Meet The Professor

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

Wednesday, August 31, 2022
5:00 PM – 6:00 PM ET

Faculty

Lecia V Sequist, MD, MPH

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, 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 Genzyme, 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	AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim Pharmaceuticals Inc, Delfi Diagnostics, Genentech, a member of the Roche Group, Novartis
Data and Safety Monitoring Board/Committee	Genentech, a member of the Roche Group

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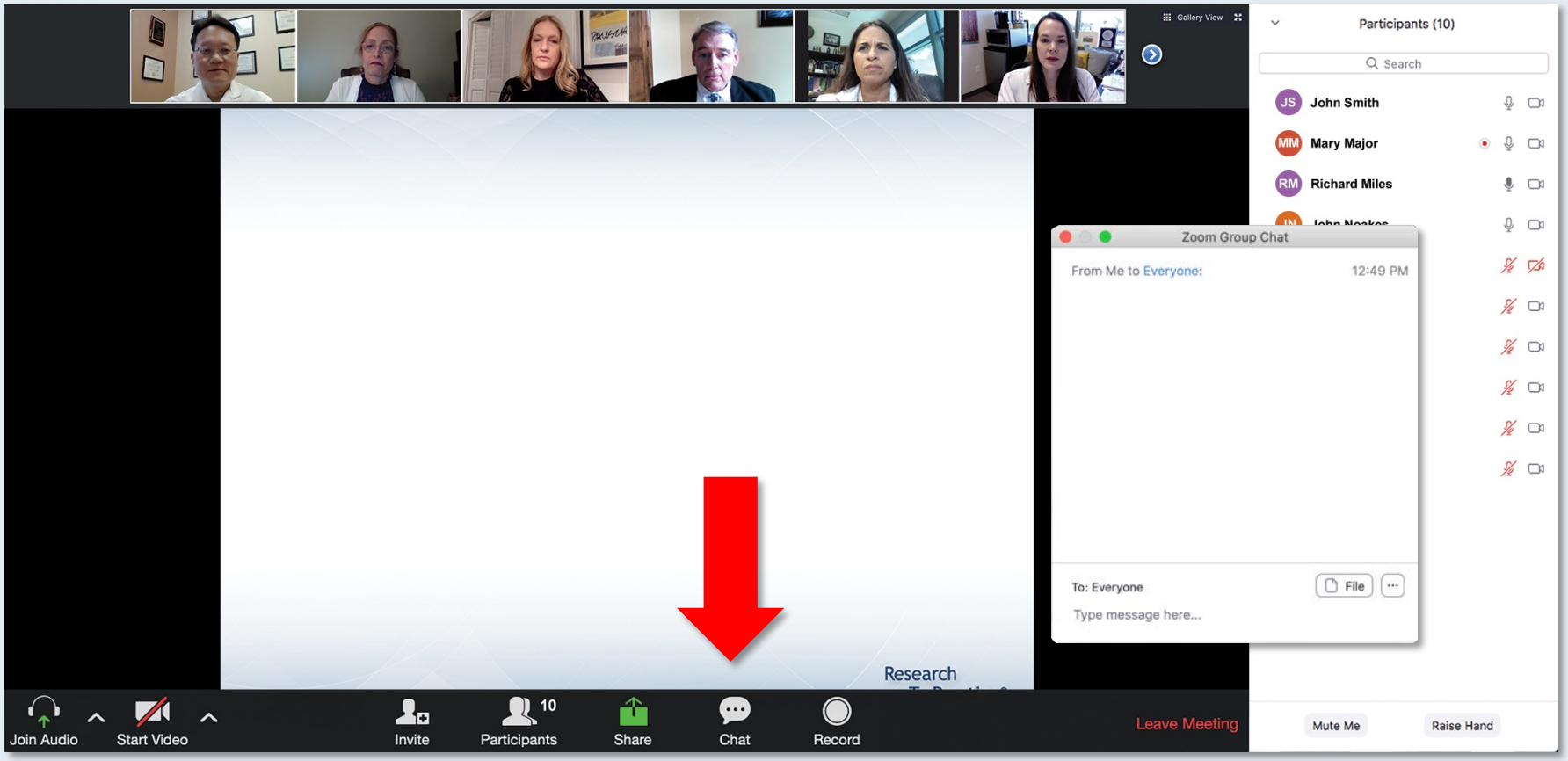

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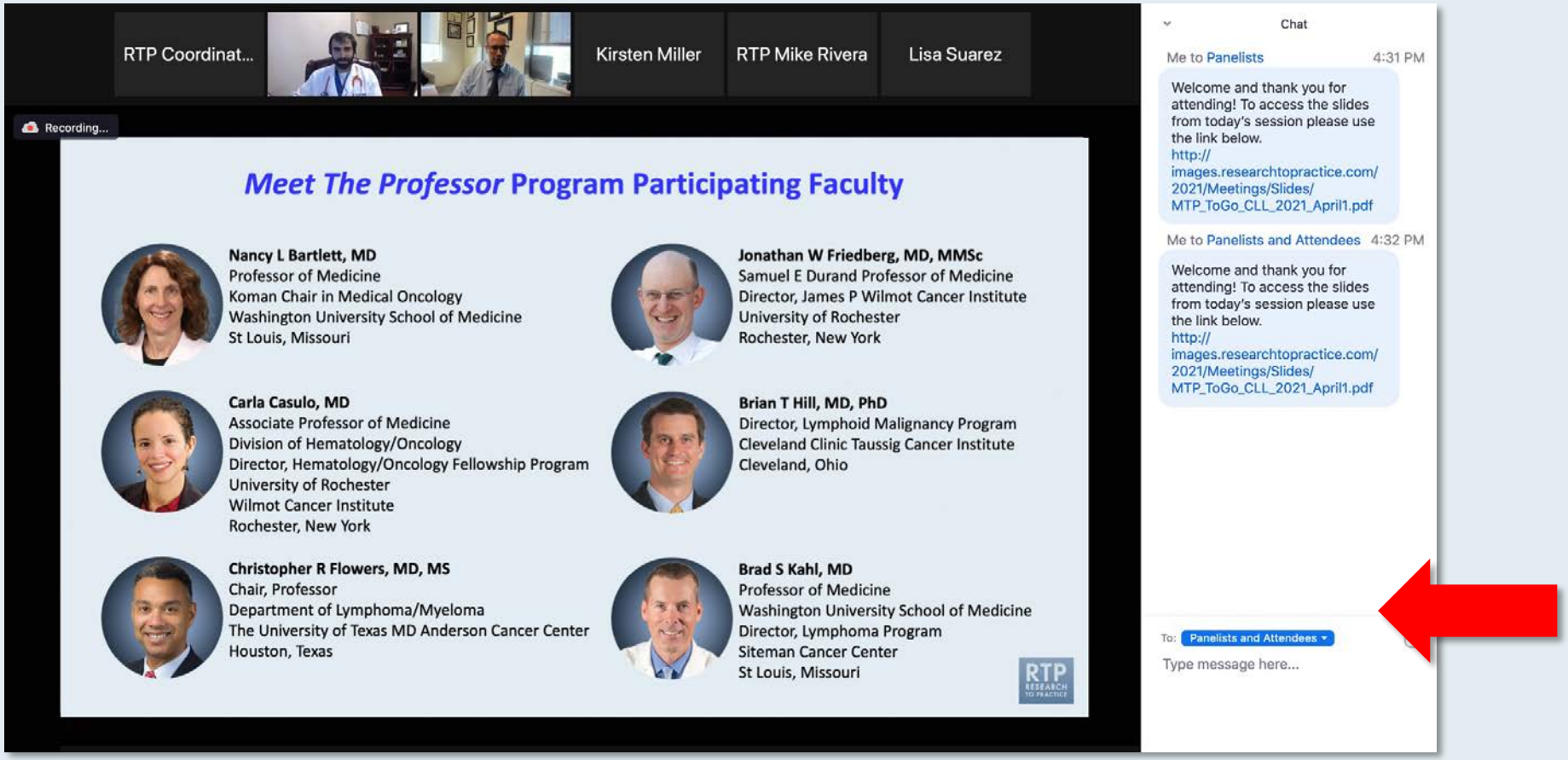
Familiarizing Yourself with the Zoom Interface

Expand chat submission box



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

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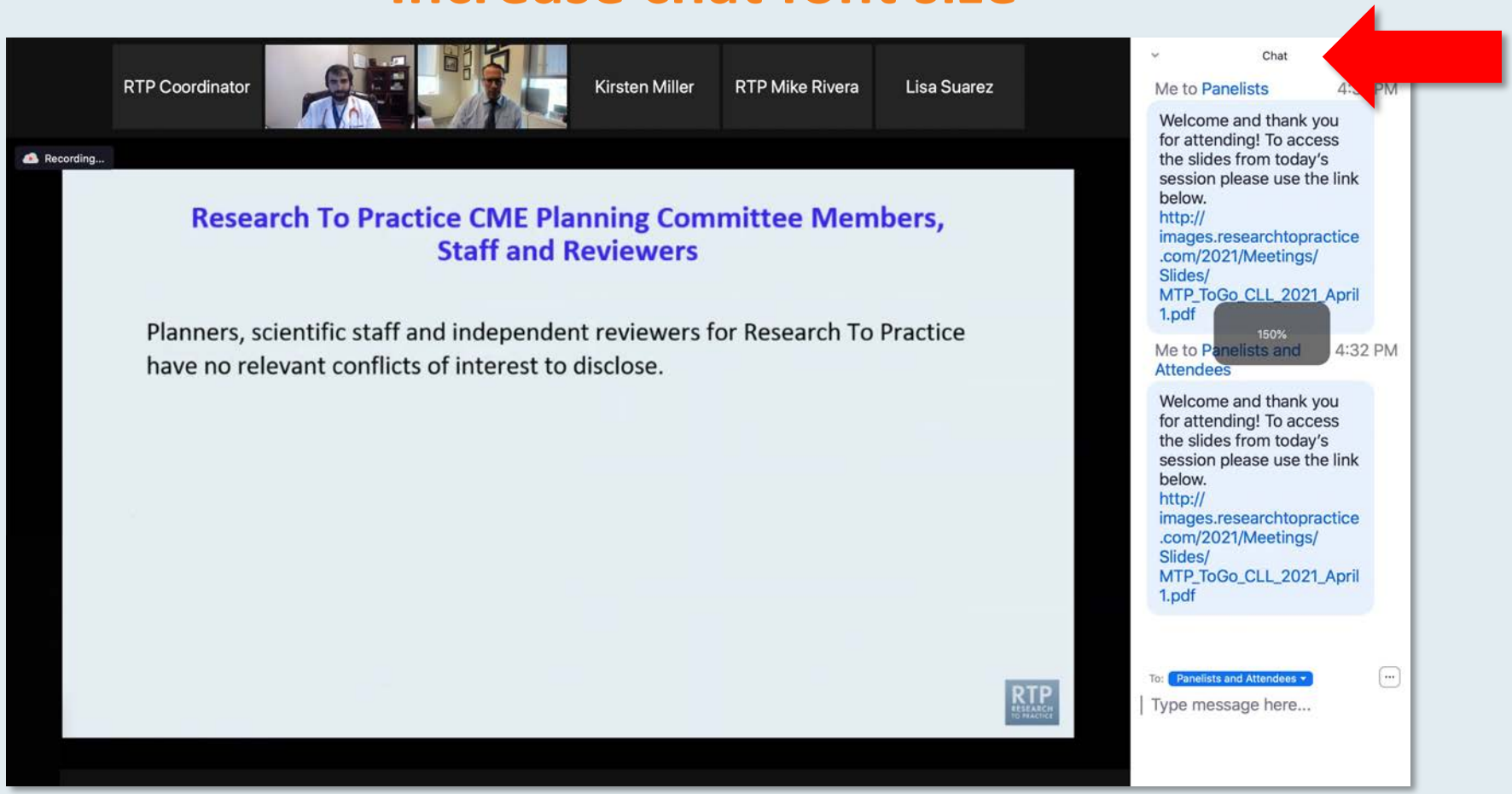

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You may do this as many times as you need for readability.

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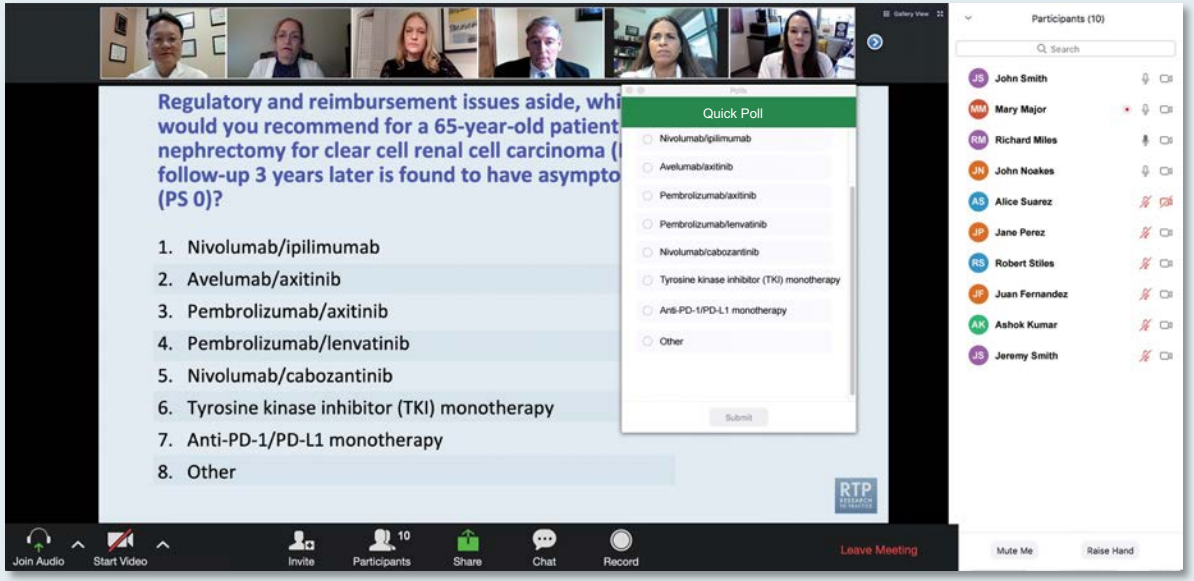

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ONCOLOGY TODAY

WITH DR NEIL LOVE

Management of Unresectable Stage III Non-Small Cell Lung Cancer

DR JEFFREY BRADLEY

EMORY UNIVERSITY SCHOOL OF MEDICINE

DR DAVID R SPIGEL

SARAH CANNON RESEARCH INSTITUTE

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Meet The Professor

Optimizing the Management of HER2-Positive Breast Cancer

Thursday, September 1, 2022
5:00 PM – 6:00 PM ET

Faculty

Mark D Pegram, MD

Moderator

Neil Love, MD

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Exploring Current Considerations and Promising Investigational Approaches for Patients with Myelodysplastic Syndromes

A CME/MOC-Accredited Virtual Event

Thursday, September 8, 2022

5:00 PM – 6:00 PM ET

Faculty

Guillermo Garcia-Manero, MD
Gail J Roboz, MD
David Sallman, MD

Moderator

Neil Love, MD

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RESEARCH TO PRACTICE

Challenging Cases from the Community: Investigators Provide Perspectives on the Optimal Management of Diffuse Large B-Cell Lymphoma

A CME/MOC-Accredited Virtual Event

Tuesday, September 13, 2022
5:00 PM – 6:00 PM ET

Faculty

Sonali M Smith, MD
Jason Westin, MD, MS
Additional faculty to be announced

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Current Paradigm and Future Directions for Immunotherapy in the Treatment of Metastatic Non-Small Cell Lung Cancer

A CME/MOC-Accredited Virtual Event

Tuesday, September 27, 2022
5:00 PM – 6:00 PM ET

Faculty

Faculty to be announced

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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Meet The Professor

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

Lecia V Sequist, MD, MPH
Director, Center for Innovation in Early Cancer Detection
Massachusetts General Hospital Cancer Center
The Landry Family Professor of Medicine
Harvard Medical School
Boston, Massachusetts

Meet The Professor Program Participating Faculty

Pasi A Jänne, MD, PhD
Director, Lowe Center for Thoracic Oncology
Director, Robert and Renée Belfer Center for Applied Cancer Sciences
Director, Chen-Huang Center for EGFR Mutant Lung Cancers
Dana-Farber Cancer Institute
Professor of Medicine
Harvard Medical School
Boston, Massachusetts

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
The Landry Family Professor of Medicine
Harvard Medical School
Boston, Massachusetts

David R Spigel, MD
Chief Scientific Officer
Sarah Cannon Research Institute
Nashville, Tennessee

MODERATOR
Neil Love, MD
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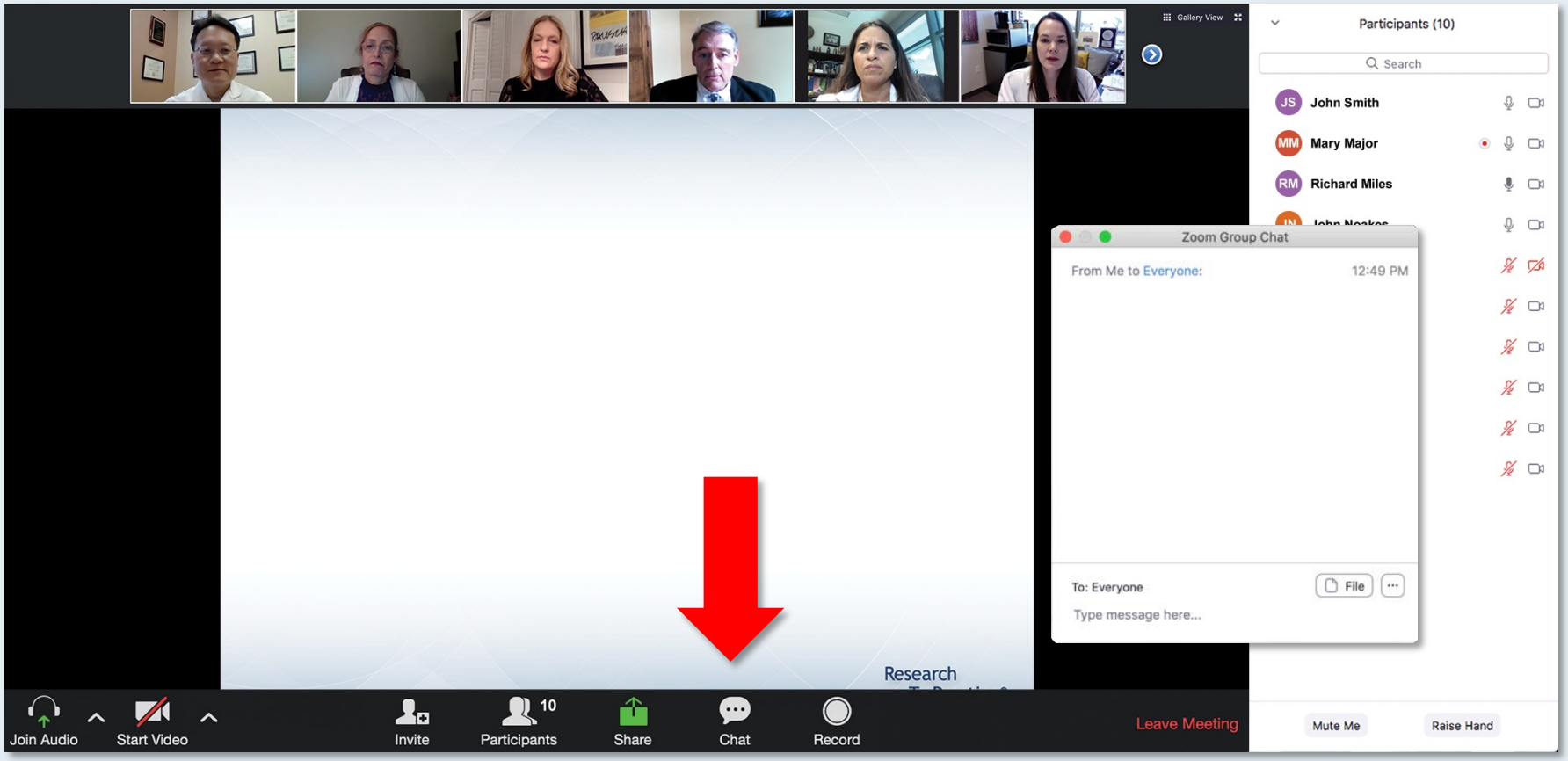

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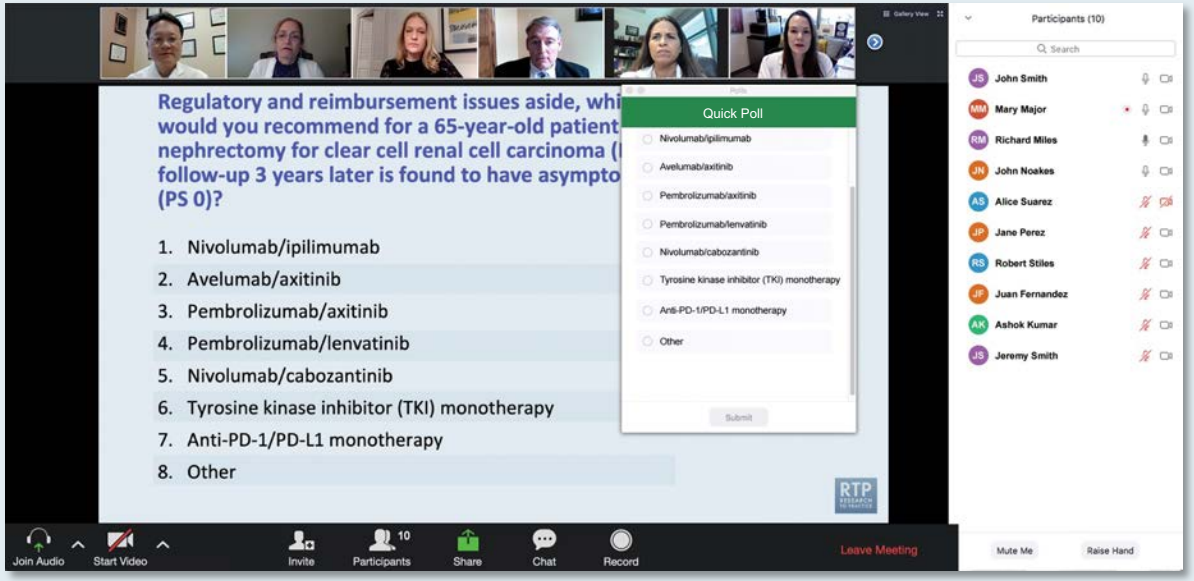

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Data and Safety Monitoring Board/Committee	Genentech, a member of the Roche Group

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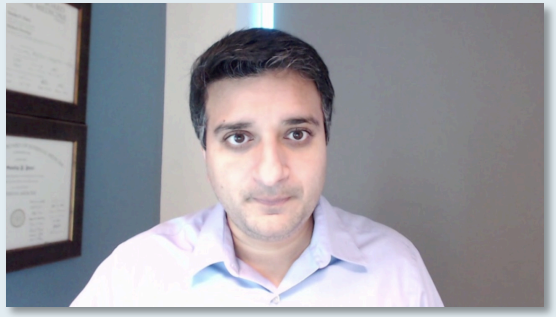
Syed M Ahmed, MD, PhD
Advocate Medical Group
Libertyville, Illinois

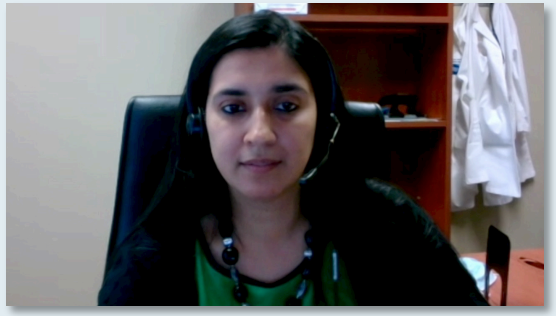
Gigi Chen, MD
John Muir Health
Pleasant Hill, California

Justin Peter Favaro, MD, PhD
Oncology Specialists of Charlotte
Charlotte, North Carolina

Adam R Miller, MD
Mass General/North Shore
Cancer Center
Danvers, Massachusetts



Sandip Patel, MD
San Diego Center for Precision
Immunotherapy
San Diego, California



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

Priya Rudolph, MD
Georgia Cancer Specialists
Athens, Georgia

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Meet The Professor with Dr Sequist

INTRODUCTION: Journal Club with Dr Sequist – Part 1

MODULE 1: Case Presentations

MODULE 2: Faculty Survey

MODULE 3: Journal Club with Dr Sequist – Part 2

MODULE 4: Appendix of Key Publications

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Patients with metastatic non-small cell lung cancer with a high PD-L1 level and an activating EGFR mutation may have a robust response to a single-agent checkpoint inhibitor.

1. Agree
2. Disagree
3. I'm not sure

Meet The Professor with Dr Sequist

INTRODUCTION: Journal Club with Dr Sequist – Part 1

MODULE 1: Case Presentations

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Lancet 2021;398:535-54.

Seminar

Lung cancer

Alesha A Thai, Benjamin J Solomon, Lecia V Sequist, Justin F Gainor, Rebecca S Heist

Lung cancer is one of the most frequently diagnosed cancers and the leading cause of cancer-related deaths worldwide with an estimated 2 million new cases and 1·76 million deaths per year. Substantial improvements in our understanding of disease biology, application of predictive biomarkers, and refinements in treatment have led to remarkable progress in the past two decades and transformed outcomes for many patients. This seminar provides an overview of advances in the screening, diagnosis, and treatment of non-small-cell lung cancer and small-cell lung cancer, with a particular focus on targeted therapies and immune checkpoint inhibitors.

Long Term Survival Outcomes in NSCLC Patients with Targeted Therapy and Immunotherapy: An IASLC Analysis of ASCO CancerLinQ Discovery Data

Behera M et al.

IASLC 2022;Abstract EP08.01-060.

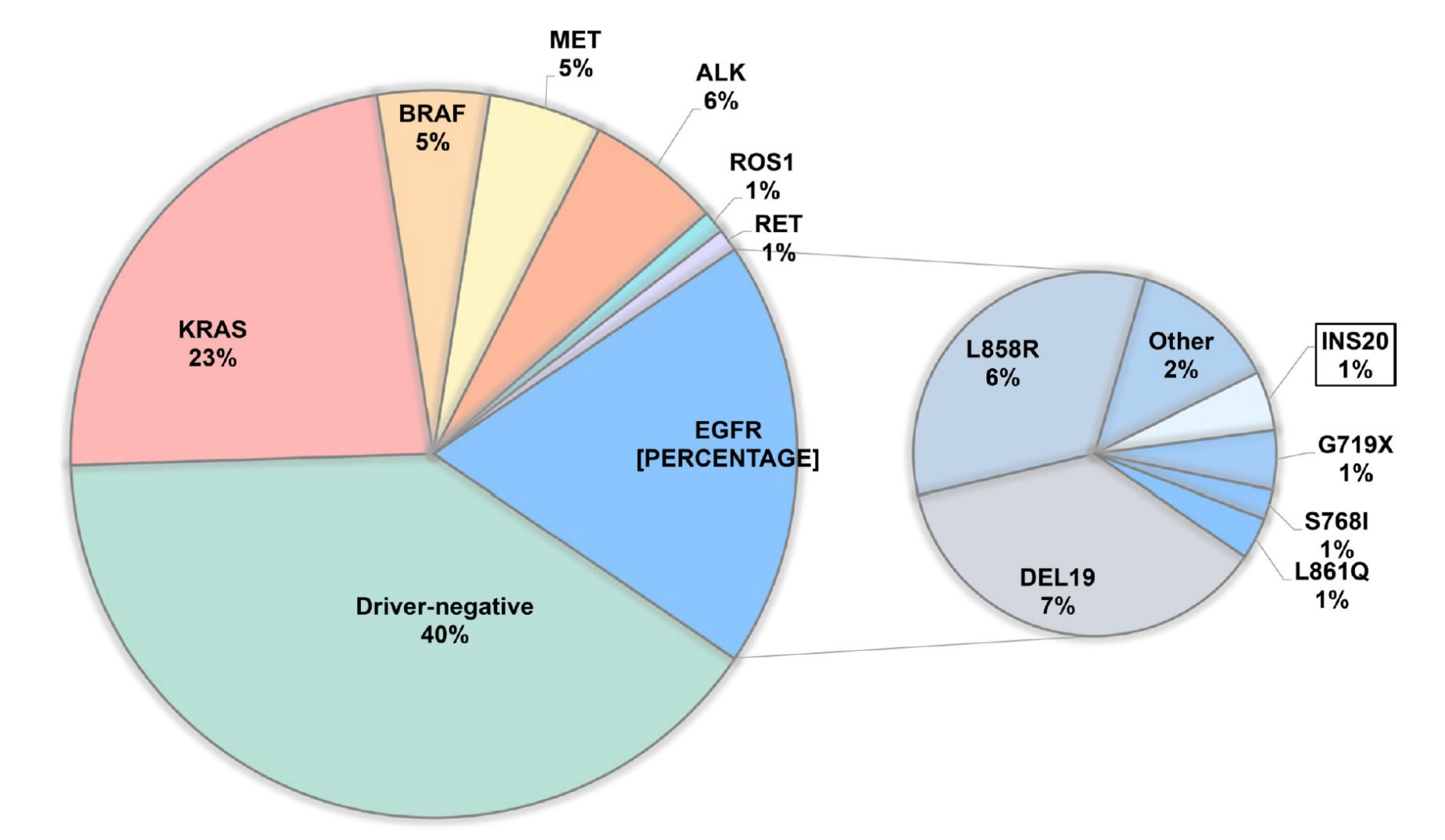
Targeting *EGFR* Exon 20 Insertions in NSCLC: Recent Advances and Clinical Updates

Catherine B. Meador[1], **Lecia V. Sequist**[1,2], **Zofia Piotrowska**[1]

[1]Department of Medicine, Division of Hematology/Oncology, Massachusetts General Hospital/ Harvard Medical School, Boston, MA

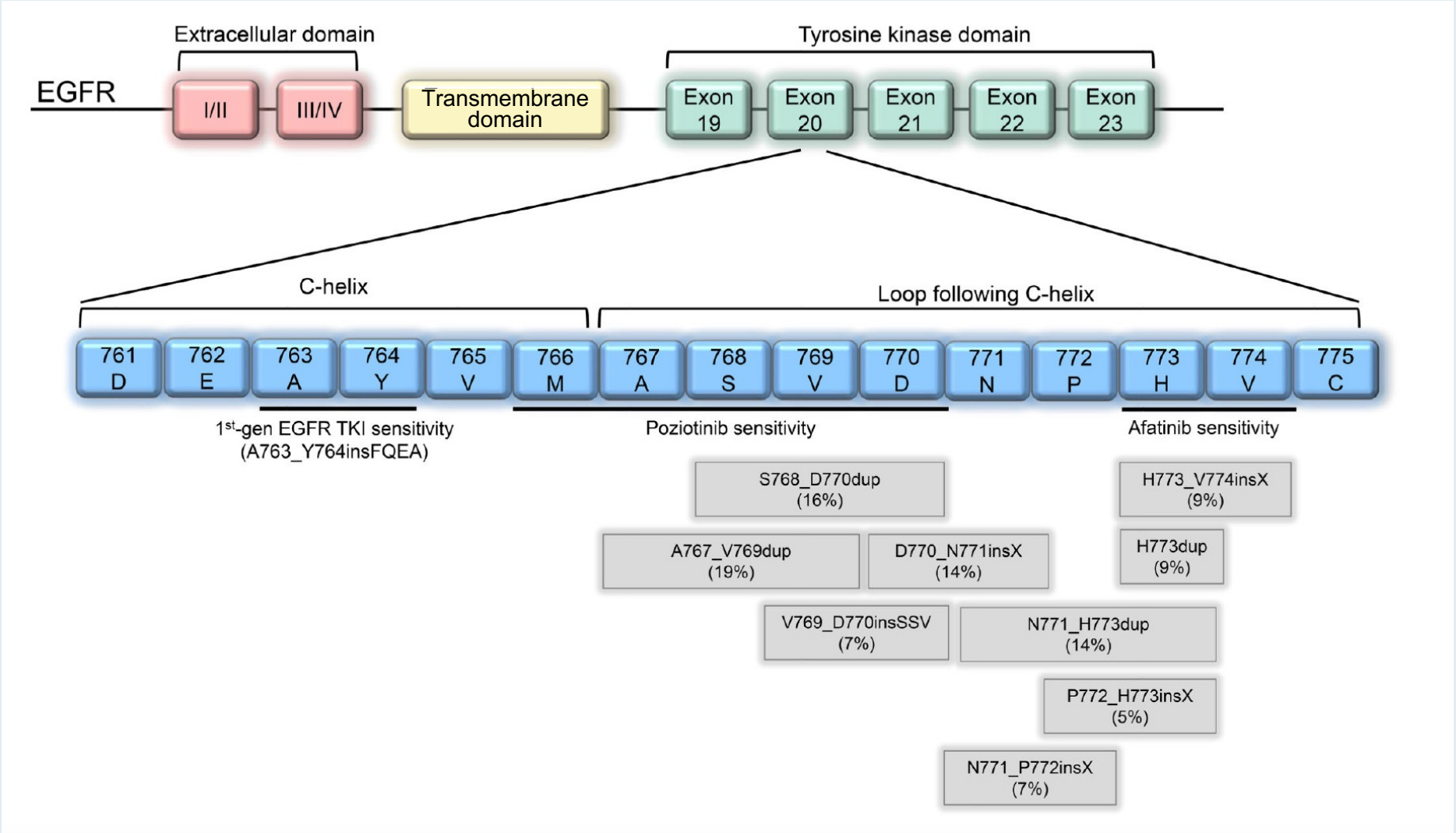
Cancer Discov **2021;11(9):2145-57.**

Frequency of EGFR Exon 20 Insertion Mutations



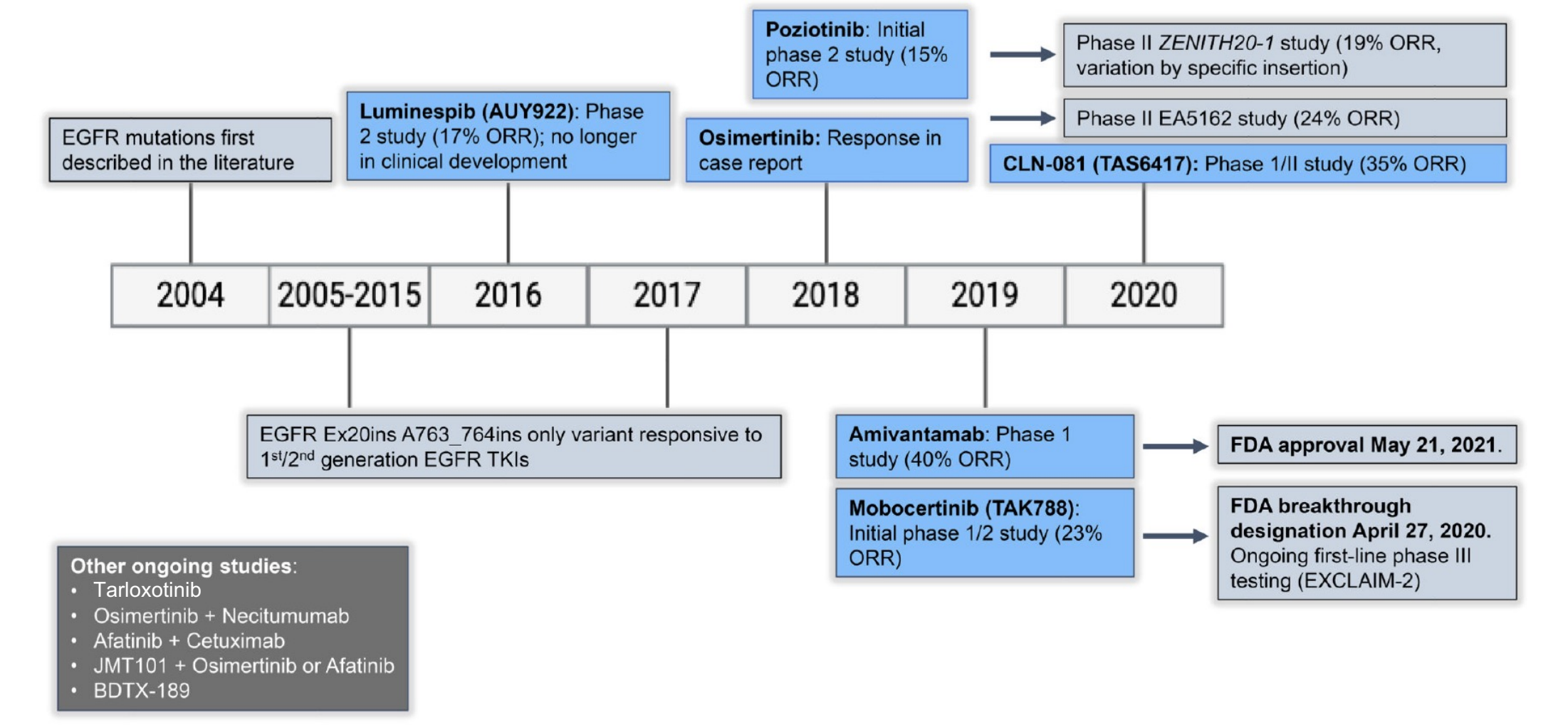
Meador CB et al. *Cancer Discov* 2021;11(9):2145-57.

Location of EGFR Exon 20 Insertion Mutations



Meador CB et al. *Cancer Discov* 2021;11(9):2145-57.

Timeline of Development of Targeted Therapies for EGFR 20 Insertion Mutations



Meador CB et al. *Cancer Discov* 2021;11(9):2145-57.

STATE OF THE ART: CONCISE REVIEW

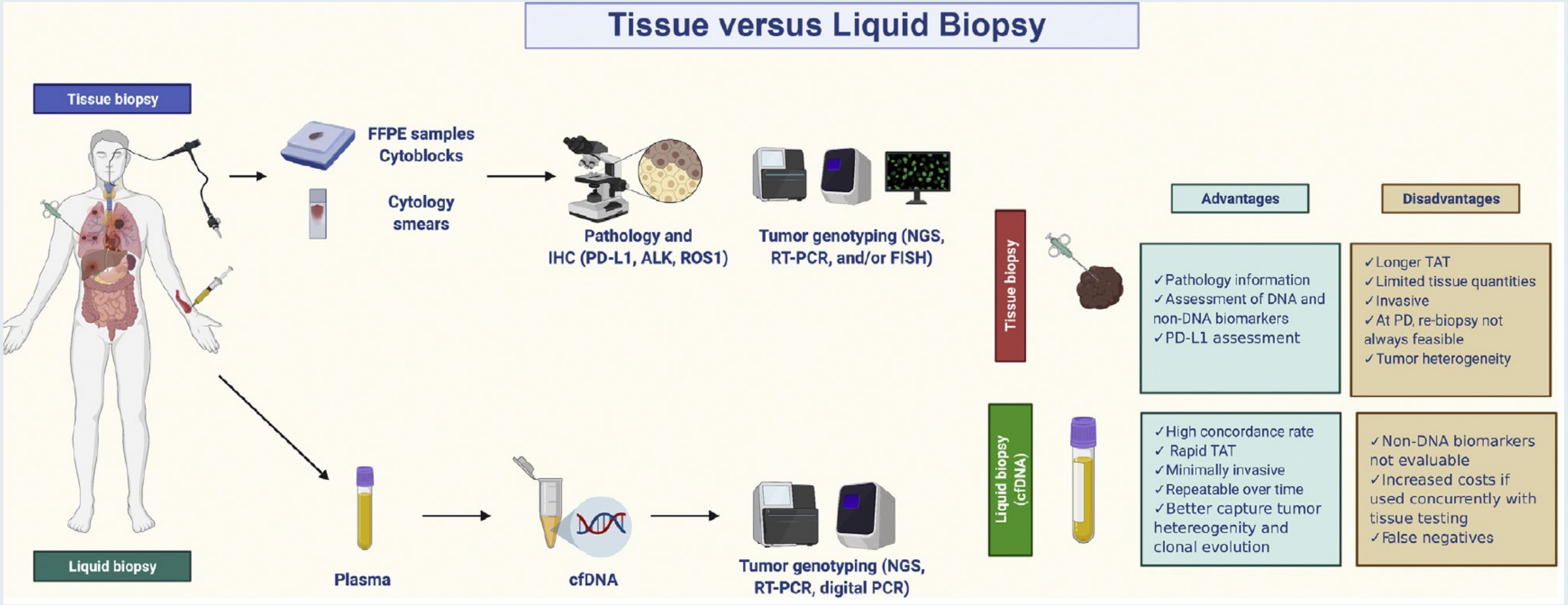
IASLC

Liquid Biopsy for Advanced NSCLC: A Consensus Statement From the International Association for the Study of Lung Cancer

Christian Rolfo, MD, PhD, MBA, Dr.hc.,[a] Philip Mack, PhD,[a]
Giorgio V. Scagliotti, MD, PhD,[b] Charu Aggarwal, MD, MPH,[c] Maria E. Arcila, MD,[d]
Fabrice Barlesi, MD, PhD,[e,f] Trever Bivona, MD, PhD,[g,h,i]
Maximilian Diehn, MD, PhD,[j,k] Caroline Dive, PhD,[l,m] Rafal Dziadziuszko, MD, PhD,[n]
Natasha Leighl, BSc, MMSc, MD,[o] Umberto Malapelle, PhD,[p] Tony Mok, MD,[q]
Nir Peled, MD, PhD,[r] Luis E. Raez, MD,[s] Lecia Sequist, MD, MPH,[t,u,v]
Lynette Sholl, MD,[w] Charles Swanton, BSc, PhD, FRCP,[x,y] Chris Abbosh, MD, PhD,[y]
Daniel Tan, MBBS, PhD,[z,aa] Heather Wakelee, MD,[bb] Ignacio Wistuba, MD,[cc]
Rebecca Bunn, MSc,[dd] Janet Freeman-Daily, MS, ENG,[ee] Murry Wynes, PhD,[cc]
Chandra Belani, MD,[ff] Tetsuya Mitsudomi, MD, PhD,[gg] David Gandara, MD[hh,*]

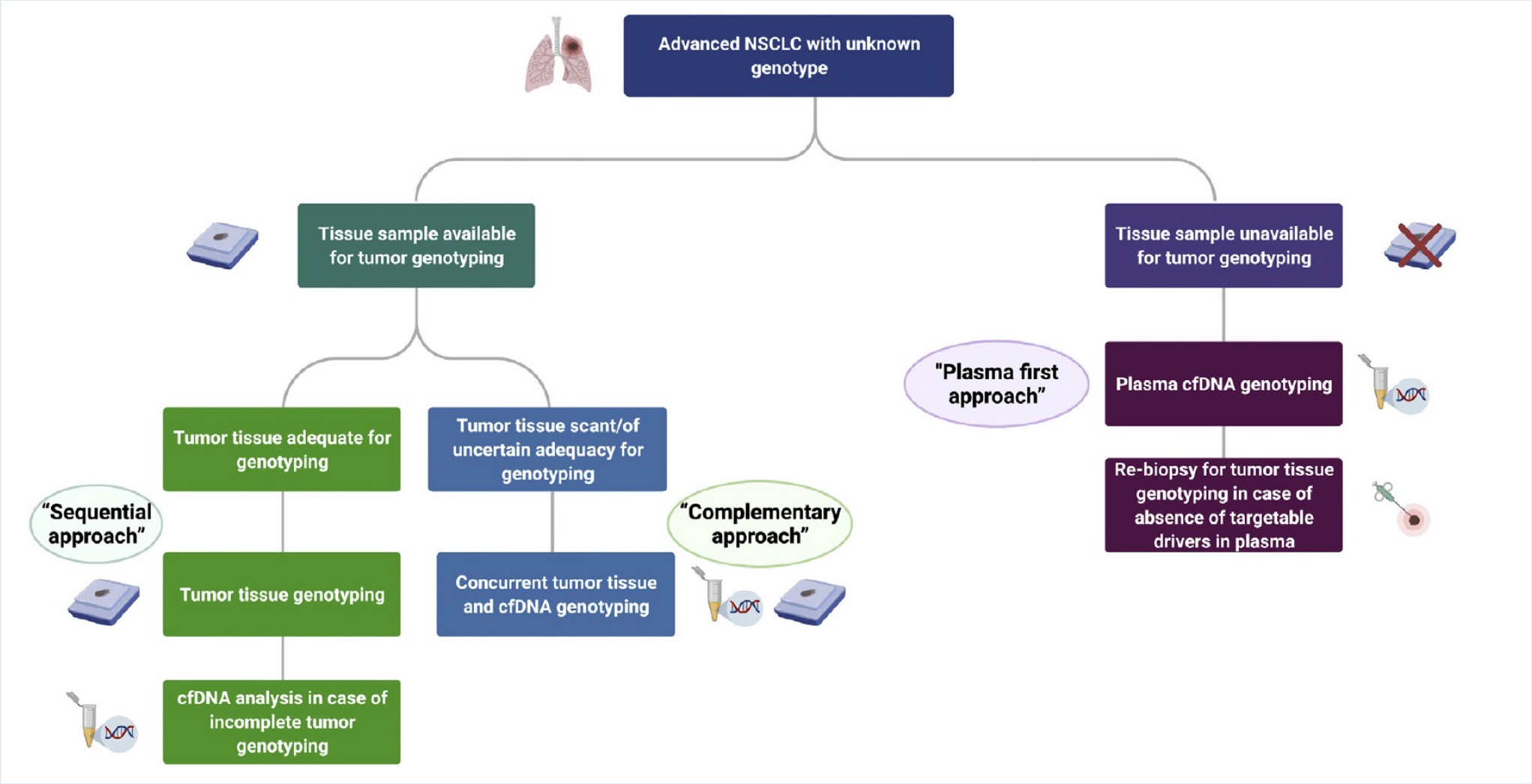
***J Thorac Oncol* 2021;16(10):1647-62.**

Advantages and Disadvantages of Tissue and Liquid Biopsy for Tumor Genotyping in Advanced or Metastatic NSCLC



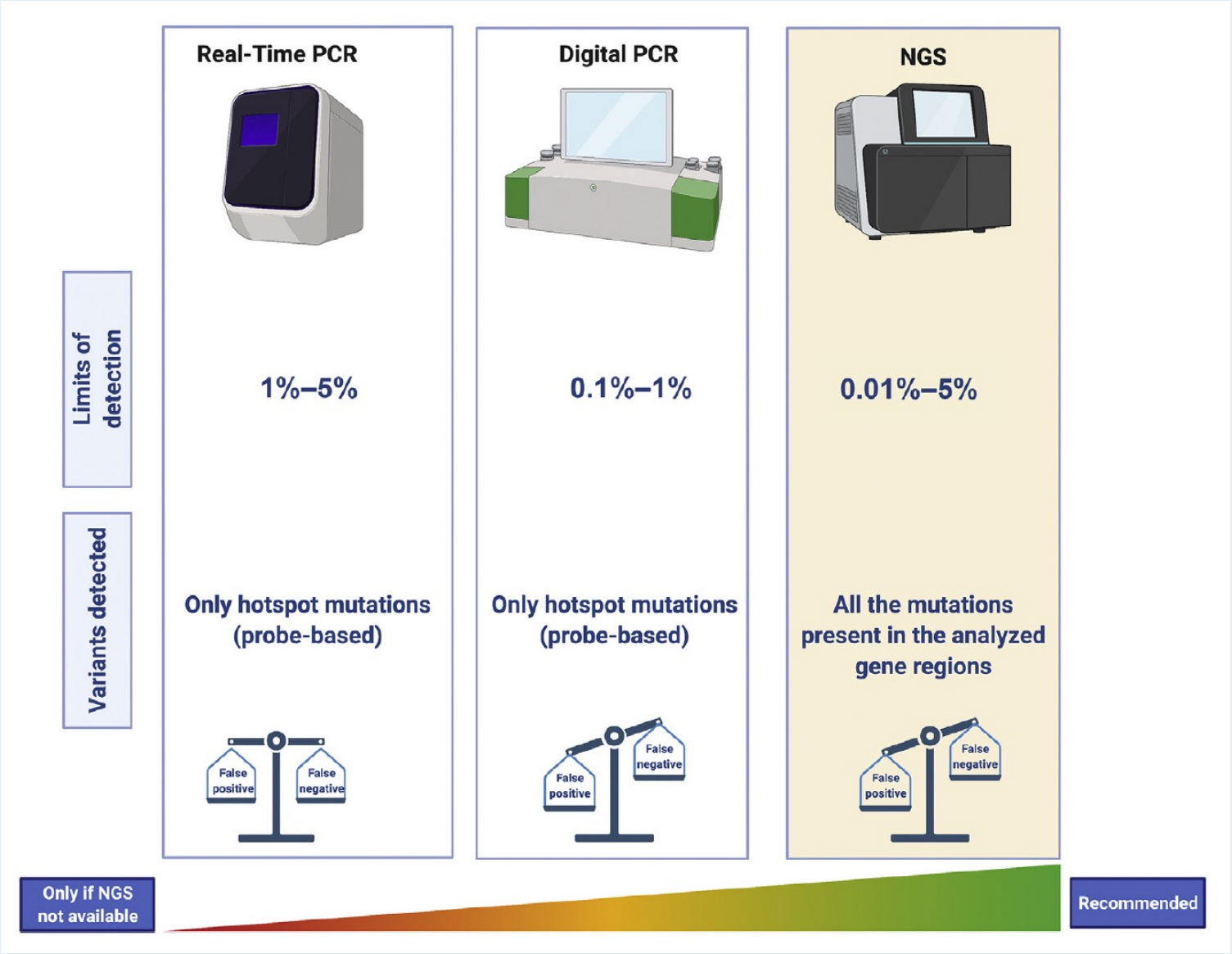
Rolfo C et al. *J Thorac Oncol* 2021;16(10):1647-62.

Diagnostic Algorithm for Liquid Biopsy Use in Treatment-Naïve Advanced or Metastatic NSCLC



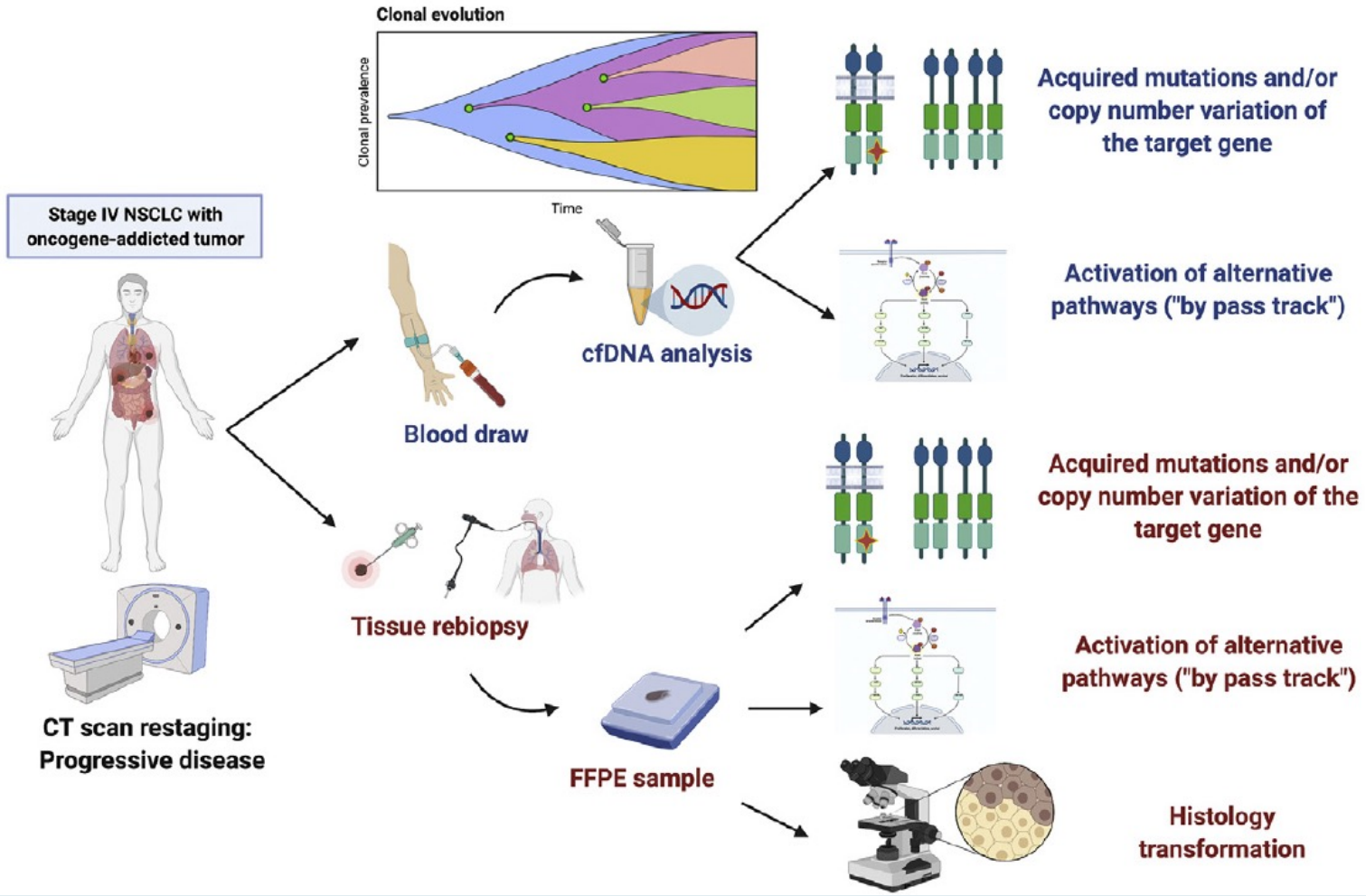
Rolfo C et al. *J Thorac Oncol* 2021;16(10):1647-62.

Comparison of Major Methodologies for ctDNA Analysis



Rolfo C et al. *J Thorac Oncol* 2021;16(10):1647-62.

Liquid Biopsy and Tissue Rebiopsy After Acquired Resistance to Targeted Therapies for Oncogene-Addicted NSCLC



Main liquid biopsy techniques used

NGS-based approaches:
- ✓High sensitivity
- ✓Multiplex
- ✓Gene rearrangements
- ✓Gene amplifications

PCR-based approaches:
- ✓Variable sensitivity
- ✓Single gene testing
- ✓Only for mutations

Main techniques used for tumor tissue

NGS-based approaches:
- ✓High sensitivity
- ✓Multiplex
- ✓Gene rearrangements
- ✓Gene amplifications

FISH:
- ✓Gene rearrangements & amplifications

PCR-based approaches:
- ✓Variable sensitivity
- ✓Single/Multiplex gene testing
- ✓Only for mutations

IHC:
- ✓Protein expression

Rolfo C et al. *J Thorac Oncol* 2021;16(10):1647-62.

Meet The Professor with Dr Sequist

MODULE 1: Case Presentations

- Dr Miller: 72-year-old woman with Stage IIB EGFR exon 19-mutant adenocarcinoma of the lung
- Dr Rudolph: 77-year-old man with EGFR L858R-mutant metastatic adenocarcinoma of the lung develops hemoptysis from an “escape lesion” on osimertinib
- Dr Patel: 72-year-old man with EGFR L858R-mutant, PD-L1-high metastatic adenocarcinoma of the lung with disease progression on pembrolizumab
- Dr Favaro: 65-year-old woman with metastatic adenocarcinoma of the lung with an EGFR exon 20 insertion with multiple brain and bone metastases (PD-L1 <1%)
- Dr Chen: 55-year-old woman with EGFR-mutant metastatic adenocarcinoma of the lung with disease progression after response to osimertinib x 3 years (PD-L1 TPS 80%)
- Dr Peswani: 50-year-old man with EGFR exon 19-mutant adenocarcinoma of the lung with brain metastases and disease progression on both osimertinib and carboplatin/paclitaxel/pembrolizumab/bevacizumab (ROS fusion detected on RNA assay)
- Dr Ahmed: 76-year-old woman with metastatic adenocarcinoma of the lung and EGFR exon 18 G719S and E709A mutations

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Case Presentation: 72-year-old woman with Stage IIB EGFR exon 19-mutant adenocarcinoma of the lung

Dr Adam Miller (Danvers, Massachusetts)

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Case Presentation: 77-year-old man with EGFR L858R-mutant metastatic adenocarcinoma of the lung develops hemoptysis from an “escape lesion” on osimertinib

Dr Priya Rudolph (Athens, Georgia)

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Case Presentation: 72-year-old man with EGFR L858R-mutant, PD-L1-high metastatic adenocarcinoma of the lung with disease progression on pembrolizumab

Dr Sandip Patel (San Diego, California)

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Case Presentation: 72-year-old man with EGFR L858R-mutant, PD-L1-high metastatic adenocarcinoma of the lung with disease progression on pembrolizumab (continued)

Dr Sandip Patel (San Diego, California)

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Case Presentation: 65-year-old woman with metastatic adenocarcinoma of the lung with an EGFR exon 20 insertion with multiple brain and bone metastases (PD-L1 <1%)

Dr Justin Favaro (Charlotte, North Carolina)

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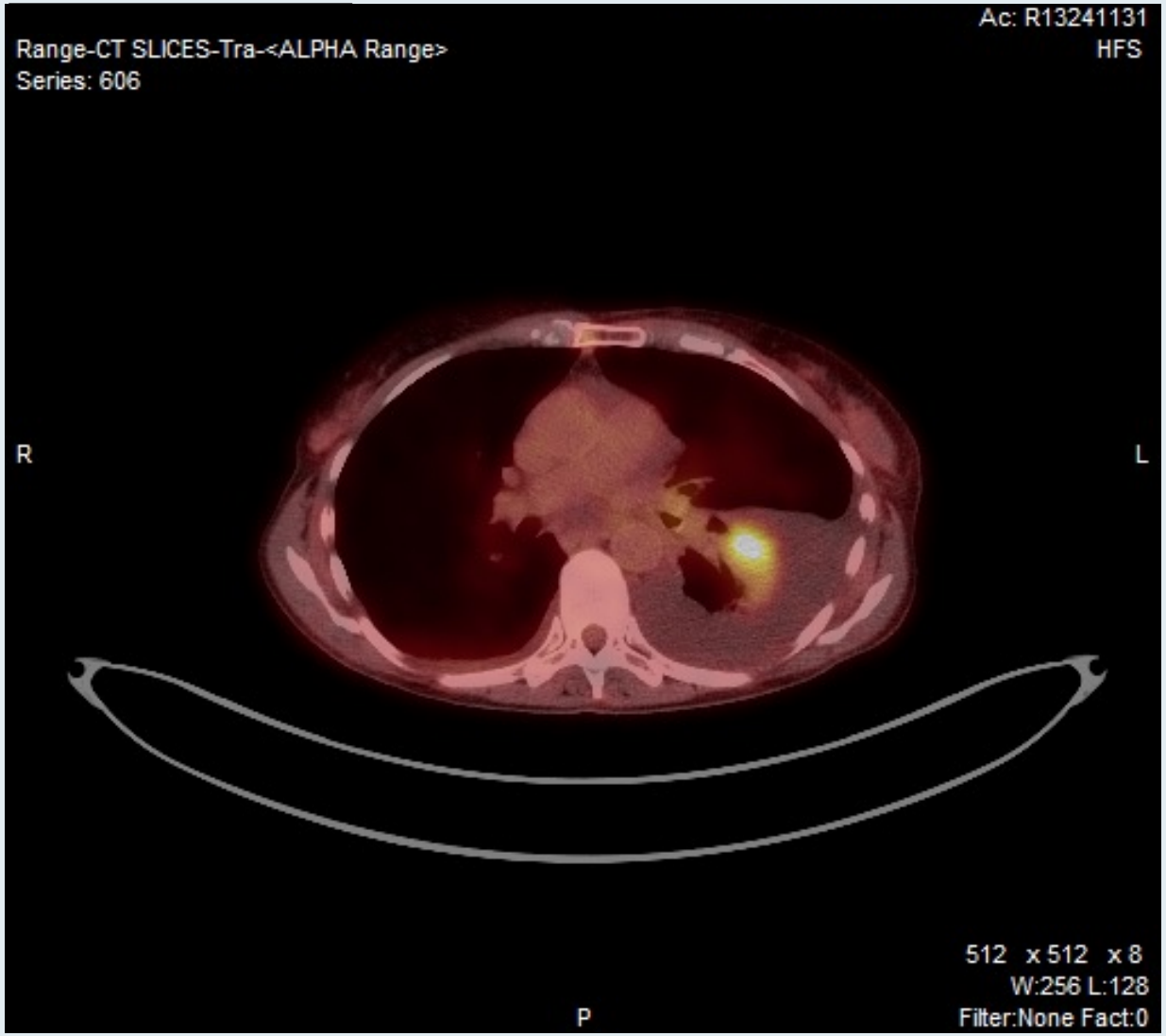

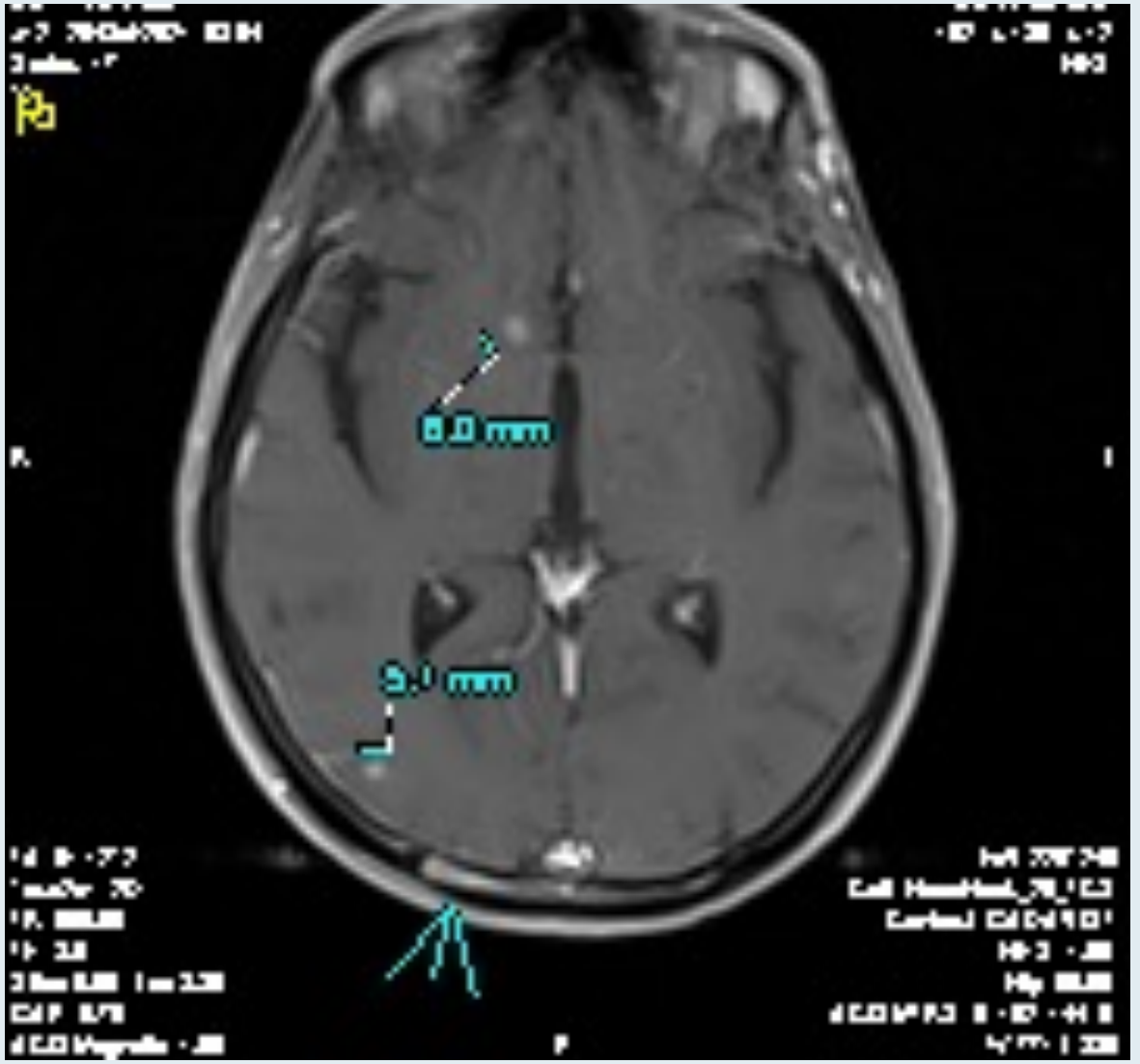

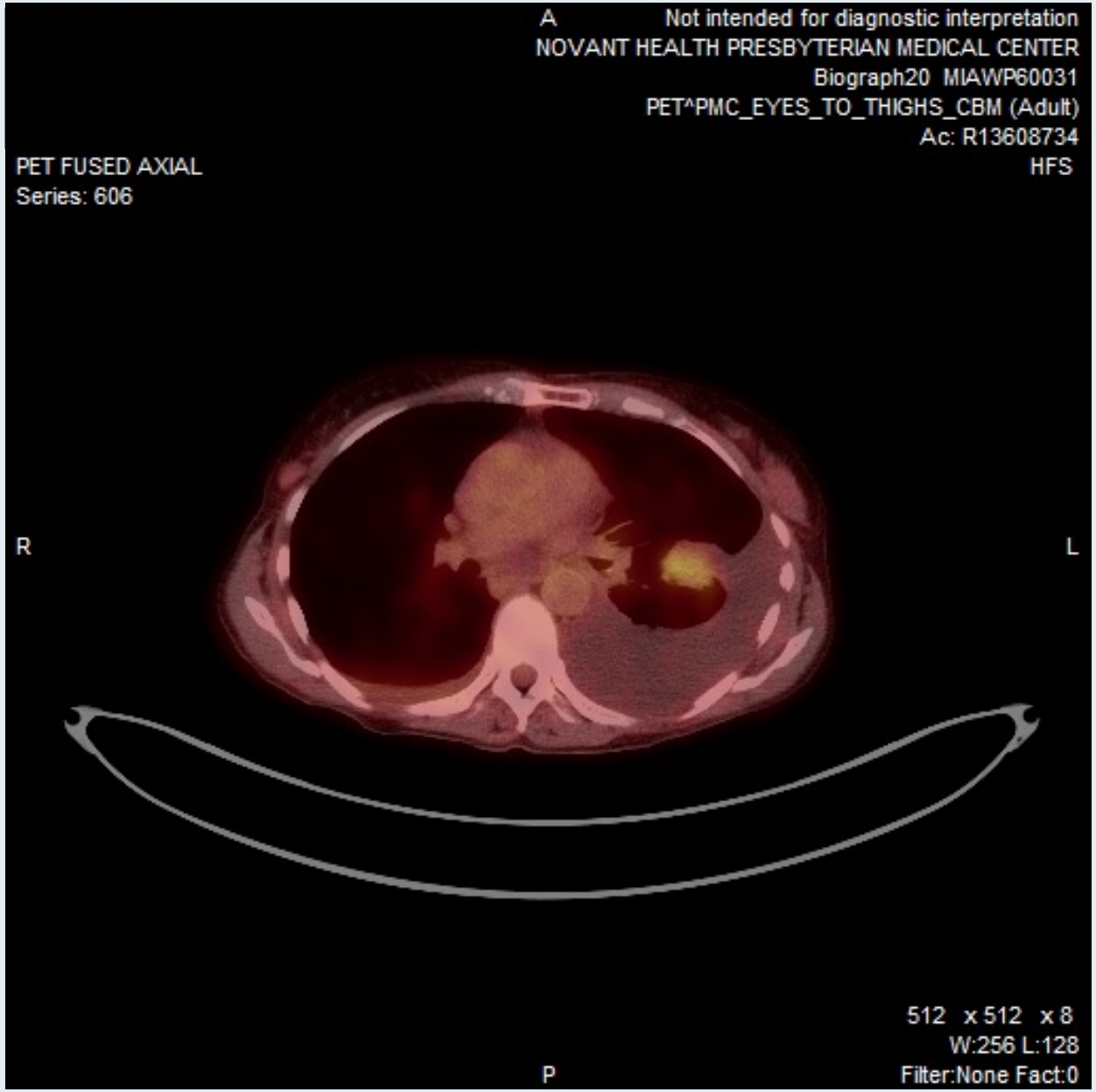
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Case Presentation: 55-year-old woman with EGFR-mutant metastatic adenocarcinoma of the lung with disease progression after response to osimertinib x 3 years (PD-L1 TPS 80%)

Dr Gigi Chen (Pleasant Hill, California)

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RESEARCH ARTICLE

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

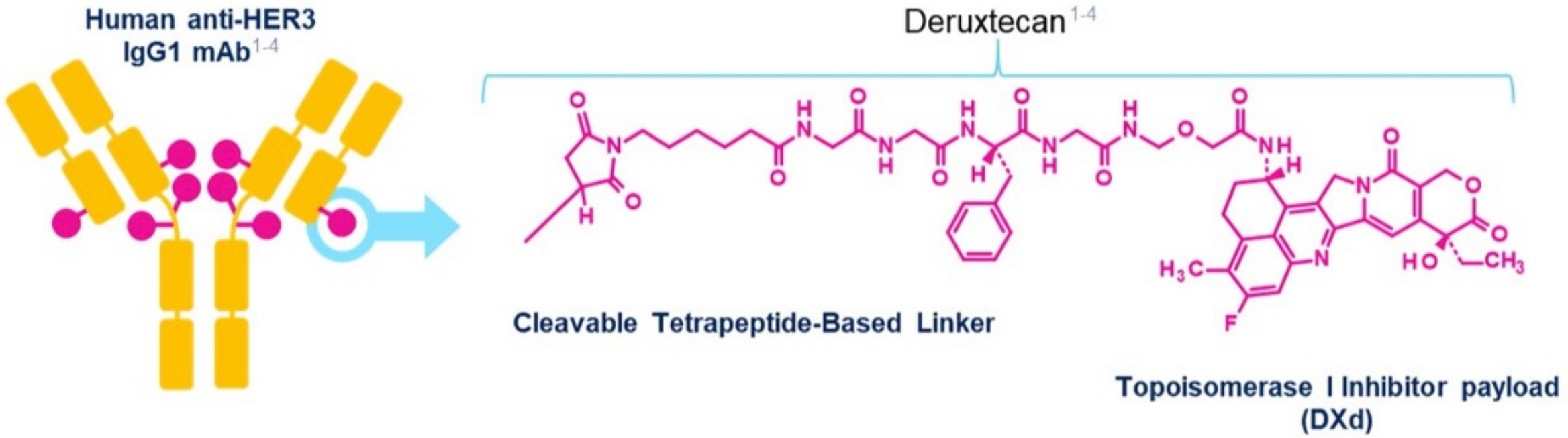
Efficacy and Safety of Patritumab Deruxtecan (HER3-DXd) in EGFR Inhibitor–Resistant, *EGFR*-Mutated Non–Small Cell Lung Cancer

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.

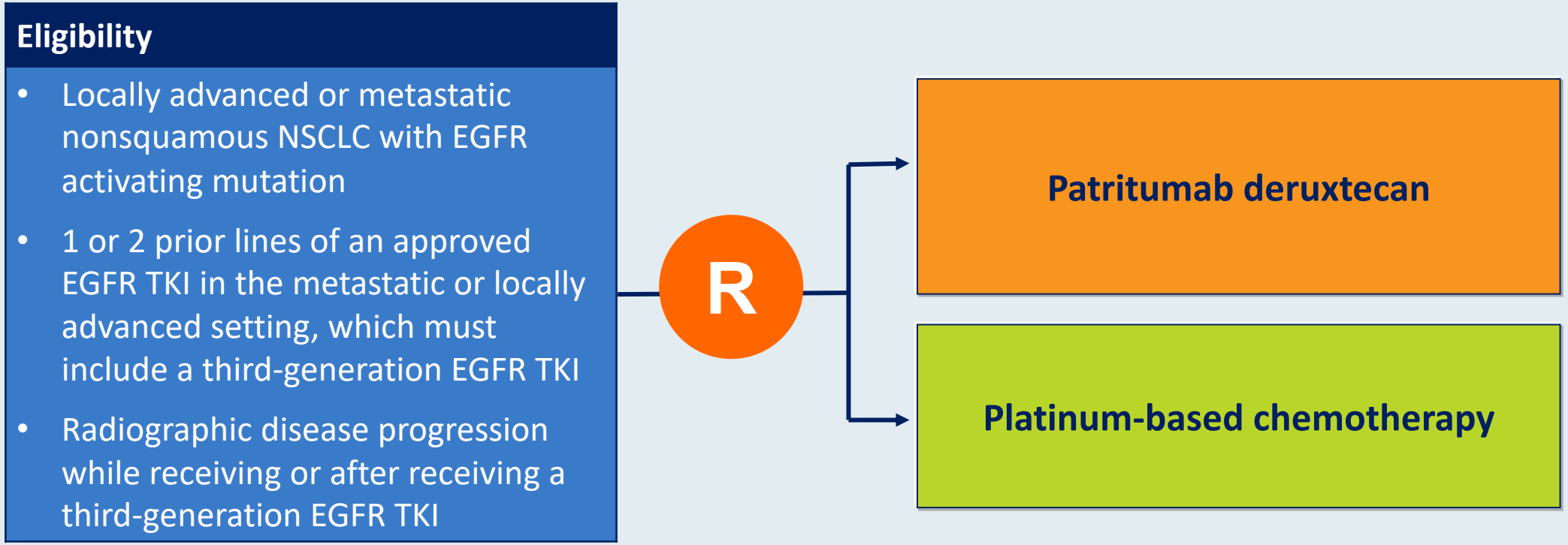
Select Grade ≥3 Treatment-Emergent Adverse Events (TEAEs)

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

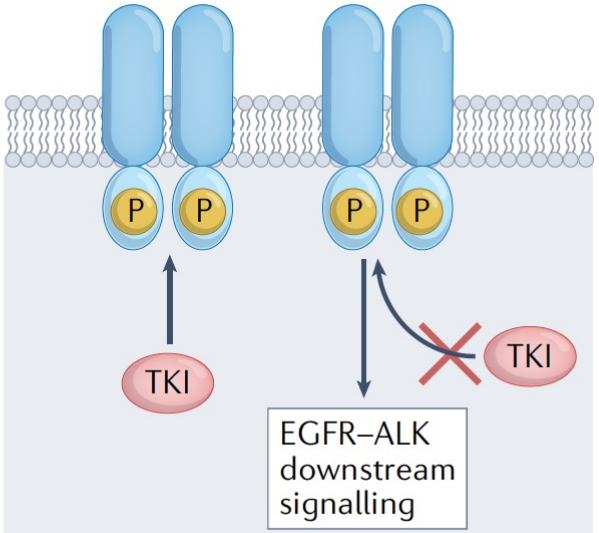
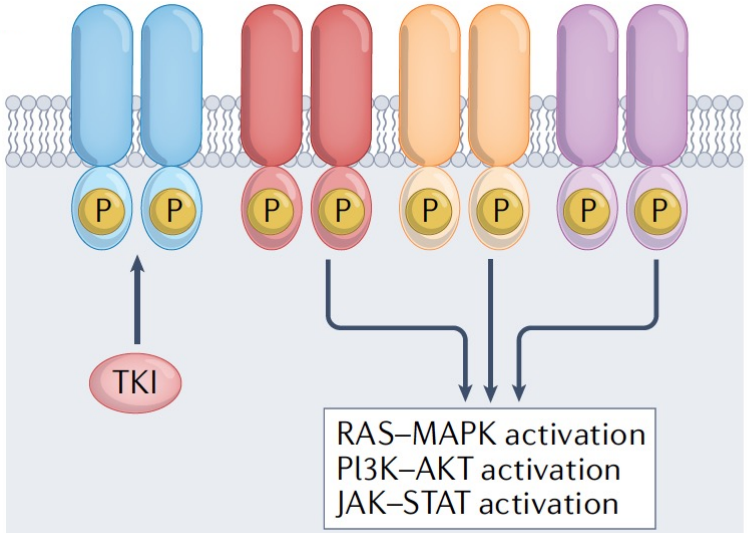
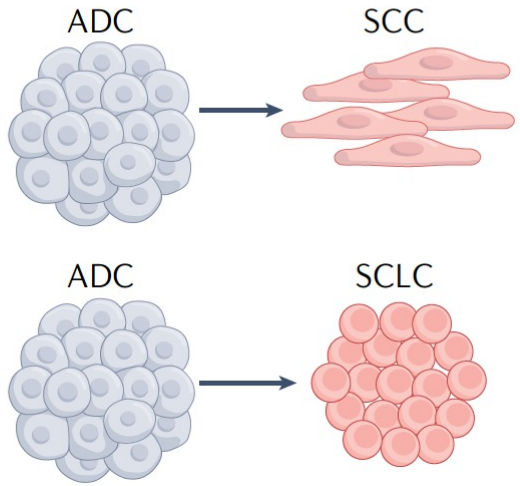
Nat Rev Clin Oncol 2022 August;19(8):499-514.

REVIEWS

Third-generation EGFR and ALK inhibitors: mechanisms of resistance and management

Alissa J. Cooper, Lecia V. Sequist and Jessica J. Lin ✉

Mechanisms of Acquired Resistance to Osimertinib for NSCLC with EGFR Mutations

	Alterations in TKI Signaling	Activation of Bypass and/or Downstream Signaling Pathways	Changes in Tumor Cell Lineage
			
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.

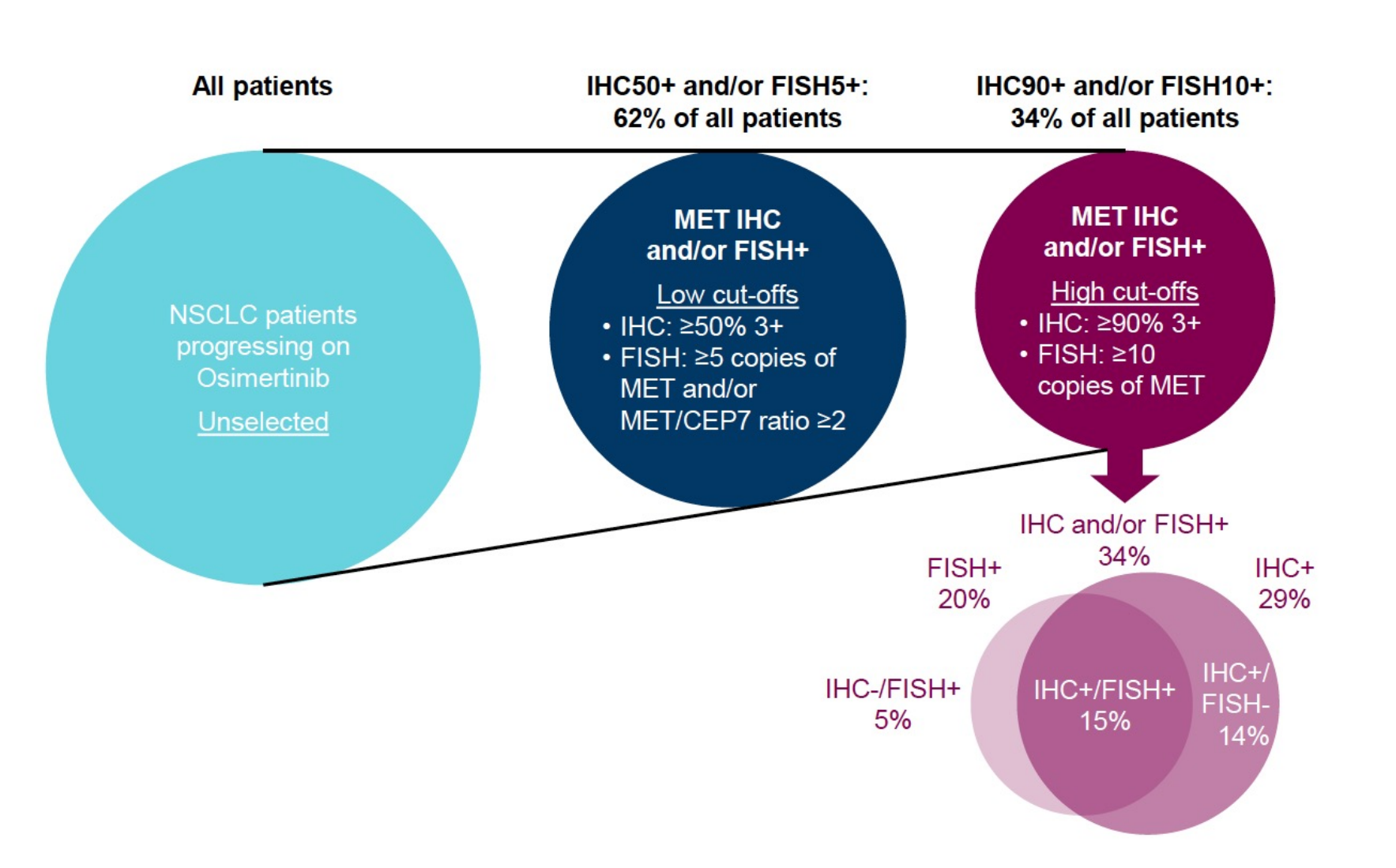
#EP08.02-140

IASLC 2022

MET Biomarker-based Preliminary Efficacy Analysis in SAVANNAH: savolitinib+osimertinib in EGFRm NSCLC Post-osimertinib

Myung-Ju Ahn[1], Filippo de Marinis[2], Laura Bonanno[3], Byoung Chul Cho[4], Tae Min Kim[5], Susanna Cheng[6], Silvia Novello[7], Claudia Proto[8], Sang-We Kim[9], Jong Seok Lee[10], Giulio Metro[11], James CH Yang[12], Wanning Xu[13], Ryan Hartmaier[14], Aino Telaranta-Keerie[15], Lynne Poole[16], Lecia Sequist[17]

Estimated Prevalence of MET Overexpression and/or Amplification



Ahn M-J et al. IASLC 2022;Abstract EP08.02-140.

Case Presentation: 50-year-old man with EGFR exon 19-mutant adenocarcinoma of the lung with brain metastases and disease progression on both osimertinib and carboplatin/paclitaxel/pembrolizumab/bevacizumab (ROS fusion detected on RNA assay)

Dr Namrata Peswani (Richardson, Texas)

RTP RESEARCH TO PRACTICE

Case Presentation: 76-year-old woman with metastatic adenocarcinoma of the lung and EGFR exon 18 G719S and E709A mutations

Dr Syed Ahmed (Libertyville, Illinois)

RTP RESEARCH TO PRACTICE

Meet The Professor with Dr Sequist

INTRODUCTION: Journal Club with Dr Sequist – Part 1

MODULE 1: Case Presentations

MODULE 2: Faculty Survey

MODULE 3: Journal Club with Dr Sequist – Part 2

MODULE 4: Appendix of Key Publications

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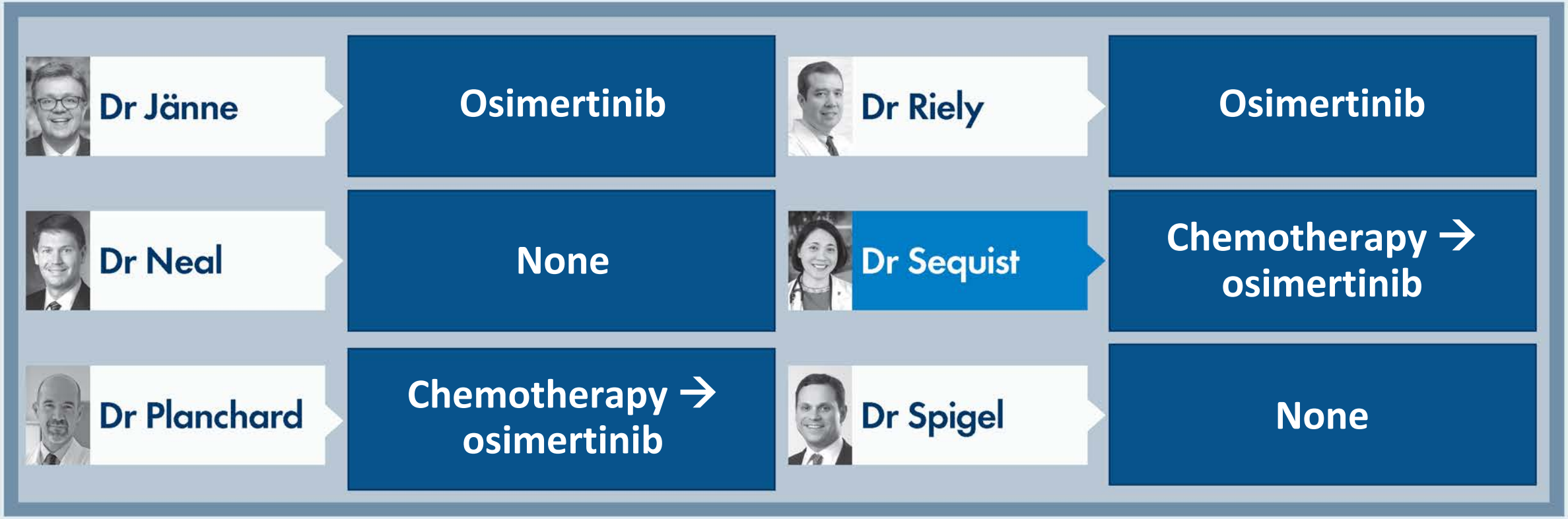
Adjuvant Therapy

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

RTP RESEARCH TO PRACTICE

Locally Advanced Disease

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

Metastatic Disease

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 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

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

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

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Exon 20 Insertions

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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

RTP RESEARCH TO PRACTICE

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

RTP RESEARCH TO PRACTICE

Meet The Professor with Dr Sequist

INTRODUCTION: Journal Club with Dr Sequist – Part 1

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MODULE 4: Appendix of Key Publications

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RESEARCH
TO PRACTICE

Original Study

Chemotherapy Plus Immunotherapy Versus Chemotherapy Plus Bevacizumab Versus Chemotherapy Alone in EGFR-Mutant NSCLC After Progression on Osimertinib

Maya N. White,[1] Andrew J Piper-Vallillo,[2,3] Rebecca M. Gardner,[4] Kristen Cunanan,[4] Joel W. Neal,[1] Millie Das,[1,5] Sukhmani K. Padda,[1] Kavitha Ramchandran,[1] Thomas T. Chen,[6] Lecia V. Sequist,[3] Zofia Piotrowska,[3] Heather A. Wakelee[1]

***Clin Lung Cancer* 2022;23(3):e210-21.**

Combining Osimertinib With Chemotherapy in EGFR-Mutant NSCLC at Progression

Maya N White, MD MS[*,1], Zofia Piotrowska, MD MHS[*,2], Kevin Stirling, MD[3], Stephen V Liu, MD[4], Mandeep K Banwait, BS[5], Kristen Cunanan, PhD[6], Lecia V Sequist, MD MPH[2], Heather A Wakelee, MD[1], Daniel Hausrath, MD[7], Joel W Neal, MD PhD[1]

Clin Lung Cancer 2021;22(3):201-9.

JC JOURNAL CLUB RTP RESEARCH TO PRACTICE

Optimizing Supportive Care for Patients with Metastatic Lung Cancer in the Era of Precision Oncology

Authors: Kelly Hsu, BA, Lecia Sequist, MD, MPH, Vicki Jackson, MD, MPH, Elyse Park, PhD, MPH, Dustin Rabideau, PhD, Joseph Greer, PhD, Jennifer Temel, MD, and Laura Petrillo, MD

ASCO 2022;Abstract TPS12150.

JC JOURNAL CLUB

RTP RESEARCH TO PRACTICE

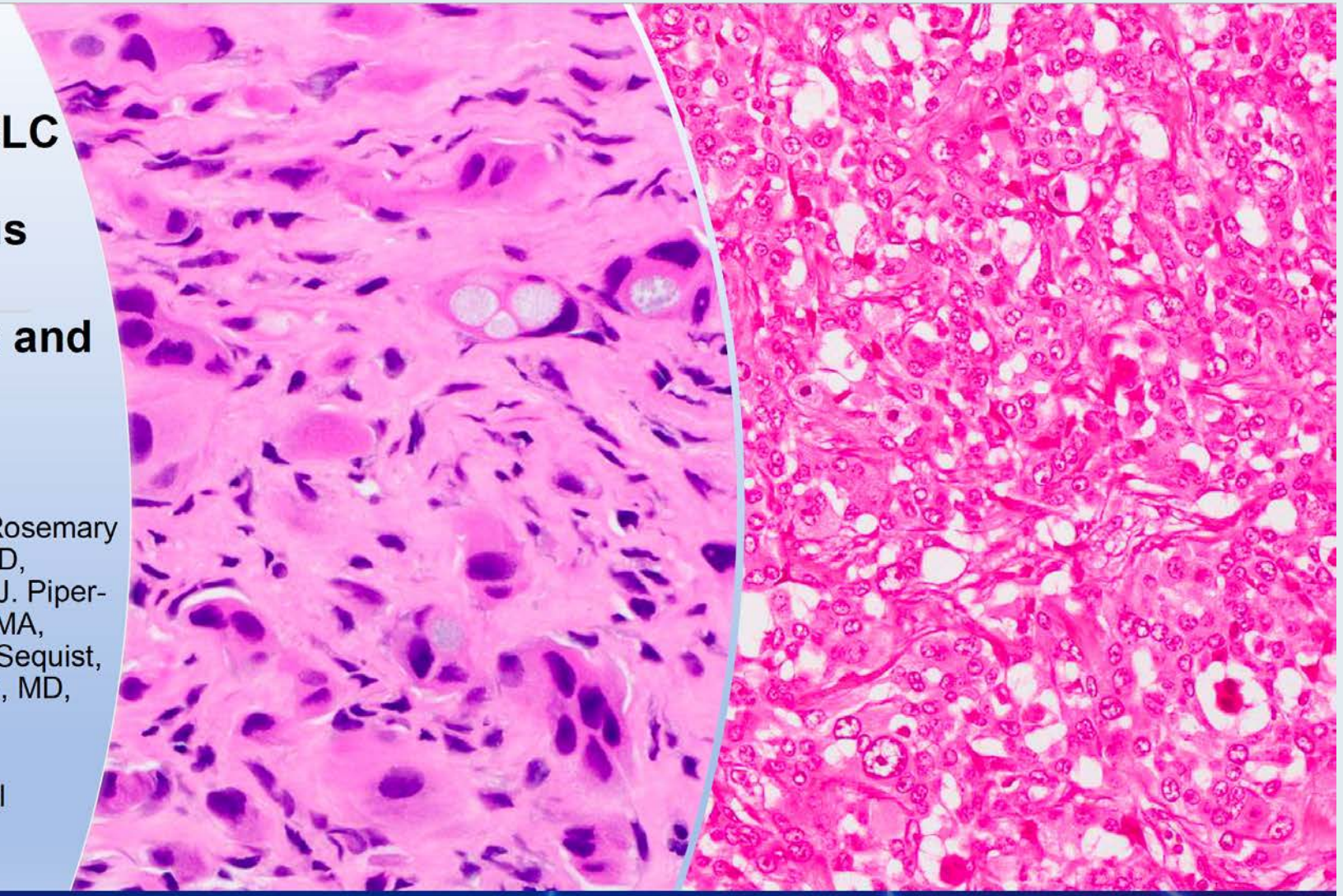
EGFR-mutant NSCLC with *de novo* or acquired squamous histology:

Molecular features and clinical outcomes

Catherine Meador, MD, PhD, Rosemary Cobb, BA , Yin P. Hung, MD, PhD, Mandeep Banwait, BA, Andrew J. Piper-Vallillo, MD, Alona Muzikansky, MA, Aaron Hata, MD, PhD, Lecia V. Sequist, MD, MPH, and Zofia Piotrowska, MD, MHS

Massachusetts General Hospital

Boston, MA, USA

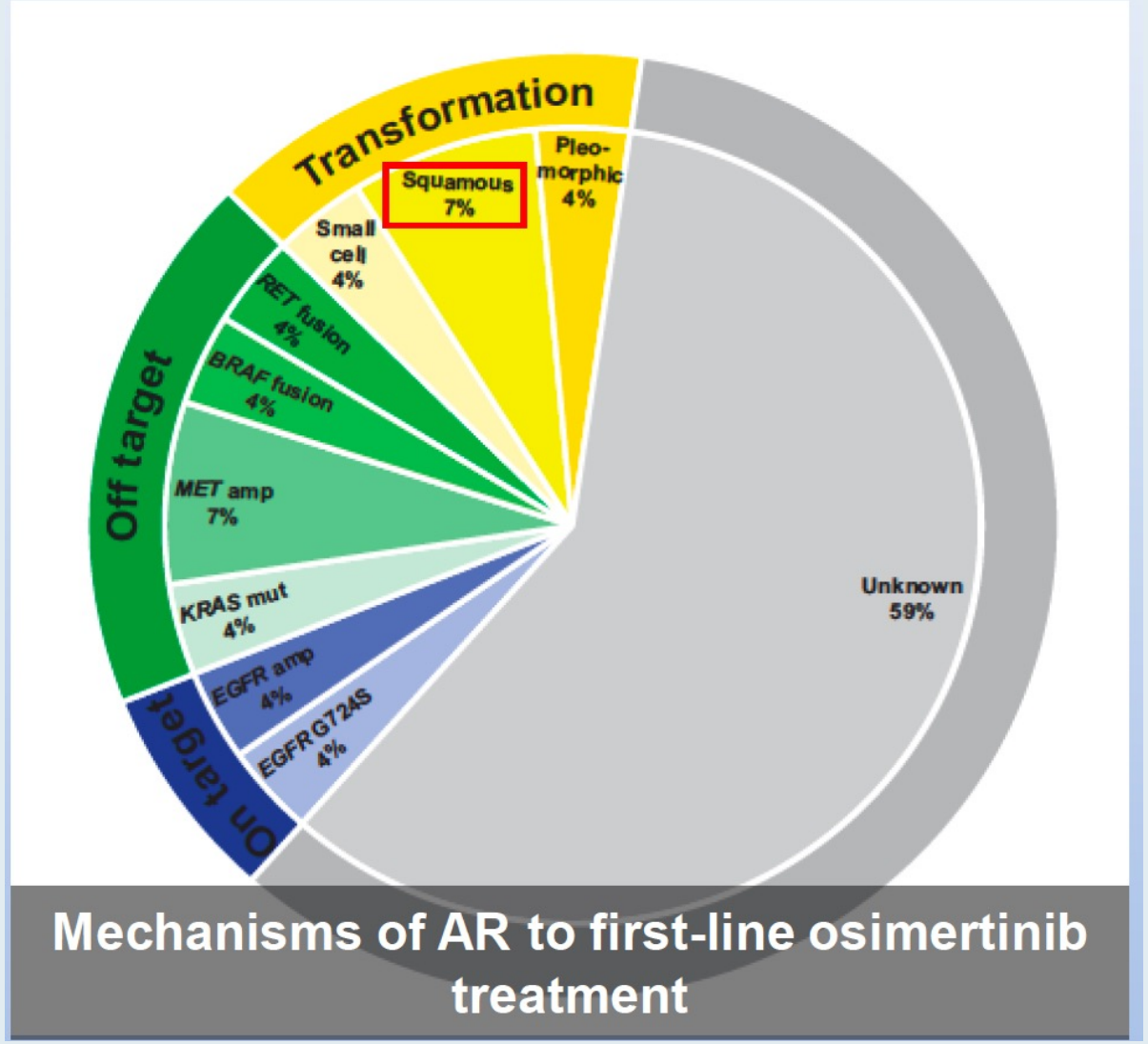


IASLC | 2021 World Conference on Lung Cancer

SEPTEMBER 8 - 14, 2021 I WORLDWIDE VIRTUAL EVENT

Meador C et al. IASLC 2021;Abstract MA14.07.

Squamous Transformation as a Mechanism of Acquired Resistance (AR) to EGFR TKIs



Meador C et al. IASLC 2021;Abstract MA14.07.

JCO Precis Oncol 2021 February 1;5:325-32.

TARGETED DRUG THERAPY

original reports

Randomized Phase II Study of 3 Months or 2 Years of Adjuvant Afatinib in Patients With Surgically Resected Stage I-III *EGFR*-Mutant Non–Small-Cell Lung Cancer

Joel W. Neal, MD, PhD[1]; Daniel B. Costa, MD, PhD, MSc[2]; Alona Muzikansky, MS[3]; Joseph B. Shrager, MD[1]; Michael Lanuti, MD[1]; James Huang, MD[4]; Kavitha J. Ramachandran, MD[1]; Deepa Rangachari, MD[2]; Mark S. Huberman, MD[2]; Zofia Piotrowska, MD, MHS[3]; Mark G. Kris, MD[5]; Christopher G. Azzoli, MD[3]; Lecia V. Sequist, MD, MPH[3]; and Jamie E. Chaft, MD[5]

Complete Evaluation of Resistance Mechanisms to First-Line Osimertinib Requires Tissue Biopsy

Piotrowska Z et al.

ASCO 2022;Abstract e21154.

JTO Clin Res Rep 2022 April 21;3(6):100328.

ORIGINAL ARTICLE

High-Dose Osimertinib for CNS Progression in EGFR+ NSCLC: A Multi-Institutional Experience

A. J. Piper-Vallillo, MD,[a,b] Julia K. Rotow, MD,[c,d] Jacqueline V. Aredo, MD,[e] Khvaramze Shaverdashvili, MD, PhD,[f] Jia Luo, MD,[c,d,g] Jennifer W. Carlisle, MD,[h] Hatim Husain, MD,[i] Alona Muzikansky, MA,[a] Rebecca S. Heist, MD,[a,c] Deepa Rangachari, MD,[b,c] Suresh S. Ramalingam, MD,[h] Heather A. Wakelee, MD,[e] Helena A. Yu, MD,[g] Lecia V. Sequist, MD,[a,c] Joshua M. Bauml, MD,[f] Joel W. Neal, MD, PhD,[e] Zofia Piotrowska, MD, MHS[a,c,*]

COMPEL: chemotherapy with / without osimertinib in patients with EGFRm advanced NSCLC and progression on first-line osimertinib

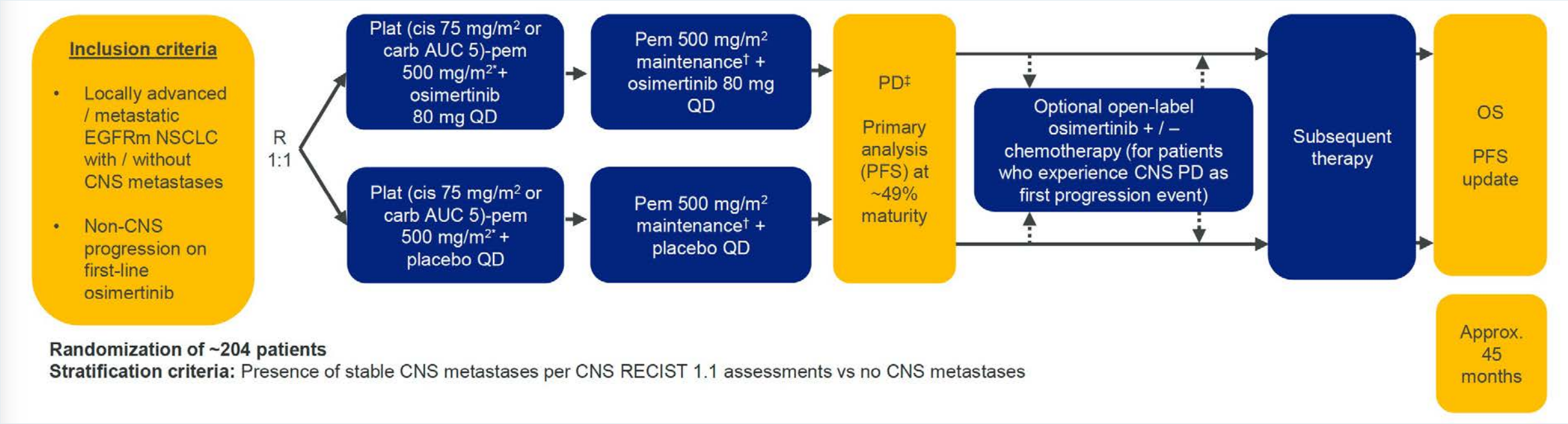
https://bit.ly/3yuWJOk
Scan the QR code or visit the link for:
- A copy of these slides
- An infographic summary

Lecia V. Sequist[1], Nir Peled[2], Amanda Tufman[3], Leslie Servidio[4], Jingyi Li[4], Rosemary Taylor[5], Jun Zhao[6]

[1]Massachusetts General Hospital Cancer Center, Boston, Massachusetts, USA; [2]Division of Oncology, Shaare Zedek Medical Center, Jerusalem, Israel, & The Hebrew University, Jerusalem, Israel; [3]Division of Respiratory Medicine V, University of Munich, Comprehensive Pneumology Center, Member of the German Center for Lung Research, Munich, Germany; [4]Global Medical Affairs, Oncology Business Unit, AstraZeneca, Gaithersburg, Maryland, USA; [5]Oncology R&D, Astrazeneca, Melbourn, UK; [6]Peking University School of Oncology, Beijing Cancer Hospital, Beijing, China

Poster number: P47.11

COMPEL Phase III Study Design



Sequist LV et al. IASLC 2021;Abstract P47.11.

European Journal of Cancer 172 (2022) 276–286
https://doi.org/10.1016/j.ejca.2022.05.023

ELSEVIER

Available online at www.sciencedirect.com

ScienceDirect

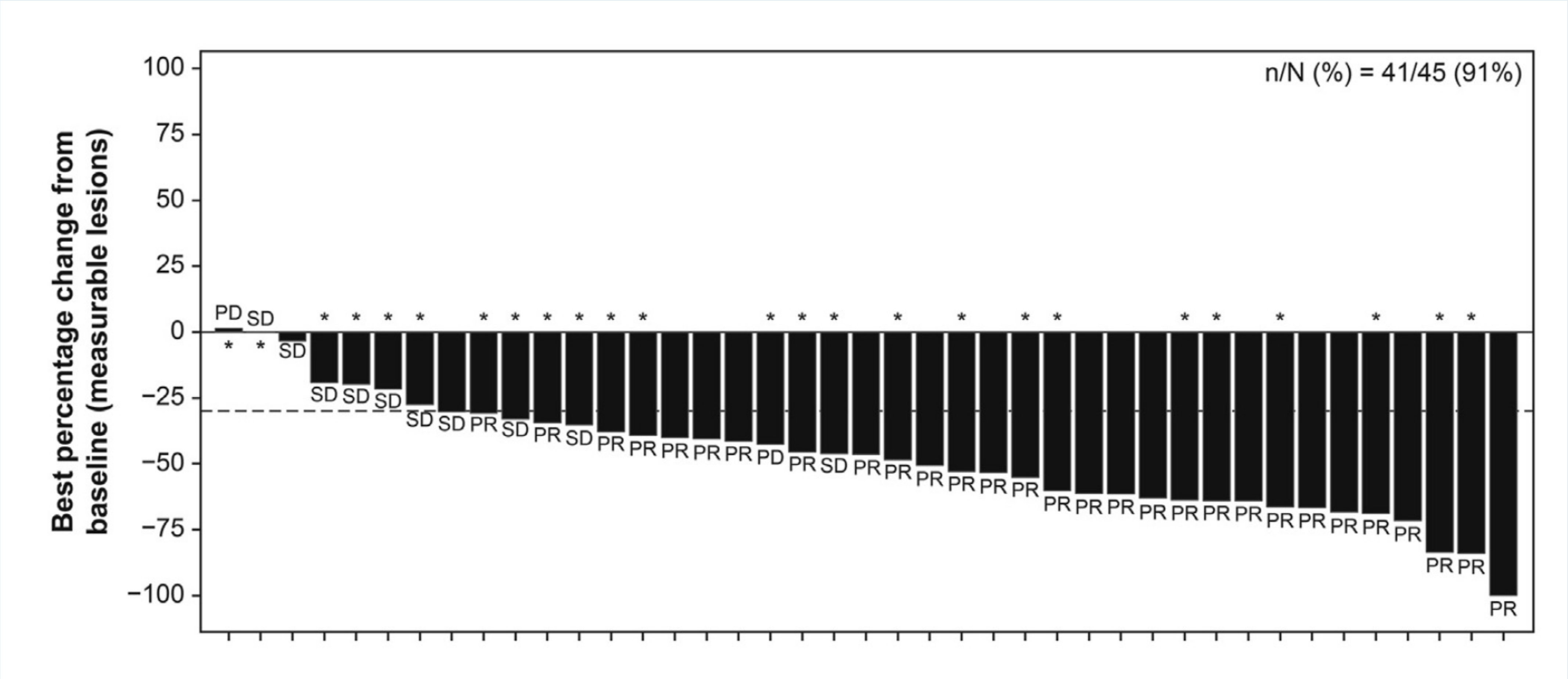
journal homepage: www.ejcancer.com

Original Research

Nazartinib for treatment-naive *EGFR*-mutant non–small cell lung cancer: Results of a phase 2, single-arm, open-label study

Daniel S.W. Tan [a,*], Sang-We Kim [b], Santiago Ponce Aix [c], Lecia V. Sequist [d], Egbert F. Smit [e], James C.H. Yang [f], Toyoaki Hida [g], Ryo Toyozawa [h], Enriqueta Felip [i], Juergen Wolf [j], Christian Grohé [k], Natasha B. Leighl [l], Gregory Riely [m], Xiaoming Cui [n], Mike Zou [o], Samson Ghebremariam [o], Leslie O'Sullivan-Djentuh [p], Riccardo Belli [p], Monica Giovannini [o], Dong-Wan Kim [q]

Best Change from Baseline in Sum of Longest Lesion Diameters by BIRC Assessment for All Patients



BIRC = blinded independent review committee; PD = progressive disease; SD = stable disease; PR = partial response

Tan DSW et al. *Eur J Cancer* 2022;172:276-86.

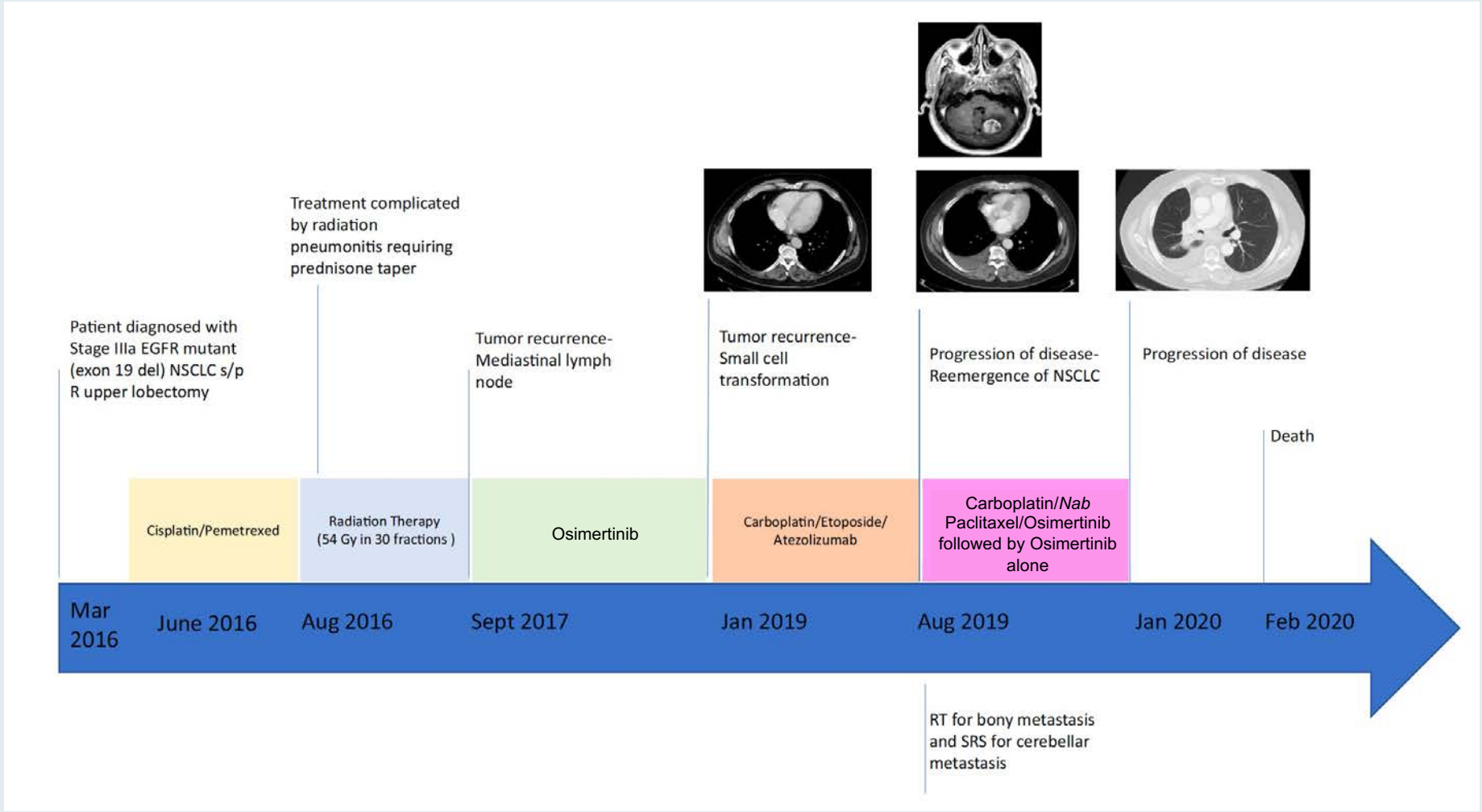
JTO Clin Res Rep 2020 December 3;2(2):100128.

CASE REPORT

Revolving Door of Histologic Transformation—Tumor Heterogeneity Complicating the Management of *EGFR*-Mutated Lung Adenocarcinoma: A Case of Jekyll and Hyde

Michael Wysota, MD,[a,b,c] Saeed Asiry, MD,[a,b,c] Yitzhak Goldstein, MD,[a,b,c] Lecia V. Sequist, MD,[d] Samer Khader, MD,[a,b,c] Balazs Halmos, MD[a,b,c,*]

Timeline of a Patient's NSCLC and Dates of Therapy



Wysota M et al. *JTO Clin Res Rep* 2020 December 3;2(2):100128.

Effect of Participation in the EGFR Resisters Research Summit on Competence, Performance, and Professional Productivity of Young Researchers

Fowler JB et al.

ASCO 2022;Abstract e23010.

JC JOURNAL CLUB RTP RESEARCH TO PRACTICE

Meet The Professor with Dr Sequist

INTRODUCTION: Journal Club with Dr Sequist – Part 1

MODULE 1: Case Presentations

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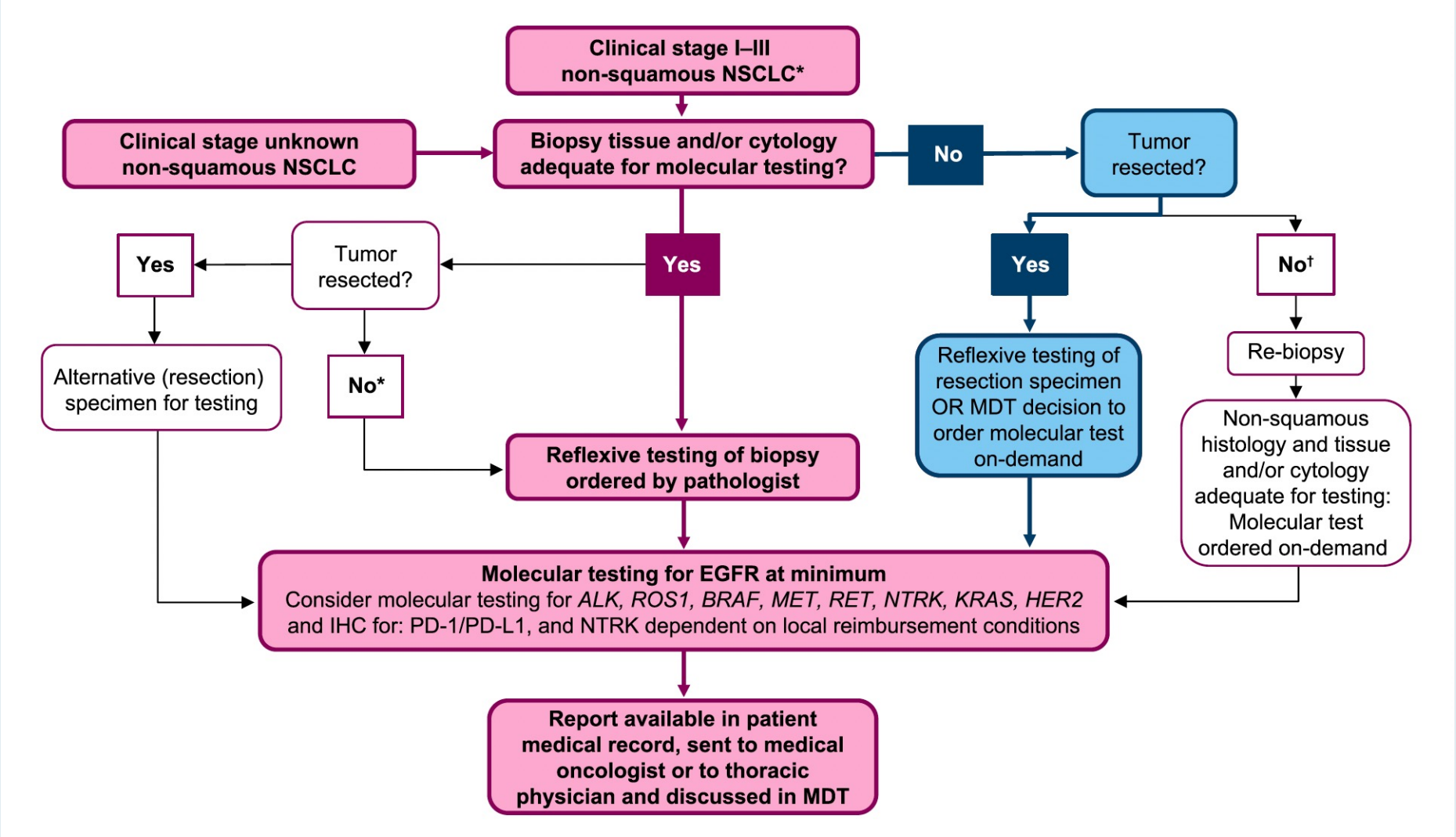
RESEARCH
TO PRACTICE

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.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 29, 2020 VOL. 383 NO. 18

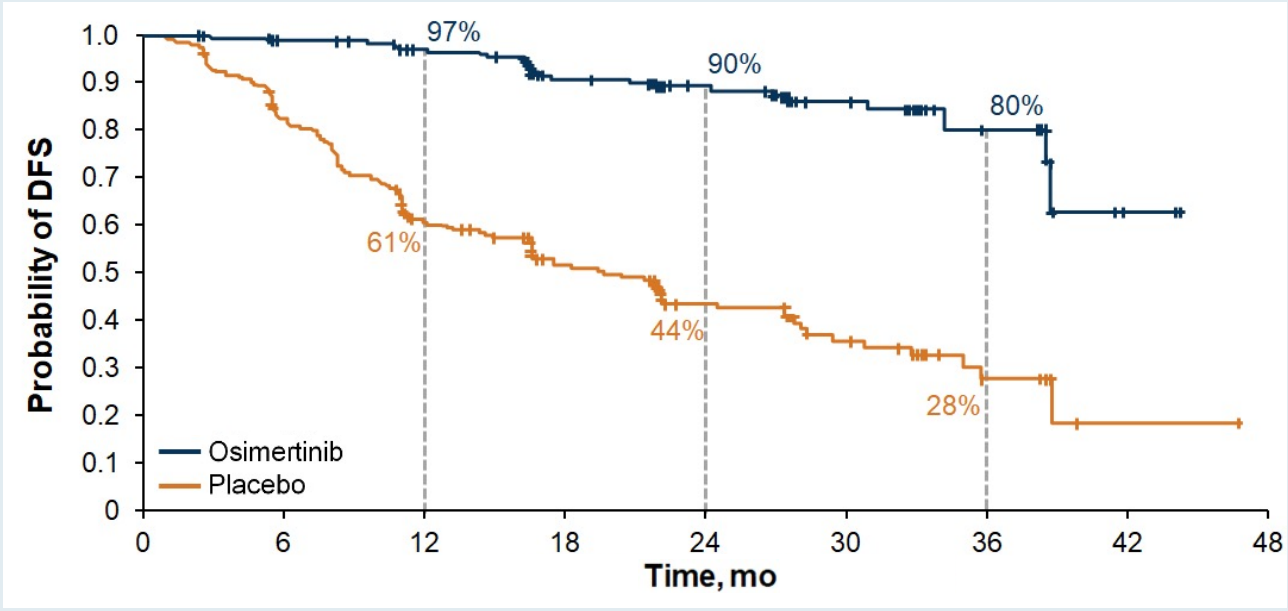
Osimertinib in Resected *EGFR*-Mutated Non–Small-Cell Lung Cancer

Yi-Long Wu, M.D., Masahiro Tsuboi, M.D., Jie He, M.D., Thomas John, Ph.D., Christian Grohe, M.D., Margarita Majem, M.D., Jonathan W. Goldman, M.D., Konstantin Laktionov, Ph.D., Sang-We Kim, M.D., Ph.D., Terufumi Kato, M.D., Huu-Vinh Vu, M.D., Ph.D., Shun Lu, M.D., Kye-Young Lee, M.D., Ph.D., Charuwan Akewanlop, M.D., Chong-Jen Yu, M.D., Ph.D., Filippo de Marinis, M.D., Laura Bonanno, M.D., Manuel Domine, M.D., Ph.D., Frances A. Shepherd, M.D., Lingmin Zeng, Ph.D., Rachel Hodge, M.Sc., Ajlan Atasoy, M.D., Yuri Rukazenkov, M.D., Ph.D., and Roy S. Herbst, M.D., Ph.D., for the ADAURA Investigators*

Phase III ADAURA Trial: Adjuvant Osimertinib

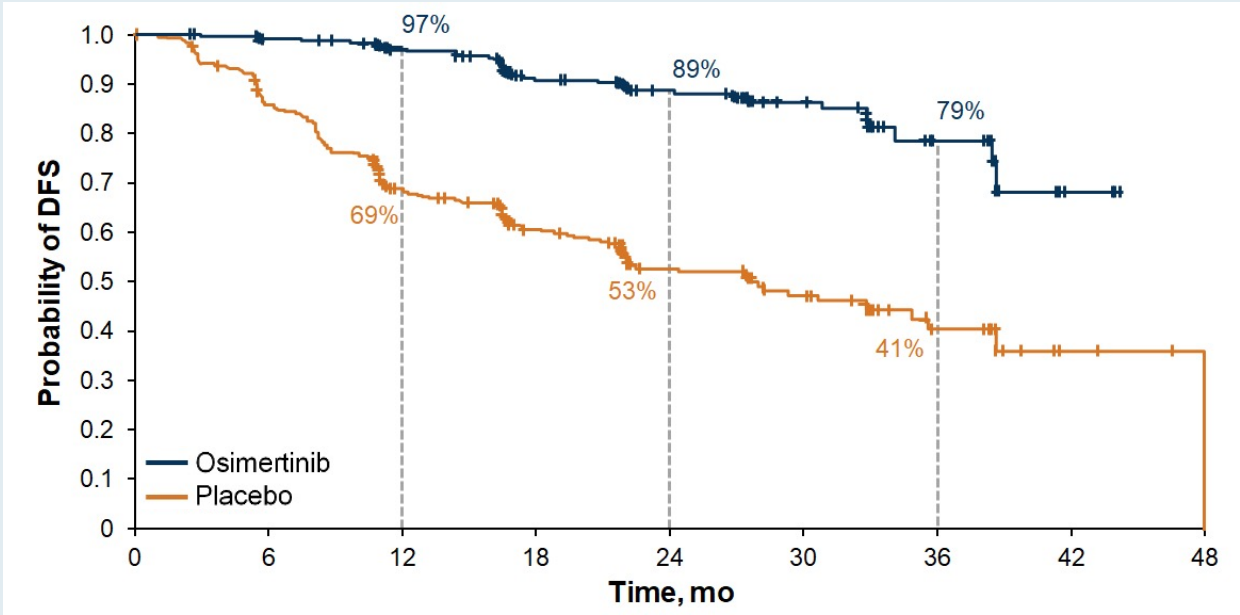
Disease-Free Survival (DFS)

Stage II to IIIA disease



HR = 0.17; $p < .001$ → 83% reduction in risk of disease recurrence or death

Stage IB to IIIA disease

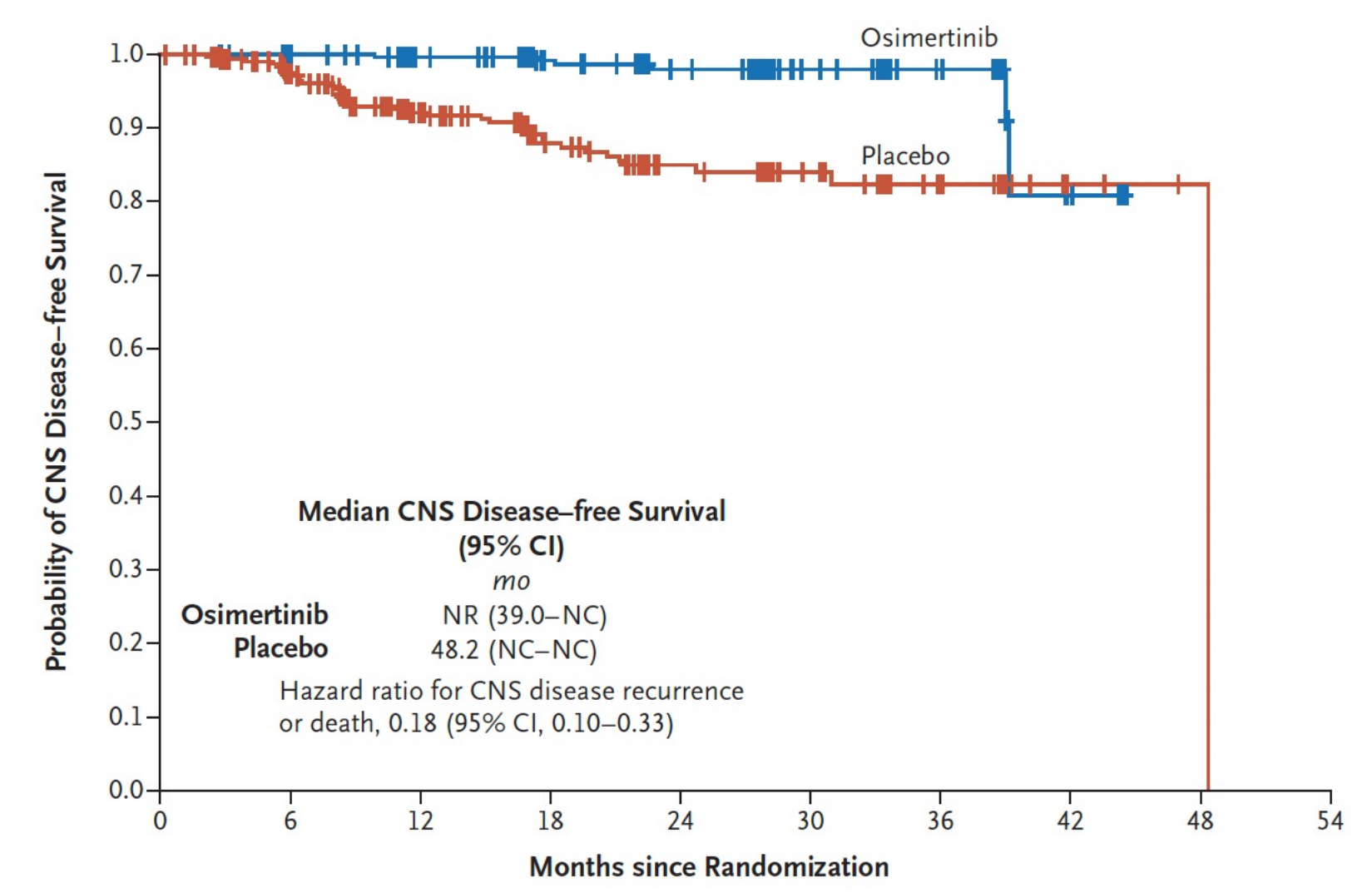


HR = 0.20; $p < .001$ → 80% reduction in risk of disease recurrence or death

Wu Y-L et al. *N Engl J Med* 2020;383(18):825-35.

RTP RESEARCH TO PRACTICE

ADAURA: CNS Disease-Free Survival According to Investigator Assessment in the Overall Population



Wu Y-L et al. *N Engl J Med* 2020;383(18):825-35.

RTP RESEARCH TO PRACTICE

ORIGINAL ARTICLE

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

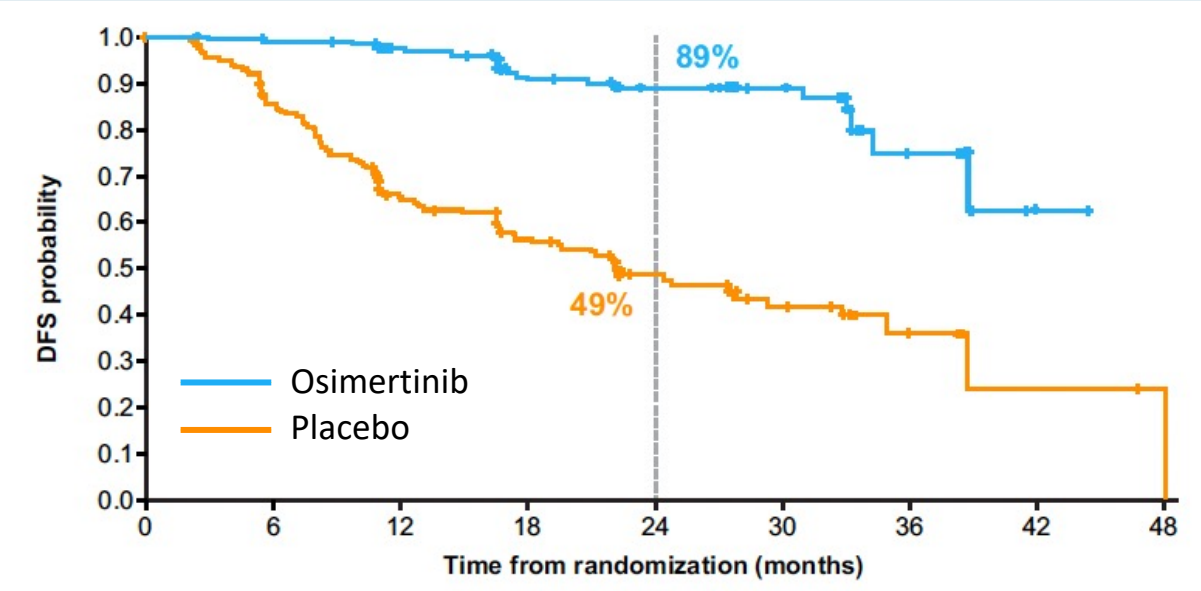
IASLC

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

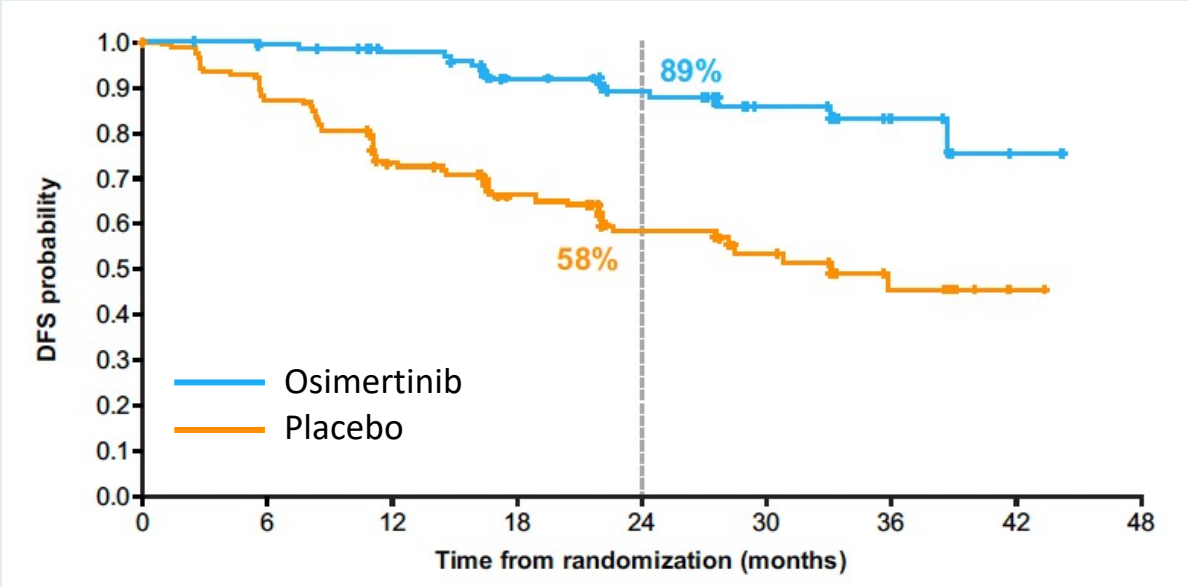
Yi-Long Wu, MD,[a,*] Thomas John, PhD,[b] Christian Grohe, MD,[c] Margarita Majem, MD, PhD,[d] Jonathan W. Goldman, MD,[e] Sang-We Kim, MD, PhD,[f] Terufumi Kato, MD,[g] Konstantin Laktionov, PhD,[h] Huu Vinh Vu, MD, PhD,[i] Zhijie Wang, MD,[j] Shun Lu, MD,[k] Kye Young Lee, MD, PhD,[l] Charuwan Akewanlop, 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



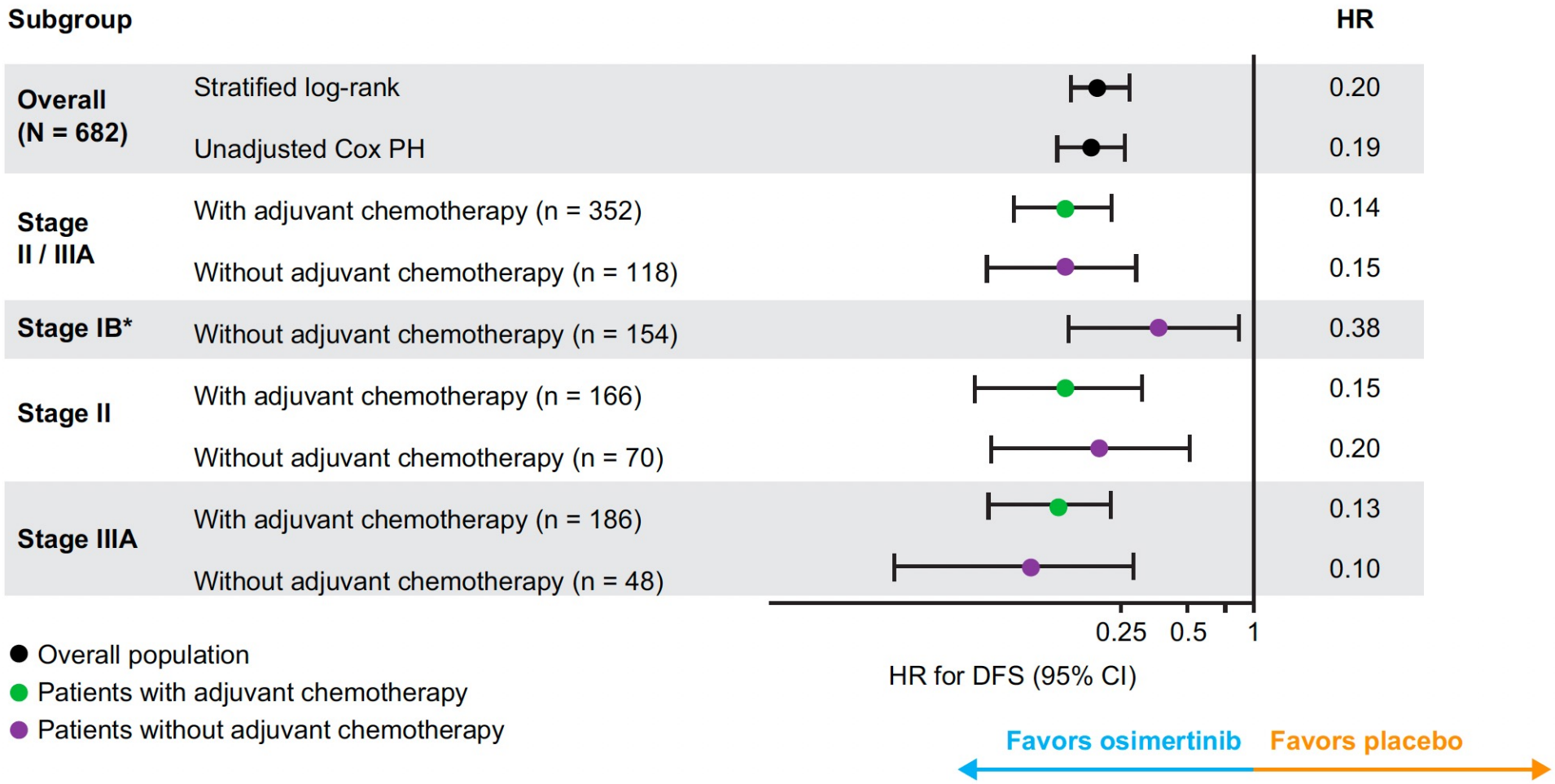
Without adjuvant chemotherapy



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.

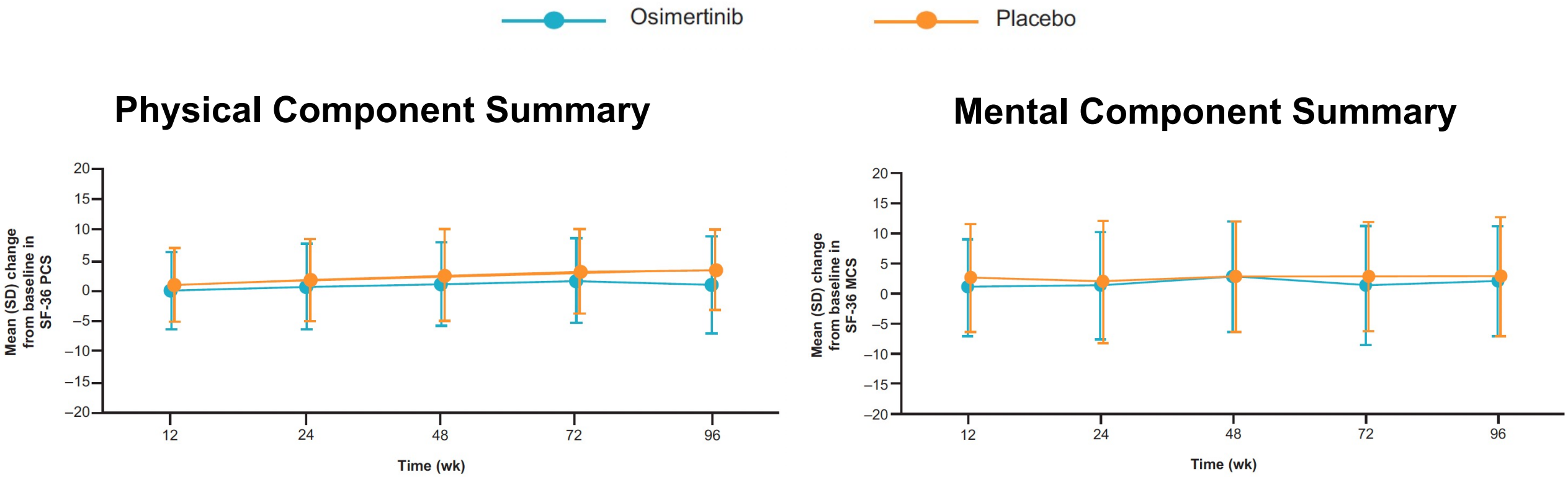
CLINICAL CANCER RESEARCH | CLINICAL TRIALS: TARGETED THERAPY

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."

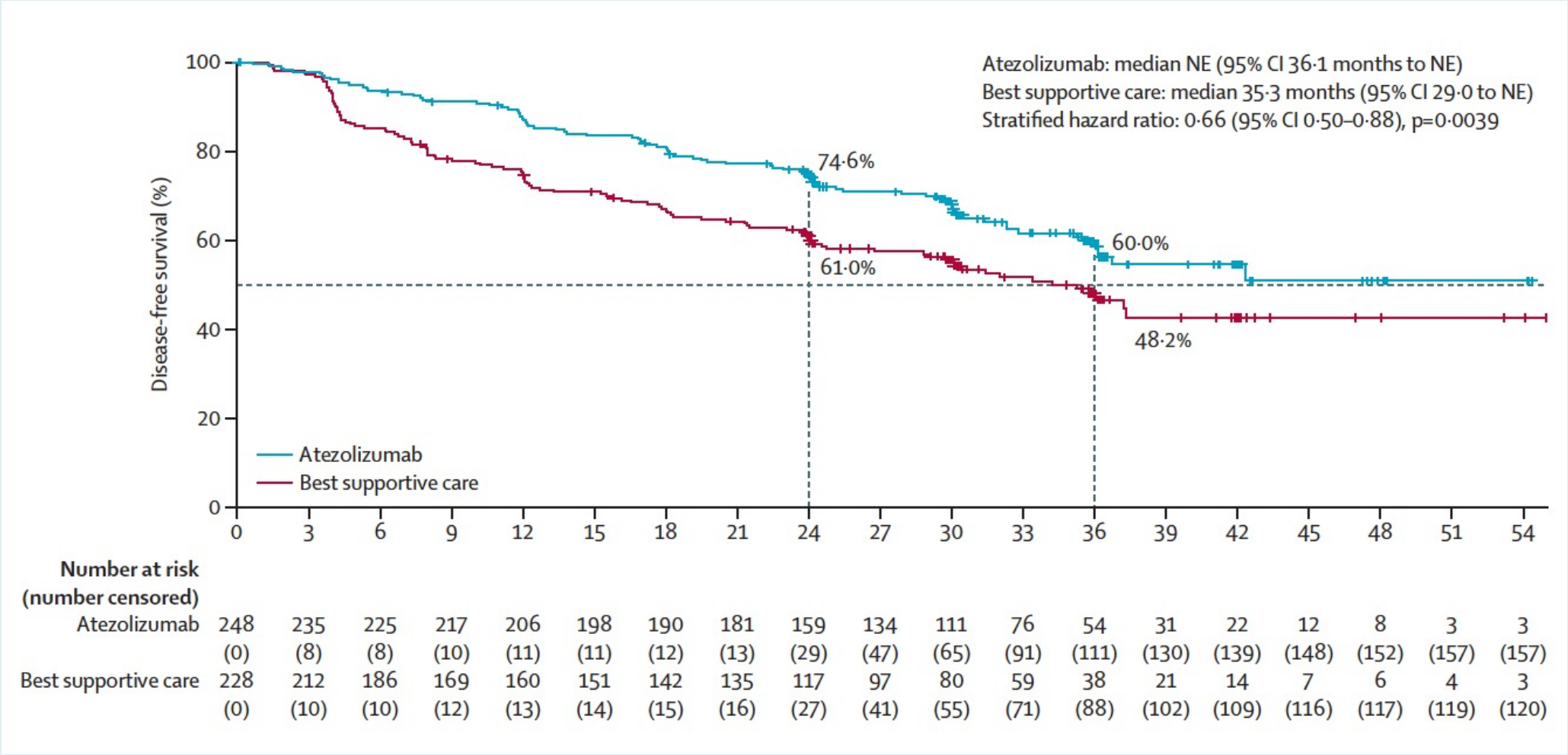
https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-atezolizumab-adjuvant-treatment-non-small-cell-lung-cancer

Lancet 2021;398:1344-57.

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**

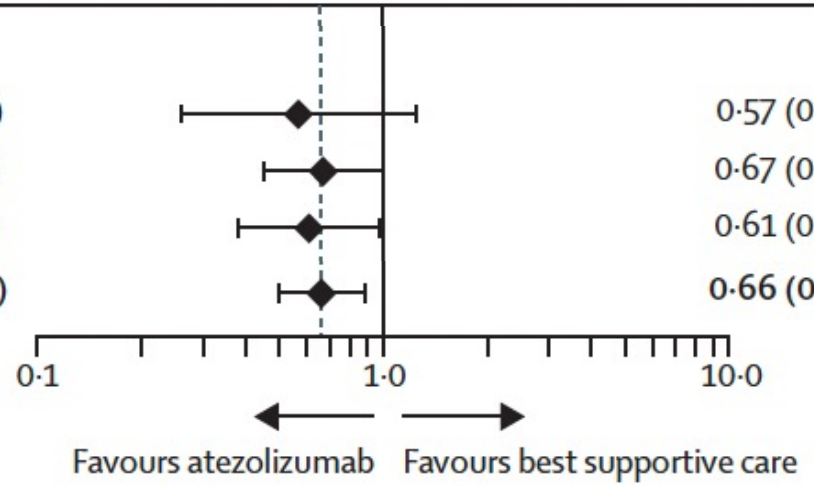
IMpower010 Primary Endpoint: Disease-Free Survival in the PD-L1 ≥1% Tumor Cells Stage II-IIIA Population



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

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

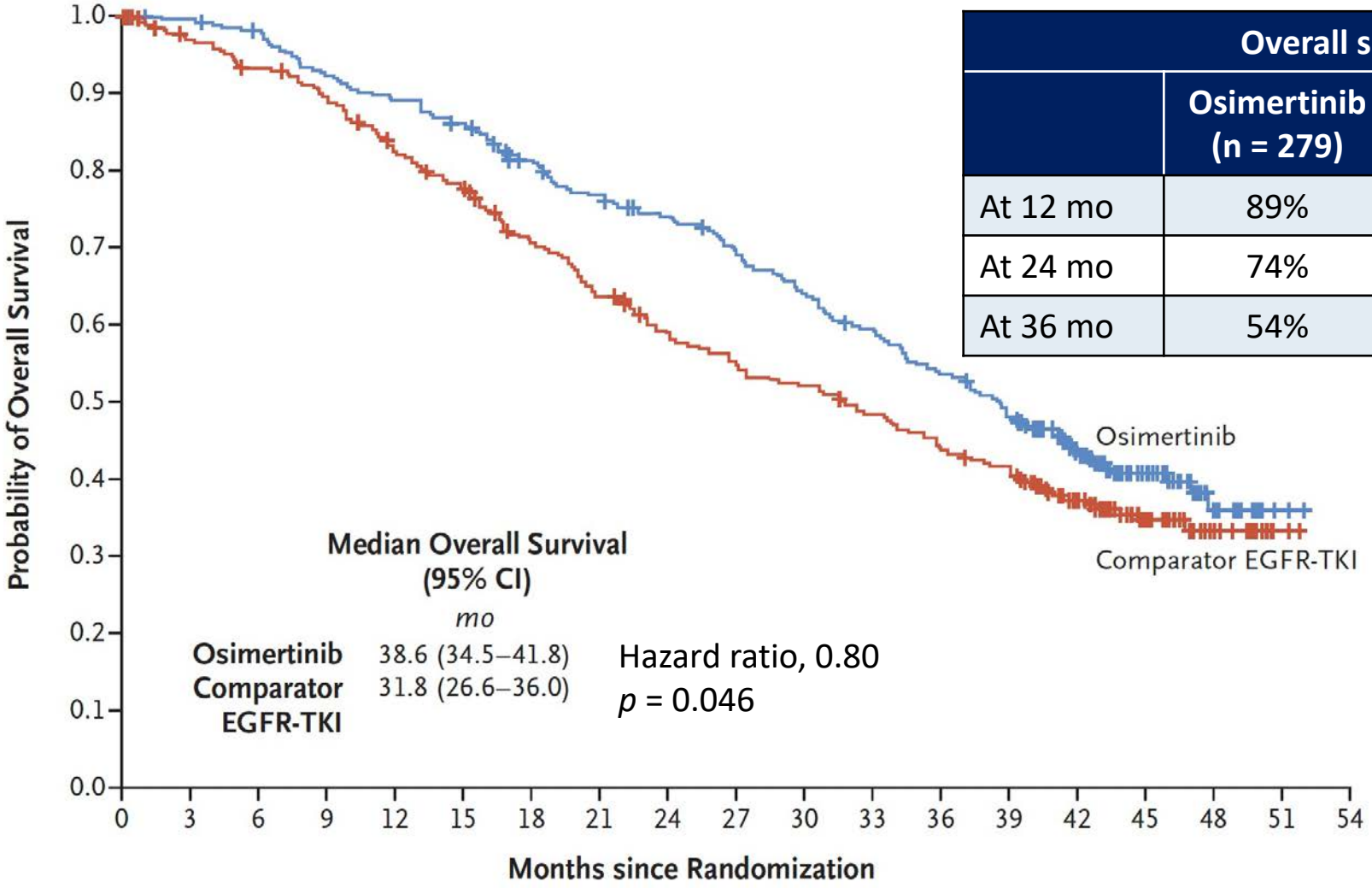
The NEW ENGLAND JOURNAL of MEDICINE

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.

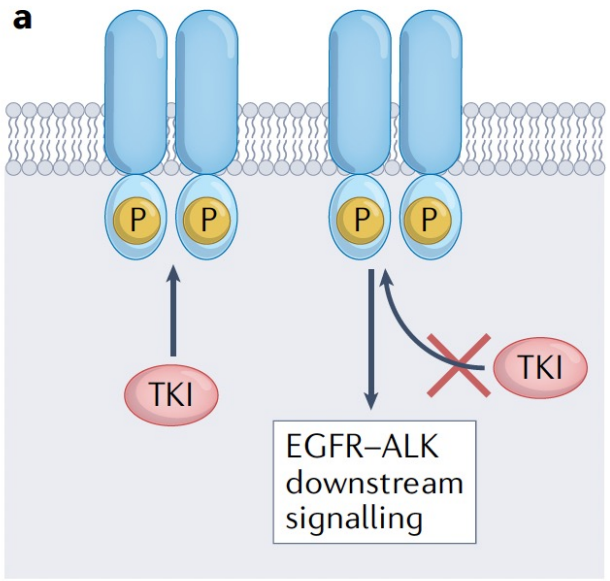
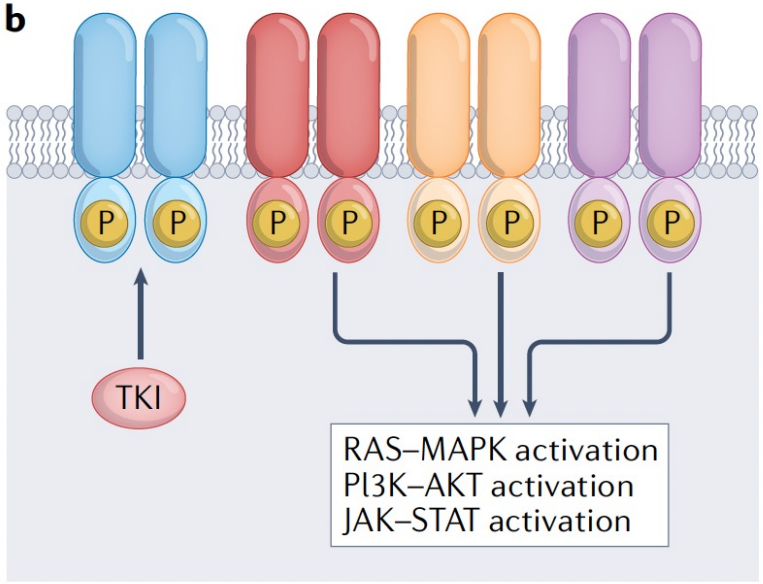
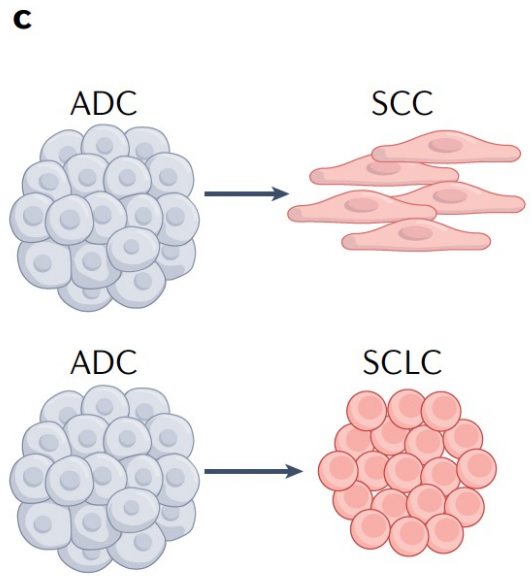
Select Ongoing Phase III Studies of First-Line Therapy for Patients with Metastatic NSCLC and Activating EGFR Mutations

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

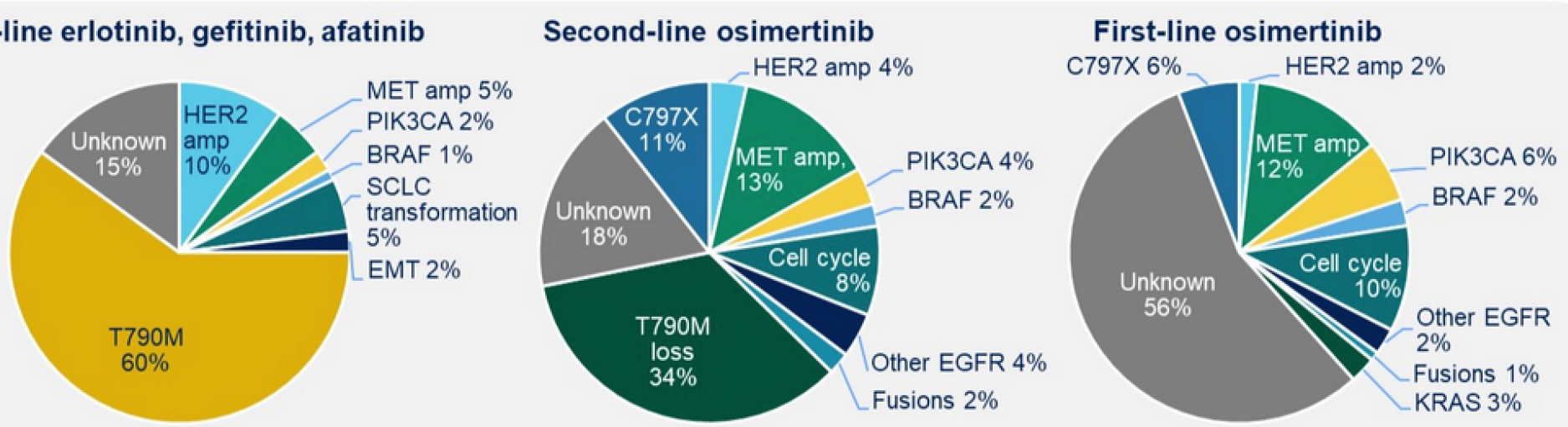
	Alterations that prevent inhibition of the target receptor tyrosine	Activation of bypass and/or downstream signalling pathways	Changes in tumour cell lineage such as transformation
			
Osimertinib resistance	*EGFR* C797X, G796X, L792X, G724S, L718Q	• Amplifications in *MET*, *HER2*, *KRAS*, *NRAS*, *YES1* • 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;[Online ahead of print].

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).

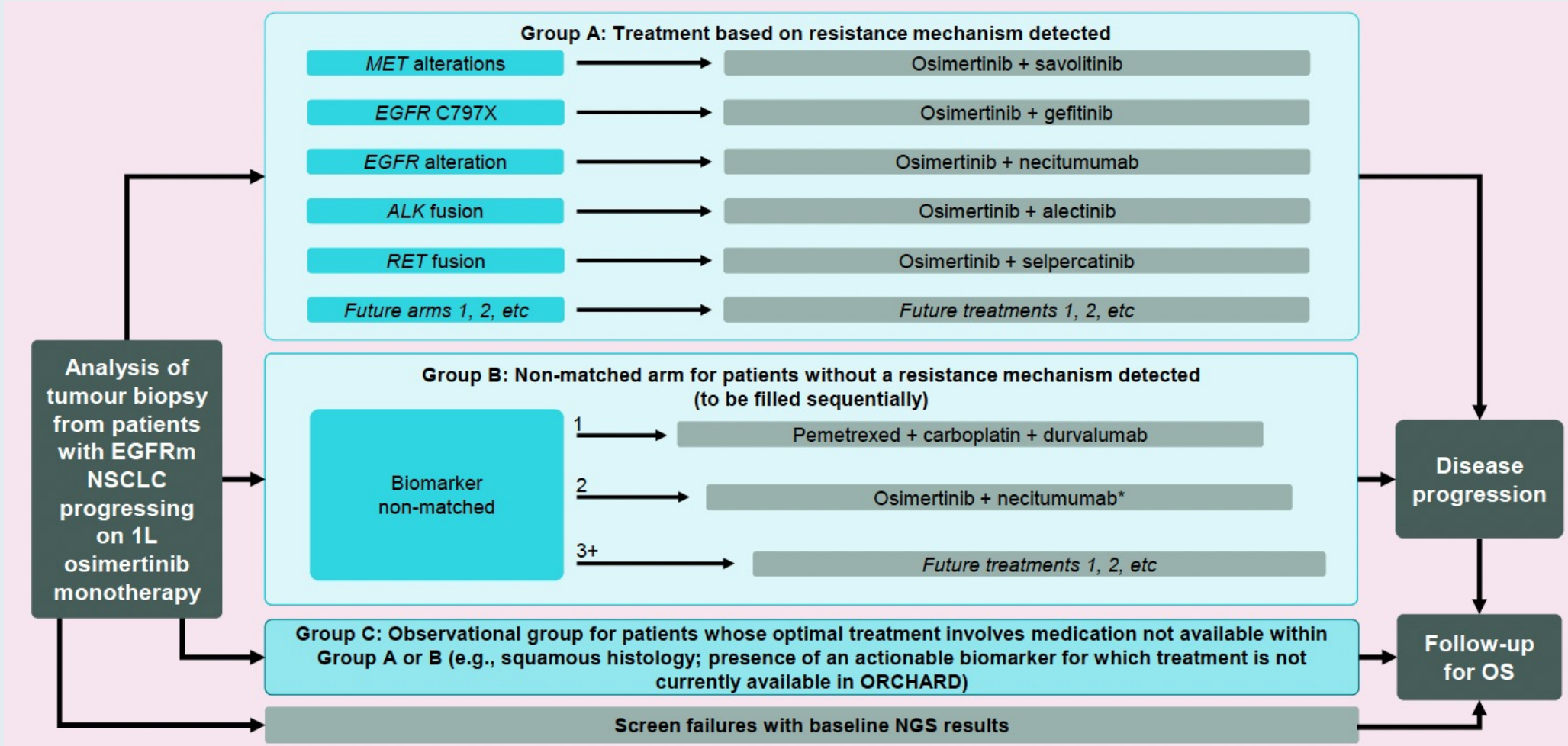
Janne PA et al. ASCO 2021;Abstract 9007.

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.

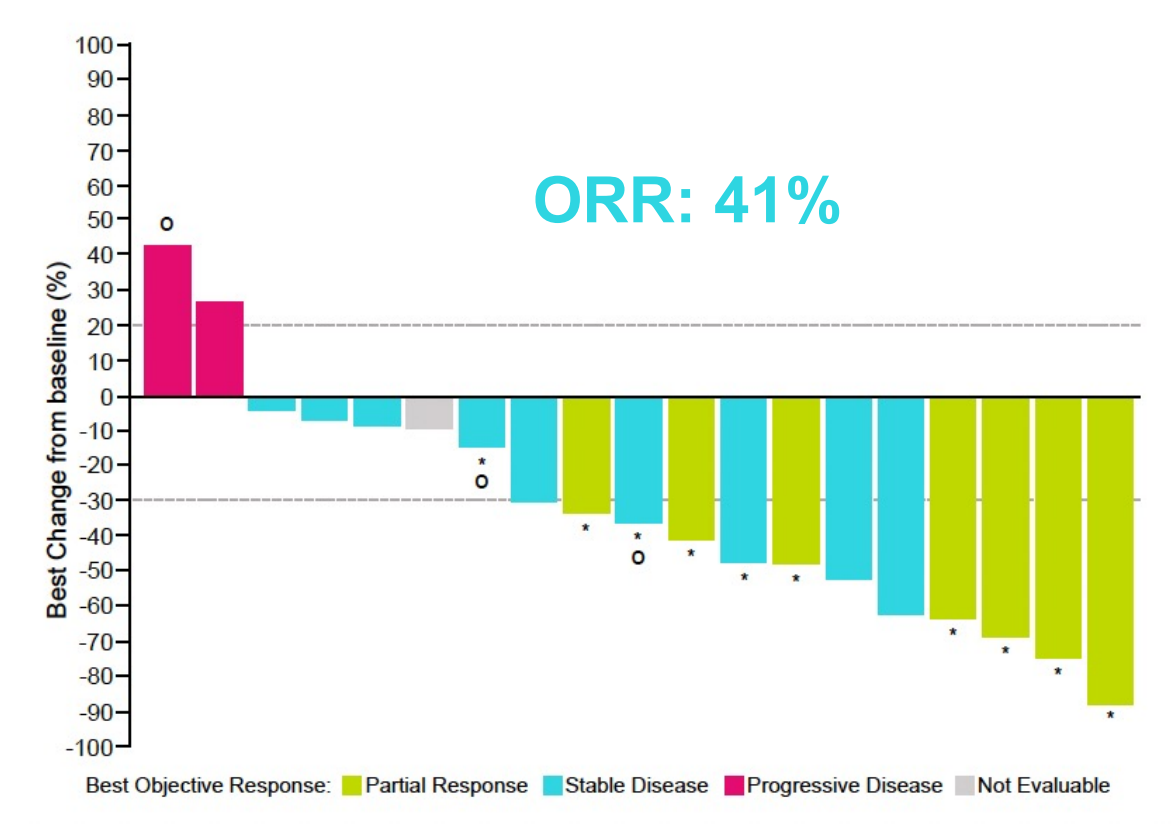
ORCHARD Study Design

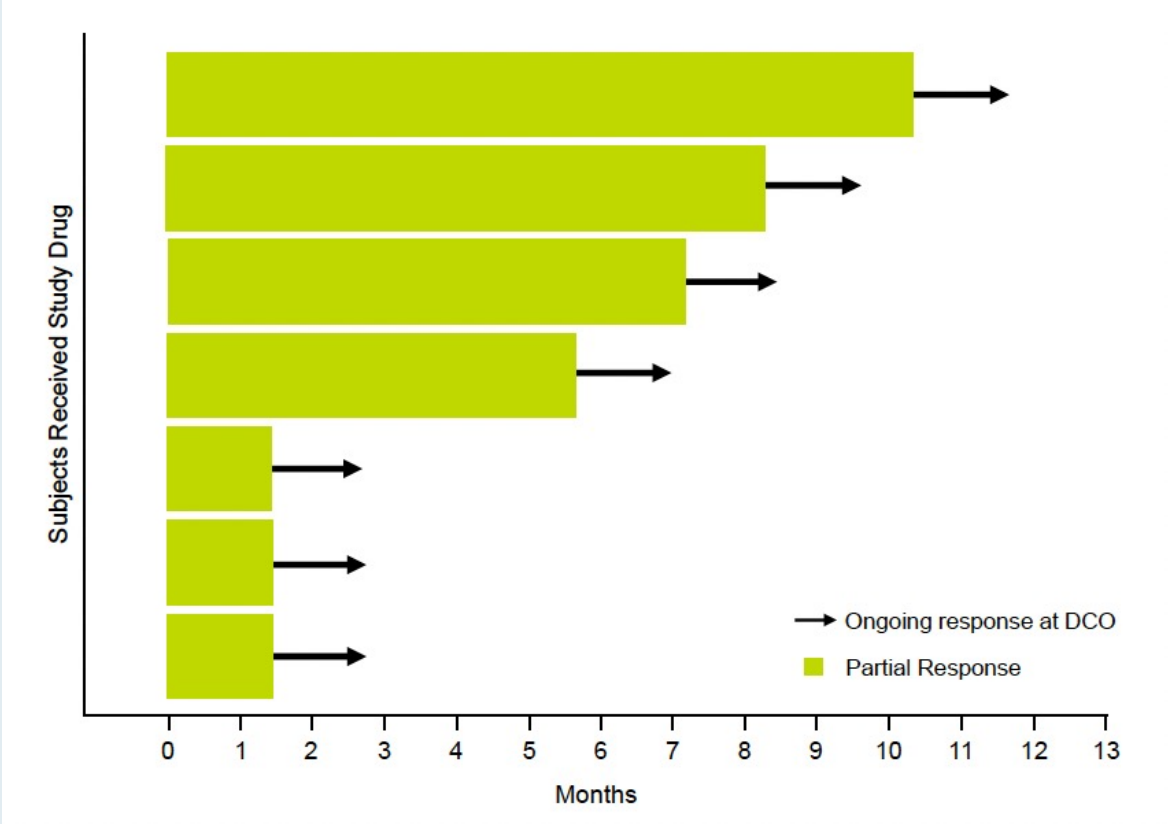


Group A: Patients who are positive for protocol-determined biomarker; Group B: patients without an available protocol-determined biomarker match, allocated sequentially, once first cohort cap has been reached, the next cohort allocation will begin; Group C: observational cohort, treated in accordance 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.

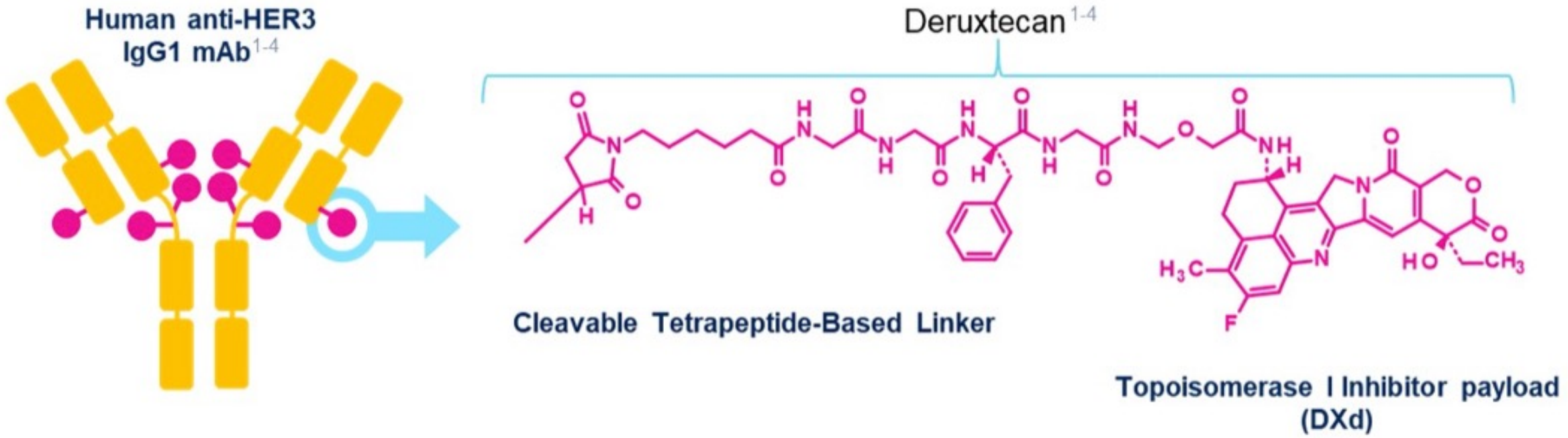
Efficacy and Safety of Patritumab Deruxtecan (HER3-DXd) in EGFR Inhibitor–Resistant, *EGFR*-Mutated Non–Small Cell Lung Cancer

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.

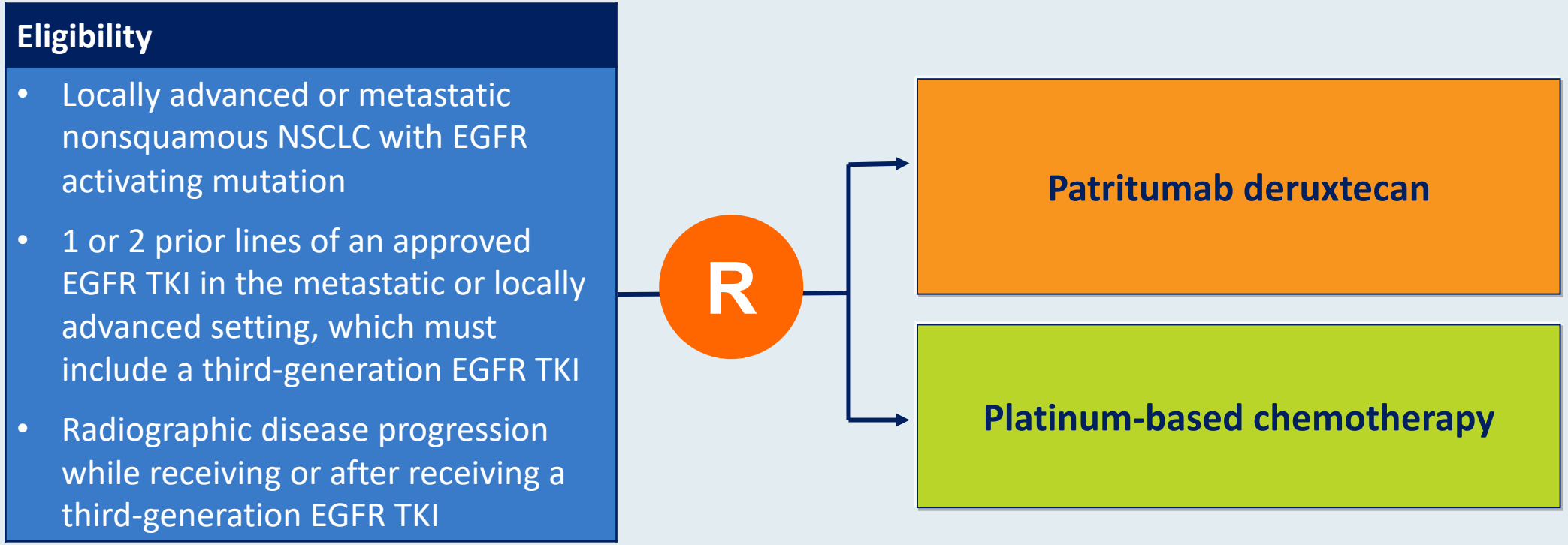
Select Grade ≥3 Treatment-Emergent Adverse Events (TEAEs)

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

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

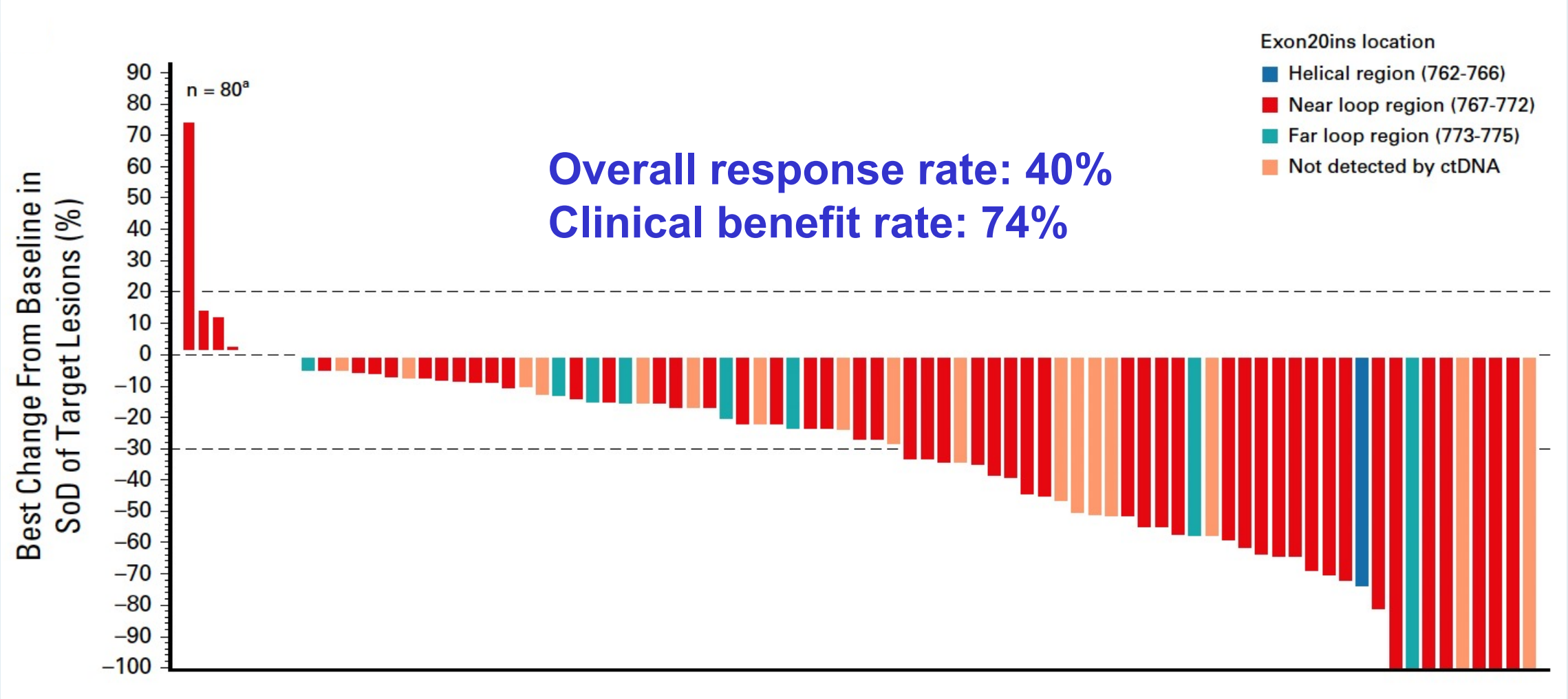
original reports

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;39:3391-402.

CHRYSALIS: Tumor Reduction and Response



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

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;39:3391-402.

RTP RESEARCH TO PRACTICE

2022 ASCO® ANNUAL MEETING

Abstract 9006

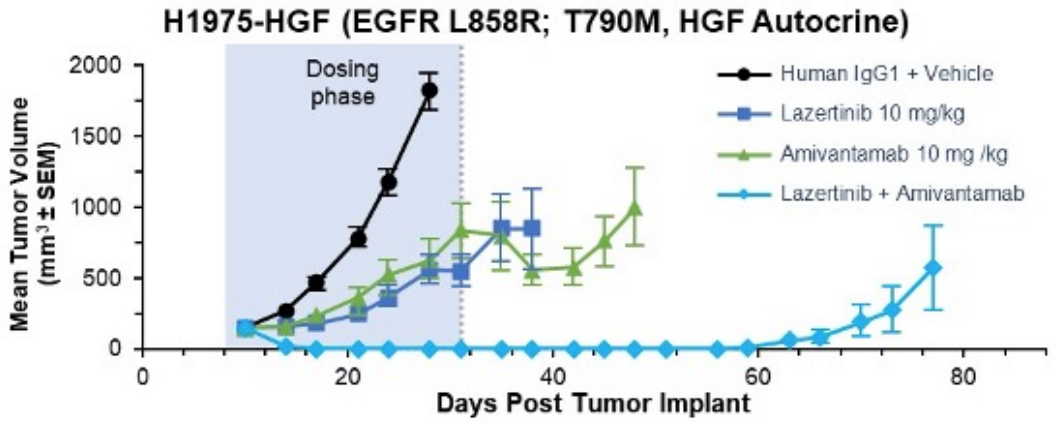
Amivantamab and lazertinib in patients with EGFR-mutant non-small cell lung cancer (NSCLC) after progression on osimertinib and platinum-based chemotherapy: Updated results from CHRYSALIS-2

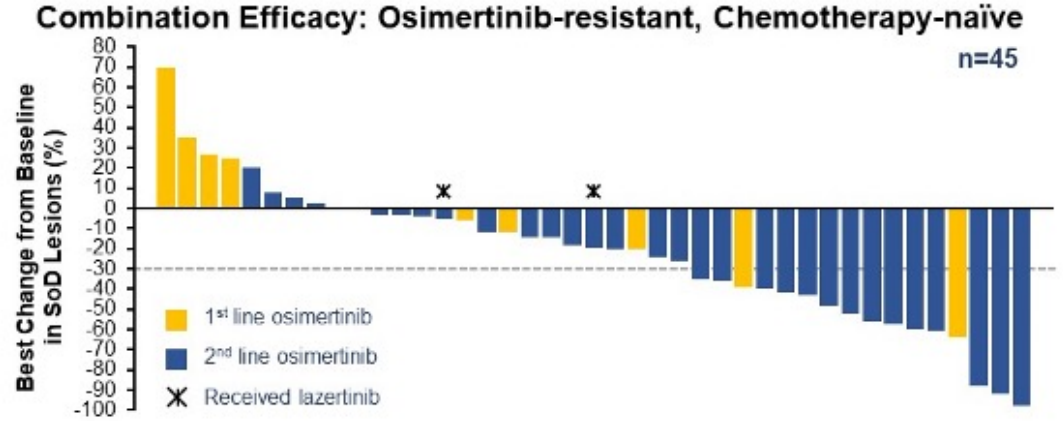
Catherine A. Shu,[1] Koichi Goto,[2] Yuichiro Ohe,[3] Benjamin Besse,[4] Se-Hoon Lee,[5] Yongsheng Wang,[6] Frank Griesinger,[7] James Chih-Hsin Yang,[8] Enriqueta Felip,[9] Rachel E. Sanborn,[10] Reyes Bernabe Caro,[11] Joshua C. Curtin,[12] Jun Chen,[12] Janine Mahoney,[12] Leonardo Trani,[12] Joshua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

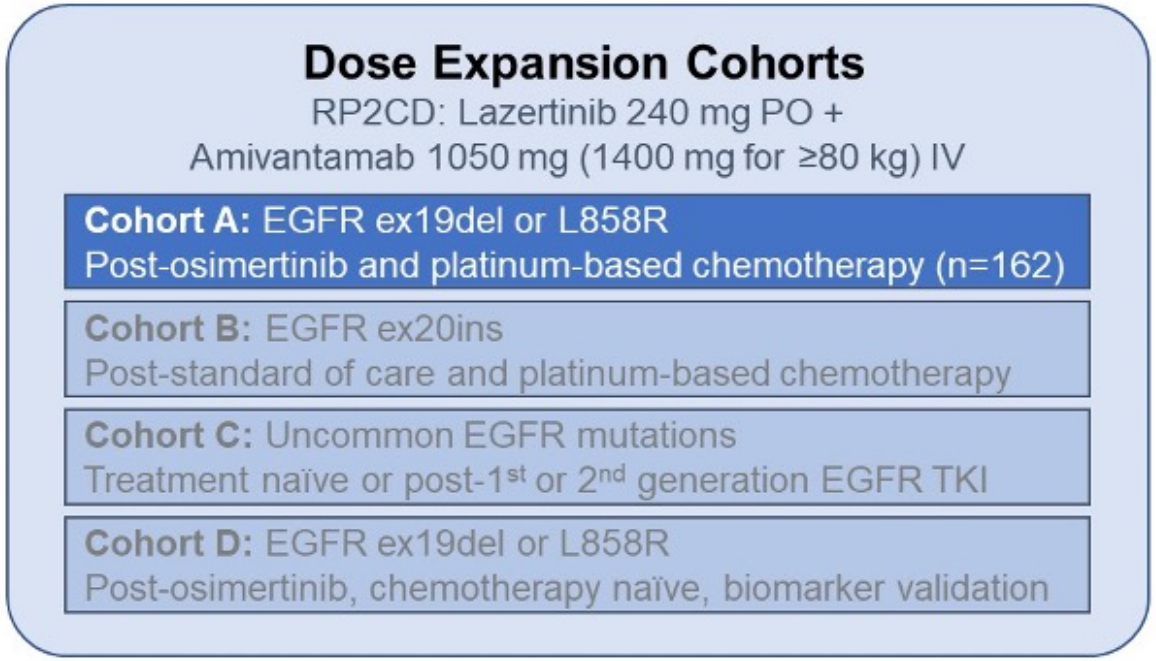




Shu CA et al. ASCO 2022;Abstract 9006.

RTP RESEARCH TO PRACTICE

CHRYSALIS-2 Study Design



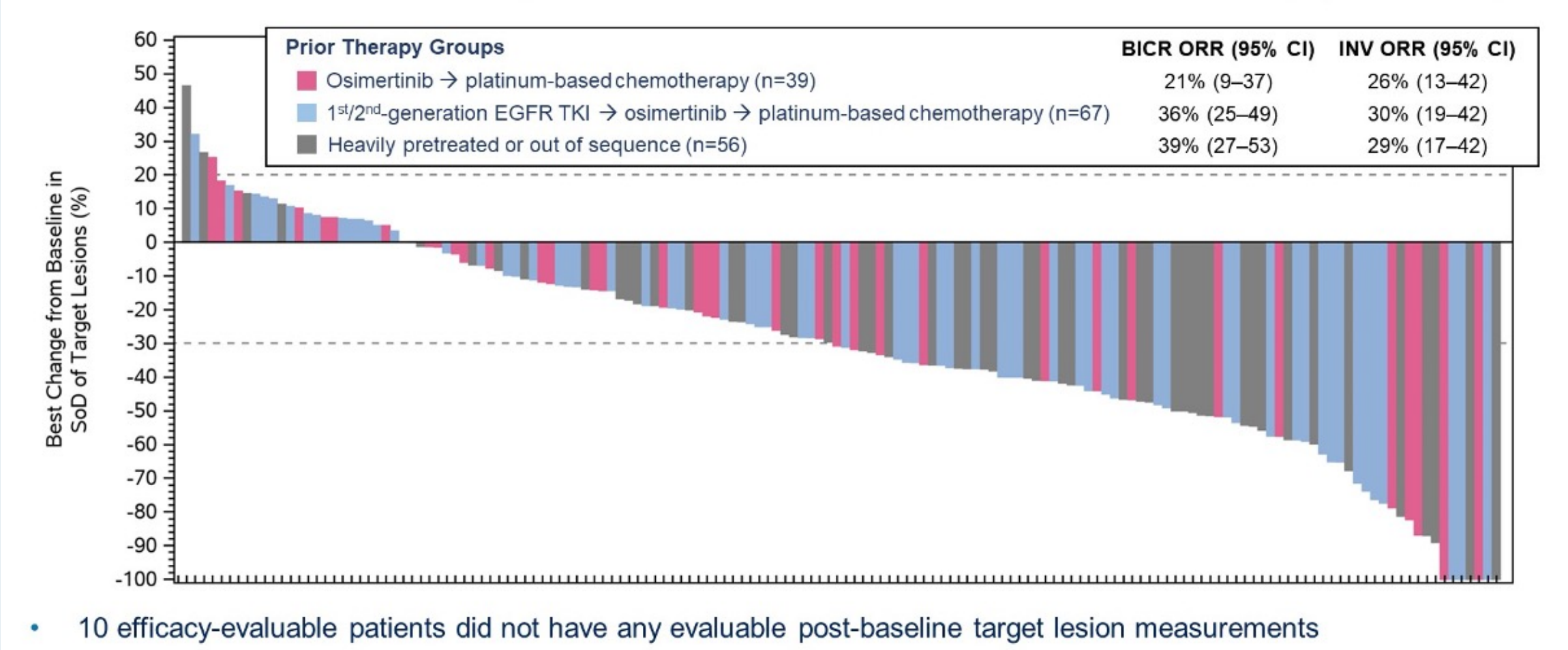
Endpoints

- 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).

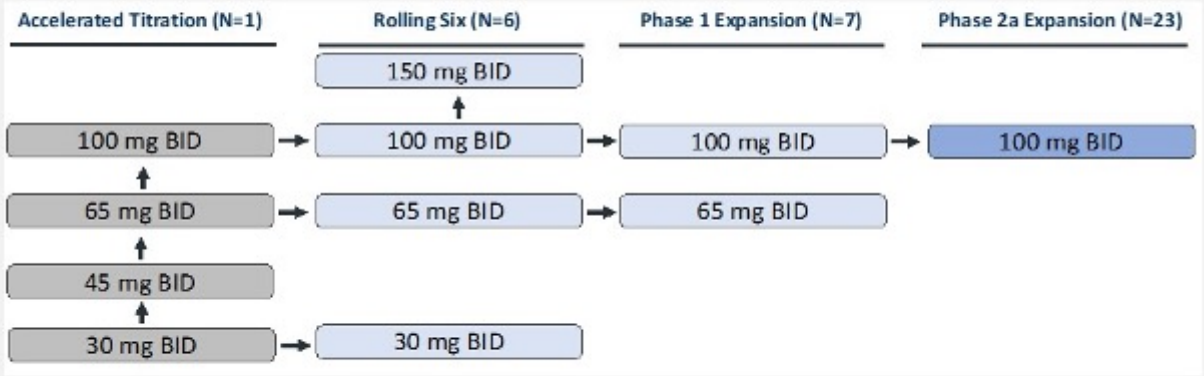
2. Leal JL, et al. Clin Lung Cancer. 2021;22(6).

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)	

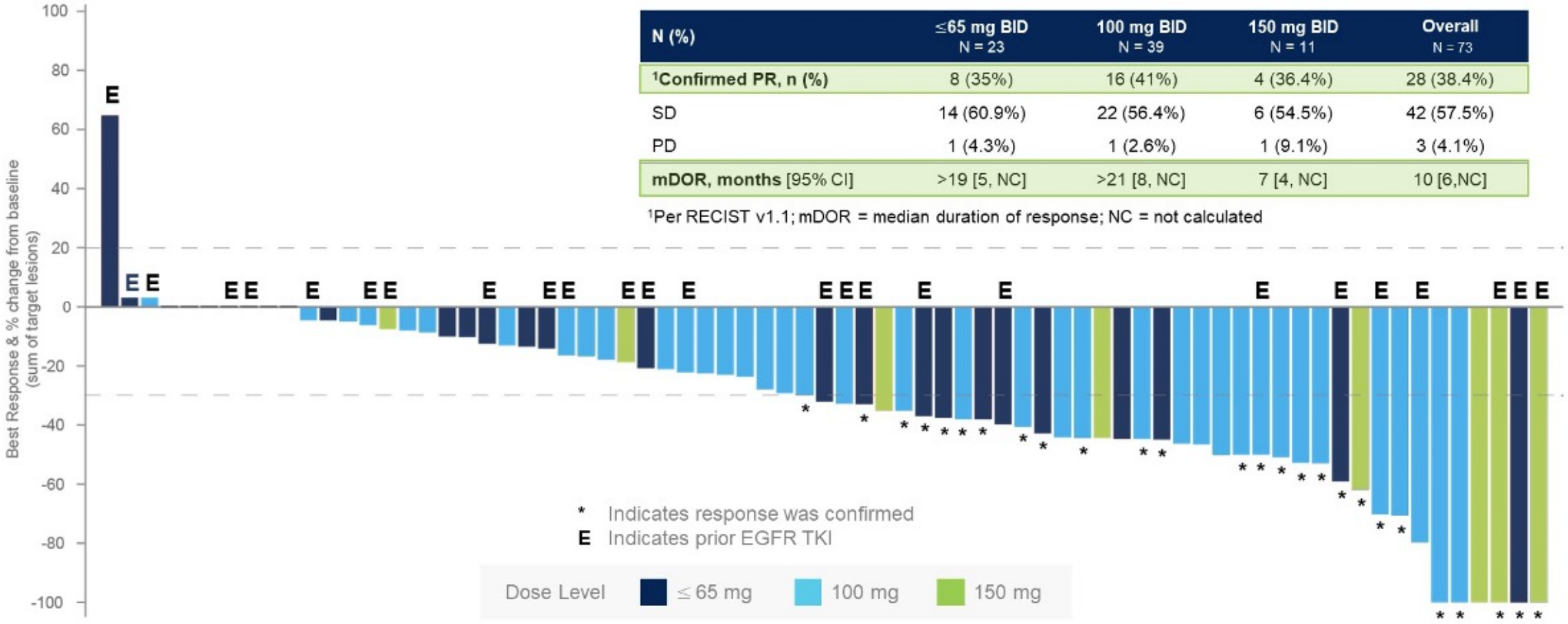
- Most AEs Grade 1/2
- Dose reductions and discontinuations were uncommon at doses below 150 mg
- No Grade ≥3 rash or diarrhea observed at doses <150 mg
- Treatment-emergent pneumonitis was observed in 4 patients (1 at 65, 2 at 100, and 1 at 150 mg), but cases were asymptomatic (1) or confounded by comorbid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

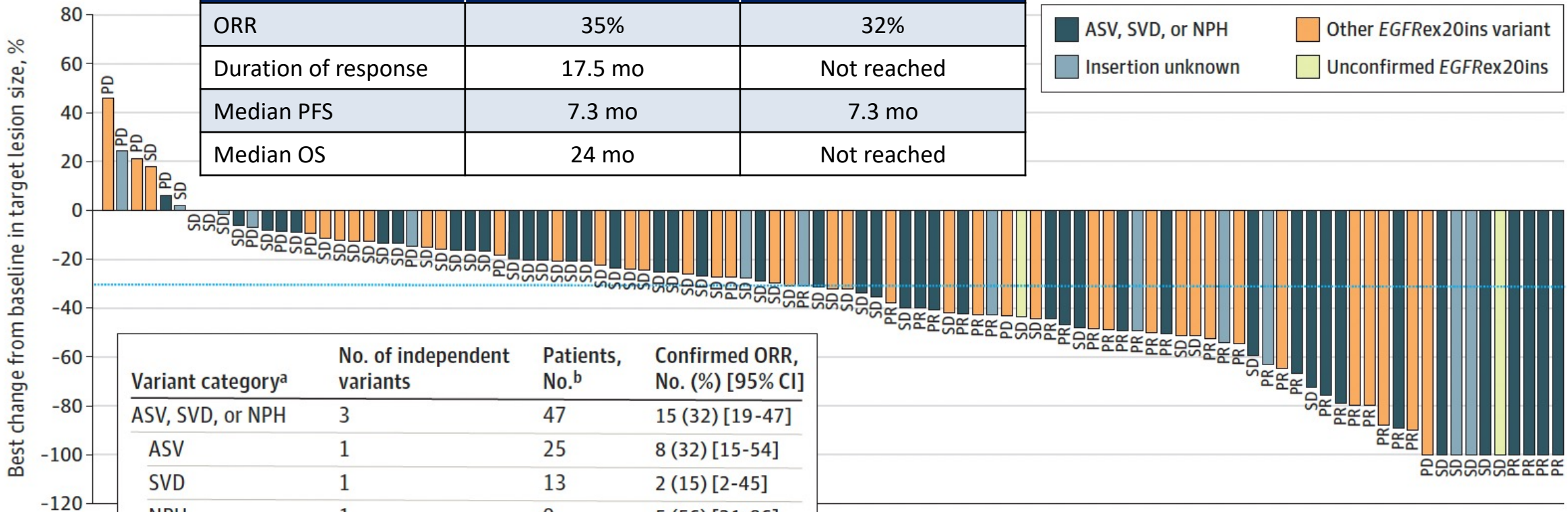
Treatment Outcomes and Safety of Mobocertinib in Platinum-Pretreated Patients With *EGFR* Exon 20 Insertion–Positive Metastatic Non–Small Cell Lung Cancer

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 HER2-Positive Breast Cancer

Thursday, September 1, 2022
5:00 PM – 6:00 PM ET

Faculty

Mark D Pegram, 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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