Liquid Biopsy

Targeted Therapies for NSCLC in the Era of Precision Medicine

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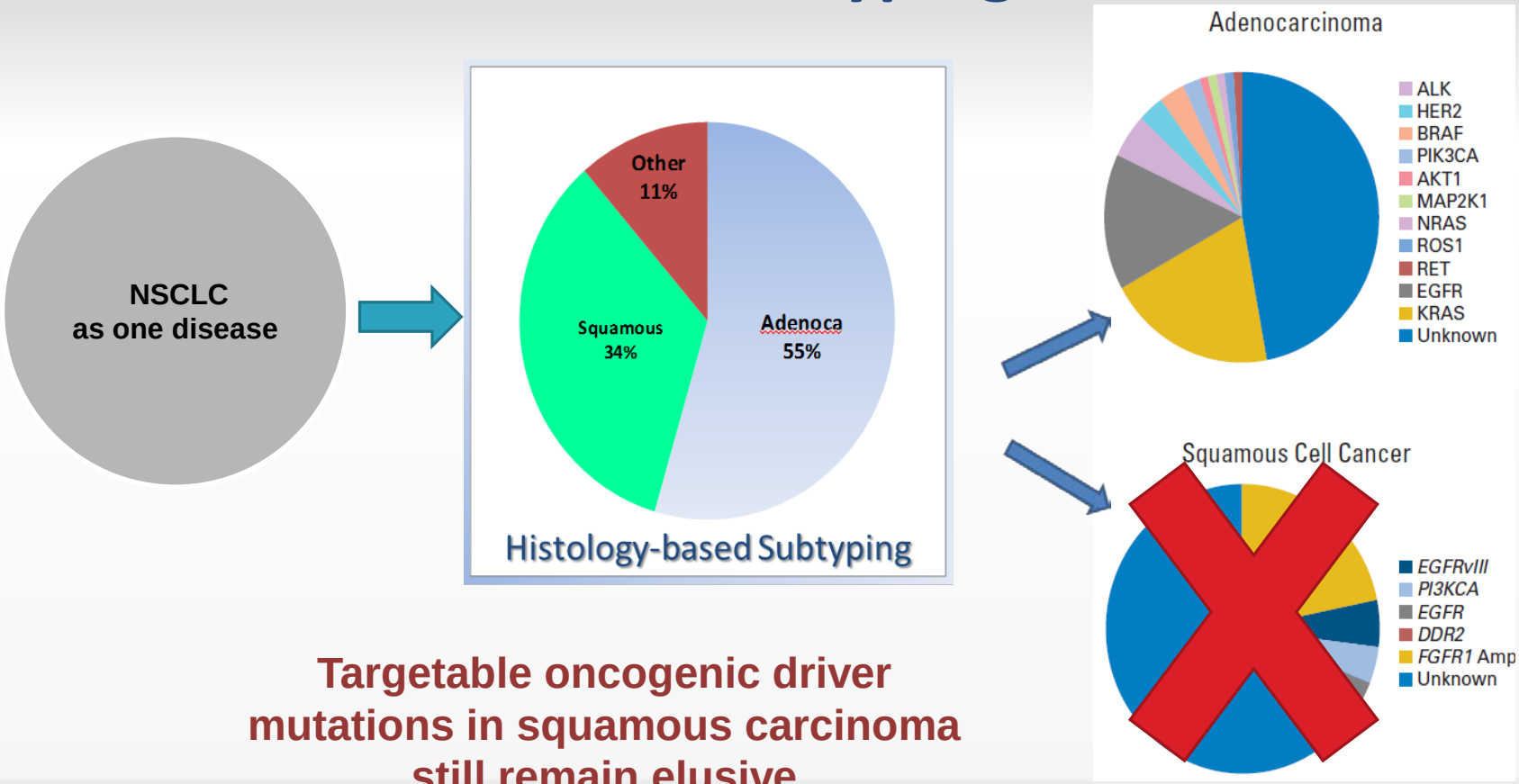
DISCLOSURES: Philip C. Mack, PhD

Research Funding:	**Boehringer Ingelheim**
Educational Honoraria:	**Guardant Health**
Advisory Board:	**AstraZeneca**
	Novartis
	Lilly
	Pfizer
Consulting:	**Apton Biosystems**
	Guardant Health

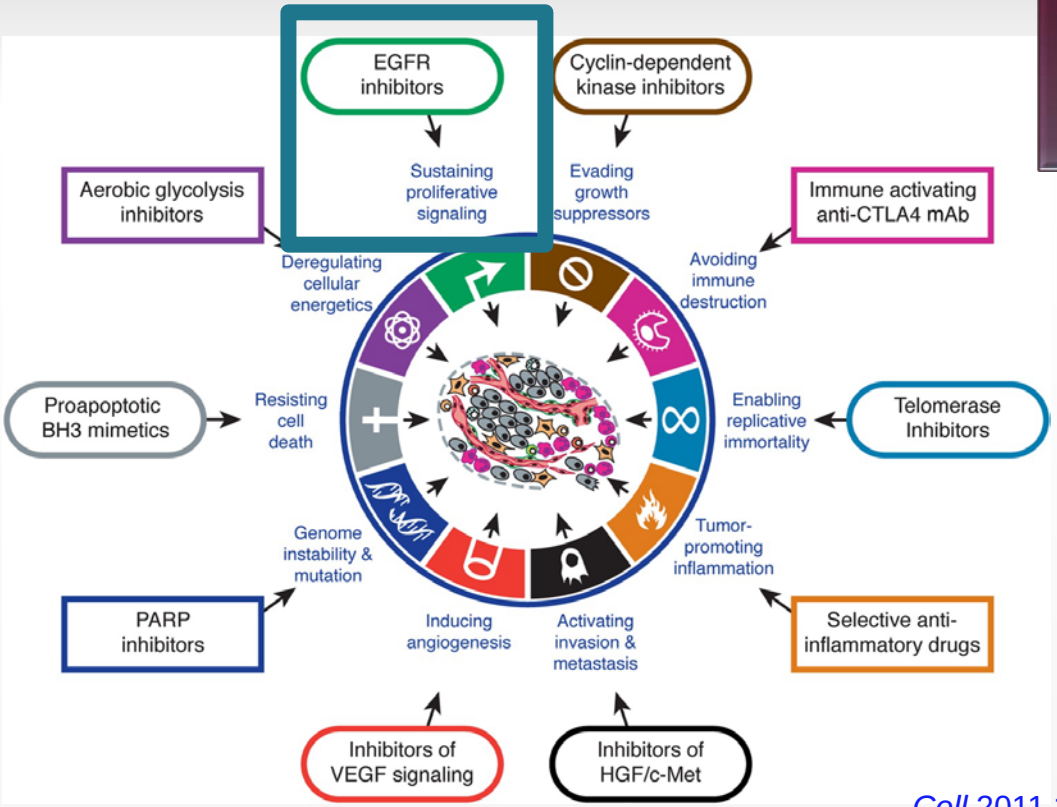
Evolution of NSCLC Subtyping



Targetable oncogenic driver mutations in squamous carcinoma still remain elusive

Philip C. Mack, PhD, UC Davis Comprehensive Cancer Center and California Northstate University

The “Hallmarks” of Cancer

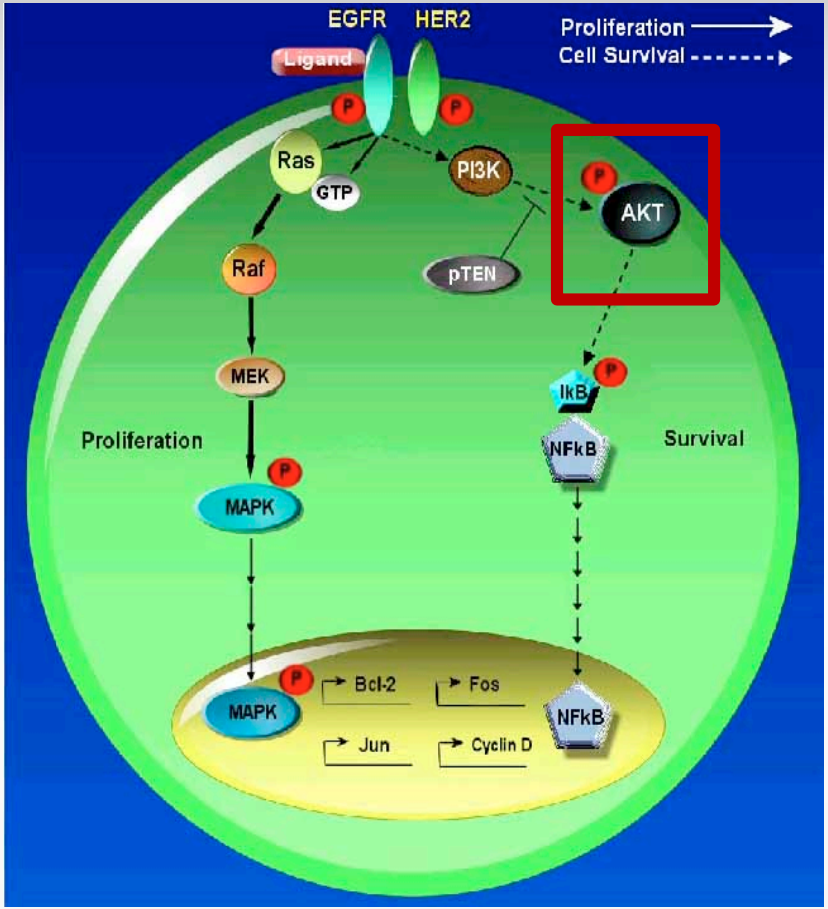


A lot of very specific processes must be corrupted to form a metastatic cancer.

In NSCLC, successful targeted therapies inhibit signal transduction-associated drivers

Hallmarks of Cancer: The Next Generation
Douglas Hanahan, Robert A. Weinberg

Cell 2011 144, 646-674DOI: (10.1016/j.cell.2011.02.013)



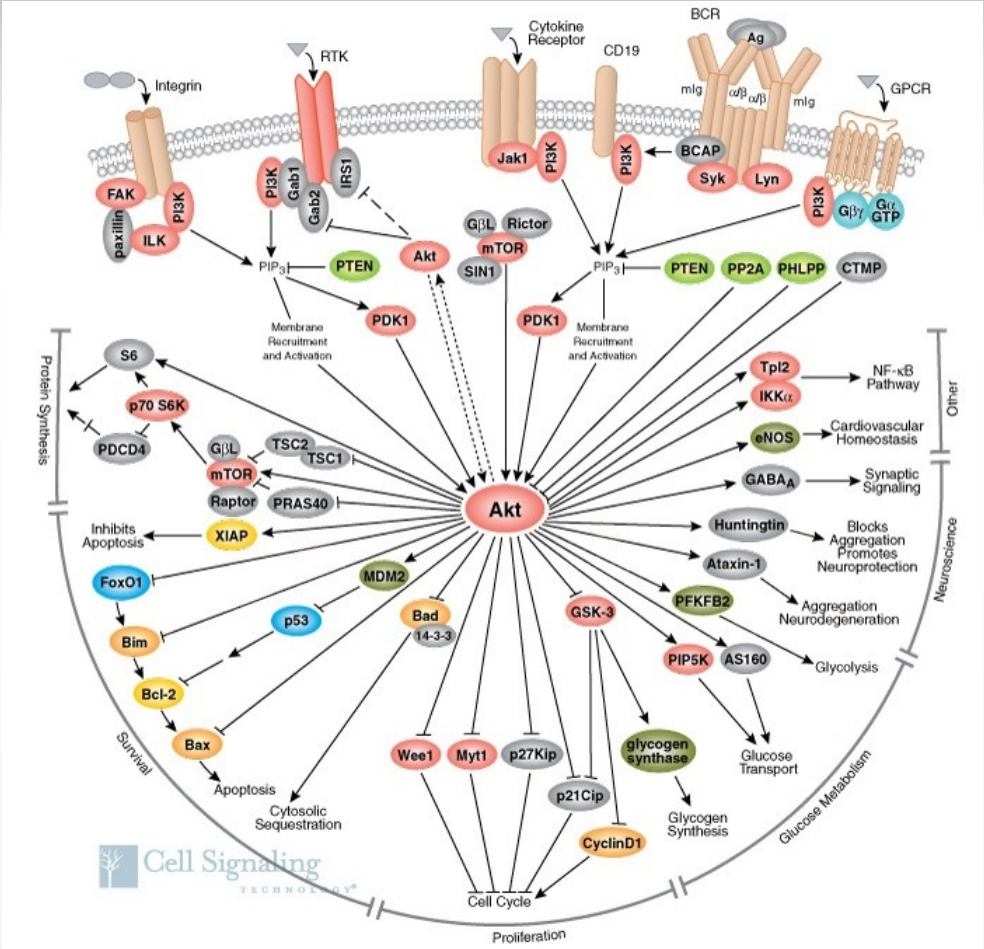
Signal Transduction -

If only it were that simple

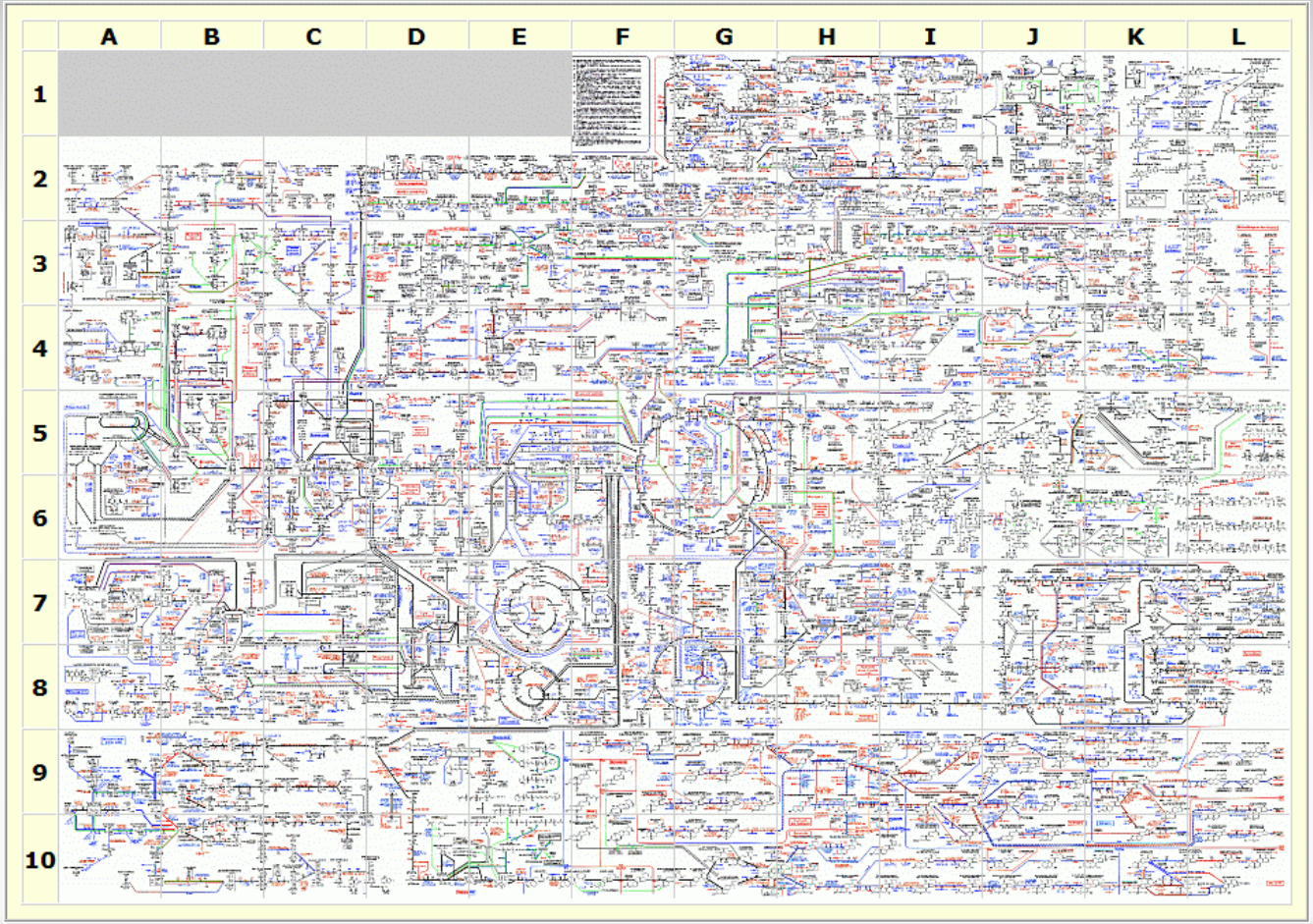
- An idealized diagram of signal transduction: two pathways controlling proliferation and survival

Signal Transduction

- Slightly more complex



- A diagram of AKT interactions: It's more of a network than a pathway.
- Still understates true complexity
  - Feedback loops
  - Cellular localization
  - Post-translational modifications



Reality hurts

Cancer signal transduction is miswired and constitutively active

Modern day oncologist?

Fortunately, tumors with actionable drivers are relatively simple

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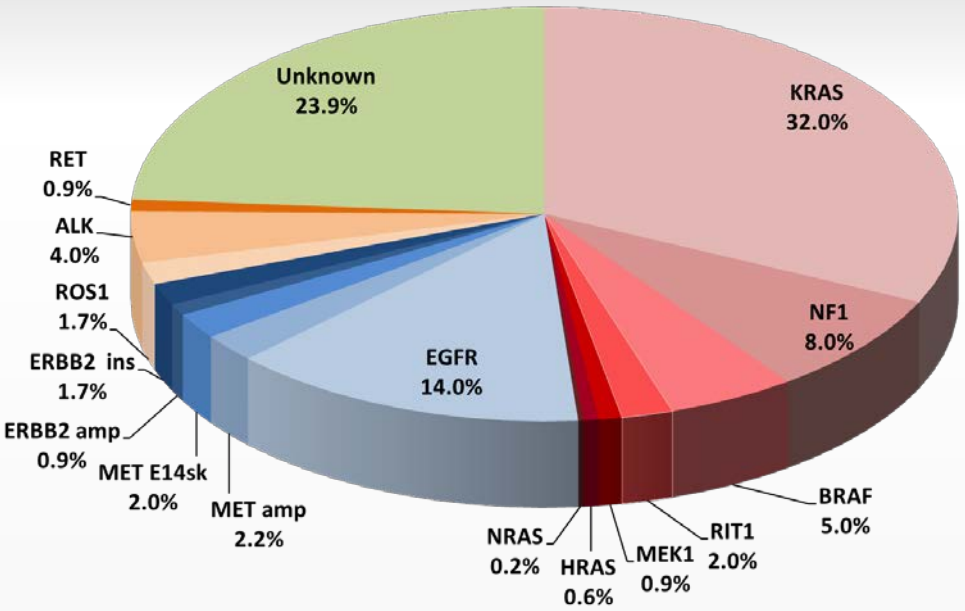
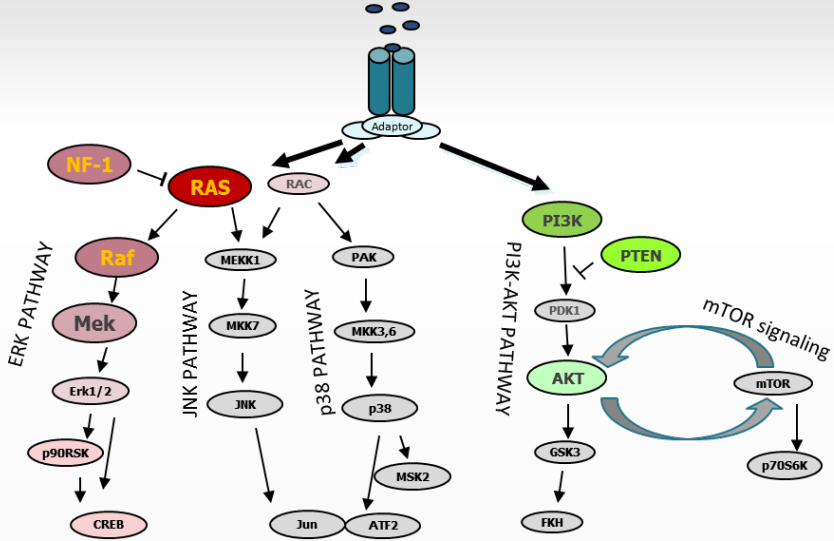
The Genomic Landscape of Lung Adenocarcinoma





Blue sections indicate RTK signaling abnormalities

Mutual exclusion with each other and with other known drivers

A key indicator of tumor dependency

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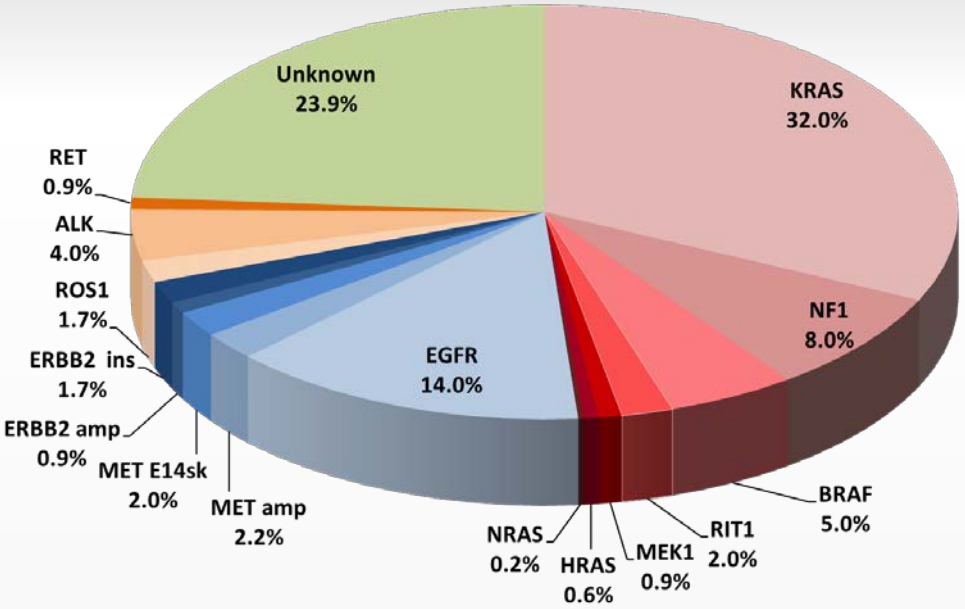
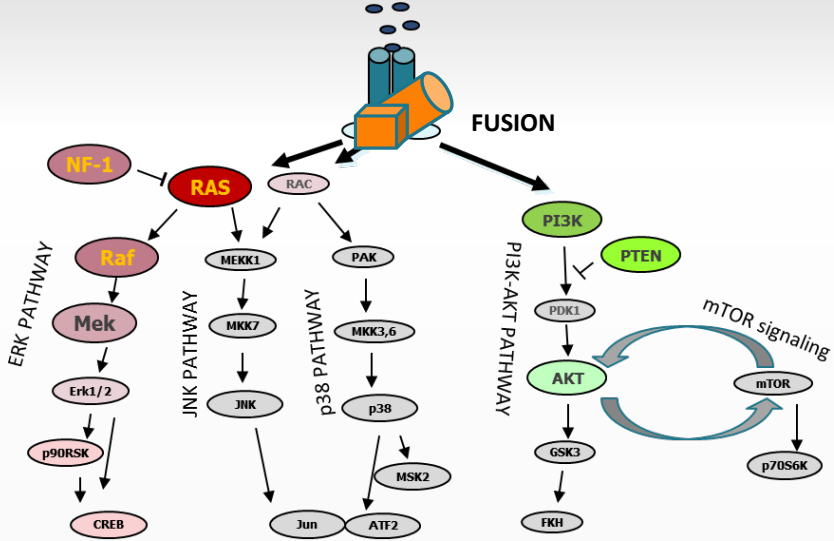
The Genomic Landscape of Lung Adenocarcinoma





Gold sections indicate transforming fusion events

Mutual exclusion with each other and with other known drivers

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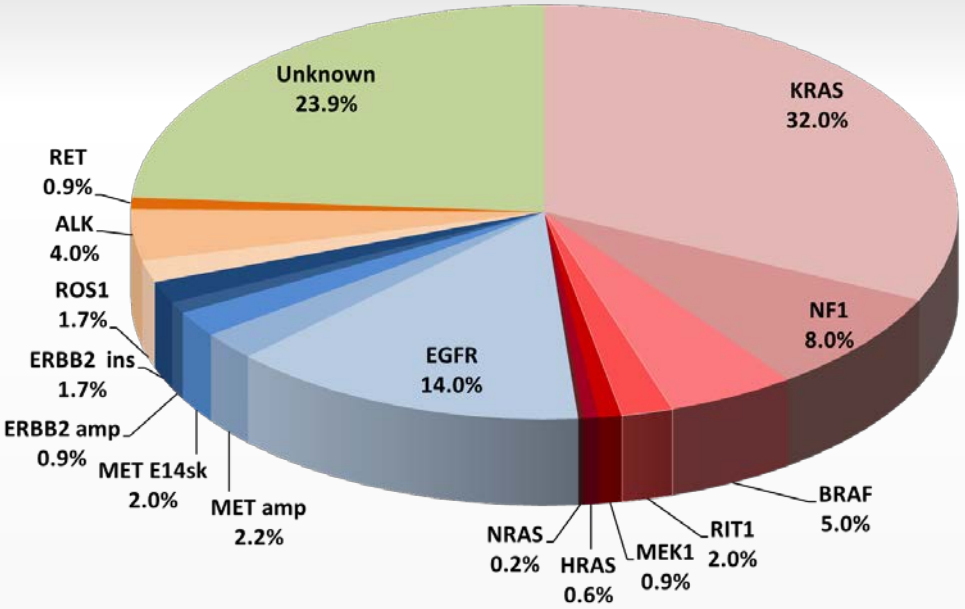
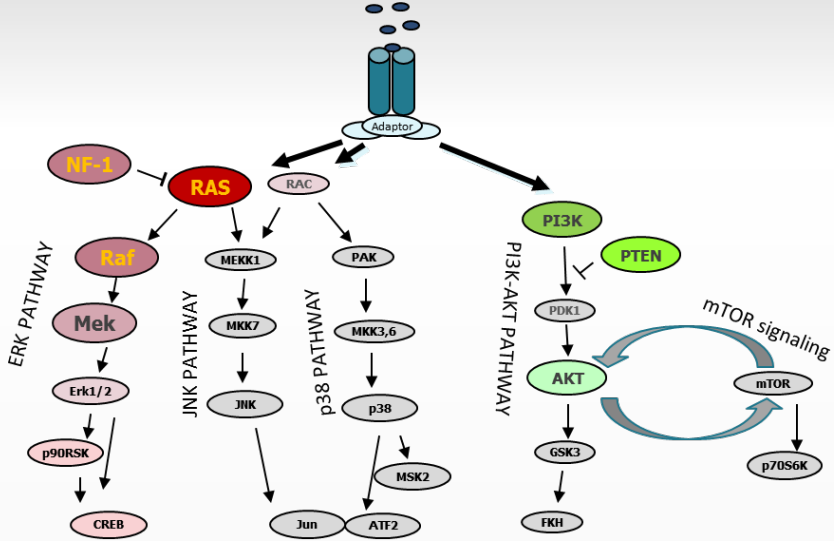
The Genomic Landscape of Lung Adenocarcinoma





Red sections indicate MAPK signaling abnormalities

Mutual exclusion with each other and with other known drivers

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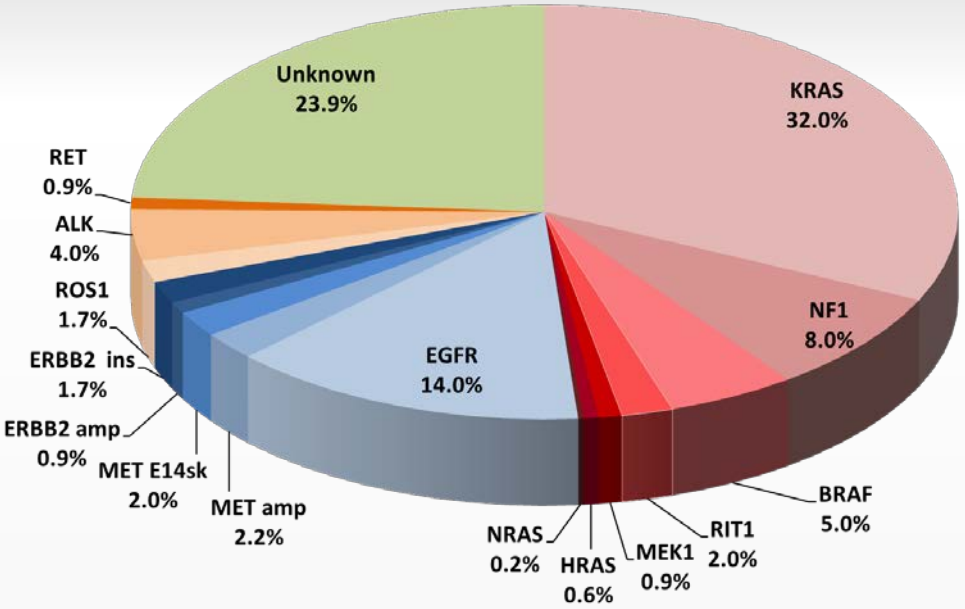
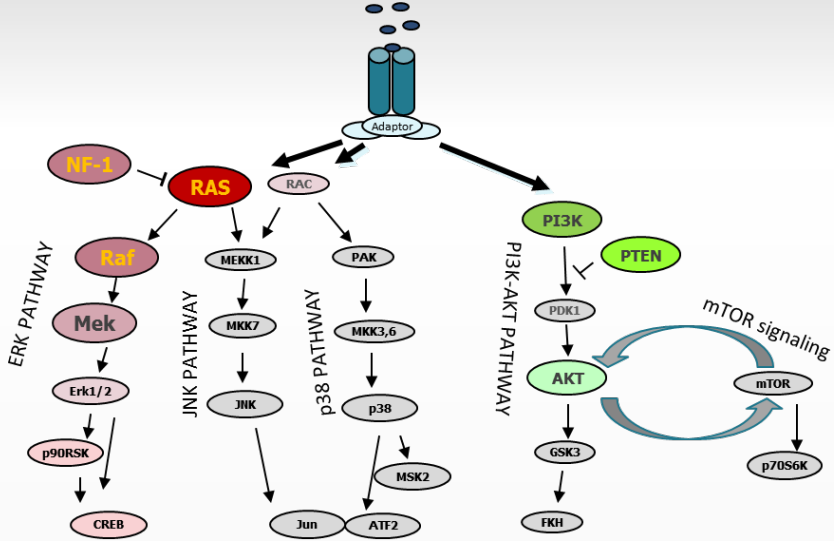
The Genomic Landscape of Lung Adenocarcinoma





Green section indicates the proportion of cases with no known signaling abnormalities (undiscovered, underappreciated, non-existent)

PI3K pathway abnormalities often overlap with other drivers

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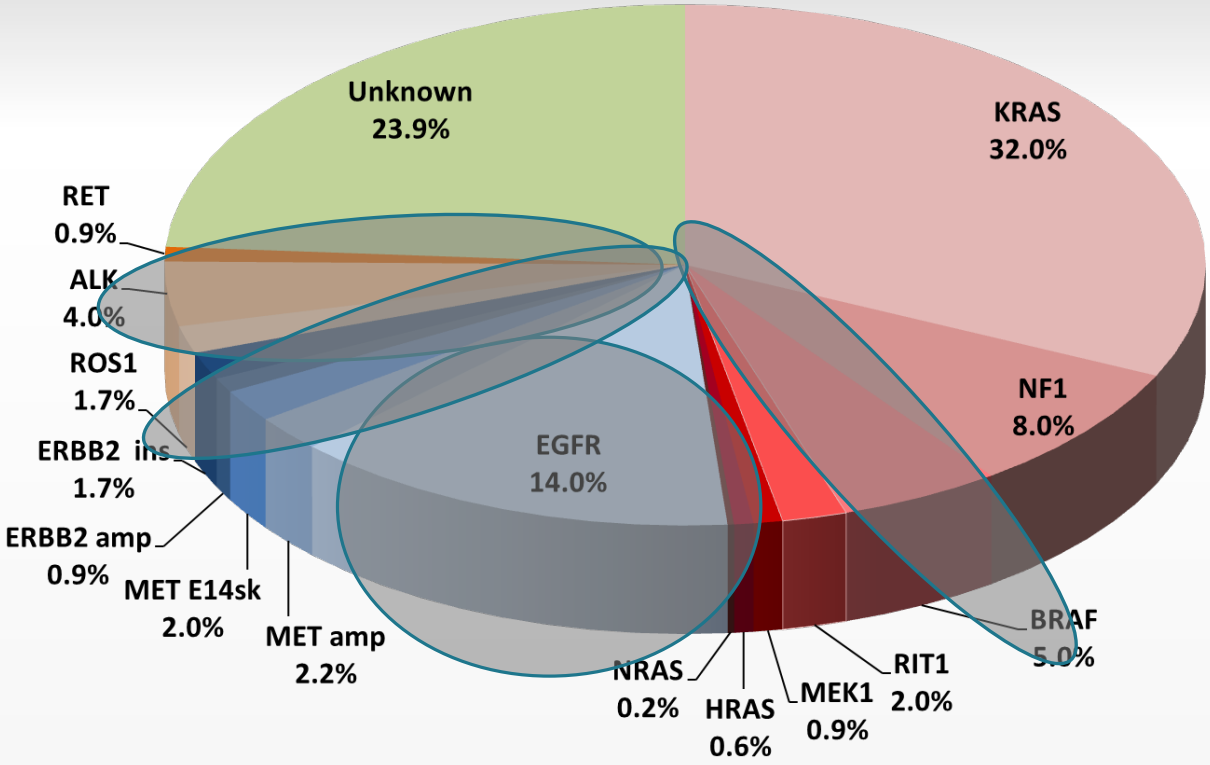
Actionable Drivers in Lung Adenocarcinoma



Currently or potentially actionable abnormalities

- 17 – 20%: ALK, ROS1, EGFR
- 10 – 12%: MET, Her2, BRAF, RET
- NTRK
- FGFR3

Largely adopted | **Poorly adopted**

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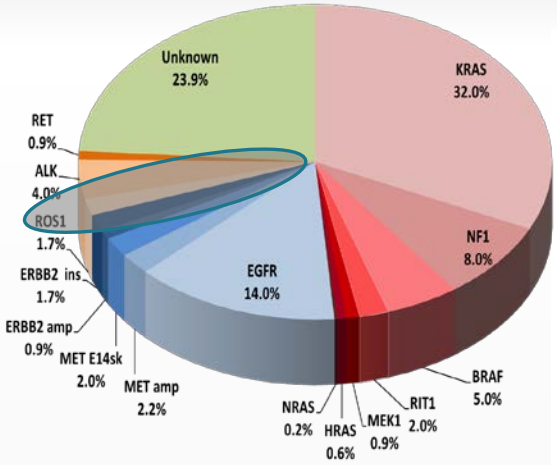
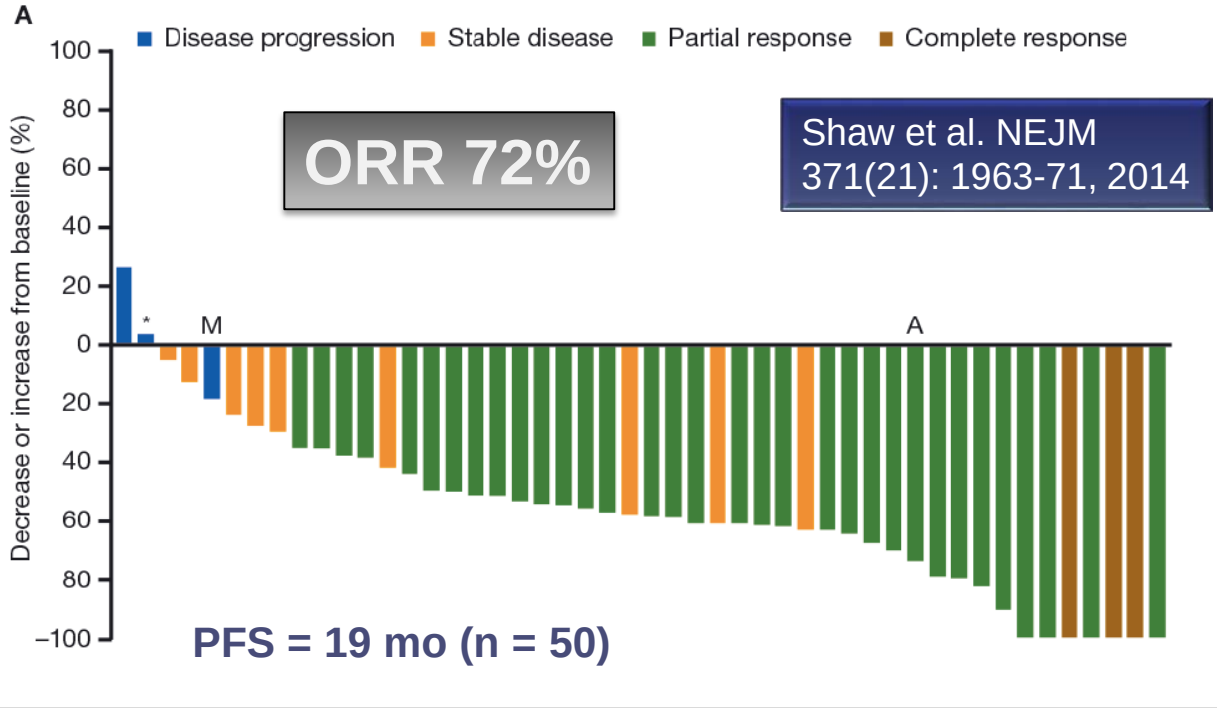
Clinical Activity of Crizotinib in Advanced ROS1+ NSCLC: PROFILE 1001 Study



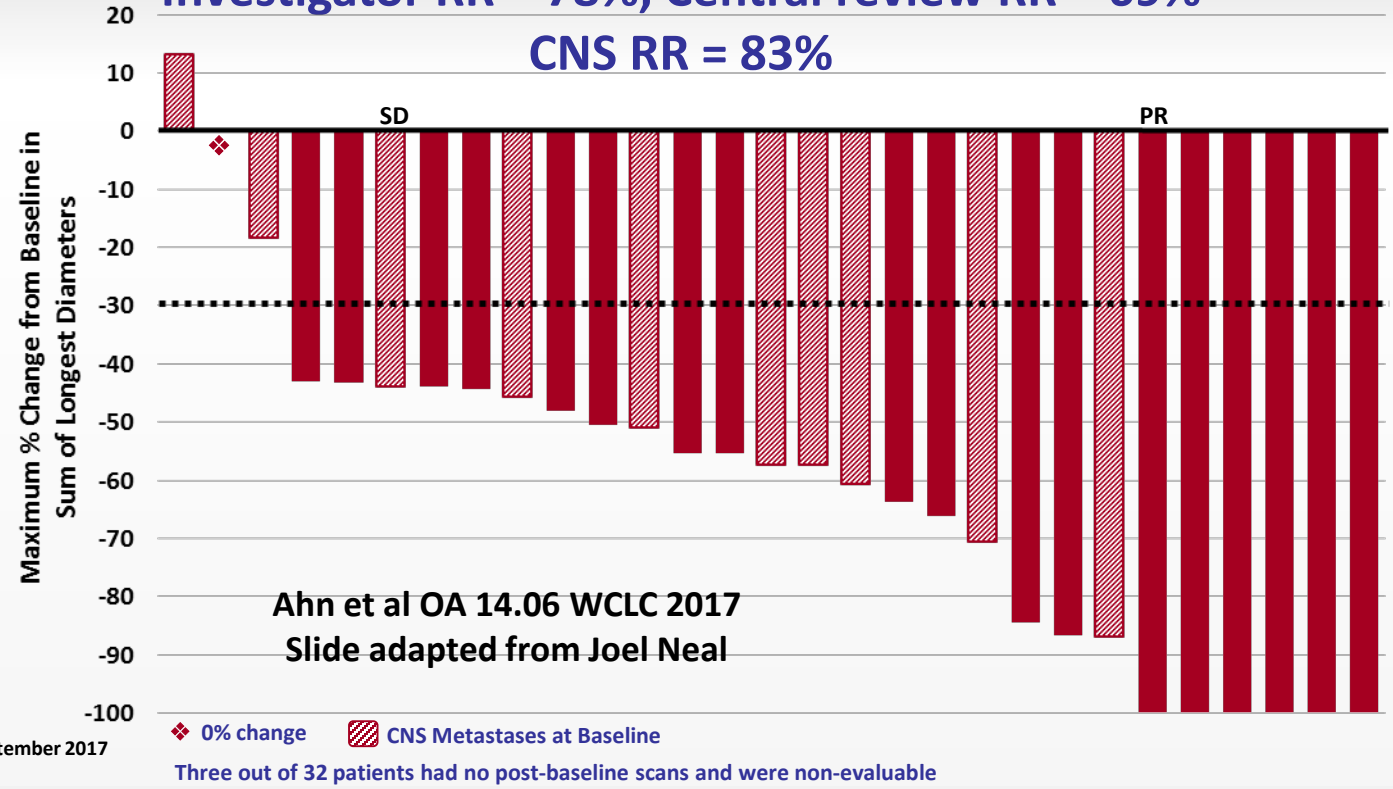


Best Response to Entrectinib in ROS1 Fusion+, Inhibitor-Naïve NSCLC

34% (11 out of 32) of the patients had CNS disease at baseline

Investigator RR = 78%, Central review RR = 69%

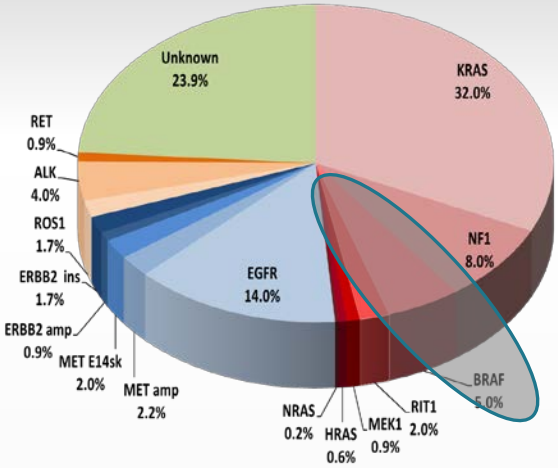
CNS RR = 83%

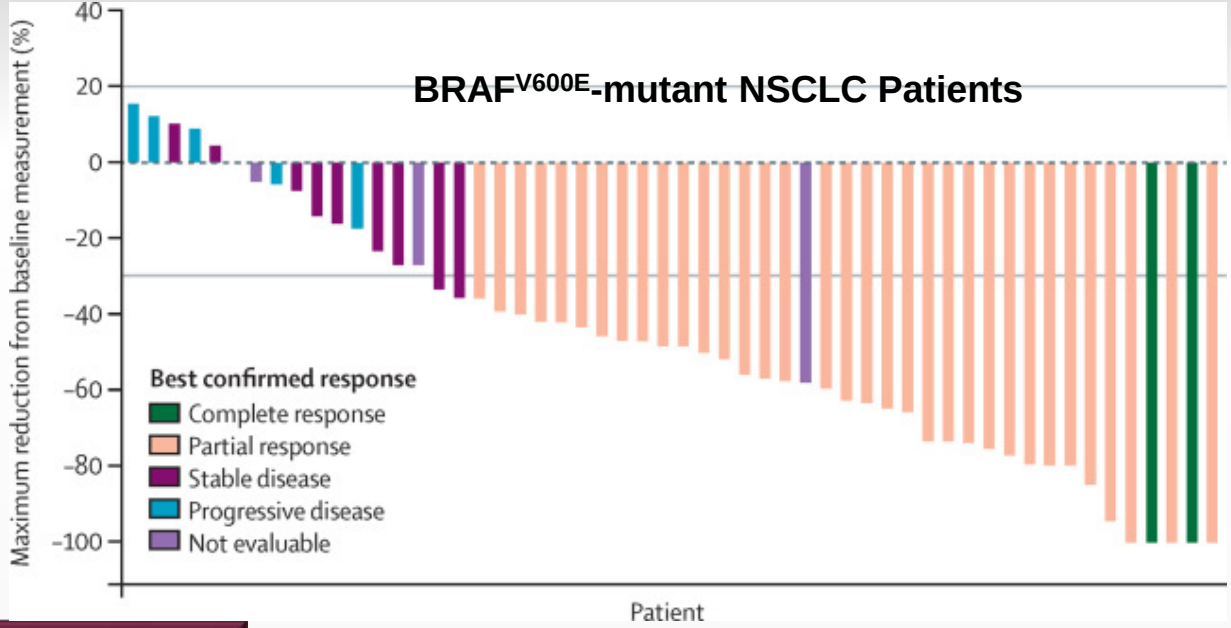


Data cutoff date: 13 September 2017

Three out of 32 patients had no post-baseline scans and were non-evaluable

Lung Adenocarcinoma: BRAF as a driver





Dabrafenib plus trametinib receives "breakthrough therapy" designation for BRAF-mutant NSCLC July 2015; full FDA approval June 2017

David Planchard et al, **Dabrafenib plus trametinib in patients with previously treated BRAFV600E-mutant metastatic non-small cell lung cancer: an open-label, multicentre phase 2 trial**. Lancet Oncology Volume 17, Issue 7, 2016, 984–993

Liquid biopsies: cell-free circulating tumor DNA

- Advanced malignancies shed DNA into circulation
  - **DNA is highly fragmented**
  - **Stable for a few hours**
- **Technology is already in routine clinical practice**
  - **Identify emergent resistance factors**
  - **Expand biomarker detection in patients with insufficient biopsies**
  - **Monitor disease progression & evolution**

How much information can we get from ctDNA?

Analysis of Guardant Health Cancer Database

Goal: Evaluate mutation distribution in cancer cases submitted to Guardant Health in comparison to The Cancer Genome Atlas (TCGA)

The landscape of actionable genomic alterations in cell-free circulating tumor DNA from 21,807 advanced cancer patients. Zill et al, Clinical Cancer Research 2018 in press

8,388 NSCLC cases reported at WCLC 2016 (Mack et al, OA06.01)
Manuscript near complete

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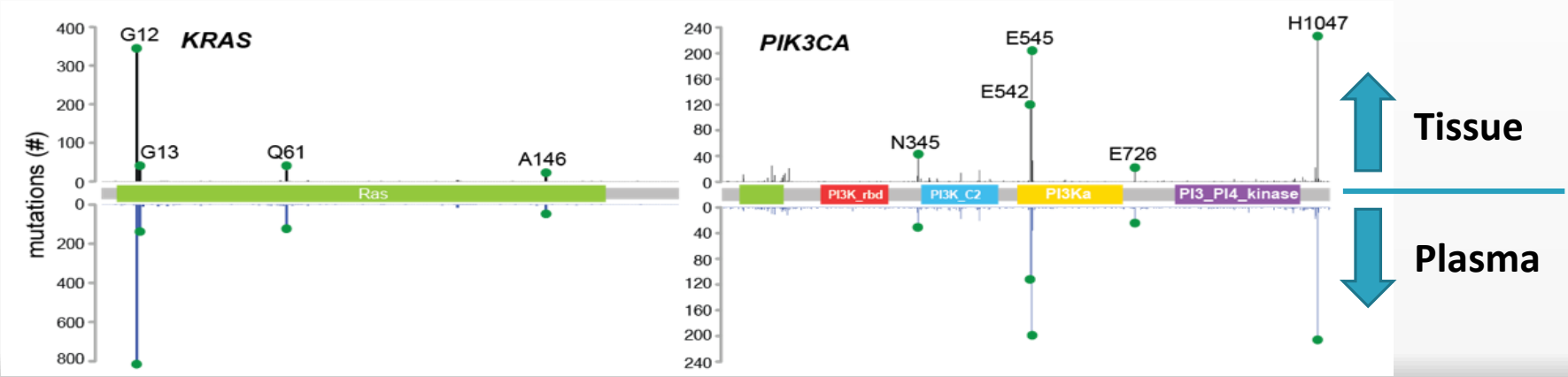
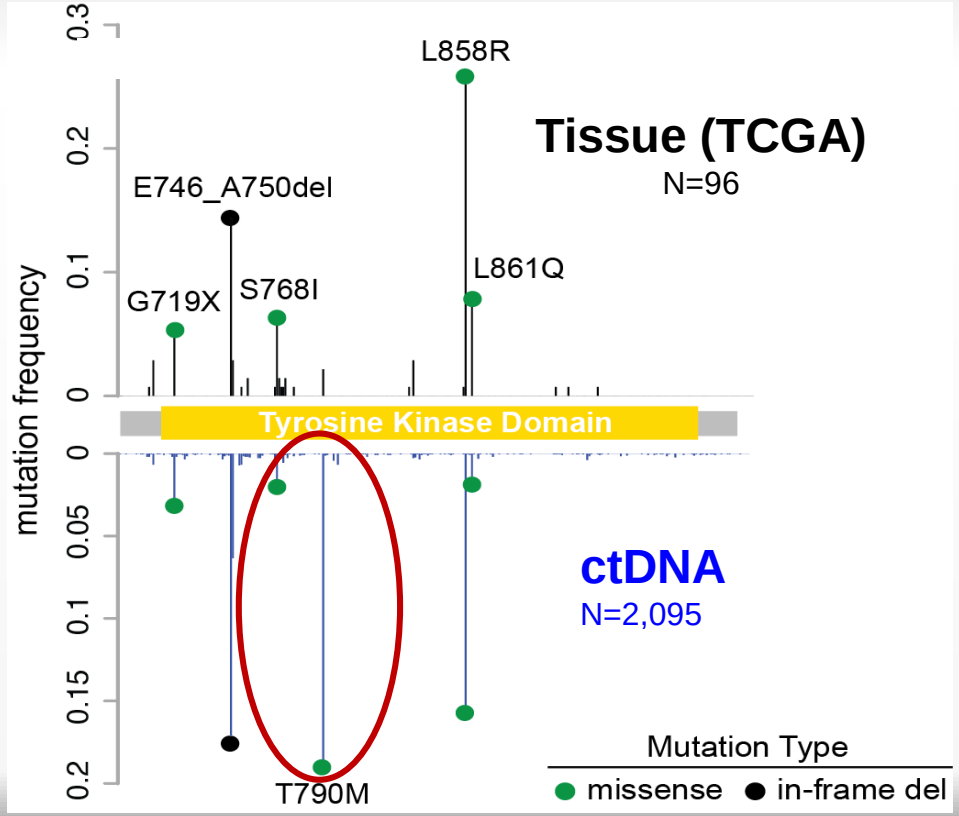
Mutation frequency and distribution in plasma is synonymous with tissue

- Plasma ctDNA NGS found truncal alterations at frequencies predicted from the TCGA
  - **Also identified resistance mutations at progression**



Population-scale genomics: TCGA and GH360 ctDNA have similar mutation patterns



The EGFR secondary resistance mutation T790M frequently found in ctDNA cohort, but rare in TCGA (surgical/treatment naïve)

EGFR (**r = 0.9** excluding T790M and C797S)

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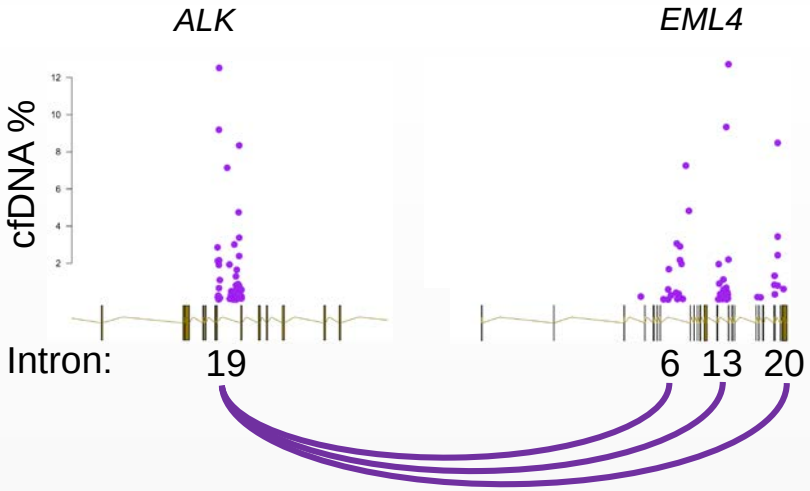
Population-scale genomics: Guardant ctDNA fusion patterns mirror tumor tissue (r=0.99)

EML4 intron (EML4-ALK)	Breakpoints in ctDNA (n=47)	Breakpoints in COSMIC (n=375)
13	46%	47%
6	37%	35%
20	5%	14%
KIF5B intron (KIF5B-RET)	**Breakpoints in ctDNA (n=28)**	**Breakpoints in COSMIC (n=589)**
15	66%	67%
16	18%	18%
23	5%	5%
20	3%	0%
24	0%	5%
CCDC6 intron (CCDC6-RET)	**Breakpoints in ctDNA (n=18)**	**Breakpoints in COSMIC (n=60)**
1	96%	99%
3	4%	0%
2	0%	1%
8	0%	0%



N=93 cases of fusions detected by G360

Comparator: Morán T, et al. 2013 *Transl Lung Cancer Res*

Results: GH360 ctDNA Genomic Landscape in Lung Adenocarcinoma

Alteration	N	%
EGFR mutations	1361	26.4%
ALK fusion	65	1.3%
RET fusion	45	0.9%
ROS1 fusion	9	0.2%
MET E14 skip	49	1.0%
BRAF mutations	139	2.7%
ERBB2 mutations	119	2.3%
KRAS mutations	888	17.2%
MET amp	295	5.7%
ERBB2 amp	229	4.4%

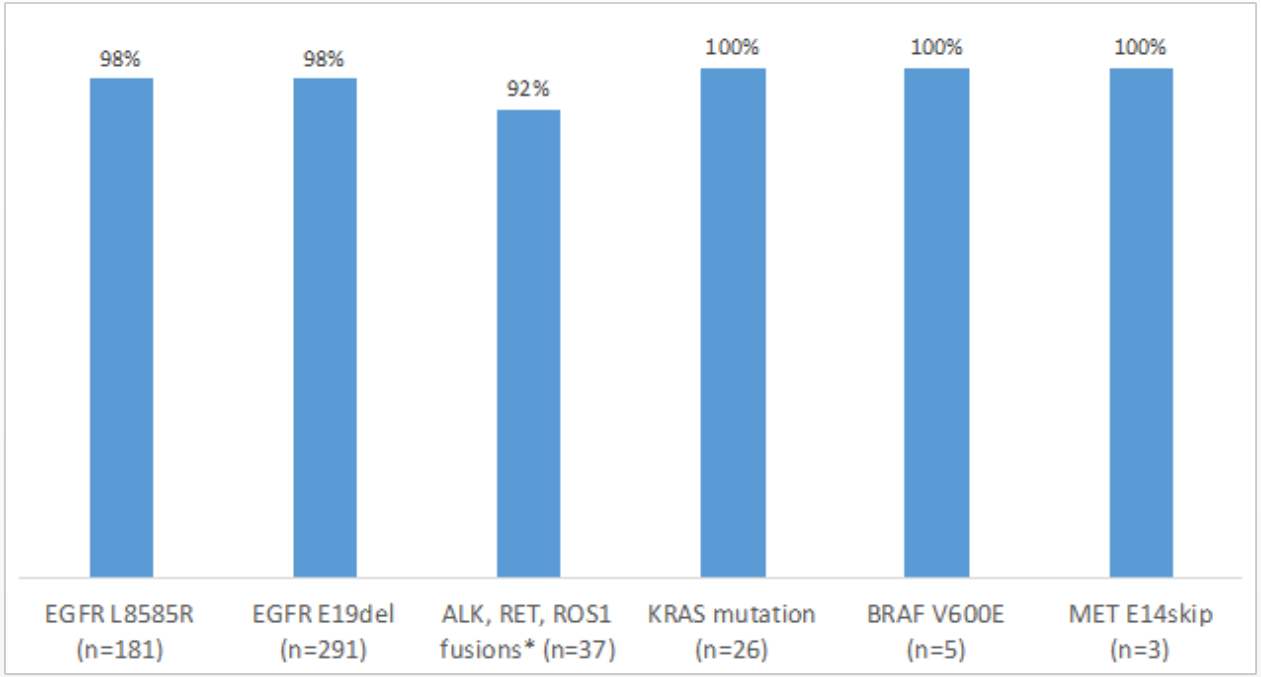
Cases from 70-gene panel only

EGFR Driver Mutations

- 52% E19 del
- 34% L858R
- 4% E20 ins
- 10% other
  - G719
  - L861
  - S768
  - E709
  - Other rare mutations

Not a random cross-section of US patients (Enriched for patients progressing on targeted agents)

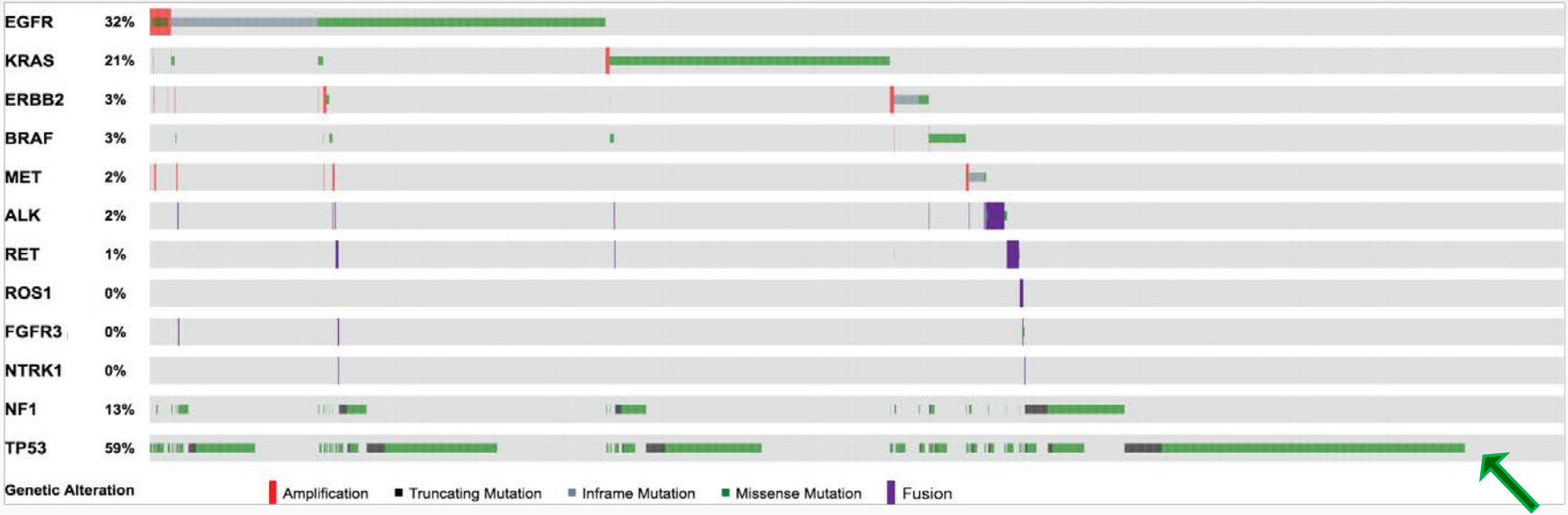
Clinical Accuracy: Matched ctDNA vs. Tissue Biopsy: Positive Predictive Value (PPV)



* Three cases with ctDNA-positive, tissue-negative *ALK* fusion responded to crizotinib.

likely representing a false negative in tissue

Mutual Exclusivity of Driver Oncogenes



Secondary mutations at resistance to EGFR TKI

Rare secondary KRAS mutations at resistance to targeted therapy?

TP53 mutations distributed evenly across drivers

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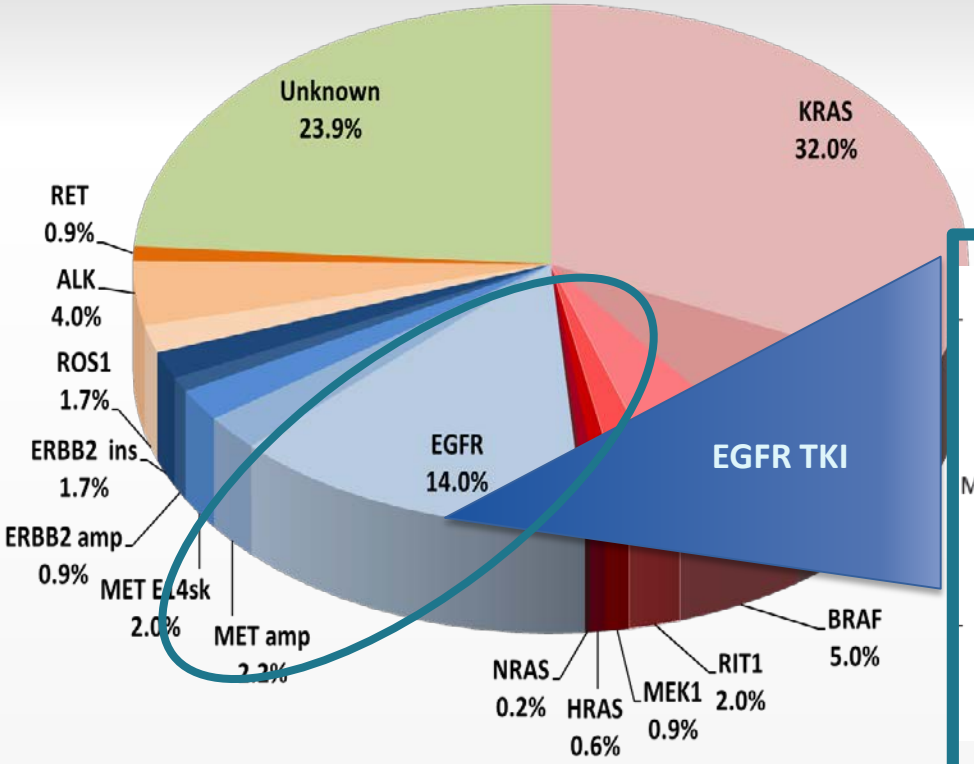
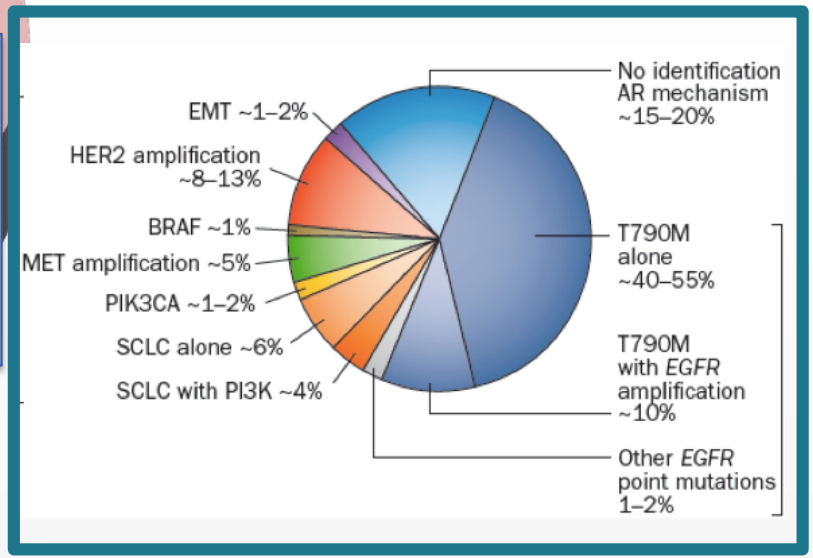
Lung Adenocarcinoma: Acquired Resistance



Almost all tumors have the capacity to evolve treatment resistance mechanisms

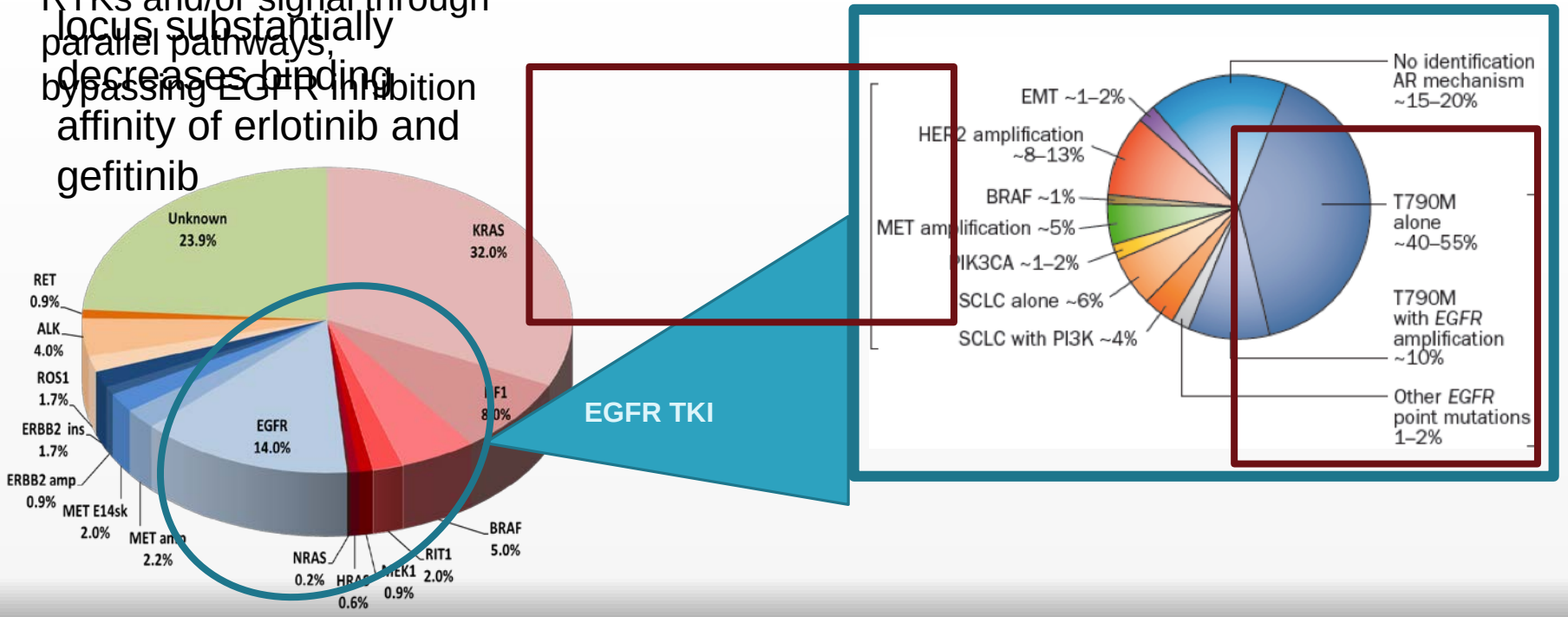


Camidge Nature Rev Clin Oncol 2014

The Genomic Landscape of Lung Cancer

EGFR mutant driven cancers may acquire the ability to activate additional RTKs and/or signal through parallel pathways, bypassing EGFR inhibition

Acquisition of an additional mutation in EGFR at the **T790M** locus substantially decreases binding affinity of erlotinib and gefitinib

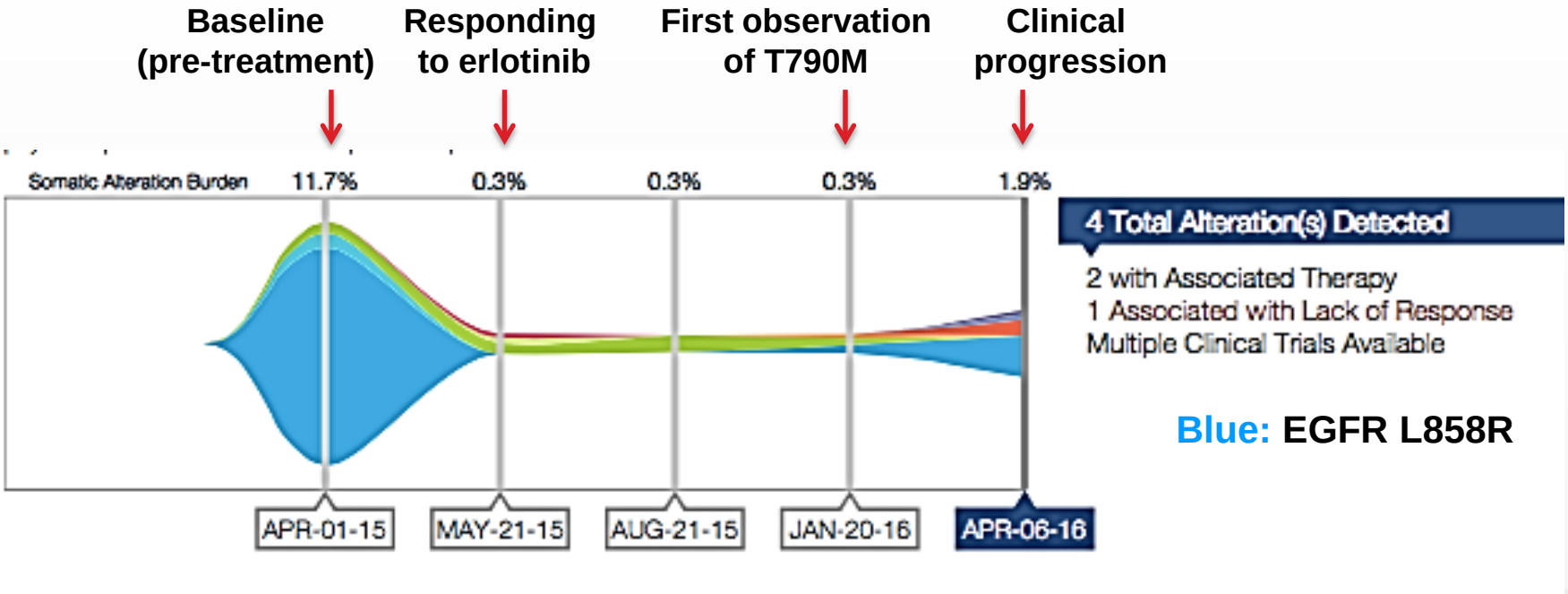


How to identify emergent resistance

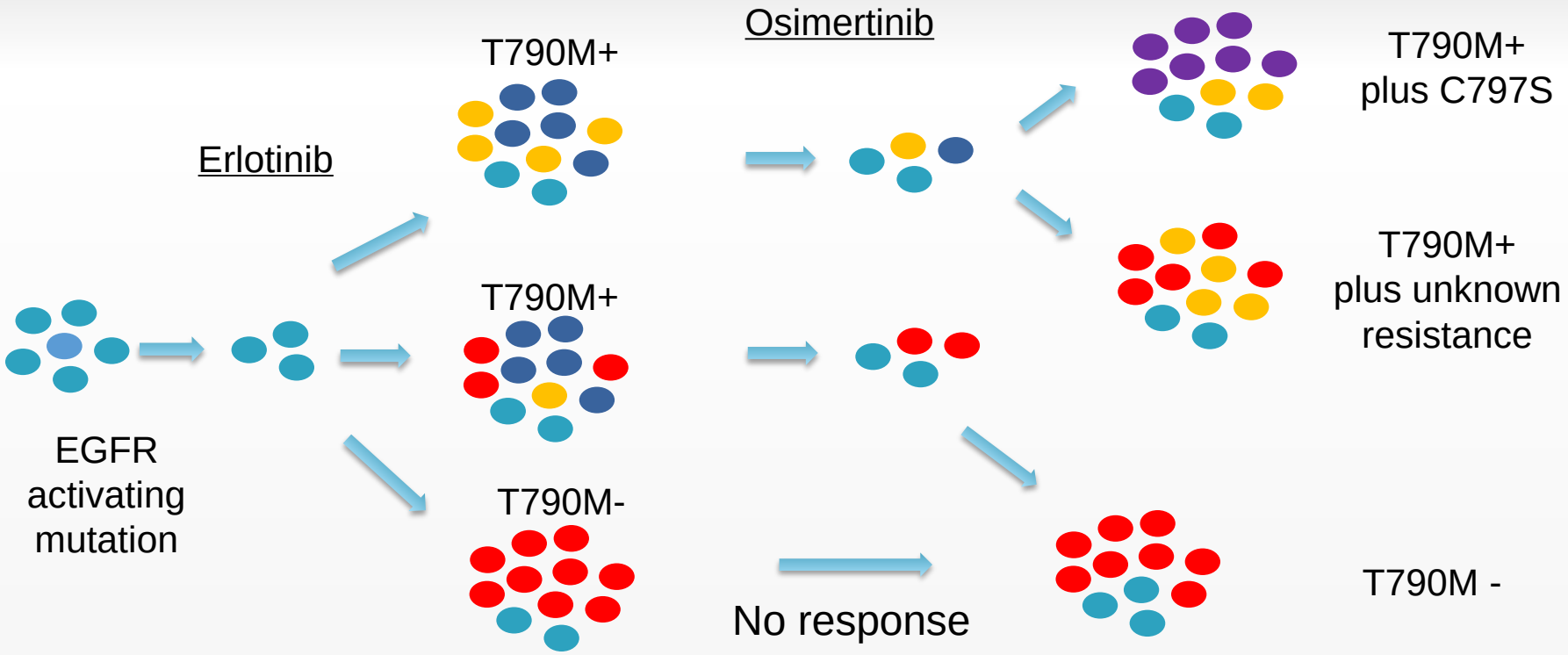
- Tissue biopsies at tumor progression

- Liquid biopsies
  - **circulating tumor DNA**

Treatment-induced changes in plasma mutant allele frequencies

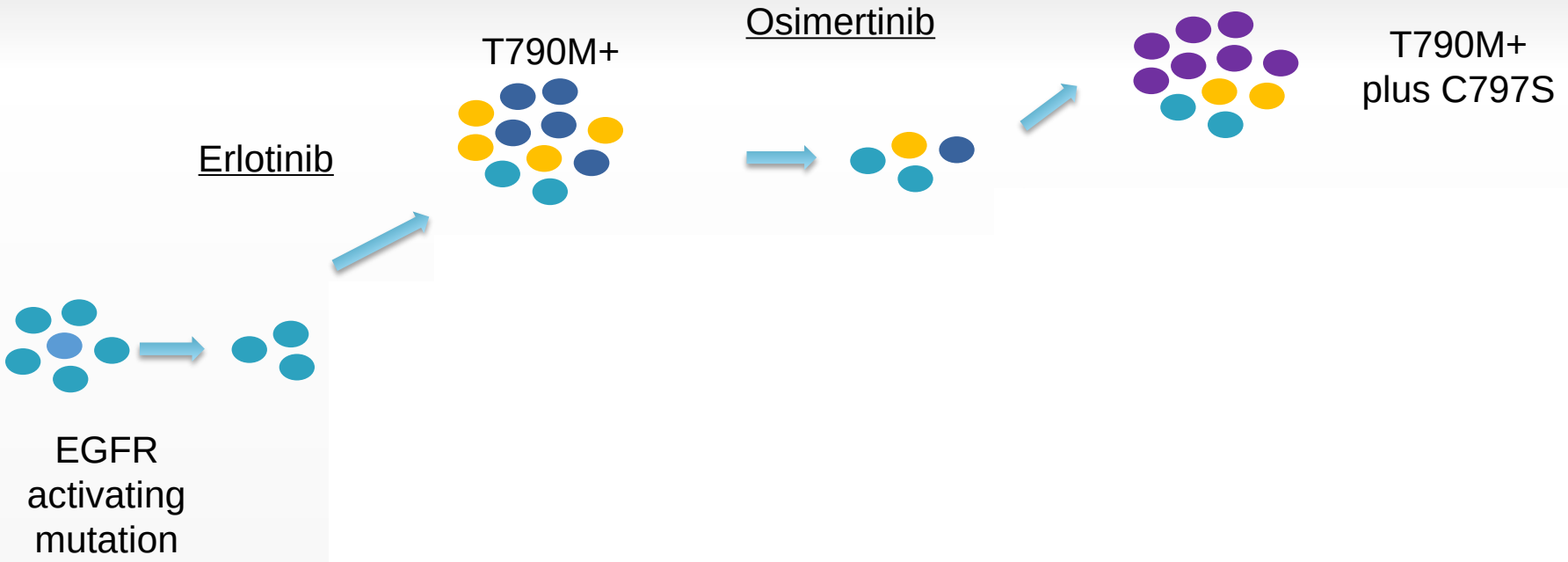


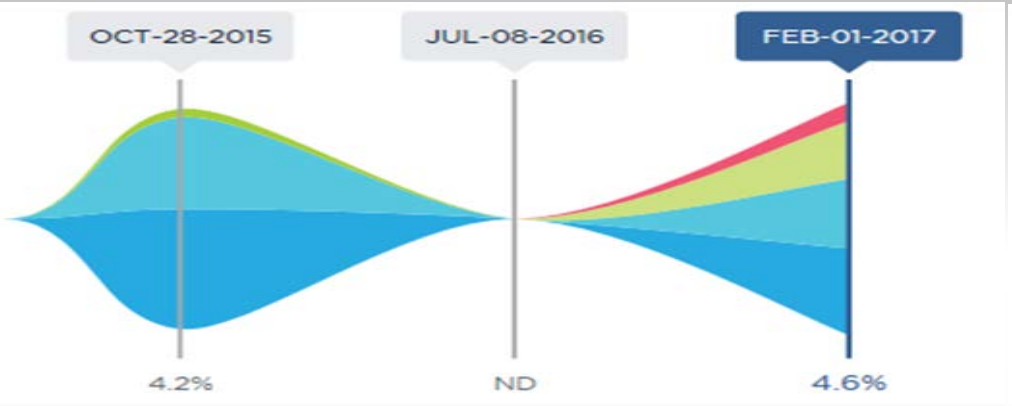
Evolution of resistance mechanisms in EGFR mutant lung cancer following EGFR TKI therapy



Janne, PLENARY SESSION 3 WCLC 2015

Evolution of resistance mechanisms in EGFR mutant lung cancer following EGFR TKI therapy



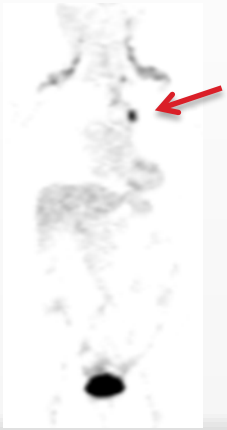


75YO F NS

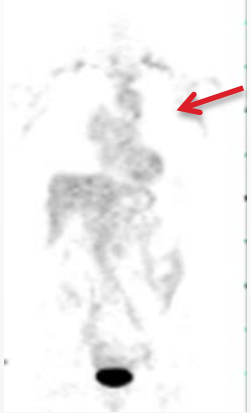
Progressing after durable PR on erlotinib

Courtesy of J. Riess, UCD

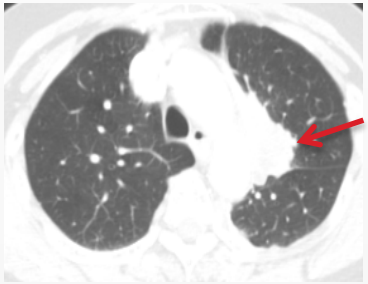
PD on erlotinib T790M-positive

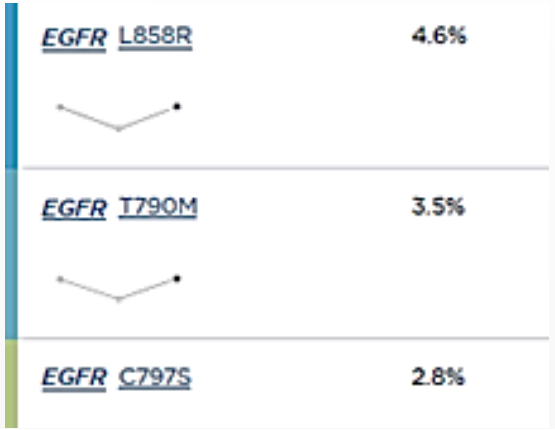


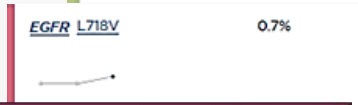
PR on osimertinib



PD on osimertinib L858R/T790M/C797S







The functional consequences and clinical significance of this gene variant are not established. Similar to other alterations in circulating cfDNA, the amount (% cfDNA) of this variant may reflect disease progression or response to treatment; clinical correlation is advised.

On trial: osimertinib + necitumumab

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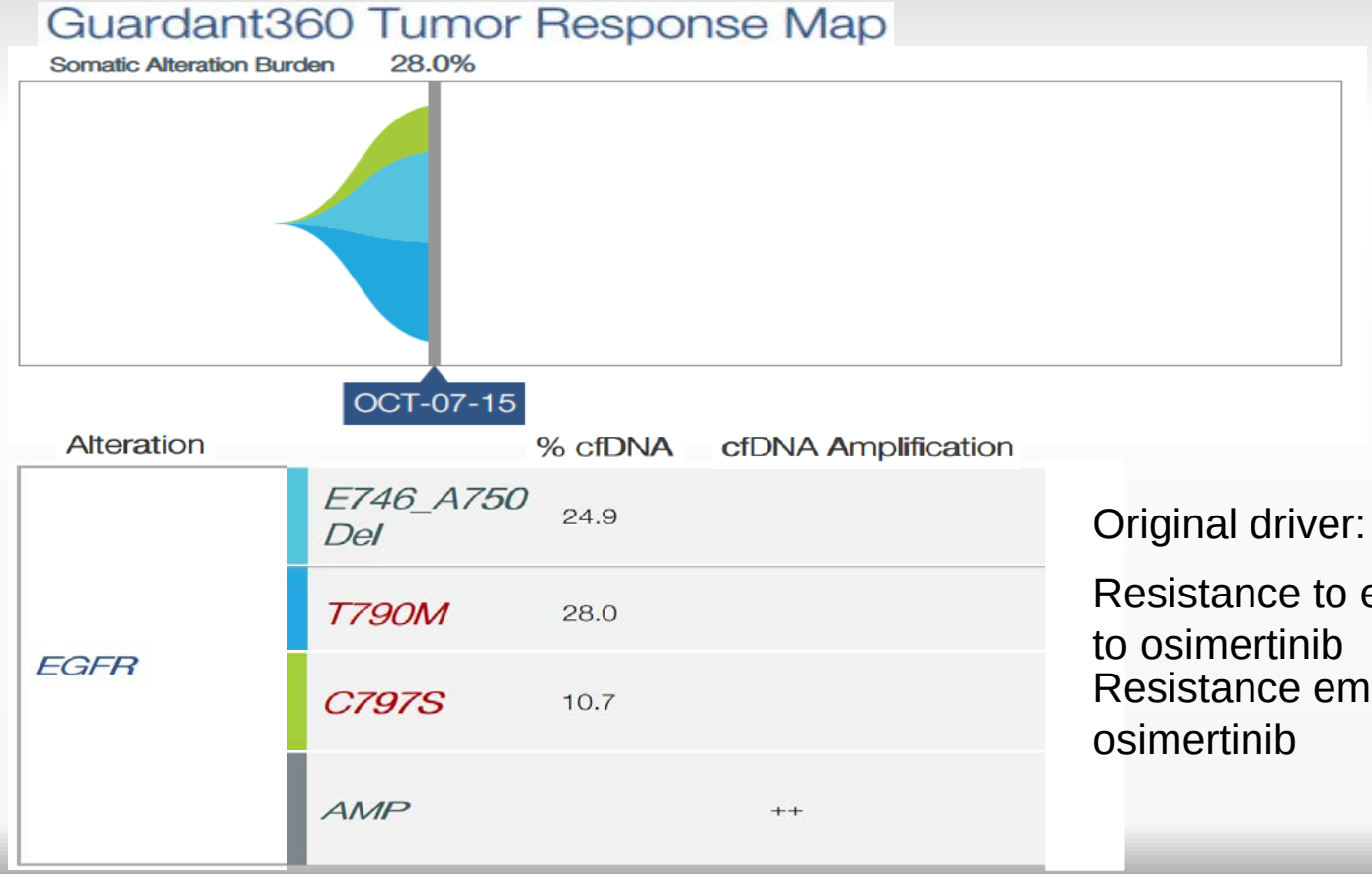
EGFR resistance mutations: single time point



Original driver: Rx erlotinib

Resistance to erlotinib: change to osimertinib

Resistance emerges again: stop osimertinib

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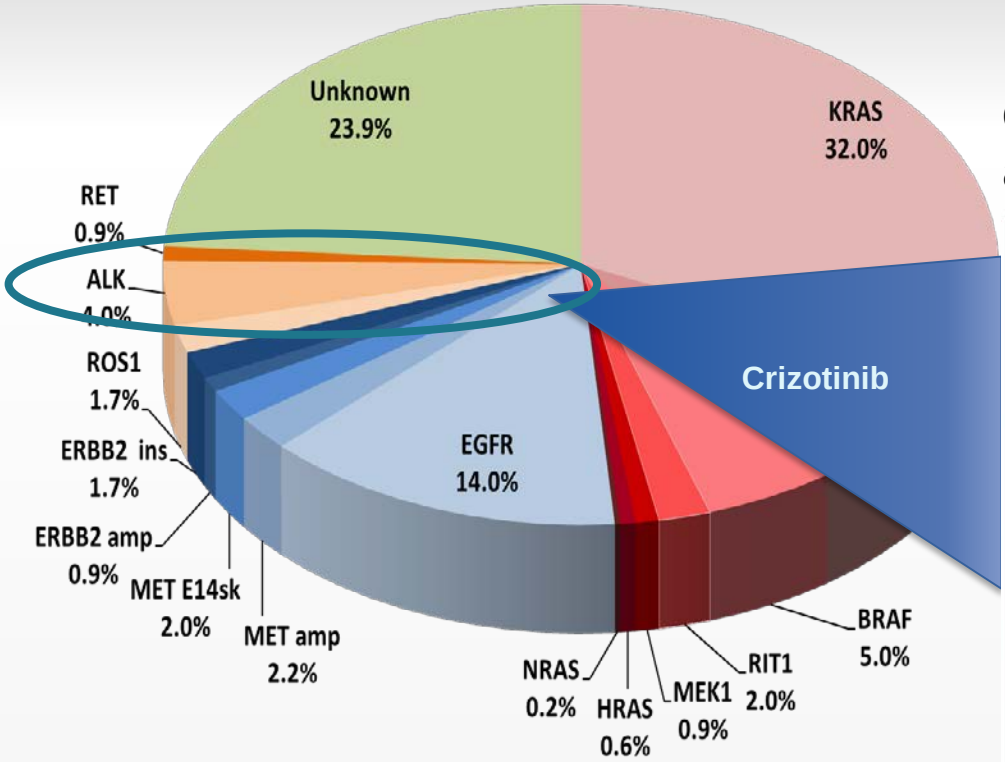
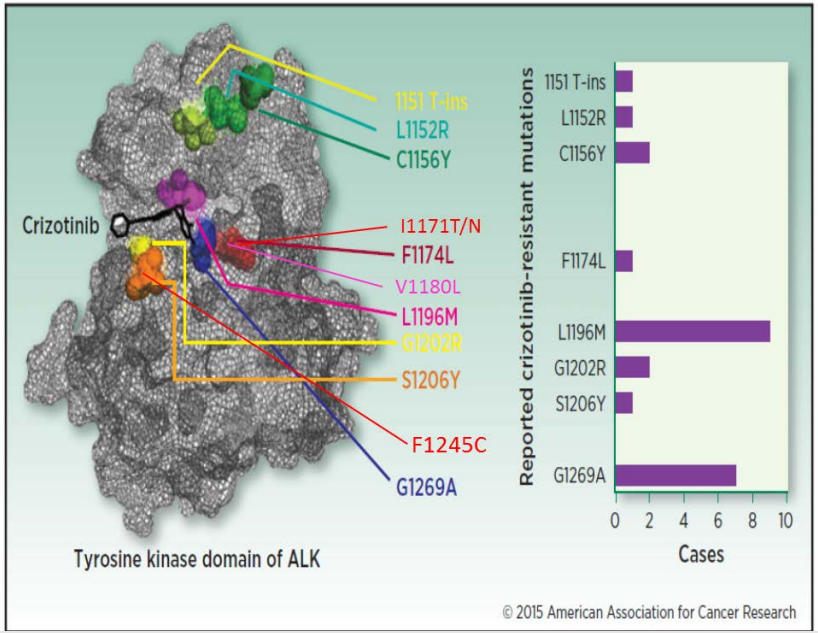
Courtesy Suresh Ramalingam MD, Emory University

Lung Adenocarcinoma: Acquired Resistance



Resistance to crizotinib characterized by ALK-dependent and independent mechanisms



Next-gen ALK Inhibitors in

- Ceritinib FDA and EMEA approved based on ASCEND-1, ASCENT 2
- Alectinib, FDA approval Dec. 2015

	Ceritinib[1] ASCEND-1	Ceritinib[2] ASCEND-2	Alectinib[3] NP28673	Alectinib[4] NP28761	Brigatinib[5] AP26113	Lorlatinib[6] PF-064639224
Phase	1	2	1-2		1-2	1-2
Number of pts	163	140	138	87	70	34
ORR (%)	**56**	**54**	**50**	**48**	**71**	**44**
DCR (%)	74	77	79	-	-	nr
Median PFS (mo)	6.9	5.7	8.9	6.3	13.4	nr
CNS activity	-	Yes (45%)	Yes (43%)	**Yes!** (69%)	Yes (53%)	Yes (36%)
Ethnicity	Global	Global	Global	USA	US/Spain	-

[1] Felip ESMO 2014* [2]Mok, ASCO 2015; [3]Seto ASCO 2015 ; [4] Ghandi, ASCO 20152; [5] Camidge , ASCO 2015; [6] Shaw, ASCO 2015

ALK kinase domain mutations – drug efficacy

Sensitive to alectinib, resistant to ceritinib

Sensitive to ceritinib, resistant to alectinib

Resistant to 2nd gen inhibitors, Sensitive to lorlatinib

	1st gen	2nd gen			3rd gen
	Crizotinib	Alectinib	Brigatinib	Ceritinib	Lorlatinib
G1123S	Res	Sens[2]	N/D	Res[2]	N/D
1151Tins	Res	Res[3]	N/D	Res[7]	Sens[9]
L1152P/R	Res	Sens	N/D	Res[7]	Sens[9]
C1156Y/T	Res	Sens	N/D	Res[7]	Sens[9]
I1171T/N	Res	Res[4,5]	N/D	Sens[4,5,7]	N/D
F1174C/L/V	Res	Sens	Sens[6]	Res[7]	Sens[9]
V1180L	Res	Res [4]	N/D	Sens[4]	N/D
L1196M	Res	Sens[3]	Sens[6]	Sens[7]	Sens[9]
L1198F	Sens [1]	Res[1]	Res[1]	Res[1]	Res[1]
G1202R	Res	Res[3]	N/D	Res[7]	Sens[9]
S1206C/Y	Res	Sens[3]	Res[6]	Sens[7]	Sens[9]
F1245C	Res[8]	N/D	N/D	Sens[8]	N/D
G1269A/S	Res	Sens	N/D	Sens[7]	Sens[9]

REFERENCES

1. Shaw NEJM 2016
2. Toyokawa JTO 2015
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10. Bayliss Cel Mol Lif Sci 2015

Data compiled Dr. Christine Lovly

ALK fusion case example showing emergence of sequential resistance mutations

Initial diagnosis

- *ALK* fusion detected in tissue
  → Crizotinib

Durable response,
But patient is progressing

Courtesy Collin Blakely MD, UCSF

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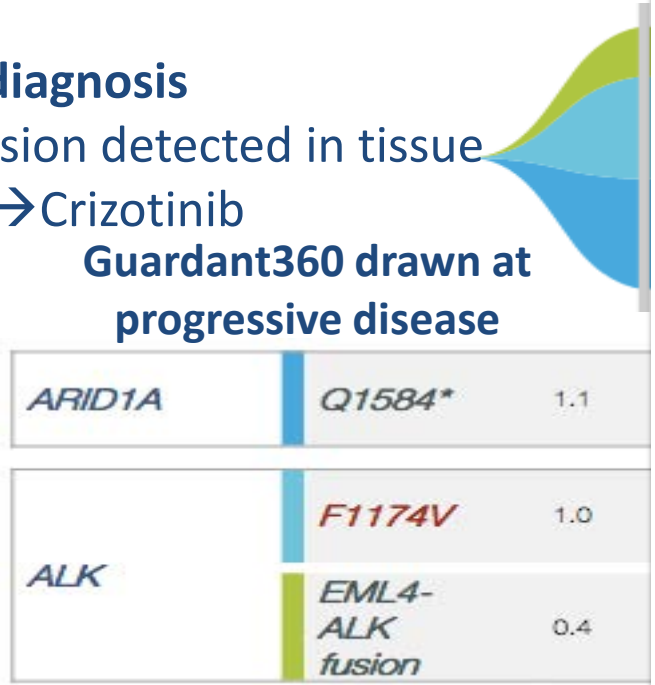
Guardant360 drawn at progressive disease



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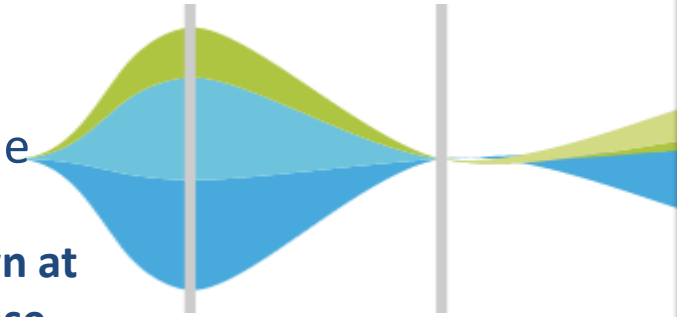

ARID1A	*Q1584**	1.1
ALK	*F1174V*	1.0
	EML4-ALK fusion	0.4

crizotinib, ceritinib resistance

Switched to alectinib with response

Courtesy Collin Blakely MD, UCSF

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crizotinib, certinib resistance

Switched to alectinib with initial response, then progressive disease

Guardant360 again drawn at progressive disease

ALK	*G1202R*
	EML4-ALK fusion
	F1174V

Courtesy Collin Blakely MD, UCSF

GUARDANT HEALTH

ALK kinase domain mutations – drug efficacy

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crizotinib, certinib resistance

Switched to alectinib with initial response, then progressive disease

Guardant360 again drawn at progressive disease

ALK	*G1202R*	
	EML4-ALK fusion	
	F1174V	

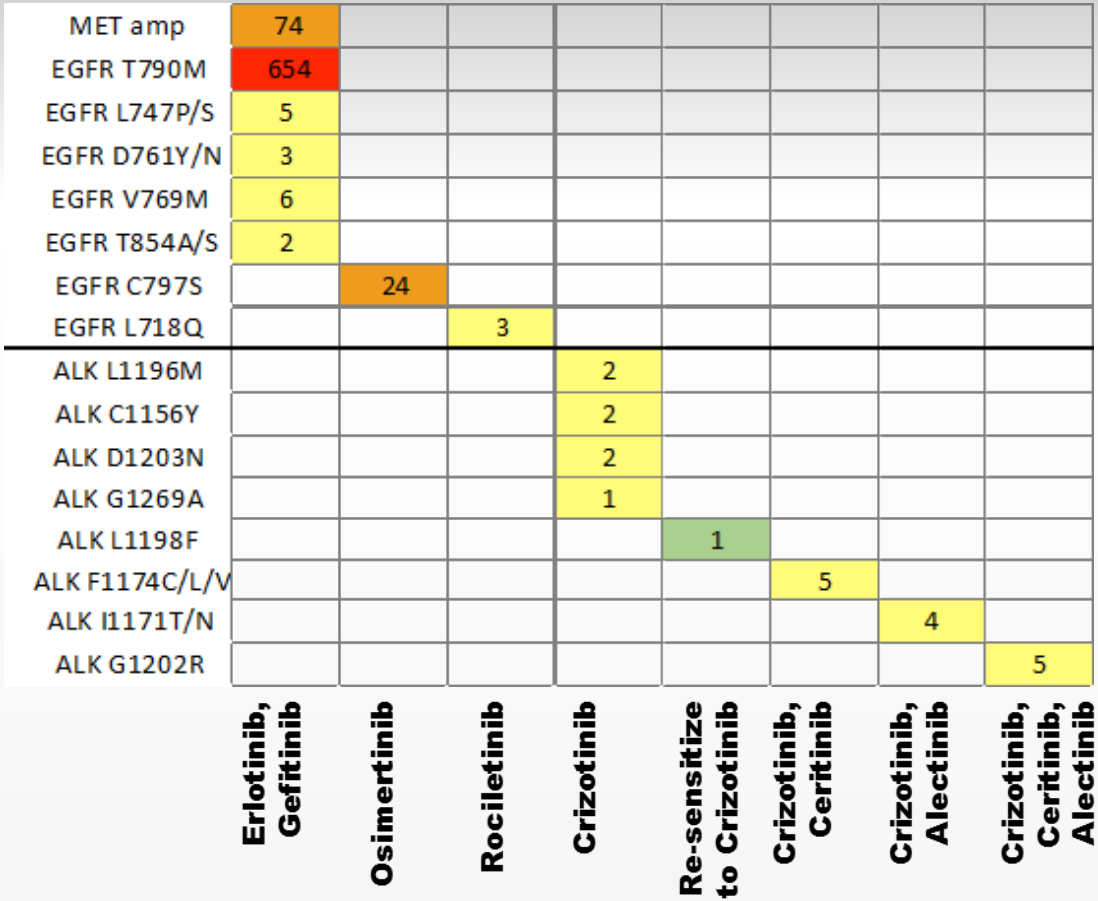
crizotinib, ceritinib, alectinib resistance

Candidate for Lorlatinib Clinical Trial

Courtesy Collin Blakely MD, UCSF

GUARDANT HEALTH

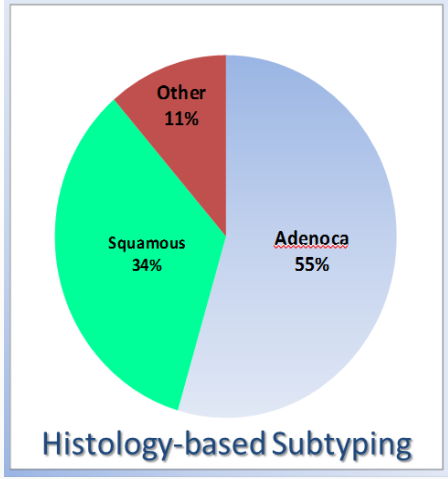
Actionable Resistance Mutations Observed in Guardant 360 ctDNA



40% of *ALK* fusion cases and 50% of *EGFR* cases had one of these potentially actionable resistance targets at progression

Philip C. Mack, PhD, UC Davis Comprehensive Cancer Center and California Northstate University

NSCLC Subtyping in the era of Immune Oncology



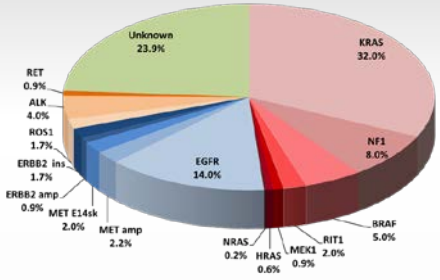
Low Mutation Burden

Usually Never/light Smokers

Often have oncogenic driver

Typically non-squamous

Often poorly responsive to immune therapies



High Mutation Burden

Usually Smokers

Actionable driver oncogenes uncommon

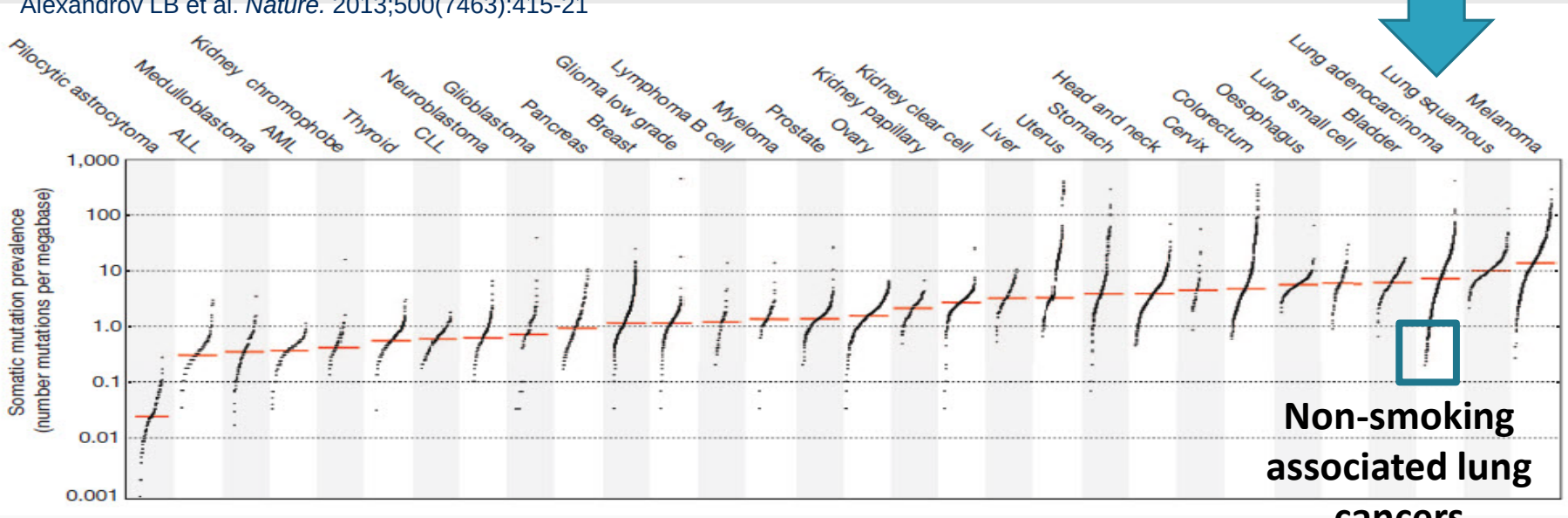
Often responsive to immune therapies

Philip C. Mack, PhD, UC Davis Comprehensive Cancer Center and California Northstate University

Mutational Burden

NSCLC Adeno

Alexandrov LB et al. *Nature.* 2013;500(7463):415-21

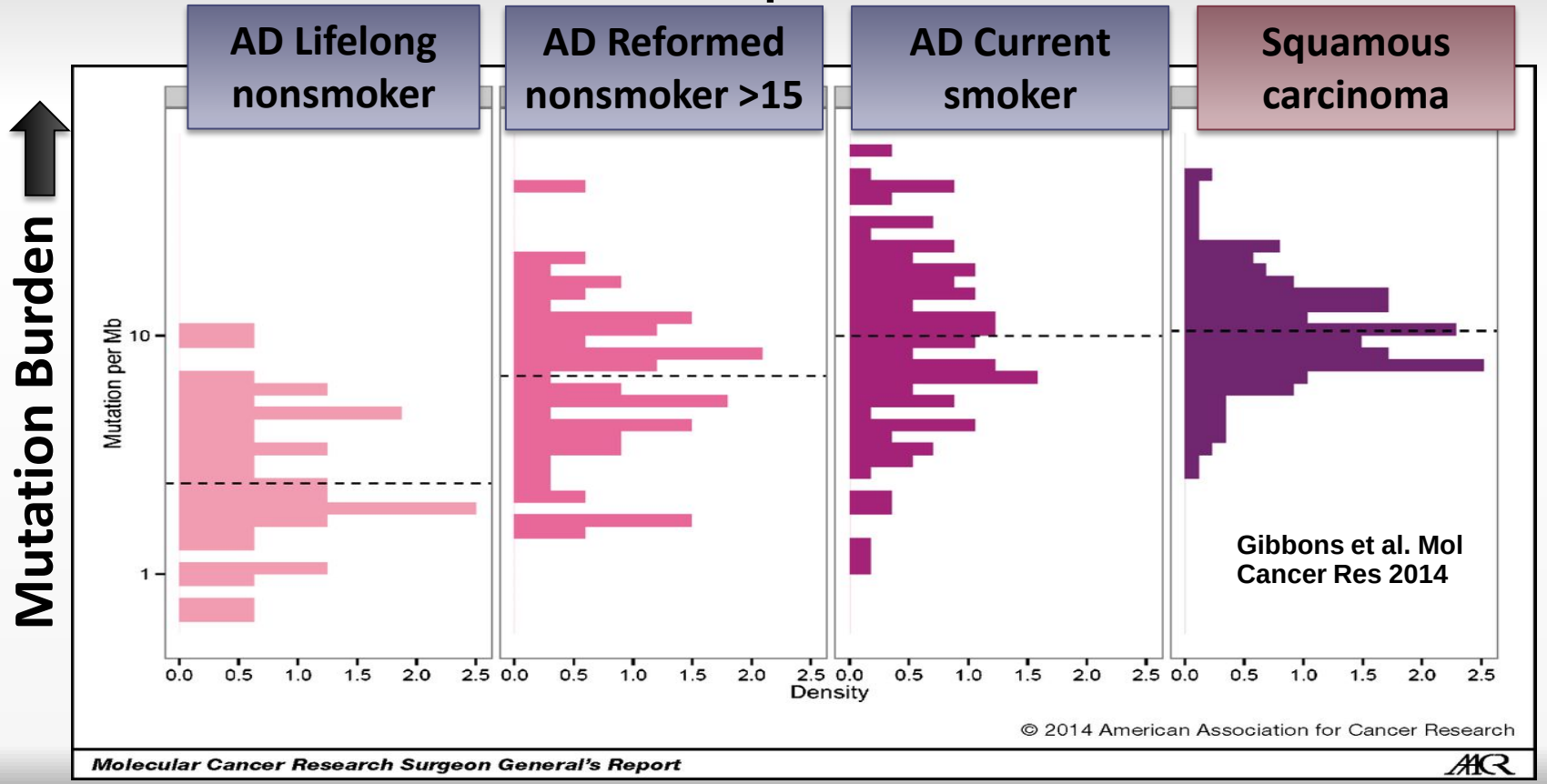


Targetable oncogene-driven tumors (EGFR, ALK, ROS etc) are:

1. typically genomically simple (relatively speaking)

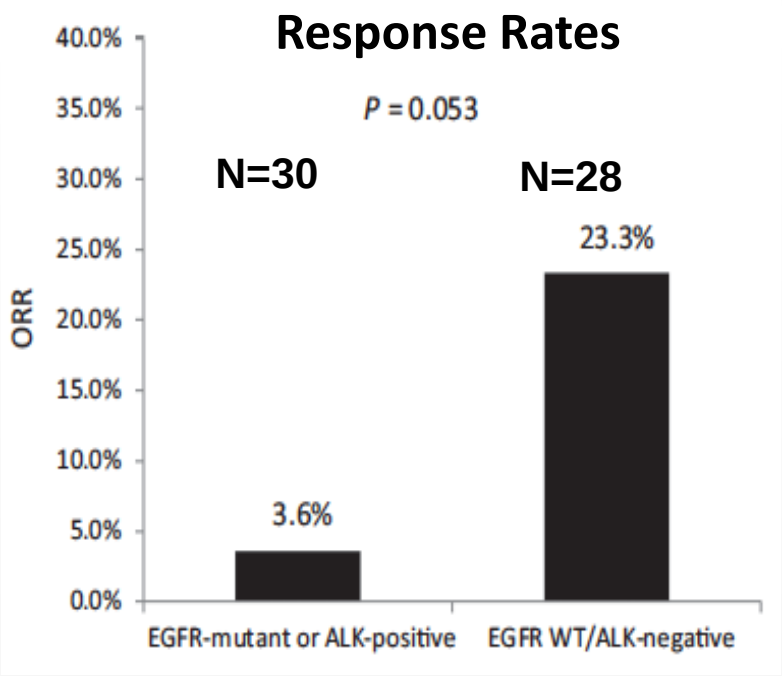
2. dependent on a single altered signal transduction factor

Genome-wide Mutation Density from the TCGA datasets for lung adenocarcinoma and squamous cell carcinoma.

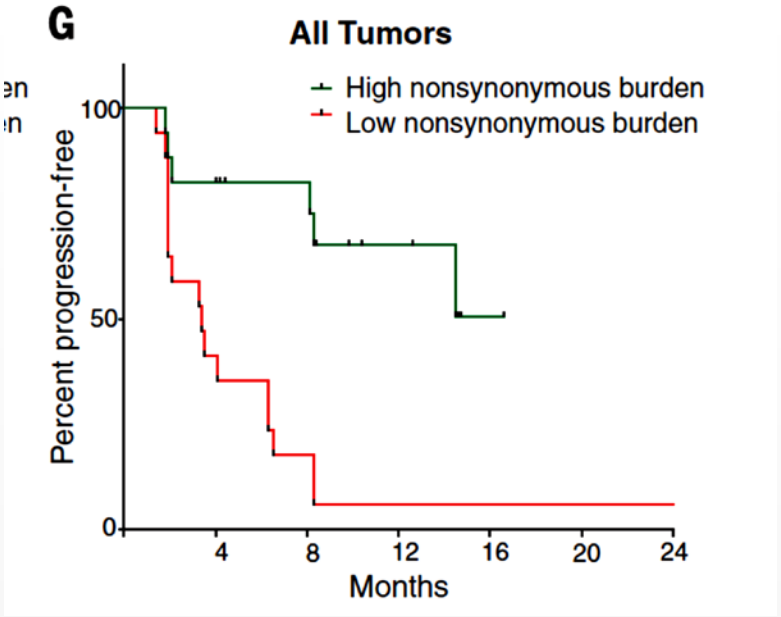


Philip C. Mack, PhD, UC Davis Comprehensive Cancer Center and California Northstate University

EGFR and ALK-positive NSCLC are less responsive to immune therapies



Gainor (Mino-Kenudson) et al. 2017 *Clinical Cancer Research*



Rizvi et al. Science 2015;348:124-8.

Conclusions

Mutations detected in plasma have a synonymous frequency and distribution as reported in tissue

This applies to truncal mutations present in all lineages of the tumor

Liquid biopsies are capable of identifying and tracking actionable emergent resistance mutations

IO drugs are generally more effective in NSCLC with high TMB. Biomarker-driven adenocarcinoma (EGFR, ALK, ROS1 etc) are typically low TMB and are best treated with targeted therapies

Philip C. Mack, PhD, UC Davis Comprehensive Cancer Center and California Northstate University

Plasma Analysis Considerations

For treatment-naïve patients, tissue is the standard and is required for complete diagnosis

Plasma can complement tissue

Serve as a baseline for future draws

For validated plasma analysis, a positive result is actionable but a negative result should be considered **inconclusive**

Unknown if true negative or insufficient shed DNA

At progression, consider a “plasma-first” option for patients if applicable

Philip C. Mack, PhD, UC Davis Comprehensive Cancer Center and California Northstate University

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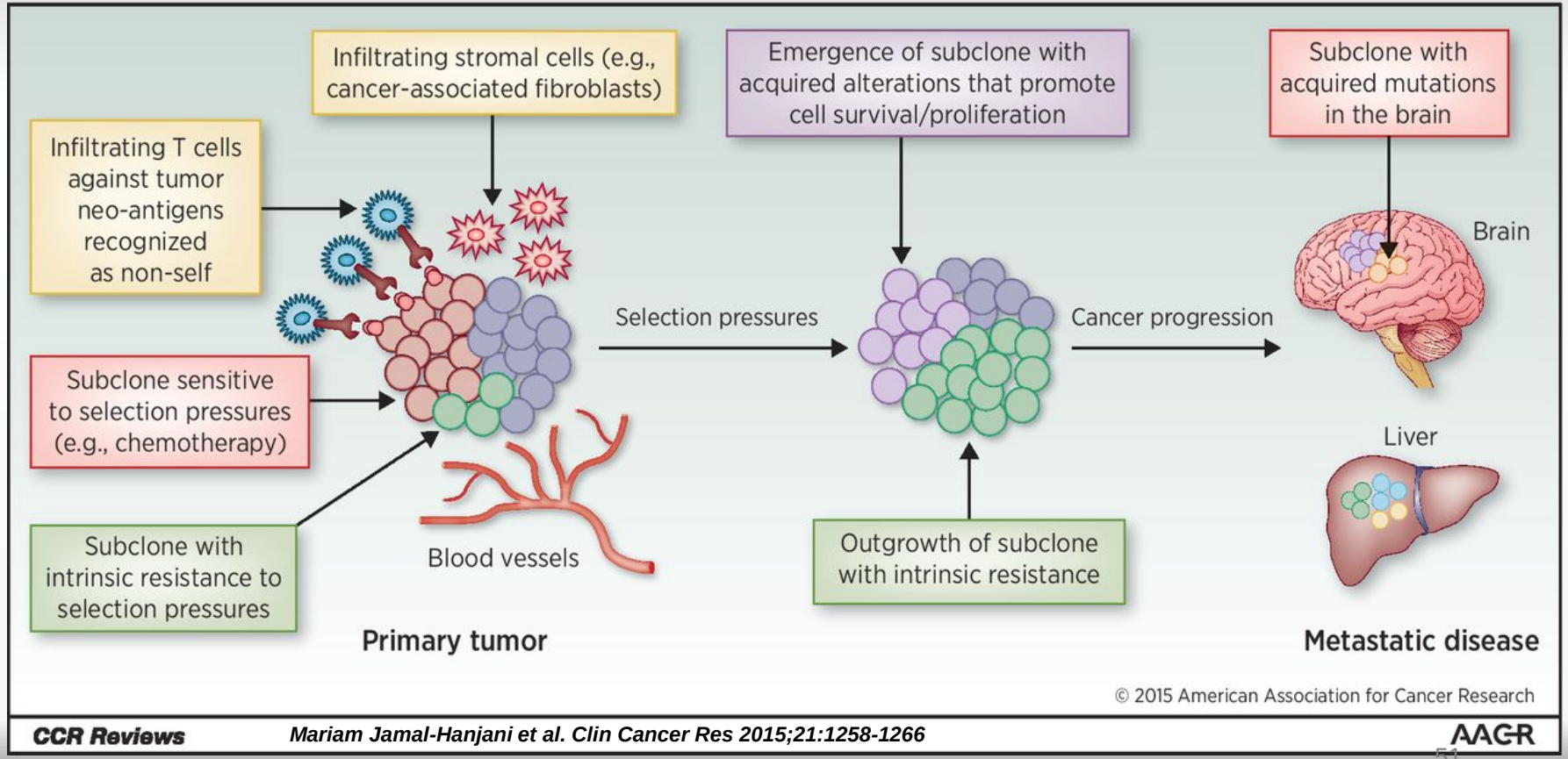
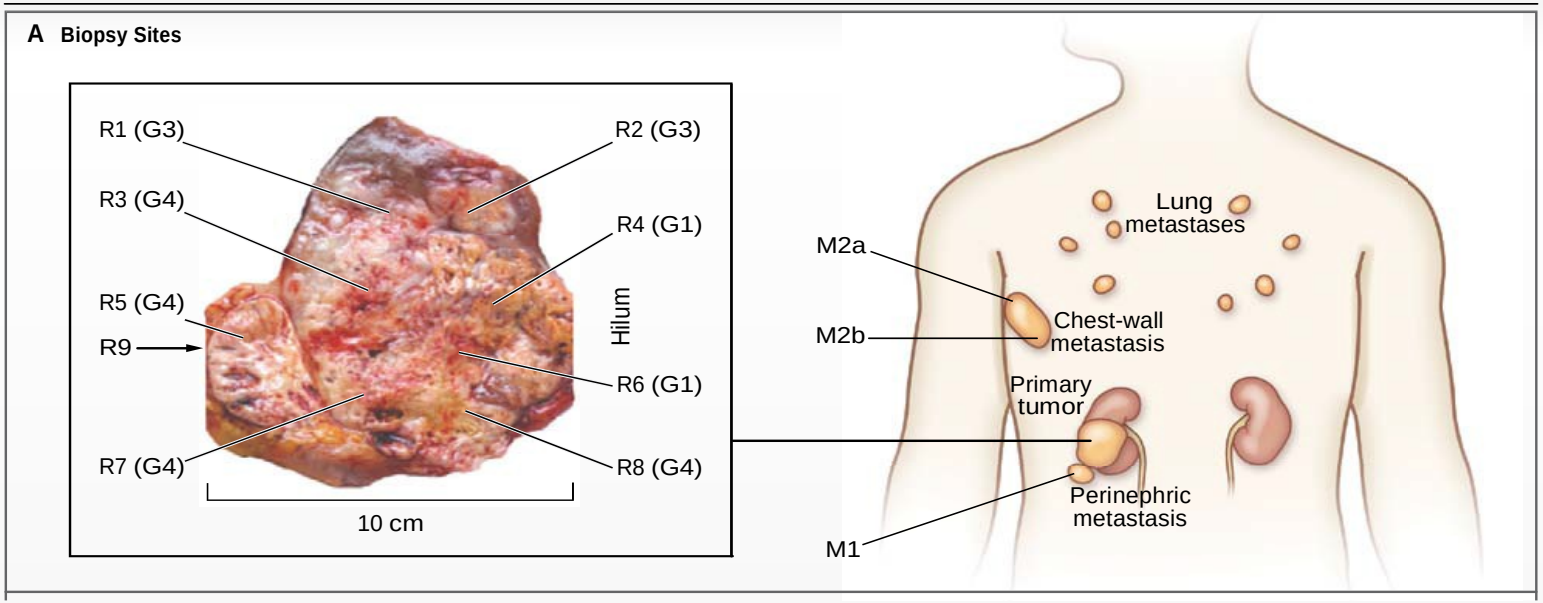
Intratumor Heterogeneity (ITH) and Clonal Evolution



CCR Reviews *Mariam Jamal-Hanjani et al. Clin Cancer Res 2015;21:1258-1266* AACR

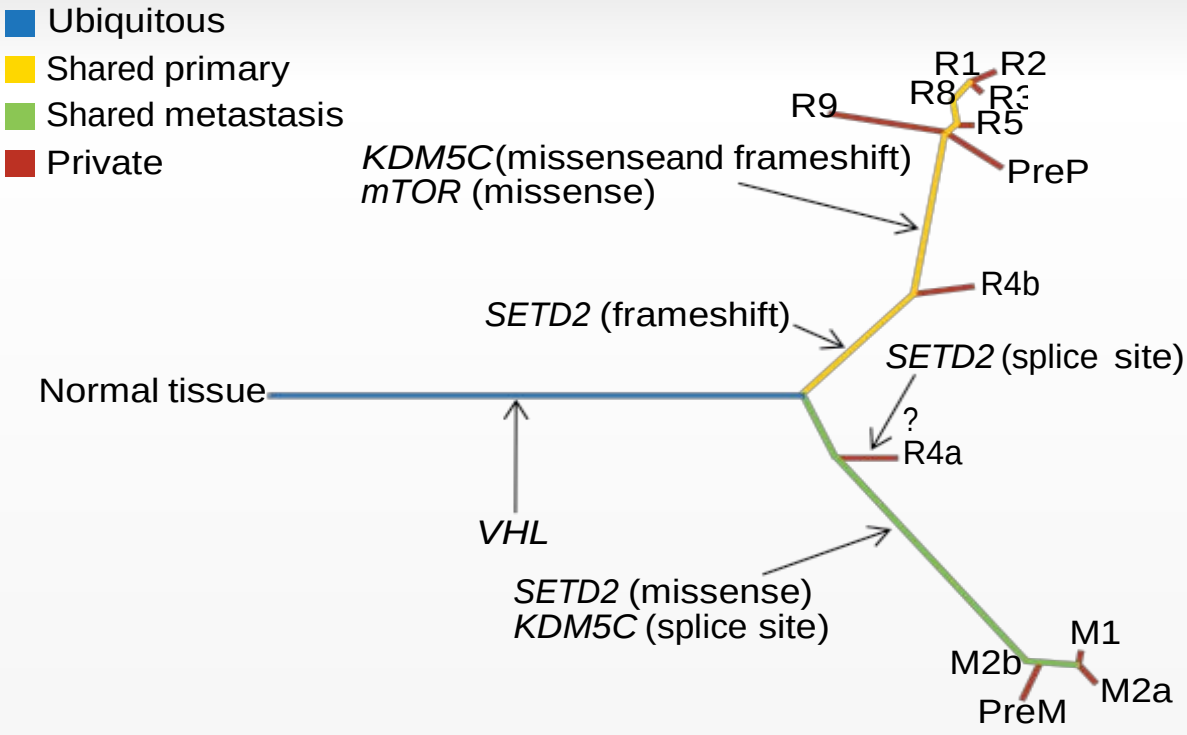
Massively Parallel Sequencing to Document Tumor Evolution



Researchers acquired biopsies from different regions of the tumor and from metastatic lesions

Gerlinger et al, NEJM 366:883, 2012

Phylogenetic Relationships of Tumor Regions



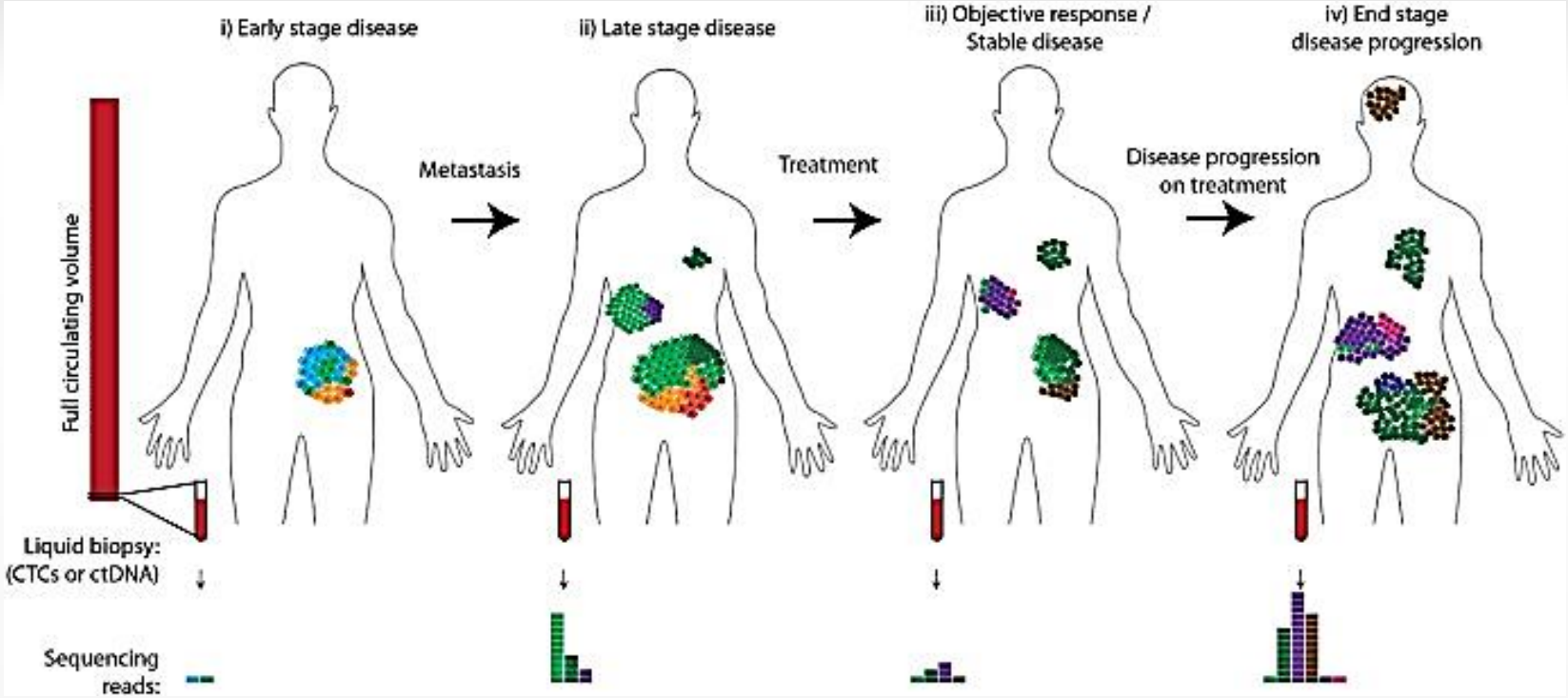
Truncal mutation: VHL

Branch mutations: SETD2 and KDM5C

Note different mechanisms to acquire the same mutation (convergent evolution)

Gerlinger et al, NEJM 366:883, 2012

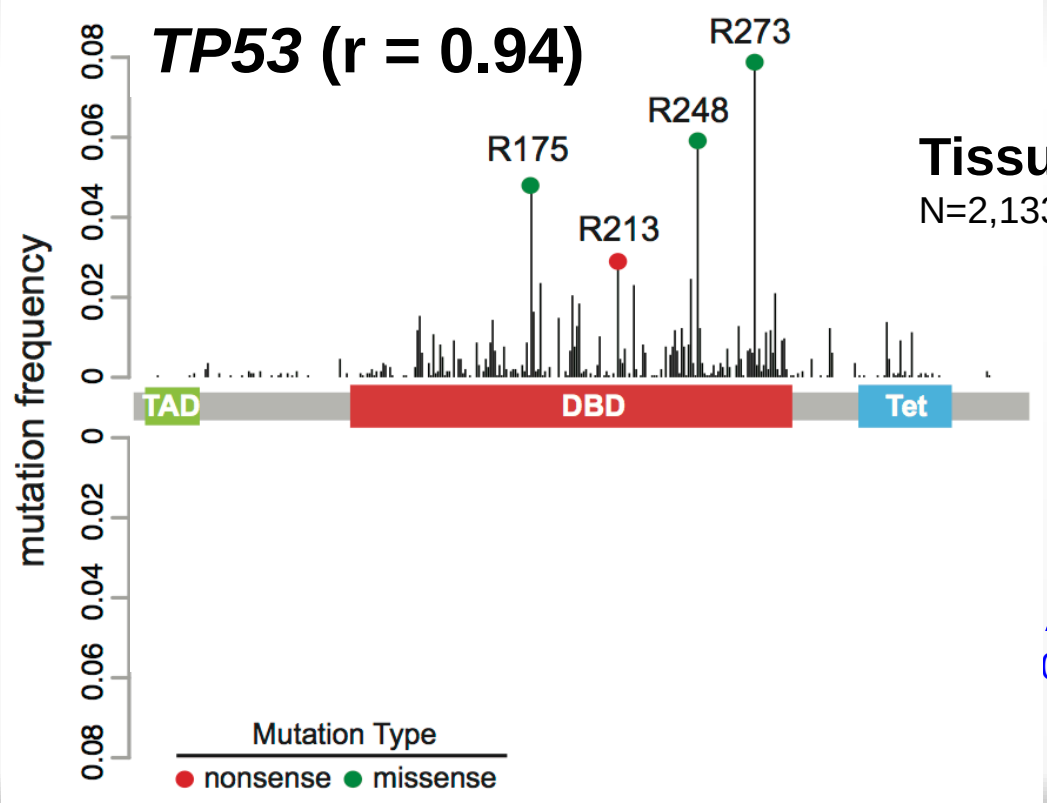
Clonal Evolution – Role of Liquid Biopsy



R. Burrell and C. Swanton, Molecular Oncology, Volume 8, 2014, 1095 - 1111

Guardant Database (15,000 cases, reported at ASCO 2016)

Over 5,000 from NSCLC



TCGA and ctDNA have synonymous TP53 mutation patterns…

…including "hot-spot" Gain-of-Function (GOF) mutations

Lorlatinib potently inhibits ALK resistance mutations, including ALK G1202R.

Cellular ALK phosphorylation mean IC_{50} (nmol/L)

Mutation status	Crizotinib	Ceritinib	Alectinib	Brigatinib	Lorlatinib
Parental Ba/F3	763.9	885.7	890.1	2774.0	11293.8
EML4–ALK V1	38.6	4.9	11.4	10.7	2.3
EML4–ALK C1156Y	61.9	5.3	11.6	4.5	4.6
EML4–ALK I1171N	130.1	8.2	397.7	26.1	49.0
EML4–ALK I1171S	94.1	3.8	177.0	17.8	30.4
EML4–ALK I1171T	51.4	1.7	33.6[a]	6.1	11.5
EML4–ALK F1174C	115.0	38.0[a]	27.0	18.0	8.0
EML4–ALK L1196M	339.0	9.3	117.6	26.5	34.0
EML4–ALK L1198F	0.4	196.2	42.3	13.9	14.8
EML4–ALK G1202R	381.6	124.4	706.6	129.5	49.9
EML4–ALK G1202del	58.4	50.1	58.8	95.8	5.2
EML4–ALK D1203N	116.3	35.3	27.9	34.6	11.1
EML4–ALK E1210K	42.8	5.8	31.6	24.0	1.7
EML4–ALK G1269A	117.0	0.4	25.0	ND	10.0
EML4–ALK D1203N+F1174C	338.8	237.8	75.1	123.4	69.8
EML4–ALK D1203N+E1210K	153.0	97.8	82.8	136.0	26.6

$IC_{50} \leq 50$ nmol/L

$IC_{50} > 50 < 200$ nmol/L

$IC_{50} \geq 200$ nmol/L

Lorlatinib is effective against G1202R

Evidence that it is effective in the clinic

Justin F. Gainor et al. Cancer Discov 2016;6:1118-1133