CLINICAL COMPENDIUM: METASTATIC SQUAMOUS NON-SMALL CELL LUNG CANCER

QUESTIONS, ANSWERS, AND TEXT SUMMARY OF RATIONALES

QUESTION 1:

1. Which of these is TRUE about NSCLC of squamous histology?

a. *EGFR* and *KRAS* mutations are common in squamous NSCLC, occurring in 35%-40% of cases at initial diagnosis
b. TTF1 and Napsin A are considered markers of squamous histology
c. Squamous NSCLC tumors are characterized by the presence of intercellular bridges and keratinization
d. Squamous NSCLC tumors present in a glandular pattern with papillary structures

The correct answer is c. **Squamous NSCLC tumors are characterized by the presence of intercellular bridges and keratinization**

Text Summary of Rationale:

- Accurate histological subtyping of NSCLC is a crucial component of the care paradigm as it can drive subsequent molecular/genetic testing and treatment decisions.[1]
- Squamous cell carcinoma (sqCC) is characterized by the presence of intracellular bridges and keratinization, while a glandular pattern or cytoplasmic mucus is characteristic of lung adenocarcinomas (ADCs).[2,3]
- Polygonal cells with intercellular bridges and crisp eosinophilic cytoplasm are hallmarks of sqCC tumors;4 squamous tumors may also contain keratinization, as keratin pearls or as deeply eosinophilic dyskeratotic malignant cells.[4]
- While mutations in EGFR and KRAS, along with EML4-ALK fusions, are the 3 most frequent driver alterations in ADC,[1,5] the prevalence of EGFR mutations is much lower in sqCC.[1]

References:

1. Socinski MA, Obasaju C, Gandara D, et al. Clinicopathologic features of advanced squamous NSCLC. *J Thorac Oncol*. 2016;11(9):1411-1422. doi:10.1016/j.jtho.2016.05.024
2. Kashima J, Kitadai R, Okuma Y. Molecular and morphological profiling of lung cancer: A foundation for "next-generation" pathologists and oncologists. *Cancers*. 2019;11(5):599. doi:10.3390/cancers11050599
3. Petersen I. The morphological and molecular diagnosis of lung cancer. *Dtsch Arzteblatt Int*. 2011;108(31-32):525-531. doi:10.3238/arztebl.2011.0525
4. Suarez E, Knollmann-Ritschel BEC. Squamous cell carcinoma of the lung. *Acad Pathol*. 2017;4. doi:10.1177/2374289517705950
5. Pikor LA, Ramnarine VR, Lam S, Lam WL. Genetic alterations defining NSCLC subtypes and their therapeutic implications. *Lung Cancer Amst Neth*. 2013;82(2):179-189. doi:10.1016/j.lungcan.2013.07.025

QUESTION 2.

2. What fraction of lung cancers exhibit morphological features of both adenocarcinoma and squamous histologic subtypes?

a. 30%
b. 10%
c. 50%
d. None

The correct answer is b. **10% of lung cancers**

Text Summary of Rationale:

- Small biopsy and cytologic samples, rather than resection samples, are used in diagnosis of most advanced lung cancers.[1]
- Non-small cell lung cancer (NSCLC) includes adenocarcinoma (around 50% of NSCLC) and squamous cell carcinoma (around 30% of NSCLC) subtypes.[2]
- The NCCN defines squamous cell carcinoma as a malignant epithelial tumor that 1) shows either keratinization and/or intercellular bridges; or 2) is an undifferentiated NSCLC positive for squamous cell carcinoma markers by immunohistochemistry (IHC).[3]
- Tumors with mixed adenocarcinoma and squamous cell carcinoma components, with each component comprising ≥10% of the tumor, are classified as "adenosquamous".[1,3]

References:

1. Socinski MA, Obasaju C, Gandara D, et al. Clinicopathologic features of advanced squamous NSCLC. *J Thorac Oncol*. 2016;11(9):1411-1422. doi:10.1016/j.jtho.2016.05.024
2. Sabbula B, Anjum F. Squamous cell lung cancer. *StatPearls Internet*. Published online January 2021. Accessed March 25, 2021. https://pubmed.ncbi.nlm.nih.gov/33232091/
3. Ettinger DS, Wood DE, Aisner DL, Akerley W. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Non-Small Cell Lung Cancer Version 5.2021. Published June 15, 2021. Accessed March 25, 2021. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

QUESTION 3.

3. Which of these markers, assessed using immunohistochemical analysis, is best suited to help identify the histologic subtype in cases of poorly differentiated or undifferentiated NSCLC?

a. p63 and Napsin A
b. TTF-1 and Napsin A
c. Cytokeratin 5/6 and p40
d. None of the above

The correct answer is c. **Cytokeratin 5/6 and p40**

Text Summary of Rationale:

- When limited tissue is available and/or the tumor is poorly differentiated, IHC should be utilized to distinguish between lung sqCC, lung ADC, metastatic malignancy, and primary pleural mesothelioma (particularly for pleural samplings).[1,2]
- In small specimens, a limited number of immunostains with 1 lung ADC marker (TTF1, napsin A) and 1 sqCC marker (p40, p63) should suffice for most diagnostic problems.[2]
- While nearly all tumors lacking squamous cell morphology and co-expressing p63 and TTF1 are preferably classified as ADC, a limitation of p63 is low specificity.[2,3]
- p40 is a relatively new predictive marker for sqCC with sensitivity comparable to that of p63, but superior specificity.[3]
- Cytokeratin 5/6 may also be a useful marker for sqCC, particularly in cases of poorly differentiated or undifferentiated NSCLC.[3]

References:

1. Kashima J, Kitadai R, Okuma Y. Molecular and morphological profiling of lung cancer: A foundation for "next-generation" pathologists and oncologists. *Cancers*. 2019;11(5):599. doi:10.3390/cancers11050599
2. Ettinger DS, Wood DE, Aisner DL, Akerley W. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Non-Small Cell Lung Cancer Version 5.2021. Published June 15, 2021. Accessed March 25, 2021. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf
3. Socinski MA, Obasaju C, Gandara D, et al. Clinicopathologic features of advanced squamous NSCLC. *J Thorac Oncol*. 2016;11(9):1411-1422. doi:10.1016/j.jtho.2016.05.024

QUESTION 4.

4. Which of these clinicopathologic features is associated with squamous NSCLC?

a. Peripherally located and related to surface alveolar epithelium or bronchial mucosal glands
b. Better prognosis than patients with adenocarcinoma subtypes of NSCLC
c. Accounts for 85% of all lung cancers
d. Associated with central tumors and cavitation

The correct answer is d. **Squamous NSCLC is associated with central tumors and cavitation**

Text Summary of Rationale:

The histologic subtype of NSCLC correlates with the site of origin of the tumor.

- Squamous cell tumors are usually centrally located (within 2 cm in all directions of any mediastinal critical structure), typically beginning in early versions of flat cells that line the inside of the lung airways and arising in the proximal bronchi.[1,2]
- Given this location, these tumors are more likely to invade larger blood vessels and vital structures in the mediastinum, leading to bronchial obstruction.[1] Squamous lung tumors are also associated with tumor cavitation, with more than 80% of cavitating tumors identified as sqCC.[1]
- Conversely, ADC are usually located peripherally and related to surface alveolar epithelium or bronchial mucosal glands.[1]
- These clinical features, particularly cavitation, may account for the increased risk for potentially fatal pulmonary hemorrhage in patients with sqCC, compared with those diagnosed with lung ADC.[1]

References:

1. Socinski MA, Obasaju C, Gandara D, et al. Clinicopathologic features of advanced squamous NSCLC. *J Thorac Oncol*. 2016;11(9):1411-1422. doi:10.1016/j.jtho.2016.05.024
2. Ettinger DS, Wood DE, Aisner DL, Akerley W. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Non-Small Cell Lung Cancer Version 5.2021. Published June 15, 2021. Accessed March 25, 2021. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

QUESTION 5.

5. What is the frequency of EGFR mutations and ALK rearrangements in squamous NSCLC?

a. 10%-12% and 4%-6%
b. 2.5%-3% and 1.5%-2.5%
c. 5%-10% and 0%
d. 2.5%-5% and 20%-25%

The correct answer is b. **EGFR mutations and ALK rearrangements occur in 2.5%-3% and 1.5%-2.5% of squamous NSCLC, respectively**

Text Summary of Rationale:

- Mutations in EGFR and KRAS, along with EML4-ALK fusions, are the 3 most frequent driver alterations in ADC, occurring with mutual exclusivity in approximately 35%–40% of tumors.[1,2]
- However, the prevalence of EGFR mutations and ALK rearrangements is much lower in squamous lung tumors, occurring in approximately 2.5%–3% and 1.5%–2.5%, respectively, of squamous NSCLC.[1-3]
- Despite the low frequency of EGFR mutations or ALK rearrangements, squamous NSCLC nevertheless has a high overall mutation rate and marked genomic complexity.[1]
- Moreover, EGFR overexpression is observed in 60%–80% of squamous cell tumors; 7%–10% of these tumors also demonstrate EGFR gene copy-number alterations.[3]

References:

1. Socinski MA, Obasaju C, Gandara D, et al. Clinicopathologic features of advanced squamous NSCLC. *J Thorac Oncol*. 2016;11(9):1411-1422. doi:10.1016/j.jtho.2016.05.024
2. Ettinger DS, Wood DE, Aisner DL, Akerley W. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Non-Small Cell Lung Cancer Version 5.2021. Published June 15, 2021. Accessed March 25, 2021. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf
3. Hirsh V. New developments in the treatment of advanced squamous cell lung cancer: focus on afatinib. *Onco Targets Ther.* 2017;10:2513-2526. Published 2017 May 11. doi:10.2147/OTT.S104177

QUESTION 6.

6. Which biomarkers should you consider testing for a patient with confirmed advanced squamous NSCLC, based on the latest NCCN clinical practice guidelines for NSCLC?

a. No molecular testing is indicated for squamous NSCLC
b. EGFR mutation, ALK, ROS1, BRAF, NTRK1/2/3, MET exon 14 skipping, RET, and PD-L1
c. EGFR mutation, ALK, ROS1, BRAF, NTRK1/2/3, MET exon 14 skipping, RET, and PD-L1, but only in patients without a history of smoking
d. PD-L1 only

The correct answer is b. **EGFR mutation, ALK, ROS1, BRAF, NTRK1/2/3, MET exon 14 skipping, RET, and PD-L1 are the markers recommended for testing in patients with confirmed advanced squamous NSCLC**

Text Summary of Rationale:

The NCCN Clinical Practice Guidelines in Oncology for NSCLC (Version 4.2021) include recommendations for considering molecular testing for – EGFR mutation, ALK rearrangements, ROS1 rearrangements, BRAF mutation, NTRK1/2/3 mutation, MET exon 14 skipping, RET rearrangements, and PD-L1 expression – for all patients with advanced/metastatic NSCLC.

- This testing is recommended in the context of broader molecular profiling to help identify rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding clinical trials.
- Given the collective significance of molecular testing for guiding targeted therapy decisions, the guidelines no longer include the qualifiers of never smokers, small biopsy specimens, or mixed histology for molecular testing in patients with advanced squamous NSCLC.

References:

1. Ettinger DS, Wood DE, Aisner DL, Akerley W. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Non-Small Cell Lung Cancer Version 5.2021. Published June 15, 2021. Accessed March 25, 2021. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

QUESTION 7.

7. Based on the updated NCCN guidelines, molecular testing for patients with advanced/metastatic squamous NSCLC should be considered

a. In never smokers, with mixed histology only
b. In patients with a history of smoking, regardless of histologic subtype
c. Regardless of smoking history, but only in patients with mixed histology
d. Regardless of smoking history or presence of mixed histology

The correct answer is d. **Molecular testing should be considered for all patients with advanced/metastatic squamous NSCLC regardless of smoking history or presence of mixed histology**

Text Summary of Rationale:

Based on the collective significance of molecular testing for guiding targeted therapy decisions, the qualifiers of never smokers, small biopsy specimens, and mixed histology have been removed from the March 2021 update of the NCCN guideline recommendations for molecular testing in patients with advanced squamous NSCLC.

References:

1. Ettinger DS, Wood DE, Aisner DL, Akerley W. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Non-Small Cell Lung Cancer Version 5.2021. Published June 15, 2021. Accessed March 25, 2021. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

QUESTION 8.

2. Which of these molecular testing data are required for a patient diagnosed with advanced squamous NSCLC to be considered for first-line pembrolizumab monotherapy?

a. Programmed death ligand 1 (PD-L1) Tumor Proportion Score (TPS) ≥1% as determined by an FDA-approved test, with no EGFR or ALK genomic tumor changes
b. PD-L1 TPS =10% as determined by an FDA-approved test, with no EGFR or ALK genomic tumor changes
c. PD-L1 TPS =1% as determined by an FDA-approved test, regardless of EGFR or ALK genomic tumor status
d. PD-L1 TPS =0% as determined by an FDA-approved test, regardless of other actionable mutations

The correct answer is a. **Programmed death ligand 1 (PD-L1) Tumor Proportion Score (TPS) ≥1% as determined by an FDA-approved test, with no EGFR or ALK genomic tumor changes**

Text Summary of Rationale:

The US FDA approved pembrolizumab as a single agent for the first-line treatment of patients with metastatic NSCLC expressing PD-L1 (Tumor Proportion Score [TPS] ≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations.[1,2]

- The approval was based on KEYNOTE-042 (NCT02220894), a randomized, multicenter, open-label, active-controlled trial of patients with stage III or IV NSCLC who had not received prior systemic treatment for metastatic NSCLC and whose tumors expressed PD-L1 (TPS ≥1%), as determined by an immunohistochemistry assay using the PD-L1 IHC 22C3 pharmDx Kit.[3]
- Of the 1274 patients, 599 (47%) had a TPS ≥50% and 818 patients (64%) had a TPS ≥20%. Overall survival was significantly longer in the pembrolizumab group than in the chemotherapy group in all 3 TPS populations (≥50% hazard ratio [HR] 0.69, 95% CI 0.56–0·.5, *P*=0.0003; ≥20% 0.77, 0.64–0.92, *P*=0.0020, and ≥1% 0.81, 0.71–0.93, *P*=0.0018).
- Notably, most of the benefit from pembrolizumab in this trial was driven by a subset of NSCLC with PD-L1 TPS ≥50%.[3,4]

References:

1. FDA Press Release. FDA expands pembrolizumab indication for first-line treatment of NSCLC (TPS ≥1%). Published April 11, 2019. Accessed August 11, 2021. https://www.fda.gov/drugs/fda-expands-pembrolizumab-indication-first-line-treatment-nsclc-tps-1
2. Merck. KEYTRUDA® (pembrolizumab) injection, for intravenous use [package insert]. U.S. Food and Drug Administration website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125514s102lbl.pdf. Revised 08/2021. Accessed August 11, 2021.
3. Mok TSK, Wu YL, Kudaba I, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. *Lancet*. 2019;393(10183):1819-1830. doi:10.1016/S0140-6736(18)32409-7
4. Lantuejoul S, Sound-Tsao M, Cooper WA, et al. PD-L1 testing for lung cancer in 2019: Perspective from the IASLC Pathology Committee. *J Thorac Oncol*. 2020;15(4):499-519. doi:10.1016/j.jtho.2019.12.107

QUESTION 9.

3. In metastatic squamous NSCLC, MET exon 14 skipping

a. Occurs with similar frequency as in adenocarcinoma (4%)
b. Occurs in 20% of squamous lung cancers
c. Occurs in 1% of squamous lung cancers
d. Never occurs

The correct answer is c. **MET exon 14 skipping occurs in 1% of squamous lung cancers**

Text Summary of Rationale:

In NSCLC, MET exon 14 (METex14) skipping occurs in approximately 3%–4% of cases and typically occurs in the absence of other driver mutations.

- This incidence rate is on par with or greater than those of other actionable oncogenic drivers in NSCLC, such as ROS1, NTRK1/2/3, RET, BRAF, and ALK alterations.
- METex14 skipping occurs in approximately 2% of adenocarcinomas, approximately 1% of squamous cell carcinomas, and approximately 6% in adenosquamous cell carcinomas.

References:

1. Socinski MA, Obasaju C, Gandara D, et al. Clinicopathologic features of advanced squamous NSCLC. *J Thorac Oncol*. 2016;11(9):1411-1422. doi:10.1016/j.jtho.2016.05.024

QUESTION 10.

4. _____ is/are approved and is/are considered the first-line standard(s) of care patients with newly diagnosed metastatic squamous cell lung cancer.

a. Pembrolizumab monotherapy (PD-L1 TPS ≥ 50%, no EGFR or ALK genomic tumor alterations) and pembrolizumab in combination with platinum doublet chemotherapy
b. Nivolumab and ipilimumab (PD-L1 TPS ≥ 50%, no EGFR or ALK genomic tumor alterations) in combination with platinum doublet chemotherapy
c. Atezolizumab with bevacizumab and chemotherapy (PD-L1 TPS ≥ 50%, no EGFR or ALK genomic tumor alterations)
d. Atezolizumab monotherapy (PD-L1 TPS ≥ 50%, no EGFR or ALK genomic tumor alterations)

The correct answer is a. **Pembrolizumab monotherapy (PD-L1 TPS ≥ 50%, no EGFR or ALK genomic tumor alterations) and pembrolizumab in combination with platinum doublet chemotherapy are approved for first-line treatment of advanced squamous NSCLC**

Text Summary of Rationale:

Pembrolizumab monotherapy is approved for the first-line treatment of patients with metastatic NSCLC expressing PD-L1 (Tumor Proportion Score [TPS] ≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, based on a significantly improved overall survival with pembrolizumab, compared to platinum-based doublets, in the KEYNOTE-042 study.[1,2]

- Notably, the greatest benefit from pembrolizumab in this trial was seen in a subset of NSCLC with PD-L1 TPS ≥50%.[2,3]
- Pembrolizumab is also approved in combination with carboplatin and either paclitaxel or paclitaxel protein-bound, as first-line treatment of patients with metastatic squamous NSCLC, based on data from KEYNOTE-407 (NCT02775435).[4]

References:

1. Merck. KEYTRUDA® (pembrolizumab) injection, for intravenous use [package insert]. U.S. Food and Drug Administration website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125514s102lbl.pdf. Revised 08/2021. Accessed August 11, 2021.
2. Mok TSK, Wu YL, Kudaba I, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. Lancet. 2019;393(10183):1819-1830. doi:10.1016/S0140-6736(18)32409-7
3. Lantuejoul S, Sound-Tsao M, Cooper WA, et al. PD-L1 testing for lung cancer in 2019: Perspective from the IASLC Pathology Committee. J Thorac Oncol. 2020;15(4):499-519. doi:10.1016/j.jtho.2019.12.107
4. Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. N Engl J Med. 2018;379(21):2040-2051. doi:10.1056/NEJMoa1810865
5. Paz-Ares L, Vicente D, Tafreshi A, et al. A randomized, placebo-controlled trial of pembrolizumab plus chemotherapy in patients with metastatic squamous NSCLC: Protocol-specified final analysis of KEYNOTE-407. J Thorac Oncol. 2020;15(10):1657-1669. doi:10.1016/j.jtho.2020.06.015

QUESTION 11.

5. Select the best first-line option for management of a patient with advanced metastatic squamous NSCLC, ECOG PS 0-2, without EGFR or ALK actionable alterations, found to be PD-L1–negative (TPS 1<%).

a. Atezolizumab monotherapy
b. Pembrolizumab with carboplatin and nab-paclitaxel
c. Ramucirumab with docetaxel
d. Cytotoxic chemotherapy

The correct answer is b. **Pembrolizumab with carboplatin and nab-paclitaxel**

Text Summary of Rationale:

Pembrolizumab is approved in combination with carboplatin and either paclitaxel or paclitaxel protein-bound, as first-line treatment of patients with metastatic squamous NSCLC, based on data from KEYNOTE-407.[1-3]

- In this study, the median overall survival (OS) was 15.9 months (95% confidence interval [CI], 13.2 to not reached) in the pembrolizumab-combination group and 11.3 months (95% CI, 9.5 to 14.8) in the placebo-combination group (hazard ratio for death, 0.64; 95% CI, 0.49 to 0.85; *P*<0.001). Notably, the OS benefit was consistent regardless of the PD-L1 expression level.
- Updated efficacy outcomes from the protocol-specified final analysis for this trial confirmed that substantially improved OS (median, 17.1 months [95% confidence interval (CI): 14.4–19.9] vs 11.6 months [95% CI: 10.1–13.7]; HR, 0.71 [95% CI: 0.58–0.88]) and PFS (median, 8.0 months [95% CI: 6.3–8.4] vs 5.1 months [95% CI: 4.3–6.0]; HR, 0.57 [95% CI: 0.47–0.69]) persisted with pembrolizumab plus chemotherapy.[3]

References:

1. Merck. KEYTRUDA® (pembrolizumab) injection, for intravenous use [package insert]. U.S. Food and Drug Administration website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125514s102lbl.pdf. Revised 08/2021. Accessed August 11, 2021.
2. Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. *N Engl J Med*. 2018;379(21):2040-2051. doi:10.1056/NEJMoa1810865
3. Paz-Ares L, Vicente D, Tafreshi A, et al. A randomized, placebo-controlled trial of pembrolizumab plus chemotherapy in patients with metastatic squamous NSCLC: Protocol-specified final analysis of KEYNOTE-407. *J Thorac Oncol*. 2020;15(10):1657-1669. doi:10.1016/j.jtho.2020.06.015

QUESTION 12.

6. A 50-year-old male patient, who was a former light smoker, without prior or family history of cancer, presenting with an irritable cough and left chest pain is found to have a pulmonary left upper lobe mass (5.3 cm) with enlarged mediastinal lymph nodes. Fine needle biopsy of the primary tumor confirms NSCLC of squamous histology. Expanded panel molecular testing reveals compound occurrence of EGFR exon 19 deletion and T790M mutation, but no alterations in ALK, ROS, or c-MET. PD-L1 TPS is 50%. What treatment would you recommend for this patient?

a. Erlotinib

b. Osimertinib

c. Platinum-doublet chemotherapy

d. Atezolizumab with bevacizumab–carboplatin–paclitaxel

The correct answer is b. **Osimertinib**

Text Summary of Rationale:

In patients with advanced/metastatic NSCLC whose tumors are found to have an EGFR-TKI–sensitizing mutations, osimertinib is the preferred agent for both treatment-naïve (if EGFR status is known prior to first-line systemic therapy) patients and those on treatment with systemic therapy (if EGFR status is discovered during first-line systemic therapy).[1]

- Osimertinib is also recommended as second-line and beyond (subsequent) therapy for patients with EGFR T790M–positive metastatic NSCLC who have progressed on other EGFR-TKIs.[1]
- In-frame deletion mutations in EGFR exon 19 (19Del) and the exon 21 Leu858Arg point mutation (L858R), both EGFR-tyrosine kinase inhibitor (TKI)-sensitizing mutations, account for 90% of all EGFR mutations.[2]
- The T790M mutation is prevalent in 60% of patients with disease progression after initial response to other TKIs; it is 1 mechanism of resistance to first- and second-generation EGFR TKIs and is indicated for treatment with osimertinib.[1]
- Osimertinib is a third-generation, irreversible TKI that selectively inhibits both EGFR-TKI–sensitizing and EGFR T790M resistance mutations.[3]
- In the FLAURA study, osimertinib showed superior efficacy superior and longer OS, compared to standard EGFR-TKIs, in the first-line treatment of EGFR-mutated (19Del or L858R) advanced NSCLC.[3,4]
- The clinical activity of osimertinib in patients with EGFR T790M-positive NSCLC, with disease progression after previous EGFR-TKI therapy, was demonstrated in the AURA extension and AURA2 phase 2 studies.[5,6]

References:

1. Ettinger DS, Wood DE, Aisner DL, Akerley W. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Non-Small Cell Lung Cancer Version 5.2021. Published June 15, 2021. Accessed March 25, 2021. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf
2. Karlsen EA, Kahler S, Tefay J, Joseph SR, Simpson F. Epidermal growth factor receptor expression and resistance patterns to targeted therapy in non-small cell lung cancer: A review. Cells. 2021;10(5):1206. Published 2021 May 14. doi:10.3390/cells10051206
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4. Ramalingam SS, Vansteenkiste J, Planchard D, et al. Overall survival with osimertinib in untreated, EGFR-mutated advanced NSCLC. *N Engl J Med*. 2020;382(1):41-50. doi:10.1056/NEJMoa1913662
5. Goss G, Tsai CM, Shepherd FA, et al. Osimertinib for pretreated EGFR Thr790Met-positive advanced non-small-cell lung cancer (AURA2): a multicentre, open-label, single-arm, phase 2 study. Lancet Oncol. 2016;17(12):1643-1652. doi:10.1016/S1470-2045(16)30508-3
6. Jänne PA, Yang JC, Kim DW, et al. AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. *N Engl J Med*. 2015;372(18):1689-1699. doi:10.1056/NEJMoa1411817

QUESTION 13.

7. Your patient with metastatic squamous cell lung cancer is about to receive immune checkpoint inhibitor therapy as first-line treatment. Select the factor indicating a requirement for additional supportive care during the use of PD-(L)1 inhibitors.

a. Symptomatic rheumatoid arthritis
b. Hepatitis B
c. Hypertension
d. HIV

The correct answer is a. **Symptomatic rheumatoid arthritis**

Text Summary of Rationale:

- Chronic viral infections such as hepatitis B and C and HIV have not been associated with a toxicity signal with immune checkpoint inhibitor therapy and this class of agents is now approved for use in viral hepatitis-associated hepatocellular cancers.[1]
- Retrospective analyses of data from patients with NSCLC and a history of AD who received monotherapy with a PD-[L]1 inhibitor found that AD exacerbation occurred in a minority of patients.[2] Moreover, immune-related adverse events irAEs were generally manageable and did not often lead to permanent discontinuation of immunotherapy.[2]
- Toxicity risk needs to be weighed against the benefit of first-line immunotherapy with PD-[L]1 inhibitors for patients with advanced NSCLC who also have severe and/or symptomatic ADs, such as symptomatic rheumatoid arthritis.[1]
- Adequate supportive care measures, including systemic corticosteroids and systemic immunosuppression, if needed, should be an essential component in the treatment plan for patients with advanced squamous NSCLC being considered for PD-[L]1 inhibitor therapy;[1] this is especially important considering the relatively high prevalence of ADs (14%–25%) in lung cancer patients.[3]

References:

1. Peters S, Reck M, Smit EF, Mok T, Hellmann MD. How to make the best use of immunotherapy as first-line treatment of advanced/metastatic non-small-cell lung cancer. *Ann Oncol.* 2019;30(6):884-896. doi:10.1093/annonc/mdz109
2. Leonardi GC, Gainor JF, Altan M, et al. Safety of programmed death-1 pathway inhibitors among patients with non-small-cell lung cancer and preexisting autoimmune disorders. *J Clin Oncol.* 2018;36(19):1905-1912. doi:10.1200/JCO.2017.77.0305
3. Khan SA, Pruitt SL, Xuan L, Gerber DE. Prevalence of autoimmune disease among patients with lung cancer: Implications for immunotherapy treatment options. *JAMA Oncol.* 2016;2(11):1507-1508. doi:10.1001/jamaoncol.2016.2238

QUESTION 14.

8. A 45-year-old male Asian patient, never-smoker, ECOG PS of 1 is diagnosed with advanced squamous lung cancer. Molecular testing indicates the presence of EGFR exon 20 insertion mutation and PD-L1 TPS of 25% using the PD-L1 IHC 22C3 pharmDx test. The patient has not received prior therapy for advanced squamous NSCLC. Which of these first-line treatment options is optimal for this patient?

a. Platinum-doublet chemotherapy
b. Pembrolizumab monotherapy
c. Amivantamab
d. Atezolizumab with bevacizumab–carboplatin–paclitaxel

The correct answer is c. Amivantamab

Text Summary of Rationale:

- In May 2021, the US FDA approved amivantamab-vmjw as first-line treatment for patients with NSCLC whose tumors have EGFR exon 20 insertion (ex20ins) mutations, along with the Guardant360 CDx as a companion diagnostic.1
- Amivantamab is a bispecific antibody that targets EGFR and c-MET simultaneously. Updated data from the CHRYSALIS study showed that amivantamab had promising efficacy with durable responses.2
- Approximately 2%–3% of patients with NSCLC have EGFR ex20ins mutations; unlike most common EGFR mutations, tumors with ex20ins have poor response to EGFFR-TKI therapy.3
- Limited data available for the frequency of EGFR ex20ins mutations in NSCLC of squamous histology puts it in the range of 0.5%.4

References:

1. FDA Press Release. FDA Approves First Targeted Therapy for Subset of Non-Small Cell Lung Cancer. Published May 21, 2021. Accessed August 11, 2021. https://www.fda.gov/news-events/press-announcements/fda-approves-first-targeted-therapy-subset-non-small-cell-lung-cancer
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3. Remon J, Hendriks LEL, Cardona AF, Besse B. EGFR exon 20 insertions in advanced non-small cell lung cancer: A new history begins. *Cancer Treat Rev.* 2020;90:102105. doi:10.1016/j.ctrv.2020.102105
4. Lam V et al. P2.03b-023 Circulating tumor DNA (ctDNA)-based genomic profiling of known cancer genes in lung squamous cell carcinoma (LUSC). Presented at: 2017 World Conference on Lung Cancer; October 15-18, 2017; Yokohoma, Japan

QUESTION 15.

9. Although EGFR mutations are not as common in squamous as they are in nonsquamous NSCLC, EGFR overexpression and gene copy alterations occur in 60–80% and 7–10% of squamous lung tumors, respectively. Which of these EGFR-targeted agents has gained approval for metastatic squamous NSCLC that has progressed following platinum-based chemotherapy?

a. Osimertinib
b. Dacomitinib
c. Afatinib
d. Gefinitib

The correct answer is c. **Afatinib**

Text Summary of Rationale:

Afatinib gained FDA approval for the treatment of patients with advanced squamous NSCLC following progression on platinum-based chemotherapy, based on data from the phase 3 LUX-Lung 8 study.[1]

- In this study, afatinib reduced the risk of death by 19% and disease progression by 18% compared with erlotinib.[2]
- Subsequent analyses showed that second-line afatinib was associated with improved prespecified disease-related symptoms and global health status (GHS)/quality of life (QoL), compared to erlotinib.[3]

References:

1. Gadgeel SM. FDA Approves Afatinib for squamous cell lung cancer. Published April 15, 2016. Accessed August 11, 2021. https://www.onclive.com/view/fda-approves-afatinib-for-squamous-cell-lung-cancer
2. Soria JC, Felip E, Cobo M, et al. Afatinib versus erlotinib as second-line treatment of patients with advanced squamous cell carcinoma of the lung (LUX-Lung 8): an open-label randomised controlled phase 3 trial. *Lancet Oncol.* 2015;16(8):897-907. doi:10.1016/S1470-2045(15)00006-6
3. Felip E, Hirsh V, Popat S, et al. Symptom and quality of life improvement in LUX-Lung 8, an open-label phase III study of second-line afatinib versus erlotinib in patients with advanced squamous cell carcinoma of the lung after first-line platinum-based chemotherapy. *Clin Lung Cancer.* 2018;19(1):74-83.e11. doi:10.1016/j.cllc.2017.06.002

QUESTION 16.

10. Based on subgroup analyses of studies of EGFR-targeted tyrosine kinase inhibitor therapy in NSCLC, this class of agents may be appropriate to consider for selected patients with advanced squamous NSCLC as _____.

a. First-line option, in patients with any EGFR alterations
b. First-line option, in combination with cytotoxic chemotherapy, in patients with any EGFR alterations
c. Second- or third-line options, in combination with platinum-based chemotherapy
d. Second- or third-line options, following progression on platinum-based chemotherapy

The correct answer is d. EGFR-targeted TKIs may be appropriate as second- or third-line management of patients with advanced squamous NSCLC following progression on platinum-based chemotherapy

Text Summary of Rationale:

- While EGFR-targeted TKIS may be considered for first-line treatment of patients with advanced NSCLC in patients with tumors with confirmed EGFR-TKI–sensitizing mutations, this class of agents is not recommended as monotherapy or in combination with chemotherapy in the first-line treatment of unselected patients with squamous cell lung cancer.[1]
- Data from subanalyses of studies of second- or third-line EGFR TKI monotherapy suggest a potential role for these agents in pretreated NSCLC patients.[1]
- Afatinib is FDA-approved for the treatment of patients with advanced squamous NSCLC following progression on platinum-based chemotherapy, based on data from the LUX-Lung 8 study.[2]
- Retrospective, adhoc biomarker analyses of a subset of patients from LUX-Lung 8 suggested that patients with ErbB family mutations derived particular benefit from afatinib, especially those with ErbB2 (HER2) mutations.3

References:

1. Santos ES, Hart L. Advanced squamous cell carcinoma of the lung: Current treatment approaches and the role of afatinib. *Onco Targets Ther.* 2020;13:9305-9321. Published 2020 Sep 22. doi:10.2147/OTT.S250446
2. Gadgeel SM. FDA Approves Afatinib for squamous cell lung cancer. Published April 15, 2016. Accessed August 11, 2021. https://www.onclive.com/view/fda-approves-afatinib-for-squamous-cell-lung-cancer
3. Bonomi PD, Gandara D, Hirsch FR, et al. Predictive biomarkers for response to EGFR-directed monoclonal antibodies for advanced squamous cell lung cancer. *Ann Oncol.* 2018;29(8):1701-1709. doi:10.1093/annonc/mdy196

QUESTION 17.

11. Which of these tyrosine kinase inhibitors is an irreversible inhibitor of the ErbB family approved for treating cancers with common and uncommon EGFR mutations?

a. Erlotinib
b. Gefitinib
c. Afatinib
d. Icotinib

The correct answer is c. **Afatinib**

Text Summary of Rationale:

- Afatinib, a second-generation TKI, is an ATP-competitive anilinoquinazoline derivative that covalently binds and irreversibly blocks enzymatically active ErbB receptor family members.[1]
- Afatinib is indicated for:[2]
  - First-line treatment of patients with metastatic NSCLC whose tumors have nonresistant EGFR mutations as detected by an FDA-approved test
  - Treatment of patients with metastatic, squamous NSCLC progressing after platinum-based chemotherapy
- Erlotinib, gefitinib, and icotinib are first-generation EGFR-targeted TKIs that reversibly bind to EGFR and inhibit the binding of ATP to the tyrosine kinase domain.[1]

References:

1. Karachaliou N, Fernandez-Bruno M, Bracht JWP, et al. EGFR first- and second-generation TKIs—there is still place for them in EGFR-mutant NSCLC patients. *Transl Cancer Res* 2019;8(Suppl 1):S23-S47.
2. Boehringer Ingelheim Pharmaceuticals, Inc. GILOTRIF® (afatinib) tablets, for oral use [package insert]. U.S. Food and Drug Administration website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/201292s015lbl.pdf. Revised 10/2019. Accessed August 11, 2021.

QUESTION 18.

12. In the phase 3 REVEL study of patients with stage IV NSCLC who had disease progression on platinum-based therapy, treatment with _____ in combination with docetaxel improved survival compared to placebo with docetaxel (median OS 10.5 vs 9.1 months; hazard ratio 0·86, 95% CI 0·75-0·98; p=0·023).

a. Nivolumab
b. Bevacizumab
c. Nintedanib
d. Ramucirumab

The correct answer is d. **Ramucirumab**

Text Summary of Rationale:

- Ramucirumab is the first and only antiangiogenetic agent approved in the treatment both of squamous and non-squamous NSCLC.[1]
- Bevacizumab, another antiangiogenetic agent approved for NSCLC, is contraindicated for patients with squamous cell lung cancers due to an increased risk of pulmonary hemorrhage.[2]
- The US FDA approved ramucirumab in combination with docetaxel for treatment of patients with metastatic NSCLC with disease progression during or following treatment with platinum-based chemotherapy, based on data from the REVEL study.[3]

References:

1. Maione P, Sgambato A, Casaluce F, et al. The role of the antiangiogenetic ramucirumab in the treatment of advanced non-small cell lung cancer. *Curr Med Chem*. 2017;24(1):3-13. doi:10.2174/0929867324666161118125103
2. Tsironis G, Ziogas DC, Kyriazoglou A, et al. Breakthroughs in the treatment of advanced squamous-cell NSCLC: not the neglected sibling anymore?. *Ann Transl Med*. 2018;6(8):143. doi:10.21037/atm.2018.02.18
3. Garon EB, Ciuleanu TE, Arrieta O, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. *Lancet*. 2014;384(9944):665-673. doi:10.1016/S0140-6736(14)60845-X

QUESTION 19.

13. All these statements accurately describe the immune-related adverse event (irAE) profile with immune checkpoint inhibitor (ICI) therapy EXCEPT

a. All irAEs associated with ICI therapy present soon after starting therapy, with onset between 1 to 3 weeks after initiation of ICI therapy
b. The incidence of pneumonitis in NSCLC is higher than that in other tumor types
c. Rash, colitis, hepatitis, myocarditis, endocrinopathies, and pneumonitis are common irAEs with ICI therapy
d. Diabetes mellitus, and particularly insulin-dependent or type 1 diabetes mellitus (T1DM), is a rare but serious endocrinopathy associated with ICI therapy

The correct answer is a. **All irAEs associated with ICI therapy present soon after starting therapy, with onset between 1 to 3 weeks after initiation of ICI therapy**

Text Summary of Rationale:

- irAEs have a variable onset – they may present soon after starting therapy, after extended therapy, or, in some cases, after completion of therapy.
- While most irAEs are mild to moderate in severity and can be managed without the permanent termination of immune checkpoint inhibitor therapy, rare but serious and even life-threatening irAEs may occur during therapy with this class of agents, requiring immediate attention.

References:

1. Davies MJ. PD-1/PD-L1 inhibitors for non-small cell lung cancer: Incorporating care step pathways for effective side-effect management. *J Adv Pract Oncol.* 2019;10(Suppl 1):21-35. doi:10.6004/jadpro.2019.10.2.11

QUESTION 20.

14. The NCCN recommends _____ to diagnose pneumonitis.

a. Chest X-ray and spirometry
b. Computed tomography (CT) scan with contrast, and biopsy or bronchoscopy with bronchoalveolar lavage (BAL), if needed, to exclude other causes
c. Spirometry, followed by bronchoscopy with BAL, if needed, to exclude other causes
d. Chest X-ray, followed by biopsy or bronchoscopy with BAL, if needed, to exclude other causes

The correct answer is b. **Computed tomography (CT) scan with contrast, and biopsy or bronchoscopy with bronchoalveolar lavage (BAL), if needed, to exclude other causes**

Text Summary of Rationale:

- Pneumonitis presentation includes dyspnea, dry cough, wheezing, tachycardia, and increased oxygen requirements for patients already on oxygen supplementation.[1]
- The NCCN guidelines for management of immune checkpoint inhibitor-related toxicities include recommendations for Chest CT with contrast to evaluate for pneumonitis, biopsy, or bronchoscopy with bronchoalveolar lavage (BAL) if needed to exclude other causes.[2]
- Pneumonitis is a relatively rare irAE, occurring in approximately 3% to 5% of all patients receiving immune checkpoint inhibitor therapy. Pneumonitis incidence is higher with combination immunotherapy, compared to monotherapy.[1]

References:

1. Davies MJ. PD-1/PD-L1 inhibitors for non-small cell lung cancer: Incorporating care step pathways for effective side-effect management. *J Adv Pract Oncol.* 2019;10(Suppl 1):21-35. doi:10.6004/jadpro.2019.10.2.11

2. Thompson JA, Schneider JA, Brahmer J, et al. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Management of Immune Checkpoint Inhibitor-Related Toxicities V3.2021. Published May 14, 2021. Accessed August 11, 2021. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

QUESTION 21.

15. A 68-year-old male diagnosed with Stage IV squamous NSCLC progressed after at 4 cycles of platinum-based-chemotherapy is currently receiving afatinib (40 mg daily). Common toxicities associated with afatinib treatment that have the potential to be dose-limiting. Which of these would NOT require withholding afatinib?

a. Development of Grade 2 diarrhea lasting longer than 48 hours while taking antidiarrheal medication
b. Suspected interstitial lung disease
c. Grade 2 cutaneous reactions characterized by bullous, blistering, and exfoliating lesions
d. Suspected keratitis

The correct answer is c. **Grade 2 cutaneous reactions characterized by bullous, blistering, and exfoliating lesions**

Text Summary of Rationale:

The prescribing information for afatinib includes these indications for withholding afatinib:

- Any National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), v 3.0, of Grade 3 or higher
- Diarrhea of Grade 2 or higher persisting for 2 or more consecutive days while taking antidiarrheal medication
- Cutaneous reactions of Grade 2 that are prolonged (lasting more than 7 days) or intolerable
- Renal impairment of Grade 2 or higher

References:

1. Boehringer Ingelheim Pharmaceuticals, Inc. GILOTRIF® (afatinib) tablets, for oral use [package insert]. U.S. Food and Drug Administration website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/201292s015lbl.pdf. Revised 10/2019. Accessed August 11, 2021.

QUESTION 22.

2. Ramucirumab, an anti–VEGFR-2 mAb, was approved for metastatic NSCLC based on data from the REVEL study. In this trial, rates of pulmonary hemorrhage with ramucirumab plus docetaxel vs docetaxel were

a. Similar in patients with squamous and nonsquamous histology (any grade, 8% vs 7%)
b. Higher in patients with squamous histology, compared to nonsquamous histology (any grade, 13% vs 2.5%)
c. Higher in patients with nonsquamous histology, compared to squamous histology (any grade, 15% vs 5%)
d. Only seen in patients with nonsquamous histology (10%)

The correct answer is a. **Rates of pulmonary hemorrhage with ramucirumab plus docetaxel versus docetaxel were similar in patients with squamous and nonsquamous histology (any grade, 8% vs 7%)**

Text Summary of Rationale:

- Ramucirumab, an anti–vascular endothelial growth factor receptor 2-directed monoclonal antibody, is approved in combination with docetaxel for metastatic NSCLC of both squamous and non-squamous histology, based on the results of the REVEL trial.[1]
- Patients with squamous and non-squamous NSCLC in REVEL had comparable rates of pulmonary hemorrhage with ramucirumab plus deoctaxel vs docetaxel (any grade, 8% vs. 7%, respectively; grade ≥3, 1% in each group).[1,2]

References:

1. Garon EB, Ciuleanu TE, Arrieta O, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. *Lancet.* 2014;384(9944):665-673. doi:10.1016/S0140-6736(14)60845-X
2. Kurzrock R, Stewart DJ. Exploring the benefit/risk associated with antiangiogenic agents for the treatment of non-small cell lung cancer patients. *Clin Cancer Res.* 2017;23(5):1137-1148. doi:10.1158/1078-0432.CCR-16-1968

QUESTION 23.

3. A 63-year-old male, former smoker, ECOG 1, was diagnosed with metastatic squamous NSCLC and received treatment with platinum-doublet chemotherapy. Pembrolizumab (200 mg every 3 weeks) maintenance therapy was initiated for this patient after confirmation of partial response after 4 cycles of chemotherapy. Six weeks after initiation of pembrolizumab, the patient presents with widespread rash with pruritis. Further assessment indicates maculopapular rash grade 2 in severity. What is appropriate course of action for managing this patient?

a. Consider dose reduction of pembrolizumab and monitor for improvement weekly. If no improvement, initiate oral/topical corticosteroid therapy
b. Consider holding pembrolizumab and monitor for improvement weekly. If no improvement, initiate oral/topical corticosteroid therapy
c. Consider holding pembrolizumab and monitor for improvement weekly. If no improvement, consider treatment with GABA agonist, aprepitant, or omalizumab
d. Withhold pembrolizumab and monitor for improvement weekly. If no improvement, discontinue pembrolizumab permanently

The correct answer is b. **Consider holding pembrolizumab and monitor for improvement weekly. If no improvement, initiate oral/topical corticosteroid therapy**

Text Summary of Rationale:

- The skin is the most common site of immune-related adverse vents (irAEs) with checkpoint inhibitor therapy.[1]
- Cutaneous irAEs can range widely in morphologies and severity – including pruritus, morbilliform or maculopapular rash, vitiligo-like depigmentation, bullous pemphigoid, and severe dermatologic irAEs.[1]
- Management approaches for irAEs with pembrolizumab (and other immune checkpoint inhibitors) vary by severity[2-4] –

- o No dose reduction for pembrolizumab is recommended.
- o In general, withholding of pembrolizumab is indicated for severe (Grade 3) irAEs.
- o Permanent discontinuation of pembrolizumab is indicated for life-threatening (Grade 4) irAEs, recurrent severe (Grade 3) irAEs that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating steroids.

References:

1. Tattersall IW, Leventhal JS. Cutaneous toxicities of immune checkpoint inhibitors: The role of the dermatologist. *Yale J Biol Med.* 2020;93(1):123-132. Published 2020 Mar 27.
2. AIM with Immunotherapy Foundation. Care Step Pathway - Skin Toxicities. Immuno-oncology Essentials. Published 2018. Accessed August 11, 2021. http://aimwithimmunotherapy.org/wp-content/uploads/2019/05/IOE-CSP1-skintoxicity_final.pdf
3. Thompson JA, Schneider JA, Brahmer J, et al. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Management of Immune Checkpoint Inhibitor-Related Toxicities V3.2021. Published May 14, 2021. Accessed August 11, 2021. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf
4. Merck. KEYTRUDA® (pembrolizumab) injection, for intravenous use [package insert]. U.S. Food and Drug Administration website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125514s102lbl.pdf. Revised 08/2021. Accessed August 11, 2021.