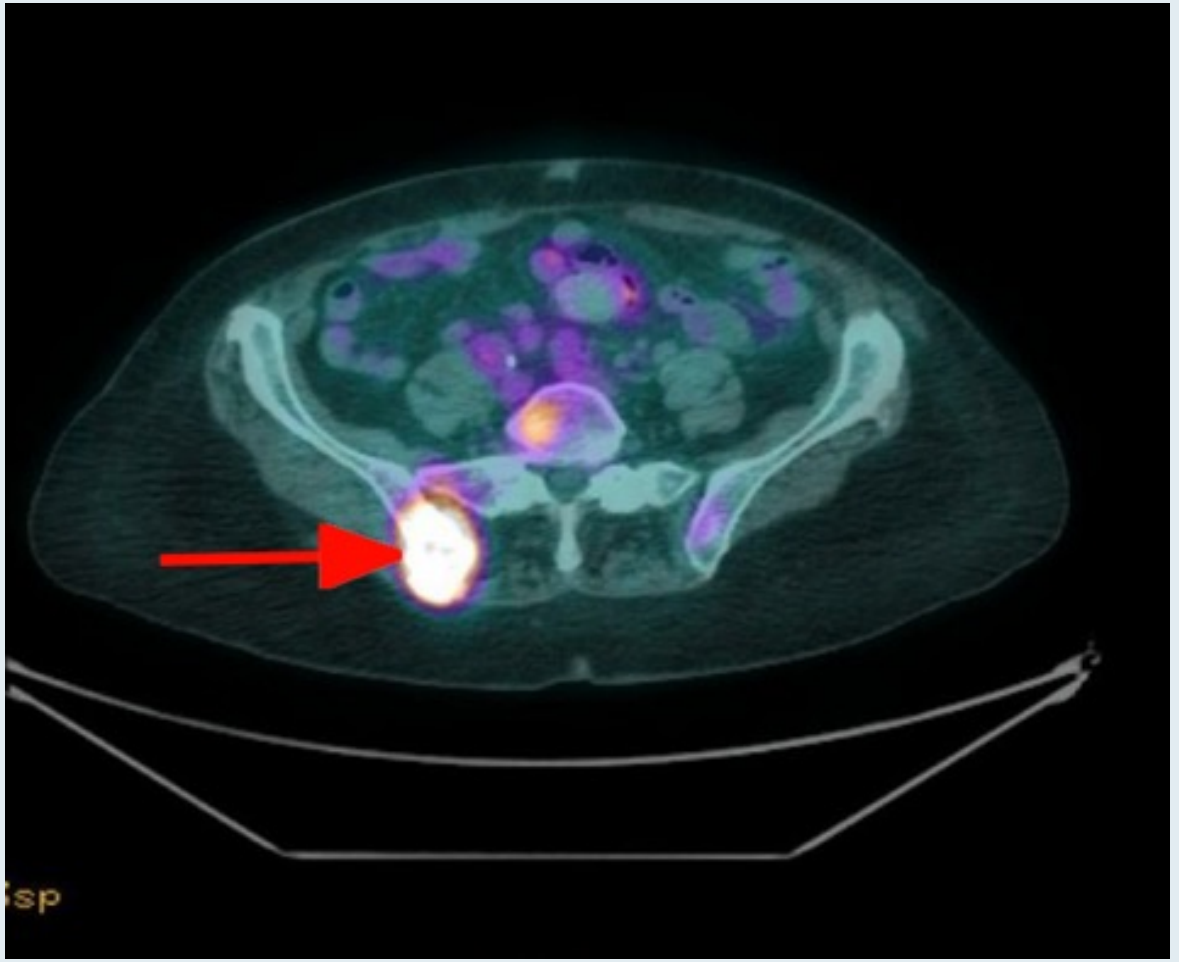
Case Presentation: 70-year-old woman with EGFR mutation-positive metastatic adenocarcinoma of the lung and brain and bone metastases s/p SRS and osimertinib

Dr Rao Mushtaq (Thornton, Colorado)

RTP RESEARCH TO PRACTICE







Meet The Professor with Dr Jänne

INTRODUCTION: Journal Club with Dr Jänne – Part 1

MODULE 1: Case Presentations

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MODULE 4: Appendix of Key Publications

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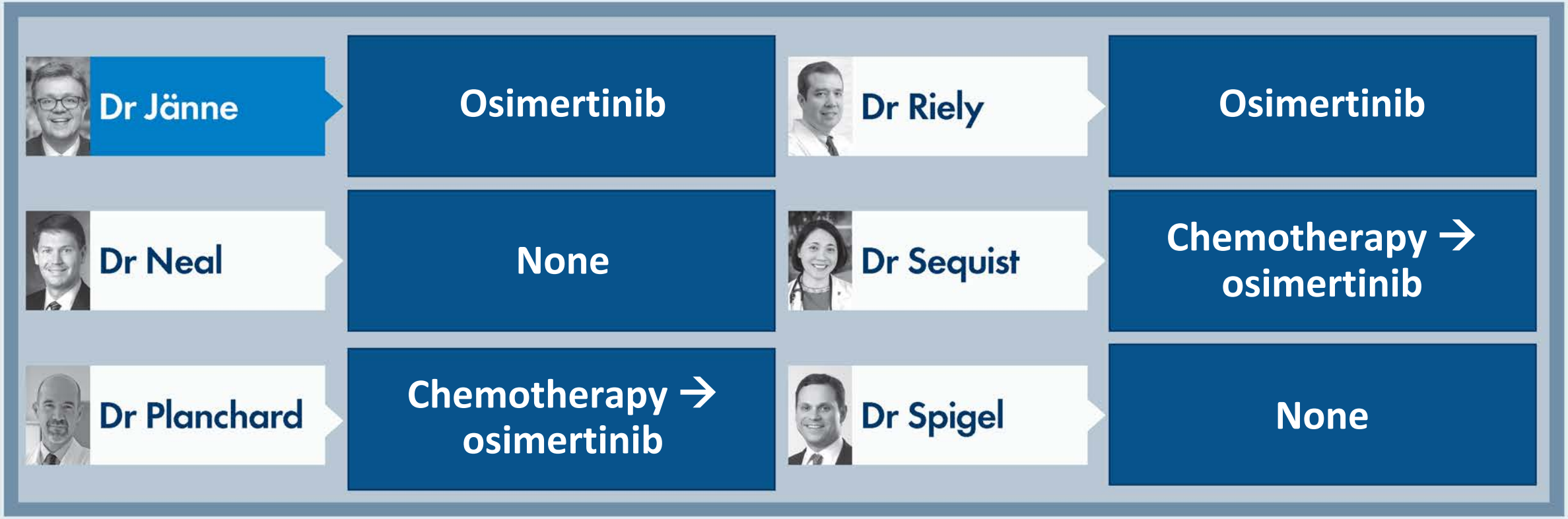
Regulatory and reimbursement issues aside, in general, what adjuvant treatment, if any, would you recommend for an otherwise healthy 65-year-old patient with Stage IB nonsquamous NSCLC with an EGFR exon 19 deletion and a PD-L1 TPS of 50%?



TPS = tumor proportion score

Regulatory and reimbursement issues aside, in general, what adjuvant treatment, if any, would you recommend for an otherwise healthy 65-year-old patient with Stage IIA nonsquamous NSCLC with an EGFR exon 19 deletion and a PD-L1 TPS of 50%?

 Dr Jänne	Chemotherapy → osimertinib	 Dr Riely	Chemotherapy → osimertinib
 Dr Neal	Chemotherapy → osimertinib	 Dr Sequist	Chemotherapy → osimertinib
 Dr Planchard	Chemotherapy → osimertinib	 Dr Spigel	Chemotherapy → osimertinib

What would you most likely recommend as consolidation treatment for a patient with locally advanced NSCLC who has completed chemoradiation therapy and is found to have an EGFR mutation?

 Dr Jänne	Osimertinib	 Dr Riely	Osimertinib
 Dr Neal	Consider durvalumab if PD-L1 high, or osimertinib	 Dr Sequist	Osimertinib
 Dr Planchard	Durvalumab or observation	 Dr Spigel	Durvalumab followed by osimertinib

RTP RESEARCH TO PRACTICE

For a patient with metastatic cancer with an EGFR mutation that responds to but then progresses on osimertinib, do you generally continue osimertinib when switching to chemotherapy?

- Yes
- Yes, if the patient has brain metastases
- No
- I'm not sure

RTP RESEARCH TO PRACTICE

If an asymptomatic patient with metastatic nonsquamous NSCLC with an EGFR exon 19 deletion and a PD-L1 TPS of 10% responded to first-line osimertinib followed by disease progression, what would be your second-line treatment recommendation if the patient had acquired no further actionable mutations?

 Dr Jänne	Continue osimertinib and add carboplatin/ pemetrexed	 Dr Riely	Platin/pemetrexed + bevacizumab
 Dr Neal	Carboplatin/pemetrexed + bevacizumab	 Dr Sequist	Continue osimertinib and add carboplatin/ pemetrexed
 Dr Planchard	Platin/pemetrexed + pembrolizumab	 Dr Spigel	Continue osimertinib and add carboplatin/ pemetrexed

Regulatory and reimbursement issues aside, in which line of therapy would you generally offer an immune checkpoint inhibitor (alone or in combination with chemotherapy) to a patient with metastatic nonsquamous NSCLC and an EGFR exon 19 deletion? Would level of PD-L1 expression have any bearing on this decision?

 Dr Jänne	Third line. No	 Dr Riely	Beyond third line. No
 Dr Neal	Beyond third line. Yes	 Dr Sequist	None
 Dr Planchard	Second line. No	 Dr Spigel	Third line. No

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, what would be your preferred first-line treatment for a patient with metastatic nonsquamous NSCLC with an EGFR exon 20 insertion mutation and a TPS of 10%?

 Dr Jänne	Chemotherapy	 Dr Riely	Chemotherapy + bevacizumab
 Dr Neal	Chemotherapy + bevacizumab	 Dr Sequist	Chemotherapy
 Dr Planchard	Amivantamab	 Dr Spigel	Anti-PD-1/PD-L1 and carboplatin/pemetrexed

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, in which line of therapy would you generally offer amivantamab or mobocertinib to a patient with metastatic NSCLC and an EGFR exon 20 insertion mutation?

 Dr Jänne	Second line	 Dr Riely	Second line
 Dr Neal	Second line	 Dr Sequist	Second line
 Dr Planchard	Second line	 Dr Spigel	Second line

RTP RESEARCH TO PRACTICE

For a patient with metastatic nonsquamous NSCLC with an EGFR exon 20 insertion mutation to whom you've made the determination to administer targeted therapy, which agent do you prefer?

 Dr Jänne	Mobocertinib	 Dr Riely	Mobocertinib
 Dr Neal	Mobocertinib	 Dr Sequist	Amivantamab
 Dr Planchard	Amivantamab	 Dr Spigel	No preference

If you could access amivantamab/lazertinib today, would you attempt to administer it prior to chemotherapy in select situations for your patients with metastatic nonsquamous NSCLC with an EGFR mutation experiencing disease progression on osimertinib?

 Dr Jänne	Yes	 Dr Riely	Yes
 Dr Neal	Yes	 Dr Sequist	Yes
 Dr Planchard	Yes	 Dr Spigel	No

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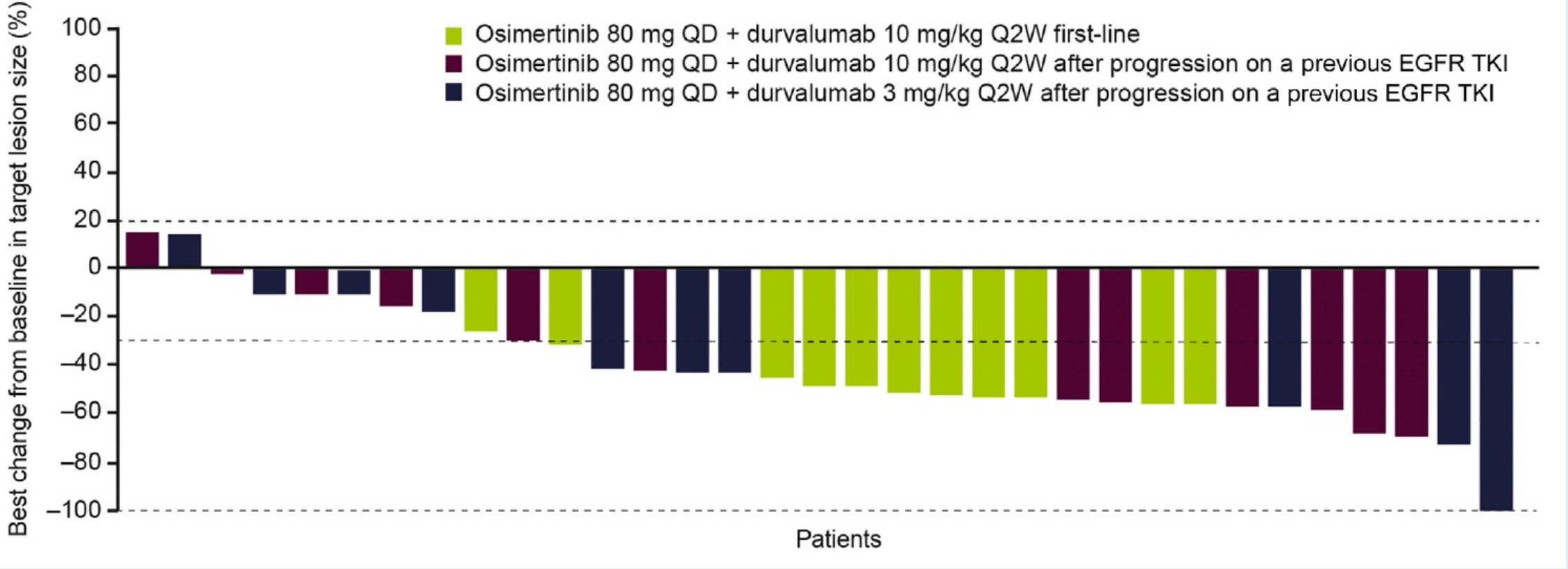
J Thorac Oncol 2022 May;17(5):718-23.

BRIEF REPORT

Osimertinib Plus Durvalumab in Patients With EGFR-Mutated, Advanced NSCLC: A Phase 1b, Open-Label, Multicenter Trial

Myung-Ju Ahn, MD, PhD,[a,*] Byoung Chul Cho, MD, PhD,[b] Xiaoling Ou, PhD,[c] Andrew Walding, MSc,[d] Angela W. Dymond, MSc,[e] Song Ren, PhD,[f] Mireille Cantarini, MbChB,[g] Pasi A. Jänne, MD, PhD[h]

Waterfall Plot of the Best Percent Change from Baseline in Target Lesion Size with Osimertinib and Durvalumab in the First Line and After Disease Progression on a Previous EGFR TKI



Ahn MJ et al. *J Thorac Oncol* 2022 May;17(5):718-23.

original reports

BIOMARKERS

Plasma ctDNA Response Is an Early Marker of Treatment Effect in Advanced NSCLC

Michael L. Cheng, MD[1,2]; Christie J. Lau, BS[3]; Marina S. D. Milan, BA[1]; Julianna G. Supplee, MA[3]; Jonathan W. Riess, MD[4]; Penelope A. Bradbury, MD[5]; Pasi A. Jänne, MD, PhD[1,2,3]; Geoffrey R. Oxnard, MD[1,2]; and Cloud P. Paweletz, PhD[3]

JCO Precis Oncol 2021 February 17;5:PO.20.00419.

JC JOURNAL CLUB

RTP RESEARCH TO PRACTICE

J Thorac Imaging 2021 September 15:[Online ahead of print].

ORIGINAL ARTICLE

Prediction Model for Tumor Volume Nadir in *EGFR*-mutant NSCLC Patients Treated With EGFR Tyrosine Kinase Inhibitors

Mizuki Nishino, MD, MPH,† Junwei Lu, PhD,‡ Takuya Hino, MD,*†*
Natalie I. Vokes, MD,§ Pasi A. Jänne, MD, PhD,§
Hiroto Hatabu, MD, PhD,† and Bruce E. Johnson, MD§‖*

J Thorac Oncol 2022 June;17(6):779-92.

ORIGINAL ARTICLE

Concurrent TP53 Mutations Facilitate Resistance Evolution in EGFR-Mutant Lung Adenocarcinoma

Natalie I. Vokes, MD,[a,b] Emily Chambers, MLA,[c] Tom Nguyen, BS,[c] Alexis Coolidge, MD,[d] Christine A. Lydon, BA,[c] Xiuning Le, MD, PhD,[a] Lynette Sholl, MD,[e] John V. Heymach, MD, PhD,[a] Mizuki Nishino, MD,[f,g] Eliezer M. Van Allen, MD,[h,i] Pasi A. Jänne, MD, PhD[c,*]

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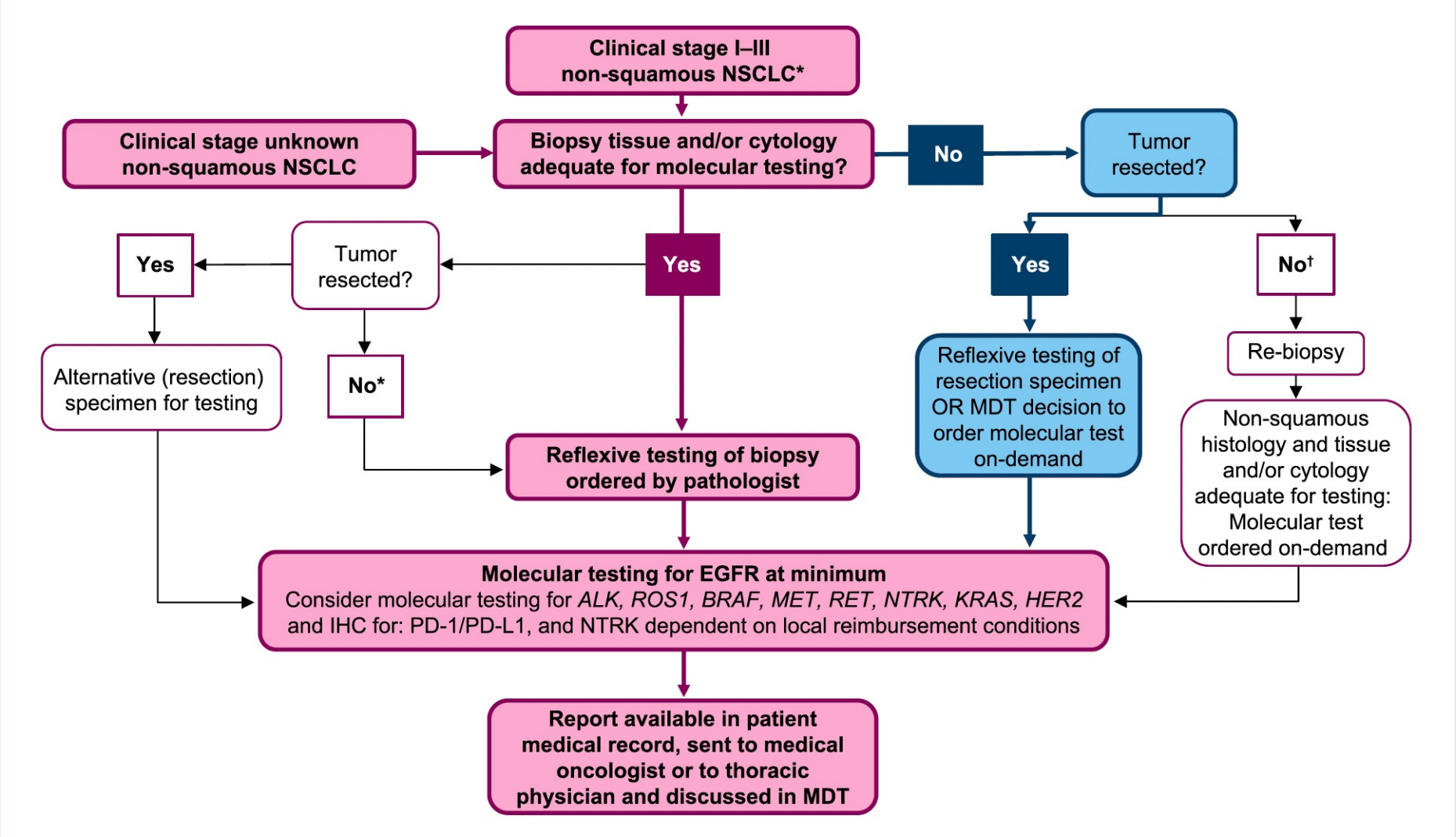
TO PRACTICE

Localized NSCLC with EGFR Mutation

Proposed Algorithm for Molecular Testing in Patients with Stage I to Stage III NSCLC (Resectable and Unresectable)



MDT = multidisciplinary team

Aggarwal C et al. *Lung Cancer* 2021;162:42-53.

Phase III Trials of Adjuvant EGFR Inhibitors for Localized NSCLC

Study	N	Setting	Regimens	Median F/U	DFS Hazard ratio	OS Hazard ratio
BR 19	503	Stage IB, II, IIA 4% mEGFR	Gefitinib x 2 y Placebo x 2 y	56.4 mo	1.22	1.24
RADIANT	973	Stage IB-IIIA 6.5% mEGFR	Erlotinib x 2 y Placebo x 2 y	47 mo	0.90	1.13
CTONG1104	222	Stage II-IIIA (N1-N2) 100% mEGFR	Gefitinib x 2 y Cis/vin x 4	76.9 mo	5-y DFS: 22.6% vs 23.2%	0.92
IMPACT	232	Stage IIA-IIIB 100% mEGFR	Gefitinib x 2 y Cis/vin x 4	70.1 mo	0.92	1.03

F/U = follow-up; DFS = disease-free survival; OS = overall survival; mEGFR = EGFR mutation-positive; cis/vin = cisplatin/vinorelbine

Melosky B et al. *Ther Adv Med Oncol* 2021;13:1-15. Sotelo MJ et al. *World J Clin Oncol* 2021;12(10):912-25.
Belluomini L et al. *Cells* 2021;10(10):2685.

N Engl J Med 2020;382:41-50.

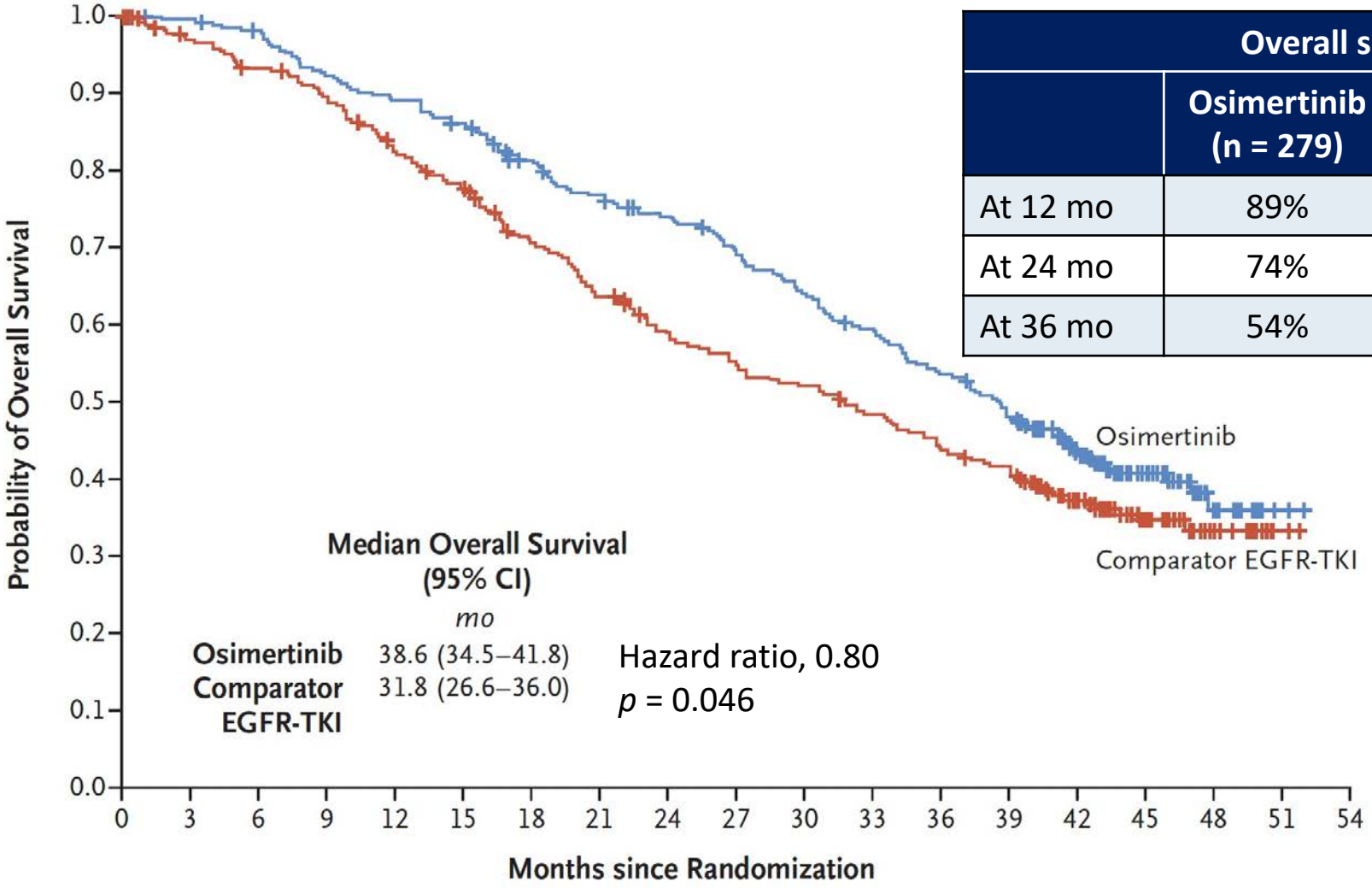
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Overall Survival with Osimertinib in Untreated, *EGFR*-Mutated Advanced NSCLC

S.S. Ramalingam, J. Vansteenkiste, D. Planchard, B.C. Cho, J.E. Gray, Y. Ohe, C. Zhou, T. Reungwetwattana, Y. Cheng, B. Chewaskulyong, R. Shah, M. Cobo, K.H. Lee, P. Cheema, M. Tiseo, T. John, M.-C. Lin, F. Imamura, T. Kurata, A. Todd, R. Hodge, M. Saggese, Y. Rukazenkov, and J.-C. Soria, for the FLAURA Investigators*

FLAURA: Overall Survival



Overall survival		
	Osimertinib (n = 279)	Comparator EGFR TKI (n = 277)
At 12 mo	89%	83%
At 24 mo	74%	59%
At 36 mo	54%	44%

Ramalingam SS et al. *N Engl J Med* 2020;382;41-50.

PARIS 2022 ESMO congress

Abstract LBA47

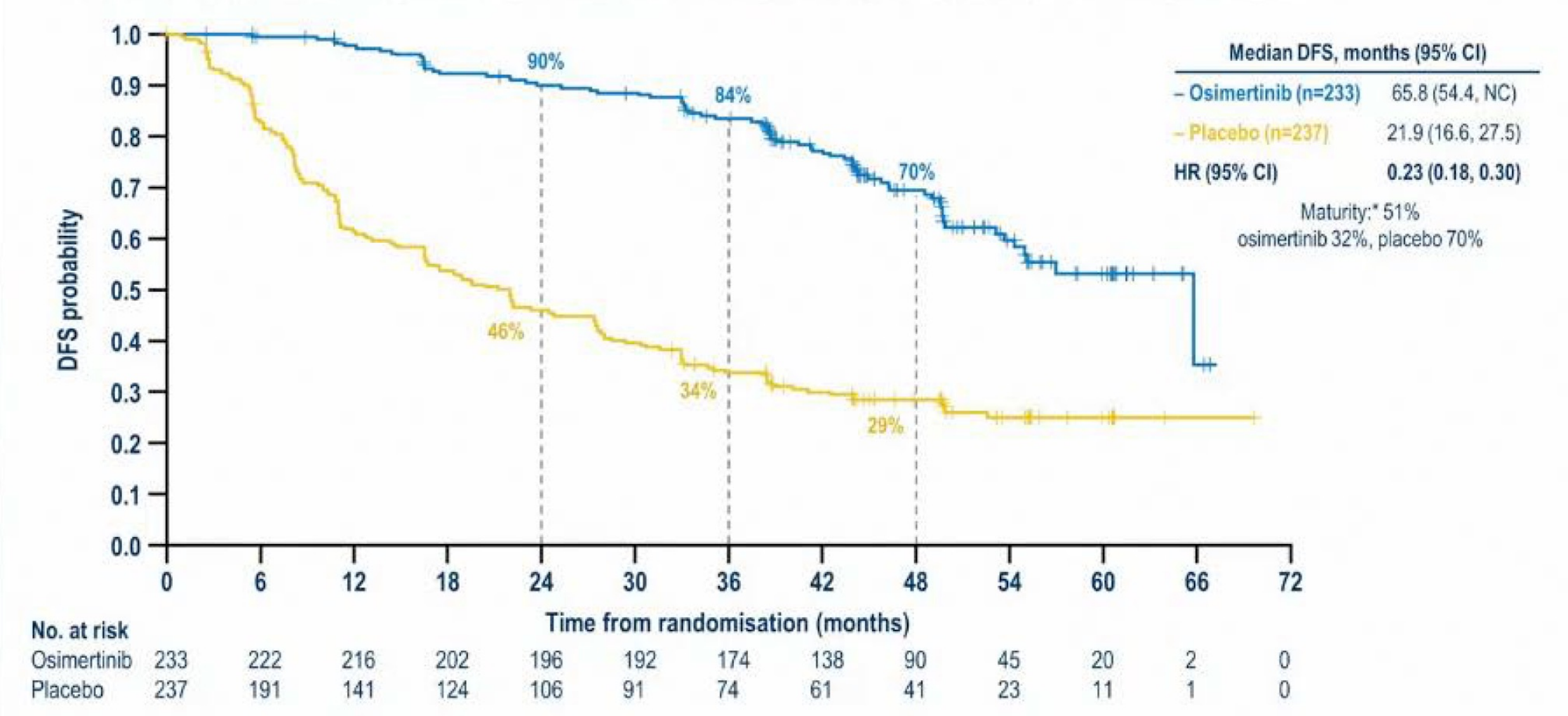
Osimertinib as adjuvant therapy in patients with resected EGFRm stage IB–IIIA NSCLC: updated results from ADAURA

Masahiro Tsuboi[1], Yi-Long Wu[2], Christian Grohe[3], Thomas John[4], Margarita Majem[5], Jie Wang[6], Terufumi Kato[7], Jonathan W. Goldman[8], Sang-We Kim[9], Chong-Jen Yu[10], Huu Vinh Vu[11], Guzel Mukhametshina[12], Charuwan Akewanlop[13], Filippo de Marinis[14], Frances A. Shepherd[15], Damien Urban[16], Marta Stachowiak[17], Ana Bolanos[18], Xiangning Huang[19], Roy S. Herbst[20]

[1]Department of Thoracic Surgery and Oncology, National Cancer Center Hospital East, Kashiwa, Japan; [2]Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital and Guangdong Academy of Medical Sciences, Guangzhou, China; [3]Klinik für Pneumologie - Evangelische Lungenklinik Berlin Buch, Berlin, Germany; [4]Department of Medical Oncology, Austin Health, Melbourne, Australia; [5]Department of Medical Oncology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; [6]Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China; [7]Department of Thoracic Oncology, Kanagawa Cancer Center, Asahi Ward, Yokohama, Japan; [8]David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA, USA; [9]Department of Oncology, Asan Medical Center, Seoul, South Korea; [10]Department of Internal Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan; [11]Department Thoracic Surgery, Choray Hospital, Ho Chi Minh City, Vietnam; [12]Republican Clinical Oncology Center, Kazan, Republic of Tatarstan, Russia; [13]Division of Medical Oncology, Faculty of Medicine, Siriraj Hospital, Bangkok, Thailand; [14]Thoracic Oncology Division, European Institute of Oncology (IEO), IRCCS, Milan, Italy; [15]Department of Medical Oncology and Hematology, University Health Network, Princess Margaret Cancer Centre, Canada; [16]Department of Oncology, Sheba Medical Center, Tel Hashomer, Israel and Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel; [17]Late Oncology Research & Development, AstraZeneca, Warsaw, Poland; [18]Oncology Research & Development, AstraZeneca, Mississauga, Canada; [19]Oncology Biometrics, AstraZeneca, Cambridge, United Kingdom; [20]Medical Oncology, Yale School of Medicine and Yale Cancer Center, New Haven, CT, USA

RTP RESEARCH TO PRACTICE

ADAURA Updated Results: DFS in Stage II/IIIA Disease

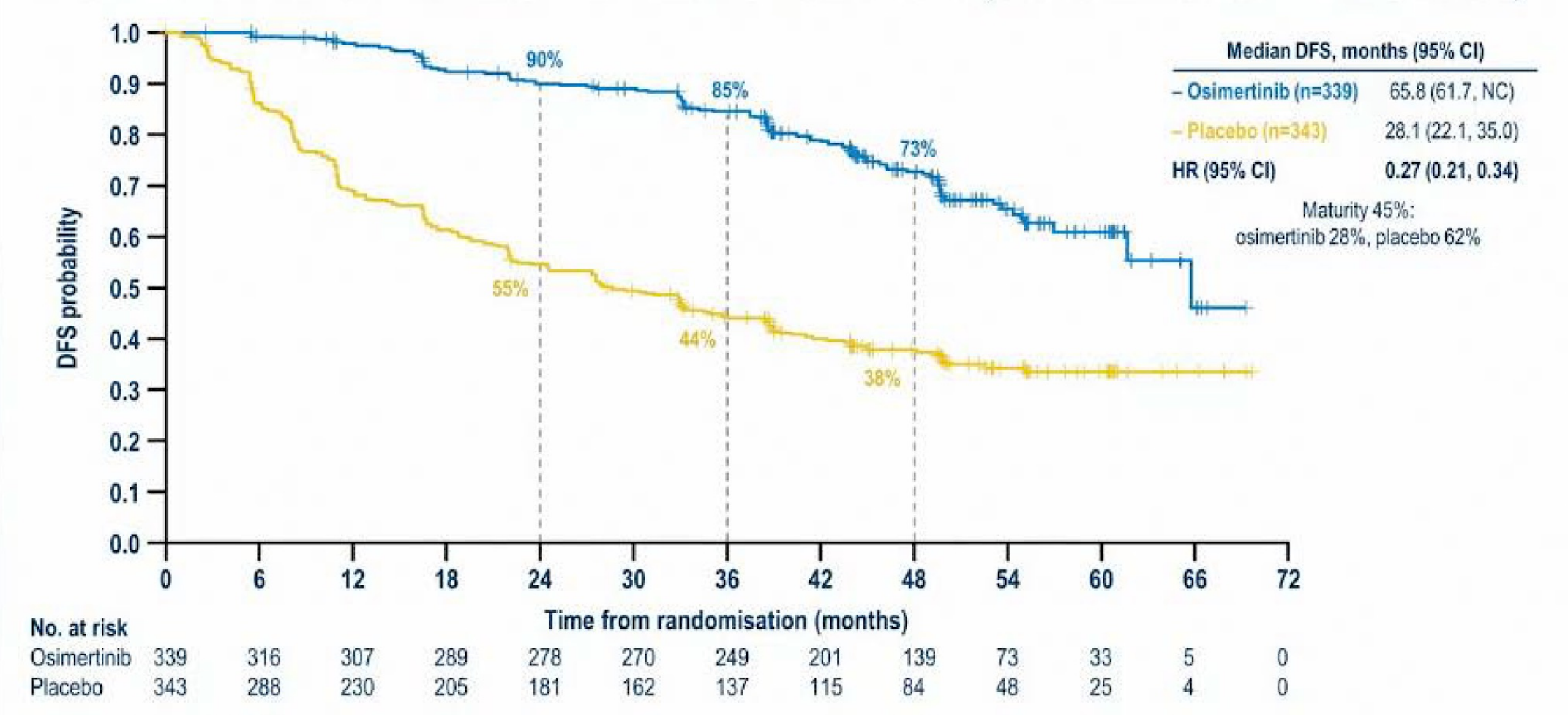


DFS = disease-free survival

Tsuboi M et al. ESMO 2022;Abstract LBA47.

RTP RESEARCH TO PRACTICE

ADAURA Updated DFS Results in the Overall Population (Stage IB/II/IIIA Disease)

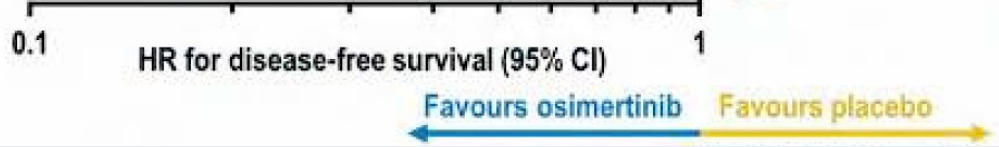


Tsuboi M et al. ESMO 2022;Abstract LBA47.

ADAURA Updated DFS Results in Subgroups in the Overall Population

- A DFS benefit with osimertinib was observed across all predefined subgroups

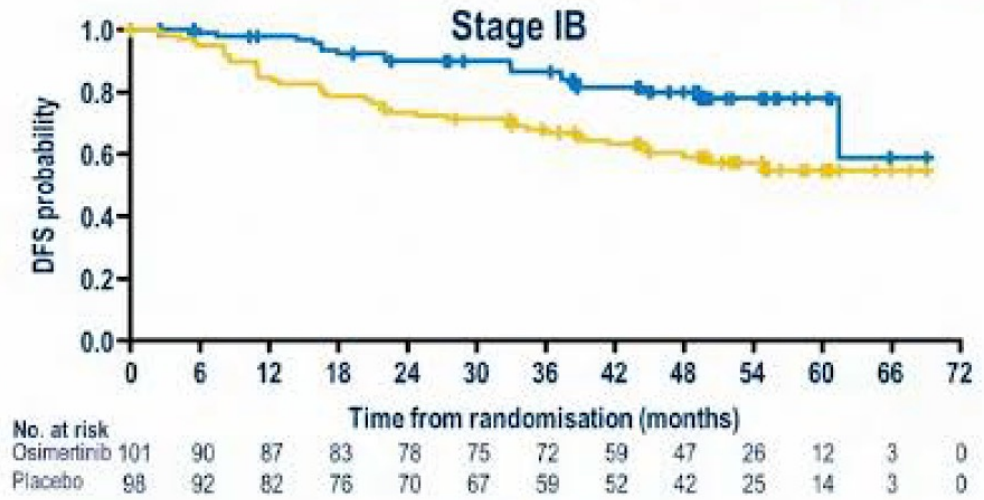
Subgroup		HR	95% CI
Overall (N=682)	Stratified log-rank	0.27	0.21, 0.34
	Unadjusted Cox PH	0.32	0.25, 0.40
Sex	Male (n=204)	0.31	0.20, 0.48
	Female (n=478)	0.31	0.23, 0.42
Age	<65 yr (n=380)	0.31	0.22, 0.42
	≥65 yr (n=302)	0.33	0.23, 0.48
Smoking history	Yes (n=194)	0.26	0.16, 0.40
	No (n=488)	0.34	0.26, 0.45
Race	Asian (n=434)	0.34	0.25, 0.45
	Non-Asian (n=248)	0.28	0.18, 0.43
Stage*	IB (n=212)	0.41	0.23, 0.69
	II (n=236)	0.34	0.23, 0.52
	IIIA (n=234)	0.20	0.14, 0.29
EGFR mutation	Ex19Del (n=378)	0.24	0.17, 0.33
	L858R (n=304)	0.45	0.31, 0.64
Adjuvant chemotherapy	Yes (n=410)	0.29	0.21, 0.39
	No (n=272)	0.36	0.24, 0.55

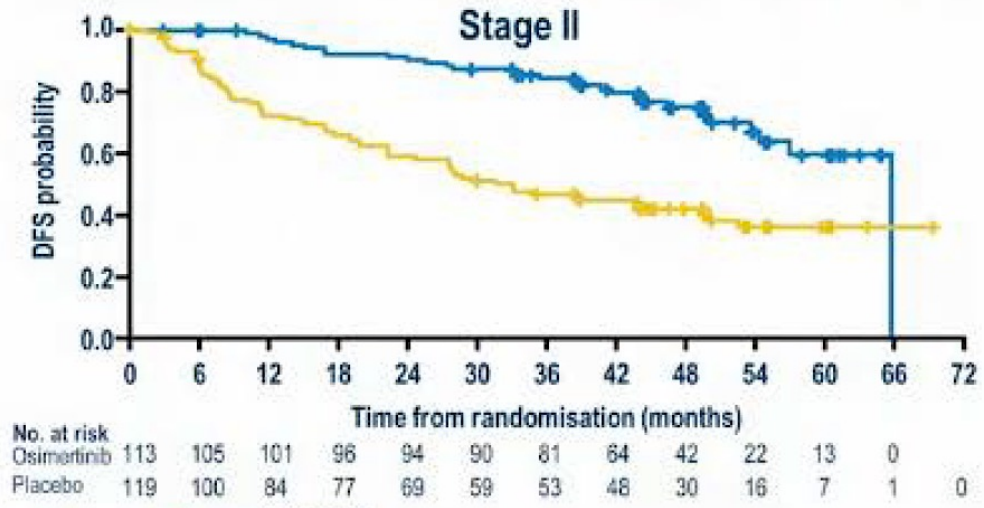


Tsuboi M et al. ESMO 2022;Abstract LBA47.

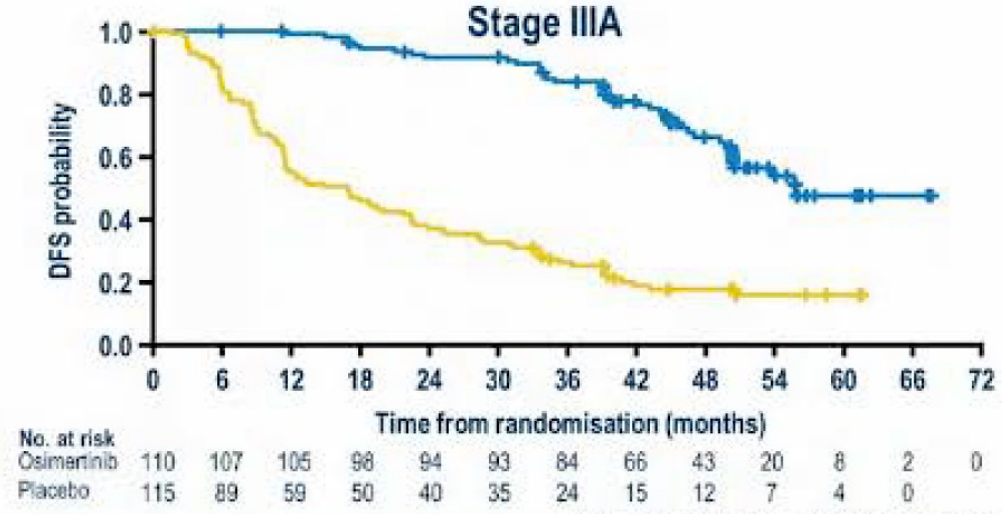
RTP RESEARCH TO PRACTICE

ADAURA Updated DFS by Stage (AJCC/UICC 8th Edition)





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



Tsuboi M et al. ESMO 2022;Abstract LBA47.

RTP RESEARCH TO PRACTICE

ADAURA Updated Safety Summary

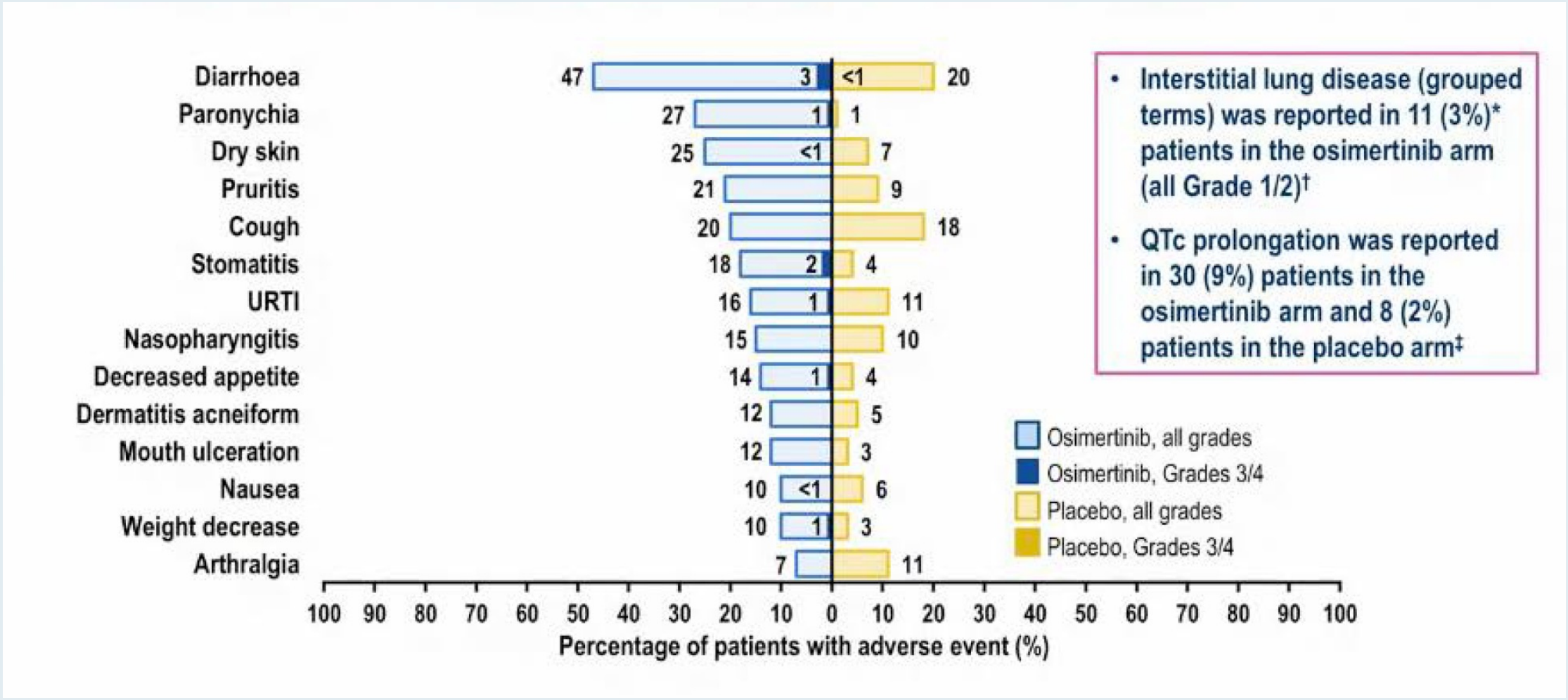
- Completed planned duration of treatment of 3 years: osimertinib n=222 (66%), placebo n=139 (41%)
- Median total duration of exposure: osimertinib: 35.8 months (range 0 to 38), placebo: 25.1 months (range 0 to 39)

AE, any cause*, n (%)	Osimertinib (n=337)	Placebo (n=343)
Any AE	330 (98)	309 (90)
Any AE Grade ≥3	79 (23)	48 (14)
Any AE leading to death	1 (<1)	2 (1)
Any serious AE	68 (20)	47 (14)
Any AE leading to discontinuation	43 (13)	9 (3)
Any AE leading to dose reduction	42 (12)	3 (1)
Any AE leading to dose interruption	91 (27)	43 (13)
AE, possibly causally related†, n (%)		
Any AE	308 (91)	199 (58)
Any AE Grade ≥3	36 (11)	7 (2)
Any AE leading to death	0	0
Any serious AE	10 (3)	2 (1)

AE = adverse event

Tsuboi M et al. ESMO 2022;Abstract LBA47.

ADAURA Updated Results: All Causality Adverse Events (≥10% of Patients)



URTI = upper respiratory tract infection

Tsuboi M et al. ESMO 2022;Abstract LBA47.

ORIGINAL ARTICLE

J Thorac Oncol 2022;17(3):423-33.

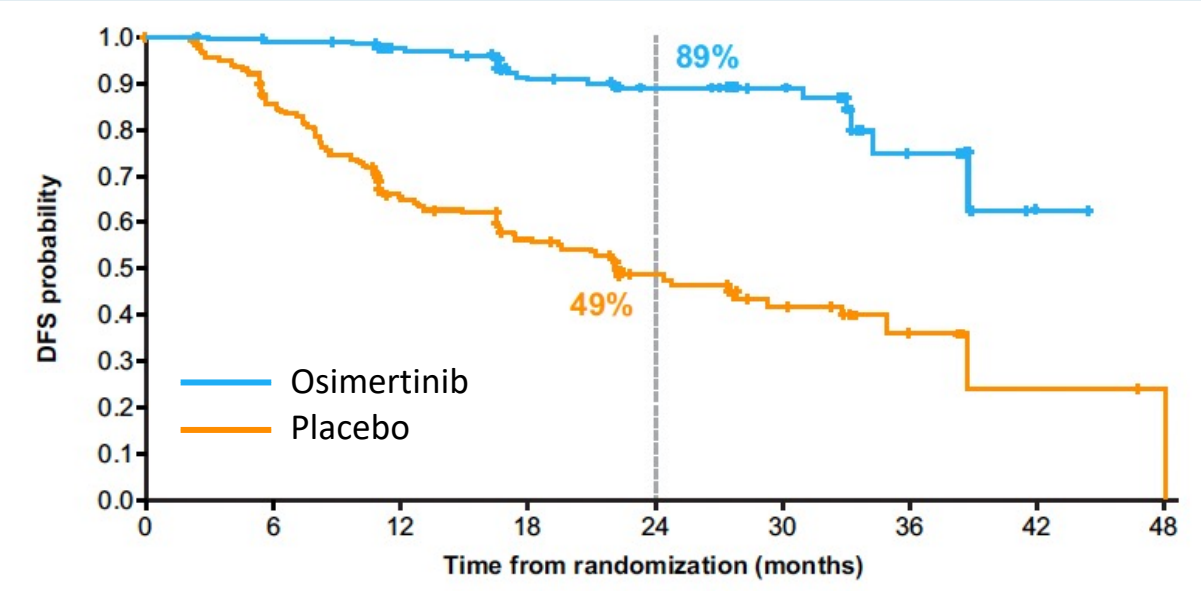
IASLC

Postoperative Chemotherapy Use and Outcomes From ADAURA: Osimertinib as Adjuvant Therapy for Resected EGFR-Mutated NSCLC

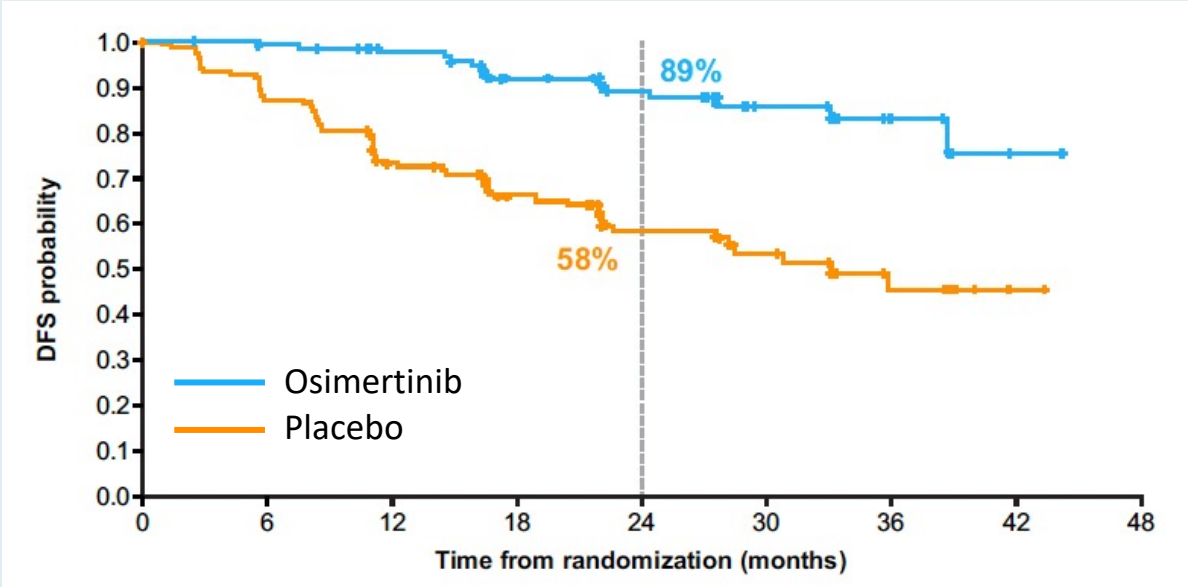
Yi-Long Wu, MD,[a,*] Thomas John, PhD,[b] Christian Grohe, MD,[c] Margarita Majem, MD, PhD,[d] Jonathan W. Goldman, MD,[e] Sang-We Kim, MD, PhD,[f] Terufumi Kato, MD,[g] Konstantin Laktionov, PhD,[h] Huu Vinh Vu, MD, PhD,[i] Zhijie Wang, MD,[j] Shun Lu, MD,[k] Kye Young Lee, MD, PhD,[l] Charuwan Akewanlop, MD,[m] Chong-Jen Yu, MD, PhD,[n] Filippo de Marinis, MD,[o] Laura Bonanno, MD,[p] Manuel Domine, MD, PhD,[q] Frances A. Shepherd, MD,[r] Lingmin Zeng, PhD,[s] Ajlan Atasoy, MD,[t] Roy S. Herbst, MD, PhD,[u] Masahiro Tsuboi, MD[v]

ADAURA: Updated DFS with Adjuvant Osimertinib for Patients Receiving and Not Receiving Adjuvant Chemotherapy

With adjuvant chemotherapy



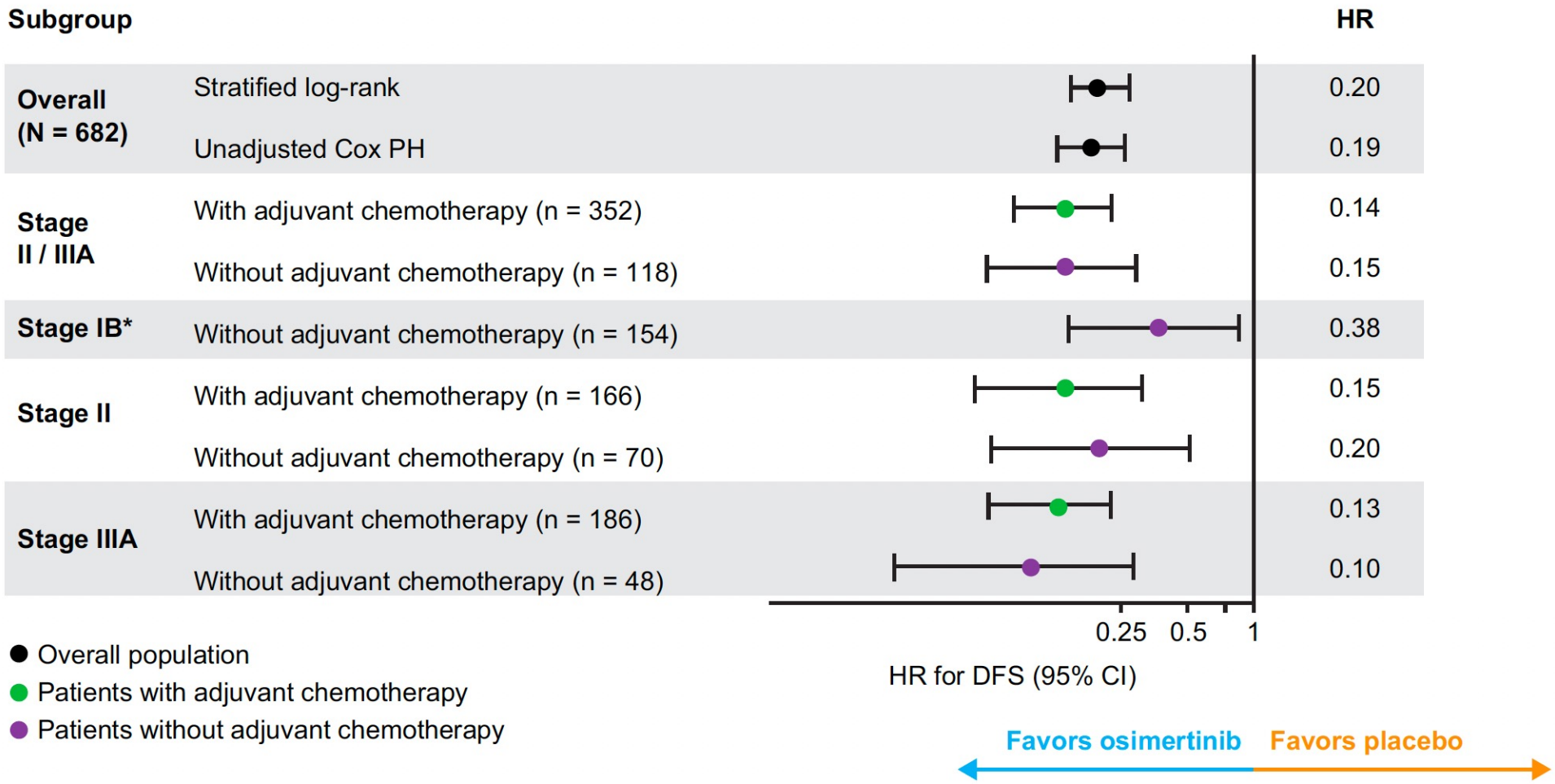
Without adjuvant chemotherapy



Wu Y-L et al. *J Thorac Oncol* 2022;17(3):423-33.

RTP RESEARCH TO PRACTICE

ADAURA: Updated DFS with Adjuvant Osimertinib for Patients Receiving and Not Receiving Adjuvant Chemotherapy — Subgroups



Wu Y-L et al. *J Thorac Oncol* 2022;17(3):423-33.

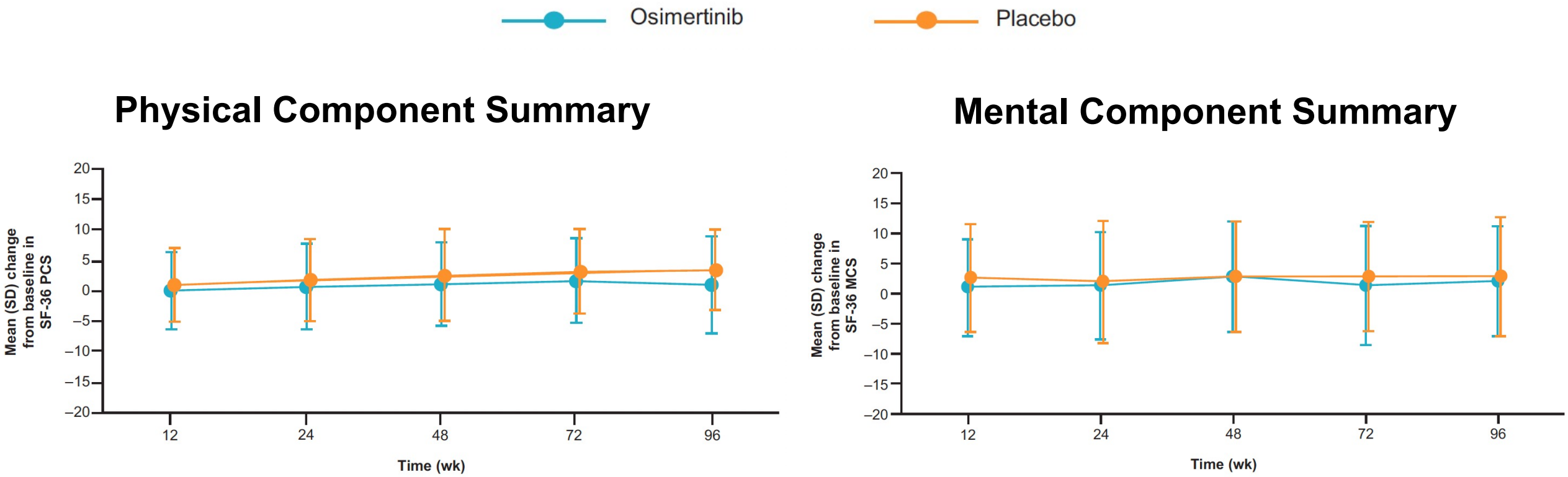
CLINICAL CANCER RESEARCH | CLINICAL TRIALS: TARGETED THERAPY

Health-Related Quality of Life Outcomes in Patients with Resected Epidermal Growth Factor Receptor–Mutated Non–Small Cell Lung Cancer Who Received Adjuvant Osimertinib in the Phase III ADAURA Trial

Margarita Majem[1], Jonathan W. Goldman[2], Thomas John[3], Christian Grohe[4], Konstantin Laktionov[5], Sang-We Kim[6], Terufumi Kato[7], Huu Vinh Vu[8], Shun Lu[9], Shanqing Li[10], Kye Young Lee[11], Charuwan Akewanlop[12], Chong-Jen Yu[13], Filippo de Marinis[14], Laura Bonanno[15], Manuel Domine[16], Frances A. Shepherd[17], Shinji Atagi[18], Lingmin Zeng[19], Dakshayini Kulkarni[20], Nenad Medic[21], Masahiro Tsuboi[22], Roy S. Herbst[23], and Yi-Long Wu[24]

***Clin Cancer Res* 2022;[Online ahead of print].**

ADAURA: Health-Related Quality of Life over Time



Majem M et al. *Clin Cancer Res* 2022;[Online ahead of print].

RTP RESEARCH TO PRACTICE

Select Ongoing Phase III Studies of TKIs for Unresected or Unresectable NSCLC with EGFR Mutation

Study	No. of patients	NSCLC stage	Randomization	Est primary completion
NeoADAURA (NCT04351555)	328	Unresected II-IIIB N2	• Osimertinib • Osimertinib + chemotherapy • Chemotherapy	March 2024
PACIFIC-4/RTOG-3515 (NCT03833154)	733	Unresected IA2-IA3	• SBRT + osimertinib • SBRT + durvalumab • SBRT + placebo	June 2025
LAURA (NCT03521154)	197	Unresectable III	• Chemotherapy → osimertinib maintenance • Chemotherapy → placebo maintenance	January 2023

TKI = tyrosine kinase inhibitor; SBRT = stereotactic body radiation therapy

www.clinicaltrials.gov. Accessed June 2022.

RTP RESEARCH TO PRACTICE

Select Ongoing Phase III Studies of TKIs in the Adjuvant Setting for NSCLC with EGFR Mutation

Study	No. of patients	NSCLC stage	Randomization	Est primary completion
ADAURA2 (NCT05120349)	380	IA2-IA3	• Osimertinib • Placebo	August 2027
FORWARD (NCT04853342)	318	II-IIIA	• Furmonertinib (AST2818) • Placebo	December 2023
EVIDENCE (NCT02448797)	320	II-IIIA	• Icotinib • Standard chemotherapy	June 2022
ICTAN (NCT01996098)	318	IIA-IIIA	• Chemotherapy → icotinib for 6 mo • Chemotherapy → icotinib for 12 mo • Chemotherapy	January 2020*

*Recruitment ongoing

www.clinicaltrials.gov. Accessed June 2022.

FDA Approves Atezolizumab as Adjuvant Treatment for NSCLC

Press Release: October 15, 2021

"The Food and Drug Administration approved atezolizumab for adjuvant treatment following resection and platinum-based chemotherapy in patients with stage II to IIIA non-small cell lung cancer (NSCLC) whose tumors have PD-L1 expression on ≥ 1% of tumor cells, as determined by an FDA-approved test.

Today, the FDA also approved the VENTANA PD-L1 (SP263) Assay as a companion diagnostic device to select patients with NSCLC for adjuvant treatment with atezolizumab.

The major efficacy outcome measure was disease-free survival (DFS) as assessed by the investigator in the primary efficacy analysis population (n = 476) of patients with stage II-IIIA NSCLC with PD-L1 expression on ≥1% of tumor cells (PD-L1 ≥1% TC). Median DFS was not reached in patients on the atezolizumab arm compared with 35.3 months on the BSC arm (HR 0.66; p = 0.004). In a pre-specified secondary subgroup analysis of patients with PD-L1 TC ≥ 50% stage II-IIIA NSCLC, the DFS HR was 0.43. In an exploratory subgroup analysis of patients with PD-L1 TC 1-49% stage II-IIIA NSCLC, the DFS HR was 0.87.

The recommended atezolizumab dose for this indication is 840 mg every 2 weeks, 1,200 mg every 3 weeks, or 1,680 mg every 4 weeks for up to 1 year."

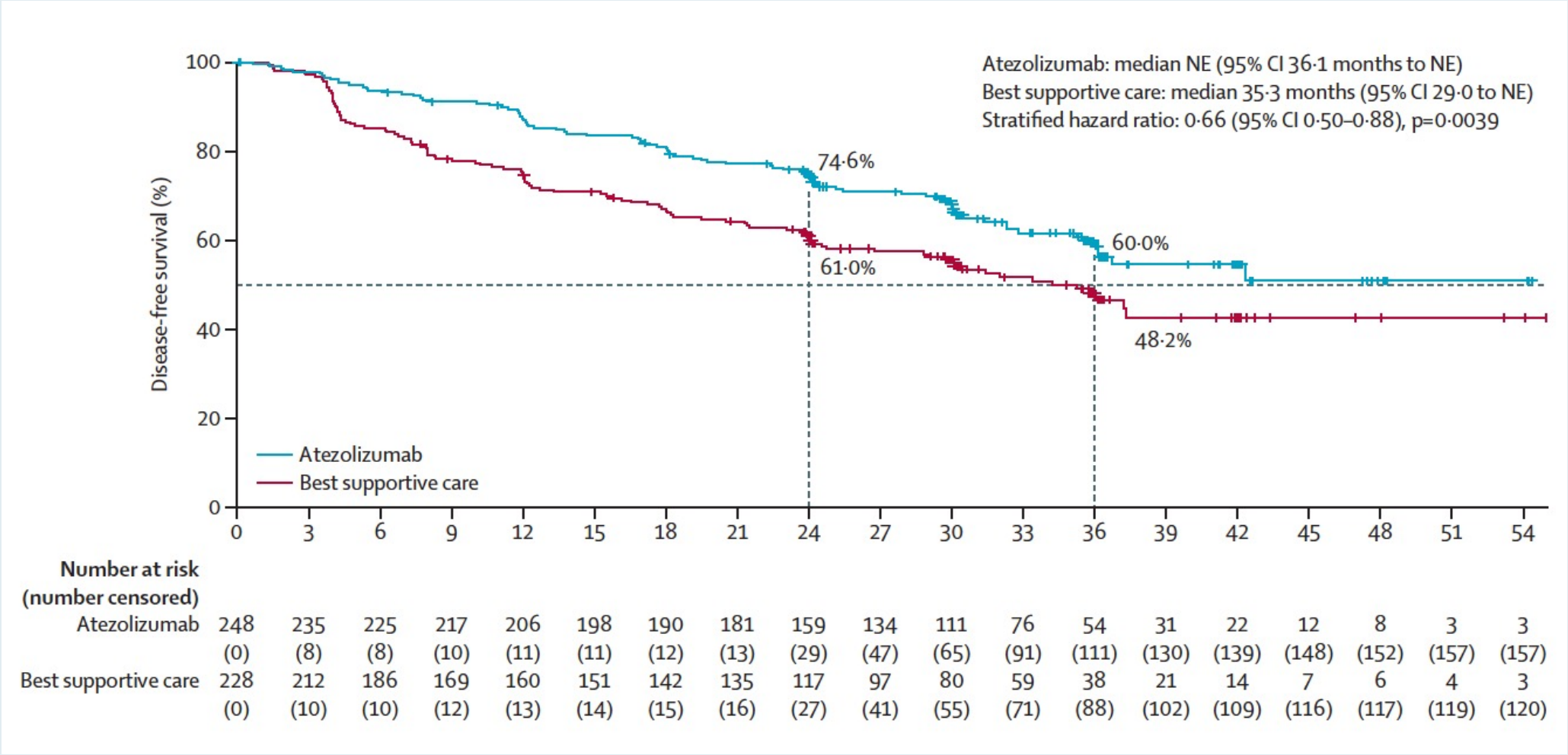
https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-atezolizumab-adjuvant-treatment-non-small-cell-lung-cancer

Lancet 2021;398(10308):1344-57.

Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB–IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial

*Enriqueta Felip, Nasser Altorki, Caicun Zhou, Tibor Csőszi, Ihor Vynnychenko, Oleksandr Goloborodko, Alexander Luft, Andrey Akopov, Alex Martinez-Marti, Hirotsugu Kenmotsu, Yuh-Min Chen, Antonio Chella, Shunichi Sugawara, David Voong, Fan Wu, Jing Yi, Yu Deng, Mark McCleland, Elizabeth Bennett, Barbara Gitlitz, Heather Wakelee, for the IMpower010 Investigators**

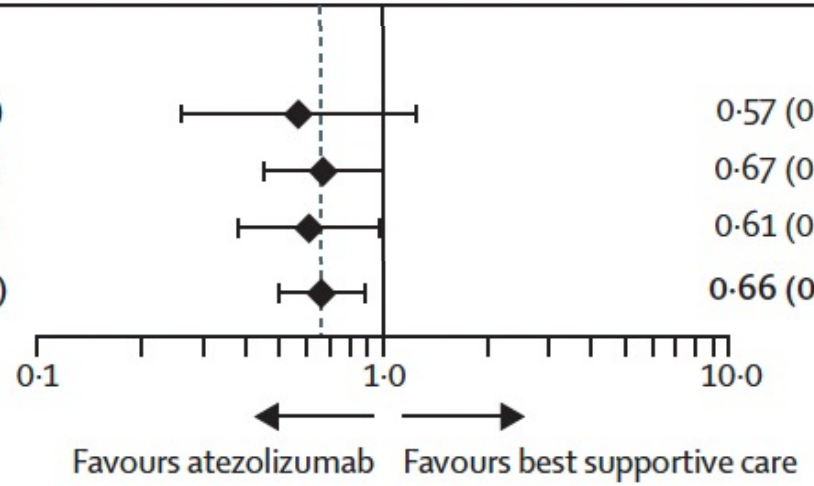
IMpower010 Primary Endpoint: Disease-Free Survival in the PD-L1 ≥1% Tumor Cells Stage II-IIIA Population



Felip E et al. *Lancet* 2021;398(10308):1344-57.

IMpower010: Disease-Free Survival by EGFR Mutation Status

	Atezolizumab group		Best supportive care group		Hazard ratio (95% CI)
	Events/patients, n/N	Median DFS (95% CI), months	Events/patients, n/N	Median DFS (95% CI), months	
***EGFR* mutation status**					
Yes	23/43	29·7 (18·0–NE)	20/43	16·6 (6·7–31·4)	0·57 (0·26–1·24)
No	123/248	NE (35·5–NE)	125/248	36·0 (26·7–NE)	0·67 (0·45–1·00)
Unknown	102/185	NE (36·1–NE)	83/185	35·3 (23·9–NE)	0·61 (0·38–0·98)
All patients	**248/476**	**NE (36·1–NE)**	**228/476**	**35·3 (29·0–NE)**	**0·66 (0·50–0·88)**



Felip E et al. *Lancet* 2021;398(10308):1344-57.

Current and Future Management of Metastatic NSCLC with EGFR Mutation

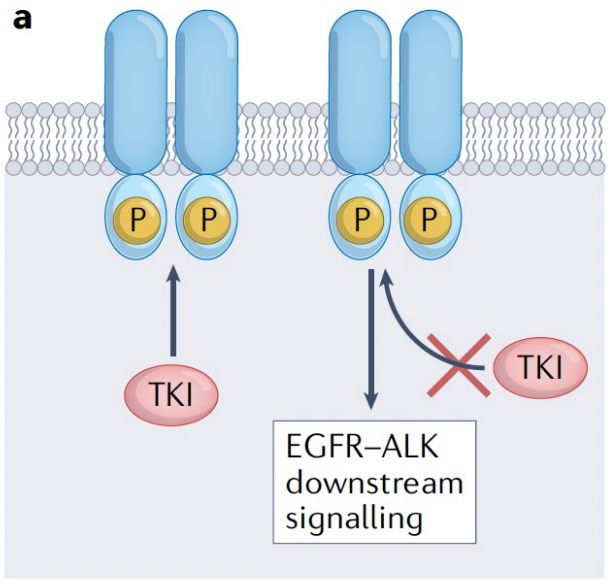
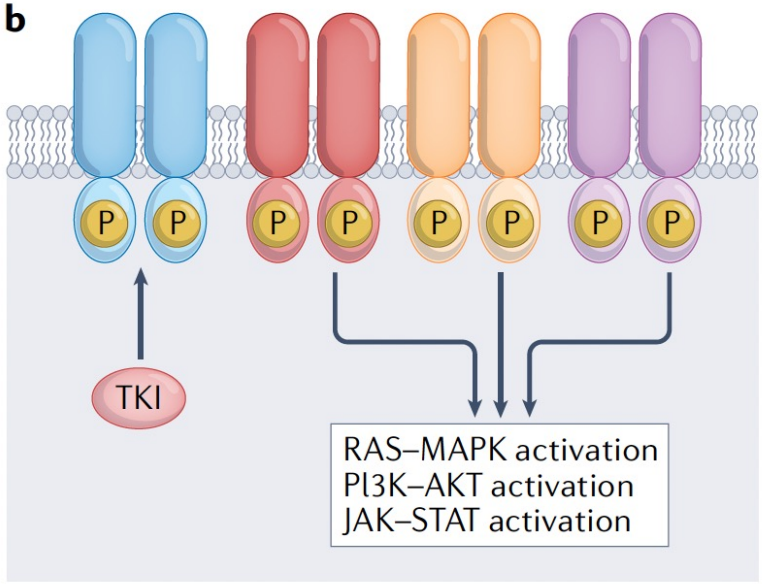
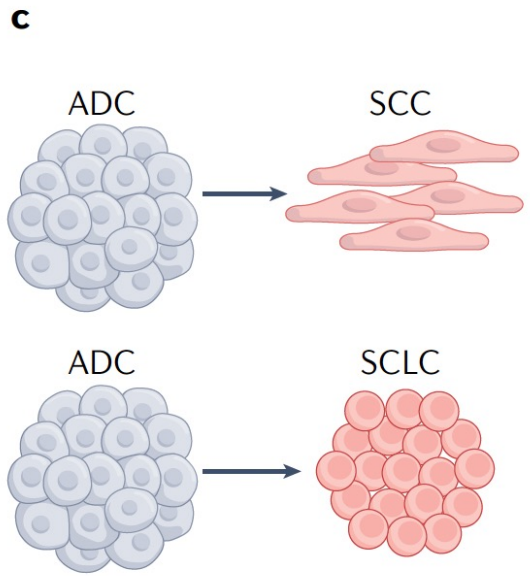
Select Ongoing Phase III Studies of First-Line Therapy for Patients with Metastatic NSCLC and Activating EGFR Mutations

Study	No. of patients	Randomization	Est primary completion
FLAURA2	587	• Osimertinib • Osimertinib + platinum-based chemo	April 2023
MARIPOSA	1,000	• Amivantamab + lazertiniib • Osimertinib + placebo • Lazertinib + placebo	April 2024
ECOG-ACRIN EA5182	300	• Osimertinib • Osimertinib + bevacizumab	September 2025
SANOVO*	320	• Osimertinib + savolitinib • Osimertinib + placebo	November 2024
FLETEO	680	• Osimertinib • TY-9591	May 2025

* Sensitizing EGFR mutation and c-MET overexpression

www.clinicaltrials.gov. Accessed June 2022.

Mechanisms of Acquired Resistance to Osimertinib

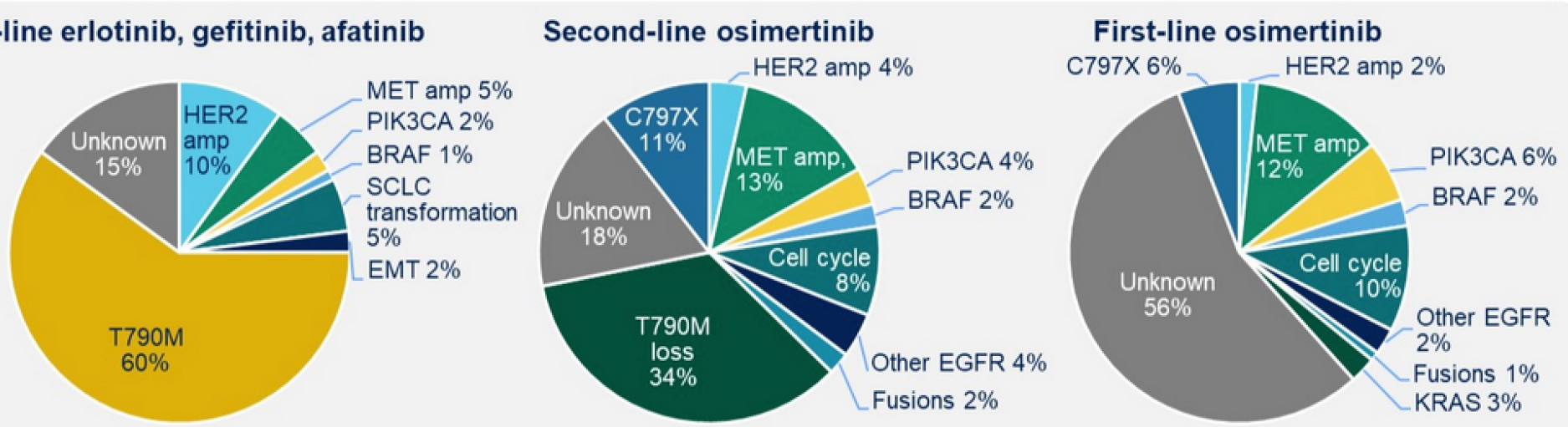
	Alterations that prevent inhibition of the target receptor tyrosine	Activation of bypass and/or downstream signalling pathways	Changes in tumour cell lineage such as transformation
			
Osimertinib resistance	*EGFR* C797X, G796X, L792X, G724S, L718Q	• Amplifications in *MET*, *HER2*, *KRAS*, *NRAS*, *YES1* • Rearrangements in *RET*, *NTRK1*, *ALK*, *BRAF*, *ROS1*, *FGFR3* • Mutations in *BRAF*, *HER2*, *KRAS*, *NRAS*, *PIK3CA* • Others: *AXL* overexpression, IGF1R activation	• Small-cell transformation • Squamous-cell transformation • EMT

Cooper AJ et al. *Nat Rev Clin Oncol* 2022;19(8):499-514.

RTP RESEARCH TO PRACTICE

Broad Range of Resistance Mechanisms in NSCLC with EGFR Mutation After Failure of EGFR TKI Therapy

Wide variety of genomic alterations associated with EGFR TKI resistance[1,2]



1. Engelman JA, et al. *Science*. 2007;316:1039-1043. 2. Schoenfeld AJ, Yu HA. *J Thorac Oncol*. 2020;15:18-21. 3. Han B, et al. *Onco Targets Ther*. 2018;11:2121-9. 4. Yang CJ, et al. *BMC Pharmacol Toxicol*. 2017;18(1).

Janne PA et al. ASCO 2021;Abstract 9007.

PARIS 2022 ESMO congress

Abstract LBA53

ELIOS: a multicentre, molecular profiling study of patients with EGFRm advanced NSCLC treated with first-line osimertinib

Zofia Piotrowska[1], Myung-Ju Ahn[2], Yong Kek Pang[3], Soon Hin How[4], Sang-We Kim[5], Pei Jye Voon[6], Diego Cortinovis[7], Javier de Castro Carpeno[8], Marcello Tiseo[9], Delvys Rodriguez Abreu[10], Suresh S. Ramalingam[11], Jingyi Li[12], Leslie Servidio[12], Samuel Sadow[13], Ryan Hartmaier[14], Byoung Chul Cho[15]

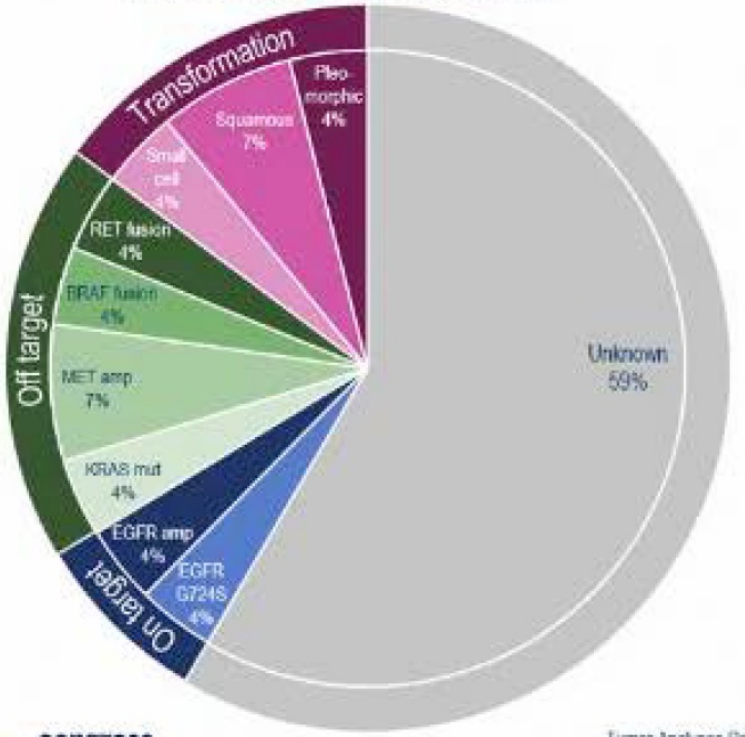
[1]Department of Medicine, Massachusetts General Hospital, Boston, MA, USA; [2]Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [3]Department of Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia; [4]Department of Medicine, Kulliyyah of Medicine, International Islamic University Malaysia, Kuantan, Malaysia; [5]Department of Oncology, Asan Medical Center, Seoul, South Korea; [6]Radiotherapy and Oncology Department, Hospital Umum Sarawak, Kuching, Malaysia; [7]Oncology Unit, San Gerardo Hospital, Monza, Italy; [8]Department of Medical Oncology, Hospital Universitario La Paz, IdiPAZ, Madrid, Spain; [9]Department of Medicine and Surgery, University of Parma, Parma, Italy and Medical Oncology Unit, University Hospital of Parma, Parma, Italy; [10]Department of Medical Oncology, Gran Canaria University Hospital, Las Palmas de Gran Canaria, Spain; [11]The Winship Cancer Institute of Emory University, Atlanta, GA, USA; [12]AstraZeneca, Oncology Business Unit, Global Medical Affairs, Gaithersburg, MD, USA; [13]Biometrics & Information Sciences, AstraZeneca, Gaithersburg, MD, USA; [14]Translational Medicine, AstraZeneca Oncology R&D, Boston, MA, USA; [15]Division of Medical Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea

RTP RESEARCH TO PRACTICE

Alterations Observed at the Time of First-Line Osimertinib Resistance

- To date, most data are liquid biopsy-based, although limited tissue-based data are available

Tissue biopsy analysis (n=27)[1]



Liquid biopsy analysis (FLAURA; n=91)[2]

Alteration	Frequency (%)
MET amplification	15
Secondary EGFR mutations	
C797X	7
PIK3CA mutations	7
Cell cycle gene alterations	
CDK4/5 amplification	5
CCND amplification	3
CCNE1 amplification	2
BRAF mutations	3
KRAS mutations	3
HER2 amplification	2

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Zofia Piotrowska, MD

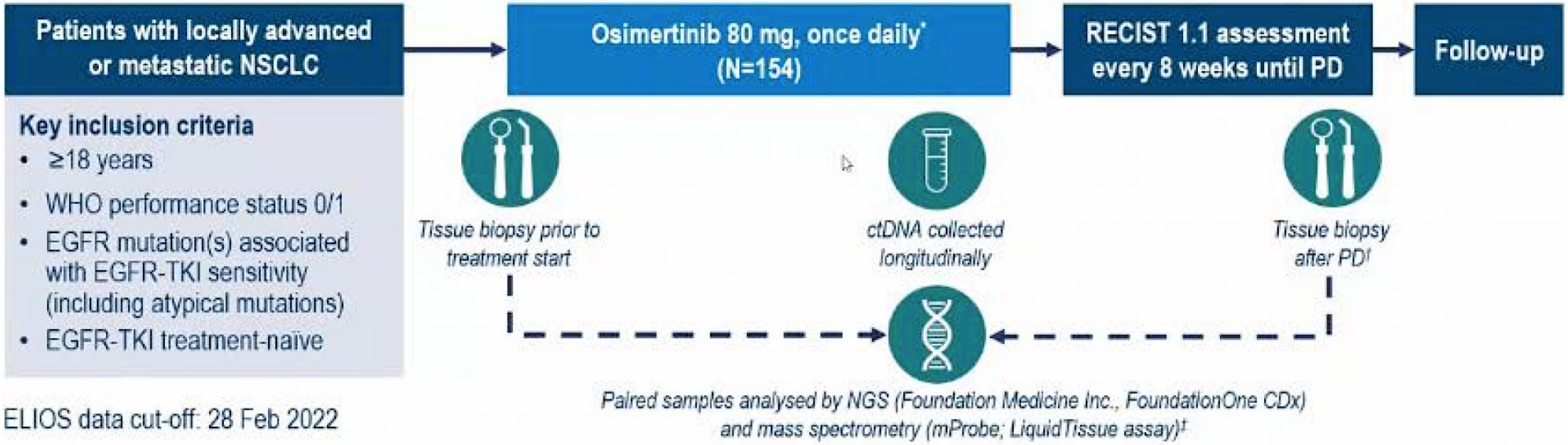
Figure adapted from Clin Cancer Res, 2020; 26(11); 2654–2663, Schoenfeld et al., Tumor Analyses Reveal Squamous Transformation and Off-Target Alterations As Early Resistance Mechanisms to First-line Osimertinib in EGFR-Mutant Lung Cancer, with permission from AACR

1. Schoenfeld et al. Clin Cancer Res 2020;26:2654–2663; 2. Ramalingam et al. Ann Oncol 2018;29(Suppl 8):viii740.

EGFR, epidermal growth factor receptor.

Piotrowska Z et al. ESMO 2022;Abstract LBA53.

ELIOS Phase II Study Design



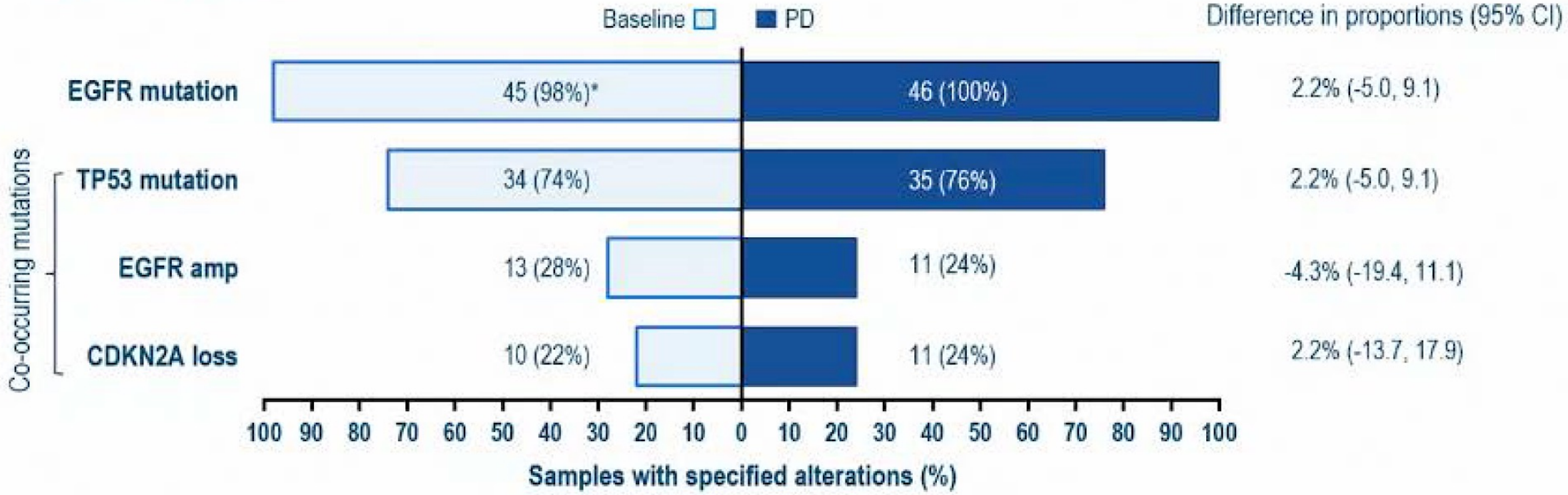
- **Primary endpoint**: proportion of patients with a given tumour genetic and proteomic marker (including, but not limited to, EGFR mutations, HER2 and MET expression and / or amplification) at PD
- Secondary endpoints: PFS (investigator-assessed), ORR, DoR, DCR, TTD, TFST, and safety

PD = disease progression; PFS = progression-free survival; ORR = objective response rate; DoR = duration of response; DCR = disease control rate; TTD = time to treatment discontinuation or death; TFST = time to first subsequent therapy or death

Piotrowska Z et al. ESMO 2022;Abstract LBA53.

ELIOS Primary Endpoint: High-Frequency Mutations from Baseline to Disease Progression (PAS-ITT)

- High frequency mutations at baseline (EGFR, TP53 mutations, EGFR amplification and CDKN2A loss) did not differ significantly at PD



Piotrowska Z et al. ESMO 2022;Abstract LBA53.

ELIOS Primary Endpoint: Summary of Major Alterations at Baseline and PD (PAS-ITT)

- Selected genetic alterations based on high frequency of detection and / or prior knowledge of involvement in osimertinib resistance are shown below

Gene alteration, N (%)	Baseline (n=46)	PD (n=46)	Acquired* (n=46)	Evidence of sensitivity
MET amp	2 (4)	9 (20)	**8 (17)**	✓[1,2]
CDKN2A del	10 (22)	11 (24)	**7 (15)**	
CDKN2B del	9 (20)	11 (24)	**7 (15)**	
MTAP del	7 (15)	10 (22)	**7 (15)**	
EGFR C797S	0 (0)	7 (15)	**7 (15)**	✓[3]
NKX2-1 amp	4 (9)	9 (20)	**5 (11)**	
EGFR amp	13 (28)	11 (24)	**5 (11)**	
CCNE1 amp	3 (7)	6 (13)	**3 (7)**	
ARAF amp	0 (0)	2 (4)	**2 (4)**	
ALK fusion	0 (0)	1 (2)	**1 (2)**	✓[4]

Piotrowska Z et al. ESMO 2022;Abstract LBA53.

PARIS 2022 ESMO congress

Abstract LBA51

EORTC European Organisation for Research and Treatment of Cancer

Osimertinib treatment based on plasma T790M monitoring in patients with *EGFR*-mutant advanced non-small cell lung cancer: EORTC Lung Cancer Group 1613 APPLE phase II randomized clinical trial

Jordi Remon[1], Benjamin Besse[1], Santiago Ponce[2], Ana Callejo[3], Kamal Al-Rabi[4], Reyes Bernabe[5], Laurent Greillier[6], Margarita Majem[7], Noemi Reguart[8], Isabelle Monnet[9], Sophie Cousin[10], Pilar Garrido[11], Gilles Robinet[12], Rosario Garcia-Campelo[13], Anne Madroszyk[14], Julien Mazières[15], Yassin Pretzenbacher[16], Beatrice Fournier[16], Anne-Marie C. Dingemans[17], Rafal Dziadziuszko[18]

[1]Institut Gustave Roussy (CLCC), Paris, France; [2]Hospital Universitario 12 De Octubre, Madrid, Spain; [3]Hospital Universitari Vall d'Hebron - Vall d'Hebron Institut Oncologia, Barcelona, Spain; [4]King Hussein Cancer Center, Amman, Jordan; [5]University Hospital Virgen del Rocio, Sevilla, Spain; [6]Aix Marseille University, Assitance Publique – Hôpitaux de Marseille (APHM), Marseille, France; [7]Hospital De La Santa Creu I Sant Pau, Barcelona, Spain; [8]Hospital Clinic Universitari de Barcelona, IDIBAPS, Barcelona, Spain; [9]Centre Hospitalier Intercommunal De Creteil, Creteil, France; [10]Institut Bergonie, Bordeaux, France; [11]Hospital Universitario Ramon y Cajal, Madrid, Spain; [12]CHU de Brest, Brest, France; [13]University Hospital A Coruna-Hospital Teresa Herrera, A Coruna, Spain; [14]Institut Paoli-Calmettes, Marseille, France; [15]CHU de Toulouse - Hopital Larrey, Toulouse, France; [16]EORTC Headquarters, Brussels, Belgium; [17]Erasmus Medical Center, Rotterdam, Netherlands; [18]Medical University of Gdansk, Gdansk, Poland

RTP RESEARCH TO PRACTICE

APPLE Phase II Study Design

- Advanced NSCLC.
- Del19, L858R *EGFR* mut.
- EGFR TKI naïve.
- ECOG PS 0-2.
- Stable BM allowed w/o steroids.

R 1:1:1

A N=53 → Osimertinib 80 mg daily (QD) until RECIST 1.1 PD

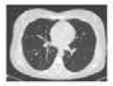
B N=52 → Gefitinib 250 mg QD until central ct-DNA T790M + or RECIST 1.1 PD → Osimertinib 80 mg QD until RECIST 1.1 PD

C N=51 → Gefitinib 250 mg QD until RECIST 1.1 PD → Osimertinib 80 mg QD until RECIST 1.1 PD

Stratification criteria:

- *EGFR* mutation subtype (Del19 *vs*. L858R)
- Brain metastasis (present *vs*. absent)
- T790M at baseline (positive *vs*. negative)

CENTRAL ct-DNA cobas *EGFR* Mutation Test v2, performed Q4W.
Only applied as a predictive for making treatment decisions in arm B



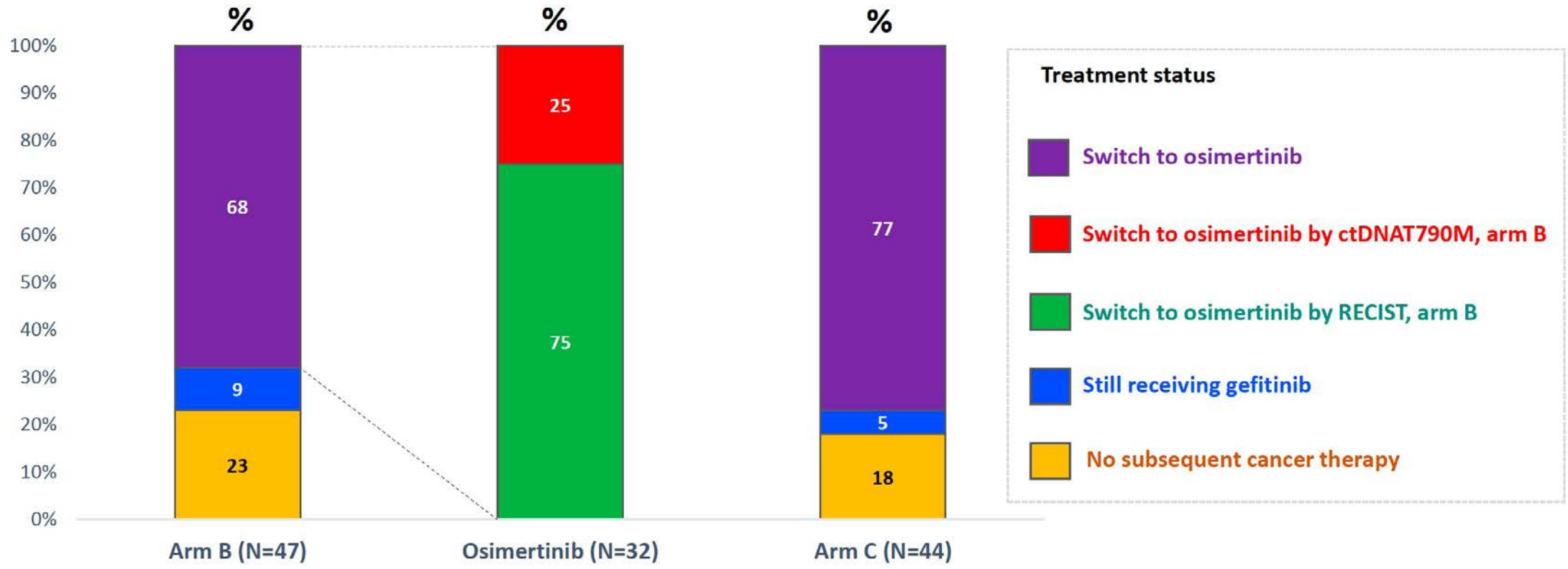
RECIST 1.1 assessment with thorax, abdomen and brain CT-scans Q8W.

- **Primary End Point:** Progression Free Survival rate at 18 months on osimertinib by investigator (RECIST 1.1)
- **Secondary End Points:** Overall Response Rate, Overall Survival.

BM = brain metastases; PD = disease progression

Remon J et al. ESMO 2022;Abstract LBA51.

APPLE: Switch to Osimertinib

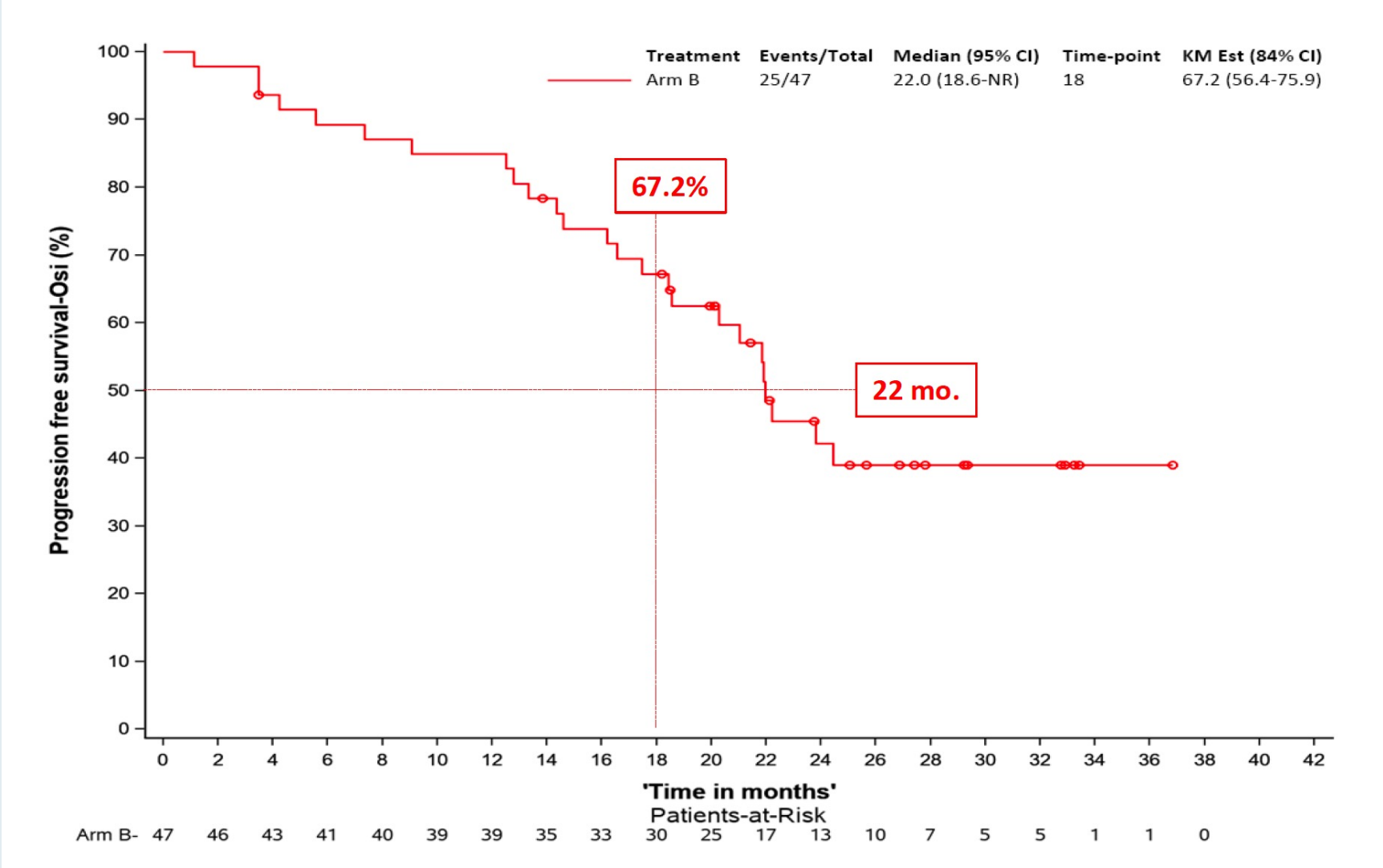


- In arm B, **17% (8/47) of PPP switched to osimertinib due to molecular progression** (ctDNA *EGFR* T790M positive)
- Median time to molecular progression was 266 days (range: 56-672 days)

Remon J et al. ESMO 2022;Abstract LBA51.

RTP RESEARCH TO PRACTICE

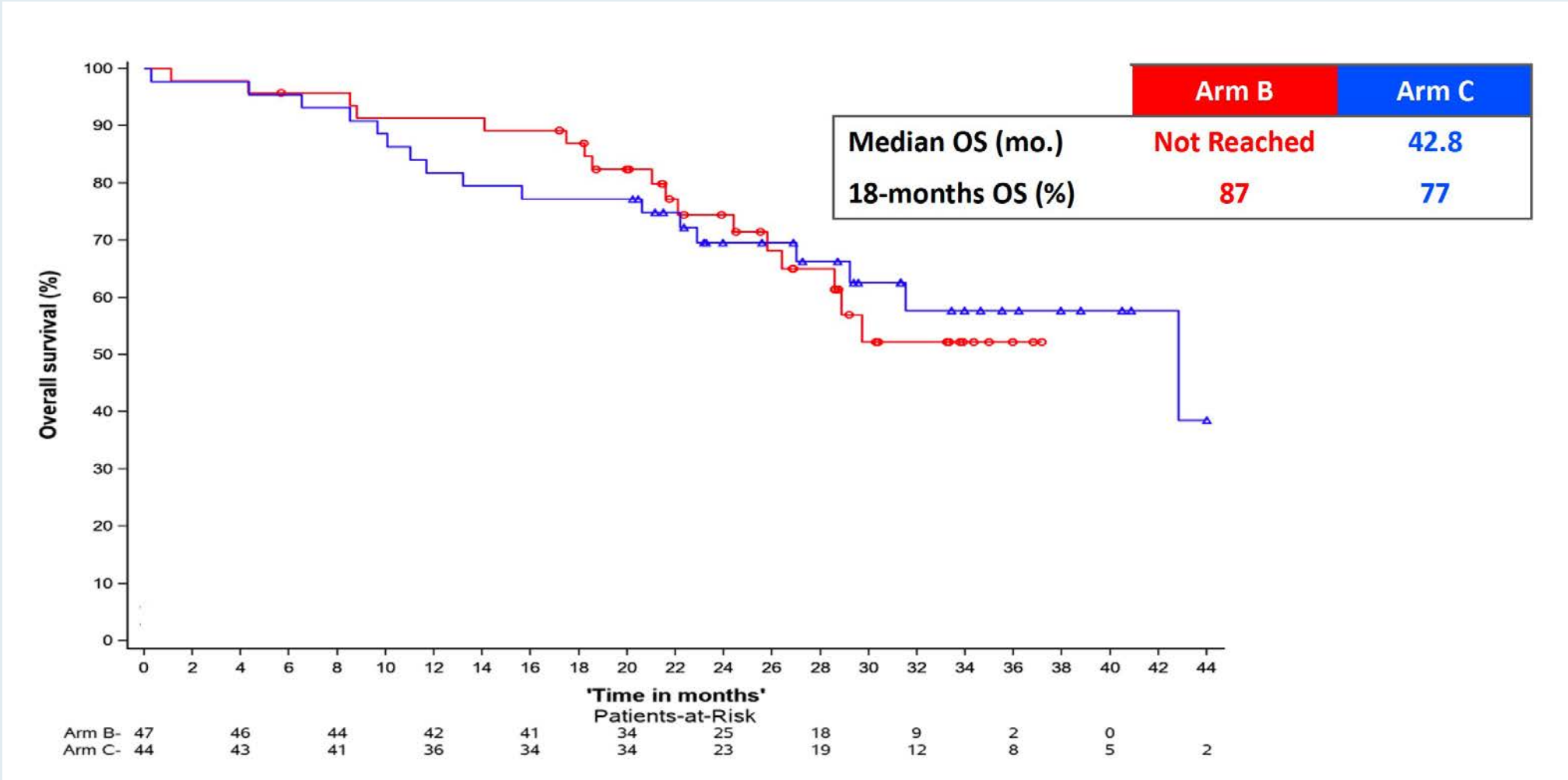
APPLE Primary Endpoint: PFS Rate at 18 Months by Investigator Assessment Arm B



Osi = osimertinib

Remon J et al. ESMO 2022;Abstract LBA51.

APPLE: Overall Survival (OS)



Remon J et al. ESMO 2022;Abstract LBA51.

LBA52

PARIS 2022 ESMO congress

Tepotinib + osimertinib for *EGFR*m NSCLC with *MET* amplification (*MET*amp) after progression on first-line (1L) osimertinib:

Initial results from the INSIGHT 2 study

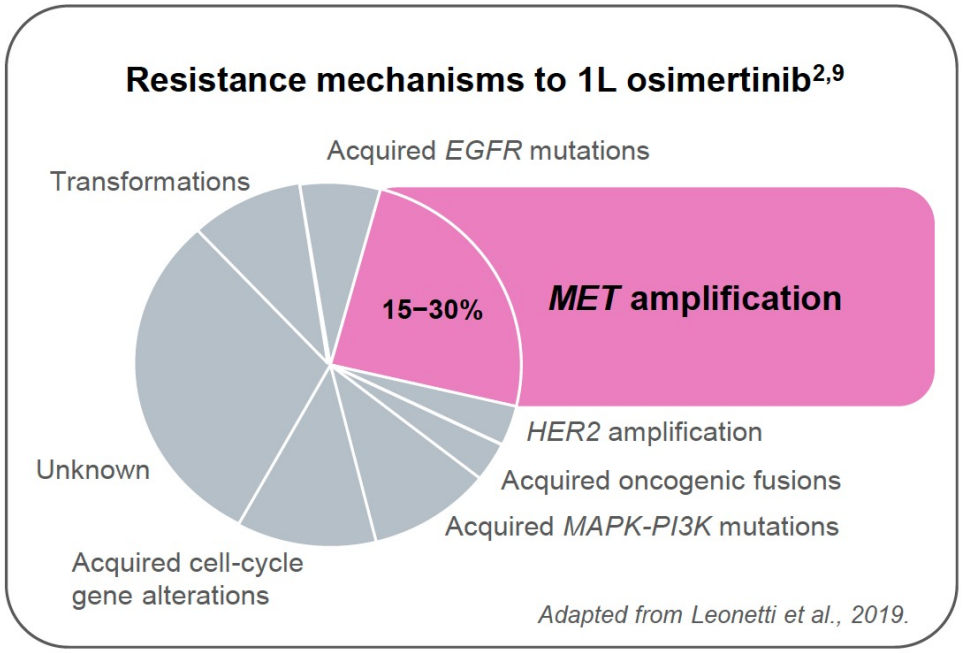
Julien Mazieres, Tae Min Kim, Boon Khaw Lim, Marie Wislez, Christophe Dooms, Giovanna Finocchiaro, Hidetoshi Hayashi, Chong Kin Liam, Jo Raskin, Lye Mun Tho, Filippo de Marinis, Ernest Nadal, Egbert F. Smit, Xiuning Le, Sabine Brutlach, Aurora O'Brate, Svenja Adrian, Barbara Ellers-Lenz, Niki Karachaliou, Yi-Long Wu

Toulouse, France

RTP RESEARCH TO PRACTICE

INSIGHT 2 Study Background

- 15–30% of patients with *EGFR*m NSCLC treated with osimertinib develop resistance through *MET* amplification (*MET*amp)[1,2]
  - TBx FISH, the gold standard *MET*amp detection method has detection rates of ~30% compared with ~15% with NGS LBx[2–5]
- *MET*amp is associated with a poor prognosis[2,6]
- Tepotinib + an EGFR TKI have shown clinical activity in *EGFR*m NSCLC with *MET*amp
  - INSIGHT study (tepotinib + gefitinib)[7]
  - Real-world evidence (tepotinib + osimertinib)[8]



The combination of tepotinib plus osimertinib is being investigated in patients with *EGFR*m NSCLC with *MET*amp in INSIGHT 2: here we present initial results from this study

1. Ramalingam SS, et al. *Ann. Oncol.* 2018;29(suppl 8):viii740; 2. Wang Y, et al. *Lung Cancer.* 2018;118:105–110; 3. Smit EF, et al. *Future Oncol.* 2022;18:1039–1054;
4. Heydt C, et al. *Comput. Struct. Biotechnol. J.* 2019;17:1339–1347; 5. Cho BC, et al. *Ann. Oncol.* 2018;29:ix177. Abstract LBA8; 6. Koulouris A, et al. *Cancers.* 2022;14:3337;
7. Wu YL, et al. *Lancet Respir Med.* 2020:8(11);1132–1143; 8. Le X, et al. Poster presentation at WCLC 2022. [EP08.02-162]; 9. Leonetti A, et al. *Br J Cancer.* 2019;121(9):725–737.

TKI = tyrosine kinase inhibitor; 1L = first-line

Mazieres J et al. ESMO 2022;Abstract LBA52.

INSIGHT 2 Phase II Study Design

An open-label, two-arm Phase II study of advanced *EGFR*m NSCLC with *MET*amp after progression on 1L osimertinib (N=~120)

Key inclusion criteria

- Locally advanced or metastatic NSCLC with activating *EGFR* mutation
- Acquired resistance to 1L osimertinib
- *MET*amp detected by either central or local* FISH testing (TBx) or central NGS testing (LBx)†
- ECOG PS of 0 or 1
- Stable, treated brain metastases allowed

Tepotinib 500 mg QD
+
Osimertinib 80 mg QD‡

Tepotinib monotherapy arm#

Primary objective

- ORR by IRC for patients with *MET*amp centrally confirmed by TBx FISH treated with tepotinib plus osimertinib

Secondary objectives include:

- ORR by IRC in patients with:
  - *MET*amp by LBx NGS treated with tepotinib plus osimertinib
  - *MET*amp centrally confirmed by TBx FISH treated with tepotinib monotherapy

Initial results are presented; global enrollment is complete, primary analysis is planned when all patients have ≥9 months' follow-up

ORR = objective response rate; IRC = independent review committee

Mazieres J et al. ESMO 2022;Abstract LBA52.

INSIGHT 2: Objective Response Rate of Tepotinib with Osimertinib

Tepotinib plus osimertinib (IRC)

	*MET*amp by central TBx FISH		*MET*amp by central LBx NGS	
Follow-up	≥9 months (N=22)	≥3 months (N=48)	≥9 months (N=16)	≥3 months (N=23)
ORR (95% CI)	**54.5%** (32.2, 75.6)	**45.8%** (31.4, 60.8)	**50.0%** (24.7, 75.3)	**56.5%** (34.5, 76.8)
BOR, n (%)				
PR	12 (54.5)	22 (45.8)	8 (50.0)	13 (56.5)
SD	2 (9.1)	5 (10.4)	1 (6.3)	1 (4.3)
PD	4 (18.2)	10 (20.8)	5 (31.3)	5 (21.7)
NE	4 (18.2)	11 (22.9)*	2 (12.5)	4 (17.4)

Similar ORRs were reported according to *MET*amp GCN (TBx FISH):

Patients with ≥3 months' follow-up (N=48): **≥10 GCN**: 51.9% (95% CI: 31.9, 71.3) (N=27);
5–<10 GCN: 40.0% (95% CI: 19.1, 63.9) (N=20)†

Tepotinib monotherapy (IRC)

	*MET*amp by central TBx FISH
Follow-up	≥6 months (N=12)
ORR (95% CI)	**8.3%** (0.2, 38.5)
BOR, n (%)	
PR	1 (8.3)
SD	2 (16.7)
PD	8 (66.7)
NE	1 (8.3)

Seven patients switched to tepotinib plus osimertinib and five of them are still on combination treatment

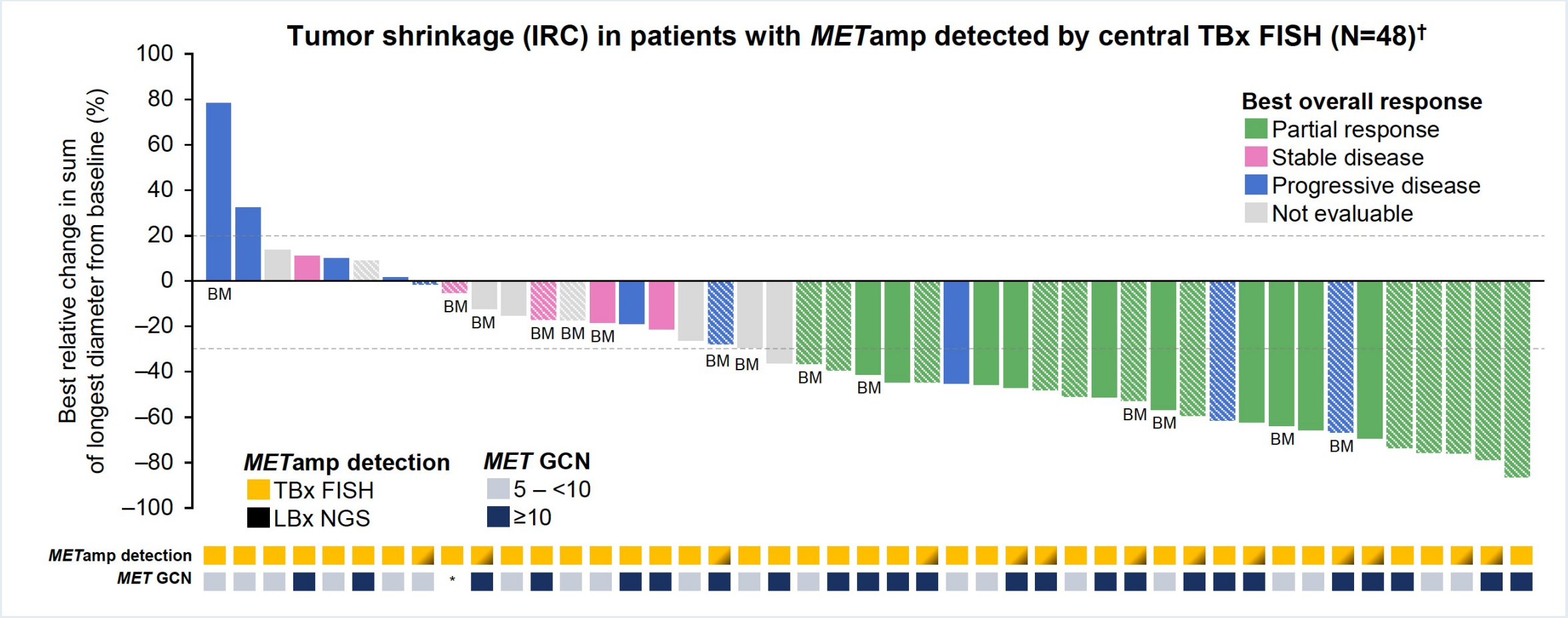
Confirmed ORR was 54.5% in patients with *MET*amp detected by TBx FISH with ≥9 months' follow-up

*Incomplete post-baseline assessments (n=2), SD <12 weeks (n=3), COVID-19-related early discontinuation (n=1), and PD/AE-related early discontinuations (n=5). †One patient had GCN 4.96 and enrolled through a *MET/CEP7* ratio ≥2.

ORR = objective response rate; BOR = best overall response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluated; GCN = gene copy number; AE = adverse event

Mazieres J et al. ESMO 2022;Abstract LBA52.

INSIGHT 2: Antitumor Activity of Tepotinib with Osimertinib



Mazieres J et al. ESMO 2022;Abstract LBA52.

INSIGHT 2: Safety Profile

TRAEs of any grade in >10% all patients, n (%)	Tepotinib + osimertinib N=88	
	Any grade	Grade ≥3
Any	**65 (73.9)**	**21 (23.9)**
Diarrhea	36 (40.9)	0
Peripheral edema	21 (23.9)	4 (4.5)
Paronychia	15 (17.0)	1 (1.1)
Nausea	12 (13.6)	0
Decreased appetite	10 (11.4)	2 (2.3)
Vomiting	10 (11.4)	1 (1.1)

- AEs led to a dose reduction in 16 patients (18.2%)
  - Tepotinib dose was reduced in 14 patients (15.9%)
  - Osimertinib dose was reduced in four patients (4.5%)
  - Two patients had a dose reduction in both drugs
- Primary reason for treatment discontinuation was AEs in six patients (6.8%)
- Two patients had AEs leading to death that were considered potentially related to either trial drug by the investigator
  - One patient had pneumonia/pneumonitis
  - One patient had pleural effusion

The safety profile of the combination was consistent with the known safety profiles of tepotinib and osimertinib

AEs = adverse events; TRAEs = treatment-related AEs

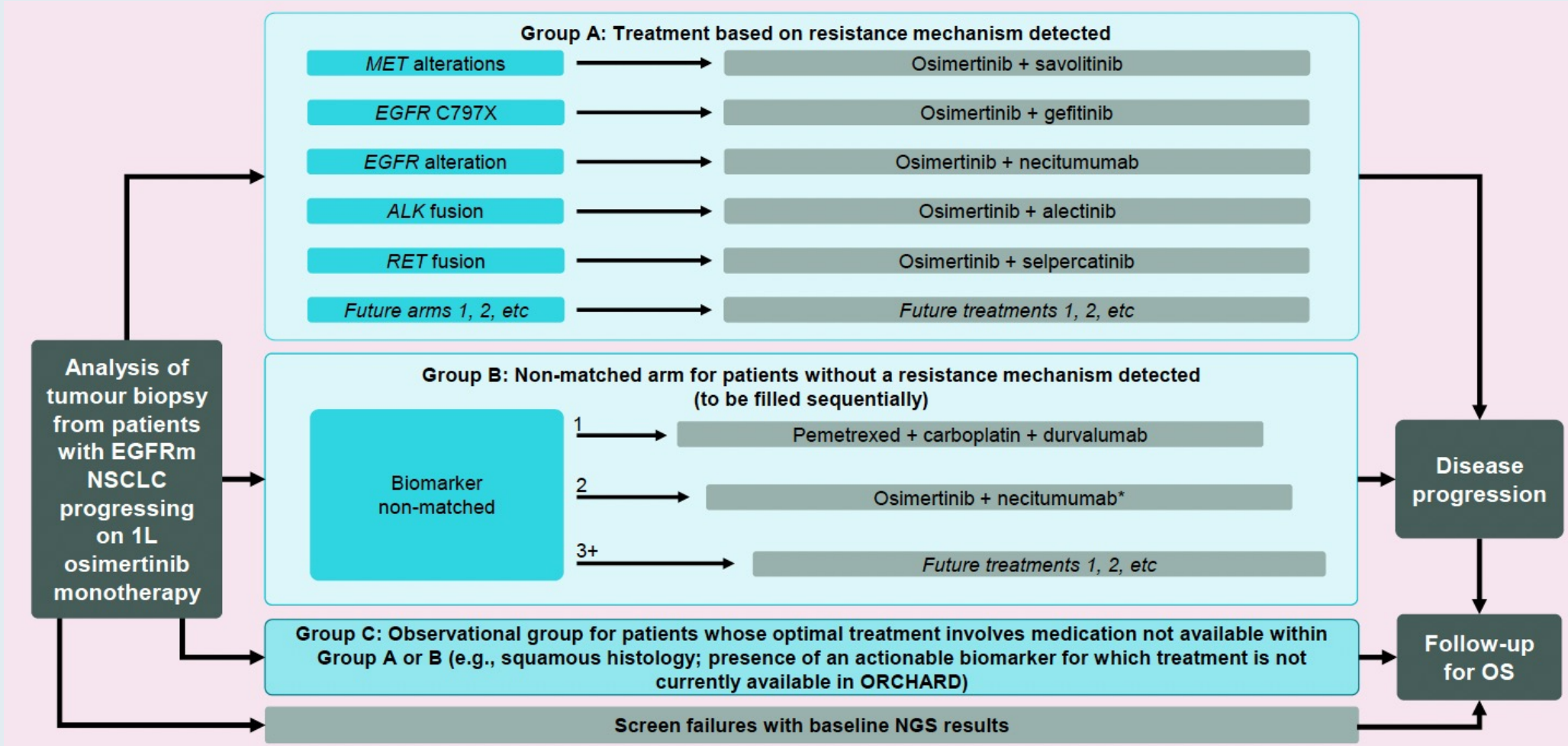
Mazieres J et al. ESMO 2022;Abstract LBA52.

ORCHARD Osimertinib + Savolitinib Interim Analysis: A Biomarker-Directed Phase II Platform Study in Patients with Advanced Non-Small Cell Lung Cancer (NSCLC) Whose Disease Has Progressed on First-Line (1L) Osimertinib

Yu HA et al.

ESMO 2021;Abstract 1239P.

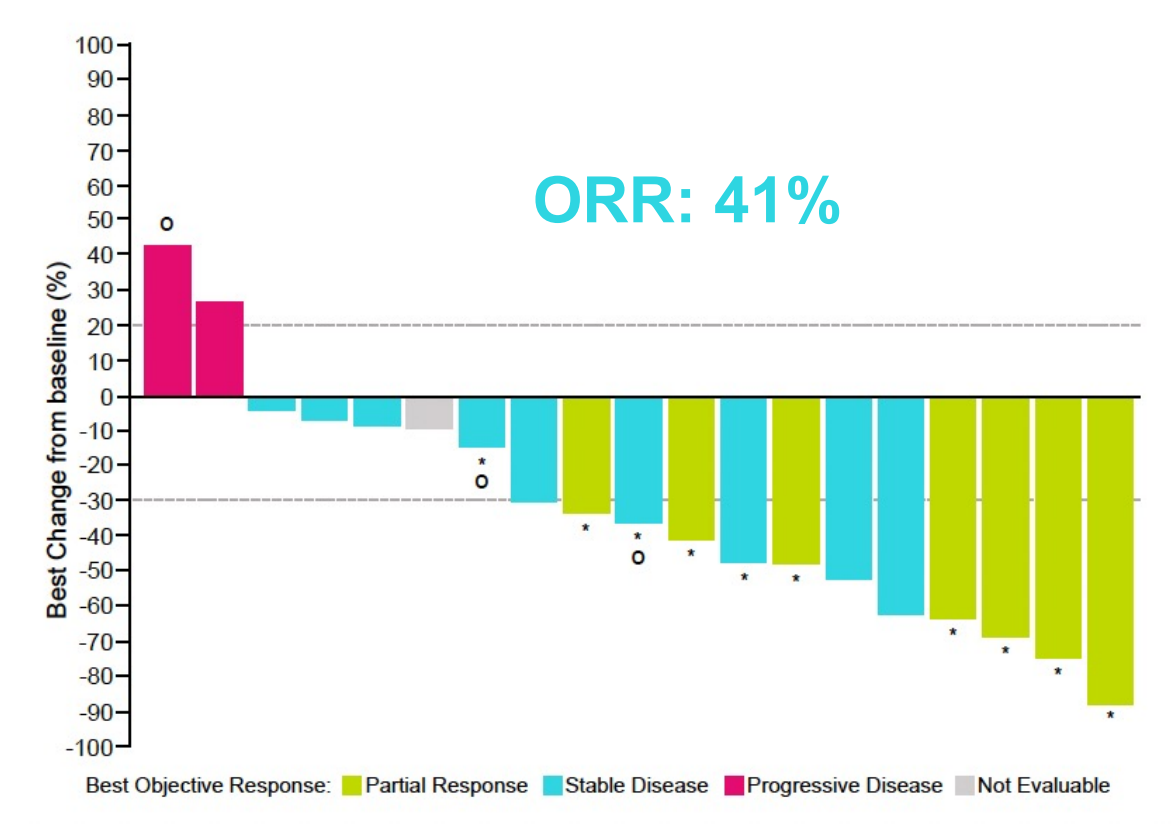
ORCHARD Study Design

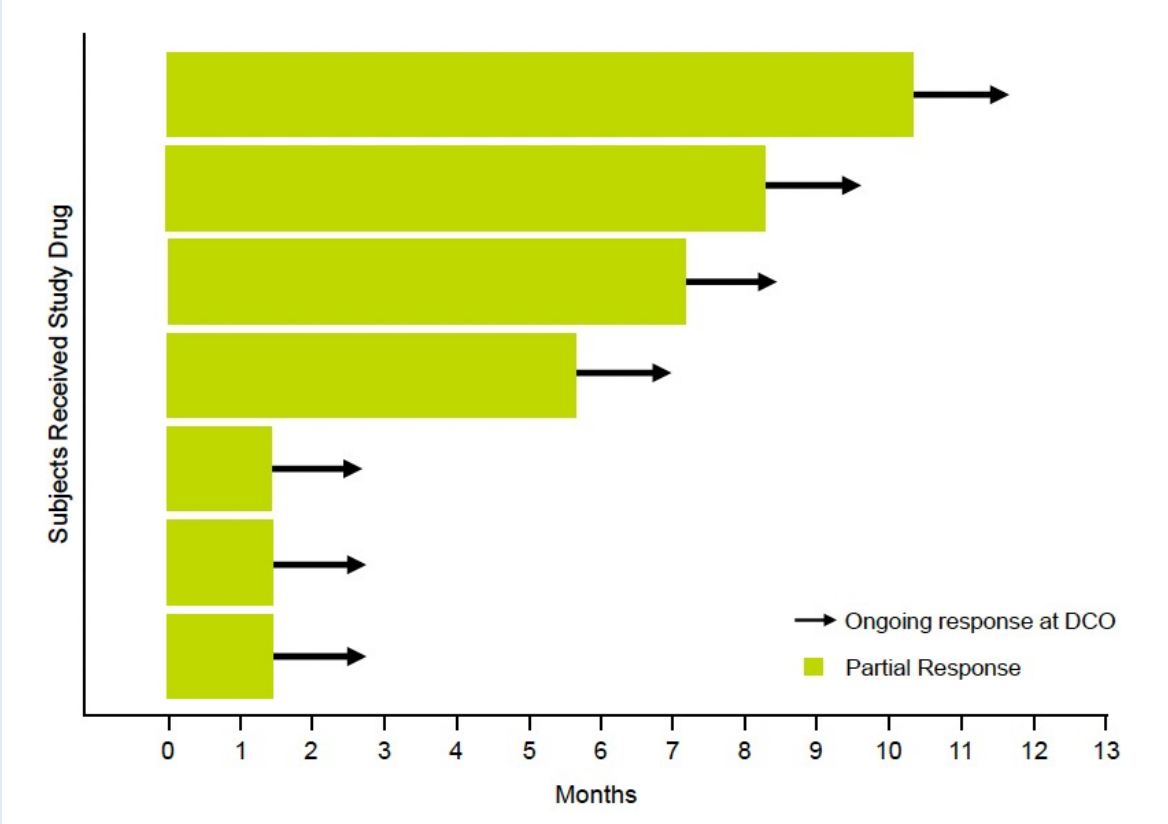


Group A: Patients who are positive for protocol-determined biomarker; Group B: patients without an available protocol-determined biomarker match, allocated sequentially, once first cohort cap has been reached, the next cohort allocation will begin; Group C: observational cohort, treated in accordance with local practice.
*Recruitment dependent on the outcome of planned interim analyses of the osimertinib + necitmumab combination arm in the biomarker matched cohort.
1L; first-line; *ALK*, anaplastic lymphoma kinase; *EGFR*, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; NGS, next generation sequencing; ORR, objective response rate; OS, overall survival

Yu HA et al. ESMO 2021;Abstract 1239P.

ORCHARD: Response and Duration of Response





ORR = objective response rate; DCO = data cutoff

Yu HA et al. ESMO 2021;Abstract 1239P.

RTP RESEARCH TO PRACTICE

ORCHARD: Incidence of Grade ≥3 Adverse Events

Most common AEs*, n (%)	Osimertinib + savolitinib N=20
Neutrophil count decrease	2 (10)
Pneumonia	2 (10)
Pneumonitis	1 (5)
Influenza	1 (5)
Hypersensitivity	1 (5)
Ischaemic stroke	1 (5)
Deep vein thrombosis	1 (5)
Pulmonary embolism	1 (5)
Alanine aminotransferase increase	1 (5)
Aspartate aminotransferase increase	1 (5)
Amylase increase	1 (5)
Blood fibrinogen decrease	1 (5)
Lymphocyte count decrease	1 (5)
White blood cell count decrease	1 (5)

Yu HA et al. ESMO 2021;Abstract 1239P.

Select Ongoing Studies to Overcome Mechanisms of Resistance to EGFR TKIs for Advanced NSCLC

Study/phase	No. of patients	Eligibility	Treatment
SAVANNAH Phase II	294	• Locally advanced/metastatic • EGFR mutation • MET amplified/overexpressed • PD on osimertinib	• Osimertinib + savolitinib
SAFFRON Phase III	324	• Locally advanced/metastatic • EGFR mutation • MET amplified/overexpressed • PD on osimertinib	• Osimertinib + savolitinib • Platinum-based doublet
COMPEL Phase III	204	• Locally advanced/metastatic • EGFR mutation • Extracranial PD on first-line osimertinib	• Platinum/pemetrexed + osimertinib • Platinum/pemetrexed + placebo
MARIPOSA-2 Phase III	500	• Locally advanced/metastatic • EGFR mutation • PD on osimertinib	• Platinum-based chemotherapy + amivantamab + lazertinib • Platinum-based chemotherapy

PD = disease progression

www.clinicaltrials.gov. Accessed June 2022.

RTP RESEARCH TO PRACTICE

FDA Grants Breakthrough Therapy Status to Patritumab Deruxtecan for Metastatic NSCLC with EGFR Mutation

Press Release: January 4, 2022

"Patritumab deruxtecan (U3-1402), a potential first-in-class HER3 directed antibody-drug conjugate, was granted breakthrough therapy designation by the FDA for the treatment of patients with metastatic or locally advanced, *EGFR*-mutant non–small cell lung cancer (NSCLC).

The regulatory decision, which is designed to accelerate the development and regulatory review process of potential new therapies, was based on data from a dose escalation study and 2 expansion cohorts from a 3-cohort trial.

Data from a phase 1 trial (NCT03260491) assessing the efficacy of patritumab deruxtecan in a heavily pretreated population of patients with EGFR-mutant NSCLC that have become resistant to other TKIs were read out at the 2021 American Society of Clinical Oncology Annual Meeting: Lung Cancer. A 5.6 mg/kg dose of the treatment resulted in a confirmed objective response rate of 39% (95% CI, 26%-52%) in a population of patients who were previously treated with a TKI and platinum-based therapy (n = 57). Additionally, treatment with patritumab deruxtecan resulted in a disease control rate of 72% (95% CI, 59%-83%), as well as a median progression-free survival of 8.2 months (95% CI, 4.0-not evaluable).

https://www.cancernetwork.com/view/fda-grants-breakthrough-therapy-status-to-patritumab-deruxtecan-for-egfr-metastatic-nsclc

RTP RESEARCH TO PRACTICE

RESEARCH ARTICLE

Cancer Discov 2022;12(1):74-89.

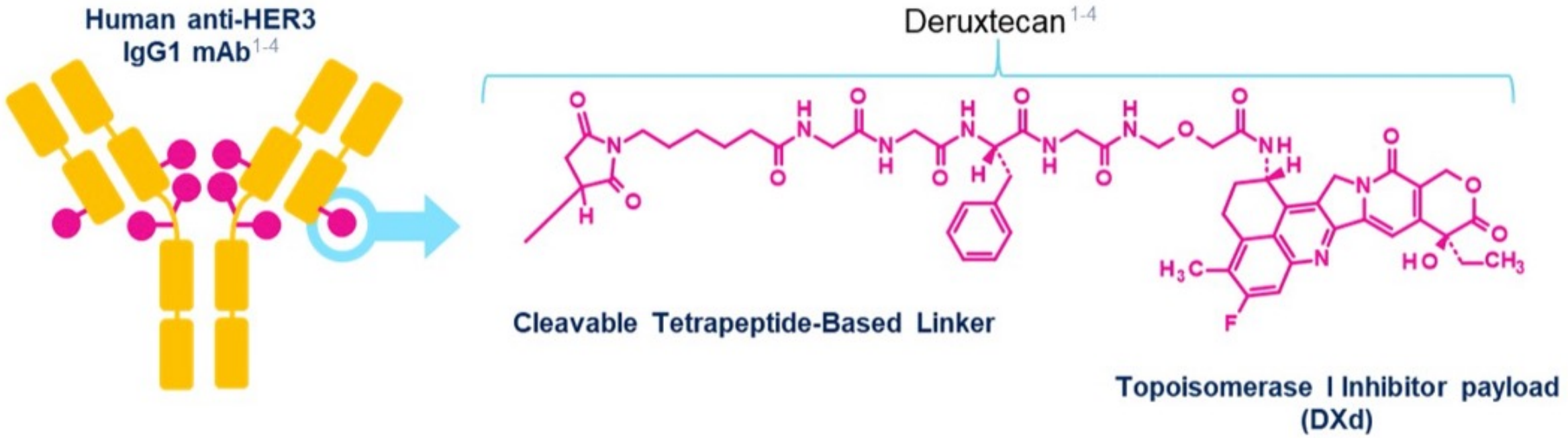
Efficacy and Safety of Patritumab Deruxtecan (HER3-DXd) in EGFR Inhibitor–Resistant, *EGFR*-Mutated Non–Small Cell Lung Cancer

Pasi A. Jänne[1], Christina Baik[2], Wu-Chou Su[3], Melissa L. Johnson[4], Hidetoshi Hayashi[5], Makoto Nishio[6], Dong-Wan Kim[7], Marianna Koczywas[8], Kathryn A. Gold[9], Conor E. Steuer[10], Haruyasu Murakami[11], James Chih-Hsin Yang[12], Sang-We Kim[13], Michele Vigliotti[14], Rong Shi[14], Zhenhao Qi[14], Yang Qiu[14], Lihui Zhao[14], David Sternberg[14], Channing Yu[14], and Helena A. Yu[15]

Patritumab Deruxtecan (HER3-DXd) Targeting HER3 May Address Multiple EGFR TKI Resistance Mechanisms

HER3-DXd is an antibody-drug conjugate with 3 components:

- A fully human anti-HER3 IgG1 mAb (patritumab), covalently linked to:
- A topoisomerase I inhibitor payload, an exatecan derivative, via
- A tetrapeptide-based cleaver linker



Janne PA et al. ASCO 2021;Abstract 9007.

Responses by Blinded Independent Central Review

Characteristics	Pooled RDE (5.6 mg/kg)	
	All pooled ($n = 57$)	Prior PBC and osimertinib ($n = 44$)
Confirmed ORR, % (n) [95% CI]	39 (22) [26.0–52.4]	39 (17) [24.4–54.5]
BOR, n (%)		
CR	1 (2)	1 (2)
PR	21 (37)	16 (36)
SD	19 (33)	13 (30)
PD	9 (16)	8 (18)
NE	7 (12)	6 (14)
DCR,[a] % (n) [95% CI]	72 (41) [58.5–83.0]	68 (30) [52.4–81.4]
TTR, median (range), months	2.6 (1.2–5.4)	2.7 (1.2–5.4)
Duration of response, median (95% CI), months	6.9 (3.1–NE)	7.0 (3.1–NE)
Progression-free survival, median (95% CI), months	8.2 (4.4–8.3)	8.2 (4.0–NE)
Overall survival, median (95% CI), months	NE (9.4–NE)	NE (8.2–NE)

Abbreviation: PBC, platinum-based chemotherapy.

[a]DCR = rate of confirmed BOR of CR, PR, or SD.

Jänne PA et al. *Cancer Discov* 2022;12(1):74-89.

Summary of Treatment-Emergent Adverse Events (TEAEs)

TEAEs	Pooled RDE 5.6 mg/kg ($n = 57$), n (%)	All patients 3.2/4.8/5.6/6.4 mg/kg ($n = 81$), n (%)
Any TEAE	57 (100)	81 (100)
Grade ≥3 TEAEs	42 (74)	52 (64)
Serious TEAEs	25 (44)	32 (40)
TEAEs associated with treatment discontinuation	6 (11)[a]	7 (9)[b]
TEAEs associated with dose reduction	12 (21)	18 (22)
TEAEs associated with dose interruption	21 (37)	30 (37)
TEAEs associated with death	4 (7)[c]	5 (6)[d]
Treatment-related TEAEs	55 (96)	78 (96)
Grade ≥3 treatment-related TEAEs	31 (54)	38 (47)
Treatment-related TEAEs associated with death	0	0
Serious treatment-related TEAEs	12 (21)	15 (19)

RDE = recommended dose for expansion

Jänne PA et al. *Cancer Discov* 2022;12(1):74-89.

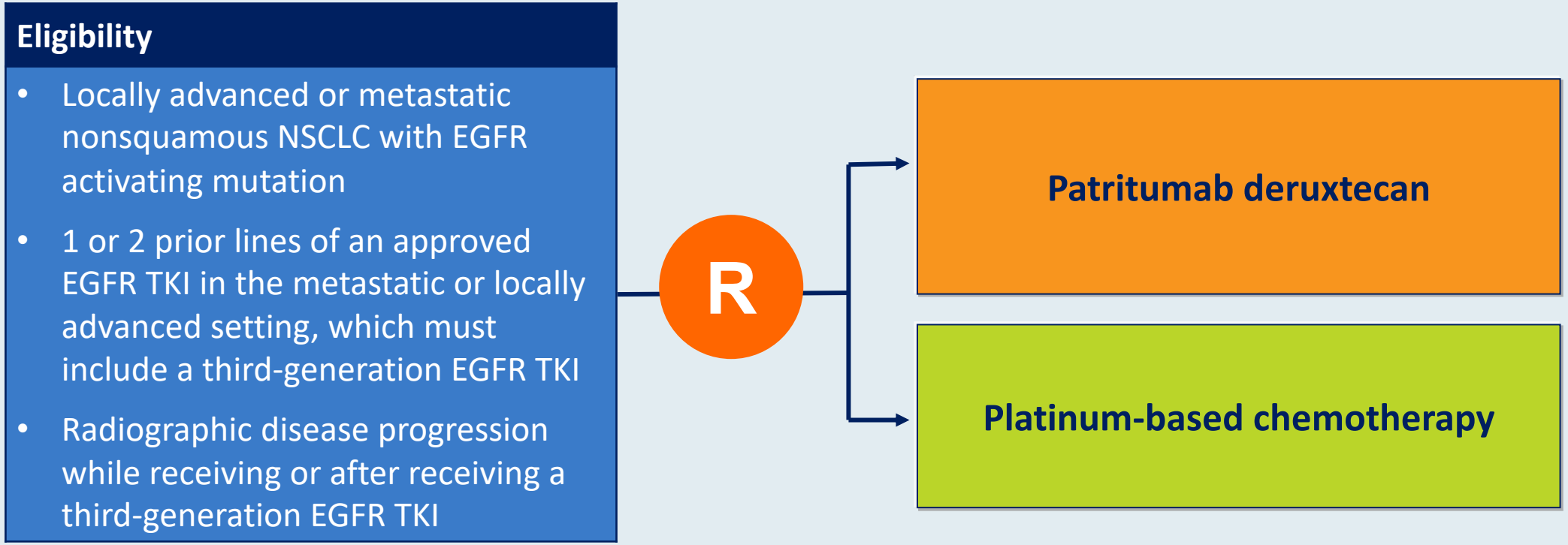
Select Grade ≥3 Treatment-Emergent Adverse Events (TEAEs)

TEAEs	Pooled RDE 5.6 mg/kg ($n = 57$), n (%)	All patients 3.2/4.8/5.6/6.4 mg/kg ($n = 81$), n (%)
Grade ≥3 TEAEs occurring in ≥5% of patients		
Platelet count decrease/thrombocytopenia	17 (30)	21 (26)
Neutrophil count decrease/neutropenia	11 (19)	12 (15)
Fatigue	8 (14)	8 (10)
Anemia/hemoglobin decrease	5 (9)	6 (7)
Dyspnea	5 (9)	5 (6)
Febrile neutropenia	5 (9)	5 (6)
Adjudicated ILD	5 (9)[e]	5 (6)[e]
Adjudicated treatment-related ILD	4 (7)[f]	4 (5)[f]

Jänne PA et al. *Cancer Discov* 2022;12(1):74-89.

HERTHENA-Lung02: An Ongoing Phase III Trial of Patritumab Deruxtecan for NSCLC with EGFR Mutation After Failure of an EGFR TKI

Trial identifier: NCT05338970 (Open)
Estimated enrollment: 560



Primary endpoint: Progression-free survival by blinded independent central review

www.clinicaltrials.gov. Accessed June 2022.

RTP RESEARCH TO PRACTICE

A patient with locally advanced NSCLC who receives definitive chemoradiation therapy followed by 1 year of consolidation durvalumab experiences disease progression 3 months later and is found to have an EGFR exon 19 deletion. Assuming the patient is clinically stable, how long would you like to wait before starting osimertinib?

 Dr Jänne	Would start now	 Dr Riely	3 mo from last dose of ICI
 Dr Neal	Consider starting now, but likely erlotinib for 3-6 mo then consider switching	 Dr Sequist	As long as possible depending on the disease tempo
 Dr Planchard	Would start now if local tx not possible	 Dr Spigel	Would start now

ICI = immune checkpoint inhibitor therapy

RTP RESEARCH TO PRACTICE

If an asymptomatic patient with metastatic nonsquamous NSCLC with an EGFR exon 19 deletion and a PD-L1 TPS of 10% responded to first-line osimertinib followed by disease progression, what would be your second-line treatment recommendation if the patient had acquired a MET amplification?

 Dr Jänne	Continue osimertinib and add capmatinib or tepotinib	 Dr Riely	Continue osimertinib and add capmatinib or tepotinib
 Dr Neal	Continue osimertinib and add tepotinib Carboplatin/pemetrexed/ bevacizumab	 Dr Sequist	Continue osimertinib and add crizotinib or capmatinib
 Dr Planchard	Continue osimertinib and add capmatinib, tepotinib or savolitinib	 Dr Spigel	Continue osimertinib and add carboplatin/ pemetrexed*

* If MET highly amplified and no EGFRm, capmatinib alone; if MET and EGFRm, then osimertinib/capmatinib (cautiously)

If an asymptomatic patient with metastatic nonsquamous NSCLC with an EGFR exon 19 deletion and a PD-L1 TPS of 10% responded to first-line osimertinib followed by disease progression, what would be your second-line treatment recommendation if the patient had acquired a BRAF V600E mutation?

 Dr Jänne	Continue osimertinib and add carboplatin/ pemetrexed	 Dr Riely	Continue osimertinib and add dabrafenib/ trametinib
 Dr Neal	Carboplatin/ pemetrexed + bevacizumab	 Dr Sequist	Continue osimertinib and add carboplatin/ pemetrexed
 Dr Planchard	Continue osimertinib and add dabrafenib/ trametinib	 Dr Spigel	Continue osimertinib and add carboplatin/ pemetrexed*

* If BRAFm alone and no EGFRm, BRAFi/MEKi

RTP RESEARCH TO PRACTICE

A patient with nonsquamous NSCLC with an EGFR exon 19 deletion and systemic and brain metastases has a good response to first-line osimertinib but experiences disease progression and is switched to chemotherapy. Would you continue the osimertinib?

 Dr Jänne	Yes, indefinitely	 Dr Riely	Yes, indefinitely
 Dr Neal	Yes, indefinitely, but depends on brain met PD vs systemic PD	 Dr Sequist	Yes, indefinitely
 Dr Planchard	No	 Dr Spigel	Yes, indefinitely

PD = disease progression

Available Therapeutic Strategies for Patients with NSCLC Harboring an EGFR Exon 20 Insertion Mutation

RTP
RESEARCH
TO PRACTICE

PLOS ONE 2021;16(3):e0247620.

RESEARCH ARTICLE

Epidemiological and clinical burden of *EGFR* Exon 20 insertion in advanced non-small cell lung cancer: A systematic literature review

Heather Burnett[1]*, Helena Emich[2], Chris Carroll[3], Naomi Stapleton[2], Parthiv Mahadevia[4], Tracy Li[4]

Global Exon 20 Insertion Rates

Region	EGFR exon 20 insertion among all patients with NSCLC	EGFR exon 20 insertion among patients with NSCLC and EGFR mutations
USA	0.5%-2.6%	5%-12%
Latin America	1.3%-2.1%	5%-8%
Europe	0.3%-1.3%	4%-12%
Asia Pacific	0.1%-4.0%	1%-5%

Burnett H et al. *PLoS One* 2021;16(3):e0247620.

FDA Grants Accelerated Approval to Amivantamab-vmjw for Metastatic NSCLC

Press Release: May 21, 2021

"The Food and Drug Administration granted accelerated approval to amivantamab-vmjw, a bispecific antibody directed against epidermal growth factor (EGF) and MET receptors, for adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.

FDA also approved the Guardant360® CDx as a companion diagnostic for amivantamab-vmjw.

Approval was based on CHRYSALIS, a multicenter, non-randomized, open label, multicohort clinical trial (NCT02609776) which included patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations. Efficacy was evaluated in 81 patients with advanced NSCLC with EGFR exon 20 insertion mutations whose disease had progressed on or after platinum-based chemotherapy. Patients received amivantamab-vmjw once weekly for 4 weeks, then every 2 weeks thereafter until disease progression or unacceptable toxicity."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-amivantamab-vmjw-metastatic-non-small-cell-lung-cancer

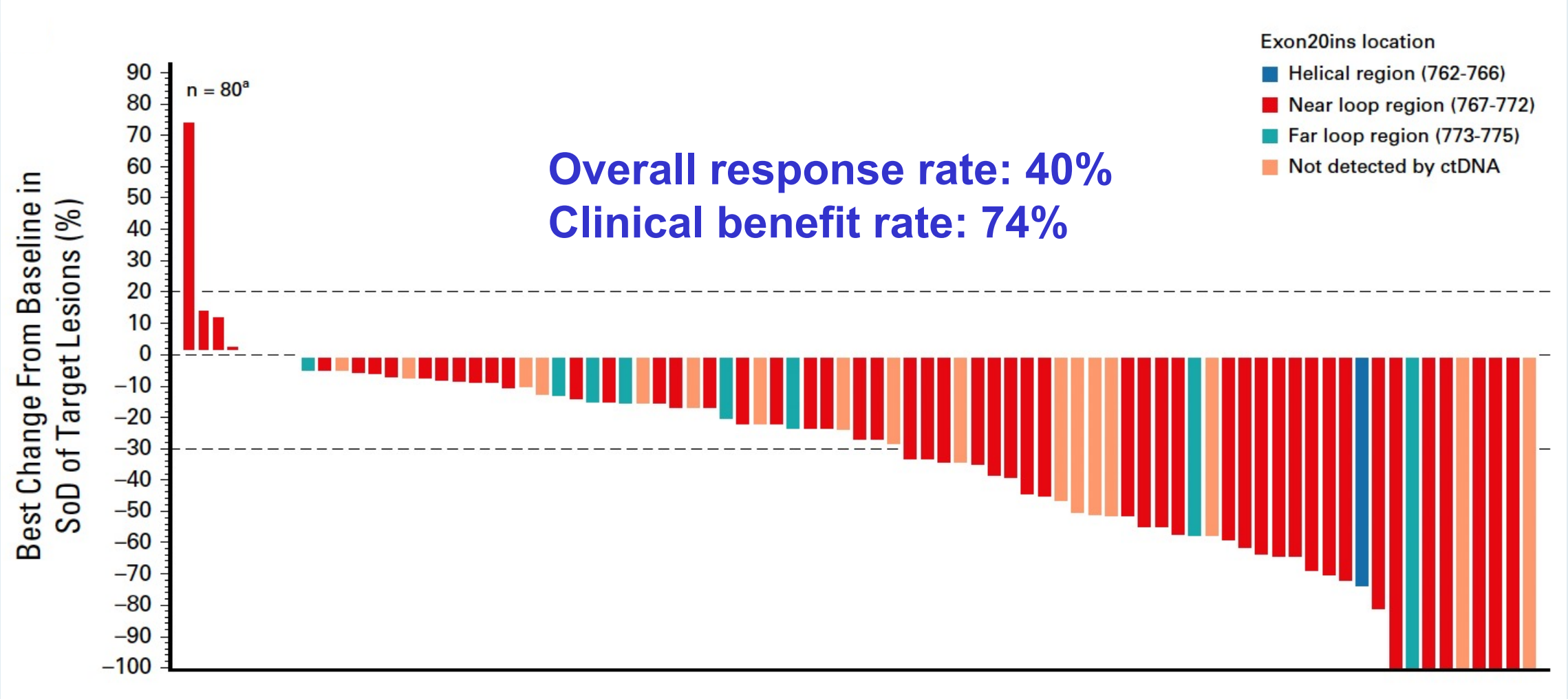
original reports

Amivantamab in EGFR Exon 20 Insertion–Mutated Non–Small-Cell Lung Cancer Progressing on Platinum Chemotherapy: Initial Results From the CHRYSALIS Phase I Study

Keunchil Park, MD, PhD[1]; Eric B. Haura, MD[2]; Natasha B. Leighl, MD[3]; Paul Mitchell, MD[4]; Catherine A. Shu, MD[5]; Nicolas Girard, MD, PhD[6]; Santiago Viteri, MD[7]; Ji-Youn Han, MD, PhD[8]; Sang-We Kim, MD, PhD[9]; Chee Khoon Lee, MD[10]; Joshua K. Sabari, MD[11]; Alexander I. Spira, MD, PhD[12]; Tsung-Ying Yang, MD, PhD[13]; Dong-Wan Kim, MD, PhD[14]; Ki Hyeong Lee, MD, PhD[15]; Rachel E. Sanborn, MD[16]; José Trigo, MD[17]; Koichi Goto, MD, PhD[18]; Jong-Seok Lee, MD, PhD[19]; James Chih-Hsin Yang, MD, PhD[20]; Ramaswamy Govindan, MD[21]; Joshua M. Bauml, MD[22]; Pilar Garrido, MD, PhD[23]; Matthew G. Krebs, MD, PhD[24]; Karen L. Reckamp, MD[25]; John Xie, PhD[26]; Joshua C. Curtin, PhD[26]; Nahor Haddish-Berhane, PhD[26]; Amy Roshak, BS[26]; Dawn Millington, MS[26]; Patricia Lorenzini, MS[26]; Meena Thayu, MD[26]; Roland E. Knoblauch, MD, PhD[26]; and Byoung Chul Cho, MD, PhD[27]

J Clin Oncol 2021;39(30):3391-402.

CHRYSALIS: Tumor Reduction and Response



Park K et al. *J Clin Oncol* 2021;39(30):3391-402.

RTP RESEARCH TO PRACTICE

CHRYSALIS: Summary of Adverse Events (AEs) and Most Common AEs

Event	Safety Population (n = 114), No. (%)	Patients Treated at the RP2D (n = 258), No. (%)
Any AE	113 (99)	257 (100)
Grade ≥ 3 AE	40 (35)	101 (39)
Serious AE	34 (30)	79 (31)
AE leading to death	8 (7)	13 (5)
AE leading to discontinuation	11 (10)	17 (7)
AE leading to dose reduction	15 (13)	26 (10)
AE leading to dose interruption[a]	40 (35)	88 (34)

Most Common AEs in the Safety Population

Adverse Events	Any Grade	Grade ≥3
Rash	86%	4%
Infusion-related reactions	66%	3%
Paronychia	45%	1%

RP2D = recommended Phase II dose

Park K et al. *J Clin Oncol* 2021;39(30):3391-402.

RTP RESEARCH TO PRACTICE

2022 ASCO® ANNUAL MEETING

Abstract 9006

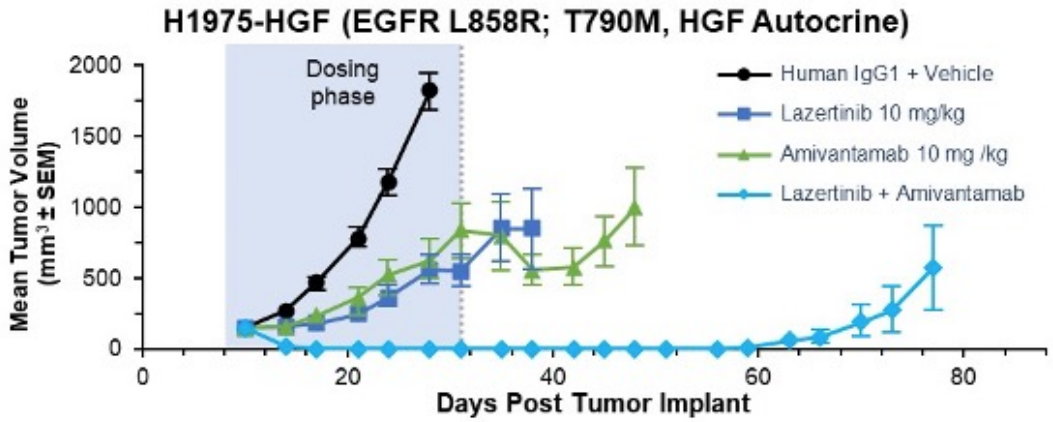
Amivantamab and lazertinib in patients with EGFR-mutant non-small cell lung cancer (NSCLC) after progression on osimertinib and platinum-based chemotherapy: Updated results from CHRYSALIS-2

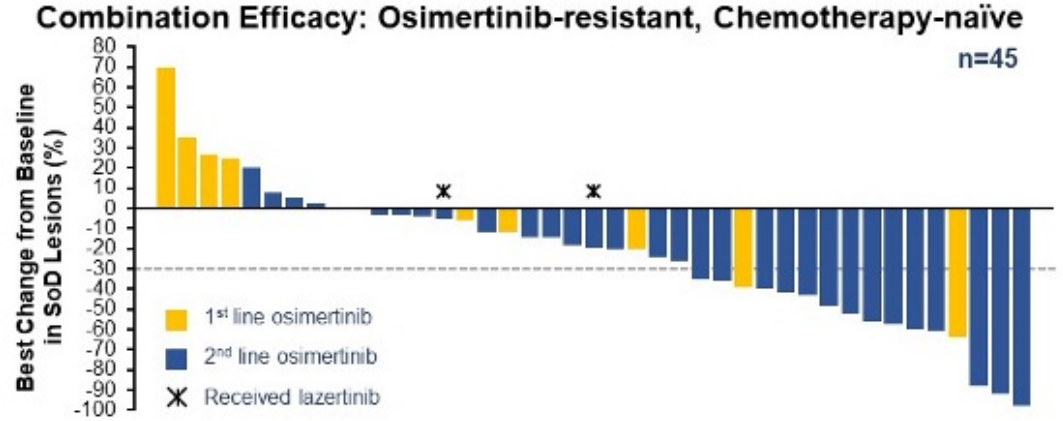
Catherine A. Shu,[1] Koichi Goto,[2] Yuichiro Ohe,[3] Benjamin Besse,[4] Se-Hoon Lee,[5] Yongsheng Wang,[6] Frank Griesinger,[7] James Chih-Hsin Yang,[8] Enriqueta Felip,[9] Rachel E. Sanborn,[10] Reyes Bernabe Caro,[11] Joshua C. Curtin,[12] Jun Chen,[12] Janine Mahoney,[12] Leonardo Trani,[12] Joshua M. Bauml,[12] Meena Thayu,[12] Roland E. Knoblauch,[12] Byoung Chul Cho[13]

[1]Columbia University Medical Center, New York, NY, USA; [2]National Cancer Center Hospital East, Kashiwa, Japan; [3]National Cancer Center Hospital, Tokyo, Japan; [4]Paris-Sacaly University, Institut Gustave Roussy, Villejuif, France; [5]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [6]Institute of Clinical Trial Center and Cancer Center, West China Hospital, Sichuan University, Chengdu, China; [7]Pius-Hospital, University of Oldenburg, Oldenburg, Germany; [8]National Taiwan University Cancer Center, Taipei, Taiwan; [9]Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Spain; [10]Earle A. Chiles Research Institute, Providence Cancer Institute, Portland, OR, USA; [11]Hospital Universitario Virgen Del Rocio, Seville, Spain; [12]Janssen R&D, Spring House, PA, USA; [13]Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea

CHRYSALIS-2: Rationale for Combining Amivantamab and Lazertinib

- Amivantamab[a] is an EGFR-MET bispecific antibody with immune cell-directing activity[1-3]
- Lazertinib is a highly selective, brain-penetrant, third-generation EGFR TKI with efficacy in activating EGFR mutations, T790M, and CNS disease[4,5]
- Preclinical studies demonstrate improved antitumor activity when both extracellular and catalytic EGFR domains are simultaneously targeted
- Among 45 patients who progressed on osimertinib but were chemotherapy naïve, the overall response rate was 36% and median DOR was 9.6 months without biomarker selection[6,7]
- This analysis explores the combination in patients with EGFRm NSCLC who have failed all standard of care (osimertinib and platinum-based chemotherapy)

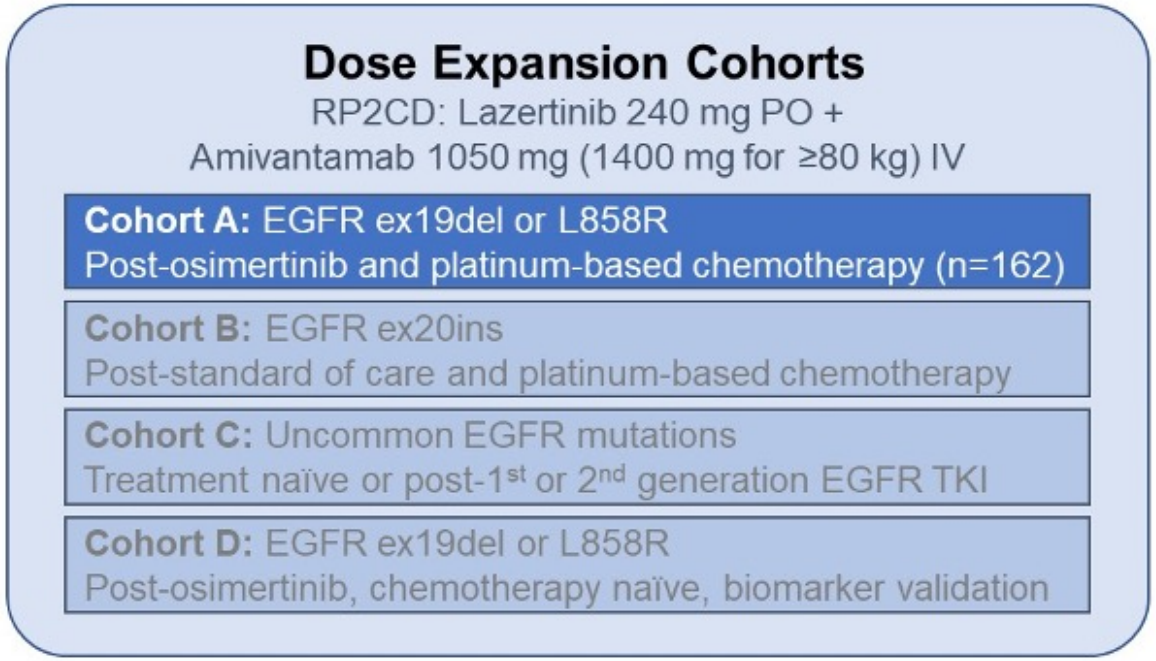




Shu CA et al. ASCO 2022;Abstract 9006.

RTP RESEARCH TO PRACTICE

CHRYSALIS-2 Study Design



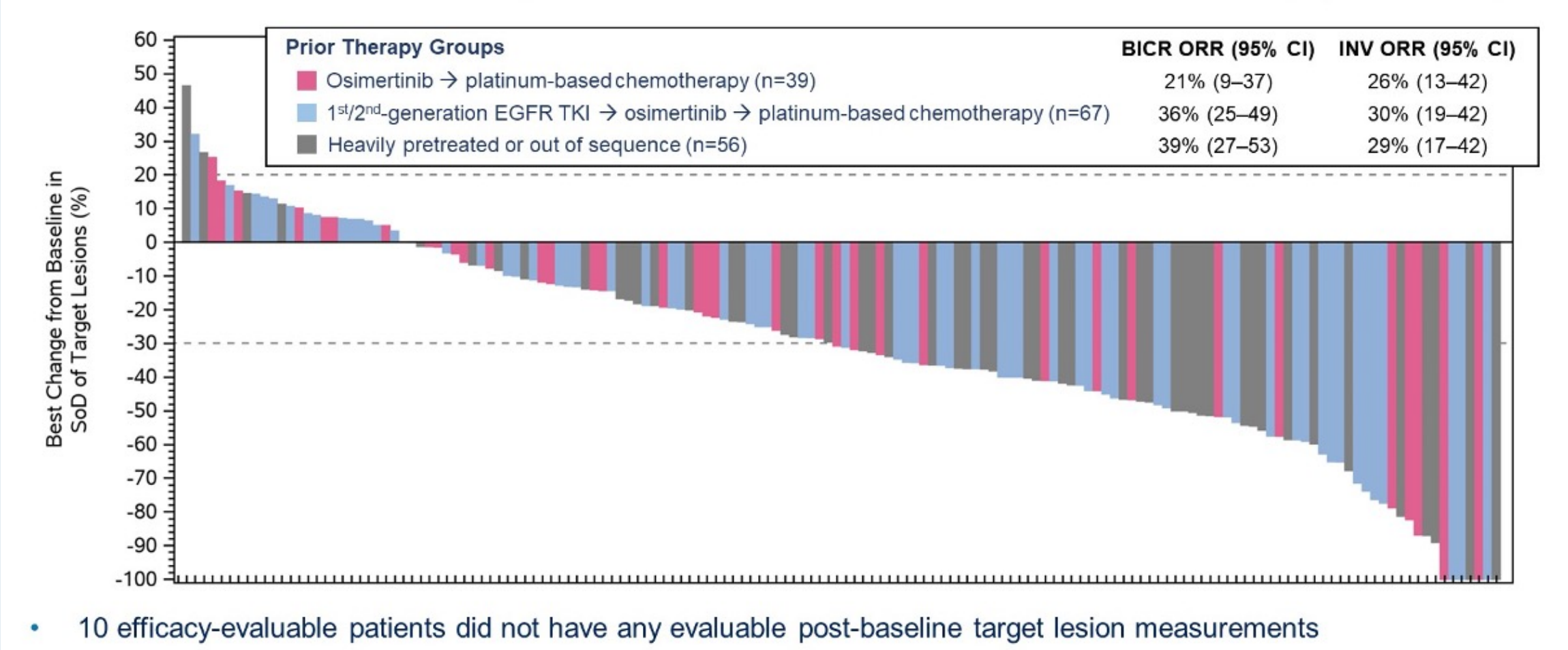
Endpoints

- Overall response rate (primary)
- Duration of response
- Clinical benefit rate[a]
- Progression-free survival
- Overall survival
- Adverse events

Here we present updated **safety** and **efficacy** results of the **amivantamab and lazertinib combination** from **fully enrolled Cohort A**

Shu CA et al. ASCO 2022;Abstract 9006.

CHRYSALIS-2: Best Antitumor Response and ORR by Prior Therapy Group



BICR = blinded independent central review; ORR = overall response rate; INV = investigator

Shu CA et al. ASCO 2022;Abstract 9006.

CHRYSALIS-2: Safety Profile

TEAEs (≥15%) by Preferred Term, n (%)	n=162	
	All grade	Grade ≥3
EGFR-related		
Rash	71 (44)	4 (2)
Dermatitis acneiform	55 (34)	8 (5)
Paronychia	84 (52)	6 (4)
Stomatitis	63 (39)	2 (1)
Diarrhea	36 (22)	1 (1)
Pruritus	30 (19)	1 (1)
MET-related		
Hypoalbuminemia	70 (43)	11 (7)
Peripheral edema	43 (27)	2 (1)
Other		
Infusion related reaction	108 (67)	13 (8)
Increased ALT	46 (28)	5 (3)
Nausea	40 (25)	3 (2)
Decreased appetite	39 (24)	1 (1)
Constipation	38 (23)	0
Asthenia	37 (23)	7 (4)
Dry skin	37 (23)	0
Vomiting	36 (22)	1 (1)
Increased AST	35 (22)	3 (2)
Dyspnea	33 (20)	13 (8)
Thrombocytopenia	33 (20)	2 (1)
Fatigue	32 (20)	4 (2)
Headache	29 (18)	2 (1)
Anemia	27 (17)	4 (2)
Hypocalcemia	26 (16)	1 (1)

- Individual AEs were mostly grade 1-2
- Dose interruptions, reductions, and discontinuations of both amivantamab and lazertinib due to toxicity were seen in 57 (35%), 15 (9%), and 12 (7%) patients, respectively
- Pneumonitis/ILD was seen in 11 (7%) patients, of which 6 (4%) were grade ≥3 (no grade 5)
- Cumulative grouped rash-related AEs[a] occurred in 129 (80%) patients, with 17 grade ≥3 (10%)
- Safety profile consistent with what was previously reported; no new safety signals identified

[a]Rash-related terms include rash, dermatitis acneiform, acne, dermatitis, drug eruption, erythema, erythema multiforme, folliculitis, macule, papule, pustule, rash erythematous, rash macular, rash maculo-papular, rash pustular, rash papular, rash pruritic, rash vesicular, skin exfoliation, and skin lesion.

AE, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase; EGFR, epidermal growth factor receptor; TEAE, treatment-emergent adverse events.

Shu CA et al. ASCO 2022;Abstract 9006.

2022 ASCO ANNUAL MEETING

Abstract 9007

Phase1/2a Study of CLN-081 in NSCLC Patients with EGFR Exon 20 Insertion (ex20ins) Mutations

Helena Yu[1], Daniel Shao-Weng Tan[2], Egbert F. Smit[3], Alexander I. Spira[4], Ross A. Soo[5], Danny Nguyen[6], Victor Ho-FunLee[7], James Chih-Hsin Yang[8], Vamsidhar Velcheti[9], John M. Wrangle[10], Mark A. Socinski[11], Marianna Koczywas[12], David Witter[13], Asher Page[13], Leigh Zawel[13], John E. Janik[13], Zofia Piotrowska[14]

[1]Memorial Sloan Kettering Cancer Center; [2]National Cancer Centre Singapore; [3]The Netherlands Cancer Institute; [4]Virginia Health Specialists; [5]National University Hospital; [6]City of Hope National Medical Center; [7]Queen Mary Hospital, The University of Hong Kong; [8]National Taiwan University Hospital and National Taiwan University Cancer Center; [9]Cleveland Clinic Foundation; [10]Johns Hopkins University School of Medicine; [11]AdventHealth Cancer Institute; [12]Department of Medical Oncology and Therapeutics Research, City of Hope; [13]Cullinan Oncology, LLC; [14]Massachusetts General Hospital

PRESENTED BY:
Helena Yu, Memorial Sloan Kettering Cancer Center, New York, NY

EGFR Exon 20 Insertion Mutations in NSCLC

~2-3% of all non-small cell lung cancer (NSCLC) cases harbor EGFR ex20ins mutations[1]

- This frequency is higher than RET, ROS1, and NTRK fusions are observed in NSCLC

Patients with ex20ins have poorer outcomes than those with more common EGFR mutations[2]

- Survival for ex20ins patients is inferior to patients with sensitive mutations

Agents targeting EGFR ex20ins mutations have been recently approved for the treatment of patients with NSCLC

- Currently approved agents demonstrate significant toxicity

Toxicities related to inhibition of wild-type EGFR, including rash and diarrhea, may limit the tolerability of some ex20ins inhibitors

- Therapeutic window between wild-type EGFR and EGFR ex20ins is narrow

1. Burnett H, et al. PLOS ONE. 2021;16(3).

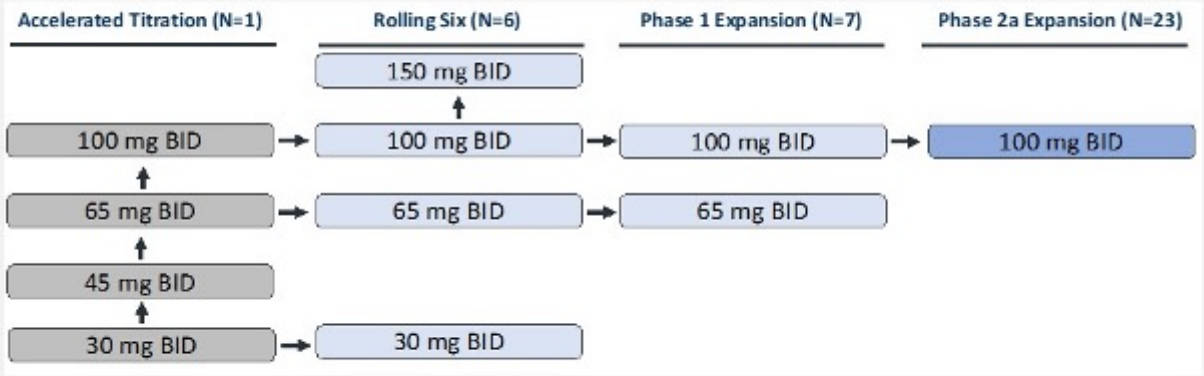
2. Leal JL, et al. Clin Lung Cancer. 2021;22(6).

Safer and more effective novel therapies to treat ex20ins NSCLC remain an unmet medical need

Yu H et al. ASCO 2022;Abstract 9007.

CLN-081-001 Study Schema

STUDY SCHEMA



- Dose escalation used both an accelerated titration and rolling-six design
- Phase 1 and Phase 2a dose expansion cohorts enrolled additional patients at dose levels meeting pre-defined thresholds for efficacy and tolerability

KEY ELIGIBILITY

- Confirmed recurrent or metastatic NSCLC with documented EGFR ex20ins mutation demonstrated by local laboratory
- Prior treatment in the recurrent/metastatic setting including a platinum-based chemotherapy regimen unless declined
- Prior treatment with an EGFR exon20in-targeting drug was allowed only in dose-escalation cohorts
- Patients with CNS metastases stable for ≥4 weeks prior to C1D1 were eligible

TREATMENT PLAN

- Patients receive CLN-081 twice daily and may continue to receive treatment until disease progression, unacceptable toxicity or withdrawal of consent
- Tumor response was assessed by investigators according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1) at 6 weeks and every 9 weeks thereafter

Yu H et al. ASCO 2022;Abstract 9007.

CLN-081-001: Baseline Characteristics

CHARACTERISTIC	ALL PATIENTS (N=73)
Median age (range)	64 (36-82)
Female	41 (56%)
ECOG PS (0, 1)	22 (30%), 51(70%)
Number of prior systemic anticancer regimens[1]	
1 (%)	22 (30%)
2 (%)	**32 (44%)**
≥3 (%)	**16 (22%)**
Median (range)	2 (1-9)
Prior EGFR TKI (non-Ex20)	**26 (36%)**
Prior afatinib or gefitinib	13 (18%)
Prior osimertinib	13 (18%)
Prior poziotinib and/or mobocertinib (%)	**3 (4%)**
Prior immunotherapy (%)	40 (55%)
History of CNS involvement (%)	**28 (38%)**

[1]Three patients with no prior therapy (declined chemotherapy)

- Heavily pre-treated patients
- 66% of patients with ≥2 prior lines of treatment
- Prior EGFR TKI treatment in 36% of patients, including 3 patients who had received prior poziotinib and/or mobocertinib
- 55% of patients received prior immunotherapy
- 38% had history of CNS metastases at baseline

Yu H et al. ASCO 2022;Abstract 9007.

CLN-081-001: Safety Profile

Dose BID	≤65 mg (N = 23)		100 mg (N = 39)		150 mg (N = 11)		Overall (N = 73)	
AE Term, n (%)	All grade[1]	Grade ≥ 3	All grade	Grade ≥ 3	All grade	Grade ≥ 3	All grade	Grade ≥3
Rash	19 (83)	0	32 (82)	0	7 (64)	1 (9)	58 (80)	1 (1)
Paronychia	6 (26)	0	12 (31)	0	5 (45)	0	23 (32)	0
Diarrhea	4 (17)	0	14 (36)	0	4 (36)	2 (18)	22 (30)	2 (3)
Fatigue	5 (22)	0	8 (21)	0	2 (18)	0	15 (21)	0
Anemia	7 (30)	4 (17)	5 (13)	1 (3)	2 (18)	2 (18)	14 (19)	7 (10)
Dry skin	6 (26)	0	7 (18)	0	0	0	13 (18)	0
Nausea	5 (22)	0	4 (10)	0	3 (27)	0	12 (16)	0
Stomatitis	2 (9)	0	5 (13)	0	3 (27)	1 (9)	10 (14)	1 (1)
Alopecia	3 (13)	0	6 (15)	0	0	0	9 (12)	0
Dry eye	1 (4)	0	7 (18)	0	1 (9)	0	9 (12)	0
AST increased	3 (13)	1 (4)	3 (8)	1 (3)	2 (18)	1 (9)	8 (11)	3 (4)
Decreased appetite	4 (17)	0	4 (10)	0	0	0	8 (11)	0
Dose Interruptions	5 (22)		13 (33)		6 (55)		24 (33)	
Dose Reductions	2 (9)		5 (13)		3 (27)		10 (14)	
Dose Discontinuations	2 (9)		2 (5)		2 (18)		6 (8)	

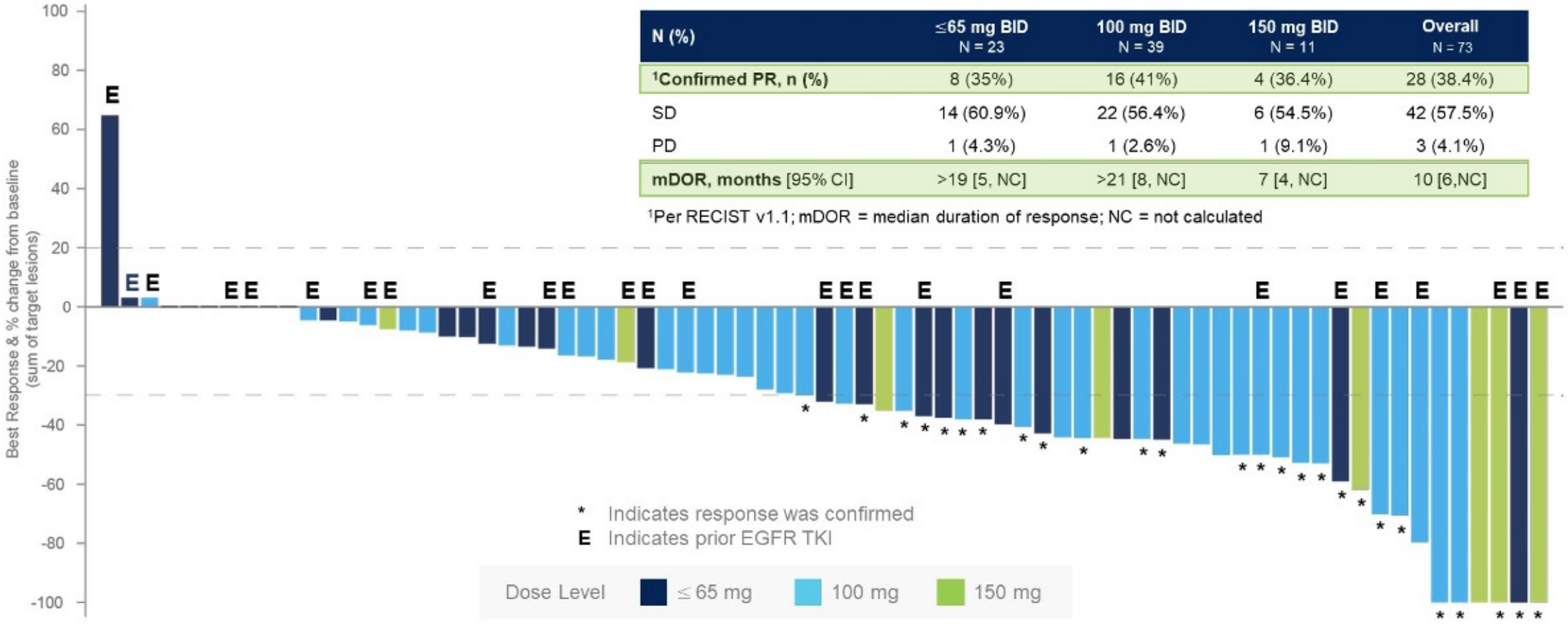
- Most AEs Grade 1/2
- Dose reductions and discontinuations were uncommon at doses below 150 mg
- No Grade ≥3 rash or diarrhea observed at doses <150 mg
- Treatment-emergent pneumonitis was observed in 4 patients (1 at 65, 2 at 100, and 1 at 150 mg), but cases were asymptomatic (1) or confounded by comorbid medical illness (3)[2]

Yu H et al. ASCO 2022;Abstract 9007.

CLN-081-001: Best Percent Change from Baseline and Confirmed Response by Dose Level

N (%)	≤65 mg BID N = 23	100 mg BID N = 39	150 mg BID N = 11	Overall N = 73
[1]Confirmed PR, n (%)	8 (35%)	16 (41%)	4 (36.4%)	28 (38.4%)
SD	14 (60.9%)	22 (56.4%)	6 (54.5%)	42 (57.5%)
PD	1 (4.3%)	1 (2.6%)	1 (9.1%)	3 (4.1%)
mDOR, months [95% CI]	>19 [5, NC]	>21 [8, NC]	7 [4, NC]	10 [6,NC]

[1]Per RECIST v1.1; mDOR = median duration of response; NC = not calculated



Yu H et al. ASCO 2022;Abstract 9007.

RTP RESEARCH TO PRACTICE

CLN-081-001: Conclusions

Safety

Safety profile amenable for long-term treatment at doses <150 mg BID

- Most adverse events Grade 1/2
- **No Grade ≥3 rash or diarrhea at doses <150 mg BID**

Efficacy

Objective responses observed in heavily pre-treated patients, including patients who progressed on treatment with other EGFR TKIs

- **At 100 mg BID: ORR 41%, mDOR >21 mos, mPFS 12 mos**

Summary

Enrollment to the phase 2b portion of the study is planned for 2H 2022

- Studies in patients with active CNS metastases and those who have relapsed after prior ex20ins therapies are planned

Yu H et al. ASCO 2022;Abstract 9007.

FDA Grants Accelerated Approval to Mobocertinib for Metastatic NSCLC with EGFR Exon 20 Insertion Mutations

Press Release: September 15, 2021

"The Food and Drug Administration granted accelerated approval to mobocertinib for adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.

Today, the FDA also approved the Oncomine Dx Target Test as a companion diagnostic device to select patients with the above mutations for mobocertinib treatment.

Approval was based on Study 101, an international, non-randomized, open-label, multicohort clinical trial (NCT02716116) which included patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations. Efficacy was evaluated in 114 patients whose disease had progressed on or after platinum-based chemotherapy. Patients received mobocertinib 160 mg orally daily until disease progression or intolerable toxicity."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-mobocertinib-metastatic-non-small-cell-lung-cancer-egfr-exon-20

Research

JAMA Oncol 2021;7(12):e214761

JAMA Oncology | Original Investigation

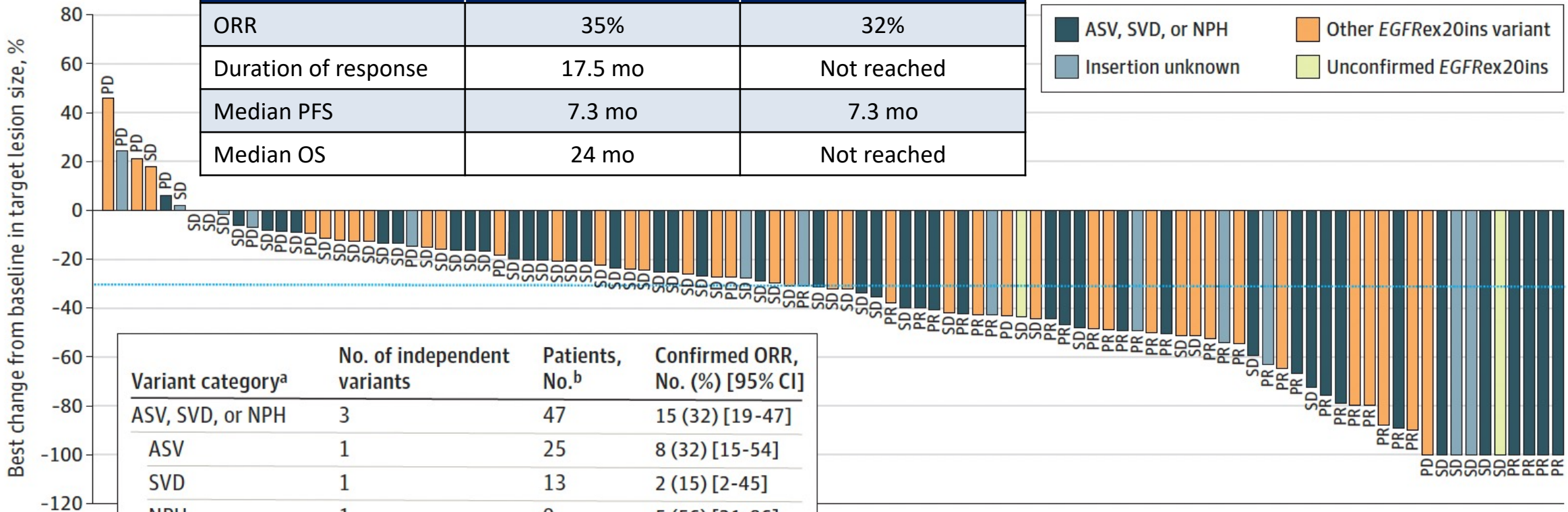
Treatment Outcomes and Safety of Mobocertinib in Platinum-Pretreated Patients With *EGFR* Exon 20 Insertion–Positive Metastatic Non–Small Cell Lung Cancer

A Phase 1/2 Open-label Nonrandomized Clinical Trial

Caicun Zhou, PhD, MD; Suresh S. Ramalingam, MD; Tae Min Kim, MD, PhD; Sang-We Kim, MD; James Chih-Hsin Yang, MD; Gregory J. Riely, MD; Tarek Mekhail, MD; Danny Nguyen, MD; Maria R. Garcia Campelo, MD; Enriqueta Felip, MD; Sylvie Vincent, PhD; Shu Jin, MS; Celina Griffin, PharmD; Veronica Bunn, PhD; Jianchang Lin, PhD; Huamao M. Lin, PhD; Minal Mehta, MBBS; Pasi A. Jänne, MD, PhD

Mobocertinib Activity in Patients with Platinum-Pretreated Metastatic NSCLC with EGFRex20ins Mutation (PPP Cohort)

	PPP cohort (n = 114)	EXCLAIM cohort (n = 96)
ORR	35%	32%
Duration of response	17.5 mo	Not reached
Median PFS	7.3 mo	7.3 mo
Median OS	24 mo	Not reached



Variant category[a]	No. of independent variants	Patients, No.[b]	Confirmed ORR, No. (%) [95% CI]
ASV, SVD, or NPH	3	47	15 (32) [19-47]
ASV	1	25	8 (32) [15-54]
SVD	1	13	2 (15) [2-45]
NPH	1	9	5 (56) [21-86]
Other *EGFR*ex20ins	29	48	12 (25) [14-40]
Insertion unknown		16	5 (31) [11-59]

PPP = platinum pretreated patients; ORR = objective response rate

Zhou C et al. *JAMA Oncol* 2021;7(12):e214761.

RTP RESEARCH TO PRACTICE

Summary of Adverse Events (AEs) and Most Common AEs with Mobocertinib

	Patients, No. (%)			
	PPP cohort (n = 114)		EXCLAIM cohort (n = 96)	
Adverse event	Any grade	Grade ≥3	Any grade	Grade ≥3
Overview of AEs				
Any	114 (100)	79 (69)	96 (100)	63 (66)
Any treatment-related	113 (99)	54 (47)	95 (99)	40 (42)
Serious	56 (49)	52 (46)	45 (47)	42 (44)
Leading to dose reduction	29 (25)	NA[a]	21 (22)	NA[a]
Leading to treatment discontinuation	19 (17)	NA[a]	10 (10)	NA[a]
Treatment-related AEs of any grade reported in ≥10% or of grade ≥3 reported in ≥3% of patients				
Diarrhea	104 (91)	24 (21)	89 (93)	15 (16)
Rash	51 (45)	0	43 (45)	0
Paronychia	43 (38)	1 (<1)	37 (39)	1 (1)

Zhou C et al. *JAMA Oncol* 2021;7(12):e214761.

Meet The Professor

Optimizing the Management of Multiple Myeloma

Tuesday, October 11, 2022
5:00 PM – 6:00 PM ET

Faculty

Sagar Lonial, MD

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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