The Role Of EBUS & Lung Biopsy For Biomarker Testing In The Community & Academic Settings

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Disclosures

i3 Health and FLASCO have mitigated all relevant financial relationships

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

Overview of NSCLC Treatment

		5 yr. survival
Stage I	**Surgery (Radiation if inoperable)** **Post op Targeted therapy for 1B EGFR/ALK** **or** **Neo adjuvant chemo immune followed by surgery if EGFR-**	**68-90%**
Stage II	**Surgery With Adjuvant Chemotherapy or** **Targeted therapy for EGFR/ALK +** **Neo adjuvant chemo immune followed by surgery if EGFR-**	**50-60%**

Survival based on IASLC 8th ed

Overview of NSCLC Treatment

5 yr. survival

Stage III → **Chemotherapy with radiation therapy, Adjuvant Immunotherapy or Targeted therapy in EGFR/ALK+**

Neo adjuvant chemo immune followed by surgery if EGFR- → **13-35%**

Stage IV or Recurrent Disease → **Chemotherapy Targeted Therapy Immunotherapy Supportive Care** → **10-20%**

Survival based on IASLC 8th ed

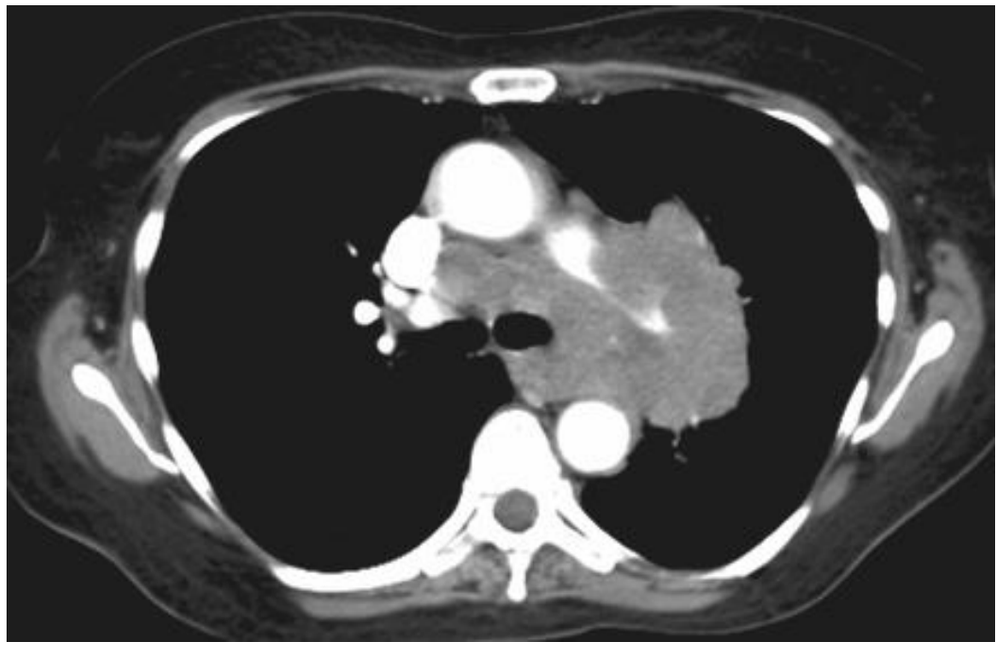
Role of EBUS in Lung Cancer Care

- Diagnosis
- Staging
- Biomarker Testing

Confirmation of Intrathoracic Stage

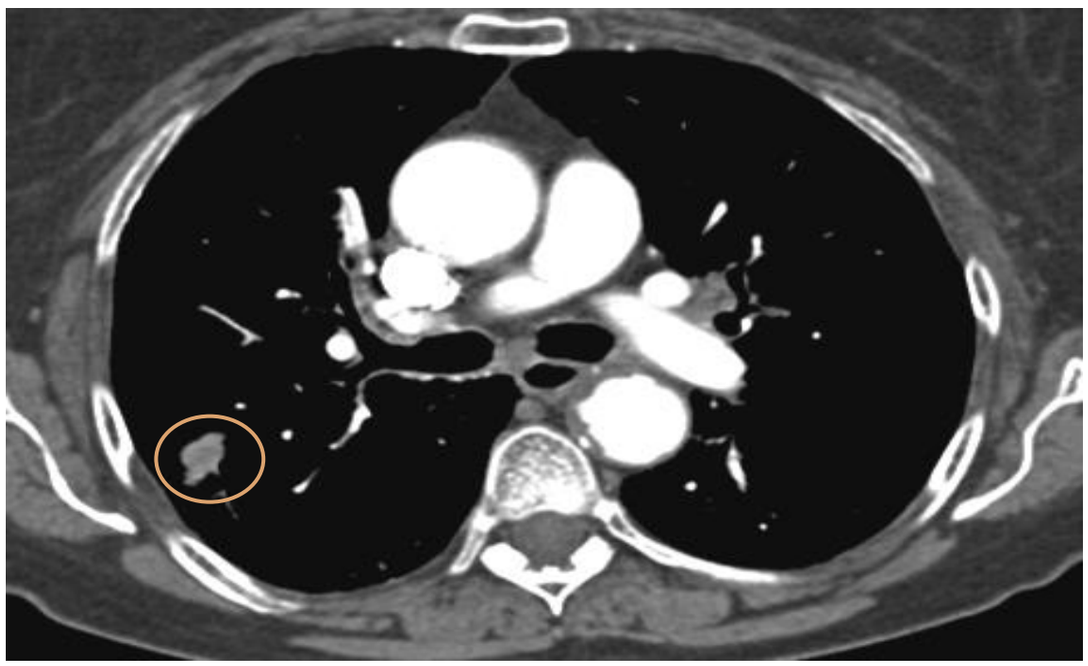
CHEST
AMERICAN COLLEGE of CHEST PHYSICIANS

Extensive Infiltration



CT neg. but central, adeno, N1

Discrete N2, 3 enlargement



Peripheral clinical stage I

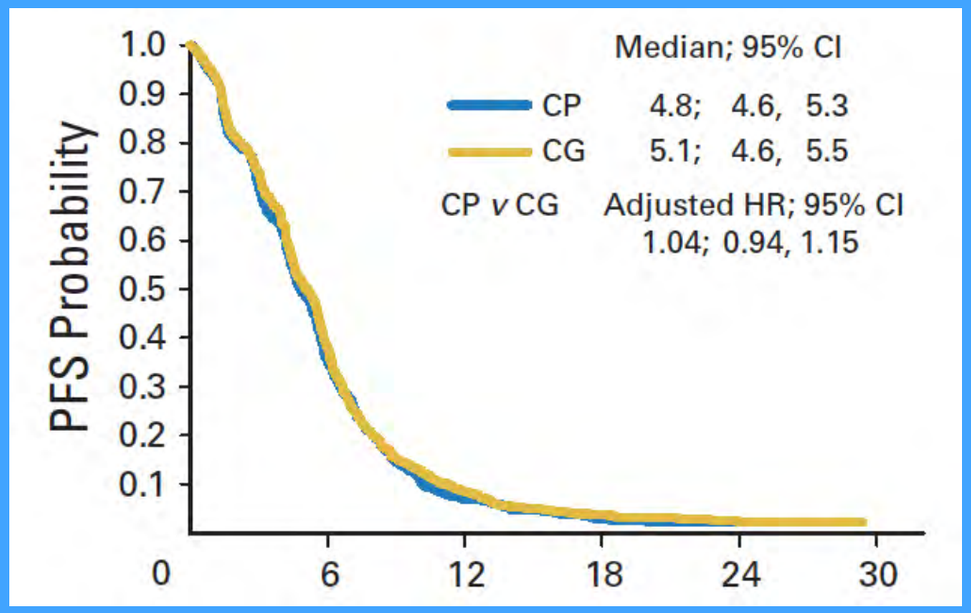
Accuracy of Staging Tests in Lung Cancer Patients

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 *CHEST 2013*

Biomarker testing in NSCLC

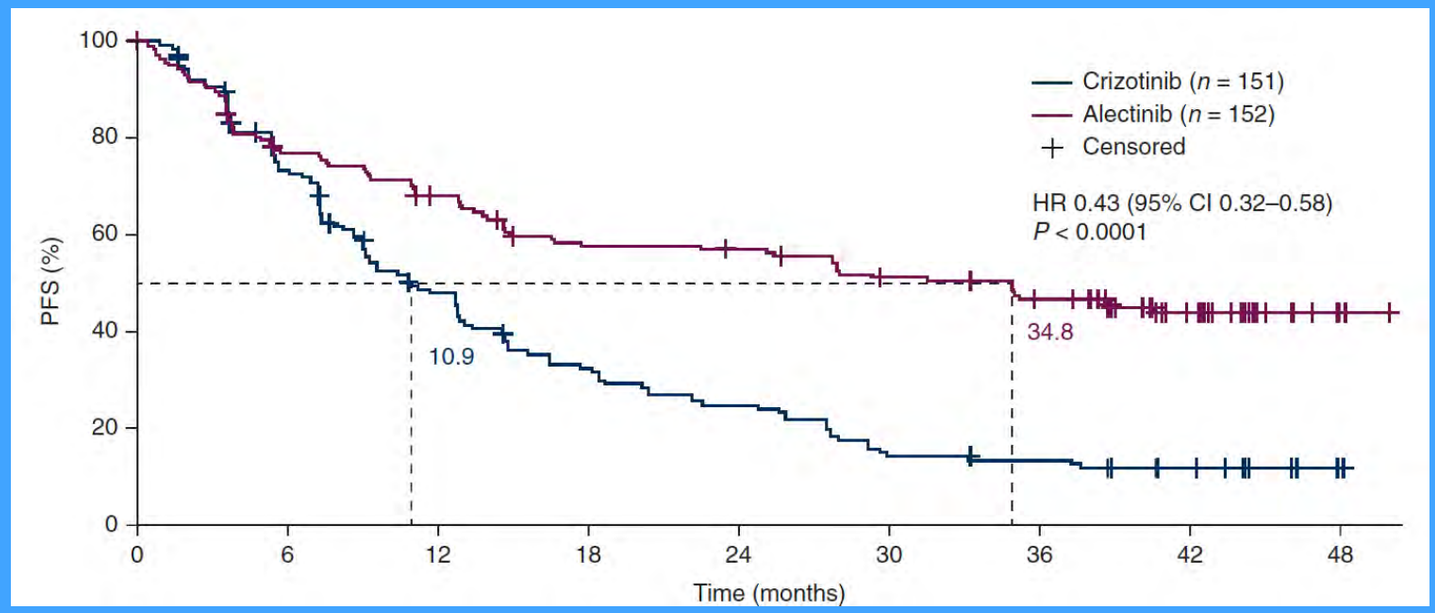
Scagliotti et al. J Clin Oncol. 2008 Jul 20;26(21):3543-51



Cisplatin/pemetrexed vs Cisplatin/gemcitabine; Stage IIIB/IV NSCLC

Median PFS ~5 months with either

Mok et al. Ann Oncol. 2020 Aug;31(8):1056-1064

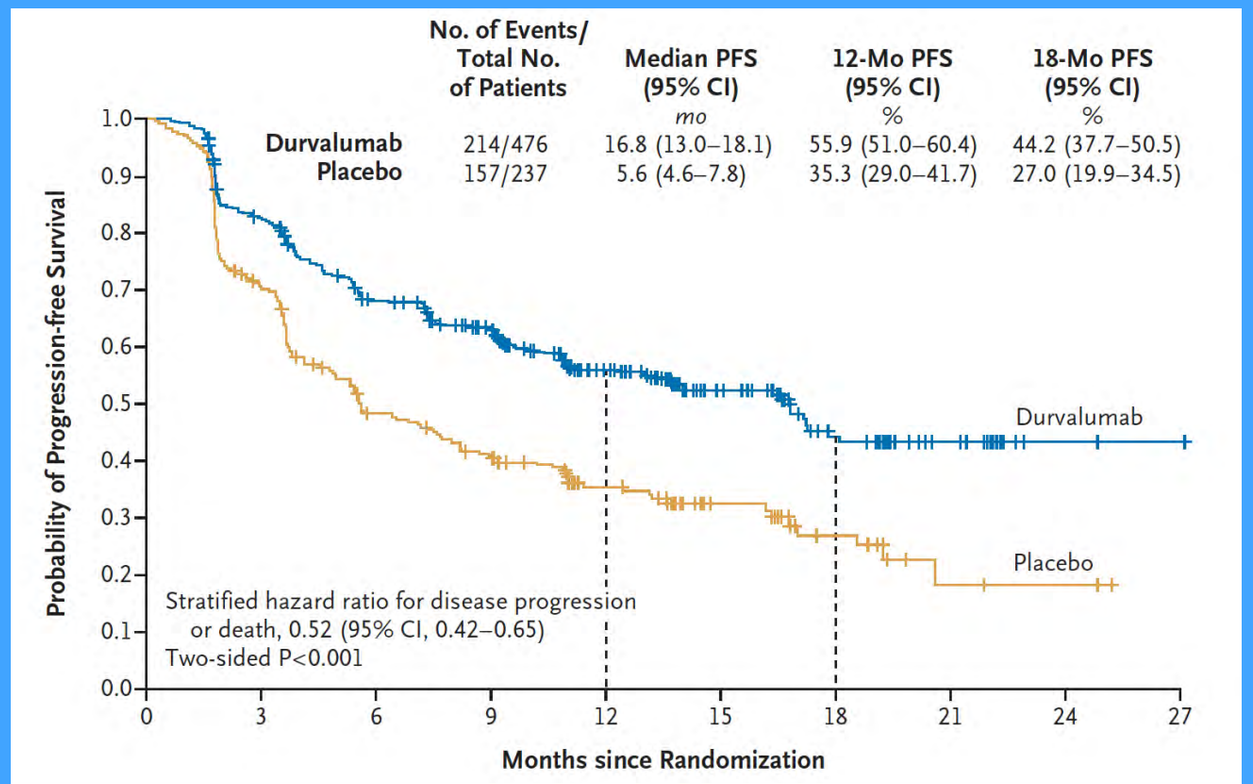


Alectinib vs Crizotinib Stage III/IV ALK (+) NSCLC

Median PFS 34.8 months with Alectinib

Biomarker testing in NSCLC

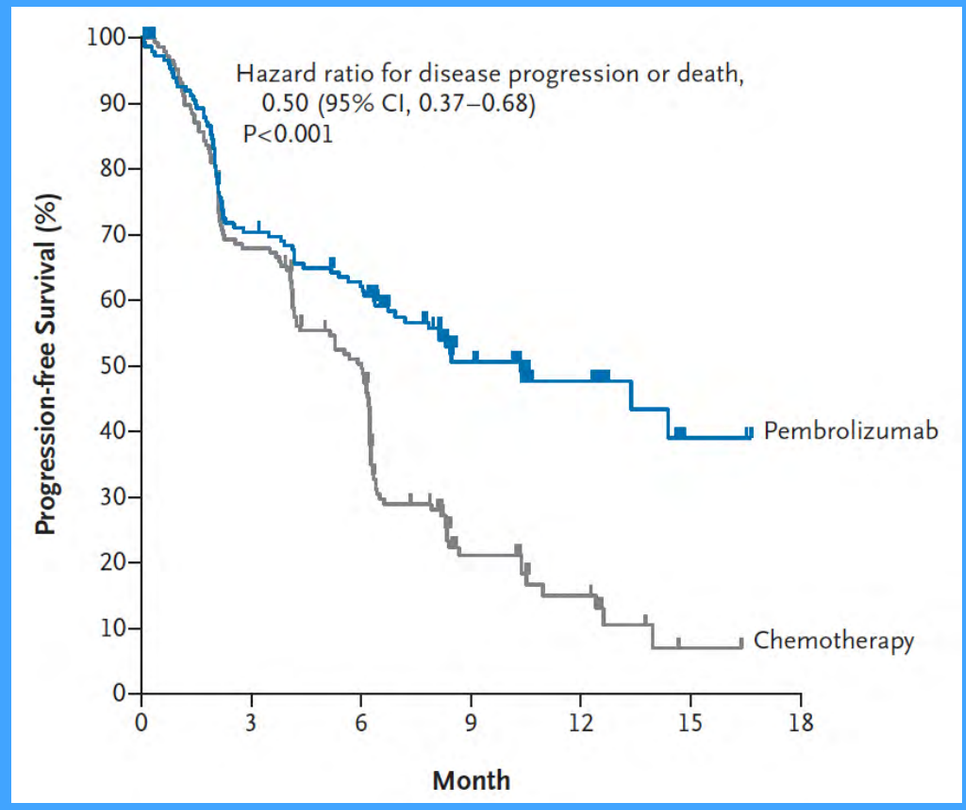
PACIFIC TRIAL. Antonia N Engl J Med.



Chemo + (Immunotherapy vs placebo)
Stage III NSCLC

Median PFS 16 vs 5 months

Reck N Engl J Med. 2016



Immunotherapy vs Chemotherapy
Stage IV NSCLC with PD-L1 > 50%

Median PFS 10.3 vs 6.7 months

The expanding role of biomarker testing

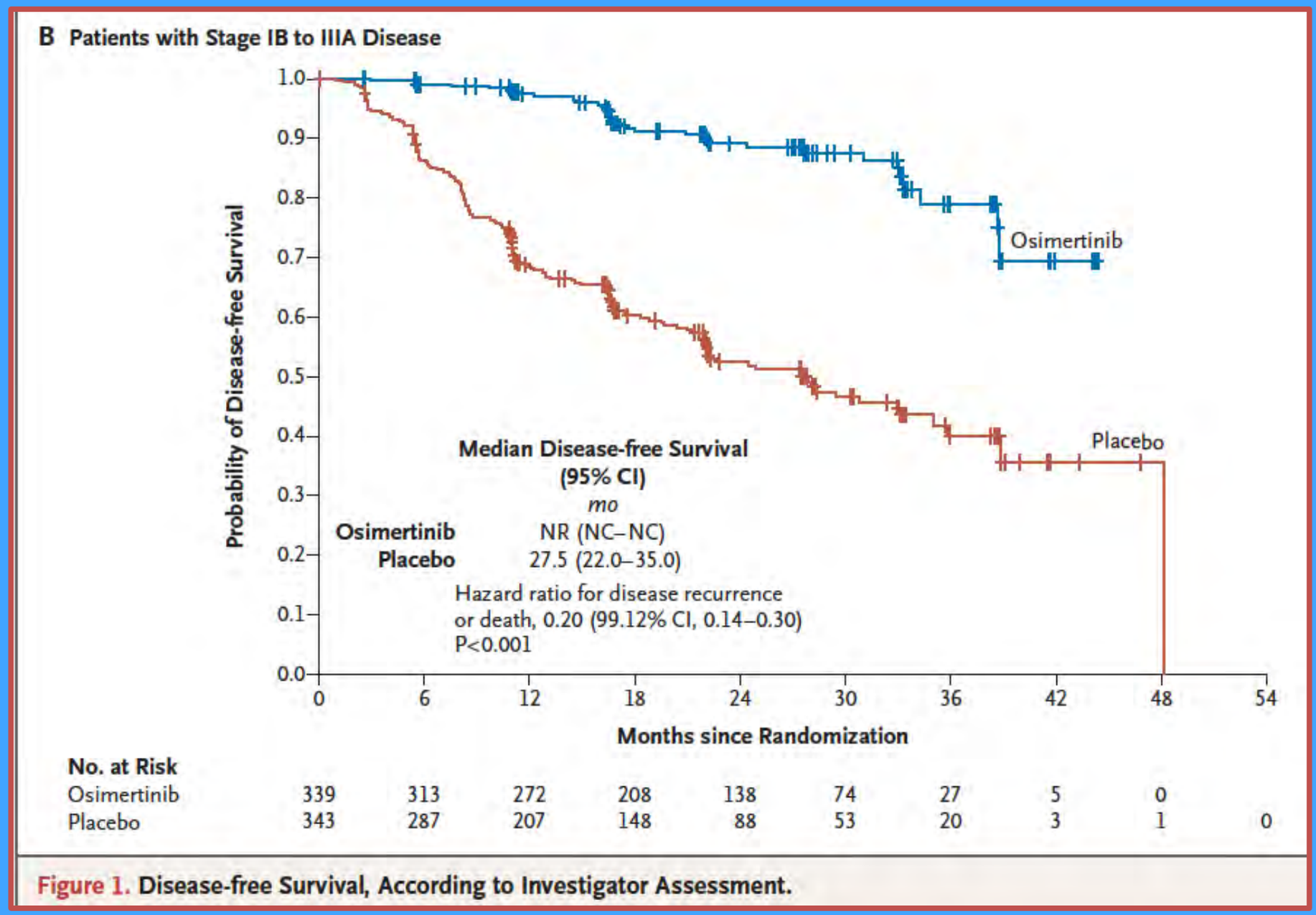
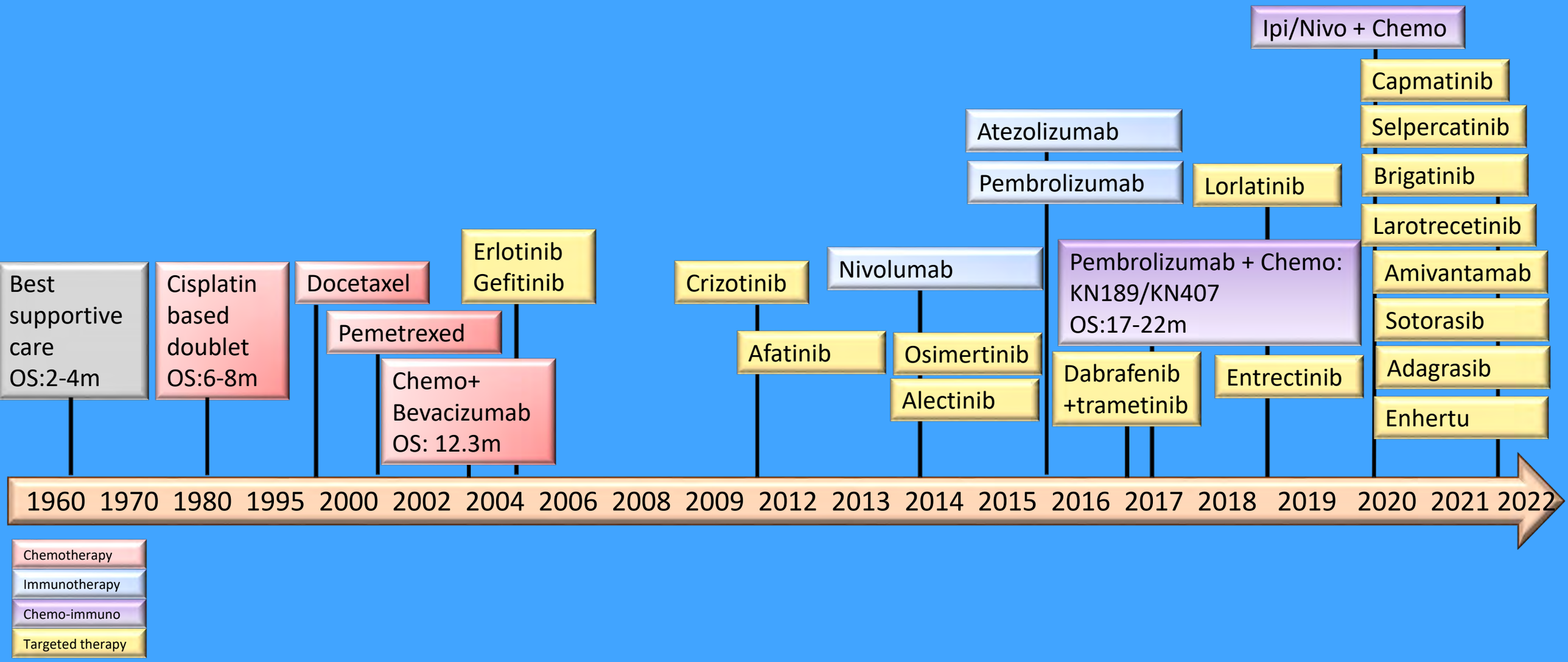


Figure 1. Disease-free Survival, According to Investigator Assessment.

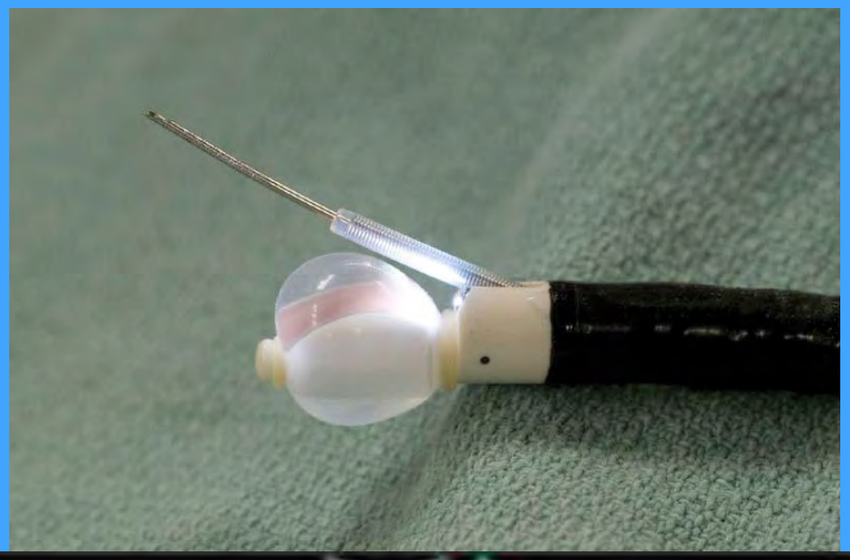
Wu et al. NEJM 2020, 383: 1711-1723

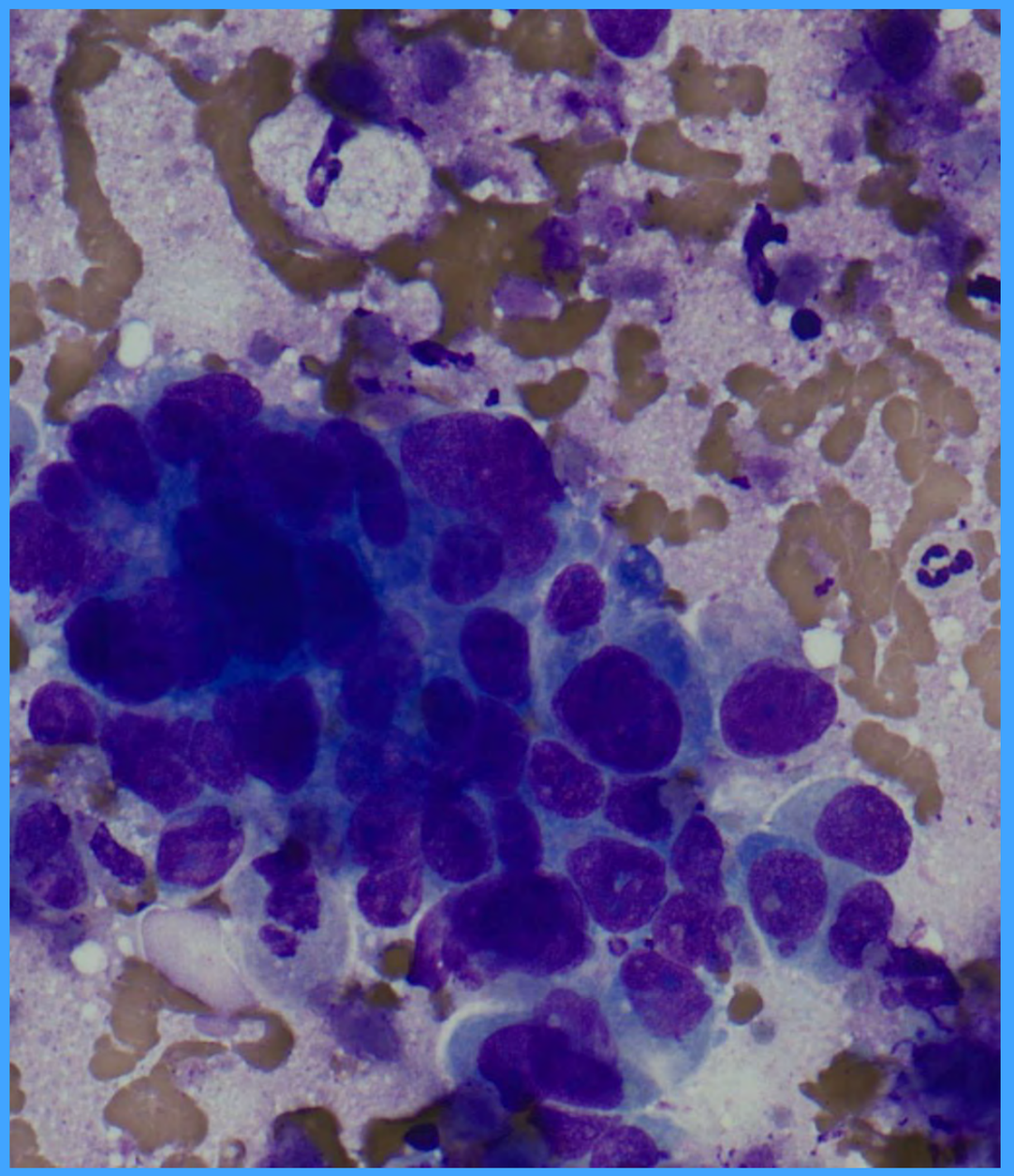
State of Non-small cell lung cancer (NSCLC)

Metastatic NSCLC



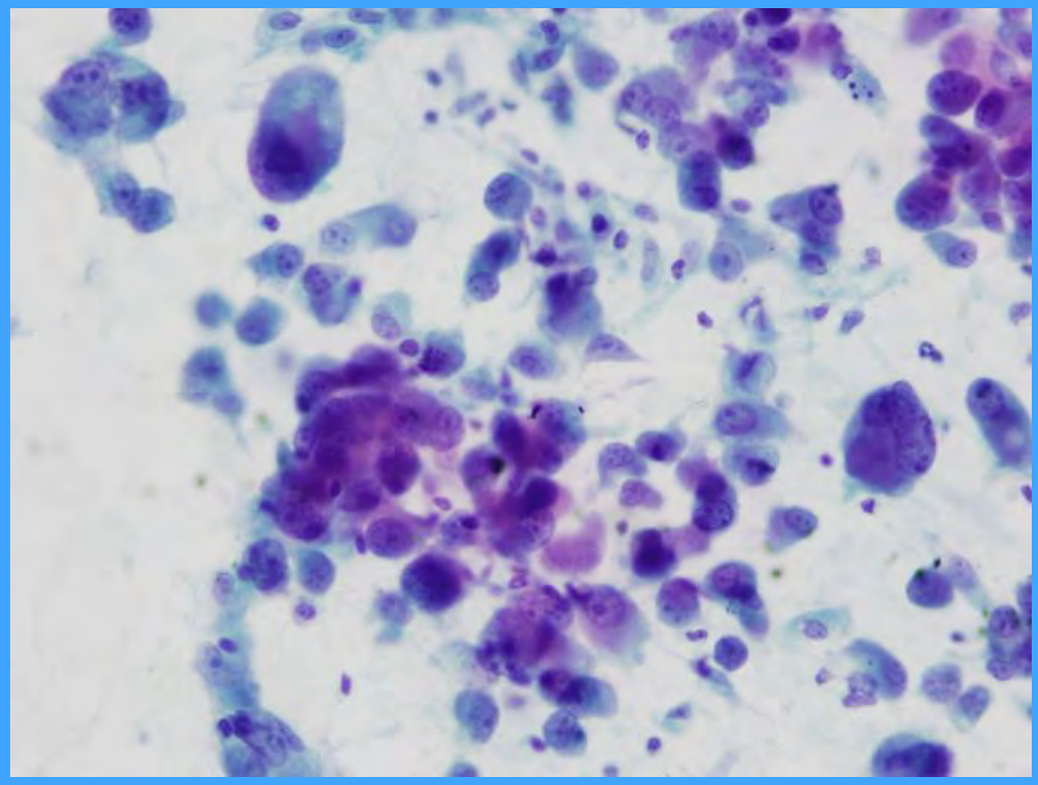
Options for tissue?





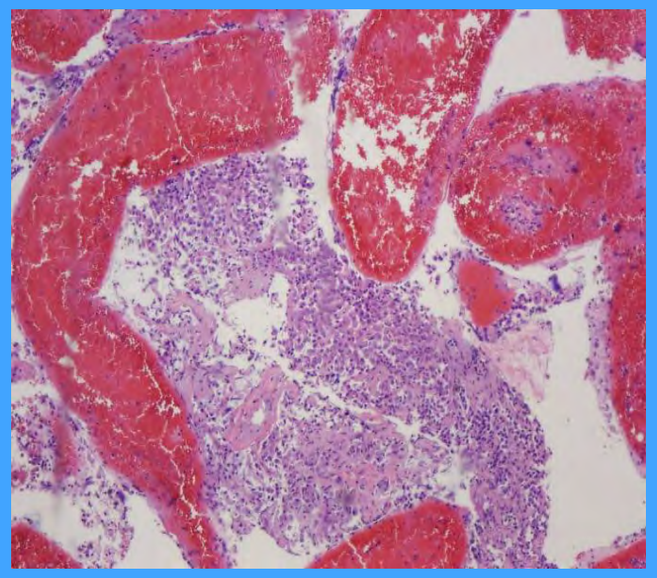
Cytology Specimens

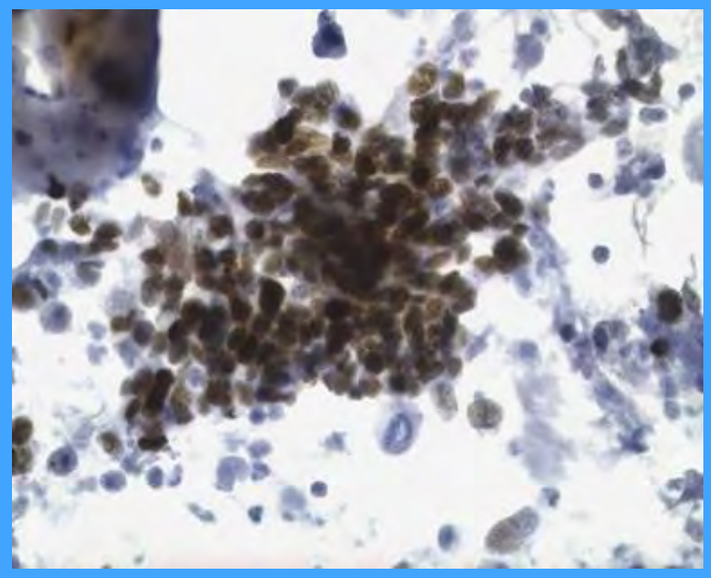
- **Bronchoscopic**
  - **Wash**
  - **Brush**
  - **Lavage**
- **FNA**
  - **Transbronchial**
  - **Transthoracic**
  - **EBUS or EUS**



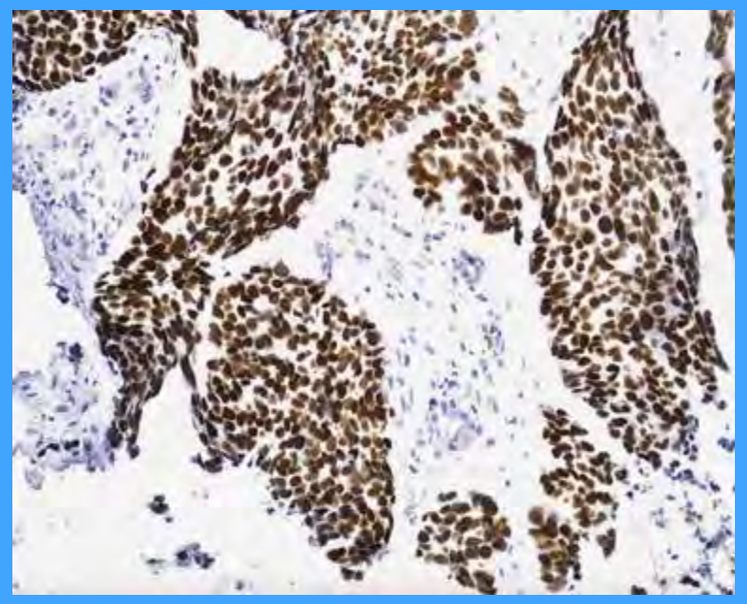
Cell Block

- Morphololology
- Immunohistochemistry
- Mutational analysis





TTF1



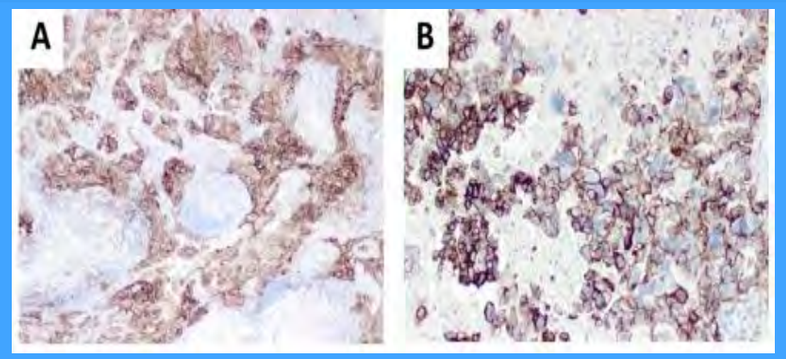
TTF1

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

PD-L1 testing on the EBUS-FNA cytology specimens of non-small cell lung cancer



- Consecutive patients with NSCLC undergoing EBUS
- Cell blocks used for PD-L1 testing 265 EBUS-FNA specimens
- **230 (86.8%) adequate for PD-L1 testing.**
- 34 NSCLC patients with both histology and EBUS-FNA cytology specimens PD-L1 - concordance of 91.3%.
- The PD-L1 results from 16 paired specimens from the same anatomic site had 100% agreement.

Wang et al. Lung Cancer 2019, 136:1-5.

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

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

The Critical Need for Sufficient Tissue

- NCCN Guidance: A major limitation in obtaining tissue molecular testing results for NSCLC occurs when minimally invasive techniques are used to obtain samples; the yield may be insufficient for molecular, biomarker, and histologic testing.

- *Therefore, bronchoscopists and interventional radiologists should procure sufficient tissue to enable all appropriate testing.*

  - NCCN Guidelines. Non–small Cell Lung Cancer. v5.2022.

EBUS: How Many Aspirations per Node?

Three aspirations per node is standard; fourth passes did not increase yield for **diagnosis.**

Cumulative Diagnostic Values of EBUS-TBNA Shown by the Number of Aspirations*

Variables	Aspirations, No.			
	1	2	3	4
Sensitivity	69.8 (30/43)	83.7 (36/43)	95.3 (41/43)	95.3 (41.43)
Specificity	100 (83/83)	100 (83/83)	100 (83/83)	100 (83/83)
PPV	100 (30/30)	100 (36/36)	100 (41/41)	100 (41/41)
NPV	86.5 (83/96)	92.2 (83/90)	97.6 (83/85)	97.6 (83/85)
Accuracy	89.7 (113/126)	94.4 (119/126)	98.4 (124/126)	98.4 (124/126)

*Data are presented at % (No./total). We considered inadequate samples as negative results.

Lee HS, et al. *Chest.* 2008.

How Many Passes For NGS or Mutational Testing

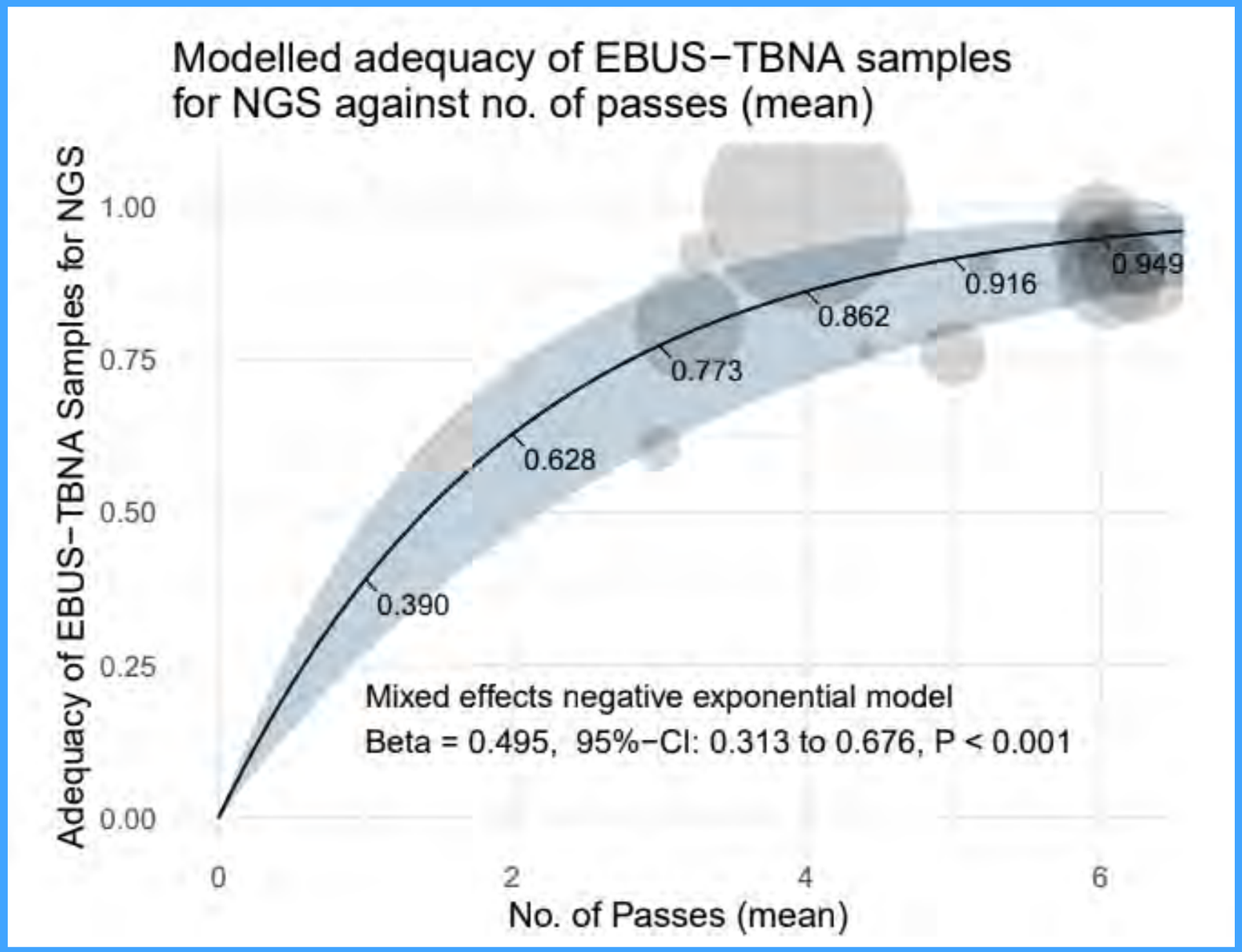
- **Twenty-one studies 1,175 patients**

- **The pooled proportion of adequate EBUS-TBNA samples for NGS (yield) was 86.5% (95%-CI: 80.9% to 91.4%).**

- **Modeled yield rates were 77%, 86%, 92% and 95% at mean passes of 3, 4, 5 & 6 respectively.**

Zhao et al. Lung Cancer 166 (2022) 17–26

6 Passes Get You to 95% Yield On NGS

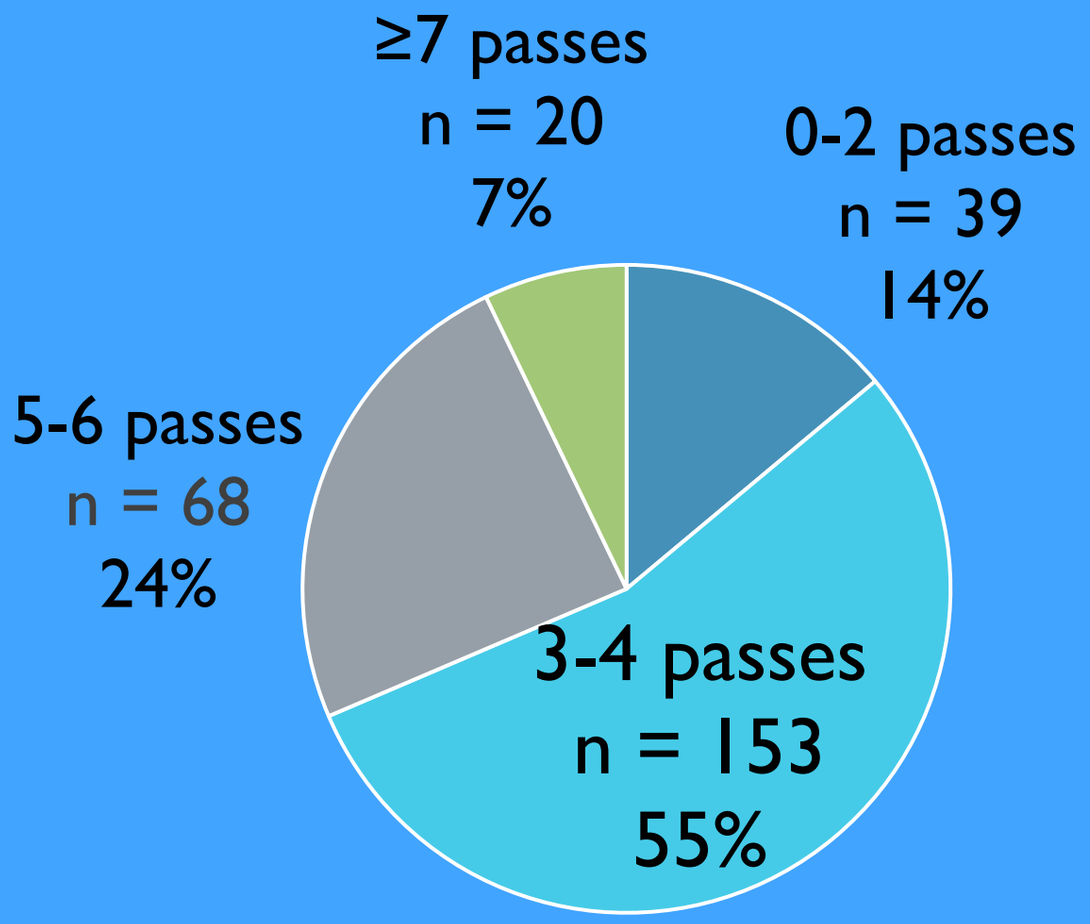


PULMONOLOGISTS ROLE IN BIOMARKER TESTING

Knowledge and Practice Patterns Among Pulmonologists for Molecular Biomarker Testing in Advanced Non-small Cell Lung Cancer

Adam H. Fox, MD • James R. Jett, MD • Upal Basu Roy, PhD, MPH • Bruce E. Johnson, MD
Jennifer C. King, PhD • Nikki Martin, MA • Raymond U. Osarogiagbon, MBBS • M. Patricia Rivera, MD
Lauren S. Rosenthal, MPH • Robert A. Smith, PhD • Gerard A. Silvestri, MD • Show less

Number of Needle Passes During EBUS to Collect Tissue for Biomarker Testing



- Responsible for ordering:
  - Oncologists (37%)
  - Pathologists (31%)
  - Pulmonologists (23%)
  - Tumor board (7%)
- 48% reported an institutional policy to guide biomarker testing
- Location:
  - In-house (20%)
  - Outside testing (44%)
  - Combination (31%)

Survey of Pulmonologists

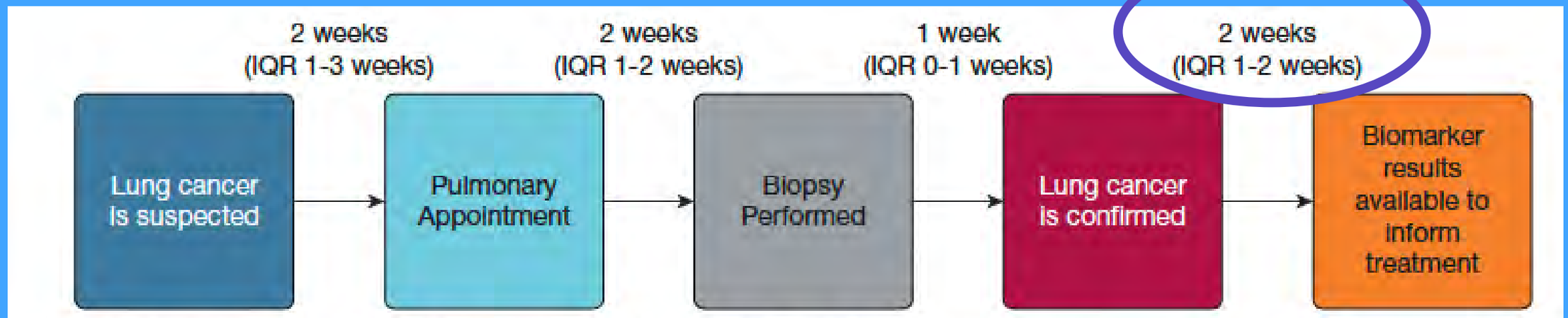
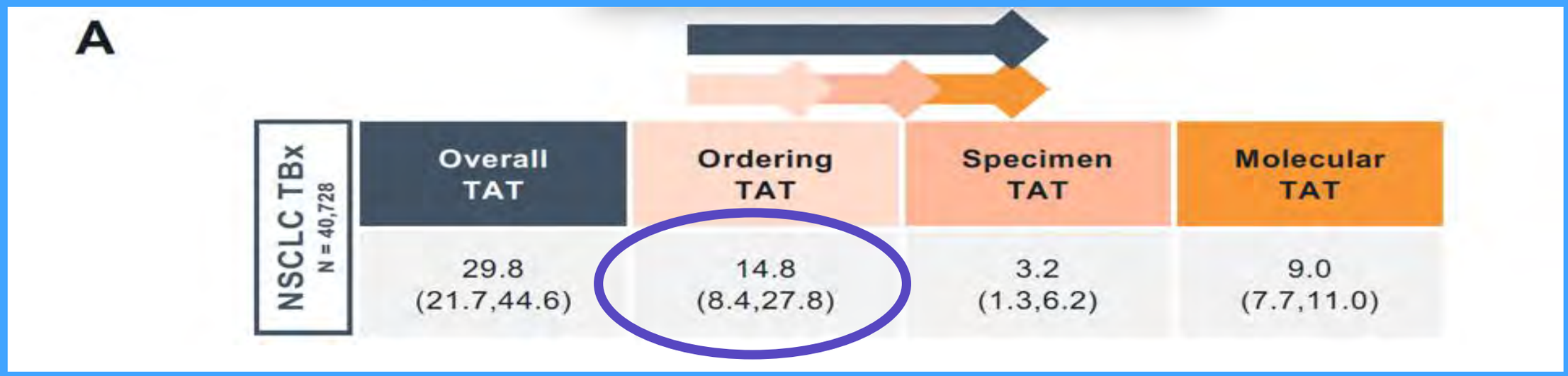


Figure 3 – *Estimates of times to complete diagnostic steps by respondents. IQR = interquartile range.*

Fox Chest. 2021

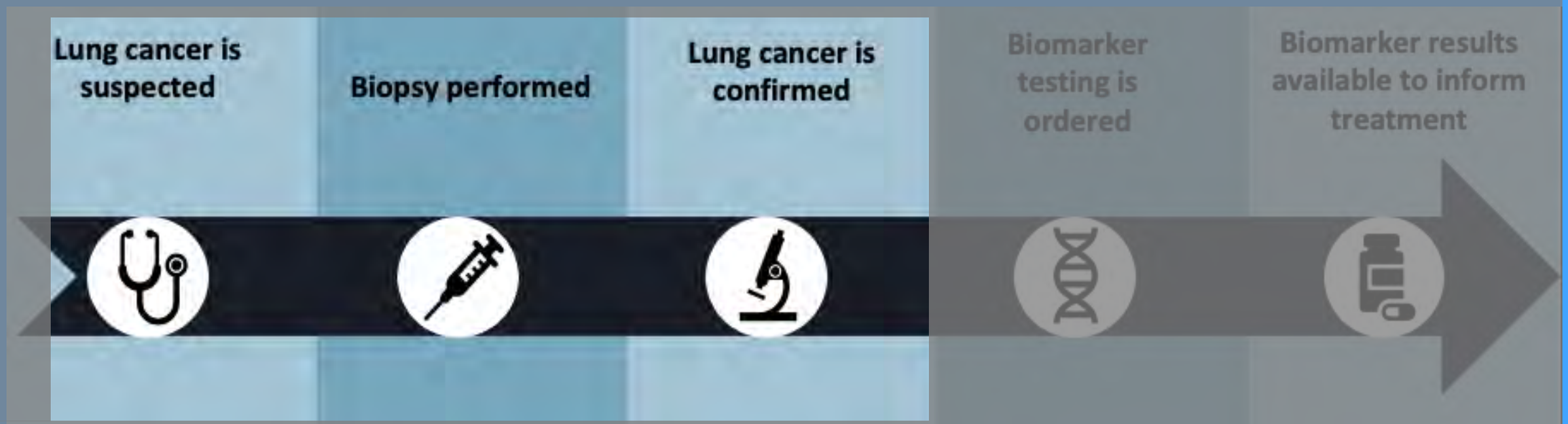
Preliminary data on >40,000 specimens



Pulmonologist's Perspective

Fox Cancer J Clin. 2023

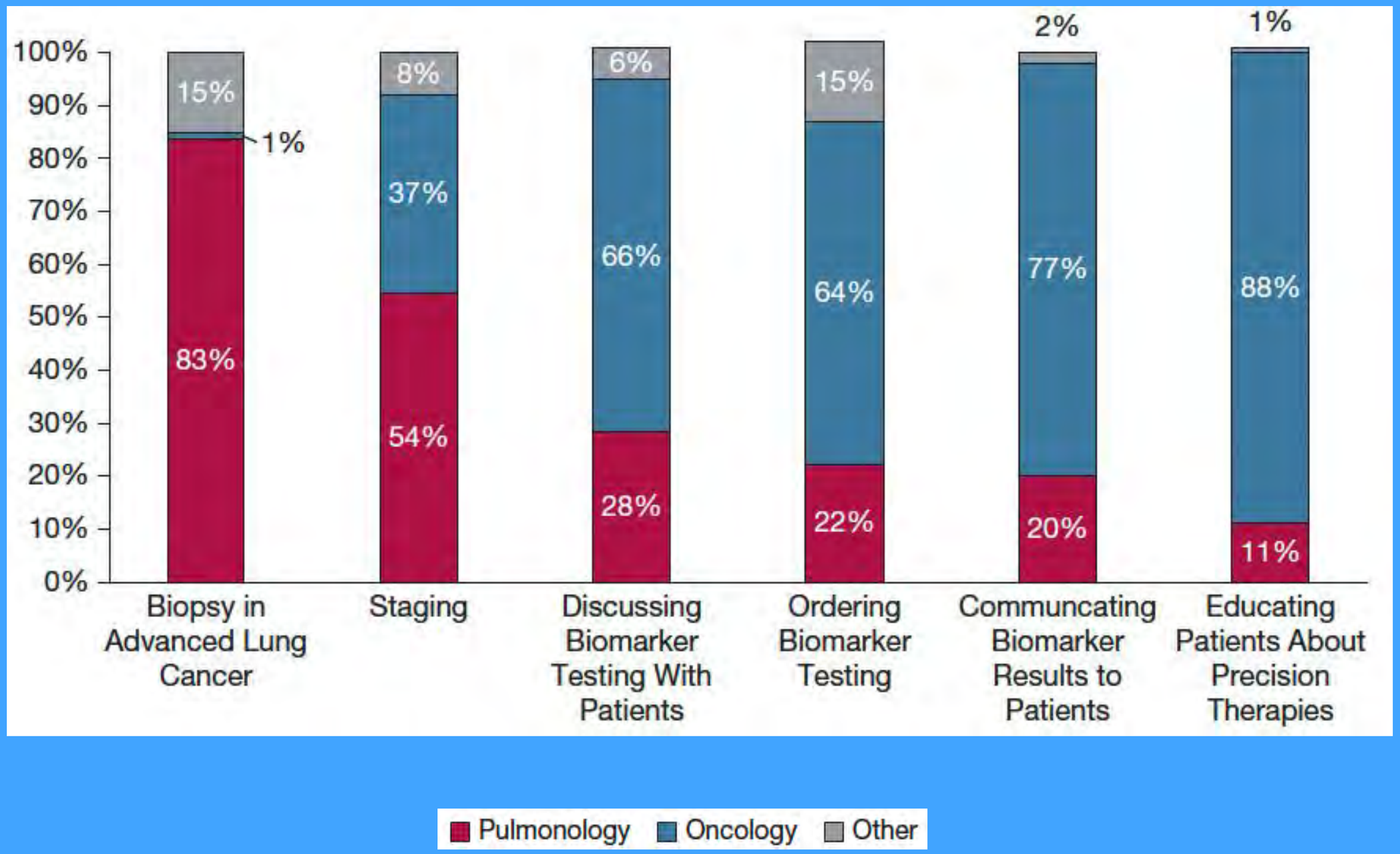
Pulmonologist's Perspective



Fox Cancer J Clin. 2023

Survey of Pulmonologists

Who leads diagnostic activities?



Fox *Chest*. 2024

Pulmonologist perspective

Perceived Role

- **~ Half (46%) biomarker testing is out their scope of practice**
- **~ Half (51%) lack knowledge for which tests to order**

Tumor Board

- **Only 2/3 participate in a tumor board**
- **Time being the most common barrier**

Associated with ordering biomarker testing (P<0.5)

- **Longer practice tenure (16+, 64% vs <15, 53%)**
- **Higher case volumes (≥6, 72% vs <5, 50%)**
- **Tumor board participation (yes, 62% vs no, 48%)**

Fox AH, *Chest*. 2024

Summary

- **EBUS - first line test in NSCLC for diagnostic and staging**
- **EBUS is a validated method for acquiring tissue for biomarker analysis and PDL-1 testing.**
- **Pulmonologists need to own beyond biopsy and referral**
- **Pulmonologists must consider adequate tissue for biomarker testing during procedure selection**
- **Pulmonologists lack MDT support, knowledge, and time**
- **Communication between Pulmonary, Oncology and Pathology is critical for the success of biomarker testing and treatment of patients with lung cancer.**
- **These are all targets for intervention**