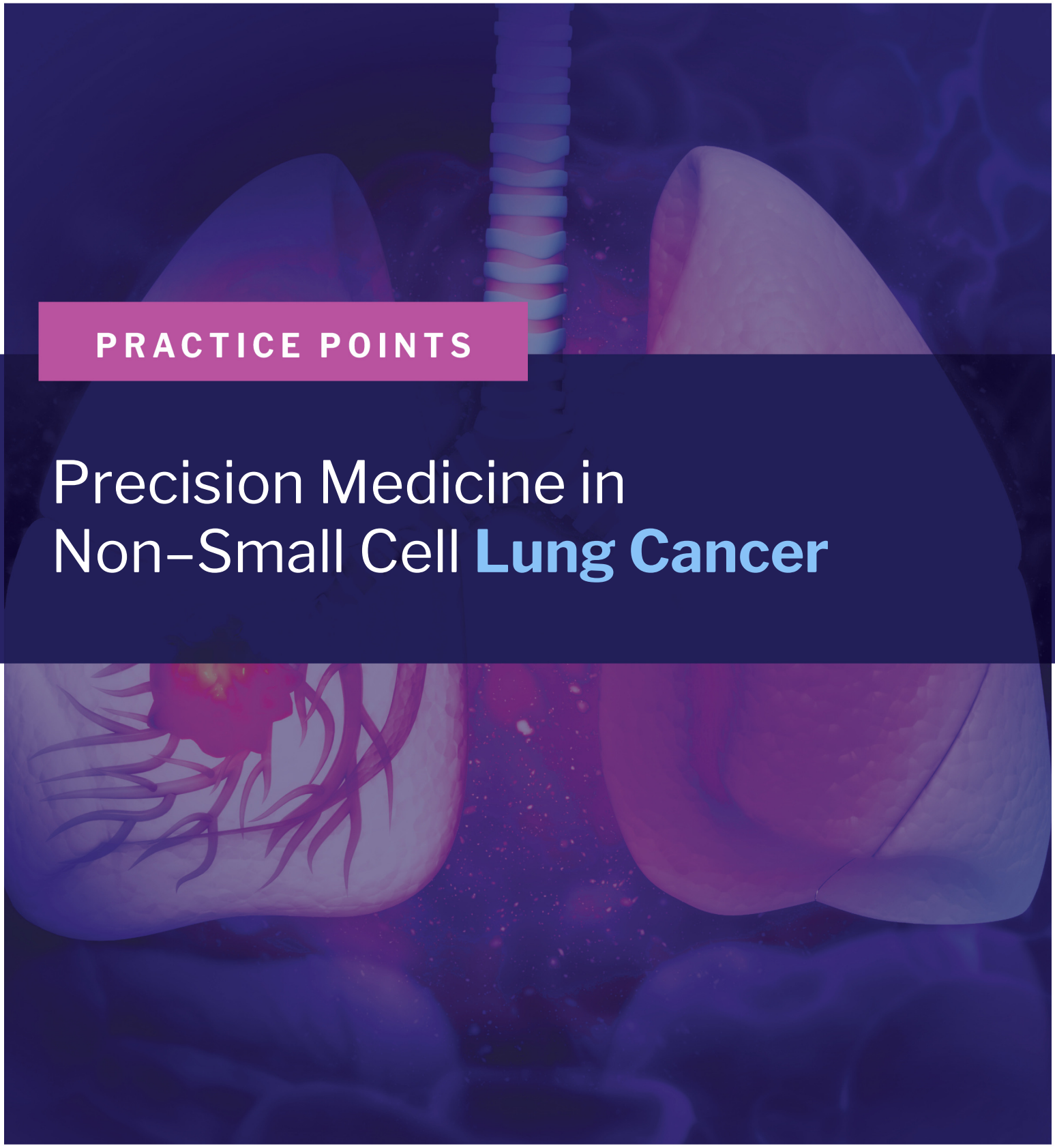

PRACTICE POINTS

Precision Medicine in Non–Small Cell **Lung Cancer**

This activity is jointly provided by PIM Postgraduate Institute for Medicine Bio Ascend™

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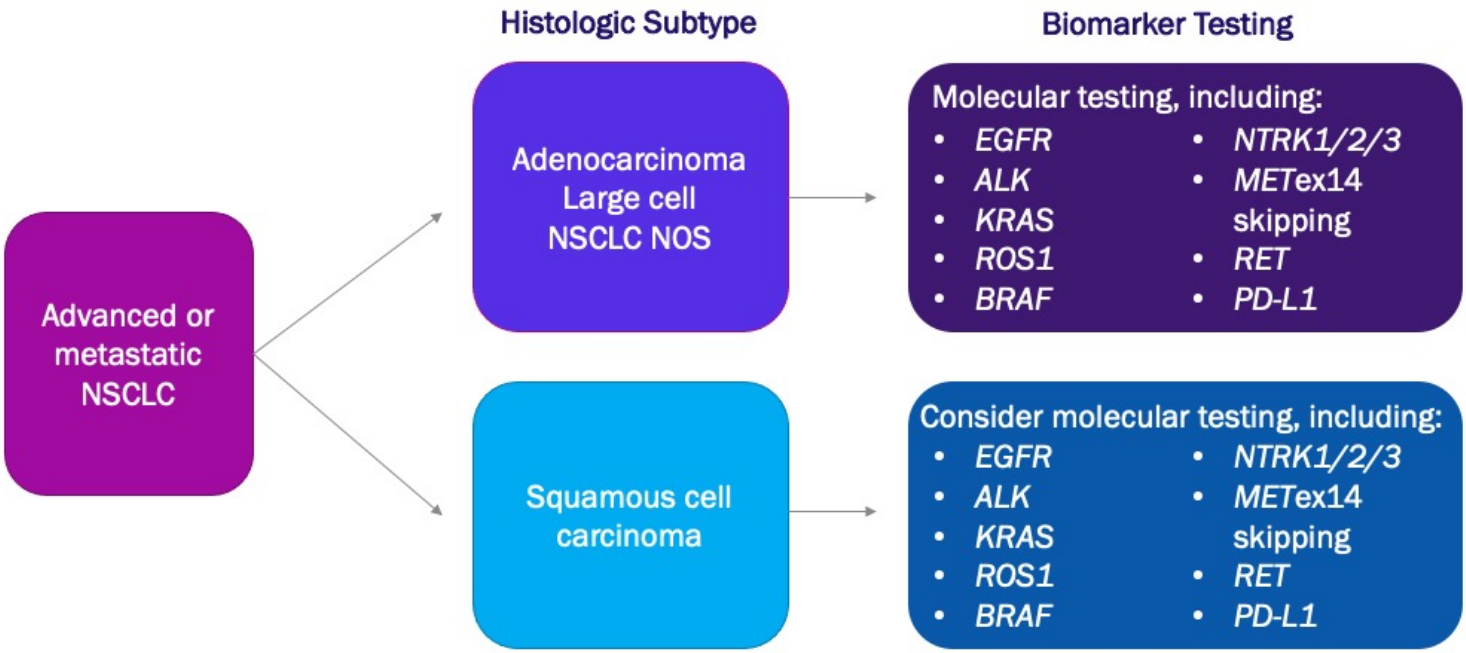
Biomarkers in Lung Cancer



- Biomarker testing detects molecular differences between NSCLCs and should be conducted as part of broad molecular profiling

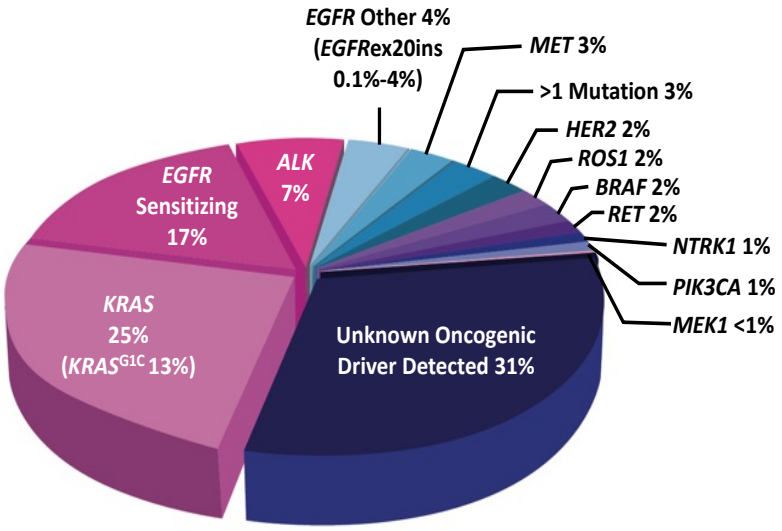
- Biomarker testing impacts treatment and should be conducted regardless of smoking history

ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; NSCLC NOS, non-small cell lung cancer not otherwise specified; PD-L1, programmed death-ligand 1.

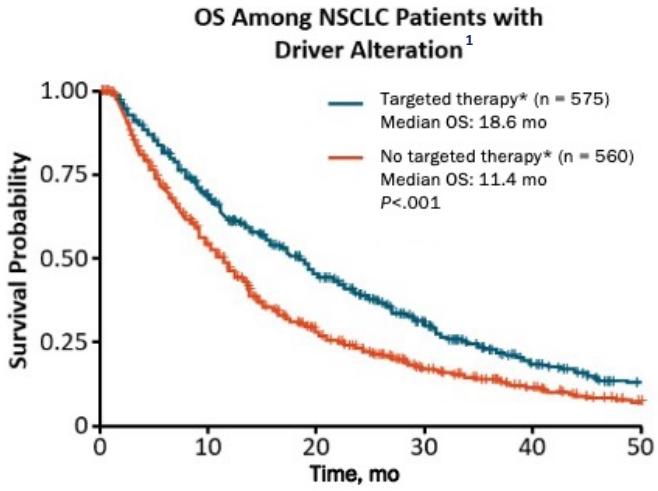
NCCN Guidelines. Non-Small Cell Lung Cancer. V3.2022.

PRACTICE POINTS

Evolving Treatments for NSCLC With Driver Mutations



Driver Mutation	FDA-Approved Therapies
EGFR (del 19 or L858R	Osimertinib (preferred), erlotinib, afatinib, gefitinib, dacomitinib
EGFR Exon 20 ins	Amivantamab, mobocertinib
ALK	Alectinib, brigatinib, lorlatanib, ceritinib, crizotinib
ROS1	Crizotinib, entrectanib
BRAF V600E	Dabrafanib/trametinib
NTRK 1,2,3	Entrectanib, larotrectinib
RET	Selpercatinib, pralsetinib
*MET*ex14 skip	Capmatinib, tepotinib
KRAS G12C	Sotorasib



*Agents selected per NCCN recommendations for specific driver mutations

- Patients with identified driver mutations that receive biomarker-driven targeted therapies have improved clinical outcomes[2]

ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; NCCN, National Comprehensive Cancer Network; NSCLC; non-small cell lung cancer; OS, overall survival

1. NCCN Guidelines. Non-Small Cell Lung Cancer. V3.2022. 2. Singal G, et al. *JAMA*. 2019;321: 1391-1399.

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Select Common Toxicities With Targeted Therapies for NSCLC

Adverse Event	Commonly occurs with:
Rash	Osimertinib, amivantamab, mobocertinib
Paronychia	Osimertinib, amivantamab
Diarrhea	Osimertinib, mobocertinib, sotorasib, selpercatinib
Nausea	Sotorasib, tepotinib/capmatinib
Edema	Tepotinib/capmatinib
Constipation	Pralsetinib
Infusion-related reactions	Amivantamab
Hypertension	Selpercatinib, pralsetinib

Key Strategies to Manage Treatment-Related AEs

- Determine baseline prior to starting treatment
- Establish realistic expectations of treatment and possible AEs
- Stress the importance of reporting all symptoms
- Utilize CTCAE to help determine appropriate intervention

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; NSCLC, non-small cell lung cancer.
NCCN Guidelines. Non-Small Cell Lung Cancer. V3.2022.

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EGFR Inhibitors: Dosing and Side Effects/Precautions

Actionable Target	Agents	Dosage and Administration	Warning/Precautions and Common Toxicities
***EGFR* T790M, L858R**	Osimertinib (preferred frontline treatment)	80 mg daily with or without food	**AEs:** diarrhea, rash, dry skin, nail toxicity, fatigue **Precautions:** ILD/pneumonitis, QTc interval prolongation, cardiomyopathy, keratitis **Drug-drug interactions:** AVOID, if possible, strong CYP3A inducers or Osimertinib 160 mg daily
***EGFR* exon 20 Insertion**	Amivantamab	Weight-based: <80 kg: 1050 mg >80 kg: 1400 mg Administration: IV	**AEs:** rash, fatigue, edema, paronychia, musculoskeletal pain, dyspnea, cough, nausea, vomiting, stomatitis, constipation, IRR **Precautions:** IRR, ILD/pneumonitis, dermatologic AEs, ocular toxicity **Lab abnormalities:** ↓ albumin, phosphate, electrolytes, lymphocytes ↑ glucose, creatinine, liver function tests: alk. phos, ALT, AST, GGT
	Mobocertinib	160 mg daily with food (40 mg capsules, 4 capsules daily)	**AEs:** diarrhea, stomatitis, ↓ appetite, nausea, vomiting, ↓ weight, dry skin, rash, paronychia, fatigue, cough **Precautions:** ILD/pneumonitis, cardiac toxicity, diarrhea **Drug-drug interactions:** strong, moderate CYP3A inhibitors, inducers **Lab abnormalities:** ↓ RBC, lymphocytes, platelets, leukocytes, potassium ↑ creatinine, amylase, lipase, alk phos

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CYP3A, cytochrome P450, family 3, subfamily A; EGFR, epidermal growth factor receptor; GGT, gamma-glutamyl transferase; ILD, interstitial lung disease; IRR, infusion-related reaction; IV, intravenous; RBC, red blood cell.
Prescribing Information.

PRACTICE POINTS

KRAS Inhibitors: Dosing and Side Effects/Precautions

Actionable Target	Agent	Dosage and Administration	Warning/Precautions and Common Toxicities
***KRAS* G12C**	Sotorasib	960 mg daily with or without food Dosage: 8 tables po daily	**AEs:** diarrhea, nausea, musculoskeletal pain, fatigue, hepatoxicity, ILD/pneumonitis, rash, cough **Precautions:** ILD, pneumonitis, hepatoxicity **Drug-drug interactions:** AVOID concurrent use of PPI and H2RA. *Could use OTC acid-reducing medication.* Avoid strong CYP3A4 inducers **Lab abnormalities:** ↓ calcium, sodium, lymphocytes, hemoglobin ↑ AST, ALT, alkaline phosphatase, urine protein

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CYP3A, cytochrome P450, family 3, subfamily A; H2RA, histamine H2 receptor antagonist; ILD, interstitial lung disease; OTC, over the counter; PO, by mouth; PPI, proton pump inhibitor.
Prescribing Information.

PRACTICE POINTS

MET Inhibitors: Dosing and Side Effects/Precautions

Actionable Target	Agents	Dosage and Administration	Warning/Precautions and Common Toxicities
***MET* Exon 14 Skipping**	Capmatinib	400 mg BID with or without food Dosage: 150 mg or 200 mg tablets	**AEs:** Peripheral edema, fatigue, nausea, vomiting, decreased appetite, dyspnea **Precautions:** ILD/pneumonitis, hepatotoxicity, photosensitivity, embryo-fetal toxicity **Drug-drug interactions:** strong, moderate CYP3A inducers **Lab abnormalities:** ↓ albumin ↑ creatinine, ALT, AST, GGT, amylase, lipase, alk phos
	Tepotinib	450 mg daily with food Dosage: 225 mg tablets	**AEs:** Edema, fatigue, nausea, diarrhea, musculoskeletal pain, dyspnea **Precautions:** ILD/pneumonitis, hepatotoxicity, embryo-fetal toxicity **Drug-drug interactions:** Dual strong CYP3A + P-gp inhibitors, strong CYP3A inducers **Lab abnormalities:** ↓ albumin, sodium ↑ creatinine, ALT, AST, GGT, amylase, alk phos., potassium

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, two times a day; CYP3A, cytochrome P450, family 3, subfamily A; GGT, gamma-glutamyl transferase; ILD, interstitial lung disease; IRR, infusion-related reaction; P-gp, P-glycoprotein.
Prescribing Information.

PRACTICE POINTS

RET Inhibitors: Dosing and Side Effects/Precautions

Actionable Target	Agents	Dosage and Administration	Warning/Precautions and Common Toxicities
***RET* Fusion**	Selpercatinib	Dose: weight-based <50 kg: 120 mg BID with or w/o food ≥50 kg: 160 mg BID with or w/o food Dosage: 40 mg, 80 mg capsules	**AEs:** dry mouth, diarrhea, constipation, nausea, abdominal pain, hypertension, fatigue, edema, rash **Precautions:** hepatotoxicity, hypertension, QT prolongation, hemorrhagic events, TLS, impaired wound healing, embryo-fetal toxicity **Drug-drug interactions:** PPIs-may take with food with PPI, AVOID strong, moderate CYP3A4 inducers **Lab abnormalities:** ↓ albumin, calcium, sodium, leukocytes, platelets ↑ AST, ALT, glucose, creatinine, alkaline phosphatase, total cholesterol
	Pralsetinib	400 mg daily on an empty stomach Dosage: 100 mg capsules	**AEs:** constipation, hypertension, fatigue, edema, musculoskeletal pain, diarrhea, fever, cough **Precautions:** ILD/pneumonitis, hepatotoxicity, hypertension, hemorrhagic events, TLS, impaired wound healing, embryo-fetal toxicity **Drug-drug interactions:** Strong CYP3A4 inhibitors and inducers, combined P-gp and strong CYP3A4 inhibitors **Lab abnormalities:** ↓ calcium, albumin, phosphate, sodium, neutrophils, hemoglobin, lymphocytes, platelets ↑ AST, ALT, alkaline phosphatase, creatinine, potassium

AEs, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, two times a day; CYP3A, cytochrome P450, family 3, subfamily A; ILD, interstitial lung disease; P-gp, P-glycoprotein; PPI, proton pump inhibitor; TLS, tumor lysis syndrome.
Prescribing Information.

PRACTICE POINTS

AE Management Strategies: Dermatologic Toxicity

Rash

- Mild to moderate rash:
  - Topical corticosteroid +/- clindamycin
  - Oral tetracycline antibiotic
- Mild to moderate pruritus:
  - Topical antipruritics
- Rash on scalp:
  - Topical corticosteroids solutions/ lotions
  - Aluminum acetate soak for confluent crusting

Paronychia

- Mild to moderate paronychia:
  - Topical corticosteroids, antibiotics, antifungals, antiseptics
  - White vinegar soaks
  - Oral antibiotics

AE, adverse event.
Chu C, et al. *Oncologist*. 2018;23:891–899; Califano R, et al. *Drugs*. 2015;75(12):1335-1348.

PRACTICE POINTS

AE Management Strategies: GI Toxicity

Diarrhea

- Mild to moderate diarrhea should have dietary modifications
  - Eliminating lactose containing products
  - Avoid alcohol and caffeinated drinks
- Start loperamide 4 mg initially, then 2 mg after every loose stool (maximum 16 mg/day)
- If diarrhea persist, evaluate for possible infection
- Increase oral hydration for mild diarrhea, IV hydration for grade 3–4 diarrhea and electrolyte replacement

Nausea

- Can consider to take oral therapeutic treatment with food if not contraindicated per the PI
- 5-HT3 receptor antagonist
- Dopamine receptor antagonist
- Cannabinoid receptor agonists (eg., dronabinol)
- Complementary alternative therapies
  - Ginger supplementation
  - Acupressure

Constipation

- Increase dietary fiber, fluids, and exercise
- Start laxative
  - Senna, lactulose, polyethylene glycol
- Can add bisacodyl and 2 or more laxatives (stimulant and osmotic)

5-HT3, 5-hydroxytryptamine; AE, adverse event; GI, gastrointestinal; IV, intravenous; PI, prescribing information.

Benson A, et al. *J Clin Oncol*. 2004;22:2918-2926; Bossi P, et al. *Ann Oncol*. 2018;29 (Suppl 4):iv126-iv142. Ryan J., *Eur Oncol.* 2010;6(2):14-16; Hesthketh, P. et al. *J Clin Oncol*. 2017;28:3240-3261. Wickham R J, et al. J *Adv Prac Oncol*. 2017;8:149-161.

PRACTICE POINTS

AE Management Strategies: Other Select AEs

Edema

- Compression stockings 20–30mmHg
- Lymphedema treatment
- Can consider diuretics
  - Monitoring of electrolytes and renal function

Hypertension

- Optimal antihypertensive control prior to starting treatment
- Monitor blood pressure after one week and at least monthly thereafter
- Educate patients on the importance of self-monitoring BP
- If blood pressure is uncontrolled despite maximum optimal antihypertensive control, dose interruption, reduction, or permanent discontinuation may be needed based on PI and severity

AE, adverse event; BP, blood pressure; PI, prescribing information.
Goodwin K, et al. *J Thor Oncol*. 2021;16(1):S16-S17.

PRACTICE POINTS

Strategies to Help Patients Navigate Treatment

- Direct patients to reliable resources, for example
  - LUNGEVITY Foundation - www.lungevity.org
  - American Lung Association - www.lung.org

- Discuss social determinants of health, financial implications, and barriers to optimal care

- Recognize patient's voice
  - Use shared decision-making models

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Summary

- Because of highly effective targeted therapies (and lack of efficacy with immunotherapy), testing for *EGFR/ALK/ROS1/BRAF/NTRK/MET*ex14*/RET* at diagnosis is mandatory for all patients with advanced NSCLC
  - Broad testing with next-generation sequencing for both required and emerging biomarkers is highly recommended!
- PD-L1 testing still important in initial decision making, but biomarker testing is necessary to determine optimal treatment for the patient. For patients with most actionable mutations, targeted therapy is preferred regardless of PD-L1 status
- Molecular testing is moving into the early-stage setting—biomarker-directed targeted therapy and immunotherapy options now approved as adjuvant therapy for these patients
  - Approval of neoadjuvant nivolumab in combination with chemotherapy regardless of PD-L1 expression

ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death ligand 1.

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