NATIONAL LUNG CANCER ROUNDTABLE

American Cancer Society®

Project ECHO®

Addressing Lung Cancer Biomarker Testing Through Project ECHO: 2022-2023 Expansion

Session Six: "Genomic testing at the time of resistance"

Welcome to Session Six:
ACS/NLCRT Lung Cancer Biomarker Testing Project ECHO

Each ECHO session will be recorded

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Today's materials will be made available on www.echo.cancer.org

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Today's Agenda

Agenda Preview & Introductions (5 min)

Didactic Presentation: Dr. Rick Hall, UVA
Genomic testing at the time of resistance (15 min)

Didactic Q/A (5 min)

Case Presentation: Dr. Nathan Roberts
Hematology/Oncology Fellowship Program, UVA (5 min)

Case Presentation Recommendation/Discussion (10 min)

Post-Session Poll & Wrap Up (5 min)

This ACS/NLCRT Lung Cancer Biomarker Testing ECHO series is made possible by funding provided by:

Additional thanks to Foundation Medicine

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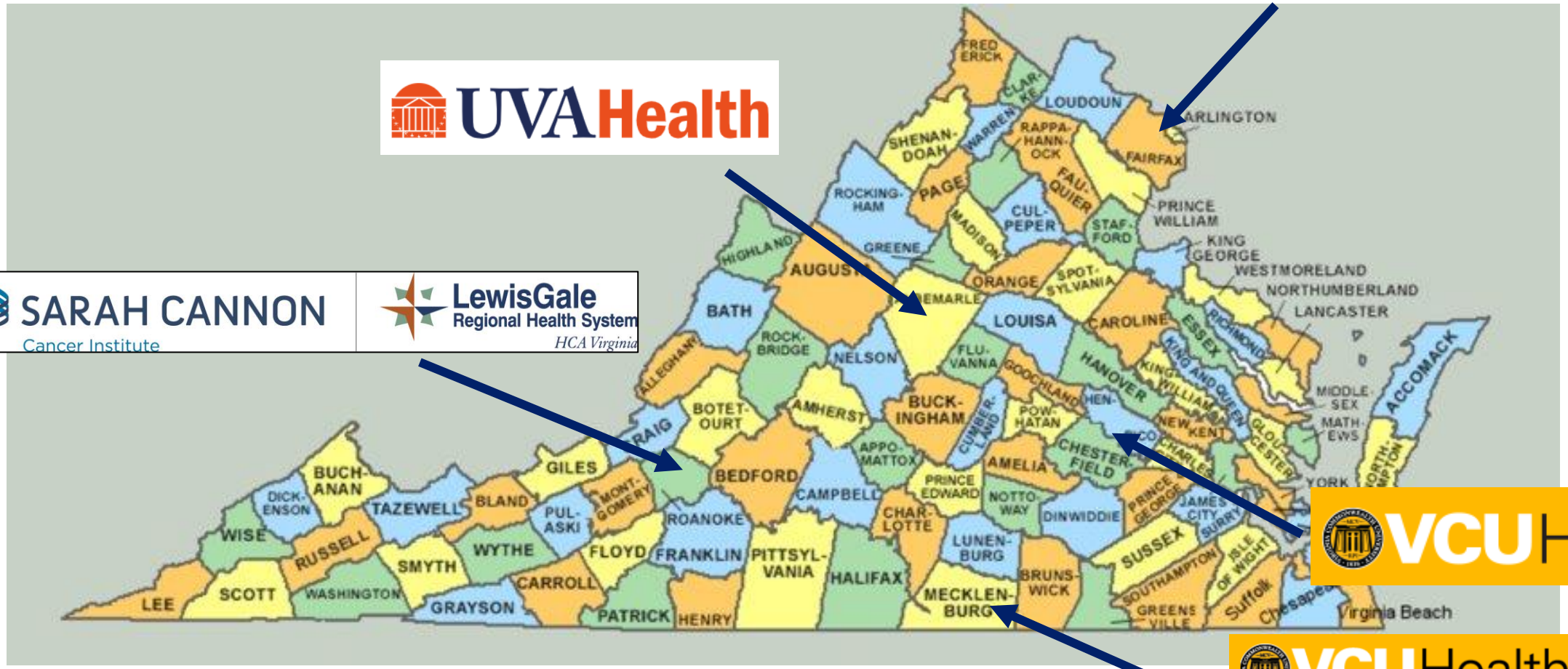

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DIDACTIC PRESENTATION

"Genomic testing at the time of resistance"

Richard D. Hall, MD, MS
University of Virginia
Associate Professor of Medicine
Hematology/Oncology Fellowship Program Director

UVAHealth

ONCOGENE MUTATION TESTING AT THE TIME OF RESISTANCE
TISSUE, BLOOD, OR EVEN PERFORM AT ALL?

RICHARD HALL MD, MS

ASSOCIATE PROFESSOR OF MEDICINE, DIVISION OF HEMATOLOGY/ONCOLOGY

AMERICAN CANCER SOCIETY – PROJECT ECHO

APRIL 27, 2023

UNIVERSITY of VIRGINIA HEALTH SYSTEM

LEARNING OBJECTIVES

Identify molecular targets for therapy in NSCLC

Understand role of ctDNA and tissue testing in NSCLC

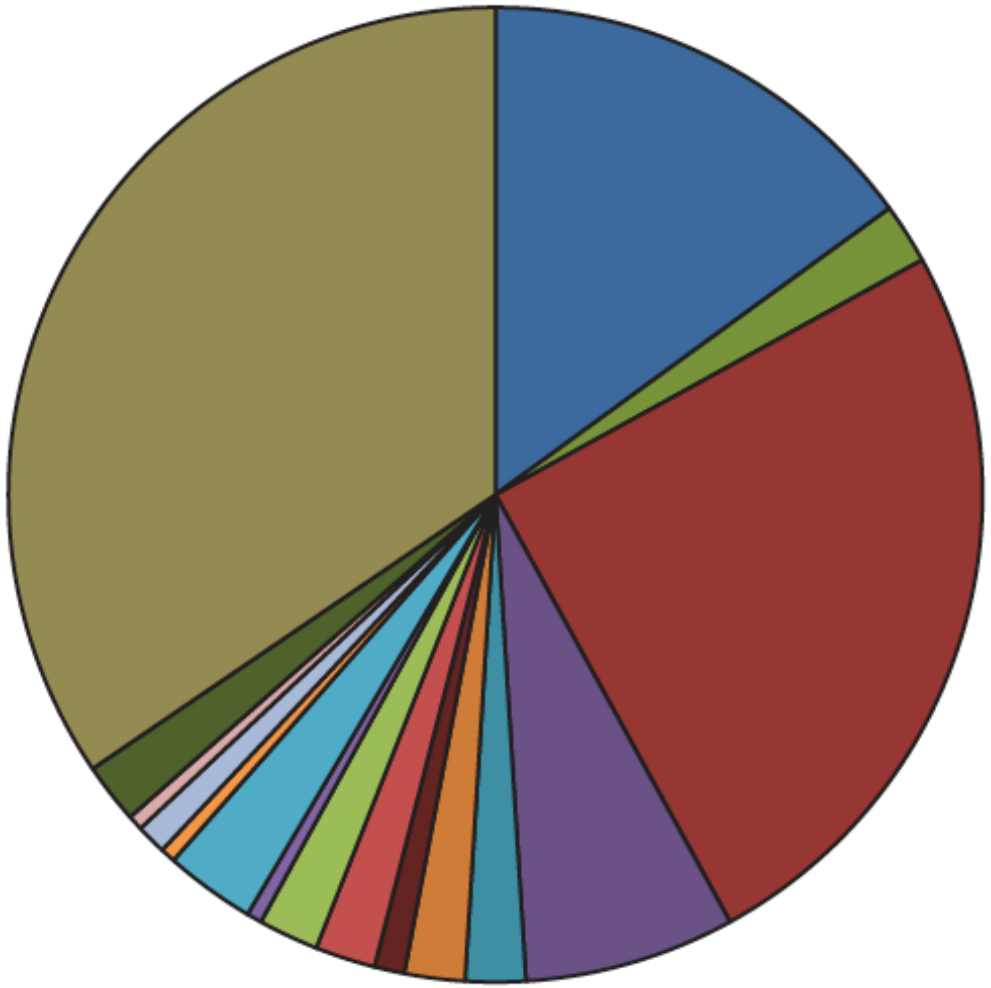
Identify reasons for molecular testing in EGFR positive NSCLC

TESTING HISTORY:

2011 ASCO:	**EGFR (provisional)**
2013 CAP / IASLC / AMP:	**EGFR, ALK, ALL PATIENTS WITH ADVANCED STAGE, <14 DAY TAT**
2018 CAP/ IASLC / AMP:	**EGFR, ALK, ROS1, PD-L1**
2018 ASCO:	**EGFR, ALK, ROS1, BRAF, PD-L1**
NCCN v3.2023:	**NGS (preferred) or broad panel testing targets with therapeutic options**

ASCO Education Book 2019, Pennell et al

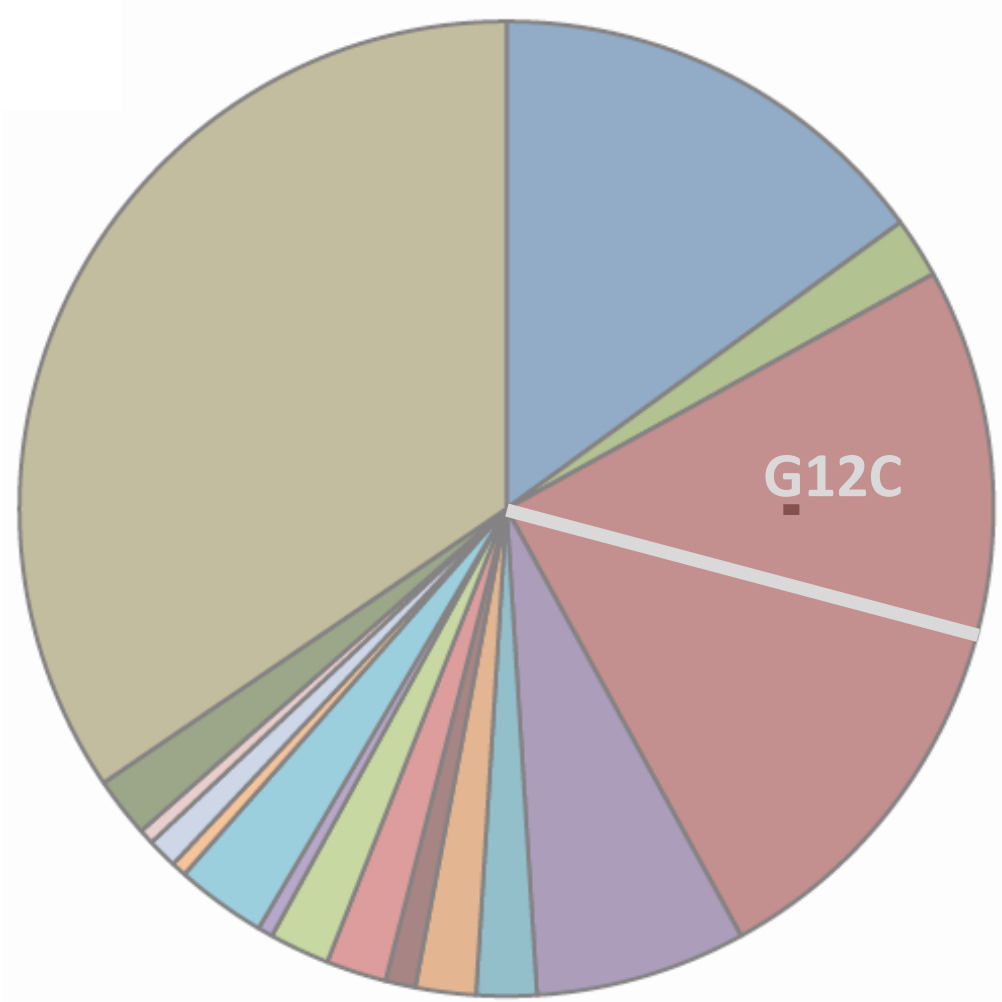
NSCLC ADENOCARCINOMA ONCOGENES



- *EGFR*-sensitising (15%)
- *EGFR* other (2%)
- *KRAS* (25%)
- *ALK* (7%)
- *HER2* (2%)
- *BRAFV600E* (2%)
- *BRAF* other (1%)
- *ROS1* (2%)
- *RET* (2%)
- *NTRK1* (0·5%)
- *MET* (3%)
- *MAP2K1* (0·5%)
- *PIK3CA* (1%)
- *NRAS* (0·5%)
- >1 mutation (3%)
- Unknown (31%)

Lancet 2016; 388: 1012-1024

TREATMENT OPTIONS FOR ONCOGENE DRIVEN NSCLC



- *EGFR*-sensitising (15%) **OSIMERTINIB**
- *EGFR* other (2%) **AFATINIB, AMIVANTAMAB, MOBOCERTINIB**
- *KRAS* (25%) **G12C: ADAGRASIB, SOTORASIB**
- *ALK* (7%) **ALECTINIB, BRIGATINIB, LORLATINIB**
- *HER2* (2%) **TRASTUZUMAB-DERUXTECAN**
- *BRAFV600E* (2%) **DABRAFENIB / TRAMETINIB**
- *BRAF* other (1%)
- *ROS1* (2%) **ENTRECTINIB, LORLATINIB**
- *RET* (2%) **SELPERCATINIB, PRALSETINIB**
- *NTRK1* (0·5%) **ENTRECTINIB, LAROTRECTINIB**
- *MET* (3%) **CAPMATINIB, TEPOTINIB**
- *MAP2K1* (0·5%)
- *PIK3CA* (1%)
- *NRAS* (0·5%)
- >1 mutation (3%)
- Unknown (31%)

Lancet 2016; 388: 1012-1024

TESTING OPTIONS: TISSUE VS BLOOD

	Benefits	Limitations
ctDNA	Quick turnaround time	Variable ctDNA shedding decreases sensitivity
	Minimally invasive	More technically challenging for fusions or copy number alterations
	Captures tumoral heterogeneity	
	Ability to detect disease when none is detectable on imaging	
	Temporal monitoring	
Tissue	Direct observation of the tumor to establish tumor purity	Often requires invasive procedure
	Preferred method of biomarker testing (HER2, ER, PR, PD-L1, etc.)	Generally longer turnaround time
	Ability to validate tumor somatic alterations compared to germline and/or CHIP	

Other issues pertinent to lung cancer:

- **PD-L1 IHC**
- **Histology**

ASCO Post, 1 Dec 2021, Huffman and Parikh

TESTING OPTIONS: TISSUE VS BLOOD

NILE Study

Non-inferiority study of ctDNA vs SOC tissue genotyping

282 treatment naïve non-squamous NSCLC patients

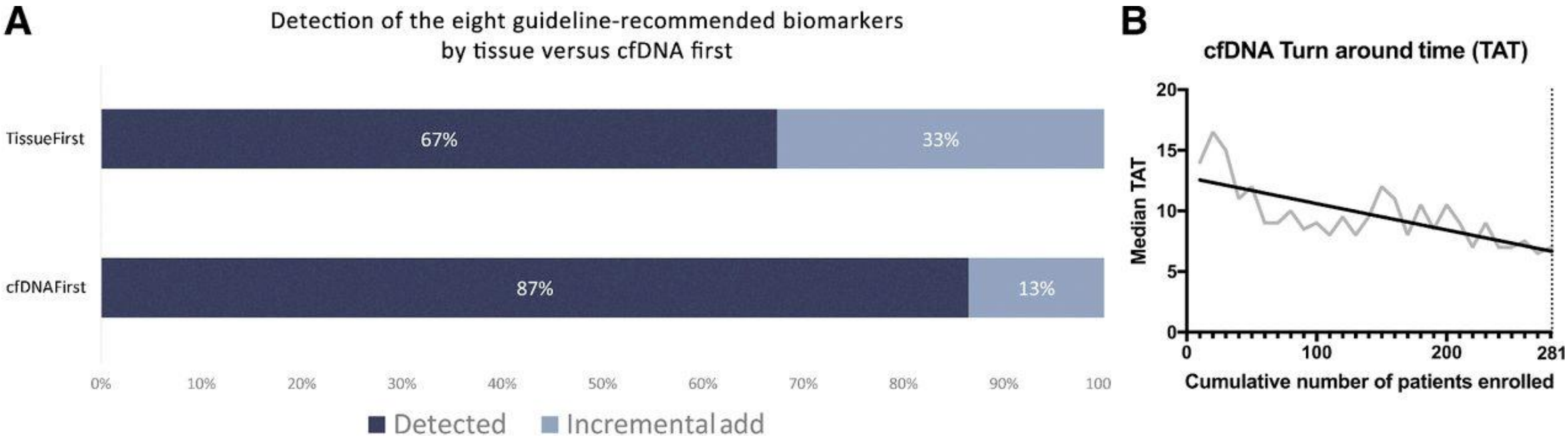
Paired ctDNA and SOC tissue testing

SOC tissue testing was deemed QNS if < 8 guideline recommended biomarkers

EGFR, ALK, ROS1, BRAF, RET, MET amp, MET exon 14, ERBB2

Clin Cancer Res (2019) 25 (15): 4691–4700

TESTING OPTIONS: TISSUE VS BLOOD



MEAN TAT:

Tissue: 15 days **ctDNA: 9 days** **p < 0.0001**

Clin Cancer Res (2019) 25 (15): 4691–4700

TESTING OPTIONS: TISSUE VS BLOOD

Guideline-recommended biomarker positivity by sample type		Tissue		
		Positive	Negative	Total
cfDNA	Positive	48	29	77
	Negative	12	193	205
	Total	60	222	282

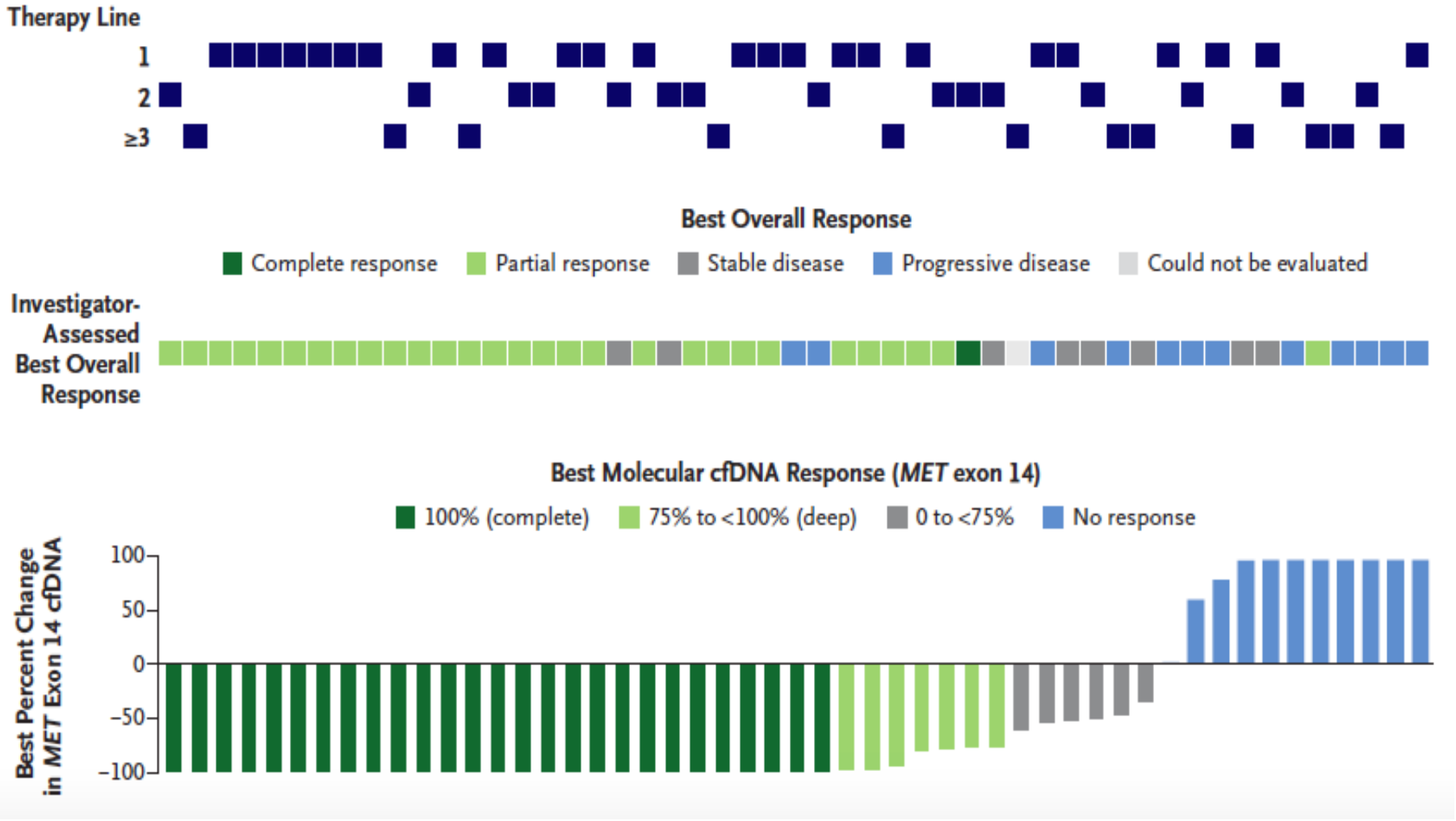
Tissue rate: 60/282 (21.3%) **ctDNA rate: 77/282 (27.3%)**

Tissue “undergenotyping:” 82% of tissue < 8 biomarkers

ctDNA increased target identification by 32% over tissue

Clin Cancer Res (2019) 25 (15): 4691–4700

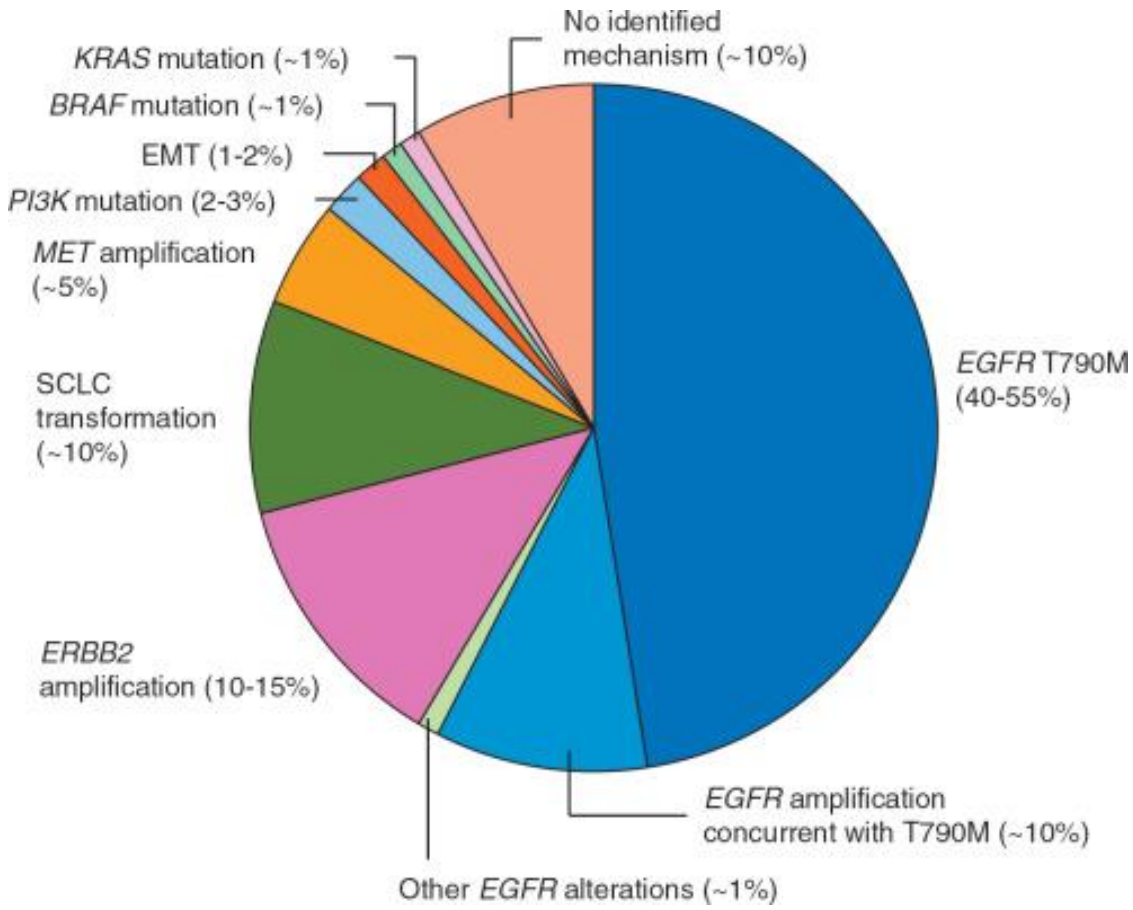
ctDNA TO MONITOR RESPONSE - TEPOTINIB



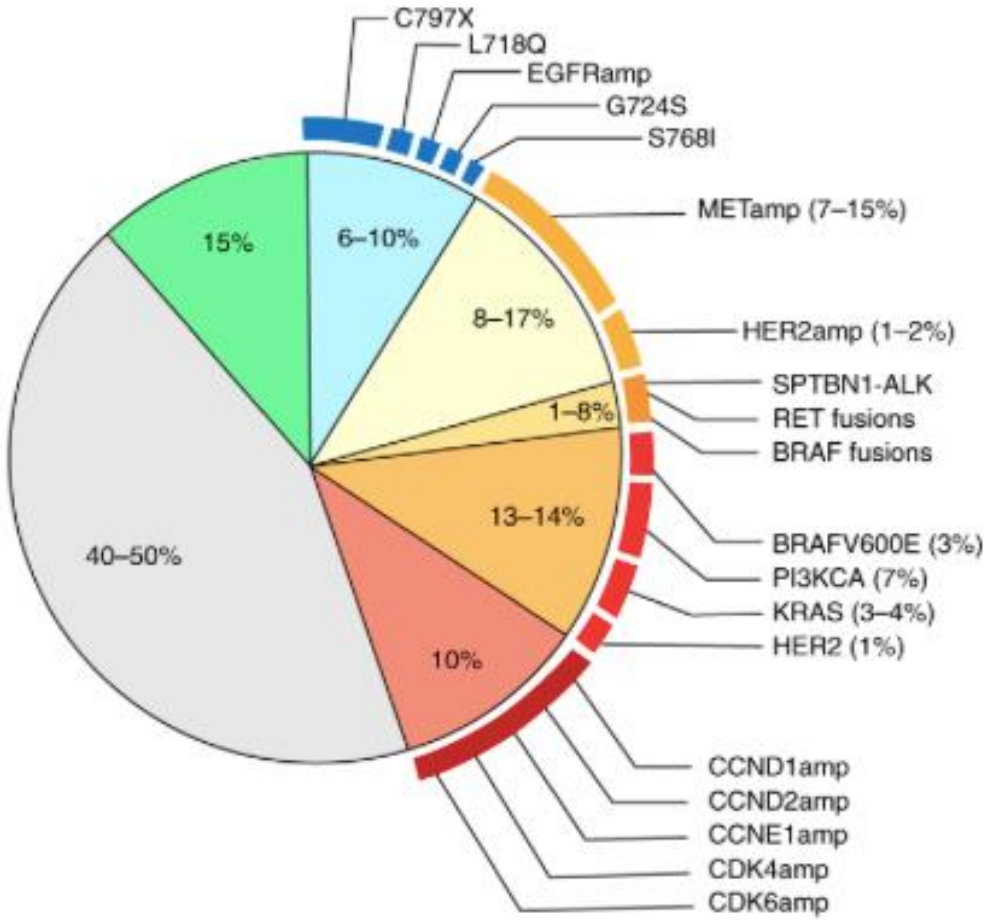
N Engl J Med 2020;383:931-43.

EGFR AND CHANGING RESISTANCE

Old Paradigm: Post 1st Gen TKI



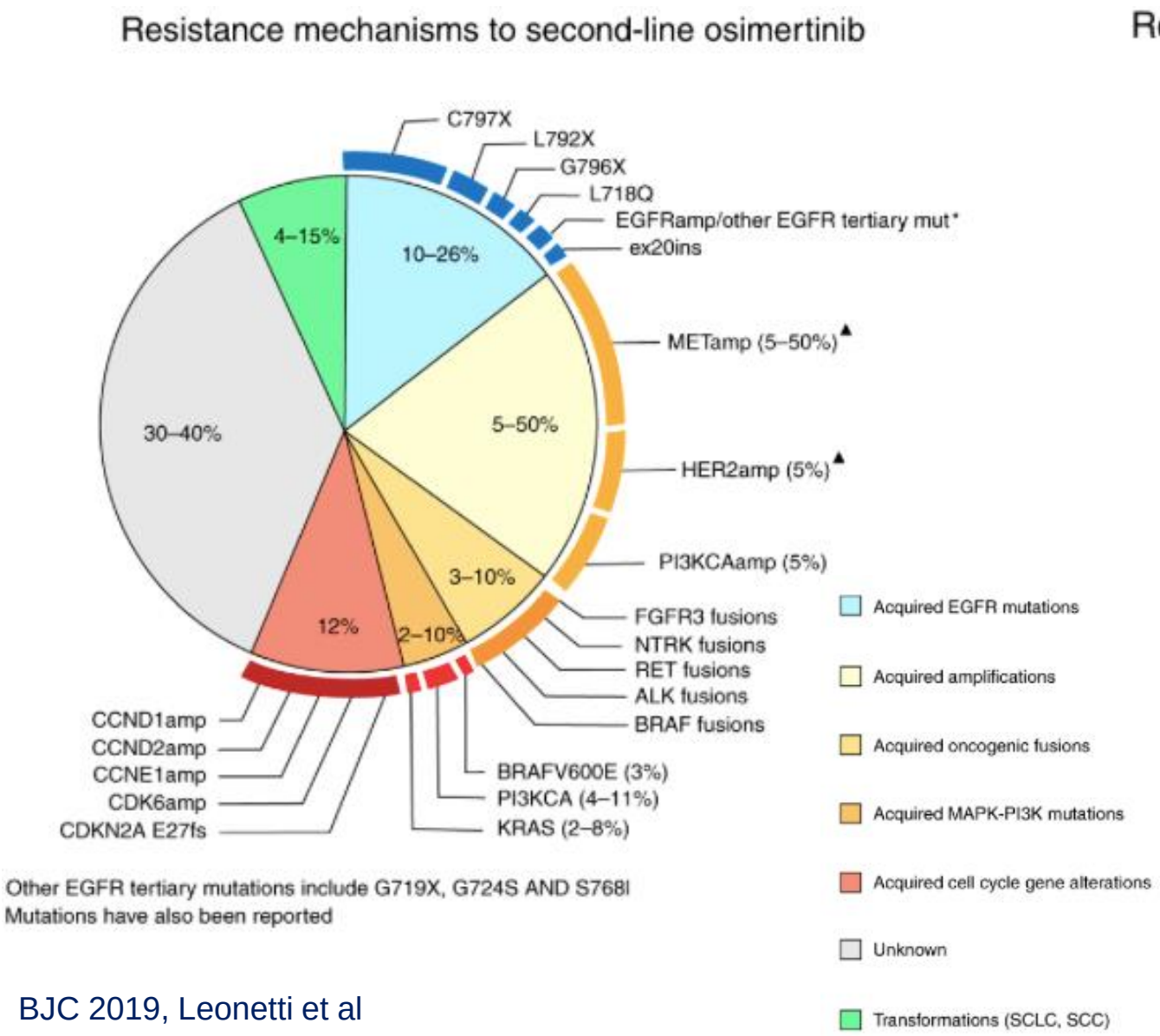
New Paradigm: Post 3rd Gen TKI

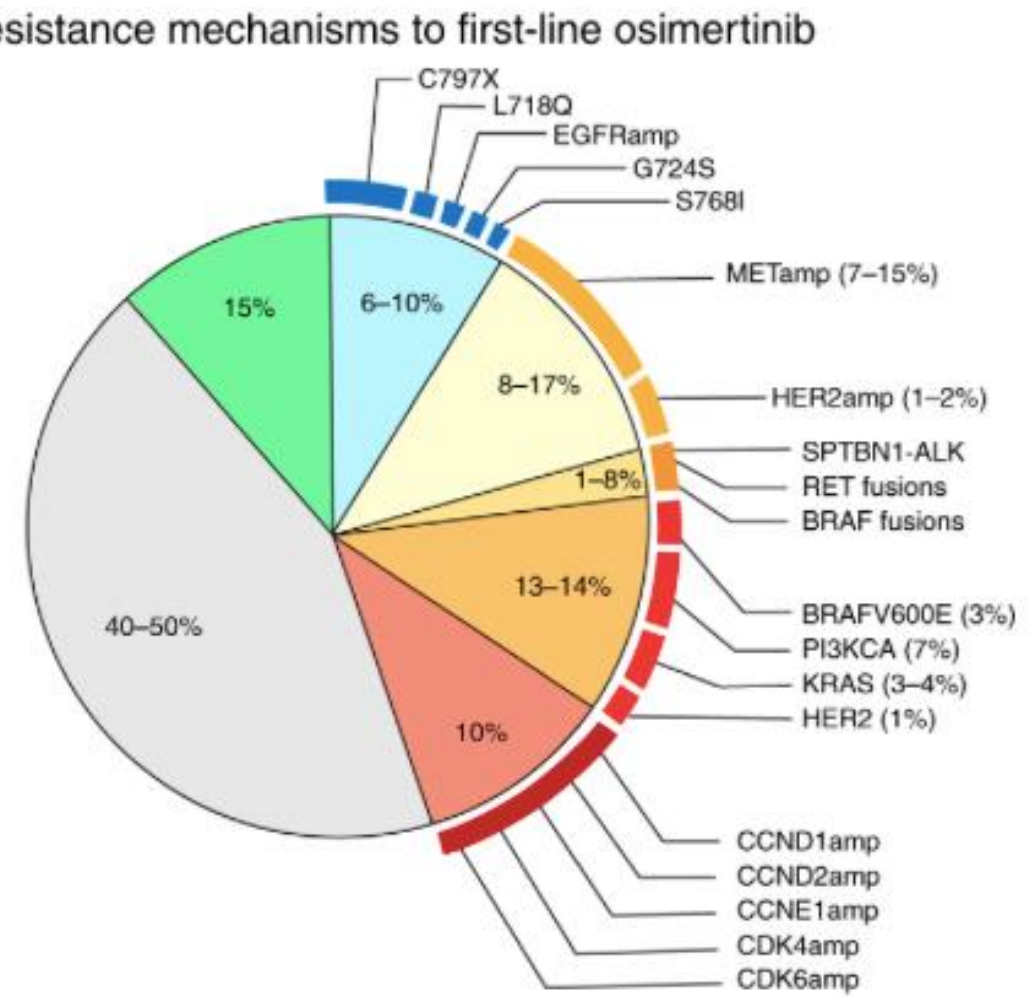


Annals of Oncology, Volume 29, Supplement 1, January 2018, Pages i10-i19

BJC 2019, Leonetti et al

RESISTANCE: LINE OF THERAPY MATTERS





BJC 2019, Leonetti et al

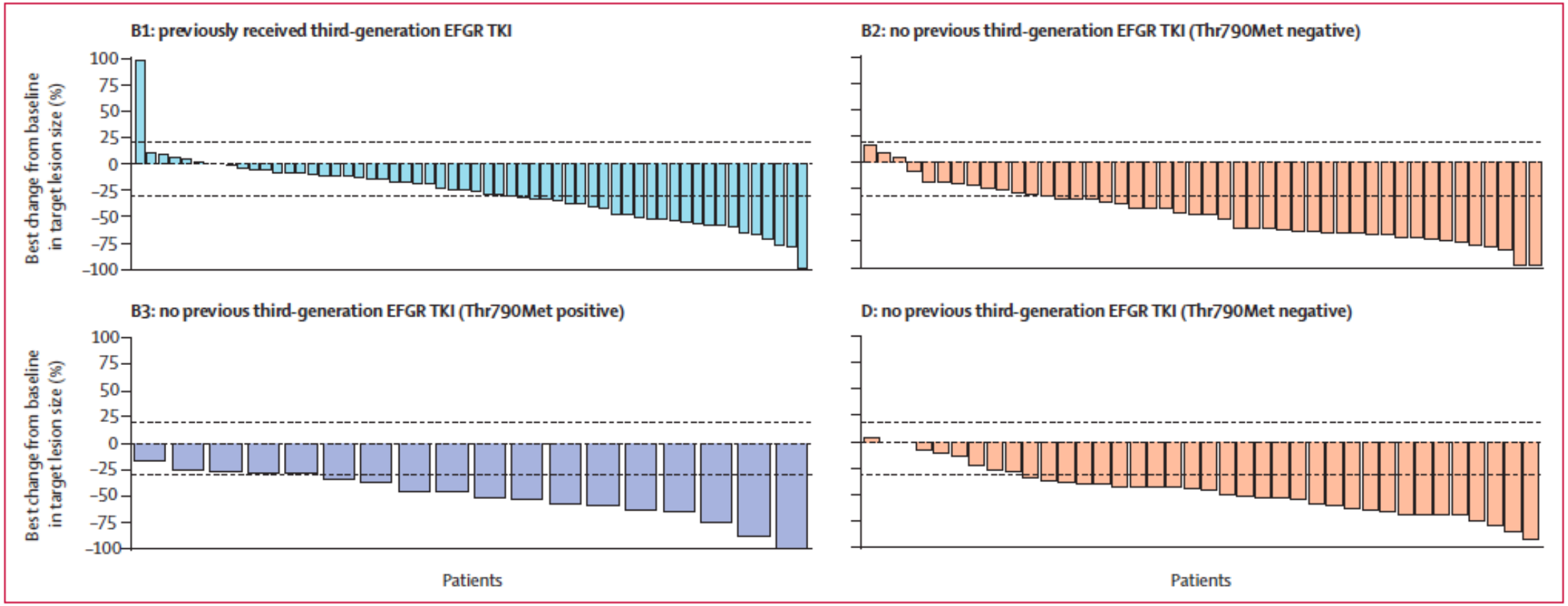
WHY TEST AT RESISTANCE

Osimertinib plus savolitinib in patients with *EGFR* mutation-positive, *MET*-amplified, non-small-cell lung cancer after progression on EGFR tyrosine kinase inhibitors: interim results from a multicentre, open-label, phase 1b study

Lecia V Sequist, Ji-Youn Han*, Myung-Ju Ahn, Byoung Chul Cho, Helena Yu, Sang-We Kim, James Chih-Hsin Yang, Jong Seok Lee, Wu-Chou Su, Dariusz Kowalski, Sergey Orlov, Mireille Cantarini, Remy B Verheijen, Anders Mellemgaard, Lone Ottesen, Paul Frewer, Xiaoling Ou, Geoffrey Oxnard*

TATTON Study: Lancet Oncol 2020; 21: 373–86

WHY TEST AT RESISTANCE



48% ORR in part B (post TKI)
64% in part D (T790M neg and no prior 3rd gen TKI)

Other studies ongoing: ORCHARD, SAVANNAH, others

Lancet Oncol 2020; 21: 373–86

SUMMARY

In NSCLC, there are numerous 1st line (seven) and 2nd line (three) molecular targets for treatment

ctDNA offers advantages in time and coverage in newly diagnosed patients

ctDNA will likely be used to monitor response in the future

Resistance to therapy will drive new treatments in *EGFR* positive disease and likely other targets

Case presentation

- Patient is a a 71 yo F who is referred to medical oncology by her gastroenterologist for evaluation of elevated CEA and hepatic lesion.
- PET/CT is obtained which reveals 3x2 cm left perihilar hypermetabolic lesion, ipsilateral mediastinal and hilar hypermetabolic lymph nodes, and FDG avid lesions within the thoracic spine, lumbar spine, and sacrum.
- Left upper lobe lung biopsy is obtained which confirms adenocarcinoma (PD-L1 5%), initial stage at diagnosis T2aN2M1b, stage IVB.
- Genomic analysis is sent on the primary tumor biopsy.

Molecular analysis reveals EGFR exon 21 mutation (L858R)

Molecular Markers by PCR and FISH:

EGFR:	Exon 21 Mutation **DETECTED** c.2573T>G (p.L858R)
ALK:	Not performed
ROS:	Not performed
BRAF:	NEGATIVE
NTRK1-3:	NEGATIVE
RET:	NEGATIVE

Results:

Test	Result	Mutations
EGFR Mutation		
EGFR Exon 18	Not Detected	N/A
EGFR Exon 19	Not Detected	N/A
EGFR Exon 20 T790M	Not Detected	N/A
EGFR Exon 20 Other Mutations	Not Detected	N/A
EGFR Exon 21	Detected	c.2573T>G (p.L858R)

Case presentation (Cont'd)

- The patient begins 1st-line therapy with osimertinib 80 mg daily and receives palliative radiation to thoracic spine and sacrum.
- Initial restaging imaging ~4 months after beginning osimertinib reveals near total resolution (~1.2 cm residual lesion) of left perihilar mass, resolution of mediastinal and hilar adenopathy, and stability of multiple now sclerotic-appearing osseous metastases.
- Approximately 27 months after starting osimertinib, a PET/CT is obtained for worsening low back and left flank pain. This demonstrates clear evidence of disease progression with findings of new multifocal osseous metastatic lesions.
- Patient is referred to UVA for second opinion.

GUARDANT 360 testing on peripheral blood reveals emergence of BRAF V600E mutation in ctDNA

DETECTED ALTERATION(S) / BIOMARKER(S)	% CFDNA OR AMPLIFICATION	ASSOCIATED FDA-APPROVED THERAPIES	CLINICAL TRIAL AVAILABILITY
EGFR L858R	41.7%	Afatinib, Dacomitinib, Erlotinib, Erlotinib+ramucirumab, Gefitinib, Osimertinib	Yes
BRAF V600E	11.0%	Dabrafenib+trametinib, Binimetinib, Cobimetinib, Dabrafenib, Encorafenib+binimetinib, Trametinib, Vemurafenib, Vemurafenib+cobimetinib	Yes
TP53 R342*	30.2%	None	Yes
PIK3CA Amplification	High (+++) Plasma Copy Number: 4.2	None	Yes
EGFR Amplification	Medium (++) Plasma Copy Number: 2.7	None	Yes

Case presentation (conclusion)

- While awaiting referral to UVA, the patient's local oncologist opted to add bevacizumab and to continue osimertinib. Palliative radiation to lumbar spine and left hip are completed as well.
- Thoracic oncology at UVA recommends discontinuation of bevacizumab in favor of starting dabrafenib 150 mg BID, trametinib 1 mg daily, and to continue osimertinib.
- Patient is lost to oncology follow up at UVA, however last medical contact in the EHR occurred ~2 months after last visit with UVA providers, and at this time both dabrafenib and trametinib appeared on her medication list.

Wrap-Up & Post-Session Poll Questions

A Few Reminders:

Next ECHO Session: Monday, June 12th at 4:30 – 5:15 PM (EST)

Didactic Presentation will include ACSO updates and Biomarker Testing

Materials and Resources will be made available via the ACS ECHO Website

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

Additional Feedback on Today's Session? Tell us in the Post Session Feedback Forum
(URL in chat box) https://forms.office.com/r/TNR4UT0uc1

Questions: Contact Korey.Hofmann@cancer.org or Annika.Dean@cancer.org

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PLEASE MARK YOUR CALENDAR

MONDAY, JUNE 12TH AT 4:30PM EST

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NATIONAL LUNG CANCER ROUNDTABLE