Tumor Board Tuesday – Dr. Estelamari Rodriguez, 5/24/2022: MET Exon 14 Lung Cancer

Posttest Rationale

1. How common are METex14-skipping mutations in NSCLC (Non-Small Cell Lung Cancer)?
    a. 1%
    b. 3-4%
    c. 10%
    d. 25%

Rationale: Answer B. MET exon14 skipping mutations are found in about 3-4% of Non-Small Cell Lung Cancer (NSCLC) overall. MET exon14 mutations are usually independent of other driver mutations (EGFR, ALK, ROS, KRAS). When co-occurring mutations are present (such as EGFR and METex14) it is often in the setting of EGFR mutated NSCLC with acquired resistance to EGFR TKI therapy.

Socinski MA, Pennell NA, Davies KD. *MET* Exon 14 Skipping Mutations in Non-Small-Cell Lung Cancer: An Overview of Biology, Clinical Outcomes, and Testing Considerations. *JCO Precis Oncol*. 2021;5:PO.20.00516. Published 2021 Apr 13. doi:10.1200/PO.20.00516

Le X, Hong L, Hensel C, et al. Landscape and Clonal Dominance of Co-occurring Genomic Alterations in Non-Small-Cell Lung Cancer Harboring *MET* Exon 14 Skipping [published correction appears in JCO Precis Oncol. 2022 Mar;6:e2200175]. *JCO Precis Oncol*. 2021;5:PO.21.00135. Published 2021 Dec 13. doi:10.1200/PO.21.00135

2. Which of the following is the most sensitive testing assay for detection of METex14-skipping mutations?
    a. DNA next-generation sequencing (NGS)
    b. FISH
    c. IHC
    d. RNA NGS

Rationale: Answer D. Many different genetic alterations (deletions, insertions, point mutations, and even full exon deletions) in the exon14 region can result in mRNA with absent expression of METexon14. Most NGS testing for oncology diagnostic purposes is NOT full exon sequencing, but rather relies on "capture" of mutations in areas of interest using DNA primers. Since the mutations leading to METex14 skipping are so varied, the DNA primers used may not capture the particular mutation, leading to false negatives. RNA based NGS testing, in contrast, can detect the common end-result: fusion of exons 13 and 15 and thus is more sensitive than DNA NGS testing. Many testing platforms use DNA NGS primarily with RNA testing in parallel or as a reflex test for MET exon. Importantly, MET protein expression by immunohistochemistry (IHC) is NOT a reliable test for identifying METex14 positive patients.

Socinski MA, Pennell NA, Davies KD. *MET* Exon 14 Skipping Mutations in Non-Small-Cell Lung Cancer: An Overview of Biology, Clinical Outcomes, and Testing Considerations. *JCO Precis Oncol*. 2021;5:PO.20.00516. Published 2021 Apr 13. doi:10.1200/PO.20.00516

Davies KD, Lomboy A, Lawrence CA, et al. DNA-Based versus RNA-Based Detection of MET Exon 14 Skipping Events in Lung Cancer. *J Thorac Oncol*. 2019;14(4):737-741. doi:10.1016/j.jtho.2018.12.020

3. Which lung cancer histologies are MORE likely to present with a met-exon 14 skipping mutations?
    a. Adenocarcinoma
    b. Sarcomatoid
    c. Squamous
    d. Small cell carcinoma

Rationale: Answer A: Although the incidence of METex14 varies within NSCLC histologies, adenocarcinoma is more common overall (representing ~50% of NSCLC). Notably, NGS testing is still valuable in less common and mixed-histology tumors (sarcomatoid, adenosquamous) as actionable driver mutations with therapeutic benefit may be identified.

4. Which treatments are FDA approved for METex14-skipping mutations?
    a. Cabozantinib
    b. Capmatinib+ Tepotinib
    c. Crizotinib
    d. Amivantamab

Rationale: Answer B: While all the listed drugs have been used for treatment of METex14 NSCLC in clinical trials or real-world used), only capmatinib and tepotinib are FDA-approved specifically for the treatment of METex14 NSCLC based on results of the GEOMETRYmono-1 and VISION trials, respectively.

Mathieu LN, Larkins E, Akinboro O, et al. FDA Approval Summary: Capmatinib and Tepotinib for the Treatment of Metastatic NSCLC Harboring MET Exon 14 Skipping Mutations or Alterations. *Clin Cancer Res*. 2022;28(2):249-254. doi:10.1158/1078-0432.CCR-21-1566