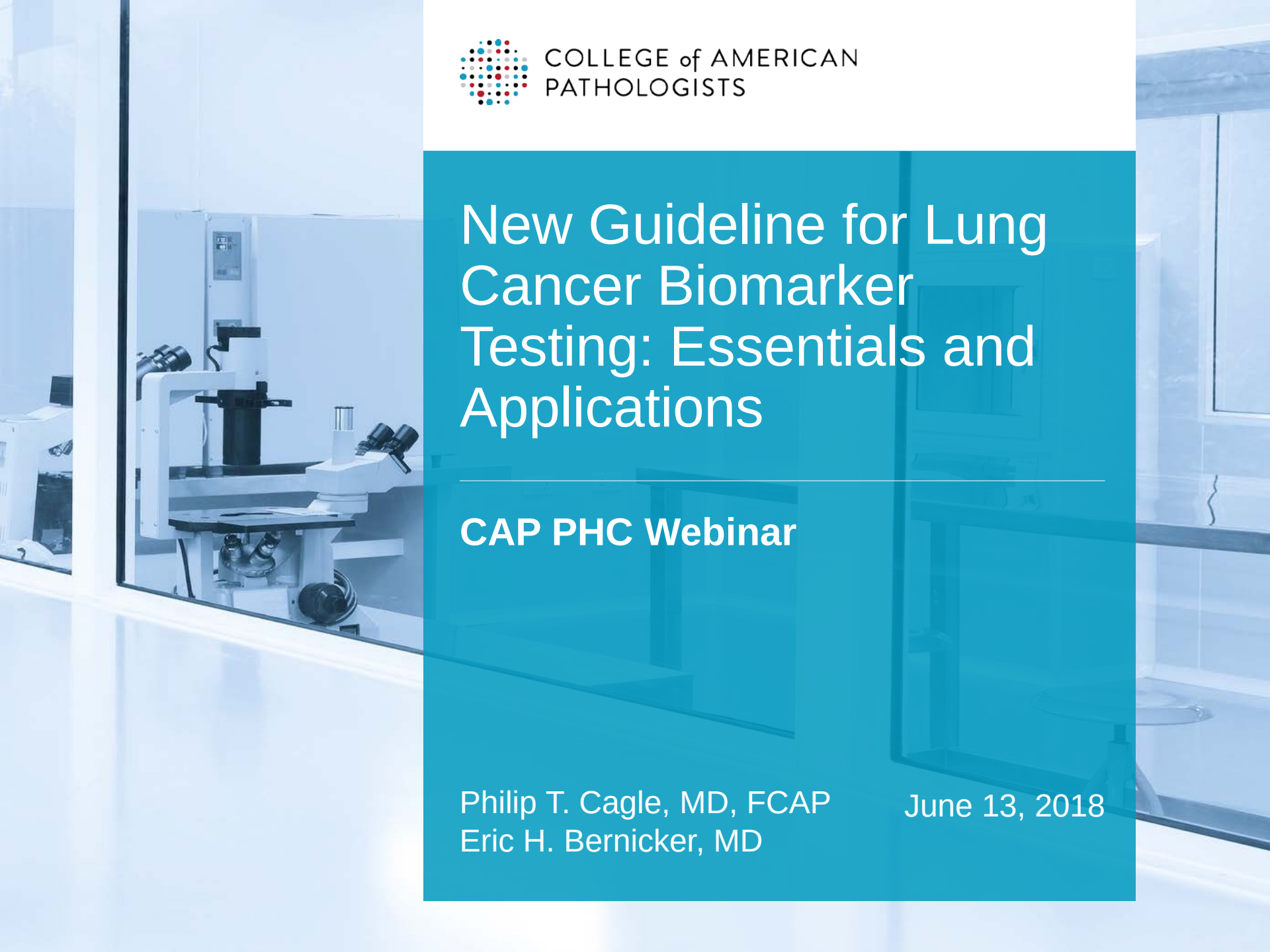

COLLEGE of AMERICAN PATHOLOGISTS

New Guideline for Lung Cancer Biomarker Testing: Essentials and Applications

CAP PHC Webinar

Philip T. Cagle, MD, FCAP
Eric H. Bernicker, MD

June 13, 2018

Webinar Host

- **This series is sponsored by the Personalized Healthcare Committee (PHC)**
- **Today's webinar host is PHC member, Dr. Joseph Willis**

Housekeeping

- **This presentation will be recorded. The recording and PDF will go out to all registrants in one week**
- **All lines are muted during the presentation**
- **Please send in your questions as you think of them via the “Question Box” in your control panel**

Philip T. Cagle, MD, FCAP

- **Director of Pulmonary Pathology at Houston Methodist**
- **Editor-in-chief of the *Archives of Pathology and Laboratory Medicine***
- **Co-chair of the “Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment With Targeted Tyrosine Kinase Inhibitors”**

Eric H. Bernicker, MD

- **Assistant clinical professor of medicine at Weill Cornell Medicine**
- **Primary investigator for a number of cooperative group, industry-sponsored, and investigator-initiated trials looking at different novel therapies for lung cancer, including immunotherapy**
- **Expert Panel member of the “Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment With Targeted Tyrosine Kinase Inhibitors”**

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- **Opinions expressed by the speaker are the speaker's own and do not necessarily reflect an endorsement by the CAP of any organizations, equipment, reagents, materials, or services used by participating laboratories.**

Dr. Cagle's Conflicts of Interest

- **None**

Dr. Bernicker's Conflicts of Interest

Advisory board: Astra Zeneca, Abbvie, and Guardant Health

Practical Description and Application of the Guidelines for Anatomic Pathologists

- **Background and general perspectives/caveats-Dr. Cagle**
- **Approach to guidelines from anatomic pathologist perspective-Dr. Cagle**
- **Approach to guidelines from oncologist perspective-Dr. Bernicker**

Coming Related Guidelines

Collection and Handling of Thoracic Small Biopsy and Cytology Specimens for Ancillary Studies

Sinchita Roy Chowdhuri, MD, PhD

Coming Related Guidelines

PD1-PD-L1 Testing of Patients with Lung Cancer for Selection of Immunooncology Therapies

Lynette Sholl, MD

Molecular Testing Guideline for Selection of Lung Cancer Patients for EGFR and ALK Tyrosine Kinase Inhibitors

Guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology

Neal I. Lindeman, MD; Philip T. Cagle, MD; Mary Beth Beasley, MD; Dhananjay Arun Chitale, MD; Sanja Dacic, MD, PhD; Giuseppe Giaccone, MD, PhD; Robert Brian Jenkins, MD, PhD; David J. Kwiatkowski, MD, PhD; Juan-Sebastian Saldivar, MD; Jeremy Squire, PhD; Erik Thunnissen, MD, PhD; Marc Ladanyi, MD

Published in *Archives of Pathology & Laboratory Medicine* (CAP), *Journal of Thoracic Oncology* (IASLC) and *Journal of Molecular Diagnostics* (AMP)

1533 articles screened to identify 521 pertinent articles

Drafts circulated to writing panel (Version 1), advisory panel (Version 2), and the public (Version 3), before submission (Version 4)

March 2010 Initiated to ePublication in April 2013

Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment With Targeted Tyrosine Kinase Inhibitors

Guideline From the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology

Neal I. Lindeman, MD; Philip T. Cagle, MD; Dara L. Aisner, MD, PhD; Maria E. Arcila, MD; Mary Beth Beasley, MD; Eric Bernicker, MD; Carol Colasacco, MLIS, SCT(ASCP); Sanja Dacic, MD, PhD; Fred R. Hirsch, MD, PhD; Keith Kerr, MB, ChB; David J. Kwiatkowski, MD, PhD; Marc Ladanyi, MD; Jan A. Nowak, MD, PhD; Lynette Sholl, MD; Robyn Temple-Smolkin, PhD; Benjamin Solomon, MBBS, PhD; Lesley H. Souter, PhD; Erik Thunnissen, MD, PhD; Ming S. Tsao, MD; Christina B. Ventura, MPH, MT(ASCP); Murry W. Wynes, PhD; Yasushi Yatabe, MD, PhD

PUBLISHED JANUARY 2018

Bethesda, February, 2016

CAP/IASLC/AMP Biomarkers Guideline
CAP Expert Panel Members

Sanja Dacic, MD, PhD

Mary Beth Beasley, MD

Eric Bernicker, MD

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Keith Kerr BSc, MBChB, FRCPath, FRCPE

COLLEGE of AMERICAN PATHOLOGISTS

A Consideration for Testing: Writing Guidelines and In Practice

- **70% of lung cancer patients present in advanced stage**
- **Typically get only small biopsy and/or cytology specimen for diagnosis: limited tissue in 70% of lung cancers**
- **May be potentially eligible for TKI targeted therapy or immunotherapy**
- **Small sample size for testing is a potential concern**

Philosophy for Biomarker Testing of Lung Cancer Biopsies: Writing Guidelines and In Practice

1. **Give maximum number of patients a chance at therapy**
2. **Maximum use of minimal tissue**

Rules and Philosophies of the Lung Cancer Biomarker Testing Guidelines

- **Very strict, evidence-based: Actual practice is off-label, doesn't always wait for prospective clinical trials, FDA approval, etc**
- **National Academy of Medicine (formerly Institute of Medicine) criteria and protocols**
- **International—differing practices and resources**
- **Avoid boxing in practitioners; legal implications**

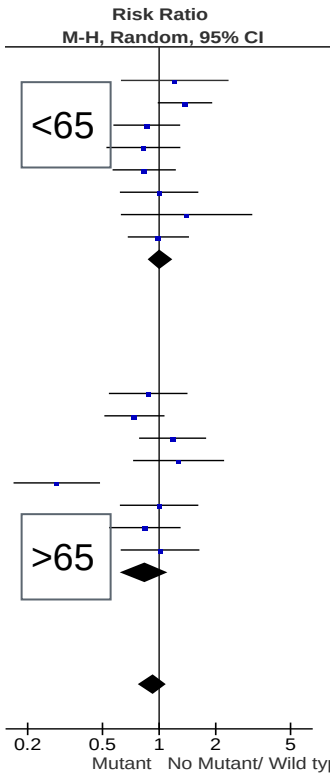
2018 Guidelines

1. **Reaffirmed EGFR and ALK testing recommended for adenocarcinomas**
2. **To select patients for ROS1 targeted therapy, ROS1 testing on all lung adenocarcinomas**
3. **Testing for RET, BRAF, MET or ERBB2/HER2 in lung adenocarcinomas,**
   a. **not indicated as a routine stand-alone assay outside the context of a clinical trial**
   b. **but can be part of larger testing panels performed either initially**
   c. **or when routine EGFR, ALK, and ROS1 testing are negative**

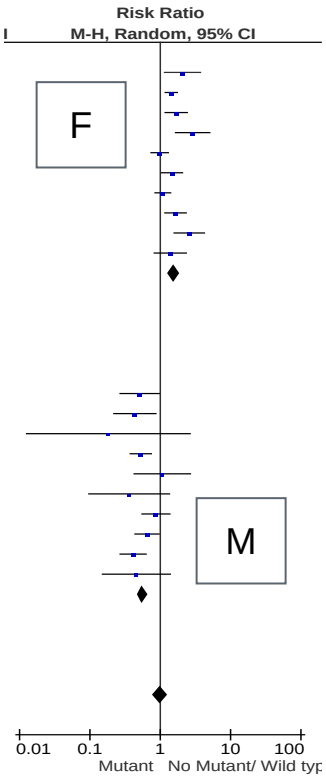
WHOM to Test?

- **Clinical criteria: Inadequate predictors**

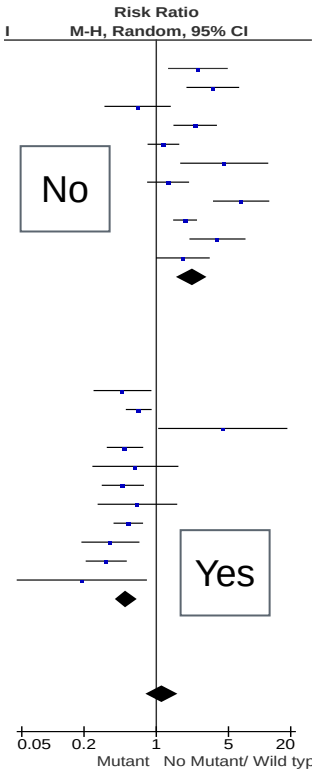
AGE



GENDER



TOBACCO



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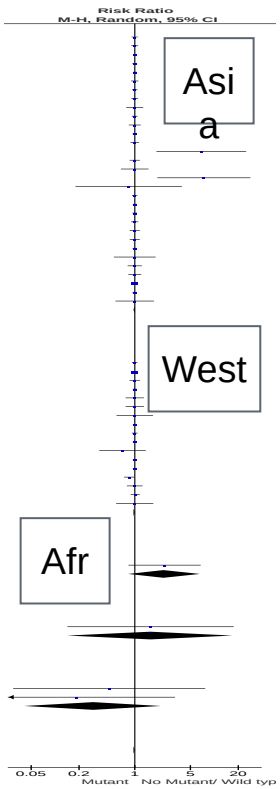


EGFR Mutations: Adeno versus Squamous Cell

Source, y	Predominant Ethnic Origin of Study Population	*EGFR* Mutations in Resected Adenocarcinomas, No. (%)	*EGFR* Mutations in Resected Squamous Cell Carcinomas, No. (%)
Marchetti, *et al*., 2005	European	39/375 (10.4)	0/454
Sugio, *et al*., 2006	Asian	136/322 (42.2)	0/102
Tsao, *et al*., 2006	North American	14/96 (14.6)	0/63
Tsao, *et al.,* 2011	North American	32/231 (13.9)	8/162 (4.9)
Bae, *et al*., 2007	Asian	20/55 (36.4)	0/60
Lee, *et al*., 2010	Asian	36/117 (30.8)	0/56
Miyamae, *et al*., 2011	Asian	-	3/87 (3.4)
Rekhtman, *et al*., 2012	North American	-	0/95
TCGA, 2012	North American	-	2/178 (1.1)

ALK Rearrangements in Squamous Cell Carcinoma

	n	*ALK* Rearrangement Positive, %
Takeuchi, et al., 2008	**71**	**0**
Takahashi, et al., 2010	**75**	**0**
Inamura, et al.,2008	**48**	**0**

2013 Guideline Which Patients Should be Tested for EGFR Mutations and ALK Rearrangements

- **EGFR molecular testing should be used to select patients for EGFR-targeted TKI therapy in adenocarcinomas or tumors with adenocarcinoma component**
- **ALK molecular testing should be used to select patients for ALK-targeted TKI therapy in adenocarcinomas or tumors with adenocarcinoma component**

2013 Guideline Which Patients Should be Tested for EGFR Mutations and Rearrangements

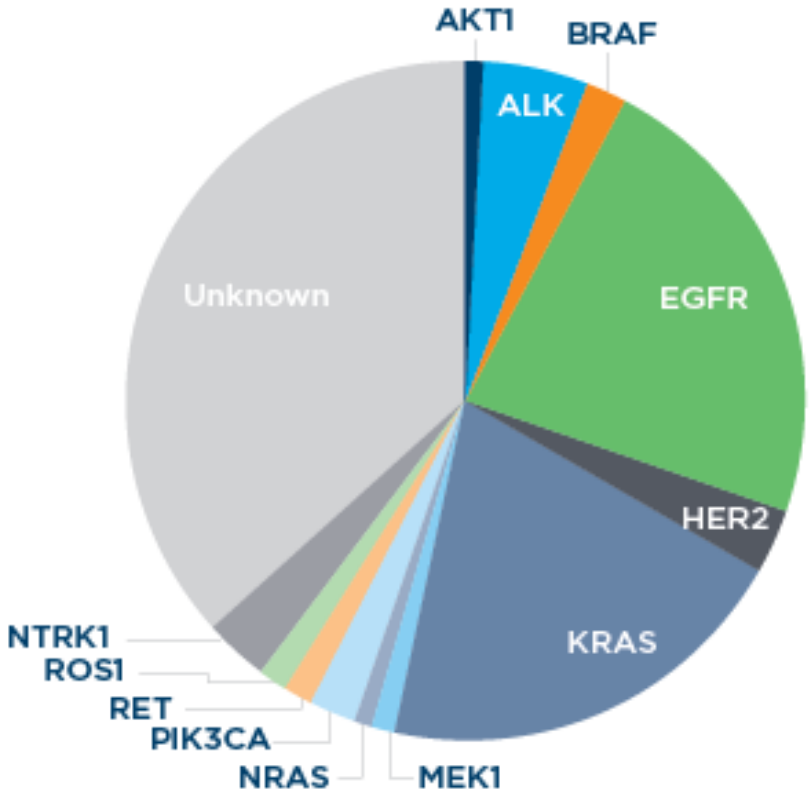
- **In limited samples (like small biopsies) when an adenocarcinoma component cannot be completely excluded, EGFR and ALK testing may be done**
- **(Give maximum number of patients a chance at therapy)**

2018 Revision

Expert Consensus Opinion: **Physicians may use molecular biomarker testing in tumors with histologies other than adenocarcinoma when clinical features indicate a higher probability of an oncogenic driver.**

(Give maximum number of patients a chance at therapy)

Molecular Profile of Adenocarcinoma



Frequency of Mutations	
AKT1	1%
ALK	3–7%
BRAF	1–3%
EGFR	10–35%
HER2	2–4%
KRAS	15–25%
MEK1	1%
NRAS	1%
PIK3CA	1–3%
RET	1–2%
ROS1	1–2%
NTRK1	~3%

http://www.lungevity.org/about-lung-cancer/lung-cancer-101/treatment-options/targeted-therapy

2018 KQ I. What other genes, previously not addressed, should be tested in lung adenocarcinoma?

- **ROS1: 1-2% rearrangement**
- **RET: 1-2% rearrangement**
- **BRAF: 4% half are non-V600E**
- **MET: 3% exon 14 deletion and amplification**
- **ERBB2/ HER2: 2% mutations, exon 20 insertions**
- **(KRAS: 30%)**

2018 Guidelines

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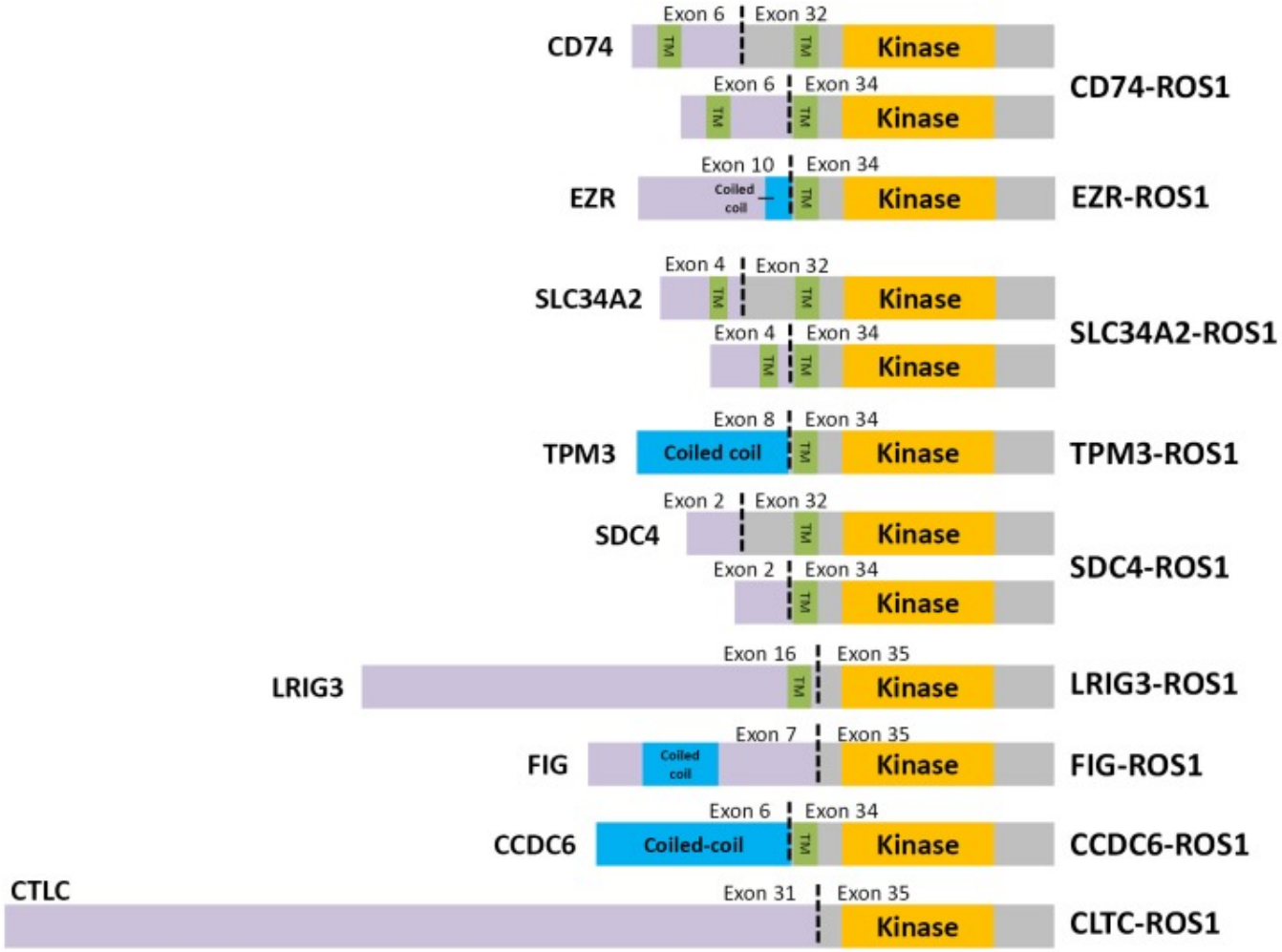
   c. **or when routine EGFR, ALK, and ROS1 testing are negative**

ROS1 REARRANGEMENTS IN NSCLC



Kohno T, et al. Transl Lung Cancer Res. 2015;4:156-64.

Tests for ROS1 Rearrangements in NSCLC

NO GOLD STANDARD METHOD

- **FISH**
- **Immunohistochemistry (IHC)**
- **Anchored multiplex PCR**
- **Reverse-transcriptase PCR**
- **Next generation sequencing**
- **FDA approved the Oncomine™ Dx Target Test (Thermo Fisher Scientific), NGS test**

2018 Guidelines

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   c. **or when routine EGFR, ALK, and ROS1 testing are negative**

On June 22, 2017, FDA granted approvals to dabrafenib and trametinib in combination for patients with metastatic NSCLC with BRAF V600E mutation as detected by an FDA-approved test.

June 22, 2017, FDA approved the Oncomine™ Dx Target Test (Thermo Fisher Scientific), NGS test to detect BRAF, ROS1, and EGFR gene mutations or alterations in tumor tissue of patients with NSCLC.

2018 BRAF Recommendation

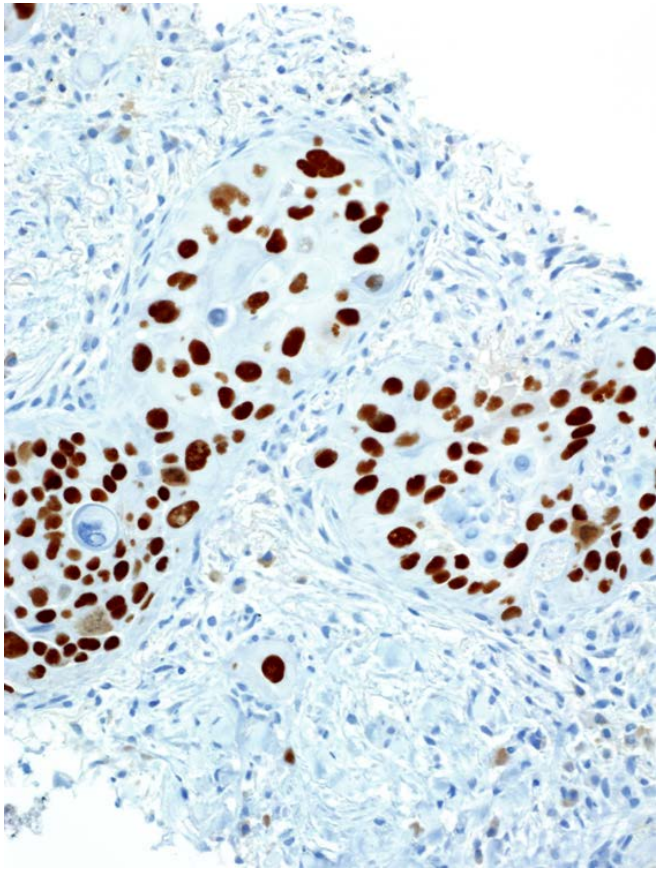
- **The most controversial of all recommendations among the Expert Panel**
- **Published evidence lacked controlled prospective trials**
- **Lacked strength to warrant an international recommendation for single-gene testing for BRAF for all lung adenocarcinoma**

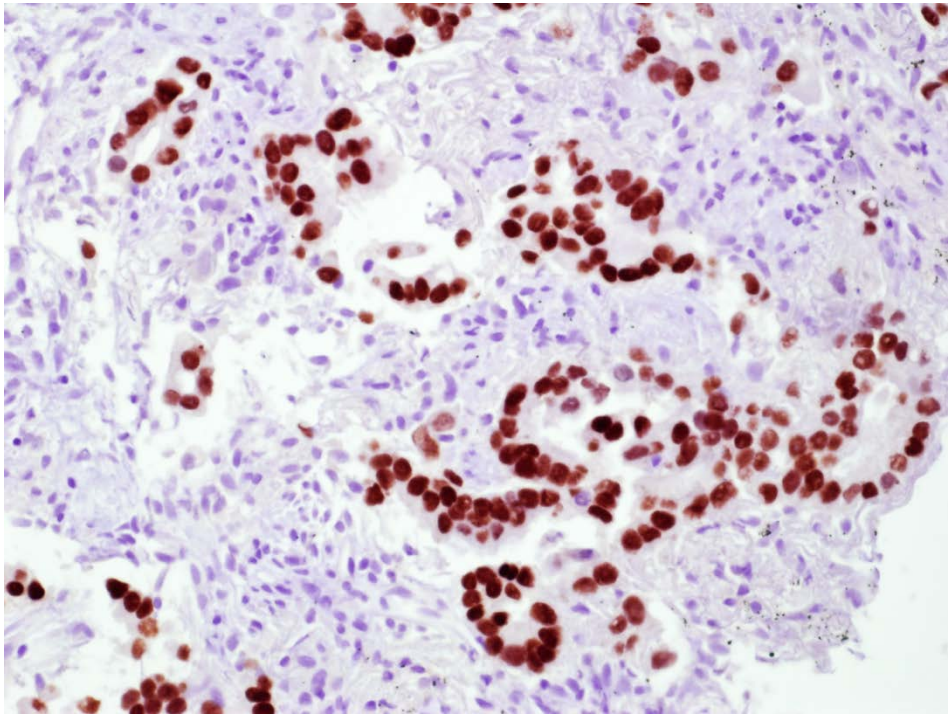
Emerging Markers for Molecular Testing in Lung Cancer

Mitogen-Activated Protein Kinase Kinase 1 (*MEK1/MAP2K1*)
Fibroblast Growth Factor Receptor 1-4 (*FGFR 1-4*)
Neurotrophic Tyrosine Kinase, Receptor, Type 1 – 3 (*NTRK1-3*)
Neuregulin 1 (*NRG1*)
***Ras*-Like Without CAAX 1 (*RIT1*)**
Neurofibromin 1 (*NF1*)
Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha (*PIK3CA*)
AKT Serine/Threonine Kinase 1 (*AKT1*)
NRAS Proto-Oncogene, GTPase (*NRAS*)
Mechanistic Target Of Rapamycin (*MTOR*)
Tuberous Sclerosis 1 (*TSC1*)
Tuberous Sclerosis 2 (*TSC2*)
KIT Proto-Oncogene Receptor Tyrosine Kinase (*KIT*)
Platelet Derived Growth Factor Receptor Alpha (*PDGFRA*)
Discoidin Domain Receptor Tyrosine Kinase 2 (*DDR2*)

A Word on Cell Type and Cell Subtype

Adenocarcinoma TTF-1

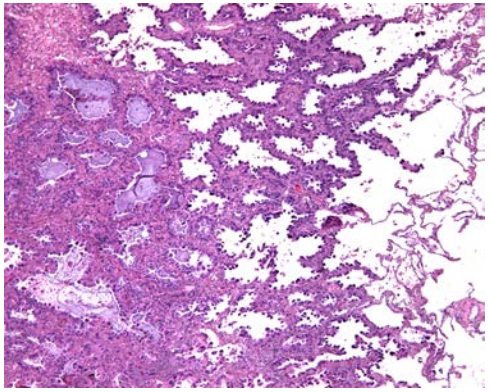




Squamous Cell Carcinoma p40

1% to 2% NSCLC cannot be classified as adenocarcinoma or squamous cell carcinoma

NSCLC, NOS
Large Cell Carcinoma



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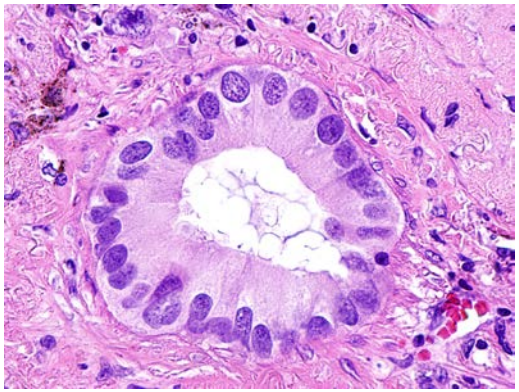
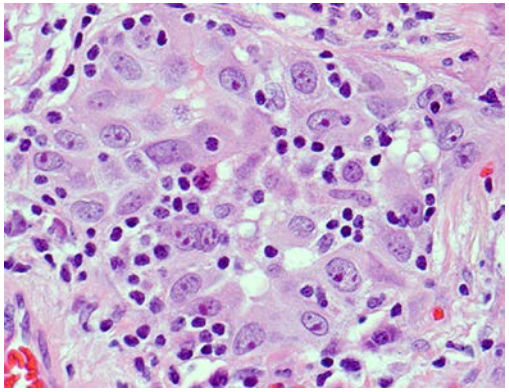
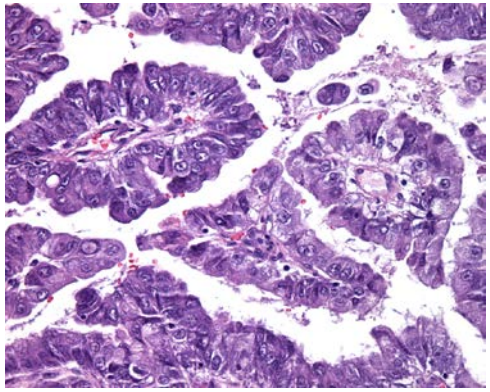


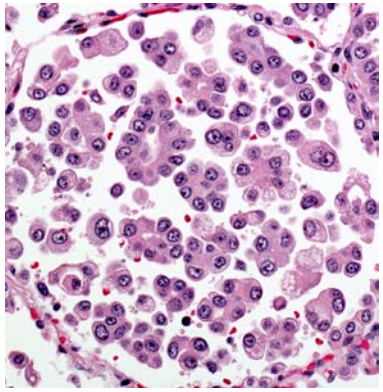
ACINAR



SOLID



PAPILLARY



MICROPAPILLARY

5 Year Disease Free Survival Stage I Based on 2015 Classification

- **Adenocarcinoma-in-situ 100%**
- **Minimally invasive adeno 100%**
- **Lepidic predominant 90%**
- **Papillary predominant 83%**
- **Acinar predominant 84%**
- **Mucinous 75%**
- **Colloid predominant 71%**
- **Solid predominant 70%**
- **Micropapillary predominant 67%**

Coming Soon?

- **Cribriform**
- **Fused Acinar**
- **Filiform Micropapillary**

Is there a relationship between histologic subtype and frequency of biomarkers?

Correlation of EGFR Mutation Status With Predominant Histologic Subtype of Adenocarcinoma According to the New Lung Adenocarcinoma Classification of the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society

Celina Villa, Philip T. Cagle, Melissa Johnson, Jyoti D. Patel, Anjana V. Yeldandi, Rishi Raj, Malcolm M. DeCamp and Kirtee Raparia

Archives of Pathology & Laboratory Medicine Oct 2014, Vol. 138, No. 10 (October 2014) pp. 1353-1357

Kirtee Raparia

Conclusions

- **Certain subtypes of adenocarcinoma are more commonly associated with specific biomarkers.**
- **However, biomarkers are also found in other subtypes, just less frequently.**
- **Subtype should not be used to exclude patients from TKI therapy**

(Give maximum number of patients a chance at therapy)

Testing

- **NGS versus sequential individual assays**
- **Immunohistochemistry**
- **Cytology Specimens**
- **Liquid Biopsy**

Advantages of Targeted Gene Sequencing

- **Analyzes multiple genes in a single assay**
- **Optimizes use of limited tissue samples by reducing need for sequential testing**

  (Maximum use of minimal tissue)

- **Not available in some situations**

Expert Consensus Opinion: Multiplexed genetic sequencing panels are preferred over multiple single-gene tests to identify other treatment options beyond EGFR, ALK, and ROS1.

PD-L1 IHC

- **Many NSCLC, both adenocarcinoma and squamous cell carcinoma positive**
- **Many issues regarding PD-L1 as biomarker:**
  Heterogeneity (limited sample), different antibodies, different cut-offs for different drugs, Is it even the correct biomarker for this purpose?
- **FDA: Immune checkpoint therapy if negative for biomarker for TKI target**
- **Oncologists request**
- **Reflex test**
- **Limited sample: Talk to Oncologist before sacrificing tissue**

What is the role of testing to select patients for treatment with immunomodulatory therapies?

Opinion: Samples should be preserved for assessment of biomarkers that predict response to immunomodulatory therapies (eg, *PD-1* and *PD-L1*), in accordance with the labeling requirements of the drugs under consideration.

Because of the lack of firm evidence supporting specific methodology or agents, we cannot make evidence-based recommendations regarding testing for these drugs in this guideline.

A subsequent practice guideline is being planned to focus specifically on evidence-based assessment of methods for selecting patients to receive immunomodulatory therapies.

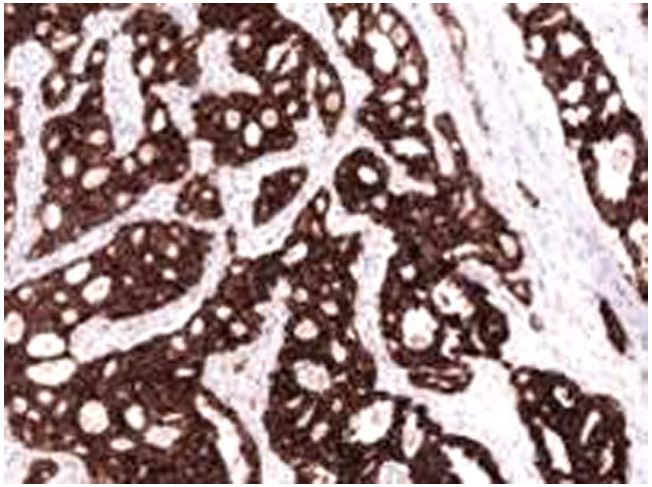
Coming Related Guidelines

PD1-PD-L1 Testing of Patients with Lung Cancer for Selection of Immunooncology Therapies

Lynette Sholl, MD

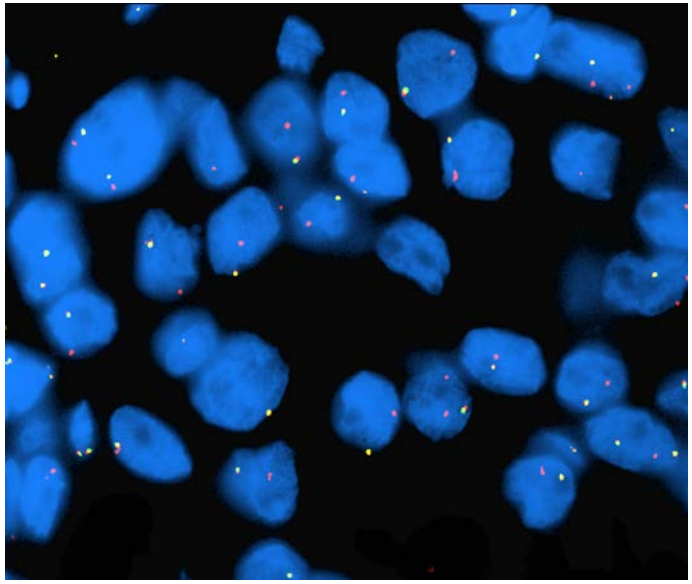
FDA Approval 6-12-2015

VENTANA ALK (D5F3) CDx Assay is intended for the qualitative detection of the ALK protein in FFPE NSCLC tissue stained with a BenchMark XT automated staining instrument. It is indicated as an aid in identifying patients eligible for treatment with XALKORI® (crizotinib).



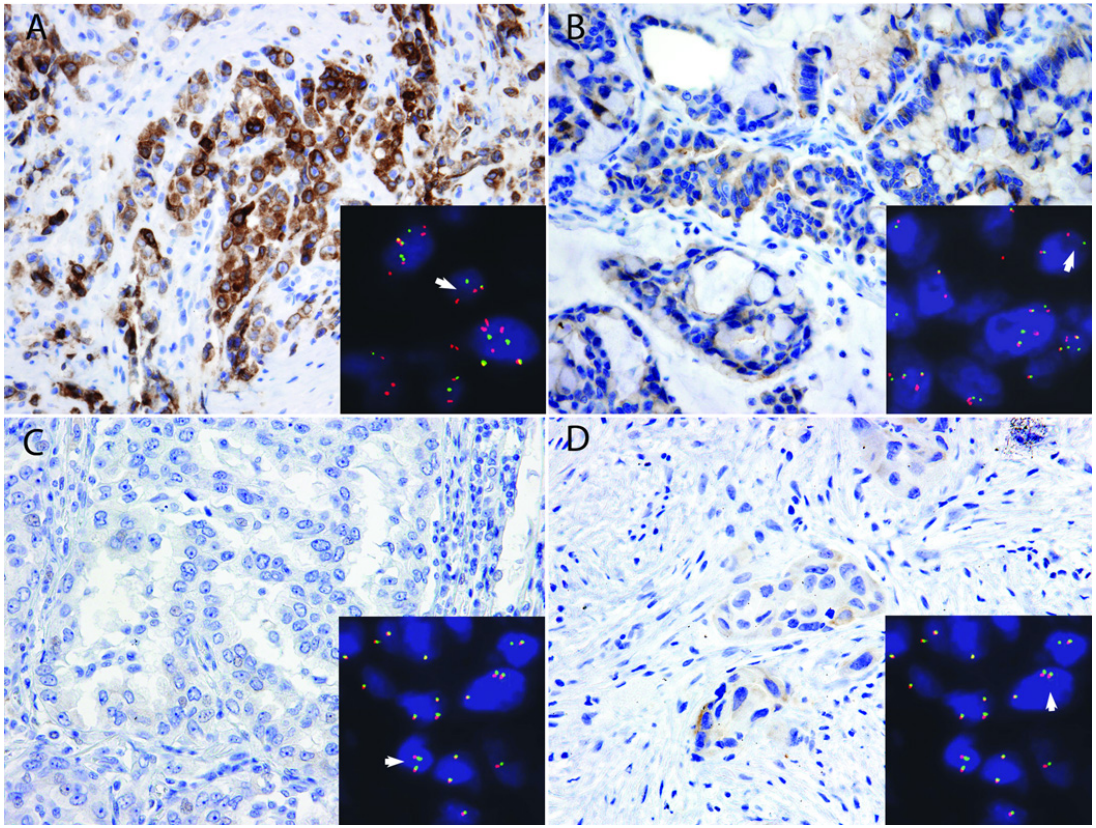
2018 ALK IHC Recommendation

- **IHC is an equivalent alternative to FISH for ALK testing.**



ROS1 IHC versus FISH

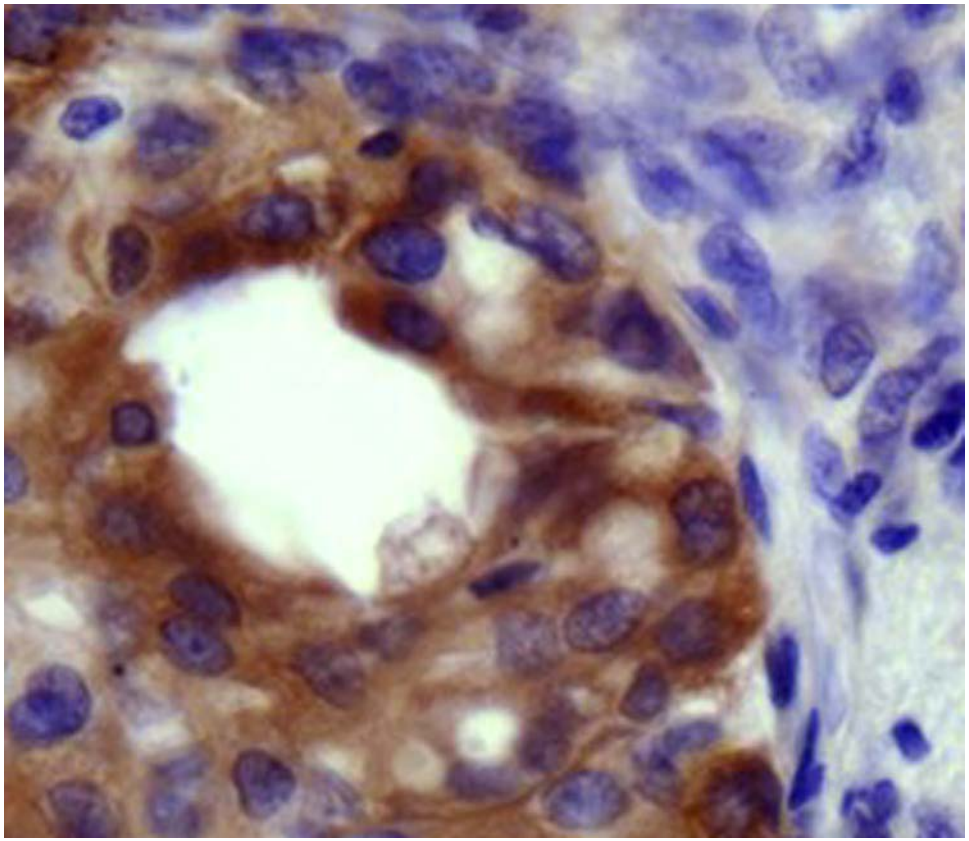
A) **Strong, diffuse (3+) case with ROS1 FISH rearrangement**
B) **Weak to moderate but diffuse (3+) staining in case with ROS1 FISH rearrangement**
C) **Absent ROS1 IHC in a case with no rearrangement by FISH**
D) **Weak staining in scattered cells (2+) in a case with no rearrangement by FISH**



Sholl LM, et al. Am J Surg Pathol. 2013 Sep;37:1441-9.

Expert Consensus Opinion: *ROS1* IHC may be used as a screening test in advanced stage lung adenocarcinoma patients; however, positive *ROS1* IHC results should be confirmed by a molecular or cytogenetic method.

EGFR exon 19 deletion-specific antibody



Negative result does not exclude the possibility of other EGFR mutations

Recommendation: Laboratories should not use *EGFR* mutation specific IHC testing to select patients for EGFR-targeted tyrosine kinase inhibitor therapy.

Principles for Biomarker Testing of Lung Cancer Biopsies

1. ***Give maximum number of patients a chance at therapy***
2. ***Maximum use of minimal tissue***

Practical Rules For Small Samples

1. ***Minimize using tissue for diagnosis of cell type (limit to TTF-1 and p40)***
2. ***If choice between biomarker testing and pinning down cell type err on side of biomarker testing***
3. ***NGS over stand-alone tests whenever possible***
4. ***EGFR> ALK> ROS1> other***
5. ***PD-L1 IHC***

2018 CAP/IASLC/AMP Lung Cancer Biomarker Testing Guideline Cytology Specimen Revision

- **Previously, cell blocks preferred over cytology smears**
- **Cytology smears or cell blocks, both suitable for lung cancer biomarker molecular testing.**

Coming Related Guidelines

Collection and Handling of Thoracic Small Biopsy and Cytology Specimens for Ancillary Studies

Sinchita Roy Chowdhuri MD, PhD

2018 CAP/IASLC/AMP Lung Cancer Biomarker Testing Guideline "Liquid Biopsy"

New Recommendation Statements

Key Question 5: What is the role of testing for circulating, cell-free DNA for lung cancer patients?

No Recommendation: There is currently insufficient evidence to support the use of circulating cell-free plasma DNA (cfDNA) molecular methods for the diagnosis of primary lung adenocarcinoma.

Recommendation: In some clinical settings in which tissue is limited and/or insufficient for molecular testing, physicians may use a cell-free plasma DNA (cfDNA) assay to identify *EGFR* mutations.

New Recommendation Statements

Key Question 5: What is the role of testing for circulating cell-free DNA for lung cancer patients?

Expert Consensus Opinion: Physicians may use cell-free plasma DNA (cfDNA) methods to identify *EGFR* T790M mutations in lung adenocarcinoma patients with progression or secondary clinical resistance to EGFR-targeted tyrosine kinase inhibitors; testing of the tumor sample is recommended if the plasma result is negative.

No Recommendation: There is currently insufficient evidence to support the use of circulating tumor cell (CTC) molecular analysis for the diagnosis of primary lung adenocarcinoma, the identification of *EGFR* or other mutations, or the identification of *EGFR* T790M mutations at the time of *EGFR* TKI-resistance.

And now Dr. Bernicker….

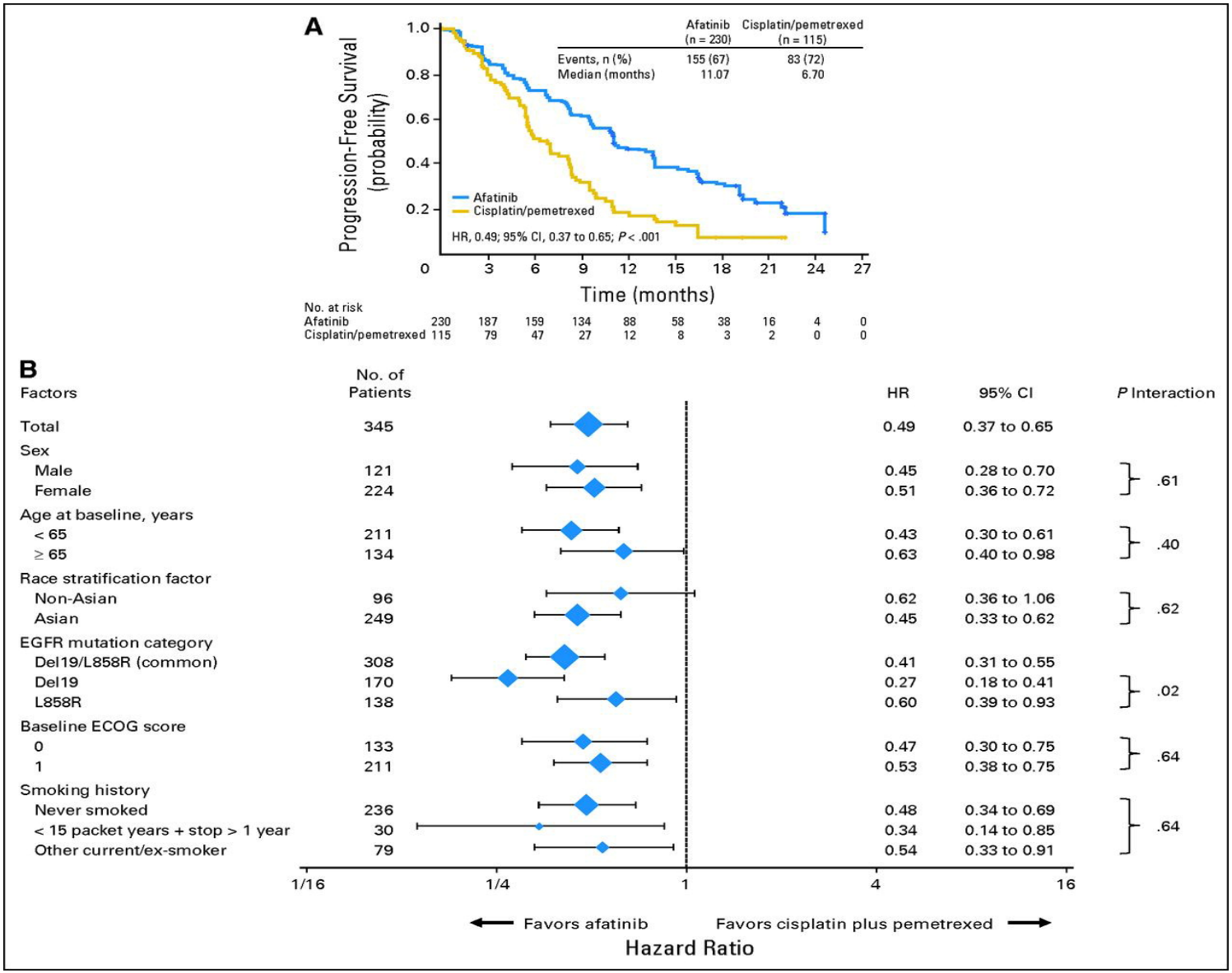
Please Sir, I want some more…biomarkers

EGFR mutations heralded a new age of targeted therapies

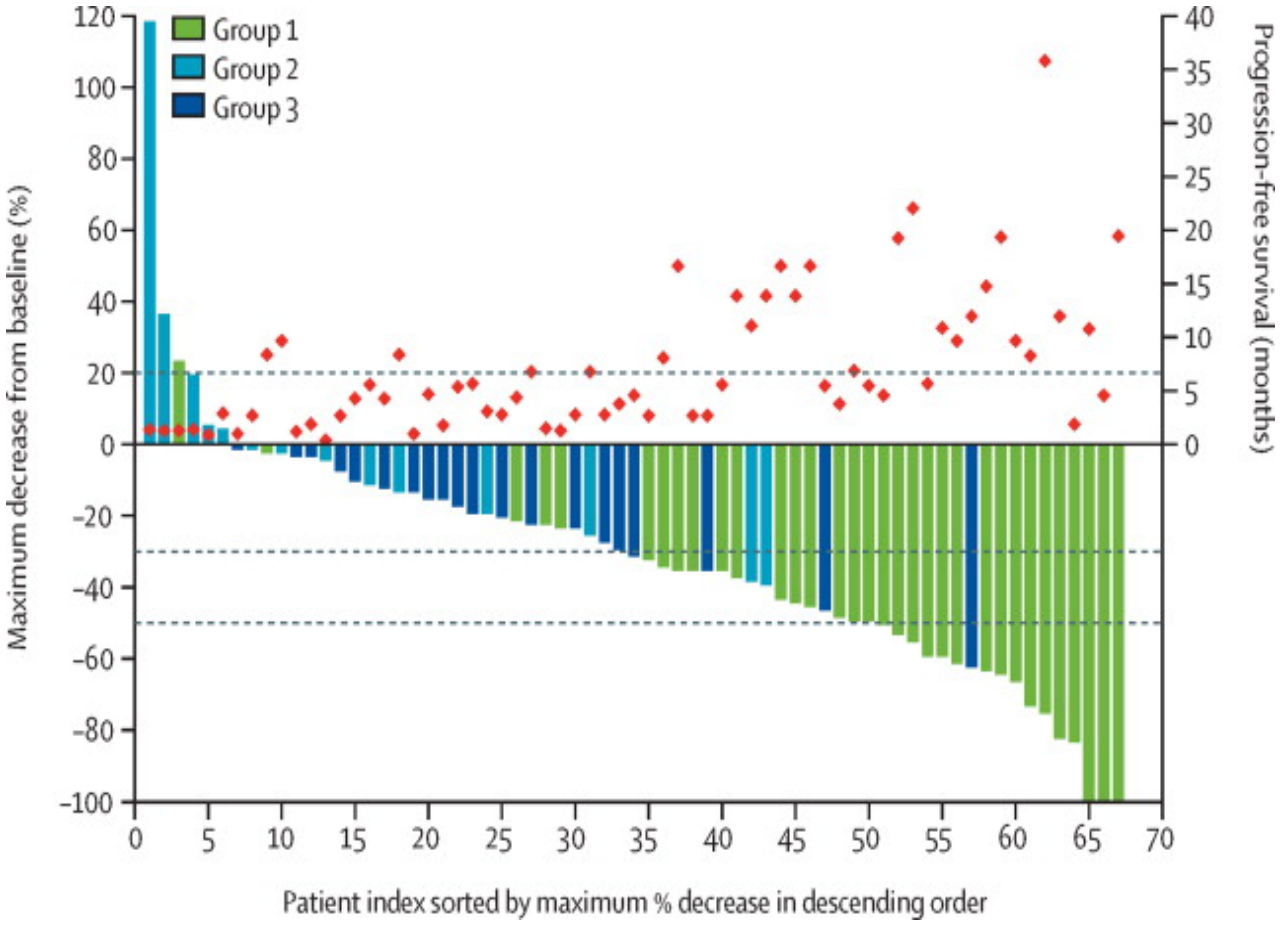
- **15% of adenocarcinomas in the US**
- **Much more common in patients of East Asian descent**
- **Patients tend to be never or light smokers**
- **Higher incidence of CNS disease**

Selected EGFR Mutations: Differential Response to TKIs

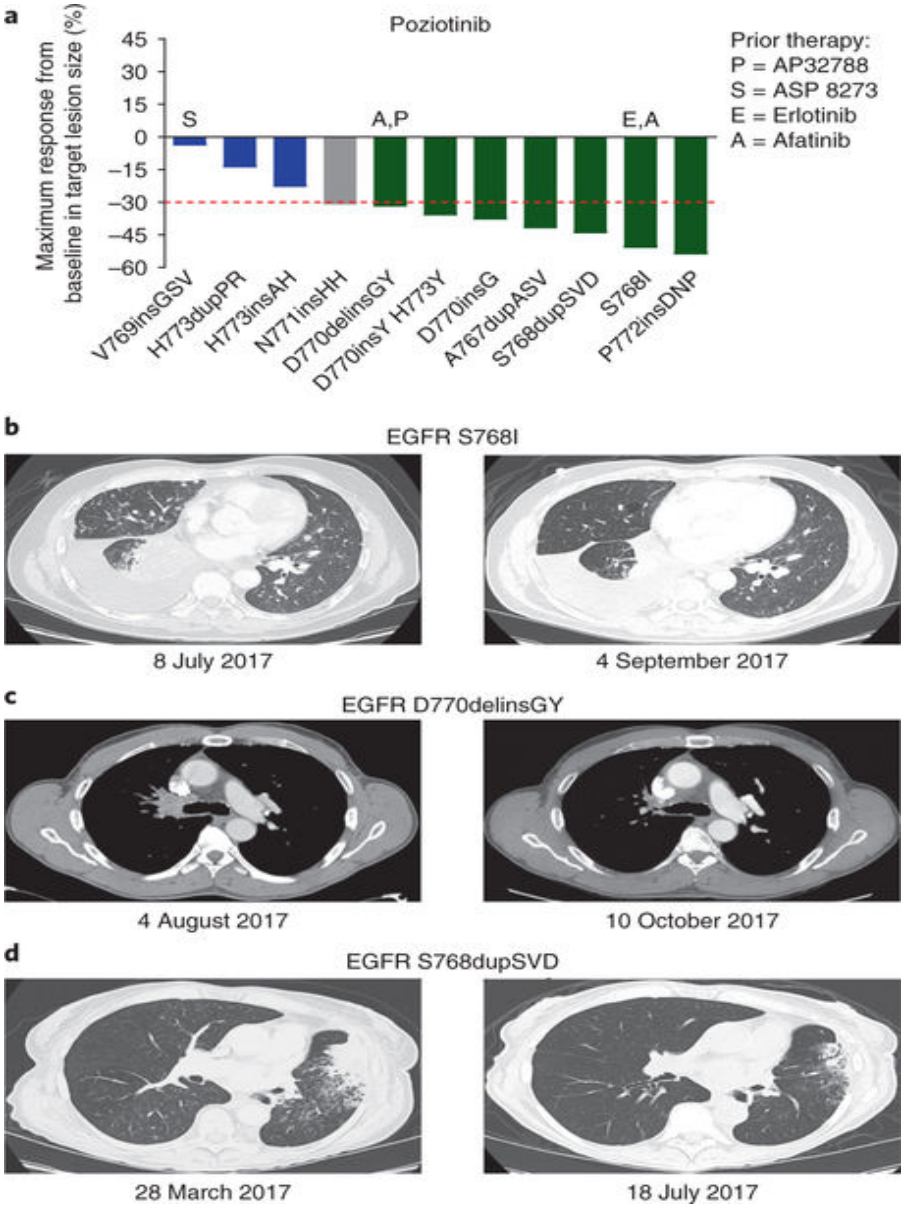
Mutation	Frequency	Response to EGFR TKIs	Median PFS	Median OS
Exon 19 deletions	45 %	70-83%	11.5 months	30.8 months
L858R (exon 21)	40%	50-67%	8-11 months	8-20.5 months
G719X	3%	50%	8 months	16 months
T790M	0.5-3 %	Lack of response		



Sequist JCO 2015



Group 1=point mutations or duplications in exons 18–21;
Group 2=de-novo Thr790Met mutations;
Group 3=exon 20 insertions.
Yang et al Lancet Oncology 2015



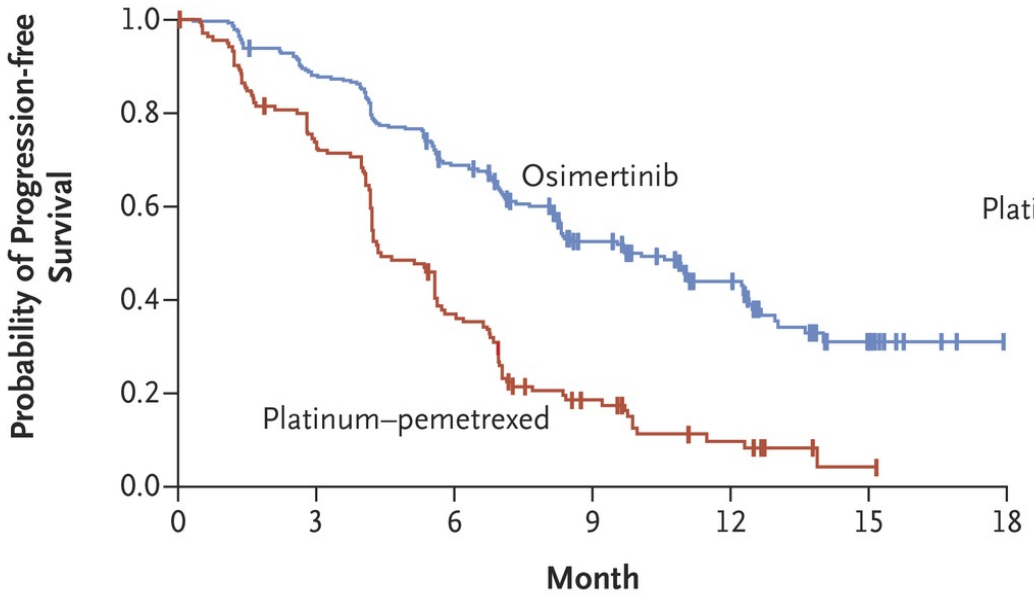
Robichaux et al Nature Medicine 2018

Success of treatment limited by the development of acquired resistance

- **All patients who initially respond eventually progress clinically**
- **Often the cause is the development of a T790 mutation**
- **Other causes: MET amplification, HER2 amplification, small cell transformation**
- **Take home point: patients losing response to frontline TKI need re-biopsy to characterize resistance mutations and to guide next line of therapy**

Osimertinib in T790 + patients

A **Patients in Intention-to-Treat Population**



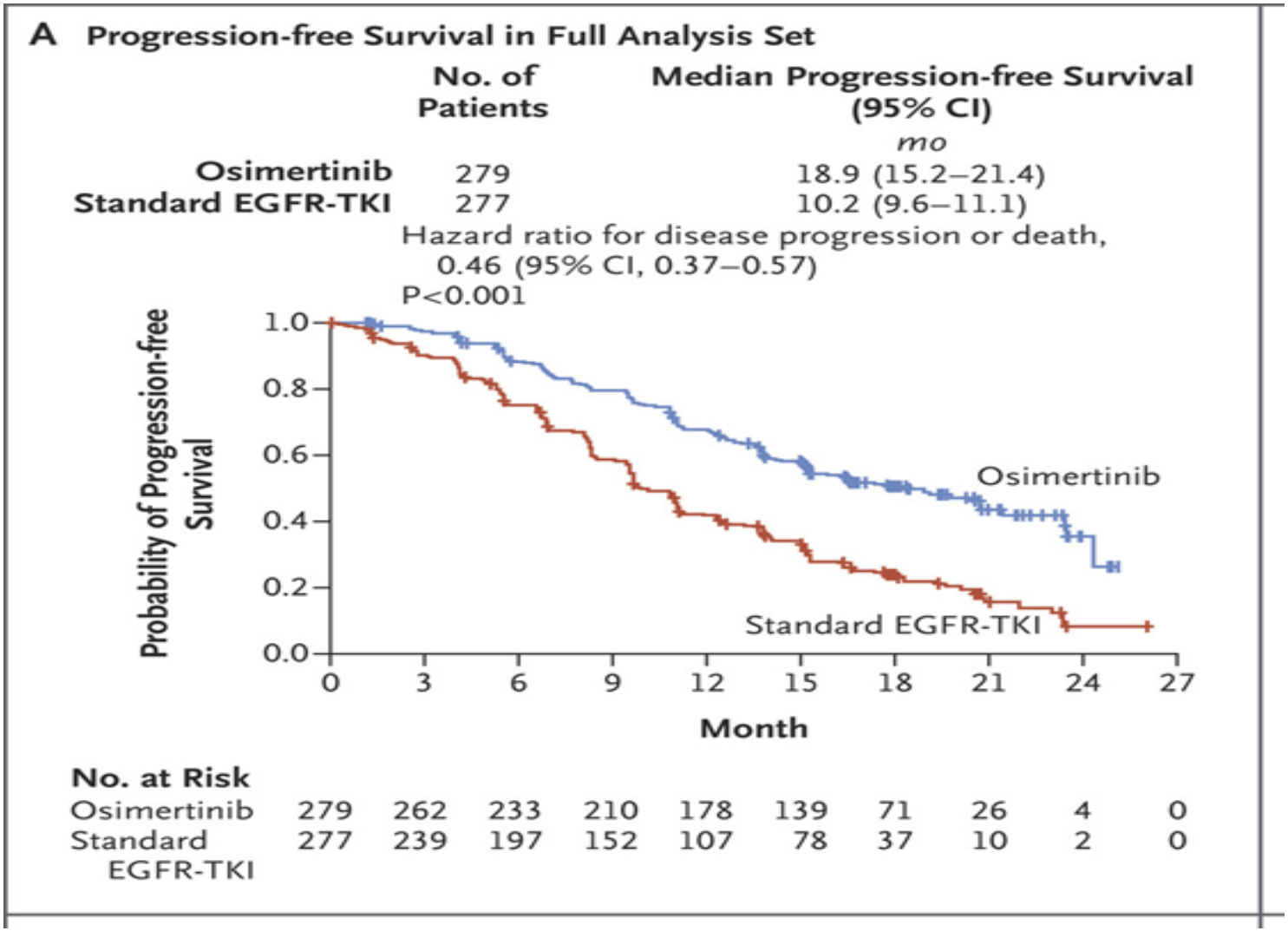
No. at Risk							
Osimertinib	279	240	162	88	50	13	0
Platinum–pemetrexed	140	93	44	17	7	1	0

	No. of Patients	Median Progression-free Survival *mo (95% CI)*
Osimertinib	279	10.1 (8.3–12.3)
Platinum–pemetrexed	140	4.4 (4.2–5.6)

Hazard ratio for disease progression or death, 0.30 (95% CI, 0.23–0.41)
P<0.001

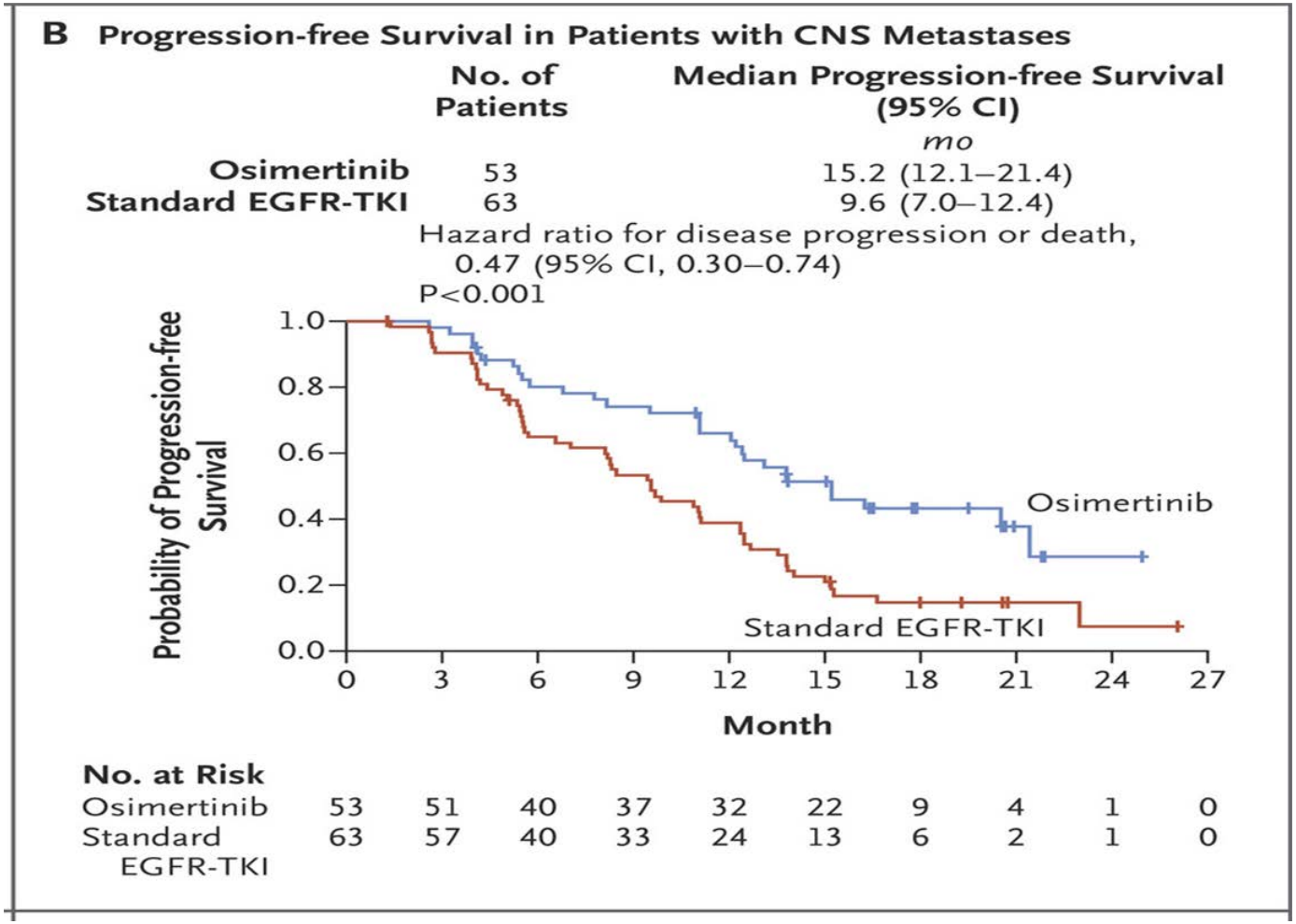
Mok NEJM 2017

Osimertinib in treatment-naïve patients



Soria et al NEJM 2017

Osimertinib : Efficacy in Patients with CNS disease

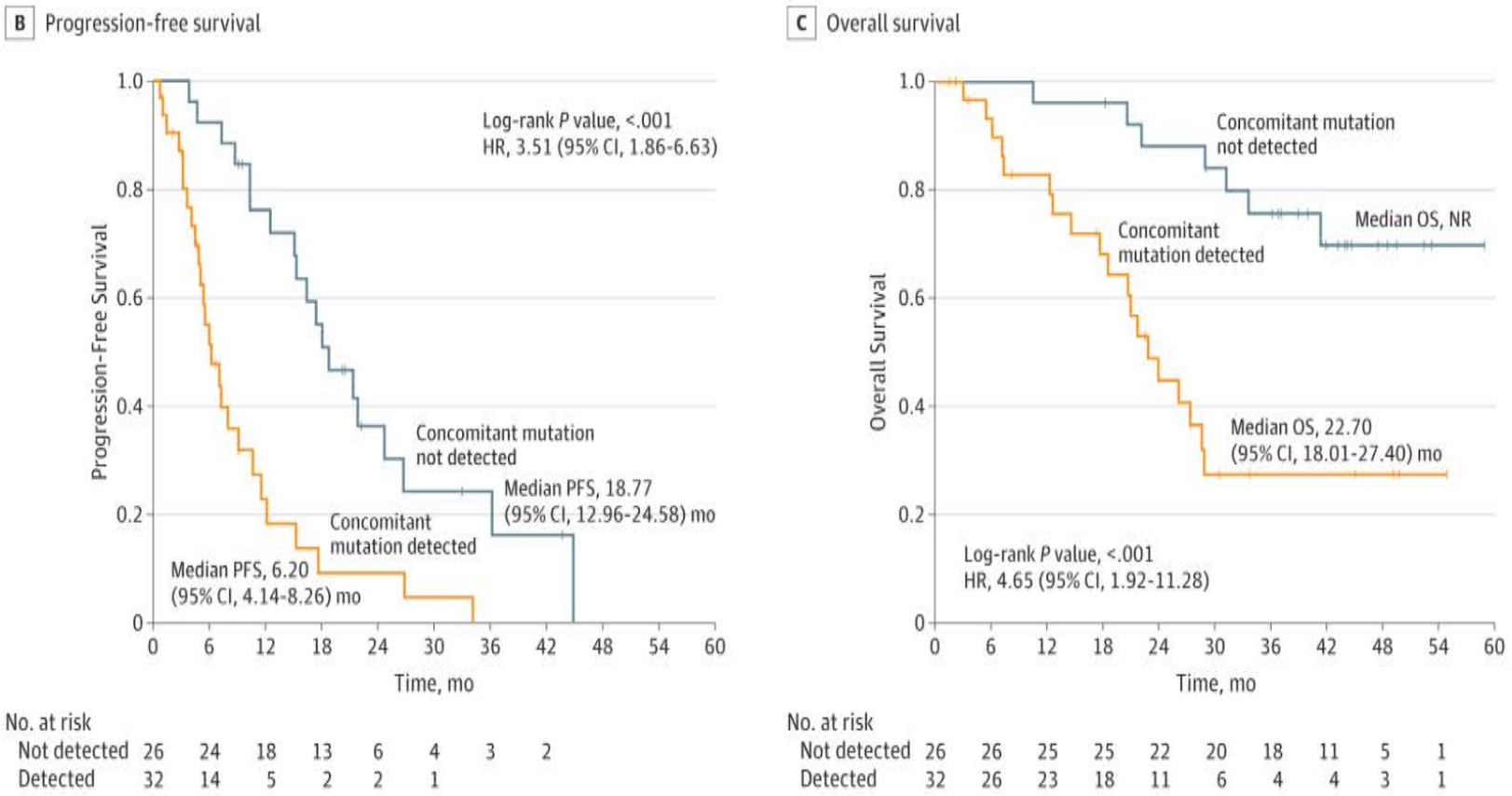


Soria et al NEJM 2017

Should EGFR TKI therapy be sequenced?

- **Would an earlier generation TKI followed by osimeritnib provide longer disease control?**
- **Concern is that therapies for resistance mechanisms to osimertinib not available yet**
- **However 40% of patients don’t develop the T790 mutation and thus need to go on to chemotherapy**

Concomitant Mutations in EGFR-positive Lung Cancers



Hong et al Jama Onc 2018

Small Cell Transformation

- **Rare but consistently reported events**
- **Cells retain the initial activating EGFR mutation**
- **Increased neuroendocrine markers and decreased EGFR expression**
- **100% loss of RB expression**

ALK + Positive Lung Cancers

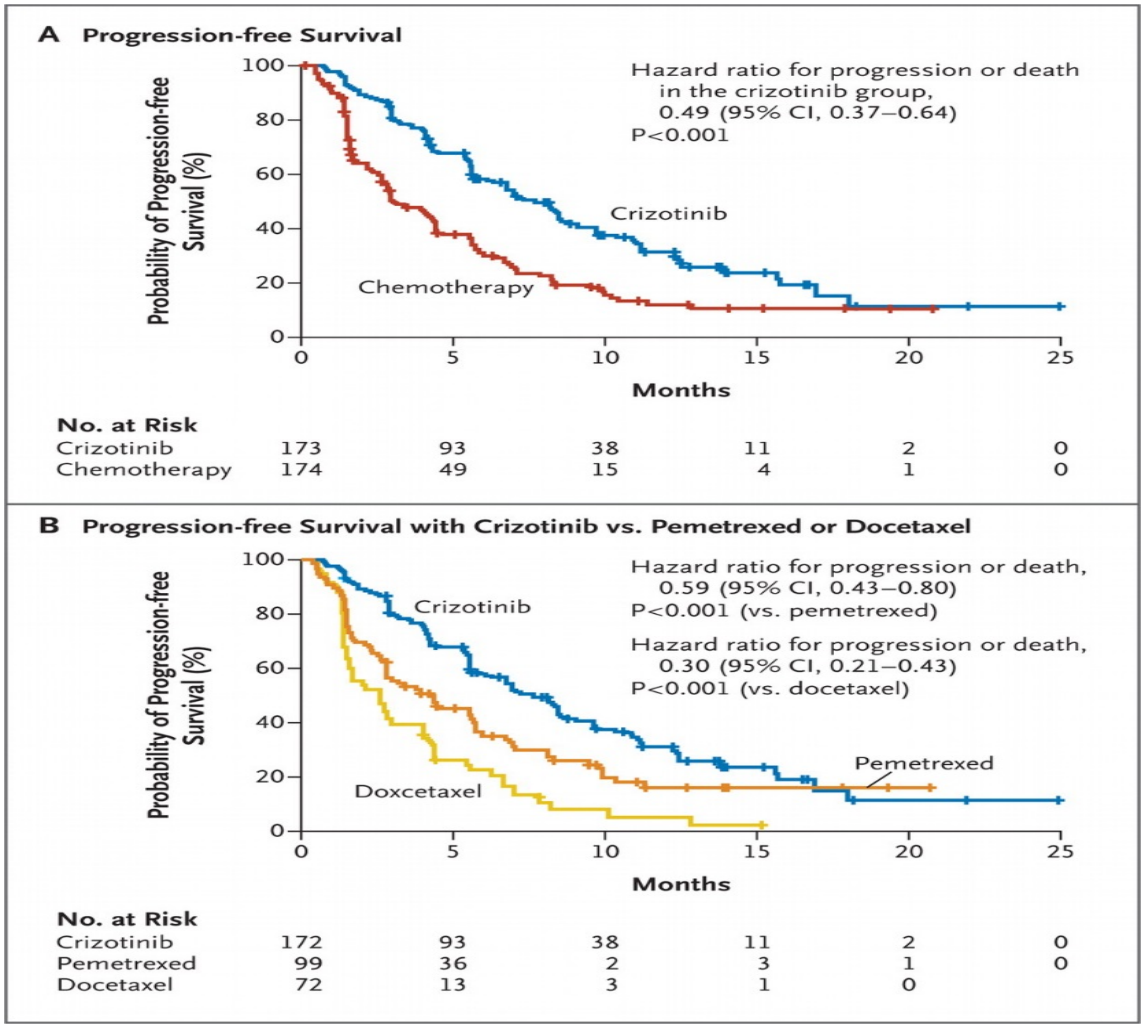
- **Translocations found in approximately 5% of adenocarcinomas**
- **First described in 2007**
- **Initial fusion partner was EML.4—others now recognized**
- **ALK kinase domain conserved**
- **All ALK fusions show gain of function properties**

ALK Clinical Features

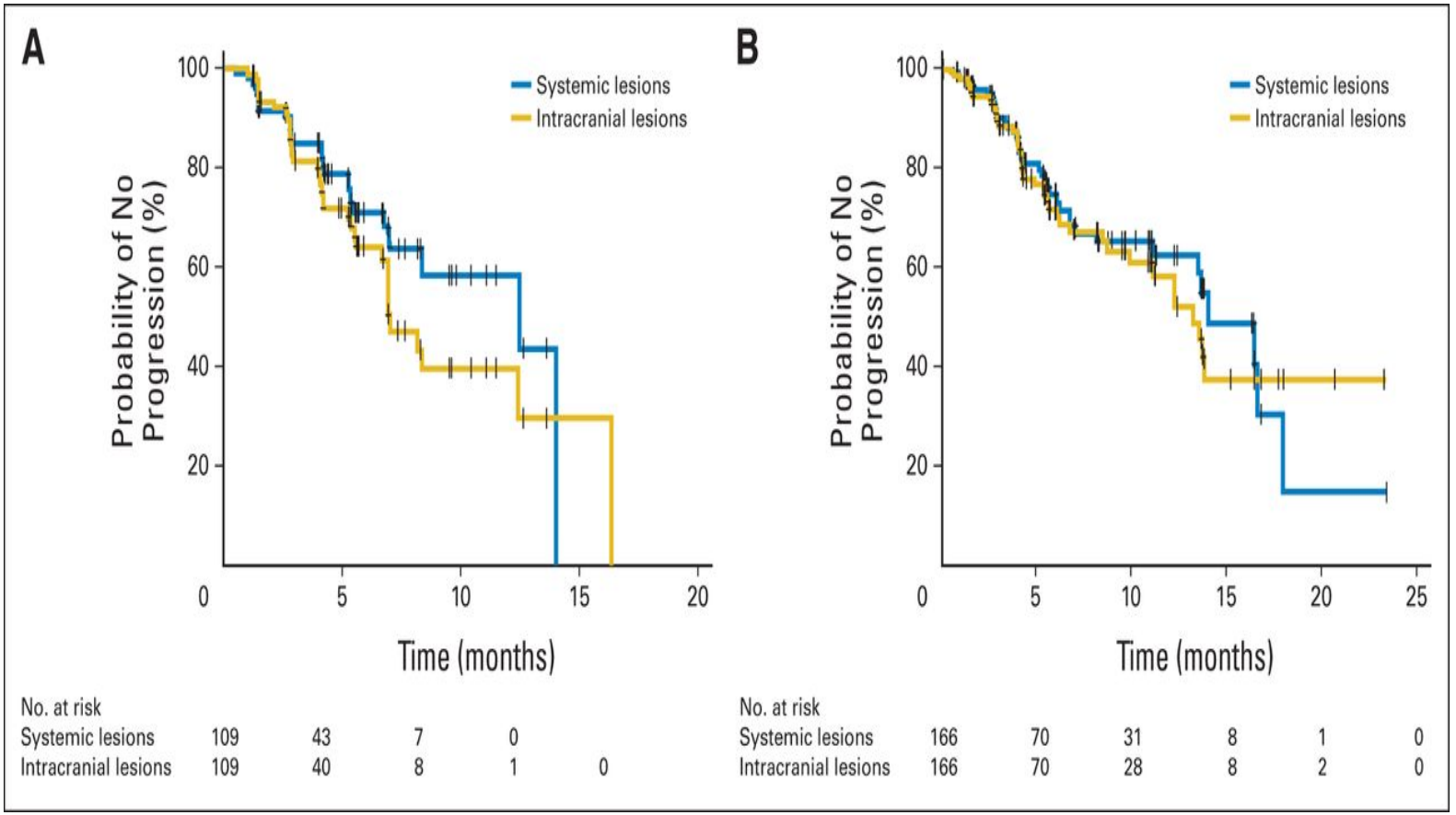
- **Histology: adenocarcinomas**
- **Never or light smokers**
- **Generally younger patients**
- **High incidence of CNS relapse**
- **Tend to be quite sensitive to Pemetrexed chemotherapy**

Crizotinib vs Chemotherapy Frontline

Solomon et al NEJM 2014

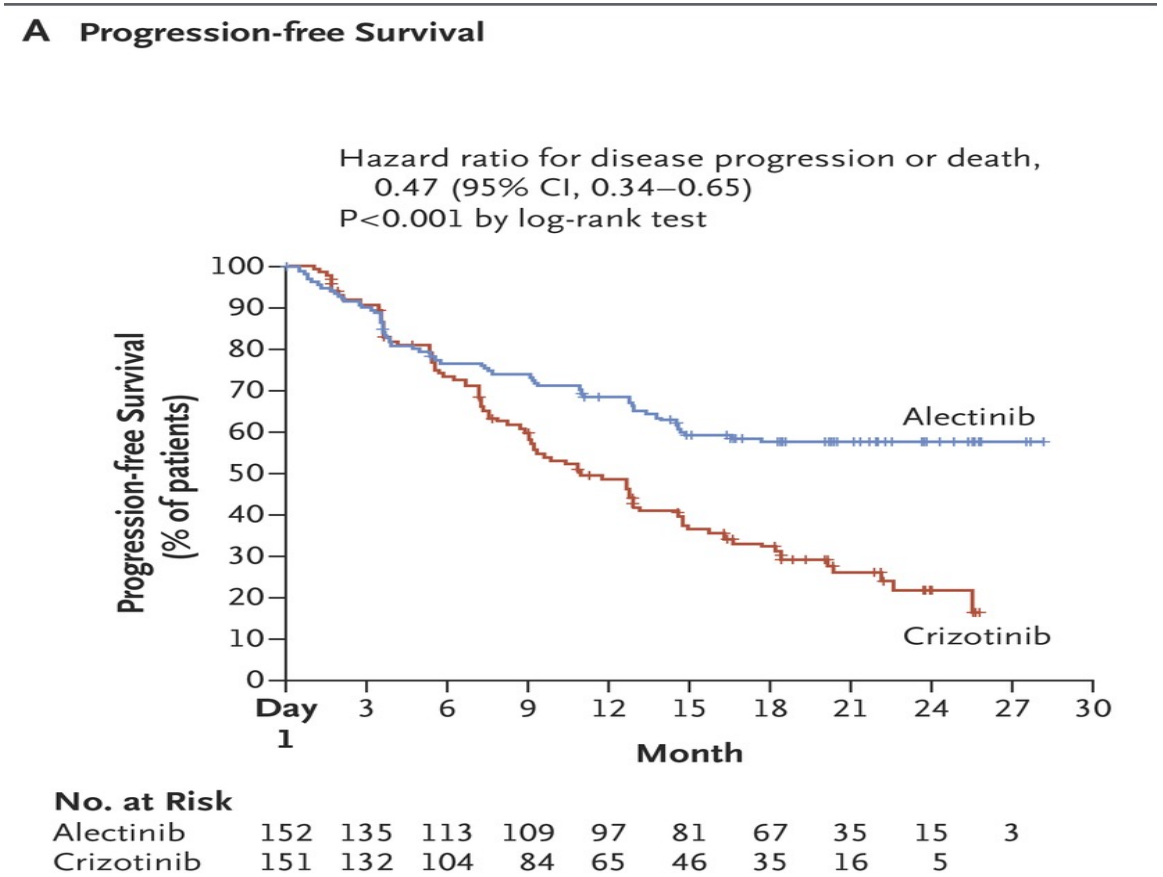


Systemic and intracranial time to progression in patients with previously (A) untreated and (B) treated brain metastases.



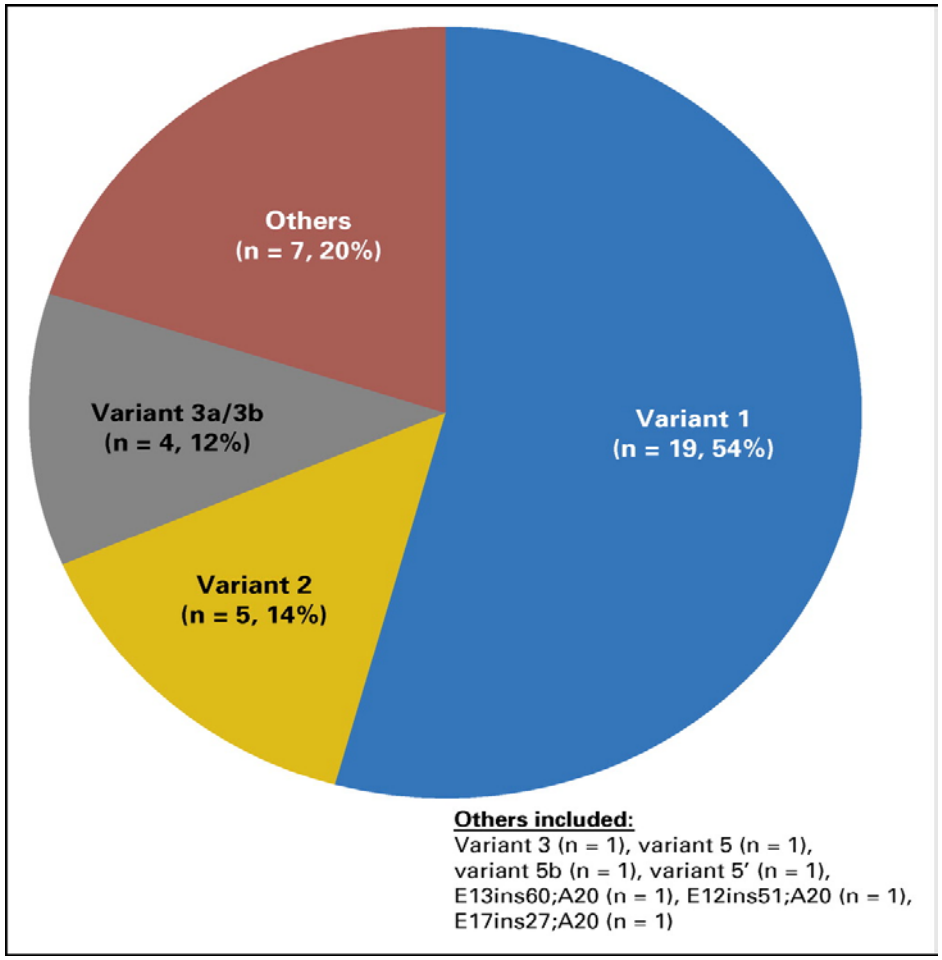
Daniel B. Costa et al. JCO 2015

Alectinib vs Crizotinib in ALK positive lung cancer: PFS



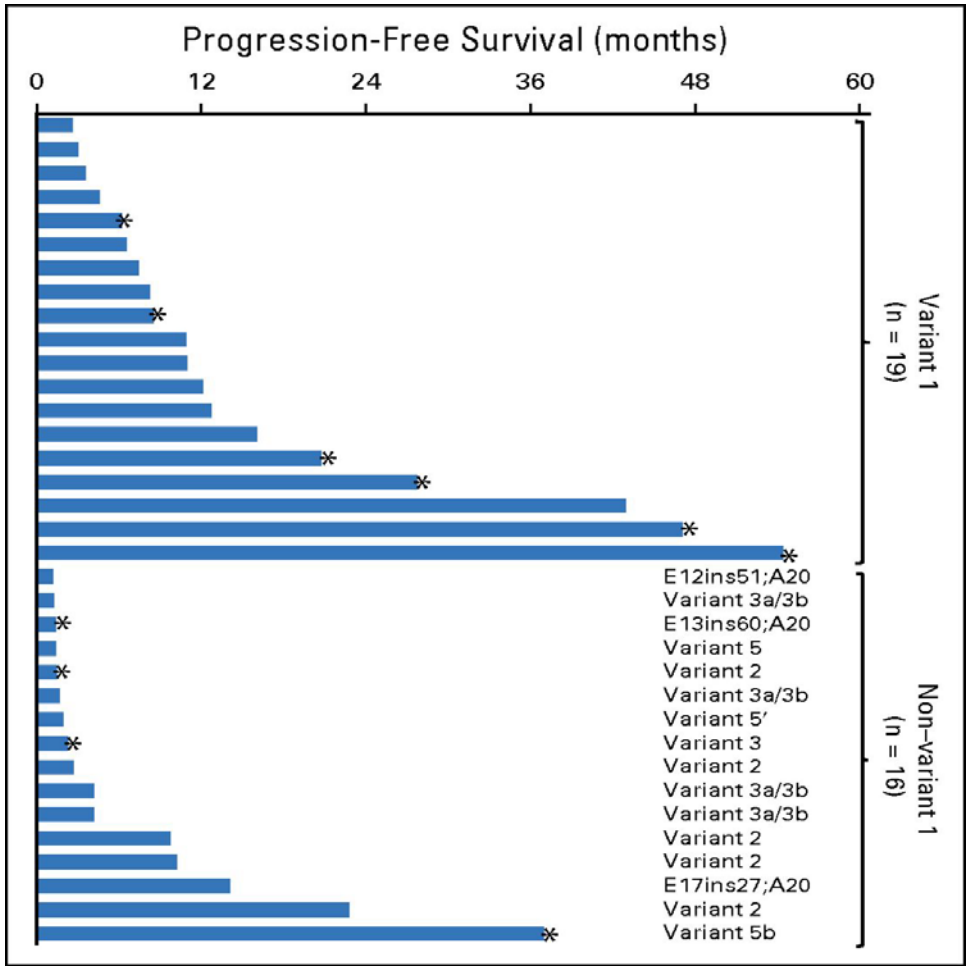
Peters et al NEJM 2017

Differential Response to Crizotinib According to ALK variant



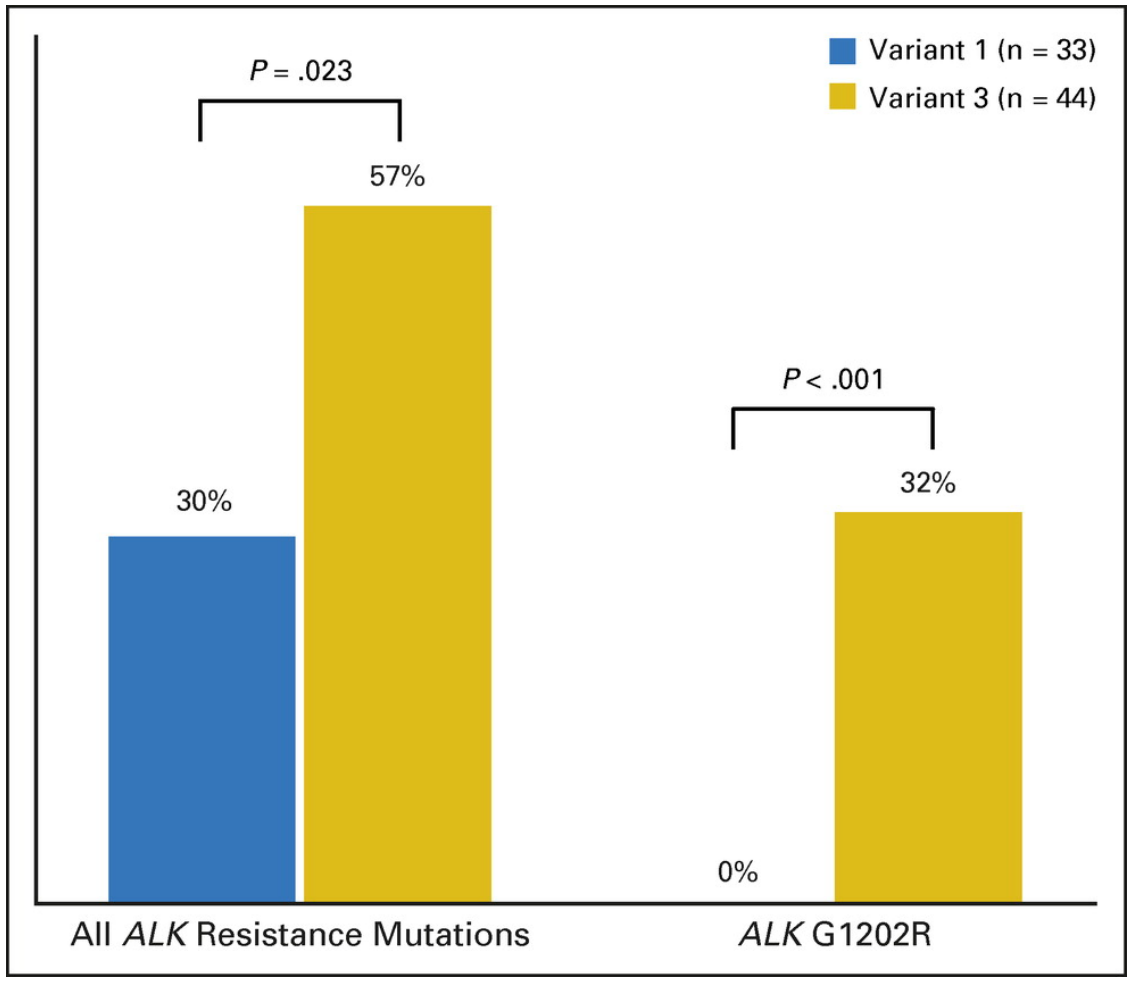
Yoshida et al, JCO 2016

Progression-free survival according to the differences in ALK variant status



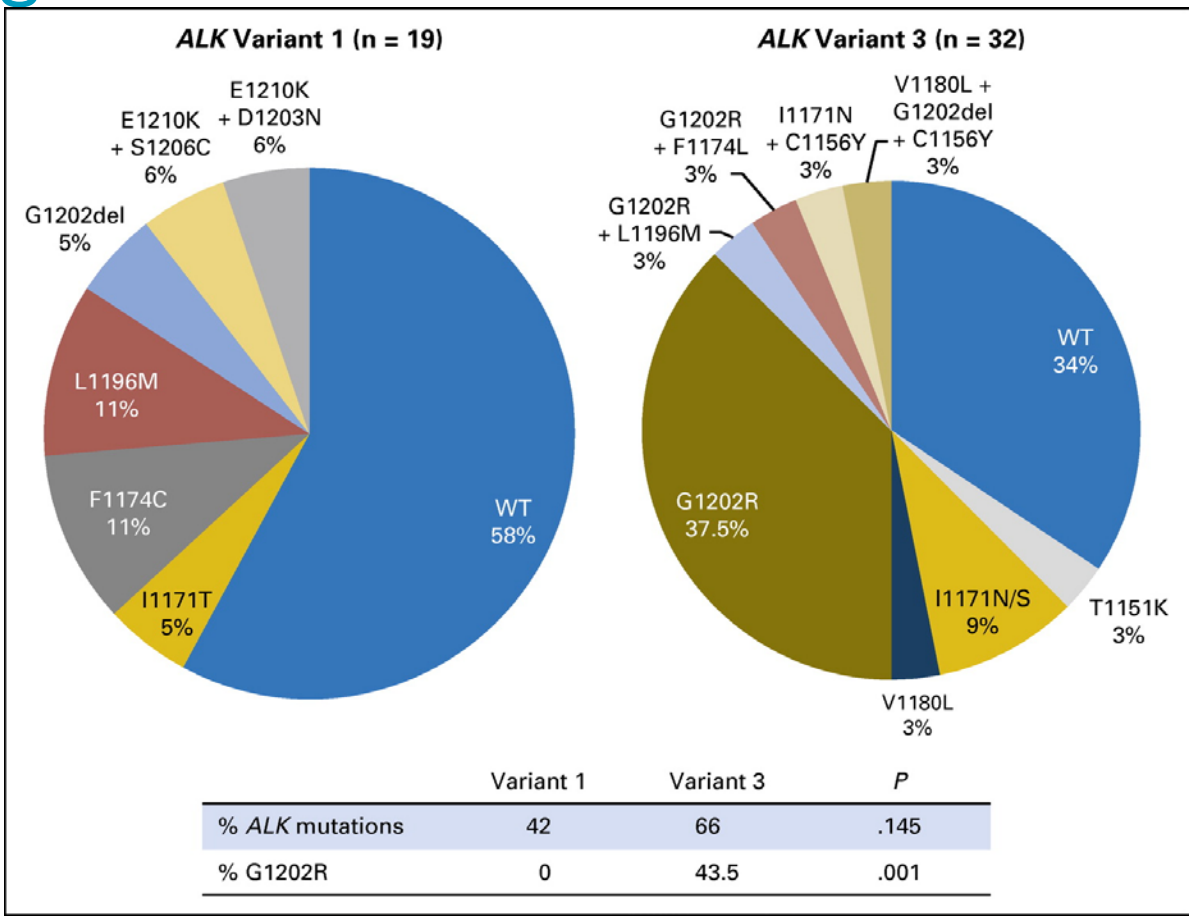
Yoshida et al JCO 2016

ALK resistance mutations according to EML4-ALK variant



Lin et al, JCO 2018

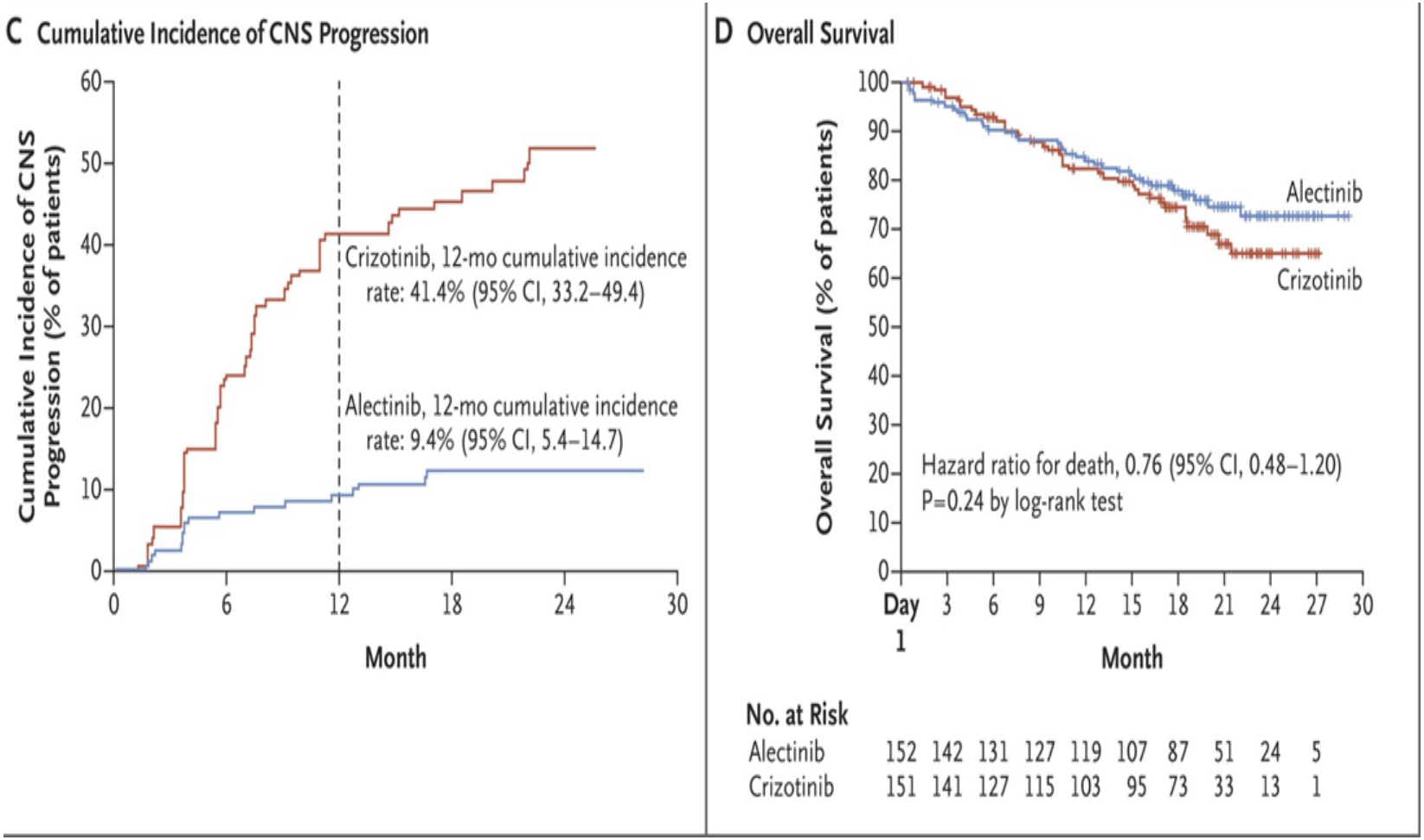
Distribution of resistance mutations after progression on second generation ALK inhibitors



	Variant 1	Variant 3	*P*
% *ALK* mutations	42	66	.145
% G1202R	0	43.5	.001

Lin et al JCO 2018

Alectinib vs Crizotinib in ALK + NSCLC

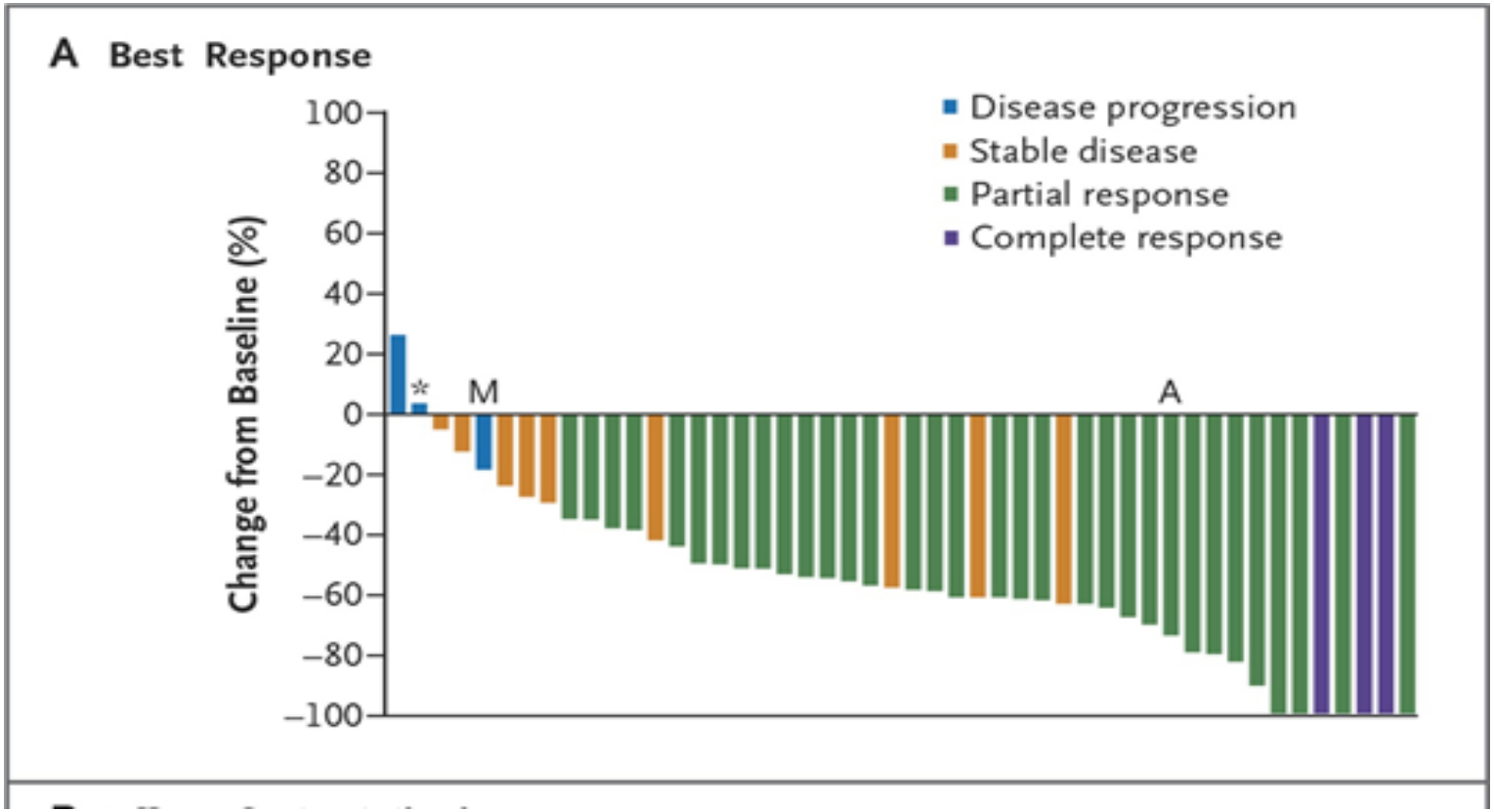


Peters et al NEJM 2018

ROS1

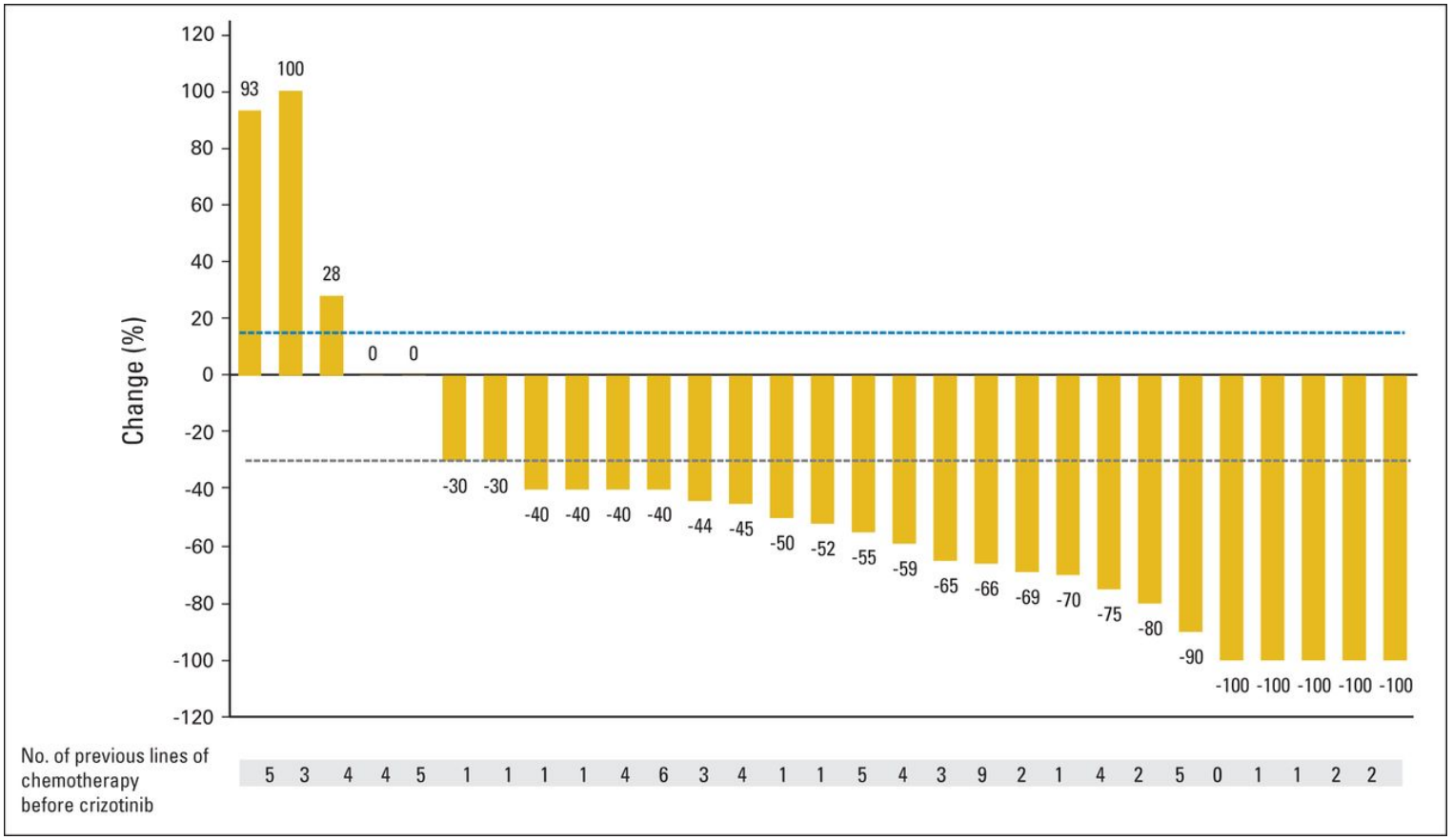
- **Incidence: approximately 1% of lung adenocarcinomas**
- **Often seen in women and non-smokers**
- **Profound sensitivity to ALK inhibitors as well as pemetrexed chemotherapy**

Crizotinib in ROS1 mutated lung cancer



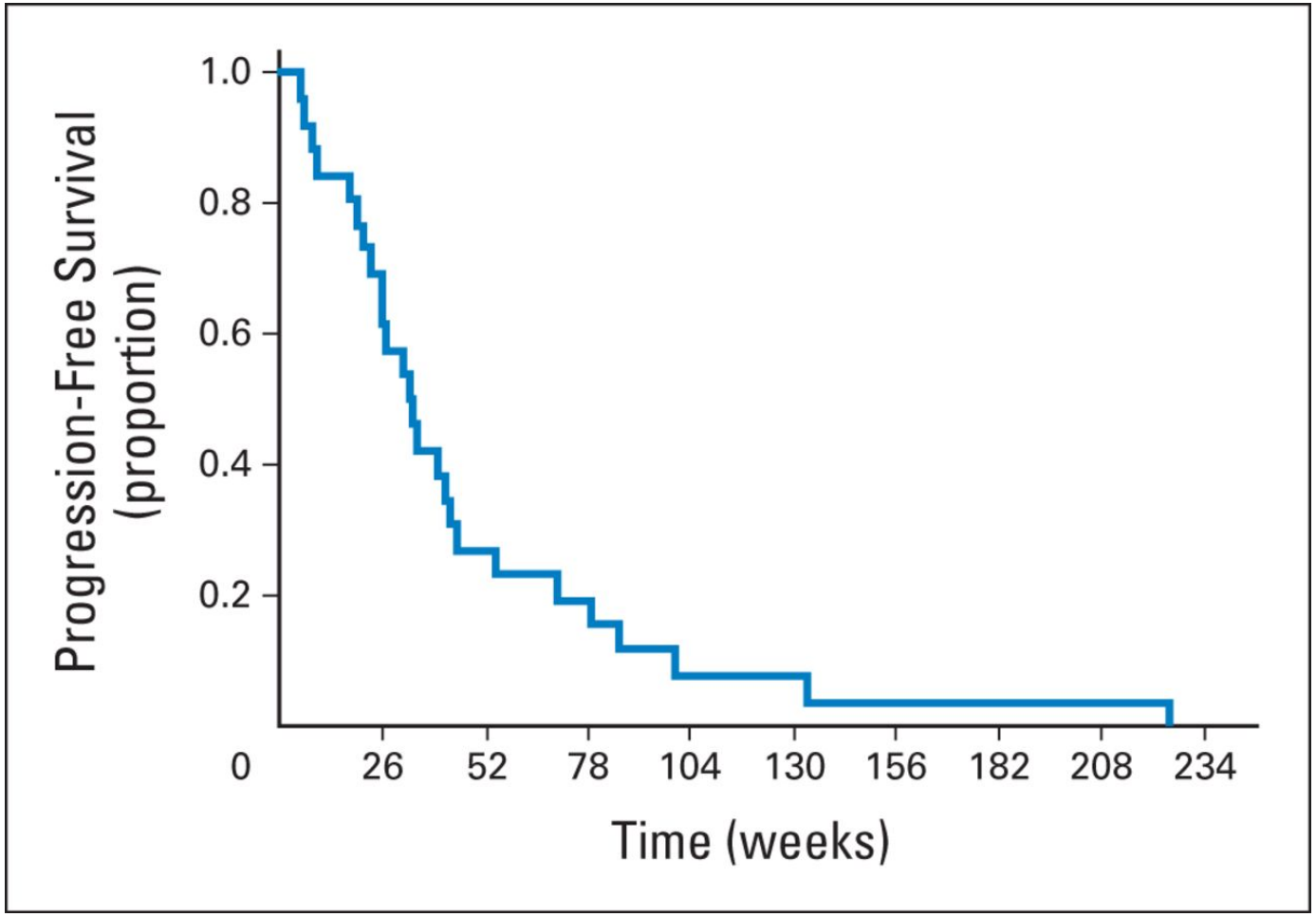
Shaw et al NEJM 2014

Waterfall plot of the best response to crizotinib in patients with lung cancer and an ROS1 rearrangement.



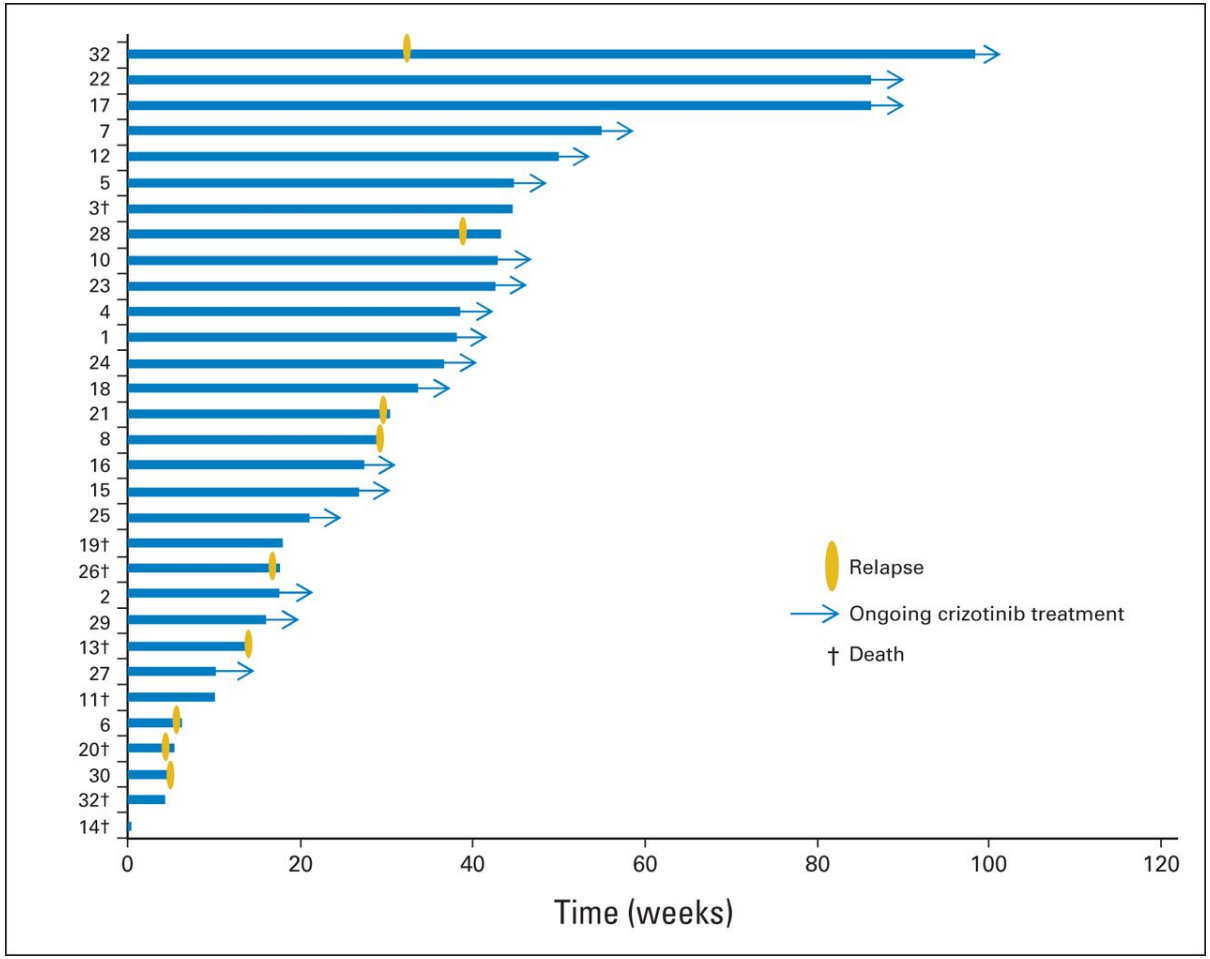
Mazières et al. JCO 2015

Progression-free survival on pemetrexed-based chemotherapy in patients with lung cancer and an ROS1 rearrangement.



Mazières et al. JCO 2015;33:992-999

Duration of crizotinib treatment in patients with lung cancer and an ROS1 rearrangement.



Mazières et al. JCO 2015

Targeted Therapy for Metastatic Disease (NCCN Guidelines)

Sensitizing EGFR mutation	ALK Rearrangement	ROS1 Rearrangement	BRAF V600E mutation
First-line Therapy:	First-line Therapy	First-line Therapy	Dabrafenib/trametinib
Osimertinib	Alectinib	Ceritinib	
Erlotinib	Ceritinib	Crizotinib	
Gefitinib	Crizotinib		
Subsequent Therapy:	Subsequent Therapy:		
Osimertinib	Alectinib, Brigantinib, Ceritnib		

Emerging Targeted Agents (NCCN Guidelines)

Genetic Alteration	Available Targeted Agents
High-level MET amplification or MET exon 14 skipping mutation	Crizotinib
RET rearrangements	Cabozantinib Vandetanib
HER2 mutations	Ado-trastuzumab

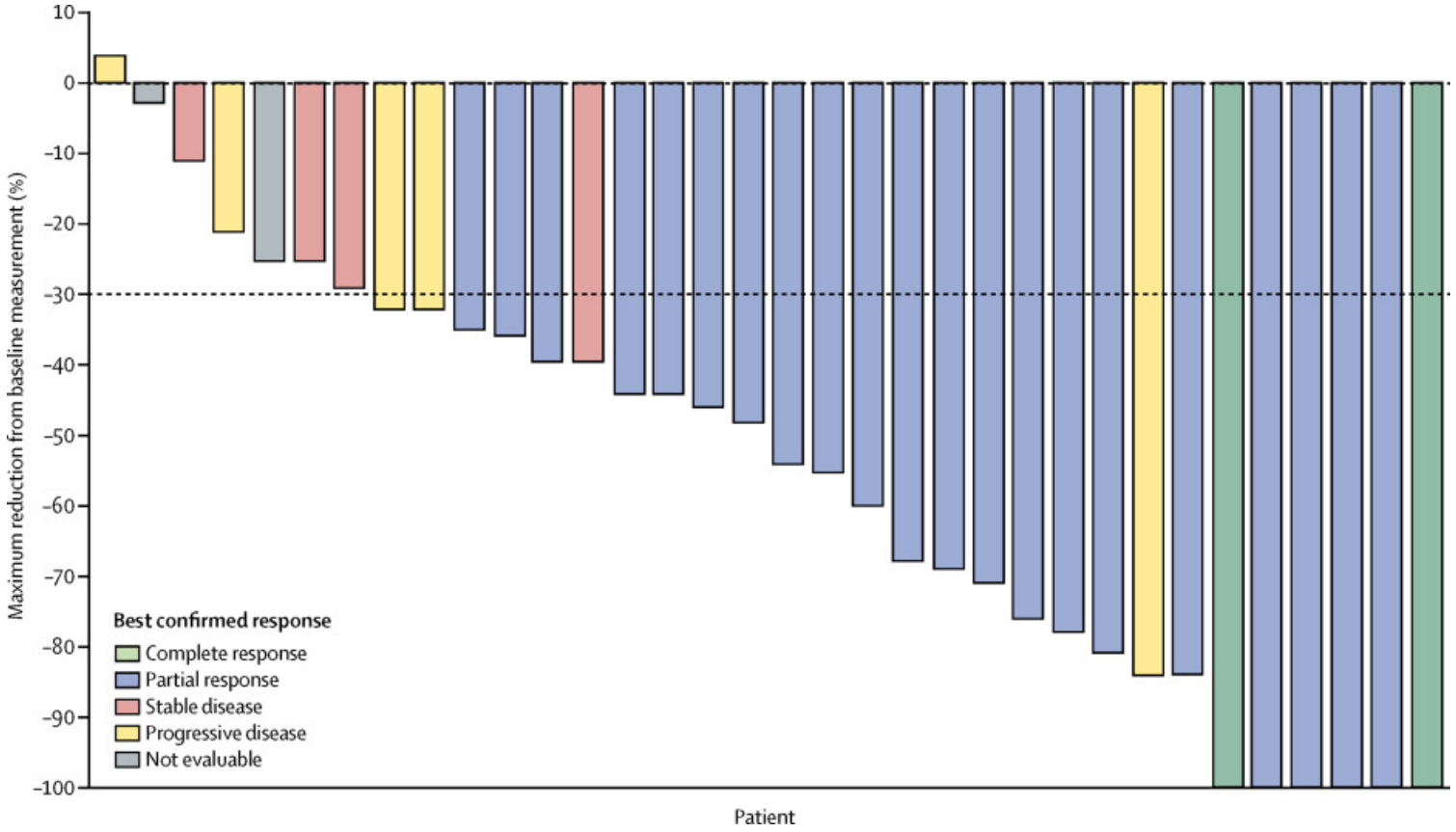
BRAF Mutated Lung Cancer

- **Mutually exclusive with ALK and EGFR mutations**
- **V600E seen in 1-2% of NSCLC patients**
- **Seems to confer a lower response to platinum-based chemotherapy and a more aggressive behavior**
- **Success of BRAF-directed therapy led to trials in patients with NSCLC**

BRAF Targeted Therapy in NSCLC

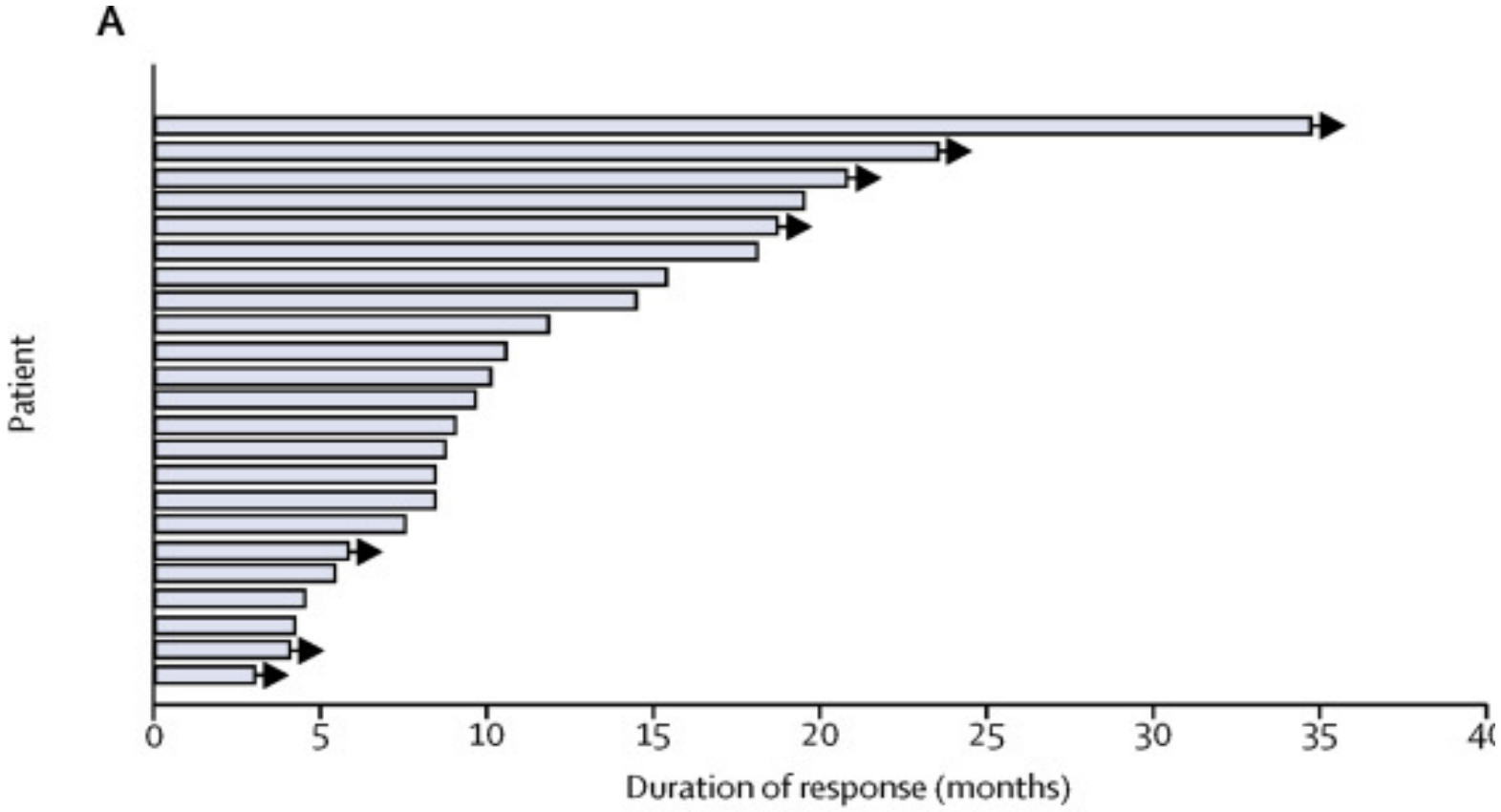
- **Dabrafenib monotherapy has a ORR of 32%**
- **Combination therapy of Debrafenib with Trametinib has been tested in BRAF-mutated lung cancer (V600E)**
- **64% female, 73% former smokers; all had failed frontline chemo.**
- **ORR 63.2% all PRs.**
  Median duration of therapy 10.6 months; 30% of patients on Rx over 12 months

Dabrafenib + trametinib in untreated BRAF V600E + patients



Planchard et al Lancet Oncology 2017

Duration of response



Planchard et al Lancet Oncology 2017

MET Exon 14 Skipping and Amplification

- **Found in 4% of lung cancers**
- **The mutation causes MET amplification and sensitivity to MET inhibitors in vitro**
- **Crizotinib active in both situations**
- **ORR around 40% with median duration of response 6 months**

RET Fusions in NSCLC

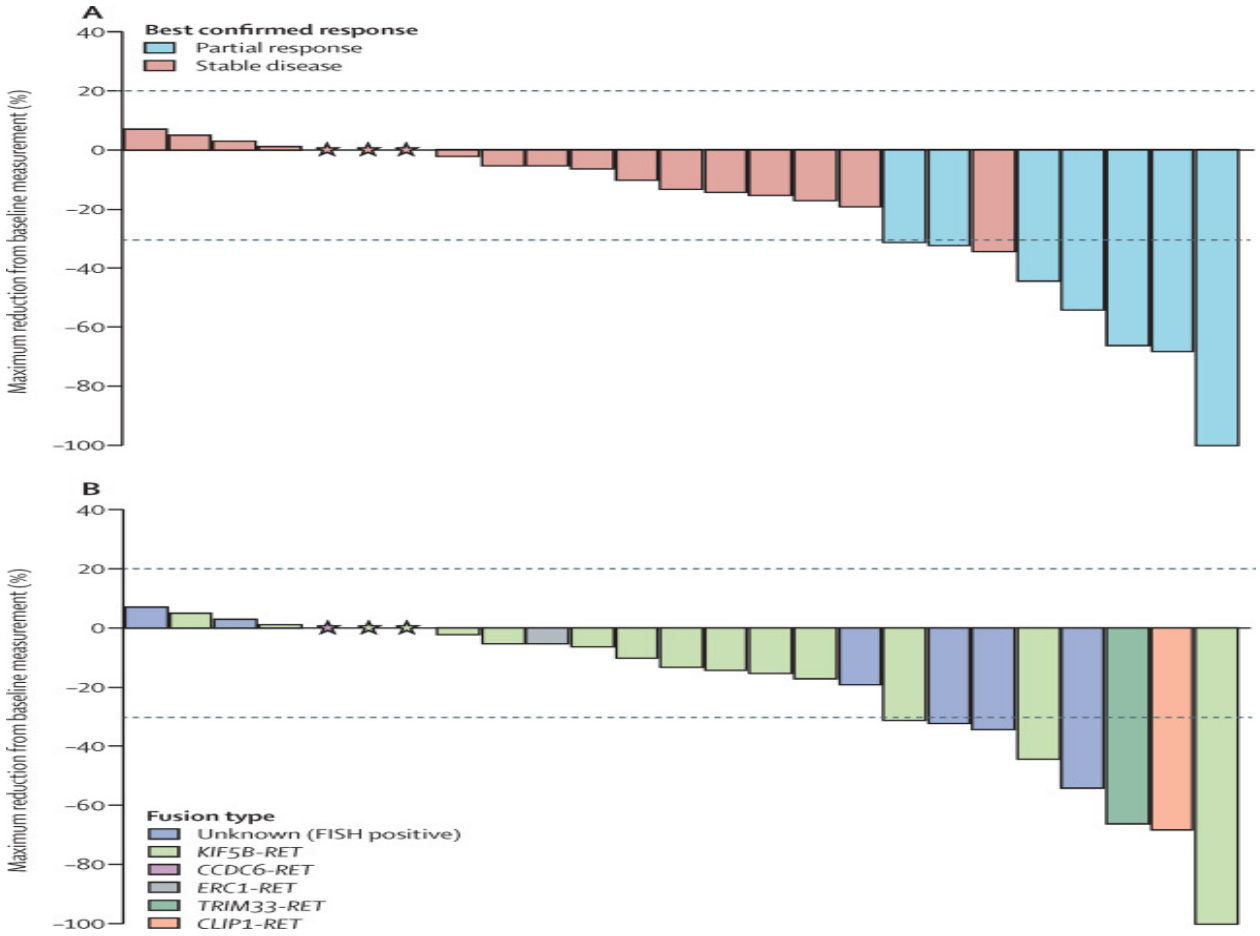
- **1-2 % of patients with adenocarcinoma, higher in patients who are never smokers and lack other driver mutations.**
- **Younger patients with early nodal spread and poorly differentiated histology**
- **Drilon et al published their experience with cabozantinib in 3 patients**
- **2 PRs and 1 stable disease (8 months) in the first 3 patients treated**
- **All 3 remain on therapy**
- **Lee et al ASCO 2016: Vandetanib: 17% PR, 44% stable**

RET: less responsive ?

- **Gautschi, ASCO 2016: Global registry**
- **132 patients;62% never smokers, 97% adenocarcinoma, 52% women**
- **Various RET inhibitors used, often third line**
- **Median PFS 2.9 months**
- **ORR 23%**
- **Median duration of therapy: 2.2 months**

Cabozantinib in RET translocated patients

(Drilon Lancet Onc 2018)



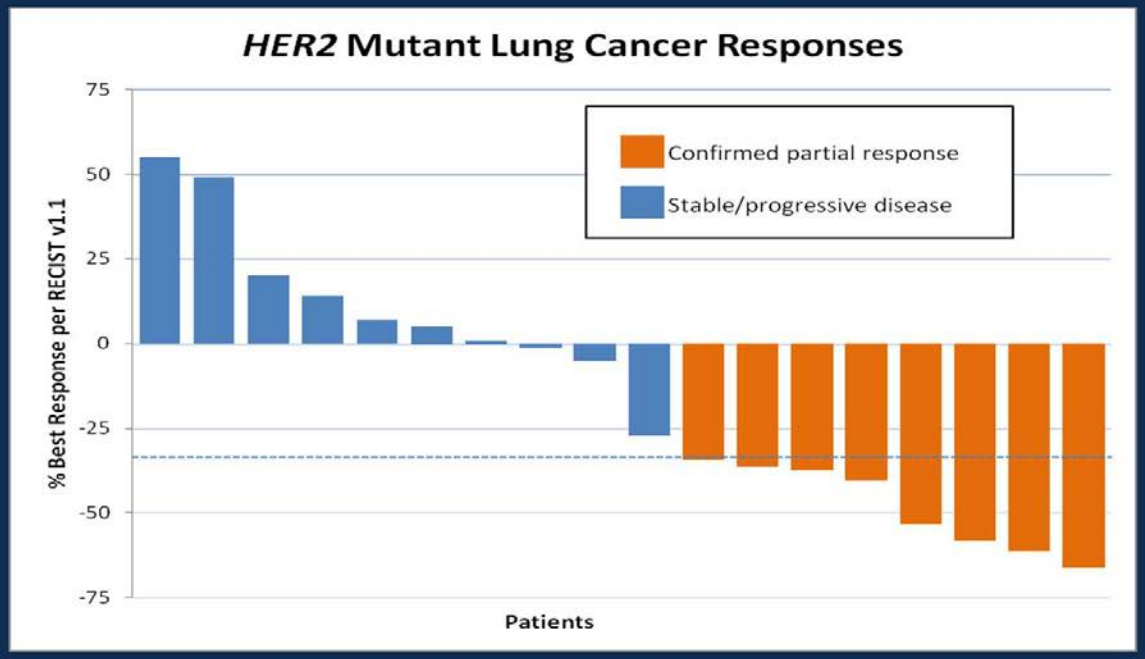
LOXO-292 in RET Fusion Positive Lung Cancer

- **Drilon et al presented data on Loxo-292 in patients with RET + cancers (27 lung, 20 MTC, 7 PTC, 1 pancreatic)**
- **ORR was 69%; 65% in the lung cohort and occurred in treatment naïve and previously treated patients**
- **Toxicities have been mild and 52/57 patients have remained on therapy with all responses ongoing; the longest > 6 months**

HER-2 and Lung Cancer

- **1-2% of adenocarcinomas**
- **Female predominant**
- **Early studies often lumped over-expressors in with patients with the exon 20 mutation**
- **Responses to therapy are seen more often in the mutated cohort although patients with IHC 3+ also seem to respond**

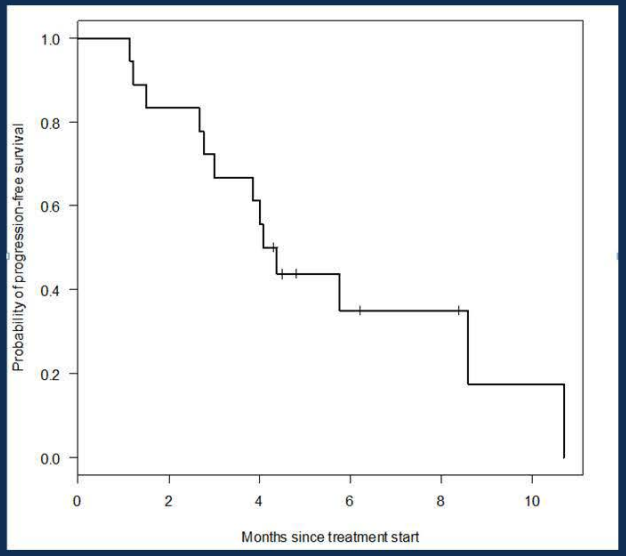
Overall response rate (ORR) by RECIST v1.1

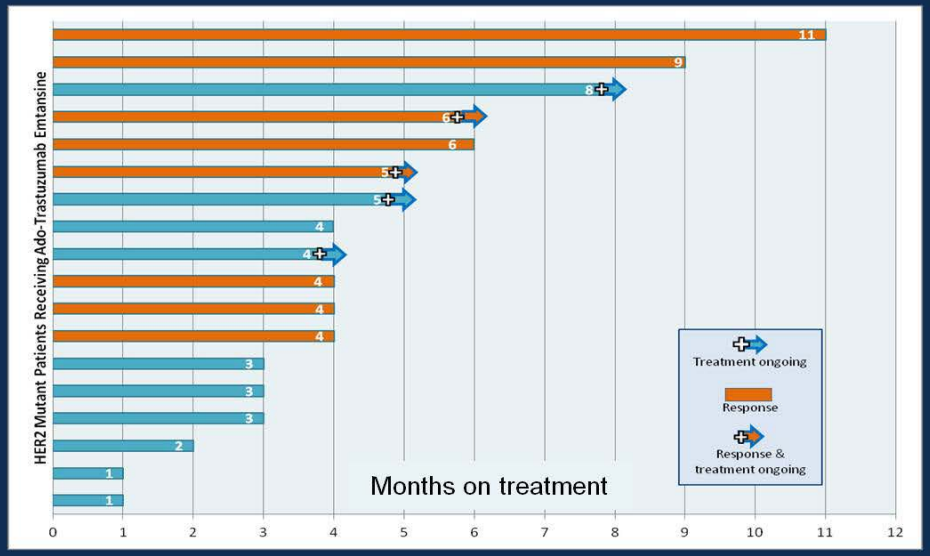


ORR 44% (8/18, 95% CI 22-69%), study met primary endpoint

Li et al ASCO Annual Meeting 2017

Progression free survival (PFS)





Median PFS: 4 months (95% CI 3.0 to NR, n=18 with 13 events)
Median duration of response: 5 months (95% CI 3.0 to NR, n=8 with 6 events)

Li et al ASCO Annual Meeting 2017

Mutations can also help guide IO decisions

- **Driver-mutated lung cancers are less responsive to IO although they differ in the response rates**
- **EGFR seems least responsive, BRAF maybe the most**
- **Progressing patients will still be offered IO but hopefully on a clinical trial**

Efficacy of IO in NSCLC Patients with Driver Mutations

Driver	n	CR/PR	SD/PD	Median PFS	1 yr PFS	Median OS
BRAF	38	28.1	28.1/43.8	3.0 months	19%	13.6 months
KRAS	252	27.2	23.1/49.8	3.2 months	26%	13.5 months
ROS1	5	20	0/80	NA	NA	NA
MET	36	15.6	34.3/50	3.4 months	23%	18.4 months
EGFR	110	11.0	18.0/71.0	2.0 months	6%	8.8 months
HER2	23	9.5	28.6/61.9	3.5 months	17 %	10.0 months
RET	14	7.1	21.4/71.4	2.2 months	8	6.5 months
ALK	18	0	21.4/78.6	2.1 months	8	17 months

Mazieres et al ASCO Annual Meeting 2018

KRAS and STK11/LKB1 and Resistance to IO

There are distinct molecular subgroups in KRAS mutated adenocarcinoma of the lung and they have different responses to PD1 blockade

KRAS and STK11/LKB1: ORR 7.4%

KRAS: and p53 : ORR 35.7%

KRAS alone: ORR 28.6%

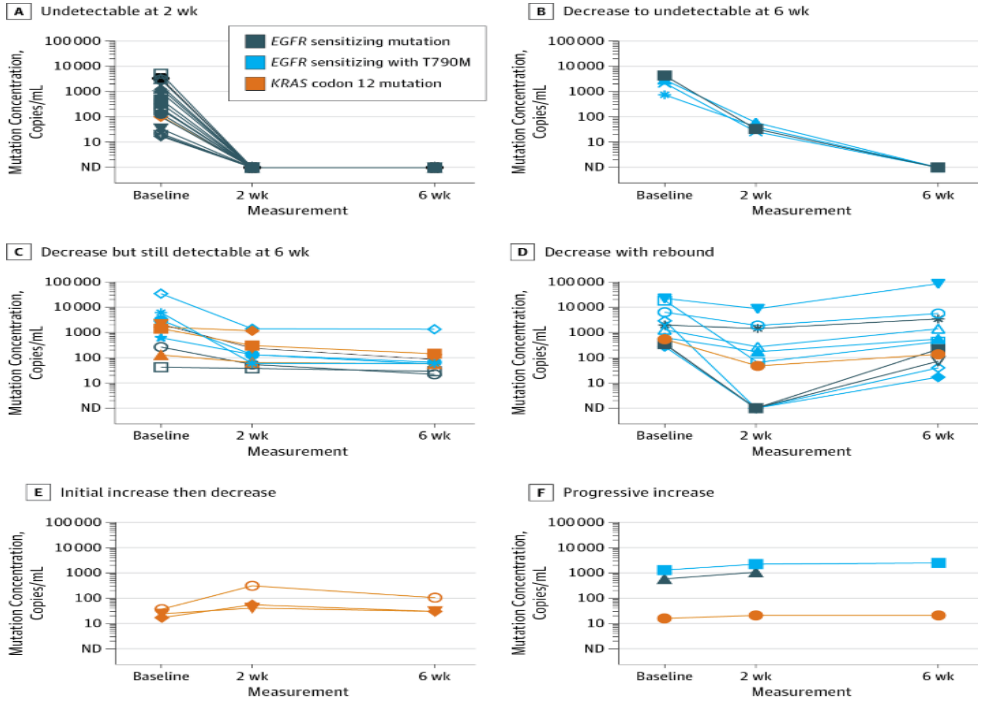
Among 924 patients, KRAS and STK11/LKB1 was the only marker significantly associated with failure to respond to Io in the TMB int/high group

Heymach Cancer Discovery 2018

The JAMA Network

From: **Prospective Validation of Rapid Plasma Genotyping for the Detection of EGFR and KRAS Mutations in Advanced Lung Cancer**

JAMA Oncol. Published online April 07, 2016. doi:10.1001/jamaoncol.2016.0173



THANK YOU!

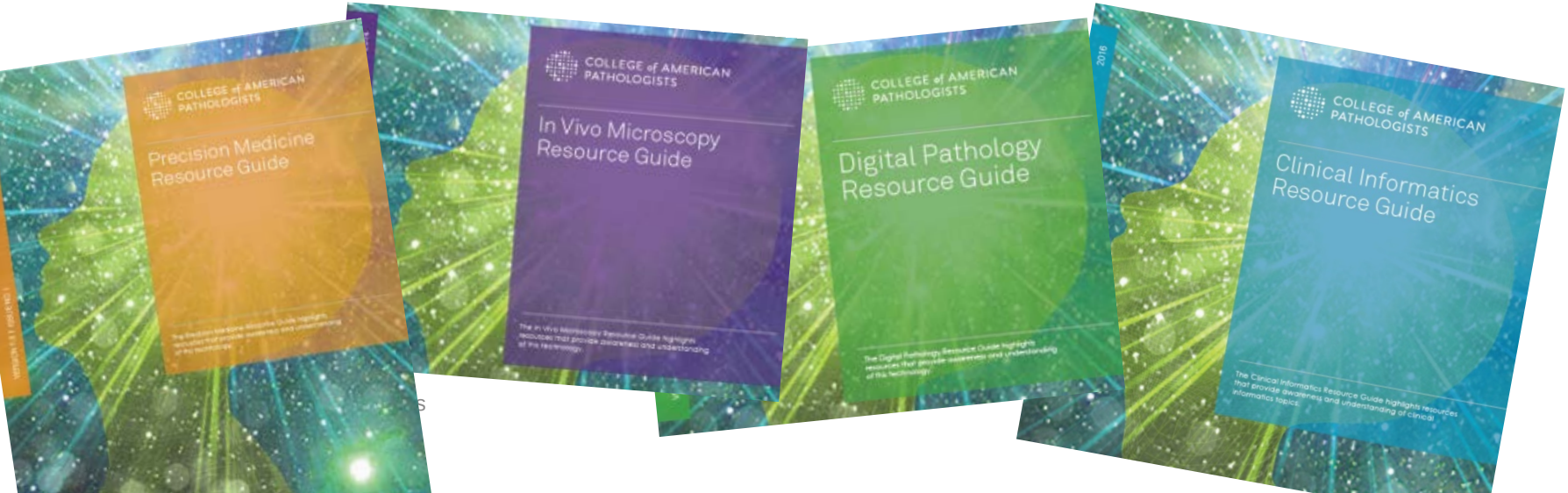
Register for Upcoming Webinar

DATE	TOPIC	SPEAKER
Tuesday, July 17 11:00 AM CT	Incidental Findings Webinar	Sophia L. Yohe, MD

Register for upcoming & archived webinars:
www.cap.org > Calendar > Webinars > Previous

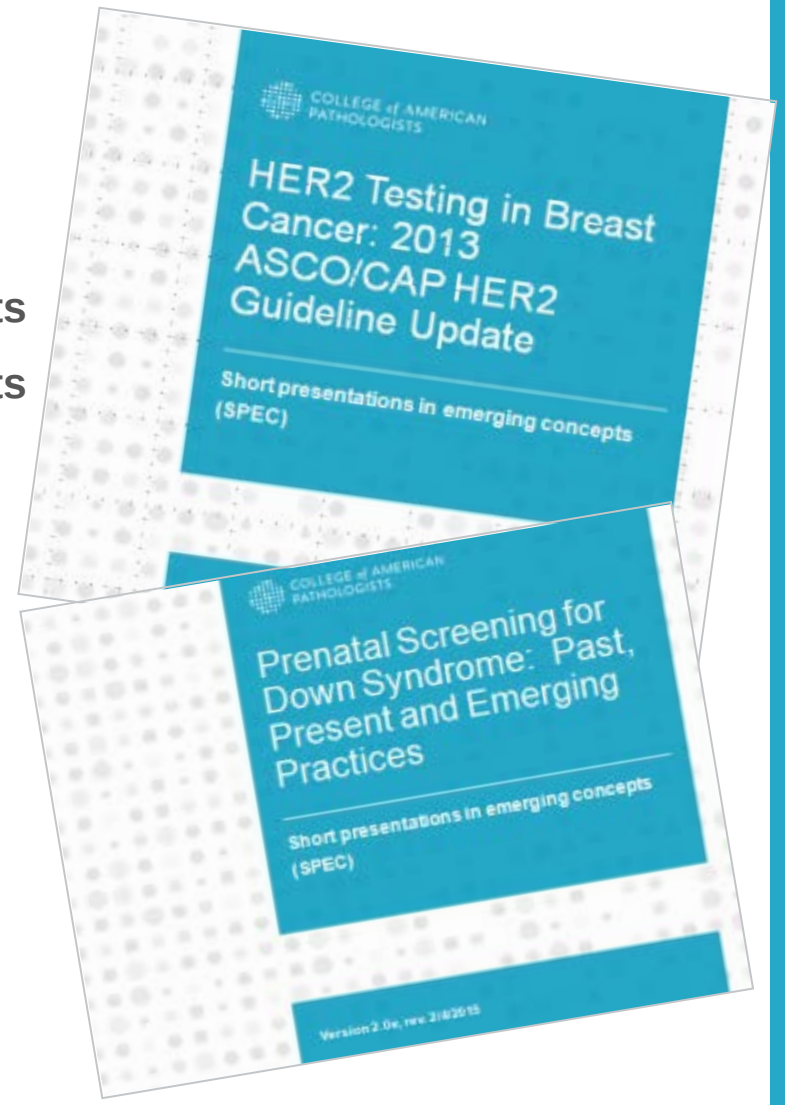
CAP's Pathology Resource Guide: Precision Medicine

- **The CAP has created the Pathology Resource Guides to assist pathologists in understanding key emerging technologies.**
  - **Printed guides are now available for members ($39) and non-members ($69)**
  - **The digital copy of the Resource Guides are a complimentary member benefit**
  - **Access them www.cap.org > Resources and Publications**



Short Presentations on Emerging Concepts (SPECS)

- **Pathology SPECs are:**
  - **Short PowerPoints, created for pathologists**
  - **Focused on diseases where molecular tests play a key role in patient management**
- **Recent topics include:**
  - **Microbiome**
  - **Biomarkers in Lung Cancer**
  - **MDS**
  - **Other emerging topics**
- **Access them at www.cap.org > Resources and Publications**



See, Test & Treat® brings cancer screenings to women in need!

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- CAP member pathologists' partner with gynecologists, radiologists and other medical professionals to lead See, Test & Treat programs in hospitals, clinics and other facilities

- Women learn the importance of preventive care through annual exams, a Pap test, Mammogram and a healthy lifestyle

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THANK YOU!

Thank you for attending our webinar, "New Guideline for Lung Cancer Biomarker Testing: Essentials and Applications" by Philip Cagle, MD, FCAP and Eric Bernicker, MD

For comments about this webinar or suggestions for upcoming webinars, please contact phcwebinars@cap.org.

NOTE: There is no CME/CE credit available for today's free webinar. The PDF of the presentation will be sent out in a week.

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