NCCN Virtual Nursing Program:
Advancing Oncology Nursing™

Wednesday, March 17, 2021
1:25 PM – 2:10 PM EDT

Keeping up with the Molecular Targets in the Treatment of Advanced Non-Small Cell Lung Cancer

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Learning Objectives

- Identify molecular targets for metastatic non-small cell lung cancer (NSCLC)
- Discuss the recommended targeted therapies for metastatic NSCLC
- Describe side effects that may occur with targeted therapies

Q: NCCN recommends molecular testing for which patients with metastatic NSCLC?

- A: All patients with NSCLC
- B: Patients with adenocarcinoma NSCLC histology
- C: Only non-smokers
- D: Patients with squamous NSCLC histology

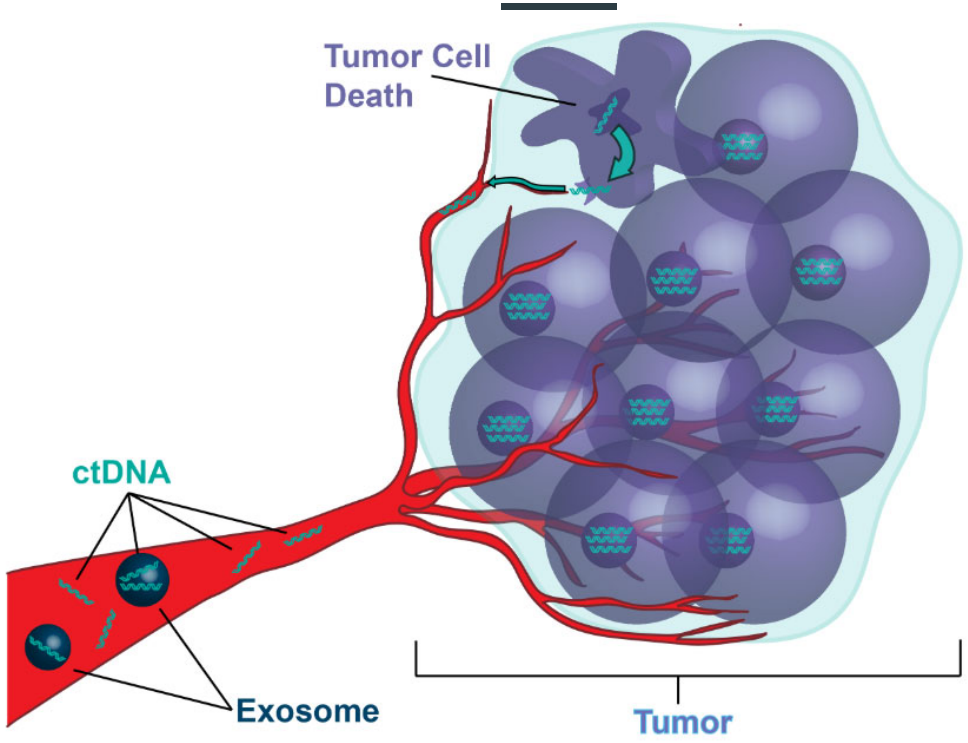
Oncogenic Molecular Biomarkers

- Molecular testing should be conducted on every patient with metastatic NSCLC with histologic subtype adenocarcinoma, large cell, NSCLC not otherwise specified (NOS), if clinically feasible
  - Testing should be considered in squamous cell histology
- Survival is longer for patients with metastatic NSCLC with driver mutations who receive appropriate targeted therapies; 5-year survival rates range from 15-50% for patients who receive targeted therapy, depending on the different biomarkers, vs 6% of patients who are not eligible for targeted therapy and receive chemotherapy regimens.
- Re-biopsy should be considered in certain patients at progression to evaluate for mechanisms of resistance
- Actionable molecular biomarkers are more common in never smokers, younger patients, adenocarcinoma

Testing Methodologies

- Next-generation sequencing (NGS)
- Real-time polymerase chain reaction (PCR)
- Sanger sequencing
- Fluorescence in situ hybridization (FISH)
- Immunohistochemistry (IHC)

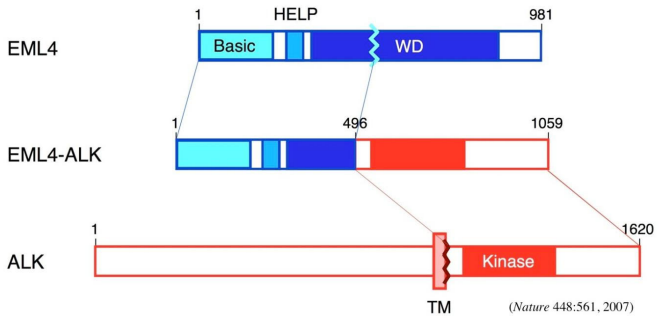
Liquid Biopsy: ctDNA Testing (Plasma Testing) for Molecular Biomarkers



Lovly, C., M. et al. 2016. Circulating Tumor DNA. *My Cancer Genome*

ALK rearrangements

- Account for roughly 5% of patients with NSCLC
- EML4 is most common fusion partner seen with ALK
- 1st generation ALK inhibitor: crizotinib
- 2nd generation ALK inhibitors: alectinib, brigatinib, ceritinib
- 3rd generation ALK inhibitor: lorlatinib



American Cancer Society. Targeted therapy drugs for non-small cell lung cancer; Hofman. Cancers (Basel). 2017;9:107.

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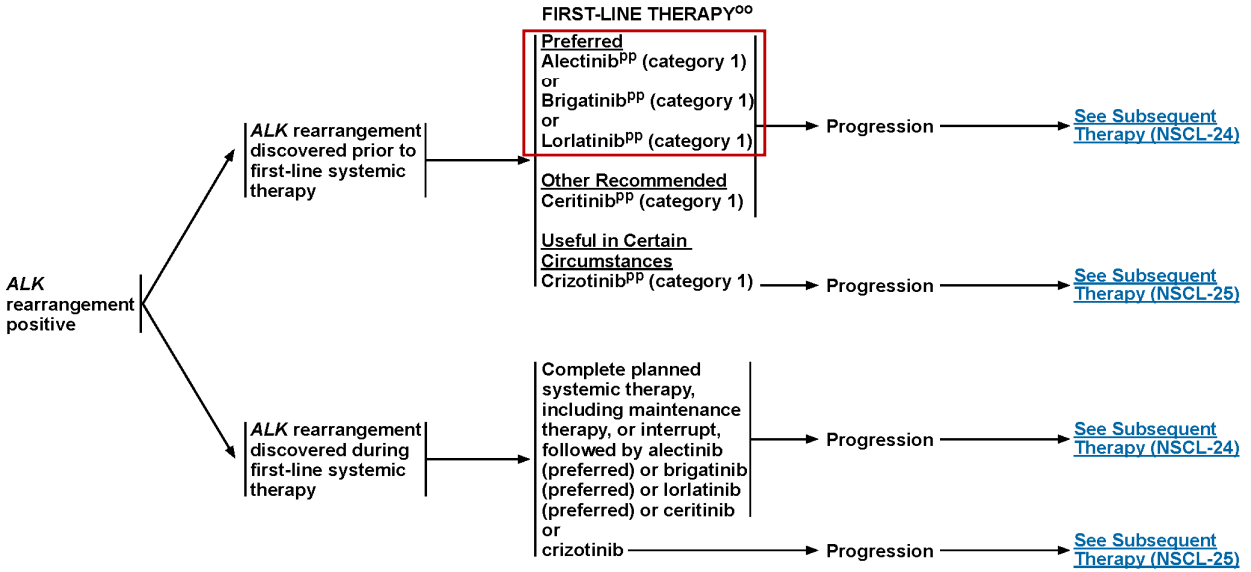
***ALK* REARRANGEMENT POSITIVE**[ll]



[ll] See Principles of Molecular and Biomarker Analysis (NSCL-H).
[oo] See Targeted Therapy or Immunotherapy for Advanced or Metastatic Disease (NSCL-J).
[pp] For performance status 0–4.

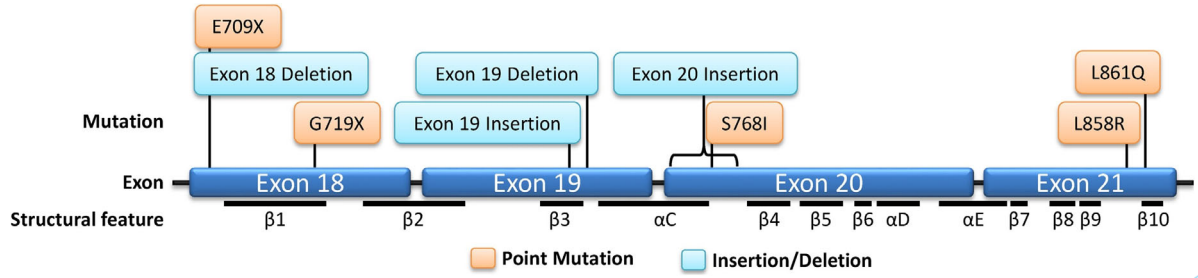
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

ALK Inhibitor Side Effects

- Pulmonary toxicity; can be early onset with brigatinib (3-9% incidence)
- Nausea and vomiting
- Constipation (over a third of patients on alectinib)
- Fatigue
- Edema
- Cardiac toxicity: hypertension (brigatinib), sinus bradycardia and QT prolongation (crizotinib)
- Myalgias (alectinib and brigatinib)
- Hypercholesterolemia (lorlatinib)
- Neurologic toxicity (lorlatinib)

EGFR mutations

- More common: exon 19 del, exon 21 L858R
- Occurs in about 10% Caucasian patients with NSCLC, up to 50% in Asian
- 1st generation EGFR TKIs: erlotinib, gefitinib
- 2nd generation EGFR TKIs: afatinib, dacomitinib
- 3rd generation EGFR TKI: osimertinib



Harrison, et al. 2020. Rare epidermal growth factor receptor (EGFR) mutations in non-small cell lung cancer. 61(167-179)

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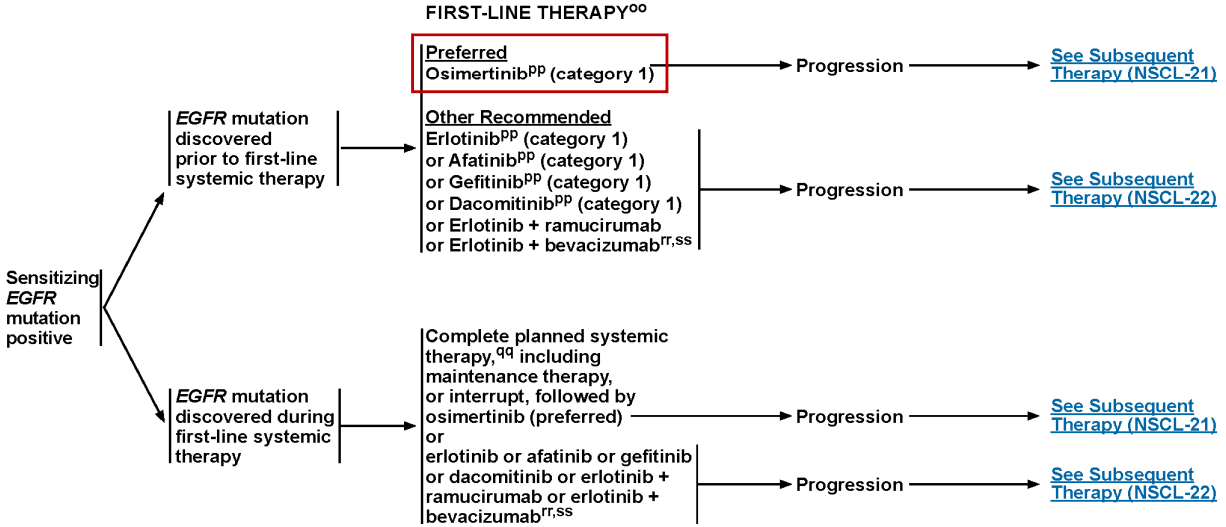
SENSITIZING *EGFR* MUTATION POSITIVE[ll]



[ll] See Principles of Molecular and Biomarker Analysis (NSCL-H).
[oo] See Targeted Therapy or Immunotherapy for Advanced or Metastatic Disease (NSCL-J).
[pp] For performance status 0–4.
[qq] If systemic therapy regimen contains an immune checkpoint inhibitor, physicians should be aware of the long half-life of such drugs and data reporting adverse events when combining checkpoint inhibitors with osimertinib. Schoenfeld AJ, et al. Ann Oncol 2019;30:839-844; Oshima Y, et al. JAMA Oncol 2018;4:1112-1115; Oxnard GR, et al. Ann Oncol 2020;31:507-516.
[rr] Criteria for treatment with bevacizumab: non-squamous NSCLC, and no recent history of hemoptysis.
[ss] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.

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EGFR Inhibitor Side Effects

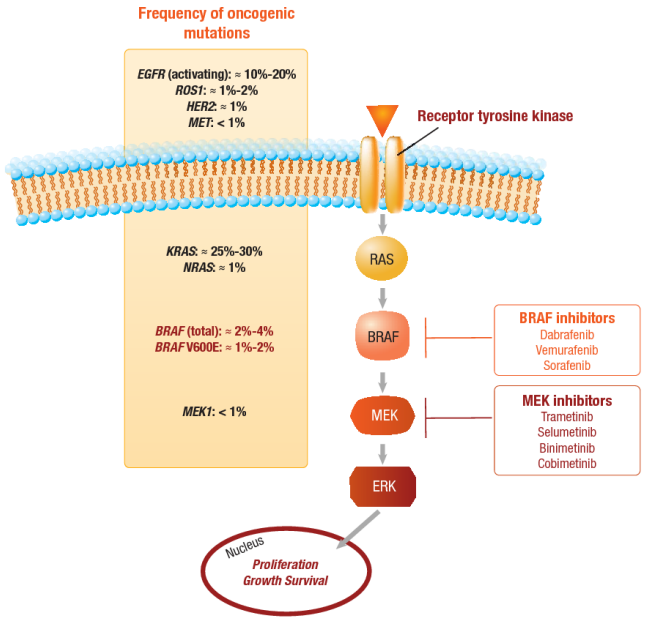
- Cutaneous reactions: rash, xerosis, hair/nail changes (59% osimertinib)
- Diarrhea (60% osimertinib)
- Mouth sores
- Eye problems: conjunctivitis, dry eyes, trichiasis
- Pulmonary toxicity: interstitial lung disease (ILD) with all EGFR inhibitors, (potentially fatal)
- Hepatic toxicity: failure and hepatorenal syndrome reported in erlotinib (potentially fatal)

Q: Patient on osimertinib develops asymptomatic new lung lesion. Now what?

- A: consider other EGFR TKIs
- B: continue osimertinib and consider local therapy
- C: discontinue osimertinib and start chemotherapy
- D: unsure

BRAF mutation

- Point mutation in amino acid position 600 (V600E) most common
- There are others, of which significance is not understood at this time
- Occurs in 1-2% of patients with lung adenocarcinoma, about half of which are V600E driver mutations
- BRAF inhibition is combined with MEK inhibition



Baik, et al. Targeting BRAF-Mutant Non-Small Cell Lung Cancer: From Molecular Profiling to Rationally Designed Therapy. The Oncologist 2017;22:786–796

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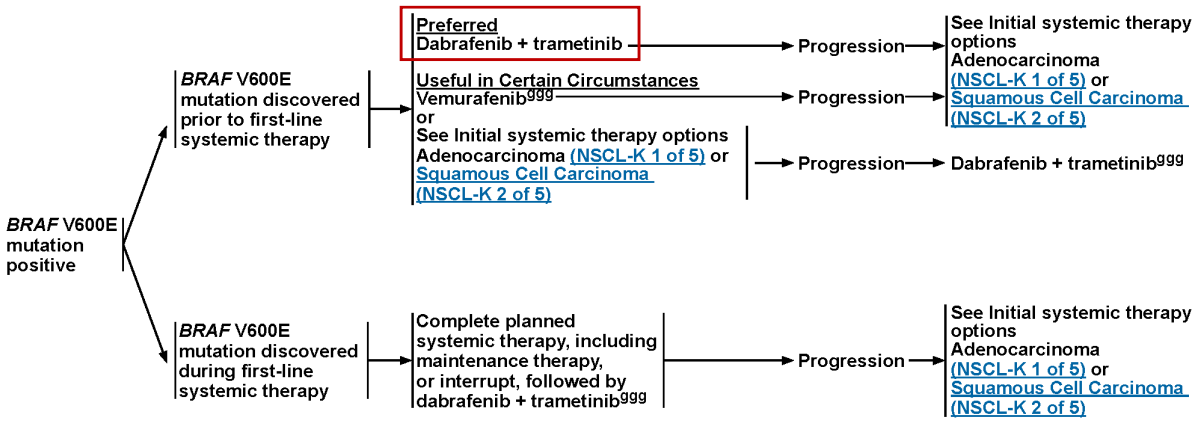
***BRAF* V600E MUTATION POSITIVE**[ll]



[ll] See Principles of Molecular and Biomarker Analysis (NSCL-H).
[oo] See Targeted Therapy or Immunotherapy for Advanced or Metastatic Disease (NSCL-J).
[ggg] Single-agent vemurafenib is a treatment option if the combination of dabrafenib + trametinib is not tolerated.

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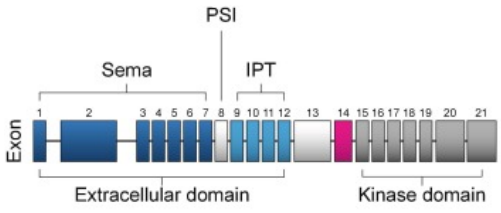
BRAF Inhibitor Side Effects

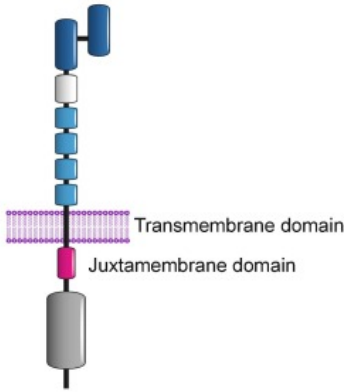
- Fever (50-60%)
- Arthralgias (~25%)
- Nausea (~40%)
- Fatigue (~55%)
- Cutaneous reactions: rash, palmar-plantar erythrodysesthesia, dry skin (~35%)
- Hyperglycemia (60-70%), or exacerbation of DM

MET Exon 14 Skipping Mutations

- MET exon 14 skipping mutation, occurs in about 3-4% patients with lung adenocarcinoma, 1-2% other histologies
- MET amplification also important, based on the ratio of MET/CEP7, but no current drug approvals for this
  - Potential resistance mechanism seen in patients treated with EGFR-TKIs



MET gene



MET receptor

Salgia, et al. The promise of selective MET inhibitors in non-small cell lung cancer with MET exon 14 skipping. Cancer Treatment Reviews 87 (2020) 102022

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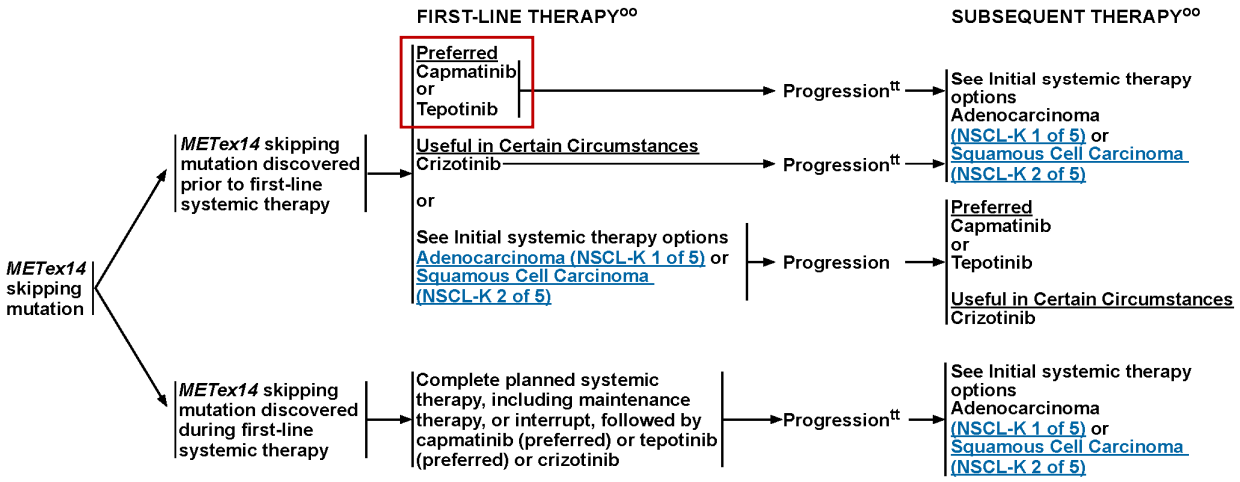
***METex14* SKIPPING MUTATION**[ll]



[ll] See Principles of Molecular and Biomarker Analysis (NSCL-H).
[oo] See Targeted Therapy or Immunotherapy for Advanced or Metastatic Disease (NSCL-J).
[tt] Beware of flare phenomenon in subset of patients who discontinue TKI. If disease flare occurs, restart TKI.

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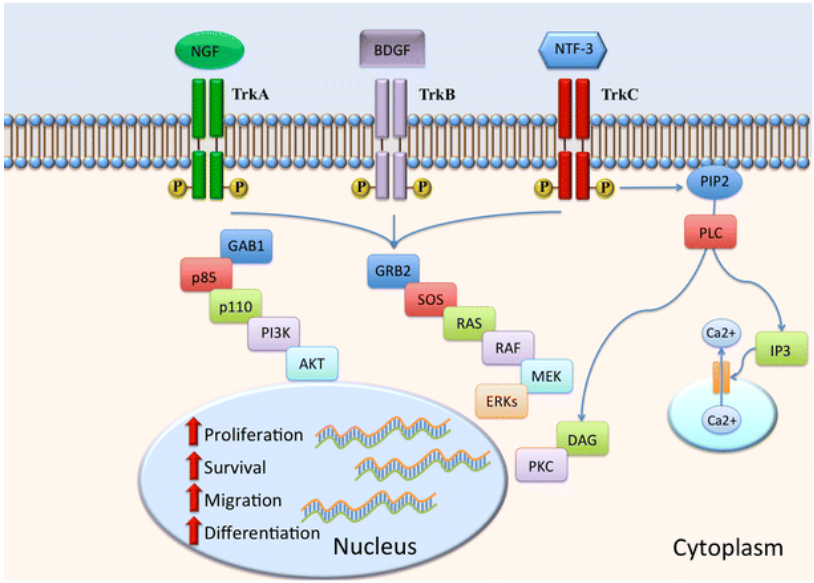
MET Inhibitor Side Effects

- Peripheral edema (52% capmatinib), edema (70% tepotinib)
- Nausea (44%) and vomiting (28%) with capmatinib, less with tepotinib
- Fatigue (32%-similar for both drugs)
- ILD/pneumonitis (4.5% capmatinib, 2.2% tepotinib)
- Hepatotoxicity: increased ALT/AST (13% both capmatinib and tepotinib)

NTRK Gene Fusions



- Occurs in about 0.2% of patients with NSCLC
- Studied in phase I studies in tumor agnostic patient population

Riciuti, et al. 2017. Targeting NTRK fusion in non-small cell lung cancer: rationale and clinical evidence. *Medical Oncology*. 34(105)

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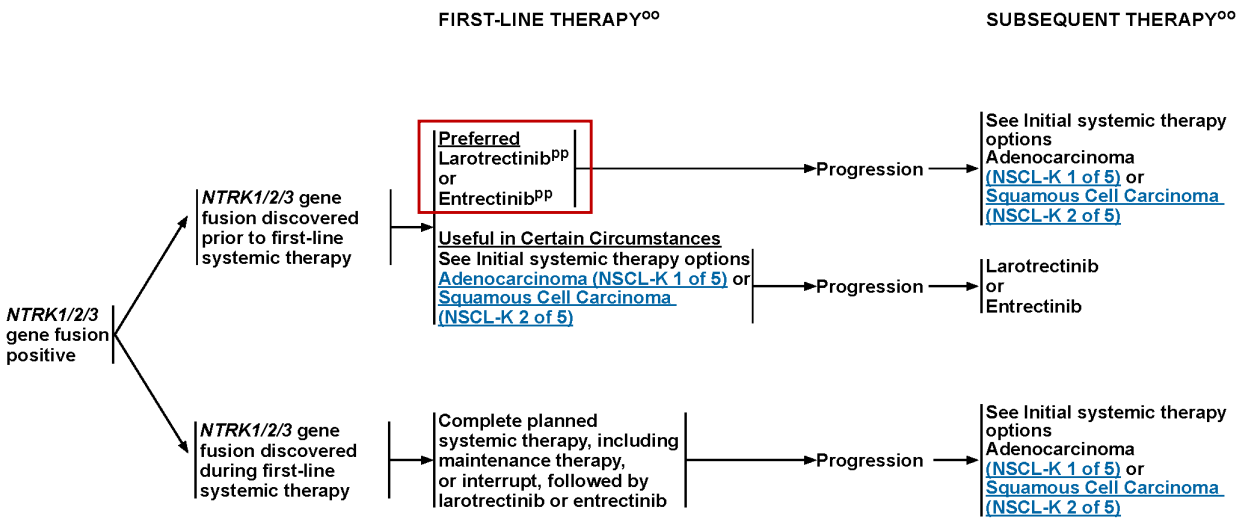
***NTRK* GENE FUSION POSITIVE**[ll]



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[pp] For performance status 0–4.

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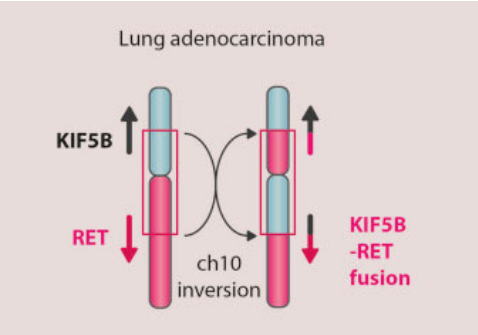
NTRK Inhibitor Side Effects

- Neurotoxicity: dizziness
- Hepatotoxicity: increased AST/ALT
- Edema
- Fatigue
- Diarrhea
- >20% incidence for larotrectinib and entrectinib

RET Rearrangements

- Common fusion partners are KIF5B, NCOA4, CCDC6, but there are others
- Occurs in 1-2% patients with NSCLC, more common in adenocarcinoma



Ferrara, et al. 2018 Clinical and Translational Implications of *RET* Rearrangements in Non–Small Cell Lung Cancer. JTO, 13(1)27-45

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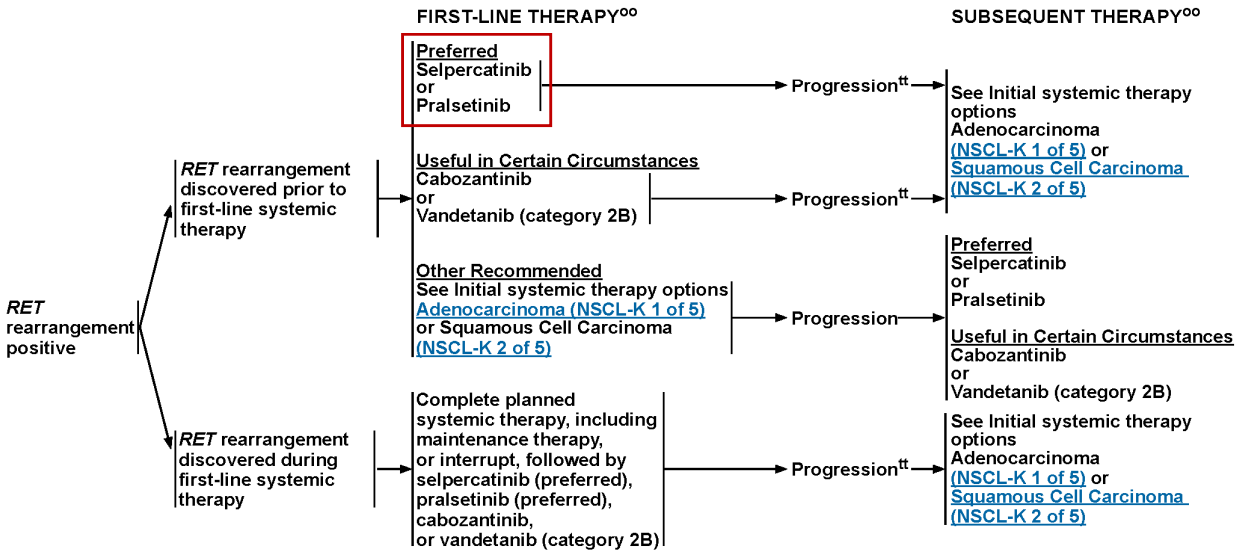
***RET* REARRANGEMENT POSITIVE**[ll]



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[tt] Beware of flare phenomenon in subset of patients who discontinue TKI. If disease flare occurs, restart TKI.

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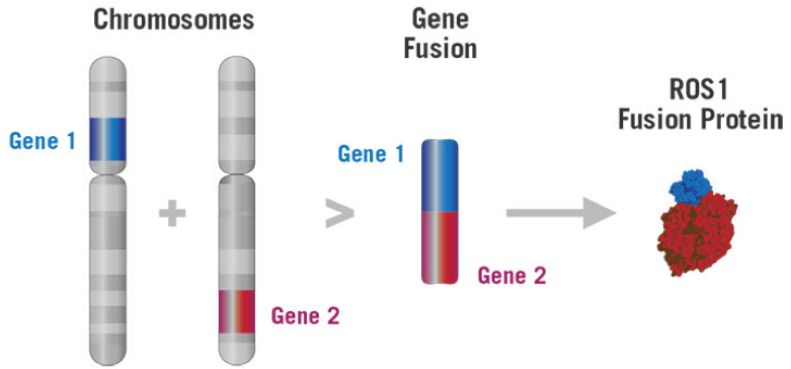
RET Inhibitor Side Effects

- Pralsetinib: most common adverse reactions (≥25%) were constipation, hypertension, fatigue, musculoskeletal pain and diarrhea
- Selpercatinib: most common adverse reactions (>15%) were gastrointestinal (dry mouth, diarrhea/constipation, nausea/vomiting), hypertension, fatigue, rash

ROS1 Fusions

- Common fusion partners are CD74, SLC34A2, CCDC6, and FIG, but there are others
- Occurs in 1-2% of patients with NSCLC
- Closely related and structurally similar to ALK oncogene



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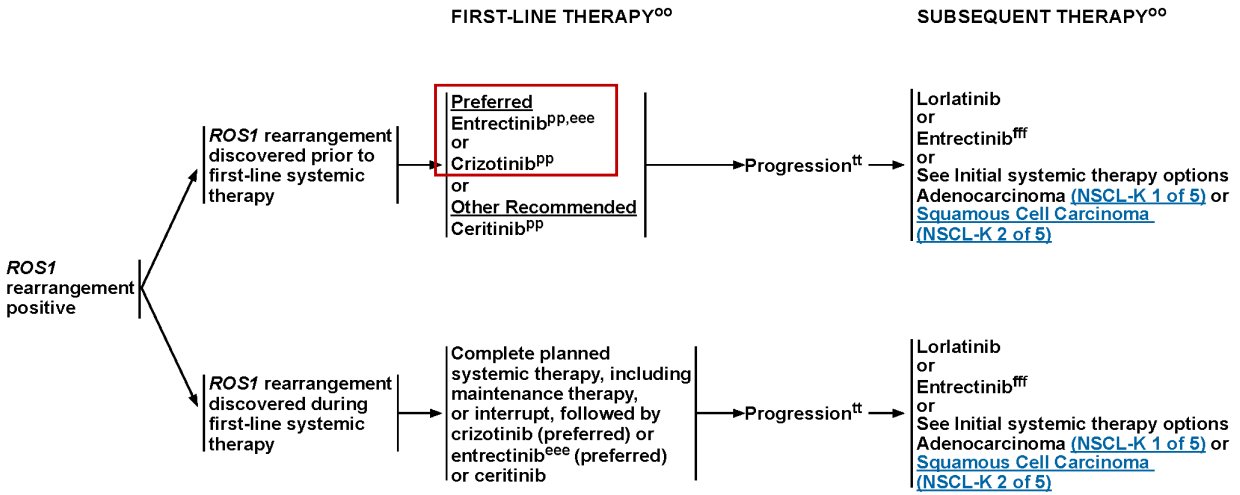
***ROS1* REARRANGEMENT POSITIVE**[ll]



[ll] See Principles of Molecular and Biomarker Analysis (NSCL-H).
[oo] See Targeted Therapy or Immunotherapy for Advanced or Metastatic Disease (NSCL-J).
[pp] For performance status 0–4.
[tt] Beware of flare phenomenon in subset of patients who discontinue TKI. If disease flare occurs, restart TKI.
[eee] Entrectinib may be better for patients with brain metastases.
[fff] Entrectinib is primarily for patients with CNS progression after crizotinib.

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ROS1 Inhibitor Side Effects

- Crizotinib: most common adverse reactions (≥25%) were vision disorders, nausea, diarrhea, vomiting, edema, constipation, elevated transaminases, fatigue, decreased appetite, upper respiratory infection, dizziness, and neuropathy
- Entrectinib: most common adverse reactions (≥ 20%) were fatigue, constipation, dysgeusia, edema, dizziness, diarrhea, nausea, dysesthesia, dyspnea, myalgia, cognitive impairment, increased weight, cough, vomiting, pyrexia, arthralgia, and vision disorder

Q: What treatment is recommended if there are no actionable molecular biomarkers but PD-L1 is positive, in patients with metastatic nonsquamous NSCLC?

- A: carboplatin + (pemetrexed or albumin-bound paclitaxel) + pembrolizumab
- B: pembrolizumab monotherapy
- C: nivolumab + ipilimumab ± pemetrexed + (carboplatin or cisplatin)
- D: All of the above

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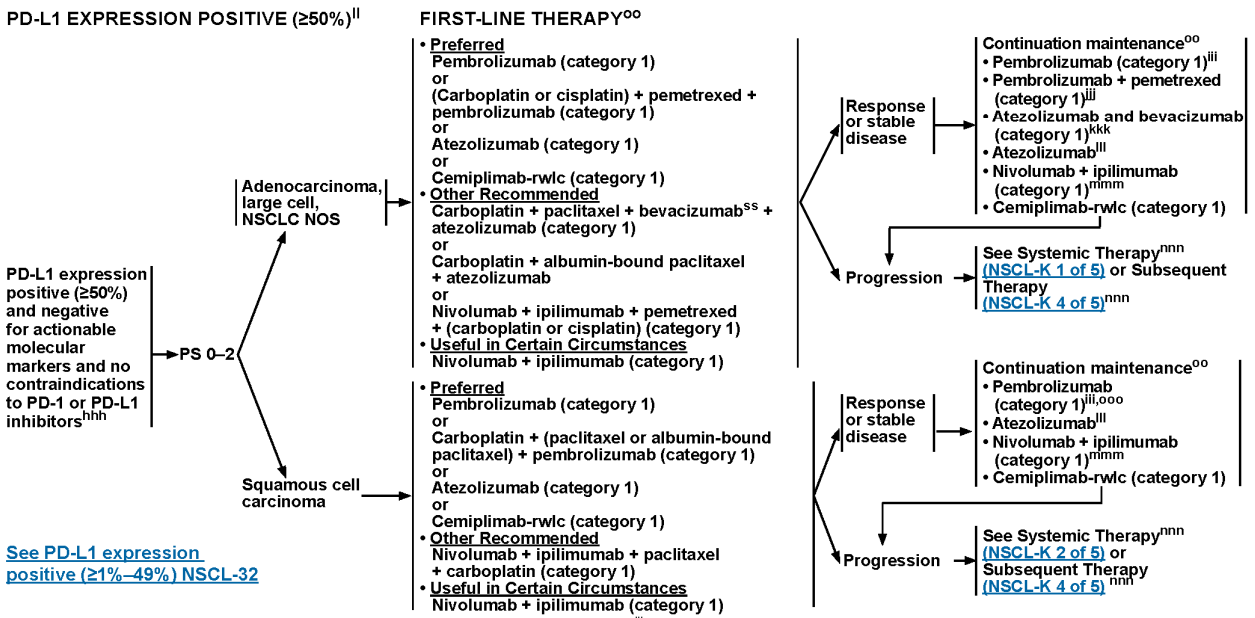

[ll] See Principles of Molecular and Biomarker Analysis (NSCL-H).
[oo] See Targeted Therapy or Immunotherapy for Advanced or Metastatic Disease (NSCL-J).
[ss] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[hhh] Contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or current use of immunosuppressive agents or presence of an oncogene, which would predict lack of benefit. If there are contraindications, refer to NSCL-K 1 of 5 (adenocarcinoma) or NSCL-K 2 of 5 (squamous cell carcinoma).
[iii] If pembrolizumab monotherapy given.
[jjj] If pembrolizumab/carboplatin/pemetrexed or pembrolizumab/cisplatin/pemetrexed given.
[kkk] If atezolizumab/carboplatin/paclitaxel/bevacizumab given.
[lll] If atezolizumab/carboplatin/albumin-bound paclitaxel or atezolizumab given (category 1 following atezolizumab alone).
[mmm] If nivolumab + ipilimumab ± chemotherapy given.
[nnn] If patient has not received platinum-doublet chemotherapy, refer to "systemic therapy." If patient received platinum chemotherapy and anti-PD-1/PD-L1, refer to "subsequent therapy."
[ooo] If pembrolizumab/carboplatin/(paclitaxel or albumin-bound paclitaxel) given.

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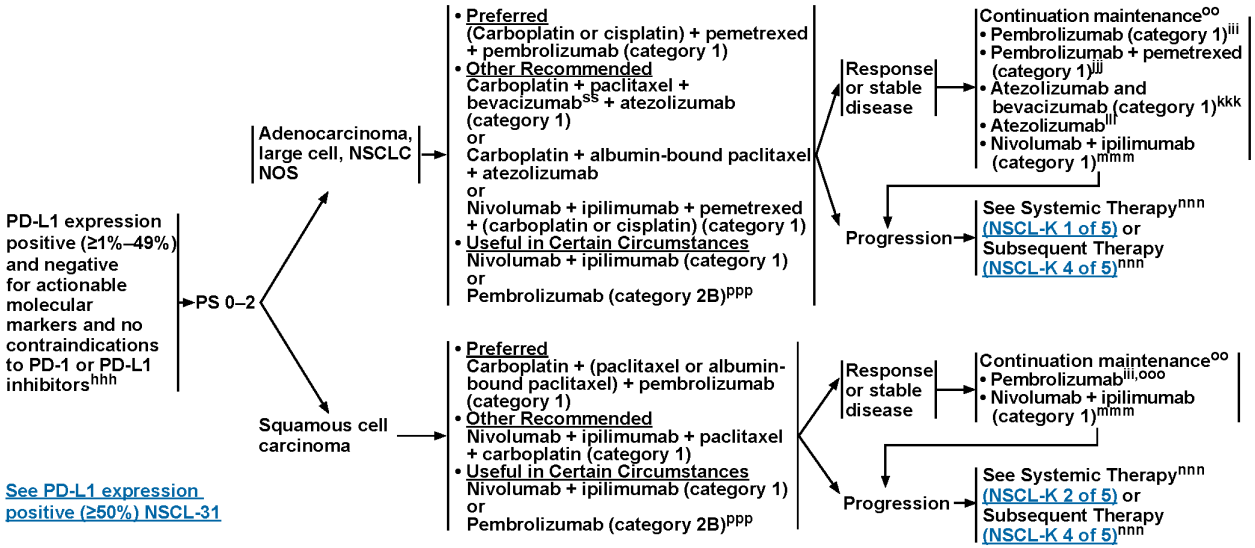
PD-L1 EXPRESSION POSITIVE (≥1%–49%)[ll] **FIRST-LINE THERAPY[oo]**



See PD-L1 expression positive (≥50%) NSCL-31

[ll] See Principles of Molecular and Biomarker Analysis (NSCL-H).
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[ooo] If pembrolizumab/carboplatin/(paclitaxel or albumin-bound paclitaxel) given.
[ppp] Pembrolizumab monotherapy can be considered in PD-L1 1%–49%, in patients with poor PS or other contraindications to combination chemotherapy.

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Immunotherapy side effects

- Any –itis!
- Pneumonitis
- Colitis
- Rash
- Hypothyroidism

Other considerations

- Adjuvant osimertinib is now approved (ADAURA trial) in eligible patients with completely resected stage IB-IIIA NSCLC
- KRAS G12C inhibitor, sotorasib, undergoing priority review by FDA.
  - KRAS mutations in about 25% patients with adenocarcinoma in North America

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  To improve and facilitate quality, effective, efficient, and accessible cancer care so patients can live better lives
- **Our Vision**
  To define and advance high-quality, high-value, patient-centered cancer care globally

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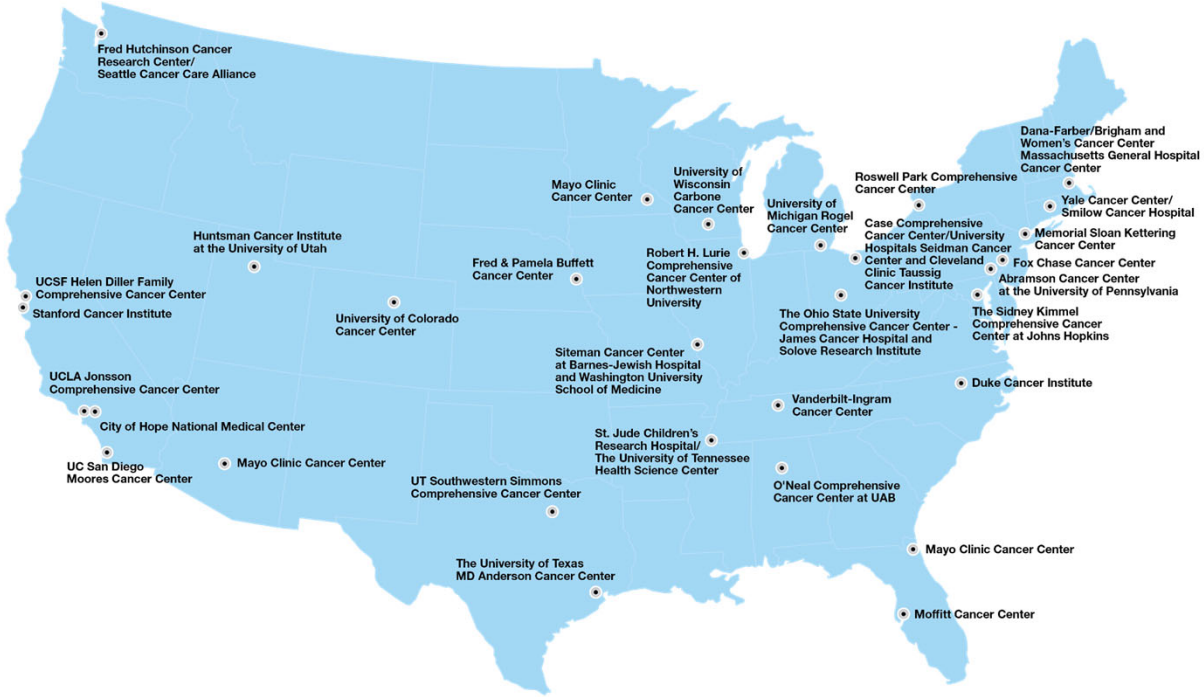

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