



*Continuous Evolution:  
Current and Emerging Indications for  
Molecular Pathology in Lung Cancer*

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*Annual Park City Pathology Update  
Park City, Utah  
February 6, 2022*





# *Introductions*



I have no conflicts of interest



But there's always hope...

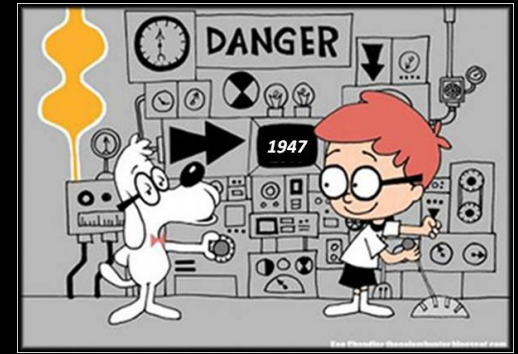


# *Case Presentation:*

- 52 yr old female
- Symptoms (months):
  - Headaches
  - Light/dark sensitivity
  - Chronic dry cough
- MRI:
  - Enhancing dural mass

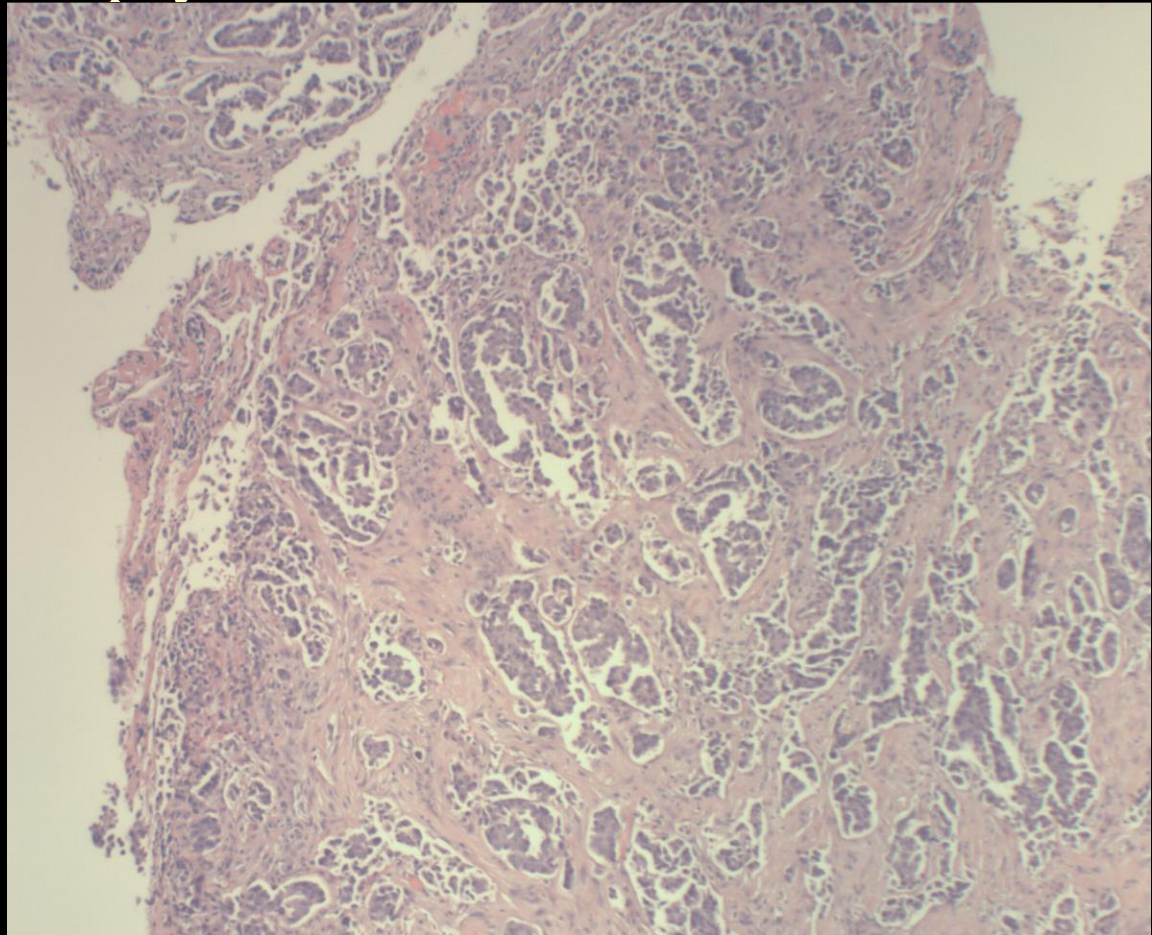
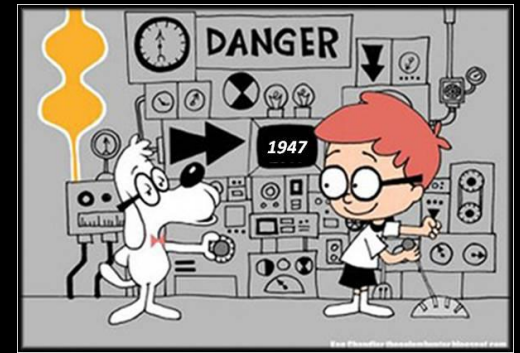
## □ Differential Dx:

- Tumor
  - Meningioma
  - Lymphoma
  - Metastasis
  - Primary CNS tumor
- Granuloma
  - Sarcoidosis
  - Tuberculosis
- Chronic meningitis
  - Wegener's



# *Case presentation:*

□ Brain biopsy:

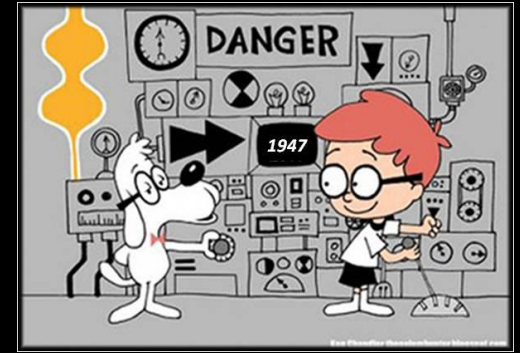


# *Case Presentation*

## ❑ Follow-up imaging studies

- 5 cm lung mass
- Additional masses:
  - Lung (x2), liver (x2), bone

## ❑ Non-small Cell Lung Cancer, Stage IV



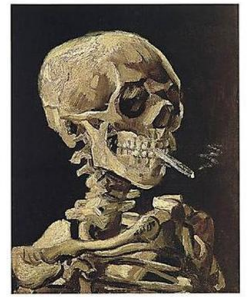
# *Lung Cancer is Bad*

## □ Survival @ 18 months:

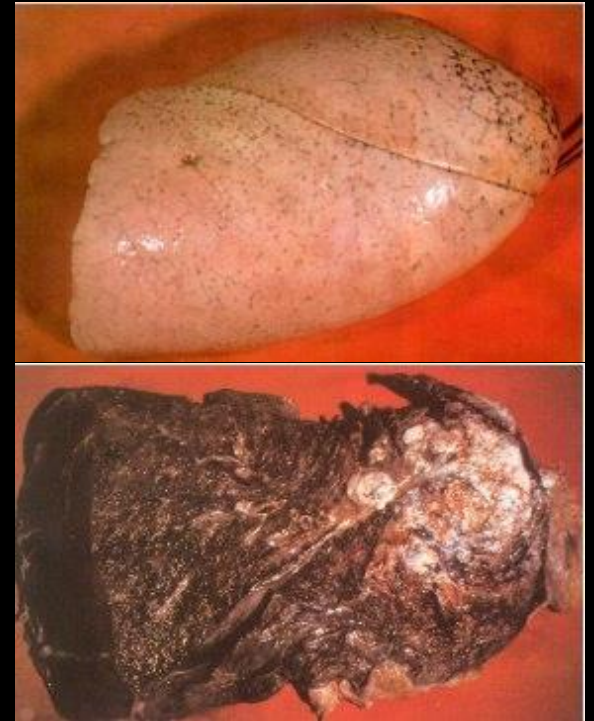
- Stage I: 49 – 65%
- Stage II: 39 - 55%
- Stage III: 4 – 15%
- **Stage IV: 1%**

## □ Median survival:

- Stage I/II: 17 – 32 months
- Stage III: 9 - 22 months
- **Stage IV: 16 – 36 weeks**



*Van Gogh, 1885*

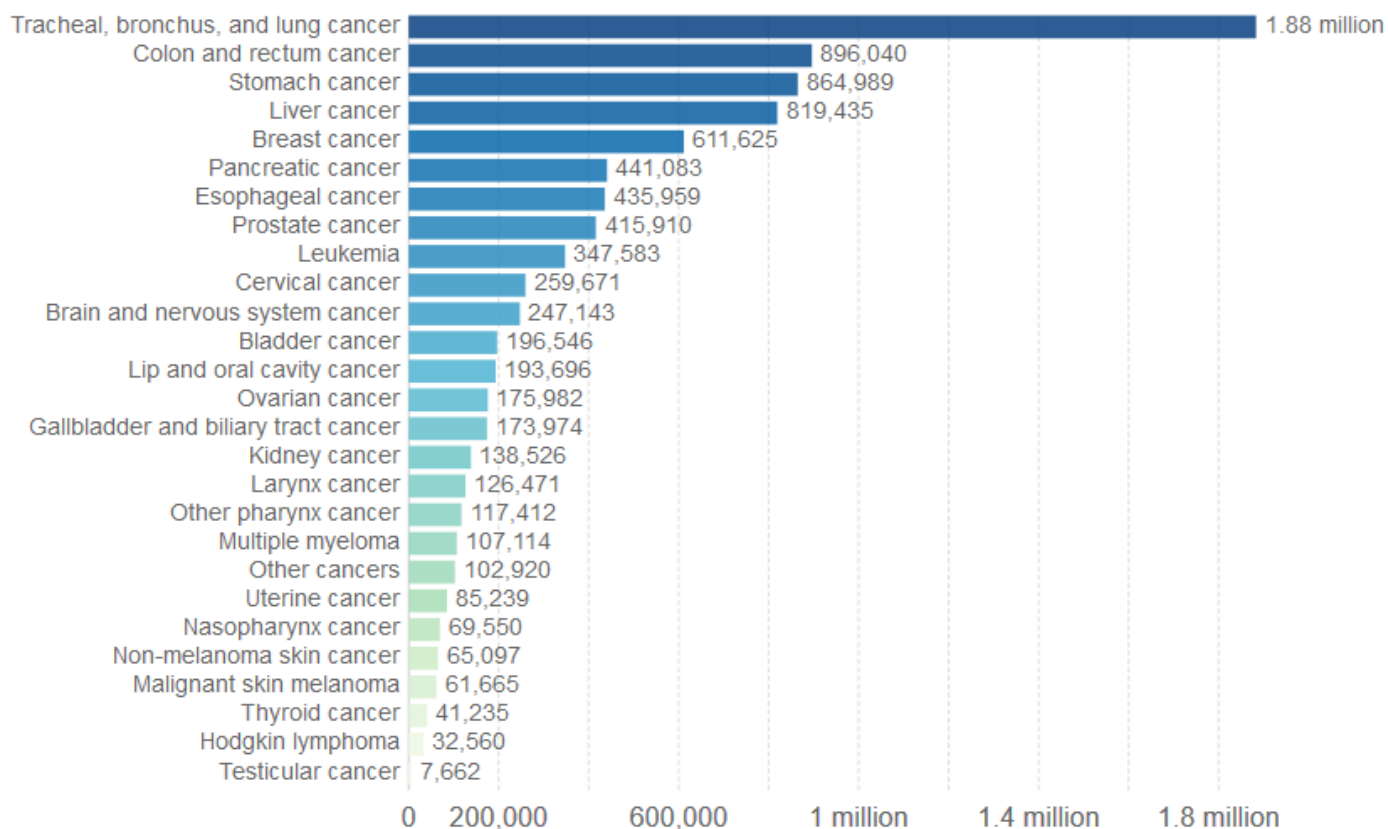


# *Lung Cancer is Bad for society*

## Cancer deaths by type, World, 2017

Total annual number of deaths from cancers across all ages and both sexes, broken down by cancer type.

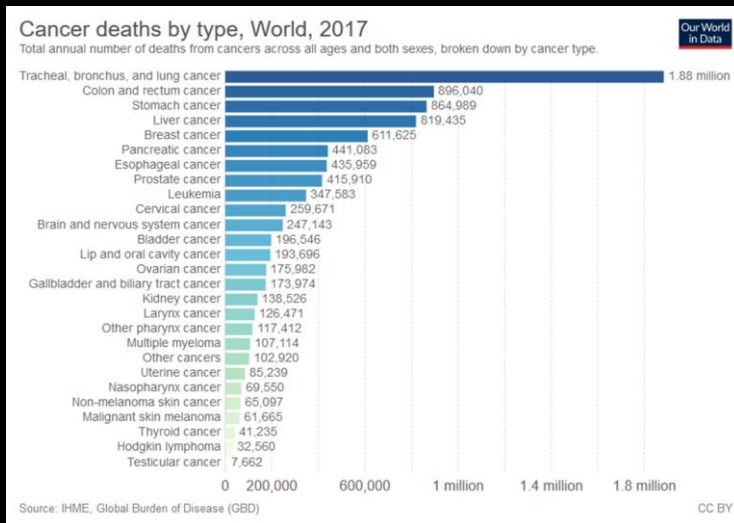
Our World  
in Data



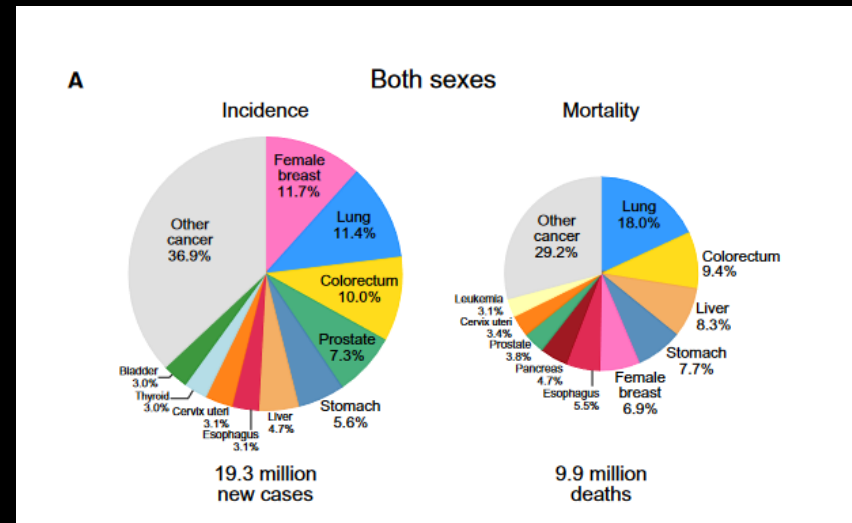
Source: IHME, Global Burden of Disease (GBD)

CC BY

# *It is getting better...slightly*



2017: 1.88 M deaths

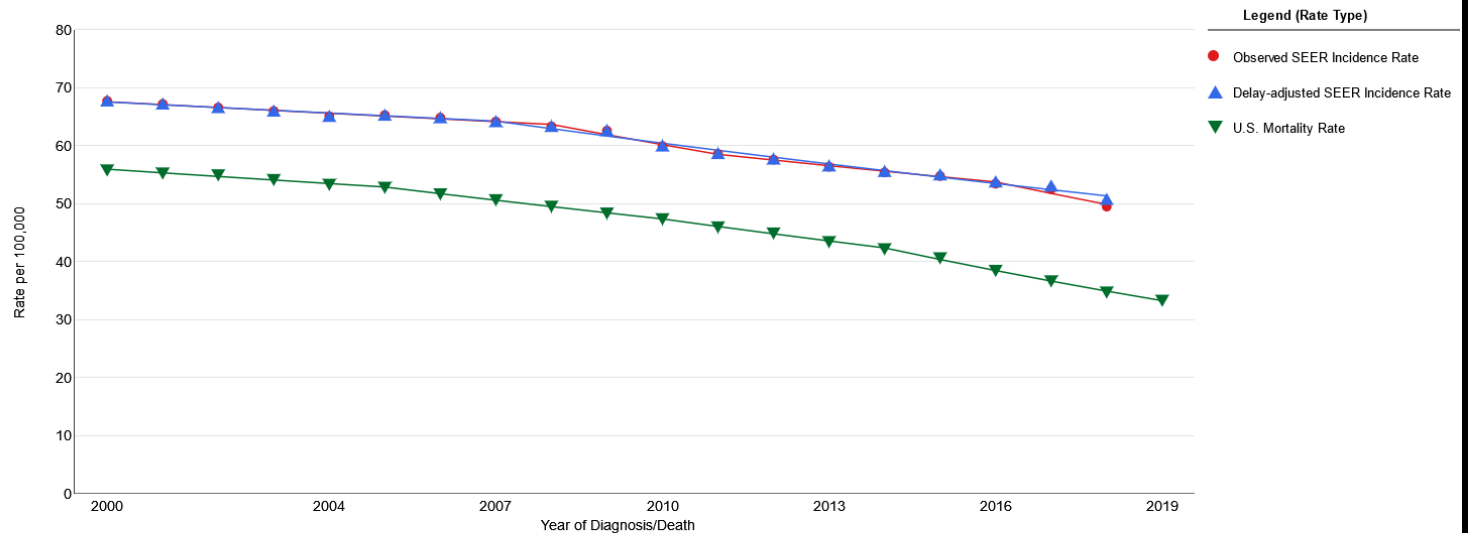


*Sung, et al., CA Cancer J Clin, 2021*

2020: 1.79 M deaths

# *It is getting better*

## Lung and Bronchus Recent Trends in SEER Incidence(2000-2018) and U.S. Mortality(2000-2019) Rates By Rate Type, Both Sexes, All Races (includes Hispanic), All Ages

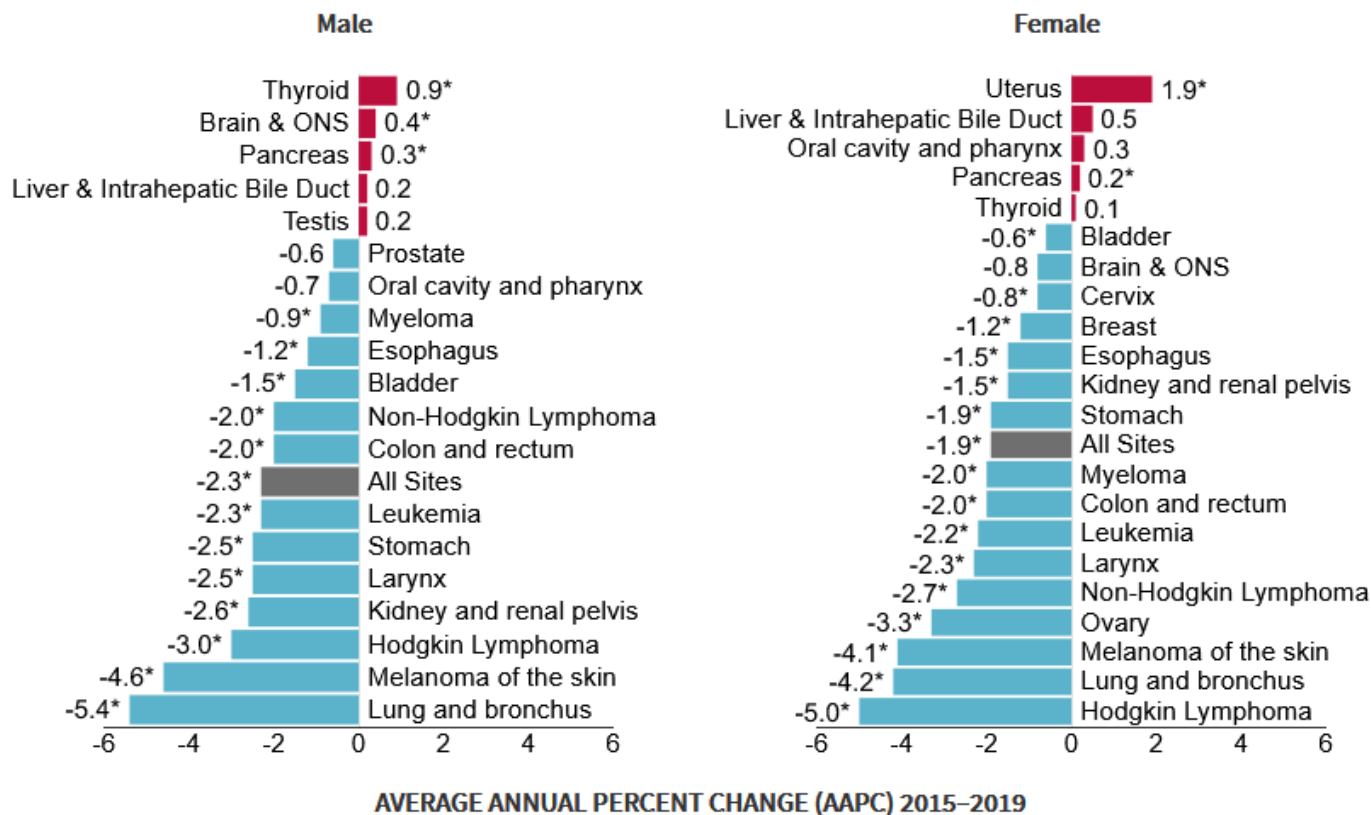


Created by <https://seer.cancer.gov/explorer> on Mon Jan 10 2022.  
 Mortality Estimates: US Mortality Files, National Center for Health Statistics, CDC.  
 Incidence Estimates: SEER 21 areas (<http://seer.cancer.gov/registries/terms.html>) (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, San Jose-Monterey, Los Angeles, Alaska Native Registry, Rural Georgia, California excluding SF/SJ/LA, Kentucky, Louisiana, New Jersey, Georgia excluding ATL/RG, Idaho, New York and Massachusetts).  
 Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130).  
 The Annual Percent Change (APC) and Average Annual Percent Change (AAPC) estimates were calculated from the underlying rates using the Joinpoint Trend Analysis Software (<http://surveillance.cancer.gov/joinpoint>), Version 4.9, March 2021, National Cancer Institute.  
 The APCs/AAPCs direction is "Rising" (↑) when the entire 95% confidence interval (C.I.) is above 0, "Falling" (↓) when the entire 95% C.I. is lower than 0, otherwise, the trend is considered "Not Significant".  
 Rates for American Indians/Alaska Natives only include cases that are in a Purchased/Referred Care Delivery Area (PRCDA). See SEER Race Recode Documentation for American Indian/Alaskan Native Statistics ([http://seer.cancer.gov/seerstat/variables/seer\\_race\\_ethnicity/#ai-an](http://seer.cancer.gov/seerstat/variables/seer_race_ethnicity/#ai-an)).  
 Hispanics and Non-Hispanics are not mutually exclusive from whites, blacks, Asian/Pacific Islanders, and American Indians/Alaska Natives. Incidence data for Hispanics and Non-Hispanics are based on the NAACCR Hispanic/Latino Identification Algorithm (NHIA) and exclude cases from the Alaska Native Registry. See SEER Race Recode Documentation for Spanish-Hispanic/Latino Ethnicity ([http://seer.cancer.gov/seerstat/variables/seer\\_race\\_ethnicity/#hispanic](http://seer.cancer.gov/seerstat/variables/seer_race_ethnicity/#hispanic)).  
 Mortality Estimates: Cancer sites are defined using the SEER Cause of Death Recode 1969+ (04/16/2012) ([https://seer.cancer.gov/coderecode/1969+\\_d04162012/index.html](https://seer.cancer.gov/coderecode/1969+_d04162012/index.html)).  
 Incidence Estimates: See SEER Explorer Cancer Site Definitions (<https://seer.cancer.gov/explorer/cancer-sites.html>) for details about the coding used for SEER incidence data.

*SEER, NIH website, accessed 1/10/22*

*It is getting better*

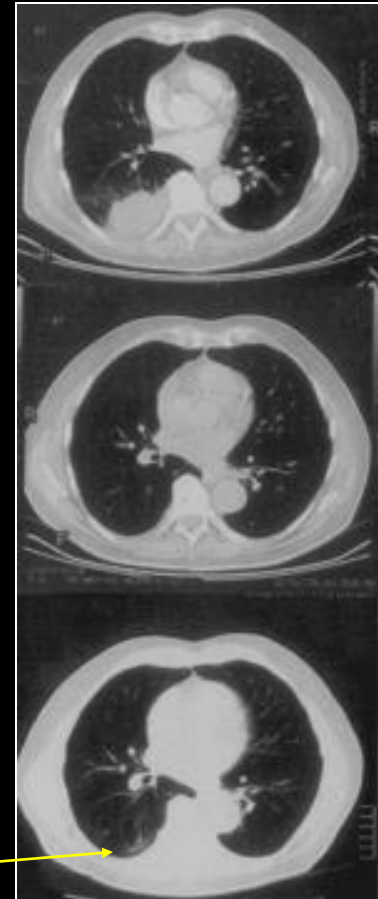
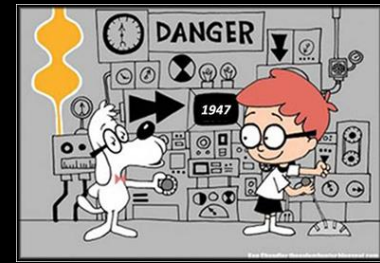
TRENDS IN DEATH RATES



# *Return to Case:*

## □ History:

- **Never smoked**
- Course:
- 4/01: Carboplatin-Paclitaxel
  - Response for 6 wks
  - Progression by 12/01
- 12/01: Cetuximab (Erbix)
  - Stabilization for 4 mos
  - Progression by 7/02
- **8/02: Gefitinib (Iressa)**
  - **Sustained response for 30 mos**
  - **Relapse in 2/05**

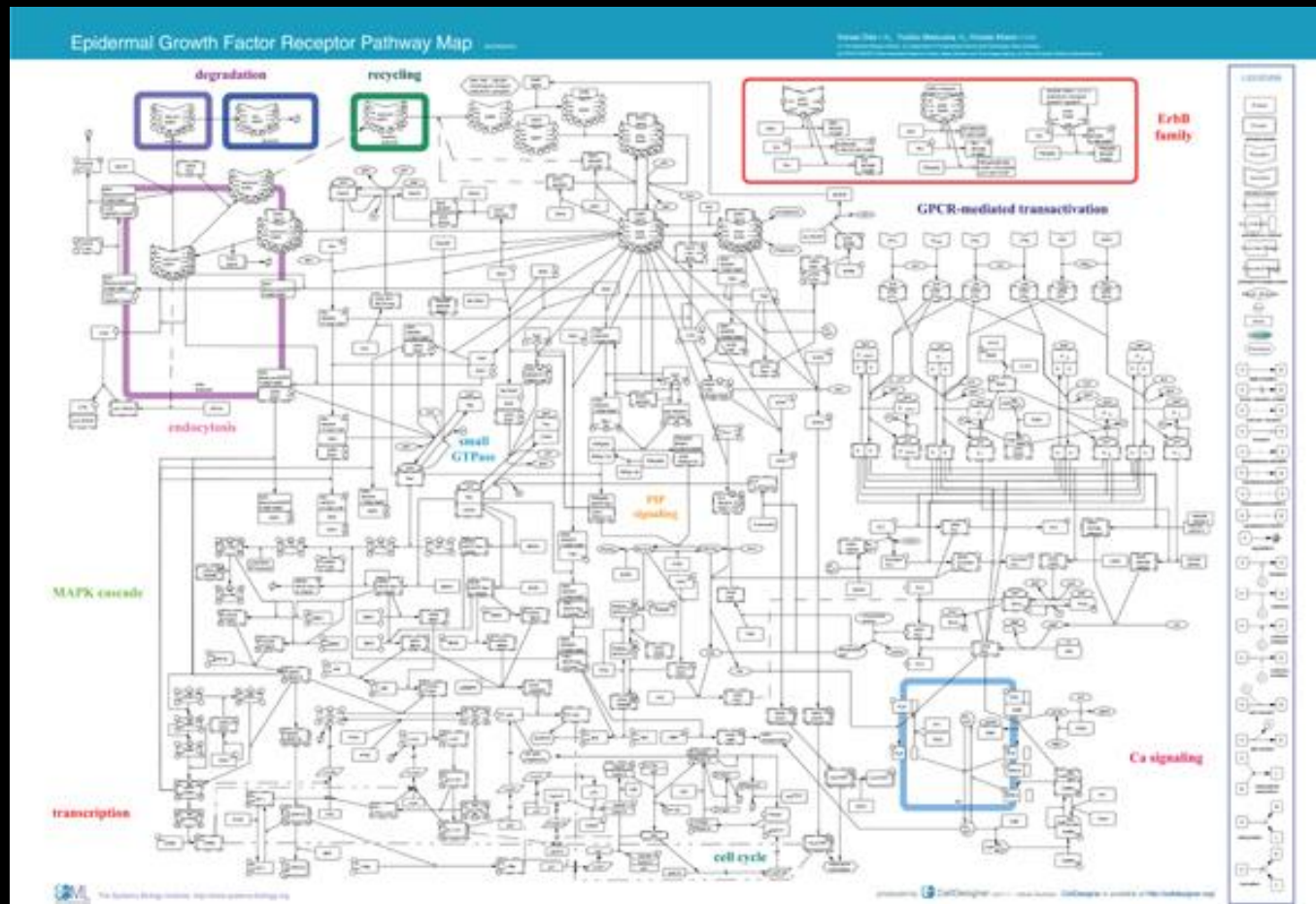


8/02

5/03

2/05

# What is *EGFR* and why target it?



Oda, et al., *Molec Systems Biol*, 2005

# *EGFR signaling simplified:*



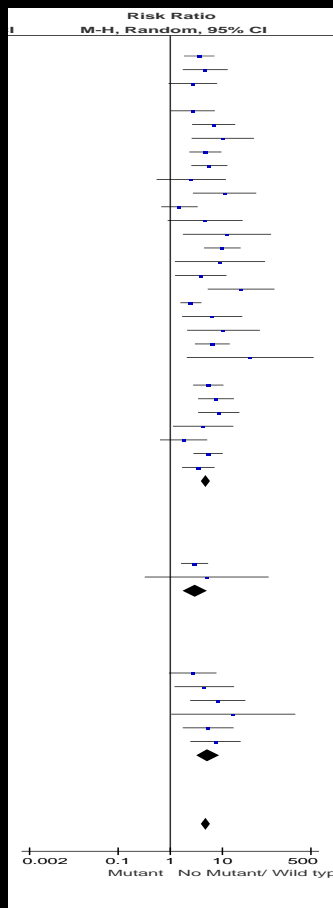
- ❑ Ligand binds
- ❑ Receptor Dimerization
- ❑ Phosphorylation
- ❑ Downstream signaling
  - RAS→RAF→ERK
  - JAK→STAT
  - PIK3CA→AKT→mTOR
- ❑ Cells proliferate, survive

Very commonly overexpressed in human carcinomas

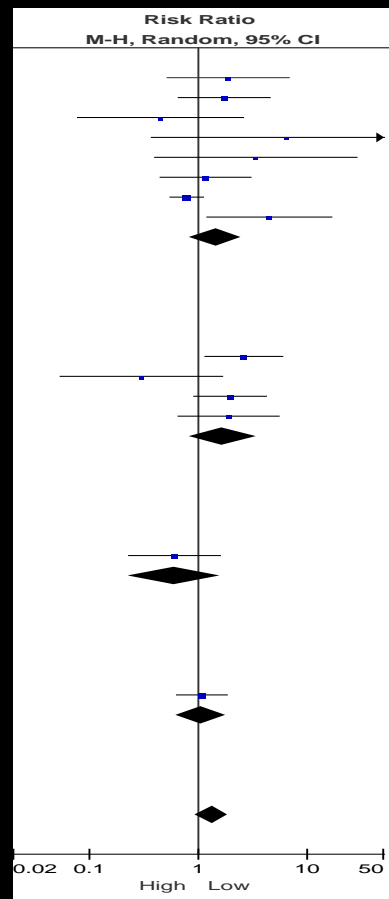
# *How to test for EGFR?*

## *Molecular Diagnosis!*

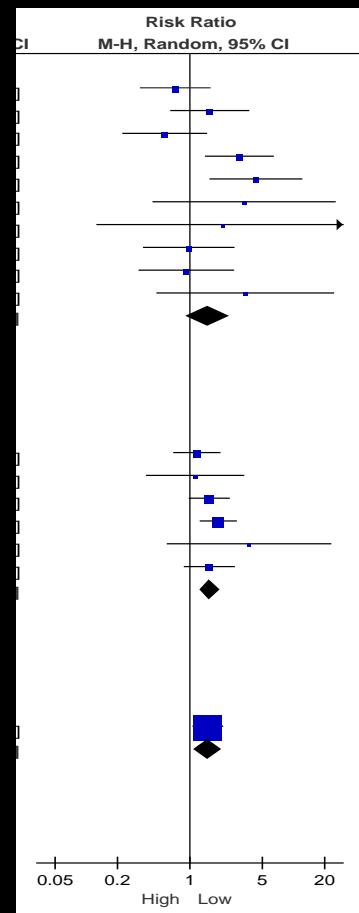
### Mol Dx



### FISH

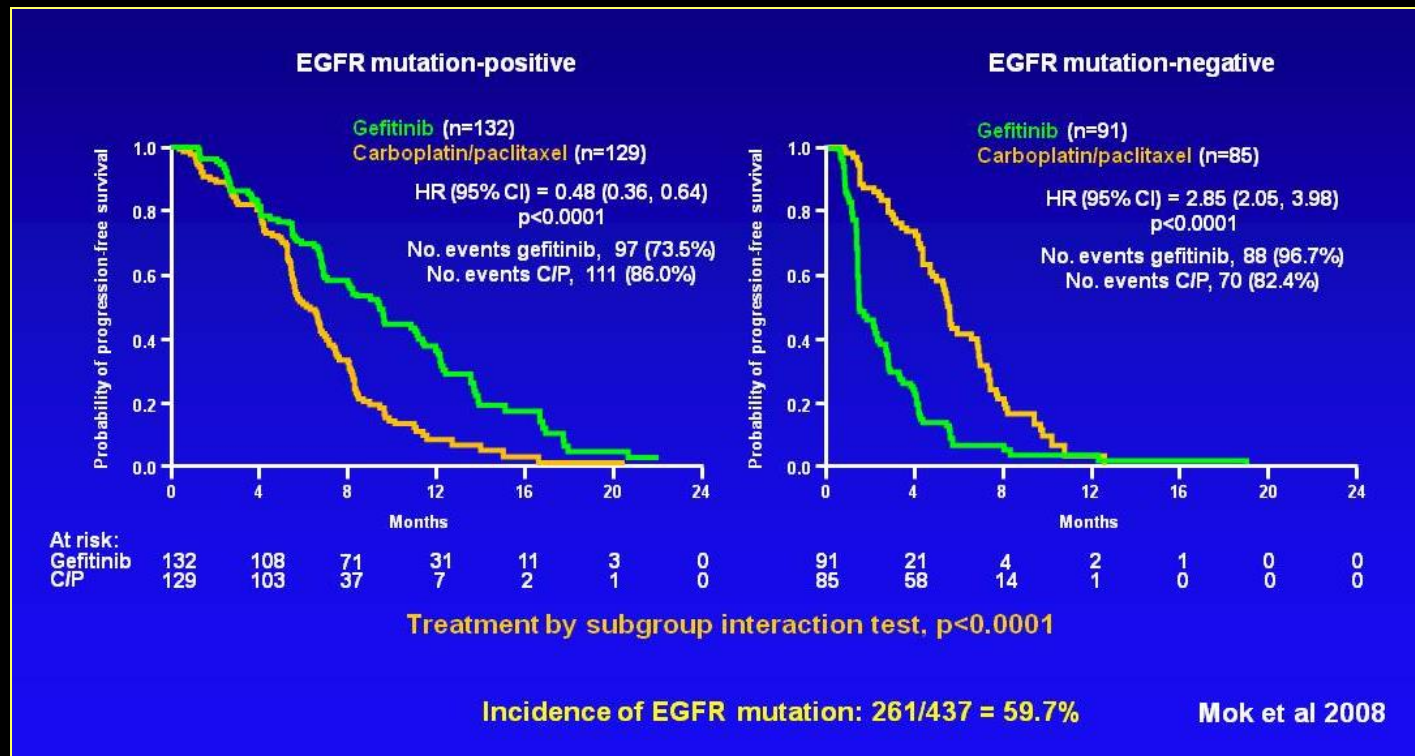
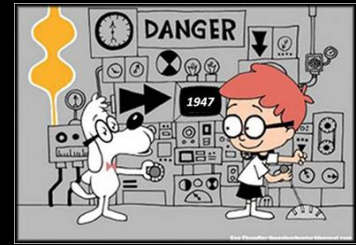


### IHC



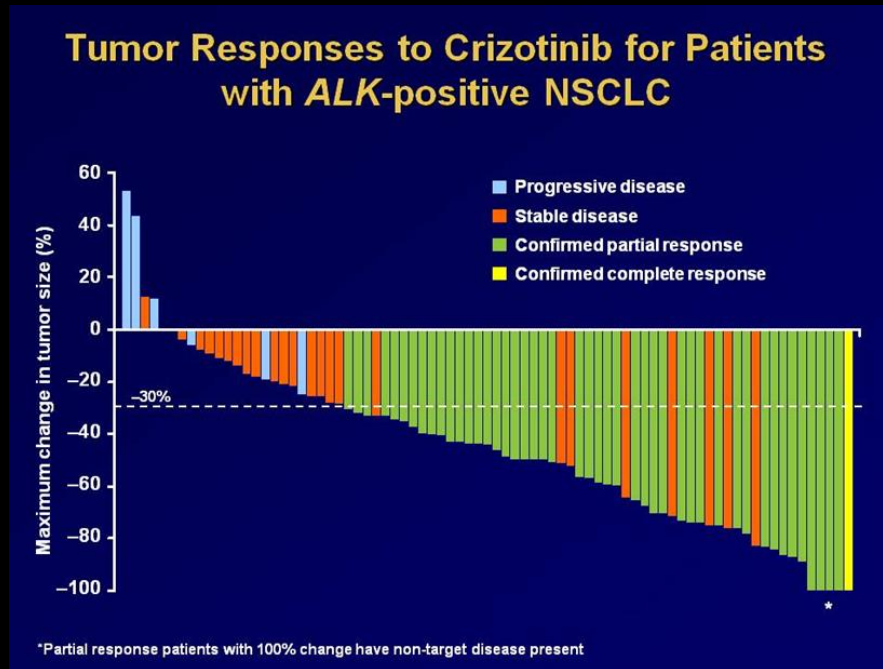
# *Why test at all?*

## *Empiric therapy is not harmless*



*But wait...*

*... there's MORE!*

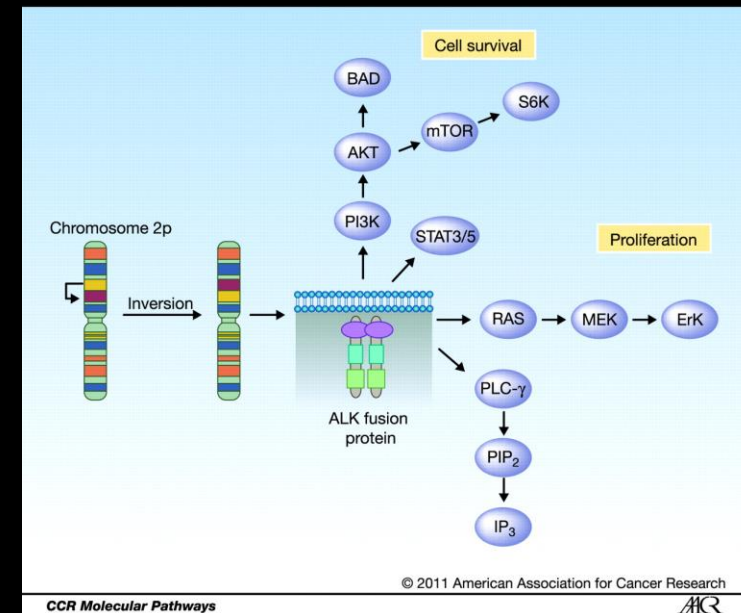
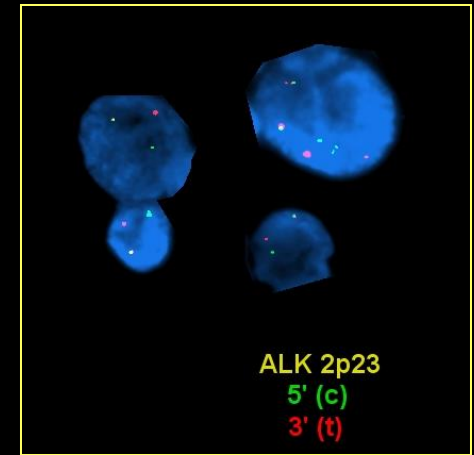


*ALK rearrangement predicts crizotinib response*

Crizotinib and ALK FISH both approved by FDA, 2011

# ALK rearrangement

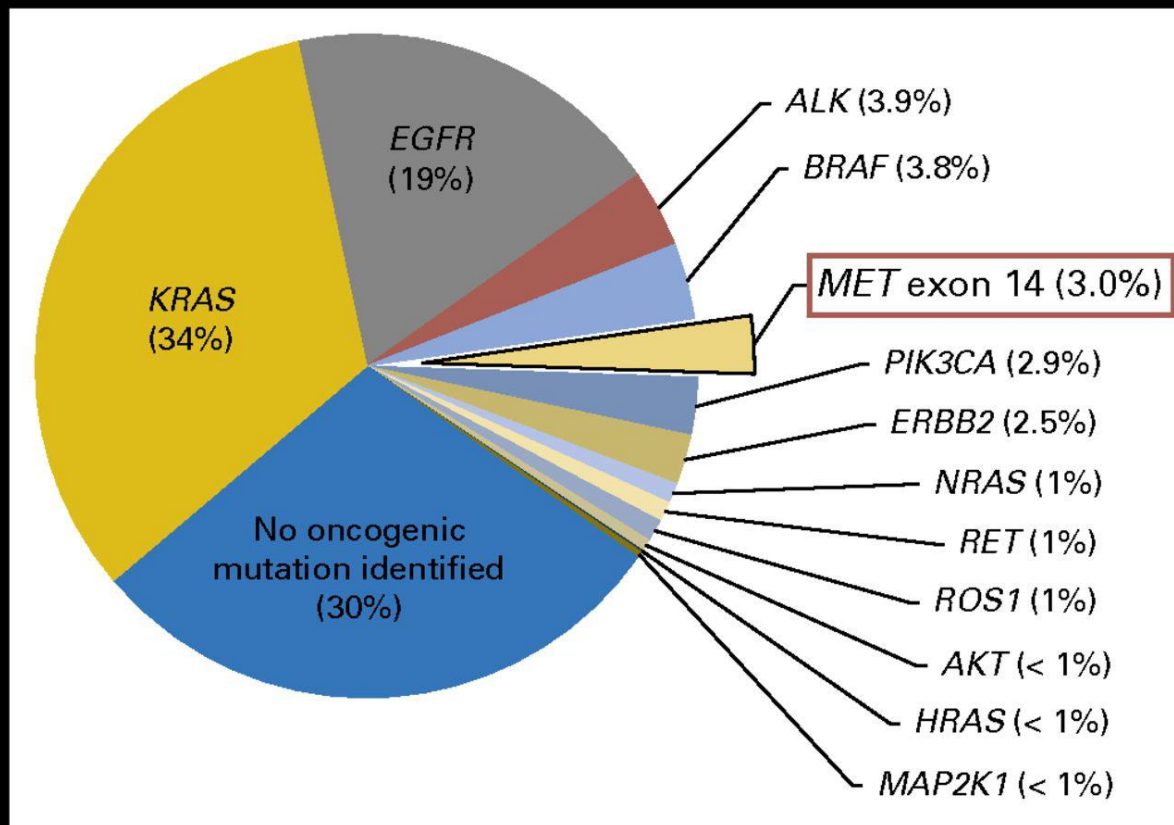
- ❑ First report: Soda, et al, Nature, 2007
- ❑ Typical : Inversion on 2p
  - EML4-ALK fusion
  - Rare Chromosomal variants
    - KIF5B-ALK, TFG-ALK
- ❑ Activates ALK kinase
- ❑ ~5% of lung adenocarcinomas
- ❑ Therapy: crizotinib



Trivia: More patients have EML4-ALK lung cancer than NPM-ALK lymphoma!



# 2017: *EGFR/ALK not the whole story*





CAP Laboratory Improvement Programs

## 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. Wynnes, PhD; Yasushi Yatabe, MD, PhD

Article in Press

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DOI: <https://doi.org/10.1016/j.jtho.2017.12.001>

The Journal of Molecular Diagnostics, Vol. 20, No. 1, 2018



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Diagnostics  
[jmd.ampjpathol.org](http://jmd.ampjpathol.org)

## SPECIAL ARTICLE

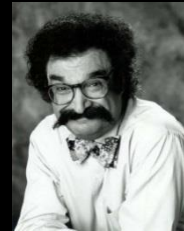
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# *What other genes should be tested in lung adenocarcinoma?*

*ROS1*: 1-2% rearrangement



*RET*: 1-2% rearrangement

*BRAF*: 4% mutation half are non-V600E



*MET*: 3% exon 14 skipping mutations, amplification

*ERBB2/HER2*: 2% mutation



*KRAS*: 30% mutation



# *ABRUPT AND JARRING FORMAT CHANGE*



# Abrupt and jarring format change



# New in 2018: *ROS1*

- **Clinical utility**

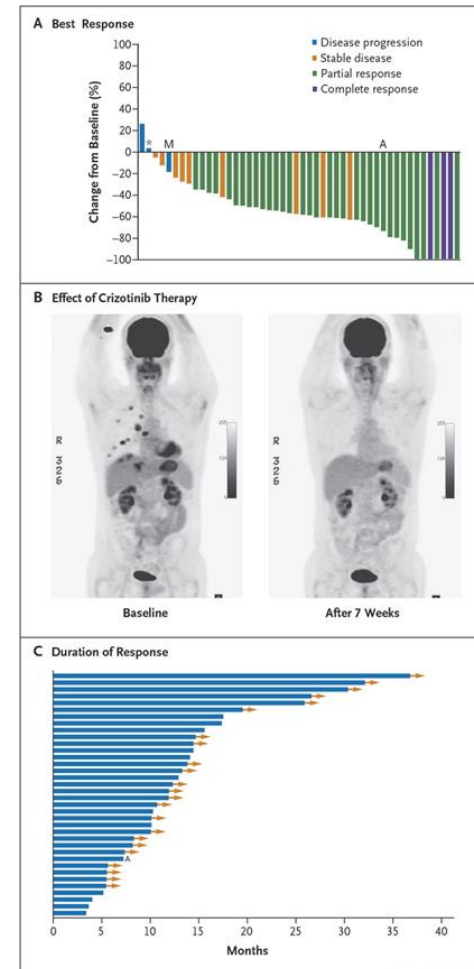
- *ROS1*+ tumors respond to crizotinib
- RR 70-80%
- Phase I, I/II, II trials
- No Phase III

- **Oncologists treat with crizotinib**

- Oncologists use *ROS1* testing

- **Crizotinib approved by FDA**

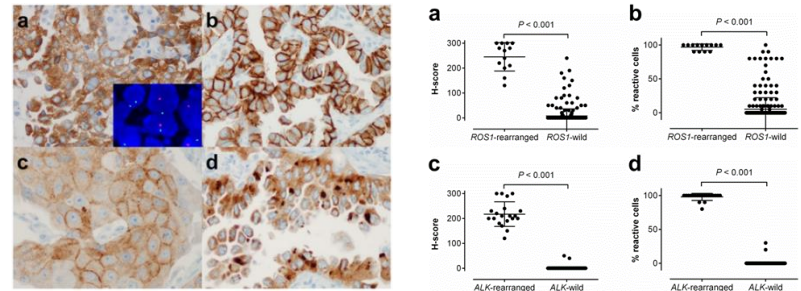
- *ALK*+, *ROS1*+ lung cancers



# New in 2018: *ROS1*

## •Methodology

- Adenocarcinomas, but no sensitive clinical predictors
- No designated companion diagnostic
- FISH is predicate method
- Immunohistochemistry (IHC) for screening; confirm + with FISH
- RNA methods (RT-PCR, anchored multiplexed PCR)
- Next generation DNA sequencing



Cha, et al., PLoS One, 2014

# Others: *RET*, *BRAF*, *ERBB2*, *KRAS*, *MET*

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- As with *EGFR*, *ALK*, *ROS1*, typically mutually exclusive

- Adenocarcinomas, but no sensitive clinical predictors

- Clinical trials and/or potential drugs for each:

- *RET*: cabozantinib, vandetinib

- *BRAF*: vemurafenib, dabrafenib, +/- trametinib

- *ERBB2/HER2*: ?pulsed afatinib?, ?neratinib?, ?dacomitinib?

- *KRAS*: trametinib, selumetinib

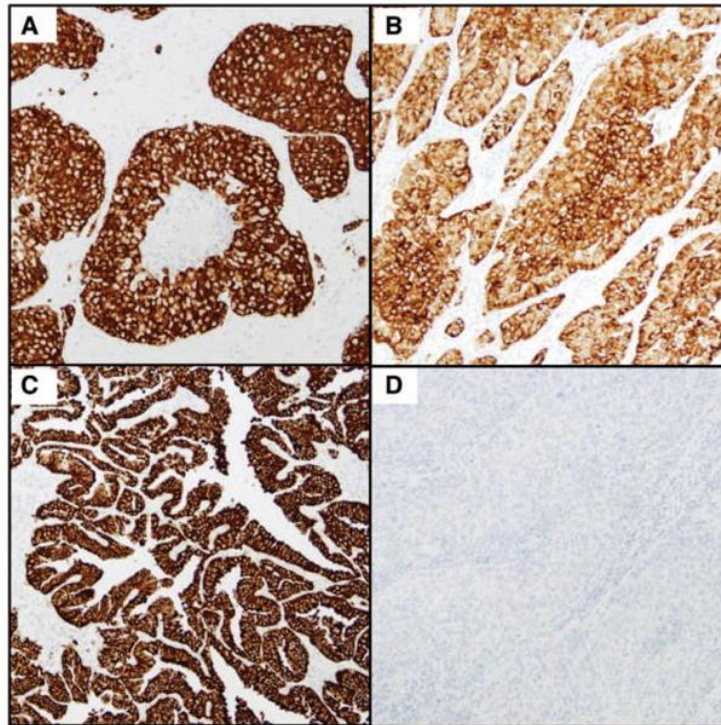
- *MET*: crizotinib

- Not recommended as single tests for lung cancer patients
- If a large panel is being performed, include these
- If *ALK*, *EGFR*, *ROS1* all negative, include these

- Limited evidence for clinical utility (Case reports & small series\*)

# KQ II. Is immunohistochemistry reliable for *ALK* translocations?

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Wynes, et al., JTO, 2014



# KQ II. Is immunohistochemistry reliable for *ALK* translocations?

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**YES**



# KQ II. Is immunohistochemistry reliable for *ALK* translocations?

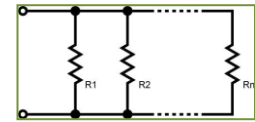


Table 3.  
Comparative FISH/IHC Analysis in 3244 NSCLC Patients

FISH					
IHC		Positive	Negative	NC	Total
	Positive	80	19	15	114
	Negative	36	2579	435	3050
	NC	0	49	31	80
	Total	116	2647	481	3244

FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; NC, noncontributive analysis or technical failure; NSCLC, non-small-cell lung cancer.

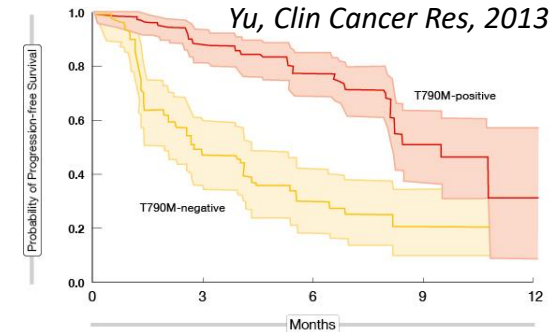
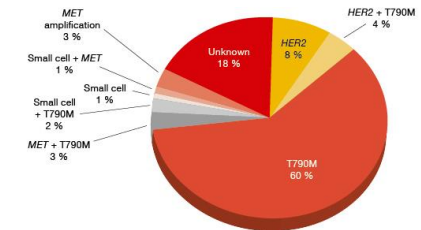
- Numerous studies showed excellent concordance
- Discordances seen in both directions
  - both FISH and IHC can be either false negative or positive
- No scientific need to perform both methods
- Do NOT use the ALK1 antibody developed for Anaplastic Lymphoma



# KQIII: Testing in acquired resistance

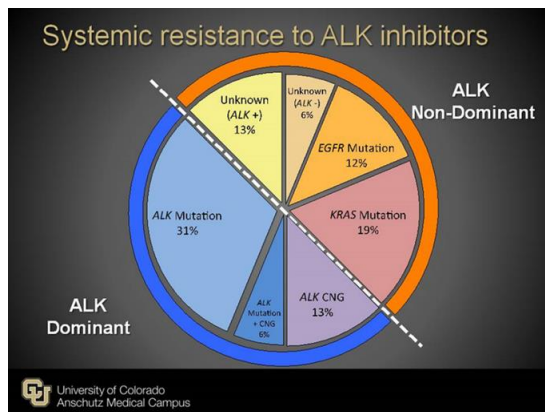
## • **EGFR:** all about T790M, and ultrasensitivity

- T790M responds to specific inhibitor
- Relapsed specimens are heterogeneous
- Recommended cutoff is 5% mutant alleles
- Circulating cell-free DNA may be superior\*



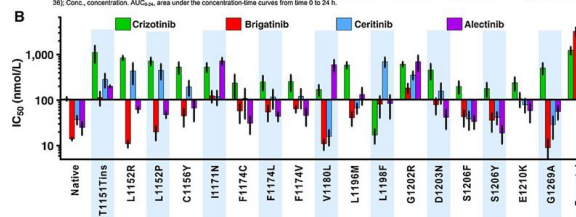
## • **ALK:** unclear value of identifying resistance mutations

Janne, NEJM, 2015



TKI	Clinical trial data				In vitro mutagenesis screen results	
	Dose*	C <sub>50</sub> † (nmol/L)	PPB (%)	ALK Secondary mutations previously associated with clinical resistance‡	TKI Conc. (nmol/L)	ALK Secondary mutations that emerged§
Crizotinib	250 mg bid	718	90.7	T1151Tins, L1152R, C1156Y, L1173N†, E1174L, L1198M, G1202R, G1203R, S1206Y, G1288A	500	T1151K, H1717, E1174L, S1206A, F1245C, G1288A
	90 mg qd	582	85.7	N/A¶	750	C1156Y, L1173N†, L1174C, L1198M, L1198M
Brigatinib	180 mg qd	1447	85.7	N/A¶	1000	L1198M
	750 mg qd	1232	97.2	G1123S, E1174C/V, G1202R	200	E1174C/V, L1198M, S1206A, E1210K
Ceritinib	750 mg qd	1232	97.2	G1123S, E1174C/V, G1202R	200	E1174C/V, L1198M, S1206A
	750 mg qd	1232	97.2	G1123S, E1174C/V, G1202R	500	L1198M
Alectinib	600 mg bid	1120	96.7	L1173N/Tin, G1202R	1000	None
	600 mg bid	1120	96.7	L1173N/Tin, G1202R	200	L1173N, V1186L, L1198M
					500	L1173N
					1000	L1173N

\*Approved or recommended phase 2 doses. †C<sub>50</sub>, Steady-state plasma levels (AUC<sub>0-24</sub>) corrected for 24 h exposures. ‡Crizotinib (32), brigatinib (33), ceritinib (11), alectinib (24). §Crizotinib (32), ceritinib (33), alectinib (24). ¶Mutations associated with resistance to brigatinib in the phase III trial have not yet been reported. †Indicated mutations were included in the panel of 17 mutants analyzed further (Fig. 4B). ‡Mutations are at amino acids not previously associated with clinical resistance. PPB, Plasma protein binding (32, 33, 35, 36). Conc., concentration; AUC<sub>0-24</sub>, area under the concentration-time curve from time 0 to 24 h.



Zhang, et al., Clin Cancer Res 2016; 22(22): 5527-38

# KQ IV. Test squamous or small cell carcinomas?

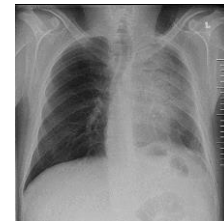
•Small cell carcinomas: No

•Squamous cell carcinomas: Maybe

- “Squamous carcinoma genes”: *FGFRs*, *DDR2*
  - Insufficient evidence to support for/against testing
- “Adenocarcinoma genes”: *EGFR*, *ALK*, *ROS1*
  - If clinical or pathologic features are “high risk”
    - Can’t exclude unsampled adenocarcinoma histology
    - Young patient
    - No history of tobacco use
- Other therapies: EGFR antibodies, immunotherapy



1 cycle  
gemcitabine/cisplatin



Switch to  
crizotinib

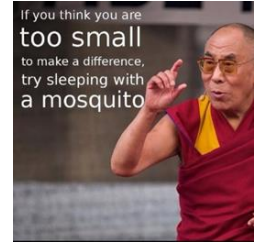


Images courtesy of Erick  
Bernicker, MD

# KQ V. What is the role of testing cell-free DNA or circulating tumor cells?

## • Initial diagnosis:

- Appropriate when tissue testing unavailable
  - No adequate sample
  - Patient cannot undergo biopsy

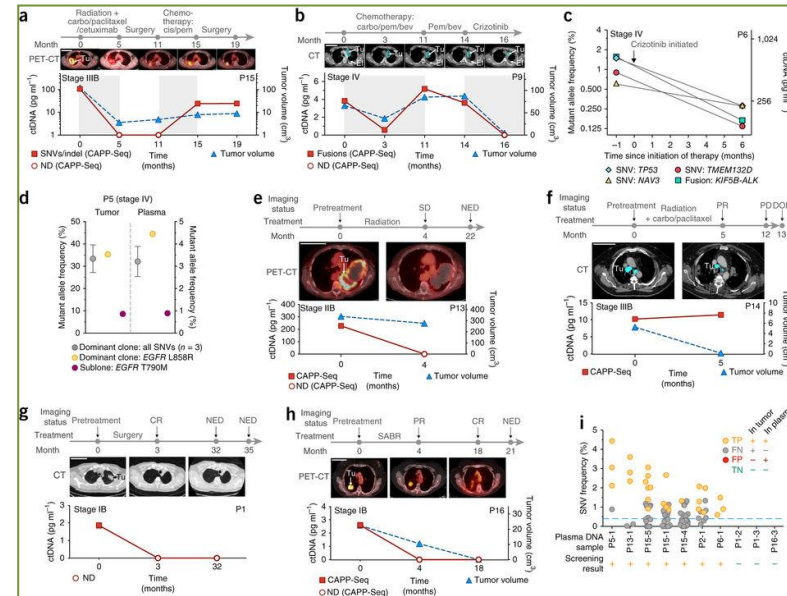


## • Monitoring on therapy:

- Very exciting and very unproven
- Cannot recommend at this time

## • Acquired resistance:

- Appropriate alternative to tissue testing
  - Sensitivity poor, specificity high
  - Treat if plasma positive
  - Biopsy and test tissue if plasma negative



Newman, et al., Nature Med 2014

# KQ VI: What is the role of sequencing panels in lung cancer?

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- **2013: insufficient evidence to support NGS panels**
- **2018: NGS panels preferred over single gene tests**
  - Single gene methods still acceptable, provided TAT met
  - Results returned quicker
  - Spares sample, which is often limiting
  - Enables expanded testing beyond *EGFR*, *ALK*, *ROS1*
    - Help patients find appropriate clinical trials
- **TAT recommendation: two weeks, for all testing**

# Not a KQ, but should have been: What is the role of PD-1/PD-L1 IHC?

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- **Pulling up lame: Out of scope for us**

- Wrong panel constituency to assess this properly
- Not included in initial search or data evaluation tools
- Incorporating it would entail a near-restart and a 1+ yr delay
- Another project is addressing this in a broader disease context



- **Non-evidence based opinion**

- Immune checkpoint therapies are proven effective in lung cancer
- Test methods, in a global sense, are not yet established
  - IHC: PD-1, PD-L1, CTLA-4, with multiple different antibodies
  - Tumor lymphocytes, mutational load, neoantigen expression

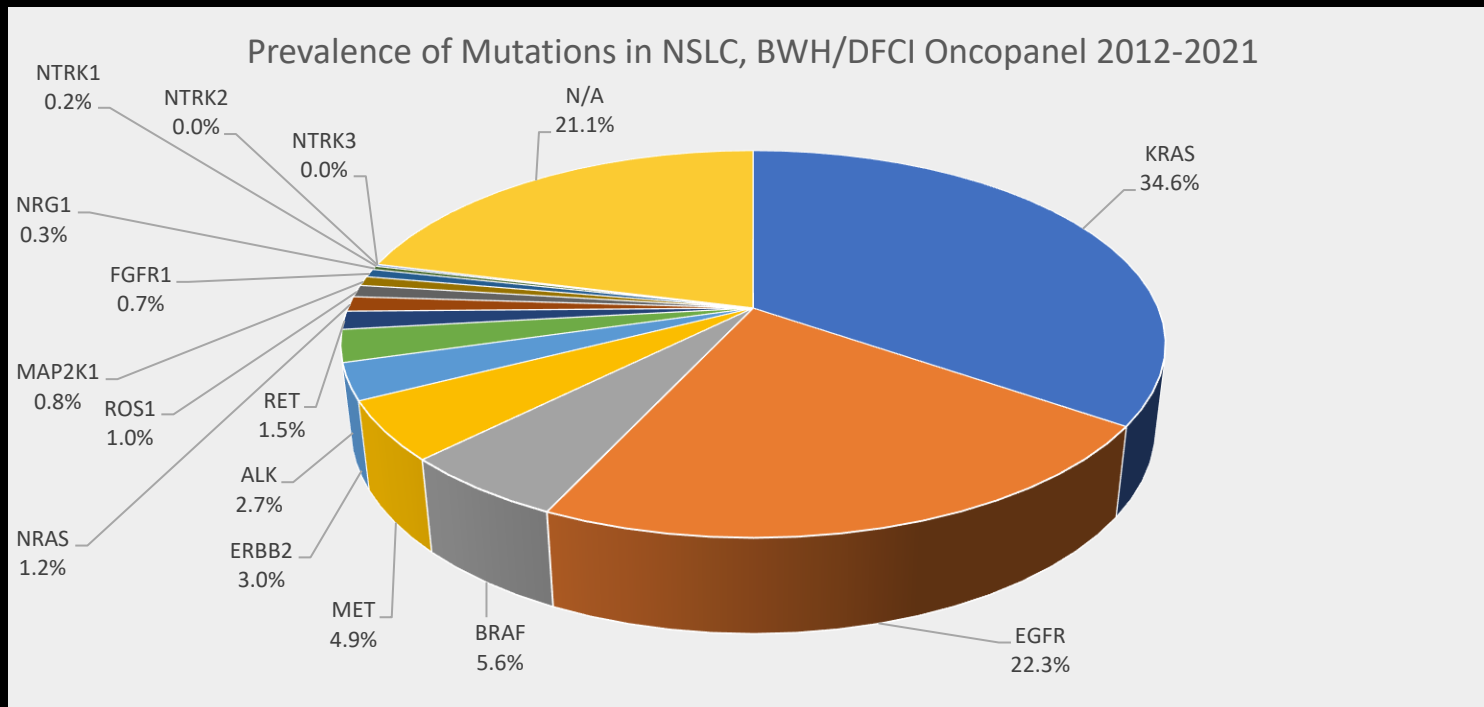
- **Some agents require specific tests to determine eligibility**

- **Opinion: for now, use the tests required for the agents being considered**

*2021: Time for a new guideline*

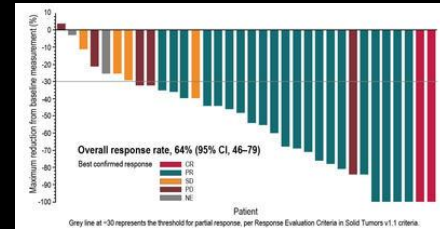


# *Landscape evolution*

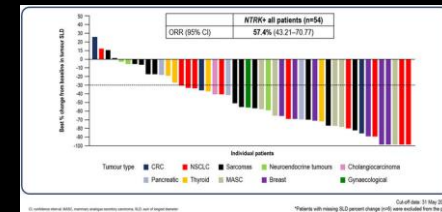


# Treatment evolution:

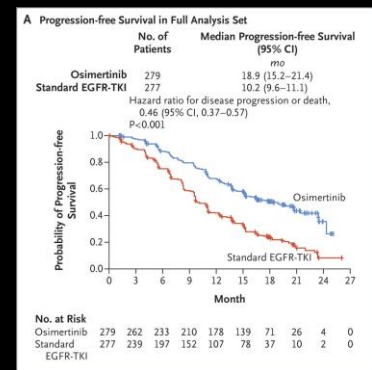
- ❑ BRAF inhibitor approved
- ❑ NTRK inhibitor approved
- ❑ T790M inhibitor now first line
- ❑ RET inhibitor approved
- ❑ MET inhibitor approved
- ❑ Inhibitor for EGFR exon 20 insertions
- ❑ Immune therapies exploded
- ❑ KRAS G12C inhibitors
- ❑ Coming: ERBB2 conjugates



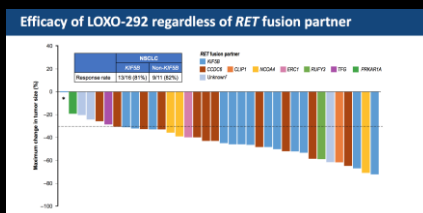
Planchard, ESMO, 2017



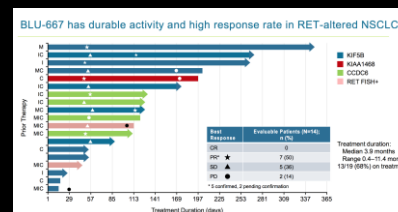
Demetri, ESMO 2018



Soria, et al., NEJM, 2018



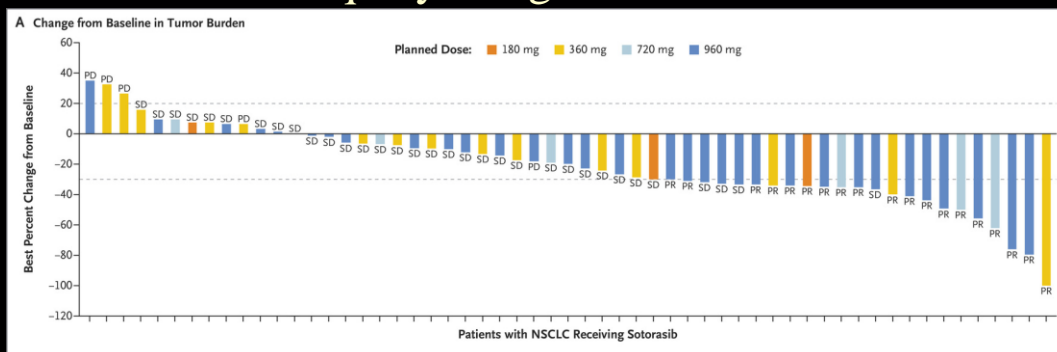
Koski, 2018





# KRAS G12C in NSCLC

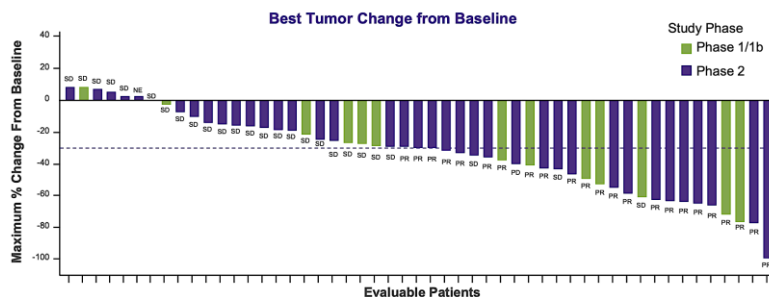
- Creates a novel binding pocket
- Clinical utility: G12C mutation and sotorasib, adagrasib
- Inhibitors uniquely designed for this exact mutation



sotorasib:  
response rate 32%  
disease control 88%

-Hong, et al., NEJM, 2020

## Adagrasib 600 mg BID in Patients With NSCLC: Best Tumor Change From Baseline



- Clinical benefit (DCR) observed in 96% (49/51) of patients
- 70% (16/23) of responders had a best tumor response greater than 40% from baseline

\*Two timepoint assessments of CR were separated by recurrent disease associated with treatment interruption due to hypoxia; this patient remains on treatment and in two consecutive scans (1 after August 30 data cutoff) demonstrated 100% tumor regression in target and non-target lesions after resuming treatment.

Data as of 30 August 2020. Pooled includes NSCLC Phase 1/1b and Phase 2 600 mg BID.

NSCLC: non-small cell lung cancer; BID: twice daily dosing; DCR: disease control rate

Presented at the 32nd EORTC-NCIC AACR Symposium, October 24-25, 2020



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# *KRAS Mutations in NSCLC*

- Useful to “rule out” other less common alterations

A	B	Neither	A Not B	B Not A	Both	p-Value	Tendency
KRAS	EGFR	2225	1431	1032	56	<0.001	Mutual exclusivity
KRAS	MET	2929	1435	328	52	<0.001	Mutual exclusivity
KRAS	ERBB2	3050	1446	207	41	<0.001	Mutual exclusivity
BRAF	EGFR	3379	277	1046	42	<0.001	Mutual exclusivity
ALK	EGFR	3282	374	1022	66	<0.001	Mutual exclusivity
KRAS	BRAF	3005	1420	252	67	<0.001	Mutual exclusivity
KRAS	ROS1	2987	1407	270	80	<0.001	Mutual exclusivity
MET	EGFR	3340	316	1024	64	0.002	Mutual exclusivity
ERBB2	EGFR	3450	206	1046	42	0.011	Mutual exclusivity
KRAS	ALK	2935	1369	322	118	0.017	Mutual exclusivity

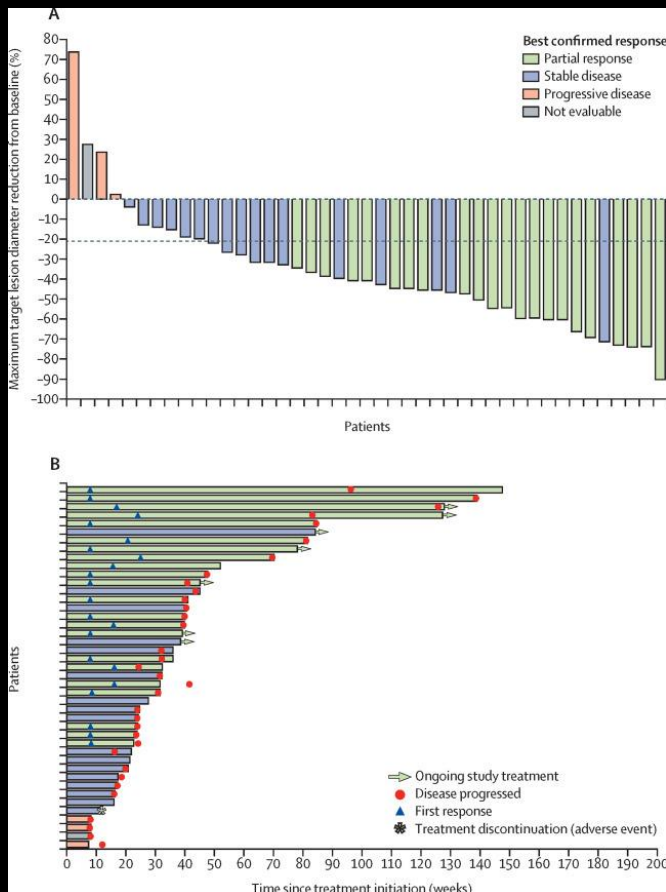
- Mutually exclusive with other driver alterations
- ~30% of lung adenocarcinomas
- Simple and widely available single gene assays
  - **Many cannot distinguish G12C from others, however**



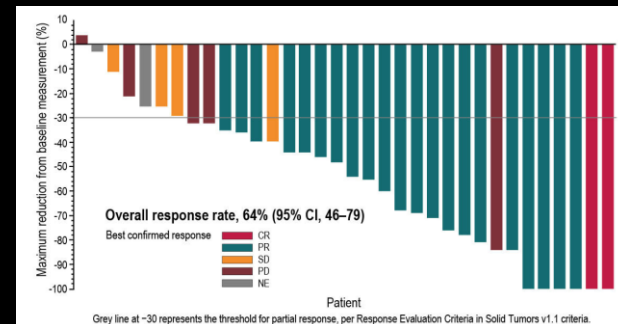
# *BRAF V600E mutations*



## • Clinical utility: response to BRAF+MEK inhibition

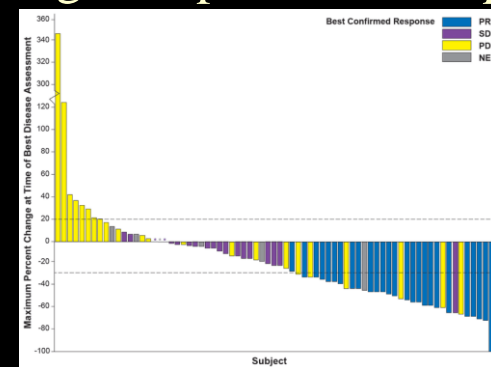


*Subbiah, et al., Lancet Oncol, 2020*



*Planchard, et al., Lancet Onc, 2017*

## Single target response less impressive



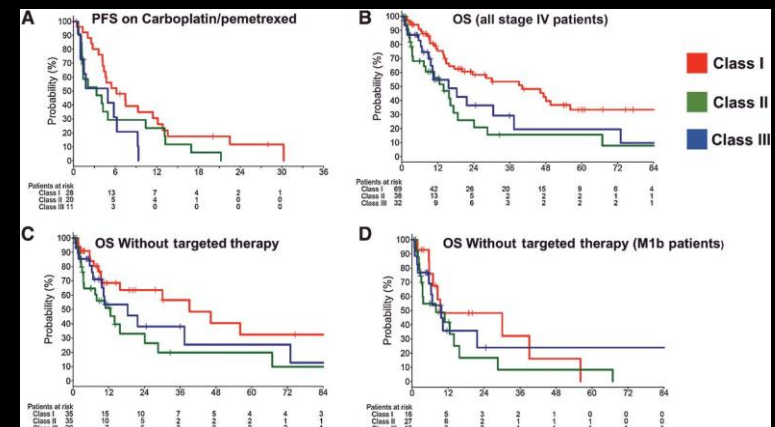
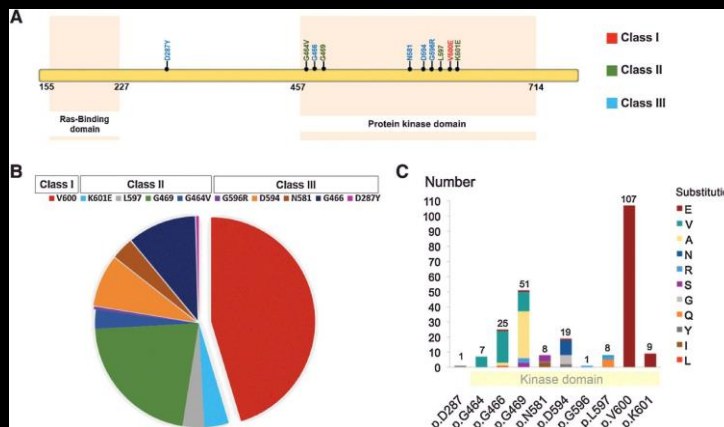
*Planchard, et al., Lancet Onc, 2016*



# Other *BRAF* mutations



- Class I: activating, as monomers → readily inhibited
- Class II: activating, require dimerization
- Class III: kinase null, but activate through other mechanisms
- Typically co-occur with RAS activating alterations



Dagogo-Jack, et al., Clin Cancer Res, 2019





# ***ERBB2 (HER2)***



## ❑ Critical gene in breast cancer

- Amplification (FISH) or overexpression (IHC)
- Responds to treatment with trastuzumab

## ❑ Different role in lung cancer

- Mutations, typically insertions in exon 20
  - Amplifications do occur as well
- FISH, IHC are not useful for lung cancer
- 

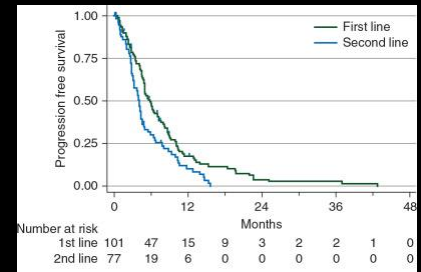


# ERBB2 (HER2)

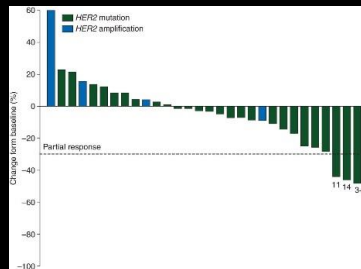


## Clinical Utility

- Do not respond to therapeutic antibodies
- Treatment with TKIs disappointing

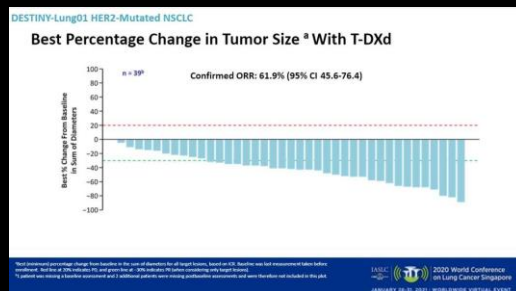


Mazieres., *Ann Oncol*, 2016

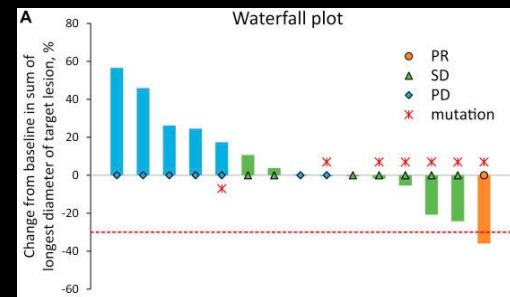


Response rate: 12%  
Kris, *et al.*, *Ann Oncol*, 2015

- Trastuzumab conjugates (toxic payload) maybe promising



TopoI inhibitor  
Response rate: 61%  
*Smit. et al.*, *World Lung*, 2021



Microtubule inhibitor  
Response rate: 7%  
*Hotta, et al.*, *JTO*, 2018

# RET

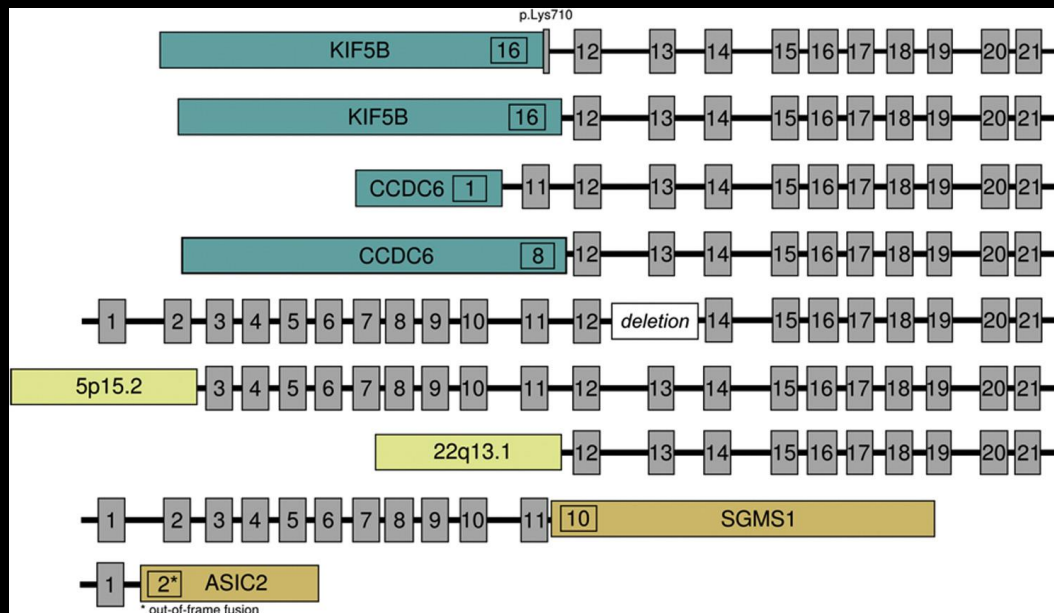


- **Characteristic mutations in thyroid cancer**

- Mutations in MEN II syndrome, medullary carcinoma
- *RET/PTC* fusions in papillary carcinoma

- **Overlapping alterations in lung cancer**

- Multiple fusions, including *KIF5B*, *CCDC6*, *NCOA4*

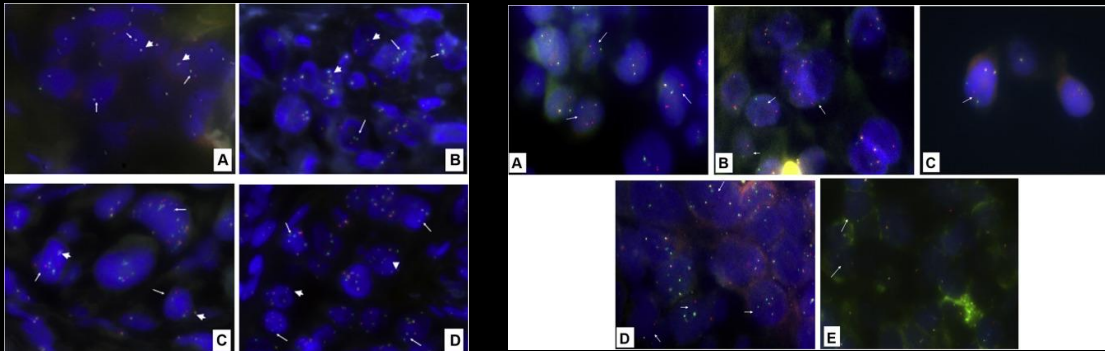


# RET methodology

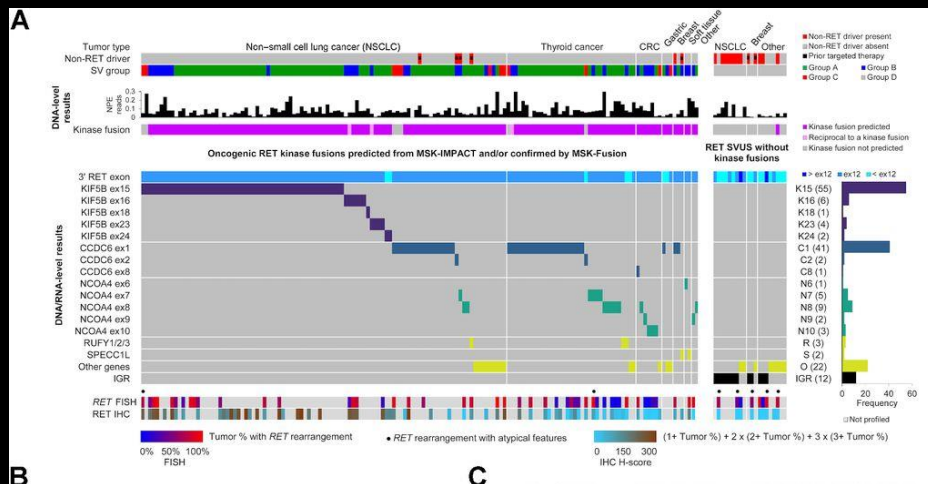


## •Challenging!

- Discovered by DNA NGS
- FISH and IHC can be challenging
- RT-PCR may be best



*Radonic, JTO, 2021*



*Yang, Clin Cancer Res, 2021*

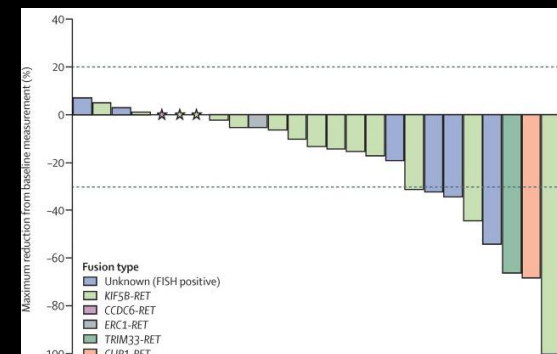


# RET

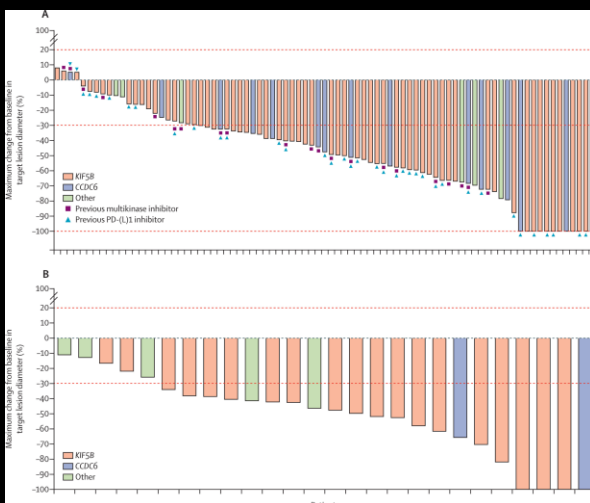


## • Response to TKIs:

- Broad TKIs: ~30-50% ORR, PFS 5-8 mos
- Selective RET TKIs: 50-70% ORR, PFS 18.4mos

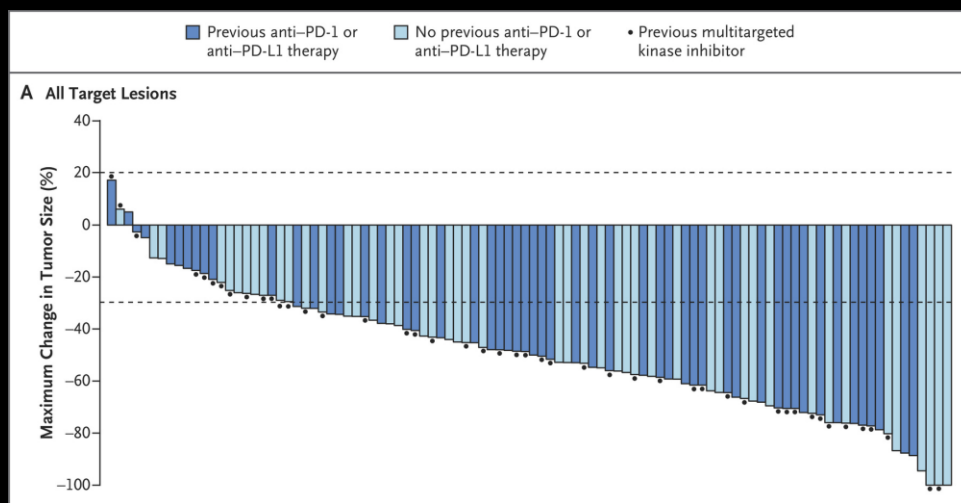


*Drilon Lancet Onc, 2016*



**Pralsetinib: 61% response**

*Gainor, Lancet Onc, 2021*



**Selpercatinib: 64% response**

*Drilon, NEJM, 2020*



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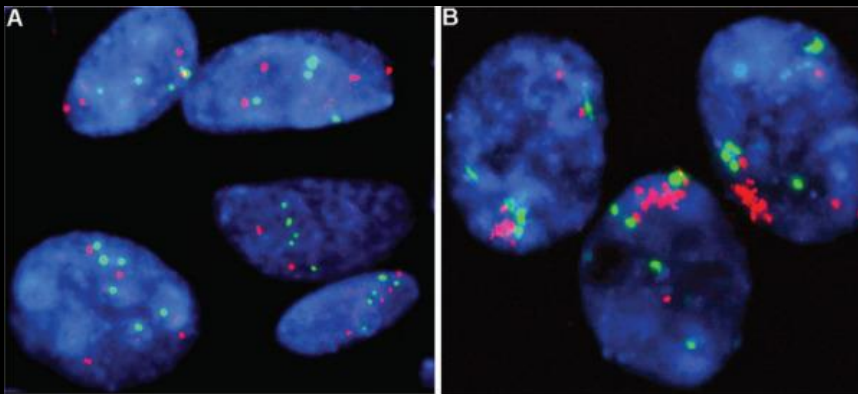
# ***MET***



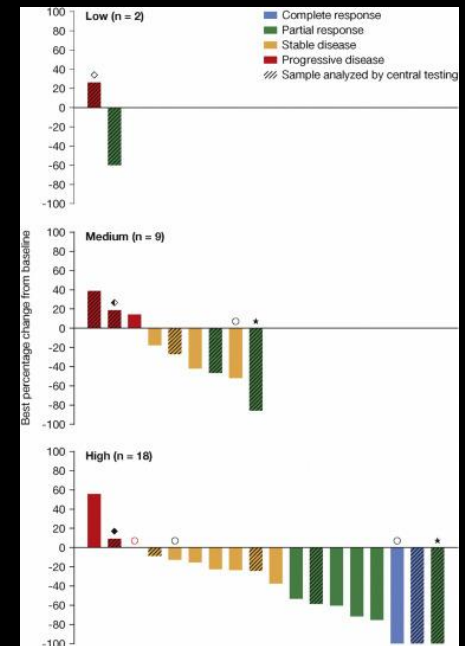
## • Clinical utility - a complicated story...

— *MET* copy gain first seen in who relapsed on anti-EGFR therapy

- Confusion : “copy gain” vs “amplification”
- Can co-exist with other oncogene mutations



*Cappuzzo, Ann Onc, 2009*



*Camidge, JTO, 2021*

— MET inhibitors were developed (crizotinib), but didn't work in general

- Rare “true” MET amplification does respond to crizotinib (~40% rr)

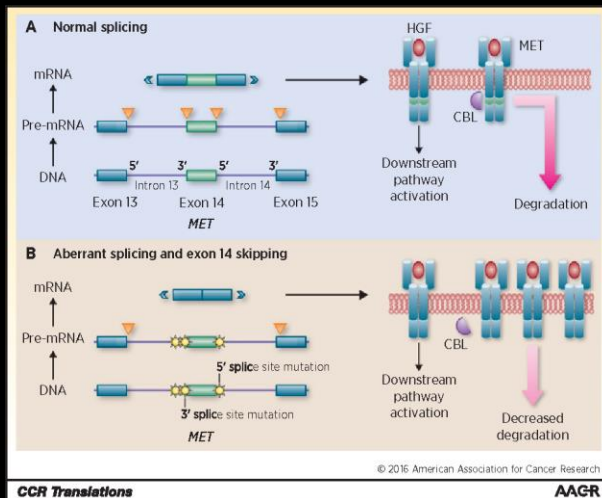
# MET



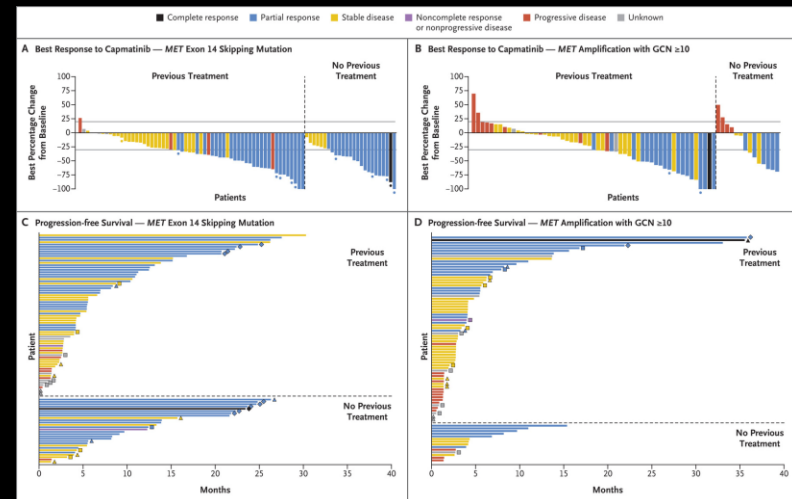
## • Clinical utility – fast forward...

### – NGS discovers mutations affecting splicing of exon 14

- Common: ~3% of lung cancers
- exon 14 skipping mutations do respond to targeted inhibitors



*Drilon, Clin Cancer Res, 2016*



*Wolf, NEJM, 2020*

- Methodology: many choices still, but RNA favored



# Rare mutations

## • Insufficient evidence for review in 2018:

— NTRK1,2,3 fusions in all solid tumors

— Specific Trk inhibitors

— NRG1 fusions

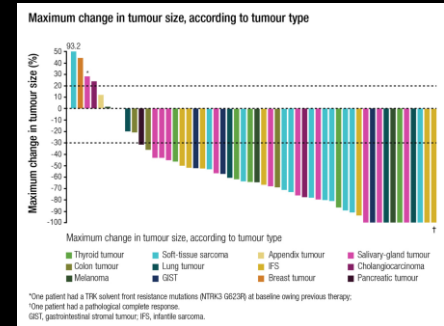
— ~30% in mucinous tumors

— Ligand for HER3

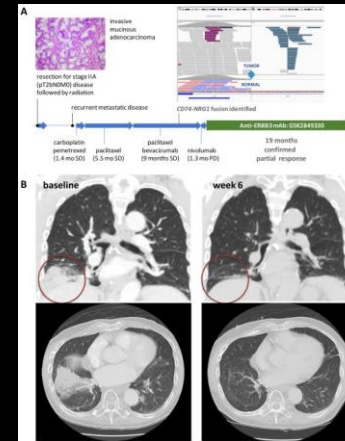
— Anti-HER3 antibodies?

— FGFR1,2 amplification

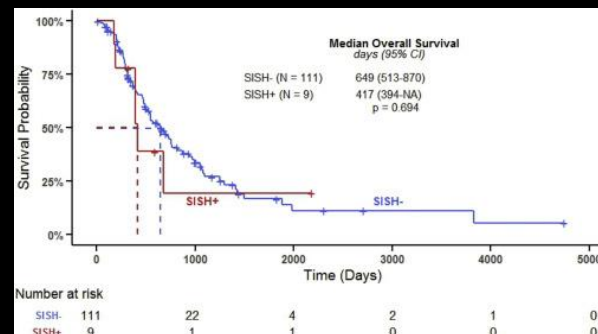
— disappointing



*Drilon, NEJM, 2018*



*Drilon, Cancer Disc, 2018*



*Ng, Clin Lung Cancer, 2018*

# *New issues with old genes*

## □ EGFR

- 3<sup>rd</sup> generation inhibitors in first line
- Novel resistance mechanisms
- Early stage disease
- Exon 20 insertion therapies

## □ ALK

- Secondary resistance

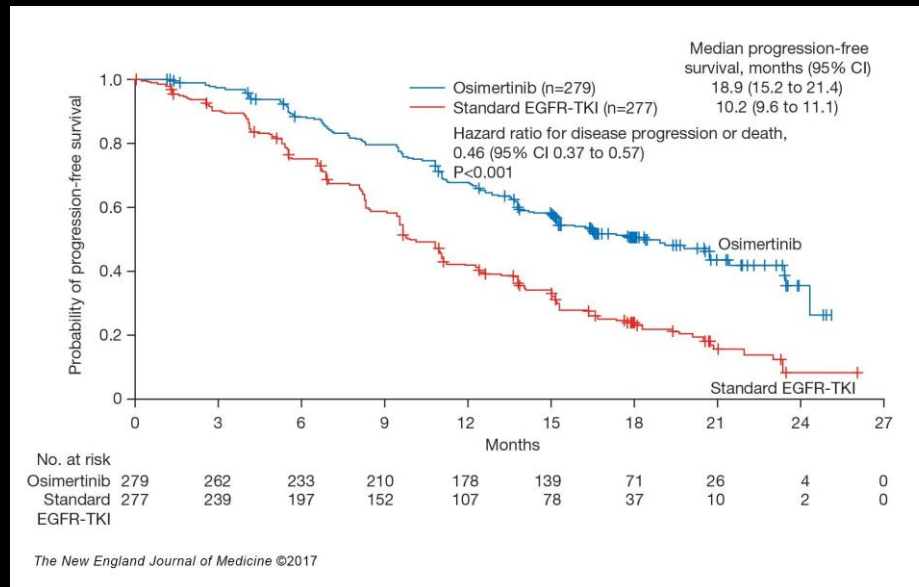




# *New issues with old genes*

## □ EGFR

- Third generation inhibitors now used in first line
  - Covalently binds EGFR, rather than competing with ATP



Overall survival  
1<sup>st</sup> gen: 31.8 mos  
3<sup>rd</sup> gen: 38.6 mos

Recall slide 7:  
placebo: 6 mos

*Ramalingam, NEJM, 2020*



# New issues with old genes



- 3<sup>rd</sup> Gen EGFR inhibitors in first line
- New profile for secondary resistance



Leonetti, BJC, 2019

- Requires broad-spectrum technology, or multiple assays



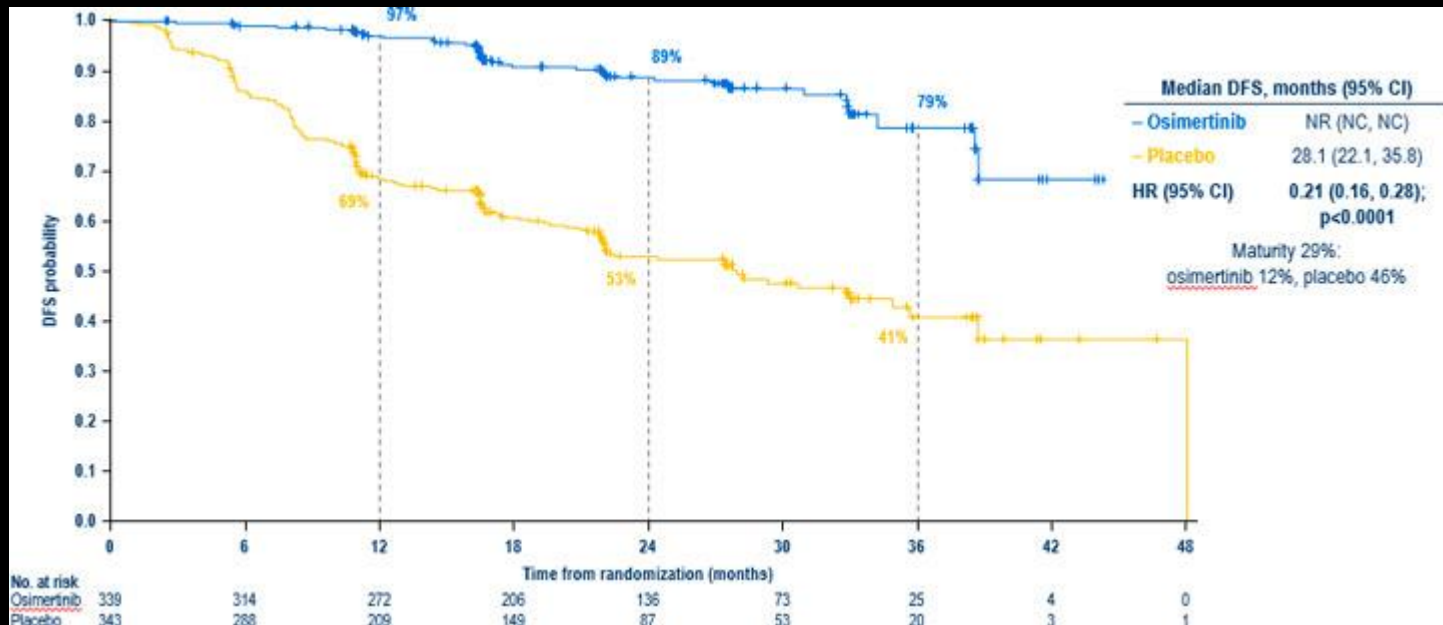


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# *New issues with old genes*



## □ EGFR inhibition in early stage disease



*Herbst, ASCO, 2020*



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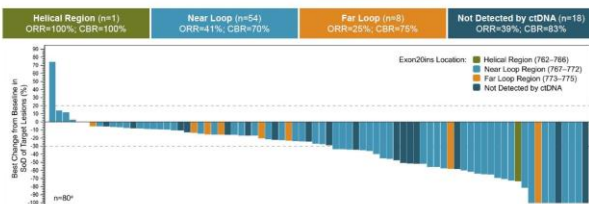
# New issues with old genes



## EGFR exon 20 insertions

- Resistant to first, second, and third generation inhibitors
- New drugs:

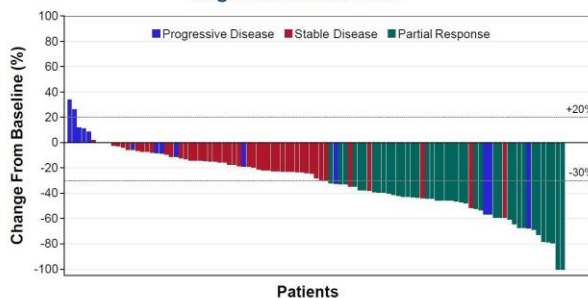
Best ORR by Insertion Region of Exon 20 (detected by ctDNA)



25 distinct Exon20ins variants identified by NGS of ctDNA (Guardant360®) from 63 evaluable patient samples

\*One patient in the efficacy population discontinued before any disease assessment and is not included in the plot. NGS, next-generation sequencing; SLD, sum of diameters

Change From Baseline in Sum of Target Lesion Diameter



Amivantamab:

bispecific antibody (EGFR-MET)  
ORR 40%, PFS 8.3 mos

Mobocertinib:

specialized TKI  
ORR 26%, PFS 7.3 mos



jpg

# New issues with old genes



## ALK resistance mutations

- Different inhibitors have different sensitivity profiles
- More analogous to BCR-ABL than to EGFR

**Table 2**

Pharmacologic properties of ALK inhibitors approved by the US FDA or in clinical testing.

ALK TKI	Crizotinib (PF-02341066)	Ceritinib (LDK378)	Alectinib (RO/CH5424802)	Brigatinib (AP26113)	Lorlatinib (PF-06463922)	Entrectinib (RXDX-101)	Ensartinib (X-396)
Manufacturer	Pfizer	Novartis	Genentech	Ariad	Pfizer	Ignitya	Xcovery
Targets other than ALK	ROS1 ROS1MET	ROS1 IGF-1R IR	GAK LTK RET	ROS1	ROS1	NTRK1 NTRK2 NTRK3 ROS1	ROS1 MET AXL
Resistance mutations known to be targeted by TKI	L1196F	I1171T/N L1196M S1206C/Y G1269A/S	L1152P/R C1156V/T F1174C/L/V L1196M S1206C/Y G1269A/S	I1151Tins L1152P/R C1156V/T F1174C/L/V L1196M <b>G1202R<sup>a</sup></b> G1269A/S	I1151Tins L1152P/R C1156V/T I1171T/N/S F1174C/L/V L1196M <b>G1202R<sup>a</sup></b> S1206C/Y E1210K G1269A/S	C1156V/T L1196M	C1156V/T L1196M
Reported resistance mutations to the TKI	I1151Tins L1152P/R C1156V/T I1171T/N/S F1174C/L/V V1180L L1196M G1202R S1206C/Y E1210K G1269A/S	I1151Tins L1152P/R C1156V/T F1174C/L/V G1202R	I1171T/N/S V1180L G1202R	<b>G1202R<sup>a</sup></b> E1210K + S1206C E1210K + D1203N	<b>L1198F + C1156V<sup>b</sup></b>	G1202R	N.D.

## Notable mutations

L1196M “gatekeeper”  
blocks sterically like T790M  
G1269A  
also steric hindrance  
G1202R “solvent front”  
adjacent to binding site  
alter binding affinity

*Lin, Europe PMC, 2017*

- Also: ALK amplification, bypass, epigenetics

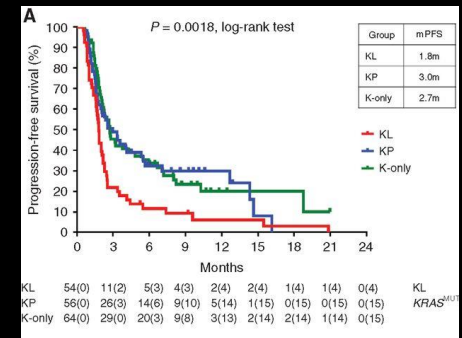
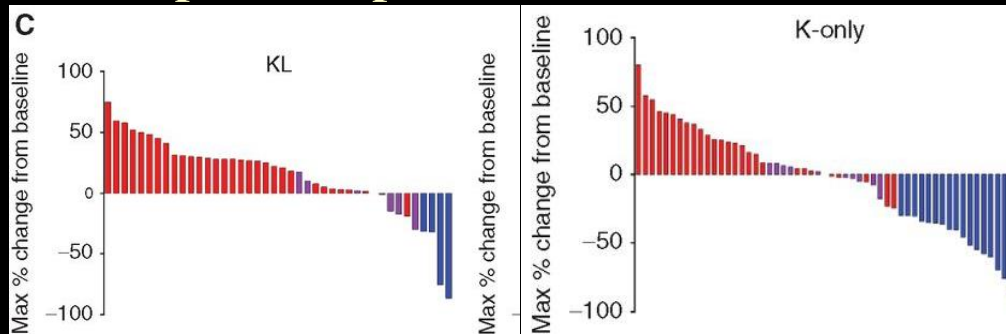


# Influential passengers



## □ STK11 (aka LKB1):

- causes Peutz-Jeghers in germline
- Impairs response to PD1 blockade in KRAS mutant cancer



*Sikoulidis, Cancer Disc, 2018*

## □ PIK3CA

- Often co-exist with other targetable mutations
- Treatment under investigation



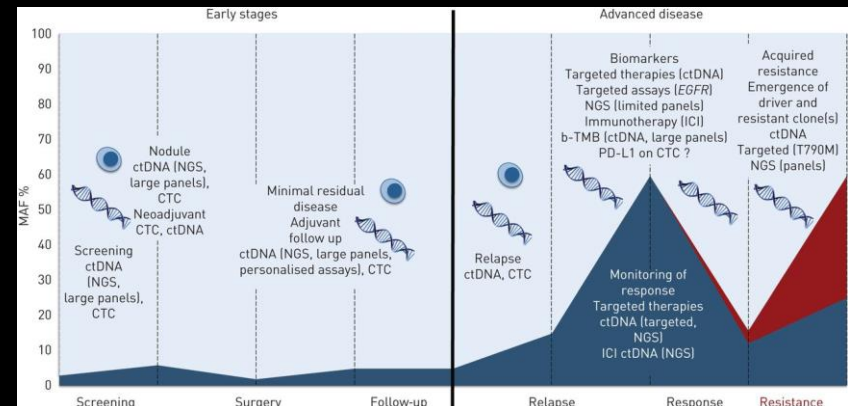
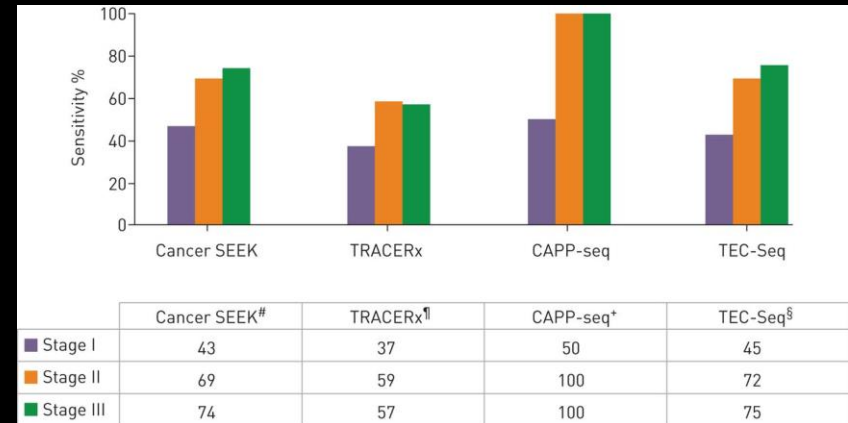
# Expansion of “liquid biopsy”

## Early detection

- Screening?
- Avoid biopsy?

## Monitoring

- Indication of response?
- Resistance mechanisms?

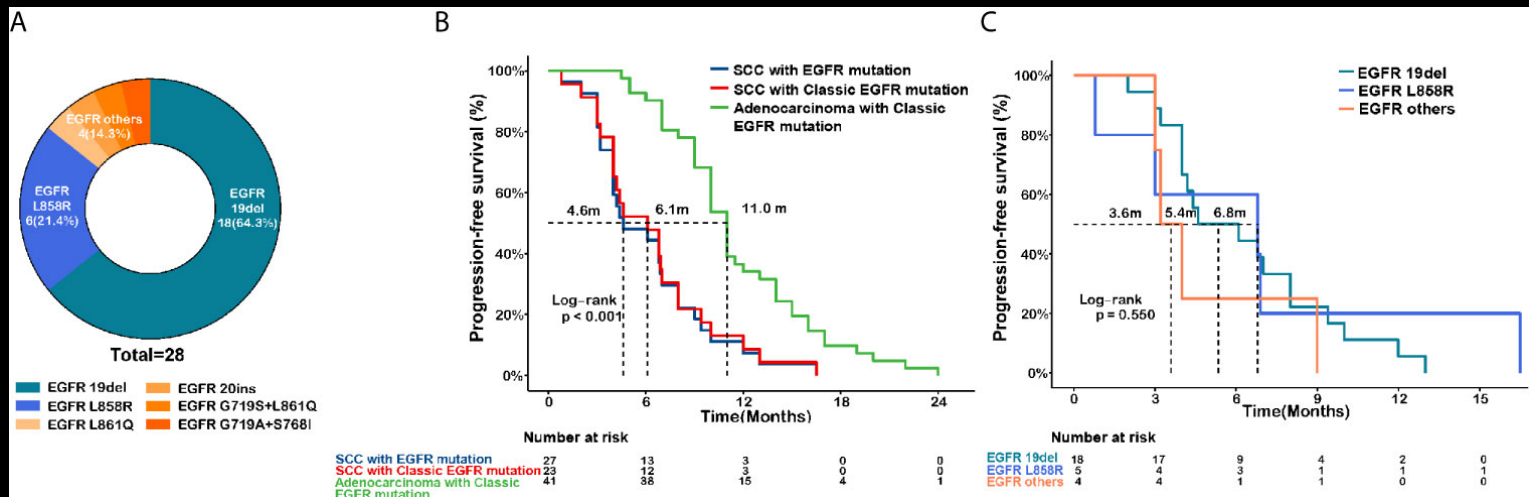


Guibert, Eur Resp Rev, 2020



# Other cancers

- We test for variants in <1% of adenocarcinomas
- EGFR mutation is seen in ~5% of squamous carcinomas
- Not great evidence about treatment response yet



Jin, Front Oncol, 2021



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