Video Consensus or Controversy? Clinical Investigators Provide Perspectives on the Current and Future Management of Non-Small Cell Lung Cancer

A CME Symposium Held in Conjunction with the 2023 ASCO® Annual Meeting

Friday, June 2, 2023

6:30 PM – 9:00 PM CT

Faculty

Edward B Garon, MD, MS
John V Heymach, MD, PhD
Corey J Langer, MD
Ticiana Leal, MD
David R Spigel, MD
Helena Yu, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Faculty

Edward B Garon, MD, MS
Professor
Director, Thoracic Oncology Program
Director, Signal Transduction and Therapeutics Research Program
David Geffen School of Medicine at UCLA
Jonsson Comprehensive Cancer Center
Los Angeles, California

John V Heymach, MD, PhD
Professor and Chair
Thoracic/Head and Neck Medical Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Corey J Langer, MD
Director of Thoracic Oncology
Abramson Cancer Center
Professor of Medicine
Perelman School of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania

Ticiana Leal, MD
Associate Professor
Department of Hematology and Oncology
Director, Thoracic Medical Oncology
Winship Cancer Institute
Emory University
Atlanta, Georgia

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

Helena Yu, MD
Medical Oncologist
Associate Attending
Memorial Sloan Kettering Cancer Center
New York, New York

Moderator
Neil Love, MD
Research To Practice
Miami, Florida

RTP
RESEARCH TO PRACTICE

Contributing Investigators

Matthew Gubens, MD, MS
Associate Professor, Thoracic Medical Oncology
University of California, San Francisco
San Francisco, California

Jarushka Naidoo, MB BCH, MHS
Professor of Oncology
Beaumont RCSI Cancer Centre
Beaumont Hospital
Dublin, Ireland
Adjunct Professor
Johns Hopkins University
Baltimore, Maryland

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

RTP
RESEARCH TO PRACTICE

The consulting investigator interviews will be developed into a special program featuring more than 60 video segments with over 1 hour of content.

Melissa Johnson, MD

Matthew Gubens, MD, MS

Jarushka Naidoo, MB BCH, MHS

An email will be sent to all attendees when the activity is available.

RTP RESEARCH TO PRACTICE

Dr Garon — Disclosures

Consulting Agreements	ABL Bio, AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim Pharmaceuticals Inc, Bristol Myers Squibb, Dracen Pharmaceuticals, Eisai Inc, EMD Serono Inc, Gilead Sciences Inc, GSK, Lilly, Merck, Natera Inc, Novartis, Personalis, Regeneron Pharmaceuticals Inc, Sanofi, Shionogi Inc, Xilio Therapeutics, Zymeworks Inc
Contracted Research	ABL Bio, AstraZeneca Pharmaceuticals LP, BioNTech SE, Bristol Myers Squibb, Daiichi Sankyo Inc, Dynavax Technologies, EMD Serono Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, lovance Biotherapeutics, Lilly, Merck, Mirati Therapeutics Inc, Novartis
Data and Safety Monitoring Board/Committee	Nuvalent
Sponsored Independent Medical Education	Daiichi Sankyo Inc, Ipsen Biopharmaceuticals Inc
Travel	A2 Bio, Novartis

RTP
RESEARCH
TO PRACTICE

Dr Gubens — Disclosures

Consulting Agreements	AnHeart Therapeutics, AstraZeneca Pharmaceuticals LP, Bristol Myers Squibb, Cardinal Health, Genentech, a member of the Roche Group, Genzyme Corporation, Gilead Sciences Inc, Guardant Health, iTeos Therapeutics, Sanofi, Summit Therapeutics, Surface Oncology
Contracted Research (Funding to Institution as Site PI)	Amgen Inc, Celgene Corporation, Johnson & Johnson Pharmaceuticals, Merck, Novartis, OncoMed Pharmaceuticals Inc, Trizell

RTP
RESEARCH
TO PRACTICE

Dr Heymach — Disclosures

Advisory Committee	AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim Pharmaceuticals Inc, BrightPath Biotherapeutics Co Ltd, Bristol Myers Squibb, Catalyst Pharmaceuticals, Chugai Pharmaceutical Co Ltd, EMD Serono Inc, Genentech, a member of the Roche Group, GSK, Hengrui Therapeutics Inc, Janssen Biotech Inc, Lilly, Mirati Therapeutics Inc, Nexus Health Systems, Pneuma Respiratory, RefleXion, Sanofi, Spectrum Pharmaceuticals Inc, Takeda Pharmaceuticals USA Inc
Research Support	AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim Pharmaceuticals Inc, Spectrum Pharmaceuticals Inc, Takeda Pharmaceuticals USA Inc
Royalties and Licensing Fees	Spectrum Pharmaceuticals Inc

Dr Johnson — Disclosures

Consulting Agreements	AbbVie Inc, Amgen Inc, Arcus Biosciences, ArriVent Biopharma, Astellas, AstraZeneca Pharmaceuticals LP, Axelia Oncology, Black Diamond Therapeutics Inc, Calithera Biosciences, Daiichi Sankyo Inc, EcoR1 Capital LLC, Genentech, a member of the Roche Group, Genmab US Inc, Genocea, Gritstone bio, GSK, IDEAYA Biosciences, Immunocore, iTeos Therapeutics, Janssen Biotech Inc, Jazz Pharmaceuticals Inc, Merck, Mirati Therapeutics Inc, Molecular Axiom, Novartis, Oncorus, Pyramid Biosciences, Regeneron Pharmaceuticals Inc, Revolution Medicines, Sanofi, Seagen Inc, Synthekine, Takeda Pharmaceuticals USA Inc, Turning Point Therapeutics Inc, VBL Therapeutics
Contracted Research	AbbVie Inc, Acerta Pharma — A member of the AstraZeneca Group, Adaptimmune, Amgen Inc, Apexigen, Arcus Biosciences, Array BioPharma Inc, a subsidiary of Pfizer Inc, AstraZeneca Pharmaceuticals LP, Atreca, BeiGene Ltd, BerGenBio ASA, BioAtla, Birdie Biopharmaceuticals, Black Diamond Therapeutics Inc, Boehringer Ingelheim Pharmaceuticals Inc, Bristol Myers Squibb, Calithera Biosciences, Carisma Therapeutics, Checkpoint Therapeutics Inc, Corvus Pharmaceuticals, Curis Inc, CytomX Therapeutics, Daiichi Sankyo Inc, Dracen Pharmaceuticals, Dynavax Technologies, Elicio Therapeutics, EMD Serono Inc, EQRx, Erasca, Exelixis Inc, Fate Therapeutics, Genentech, a member of the Roche Group, Genmab US Inc, Genocea, Gritstone bio, GSK, Guardant Health, Harpoon Therapeutics, Helsinn Healthcare SA, Hengrui Therapeutics Inc, Hutchison MediPharma, IDEAYA Biosciences, Immunitas Therapeutics, Immunocore, Incyte Corporation, Janssen Biotech Inc, Jounce Therapeutics, Kadmon, Kartos Therapeutics, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Lycera, Merck, Merus BV, Mirati Therapeutics Inc, Mythic Therapeutics, NeolummuneTech, Neovia Oncology, Novartis, Nuvalent, OncoMed Pharmaceuticals Inc, Palleon Pharmaceuticals, Pfizer Inc, PMV Pharma, Rain Therapeutics, Rascal Therapeutics, Regeneron Pharmaceuticals Inc, Relay Therapeutics, Revolution Medicines, Ribon Therapeutics, Roivant Sciences Ltd, Rubius Therapeutics, Sanofi, Seven and Eight Biopharmaceuticals Inc, Shattuck Labs, Stemcentrx, Syndax Pharmaceuticals Inc, Takeda Pharmaceuticals USA Inc, Tarveda Therapeutics, TCR^2 Therapeutics, Tempest Therapeutics, Tizona Therapeutics Inc, Tmunity Therapeutics, Turning Point Therapeutics Inc, Vyriad, WindMIL Therapeutics, Y-mAbs Therapeutics Inc
Nonrelevant Financial Relationship	City of Hope National Medical Center, Memorial Sloan Kettering Cancer Center, University of Michigan

RTP RESEARCH TO PRACTICE

Dr Langer — Disclosures

Consulting Fees	AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim Pharmaceuticals Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, GSK, Heat Biologics, Merck, Mirati Therapeutics Inc, Novocure Inc, Pfizer Inc, Regeneron Pharmaceuticals Inc, Sanofi, Takeda Pharmaceuticals USA Inc
Data Safety Monitoring Board or Advisory Board (Co-Chair)	Amgen Inc, Oncocyte
Medical Writing	Novartis
Research Funding	AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim Pharmaceuticals Inc, Inovio Pharmaceuticals Inc, Lilly, Merck, Oncocyte, Takeda Pharmaceuticals USA Inc, Trizell
Nonrelevant Financial Relationship	US Department of Veterans Affairs

RTP
RESEARCH
TO PRACTICE

Dr Leal — Disclosures

Consultant/Advisory Boards	Amgen Inc, AstraZeneca Pharmaceuticals LP, Catalyst Pharmaceuticals, Daiichi Sankyo Inc, Eisai Inc, EMD Serono Inc, Janssen Biotech Inc, Jazz Pharmaceuticals Inc, Merck, Novocure Inc, Regeneron Pharmaceuticals Inc, Roche Laboratories Inc, Takeda Pharmaceuticals USA Inc
Contracted Research	Advaxis Inc, Bayer HealthCare Pharmaceuticals, Pfizer Inc
Data and Safety Monitoring Board/Committee	OncoC4
Speaker	Aptitude Health, Cardinal Health, Curio Bioscience
Nonrelevant Financial Relationship	ASTRO, GASCO, GRACE, IDEOlogy Health, Medscape, National Cancer Institute, Nebraska Oncology Society, OncLive, Opinions in Lung Cancer, PeerView, SITC, Targeted Oncology

RTP
RESEARCH
TO PRACTICE

Dr Naidoo — Disclosures

Advisory Committee and Consulting Agreements	AbbVie Inc, Amgen Inc, Arcus Biosciences, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Bristol Myers Squibb, Daiichi Sankyo Inc, Elevation Oncology, Genentech, a member of the Roche Group, Kaleido Biosciences, Mirati Therapeutics Inc, NGM Biopharmaceuticals, Pfizer Inc, Regeneron Pharmaceuticals Inc, Takeda Pharmaceuticals USA Inc
Contracted Research	Amgen Inc, Arcus Biosciences, AstraZeneca Pharmaceuticals LP, Bristol Myers Squibb, Genentech, a member of the Roche Group, Mirati Therapeutics Inc, Pfizer Inc, Takeda Pharmaceuticals USA Inc
Data and Safety Monitoring Board/Committee	Bristol Myers Squibb, Daiichi Sankyo Inc

RTP
RESEARCH
TO PRACTICE

Dr Spigel — Disclosures

Consulting Agreements	AbbVie Inc, AstraZeneca Pharmaceuticals LP, BeiGene Ltd, Bristol Myers Squibb, Evidera, Genentech, a member of the Roche Group, GSK, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, Jazz Pharmaceuticals Inc, Lilly, Molecular Templates, Monte Rosa Therapeutics, Novartis, Novocure Inc, Pfizer Inc, Regeneron Pharmaceuticals Inc, Sanofi
Contracted Research	AbbVie Inc, Aeglea BioTherapeutics, Agios Pharmaceuticals Inc, Amgen Inc, AnHeart Therapeutics, Apollomics Inc, Arcus Biosciences, Arrys Therapeutics, a wholly owned subsidiary of Kyn Therapeutics, Ascendis Pharma, Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, BIND Therapeutics Inc, BioNTech SE, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Bristol Myers Squibb, Calithera Biosciences, Celgene Corporation, Celldex Therapeutics, Clovis Oncology, Cyteir Therapeutics, Daiichi Sankyo Inc, Denovo Biopharma, Eisai Inc, Elevation Oncology, Endeavor Biomedicines, Erasca, Faeth Therapeutics, FUJIFILM Pharmaceuticals USA Inc, G1 Therapeutics Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, Grail Inc, GSK, Hutchison MediPharma, ImClone Systems, a wholly owned subsidiary of Eli Lilly and Company, Incyte Corporation, Inspirna, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, Jazz Pharmaceuticals, Kronos Bio, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Lyell Immunopharma, MacroGenics Inc, Merck, Moderna, Molecular Templates, Monte Rosa Therapeutics, Nektar, Novartis, Novocure Inc, Peloton Therapeutics Inc, a wholly-owned subsidiary of Merck & Co Inc, PureTech Health, Razor Genomics, Repare Therapeutics, Seagen Inc, Shenzhen Chipscreen Biosciences Co Ltd, Stemline Therapeutics Inc, Synthekine, Taiho Oncology Inc, Takeda Pharmaceuticals USA Inc, Tango Therapeutics, Tarveda Therapeutics, Tesaro, A GSK Company, Tizona Therapeutics Inc, Transgene, Verastem Inc, Zai Lab
Nonrelevant Financial Relationship	UT Southwestern Medical Center

RTP
RESEARCH TO PRACTICE

Dr Yu — Disclosures

Consulting Agreements	AbbVie Inc, AstraZeneca Pharmaceuticals LP, Black Diamond Therapeutics Inc, Blueprint Medicines, C4 Therapeutics, Cullinan Oncology, Daiichi Sankyo Inc, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, Takeda Pharmaceuticals USA Inc
Data and Safety Monitoring Board/Committee	Janssen Biotech Inc
Research Funding to My Institution	AstraZeneca Pharmaceuticals LP, Black Diamond Therapeutics Inc, Blueprint Medicines, Cullinan Oncology, Daiichi Sankyo Inc, Erasca, Janssen Biotech Inc, Novartis, Pfizer Inc

Commercial Support

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

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.

Friday June 2	**Gastroesophageal Cancers** 11:45 AM – 12:45 PM CT (12:45 PM – 1:45 PM ET)
	Non-Small Cell Lung Cancer 6:30 PM – 9:00 PM CT (7:30 PM – 10:00 PM ET)
Saturday June 3	**Hepatobiliary Cancers** 6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)
	Prostate Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Sunday June 4	**Ovarian Cancer** 6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)
	Lymphoma, Chronic Lymphocytic Leukemia and Multiple Myeloma 7:00 PM – 9:30 PM CT (8:00 PM – 10:30 PM ET)
Monday June 5	**Urothelial Bladder Cancer** 6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)
	Breast Cancer 7:00 PM – 9:30 PM CT (8:00 PM – 10:30 PM ET)
Tuesday June 6	**Renal Cell Carcinoma (Webinar)** 7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)

RTP
RESEARCH TO PRACTICE

Exciting CME Events in Chicago You Do Not Want to Miss

A CME Hybrid Symposium Series Held in Conjunction with the 2023 ASCO® Annual Meeting

Gastroesophageal Cancers

Friday, June 2, 2023

11:45 AM – 12:45 PM CT (12:45 PM – 1:45 PM ET)

Faculty

Yelena Y Janjigian, MD
Manish A Shah, MD
Harry H Yoon, MD, MHS

Hepatobiliary Cancers

Saturday, June 3, 2023

6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)

Faculty

Anthony El-Khoueiry, MD
Robin K (Katie) Kelley, MD
Professor Arndt Vogel, MD

Non-Small Cell Lung Cancer

Friday, June 2, 2023

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

Faculty

Edward B Garon, MD, MS
John V Heymach, MD, PhD
Corey J Langer, MD
Ticiana Leal, MD
David R Spigel, MD
Helena Yu, MD

Prostate Cancer

Saturday, June 3, 2023

7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)

Faculty

Emmanuel S Antonarakis, MD
Prof Karim Fizazi, MD, PhD
Rana R McKay, MD
Alicia K Morgans, MD, MPH
A Oliver Sartor, MD

Exciting CME Events in Chicago You Do Not Want to Miss

A CME Hybrid Symposium Series Held in Conjunction with the 2023 ASCO® Annual Meeting

Ovarian Cancer

Sunday, June 4, 2023
6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)

Faculty
Philipp Harter, MD, PhD
David M O'Malley, MD
Shannon N Westin, MD, MPH

Urothelial Bladder Cancer

Monday, June 5, 2023
6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)

Faculty
Matthew D Galsky, MD
Andrea Necchi, MD
Scott T Tagawa, MD, MS

Lymphoma, Chronic Lymphocytic Leukemia and Multiple Myeloma

Sunday, June 4, 2023
7:00 PM – 9:30 PM CT (8:00 PM – 10:30 PM ET)

Faculty
John N Allan, MD
Shaji K Kumar, MD
Ann S LaCasce, MD, MMSc
Sagar Lonial, MD
Loretta J Nastoupil, MD
Susan O'Brien, MD

Breast Cancer

Monday, June 5, 2023
7:00 PM – 9:30 PM CT (8:00 PM – 10:30 PM ET)

Faculty
Komal Jhaveri, MD
Kevin Kalinsky, MD, MS
Ian E Krop, MD, PhD
Joyce O'Shaughnessy, MD
Hope S Rugo, MD
Professor Peter Schmid, FRCP, MD, PhD

Exciting CME Events in Chicago You Do Not Want to Miss

A CME Hybrid Symposium Series Held in Conjunction with the 2023 ASCO® Annual Meeting

Renal Cell Carcinoma Webinar

Tuesday, June 6, 2023

7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)

Faculty

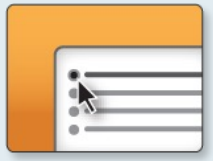
David F McDermott, MD

Sumanta Kumar Pal, MD

Clinicians in the Meeting Room

Networked iPads are available.

Review Program Slides: Tap the Program Slides button to review speaker presentations and other program content.



Answer Survey Questions: Complete the pre- and postmeeting surveys.

Ask a Question: Tap Ask a Question to submit a challenging case or question for discussion. We will aim to address as many questions as possible during the program.

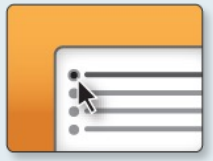
Complete Your Evaluation: Tap the CME Evaluation button to complete your evaluation electronically to receive credit for your participation.

For assistance, please raise your hand. Devices will be collected at the conclusion of the activity.

RTP RESEARCH TO PRACTICE

Clinicians Attending via Zoom

Review Program Slides: A link to the program slides will be posted in the chat room at the start of the program.



Answer Survey Questions: Complete the pre- and postmeeting surveys.

Ask a Question: Submit a challenging case or question for discussion using the Zoom chat room.

Get CME Credit: A CME credit link will be provided in the chat room at the conclusion of the program.

RTP
RESEARCH
TO PRACTICE

PREMEETING SURVEY – Available Now

Clinicians in Attendance: If you have not already done so, please take a moment to complete the premeeting survey on the iPads for attendees in the room and on Zoom for those attending virtually. Your input on this survey will be integral to the program today.

A postmeeting survey will be posted toward the end of the session.

Thank you for your input.

RTP
RESEARCH
TO PRACTICE

About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based video/PowerPoint program.
  An email will be sent to all attendees when the activity is available.
- To learn more about our education programs, visit our website, **www.ResearchToPractice.com**

RTP
RESEARCH
TO PRACTICE

Video Consensus or Controversy? Clinical Investigators Provide Perspectives on the Current and Future Management of Non-Small Cell Lung Cancer

A CME Symposium Held in Conjunction with the 2023 ASCO® Annual Meeting

Friday, June 2, 2023

6:30 PM – 9:00 PM CT

Faculty

Edward B Garon, MD, MS
John V Heymach, MD, PhD
Corey J Langer, MD
Ticiana Leal, MD
David R Spigel, MD
Helena Yu, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Agenda

Module 1: Incorporation of Immunotherapeutic Strategies into the Management of Nonmetastatic Non-Small Cell Lung Cancer (NSCLC) — Dr Heymach

Module 2: Contemporary Treatment for Localized or Metastatic NSCLC with an EGFR Mutation — Dr Yu

Module 3: Research Advances Shaping the Current and Future Treatment of Metastatic NSCLC with ALK Rearrangements, ROS1 Rearrangements or RET Fusions — Dr Langer

Module 4: Targeting MET, HER2 and KRAS Alterations in NSCLC — Dr Spigel

Module 5: Current Management of Metastatic NSCLC without a Targetable Tumor Mutation — Dr Garon

Module 6: Future Directions in the Management of Metastatic NSCLC — Dr Leal

Agenda

Module 1: Incorporation of Immunotherapeutic Strategies into the Management of Nonmetastatic Non-Small Cell Lung Cancer (NSCLC) — Dr Heymach

Module 2: Contemporary Treatment for Localized or Metastatic NSCLC with an EGFR Mutation — Dr Yu

Module 3: Research Advances Shaping the Current and Future Treatment of Metastatic NSCLC with ALK Rearrangements, ROS1 Rearrangements or RET Fusions — Dr Langer

Module 4: Targeting MET, HER2 and KRAS Alterations in NSCLC — Dr Spigel

Module 5: Current Management of Metastatic NSCLC without a Targetable Tumor Mutation — Dr Garon

Module 6: Future Directions in the Management of Metastatic NSCLC — Dr Leal

Strategies to cope with platinum shortages

Melissa Johnson, MD

Matthew Gubens, MD, MS

Jarushka Naidoo, MB BCH, MHS

RTP
RESEARCH
TO PRACTICE

What are you currently doing in the case of patients to whom you wish to administer first-line carboplatin/pemetrexed/pembrolizumab but carboplatin is not available?

 Dr Garon	I have not been faced with this issue
 Dr Heymach	Nivo/ipi if low tumor bulk; substitute cis if high tumor bulk
 Dr Langer	Cis/pem/pembro OR nivo/ipi +/- pem if neither carbo nor cis available
 Dr Leal	NA
 Dr Spigel	NA
 Dr Yu	Pemetrexed/ pembrolizumab
 Dr Gubens	Nivolumab/ipilimumab
 Dr Johnson	Substitute cisplatin for carboplatin
 Dr Naidoo	No platinum shortages in Europe

Cis = cisplatin; pem = pemetrexed; pembro = pembrolizumab; nivo = nivolumab; ipi = ipilimumab; carbo = carboplatin

RTP RESEARCH TO PRACTICE

Selection of appropriate candidates for neoadjuvant chemoimmunotherapy

Melissa Johnson, MD

Matthew Gubens, MD, MS

Jarushka Naidoo, MB BCH, MHS

RTP
RESEARCH
TO PRACTICE

In which specific clinical situations do you or would you administer neoadjuvant chemotherapy combined with an anti-PD-1/PD-L1 antibody?

 Dr Garon	Node-positive NSCLC (based on radiographs)
 Dr Heymach	Any nondriver tumor >4 cm, up to N2 disease as long as mediastinal disease is not bulky
 Dr Langer	Potentially resectable Stage IIIA, predominantly
 Dr Leal	Resectable Stage II-III w/o EGFR/ALK; preferred for Stage III PD-L1 high
 Dr Spigel	All resectable settings if able
 Dr Yu	Any resectable Stage II/III w/o EGFR/ALK/ROS1/RET
 Dr Gubens	PD-L1+, especially high; resectable but would benefit from cytoreduction; pts who would benefit from preop medical optimization or need for tobacco cessation
 Dr Johnson	Stage II-III (T2b,3-4 N0-1, consider for N2 if surgeon on board)
 Dr Naidoo	Stage IB-IIIA, any PD-L1, no EGFR or ALK

RTP RESEARCH TO PRACTICE

In general, for a patient with localized NSCLC to whom you have made the decision to administer an anti-PD-1/PD-L1 antibody in the neoadjuvant setting, what do you consider to be the optimal approach?

 Dr Garon	Chemo/nivo → resection	 Dr Yu	Chemo/nivo → resection
 Dr Heymach	Chemo/durva → resection → durva	 Dr Gubens	Chemo/nivo → resection
 Dr Langer	No preference	 Dr Johnson	Chemo/pembro → resection → pembro
 Dr Leal	Chemo/nivo → resection	 Dr Naidoo	Chemo/nivo → resection
 Dr Spigel	Chemo/pembro → resection → pembro OR chemo/durva → resection → durva		

Nivo = nivolumab; durva = durvalumab; pembro = pembrolizumab

RTP RESEARCH TO PRACTICE

Current clinical role of adjuvant anti-PD-1/PD-L1 antibodies

Melissa Johnson, MD

Matthew Gubens, MD, MS

Jarushka Naidoo, MB BCH, MHS

Regulatory and reimbursement issues aside, in general, which adjvuant treatment would you recommend for an otherwise healthy 65-year-old patient with Stage IIA nonsquamous NSCLC and a PD-L1 TPS of 0%?

 Dr Garon	None
 Dr Heymach	Cisplatin-based chemo → pembro
 Dr Langer	Cisplatin-based chemo → pembro
 Dr Leal	Cisplatin-based chemo → pembro
 Dr Spigel	Carboplatin-based chemo → pembro
 Dr Yu	Cisplatin-based chemo → pembro
 Dr Gubens	Cisplatin-based chemo
 Dr Johnson	Carboplatin-based chemo → pembro
 Dr Naidoo	Cisplatin-based chemo

Pembro = pembrolizumab

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, in general, which adjvuant treatment would you recommend for an otherwise healthy 65-year-old patient with Stage IIA nonsquamous NSCLC and a PD-L1 TPS of 50%?

 Dr Garon	None	 Dr Yu	Cisplatin-based chemo → pembro
 Dr Heymach	Carboplatin-based chemo → atezo	 Dr Gubens	Cisplatin-based chemo → atezo
 Dr Langer	Cisplatin-based chemo → atezo	 Dr Johnson	Carboplatin-based chemo → atezo
 Dr Leal	Cisplatin-based chemo → atezo	 Dr Naidoo	Cisplatin-based chemo → atezo
 Dr Spigel	Carboplatin-based chemo → pembro		

Atezo = atezolizumab; pembro = pembrolizumab

RTP RESEARCH TO PRACTICE

For a patient who does not wish to receive chemotherapy, in which situations, if any, would you be comfortable administering an adjuvant anti-PD-1/PD-L1 antibody alone?

 Dr Garon	Node-positive and PD-L1 ≥50%; would consider for high TMB
 Dr Heymach	Resectable stage IB-III, any PD-L1 level
 Dr Langer	PD-L1+, Stage II/IIIA, but if they are declining chemo, I might be VERY leery of giving them IO
 Dr Leal	Negative EGFR status and PD-L1-high tumor
 Dr Spigel	Probably any (EGFR WT)
 Dr Yu	Stage II-III w/ contraindication to chemo
 Dr Gubens	Any candidate for adj IO, after discussion of potential curative benefit the pt is choosing to forgo
 Dr Johnson	As long as PD-L1+
 Dr Naidoo	Cisplatin ineligible

TMB = tumor mutational burden

RTP RESEARCH TO PRACTICE

Patient selection for and practical implementation of consolidation durvalumab

Melissa Johnson, MD

Matthew Gubens, MD, MS

Jarushka Naidoo, MB BCH, MHS

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, 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-activating mutation?

 Dr Garon	None	 Dr Yu	Osimertinib
 Dr Heymach	Osimertinib	 Dr Gubens	Osimertinib
 Dr Langer	Osimertinib	 Dr Johnson	Durvalumab
 Dr Leal	None	 Dr Naidoo	Osimertinib
 Dr Spigel	Osimertinib		

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, 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 a RET fusion?

 Dr Garon	None	 Dr Yu	Selpercatinib
 Dr Heymach	Durvalumab	 Dr Gubens	Durvalumab
 Dr Langer	Shared decision with pt on durvalumab vs selpercatinib vs sequential	 Dr Johnson	Selpercatinib
 Dr Leal	Durvalumab	 Dr Naidoo	Durvalumab
 Dr Spigel	Durvalumab		

RTP RESEARCH TO PRACTICE

Incorporation of Immunotherapeutic Strategies into the Management of Nonmetastatic Non-Small Cell Lung Cancer (NSCLC)

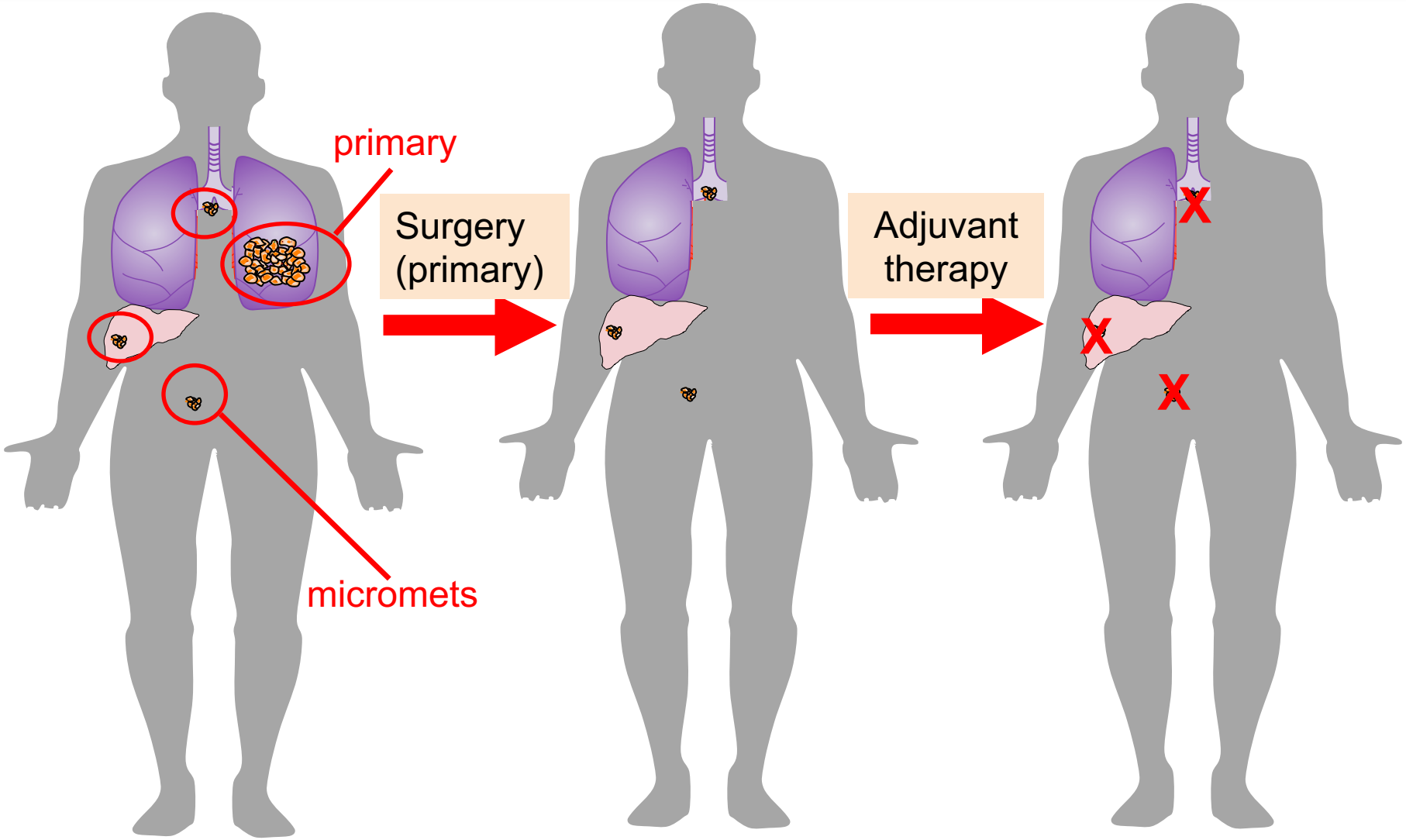
John Heymach MD, PhD
Chair, Thoracic/Head and Neck Medical Oncology
David Bruton, Jr. Chair in Cancer Research
MD Anderson Cancer Center

ASCO Lung Cancer Satellite with Research To Practice

June 2, 2023

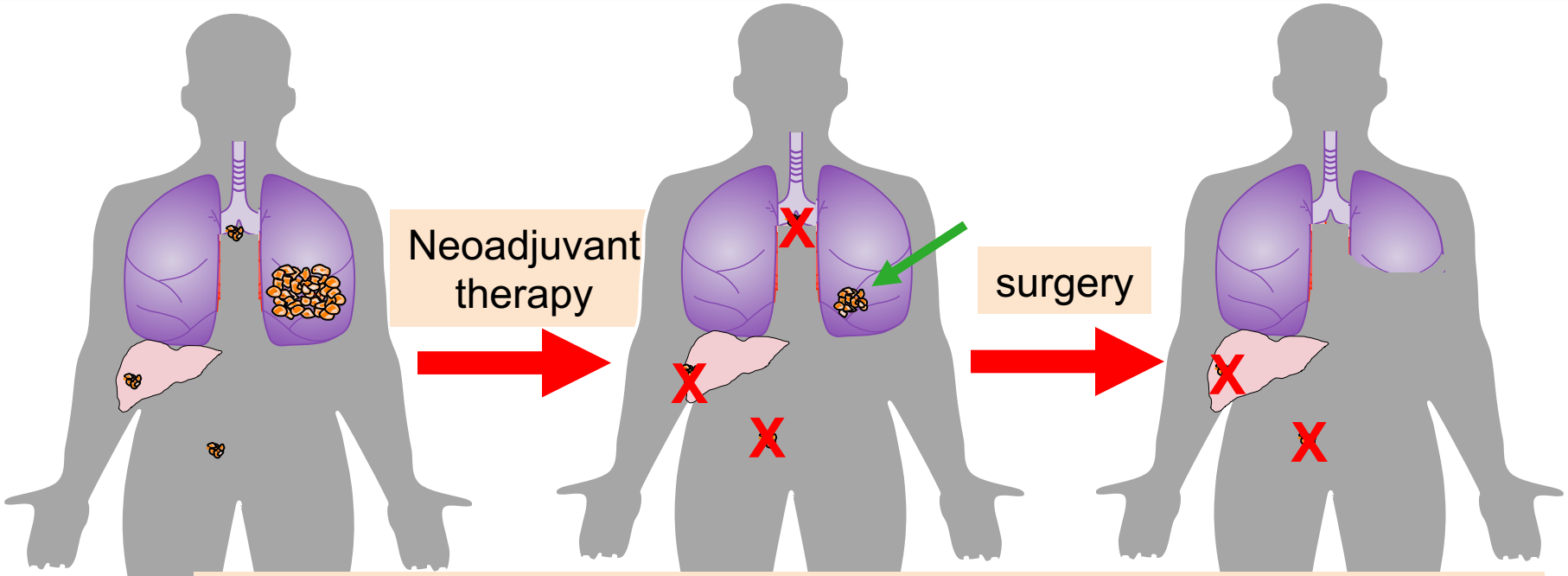
THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

The primary goal of adjuvant treatment is to eliminate micrometastatic disease



THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Neoadjuvant treatment can “downstage” the primary tumor, potentially making surgery less morbid and clearing mediastinum



Other potential advantages of neoadjuvant treatment

- Analysis of tumor response (MPR, pCR)
- Enhance anti-tumor immunity when greater burden of tumor and tumor antigens are present
- Earlier treatment of micromets and increased compliance

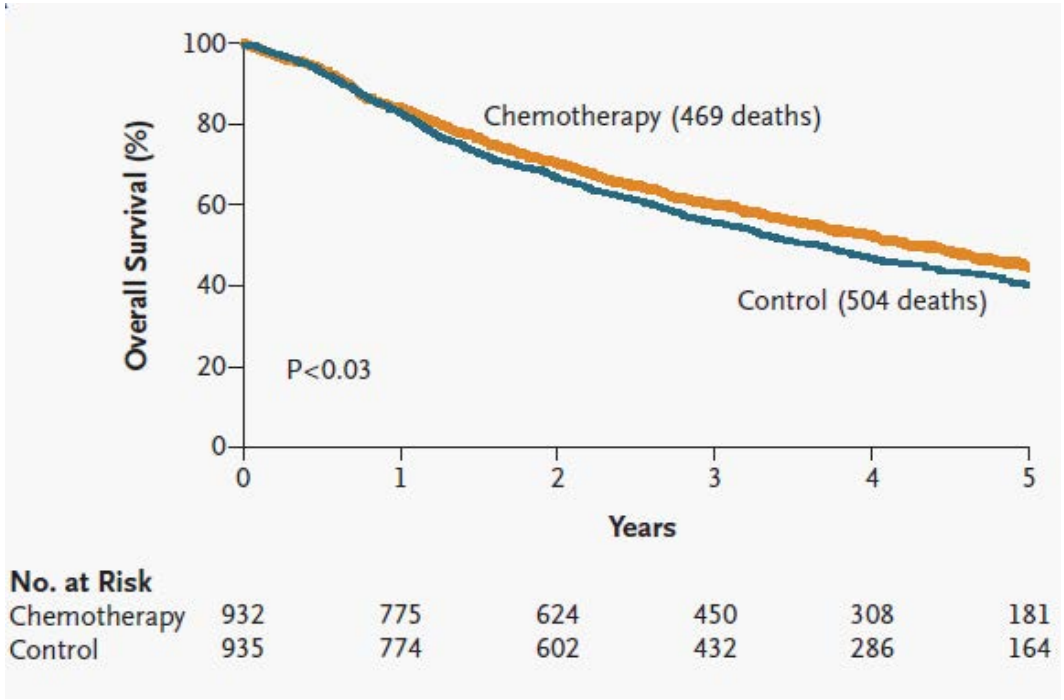
Adjuvant chemo in resected NSCLC prolongs OS and reduces likelihood of recurrence at 5y by ~5% : The IALT study

Stage I-III NSCLC
Post resection
No prior tx
N=1867

R

Adjuvant chemo 3-4 cycles
cisplatin + vinca or etoposide

Observation



HR: 0.86
P<0.003

The International Lung Cancer Trial Collaborative (IALT) Group; N Engl J Med, 2004

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Rationale for ICB in early stage NSCLC: Role of PD-L1 in facilitating metastatic spread

nature COMMUNICATIONS

ARTICLE

Received 13 Jul 2014 | Accepted 11 Sep 2014 | Published xx xxx 2014

DOI: 10.1038/ncomms6241

Metastasis is regulated via microRNA-200/ZEB1 axis control of tumour cell PD-L1 expression and intratumoral immunosuppression

Limo Chen[1,2,*], Don L. Gibbons[1,3,*], Sangeeta Goswami[1], Maria Angelica Cortez[1], Young-Ho Ahn[1,4], Lauren A. Byers[1], Xuejun Zhang[2], Xiaohui Yi[2], David Dwyer[2], Wei Lin[1], Lixia Diao[5], Jing Wang[5], Jonathon Roybal[1], Mayuri Patel[1], Christin Ungewiss[1], David Peng[1], Scott Antonia[6], Melanie Mediavilla-Varela[6], Gordon Robertson[7], Milind Suraokar[1,8], James W. Welsh[9], Baruch Erez[1], Ignacio I. Wistuba[1,8], Lieping Chen[10], Di Peng[11], Shanshan Wang[11], Stephen E. Ullrich[2], John V. Heymach[1], Jonathan M. Kurie[1] & F. Xiao-Feng Qin[1,2,11]

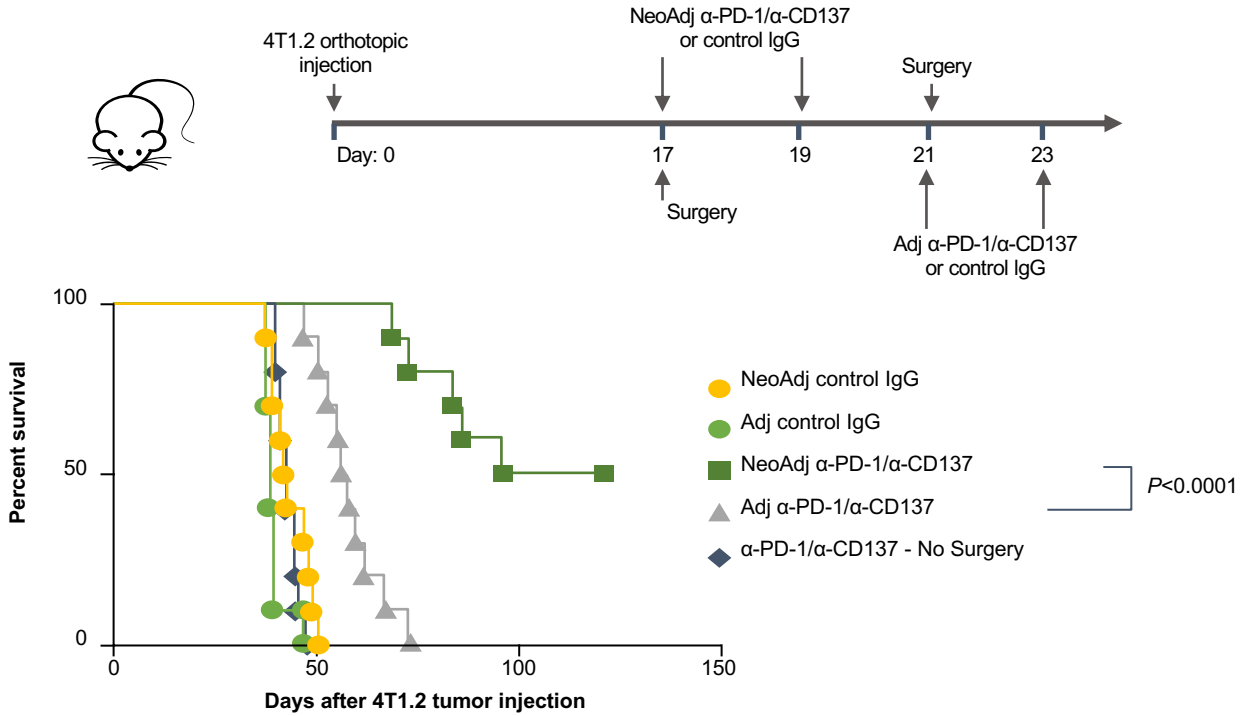
THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Making Cancer History®

Neoadjuvant ICB combination is superior to adjuvant therapy in murine models of breast cancer

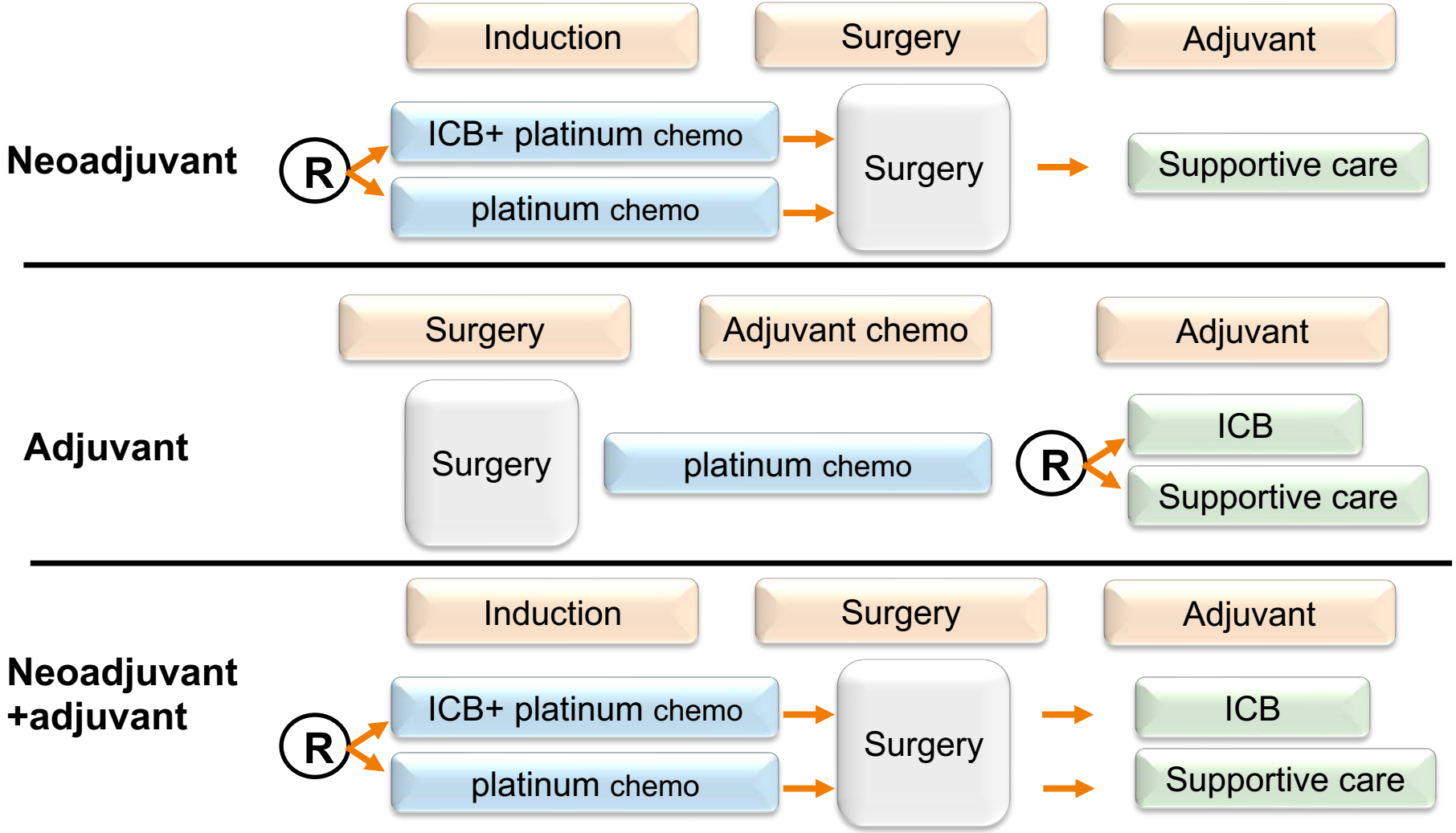
- In early stage disease, neoadjuvant IO may activate the immune system robustly prior to surgery, when tumor is intact, neoantigens are present and clonal resistance is minimal[1-4]

Neoadjuvant immunotherapy is superior to adjuvant in a mouse model of breast cancer[6]



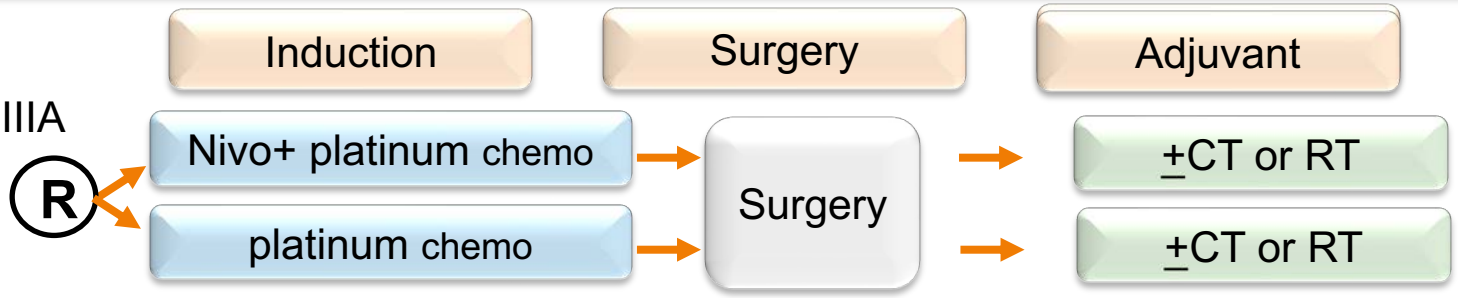
1. Gonzalez H et al. *Genes Dev*. 2018. 2. McGranahan N et al. *Science*. 2016. 3. Tohme S et al. *Cancer Res*. 2017. 4. Topalian SL et al. *Science*. 2020. 6. Liu J et al. *Cancer Discov*. 2016.

Randomized studies of neoadjuvant ICB, adjuvant ICB, or both

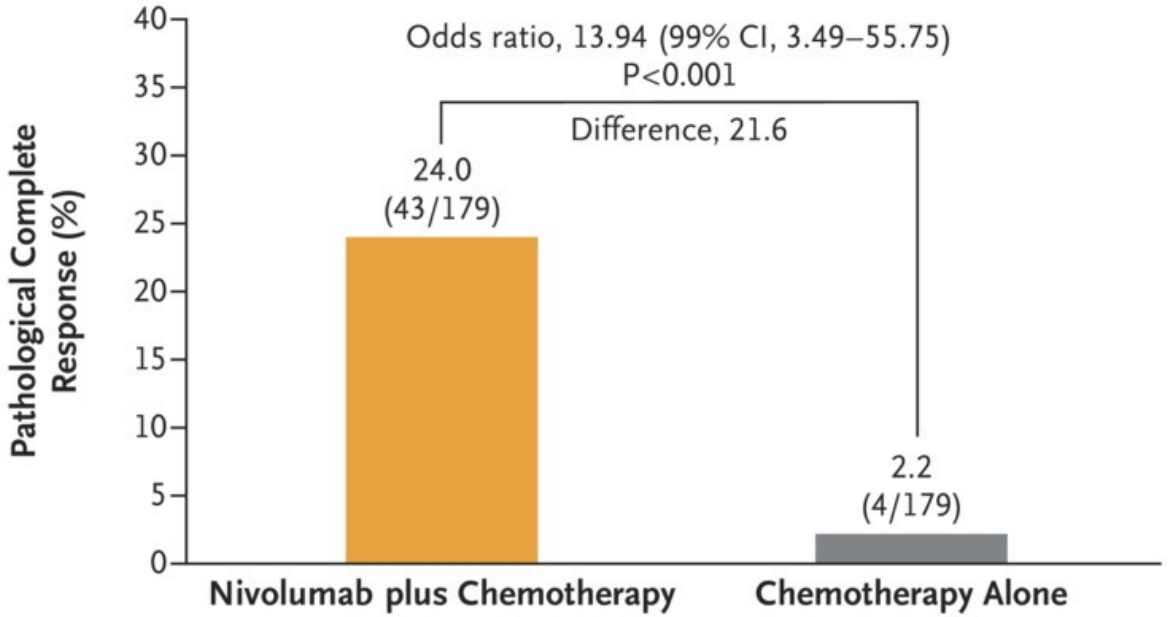


CheckMate 816 study: addition of neoadjuvant nivolumab to CT improves path CR in resectable stage IB-IIIA NSCLC

CM816
Stage IB (>4cm)-IIIA
N=358
1EP: pCR, EFS
2EP: MPR, OS



Path CR: 24.0 vs 2.2% (P<.001)

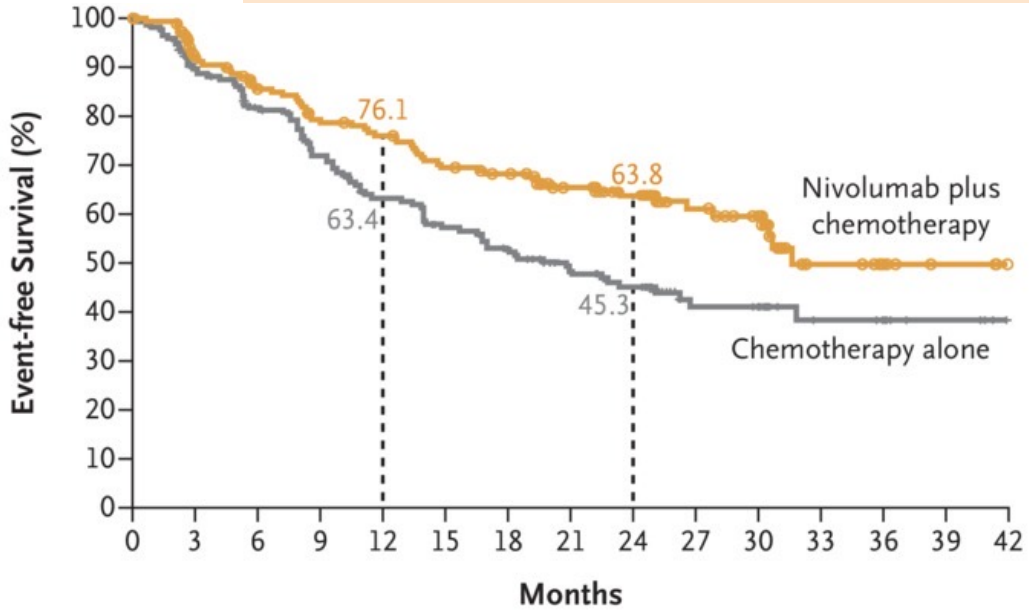


Forde et al. N Engl J Med 2022;386:1973-1985

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

CheckMate 816 study: addition of neoadjuvant nivolumab to CT improves EFS in resectable stage IB-IIIA NSCLC

EFS HR: 0.63 (P=.005)
18.5% improvement in 2Y EFS



	No. of Patients	Median Event-free Survival (95% CI) *mo*
Nivolumab plus Chemotherapy	179	31.6 (30.2–NR)
Chemotherapy Alone	179	20.8 (14.0–26.7)

Hazard ratio for disease progression, disease recurrence, or death, 0.63 (97.38% CI, 0.43–0.91)
P=0.005

No. at Risk

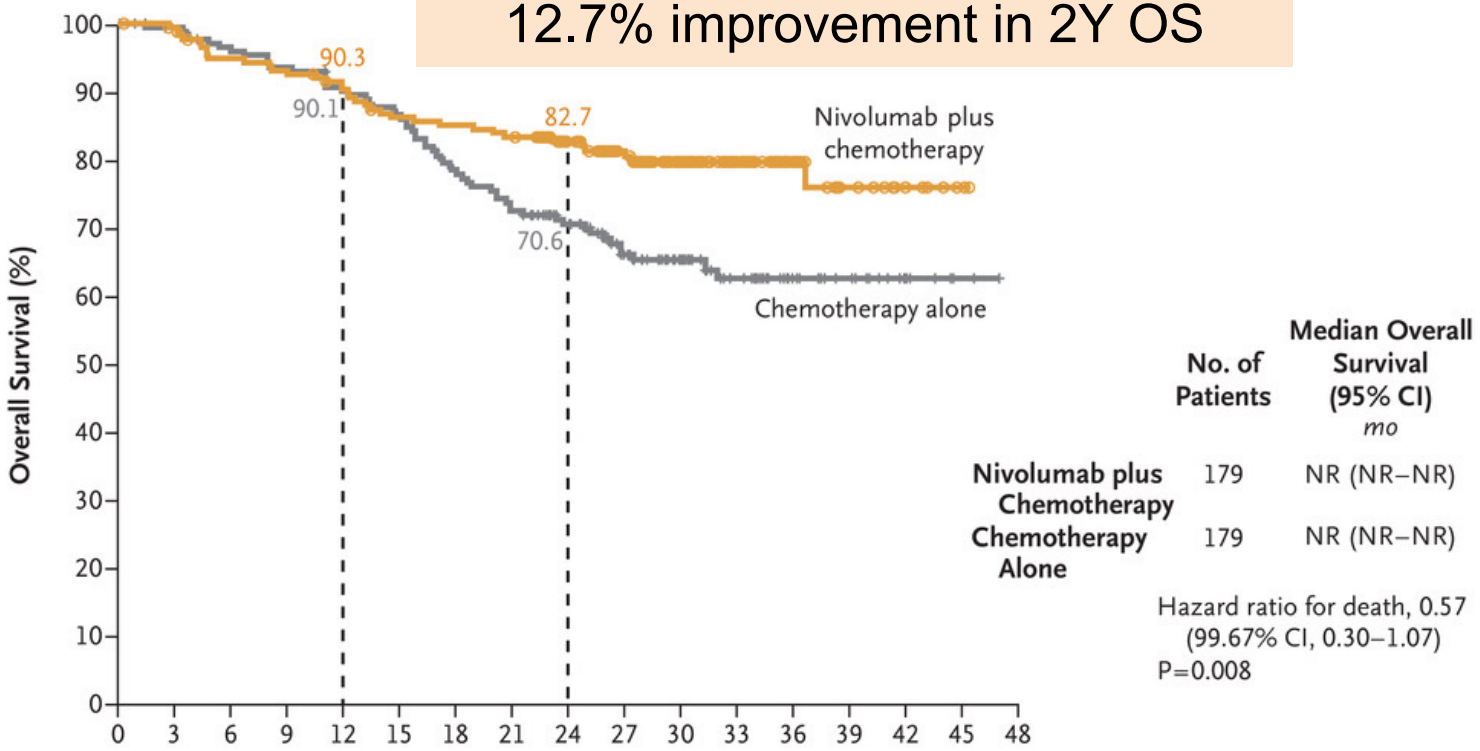
Nivolumab plus chemotherapy	179	151	136	124	118	107	102	87	74	41	34	13	6	3	0
Chemotherapy alone	179	144	126	109	94	83	75	61	52	26	24	13	11	4	0

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Forde et al. N Engl J Med 2022;386:1973-1985

CheckMate 816 study: addition of neoadjuvant nivolumab to CT improves OS in resectable stage IB-IIIA NSCLC

<u>OS HR</u>: 0.57 (P=.008)*
12.7% improvement in 2Y OS



	No. of Patients	Median Overall Survival (95% CI) *mo*
Nivolumab plus Chemotherapy	179	NR (NR–NR)
Chemotherapy Alone	179	NR (NR–NR)

Hazard ratio for death, 0.57
(99.67% CI, 0.30–1.07)
P=0.008

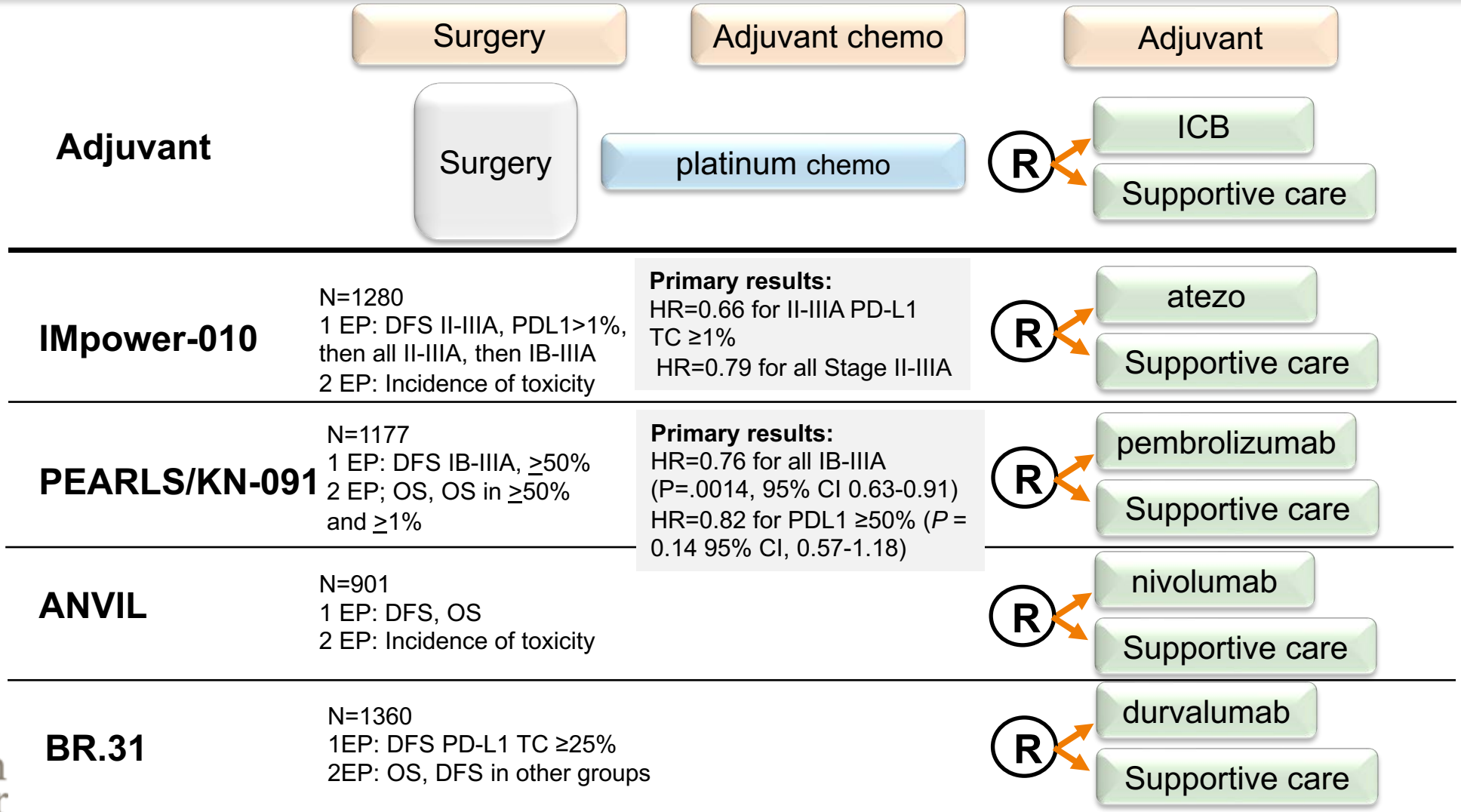
March 4, 2022: FDA approves neoadjuvant nivo/chemo for resectable NSCLC

*prespecific interim OS analysis did not cross boundry for statistical significance

Forde et al. N Engl J Med 2022;386:1973-1985

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

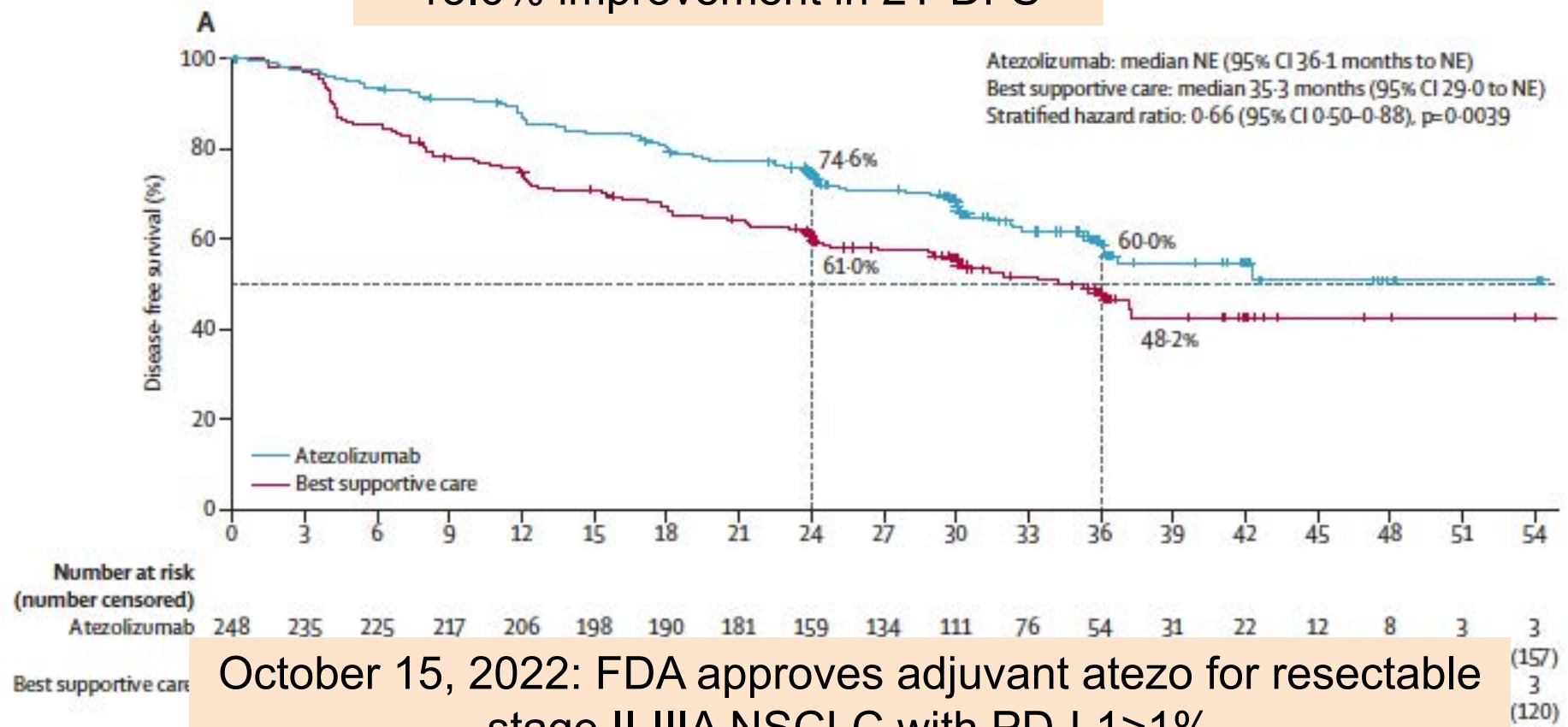
Randomized studies of adjuvant ICB for resectable NSCLC



Felip, Lancet 2021; Paz-Ares, et al. *Annals Oncology*. 2022;33(4):451

IMpower-010 randomized study of adjuvant atezolizumab vs BSC: Primary endpoint of DFS (PD-L1>1%, stage II-IIIA)

HR 0.66 (p=.0039)
13.6% improvement in 2Y DFS

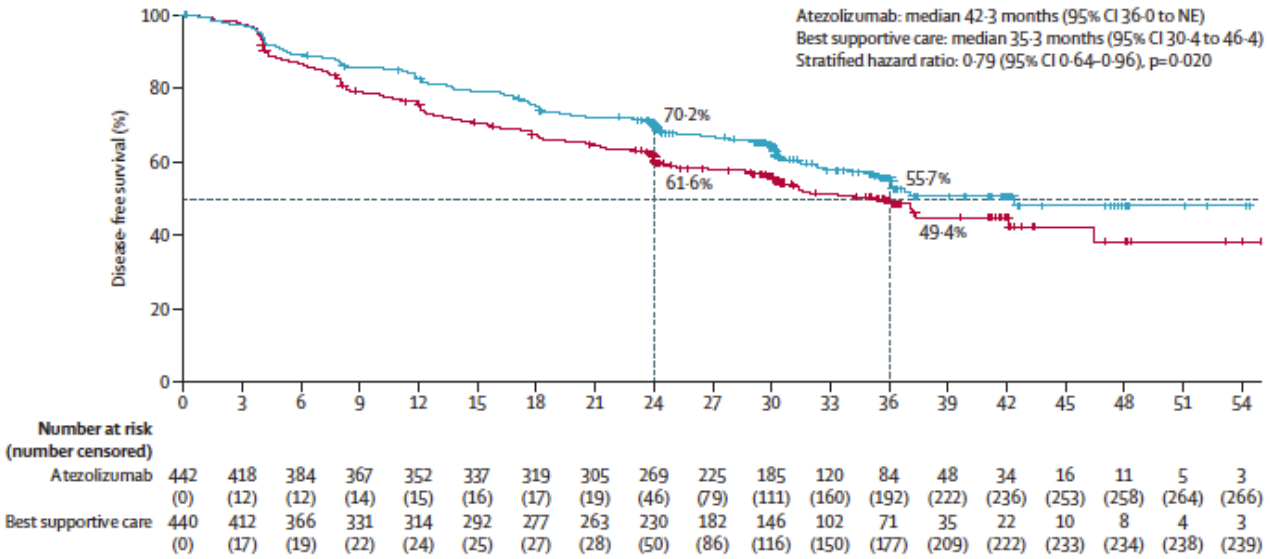


October 15, 2022: FDA approves adjuvant atezo for resectable stage II-IIIA NSCLC with PD-L1≥1%

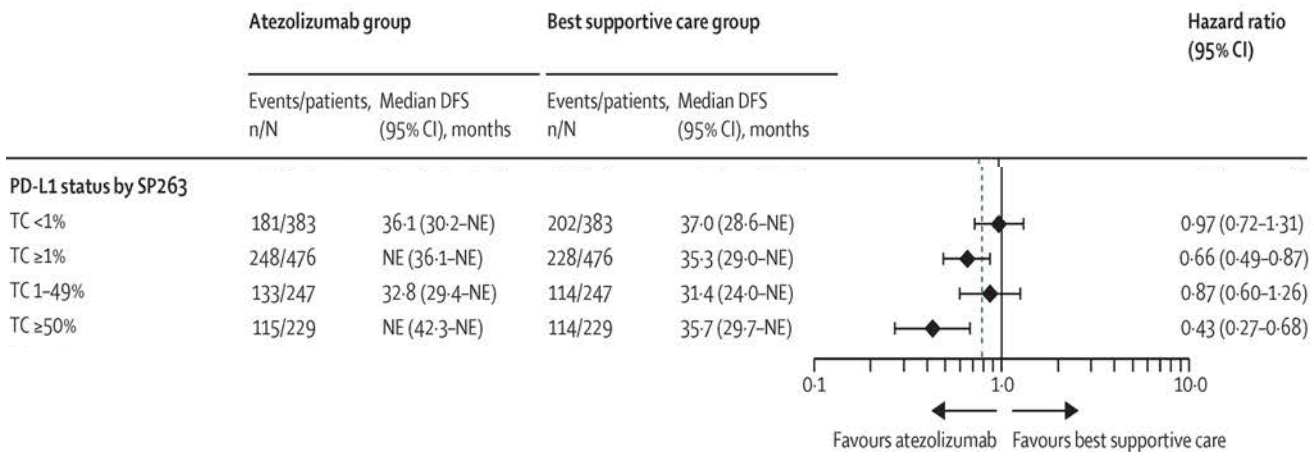
Felip et al, Lancet 2021

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

IMpower-010 randomized study of adjuvant atezolizumab vs BSC: DFS (all stage II-IIIA)



All stage II-IIIA:
HR 0.79 (p=.0039)
8.6% improvement in 2Y DFS



TC<1%:
no benefit
(HR 0.97)

Felip et al, Lancet 2021

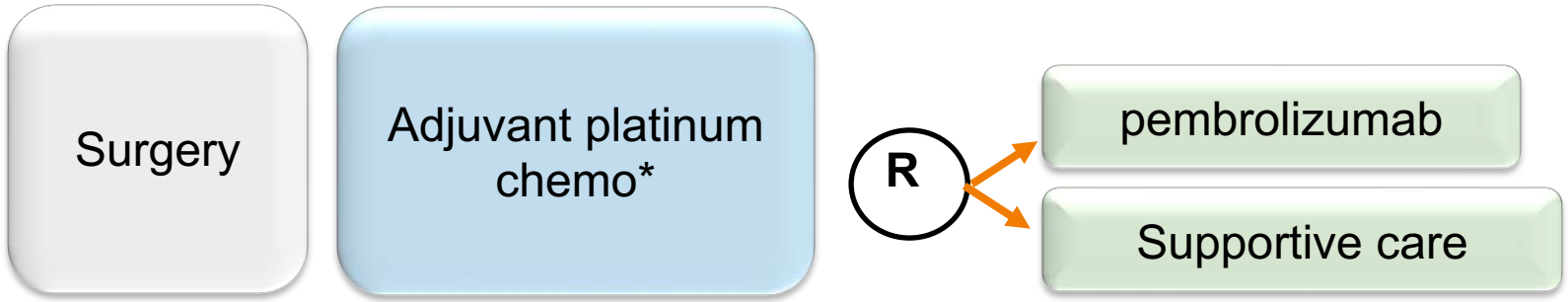
THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

KEYNOTE-091/PEARLS RP3 study of adjuvant pembrolizumab vs BSC for resectable NSCLC

N=1177

- Stage 1B (≥4cm)-IIIA (AJCC 7th edition)
- Any PD-L1 level
- Stratification: stage, prior adjuvant, PD-L1

- Primary endpoint#1: DFS IB-IIIA, ≥50%
- Primary endpoint #2: OS, OS in ≥50% and ≥1%



THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

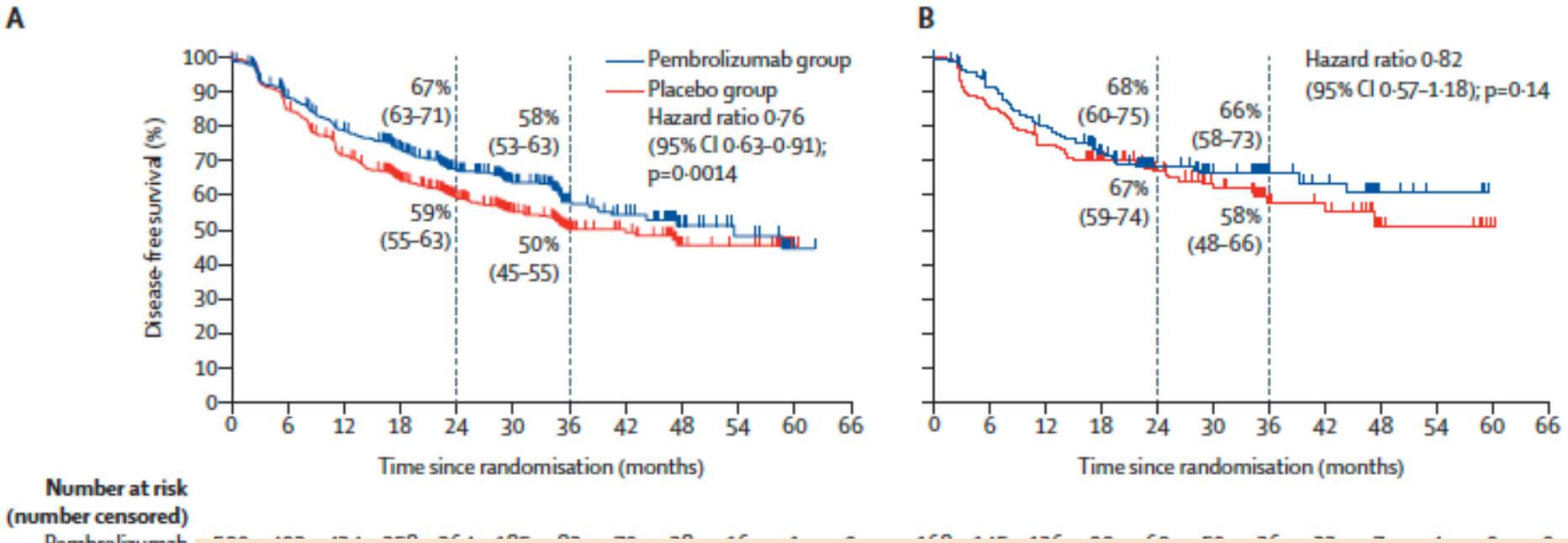
*adjuvant chemo recommended for stage II-IIIA, to be considered for stage IB.

O'Brien et al, Lancet Oncology 2022

KEYNOTE-091/PEARLS RP3 study of adjuvant pembrolizumab vs BSC for resectable NSCLC

Stage IB-IIIA
HR=0.76 (P=.0014,
95% CI 0.63-0.91)

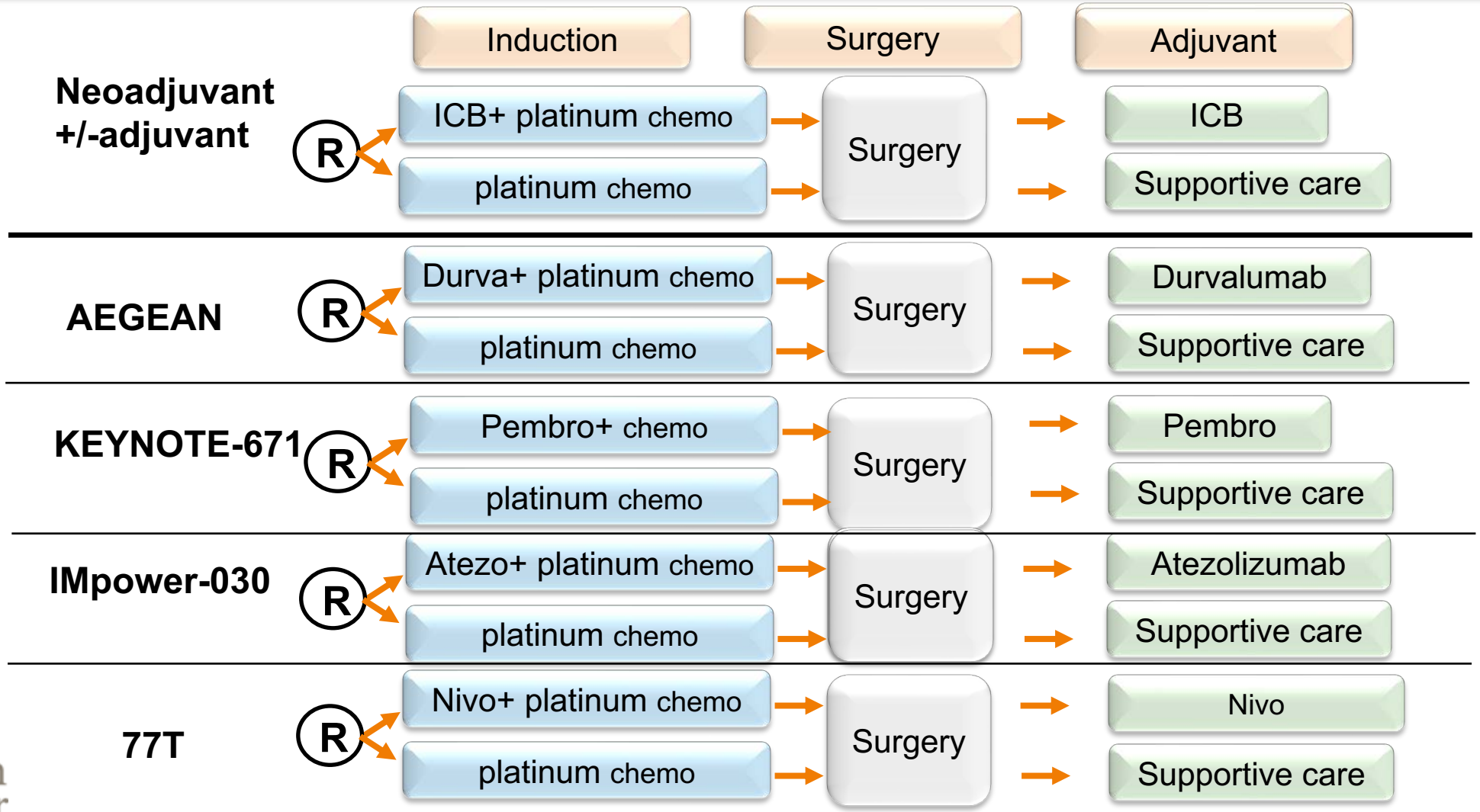
PD-L1>50%
HR=0.82 (P=.14,
95% CI , 0.57-1.18)



January 26, 2023: FDA approves adjuvant pembro following resection and platinum-based chemotherapy for Stage IB, II or IIIA NSCLC

O'Brien et al, Lancet Oncology 2022

Randomized studies of perioperative (neoadjuvant+adjuvant) ICB for resectable NSCLC

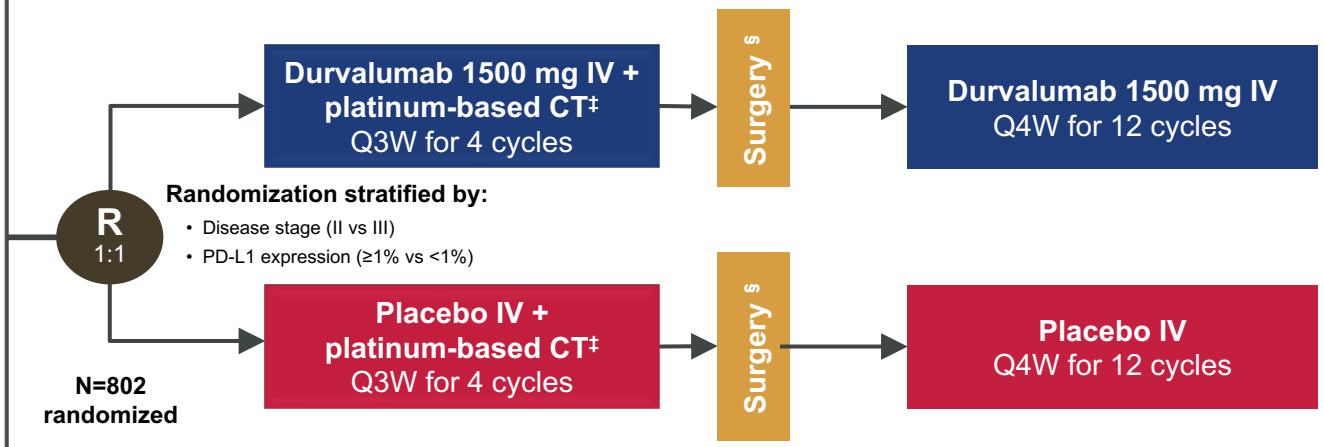


AEGEAN (CT.gov: NCT03800134; WCLC19 abstract P1.18-02), KN671 (CT.gov: NCT03425643, ESMO20 1235 TPS), IMpower030 (CT.gov: NCT03456063, WCLC18 P2.17-27 TPS), CM77T (CT.gov: NCT04025879).

AEGEAN: a phase 3, global, randomized, double-blind, placebo-controlled study of neoadjuvant+adjuvant durvalumab plus neoadjuvant chemo for resectable NSCLC

Study population

- Treatment-naïve
- ECOG PS 0 or 1
- Resectable NSCLC* (stage IIA–IIIB[N2]; AJCC 8th ed)
- Lobectomy, sleeve resection, or bilobectomy as planned surgery*
- Confirmed PD-L1 status†
- No documented *EGFR/ALK* aberrations*



Endpoints: modified ITT population excludes patients with *EGFR/ALK* aberrations¶

Primary:

- pCR by central lab (per IASLC 2020[1])
- EFS using BICR (per RECIST v1.1)

Key secondary:

- MPR by central lab (per IASLC 2020[1])
- DFS using BICR (per RECIST v1.1)
- OS

*The protocol was amended while enrollment was ongoing to exclude (1) patients with tumors classified as T4 for any reason other than size; (2) patients with planned pneumonectomies; and (3) patients with documented *EGFR/ALK* aberrations. †Ventana SP263 immunohistochemistry assay. ‡Choice of CT regimen determined by histology and at the investigator's discretion. For non-squamous: cisplatin + pemetrexed or carboplatin + pemetrexed. For squamous: carboplatin + paclitaxel or cisplatin + gemcitabine (or carboplatin + gemcitabine for patients who have comorbidities or who are unable to tolerate cisplatin per the investigator's judgment). §Post-operative radiotherapy (PORT) was permitted where indicated per local guidance. ¶All efficacy analyses reported in this presentation were performed on the mITT population, which includes all randomized patients who did not have documented *EGFR/ALK* aberrations. AJCC, American Joint Committee on Cancer; BICR, blinded independent central review; DFS, disease-free survival; EFS, event-free survival; mITT, modified intent-to-treat; MPR, major pathologic response; pCR, pathologic complete response.

[1]Travis WD, et al. *J Thorac Oncol* 2020;15:709-40.

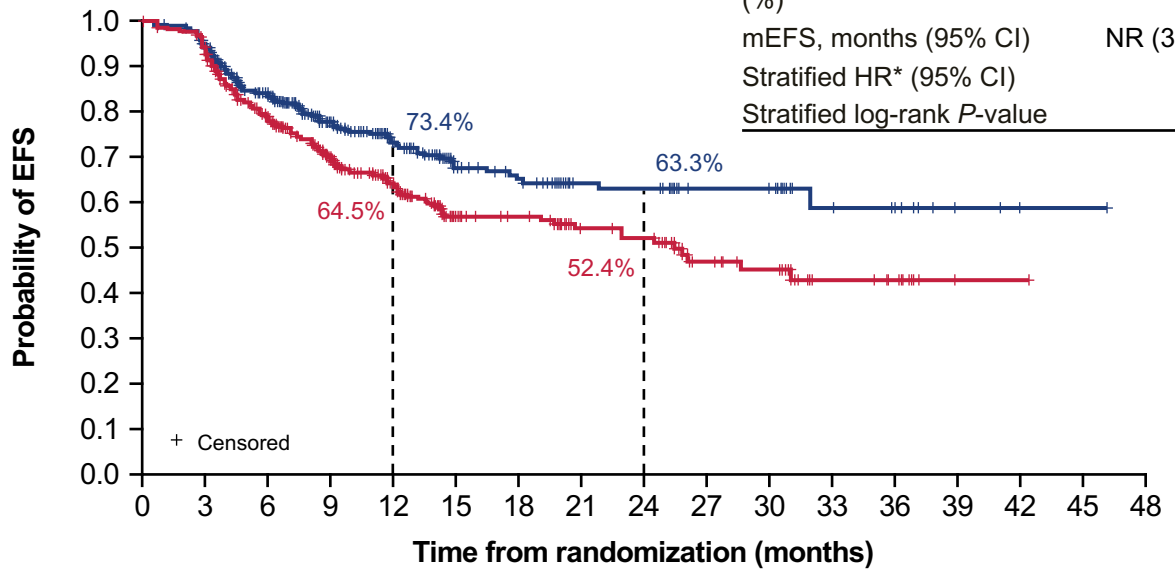
THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Heymach et al, AACR 2023

AEGEAN EFS primary endpoint (BICR in mITT)

First planned interim analysis of EFS

	D arm	PBO arm
No. events / no. patients (%)	98/366 (26.8)	138/374 (36.9)
mEFS, months (95% CI)	NR (31.9–NR)	25.9 (18.9–NR)
Stratified HR* (95% CI)	0.68 (0.53–0.88)	
Stratified log-rank *P*-value	0.003902	



No. at risk:

D arm	366	336	271	194	140	90	78	50	49	31	30	14	11	3	1	1	0
PBO arm	374	339	257	184	136	82	74	53	50	30	25	16	13	1	1	0	0

AEGEAN regimen achieved primary endpoint of EFS (HR 0.68) with 11% improvement in 2Y EFS

Median follow-up (range) in censored patients: 11.7 months (0.0–46.1)

EFS maturity: 31.9%

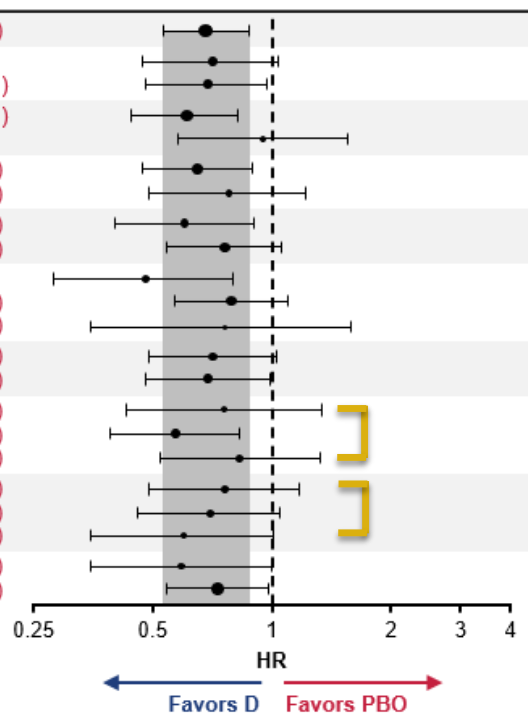
DCO = Nov 10, 2022. EFS is defined as time from randomization to the earliest of: (A) progressive disease (PD) that precludes surgery; (B) PD discovered and reported by the investigator upon attempting surgery that prevents completion of surgery; (C) local/distant recurrence using BICR per RECIST v1.1; or (D) death from any cause. *HR <1 favors the D arm versus the PBO arm. Median and landmark estimates calculated using the Kaplan–Meier method; HR calculated using a stratified Cox proportional hazards model; and *P*-value calculated using a stratified log rank test. Stratification factors: disease stage (II vs III) and PD-L1 expression status (<1% vs ≥1%). Significance boundary = 0.009899 (based on total 5% alpha), calculated using a Lan-DeMets alpha spending function with O'Brien Fleming boundary. mEFS, median EFS; NR, not reached.

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Heymach et al, AACR 2023

AEGEAN EFS by subgroup (BICR in mITT)

Subgroup		n	Median EFS, months (95% CI) D arm (N=366)	PBO arm (N=374)	HR (95% CI)
All patients		740	NR (31.9–NR)	25.9 (18.9–NR)	0.68 (0.53–0.88)
Age at randomization	<65 years	358	NR (NR–NR)	NR (18.9–NR)	0.71 (0.47–1.04)
	≥65 years	382	NR (17.9–NR)	24.5 (13.6–31.1)	0.69 (0.48–0.97)
Sex	Male	530	NR (31.9–NR)	22.9 (14.3–31.1)	0.61 (0.44–0.82)
	Female	210	NR (17.5–NR)	NR (13.6–NR)	0.95 (0.58–1.56)
ECOG PS	0	506	NR (31.9–NR)	25.4 (14.3–NR)	0.65 (0.47–0.89)
	1	234	NR (21.8–NR)	25.9 (14.3–NR)	0.78 (0.49–1.22)
Race*	Asian	307	NR (NR–NR)	25.4 (13.9–NR)	0.60 (0.40–0.90)
	Non-Asian	433	31.9 (21.8–NR)	26.2 (14.3–NR)	0.76 (0.54–1.06)
Smoking	Current	190	NR (NR–NR)	14.3 (8.1–NR)	0.48 (0.28–0.80)
	Former	443	NR (31.9–NR)	25.9 (19.5–NR)	0.79 (0.57–1.10)
	Never	107	NR (NR–NR)	24.5 (14.3–NR)	0.76 (0.35–1.58)
Histology	Squamous	360	NR (31.9–NR)	26.2 (13.0–NR)	0.71 (0.49–1.03)
	Non-squamous	375	NR (NR–NR)	25.4 (14.3–NR)	0.69 (0.48–0.99)
Disease stage (AJCC 8th ed.)	Stage II	214	NR (NR–NR)	31.1 (25.4–NR)	0.76 (0.43–1.34)
	Stage IIIA	338	NR (NR–NR)	19.5 (11.7–NR)	0.57 (0.39–0.83)
	Stage IIIB	186	31.9 (11.7–NR)	18.9 (11.8–NR)	0.83 (0.52–1.32)
PD-L1 expression at baseline†	TC <1%	247	NR (14.9–NR)	20.6 (13.9–NR)	0.76 (0.49–1.17)
	TC 1–49%	277	NR (31.9–NR)	25.4 (12.2–NR)	0.70 (0.46–1.05)
	TC ≥50%	216	NR (NR–NR)	26.2 (14.3–NR)	0.60 (0.35–1.01)
Planned neoadjuvant platinum agent	Cisplatin	196	NR (NR–NR)	31.1 (14.3–NR)	0.59 (0.35–1.00)
	Carboplatin	544	NR (31.9–NR)	25.4 (14.3–NR)	0.73 (0.54–0.98)



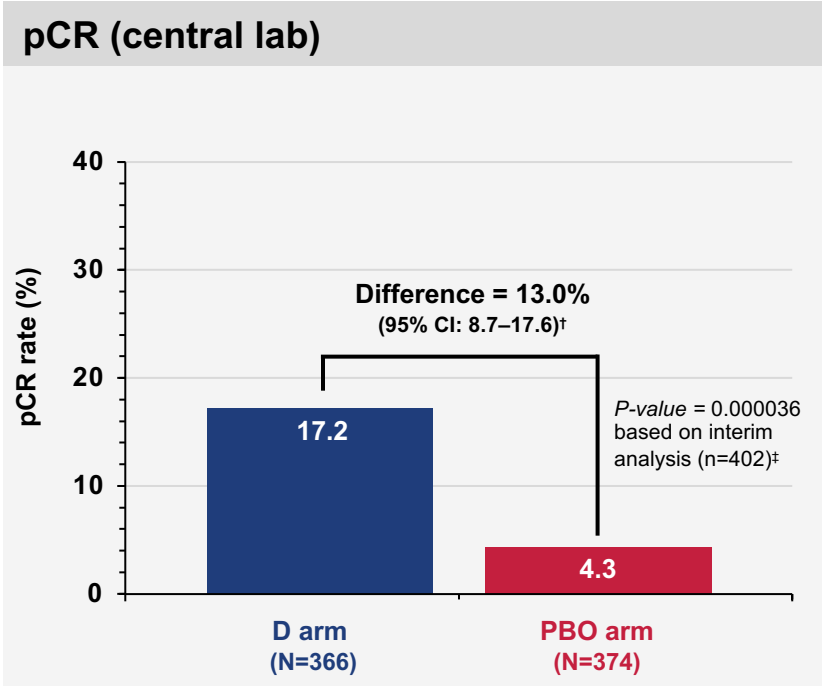
DCO = Nov 10, 2022; median EFS follow-up in censored patients: 11.7 months (range: 0.0–46.1); EFS maturity: 31.9%. Median calculated using the Kaplan–Meier method; HR for all patients (mITT) calculated using a stratified Cox proportional hazards model. HRs for subgroups calculated using unstratified Cox proportional hazards models. The size of circles is proportional to the number of events for each subgroup, and the horizontal bars represent the 95% CIs. *Race was self-reported per the electronic case report form. †Determined using the Ventana SP263 immunohistochemistry assay.

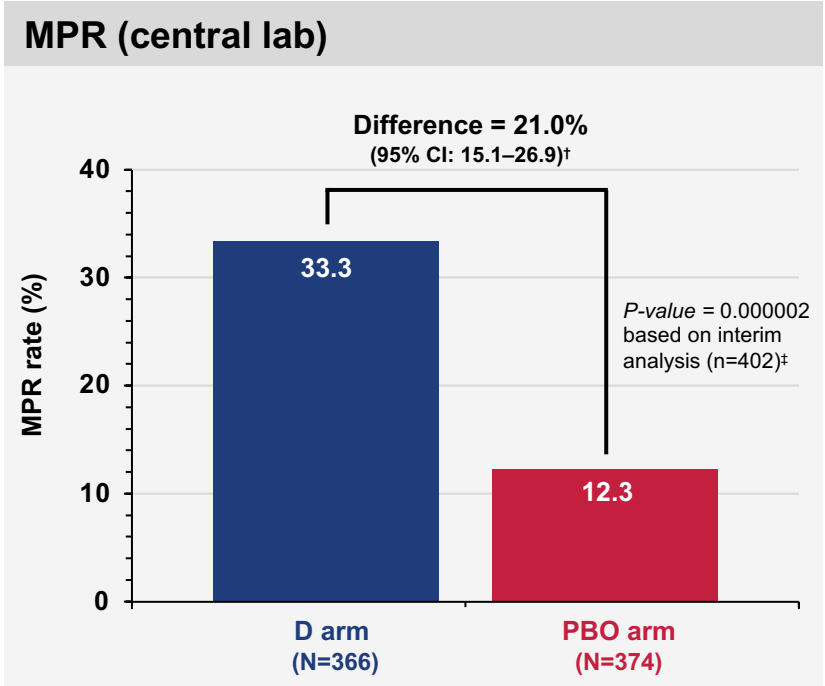
EFS benefit across subgroups including stages, platinum chemo, and PD-L1 levels (HR in PD-L1>50%=.60, PD-L1<1%= 0.76)

Heymach et al, AACR 2023

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

AEGEAN primary endpoint of pathologic complete response (Final analysis in mITT; per IASLC 2020 methodology*)





Achieved primary endpoint of significant improvement in path CR as well as MPR

*Using IASLC recommendations for pathologic assessment of response to therapy, including gross assessment and processing of tumor bed (Travis WD, et al. *J Thorac Oncol* 2020;15:709-40). pCR = a lack of any viable tumor cells after complete evaluation of the resected lung cancer specimen
and all sampled regional lymph nodes. MPR = less than or equal to 10% viable tumor cells in lung primary tumor after complete evaluation of the resected lung cancer specimen. To be eligible for pathologic assessment, patients needed to have received three cycles of neoadjuvant study Tx per protocol. Patients who were not evaluable were classified as non-responders. †CIs calculated by stratified Miettinen and Nurminen method. ‡No formal statistical testing was performed at the pCR final analysis (DCO: Nov 10, 2022; n=740 [data shown]). Statistical significance was achieved at the interim pCR analysis (DCO: Jan 14, 2022; n=402; *P*-value for pCR/MPR calculated using a stratified Cochran-Mantel-Haenszel test with a significance boundary = 0.000082 calculated using a Lan-DeMets alpha spending function with O'Brien Fleming boundary).

Heymach et al, AACR 2023

AEGEAN AE summary (safety analysis set)*

Overall study period (inclusive of the neoadjuvant, surgical, and adjuvant Tx phases)†	**D arm (N=400)**	**PBO arm (N=399)**
Any-grade all-causality AEs, n (%)	386 (96.5)	378 (94.7)
Max. grade 3 or 4	169 (42.3)	173 (43.4)
SAE	150 (37.5)	126 (31.6)
Outcome of death	23 (5.8)	15 (3.8)
Leading to discontinuation of D / PBO	48 (12.0)	24 (6.0)
Leading to cancellation of surgery	7 (1.8)	4 (1.0)
Any-grade AEs possibly related to D / PBO / CT, n (%)	346 (86.5)	322 (80.7)
Max. grade 3 or 4	129 (32.3)	132 (33.1)
Outcome of death‡	7 (1.8)	2 (0.5)
Any-grade immune-mediated AEs§, n (%)	94 (23.5)	39 (9.8)
Grade 3 or 4	16 (4.0)	10 (2.5)
Pneumonitis (any grade)¶	15 (3.8)	7 (1.8)

No increase in Gr3/4 AEs; IrAEs rare and largely Gr1/2 for AEGEAN regimen

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

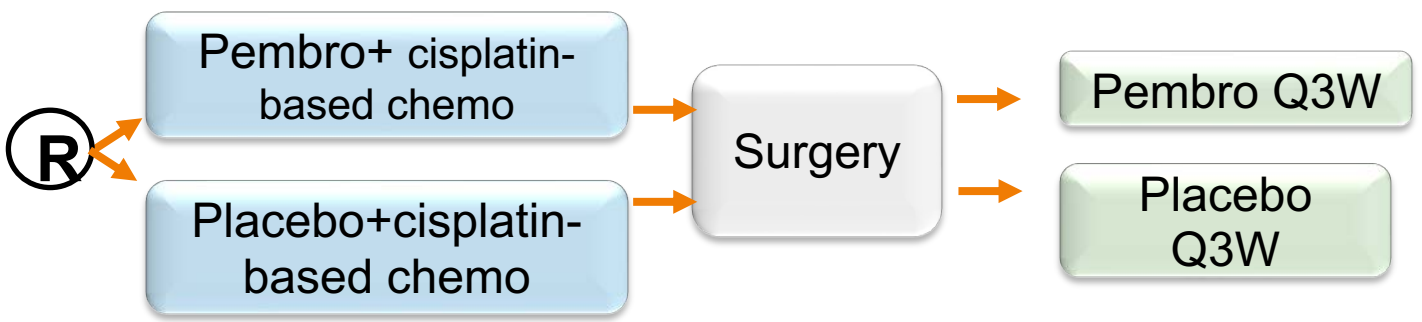
DCO = Nov 10, 2022. *The safety analysis set includes all randomized patients who received ≥1 dose of study Tx; AEs were graded using Common Terminology Criteria for Adverse Events v5.0. †First dose of study Tx (D / PBO / CT) until the earliest of: the last dose of study Tx or surgery + 90 days (taking the latest dose of D / PBO / CT / date of surgery, + 90 days); the DCO date; or the date of the first dose of subsequent anti-cancer Tx. ‡Included interstitial lung disease (n=2) and immune-mediated lung disease, pneumonitis, hemoptysis, myocarditis, and decreased appetite (n=1 each) in the D arm and pneumonia and infection (n=1 each) in the PBO arm. §An AE of special interest consistent with an immune-mediated mechanism of action, where there is no clear alternate etiology, and requiring the use of systemic corticosteroids or other immunosuppressants and/or, for specific endocrine events, endocrine therapy. ¶Pneumonitis is summarized as a grouped term comprising the 'pneumonitis', 'interstitial lung disease', and 'immune-mediated lung disease' preferred terms. AE, adverse event; SAE, serious AE.

Heymach et al, AACR 2023

KEYNOTE-671: perioperative pembrolizumab plus neoadjuvant chemo for resectable NSCLC

Study population

- N=786
- Resectable stage II, IIIA, or IIIB (T3-4N2)
- ECOG PS 0 or 1

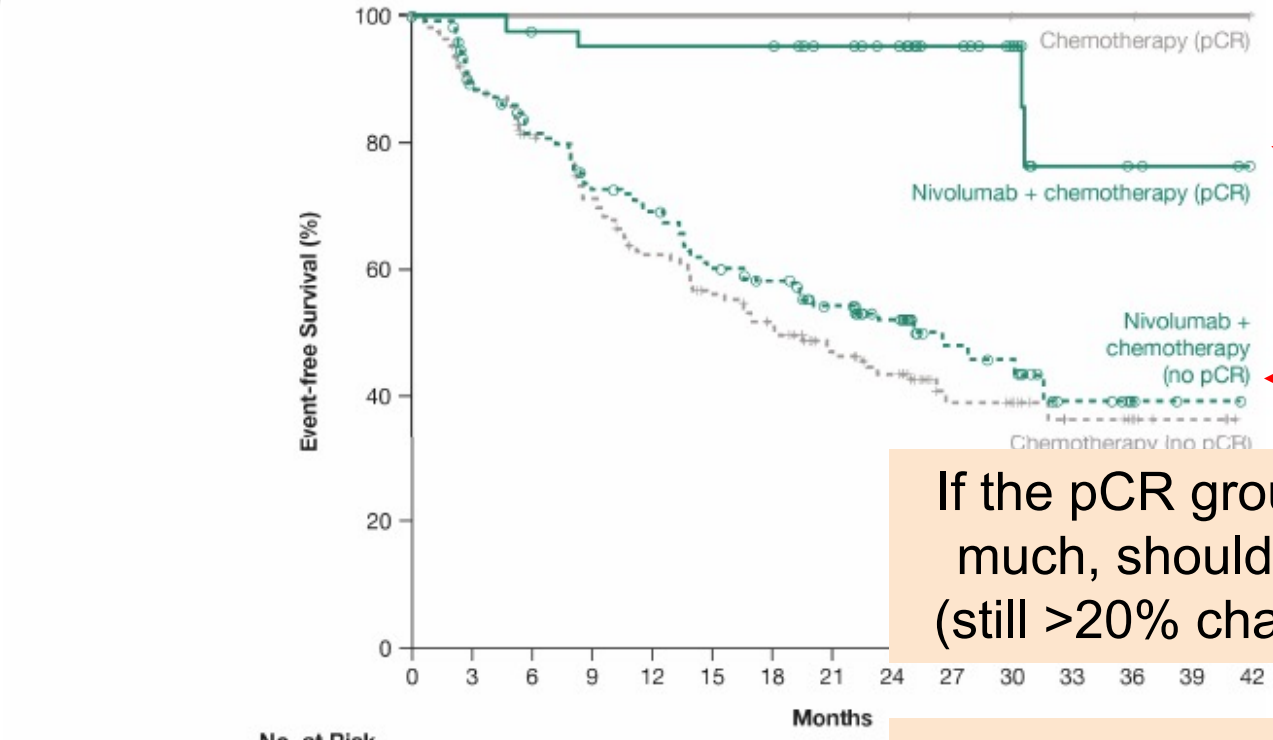


Press release March 1, 2023: pembrolizumab showed statistically significant improvement in EFS as well as key secondary endpoints (pCR, MPR). No new safety signals detected.
PDUFA data Oct 16, 2023

ClinicalTrials.gov, NCT03425643

Adjuvant, neoadjuvant, or both?
Where do we go from here?

Can pathological response help risk-stratify patients and identify those needing intensification?



pCR vs no pCR patients for nivo+chemo: **HR 0.13** (arm)

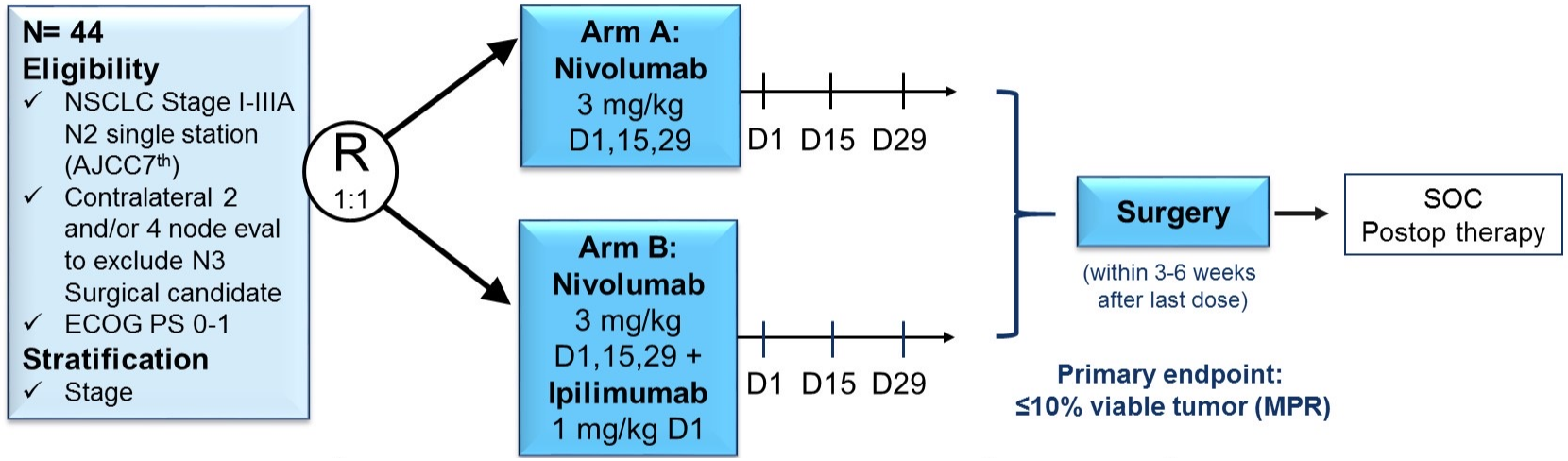
If the pCR group is benefitting so much, shouldn't they continue? (still >20% chance of recurrence)

If the no pCR group hasn't responded as well, should they get a different type of therapy?

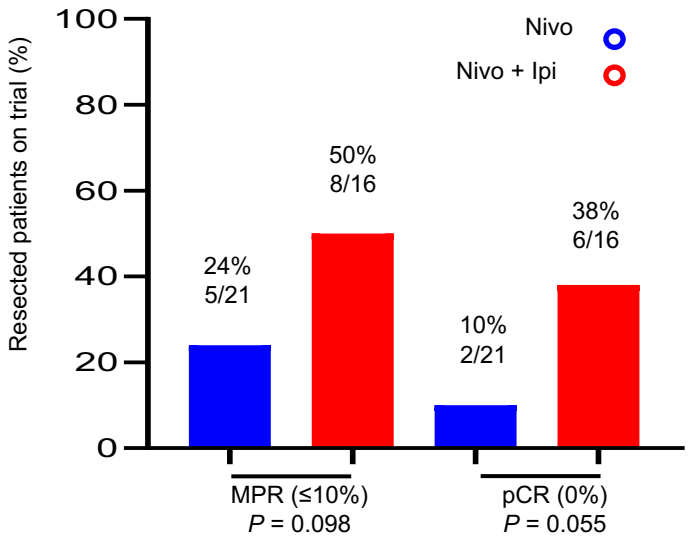
THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Forde et al. N Engl J Med 2022;386:1973-1985

Testing neoadjuvant combinations: the phase II NEOSTAR study



Path CR rate:
Nivo: 10%
Nivo/Ipi: 38%



Cascone et al, Nat Med 2021

NeoCOAST platform study of neoadjuvant ICB combinations in resectable NSCLC

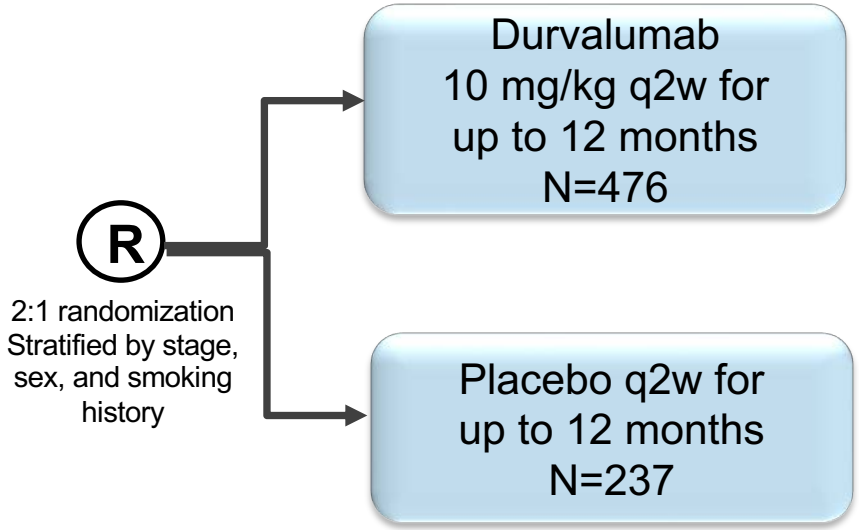
- Durva combinations with:
  - Oleclumab: CD73 (adenosine pathway)
  - Monalizumab: NKG2A target (NK, CD8+)
  - Danvatirsen: STAT3 antisense

	Durva (n=27)	Durva + Ole (n=21)	Durva + Mona (n=20)	Durva + Danva (n=16)
Pathologic responses				
MPR, n (%)	**3 (11.1)**	**4 (19.0)**	**6 (30.0)**	**5 (31.3)**
pCR, n (%)	1 (3.7)	2 (9.5)	2 (10.0)	2 (12.5)
Responses by RECIST v1.1				
ORR, n (%)	2 (7.4)	1 (4.8)	3 (15.0)	1 (6.3)
Objective responses, n (%)				
PR	2 (7.4)	1 (4.8)	3 (15.0)	1 (6.3)
SD	22 (81.5)	17 (81.0)	15 (75.0)	14 (87.5)
PD	1 (3.7)	3 (14.3)	1 (5.0)	1 (6.3)
NE	1 (3.7)	0	1 (5.0)	0

Cascone T et al,. AACR Annual Meeting 2022

PACIFIC: phase III RCT comparing consolidation durvalumab vs placebo after cCRT for stage III unresectable NSCLC

- N=713
- Stage III, locally advanced, unresectable NSCLC who have not progressed following definitive platinum-based cCRT (≥2 cycles)
- PS 0 -1, life expectancy >12w



Primary endpoints

- PFS by BICR
- OS

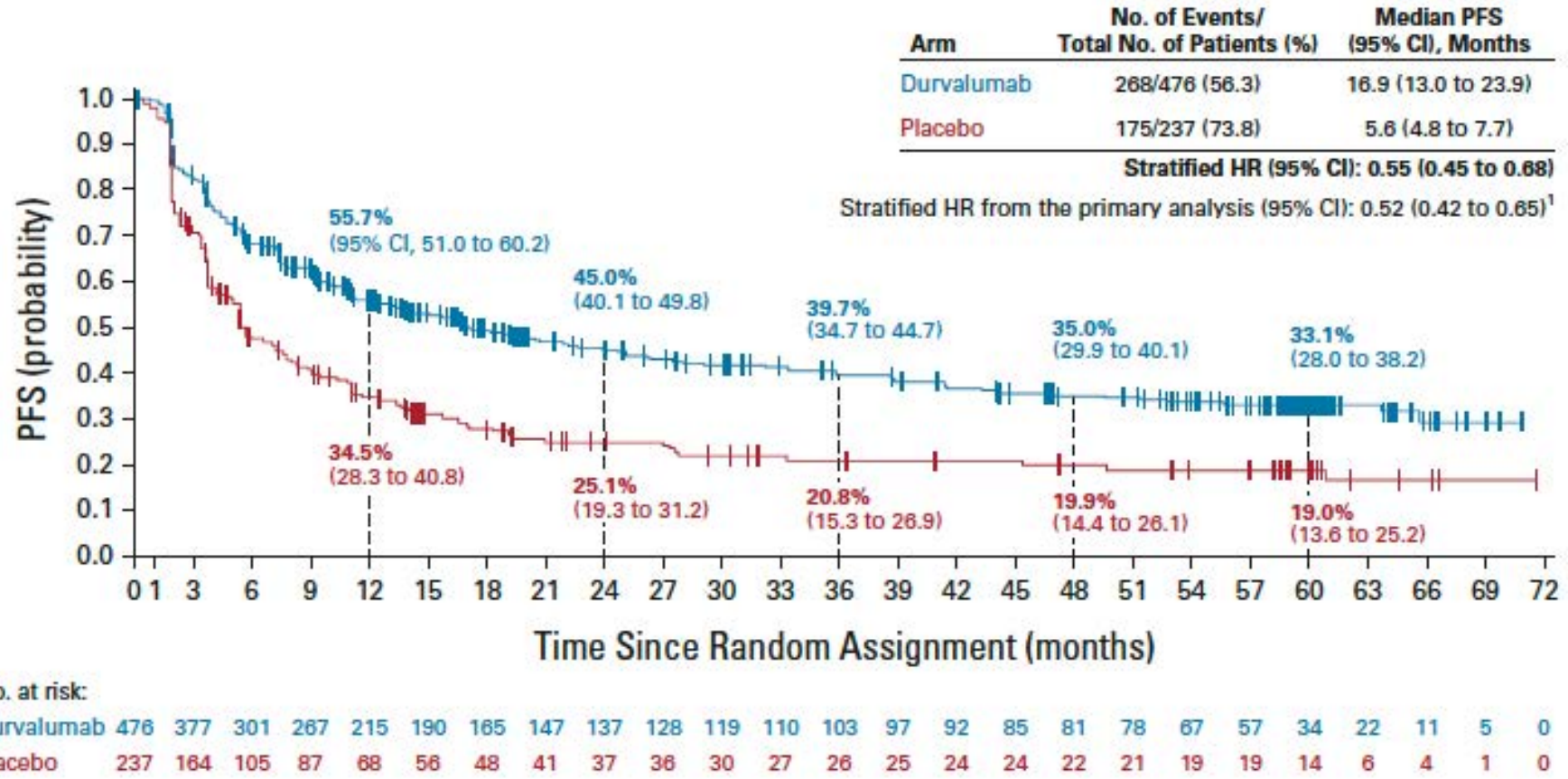
Key secondary endpoints

- ORR (per BICR)
- DoR (per BICR)
- Safety and tolerability
- PROs

*ClinicalTrials.gov number: NCT02125461 BICR, blinded independent central review; cCRT, concurrent chemoradiation therapy; PROs, patient-reported outcomes;

Antonia et al, NEJM 2017; Spigel et al, JCO 2022

PACIFIC: 5-year PFS outcomes



PFS HR 0.55

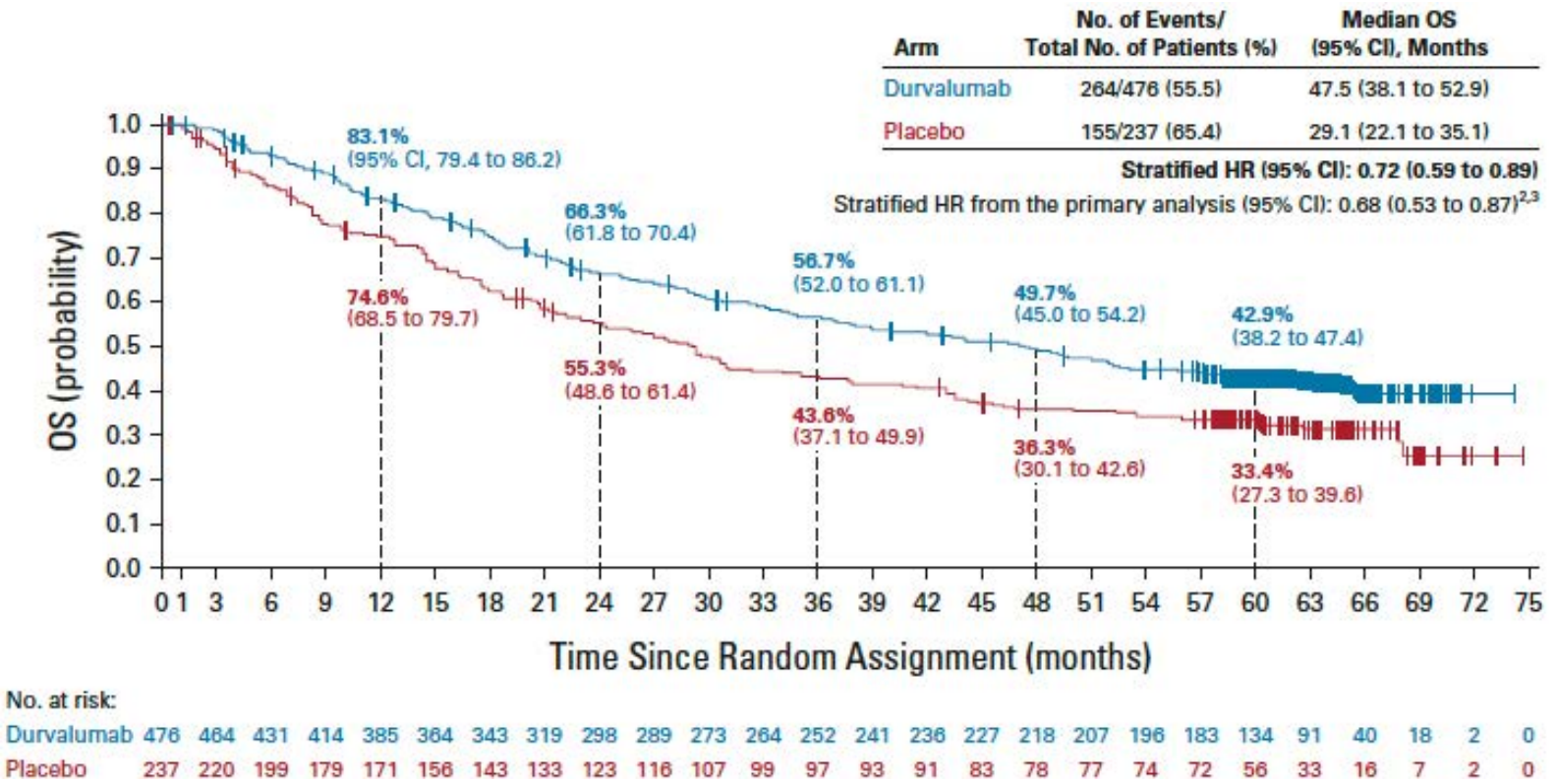
mPFS: 16.9m vs 5.6m

~14% improvement in 5Y PFS

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Spigel et al, JCO 2022

PACIFIC: 5-year overall survival outcomes



OS HR 0.72

mOS: 47.5m vs 29.1m

~9.5% improvement in 5Y survival

Sustained and meaningful PFS + OS benefits observed for PACIFIC regimen

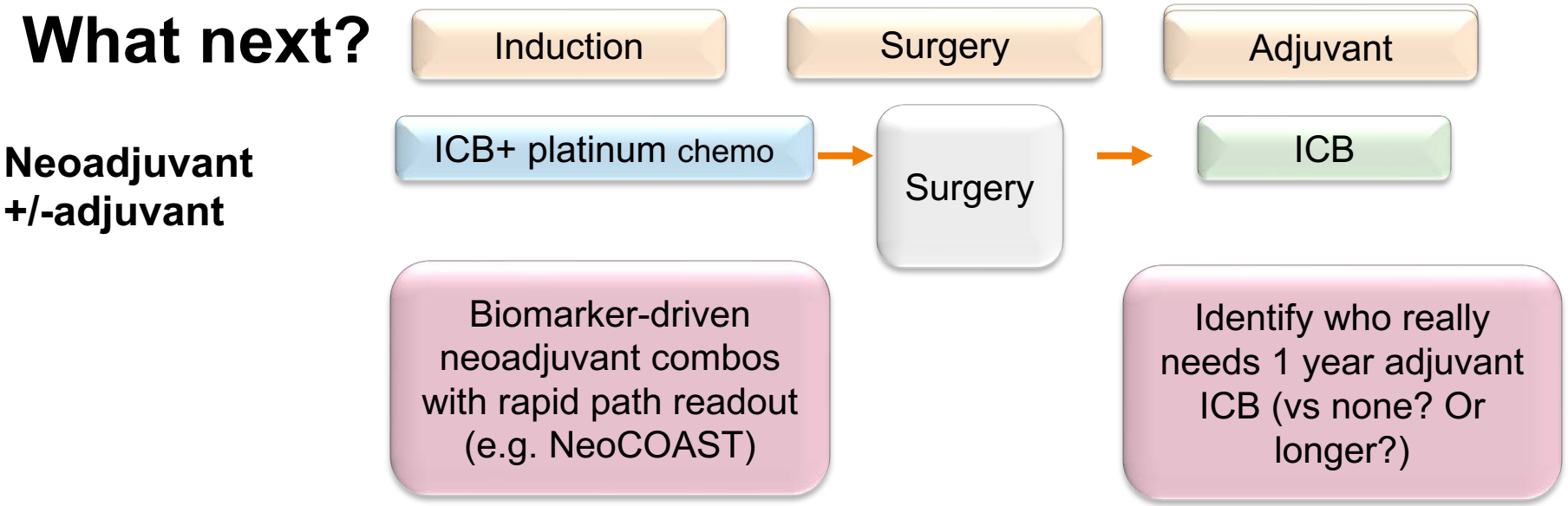
THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Spigel et al, JCO 2022

ICB for non-metastatic NSCLC: the bottom line

- Both neoadjuvant (nivo) and adjuvant ICB (atezo, pembro) significantly improve outcomes and are FDA approved; neoadjuvant may give more benefit with shorter duration
- Perioperative ICB (durvalumab in AEGEAN; pembrolizumab in KEYNOTE-671) improve outcomes, although long term benefits, advantages vs neoadjuvant or adjuvant will require longer follow-up
- Consolidation durvalumab in PACIFIC: sustained, robust PFS/OS gains

What next?



Agenda

Module 1: Incorporation of Immunotherapeutic Strategies into the Management of Nonmetastatic Non-Small Cell Lung Cancer (NSCLC) — Dr Heymach

Module 2: Contemporary Treatment for Localized or Metastatic NSCLC with an EGFR Mutation — Dr Yu

Module 3: Research Advances Shaping the Current and Future Treatment of Metastatic NSCLC with ALK Rearrangements, ROS1 Rearrangements or RET Fusions — Dr Langer

Module 4: Targeting MET, HER2 and KRAS Alterations in NSCLC — Dr Spigel

Module 5: Current Management of Metastatic NSCLC without a Targetable Tumor Mutation — Dr Garon

Module 6: Future Directions in the Management of Metastatic NSCLC — Dr Leal

RTP RESEARCH TO PRACTICE

FDA Approved Agents For Various Oncogenic Targets in NSCLC

EGFR	ALK	ROS1	BRAF	MET	RET	TRK	KRAS G12C	HER2
Erlotinib	Crizotinib	Crizotinib	Dabrafenib	Capmatinib	Selpercatinib	Larotrectinib	Sotorasib	Trastuzumab deruxtecan
Gefitinib	Ceritinib	Entrectinib	Trametinib	Tepotinib	Pralsetinib	Entrectinib	Adagrasib	
Afatinib	Brigatinib							
Osimertinib	Alectinib							
Dacomitinib	Lorlatinib							
Ramucirumab + erlotinib								
Amivantamab								
Mobocertinib								

https://www.fda.gov/drugs/resources-information-approved-drugs/oncology-cancer-hematologic-malignancies-approval-notifications; Accessed June 2023.

RTP RESEARCH TO PRACTICE

Use of adjuvant osimertinib for patients with EGFR mutation-positive localized NSCLC

Melissa Johnson, MD

Matthew Gubens, MD, MS

Jarushka Naidoo, MB BCH, MHS

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, in general, which adjuvant treatment 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%?

 Dr Garon	Osimertinib
 Dr Heymach	Chemotherapy → osimertinib
 Dr Langer	Chemotherapy → osimertinib
 Dr Leal	Chemotherapy → osimertinib
 Dr Spigel	Osimertinib
 Dr Yu	Osimertinib
 Dr Gubens	Osimertinib
 Dr Johnson	Chemotherapy → osimertinib
 Dr Naidoo	None

RTP RESEARCH TO PRACTICE

For a patient with an EGFR mutation who does not wish to receive chemotherapy, in which situations, if any, would you be comfortable administering adjuvant osimertinib alone?

 Dr Garon	The same situations in which I would be willing to give it after chemo
 Dr Heymach	Resectable Stage IB-III
 Dr Langer	Stage IB-IIIA, but would carefully explore reasons for rejecting chemo
 Dr Leal	Resected Stage IB-IIIA
 Dr Spigel	Probably any
 Dr Yu	Stage IB, II or III
 Dr Gubens	Any candidate for adj osi, after discussion of potential curative benefit the pt is choosing to forgo
 Dr Johnson	Stage IB-IIIA
 Dr Naidoo	If they refuse/have a contraindication to chemo

Osi = osimertinib

Potential implications of FLAURA2

Melissa Johnson, MD

Matthew Gubens, MD, MS

Jarushka Naidoo, MB BCH, MHS

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, in which situations, if any, would you like to use osimertinib in combination with chemotherapy for your patients with metastatic NSCLC with an EGFR mutation?

 Dr Garon	Would consider in young pts
 Dr Heymach	Bulky disease, bad genetics (eg, p53 mutation)
 Dr Langer	Highly symptomatic disease, large tumor burden
 Dr Leal	Resistance setting w/ no targetable mechanism of resistance and no evidence of CNS progression
 Dr Spigel	After osimertinib
 Dr Yu	High-risk disease — lack of ctDNA clearance or atypical EGFR mutation
 Dr Gubens	Pts who do not clear ctDNA shortly after starting osi; may also consider co-mutations TP53/RB1 at diagnosis
 Dr Johnson	Young pt "wanting to do everything" or concurrent mutations such as PIK3CA or TP53
 Dr Naidoo	None yet

Osi = osimertinib

Promising investigational strategies for progressive EGFR-mutant disease

Melissa Johnson, MD

Matthew Gubens, MD, MS

Jarushka Naidoo, MB BCH, MHS

If you could access patritumab deruxtecan today, would you attempt to administer it prior to chemotherapy for your patients with metastatic nonsquamous NSCLC with an EGFR mutation experiencing disease progression on osimertinib?

 Dr Garon	No	 Dr Yu	No
 Dr Heymach	Yes	 Dr Gubens	Yes
 Dr Langer	Yes	 Dr Johnson	Yes
 Dr Leal	No	 Dr Naidoo	No
 Dr Spigel	Yes		

RTP RESEARCH TO PRACTICE

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

 Dr Garon	No	 Dr Yu	No
 Dr Heymach	Yes	 Dr Gubens	Yes
 Dr Langer	Yes	 Dr Johnson	Yes
 Dr Leal	No	 Dr Naidoo	Yes
 Dr Spigel	No		

RTP RESEARCH TO PRACTICE

Sequencing of therapies for metastatic NSCLC with EGFR exon 20 insertion mutations

Melissa Johnson, MD

Matthew Gubens, MD, MS

Jarushka Naidoo, MB BCH, MHS

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, what would be your preferred first-line treatment for a patient with metastatic nonsquamous NSCLC with an EGFR exon 20 insertion mutation and a TPS of 50%?

 Dr Garon	Carboplatin/ pemetrexed
 Dr Heymach	Chemo + amivantamab
 Dr Langer	Carbo/pem/bev or carbo/pem/pembro
 Dr Leal	Platinum/pemetrexed +/- bevacizumab
 Dr Spigel	Carbo/pem/pembro
 Dr Yu	Carbo/pem/bev
 Dr Gubens	Carbo/pem/bev
 Dr Johnson	Carboplatin/ pemetrexed
 Dr Naidoo	Amivantamab or mobocertinib

Carbo = carboplatin; pem = pemetrexed; bev = bevacizumab; pembro = pembrolizumab

RTP RESEARCH TO PRACTICE

What would be your preferred initial targeted therapy for a 65-year-old asymptomatic patient with metastatic nonsquamous NSCLC and an EGFR exon 20 insertion mutation?

 Dr Garon	Amivantamab
 Dr Heymach	Amivantamab
 Dr Langer	Amivantamab
 Dr Leal	Amivantamab
 Dr Spigel	No preference
 Dr Yu	Amivantamab
 Dr Gubens	Mobocertinib
 Dr Johnson	Amivantamab
 Dr Naidoo	No preference

RTP RESEARCH TO PRACTICE

Memorial Sloan Kettering Cancer Center

Contemporary treatment for localized or metastatic NSCLC with an EGFR mutation

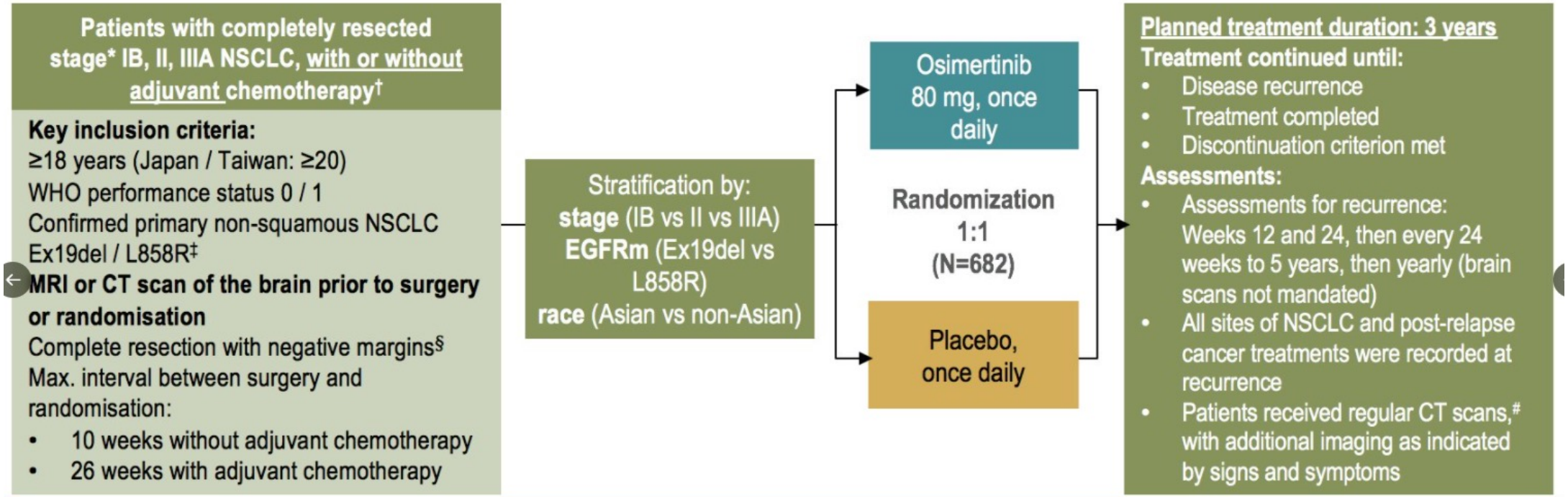
Helena Yu, MD
Associate Attending
Research Director, Thoracic Oncology Service
Memorial Sloan Kettering Cancer Center

Outline

- Targeted therapy in early-stage EGFR+ NSCLC
- First-line treatment for metastatic EGFR+ NSCLC
- Mechanisms of resistance to osimertinib
- Osimertinib-based combinations
- Targeted therapies after osimertinib
- Treatment of metastatic EGFR exon 20 positive NSCLC

Osimertinib in Early-Stage Disease

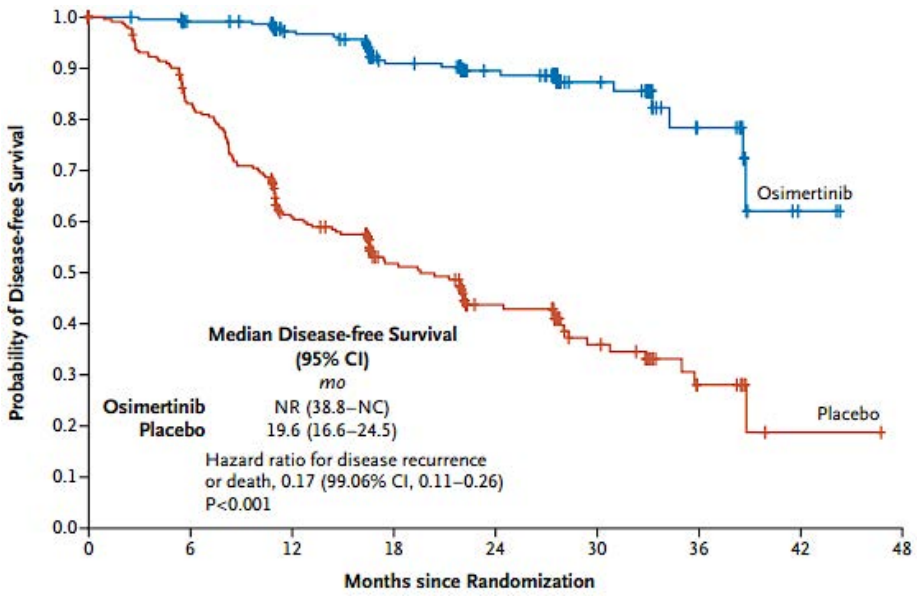
ADAURA: Phase III double-blind study design



- The primary and key secondary endpoints of DFS¶ in stage II/IIIA patients and the overall population, respectively, have been reported previously[1]
- **Here we report results from a pre-specified exploratory analysis of disease recurrence patterns in ADAURA, including CNS**

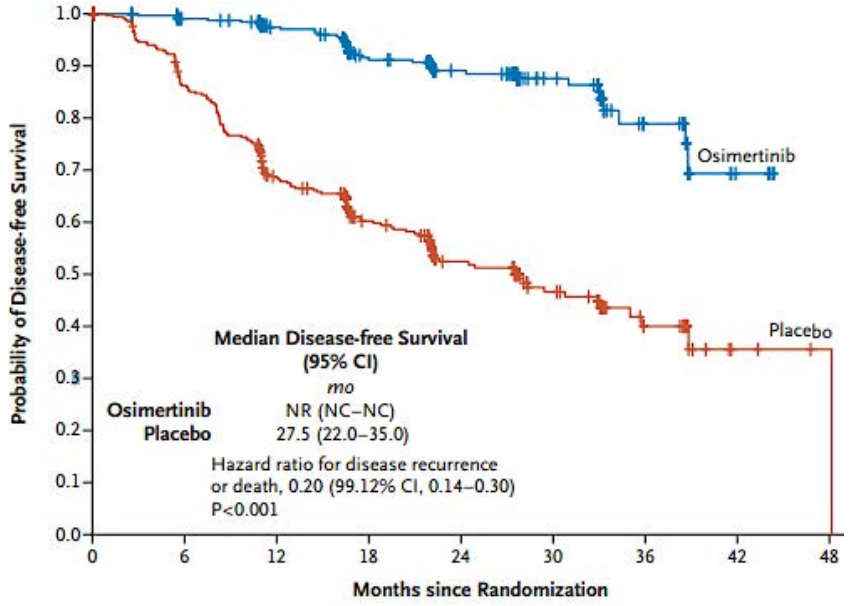
Osimertinib in Early-Stage Disease

Stage 2-3A



	Median DFS, months (95% CI)	HR (99.06% CI)
– Osimertinib	NR (38.8, NC)	0.17 (0.11, 0.26)
– Placebo	19.6 (16.6, 24.5)	P<0.0001

Stage 1B-3A



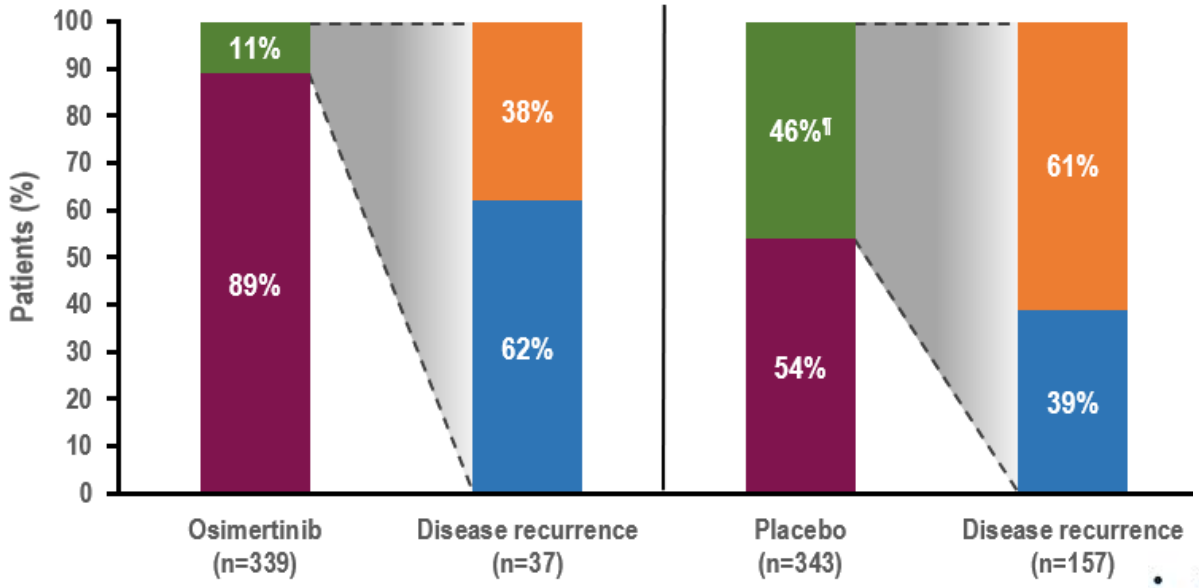
	Median DFS, months (95% CI)	HR (99.12% CI)
– Osimertinib	NR (NC, NC)	0.20 (0.14, 0.30)
– Placebo	27.5 (22.0, 35.0)	P<0.0001

- Benefit deepened with higher stage but remained across all stages, all subgroups and with/without adjuvant chemotherapy
- Update ESMO 2022 with continued HR DFS benefit (HR 0.23).
- Two things can be true- delaying recurrence for some, curing others

Memorial Sloan Kettering Cancer Center

Tsuboi M et al. 2022 ESMO Congress. Abstract LBA47. Wu YL et al. *N Engl J Med*. 2020;383(18):1711-1723.

Osimertinib in Early-Stage Disease



Patient disposition*
- DFS event
- No DFS event

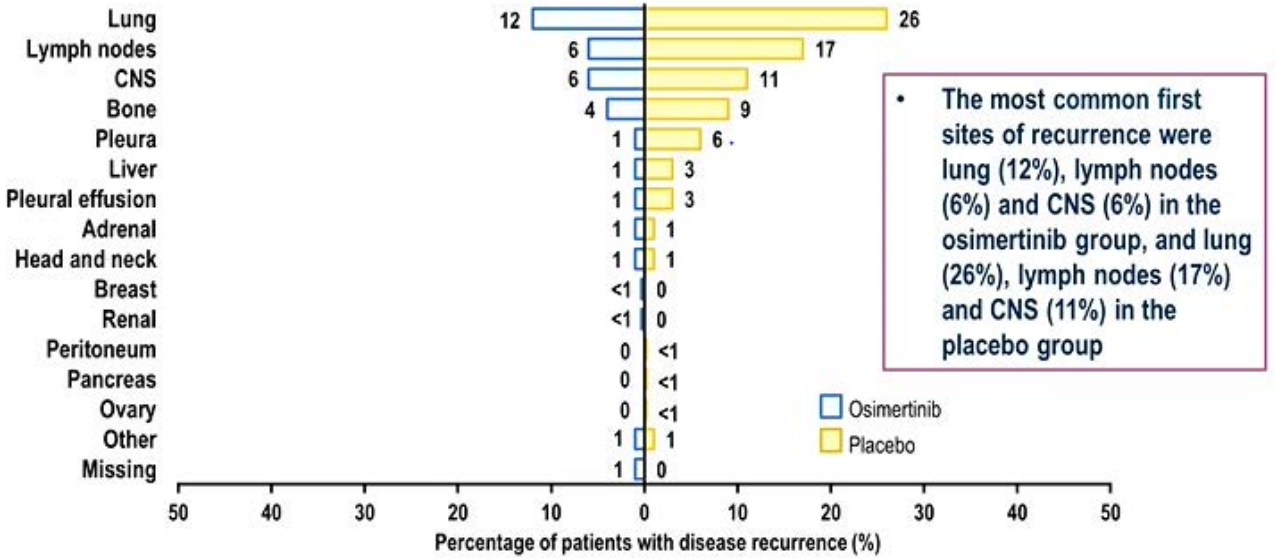
Type of disease recurrence
- Distant† recurrence
- Local/regional‡ recurrence only

CNS recurrence
6% vs 11%

ASCO Plenary session
June 4th, 1PM
OS analysis from ADAURA

"statistically significant and clinical meaningful improvement in OS"

- In the overall population, fewer patients treated with osimertinib had disease recurrence (93/339; 27%) compared with placebo (205/343; 60%)*



- The most common first sites of recurrence were lung (12%), lymph nodes (6%) and CNS (6%) in the osimertinib group, and lung (26%), lymph nodes (17%) and CNS (11%) in the placebo group

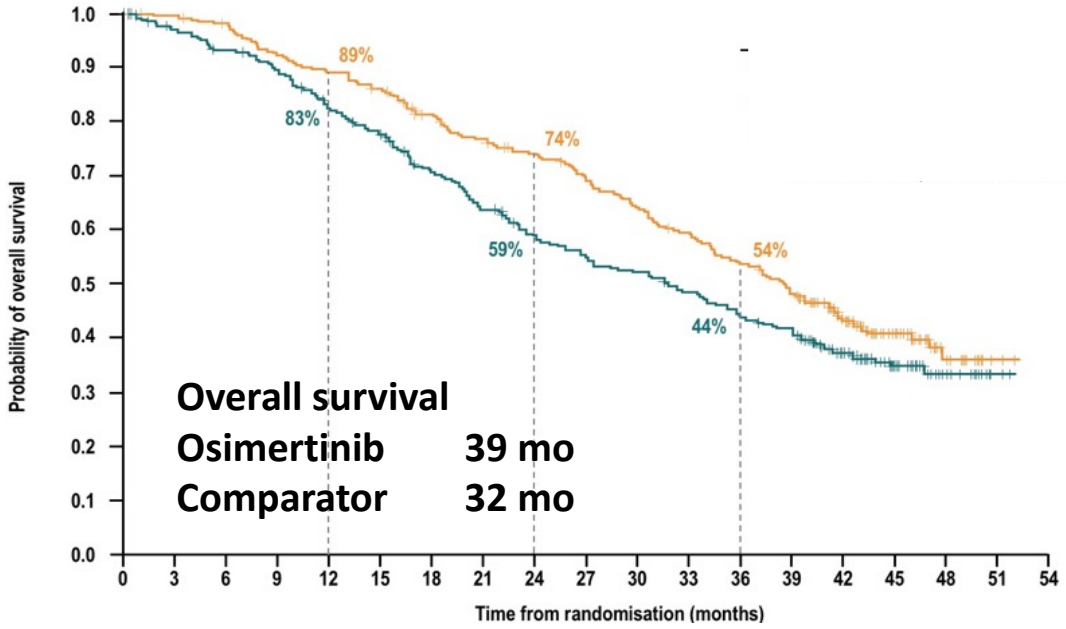
Memorial Sloan Kettering Cancer Center

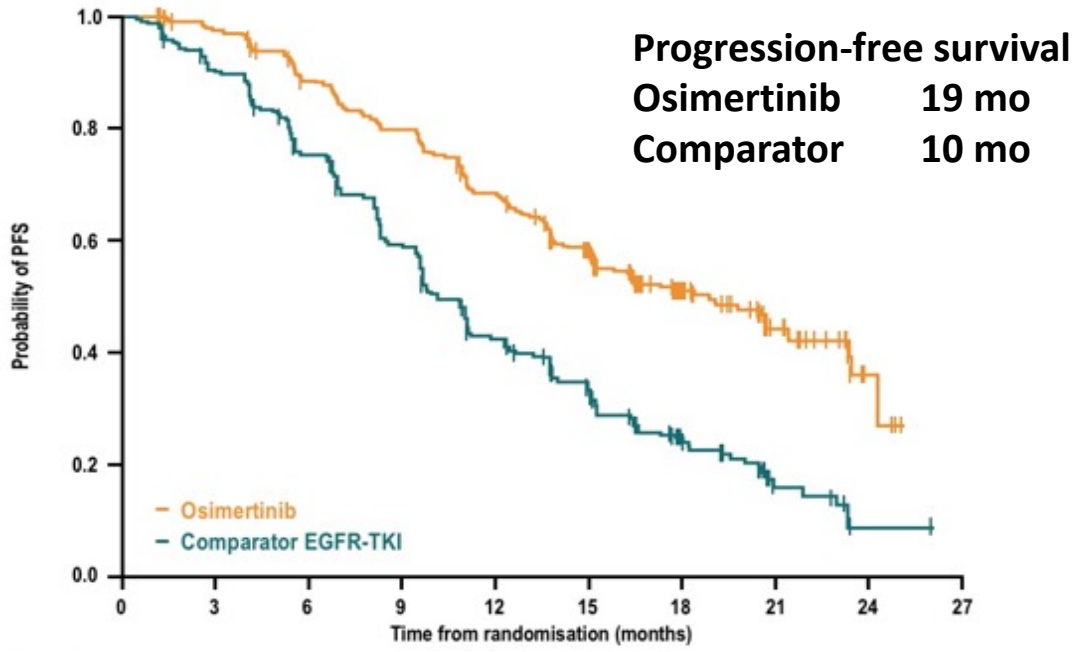
Tsuboi M et al. 2022 ESMO Congress. Abstract LBA47.

Outline

- Targeted therapy in early-stage EGFR+ NSCLC
- First-line treatment for metastatic EGFR+ NSCLC
- Mechanisms of resistance to osimertinib
- Targeted therapies after osimertinib
- Treatment of metastatic EGFR exon 20 positive NSCLC

Osimertinib as Best-in-Class EGFR TKI





- Osimertinib is a third-generation, irreversible, mutant-specific EGFR TKI
- Osimertinib initially approved for use after earlier generation EGFR TKIs with acquisition of EGFR T790M
- Improved PFS and OS compared to earlier generation EGFR TKIs
- Even so, PFS and OS still relatively short with acquired resistance a certainty

Memorial Sloan Kettering Cancer Center

Soria JC et al. *N Engl J Med*. 2018;378(2):113-125. Ramalingam SS et al. 2019 ESMO Congress. Abstract 567.

Osimertinib Better at Treating and Preventing CNS Metastases

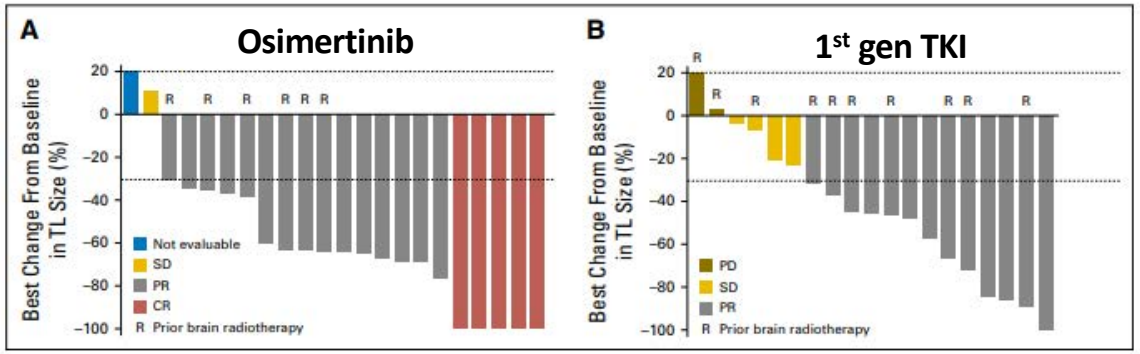
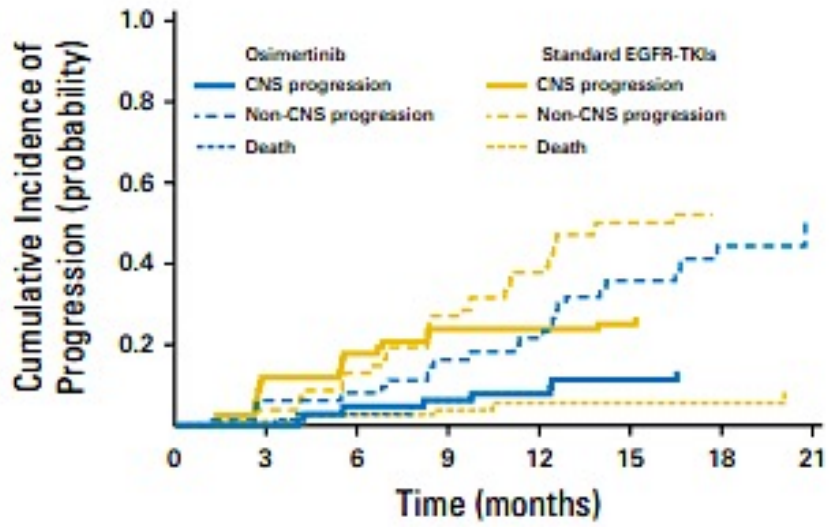


Fig 3. Best percentage change from baseline in CNS target lesion (TL) size (cEFR) with (A) osimertinib and (B) standard epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs).



CNS Progression
Osimertinib: 20%
1st gen TKI: 39%

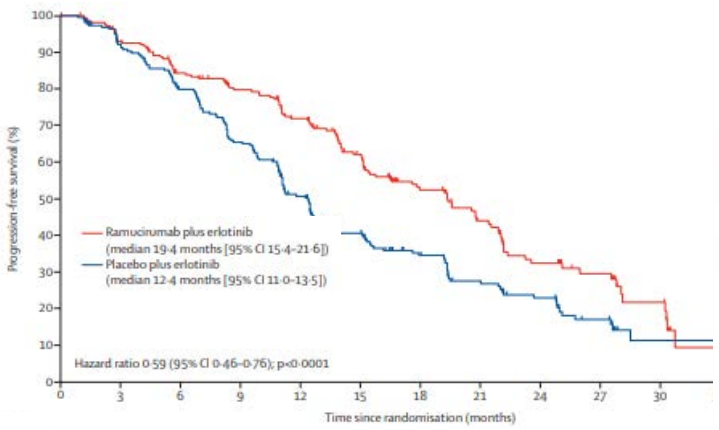
- FLAURA assessed osimertinib vs SOC TKI as 1st line treatment (mPFS 19 vs 10 mo)
- Baseline MRI not mandated, and interval MRIs only in pts with known BM (128 with BM/200 baseline scan/556 total pts)
- Rate of symptomatic CNS PD lower with osimertinib (15 vs 6%)
- CNS progression was mostly in new lesions

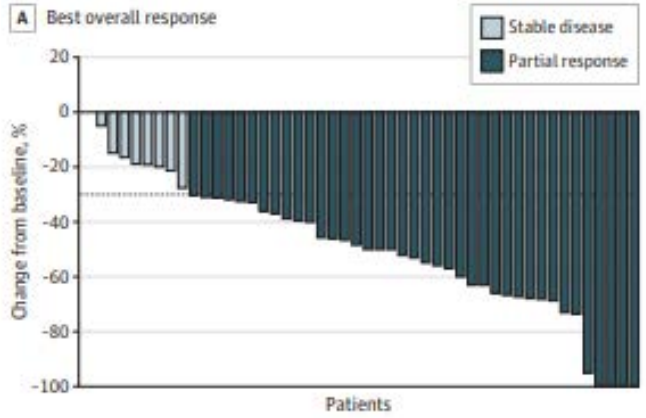
Evaluation of new therapies should include routine CNS imaging as CNS efficacy is a key factor in treatment choice. Lack of routine imaging seriously limits interpretation.

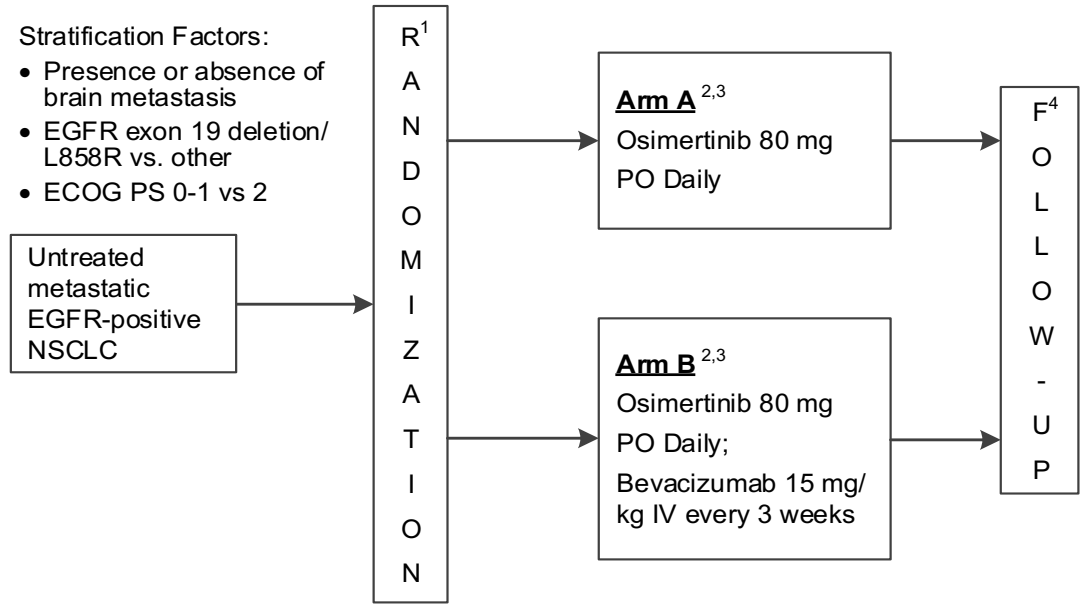
Memorial Sloan Kettering Cancer Center

Soria JC et al. *N Engl J Med*. 2018;378(2):113-125. Reungwetwattana T et al. *J Clin Oncol*. 2018; JCO2018783118.

Osimertinib First-Line Combinations - VEGF







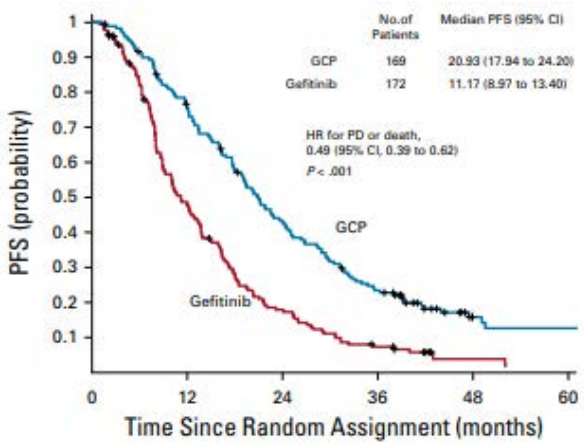
Accrual Goal = 300 patients

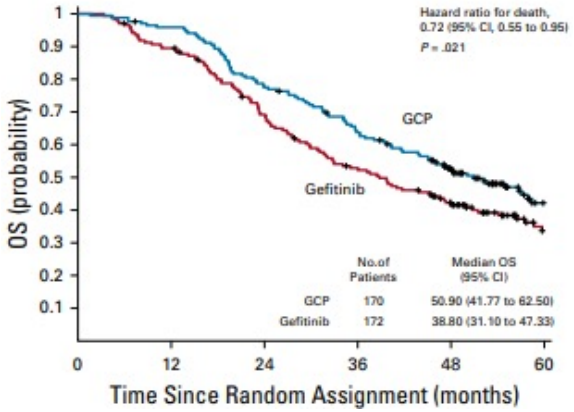
- Erlotinib and bevacizumab in Phase 2/3 studies with clear PFS benefit (but no OS), approval in EU, Japan.
- Erlotinib and ramucirumab in phase 3 study with improved PFS with US approval
- Osimertinib and bevacizumab single-arm Phase 1 study demonstrated safety and feasibility
- EA5182 is assessing osimertinib +/- bevacizumab
- Study allows for CNS metastases and interval MRI imaging will be obtained
- Ongoing randomized studies will definitively demonstrate whether there is utility in EGFR TKI/VEGF inhibition combination

Memorial Sloan Kettering Cancer Center

Nakagawa K et al. *Lancet Oncol*. 2019;20(12):1655-1669. Yu HA et al. *JAMA Oncol*. 2020;6(12):1983.

Osimertinib First-Line Combinations - Chemo





PFS

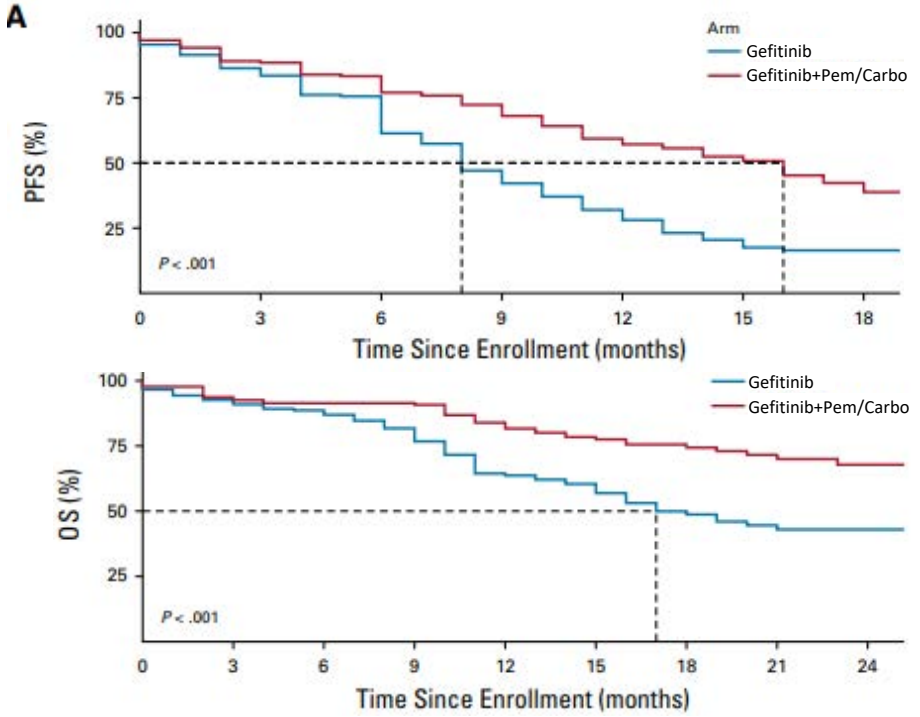
NEJ009: 11 vs 21 mo (HR 0.49)

Tata: 8 vs 16 mo (HR 0.51)

OS

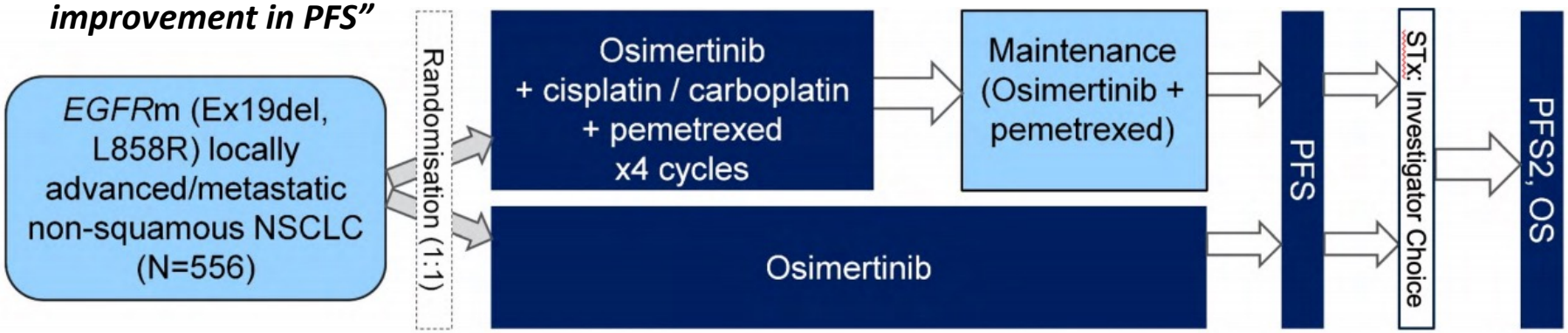
NEJ009: 39 vs 51mo (HR 0.72)

Tata: 17 v NR (HR 0.45)



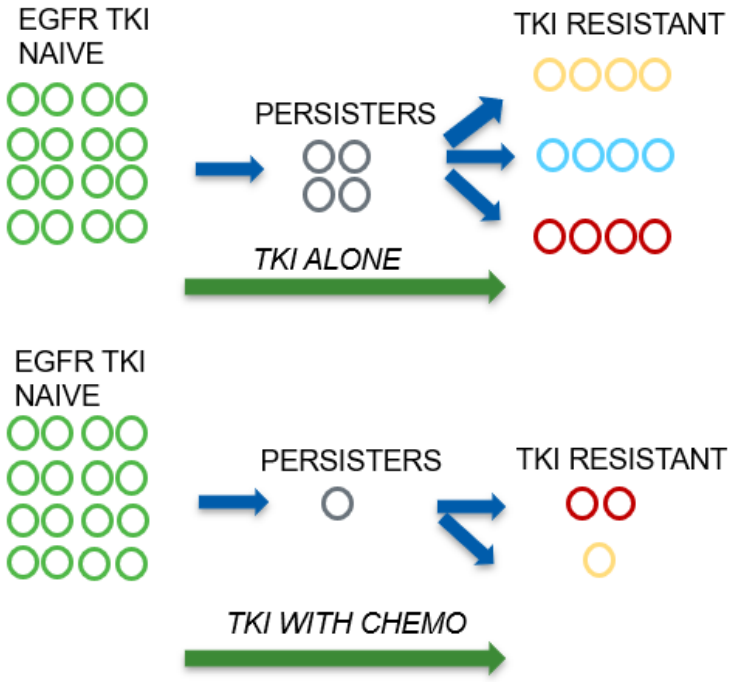
"statistically significant and clinically meaningful improvement in PFS"

FLAURA2

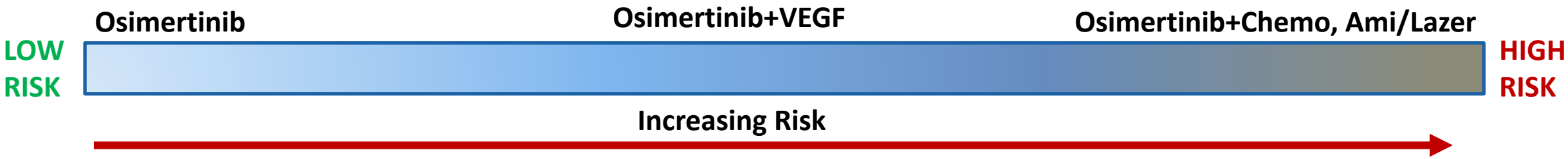


Hosomi Y et al. *J Clin Oncol*. 2020;38(2):115-12. Noronha V et al. *J Clin Oncol*. 2020;38(2):124-136.

Osimertinib First-Line Combinations



- To combine two active therapies, there needs to be clear improvement in PFS more than the sum of sequencing OR improvement in overall survival. PFS benefit but how much and any OS benefit?
- EGFR TKI and chemotherapy combination therapy may further eradicate subclones that survive EGFR TKI monotherapy (PERSISTERS)
- Need to personalize therapy to a patient's risk. Biomarkers for escalation of care include EGFR mutation subtype (ex 19/L858R vs atypical), co-mutations (TP53, RB1) and ctDNA clearance.
- Envision low-risk patients getting osimertinib alone and escalating to the most aggressive combinations for the highest-risk patients

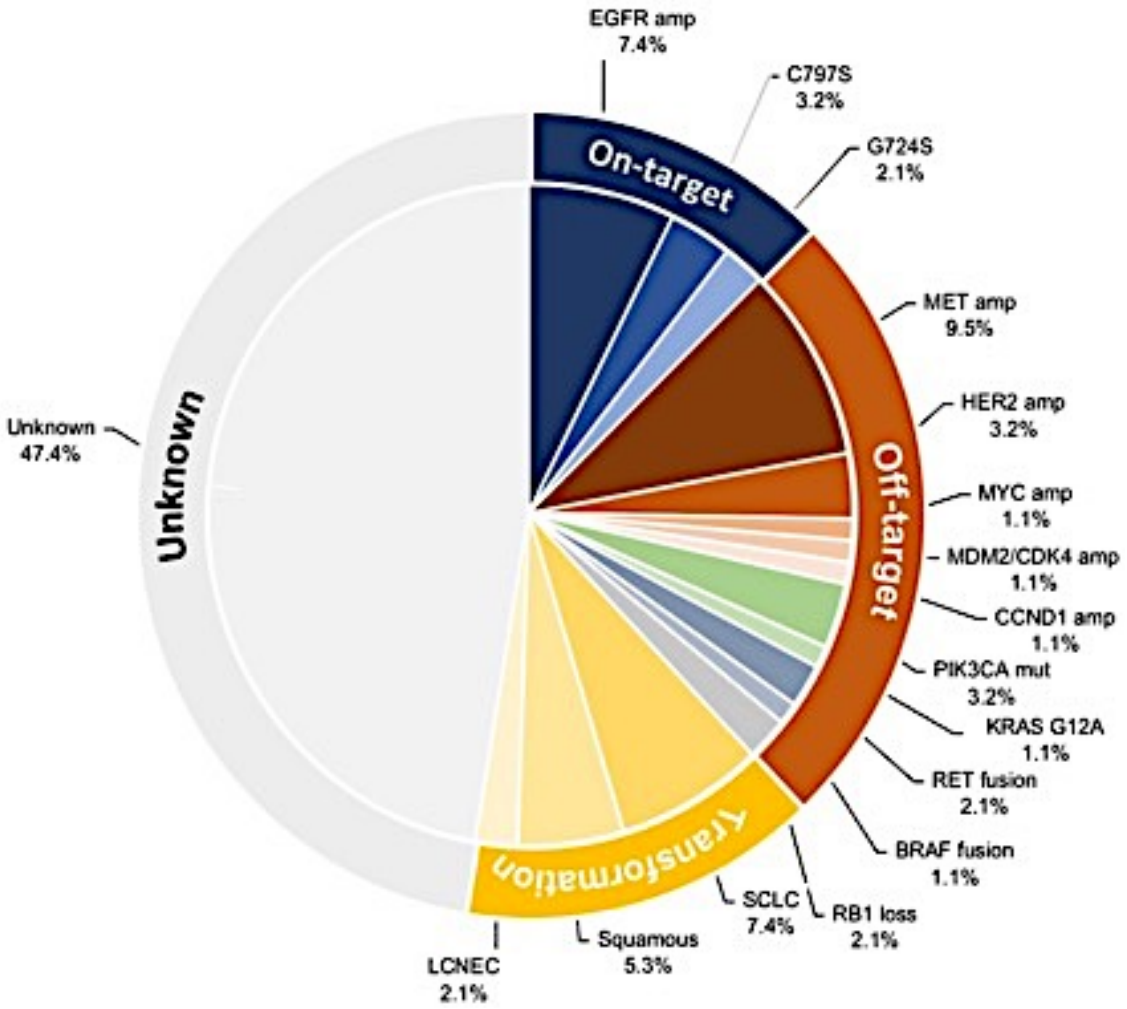


Memorial Sloan Kettering Cancer Center

Outline

- Targeted therapy in early-stage EGFR+ NSCLC
- First-line treatment for metastatic EGFR+ NSCLC
- Mechanisms of resistance to osimertinib
- Targeted therapies after osimertinib
- Treatment of metastatic EGFR exon 20 positive NSCLC

Mechanisms of Resistance to First-Line Osimertinib



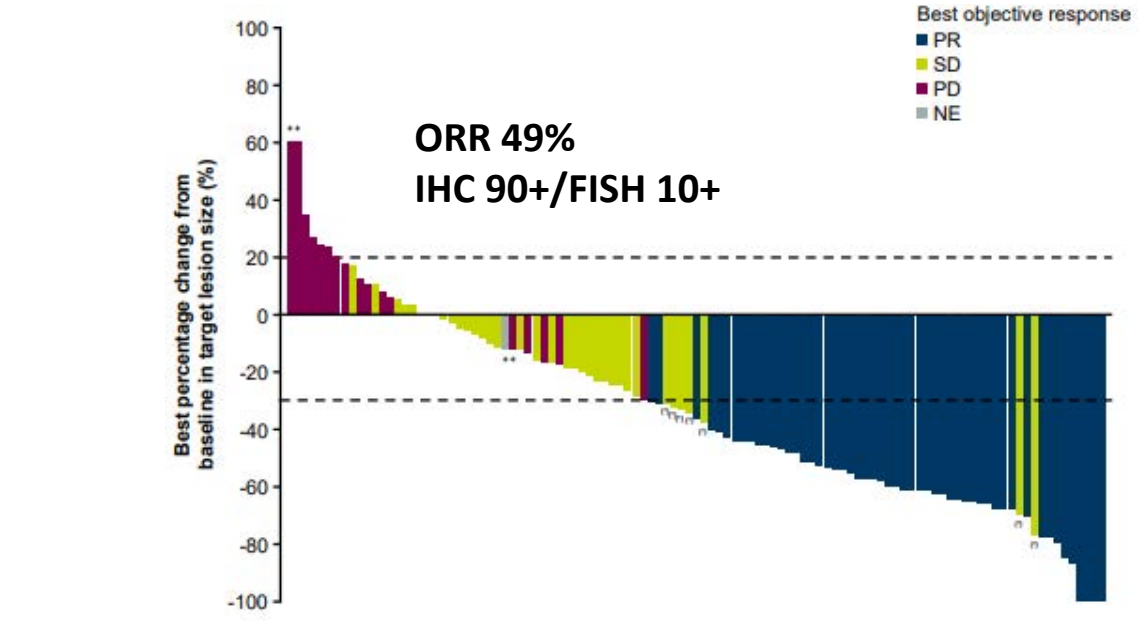
- Mechanisms of resistance to first-line osimertinib are diverse, with no dominant mechanism so upfront combinations to prevent resistance not appropriate without a biomarker
- With development of better EGFR inhibitors, there is more off target resistance seen
- High incidence of lineage plasticity including both small cell and squamous transformation
- Frequent acquired gene alterations such as gene fusions which are rare de novo
- There will be a role for non-biomarker selected therapies that focus on enhanced EGFR on-target inhibition or address general tumor biology

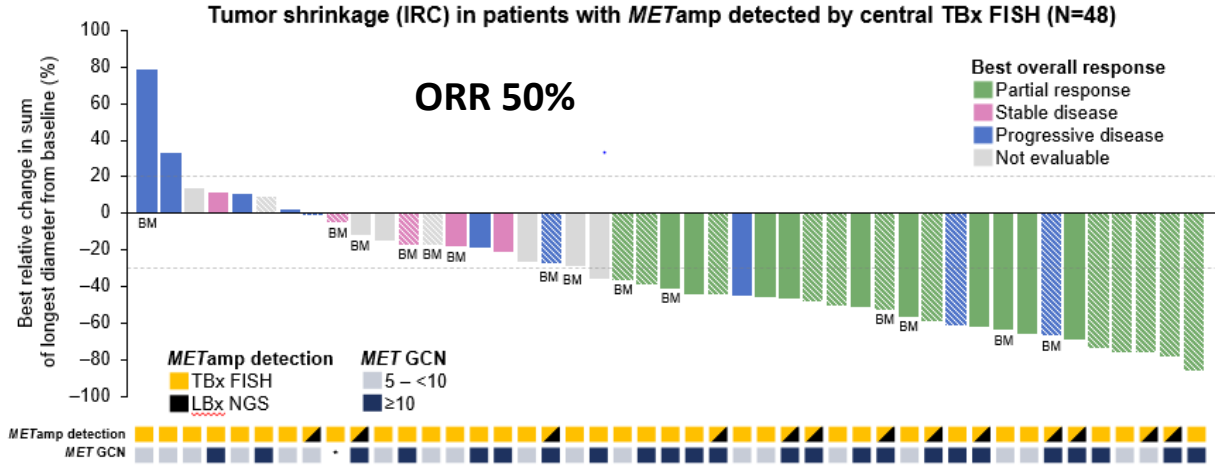
Yu H. Submitted Paper.

Mechanisms of Resistance to Osimertinib

On target	EGFR 2nd mtn: 1st/2nd gen EGFR TKI
Off target	MET amp: crizotinib, capmatinib
	RET fusion: selpercatinib
	ALK fusion: alectinib
	BRAF mtn: trametinib+/-dabrafenib
	HER2 amp/mtn: T-DM1, T-DXd
None identified	Chemo or clinical trial
Lineage plasticity	SCLC transform: chemo
	Squamous transform: chemo

Acquired MET Amplification/Mutation Drives Resistance to Osimertinib





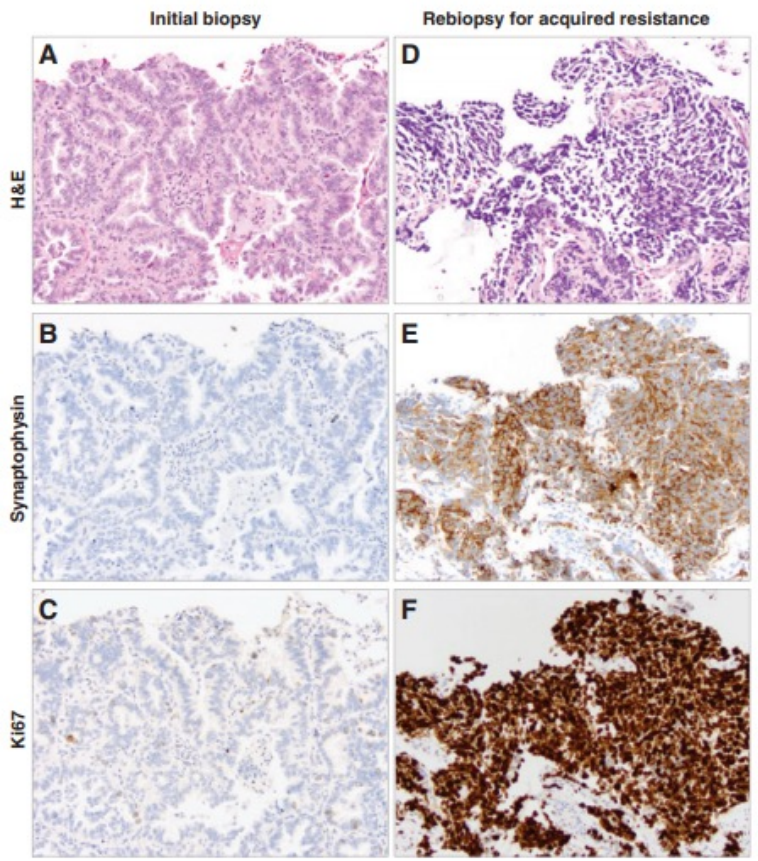
- Approved/available MET inhibitors include crizotinib, tepotinib and capmatinib
- Osimertinib and savolitinib studied in SAVANNAH with ORR was 49%, in IHC90+/FISH 10+
- In INSIGHT2, osimertinib + tepotinib for pts with MET amp post 1L osimertinib with ORR 45.8%
- Multiple studies ongoing looking at osimertinib + MET inhibitor combination (tepotinib NCT03940703, savolitinib SAVANNAH NCT03778229, ORCHARD NCT03944772, SAFFRON NCT05261399)

Memorial Sloan Kettering Cancer Center

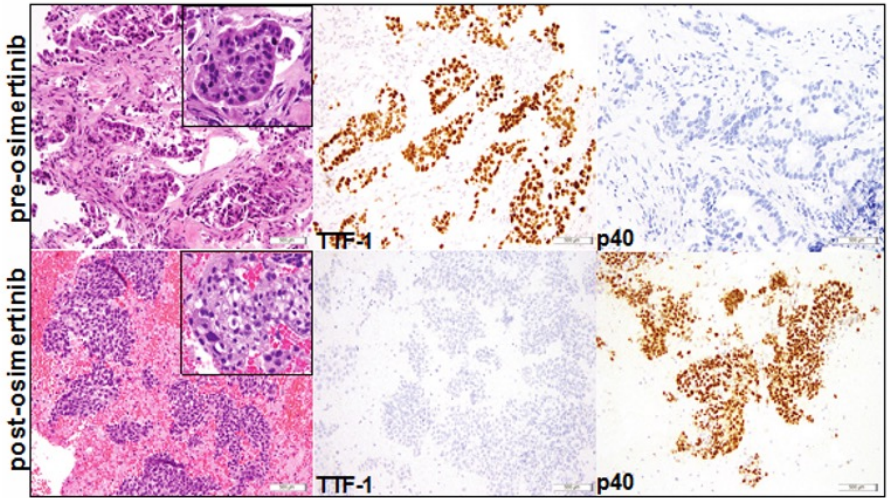
Ahn, MJ 2022 WCLC Congress. EP08.02-140. Abstract . Suzawa K et al. *JCO Precis Oncol*. 2019;3:PO.19.00011. Mazieres J et al. 2022 ESMO Congress. Abstract LBA52.

Histologic Transformation

Small Cell Transformation



Squamous Cell Transformation

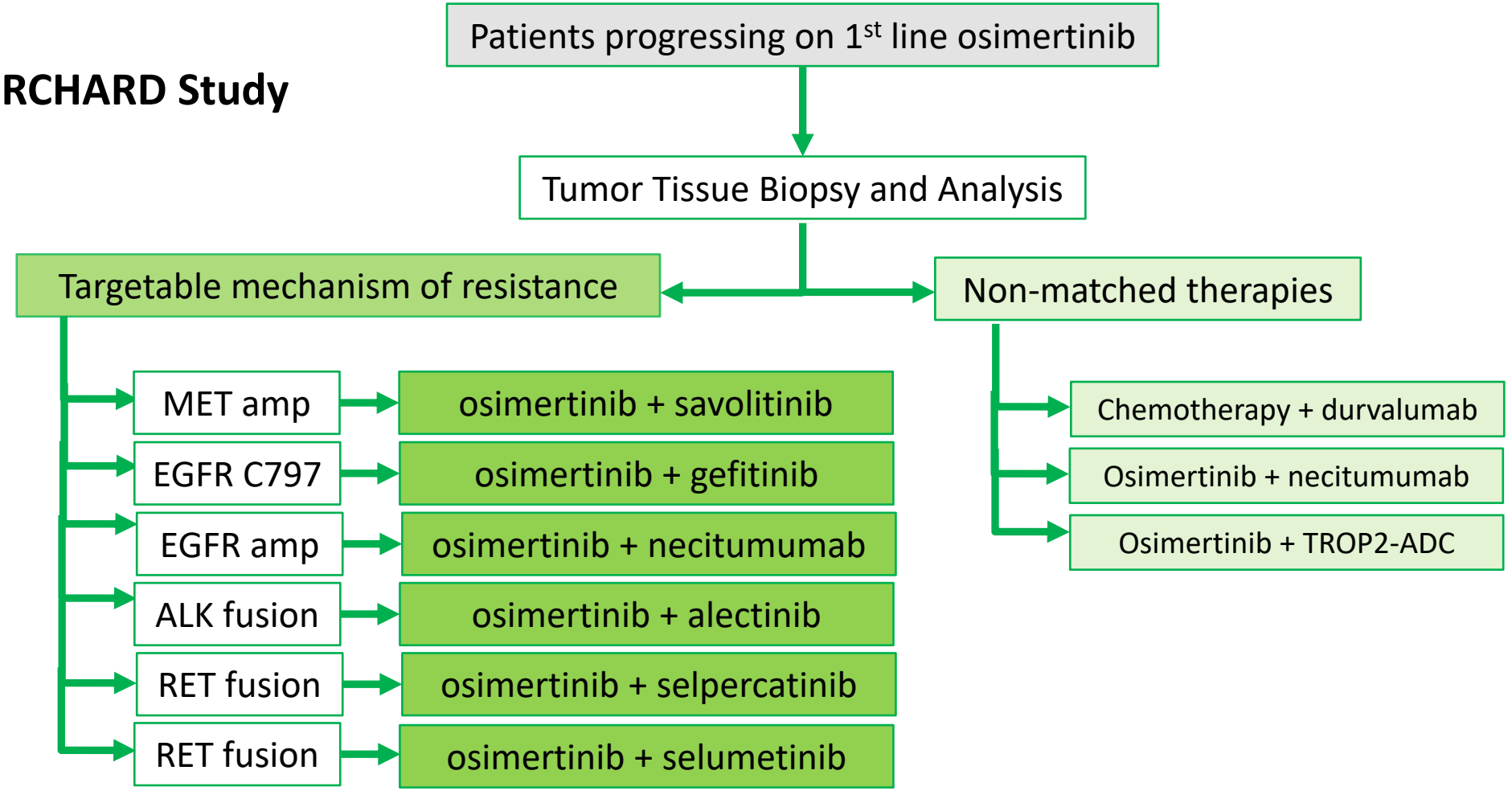


- With first-line osimertinib, we see more lineage plasticity (~15%). This is a complete histologic transformation that makes the tumor no longer dependent on EGFR signaling
- Once transformation occurs, outcomes are poor (median OS 10.9mo) and treatment options limited. Work ongoing to try to prevent transformation.
- Presence of EGFR/TP53/RB1 alterations increases risk

Yu HA et al. *Clin Cancer Res*. 2013;19(8):2240-2247. Schoenfeld AJ et al. *Clin Cancer Res*. 2020;26(11):2654-2663.

Exploring Biomarker-Driven Treatment of Osimertinib Resistance

ORCHARD Study



Memorial Sloan Kettering Cancer Center

MSK IRB# 19-312, NCT03944772. Global PI: Yu.

Outline

- Targeted therapy in early-stage EGFR+ NSCLC
- First-line treatment for metastatic EGFR+ NSCLC
- Mechanisms of resistance to osimertinib
- Targeted therapies after osimertinib
- Treatment of metastatic EGFR exon 20 positive NSCLC

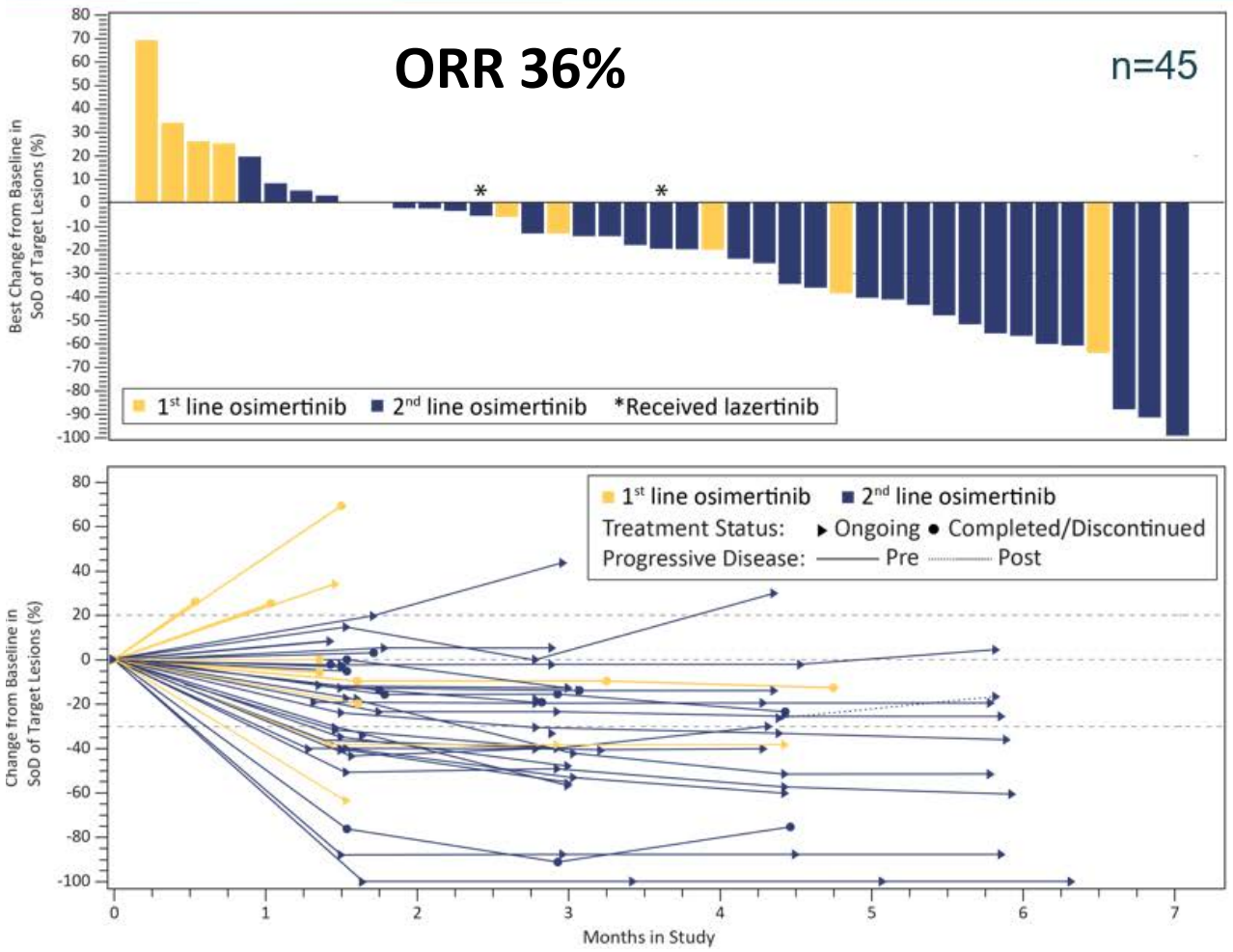
Treatments Post Osimertinib: Patritumab Deruxtecan

- 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

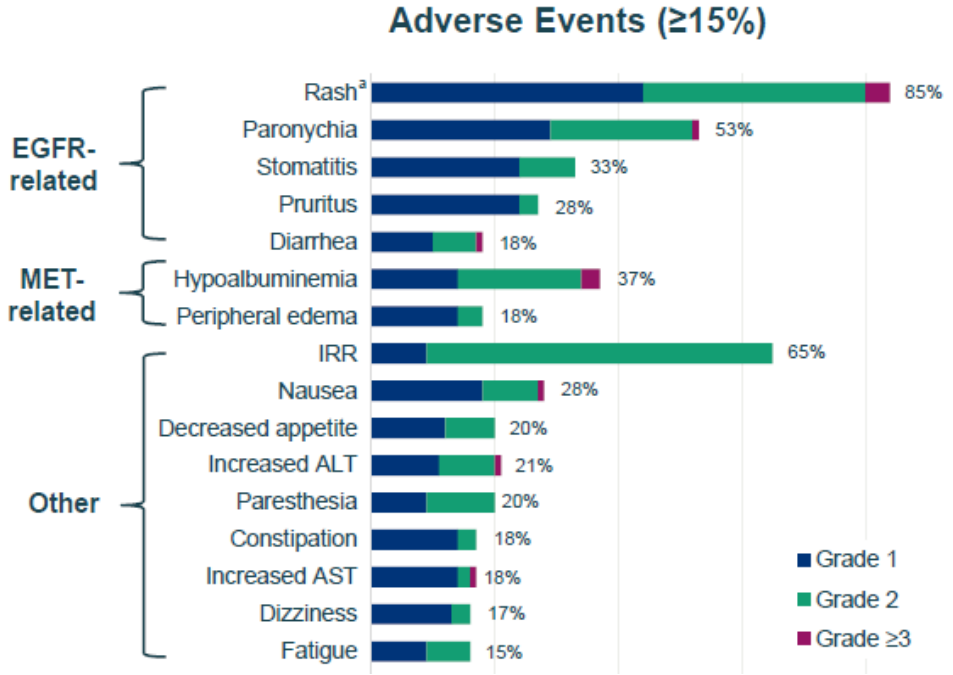
Memorial Sloan Kettering Cancer Center

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

Treatments Post Osimertinib: Amivantamab and Lazertinib



- Amivantamab is a MET/EGFR antibody and Lazertinib is a 3rd gen EGFR TKI
- The combo was assessed after osimertinib before chemo
- Ongoing and future studies are looking at first-line and later-line treatment



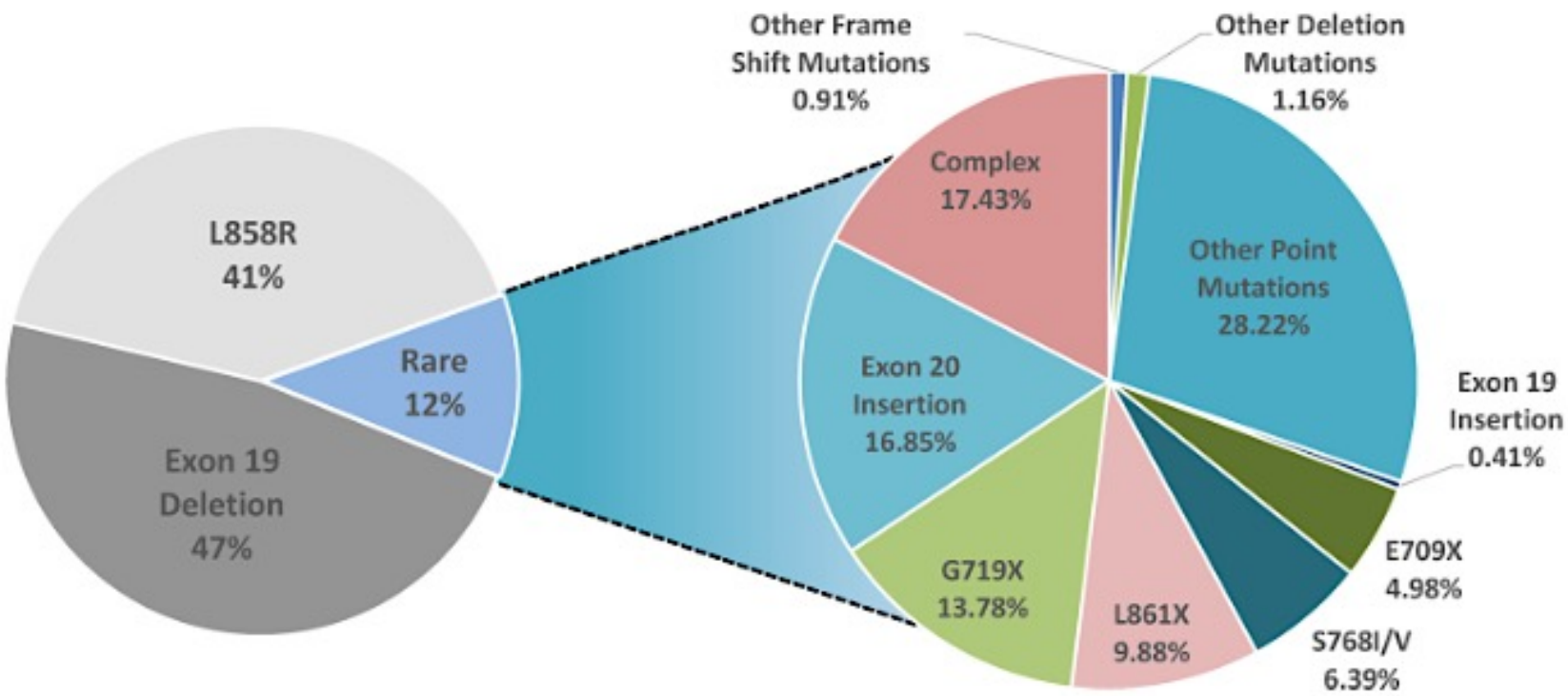
Memorial Sloan Kettering Cancer Center

Cho BC et al. 2020 ESMO Congress. Abstract 12580.

Outline

- Targeted therapy in early-stage EGFR+ NSCLC
- First-line treatment for metastatic EGFR+ NSCLC
- Mechanisms of resistance to osimertinib
- Targeted therapies after osimertinib
- Treatment of metastatic EGFR exon 20 positive NSCLC

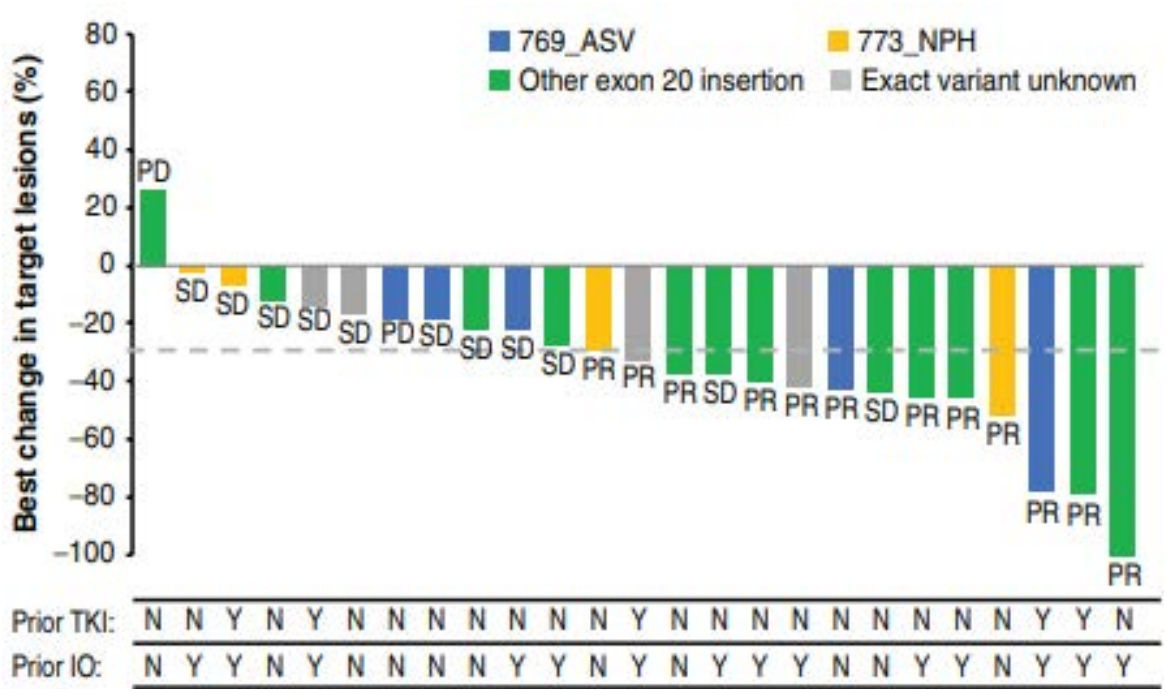
EGFR Exon 20 Insertions



- Subset of EGFR mutations that are activating but not sensitizing to traditional EGFR TKIs (erlotinib, osimertinib)
- Recent first approvals for targeted therapies for these lung cancers

Harrison PT et al. *Sem Cancer Biol*. 2019;61:167-179.

Mobocertinib



Efficacy endpoint	5–40 mg/d (*n* = 12)	80 mg total daily dose[a] (*n* = 9)	120 mg/d (*n* = 21)	160 mg/d[b] (*n* = 28)
Best confirmed response, *n* (%)[c]				
Complete response	0	1 (11)	1 (5)	0
Partial response	0	1 (11)	3 (14)	12 (43)
Stable disease[d]	3 (25)	6 (67)	11 (52)	12 (43)
Progressive disease	7 (58)	1 (11)	3 (14)	2 (7)
Not evaluated	2 (17)	0	3 (14)	2 (7)
Confirmed ORR, *n* (%) [95% CI]	0 [0–26]	2 (22) [3–60]	4 (19) [5–42]	12 (43) [24–63]
Confirmed disease control rate, *n* (%) [95% CI]	3 (25) [5–57]	8 (89) [52–100]	15 (71) [48–89]	24 (86) [67–96]

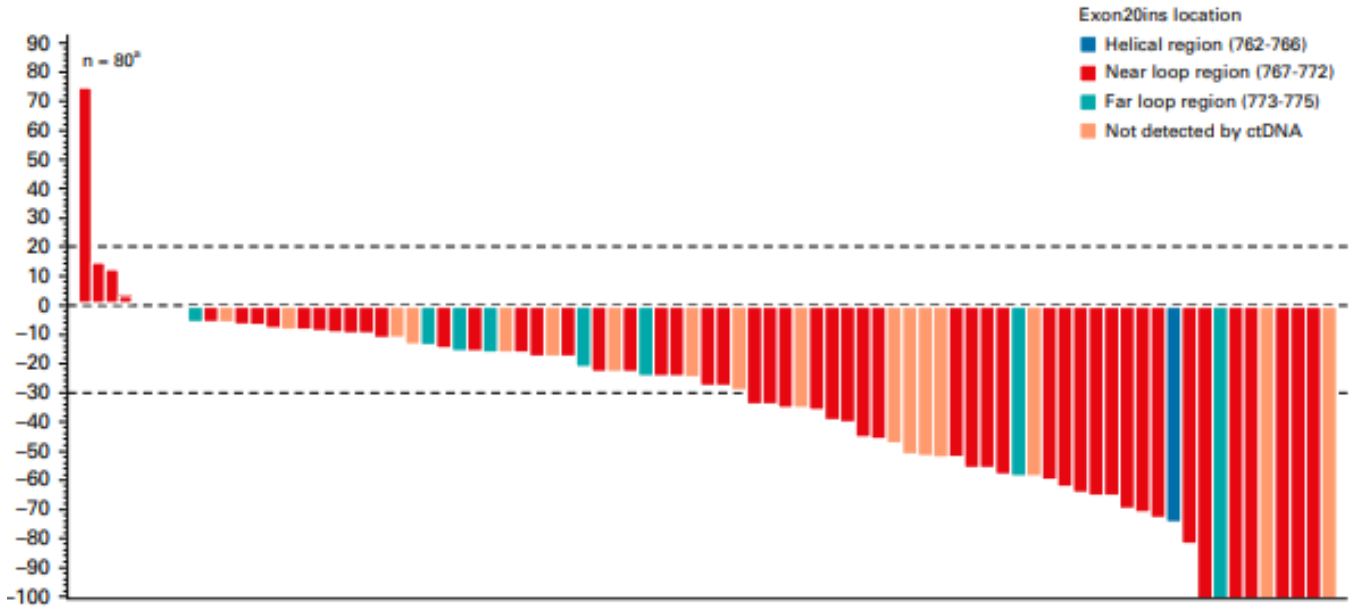
	Patients with *EGFR*ex20ins treated at 160 mg/d[a] (*n* = 28)	
TEAE	Any grade	Grade ≥3
Diarrhea	23 (82)	9 (32)
Nausea	11 (39)	3 (11)
Rash	13 (46)	0
Vomiting	10 (36)	2 (7)
Dry skin	5 (18)	0
Decreased appetite	11 (39)	0
Stomatitis	6 (21)	2 (7)
Fatigue	4 (14)	1 (4)
Rash maculopapular	7 (25)	1 (4)
Paronychia	8 (29)	0
Anemia	5 (18)	0
Dermatitis acneiform	5 (18)	0
GERD	3 (11)	0
Dyspepsia	6 (21)	0
Increased lipase	7 (25)	2 (7)
Pruritus	5 (18)	0

- Oral EGFR exon 20 inhibitor
- ORR at 160mg was 43% (0-19% ORR at lower doses), mPFS 7.3mo
- ORR 56% in pts w/o brain mets, 25% in pts with brain mets

Memorial Sloan Kettering Cancer Center

Riely GJ et al. *Cancer Disc*. 2021;11(7):1688-1699.

Amivantamab



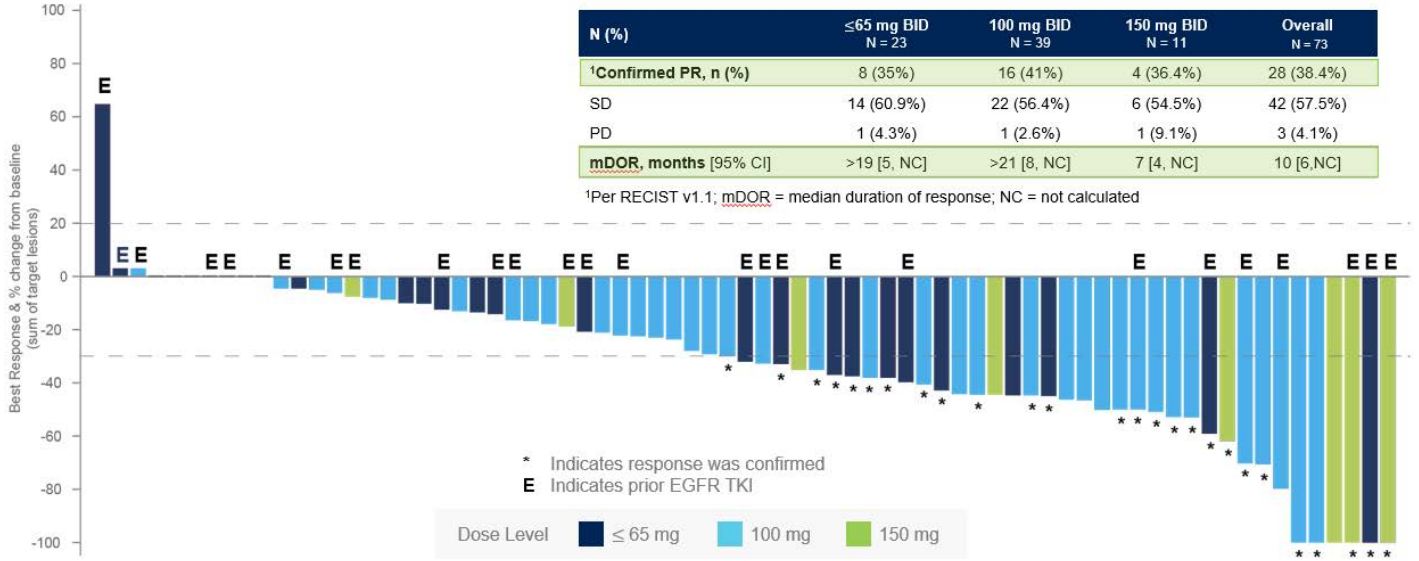
AE (≥15% of Treatment-emergent AEs), n (%)	Safety Population (N=114)			
	Treatment-emergent AE		Treatment-related AE	
	Total	Grade ≥3	Total	Grade ≥3
EGFR-related				
Rash[a]	98 (86)	4 (4)	98 (86)	4 (4)
Paronychia	51 (45)	1 (1)	48 (42)	1 (1)
Stomatitis	24 (21)	0	21 (18)	0
Pruritus	19 (17)	0	19 (17)	0
MET-related				
Hypoalbuminemia	31 (27)	3 (3)	17 (15)	2 (2)
Peripheral edema	21 (18)	0	11 (10)	0
Other				
Infusion related reaction	75 (66)	3 (3)	75 (66)	3 (3)
Constipation	27 (24)	0	7 (6)	0
Nausea	22 (19)	0	13 (11)	0
Dyspnea	22 (19)	2 (2)	6 (5)	0
Fatigue	21 (18)	2 (2)	14 (12)	1 (1)
Increased ALT	17 (15)	1 (1)	14 (12)	1 (1)

- Bispecific EGFR/MET antibody that is given intravenously
- ORR 40%, DoR 11.1mo, mPFS 8.3mo, mOS 22.8mo
- Also being assessed in sensitizing EGFR mutations

Memorial Sloan Kettering Cancer Center

Park K et al. *J Clin Oncol*. 2021;39(30):3391-3402.

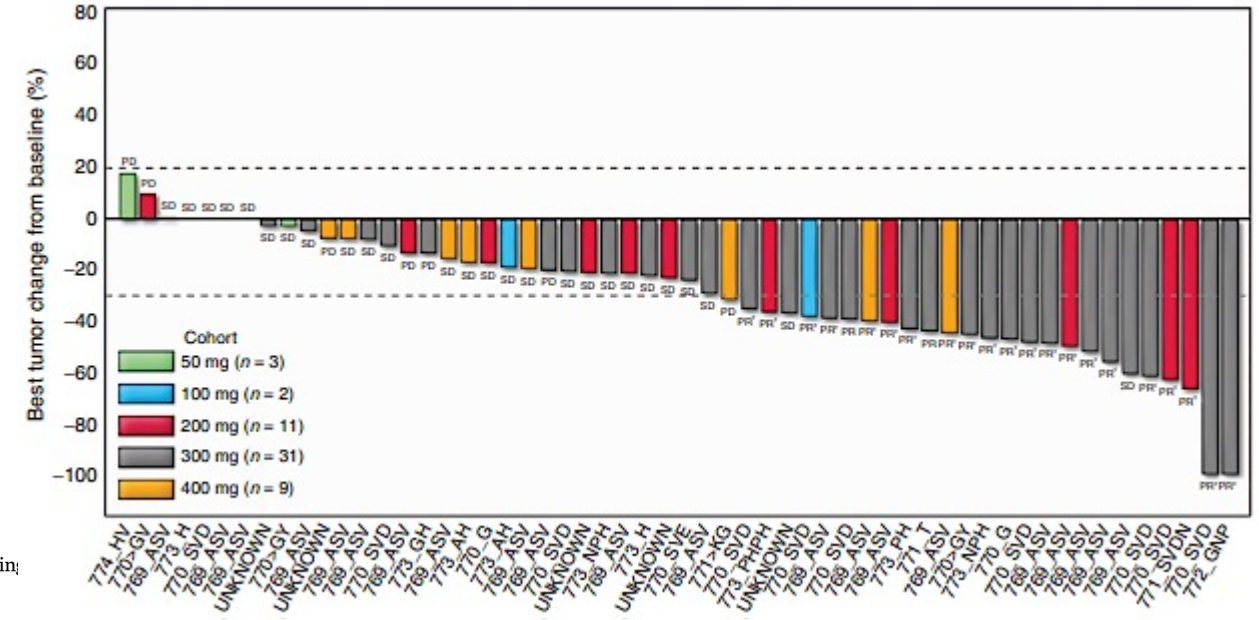
Exon 20 Inhibitors in Development



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

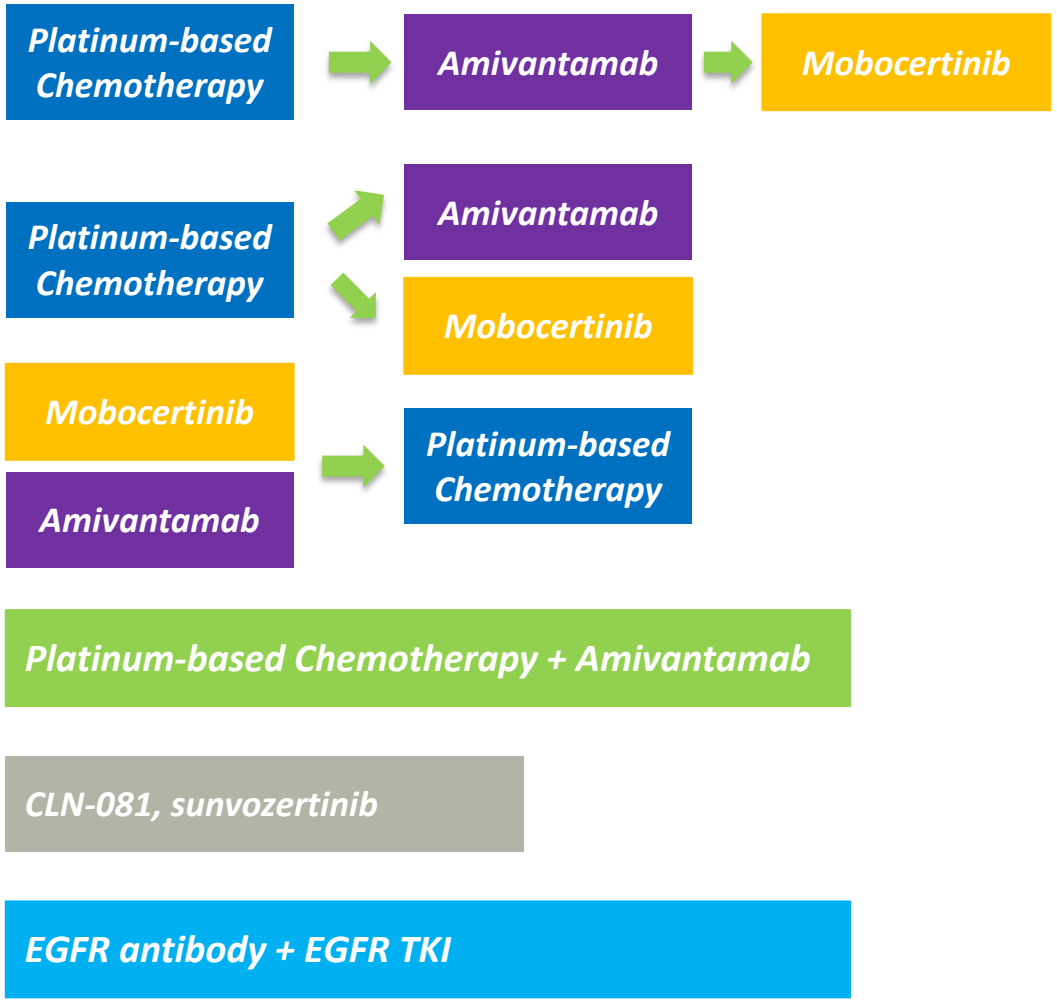
CLN-081
ORR 38.4%
mPFS 10mo



Sunvozertinib
ORR 37.5%
mPFS not reached

Memorial Sloan Kettering Cancer Center

Outstanding Questions for EGFR Exon 20



- First-line treatment versus second-line treatment
- Sequencing without cross-resistance, especially with EGFR TKI and antibody
- CNS penetration and efficacy
- Combination strategies: chemo + exon 20 drugs
- New exon 20 inhibitors in development

Conclusions

- **Early-stage EGFR+ NSCLC**
  - Make sure to do molecular testing, use osimertinib when appropriate with both PFS and OS benefit.
- **First-line treatment**
  - Osimertinib monotherapy is the standard of care, but studies are ongoing looking at osimertinib-based combinations. Risk stratifying will be important when making treatment choices.
- **Mechanisms of resistance**
  - No dominant mechanism, off-target and histologic transformation are common.
- **Targeted therapies after osimertinib**
  - Focus on targeted therapies that transcend resistance mechanism, interest in patritumab deruxtecan and amivantamab/lazertinib.
- **EGFR exon 20**
  - Amivantamab and mobocertinib are both approved but with limitations. New inhibitors also currently in development, many unanswered questions.

Agenda

Module 1: Incorporation of Immunotherapeutic Strategies into the Management of Nonmetastatic Non-Small Cell Lung Cancer (NSCLC) — Dr Heymach

Module 2: Contemporary Treatment for Localized or Metastatic NSCLC with an EGFR Mutation — Dr Yu

Module 3: Research Advances Shaping the Current and Future Treatment of Metastatic NSCLC with ALK Rearrangements, ROS1 Rearrangements or RET Fusions — Dr Langer

Module 4: Targeting MET, HER2 and KRAS Alterations in NSCLC — Dr Spigel

Module 5: Current Management of Metastatic NSCLC without a Targetable Tumor Mutation — Dr Garon

Module 6: Future Directions in the Management of Metastatic NSCLC — Dr Leal

RTP
RESEARCH
TO PRACTICE

Selection of first- and later-line treatment for patients with ALK-rearranged NSCLC

Melissa Johnson, MD

Matthew Gubens, MD, MS

Jarushka Naidoo, MB BCH, MHS

RTP RESEARCH TO PRACTICE

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

 Dr Garon	Alectinib	 Dr Yu	Alectinib
 Dr Heymach	Alectinib	 Dr Gubens	Alectinib
 Dr Langer	Alectinib	 Dr Johnson	Alectinib
 Dr Leal	Alectinib	 Dr Naidoo	Alectinib
 Dr Spigel	Alectinib		

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, in general, what would be your preferred next therapy for a patient with metastatic nonsquamous NSCLC with an ALK rearrangement and a TPS of 50% who was responding to but was not able to tolerate first-line alectinib?

 Dr Garon	Lorlatinib	 Dr Yu	Brigatinib
 Dr Heymach	Brigatinib	 Dr Gubens	Lorlatinib
 Dr Langer	Brigatinib	 Dr Johnson	Lorlatinib
 Dr Leal	Brigatinib	 Dr Naidoo	Brigatinib
 Dr Spigel	Brigatinib		

RTP RESEARCH TO PRACTICE

Role of RET-targeted therapy in current clinical practice

Melissa Johnson, MD

Matthew Gubens, MD, MS

Jarushka Naidoo, MB BCH, MHS

RTP
RESEARCH
TO PRACTICE

What would be your preferred initial targeted therapy for a 65-year-old asymptomatic patient with metastatic nonsquamous NSCLC and a RET fusion?

 Dr Garon	Selpercatinib	 Dr Yu	Selpercatinib
 Dr Heymach	Selpercatinib	 Dr Gubens	No preference
 Dr Langer	Selpercatinib	 Dr Johnson	Selpercatinib
 Dr Leal	No preference	 Dr Naidoo	No preference
 Dr Spigel	No preference		

RTP RESEARCH TO PRACTICE

Would you generally offer targeted treatment prior to attempting whole-brain radiation therapy for an asymptomatic patient with newly diagnosed nonsquamous NSCLC, diffuse bilateral brain metastases and a RET fusion?

 Dr Garon	Yes	 Dr Yu	Yes
 Dr Heymach	No	 Dr Gubens	Yes
 Dr Langer	Yes	 Dr Johnson	Yes
 Dr Leal	Yes	 Dr Naidoo	Yes
 Dr Spigel	Yes		

RTP RESEARCH TO PRACTICE

Selection of therapy for ROS1-positive NSCLC, including for patients with CNS involvement

Melissa Johnson, MD

Matthew Gubens, MD, MS

Jarushka Naidoo, MB BCH, MHS

RTP RESEARCH TO PRACTICE

What would be your preferred initial targeted therapy for a 65-year-old asymptomatic patient with metastatic nonsquamous NSCLC and a ROS1 rearrangement?

 Dr Garon	Entrectinib
 Dr Heymach	Entrectinib
 Dr Langer	Crizotinib
 Dr Leal	Crizotinib
 Dr Spigel	Entrectinib
 Dr Yu	Entrectinib
 Dr Gubens	Entrectinib
 Dr Johnson	Crizotinib
 Dr Naidoo	Crizotinib

RTP RESEARCH TO PRACTICE

What would be your preferred initial targeted therapy for a 65-year-old asymptomatic patient with metastatic nonsquamous NSCLC, a ROS1 rearrangement and brain metastases?

 Dr Garon	Entrectinib	 Dr Yu	Entrectinib
 Dr Heymach	Entrectinib	 Dr Gubens	Entrectinib
 Dr Langer	Entrectinib	 Dr Johnson	Entrectinib
 Dr Leal	Entrectinib	 Dr Naidoo	Entrectinib
 Dr Spigel	Entrectinib		

RTP RESEARCH TO PRACTICE

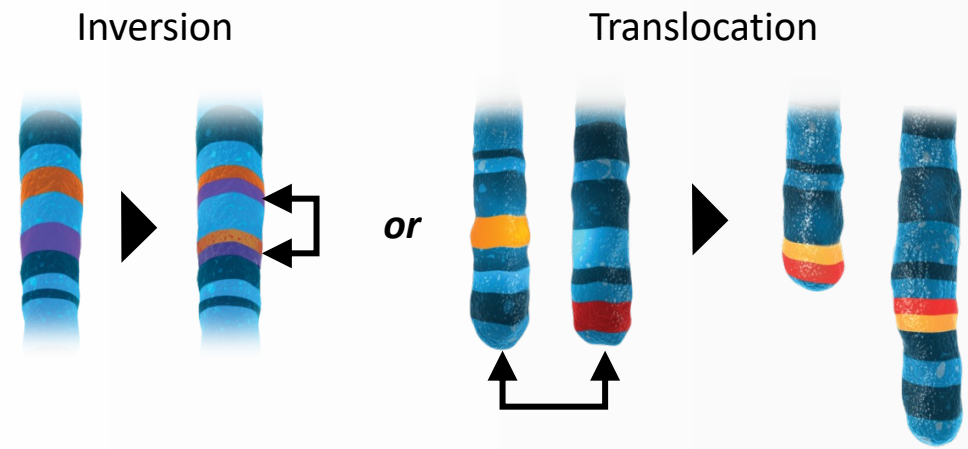
Research Advances Shaping the Current and Future Treatment of Metastatic NSCLC with ALK Rearrangements, ROS1 Rearrangements or RET Fusions

Corey J. Langer, MD, FACP
Director of Thoracic Oncology
Abramson Cancer Center
Professor of Medicine
Perelman School of Medicine
University of Pennsylvania
Philadelphia, PA 19104

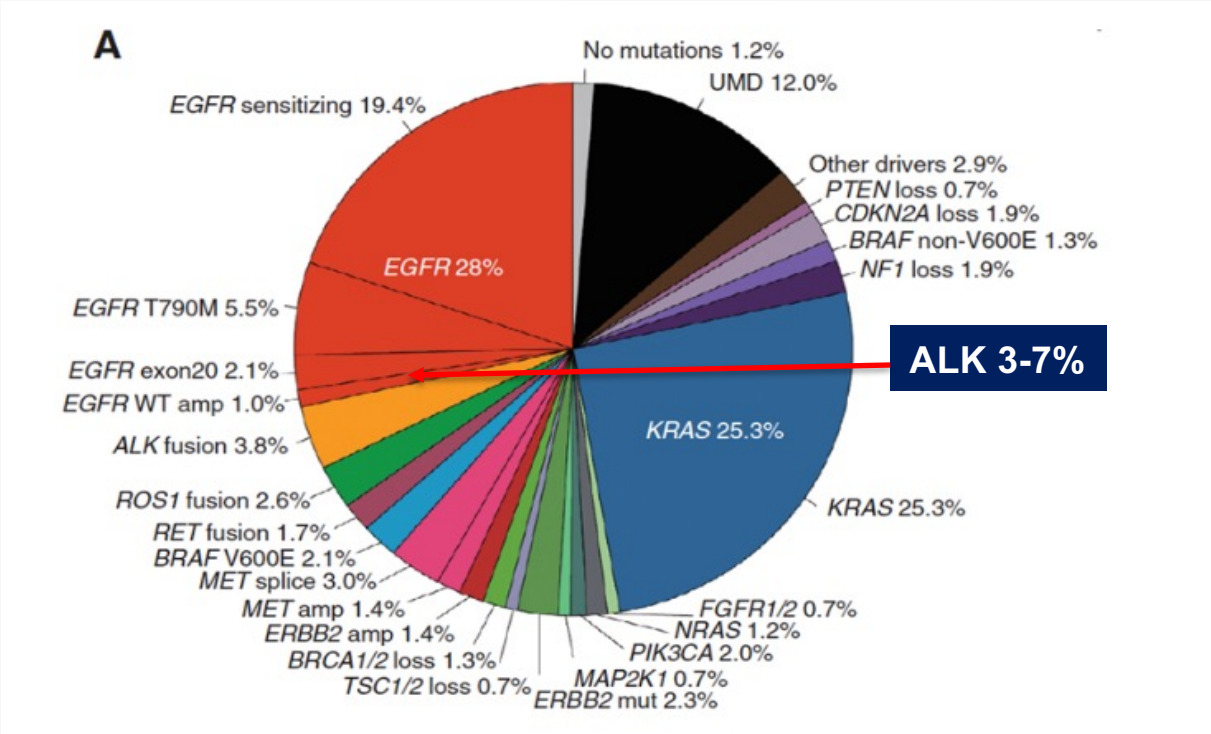
ALK-Rearranged Lung Cancer

Identification of the transforming *EML4–ALK* fusion gene in non-small-cell lung cancer

Manabu Soda[1,2], Young Lim Choi[1], Munehiro Enomoto[1,2], Shuji Takada[1], Yoshihiro Yamashita[1], Shunpei Ishikawa[5], Shin-ichiro Fujiwara[1], Hideki Watanabe[1], Kentaro Kurashina[1], Hisashi Hatanaka[1], Masashi Bando[2], Shoji Ohno[2], Yuichi Ishikawa[6], Hiroyuki Aburatani[5,7], Toshiro Niki[3], Yasunori Sohara[4], Yukihiko Sugiyama[2] & Hiroyuki Mano[1,7]



Soda M, et al. *Nature*. 2007;448:561-567

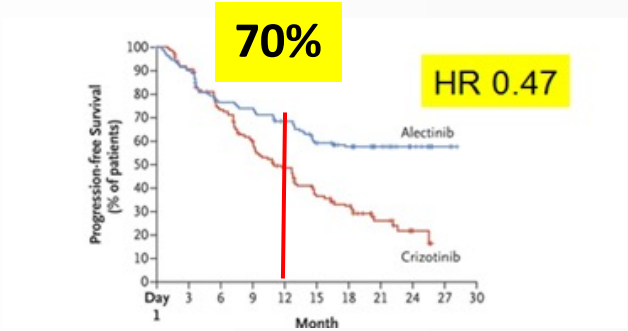


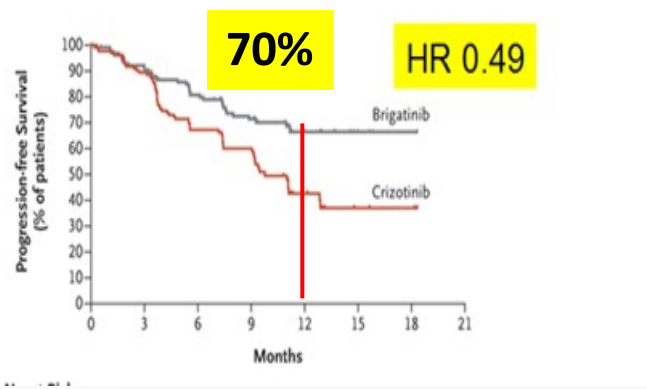
ALK-positive patients:

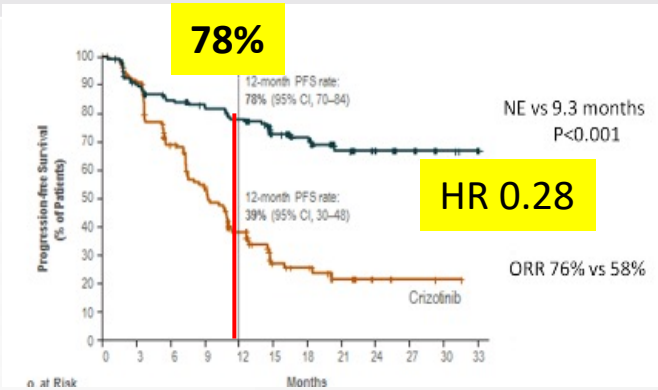
- Never or minimal smokers
- Young (average age 50 y)
- Adenocarcinoma type (signet ring morphology)
- Poor prognosis without Tx

First-Line *ALK*+: PFS Outcomes From the ALEX, ALTA-1L, and CROWN Trials

Efficacy Data	ALEX[1]		ALTA-1L[2]		CROWN[3]	
	Alectinib (n = 152)	Crizotinib (n = 151)	Brigatinib (n = 137)	Crizotinib (n = 138)	Lorlatinib (n = 147)	Crizotinib (n = 149)
Median PFS, months	34.8	10.9	24.0	11.1	Not reached	9.3
HR (95% CI)	0.47 (0.32–0.58)		0.49 (0.35–0.66)		0.27 (0.18–0.39)	
PFS rate at 36 months, % (95% CI)	46.4 (CI not reported)	13.5 (CI not reported)	43.0 (34.0–51.0)	19.0 (12.0–27.0)	63.5 (CI not reported)	18.9 (CI not reported)
Median duration of follow-up, months	37.8		40.4		36.7	

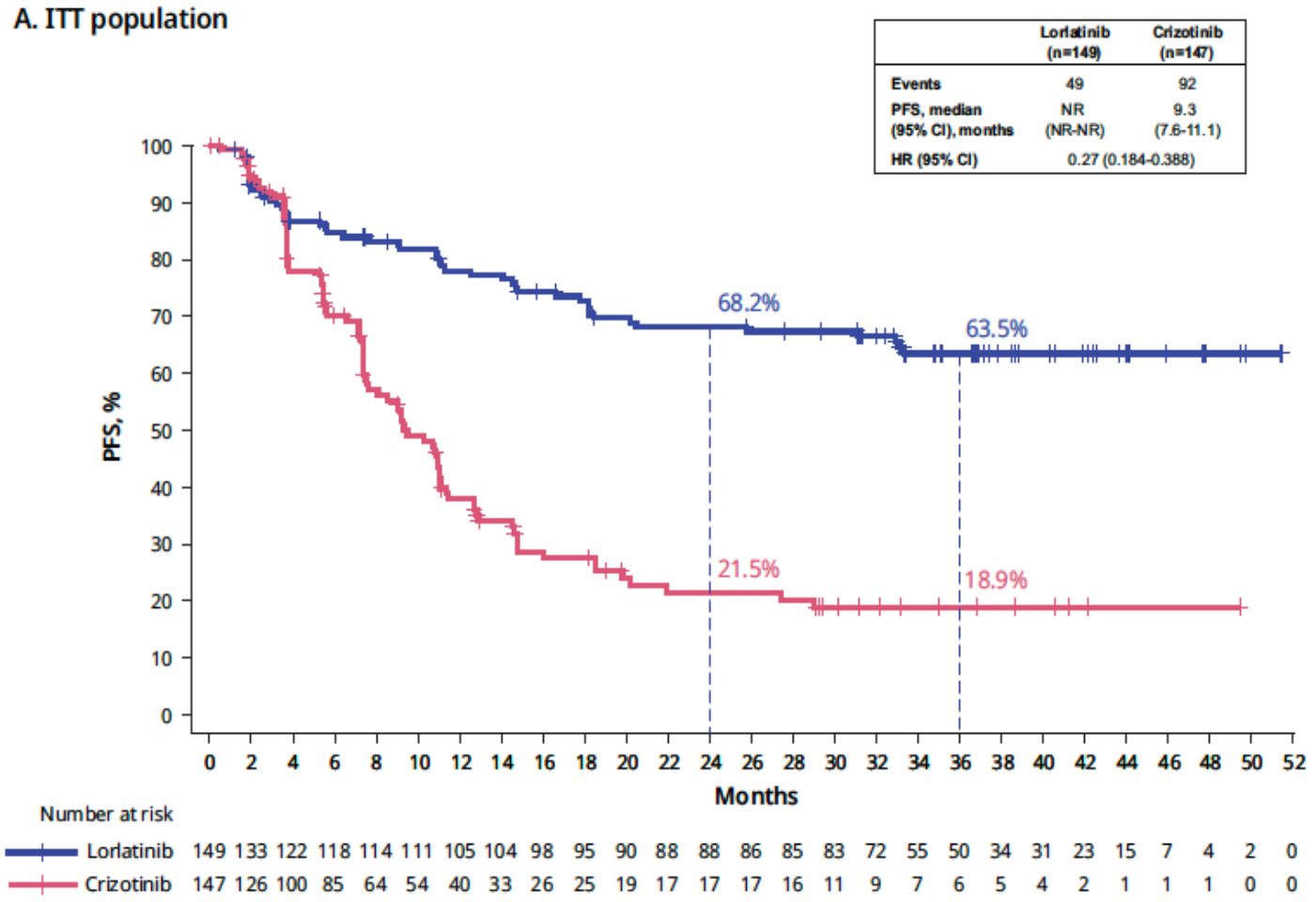






- 1. Mok T, et al. *Ann Oncol*. 2020;31:1056-1064; 2. Tiseo M, et al. ELCC 2022. Abstract 29P; 3. Solomon B, et al. AACR 2022. Abstract CT223.

Updated Efficacy from the Phase 3 CROWN Study of 1L Lorlatinib



Updated analysis of CROWN with approximately 3 years of follow-up

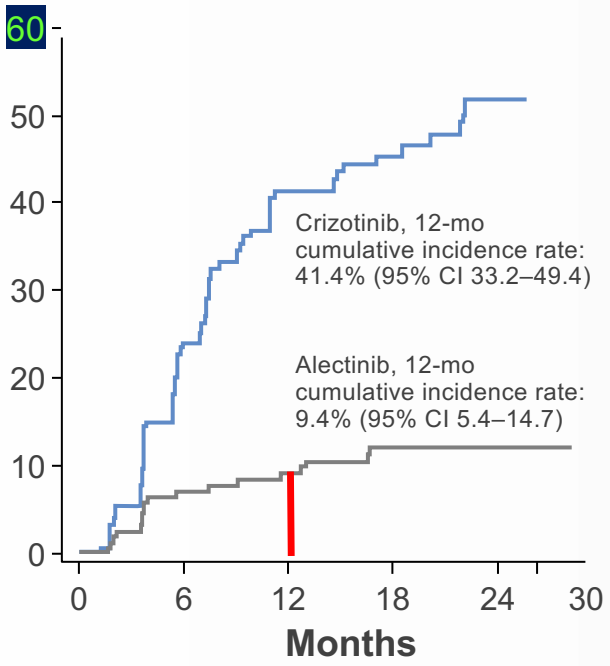
- **Median PFS by BICR:**
  - NR (95% CI, NR-NR) with lorlatinib
  - 9.3 months (95% CI, 7.6-11.1) with crizotinib
  - HR 0.27 (95% CI, 0.18-0.39)

- **3-year PFS rate with lorlatinib: 63.5%**

Solomon BJ, et al. Presented at: AACR;2022. Abstract CT223.

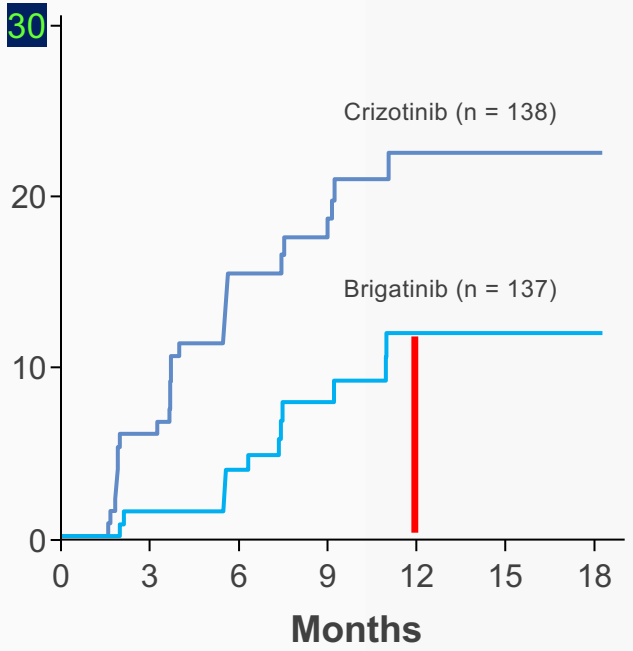
CNS Progression: Standard ALK TKIs

Alectinib (ALEX)



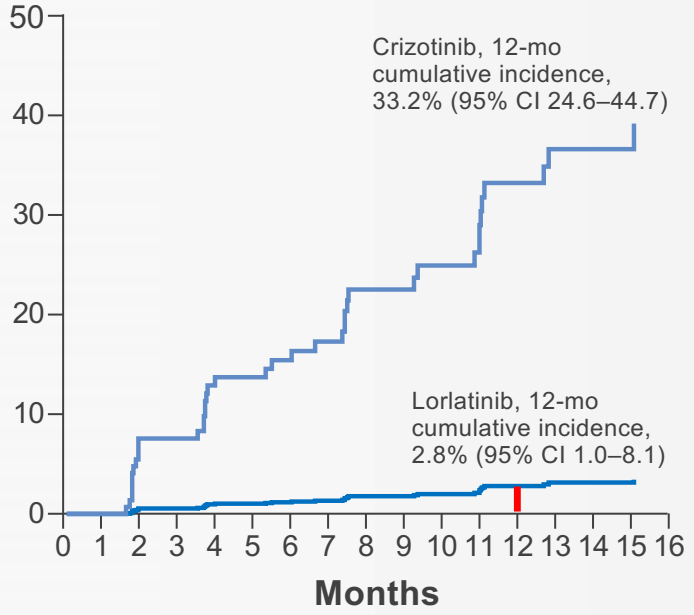
Cause-specific HR 0.16; 95% CI 0.10-0.28; *P*<0.001).

Brigatinib (ALTA-1L)



Cause-specific HR for CNS progression = 0.30 (0.15–0.60)

Lorlatinib (CROWN)[3]



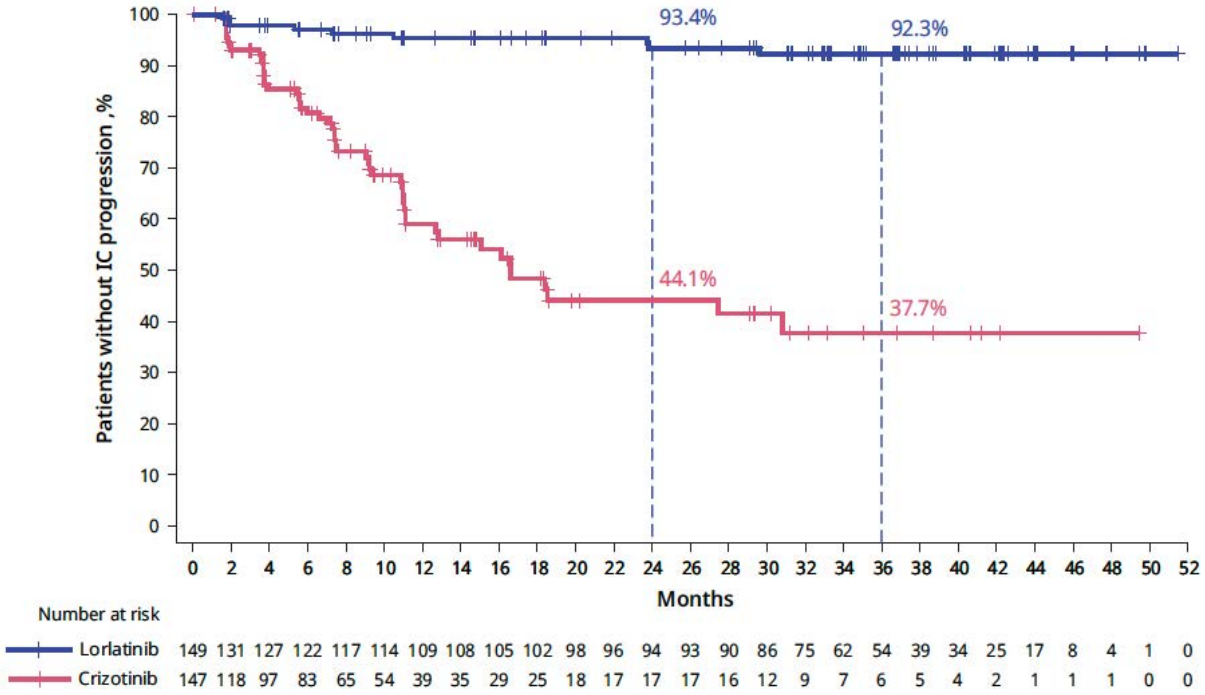
Hazard ratio for CNS progression without previous non-CNS progression or death, 0.06 (95% CI, 0.02–.18)

Peters S, et al. *N Engl J Med.* 2017;377:829-838; Popat S, et al. *Ann Oncol.* 2018;29(suppl_8):vii76 and presentation at ESMO 2018; Shaw AT, et al. *N Engl J Med.* 2020;383:2018-2029.

CNS Protective Effect of 1L Lorlatinib (CROWN))

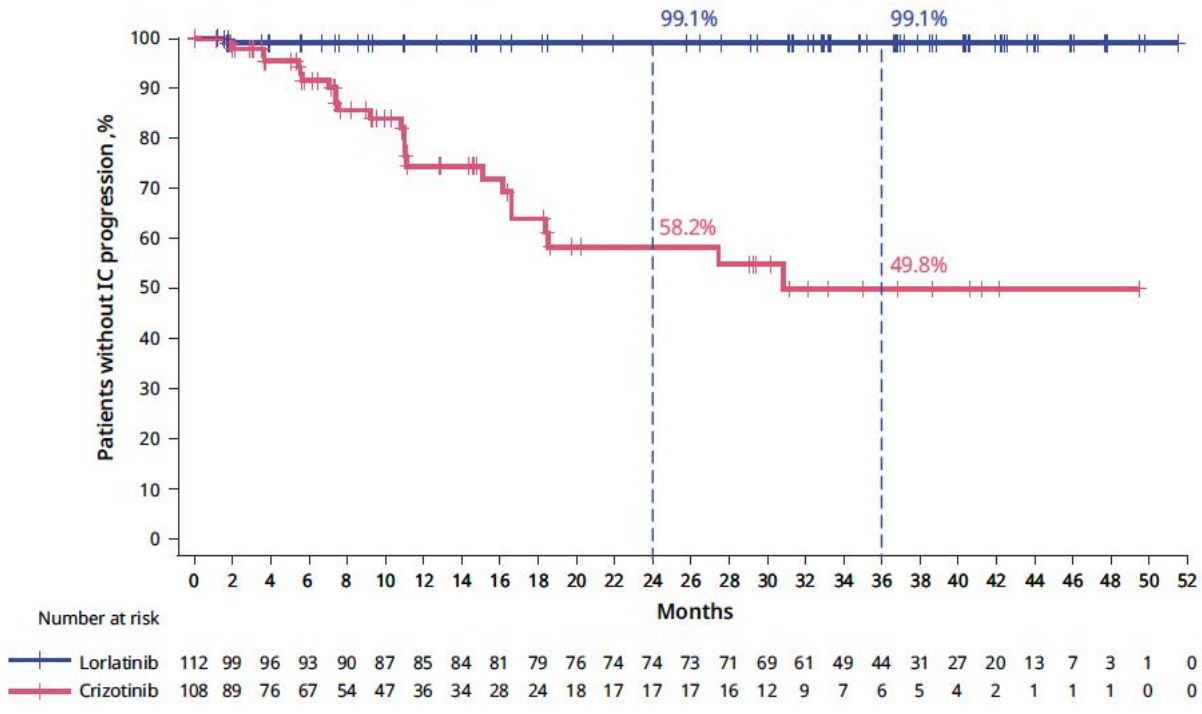
A. ITT population

	Lorlatinib (n=149)	Crizotinib (n=147)
Events	9	51
PFS, median (95% CI), months	NR (NR-NR)	16.6 (11.1-NR)
HR (95% CI)	0.08 (0.040-0.174)	



C. Patients without baseline brain metastases

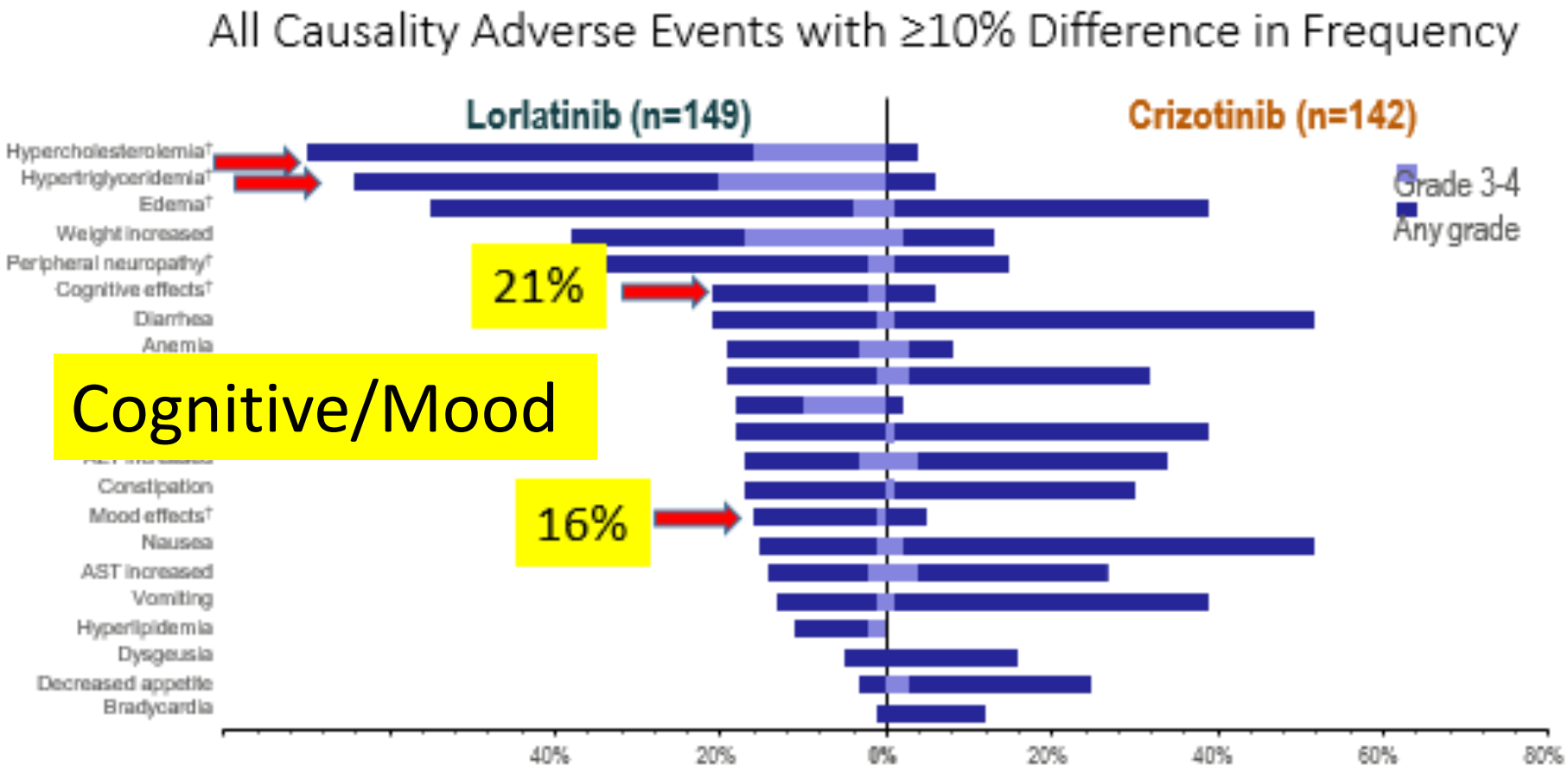
	Lorlatinib (n=112)	Crizotinib (n=108)
Events	1	25
TTP, median (95% CI), months	NR (NR-NR)	30.8 (18.4-NR)
HR (95% CI)	0.02 (0.002-0.136)	



Only 1 of 112 pts without baseline brain metastases had IC progression on lorlatinib

Solomon BJ, et al. Presented at: AACR;2022. Abstract CT223.

Lorlatinib Adverse Events



<u>Weight gain</u> reported in <u>38%</u> and associated with increased appetite. (17% grade 3: 20% increase)

Both weight gain and cognitive and mood changes due to off-target inhibition of <u>tropomyosin receptor kinase B in the CNS</u>

Big Questions in ALK

- Can “apparent” enhancements in PFS and CNS penetrance for lorlatinib offset its increased toxicity?
- Would we have equipoise conducting a RP3 trial of lorlatinib vs either alectinib or brigatinib?
- If lorlatinib were used upfront, what would 2nd line Tx entail?

In vitro sensitivity to ALKi in BA/F3 cell lines with different resistance mutations: IC50 ranking

A

	Crizotinib	Ceritinib	Ensartinib	Alectinib	Brigatinib	Lorlatinib
WT	23.30 16.23 to 33.46	12.47 7.813 to 19.92	1.281 1.073 to 1.530	1.377 1.044 to 1.818	0.959 0.794 to 1.158	0.267 0.212 to 0.337
G1123S	27.17 16.75 to 44.09	661.6 271.7 to 1611	0.983 0.711 to 1.358	1.559 1.167 to 2.082	11.14 7.082 to 17.53	2.855 2.238 to 3.642
L1152R	361.3 205.5 to 635.1	167.3 145.2 to 968.4	34.75 23.42 to 51.56	3.501 3.110 to 3.943	0.798 0.640 to 0.995	7.402 8.190 to 20.24
C1156Y	306.0 100.6 to 931.3	199.7 54.09 to 737.4	27.27 9.057 to 82.12	13.61 5.461 to 33.91	7.659 3.999 to 14.67	8.938 4.206 to 18.99
I1171T	471.9 190.3 to 1171	165.1 59.20 to 460.4	69.25 339.21 to 122.3	379.8 126.4 to 1141	25.85 10.58 to 63.14	52.53 23.42 to 117.8
F1174C	294.4 72.52 to 1195	205.1 69.89 to 601.6	58.55 24.82 to 138.1	19.22 9.222 to 40.05	29.10 12.31 to 68.78	9.786 5.047 to 18.98
F1174V	57.91 33.13 to 100.7	51.28 24.74 to 106.3	6.992 5.689 to 8.593	1.988 1.700 to 2.325	5.165 4.110 to 6.491	2.100 1.732 to 2.545
V1180L	114.5 44.44 to 295.0	11.87 7.962 to 17.70	4.436 3.401 to 5.786	1902 1186 to 3051	1.563 1.233 to 1.983	1.650 1.394 to 1.953
L1196M	637.1 246.7 to 1645	133.8 59.24 to 302.4	59.53 31.25 to 113.4	58.74 23.75 to 145.3	20.09 8.841 to 45.65	56.52 30.07 to 106.2
L1198F	27.97 14.30 to 54.73	1722 587.6 to 5045	0.323 0.199 to .524	201.9 125.2 to 325.5	48.53 29.15 to 80.80	56.61 26.51 to 120.9
G1202del	179.9 59.72 to 541.6	319.1 165.9 to 614.0	138.9 68.17 to 283.0	963 614.7 to 1509	25.02 14.85 to 42.15	11.15 5.858 to 21.21
G1202R	289.5 197.4 to 424.4	252.4 147.7 to 413.3	316.0 212.4 to 470.2	1918 1151 to 3197	30.92 233.47 to 40.72	31.18 26.41 to 36.81
S1206Y	177.5 65.38 to 482.0	53.14 25.64 to 110.1	31.45 21.92 to 45.14	7.216 3.878 to 13.43	17.56 8.543 to 36.10	4.704 2.795 to 7.918
E1210K	4027 887.6 to 20981	345.6 147.4 to 809.1	3010 1015 to 9077	5065 2991 to 8557	299.2 144.7 to 622	38.04 10.67 to 139.3
F1245C	197.6 68.43 to 571.3	216.3 87.17 to 536.6	22.03 11.88 to 40.85	13.62 6.995 to 26.53	26.00 12.48 to 54.18	7.357 4.538 to 11.93
G1269A	699.3 176.9 to 2765	67.13 29.22 to 154.3	221.8 97.82 to 503.1	58.66 42.83 to 80.35	11.41 5.492 to 23.72	76.39 31.93 to 182.7

1000nM
800nM
600nM
400nM
200nM

B

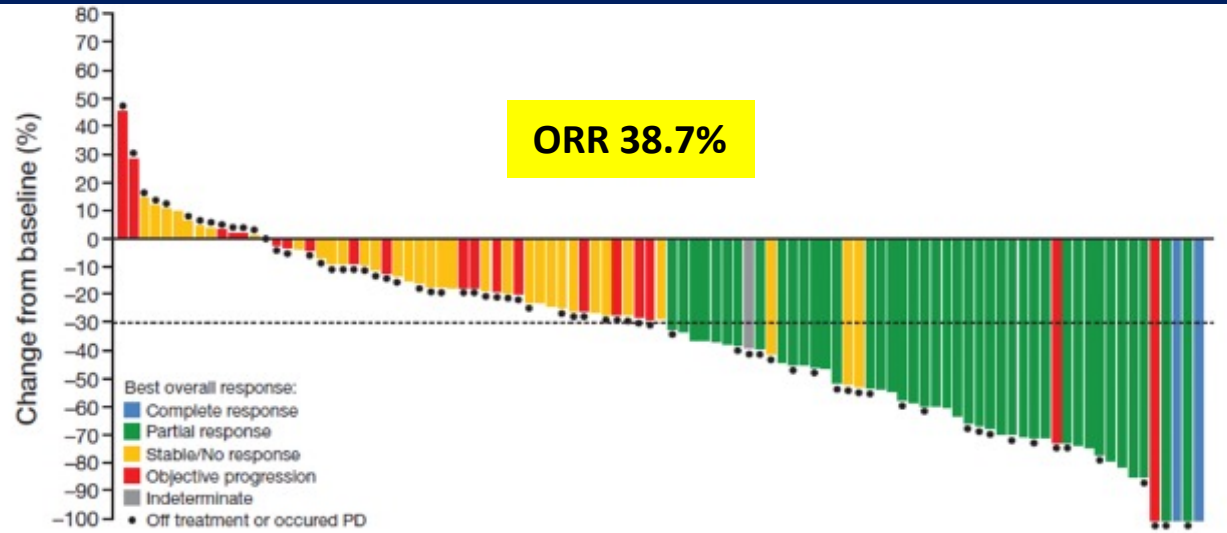
	Crizotinib	Ceritinib	Ensartinib	Alectinib	Brigatinib	Lorlatinib
WT	205.3 70.5 to 597.9	75.1 29.72 to 189.8	24.92 9.450 to 65.70	29.51 15.53 to 56.05	16.75 10.10 to 27.77	4.456 2.376 to 8.357
G1123S	54.50 23.65 to 125.6	651.2 179.3 to 2365	1.309 0.701 to 2.446	3.000 1.424 to 6.319	25.79 9.503 to 69.99	3.557 2.111 to 5.992
L1152R	124.3 66.44 to 232.6	165.7 533.61 to 511.9	14.80 7.863 to 27.86	3.300 2.502 to 4.354	0.190 0.126 to 0.287	4.246 2.228 to 8.091
C1156Y	110.4 69.28 to 176.1	58.66 38.68 to 88.98	10.92 7.338 to 16.25	5.266 3.842 to 7.218	2.263 3.842 to 7.218	2.313 1.570 to 3.407
I1171T	152.8 79.26 to 294.5	17.60 13.11 to 23.62	13.84 6.726 to 28.50	24.78 14.50 to 42.36	3.135 2.297 to 4.278	7.450 4.528 to 12.26
F1174C	257.7 85.86 to 773.5	248.5 110.2 to 560.4	64.79 23.95 to 175.3	286.2 123.0 to 665.8	28.06 13.40 to 58.75	13.11 6.494 to 26.48
F1174V	238.8 170.4 to 1003	157.4 60.73 to 408.0	33.28 22.67 to 48.86	38.43 21.25 to 69.52	31.92 20.08 to 50.75	8.258 5.731 to 11.90
V1180L	98.12 43.35 to 222.6	18.63 7.693 to 45.10	9.423 5.058 to 17.56	2166 601.8 to 7798	3.523 1.950 to 6.365	2.653 1.569 to 4.484
L1196M	924.5 415.4 to 2057	205.9 58.74 to 721.6	81.31 37.03 to 178.6	929.6 422.2 to 2047	26.66 11.10 to 64.04	69.81 28.04 to 173.8
L1198F	46.52 17.84 to 121.3	2072 382.2 to 11228	3.807 2.080 to 6.966	1205 494.7 to 2933	157.0 59.32 to 415.5	59.47 313.53 to 112.2
G1202del	322.0 125.6 to 765.0	586.7 173.2 to 1988	474.7 169.0 to 1333	>10000 N/A	104.6 337.6 to 290.8	26.19 12.51 to 54.86
G1202R	440.5 175.7 to 1105	405.6 189.5 to 868.1	315.9 194.1 to 514.1	>10000 N/A	83.82 50.43 to 139.3	35.72 20.46 to 62.36
D1203N	332.0 170.1 to 648.2	329.2 172.0 to 630.1	21.10 11.73 to 37.98	142.7 46.29 to 439.7	33.42 20.19 to 55.30	19.73 12.16 to 32.01
S1206C	308.1 152.9 to 620.9	222.2 91.30 to 541.0	42.49 20.41 to 88.46	30.94 14.02 to 68.29	81.80 27.80 to 240.6	6.129 3.167 to 11.86
S1206Y	175.7 60.74 to 508.3	90.05 24.02 to 337.6	48.24 23.47 to 99.14	9.804 6.057 to 15.87	16.29 8.313 to 31.94	3.238 3.042 to 5.134
E1210K	482.6 170.5 to 1366	178.2 83.58 to 380.1	527.6 198.5 to 1402	759.3 255.7 to 2255	162.9 58.92 to 450.3	7.565 3.780 to 15.14
F1245C	289.9 119.2 to 704.8	208.0 63.52 to 680.9	52.90 23.83 to 117.5	65.55 27.22 to 157.9	46.16 21.58 to 98.70	14.82 6.461 to 34.00
G1269A	511.4 169.3 to 1544	52.65 23.98 to 115.6	123.1 65.00 to 268.6	100.4 45.83 to 220.0	10.02 5.337 to 18.82	42.70 20.85 to 87.42

1000nM
800nM
600nM
400nM
200nM

Horn et al, J Thorac Oncol 2019; 14:1901-1911In

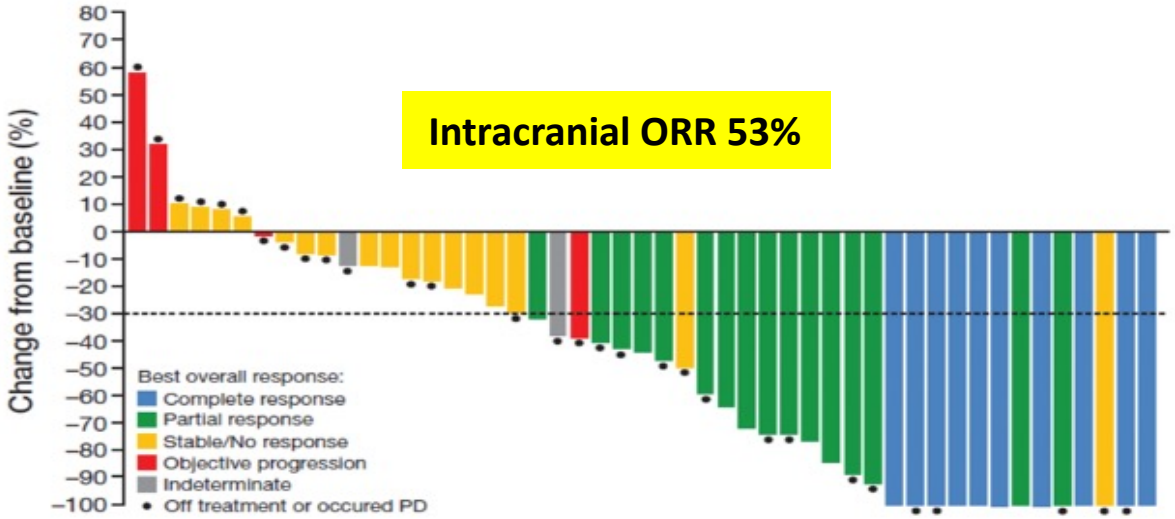
Lorlatinib in *ALK*+ Patients Treated With ≥2 Prior ALK Inhibitors (2–3 ALK TKIs ± chemo)

N = 111



ORR 38.7%

PFS 6.9 months

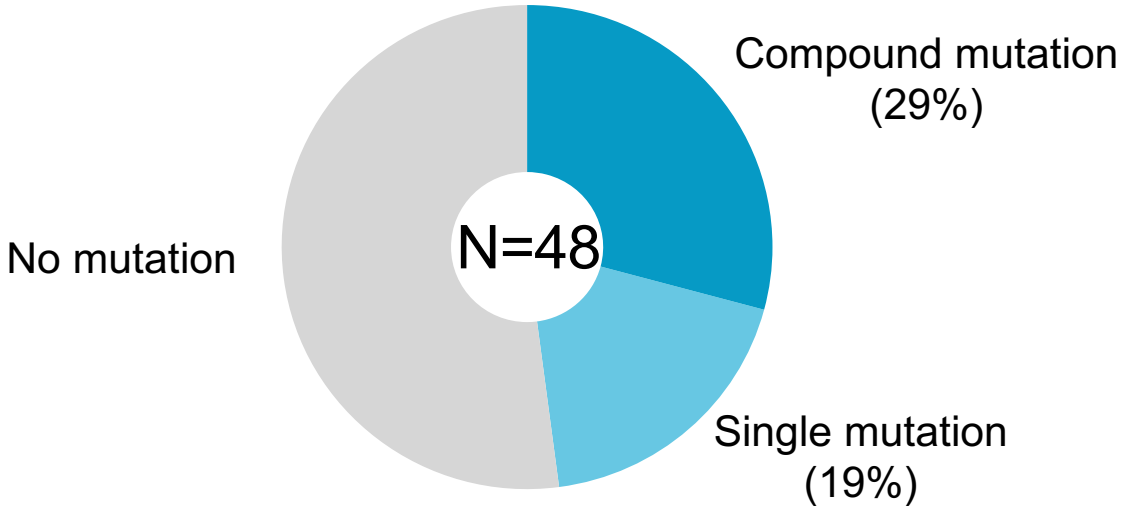


Intracranial ORR 53%

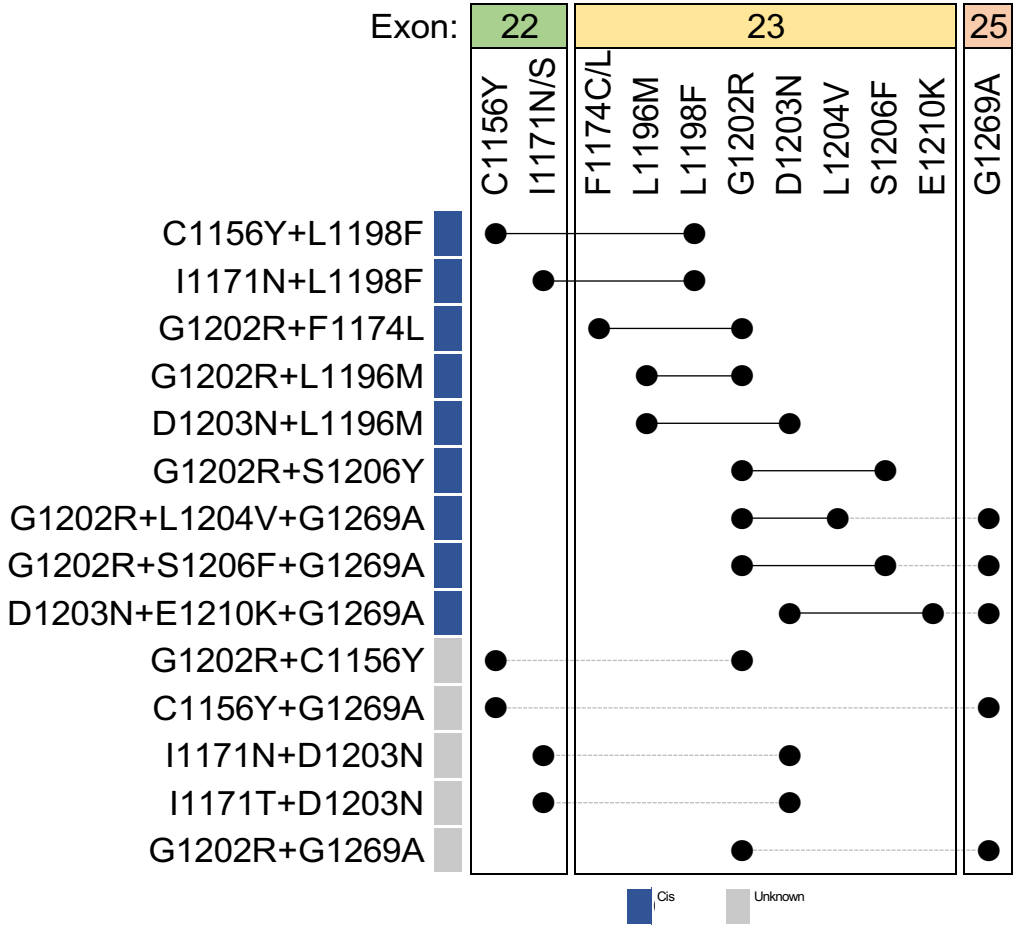
Solomon BJ, et al. *Lancet Oncol*. 2018;19:1654-1667.

Resistance to Lorlatinib Following Prior ALK TKI(s): Compound *ALK* Mutations

Post-lorlatinib tissue biopsies (with prior ALK TKI)



- No single predominant compound *ALK* mutation was identified; *however*…
- Among the 14 cases with ≥2 *ALK* mutations, 8 (57%) harbored *ALK* G1202R and 3 (21%) harbored *ALK* I1171N

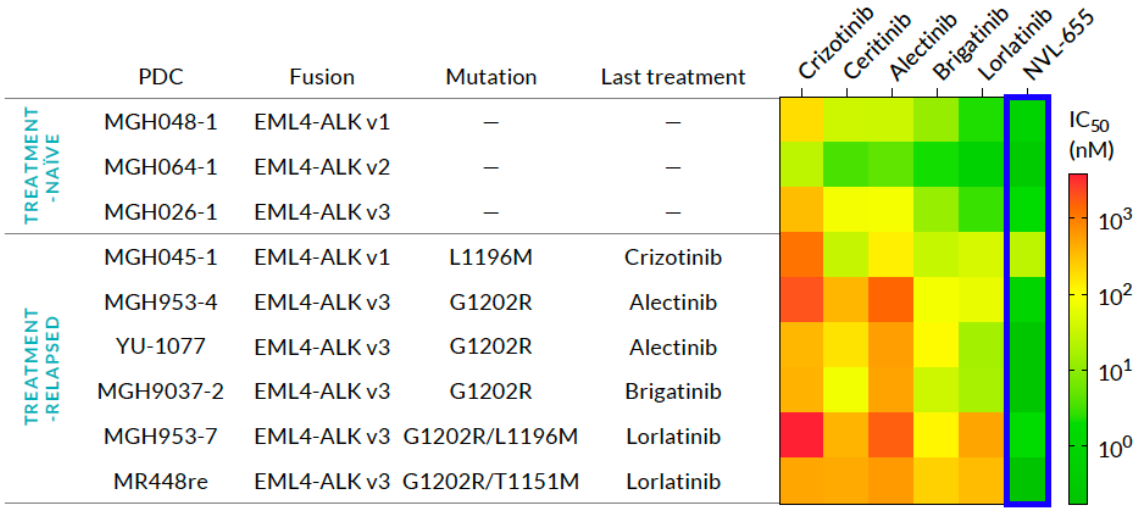


Shiba-Ishii A, et al. *Nat Cancer*. 2022;3:710-22.

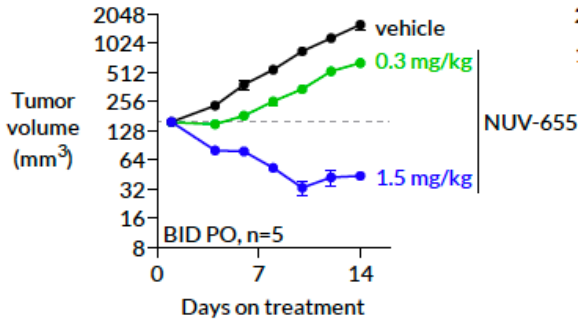
Overcoming Lorlatinib-Resistant Compound Mutations: 4G ALK TKI

NVL-655 (ALKOVE-1; NCT05384626)

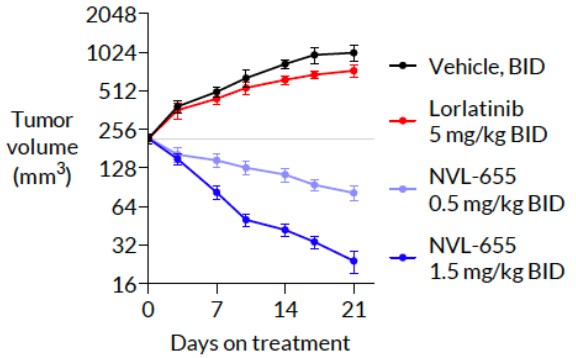
	Cell with ALK fusion	NUV-655	Crizotinib	Ceritinib	Alectinib	Brigatinib	Lorlatinib
No kinase domain mutations	NCI-H2228 (EML4-ALK v3)	0.70	90	55	13	13	< 1.1
	NCI-H3122 (EML4-ALK v1)	2.0	180	48	22	22	3.5
	Wild-type	1.6	270	90	25	42	4.2
G1202R+ mutations	G1202R	< 0.73	950	570	1600	400	120
	G1202R/L1196M	7.0	1500	1400	2200	820	3900
	G1202R/G1269A	3.0	1100	350	1300	240	970
	G1202R/L1198F	2.0	170	1300	2200	470	720



EML4-ALK G1202R/L1196M fusion Ba/F3 xenograft model

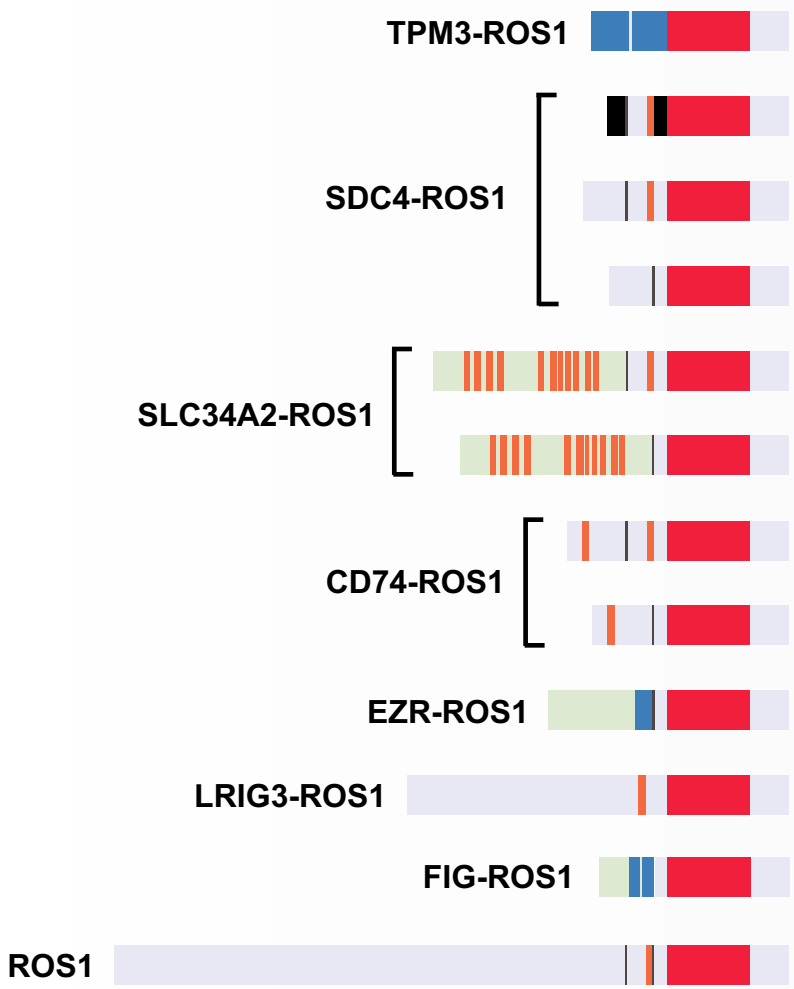


EML4-ALK G1202R/L1196M fusion MGH953-7 PDX

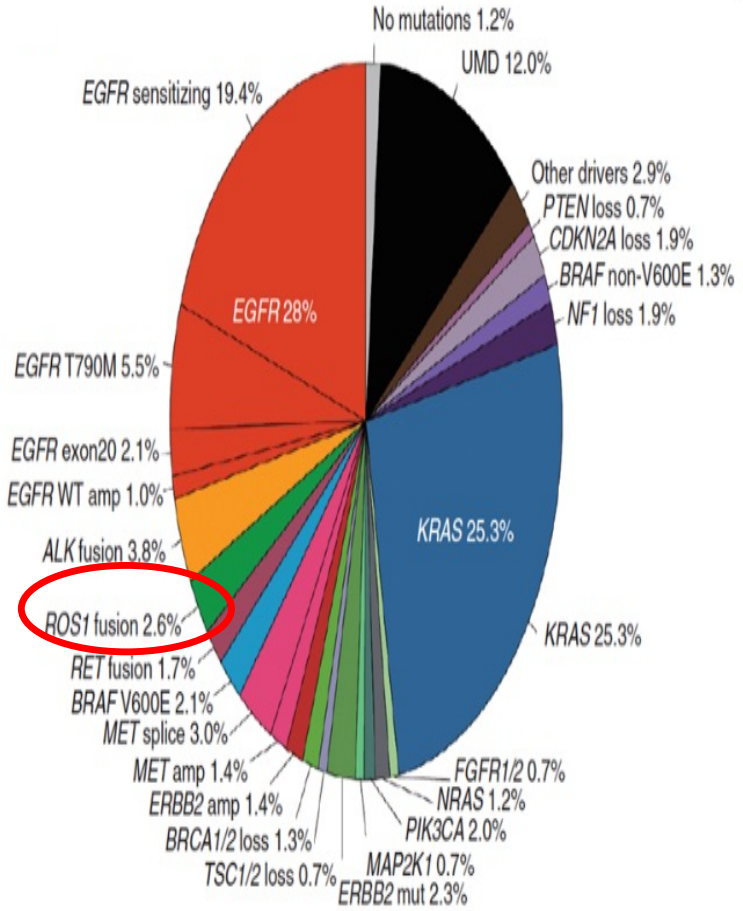


Pelish HE, et al. Presented at: AACR;2021. Fujino T, et al. Presented at: EORTC-NCI-AACR;2022.

ROS1 Rearrangements in NSCLC



- Identified in ~2% of NSCLC
- Also found in some GBMs, cholangiocarcinomas, and other tumor types
- Activated by chromosomal rearrangement, leading to constitutive kinase activation and oncogene addiction
- No overlap with ALK

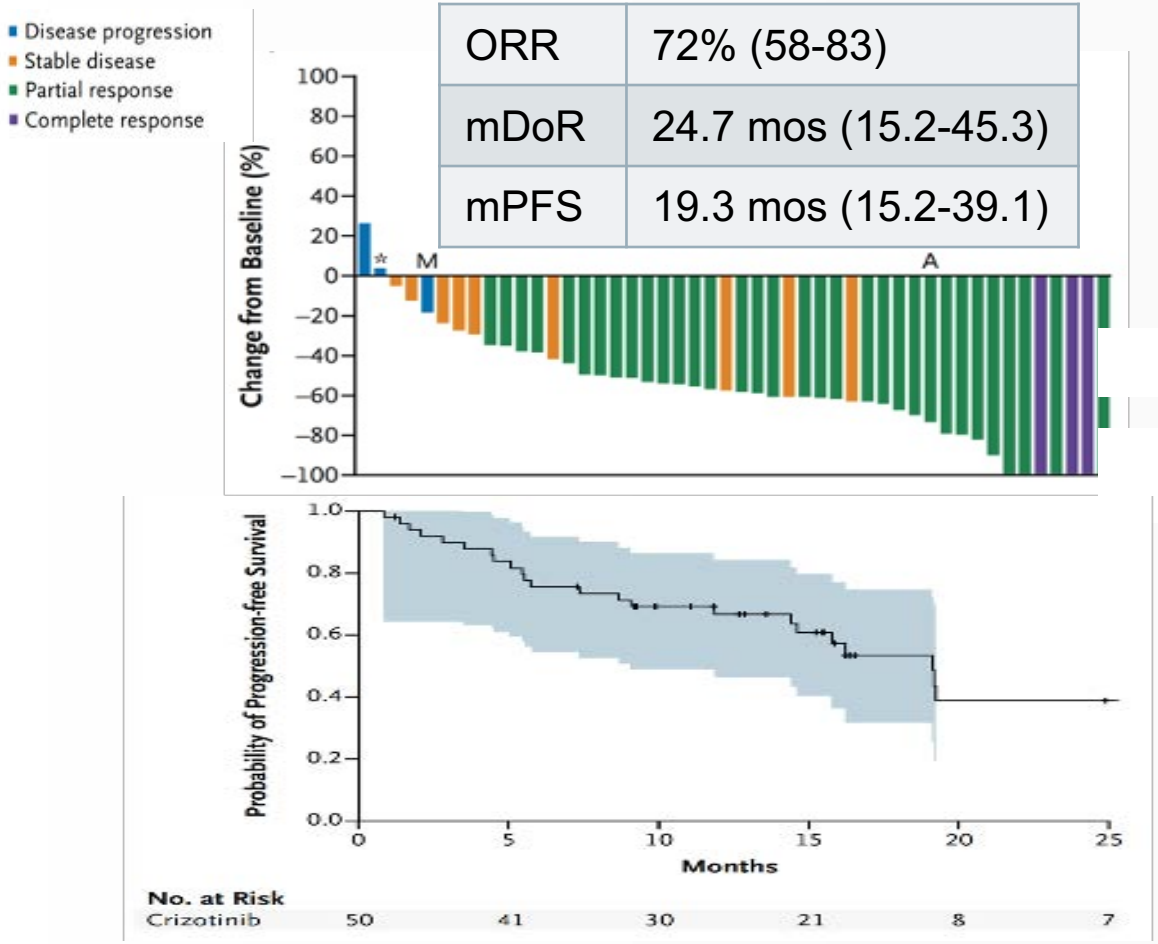


Bergethon et al., JCO 30(8): 863-70, 2012; Takeuchi et al., Nat Med 18(3): 378-81, 2012; Rimkunas et al., CCR 18(16): 4449-57, 2012

Crizotinib and Entrectinib: Systemic Efficacy

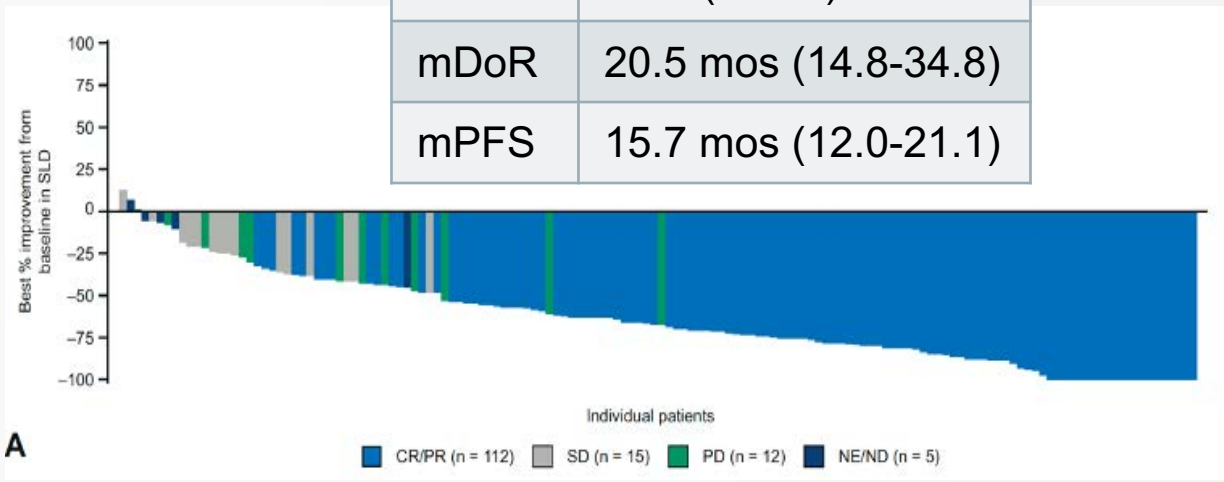
Crizotinib

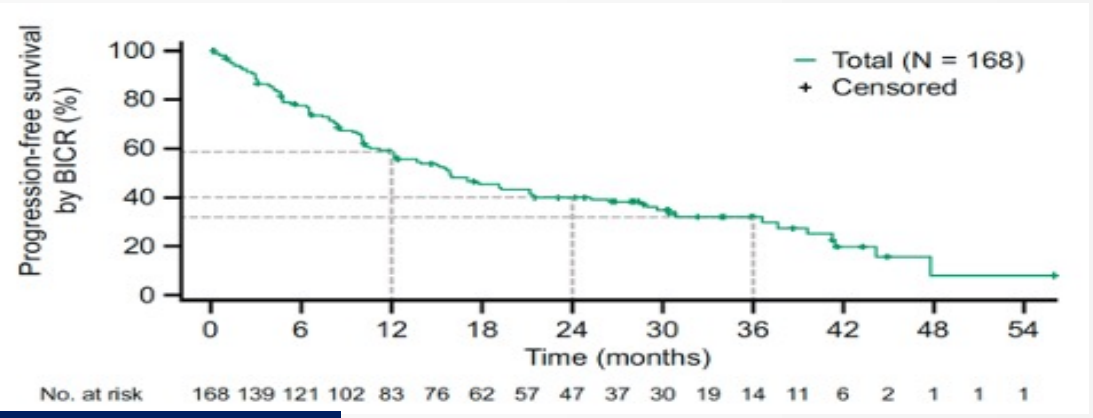
ORR	72% (58-83)
mDoR	24.7 mos (15.2-45.3)
mPFS	19.3 mos (15.2-39.1)



Entrectinib

ORR	68% (60-75)
mDoR	20.5 mos (14.8-34.8)
mPFS	15.7 mos (12.0-21.1)





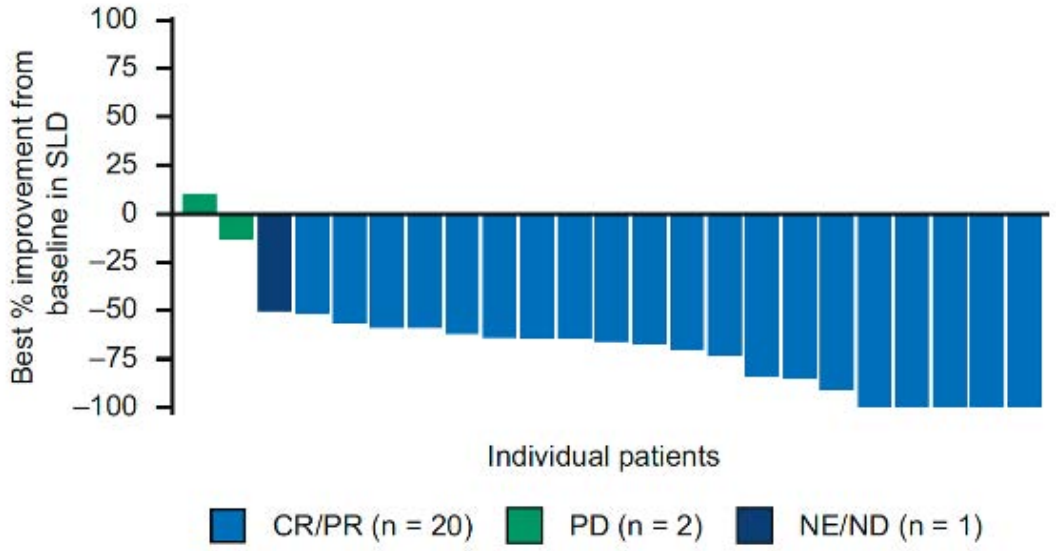
Crizotinib approved by FDA March 2016

Entrectinib approved by FDA August 2019

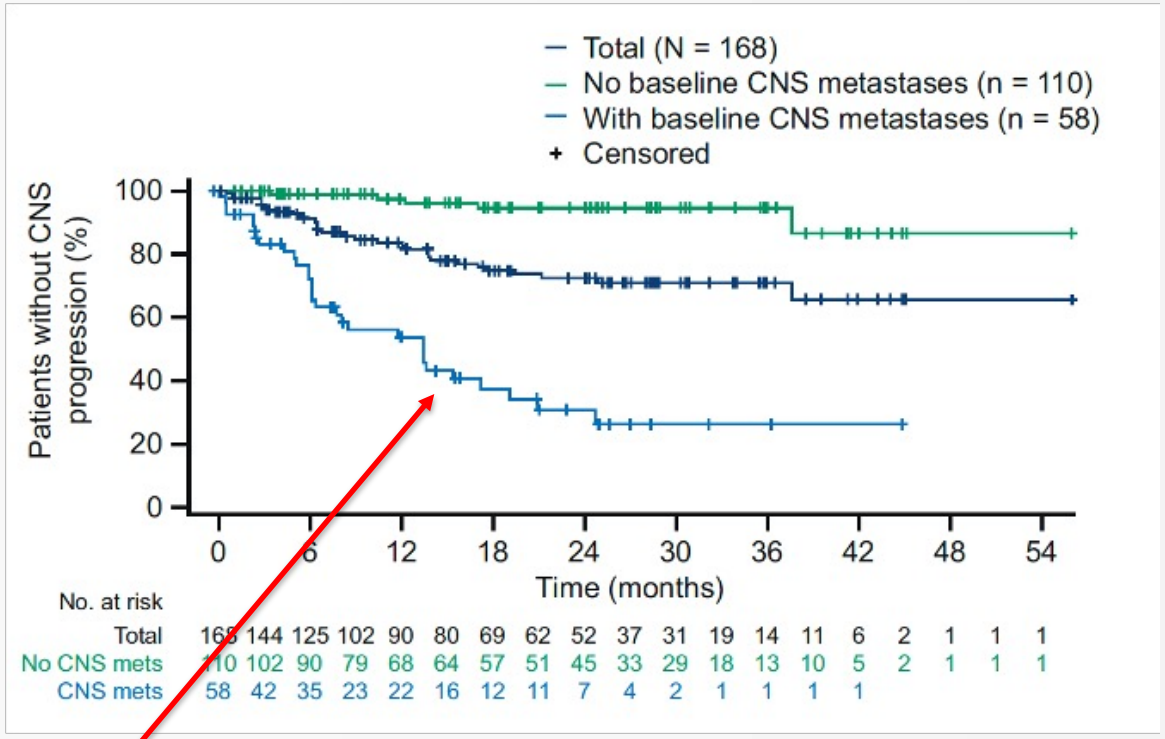
Shaw AT, et al. ***N Engl J Med.*** **2014;371:1963-71.**
Shaw AT, et al. ***Ann Oncol.*** **2019;30:1121-6.**
Drilon A, et al. ***JTO Clin Res Rep.*** **2022;3:100332.**

Entrectinib: CNS efficacy

Best intracranial responses, patients with baseline measurable CNS metastases



Time to CNS progression



- **Intracranial ORR**: 80% (59.3-93.2) among 25 patients with measurable baseline CNS metastases
- **Median intracranial PFS**: 8.4 months (6.4-13.8)
- **Time to CNS progression**: not estimable overall; 13.6 months (6.7-19.3) in patients with baseline CNS metastases

- Drilon A, et al. *JTO Clin Res Rep*. 2022;3(6):100332.

Crizotinib and Entrectinib: Toxicities

	Crizotinib		Entrectinib	
	All grades (%)	Grade 3 (%)	All grades (%)	Grade 3-4 (%)
Vision disorder	87	0	NR	NR
Nausea	51	2	17	0
Edema	47	0	16	0
Diarrhea	45	0	26	2
Vomiting	38	4	14	0
Elevated transaminases	36	4	10/10	2/2
Constipation	34	0	33	0
Bradycardia	21	0	NR	NR
Fatigue	21	0	24	0
Dizziness	19	0	32	<1
Dysgeusia	19	0	42	<1
Hypophosphatemia	17	15	1	<1
Decreased appetite	15	2	NR	NR
Neutropenia	15	9	4	4
Rash	13	0	7	1
Weight increase	NR	NR	19	7
Paresthesia	NR	NR	17	0
Myalgia	NR	NR	14	2
Blood creatinine increase	NR	NR	13	<1

Shaw AT, et al. *Ann Oncol*. 2019;30(7):1121-1126. Drilon A, et al. *Lancet Oncol*. 2020;21(2):261-270.

Summary of ROS1 TKIs in TKI-Naïve *ROS1* Fusion+ NSCLC (1L)

	Crizotinib* (PROFILE 1001)	Entrectinib* (ALKA-372-001, STARTRK-1, STARTRK-2)	Ceritinib (Korean Phase 2)	Taletrectinib (TRUST Chinese Phase 2)	Lorlatinib (Phase 1/2)	Repotrectinib# (TRIDENT-1 Phase 1/2)
N	53	168	20	67	21	22
ORR	72%	68%	67%	93%	62%	91%
Median PFS	19.3 months	15.7 months	19.3 months	Not available	21.0 months	Not available
CNS activity	N/A	25/48 (52%) patients with measurable or nonmeasurable intracranial disease	2/5 (40%) patients with measurable or nonmeasurable intracranial disease	11/12 (92%) patients with baseline measurable CNS metastases	7/11 (64%) patients with measurable or nonmeasurable intracranial disease	3/3 (100%) patients with measurable intracranial disease
Reference	Shaw et al. Ann Oncol 2019	Drilon et al. JTO CRR 2022	Lim et al. JCO 2017	Li W et al., ASCO 2022	Shaw et al. Lancet Oncol 2019	Cho et al. WCLC 2020; ASCO 2019

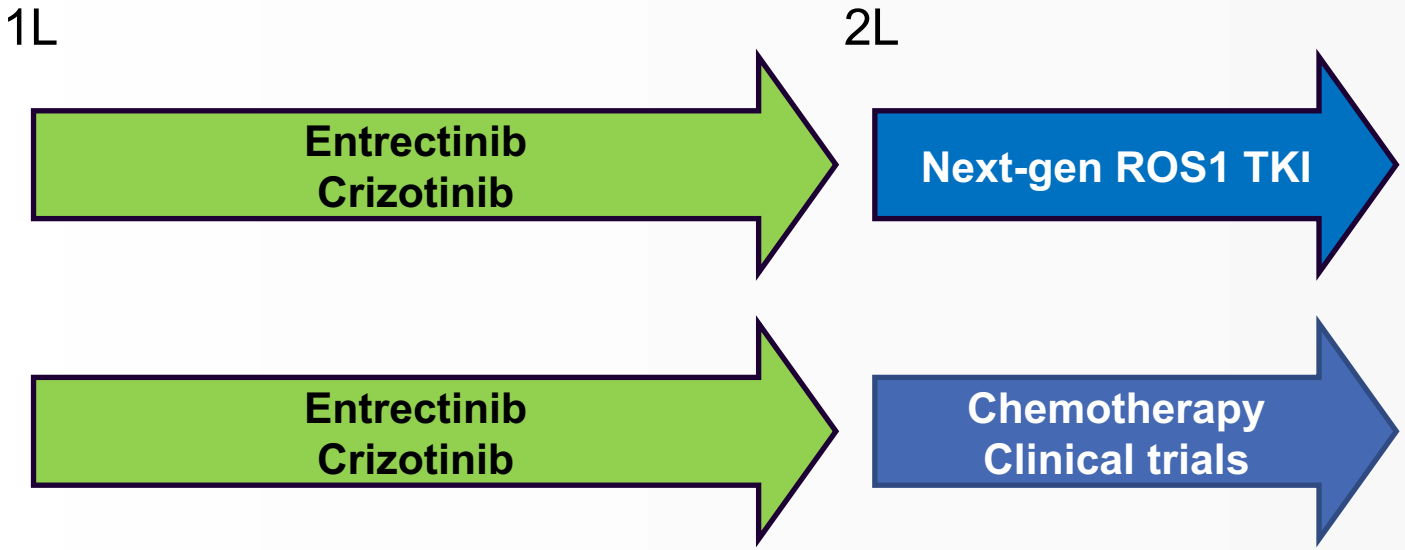
**FDA/EMA-approved* *#granted FDA breakthrough therapy designation in 2020; granted priority review May 2023*

Shaw AT, et al. *Ann Oncol*. 2019;30:1121-6. Drilon A, et al. *JTO Clin Res Rep.* 2022;3:100332. Lim SM, et al. *J Clin Oncol.* 2017;35(23):2613-2618. Li W, et al. *J Clin Oncol*. 2022;40(16_suppl):8572. Shaw AT, et al. *Lancet Oncol.* 2019;20(12):1691-1701. Cho BC, et al. *J Clin Oncol*. 2019;37(15_suppl):9011.

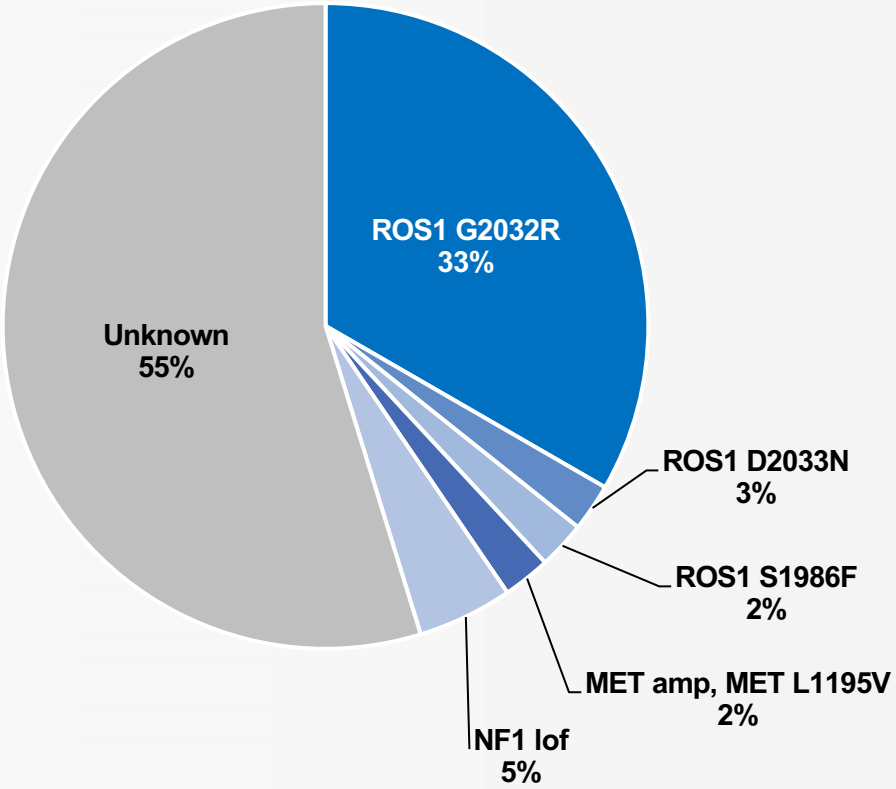
Big Questions in *ROS 1*

- Which agent is preferred front line?
- Does superior CNS penetrance give Entrectinib a leg up?
- What is the optimal approach 2nd line?
- At what point do we intervene with chemo (e.g. Pem/Carbo +/- Bev)?

Advanced ROS1 Fusion+ NSCLC: Current Treatment Paradigm: 2L



Mechanisms of resistance to crizotinib (n=42)



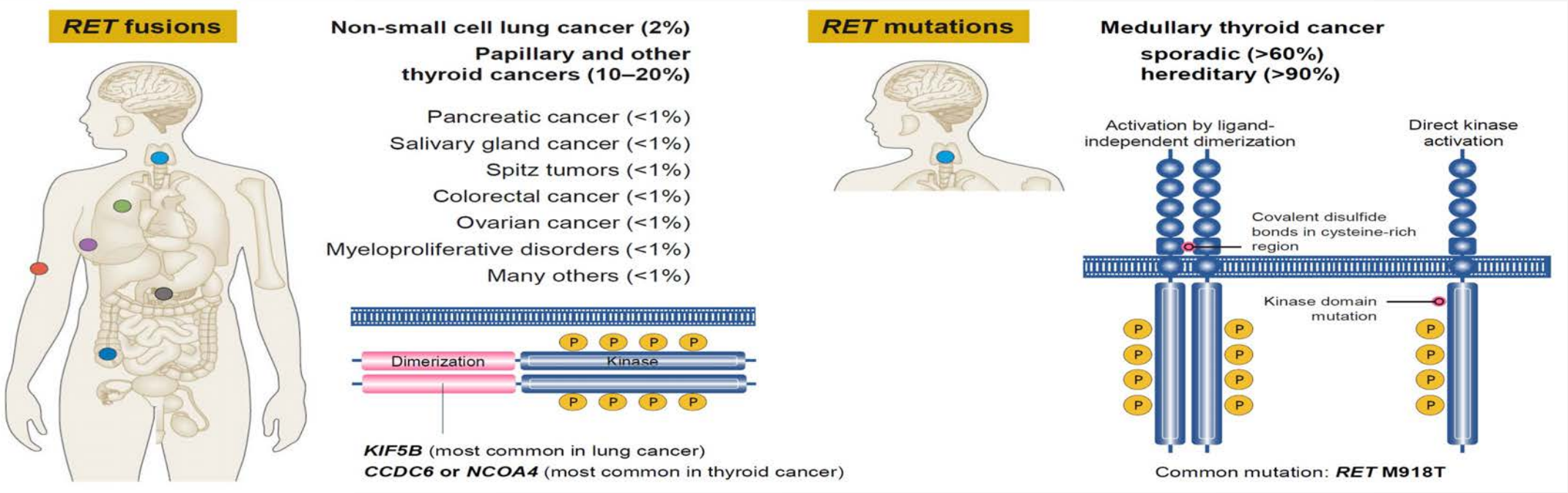
Lin JJ, et al. *Clin Cancer Res.* 2021;27:2899-909.

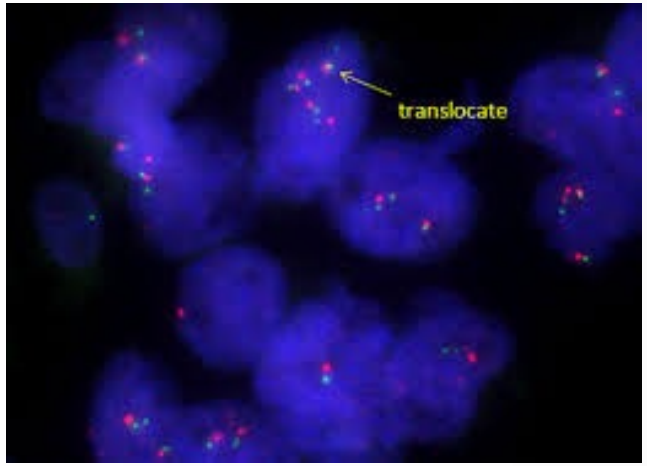
Addressing Systemic Progression on 1L TKI: ROS1 TKIs in Crizotinib/TKI-Pretreated *ROS1* Fusion+ NSCLC (2L)

	Lorlatinib (Phase 1/2)	Repotrectinib (TRIDENT-1 Phase 1/2)	Taletrectinib (TRUST Chinese Phase 2)
Patients	N=40	N=56	N=38
ORR	35%	38% (1 prior ROS1 TKI, no chemo)	50%
Median PFS	8.5 months	NR	NR
CNS activity	12/24 (50%) patients with measurable or nonmeasurable intracranial disease	5/12 (42%) patients with baseline measurable CNS metastases	11/12 (92%) patients with baseline measurable CNS metastases (TKI-naive and crizotinib-pretreated combined)
Clinical ROS1 G2032R activity	Response in 0/6 (0%) patients with a baseline ROS1 G2032R in plasma	Responses in 10/17 (59%) patients with a baseline ROS1 G2032R (1-2 prior ROS1 TKIs, +/- chemo)	Response in 4/5 (80%) patients with a baseline ROS1 G2032R
Most common treatment-related or treatment-emergent AEs (all grades)	Hypercholesterolemia, hypertriglyceridemia, edema, peripheral neuropathy, cognitive effects, weight increased, dizziness, mood effects, lipase increased	Dizziness, dysgeusia, constipation, paresthesia, dyspnea, anemia, fatigue, nausea, muscular weakness, ataxia	Diarrhea, nausea, vomiting, ALT increase, AST increase, anemia, neutrophil count decrease
Reference	Shaw et al., Lancet Oncol 2019	Cho et al., AACR-NCI-EORTC 2022	Li W et al., ASCO 2022

Shaw AT, et al. *Lancet Oncol.* 2019;20(12):1691-1701. Li W, et al. Presented at: ASCO;2022. Cho BC, et al. Presented at: AACR-NCI-EORTC;2022. Abstract 2LBA.

RET fusions occur in multiple diseases

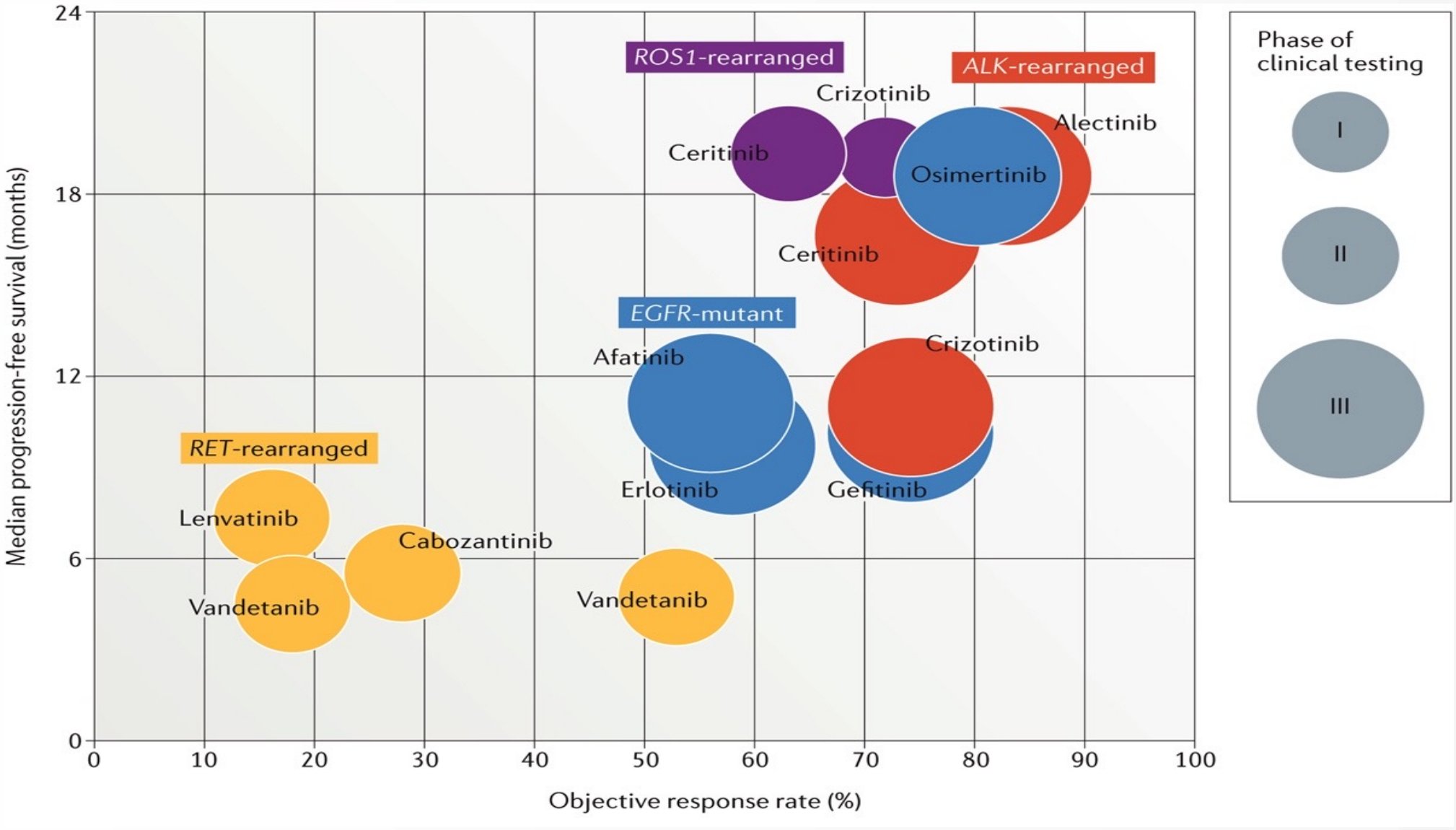




- Receptor tyrosine kinase that plays a crucial role in cell growth and differentiation
- RET gain of function leads to activation of cells like the MEN 2 syndrome
- RET loss of function leads to developmental disorders like Hirschsprung's disease or aganglionosis of the gut
- Fusions in NSCLC: younger, never smokers, almost always adenoca
- Solid and signet ring cell histologies most common
- KIF5B is most common partner; CCDC6 and NCOA4 can also partner

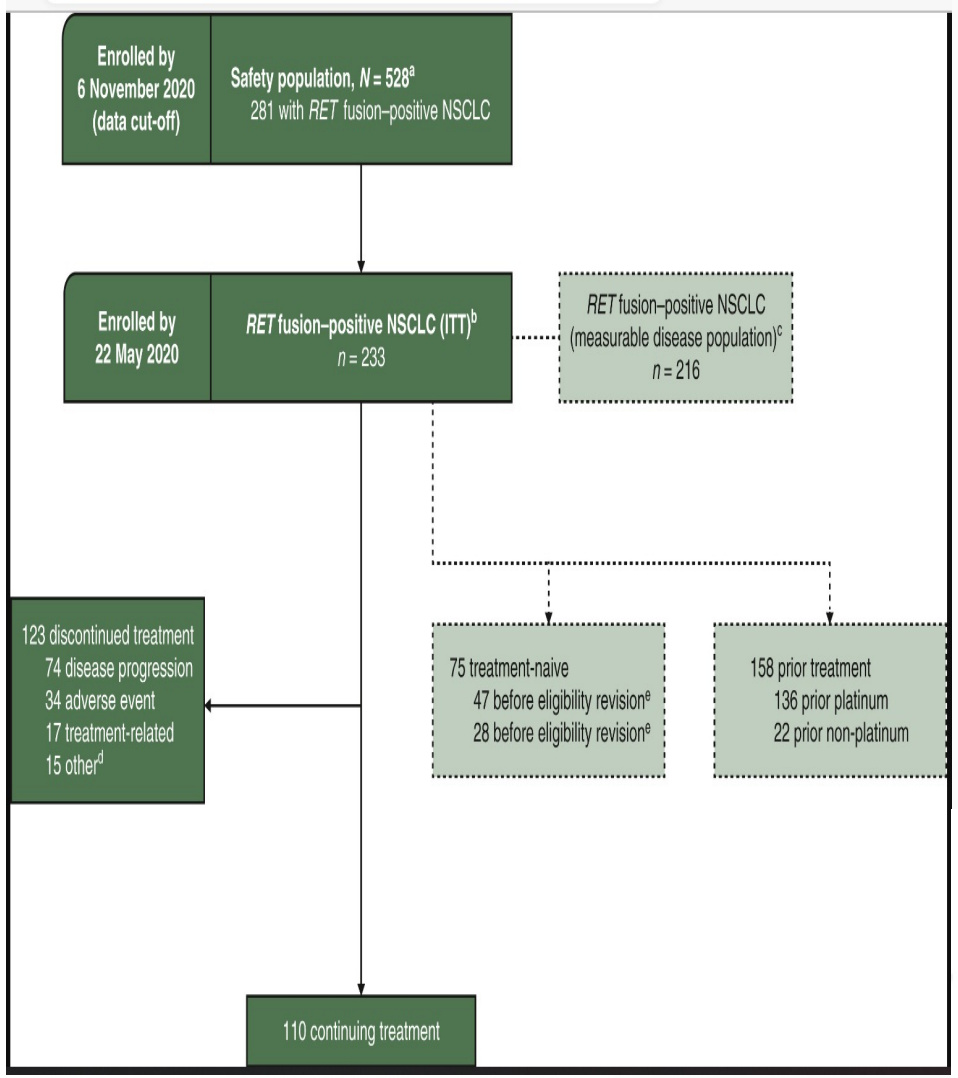
Drilon et al. Nat Rev Clin Oncol 2017

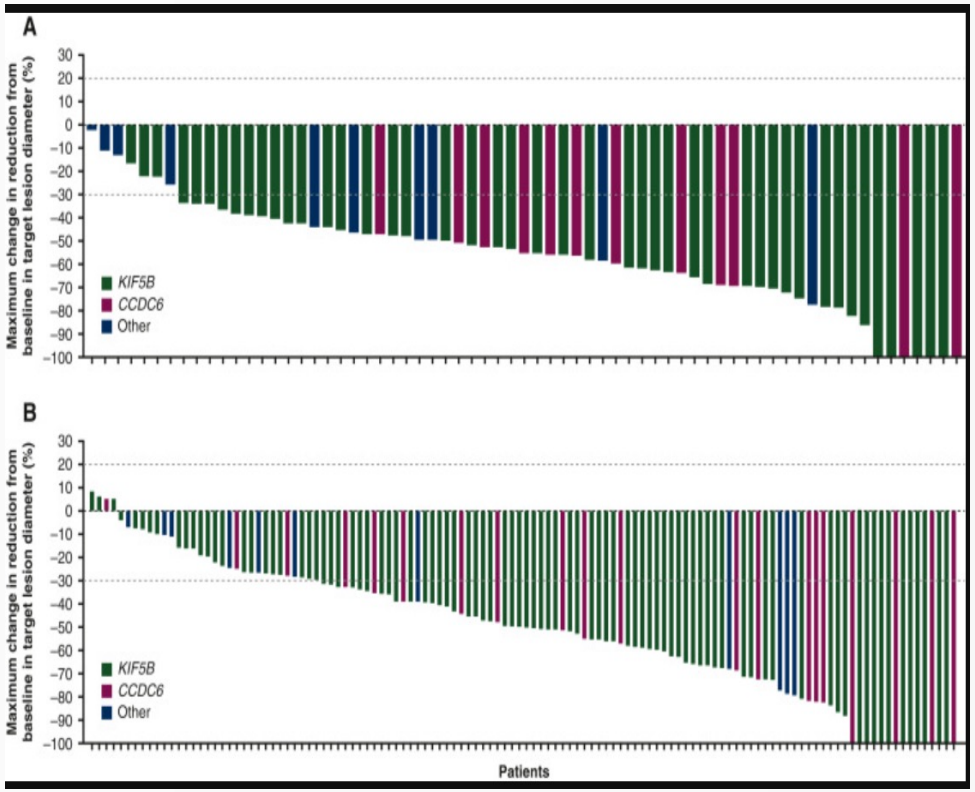
Older less selective RET TKIs had modest efficacy



Drilon et al. Nat Rev Clin Oncol 2017

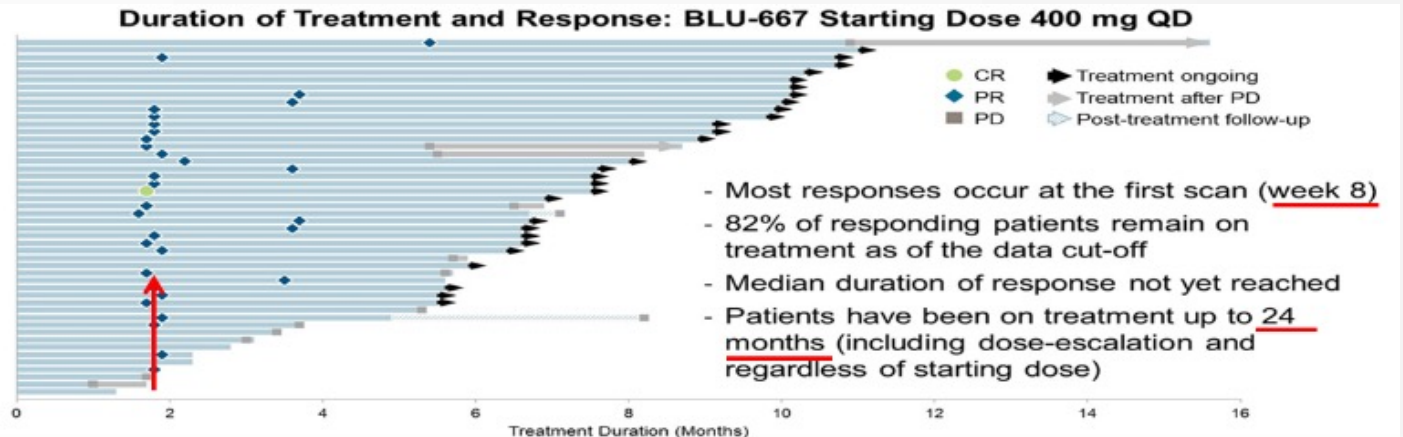
Pralsetinib: ARROW trials





Treatment naive (N=75):
ORR 72% (95% CI 60-82)

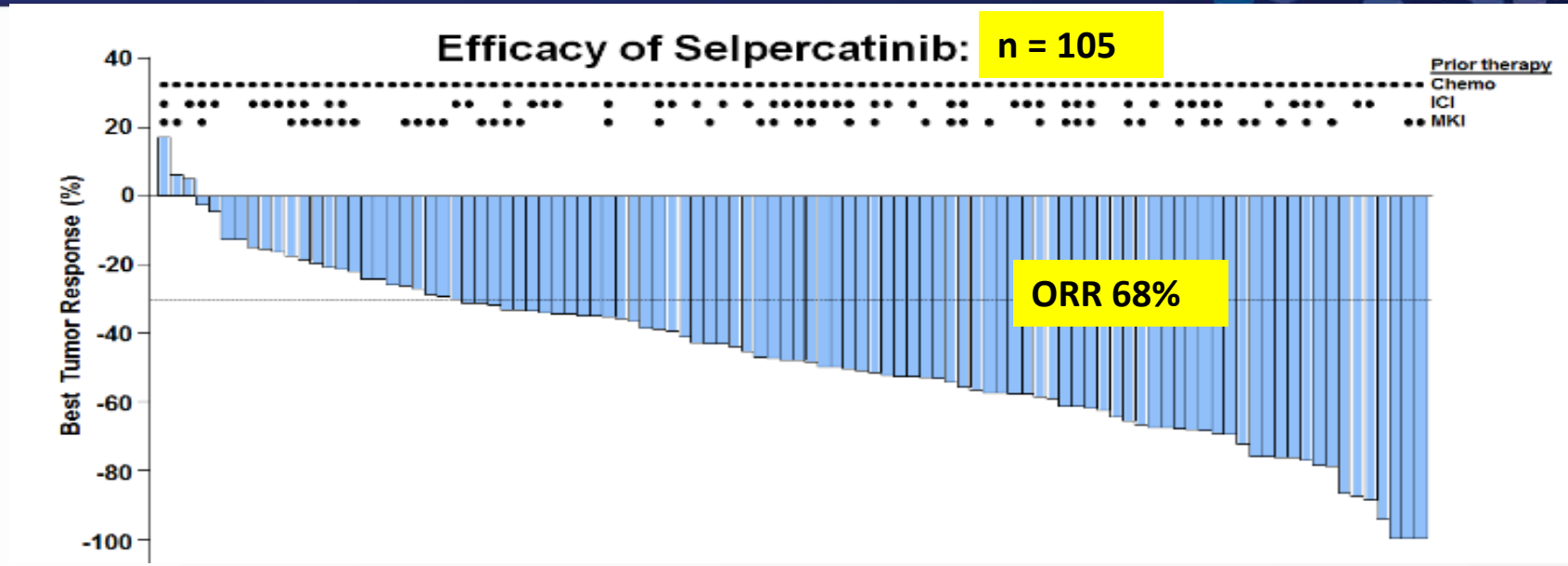
Prior treatment (N=136)
ORR 59% (95% CI 50-67)

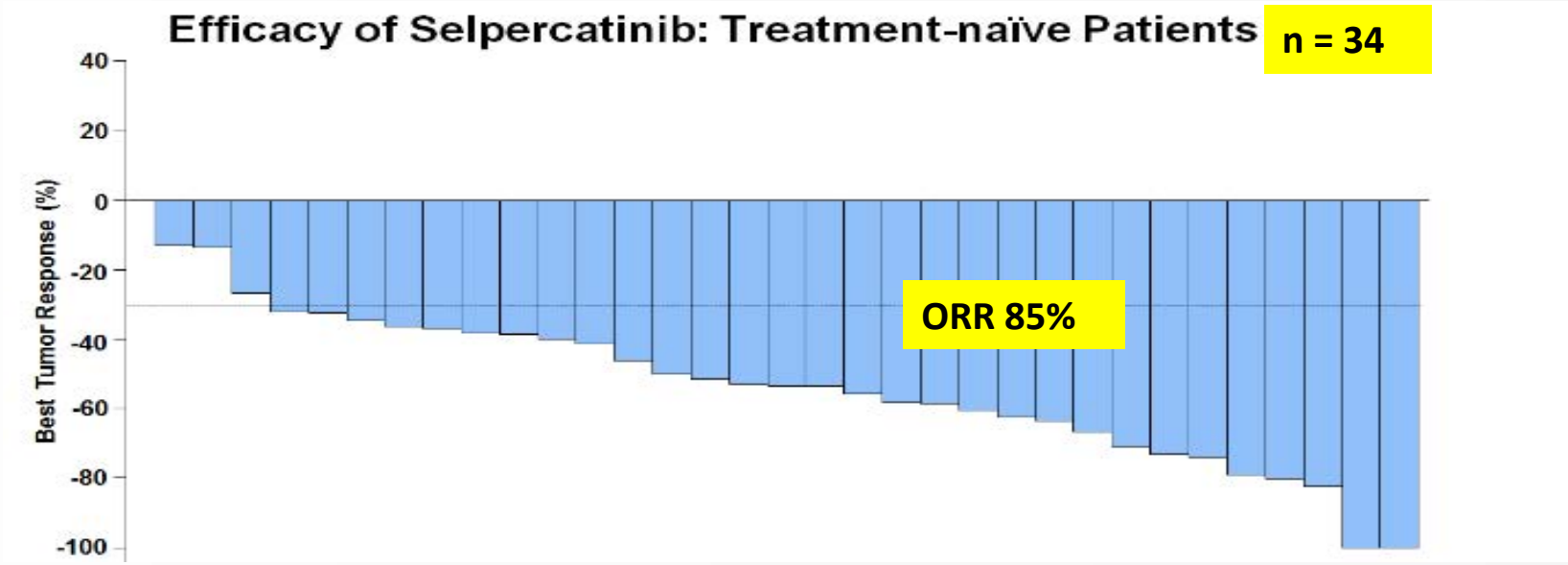


Griesinger, *Annals of Oncology 2022;33:1168-11778*

LIBRETTO-001: Selpercatinib in *RET*-Altered NSCLC

WCLC 2019





Drillon A, et al. WCLC 2019. Abstract PL02.08.

RET translocation

	Selpercatinib		Pralsetinib		
	untreated	pretreated	untreated	Pretreated platinum	Pretreated non-platinum
N	39	105	75	136	22
Dose	160 mg QD		400 OD		
ORR (%(95% CI)	85 (70-94)	64 (54-73)	72 (60-82)	59 (50-67)	73 (50-89)
Time to response			1.8 (0.9-6.1)	1.8 (1.3-11.4)	1.8 (1.6-5.5)
DoR (mo) (95% CI)	NE (12 –NE)	17.5 (12-NE)	NR (9.0 – NR)	22.3 (15.1-NR)	NR (9.2-NR)
Intracranial RR	82% 19/22		70% 7/10, 3 CR		
mPFS (mo)	NE	19.3	13.0	16.5	12.8
Toxicity gr ¾	38%		52%	56%	
Special toxicity	Hypertension, increase transaminases		Hypertension, neutropenia, anemia, increase transaminases, pneumonitis (2%)		

This is not intended as a head-to-head comparison

Drilon, *NEJM 2020;383:813*
Subbiah, *Clin Cancer Res. 2021;27(15):4160-4167*
Griesinger, *Annals of Oncology 2022;33:1168-11778*

Key Ongoing Clinical Trials of Selective RET Inhibitors

Trial	Phase	Planned N	Treatment Arms	Study Population	Primary Endpoint(s)
LIBRETTO-431 (NCT04194944)	III	250	Selpercatinib vs SoC plt-based CT ± pembrolizumab	RET fusion–positive advanced NSCLC and no prior systemic therapy	PFS by BICR
AcceleRET-Lung (NCT04222972)	III	250	Pralsetinib vs SoC plt-based CT ± pembrolizumab	RET fusion–positive advanced NSCLC and no prior systemic therapy	PFS
LIBRETTO-531 (NCT04211337)	III	400	Selpercatinib vs cabozantinib or vandetanib	RET-mutant advanced MTC and no prior kinase inhibitor therapy	TFFS by BICR
NCT04161391	I/II	362	TPX-0046 (RET/SRC inhibitor)	Advanced solid tumors (including NSCLC and thyroid cancer) with RET mutations or fusions*	DLT, RP2D, ORR
NCT03780517	I	114	BOS172738 (RET inhibitor)	Advanced solid tumors (including NSCLC and MTC) with RET alterations*	MTD, RP2D, safety

*Cohorts to include RET TKI therapy naive and those pretreated with prior RET TKI. All trials recruiting as of March 2021.

NCT04194944 [clinicaltrials.gov]. Accessed July 14, 2022. https://clinicaltrials.gov/ct2/show/NCT04194944. NCT04222972 [clinicaltrials.gov]. Accessed July 14, 2022. https://www.clinicaltrials.gov/ct2/show/NCT04222972. NCT04211337 [clinicaltrials.gov]. Accessed July 14, 2022. https://www.clinicaltrials.gov/ct2/show/NCT04211337. NCT04161391 [clinicaltrials.gov]. Accessed July 14, 2022. https://clinicaltrials.gov/ct2/show/NCT04161391. NCT03780517 [clinicaltrials.gov]. Accessed July 14, 2022. https://clinicaltrials.gov/ct2/show/NCT03780517.

Summary

- *ALK*, *ROS1* and RET fusion-positive lung cancers represent disease subsets of NSCLC for which we've highly effective targeted therapies
- Standard 1L agents in ALK fusion-positive NSCLC are next-generation ALK TKIs (alectinib, brigatinib, lorlatinib)
- Standard 1L agents in ROS1 fusion-positive NSCLC are crizotinib or Entrectinib
- Standard 1L agents in RET fusion (+) NSCLC are selpercatinib and pralsetinib
- Emerging data show our capacity to sequence TKI(s) at the time acquired resistance to the 1L TKI(s)
- Re-biopsies and ctDNA can be helpful in determining the mechanism of resistance (eg, on-target resistance mutation versus off-target mechanism)

Agenda

Module 1: Incorporation of Immunotherapeutic Strategies into the Management of Nonmetastatic Non-Small Cell Lung Cancer (NSCLC) — Dr Heymach

Module 2: Contemporary Treatment for Localized or Metastatic NSCLC with an EGFR Mutation — Dr Yu

Module 3: Research Advances Shaping the Current and Future Treatment of Metastatic NSCLC with ALK Rearrangements, ROS1 Rearrangements or RET Fusions — Dr Langer

Module 4: Targeting MET, HER2 and KRAS Alterations in NSCLC — Dr Spigel

Module 5: Current Management of Metastatic NSCLC without a Targetable Tumor Mutation — Dr Garon

Module 6: Future Directions in the Management of Metastatic NSCLC — Dr Leal

RTP RESEARCH TO PRACTICE

Current clinical role of trastuzumab deruxtecan in NSCLC

Melissa Johnson, MD

Matthew Gubens, MD, MS

Jarushka Naidoo, MB BCH, MHS

RTP
RESEARCH
TO PRACTICE

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

 Dr Garon	Carbo/pem/pembro	 Dr Yu	Trastuzumab deruxtecan
 Dr Heymach	Trastuzumab deruxtecan	 Dr Gubens	Trastuzumab deruxtecan
 Dr Langer	Carbo/pem/pembro	 Dr Johnson	Trastuzumab deruxtecan
 Dr Leal	Carbo/pem +/- bev	 Dr Naidoo	Pembrolizumab
 Dr Spigel	Trastuzumab deruxtecan		

Carbo = carboplatin; pem = pemetrexed; pembro = pembrolizumab; bev = bevacizumab

RTP RESEARCH TO PRACTICE

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

 Dr Garon	Trastuzumab deruxtecan	 Dr Yu	Trastuzumab deruxtecan
 Dr Heymach	Trastuzumab deruxtecan	 Dr Gubens	Trastuzumab deruxtecan
 Dr Langer	Trastuzumab deruxtecan	 Dr Johnson	Trastuzumab deruxtecan
 Dr Leal	Trastuzumab deruxtecan	 Dr Naidoo	Trastuzumab deruxtecan
 Dr Spigel	Trastuzumab deruxtecan		

RTP RESEARCH TO PRACTICE

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

 Dr Garon	Second line	 Dr Yu	Third line
 Dr Heymach	Second line	 Dr Gubens	Second line
 Dr Langer	Third line	 Dr Johnson	Second line
 Dr Leal	Third line	 Dr Naidoo	Third line or beyond
 Dr Spigel	First line		

RTP RESEARCH TO PRACTICE

Therapeutic sequencing for patients with NSCLC and KRAS G12C mutations

Melissa Johnson, MD

Matthew Gubens, MD, MS

Jarushka Naidoo, MB BCH, MHS

RTP RESEARCH TO PRACTICE

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

 Dr Garon	Second line	 Dr Yu	Second line
 Dr Heymach	Second line	 Dr Gubens	Second line
 Dr Langer	Second line	 Dr Johnson	Second line
 Dr Leal	Second line	 Dr Naidoo	Second line
 Dr Spigel	Second line		

RTP RESEARCH TO PRACTICE

Management of MET exon 14 mutation-positive NSCLC

Melissa Johnson, MD

Matthew Gubens, MD, MS

Jarushka Naidoo, MB BCH, MHS

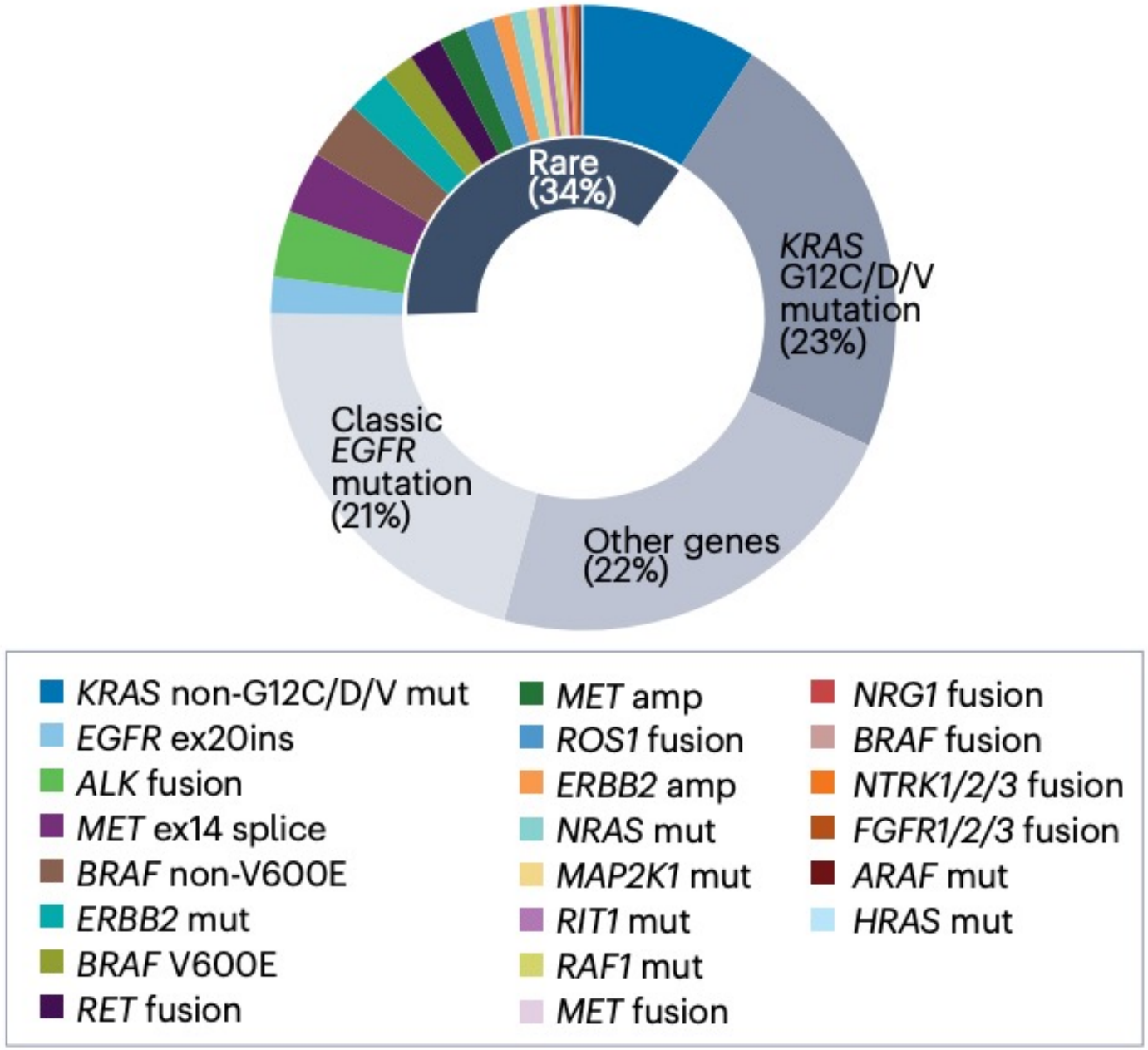
RTP
RESEARCH
TO PRACTICE

Targeting *MET*, *HER2*, and *KRAS* Alterations in NSCLC

David R. Spigel, M.D.

Chief Scientific Officer

SARAH CANNON
Research Institute



Harada, Nat Rev Clin Onc, 2023

SARAH CANNON Research Institute

MOLECULAR AND BIOMARKER-DIRECTED THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b]

***EGFR* Exon 19 Deletion or Exon 21 L858R**
- First-line therapy
  - Afatinib[1]
  - Erlotinib[2]
  - Dacomitinib[3]
  - Gefitinib[4,5]
  - Osimertinib[6]
  - Erlotinib + ramucirumab[7]
  - Erlotinib + bevacizumab[c] (nonsquamous)[8]
- Subsequent therapy
  - Osimertinib[9]

***EGFR* S768I, L861Q, and/or G719X**
- First-line therapy
  - Afatinib[1,10]
  - Erlotinib[2]
  - Dacomitinib[3]
  - Gefitinib[4,5]
  - Osimertinib[6,11]
- Subsequent therapy
  - Osimertinib[9]

***EGFR* Exon 20 Insertion Mutation**
- Subsequent therapy
  - Amivantamab-vmjw[12]
  - Mobocertinib[13]

***KRAS* G12C Mutation**
- Subsequent therapy
  - Sotorasib[14]
  - Adagrasib[15]

***ALK* Rearrangement**
- First-line therapy
  - Alectinib[16,17]
  - Brigatinib[18]
  - Ceritinib[19]
  - Crizotinib[16,20]
  - Lorlatinib[21]
- Subsequent therapy
  - Alectinib[22,23]
  - Brigatinib[24]
  - Ceritinib[25]
  - Lorlatinib[26]

***ROS1* Rearrangement**
- First-line therapy
  - Ceritinib[27,28]
  - Crizotinib[29]
  - Entrectinib[30]
- Subsequent therapy
  - Lorlatinib[31]
  - Entrectinib[30]

***BRAF* V600E Mutation**
- First-line therapy
  - Dabrafenib/trametinib[32]
  - Dabrafenib[32]
  - Vemurafenib
- Subsequent therapy
  - Dabrafenib/trametinib[33,34]

***NTRK1/2/3* Gene Fusion**
- First-line/Subsequent therapy
  - Larotrectinib[35]
  - Entrectinib[36]

***MET* Exon 14 Skipping Mutation**
- First-line therapy/Subsequent therapy
  - Capmatinib[37]
  - Crizotinib[38]
  - Tepotinib[39]

***RET* Rearrangement**
- First-line therapy/Subsequent therapy
  - Selpercatinib[40]
  - Pralsetinib[41]
  - Cabozantinib[42,43]

***ERBB2 (HER2)* Mutation**
- Subsequent therapy
  - Fam-trastuzumab deruxtecan-nxki[44]
  - Ado-trastuzumab emtansine[45]

PD-L1 ≥50% First-line Therapy

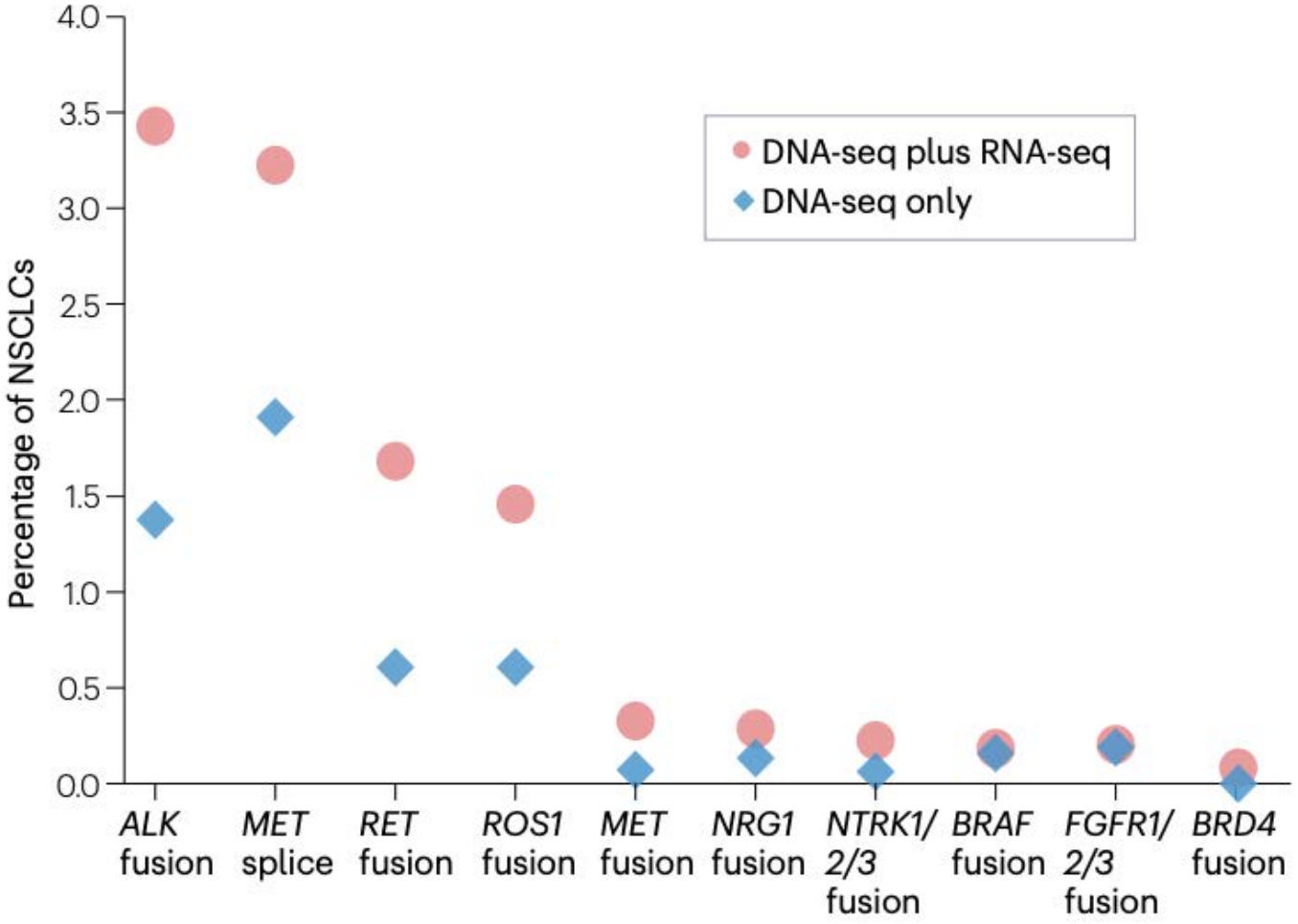
PD-L1 ≥1-49% First-line Therapy

EMERGING BIOMARKERS TO IDENTIFY NOVEL THERAPIES FOR PATIENTS WITH METASTATIC NSCLC

Genetic Alteration (ie, Driver event)	Available Targeted Agents with Activity Against Driver Event in Lung Cancer
High-level *MET* amplification*	Capmatinib[1] Tepotinib[2] Crizotinib[3,4]

* The definition of high-level *MET* amplification is evolving and may differ according to the assay used for testing. For NGS-based results, a copy number greater than 10 is consistent with high-level *MET* amplification.

DNA +/- RNA



Harada, Nat Rev Clin Onc, 2023

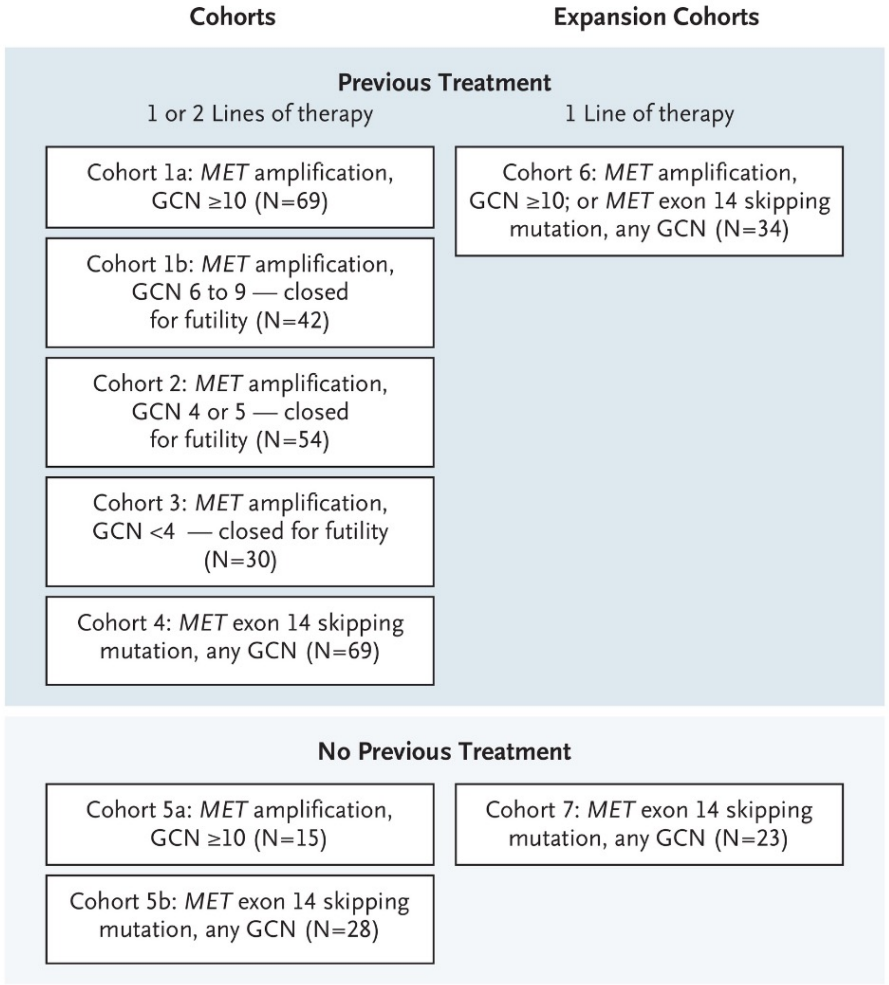
SARAH CANNON Research Institute

Capmatinib in *MET* Exon 14 Mutated and *MET* Amplified NSCLC

Stage IIIB or IV NSCLC
EGFR nonmutated (negative for L858R and exon 19 deletion) and *ALK*-rearrangement negative
ECOG performance-status score of 0 or 1
≥1 Measurable lesion (RECIST, version 1.1)
Asymptomatic or neurologically stable brain metastases allowed

↓

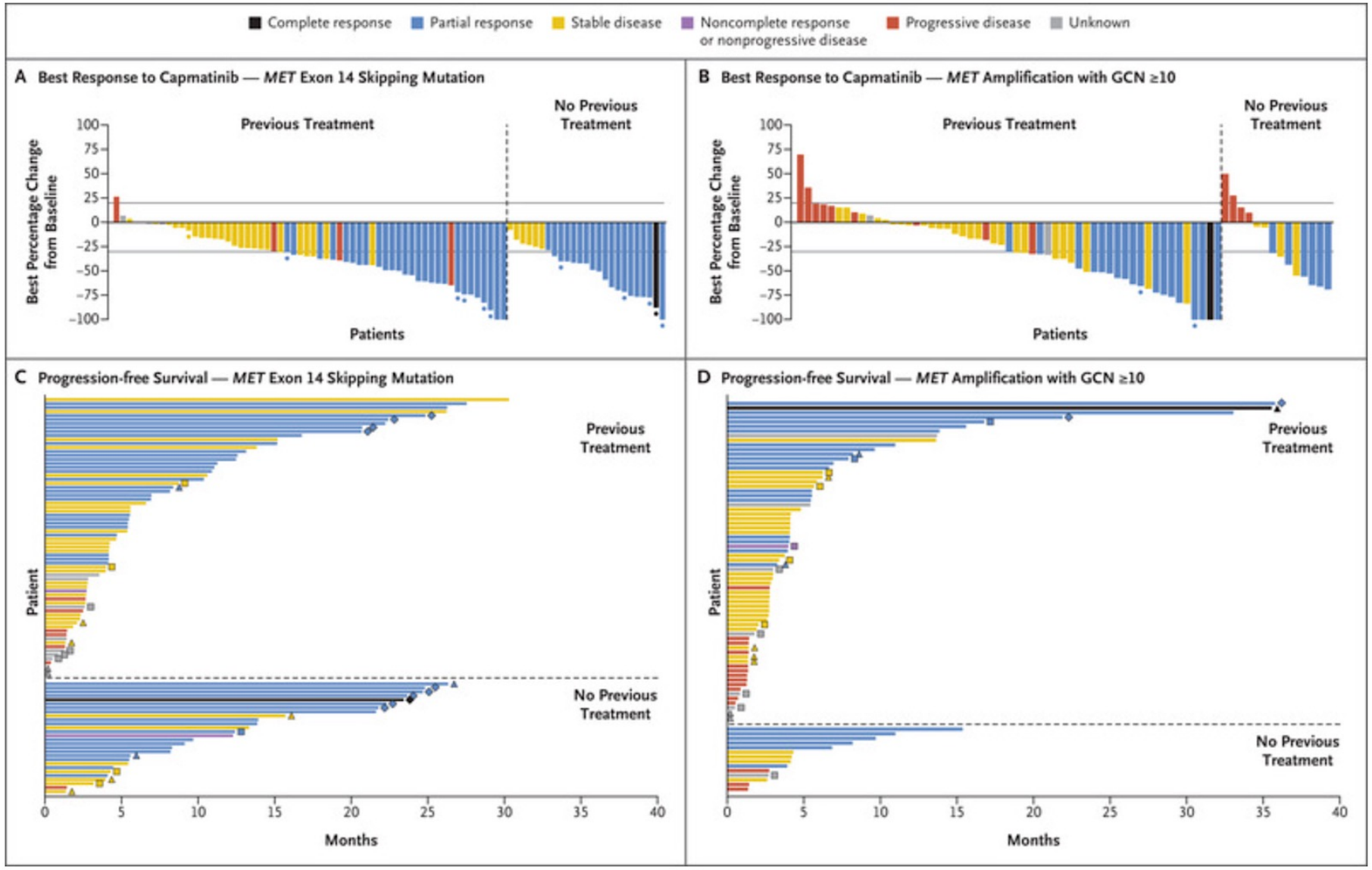
Capmatinib, 400 mg tablet twice daily



Wolf, NEJM 2020

SARAH CANNON Research Institute

Capmatinib in *MET* Exon 14 Mutated and *MET* Amplified NSCLC



Wolf, NEJM 2020

SARAH CANNON
Research Institute

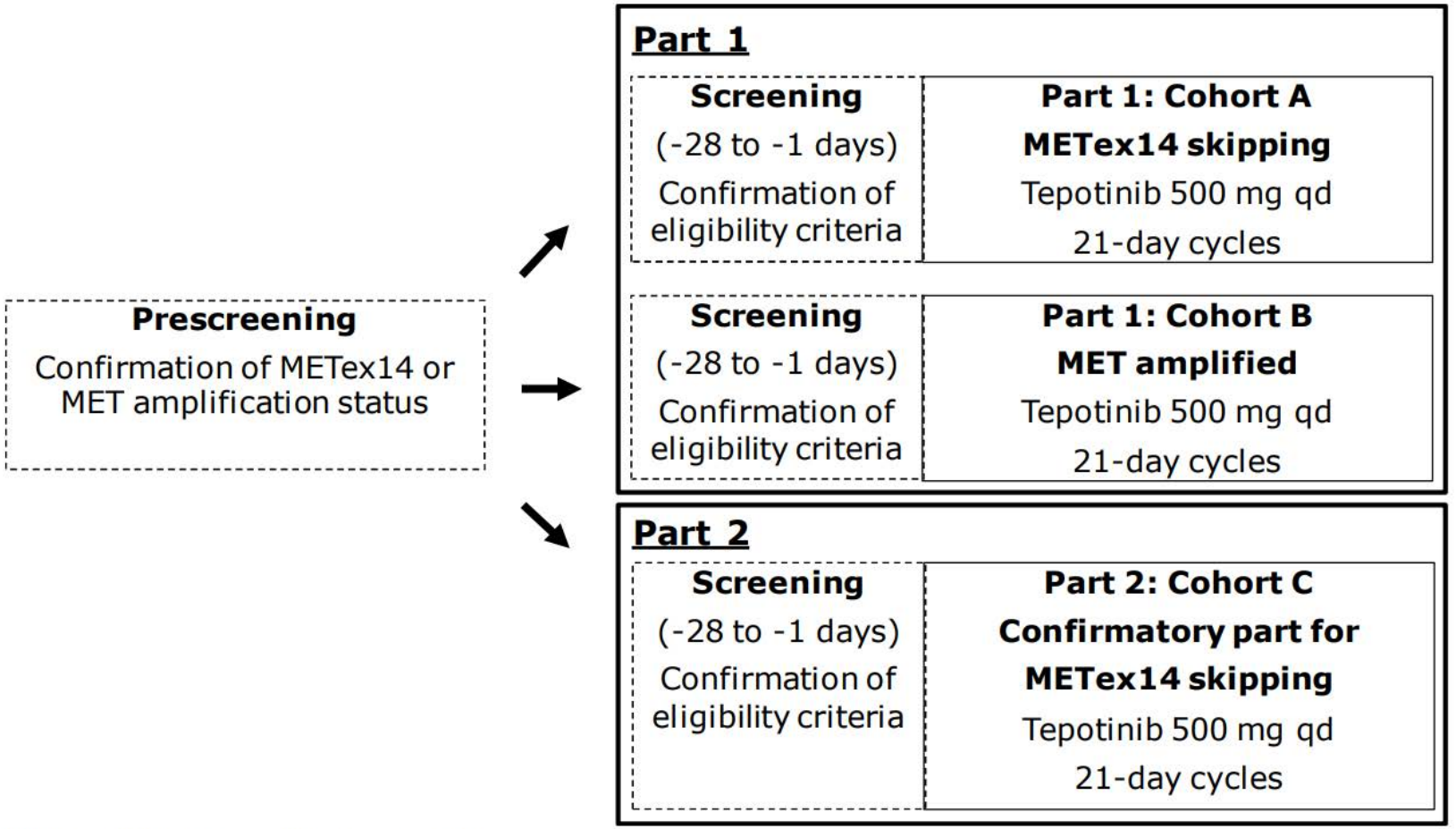
Capmatinib Safety

Variable	NSCLC with *MET* Exon 14 Skipping Mutation				NSCLC with *MET* Amplification								All Cohorts (N=364)	
	Cohort 4 (N=69)		Cohort 5b (N=28)		Cohort 1a (N=69)		Cohort 5a (N=15)		Cohort 1b (N=42)		Cohort 2 (N=54)		Cohort 3 (N=30)		Total	Grade 3 or 4
	Total	Grade 3 or 4	Total	Grade 3 or 4	Total	Grade 3 or 4	Total	Grade 3 or 4	Total	Grade 3 or 4	Total	Grade 3 or 4	Total	Grade 3 or 4		
Adverse events																
Any event — no. (%)	68 (99)	52 (75)	28 (100)	21 (75)	67 (97)	48 (70)	15 (100)	10 (67)	42 (100)	27 (64)	54 (100)	35 (65)	28 (93)	22 (73)	355 (98)	244 (67)
Most common events — no. (%)†																
Peripheral edema	37 (54)	10 (14)	21 (75)	3 (11)	34 (49)	5 (7)	11 (73)	3 (20)	18 (43)	3 (7)	24 (44)	3 (6)	11 (37)	1 (3)	186 (51)	33 (9)
Nausea‡	32 (46)	0	13 (46)	0	32 (46)	5 (7)	9 (60)	0	17 (40)	3 (7)	24 (44)	0	15 (50)	0	163 (45)	9 (2)
Vomiting‡	18 (26)	0	7 (25)	0	24 (35)	5 (7)	4 (27)	1 (7)	16 (38)	1 (2)	12 (22)	0	9 (30)	1 (3)	102 (28)	9 (2)
Blood creatinine increased	23 (33)	0	10 (36)	0	16 (23)	0	3 (20)	0	8 (19)	0	14 (26)	0	5 (17)	0	89 (24)	0

Wolf, NEJM 2020

SARAH CANNON Research Institute

Tepotinib in *MET* Exon 14 Mutated NSCLC

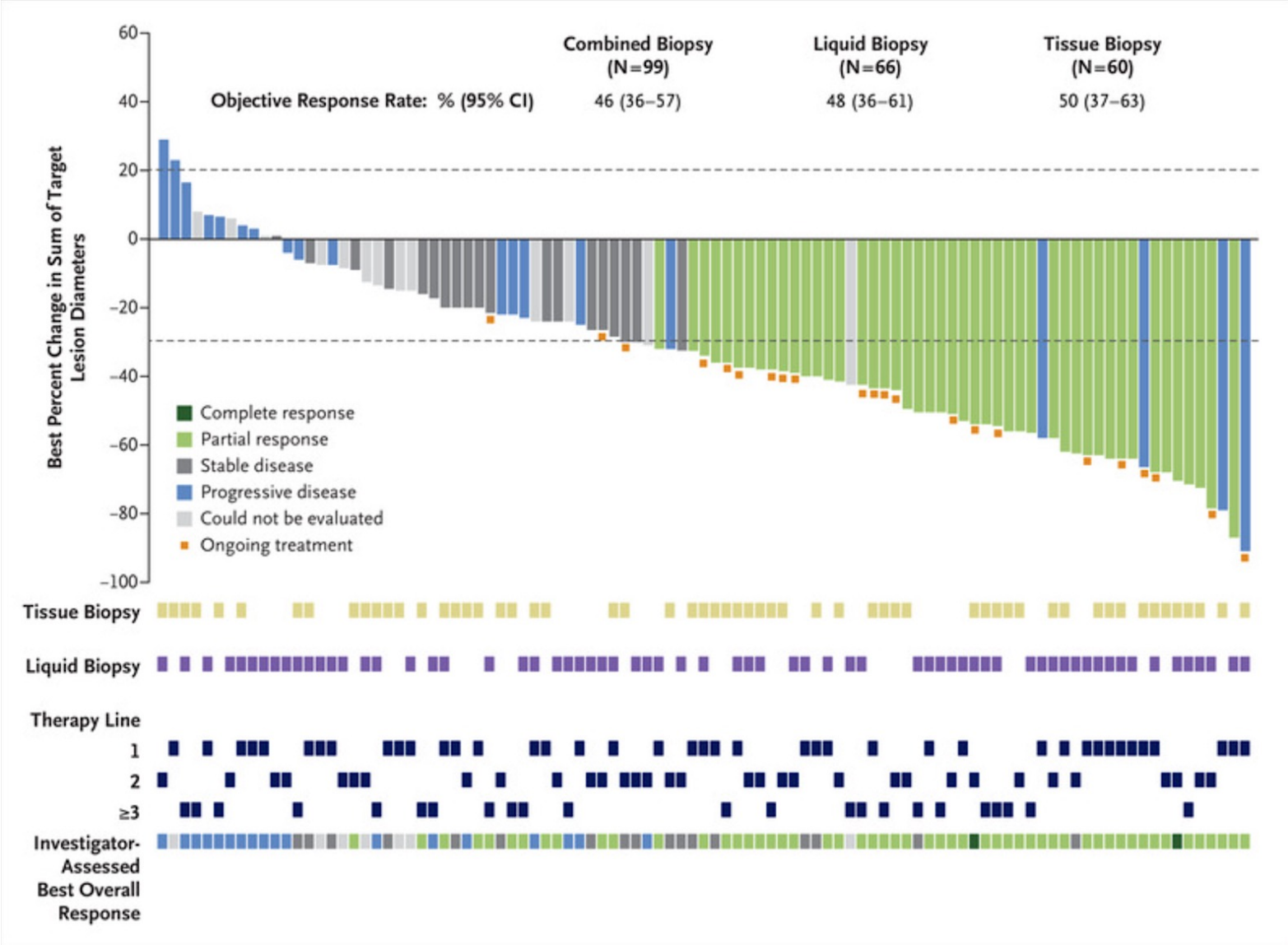


METex14: MET exon 14; qd: once daily.

Paik, NEJM 2020

SARAH CANNON Research Institute

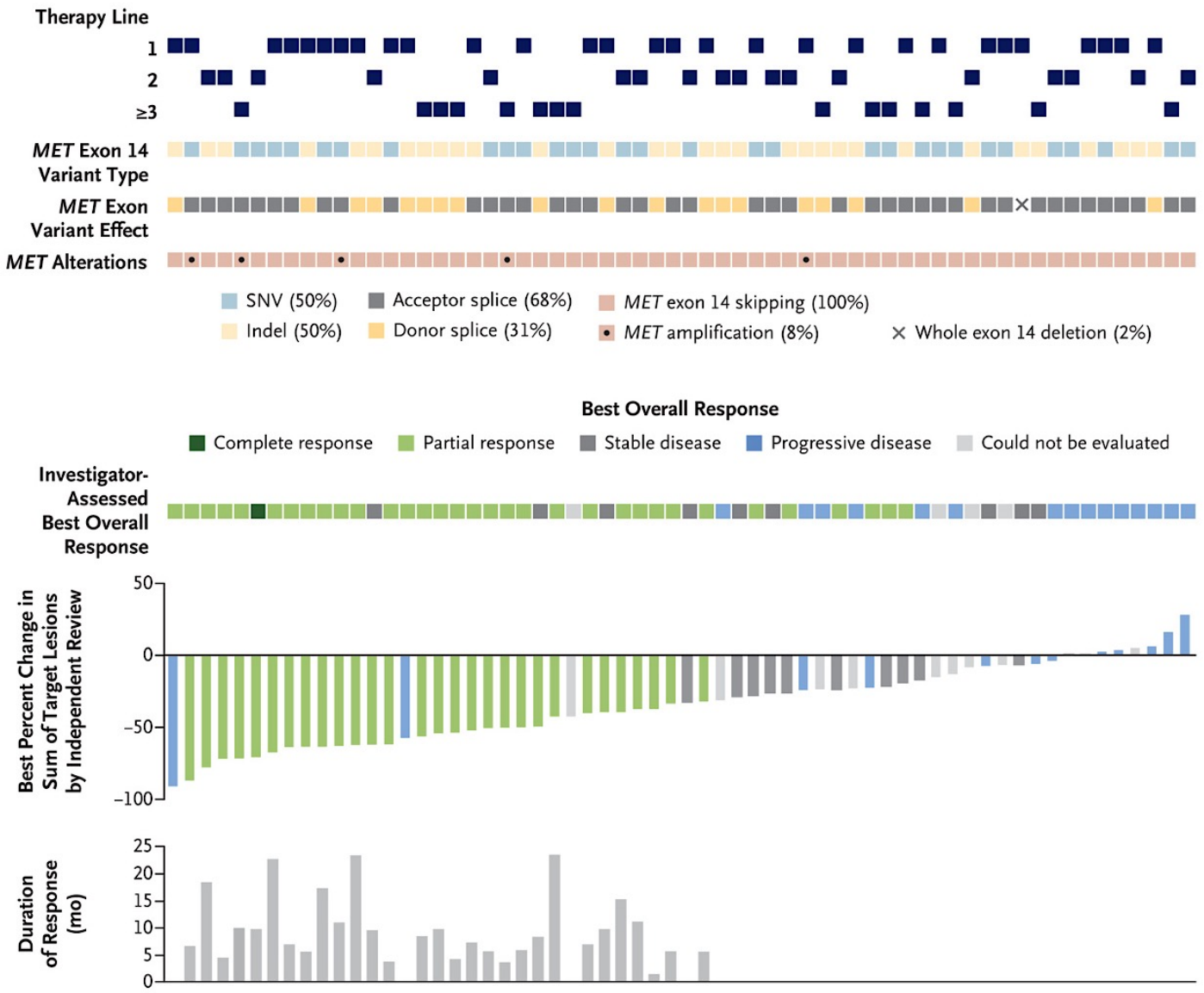
Tepotinib in *MET* Exon 14 Mutated NSCLC



Paik, NEJM 2020

SARAH CANNON Research Institute

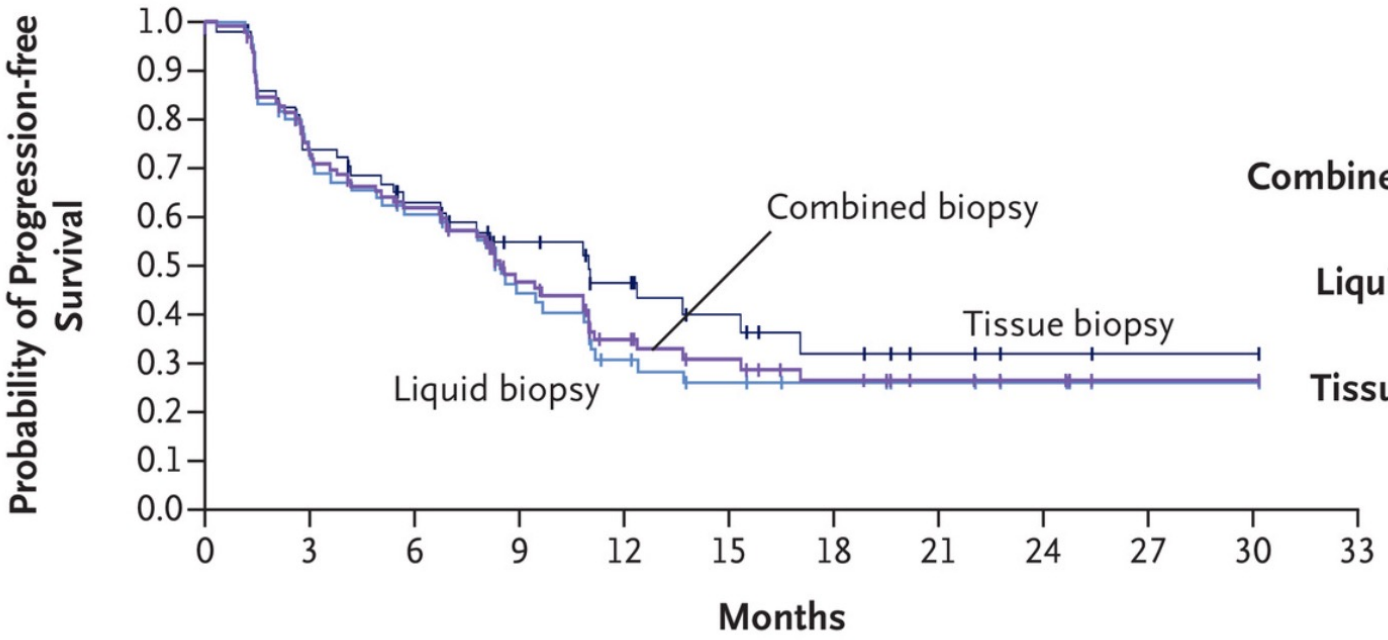
Tepotinib in *MET* Exon 14 Mutated and *MET* Amplified NSCLC



Paik, NEJM 2020

SARAH CANNON Research Institute

Tepotinib in *MET* Exon 14 Mutated NSCLC



	No. of Events	Median Duration (95% CI)
		mo
Combined Biopsy (N=99)	60	8.5 (6.7–11.0)
Liquid Biopsy (N=66)	43	8.5 (5.1–11.0)
Tissue Biopsy (N=60)	32	11.0 (5.7–17.1)

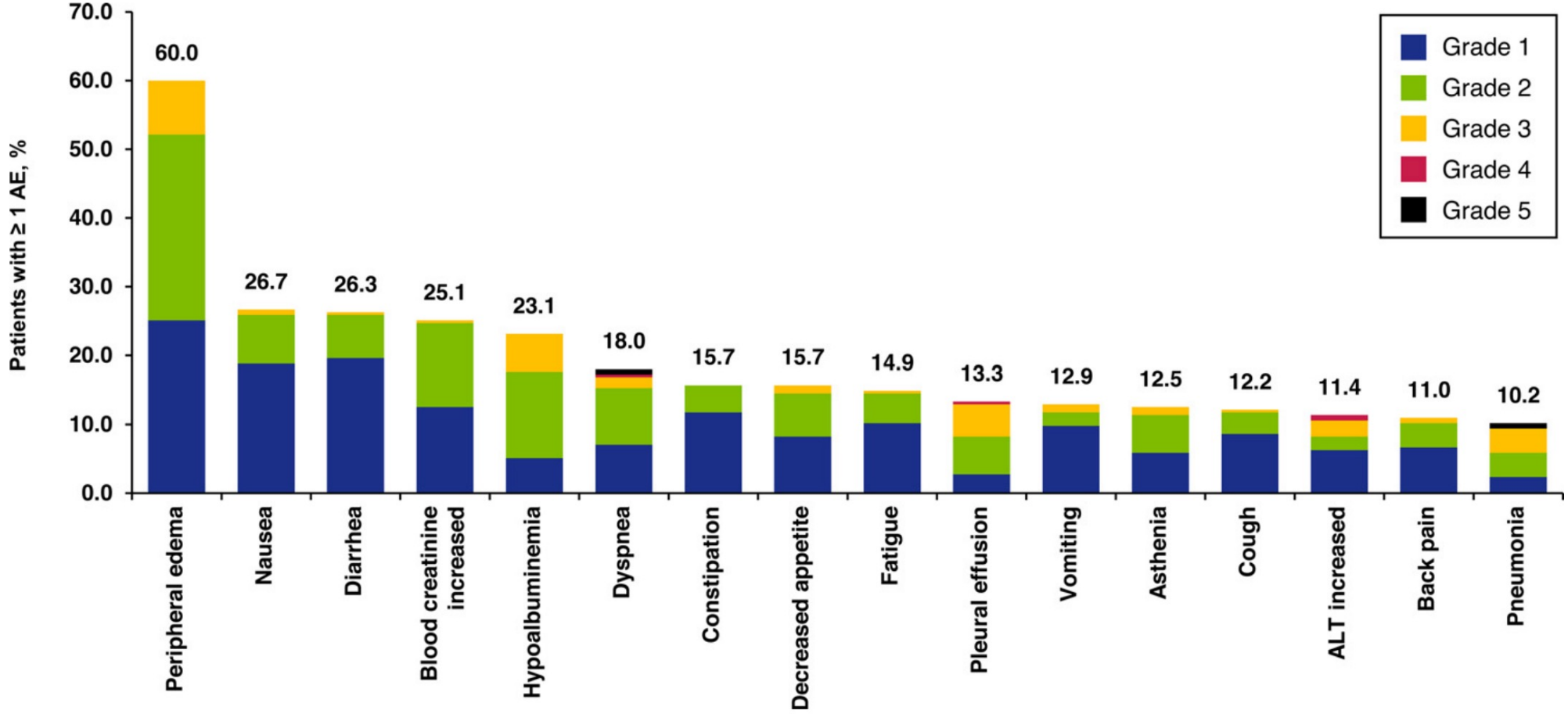
No. at Risk

Combined biopsy	99	67	53	33	20	15	10	6	4	1	1	0
Liquid biopsy	66	44	36	23	14	10	8	6	4	1	1	0
Tissue biopsy	60	42	32	22	16	11	7	4	2	1	1	0

Paik, NEJM 2020

SARAH CANNON Research Institute

Tepotinib Safety



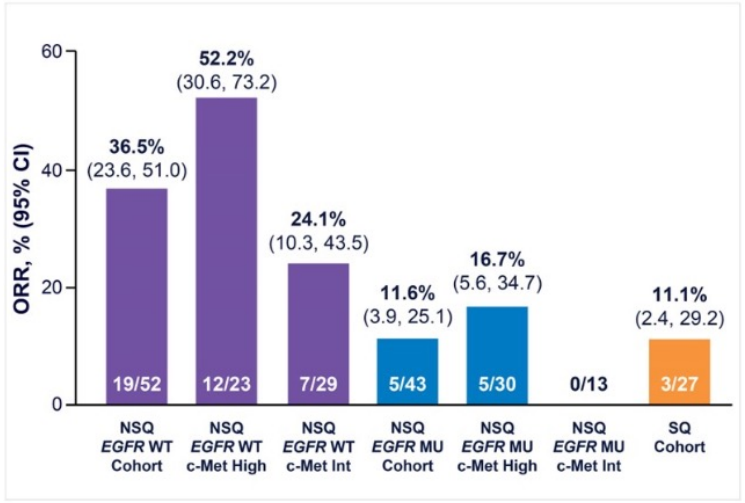
Veillon, Clin Lung Ca 2022

SARAH CANNON Research Institute

Telisotuzumab Vedotin (teliso-v) in NSCLC
LUMINOSITY

Interim Efficacy

ORR per Central Review by Cohort/Group



CI, confidence interval; *EGFR*, epidermal growth factor receptor; Int, intermediate; MU, mutant; NSQ, non-squamous; ORR, overall response rate; SQ, squamous; WT, wild-type.

- The NSQ *EGFR* WT NSCLC cohort met protocol-specified criteria for expansion in Stage 2 at interim analysis 3. Updated data at the time of interim analysis 4 are shown
- The NSQ *EGFR* MU NSCLC cohort met protocol-specified criteria for futility at interim analysis 4. The SQ cohort met criteria for futility at the previous interim analysis; final data shown

DOR per Central Review by Cohort/Group

Cohort/Group	mDOR by ICR, No. of Events/No. of Responders, Months [95% CI]
NSQ *EGFR* WT	8/19, 6.9 [4.1, NR]
c-Met high	5/12, 6.9 [2.4, NR]
c-Met int	3/7, NR [4.1, NR]
NSQ *EGFR* MU	2/5, NR [3.0, NR]
c-Met high	2/5, NR [3.0, NR]
c-Met int	NA
SQ	2/3, 4.4 [3.0, NR]

CI, confidence interval; DOR, duration of response; *EGFR*, epidermal growth factor receptor; ICR, independent central review; int, intermediate; mDOR, median duration of response; MU, mutant; NA, not available; NR, not reached; NSQ, non-squamous; SQ, squamous; WT, wild-type.

Objective Response Rate per Central Review for Subgroups Defined by Prior Therapies: NSQ *EGFR* WT Cohort

Cohort/Group	Prior Platinum, n/N (%)	Prior Platinum and Immune Checkpoint Inhibitor, n/N (%)
NSQ *EGFR* WT	18/50 (36.0)	15/37 (40.5)
c-Met high	11/21 (52.4)	9/16 (56.3)
c-Met int	7/29 (24.1)	6/21 (28.6)

EGFR, epidermal growth factor receptor; int, intermediate; NSQ, non-squamous; WT, wild-type.

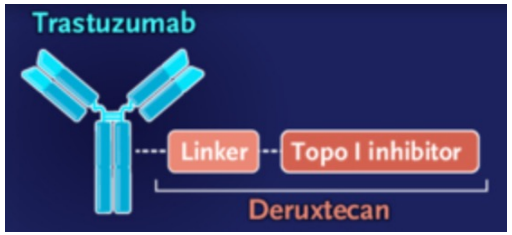
Molecular oncogene analyses in tumors of patients with available tissue are underway.

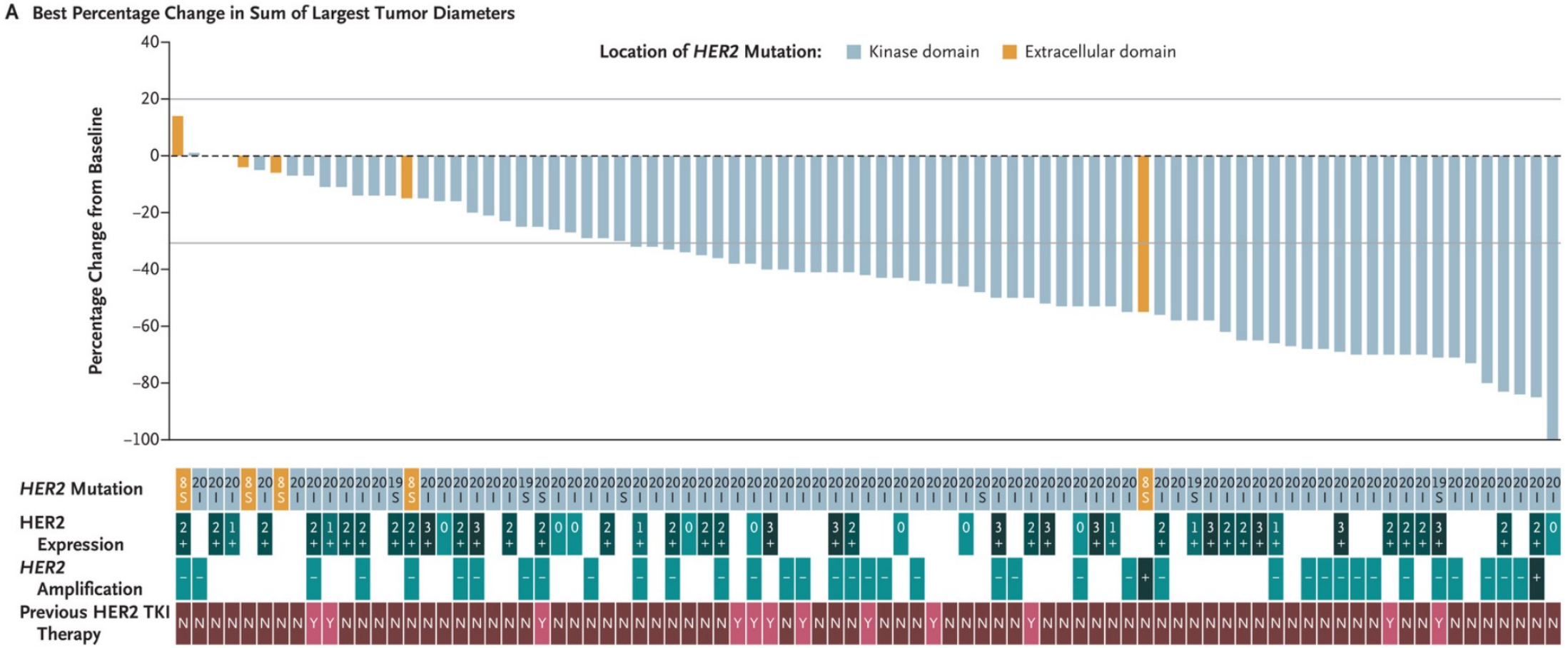
DOR, duration of response; EGFR, epidermal growth factor receptor; MU, mutant; NSCLC, non-small cell lung caner; NSQ, non-squamous; OE, overexpressing; ORR, overall response rate; SQ, squamous; Teliso-V, telisotuzumab vedotin; WT, wild-type.

Camidge, JCO 2022

SARAH CANNON Research Institute

Trastuzumab Deruxtecan in *HER2*-Mutant NSCLC

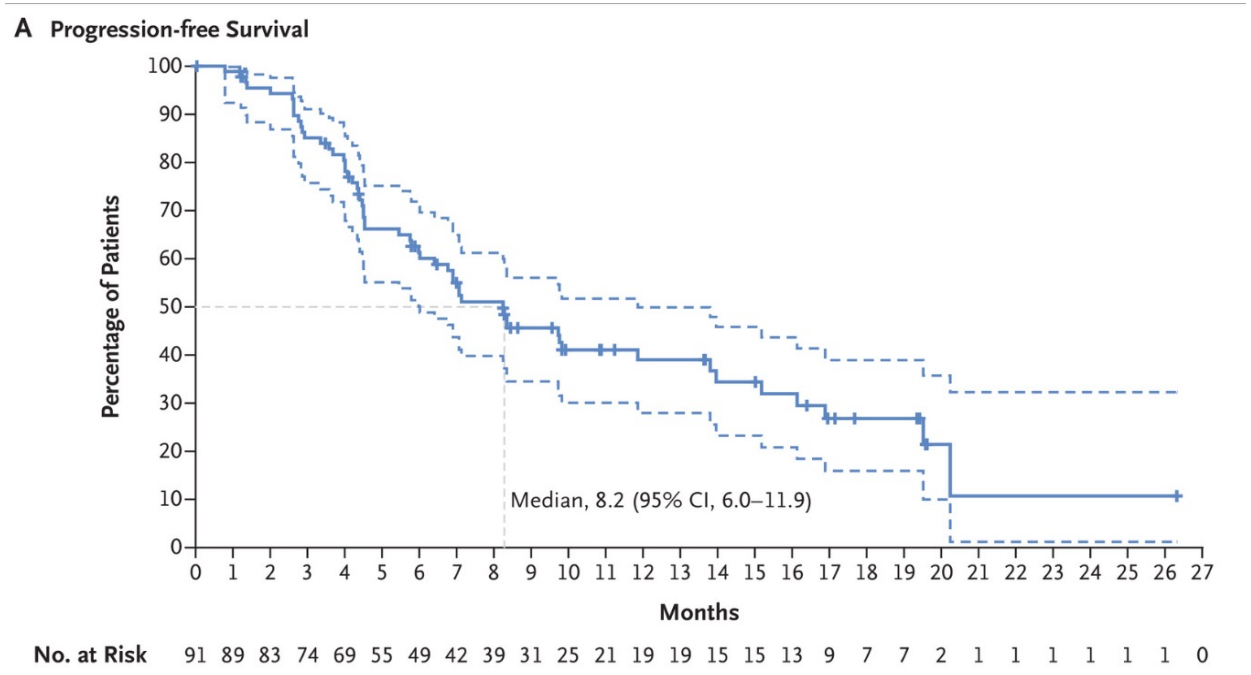


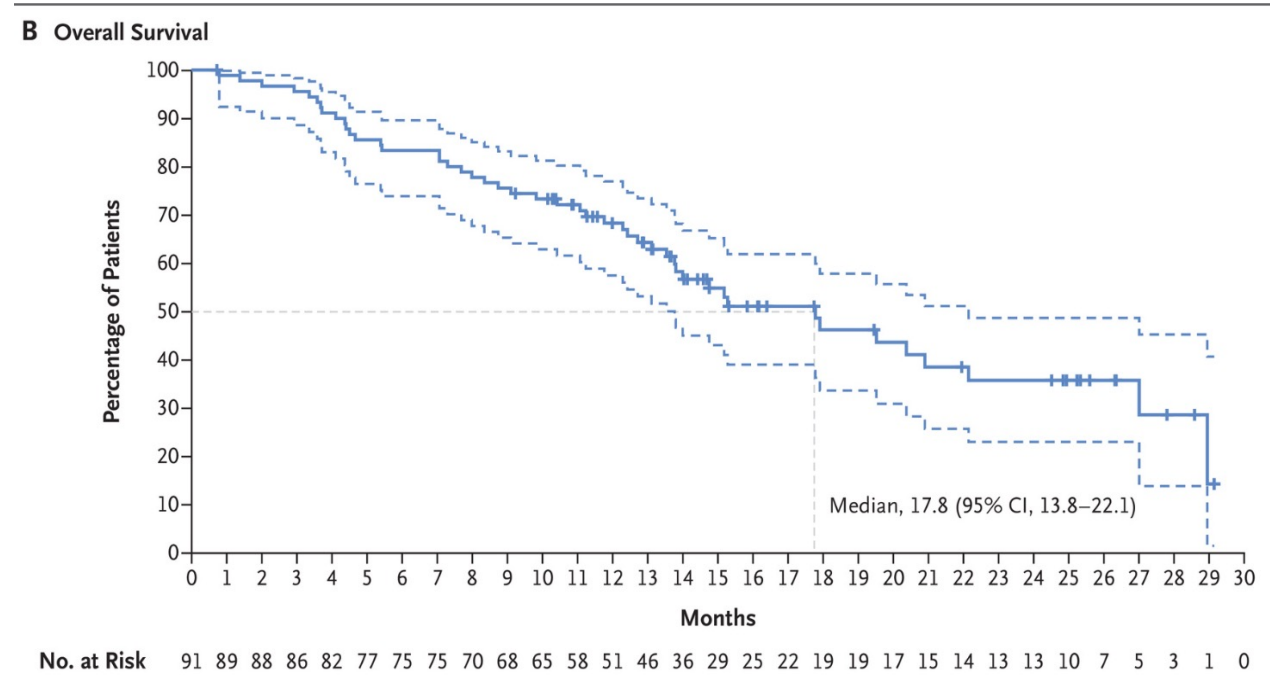


Li, NEJM 2022

SARAH CANNON Research Institute

Trastuzumab Deruxtecan in *HER2*-Mutant NSCLC





Li, NEJM 2022

SARAH CANNON Research Institute

Trastuzumab Deruxtecan in *HER2*-Mutant NSCLC

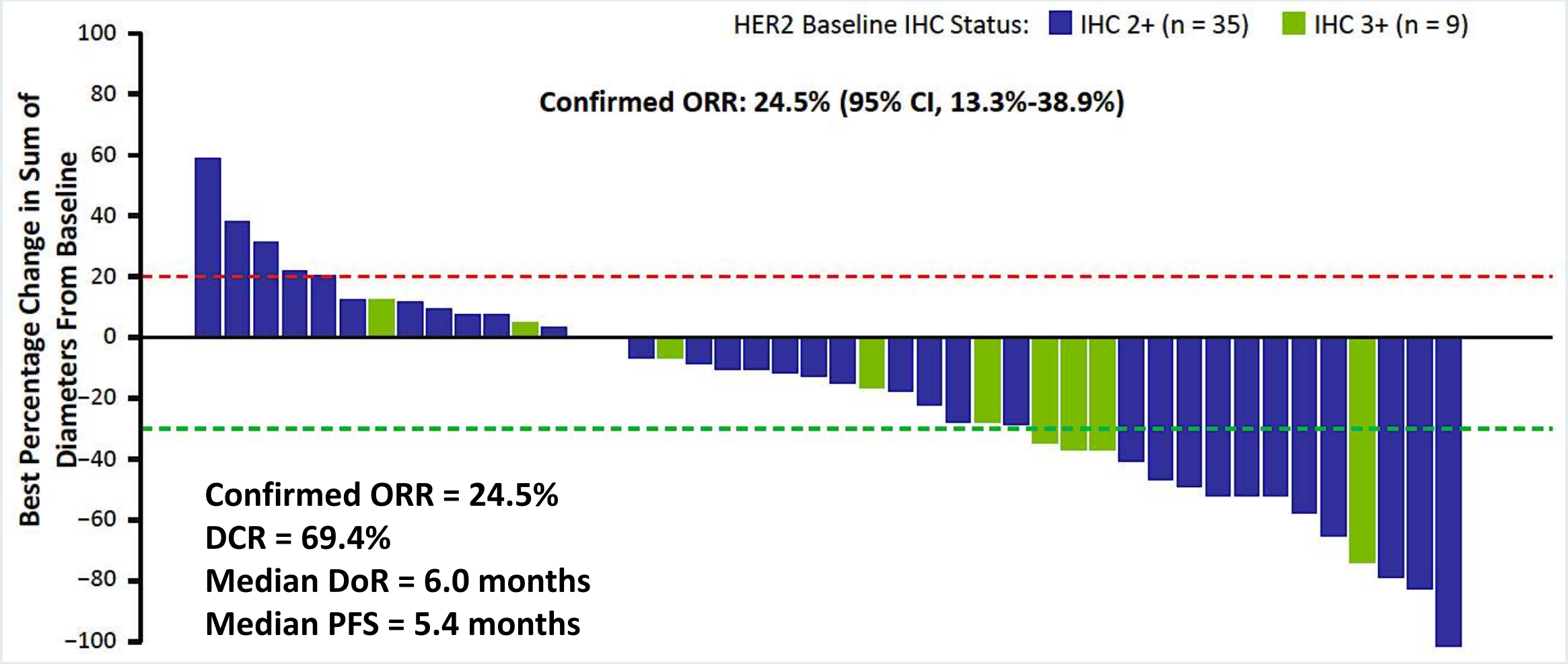
Event	Grade 1–2	Grade 3	Grade 4	Grade 5	Overall
			number of patients (percent)		
Drug-related adverse event	46 (51)	37 (41)	4 (4)	1 (1)*	88 (97)
Drug-related adverse events with ≥20% incidence					
Nausea	58 (64)	8 (9)	0	0	66 (73)
Fatigue†	42 (46)	6 (7)	0	0	48 (53)
Alopecia	42 (46)	0	0	0	42 (46)
Vomiting	33 (36)	3 (3)	0	0	36 (40)
Neutropenia‡	15 (16)	14 (15)	3 (3)	0	32 (35)
Anemia§	21 (23)	9 (10)	0	0	30 (33)
Diarrhea	26 (29)	2 (2)	1 (1)	0	29 (32)
Decreased appetite	27 (30)	0	0	0	27 (30)
Leukopenia¶	17 (19)	4 (4)	0	0	21 (23)
Constipation	20 (22)	0	0	0	20 (22)

* One patient had grade 5 (i.e., fatal) pneumonitis that was assessed as drug-related by the investigator (subsequently adjudicated as interstitial lung disease). Another patient had grade 3 interstitial lung disease, as reported by the investigator, and died; the reported interstitial lung disease was subsequently adjudicated as grade 5 by the interstitial lung disease adjudication committee. All adjudicated events of drug-related interstitial lung disease are reported in Table S5.

Li, NEJM 2022

SARAH CANNON Research Institute

DESTINY-Lung01 Trial: Best Percent Change in Tumor Size with T-DXd for NSCLC with HER2 Overexpression



ORR = objective response rate; DCR = disease control rate; DoR = duration of response

Nakagawa K et al. IASLC/WCLC 2020;Abstract OA04.05.

DESTINY-Lung02: Response by Blinded Independent Central Review (BICR)

Response Assessment by BICR	Prespecified early cohort	
	T-DXd 5.4 mg/kg n = 52	T-DXd 6.4 mg/kg n = 28
Confirmed ORR,[a] n (%) [95% CI]	28 (53.8) [39.5, 67.8]	12 (42.9) [24.5, 62.8]
Best overall response, n (%)		
CR	1 (1.9)	1 (3.6)
PR	27 (51.9)	11 (39.3)
SD	19 (36.5)	14 (50.0)
PD	2 (3.8)	1 (3.6)
Not evaluable[b]	3 (5.8)	1 (3.6)
DCR,[c] n (%) [95% CI]	47 (90.4) [79.0, 96.8]	26 (92.9) [76.5, 99.1]
Median DoR, months [95% CI]	NE [4.2, NE]	5.9 [2.8, NE]
Median TTIR, months [range]	1.4 [1.2-5.8]	1.4 [1.2-3.0]
Median follow-up, months [range]	5.6 (1.1-11.7)	5.4 (0.6-12.1)

ORR = objective response rate; DCR = disease control rate; DoR = duration of response; NE = nonevaluable; TTIR = time to initial response

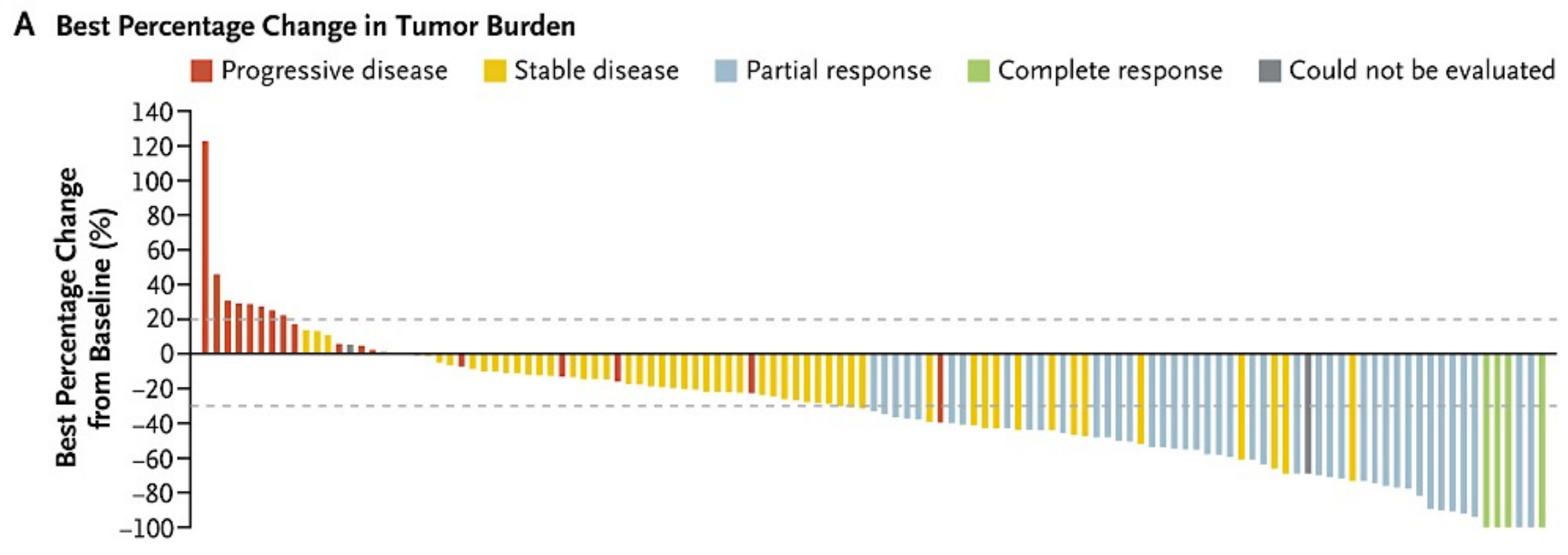
Goto K et al. ESMO 2022;Abstract LBA55.

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

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

Goto K et al. ESMO 2022;Abstract LBA55.

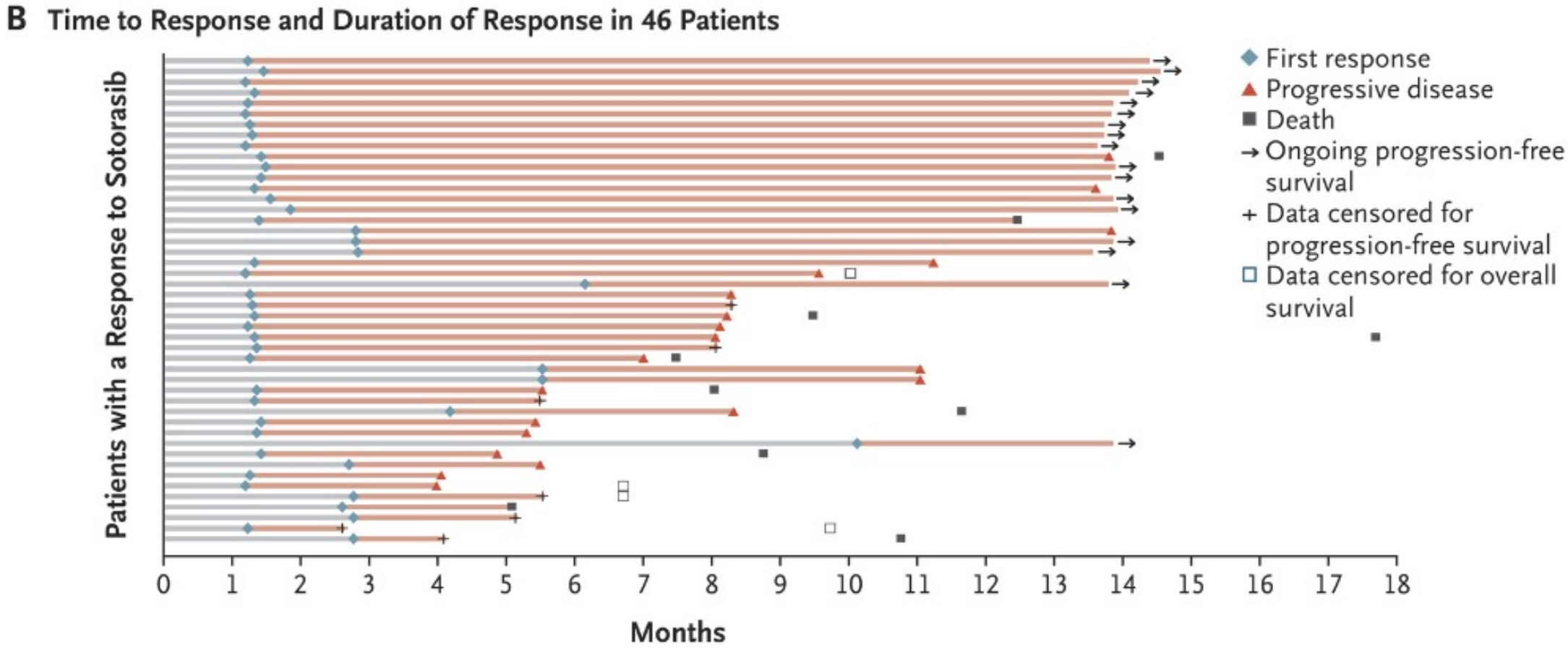
Sotorasib in *KRAS* G12C Mutated NSCLC



Skoulidis, NEJM 2021

SARAH CANNON Research Institute

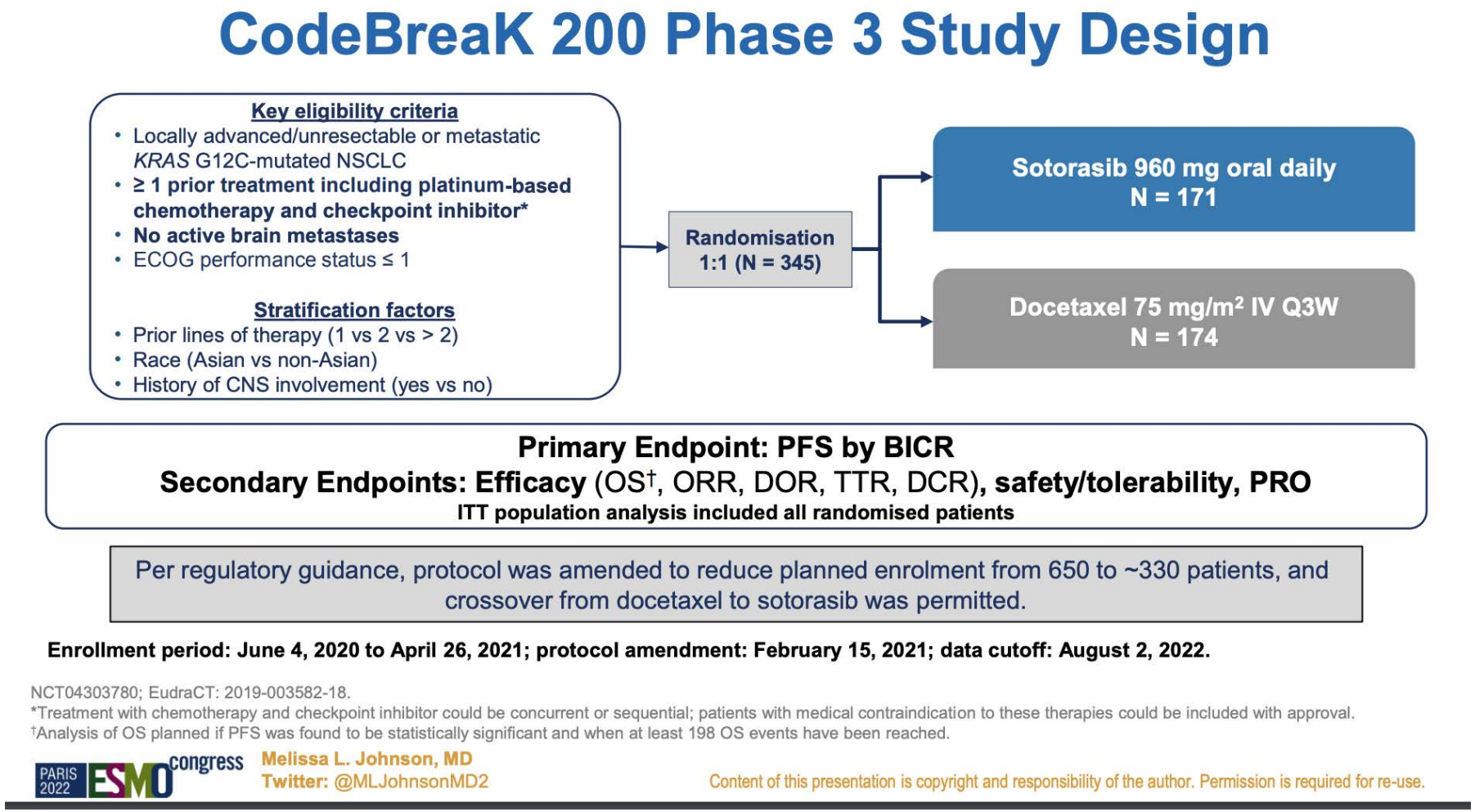
Sotorasib in *KRAS* G12C Mutated NSCLC



Skoulidis, NEJM 2021

SARAH CANNON Research Institute

Sotorasib v. Docetaxel in *KRAS* G12C Mutated NSCLC

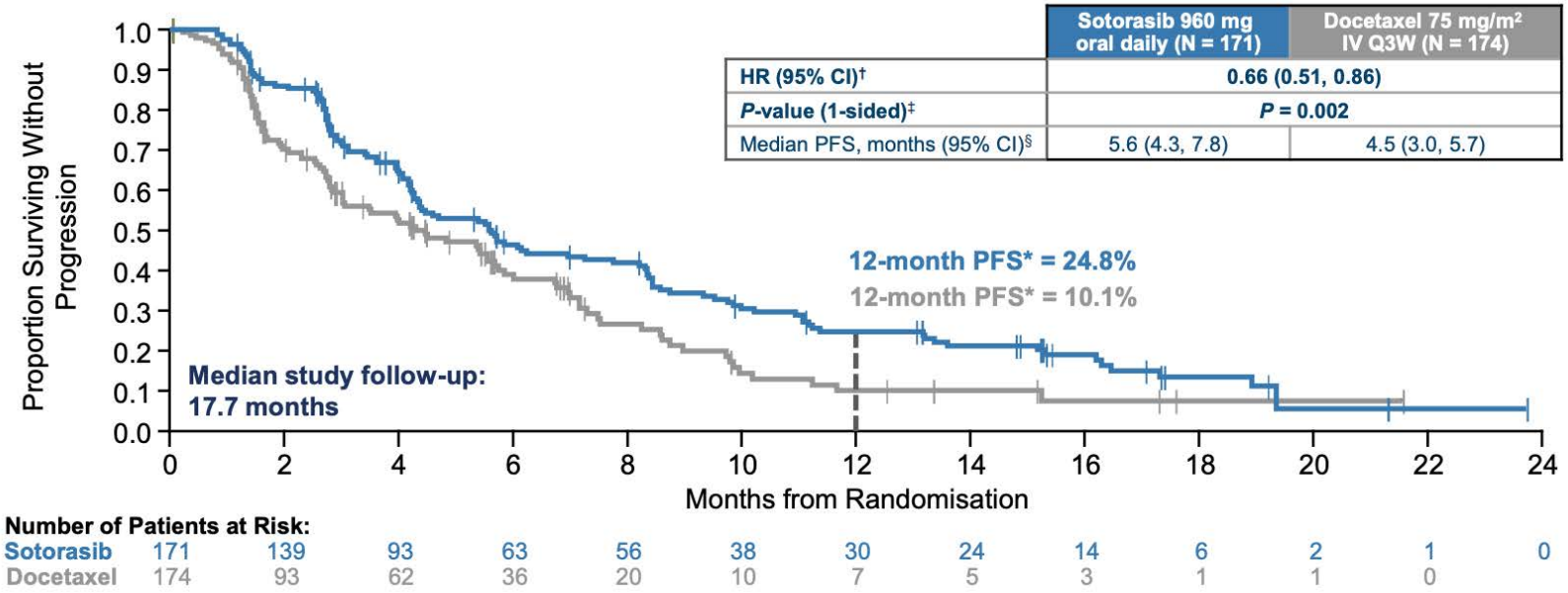


Johannes de Langen, Lancet 2023

SARAH CANNON Research Institute

Sotorasib v. Docetaxel in *KRAS* G12C Mutated NSCLC

Primary Endpoint: PFS by BICR



	Sotorasib 960 mg oral daily (N = 171)	Docetaxel 75 mg/m² IV Q3W (N = 174)
HR (95% CI)†	0.66 (0.51, 0.86)	
P-value (1-sided)‡	*P* = 0.002	
Median PFS, months (95% CI)§	5.6 (4.3, 7.8)	4.5 (3.0, 5.7)

Number of Patients at Risk:

Sotorasib	171	139	93	63	56	38	30	24	14	6	2	1	0
Docetaxel	174	93	62	36	20	10	7	5	3	1	1	0	

CodeBreaK 200 met its primary endpoint with sotorasib demonstrating superior PFS over docetaxel (HR 0.66, *P* = 0.002); 12-month PFS rate was 24.8% for sotorasib and 10.1% for docetaxel

*PFS rates estimated using Kaplan-Meier method; ITT population.
†HR and 95% CIs estimated using a stratified Cox proportional hazards model.
‡*P*-value calculated using a stratified log-rank test.
§Medians estimated using Kaplan-Meier method; 95% CIs estimated using the method by Klein and Moeschberger with log-log transformation.

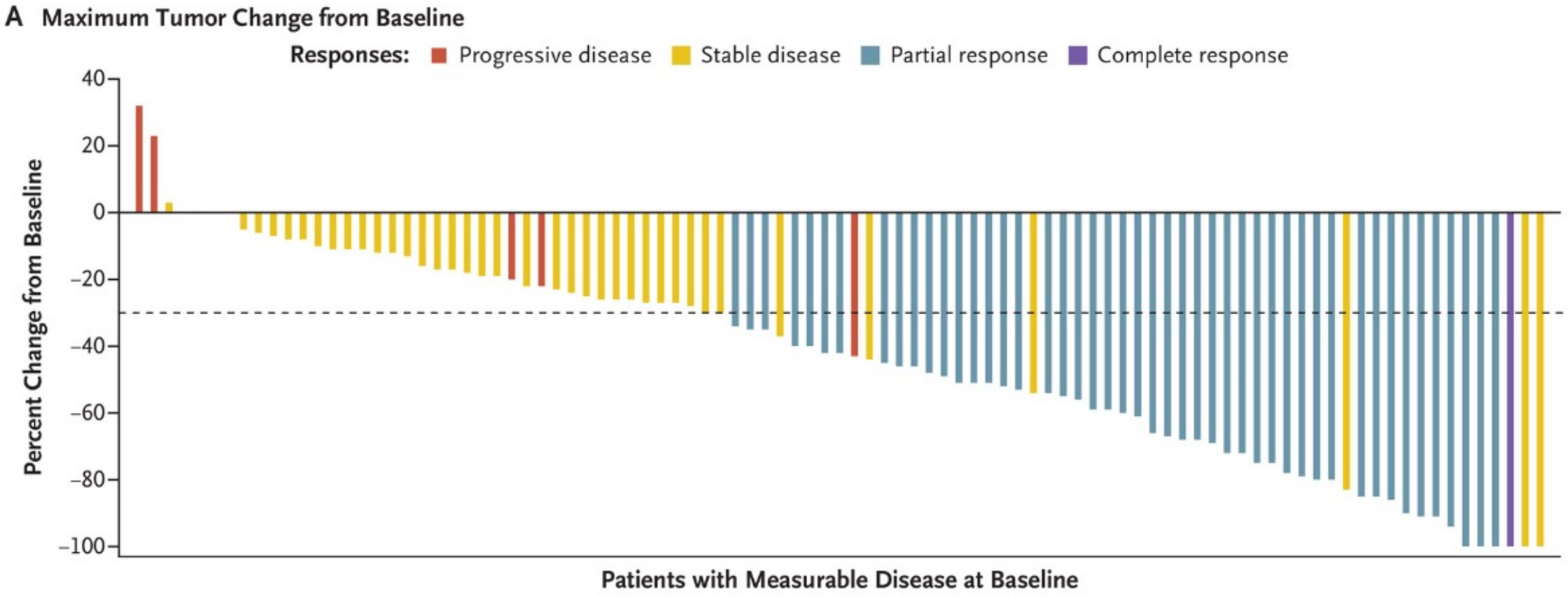
PARIS 2022 ESMO congress

Melissa L. Johnson, MD
Twitter: @MLJohnsonMD2

Johannes de Langen, Lancet 2023

SARAH CANNON Research Institute

Adagrasib in *KRAS* G12C Mutated NSCLC



Janne, NEJM 2022

SARAH CANNON
Research Institute

Summary

- **Standard Therapies are approved for *MET*, *KRAS*, and *HER2* altered NSCLC**
- **Comprehensive NGS for Squamous and Non-Squamous NSCLC is needed to identify these and other molecular alterations for treatment Planning**
- **Antibody-Drug Conjugates (ADCs) and combination strategies are in development – including earlier treatment settings**

Agenda

Module 1: Incorporation of Immunotherapeutic Strategies into the Management of Nonmetastatic Non-Small Cell Lung Cancer (NSCLC) — Dr Heymach

Module 2: Contemporary Treatment for Localized or Metastatic NSCLC with an EGFR Mutation — Dr Yu

Module 3: Research Advances Shaping the Current and Future Treatment of Metastatic NSCLC with ALK Rearrangements, ROS1 Rearrangements or RET Fusions — Dr Langer

Module 4: Targeting MET, HER2 and KRAS Alterations in NSCLC — Dr Spigel

Module 5: Current Management of Metastatic NSCLC without a Targetable Tumor Mutation — Dr Garon

Module 6: Future Directions in the Management of Metastatic NSCLC — Dr Leal

RTP RESEARCH TO PRACTICE

Use of anti-PD-1/PD-L1 antibodies in patients for whom biomarker testing is pending

Melissa Johnson, MD

Matthew Gubens, MD, MS

Jarushka Naidoo, MB BCH, MHS

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

 Dr Garon	No	 Dr Yu	No
 Dr Heymach	No	 Dr Gubens	No
 Dr Langer	No	 Dr Johnson	No
 Dr Leal	No	 Dr Naidoo	No
 Dr Spigel	No		

RTP RESEARCH TO PRACTICE

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

 Dr Garon	Yes	 Dr Yu	Yes
 Dr Heymach	Yes	 Dr Gubens	No
 Dr Langer	Yes	 Dr Johnson	Yes
 Dr Leal	No	 Dr Naidoo	Yes
 Dr Spigel	No		

RTP RESEARCH TO PRACTICE

Selection of first-line therapy for newly diagnosed metastatic NSCLC without a targetable tumor mutation

Melissa Johnson, MD

Matthew Gubens, MD, MS

Jarushka Naidoo, MB BCH, MHS

Which of the available anti-PD-1/PD-L1 antibodies has the best risk-benefit profile when administered as monotherapy for a patient with metastatic NSCLC with no targetable mutations and a high PD-L1 TPS (≥50%)?

 Dr Garon	Pembrolizumab and cemiplimab
 Dr Heymach	There is no significant difference
 Dr Langer	There is no significant difference
 Dr Leal	There is no significant difference
 Dr Spigel	There is no significant difference
 Dr Yu	There is no significant difference
 Dr Gubens	There is no significant difference
 Dr Johnson	There is no significant difference
 Dr Naidoo	Atezolizumab

RTP RESEARCH TO PRACTICE

Which first-line treatment regimen would you recommend for an asymptomatic 65-year-old patient with metastatic nonsquamous NSCLC with modest disease burden, no identified targetable mutations and a PD-L1 TPS of 50%?

 Dr Garon	Pembrolizumab
 Dr Heymach	Pembrolizumab
 Dr Langer	Pembrolizumab
 Dr Leal	Pembrolizumab
 Dr Spigel	Cemiplimab
 Dr Yu	Pembrolizumab
 Dr Gubens	Pembrolizumab
 Dr Johnson	Carbo/pem/pembro
 Dr Naidoo	Pembrolizumab

Carbo = carboplatin; pem = pemetrexed; pembro = pembrolizumab

RTP RESEARCH TO PRACTICE

Role of first-line immunotherapy in PD-L1-negative metastatic NSCLC

Melissa Johnson, MD

Matthew Gubens, MD, MS

Jarushka Naidoo, MB BCH, MHS

RTP RESEARCH TO PRACTICE

Which first-line treatment regimen would you recommend for a 65-year-old patient with metastatic nonsquamous NSCLC, no identified targetable mutations and a PD-L1 TPS of 0%?

 Dr Garon	Carbo/pem/pembro	 Dr Yu	Carbo/pem/pembro
 Dr Heymach	Durvalumab/ tremelimumab + chemo	 Dr Gubens	Ipilimumab/nivolumab
 Dr Langer	Carbo/pem/pembro	 Dr Johnson	Carbo/pem/pembro
 Dr Leal	Carbo/pem/pembro	 Dr Naidoo	Ipilimumab/nivolumab + chemotherapy
 Dr Spigel	Carbo/pem/pembro		

Carbo = carboplatin; pem = pemetrexed; pembro = pembrolizumab

RTP RESEARCH TO PRACTICE

Implications of antibiotic use and autoimmune toxicity for checkpoint inhibitor efficacy

Melissa Johnson, MD

Matthew Gubens, MD, MS

Jarushka Naidoo, MB BCH, MHS

Do you believe that patients who receive antibiotics while receiving anti-PD-1/PD-L1 antibodies derive less benefit than those who do not?

 Dr Garon	Yes	 Dr Yu	Yes
 Dr Heymach	No	 Dr Gubens	No
 Dr Langer	No	 Dr Johnson	No
 Dr Leal	No	 Dr Naidoo	No
 Dr Spigel	No		

RTP
RESEARCH
TO PRACTICE

Do you believe that a correlation exists between autoimmune toxicity and treatment benefit in patients receiving immune checkpoint inhibitors?

 Dr Garon	Yes	 Dr Yu	Yes
 Dr Heymach	Yes	 Dr Gubens	Yes
 Dr Langer	Yes	 Dr Johnson	No
 Dr Leal	Yes	 Dr Naidoo	Yes
 Dr Spigel	Yes		

RTP
RESEARCH
TO PRACTICE

Current Management of Metastatic NSCLC without a Targetable Tumor Mutation

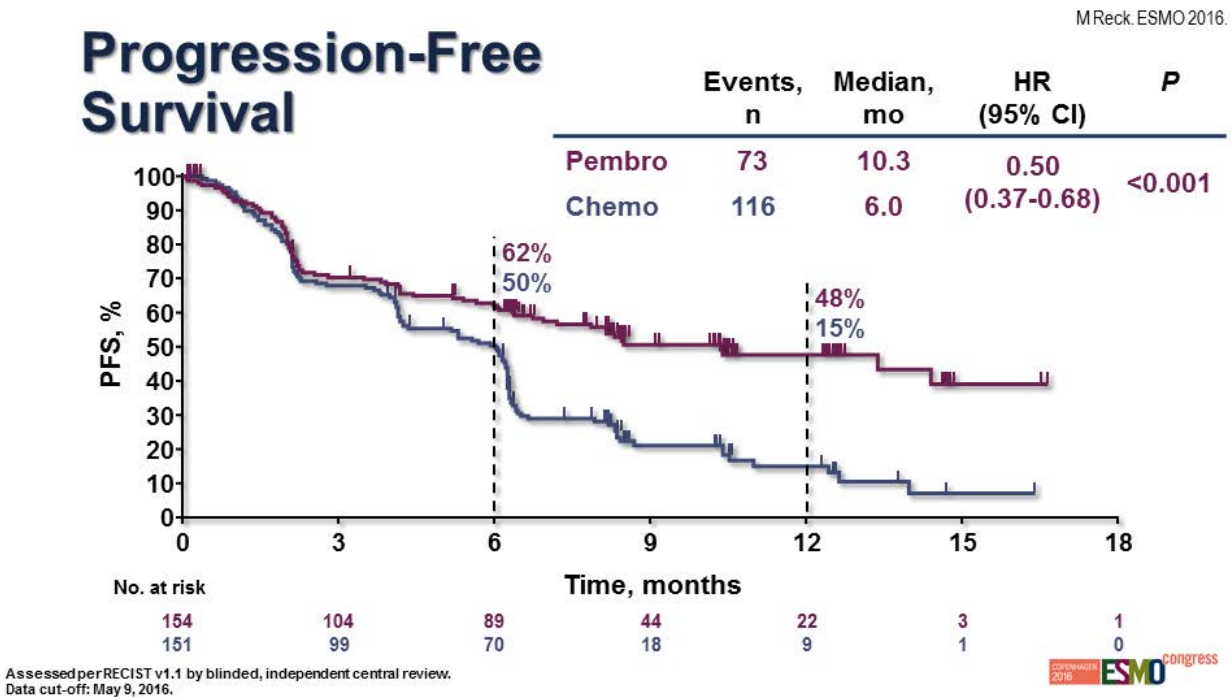
Edward B. Garon, MD, MS

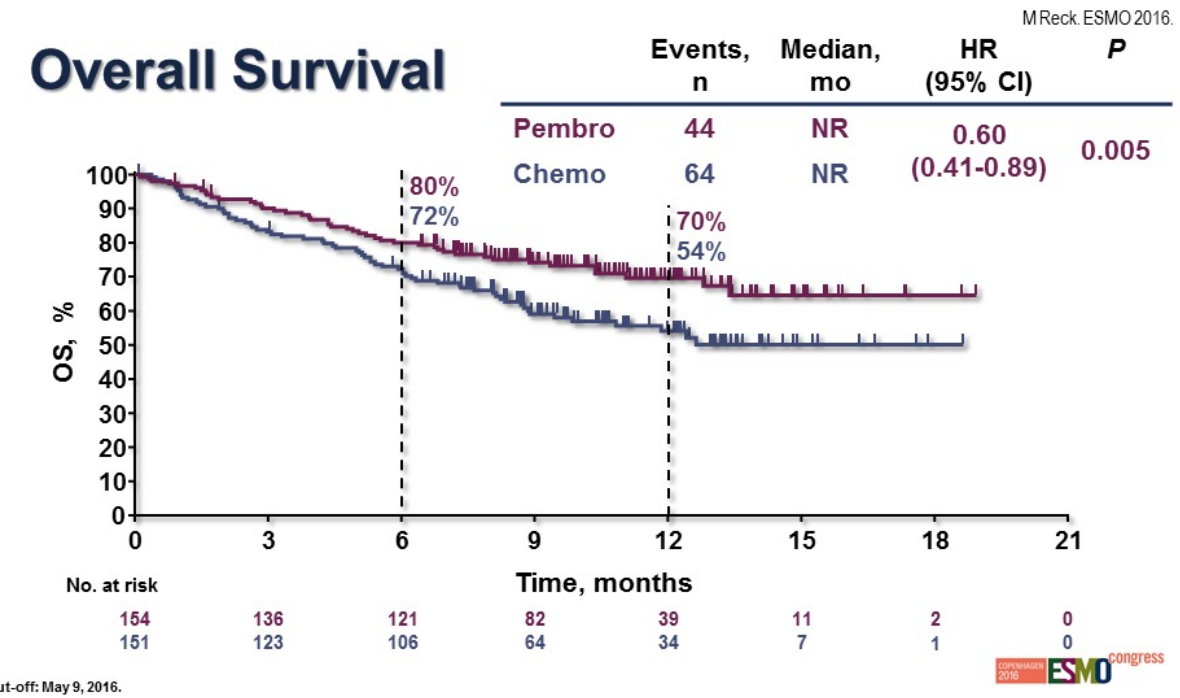
Professor

David Geffen School of Medicine at UCLA

Los Angeles, CA

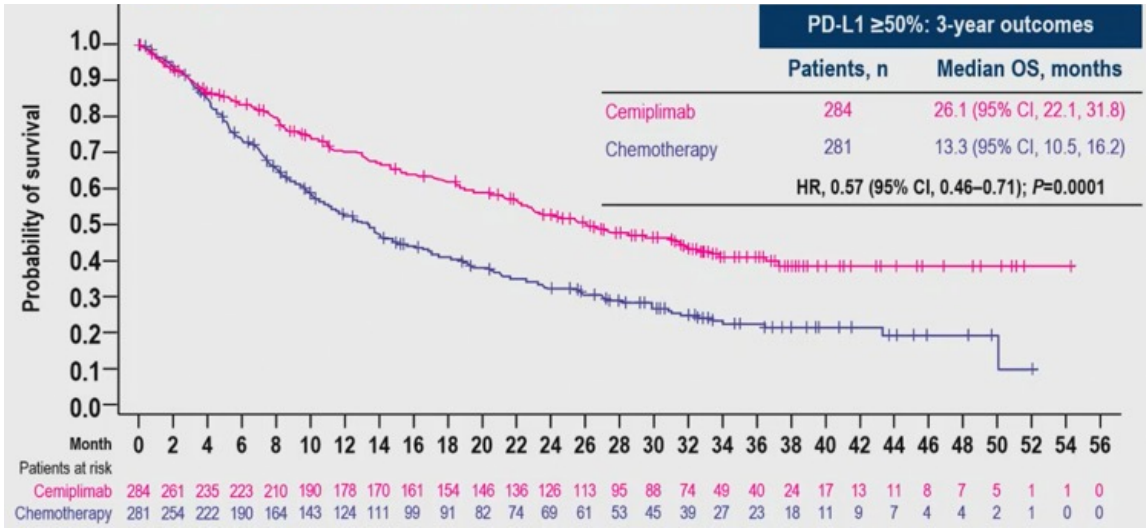
Pembrolizumab vs. Chemo in NSCLC with PD-L1 Expression in ≥50% of Tumor Cells



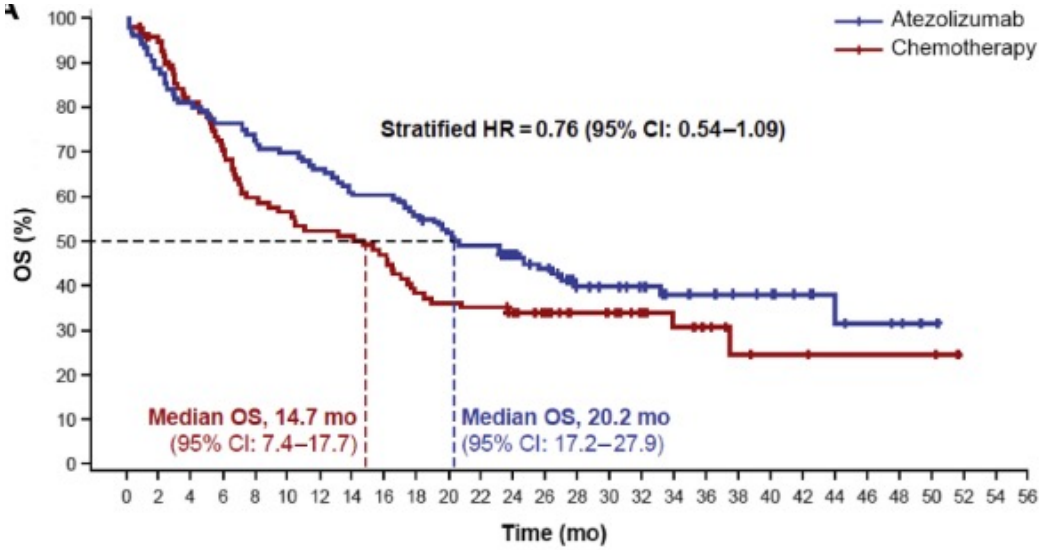


Long Term Update of Monotherapy Experience

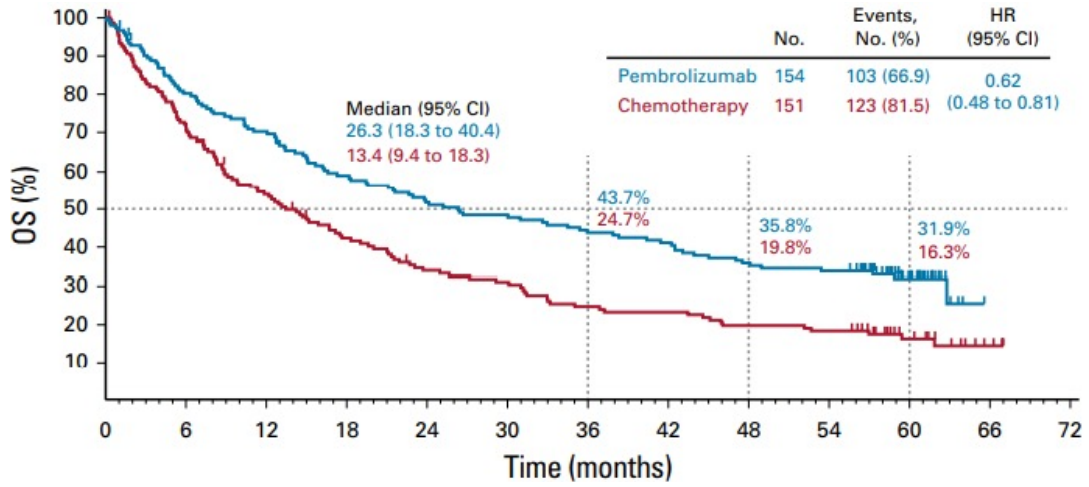
EMPOWER-1: 3 Years[a]



IMpower110: Updated Analysis[b]



KEYNOTE 024: 5 Years[c]



a. Ozguroglu M, et al. Presented at: European Society for Medical Oncology annual congress; September 9-13; 2022; Paris, France Abstract LBA54;

b. Jassem J, et al. J Thorac Oncol. 2021;16:1872-1882;

c. Reck M, et al. J Clin Oncol. 2021;39:2339-2349.

KEYNOTE-042: Progression-Free Survival – TPS ≥50%

(RECIST v1.1, BICR)

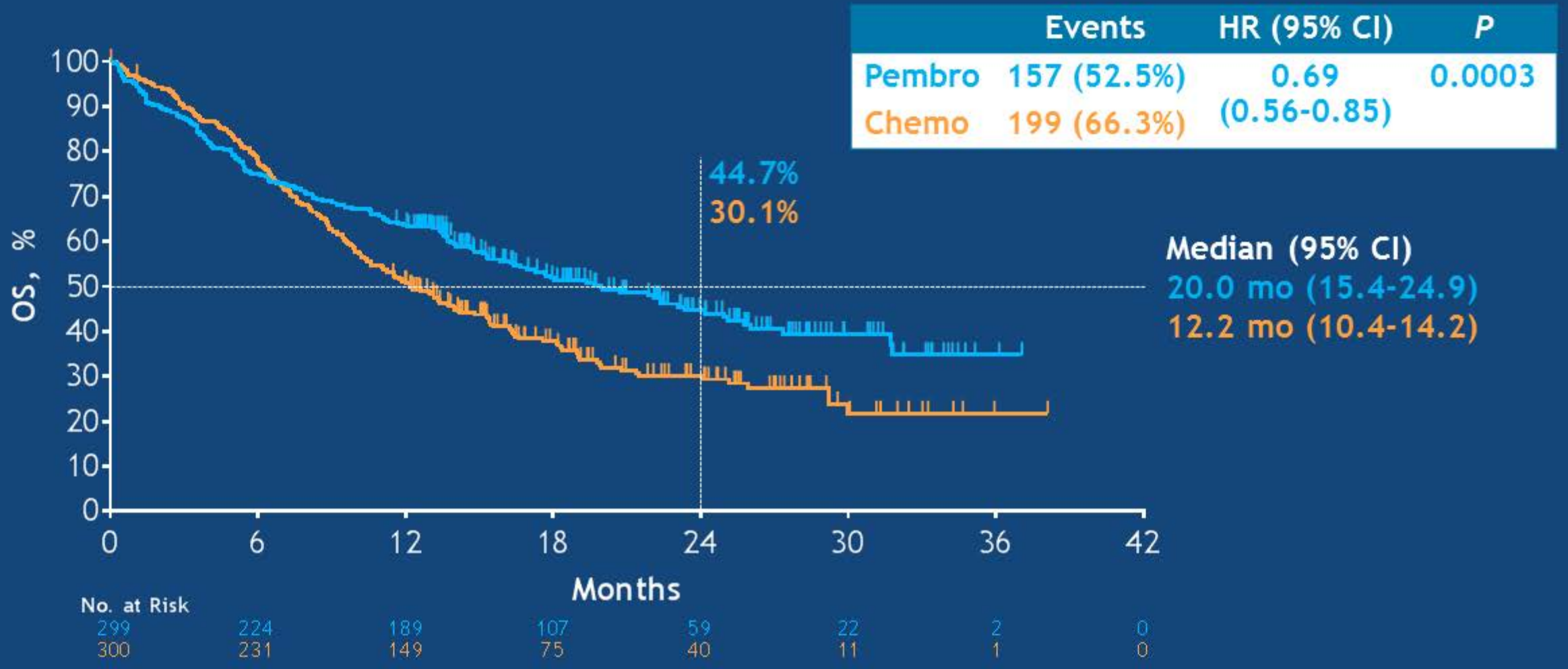
	Events	HR (95% CI)	*P*
Pembro	221 (73.9%)	0.81 (0.67-0.99)	0.0170[a]
Chemo	233 (77.7%)		

Median (95% CI)
7.1 mo (5.9-9.0)
6.4 mo (6.1-6.9)

[a]Protocol-specified significance boundary not met. BICR, blinded independent central review.

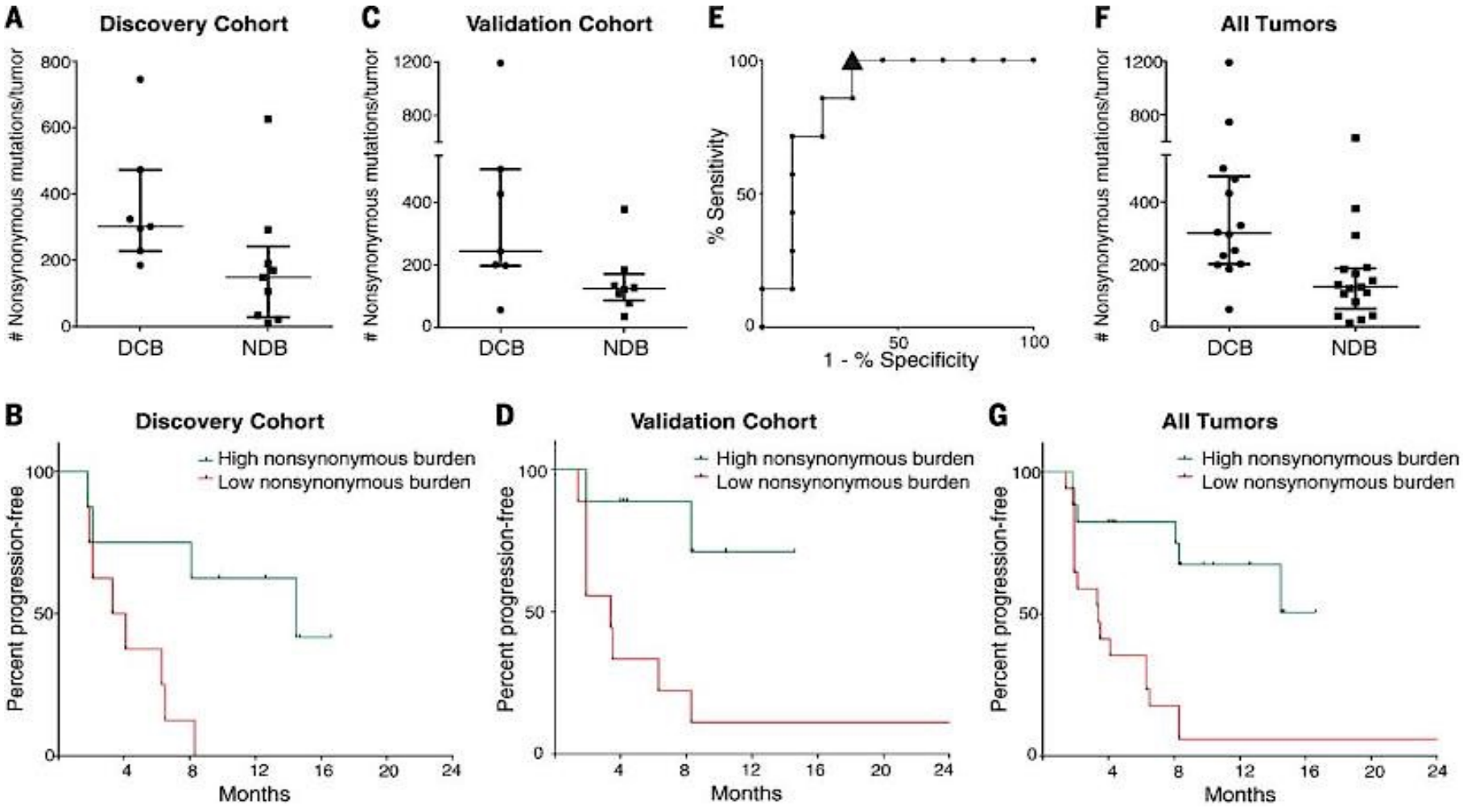
Mok TSK et al. *Lancet* 2019;393(10183):1819-30; Lopes ASCO 2018.

KEYNOTE-042: Overall Survival – TPS ≥50%



Mok TSK et al. *Lancet* 2019;393(10183):1819-30; Lopes ASCO 2018.

Nonsynonymous mutation burden is associated with PFS benefit of anti–PD-1 therapy



Rizvi NA. *Science* 2015;348:124-128

Tumor Mutational Burden as a Continuous Variable

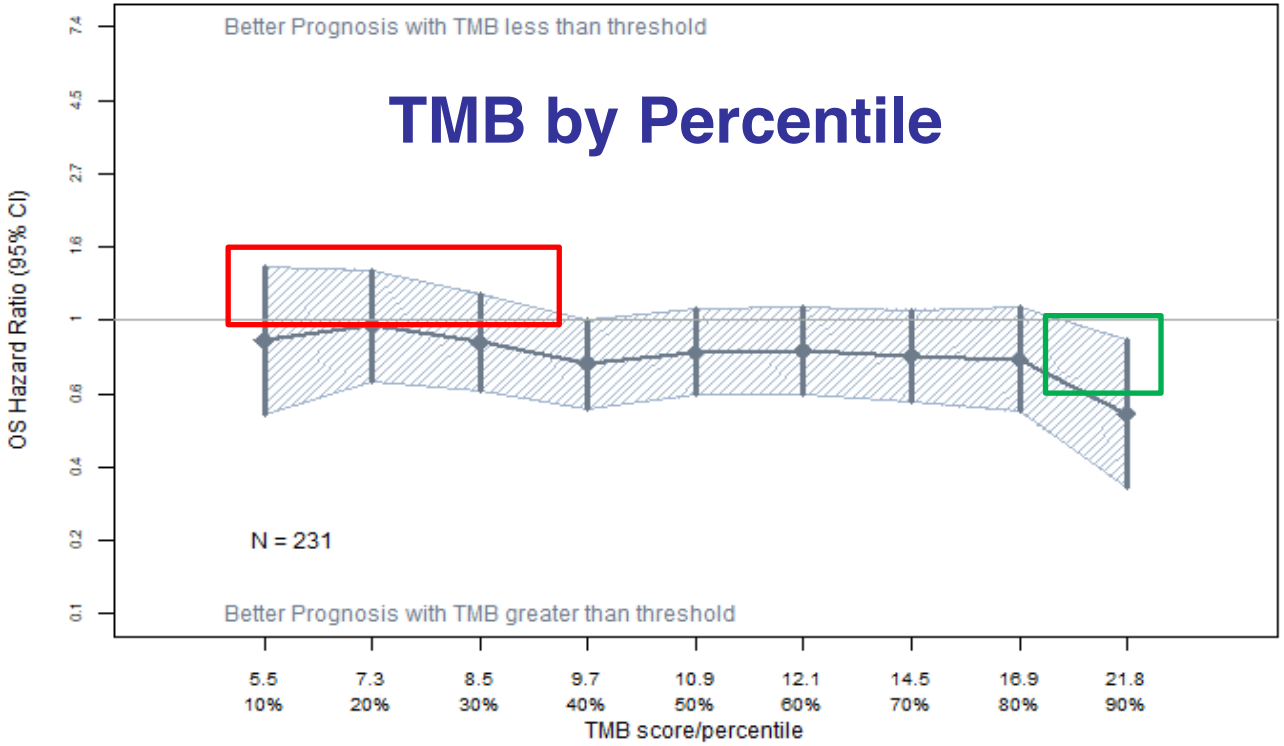
TMB by Value (per 10-unit difference)

Total pts: 252 on S1400I
68 on S1400A

<u>Overall Survival</u>: higher TMB; HR; 0.80 (95% CI: 0.67;0.94), p=0.008

<u>Progression Free Survival</u>: HR: 0.80 (95% CI; 0.69;0.93), p=0.004

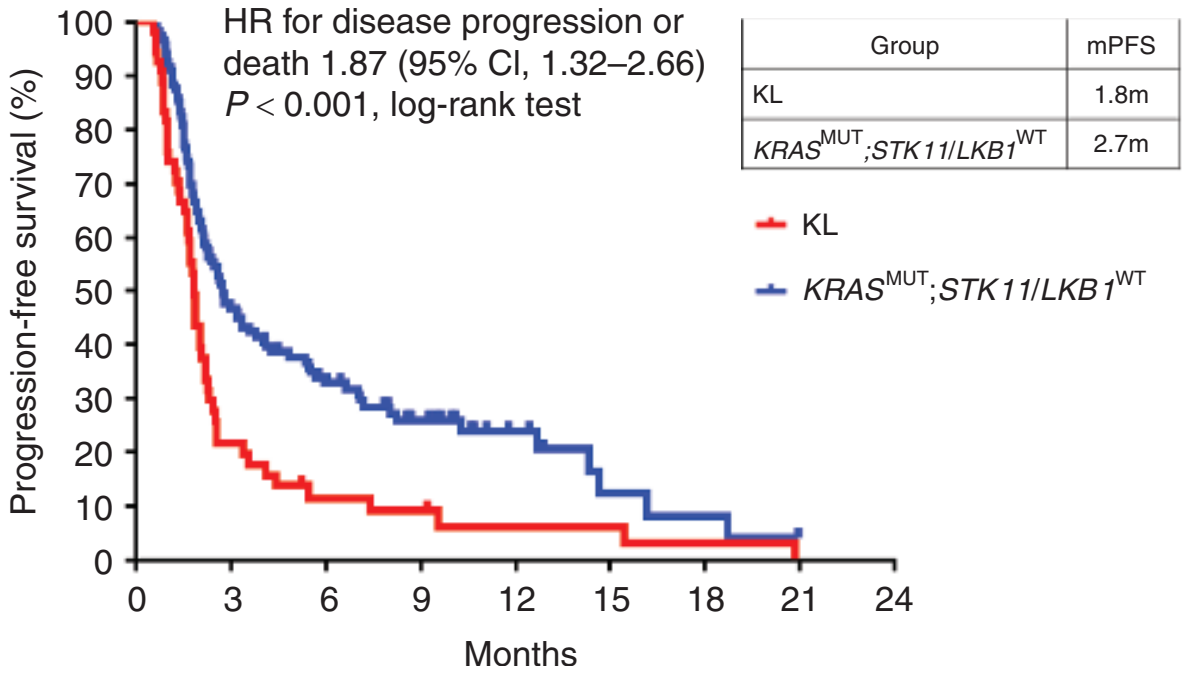
HIGHER TMB WAS SIGNIFICANTLY ASSOCIATED WITH IMPROVED OS AND PFS.

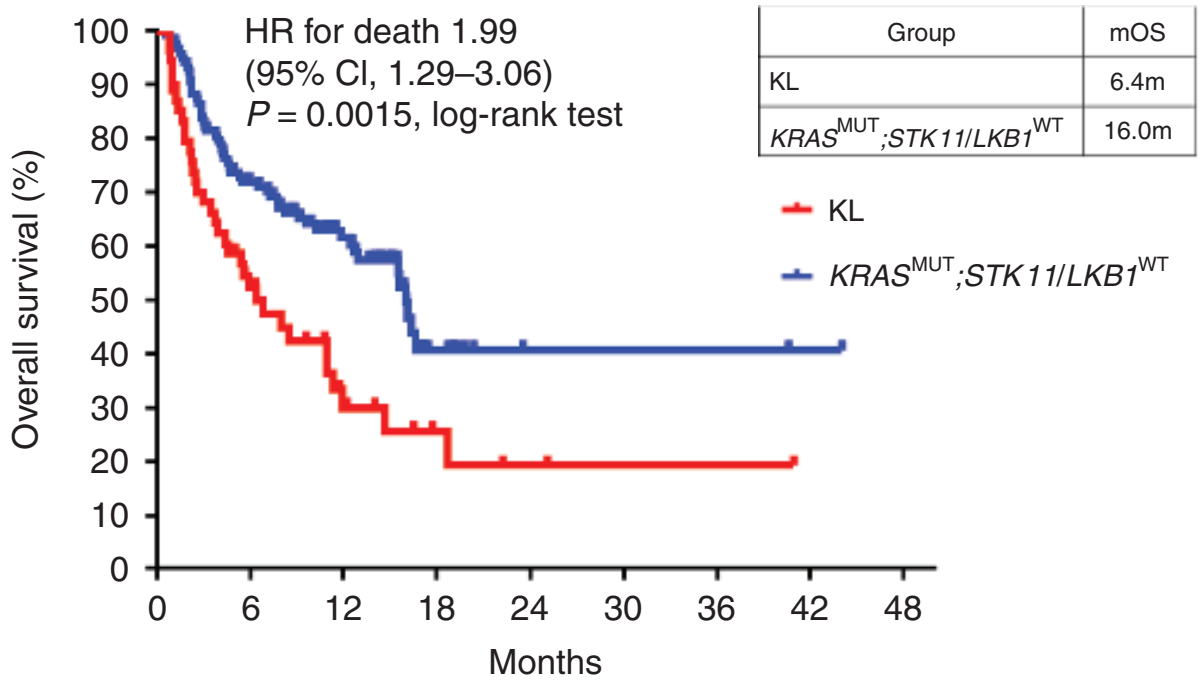


The relative risk of death comparing OS between patients with TMB levels above versus below the thresholds

Negative Predictors

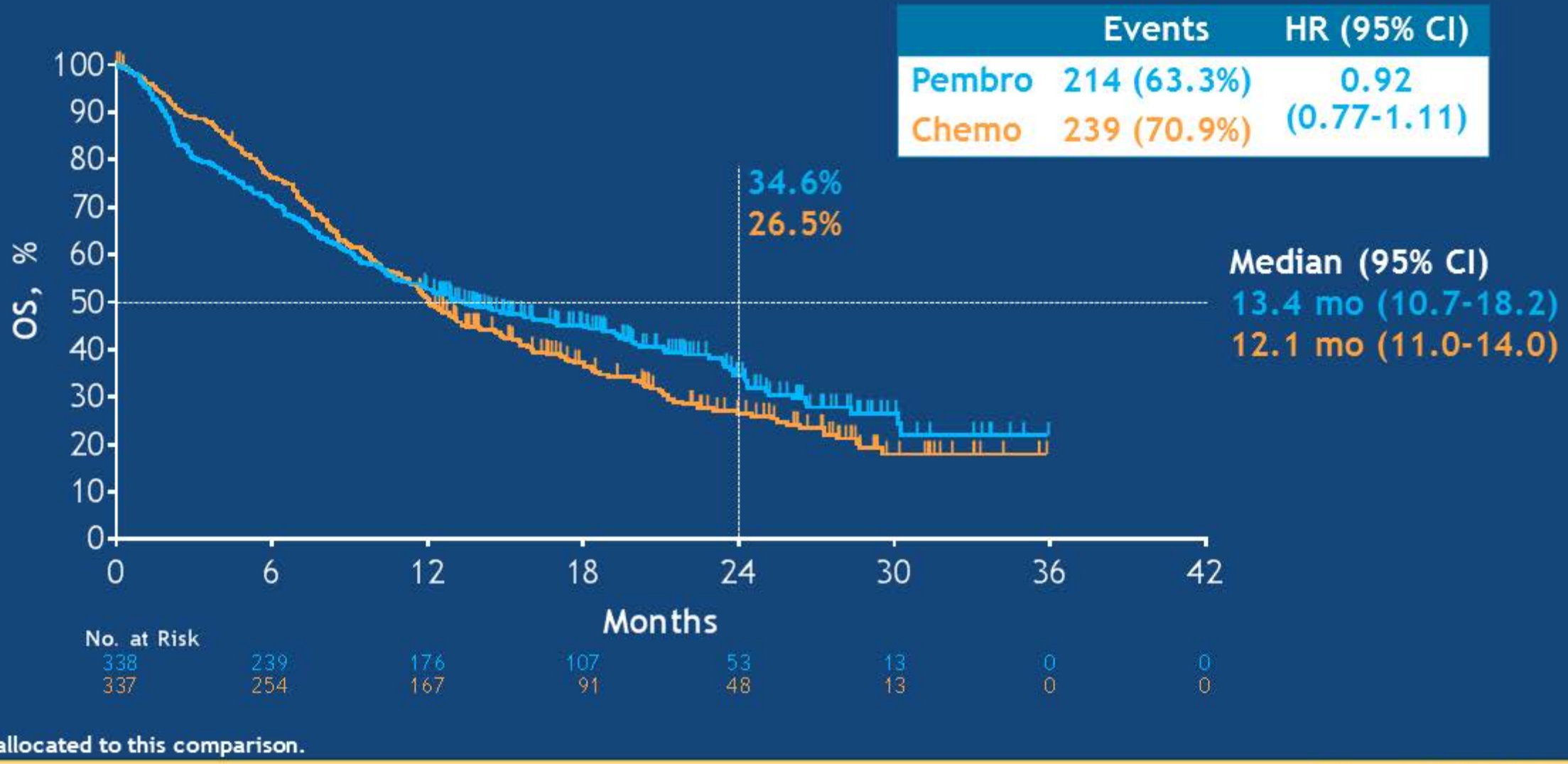
- In KRAS mutant NSCLC, co-mutations correlated with clinical efficacy
  - STK11/LKB1 with KRAS led to worse outcomes





Skoulidis F, Cancer Disc 2017

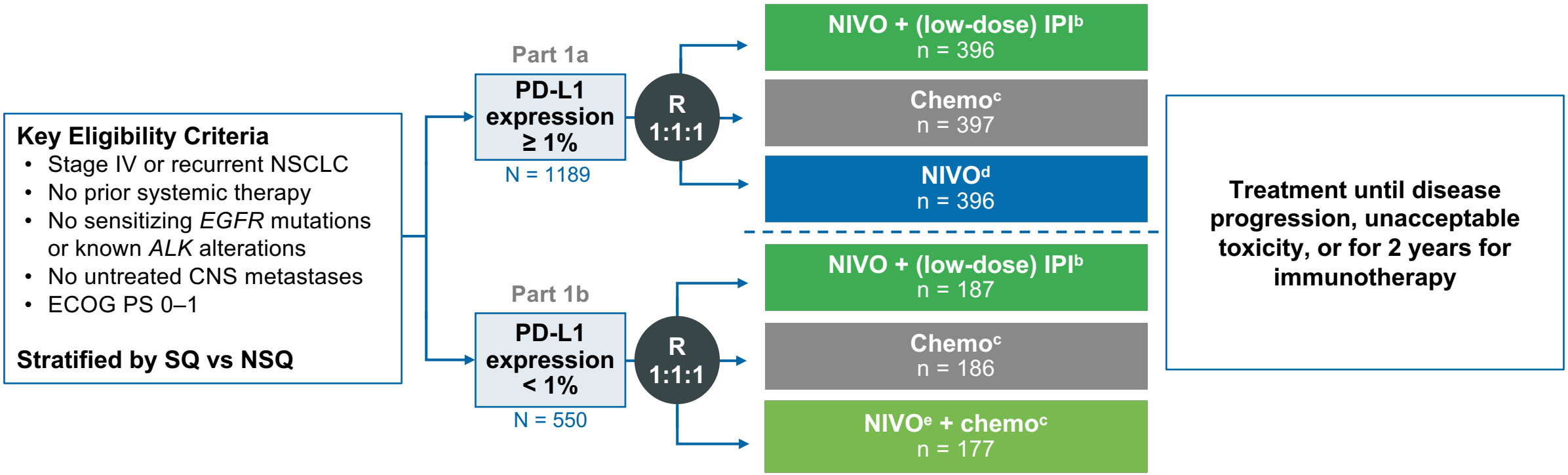
KEYNOTE-042: Overall Survival – TPS ≥ 1-49%
(Exploratory Analysis)



[a]No alpha allocated to this comparison.

Mok TSK et al. *Lancet* 2019;393(10183):1819-30; Lopes ASCO 2018.

CheckMate 227 Part 1 Study Design[a]



Independent co-primary endpoints: NIVO + IPI vs chemo

- PFS in high TMB (≥10 mut/Mb) population[f]
- OS in PD-L1 ≥ 1% population[g]

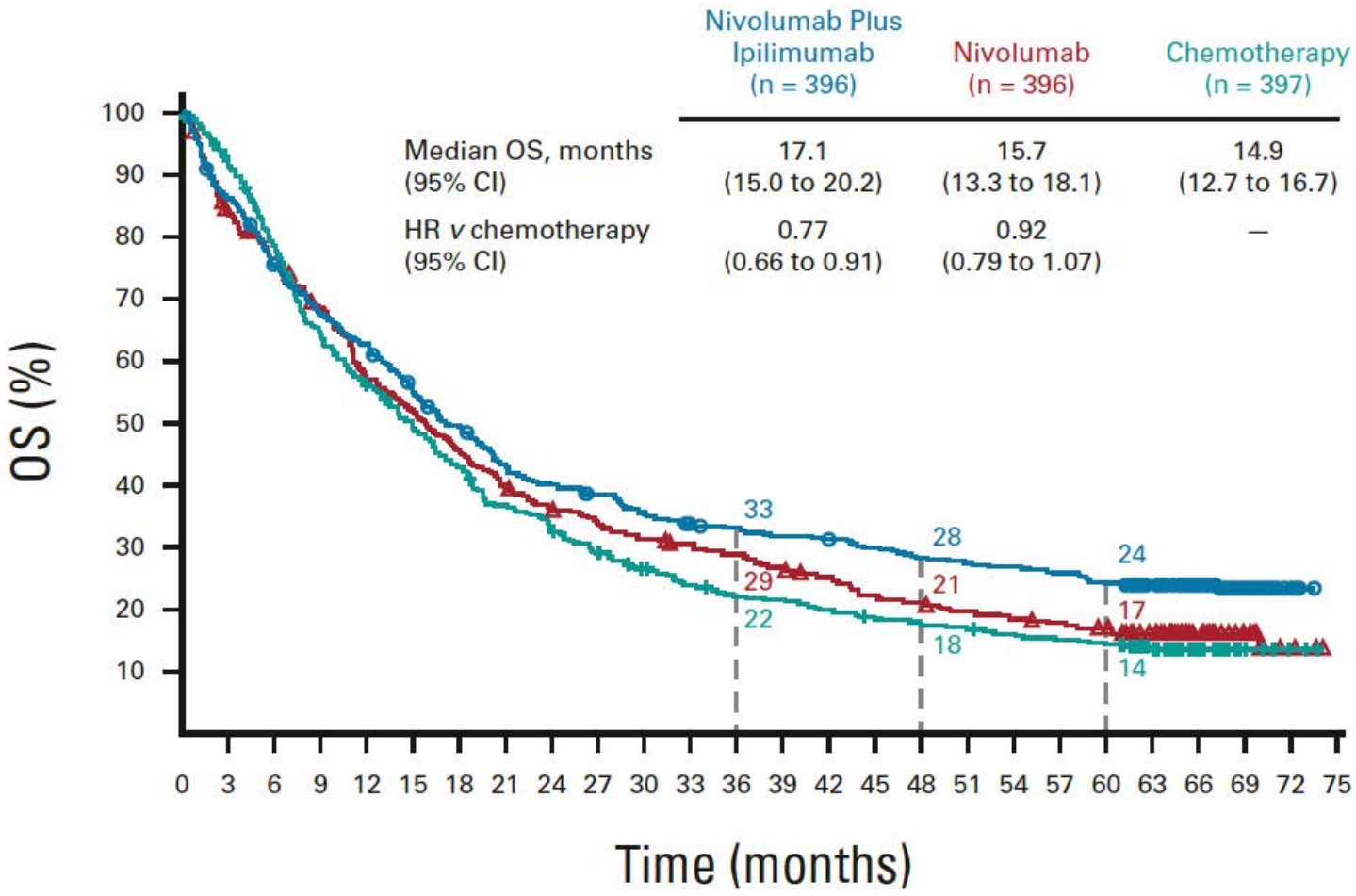
Secondary endpoints (PD-L1 hierarchy):

- PFS: **NIVO + chemo vs chemo** in PD-L1 < 1%
- OS: **NIVO + chemo vs chemo** in PD-L1 < 1%
- OS: **NIVO vs chemo** in PD-L1 ≥ 50%

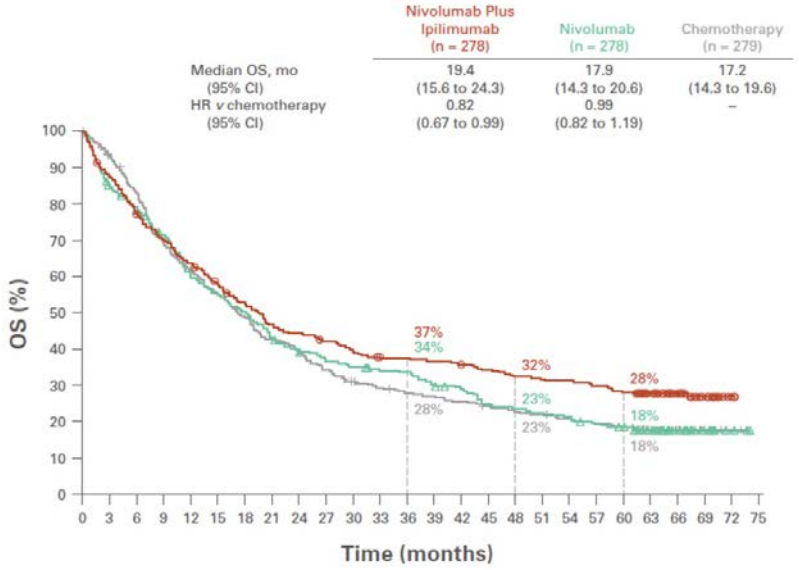
Peters S. ESMO 2019

CheckMate 227: 5-Year OS in patients with PD-L1 ≥1%

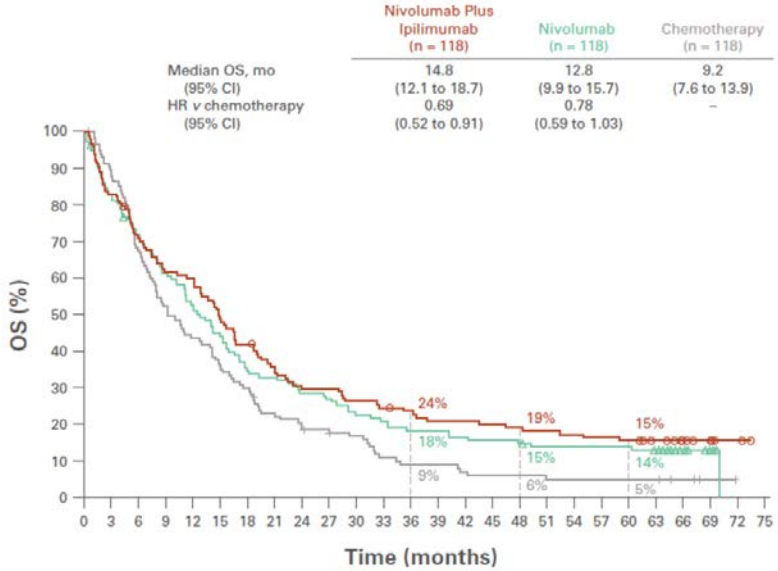
All patients (NSQ + SQ)



NSQ

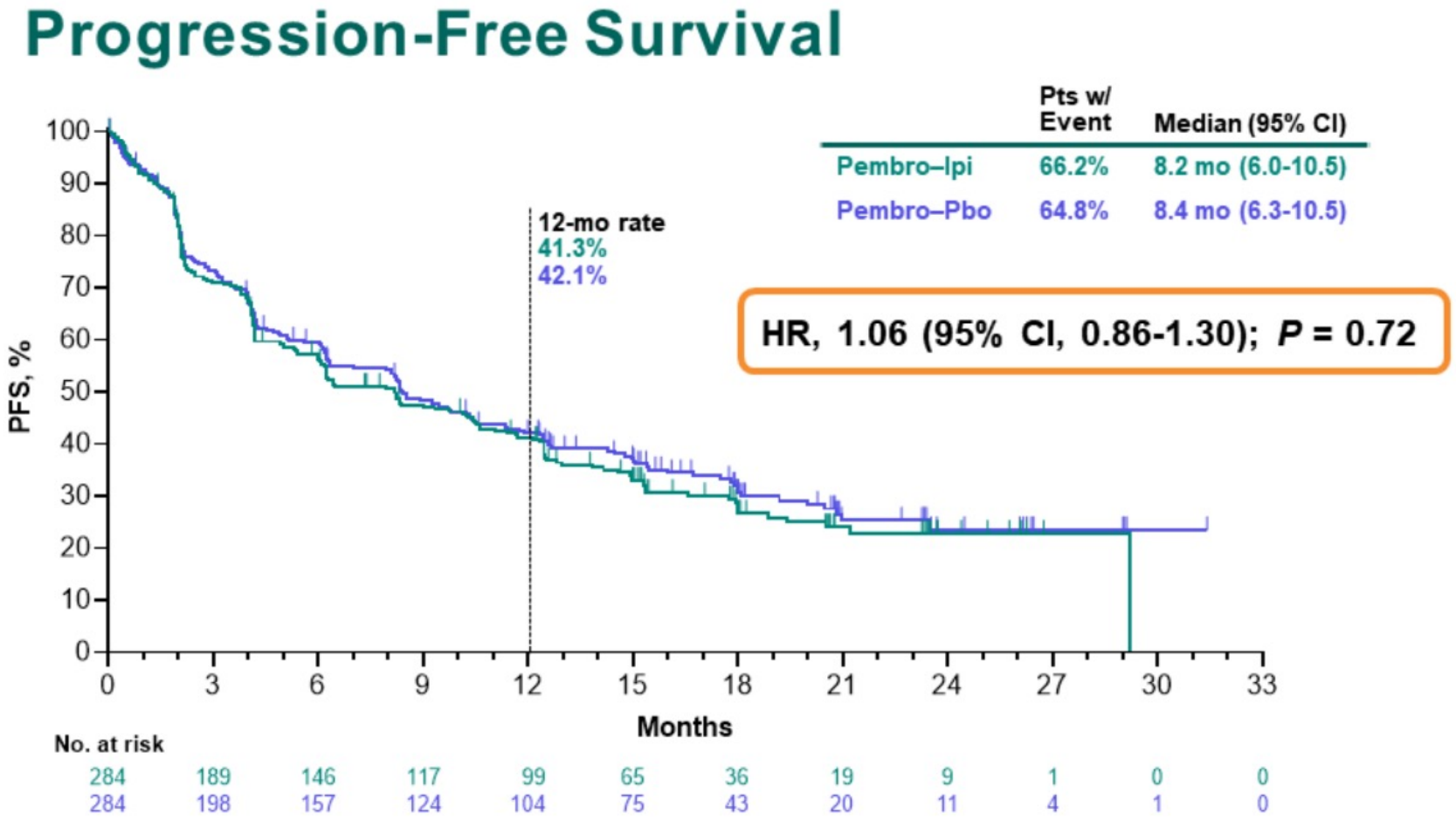


SQ



Brahmer JR et al. *J Clin Oncol* 2023;41(6):1200-12.

Pembrolizumab +/- Ipilimumab



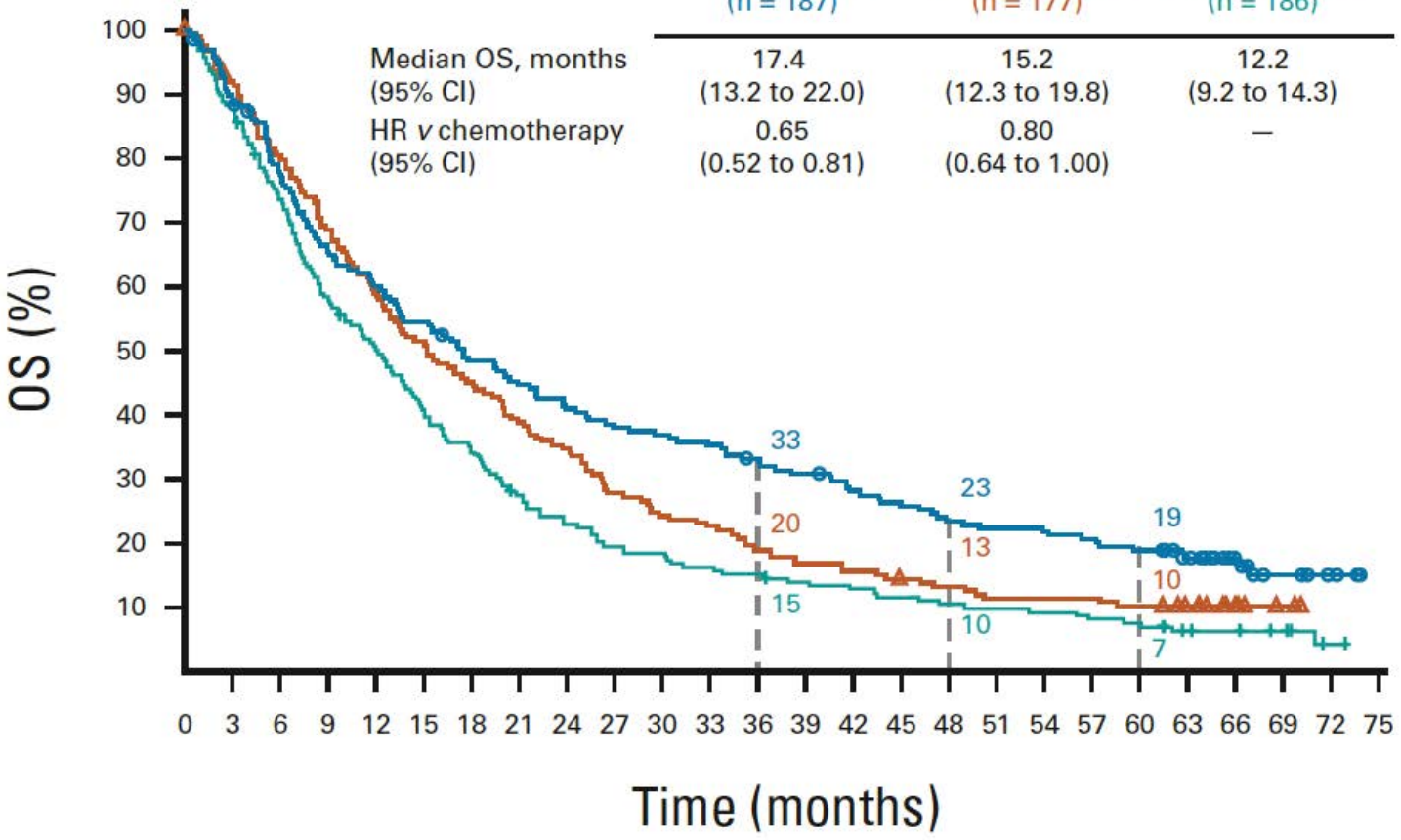
HR = hazard ratio.

Boyer M, et al. *J Clin Oncol.* 2021;39(21):2327-2338.

CheckMate 227: 5-Year OS in patients with PD-L1 < 1%

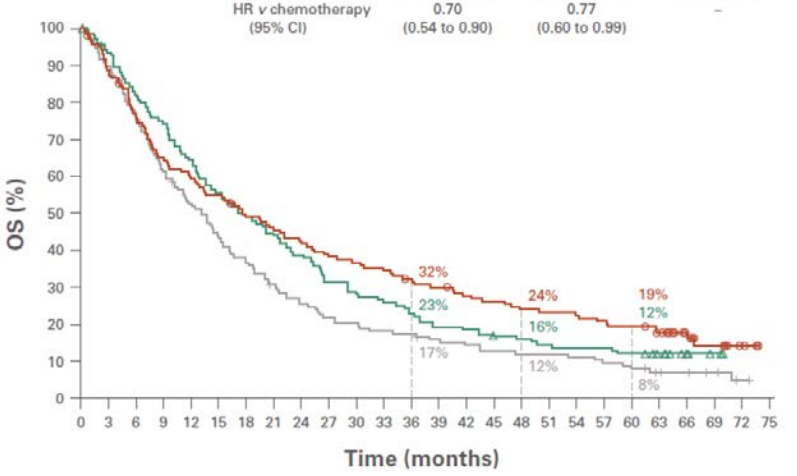
All patients (NSQ + SQ)

	Nivolumab Plus Ipilimumab (n = 187)	Nivolumab Plus Chemotherapy (n = 177)	Chemotherapy (n = 186)
Median OS, months (95% CI)	17.4 (13.2 to 22.0)	15.2 (12.3 to 19.8)	12.2 (9.2 to 14.3)
HR *v* chemotherapy (95% CI)	0.65 (0.52 to 0.81)	0.80 (0.64 to 1.00)	—



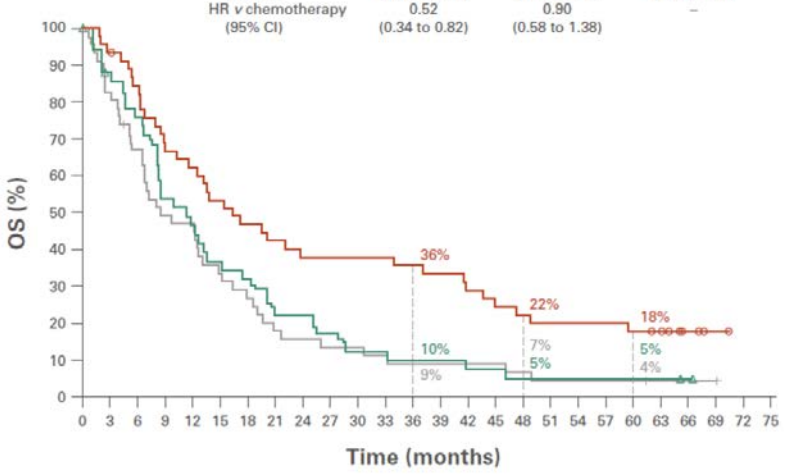
NSQ

	Nivolumab Plus Ipilimumab (n = 141)	Nivolumab Plus Chemotherapy (n = 134)	Chemotherapy (n = 140)
Median OS, mo (95% CI)	17.5 (12.3 to 23.9)	17.7 (13.5 to 21.6)	13.1 (9.8 to 15.3)
HR *v* chemotherapy (95% CI)	0.70 (0.54 to 0.90)	0.77 (0.60 to 0.99)	–



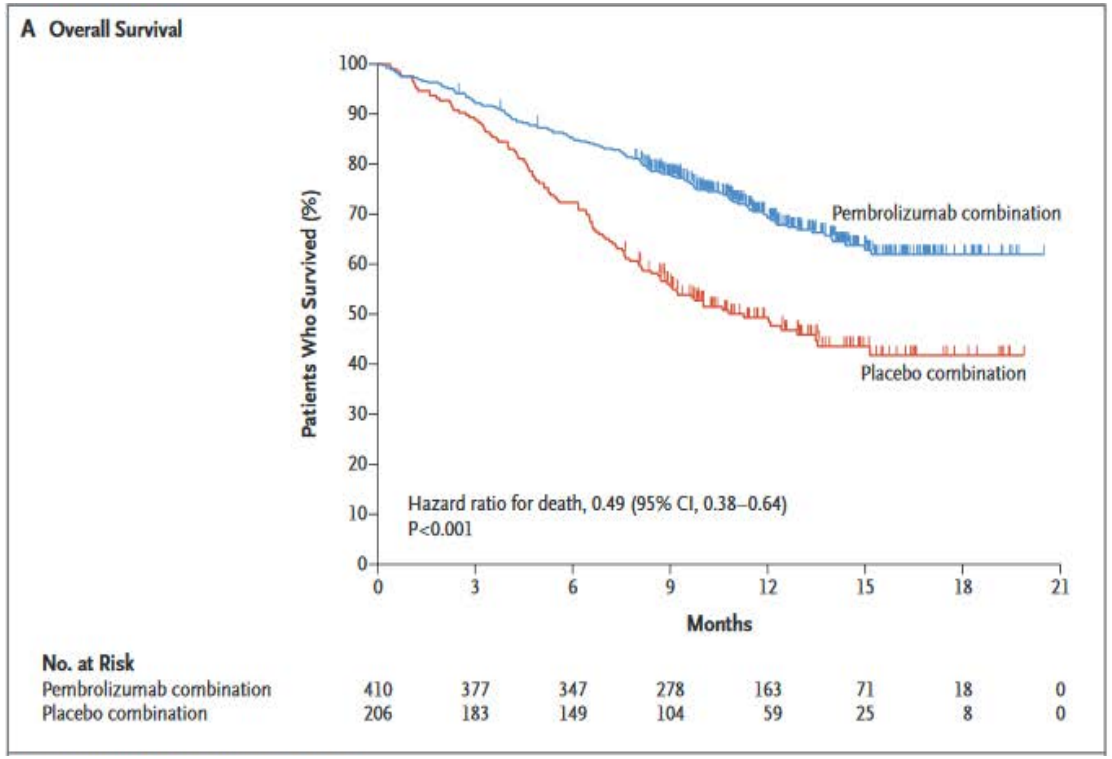
SQ

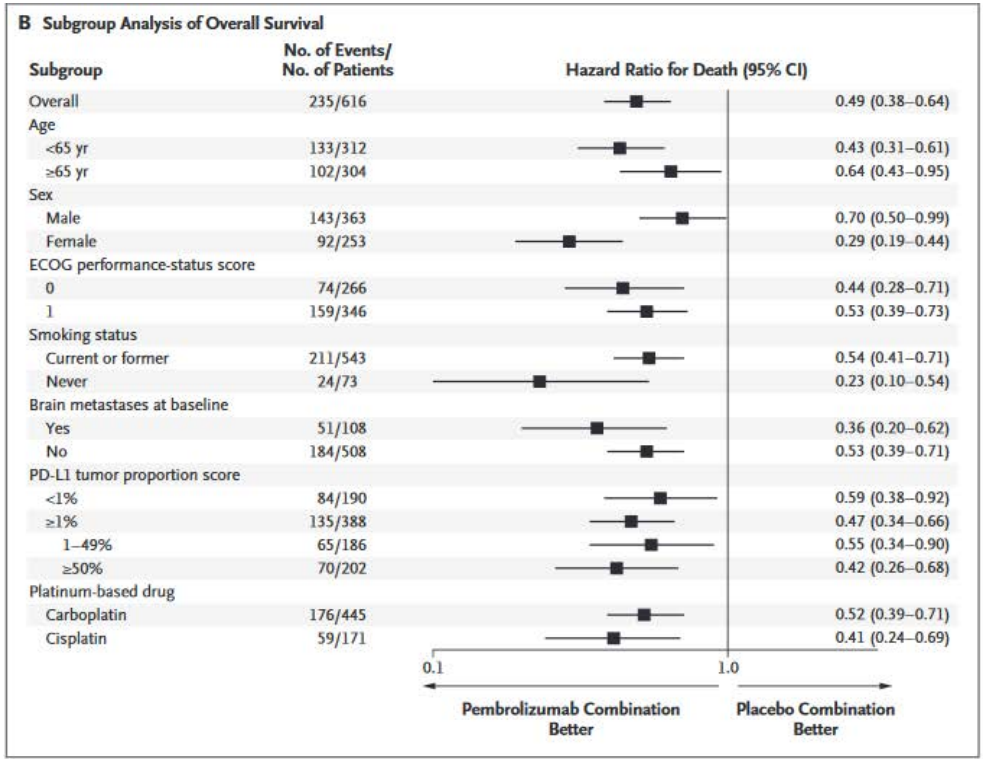
	Nivolumab Plus Ipilimumab (n = 46)	Nivolumab Plus Chemotherapy (n = 43)	Chemotherapy (n = 46)
Median OS, mo (95% CI)	16.3 (10.3 to 33.9)	11.3 (8.1 to 15.2)	8.5 (6.4 to 13.0)
HR *v* chemotherapy (95% CI)	0.52 (0.34 to 0.82)	0.90 (0.58 to 1.38)	–



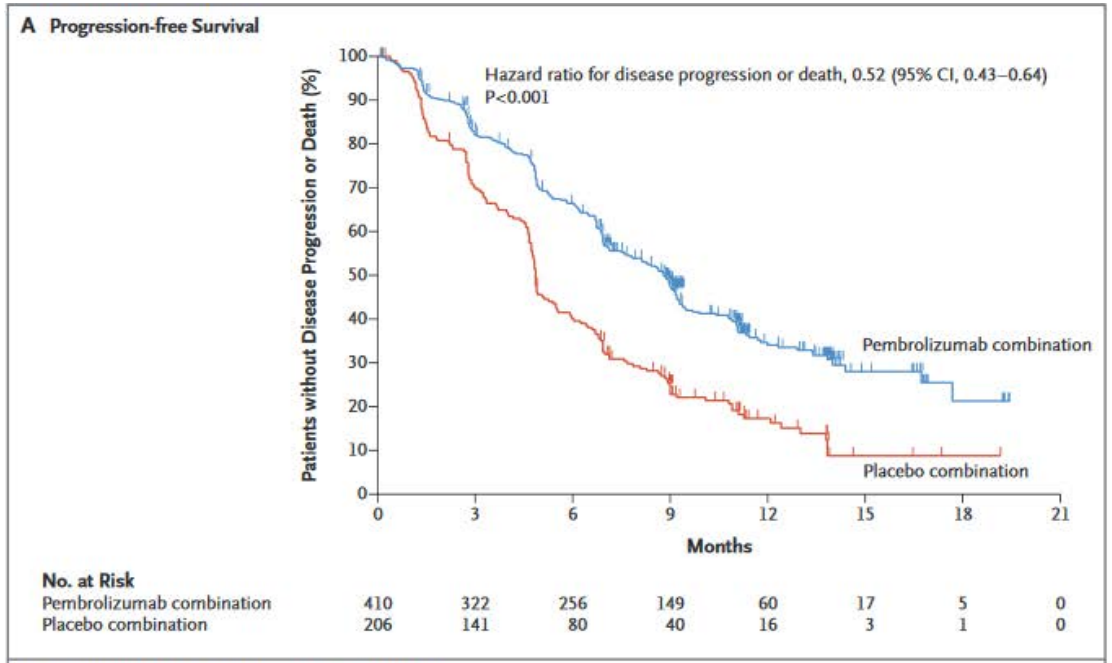
Brahmer JR et al. *J Clin Oncol* 2023;41(6):1200-12.

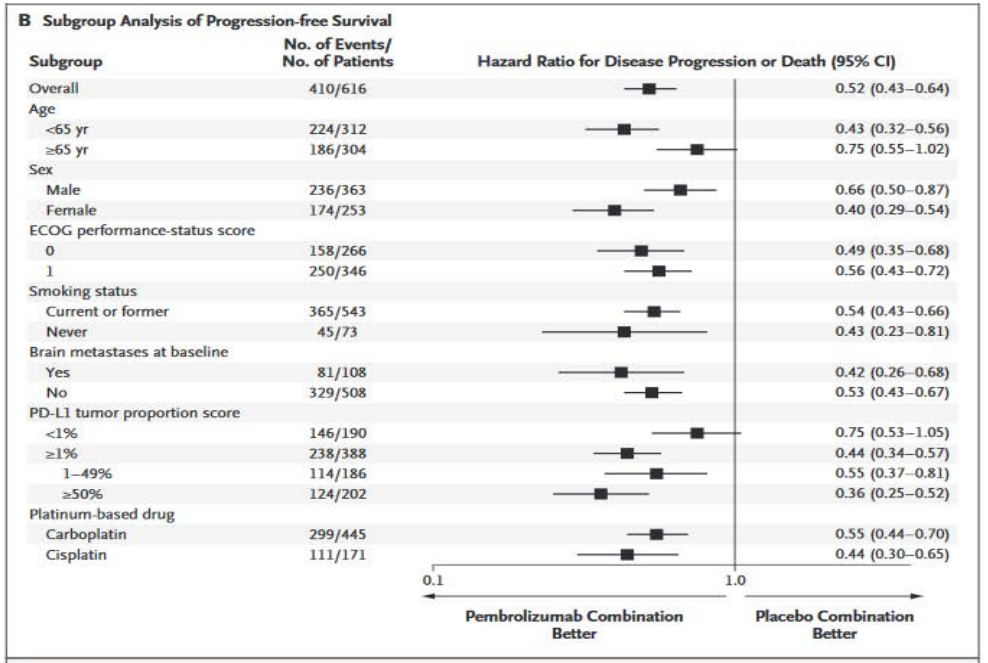
KEYNOTE-189



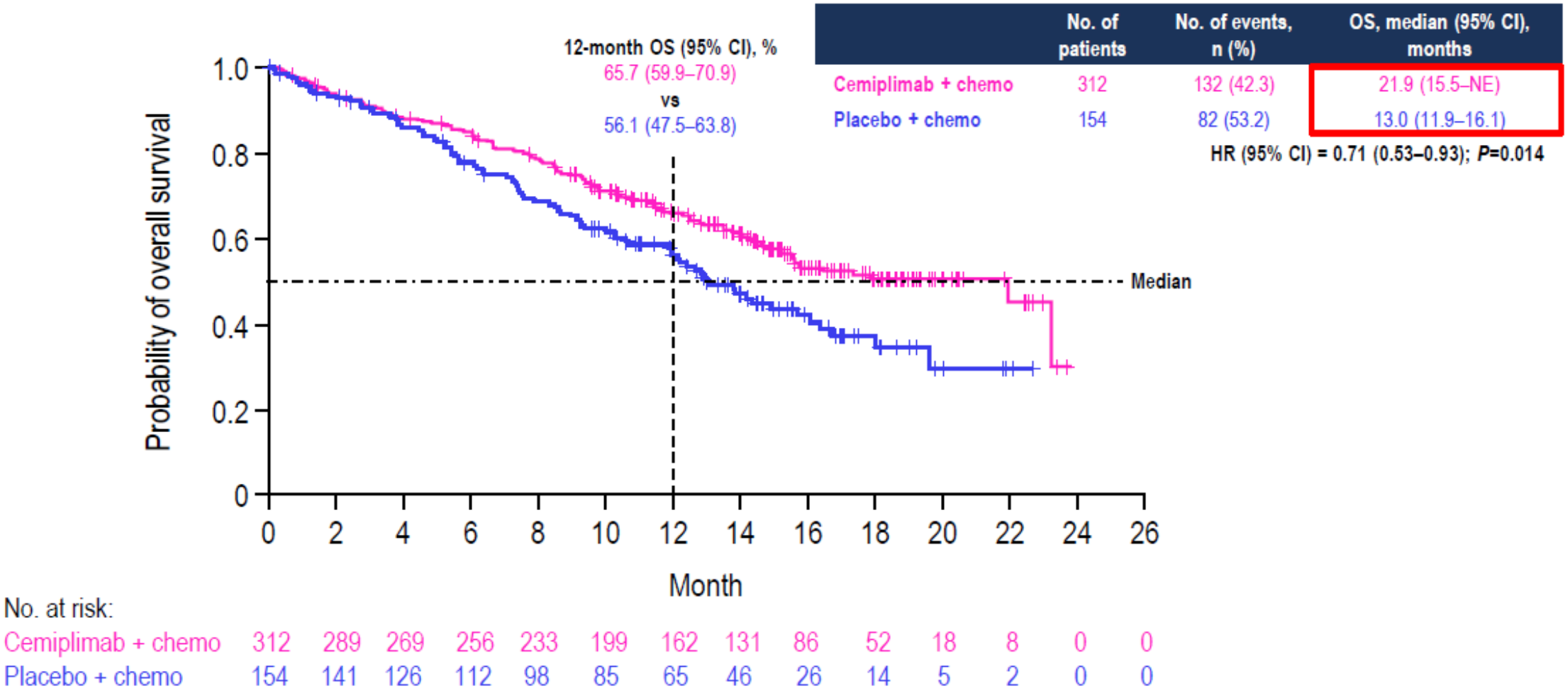


Gandhi L et al. N Engl J Med 2018





EMPOWER-Lung 3

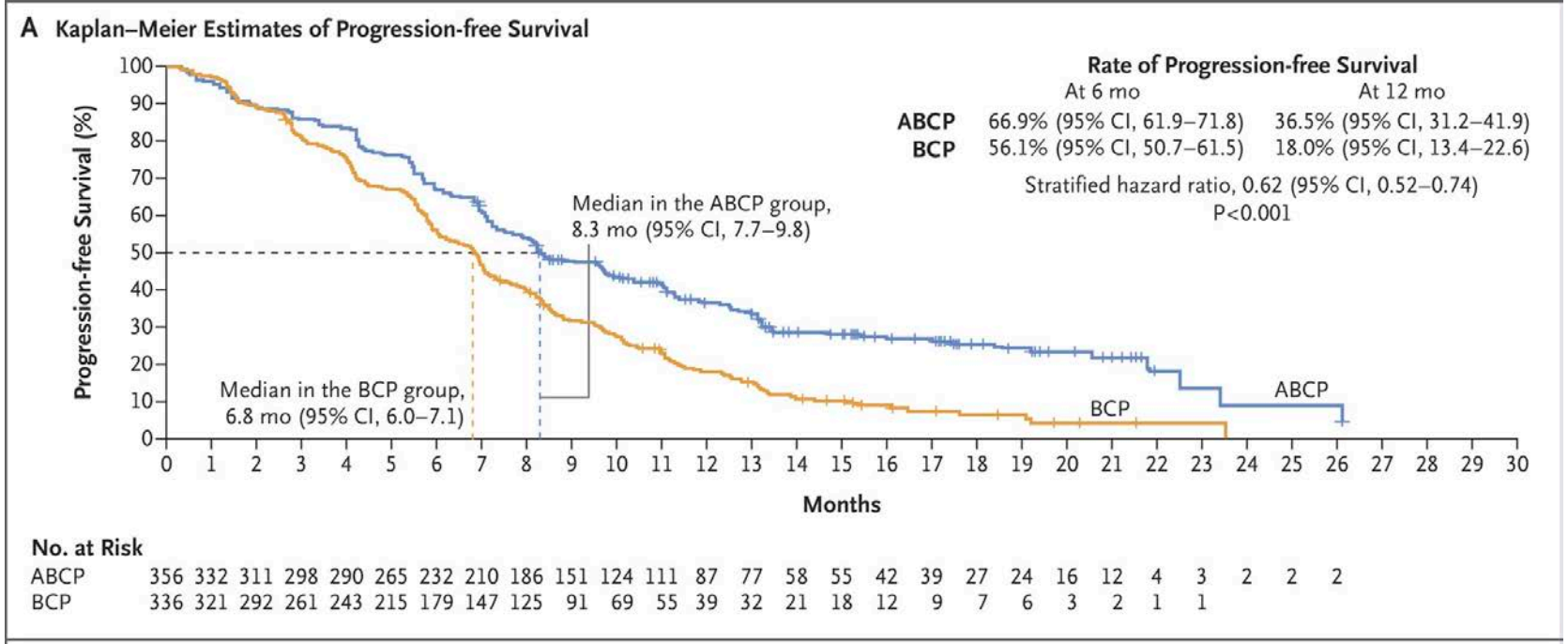


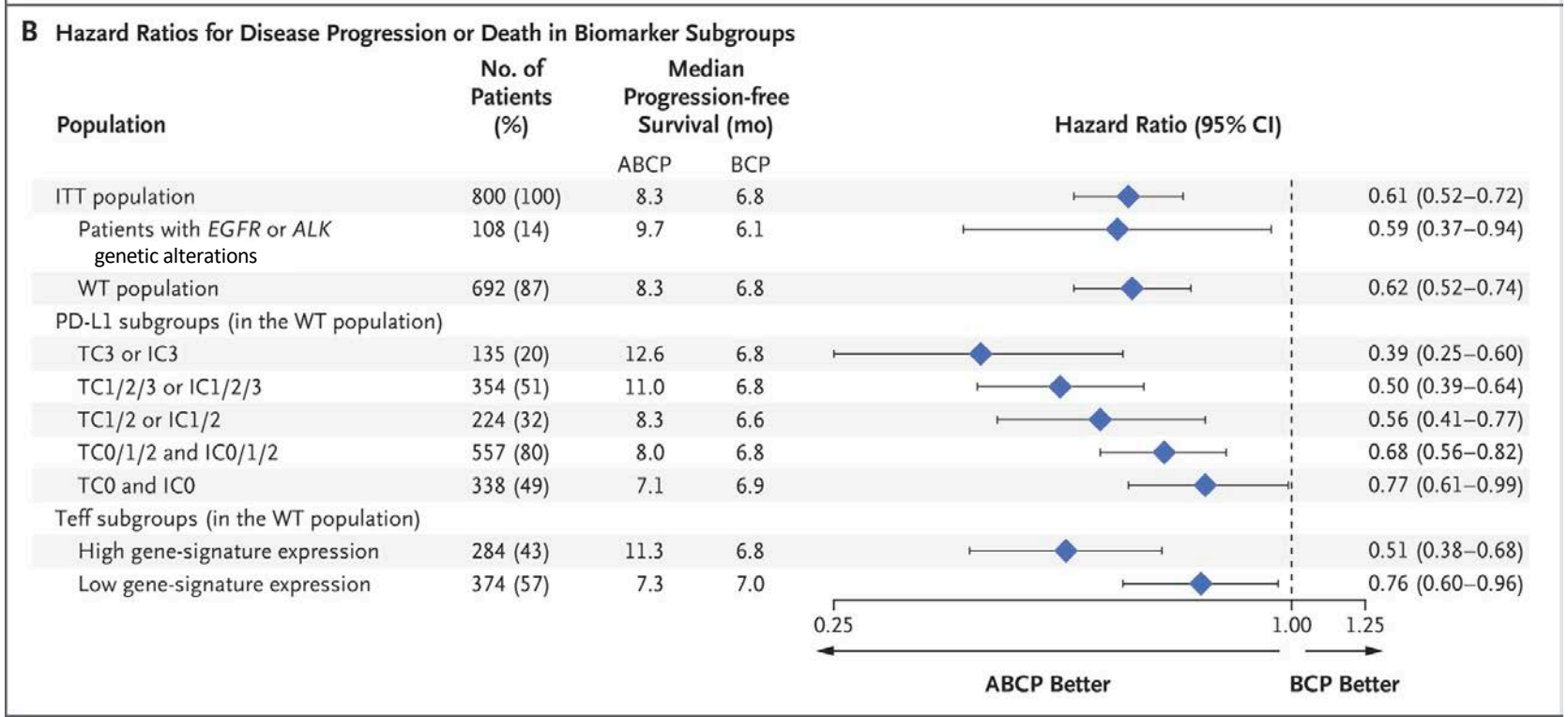
	No. of patients	No. of events, n (%)	OS, median (95% CI), months
Cemiplimab + chemo	312	132 (42.3)	21.9 (15.5–NE)
Placebo + chemo	154	82 (53.2)	13.0 (11.9–16.1)

HR (95% CI) = 0.71 (0.53–0.93); *P*=0.014

Gogishvili M et al. *Nat Med* 2022;28(11):2374-80.

IMpower 150





Socinski MA et al.
N Engl J Med
2018;378:2288-2301

CheckMate 9LA study design[a]

Key eligibility criteria
- Stage IV or recurrent NSCLC
- No prior systemic therapy
- No sensitizing *EGFR* mutations or known *ALK* alterations
- ECOG PS 0-1

Stratified by PD-L1[b] (< 1%[c] vs ≥ 1%), sex, and histology (SQ vs NSQ)

N = 719

R 1:1

n = 361: **NIVO** 360 mg Q3W + **IPI** 1 mg/kg Q6W + **Chemo[d]** Q3W (2 cycles)

n = 358: **Chemo[d]** Q3W (4 cycles) with optional pemetrexed maintenance (NSQ)

Until disease progression, unacceptable toxicity, *or* for 2 years for immunotherapy

Primary endpoint
- OS

Secondary endpoints
- PFS by BICR[e]
- ORR by BICR[e]
- Efficacy by tumor PD-L1 expression

Exploratory endpoints
- Safety

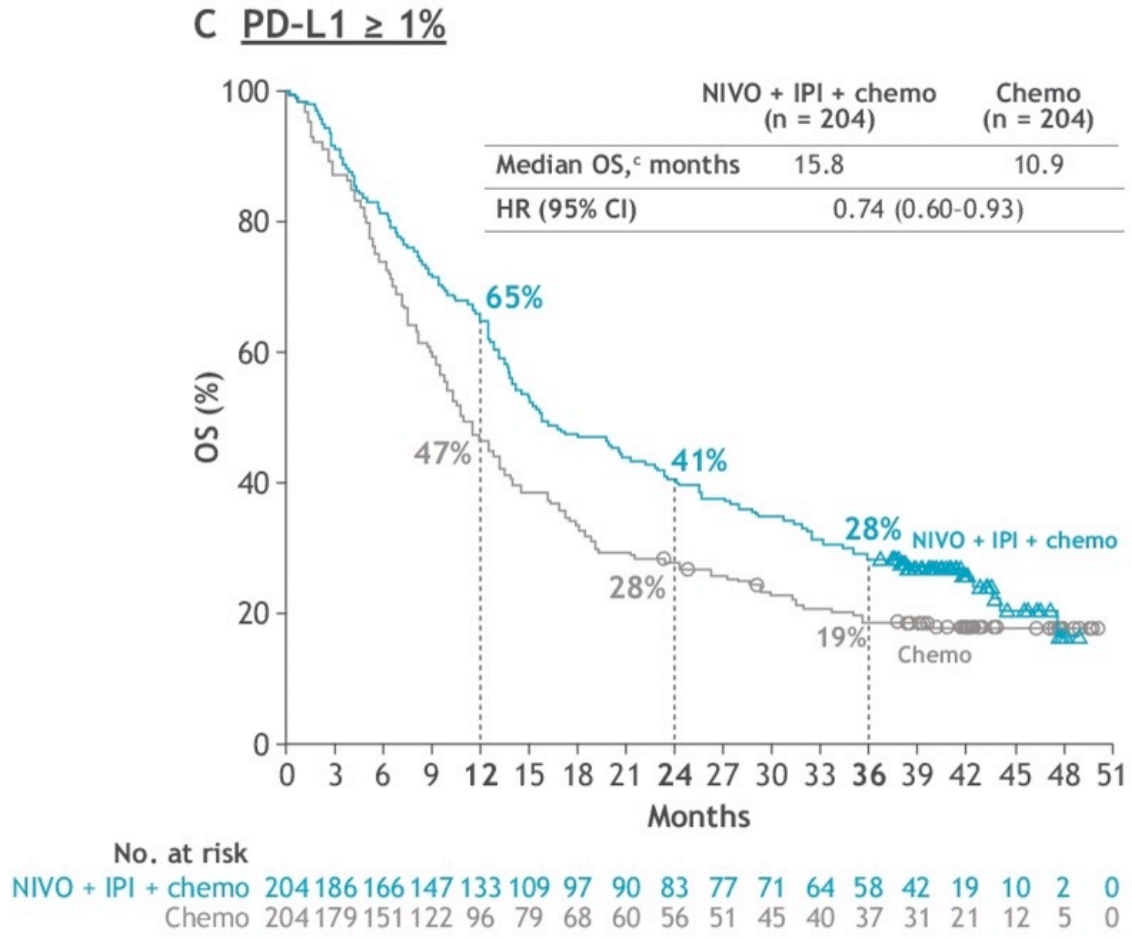
DBL: February 18, 2021; minimum / median follow-up for OS: 24.4 months / 30.7 months.

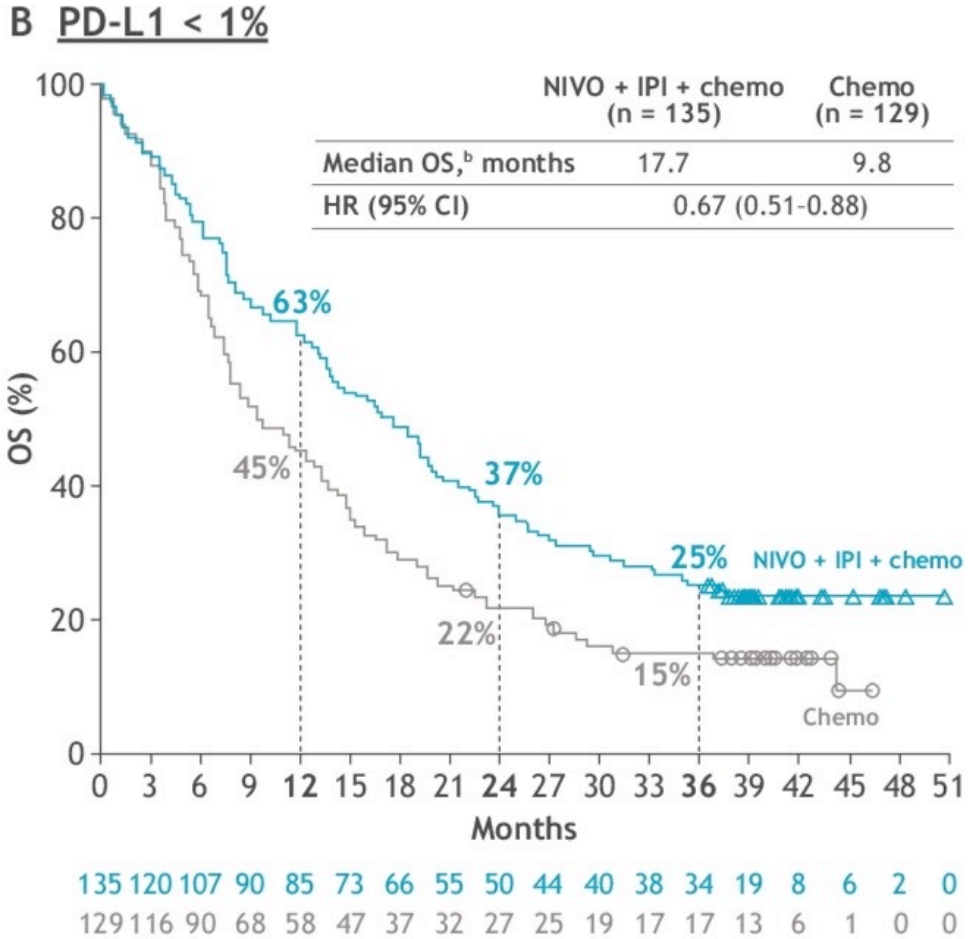
[a]NCT03215706; [b]Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako); [c]Patients unevaluable for PD-L1 were stratified to PD-L1 < 1% and capped to 10% of all randomized patients; [d]NSQ: pemetrexed + cisplatin or carboplatin; SQ: paclitaxel + carboplatin; [e]Hierarchically statistically tested.

Reck M. ASCO 2021.

CheckMate 9LA: 3-Year Update

OS in subgroups by PD-L1 expression





Paz-Ares, et al. ASCO 2022. Abstract 9026.

POSEIDON Study Design

Johnson ML. ASCO 2021

Phase 3, global, randomized, open-label, multicenter study

- Stage IV NSCLC
- No *EGFR* or *ALK* alterations
- ECOG PS 0 or 1
- Treatment-naïve for metastatic disease

N=1013 (randomized)

R 1:1:1

Stratified by:
- PD-L1 expression (TC ≥50% vs <50%)
- Disease stage (IVA vs IVB)
- Histology

Durvalumab 1500 mg + CT* q3w (4 cycles) → **Durvalumab 1500 mg q4w + pemetrexed† until PD**

Durvalumab 1500 mg + tremelimumab 75 mg + CT* q3w (4 cycles) → **Durvalumab 1500 mg q4w + tremelimumab 75 mg (week 16 only)‡ + pemetrexed† until PD**

Platinum-based CT* q3w (up to 6 cycles) → **Pemetrexed† until PD**

Primary endpoints
- PFS by BICR (D+CT vs CT)
- OS (D+CT vs CT)

Key secondary endpoints
- PFS by BICR (D+T+CT vs CT)
- OS (D+T+CT vs CT)
- OS in patients with bTMB ≥20 mut/Mb (D+T+CT vs CT)

Additional secondary endpoints
- ORR, DoR, and BOR by BICR
- PFS at 12 months
- HRQoL
- Safety and tolerability

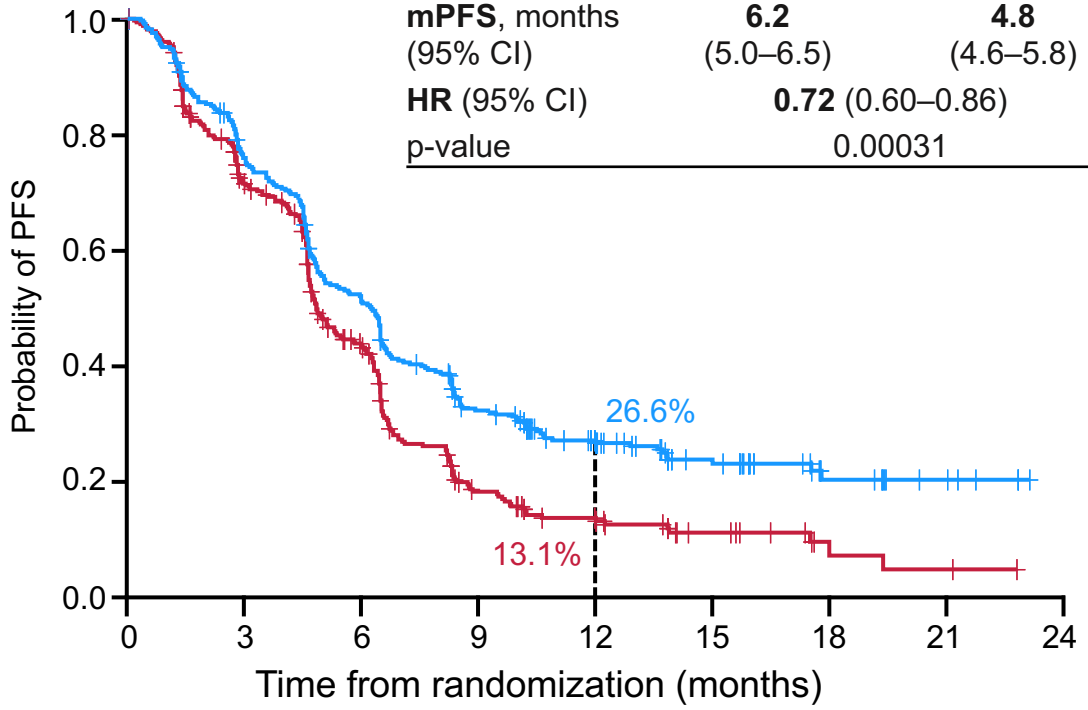
*CT options: gemcitabine + carboplatin/cisplatin (squamous), pemetrexed + carboplatin/cisplatin (non-squamous), or nab-paclitaxel + carboplatin (either histology);
†Patients with non-squamous histology who initially received pemetrexed during first-line treatment only (if eligible); ‡Patients received an additional dose of tremelimumab post CT (5th dose)

BICR, blinded independent central review; BOR, best objective response; bTMB, blood tumor mutational burden; D, durvalumab; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; HRQoL, health-related quality of life; Mb, megabase; mut, mutations; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PS, performance status; q3w, every 3 weeks; q4w, every 4 weeks; T, tremelimumab; TC, tumor cell

Durvalumab + Tremelimumab + CT vs CT: PFS and OS

PFS

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

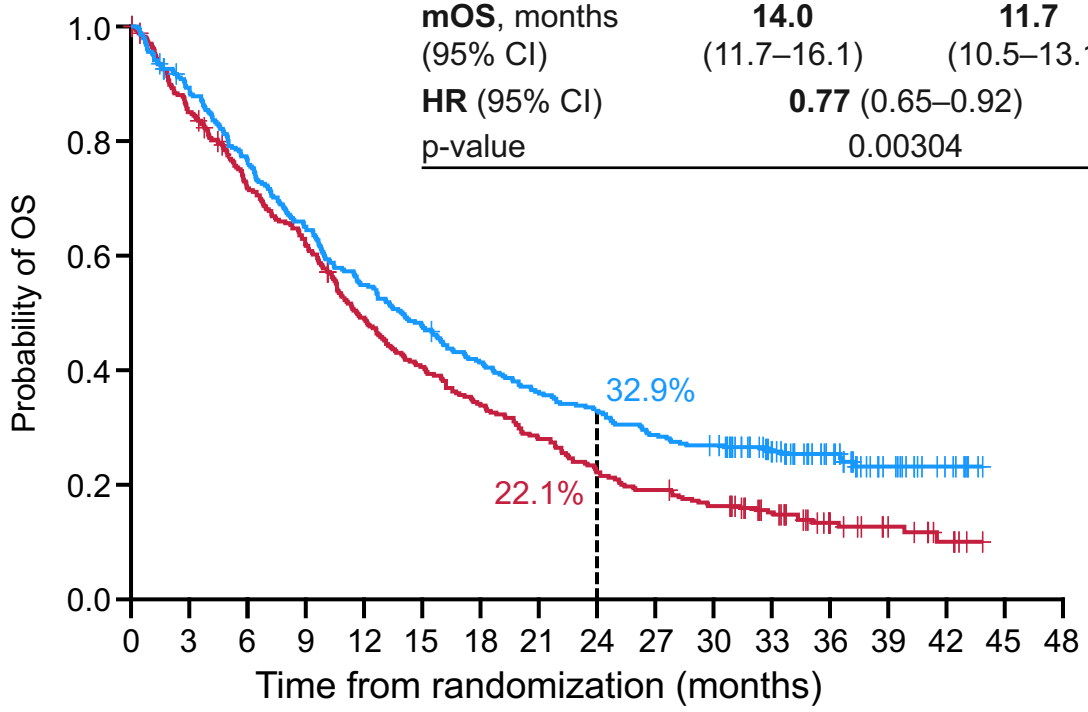


No. at risk

D+T+CT	338	243	161	94	56	32	13	5	0
CT	337	219	121	43	23	12	3	2	0

OS

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



No. at risk

D+T+CT	338	298	256	217	183	159	137	120	109	95	88	64	41	20	9	0	0
CT	337	284	236	204	160	132	111	91	72	62	52	38	21	13	6	0	0

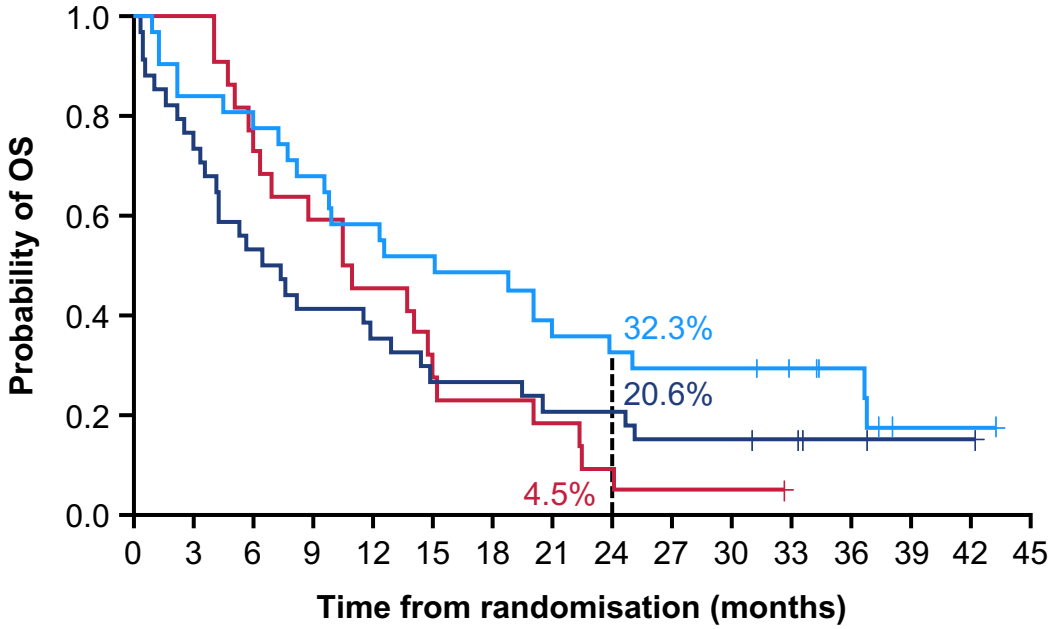
Johnson ML et al. *J Clin Oncol* 2023 Feb 20;41(6):1213-27; Johnson ML et al. WCLC 2021

OS by *STK11* Mutation Status

OS benefit observed for T+D+CT vs CT in STK11m with HR 0.56 and estimated 32.3% alive at 2 yrs vs 4.5%

*STK11*m

	T+D+CT	D+CT	CT
Events, n/N	24/31	29/34	21/22
mOS, mo (95% CI)	**15.0** (8.2–23.8)	**6.9** (3.6–12.9)	**10.7** (6.0–14.9)
HR* (95% CI)	**0.56** (0.30–1.03)	**1.03** (0.59–1.84)	–

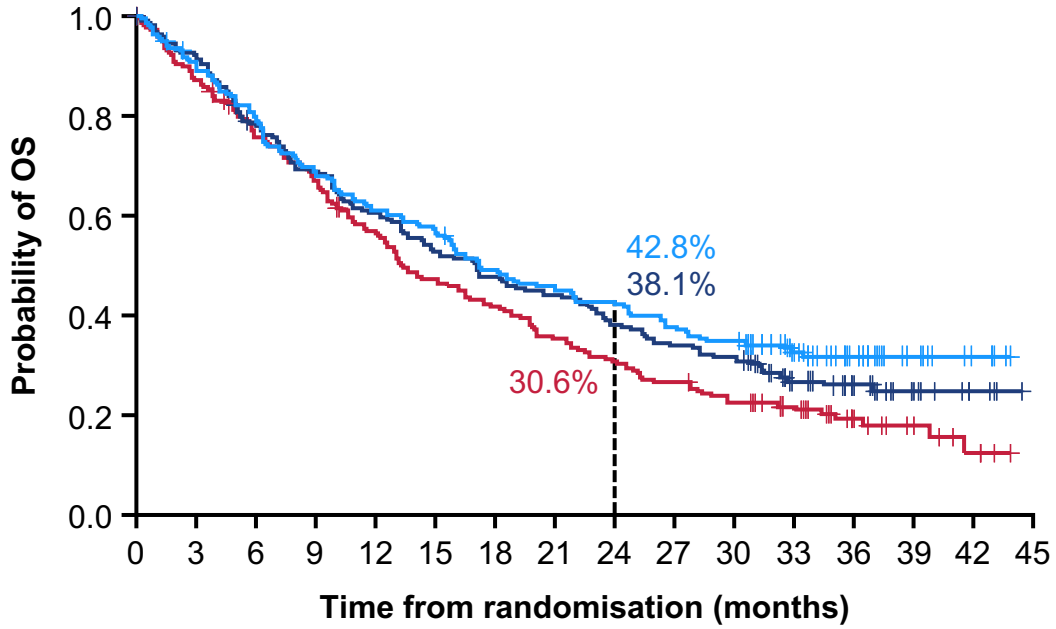


No. at risk

T+D+CT	31	26	24	21	18	15	15	11	10	9	9	7	5	1	1	0
D+CT	34	26	18	14	12	9	9	7	7	5	5	4	2	1	0	0
CT	22	22	16	13	10	6	5	4	1	1	1	0	0	0	0	0

*STK11*wt

	T+D+CT	D+CT	CT
Events, n/N	118/177	123/169	141/179
mOS, mo (95% CI)	**17.2** (14.9–22.1)	**17.1** (13.3–22.3)	**13.4** (11.5–17.5)
HR* (95% CI)	**0.73** (0.57–0.93)	**0.81** (0.64–1.04)	–



No. at risk

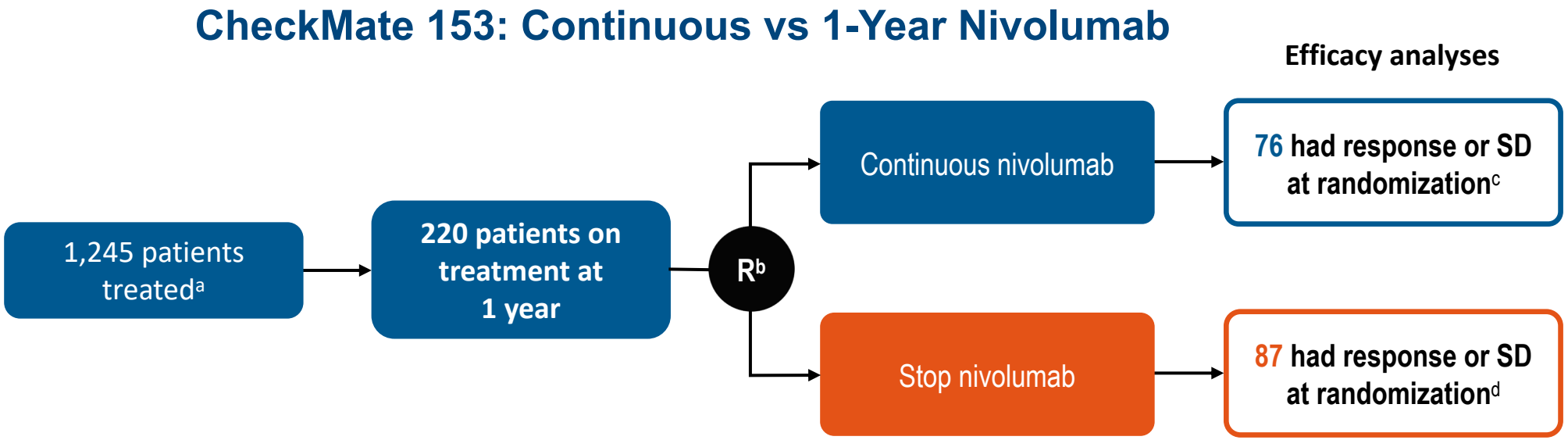
T+D+CT	177	159	140	120	107	100	85	79	74	65	60	40	25	11	5	0
D+CT	169	155	130	114	100	87	79	73	63	56	52	33	23	10	4	0
CT	179	154	131	116	97	80	71	60	52	45	37	29	15	8	4	0

DCO, data cut-off; mo, months; mOS, median OS

*HR <1 favours D (± T) + CT versus CT (unstratified analysis)
Assessed among mutation-evaluable patients with NSQ tumour histology; DCO, 12 Mar 2021

DURATION OF THERAPY

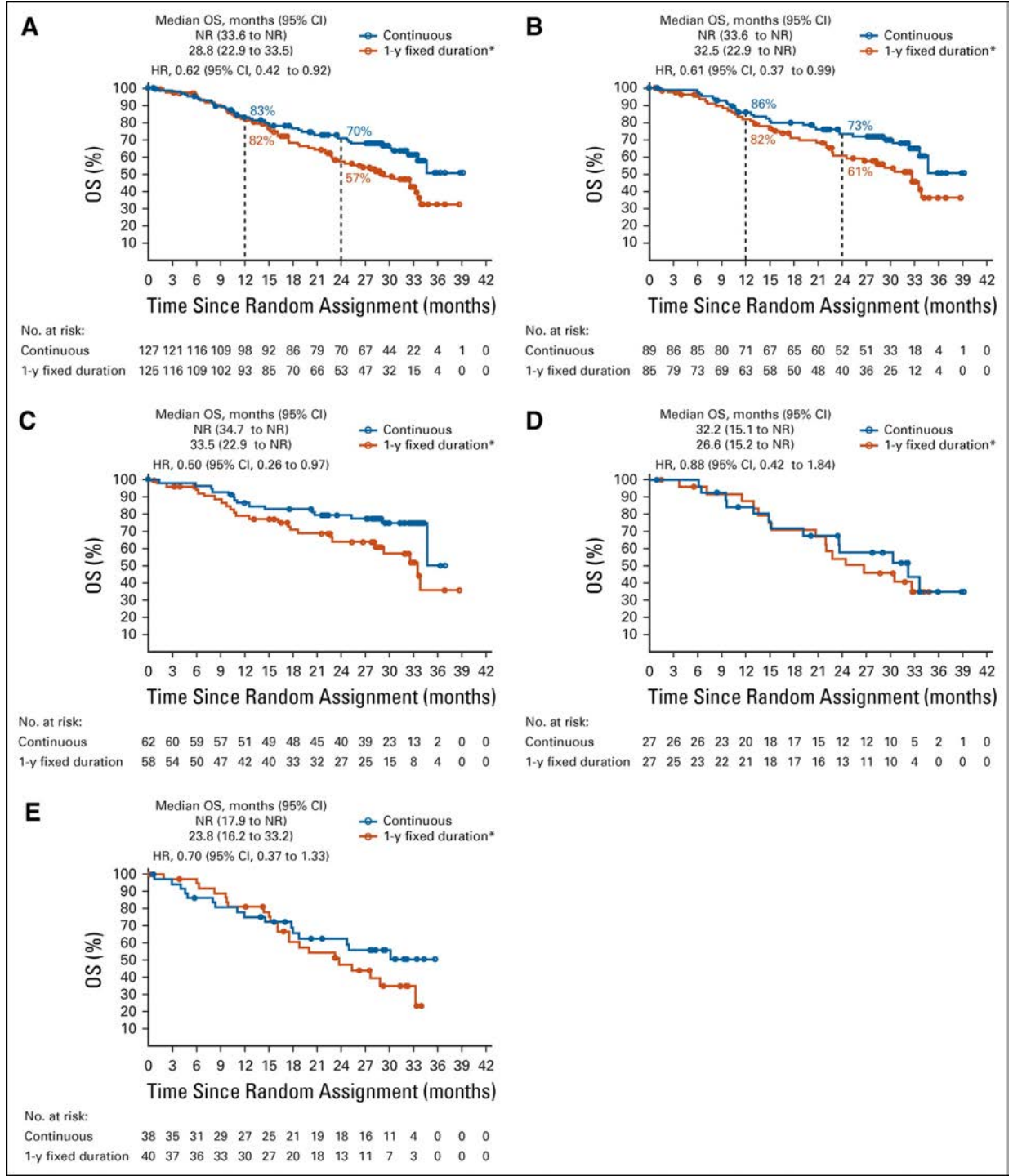
Among patients benefiting



a: Main US cohort; 1,025 patients discontinued prior to 1 year due to progression, death, study withdrawal, toxicity, or other reasons;
b: All 220 patients continuing on treatment at 1 year were randomized regardless of response status; 57 of these 220 patients had PD and were randomized as allowed per protocol; safety analyses were based on all 220 patients, 107 in the continuous arm and 113 in the stop arm; c8 patients discontinued treatment due to patient request or withdrawal of consent; d12 patients discontinued treatment due to patient request or withdrawal of consent

Spigel DR et al. *ESMO Congress*. 2017 Sep 8; Madrid, Spain.

Duration of Therapy



Waterhouse DM, et al. Journal of Clinical Oncology 2020;38(33):3863-73

Conclusions

- Monotherapy options include
  - Pembrolizumab PD-L1 $\geq$ 1%
  - Cemiplimab PD-L1 $\geq$ 50%
  - Atezolizumab PD-L1 $\geq$ 50%, but weakening OS data over time
- Nivolumab ipilimumab approved in PD-L1 positive patients
- Chemotherapy plus PD-1 inhibitor options
  - Chemo plus pembrolizumab or cemiplimab
- Chemotherapy plus PD-(L)1 inhibitor plus CTLA-4 options
  - 2 chemo cycles plus nivolumab ipilimumab, durvalumab plus tremelimumab

Agenda

Module 1: Incorporation of Immunotherapeutic Strategies into the Management of Nonmetastatic Non-Small Cell Lung Cancer (NSCLC) — Dr Heymach

Module 2: Contemporary Treatment for Localized or Metastatic NSCLC with an EGFR Mutation — Dr Yu

Module 3: Research Advances Shaping the Current and Future Treatment of Metastatic NSCLC with ALK Rearrangements, ROS1 Rearrangements or RET Fusions — Dr Langer

Module 4: Targeting MET, HER2 and KRAS Alterations in NSCLC — Dr Spigel

Module 5: Current Management of Metastatic NSCLC without a Targetable Tumor Mutation — Dr Garon

Module 6: Future Directions in the Management of Metastatic NSCLC — Dr Leal

RTP RESEARCH TO PRACTICE

Future directions in NSCLC: Tumor treating fields and datopotamab deruxtecan

Melissa Johnson, MD

Matthew Gubens, MD, MS

Jarushka Naidoo, MB BCH, MHS

RTP RESEARCH TO PRACTICE

On a scale of 1 to 5, with 1 being not at all and 5 being very well, to what extent do you feel you understand the translational science underlying tumor treating fields?

 Dr Garon	2	 Dr Yu	1
 Dr Heymach	1	 Dr Gubens	1
 Dr Langer	4	 Dr Johnson	3
 Dr Leal	5	 Dr Naidoo	1
 Dr Spigel	5		

RTP
RESEARCH
TO PRACTICE

Based on the published literature and your clinical experience, if any, with the tolerability and practical requirements of tumor treating fields, what degree of benefit would you need to see in the pivotal Phase III LUNAR trial to justify their use?

 Dr Garon	I will need to be convinced it is real, rather than a specific number	 Dr Yu	Significant benefit
 Dr Heymach	OS HR 0.7	 Dr Gubens	Perhaps HR for OS <0.8 and reasonable QoL data
 Dr Langer	OS HR <0.8 with *p*-value <0.05	 Dr Johnson	HR of 0.7 for median OS
 Dr Leal	Improvement in OS by 3 months	 Dr Naidoo	A major benefit, OS HR 0.4 or so
 Dr Spigel	Substantial OS advantage (4+ months)		

OS = overall survival; HR = hazard ratio; QoL = quality of life

RTP RESEARCH TO PRACTICE

If datopotamab deruxtecan were available today, in which situations would you want to use it for your patients with metastatic NSCLC?

 Dr Garon	Progression on or after chemo and a PD-1/PD-L1 inhibitor	 Dr Yu	After chemotherapy and immunotherapy
 Dr Heymach	Second line after chemo/IO	 Dr Gubens	Probably second line to start
 Dr Langer	Second or third line after failure of CPIs	 Dr Johnson	After chemo/IO for EGFR wild-type disease
 Dr Leal	After docetaxel	 Dr Naidoo	After progression on IO
 Dr Spigel	Second line and beyond (in wild-type settings)		

CPI = checkpoint inhibitor

RTP RESEARCH TO PRACTICE

EMORY
WINSHIP
CANCER
INSTITUTE
National Cancer Institute-Designated
Comprehensive Cancer Center

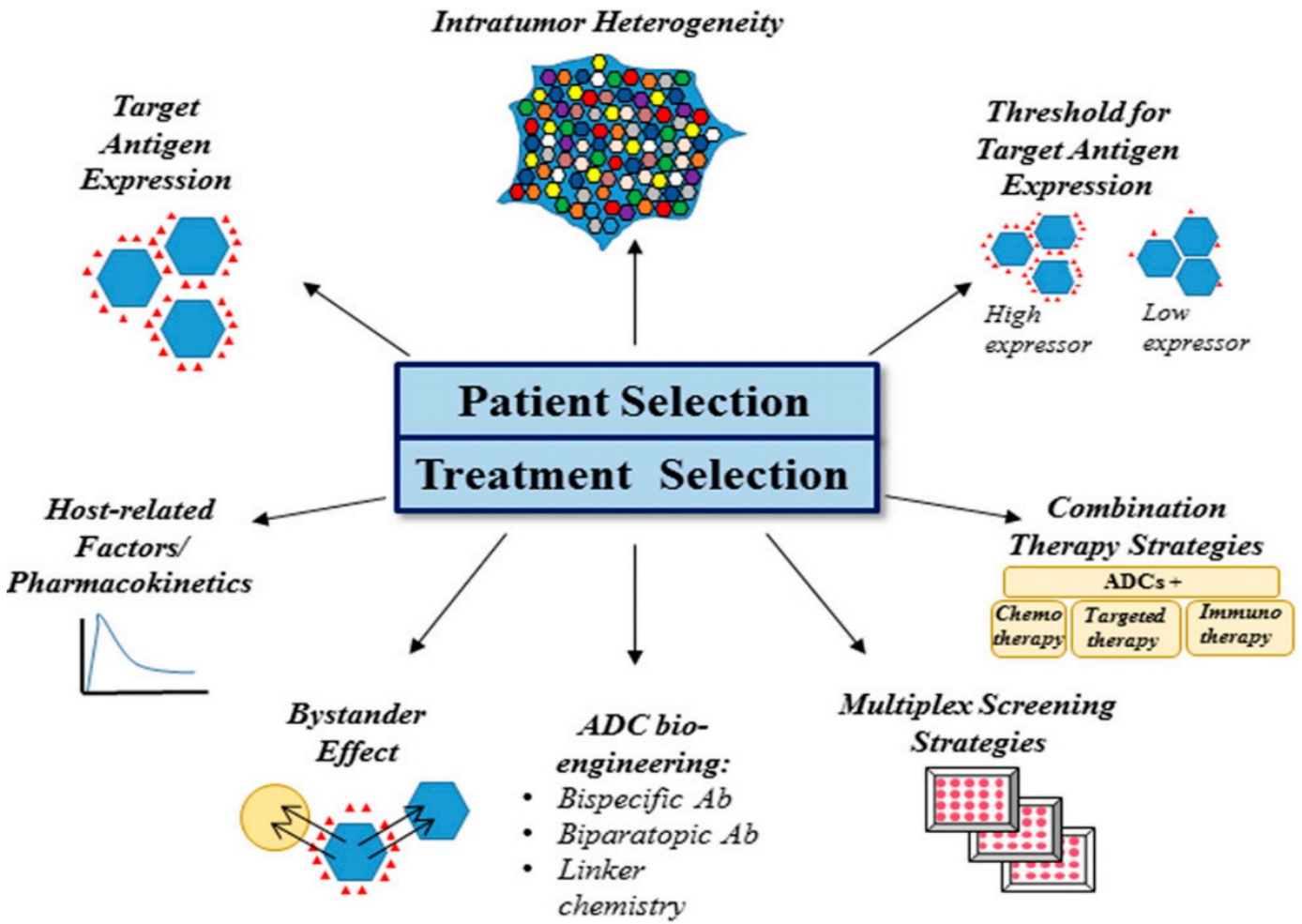
Future Directions in the Management of Metastatic NSCLC

Ticiana Leal, MD
Associate Professor of Medicine
Director, Thoracic Medical Oncology Program
Winship Cancer Institute
Emory University

Antibody-drug conjugates (ADCs)

- Antibody-drug conjugates (ADCs) are a promising drug platform designed to enhance the therapeutic index and minimize the toxicity of anticancer agents.

- Various ADCs have now entered the clinic and others are in clinical trials against a variety of solid tumors, including breast cancer, lung, ovarian, renal cell, mesothelioma, melanoma, and prostate cancer.



Teicher et al. Clin Cancer Res 2011
Makawita S, Meric-Bernstam F. ASCO Educational Book 2020.

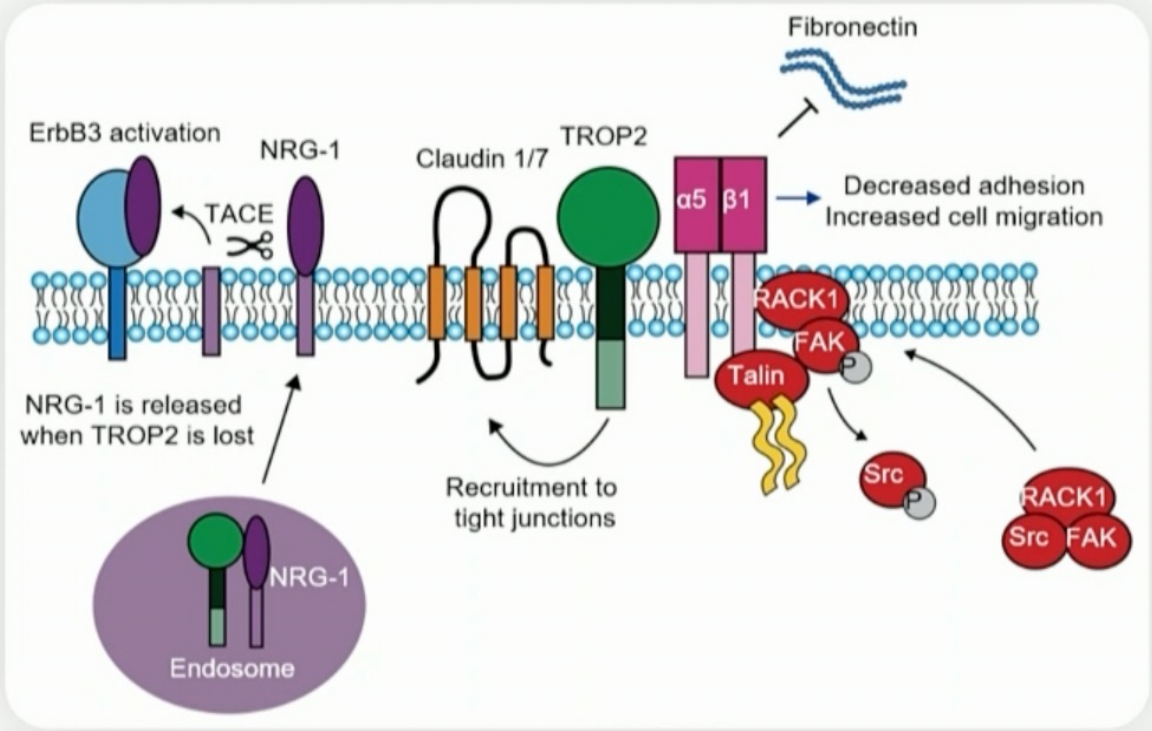
ADC Targets and Therapeutics in NSCLC

Target	Agent	Study	Sample Size—Patients (No.)	Treatment (RP2D or RDE)	ORR, No. (%)	Median PFS, months (95% CI)	Median OS, months (95% CI)	Safety and Toxicities (%)	References
TROP-2	Dato-DXd	Phase I, dose-escalation and expansion study	180	6 mg/kg every 3 weeks	25	6 (NE)	NE	Grade 3 stomatitis (2%), nausea (1%), neutropenia (1%). ILD by independent adjudication any grade: 4 mg/kg 10% (one grade 1, three grade 2, one grade 3), 6 mg/kg 4% (two grade 2), and 8 mg/kg 15% (three grade 1, five grade 2, one grade 3, three grade 5	Meric-Bernstam et al,[42] Spira et al,[43] Garon et al[44]
	SG	Phase I/II basket trial	54	10 mg/kg D1 D8 every 3 weeks	16.7	4.4 (3.6 to 9.7)	16.8 (9.0 to 21.9)	Grade 3 nausea (3.6%), diarrhea (7.9%), vomiting (2.8%) grade 3 anemia (10.3%) Neutropenia: grade 3 28.9%, grade 4 13.5% Febrile neutropenia: grade 3 4.2%, grade 4 1.0%	Bardia et al[23]
HER3	HER3-DXd	Phase I dose-escalation/ expansion study	57 (EGFRm) 47 (EGFRwt)	5.6 mg/kg every 3 weeks	39 (EGFRm) 28 (EGFRwt)	EGFRm 8.2 (4.4 to 8.3) EGFRwt 5.4 (3. 9 to 12.7)	NE	Grade 3 thrombocytopenia 30%, anemia 9%, neutropenia 19%, Adjudicated treatment-related ILD 7% (two grade 1, one grade 2, one grade 3)	Janne et al[45] Steuer et al[46]
MET	Teliso-V	Phase I dose-escalation/ expansion study	16 c-MET+ by IHC	2.7 mg/kg every 3 weeks	18.8	5.7 (1.2 to 15.4)	NE	Grade 3 fatigue (14.3%), grade 3 anemia (7.1%), grade 3 neutropenia (7.1%) grade 3 hypoalbuminemia (4%), grade 3 peripheral edema (2.1%), grade 3 hypophosphatemia (2.1%)	Strickler et al[47]
		Phase II	136 c-MET+ by IHC: OE ≥25% 3+	1.9 mg/kg every 2 weeks	36.5	NE	NE	Any grade AEs: peripheral sensory neuropathy (25%), nausea (22.1%), hypoalbuminemia (20.6%)	Camidge et al[48]
CEACAM-5	TUSA	Phase I dose-expansion study	92 CEACAM+ by IHC: 64 high 28 moderate	100 mg/kg every 2 weeks	20.1 (high) 7.1 (moderate)	NE	NE	Grade 3 keratopathy (10.9%), dyspnea (11%), asthenia (4.3%)	Gazzah et al[49]
B7-H3	I-DXd	Phase I dose escalation/ expansion study. SCLC cohort	19	12 mg/kg every 3 weeks	58	NE	NE	Grade 3 anemia (19%), neutropenia (7%), nausea (3%), pneumonia (3%). Any grade IRR 32%, one grade 3, one case of grade 5 ILD	Doi et al[50]

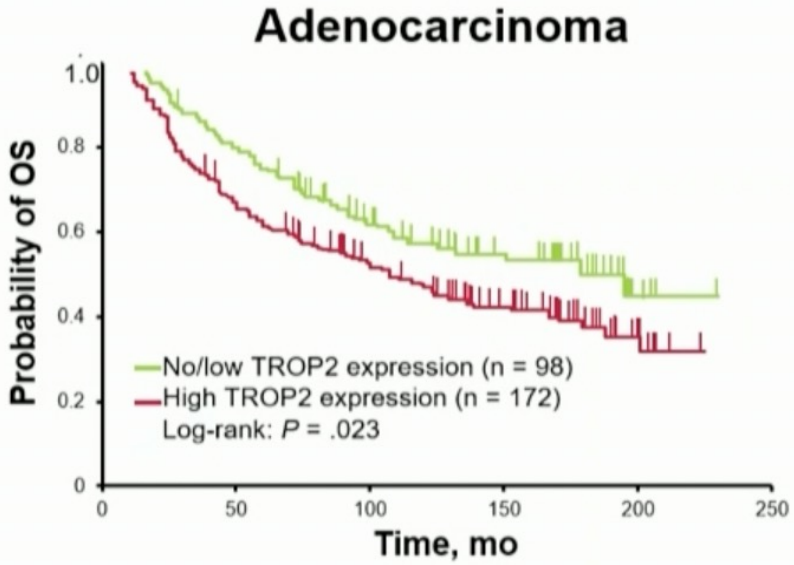
Rosner et al. ASCO Educational Book 2023.

TROP2 in NSCLC[1]

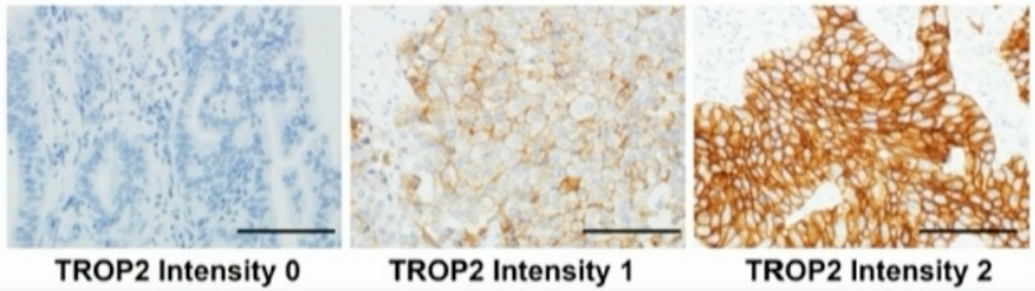
- TROP2, a transmembrane glycoprotein, is highly expressed in NSCLC and other solid tumors
  - High TROP2 expression is associated with poor prognosis, making it a promising therapeutic target



Lenart S et al. *Cancers (Basel)*. 2020;12:3328

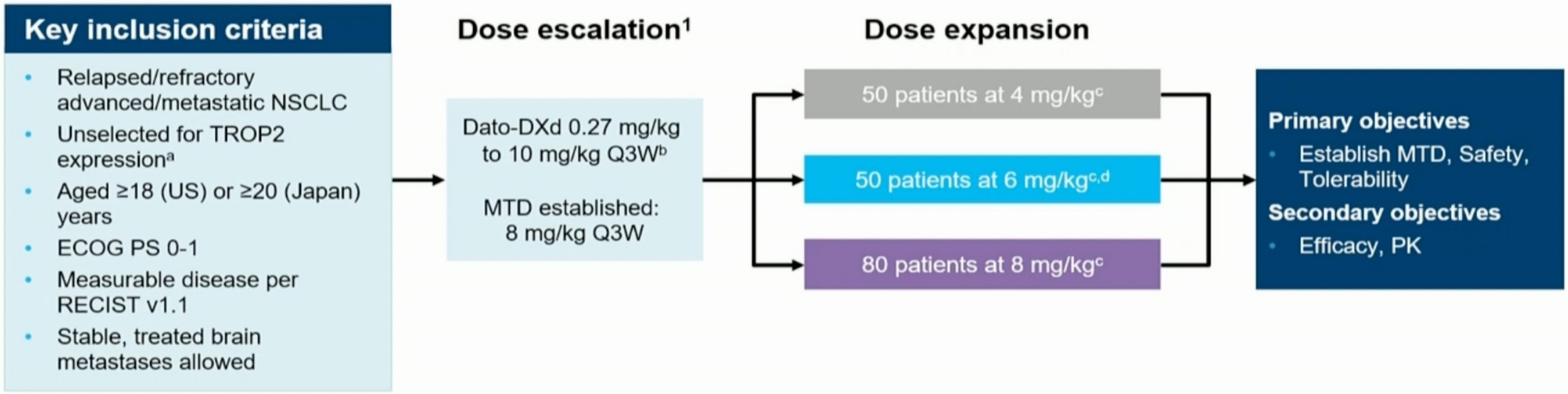


- There is no current testing recommendation for TROP2
- Identified by IHC



TROPION-PanTumor01 (NCT03401385) Study Design

Phase 1 FIH Dose Escalation and Expansion Study



- NSCLC enrollment complete[d]
- TNBC cohort 6 mg/kg Q3W is enrolling; cohorts in other tumor types may be added
- Here we report updated results for the NSCLC dose expansion cohort (175 patients treated at 4, 6, or 8 mg/kg of Dato-DXd)

[a]Pretreatment tumor tissue was required for retrospective analysis of TROP2 expression. [b]The 4, 6, and 8 mg/kg dose levels are being further evaluated for safety and efficacy. A TNBC cohort is currently open for enrollment at 6 mg/kg, although no TNBC patients are included in this analysis. [c]Inclusive of patients treated in dose escalation and dose expansion. [d]The current analysis includes 45 patients treated at the 6 mg/kg dose (data cutoff: 4 September 2020).
ECOG PS, Eastern Cooperative Oncology Group performance status; FIH, first-in-human; MTD, maximum tolerated dose; NSCLC, non–small cell lung cancer; PK, pharmacokinetics; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TNBC, triple-negative breast cancer; TROP2, trophoblast cell surface antigen 2; Q3W, once every 3 weeks; US, United States.

1. Lisberg AE, et al. Presented at: ASCO Annual Meeting; May 29-June 2, 2020; virtual meeting. Abstract 9619.

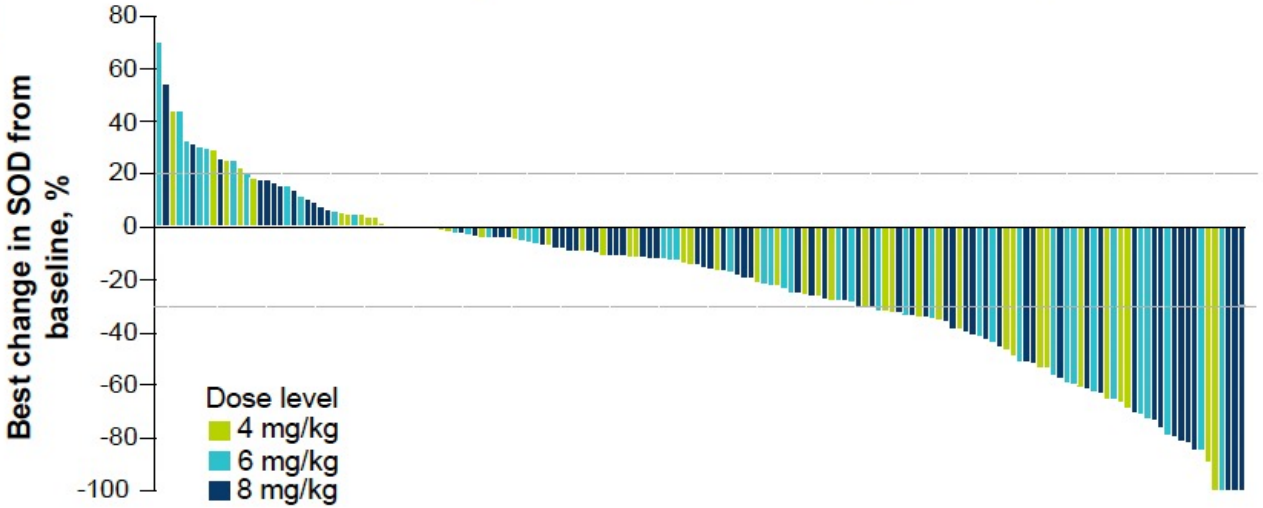
TROPION-PanTumor01: Antitumor Activity of Dato-DXd

Best Overall Response (BICR)

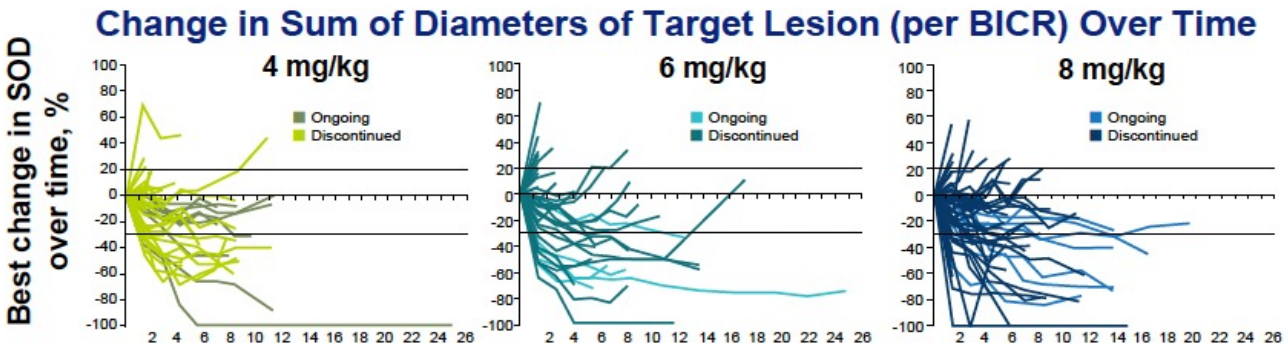
Patients[a]	Dato-DXd dose		
	4 mg/kg (n=50)	6 mg/kg (n=50)	8 mg/kg (n=80)
ORR, n (%)[b]	12 (24)	14 (28)	19 (24)
CR, n (%)	0	0	1 (1)
PR, n (%)[b]	12 (24)	14 (28)	18 (23)
SD, n (%)	25 (50)	20 (40)	42 (53)
Non-CR/PD, n (%)	1 (2)	2 (4)	2 (3)
PD, n (%)	7 (14)	10 (20)	8 (10)
NE, n (%)	5 (10)	5 (10)	9 (11)
DOR, median (95% CI), mo	NE (2.8-NE)	10.5 (5.6-NE)	9.4 (5.8-NE)

- Antitumor activity was observed at 4-, 6-, and 8-mg/kg doses of Dato-DXd
- Most responses were durable over time, including a median duration of response of 10.5 months in the 6-mg/kg cohort

Best Change in Sum of Diameters (per BICR)



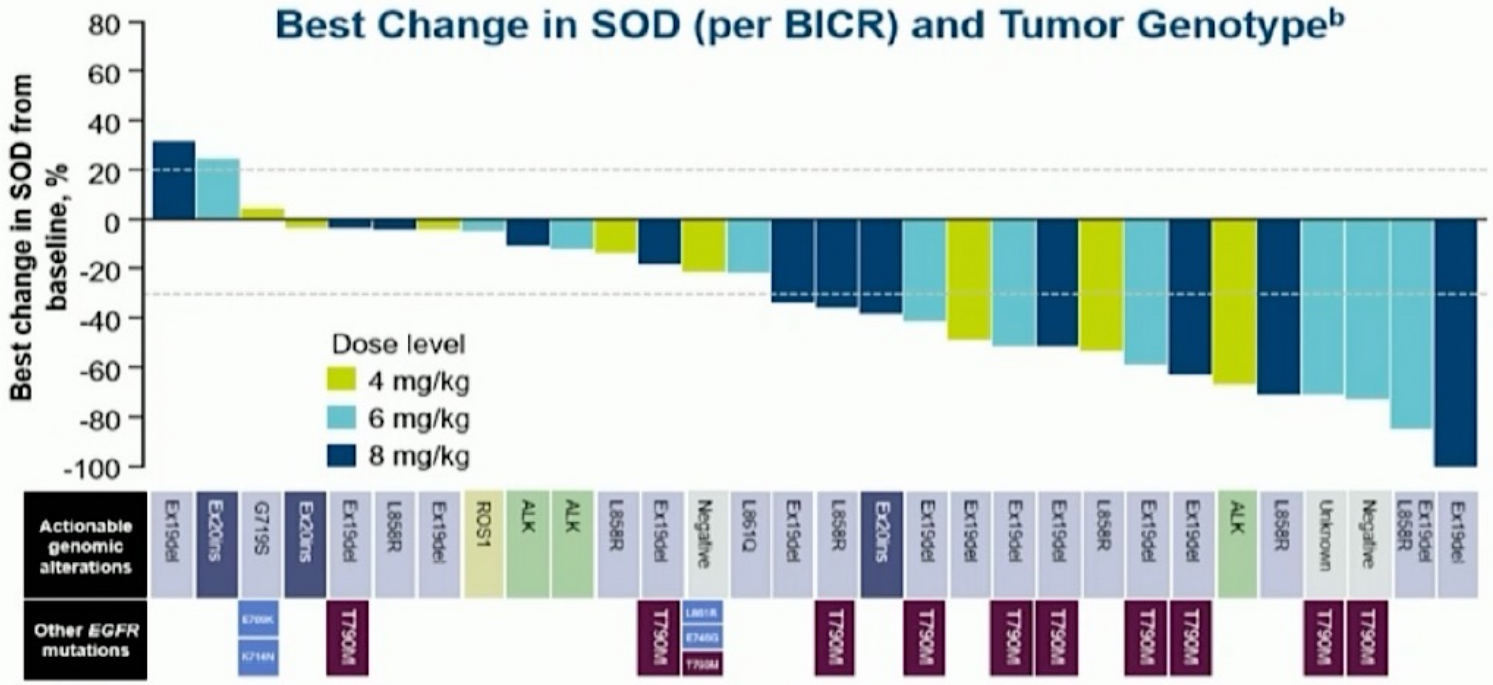
Change in Sum of Diameters of Target Lesion (per BICR) Over Time



PanTumor01 AGA Subset Efficacy Analysis

Patients[a]	Dato-DXd n=34
ORR, n (%)	12 (35)
CR	0
PR	12 (35)
SD, n (%)	14 (41)
Non-CR/PD, n (%)	2 (6)
PD, n (%)	2 (6)
NE, n (%)	4 (12)
DOR, median (95% CI), mo	9.5 (3.3-NE)

Clinical activity was observed in *EGFR*-sensitizing mutations (Ex19del, L858R), including after osimertinib, and across other AGAs



Data cutoff: April 6, 2021.

[a]Includes response-evaluable patients who had ≥1 postbaseline tumor assessment or discontinued treatment. [b]Four patients were not included in the waterfall plot: 2 who did not have a target lesion per BICR and 2 who did not have on-study treatment images.

AGA, actionable genomic alteration; ALK, anaplastic lymphoma kinase; BICR, blinded independent central review; CR, complete response; Dato-DXd, datopotamab deruxtecan; DOR, duration of response; *EGFR*, epidermal growth factor receptor; ESMO, European Society for Medical Oncology; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; ROS1, ROS proto-oncogene 1; SD, stable disease; SOD, sum of diameters.

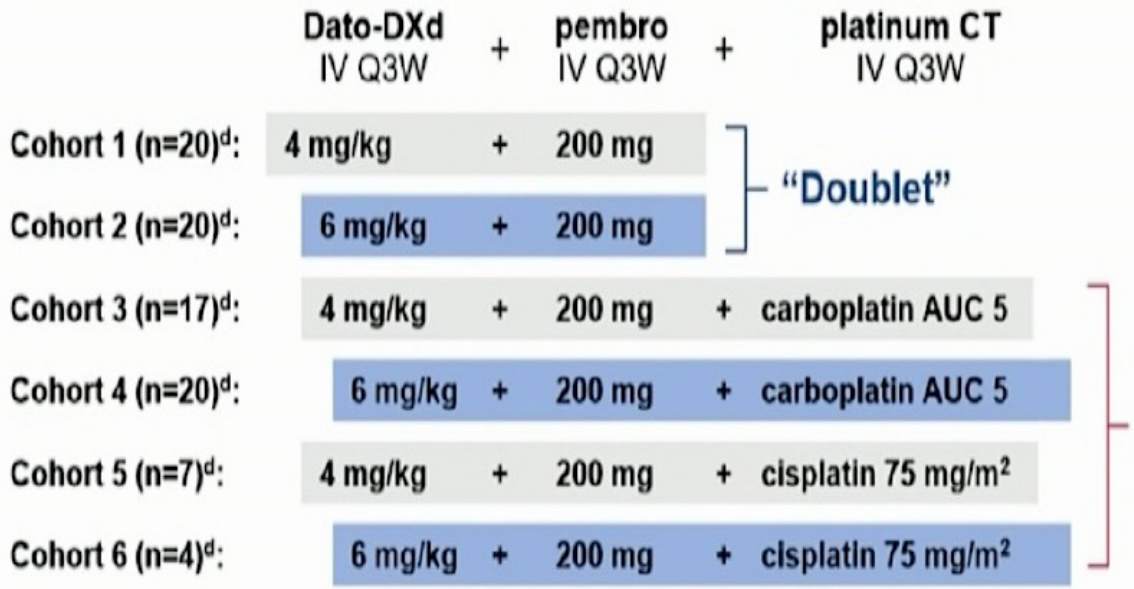
Garon EB, et al. ESMO 2021. Abstract LBA49.

TROPION-Lung02: Study Design and Endpoints

Phase 1b study evaluating Dato-DXd + pembrolizumab +/- platinum CT in advanced NSCLC without actionable mutations (NCT04526691)

Key eligibility

- Advanced/metastatic NSCLC
- Dose confirmation[b]: ≤2 lines of prior therapy[c]
- Dose expansion
  - ≤1 line of platinum-based CT (cohorts 1 and 2)[c]
  - No prior therapy (cohorts 3-6)[c]



- **Primary objectives:** safety and tolerability
- **Secondary objectives:** efficacy, pharmacokinetics, and anti-drug antibodies

Levy et al. WCLC 2022.

TROPION-Lung02: Efficacy

Antitumor Activity

In the overall population:

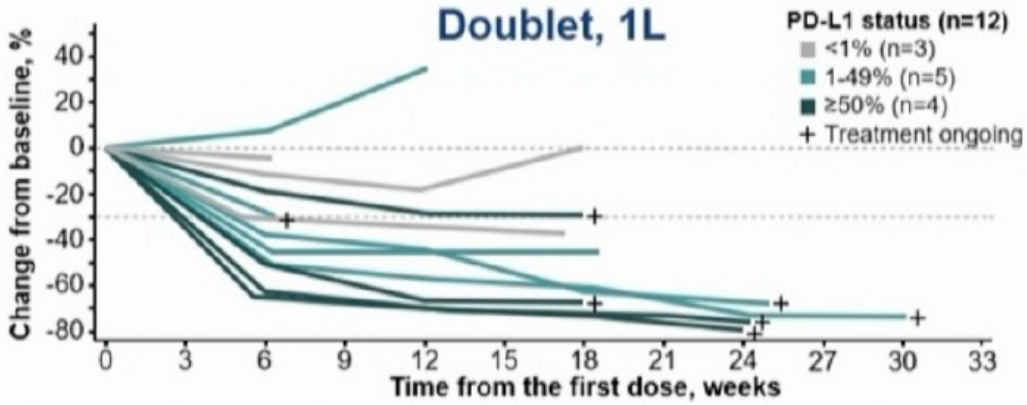
ORRs (confirmed + pending) of 37% and 41% were seen with doublet (n=38) and triplet (n=37) therapy, respectively; both groups had 84% DCR

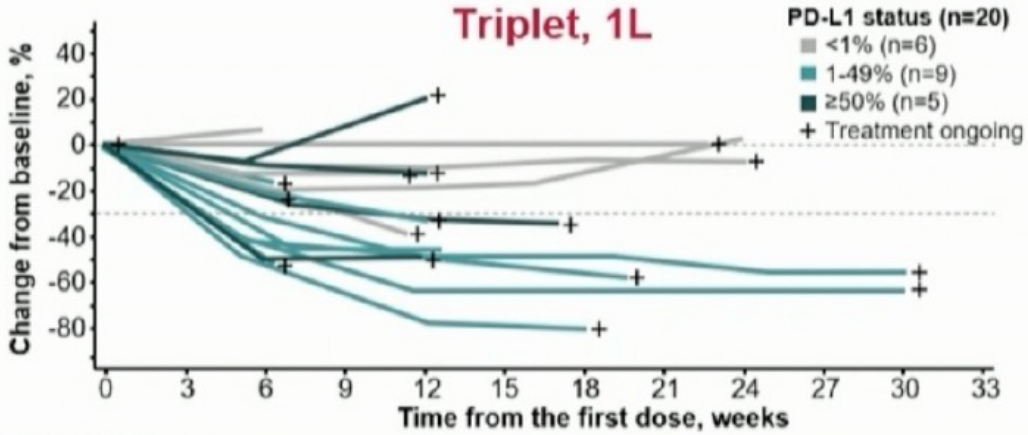
BOR With 1L Therapy For Advanced NSCLC[a,b]

Response, n (%)	Doublet (n=13)	Triplet (n=20)
ORR confirmed + pending	**8 (62%)**	**10 (50%)**
CR	0	0
PR confirmed	8 (62%)	7 (35%)
PR pending	0	3 (15%)
SD	5 (39%)	8 (40%)
DCR	13 (100%)	18 (90%)

- As 1L therapy, the doublet and triplet yielded ORRs (confirmed + pending) of 62% and 50%, respectively
- As 2L+ therapy, respective ORRs (confirmed + pending) were 24% and 29%

Percent Change in Sum of Diameters[a]





Data cutoff: May 2, 2022.
BOR, best overall response; CR, complete response; DCR, disease control rate; ORR, overall response rate; PR, partial response; SD, stable disease.
[a] By investigator. [b] BOR is based on response evaluable patients who have ≥1 postbaseline tumor assessment or discontinued.

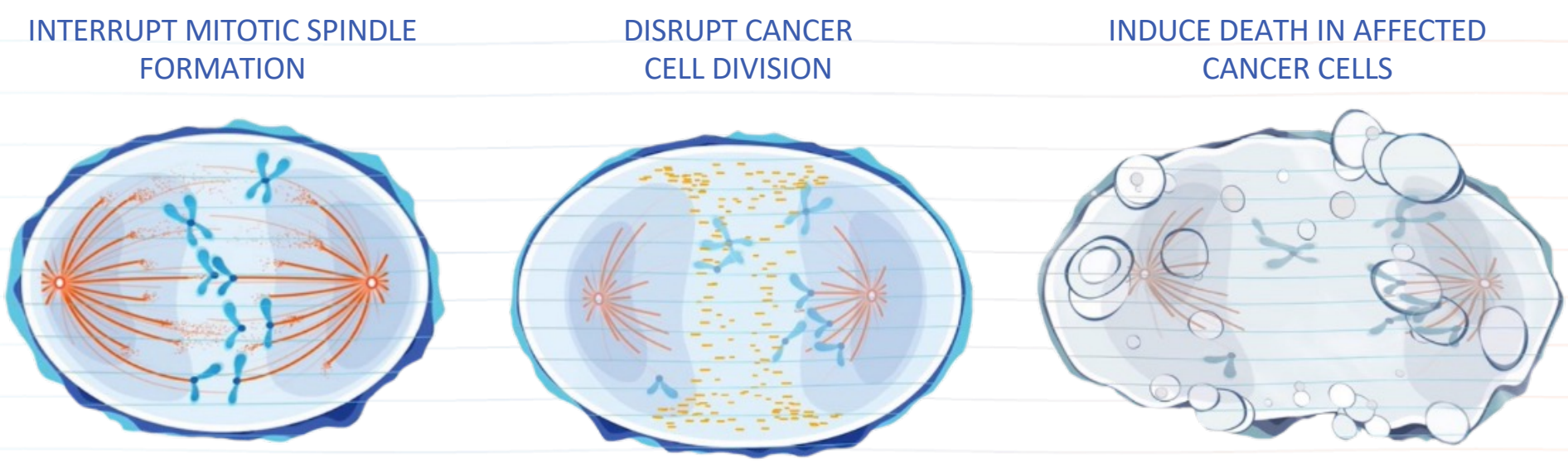
Levy et al. WCLC 2022.

Dato-DXd Clinical Development

Disease	Phase/Description	2018	2019	2020	2021	2022	2023	2024
Advanced Solid Tumors	Phase 1 2L+ monotherapy	TROPION-PanTumor01 Relapsed/refractory advanced/metastatic NSCLC, TNBC, HR+/HER2– negative BC, urothelial cancer, gastric cancer, esophageal cancer, SCLC, and other solid tumors (DS1062-A-J101, NCT03401385)						Recruiting North America, Asia
	Phase 1/2 2L+ monotherapy					TROPION-PanTumor02 Advanced/metastatic NSCLC, TNBC, and other solid tumors (NCT05460273)		Recruiting China
Advanced/ Metastatic NSCLC	Phase 3 2L+ monotherapy vs docetaxel			TROPION-Lung01 Without or with AGA and previously treated with platinum CT + immunotherapy (DS1062-A-U301, NCT04656652)				Recruiting North America, Europe, Asia
	Phase 2 3L+ monotherapy				TROPION-Lung05 With AGA who progressed on platinum CT and ≥1 line of targeted therapy (DS1062-A-U202, NCT04484142)			Recruiting North America, Europe, Asia
	Phase 1b 1L+ combination with pembrolizumab ± platinum CT			TROPION-Lung02 Without AGA and previously treated or treatment-naive in a metastatic setting (DS1062-A-U102, NCT04526691)				Recruiting North America, Europe, Asia
	Phase 3 1L combination with pembrolizumab				TROPION-Lung08 Without AGA and treatment-naive in a metastatic setting with high PD-L1 (DS1062-A-U304, NCT05215340)			Recruiting North America, Europe, Asia
	Phase 1b 1L+ combination with durvalumab ± carboplatin			TROPION-Lung04 Without AGA and previously treated or treatment-naive in a metastatic setting (DS1062-A-U104, NCT04612751)				Recruiting North and South America, Europe, Asia

TROPION-Lung07 (September 2022): Phase III first-line combination with pembrolizumab ± platinum chemotherapy, without actionable genomic alterations (Recruiting, United States, Asia, Australia)

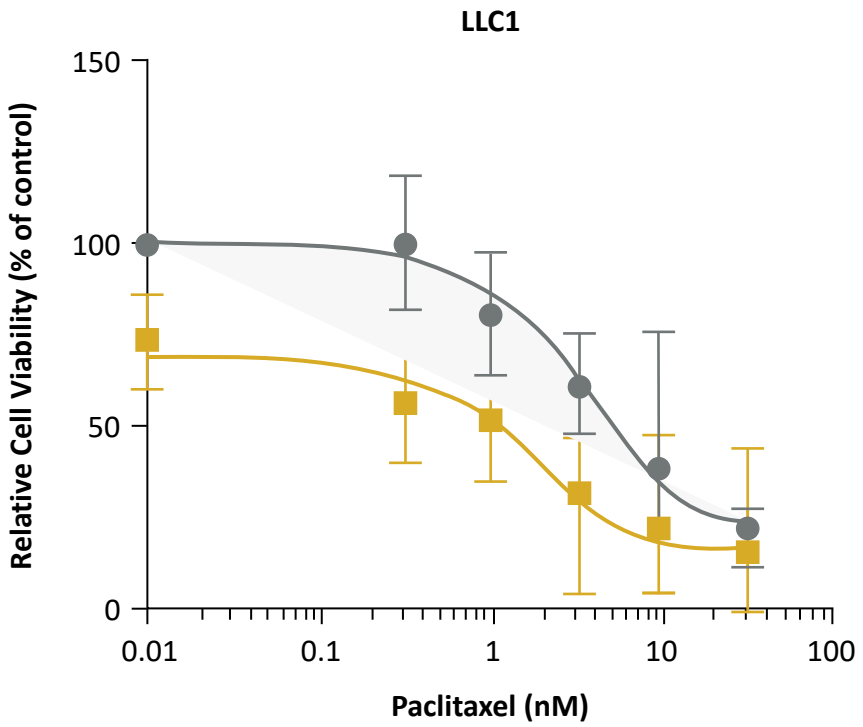
Tumor Treating Fields: A Platform Therapy Targeting Dividing Cancer Cells

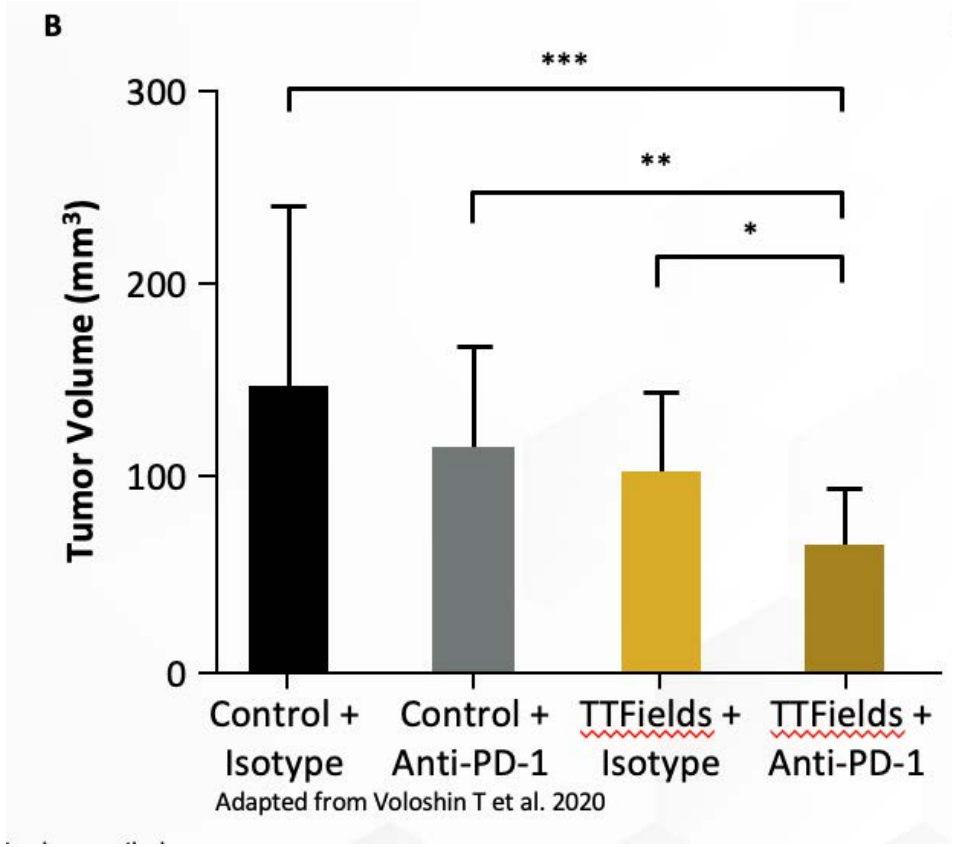


Tumor treating fields are alternating electric fields tuned to specific frequencies that disrupt cancer cell division (mitosis)

Arvind R, et al. *Crit Rev Oncol Hematol* 2021;168:103535.

Preclinical studies have demonstrated the effficay of TTFields Treatment in combination with taxanes or immunotherapy





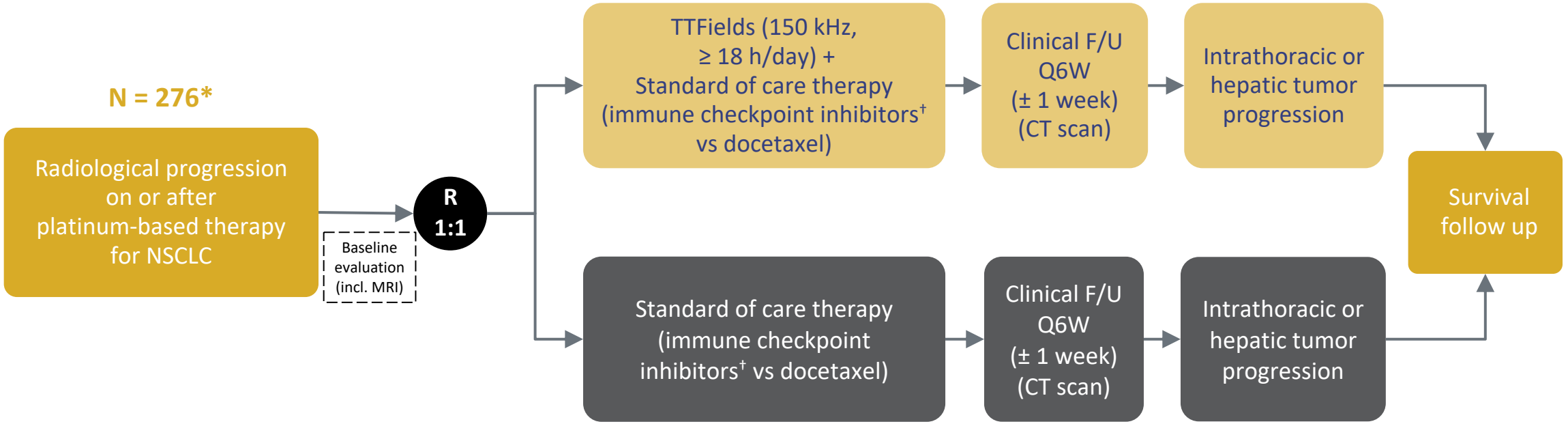
Paclitaxel Paclitaxel + TTFields

LLC1, murine Lewis Lung Carcinoma cell line.

Giladi M, et al. *Semin Oncol.* 2014;41(suppl 6):S35–S41. 2. Mumblat H, et al. *Lung Cancer.* 2021;160;99–110. 3. Voloshin T, et al. *Cancer Immunol Immunother.* 2020;69(7):1191–1204.

LUNAR
Lung Cancer

LUNAR: Phase 3 Trial Design[1,2]



Start date: Dec 2016
Primary completion: Sept 2023
Study sites: 124 (North America, Europe, Asia)

Stratification:
- Standard of care therapy (immune checkpoint inhibitors vs docetaxel)
- Histology (squamous vs non-squamous)
- Geographic region

Primary endpoint:
- OS

Key secondary endpoints:
- PFS (RECIST v1.1), ORR (RECIST v1.1), QoL (EORTC QLQ-C30, EORTC QLQ-LC13), AEs (frequency and severity)

- *After the pre-specified interim analysis, the independent data monitoring committee recommended reducing patient accrual to 276 patients with 12 months follow-up. Initial accrual was 534 patients with 18 months follow-up. The expected hazard ratio for overall survival is <0.75. †Pembrolizumab, nivolumab or atezolizumab.

- 1. NCT02973789 [ClinicalTrials.gov]. Accessed October 7, 2022. https://clinicaltrials.gov/ct2/show/NCT02973789. 2. Leal et al. Swedish Oncology Days. March 2022.

LUNAR: Preliminary Safety Results

- March 2020, a planned interim review of LUNAR study data showed no unexpected safety issues, or increased systemic toxicity in patients treated with TTFields plus immune checkpoint inhibitors

- **The LUNAR study met its primary endpoint, demonstrating a statistically significant and clinically meaningful improvement in overall survival**

Abstract Number for Publication: LBA9005

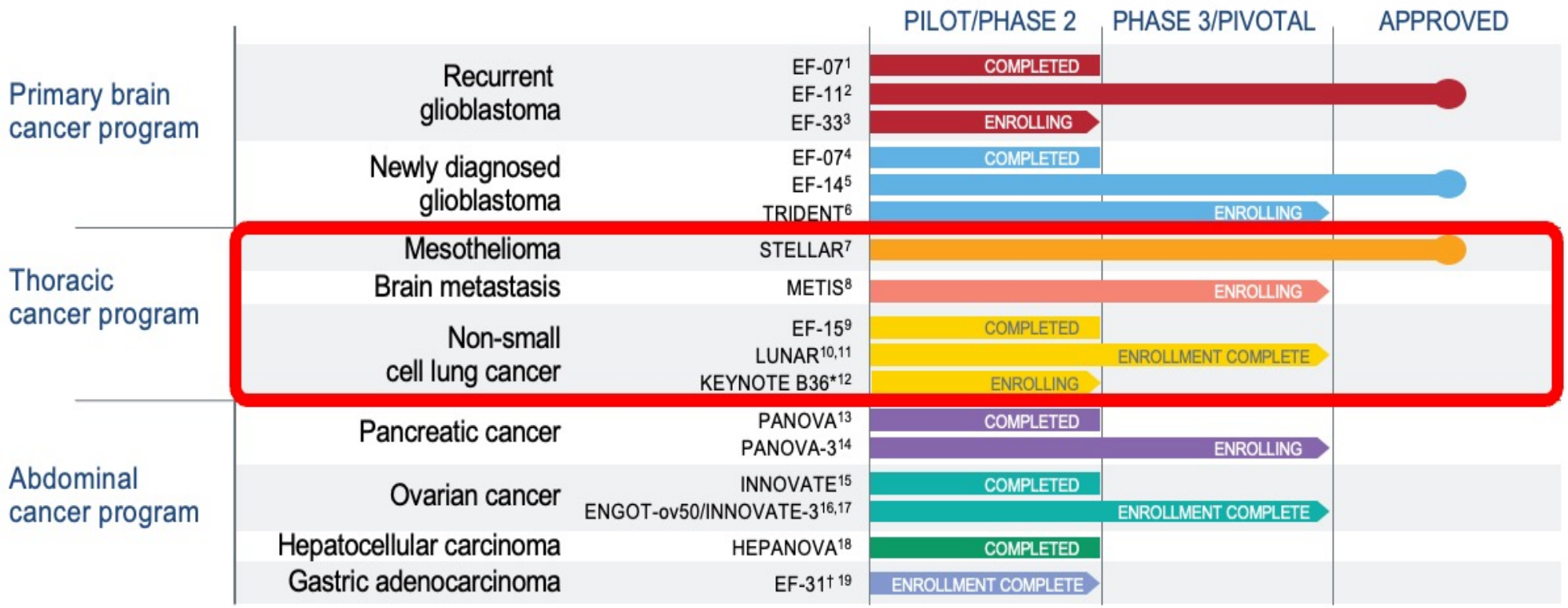
Abstract Title: *Tumor Treating Field (TTFields) therapy with standard of care (SOC) in metastatic non-small cell lung cancer (mNSCLC) following platinum failure: Randomized, phase 3 LUNAR study.*

Session Type – Session Title:
Oral Abstract Session: Lung Cancer—Non-Small Cell Metastatic

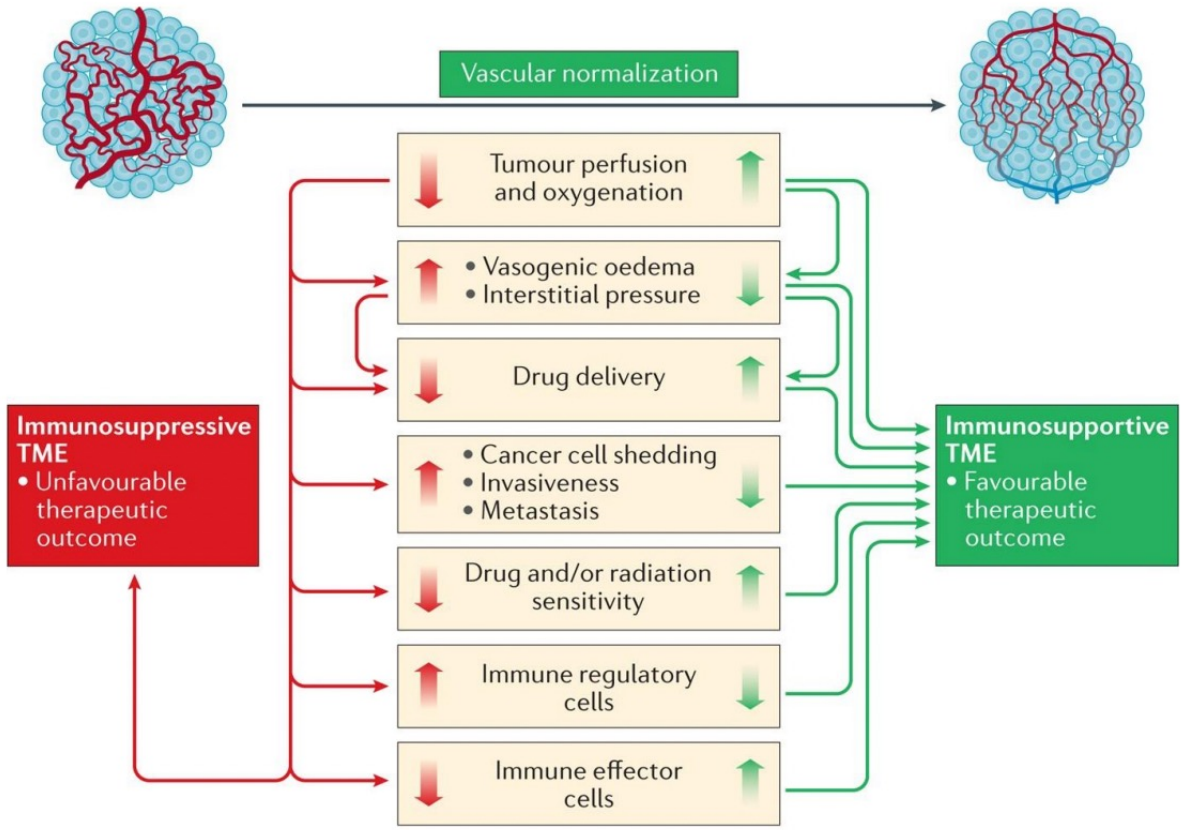
Session Date and Time:
6/6/2023, 9:45 AM-12:45 PM

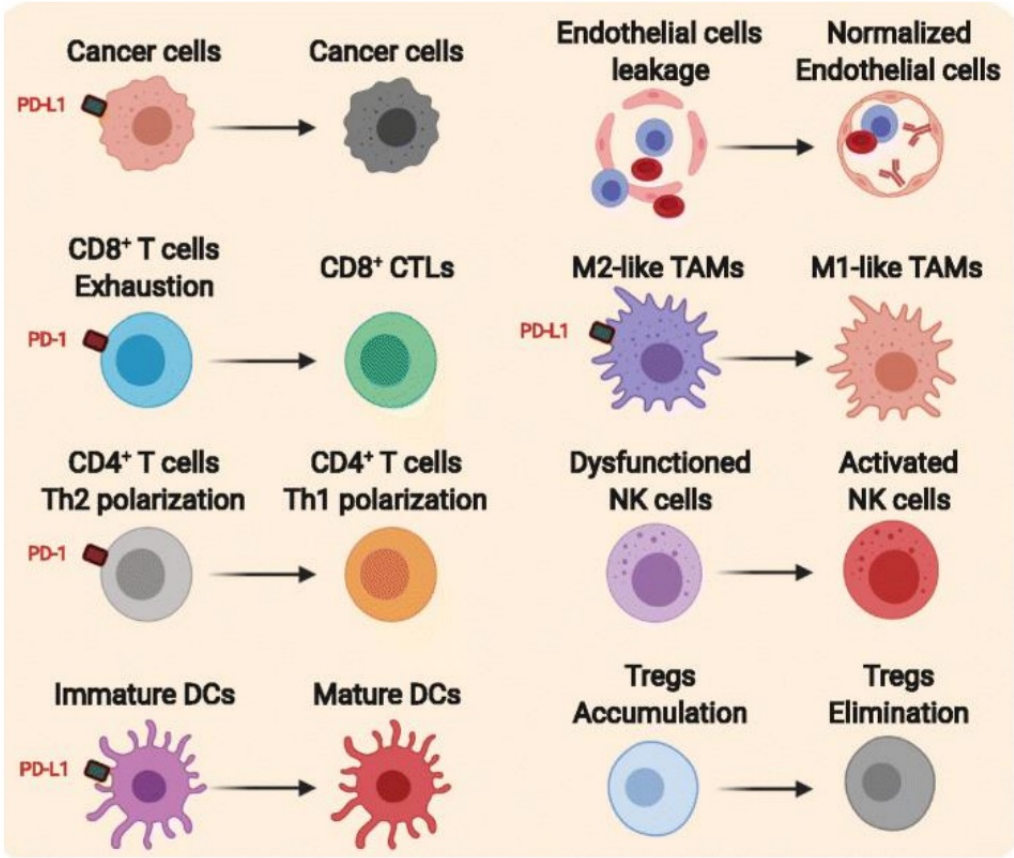
Leal et al. Swedish Oncology Days. March 2022.

TTFields Clinical Trials



Targeting angiogenesis to overcome ICI resistance





Fukumura et al., *Nat Rev Clin Oncol* 2018; Chen et al., *Biomarker Res* 2021

S1800A: Pembrolizumab + Ramucirumab

- Advanced NSCLC
- Previously received PD-(L)1 inhibitor and platinum doublet chemotherapy
- PD after ≥ 84 days of ICI
- ECOG 0-1

R
1:1

Investigator's choice
SOC
Docetaxel/ram
Docetaxel
Gemcitabine
Pemetrexed (nonSq)

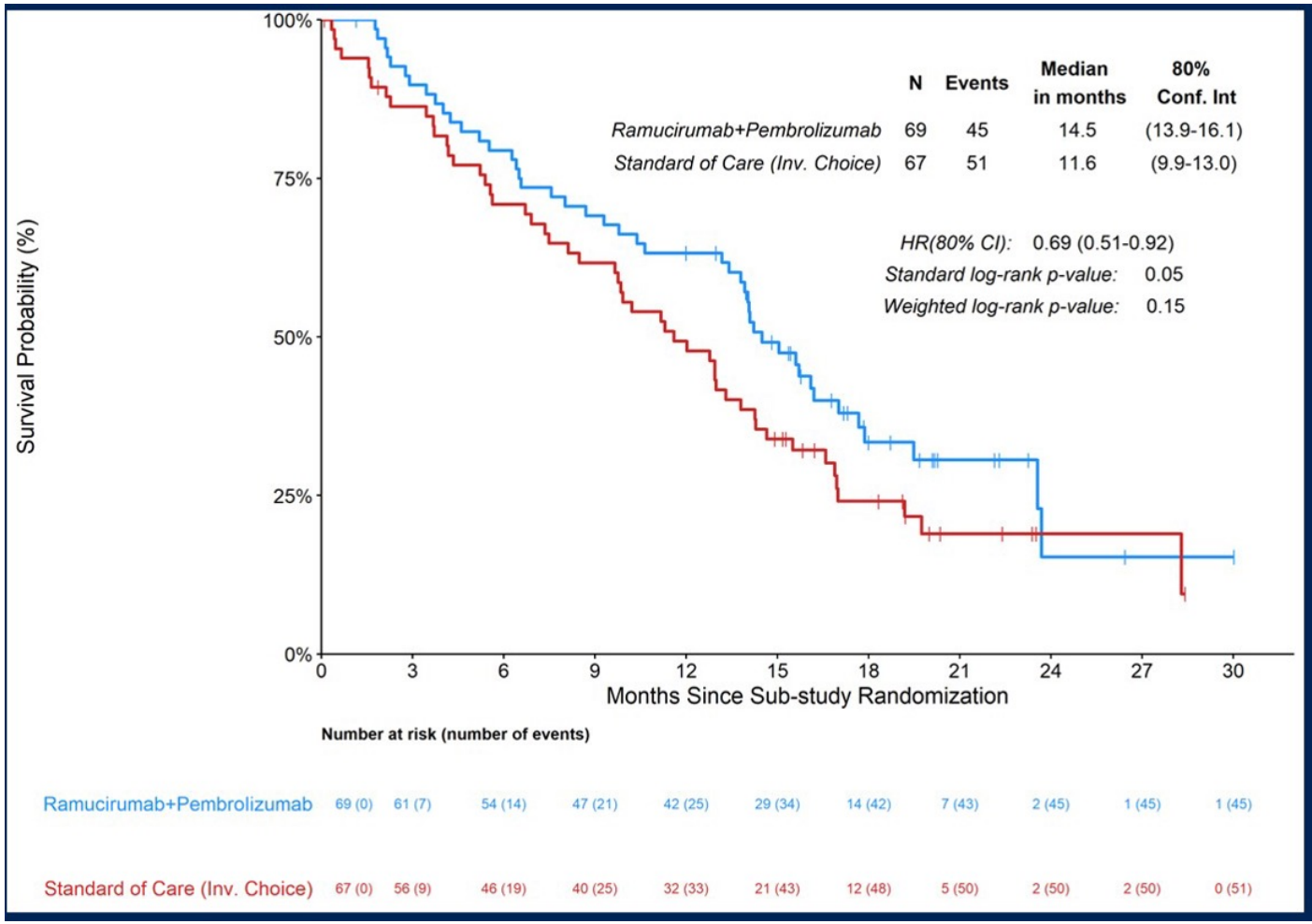
Pembrolizumab
+
Ramucirumab

Primary endpoint: OS
Secondary endpoints: RR, DCR, DoR, PFS, tox

Stratified by:
1) PD-L1 expression
2) Histology
3) Intent to give ram in SOC arm

Reckamp et al JCO 2022. Leal, Ramalingam et al. JCO 2022

S1800A: Pembrolizumab + Ramucirumab



- Median OS for RP 14.5 months v. SOC 11.6 months
- HR= 0.69; SLR p-value 0.05

Standard of care therapy received:

- Docetaxel + Ramucirumab (n = 45)
- Docetaxel (n = 3)
- Gemcitabine (n = 12)
- Pemetrexed (n = 1)
- No treatment (n = 6)

Reckamp et al JCO 2022. Leal, Ramalingam et al. JCO 2022

Project Pragmatica-Lung

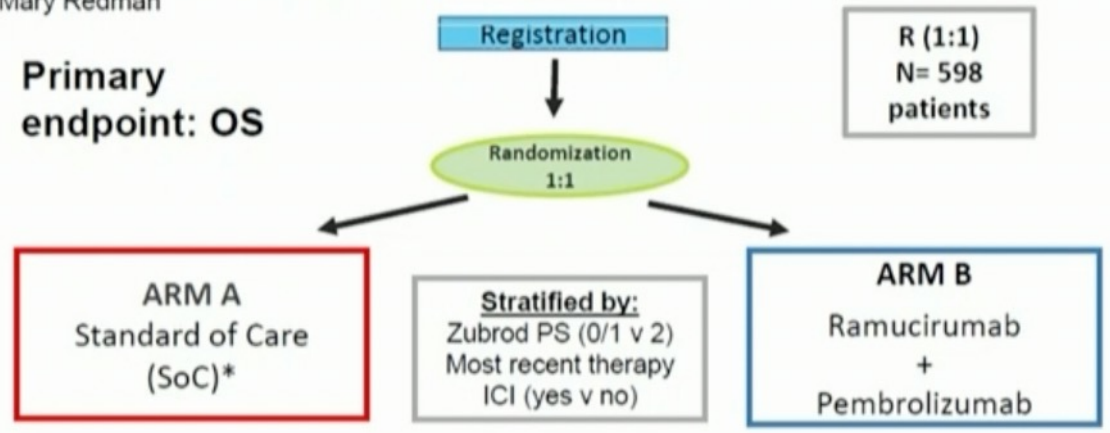
Phase III Rationale

- Effective therapy following frontline ICI for NSCLC is needed with limited FDA-approved options.
- We propose a pragmatic clinical trial design to promote diversity and inclusion in clinical trials.
- The aim of the trial is to validate the improvement in overall survival demonstrated in S1800A.
- The purpose is to empower investigators to treat patients as would be done in real world practice.
- The design is novel and potentially paradigm-changing to decrease barriers to enrollment and minimize the data collection burden.

S2302 Treatment/Schema

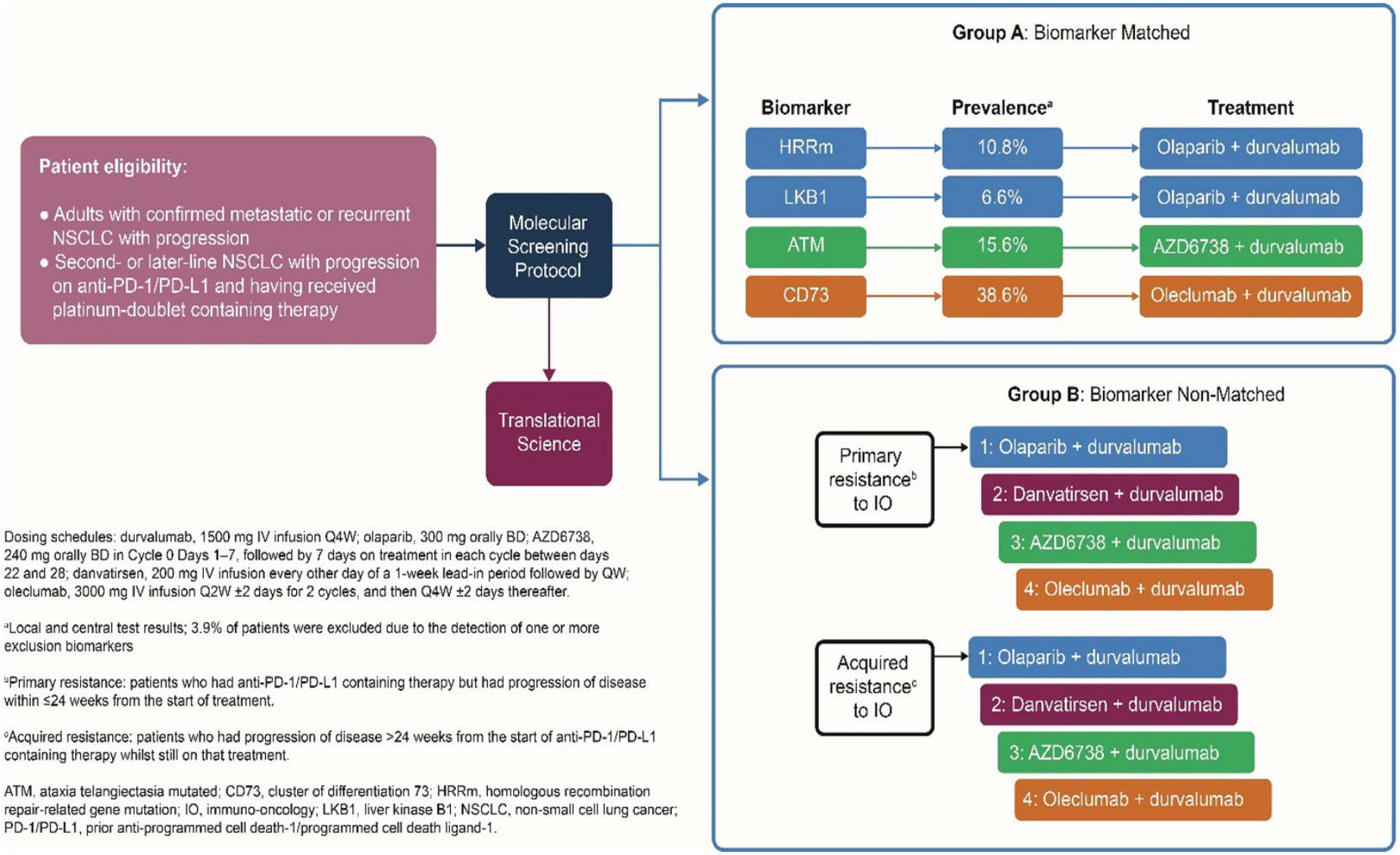
S2302, PROJECT PRAGMATICA: A PROSPECTIVE RANDOMIZED STUDY OF RAMUCIRUMAB (NSC 749128) PLUS PEMBROLIZUMAB (MK-3475; NSC 776864) VERSUS STANDARD OF CARE FOR PARTICIPANTS PREVIOUSLY TREATED WITH IMMUNOTHERAPY FOR STAGE IV OR RECURRENT NON-SMALL CELL LUNG CANCER

Chair: Karen Reckamp, MD; Co-chair: Konstantin Dragnev, MD; TBD
Statistician: Mary Redman



*SoC treatment is to be determined by the treating investigator and participant. It is recommended that the choice of SoC drug(s) is based on NCCN guidelines for a "systemic therapy for advanced or metastatic disease-subsequent."

HUDSON Umbrella Study of Durvalumab with Novel Anticancer Agents After Progression on an Anti-PD-1/PD-L1-Containing Therapy



Dosing schedules: durvalumab, 1500 mg IV infusion Q4W; olaparib, 300 mg orally BD; AZD6738, 240 mg orally BD in Cycle 0 Days 1–7, followed by 7 days on treatment in each cycle between days 22 and 28; danvatirsen, 200 mg IV infusion every other day of a 1-week lead-in period followed by QW; oleclumab, 3000 mg IV infusion Q2W ±2 days for 2 cycles, and then Q4W ±2 days thereafter.

[a]Local and central test results; 3.9% of patients were excluded due to the detection of one or more exclusion biomarkers

[b]Primary resistance: patients who had anti-PD-1/PD-L1 containing therapy but had progression of disease within ≤24 weeks from the start of treatment.

[c]Acquired resistance: patients who had progression of disease >24 weeks from the start of anti-PD-1/PD-L1 containing therapy whilst still on that treatment.

ATM, ataxia telangiectasia mutated; CD73, cluster of differentiation 73; HRRm, homologous recombination repair-related gene mutation; IO, immuno-oncology; LKB1, liver kinase B1; NSCLC, non-small cell lung cancer; PD-1/PD-L1, prior anti-programmed cell death-1/programmed cell death ligand-1.

ORR

Olaparib HRRm 9.5%

Ceralasertib (AZD6738) 11.1%

Oleclumab 0

Ceralasertib (AZD6738) 10.5%

no other responses with other agents

Olaparib 4.3%

Ceralasertib (AZD6738) 8.3%

Oleclumab 4.2%

Lao-Sirieix S et al. IASLC 2019;Abstract P2.01.07. Besse B et al. 2020 IASLC;Abstract OA07.08.

Ongoing LATIFY Phase III Trial Schema

Estimated enrollment: N = 580

- Locally advanced or metastatic NSCLC with documented radiological progression on most recent treatment regimen
- EGFR and ALK wild type gene status
- Eligible for second-line or third-line therapy
- Prior treatment with an anti-PD-(L)1 therapy and a platinum doublet-containing therapy either separately or in combination

Primary endpoint: Overall survival

Secondary endpoints include PFS, objective response rate, duration of response time and adverse events

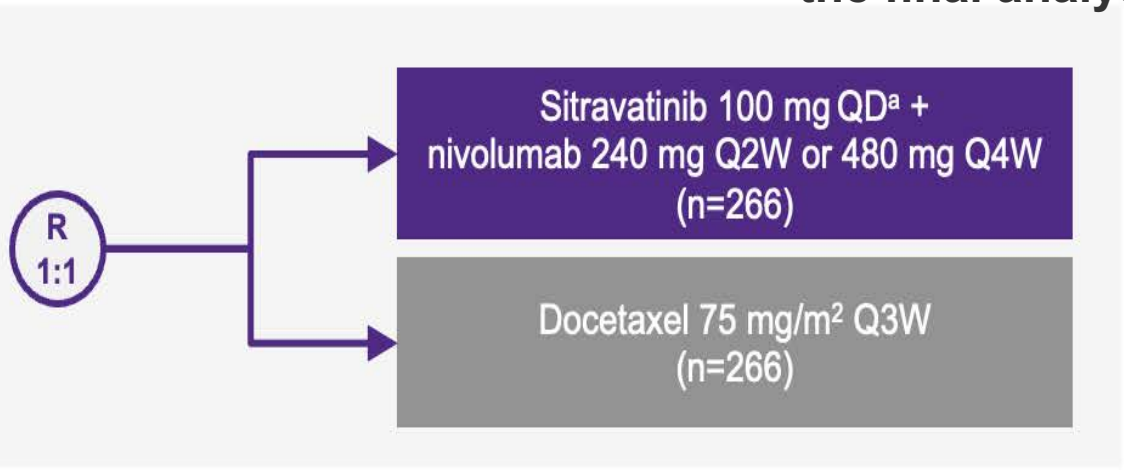
www.clinicaltrials.gov. NCT05450692. Accessed June 2023.

SAPPHIRE: Phase 3, Randomized, Open-Label Trial of 2L/3L Sitravatinib + Nivolumab vs Docetaxel After Progression on or Following CPI in Advanced NSCLC

05/24/2023
The SAPPHIRE study did not meet its primary endpoint of overall survival at the final analysis.

Key Eligibility Criteria (n=532)

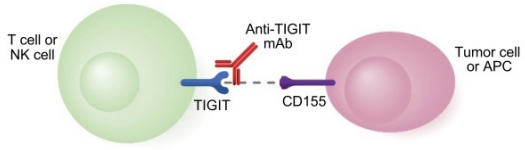
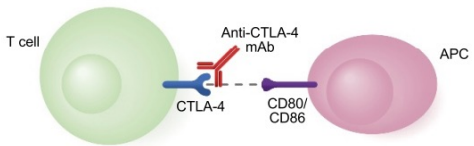
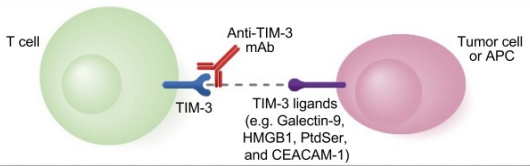
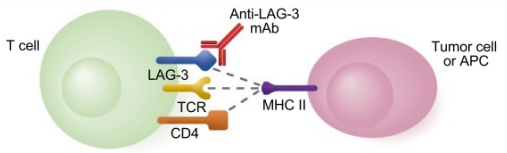
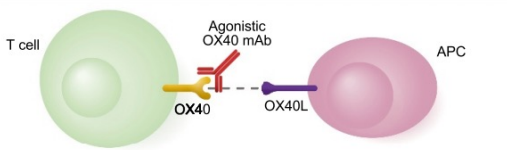
- Advanced, nonsquamous NSCLC
- Prior PD-1/L1 therapy for ≥4 months (prior anti–CTLA-4 therapy allowed)
- Progression on or following PD-1/L1 inhibitor in combination with or following chemotherapy
- Excludes patients with known driver mutations

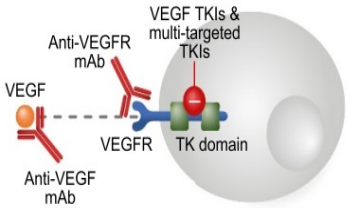
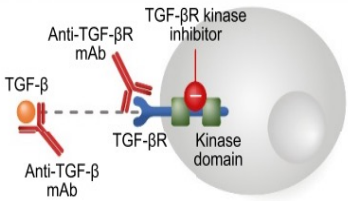
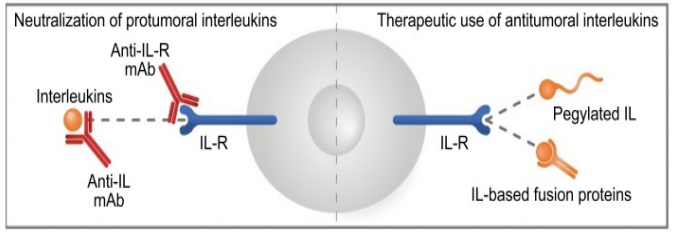
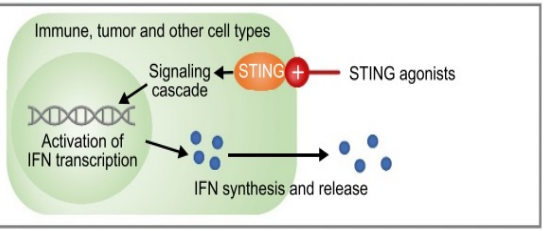


Primary Endpoint:
- OS

Secondary Endpoints:
- PFS
- ORR
- Safety

Potential pathways contributing to sensitivity and resistance to PD-(L)1 inhibitors in NSCLC

Pathways & targets		Potential role of pathway in sensitivity or resistance to PD-(L)1 inhibition	Mechanism of action of investigational agents
Upregulation of co-inhibitory checkpoints	TIGIT[7,21–24]	Downregulation of T-cell responses Inhibition of T-cell activation T-cell exhaustion **Immunosuppression**	
	CTLA-4[2,25]	Suppression of T-cell priming Inhibition of T-cell activation Increased regulatory T-cell activity **Immunosuppression**	
	TIM-3[17,26]	Inhibition of T-cell activation Suppression of T-cell proliferation T-cell exhaustion **Immunosuppression**	
	LAG-3[18,25,27]	Inhibition of T-cell activation Suppression of T-cell proliferation T-cell exhaustion **Immunosuppression**	
Co-stimulatory checkpoint activity	OX40[28,29]	Enhanced T-cell survival & proliferation Generation of memory T cells Inhibition of regulatory T cell function **Enhanced immune response**	

Pathways & targets		Potential role of pathway in sensitivity or resistance to PD-(L)1 inhibition	Mechanism of action of investigational agents
Immunosuppressive tumor immune microenvironment	VEGF[30,31]	Promotion of tumor angiogenesis Suppression of DC maturation Inhibition of T-cell proliferation & infiltration **Immunosuppression**	
	TGF-β[32–37]	Promotion of tumor progression Suppression of T-cell activity Promotion of regulatory T cell-mediated immunosuppression **Immunosuppression**	
	Interleukins[33,38]	Promotion of inflammation Control of T-cell mediated immune responses **Pleiotropic effects – may promote carcinogenesis or antitumoral immune responses**	
Oncogenic signaling pathways	Disruption of IFN signaling[17,30,35,39,40]	Suppression of T-cell infiltration Impaired T-cell response Loss of IFNγ-mediated cell-growth inhibition **Immune resistance and escape**	

Villacruz L, Blumenschein G, Otterson G, Leal T. Cancer. 2023;129:1319–1350. 2022.

Take Home Messages

- Dato-DXd has shown promising activity as monotherapy or in combination with immunotherapy +/- CT in NSCLC.
- Pembrolizumab + ramucirumab in patients with immunotherapy-resistant advanced NSCLC improved OS compared to SOC.
- The combination of sitravatinib and nivolumab demonstrated promising OS in patients with immunotherapy-resistant advanced NSCLC. However, the phase 3 study did not meet its primary endpoint.
- The LUNAR study demonstrated that TTFields with immunotherapy or docetaxel led to a statistically significant and clinically meaningful improvement in overall survival.

Video Consensus or Controversy? Clinical Investigators Provide Perspectives on the Current and Future Management of Non-Small Cell Lung Cancer

A CME Symposium Held in Conjunction with the 2023 ASCO® Annual Meeting

Friday, June 2, 2023

6:30 PM – 9:00 PM CT

Faculty

Edward B Garon, MD, MS
John V Heymach, MD, PhD
Corey J Langer, MD
Ticiana Leal, MD
David R Spigel, MD
Helena Yu, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Contributing Investigators

Matthew Gubens, MD, MS
Associate Professor, Thoracic Medical Oncology
University of California, San Francisco
San Francisco, California

Jarushka Naidoo, MB BCH, MHS
Professor of Oncology
Beaumont RCSI Cancer Centre
Beaumont Hospital
Dublin, Ireland
Adjunct Professor
Johns Hopkins University
Baltimore, Maryland

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

RTP
RESEARCH TO PRACTICE

POSTMEETING SURVEY – Available Now

Clinicians in Attendance: The postmeeting survey is now available on the iPads for attendees in the room and on Zoom for those attending virtually. We appreciate your completing this survey before the end of the program.

Thank you for your input.

RTP
RESEARCH
TO PRACTICE

Breakfast with the Investigators: Hepatobiliary Cancers

A CME Symposium Held in Conjunction with the 2023 ASCO® Annual Meeting

Saturday, June 3, 2023

6:45 AM – 7:45 AM CT

Faculty

Anthony El-Khoueiry, MD

Robin K (Katie) Kelley, MD

Prof Arndt Vogel, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Thank you for joining us!
Your feedback is very important to us.

Please complete the survey currently up on the iPads for attendees in the room and on Zoom for those attending virtually. The survey will remain open up to 5 minutes after the meeting ends.

How to Obtain CME Credit

In-person attendees: Please refer to the program syllabus for the CME credit link or QR code. You may also use the iPads available in the meeting room to complete the course evaluation.

Online/Zoom attendees: The CME credit link is posted in the chat room.

RTP
RESEARCH
TO PRACTICE