Which biomarker tests should a patient with non-small cell lung cancer receive?

Fact Sheet

ID.LUNG

Unmet need in lung cancer

- Lung cancer is the second most commonly diagnosed cancer and the leading cause of cancer-related death worldwide[1]
- Non-small cell lung cancer (NSCLC) accounts for the majority (80–85%) of all cases of lung cancer[2]

At **diagnosis, ~70%** of patients with NSCLC have **locally advanced or metastatic** disease[3]

- Although treatment advances have led to improvements in survival, the overall prognosis for NSCLC remains poor[4]

Specific subtyping of all NSCLCs is necessary for therapeutic decision making

Predictive biomarker testing aims to match patients with the **most appropriate treatment** for their tumour[5,6]

- The biomarkers used in advanced NSCLC fall into two main categories:

Mutation testing[7–9]

EGFR mutation | *ALK* fusion | *ROS1* fusion | *BRAF* mutation | *ERBB2* (*HER2*) mutation | *KRAS G12C* mutation | *MET* exon 14 skipping mutation | *NTRK* fusion | *RET* rearrangement

PD-L1 testing[6–8]

PD-L1 expression

Mutation testing

- Patients are tested for specific activating or sensitising mutations that have been identified in the *EGFR, ALK, ROS1, BRAF, ERBB2 (HER2), KRAS G12C, MET, NTRK* and *RET* genes of advanced NSCLC tumours[5,7–9]
  - *EGFR* mutations include activating and sensitising mutations in exons 18–21 of *EGFR*[7]
  - Most common *EGFR* mutations comprise deletions in exon 19 and the L858R substitution mutation in exon 21. The T790M exon 20 substitution mutation is only rarely found in EGFR-TKI-naïve disease but is the most frequent cause of resistance to first- and second-generation EGFR-TKIs[7]
- Drugs that have been designed to specifically target the relevant mutant proteins or molecular pathways can be used for treatment following a positive test[5,7,8]
- Studies have shown that targeted therapies have greater efficacy than the previous standard of care in patients with *EGFR, ALK, ROS1, BRAF, ERBB2 (HER2), KRAS G12C, MET, NTRK* and *RET* mutation positive NSCLC tumours[10]
- If available, multiplex platforms (NGS) for molecular testing are preferable[7]
  - cfDNA (liquid biopsy) can be used to test for oncogenic drivers as well as resistance mutations, but all patients with a negative cfDNA blood test still require tissue biopsy[7]

PD-L1 testing

- Anti-programmed cell death-1 (PD-1)/programmed cell death ligand-1 (PD-L1) immunotherapy is a treatment option for advanced NSCLC tumours that have tested negative for *EGFR (select mutations), ALK, ROS1, BRAF, MET, NTRK* and *RET* mutations[6–9]
- PD-L1 testing allows tumours to be classed as either PD-L1 high or PD-L1 low/negative based on the level of PD-L1 expression in tumour cells and/or tumour infiltrating immune cells[6]
- Studies have shown that anti-PD-1/PD-L1 immunotherapy, alone or in combination with chemotherapy, can have greater efficacy in patients with tumours expressing higher levels of PD-L1[6,7,11]
  - The predictive nature of PD-L1 expression levels in patients with NSCLC has been reported in a number of key trials evaluating anti-PD-1/PD-L1 immunotherapy, including KEYNOTE-001 (NCT01295827), KEYNOTE-024 (NCT02142738), CheckMate 057 (NCT01673867) and POSEIDON (NCT03164616)[11–14]

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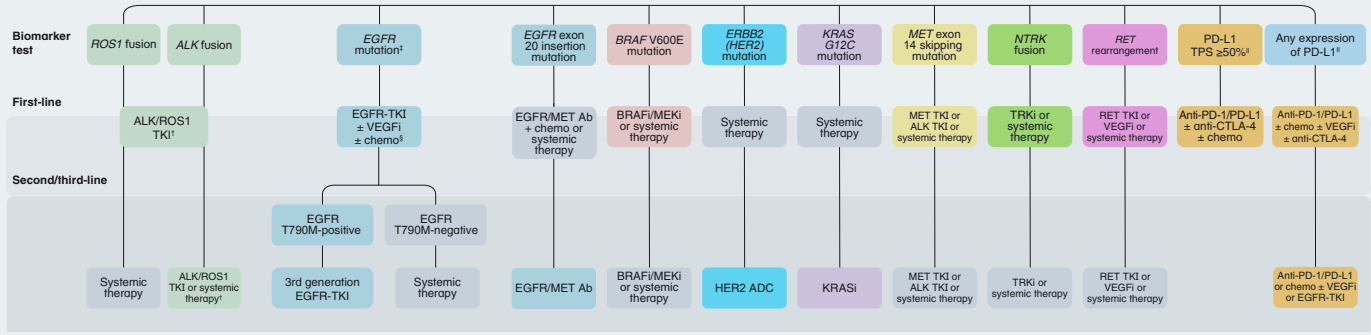
Figure. Summary of guidelines for selecting treatments on the basis of test results[7,9]



*The information is a broad representation of biomarker testing in NSCLC, adapted from guidelines, and does not summarise all aspects of testing. Routine mutation testing is not recommended in patients with unequivocal diagnosis of squamous cell carcinoma; †ALK specific TKI is also recommended for patients with *ALK*-positive advanced NSCLC; ‡including exon 19 deletion, exon 21 L858R mutation, S768I, L861Q and/or G719X mutations;[7,9] §VEGFi only in combination with erlotinib; ¶Recommendations for patients with Performance Status 0–2 and who have tested negative for *EGFR, ALK, ROS1, BRAF, ERBB2 (HER2), KRAS G12C, MET, NTRK* and *RET* mutations[7,9]

Ab, antibody; BRAFi, BRAF V600E inhibitor; chemo, chemotherapy; KRASi, Kirsten rat sarcoma viral oncogene homolog inhibitor; MEKi, MEK inhibitor; TKI, tyrosine kinase inhibitor; TPS, tumour proportion score; TRK, tropomycin receptor kinase; VEGFi, vascular endothelial growth factor inhibitor

Implications in the clinic

- Testing a portfolio of established biomarkers can help identify patients with NSCLC who are most likely to benefit from particular treatment options[5–8]

Summary

- There remains significant unmet need for improving outcomes in patients with NSCLC
- Testing for predictive biomarkers provides an opportunity to improve outcomes by assigning patients to the most appropriate treatment
- Patients with NSCLC whose tumours habour *EGFR, ALK, BRAF, ROS1, ERBB2 (HER2), KRAS G12C, MET, NTRK* and *RET* aberrations should be assigned to the appropriate targeted therapy
- Broad genomic profiling may be the most informative approach to identify potential resistance mechanisms, and repeat profiling may be necessary throughout a patient's treatment plan
- NSCLC patients who have PD-L1 high (TC ≥50%) tumours (but are negative for the *EGFR, ALK, ROS1, BRAF, ERBB2 (HER2), KRAS G12C, MET, NTRK* and *RET* tests) should be considered for anti-PD-1/PD-L1 immunotherapy

References

1. Sung H, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71:209–49
2. American Cancer Society. What is non-small cell lung cancer? Available at: https://www.cancer.org/cancer/non-small-cell-lung-cancer/about/what-is-non-small-cell-lung-cancer.html (accessed January 2024)
3. Cancer.Net. Lung Cancer - Non-Small Cell: Statistics. Available at: https://www.cancer.net/cancer-types/lung-cancer-non-small-cell/statistics. (accessed January 2024)
4. Vicidomini G. Current Challenges and Future Advances in Lung Cancer: Genetics, Instrumental Diagnosis and Treatment. Cancers (Basel) 2023;15:3710
5. Sundar R, et al. Imprecision in the era of precision medicine in non-small cell lung cancer. Front Med 2017;4:39
6. Peters S, et al. PD-1 blockade in advanced NSCLC: A focus on pembrolizumab. Cancer Treat Rev 2018;62:39–49
7. Planchard D, et al. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2020;27:v1–27
8. Lindeman NI, et al. Updated molecular testing guideline for the selection of lung cancer patients for treatment with targeted tyrosine kinase inhibitors. J Thorac Oncol 2018;13:323–58
9. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer V.1.2024. © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. Accessed January 09, 2024. 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
10. Guo H, et al. Biomarker-targeted therapies in non–small cell lung cancer: current status and perspectives. Cells 2022;11:3200
11. Johnson ML, et al. Durvalumab with or without tremelimumab in combination with chemotherapy as first-line therapy for metastatic non–small-cell lung cancer: the Phase III POSEIDON study. J Clin Oncol 2023;41:1213–27
12. Reck M, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med 2016;375:1823–33
13. Garon EB, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med 2015;372:2018–28
14. Borghaei H, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med 2015;373:1627–39