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Targeted Therapy in NSCLC

Master Lecture Series: Evolving Treatments in Immunotherapy and Targeted Therapies

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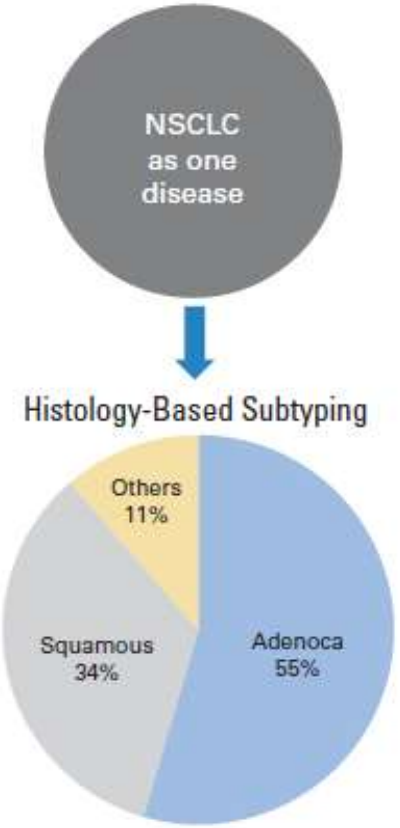
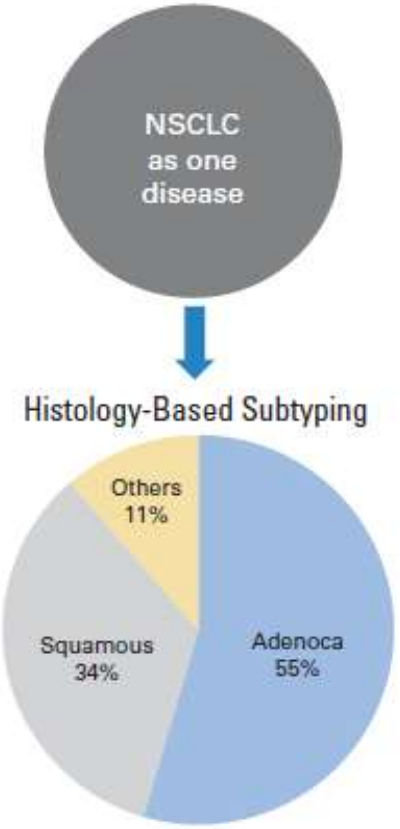
Disclosures

- Consulting
  - AstraZeneca, Beyond Spring, Boehringer Ingelheim, Bristol-Myers Squibb, Inivata, Takeda
- 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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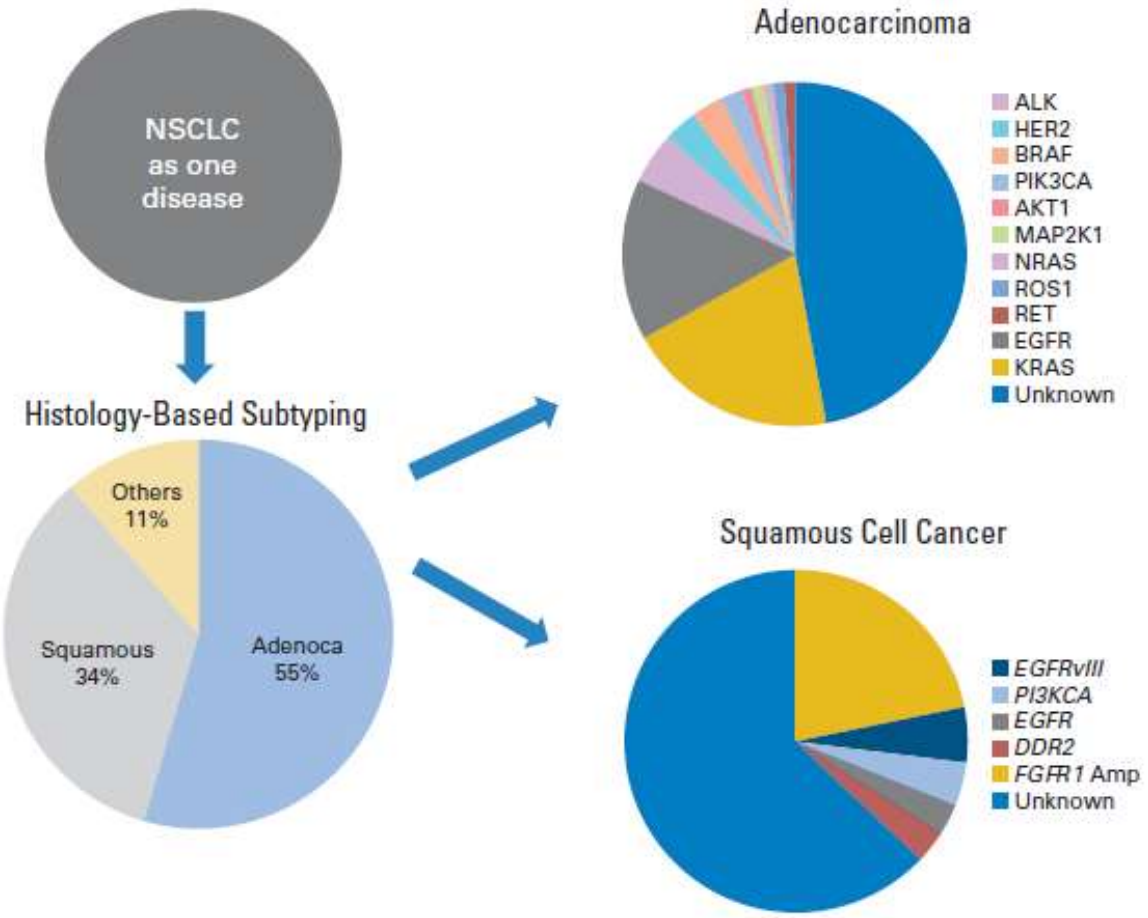
Li, JCO 2013.


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 and 3rd generation approaches in EGFR and ALK
- 1st generation approaches in “emerging” alterations

Targeted therapies for oncogene-driven NSCLC

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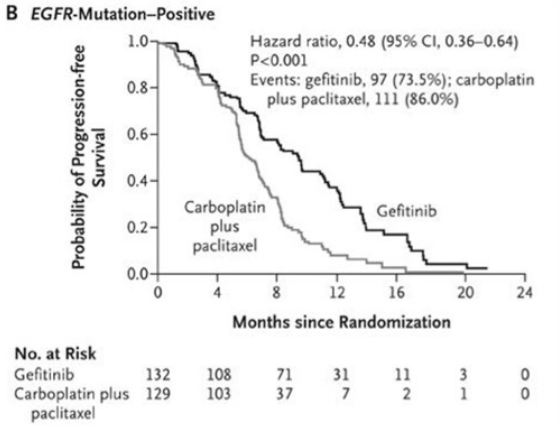
EGFR

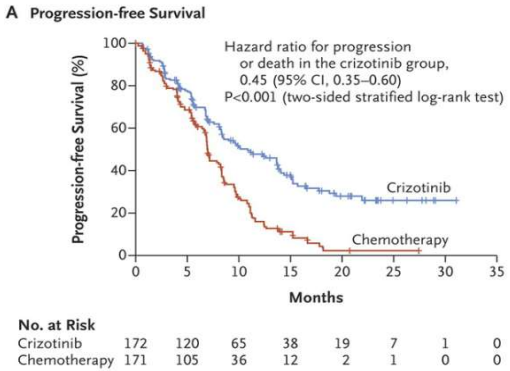
- 2009 IPASS study– gefitininb (Mok et al in NEJM)



- …but resistance inevitably develops
- ~50-60% T790M “gatekeeper”

ALK

- 2014 PROFILE 1014– crizotinib (Solomon et al in NEJM)



- …but resistance inevitably develops
- Middling ALK inhibitor
- Poor CNS penetration

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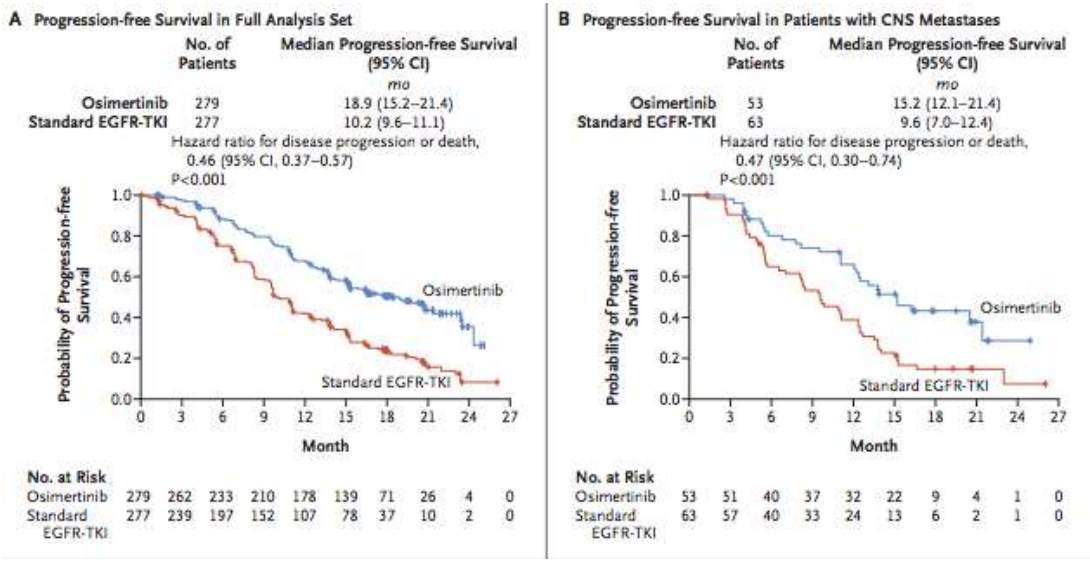
EGFR– Osimertinib first line: FLAURA trial

- Osimertinib vs gefitinib or erlotinib



- And overall survival advantage: 38.6 vs 31.8mo
- And superior safety profile

Soria, NEJM 2017, Ramalingam, NEJM 2020

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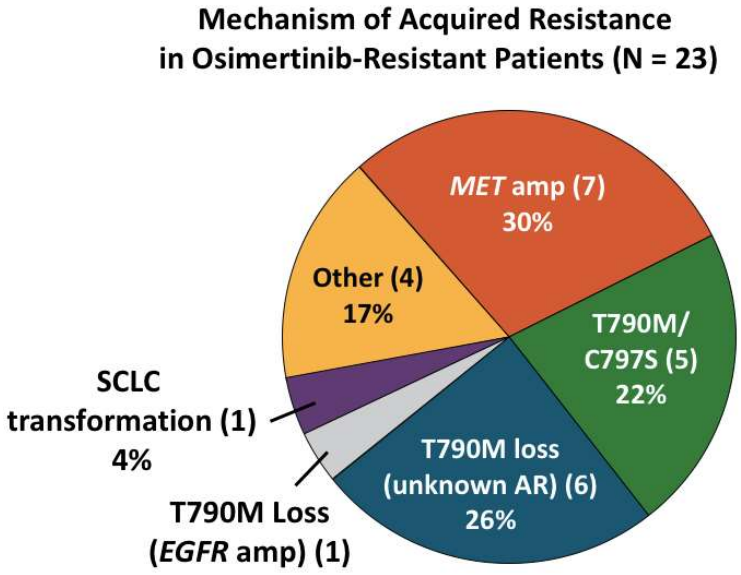
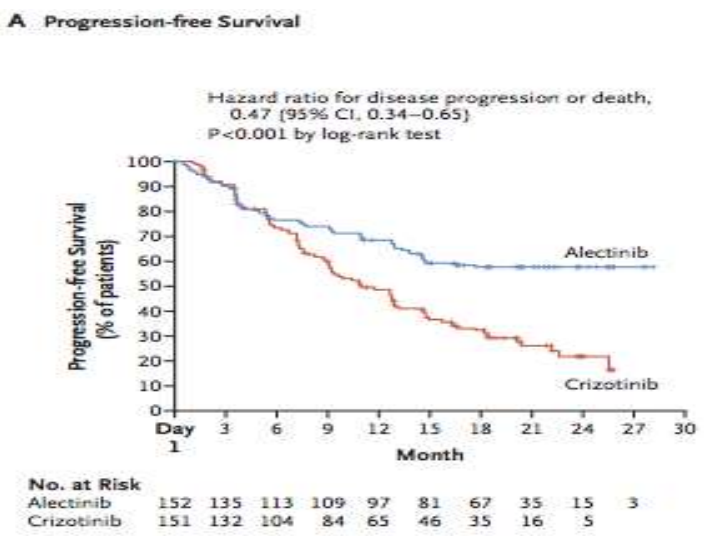
After osimertinib first-line?

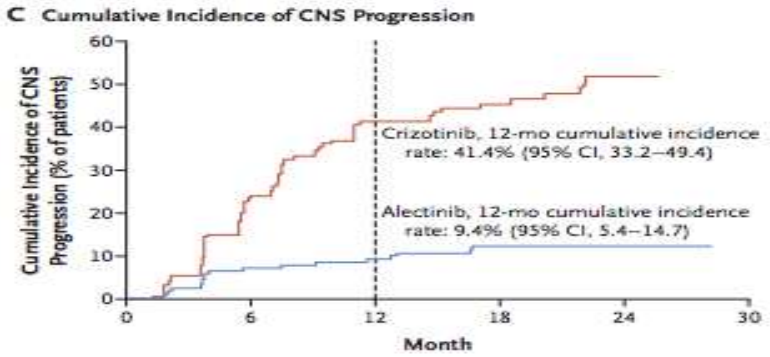
- Cancers evolve…
- …resistance inevitably develops
- Role for repeat biopsy?
  - MET amp → add MET inhibitor?
  - SCLC transformation → SCLC chemo?
  - Clinical trials
    - Specific to mechanism of resistance
      - Eg C797S inhibitor
    - Broader mechanisms
      - Eg osimertinib + alisertib (aurora kinase inhibitor)



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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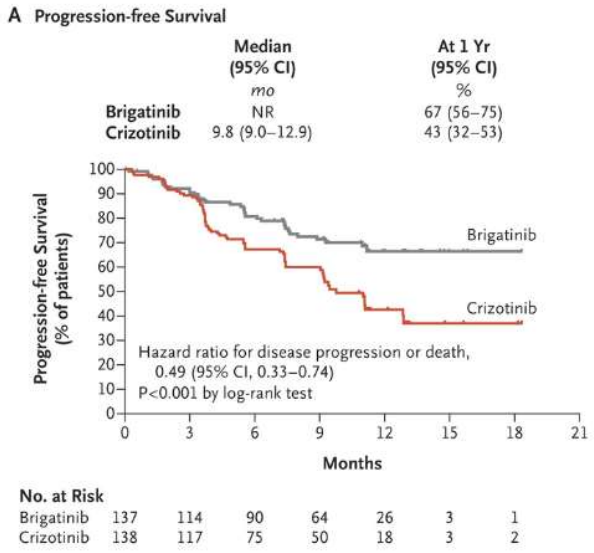
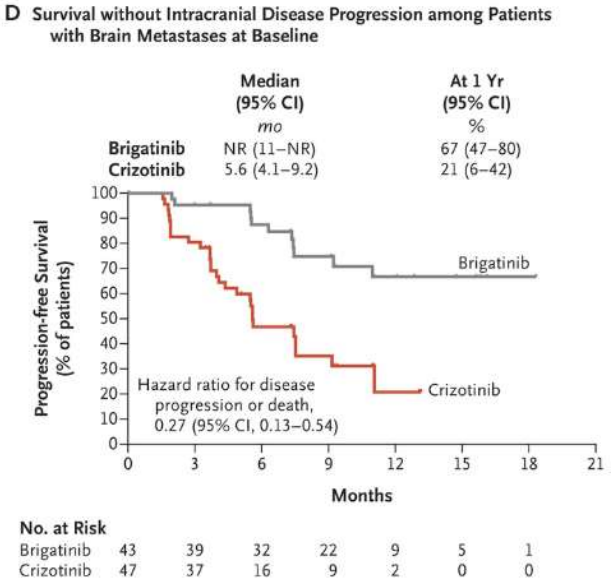
ALK– Moving 2nd generation to 1st line?

- ALTA-1L (NEJM 2018), alectinib vs crizotinib
  - 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)

After alectinib first line?

- Cancers evolve…
- ...resistance inevitably develops
- 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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Immunotherapy in metastatic EGFR-Mutated NSCLC?

- Phase 2 study– advanced EGFR TKI-naïve– planned 25 EGFR+ patients
  - Pembrolizumab single agent
  - Primary endpoint ORR
- Results: Stopped after stage 1, 11 patients
  - 1/11 had an objective response
  - …and that responder was later found to be EGFR negative
  - This despite 73% with PD-L1 expression >=50%
  - 2 deaths within 6 months of enrollment, including 1 attributed to pneumonitis
- Take-home messages: first line IO not appropriate for EGFR and likely other driver mutations where targeted therapy available– poor effectiveness *even* with high PD-L1... and potential toxic interaction with TKI

Targeted therapies for oncogene-driven NSCLC

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FDA-approved oncogene-targeted agents in NSCLC

- EGFR
  - Erlotinib (2009)
  - Gefitinib (2015)
    - Afatinib (2013)
    - Dacomitinib (2018)
      - Osimertinib (2015)
- ALK
  - Crizotinib (2011)
    - Ceritinib (2014)
    - Alectinib (2015)
    - Brigatinib (2017)
      - Lorlatinib (2018)
- ROS1
  - Crizotinib (2016)
    - n=53
    - ORR 70%, mPFS 19.3mo
  - Entrectinib (2019)
    - N=51
    - ORR 78%, DoR 24.6mo
- BRAF
  - Dabrafenib/trametinib approved 2017
    - 1st line n=36
    - ORR 64%. 14.6mo

Bare minimum for non-squamous NSCLC: EGFR, ALK, ROS1, and BRAF

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

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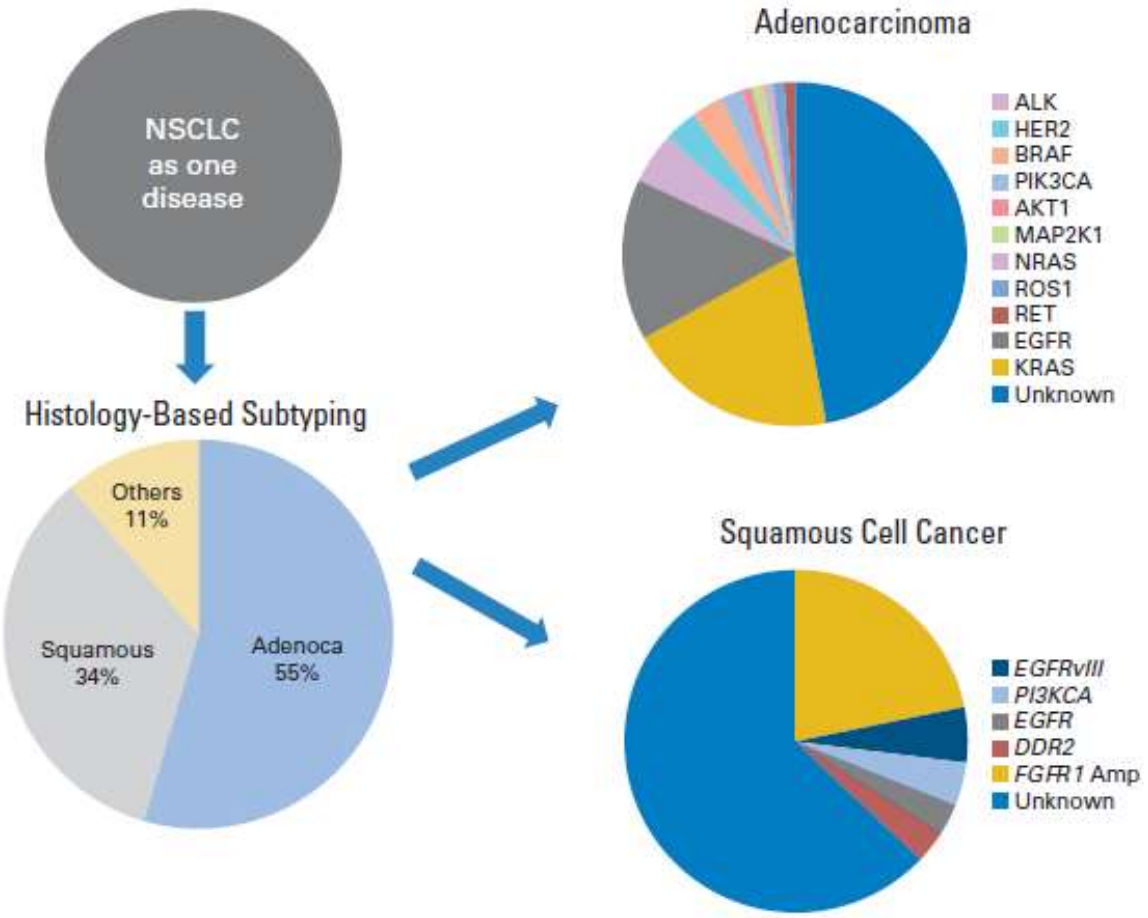
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FGFR1 Amp
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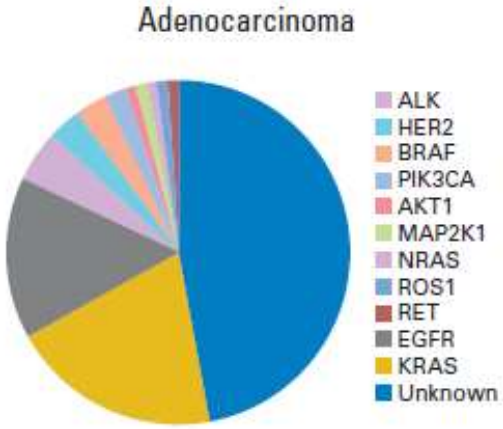
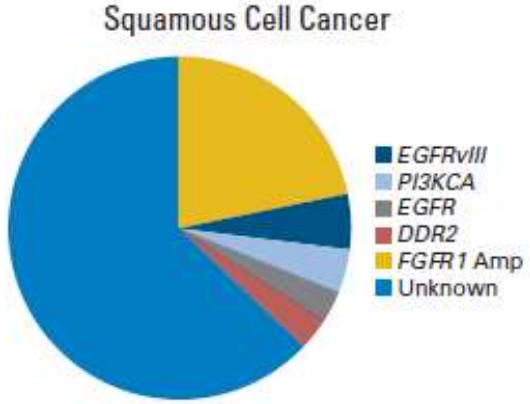
Li, JCO 2013





Li, JCO 2013.

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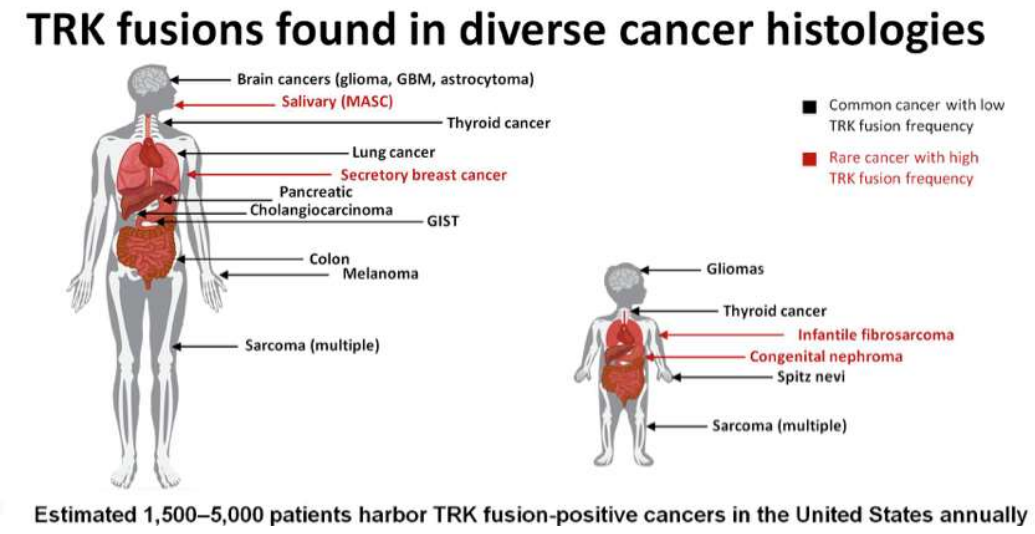
Emerging targets

- TRK fusions
  - Larotrectinib
    - N=55
    - 4 lung
  - RR 76%
    - Including 22% CR
  - mDOR NR



- FDA approved, tumor site agnostic, 11/18
- Entrectinib also now approved, 2019 (n=54, RR 57%)

Hyman DM, ASCO Proc 2017.

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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)
      - Selpercatinib (LOXO-292) ORR 85%, CNS ORR 91%, mPFS 18.4mo
- HER2 mutation
    - T-DM1 ORR 33% (ASCO 2017)

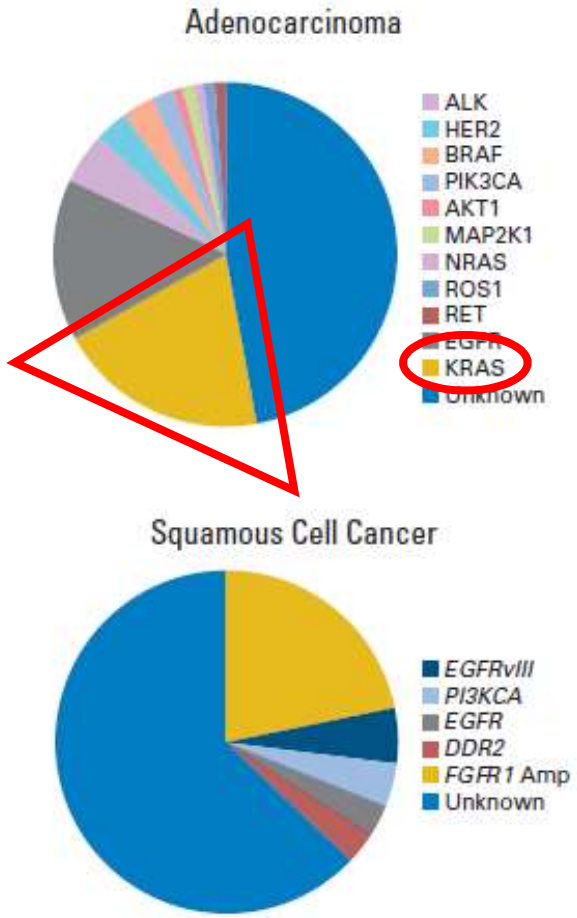
EMERGING BIOMARKERS TO IDENTIFY NOVEL THERAPIES FOR PATIENTS WITH METASTATIC NSCLC

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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Emerging targets

- KRAS ~30% of NSCLC
  - Difficult to “drug”
  - KRAS G12C ~1/3 of KRAS NSCLC
    - Direct inhibitors include AMG510, MRTX849, JNJ-74699157
  - Registrational and combo studies available

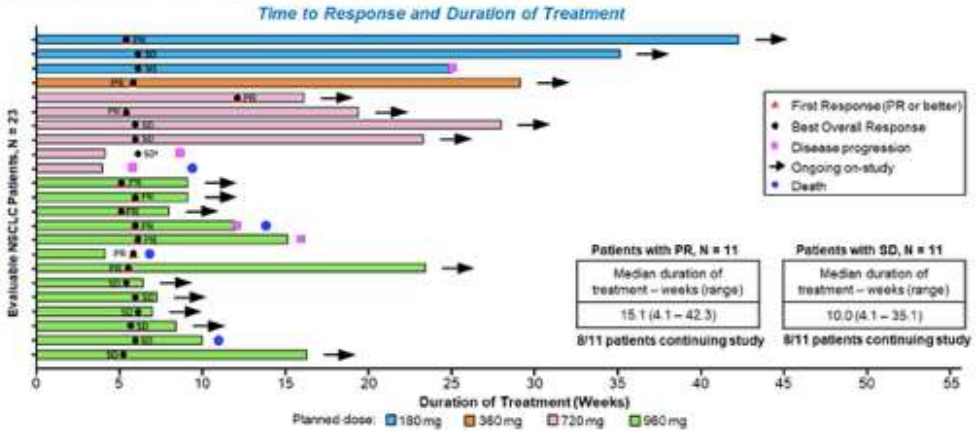
Phase 1 Study of AMG 510, a Novel KRAS^{G12C} Inhibitor, in Advanced Solid Tumors With *KRAS p.G12C* Mutation: ESMO 2019

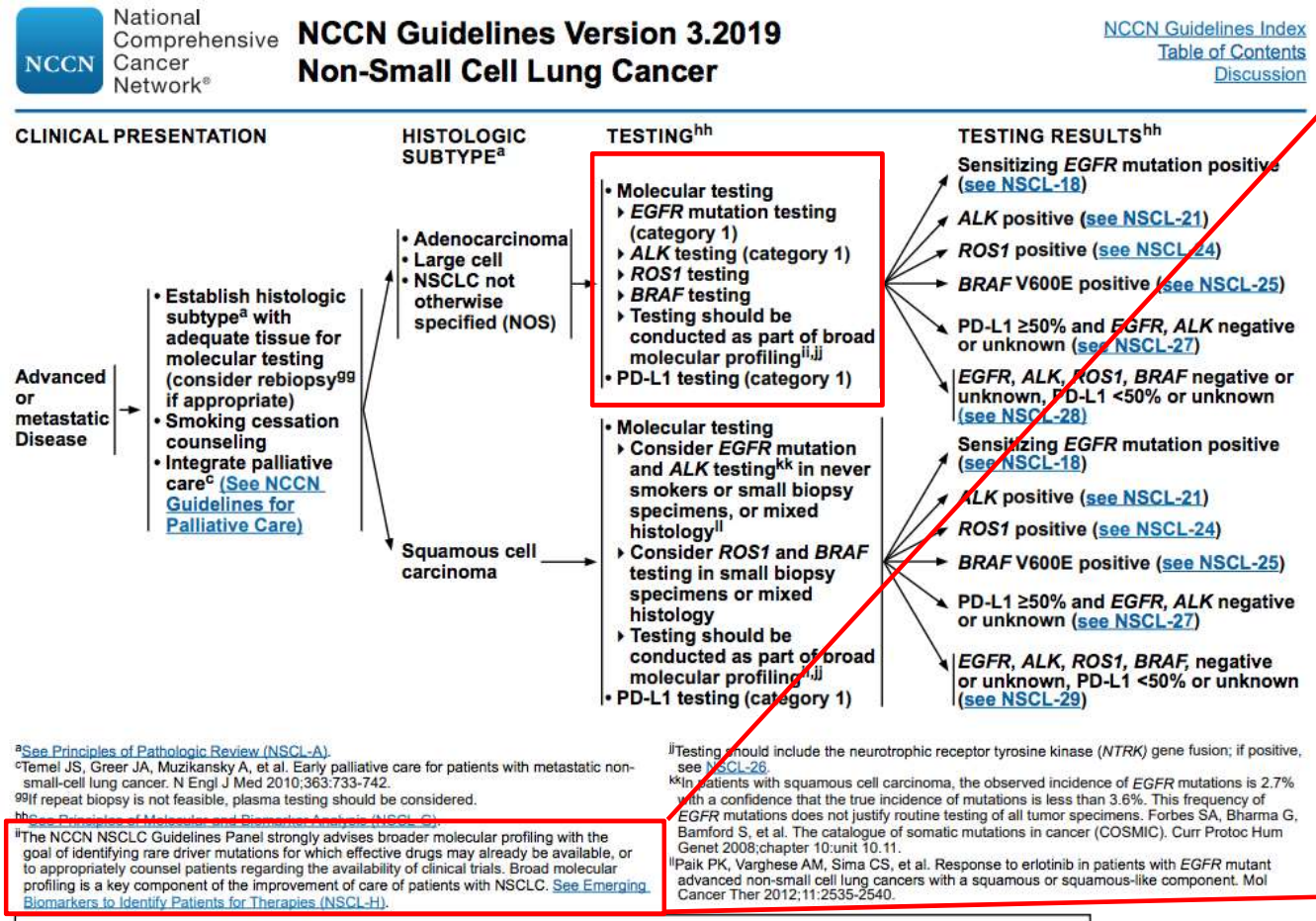
BEST TUMOR RESPONSE WITH ALL DOSE LEVELS, ALL TUMOR TYPES

Efficacy outcomes	NSCLC, evaluable patients N = 23	CRC, evaluable patients N = 29	Other tumor types, evaluable patients N = 3
Best overall response			
PR – n (%)	11 (48)	1 (3)	1 (33)[c]
SD – n (%)	11 (48)	22 (76)	1 (33)[d]
PD – n (%)	1 (4)	6 (21)	1 (33)[e]
Objective response rate[a]	**48%**	**3%**	**N/A**
Disease control rate[b]	**96%**	**79%**	**N/A**

Phase 1 Study of AMG 510, a Novel KRAS^{G12C} Inhibitor, in Advanced Solid Tumors With *KRAS p.G12C* Mutation: ESMO 2019

EFFICACY IN NSCLC





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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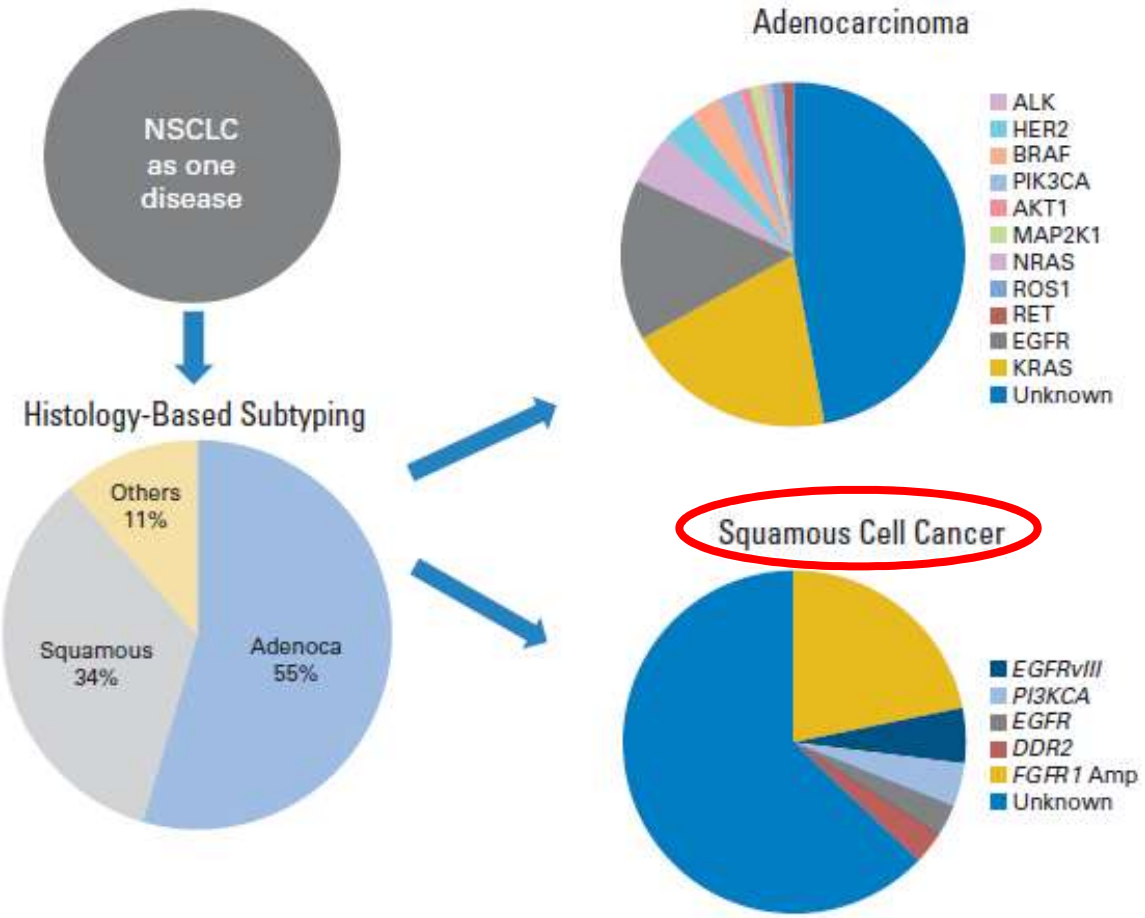
You can't treat a mutation you don't know!



Li, JCO 2013.

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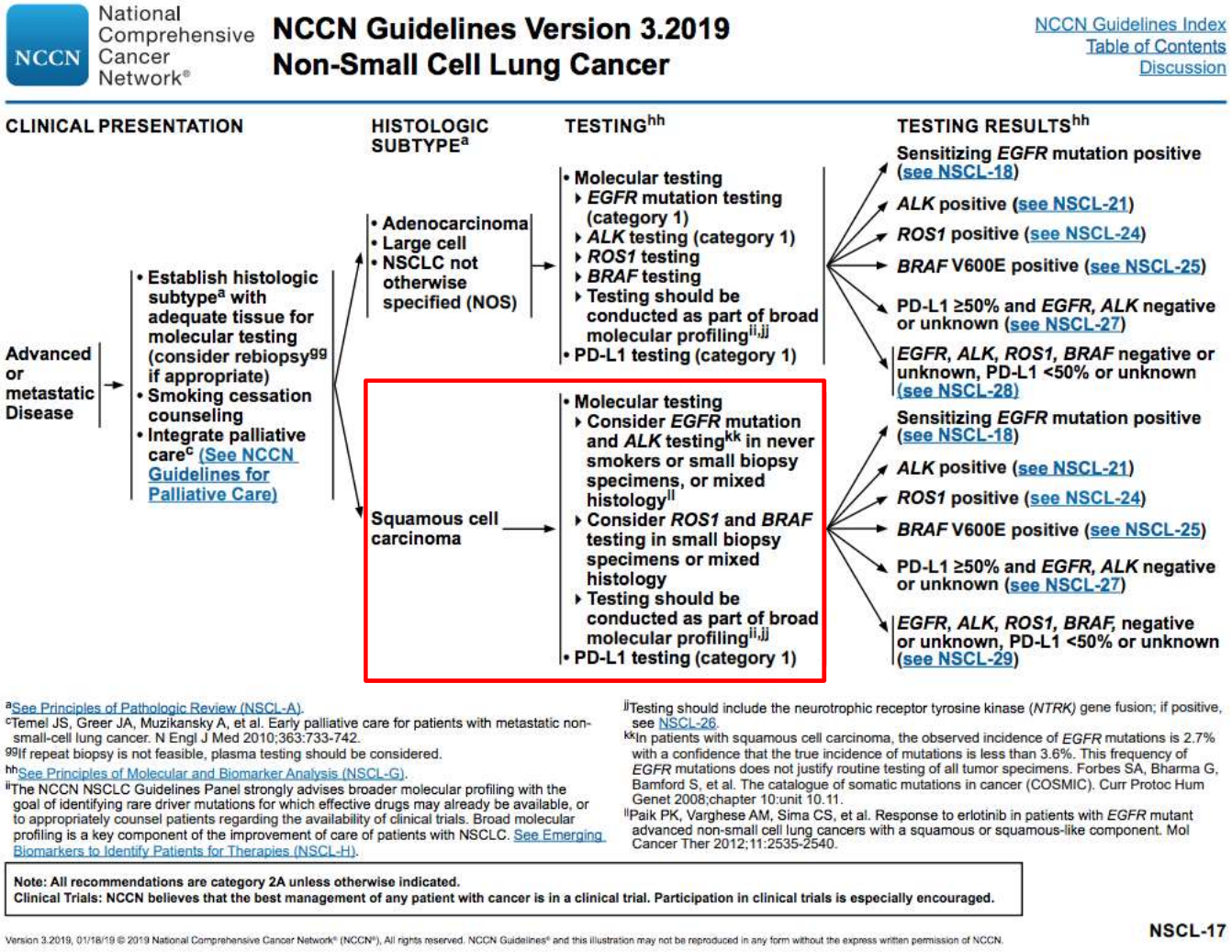

Squamous cell lung ca

- 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 (immunotherapy)

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Targeted therapies for oncogene-driven NSCLC

- EGFR:
  - Osimertinib with clear survival benefit
  - Consider biopsy to determine mechanism of resistance
- ALK:
  - Alectinib clear standard of care in first line
  - Lorlatinib appropriate empirically in subsequent line
  - But again, may consider biopsy to determine mechanism of resistance
- And a cautionary tale
  - Single agent immunotherapy does NOT work well

Targeted therapies for oncogene-driven NSCLC

- 1st generation approaches in “emerging” alterations
  - FDA approvals for ROS1, BRAF, NTRK
  - Other targets like MET, RET, HER2 “on deck,” some with off-label opportunities (NCCN can help)
  - KRAS is (finally) coming!
- You can’t treat what you haven’t identified
- **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!