Meet The Professor

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

Joel W Neal, MD, PhD
Associate Professor of Medicine
Division of Oncology, Department of Medicine
Stanford Cancer Institute
Stanford University
Palo Alto, California

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

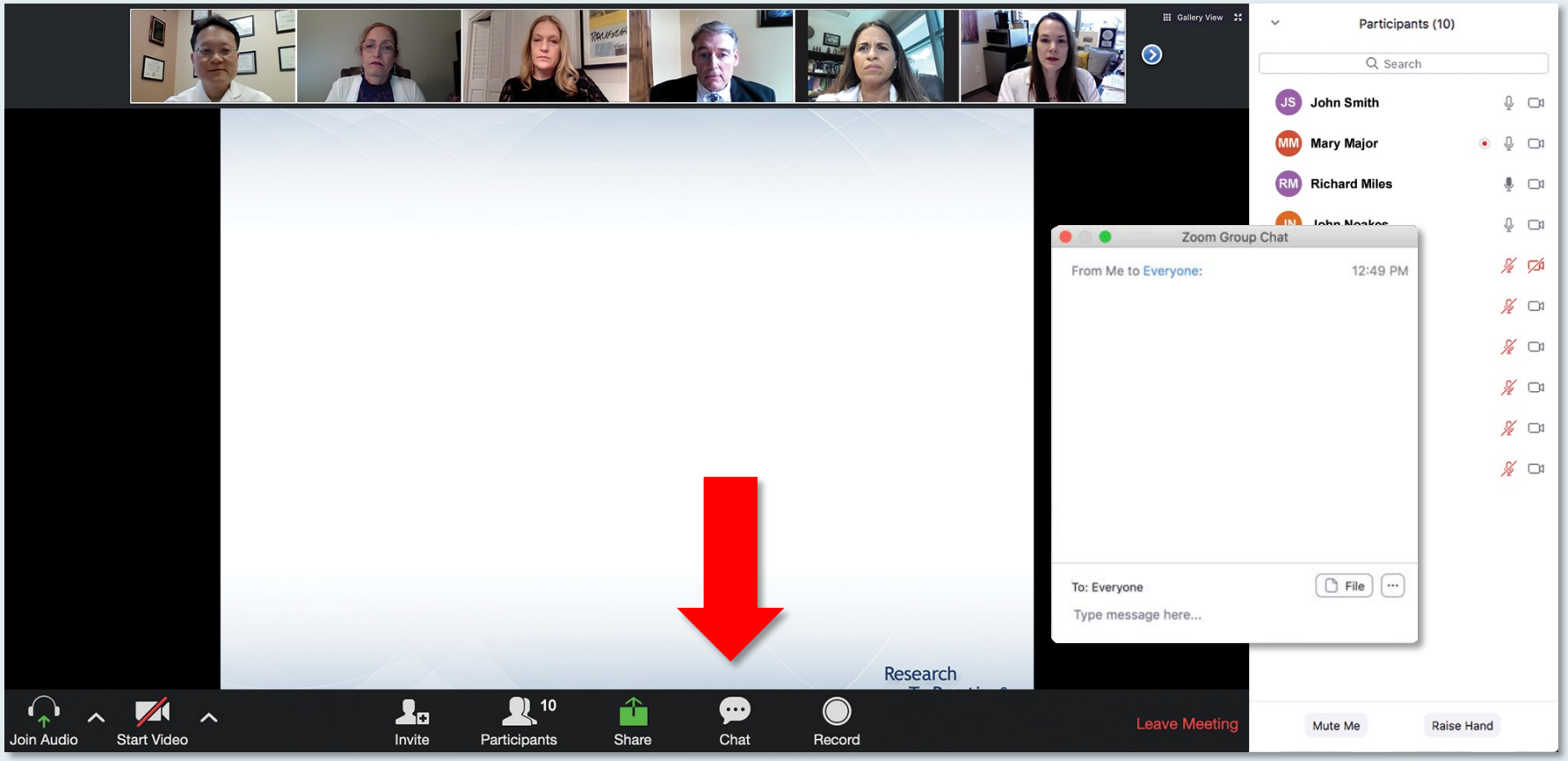
Gregory J Riely, MD, PhD
Attending
Memorial Sloan Kettering Cancer Center
New York, New York

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

MODERATOR
Neil Love, MD
Research To Practice

RTP
RESEARCH TO PRACTICE

We Encourage Clinicians in Practice to Submit Questions



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

RTP RESEARCH TO PRACTICE

ONCOLOGY TODAY

WITH DR NEIL LOVE

NSCLC with EGFR Exon 20 Insertion Mutations

DR GREGORY RIELY
MEMORIAL SLOAN KETTERING CANCER CENTER

Listen on Apple Podcasts

Spotify

Listen on Google Podcasts

Meet The Professor

Optimizing the Management of Ovarian Cancer

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

Faculty

Ursula Matulonis, MD

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Meet The Professor

Optimizing the Management of Hepatobiliary Cancers

Thursday, July 7, 2022
5:00 PM – 6:00 PM ET

Faculty

Ghassan Abou-Alfa, MD, MBA

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Meet The Professor

Optimizing the Management of Gastroesophageal Cancers

Tuesday, July 12, 2022
5:00 PM – 6:00 PM ET

Faculty

Samuel J Klempner, MD

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Management of Acute Myeloid Leukemia and Myelodysplastic Syndromes – A Review of the 2022 ASCO Annual Meeting and EHA Congress

Wednesday, July 13, 2022
5:00 PM – 6:00 PM ET

Faculty

Richard M Stone, MD

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Meet The Professor

Optimizing the Management of Chronic Myeloid Leukemia

Tuesday, July 19, 2022
5:00 PM – 6:00 PM ET

Faculty

Daniel J DeAngelo, MD, PhD

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Recent Advances in Medical Oncology:
A daylong CME hybrid (live/online) event

Saturday, August 6, 2022

9:00 AM – 4:30 PM PT (12:00 PM – 7:30 PM ET)

Bellagio Las Vegas | Las Vegas, Nevada

Faculty

Neeraj Agarwal, MD
Harold J Burstein, MD, PhD
Ibiayi Dagogo-Jack, MD
Rafael Fonseca, MD
Brad S Kahl, MD
Rutika Mehta, MD, MPH
Craig Moskowitz, MD
Joyce O'Shaughnessy, MD
Krina Patel, MD, MSc
Philip A Philip, MD, PhD, FRCP
Suresh S Ramalingam, MD
Sandy Srinivas, MD

Moderator

Neil Love, MD

In Partnership with the American Oncology Network

RTP RESEARCH TO PRACTICE

Meet The Professor

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

Joel W Neal, MD, PhD
Associate Professor of Medicine
Division of Oncology, Department of Medicine
Stanford Cancer Institute
Stanford University
Palo Alto, California

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.

Research To Practice CME Planning Committee Members, Staff and Reviewers

Planners, scientific staff and independent reviewers for Research To Practice have no relevant conflicts of interest to disclose.

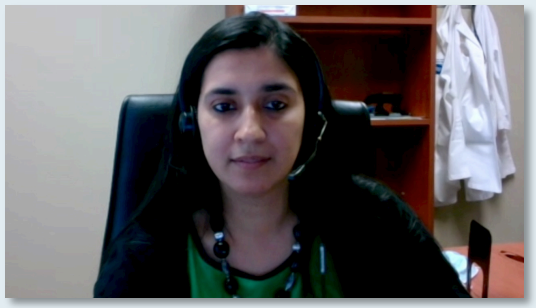
Dr Neal — Disclosures

Advisory and Consulting Roles	Amgen Inc, AstraZeneca Pharmaceuticals LP, Blueprint Medicines, Calithera Biosciences, D2G Oncology Inc, Exelixis Inc, Genentech, a member of the Roche Group, Iovance Biotherapeutics, Jounce Therapeutics, Lilly, Natera Inc, Regeneron Pharmaceuticals Inc, Sanofi Genzyme, Surface Oncology, Takeda Pharmaceuticals USA Inc, Turning Point Therapeutics Inc
Contracted Research	AbbVie Inc, Adaptimmune, Boehringer Ingelheim Pharmaceuticals Inc, Exelixis Inc, Genentech, a member of the Roche Group, GlaxoSmithKline, Janssen Biotech Inc, Merck, Nektar, Novartis, Takeda Pharmaceuticals USA Inc

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

Neil Morganstein, MD
Atlantic Health System
Summit, New Jersey

Gigi Chen, MD
John Muir Health
Pleasant Hill, California



Namrata I Peswani, MD
UT Southwestern Medical Center
Richardson, Texas

Joanna Metzner-Sadurski, MD
Self Regional Healthcare Cancer Center
Greenwood, South Carolina

Julia Saylors, MD
Charleston Oncology
North Charleston, South Carolina

William R Mitchell, MD
Southern Oncology Specialists
Charlotte, North Carolina

Nasfat Shehadeh, MD
Oncology Specialists of Charlotte, PA
Charlotte, North Carolina

RTP
RESEARCH
TO PRACTICE

Meet The Professor with Dr Neal

INTRODUCTION: Journal Club with Dr Neal – Part 1

MODULE 1: Adjuvant Therapy

MODULE 2: Locally Advanced Disease

MODULE 3: Exon 20 Insertions

MODULE 4: Metastatic Disease

MODULE 5: Journal Club with Dr Neal – Part 2

MODULE 6: Appendix of Key Publications

RTP
RESEARCH
TO PRACTICE

Durvalumab with Chemotherapy Significantly Improved pCR for Resectable NSCLC in the AEGEAN Phase III Trial

Press Release: June 30, 2022

"Positive high-level results from a planned interim analysis of the AEGEAN Phase III trial showed treatment with durvalumab in combination with neoadjuvant chemotherapy before surgery demonstrated a statistically significant and meaningful improvement in pathologic complete response (pCR) compared to neoadjuvant chemotherapy alone for patients with resectable non-small cell lung cancer (NSCLC).

A statistically significant improvement in major pathologic response (MPR) was also observed. The trial will continue as planned to assess the additional primary endpoint of event-free survival (EFS).

The safety and tolerability of adding durvalumab to neoadjuvant chemotherapy was consistent with the known profile for this combination and did not decrease the number of patients able to undergo successful surgery versus chemotherapy alone.

These pCR data will be shared with global health authorities and presented at a forthcoming medical meeting when EFS results are available."

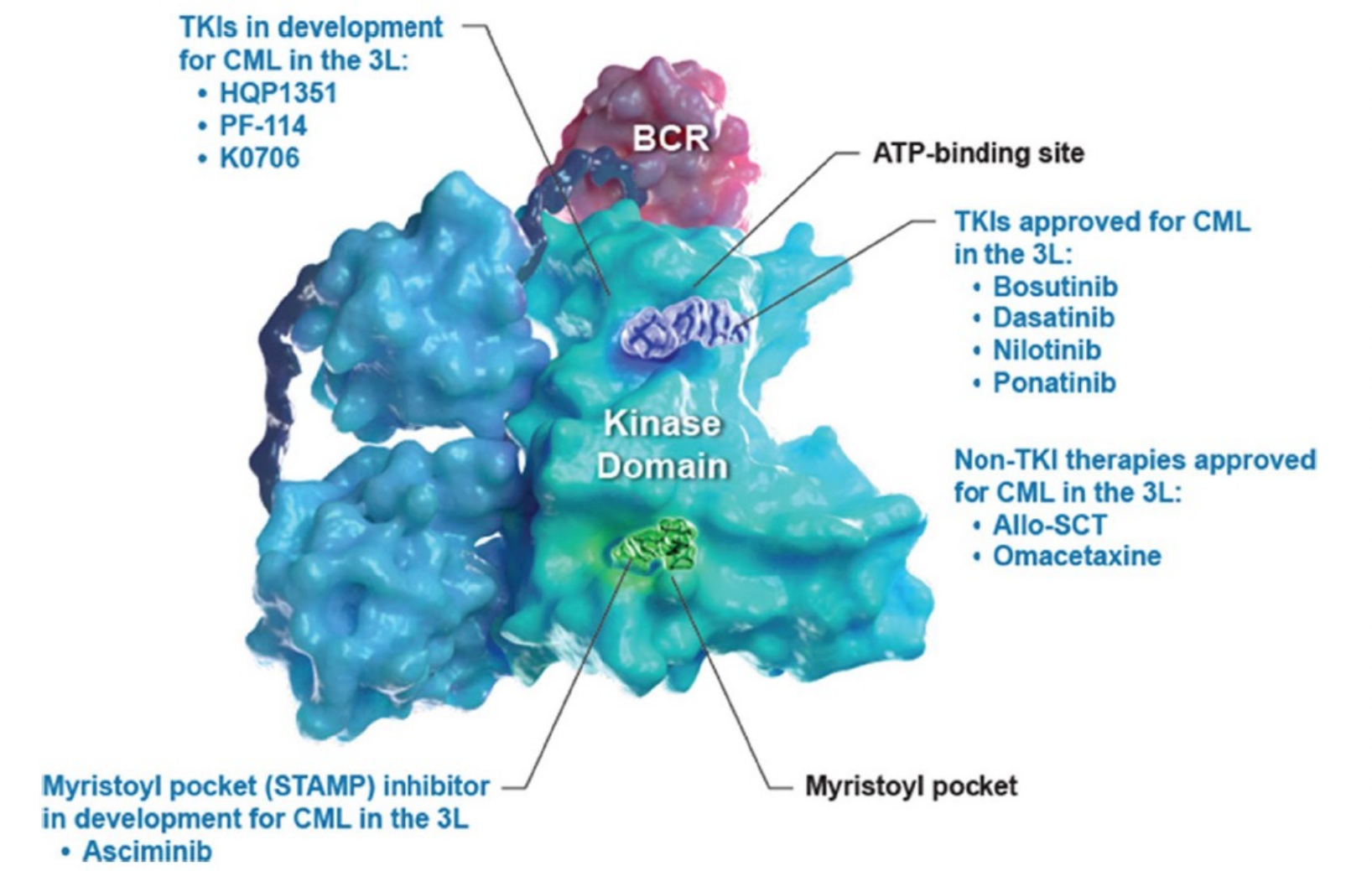
https://finance.yahoo.com/news/imfinzi-durvalumab-plus-chemotherapy-significantly-110000161.html

RTP RESEARCH TO PRACTICE

Meet The Professor
Optimizing the Management of Chronic Myeloid Leukemia

Jorge Cortes, MD
Director, Georgia Cancer Center
Cecil F Whitaker Jr, MD/GRA Eminent Scholar Chair in Cancer
Augusta University
Augusta, Georgia

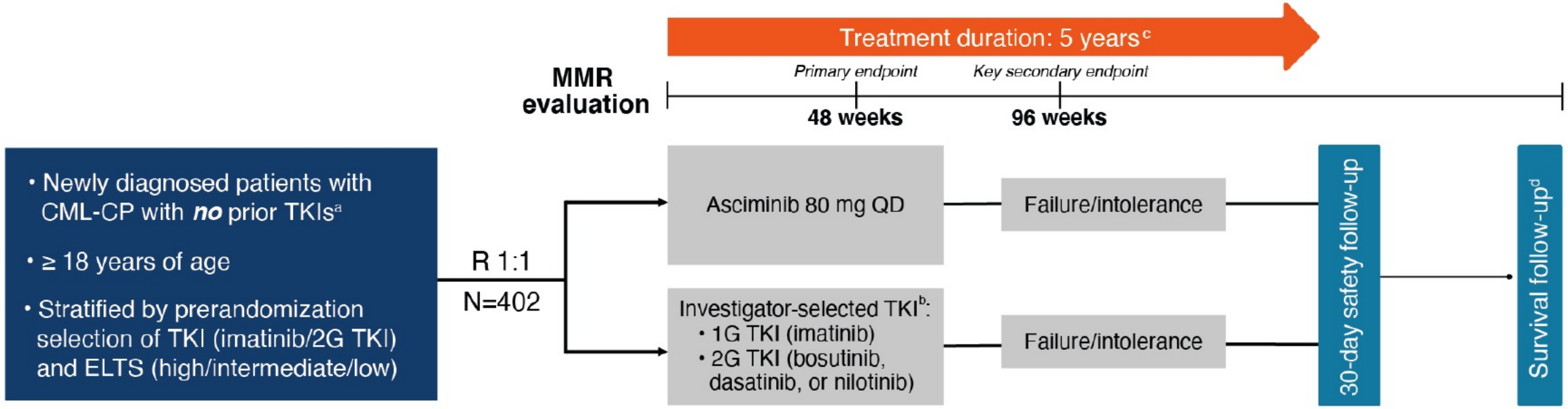
Therapies in Development versus Approved Therapies for CML in the Third-Line Setting or Later



TKI = tyrosine kinase inhibitor

Cortes J, Lang F. *J Hematol Oncol* 2021;14:44.

Schema of a Phase III Trial of Asciminib versus TKI for Newly Diagnosed CP-CML



1G, 1st generation; 2G, 2nd generation; CML-CP, chronic myeloid leukemia in chronic phase; ELTS, EUTOS long-term survival; EUTOS, European Treatment and Outcome Study; IS, International Scale; MMR, major molecular response (*BCR::ABL1*^{IS} ≤0.1%); QD, once daily; R, randomized; TKI, tyrosine kinase inhibitor.
[a] Only imatinib therapy ≤2 weeks is allowed. [b] The investigator-selected TKI treatment group will be distributed evenly between patients prerandomized to either 1G TKI or 2G TKI at their approved dose, with dose modifications for intolerance allowed at the investigator's discretion and in accordance with local labels.
[c] Patients will remain on study for 5 years after the last patient's 1st dose, unless they have discontinued early due to treatment failure, disease progression, intolerance, or investigator or patient decision. [d] Patients who discontinue early will continue to be followed up for survival and disease progression until the end of the study.

Hughes T et al. *EHA* 2022;Abstract PB1904.

Meet The Professor with Dr Neal

INTRODUCTION: Journal Club with Dr Neal – Part 1

MODULE 1: Adjuvant Therapy

MODULE 2: Locally Advanced Disease

MODULE 3: Exon 20 Insertions

MODULE 4: Metastatic Disease

MODULE 5: Journal Club with Dr Neal – Part 2

MODULE 6: Appendix of Key Publications

Clin Lung Cancer. 2021 May ; 22(3): 201–209.

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]

Original Study

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

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]

JC JOURNAL CLUB RTP RESEARCH TO PRACTICE

JTO Clin Res Rep 2022;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,*]

Cancer Chemotherapy and Pharmacology (2022) 89:105–115
https://doi.org/10.1007/s00280-021-04369-0

ORIGINAL ARTICLE

A phase 1b study of erlotinib and momelotinib for the treatment of *EGFR*-mutated, tyrosine kinase inhibitor-naive metastatic non-small cell lung cancer

Sukhmani K. Padda[1,2] · Karen L. Reckamp[2,3] · Marianna Koczywas[3] · Joel W. Neal[1] · Jun Kawashima[4,6] · Shengchun Kong[4,7] · Daniel B. Huang[5] · Mark Kowalski[4,6] · Heather A. Wakelee[1]

A patient who never smoked presents with highly symptomatic metastatic nonsquamous NSCLC requiring immediate treatment, and chemotherapy is started while awaiting next-generation sequencing. PD-L1 TPS is 90%. Would you recommend adding an anti-PD-1/PD-L1 antibody as well?

TPS = tumor proportion score

A patient with a long smoking history presents with highly symptomatic metastatic nonsquamous NSCLC requiring immediate treatment, and chemotherapy is started while awaiting next-generation sequencing. PD-L1 TPS is 90%. Would you recommend adding an anti-PD-1/PD-L1 antibody as well?

Meet The Professor with Dr Neal

INTRODUCTION: Journal Club with Dr Neal – Part 1

MODULE 1: Adjuvant Therapy

- Dr Metzner-Sadurski: A 65-year-old woman with Stage I NSCLC with an EGFR mutation and emphysema
- Dr Mitchell: A 68-year-old woman with localized papillary NSCLC and an EGFR L864Q mutation

MODULE 2: Locally Advanced Disease

MODULE 3: Exon 20 Insertions

MODULE 4: Metastatic Disease

MODULE 5: Journal Club with Dr Neal – Part 2

MODULE 6: Appendix of Key Publications

RTP
RESEARCH
TO PRACTICE

Case Presentation: A 65-year-old woman with Stage I NSCLC with an EGFR mutation and emphysema

Dr Joanna Metzner-Sadurski (Greenwood, South Carolina)

RTP
RESEARCH
TO PRACTICE

From: "Mallidi, Padmaja V"
Date: June 29, 2022 at 8:37:05 AM EDT
To: Neil Love <nlove@researchtopractice.com>
Subject: RE: Case for tonight

Dear Dr Love.

I like to get an opinion on a case, patient that I met last week and wanted to put this in chat room tonight. But wanted to send this to you, in case if it helps to have it before the meeting.

[redacted] is a pleasant 65 yr old with history of very minimal smoking decades ago, no other comorbidities, had imaging done in trauma center after MVA. Found to have lung nodule confirmed to be FDG avid on PET , but no adenopathy on CT or PET.
Went for surgery.
Path - RUL mod-poorly diff adenoca, T1cN2M0, s/p RUL lobectomy and MLND. EGFR exon 21 L861R, PDL1 TPS score 70% by 22C3 assay, Atezo (SP263) assay pnd; rest of the mutation panel negative

Stage IIIA NSCLC, she is starting chemo soon with Pemetrexed/cisplatin x 4 cycles.

Adaura trial only included pts with tumors that harbored EGFR mutations like exon 19 or exon 21 L858R.
I understand from literature review that the tumors with EGFR exon 21 L861R can be responsive to EGFR inh like afatinib or Osimertinib. But not a whole literature out there for this specific one as it is quite rare. Trying to avoid Atezo as it may not benefit and potential future incr toxicity esp pneumonitis.

Wondering if subject experts would consider EGFR inh or atezo or none after chemo.

On the same thread, was wondering if consolidative durvalumab is skipped routinely in pts with known EGFR/ ALK/ROS mutation pts after chemo XRT in stage 3B.
(Since pacific trial had some pts with these mutations and did not seem to benefit and potential increased toxicity if they relapse soon after and had to be stated on TKI)

As always enjoy your conferences.

Padma Mallidi

Case Presentation: A 68-year-old woman with localized papillary NSCLC and an EGFR L864Q mutation

Dr William Mitchell (Charlotte, North Carolina)

RTP
RESEARCH
TO PRACTICE

JCO Precis Oncol 2021;5:325-32.

original reports

TARGETED DRUG THERAPY

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]

Efficacy of Osimertinib in Patients with *EGFR* Mutant Lung Cancer Harboring the Uncommon Exon 19 Deletion, L747_A750>P

Grant MJ et al.

ASCO 2022;Abstract e21112.

ORIGINAL ARTICLE

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

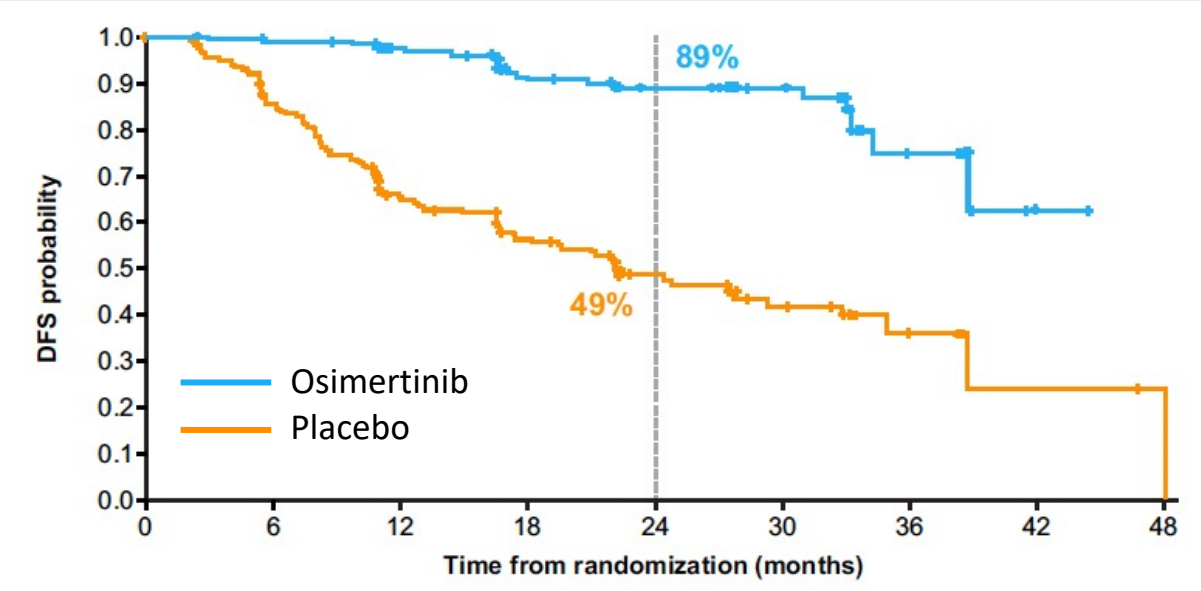
IASLC

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

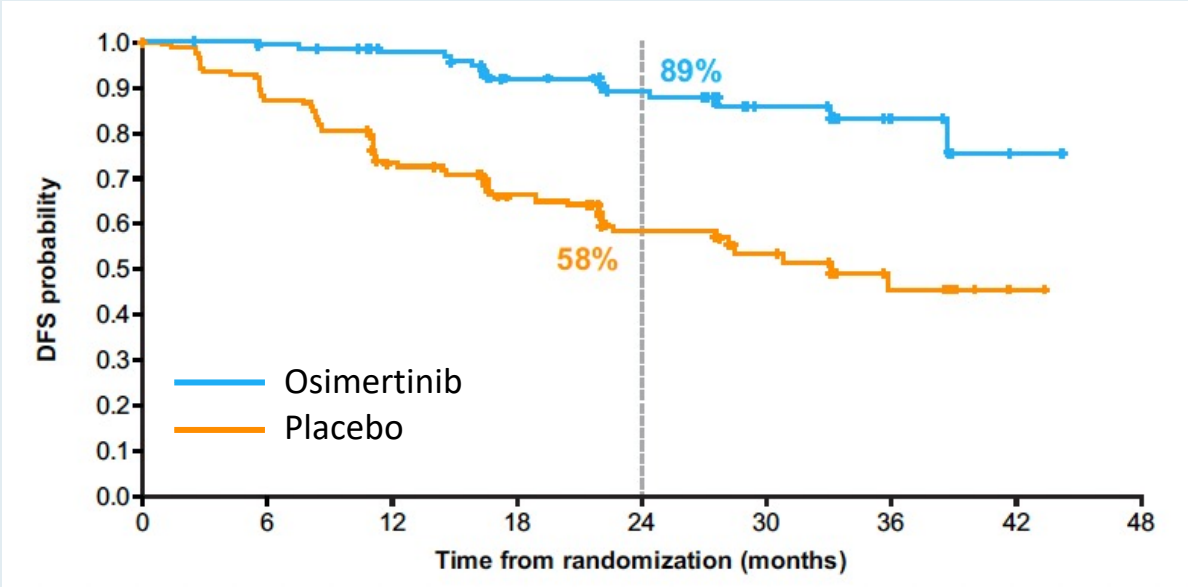
Yi-Long Wu, MD,[a,*] Thomas John, PhD,[b] Christian Grohe, MD,[c] Margarita Majem, MD, PhD,[d] Jonathan W. Goldman, MD,[e] Sang-We Kim, MD, PhD,[f] Terufumi Kato, MD,[g] Konstantin Laktionov, PhD,[h] Huu Vinh Vu, MD, PhD,[i] Zhijie Wang, MD,[j] Shun Lu, MD,[k] Kye Young Lee, MD, PhD,[l] Charuwan Akewanlop,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



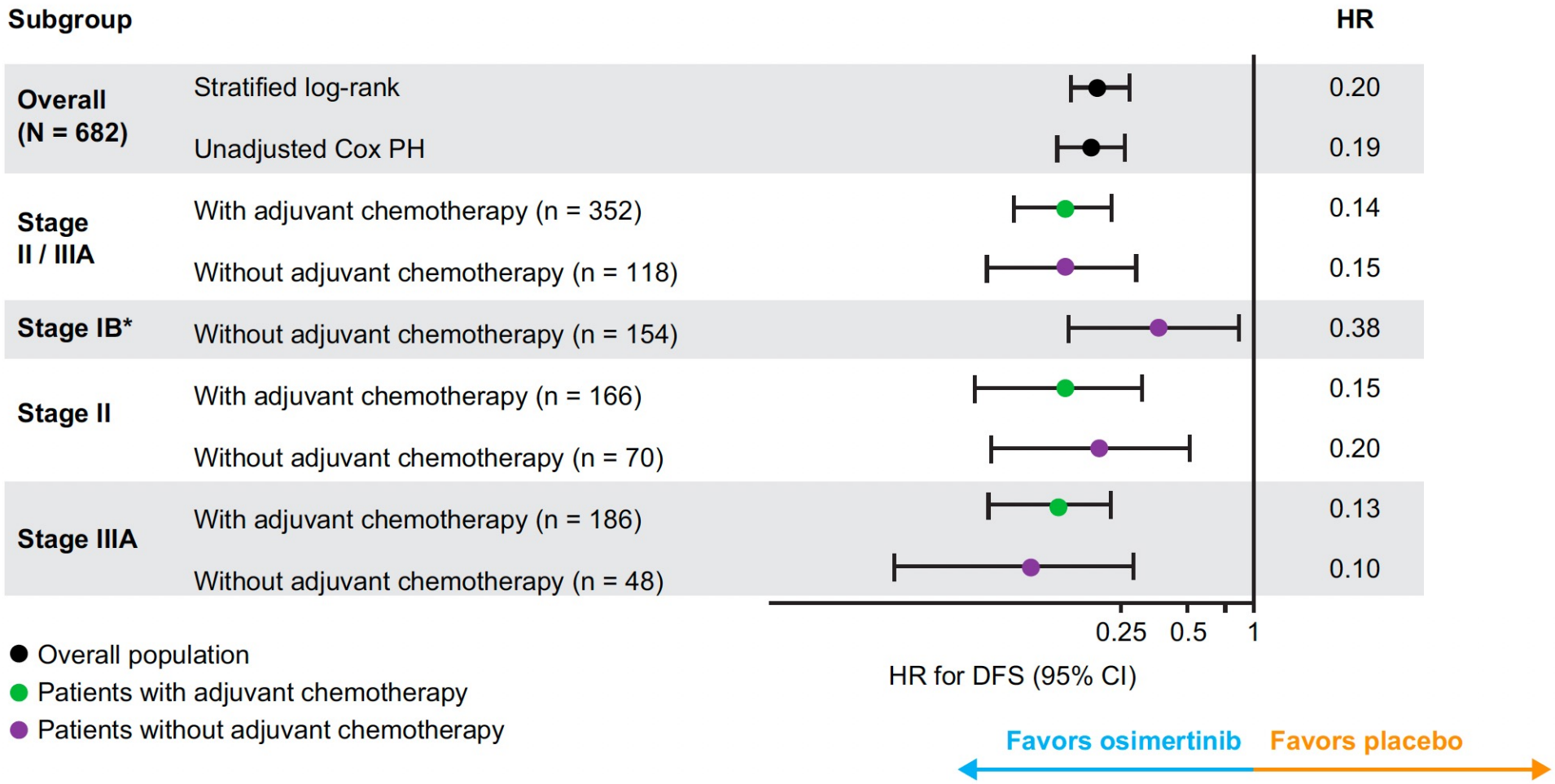
Without adjuvant chemotherapy



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.

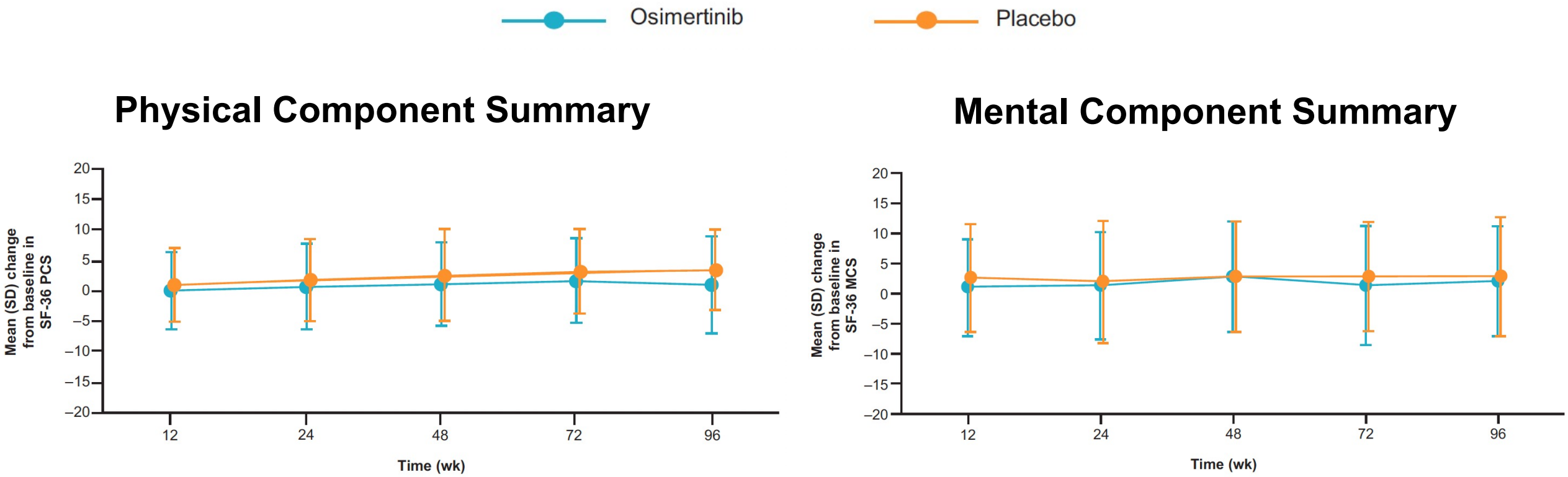
CLINICAL CANCER RESEARCH | CLINICAL TRIALS: TARGETED THERAPY

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.

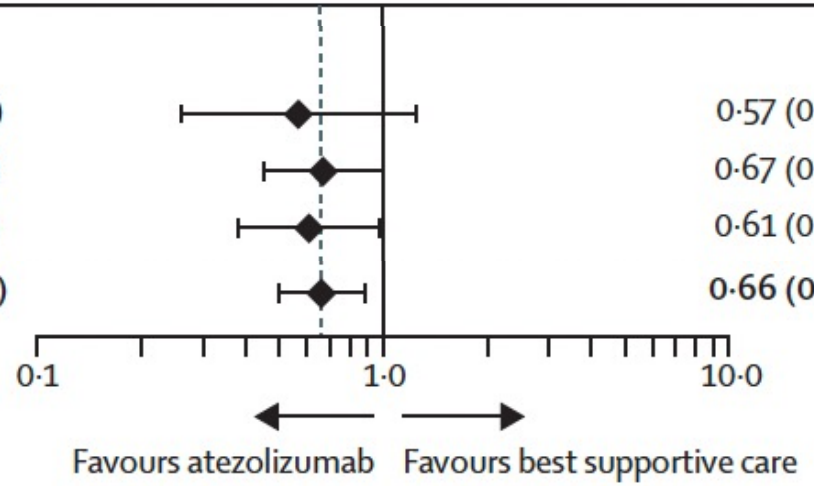
Lancet 2021;398:1344-57.

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**

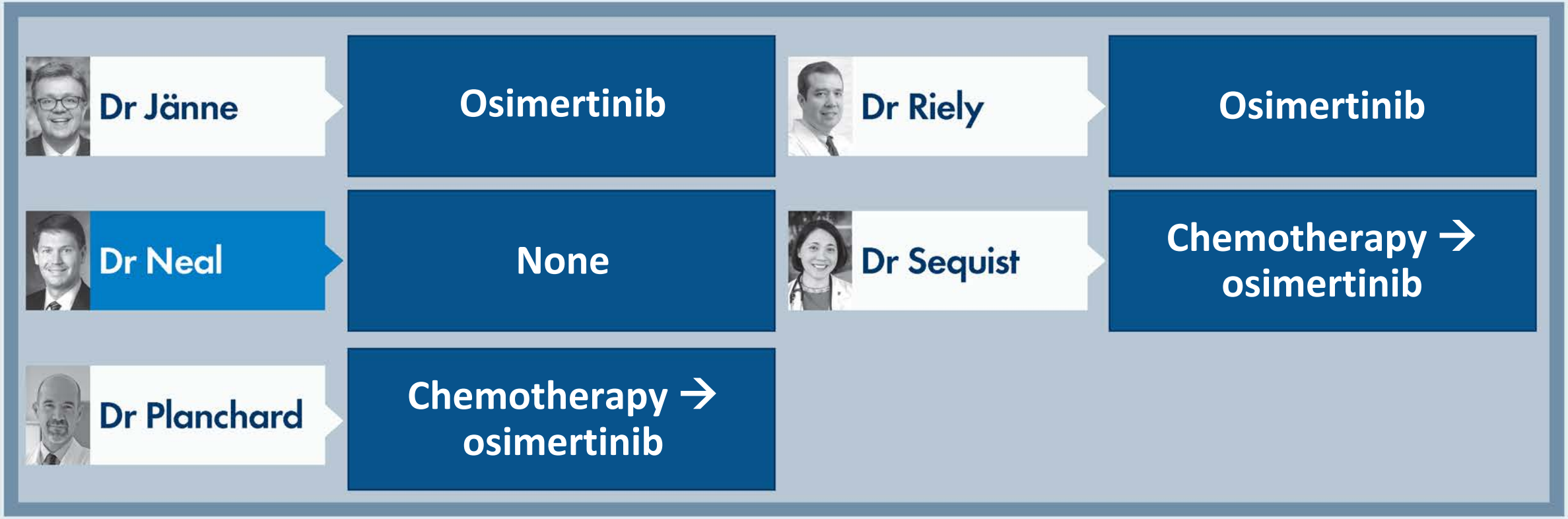
IMpower010: Disease-Free Survival by EGFR Mutation Status

	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)**



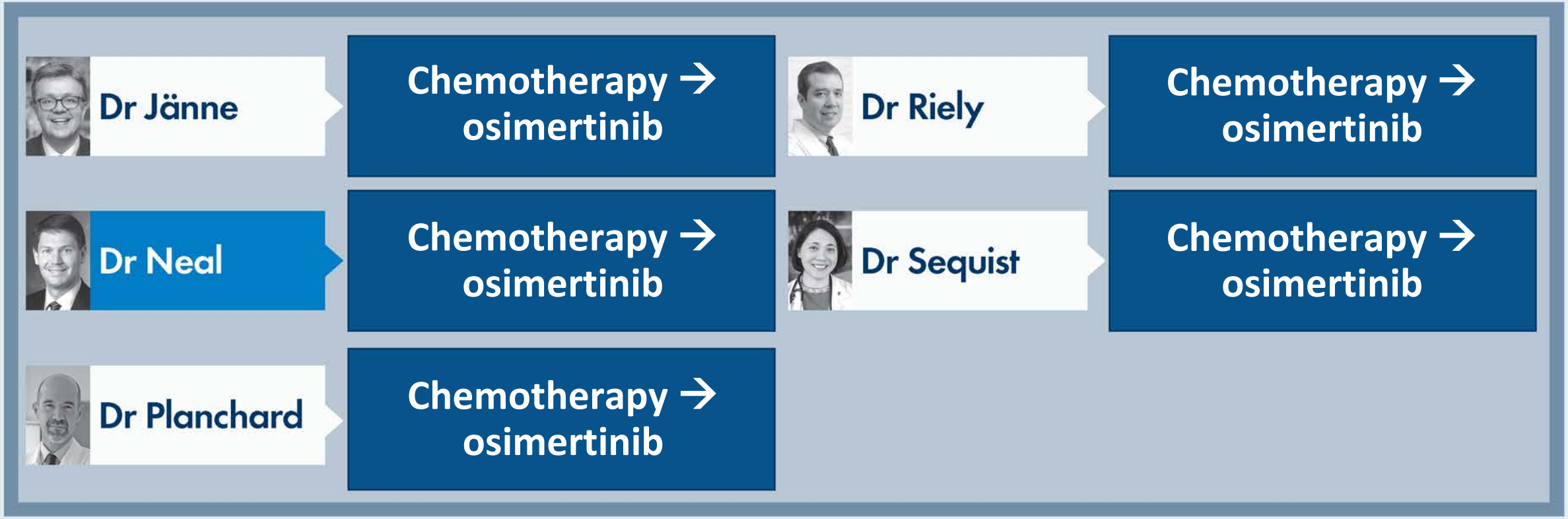
Felip E et al. *Lancet* 2021;398(10308):1344-57.

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%?



RTP RESEARCH TO PRACTICE

Meet The Professor with Dr Neal

INTRODUCTION: Journal Club with Dr Neal – Part 1

MODULE 1: Adjuvant Therapy

MODULE 2: Locally Advanced Disease

- Dr Morganstein: A 73-year-old woman with Stage IIIA NSCLC and EGFR L858R, ROS1 and TP53 mutations

MODULE 3: Exon 20 Insertions

MODULE 4: Metastatic Disease

MODULE 5: Journal Club with Dr Neal – Part 2

MODULE 6: Appendix of Key Publications

RTP RESEARCH TO PRACTICE

Case Presentation: A 73-year-old woman with Stage IIIA NSCLC and EGFR L858R, ROS1 and TP53 mutations

Dr Neil Morganstein (Summit, New Jersey)

RTP RESEARCH TO PRACTICE

J Thorac Oncol 2021;16(12):1994-8.

IASLC

CONTROVERSIES IN THORACIC ONCOLOGY

Consolidation Durvalumab Should Not Be Administered to Patients With Stage III *EGFR*-Mutant NSCLC

Jacqueline V. Aredo, MD, MS,[a] Jessica A. Hellyer, MD,[b] Joel W. Neal, MD, PhD,[c] Heather A. Wakelee, MD[c,*]

JC JOURNAL CLUB RTP RESEARCH TO PRACTICE

The NEW ENGLAND JOURNAL of MEDICINE

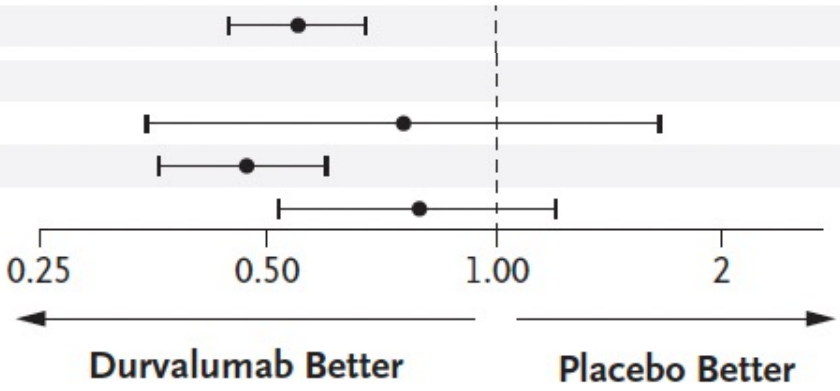
ESTABLISHED IN 1812 NOVEMBER 16, 2017 VOL. 377 NO. 20

Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer

S.J. Antonia, A. Villegas, D. Daniel, D. Vicente, S. Murakami, R. Hui, T. Yokoi, A. Chiappori, K.H. Lee, M. de Wit, B.C. Cho, M. Bourhaba, X. Quantin, T. Tokito, T. Mekhail, D. Planchard, Y.-C. Kim, C.S. Karapetis, S. Hiret, G. Ostoros, K. Kubota, J.E. Gray, L. Paz-Ares, J. de Castro Carpeño, C. Wadsworth, G. Melillo, H. Jiang, Y. Huang, P.A. Dennis, and M. Özgüroğlu, for the PACIFIC Investigators*

PACIFIC Trial: EGFR Mutation Subgroup Analysis for Progression-Free Survival in the Intention-to-Treat Population

Subgroup	Durvalumab	Placebo	Unstratified Hazard Ratio for Disease Progression or Death (95% CI)
	no. of patients		
All patients	476	237	0.55 (0.45–0.68)
EGFR mutation			
Positive	29	14	0.76 (0.35–1.64)
Negative	315	165	0.47 (0.36–0.60)
Unknown	132	58	0.79 (0.52–1.20)



Antonio SJ et al. *N Engl J Med* 2017;377(20):1919-29.

J Thorac Oncol 2021;16(5):868-72.

IASLC

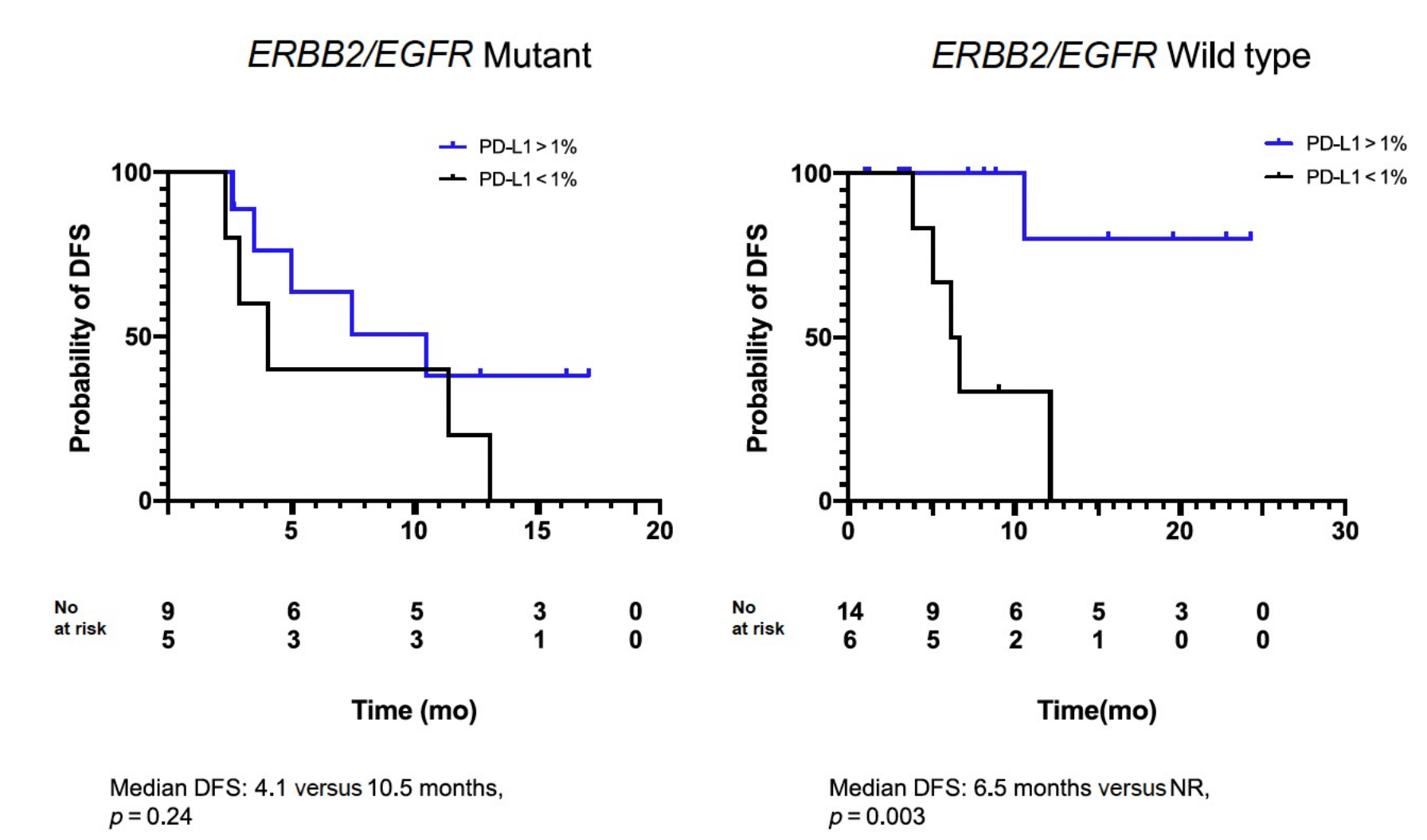
BRIEF REPORT

Role of Consolidation Durvalumab in Patients With *EGFR*- and *HER2*-Mutant Unresectable Stage III NSCLC

Jessica A. Hellyer, MD,[a] Jacqueline V. Aredo, BS,[a] Millie Das, MD,[a,b] Kavitha Ramchandran, MD,[a] Sukhmani K. Padda, MD,[a] Joel W. Neal, MD, PhD,[a] Heather A. Wakelee, MD[a,*]

JC JOURNAL CLUB RTP RESEARCH TO PRACTICE

Disease-Free Survival (DFS) for ERBB2/EGFR Mutation and ERBB2/EGFR Wild-Type Cohorts by PD-L1 <1% versus PD-L1 >1%



Hellyer JA et al. *J Thorac Oncol* 2021;16(5):868-72.

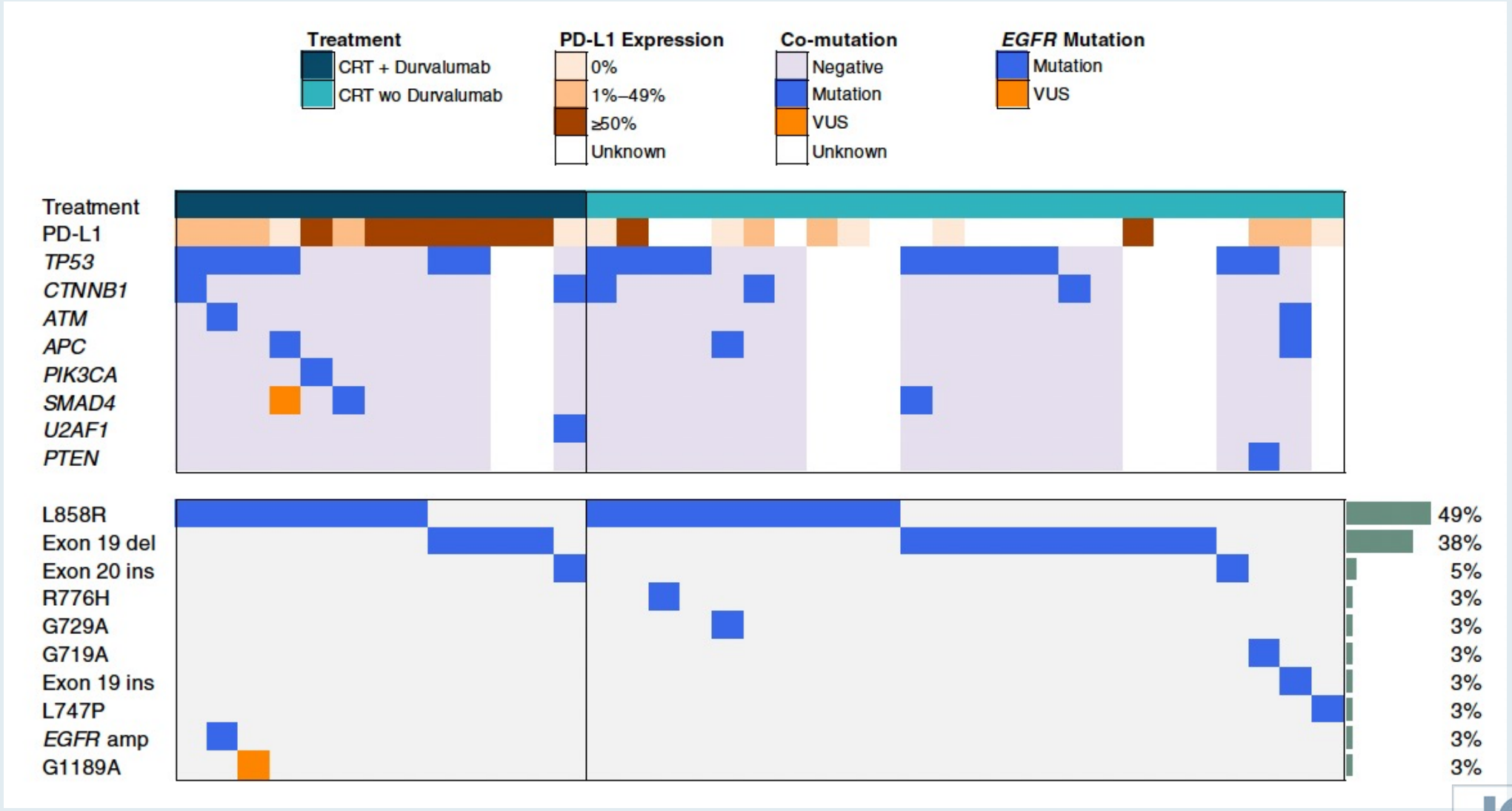
J Thorac Oncol 2021;16(6):1030-41.

ORIGINAL ARTICLE

Durvalumab for Stage III *EGFR*-Mutated NSCLC After Definitive Chemoradiotherapy

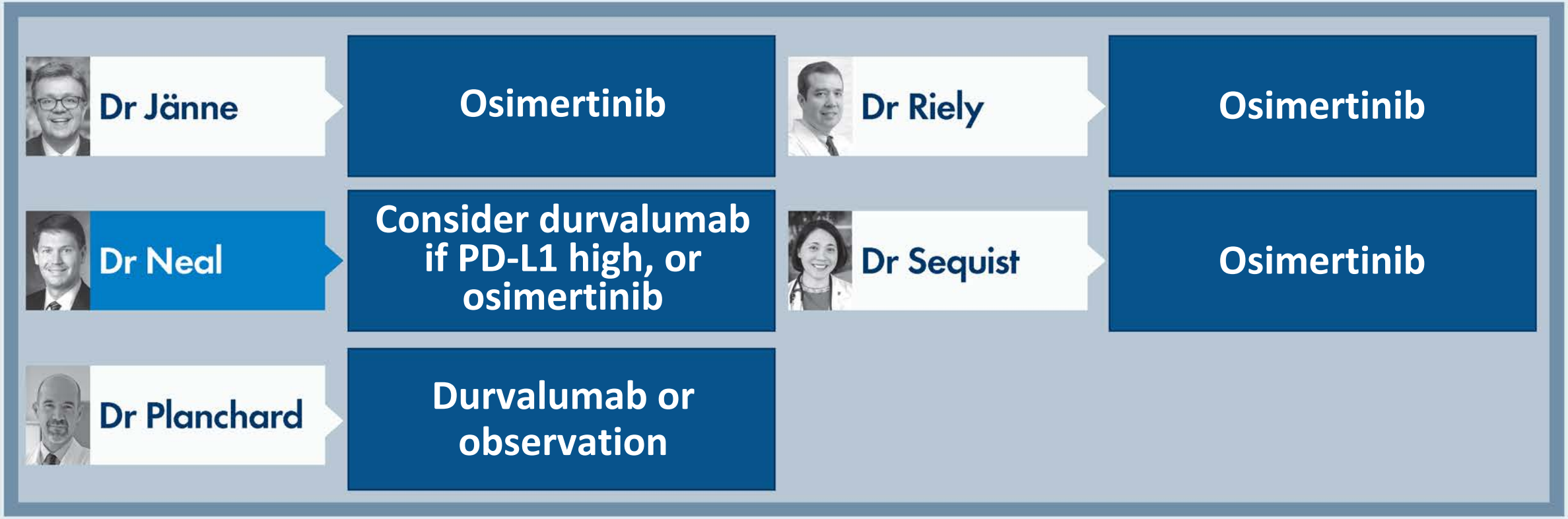
Jacqueline V. Aredo, BS,[a] Isa Mambetsariev, BA,[b] Jessica A. Hellyer, MD,[c] Arya Amini, MD,[d] Joel W. Neal, MD, PhD,[c] Sukhmani K. Padda, MD,[c] Caroline E. McCoach, MD, PhD,[e] Jonathan W. Riess, MD, MS,[f] Elwyn C. Cabebe, MD,[g] Jarushka Naidoo, MBBCH, MHS,[h,i] Tariq Abuali, BS,[d] Ravi Salgia, MD, PhD,[b] Billy W. Loo Jr., MD, PhD,[j] Maximilian Diehn, MD, PhD,[j] Summer S. Han, PhD,[k] Heather A. Wakelee, MD[c,*]

Molecular Features of the NSCLC Cohort with EGFR Mutations



Aredo JV et al. *J Thorac Oncol* 2021;16(6):1030-41.

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?



Meet The Professor with Dr Neal

INTRODUCTION: Journal Club with Dr Neal – Part 1

MODULE 1: Adjuvant Therapy

MODULE 2: Locally Advanced Disease

MODULE 3: Exon 20 Insertions

- Dr Saylors: A 52-year-old woman with metastatic NSCLC and an EGFR exon 20 insertion – PD-L1 TPS 20%

MODULE 4: Metastatic Disease

MODULE 5: Journal Club with Dr Neal – Part 2

MODULE 6: Appendix of Key Publications

Case Presentation: A 52-year-old woman with metastatic NSCLC and an EGFR exon 20 insertion – PD-L1 TPS 20%

Dr Julia Saylors (North Charleston, South Carolina)

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.

Original Study

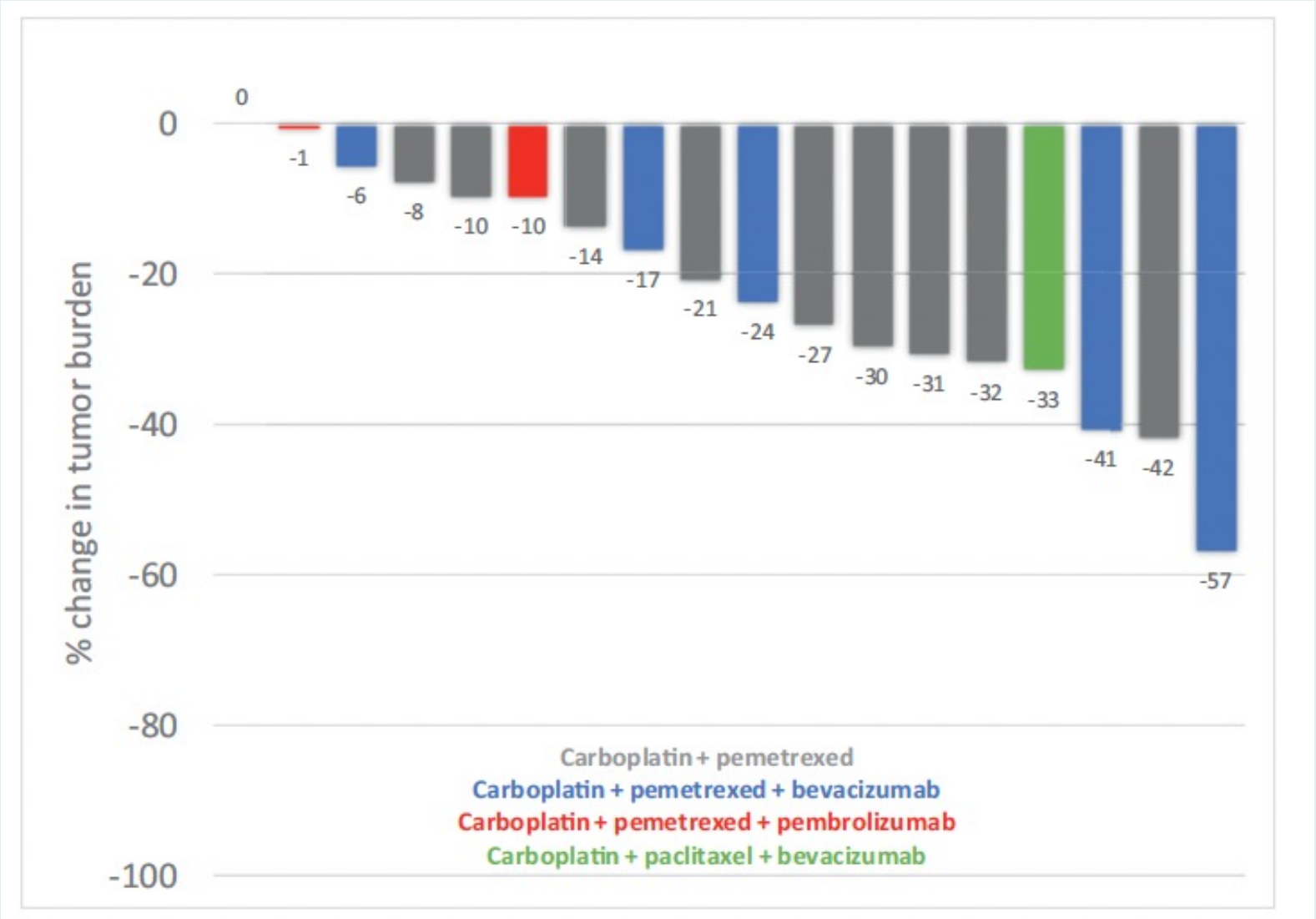
Clin Lung Cancer 2022;23(2):e148-53.

EGFR exon 20 Insertion NSCLC and Response to Platinum-Based Chemotherapy

Manan P. Shah, Jacqueline V. Aredo, Sukhmani K. Padda, Kavitha J. Ramchandran, Heather A. Wakelee, Millie S. Das, Joel W. Neal

JC JOURNAL CLUB RTP RESEARCH TO PRACTICE

Best Change in Tumor Burden for 18 Patients with EGFR ex20ins NSCLC Treated with Platinum-Based Chemotherapy



Shah MP et al. *Clin Lung Cancer* 2022;23(2):e148-53.

2022 ASCO ANNUAL MEETING

Abstract 9115.

Matching-Adjusted Indirect Comparison (MAIC) of Mobocertinib vs Amivantamab in Patients with Non-Small Cell Lung Cancer (NSCLC) with *EGFR* Exon 20 Insertions (ex20ins)

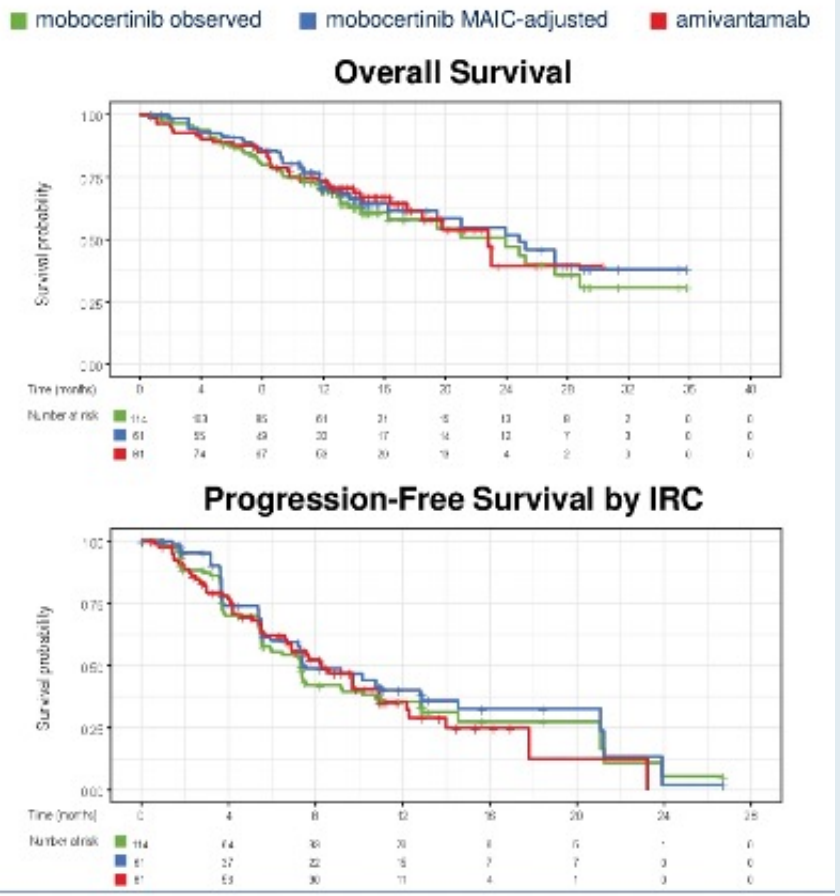
Sai-Hong I. Ou[1], Thibaud Prawitz[2], Huamao M. Lin[3], Jin-Liern Hong[3], Min Tan[2], Irina Proskorovsky[2], Luis Hernandez[4], Shu Jin[3], Pingkuan Zhang[3], Jianchang Lin[3], Jyoti Patel[5], Danny Nguyen[6], Joel W. Neal[7]

[1]Chao Family Comprehensive Cancer Center, University of California Irvine School of Medicine, Orange, CA, USA; [2]Evidera, Inc, Lexington, MA, USA; [3]Takeda Development Center Americas, Inc, Lexington, MA, USA; [4]Takeda Pharmaceuticals America, Inc, Lexington, MA, USA; [5]Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, IL, USA; [6]City of Hope National Medical Center, Los Angeles, CA, USA; [7]Stanford Cancer Institute, Stanford University, Stanford, CA, USA

Similar Efficacy for Mobocertinib and Amivantamab

Outcome	Statistic	Unweighted comparison	P value	Weighted comparison	P value
OS	HR (95% CI)	1.12 (0.71, 1.77)	0.637	0.95 (0.55, 1.67)	0.865
PFS (IRC)	HR (95% CI)	1.00 (0.69, 1.44)	0.988	0.82 (0.52, 1.32)	0.417
cORR (IRC)	OR (95% CI)	0.60 (0.32, 1.10)	0.099	0.64 (0.31, 1.33)	0.230
cORR (INV)	OR (95% CI)	0.97 (0.53, 1.77)	0.919	0.99 (0.48, 2.02)	0.974

HR <1 and OR >1 suggest better outcome for mobocertinib vs amivantamab.
For amivantamab, reconstructed individual-patient data were derived using the Guyot et al. algorithm.[4]



4. Guyot P, et al. BMC medical research 2012;12.1:1:13

Ou S-HI et al. ASCO 2022;Abstract 9115.

Conclusions

- Efficacy of mobocertinib and amivantamab were similar in patients with *EGFR* ex20ins-mutant NSCLC that have progressed during or after platinum-based chemotherapy.
- Having two treatment options with distinct mechanisms of action and routes of administration could benefit patients with *EGFR* ex20ins-mutant NSCLC, especially in the case of resistance or intolerance.
- A better understanding of where these agents fit in the treatment paradigm could maximize patient outcomes.
- Ongoing phase 3 studies may establish a role for these agents as first-line treatment.

Ou S-HI et al. ASCO 2022;Abstract 9115.

MOBOCERTINIB IN *EGFR* EXON 20 INSERTION–POSITIVE METASTATIC NSCLC PATIENTS WITH DISEASE CONTROL ON PRIOR EGFR TKI THERAPY

Alexander I Spira[1], Suresh S Ramalingam[2], Joel W Neal[3], Zofia Piotrowska[4], Tarek Mekhail[5], Anne Tsao[6], Ryan Gentzler[7], Gregory J Riely[8], Lyudmila Bazhenova[9], Shirish Gadgeel[10], Danny Nguyen[11], Melissa L Johnson[12], Sylvie Vincent[13], Shu Jin[13], Celina Griffin[13], Veronica Bunn[13], Jianchang Lin[13], Eric N Churchill[13], Minal Mehta[13], Pasi A Jänne[14]

[1]Virginia Cancer Specialists and US Oncology Research, Fairfax, VA, USA; [2]Emory University, Atlanta, GA, USA; [3]Stanford Cancer Institute, Stanford University, Stanford, CA, USA; [4]Massachusetts General Hospital Cancer Center, Boston, MA, USA; [5]AdventHealth Orlando, Orlando, FL, USA; [6]University of Texas MD Anderson Cancer Center, Houston, TX, USA; [7]University of Virginia Cancer Center, Charlottesville, VA, USA; [8]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [9]University of California San Diego Moores Cancer Center, La Jolla, CA, USA; [10]University of Michigan, Ann Arbor, MI, USA; [11]Pacific Shores Medical Group, Long Beach, CA, USA; [12]Sarah Cannon Research Institute, Nashville, TN, USA; [13]Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited; [14]Dana-Farber Cancer Institute, Boston, MA, USA

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

Abstract OA15.01.

Research

JAMA Oncol 2021;7(12):e214761

JAMA Oncology | Original Investigation

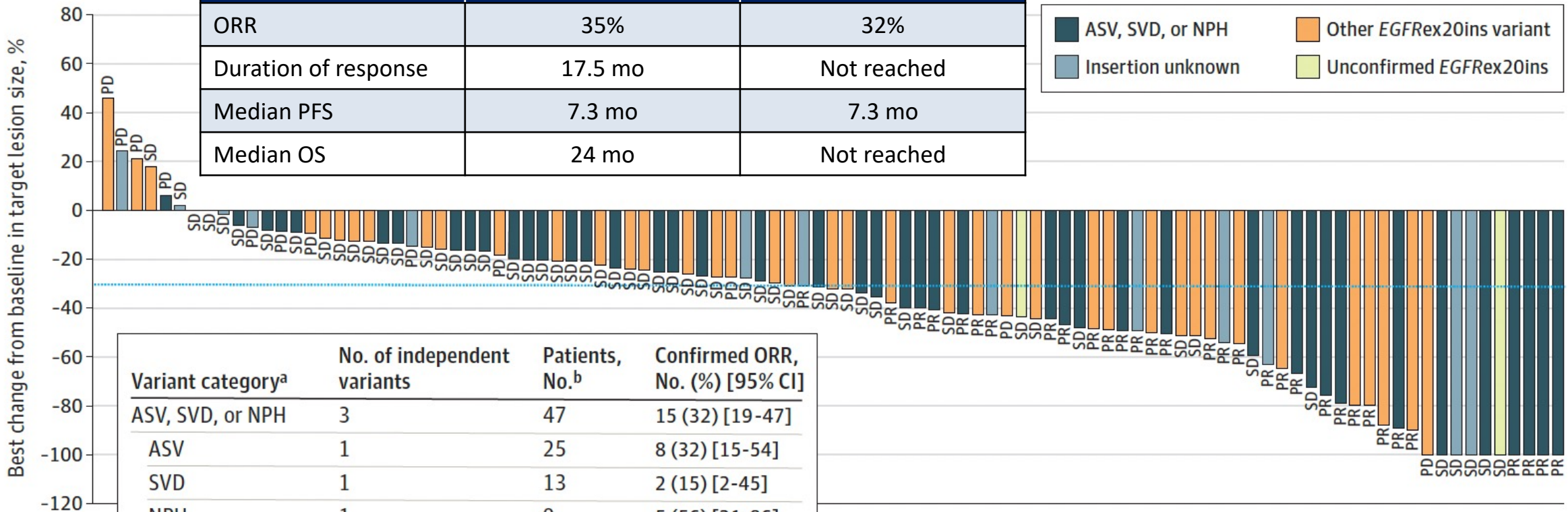
Treatment Outcomes and Safety of Mobocertinib in Platinum-Pretreated Patients With *EGFR* Exon 20 Insertion–Positive Metastatic Non–Small Cell Lung Cancer

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.

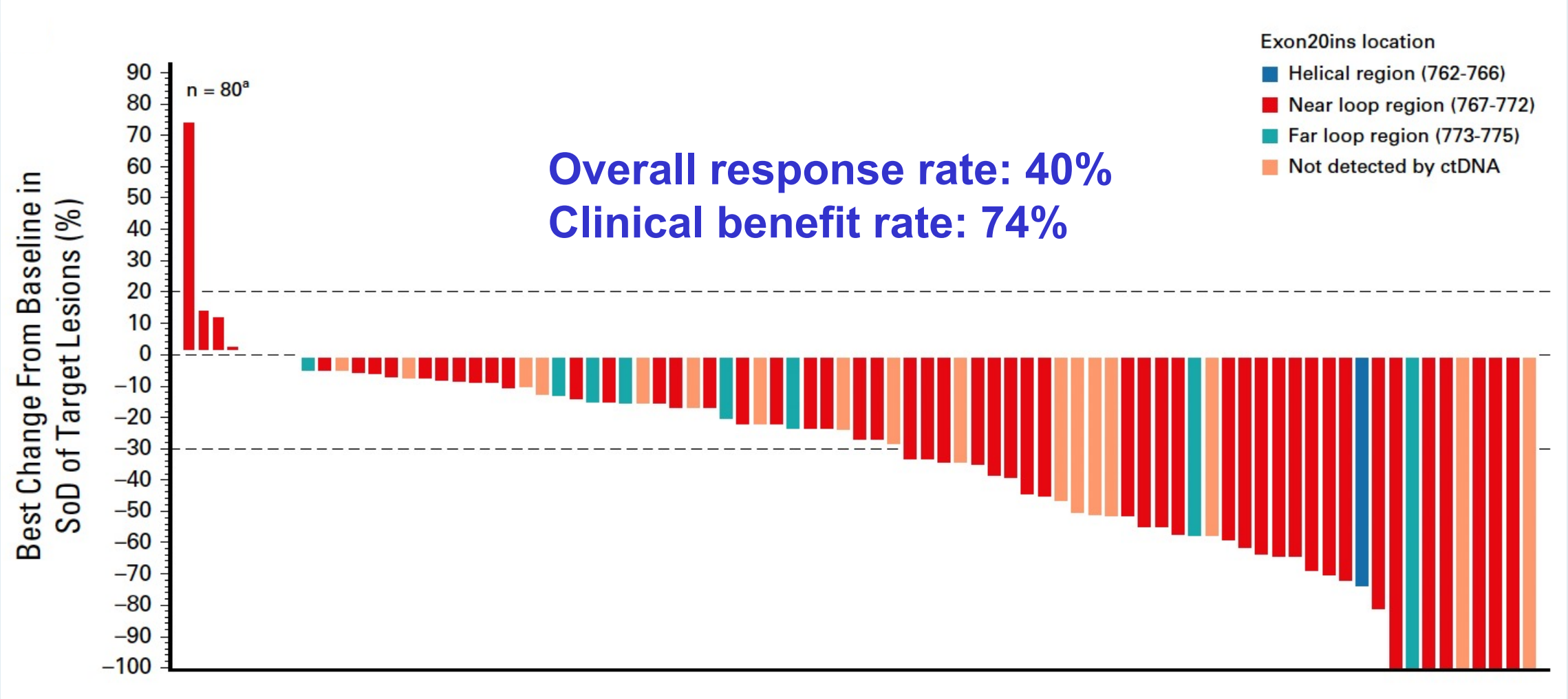
original reports

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 9007

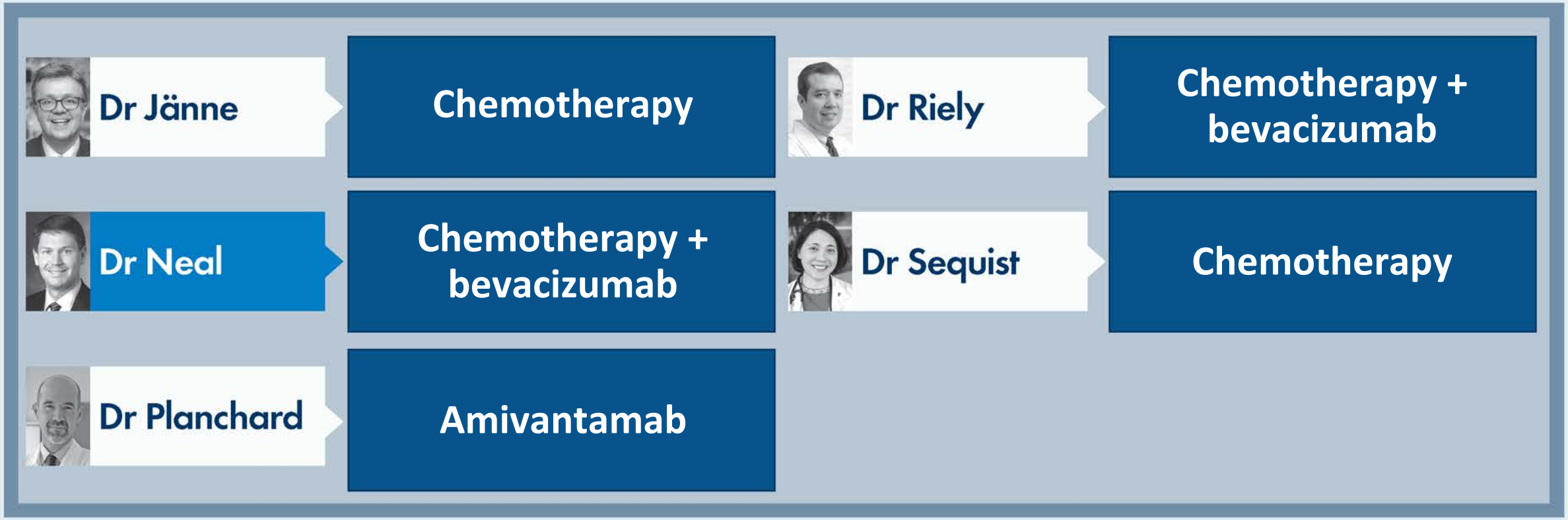
Phase1/2a Study of CLN-081 in NSCLC Patients with EGFR Exon 20 Insertion (ex20ins) Mutations

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

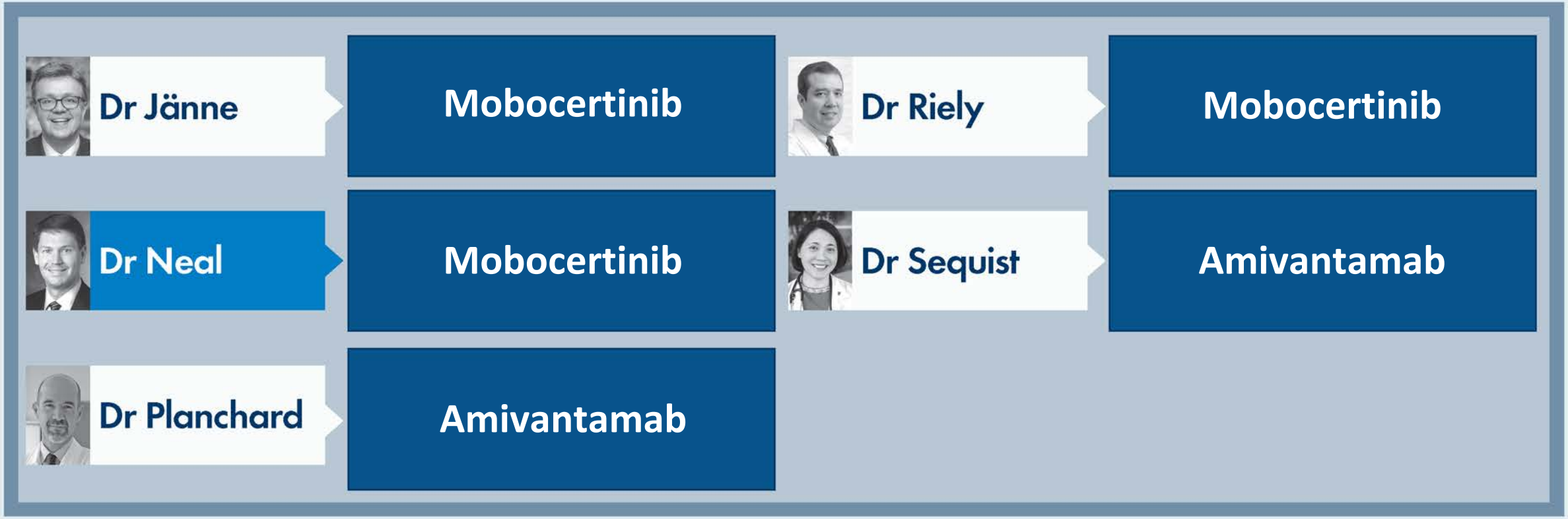
PRESENTED BY:
Helena Yu, Memorial Sloan Kettering Cancer Center, New York, NY

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%?

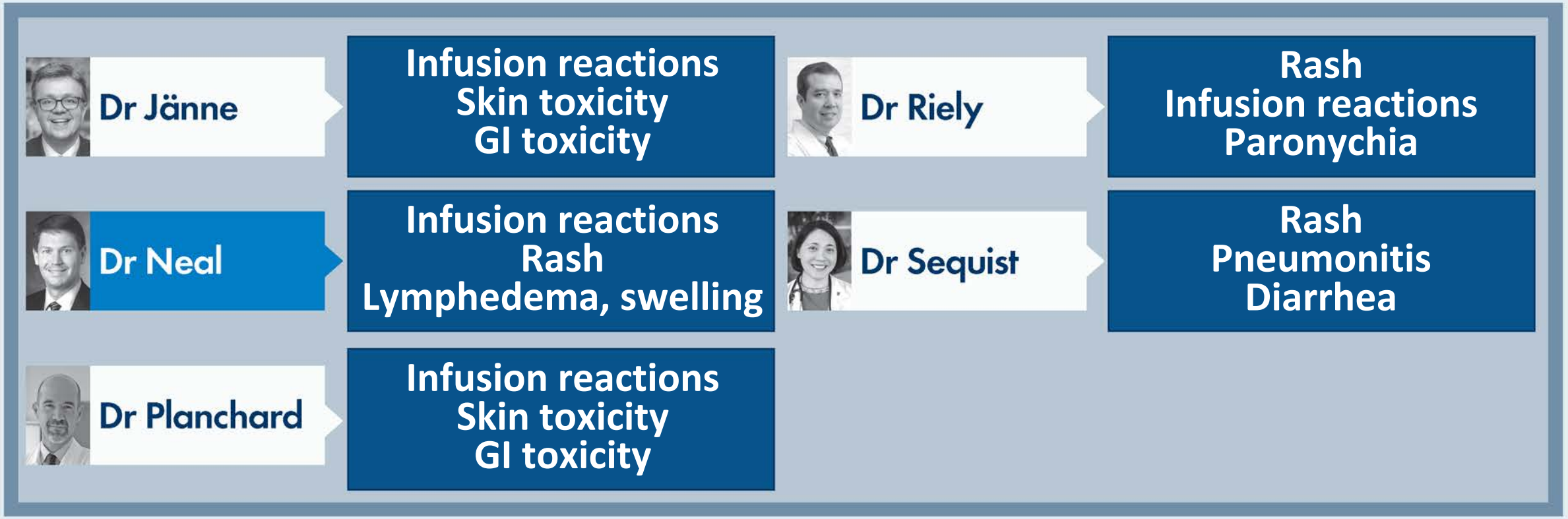


Regulatory and reimbursement issues aside, in which line of therapy would you generally offer amivantamab or mobocertinib to a patient with metastatic NSCLC and an EGFR exon 20 insertion mutation?

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?



When a patient is about to begin treatment with amivantamab, what are your 3 most important tolerability concerns?



When a patient is about to begin treatment with mobocertinib, what are your 3 most important tolerability concerns?

 Dr Jänne	Diarrhea Skin toxicity
 Dr Neal	Diarrhea Paronychia Anorexia
 Dr Planchard	GI toxicity Skin toxicity Hepatic toxicity
 Dr Riely	Diarrhea Rash Fatigue
 Dr Sequist	Rash Diarrhea Fatigue

RTP RESEARCH TO PRACTICE

Meet The Professor with Dr Neal

INTRODUCTION: Journal Club with Dr Neal – Part 1

MODULE 1: Adjuvant Therapy

MODULE 2: Locally Advanced Disease

MODULE 3: Exon 20 Insertions

MODULE 4: Metastatic Disease

- Dr Peswani: A 70-year-old woman with metastatic NSCLC with an EGFR exon 19 mutation – PD-L1 TPS 50%
- Dr Shehadeh: A 54-year-old woman with metastatic NSCLC with an EGFR exon 19 deletion
- Dr Chen: A 55-year-old woman with metastatic NSCLC and an EGFR exon 19 deletion – PD-L1 80%
- Dr Ahmed: A 76-year-old woman with metastatic NSCLC and EGFR exon 18 G719S and E709A mutations – PD-L1 TPS 0

MODULE 5: Journal Club with Dr Neal – Part 2

MODULE 6: Appendix of Key Publications

RTP RESEARCH TO PRACTICE

Under which circumstances, if any, do you administer afatinib as first-line therapy to patients with metastatic NSCLC and an EGFR mutation?

Dr Jänne

Atypical mutation in absence of CNS mets

Dr Neal

Perhaps with EGFR mutation and HER2 amplification as acquired resistance

Dr Planchard

Only in case of atypical EGFR mutation, especially exon 20 insertion

Dr Riely

None

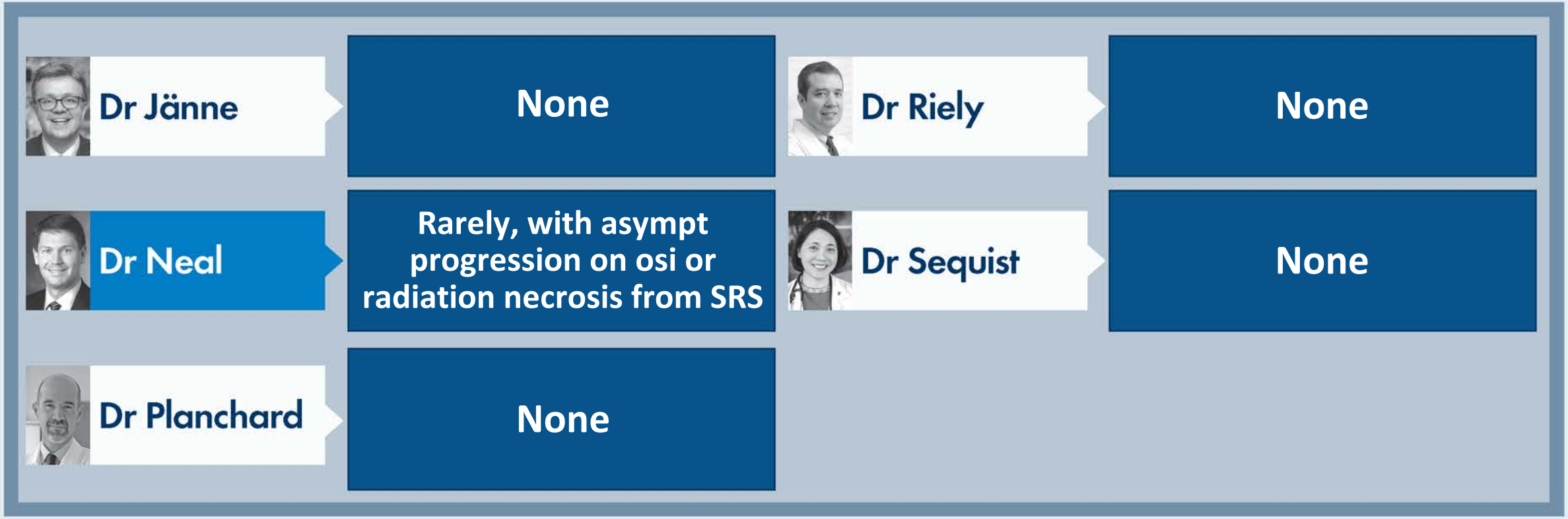
Dr Sequist

None

RTP RESEARCH TO PRACTICE

Under which circumstances, if any, do you administer erlotinib/ramucirumab as first-line therapy to patients with metastatic NSCLC and an EGFR mutation?

Under which circumstances, if any, do you administer osimertinib in combination with bevacizumab as first-line therapy to patients with metastatic NSCLC and an EGFR mutation?



SRS = stereotactic radiosurgery

Under which circumstances, if any, do you administer osimertinib in combination with ramucirumab as first-line therapy to patients with metastatic NSCLC and an EGFR mutation?

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?

Case Presentation: A 70-year-old woman with metastatic NSCLC with an EGFR exon 19 mutation – PD-L1 TPS 50%

Dr Namrata Peswani (Richardson, Texas)

RTP
RESEARCH
TO PRACTICE

Case Presentation: A 54-year-old woman with metastatic NSCLC with an EGFR exon 19 deletion

Dr Nasfat Shehadeh (Charlotte, North Carolina)

RTP
RESEARCH
TO PRACTICE

Case Presentation: A 55-year-old woman with metastatic NSCLC and an EGFR exon 19 deletion – PD-L1 80%

Dr Gigi Chen (Pleasant Hill, California)

RTP
RESEARCH
TO PRACTICE

Case Presentation: A 76-year-old woman with metastatic NSCLC and EGFR exon 18 G719S and E709A mutations – PD-L1 TPS 0

Dr Syed Ahmed (Libertyville, Illinois)

2022 ASCO® ANNUAL MEETING

Abstract 9006

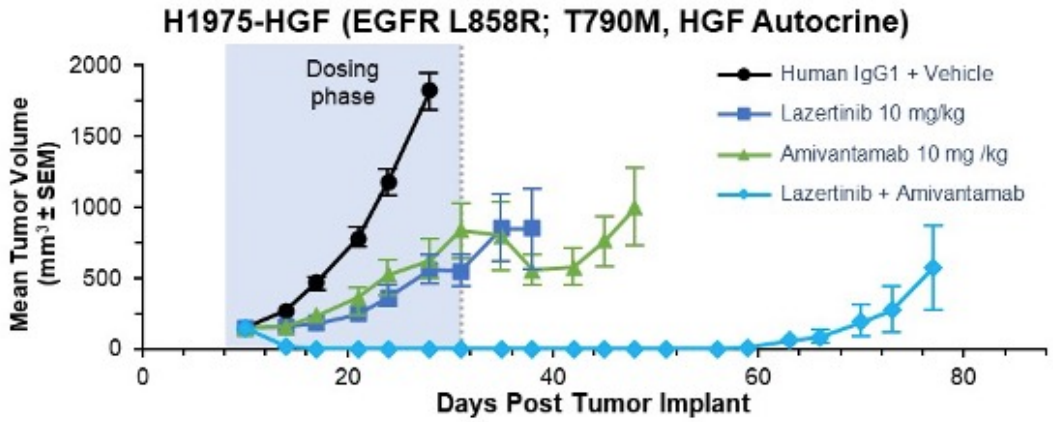
Amivantamab and lazertinib in patients with EGFR-mutant non-small cell lung cancer (NSCLC) after progression on osimertinib and platinum-based chemotherapy: Updated results from CHRYSALIS-2

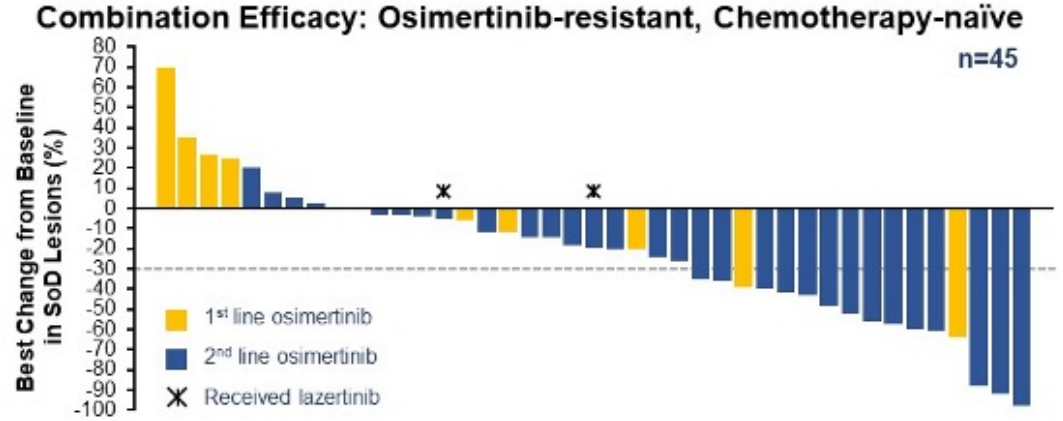
Catherine A. Shu,[1] Koichi Goto,[2] Yuichiro Ohe,[3] Benjamin Besse,[4] Se-Hoon Lee,[5] Yongsheng Wang,[6] Frank Griesinger,[7] James Chih-Hsin Yang,[8] Enriqueta Felip,[9] Rachel E. Sanborn,[10] Reyes Bernabe Caro,[11] Joshua C. Curtin,[12] Jun Chen,[12] Janine Mahoney,[12] Leonardo Trani,[12] Joshua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

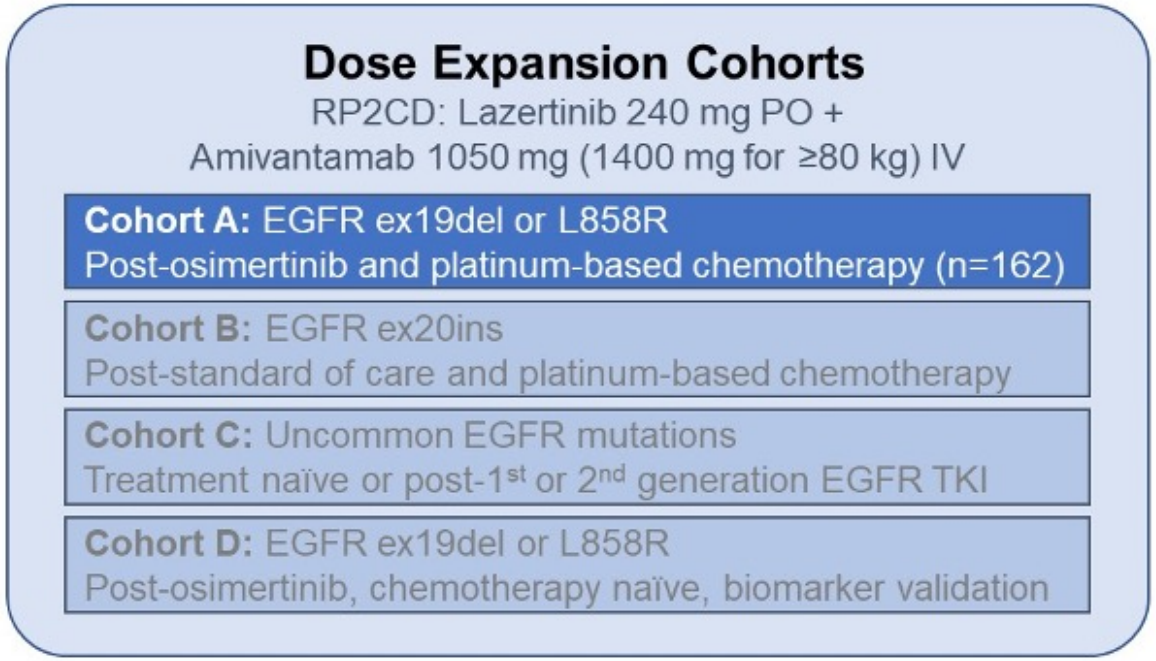




Shu CA et al. ASCO 2022;Abstract 9006.

RTP RESEARCH TO PRACTICE

CHRYSALIS-2 Study Design



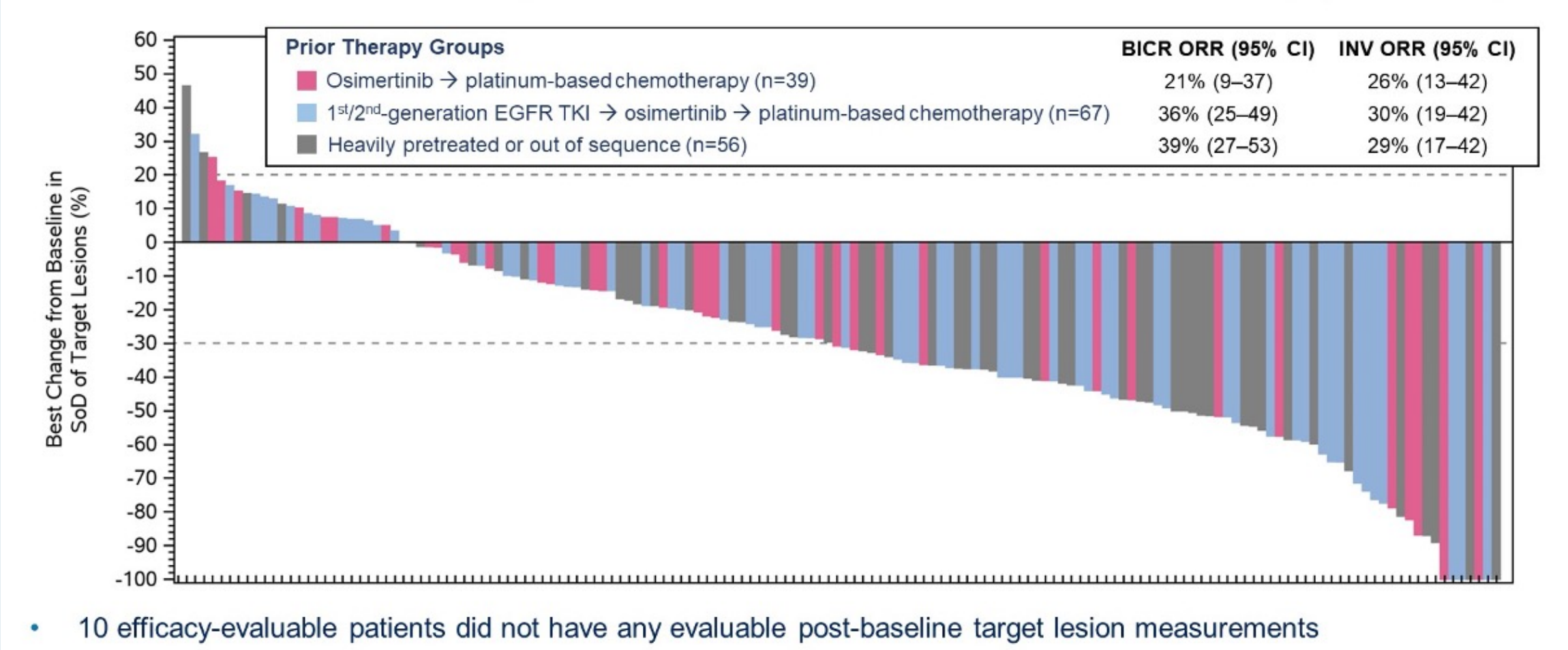
Endpoints

- 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.

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.

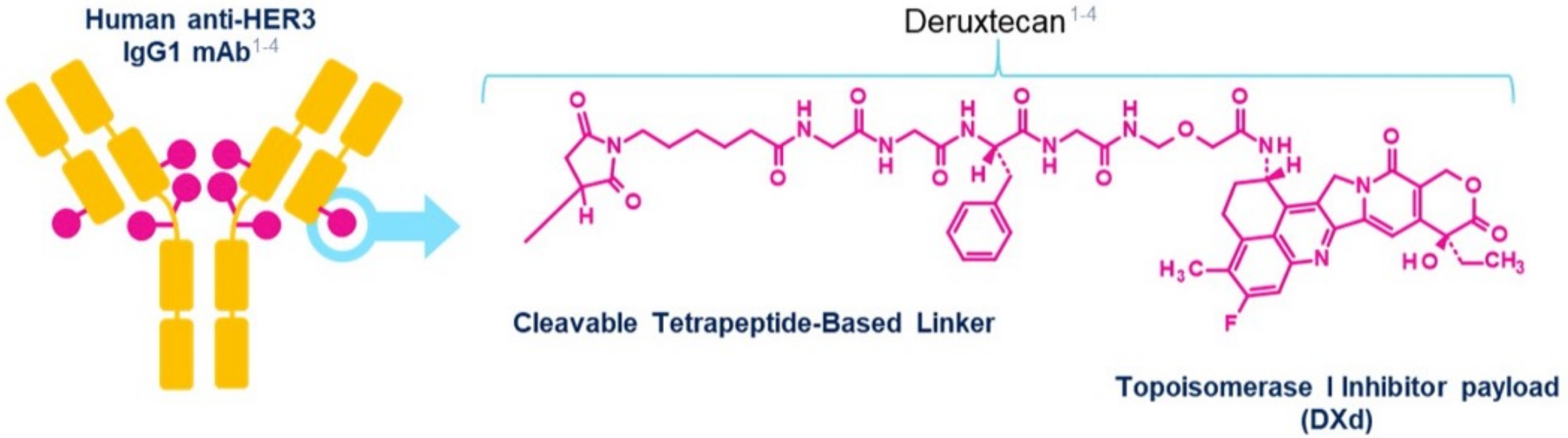
Efficacy and Safety of Patritumab Deruxtecan (HER3-DXd) in EGFR Inhibitor–Resistant, *EGFR*-Mutated Non–Small Cell Lung Cancer

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

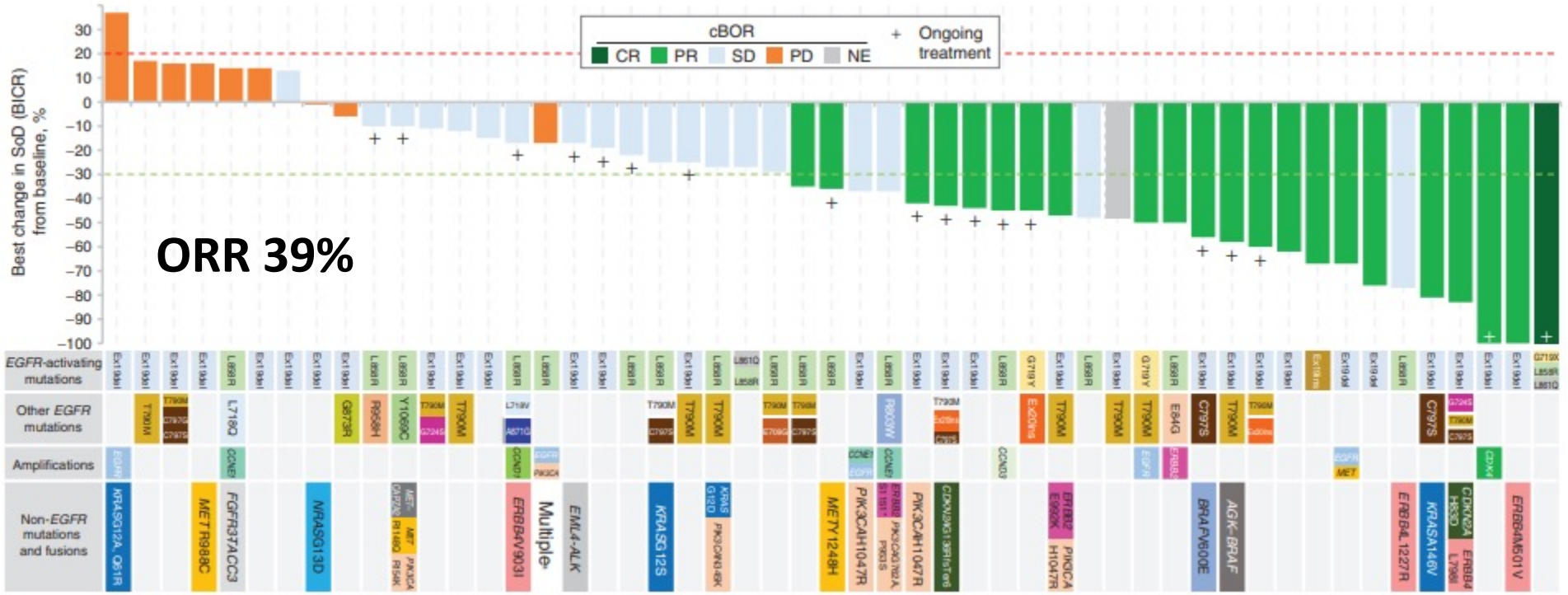
HER3-DXd is an antibody-drug conjugate with 3 components:

- 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.

Treatments post osimertinib: Patritumab deruxtecan



- Platinum-based chemotherapy is the standard of care post osimertinib.
- HER3-DxD is a HER3-directed antibody drug conjugate. HER3 is expressed in the majority of EGFR-mutant NSCLCs.
- After osimertinib and after chemotherapy, patritumab deruxtecan was active.
- It is now being assessed in further studies as monotherapy and in combination with osimertinib.

Memorial Sloan Kettering Cancer Center

Courtesy of Helena Yu, MD

Jänne Canc Disc 2022

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.

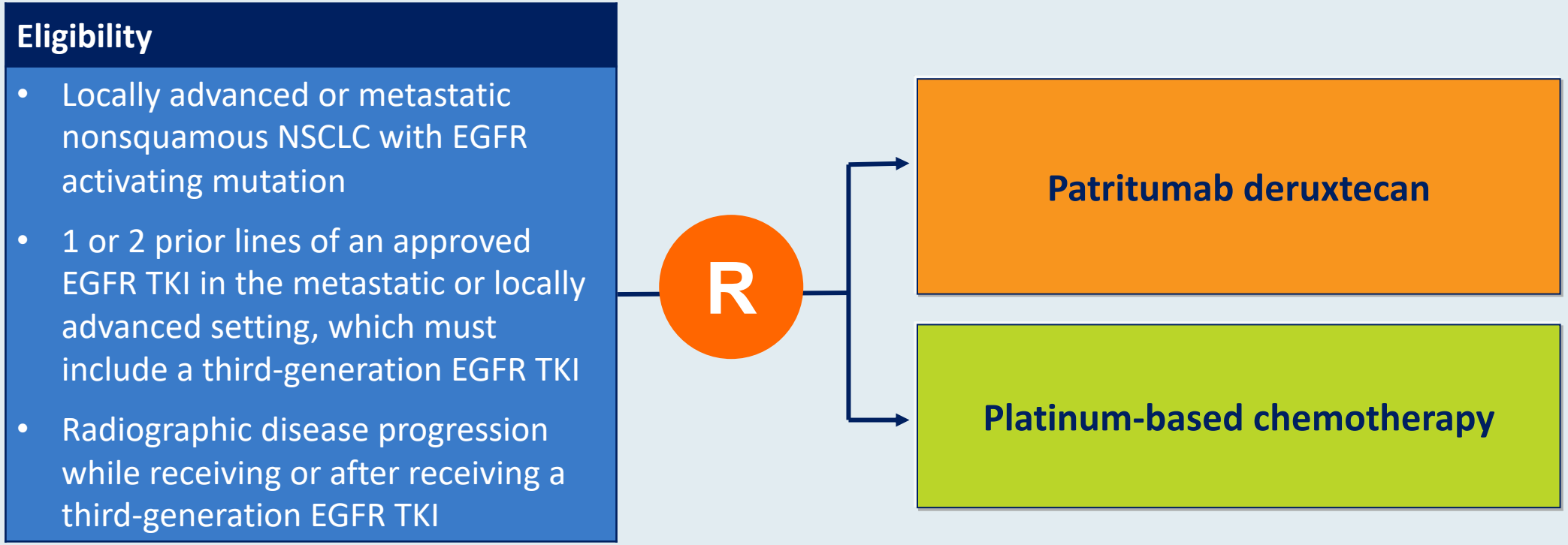
Select Grade ≥3 Treatment-Emergent Adverse Events (TEAEs)

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

Meet The Professor with Dr Neal

INTRODUCTION: Journal Club with Dr Neal – Part 1

MODULE 1: Adjuvant Therapy

MODULE 2: Locally Advanced Disease

MODULE 3: Exon 20 Insertions

MODULE 4: Metastatic Disease

MODULE 5: Journal Club with Dr Neal – Part 2

MODULE 6: Appendix of Key Publications

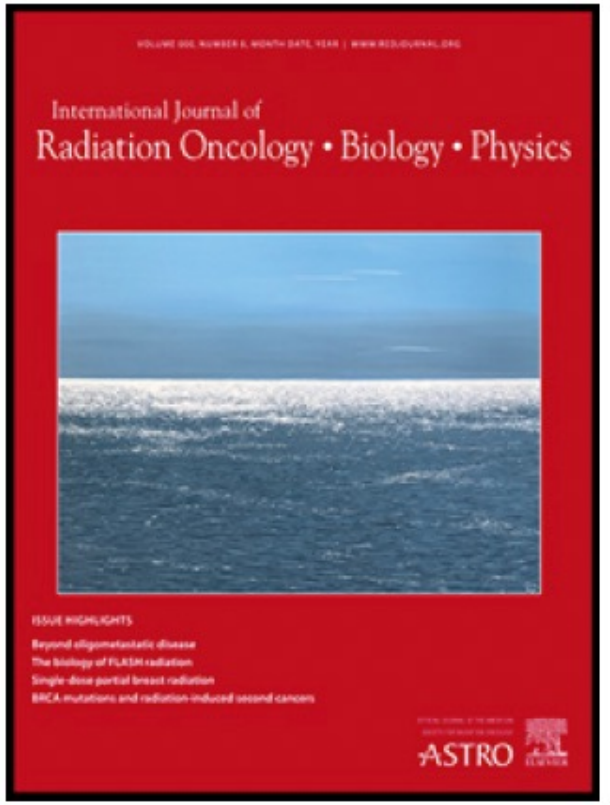
RTP
RESEARCH
TO PRACTICE

Int J Radiat Oncol Biol Phys 2022;[Online ahead of print].

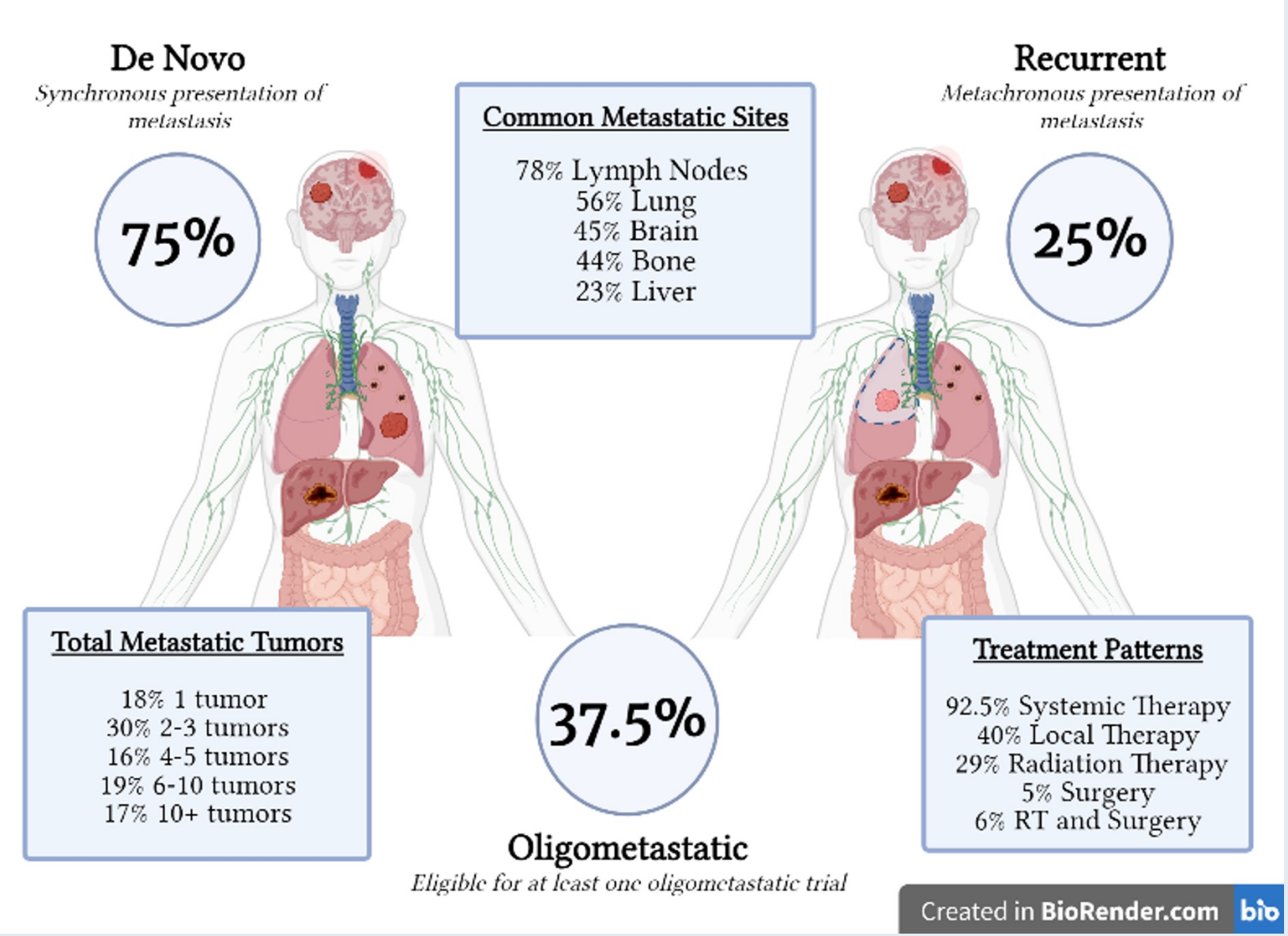
Journal Pre-proof

Characterization of Metastatic Non-Small Cell Lung Cancer and Oligometastatic Incidence in an Era of Changing Treatment Paradigms

Hyunsoo Joshua No MD, CMD , Neelufar Raja BS ,
Rie Von Eyben MS , Millie Das MD , Mohana Roy MD ,
Nathaniel Myall MD, MS , Joel Neal MD, PhD ,
Heather Wakelee MD , Alexander Chin MD, MBA ,
Maximilian Diehn MD, PhD , Billy Wiseman Loo MD, PhD ,
Daniel Tandel Chang MD , Erqi Liu Pollom MD, MS ,
Lucas Kas Vitzthum MD, MAS

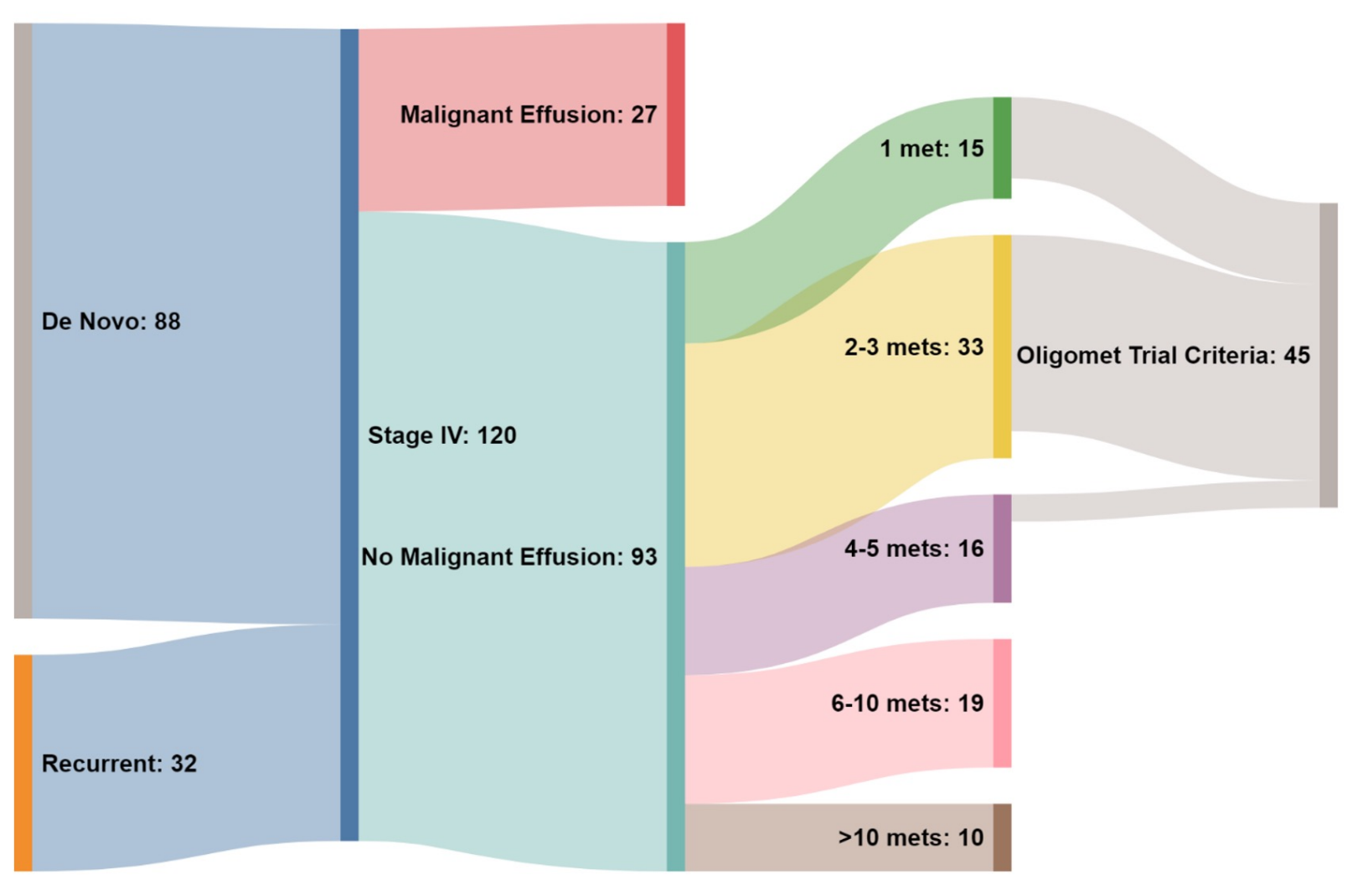


Initial Presentation of Metastatic NSCLC



No HJ et al. *Int J Radiat Oncol Biol Phys* 2022;[Online ahead of print].

Sankey Diagram Showing Numbers of Patients with Metastatic NSCLC Who Met Eligibility Criteria for the 4 Representative Oligometastatic Trials



No HJ et al. *Int J Radiat Oncol Biol Phys* 2022;[Online ahead of print].

JC JOURNAL CLUB RTP RESEARCH TO PRACTICE

Original Study

Clin Lung Cancer 2022;23(3):264-72.

Impact of Tumor Suppressor Gene Co-Mutations on Differential Response to EGFR TKI Therapy in *EGFR* L858R and Exon 19 Deletion Lung Cancer

Jessica A. Hellyer,[1] Maya N. White,[1] Rebecca M. Gardner,[2] Kristen Cunanan,[2] Sukhmani K. Padda,[1] Millie Das,[1,3] Kavitha Ramchandran,[1] Joel W. Neal,[1] Heather A. Wakelee[1]

JC JOURNAL CLUB RTP RESEARCH TO PRACTICE

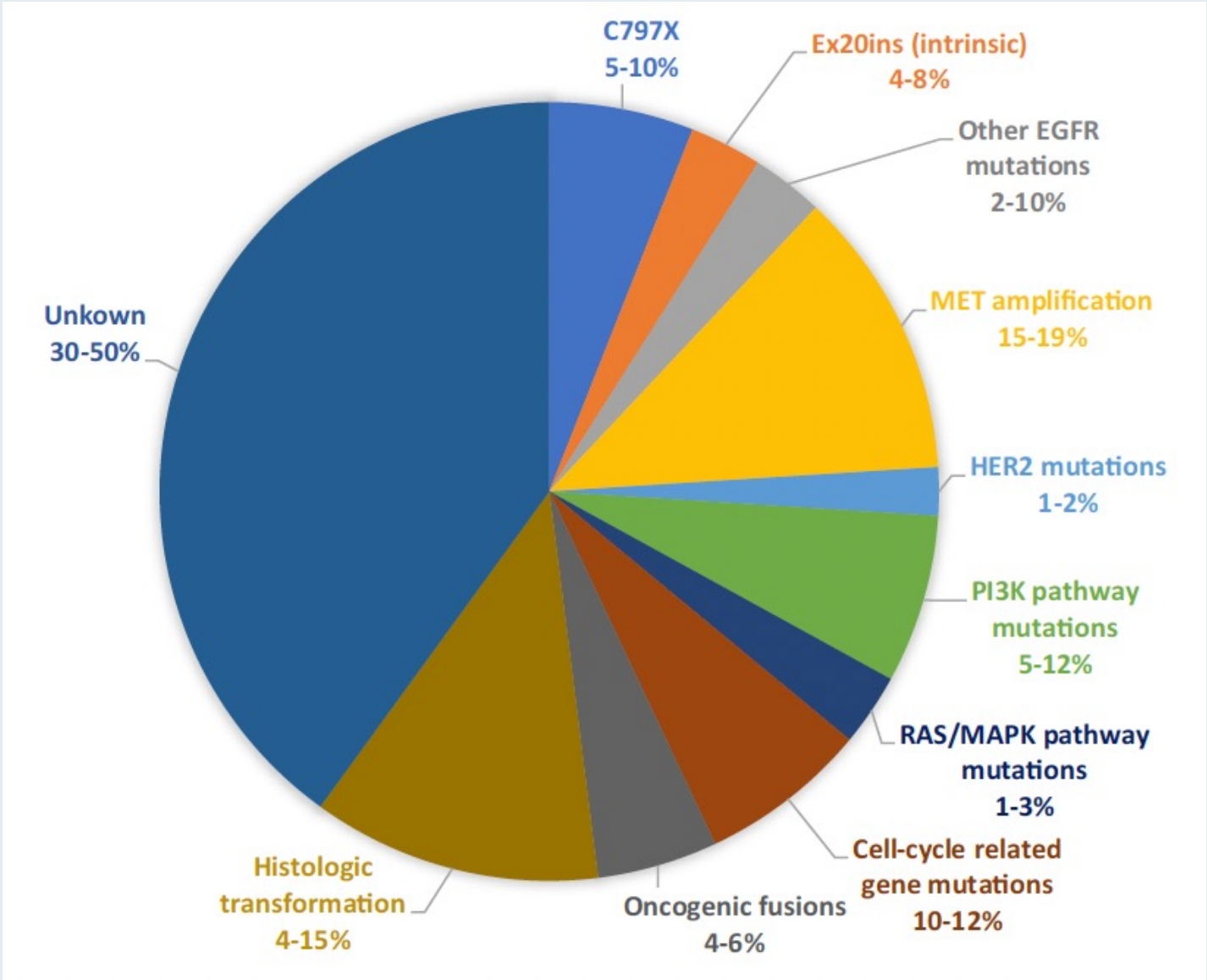
Drugs (2022) 82:649–662
https://doi.org/10.1007/s40265-022-01698-z

REVIEW ARTICLE

Targeting Acquired and Intrinsic Resistance Mechanisms in Epidermal Growth Factor Receptor Mutant Non-Small-Cell Lung Cancer

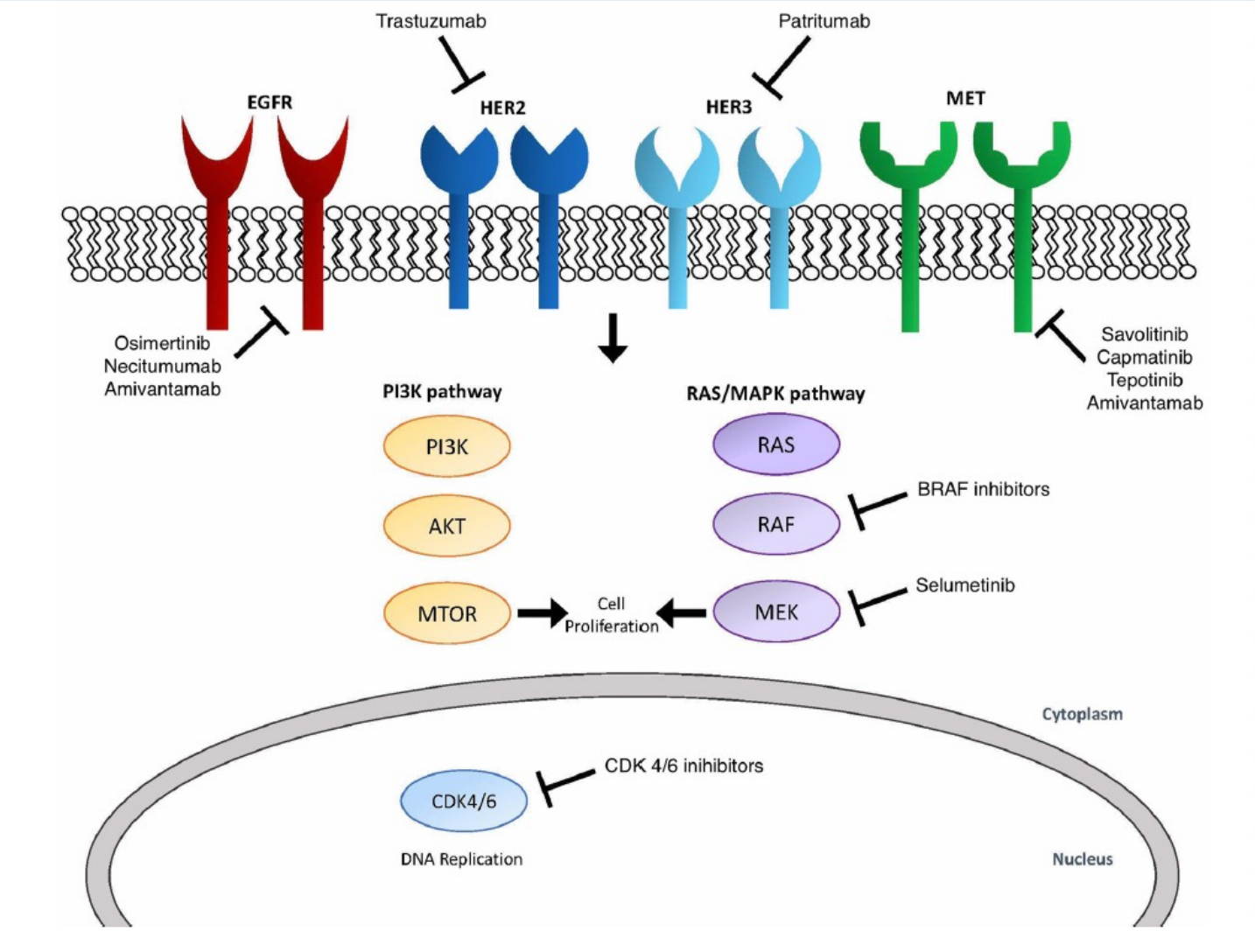
Manan P. Shah[1] · Joel W. Neal[1]

Resistance Mechanisms to First-Line Osimertinib



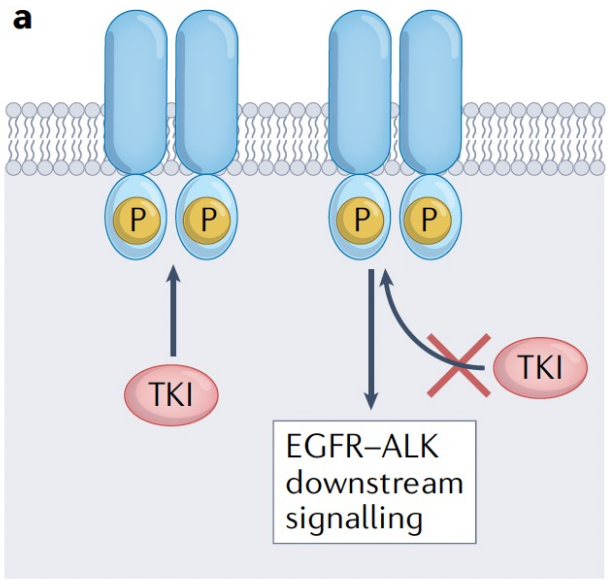
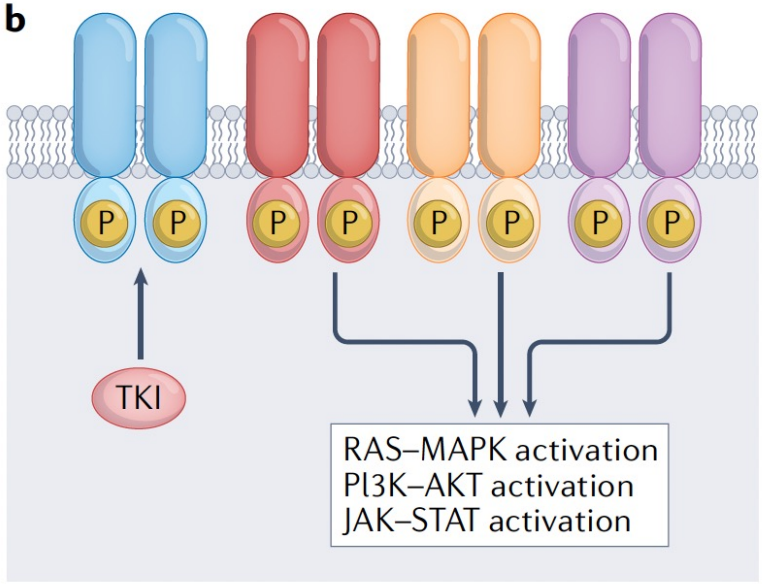
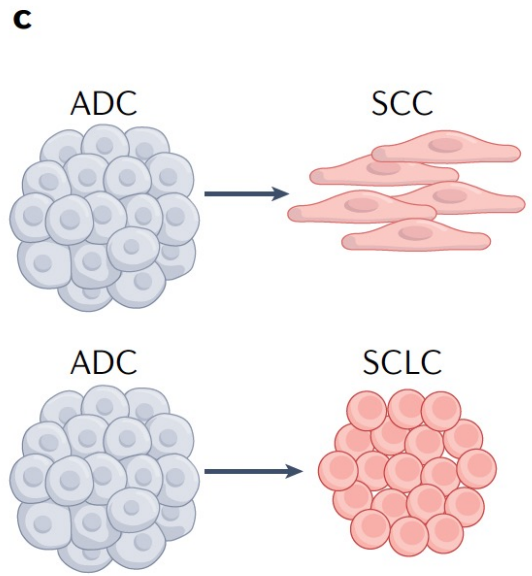
Shah MP, Neal JW. *Drugs* 2022;82:649-62.

Overview of Oncogenic Pathways and Examples of Targeted Inhibitors to Overcome Resistance to Treatment for NSCLC with EGFR Mutation



Shah MP, Neal JW. *Drugs* 2022;82:649-62.

Mechanisms of Acquired Resistance to Osimertinib

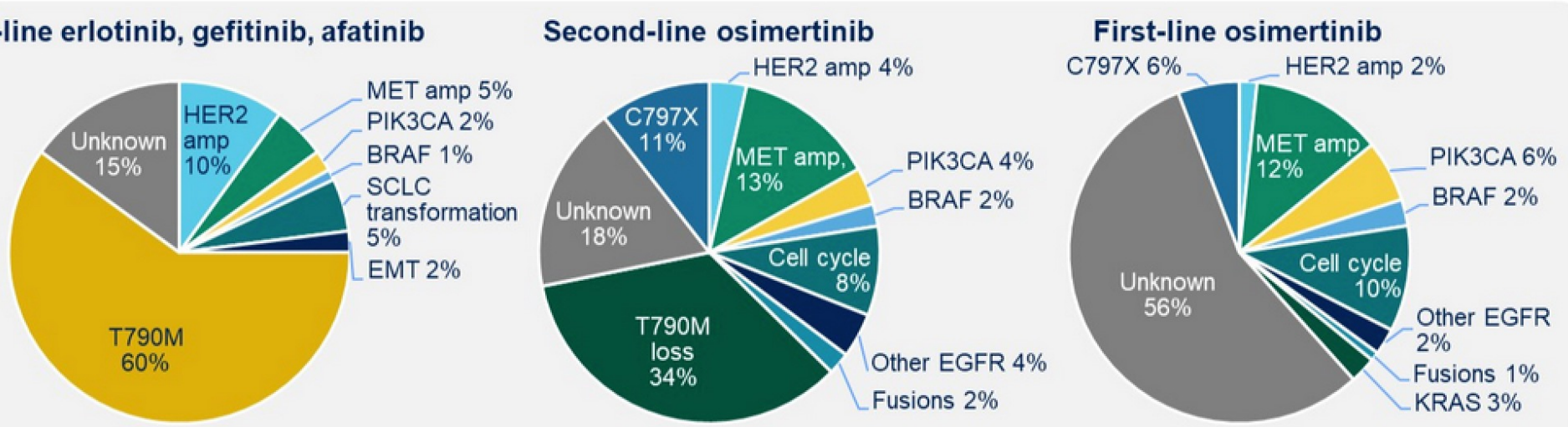
	Alterations that prevent inhibition of the target receptor tyrosine	Activation of bypass and/or downstream signalling pathways	Changes in tumour cell lineage such as transformation
			
Osimertinib resistance	*EGFR* C797X, G796X, L792X, G724S, L718Q	• Amplifications in *MET*, *HER2*, *KRAS*, *NRAS*, *YES1*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

Generalova *et al. J Patient Rep Outcomes* (2021) 5:91
https://doi.org/10.1186/s41687-021-00358-2

Journal of Patient-Reported Outcomes

SHORT REPORT

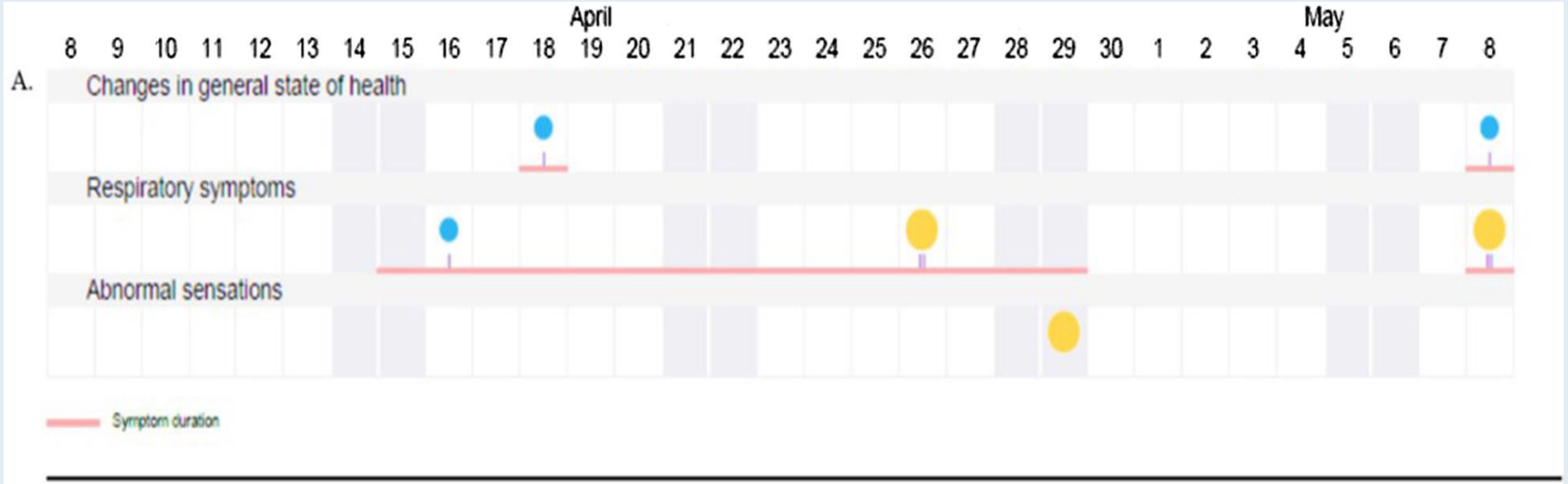
Open Access

Implementation of a cloud-based electronic patient-reported outcome (ePRO) platform in patients with advanced cancer

Olga Generalova[1†], Mohana Roy[1,2*†], Evan Hall[3,4], Sumit A. Shah[1,2], Kristen Cunanan[5], Touran Fardeen[6], Brianna Velazquez[1], Gilbert Chu[1,2], Bianca Bruzzone[6], Anna Cabot[6], George A. Fisher[1,2], Sandy Srinivas[1,2], Alice C. Fan[1,2], Sigurdis Haraldsdottir[1,2], Heather A. Wakelee[1,2], Joel W. Neal[1,2], Sukhmani K. Padda[1,2], Tyler Johnson[1,2], Gregory M. Heestand[1,2], Robert W. Hsieh[1,2] and Kavitha Ramchandran[1,2]

Visualization of Symptoms: Calendar Format for Symptom Type, Severity and Duration, and Symptom Report Summary

A.



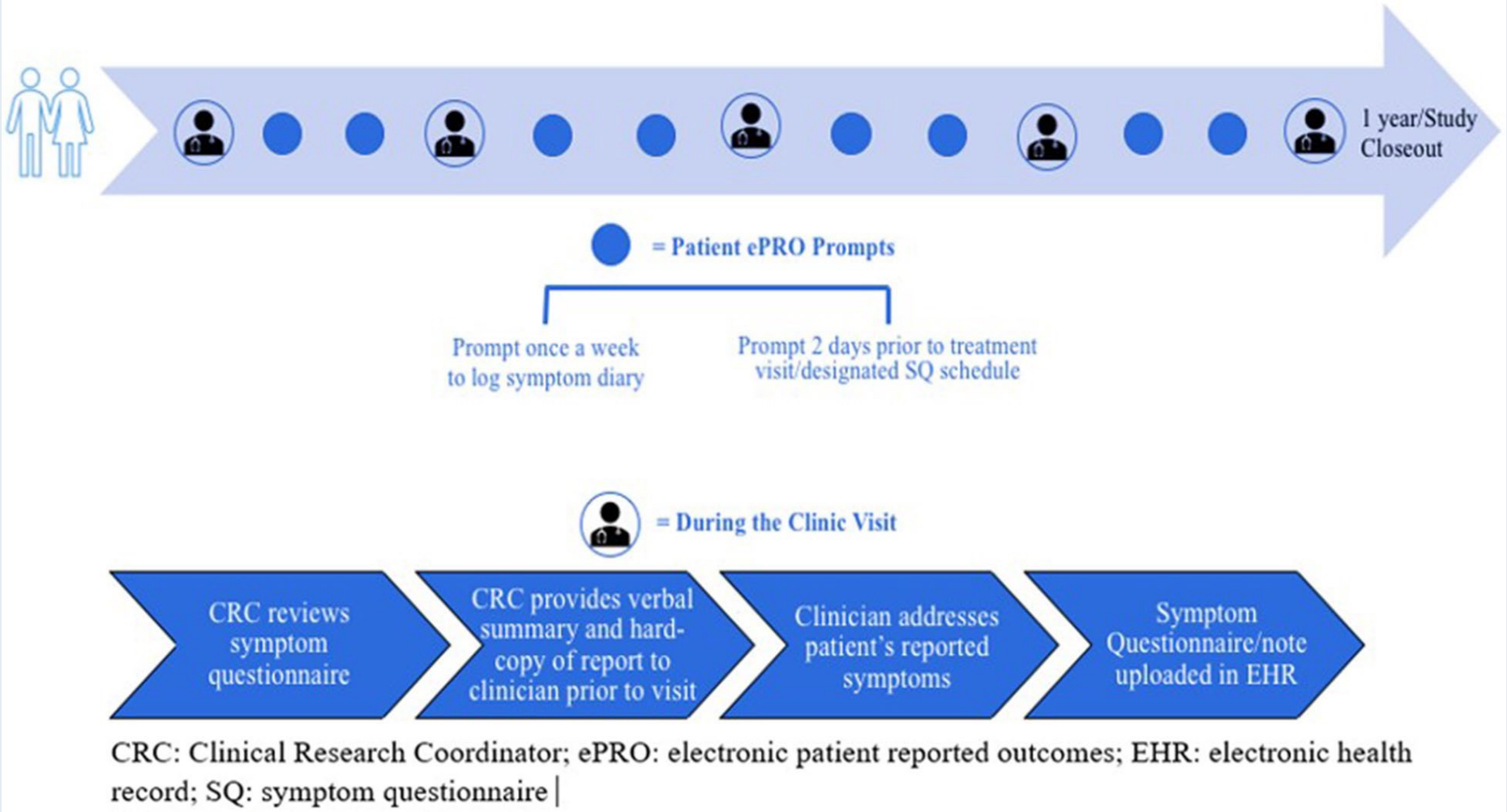
B. **Symptom report summary**

Symptom	Grade	Max	Min	Average	Symptom days (of 30)	Trend
Changes in general state of health	Mild	1	1	1 (ECOG)	-	−
Distress	Mild	2.0	2.0	2.0 (ESAS)	-	−
Weight	No grading	-	-	-	-	–
Respiratory symptoms	Moderate	2	1	1.7 (CTCAE)	16	↑
Abnormal sensations	No grading	-	-	-	Symptom is persistent	−

Generalova O et al. *J Patient Rep Outcomes* 2021;5(1):91.

RTP RESEARCH TO PRACTICE

Schema of ePRO Intervention: Overall Schema of the ePRO Intervention with Symptom Logs, Questionnaires, and In-Clinic Review



CRC: Clinical Research Coordinator; ePRO: electronic patient reported outcomes; EHR: electronic health record; SQ: symptom questionnaire

Generalova O et al. *J Patient Rep Outcomes* 2021;5(1):91.

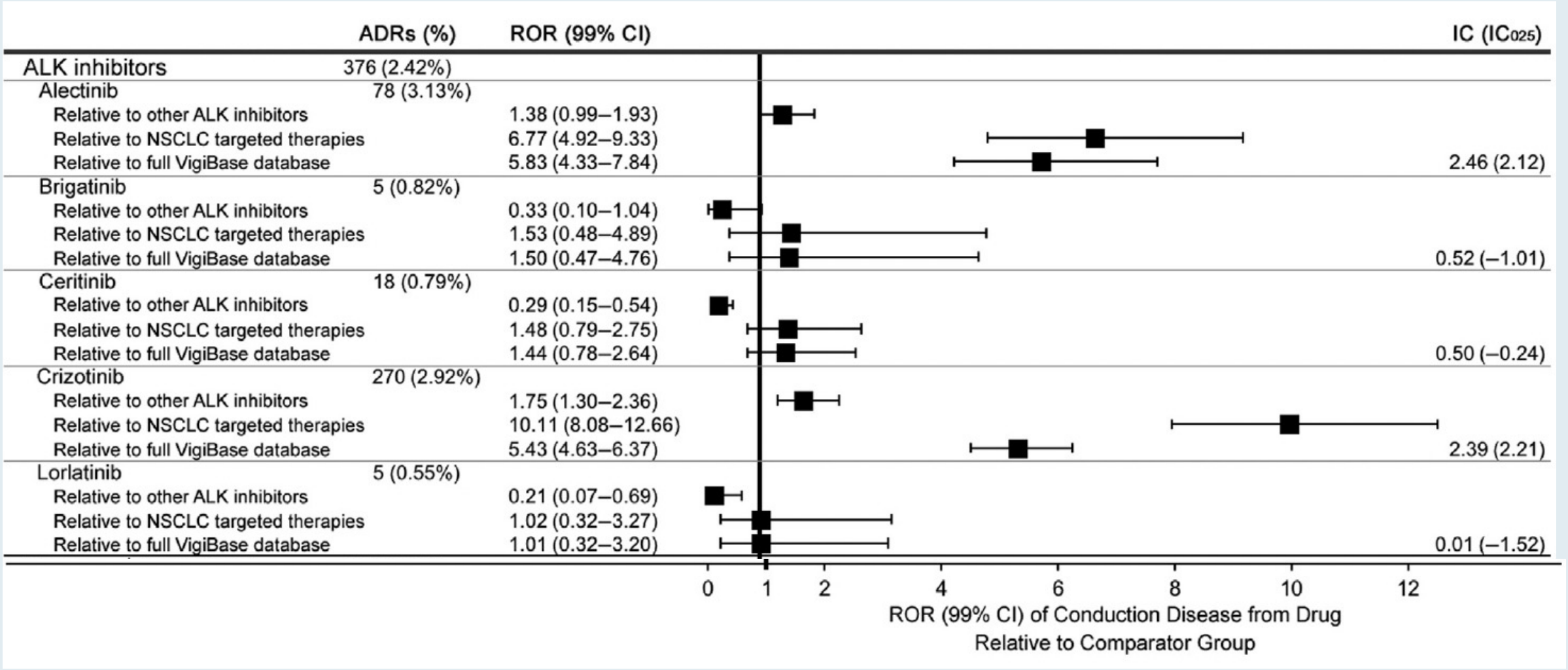
J Thorac Oncol 2021;16(12):2029-39.

ORIGINAL ARTICLE

Pharmacovigilance Analysis of Cardiac Toxicities Associated With Targeted Therapies for Metastatic NSCLC

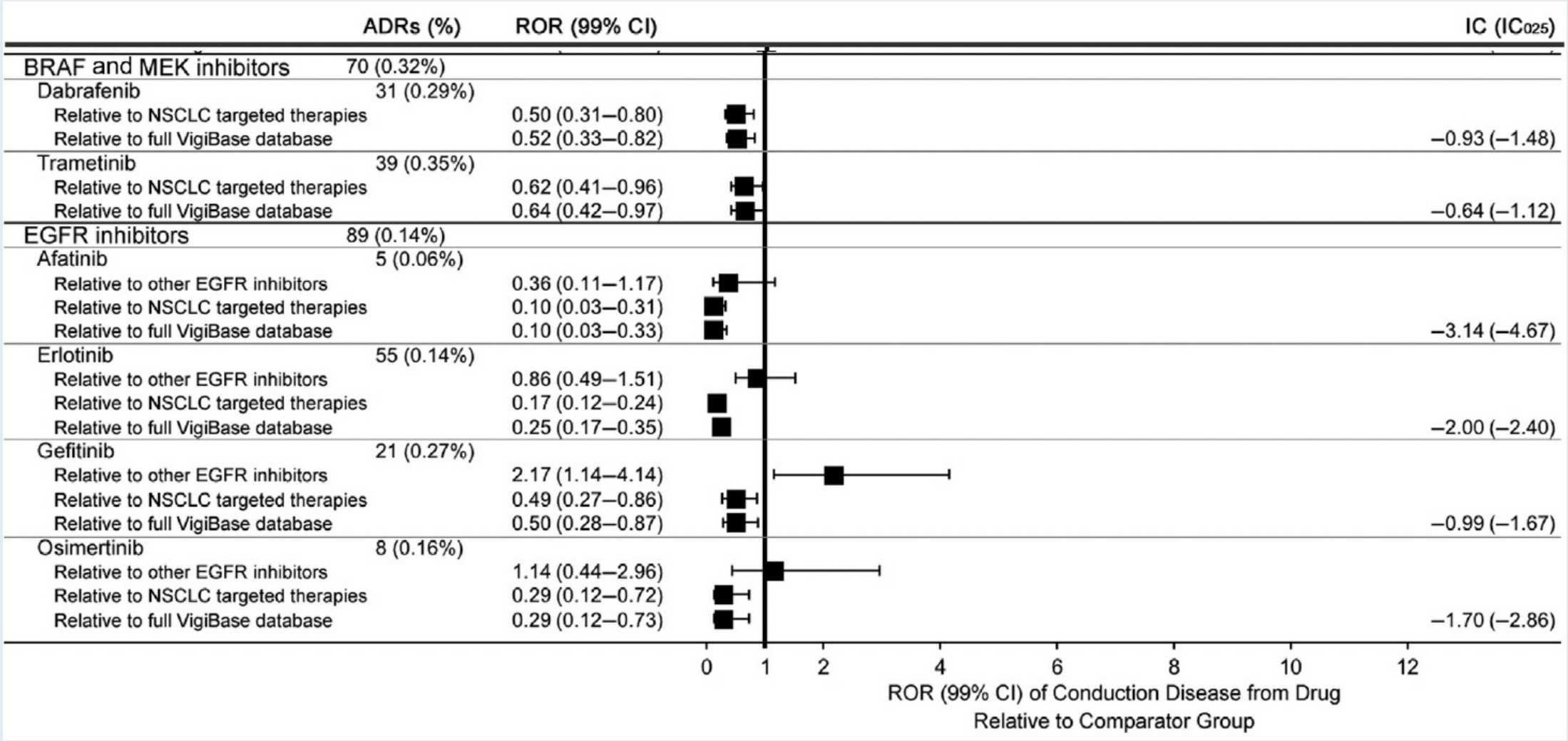
Sarah Waliany, MD, MS,[a] Han Zhu, MD,[a,b,c] Heather Wakelee, MD,[a,d,e] Sukhmani K. Padda, MD,[a,d,e] Millie Das, MD,[a,d,e,f] Kavitha Ramchandran, MD,[a,d,e] Nathaniel J. Myall, MD,[a,d,e] Thomas Chen, MD, PhD,[g] Ronald M. Witteles, MD,[a,b] Joel W. Neal, MD, PhD[a,d,e,*]

Assessment of Odds of Conduction Disease Associated with NSCLC Targeted Therapies: ALK Inhibitors



Waliany S et al. *J Thorac Oncol* 2021;16(12):2029-39.

Assessment of Odds of Conduction Disease Associated with NSCLC Targeted Therapies: BRAF, MEK and EGFR Inhibitors



Waliany S et al. *J Thorac Oncol* 2021;16(12):2029-39.

Meet The Professor with Dr Neal

INTRODUCTION: Journal Club with Dr Neal – Part 1

MODULE 1: Adjuvant Therapy

MODULE 2: Locally Advanced Disease

MODULE 3: Exon 20 Insertions

MODULE 4: Metastatic Disease

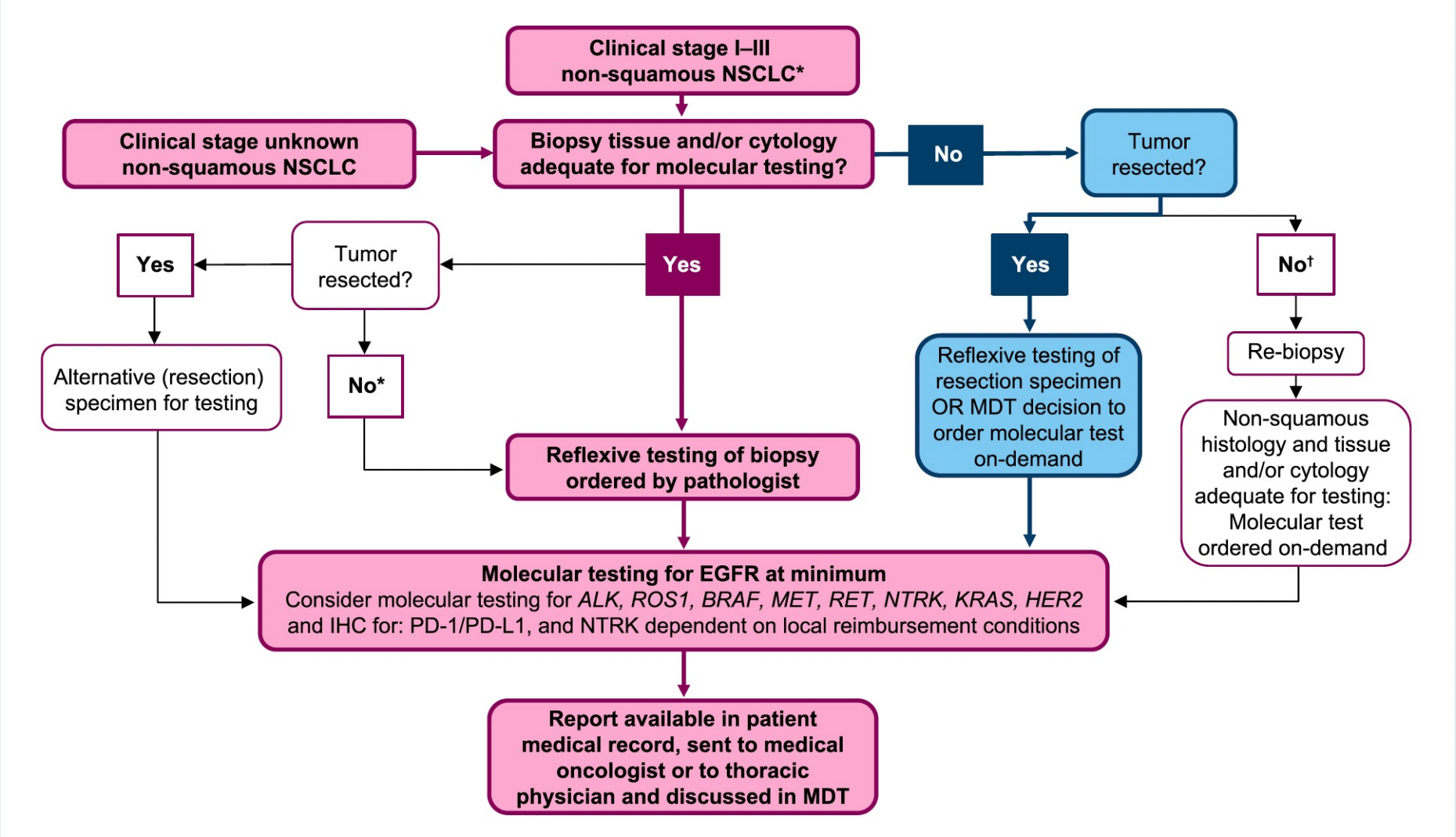
MODULE 5: Journal Club with Dr Neal – Part 2

MODULE 6: Appendix of Key Publications

RTP
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

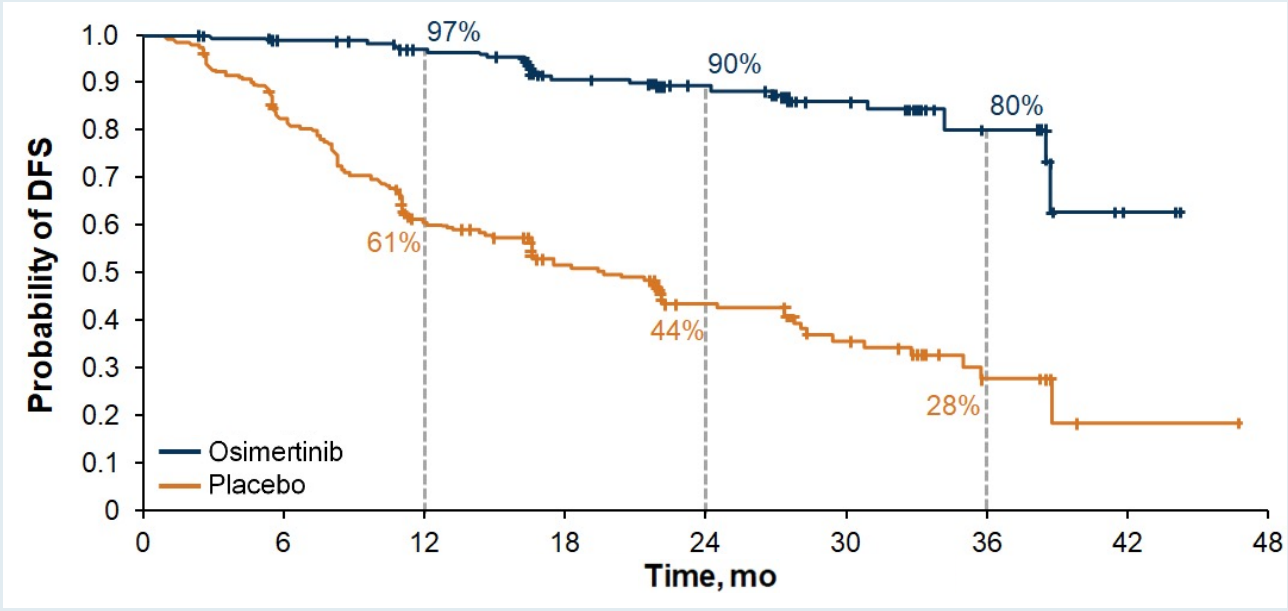
Osimertinib in Resected *EGFR*-Mutated Non–Small-Cell Lung Cancer

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

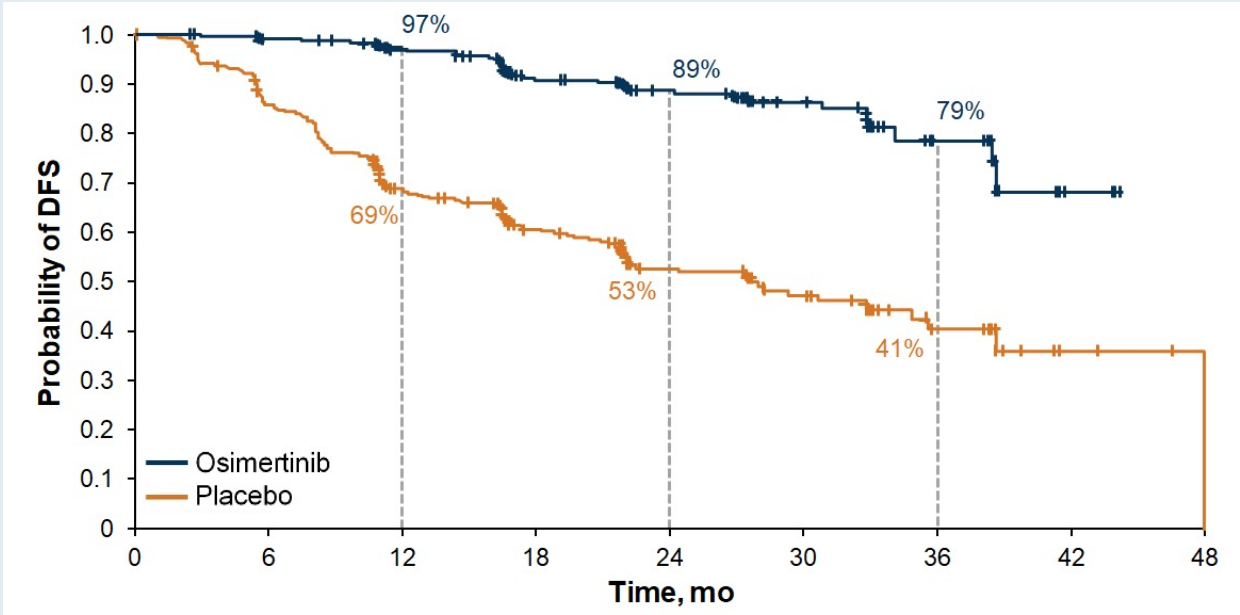
Disease-Free Survival (DFS)

Stage II to IIIA disease



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

Stage IB to IIIA disease

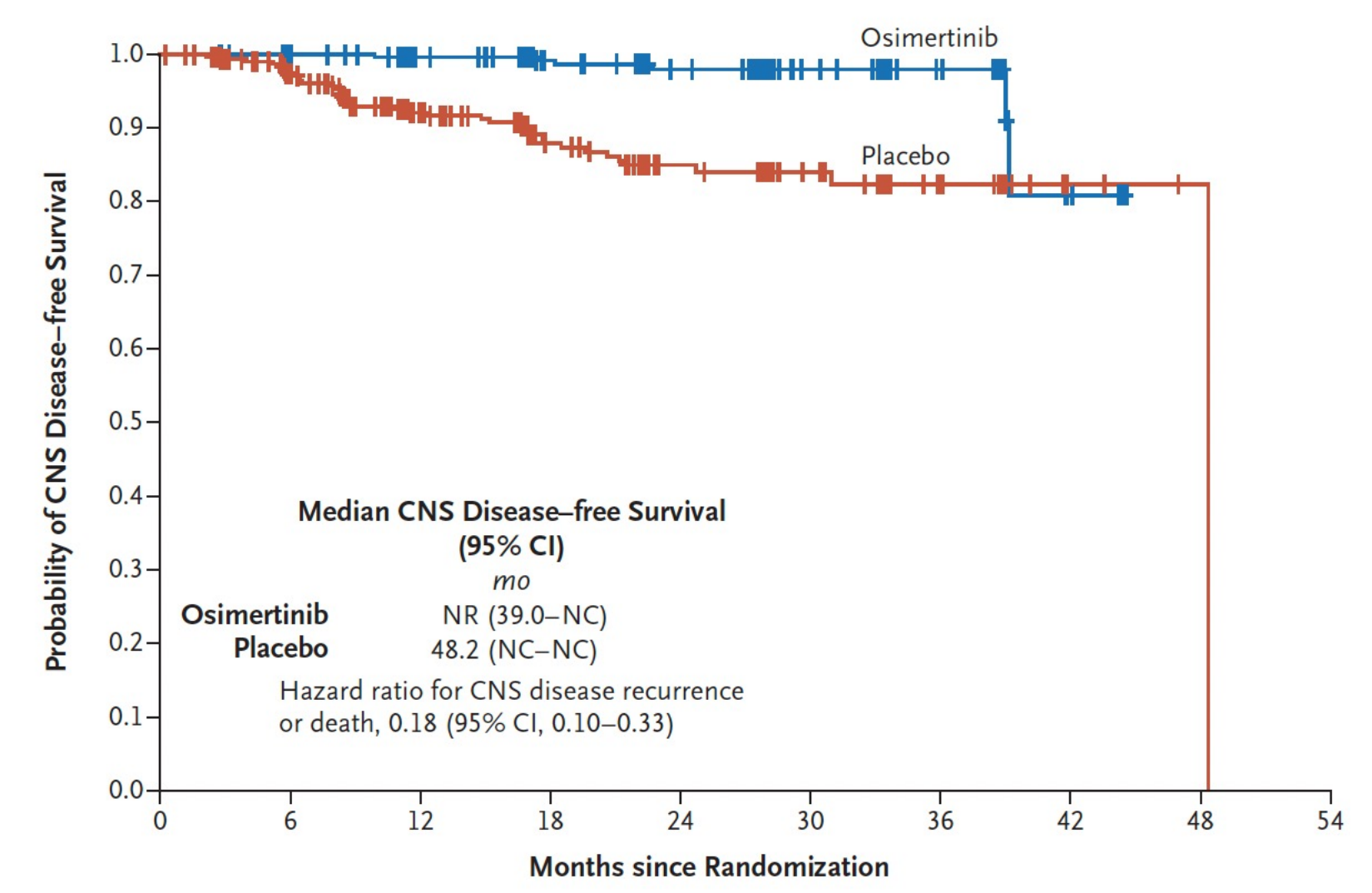


HR = 0.20; $p < .001$ → 80% reduction in risk of disease recurrence or death

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.

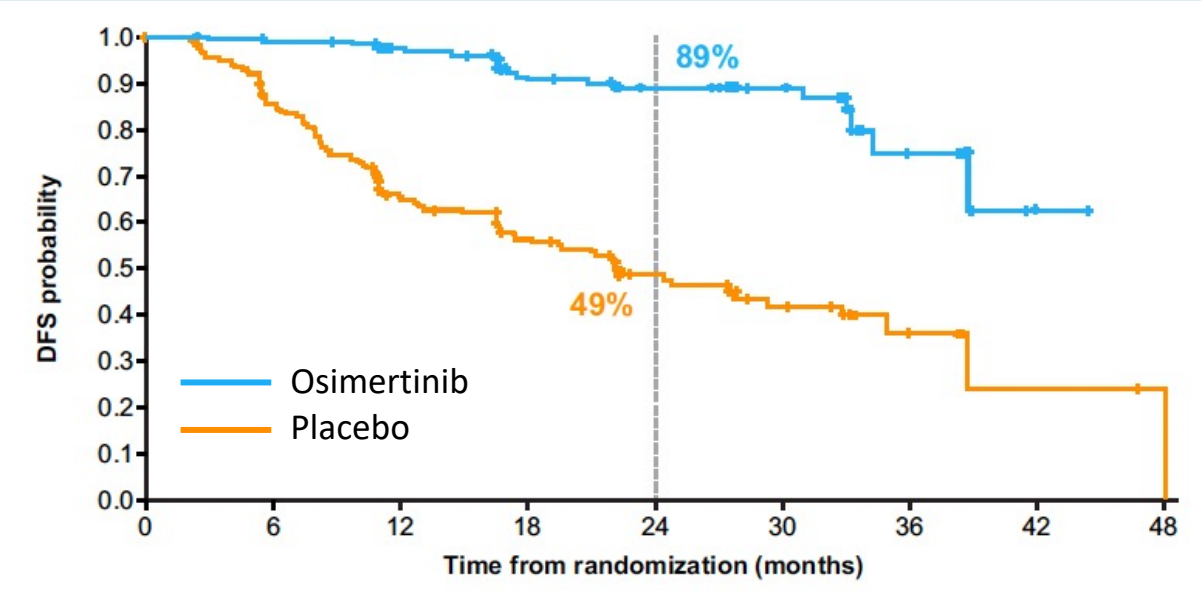
IASLC

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

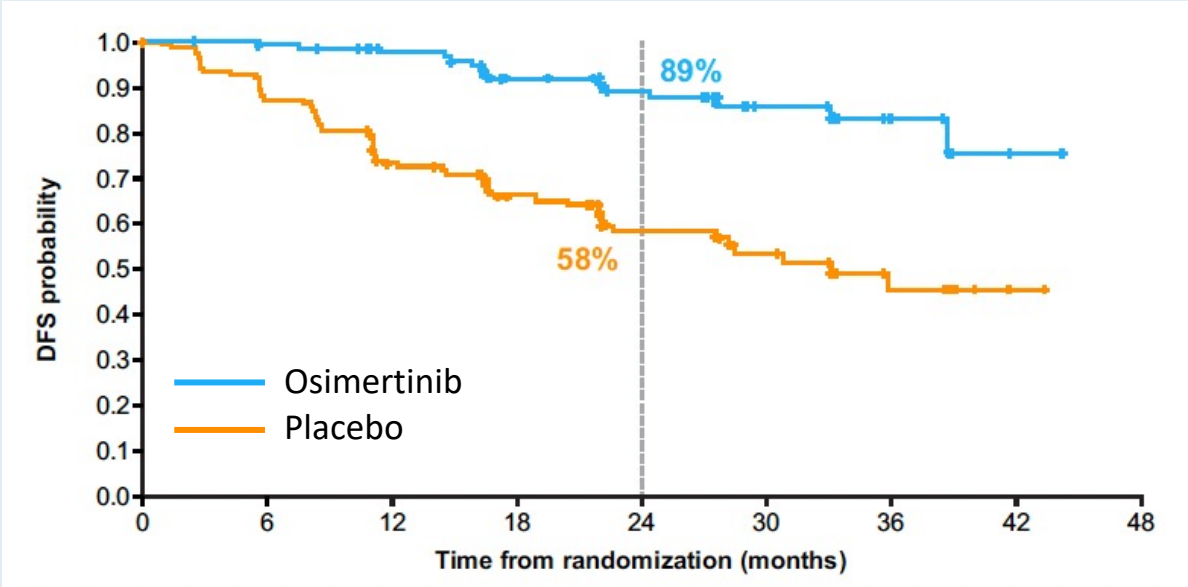
Yi-Long Wu, MD,[a,*] Thomas John, PhD,[b] Christian Grohe, MD,[c] Margarita Majem, MD, PhD,[d] Jonathan W. Goldman, MD,[e] Sang-We Kim, MD, PhD,[f] Terufumi Kato, MD,[g] Konstantin Laktionov, PhD,[h] Huu Vinh Vu, MD, PhD,[i] Zhijie Wang, MD,[j] Shun Lu, MD,[k] Kye Young Lee, MD, PhD,[l] Charuwan Akewanlop,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



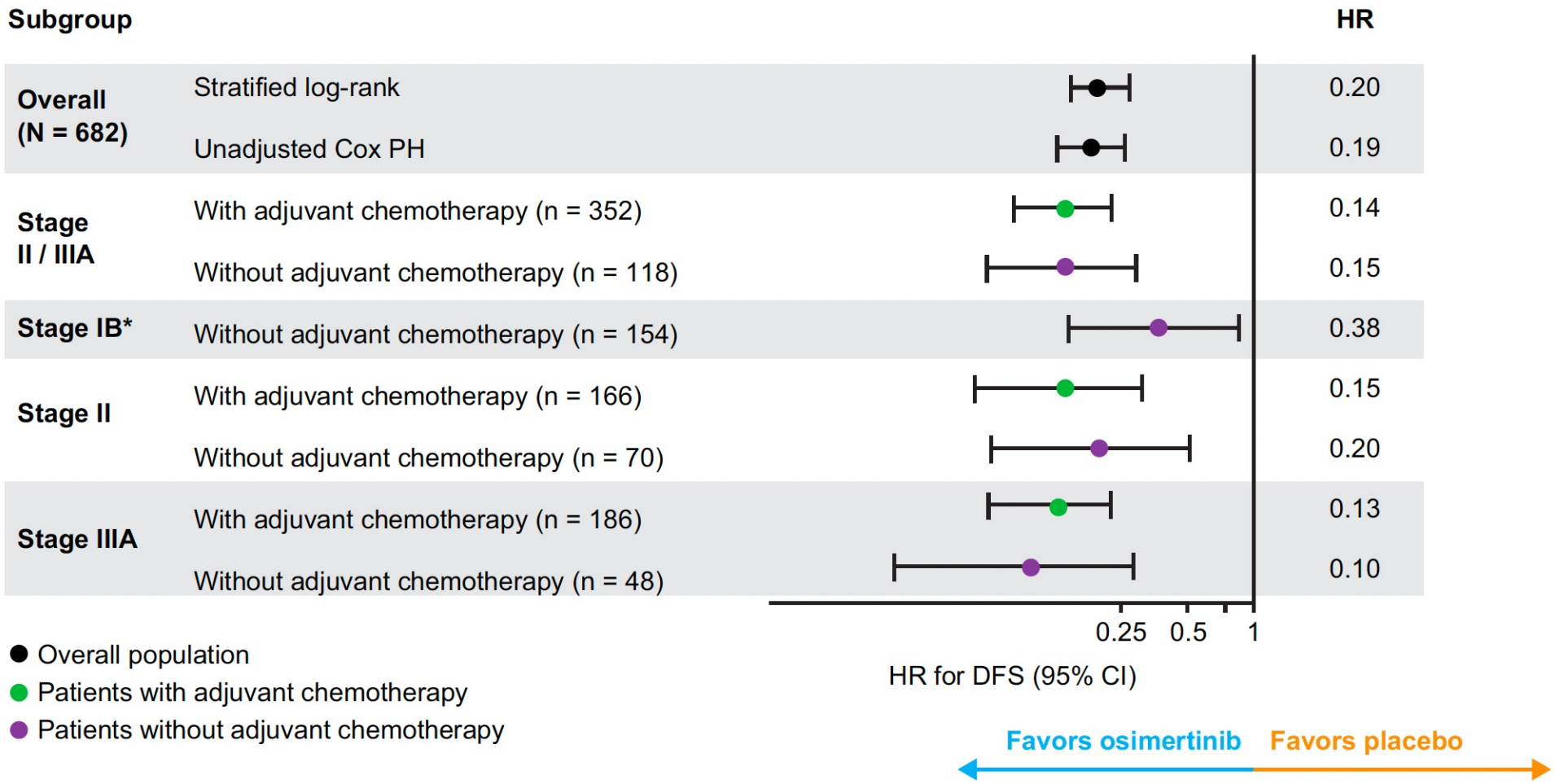
Without adjuvant chemotherapy



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.

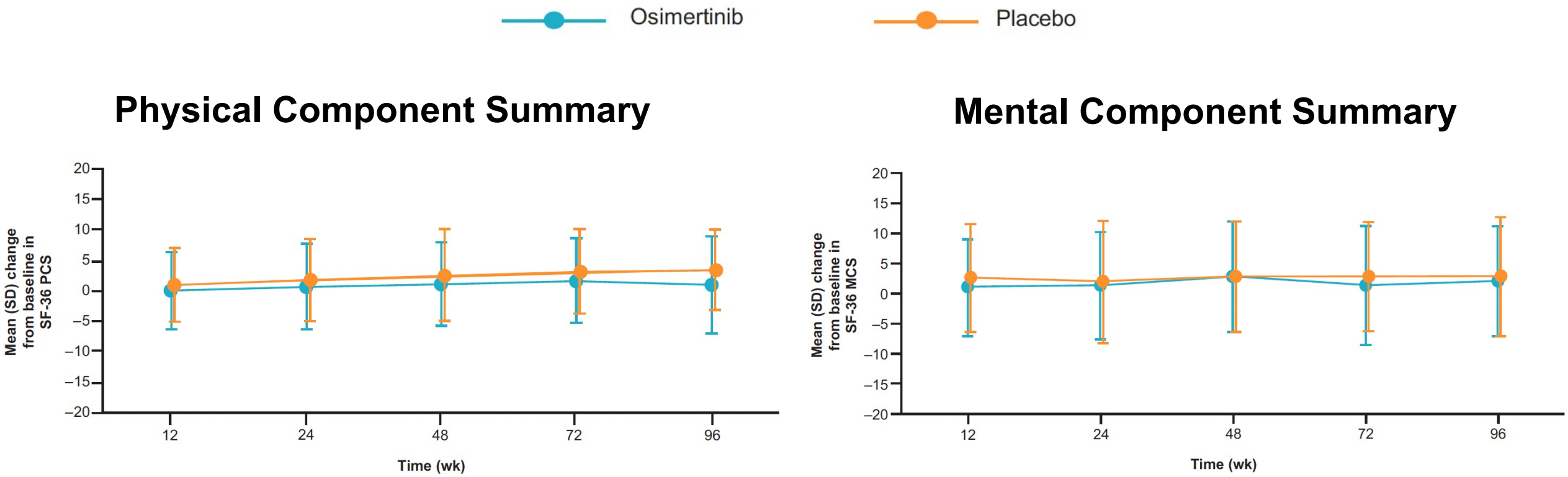
CLINICAL CANCER RESEARCH | CLINICAL TRIALS: TARGETED THERAPY

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."

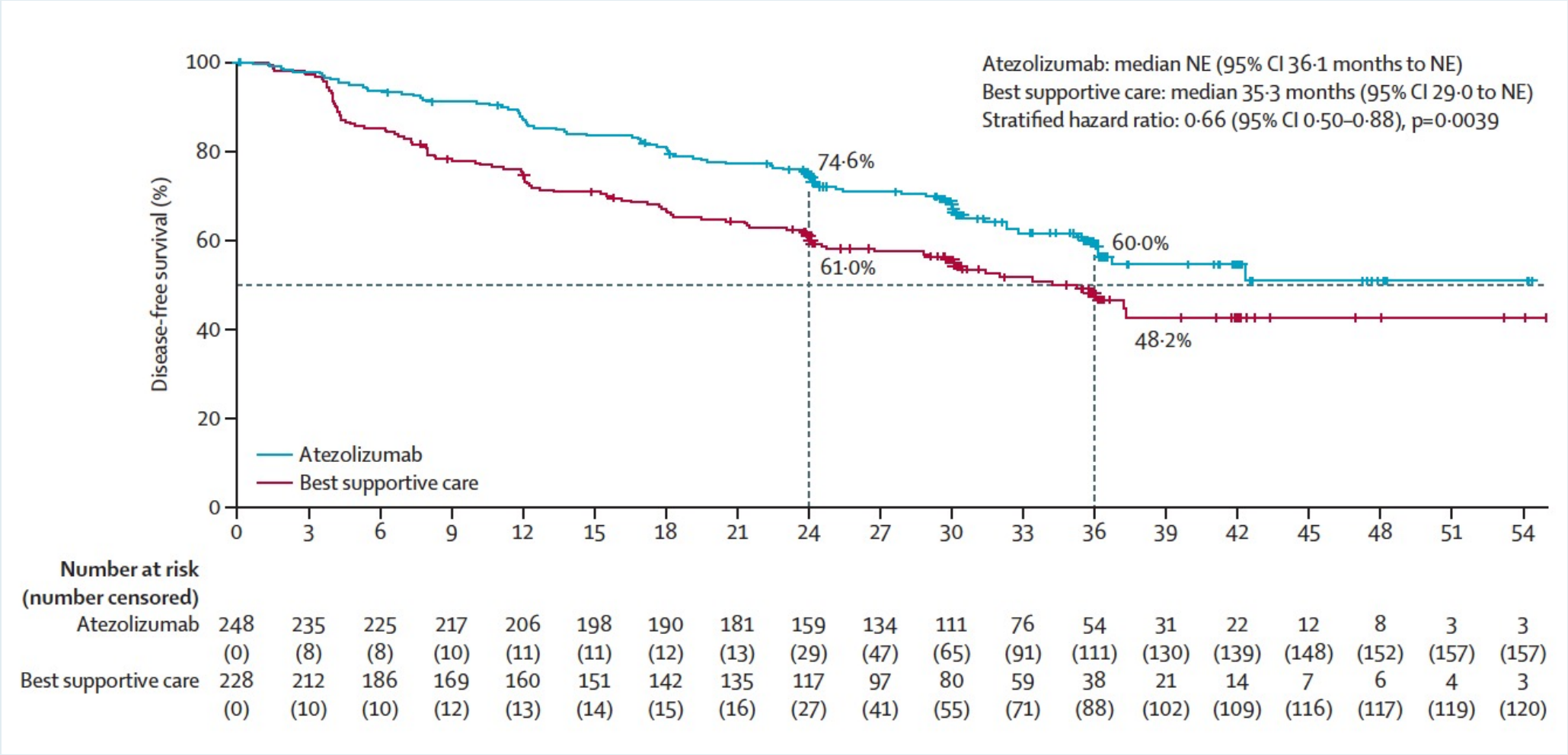
https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-atezolizumab-adjuvant-treatment-non-small-cell-lung-cancer

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**

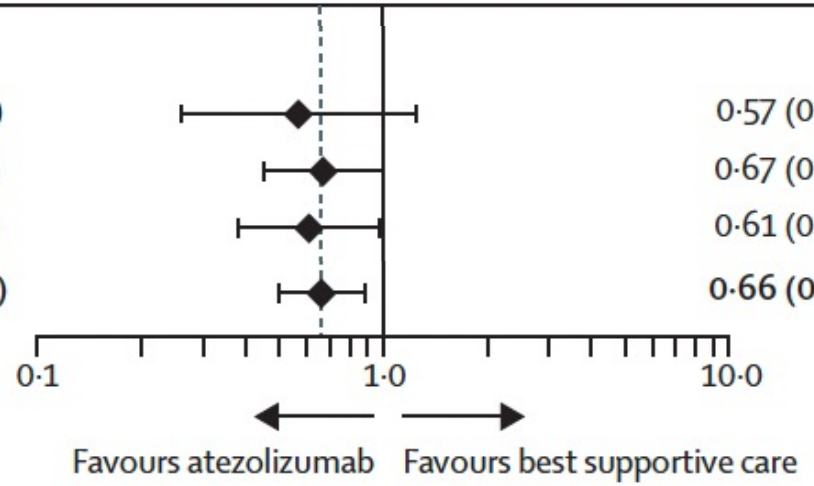
IMpower010 Primary Endpoint: Disease-Free Survival in the PD-L1 ≥1% Tumor Cells Stage II-IIIA Population



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

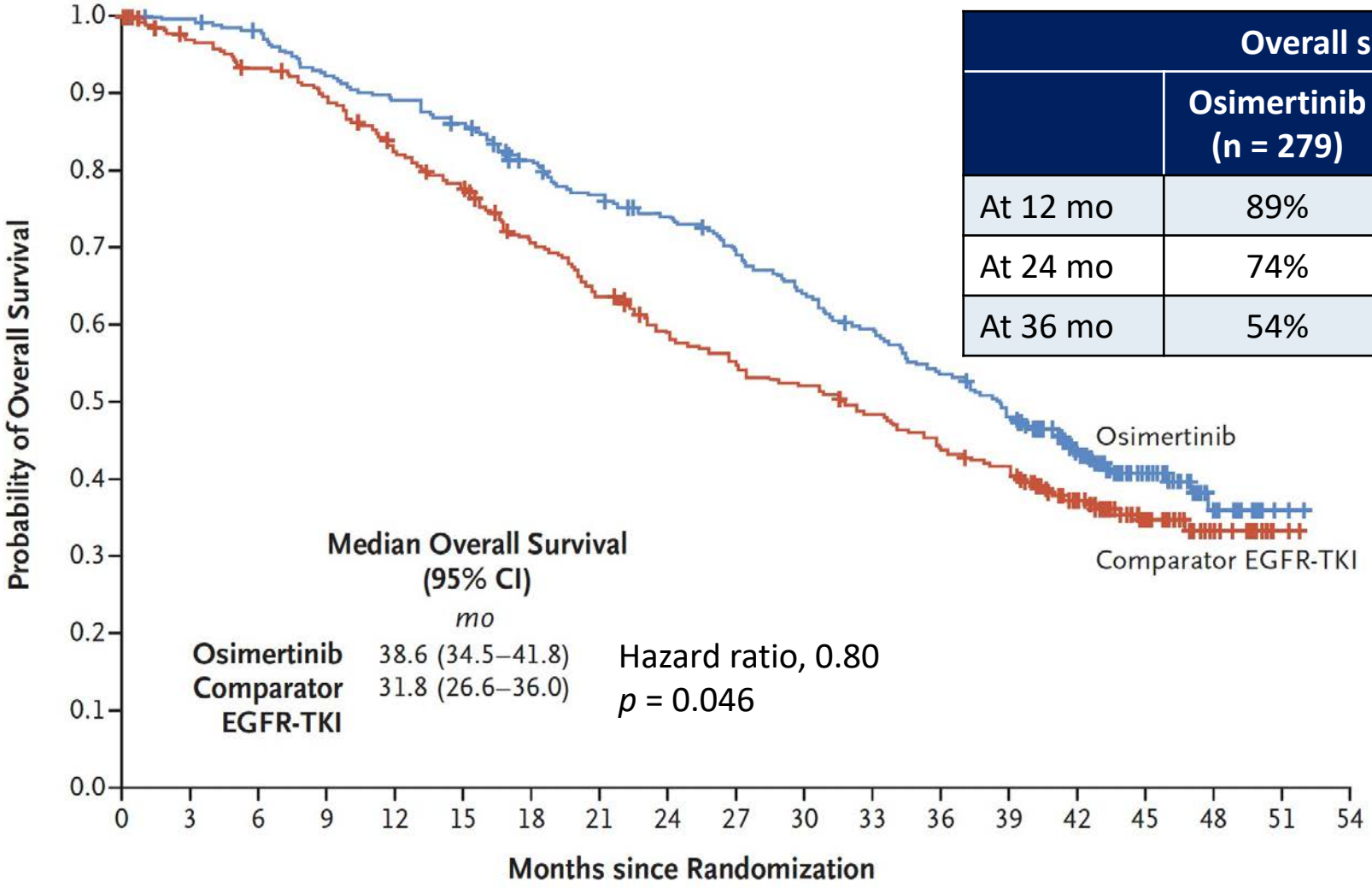
The NEW ENGLAND JOURNAL of MEDICINE

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.

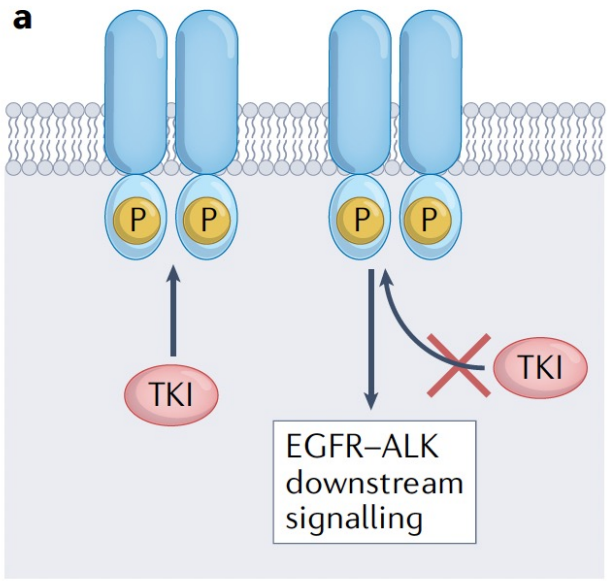
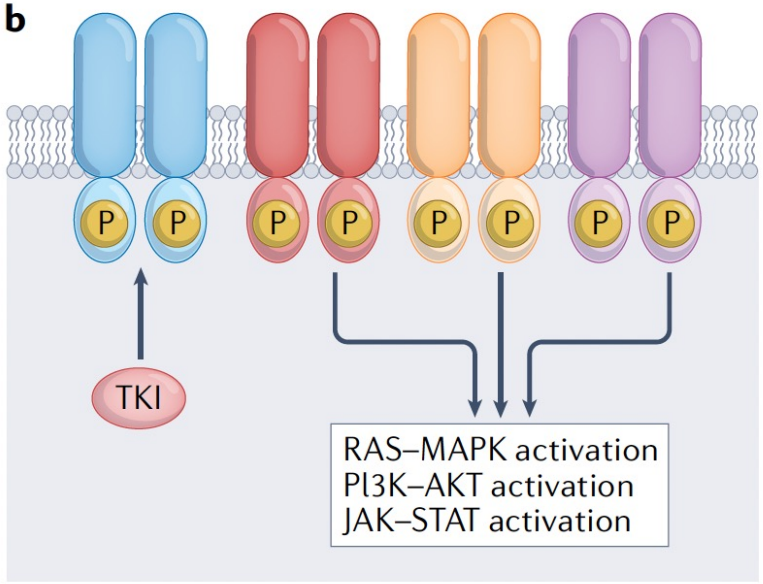
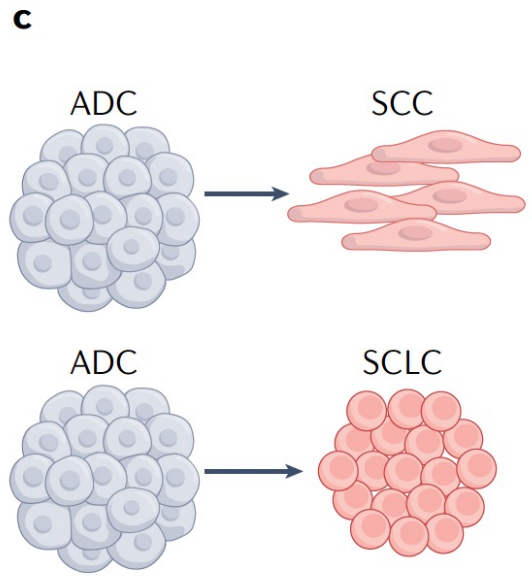
Select Ongoing Phase III Studies of First-Line Therapy for Patients with Metastatic NSCLC and Activating EGFR Mutations

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

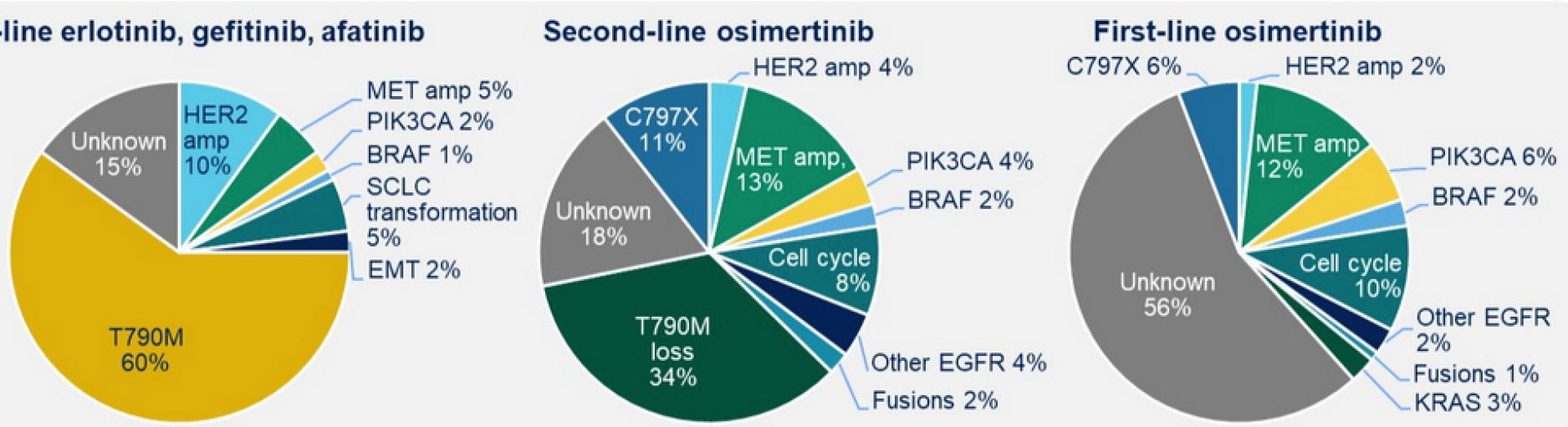
	Alterations that prevent inhibition of the target receptor tyrosine	Activation of bypass and/or downstream signalling pathways	Changes in tumour cell lineage such as transformation
			
Osimertinib resistance	*EGFR* C797X, G796X, L792X, G724S, L718Q	• Amplifications in *MET*, *HER2*, *KRAS*, *NRAS*, *YES1*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

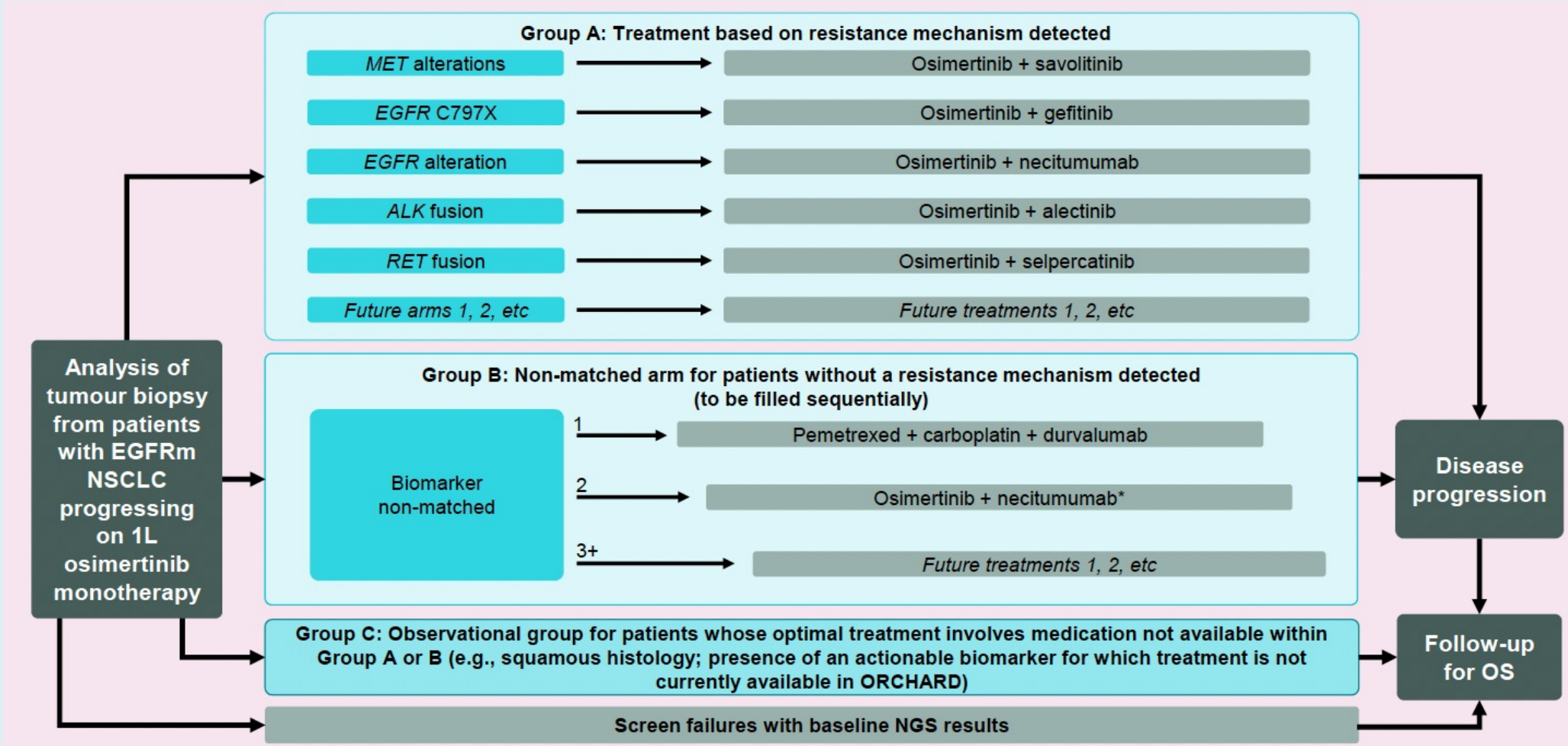
Janne PA et al. ASCO 2021;Abstract 9007.

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.

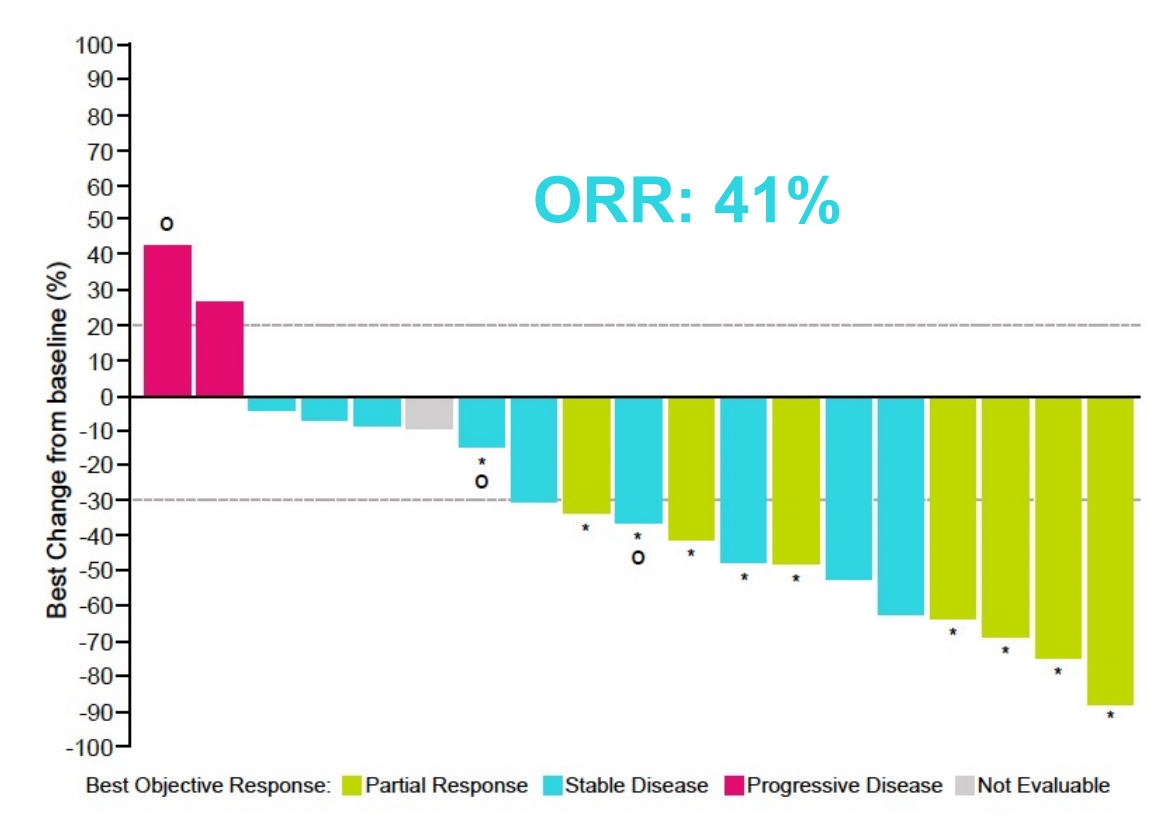
ORCHARD Study Design

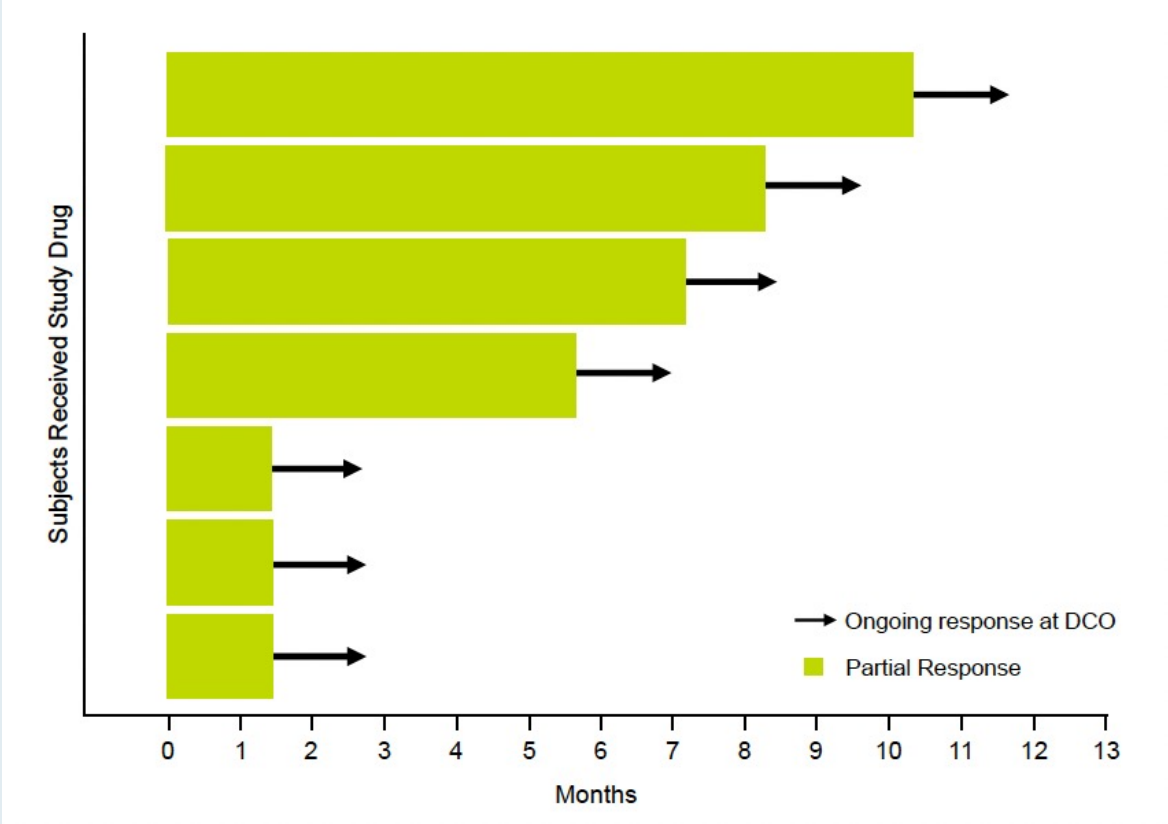


Group A: Patients who are positive for protocol-determined biomarker; Group B: patients without an available protocol-determined biomarker match, allocated sequentially, once first cohort cap has been reached, the next cohort allocation will begin; Group C: observational cohort, treated in accordance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

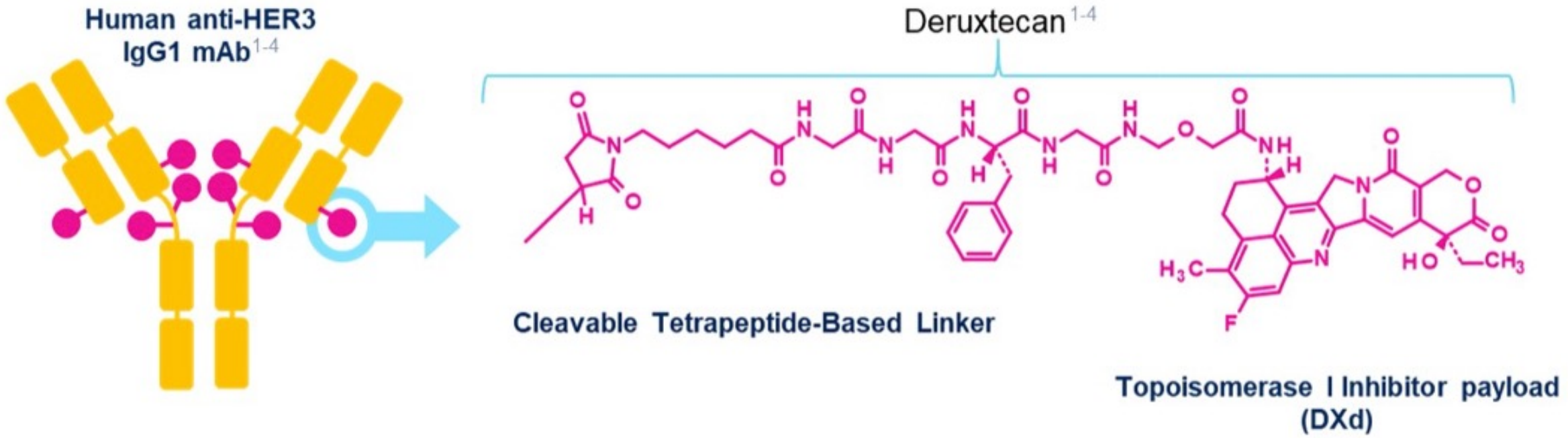
Efficacy and Safety of Patritumab Deruxtecan (HER3-DXd) in EGFR Inhibitor–Resistant, *EGFR*-Mutated Non–Small Cell Lung Cancer

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.

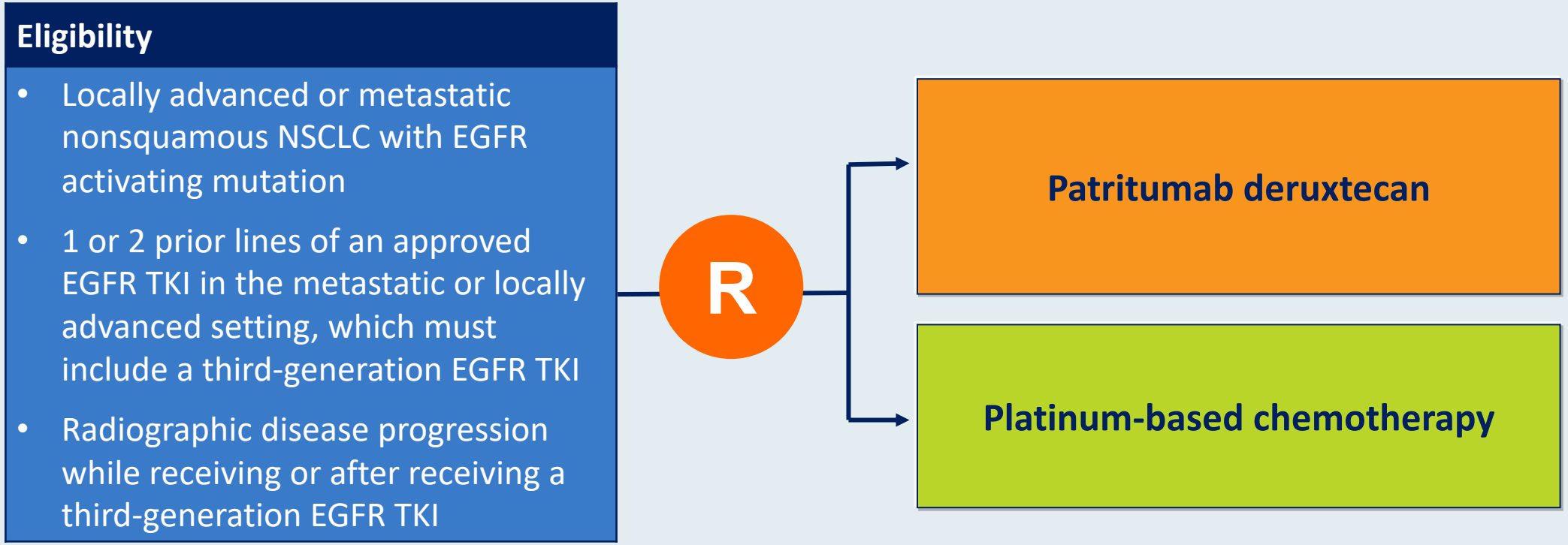
Select Grade ≥3 Treatment-Emergent Adverse Events (TEAEs)

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

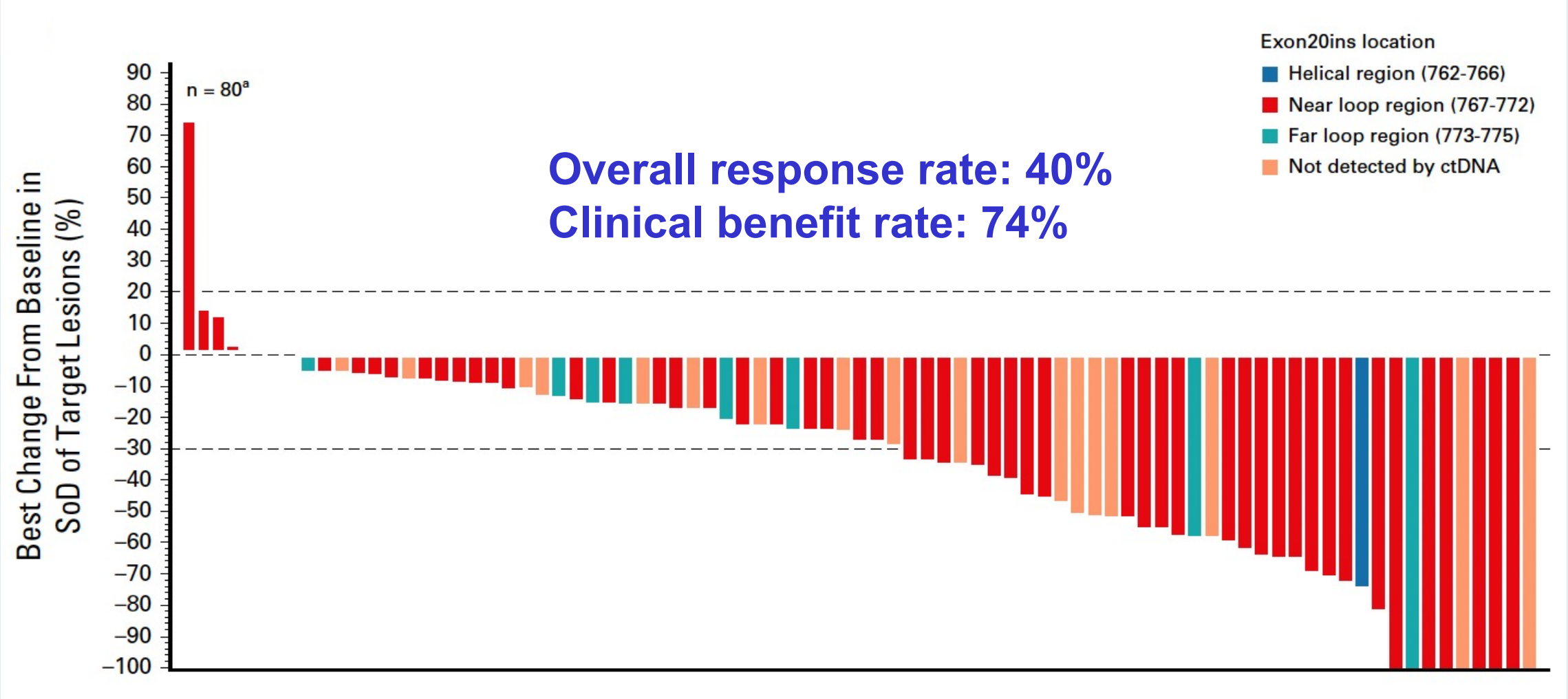
original reports

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

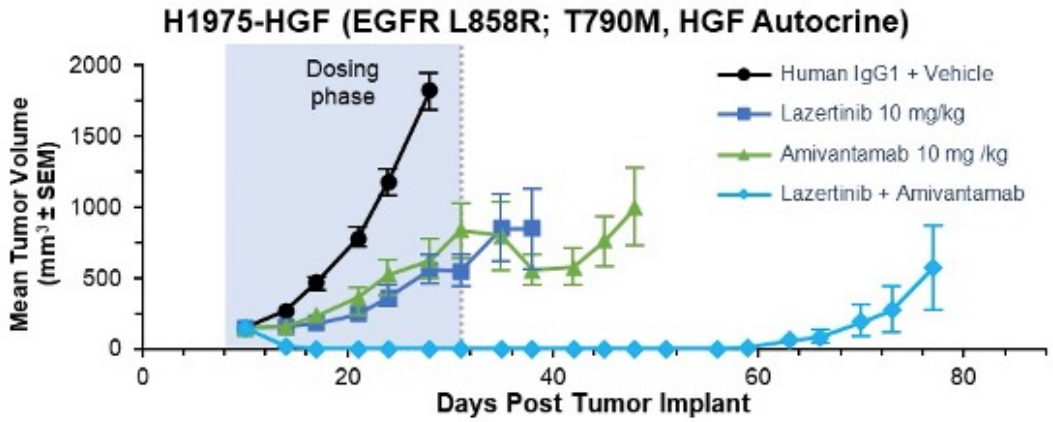
Amivantamab and lazertinib in patients with EGFR-mutant non-small cell lung cancer (NSCLC) after progression on osimertinib and platinum-based chemotherapy: Updated results from CHRYSALIS-2

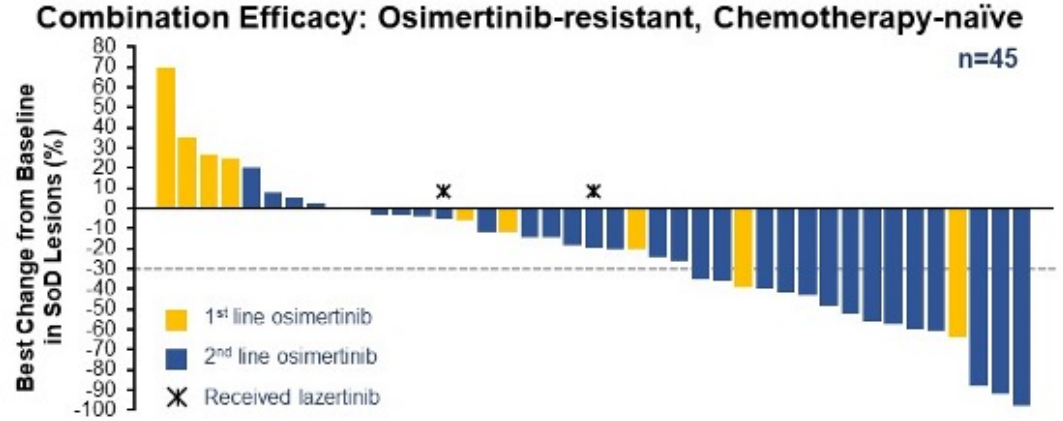
Catherine A. Shu,[1] Koichi Goto,[2] Yuichiro Ohe,[3] Benjamin Besse,[4] Se-Hoon Lee,[5] Yongsheng Wang,[6] Frank Griesinger,[7] James Chih-Hsin Yang,[8] Enriqueta Felip,[9] Rachel E. Sanborn,[10] Reyes Bernabe Caro,[11] Joshua C. Curtin,[12] Jun Chen,[12] Janine Mahoney,[12] Leonardo Trani,[12] Joshua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

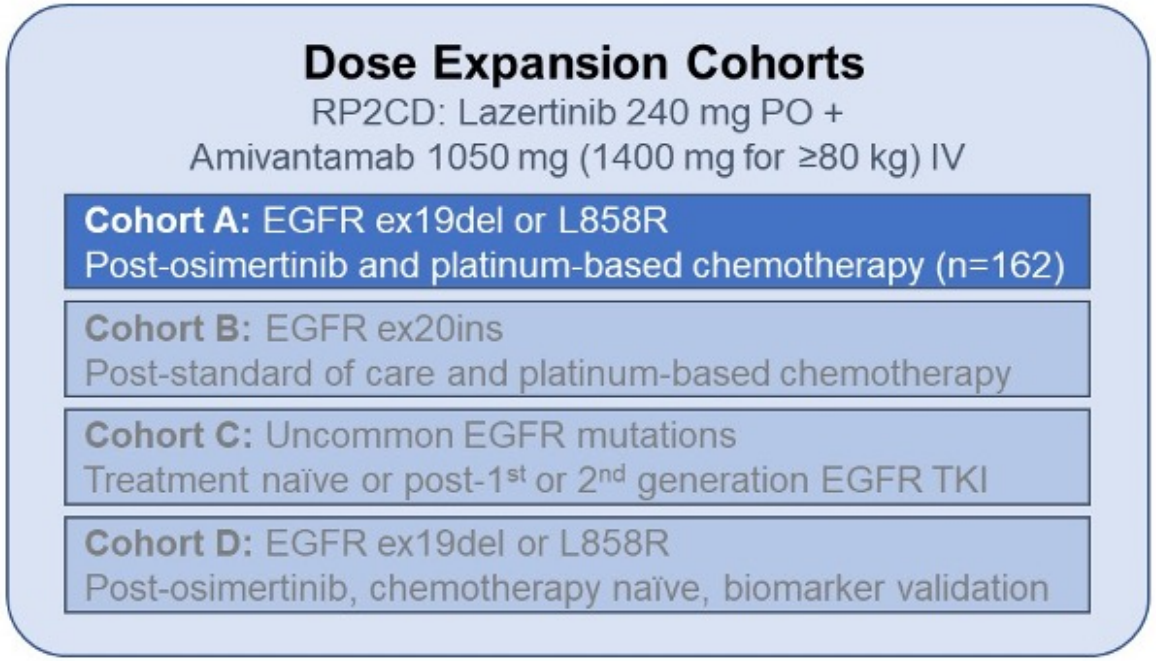




Shu CA et al. ASCO 2022;Abstract 9006.

RTP RESEARCH TO PRACTICE

CHRYSALIS-2 Study Design



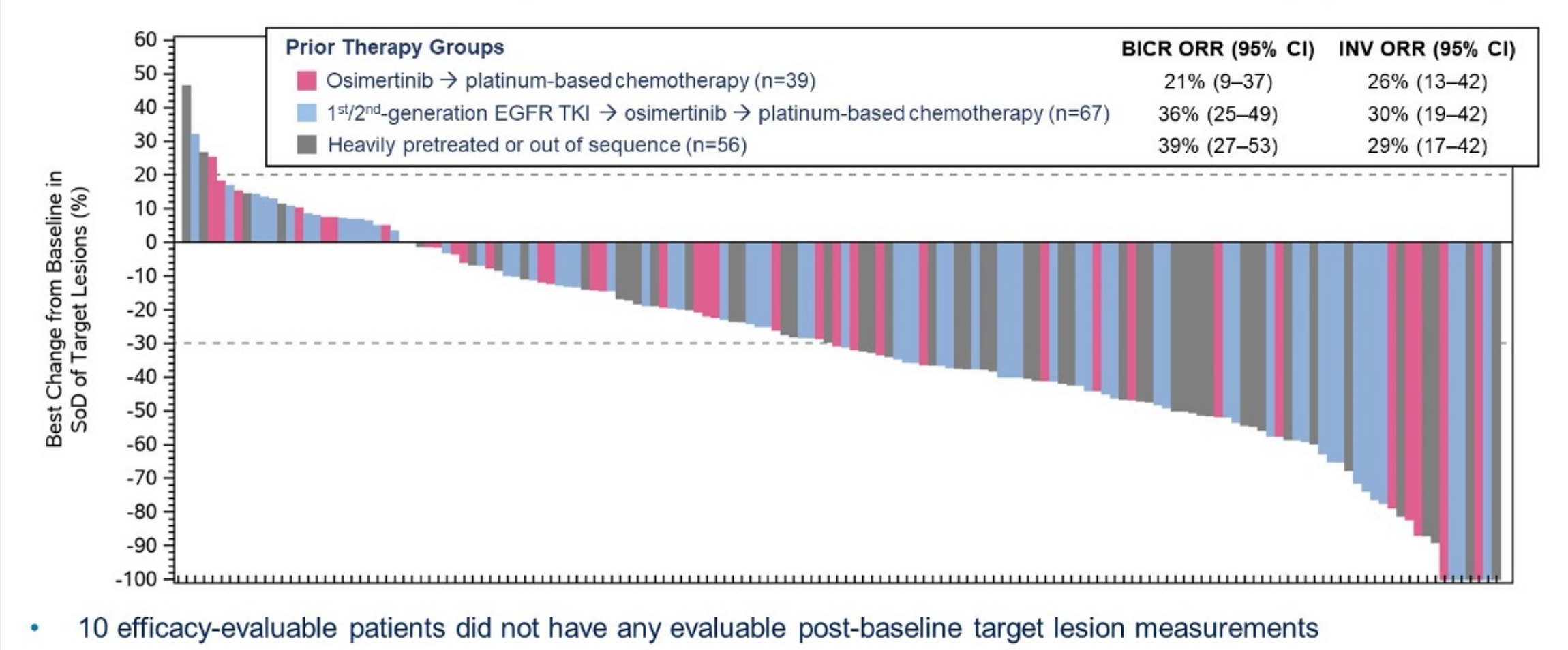
Endpoints

- 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).

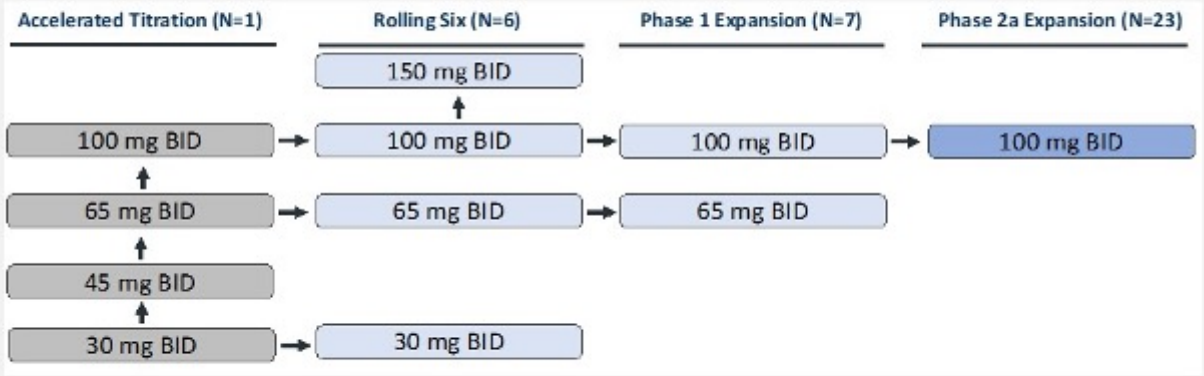
2. Leal JL, et al. Clin Lung Cancer. 2021;22(6).

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)	

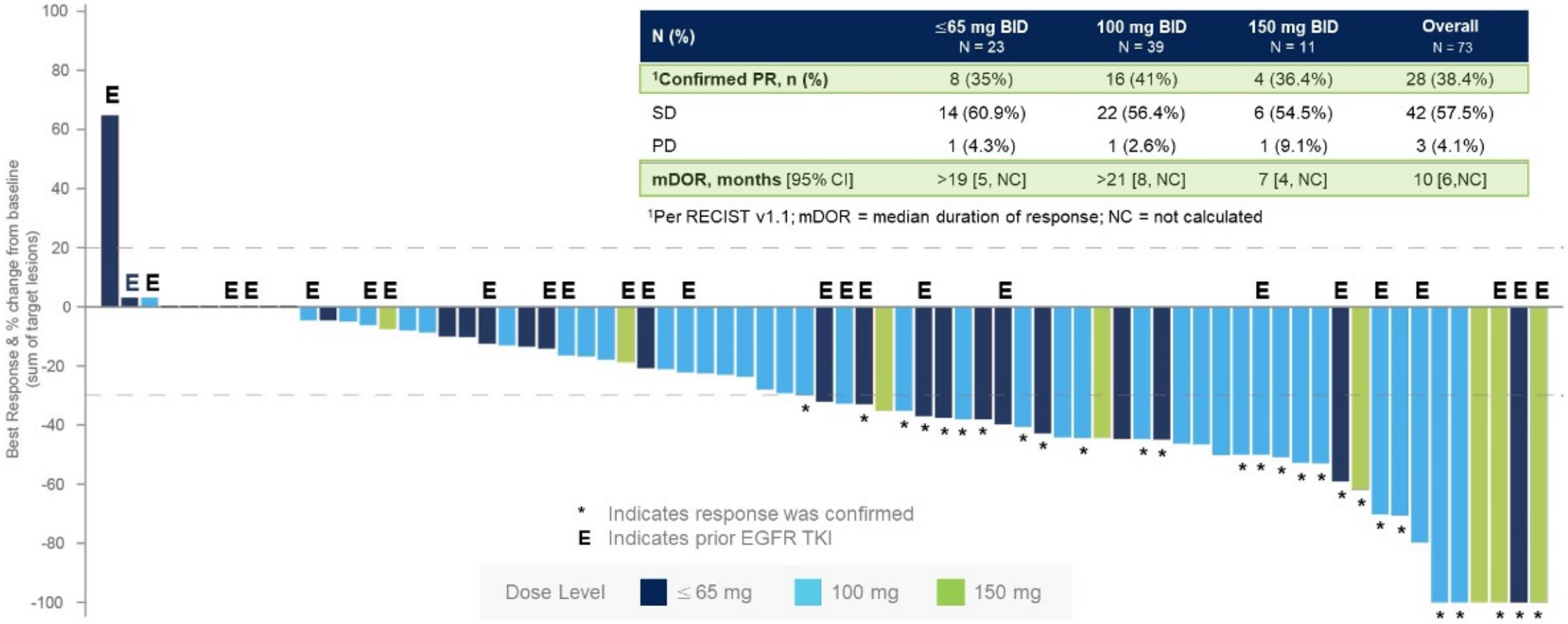
- Most AEs Grade 1/2
- Dose reductions and discontinuations were uncommon at doses below 150 mg
- No Grade ≥3 rash or diarrhea observed at doses <150 mg
- Treatment-emergent pneumonitis was observed in 4 patients (1 at 65, 2 at 100, and 1 at 150 mg), but cases were asymptomatic (1) or confounded by comorbid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

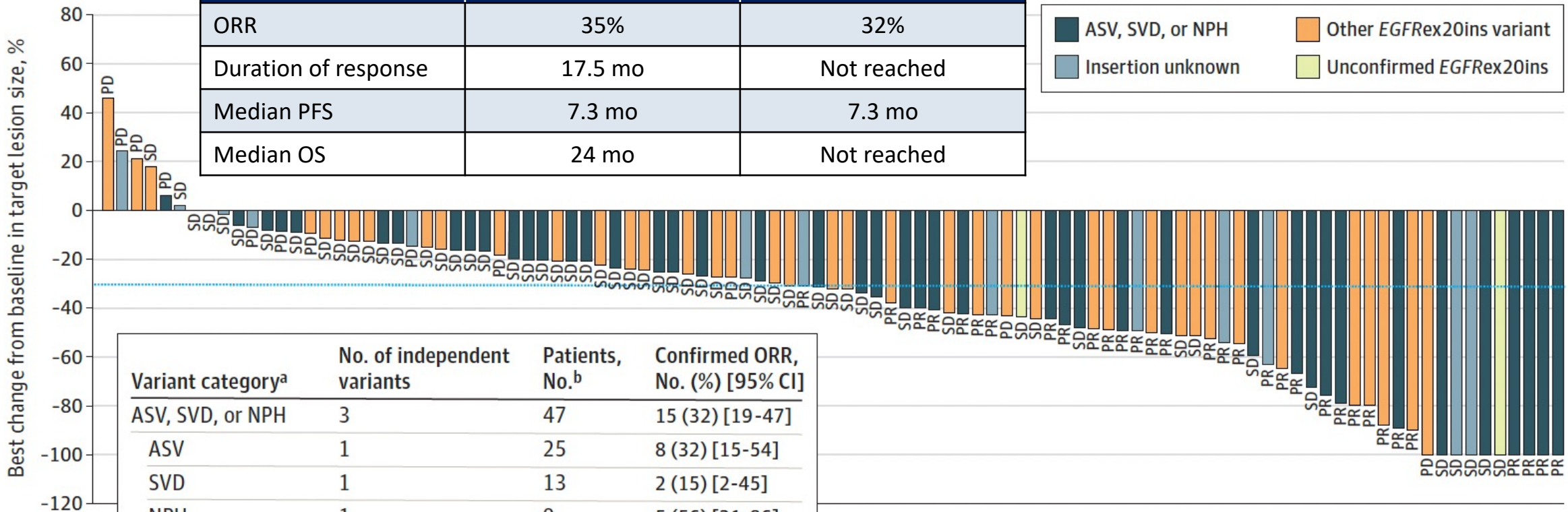
Treatment Outcomes and Safety of Mobocertinib in Platinum-Pretreated Patients With *EGFR* Exon 20 Insertion–Positive Metastatic Non–Small Cell Lung Cancer

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 Ovarian Cancer

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

Faculty

Ursula Matulonis, MD

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Thank you for joining us!

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

RTP
RESEARCH
TO PRACTICE