UCSF
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Oncogene-Driven NSCLC

Master Lecture Series: Evolving Treatment Options in Lung Cancer

Matthew Gubens, MD, MS
Associate Professor, Thoracic Oncology

February 9, 2019

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Oncogene-Driven NSCLC *(except EGFR)*

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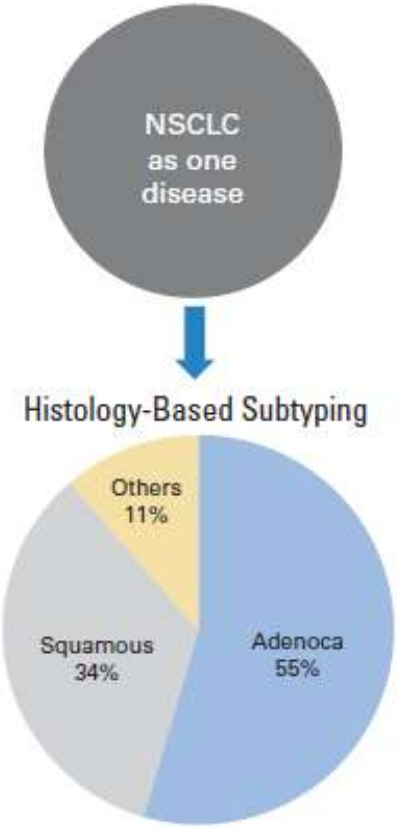
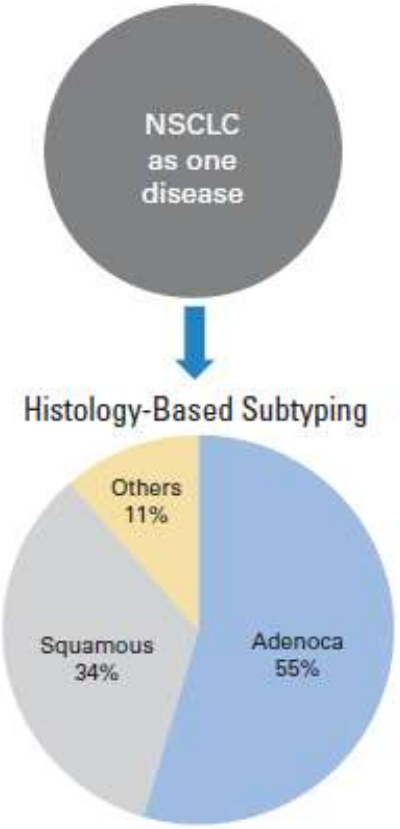
Disclosures

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

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


NSCLC
as one
disease


NSCLC
as one
disease
Histology-Based Subtyping
Others
11%
Squamous
34%
Adenoca
55%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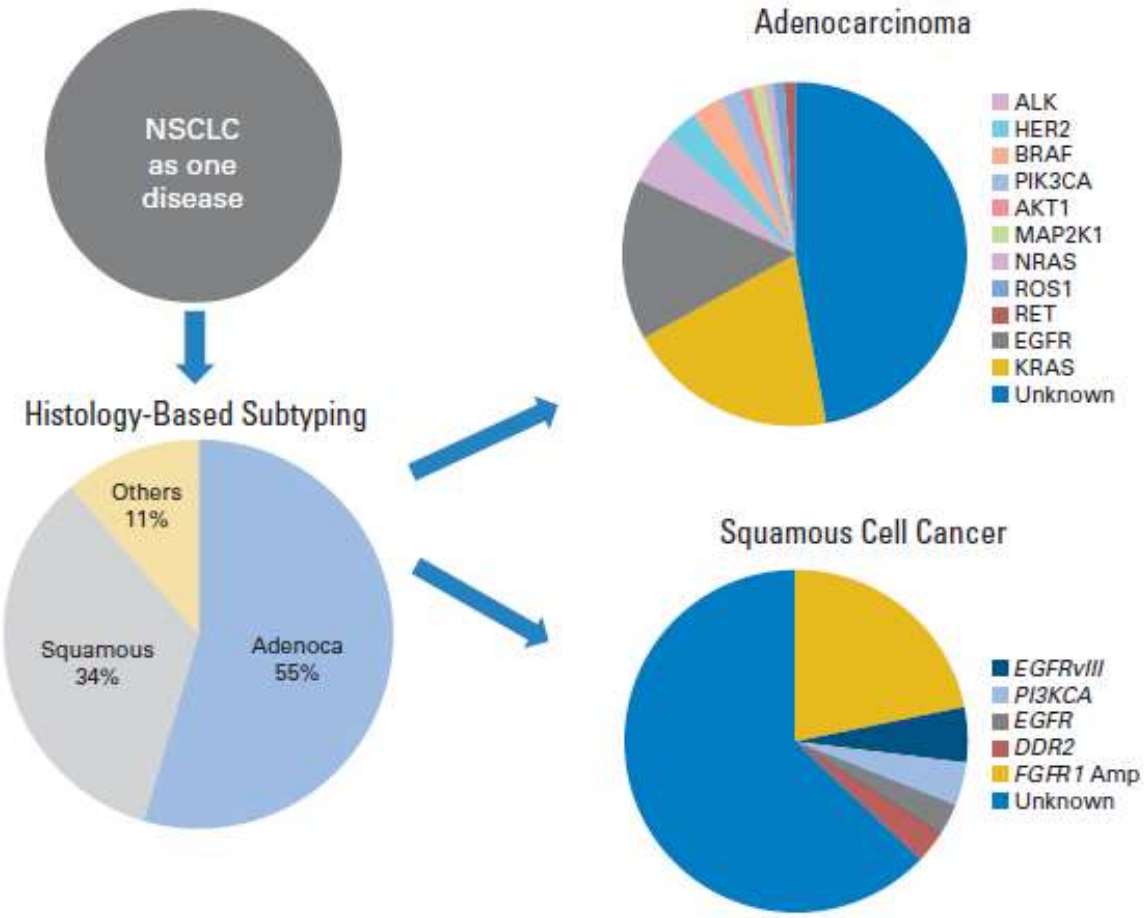
Li, JCO 2013.


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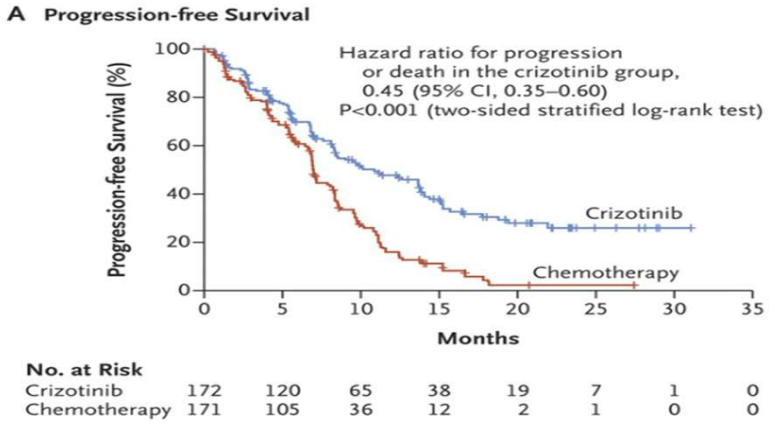
ALK rearrangements

- 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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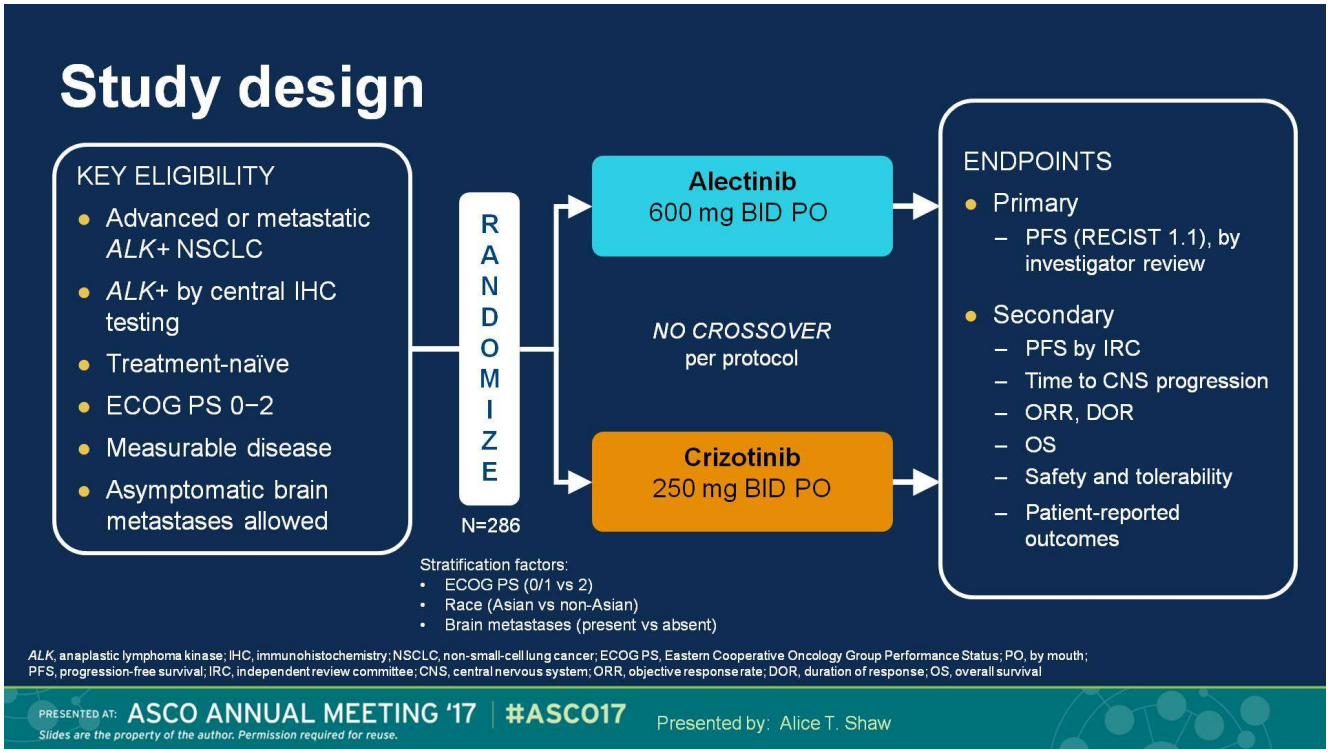
ALK rearrangements

- …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?

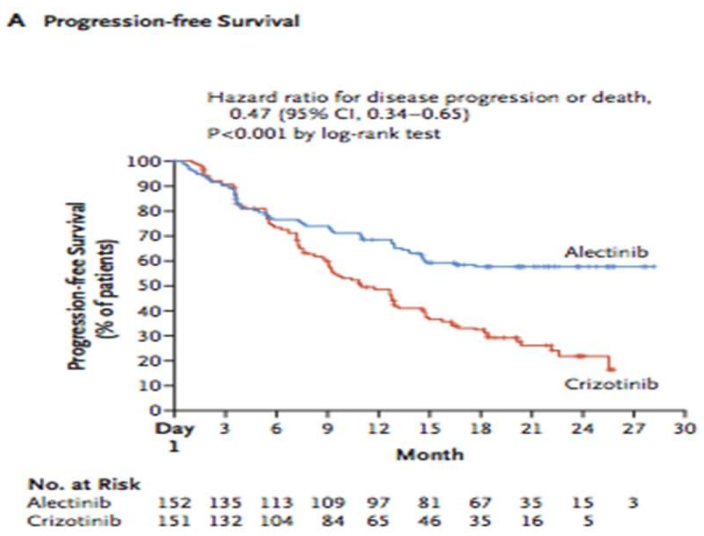
- ALEX trial

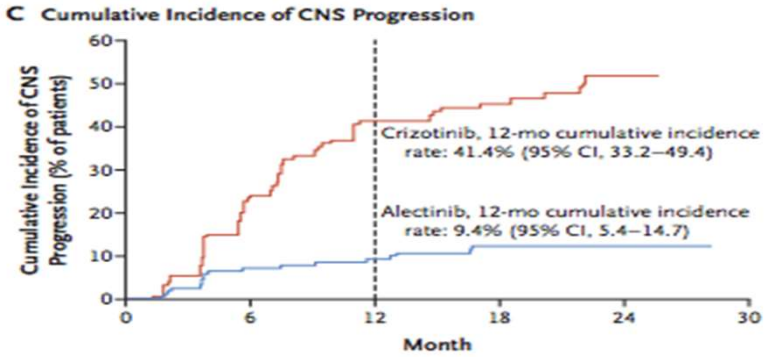


Shaw, ASCO 2017.

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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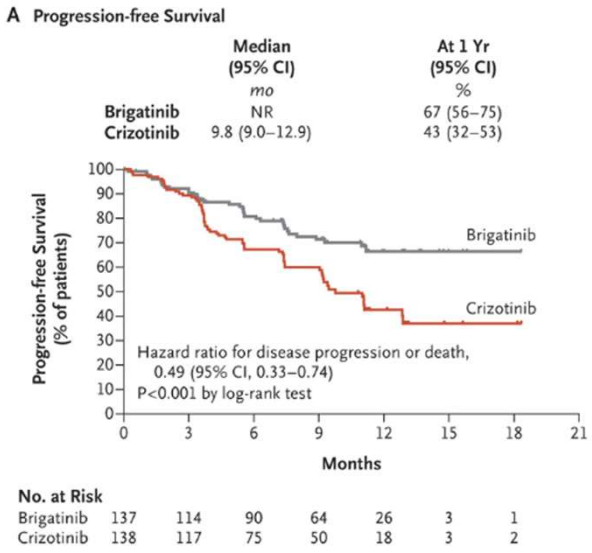
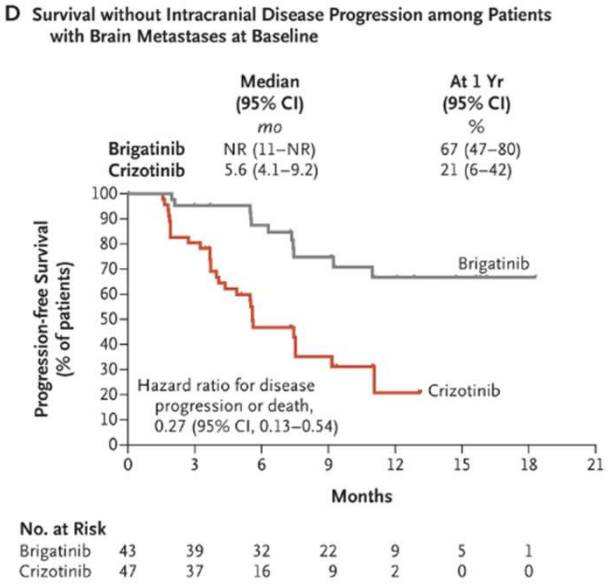
ALK– Moving 2nd generation to 1st line?

- ALTA-1L (NEJM 2018), alectinib vs criztoinib
  - RR 71 vs 60%





Not yet FDA approved for 1L

Camidge, NEJM 2018

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ALK– 3rd generation

- Lorlatinib
  - ORR in pts after previous TKI failure, n=215: 48%
    - Median DoR 12.5 mos
  - Intracranial ORR, n=89, 60%
- FDA approved 11/18 for 2nd line (after 2nd gen) or 3rd line (after 1st and 2nd gen)

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:
    - ORR 44% after 1 prior TKIs
    - ORR 25% after 2 prior TKIs
    - ORR 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; ASCO Proc 2017 #9006

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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
  - Gefitinib approved 2015
    - Afatinib approved 2013
    - Dacomitinib approved 2018
      - Osimertinib approved 2015
- ALK
  - Crizotinib approved 2011
    - Ceritinib approved 2014
    - Alectinib approved 2015
    - Brigatinib approved 2017
      - Lorlatinib approved 2018
- 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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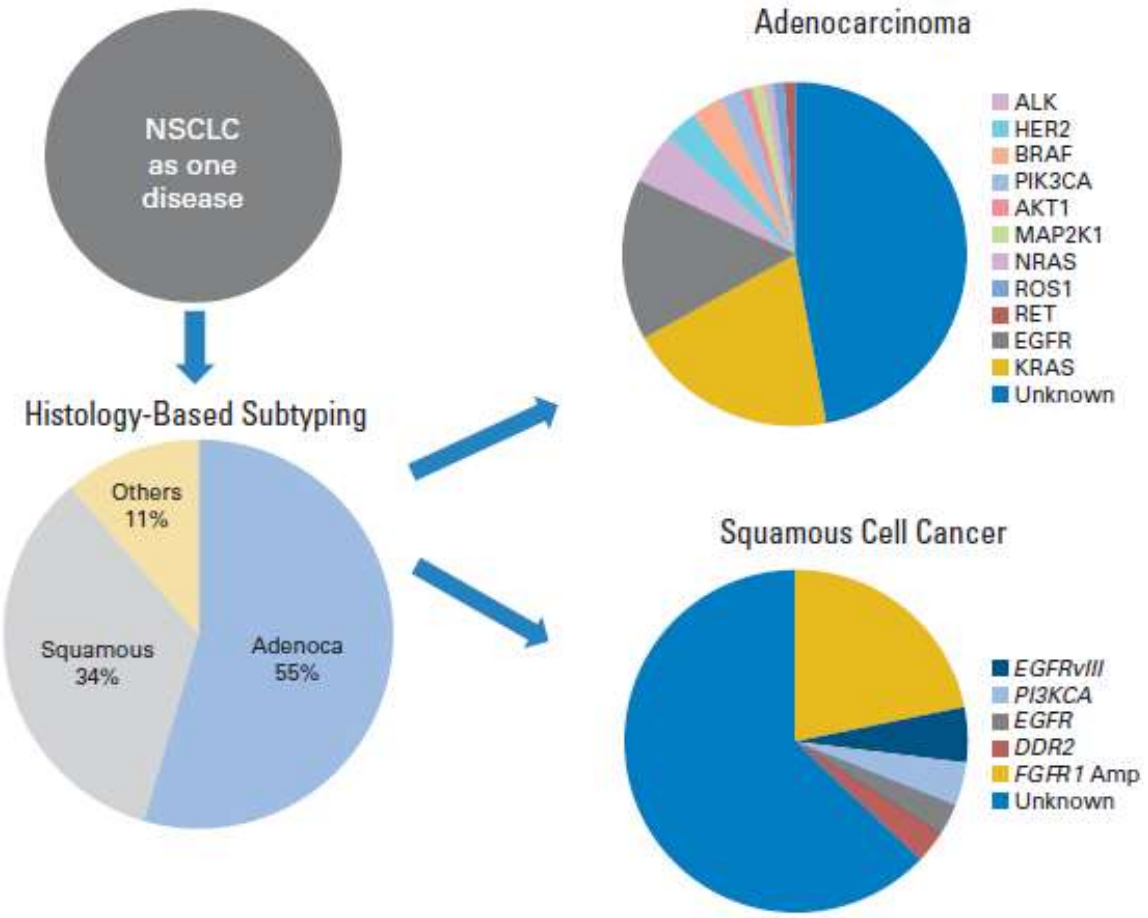
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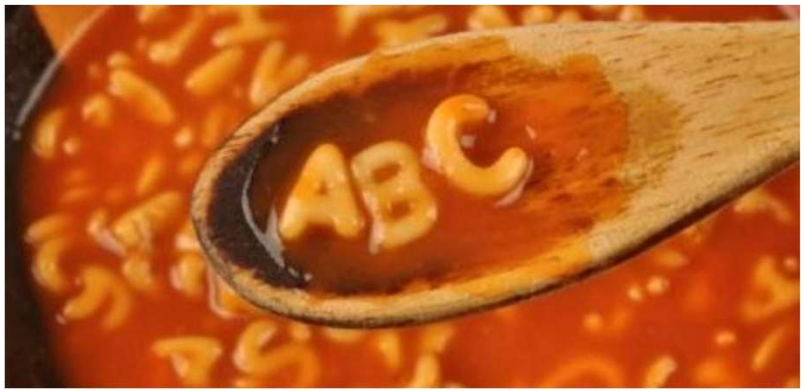
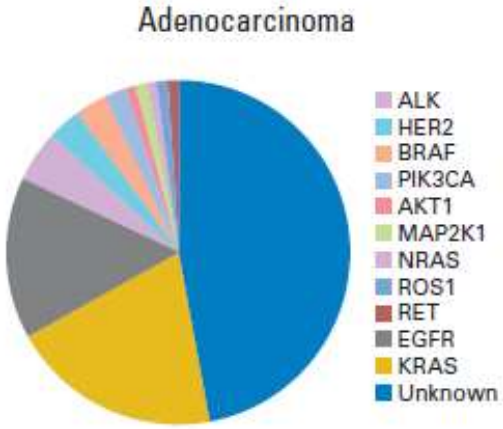
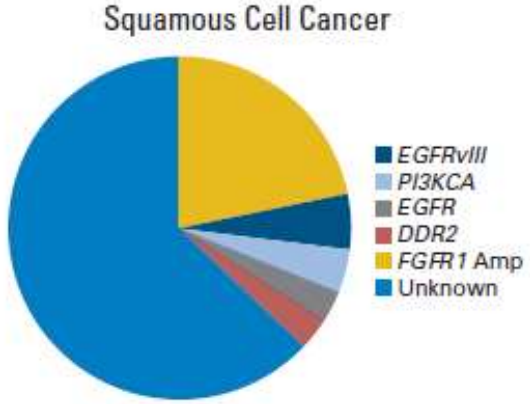
Li, JCO 2013







Li, JCO 2013.

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Emerging targets

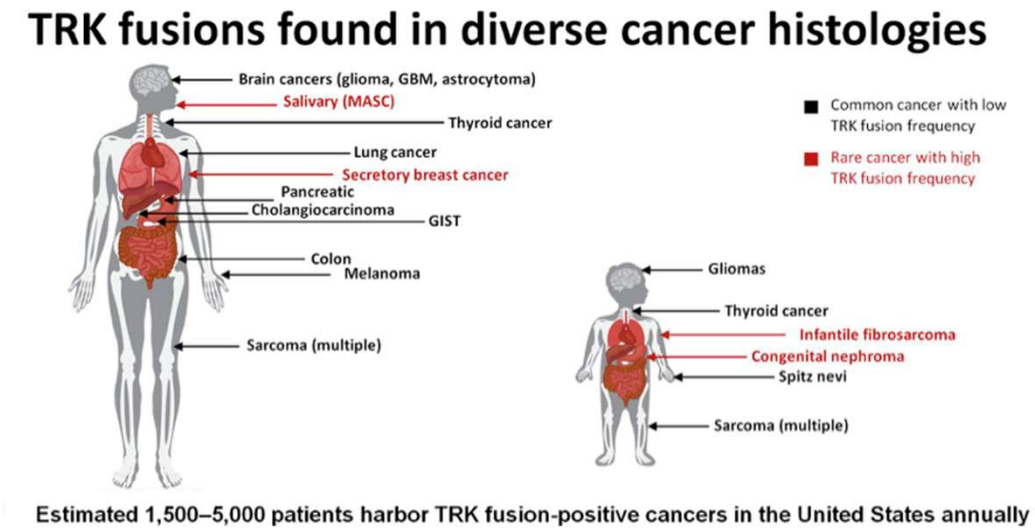
- MET exon 14 skipping mutation
  - Often older patients, current/former smokers, sarcomatoid pathology
  - 3-4% of NSCLC
    - Crizotinib ORR 44%, PFS not yet reached (ASCO 2016)
      - FDA breakthrough designation

- 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%
    - Including 22% CR
  - mDOR NR
- FDA approved, tumor site agnostic, 11/18



Hyman DM, ASCO Proc 2017.

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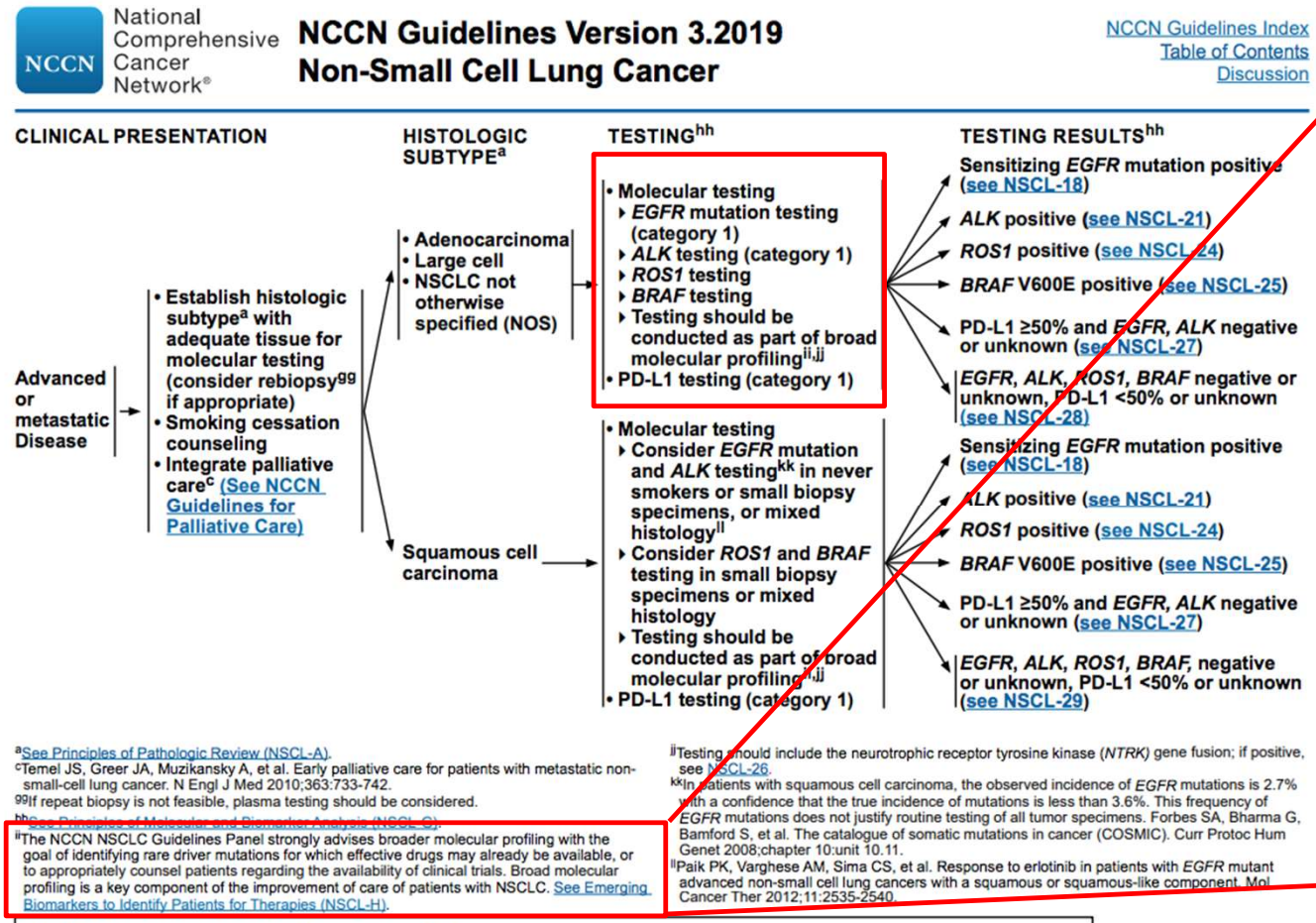

The NCCN NSCLC Guidelines panel strongly advises broader molecular profiling with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials. Broad molecular profiling is a key component of the improvement of care of patients with NSCLC.

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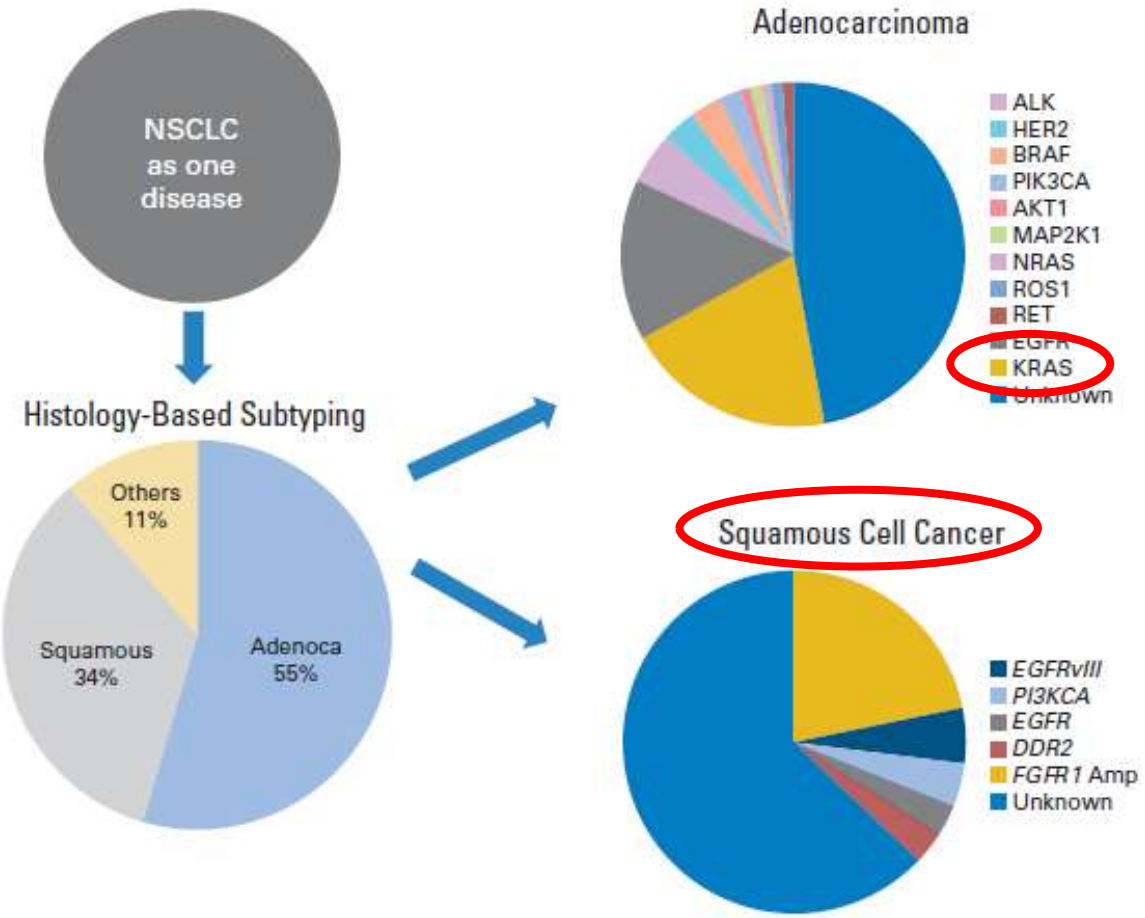
EMERGING BIOMARKERS TO IDENTIFY NOVEL THERAPIES FOR PATIENTS WITH METASTATIC NSCLC

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]
ERBB2 (HER2) mutations	Ado-trastuzumab emtansine[9]
Tumor mutational burden (TMB)*	Nivolumab + ipilimumab[10] Nivolumab[11]

*TMB is an evolving biomarker that may be helpful in selecting patients for immunotherapy. There is no consensus on how to measure TMB.

[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 A, Rekhtman N, Arcila M, et al. Cabozantinib in patients with advanced RET-rearranged non-small-cell lung cancer: an open-label, single-centre, phase 2, single-arm trial. Lancet Oncol 2016;17:1653-1660.
[8]Lee SH, Lee JK, Ahn MJ, et al. Vandetanib in pretreated patients with advanced non-small cell lung cancer-harboring RET rearrangement: a phase II clinical trial. Ann Oncol 2017;28:292-297.
[9]Li BT, Shen R, Buonocore D, et al. Ado-trastuzumab emtansine in patients with HER2 mutant lung cancers: Results from a phase II basket trial. J Clin Oncol 2018;36:2532-2537.
[10]Hellmann MD, Ciuleanu TE, Pluzanski A et al. Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. N Engl J Med 2018; 378:2093-2104.
[11]Carbone DP, Reck M, Paz-Ares L et al. First-line nivolumab in stage IV or recurrent non-small-cell lung cancer. N Engl J Med 2017;376:2415–2426.

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.



Li, JCO 2013.

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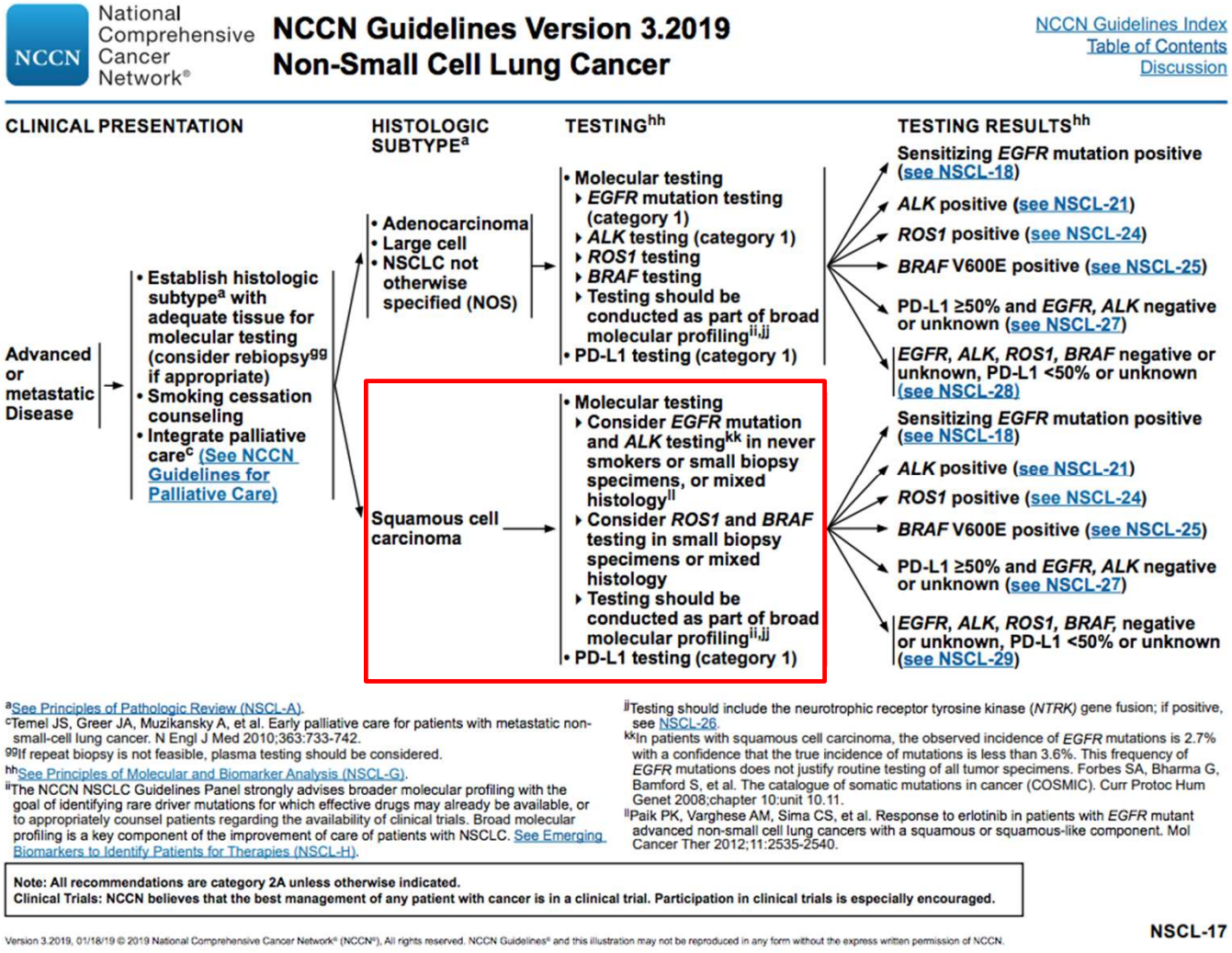

Squamous cell lung ca

- 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 standard of care in first line
  - Lorlatinib the new standard of care in refractory disease
  - But may eventually consider biopsy to determine mechanism of resistance
- 1st generation approaches in “emerging” alterations
  - FDA approvals for ROS1, BRAF, NTRK
  - 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!