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

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Faculty

Marc Ladanyi, MD
Chief, Molecular Diagnostics Service
William J Ruane Chair in Molecular Oncology
Memorial Sloan Kettering Cancer Center
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Helena Yu, MD
Medical Oncologist
Associate Attending
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Scientific Director, Genospace
Sarah Cannon
Nashville, Tennessee

Moderator

Neil Love, MD
Research To Practice
Miami, Florida

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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

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Dr McKenzie — Disclosures

No relevant conflicts of interest to disclose.

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Dr Yu — Disclosures

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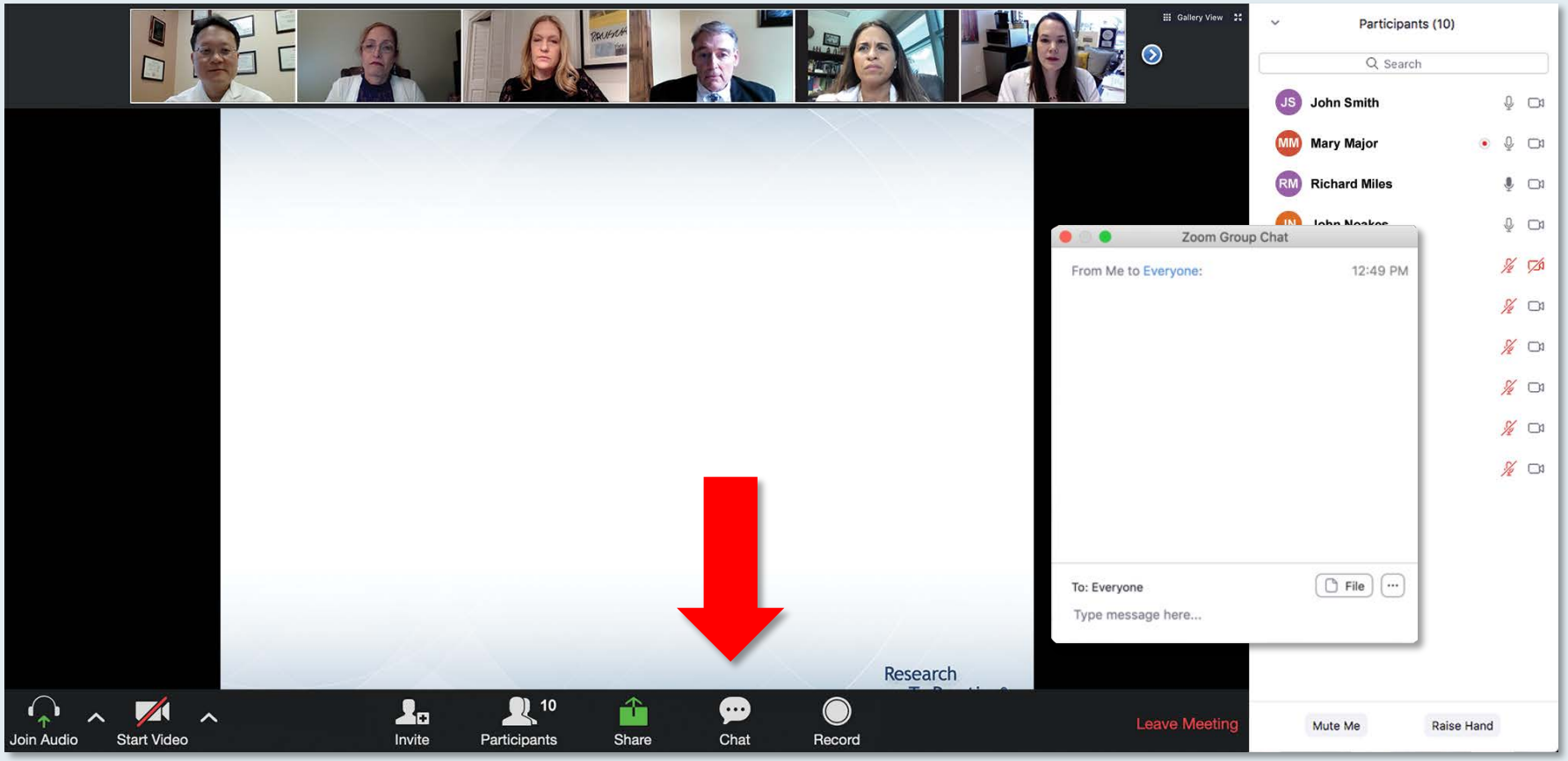
Contracted Research (to Institution)	AstraZeneca Pharmaceuticals LP, Cullinan Oncology, Daiichi Sankyo Inc, Janssen Biotech Inc, Lilly, Novartis, Pfizer Inc

We Encourage Clinicians in Practice to Submit Questions



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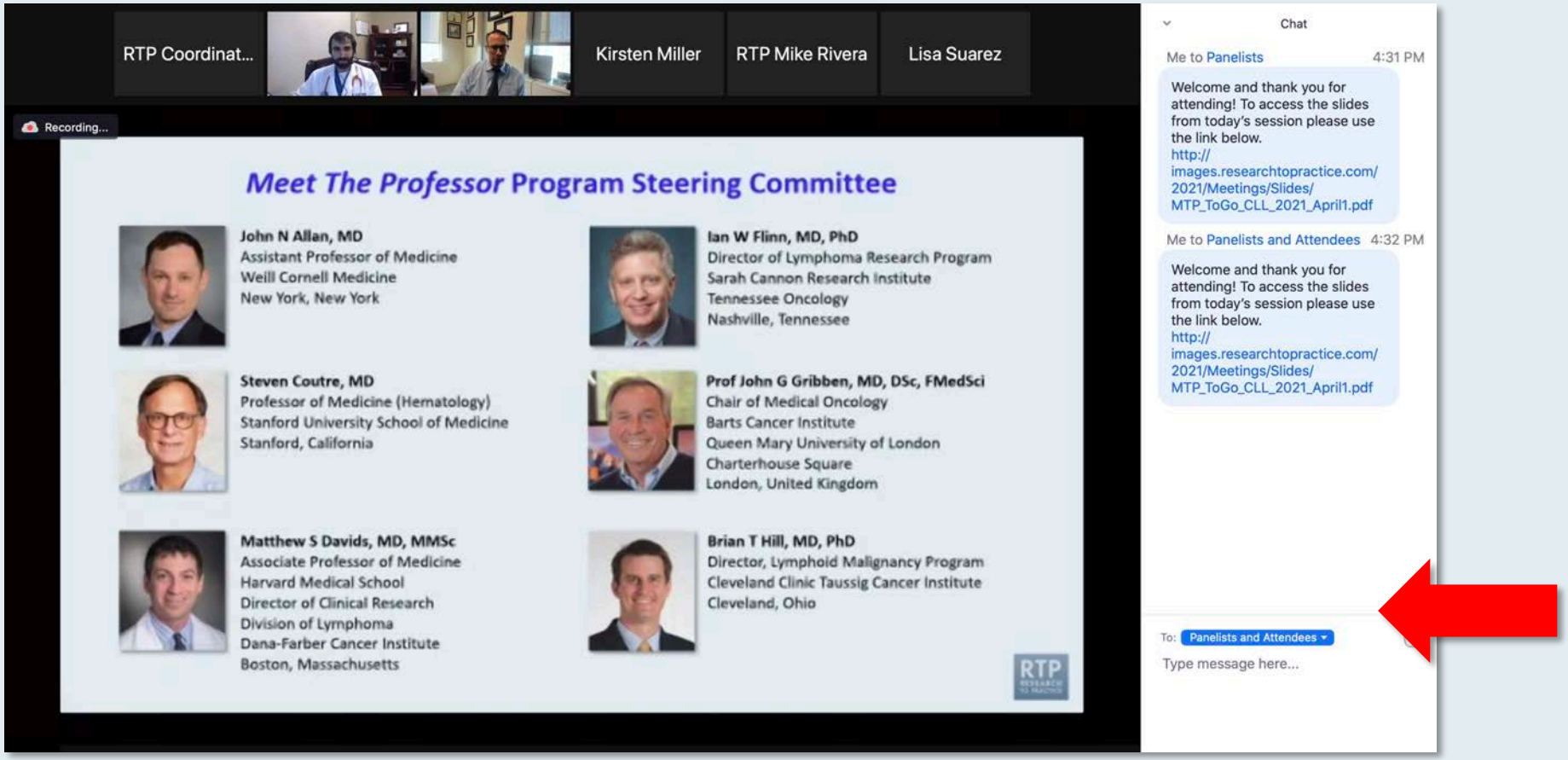

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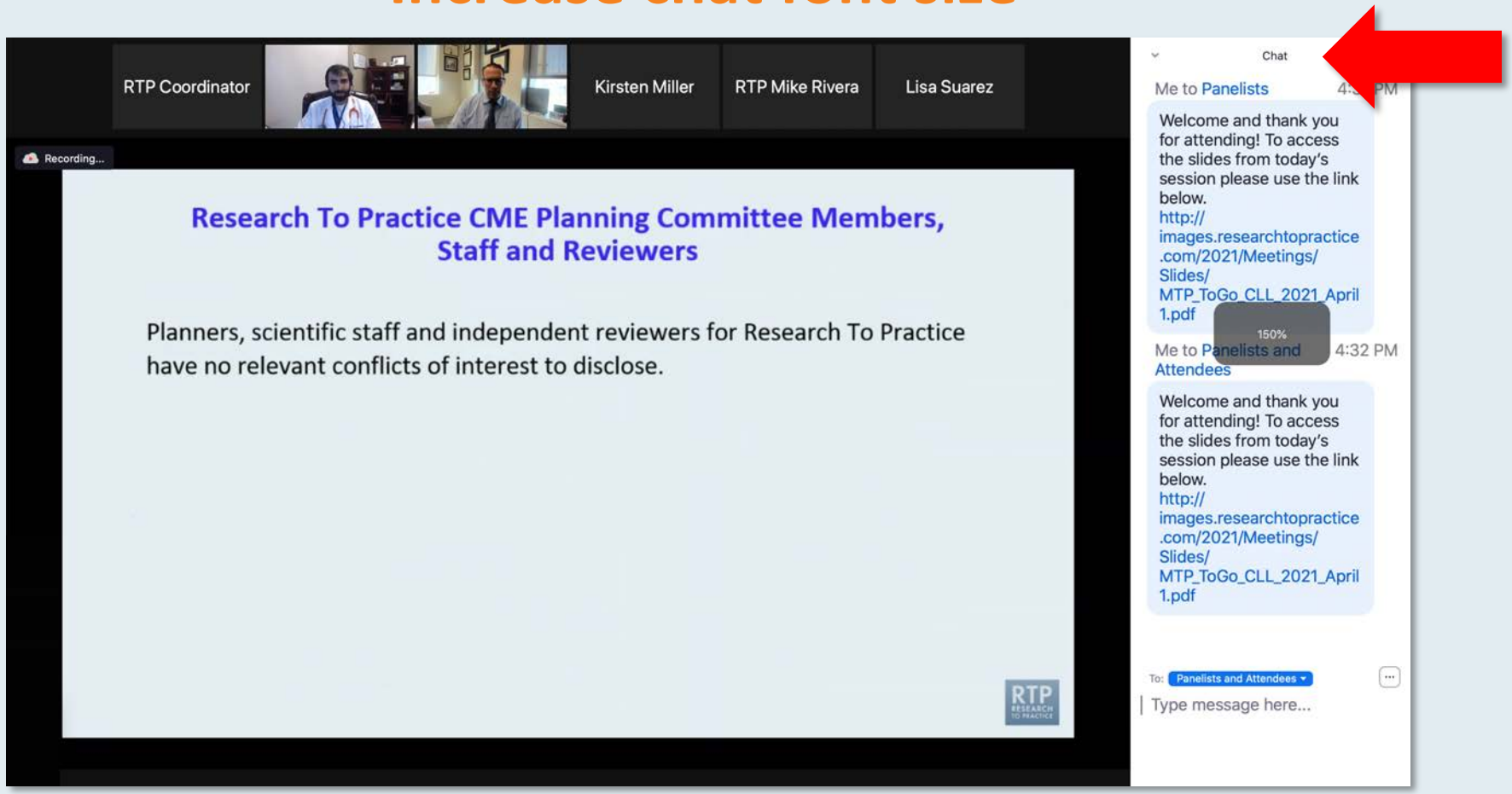

Press Command (for Mac) or Control (for PC) and the + symbol.
You may do this as many times as you need for readability.

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WITH DR NEIL LOVE

Key Presentations on Lung Cancer from the 2021 ASCO Annual Meeting

DR JOEL NEAL

STANFORD UNIVERSITY

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Meet The Professor

Optimizing the Clinical Management of Hodgkin and Non-Hodgkin Lymphomas

Monday, November 15, 2021
5:00 PM – 6:00 PM ET

Faculty

Christopher R Flowers, MD, MS

Moderator

Neil Love, MD

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Meet The Professor

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

Wednesday, November 17, 2021
5:00 PM – 6:00 PM ET

Faculty

Kevin Kalinsky, MD, MS

Moderator

Neil Love, MD

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Current and Future Role of Immunotherapy in the Management of Lung Cancer

Thursday, November 18, 2021
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Management of BRAF-Mutant Melanoma

Monday, November 29, 2021
5:00 PM – 6:00 PM ET

Faculty

Jason J Luke, MD

Moderator

Neil Love, MD

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Meet The Professor

Optimizing the Management of Metastatic Castration-Resistant Prostate Cancer

Tuesday, November 30, 2021
5:00 PM – 6:00 PM ET

Faculty

A Oliver Sartor, MD

Moderator

Neil Love, MD

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Meet The Professor

Optimizing the Management of Acute Myeloid Leukemia

Wednesday, December 1, 2021
5:00 PM – 6:00 PM ET

Faculty

Andrew H Wei, MBBS, PhD

Moderator

Neil Love, MD

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Thank you for joining us!

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

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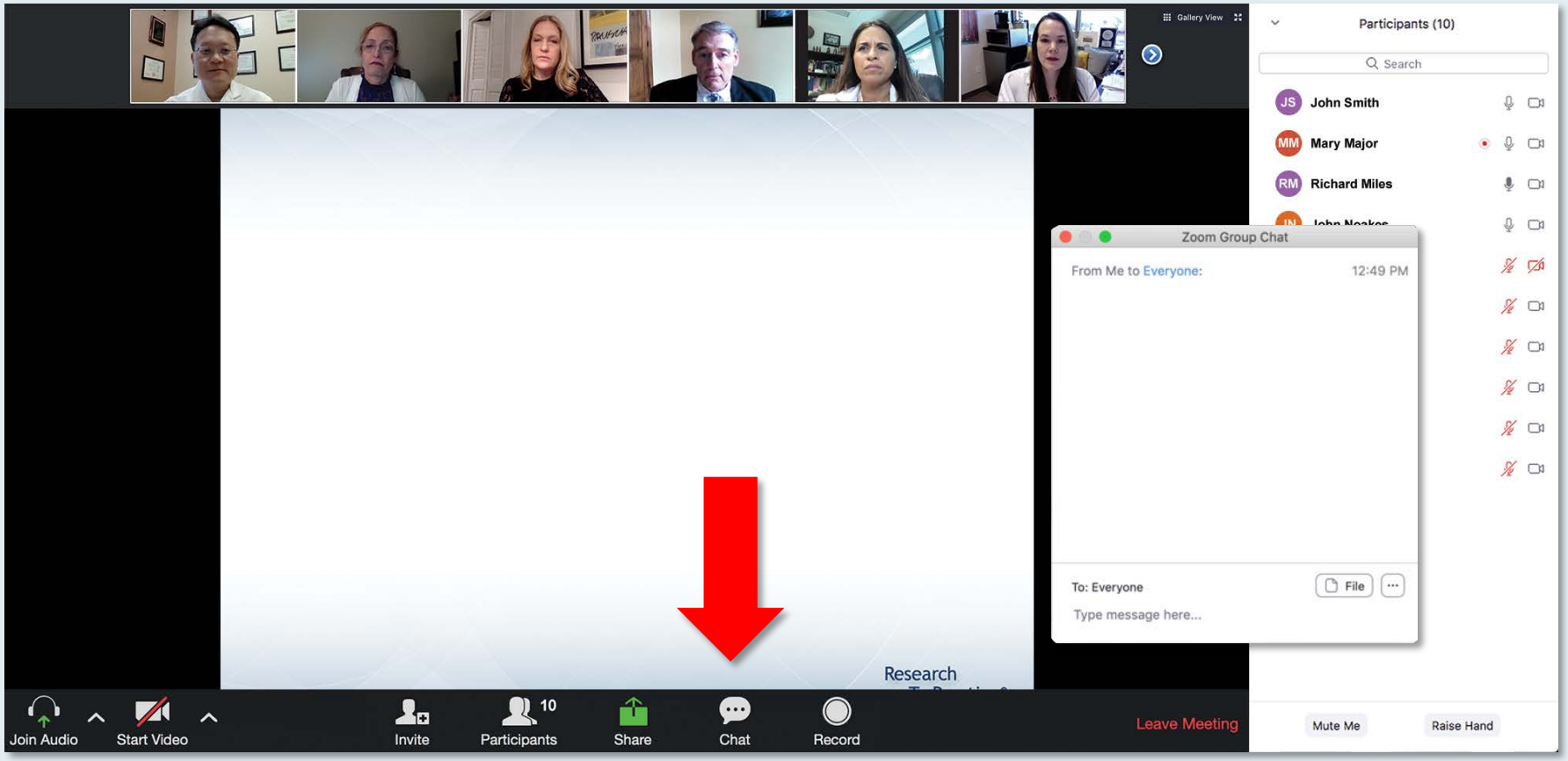

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Case Presentations

- Dr Yu: A 44-year-old woman with newly diagnosed Stage IIB adenocarcinoma of the lung and an EGFR L858R mutation
- Dr Ladanyi: A 78-year-old man with metastatic NSCLC and osimertinib resistance due to acquired RET fusion
- Dr Yu: A 64-year-old woman with newly diagnosed adenocarcinoma of the lung and an EGFR exon 20 mutation
- Dr McKenzie: A 78-year-old man with Stage IV adenocarcinoma of the lung and a RET fusion
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- Dr Jasani: A 35-year-old woman with newly diagnosed metastatic NSCLC and an ALK mutation
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- 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

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Types of Molecular Testing

	Piecemeal testing	Next-generation sequencing
PROS	Cheaper, quicker	All mutations tested for
CONS	More tissue needed	Cost, turnaround time

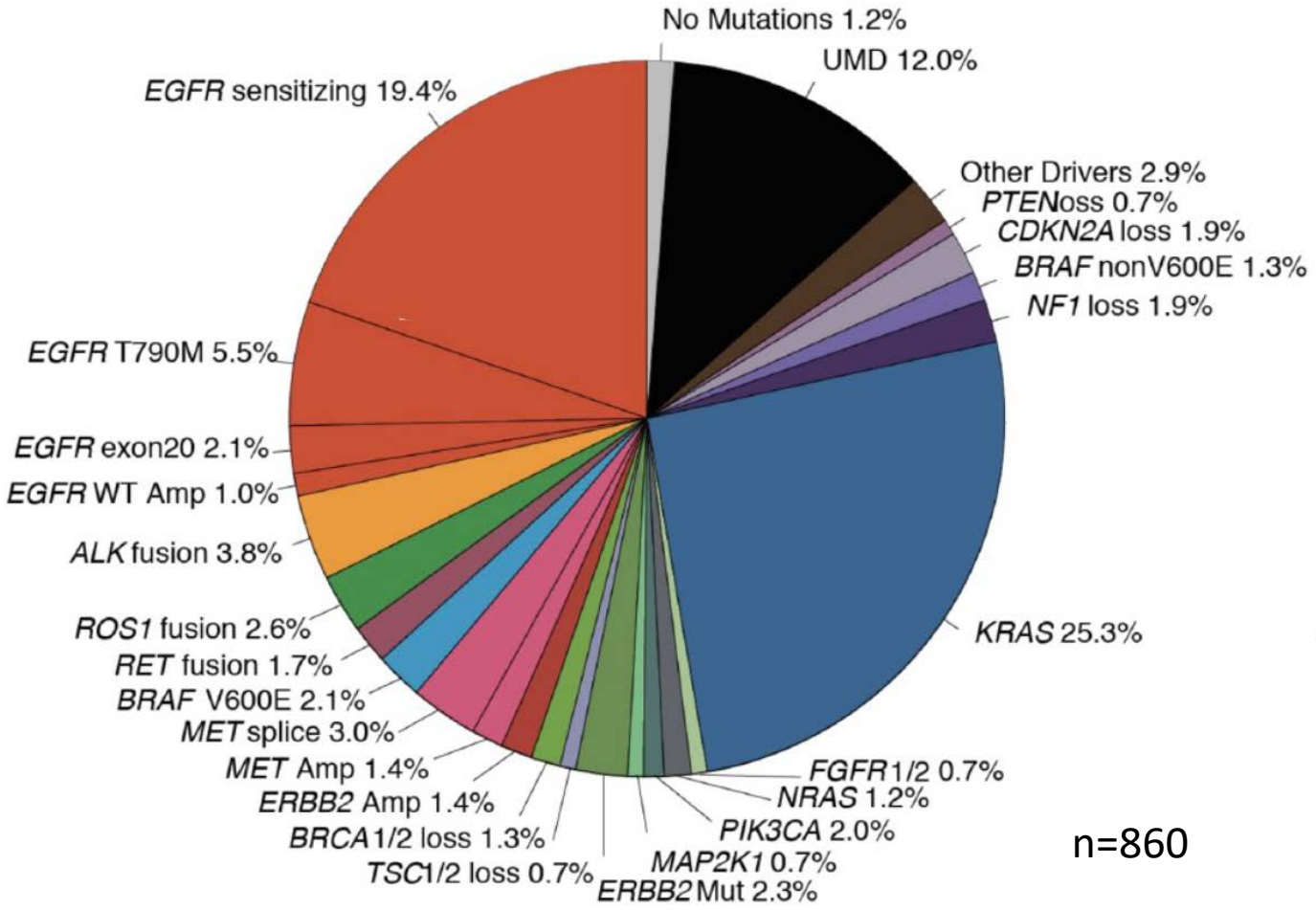
	Liquid (plasma ctDNA)	Tumor tissue
PROS	Faster, more readily available	Greater sensitivity, gold standard
CONS	Not all tumors with circulating tumor DNA, less sensitive for fusions, amplification	Need tumor tissue, slower turnaround

- What usually happens is a combination of both. Encourage whatever is easiest for a provider's workflow.
- If plasma testing is negative, would always recommend following up with tumor tissue molecular testing

Courtesy of Helena Yu, MD

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

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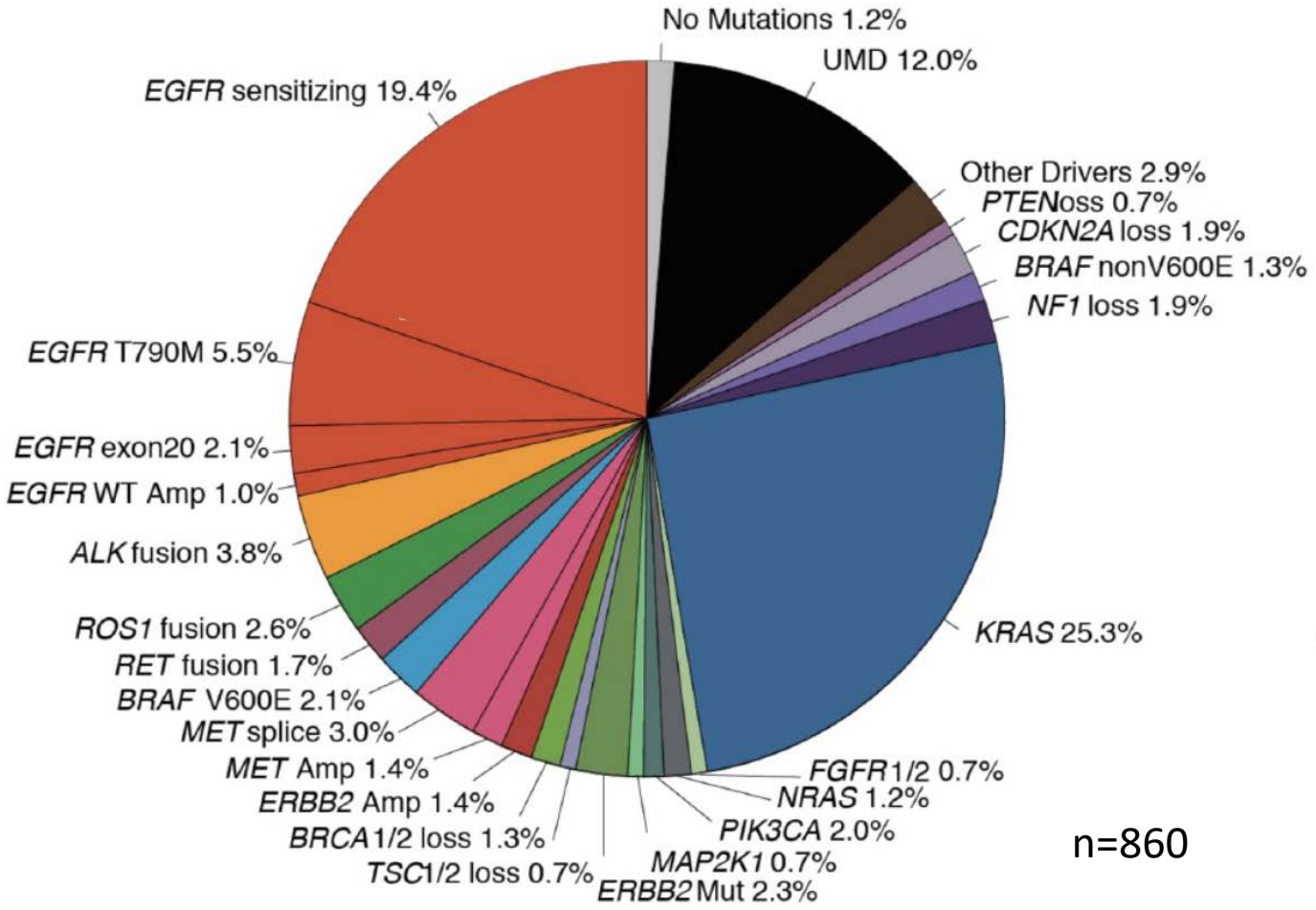

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KRAS 25.3%
UMD 12.0%
No Mutations 1.2%

Courtesy of Marc Ladanyi, MD

Jordan EJ et al. *Cancer Discovery* 2017

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

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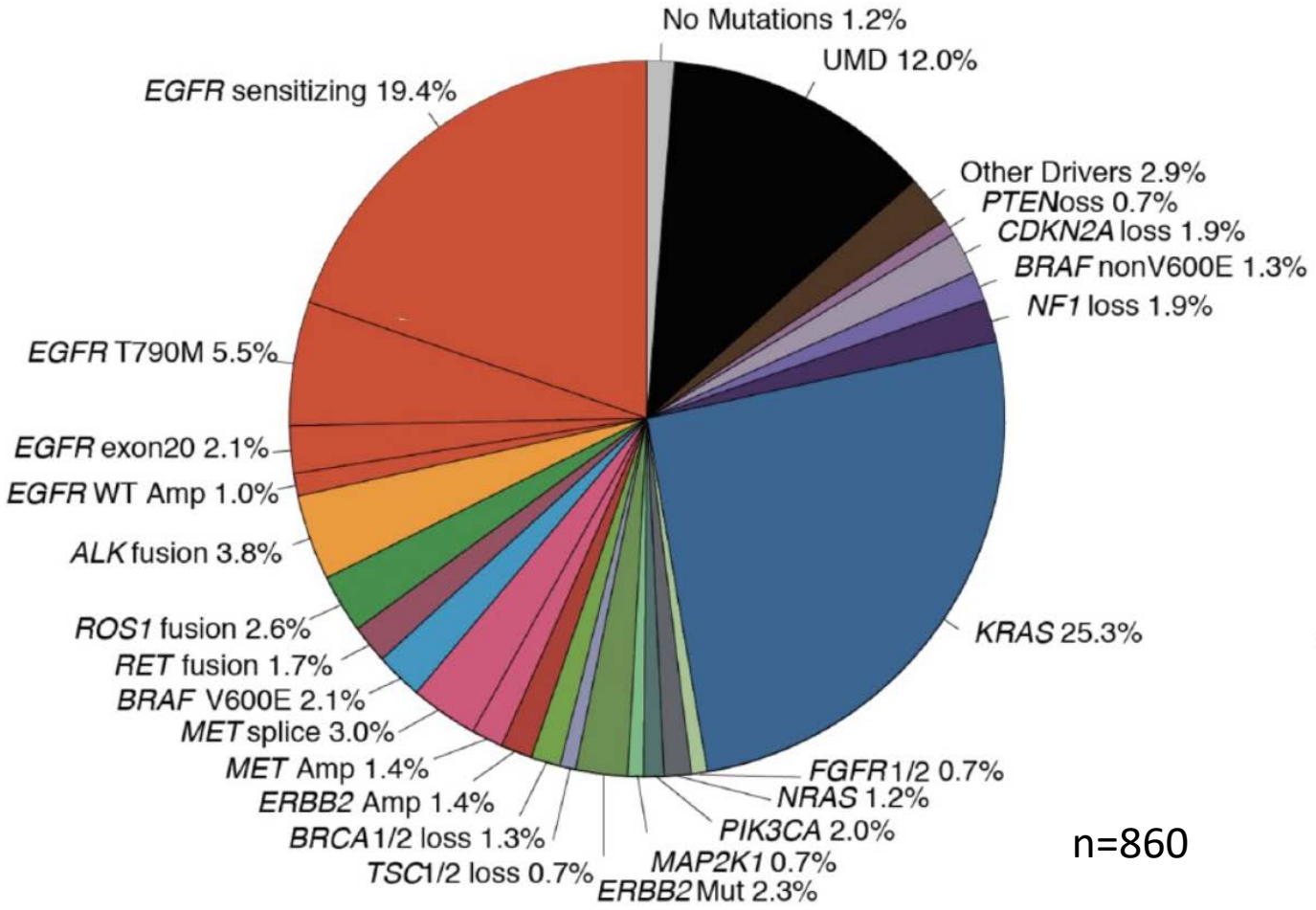

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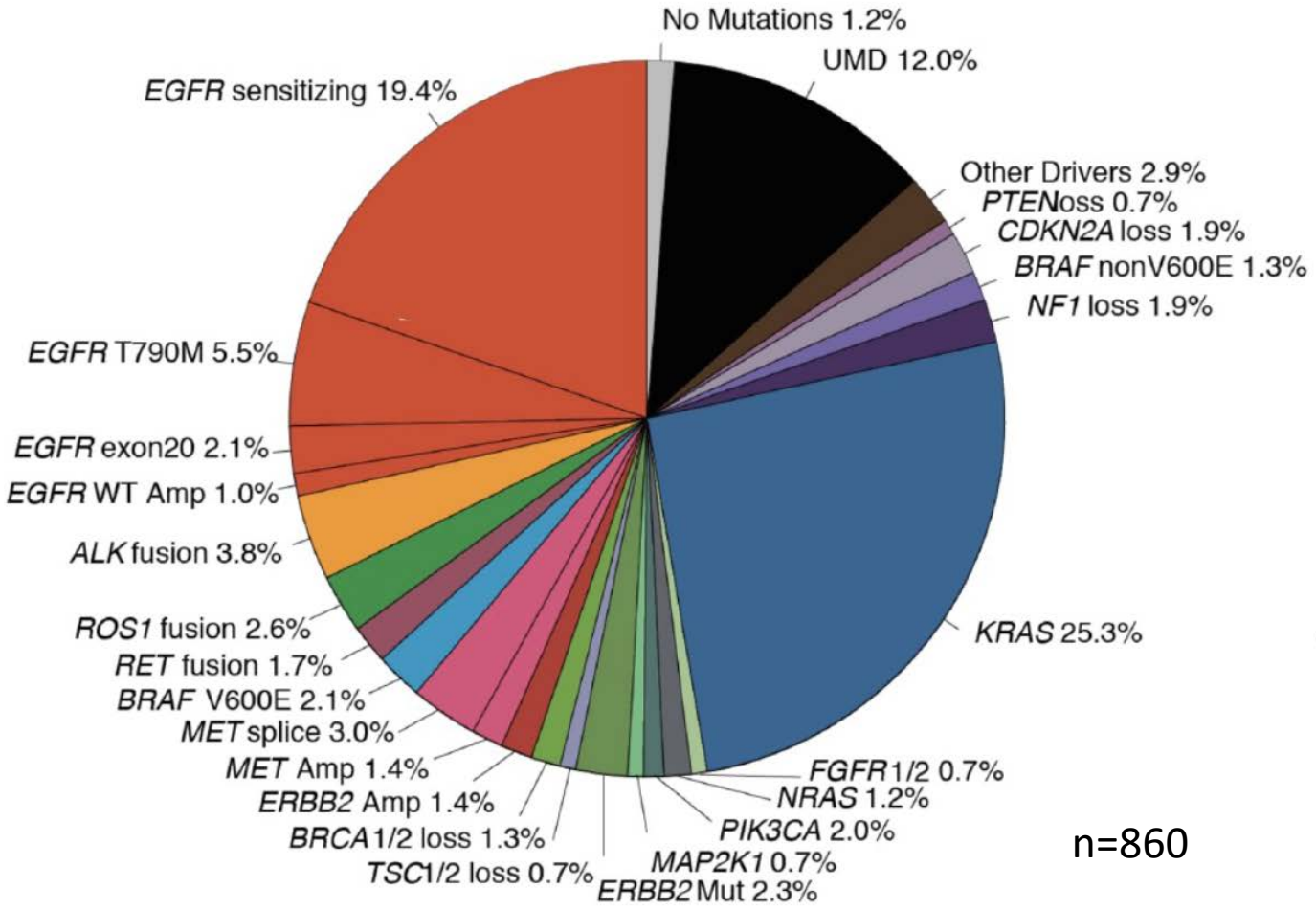
ALK fusion 3.8%
ROS1 Fusion 2.6%
RET Fusion 1.7%
BRAF V600E 2.1%
MET Splice 3.0%
MET Amp 1.4%
ERBB2 Amp 1.4%
ERBB2 Mut 2.3%

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



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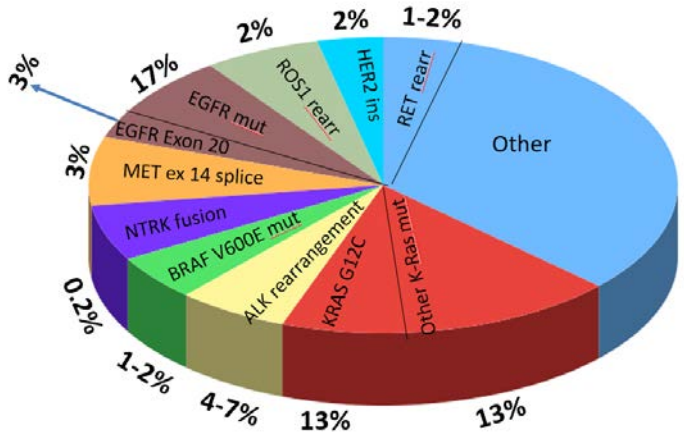
BRCA 1/2 loss 1.3%
TSC 1/2 loss 0.7%
MAP2K1 0.7%
PIK3CA 2.0%
NRAS 1.2%
FGFR 1/2 0.7%
NF1 loss 1.9%
BRAF nonV600E 1.3%
CDKN2A loss 1.9%
PTEN loss 0.7%
Other drivers 2.9%

Courtesy of Marc Ladanyi, MD

Jordan EJ et al. *Cancer Discovery* 2017

NSCLC: How to test for targets



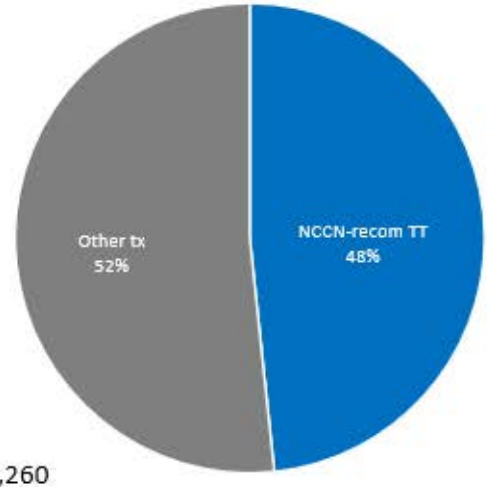
Target	Direct/ hotspot seq	FISH testing	IHC staining	NGS DNA tumor seq	NGS plasma seq	NGS RNA tumor seq
KRAS mutations	++	-	-	++	+	++
EGFR mutations (including exon 20 insertions)	++	-	+/-	++	+	++
ALK rearrangements	-	++	+	+	+	++
ROS1 rearrangements	-	++	-	+	+	++
BRAF mutations (including V600E)	++	-	-	++	+	++
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

Why does upfront testing matter?

- ***Less than half (48%)*** of patients with advanced NSCLC and an NCCN-driver alteration (EGFR, ALK, ROS1, BRAF, MET, RET, ERBB2) ***received an NCCN-recommended targeted therapy.***
- Patients with ALK (70.1%) and EGFR (64.3%) were mostly likely to get the recommended treatment.
- For patients with driver mutations, ***improved OS was observed in those receiving targeted therapies*** (median 18.6 mo vs. 11.4 mo; p<.001)



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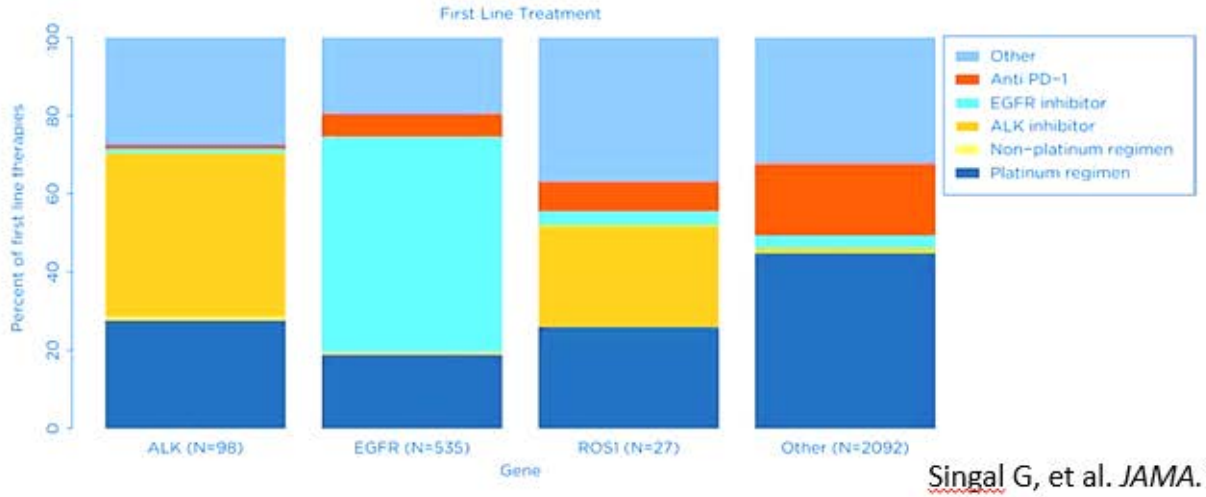


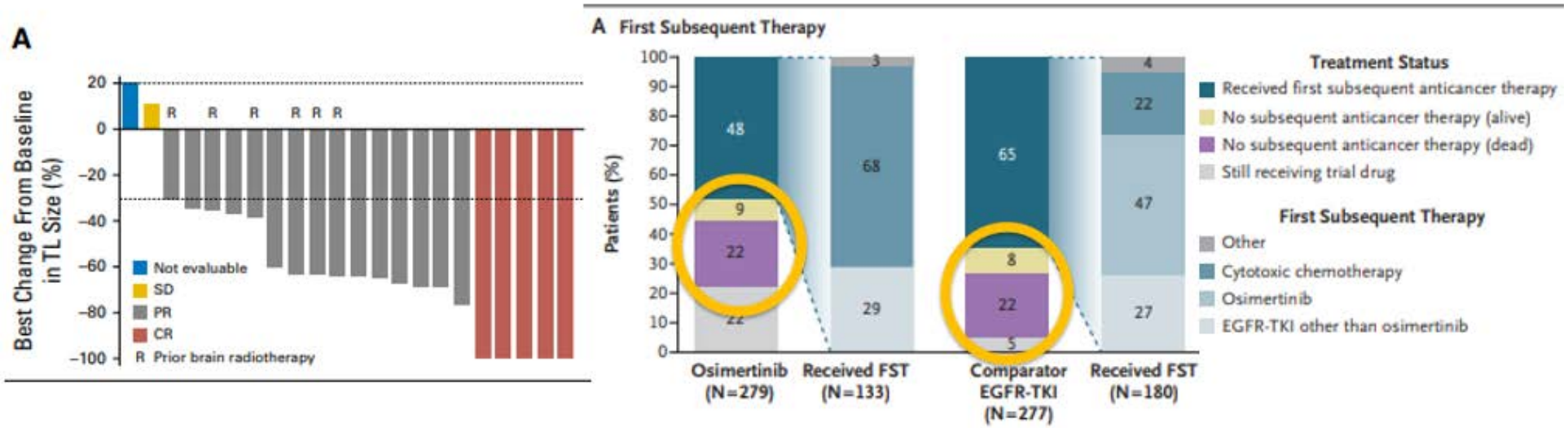
Singal G, et al. *JAMA*. 2019.

Memorial Sloan Kettering Cancer Center

Courtesy of Helena Yu, MD

Why does upfront testing matter?

- Always give your best treatments first! ***Not all patients receive second-line treatment.***
- Starting with the best treatment may allow you to forego radiation, surgery or other treatments upfront



Reungwetwattana JCO 2018, Ramalingam NEJM 2020

Memorial Sloan Kettering Cancer Center

Courtesy of Helena Yu, MD

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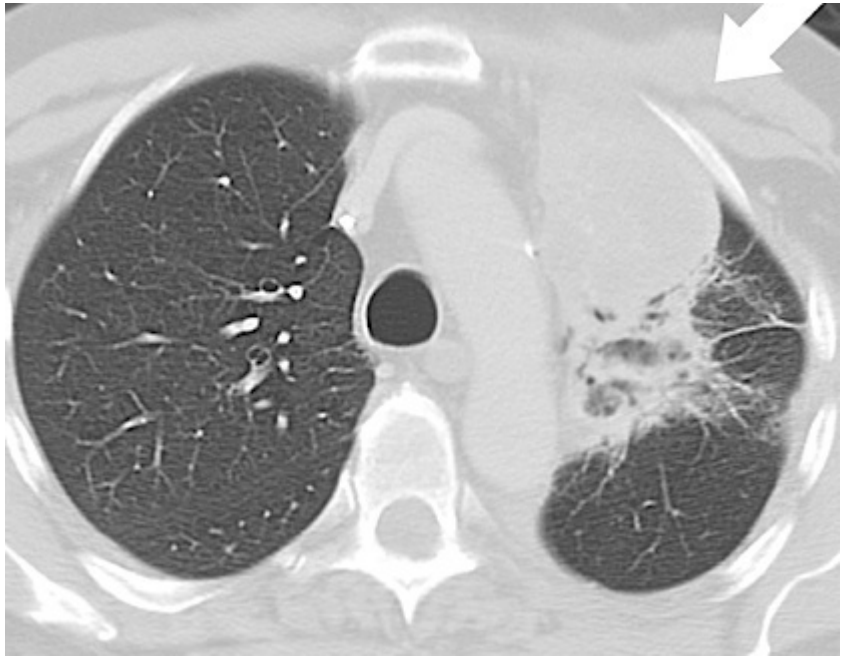
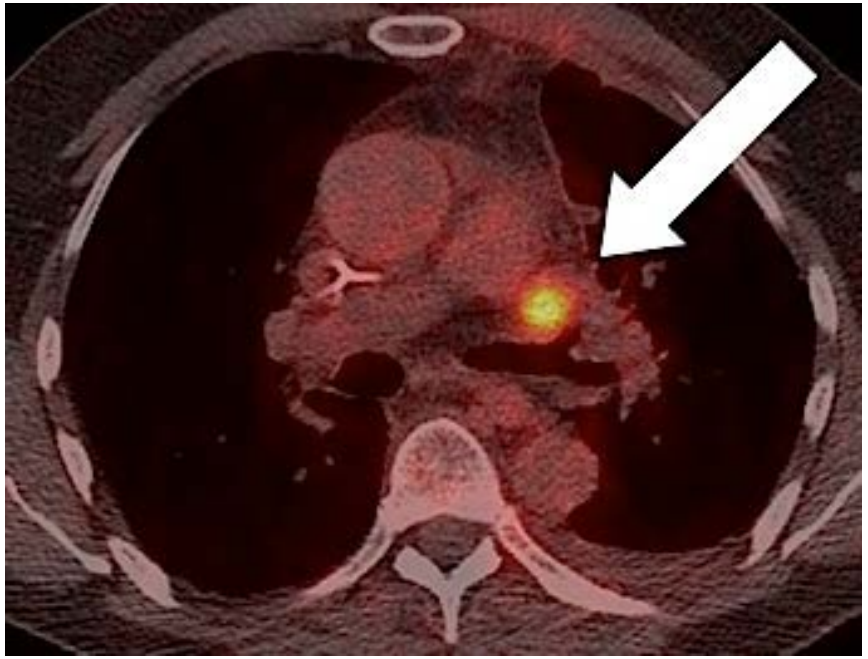
Case Presentation – Dr Yu: A 44-year-old woman with newly diagnosed Stage IIB adenocarcinoma of the lung and an EGFR L858R mutation

44 yo woman, never smoker, gets into a MVA and a CXR is done that identifies a L sided lung mass. CT scan shows a left sided lung nodule. Bronchoscopy with biopsy confirms primary lung adenocarcinoma and PET/MRI indicate no distant metastatic disease but ipsilateral hilar lymph node involvement.





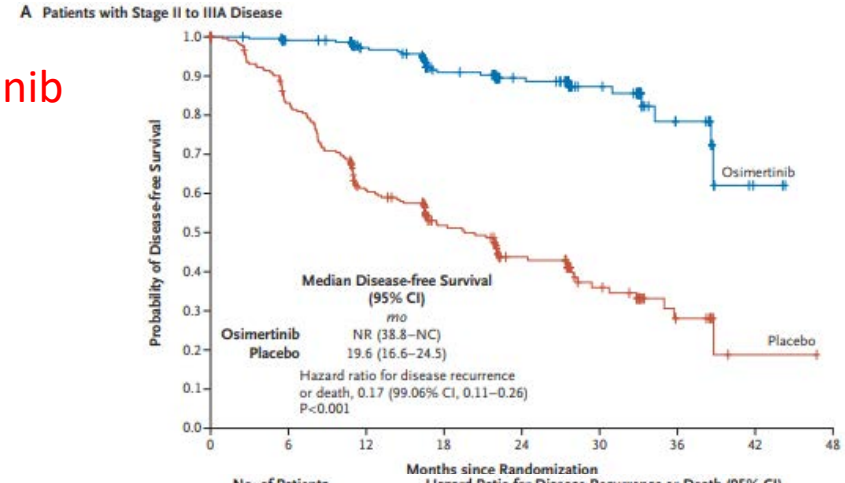
Case Presentation – Dr Yu: A 44-year-old woman with newly diagnosed Stage IIB adenocarcinoma of the lung and an EGFR L858R mutation (continued)

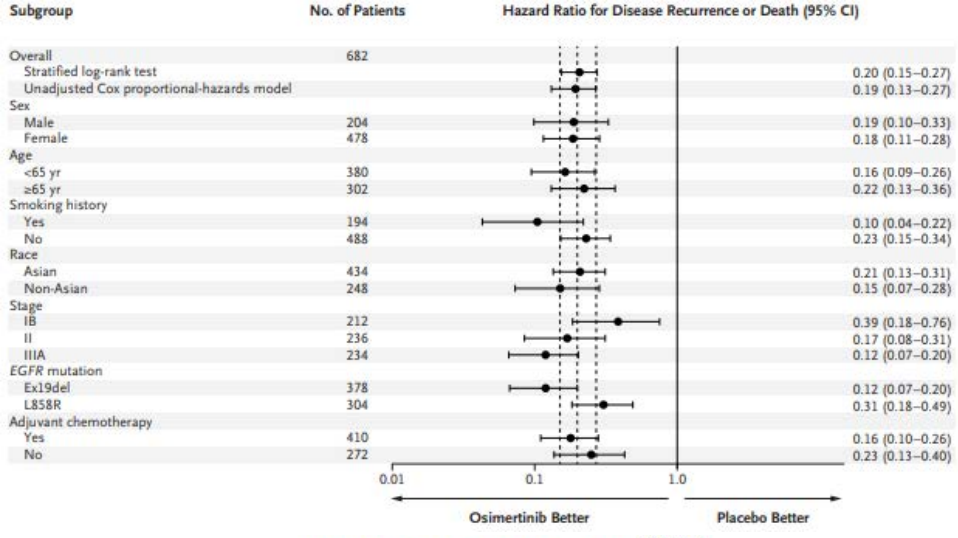
She undergoes a lobectomy and lymph node dissection. Final pathology indicates a T2AN1M0 lung adenocarcinoma, Stage 2B (PDL1 1%).

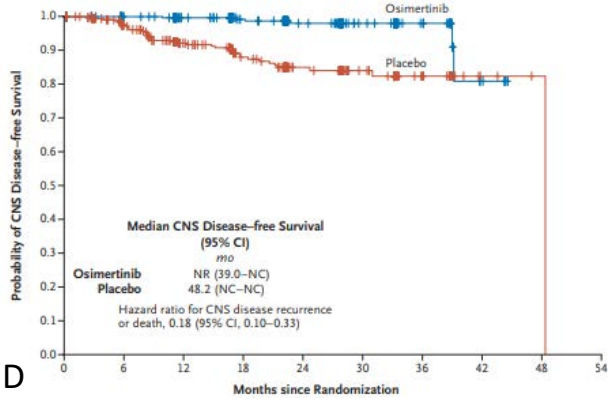
She recovers from surgery well and presents to your office to discuss any post-operative treatment. Reflex rapid testing confirms an EGFR L858R mutation.

What do you recommend?

Osimertinib



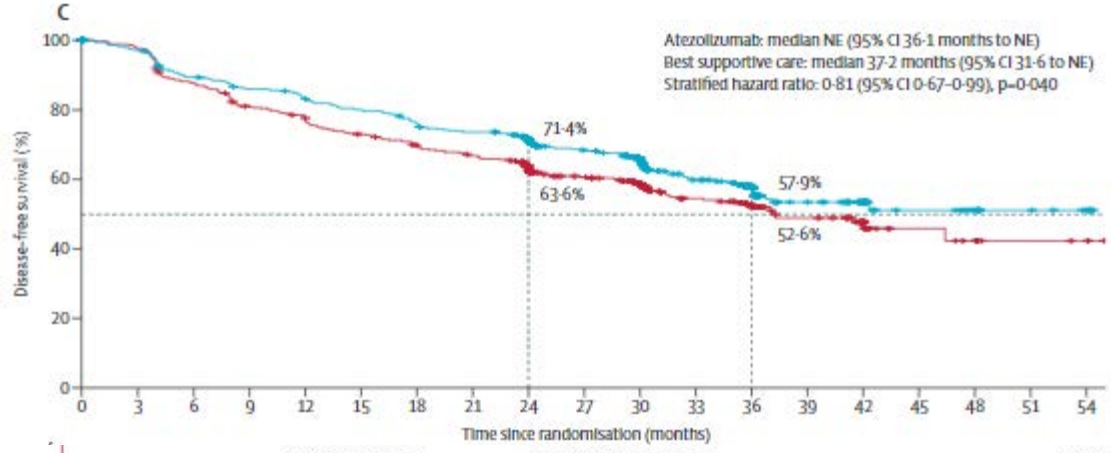




Courtesy of Helena Yu, MD

Atezolizumab

	PD-L1 TC ≥1% stage II–IIIA group (SP263)		All stage II–IIIA group		Intention-to-treat group (stage IB–IIIA)	
	Atezolizumab (n=248)	Best supportive care (n=228)	Atezolizumab (n=442)	Best supportive care (n=440)	Atezolizumab (n=507)	Best supportive care (n=498)
(Continued from previous page)						
EGFR mutation status†						
Yes	23 (9%)	20 (9%)	49 (11%)	60 (14%)	53 (10%)	64 (13%)
No	123 (50%)	125 (55%)	229 (52%)	234 (53%)	261 (52%)	266 (53%)
Unknown	102 (41%)	83 (36%)	164 (37%)	146 (33%)	193 (38%)	168 (34%)
Tobacco use history						
Never	51 (21%)	41 (18%)	100 (23%)	96 (22%)	114 (23%)	108 (22%)
Previous	163 (66%)	146 (64%)	277 (63%)	270 (61%)	317 (63%)	304 (61%)
Current	34 (14%)	41 (18%)	65 (15%)	74 (17%)	76 (15%)	86 (17%)



	Atezolizumab group		Best supportive care group		Hazard ratio (95% CI)
	Events/patients, n/N	Median DFS (95% CI), months	Events/patients, n/N	Median DFS (95% CI), months	
Age					
<65 years	156/287	NE (36·0–NE)	131/287	34·2 (29·7–NE)	0·67 (0·46–0·96)
≥65 years	92/189	42·3 (32·3–NE)	97/189	36·0 (23·0–NE)	0·64 (0·41–1·01)
Sex					
Male	171/318	NE (36·7–NE)	147/318	36·0 (29·0–NE)	0·69 (0·48–0·99)
Female	77/158	NE (31·3–NE)	81/158	30·1 (23·9–37·3)	0·61 (0·38–0·97)
Tobacco use history					
Never	51/92	31·3 (29·4–36·1)	41/92	20·5 (12·2–37·2)	0·63 (0·37–1·10)
Previous	163/309	NE (42·3–NE)	146/309	35·3 (26·7–NE)	0·54 (0·37–0·78)
Current	34/75	36·7 (27·9–NE)	41/75	NE (34·2–NE)	1·24 (0·58–2·64)
EGFR mutation status					
Yes	23/43	29·7 (18·0–NE)	20/43	16·6 (6·7–31·4)	0·57 (0·26–1·24)
No	123/248	NE (35·5–NE)	125/248	36·0 (26·7–NE)	0·67 (0·45–1·00)
Unknown	102/185	NE (36·1–NE)	83/185	35·3 (23·9–NE)	0·61 (0·38–0·98)

Case Presentation – Dr Yu: A 44-year-old woman with newly diagnosed Stage IIB adenocarcinoma of the lung and an EGFR L858R mutation (continued)

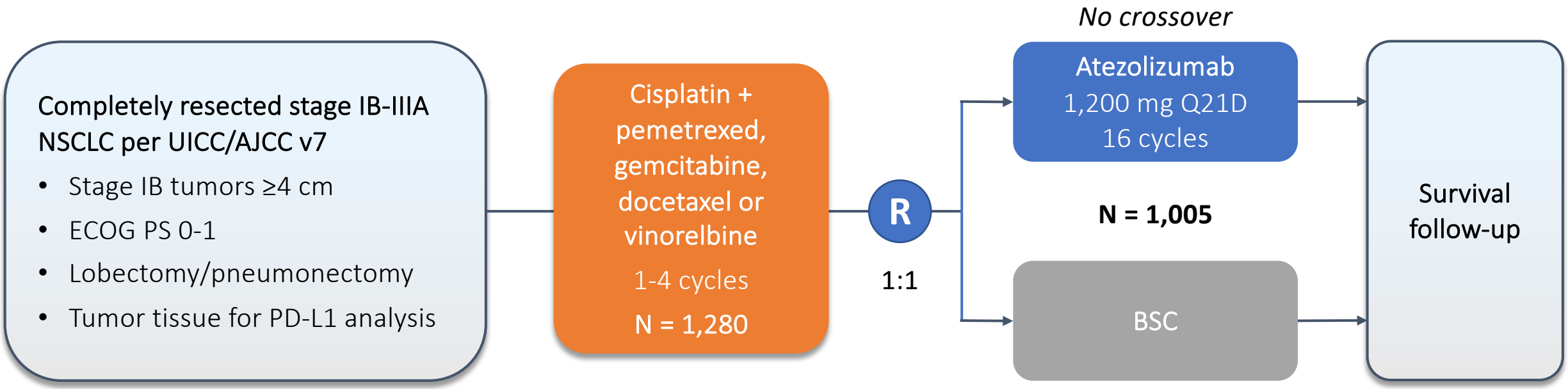
Variations:

What if she had an EGFR G719A mutation?

What if her PDL1 was 100%?

What if this was a 3B case s/p definitive chemoRT? Osimertinib or durvalumab?

Phase 3 IMpower010 Study: Schema



Stratification factors

- Male/female
- Stage (IB vs II vs IIIA)
- Histology
- PD-L1 tumor expression status[a]: TC2/3 and any IC vs TC0/1 and IC2/3 vs TC0/1 and IC0/1

Primary endpoints

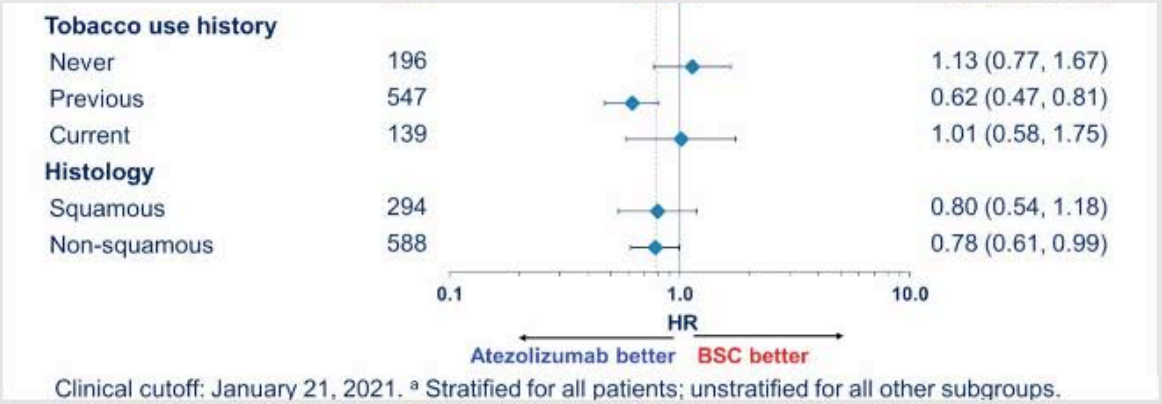
- Investigator-assessed DFS tested hierarchically:
  - PD-L1, TC ≥1% (per SP263) stage II-IIIA population
  - All-randomized stage II-IIIA population
  - ITT population (stage IB-IIIA)

Exploratory endpoints

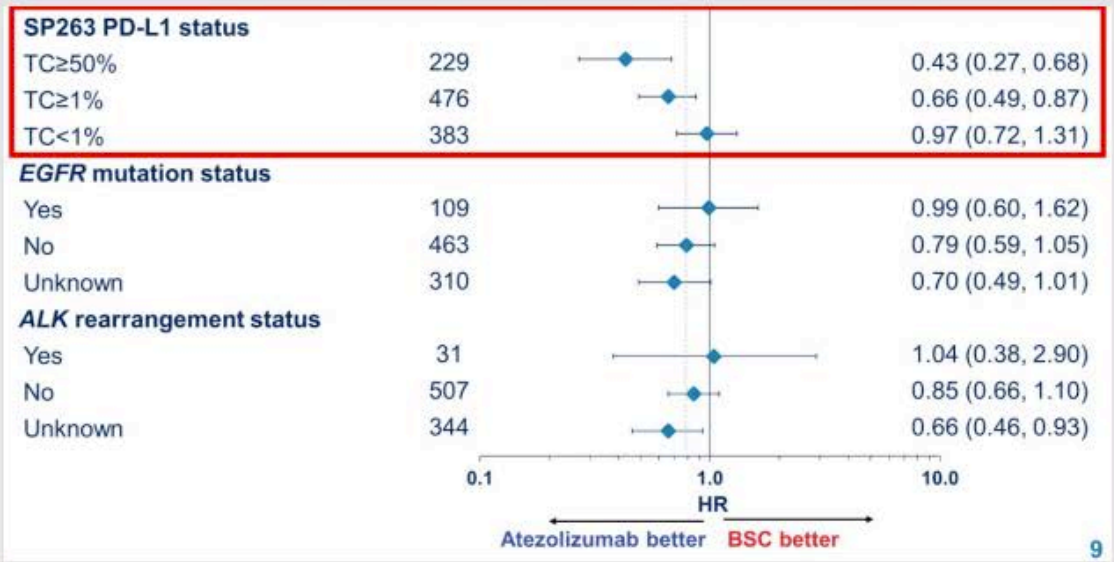
- OS in ITT population
- DFS in PD-L1 TC ≥50% (per SP263) stage II-IIIA population
- 3-year and 5-year DFS in all 3 populations

Wakelee HA. ASCO 2021; Abstract 8500

IMpower010: DFS in NSCLC ≥5cm (7th ed. St II-IIIA) Key Subsets



Clinical cutoff: January 21, 2021. [a] Stratified for all patients; unstratified for all other subgroups.



No obvious benefit in:

- Never smokers
- PD-L1 negative
- EGFR/ALK+

Adapted from Wakelee H et al. ASCO 2021;Abstract 8500

Chaft JE. IASLC 2021;Abstract PL05.04

RTP RESEARCH TO PRACTICE

The NEW ENGLAND JOURNAL of MEDICINE

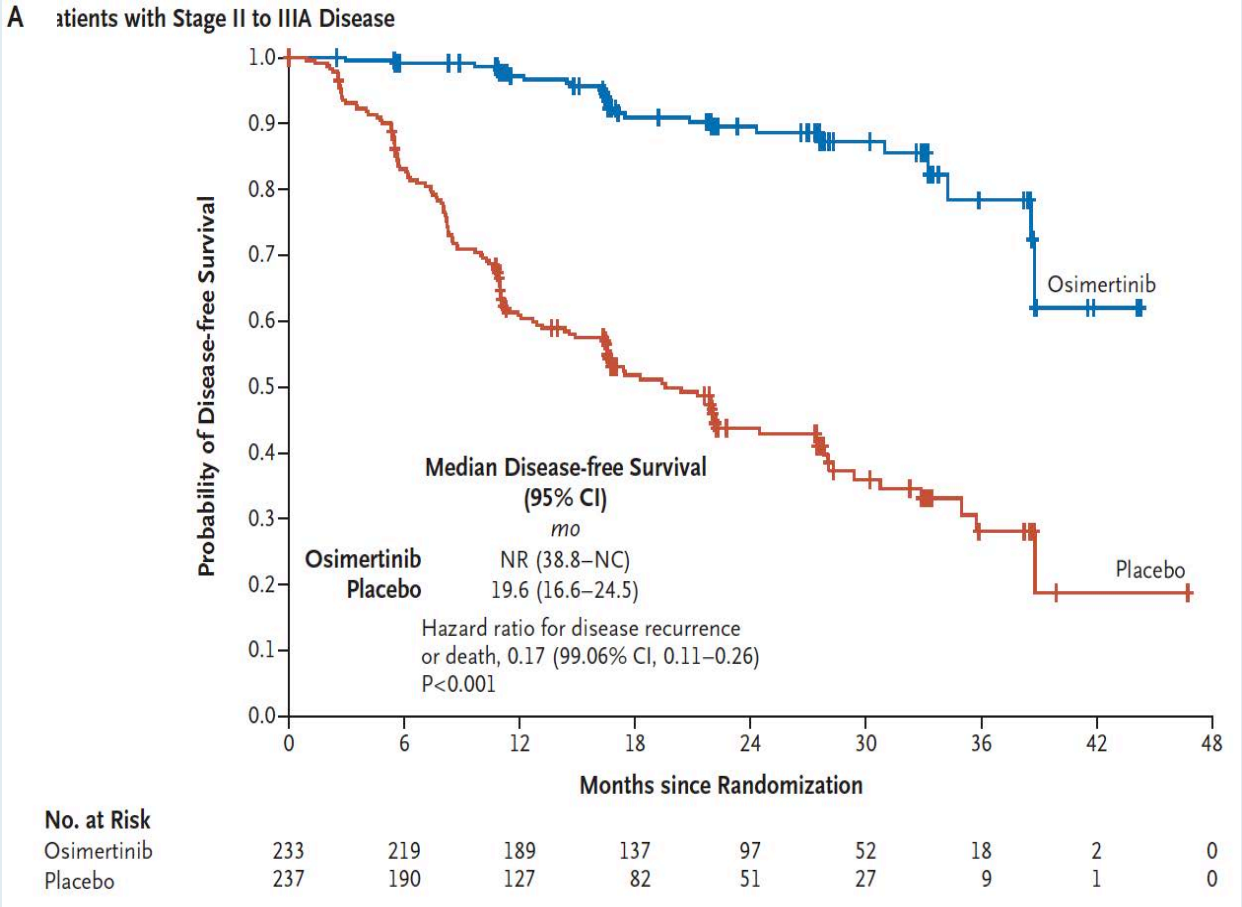
ORIGINAL ARTICLE

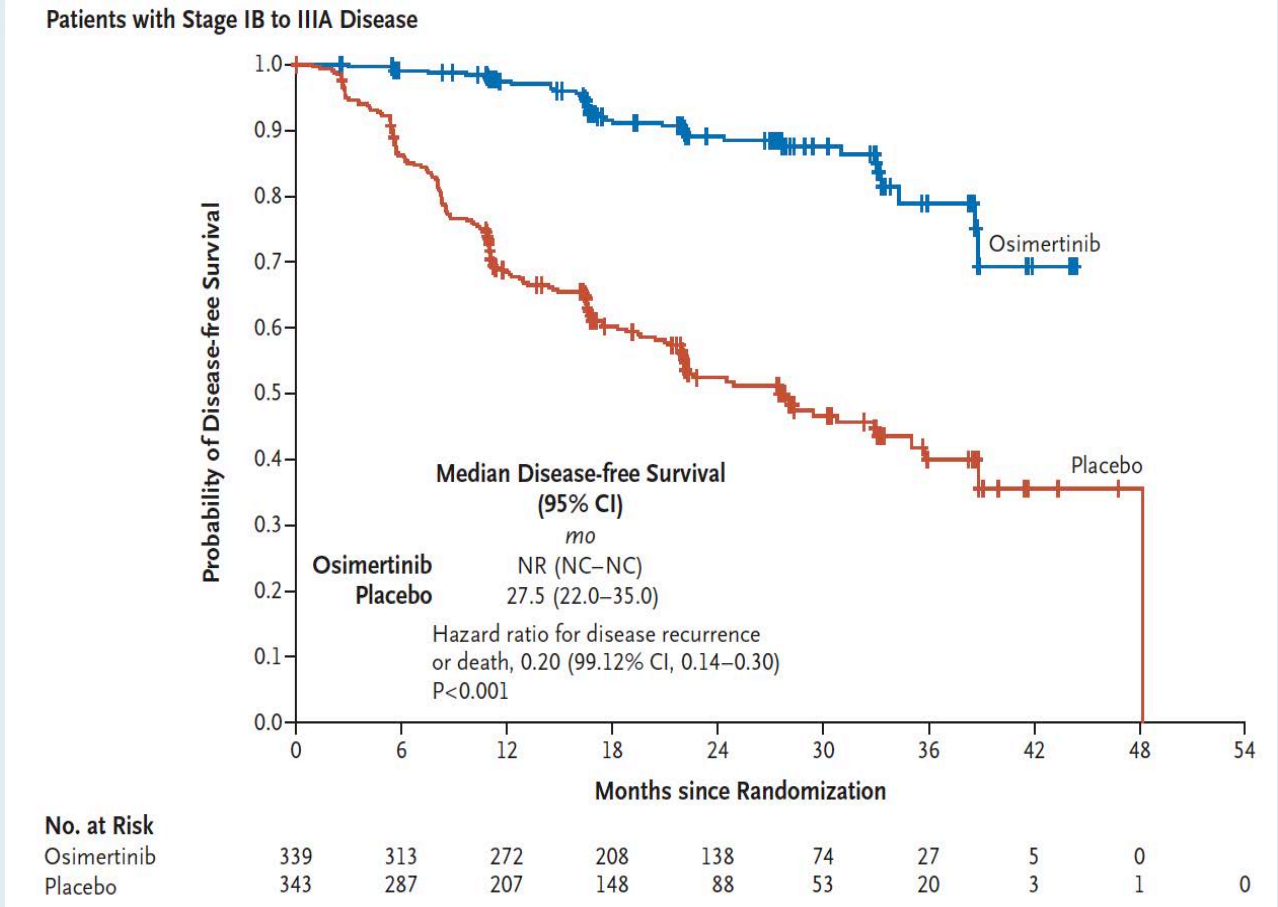
Osimertinib in Resected *EGFR*-Mutated Non–Small-Cell Lung Cancer

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.

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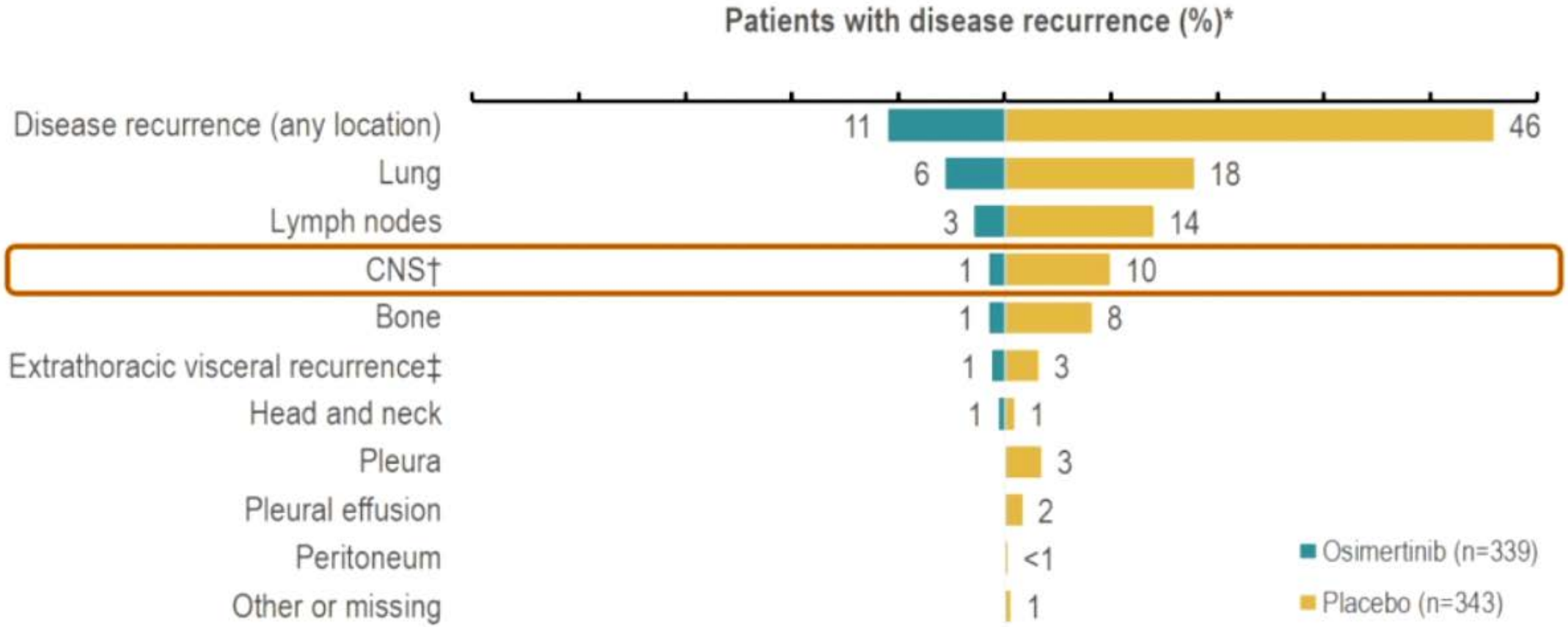
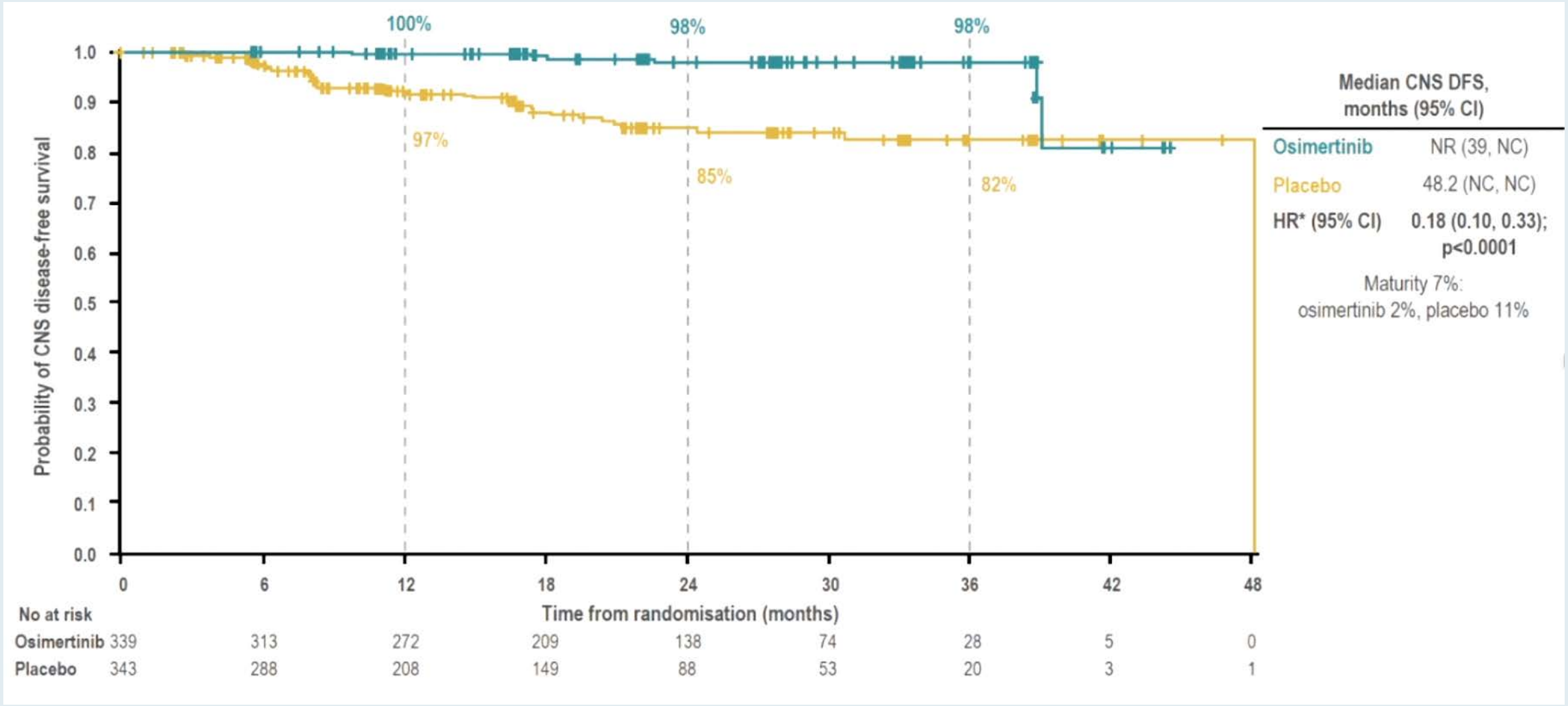
ADAURA: Sites of Disease Recurrence



Tsuboi M et al. ESMO 2020;Abstract LBA1.

RTP RESEARCH TO PRACTICE

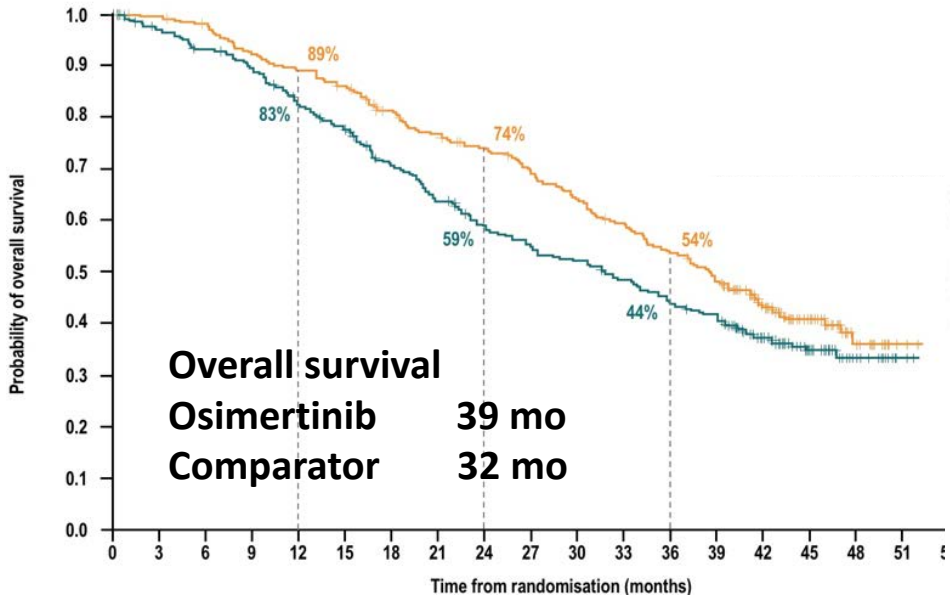
ADAURA: CNS DFS in Overall Population

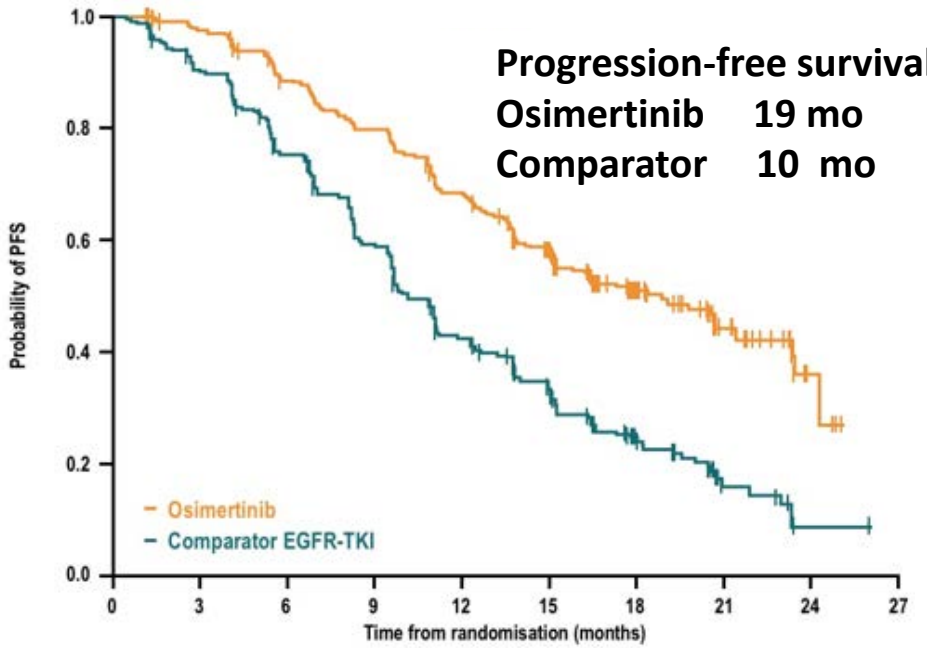


Tsuboi M et al. ESMO 2020;Abstract LBA1.

RTP RESEARCH TO PRACTICE

Osimertinib as best in class EGFR TKI





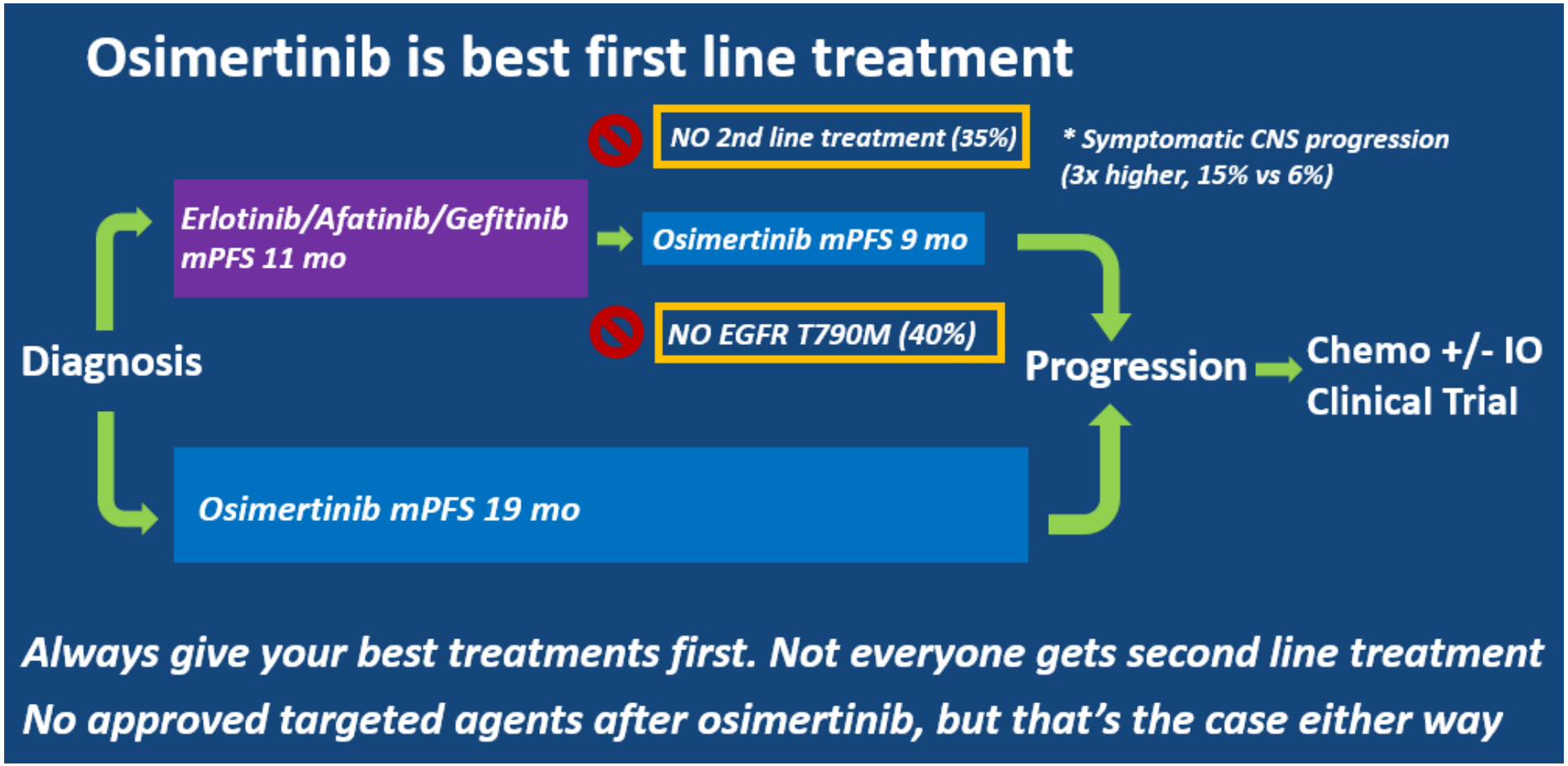
- Osimertinib is a third-generation, irreversible, mutant-specific EGFR TKI
- Improved PFS and OS compared to earlier generation EGFR TKIs
- Time on treatment and overall survival still relatively short with acquired resistance a certainty
- Ongoing/upcoming studies are focused on combinations with osimertinib and/or addressing emerging mechanisms of resistance

Memorial Sloan Kettering Cancer Center

Soria NEJM 2018, Ramalingam ESMO 2019

Courtesy of Helena Yu, MD

Osimertinib as best in class EGFR TKI



Memorial Sloan Kettering Cancer Center

Courtesy of Helena Yu, MD

Agenda

Introduction: Role of Genomic Profiling in Non-Small Cell Lung Cancer (NSCLC)

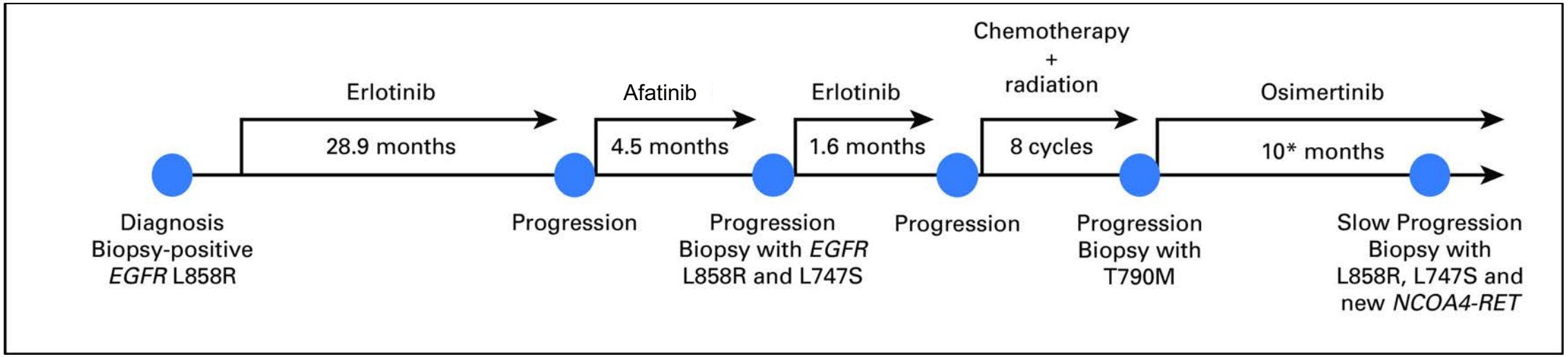
Case Presentations

- Dr Yu: A 44-year-old woman with newly diagnosed Stage IIB adenocarcinoma of the lung and an EGFR L858R mutation
- Dr Ladanyi: A 78-year-old man with metastatic NSCLC and osimertinib resistance due to acquired RET fusion
- Dr Yu: A 64-year-old woman with newly diagnosed adenocarcinoma of the lung and an EGFR exon 20 mutation
- Dr McKenzie: A 78-year-old man with Stage IV adenocarcinoma of the lung and a RET fusion
- Dr Bachow: A 69-year-old man with metastatic mucinous adenocarcinoma of the lung and a HER2 mutation
- Dr Jasani: A 35-year-old woman with newly diagnosed metastatic NSCLC and an ALK mutation
- Dr McKenzie: A 78-year-old man with NSCLC and a TRK fusion
- 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

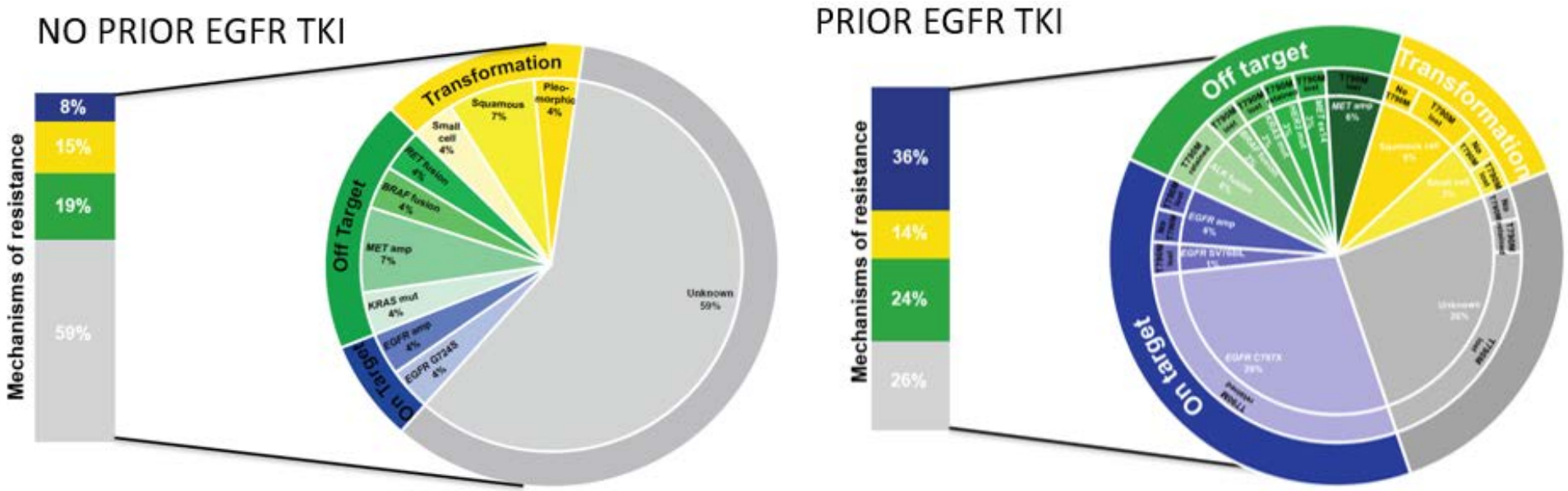
RTP RESEARCH TO PRACTICE

Case Presentation – Dr Ladanyi: A 78-year-old man with metastatic NSCLC and osimertinib resistance due to acquired RET fusion

A 78-year-old man, a never smoker, presented with a 4-cm right lung mass and a liver lesion. A biopsy of the lung revealed adenocarcinoma positive for *EGFR* L858R (staging T2aN2M1b). He started treatment with erlotinib and continued it for 29 months until progression developed in the lungs. A subsequent biopsy showed the original *EGFR* L858R and a newly acquired EGFR L747S mutation. He started combination treatment with carboplatin and pemetrexed along with palliative radiation to the right middle lobe. A repeat biopsy then showed an acquired *EGFR* T790M mutation in addition to *EGFR* L747S and L858R mutations, and he started osimertinib. The biopsy tissue was retrospectively analyzed by targeted RNAseq and showed no evidence of gene fusions. The patient developed oligoprogression after 16 months of osimertinib treatment and underwent local radiation. A right lung biopsy showed the known *EGFR* L747S and L858R mutations as well as a new *NCOA4-RET* fusion on MSK-IMPACT™; the fusion was confirmed by targeted RNAseq. The patient remained on osimertinib treatment as a result of the slow, asymptomatic progression.



Acquired resistance to osimertinib



- 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

Schoenfeld CCR 2020

Courtesy of Helena Yu, MD

Combination EGFR TKIs to address acquired second-site EGFR resistance mutations

Pretreatment	After 1st gen TKI	After 3rd gen TKI

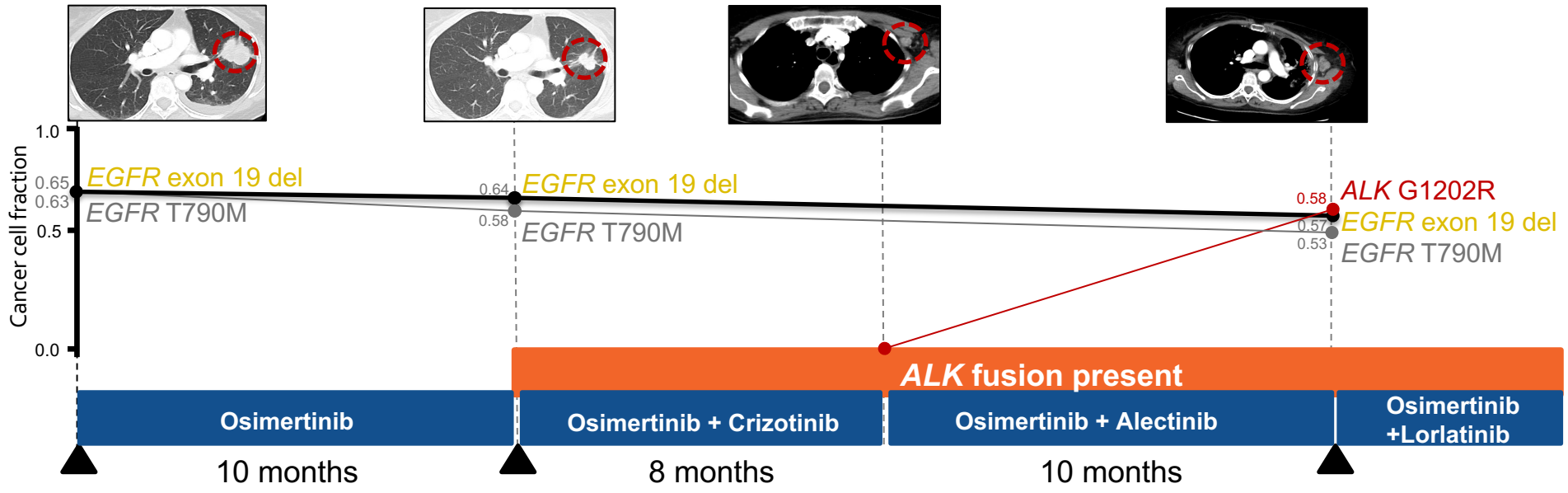
- The most common mechanism of resistance to earlier generation EGFR TKIs is T790M. Osimertinib is a T790M inhibitor.
- 3rd generation EGFR TKIs bind at EGFR C797. Acquired EGFR C797S (L718X, G724X) induce resistance to osimertinib.
- In the presence of the original EGFR mutation and C797S without T790M, cells retain sensitivity to 1st/2nd generation EGFR TKIs.

Thress Nat Med 2015, Yu JAMA Onc 2015, Ercan Canc Res 2015

Courtesy of Helena Yu, MD

Acquired ALK fusion drives resistance to osimertinib

Combined inhibition of *ALK* and *EGFR* overcomes *ALK* mediated resistance



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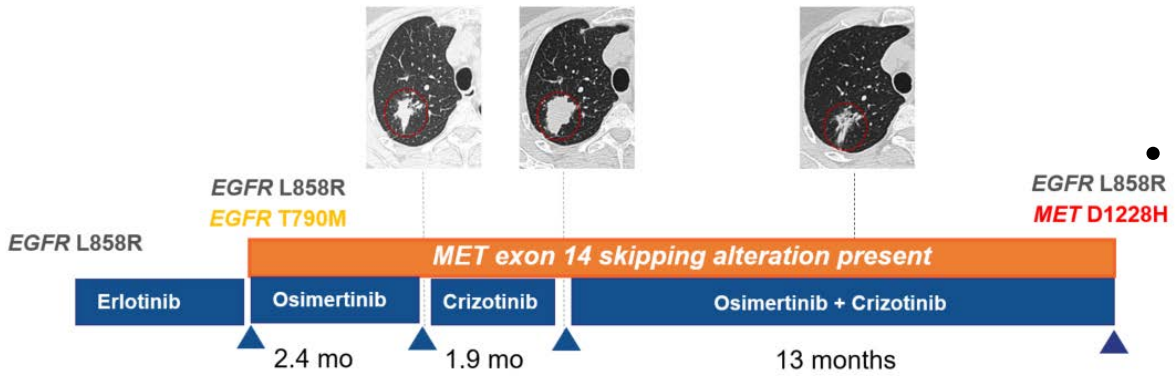
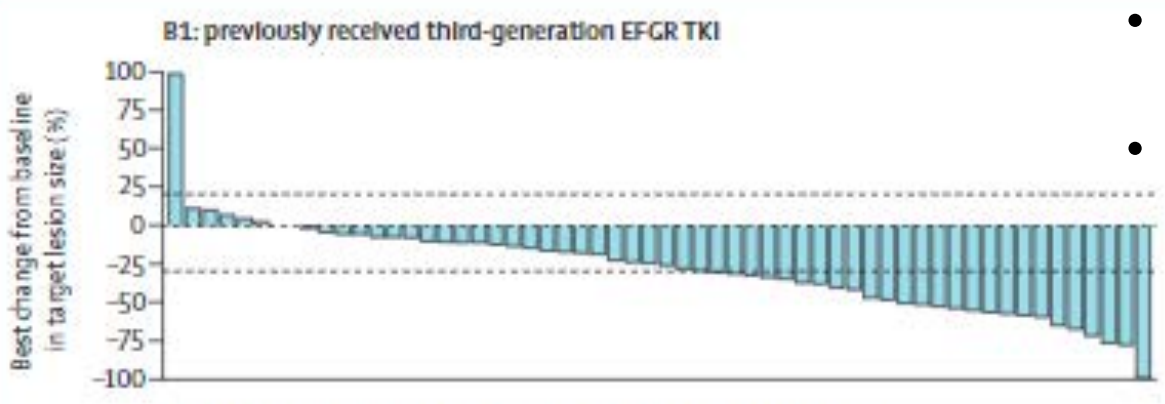
Schoenfeld et al. ASCO 2019

Courtesy of Helena Yu, MD

Acquired MET amplification/mutation drives resistance to osimertinib





- -Approved/available MET inhibitors include crizotinib, tepotinib and capmatinib.
- -Osimertinib and savolitinib studied in TATTON study with relevant cohort that received prior 3rd gen EGFR TKI (57% had 3 or more prior treatments)
- -ORR was 30%, median PFS 5.4 months
- -Multiple studies ongoing looking at osimertinib + MET inhibitor combination (tepotinib NCT03940703, savolitinib SAVANNAH NCT03778229, ORCHARD NCT03944772)

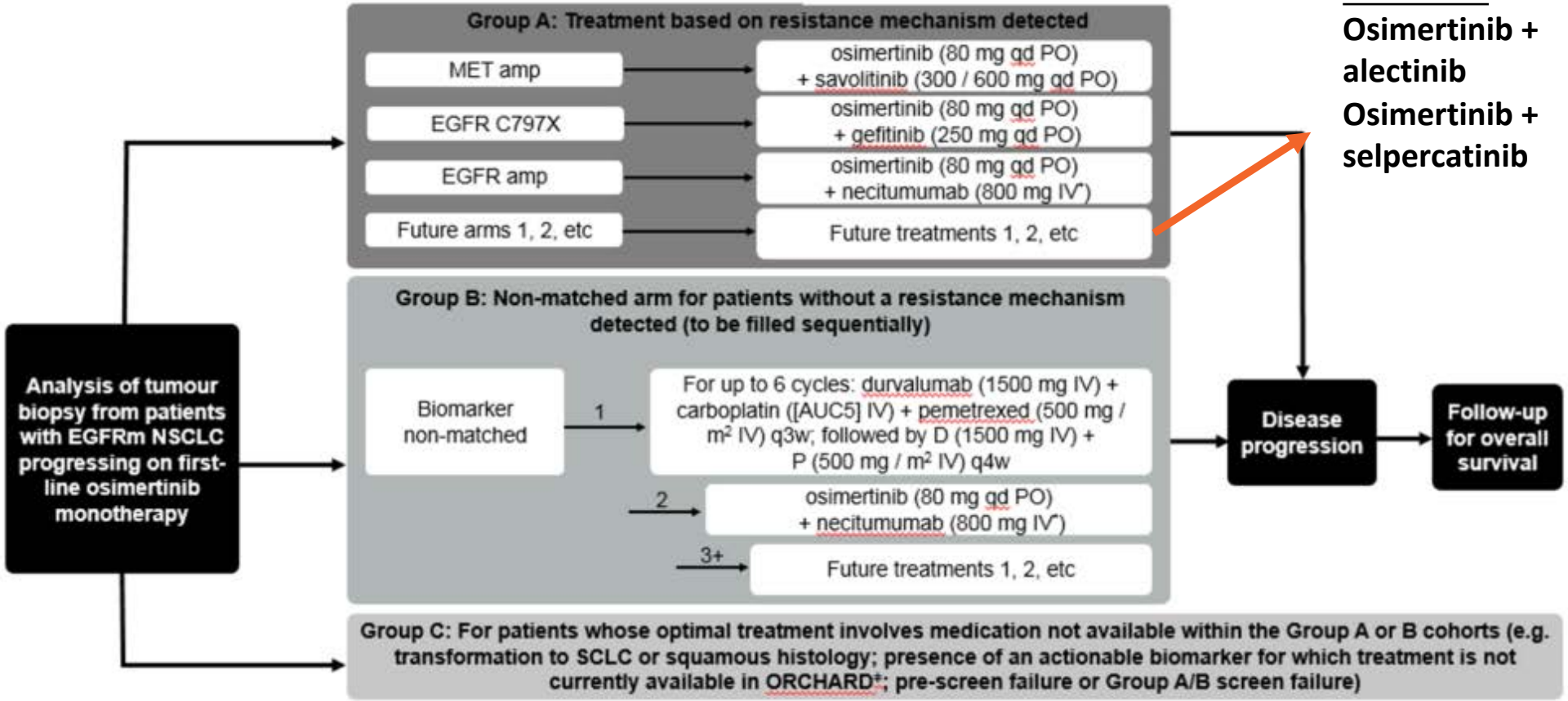
Courtesy of Helena Yu, MD

Memorial Sloan Kettering Cancer Center

Sequist Lancet Onc 2020, Suzawa JCO PO 2019

ORCHARD: Osimertinib-based combinations

Figure 1. ORCHARD study design



New arms:
Osimertinib + alectinib
Osimertinib + selpercatinib

*On Days 1 and 8 of each 3-week cycle; †e.g. ALK fusion
ALK, anaplastic lymphoma kinase; amp, amplification; AUC, area under curve; EGFR, epidermal growth factor; EGFRm, EGFR-tyrosine kinase inhibitor sensitising mutation; IV, intravenous; MET, hepatocyte growth factor receptor (HGFR); NGS, next generation sequencing; NSCLC, non-small cell lung cancer; PO, orally; q3(4)w, once every 3(4)-week cycle; qd, once a day; SCLC, small cell lung cancer

Memorial Sloan Kettering Cancer Center

Courtesy of Helena Yu, MD

Agenda

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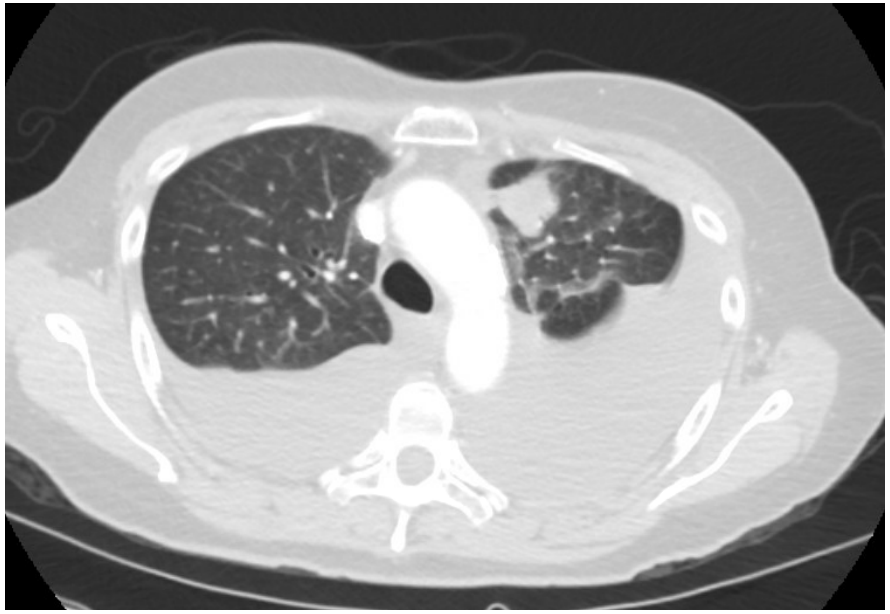
RTP RESEARCH TO PRACTICE

Case Presentation – Dr Yu: A 64-year-old woman with newly diagnosed adenocarcinoma of the lung and an EGFR exon 20 mutation

64yo, never smoker, develops back pain and shortness of breath. MRI shows lytic lesions throughout spine, CT with bilateral pleural effusions, liver lesions, lymphadenopathy. CT guided biopsy of L lung nodule consistent with lung adenocarcinoma, PDL1 0%, EGFR exon 20 p.N771_H773_dup

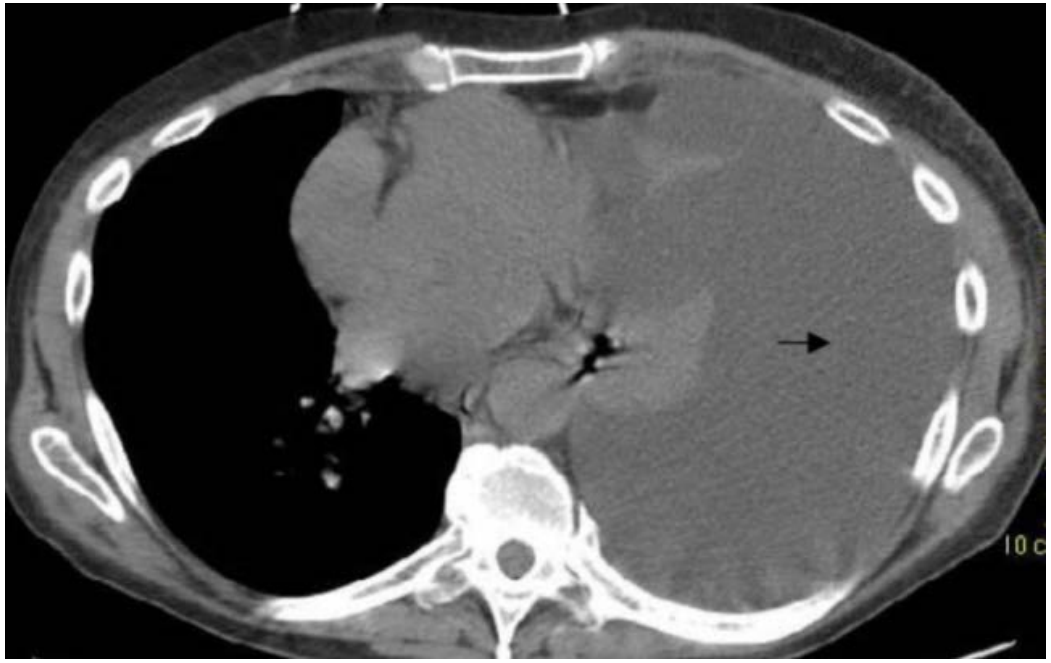


What first treatment do you recommend?

What factors contribute to your decision?

Case Presentation – Dr Yu: A 64-year-old woman with newly diagnosed adenocarcinoma of the lung and an EGFR exon 20 mutation (continued)

She received 4 cycles of carboplatin/pemetrexed/bevacizumab followed by 4 cycles of pemetrexed/bevacizumab maintenance therapy. Repeat scans show worsening now large L pleural effusion.



What treatment do you recommend?

What factors contribute to your decision?

Interval brain MRI indicates 5 punctate new brain metastases.

Does that change your treatment choice?

Landscape of Targeting EGFR Exon 20 Insertion

	Mobocertinib	Amivantamab	Osimertinib	CLN-081	Poziotinib
Type of drug	EGFR TKI	EGFR/MET antibody	EGFR TKI	EGFR TKI	EGFR TKI
Clinical trial setting	After platinum chemo Active brain mets OK (35%)	After platinum chemo Brain mets (22%)	1 prior line of treatment Stable brain mets OK	After platinum chemo Stable brain mets OK	After chemo Stable brain mets OK (10%)
Number of pts	PPP N=114 EXCLAIM N=96	N=81	N=21	N=43	N=87
Prior TKI	25% (PPP) 31% (EXCLAIM)	25%	Prior TKI unknown Median prior therapy = 2	Prior 1st/2nd gen=18% Prior osi=20% Prior pozi/mobo=9%	Prior EGFR TKI=25%
Prior IO	43% (PPP) 34% (EXCLAIM)	46%	Unknown	56%	Unknown
Toxicity (Treatment-related) >30%	91-93% Diarrhea 45% Rash 39% Paronychia 32-35% Anorexia 30-34% Nausea 31% Dry skin	66% infusion reaction 86% rash 42% paronychia	76% Diarrhea 67% Fatigue 67% thrombocytopenia 43% anemia 43% leukopenia 43% anorexia 38% mucositis 38% rash	73% Rash	79% Diarrhea 60% Rash 52% Stomatitis 45% Paronychia 38% Nausea 31% Anorexia
Dose Modifications	Dose reduction 25% PPP 22% EXCLAIM Drug discontinue 17% PPP 10% EXCLAIM	Dose reduction 13% Drug discontinue 4%	Dose reduction Unknown Drug discontinue 5%	Dose reduction 11% Drug discontinue 9%	Dose reduction 68% Drug discontinue 10%
ORR	28% (PPP) 25% (EXCLAIM)	40%	24%	31% at all levels 46% at 100 BID	15%
PFS/DOR	DOR 17.5 mo (PPP) mPFS 7.3mo (PPP) OS 24 mo (PPP)	DOR 11.1 mPFS 8.3mo OS 22.8 mo	mPFS 9.6mo	Unknown	PFS 4.2mo DOR 7.4mo
CNS as Site of PD	All: CNS 38%, Not CNS (62%) Baseline brain mets: CND 68%	Not reported	Not reported	Not reported	Not reported
EGFR ex20ins Position	Efficacy across all EGFRex20ins subtypes	Efficacy across all EGFRex20ins subtypes	Not reported	Efficacy across all EGFRex20ins subtypes	Efficacy across all EGFRex20ins subtypes

Ramalingam PASCO 2021, Piotrowska PASCO 2020
Sabari WCLC 2020, Piotrowska PASCO 2021 #ASCO21
Le AACR 2020

Courtesy of Helena Yu, MD

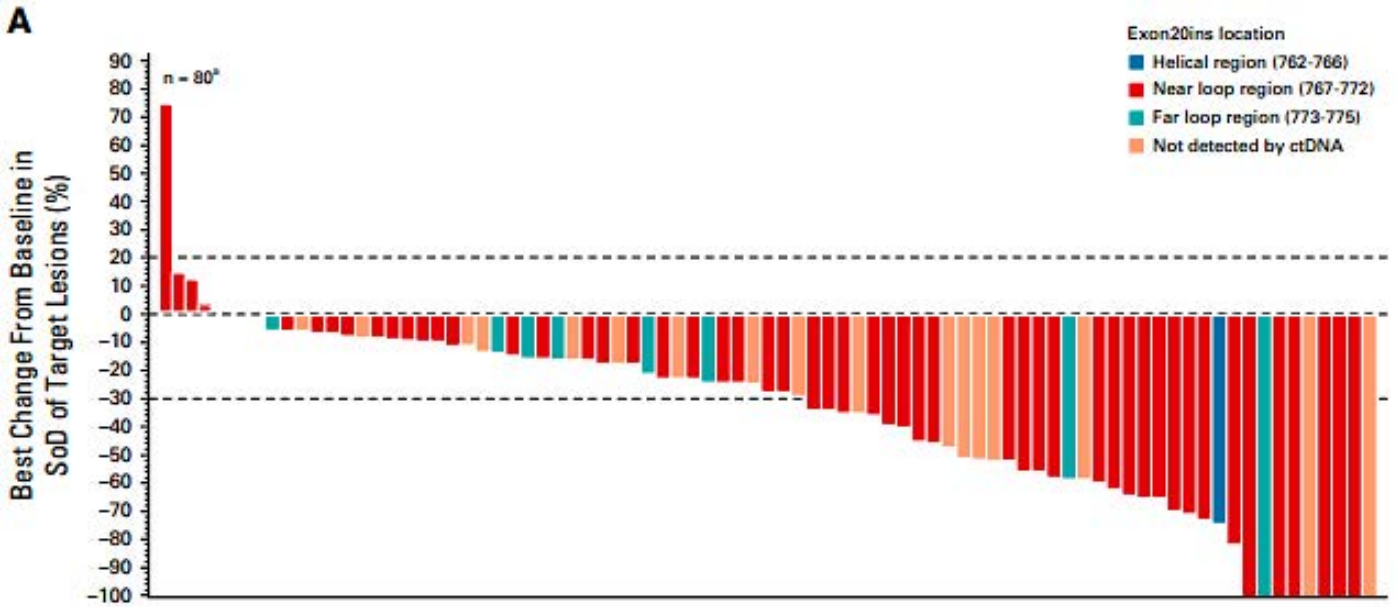
Case Presentation – Dr Yu: A 64-year-old woman with newly diagnosed adenocarcinoma of the lung and an EGFR exon 20 mutation (continued)

The decision is made to start amivantamab.

Are there any potential adverse events that are important to share with the patient?

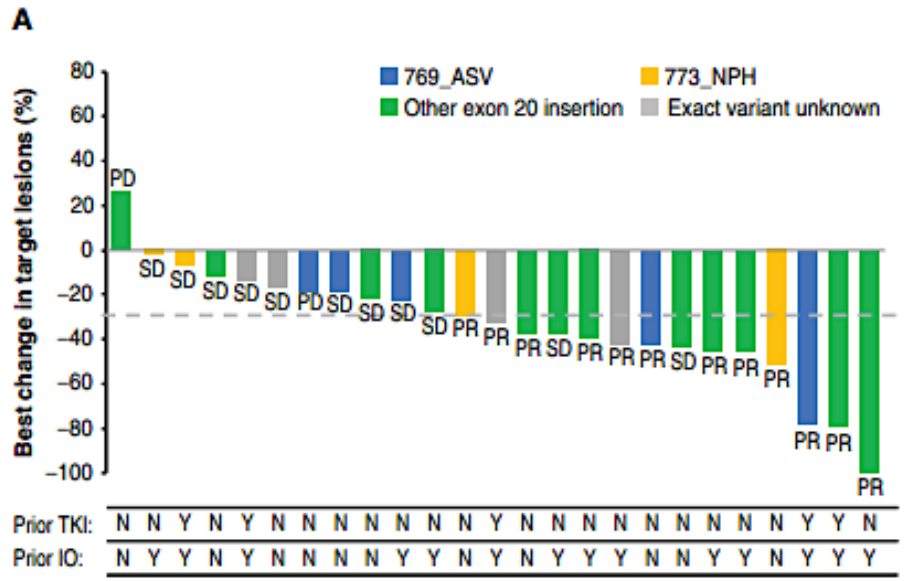
Amivantamab

Most Common AE (≥ 10%)	Safety Population (n = 114), No. (%)				Patients Treated at the RP2D (n = 258), No. (%)			
	Total	Grade 1	Grade 2	Grade ≥ 3	Total	Grade 1	Grade 2	Grade ≥ 3
Rash[b]	98 (86)	43 (38)	51 (45)	4 (4)	202 (78)	101 (39)	94 (36)	7 (3)
Infusion-related reaction	75 (66)	9 (8)	63 (55)	3 (3)	167 (65)	21 (8)	140 (54)	6 (2)
Paronychia	51 (45)	28 (25)	22 (19)	1 (1)	104 (40)	50 (19)	51 (20)	3 (1)
Hypoalbuminemia	31 (27)	6 (5)	22 (19)	3 (3)	63 (24)	21 (8)	38 (15)	4 (2)
Constipation	27 (24)	18 (16)	9 (8)	0	58 (23)	36 (14)	22 (9)	0
Nausea	22 (19)	17 (15)	5 (4)	0	55 (21)	40 (16)	14 (5)	1 (0.4)
Dyspnea	22 (19)	12 (11)	8 (7)	2 (2)	52 (20)	28 (11)	13 (5)	11 (4)
Stomatitis	24 (21)	11 (10)	13 (11)	0	50 (19)	33 (13)	17 (7)	0
Peripheral edema	21 (18)	20 (18)	1 (1)	0	50 (19)	43 (17)	5 (2)	2 (1)



Mobocertinib

TEAE	Patients with *EGFR*ex20ins treated at 160 mg/d[a] (*n* = 28)		All patients treated at 160 mg/d[b] (*n* = 136)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Diarrhea	23 (82)	9 (32)	113 (83)	28 (21)
Nausea	11 (39)	3 (11)	58 (43)	5 (4)
Rash	13 (46)	0	45 (33)	1 (1)
Vomiting	10 (36)	2 (7)	36 (26)	5 (4)
Dry skin	5 (18)	0	30 (22)	0
Decreased appetite	11 (39)	0	29 (21)	1 (1)
Stomatitis	6 (21)	2 (7)	28 (21)	5 (4)
Fatigue	4 (14)	1 (4)	28 (21)	2 (1)
Rash maculopapular	7 (25)	1 (4)	22 (16)	1 (1)
Paronychia	8 (29)	0	22 (16)	0



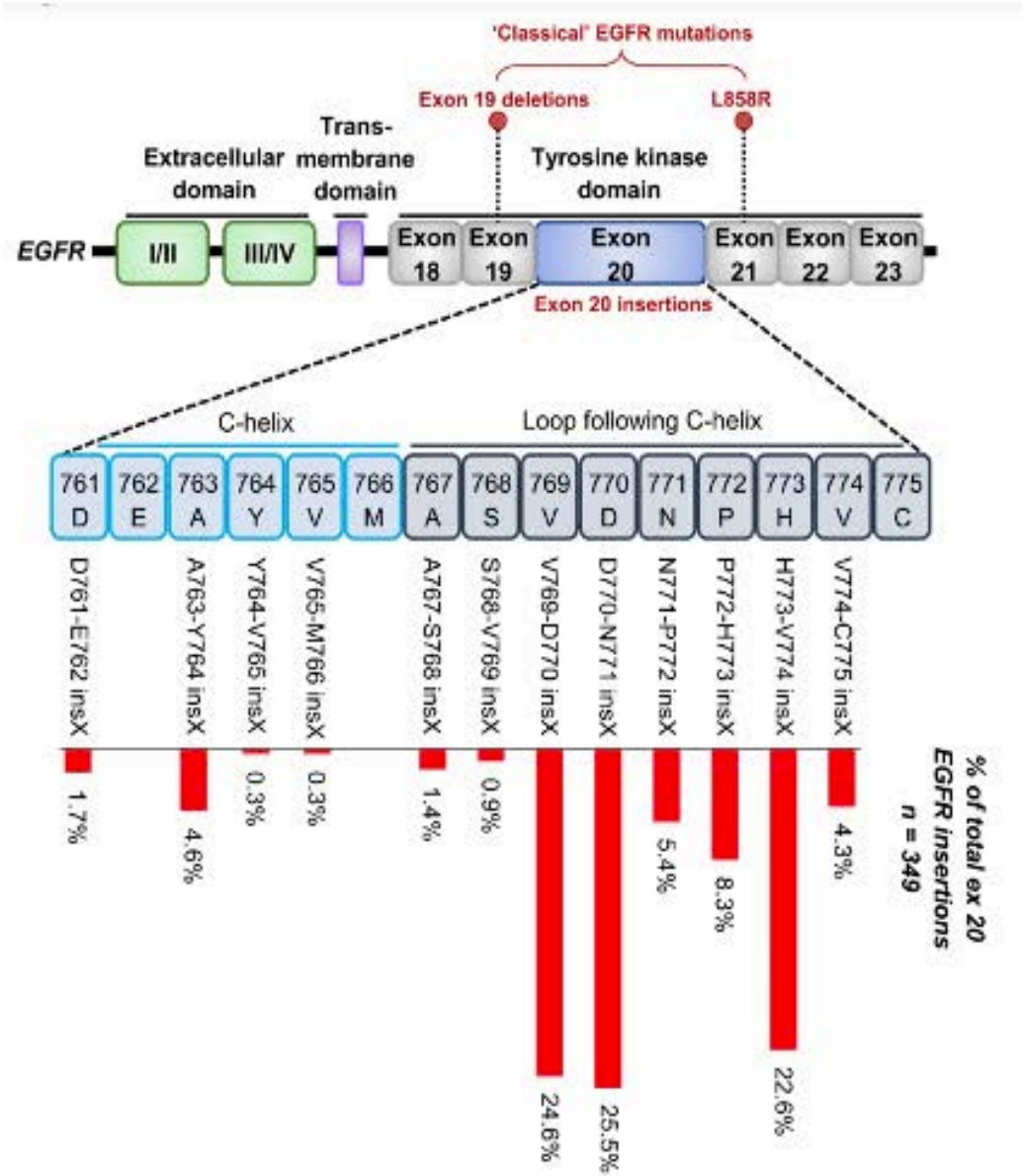
Courtesy of Helena Yu, MD

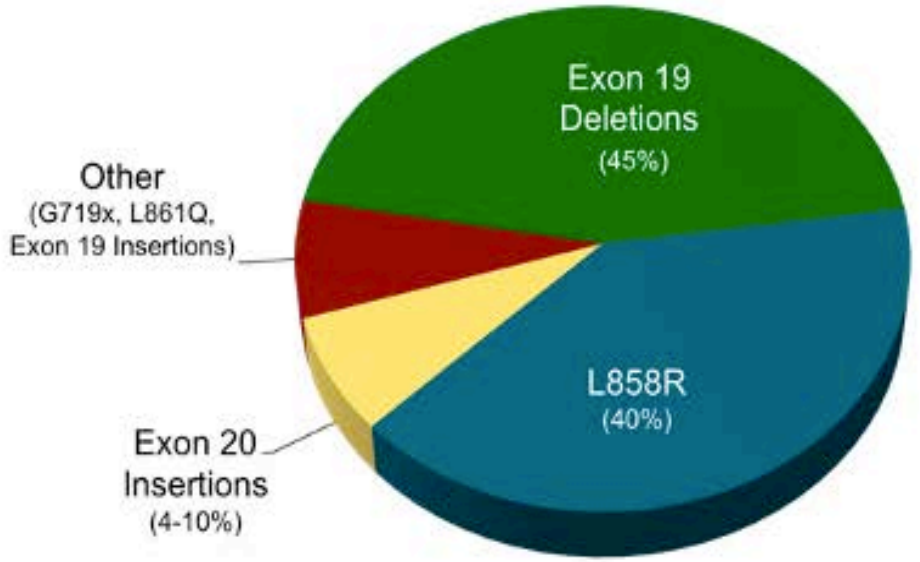
Case Presentation – Dr Yu: A 64-year-old woman with newly diagnosed adenocarcinoma of the lung and an EGFR exon 20 mutation (continued)

She had disease shrinkage with amivantamab and tolerated it well with rash, paronychia, and some peripheral edema. After 6 months on treatment, her disease progressed again.

What treatment would you consider at this point?

Frequency of EGFR Exon 20 Mutations



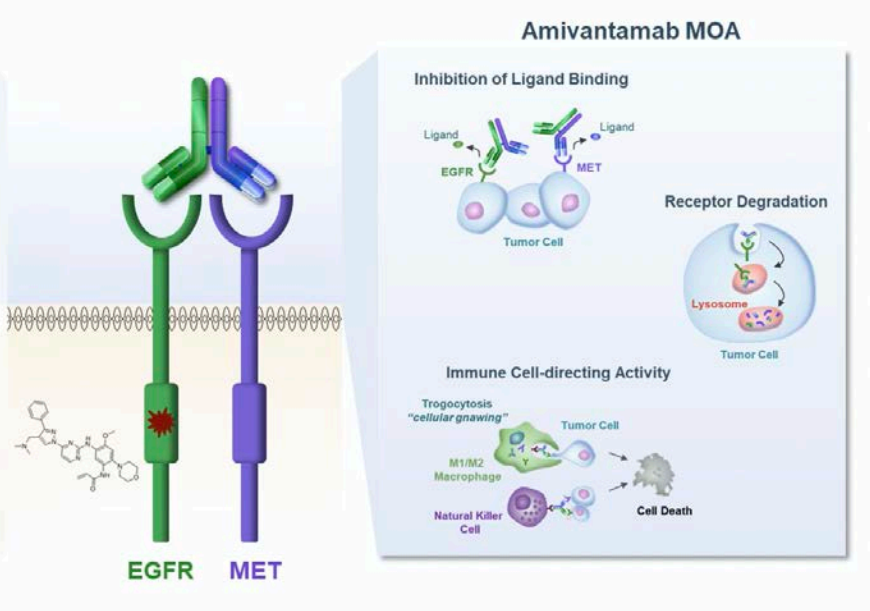


Exon 20 NSCLC: US and China				
		Exon 20 Frequency	Total Number of NSCLC Patients/year	
United States	EGFR	2.1%	3.6%	7700
	HER2	1.5%		
China	EGFR	2.4%	6.3%	41100
	HER2	3.9%		

Courtesy of Zofia Piotrowska, MD, MHS

Amivantamab

Amivantamab is a bispecific antibody targeting EGFR + MET

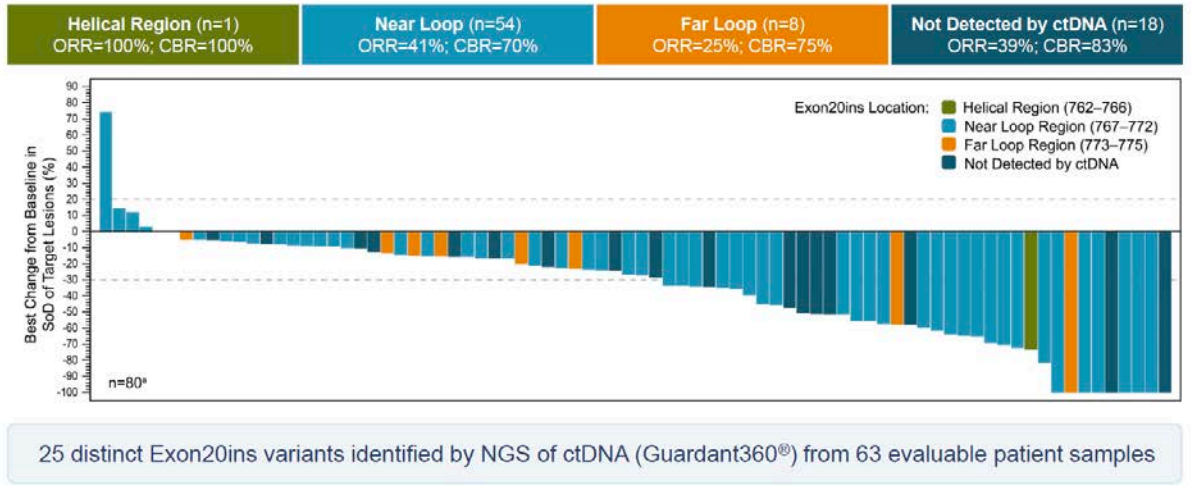


- Amivantamab recently received FDA approval for EGFR exon 20 insertion+ NSCLC

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)



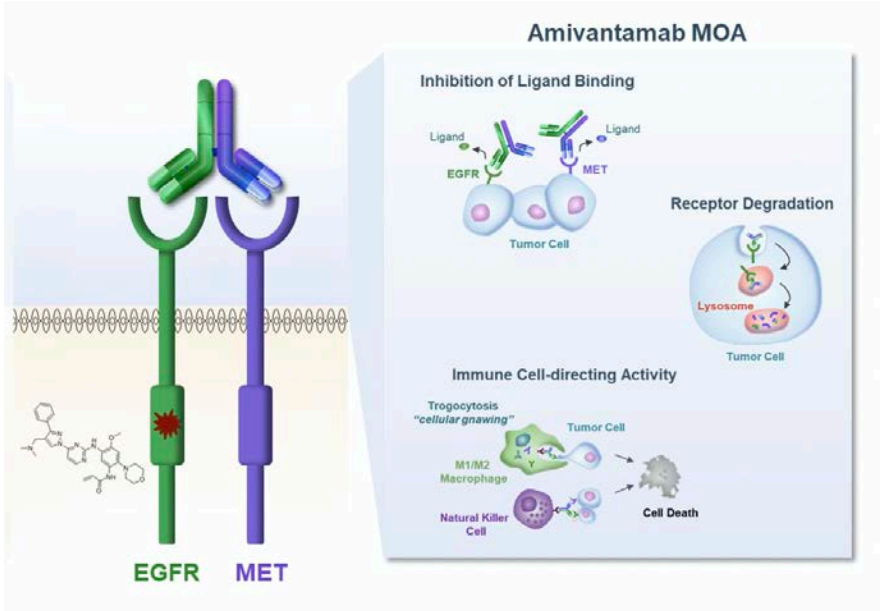
25 distinct Exon20ins variants identified by NGS of ctDNA (Guardant360®) from 63 evaluable patient samples

Courtesy of Zofia Piotrowska, MD, MHS

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

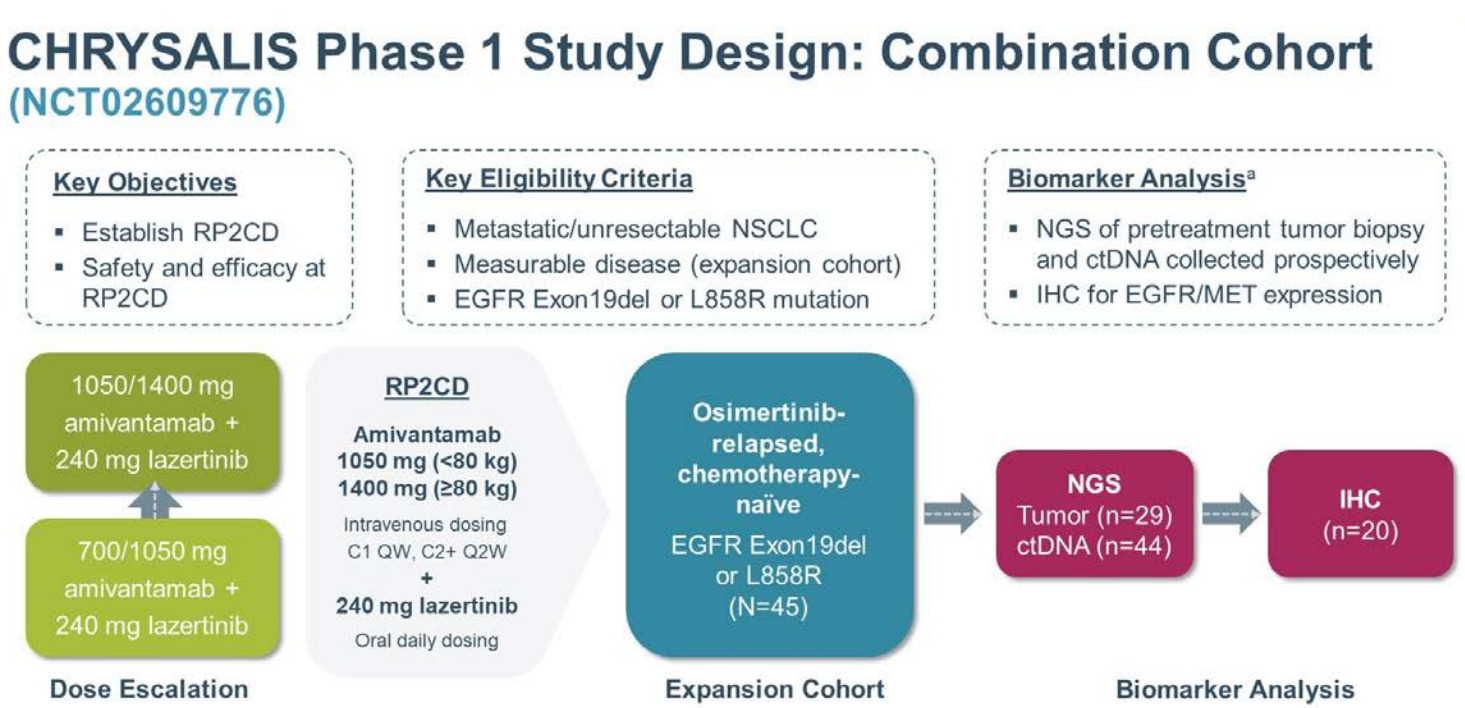
Amivantamab + Lazertinib

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

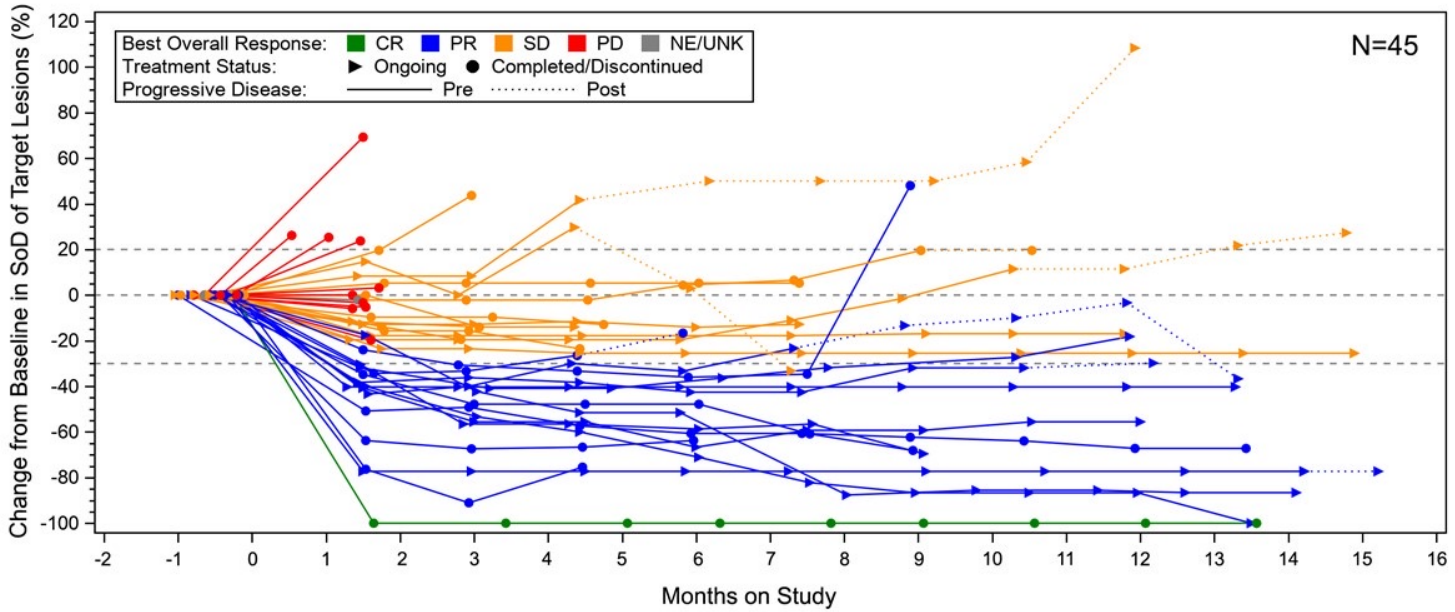
Amivantamab + Lazertinib in TKI-resistant EGFR+ NSCLC



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)

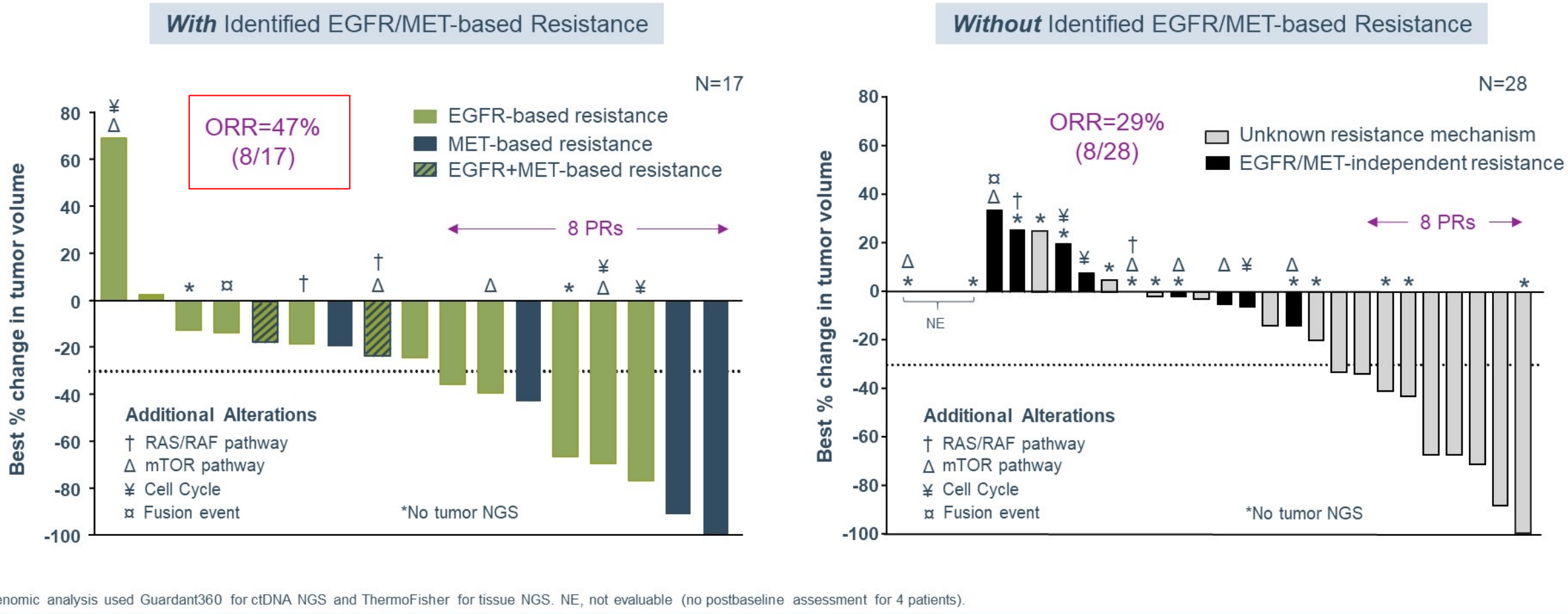
- Safety profile consistent with previous experience with amivantamab + lazertinib[1]
- Most common AEs were IRR (78%), rash (acneiform dermatitis, 51% + rash, 27%), and paronychia (49%)
  - Majority were grade 1–2
- Treatment-related: grade ≥3 AE (16%), discontinuations (4%), dose reductions (18%)

1. Chul B et al. ASCO 2021

Courtesy of Zofia Piotrowska, MD, MHS

MASSACHUSETTS GENERAL HOSPITAL CANCER CENTER

Amivantamab + Lazertinib

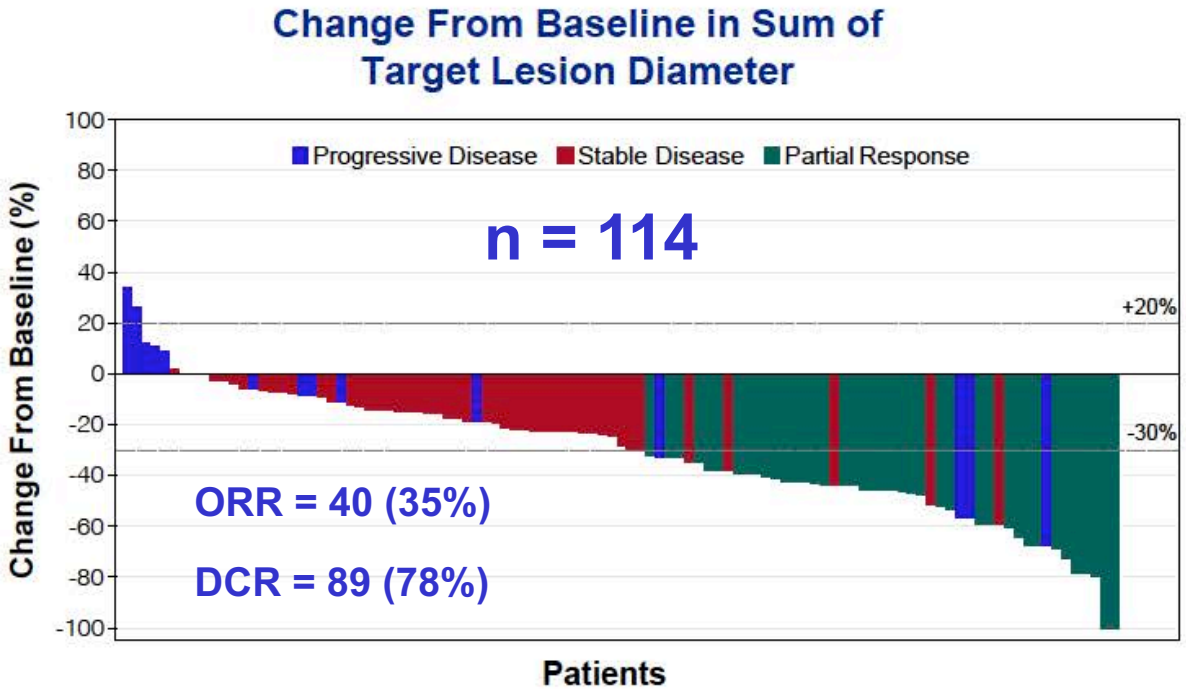


Genomic analysis used Guardant360 for ctDNA NGS and ThermoFisher for tissue NGS. NE, not evaluable (no postbaseline assessment for 4 patients).

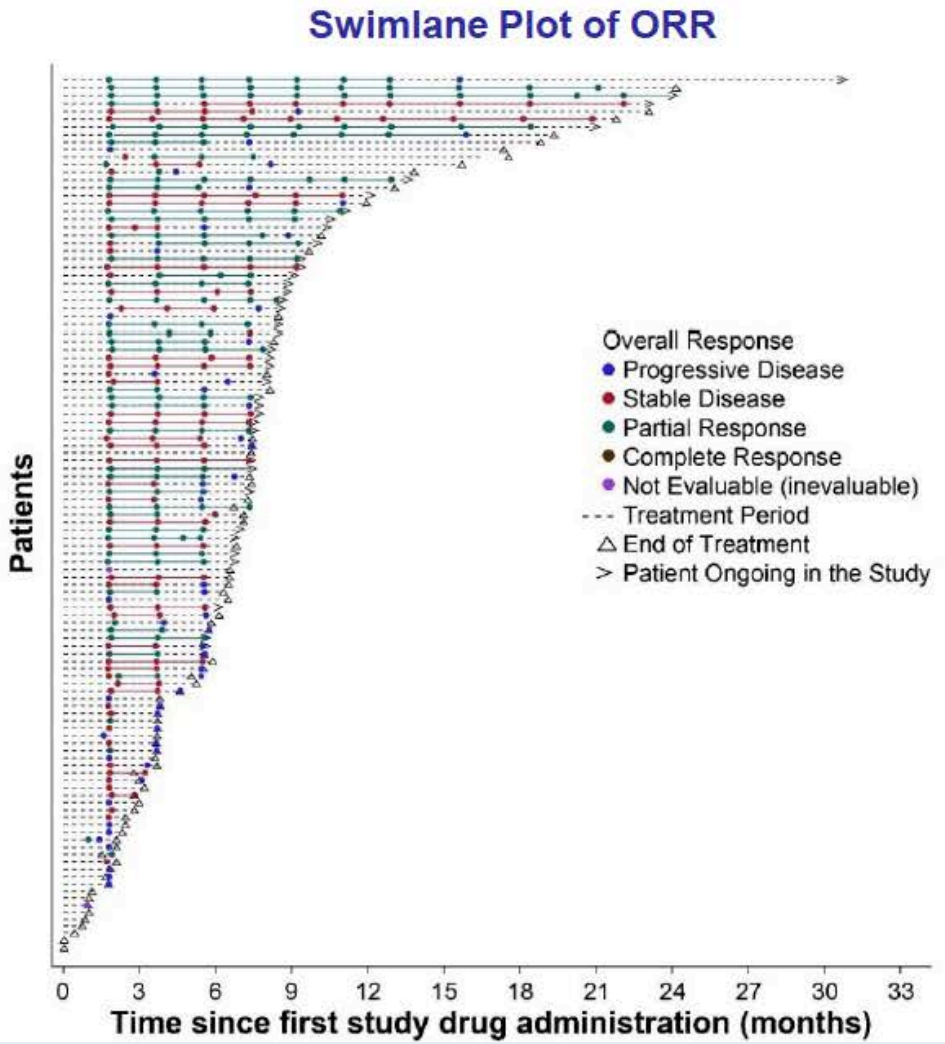
1. Chul B et al. ASCO 2021

Courtesy of Zofia Piotrowska, MD, MHS

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



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

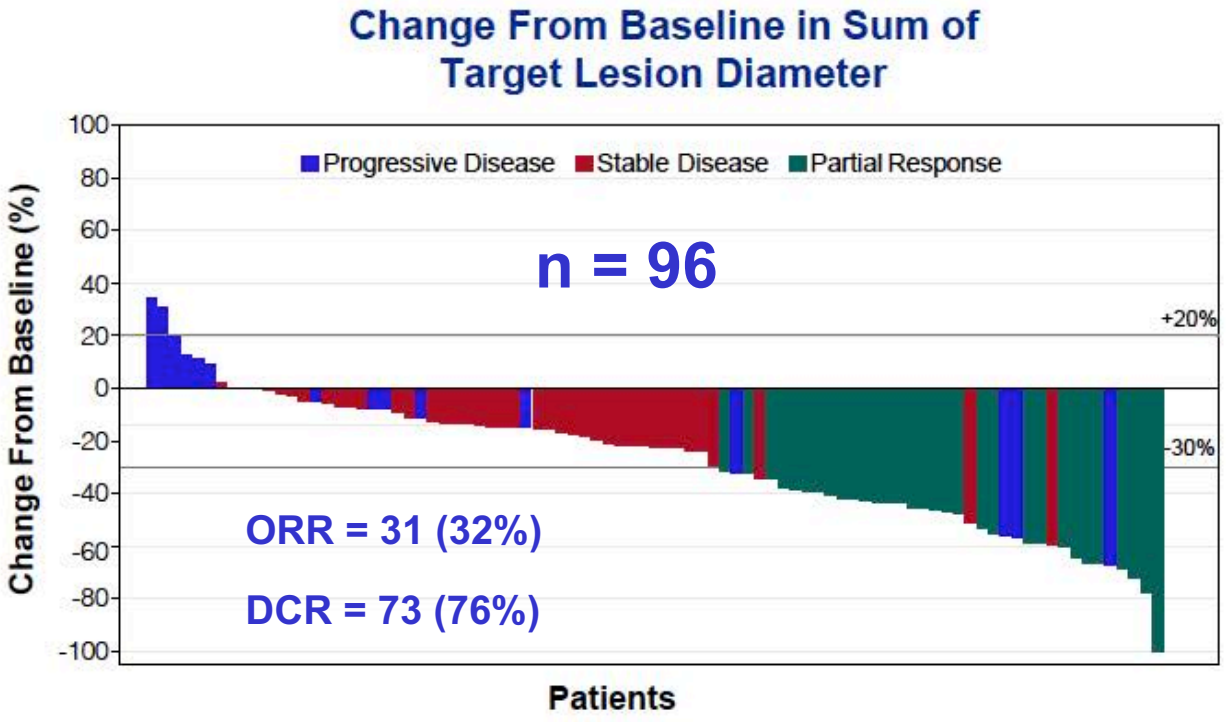


ORR, objective response rate; PPP, platinum-pretreated patients

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

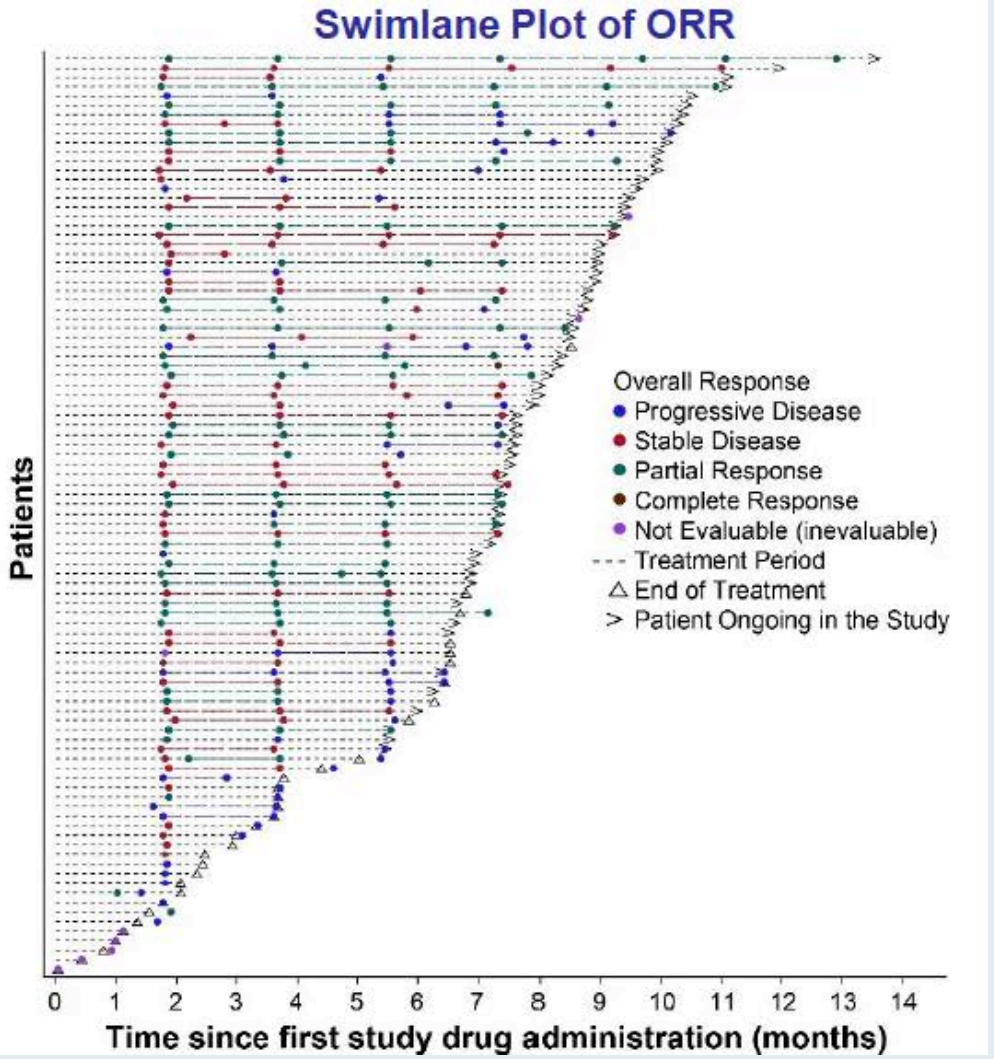
Courtesy of Zofia Piotrowska, MD, MHS

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

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- Dr Bachow: A 69-year-old man with metastatic mucinous adenocarcinoma of the lung and a HER2 mutation
- Dr Jasani: A 35-year-old woman with newly diagnosed metastatic NSCLC and an ALK mutation
- Dr McKenzie: A 78-year-old man with NSCLC and a TRK fusion
- 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 Stage IV adenocarcinoma of the lung and a RET fusion

- 78yr Male – never smoker
- Diagnosed May 2020 with Stage IV NSCLC adenocarcinoma
  - PDL1 = 20%
  - No brain mets
  - *Carbo/pem/pem planned if NGS revealed no actionable alterations*
- Tissue-based NGS (6/2020)
  - Revealed CCDC6-RET fusion
- Selpercatinib initiated 6/2020 (160mg BID)
  - Adenocarcinoma of the lung Stage IV
    - Reviewed his CTs. Shows stable appearance of the anterolateral pleural thickening within the LEFT hemithorax, small L loculated pleural effusion with stable L basilar atelectasis/consolidation, small amount of abdominal and pelvic ascites has increased without discrete peritoneal or omental nodularity
    - Tolerating treatment
    - PS and labs adequate
    - Continue Selpercatinib at 160mg bid
    - Next visit 3 months

Case Presentation – Dr McKenzie: A 78-year-old man with Stage IV adenocarcinoma of the lung and a RET fusion (continued)

Due to the low tumor purity, sensitivity for the detection of copy number alterations including ERBB2 is reduced due to sample quality. Refer to appendix for limitations statement. Sensitivity for the detection of other alterations and genomic signatures may also be reduced.

Biomarker Findings

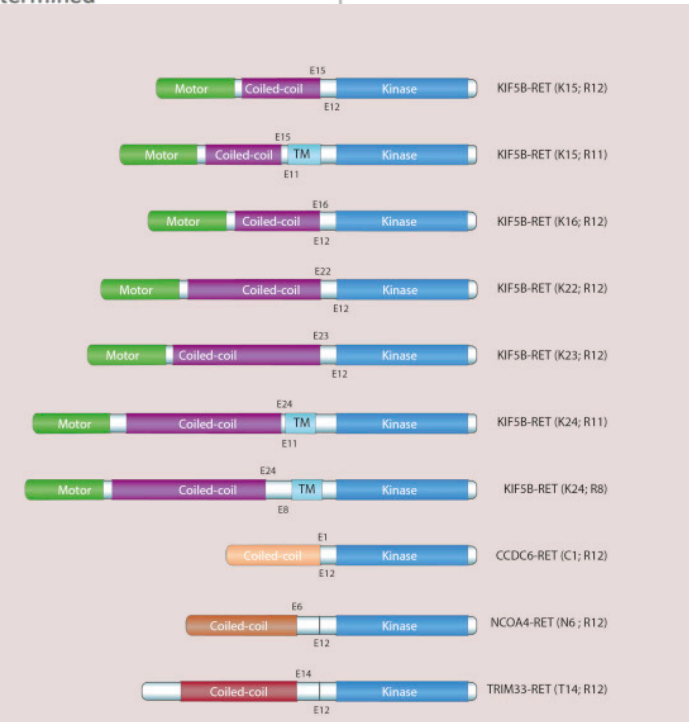
Microsatellite status - Cannot Be Determined
Tumor Mutational Burden - Cannot Be Determined

Genomic Findings

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

RET CCDC6-RET fusion
NFE2L2 W24C
TP53 S241F

7 Disease relevant genes with no reportal
EGFR, ERBB2, KRAS, MET, ROS1



- 1-2% in NSCLC
- CCDC6-RET fusions and KIF5B-RET fusions are most common
- CCDC6-RET fusions have been described as acquired resistance mutations to osimertinib
- *De novo* CCDC6-RET fusions are sensitive to selpercatinib
- *Efficacy for RET-fusion-positive NSCLC was evaluated in 105 adult patients, previously treated with platinum chemotherapy. The ORR was 64% (95% CI: 54%, 73%); 81% of responding patients had responses lasting 6 months or longer. Efficacy was also evaluated in 39 patients who never received systemic treatment. The ORR for these patients was 85% (95% CI: 70%, 94%); 58% of responding patients had responses lasting 6 months or longer.*

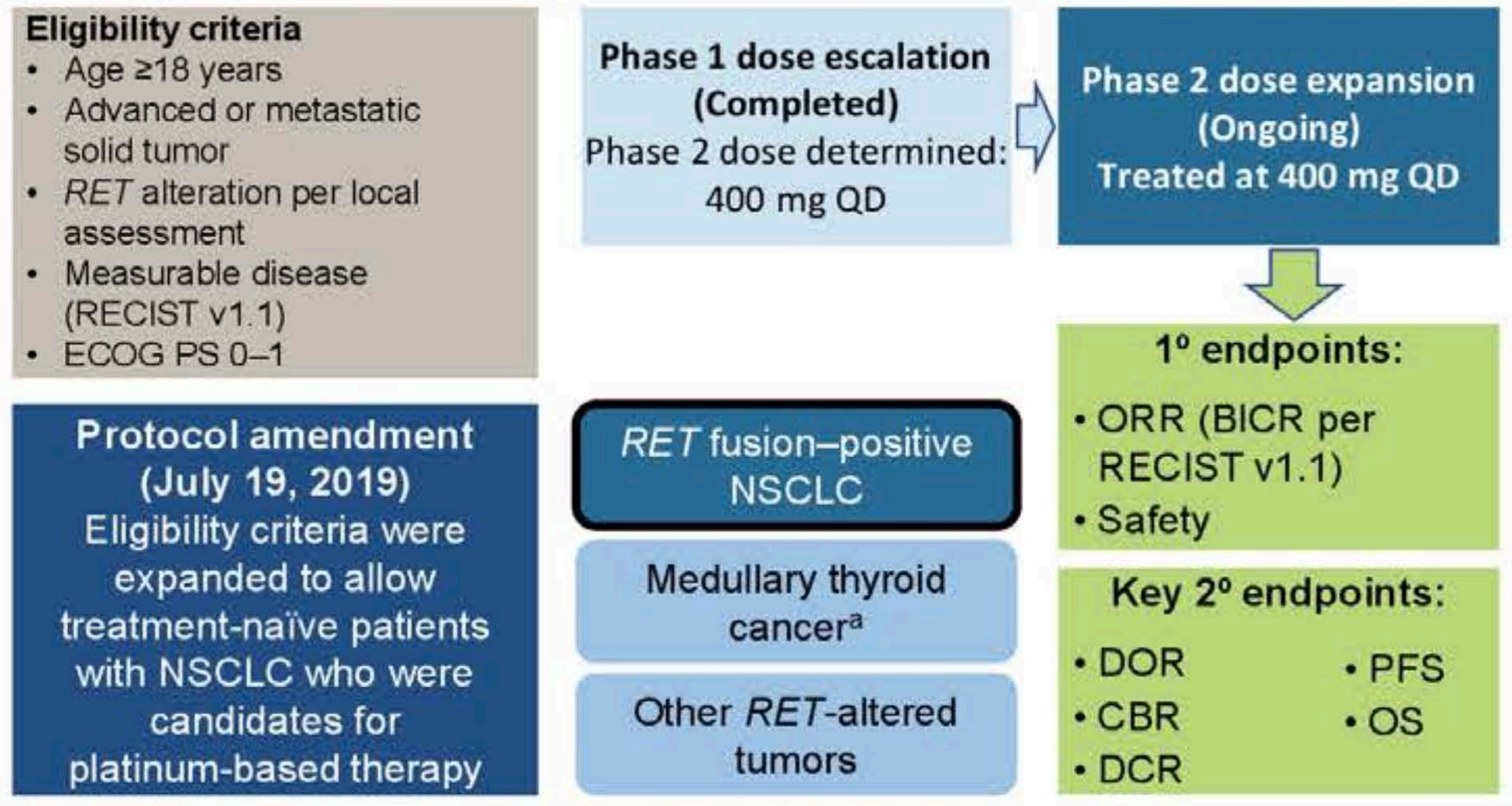
SARAH CANNON

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.

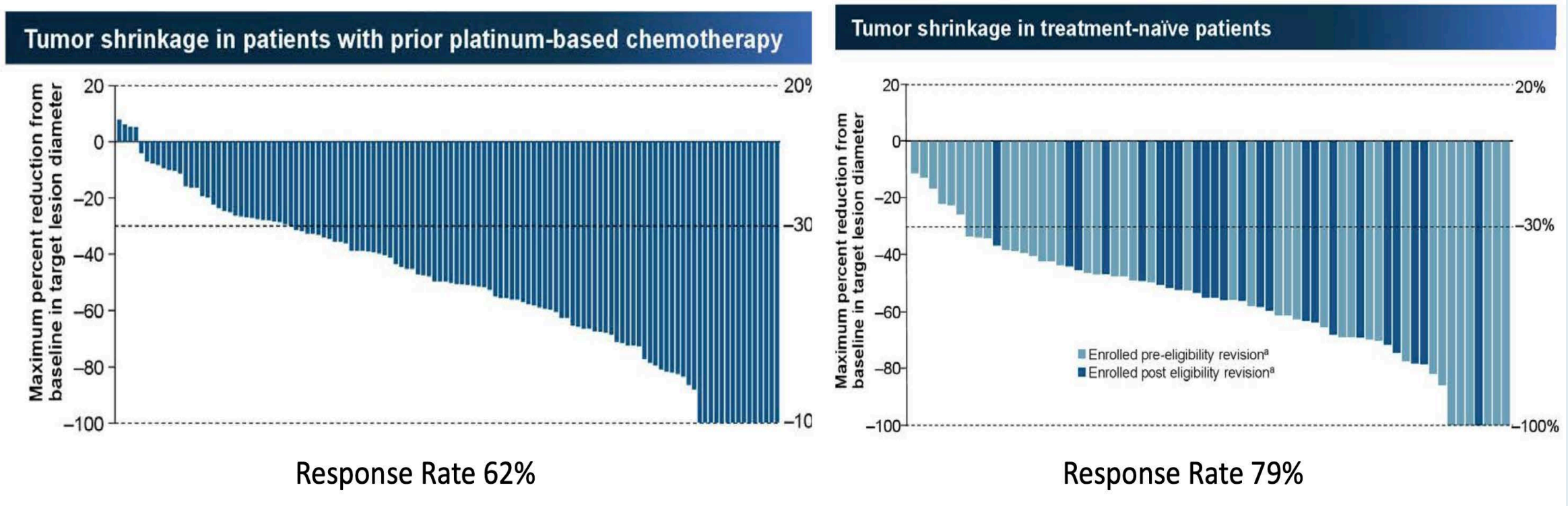
ASCO 2021;Abstract 9089.

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.

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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

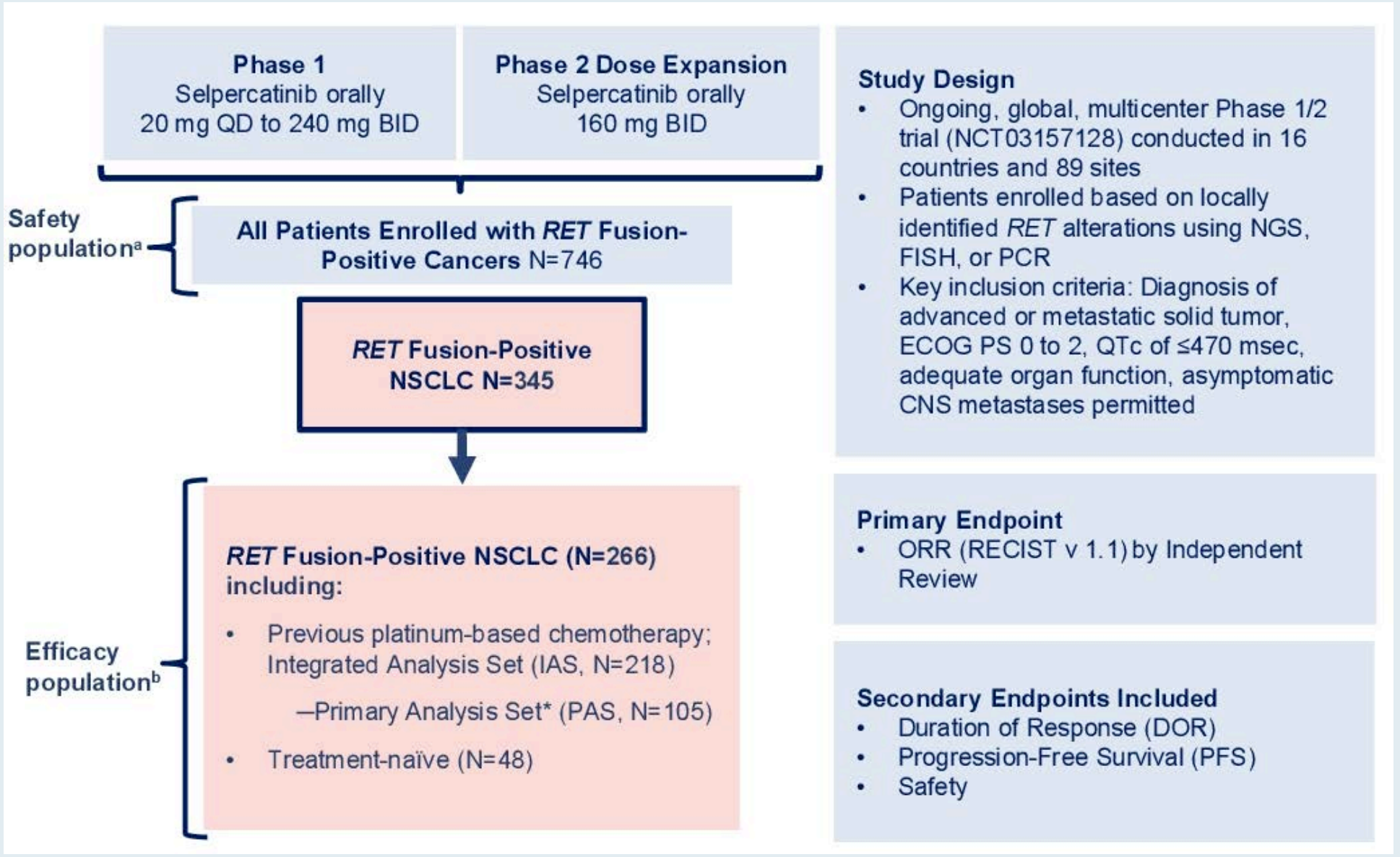
Curigliano J et al. ASCO 2021;Abstract 9089.

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.

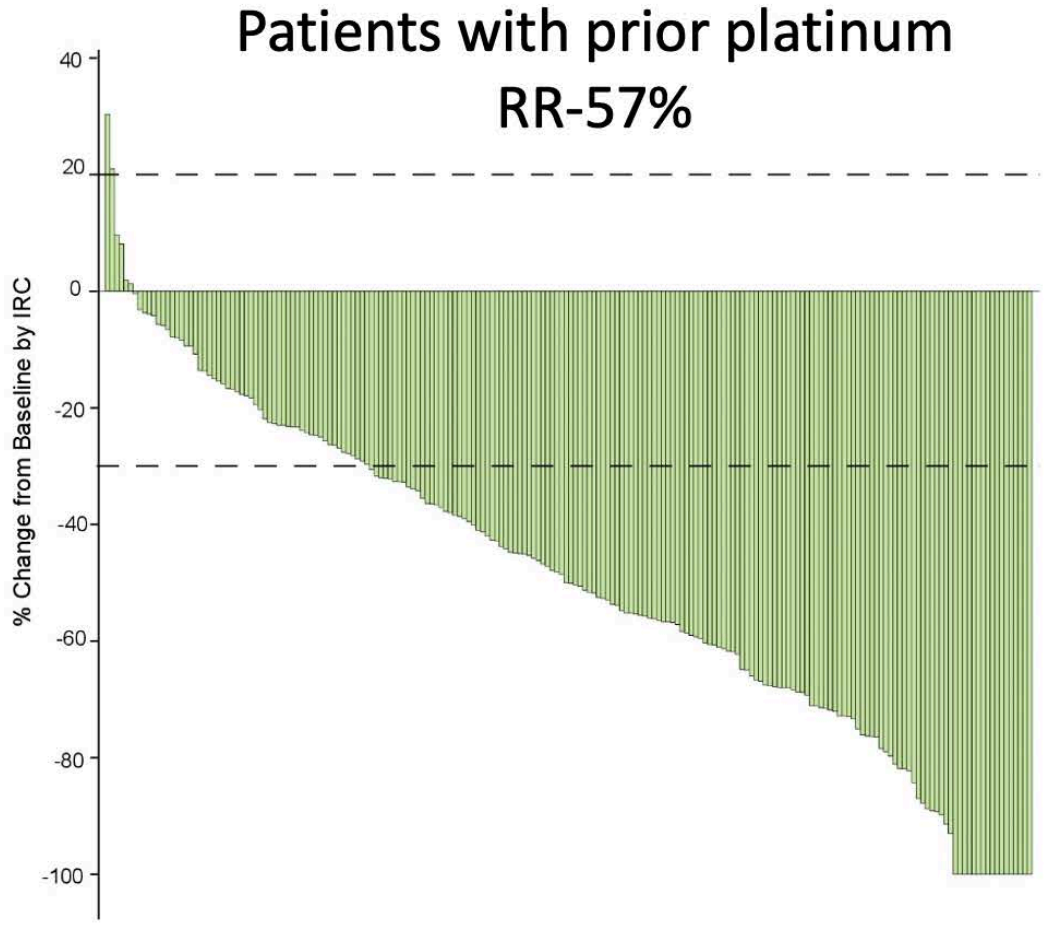
ASCO 2021;Abstract 9065.

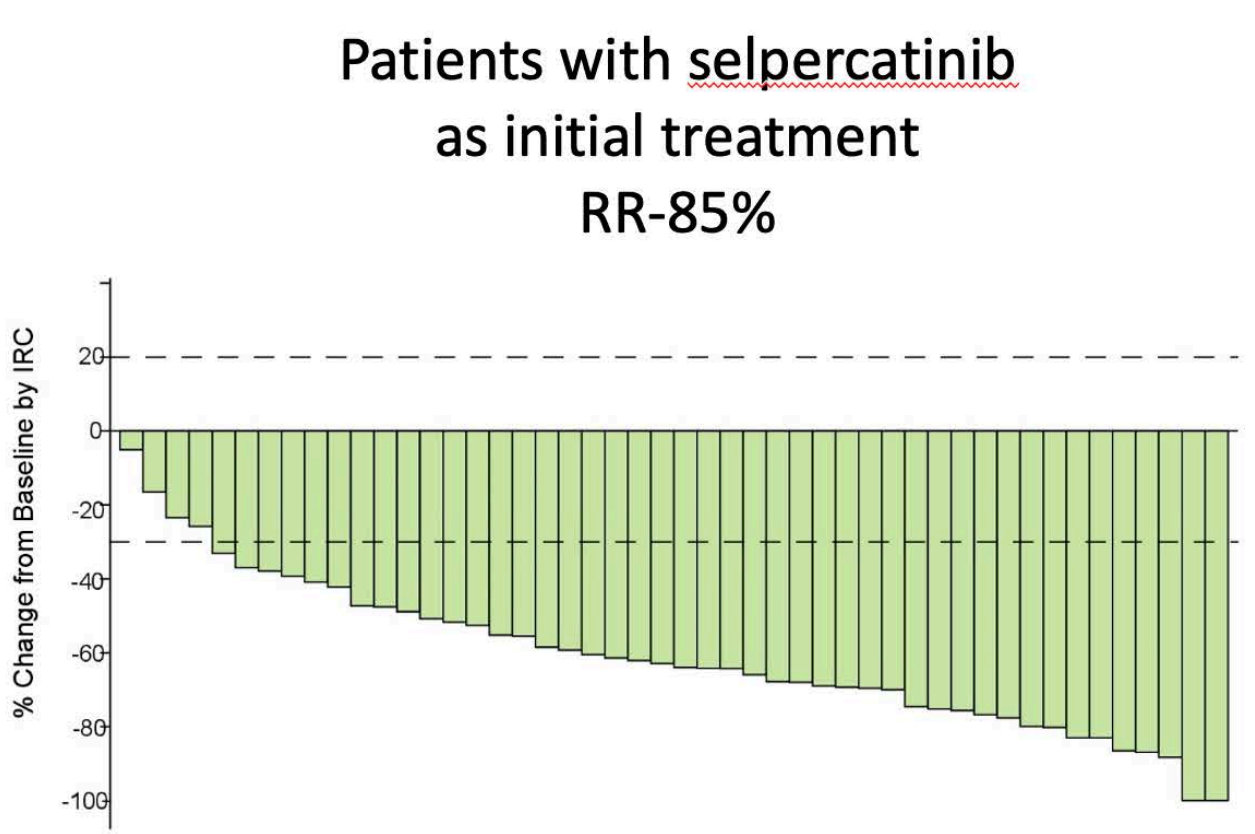
LIBRETTO-001 Study Design



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

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Case Presentation – Dr Bachow: A 69-year-old man with metastatic mucinous adenocarcinoma of the lung and a HER2 mutation

Spencer Henick Bachow, MD

- 10/2016: S/p left lower lobectomy and adjuvant cisplatin/gemcitabine x 4 for pT3N0 mucinous adenocarcinoma of the lung
- 11/2017: Recurrent disease, with HER2 V659D mutation identified → Afatinib
- 11/2020: Slow disease progression, with the development of dysphagia
  - Esophageal stent
- Plan: Palliative EBRT and trastuzumab deruxtecan
  - Patient and wife considering palliative care/best supportive care/hospice approach

Questions

- How often do you see pneumonitis and other pulmonary issues with trastuzumab deruxtecan?
- For patients receiving trastuzumab deruxtecan how do you monitor them for pulmonary toxicity? Would you do more frequent CT scans or staging CT scans? Would you do pulmonary function tests?

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

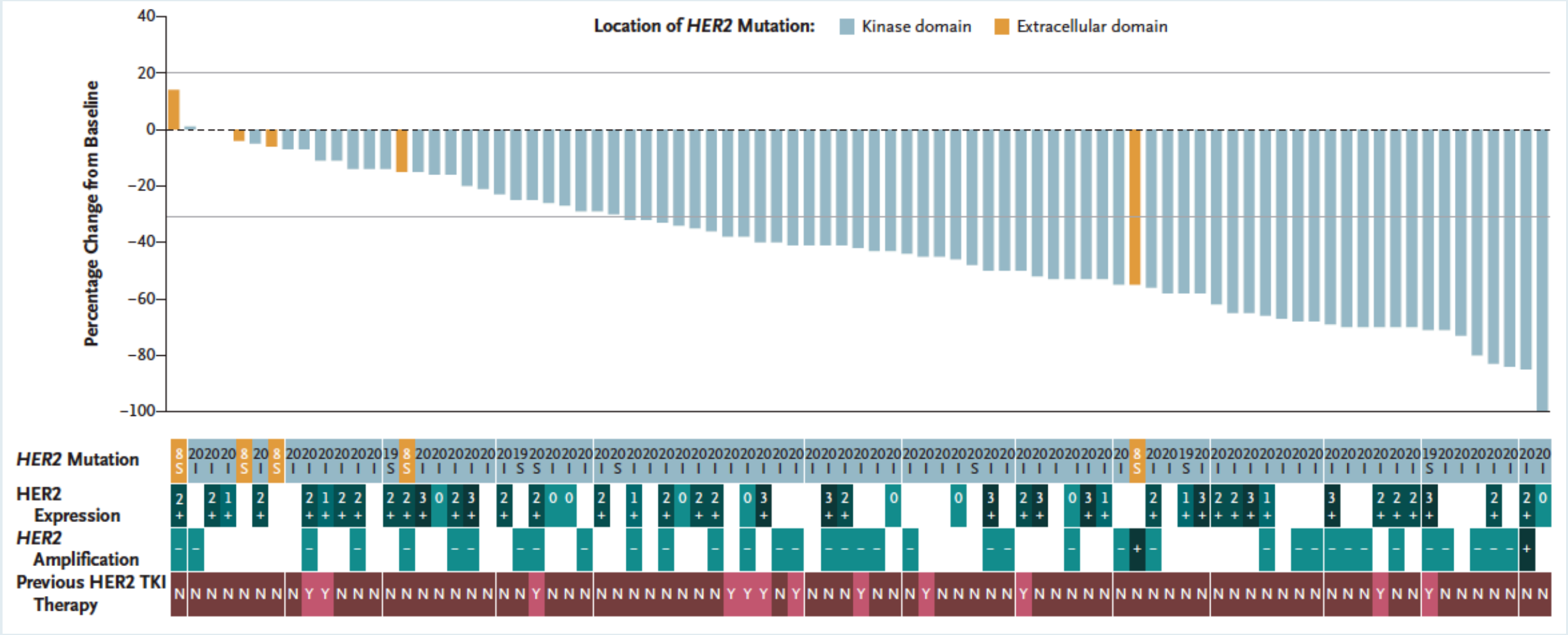
ORIGINAL ARTICLE

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].

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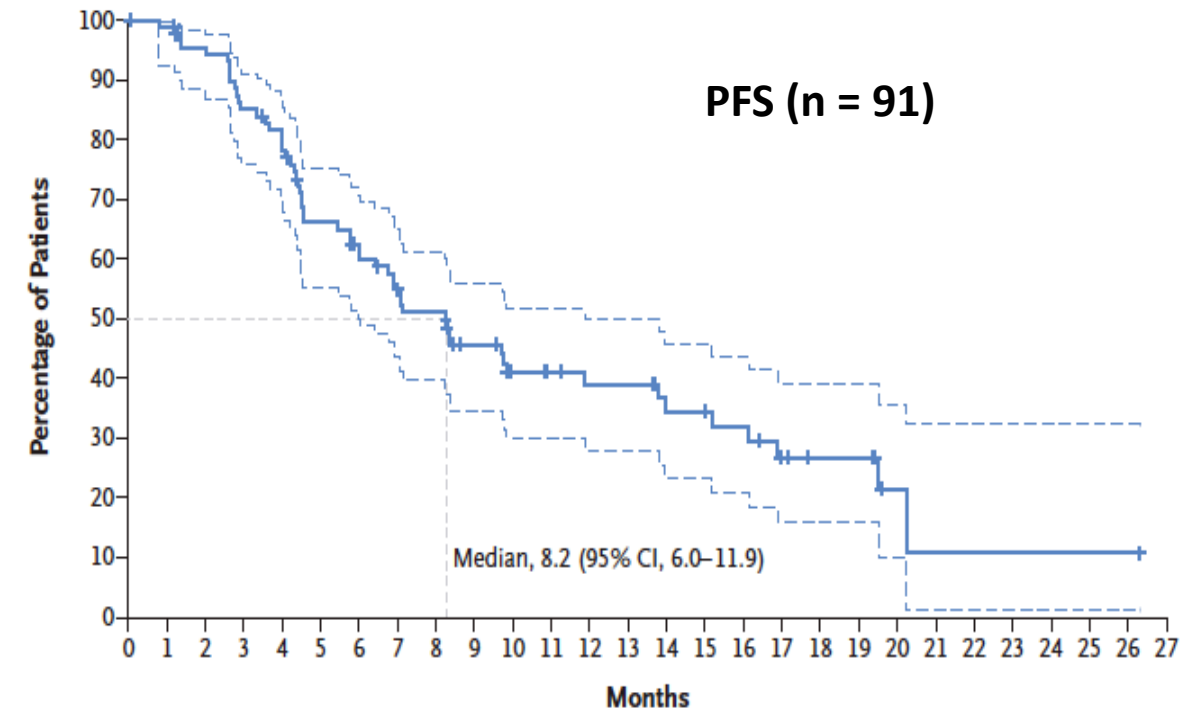
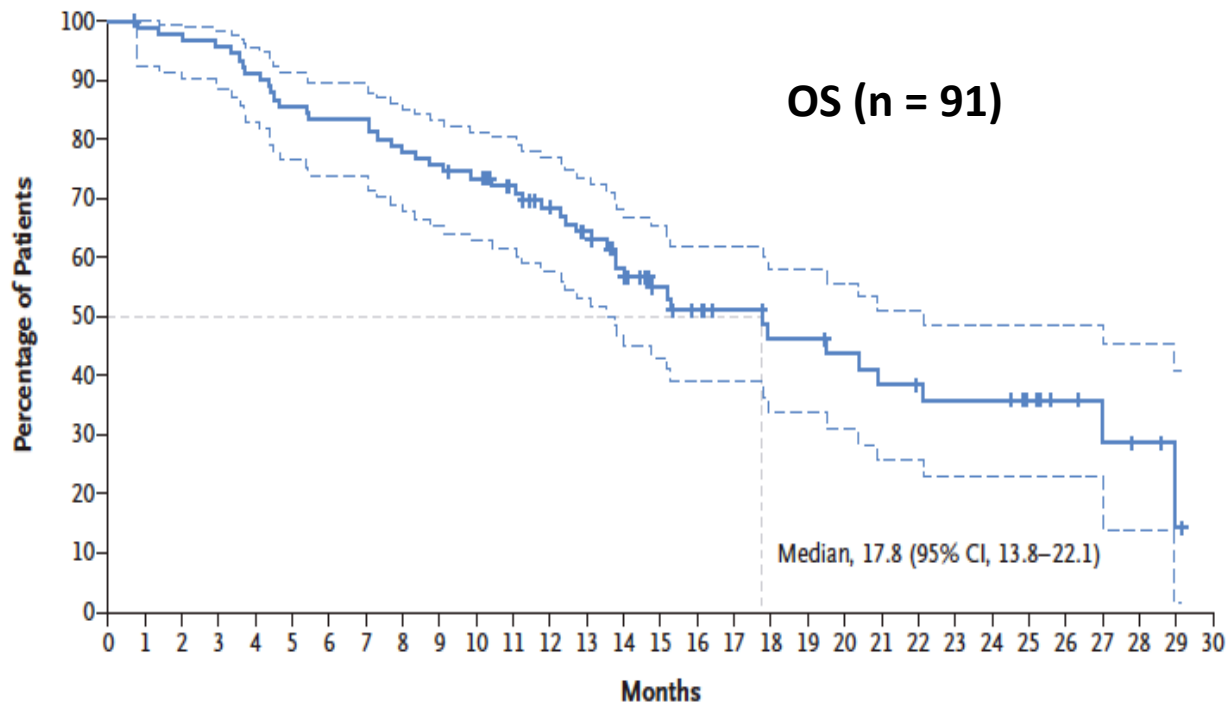
DESTINY-Lung01: Survival in the Overall Population





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RTP RESEARCH TO PRACTICE

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RTP RESEARCH TO PRACTICE

Case Presentation – Dr Jasani: A 35-year-old woman with newly diagnosed metastatic NSCLC and an ALK mutation

Nikesh Jasani, MD

- 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?

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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

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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%

Mohamed K Mohamed, MD, PhD

- 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

Introduction: Role of Genomic Profiling in Non-Small Cell Lung Cancer (NSCLC)

Case Presentations

- Dr Yu: A 44-year-old woman with newly diagnosed Stage IIB adenocarcinoma of the lung and an EGFR L858R mutation
- Dr Ladanyi: A 78-year-old man with metastatic NSCLC and osimertinib resistance due to acquired RET fusion
- Dr Yu: A 64-year-old woman with newly diagnosed adenocarcinoma of the lung and an EGFR exon 20 mutation
- Dr McKenzie: A 78-year-old man with Stage IV adenocarcinoma of the lung and a RET fusion
- Dr Bachow: A 69-year-old man with metastatic mucinous adenocarcinoma of the lung and a HER2 mutation
- Dr Jasani: A 35-year-old woman with newly diagnosed metastatic NSCLC and an ALK mutation
- Dr McKenzie: A 78-year-old man with NSCLC and a TRK fusion
- 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

Syed F Zafar, MD

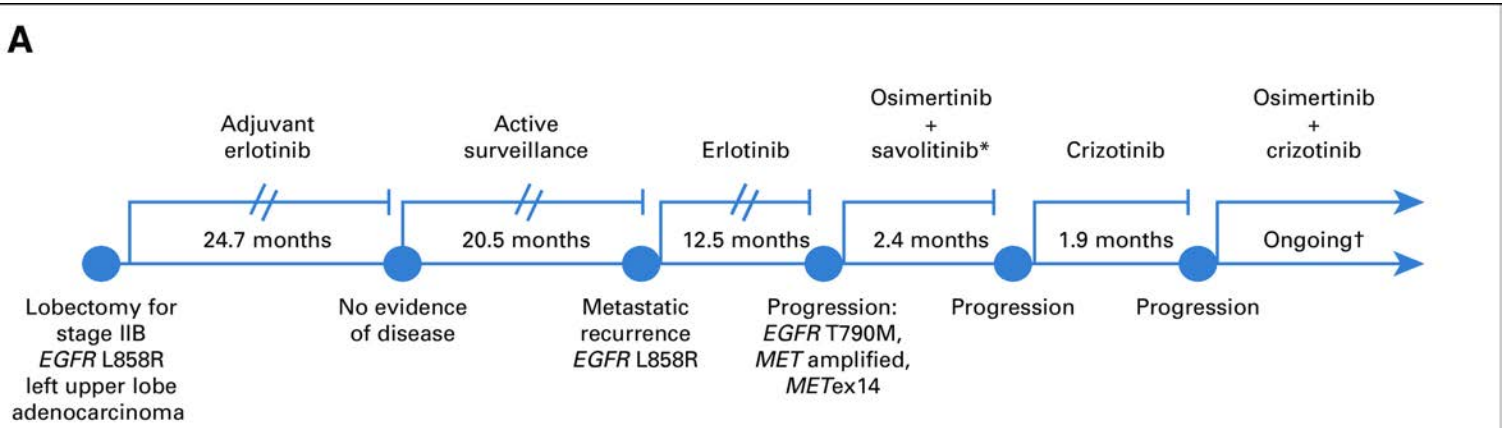
- 2020: Diagnosed with metastatic adenocarcinoma with several pulmonary lesions, mediastinal lymphadenopathy, and brain metastases
- Liquid biopsy and NGS ordered
  - Liquid biopsy reveals BRAF V600E mutation
  - NGS results do not reveal any actionable targets
- Patient is symptomatic: Cough, shortness 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

Faculty Case Appendix

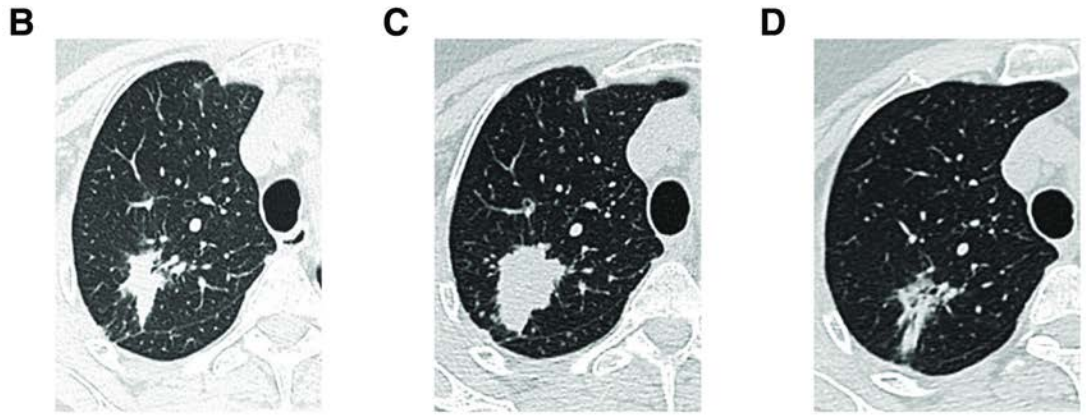
Case Presentation – Dr Ladanyi: A 74-year-old woman with metastatic NSCLC and osimertinib resistance due to acquired METex14

A 73-year-old woman who had never smoked presented with lung adenocarcinoma, which was diagnosed via bronchoscopy with biopsy of the left upper lobe, and underwent a left upper lobe lobectomy and lymph node dissection, which showed a stage IIB (pT2bN0M0) poorly differentiated adenocarcinoma. Molecular testing revealed an *EGFR* L858R mutation, and the patient received adjuvant erlotinib (100 mg daily). After 24.7 months of erlotinib, given no recurrence, adjuvant therapy was discontinued. The patient was observed for 20.5 months, when imaging revealed new bilateral pulmonary nodules, right-sided paratracheal lymphadenopathy, and a sclerotic T11 lesion. Right upper lobe biopsy confirmed recurrent disease, and MSK-IMPACT testing showed the presence of *EGFR* L858R without *EGFR* T790M mutation. The patient restarted erlotinib (100 mg daily) with clinical and radiologic response for 12.5 months, at which time computed tomography revealed an increase in the dominant right upper lobe mass. Fluorescence in situ hybridization of right upper lobe biopsy material revealed *MET* amplification, and cell-free DNA testing was positive for *EGFR* T790M. MSK-IMPACT revealed an *EGFR* L858R mutation, no evidence of *EGFR* T790M, and a new *MET*ex14 skipping alteration and *MET* amplification (fold change, 2.5). Therapy was changed to osimertinib with savolitinib daily for 1.4 months, after which savolitinib was stopped because of toxicity and single-agent osimertinib 80 mg daily was continued. Progressive disease in the lung was noted after 2.4 months of osimertinib. Crizotinib 250 mg twice daily was then administered for 1.9 months, at which time further pulmonary progression of disease was noted. Treatment was changed to combination osimertinib (80 mg daily) with crizotinib (250 mg twice daily). The combination was tolerated without any report of toxicity. At follow-up 2.3, 4.6, and 7.7 months after starting combination therapy, she had ongoing clinical benefit and stable disease by RECIST (−12.2% response). The patient continued to receive combination therapy with durable clinical and radiographic benefit for more than 9 months.

Case Presentation – Dr Ladanyi: A 74-year-old woman with metastatic NSCLC and osimertinib resistance due to acquired METex14 (continued)



	Timing of test	Type of test	Sample	Result
Molecular testing	Diagnosis stage IIB	Hotspot genotyping (a)	Tumor	*EGFR* L858R detected
	Metastatic recurrence	Digital PCR (b)	Tumor	*EGFR* T790M negative
		NGS by MSK-IMPACT (c)	Tumor	*EGFR* L858R
	Progression during erlotinib treatment	Digital PCR (b)	cfDNA	*EGFR* T790M positive
		Digital PCR (b)	Tumor	*EGFR* T790M negative
		NGS by MSK-IMPACT (c)	Tumor	*EGFR* L858R with amplification (FC, 3.8); *MET* exon 14 splicing variant (c.2888-1G>A) with amplification (FC, 2.5)
		FISH (d)	Tumor	*MET* amplification

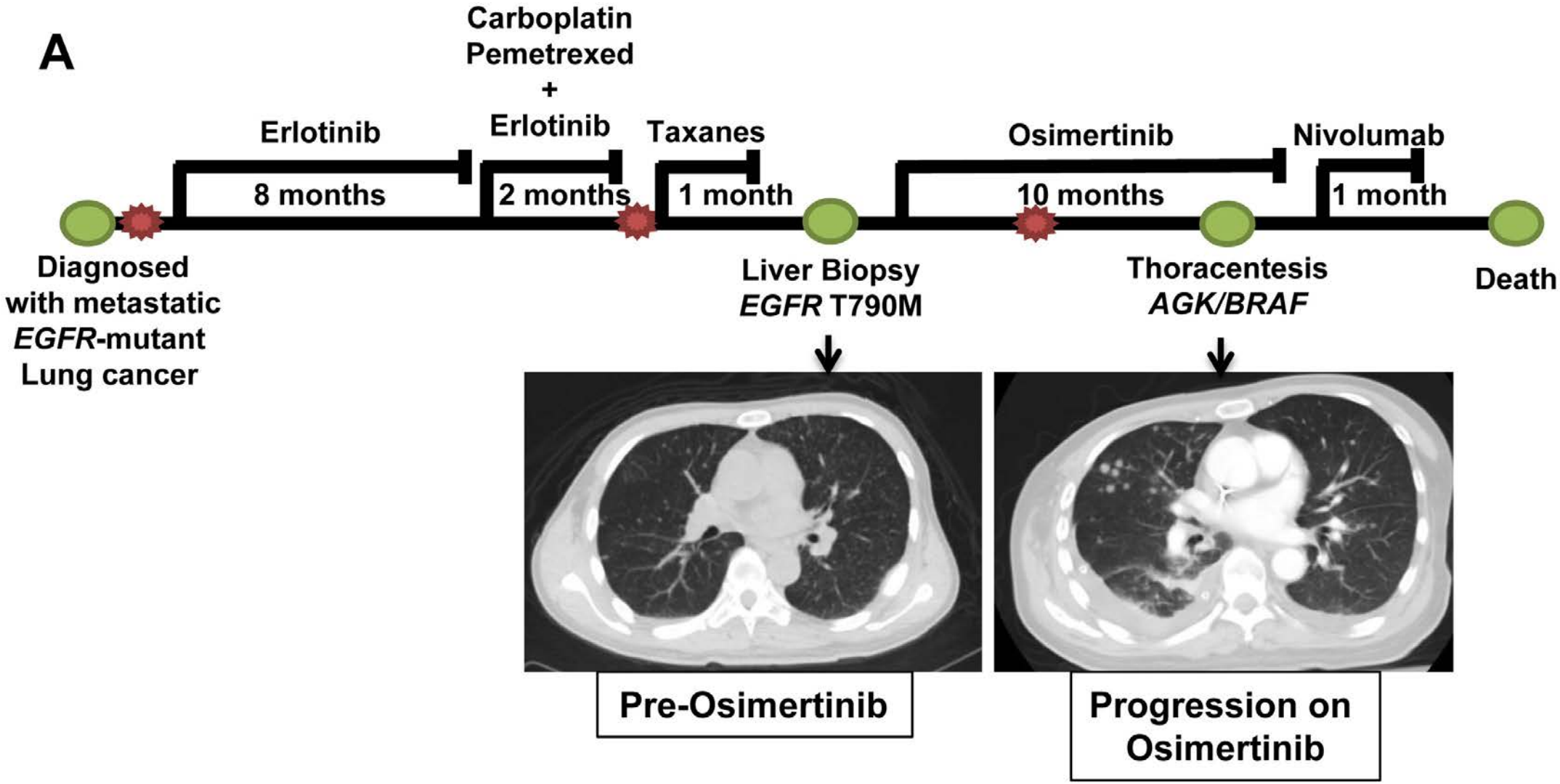


Case summary. (A) Summary of disease course, therapy, and molecular findings. (a) Sequenom mass spectrometry genotyping (Data Supplement). (b) Digital polymerase chain reaction (PCR) for *EGFR* T790M on tissue and/or cell-free DNA (cfDNA). (c) Memorial Sloan Kettering Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT) large-panel next-generation sequencing (NGS) assay. (d) Fluorescence in situ hybridization (FISH) analysis. (B-D) Representative images showing (B) baseline scan (at time of progression during osimertinib monotherapy), (C) response to crizotinib monotherapy, and (D) response to combined crizotinib and osimertinib therapy. The patient continued to show stable disease 10 months after initiation of combination therapy. FC, fold change. (*) The patient initially received 1.4 months of combination osimertinib and savolitinib in a clinical trial, but treatment was changed to monotherapy with osimertinib because of intolerable toxicity. (†) As of 10 months of ongoing treatment with osimertinib and crizotinib.

Case Presentation – Dr Ladanyi: A 48-year-old man with metastatic NSCLC and osimertinib resistance due to acquired BRAF fusion

A 48-year-old male never-smoker presented with a right 12th cranial nerve palsy and was found to have metastatic lung adenocarcinoma to the brain, liver, and bone and lymphangitic spread in the lungs. Evaluation of the right upper lobe biopsy sample by PCR revealed a 15-bp EGFR exon 19 deletion (ex19del). The patient received whole-brain radiation therapy followed by single-agent erlotinib, 150 mg daily. The patient initially had a robust clinical and radiologic response, but after 7.7 months of treatment he was noted to have progressive disease in the bone and subsequently in the liver. A biopsy was performed on the liver, and MSK-IMPACT testing revealed a newly acquired EGFR T790M mutation. The patient was subsequently given osimertinib, 80 mg daily, with an initial response. After 9.5 months, the patient had radiologic and clinical progression with right-sided chest pain and a pleural effusion. A thoracentesis was done, with MSK-IMPACT testing revealing a BRAF structural rearrangement. Targeted RNA sequencing showed the AGK-BRAF fusion. The treatment was changed to nivolumab, but he showed further clinical deterioration and died 2 weeks later.

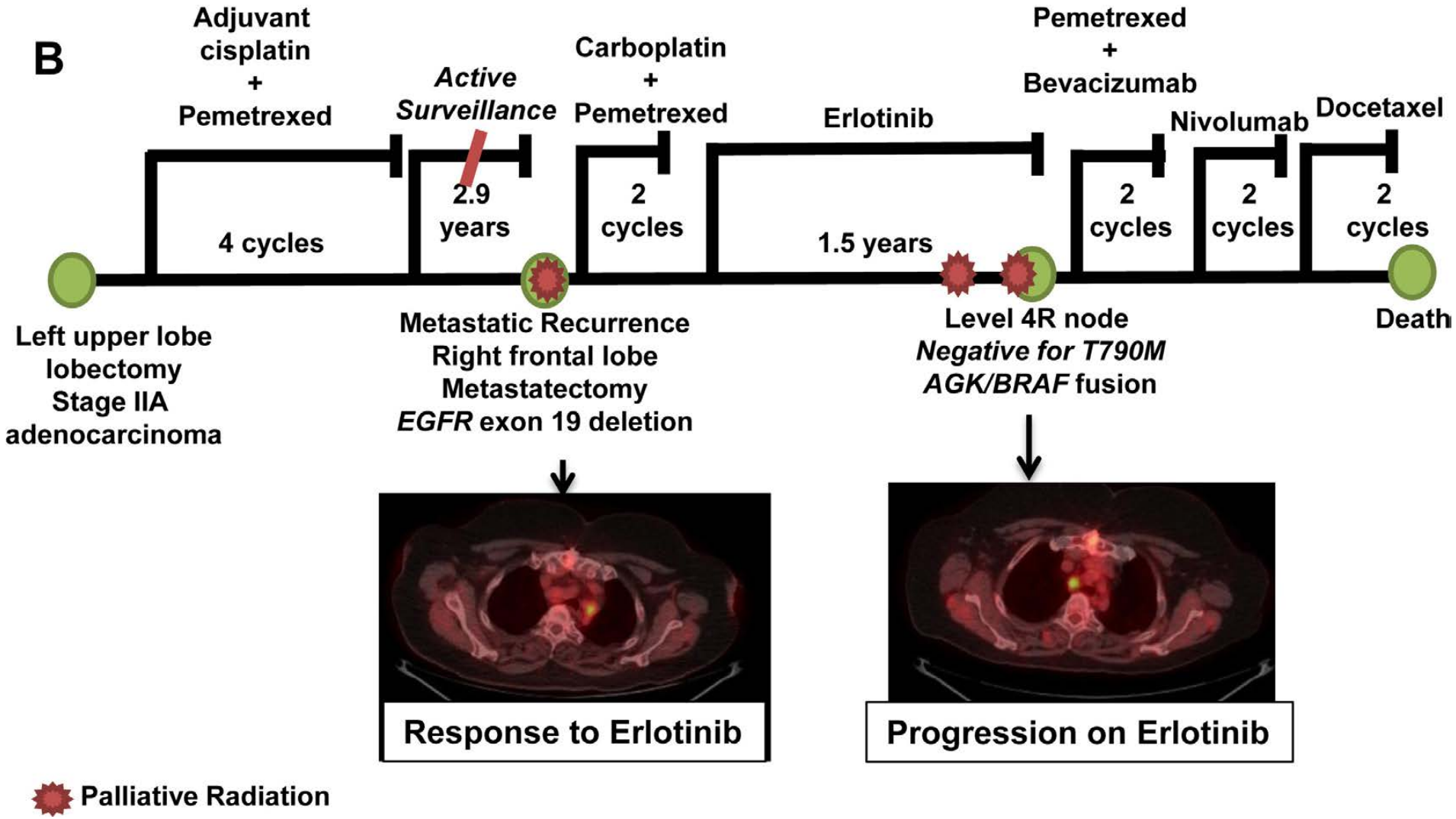
Case Presentation – Dr Ladanyi: A 48-year-old man with metastatic NSCLC and osimertinib resistance due to acquired BRAF fusion (continued)



Case Presentation – Dr Ladanyi: A 69-year-old woman with metastatic NSCLC and EGFR TKI resistance due to acquired BRAF fusion

A 69-year-old female former smoker (22 pack-years) had her cancer diagnosed as stage IIa (pT2aN1M0) lung adenocarcinoma after a left upper lobe lobectomy and mediastinal node dissection. She was treated with adjuvant cisplatin and pemetrexed for four cycles. She was maintained on active surveillance for 2.9 years, at which time she was noted to have a metastatic recurrence in the brain. She underwent a metastatectomy of a 1.8 cm right frontal lobe metastasis. MSK-IMPACT analysis revealed an EGFR ex19del. An interval CT scan found enlarging mediastinal lymph nodes, and the patient was given erlotinib, 150 mg daily. She had a clinical and radiologic response to erlotinib and continued taking it for 1.5 years, at which point she was noted to have progression in her mediastinal lymph nodes. MSK-IMPACT analysis of the post-erlotinib progression sample identified the original EGFR ex19del as well as a new AGK-BRAF fusion. The patient was placed on multiple lines of cytotoxic chemotherapy; however, she had continued disease progression and died.

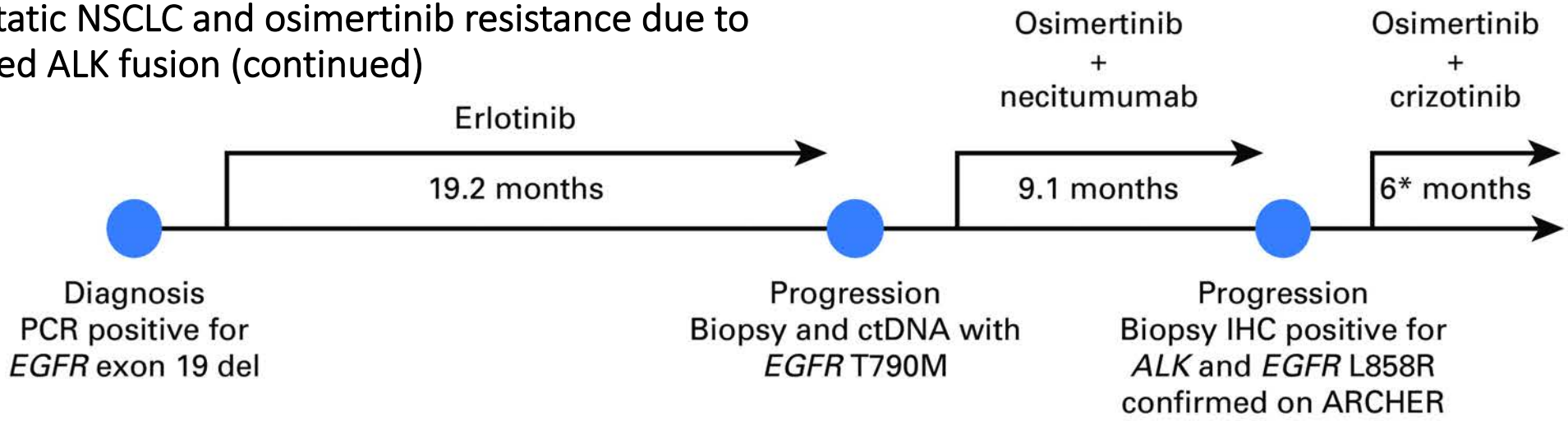
Case Presentation – Dr Ladanyi: A 69-year-old woman with metastatic NSCLC and EGFR TKI resistance due to acquired BRAF fusion (continued)

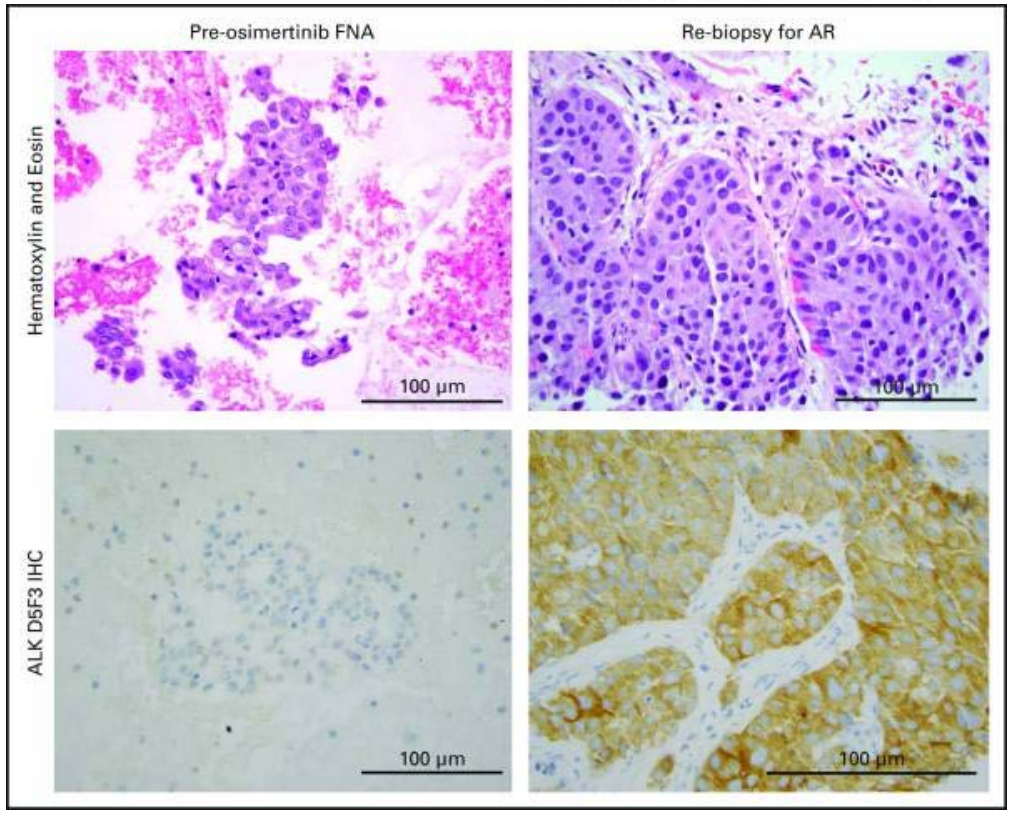


Case Presentation – Dr Ladanyi: A 65-year-old woman with metastatic NSCLC and osimertinib resistance due to acquired ALK fusion

A 65-year-old woman, with a remote 9 pack-year smoking history, presented with a 3 cm lingular primary mass, hilar adenopathy, and a liver lesion (staging: T2pN2cM1b). The biopsy revealed adenocarcinoma with a 15-bp *EGFR* exon 19 deletion (exon19del). The patient received erlotinib and continued this treatment for 19 months before progression occurred. At that time, plasma circulating tumor DNA (ctDNA) and the tumor rebiopsy were positive for *EGFR* T790M; notably, NGS showed no *ALK* rearrangement. The patient transitioned to treatment with osimertinib and necitumumab for 9 months until progression developed in the lungs. A biopsy noted an adenocarcinoma with IHC results positive for *ALK*. NGS confirmed an acquired *EML4-ALK* fusion in addition to the *EGFR* exon19del and T790M mutations. The patient started combination treatment with osimertinib 80 mg daily and crizotinib 200 mg twice daily, remained on treatment with stable disease, and continued to receive clinical benefit from treatment, with no report of toxicity. Subsequent imaging demonstrated oligoprogression in the target lesion with stable disease in nontarget lesions. The patient underwent radiation to the oligoprogressive site and remained on combination therapy with continued disease control.

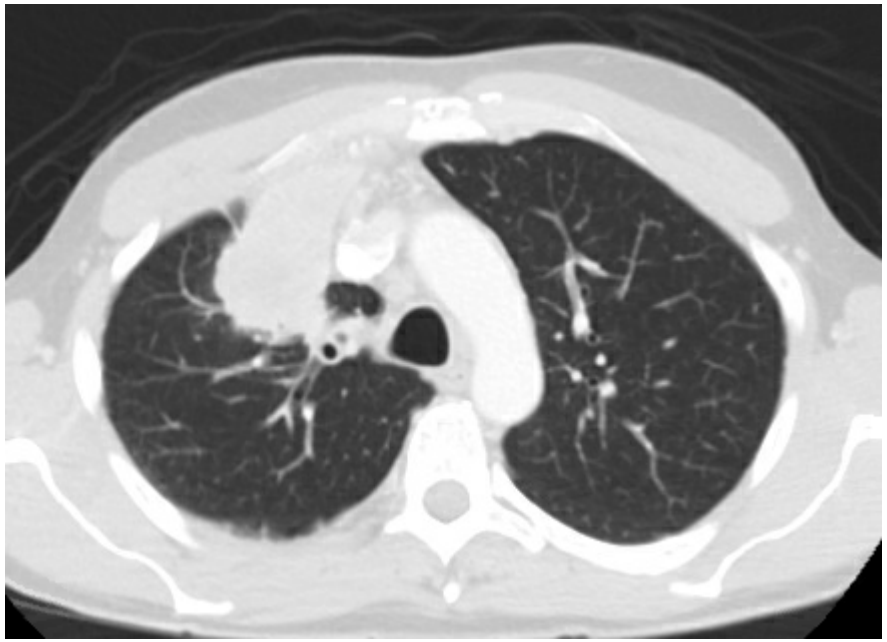
Case Presentation – Dr Ladanyi: A 65-year-old woman with metastatic NSCLC and osimertinib resistance due to acquired ALK fusion (continued)

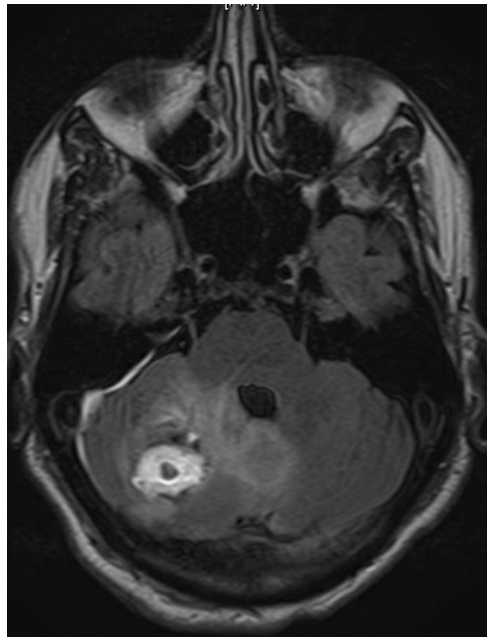




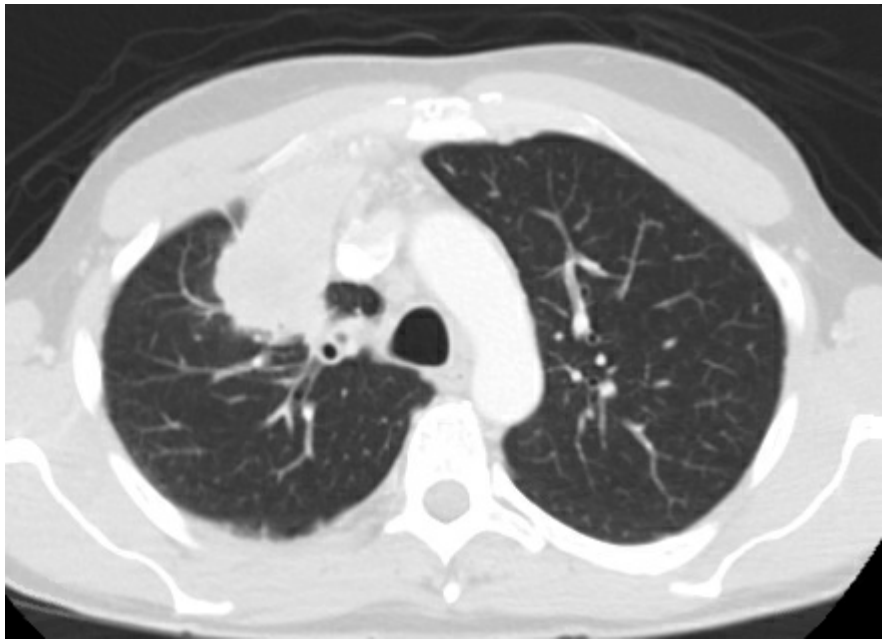
Case Presentation – Dr Yu: A 47-year-old marathon runner who presents with NSCLC and brain metastases

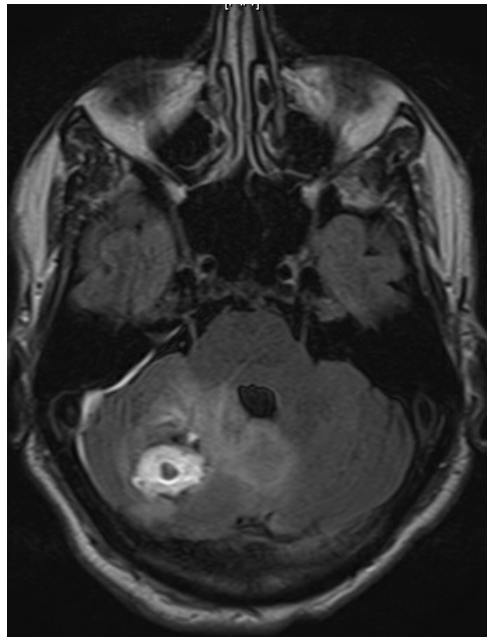
- 47 yo marathon runner with no PMH who developed headaches, unsteady gait and speech difficulties over the course of a month
- 9/17 MRI brain showed a 4.5cm R cerebellar brain tumor along with several other brain metastases.
- 9/17 CT CAP showed a 6cm R sided lung tumor, enlarged lymph nodes, liver, and bone metastases
- He underwent surgical resection of the brain tumor that confirmed lung adenocarcinoma.





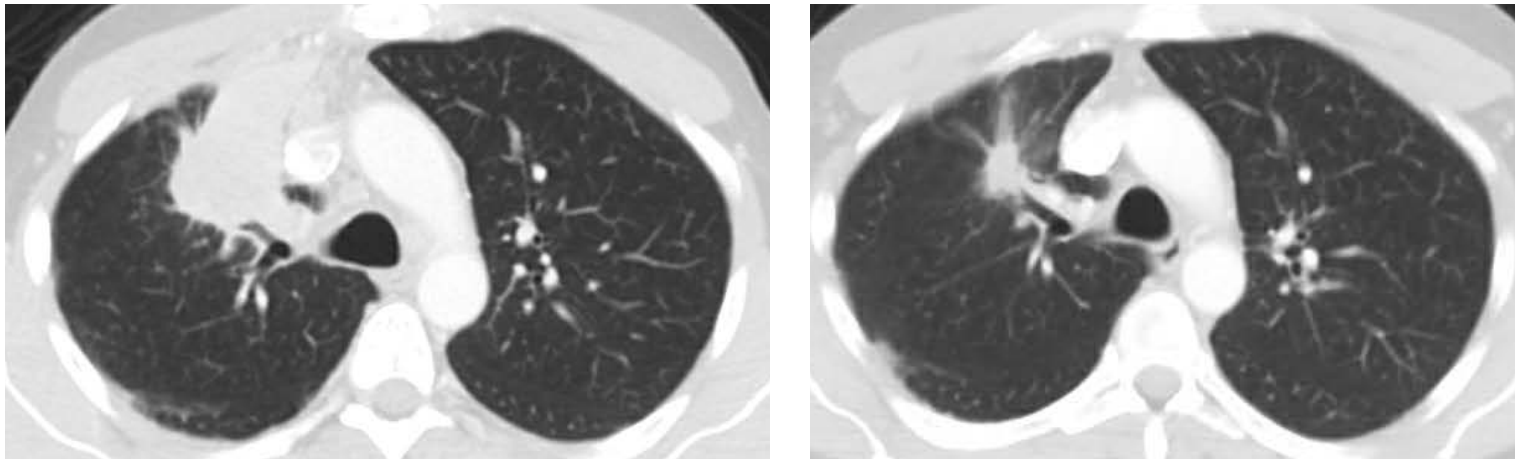
Case Presentation – Dr Yu: A 47-year-old marathon runner who presents with NSCLC and brain metastases (continued)





- Molecular testing was sent off on his brain tumor resection sample. However, he develops worsening shortness of breath and cough.
- He is a never-smoker and I am hopeful for the presence of a targetable mutation but due to his symptoms, feels he needs to start treatment now.
- Is there a concern about starting chemotherapy and immunotherapy? Are there other alternatives?

Case Presentation – Dr Yu: A 47-year-old marathon runner who presents with NSCLC and brain metastases (continued)



Luckily, molecular testing comes back the day we are set to start chemotherapy.

- He was started on osimertinib 80mg daily in Oct 2017
- In a follow up PET scan, 3 weeks after starting, lung tumor had gone from 7.2cm to 2.6cm. Lymph nodes returned to normal, liver lesions shrunk, bone metastases appeared healed.
- In Dec 2018, he had isolated progression in the liver and underwent radioembolization.
- He was also biopsied and had repeat molecular testing done on the liver lesion

Case Presentation – Dr Yu: A 47-year-old marathon runner who presents with NSCLC and brain metastases (continued)

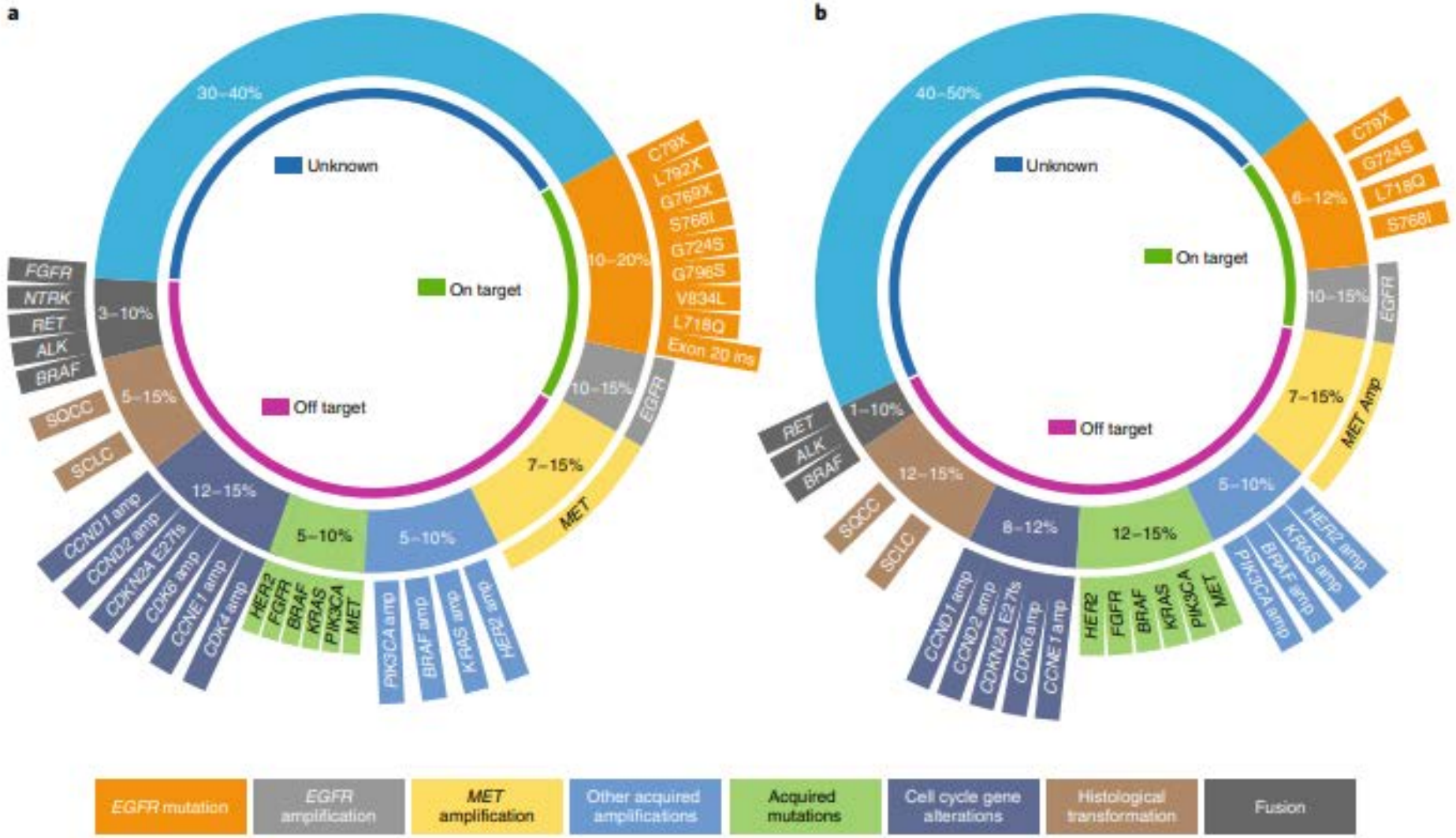
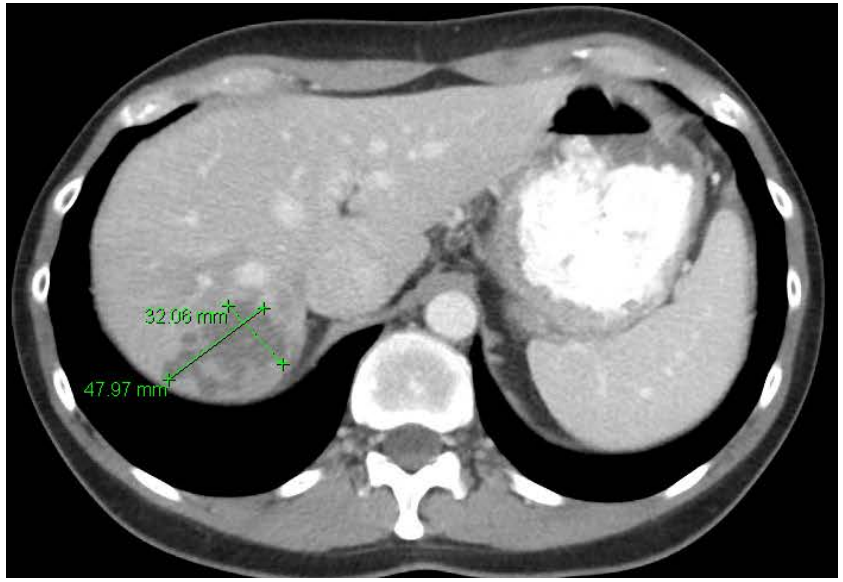
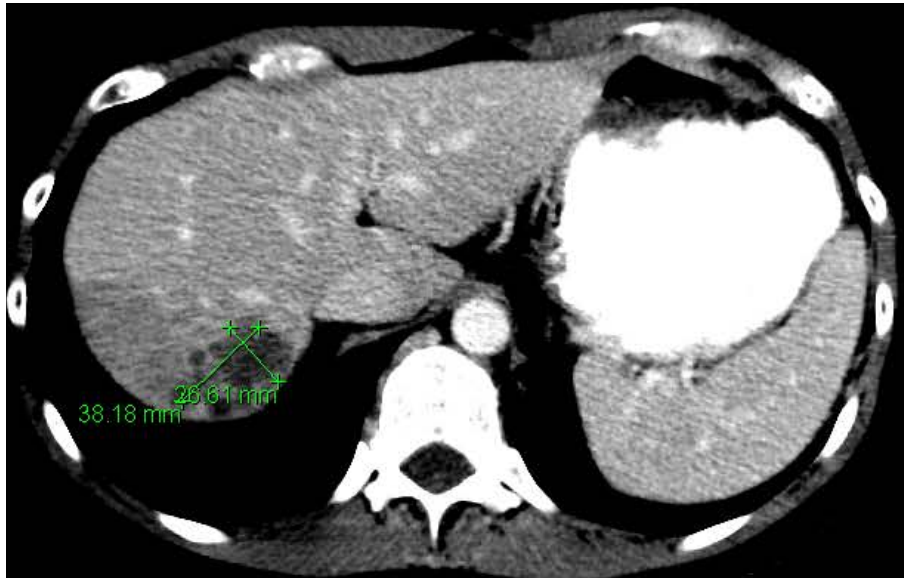


Fig. 2 | Mechanisms of resistance to osimertinib. a,**b**, Resistance mechanisms arising after second-line (**a**) and first-line (**b**) osimertinib therapy. The specific mutations are indicated, along with the incidence of each alteration and the broad classes of alterations driving resistance. Amp, amplification; Ins, insertion.

Case Presentation – Dr Yu: A 47-year-old marathon runner who presents with NSCLC and brain metastases (continued)





- He had an acquired EGFR G724S mutation on repeat biopsy and was started on dacomitinib on a clinical trial.
- He had stable disease for about 6 months and then more systemic disease progression.
- He started chemotherapy and is responding well to treatment with carboplatin/pemetrexed/bevacizumab.

Case Presentation – Dr Yu: A 47-year-old marathon runner who presents with NSCLC and brain metastases (continued): Case variations

What if he had evidence of small cell transformation? What treatment would you start?

What if he had MET amplification?

What if he acquired an ALK fusion?

Meet The Professor

Optimizing the Clinical Management of Hodgkin and Non-Hodgkin Lymphomas

Monday, November 15, 2021
5:00 PM – 6:00 PM ET

Faculty

Christopher R Flowers, MD, MS

Moderator

Neil Love, MD

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