Drugs in Context

drugsincontext.com

CASE REPORT

Nivolumab plus ipilimumab with chemotherapy in metastatic NSCLC: minireview and a case study of a patient negative for PD-L1

Alessandro Morabito

Oncologia Clinica Sperimentale Toraco-Polmonare, Istituto Nazionale dei Tumori IRCCS Fondazione "G. Pascale", Napoli, Italy

Abstract

The advent of immunotherapy, and in particular the use of immune-checkpoint inhibitors, has profoundly revolutionized the treatment of different cancers, including lung cancer. The use of immune-checkpoint inhibitors has prolonged survival in lung cancer with a strong benefit in a significant percentage of patients with non-small-cell lung cancer. Here, a clinical case of a patient who, despite testing negative for PD-L1, displayed a sustained complete response to immunotherapy treatment in advanced metastatic non-small-cell lung cancer is presented. Additionally, recent findings concerning the application of immunotherapy in this context are reviewed.

Keywords: biomarkers, immune-checkpoint inhibitors, NSCLC, response duration.

Citation

Morabito A. Nivolumab plus ipilimumab with chemotherapy in metastatic NSCLC: minireview and a case study of a patient negative for PD-L1. *Drugs Context*. 2024;13:2024-5-3. https://doi.org/10.7573/dic.2024-5-3

Introduction

The advent of immunotherapy, and in particular the use of immune-checkpoint inhibitors (ICIs), has profoundly revolutionized the treatment of different cancers. Patients with melanoma had an unprecedented advantage from the use of ICIs. In 2011, ipilimumab, an antibody targeting CTLA4, was approved for the treatment of advanced melanoma following the positive results of a phase III trial.[1] Other ICIs have been subsequently approved for advanced melanoma and different drugs and treatment options are now available for its treatment.[1]

Following the results obtained in melanoma, the number of tumours for which ICIs have been approved and are currently being used is constantly increasing. Renal cell carcinoma, urothelial carcinoma, head and neck squamous cell cancer, and Hodgkin lymphoma are some examples where the use of ICIs has demonstrated a strong impact on patient outcomes.[2,3] In some specific tumour types, such as colorectal cancer with high microsatellite instability (MSI), a sub-class of patients seem to be particularly responsive to ICIs.[4] Interestingly, significant activity has also been reported in rare tumours such as Merkel cell carcinoma, hepatocellular carcinoma or squamous cell carcinoma of the skin.[5,6] The use of ICIs has shown strong benefits in the treatment of non-small-cell lung cancer (NSCLC) in terms of overall survival (OS) and duration of response.[7–10]

However, not all patients with cancer benefit from the use of ICIs and there are still several open questions relative to the use of ICIs, including the lack of biomarkers predicting response. Finally, new emerging ICIs and combination ICIs are in clinical trials, thus possibly further enhancing the therapeutic opportunities for a larger number of patients.

Herein, a minireview is presented on the evolutionary course of NSCLC treatment over recent years, particularly emphasizing the advent of the various ICIs approved either as monotherapy or in combination. Subsequently, a case involving a patient who tested negative for PD-L1 but experienced a sustained complete response is discussed to explore strategies for addressing this specific tumour context.

Minireview

ICI therapy

ICI therapy is becoming the standard first-line therapy for patients with advanced NSCLC without molecular alterations, mainly used as monotherapy in patients with high expression of PD-L1 (≥50%) or in combination with chemotherapy in patients with PD-L1 <50%.[7,8] Several randomized phase III studies performed in recent years clearly showed a strong benefit from the use of ICIs in NSCLC, leading to their approval for the treatment of advanced NSCLC. Amongst the ICIs approved are inhibitors of PD-L1 (durvalumab[11] and atezolizumab[12]), inhibitors of PD-1 (pembrolizumab,[13] cemiplimab[14] and nivolumab[15,16]) and inhibitors of CTLA4 (ipilimumab[17,18]).

In 2015, two randomized, open-label international trials compared nivolumab (a fully human IgG4 antibody targeting PD-1) to docetaxel in patients with advanced squamous NSCLC progressing after or during chemotherapy.[15,16] These studies showed a statistically significant increase in OS in the group of patients treated with nivolumab. The study by Borghaei et al.[15] randomized 582 patients with advanced non-squamous NSCLC after failure of platinum-based chemotherapy and reported a median OS of 12.2 months in the 292 patients randomized to receive nivolumab *versus* 9.4 amongst the 290 patients treated with docetaxel, with a hazard ratio (HR) for death of 0.73 (96% CI 0.59–0.89). The second study by Brahmer et al.[16] reported, in a smaller number of patients (*n*=272), a similar HR for death of 0.59 (95% CI 0.44–0.79). These results led to a quick FDA approval of the drug for the treatment of this specific group of patients. Another study using another antibody targeting PD-1 (pembrolizumab) in patients with advanced NSCLC and an expression of PD-L1 in at least 50% of cancer cells randomized 305 patients to receive first-line pembrolizumab or platinum-based chemotherapy.[13] The results showed a significantly longer progression-free survival and OS in patients treated with pembrolizumab compared to those treated with platinum-based chemotherapy. The median progression-free survival was 10.3 months in the pembrolizumab group *versus* 6.0 months in the chemotherapy group, with a HR for disease progression or death of 0.50 (95% CI 0.37–0.68). The response rate was also higher in the pembrolizumab group (45%) than in the chemotherapy group (28%). Notably, this superiority in efficacy was associated with a lower frequency of treatment-related adverse events of any grade (which occurred in 73.4% of patients treated with pembrolizumab compared to 90.0% in the group of patients receiving chemotherapy). Even when grade 3, 4 or 5 treatment-related adverse events were considered, the pembrolizumab group showed a reduced frequency (26.6% *versus* 53.3%) compared to the chemotherapy group. Also in this case, in 2016, the study opened the way to the first FDA and EMA approval of an ICI for the first-line treatment of patients with NSCLC with more than 50% of cells positive for PD-L1.

Monotherapy *versus* combination

Although the initial studies and application were conceived for the use of ICI monotherapy, mostly in the second-line setting, the encouraging results obtained have led to the use of ICIs in combination regimens and first-line settings.

The combinations can be of either different ICIs with or without chemotherapy or a single ICI and chemotherapy. Particularly relevant for NSCLC is the association of ipilimumab (anti-CTLA4) and nivolumab (anti-PD-1), which was approved in 2020 in first-line treatment. This combination has been compared to chemotherapy in the first-line setting in a phase III study in patients with at least 1% of cells positive for PD-L1 expression.[17] The trial showed a superiority of ipilimumab and nivolumab compared to chemotherapy with a median OS duration of 17.1 months for the nivolumab-plus-ipilimumab group and 14.9 months for the chemotherapy group. The median duration of response was 23.2 months for patients receiving ICIs compared to 6.2 months for those treated with chemotherapy. The OS benefit was also maintained in patients with PD-L1 expression below 1%. The percentage of patients with grade 3 or 4 treatment-related adverse events was lower in the group receiving ICIs (32.8% *versus* 36.0% for those treated with chemotherapy).

Interestingly, the ipilimumab and nivolumab combination also confirmed its activity in patients regardless of their expression of PD-L1 in combination with two cycles of chemotherapy. The CheckMate 9LA trial enrolled patients with squamous or non-squamous advanced NSCLC, stratifying the patients by histology, sex and PD-L1 expression in the tumour (<1% or ≥1%).[18] The arms were ipilimumab plus nivolumab combined with two cycles of chemotherapy *versus* chemotherapy alone for four cycles, with a 1:1 randomization; a clear superiority of this combination regimen compared to chemotherapy was reported. At 5 years, the trial confirmed the superiority of ICIs plus chemotherapy with a HR of 0.73 (95% CI 0.62–0.85).[19] The OS rate at 5 years was 18% in the ICI–chemotherapy arm compared to 11% in the chemotherapy alone arm. Again, these favourable results were obtained regardless of PD-L1 expression. The reported HR in patients with PD-L1 expression <1% was in fact 0.63 (95% CI 0.49–0.83) compared to 0.73 (95% CI 0.59–0.90) for those with PD-L1 ≥1%. Similarly, no differences were found for histology: HR for the squamous group was 0.63 (95% CI 0.48–0.84) and for the non-squamous group it was 0.77 (95% CI 0.64–0.94).

Overall, these data offer an additional opportunity for patients with PD-L1 expression <1%, representing those with the most unmet needs.

Thus, apart for patients with NSCLC harbouring specific mutations (such as *EGFR* or *ALK*), who are treated with drugs designed to hit these targets, the remaining patients with NSCLC have the possibility to receive first-line ICIs.

Biomarkers and patient selection

There is still no clear evidence of biomarkers predicting the response to ICIs in patients with NSCLC. Amongst the tumour-based biomarkers investigated for the treatment with ICIs in NSCLC, the expression of PD-L1 in tumour biopsies, as assessed by immunohistochemistry, represents the best (and approved) biomarker to guide treatment decisions and able to predict response to therapy. High baseline PD-L1 expression is generally associated with superior outcomes following ICI monotherapy in patients who failed standard chemotherapy. However, it needs to be mentioned that ICIs have shown activity in patients negative for PD-L1.[20] The absence of PD-L1 expression is likely to be the most relevant biomarker justifying the selection of the combination of PD-1 and CTLA4 inhibitors as outlined in both the CheckMate 227 and CheckMate 9LA randomized trials.[18,21] This is consistent with the Clinical Practice Guidelines in Oncology (NCCN Guidelines) for NSCLC.[22]

Another tissue-based biomarker is the tumour mutational burden (TMB), i.e. the total number of somatic mutations per megabase of the tumour genome. The assumption is that mutations generate more neoantigens inducing stronger immune activation, and there are some data supporting that higher TMB correlates with increased responses.[23] Hellmann et al. showed clinical benefit of nivolumab plus ipilimumab in patients with NSCLC with a high TMB independently from the percentage of tumour PD-L1 expression.[24]

MSI is another potential biomarker. It has been shown that patients with high MSI better respond to ICIs.[4] However, MSI alterations are rare in NSCLC and are mostly observed in tumours like colorectal and endometrial cancer.

Considering the different landscape of mutations, there is evidence that the presence of comutations in certain genes (such as *KRAS* and *STK11*/*LKB1*) is associated with a worst response to ICIs[25,26] in patients with NSCLC. The reasons behind these reduced effects are likely to be the inherent worst prognosis of these patients, the low expression of PD-L1 and the reduced infiltrate in these tumours.[25–27] An interesting possibility comes from the evidence that the use of KRAS-G12C-specific inhibitors in preclinical models stimulates a pro-inflammatory tumour microenvironment with increased response to ICIs.[28] *KRAS-G12C* represents the most frequent *KRAS* mutation in NSCLC. Following from these data, trials are in progress to test the combination of KRAS-G12C and ICIs in advanced NSCLC that could represent an additional effective regimen to be proposed.

Finally, particularly for NSCLC, where the tissue available is often scarce, blood-based biomarkers are being evaluated as a predictor of response. These biomarkers would have the possibility to longitudinally track patient tumour evolution under the selective pressure of different treatments, including ICIs. These include the evaluation of TMB in circulating cells in blood, microRNAs, circulating tumour cells and circulating tumour DNA, which have shown promising associations with the clinical response of patients with NSCLC to ICI therapy.[3,29,30]

Table 1 reports a list of drugs currently used in NSCLC, whether they are used as monotherapy or in combination, and their respective treatment lines.

The combination of different ICIs is now in clinical practice for different cancers, including NSCLC. In particular, there are two treatment options in Italy for patients with advanced non-squamous NSCLC with an expression of PD-L1 <50%: a combination of platinum-based chemotherapy with pembrolizumab for four cycles, followed by maintenance therapy with pembrolizumab and pemetrexed (Keynote 189 schedule) or a combination of platinum-based chemotherapy with nivolumab and ipilimumab for only two cycles (CheckMate 9LA schedule), followed by maintenance therapy with nivolumab

Table 1. Immune-checkpoint inhibitors approved by the FDA for non-small-cell lung cancer.

Drug/ combination	Target	Line of therapy	Notes
Nivolumab	PD-1	Second	Any PD-L1
Pembrolizumab	PD-1	First Second	PD-L1 ≥50% PD-L1 ≥1%
Atezolizumab	PD-L1	Second First	Any PD-L1 PD-L1 ≥50%
Durvalumab	PD-L1	Locally advanced	PD-L1 ≥1%
Ipilimumab and nivolumab	CTLA4/PD-1	First	PD-L1 ≥1%
Cemiplimab	PD-1	First	PD-L1 ≥50%

and ipilimumab without further chemotherapy.[9,10,18] Although the follow-up data are longer for Keynote 189 compared to CheckMate 9LA, no substantial differences have been highlighted in terms of efficacy between these two regimens (Table 2); fewer grade 3–5 side-effects have been reported with the CheckMate 9LA scheme, probably due to the lower chemotherapy treatment used.[31,32]

Herein, a case of a patient with bulky disease at baseline, PD-L1 negative, who has been successfully treated with the CheckMate 9LA regimen with a long-lasting complete response without significant side-effects, is presented.

Case report

The clinical case here reported is described with the intent to exemplify disease management and illustrate how patients with NSCLC negative for PD-L1 expression might be approached. All the data referring to the patient are published after informed consent, in anonymous way, without any details allowing patient identification, and in accordance with the World Medical Association Declaration of Helsinki.

In May 2022, a 55-year-old patient, heavy smoker (30 cigarettes/day from the age of 15 years), was admitted in our hospital for cough and dyspnoea. Comorbidities included hypertension under treatment, chronic obstructive pulmonary disease with sleep apnoea, obesity and HBsAg-positive liver disease (hepatitis B) under treatment with entecavir.

CT and positron emission tomography revealed a suspected lung mass in the left hilar site of approximately 61 mm (SUV 12.9), with stenosis of the main bronchus and downstream atelectasis; a further nodular lesion below the first of 37 mm, a hamartomatous formation in the right upper pulmonary lobe of 14 mm, sub-carinal lymphadenopathy of 44×23 mm (SUV 11) and right adrenal lesion of 44 mm (SUV 10.7) were also detected.

The patient subsequently underwent endo bronchial ultrasound-guided transbronchial needle aspiration, and the final diagnosis was lung adenocarcinoma, PD-L1 negative. Next-generation sequencing tests on DNA and RNA (Oncomine Precision Assay from Thermo Fisher Scientific, detecting hotspot mutations in 45 genes, copy number variations in 14 genes and fusions in 18 genes) were negative for molecular alterations susceptible to targeted biological therapies and positive for *TP53* (66%).

Before starting first-line treatment, the patient repeated a total body CT scan, which displayed the onset of left pleural effusion, substantial stability of the left hilar lesion of 61×55 mm and of the sub-carinal lymph nodes, an increase in size of the nodular lesion in the retrocardiac site of 57×35 mm, and stability of the right adrenal metastasis of 44 mm (Figure 1A–D).

Following a thorough discussion with the patient regarding the various therapeutic options available (Keynote 189 *versus* CheckMate 9LA), the CheckMate 9LA regimen, which includes only two cycles of chemotherapy in the induction phase, without further chemotherapy in the maintenance phase, was chosen in order to reduce the risk of bone marrow and gastrointestinal toxicities.

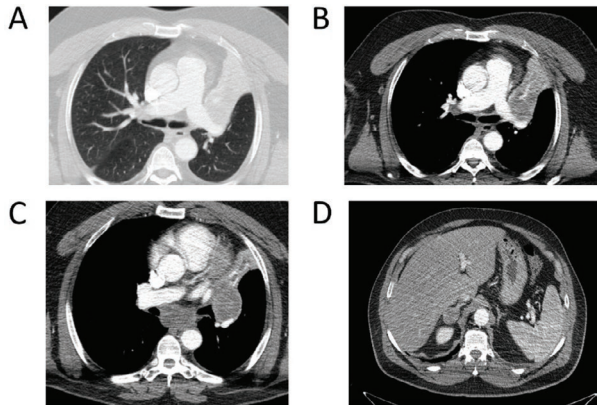
In July 2022, the patient started first-line therapy according to the CheckMate 9LA scheme, which was well tolerated, without significant side-effects. The re-evaluation of the disease after four cycles (two of chemotherapy plus immunotherapy and two of immunotherapy with nivolumab and ipilimumab) demonstrated a partial response, with a reduction of the left hilar lesion, regression of the left pleural effusion, disappearance of the lesion in the lower lung, sub-carinal lymphadenopathy

Table 2. Keynote 189 *versus* CheckMate 9LA in first-line setting of patients with advanced non-small-cell lung cancer.

Study	Ref.	Treatment	Number of patients	Histology	RR	PFS (months)	OS (months)	AEs Any grade	AEs Grade 3–5
Keynote 189	10	DDP+Pem+Pembro *vs* DDP+Pem	616	Non-squamous	48% *vs* 19.4%	9.0 *vs* 4.9 HR 0.48	22 *vs* 10.7 HR 0.56; $p<0.001$	99.8%	71.9%
CheckMate 9LA	18	CT+Nivo+IPI *vs* CT	719	Any	38% *vs* 25%	6.7 vs 5.0 HR 0.68	14.1 *vs* 10.7 HR 0.69; $p=0.0006$	91%	47%

AE, adverse events; CT, chemotherapy; DDP, platinum; IPI, ipilimumab; Nivo, nivolumab; OS, overall survival; Pem, pemetrexed; Pembro, pembrolizumab; PFS, progression-free survival; RR, response rate.

Figure 1. CT scan at baseline. Thoracic bulky disease and right adrenal metastasis were observed (A–D).



and right adrenal lesion (Figure 2A–D). The patient then continued maintenance therapy with nivolumab and ipilimumab without side-effects. The CT performed after eight cycles documented complete remission of the disease, with regression of all lungs, lymph node, and adrenal lesions and of the left pleural effusion. The patient is currently continuing maintenance therapy with nivolumab and ipilimumab (14 cycles as of February 2024), without significant toxicity and with persistent complete response (Figure 3A–D).

Conclusion

The data collected in the last year clearly show an unprecedented impact of ICIs, alone or in combination with chemotherapy, in patients with advanced NSCLC.

Figure 2. CT scan after four cycles of therapy. Partial remission is shown (A–D).

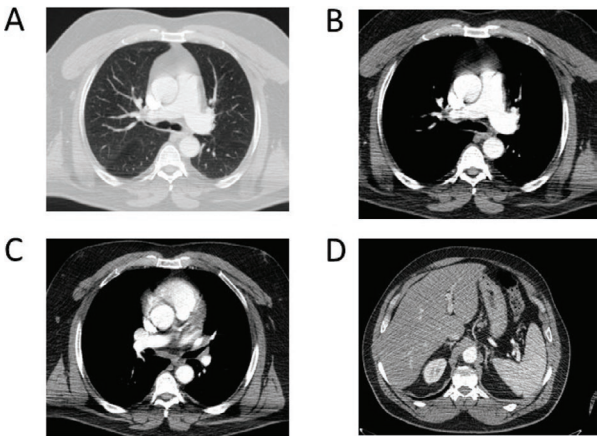
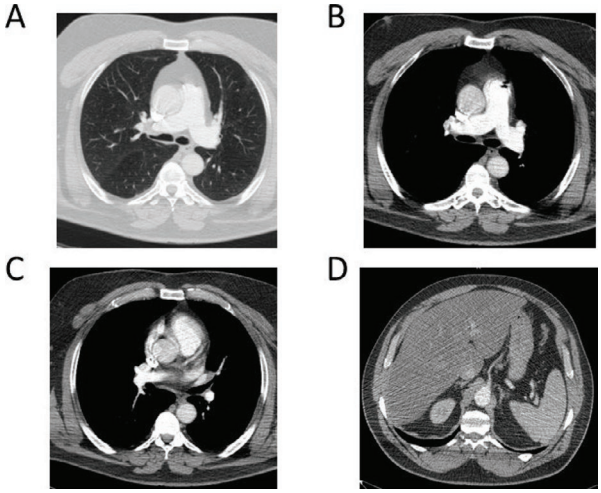


Figure 3. CT scan after 14 cycles of therapy. A long-lasting complete remission is observed (A–D).



Although the percentage of patients who benefit from this armamentarium is still not satisfactory, there is a strong effort in assessing the determinants of response to precisely assign the best treatment option for each patient. New drugs are emerging, and surely new combination approaches will help in increasing the rate of success of ICIs.

This clinical case highlights several points of discussion. Firstly, the eligibility for chemo-immunotherapy treatment of a patient with hepatitis B on antiviral therapy: this comorbidity has been an exclusion criterion for patients in the pivotal clinical trials and the lack of data from randomized studies could represent a critical issue for the proposed treatment. Secondly, the presence of bulky disease at baseline, which could be considered a contraindication for the use of a therapeutic regimen with fewer chemotherapy cycles. The patient reported a complete response, described in 2% of patients treated with the CheckMate 9LA scheme,[19] and maintained this response for almost 2 years after starting treatment. The negativity for PD-L1 does not affect the efficacy of immunotherapy, as emphasized in the CheckMate 9LA trial through sub-group analysis of PD-L1 expression, revealing no disparities in the effectiveness of nivolumab and ipilimumab amongst patients with PD-L1 <1%.[33] Furthermore, the outstanding tolerability of the treatment enabled the patient to continue their regular work activities and maintain an optimal quality of life.

In conclusion, the CheckMate 9LA regimen can be used successfully in patients with bulky disease at baseline and hepatitis B on antiviral therapy, with the possibility of obtaining long-lasting complete responses without significant side-effects.

Contributions: The named author meets the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, takes responsibility for the integrity of the work as a whole, and has given their approval for this version to be published.

Disclosure and potential conflicts of interest: AM received payment or honoraria for lectures, presentations, speakers' bureaus or educational events from Roche, AstraZeneca, BMS, MSD, Pfizer, Takeda, Boehringer, Sanofi, Lilly, Novartis and Italfarmaco and participated on an Advisory Board for Roche, AstraZeneca, Pfizer, MSD, BMS and Takeda. The International Committee of Medical Journal Editors (ICMJE) Potential Conflicts of Interests form for the authors is available for download at: https://www.drugsincontext.com/wp-content/uploads/2024/07/dic.2024-5-3-COI.pdf

Acknowledgements: The author would like to thank Dr Giovanna Damia, MD, on behalf of Content Ed Net, for medical writing and editorial assistance.

Funding declaration: There was no funding associated with the preparation of this article.

Article URL: https://www.drugsincontext.com/nivolumab-plus-ipilimumab-with-chemotherapy-in-metastatic-nsclc-minireview-and-a-case-study-of-a-patient-negative-for-pd-l1

Correspondence: Alessandro Morabito, Oncologia Clinica Sperimentale Toraco-Polmonare, Istituto Nazionale dei Tumori IRCCS Fondazione "G. Pascale", Via Mariano Semmola, 53, 80131 Napoli, Italy. Email: a.morabito@istitutotumori.na.it

Provenance: Submitted; externally peer reviewed.

Submitted: 10 May 2024; **Accepted:** 2 July 2024; **Published:** 19 July 2024.

Drugs in Context is published by BioExcel Publishing Ltd. Registered office: 6 Green Lane Business Park, 238 Green Lane, New Eltham, London, SE9 3TL, UK.

BioExcel Publishing Limited is registered in England Number 10038393. VAT GB 252 7720 07.

For all manuscript and submissions enquiries, contact the Editorial office editorial@drugsincontext.com

For all permissions, rights, and reprints, contact David Hughes david.hughes@bioexcelpublishing.com

References

1. Eggermont AMM, Maio M, Robert C. Immune checkpoint inhibitors in melanoma provide the cornerstones for curative therapies. *Semin Oncol*. 2015;42(3):429–435. https://doi.org/10.1053/j.seminoncol.2015.02.010
2. Wojtukiewicz MZ, Rek MM, Karpowicz K, et al. Inhibitors of immune checkpoints — PD-1, PD-L1, CTLA-4 — new opportunities for cancer patients and a new challenge for internists and general practitioners. *Cancer Metastasis Rev*. 2021;40(3):949–982. https://doi.org/10.1007/s10555-021-09976-0
3. Qin Y, Huo M, Liu X, Li SC. Biomarkers and computational models for predicting efficacy to tumor ICI immunotherapy. *Front Immunol*. 2024;15. https://doi.org/10.3389/fimmu.2024.1368749
4. Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. *N Engl J Med*. 2015;372(26):2509–2520. https://doi.org/10.1056/NEJMoa1500596

5. Guven DC, Stephen B, Sahin TK, Cakir IY, Erul E, Aksoy S. The efficacy of immune checkpoint inhibitors in rare tumors: a systematic review of published clinical trials. *Crit Rev Oncol Hematol*. 2022;174:103700. https://doi.org/10.1016/j.critrevonc.2022.103700
6. Petrelli F, Consoli F, Ghidini A, et al. Efficacy of immune checkpoint inhibitors in rare tumours: a systematic review. *Front Immunol*. 2021;12:720748. https://doi.org/10.3389/fimmu.2021.720748
7. Reck M, Remon J, Hellmann MD. First-line immunotherapy for non-small-cell lung cancer. *J Clin Oncol*. 2022;40(6):586–597. https://doi.org/10.1200/JCO.21.01497
8. Jaiyesimi IA, Leighl NB, Ismaila N, et al. Therapy for stage IV non-small cell lung cancer without driver alterations: ASCO Living Guideline, Version 2023.3. *J Clin Oncol*. 2024:JCO2302746. https://doi.org/10.1200/JCO.23.02746
9. Rodríguez-Abreu D, Powell SF, Hochmair MJ, et al. Pemetrexed plus platinum with or without pembrolizumab in patients with previously untreated metastatic nonsquamous NSCLC: protocol-specified final analysis from KEYNOTE-189. *Ann Oncol*. 2021;32(7):881–895. https://doi.org/10.1016/j.annonc.2021.04.008
10. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med*. 2018;378(22):2078–2092. https://doi.org/10.1056/NEJMoa1801005
11. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *N Engl J Med*. 2017;377(20):1919–1929. https://doi.org/10.1056/NEJMoa1709937
12. Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet Lond Engl*. 2017;389(10066):255–265. https://doi.org/10.1016/S0140-6736(16)32517-X
13. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med*. 2016;375(19):1823–1833. https://doi.org/10.1056/NEJMoa1606774
14. Sezer A, Kilickap S, Gümüş M, et al. Cemiplimab monotherapy for first-line treatment of advanced non-small-cell lung cancer with PD-L1 of at least 50%: a multicentre, open-label, global, phase 3, randomised, controlled trial. *Lancet*. 2021;397(10274):592–604. https://doi.org/10.1016/S0140-6736(21)00228-2
15. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med*. 2015;373(17):1627–1639. https://doi.org/10.1056/NEJMoa1507643
16. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med*. 2015;373(2):123–135. https://doi.org/10.1056/NEJMoa1504627
17. 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(21):2020–2031. https://doi.org/10.1056/NEJMoa1910231
18. Paz-Ares L, Ciuleanu TE, Cobo M, et al. First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): an international, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2021;22(2):198–211. https://doi.org/10.1016/S1470-2045(20)30641-0
19. Reck M, Ciuleanu TE, Schenker M, et al. Five-year outcomes with first-line (1L) nivolumab + ipilimumab + chemotherapy (N + I + C) vs C in patients (pts) with metastatic NSCLC (mNSCLC) in CheckMate 9LA. *J Clin Oncol*. 2024;42(Suppl. 16):8560. https://doi.org/10.1200/JCO.2024.42.16_suppl.8560
20. Shen X, Zhao B. Efficacy of PD-1 or PD-L1 inhibitors and PD-L1 expression status in cancer: meta-analysis. *BMJ*. 2018;362:k3529. https://doi.org/10.1136/bmj.k3529
21. Paz-Ares LG, Ramalingam SS, Ciuleanu TE, et al. First-line nivolumab plus ipilimumab in advanced NSCLC: 4-year outcomes from the randomized, open-label, phase 3 CheckMate 227 part 1 trial. *J Thorac Oncol*. 2022;17(2):289–308. https://doi.org/10.1016/j.jtho.2021.09.010
22. Ettinger DS, Wood DE, Aisner DL, et al. NCCN guidelines insights: non-small cell lung cancer, Version 2.2021. *J Natl Compr Cancer Netw*. 2021;19(3):254–266. https://doi.org/10.6004/jnccn.2021.0013
23. Yarchoan M, Hopkins A, Jaffee EM. Tumor mutational burden and response rate to PD-1 inhibition. *N Engl J Med*. 2017;377(25):2500–2501. https://doi.org/10.1056/NEJMc1713444
24. Hellmann MD, Ciuleanu TE, Pluzanski A, et al. Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. *N Engl J Med*. 2018;378(22):2093–2104. https://doi.org/10.1056/NEJMoa1801946
25. Skoulidis F, Goldberg ME, Greenawalt DM, et al. STK11/LKB1 mutations and PD-1 inhibitor resistance in KRAS-mutant lung adenocarcinoma. *Cancer Discov*. 2018;8(7):822–835. https://doi.org/10.1158/2159-8290.CD-18-0099
26. Ricciuti B, Arbour KC, Lin JJ, et al. Diminished efficacy of programmed death-(ligand)1 inhibition in STK11- and KEAP1-mutant lung adenocarcinoma is affected by KRAS mutation status. *J Thorac Oncol*. 2022;17(3):399–410. https://doi.org/10.1016/j.jtho.2021.10.013

27. Koyama S, Akbay EA, Li YY, et al. STK11/LKB1 deficiency promotes neutrophil recruitment and proinflammatory cytokine production to suppress T-cell activity in the lung tumor microenvironment. *Cancer Res*. 2016;76(5):999–1008. https://doi.org/10.1158/0008-5472.CAN-15-1439
28. Canon J, Rex K, Saiki AY, et al. The clinical KRAS(G12C) inhibitor AMG 510 drives anti-tumour immunity. *Nature*. 2019;575(7781):217–223. https://doi.org/10.1038/s41586-019-1694-1
29. Honrubia-Peris B, Garde-Noguera J, García-Sánchez J, Piera-Molons N, Llombart-Cussac A, Fernández-Murga ML. Soluble biomarkers with prognostic and predictive value in advanced non-small cell lung cancer treated with immunotherapy. *Cancers*. 2021;13(17):4280. https://doi.org/10.3390/cancers13174280
30. Tsai YT, Schlom J, Donahue RN. Blood-based biomarkers in patients with non-small cell lung cancer treated with immune checkpoint blockade. *J Exp Clin Cancer Res CR*. 2024;43(1):82. https://doi.org/10.1186/s13046-024-02969-1
31. Garassino MC, Gadgeel S, Speranza G, et al. Pembrolizumab plus pemetrexed and platinum in nonsquamous non-small-cell lung cancer: 5-year outcomes from the phase 3 KEYNOTE-189 study. *J Clin Oncol*. 2023;41(11):1992–1998. https://doi.org/10.1200/JCO.22.01989
32. Paz-Ares LG, Ciuleanu TE, Cobo M, et al. First-line nivolumab plus ipilimumab with chemotherapy versus chemotherapy alone for metastatic NSCLC in CheckMate 9LA: 3-year clinical update and outcomes in patients with brain metastases or select somatic mutations. *J Thorac Oncol*. 2023;18(2):204–222. https://doi.org/10.1016/j.jtho.2022.10.014
33. Carbone DP, Ciuleanu TE, Schenker M, et al. Four-year clinical update and treatment switching-adjusted outcomes with first-line nivolumab plus ipilimumab with chemotherapy for metastatic non-small cell lung cancer in the CheckMate 9LA randomized trial. *J Immunother Cancer*. 2024;12(2):e008189. https://doi.org/10.1136/jitc-2023-008189