MOLECULAR DIAGNOSIS IN **LUNG CANCER**

Knowledge Check 1

1 **In 2022, ~50% of patients with mNSCLC have an actionable alteration in 1 of 9 driver genes for which NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommends testing. What are the driver genes?**

_____, _____, _____, _____, _____,

_____, _____, _____, _____

2 **At least one of the actionable driver alterations in lung cancer may be classified as:**

a) Rearrangements, SNVs, indels, or exon skipping
b) SNVs, indels, or rearrangements
c) Rearrangements, SNVs, or CNAs
d) None of the above

3 **Which type of NGS assay cannot reliably detect fusion events or CNVs?**

a) DNA-based amplicon assays
b) Hybrid capture-based assays
c) FISH
d) RNA-based amplicon assays

4 **What percentage of patients with mNSCLC who are positive for an oncogenic driver will also have a PD-L1 tumor proportion score of at least 1%?**

a) 10%
b) 20%
c) 50%
d) 80%

5 **True or False: The National Comprehensive Cancer Network® (NCCN®) NSCLC Panel recommends that clinicians should obtain molecular testing results for actionable biomarkers before administering first-line ICI therapy, if clinically feasible, including *ALK*, *BRAF*, *EGFR*, *MET*ex14 skipping, *NTRK1/2/3*, *RET*, and *ROS1* variants**

a) True
b) False

ANSWERS

Precision Medicine

1. In 2022, NCCN Guidelines recommends testing for *ALK, BRAF, EGFR, ERBB2 (HER2), KRAS, MET*ex14 skipping, *NTRK*, *RET,* and *ROS1* (page 5)[1]

2. **A.** Actionable driver alterations in NSCLC include rearrangements (ALK, ROS1, RET, NTRK), SNVs (EGFR sensitizing, KRAS, BRAF, ERBB2 (HER2)), indels (EGFR sensitizing, EGFR exon 20, ERBB2 (HER2)), and exon skipping events (METex14 skipping) (page 3, page 7)[2]

3. **A.** Amplicon-based target enrichment is efficient for smaller panels and can reliably identify point mutations and small indels, with less nucleic acid required (5-10 ng) and a shorter turnaround time (7-10 days). However, this technique cannot reliably detect fusion events or copy number variants when using DNA. In addition, these assays have limitations in the number of genes and regions that can be covered (page 9)[3,4]

4. **C.** Oncogenic drivers are often mutually exclusive, but the presence of an oncogenic driver is not mutually exclusive with elevated PD-L1 expression. Evidence suggests that approximately 50% of patients with an oncogenic mutation will have a PD-L1 tumor proportion score of at least 1% (page 6)[5-8]

5. **True.** NCCN NSCLC Panel recommends that clinicians should obtain molecular testing results for actionable biomarkers before administering first-line ICI therapy, if clinically feasible, including *ALK*, *BRAF*, *EGFR*, *MET*ex14 skipping, *NTRK1/2/3*, *RET*, and *ROS1* variants (page 5)[1]

This knowledge check is connected to the chapter "The Importance of a Molecular Diagnosis in mNSCLC." To get a copy of this and other chapters, please visit:
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ALK; anaplastic lymphoma kinase; BRAF, v-raf murine sarcoma viral oncogene homolog B1; CNA, copy number alteration; CNV, copy number variation; DNA, deoxyribonucleic acid; EGFR, epidermal growth factor receptor; ERBB2, erb-b2 receptor tyrosine kinase 2FISH, fluorescence in situ hybridization HER2, human epidermal growth factor receptor 2; ICI, immune checkpoint inhibitor; KRAS, Kirsten rat sarcoma viral oncogene homolog; METex14, MET exon 14; mNSCLC, metastatic non-small cell lung cancer; NGS, next-generation sequencing; NCCN, National Comprehensive Cancer Network® (NCCN®); NTRK, neurotrophic tropomyosin receptor kinase; PD-L1, programmed death-ligand 1; RET, ret proto-oncogene; ROS1, receptor tyrosine kinase; SNV, single-nucleotide variant. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. To view the most recent and complete version of the guideline, go online to NCCN.org.

References: 1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer V.4.2022. ©National Comprehensive Cancer Network, Inc. 2022. All rights reserved. September 16, 2022. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.To view the most recent and complete version of the guideline, go online to NCCN.org. **2.** Chakravarty D et al. *J Clin Oncol*. 2022;40(11):1231-1258. **3.** Pennell NA et al. *Am Soc Clin Oncol Educ Book*. 2019;39:531-542. **4.** Church AJ. Next-generation sequencing. In: Tafe L, Arcila M, eds. *Genomic Medicine*. Cham, Switzerland: Springer; 2020:25-40. **5.** Evans M et al. *Pathol Oncol* Res. 2020;26(1):79-89. **6.** Mazieres J et al. *Ann Oncol*. 2019;30(8):1321-1328. **7.** Calles A et al. *Am Soc Clin Oncol Educ Book*. 2020;40:372-384. **8.** Karatrasoglou EA et al. *Virchows Arch*. 2020;477(2):207-217.

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