Addressing Current Questions and Controversies in the Management of Non-Small Cell Lung Cancer with an EGFR Mutation

A Live CME Webinar During the IASLC 2020 North America Virtual Conference on Lung Cancer

Friday, October 16, 2020
11:00 AM – 12:00 PM ET

Faculty

Roy S Herbst, MD, PhD
Suresh S Ramalingam, MD
Helena Yu, MD

Moderator

Neil Love, MD

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Commercial Support

This activity is supported by an educational grant from AstraZeneca Pharmaceuticals LP.

Dr Love — Disclosures

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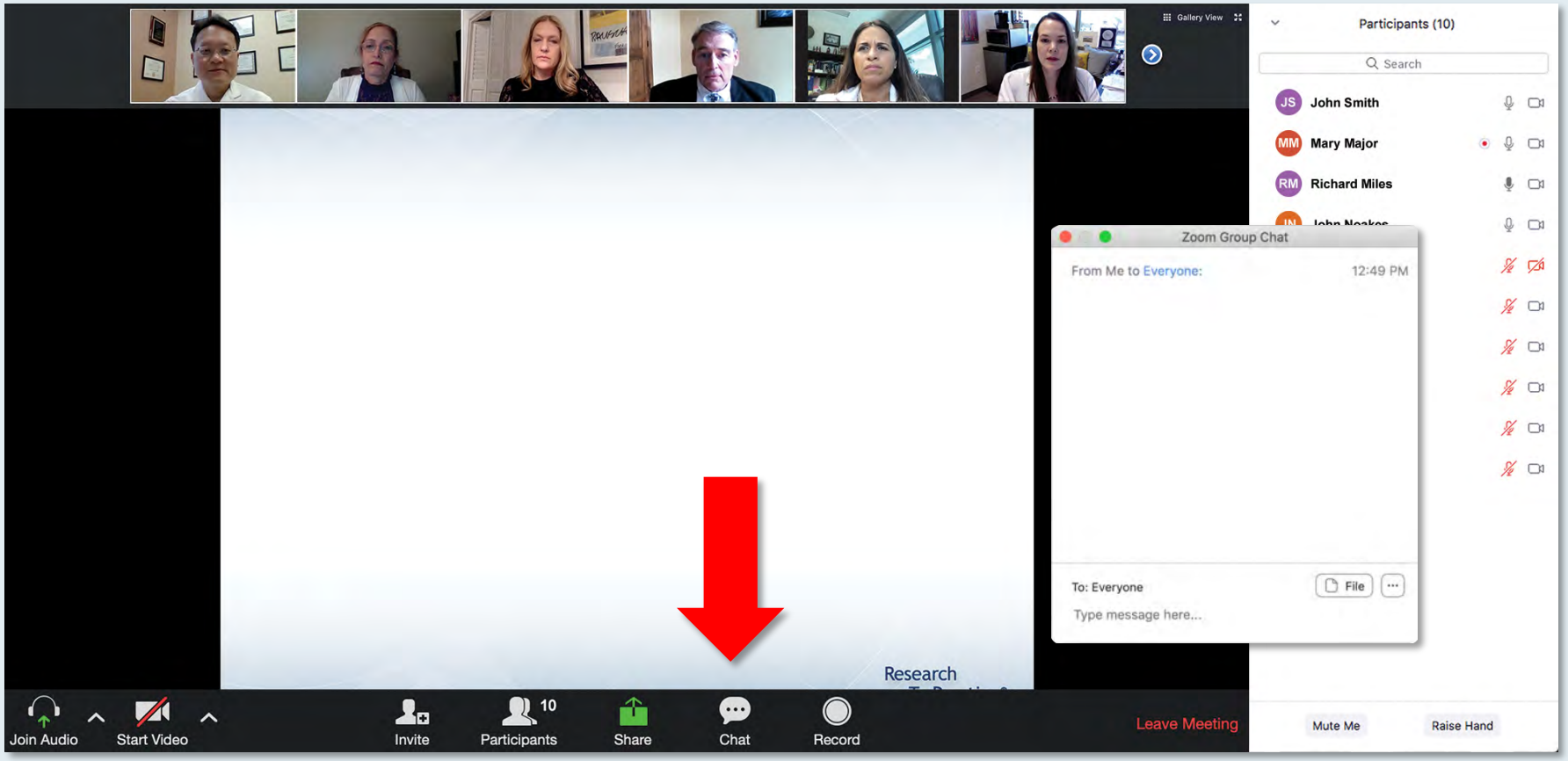
We Encourage Clinicians in Practice to Submit Questions



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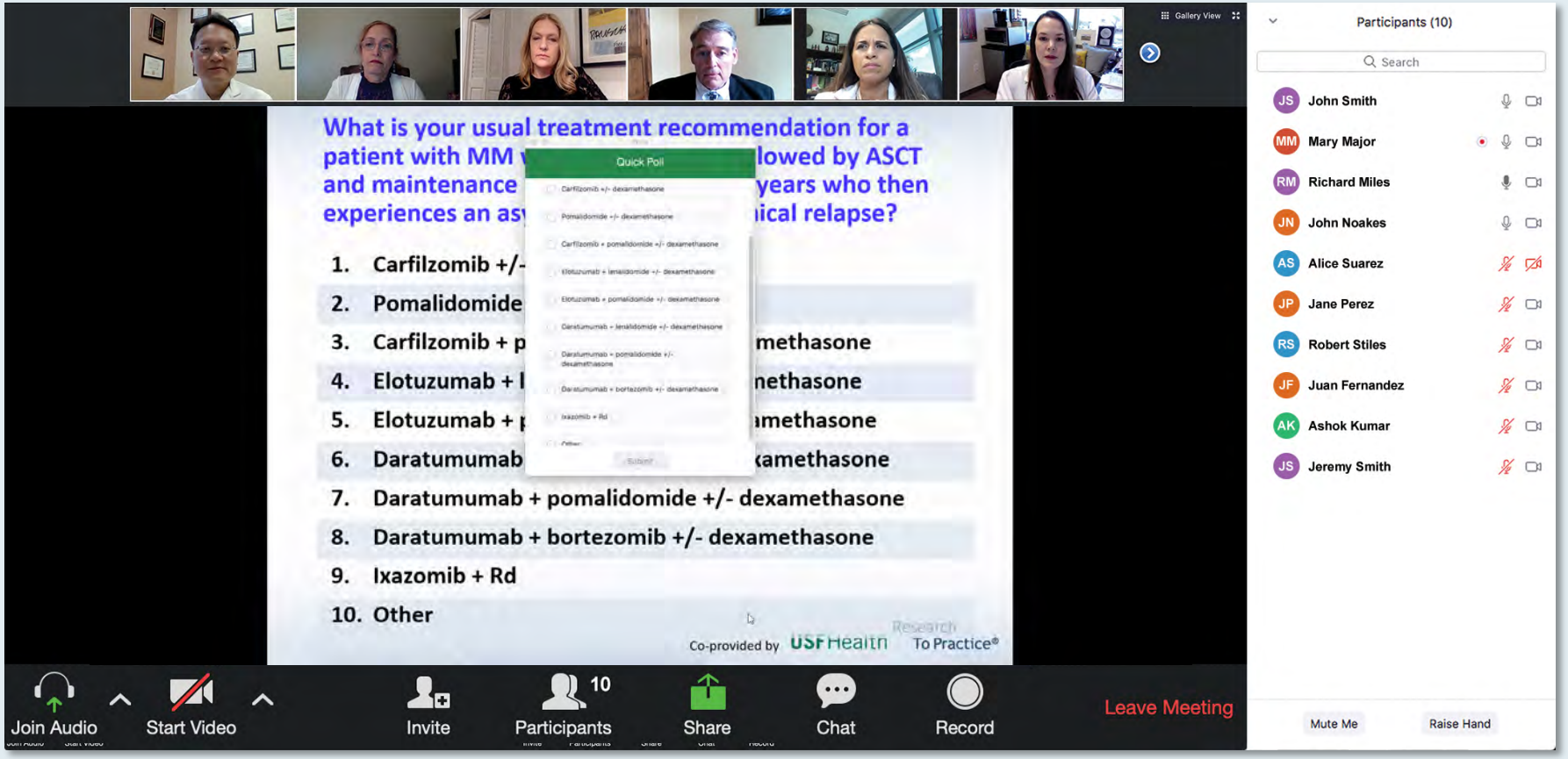

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Upcoming Webinars

Tuesday, October 20, 2020
5:00 PM – 6:00 PM ET

Optimizing the Role of Radiation Oncologists and Other Multidisciplinary Team Members in the Management of Locally Advanced Non-Small Cell Lung Cancer

Faculty
Walter J Curran Jr, MD
Camille Usher, MS, APRN, NP-C

Moderator
Neil Love, MD

Thursday, October 22, 2020
12:00 PM – 1:00 PM ET

Meet The Professor: Management of Multiple Myeloma

Faculty
Krina K Patel, MD, MSc

Moderator
Neil Love, MD

Upcoming Webinars

Saturday, October 24, 2020
8:30 AM – 4:30 PM ET

Current Concepts and Recent Advances in Oncology: A Daylong Clinical Summit Hosted in Partnership with Florida Cancer Specialists

Moderator
Neil Love, MD

Thank you for joining us!

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

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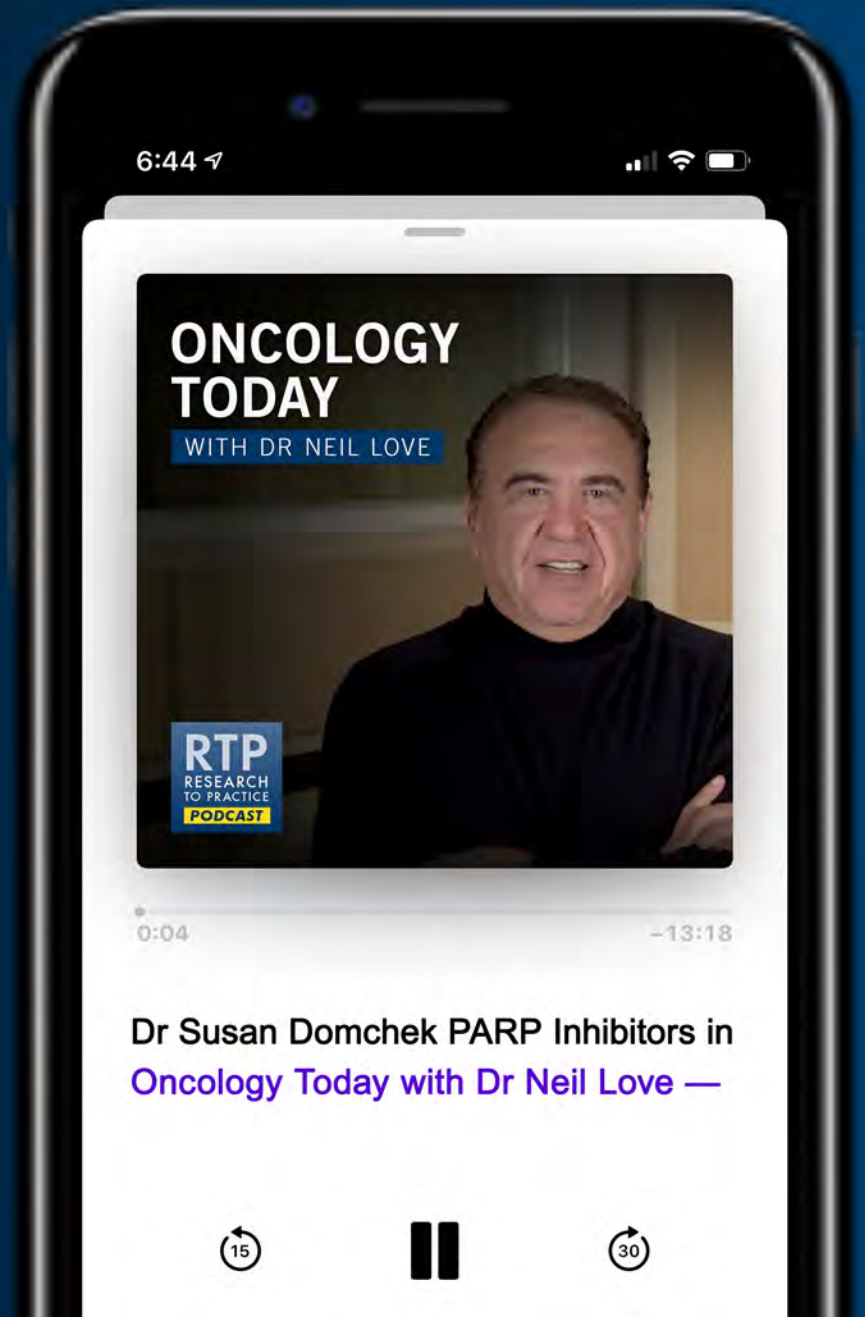

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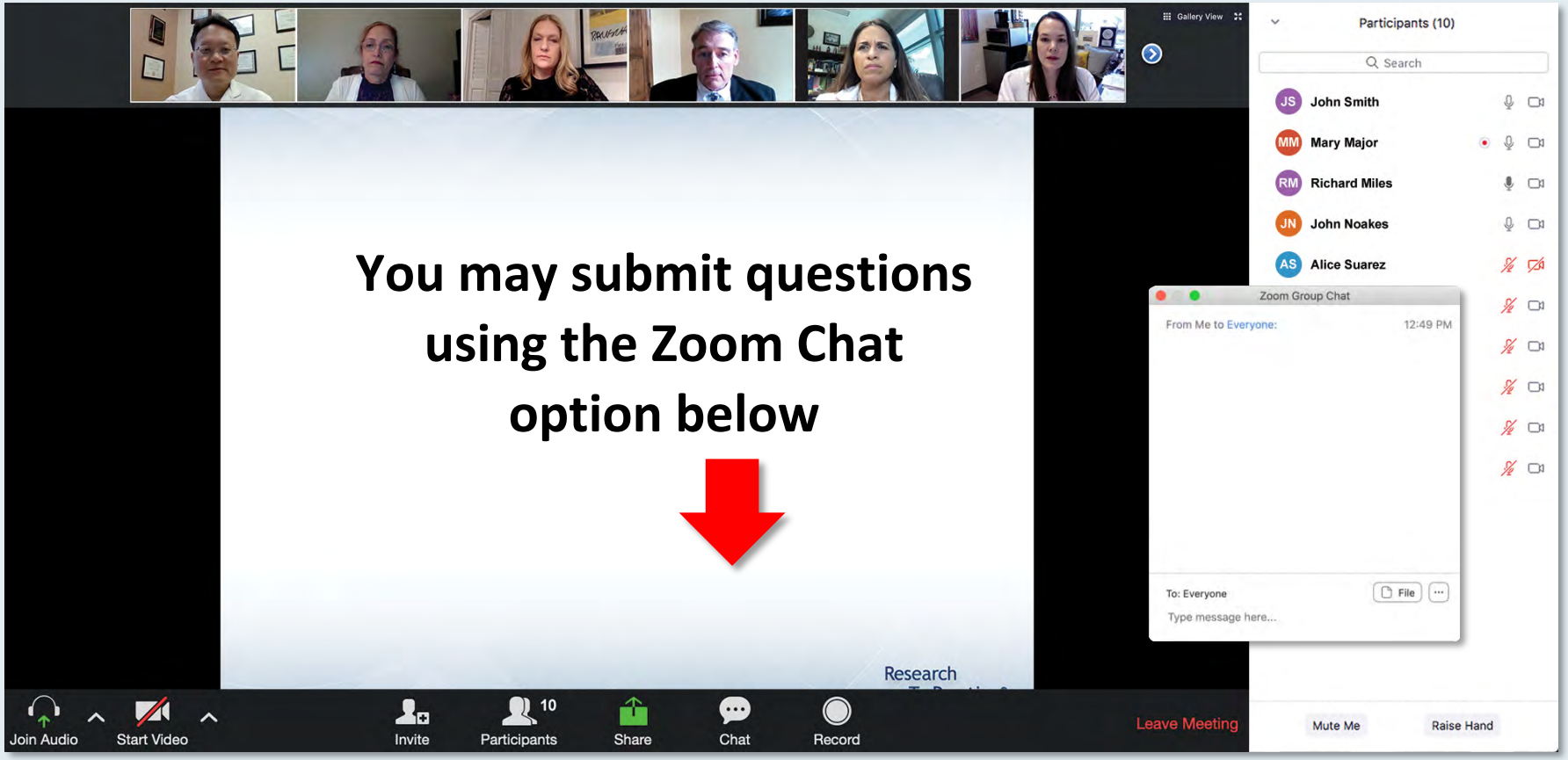

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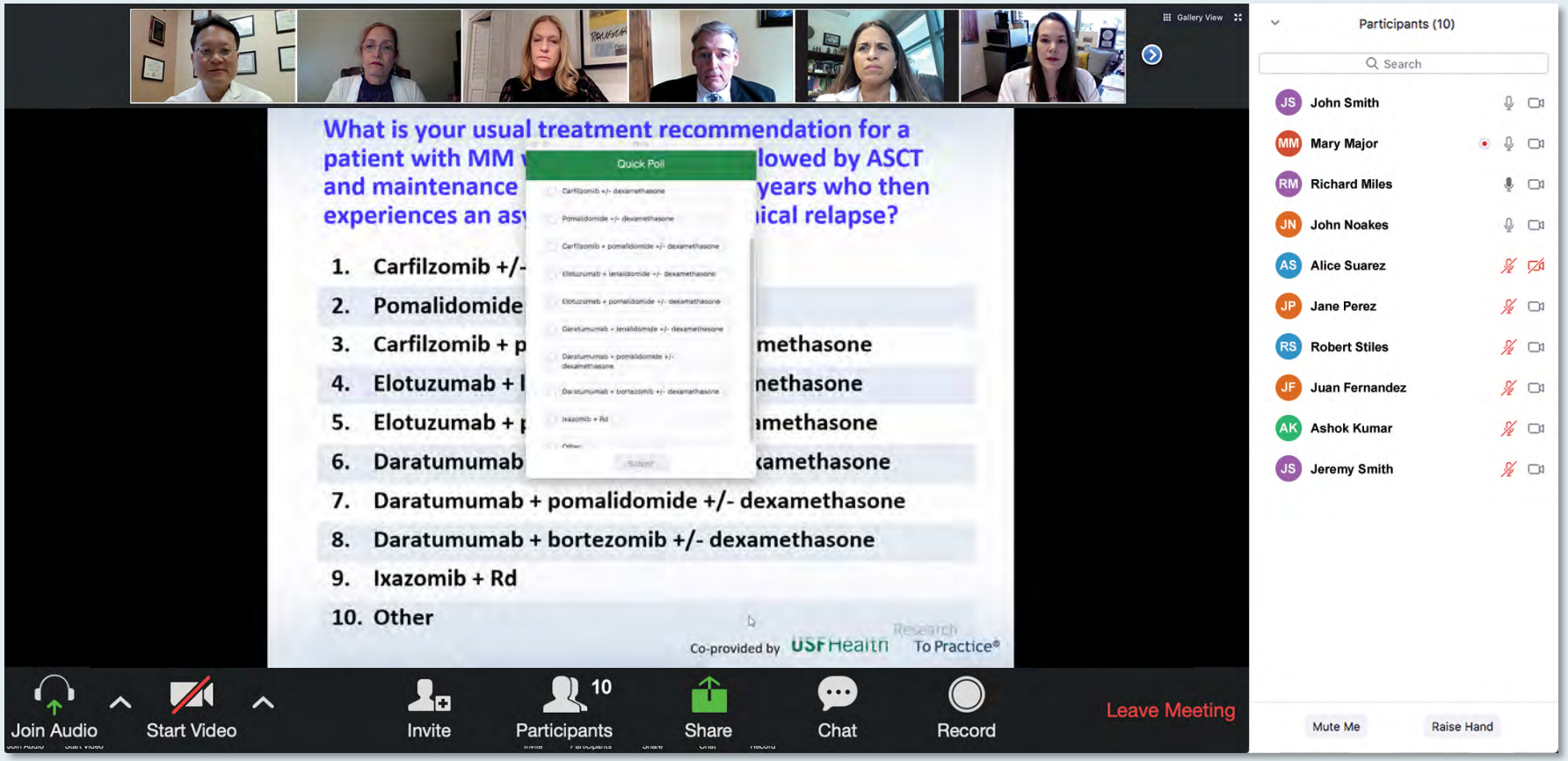

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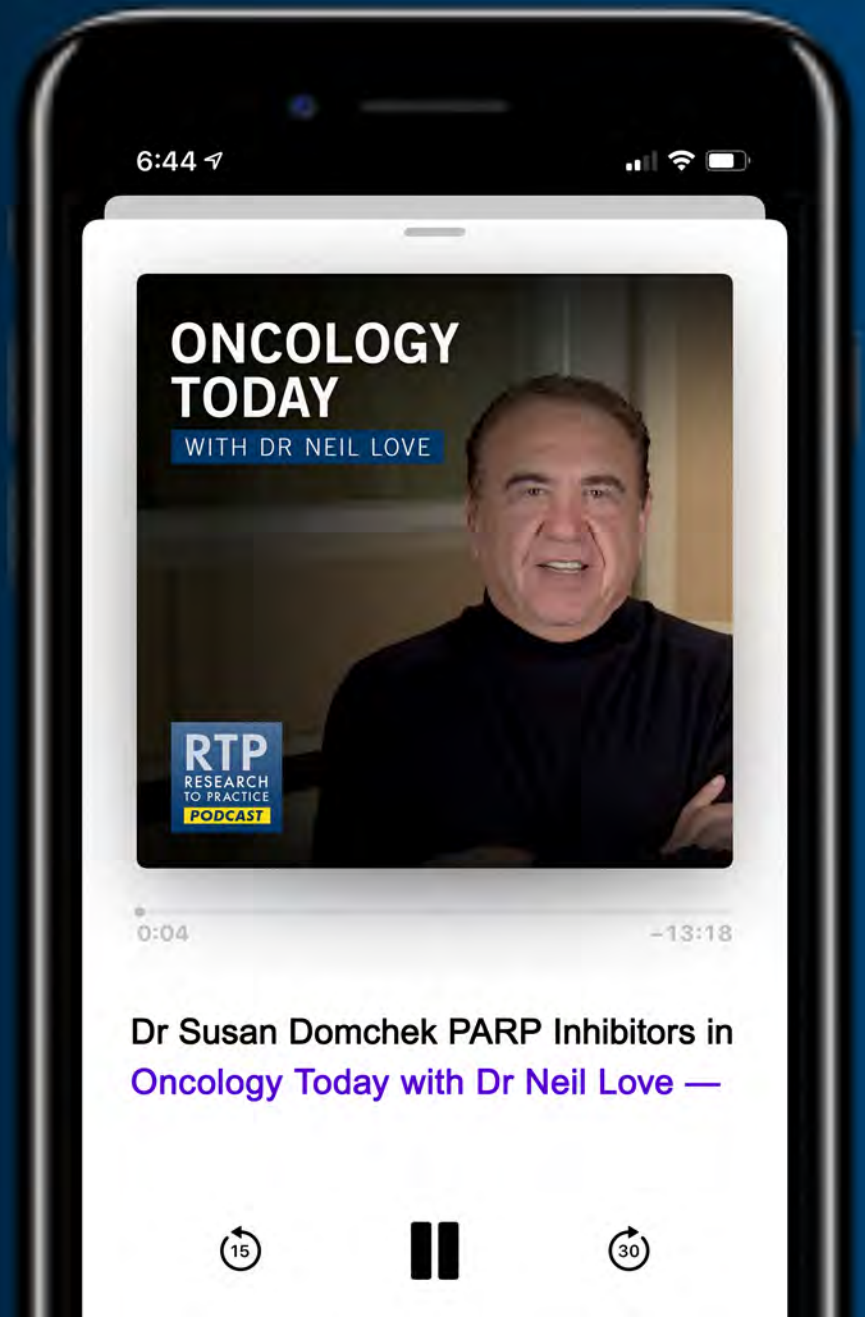

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8:30 AM – 4:30 PM ET

8:30 AM Lung Cancer
Gregory Riely, David Spigel

9:30 AM Multiple Myeloma
Shaji Kuma, Robert Orlowski

10:45 AM Chronic Lymphocytic Leukemia and Lymphomas
Brad Kahl, Loretta Nastoupil

11:45 AM Gastrointestinal Cancers
Johanna Bendell, Axel Grothey

1:30 PM Genitourinary Cancers
Arjun Balar, William Oh

2:30 PM Gynecologic Cancers
Kathleen Moore, David O'Malley

3:30 PM Breast Cancer
Hope Rugo, Sara Tolaney

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Gigi Chen, MD
Diablo Valley Oncology and
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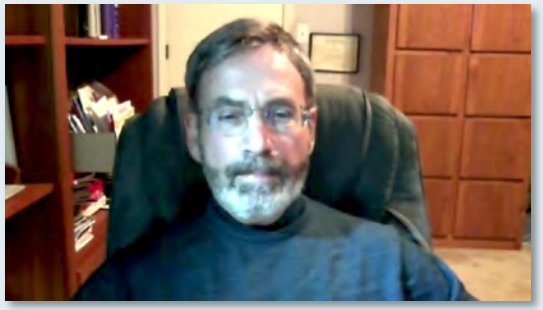
Sulfi Ibrahim, MD
Reid Health
Richmond, Indiana



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Agenda

MODULE 1: Overview of EGFR tumor mutations; selection of first-line therapy

MODULE 2: First-line treatment of NSCLC with EGFR mutation and brain metastases

MODULE 3: Progressive disease with EGFR mutation; resistance mutations

MODULE 4: Management of locally advanced disease with EGFR mutation

MODULE 5: ADAURA trial: Adjuvant therapy for NSCLC with EGFR mutation

MODULE 6: Treatment of NSCLC with EGFR exon 20 alterations

MODULE 7: Optimal approach to oligoprogression of NSCLC with EGFR mutation

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Case Presentation – Dr Ibrahim: A 74-year-old woman with metastatic NSCLC and an exon 19 insertion mutation

Sulfi Ibrahim, MD

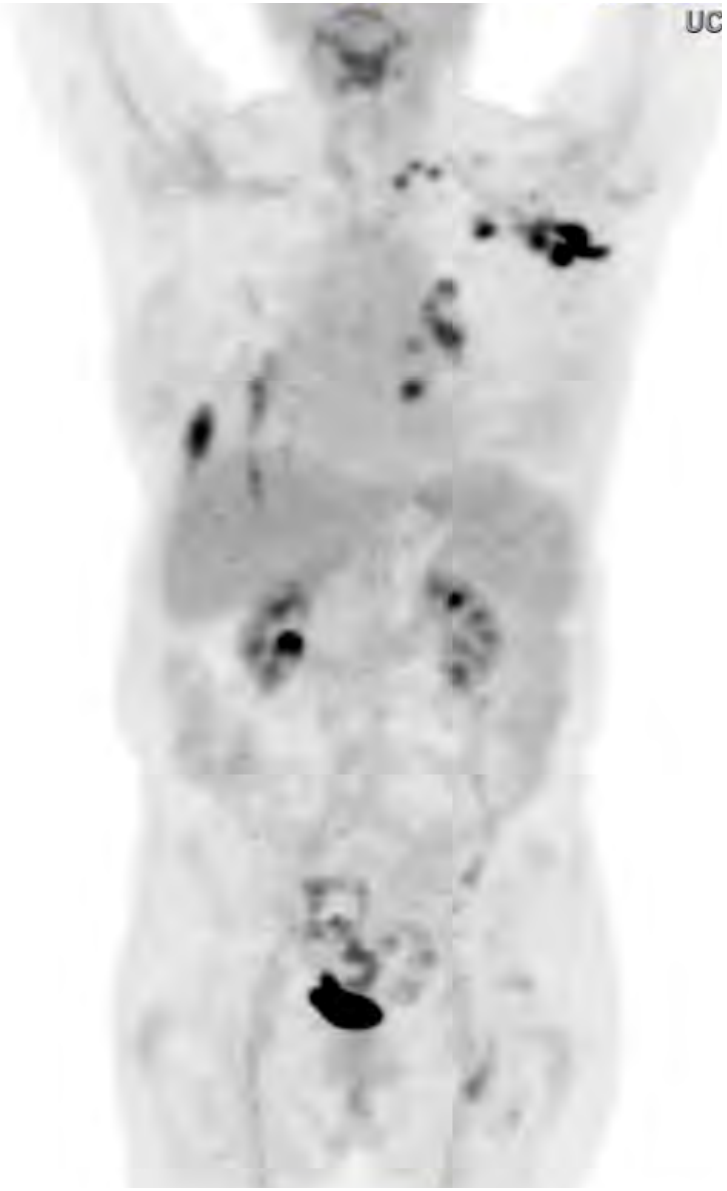
- African American never smoker who presented with increasing cough and dyspnea that did not respond to antibiotics
- Bronchoscopy revealed lung adenocarcinoma metastatic to the contralateral lung
- Exon 19 insertion mutation detected on NGS
- Started on osimertinib with a great response and off ambulatory oxygen within a month of starting therapy, with no toxicity

Questions

- Is Osimertinib the best agent to treat exon 19 insertion mutation?
- Is this seen more classically in African American never smoking women?
- Do patients who have the RB1 and P53 mutation have a shorter PFS with Osimertinib and higher risk of transformation to small cell cancer?

Case Presentation – Dr Herbst: A 68-year-old man with metastatic adenocarcinoma of the lung and an EGFR exon 19 deletion mutation

- 68-year-old man and non smoker presented with palpable L axillary lymphadenopathy.
- FNA of L axillary LN shows lung adenocarcinoma TTF1+
- PET CT with primary LUL lung mass.
  L axillary/hilar and L SCL LAD and diffuse bone metastases.
- MRI brain negative for metastatic disease.
- EGFR mutation exon 19 Deletion

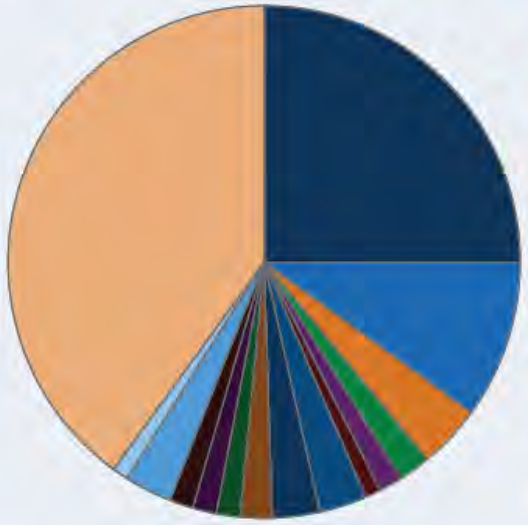


Courtesy of Roy S Herbst, MD, PhD

Molecular Complexity of NSCLC and the Importance of Genomic Profiling

All patients with NSCLC should undergo molecular profiling to identify targetable alterations

Molecular Complexity of Adenocarcinoma



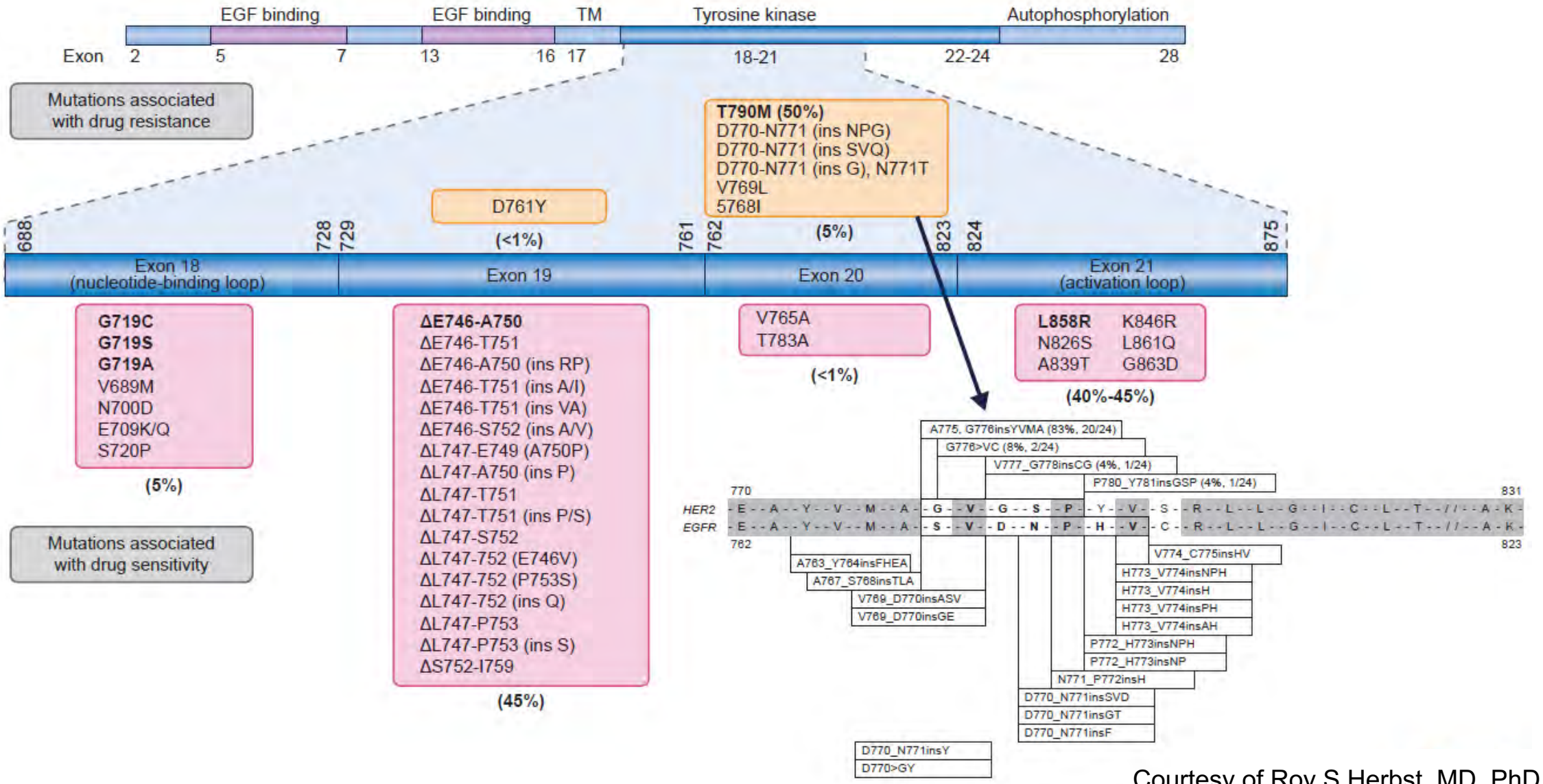
- *KRAS* mutation
- *EGFR* mutation
- *ALK* fusion
- *ROS1* fusion
- *RET* fusion
- *NTRK1* fusion
- *HER2* fusion
- *BRAF* mutation
- *PIK3CA* mutation
- *HRAS* mutation
- *NRAS* mutation
- *AKT* mutation
- *MET* exon 14 mutation
- *MAP3K1* mutation
- Unknown

There are now **7** molecular alterations with FDA-approved targeted therapies!

- *EGFR*
- *ALK*
- *ROS1*
- BRAF V600E
- *NTRK*
- *MET* exon 14
- *RET*

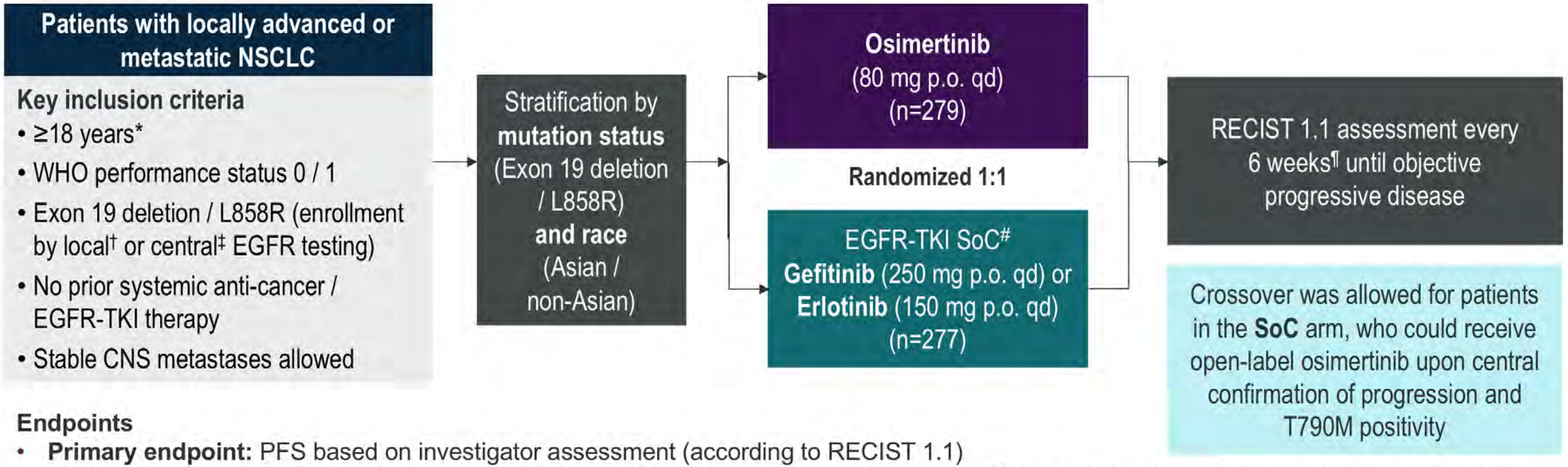
Courtesy of Roy S Herbst, MD, PhD

Complexity of *EGFR* Alterations in Lung Cancer



Courtesy of Roy S Herbst, MD, PhD

FLAURA Study Design



Endpoints

- **Primary endpoint:** PFS based on investigator assessment (according to RECIST 1.1)
  - The study had a 90% power to detect a hazard ratio of 0.71 (representing an improvement in median PFS from 10 months to 14.1 months) at a two-sided alpha-level of 5%
- **Secondary endpoints:** objective response rate, duration of response, disease control rate, depth of response, overall survival, patient reported outcomes, safety

Courtesy of Suresh Ramalingam, MD

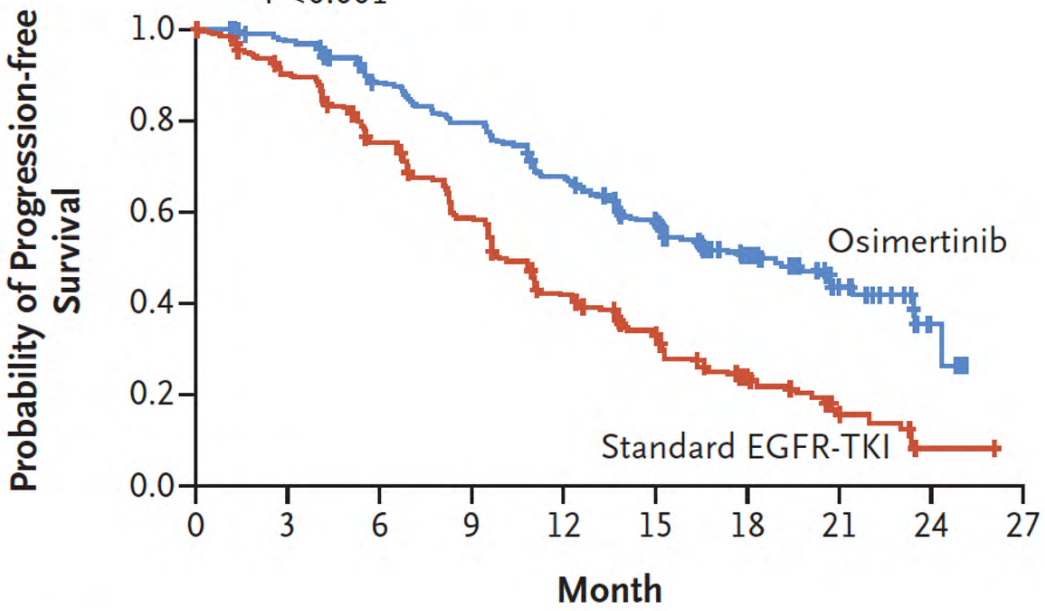
Ramalingam et al, N Engl J Med, 2020

FLAURA: PFS

Progression-free Survival in Full Analysis Set

	No. of Patients	Median Progression-free Survival (95% CI)
		mo
Osimertinib	279	18.9 (15.2–21.4)
Standard EGFR-TKI	277	10.2 (9.6–11.1)

Hazard ratio for disease progression or death, 0.46 (95% CI, 0.37–0.57)
P<0.001



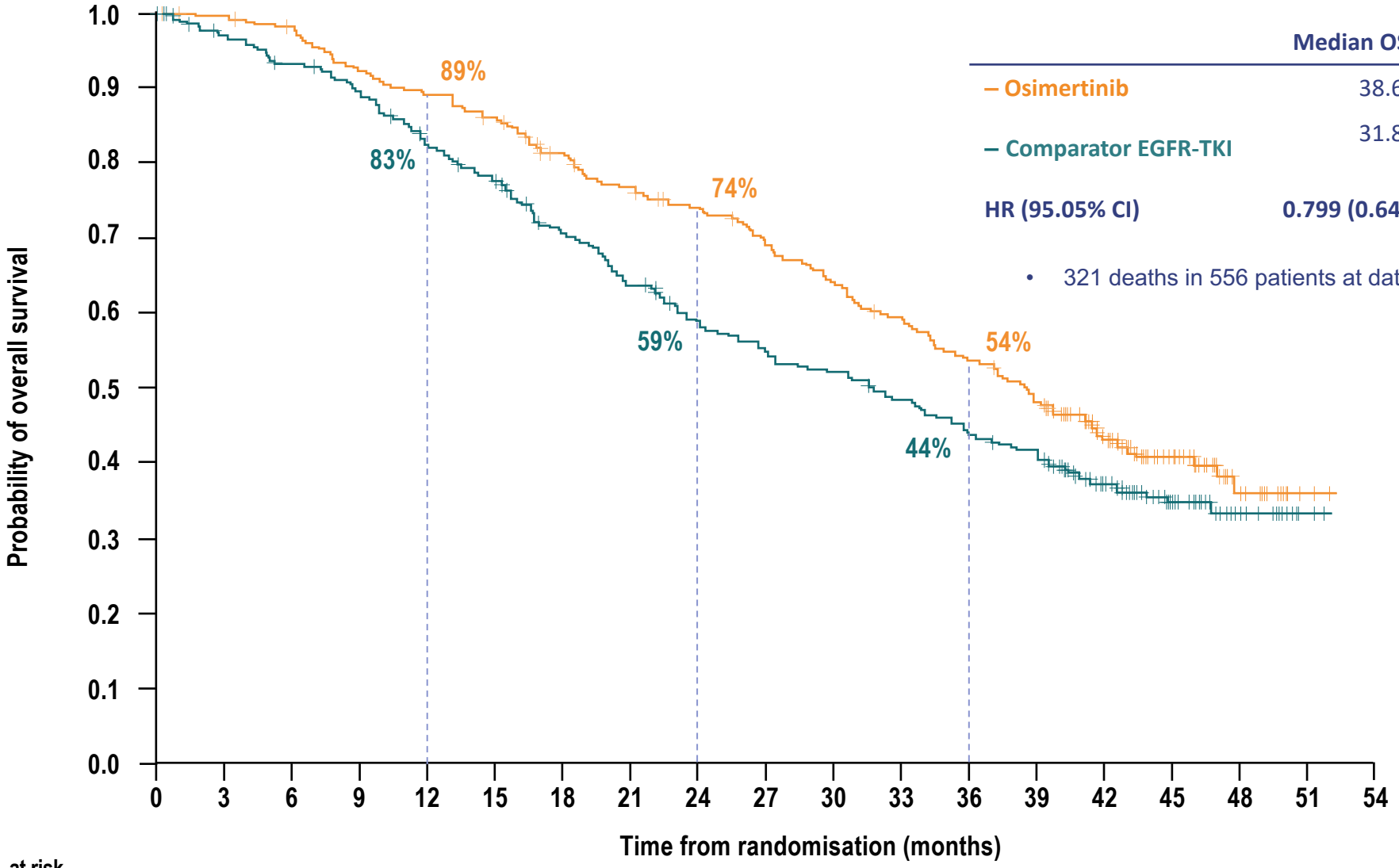
No. at Risk

Osimertinib	279	262	233	210	178	139	71	26	4	0
Standard EGFR-TKI	277	239	197	152	107	78	37	10	2	0

Soria et al, N Engl J Med, 2018.

Courtesy of Suresh Ramalingam, MD
Winship Cancer Institute | Emory University

Final analysis: Overall Survival



Median OS, months (95% CI)	
– Osimertinib	38.6 (34.5, 41.8)
– Comparator EGFR-TKI	31.8 (26.6, 36.0)
HR (95.05% CI)	**0.799 (0.641, 0.997); p=0.0462**

- 321 deaths in 556 patients at data cut-off: 58% maturity

No. at risk																			
Osimertinib	279	276	270	254	245	236	217	204	193	180	166	153	138	123	86	50	17	2	0
Comparator EGFR-TKI	277	263	252	239	219	205	182	165	148	138	131	121	110	101	72	40	17	2	0

Data cut-off: 25 June 2019

For statistical significance, a p-value of less than 0.0495, determined by O'Brien-Fleming approach, was required

Ramalingam et al, N Engl J Med, 2020

Courtesy of Suresh Ramalingam, MD
Winship Cancer Institute | Emory University

RELAY: Study Design[1,2]

Key inclusion criteria

- Stage IV NSCLC
- *EGFR* mutation-positive (Ex19del or Ex 21 L858R)
- ECOG PS 0-1

Key exclusion criteria

- Known *EGFR* T790M mutation
- Prior treatment with EGFR TKI or chemotherapy
- Brain metastases

Phase 3[a]
N=449

RANDOMIZE 1:1

- **Ramucirumab 10 mg/kg Q2W + Erlotinib 150 mg/day**
- **Placebo Q2W + Erlotinib 150 mg/day**

Treatment until progression or unacceptable toxicity

Primary end point: Progression-Free Survival

Stratification factors

- *EGFR* status (exon 19 deletion vs. exon 21 L858R)
- Sex
- Region (East Asia vs. other)
- EGFR testing method (therascreen®/cobas® vs. other)

[a]Phase 3 enrollment began after confirmation of dose and schedule in Phase 1b[2]

1. Garon EB et al. *Clin Lung Cancer* 2017; 2. Reck M et al. *Clin Lung Cancer* 2018

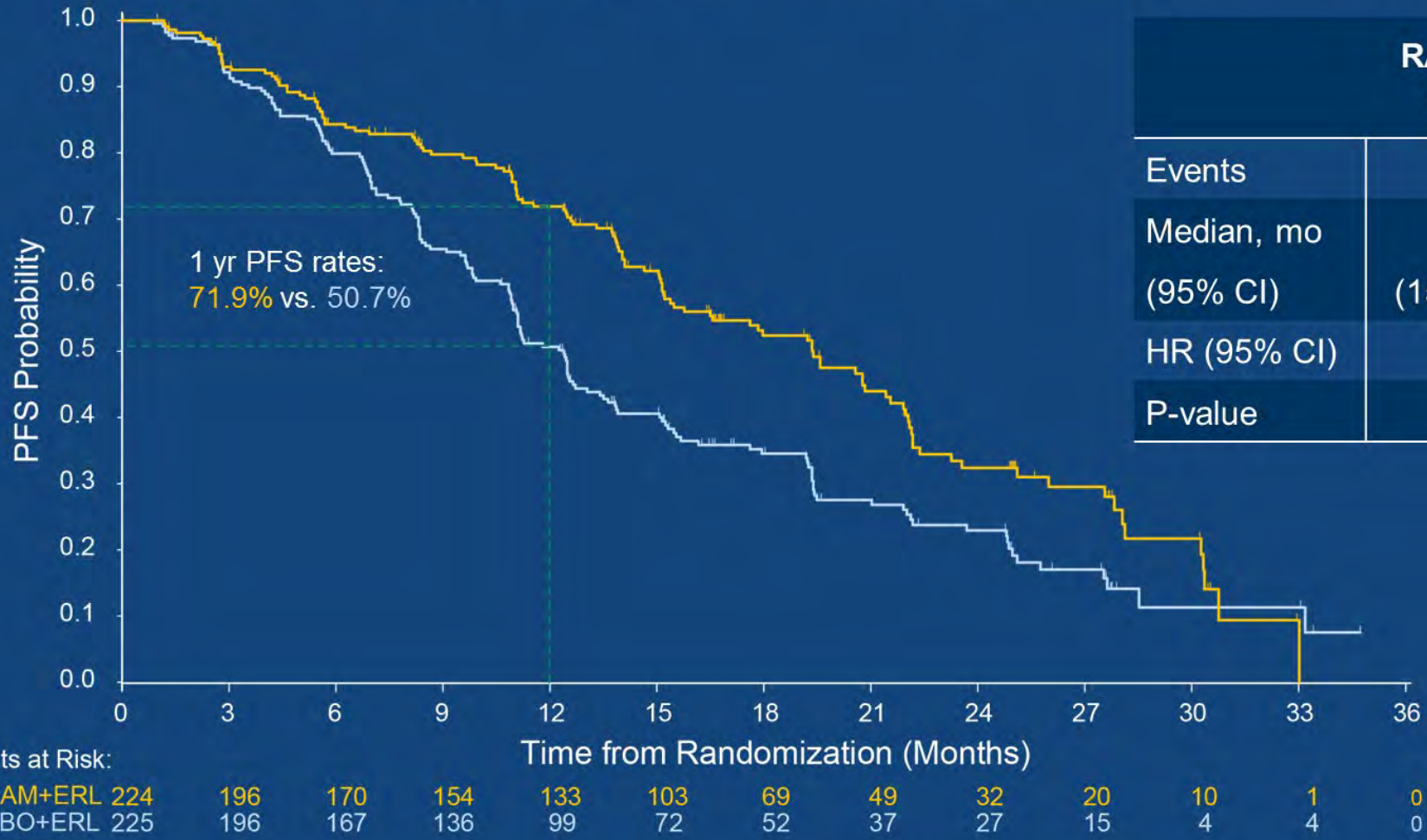
Clinicaltrials.gov NCT02411448

PRESENTED BY: Prof. Kazuhiko Nakagawa, MD, PhD
Kindai University Faculty of Medicine, Osaka, Japan

Courtesy of Suresh Ramalingam, MD
Winship Cancer Institute | Emory University

Presented By Kazuhiko Nakagawa at 2019 ASCO Annual Meeting

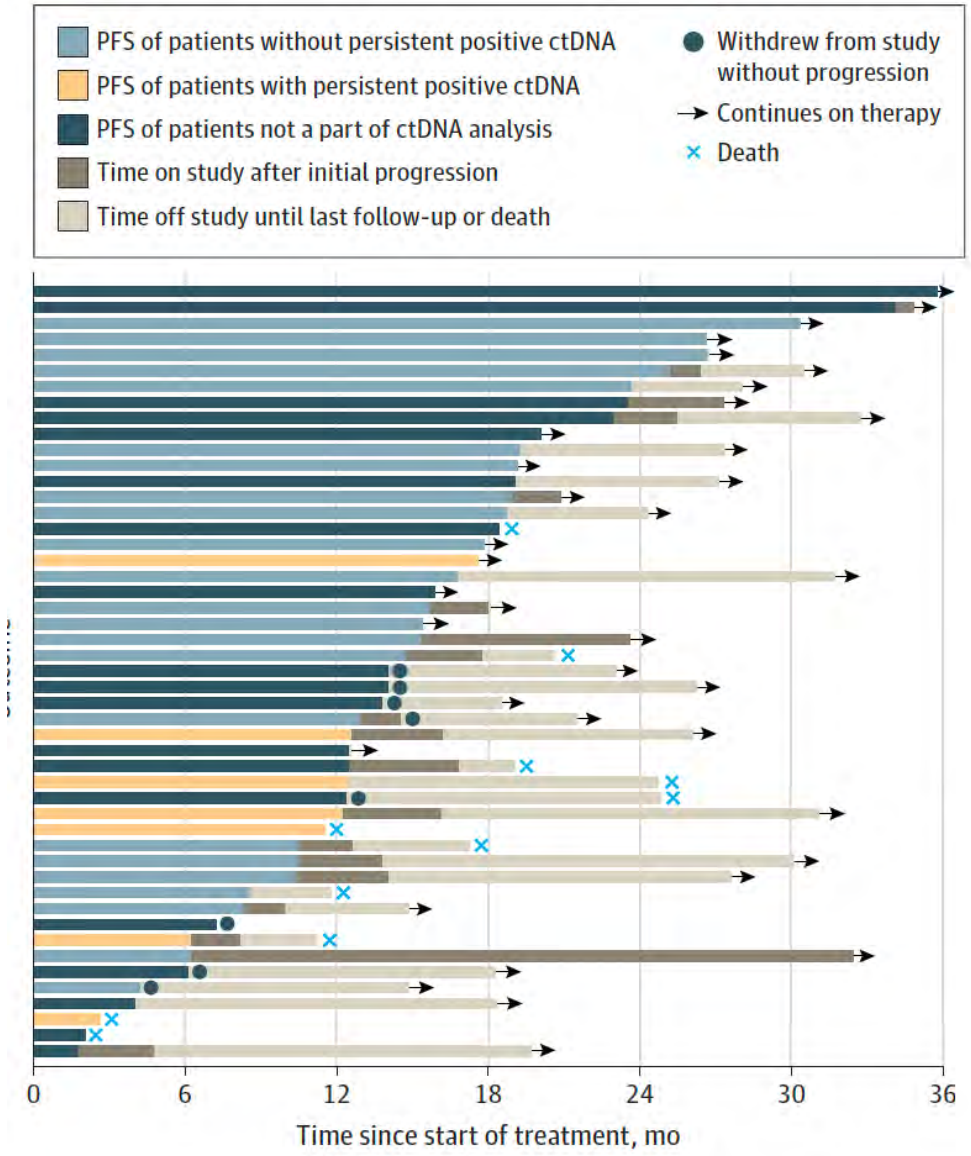
RELAY Primary Endpoint: PFS (Investigator-Assessed)

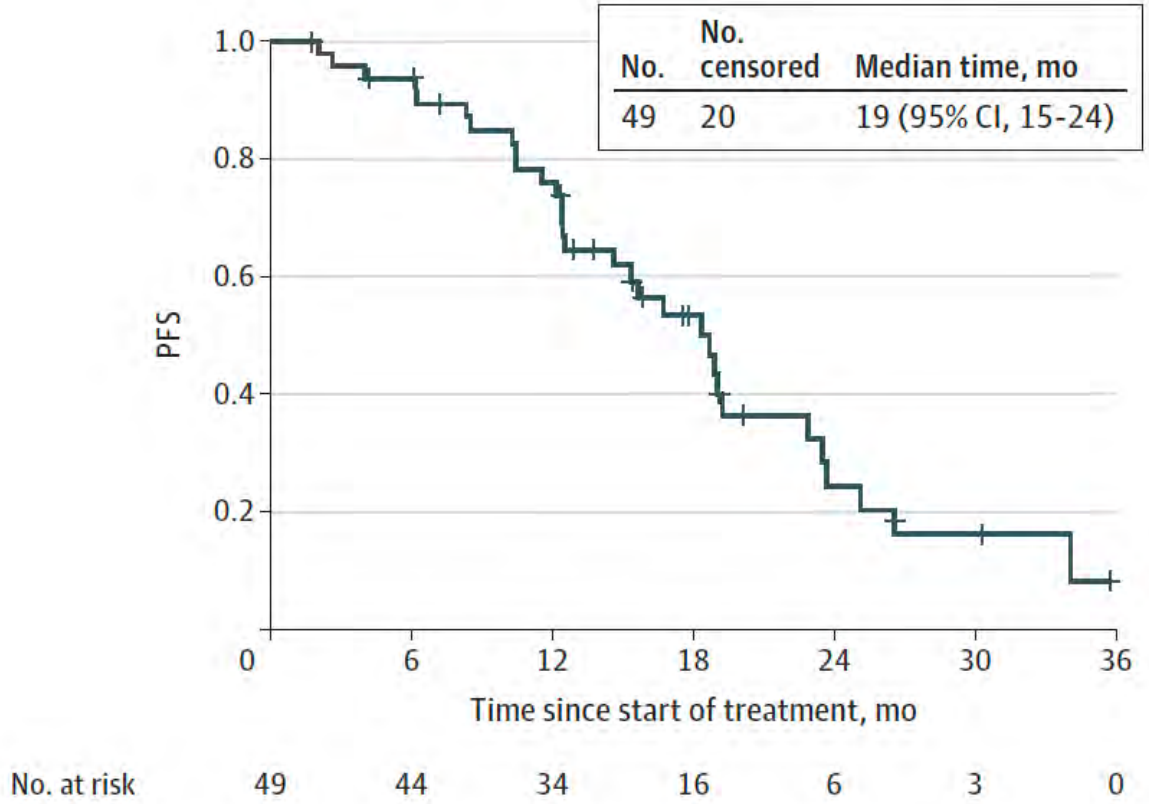


	RAM+ERL n=224	PBO+ERL n=225
Events	122	158
Median, mo	**19.4**	**12.4**
(95% CI)	(15.4–21.6)	(11.0–13.5)
HR (95% CI)	**0.591** (0.461, 0.760)	
P-value	<0.0001	

Consistent PFS benefit by independent, blinded central review (HR 0.671, 95% CI 0.518 – 0.869; p=0.0022)

Osimertinib + Bevacizumab: Phase 1/2 Study





Yu et al, JAMA Oncol, 2020.

Courtesy of Suresh Ramalingam, MD

A Randomized Phase II Study of Osimertinib with or without Bevacizumab in Advanced Lung Adenocarcinoma Patients with EGFR T790M Mutation (West Japan Oncology Group 8715L)

Toi Y et al.

ESMO 2020;Abstract 1259O.

EA5182 Study Schema

Untreated metastatic EGFR+ NSCLC
No prior treatment with EGFR TKI
No contraindications to bevacizumab

Stratification:
Presence/absence of brain mets

Randomized 1:1

N=150

Osimertinib 80mg PO daily

21 day cycles
Imaging every 3 cycles (9 weeks)
Toxicity using CTCAE v5.0

Osimertinib 80mg PO daily
Bevacizumab 15mg/kg IV q 3 weeks

N=150

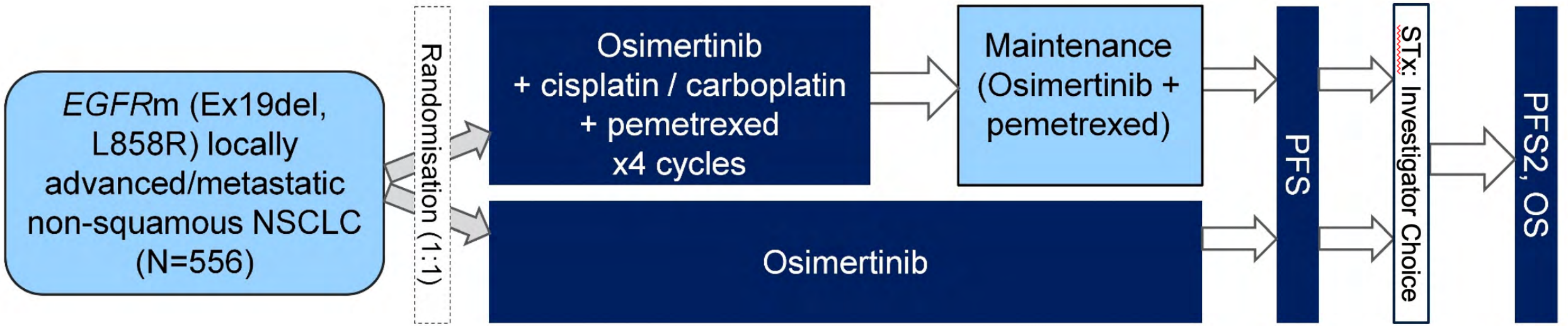
Primary endpoint: Progression-free survival
Secondary endpoints: overall survival, response rate, intracranial PFS (CNS imaging every 18 weeks), mechanisms of resistance

Changes per TMSC:
Could not change primary endpoint to OS (sample size, study duration not feasible)
Proposal to hold PFS results until OS matures, increase sample size for power to assess secondary OS endpoint

PI: Yu & Halmos

Courtesy of Suresh Ramalingam, MD
Winship Cancer Institute | Emory University

FLAURA 2 Study Scheme

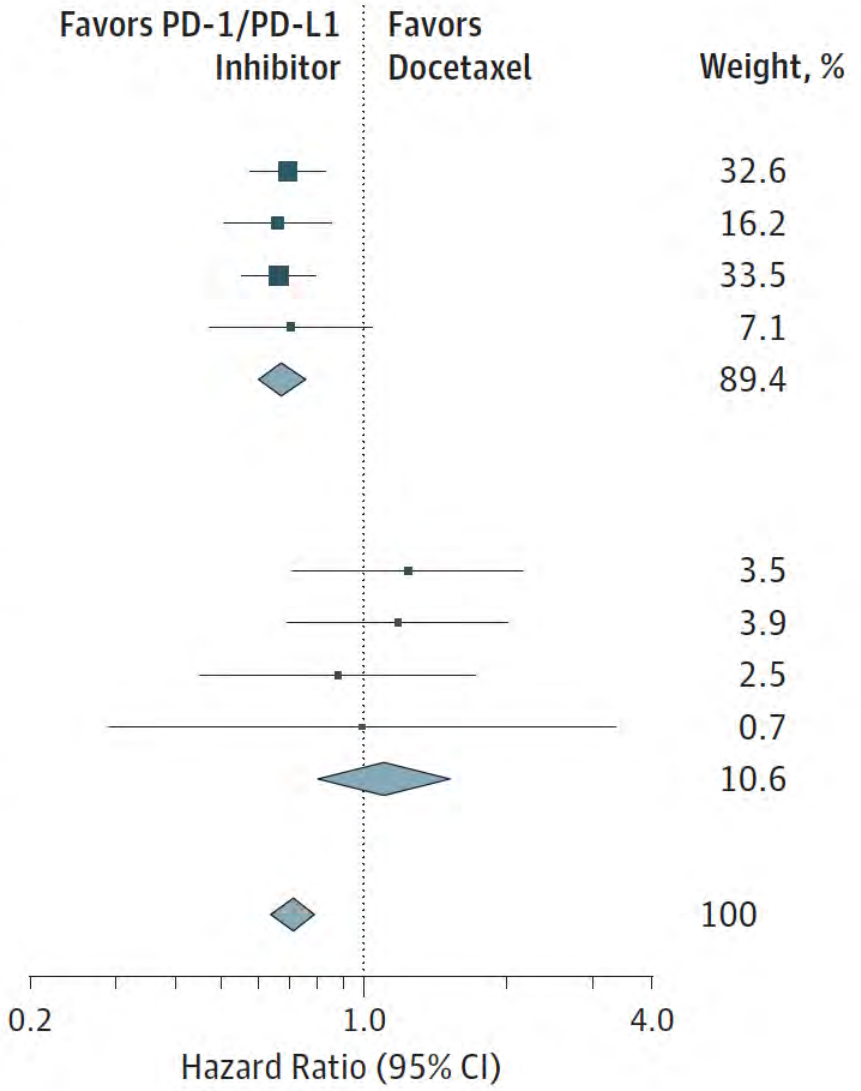


- Osimertinib given at a dose of 80 mg QD during induction and maintenance
- The osimertinib dose can be reduced to 40 mg QD for management of AEs; chemotherapy dose interruption/reduction is to be prioritised over reduction/interruption of osimertinib
- Randomisation will be stratified by race, WHO PS (0 vs 1), and tissue *EGFR* mutation test at enrolment
- Planned to involve approximately 248 sites in 27 countries

Courtesy of Suresh Ramalingam, MD
Winship Cancer Institute | Emory University

Efficacy of PD-1 Inhibitors in EGFR^{MT} NSCLC

Trial	Hazard Ratio (95% CI)	Weight, %
EGFR wild-type		
OAK	0.69 (0.57-0.83)	32.6
CheckMate 057	0.66 (0.51-0.85)	16.2
Keynote 010	0.66 (0.55-0.79)	33.5
POPLAR	0.70 (0.47-1.04)	7.1
Subtotal	0.67 (0.60-0.75)	89.4
Heterogeneity: $\chi^2_3 = 0.18$, $P = .98$; $I^2 = 0\%$		
Test for overall effect: $z = 6.94$ ($P < .001$)		
EGFR mutated		
OAK	1.24 (0.71-2.18)	3.5
CheckMate 057	1.18 (0.69-2.02)	3.9
Keynote 010	0.88 (0.45-1.72)	2.5
POPLAR	0.99 (0.29-3.40)	0.7
Subtotal	1.11 (0.80-1.53)	10.6
Heterogeneity: $\chi^2_3 = 0.69$, $P = .88$; $I^2 = 0\%$		
Test for overall effect: $z = 0.61$ ($P = .54$)		
Total	0.71 (0.64-0.79)	100
Heterogeneity: $\chi^2_7 = 8.90$, $P = .26$; $I^2 = 21\%$		
Test for overall effect: $z = 6.37$ ($P < .001$)		
Test for subgroup differences: $\chi^2 = 8.03$, $P = .005$; $I^2 = 87.6\%$		

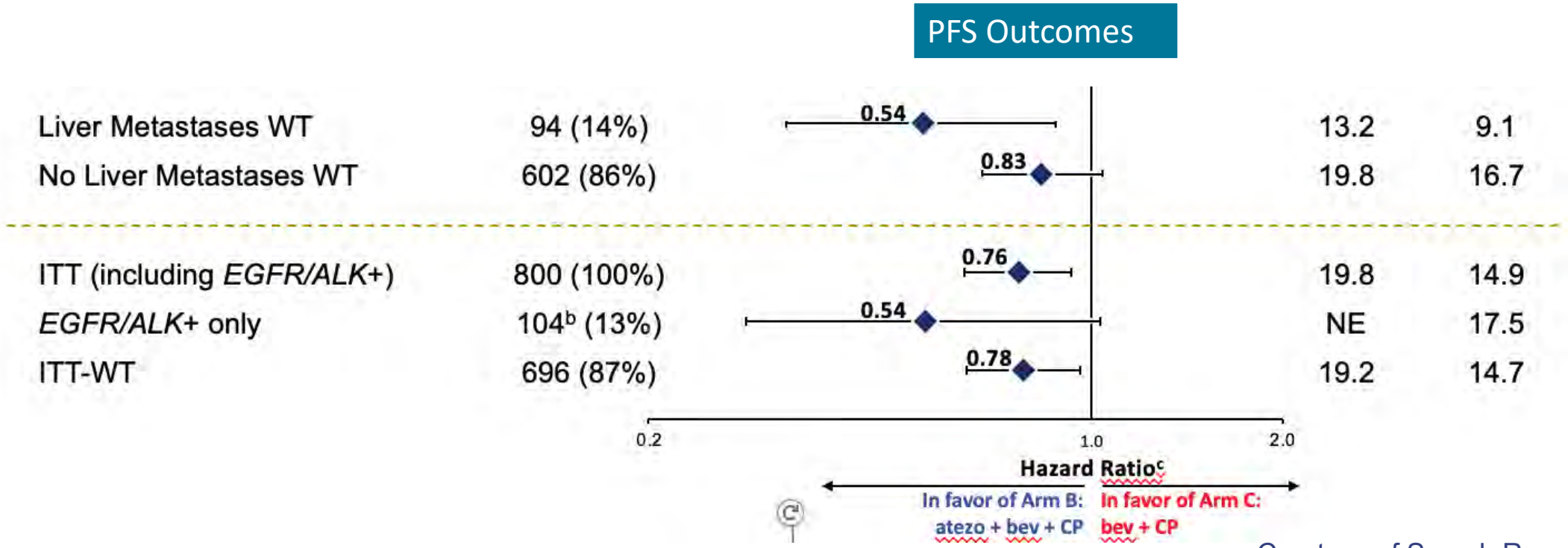


Lee et al, JAMA Oncology, 2017 (online)

Courtesy of Suresh Ramalingam, MD
Winship Cancer Institute | Emory University

What About Chemo + IO for EGFR MT NSCLC

- Post-hoc analysis from IMpower150
  - Suggestion of improved efficacy with chemo+ Bevacizumab + Atezolizumab
- Results from IMpower130 failed to demonstrate benefit with chemo + Atezo in EGFR MT NSCLC



Socinski et al, NEJM, 2018

Courtesy of Suresh Ramalingam, MD
Winship Cancer Institute | Emory University

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Case Presentation – Dr Hanna: A physician with NSCLC with 25 brain metastases and an EGFR exon 21 L858R mutation

Nasser H Hanna, MD

- Never smoking, high functioning physician presented with a lung mass with brain and bone metastases
- EGFR exon 21 L8585R mutation
- Osimertinib initiated with initial response followed by CNS progression

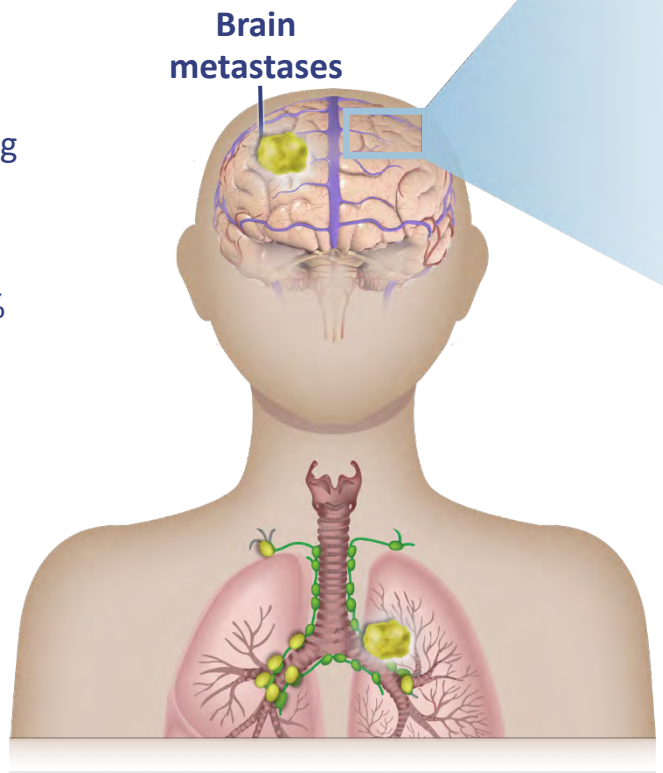
Questions

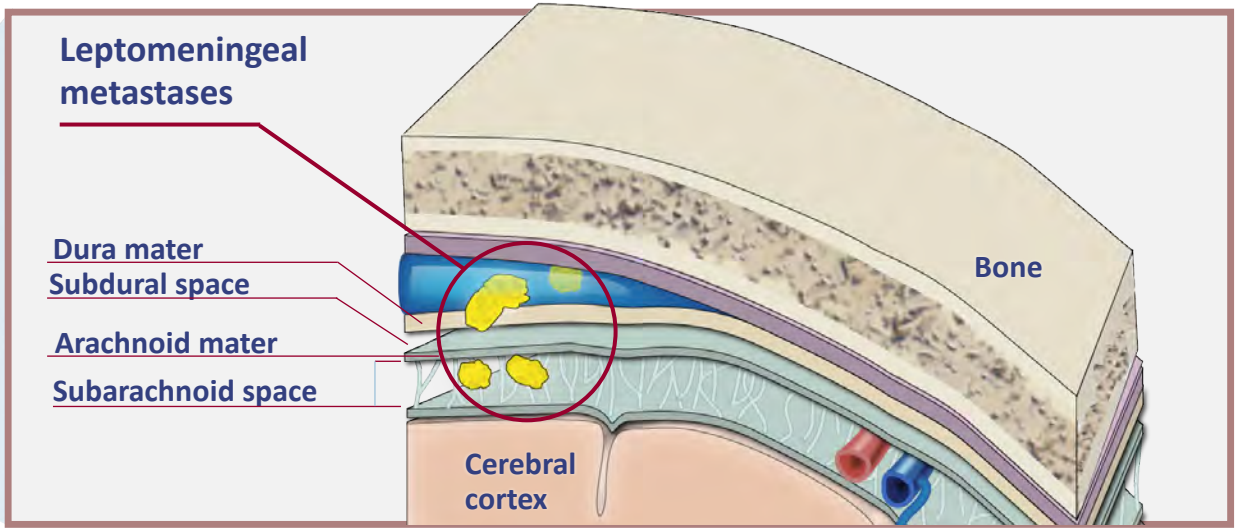
- Should chemotherapy be added to osimertinib? Is bevacizumab an option?
- What if the patient had an exon 20 insertion mutation?

CNS metastases and LM occur at higher frequency in EGFRm NSCLC[1-5]

Brain metastases

- At initial diagnosis, 19%-24% of patients with EGFRm tumors had brain metastases compared with 11%-13% of patients with WT EGFR[2-4]
- Additional patients with NSCLC develop brain metastases during the course of their disease; at final follow-up, 44% of patients with EGFRm tumors had brain metastases compared with 22% of patients with WT EGFR[2]





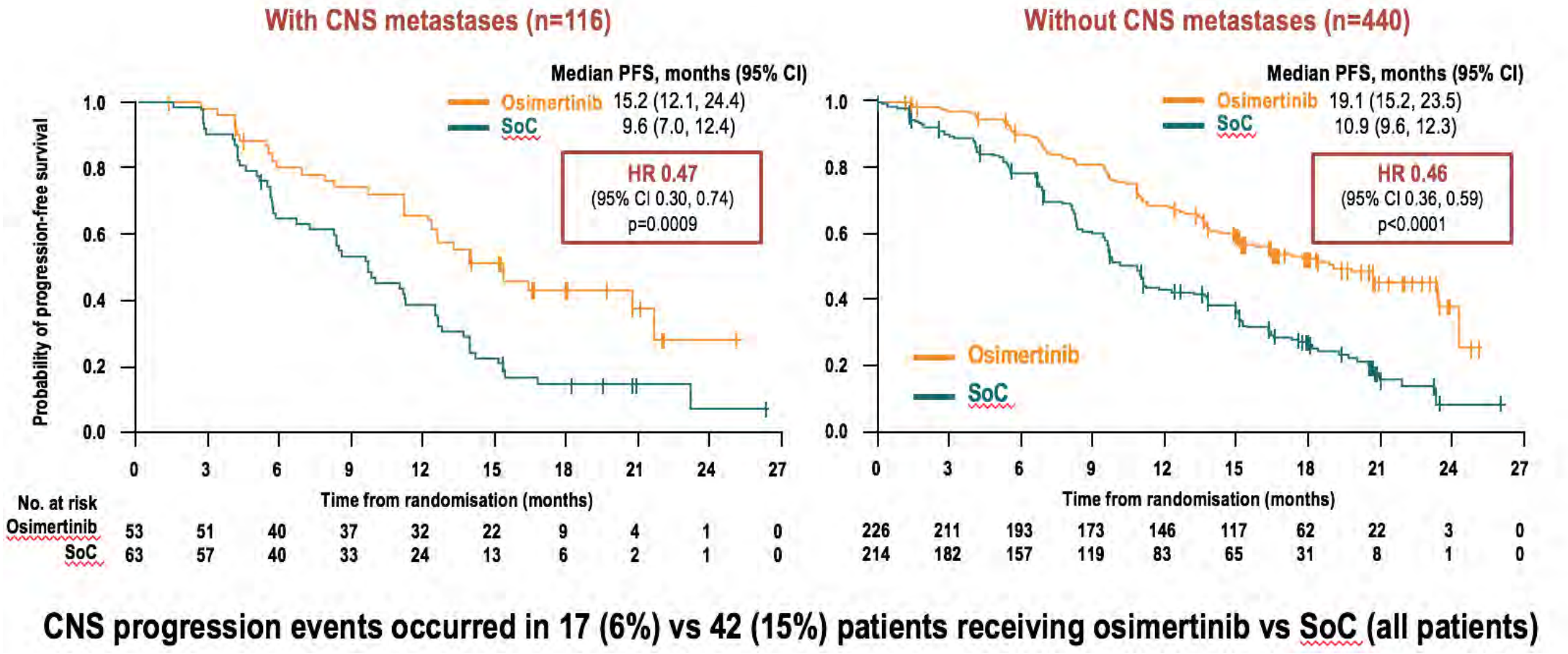
Leptomeningeal metastases

- Leptomeningeal metastasis (LM) is defined by tumor cell spread to the leptomeninges and subarachnoid space[1]
- LM is late stage development in patients with high tumor burden and often occur in patients who also have brain metastases[1]
- LM is likely underdiagnosed and has poor prognosis when not treated (survival of 4-6 weeks)[1]
- Leptomeningeal metastasis may be more frequent In patients with EGFRm NSCLC vs wild type EGFR (9.4% vs 1.7%; *P*<0.001)[5,*]

- *Data are from a retrospective analysis from January 2011 to June 2015 that included 5,387 patients—of which 1,258 patients with NSCLC were confirmed with EGFR mutations, of which 118 were diagnosed with LM.
- CNS = central nervous system; EGFR = epidermal growth factor receptor; EGFRm = epidermal growth factor receptor mutation-positive; LM = leptomeningeal metastasis; NSCLC = non-small cell lung cancer; WT = wild-type.
- 1. Mack F, et al. *Cancer Treat Rev*. 2016;43:83-91. 2. Han G, et al. *Oncotarget.* 2016;7(35):56998-57010. 3. Stanic K, et al. *Radiol Oncol*. 2014;48(2):173-183. 4. Rangachari D, et al. *Lung Cancer*. 2015;88(1):108-111. 5. Li Y-S, et al. *J Thorac Oncol*. 2016;11(11):1962-1969.

Courtesy of Suresh Ramalingam, MD
Winship Cancer Institute | Emory University

FLAURA: Efficacy Against Brain Metastases



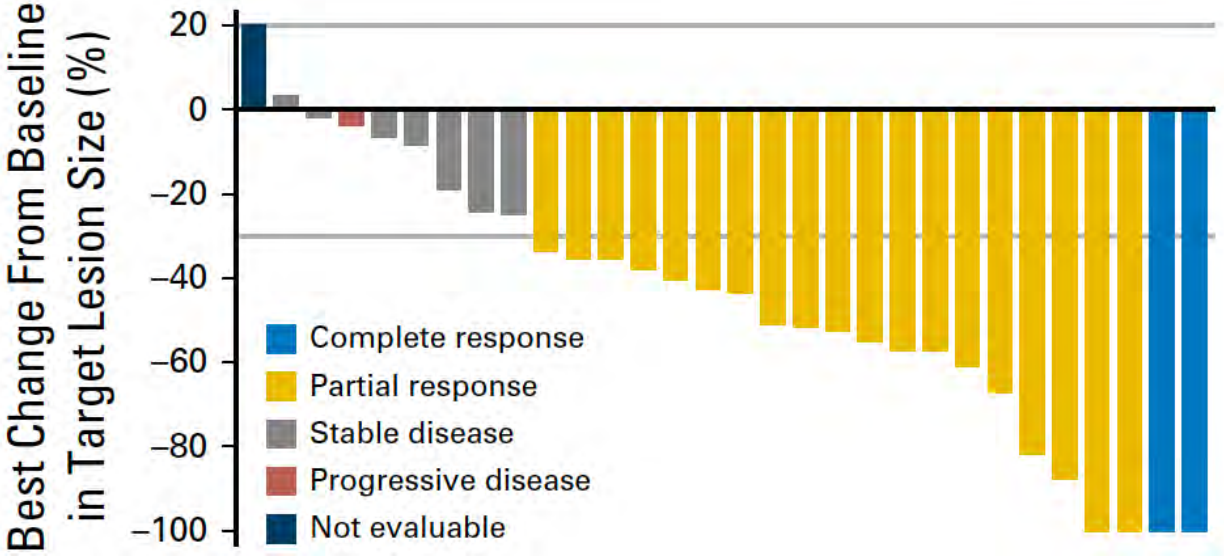
CNS progression events occurred in 17 (6%) vs 42 (15%) patients receiving osimertinib vs SoC (all patients)

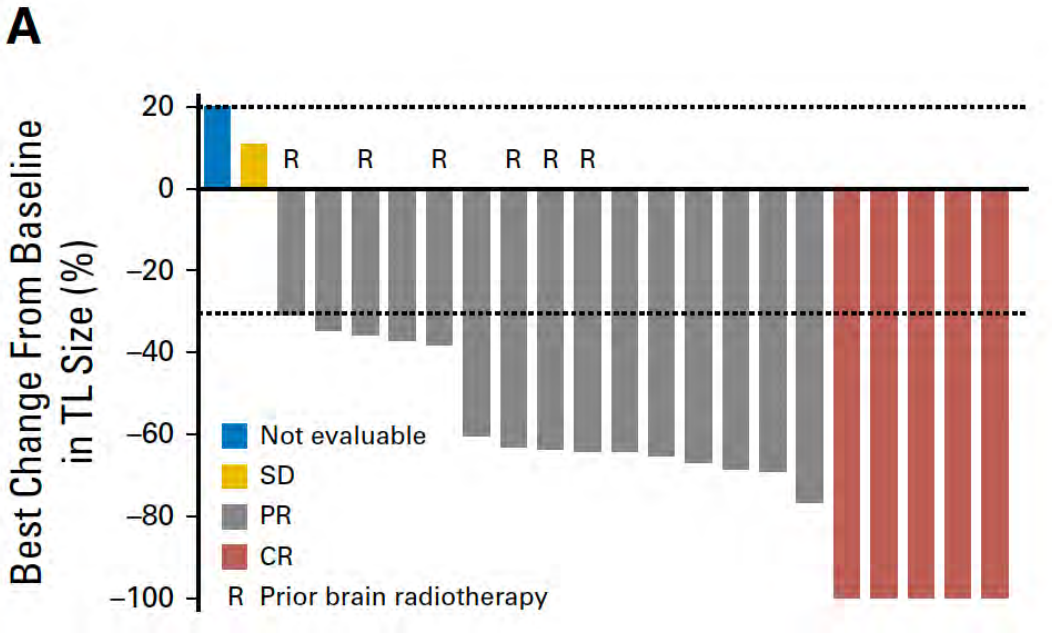
Ramalingam et al, ESMO 2017; Soria et al, N Engl J Med, 2018

Courtesy of Suresh Ramalingam, MD
Winship Cancer Institute | Emory University

Osimertinib: Activity Against CNS Metastasis

Pts with CNS Metastasis	CNS ORR	mDOR CNS	PFS CNS
AURA 3 (N=116)	70% vs. 31%	8.9 m vs. 5.7 m	11.7 m vs. 5.6 m
FLAURA (N=128)	91% vs. 68%	NR vs. 14.4 m	NR vs. 13. 9m (HR 0.48)





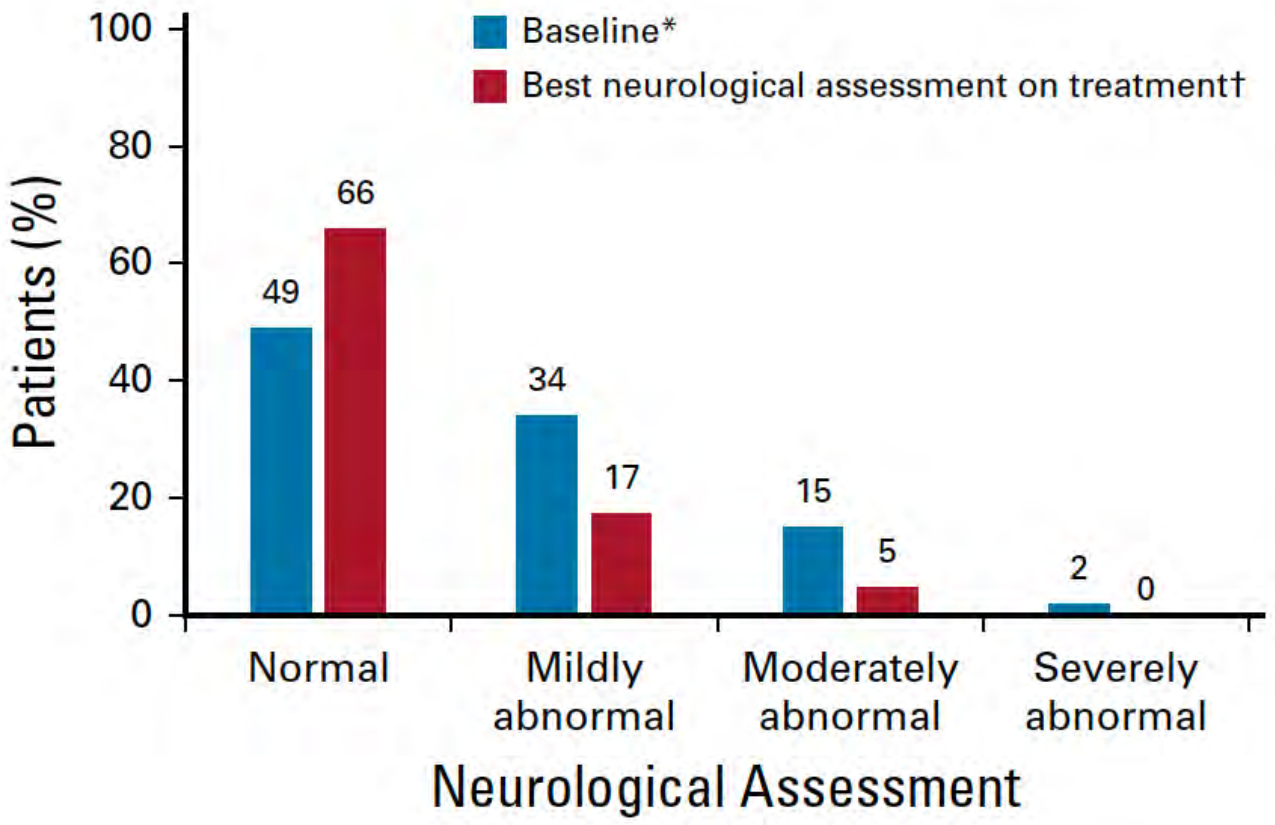
Courtesy of Suresh Ramalingam, MD

Winship Cancer Institute | Emory University

Wu et al, J Clin Oncol, 2018; Reungwetwattana et al, J Clin Oncol, 2018.

Leptomeningeal Metastasis: BLOOM Trial of Osimertinib

- N=41 patients
- Tx: Osimertinib 160 mg/d
- ORR: 62% (Ind Review)
- mDOR 8.3 m
- mOS 11.0 m



Yang et al, J Clin Oncol, 2020.

Courtesy of Suresh Ramalingam, MD

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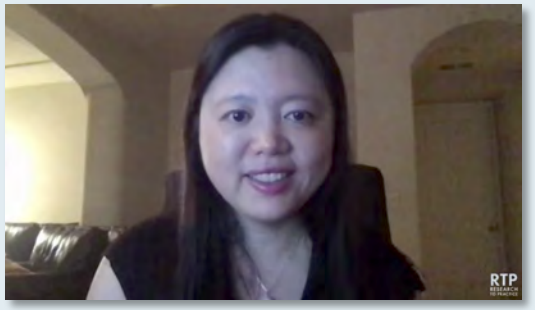
Case Presentation – Dr Chen: A 57-year-old man, never smoker with metastatic adenocarcinoma of the lung and a del(19) EGFR mutation



Gigi Chen, MD

- Work-up after skiing accident reveals metastatic adenocarcinoma of the lung
  - Involvement of the LUL, hilar and mediastinal adenopathy, liver, bone and brain
  - EGFR del19 mutation
- 8/2018: Osimertinib and zoledronic acid, with initial response systemically and in brain
- One year later: PD in bone → SBRT → Zoledronic acid switched to denosumab (severe jaw pain)
  - Reverted to zoledronic acid
- Currently, scans show multiple new bone progressions, lung disease is stable
- GUARDANT: Predominant EGFR exon 19, but also has small amount of EGFR C797s, BRAF V600E, RET fusion and MET amplification, TP53 and RB1
- Carboplatin/pemetrexed

Question

- How would you manage the denosumab-associated jaw pain? Would you have switched back to zoledronic acid?

Case Presentation – Dr Yu: A 64-year-old woman with Stage IV NSCLC and EGFR exon 19 deletion, EGFR T790M acquires an ALK fusion after treatment with osimertinib

64 yo woman, never-smoker, who initially presented with stage 4 EGFR-mutant lung cancer with metastases to bilateral lungs, lymph node and bone.

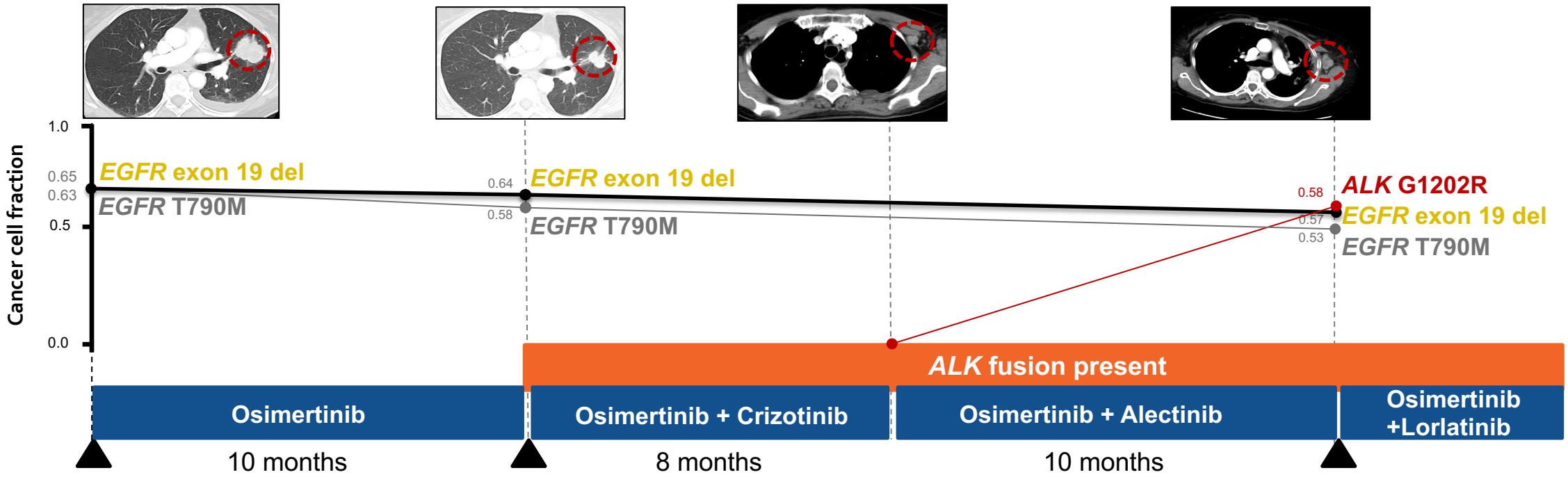
She was started on erlotinib and had disease control for 14 months followed by disease progression. She had a repeat biopsy that showed continued EGFR exon 19 deletion as well as EGFR T790M.

She started osimertinib and had disease control for 10 months. Upon rebiopsy, she had evidence of an acquired ALK fusion.

Courtesy of Helena Yu, MD

Case Presentation – Dr Yu: 64-year-old woman (continued) - ALK-mediated resistance

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

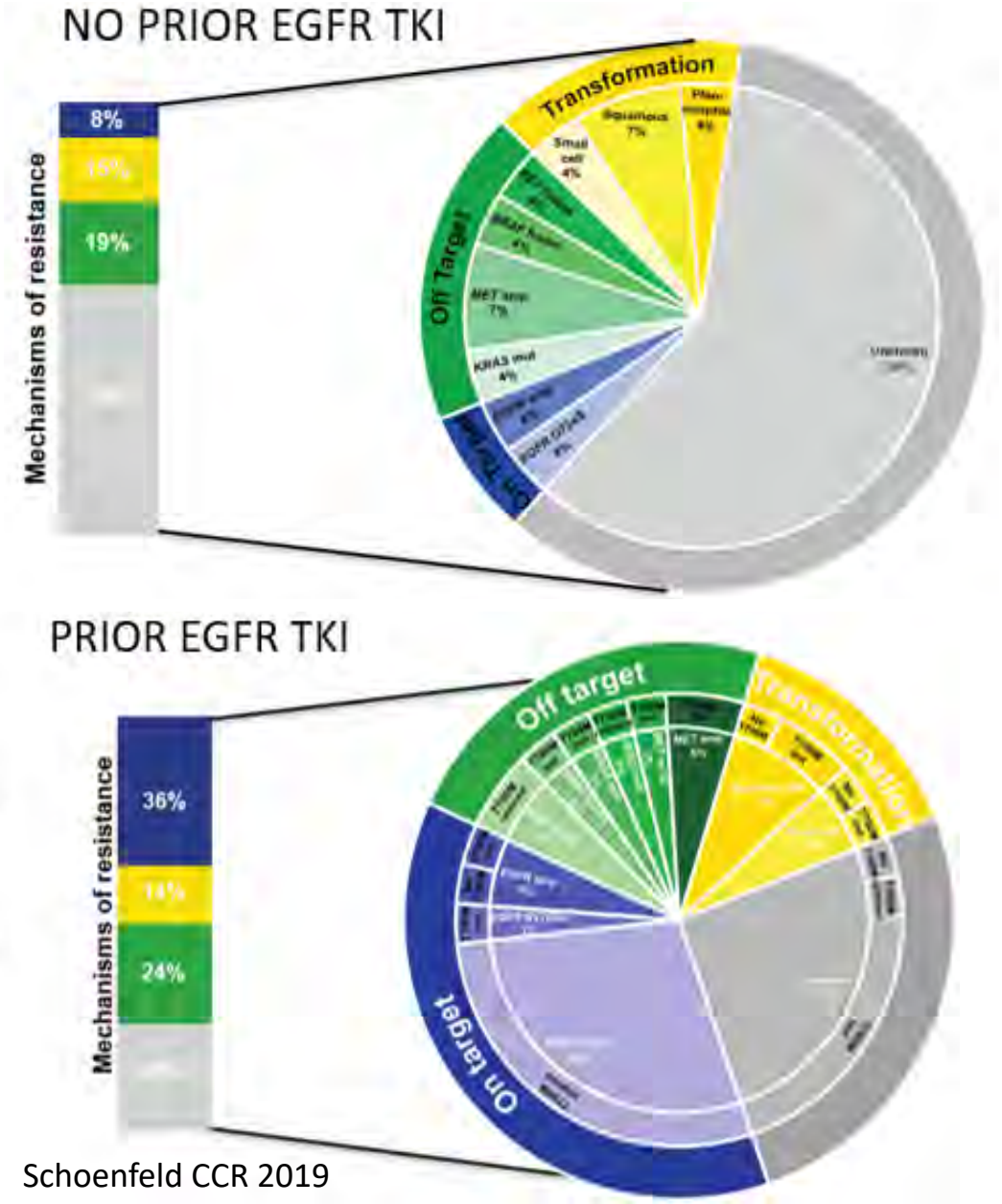


Memorial Sloan Kettering Cancer Center

Schoenfeld CCR 2019

Courtesy of Helena Yu, MD

Mechanisms of resistance to osimertinib



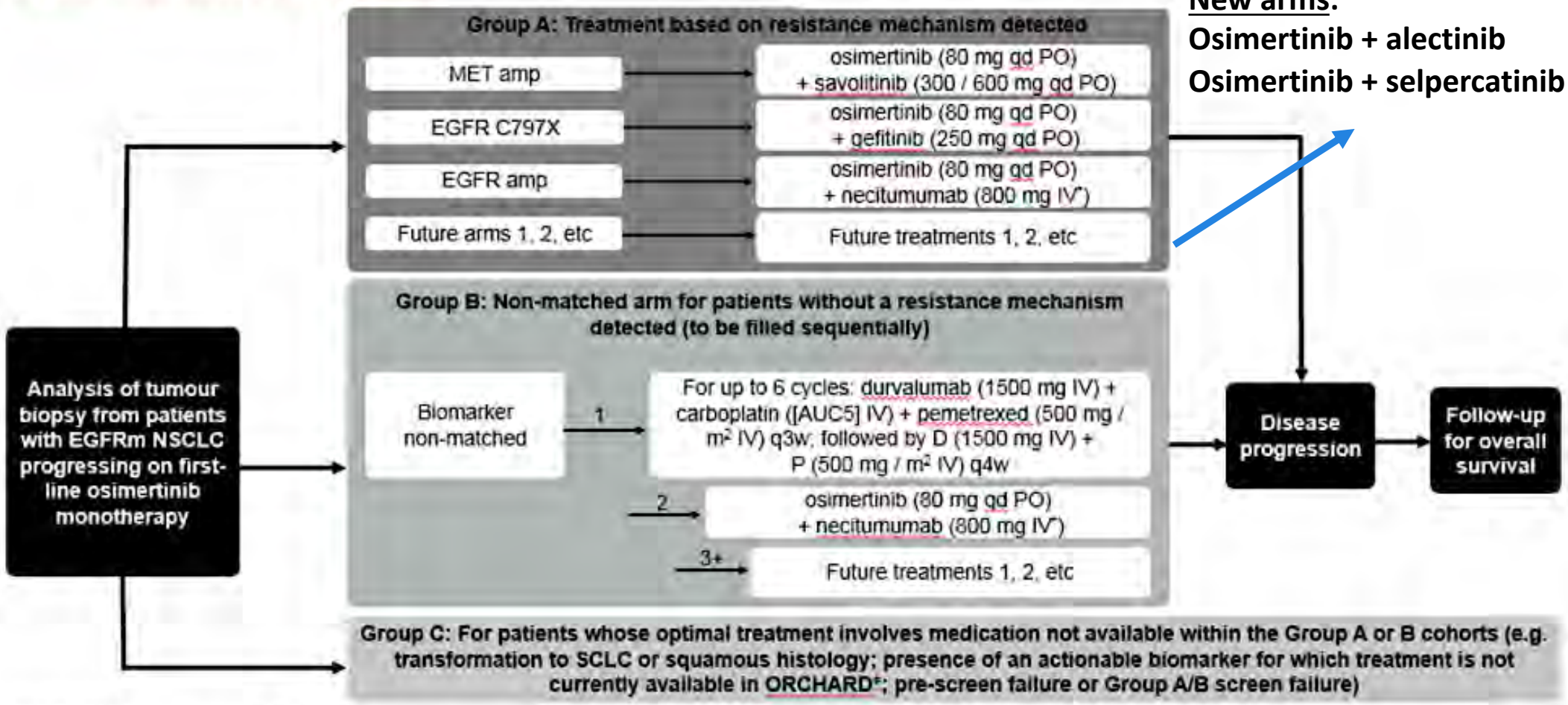
Schoenfeld CCR 2019

- **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**
- **Majority of patients without clear genomic resistance mechanism- there will be a role for non-biomarker selected therapies**

Courtesy of Helena Yu, MD

Mechanisms of resistance to osimertinib

Figure 1. ORCHARD study design



*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

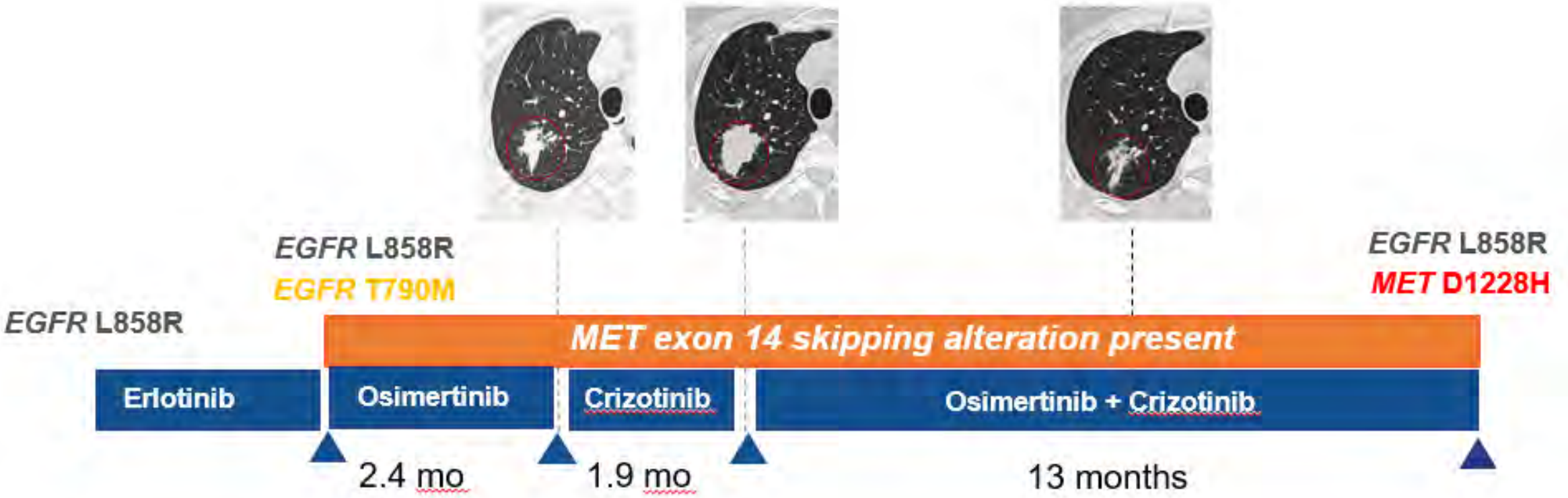
New arms:
Osimertinib + alectinib
Osimertinib + selpercatinib

Memorial Sloan Kettering Cancer Center

Courtesy of Helena Yu, MD

MET exon 14-mediated resistance

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



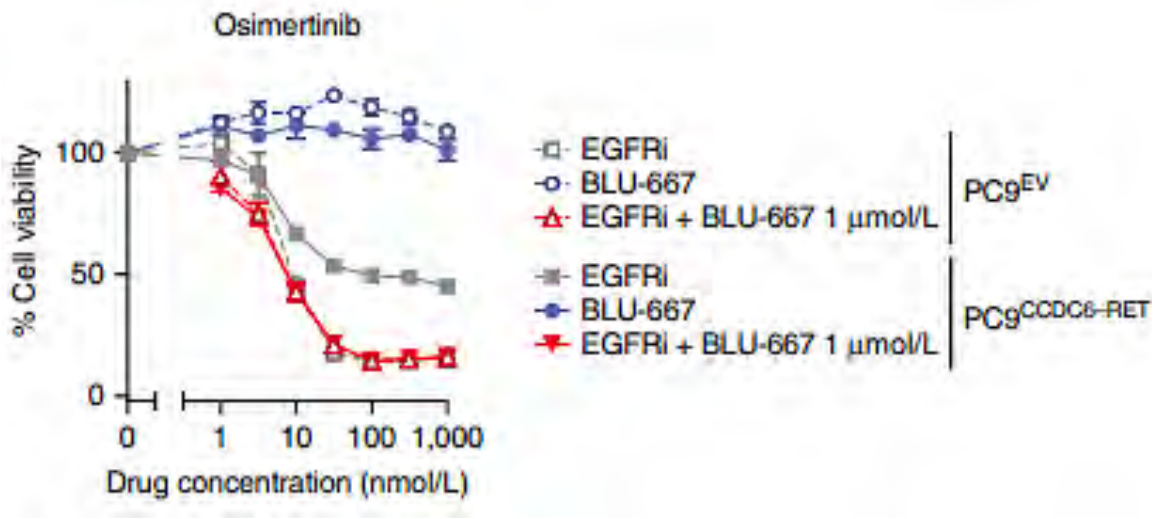
Memorial Sloan Kettering Cancer Center

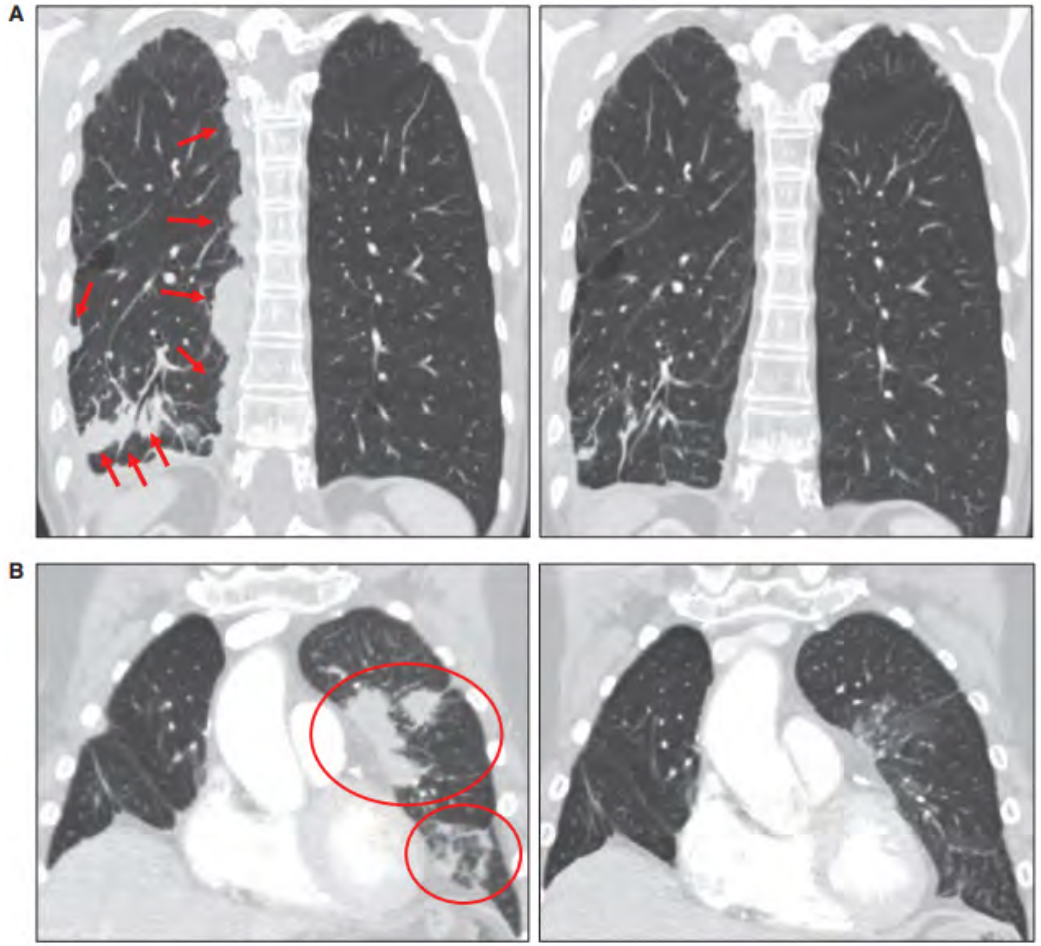
Schoenfeld CCR 2019

Courtesy of Helena Yu, MD

RET-mediated resistance

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





Piotrowska Canc Disc 2018

Courtesy of Helena Yu, MD

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Case Presentation – Dr Lamar: An 83-year-old woman with Stage IIIB NSCLC and an EGFR exon 21 mutation

Zanetta S Lamar, MD

- 2018: Diagnosed with Stage IA lung adenocarcinoma
- Left upper lobectomy, mediastinal node dissection and observation
- June 2020 repeat PET scan: Multiple hypermetabolic bilateral mediastinal lymph nodes
  - No evidence of distant disease
  - Brain MRI: Negative
  - Molecular testing: EGFR exon 21; PD-L1 TPS 0%; ALK, ROS1 and RET negative
  - Performance status: 1, occasional memory problems

Questions

- What treatment would you recommended next?
- Would you consider concurrent chemoradiation therapy? Would you consider Osimertinib?

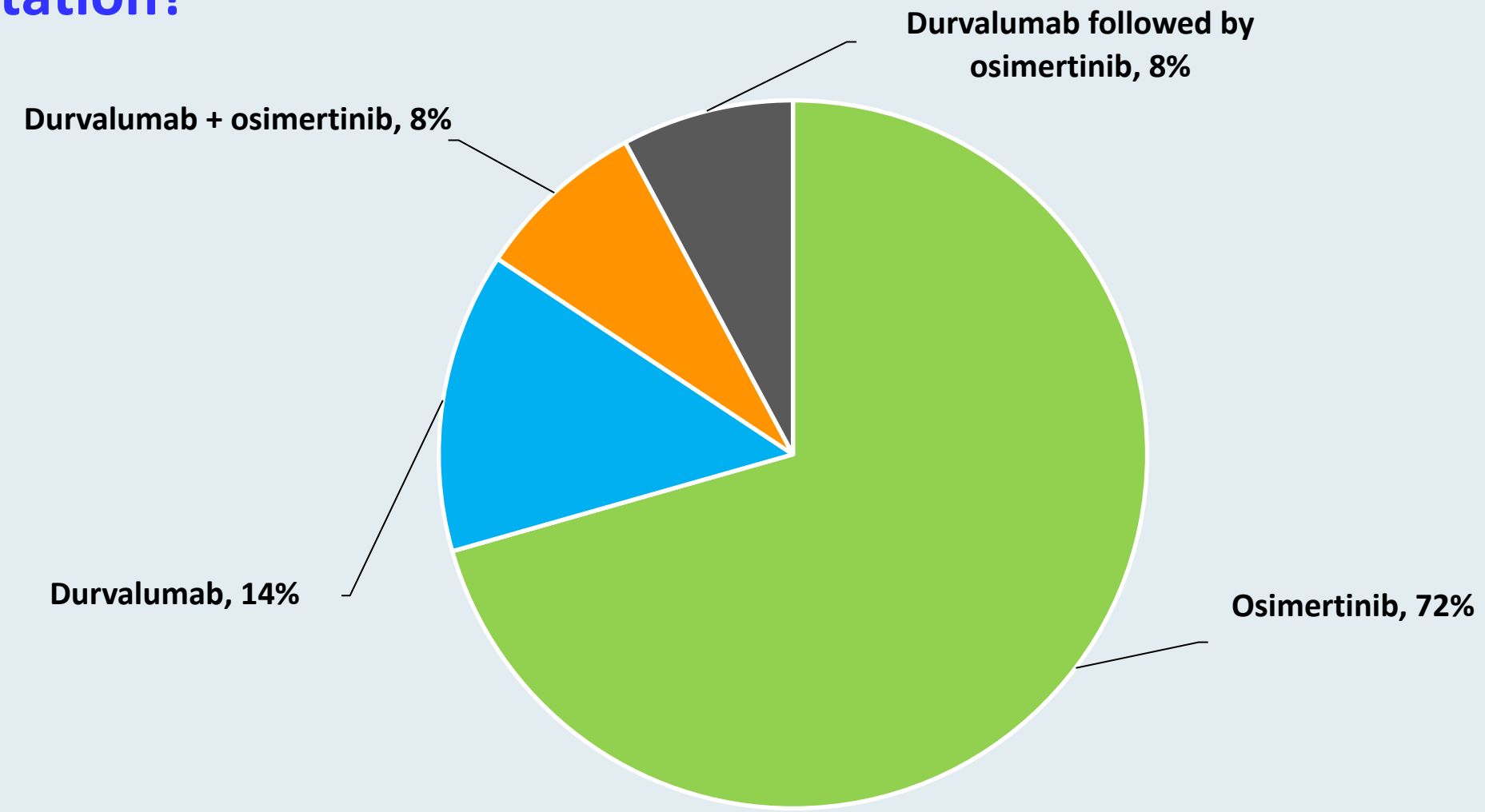
RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, what would you most likely recommend as consolidation treatment for a patient with locally advanced NSCLC who has completed chemoradiation therapy and is found to have an EGFR activating mutation?

1. Durvalumab
2. Osimertinib
3. Durvalumab + osimertinib
4. Durvalumab followed by osimertinib
5. Other

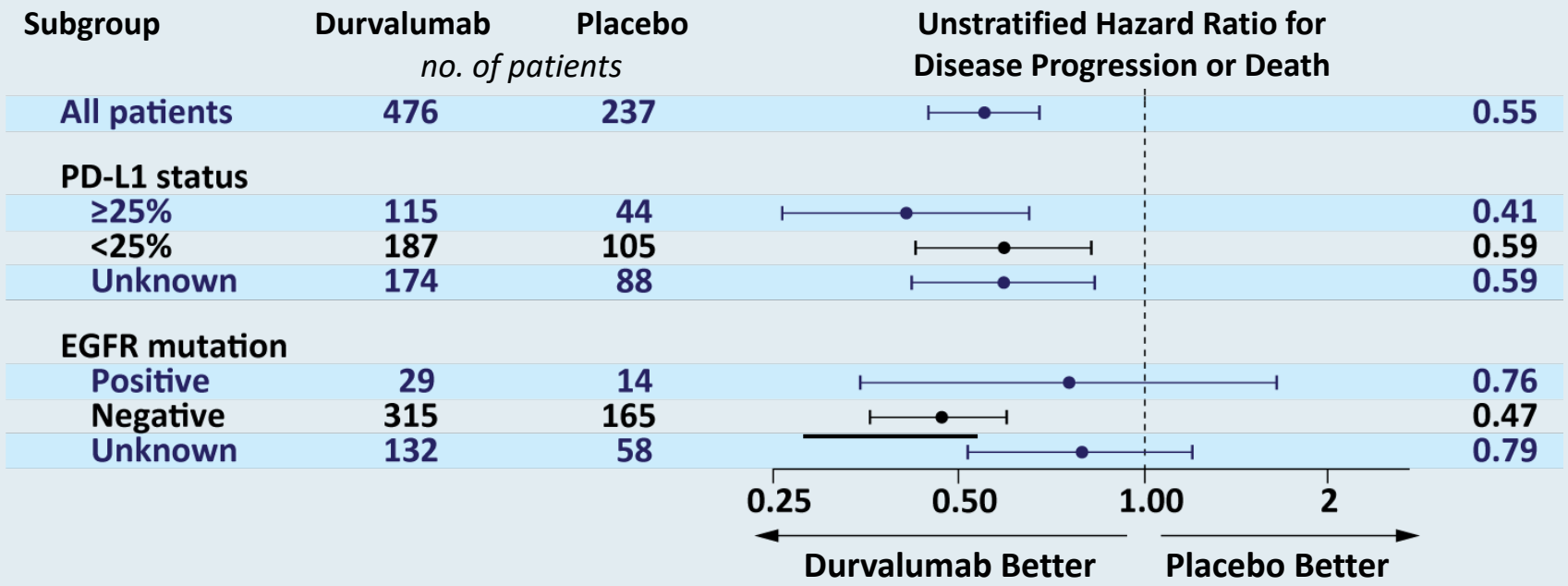
RTP
RESEARCH
TO PRACTICE

What would you most likely recommend as consolidation treatment for a patient with locally advanced NSCLC who has completed chemoradiation therapy and is found to have an EGFR activating mutation?

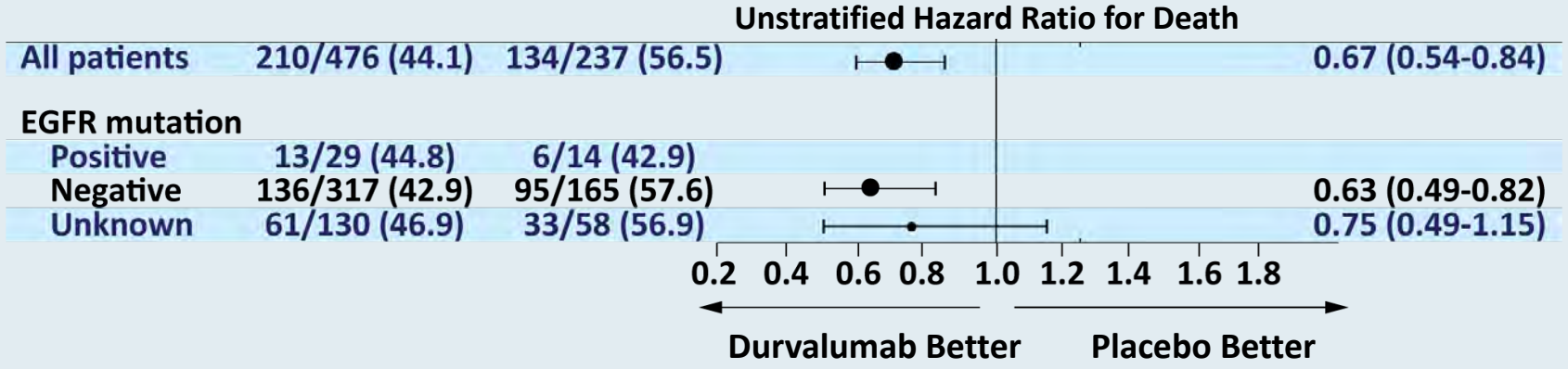


PACIFIC: Outcomes by EGFR Status

Progression-free Survival



Overall Survival



Antonia SJ et al. *N Engl J Med* 2017;377(20):1919-29; Gray JE et al. *J Thorac Oncol* 2020;15(2):288-93.

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Case Presentation — Dr Gubens: A 59-year-old woman with resected Stage IB NSCLC and an EGFR exon 19 deletion

Matthew Gubens, MD, MS

- Nonsmoker; Stage IB tumor — delayed resection due to COVID-19
- 2.9-cm high-grade adenocarcinoma with lymphovascular invasion
- EGFR exon 19 deletion

Case Presentation – Dr Ramalingam: A 71-year-old woman with metastatic adenocarcinoma of the lung and an EGFR L858R mutation

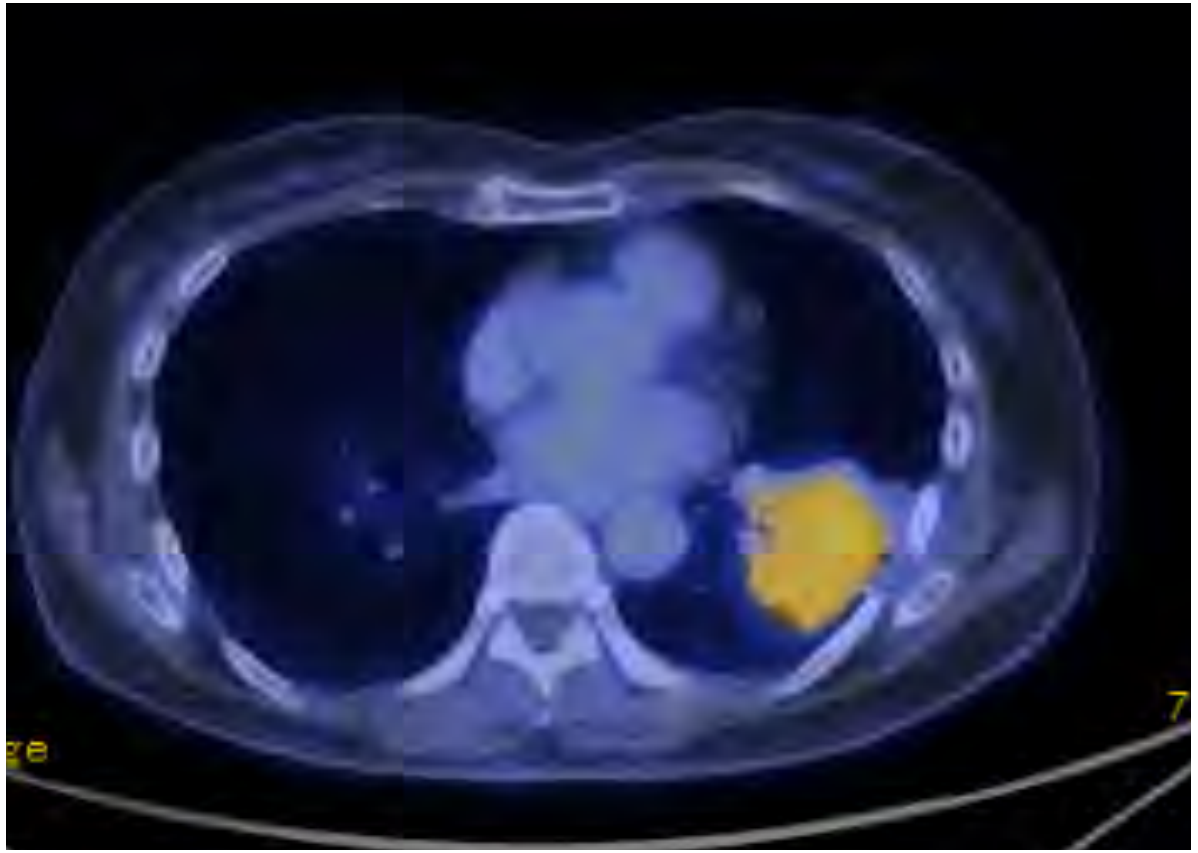
- 71-year-old female
- T2bN2 Adeno of right lower lobe
- S/P Surgery and adjuvant chemo in 2018
- Recurrence of disease diagnosed in May 2019
- EGFR L858R mutation
- No extra-thoracic disease
- Started Osimertinib in May 2019
- Tolerating well
- Partial response to therapy

Courtesy of Suresh Ramalingam, MD

Winship Cancer Institute | Emory University

Case Presentation – Dr Herbst: A 70-year-old woman with adenocarcinoma of the lung and an EGFR L858R mutation

- 70-year-old Asian never-smoking woman with persistent cough
- Chest x-ray: RUL nodule
- CT chest: 5.9 cm mass in LLL
- PET/CT: SUV max 6.6 in LLL lesion. No enlarged or FDG avid mediastinal LNs; no sites of distant metastases
- MRI brain negative
- Biopsy of LLL: NSCLC-adenocarcinoma (TTF1+)
- PFTs adequate for surgery
- EGFR L858R mutation



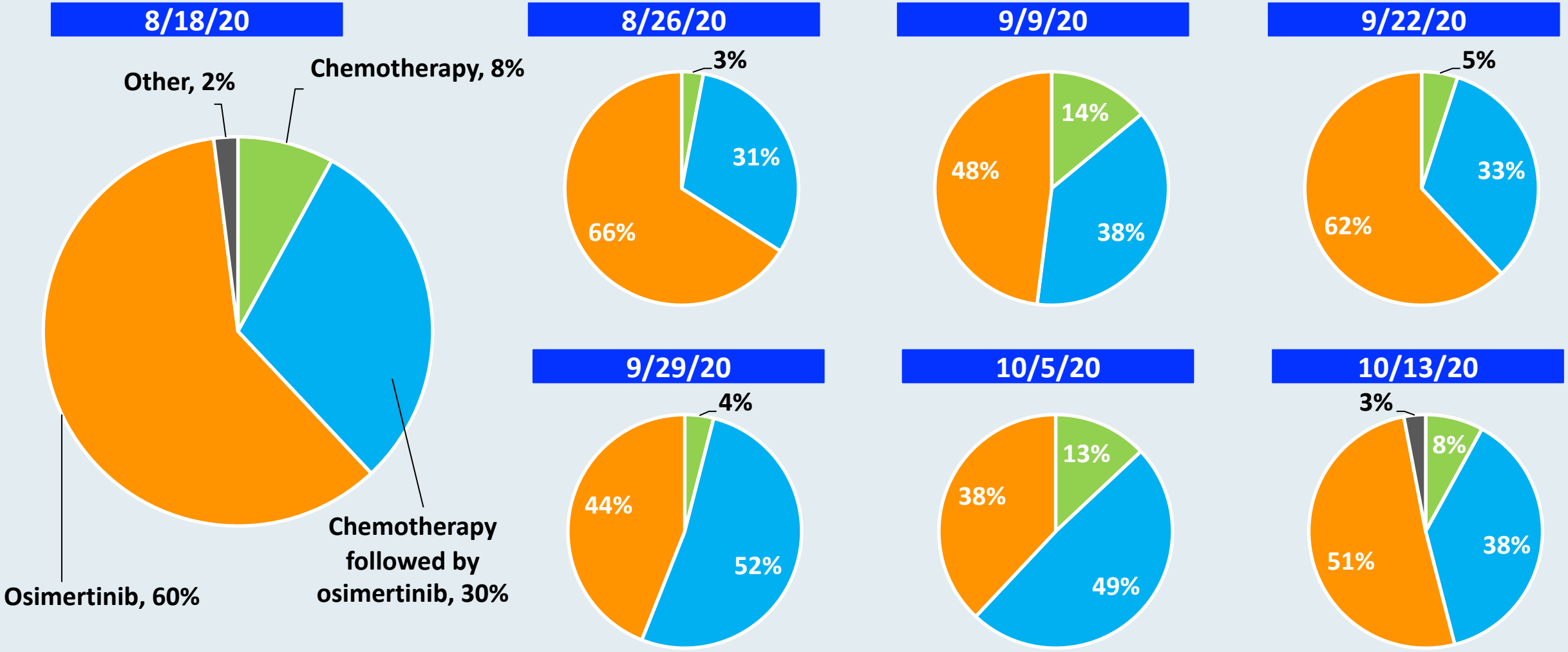
Courtesy of Roy S Herbst, MD, PhD

Regulatory and reimbursement issues aside, which adjuvant systemic therapy would you generally recommend for a patient with Stage IIB nonsquamous NSCLC and an EGFR exon 19 deletion?

1. Chemotherapy
2. Osimertinib
3. Chemotherapy followed by osimertinib
4. Other

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, which adjuvant systemic therapy would you generally recommend for a patient with Stage IIB nonsquamous NSCLC and an EGFR exon 19 deletion?



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., for the ADAURA Investigators*

N Engl J Med 2020;[Epub ahead of print].

ADAURA Phase III double-blind study design

Adult patients with completely resected stage* IB, II, IIIA EGFRm NSCLC, <u>with or without adjuvant chemotherapy</u>

Key eligibility criteria:
- WHO performance status 0 / 1
- Confirmed primary, non-squamous, non-metastatic NSCLC
- MRI or CT scan of the brain prior to surgery or randomization
- **Prior, post, or planned radiotherapy was not allowed**
- **Complete resection with negative margins (open surgery or VATS allowed; wedge resection or segmentectomy not allowed)†**
- **Max. interval between surgery and randomization 10 / 26 weeks without / with adjuvant chemotherapy**
- **Major surgery within 4 weeks of the first dose of study drug was not allowed**

Stratification by:
stage (IB vs II vs IIIA)
EGFRm (Ex19del vs L858R)‡
race (Asian vs non-Asian)

Randomization 1:1 (N=682)

Osimertinib 80 mg, once daily

Placebo, once daily

3-yr treatment until recurrence / treatment completion / discontinuation §

<u>Primary endpoint:</u> investigator-assessed DFS in stage II / IIIA (designed for superiority under assumed DFS HR 0.70)

<u>Secondary endpoints:</u>
- DFS in the overall population**
- DFS at 2, 3, 4, and 5 yr
- OS
- Safety
- HRQoL

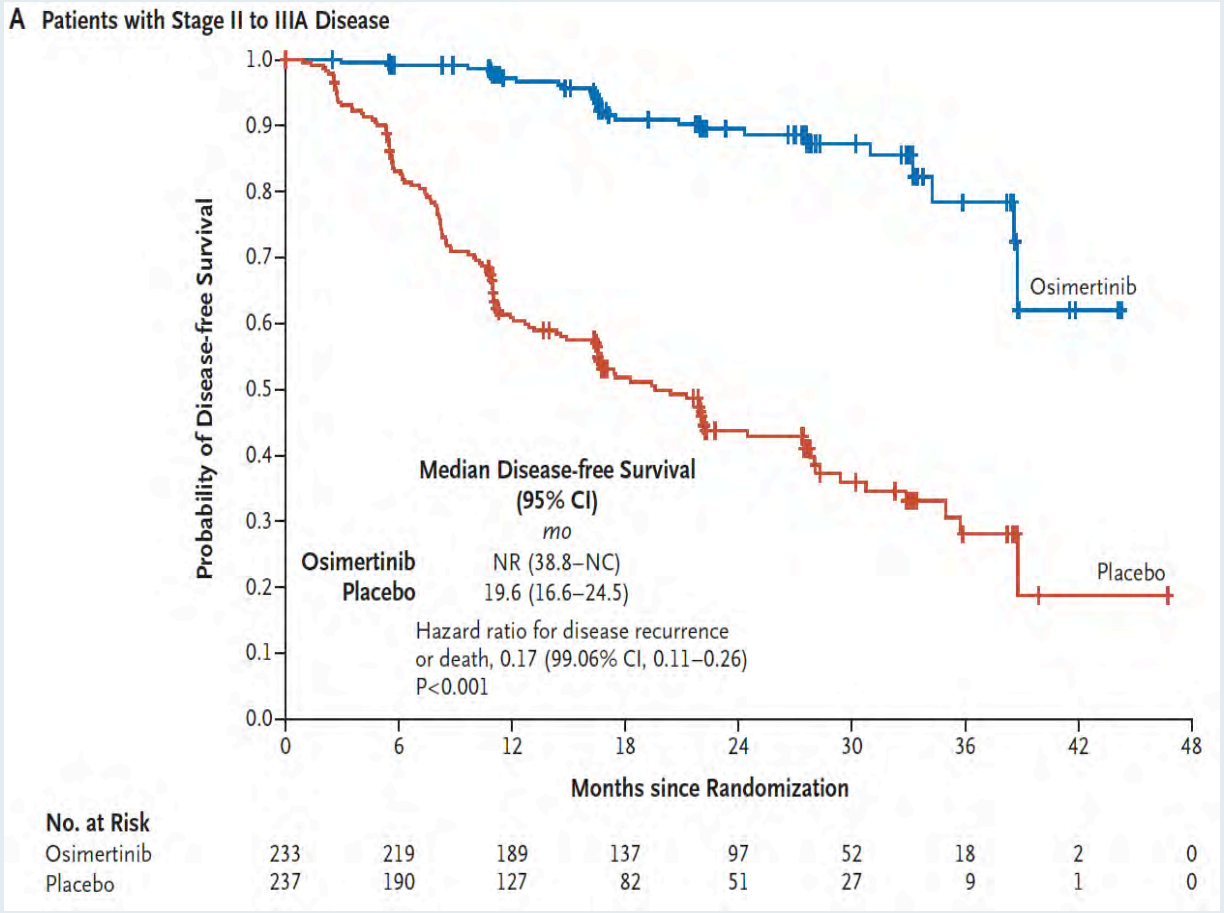
<u>Pre-specified exploratory endpoint:</u>
assessment of site(s) of recurrence, including CNS

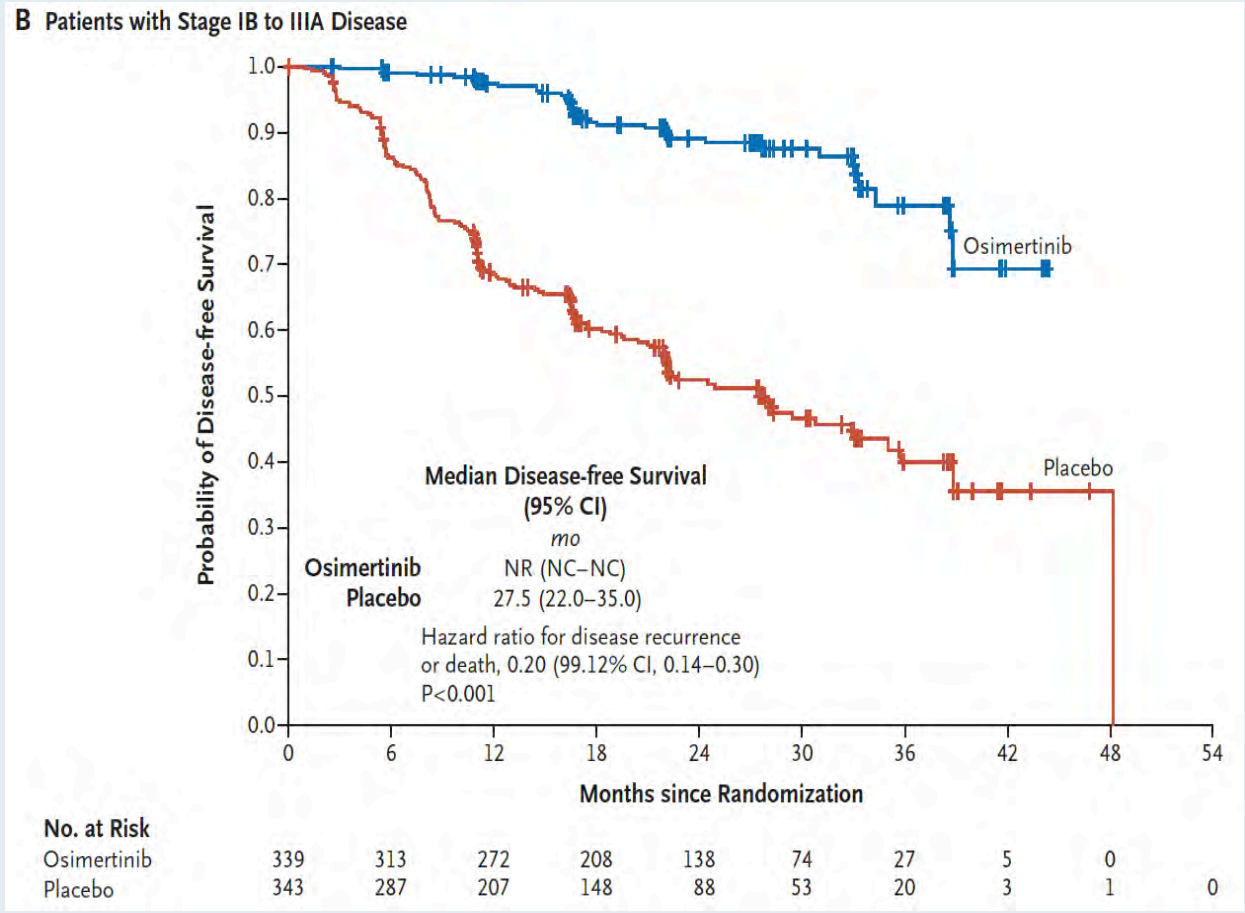
- **Following IDMC recommendation, the study was unblinded early due to efficacy; here we report an unplanned interim analysis**
  - **At the time of unblinding the study had completed enrollment and all patients were followed up for at least 1 yr**

Wu et al., DOI: 10.1056/NEJMoa2027071. NCT02511106. ADAURA data cut-off: January 17, 2020. *AJCC 7th edition; †Patients received a CT scan after resection and within 28 days prior to treatment; surgery may consist of lobectomy, sleeve resection, bilobectomy, or pneumonectomy; ‡Centrally confirmed in tissue; §Follow up until recurrence: week 12 and 24, then every 24 weeks to 5 years, then yearly; follow-up after recurrence: every 24 weeks for 5 years, then yearly. **Stage IB / II / IIIA. CT, computed tomography; Ex19del, exon 19 deletion; IDMC, Independent Data Monitoring Committee; HR, hazard ratio; HRQoL, health-related quality of life; MRI, magnetic resonance imaging; VATS, Video Associated Thoracic Surgery; WHO, World Health Organization.

Courtesy of Roy S Herbst, MD, PhD

ADAURA: Disease-Free Survival by Stage

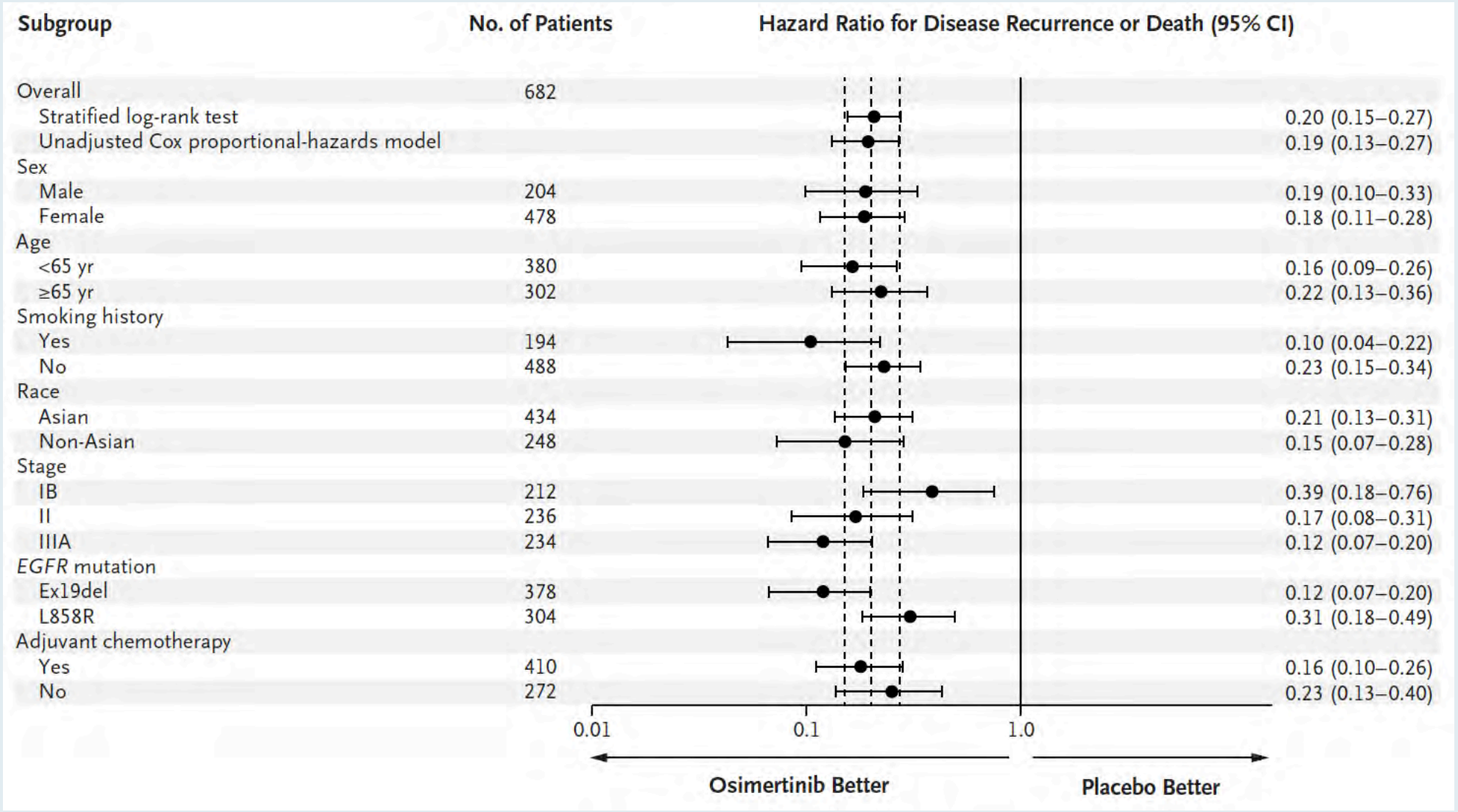




Wu YL et al. *N Engl J Med* 2020;[Epub ahead of print].

RTP RESEARCH TO PRACTICE

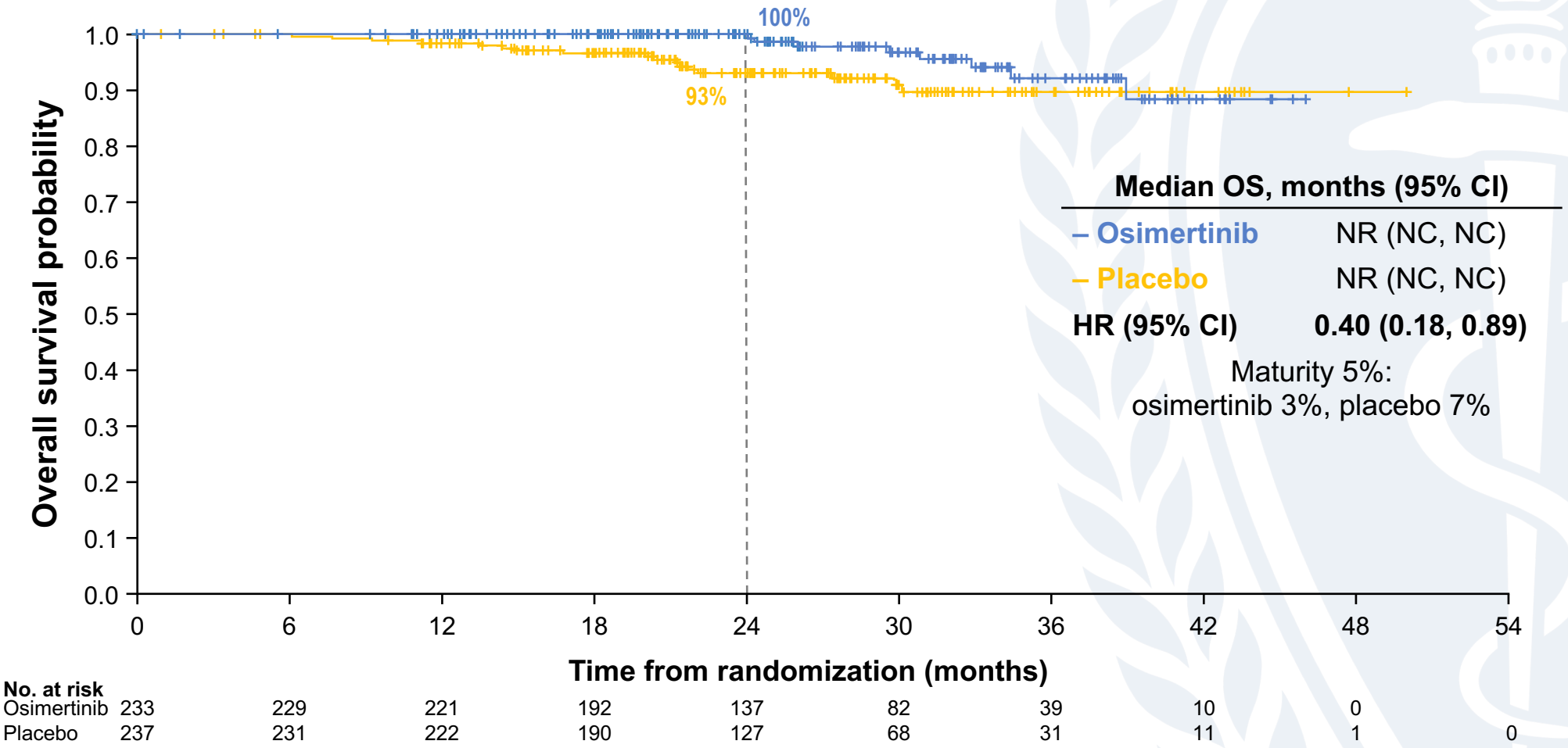
ADAURA: Subgroup Analysis of Disease-Free Survival



Wu YL et al. *N Engl J Med* 2020;[Epub ahead of print].

RTP RESEARCH TO PRACTICE

Early snapshot: overall survival in patients with stage II/IIIA disease



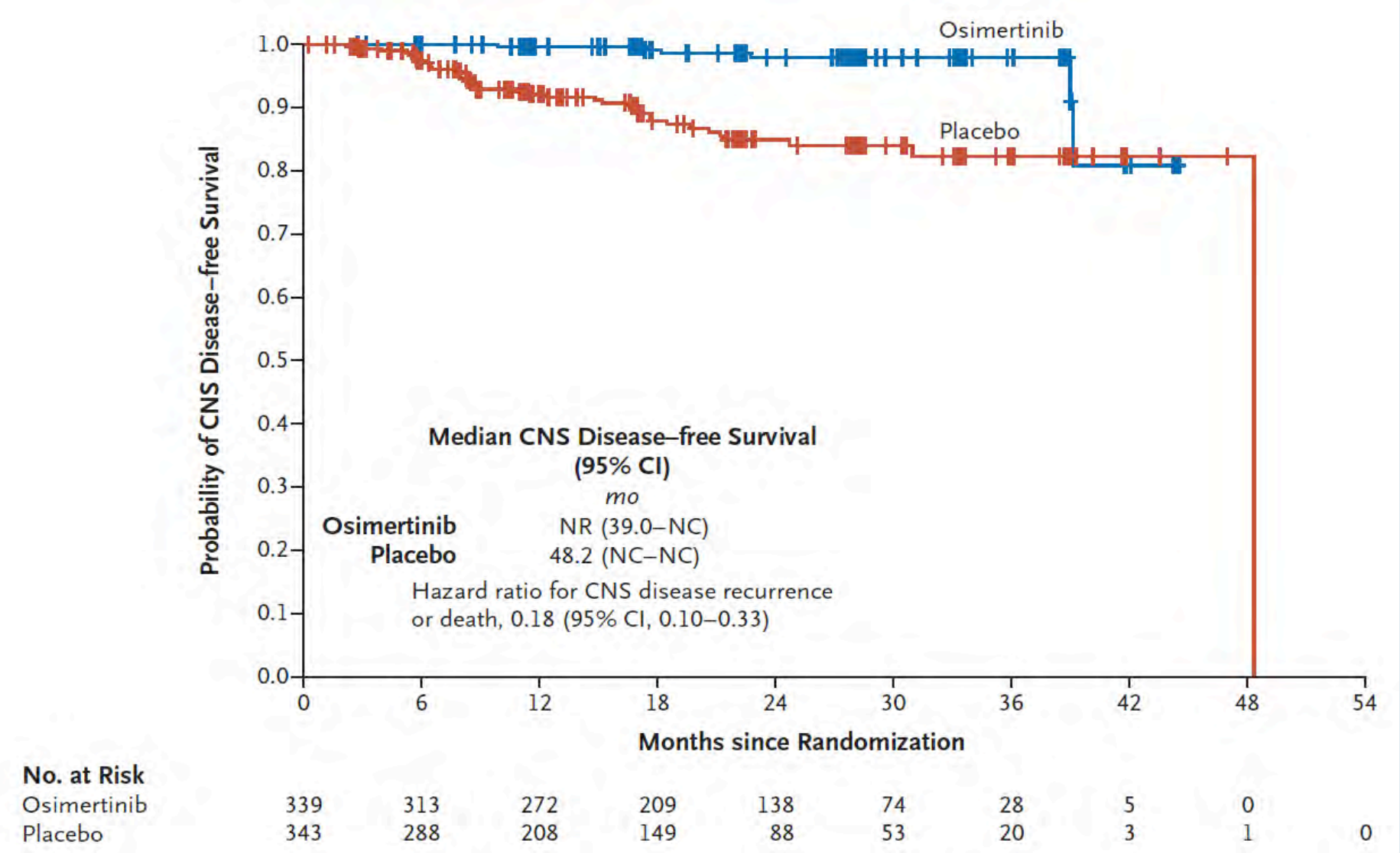
Median OS, months (95% CI)	
– Osimertinib	NR (NC, NC)
– Placebo	NR (NC, NC)
HR (95% CI)	**0.40 (0.18, 0.89)**

Maturity 5%:
osimertinib 3%, placebo 7%

ADAURA data cut-off: January 17, 2020. Median follow-up: osimertinib 26.1, placebo 24.7 months. Tick marks indicate censored data.

Courtesy of Roy S Herbst, MD, PhD

ADAURA: CNS Disease-Free Survival



Wu YL et al. *N Engl J Med* 2020;[Epub ahead of print].

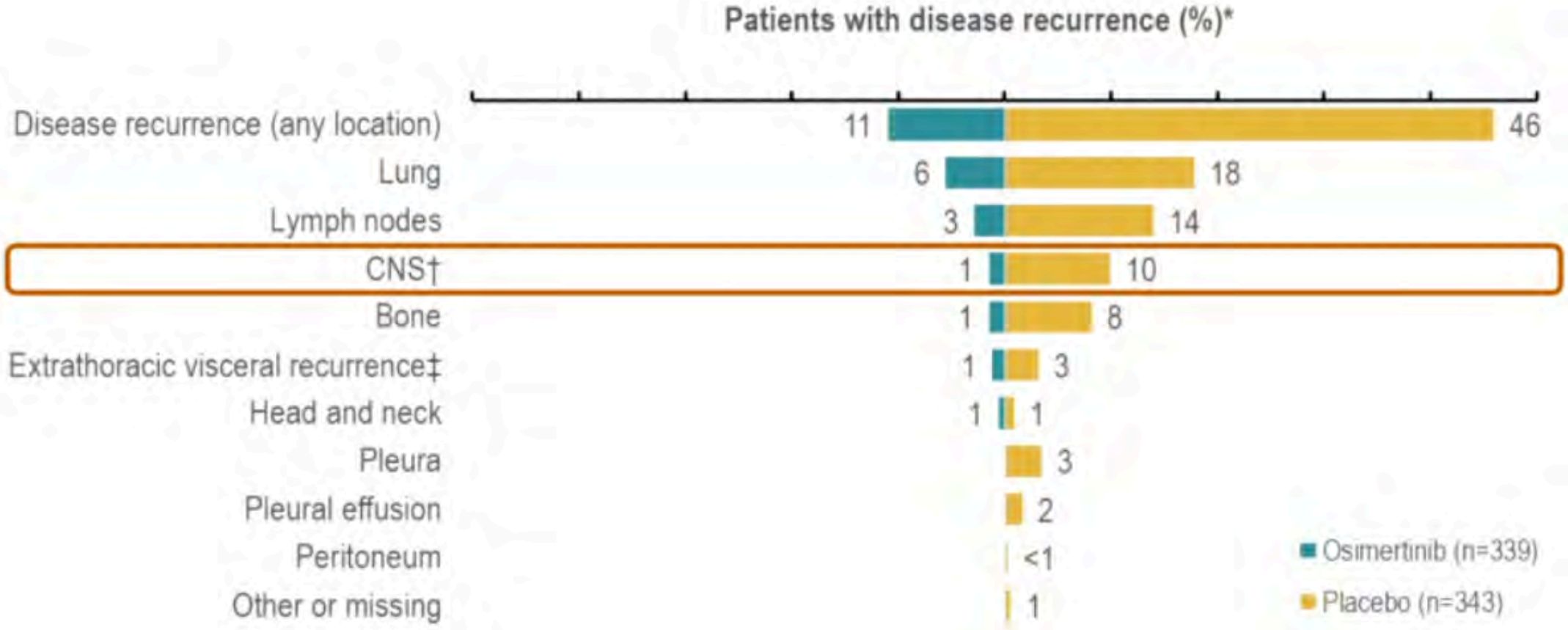
RTP RESEARCH TO PRACTICE

Osimertinib Adjuvant Therapy in Patients (pts) with Resected EGFR Mutated (EGFRm) NSCLC (ADAURA): Central Nervous System (CNS) Disease Recurrence

Tsuboi M et al.

ESMO 2020;Abstract LBA1.

ADAURA: Sites of Disease Recurrence



Tsuboi M et al. ESMO 2020;Abstract LBA1.

RTP RESEARCH TO PRACTICE

ADAURA: CNS DFS Events

- Overall, 45 patients (osimertinib n=6, placebo n=39) had CNS DFS events

	Overall population	
Patients, n (%)	**Osimertinib n=339**	**Placebo n=343**
CNS DFS events:	6 (2%)	39 (11%)
CNS recurrence	4 (1%)	33 (10%)
Death	2 (1%)	6 (2%)

Tsuboi M et al. ESMO 2020;Abstract LBA1.

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MODULE 4: Management of locally advanced disease with EGFR mutation

MODULE 5: ADAURA trial: Adjuvant therapy for NSCLC with EGFR mutation

MODULE 6: Treatment of NSCLC with EGFR exon 20 alterations

MODULE 7: Optimal approach to oligoprogression of NSCLC with EGFR mutation

Case Presentation – Dr Brenner: A 67-year-old woman with metastatic NSCLC with hepatic and blastic bone metastases and an exon 20 mutation

Warren S Brenner, MD

- November 2018: Metastatic adenocarcinoma of the lung with liver metastases and extensive blastic bone metastases predominantly in the left hip
- EGFR exon 20 mutation; PD-L1 negative
- December 2018: Initiation of carboplatin/pemetrexed/bevacizumab; palliative radiation to the hip
- Disease progression

Question

- What is the best treatment option for a patient with an EGFR exon 20 mutation?

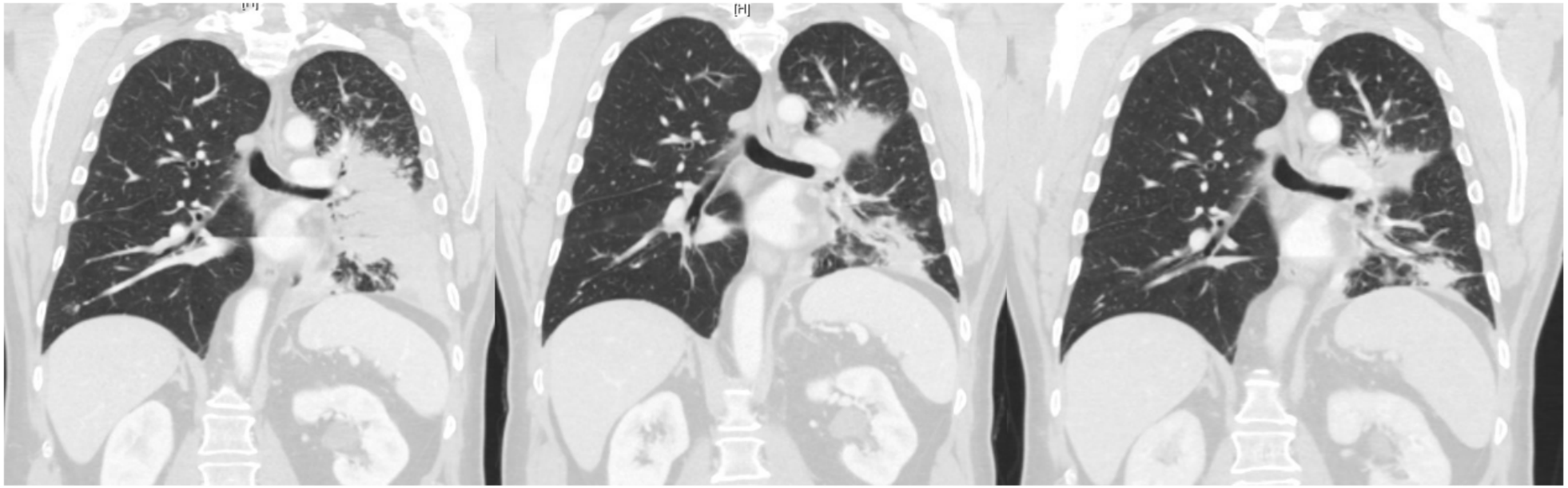
Case Presentation – Dr Yu: A 47-year-old woman with pan-wild-type Stage IV NSCLC

47 yo woman, never-smoker, who initially presented with stage 4 lung cancer with metastases to liver, bone, and brain.

- She was tested for EGFR ex19 deletion, EGFR L858R by ddPCR testing, and ALK and ROS1 by FISH and was negative for all.
- She started chemotherapy with carboplatin, pemetrexed and bevacizumab and was maintained on maintenance pemetrexed/bevacizumab for 12 months. She ultimately had PD in the liver and lung. She was then on docetaxel for 6 months with further progression in her lungs.
- She had a repeat biopsy and had genetic testing performed on the sample and an EGFR p.N771_H773dup alteration was identified.
- She was started on the TAK-788 (mobocertinib study)

Courtesy of Helena Yu, MD

Case Presentation – Dr Yu: 47-year-old woman with pan-wild-type Stage IV NSCLC (continued)



baseline 2 months 4 months

- Her cough improved within 2 weeks and she had a partial response (38% shrinkage in her target lesions)
- She was dose reduced from 160mg to 120mg QD due to diarrhea and nausea and remains on treatment 14 months later.

Courtesy of Helena Yu, MD

ECOG-ACRIN 5162: A Phase II Study of Osimertinib 160 mg in NSCLC with EGFR Exon 20 Insertions

Piotrowska Z et al.
ASCO 2020;Abstract 9513.

Agenda

MODULE 1: Overview of EGFR tumor mutations; selection of first-line therapy

MODULE 2: First-line treatment of NSCLC with EGFR mutation and brain metastases

MODULE 3: Progressive disease with EGFR mutation; resistance mutations

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Case Presentation – Dr Freedman: An 81-year-old woman with metastatic NSCLC and an EGFR C797S resistance mutation

Allen Freedman, MD

- 2018: Presented with cough and left upper back pain
- CT/PET scan showed mass in the lingula and a metastasis to the first lateral rib and T4
- Poorly differentiated non-small cell lung cancer
- EGFR mutations: Missense in exon 18; missense in exon 20
- Treated with osimertinib and palliative radiation with response
- September 2020: Developed gait instability, MRI revealed multiple brain lesions
- Liquid biopsy: Low level mutations – C797S; PIK3CA

Questions

- What is the best treatment option?
- Should current therapy be continued?

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Case Presentation – Dr Ramalingam: A 57-year-old woman with metastatic adenocarcinoma of the lung and an EGFR exon 19 deletion mutation and an EGFR C797S mutation

- 57-year-old female
- Left upper lobe wedge resection for 1.2 cm adeno in 2010
- SRS to right upper lobe lesion in 2012
- Advanced stage disease diagnosed in July 2018
- EGFR exon 19 del mutation
- Started on osimertinib in Aug 2018
- Oligo-progression in right upper lobe
- S/P right upper lobectomy
- Positive for EGFR C797S mutation
- Continues on Osimertinib

Courtesy of Suresh Ramalingam, MD

Winship Cancer Institute | Emory University

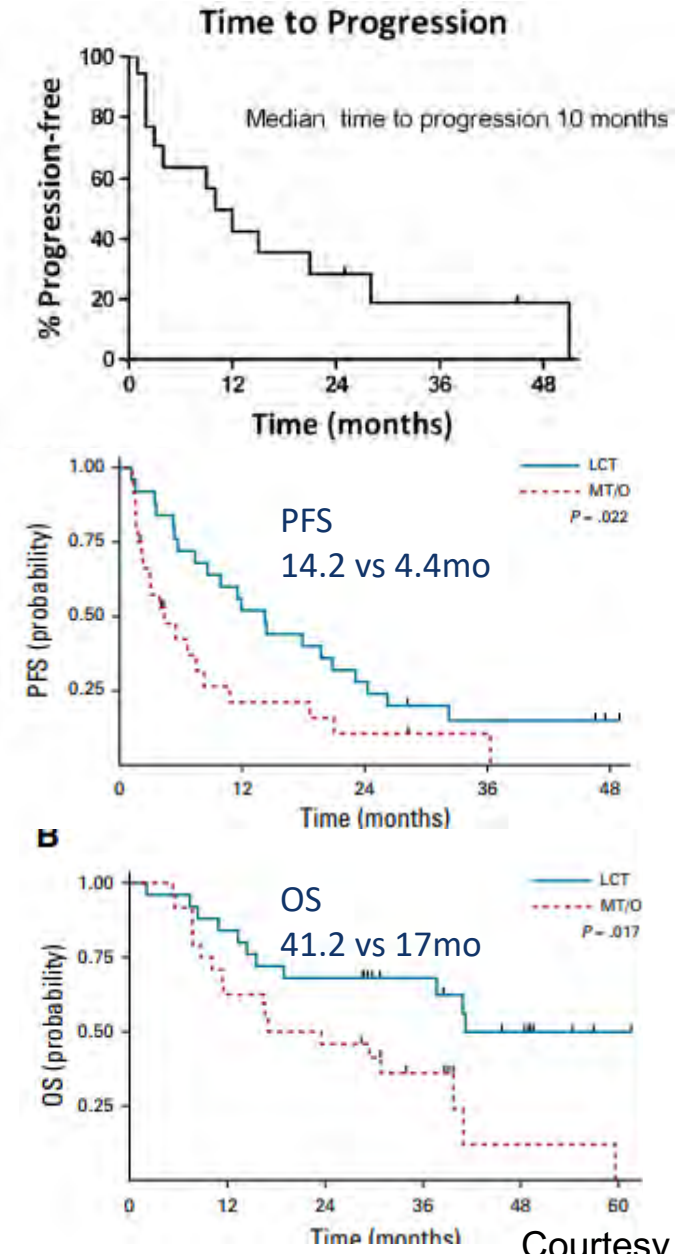
Local therapy for oligoprogression

Patients with oligoprogression are best served by local therapy and continuing same EGFR TKI

- A subset of patients have oligoprogression: ~20% progress in a solitary lesion, ~15% progress in the CNS only
- Local therapy + continued EGFR TKI delays time until new systemic treatment is required, median TTP 10 months after local therapy

Consolidative local therapy at minimal residual disease and continuing EGFR TKI is another reasonable strategy

- Another strategy is local consolidative therapy after ≥ 3 months of systemic therapy at minimal residual disease
- Study closed early by DSMB. PFS and OS benefit with local therapy



Memorial Sloan Kettering Cancer Center

Yu JTO 2013, Gomez JCO 2019

Courtesy of Helena Yu, MD

Optimizing the Role of Radiation Oncologists and Other Multidisciplinary Team Members in the Management of Locally Advanced Non-Small Cell Lung Cancer

Tuesday, October 20, 2020
5:00 PM – 6:00 PM ET

Faculty

Walter J Curran Jr, MD
Camille Usher, MS, APRN, NP-C

Moderator

Neil Love, MD

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Thank you for joining us!

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

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