Addressing Lung Cancer Biomarker Testing Through Project ECHO: Session 3

8.26.2021

This project is generously supported by Amgen Oncology

Welcome to Session 3 of the Addressing Lung Cancer Biomarker Testing Through Project ECHO Pilot

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Use the buttons in the *black* menu bar to unmute your line and to turn on your video.
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Today's materials will be made available to you

Please type your name and organization in the chat box

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COMBINED SESSION 3

Introductions, Session 1 Poll Results, & Agenda Preview

Robert Smith, PHD

Senior Vice President, Cancer Screening

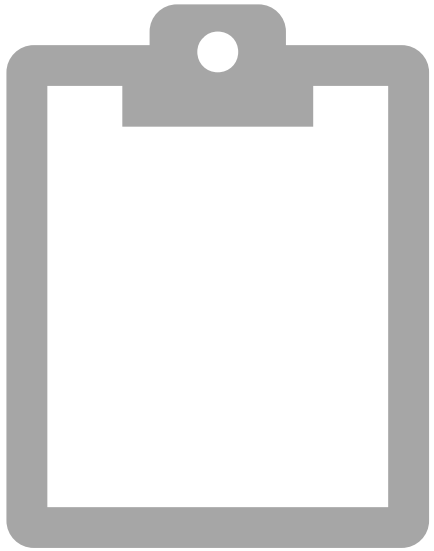
American Cancer Society

Today's Agenda

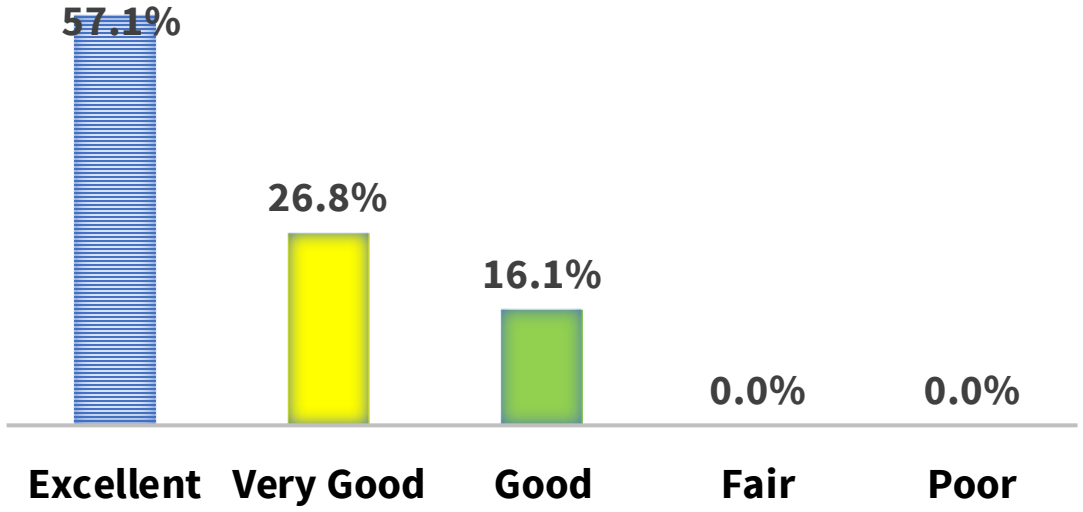
01	**Agenda Preview, Poll Results & Introductions** (10 minutes)
02	**Didactic Presentation: *Adequate Tissue for Sampling*** (15 minutes)
03	**Didactic Q/A** (5 minutes)
04	**Case Presentation** (5 minutes)
05	**Case Presentation Recommendations & Discussion** (15 minutes)
06	**Post-Session Poll & Wrap Up** (5 minutes)

Post-Session Poll Results:

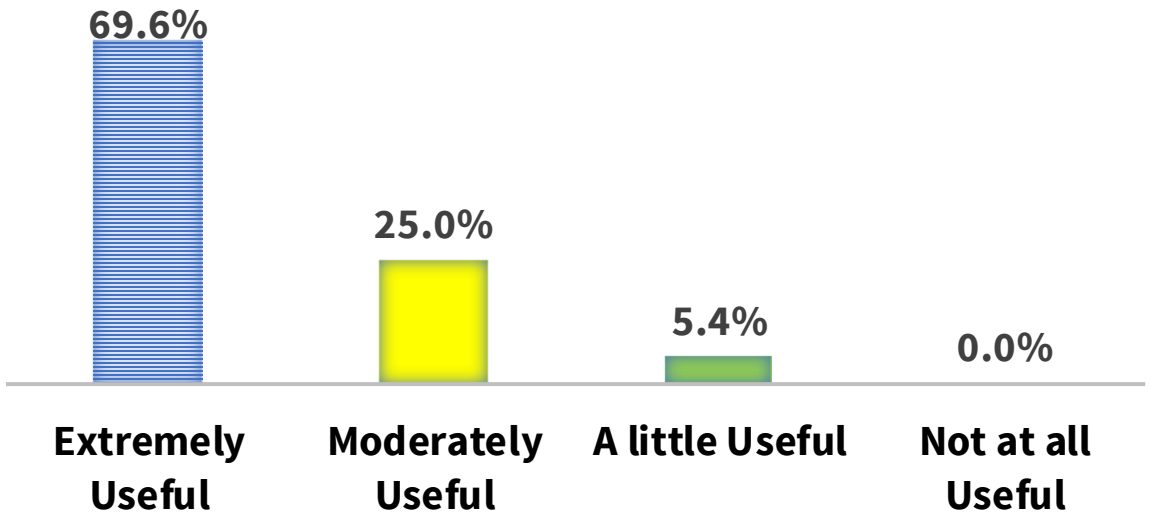
6.28.2021 Combined Session 1



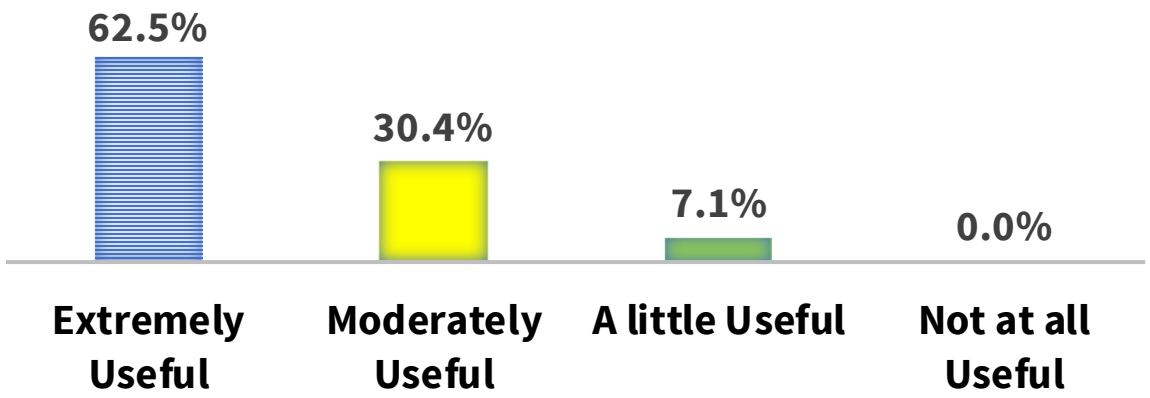
Q1: Overall, how would you rate today's ECHO session?



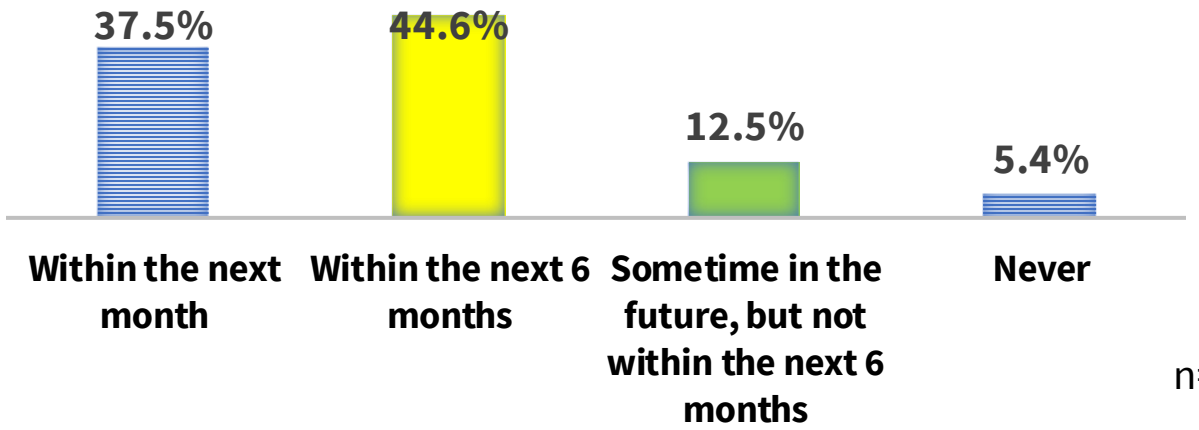
Q2: Please rate the usefulness of today's didactic presentation to your work:



Q3: Please rate the usefulness of today's case presentation section to your work:



Q4: When do anticipate putting what you learned from today's session into practice?



n=56

Faculty Introductions

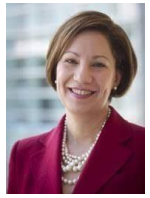
Meet Our

17

Faculty Members

Farhood Farjah, MD, MPH
University of Washington
NLCRT Faculty Member

Bruce Johnson, MD
Dana-Farber Cancer Institute
NLCRT Faculty Member

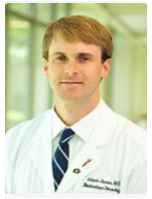


Patricia Rivera, MD
University of North Carolina
NLCRT Faculty Member

Gerard Silvestri, MD, MS
Medical University of South Carolina
NLCRT Faculty Member

Ignacio Wistuba, MD
MD Anderson Cancer Center
NLCRT Faculty Member

Eric Flenaugh, MD
Grady Health System
GA Faculty Member



Adam Jones, MD
Phoebe Putney Health System
GA Faculty Member

Suresh Ramalingam, MD
Winship Cancer Institute
GA Faculty Member

Zhonglin Hao, MD, PHD
UK Markey Cancer Center
KY Faculty Member

Jill Kolesar, PharmD, MS
UK Markey Cancer Center
KY Faculty Member

Tim Mullett, MD, MBA
UK Markey Cancer Center
KY/NLCRT Faculty Member

Shadi Qasem, MD, MBA
UK Markey Cancer Center
KY Faculty Member

John Villano, MD, PHD
UK Markey Cancer Center
KY Faculty Member

Ralph Zinner, MD
UK Markey Cancer Center
KY Faculty Member

Ray Osarogiagbon, MBBS
Baptist Cancer Center
MS/NLCRT Faculty Member

Pierre De Delva, MD
UMMC Cancer Center & Research Institute
MS Faculty Member

NLCRT= National Lung Cancer Roundtable Link

Michal Senitko, MD
UMMC Cancer Center & Research Institute
MS Faculty Member

Spoke (Chat) Introductions

Meet Our

21

Spoke Sites

Georgia Spoke Sites

Atrium Health Navicent
Augusta University/Georgia Cancer Center
Northeast Georgia Medical Center
Northside Hospital Cancer Institute
Phoebe Putney Health System
Piedmont Columbus Regional, JBACC
St. Joseph's/Candler Health System/Lewis Cancer & Research Pavilion

Kentucky Spoke Sites

Highlands ARH Regional Medical Center
Lake Cumberland Regional Hospital
St. Claire Healthcare
LifePoint Central Kentucky: Clark Regional Medical Center & Georgetown Community Hospital
Taylor Regional Hospital

All spokes in Kentucky are part of the UK Markey Affiliate Network

Mississippi Spoke Sites

Baptist Cancer Centers
Forrest General Hospital/ Hattiesburg Clinic
Jackson Oncology Associates
North Mississippi Health Services
St. Dominic's Hospital
Singing River Health System
Southwest Mississippi Regional Medical Center
UMMC Cancer Center & Research Institute
G.V. (Sonny) Montgomery VA Medical Center

Thank you for your participation!

Reminder: Please type your *name* and *organization* in the chat box

Context Setting

COMBINED SESSION 3

Didactic Presentation:
Adequate Tissue for Sampling

Gerard Silvestri, MD, MS

Hillenbrand Professor of Thoracic Oncology

Medical University of South Carolina

Tissue Acquisition and Biomarker Testing in the Community and Academic Settings

Gerard A. Silvestri MD, MS
Hillenbrand Professor of Thoracic Oncology
Division of Pulmonary and Critical Care
Medical University of South Carolina
Charleston, SC
Email: silvestri@musc.edu

Disclosures

Source	Research Funding	Consulting
NIH NCI R01	X	
PCORI	X	
Exact Sciences	X	X
Oncocyte	X	
Olympus	X	X
Biodesix	X	X
Veran medical	X	
Auris Medical	X	X
Aries pharmaceutical	X	X
Boston Scientific	X	
SEER	X	
Amgen	X	
Nucleix	X	X

Outline

- Historical perspective
- EBUS-TBNA
- Biomarker Testing
- Liquid Biopsy
- Challenges

Overview of NSCLC Treatment

		5 yr. survival
Stage I	Surgery (Radiation if inoperable) Targeted therapy for 1B EGFR +	68-90%
Stage II	Surgery With Adjuvant Chemotherapy or Targeted therapy for EGFR +	50-60%
Stage III	Chemotherapy with radiation therapy, Adjuvant Immunotherapy or Targeted therapy	13-35%
Stage IV or Recurrent Disease	Chemotherapy Targeted Therapy Immunotherapy Supportive Care	0-10%

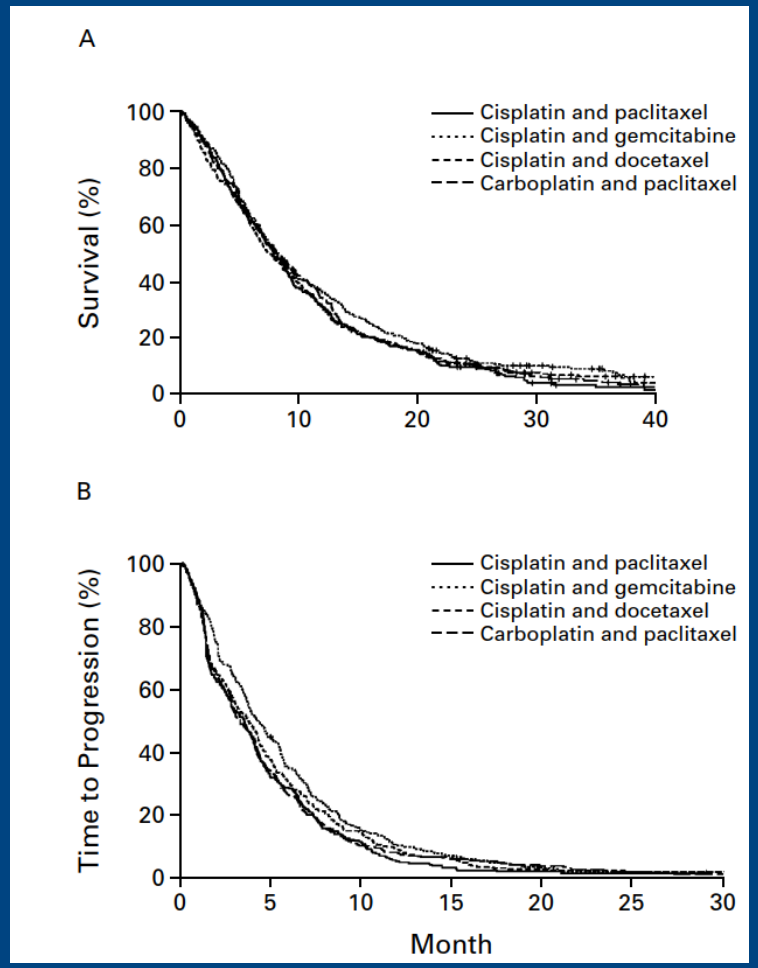
Survival based on IASLC 8th ed

Accuracy of Staging Tests in Lung Cancer Patients

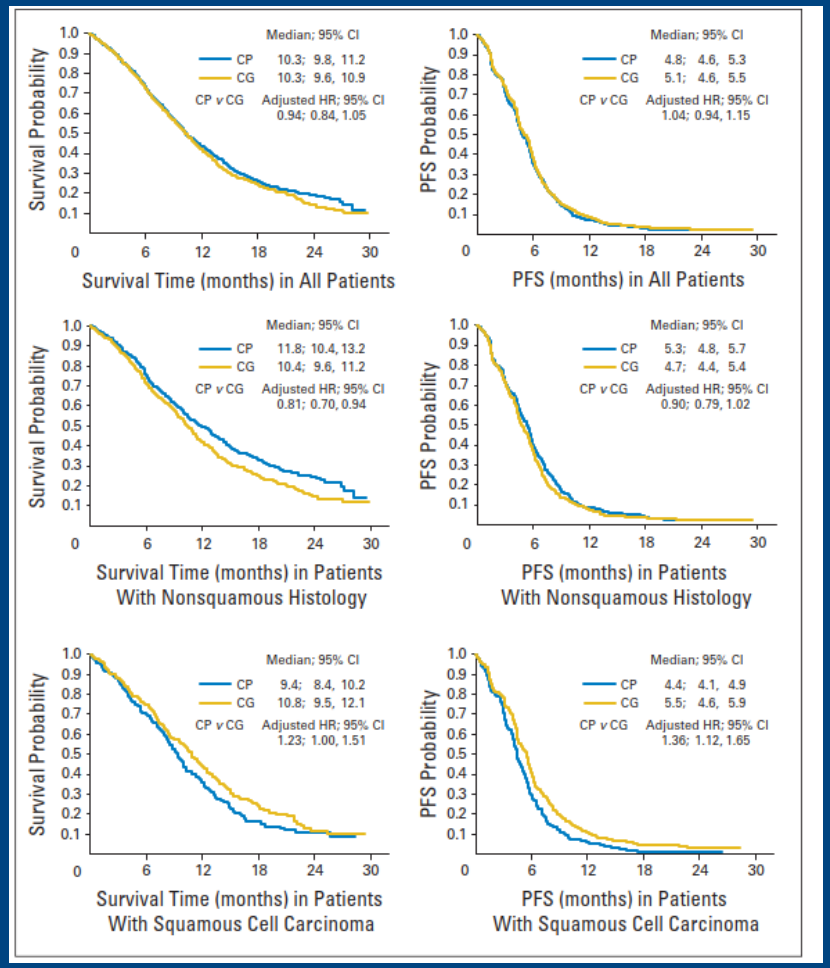
Procedure	Number of Studies	N	Sens	Spec
Mediastinoscopy	**35**	**10,648**	**81**	**100**
EUS	**26**	**2,443**	**89**	**100**
EBUS	**26**	**2,756**	**89**	**100**
EBUS/EUS	**7**	**811**	**91**	**100**

Silvestri et al, CHEST 2013;143

Lest we forget… from whence we came

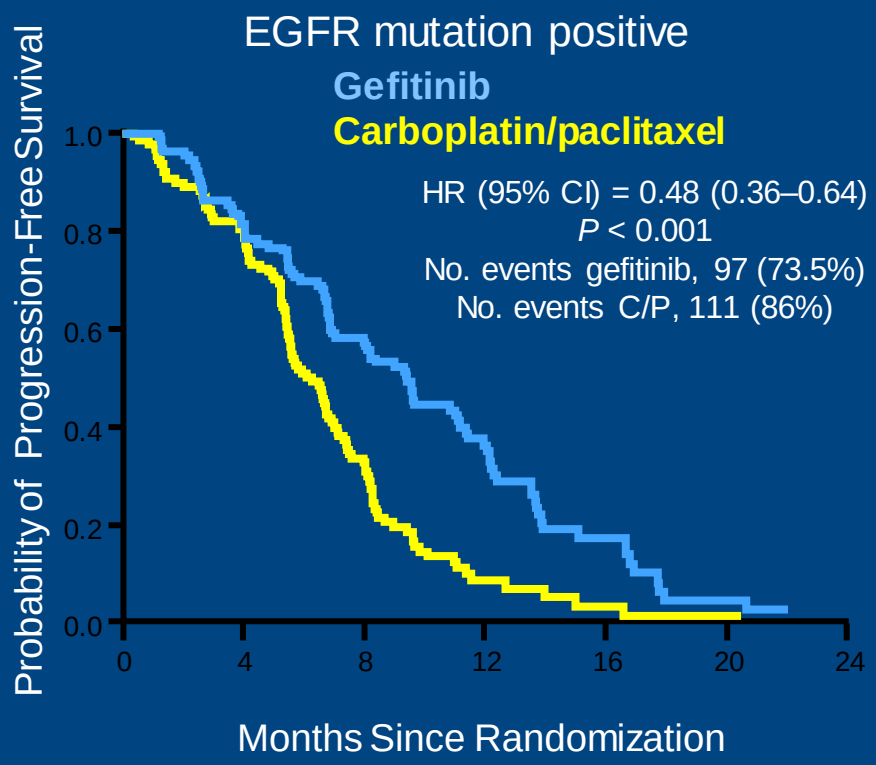


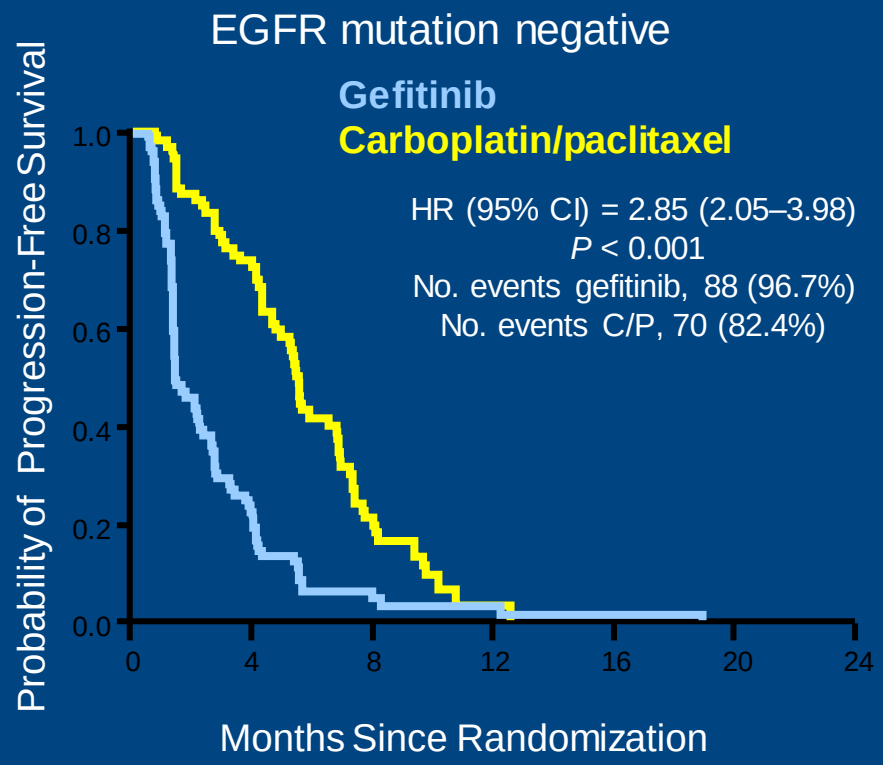
Schiller JH, et al. N Engl J Med 2002, 246:92



Scagliotti GV et al. J Clin Oncol 2008, 26:3543

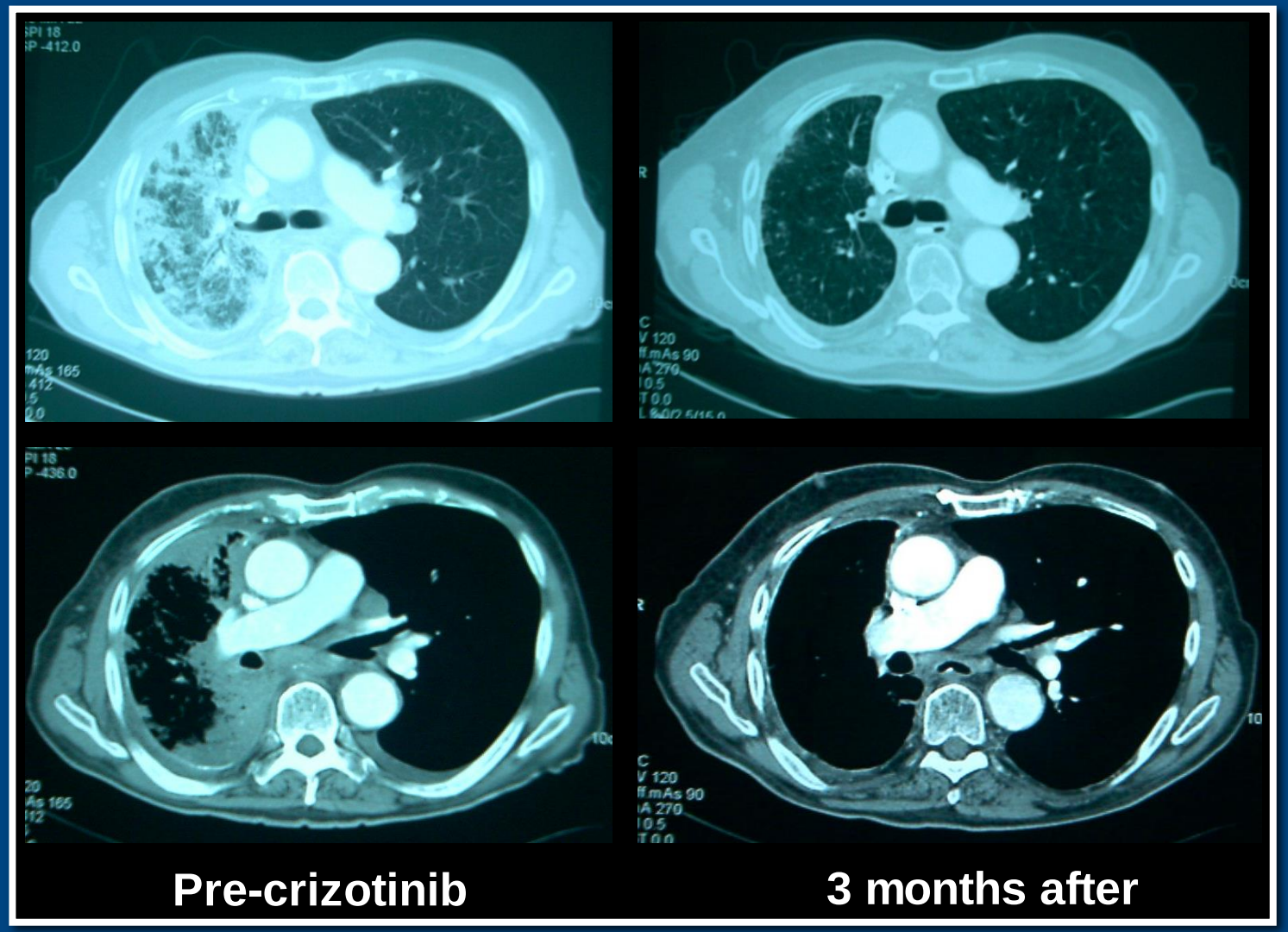
Progression-free Survival by *EGFR* Mutation and Treatment (12 month progression free survival 25% vs. 6.7%. Non-smoking Eastern Asians)



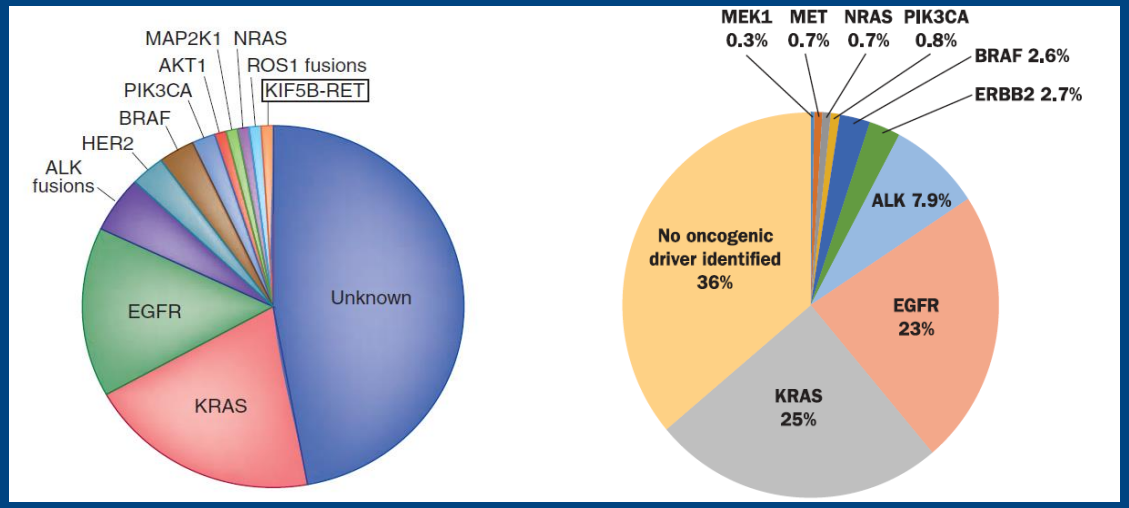


Mok TS, et al. *N Engl J Med*. 2009;361(10):947-957.

Response to EGFR TKIs

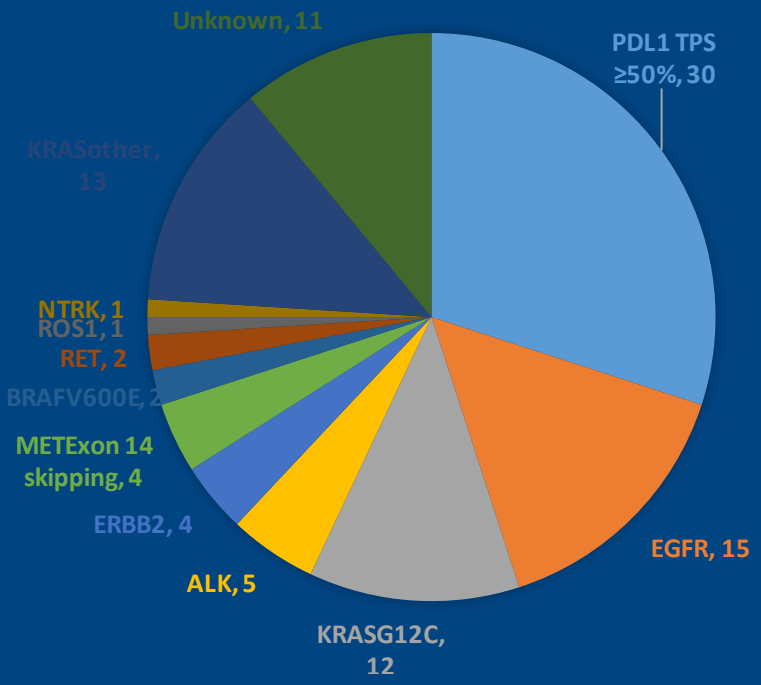


Non-Squamous Non-Small Cell Lung Cancer Biomarkers



Pao and Hutchinson 'Chipping away at the lung cancer genome'
Nature Medicine. **March 2012**

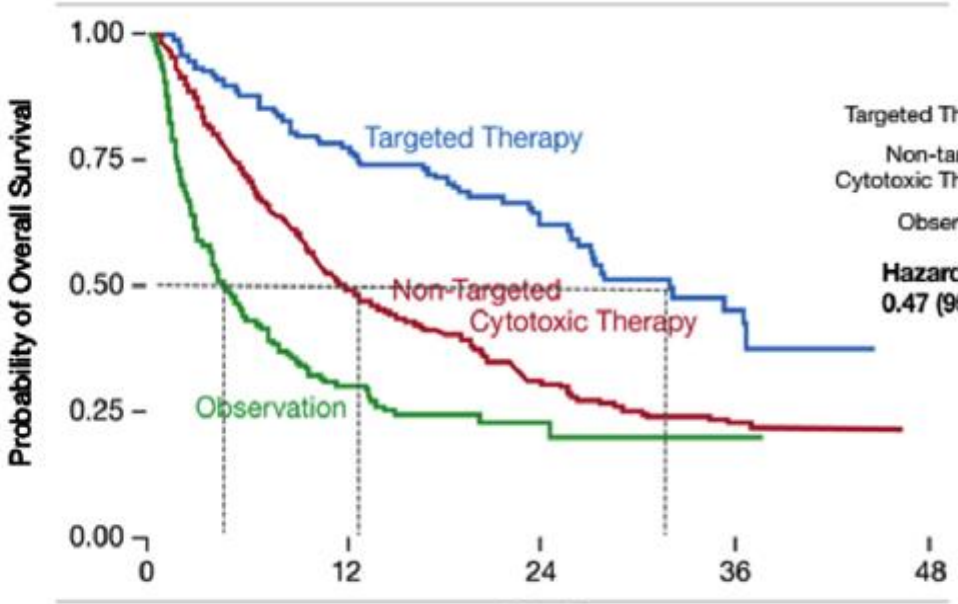
Scholl et al. Lung Cancer Mutation Consortium
J Thorac Oncol. **May 2015**



2020: biomarkers with drug targets

Are Lung Cancer Biomarkers being used?

814 patients (89% stage IV; 11% stage IIIB), 59% should have been tested but only 8% underwent genetic profiling.



	No. of Patients	Events	Median OS Mo (95% CI)
Targeted Therapy	131	58	31.8 (26.8-NA)
Non-targeted Cytotoxic Therapy	482	309	12.7 (11.0-15.5)
Observation	192	118	5.1 (3.9-7.3)

Hazard ratio for death (Targeted vs Non-targeted): 0.47 (95% CI, 0.36 to 0.63), Log rank p < 0.0001

No. at Risk					
Targeted Therapy	131	98	56	19	0
Non-targeted Cytotoxic Therapy	482	236	82	37	0
Observation	192	47	9	1	0

Gutierrez et al. Clinical Lung Cancer 2017;18:651

The expanding role of biomarker testing

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*

Wu et al. NEJM 2020, 383: 1711-1723

The expanding role of biomarker testing

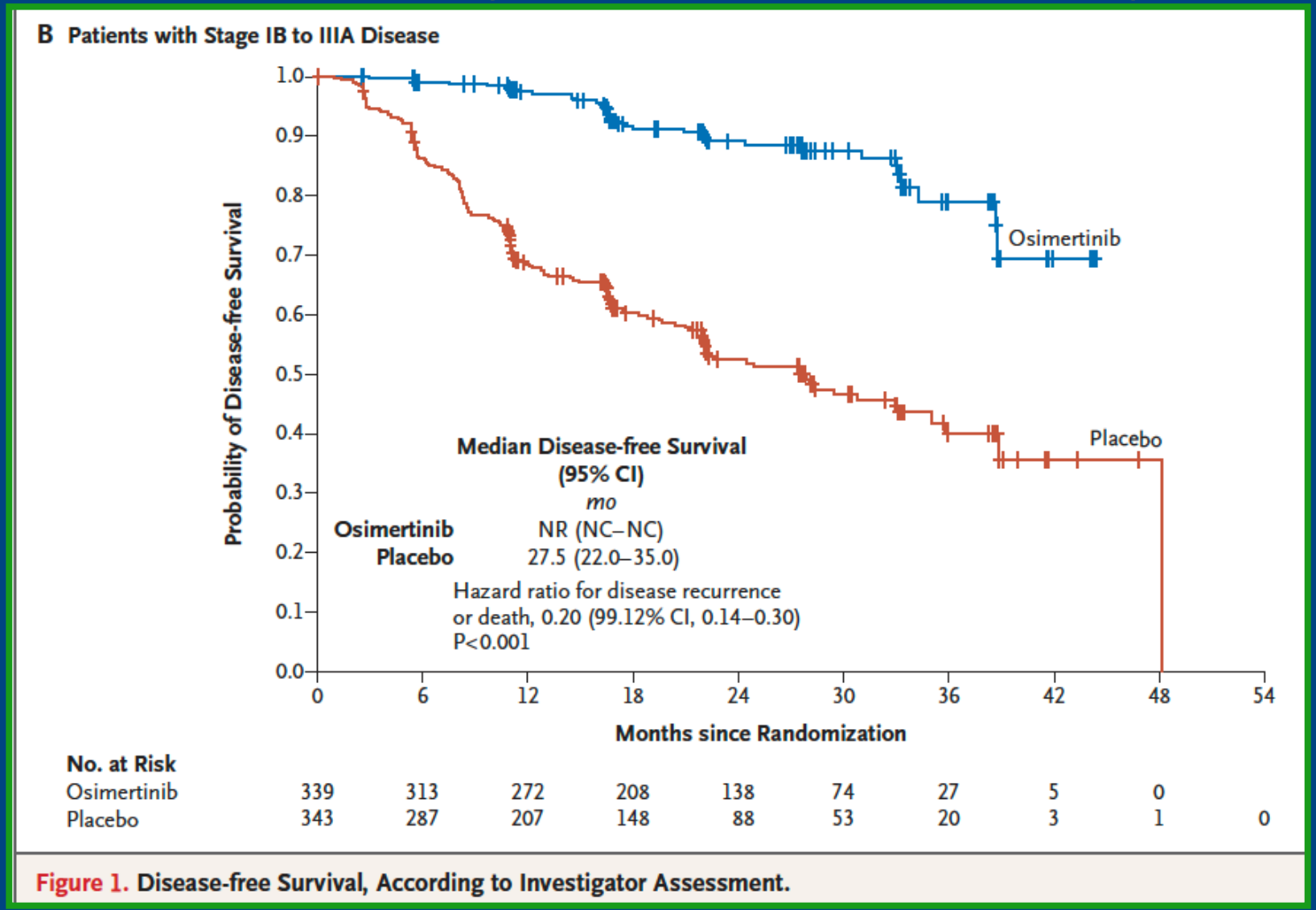


Figure 1. Disease-free Survival, According to Investigator Assessment.

Wu et al. NEJM 2020, 383: 1711-1723

Biomarkers for Lung Cancer Treatment September 2020

Target	Prevalence	Initial FDA Approval	Drugs
EGFR	10-15%	2003	Gefitinib, Erlotinib, Afatinib, Osimertinib
ALK	2-7%	2011	Crizotinib, Ceritinib, Alectinib, Lorlatinib, Brigantinib
R0S-1	1-2%	2016	Crizotinib, Entrectinib, Ceritinib, Lorlatinib
PD-L1 TPS 50%	30%	2016	Pembrolizumab, Atezolizumab
B-RAF^{V600E}	2%	2017	Dabrafenib+Trametinib, Vemurafenib
NTRK	0.2-3%	2018	Larotrectinib, Entrectinib
HER-2 (ERBB2)	2-5%	May 2020	Trastuzumab deruxtecan (Enhertu)
MET exon 14 skipping	3-4%	May 2020	Capmatinib; ?Tepotinib?, Crizotinib
RET	1-2%	September 4, 2020	Salpercatinib, Pralsetinib, Carbozantinib, Vandetanib
K-RAS ^{G12C}	12%	?	AMG510

2020 NCCN Guidelines

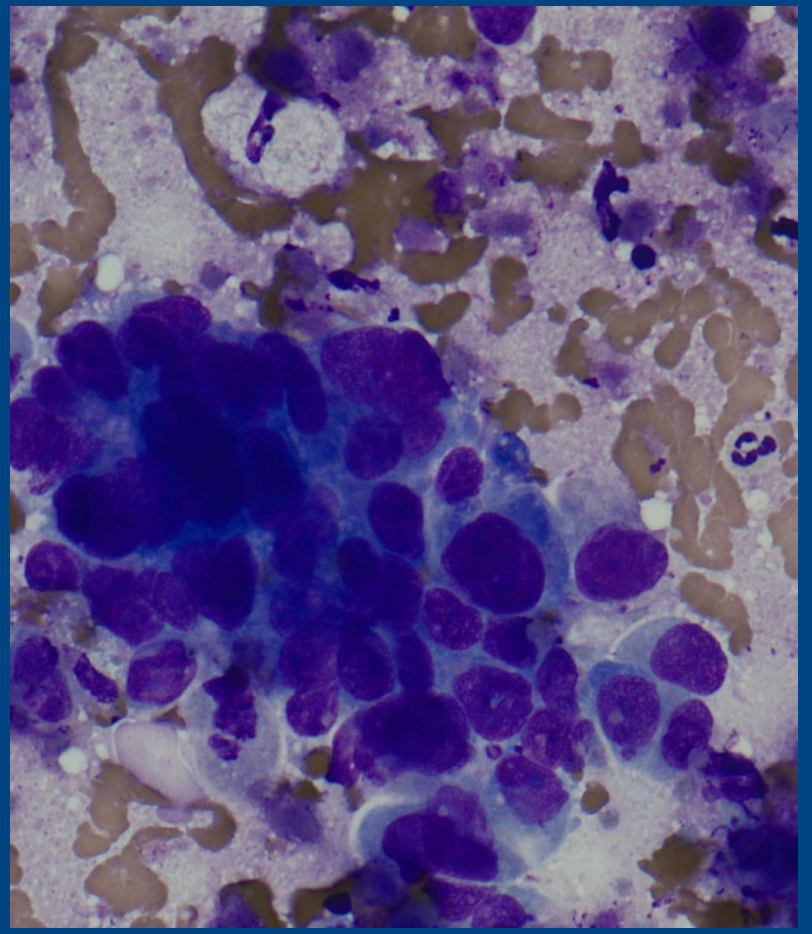
- Should have capability to perform extended gene panel testing with minute amounts of tissue through methodologies such as next generation sequencing.
- All advanced cases of adenocarcinoma, large cell carcinoma, and NSCLC not otherwise specified (NOS) be tested for EGFR, ALK, ROS1, BRAF, and broad molecular profiling such as **next generation sequencing**.
- For cases of advanced stage squamous cell carcinoma, ROS1 and BRAF testing should be considered also as part of broad molecular profiling.
- PDL-1 testing should be performed in all cases of NSCLC.
- Approximately 25-27% of lung cancer patients don't have enough material for EGFR testing after histological examination.

Advantages of NGS

- Single test identifies thousands of somatic or germline mutations from hundreds of genes (point mutations, insertions or deletions, copy number variations, and fusion oncogenes).
- Preferred over direct sequencing as it is more sensitive in specimens with low tumor cellularity. Uses less material than combining multiple conventional assays.
- May be more cost-effective than single gene testing modalities. Expensive but cost is less than a PET scan
- Driver mutations detected in 50-60% of NSCLC patients, of which 50% can be treated with a targeted agent.

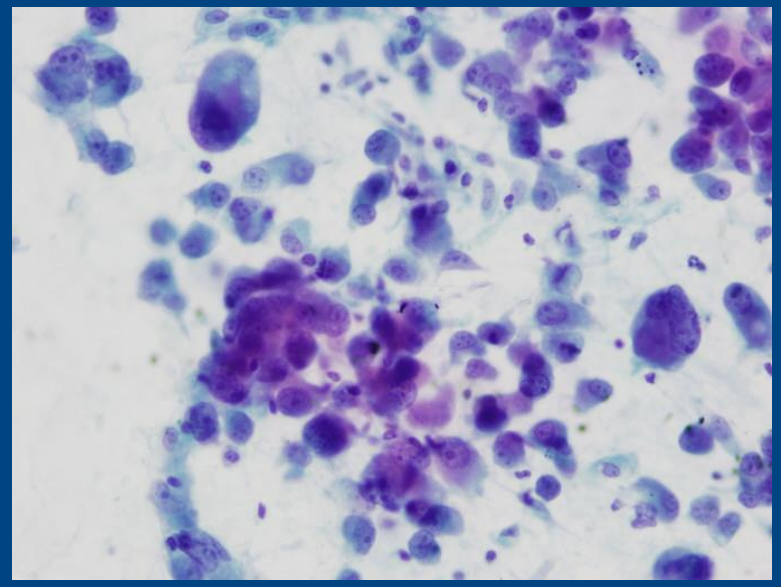
Drilon et al. Clin Cancer Res 2015;21: 3631-9
Pennel et al. J Clin Oncol 2018;36 abstr9031
Lim et al. Oncotarget 2016;7:24172-8
Kaderbai et al. Oncotarget 2016; 724860-70

Options for tissue?



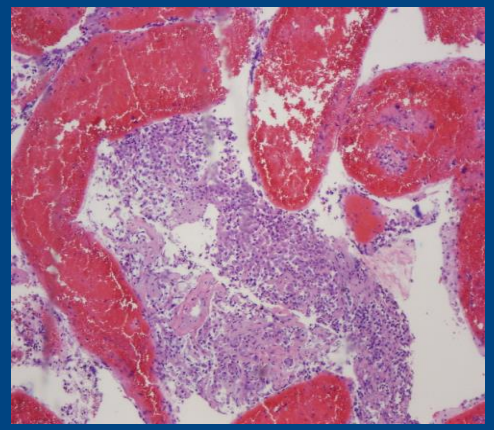
Cytology Specimens

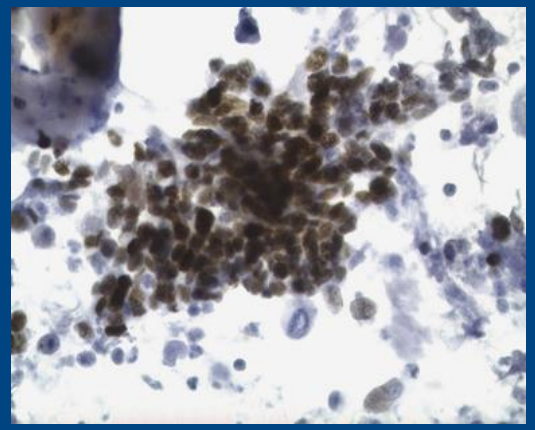
- Bronchoscopic
  - Wash
  - Brush
  - Lavage
- FNA
  - Transbronchial
  - Transthoracic
  - EBUS or EUS



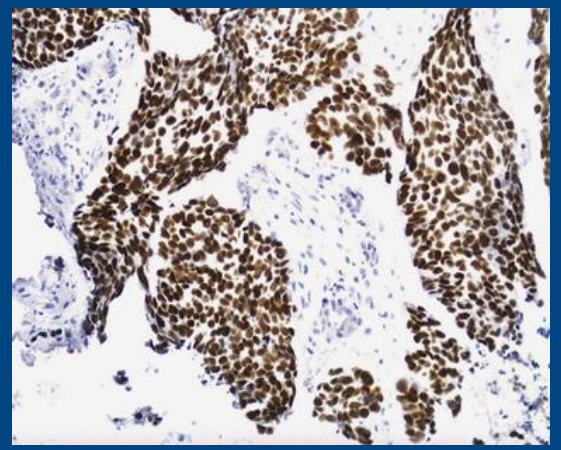
Cell Block

- Morpholology
- Immunohistochemistry
- Mutational analysis





TTF1



TTF1

Microdissection of cytology smears for molecular analysis

- Enrichment of the specimen
- Slides are examined and areas containing tumor cells are circled (pathology directed microtomy)
- Pathology assistant extracts cells from the marked areas

Treece et al. Cancer Cytopathol 2016;124:406-14

EBUS for genetic testing

- Initially evaluated for single gene testing
  - Pooled analysis of 28 studies (2,497 patients) reported sufficient sample for EGFR in 94.48%
  - Analysis of 12 studies (607 patients) reported sufficient sample for ALK in 95%
  - Smaller studies for ROS-1 showed sufficient sample in 83%

Labarca et al. Ann Am Thorac Soc 2018;15:1205-1216
Fernandez-Bussy et al. Arch Bronchopneumol 2017; 53: 172-174

Fewer studies on EBUS for NGS

- A study in 54 patients (85 samples) successful testing in 98% for a 50 gene panel and 91% for a 1,213 gene panel
- Another study 115 patients: EBUS-TBNA specimen adequacy for large NGS panels in 86% of cases (success rate improved with 76% for first 3rd and 92% for the last 3rd)

Stoy et al. Clin Lung Cancer 2018; 19: 230-238.e2
Turner et al. Lung Cancer 2018;119: 85-90

Next Generation Sequencing (NGS)

- Validation study **on FFPE specimens**
- 61 previously profiled clinical tumor specimens
- **Concordance of 100%** between NGS and conventional platforms
- Analysis of tumor cell lines indicated reliable mutation detection in samples with up **5% tumor content.** Sequencing of 50 genes was successful greater 95% of the time with > 5 ng/mL of DNA (at least 5,000 cells)

Mutation Type	Gene	Platforms	Expected	Detected	% Concordance
SNV	*EGFR*	ARMS-PCR	22	22	100%
SNV	*KRAS*	ARMS-PCR	16	16	100%
SNV	*PIK3CA*	ARMS-PCR	2	2	100%
Deletion	*EGFR*	ARMS-PCR	16	16	100%
Insertion	*EGFR*	ARMS-PCR	1	1	100%
Gene Fusion	*ROS1*	FISH	2	2	100%
Gene Fusion	*ALK*	FISH	1	1	100%
Gene Fusion	*RET*	FISH	1	1	100%
Total	–	–	61	61	100%

Table 3. Concordance of targeted NGS with conventional platforms.

Shao D et al. *Sci Rep* 2016; 6:22338

DNA Requirements

- Depends on the NGS platform
- Large panel (> 200 genes) requires up to 50ng of DNA
- A 50 gene panel may require 1-10ng of DNA (>1000 cells) while 1200 gene panels may require 25-100ng of DNA (>200,000 cells)

The challenge

- How much is enough to address competing needs?
  - IHC for cell type
  - IHC for PDL-1
  - Other tests (eg FISH) if smaller NGS panel
- Variable cellularity among lung cancers

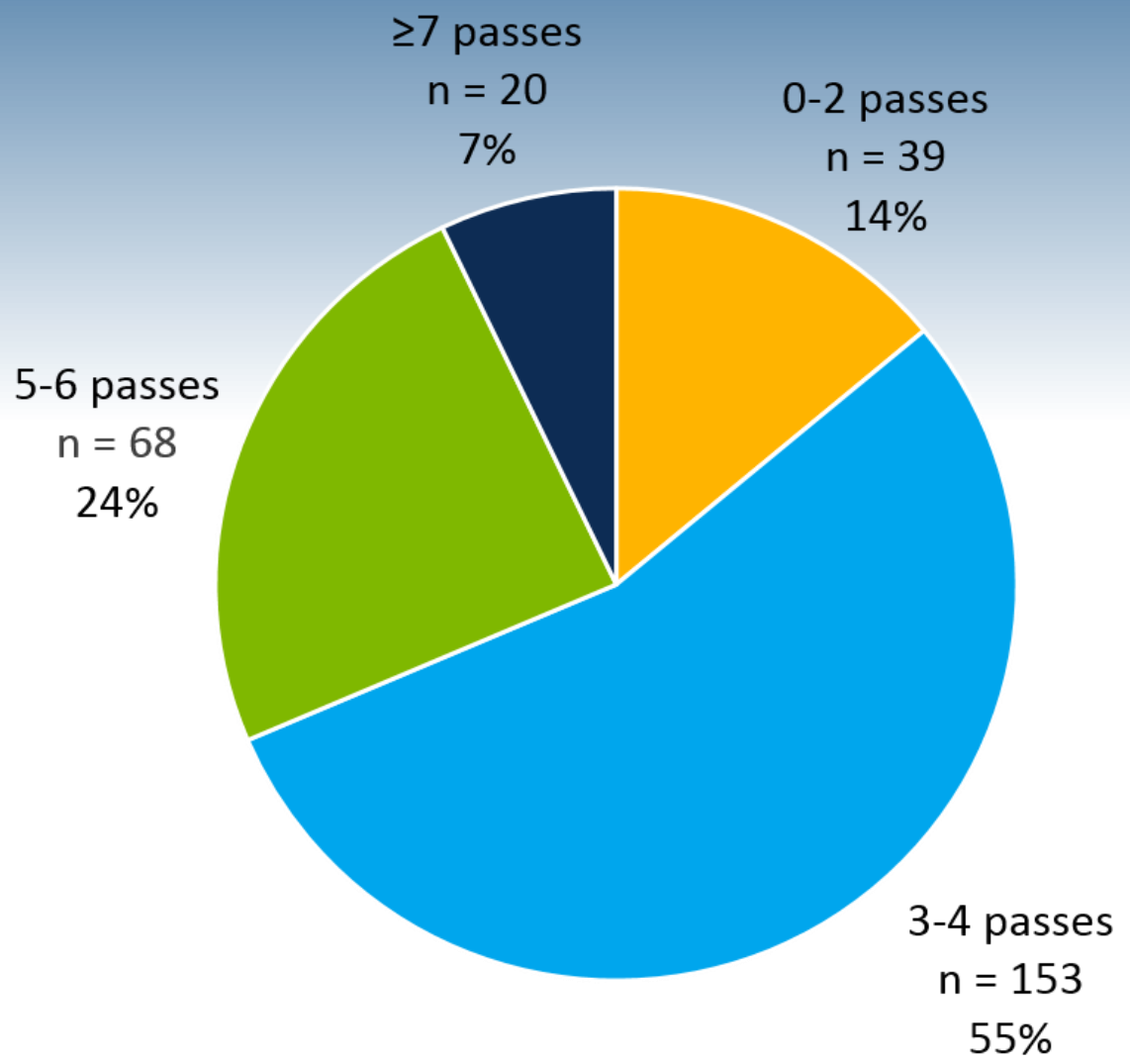
NCCN Guidelines 03.2020.

The Challenge to the Pulmonary Community

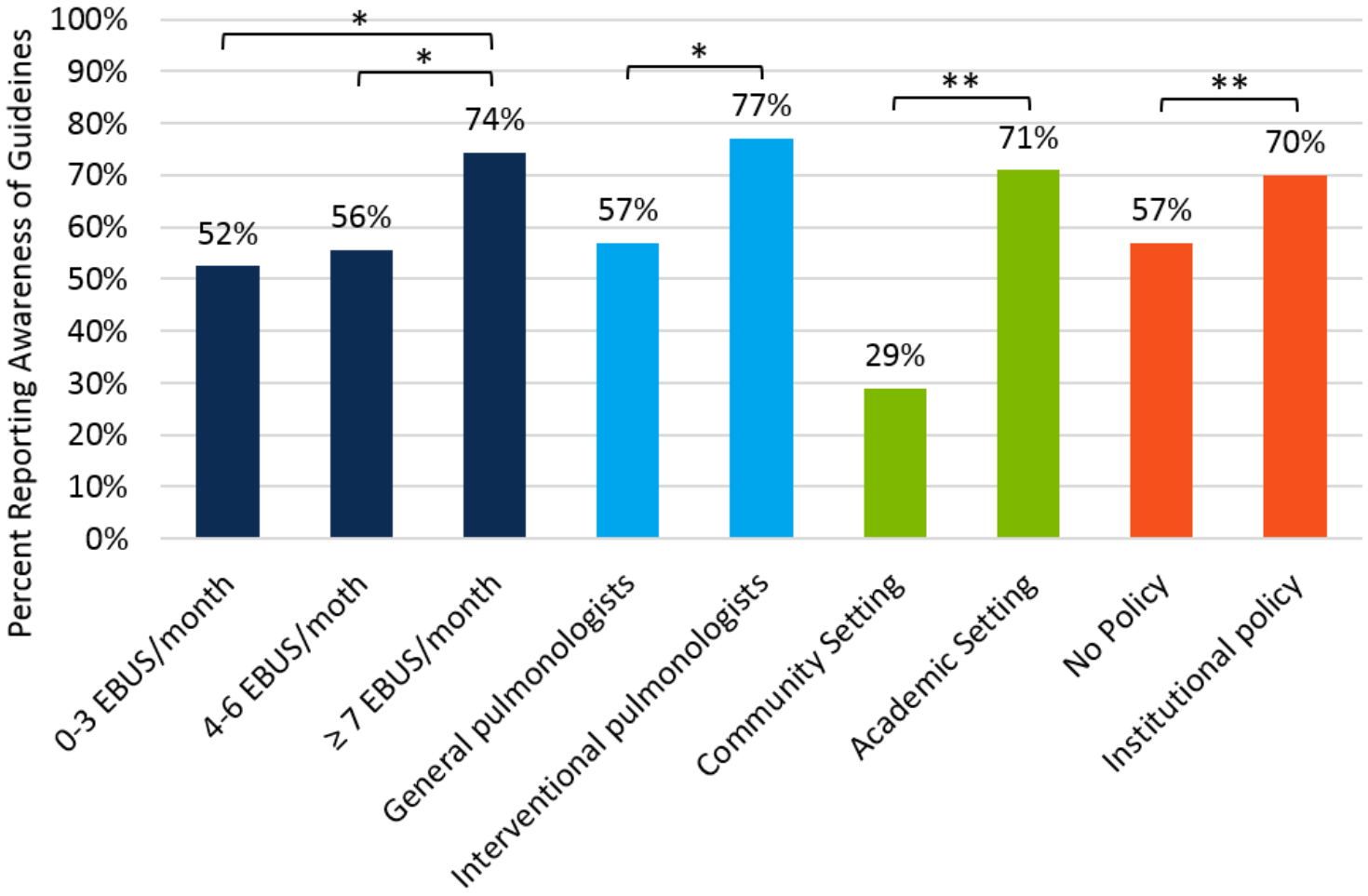
- Surveyed 453 pulmonologists
- 67% community and 33% academic
- 51% 1-4 lung cancers/month
- 19% > 10 lung cancers/month

Fox et al. Chest, In press

Number of Passes from EBUS to Obtain Tissue for Biomarker Testing



Reported awareness of guidelines



Challenge for Pulmonary Community

- Interventional training, academic practice setting, and higher volume of EBUS-TBNA associated with increased knowledge of practice guidelines for the number of recommended passes during EBUS-TBNA ($p<0.05$).
- Higher testing rates were associated with interventional training, academic setting, and the presence of an institutional policy, whereas lower testing rates were associated with being a general pulmonologist, practice in a community setting, and lack of a guiding institutional policy ($p<0.05$).

Conclusions

- EBUS-TBNA remains the cornerstone of staging the mediastinum in lung cancer and is effective in molecular analysis
- The issue is tissue no matter what method is used.
- Challenges of clinical integration include education, obtaining adequate amounts of cf-DNA, and cost/insurance coverage.
- Ordering should be considered at the time of diagnosis and in some cases of progression of advanced stage NSCLC.
- Communication between Pulmonary, Oncology and Pathology is critical for the success of biomarker testing and treatment of patients with lung cancer.

Didactic Q & A

Case Presentation:

Northside Hospital Cancer Institute/Georgia Cancer Specialists

NORTHSIDE HOSPITAL CANCER INSTITUTE
BUILT TO BEAT CANCER

GEORGIA CANCER SPECIALISTS

Rodolfo Bordoni, MD

Director of the Clinical Research

Georgia Cancer Specialists

YRP 52 y/o female patient

HPI Presented to PCP with a two-month history of back discomfort, but active, is eating well, has had no weight loss.

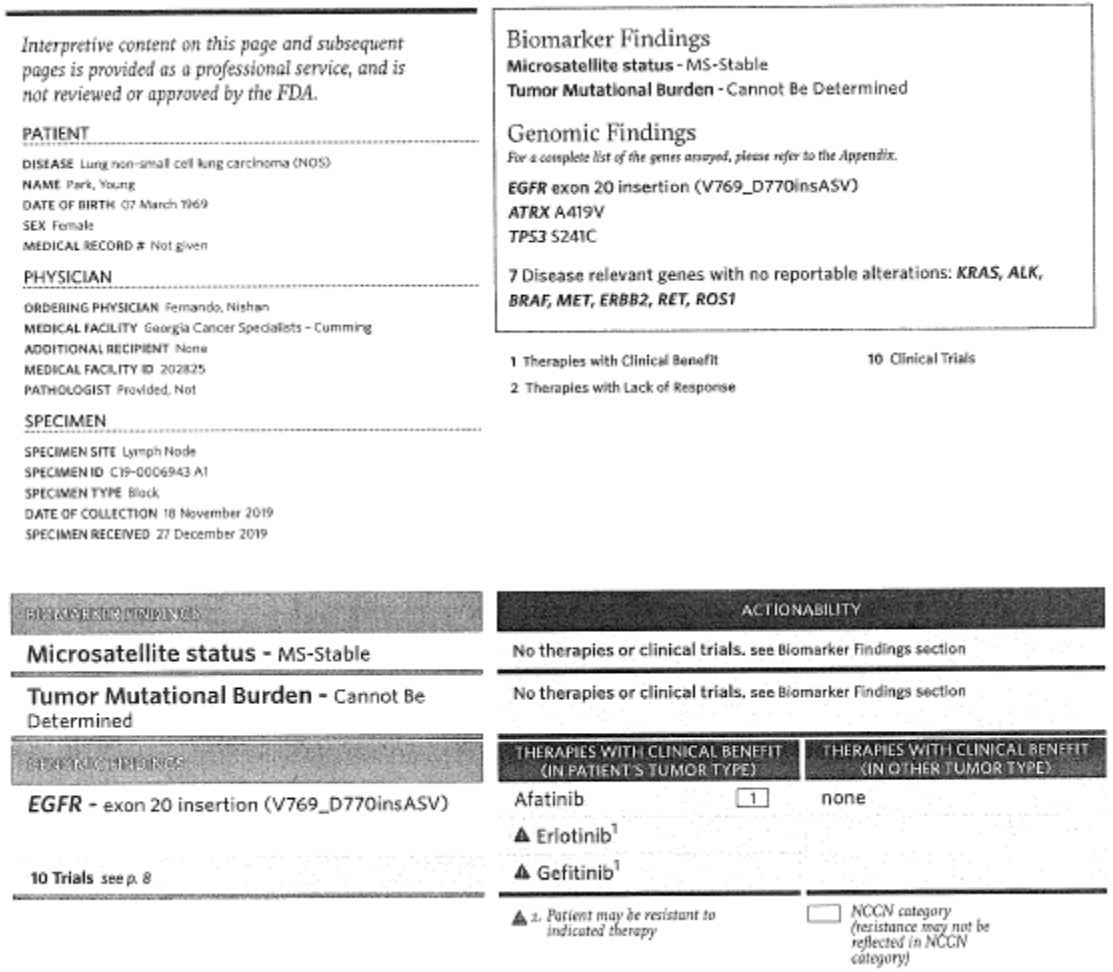
- CT/PET scan evaluation on 11/13/19 showed: 5x2 cm right lower lobe mass with additional mediastinal, bilateral hilar, right lower lobe adenopathy; also, uptake within right adrenal gland, and multiple lytic destructive bony lesions involving sternum, ribs, spine, and pelvis.

- EBUS and TBBx on 11/18/19: NSCLC, favoring adenocarcinoma.

- MRI brain on 12/17/19: scattered small 5-7 mm CNS lesions;
  s/p WBRT

YRP 52 y/o female patient

- Tissue molecular profiling: **EGFR exon 20 mutation (A767-V769dup).**
- PD-L1 TCS: **65%.**



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PATIENT

DISEASE Lung non-small cell lung carcinoma (NOS)
NAME Park, Young
DATE OF BIRTH 07 March 1969
SEX Female
MEDICAL RECORD # Not given

PHYSICIAN

ORDERING PHYSICIAN Fernando, Nishan
MEDICAL FACILITY Georgia Cancer Specialists - Cumming
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 202825
PATHOLOGIST Provided, Not

SPECIMEN

SPECIMEN SITE Lymph Node
SPECIMEN ID C19-0006943 A1
SPECIMEN TYPE Block
DATE OF COLLECTION 18 November 2019
SPECIMEN RECEIVED 27 December 2019

Biomarker Findings

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

Genomic Findings

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

EGFR exon 20 insertion (V769_D770insASV)
ATRX A419V
TP53 S241C

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

1 Therapies with Clinical Benefit
2 Therapies with Lack of Response
10 Clinical Trials

BIOMARKER FINDINGS

Microsatellite status - MS-Stable

Tumor Mutational Burden - Cannot Be Determined

GENOMIC FINDINGS

EGFR - exon 20 insertion (V769_D770insASV)

10 Trials *see p. 8*

ACTIONABILITY	
No therapies or clinical trials. see Biomarker Findings section	
No therapies or clinical trials. see Biomarker Findings section	
THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
Afatinib 1	none
▲ Erlotinib[1]	
▲ Gefitinib[1]	

▲ 1. *Patient may be resistant to indicated therapy*

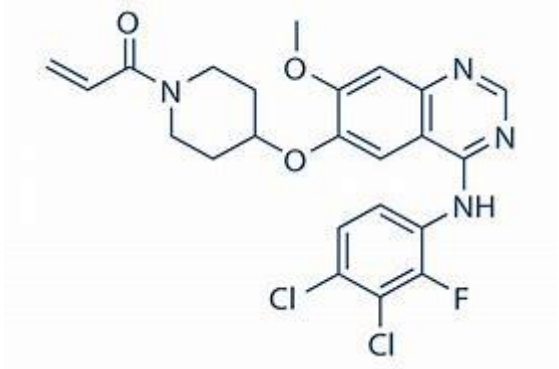
☐ *NCCN category (resistance may not be reflected in NCCN category)*

YRP 52 y/o female patient

Family History: notable for a sister with lymphoma, doing well.

Social History/Habits:

- former tobacco user, in the form of cigarettes
- Years patient has used tobacco: 3 years, in her 20's
- Tobacco quantity per day:10 or less (1/2 pack)
- Pack Years: 1
- Nonsmoking currently.



Recommendations:

- No specific treatment available for the kind of tumor genomic aberration.
- Consider participation in clinical trial/s with specific EGFR exon 20 inhibitory activity *(poziotinib).*
- Consider osimertinib, has shown some activity in case reports.
- Consider chemotherapy/bevacizumab or ramucirumab down the road.
- Denosumab to avoid SRE due to bony dz.

YRP 52 y/o female patient

Considered for clinical trial of Poziotinib but started osimertinib 80mg/day PO 12/20/19.

02/21/20: PET/CT with interval DP of lung and bony dz; MRI brain stable.

2L therapy: Carboplatin/Pemetrexed/Pembrolizumab x5 cycles (3/5/20-05/29/20; Pemetrexed/Pembrolizumab maint. (6/19/20--10/2/20).

05/01/20- CT/PET scan: PR in all areas (~50%)

10/16/20- PET/CT with widespread bony progression.

11/01/20- Guardant360 with unchanged EGFR exon 20 insertion mutation.

3L therapy: Docetaxel/Ramucitumab, started 10/30/20.

1/22/21- PET/CT with marked response in osseous dz; pleural dz stable.

5/14/21- MRI brain with stable prior treated lesions, but multiple new lesions (4-7mm); *s/p WBRT*

YRP 52 y/o female patient

06/04/21- started discussing potential new line of systemic therapy with Amivantamab (JNJ-61186372), an anti-EGFR-MET bispecific antibody, with specific anti-tumor activity in patients with EGFR exon 20 insertion (exon20ins)-mutated NSCLC.

05/21/21- The FDA approved amivantamab-vmjw (Rybrevant) as the first treatment for adult patients with NSCLC who harbor EGFR exon 20 insertion mutations.

The regulatory agency also gave the green light to Guardant360 CDx, developed by Guardant Health Inc., for use as a companion diagnostic for the drug.

Case Presentation Discussion

Specific Question(s) to the Faculty

Q1 Different than in the past, how would you treat this patient nowadays?

Post-Session Poll
Questions & Wrap Up

A Few Reminders

Next Session: 9/23/2021 @ 1:00 PM

Speake: *Ignacio I. Wistuba, MD*
Topic: *Choice of Panel, Interpretation of Results, and Next Steps*

Materials and resources will be made available to you
All resources will be available at echo.cancer.org

Case Presentations
Spokes: Interested in scheduling your Case Presentation? Let us know.
Faculty: All future case presentations will be shared with you at 24-hours in advance.

Additional Feedback on Today's Session? Tell us in the Post Session Feedback Forum
(URL in chat box)

Questions: Contact your regional leads, **Jessica Davis**, **Beth Dickson-Gavney**, **Julie Waters** or **Kelly Durden**

Thank you to Amgen for their generous support!

SEE YOU IN SEPTEMBER!