Editorial

Biomarkers for immunotherapy in non-small cell lung cancer: a current and future reality

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Immunotherapy has now become one of the mainstays in the treatment of non-small cell lung cancer (NSCLC). Immunotherapy based on immune checkpoint inhibitors (ICIs) has become a standard for treatment at all stages, ranging from neoadjuvant or adjuvant to advanced stages (*Table 1*) (1). One of the main problems encountered in clinical practice in recent years since the development of immunotherapy in NSCLC and other solid tumours is the poor prediction of response to these treatments. Different biomarkers have been validated as predictors of immunotherapy in NSCLC, however, only two have demonstrated validity and clinical applicability, namely programmed death-ligand 1 (PD-L1) and tumour mutational burden (TMB) (2). Another biomarker that is not as well known (although it has been described in multiple studies), and which is fundamental in NSCLC, is the patient's general condition measured by different scales, which marks with a high probability the possibility of response to immunotherapy in NSCLC (3).

PD-L1 and TMB

The best known and validated of all biomarkers is undoubtedly PD-L1. This molecule is the ligand of the programmed death-1 (PD-1) receptor, whose alterations are one of the most important immune evasion mechanisms (4). Different studies have validated its applicability in NSCLC, being the only biomarker, whose value so far implies changes in NSCLC therapeutics (5). Even though a high value implies a higher probability of response to ICIs, multiple obstacles have been found in its applicability that have hindered its value as a biomarker. The main one is that PD-L1 expression is heterogeneous at the tumour level, so its value depends on the tumour site analysed. Furthermore, the methods of evaluation also differ depending on the pharmaceutical company that developed it, which makes its interpretation even more complex. Nevertheless, high PD-L1 values, especially above 50%, imply a very high probability of response to immunotherapy in NSCLC, which is why, despite its limitations, it is now considered a powerful predictive biomarker in NSCLC (6). In addition, the value of amplification of the *PD-L1* gene found in the 9p24.1 region of the genome as a biomarker is under investigation due to the development of molecular diagnostic methods (7,8).

Along with PD-L1, the other validated predictive

Table 1 Main indications in NSCLC with immunotherapy

Immune checkpoint inhibitors	Immunoglobulin type	Target molecule	Approved in NSCLC
Ipilimumab (MDX-010)	IgG-1κ	CTLA-4	Advanced NSCLC in combination with chemotherapy and nivolumab in first line (CheckMate9LA)
			Advanced NSCLC in combination with nivolumab in first line with PD-L1 ≥1% (CheckMate227)
Tremelimumab (CP-675)	IgG-2	CTLA-4	Advanced NSCLC in combination with chemotherapy and durvalumab in first line (POSEIDON)
Pembrolizumab (MK-3475)	IgG-4κ	PD-1	Advanced NSCLC in combination with chemotherapy in first line (KEYNOTE-189 and KEYNOTE-407)
			Advanced NSCLC in monotherapy with PD-L1 ≥50% (KEYNOTE-024)
			Advanced NSCLC in second line with PD-L1 ≥1% (KEYNOTE-010)
Nivolumab (MDX-1106)	IgG4	PD-1	Neoadjuvant in NSCLC plus chemotherapy in stage IB–IIIA (CheckMate816)
			Advanced NSCLC (first line) in combination with chemotherapy and Ipilimumab in first line (CheckMate9LA)
			Advanced NSCLC (first line) in combination with ipilimumab in first line with PD-L1 ≥1% (CheckMate227)
			Advanced NSCLC (second line) in monotherapy (CheckMate017 and CheckMate057)
Cemiplimab (REGN-2810)	IgG4	PD-1	Advanced NSCLC (first line) in monotherapy with PD-L1 ≥50% (EMPOWER-Lung1)
			Advanced NSCLC with chemotherapy in first line (EMPOWER-Lung3)
Atezolizumab (MPDL3280A)	IgG1	PD-L1	Adjuvant in NSCLC in stage IB–III in monotherapy post-surgery and CT (IMpower010)
			Advanced NSCLC (first line) with chemotherapy +/– bevacizumab (IMpower150)
			Advanced NSCLC (first line) in monotherapy with PD-L1 ≥50% (IMpower110)
			Advanced NSCLC (second line) in monotherapy (OAK)
Durvalumab (MEDI4736)	IgG1	PD-L1	Adjuvant in locally advanced unresectable NSCLC (after CT/RT with PD-L1 ≥1% in tumour cells)
			Advanced NSCLC in combination with chemotherapy and tremelimumab in first line (POSEIDON)

NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1; PD-1, programmed death-1; CTLA-4, cytotoxic T lymphocyte-associated antigen-4; CT, computed tomography; RT, radiotherapy.

biomarker, although less applicable in clinical practice, is TMB. The accumulation of the number of mutations in the tumour leads to a greater genesis of neoantigens, so the action of the immune system and immunotherapy on these tumours is greater (9). Among the tumours with the highest mutational burden, the two with the highest TMB are melanoma and NSCLC, which has led to higher TMB being a strong predictor of greater response to immunotherapy. The main study that has validated this biomarker in NSCLC is the CheckMate227 clinical trial (10). In this study in patients with NSCLC and high TMB (≥10 mutations/megabase), the Nivolumab-Ipilimumab combination had a progression-free survival (PFS) of 7.2 months versus chemotherapy of 5.5 months [hazard ratio (HR) 0.58; P<0.001]. Thus, although its clinical applicability is currently low, it is a promising biomarker with important applications.

Performance status

The patient's general condition is key in clinical practice. In many cases of NSCLC, the need for a response due to the

high symptomatology of the patients makes it necessary to consider chemotherapy treatments in the search for a high response, regardless of other values such as PD-L1. The latency in the appearance of response with immunotherapy means that the probability of response to immunotherapy is lower in patients with poor general condition (11). The absence of immediate cytotoxicity on the tumour means that the response to ICIs in the different clinical trials takes about three months, so it is important to take this biomarker into account when making decisions. Therefore, measuring general condition using different scales such as the Karnofsky or Eastern Cooperative Oncology Group (ECOG) scales is a predictive biomarker that is possibly more predictive than others such as PD-L1 (12).

Biomarkers in development

In addition to the above, there are other biomarkers that, although they have not been validated, have a very promising future and are currently under investigation. Probably, due to their importance in other tumours, alterations in the mismatch repair (MMR) system are one of the most promising biomarkers in NSCLC. It is estimated that about 4–5% of NSCLC have MMR system alterations, although these values can vary up to 8–10% (13). The value of these MMR system genes (*MLH1*, *MSH2*, *MSH6* and *PMS2*) as predictive biomarkers in solid tumours is already known, especially in tumours of gastrointestinal origin. Several studies have investigated their association with immunotherapy in NSCLC, showing a greater benefit of immunotherapy in NSCLC with MMR alterations in terms of both response and survival (14,15). However, their use in these tumours has not been validated, so their value is still in the preclinical stages.

Along with all the biomarkers mentioned above, there are several other biomarkers which are in different stages of development and which to date have shown promising results. One of the most interesting is the microbiome, understood as the set of micro-organisms living in a particular environment (16). In the case of the gut microbiome, commensal germs that colonise the gut are considered essential for the homeostasis of the digestive tract. They have multiple functions, one of the most important of which is an anti-inflammatory effect through modification of regulatory T-cells. Alterations in the microbiome may lead to a greater or lesser effect of immunotherapy, whereby the microbiome could be altered to increase the effect of ICIs or decrease in cases of immunotoxicity. Therefore, the microbiome could be both a predictive and prognostic biomarker for immunotherapy (17). The use of antibiotics prior to and during immunotherapy treatment could modulate the effects of immunotherapy through regulation of the microbiome, although its use is in pre-clinical stages.

Tumour-infiltrating lymphocytes (TILs) are another biomarker under investigation both preclinically and clinically. TILs are lymphocytes that are found infiltrating tumours, generating a pro-inflammatory environment that enhances the anti-tumour response of the immune system (18). Multiple studies have shown that increased TILs at the tumour level led to a better response to ICIs in different solid tumours, including NSCLC (19,20). TILs are so important in the anti-tumour immune response that two types of tumours can now be distinguished according to the presence of TILs: tumours with high inflammation and a better response to immunotherapy, and non-inflamed tumours with a poorer response (21). Therefore, although TILs are not very useful in clinical practice, their role could be essential in the future in immunotherapy treatment of NSCLC.

Along with all the above-mentioned biomarkers, there are multiple biomarkers currently under development (*Table 2*). Different genomic signatures are under development to try to find patterns of response to immunotherapy in NSCLC (*STK11/LKB1* o *LAMC3*), and there are some promising genes that could have great future relevance in the treatment of NSCLC. Other biomarkers are the lactate dehydrogenase (LDH) which is a marker of tumour proliferation and whose values have been inversely related to the response to ICIs (22), the expression of interferon-γ as a marker of anti-tumour inflammatory response (23) and the neutrophil-to-lymphocyte ratio (NLR) with a high serum value being related to worse responses to immunotherapy in NSCLC (24). Finally, the main driver mutations in NSCLC (*EGFR*, *ALK* and *ROS1*) should not be forgotten. These mutations are known biomarkers predictive of non-response to immunotherapy, and therefore, targeted therapy against these mutations in NSCLC is essential over and above

Table 2 Main predictive biomarkers of response to immunotherapy in NSCLC

Biomarker	Influence on the response to immunotherapy
PD-L1	High PD-L1: better response to immunotherapy
TMB	High TMB: better response to immunotherapy
Performance status	ECOG ≥2 or KPS ≤70: worse response to immunotherapy
DNA mismatch repair	Mutations in MMR system: better response to immunotherapy
Microbiome	Rich microbiome in *Bacteroides* and *Bifidobacteria*: better response to immunotherapy
Tumor-infiltrating lymphocytes	High value of TILs in tumour: better response to immunotherapy
Lactate dehydrogenase	High LDH: worse response to immunotherapy
Interferon-γ	High interferon-γ: better response to immunotherapy
Neutrophil-to-lymphocyte ratio	High NLR: worse response to immunotherapy
Oncogenic driver mutations	*EGFR*, *ALK* or *ROS1* mutations: worse response to immunotherapy

NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1; TMB, tumour mutational burden; ECOG, Eastern Cooperative Oncology Group; KPS, Karnofsky performance status; MMR, mismatch repair; TILs, tumour-infiltrating lymphocytes; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio.

immunotherapy treatments (25).

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References

1. Reck M, Remon J, Hellmann MD. First-Line Immunotherapy for Non-Small-Cell Lung Cancer. J Clin Oncol 2022;40:586-97.
2. Negrao MV, Skoulidis F, Montesion M, et al. Oncogene-specific differences in tumor mutational burden, PD-L1 expression, and outcomes from immunotherapy in non-small cell lung cancer. J Immunother Cancer 2021;9:e002891.
3. Alessi JV, Awad MM. Immunotherapy in lung cancer: effective for patients with poor performance status? Lancet Respir Med 2020;8:838-9.
4. Han Y, Liu D, Li L. PD-1/PD-L1 pathway: current researches in cancer. Am J Cancer Res 2020;10:727-42.
5. De Marchi P, Leal LF, Duval da Silva V, et al. PD-L1 expression by Tumor Proportion Score (TPS) and Combined Positive Score (CPS) are similar in non-small cell lung cancer (NSCLC). J Clin Pathol 2021;74:735-40.
6. Proto C, Ferrara R, Signorelli D, et al. Choosing wisely first line immunotherapy in non-small cell lung cancer (NSCLC): what to add and what to leave out. Cancer Treat Rev 2019;75:39-51.
7. Xu-Monette ZY, Zhou J, Young KH. PD-1 expression

and clinical PD-1 blockade in B-cell lymphomas. Blood 2018;131:68-83.
8. Phillips WJ, Awan A, Lo B, et al. The role of concurrent amplification of PD- L1, PD-L2 and JAK2 in metastatic lung adenocarcinoma as a biomarker of immune checkpoint inhibitor response: a case report. Precis Cancer Med 2023;6:10.
9. Addeo A, Friedlaender A, Banna GL, et al. TMB or not TMB as a biomarker: That is the question. Crit Rev Oncol Hematol 2021;163:103374.
10. Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus Ipilimumab in Advanced Non-Small-Cell Lung Cancer. N Engl J Med 2019;381:2020-31.
11. Mojsak D, Kuklińska B, Dębczyński M, et al. Immunotherapy in patients with non-small cell lung cancer with ECOG PS 2. Contemp Oncol (Pozn) 2021;25:53-6.
12. Bersanelli M, Brighenti M, Buti S, et al. Patient performance status and cancer immunotherapy efficacy: a meta-analysis. Med Oncol 2018;35:132.
13. Olivares-Hernández A, Del Barco Morillo E, Parra Pérez C, et al. Influence of DNA Mismatch Repair (MMR) System in Survival and Response to Immune Checkpoint Inhibitors (ICIs) in Non-Small Cell Lung Cancer (NSCLC): Retrospective Analysis. Biomedicines 2022;10:360.
14. Jiang M, Jia K, Wang L, et al. Alterations of DNA damage response pathway: Biomarker and therapeutic strategy for cancer immunotherapy. Acta Pharm Sin B 2021;11:2983-94.
15. Fanale D, Corsini LR, Scalia R, et al. Can the tumor-agnostic evaluation of MSI/MMR status be the common denominator for the immunotherapy treatment of patients with several solid tumors? Crit Rev Oncol Hematol 2022;170:103597.
16. Gopalakrishnan V, Helmink BA, Spencer CN, et al. The Influence of the Gut Microbiome on Cancer, Immunity, and Cancer Immunotherapy. Cancer Cell 2018;33:570-80.
17. Sun JY, Yin TL, Zhou J, et al. Gut microbiome and cancer immunotherapy. J Cell Physiol 2020;235:4082-8.
18. Paijens ST, Vledder A, de Bruyn M, et al. Tumor-infiltrating lymphocytes in the immunotherapy era. Cell Mol Immunol 2021;18:842-59.
19. Creelan BC, Wang C, Teer JK, et al. Tumor-infiltrating lymphocyte treatment for anti-PD-1-resistant metastatic lung cancer: a phase 1 trial. Nat Med 2021;27:1410-8.
20. Wang SS, Liu W, Ly D, et al. Tumor-infiltrating B cells: their role and application in anti-tumor immunity in lung cancer. Cell Mol Immunol 2019;16:6-18.
21. Lee N, Zakka LR, Mihm MC Jr, et al. Tumour-infiltrating lymphocytes in melanoma prognosis and cancer immunotherapy. Pathology 2016;48:177-87.
22. Ma X, Yang S, Zhang T, et al. Bioresponsive immune-booster-based prodrug nanogel for cancer immunotherapy. Acta Pharm Sin B 2022;12:451-66.
23. Gocher AM, Workman CJ, Vignali DAA. Interferon-γ: teammate or opponent in the tumour microenvironment? Nat Rev Immunol 2022;22:158-72.
24. Diem S, Schmid S, Krapf M, et al. Neutrophil-to-Lymphocyte ratio (NLR) and Platelet-to-Lymphocyte ratio (PLR) as prognostic markers in patients with non-small cell lung cancer (NSCLC) treated with nivolumab. Lung Cancer 2017;111:176-81.
25. Liu F, Yuan X, Jiang J, et al. Immunotherapy in advanced non-small-cell lung cancer with EGFR mutations. Immunotherapy 2020;12:1195-207.

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