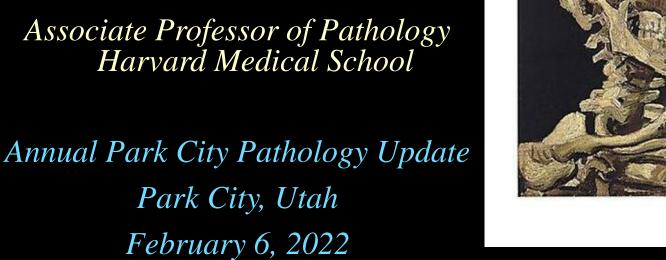


Park City, Utah

February 6, 2022







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

### □ <u>Differential Dx</u>:

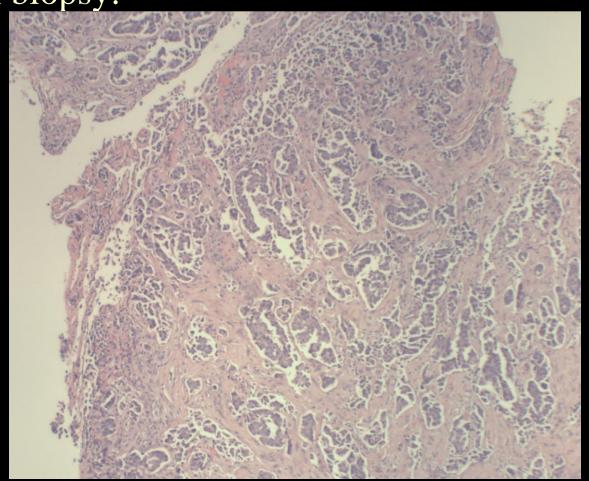
- Tumor
  - Meningioma
  - Lymphoma
  - Metastasis
  - Primary CNS tumor
- Granuloma
  - Sarcoidosis
  - Tuberculosis
- Chronic meningitis
  - Wegener's



# Case presentation:

DANGER V (I)

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



Van Gogh, 1885

- 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

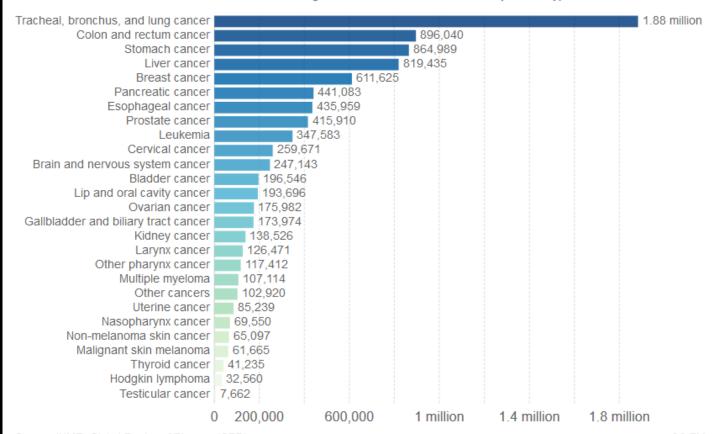


# Lung Cancer is Bad for society

### Cancer deaths by type, World, 2017

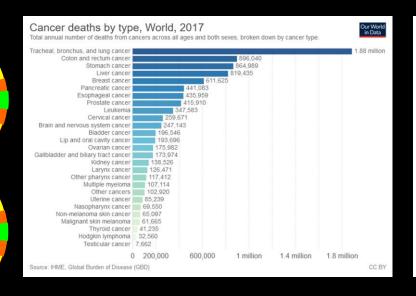
Our World in Data

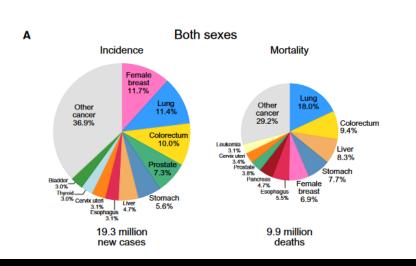
Total annual number of deaths from cancers across all ages and both sexes, broken down by cancer type.



Source: IHME, Global Burden of Disease (GBD)

# It is getting better...slightly





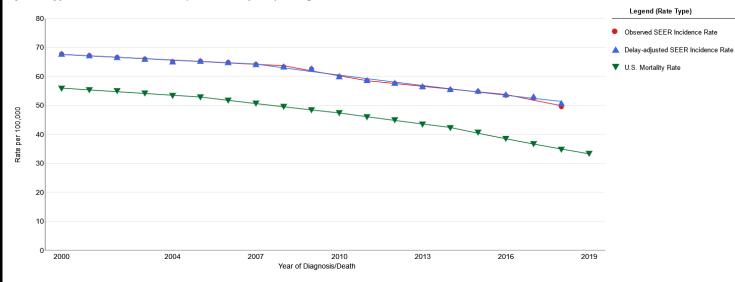
Sung, et al., CA Cancer J Clin, 2021

2017: 1.88 M deaths

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





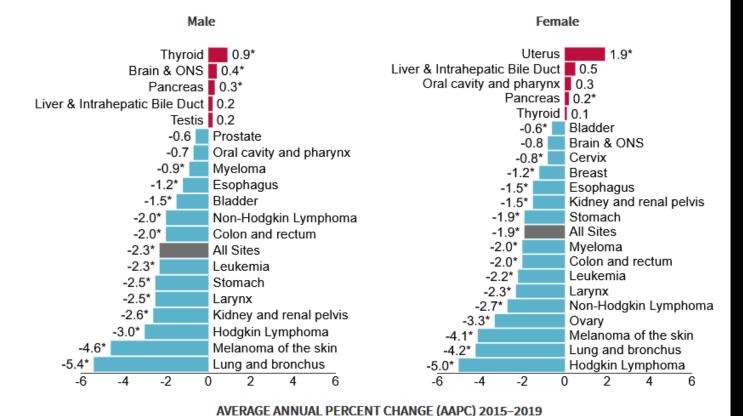
Created by https://seer.cancer.gov/explorer on Mon Jan 10 2022.
Mortally Estimates: Lis Mortality Fiesh Resistance Center for Health Statistics, CDC.
Incidence Estimates: SERR 21 areas [http://seer.cancer.gov/registries/terms.html] (San Francisco, Connecticut, Detroit, Haw aii, low a, New Mexico, Seattle, Utah, Atlanta, San Jose-Monterey, Los Angeles, Alaska Native Registry, Rural Georgia, California excluding SFS/MUA, Kentucky, Louisainan, New Jersey, Georgia excluding ATURG, Maho, 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 Revent Change (AFC) and Average Annual Percent Change (AFC) estimates were calculated from the underlying rates using the Joinpoint Trend Analysis Softw are [http://surveillance.cancer.gov/joinpoint], Version 4.9, March

The APS/AAAFS direction is "Rising" (1) when the entire 55% confidence interval (C1) is above 0. "Failing" (1) when the entire 55% C1 is lower than 0, otherwise, the trend is considered "Not Significant", Rates for American Indians/Alaskas lativers only include cases that are in a Purchased-inferender Can be only See SEER Race Recode Documentation for American Indians/Alaskas Matives Ostification Ratios Statistics

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# It is getting better

#### TRENDS IN DEATH RATES





### Return to Case:

DANGER V Q

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

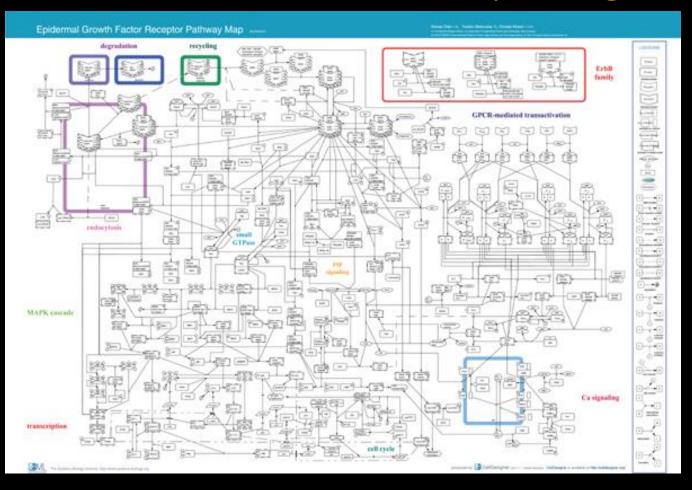


8/02

5/03

2/05

# What is EGFR and why target it?





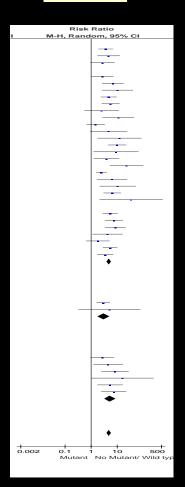


- Ligand binds
- Receptor Dimerization
- Phosphorylation
- Downstream signaling
  - $RAS \rightarrow RAF \rightarrow ERK$
  - $JAK \rightarrow STAT$
  - PIK3CA→AKT→mTOR
- Cells proliferate, survive

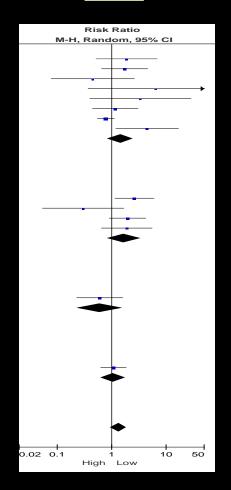
Very commonly overexpressed in human carcinomas

# How to test for EGFR? Molecular Diagnosis!

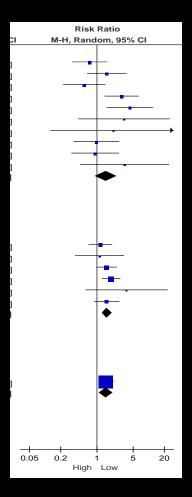
### **Mol Dx**



### **FISH**



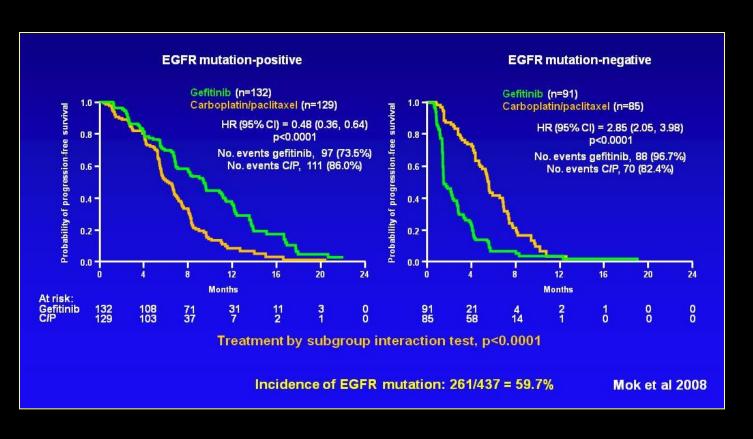
### **IHC**





# Why test at all? Empiric therapy is not harmless

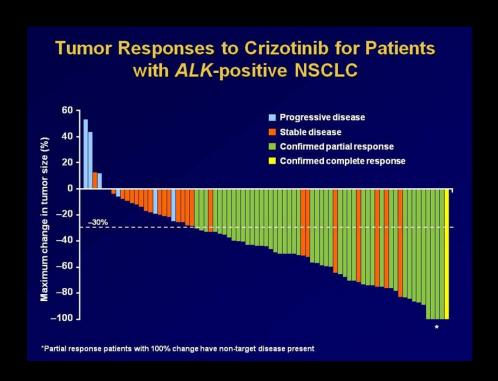
DANGER





### But wait...

### ... there's MORE!





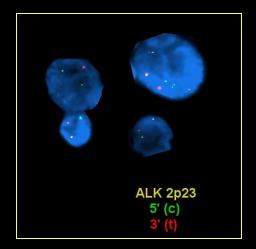
### ALK rearrangement predicts crizotinib response

Crizotinib and ALK FISH both approved by FDA, 2011

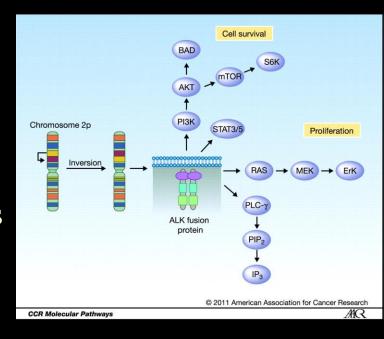


## ALK rearrangement

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

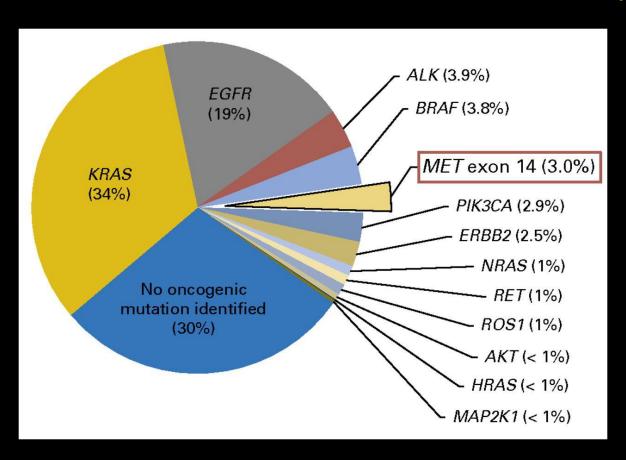


Trivia: More patients have EML4-ALK lung cancer than NPM-ALK lymphoma!

# 2013: Practice guideline for EGFR and ALK

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# 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; Hore Kink Herr, MB, ChB; David J. Kwiatkowski, MD, PhD; Marc Ladanyi, MD; Jan A. Nowak, MD, PhD; Jenete Sholl, MD; Kobyn 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

#### Article in Press

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

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

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



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#### SPECIAL ARTICLE

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# What other genes should be tested in lung adenocarcinoma?

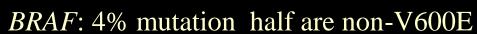








RET: 1-2% rearrangement







MET: 3% exon 14 skipping mutations, amplification















### ABRUPT AND JARRING FORMAT CHANGE



## Abrupt and jarring format change





### New in 2018: ROS1

### Clinical utility

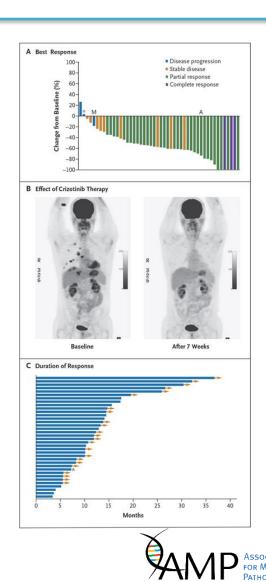
- ROS1+ tumors respond to crizotinib
- RR 70-80%
- Phase I, I/II, II trials
- No Phase III

### Oncologists treat with crizotinib

Oncologists use ROS1 testing

### Crizotinib approved by FDA

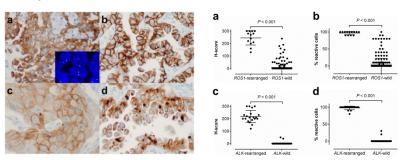
— ALK+, ROS1+ lung cancers



### 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



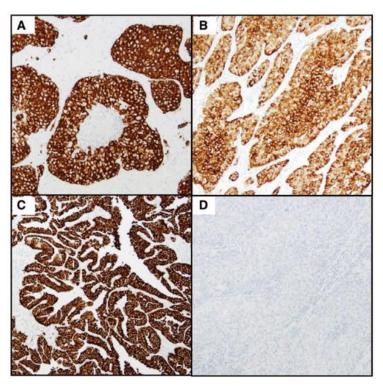
### Others: RET, BRAF, ERBB2, KRAS, MET

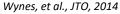
- As with EGFR, ALK, ROS1, typically mutually exclusive
- Adenocarcinomas, but no sensitive clinical predictors
- Clinical trials and/or potential drugs for each:
  - RET: cabozantinib, vandetinib

- · 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
- BRAF: vemurafenib, dabrafenib, +/- trametinib
- ERBB2/HER2: ?pulsed afatinib?, ?neratinib?, ?dacomitinib?
- KRAS: trametinib, selumetinib
- MET: crizotinib
- Limited evidence for clinical utility (Case reports & small series\*)



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







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

# **YES**

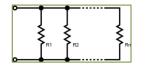


# KQ II. Is immunohistochemistry reliable for *ALK* translocations?

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

- 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



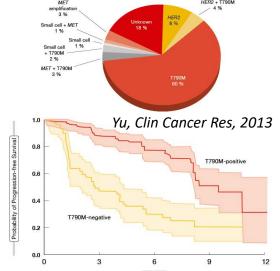


## **KQIII: Testing in acquired resistance**

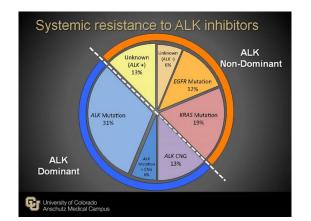
### • EGFR: all about T790M, and ultrasensivity

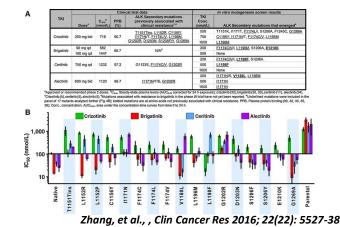
- -T790M responds to specific inhibitor
- Relapsed specimens are heterogeneous
- Recommended cutoff is 5% mutant alleles
- Circulating cell-free DNA may be superior\*





Janne, NEJM, 2015







# 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 cellfree DNA or circulating tumor cells?

### •Initial diagnosis:

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

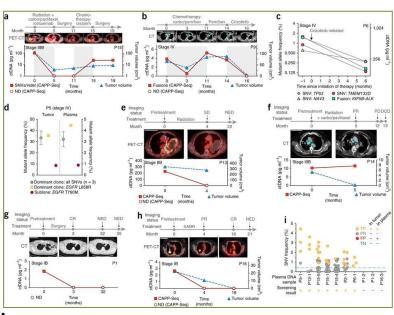
### Monitoring on therapy:

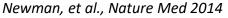
- Very exciting and very unproven
- Cannot recommend at this time

### Acquired resistance:

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









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

- •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?

#### •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



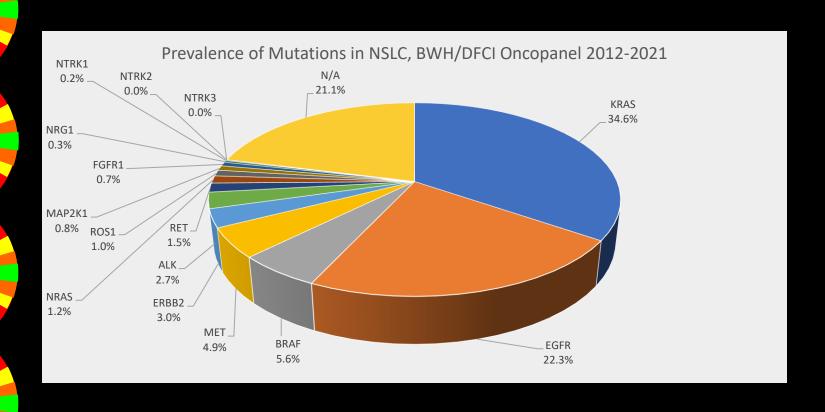




# 2021: Time for a new guideline



# Landscape evolution

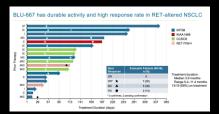


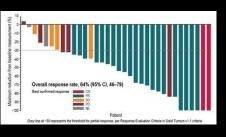
### Treatment evolution:

- 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

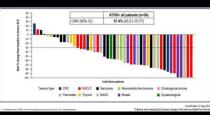
Koski, 2018



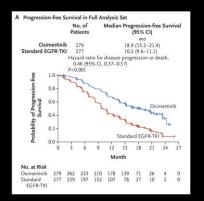




Planchard, ESMO, 2017



Demetri, ESMO 2018

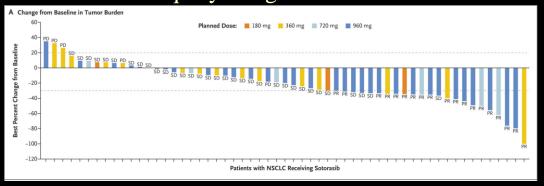


Soria, et al., NEJM, 2018



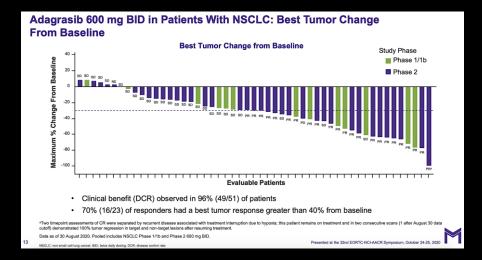


- Creates a novel binding pocket
- Clinical utility: G12C mutation and sotorasib, adagrasib
  - Inhibitors uniquely designed for this exact mutation



# sotorasib: response rate 32% disease control 88%

-Hong, et al., NEJM, 2020









#### •Useful to "rule out" other less common alterations

Α	В	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

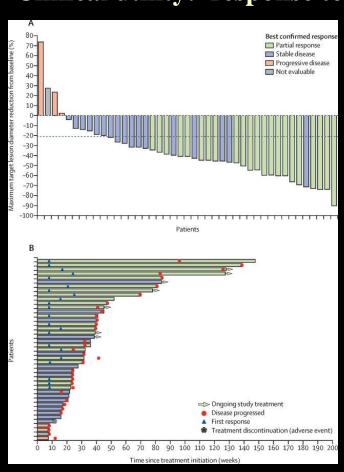


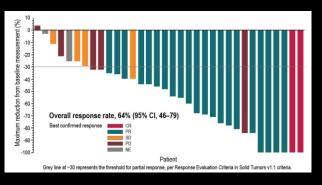


# BRAF V600E mutations



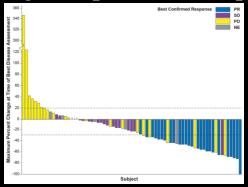
### •Clinical utility: response to BRAF+MEK inhibition





Planchard, et al., Lancet Onc, 2017

#### Single target response less impressive



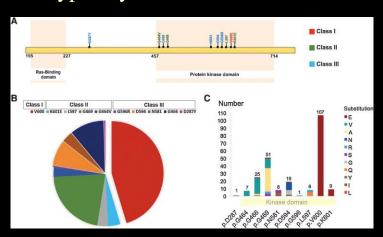
Planchard, et al., Lancet Onc, 2016

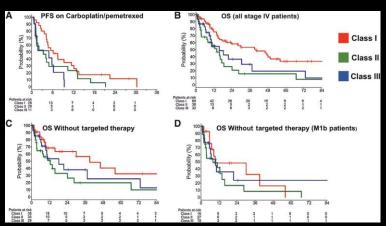






- •Class I: activating, as monomers → readily inhibited
- •Class II: activating, require dimerization
- •Class III: kinase null, but activate through other mechanisms
  - •Typically co-occur with RAS activating alterations





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**

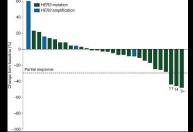
- Mutations, typically insertions in exon 20
  - Amplifications do occur as well
- FISH, IHC are not useful for lung cancer



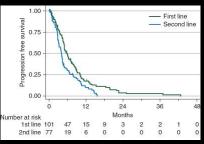


### **Clinical Utility**

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

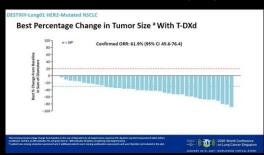


Response rate: 12% Kris, et al., Ann Oncol, 2015

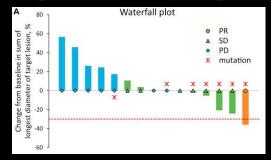


Mazieres., Ann Oncol, 2016

- 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 €



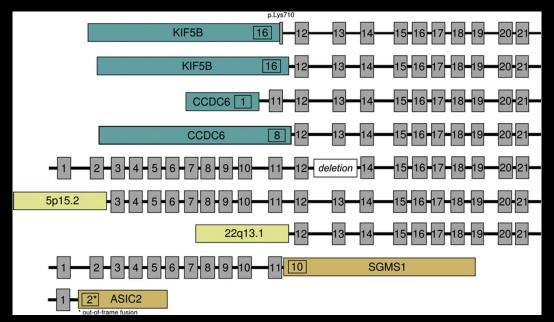


#### Characteristic mutations in thyroid cancer

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

#### Overlapping alterations in lung cancer

Multiple fusions, including KIF5B, CCD6, NCOA4



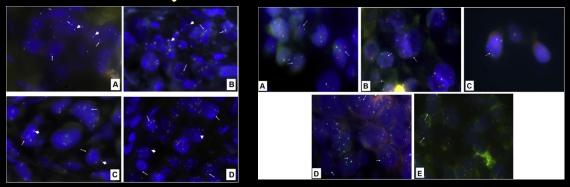


# RET methodology

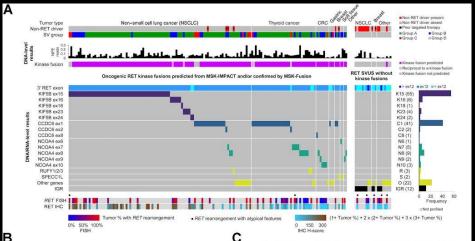


#### Challenging!

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



Radonic, JTO, 2021



Yang, Clin Cancer Res, 2021

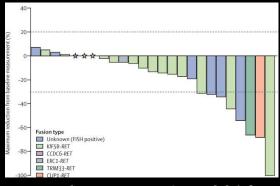




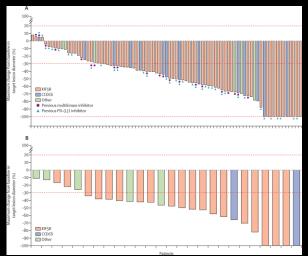


### •Response to TKIs:

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

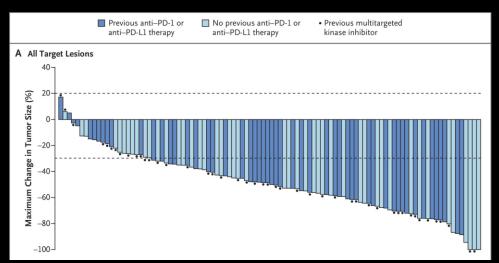


Drilon Lancet Onc, 2016



Pralsetinib: 61% response

Gainor, Lancet Onc, 2021



Selpercatinib: 64% response

Drilon, NEJM, 2020



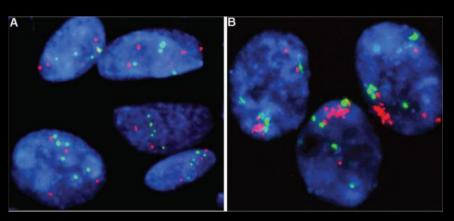
Association for Molecular Pathology



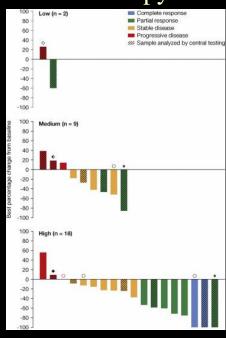


#### Clinical utility - a complicated story...

- -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

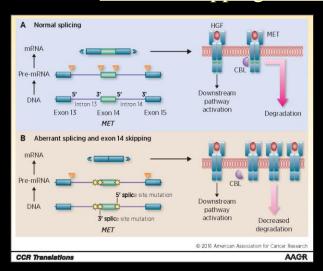
- —MET inhibitors were developed (crizotinib), but didn't work in general
  - Rare "true" MET amplification does respond to crizotinib (~40% rr)



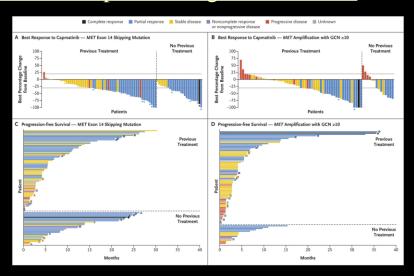


#### Clinical utility – fast forward...

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







Wolf, NEJM, 2020



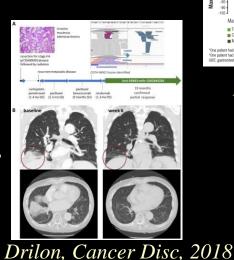


### Rare mutations

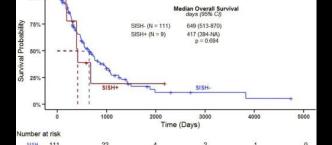


#### •Insufficient evidence for review in 2018:

- -NTRK1,2,3 fusions in all solid tumors
  - -Specific Trk inhibitors
- -NRG1 fusions
  - −~30% in mucinous tumors
  - -Ligand for HER3
  - -Anti-HER3 anitbodies?
- FGFR1,2 amplification
  - -disappointing



Drilon, NEJM, 2018



Ng, Clin Lung Cancer, 2018





### EGFR

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

### 

Secondary resistance

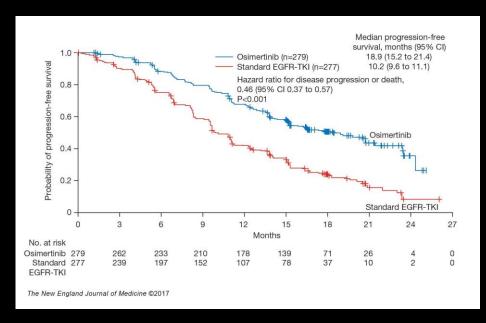






#### EGFR

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



Overall survival

1st gen: 31.8 mos

3<sup>rd</sup> gen: 38.6 mos

Recall slide 7: placebo: 6 mos

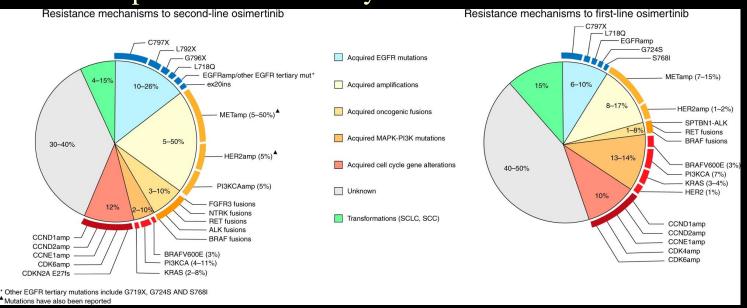
Ramalingam, NEJM, 2020







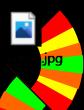
- 3<sup>rd</sup> Gen EGFR inhibitors in first line
  - New profile for secondary resistance



Leonetti, BJC, 2019

• Requires broad-spectrum technology, or multiple assays

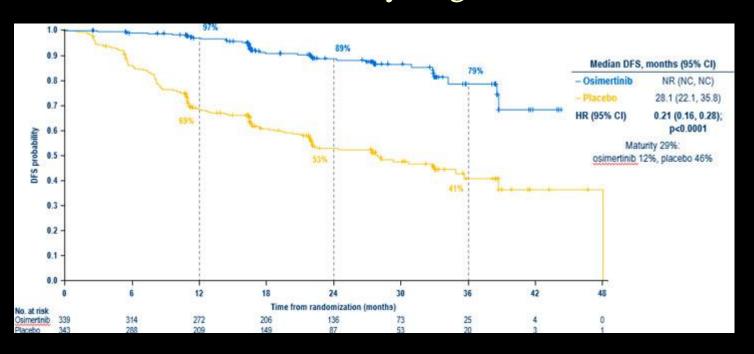






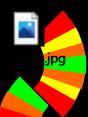


■ EGFR inhibition in early stage disease



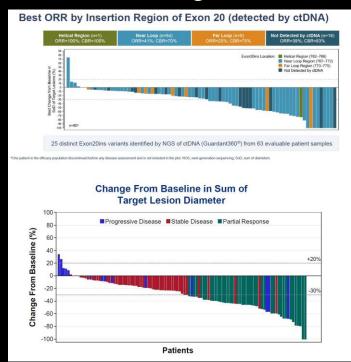
Herbst, ASCO, 2020







- EGFR exon 20 insertions
  - Resistant to first, second, and third generation inhibitors
  - New drugs:



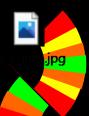
Plieth, World Lung, 2021

Amivantamab:

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

Mobocertinib: specialized TKI ORR 26%, PFS 7.3 mos









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

ALK TKI	Crizotinib (PF-02341066)	Ceritinib (LDK378)	Alectinib (RO/CH5424802)	Brigatinib (AP26113)	Lorlatinib (PF-06463922)	Entrectinib (RXDX-101)	Ensartir (X-396
Manufacturer	Pfizer	Novartis	Genentech	Ariad	Pfizer	Ignyta	Xcovery
Targets other than ALK	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	L1198F	I1171T/N L1196M S1206C/Y G1269A/S	L152P/R C1156V/T F174C/L/V L1196M S1206C/Y G1269A/S	H151Tins L1152P/R C1156V/T F1174C/L/V L1196M <b>G1202R</b> <sup>B</sup> G1269A/S	11151Tins L1152P/R C1156Y/T 11171T/N/S F1174C/L/V L1196M <b>G1202R</b> 2 S1206C/Y E1210K G1269A/S	C1156Y/T L1196M	C1156Y/ L1196M
Reported resistance mutations to the TKI	I1151Tins L1152P/R C1156Y/T I1171T/N/S F1174C/L/V V1180L L1196M G1202R S1206C/Y E1210K	I1151Tins L1152P/R C1156Y/T F1174C/L/V G1202R	I1171T/N/S V1180L G1202R	<b>G1202R<sup>B</sup></b> E1210K + 51206C E1210K + D1203N	L1198F + C1156Y <sup>⊆</sup>	G1202R	N.D.

### Notable mutations

L1196M "gatekeeper"
blocks sterically likeT790M
G1269A
also steric hindrance
G1202R "solvent front"
adjacent to binding site
alter binding affinity

Lin, Europe PMC, 2017

Also: ALK amplification, bypass, epigenetics



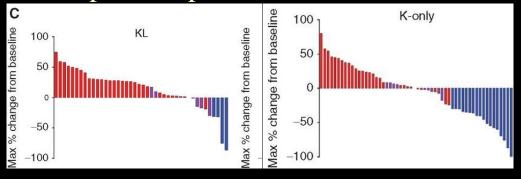


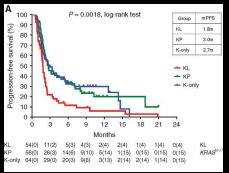
# Influential passengers



### ■ STK11 (aka LKB1):

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





Sikouldis, Cancer Disc, 2018

### PIK3CA

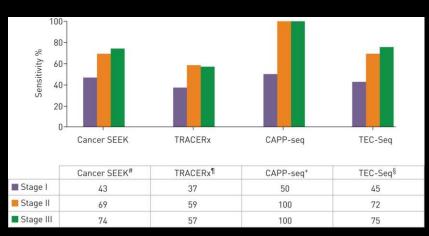
- Often co-exist with other targetable mutations
- Treatment under investigation

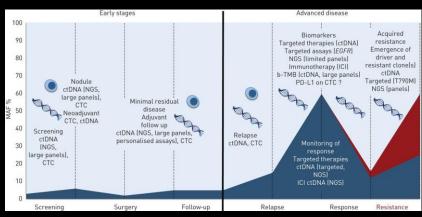




- Early detection
  - Screening?
  - Avoid biopsy?

- Monitoring
  - Indication of response?
  - Resistance mechasnisms?





Guibert, Eur Resp Rev, 2020





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

