VIRTUAL MOLECULAR TUMOR BOARD
Optimizing Biomarker-Based Decision-Making for Patients with Non-Small Cell Lung Cancer with EGFR Mutations or with Other Oncogene-Addicted Lung Cancers

A 2-Part CME/MOC-Accredited Webinar Series

Tuesday, October 26, 2021
5:00 PM – 6:00 PM ET

Faculty

Marc Ladanyi, MD
Andrew J McKenzie, PhD
Joel W Neal, MD, PhD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Faculty

Marc Ladanyi, MD
Chief, Molecular Diagnostics Service
William J Ruane Chair in Molecular Oncology
Memorial Sloan Kettering Cancer Center
New York, New York

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

Andrew J McKenzie, PhD
Director, Personalized Medicine
Scientific Director, Genospace
Sarah Cannon
Nashville, Tennessee

Moderator

Neil Love, MD
Research To Practice
Miami, Florida

RTP
RESEARCH
TO PRACTICE

Commercial Support

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

Dr Love — Disclosures

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

RTP
RESEARCH
TO PRACTICE

Research To Practice CME Planning Committee Members, Staff and Reviewers

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

Dr Ladanyi — Disclosures

Advisory Committee	AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb Company, Janssen Biotech Inc, Lilly, Paige AI, Takeda Pharmaceuticals USA Inc
Contracted Research	Boehringer Ingelheim Pharmaceuticals Inc, Elevation Oncology, Helsinn Healthcare SA, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Merus BV

Dr McKenzie — Disclosures

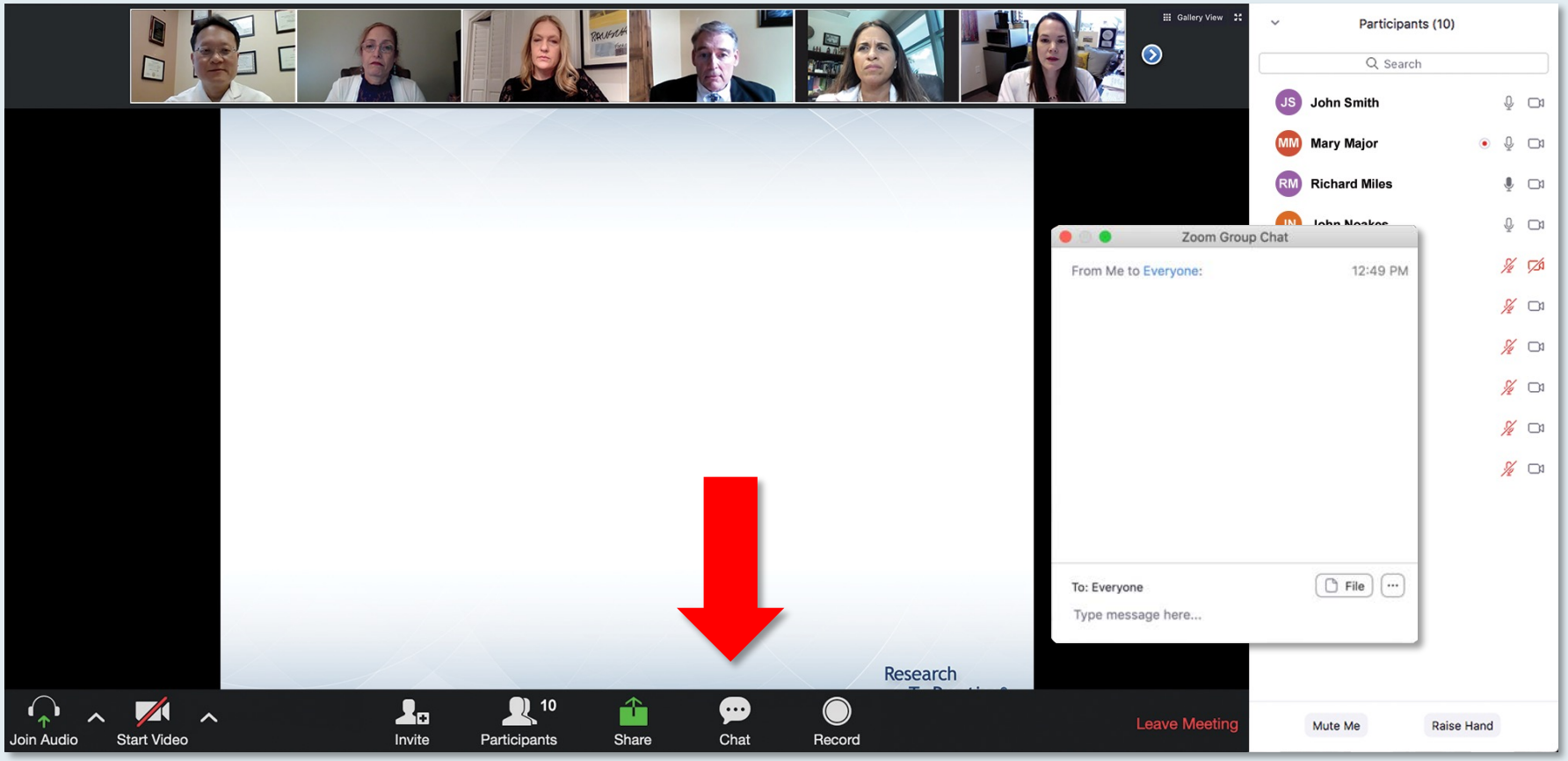
No relevant conflicts of interest to disclose.

RTP
RESEARCH
TO PRACTICE

Dr Neal — Disclosures

Advisory Committee	Amgen Inc, AstraZeneca Pharmaceuticals LP, Blueprint Medicines, Calithera Biosciences, Exelixis Inc, Genentech, a member of the Roche Group, Iovance Biotherapeutics, Jounce Therapeutics, Lilly, Natera Inc, Regeneron Pharmaceuticals Inc, Takeda Pharmaceuticals USA Inc
Contracted Research	AbbVie Inc, Adaptimmune, Boehringer Ingelheim Pharmaceuticals Inc, Exelixis Inc, Genentech, a member of the Roche Group, GlaxoSmithKline, Janssen Biotech Inc, Merck, Nektar, Novartis, Takeda Pharmaceuticals USA Inc

We Encourage Clinicians in Practice to Submit Questions

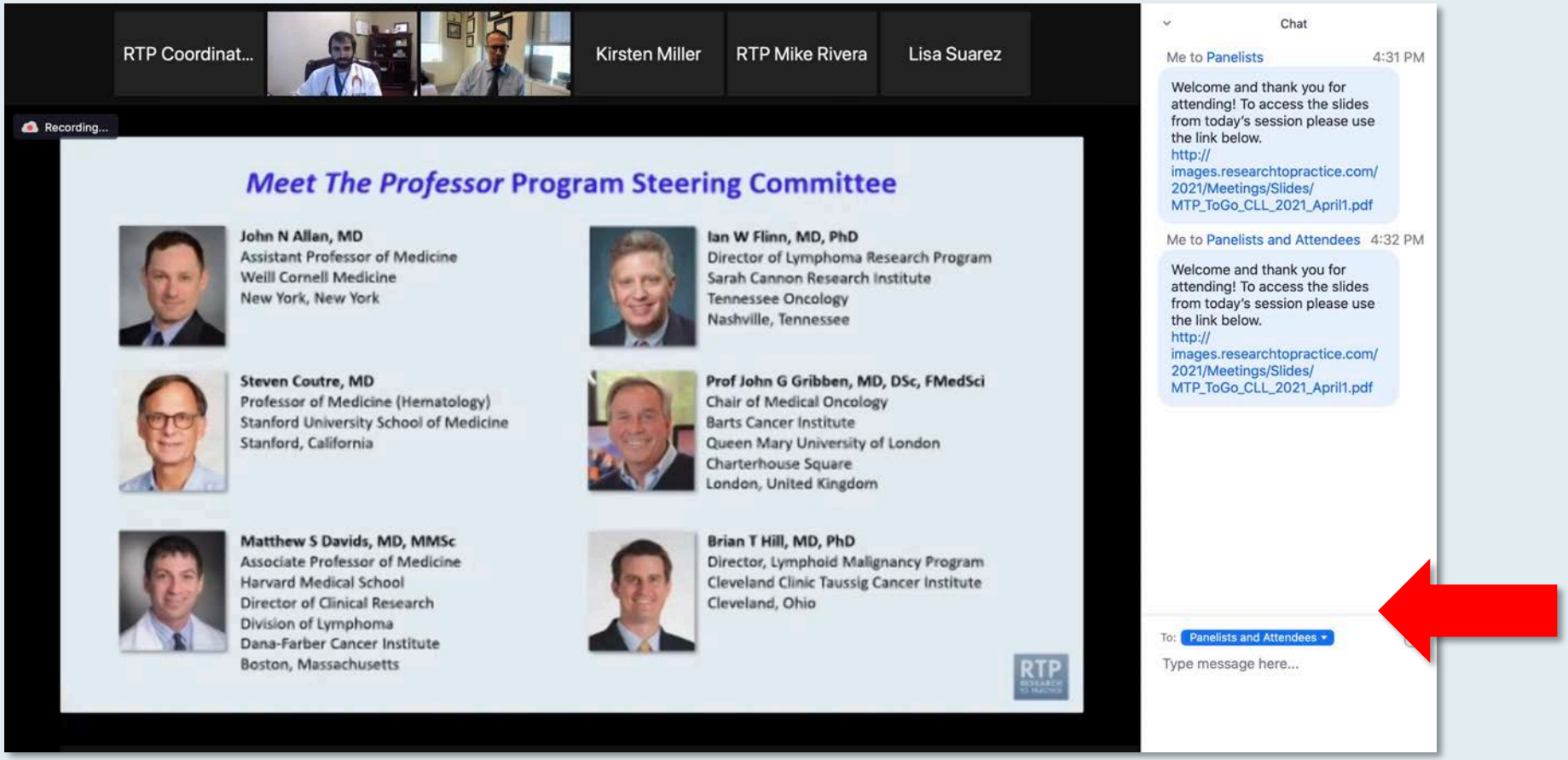


Feel free to submit questions now before the program begins and throughout the program.

RTP RESEARCH TO PRACTICE

Familiarizing Yourself with the Zoom Interface

Expand chat submission box

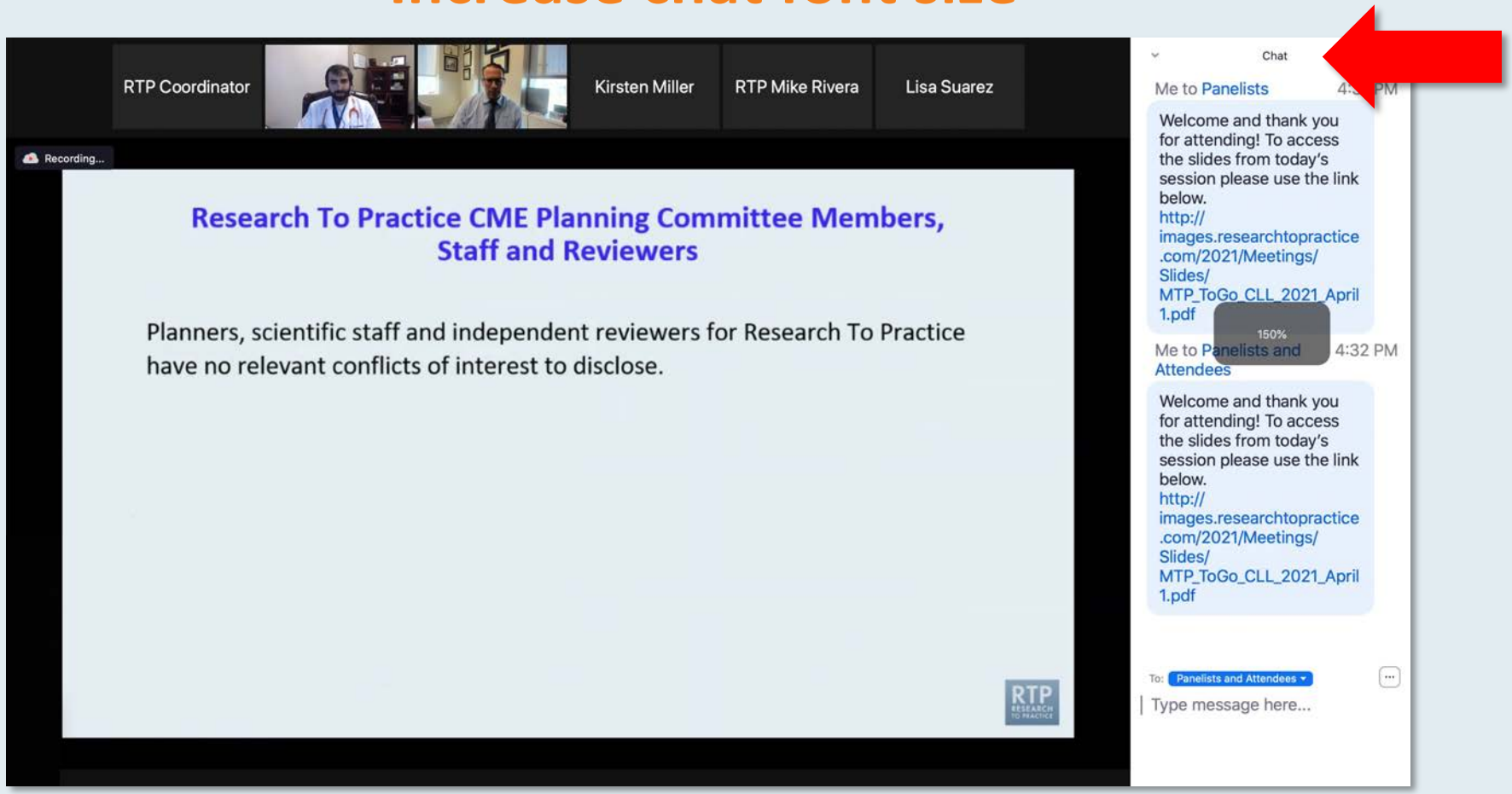


Drag the white line above the submission box up to create more space for your message.

RTP RESEARCH TO PRACTICE

Familiarizing Yourself with the Zoom Interface

Increase chat font size



Press Command (for Mac) or Control (for PC) and the + symbol.
You may do this as many times as you need for readability.

ONCOLOGY TODAY

WITH DR NEIL LOVE

Key Presentations on Lung Cancer from the 2021 ASCO Annual Meeting

DR JOEL NEAL
STANFORD UNIVERSITY

Listen on Apple Podcasts

Spotify

Listen on Google Podcasts

Meet The Professor

Optimizing the Clinical Management of Hodgkin and Non-Hodgkin Lymphomas

Wednesday, October 27, 2021
5:00 PM – 6:00 PM ET

Faculty

Jonathan W Friedberg, MD, MMSc

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Meet The Professor

Optimizing the Selection and Sequencing of Therapy for Patients with ER-Positive Breast Cancer

Thursday, October 28, 2021
5:00 PM – 6:00 PM ET

Faculty

Matthew P Goetz, MD

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Meet The Professor

Management of BRAF-Mutant Melanoma

Monday, November 1, 2021
5:00 PM – 6:00 PM ET

Faculty

Prof Georgina Long, AO, BSc, PhD, MBBS

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Meet The Professor

Optimizing the Selection and Sequencing of Therapy for Patients with Urothelial Bladder Carcinoma

Tuesday, November 2, 2021
5:00 PM – 6:00 PM ET

Faculty

Andrea Apolo, MD

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Meet The Professor

Optimizing the Selection and Sequencing of Therapy for Patients with HER2-Positive Breast Cancer

Wednesday, November 3, 2021
5:00 PM – 6:00 PM ET

Faculty

Adam M Brufsky, MD, PhD

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Key Considerations in the Optimal Clinical Care of Patients with Small Cell Lung Cancer

Thursday, November 4, 2021
5:00 PM – 6:00 PM ET

Faculty

Anne Chiang, MD, PhD
David R Spigel, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Meet The Professor

Optimizing the Management of Acute Myeloid Leukemia

Monday, November 8, 2021
5:00 PM – 6:00 PM ET

Faculty
Keith W Pratz, MD

Moderator
Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Meet The Professor

Optimizing the Management of Metastatic Castration-Resistant Prostate Cancer

Tuesday, November 9, 2021
5:00 PM – 6:00 PM ET

Faculty

Simon Chowdhury, MD, PhD

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

VIRTUAL MOLECULAR TUMOR BOARD
Optimizing Biomarker-Based Decision-Making for Patients with Non-Small Cell Lung Cancer with EGFR Mutations or with Other Oncogene-Addicted Lung Cancers

A 2-Part CME/MOC-Accredited Webinar Series

Thursday, November 11, 2021
5:00 PM – 6:00 PM ET

Faculty

Marc Ladanyi, MD
Andrew J McKenzie, PhD
Helena Yu, MD

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Thank you for joining us!

CME credit information will be emailed to each participant within 3 business days.

VIRTUAL MOLECULAR TUMOR BOARD
Optimizing Biomarker-Based Decision-Making for Patients with Non-Small Cell Lung Cancer with EGFR Mutations or with Other Oncogene-Addicted Lung Cancers

A 2-Part CME/MOC-Accredited Webinar Series

Tuesday, October 26, 2021
5:00 PM – 6:00 PM ET

Faculty

Marc Ladanyi, MD
Andrew J McKenzie, PhD
Joel W Neal, MD, PhD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Faculty

Marc Ladanyi, MD
Chief, Molecular Diagnostics Service
William J Ruane Chair in Molecular Oncology
Memorial Sloan Kettering Cancer Center
New York, New York

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

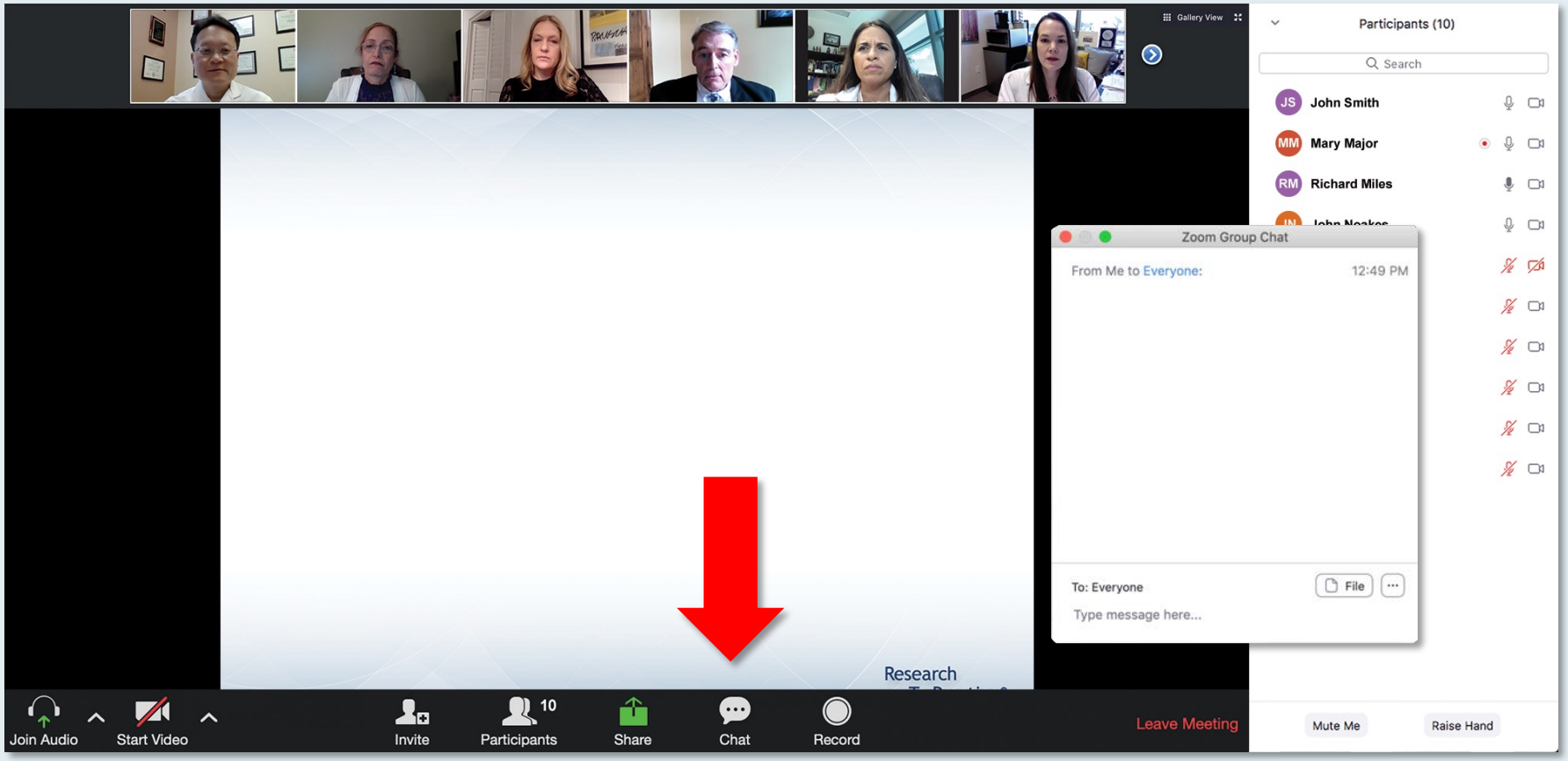
Andrew J McKenzie, PhD
Director, Personalized Medicine
Scientific Director, Genospace
Sarah Cannon
Nashville, Tennessee

Moderator

Neil Love, MD
Research To Practice
Miami, Florida

RTP
RESEARCH
TO PRACTICE

We Encourage Clinicians in Practice to Submit Questions



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

RTP RESEARCH TO PRACTICE

ONCOLOGY TODAY

WITH DR NEIL LOVE

Key Presentations on Lung Cancer from the 2021 ASCO Annual Meeting

DR JOEL NEAL
STANFORD UNIVERSITY

Listen on Apple Podcasts

Spotify

Listen on Google Podcasts

Meet The Professor

Optimizing the Clinical Management of Hodgkin and Non-Hodgkin Lymphomas

Wednesday, October 27, 2021
5:00 PM – 6:00 PM ET

Faculty

Jonathan W Friedberg, MD, MMSc

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Meet The Professor

Optimizing the Selection and Sequencing of Therapy for Patients with ER-Positive Breast Cancer

Thursday, October 28, 2021
5:00 PM – 6:00 PM ET

Faculty

Matthew P Goetz, MD

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Meet The Professor

Management of BRAF-Mutant Melanoma

Monday, November 1, 2021
5:00 PM – 6:00 PM ET

Faculty

Prof Georgina Long, AO, BSc, PhD, MBBS

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Meet The Professor

Optimizing the Selection and Sequencing of Therapy for Patients with Urothelial Bladder Carcinoma

Tuesday, November 2, 2021
5:00 PM – 6:00 PM ET

Faculty

Andrea Apolo, MD

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Meet The Professor

Optimizing the Selection and Sequencing of Therapy for Patients with HER2-Positive Breast Cancer

Wednesday, November 3, 2021
5:00 PM – 6:00 PM ET

Faculty

Adam M Brufsky, MD, PhD

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Key Considerations in the Optimal Clinical Care of Patients with Small Cell Lung Cancer

Thursday, November 4, 2021
5:00 PM – 6:00 PM ET

Faculty

Anne Chiang, MD, PhD
David R Spigel, MD

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Meet The Professor

Optimizing the Management of Acute Myeloid Leukemia

Monday, November 8, 2021
5:00 PM – 6:00 PM ET

Faculty

Keith W Pratz, MD

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Meet The Professor

Optimizing the Management of Metastatic Castration-Resistant Prostate Cancer

Tuesday, November 9, 2021
5:00 PM – 6:00 PM ET

Faculty

Simon Chowdhury, MD, PhD

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

VIRTUAL MOLECULAR TUMOR BOARD
Optimizing Biomarker-Based Decision-Making for Patients with Non-Small Cell Lung Cancer with EGFR Mutations or with Other Oncogene-Addicted Lung Cancers

A 2-Part CME/MOC-Accredited Webinar Series

Thursday, November 11, 2021
5:00 PM – 6:00 PM ET

Faculty

Marc Ladanyi, MD
Andrew J McKenzie, PhD
Helena Yu, MD

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

VIRTUAL MOLECULAR TUMOR BOARD
Optimizing Biomarker-Based Decision-Making for Patients with Non-Small Cell Lung Cancer with EGFR Mutations or with Other Oncogene-Addicted Lung Cancers

A 2-Part CME/MOC-Accredited Webinar Series

Tuesday, October 26, 2021
5:00 PM – 6:00 PM ET

Faculty

Marc Ladanyi, MD
Andrew J McKenzie, PhD
Joel W Neal, MD, PhD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Agenda

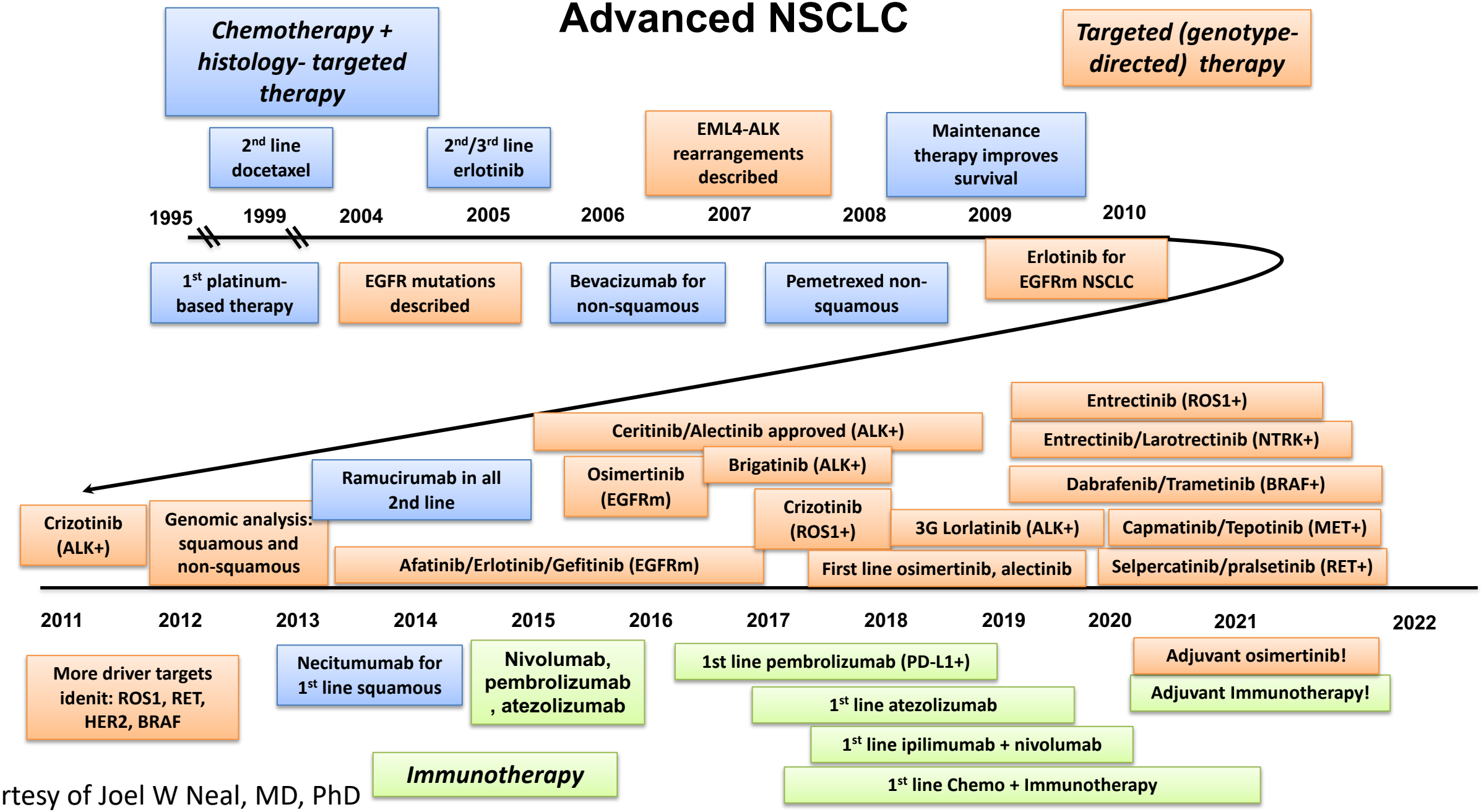
Module 1: Role of Genomic Profiling; New Developments in NSCLC with an EGFR Mutation

- Dr McKenzie: A 60-year-old woman with NSCLC and an EGFR exon 19 deletion
- Dr Hussein: A 51-year-old man with metastatic lung adenocarcinoma and an EGFR exon 20 mutation

Module 2: Other Novel Targets for Patients with NSCLC

- Dr Neal: A 51-year-old man with RET-positive NSCLC
- Dr Neal: A 64-year-old woman with metastatic NSCLC and a HER2 exon 20 insertion
- Dr McKenzie: A 78-year-old man with NSCLC and a TRK fusion
- Dr Jasani: A 35-year-old woman with newly diagnosed mNSCLC – ALK mutation
- Dr Mohamed: A 71-year-old woman with metastatic adenocarcinoma of the lung with MET exon 14 skipping and MET amplification mutations – PD-L1 TPS 95%
- Dr Zafar: A 64-year-old woman with discordant BRAF mutation testing results

Major Milestones in the Treatment of Advanced NSCLC

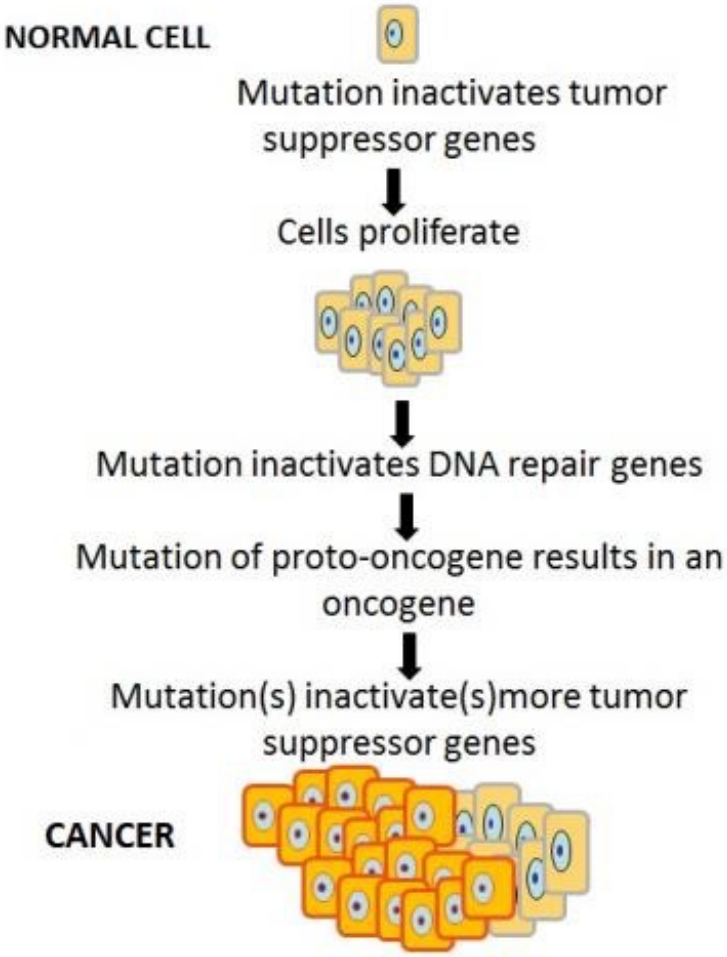


Courtesy of Joel W Neal, MD, PhD

Cancer is a Disease of the Genome

Tumorigenesis (aka carcinogenesis)

- Every type of cancer starts from a single cell (clone) with genetic mutations that confer a growth advantage over other cells (mutated cells divide and grow rapidly).
- Cancer causing mutations can occur in various classes of genes involved in cell growth and DNA repair including:
  - Oncogenes
  - Tumor Suppressor Genes
  - DNA Repair Genes
  - Cell cycle checkpoint genes
  - Cell death genes
  - Cell growth genes
  - Cellular differentiation genes
  - Cellular senescence genes
  - Metastasis/invasion genes

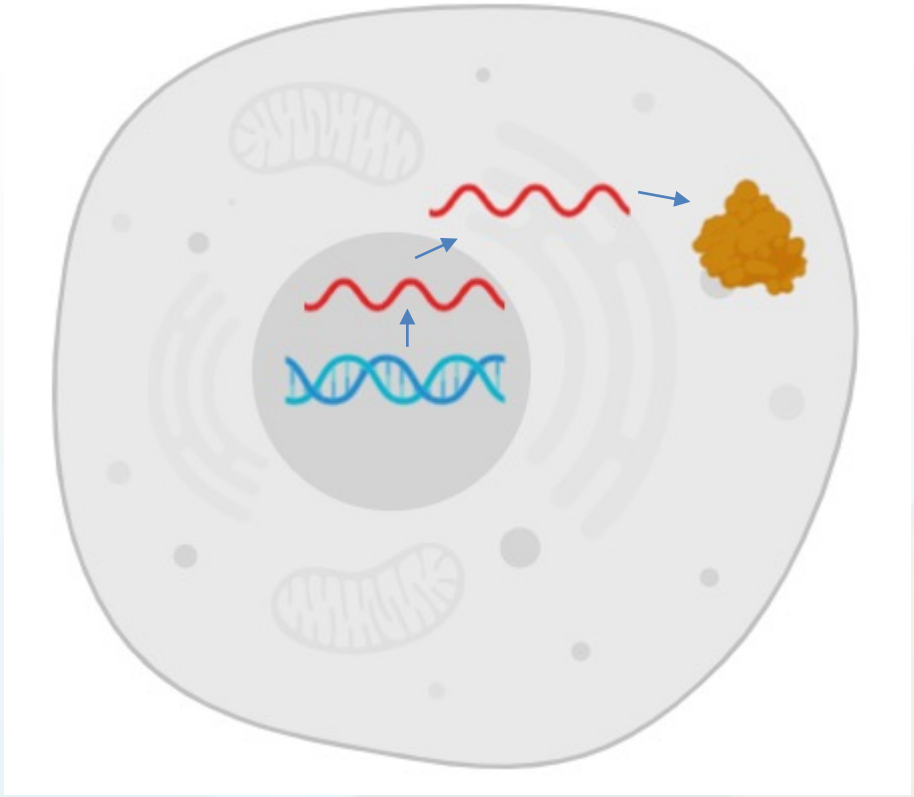


Courtesy of Andrew J McKenzie, PhD

DNA, RNA, and Protein

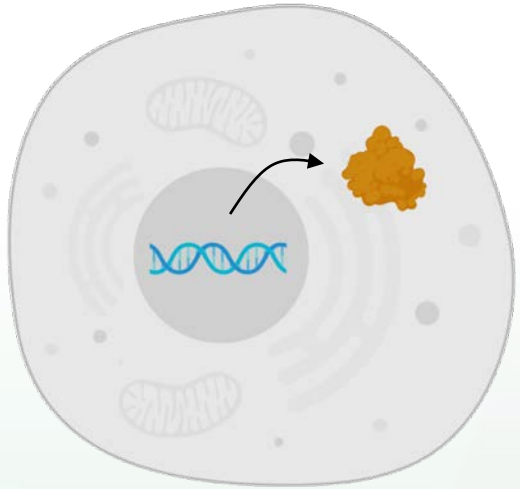
THE CENTRAL DOGMA

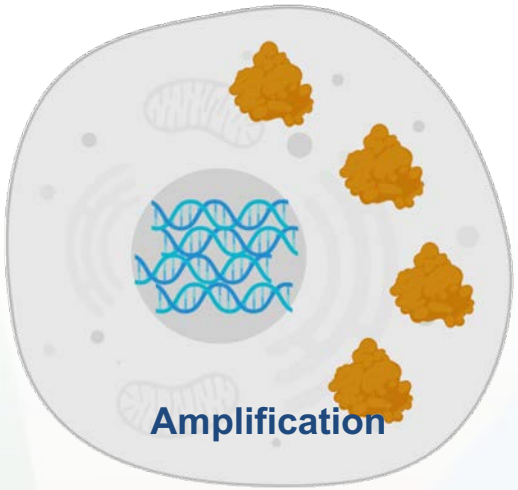
- DNA carries instructions for how to make Protein , the molecular workhorse of the cell, by way of an RNA intermediate



Courtesy of Andrew J McKenzie, PhD

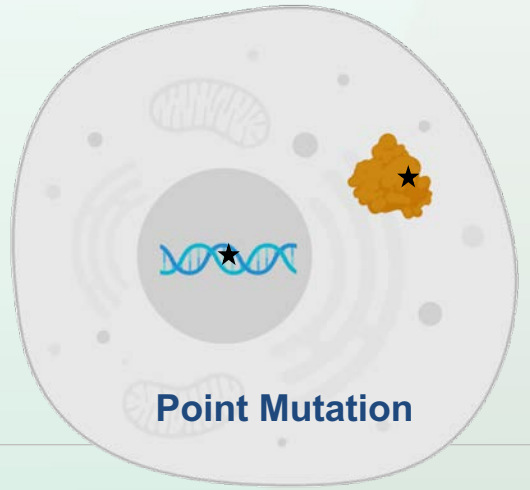
Types of Genetic Alterations (aka: mutations)



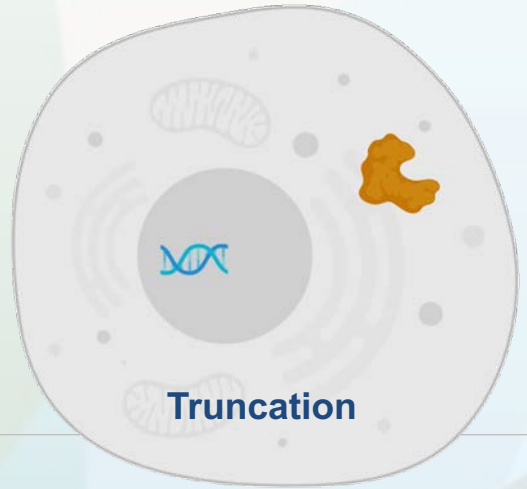


HER2

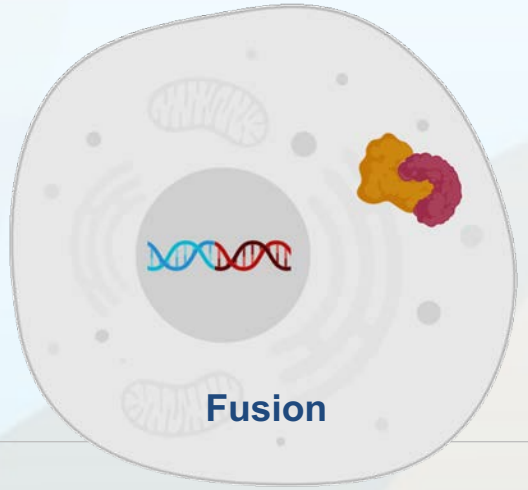
MMR



EGFR



BRCA1/2

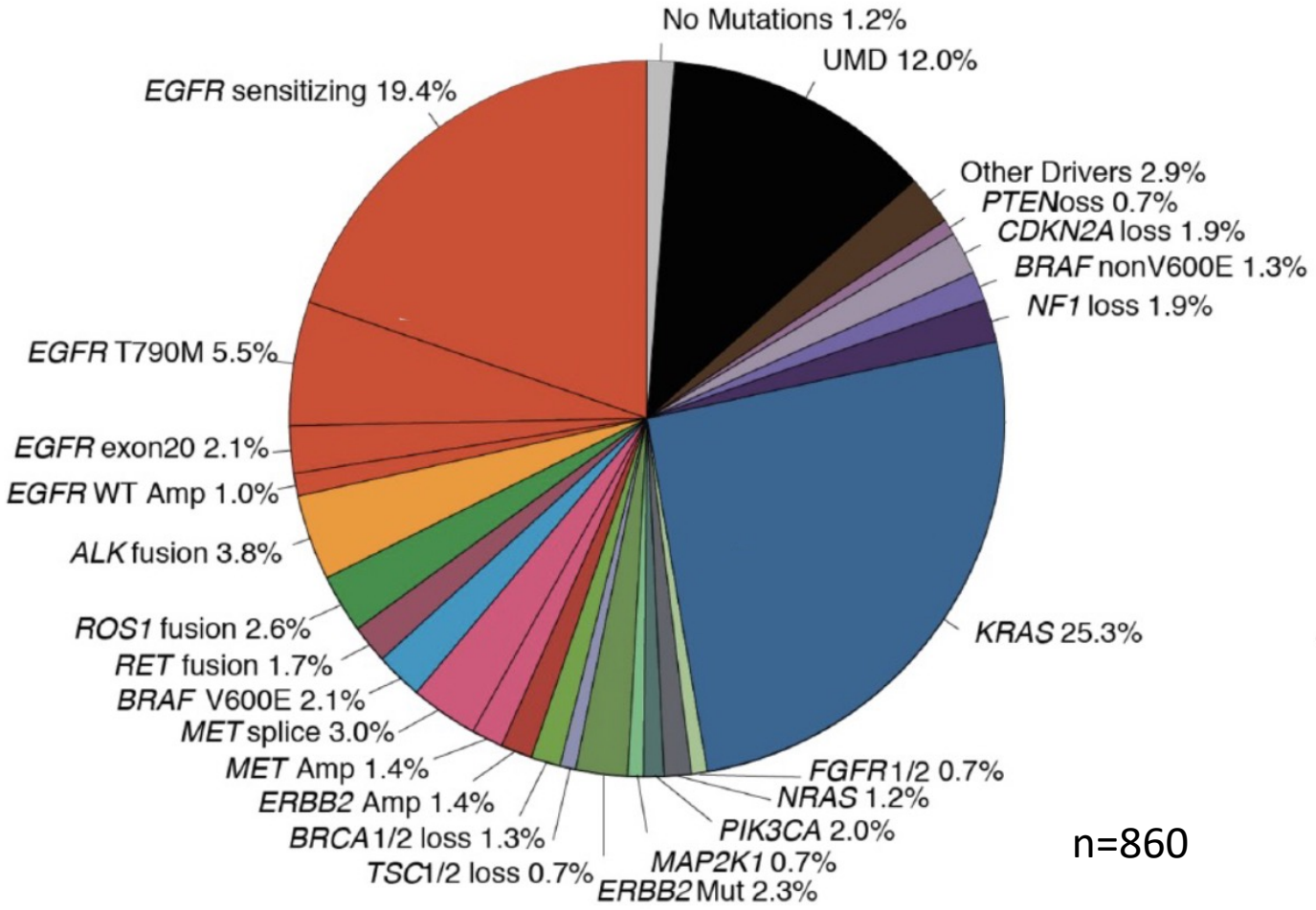


ALK/ROS1/RET

Courtesy of Andrew J McKenzie, PhD

Large panel NGS finds targets of FDA-approved targeted drugs – *circa* 2021

MSK-IMPACT data, MSKCC



n=860

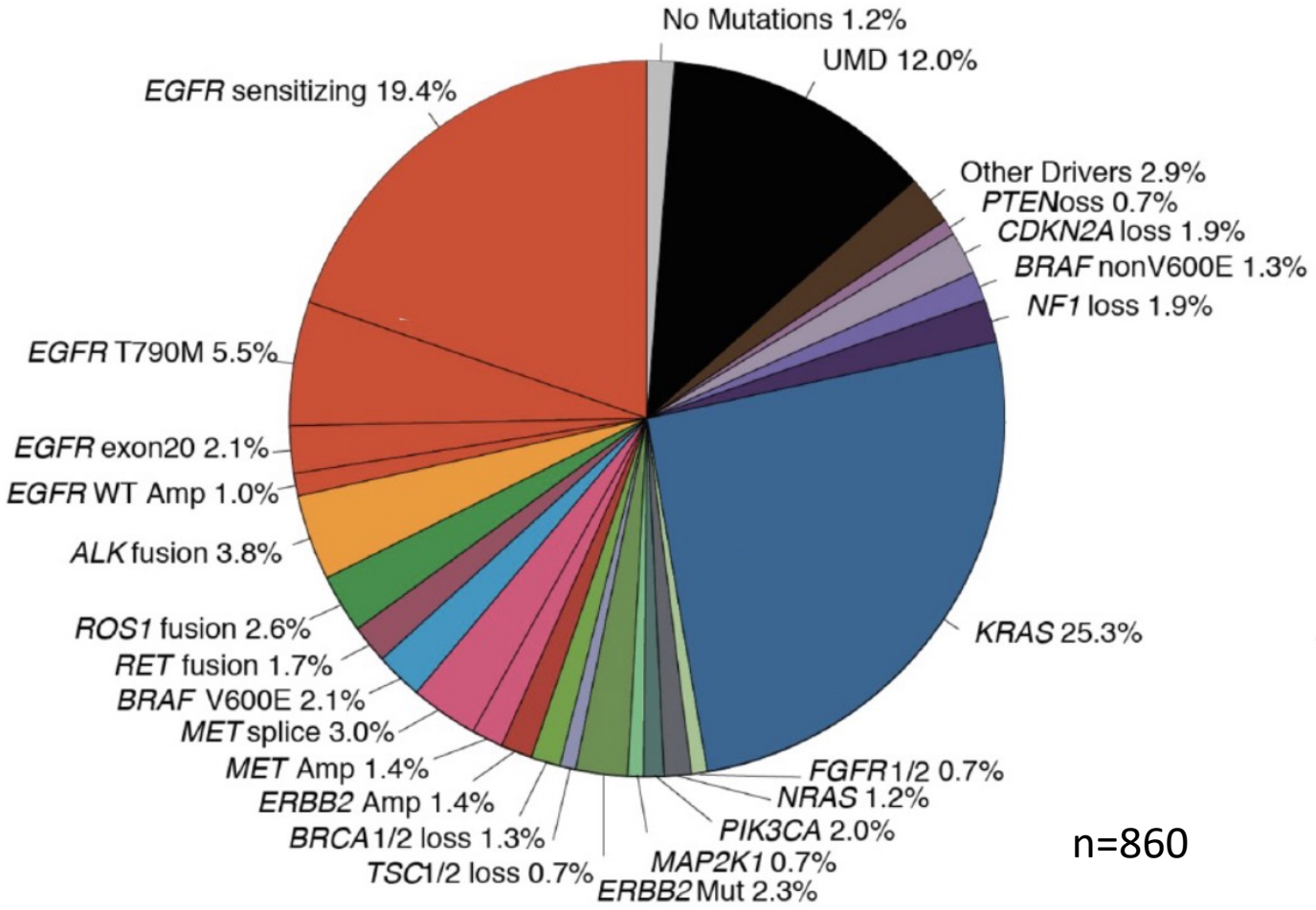
EGFR sensitizing 19.4%
EGFR T790M 5.5%
EGFR exon20 2.1%
EGFR WT Amp 1.0%

Courtesy of Marc Ladanyi, MD

Jordan EJ et al. *Cancer Discovery* 2017

Large panel NGS finds targets of FDA-approved targeted drugs – *circa* 2021

MSK-IMPACT data, MSKCC



n=860

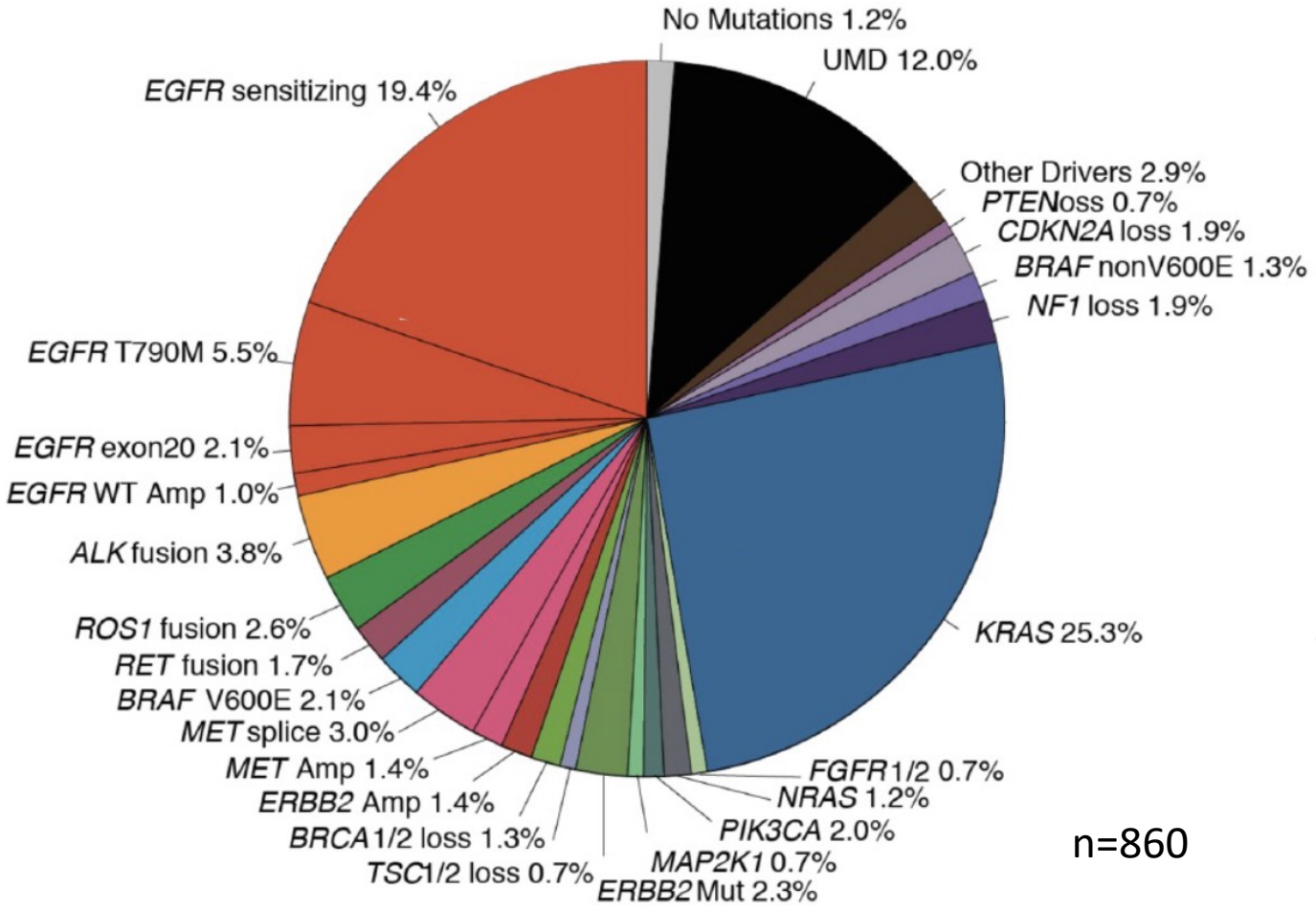
KRAS 25.3%
UMD 12.0%
No Mutations 1.2%

Courtesy of Marc Ladanyi, MD

Jordan EJ et al. *Cancer Discovery* 2017

Large panel NGS finds targets of FDA-approved targeted drugs – *circa* 2021

MSK-IMPACT data, MSKCC



n=860

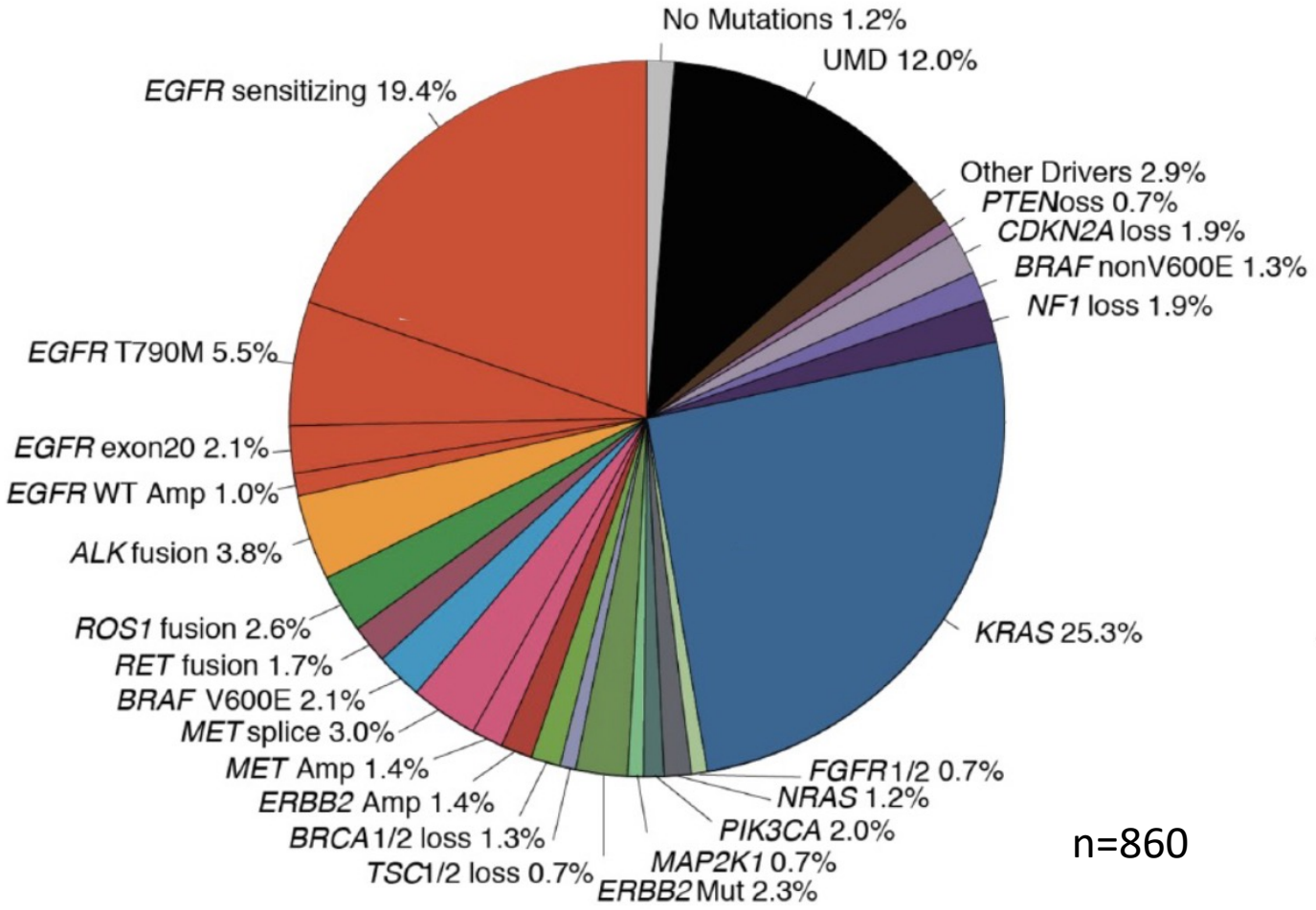
ALK fusion 3.8%
ROS1 Fusion 2.6%
RET Fusion 1.7%
BRAF V600E 2.1%
MET Splice 3.0%
MET Amp 1.4%
ERBB2 Amp 1.4%
ERBB2 Mut 2.3%

Courtesy of Marc Ladanyi, MD

Jordan EJ et al. *Cancer Discovery* 2017

Large panel NGS finds targets of FDA-approved targeted drugs – *circa* 2021

MSK-IMPACT data, MSKCC



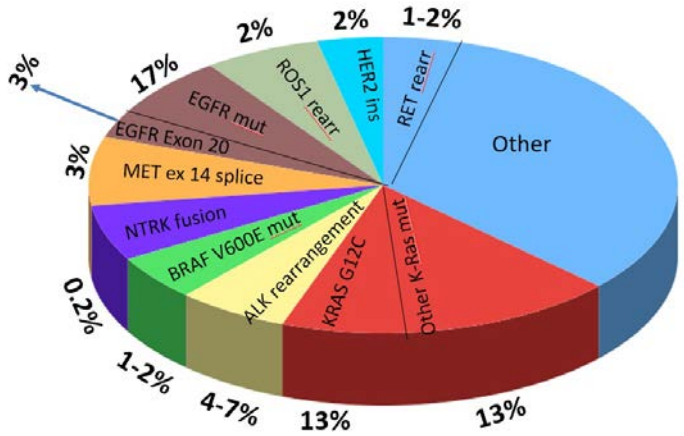
n=860

BRCA 1/2 loss 1.3%
TSC 1/2 loss 0.7%
MAP2K1 0.7%
PIK3CA 2.0%
NRAS 1.2%
FGFR 1/2 0.7%
NF1 loss 1.9%
BRAF nonV600E 1.3%
CDKN2A loss 1.9%
PTEN loss 0.7%
Other drivers 2.9%

Courtesy of Marc Ladanyi, MD

Jordan EJ et al. *Cancer Discovery* 2017

NSCLC: How to test for targets

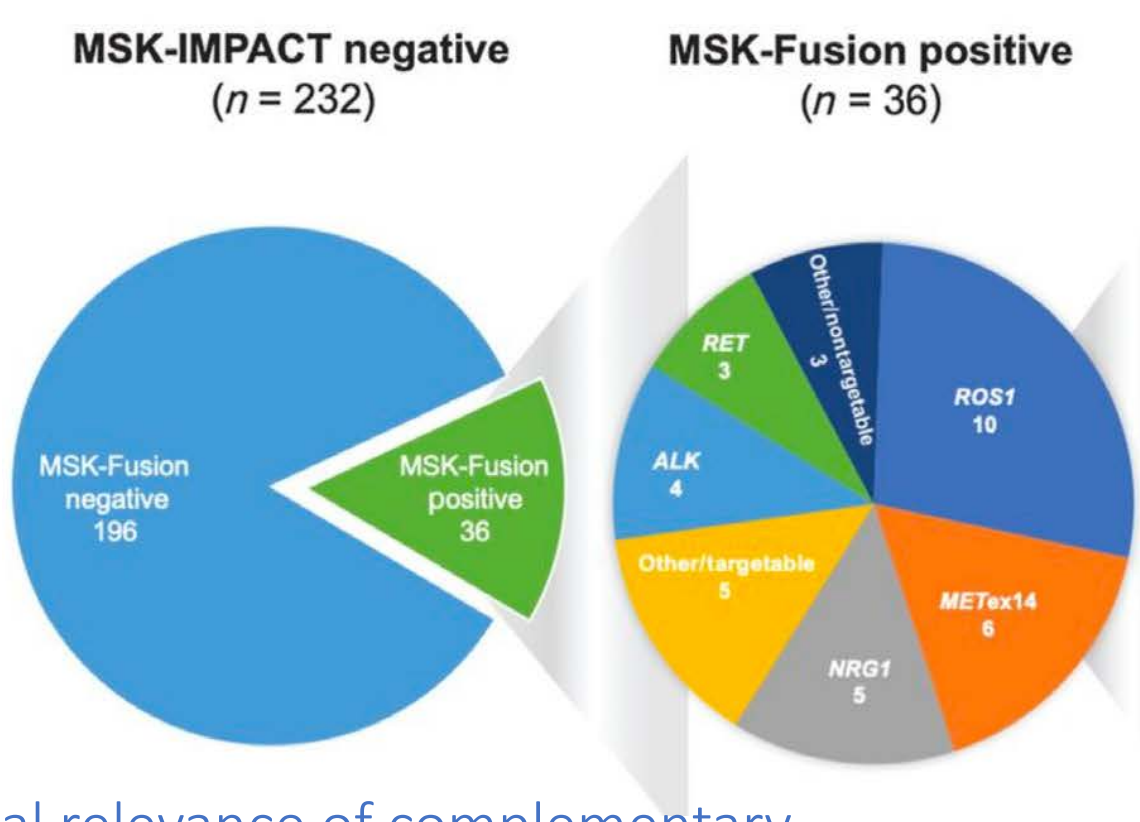


Target	Direct/ hotspot seq	FISH testing	IHC staining	NGS DNA tumor seq	NGS plasma seq	NGS RNA tumor seq
KRAS mutations	++	-	-	++	+	++
EGFR mutations (including exon 20 insertions)	++	-	+/-	++	+	++
ALK rearrangements	-	++	+	+	+	++
ROS1 rearrangements	-	++	-	+	+	++
BRAF mutations (including V600E)	++	-	-	++	+	++
MET exon 14 mutation	+/-	-	-	++	+	++
HER2 mutations	++	-	-	++	+	++
RET rearrangements	-	++	-	+	+	++
MET amplification	-	++	+/-	+	+/-	+
NTRK rearrangements	-	++	-	+	+	++
PD-L1 Protein Expression	-	-	++	-	-	-
Turnaround time (optimistically)	1-3 days	1-3 days	1 day	7-14 days	7-10 days	7-14 days

++ Most sensitive
+ Less sensitive
+/- Least sensitive (or technical limitations)
- Not appropriate

Courtesy of Joel W Neal, MD, PhD

What is the incremental value of targeted RNAseq in Lung Adenocarcinomas studied by MSK-IMPACT targeted DNAseq?



Clinical benefit of matched targeted therapy
(*n* = 10)

Rearrangement	Matched therapy	Best response*
EML4-ALK	Alectinib	SD
CD74-ROS1	Entrectinib	SD
SQSTM1-NTRK3	Larotrectinib	PR**
STRN-NTRK2	Larotrectinib	SD
CD74-ROS1	Entrectinib	PR**
CD74-NRG1	Afatinib	SD
MET Exon14 Skipping	Crizotinib	SD
SLC34A2-ROS1	Crizotinib	PD
SLC34A2-ROS1	Crizotinib	SD
SDC4-NRG1	Afatinib	PD

* Response assessment by RECIST version 1.1. **, Confirmed PR.

Clinical relevance of complementary RNA sequencing

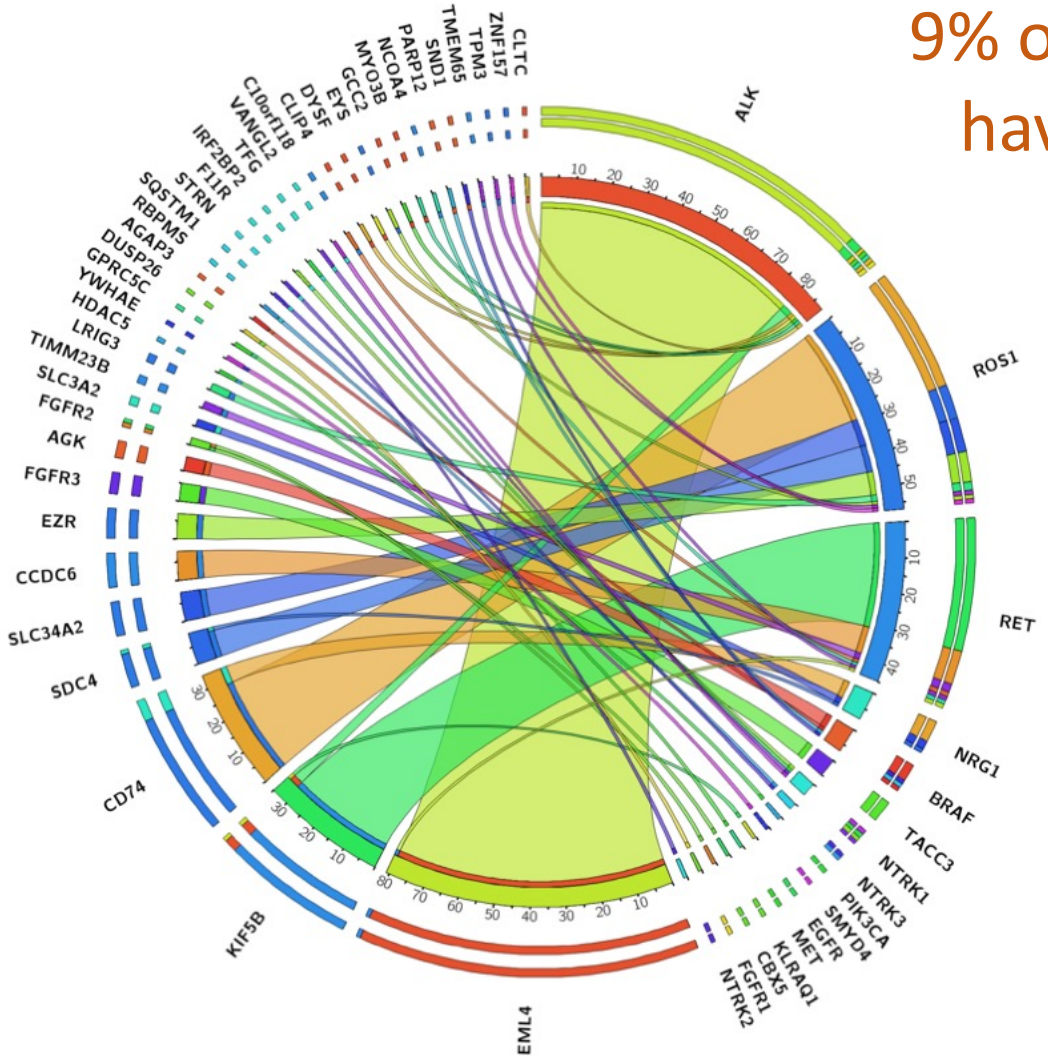
High Yield of RNA Sequencing for Targetable Kinase Fusions in Lung Adenocarcinomas with No Mitogenic Driver Alteration Detected by DNA Sequencing and Low Tumor Mutation Burden
Benayed R. et al. *Clin Cancer Res* May 2019

8 of the 10 treated pts had clinical benefit from matched therapy

Courtesy of Marc Ladanyi, MD

Gene fusions landscape in 2,522 lung adenocarcinomas

Detected by comprehensive DNASeq and RNASeq



9% of lung adenoCa patients have in-frame, targetable gene fusions.

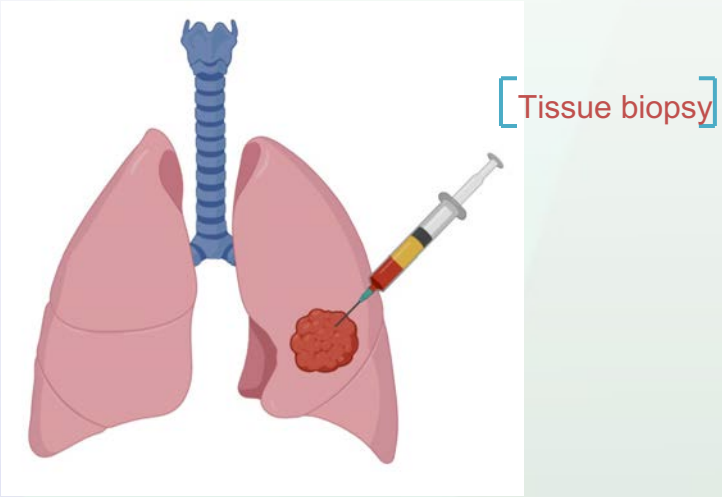
Benayed R, Offin M, Mullaney K, Sukhadia P, Rios K *et al.*, CCR 2019

Courtesy of Marc Ladanyi, MD

Tissue and Plasma Genomic Profiling

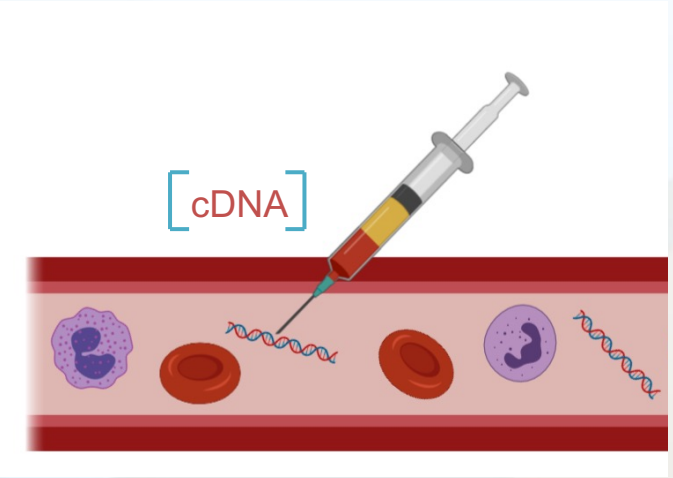
Tissue Testing

- Adequate tissue available
- High specificity and sensitivity
- Able to perform sequencing on long strands of DNA (entire coding regions) and WGS/WES
- DNA and RNA analysis capabilities
- Only tests sample that was biopsied



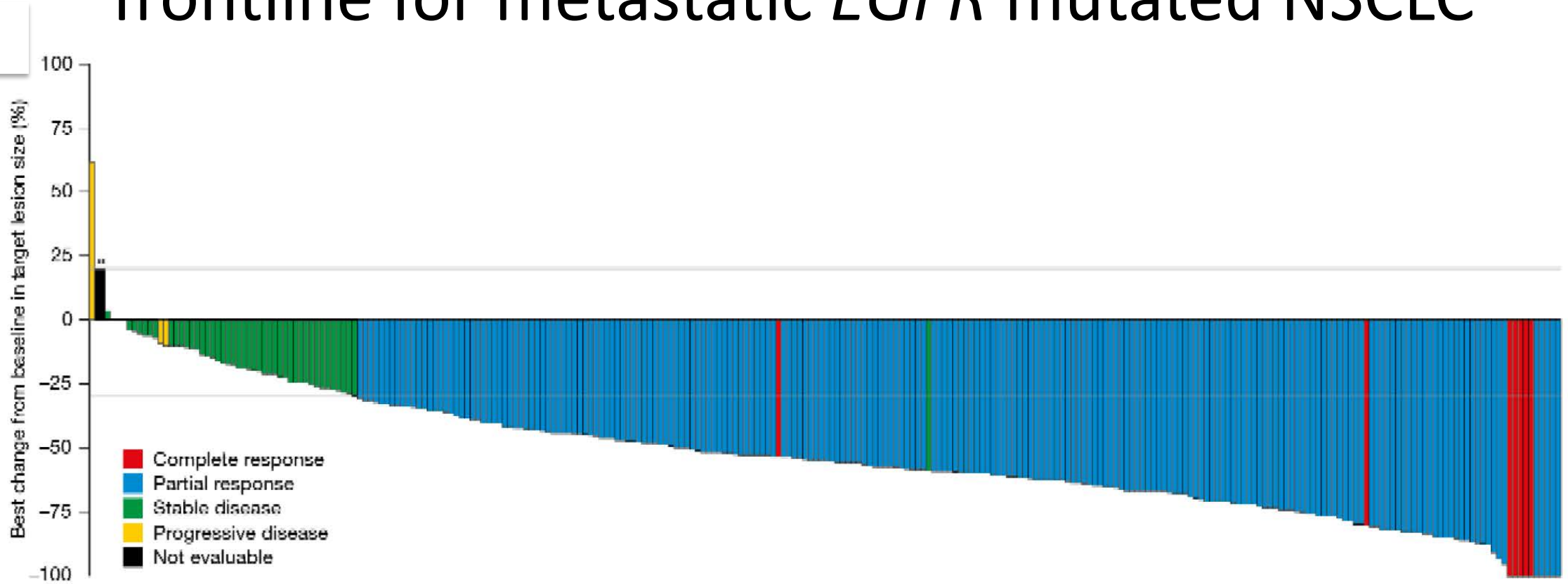
Plasma Testing

- Difficult to biopsy disease (or bone only)
- Less invasive
- Disease monitoring/resistance mechanisms
- Sequential testing
- Usually smaller panels
- DNA only (currently)
- Limited fusion detection (especially large genes i.e. NTRK)
- Monitors mutations in multiple lesions



Courtesy of Andrew J McKenzie, PhD

Osimertinib (EGFR tyrosine kinase inhibitor) frontline for metastatic *EGFR* mutated NSCLC



Objective response rate 80% (95% CI, 75 to 85)

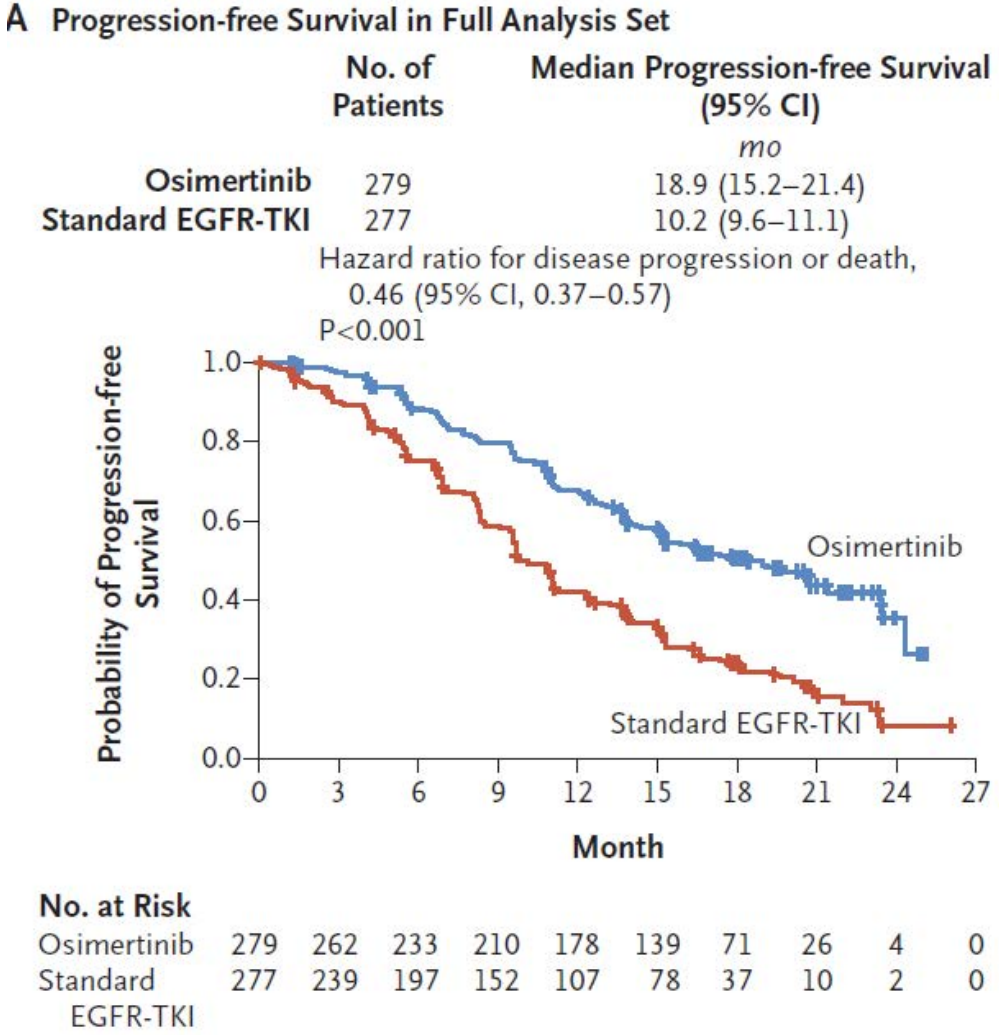
Disease-control rate was 97% (95% CI, 94 to 99)

Median best percentage change in target lesion size −54.7%

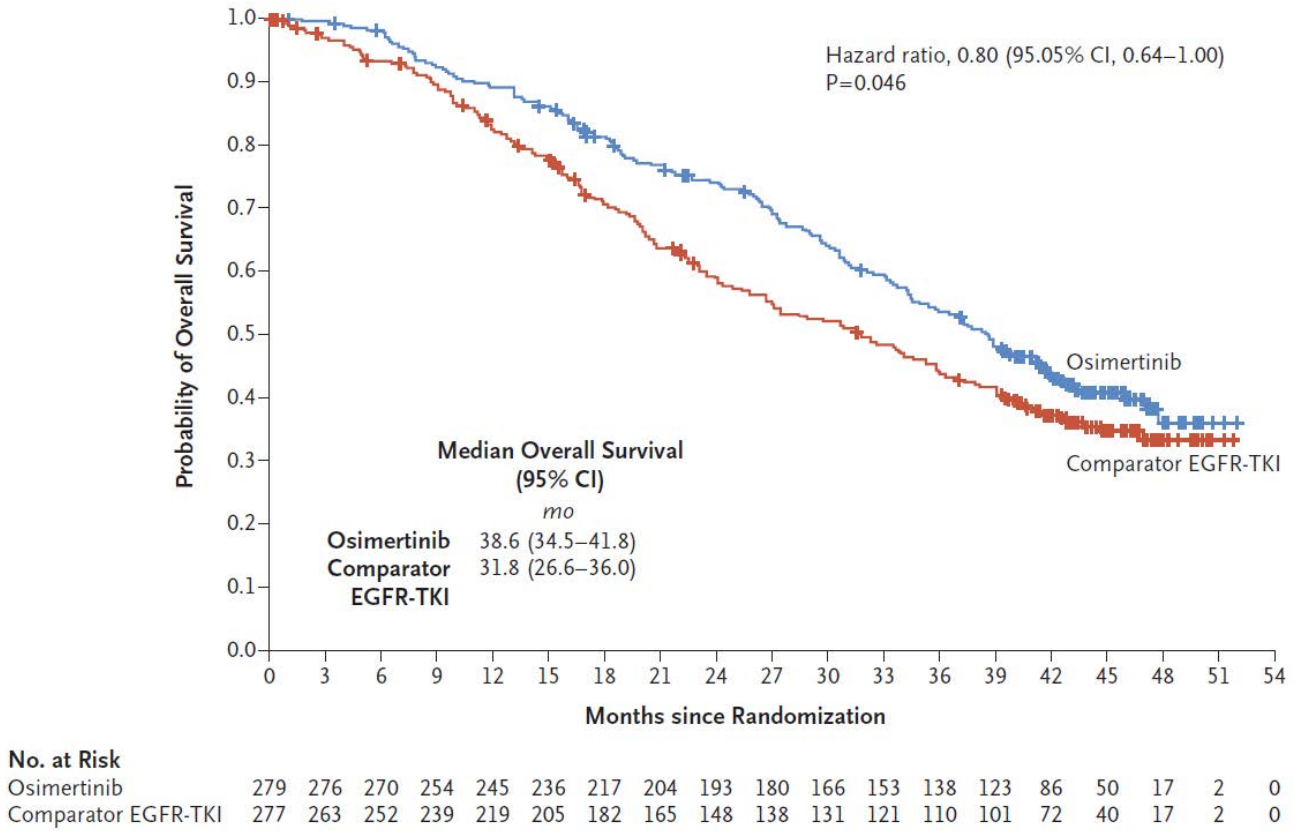
Courtesy of Joel W Neal, MD, PhD

Soria JC et al. N Engl J Med. 2018 Jan 11;378(2):113-125.

Osimertinib improves PFS & OS compared to older generation EGFR Tyrosine Kinase Inhibitors (TKIs)



Soria JC et al. N Engl J Med. 2018 Jan 11;378(2):113-125.

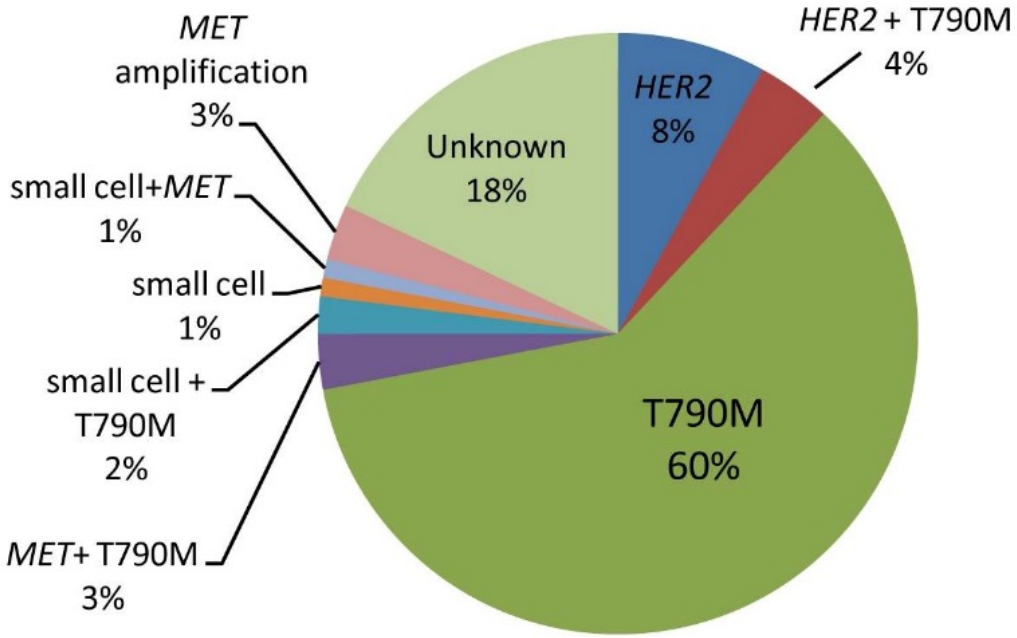


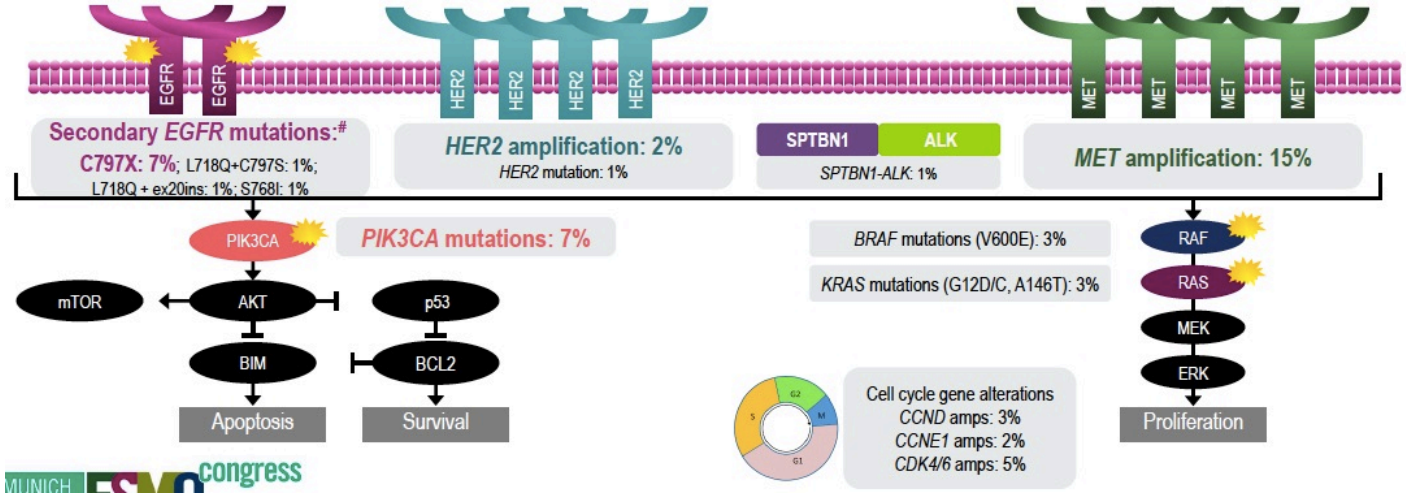
31% crossover rate

Ramalingam S et al. N Engl J Med. 2020 Jan 2;382(1):41-50.

Courtesy of Joel W Neal, MD, PhD

Resistance to targeted therapy is inevitable





Dominant mechanism of resistance for 1st generation EGFR TKIs erlotinib or gefitinib

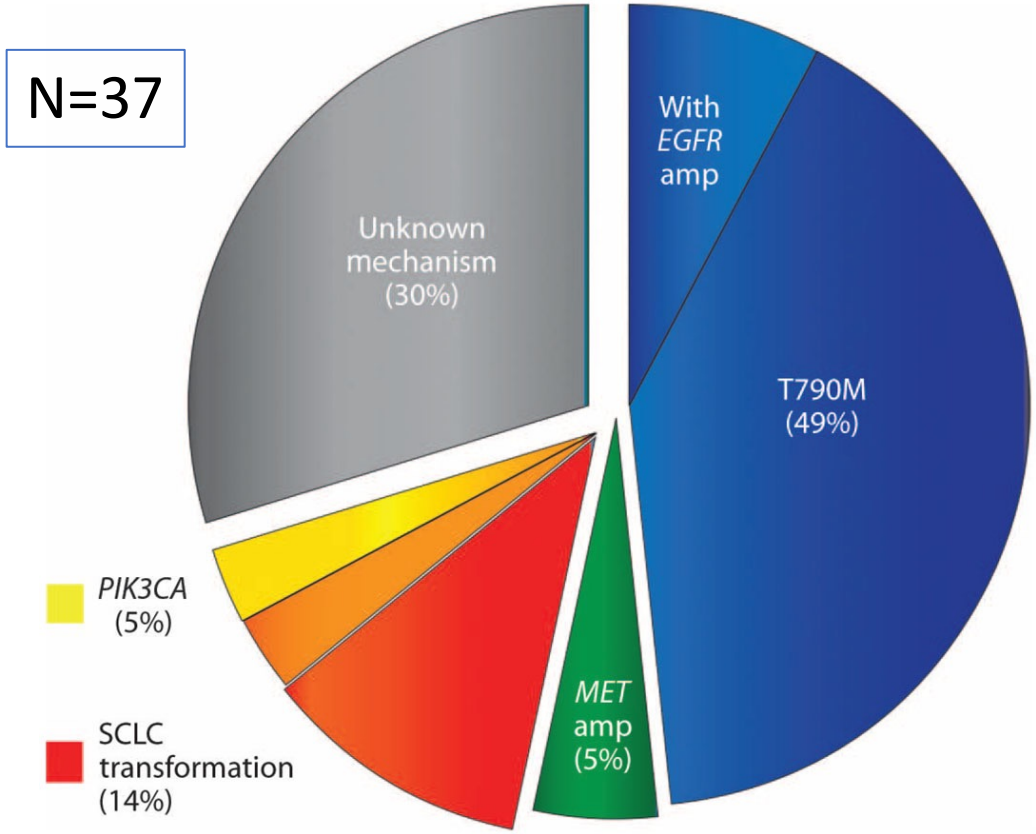
Yu H et al. Clin Cancer Res. 2013 Apr 15;19(8):2240-7.

Heterogeneous & multiple simultaneous mechanisms of resistance to 3rd generation EGFR TKI osimertinib

Ramanlingam SS et al. ESMO 2018, Munich

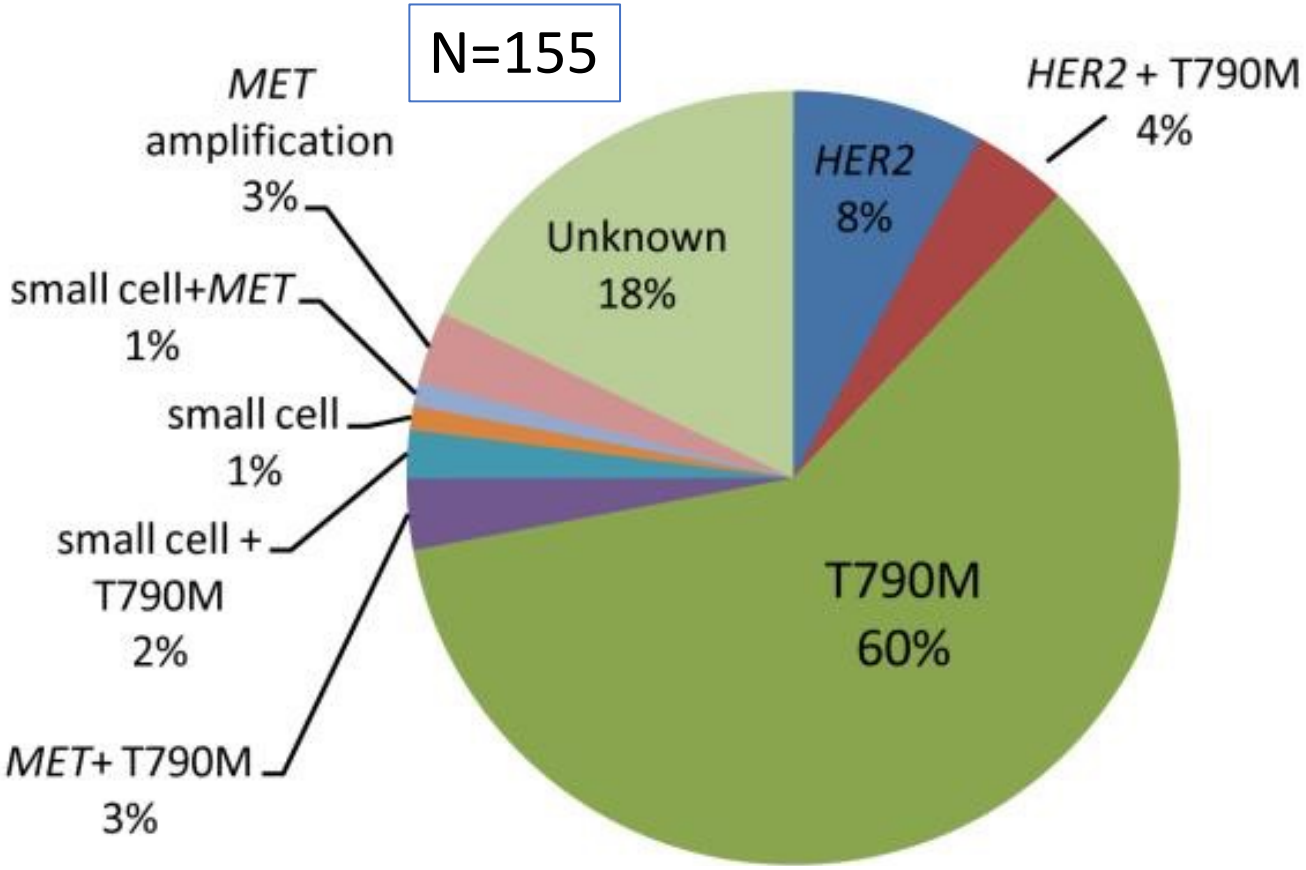
Courtesy of Joel W Neal, MD, PhD

EGFR TKI AR pie charts prior to the clinical NGS era



Genotypic and Histological Evolution of Lung Cancers Acquiring Resistance to EGFR Inhibitors

Science Transl Med March 2011



Analysis of Tumor Specimens at the Time of Acquired Resistance to EGFR-TKI Therapy in 155 Patients with *EGFR*-Mutant Lung Cancers

Clinical Cancer Res March 2013

Courtesy of Marc Ladanyi, MD

Agenda

Module 1: Role of Genomic Profiling; New Developments in NSCLC with an EGFR Mutation

- Dr McKenzie: A 60-year-old woman with NSCLC and an EGFR exon 19 deletion
- Dr Hussein: A 51-year-old man with metastatic lung adenocarcinoma and an EGFR exon 20 mutation

Module 2: Other Novel Targets for Patients with NSCLC

- Dr Neal: A 51-year-old man with RET-positive NSCLC
- Dr Neal: A 64-year-old woman with metastatic NSCLC and a HER2 exon 20 insertion
- Dr McKenzie: A 78-year-old man with NSCLC and a TRK fusion
- Dr Jasani: A 35-year-old woman with newly diagnosed mNSCLC – ALK mutation
- Dr Mohamed: A 71-year-old woman with metastatic adenocarcinoma of the lung with MET exon 14 skipping and MET amplification mutations – PD-L1 TPS 95%
- Dr Zafar: A 64-year-old woman with discordant BRAF mutation testing results

Case Presentation – Dr McKenzie: A 60-year-old woman with NSCLC and an EGFR exon 19 deletion

- 60yr Female
- Diagnosed 2017 with stage IV NSCLC adenocarcinoma
  - EGFR exon 19 deletion mutation p.E746_A751del and PDL-1 positive
- Initiated afatinib (9/2017 – 10/2018)
  - Developed EGFR T790M on liquid biopsy
- Osimertinib (10/2018 – 12/2019) until progression
  - T790M resolved; TP53 H193Y, MET/FGFR1/EGFR/CDK4/ amplifications emerge; ex19del remains
- Osimertinib + Crizotinib (2/2020 – 5/2020)
  - BRAF V600E, METD1228N (crizotinib resistant/cabozantinib sensitive), and KRAS G12V emerge
- Osimertinib + Pemetrexed/carboplatin (5/2020 – 1/2021)

Case Presentation – Dr McKenzie: A 60-year-old woman with NSCLC and an EGFR exon 19 deletion (continued)

Alteration	% cfDNA or Amp	Alter
EGFR E746_T751delinsA (Exon 19 deletion)	59.9%	0.06%
TP53 H193Y	17.0%	ND
KRAS G12V	3.7%	ND
FGFR1 I64M	0.5%	ND
EGFR S220C	0.4%	ND
BRAF V600E	0.3%	ND
MET D1228N	0.06%	ND

CDK4 Amplification Amplifications not graphed above	High (+++)	ND
EGFR Amplification Amplifications not graphed above	Medium (++)	ND
BRAF Amplification Amplifications not graphed above	Medium (++)	ND
FGFR1 Amplification Amplifications not graphed above	ND	ND
MET Amplification Amplifications not graphed above	ND	ND
HNF1A R229*	ND	ND
PDGFRA R979H	ND	ND
KIT Splice Site SNV	ND	ND
EGFR T790M	ND	ND

SARAH CANNON

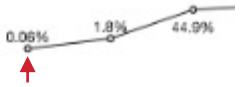
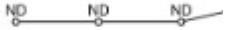
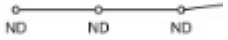
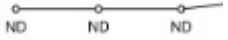
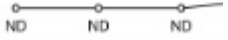
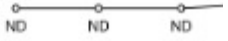
Case Presentation – Dr McKenzie: A 60-year-old woman with NSCLC and an EGFR exon 19 deletion (continued)

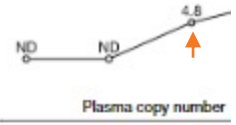
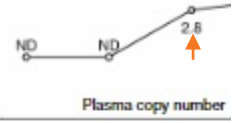
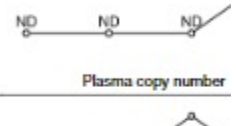
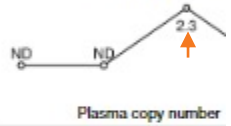
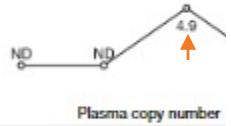
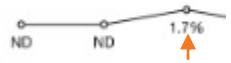
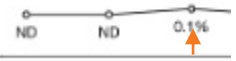
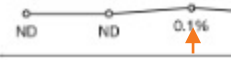
Alteration	% cfDNA or Amp	Alteration Tre
EGFR E746_T751delinsA (Exon 19 deletion)	59.9%	0.06% 1.8%
TP53 H193Y	17.0%	ND 0.2%
KRAS G12V	3.7%	ND ND
FGFR1 I64M	0.5%	ND ND
EGFR S220C	0.4%	ND ND
BRAF V600E	0.3%	ND ND
MET D1228N	0.06%	ND ND

CDK4 Amplification Amplifications not graphed above	High (+++)	ND ND Plasma
EGFR Amplification Amplifications not graphed above	Medium (++)	ND ND Plasma
BRAF Amplification Amplifications not graphed above	Medium (++)	ND ND Plasma
FGFR1 Amplification Amplifications not graphed above	ND	ND ND Plasma
MET Amplification Amplifications not graphed above	ND	ND ND Plasma
HNF1A R229*	ND	ND ND
PDGFRA R979H	ND	ND ND
KIT Splice Site SNV	ND	ND ND
EGFR T790M	ND	ND 0.3%

SARAH CANNON

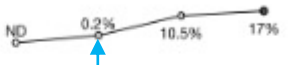
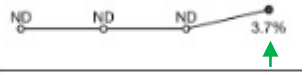
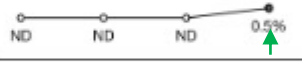
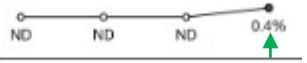
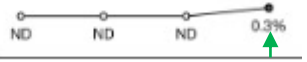
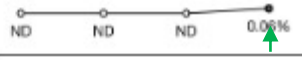
Case Presentation – Dr McKenzie: A 60-year-old woman with NSCLC and an EGFR exon 19 deletion (continued)

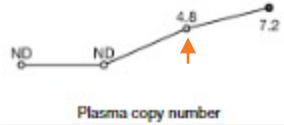
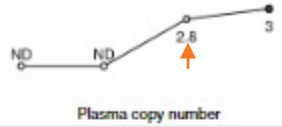
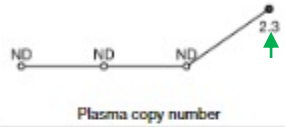
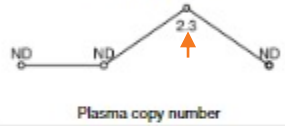
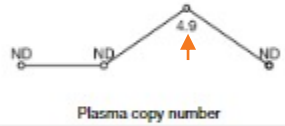
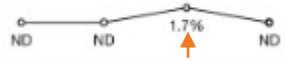
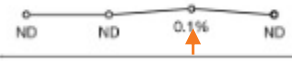
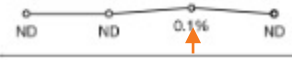
Alteration	% cfDNA or Amp	Alteration Trend
EGFR E746_T751delinsA (Exon 19 deletion)	59.9%	
TP53 H193Y	17.0%	
KRAS G12V	3.7%	
FGFR1 I64M	0.5%	
EGFR S220C	0.4%	
BRAF V600E	0.3%	
MET D1228N	0.06%	

CDK4 Amplification Amplifications not graphed above	High (+++)	
EGFR Amplification Amplifications not graphed above	Medium (++)	
BRAF Amplification Amplifications not graphed above	Medium (++)	
FGFR1 Amplification Amplifications not graphed above	ND	
MET Amplification Amplifications not graphed above	ND	
HNF1A R229*	ND	
PDGFRA R979H	ND	
KIT Splice Site SNV	ND	
EGFR T790M	ND	

SARAH CANNON

Case Presentation – Dr McKenzie: A 60-year-old woman with NSCLC and an EGFR exon 19 deletion (continued)

Alteration	% cfDNA or Amp	Alteration Trend
EGFR E746_T751delinsA (Exon 19 deletion)	59.9%	
TP53 H193Y	17.0%	
KRAS G12V	3.7%	
FGFR1 I64M	0.5%	
EGFR S220C	0.4%	
BRAF V600E	0.3%	
MET D1228N	0.06%	

CDK4 Amplification Amplifications not graphed above	High (+++)	
EGFR Amplification Amplifications not graphed above	Medium (++)	
BRAF Amplification Amplifications not graphed above	Medium (++)	
FGFR1 Amplification Amplifications not graphed above	ND	
MET Amplification Amplifications not graphed above	ND	
HNF1A R229*	ND	
PDGFRA R979H	ND	
KIT Splice Site SNV	ND	
EGFR T790M	ND	

SARAH CANNON

The NEW ENGLAND JOURNAL of MEDICINE

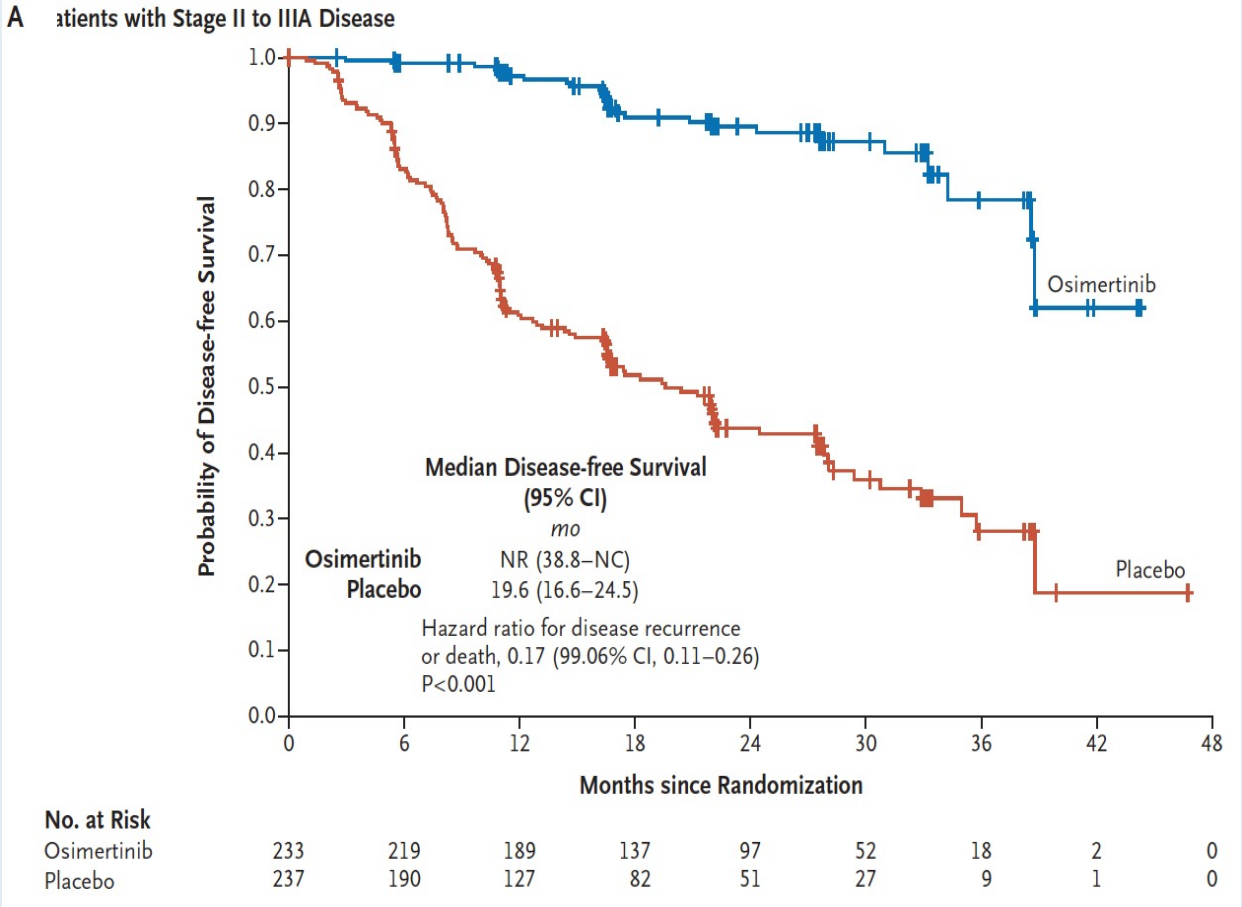
ORIGINAL ARTICLE

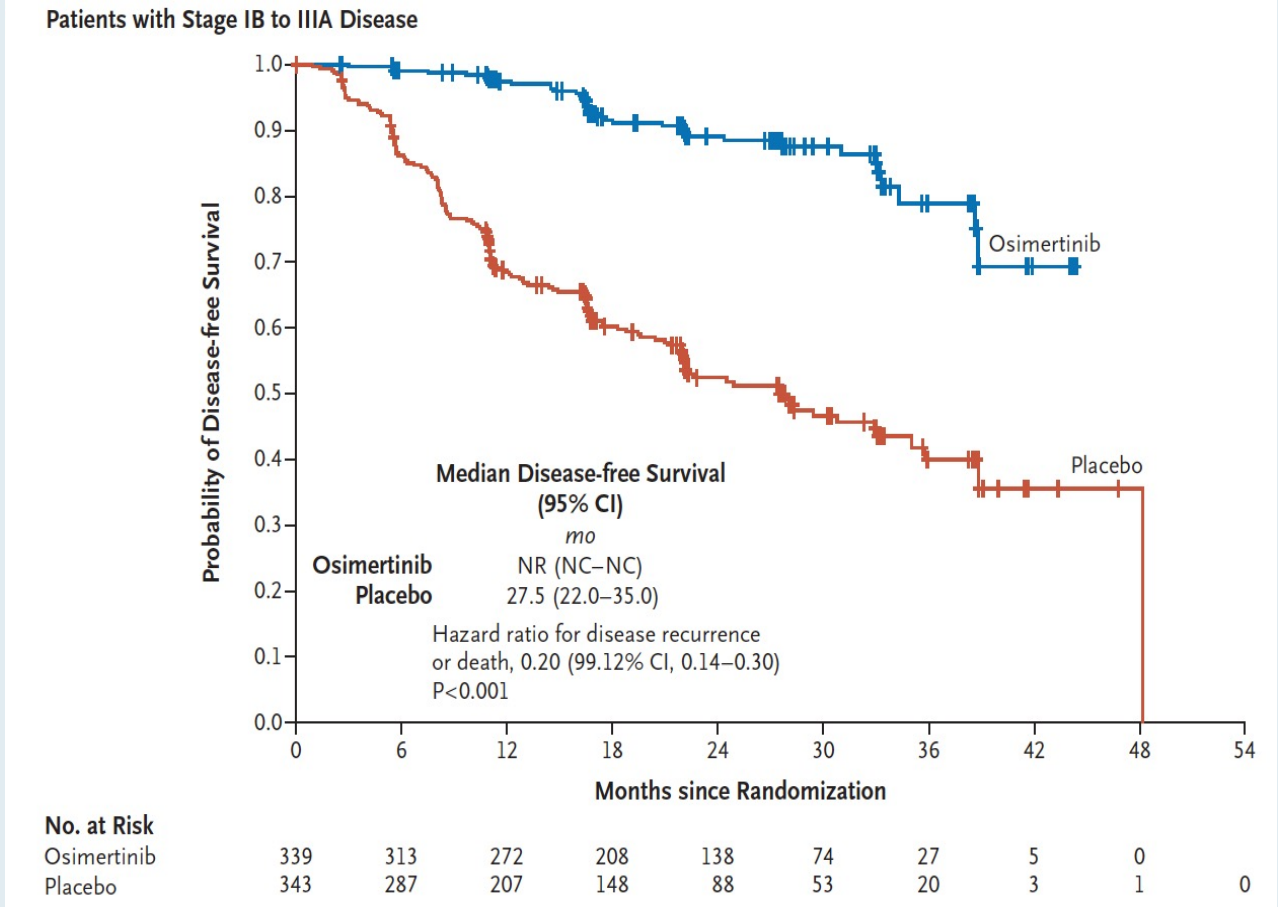
Osimertinib in Resected *EGFR*-Mutated Non–Small-Cell Lung Cancer

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

N Engl J Med 2020;383)18):1711-23.

ADAURA: Disease-Free Survival by Stage

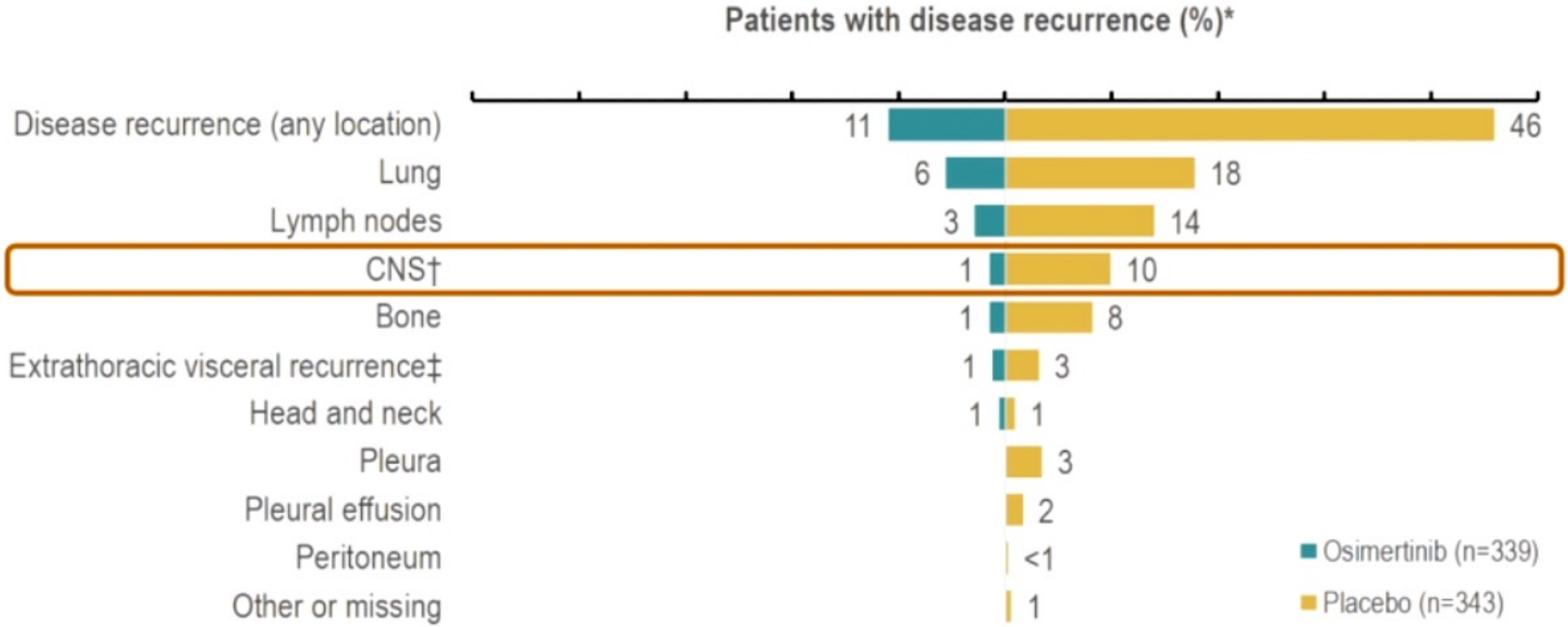




Wu YL et al. *N Engl J Med* 2020;383(18):1711-23.

RTP RESEARCH TO PRACTICE

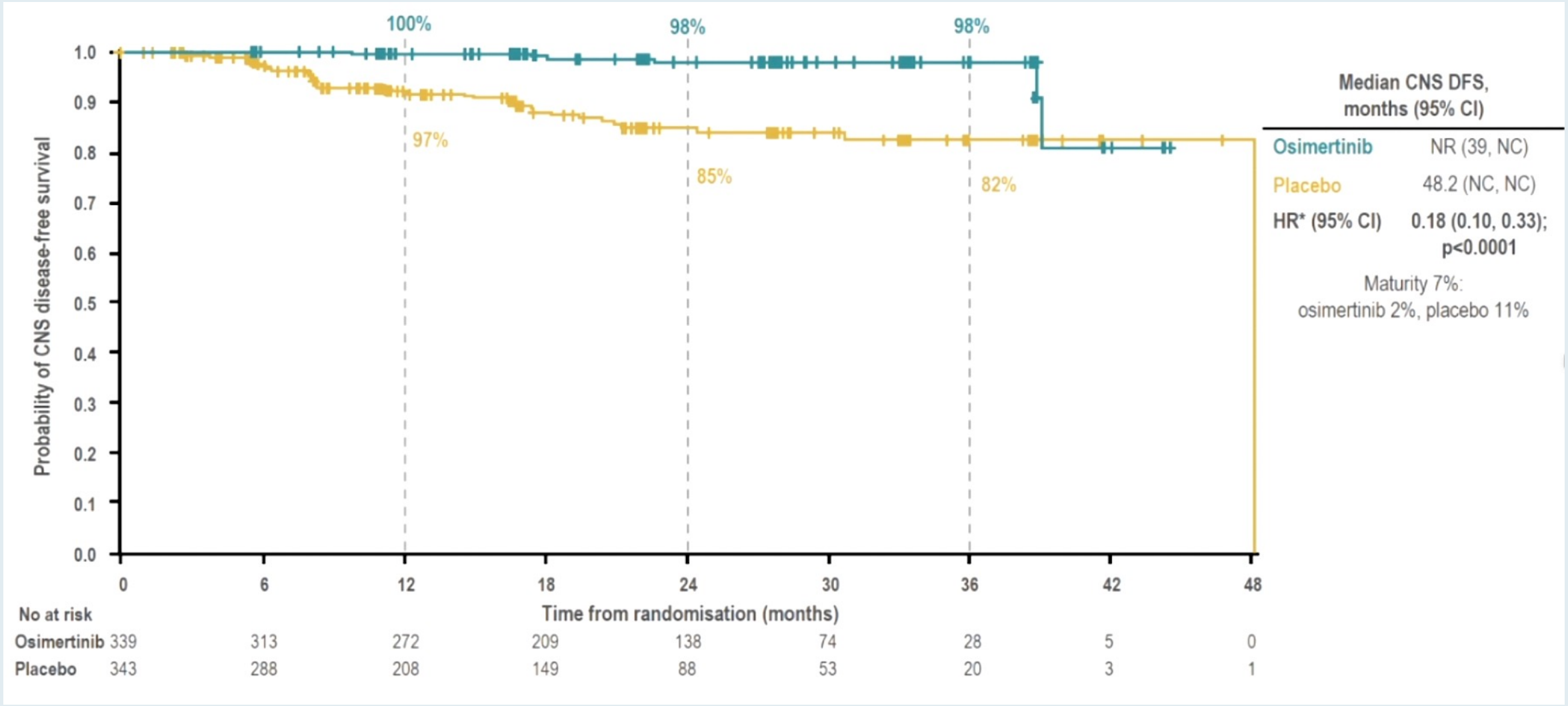
ADAURA: Sites of Disease Recurrence



Tsuboi M et al. ESMO 2020;Abstract LBA1.

RTP RESEARCH TO PRACTICE

ADAURA: CNS DFS in Overall Population



Tsuboi M et al. ESMO 2020;Abstract LBA1.

RTP RESEARCH TO PRACTICE

Agenda

Module 1: Role of Genomic Profiling; New Developments in NSCLC with an EGFR Mutation

- Dr McKenzie: A 60-year-old woman with NSCLC and an EGFR exon 19 deletion
- Dr Hussein: A 51-year-old man with metastatic lung adenocarcinoma and an EGFR exon 20 mutation

Module 2: Other Novel Targets for Patients with NSCLC

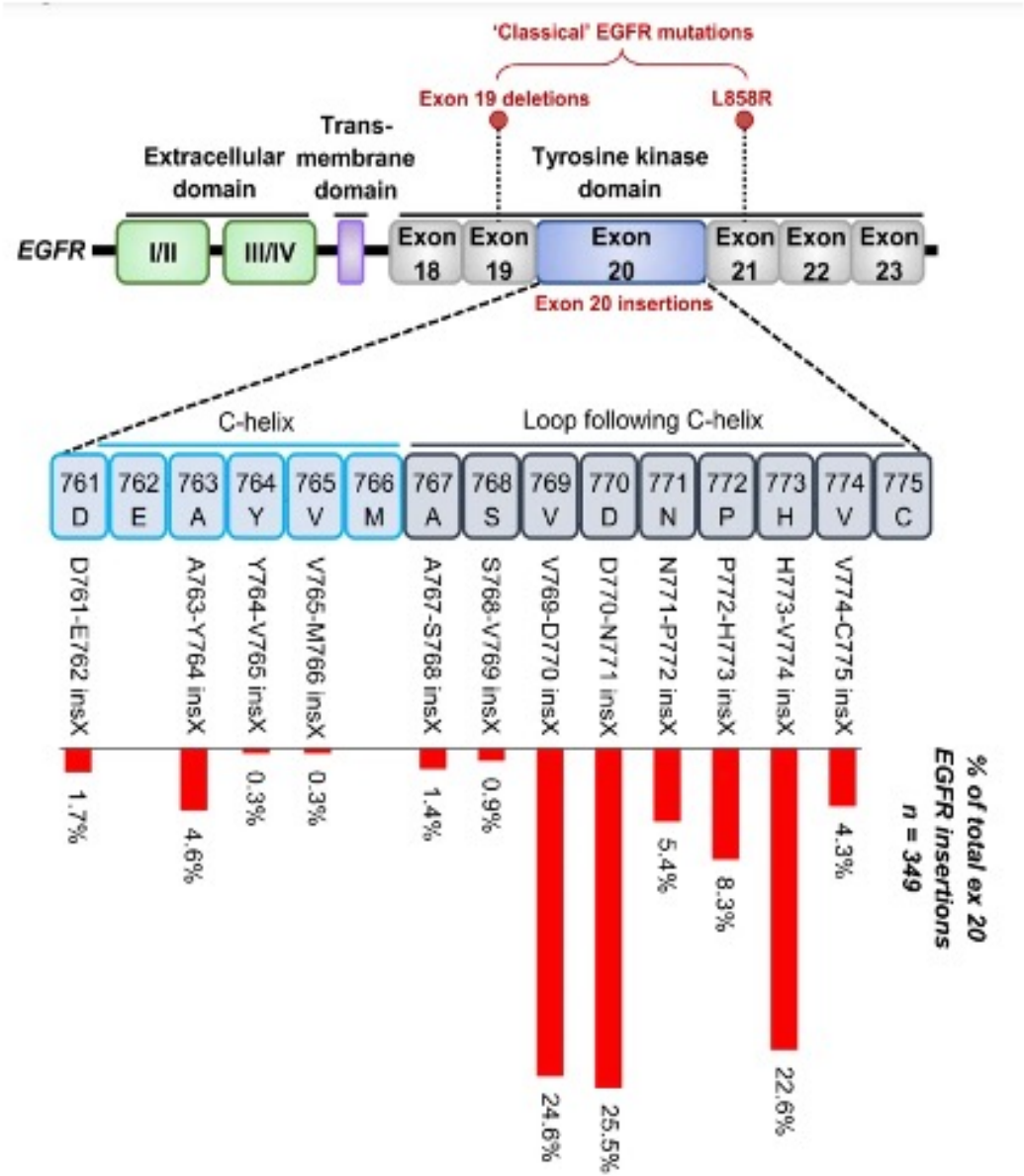
- Dr Neal: A 51-year-old man with RET-positive NSCLC
- Dr Neal: A 64-year-old woman with metastatic NSCLC and a HER2 exon 20 insertion
- Dr McKenzie: A 78-year-old man with NSCLC and a TRK fusion
- Dr Jasani: A 35-year-old woman with newly diagnosed mNSCLC – ALK mutation
- Dr Mohamed: A 71-year-old woman with metastatic adenocarcinoma of the lung with MET exon 14 skipping and MET amplification mutations – PD-L1 TPS 95%
- Dr Zafar: A 64-year-old woman with discordant BRAF mutation testing results

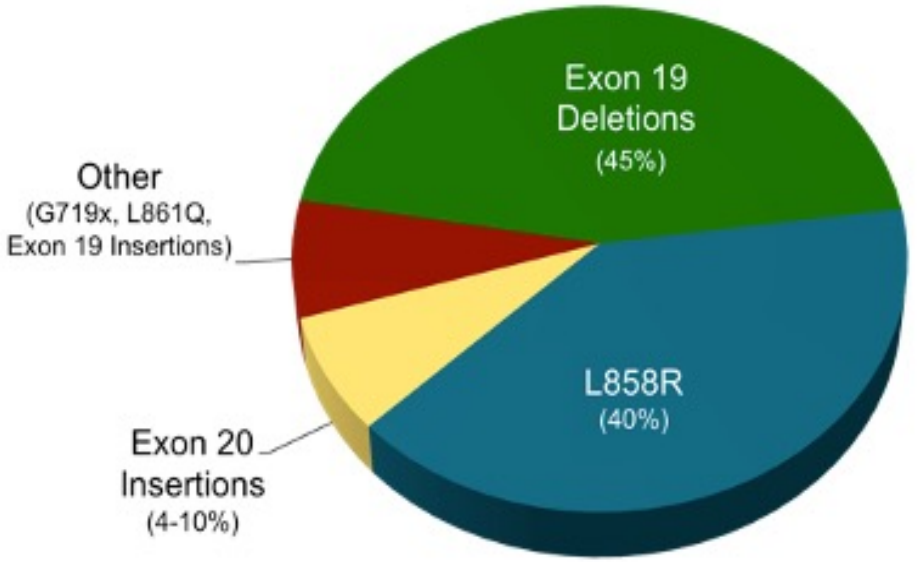
Case Presentation – Dr Hussein: A 51-year-old man with metastatic adenocarcinoma of the lung and an EGFR exon 20 mutation

Dr Atif Hussein

- Summer 2017: Patient presented with back pain
- 02/2018: Imaging revealed T9 lytic lesion and 3 cm left upper lobe lung mass
- Biopsy of T9: Metastatic adenocarcinoma
- NGS: exon 20 EGFR mutation |MSI stable |BRAF, ROS1, and ALK no abnormalities |PD-L1 negative 0%
- Radiation therapy to T9
- Started on carboplatin/pemetrexed/bevacizumab: Good PR in the lungs → maintenance pemetrexed/bevacizumab
- 5 months later PD in the lungs, bone and brain
- Cyberknife to the brain
- Started on pembrolizumab, developed autoimmune hepatitis
  - Despite steroids LFTs continued to be abnormal; pembrolizumab discontinued due to PD
- Started on TAK788 on a clinical trial → Stable disease for 3 months then worsening disease in the lungs, brain with leptomeningeal disease
- Administered high dose osimertinib with no response

Frequency of EGFR Exon 20 Mutations



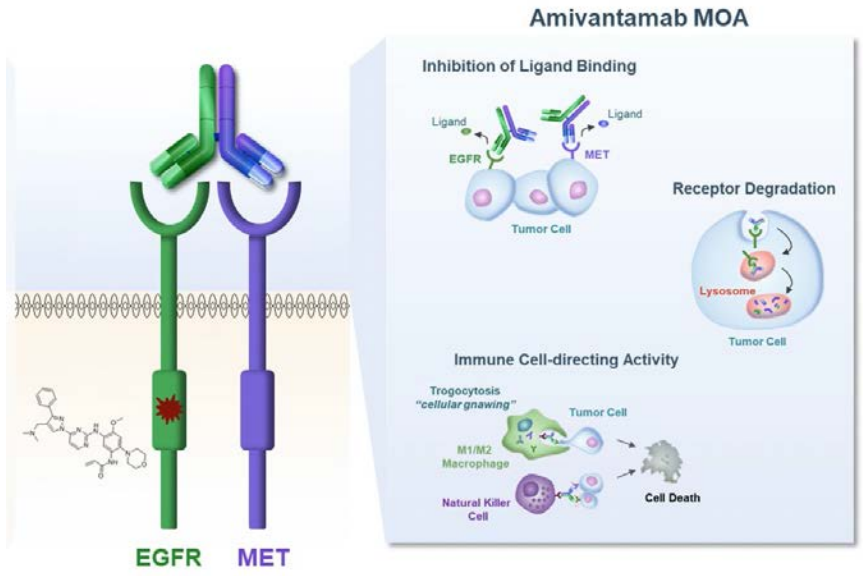


Exon 20 NSCLC: US and China				
		Exon 20 Frequency	Total Number of NSCLC Patients/year	
United States	EGFR HER2	2.1% 1.5%	3.6%	7700
China	EGFR HER2	2.4% 3.9%	6.3%	41100

Courtesy of Zofia Piotrowska, MD, MHS

Amivantamab

Amivantamab is a bispecific antibody targeting EGFR + MET

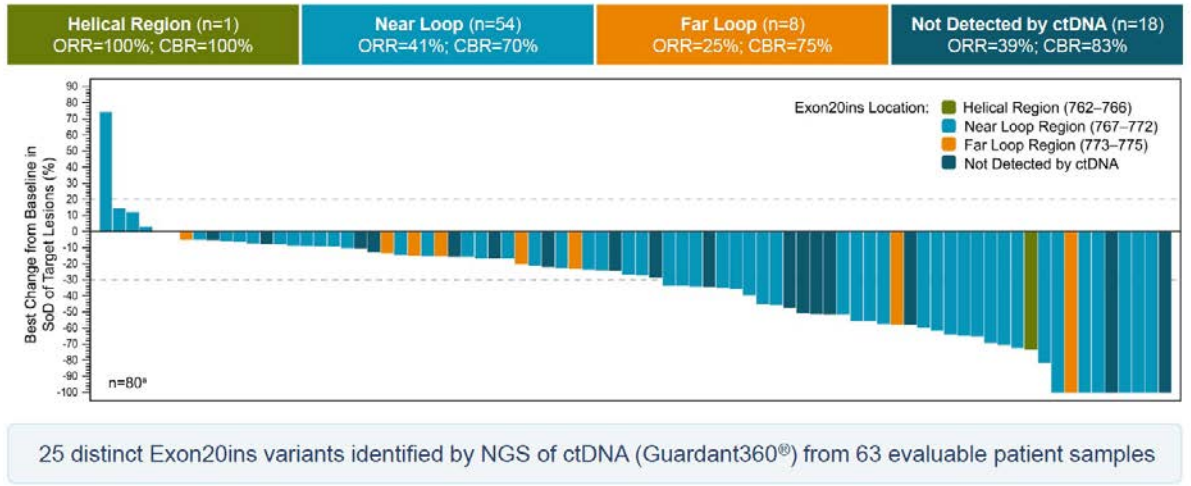


- Amivantamab recently received FDA approval for EGFR exon 20 insertion+ NSCLC

CHRYSALIS Trial

	N=81 (EGFR ins20)
ORR	40%
mDOT	11.1 mo (95% CI, 6.9-NR)
mPFS	8.3 mo (95% CI, 6.5-10.9)

Best ORR by Insertion Region of Exon 20 (detected by ctDNA)



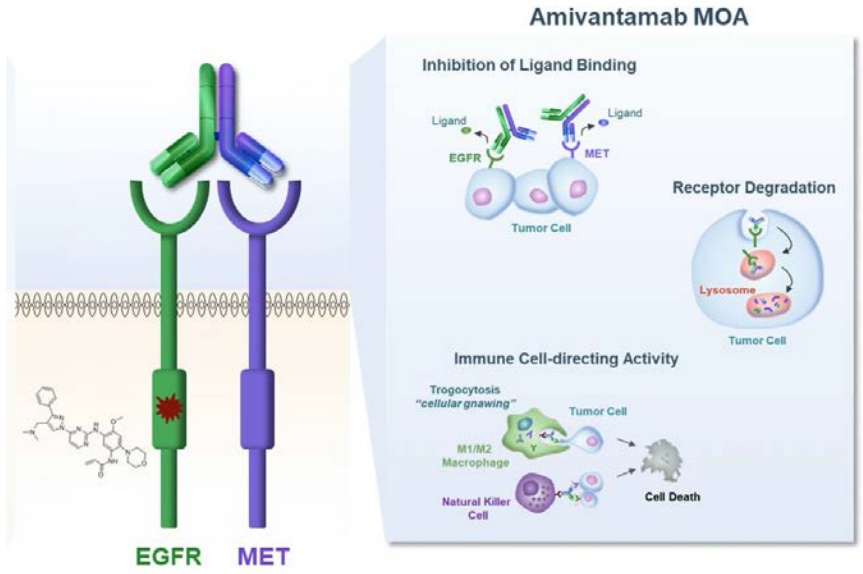
25 distinct Exon20ins variants identified by NGS of ctDNA (Guardant360®) from 63 evaluable patient samples

Courtesy of Zofia Piotrowska, MD, MHS

Chul B et al. ASCO 2021; Sabari J et al. WCLC 2021

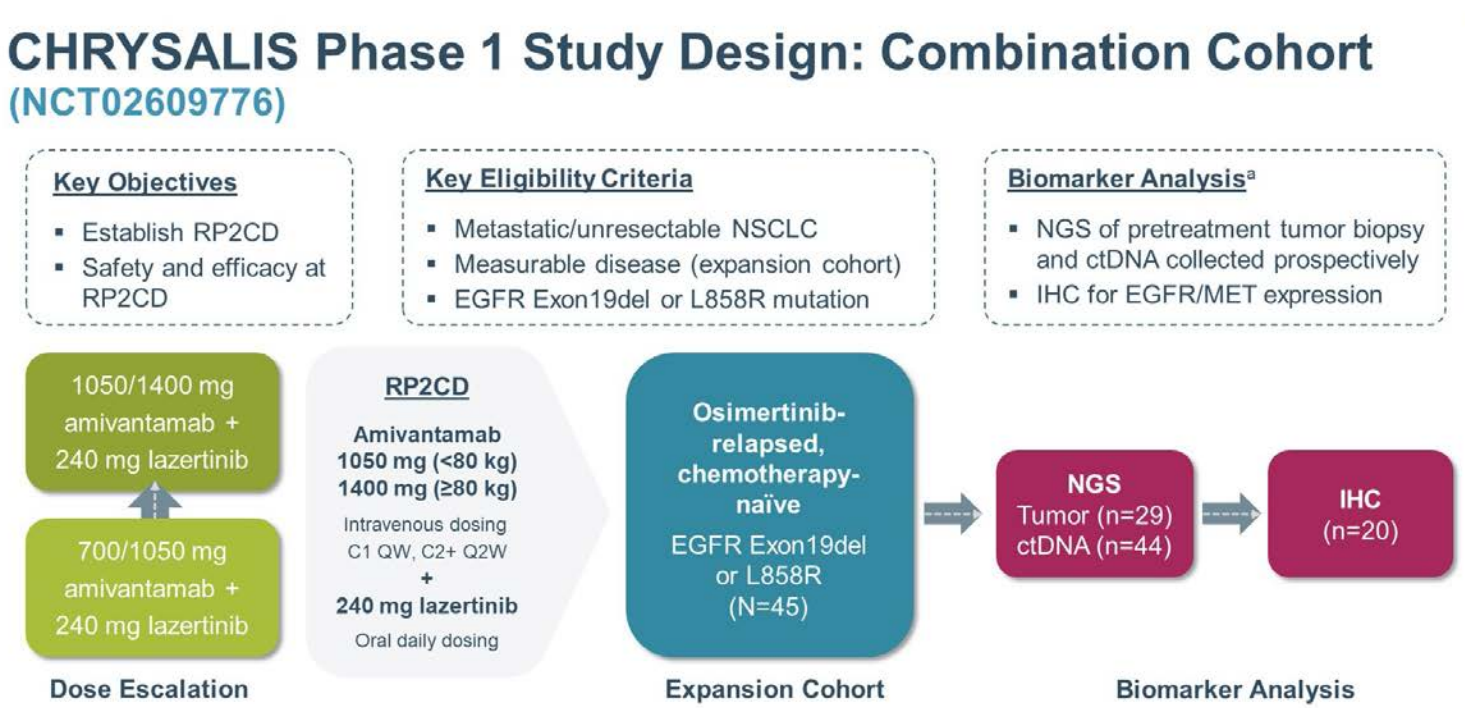
Amivantamab + Lazertinib

Amivantamab is a bispecific antibody targeting EGFR + MET



- Amivantamab recently received FDA approval for EGFR exon 20 insertion+ NSCLC
- Amivantamab + Lazertinib (3rd gen EGFR TKI) is being evaluated in TKI-resistant EGFR+ NSCLC

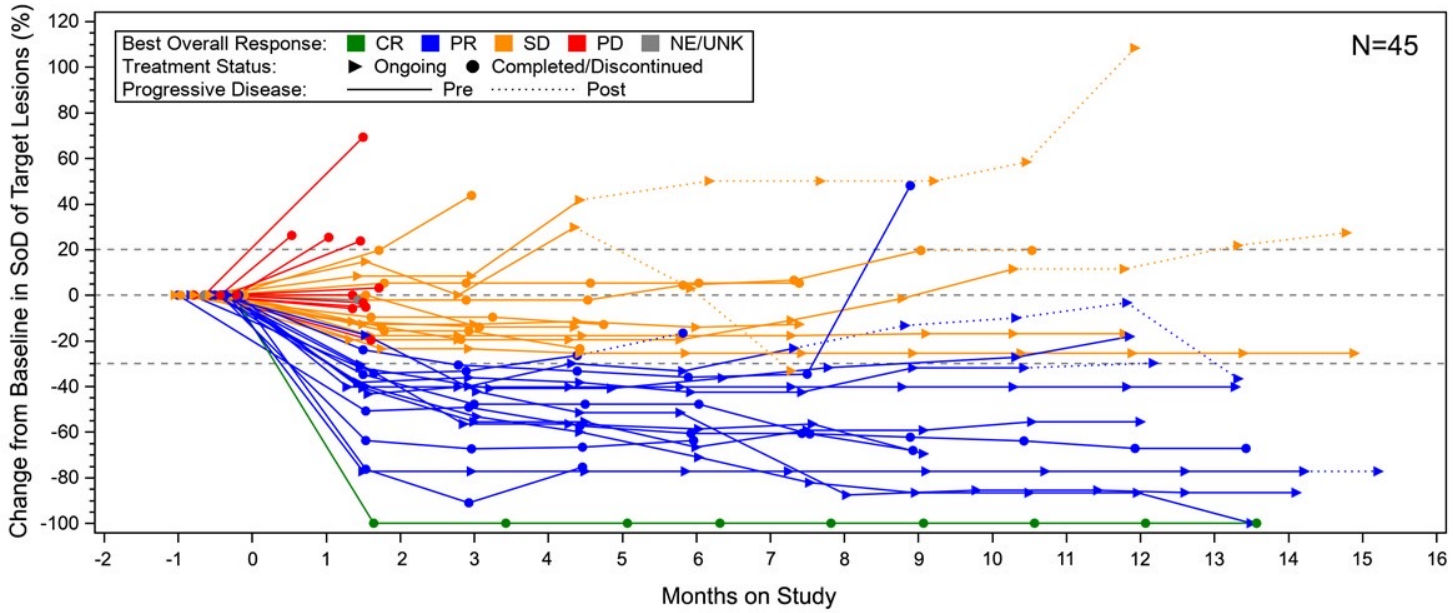
Amivantamab + Lazertinib in TKI-resistant EGFR+ NSCLC



Courtesy of Zofia Piotrowska, MD, MHS

1. Chul B et al. ASCO 2021

Amivantamab + Lazertinib



Investigator-assessed Response (N=45) *mF/U: 11.0 months (range, 1.0–15.0)* *mDOT: 5.6 months (range, 0.5–14.8)*	
ORR	36% (95% CI, 22–51)
mDOR, months	9.6 (95% CI, 5.3–NR)
DOR ≥6 months	69%
CBR	64% (95% CI, 49–78)
mPFS, months	4.9 (95% CI, 3.7–9.5)

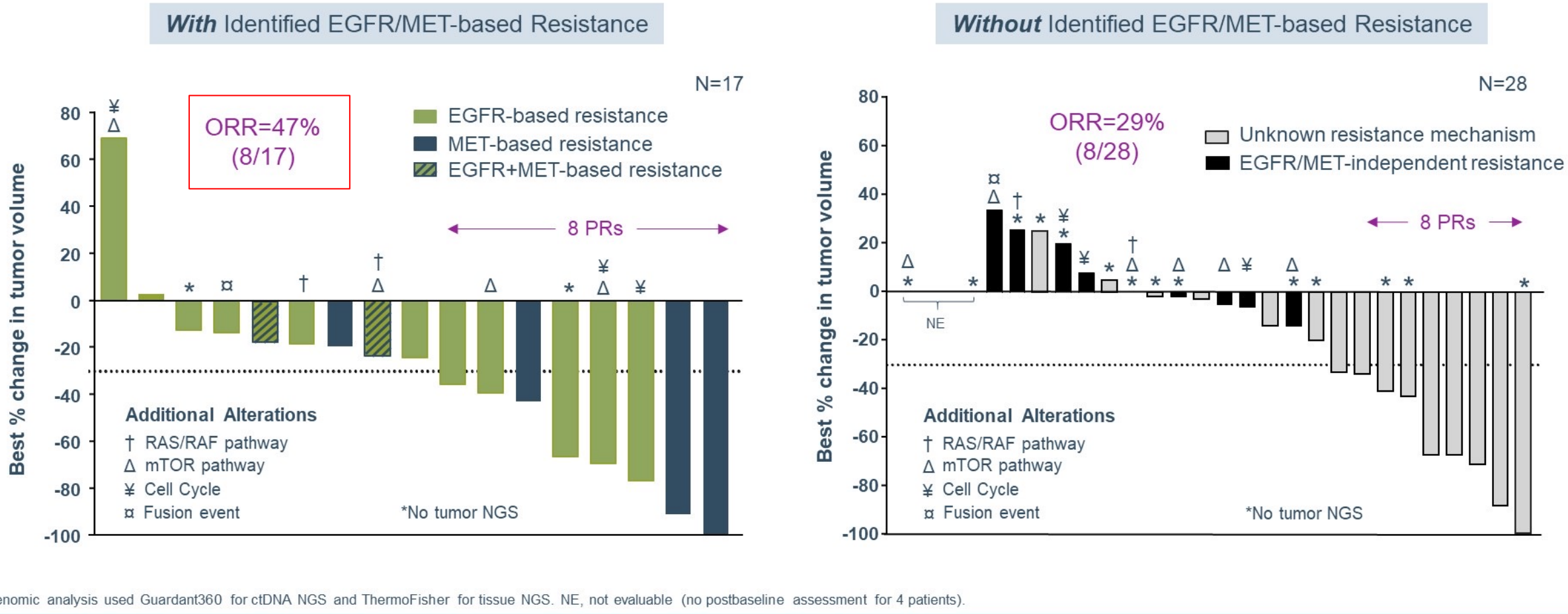
- Safety profile consistent with previous experience with amivantamab + lazertinib[1]
- Most common AEs were IRR (78%), rash (acneiform dermatitis, 51% + rash, 27%), and paronychia (49%)
  - Majority were grade 1–2
- Treatment-related: grade ≥3 AE (16%), discontinuations (4%), dose reductions (18%)

1. Chul B et al. ASCO 2021

Courtesy of Zofia Piotrowska, MD, MHS

MASSACHUSETTS GENERAL HOSPITAL CANCER CENTER

Amivantamab + Lazertinib

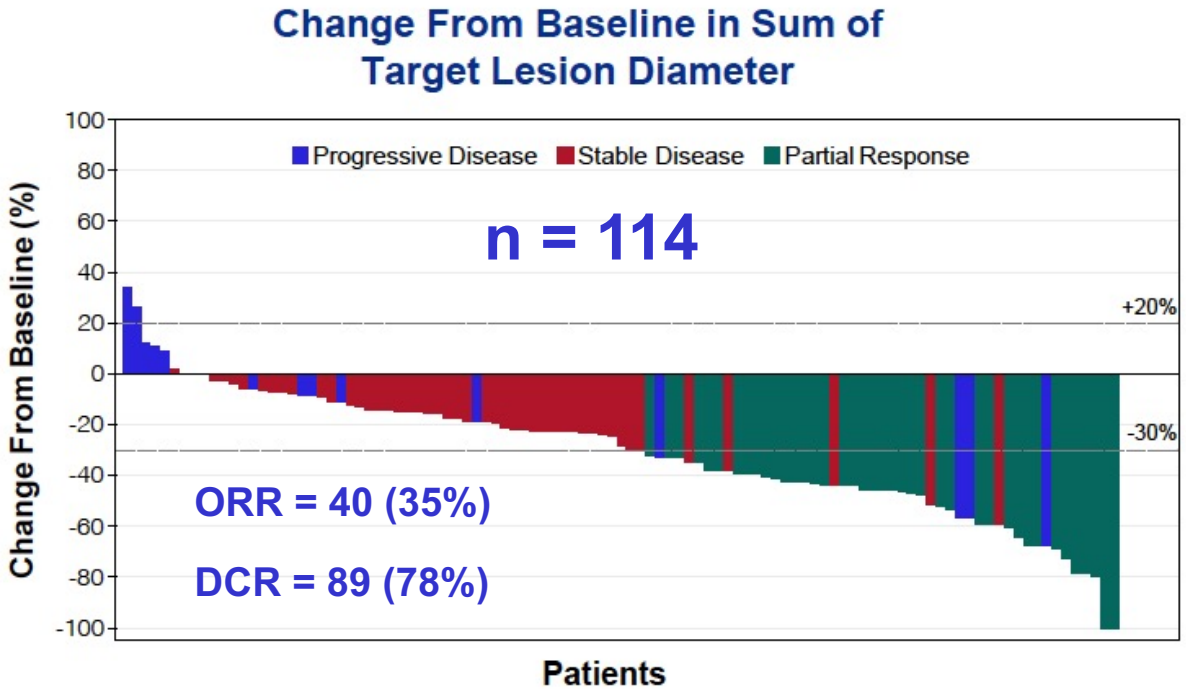


Genomic analysis used Guardant360 for ctDNA NGS and ThermoFisher for tissue NGS. NE, not evaluable (no postbaseline assessment for 4 patients).

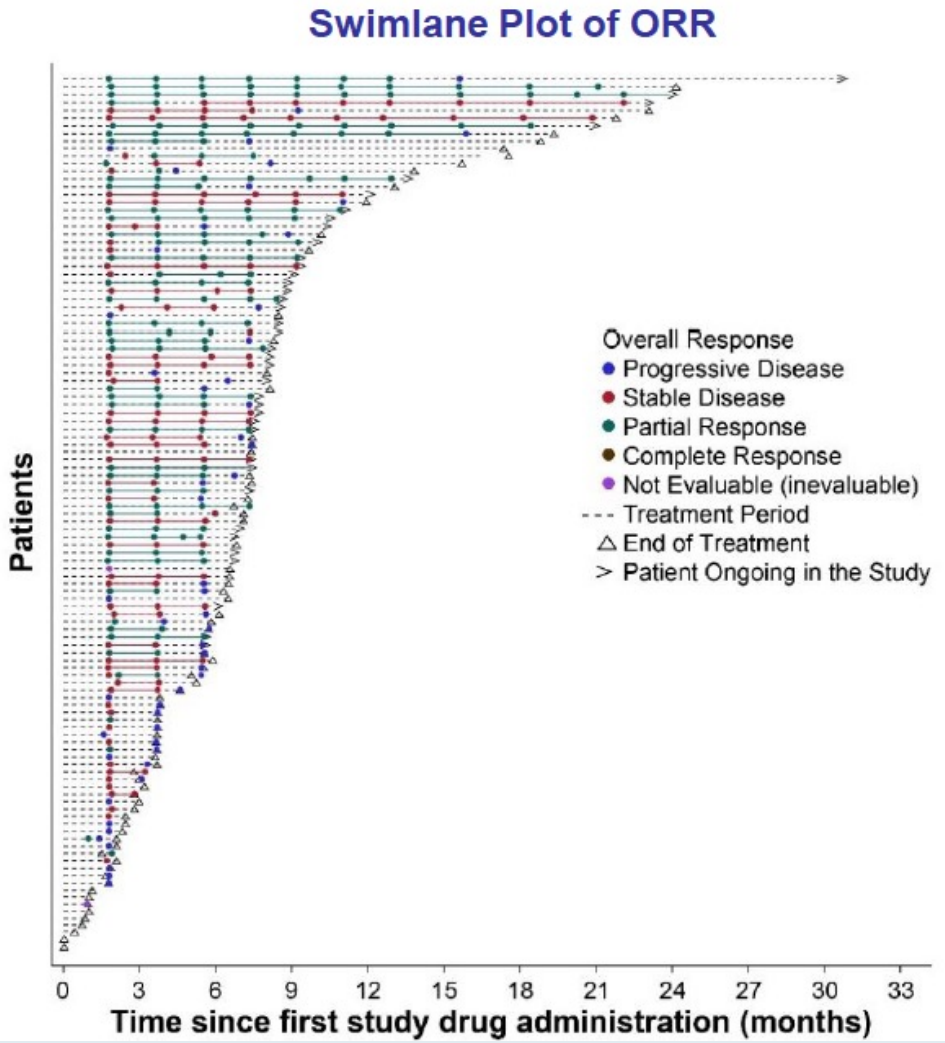
1. Chul B et al. ASCO 2021

Courtesy of Zofia Piotrowska, MD, MHS

EXCLAIM: Mobocertinib in Platinum-Pretreated NSCLC with EGFR Exon 20 Insertions



- 94 patients (82%) had a reduction from baseline in the sum of target lesion diameter



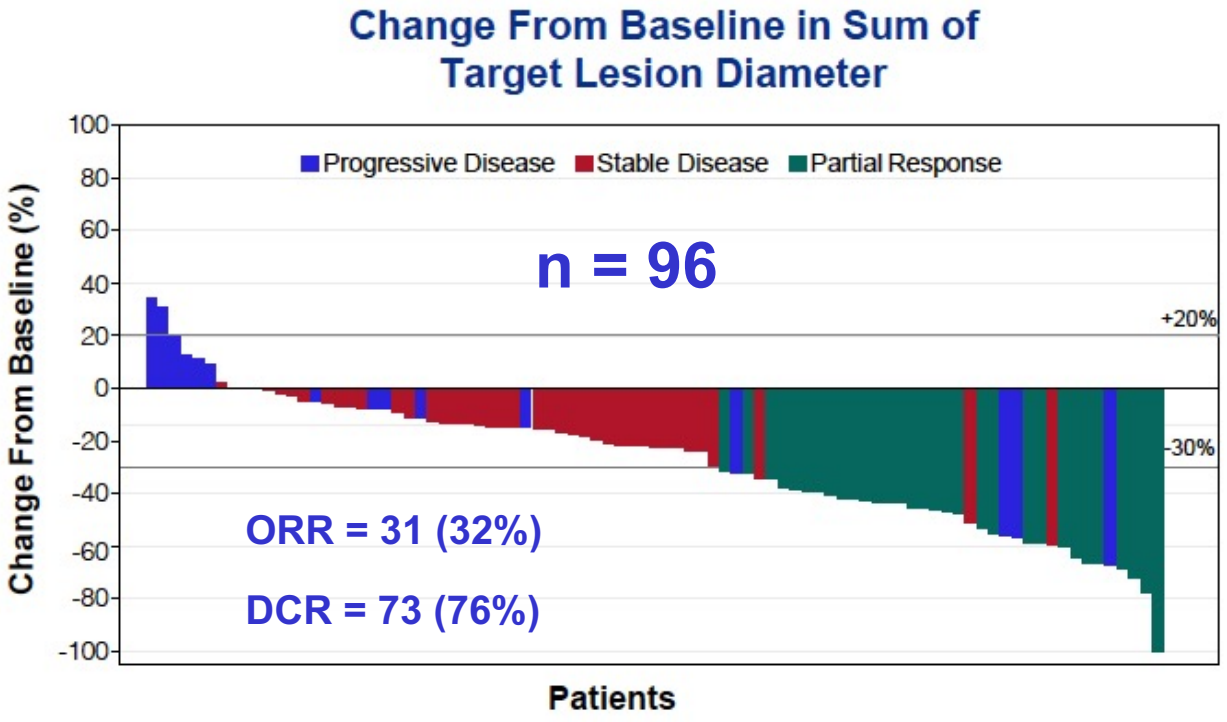
ORR, objective response rate; PPP, platinum-pretreated patients

Zhou C et al. IASLC/WCLC 2020;Abstract OA04.03

Courtesy of Zofia Piotrowska, MD, MHS

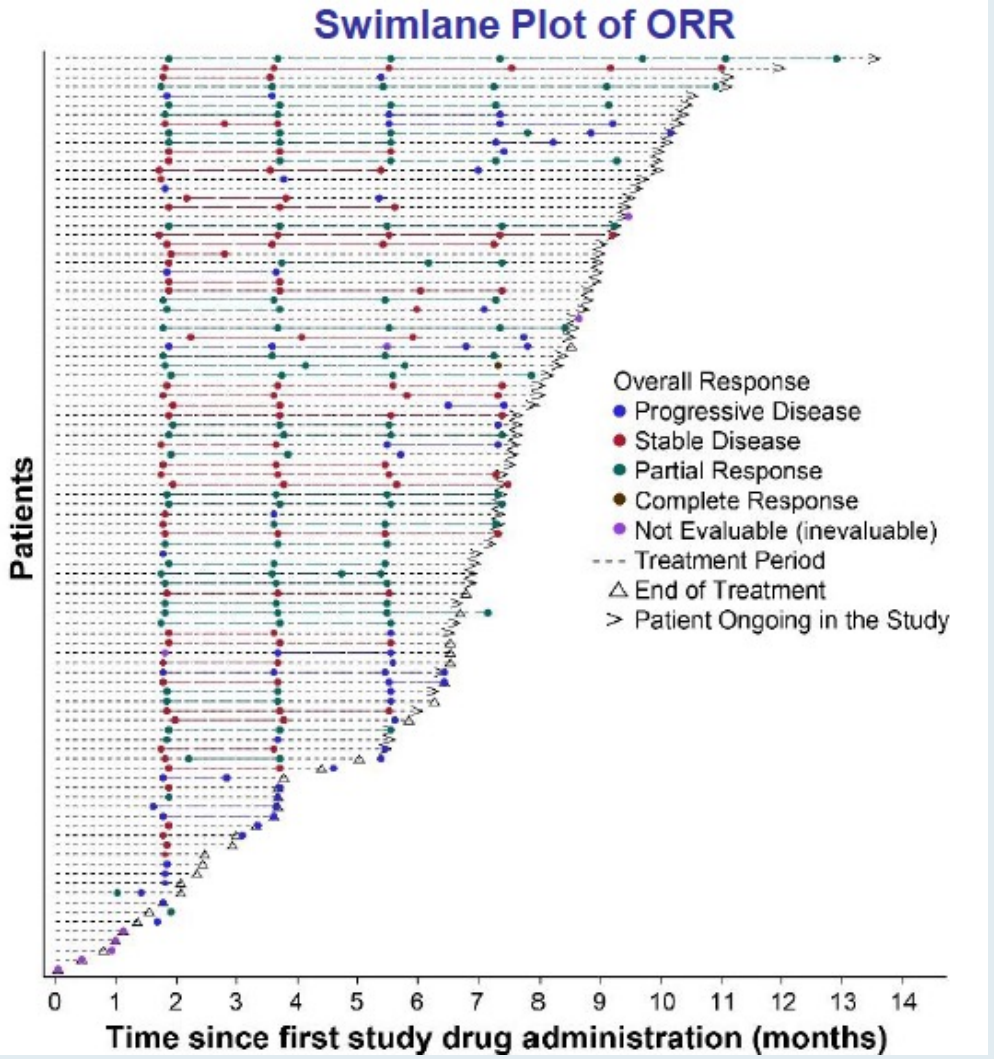
RTP RESEARCH TO PRACTICE

Mobocertinib Resulted in Reductions in Target Lesion Volume in EXCLAIM Cohort



- 77 patients (80%) had a reduction from baseline in the sum of target lesion diameter

ORR, objective response rate



Zhou C et al. IASLC/WCLC 2020;Abstract OA04.03

Courtesy of Zofia Piotrowska, MD, MHS

RTP RESEARCH TO PRACTICE

Agenda

Module 1: Role of Genomic Profiling; New Developments in NSCLC with an EGFR Mutation

- Dr McKenzie: A 60-year-old woman with NSCLC and an EGFR exon 19 deletion
- Dr Hussein: A 51-year-old man with metastatic lung adenocarcinoma and an EGFR exon 20 mutation

Module 2: Other Novel Targets for Patients with NSCLC

- Dr Neal: A 51-year-old man with RET-positive NSCLC
- Dr Neal: A 64-year-old woman with metastatic NSCLC and a HER2 exon 20 insertion
- Dr McKenzie: A 78-year-old man with NSCLC and a TRK fusion
- Dr Jasani: A 35-year-old woman with newly diagnosed mNSCLC – ALK mutation
- Dr Mohamed: A 71-year-old woman with metastatic adenocarcinoma of the lung with MET exon 14 skipping and MET amplification mutations – PD-L1 TPS 95%
- Dr Zafar: A 64-year-old woman with discordant BRAF mutation testing results

Agenda

Module 1: Role of Genomic Profiling; New Developments in NSCLC with an EGFR Mutation

- Dr McKenzie: A 60-year-old woman with NSCLC and an EGFR exon 19 deletion
- Dr Hussein: A 51-year-old man with metastatic lung adenocarcinoma and an EGFR exon 20 mutation

Module 2: Other Novel Targets for Patients with NSCLC

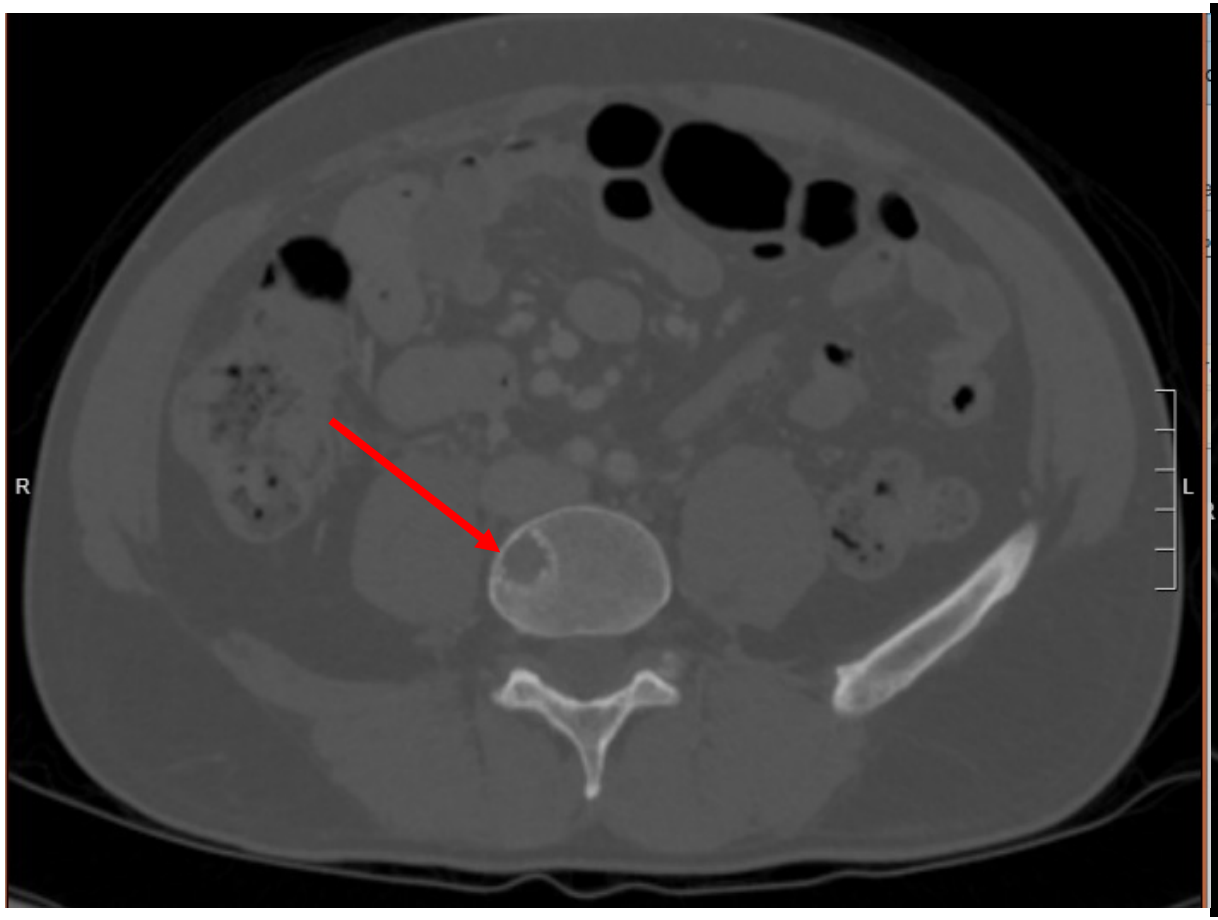
- Dr Neal: A 51-year-old man with RET-positive NSCLC
- Dr Neal: A 64-year-old woman with metastatic NSCLC and a HER2 exon 20 insertion
- Dr McKenzie: A 78-year-old man with NSCLC and a TRK fusion
- Dr Jasani: A 35-year-old woman with newly diagnosed mNSCLC – ALK mutation
- Dr Mohamed: A 71-year-old woman with metastatic adenocarcinoma of the lung with MET exon 14 skipping and MET amplification mutations – PD-L1 TPS 95%
- Dr Zafar: A 64-year-old woman with discordant BRAF mutation testing results

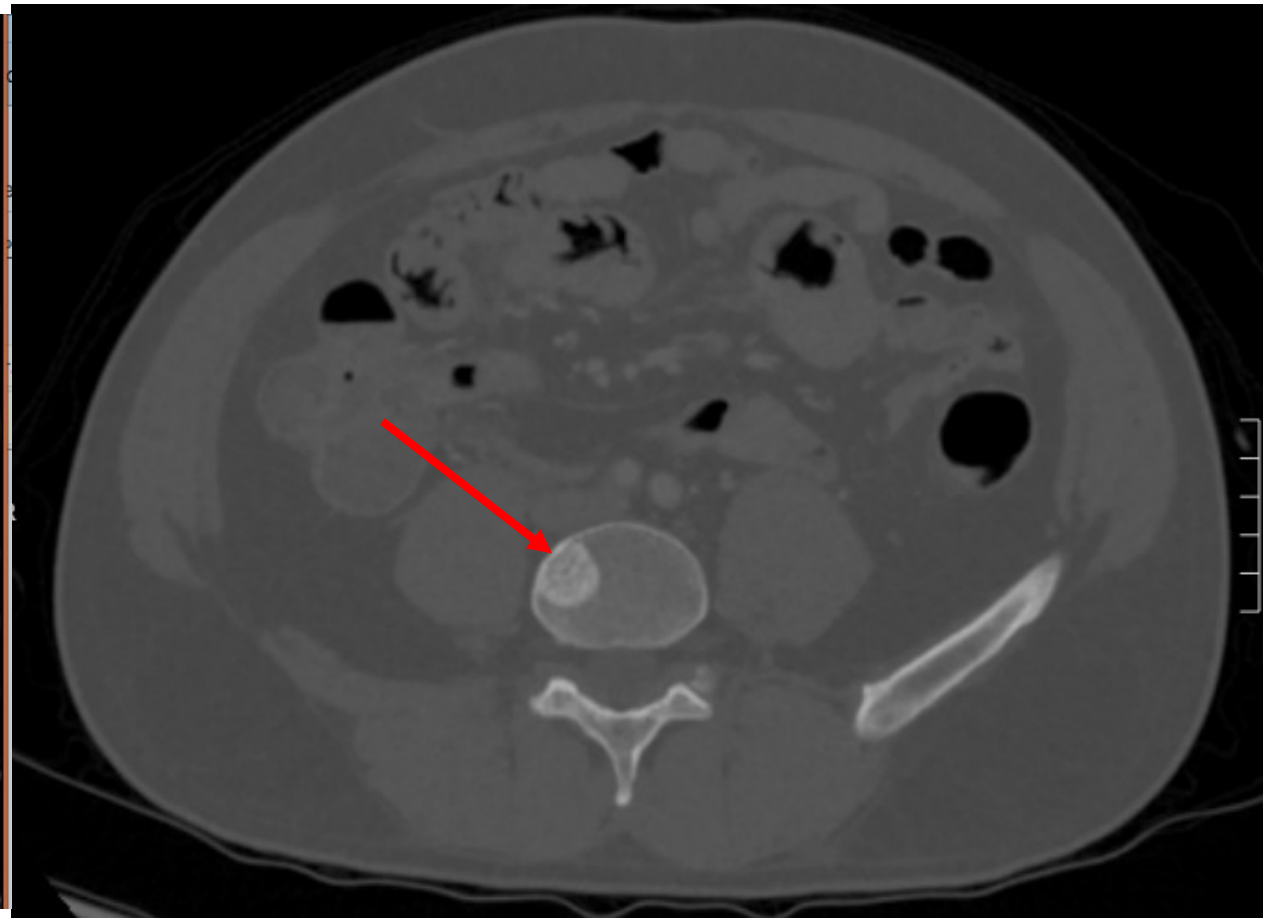
Case Presentation – Dr Neal: A 51-year-old man with RET positive NSCLC

- 51 year old Vietnamese neversmoking man presented for right sided loss of body sensation
- MRI showed right pontine hematoma with 1.3 cm underlying metastasis and other scattered mets
- CT showed 1/7 cm left lower lobe mass with hilar hode and pleural nodule, multiple bone mets
- Biospy of right radius bone – adenocarcinoma, TTF1 positive, PD-L1 10%, EGFR, ALK, ROS1 negative.
- Radiosurgery to 5 brain mets
- Systemic chemotherapy with carbo/pemetrexed/pembrolizumab
- After 5 months, progression with new liver mets and progressive brain mets. Repeat biopsy with NGS sequencing: RET fusion positive
- Started selpercatinib 160 mg BID; 6 week interval response in lungs, brain. Sclerosis of bone lesions.

Case Presentation – Dr Neal: A 51-year-old man with RET positive NSCLC (continued)

Pre- and 6 week month post selpercatinib showing bone treatment response (sclerosis/pseudoprogression)



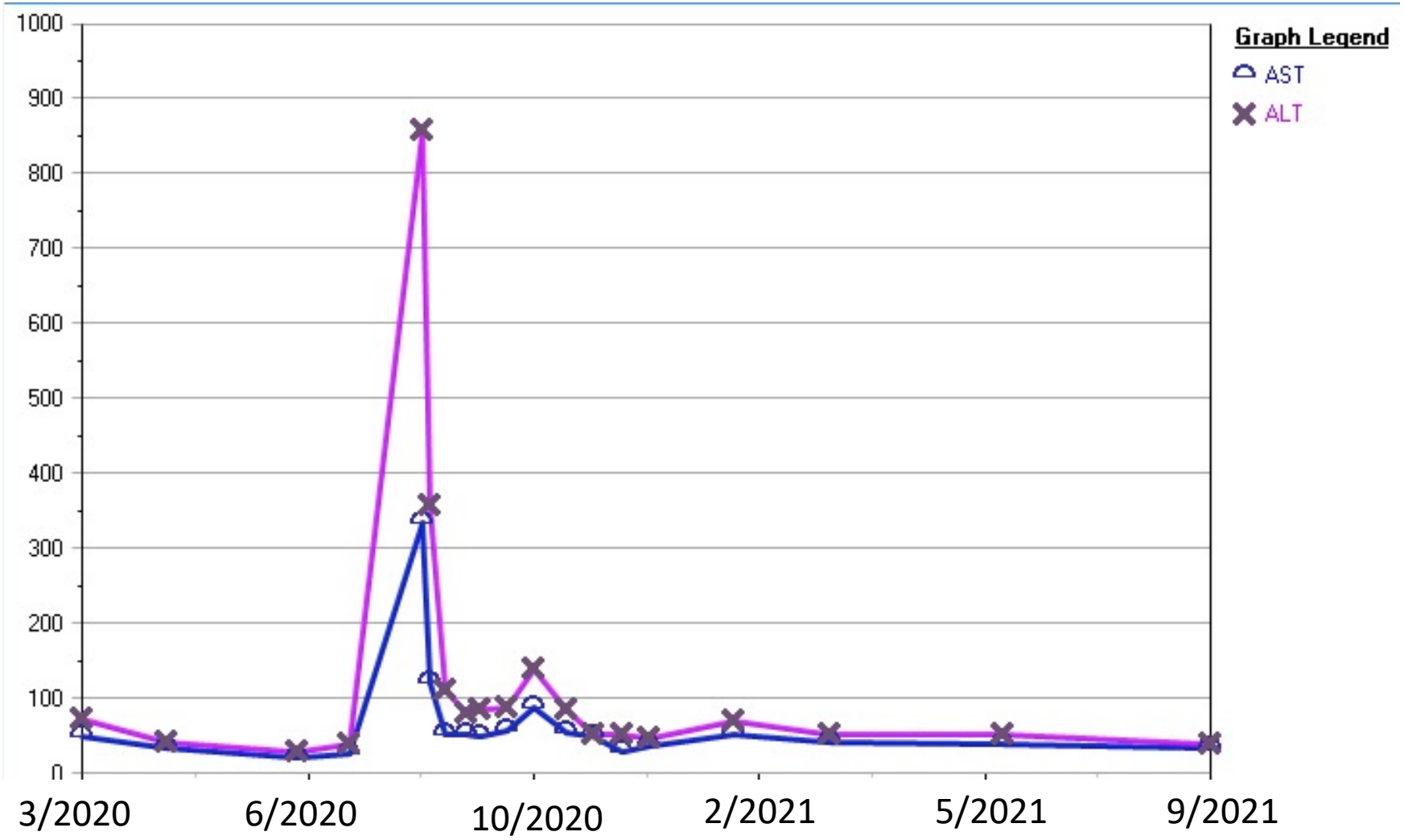


Case Presentation – Dr Neal: A 51-year-old man with RET positive NSCLC (continued)

- Aminotransferase spike 2 weeks after starting
- Held drug, reached ULN within 2 more weeks
- Restarted at 80 mg BID
- No significant LFT elevation after 4 weeks
- Escalated to 160 mg PO QAM, 80 mg PO QPM; LFTs close to ULN but stable
- Ongoing response at 14 months!

Case Presentation – Dr Neal: A 51-year-old man with RET positive NSCLC (continued)

LFT graph

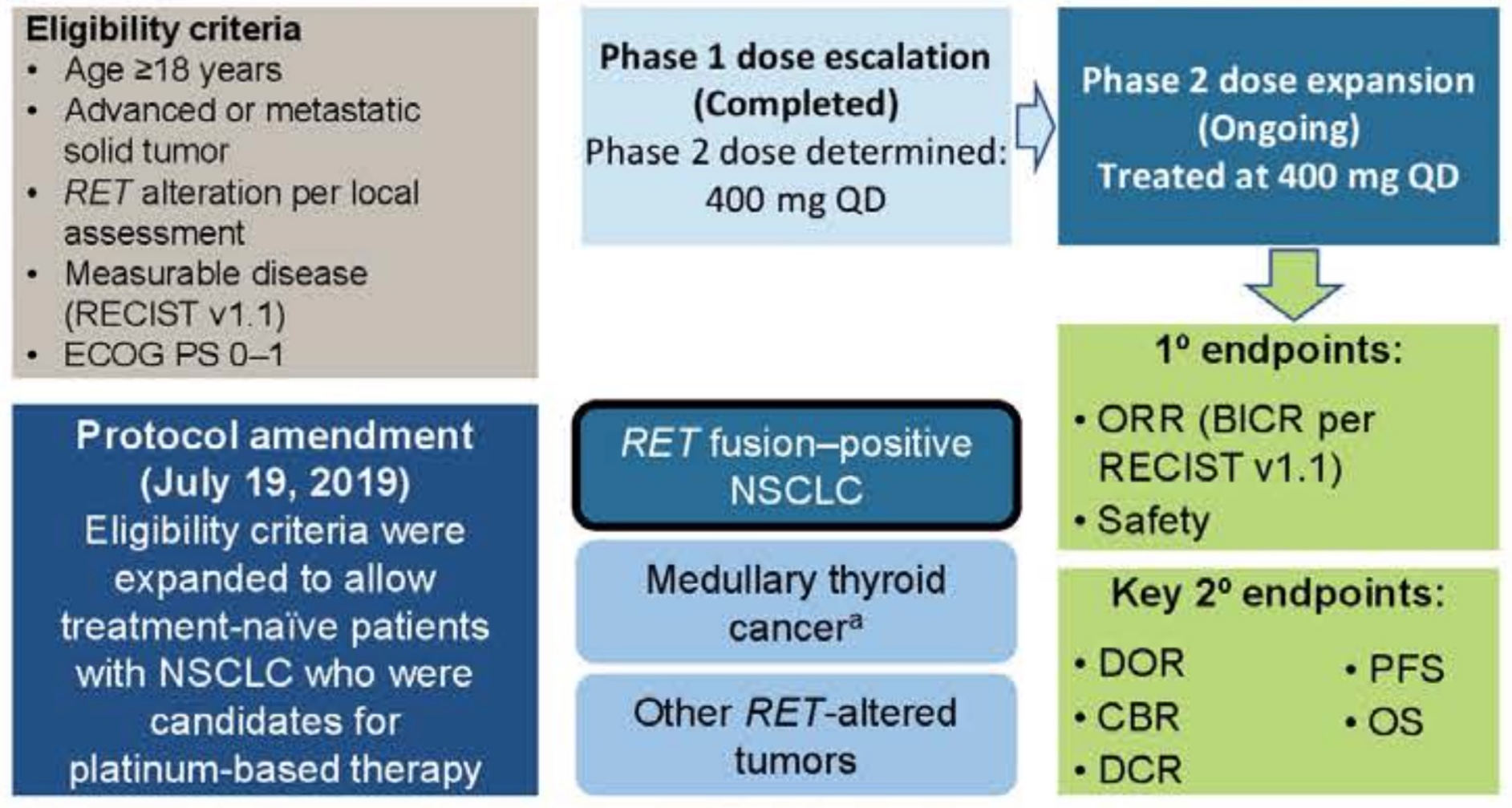


Safety and Efficacy of Pralsetinib in Patients with Advanced *RET* Fusion-Positive Non-Small Cell Lung Cancer: Update from the ARROW Trial

Curigliano G et al.

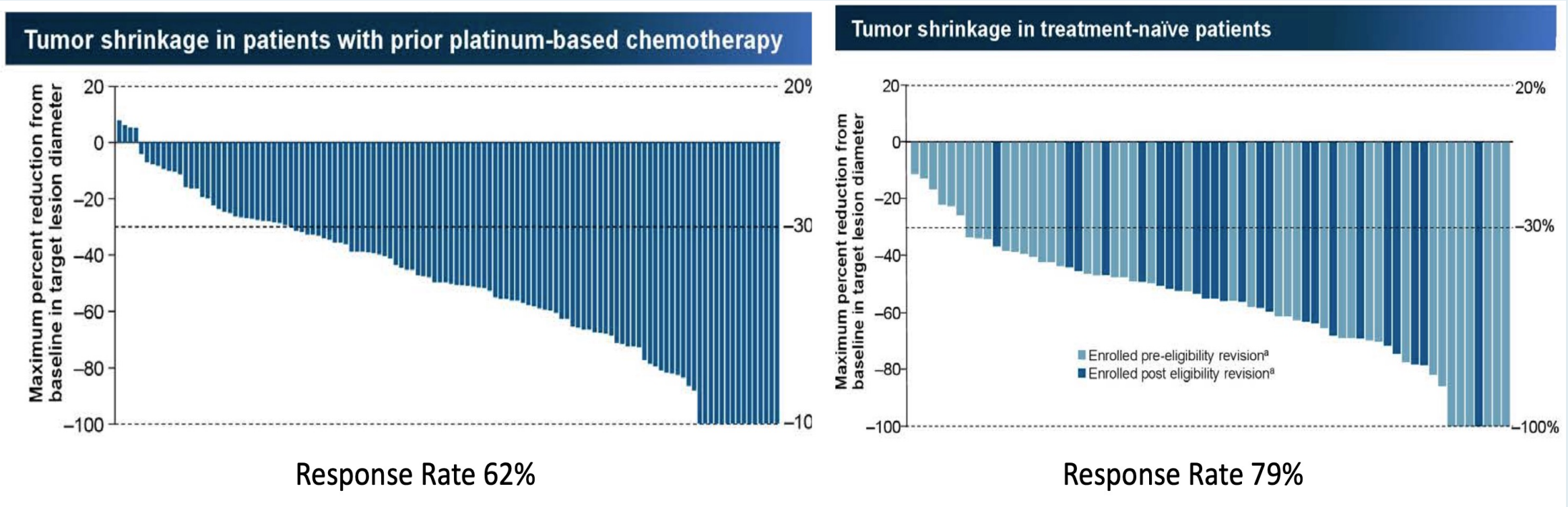
ASCO 2021;Abstract 9089.

ARROW Study Design



Curigliano J et al. ASCO 2021;Abstract 9089.

ARROW Primary Endpoint: Response to Pralsetinib



ORR (response-evaluable): All – 69%, Prior platinum – 62%, Treatment-naïve – 79%

Curigliano J et al. ASCO 2021;Abstract 9089.

ARROW: Efficacy Summary

	Measurable disease population					
	RET fusion–positive NSCLC (n=216)	Treatment-naïve			Prior treatment	
		All (n=68)	Pre-eligibility revision (n=43)[a]	Post eligibility revision (n=25)[a]	Prior platinum (n=126)	Prior non-platinum (n=22)
ORR, % (95% CI)	**69** (62–75)	**79** (68–88)	**74** (59–87)	**88** (69–98)	**62** (53–70)	**73** (50–89)
Best overall response, n (%)						
CR	9 (4)	4 (6)	4 (9)	0	5 (4)	0
PR	139 (64)	50 (74)	28 (65)	22 (88)	73 (58)	16 (73)
SD	50 (23)	9 (13)	7 (16)	2 (8)	37 (29)	4 (18)
PD	10 (5)	3 (4)	3 (7)	0	5 (4)	2 (9)
NE	8 (4)	2 (3)	1 (2)	1 (4)	6 (5)	0
DCR, % (95% CI)[b]	92 (87–95)	93 (84–98)	91 (78–97)	96 (80–100)	91 (85–96)	91 (71–99)
CBR, % (95% CI)[c]	77 (71–82)	82 (71–91)	79 (64–90)	88 (69–98)	74 (65–81)	77 (55–92)
mDOR, mo (95% CI)	22.3 (15.1–NR)	NR (9.0–NR)	11.0 (7.4–NR)	NR (NR–NR)	22.3 (15.1–NR)	NR (9.2–NR)
mPFS, mo (95% CI)[d]	16.4 (11.0–24.1) n=233	13.0 (9.1–NR) n=75	10.9 (7.7–NR) n=47	NR (NR–NR) n=28	16.5 (10.5–24.1) n=136	12.8 (9.1–NR) n=22

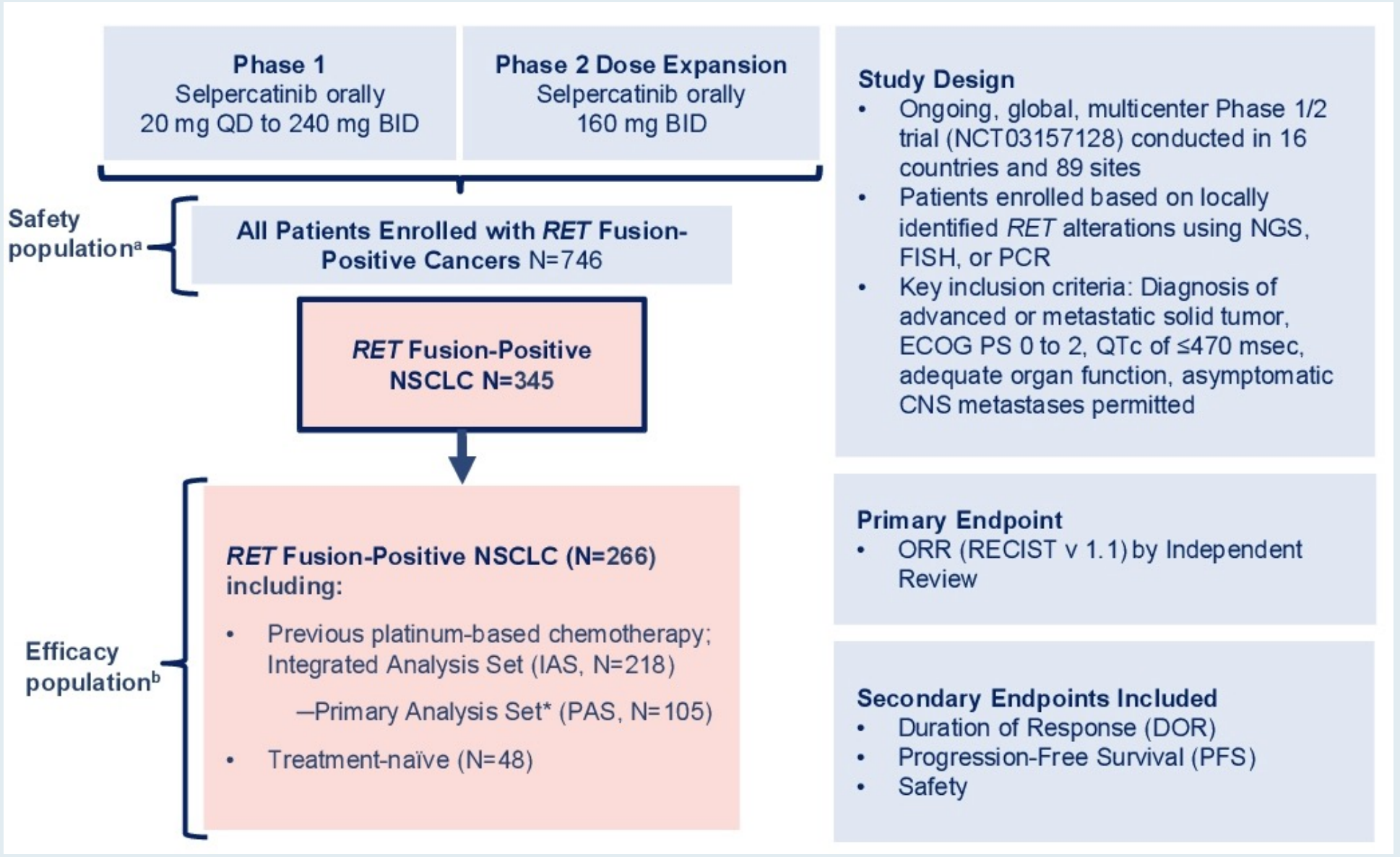
Curigliano J et al. ASCO 2021;Abstract 9089.

Updated Overall Efficacy and Safety of Selpercatinib in Patients with RET Fusion-Positive Non-Small-Cell Lung Cancer (NSCLC): LIBRETTO-001 Study

Besse B et al.

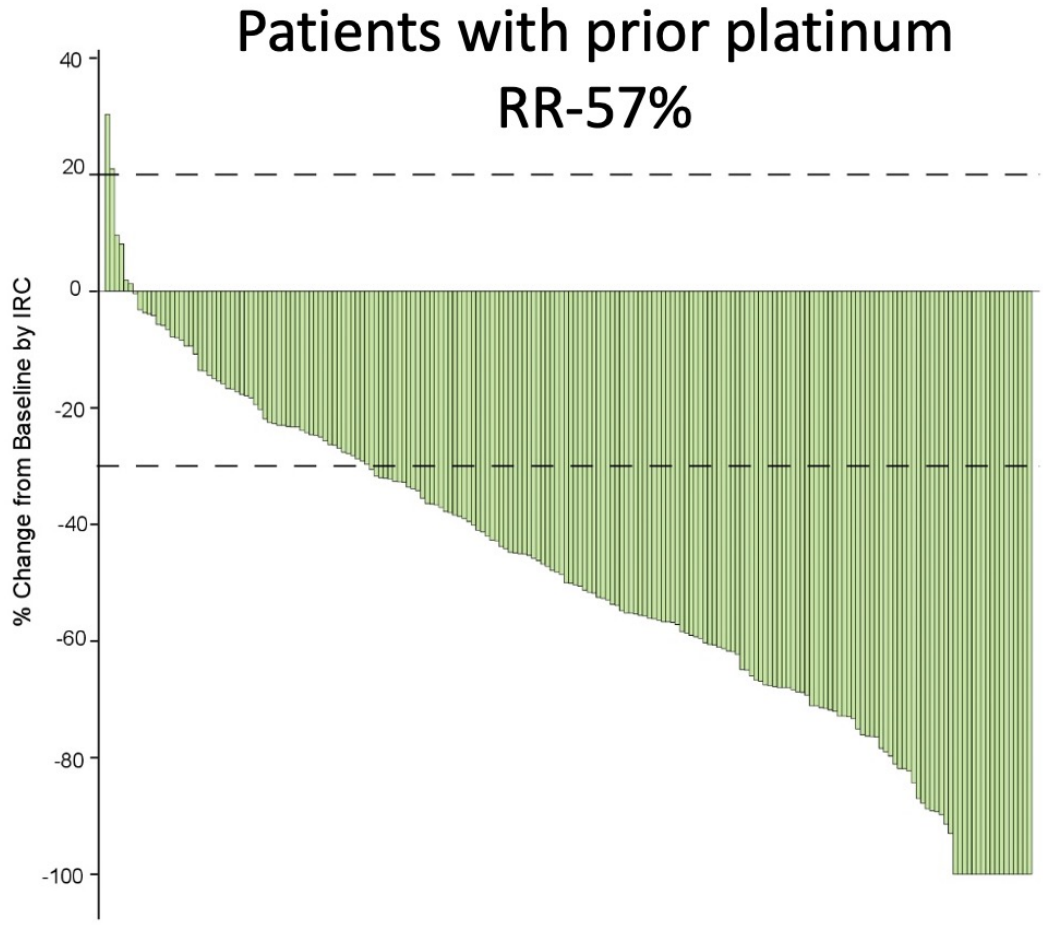
ASCO 2021;Abstract 9065.

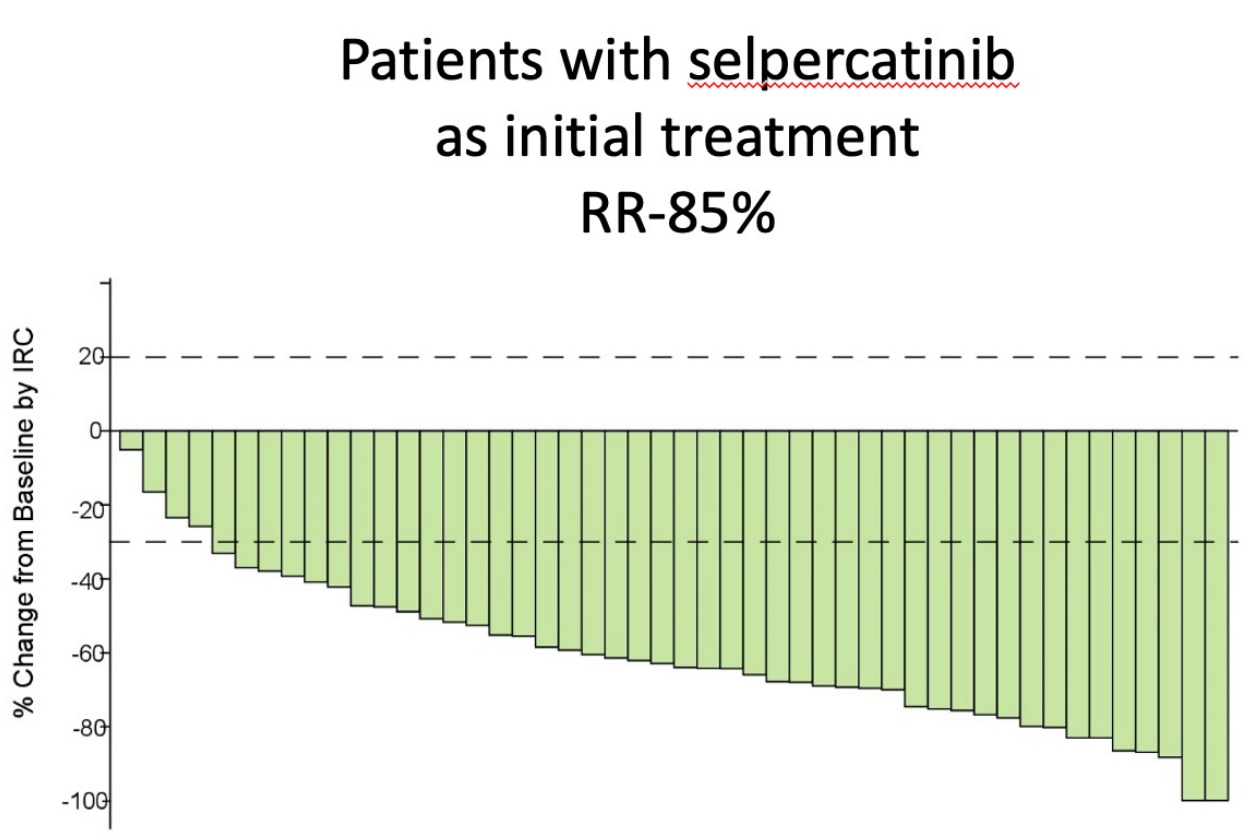
LIBRETTO-001 Study Design



Besse B et al. ASCO 2021;Abstract 9065.

LIBRETTO-001: Response to Selpercatinib





Besse B et al. ASCO 2021;Abstract 9065.

RTP RESEARCH TO PRACTICE

Agenda

Module 1: Role of Genomic Profiling; New Developments in NSCLC with an EGFR Mutation

- Dr McKenzie: A 60-year-old woman with NSCLC and an EGFR exon 19 deletion
- Dr Hussein: A 51-year-old man with metastatic lung adenocarcinoma and an EGFR exon 20 mutation

Module 2: Other Novel Targets for Patients with NSCLC

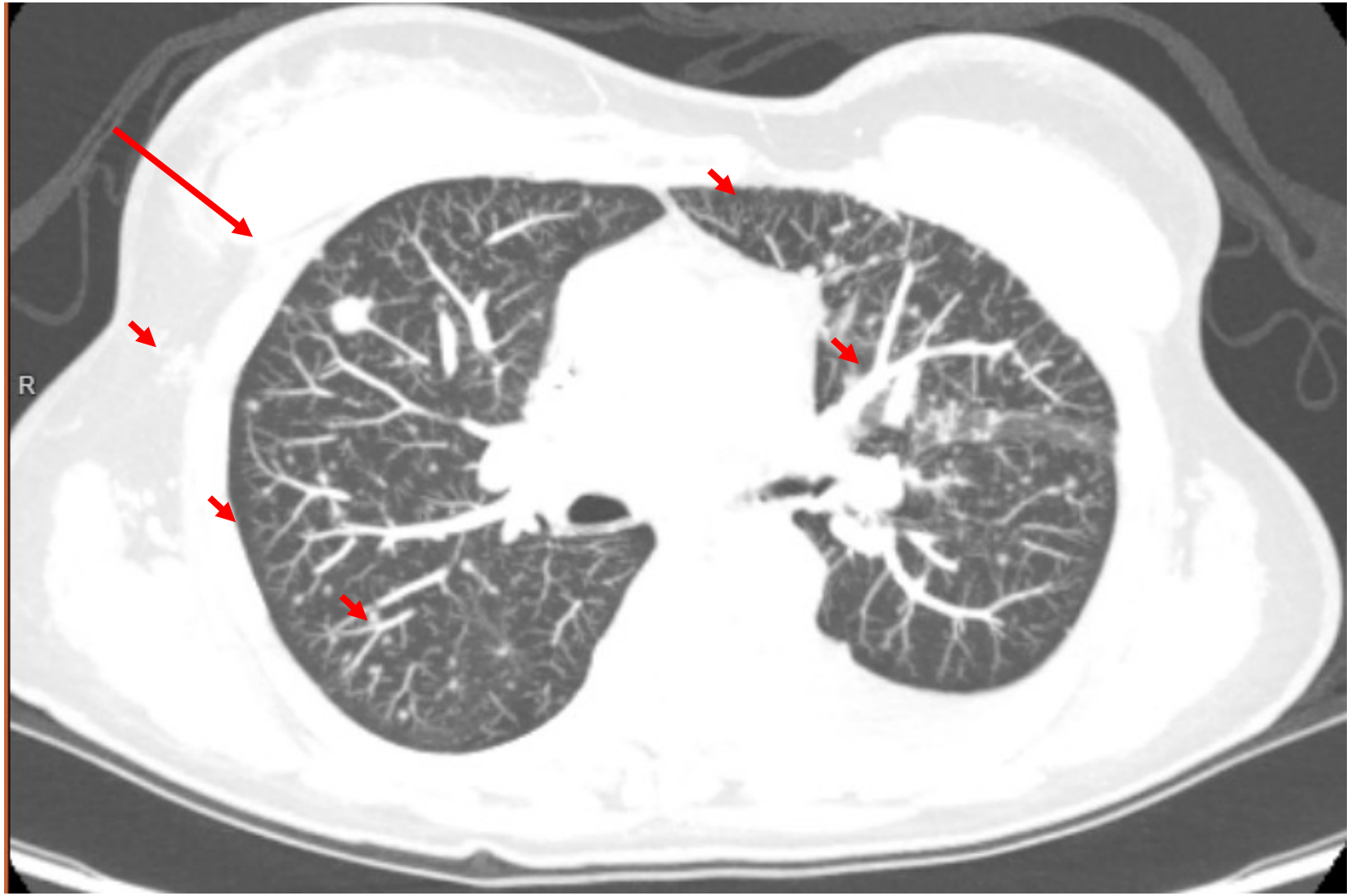
- Dr Neal: A 51-year-old man with RET-positive NSCLC
- Dr Neal: A 64-year-old woman with metastatic NSCLC and a HER2 exon 20 insertion
- Dr McKenzie: A 78-year-old man with NSCLC and a TRK fusion
- Dr Jasani: A 35-year-old woman with newly diagnosed mNSCLC – ALK mutation
- Dr Mohamed: A 71-year-old woman with metastatic adenocarcinoma of the lung with MET exon 14 skipping and MET amplification mutations – PD-L1 TPS 95%
- Dr Zafar: A 64-year-old woman with discordant BRAF mutation testing results

Case Presentation – Dr Neal: A 64-year-old woman with metastatic NSCLC and a HER2 exon 20 insertion

- 64 year old neversmoking Caucasian woman with h/o stage I breast cancer 3 years before and rheumatoid arthritis, no active therapy for either
- Productive cough for 3 months, CXR with opacities
- CT left upper lobe mass, bilateral lung nodules, liver mets, bone mets.
- FNA biopsy subcarinal and mediastinal nodes; adenocarcinoma. Ruled out for TB with AFB x 3
- MRI brain with 12 mets, 5-8 mm
- She has good pulmonary function and performance status (walks a mile in hills per day)
- EGFR
- 130 gene NGS panel (3 weeks after path diagnosis) - ERBB2 G778_P780dup
- Interpretation: HER2 exon 20 insertion mutation
- Radiosurgery to brain mets, started carbo/pemetrexed/bevacizumab with response
- Zolendronic acid for bone mets
- After 12 months: Progression predominantly in liver mets during maintenance pemetrexed/bevacizumab
- Started trastuzumab deruxtecan off label – 5.4 mg/kg IV every 3 weeks

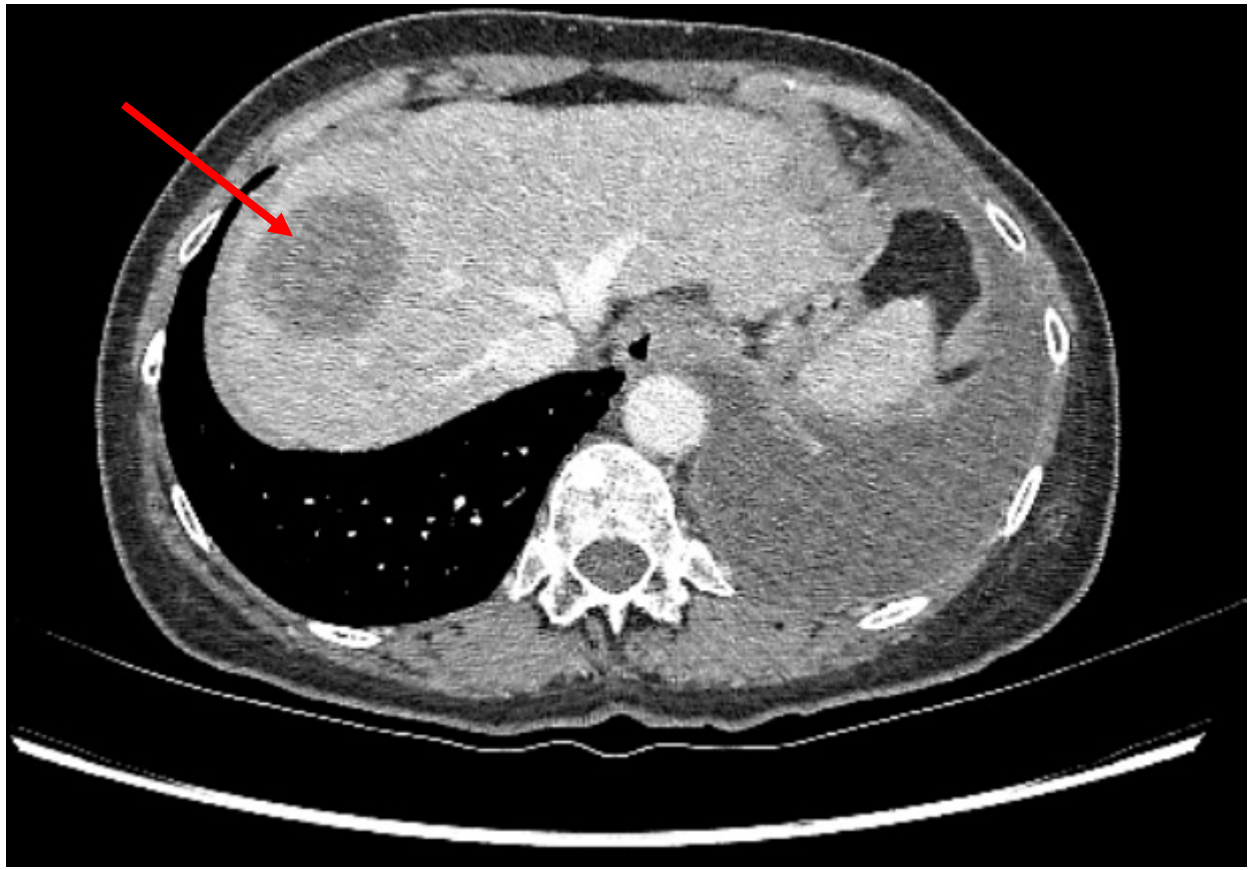
Case Presentation – Dr Neal: A 64-year-old woman with metastatic NSCLC and a HER2 exon 20 insertion (continued)

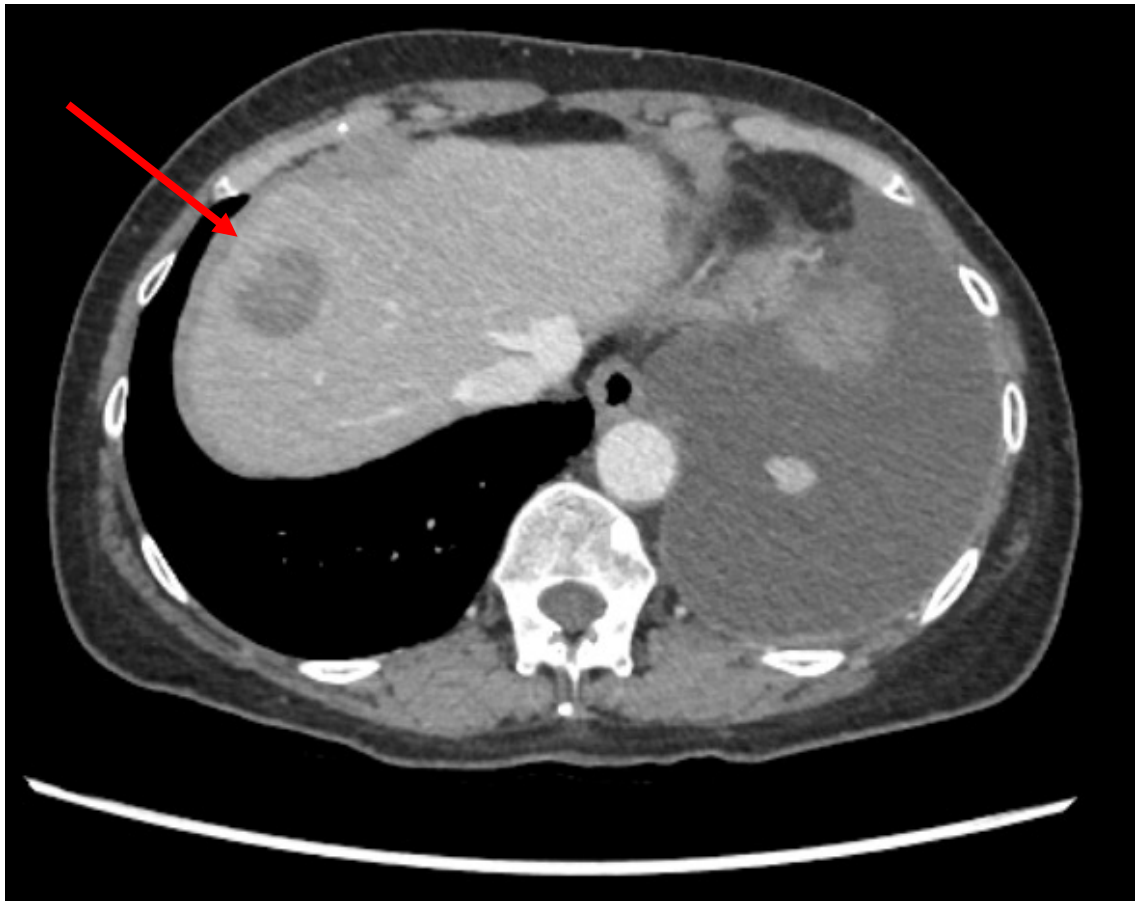
Pre-trastuzumab deruxtecan showing bilateral lung mets



Case Presentation – Dr Neal: A 64-year-old woman with metastatic NSCLC and a HER2 exon 20 insertion (continued)

Pre- and 3 month post trastuzumab deruxtecan showing liver met response





Case Presentation – Dr Neal: A 64-year-old woman with metastatic NSCLC and a HER2 exon 20 insertion (continued)

- Response after 6 weeks with continued durable response in liver mets after
- Anemia and thrombocytopenia led to dose delays for 1-2 weeks, 3-4 week cycles
- Ongoing response 10 months later

Interim Analysis of DESTINY-Lung01 in *HER2*-Overexpressing Cohort 1: Efficacy Summary

Parameter	IHC 3+ (n = 10)	IHC 2+ (n = 39)	Overall (n = 49)
Confirmed ORR, n (%; 95% CI)	2 (20.0; 2.5-55.6)	10 (25.6; 13.0-42.1)	12 (24.5; 13.3-38.9)
▪ CR	0	1 (2.6)	1 (2.0)
▪ PR	2 (20.0)	9 (23.1)	11 (22.4)
▪ SD	6 (60.0)	16 (41.0)	22 (44.9)
▪ PD	1 (10.0)	10 (25.6)	11 (22.4)
▪ Not evaluable	1 (10.0)	3 (7.7)	4 (8.2)
DCR, n (%; 95% CI)	8 (80.0; 44.4-97.5)	26 (66.7; 49.8-80.9)	34 (69.4; 54.6-81.8)
Median DoR, mos (95% CI)	6.0 (NE-NE)	5.8 (3.2-NE)	6.0 (3.2-NE)

*Full analysis set data.

Nakagawa. WCLC 2020. Abstr OA04.05.

Courtesy of Joel W Neal, MD, PhD

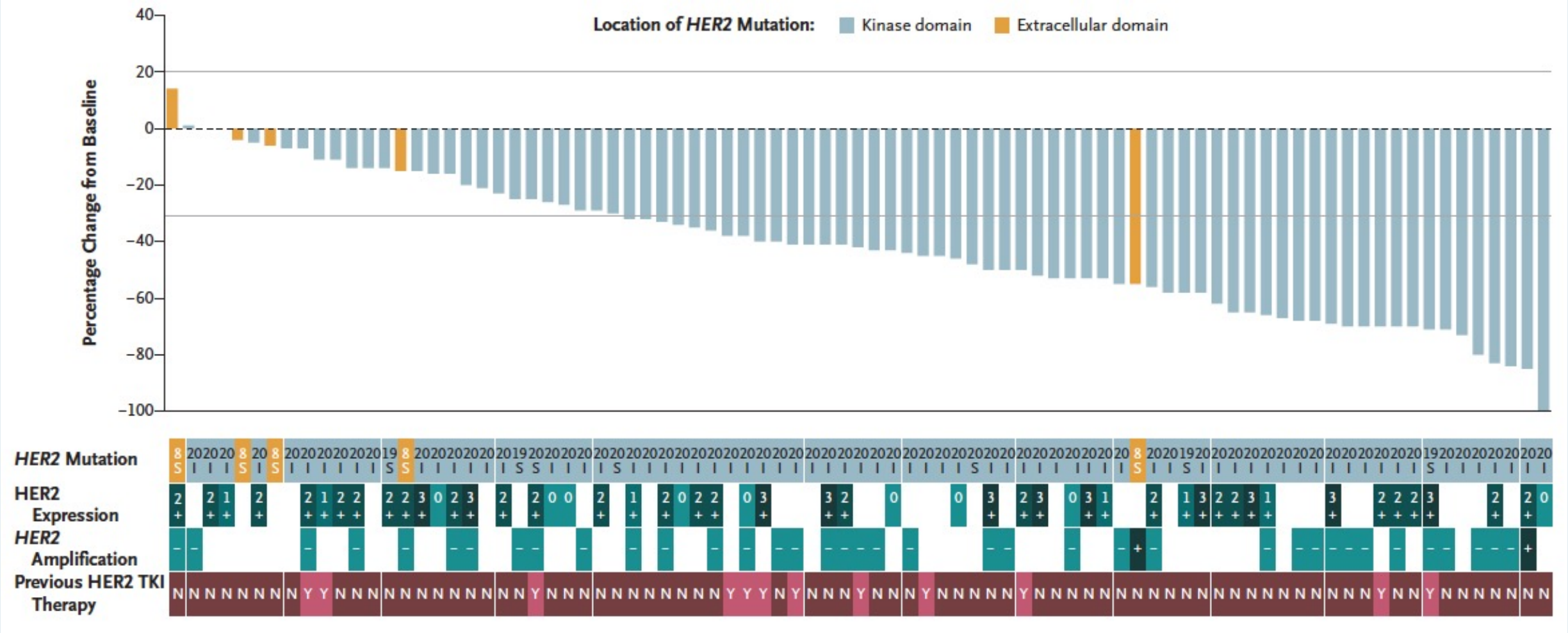
ORIGINAL ARTICLE

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

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

N Engl J Med 2021;[Online ahead of print].

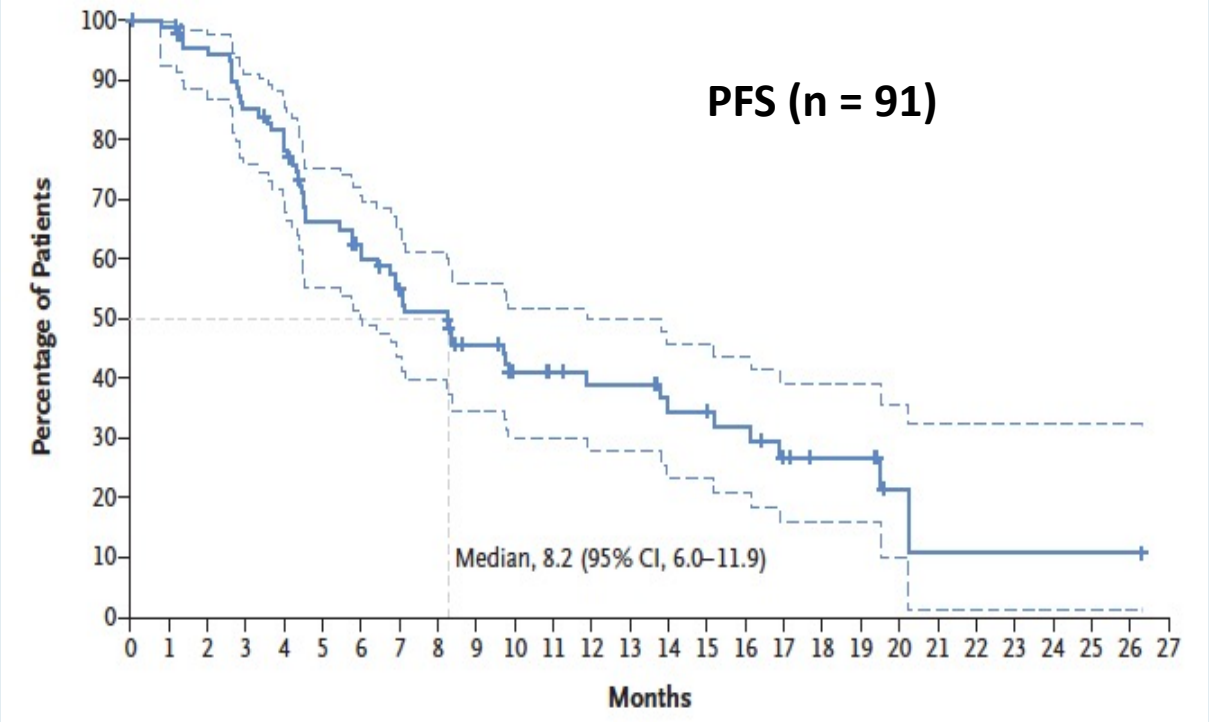
DESTINY-Lung01: Antitumor Activity

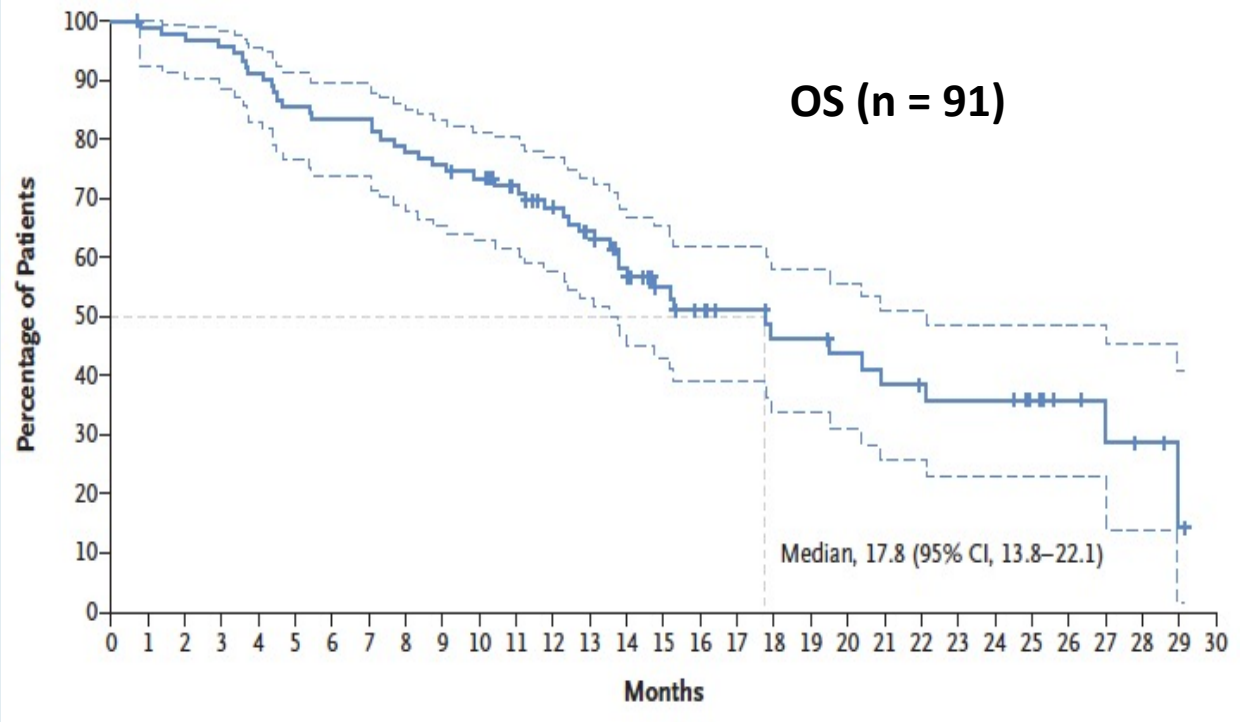


Li BT et al. *N Engl J Med* 2021;[Online ahead of print].

RTP RESEARCH TO PRACTICE

DESTINY-Lung01: Survival in the Overall Population





Li BT et al. *N Engl J Med* 2021;[Online ahead of print].

Agenda

Module 1: Role of Genomic Profiling; New Developments in NSCLC with an EGFR Mutation

- Dr McKenzie: A 60-year-old woman with NSCLC and an EGFR exon 19 deletion
- Dr Hussein: A 51-year-old man with metastatic lung adenocarcinoma and an EGFR exon 20 mutation

Module 2: Other Novel Targets for Patients with NSCLC

- Dr Neal: A 51-year-old man with RET-positive NSCLC
- Dr Neal: A 64-year-old woman with metastatic NSCLC and a HER2 exon 20 insertion
- Dr McKenzie: A 78-year-old man with NSCLC and a TRK fusion
- Dr Jasani: A 35-year-old woman with newly diagnosed mNSCLC – ALK mutation
- Dr Mohamed: A 71-year-old woman with metastatic adenocarcinoma of the lung with MET exon 14 skipping and MET amplification mutations – PD-L1 TPS 95%
- Dr Zafar: A 64-year-old woman with discordant BRAF mutation testing results

RTP
RESEARCH
TO PRACTICE

Case Presentation – Dr McKenzie: A 78-year-old man with NSCLC and a TRK fusion

- 78yr Male – never smoker
- 8/2020 - Stage 3A (cT2bN2) NSCLC squamous cell carcinoma of RUL lobe endobronchial ultrasound showed mediastinal invasion into R paratracheal space
- Started XRT 9/10.
- Weekly carbo/taxol 9/11.
  - Completed chemoRT on 10/16/20.
- Started consolidative durva 11/20/20.
- Imaging 9/24/21 followed by PET showed recurrence in lungs, liver (3 nodules), and R adrenal.
- NGS sent upon metastatic diagnosis – Tissue and plasma (both 10/2021)

Case Presentation – Dr McKenzie: A 78-year-old man with NSCLC and a TRK fusion (continued)

plasma

Summary of Detected Somatic Alterations, Immunotherapy Biomarkers & Associated Treatment Options

KEY ✓ Approved in indication ✓ Approved in other indication ⊗ Lack of response

Detected Alteration(s) / Biomarker(s)	Associated FDA-approved therapies	Clinical trial availability (see page 3)	% cfDNA or Amplification
TTC28-NTRK3 Fusion	✓ Entrectinib, Larotrectinib	Yes	2.5%
TP53 Y236S	None	Yes	17.3%
NOTCH1 Splice Site SNV	None	Yes	16.4%

Variants of Uncertain Clinical Significance
BRCA2 T1040A (21.2%), *NOTCH1* N1482K (17.6%), *GATA3* T78K (8.0%), *ESR1* D321G (0.1%), *FANCA* R874_F876del (0.3%)

tissue

Biomarker Findings

Tumor Mutational Burden - 10 Muts/Mb
Microsatellite status - MS-Stable

Genomic Findings

For a complete list of the genes assayed, please refer to the Appendix.

PIK3CA amplification - equivocal†
SOX2 amplification - equivocal†
MLL2 S2839*
NOTCH1 splice site 2588-1G>T
TP53 Y236S

8 Disease relevant genes with no reportable alterations: ***ALK, BRAF, EGFR, ERBB2, KRAS, MET, RET, ROS1***

† See About the Test in appendix for details.

- Novel TRK fusion detected in plasma, but not seen in tissue testing
- Discordance between tissue and plasma is expected
  - Tumor heterogeneity & tumor evolution
  - Test differences
  - Most discrepancies are attributed to biology and not test inferiority
- Both larotrectinib and entrectinib are approved for NTRK fused cancers
  - Indicated for patients who "*have no satisfactory alternative treatments* or that have progressed following treatment"
- Initiating entrectinib for front-line metastatic treatment

SARAH CANNON

Agenda

Module 1: Role of Genomic Profiling; New Developments in NSCLC with an EGFR Mutation

- Dr McKenzie: A 60-year-old woman with NSCLC and an EGFR exon 19 deletion
- Dr Hussein: A 51-year-old man with metastatic lung adenocarcinoma and an EGFR exon 20 mutation

Module 2: Other Novel Targets for Patients with NSCLC

- Dr Neal: A 51-year-old man with RET-positive NSCLC
- Dr Neal: A 64-year-old woman with metastatic NSCLC and a HER2 exon 20 insertion
- Dr McKenzie: A 78-year-old man with NSCLC and a TRK fusion
- Dr Jasani: A 35-year-old woman with newly diagnosed mNSCLC – ALK mutation
- Dr Mohamed: A 71-year-old woman with metastatic adenocarcinoma of the lung with MET exon 14 skipping and MET amplification mutations – PD-L1 TPS 95%
- Dr Zafar: A 64-year-old woman with discordant BRAF mutation testing results

RTP
RESEARCH
TO PRACTICE

Case Presentation – Dr Jasani: A 35-year-old woman with newly diagnosed mNSCLC – ALK mutation

Dr Nikesh Jasani

- Presented with cough, chest pain, and fatigue
- Diagnosed with stage IV NSCLC adenocarcinoma with right hilar mass, with metastases to multiple mediastinal nodes, bone and a solitary brain mass
- Molecular studies: ALK FISH +
- Stereotactic RT to brain lesion
- 1/2021: Alectinib → excellent response with resolution of all symptoms

Questions

- What is the optimal first-line therapy for NSCLC that is ALK mutation-positive?
- If her disease progresses, what would be the best next steps - repeat biopsy and assessment of resistance mutations to determine ideal treatment?
- How do you manage CNS disease in patients with NSCLC that is ALK mutation-positive?
- What are the side effects of note with the newer ALK inhibitors such as lorlatinib and brigatinib?

RTP RESEARCH TO PRACTICE

Agenda

Module 1: Role of Genomic Profiling; New Developments in NSCLC with an EGFR Mutation

- Dr McKenzie: A 60-year-old woman with NSCLC and an EGFR exon 19 deletion
- Dr Hussein: A 51-year-old man with metastatic lung adenocarcinoma and an EGFR exon 20 mutation

Module 2: Other Novel Targets for Patients with NSCLC

- Dr Neal: A 51-year-old man with RET-positive NSCLC
- Dr Neal: A 64-year-old woman with metastatic NSCLC and a HER2 exon 20 insertion
- Dr McKenzie: A 78-year-old man with NSCLC and a TRK fusion
- Dr Jasani: A 35-year-old woman with newly diagnosed mNSCLC – ALK mutation
- Dr Mohamed: A 71-year-old woman with metastatic adenocarcinoma of the lung with MET exon 14 skipping and MET amplification mutations – PD-L1 TPS 95%
- Dr Zafar: A 64-year-old woman with discordant BRAF mutation testing results

RTP
RESEARCH
TO PRACTICE

Case Presentation – Dr Mohamed: A 71-year-old woman with metastatic adenocarcinoma of the lung with MET exon 14 skipping and MET amplification mutations – PD-L1 TPS 95%

Dr Mohamed Mohamed

- Never smoker presents with bilateral flank pain and 5-month history of weight loss and fatigue
- Workup reveals Stage IV poorly differentiated adenocarcinoma of the lung; lung obstructions and 2 small, subcentimeter lesions in brain detected
- Molecular analyses: MET exon 14 skipping mutation, MET amplification
- PD-L1: 95%
- Palliative RT to the lung; SRS to the brain
- Capmatinib initiated

Questions

- If she didn't need to receive RT due to the lung obstructions, should I have initiated treatment with targeted therapy alone? Does capmatinib work on brain lesions by itself?
- With a PD-L1 of 95%, should she have been considered for immunotherapy, or should targeted therapy precede that as first-line therapy?
- Are mutations in MET regarded in the same way as mutations in EGFR and ALK in terms of immune therapy? Or are they regarded like BRAF mutations in that you could use immune therapy?

RTP RESEARCH TO PRACTICE

Agenda

Module 1: Role of Genomic Profiling; New Developments in NSCLC with an EGFR Mutation

- Dr McKenzie: A 60-year-old woman with NSCLC and an EGFR exon 19 deletion
- Dr Hussein: A 51-year-old man with metastatic lung adenocarcinoma and an EGFR exon 20 mutation

Module 2: Other Novel Targets for Patients with NSCLC

- Dr Neal: A 51-year-old man with RET-positive NSCLC
- Dr Neal: A 64-year-old woman with metastatic NSCLC and a HER2 exon 20 insertion
- Dr McKenzie: A 78-year-old man with NSCLC and a TRK fusion
- Dr Jasani: A 35-year-old woman with newly diagnosed mNSCLC – ALK mutation
- Dr Mohamed: A 71-year-old woman with metastatic adenocarcinoma of the lung with MET exon 14 skipping and MET amplification mutations – PD-L1 TPS 95%
- Dr Zafar: A 64-year-old woman with discordant BRAF mutation testing results

RTP RESEARCH TO PRACTICE

Case Presentation – Dr Zafar: A 64-year-old woman with discordant BRAF mutation testing results

Dr Syed Zafar

- 2020: Diagnosed with metastatic adenocarcinoma with several pulmonary lesions, mediastinal lymphadenopathy, and brain metastases
- Liquid biopsy and NGS ordered
  - Liquid biopsy reveals BRAF V600E mutation
  - NGS results do not reveal any actionable targets
- Patient is symptomatic: Cough, shortness of breath, effusion
- PD-L1-positive
- Considering symptomatology of patient, chemotherapy/IO combination initiated
- Patient's symptoms have improved on treatment
- Holding BRAF-targeted treatment in reserve as potential future therapy

Meet The Professor

Optimizing the Clinical Management of Hodgkin and Non-Hodgkin Lymphomas

Wednesday, October 27, 2021
5:00 PM – 6:00 PM ET

Faculty

Jonathan W Friedberg, MD, MMSc

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Thank you for joining us!

CME credit information will be emailed to each participant within 3 business days.