University of California
San Francisco

Oncogene-Driven NSCLC

Master Lecture Series: Evolving Treatment Options in Lung Cancer

Matthew Gubens, MD, MS
Associate Professor, Thoracic Oncology
Chair, UCSF Thoracic Oncology Site Committee

January 13, 2018

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Oncogene-Driven NSCLC *(except EGFR)*

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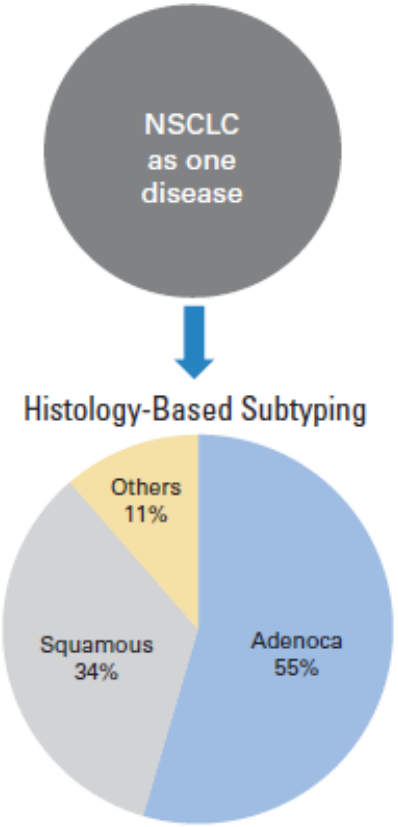
Disclosures

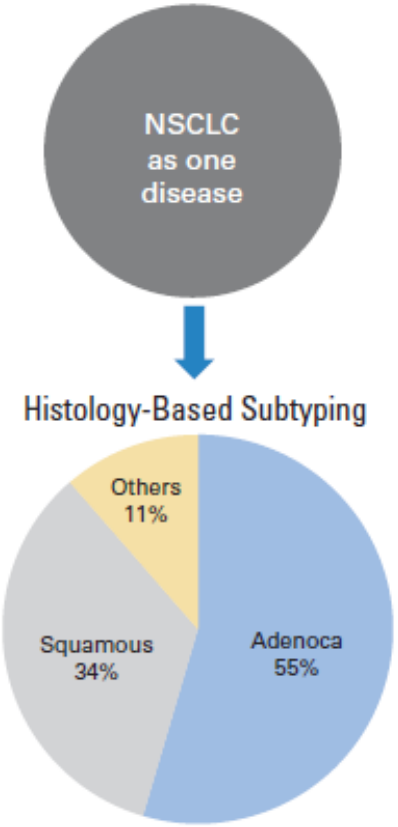
- Consulting
  - AstraZeneca, Bristol-Myers Squibb, Genentech/Roche, Mersana, Novartis
- Research Funding (to institution)
  - Celgene, Merck, Novartis, OncoMed, Roche

- I will discussing non-FDA approved treatment/ indications during my presentation today (research findings)

Li, JCO, 2013


NSCLC as one disease
Histology-Based Subtyping
Others 11%
Squamous 34%
Adenoca 55%

Li, JCO 2013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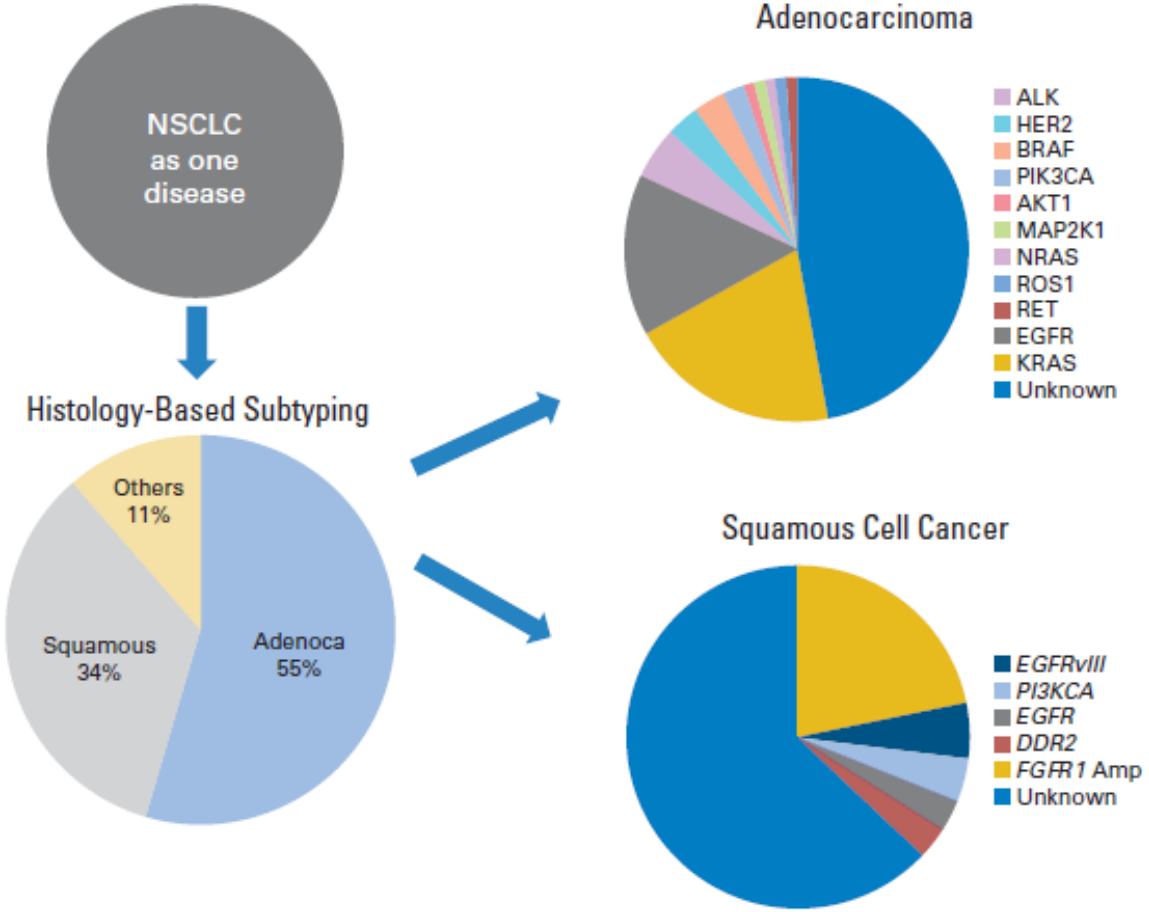
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Adenocarcinoma
ALK
HER2
BRAF
PIK3CA
AKT1
MAP2K1
NRAS
ROS1
RET
EGFR
KRAS
Unknown
Squamous Cell Cancer
EGFRvIII
PI3KCA
EGFR
DDR2
FGFR1 Amp
Unknown

Li, JCO, 2013.

Targeted therapies for oncogene-driven NSCLC

- 2nd+ generation approaches in ALK
- 1st generation approaches in “emerging” alterations

Targeted therapies for oncogene-driven NSCLC

- 2nd+ generation approaches in ALK
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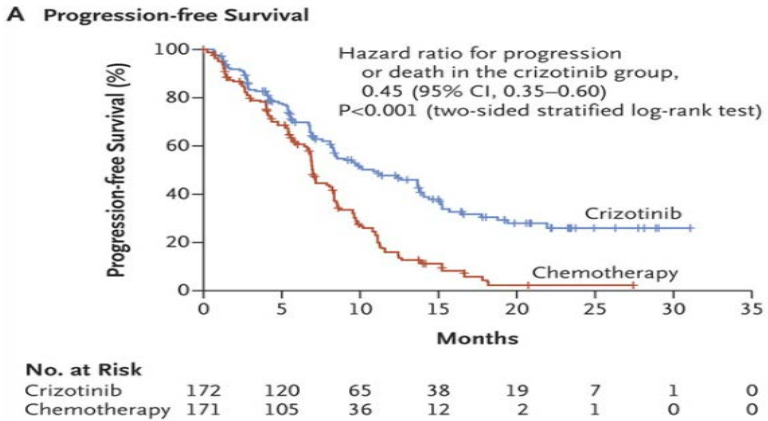
ALK rearrangements

- 2007 detected as an alteration in NSCLC
- 2011 crizotinib approved
  - Single-arm ORR 50, 61%
  - Vs docetaxel in the 2nd line
    - PFS 7.7 vs 3.0 mos
  - Vs platinum combo in the 1st line
    - PFS 10.9 vs 7.0 mos



Solomon, NEJM 2014

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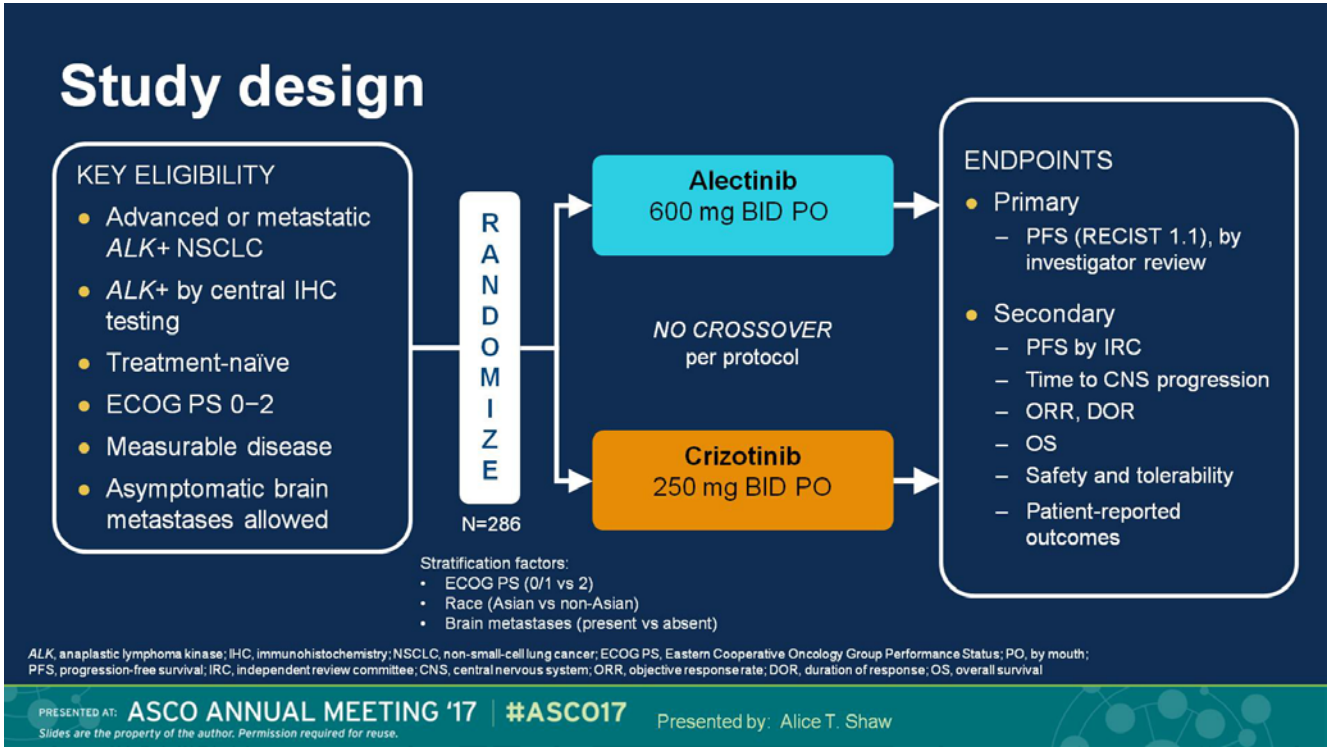
ALK rearrangements

- …but resistance inevitably develops.
- Why?
  - Crizotinib good, not great as an ALK inhibitor
  - Poor brain penetration
  - Resistance mutations develop, eg G1202R
- 2nd generation ALK inhibitors– better ALK activity, better CNS activity
  - Ceritinib approved 2014 (duration 7.1 mos post-crizotinib)
  - Alectinib approved 2015 (duration 7.5 mos post-crizotinib)

ALK– Moving 2nd generation to 1st line?

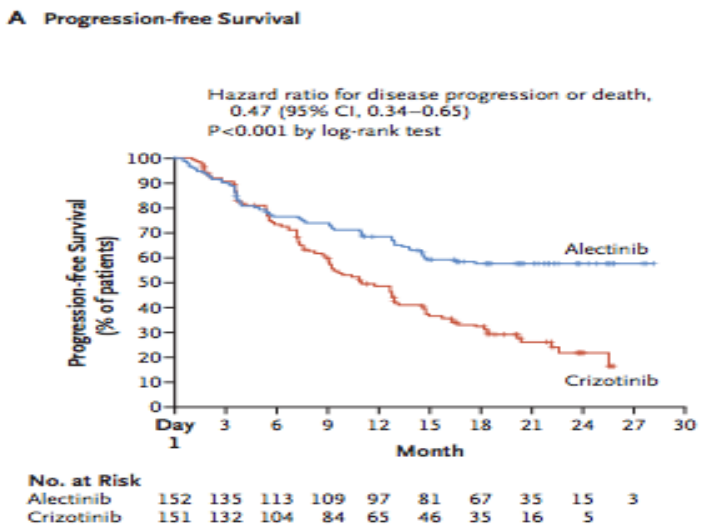
- ALEX trial

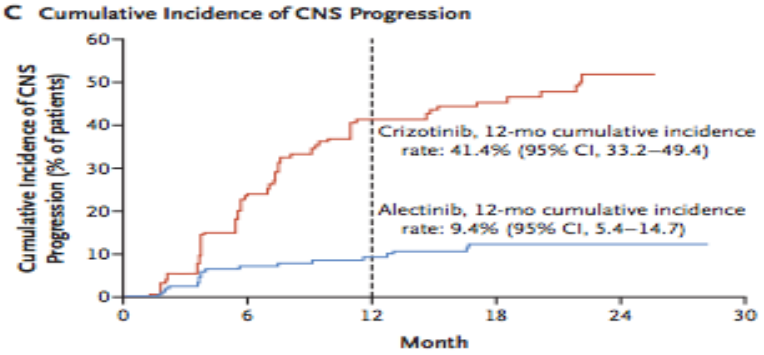


Shaw, ASCO 2017.

ALK– Moving 2nd generation to 1st line?

- ALEX (ASCO 2017, NEJM 2017), alectinib vs crizotinib
  - RR 83 vs 76%





OS immature: HR 0.76, p=0.24

FDA approved 11/17

Peters, NEJM 2017

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ALK take-home points

- Biopsy at the beginning to determine the driver mutation/rearrangement
- For ALK, 1st line SOC is alectinib
- Cancers evolve…
- Consider biopsy at progression to determine next drug?
  - Or empiric: Lorlatinib 31% after 3 prior TKIs

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

Gainor, Cancer Discovery, 2016

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Targeted therapies for oncogene-driven NSCLC

- 2nd+ generation approaches in ALK
- 1st generation approaches in “emerging” targets

FDA-approved oncogene-targeted agents in NSCLC

- EGFR
  - Erlotinib approved 2009
  - Afatinib approved 2013
  - Gefitinib approved 2015
    - Osimertinib approved 2015
- ALK
  - Crizotinib approved 2011
    - Ceritinib approved 2014
    - Alectinib approved 2015
    - Brigatinib approved 2017
- ROS1
  - Crizotinib approved 2016
- BRAF
  - Dabrafenib/trametinib approved 2017

ROS1 crizotinib
- PROFILE 1001, n=53
- ORR 70%
- mPFS 19.3mo
- Stay tuned:
  - Ceritinib (NCCN listed)
  - Entrectinib

BRAF dabrafenib/trametinib
- 1st line data, n=36
- ORR 64%
- mPFS 14.6mo

Shaw A, Ann Onc 2016. Planchard D Lancet Onc 2017.

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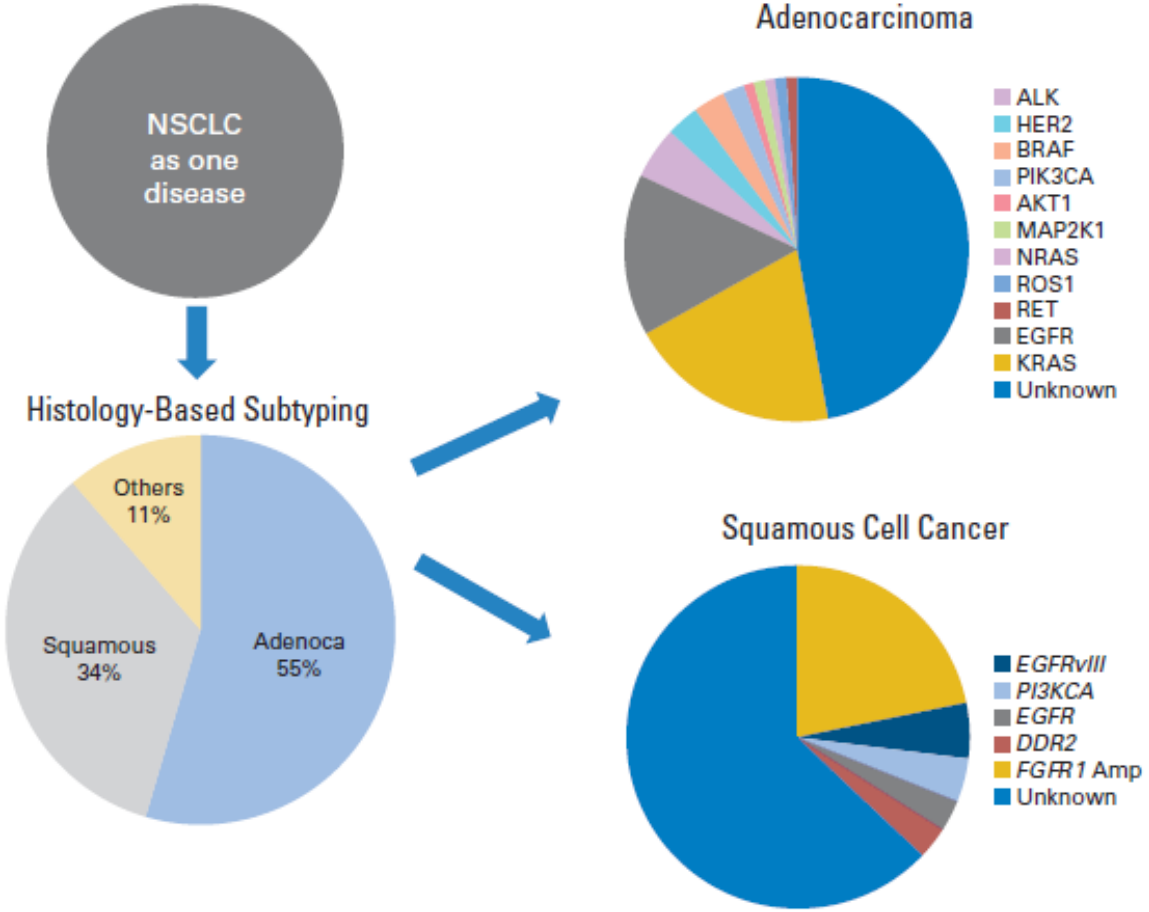
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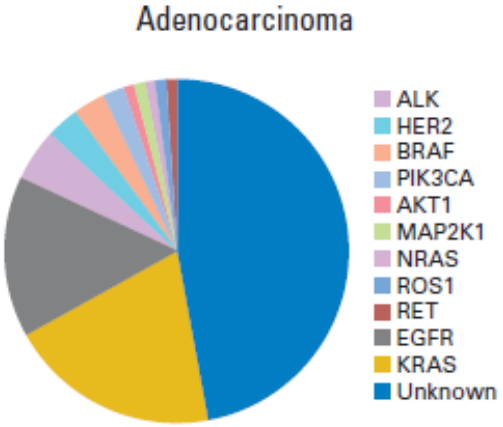
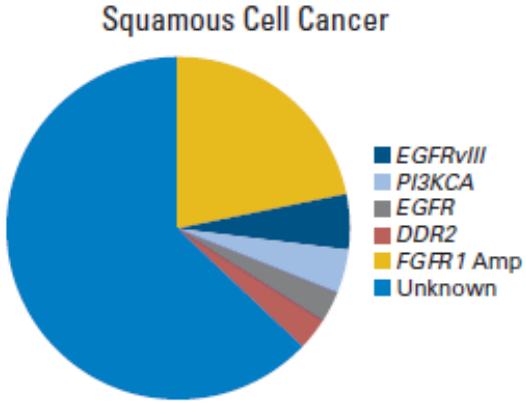
Li, JCO, 2013.





Li, JCO 2013.

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Emerging targets

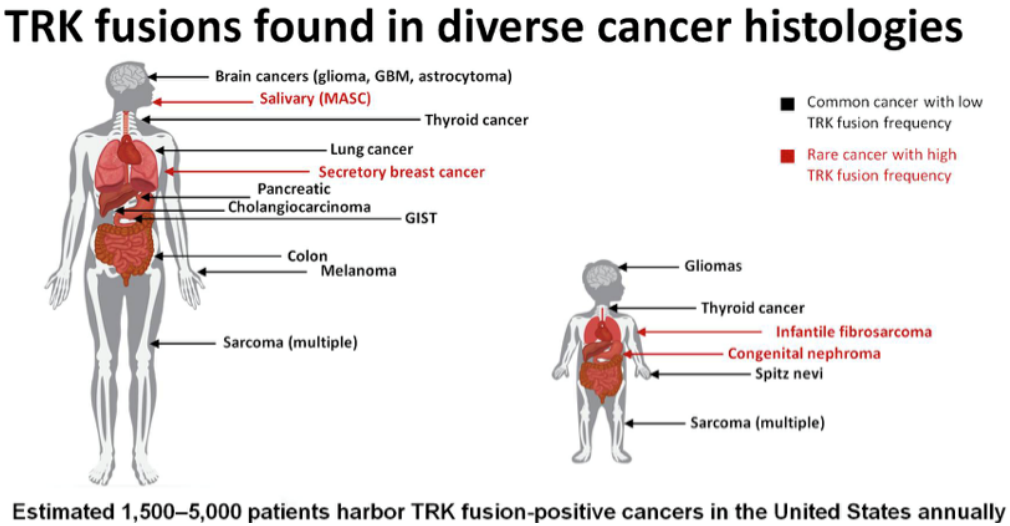
- MET exon 14 skipping mutation
  - Often older patients, current/former smokers, sarcomatoid pathology
  - 3-4% of NSCLC
    - Crizotinib ORR 44%, PFS not yet reached (ASCO 2016)

- RET rearrangement
    - Vandetanib ORR 53% (ASCO 2016)
    - Cabozantinib ORR 38% (ASCO 2016)

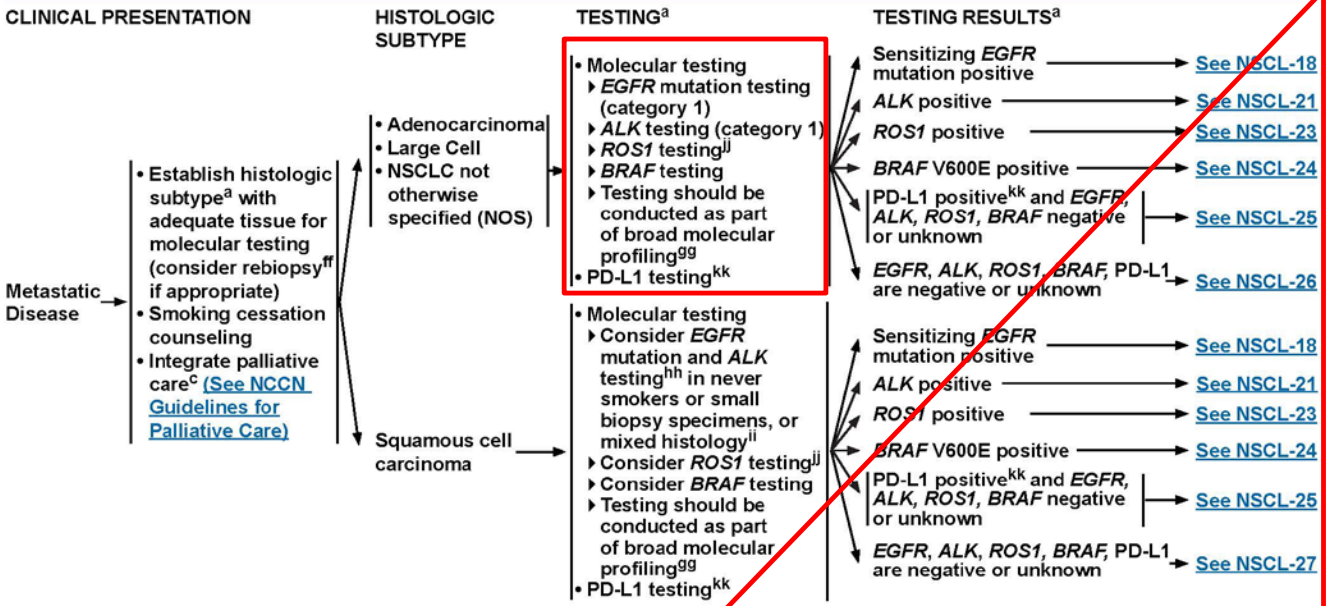
- HER2 mutation
    - T-DM1 ORR 33% (ASCO 2017)

Emerging targets

- TRK fusions
  - Larotrectinib
    - N=55
    - 4 lung
  - RR 76%
  - mDOR NR



Hyman DM, ASCO Proc 2017.



[a] See Principles of Pathologic Review (NSCL-A).

[c] Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med 2010;363:733-742.

[ff] If repeat biopsy is not feasible, plasma biopsy should be considered.

[gg] The NCCN NSCLC Guidelines Panel strongly advises broader molecular profiling with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials. Broad molecular profiling is a key component of the improvement of care of patients with NSCLC. See Emerging Targeted Agents for Patients With Genetic Alterations (NSCL-H).

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[ii] Paik PK, Varghese AM, Sima CS, et al. Response to erlotinib in patients with *EGFR* mutant advanced non-small cell lung cancers with a squamous or squamous-like component. Mol Cancer Ther 2012;11:2535-2540.

[jj] Shaw AT, Ou S-HI, Bang Y-J, et al. Crizotinib in ROS1-rearranged non-small cell lung cancer. N Engl J Med 2014;371:1963-1971.

[kk] PD-L1 expression levels of ≥50% are a positive test result for first-line pembrolizumab therapy.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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EMERGING TARGETED AGENTS FOR PATIENTS WITH GENETIC ALTERATIONS

Genetic Alteration (ie, Driver event)	Available Targeted Agents with Activity Against Driver Event in Lung Cancer
High-level *MET* amplification or MET exon 14 skipping mutation	crizotinib[1-5]
RET rearrangements	cabozantinib[6,7] vandetanib[8]
HER2 mutations	trastuzumab[9] (category 2B) afatinib[10] (category 2B)

[1]Ou SH, Kwak EL, Siwak-Tapp C, et al. Activity of crizotinib (PF02341066), a dual mesenchymal-epithelial transition (MET) and anaplastic lymphoma kinase (ALK) inhibitor, in a non-small cell lung cancer patient with de novo MET amplification. J Thorac Oncol 2011;6:942-946.
[2]Camidge RD, Ou S-HI, Shapiro G, et al. Efficacy and safety of crizotinib in patients with advanced c-MET-amplified non-small cell lung cancer. J Clin Oncol 2014;32(Suppl 5): Abstract 8001.
[3]Frampton GM, Ali SM, Rosenzweig M, et al. Activation of MET via diverse exon 14 splicing alterations occurs in multiple tumor types and confers clinical sensitivity to MET inhibitors. Cancer Discov 2015;5:850-859.
[4]Paik PK, Drilon A, Fan PD, et al. Response to MET inhibitors in patients with stage IV lung adenocarcinomas harboring MET mutations causing exon 14 skipping. Cancer Discov 2015;5:842-849.
[5]Awad MM, Oxnard GR, Jackman DM, et al. MET exon 14 mutations in non-small-cell lung cancer are associated with advanced age and stage-dependent MET genomic amplification and cMET overexpresion. J Clin Oncol 2016;34:721-730.
[6]Drilon A, Wang L, Hasanovic A, et al. Response to cabozantinib in patients with RET fusion-positive lung adenocarcinomas. Cancer Discov 2013; 3:630-635.
[7]Drilon AE, Sima CS, Somwar R, et al. Phase II study of cabozantinib for patients with advanced RET-rearranged lung cancers. J Clin Oncol 2015;33: Abstract 8007.
[8]Lee S-H, Lee J-K, Ahn M-J, et al. A phase II study of vandetanib in patients with non-small cell lung cancer harboring RET rearrangement [abstract]. J Clin Oncol 2016;34: Abstract 9013.
[9]Cappuzzo F, Bemis L, Varella-Garcia M. HER2 mutation and response to trastuzumab therapy in non-small-cell lung cancer. N Engl J Med 2006;354:2619-2621.
[10]Mazieres J, Peters S, Lepage B, et al. Lung cancer that harbors an HER2 mutation: epidemiologic characteristics and therapeutic perspectives. J Clin Oncol 2013;31:1997-2003.

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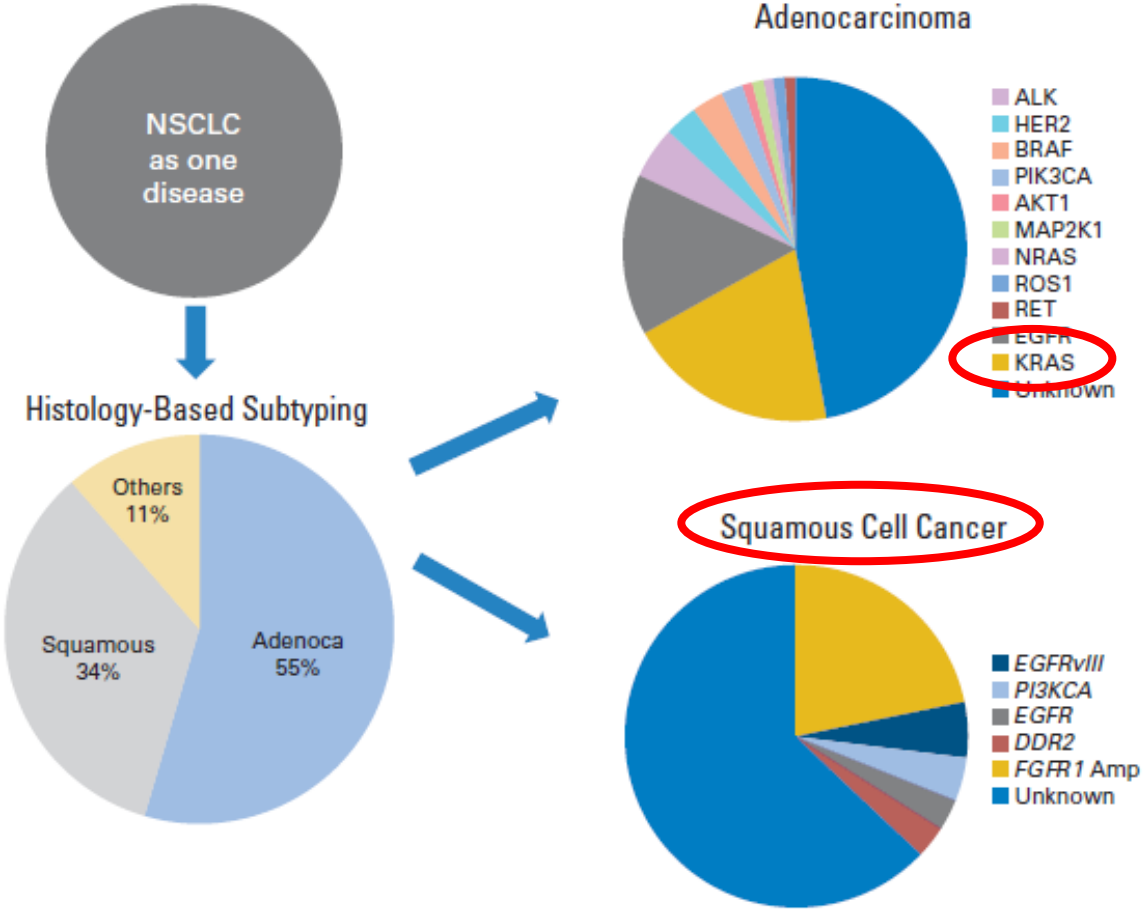

Li, JCO 2013.

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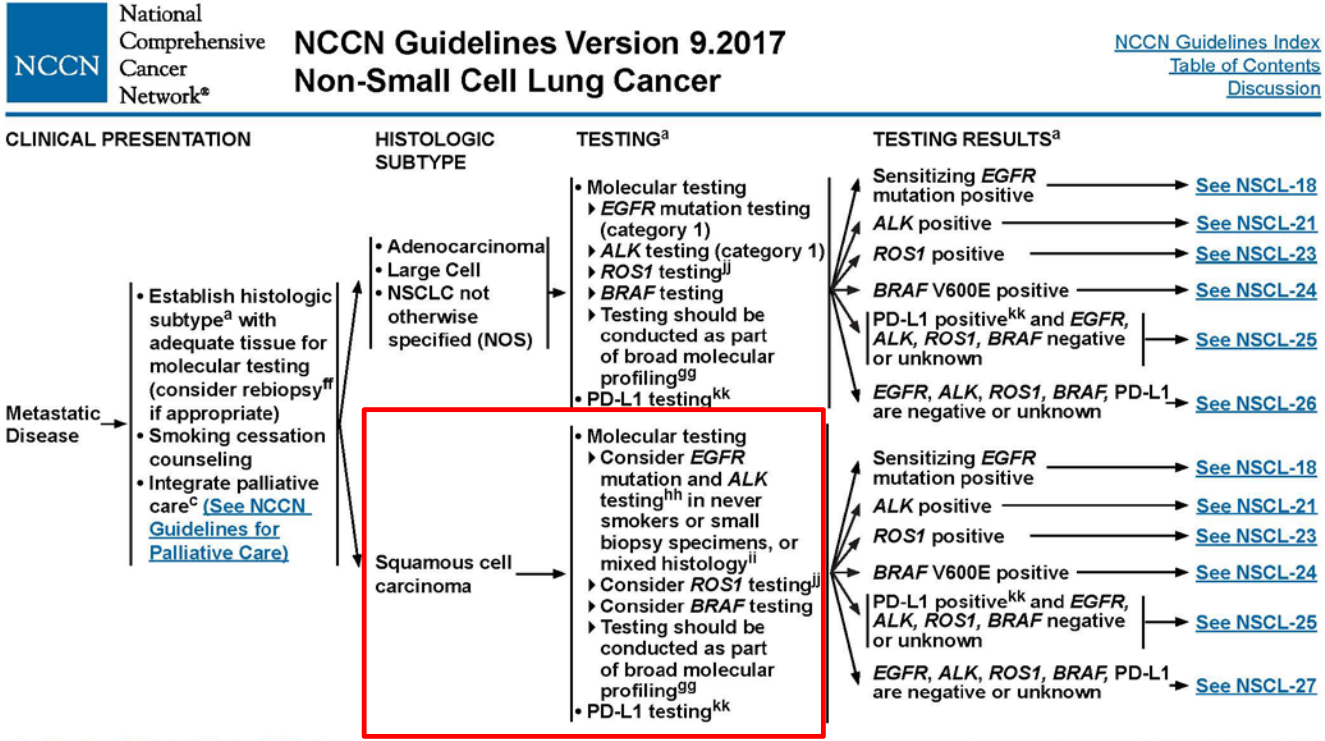

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Squamous cell lung ca

- No standard of care actionable mutations
- Lung-MAP Master Protocol
  - Mutation testing either at dx or progression
  - Start treatment after progression on chemo (+/- immunotherapy)
  - Match to a sub-study based on alteration (eg PI3K, FGFR) or non-match (currently immunotherapy)

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Targeted therapies for oncogene-driven NSCLC

- 2nd+ generation approaches in ALK
  - Alectinib the new standard of care in first line
  - Emerging TKIs (including lorlatinib) to follow, potentially empirically after alectinib
  - But may eventually consider biopsy to determine mechanism of resistance
- 1st generation approaches in “emerging” alterations
  - FDA approvals for ROS1 and BRAF
  - Other targets “on deck,” some with off-label opportunities (NCCN can help)
  - You can’t treat what you haven’t identified
  - Think about testing squamous cell patients, esp non-smokers, scant samples and mixed histology, and/or Lung-MAP
  - Clinical trials!

Thank you!