Research Article

Treatment of Metastatic Disease with Immune Checkpoint Inhibitors Nivolumab and Pembrolizumab: Effect of Performance Status on Clinical Outcomes

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ABSTRACT

Introduction: Although guidelines exist for appropriate use of chemotherapy in the metastatic setting based on performance status, such recommendations are less readily available for immune checkpoint inhibitors (ICIs). We sought to determine whether there is a relationship between Eastern Cooperative Oncology Group (ECOG) performance status and outcomes of immunotherapy in patients treated for metastatic disease at our community-based oncology practice. **Methods:** Patients ($n = 253$) were identified as receiving nivolumab or pembrolizumab for stage IV malignancy at Cancer Centers of Colorado, St. Joseph Hospital/SCL Health between June 2018 and November 2020. Patients who initiated therapy after May 2020 were excluded from analysis due to less than 6 months follow-up time. The remaining 183 patients were included in a retrospective cohort study comparing patients with ECOG 0, 1, and 2–4. Sex, age, type of cancer, line of therapy, time on therapy and best response to therapy were determined. These baseline factors and outcomes were compared using analysis of variance (ANOVA) for numeric variables and χ^2 tests of association for categorical variables. Time from initiation of ICI to death or hospice was also compared using a log-rank test as well as a multivariate Cox proportional hazards model. **Results:** Of the 183 patients included, 31.7% had an ECOG of 0, 48.6% an ECOG of 1, and 19.7% an ECOG of 2–4. Non–small cell lung cancer and melanoma represented the majority of patients in each group. Sex and line of therapy did not differ between groups. There was a significant difference in age, with mean age of 62, 66, and 70 in ECOG 0, 1, and 2–4, respectively. Patients (54.6%) remained on therapy for at least 6 months, with no significant difference between groups in ability to complete 6 months of therapy. For ECOG 0, 1, and 2–4, disease control was achieved in 67.2%, 59.6%, and 41.7%, respectively. Analysis of time to death or hospice with a log-rank test showed a significant difference between groups. A multivariate Cox proportional hazards model revealed that patients with ECOG 0 had significantly longer time to death or hospice compared with patients in both other groups after controlling for age, sex, and line of therapy. **Conclusion:** In this single institution retrospective study of patients receiving nivolumab or pembrolizumab for metastatic cancer, ECOG 0 was associated with disease control and increased time before death or transition to hospice.

Keywords: immunotherapy, ECOG, performance status

INTRODUCTION

Performance status, an estimation of a patient's ability to independently perform activities of daily living, is commonly measured in patients with cancer using the Eastern Cooperative Oncology Group (ECOG) Scale. This scale ranges from 0 to 4, with 0 being fully active and 4 indicating complete disability.[1,2] Although there are many patient and disease characteristics that affect patient outcomes when they are receiving therapy,

performance status has historically been considered one of the most important variables used to determine best treatment options for patients with cancer.[1,2] Accordingly, chemotherapy is often not recommended in patients with poor performance statuses. This is based on recent as well as historical studies from the 1980s, when chemotherapy in patients with poor performance status was first linked to high toxicity, poor response rates, and limited survival.[3]

However, the effect of performance status on outcomes in patients receiving immunotherapy is less widely studied. Lack of sufficient data in this special population is unsurprising, given the relatively recent development of immunotherapy. Though it was suggested in the mid-1900s that lymphocytes might be involved in identifying and eliminating cancer cells in the body, it was not until the late 20th century that this idea was proven. Subsequent research identified specific receptors on the surface of T cells, such as cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1), which, when activated by certain ligands on cancer cells, suppress antitumor immunity. This paved the way for the development of immune checkpoint inhibitors (ICI) such as nivolumab and pembrolizumab. These medications are monoclonal antibodies that target PD-1 on lymphocytes, preventing interaction with cancer cell surface proteins that could potentially downregulate immune function. This allows the T cells to improve immunosurveillance for the body.[4]

These medications, and other immunotherapies, have radically changed the treatment of malignancy. Nivolumab and pembrolizumab alone have indications for treating melanoma, lung cancer, head and neck squamous cell carcinomas, renal cell carcinoma, gastric cancer, ovarian cancer, and Hodgkin lymphoma. Furthermore, with a perceived better tolerance of ICIs compared with cytotoxic chemotherapy, clinicians are often more willing to use them in patients with poor performance status, though there is not sufficient data to support or refute this practice.

Notably, landmark clinical trials that led to U.S. Food and Drug Administration approval of ICIs were conducted in patients with ECOG performance status of 0 or 1, and the effect of performance status on outcomes in immunotherapy is not otherwise fully described in the literature. Available data are conflicting, with some studies indicating no relationship, while others show a link between ECOG performance status and outcomes.[2,5–8] Further studies are necessary to help determine if ECOG status should affect the decision to initiate immunotherapy. Our single-institution retrospective study seeks to contribute to this ongoing discussion.

METHODS

Institutional review board approval was obtained, and informed consent was waived due to the retrospective nature of the study. Patients ($n = 253$) were identified as receiving nivolumab or pembrolizumab for stage IV malignancy at Cancer Centers of Colorado, St. Joseph Hospital/SCL Health, between June 2018 and November 2020. Patients initiated on therapy after May 2020 were excluded from analysis due to insufficient (less than 6 months) follow-up time. The remaining 183 patients were included in a retrospective cohort study. The purpose was to compare patients with ECOG 0, 1, and 2 or greater, based on their providers' estimation of performance status at the time of initiation of immunotherapy. Sex, age, type of malignancy, and line of therapy were collected. Patients were followed throughout their course, and best response to treatment was determined by individual providers, relying on real-world clinical assessments of disease response.[9] These responses were categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). Total time on therapy prior to cessation for any reason (PD, toxicity, patient preference, or provider preference) was also calculated, and groups were specifically compared based on patients' ability to reach 6 months of therapy. Additionally, time from initiation of treatment to transition to hospice or death was followed for each patient and compared between groups.

For data analysis, categorical variables such as sex (male vs female), line of therapy (first, second, third, or more), time on therapy (greater than or equal to 6 months vs less than 6 months), and outcomes on therapy (CR, PR, SD, or PD) were compared using χ^2 tests of association. Continuous numeric variables such as age were compared using ANOVA. The outcome, the time to death or hospice, was compared with ECOG status using the log-rank test. A multivariate Cox proportional hazards model was also developed for outcome, time to death or hospice, versus the predictors ECOG status, age, sex, and treatment line. Hazard ratios (HRs) and 95% CIs were estimated. All analyses were performed in SAS version 9.4 (Cary, NC).

RESULTS

Of the 183 patients included in the study, 58 (31.7%) had an ECOG of 0, 89 (48.6%) had an ECOG of 1, and 36 (19.7%) an ECOG of 2 or greater. The latter group was mostly represented by patients with an ECOG of 2, although four patients had an ECOG of 3, and one patient had an ECOG of 4. Notably, within each ECOG group, patients had a variety of cancer types. However, in all groups, the most common diagnoses were non–small cell lung cancer and melanoma, with 60% of ECOG 0, 52% of ECOG 1, and 50% of ECOG 2–4 patients being treated for one of these types. Other cancer types, including renal cell carcinoma, upper and lower gastrointestinal, as well as head and neck, were also represented. The distribution of cancer types within each ECOG group is shown in Table 1. Overall, males were slightly more represented in our study, at 59.6% of all patients,

Table 1. Distribution of cancer diagnoses among patients in each ECOG group

Cancer Type or Location	ECOG Group 0 (*n* = 58)	1 (*n* = 89)	2–4 (*n* = 36)	Total (*N* = 183)
Bladder	2 (3.45)	1 (1.12)	0 (0.00)	3
Breast	0 (0.00)	2 (2.25)	0 (0.00)	2
CNS	0 (0.00)	1 (1.12)	0 (0.00)	1
Colorectal	5 (8.62)	3 (3.37)	0 (0.00)	8
Cutaneous BCC	0 (0.00)	1 (1.12)	0 (0.00)	1
Cutaneous SCC	1 (1.72)	0 (0.00)	0 (0.00)	1
GYN	2 (3.45)	4 (4.49)	1 (2.78)	7
HCC	1 (1.72)	2 (2.25)	1 (2.78)	4
Head/Neck	1 (1.72)	6 (6.74)	6 (16.66)	13
Hepatobiliary	1 (1.72)	1 (1.12)	0 (0.00)	2
Hodgkin	1 (1.72)	0 (0.00)	1 (2.78)	2
Kidney	7 (12.07)	15 (16.85)	2 (5.56)	24
Melanoma	22 (37.93)	17 (19.10)	2 (5.56)	41
NSCLC	13 (22.41)	29 (32.58)	16 (44.44)	58
Mesothelioma	0 (0.00)	0 (0.00)	1 (2.77)	1
Neuroendocrine	0 (0.00)	1 (1.12)	1 (2.78)	2
Penile	0 (0.00)	0 (0.00)	1 (2.78)	1
SCLC	0 (0.00)	1 (1.12)	1 (2.78)	2
Thymus	1 (1.72)	0 (0.00)	0 (0.00)	1
Thyroid	0 (0.00)	0 (0.00)	1 (2.78)	1
Upper GI	1 (1.72)	5 (5.62)	2 (5.56)	8

Values are presented as *n* (%).
BCC: basal cell carcinoma; CNS: central nervous system; ECOG: Eastern Cooperative Oncology Group; GI: gastrointestinal; GYN: gynecological; HCC: hepatocellular carcinoma; NSCLC: nonsmall cell lung cancer; SCC: squamous cell carcinoma; SCLC: small cell lung cancer.

but when ECOG groups were compared, they did not differ significantly in sex distribution ($p = 0.329$, Table 2). Age, however, was significantly different between groups, with a mean age of 62, 66, and 70 years old in ECOG 0, 1, and 2–4, respectively ($p = 0.02$, Table 2). All patients in the study received one of two therapies, with 37.2% receiving nivolumab and 63.8% receiving pembrolizumab. There was no significant difference between groups regarding which therapy patients received ($p = 0.104$, Table 2). The majority of patients in our study were receiving their first line of therapy, and a significant number were on second-line therapy. Others had failed multiple therapies and were on their third or more line of treatment. However, when comparing ECOG groups, line of therapy did not differ significantly between groups ($p = 0.224$, Table 2). Of note, once started on a PD-1 inhibitor, the majority of patients were able to tolerate at least 6 months of therapy, with no significant difference between groups in ability to achieve this landmark ($p = 0.321$, Table 2). Best response to therapy varied between groups, with the distribution of outcomes for each ECOG group noted in Table 2. Table 2 subsequently compares ECOG groups based on ability to achieve disease control, defined as SD, PR, or CR at some point in the treatment course. ECOG groups differed significantly in likelihood of having PD versus disease control as their best response ($p = 0.048$). The majority (58.3%) of ECOG 2–4 patients never achieved disease control on PD-1 inhibitors versus 40.4% in ECOG 1 and 32.8% in ECOG 0.

Table 2. Comparison of baseline characteristics of each ECOG group

Variable	Overall (*N* = 183)	ECOG Group 0 (*n* = 58)	1 (*n* = 89)	2–4 (*n* = 36)	*p*-Value
Age, mean (SD), y	65.8 (12.9)	62.5 (15.3)	66.2 (11.2)	70.0 (11.2)	0.020
Sex					0.329
Female	74 (40.4)	23 (39.7)	40 (44.9)	11 (30.6)	
Male	109 (59.6)	35 (60.3)	49 (55.1)	25 (69.4)	
Lines of immunotherapy					0.224
1	100 (54.6)	38 (65.5)	46 (51.7)	16 (44.4)	
2	55 (30.1)	13 (22.4)	27 (30.3)	15 (41.7)	
3+	28 (15.3)	7 (12.1)	16 (18.0)	5 (13.9)	
ICI					0.104
Nivolumab	68 (37.2)	28 (48.3)	28 (31.5)	12 (33.3)	
Pembrolizumab	115 (62.8)	30 (51.7)	61 (68.5)	24 (66.7)	
6-month therapy					0.321
No	83 (45.4)	22 (37.9)	45 (50.6)	16 (44.4)	
Yes	100 (54.6)	36 (62.1)	44 (49.4)	20 (55.6)	
Best response to treatment					0.043
Complete response	22 (12.0)	13 (22.4)	8 (9.0)	1 (2.8)	
Partial response	51 (27.9)	16 (27.6)	26 (29.2)	9 (25.0)	
Stable disease	34 (18.6)	10 (17.2)	19 (21.3)	5 (13.9)	
Progressive disease	76 (41.5)	19 (32.8)	36 (40.4)	21 (58.3)	
Progressive disease vs control					0.048
DisControl	107 (58.5)	39 (67.2)	53 (59.6)	15 (41.7)	
Progressive disease	76 (41.5)	19 (32.8)	36 (40.4)	21 (58.3)	

Values are presented as *n* (%).
CR, complete response; DisControl, stable disease, partial response, or complete response; ECOG: Eastern Cooperative Oncology Group; ICI, immune checkpoint inhibitors.
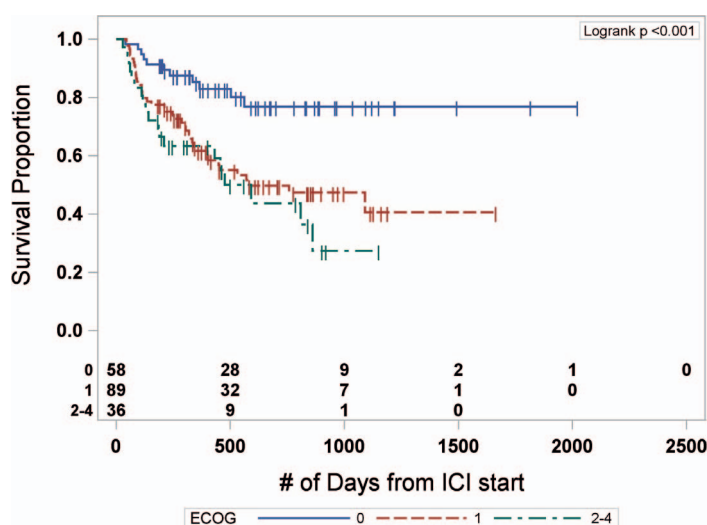
Figure 1. Kaplan-Meier plot reveals a significant difference in survival without transition to hospice between ECOG 0, 1, and 2–4, represented by blue, red, and green lines respectively. At the base of the table, the absolute number of patients alive at each time point is provided for each ECOG group. ECOG: Eastern Cooperative Oncology Group; ICI: immune checkpoint inhibitor.

Survival without transition to hospice (time to death or hospice) also differed significantly between ECOG groups, as seen in the Kaplan-Meier plot depicted in Figure 1 ($p < 0.01$). A Cox analysis subsequently breaks down how individual factors, such as age, sex, line of therapy, or ECOG performance status affect time to death or hospice when controlling for each of the other variables (Table 3). In this model, neither sex nor line of therapy had an independent effect on time to death or hospice. Age did directly affect time to death or transition to hospice, as a patient was slightly (1.026 times based on HR) more likely to transition to death or hospice with each year increase in age ($p = 0.022$). However, this plot shows that when adjusting for any differences between groups in age as well as sex or line of therapy, patients with ECOG 0 had a significantly longer time to death or hospice compared with patients in both other groups. More specifically, ECOG 1 patients were 2.5 times as likely to die or transition to hospice than those in ECOG 0 at any given time point (HR 2.5; CI 1.27–4.9). Similarly, patients in ECOG 2–4 were 2.83 times more likely to transition to hospice or die at any given time than ECOG 0 patients (HR 2.83; CI 1.31–6.13). When using this same method to compare ECOG 1 and 2–4, there was no significant difference in time to hospice transition or death ($p = 0.6633$).

DISCUSSION

As with any cancer treatment, a risk-versus-benefit discussion is essential prior to initiation of ICIs, as they are not benign drugs, physically or financially. This discussion becomes more difficult in populations not well represented in clinical trials, such as those with poor performance statuses.

Table 3. Cox proportional hazards model results

Parameter	*p*-value	HR	95% CI
ECOG 1 vs 0	0.0077	2.499	1.274–4.903
ECOG 2–4 vs 0	0.0083	2.830	1.307–6.127
ECOG 2–4 vs 1	0.6633	1.1326	0.646–1.983
Age	0.0222	1.026	1.004–1.048
Male vs female	0.4054	0.815	0.502–1.321
Tx line 2 vs 1	0.1366	1.471	0.885–2.447
Tx line 3+ vs 1	0.6016	1.222	0.575–2.598
Tx line 3+ vs 2	0.6335	0.8307	0.387–1.780

ECOG: Eastern Cooperative Oncology Group; Tx, treatment.

Clinical trials investigating the impact of performance status on patient outcomes with immunotherapy are lacking, with most data reported from meta-analyses or literature reviews. Furthermore, the findings in available studies are mixed. A 2018 meta-analysis indicated that checkpoint inhibitors improve survival in a variety of cancers, regardless of a patient's performance status.[5] In 2020, a literature review by Yang et al[6] similarly found that ECOG performance status did not affect response to immunotherapy. However, reviews focusing on individual cancer types show conflicting results. Lin et al[7] in 2018, Dall'Olio et al[8] in 2020, Sehgal et al[2] in 2021, as well as Tomasick et al[10] in 2021 studied patients with lung cancer who were on immunotherapy, noting a relationship between poor performance status, specifically an ECOG greater than 2, and worse outcomes. Similarly, a retrospective cohort study comparing outcomes on immunotherapy in patients with advanced urothelial cancer indicated ECOG affects outcomes significantly, particularly overall survival.[11]

Interestingly, though our study does not focus on a particular type of malignancy, it does point toward a relationship between ECOG status and outcomes in patients on immunotherapy for metastatic disease. In our population, ECOG greater than 0 was associated with decreased likelihood of responding to therapy as well as less time to death or transition to hospice. Although this does not indicate that the patients with ECOG of 1 or higher received no benefit from therapy, their benefits were inferior to those experienced by patients with ECOG 0.

The potential for a less robust response to treatment is particularly important to consider in the setting of known toxicities of PD-1 inhibitors. There are a variety of immune-mediated adverse events (irAEs) that can occur, and around 10% of patients on PD-1 inhibitors will experience an irAE that is severe (grade 3 or higher). Most commonly this will be in the form of a rash, endocrinopathy, colitis, pneumonitis, or hepatitis.[12] Although usually effectively treated with steroids, some toxicities can have prolonged courses despite high-dose steroid treatment.[13] Particularly severe cases can be fatal.

There is also a significant amount of financial toxicity that occurs with immunotherapy. As oncologic expenditure in the United States rises exponentially, financial stewardship will become increasingly important to consider in decisions to initiate therapy. Financial models are useful to determine the situations in which specific medications, such as nivolumab or pembrolizumab, might be considered "cost-effective" for a particular malignancy. In these models, cost effectiveness is measured against a threshold, typically $100,000 per quality adjusted life year. Previously published models have suggested PD-1 inhibitors are cost-effective for melanoma and are potentially cost-effective for non–small cell lung cancer in various scenarios.[14–16] Others show neither pembrolizumab or nivolumab to be cost-effective for genitourinary cancers and nivolumab as not cost effect for head and neck cancers.[14] In these models it is clear that specific disease and patient characteristics thought to impact outcomes on therapy can also contribute to cost effectiveness. Examples include severity of disease, molecular characteristics of disease, line of treatment, and various patient characteristics.[14–16] In the future, it would be wise to look more closely at performance status as another patient characteristic that may have an impact on cost effectiveness.

Limitations

Our study was limited by its retrospective design in which patients were started on therapy at various time points in the study window. Initiating therapy anytime between June 2018 to November 2020, subjects were followed for various lengths of time, with some followed for 1–2 months and others followed for years. Due to concern that this could skew results by allowing some patients more opportunity to respond to treatment, any patient that started after May 2020 was not included in analysis. This ensured that each patient was followed for at least 6 months, allowing sufficient time to potentially respond to treatment. As there are not any known differences in the patients who started prior to or after May 2020 and each ECOG group had a similar percentage of eliminated patients, this modification should not have introduced any new biases.

However, our data collected retrospectively from a single institution does raise questions of generalizability. The smaller number of patients available for analysis also limited our ability to investigate outcomes in individual cancer types. Although the patients in our study most commonly had melanoma or lung cancer, there were a variety of primary malignancies represented within our population. Additionally, the small number of patients with a performance status of 2 or greater required these patients to be analyzed as a singular entity. This is not optimum, as patients with ECOG 2 versus 3, and especially compared with ECOG 4, have widely different functionality. Additionally, individual providers were tasked with determining their patients' treatment response. Interprovider variability therefore affects our results and creates bias in our study. Furthermore, while we included age, sex, and line of therapy in our analysis, we did not include several other factors that can have an effect on treatment outcomes; these additional confounders include, but are not limited to, patient characteristics such as medical comorbidities, obesity, smoking status, and social determinants of health as well as clinical findings such as metastatic sites of disease, lactate dehydrogenase, albumin, lymphocyte count, baseline PD-L1 status, and toxicity rates. These factors are potential confounding variables that should be addressed.

Additionally, an investigation of how ECOG performance status affects frequency of adverse events on immunotherapy should have been included. We loosely used length of time receiving therapy before stopping treatment for any reason as a surrogate for rates of toxicity. However, this method does not distinguish between the many causes for which patients or providers might decide to stop therapy. As such, though patients were equally likely across all ECOG groups to complete 6 months of therapy, we are uncertain if this finding correlates to equivalent rates of toxicity across all groups, as we did not directly measure this. Our study could be improved in this way. Additionally, cost effectiveness of immunotherapy and how it is potentially impacted by ECOG performance status would be helpful to investigate.

CONCLUSION

In this single institution retrospective study of patients receiving nivolumab or pembrolizumab for metastatic cancer, ECOG 0 was associated with disease control and increased time before death or transition to hospice. In the future, multi-institution studies would be useful in order to have larger, more representative sample sizes. This would allow ECOG 2 to be separated from ECOG 3 and 4 in analysis, as well as allow analysis of individual cancer types. We propose that in such an expanded prospective study, more standardized methods such as RECIST (response evaluation criteria in solid tumors) be used in determining the best response to therapy.[17] It is our hope that these future studies will continue to delineate if, and how heavily, performance status should be considered in decisions regarding initiation of immunotherapy.

References

1. West H, Jin JO. Performance status in patients with cancer. *JAMA Oncol*. 2015;1:998.
2. Sehgal K, Gill RR, Widick P, et al. Association of performance status with survival in patients with advanced non–small cell lung cancer treated with pembrolizumab monotherapy. *JAMA Netw Open*. 2021;4:e2037120.
3. Pater JL, Loeb M. Nonanatomic prognostic factors in carcinoma of the lung: a multivariate analysis. *Cancer*. 1982;15;50:326–331.

4. Alsaab H, Sau S, Alzhrani R, et al. PD-1 and PD-L1 checkpoint signaling inhibition for cancer immunotherapy: mechanism, combinations, and clinical outcome. *Front Pharmacol*. 2017;8:56.

5. Bersanelli M, Brighenti M, Buti S, et al. Patient performance status and cancer immunotherapy efficacy: a meta-analysis. *Med Oncol*. 2018;35:132.

6. Yang F, Markovic SN, Molina JR, et al. Association of sex, age, and eastern cooperative oncology group performance status with survival benefit of cancer immunotherapy in randomized clinical trials: a systematic review and meta-analysis. *JAMA Netw Open*. 2020;3:e2012534.

7. Lin S, Yang C, Liao B, et al. Tumor PD-L1 expression and clinical outcomes in advanced-stage non–small cell lung cancer patients treated with nivolumab or pembrolizumab: real-world data in Taiwan. *J Cancer*. 2018;9:1813–1820.

8. Dall'Olio FG, Maggio I, Massucci M, et al. ECOG performance status ≥2 as a prognostic factor in patients with advanced non small cell lung cancer treated with immune checkpoint inhibitors–a systematic review and meta-analysis of real world data. *Lung Cancer*. 2020;145:95–104.

9. Espirito JL, Aguilar K, Boyd M, et al. RW2 retrospective real-world assessment of response outcomes in oncology. *Value in Health*. 2019;22:S389.

10. Tomasik B, Bienkowski M, Braun M, et al. Effectiveness and safety of immunotherapy in NSCLC patients with ECOG ≥ 2-systematic review and meta-analysis. *Lung Cancer*. 2021;158: 97–106.

11. Khaki AR, Li A, Diamantopoulos LN, et al. Impact of performance status on treatment outcomes: a real-world study of advanced urothelial cancer treated with immune checkpoint inhibitors. *Cancer*. 2020;126:1208–1216.

12. Martins F, Sofiya L, Sykiotis GP, et al. Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. *Nat Rev Clin Oncol*. 2019;16:563–580.

13. Weber JS, Yang JC, Atkins MB, Disis ML. Toxicities of immunotherapy for the practitioner. *J Clin Oncol*. 2015;33:2092–2099.

14. Verma V, Sprave T, Haque W, et al. A systematic review of the cost and cost-effectiveness studies of immune checkpoint inhibitors. *J Immunother Cancer*. 2018;6:128.

15. Couchoud C, Fagnoni P, Aubin F, et al. Economic evaluations of cancer immunotherapy: a systematic review and quality evaluation. *Cancer Immunol Immunother*. 2020;69:1947–1958.

16. Ding H, Xin W, Tong Y, et al. Cost effectiveness of immune checkpoint inhibitors for treatment of non–small cell lung cancer: a systematic review. *PLoS One*. 2020;15:e0238536.

17. Eisenhauer EA, Therasse P, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45:228–247.