Exploring Key Biomarkers and Actionable Genomic Alterations in NSCLC

FIRST-GENERATION EGFR tyrosine kinase inhibitors (TKIs) were first approved by the FDA 20 years ago; their efficacy was demonstrated in the treatment of non–small cell lung cancer (NSCLC) with sensitizing *EGFR* gene mutations. This marked the beginning of biomarker-driven management of NSCLC with targeted therapies.[1,2] The discovery of other actionable mutations and better understanding of the molecular basis of the disease have continued the development of targeted therapies in the treatment landscape.[1] Also, beginning in 2012, clinical guidelines strongly recommended that every patient with newly diagnosed, advanced-stage NSCLC—and some with resectable early-stage NSCLC—is tested for predictive biomarkers.[2,3] These changes and the introduction of targeted treatments resulted in improved overall survival (OS) and a rapid decline in NSCLC mortality starting in 2006 and accelerating in 2013.[2,4]

Still, NSCLC represents 76% to 90% of all diagnosed lung cancer tumors; more than half of patients present with advanced stage disease, which has an estimated 5-year survival rate of 8.2%.[2,5-7] The prevalence of predictive biomarkers among patients with NSCLC and the reduction in mortality associat-

ed with targeted therapies underscore a critical need for personalized therapies.

The **Table** summarizes the estimated frequencies for key predictive and emerging biomarkers in NSCLC and lists associated guideline-recommended testing technologies and therapies.[3,8-10]

The Role of Biomarkers
EGFR *Mutations*

Common *EGFR* mutations, including exon 19 deletions and the exon 21 L858R point mutation, account for 85% to 90% of all *EGFR* mutations in NSCLC. These mutations are strong predictors of a positive clinical response to EGFR TKIs (EGFRi).[11-13] They enable first-generation EGFRi to outcompete adenosine triphosphate (ATP) binding to the mutated receptor, preventing its activation and leading a higher response rate and extended progression-free survival (PFS).[12,13] However, the *EGFR* T790M mutation increases ATP affinity, leading to the activation of the receptor despite the presence of inhibitors.[13] Second-generation EGFRi were developed to bind irreversibly to EGFR and overcome resistance. Their efficacy has been limited by poor selectivity and toxicities. Third-generation EGFRi, like osimertinib, have shown greater selectivity for *EGFR* T790M mutations versus the wild-type *EGFR*. This has led to their

successful use in treating patients with NSCLC with *EGFR* T790M mutations.[12,13]

Uncommon *EGFR* mutations, including those within exons 18 to 25, comprise the remaining 10% to 15% of *EGFR* mutations in NSCLC; these are associated with poorer responses to EGFRi.[13,14] These mutations (including exon 18 deletions and substitutions in *EGFR* E709 and *EGFR* G719X, exon 19 insertions, exon 20 insertions, the *EGFR* S768I and exon 21 L861Q substitutions, *EGFR* kinase domain duplications, and complex mutations) exhibit varying sensitivities to EGFRi compared to common mutations. For instance, exon 20 insertion mutations induce structural changes that lead to activation of the kinase domain.[13] However, these mutations often show resistance to first- and second-generation EGFRi. Clinical trials have revealed differences in EGFRi sensitivity for distinct types of exon 20 insertions, demonstrating the heterogeneity of these mutations.[13]

ALK *Rearrangements*

ALK gene rearrangements are present in about 2% to 8% of NSCLC. These rearrangements, primarily occurring in adenocarcinomas, are more prevalent in females and never- or light smokers.[15] Compared to chemotherapy, use of the first-generation ALK TKI crizo- **»**

Table.

Established and Emerging Biomarkers for NSCLC in the United States[3,8-10]

Predictive biomarkers	Estimated frequency in NSCLC adenocarcinoma[a]	NCCN-recommended testing technologies	NCCN-recommended targeted therapy
EGFR mutations[b]	Common *EGFR* mutations, 10.0% Less common *EGFR* mutations, ≤ 10%	Real-time PCR, Sanger sequencing (ideally paired with tumor enrichment), and NGS	**First-line therapy:** afatinib, dacomitinib, erlotinib, gefitinib, osimertinib, erlotinib/ramucirumab, erlotinib/bevacizumab **Subsequent therapy:** amivantamab-vmjw, osimertinib
KRAS G12C mutations	25.0%	Real-time PCR, Sanger sequencing (ideally paired with tumor enrichment), and NGS	**Subsequent therapy:** adagrasib, sotorasib
ALK rearrangements[b]	5.0%	FISH, IHC, NGS, and real-time PCR	**First-line therapy:** alectinib, brigatinib, ceritinib, crizotinib, lorlatinib **Subsequent therapy:** alectinib, brigatinib, ceritinib, lorlatinib
ROS1 rearrangements[b]	1.0%-2.0%	FISH, IHC, NGS, and real-time PCR	**First-line therapy:** ceritinib, crizotinib, entrectinib **Subsequent therapy:** entrectinib, lorlatinib
BRAF V600E mutations[c]	1.0%-2.0%	Real-time PCR, Sanger sequencing (ideally paired with tumor enrichment), and NGS	**First-line therapy:** dabrafenib/trametinib, encorafenib/binimetinib, dabrafenib, vemurafenib **Subsequent therapy:** dabrafenib/trametinib, encorafenib/binimetinib
NTRK1/2/3 gene fusions[b]	>1.0%-3.0%	FISH, IHC, PCR, and NGS	**First-line/subsequent therapy:** larotrectinib, entrectinib
MET exon 14 skipping mutation	3.0%-4.0%	NGS	**First-line/subsequent therapy:** capmatinib, crizotinib, tepotinib
RET rearrangements	1.0%-2.0%	FISH, real-time reverse-transcriptase PCR, and NGS	**First-line/subsequent therapy:** selpercatinib, pralsetinib, cabozantinib
ERBB2 (*HER2*) mutations	3%	NGS, Sanger sequencing, and PCR	**Subsequent therapy:** fam-trastuzumab deruxtecan-nxki, ado-trastuzumab emtansine
PD-L1 expression levels[d]	TPS ≥ 50.0%, 33%; TPS = 1.0%-49.0%, 30.0%; TPS < 1.0%, 37.0%	IHC	Immune checkpoint inhibitors (pembrolizumab, nivolumab, atezolizumab, cemiplimab-rwlc, ipilimumab, tremelimumab-actl, durvalumab) alone or in combination with each other and/or with chemotherapy

Emerging biomarkers[e]	Estimated frequency in NSCLC adenocarcinoma	Potential testing technology	Targeted therapies under investigation
NRG1 rearrangement	< 1.0%	NGS	Afatinib, GSK2849330, AMG 888, seribantumab, zenocutuzumab
FGFR1 amplifications	Data not available	NGS	Infigratinib, rogaratinib

FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; NCCN, National Comprehensive Cancer Network; NGS, next-generation sequencing; NSCLC, non–small cell lung cancer; PCR, polymerase chain reaction; TPS, tumor proportion score.

[a]No specific driver known in over one-third of cases

[b]Predicts response to targeted therapy with kinase inhibitors

[c]Predicts response to BRAF with/without MEK inhibitors

[d]Predicts response to immunotherapy

[e]Under investigation as predictive biomarkers with the goal of identifying appropriate therapies for patients

The mission of the Biomarker Consortium is to bring stakeholders together to provide accurate and relevant information about the importance of testing and biomarker identification, and how to utilize biomarker status to inform treatment decisions.

tinib demonstrated superior activity and improved overall response rates (ORRs) and PFS.[15-17] This led to the development of newer ALK TKIs (eg, ceritinib, alectinib, brigatinib, lorlatinib) with greater efficacy, particularly in terms of central nervous system activity.[15-17] Despite demonstrated ORRs of up to 80%, resistance to ALK TKIs evolves.[15] This includes on-target alterations (eg, *ALK* mutations/gene amplification) and off-target bypass signaling pathways changes.[16] The treatment landscape for *ALK*-rearranged NSCLC has shifted toward using second- and third-generation ALK TKIs as first-line treatment.[15-17]

BRAF *Mutations*

BRAF mutations, specifically the V600E mutation, play a pivotal role in the development and progression of NSCLC. Occurring in 1% to 2% of lung adenocarcinomas, *BRAF* mutations, a part of the MAPK/ERK signaling pathway, are commonly found in patients with a history of smoking. These mutations contribute to the growth of cancer cells through enhanced signaling pathways.[18,19] Targeted therapies, specifically BRAF-directed TKIs, are the standard treatment for patients with advanced NSCLC with *BRAF* mutations.[3] However, affected patients often develop resistance to BRAF-targeted therapy due to intrinsic or extrinsic mechanisms.[19]

HER2 *Mutations*

HER2 (*ERBB2*) mutations and amplifications have been identified in 2% to 4% of NSCLC. Patients with *HER2*-mutated disease are more likely to be current or former smokers; they typically exhibit a worse prognosis than do patients with *EGFR* and *ALK* mutations, partially because their disease cannot yet be treated with a highly selective, targeted therapy.[20,21] *HER2* mutations primarily involve insertion or duplication events in exon 20 and other activating mutations, and they are associated with responsiveness to anti-HER2 targeted therapy.[20,21] *HER2*-mutated NSCLC demonstrates a propensity for brain metastases during treatment, with subtype *HER2* YVMA insertion showing a particularly higher estimated 12-month brain metastasis incidence when compared to the group not having this insertion.[20,22] Also, de novo *HER2* mutations are usually mutually exclusive with other driver genes, but they predominantly occur in the kinase.[20]

KRAS *Mutations*

KRAS mutations, present in up to about 35% of NSCLC diagnoses, are often early events in lung tumorigenesis that are associated with smoking, a high tumor mutation burden, and markers of immune evasion.[23-25] *KRAS* mutations in NSCLC lead to more aggressive clinical phenotypes, underscoring the importance of KRAS-targeted therapy.[23,25] KRAS was long considered "undruggable" due to the lack of good drug-binding pockets. However, the discovery of the allosteric P2 site on G12C-mutant *KRAS* enabled the development of covalent inhibitors like sotorasib and adagrasib.[23-25] These options show initial efficacy, yet intrinsic and acquired resistance eventually emerge via bypass signaling, secondary mutations, and histologic transformation. Combination therapies will likely be required for more durable responses.[24] Furthermore, the presence of comutations (eg, *STK11/LKB1*, *TP53*, *CDKN2A/B*, and *KEAP1*) adds to the heterogeneity of *KRAS*-mutated tumors and influences their biological behavior and response to treatment. Tumors with these comutations show altered immune marker expressions (eg, PD-L1), which correlate with resistance to PD-1 blockade therapy in *KRAS*-mutated lung adenocarcinoma.[23,24]

MET *Exon 14 Skipping Mutations*

MET exon 14 (*MET*ex14) skipping mutations are present in about 3% of NSCLC cases; they can lead to decreased MET receptor degradation and sustained MET signaling, which drive cancer cell proliferation and survival.[26,27] Patients with *MET*ex14 mutations show limited benefit from immunotherapy as compared with chemotherapy. Fortunately, the development of selective MET inhibitors (eg, crizotinib, capmatinib, and tepotinib) has led to improved clinical outcomes.[3,26] However, these drugs show reduced efficacy over time due to acquired resistance mediated by secondary *MET* mutations or amplification or activation of bypass signaling pathways like KRAS.[27,28] Research is focused on testing methods to identify *MET*ex14 mutations, use of combination targeted therapies to overcome resistance, and exploration of new MET inhibitors against resistance mutations.[26,28]

NTRK1/2/3 *gene fusions*

NTRK gene fusions occur in less than 1% of NSCLC cases, but they act as oncogenic drivers by causing ligand-independent activation of TRK kinases and of the downstream signaling pathways MAPK and PI3K that promote cancer cell proliferation and survival.[29,30] *NTRK* fusions are mutually exclusive with other driver mutations in NSCLC. Data are limited, yet *NTRK* fusions do not seem to be associated with high PD-L1 expression or CD8+ T-cell infiltration, »

and patients with NSCLC with *NTRK* fusions show little benefit from immunotherapy as compared to treatment with the TRK inhibitors larotrectinib and entrectinib.[30] These drugs demonstrate significant clinical activity, including against brain metastases, although acquired resistance typically develops via secondary *NTRK* mutations or activation of bypass pathways (MAPK or PI3K).[29,30]

RET *Rearrangements*

RET rearrangements occur in 1% to 2% of NSCLC cases; they function as potent oncogenic drivers through constitutive activation of the RET tyrosine kinase and the downstream signaling pathways MAPK and PI3K/AKT.[29,31,32] This leads to increased proliferation of cancer cells and the survival, migration, and invasion of these cells.[31] *RET* fusions also enable immune evasion by downregulating major histocompatibility complex class I expression. These tumors tend to have low tumor mutation burden and PD-L1 expression, contributing to poor response to immunotherapy. *RET* rearrangements confer sensitivity to RET inhibitors (eg, selpercatinib, pralsetinib, cabozantinib), but acquired resistance can develop through secondary *RET* mutations, alternate pathway activation, or new oncogenic fusions.[3,31]

ROS1 *Fusions*

ROS1 fusion proteins strongly drive tumorigenesis through constant activation of the ROS1 tyrosine kinase domain and downstream proliferative signaling pathways. Specifically, *ROS1* fusions lead to increased signaling through the MAPK, STAT3, and PI3K/AKT pathways.[33,34] This induces expression of genes involved in cell proliferation, survival, migration, and invasion.[34] *ROS1* fusions

occur in 0.9% to 2.6% of NSCLC cases, and their identification as genomic drivers of NSCLC has enabled the development of targeted inhibitors.[33,34] Crizotinib, ceritinib, and next-generation inhibitors such as lorlatinib and entrectinib are highly active against ROS1 fusion proteins, and their use often leads to dramatic tumor shrinkage.[3] By specifically blocking the fused ROS1 tyrosine kinase, these drugs can effectively shut down the progrowth signaling pathways. However, resistance to such ROS1 inhibitors inevitably develops after about 1 to 2 years through secondary mutations or activation of bypass signaling pathways.[34]

PD-L1 *Expression*

PD-1 is an immunosuppressive checkpoint expressed in immune cells, including in tumor-specific activated T cells, under conditions of chronic antigen exposure. PD-L1 is a PD-1 expressed in tumor cells, tumor-infiltrating cells, and antigen-presenting cells in many cancers, including NSCLC.[35,36] The expression of these 2 proteins suppresses T-cell function, enabling tumors to evade immune detection; although their expression levels have shown promise as prognostic biomarkers and therapeutic targets for immunotherapies that block the PD-1/PD-L1 pathway, their clinical significance varies across cancer types.[35] Higher levels of PD-L1 expression are associated with increased tumor proliferation, aggressiveness, and poorer survival.[36] The advent of immune checkpoint inhibitors that target the PD-1/PD-L1 pathway in patients with advanced NSCLC represents a significant improvement over traditional chemotherapy, especially in patients with high PD-L1 expression. However,

challenges remain; these include the occurrence of hyperprogressive disease in some patients treated with these inhibitors, which points to a need for better patient selection and understanding of resistance mechanisms.[35]

Biomarker Testing

The management of NSCLC relies heavily on the detection of biomarkers, with guidelines prioritizing comprehensive genomic testing for diagnosis and monitoring.[3] Next-generation sequencing (NGS) is crucial to identify targeted therapies and, ultimately, improve patient outcomes.[37] Fluorescence in situ hybridization, immunohistochemistry, and polymerase chain reaction assays are used to detect biomarkers in NSCLC, with each offering varying degrees of effectiveness.[3] Tests recommended for each biomarker are summarized in the Table.[3,8-10] Testing is integral to precise NSCLC diagnosis and individualized treatment.

However, genomic testing patterns indicate that recommended biomarker testing is underused—a significant number of patients with advanced NSCLC do not receive comprehensive genomic testing, and only a minority undergo testing for all recommended biomarkers.[38,39] The challenges in NSCLC biomarker testing include keeping pace with rapidly evolving guidelines, harvesting of insufficient tissue samples, needing to repeat biopsies, facing technical failures in testing, and dealing with long turnaround times and the complexity of interpreting NGS reports.[7,39] Addressing these barriers, improving guideline adherence, and enhancing the understanding of complex genomic data among oncologists are crucial unmet needs.[7,38,40] ◼

References

1. Kanellakis NI, Jacinto T, Psallidas I. Targeted therapies for lung cancer: how did the game begin? *Breathe (Sheff)*. 2016;12(2):177-179. doi:10.1183/20734735.006316

2. Howlader N, Forjaz G, Mooradian MJ, et al. The effect of advances in lung-cancer treatment on population mortality. *N Engl J Med*. 2020;383(7):640-649. doi:10.1056/NEJMoa1916623

3. National Comprehensive Cancer Network. Non-small cell lung cancer, version 5.2023. Updated November 8, 2023. Accessed November 16, 2023. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

4. Cufer T, Ovcaricek T, O'Brien MER. Systemic therapy of advanced non-small cell lung cancer: major-developments of the last 5-years. *Eur J Cancer*. 2013;49(6):1216-1225. doi:10.1016/j.ejca.2012.11.021

5. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. *CA Cancer J Clin*. 2023;73(1):17-48. doi:10.3322/caac.21763

6. Cancer stat facts: lung and bronchus cancer. National Cancer Institute. Surveillance, Epidemiology, and End Results Program. Accessed November 16, 2023. https://seer.cancer.gov/statfacts/html/lungb.html

7. Gutierrez ME, Choi K, Lanman RB, et al. Genomic profiling of advanced non-small cell lung cancer in community settings: gaps and opportunities. *Clin Lung Cancer*. 2017;18(6):651-659. doi:10.1016/j.cllc.2017.04.004

8. Villalobos P, Wistuba II. Lung cancer biomarkers. *Hematol Oncol Clin North Am*. 2017;31(1):13-29. doi:10.1016/j.hoc.2016.08.006

9. Kerr KM, Bibeau F, Thunnissen E, et al. The evolving landscape of biomarker testing for non-small cell lung cancer in Europe. *Lung Cancer*. 2021;154:161-175. doi:10.1016/j.lungcan.2021.02.026

10. Penault-Llorca F, Kerr KM, Garrido P, et al. Expert opinion on NSCLC small specimen biomarker testing - Part 2: Analysis, reporting, and quality assessment. *Virchows Arch*. 2022;481(3):351-366. doi:10.1007/s00428-022-03344-1

11. Sharma M, Basu DA, Nathany S, Amrith BP, Batra U. A narrative review of the role of common EGFR mutations in pathogenesis and treatment of non-small-cell lung carcinoma. *Cancer Res Stat Treat*. 2022;5(3):507-518. doi:10.4103/crst.crst_222_22

12. Morgillo F, Della Corte CM, Fasano M, Ciardiello F. Mechanisms of resistance to EGFR-targeted drugs: lung cancer. *ESMO Open*. 2016;1(3):e000060. doi:10.1136/esmoopen-2016-000060

13. Harrison PT, Vyse S, Huang PH. Rare epidermal growth factor receptor (EGFR) mutations in non-small cell lung cancer. *Semin Cancer Biol*. 2020;61:167-179. doi:10.1016/j.semcancer.2019.09.015

14. John T, Taylor A, Wang H, Eichinger C, Freeman C, Ahn MJ. Uncommon EGFR mutations in non-small-cell lung cancer: a systematic literature review of prevalence and clinical outcomes. *Cancer Epidemiol*. 2022;76:102080. doi:10.1016/j.canep.2021.102080

15. Schmid S, Cheng S, Chotai S, et al. Real-world treatment sequencing, toxicities, health utilities, and survival outcomes in patients with advanced ALK-rearranged non-small-cell lung cancer. *Clin Lung Cancer*. 2023;24(1):40-50. doi:10.1016/j.cllc.2022.09.007

16. Peng L, Zhu L, Sun Y, et al. Targeting ALK rearrangements in NSCLC: current state of the art. *Front Oncol*. 2022;12:863461. doi:10.3389/fonc.2022.863461

17. Chazan G, Solomon BJ. Optimal first-line treatment for metastatic ALK+ non-small cell lung cancer—a narrative review. Transl Lung Cancer Res. 2023;12(2):369-378. doi:10.21037/tlcr-22-656

18. Guaitoli G, Zullo L, Tiseo M, Dankner M, Rose AA, Facchinetti F. Non-small-cell lung cancer: how to manage BRAF-mutated disease. *Drugs Context*. 2023;12:2022-11-3. doi:10.7573/dic.2022-11-3

19. Yan N, Guo S, Zhang H, Zhang Z, Shen S, Li X. BRAF-mutated non-small cell lung cancer: current treatment status and future perspective. *Front Oncol*. 2022;12:863043. doi:10.3389/fonc.2022.863043

20. Yu X, Ji X, Su C. HER2-altered non-small cell lung cancer: biology, clinicopathologic features, and emerging therapies. *Front Oncol*. 2022;12:860313. doi:10.3389/fonc.2022.860313

21. Pillai RN, Behera M, Berry LD, et al. HER2 mutations in lung adenocarcinomas: a report from the Lung Cancer Mutation Consortium. *Cancer*. 2017;123(21):4099-4105. doi:10.1002/cncr.30869

22. Yang S, Wang Y, Zhao C, et al. Exon 20 YVMA insertion is associated with high incidence of brain metastasis and inferior outcome of chemotherapy in advanced non-small cell lung cancer patients with HER2 kinase domain mutations. *Transl Lung Cancer Res*. 2021;10(2):753-765. doi:10.21037/tlcr-20-559

23. El Osta B, Behera M, Kim S, et al. Characteristics and outcomes of patients with metastatic KRAS-mutant lung adenocarcinomas: the Lung Cancer Mutation Consortium Experience. *J Thorac Oncol*. 2019;14(5):876-889. doi:10.1016/j.jtho.2019.01.020

24. O'Sullivan E, Keogh A, Henderson B, Finn SP, Gray SG, Gately K. Treatment strategies for KRAS-mutated non-small-cell lung cancer. *Cancers (Basel)*.

2023;15(6):1635. doi:10.3390/cancers15061635

25. Xie M, Xu X, Fan Y. KRAS-mutant non-small cell lung cancer: an emerging promisingly treatable subgroup. *Front Oncol*. 2021;11:672612. doi:10.3389/fonc.2021.672612

26. 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. doi:10.1200/PO.20.00516

27. Yao Y, Yang H, Zhu B, et al. Mutations in the MET tyrosine kinase domain and resistance to tyrosine kinase inhibitors in non-small-cell lung cancer. *Respir Res*. 2023;24(1):28. doi:10.1186/s12931-023-02329-1

28. Spitaleri G, Trillo Aliaga P, Attili I, et al. MET in non-small-cell lung cancer (NSCLC): cross 'a long and winding road' looking for a target. *Cancers (Basel)*. 2023;15(19):4779. doi:10.3390/cancers15194779

29. Olmedo ME, Cervera R, Cabezon-Gutierrez L, et al. New horizons for uncommon mutations in non-small cell lung cancer: BRAF, KRAS, RET, MET, NTRK, HER2. *World J Clin Oncol*. 2022;13(4):276-286. doi:10.5306/wjco.v13.i4.276

30. Liu F, Wei Y, Zhang H, Jiang J, Zhang P, Chu Q. NTRK fusion in non-small cell lung cancer: diagnosis, therapy, and TRK inhibitor resistance. *Front Oncol*. 2022;12:864666. doi:10.3389/fonc.2022.864666

31. Novello S, Califano R, Reinmuth N, Tamma A, Puri T. RET fusion-positive non-small cell lung cancer: the evolving treatment landscape. *Oncologist*. 2023;28(5):402-413. doi:10.1093/oncolo/oyac264

32. Servetto A, Esposito D, Ferrara R, et al. RET rearrangements in non-small cell lung cancer: evolving treatment landscape and future challenges. Biochim Biophys Acta Rev Cancer. 2022;1877(6):188810. doi:10.1016/j.bbcan.2022.188810

33. Shaw AT, Ou SH, Bang YJ, et al. Crizotinib in ROS1-rearranged non-small-cell lung cancer. *N Engl J Med*. 2014;371(21):1963-1971. doi:10.1056/NEJMoa1406766

34. Gendarme S, Bylicki O, Chouaid C, Guisier F. ROS-1 fusions in non-small-cell lung cancer: evidence to date. *Curr Oncol*. 2022;29(2):641-658. doi:10.3390/curroncol29020057

35. Tang Q, Chen Y, Li X, et al. The role of PD-1/PD-L1 and application of immune-checkpoint inhibitors in human cancers. *Front Immunol*. 2022;13:964442. doi:10.3389/fimmu.2022.964442

36. Pawelczyk K, Piotrowska A, Ciesielska U, et al. Role of PD-L1 expression in non-small cell lung cancer and their prognostic significance according to clinicopathological factors and diagnostic markers. *Int J Mol Sci*. 2019;20(4); 824. doi:10.3390/ijms20040824

37. Villaruz LC, Socinski MA, Weiss J. Guidance for clinicians and patients with non-small cell lung cancer in the time of precision medicine. *Front Oncol*. 2023;13:1124167. doi:10.3389/fonc.2023.1124167

38. Hess LM, Krein PM, Haldane D, Han Y, Sireci AN. Biomarker testing for patients with advanced/metastatic nonsquamous NSCLC in the United States of America, 2015 to 2021. *JTO Clin Res Rep*. 2022;3(6):100336. doi:

39. Paz-Ares L, Gondos A, Saldana D, et al. Genomic testing among patients with newly diagnosed advanced non-small cell lung cancer in the United States: a contemporary clinical practice patterns study. *Lung Cancer*. 2022;167:41-48. doi:10.1016/j.lungcan.2022.01.021

40. Pennell NA, Arcila ME, Gandara DR, West H. Biomarker testing for patients with advanced non-small cell lung cancer: real-world issues and tough choices. *Am Soc Clin Oncol Educ Book*. 2019;39:531-542. doi:10.1200/EDBK_237863