European Journal of Cancer 109 (2019) 21–27

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Immune-related adverse events predict the therapeutic efficacy of anti–PD-1 antibodies in cancer patients

J. Rogado [a], J.M. Sánchez-Torres [a], N. Romero-Laorden [a], A.I. Ballesteros [a], V. Pacheco-Barcia [a], A. Ramos-Leví [b], R. Arranz [c], A. Lorenzo [c], P. Gullón [d], O. Donnay [a], M. Adrados [e], P. Costas [a], J. Aspa [f], A. Alfranca [g], R. Mondéjar [a], R. Colomer [a,*]

[a] *Medical Oncology Department, Instituto de Investigación Sanitaria la Princesa, HU La Princesa, Madrid, Spain*
[b] *Endocrinology Department, Instituto de Investigación Sanitaria la Princesa, HU La Princesa, Madrid, Spain*
[c] *Hematology Department, HU la Princesa, Madrid, Spain*
[d] *Social and Cardiovascular Epidemiology Research Group, Alcalá University, Madrid, Spain*
[e] *Pathology Department, Instituto de Investigación Sanitaria La Princesa, HU la Princesa, Madrid, Spain*
[f] *Neumology Department, Instituto de Investigación Sanitaria La Princesa, HU la Princesa, Madrid, Spain*
[g] *Immunology Department, Instituto de Investigación Sanitaria la Princesa, Madrid, Spain*

Received 21 June 2018; received in revised form 19 October 2018; accepted 22 October 2018
Available online 22 January 2019

KEYWORDS
Immune-related adverse events;
Nivolumab;
Pembrolizumab;
Advanced cancer;
Response predictive factor

Abstract ***Background:*** Cancer immune therapy has shown remarkable benefit in the treatment of a range of cancer types, although it may initiate autoimmune-related disorders in some patients. We have attempted to establish whether the incidence of irAEs after the use of anti–PD-1 antibodies nivolumab or pembrolizumab in advanced malignancies is associated with anti–PD-1 treatment efficacy.

Patients and methods: We studied patients treated with single-agent nivolumab or pembrolizumab for advanced cancer. irAEs (immune-related adverse events) were identified clinically and graded as per the Common Terminology Criteria for Adverse Events version 4.0. Efficacy was evaluated with objective response rate (ORR, immune-Response Evaluation Criteria in Solid Tumours [RECIST] criteria) progression-free survival (PFS) and overall survival (OS). Tests were performed to determine the association between irAEs and ORR, PFS or OS.

Results: We identified 106 patients. Primary diagnoses were lung cancer ($n = 77$), melanoma ($n = 8$), head and neck carcinoma ($n = 7$), renal carcinoma ($n = 5$), Hodgkin's lymphoma ($n = 3$), urothelial carcinoma ($n = 3$) and gallbladder adenocarcinoma, hepatocellular carcinoma and Merkel cell carcinoma ($n = 1$ each). IrAEs were observed in 40 patients (37.7%). The most

* *Corresponding author*: Medical Oncology Department, Hospital Universitario la Princesa, Instituto de Investigación La Princesa, Calle Diego de León, 62, 28006, Madrid, Spain.
E-mail address: rcolomer@seom.org (R. Colomer).

https://doi.org/10.1016/j.ejca.2018.10.014

frequent irAEs were hypothyroidism ($n = 15$), nephritis ($n = 5$) and hyperthyroidism ($n = 4$). Objective response was observed in 44 patients (41.5%), and median PFS was 5.5 months (0.5–31 months). Thirty-three of the 40 patients with irAEs had objective response (82.5%) in contrast with 11 of the 66 cases without irAEs (16.6%) (OR 23.5, $P < 0.000001$). PFS in patients with irAEs was 10 months and 3 months in those without irAEs (HR 2.2, $P = 0.016$). OS in patients with irAEs was 32 months and 22 in those without irAEs, without statistically significant differences.

Conclusion: In advanced cancer treated with single-agent anti–PD-1 antibodies, patients with irAEs showed a markedly improved efficacy over patients without irAEs (ORR of 82.5% and PFS of 10 months vs ORR of 16.6% and PFS of 3 months). Future studies of anti–PD-1 immunetherapy should address this association to explore the underlying biological mechanisms of efficacy.

1. Introduction

Anti–programmed death receptor 1 (PD-1) antibodies have been developed against the PD-1, blocking the interaction with its ligands PD-L1 and PD-L2. Nivolumab constitutes the first-in-class of new emerging cancer treatments known as the anti-cancer immune checkpoint inhibitors (ICIs).

Nivolumab has demonstrated activity in terms of progression-free survival (PFS) and overall survival (OS) in patients with advanced non-small-cell lung cancer (NSCLC) [1–3], melanoma [4–7], renal cell carcinoma [8,9], squamous cell carcinoma of head and neck (SCCHN) [10], urothelial carcinoma [11,12], Hodgkin's lymphoma (HL) [13,14] and hepatocellular carcinoma [15]. In addition, pembrolizumab, another anti-PD-1 ICI as nivolumab, has demonstrated a benefit in outcomes in patients with NSCLC [16], melanoma [17], SCCHN [18], Merkel cell carcinoma [19] and urothelial carcinoma [20]. The ICIs have been reported to have a favourable toxicity profile compared with traditional chemotherapy, although they can produce relevant immune-related adverse events (irAEs) of different grades of severity [21–24]. Mild irAEs can be developed in 30%–50% of patients, but serious irAEs currently occur in approximately 5% of the patients who received ICIs. irAEs may include colitis, hepatitis, nephritis, myocarditis, pneumonitis, dermatitis, eye disorders, endocrinopathies (especially thyroid and adrenal glands disorders), encephalitis or peripheral neuropathies (such as Guillain-Barre syndrome or myasthenia gravis) [24]. The most frequent irAEs reported in clinical trials and systematic reviews of case reports have been thyroid disorders (hypothyroidism), pneumonitis, colitis and dermatitis [21,22]. irAEs are mediated mainly by T lymphocytes acting against healthy tissue, and for this reason, they are referred to as irAEs [22]. A hyperactivated T lymphocyte response is induced, secreting high levels of T-helper lymphocytes cytokines and T-cytotoxic migration to normal tissue. The T-lymphocyte response is not specific of tissue, and subsequently to this fact, it can induce a cross-reactivity with healthy tissue [22,23]. The incidence of irAEs is lower and less severe in patients who received anti–PD-1 or anti–PD-L1 antibodies than in patients treated with CTLA-4 antibodies [25,26].

In patients with melanoma treated with nivolumab plus a peptidic vaccine, irAEs may be associated with greater antitumour responses [27]. It has also been described in patients with NSCLC [28,29] and in patients with melanoma treated with pembrolizumab [30]. However, other studies developed with NSCLC and melanoma patients found no relationship [31,32] with objective response rate (ORR).

Recently, a review concluded that irAEs are not required to obtain a benefit from immune checkpoint blockade [24]. To establish whether there is an association of irAEs with treatment efficacy of the single agents anti–PD-1 antibodies nivolumab or pembrolizumab, we have performed an observational study, in which we assessed the association between irAEs and the benefit induced by these antibodies in a series of patients with unselected malignancies in terms of antitumour response (ORR) and survival.

2. Materials and methods

2.1. Study design and patients

We reviewed medical records of all patients with advanced malignancies treated with single-agent nivolumab or pembrolizumab from January 2016 until August 2018. All patients were followed up from the start date of treatment until 30th September 2018. The dose of nivolumab was 3 mg/kg every 14 days in all cases. The dose of pembrolizumab was 200 mg as fixed dose every 21 days if it was a first-line treatment or 2 mg/kg every 21 days if it is received at second line or beyond. The study was approved by the Ethics and Research Committee of Hospital Universitario de la Princesa.

The primary end point of the study was to evaluate whether there was an association between treatment efficacy and the incidence of irAEs. Efficacy was measured using ORR (immune Response Evaluation

Criteria in Solid Tumours [RECIST] criteria) [33], PFS and OS. IrAEs were defined based on the criteria of previous studies [1–20], and their grade based on the Common Terminology Criteria for Adverse Events version 4.0. A baseline laboratory test was performed as per routine clinical practice, which included blood count, thyroid, kidney and liver function. After starting treatment, clinical and laboratory tests were carried out as clinically indicated every 2 weeks in patients receiving nivolumab or every 3 weeks in patients receiving pembrolizumab, before drug administration. Body CT scans were taken every 8–12 weeks or as clinically mandated.

2.2. Statistical analysis

For continuous variables, means and standard deviations (SDs) are shown in the case of variables with normal distribution, and median and interquartile range (IQR) in the case of variables that do not have a normal distribution. For discrete variables, the relative frequencies are shown. The PFS data were calculated from the first dose of nivolumab or pembrolizumab until progression or death or censured at the last date of the follow-up. The OS data were calculated from the diagnosis until death or censored at the last date of the follow-up. To determine the association between the incidence of irAEs and ORR, odds ratio and Chi squared test were performed. The association between the presence of irAEs with PFS, and OS was analysed using the log-rank test and Cox regression, univariate and multivariate, adjusted by age, sex, histology, smoking habit, prior lines treatment, type of anti-PD-1 antibody received, functional status as measured by the scale of the Eastern Cooperative Oncology Group (ECOG) and all the clinical and demographics variables studied. Kaplan–Meier curves showing PFS and OS based on development or no development of irAEs are presented. Statistical analyses were carried out with statistical package STATA SE, version 14.1 (StataCorp, College Station, TX, USA).

3. Results

3.1. Patient characteristics

One hundred six patients were included, with a median follow-up of 6 months (0.5–32 months). The median age was 69 years (32–86 years); 76 patients were male (71.7%), and 87 (83.6%) were smokers at diagnosis. Forty-eight patients (45%) had previous history of hypertension; 19 patients (17.9%), of diabetes; 33 patients (31.3%), of hypercholesterolaemia; five patients (4.7%), of alcoholism; eight patients (7.5%), of ischaemic cardiac events; three patients (2.8%), of atrial fibrillation. Primary malignancies were NSCLC in 77 cases (44, non-squamous; 30, squamous and 3, non-specified), melanoma in 8, SCCHN in 7, clear cell renal carcinoma in 5, HL and urothelial bladder carcinoma, 3 cases each, and gallbladder adenocarcinoma, Merkel cell carcinoma and hepatocellular carcinoma, one case each. All selected patients had metastatic disease.

The baseline ECOG status was 0–1 in 73 patients (68.8%) and 2 in 33 (31.2%). No patients had ECOG 3 or 4. Twenty-one patients (19.8%) received any prior line previous to anti–PD-1 antibody, 43 patients (40.6%) received one prior line, 20 patients (18.9%) received two prior lines, 17 patients (16.1%) received three prior lines, three patients (2.8%) received four prior lines and one patient (0.9%) received five and nine prior lines. The three patients with HL had been previously treated with bone marrow transplant. Two of them received allogeneic bone marrow transplant. Twelve patients (11.3%) received radiotherapy.

3.2. Treatment efficacy

Objective response was observed in 44 patients (41.5%): complete response in five cases (4.7%), partial response in 39 (36.8%). Stable disease was detected in 29 cases (27.4%) and progressive disease in 33 cases (31.1%). The median PFS considering all patients with all the unselected malignancies was 5.5 months (0.5–31 months) with a median follow-up of 6 months (0.5–32 months).

3.3. Immune-related adverse events

Fifty-six irAEs were detected in 40 patients (37.7%). Details are shown in Table 1. Baseline characteristics between patients with or without irAEs were not statistically different (Supplementary Table). Hypothyroidism was the most frequent irAE ($n = 19$ events; 11 cases in grade 1, 4 cases in grade II and 4 cases in grade III), followed by immune-mediated nephritis ($n = 7$; 2 cases in grade I, 2 cases in grade II and 3 cases in grade III), hyperthyroidism ($n = 6$; 1 case in grade I and 5 cases in grade II), pneumonitis ($n = 5$; all in grade I), rash ($n = 3$; all in grade I), immune-mediated hepatitis ($n = 3$; 1 case in grade I and 2 cases in grade IV), arthritis ($n = 3$; 2 cases in grade II and 1 case in grade III), panhypopituitarism ($n = 2$; grade I), hypophysitis ($n = 1$; 1 case in grade I), adrenal insufficiency ($n = 2$; grade I), diabetic ketoacidosis ($n = 1$, grade IV), immune-mediated colitis ($n = 1$, grade III), myositis ($n = 2$, grade II) and encephalitis ($n = 1$, grade IV). Nine of the patients who developed irAEs stopped treatment because of unacceptable toxicity (8.5%): one patient for grade III colitis, three patients for immune-mediated grade III nephritis, two patients due to grade III and IV hepatitis, respectively, one patient with grade III arthritis, one patient with grade IV diabetic ketoacidosis and 1 patient due to grade IV encephalitis.

Table 1
Description of irAEs occurring in individual patients and description of irAE events in patients treated with nivolumab.

		Detail of irAE events in patients treated with nivolumab	
irAE category	Number of patients with irAE (%)	Grade I–II *N.*	Grade III–IV *N.*
Hypothyroidism	15 (14.1%)	11	3
Hypothyroidism + hypophysitis + panhypopituitarism + suprarenal insufficiency + hepatitis + pneumonitis	1 (0.9%)	1 (hypophysitis + panhypopituitarism + suprarenal insufficiency + hepatitis + pneumonitis)	1 (hypothyroidism)
Hypothyroidism + panhypopituitarism + suprarenal insufficiency	1 (0.9%)	1	0
Hypothyroidism + hyperthyroidism + ketoacidotic diabetes	1 (0.9%)	1 (hypothyroidism + hyperthyroidism)	1 (Ketoacidotic diabetes)
Hypothyroidism + hyperthyroidism	1 (0.9%)	1	0
Hypothyroidism + nephritis	3 (2.8%)	3	1 (nephritis in one of the patients)
Hyperthyroidism	1 (0.9%)	1	0
Nephritis	3 (2.8%)	2	1
Nephritis + arthritis	1 (0.9%)	1 (arthritis)	1 (Nephritis)
Rash	2 (1.8%)	1	0
Rash + encephalitis	1 (0.9%)	1 (rash)	1 (encephalitis)
Pneumonitis	4 (3.7%)	4	0
Colitis	1 (0.9%)	0	1
Hepatitis	1 (0.9%)	0	1
Hepatitis + hypothyroidism	1 (0.9%)	1	0
Arthritis	1 (0.9%)	0	1
Arthritis + myositis	1 (0.9%)	1	0
Total patients irAEs	40 (37.7%)	30 irAEs in grade I–II	12 irAEs in grade II–III

irAE, immune-related adverse events.

3.4. Association between irAEs and treatment efficacy

Patients who presented irAEs of any grade showed an increase in the probability of achieving an objective response (odds ratio: 23.5, CI 95%: 15.9–93.0, $P < 0.000001$). Thirty-three of 40 (82.5%) patients who presented toxicity showed objective response versus 11 of 66 (16.6%) of the patients who did not present irAEs ($P < 0.00001$ in Chi squared test) as it is shown in Table 2.

Patients who developed irAEs had an increased median PFS when compared with patients without irAEs (10 vs 3 months, log-rank test $P = 0.001$). Details are shown in Fig. 1. In the multivariate analysis of PFS, the association of irAEs and PFS was also significant (HR: 2.3, CI 95%: 1.4–3.6, $P = 0.001$) and was being independent of age, sex, histology, ECOG PS, smoking habit, prior lines treatment, type of anti–PD-1 antibody and all the demographic and clinical variables studied. In terms of OS, we observed a trend to improvement. Patients with irAEs had an OS of 32 months versus 22 months in those patients who did not developed irAEs (log-rank test $P = 0.12$), not statistically significant in the multivariate analysis (HR: 1.1, CI 95%: 0.7–1.6, $P = 0.9$). Details are shown in Fig. 2.

The trend in improvement is maintained in the individual analysis for the different primary tumours and for the different antibodies in our series both with PFS, OS and ORR. In the subgroup of patients not having lung cancer (29 patients), we observed an increase of the probability of obtaining ORR (odds ratio: 7.0, CI 95%: 0.97–53.2, $P = 0.026$). Five of 7 patients who presented toxicity showed objective response versus 4 of 22 of the

Table 2
Relationship of objective response rate (ORR) and occurrence of irAEs in patients treated with nivolumab or pembrolizumab. IrAEs includes all grades and types.

	N	IrAE	No irAE	
ORR	44	33	11	$P < 0.00001$
No ORR	62	7	55	
Total	106	40	66	

irAE, immune- related adverse events.

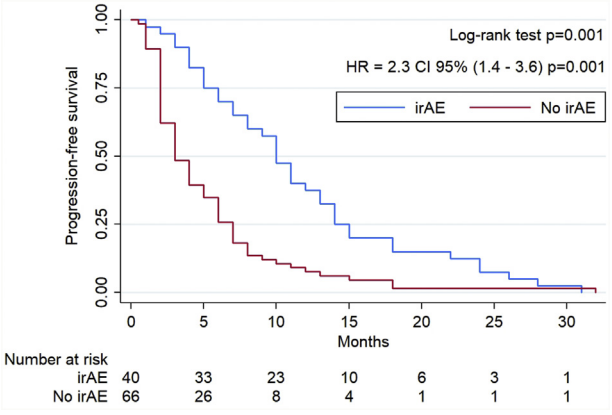

Fig. 1. Kaplan–Meier progression-free survival estimate curves by development or no development of irAE in all cancer type patients treated with anti–PD-1 antibodies. HR, hazard ratio; CI, confidence interval; irAE, immune-related adverse events.

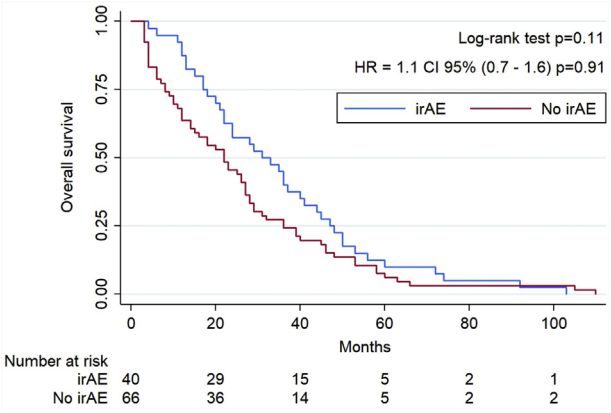

Fig. 2. Kaplan–Meier overall survival estimates curves by development or no development of irAE in all cancer type patients treated with anti–PD-1 antibodies. HR, hazard ratio; CI, confidence interval; irAE, immune-related adverse events.

patients who did no present irAEs. An increase of PFS (10.5 months in patients with irAEs versus 4 months in those patients without irAEs (log-rank $P = 0.06$) and OS (66 months vs 33 months, log-rank $P = 0.06$) was observed. In the subgroup of patients having lung cancer (77 patients), we also observed an improvement in terms of ORR, PFS and OS in patients who developed irAEs (OR: 38, CI 95% 0.97–53.2, $P < 0.00001$; PFS 10 months vs 3 months in those without irAEs, log-rank $P < 0.0001$; OS: 26 months vs 15 months, log-rank $P = 0.12$).

The subgroup of patients who stopped treatment because of unacceptable toxicity had a median PFS of 11 months (0.5–14 months). Patients with irAEs requiring corticosteroid (CEs)—20 patients—treatment (1–2 mg/kg/day), had no influence on the survival or the response. Median PFS in patients who recieved CEs was 10 months vs 4 months in those who did not recieve. In addition, patients requiring CEs had 85% (17/20 patients) of ORR versus 31.4% (27/86 patients) in those patients without CEs.

3.5. Association between PD-L1 expression and response

In 35 patients with lung cancer, PD-L1 expression was available. Ten patients (28.5%) had PD-L1 $\geq$1% and <50%, 21 patients (60%) had PD-L1 $\geq$50% and seven patients had negative expression of PD-L1. Patients who presented PD-L1 negative expression, PDL1 expression $\geq$1% and PDL1 $\geq$50% had a similar probability of response: 40% of ORR vs 40% vs 47.1%, respectively. Patients with PD-L1 negative expression had 2 months median PFS, patients with PD-L1 expression between 1% and 50% had 7 months of median PFS and patients with PDL1 $\geq$50% had 4 months of median PFS, without statistical significant differences.

3.6. Association between radiotherapy and response

Twelve patients included in our study received radiotherapy (50% received holocranial radiotherapy, 25% received haemostatic thoracic radiotherapy and 25% antialgic radiotherapy). Patients who received radiotherapy did not show more probability of response in our population: 41.6% of ORR in patients who received radiotherapy versus 41.4% in those who did not receive radiotherapy. Only three patients presented irAEs.

4. Discussion

We have found a direct association between the development of irAEs and anti–PD-1 antibodies efficacy in patients with advanced cancer. The probability of having a clinical response was 23 times higher in those patients who presented an irAE. In addition, patients with an irAE had a significant 7-month increase of PFS and had a non-significant 10-month increase of OS. It is remarkable that our patients included different tumour types (lung cancer, SCCHN, melanoma, clear cell renal carcinoma, HL, urothelial bladder carcinoma, hepatocellular carcinoma, Merkel cell carcinoma and gallbladder adenocarcinoma), different lines of therapy and also only one kind of ICI: anti–PD-1 antibodies (nivolumab or pembrolizumab). Our results confirm the suggestions of some previous studies performed with series that evaluated either number of pooled immunetherapy drugs or single tumour sites [26–32,34].

Recently, a Japanese series of 38 lung cancer patients treated with nivolumab [29] observed significantly better ORR in patients who had irAEs (63.6% vs 7.4%) and a higher PFS (median not reached vs 49 days). Notably, in this study, the incidence of irAEs (28.9%) was lower than we have observed, and pneumonitis was the most frequent irAE reported (13%), which contrasts with a lower incidence in pivotal studies, meta-analysis [1,2,15–18] or in our own series. This could be related to the higher incidence of iatrogenic pneumonitis in Asian populations that has been reported with several anticancer drugs[35]. In addition, they described a low incidence of hypothyroidism (10.5%) than meta-analysis [21–24] or our series. In a series of cases from several clinical trials at MD Anderson, patients were treated with a variety of immune-therapy approaches, and 64 received ICIs (anti–CTLA-4, anti–PD-1 or anti–PD-L1). In the whole patient population from their review, those patients with severe irAEs had better ORR (25% vs 6%) and PFS (30 weeks vs 10 weeks) than cases without severe irAEs [34]. A retrospective evaluation of Japanese lung cancer patients treated with nivolumab showed that cases with early irAEs had improved ORR (52.3%) and PFS (9.2 months) compared with cases without irAEs (27.9% and 4.8 months, respectively) [28]. A study involving patients with resected and unresected melanoma has detected a better outcome of nivolumab alone or nivolumab plus a peptide vaccine treatment in patients who developed especially cutaneous irAEs [27]. In other study, in patients with NSCLC, they did not find significant differences in ORR [32].

In our study, we show an incidence of irAES of 37.7% across all cancer types considered, and a clear relationship of the occurrence of irAEs with anti–PD-1 antibodies efficacy. Response rate increased significantly when an irAE was present (82.5% vs 16.6%), and the follow-up showed a statistically significant increase of PFS (10 vs 3 months) and a not statistically significant increase of OS (32 months vs 22 months). This marked efficacy improvement was independent of the clinical variables considered in ORR and PFS. Differences not statistically significant in terms of OS could be induced by the a short follow-up period carried out in our series.

The sample size, considering the heterogeneity in the characteristics of the patients included, may be regarded as a limitation. However, it is remarkable that the trend in ORR, PFS and OS was observed across all tumour types included in our series. Finally, our series did not explore the association of irAEs with immune-therapy combinations, but rather with single-agents Nivolumab and Pembrolizumab, therefore providing clearer basis to establishing associations. To our knowledge, this is the first study to compare a single kind of ICI's (anti–PD-1 antibodies) efficacy with the development of irAEs considering all type of tumours.

Conclusion

The occurrence of irAEs can increase up to 23 times the probability of obtaining an objective response during treatment with anti–PD-1 antibodies in patients diagnosed with cancer. In addition, irAEs can be associated with an improvement of PFS and OS in a median of 7 and 10 months, respectively compared with the patients who do not develop them. Future studies of anti–PD-1 cancer immunotherapy should address this association to reveal the underlying biological mechanisms of efficacy.

Conflict of interest statement

R. Colomer is a consultant/member of advisory board of Lilly, MSD, Roche, Servier and Novartis; received research funding from BMS, MSD, Roche, Pfizer, AstraZeneca and Astellas and is a speaker of BMS, Pfizer, Janssen, MSD and Novartis. N Romero-Laorden has received grants support from Roche, MSD, Janssen, Astellas, Pfizer and Pharmamar and travel grants from Pfizer and Janssen. No potential conflicts of interest were disclosed by the other authors.

Funding

This study was funded in part by the project Discovery, Validation and Implementation of Biomarkers for Precision Oncology, from the Instituto de Salud Carlos III, Ministerio de Economía y Competitividad (PIE15/00068), awarded to RC, and the projects JR 17/00007 and PI17/008, awarded to NR-L.

Author contributions

J.R. contributed to the conception and design of the study, data acquisition, statistical analysis, interpretation of the data and writing of the manuscript. J.M.S.T. and N.R.L. contributed to the acquisition and interpretation of the data and revision of the manuscript. P.G. and A.L. contributed to the statistical analysis and interpretation of the data. A.B., V.P.B., A.M.R.L., R.A., A.L., M.A., R.M. and P.C. contributed to the acquisition of the data. R.C. contributed to the conception of the study and reviewed the manuscript. All authors reviewed and approved the final version of the manuscript.

Acknowledgements

The authors express their gratitude to the patients and their families for participation in this observational study.This study was funded in part by the project Discovery, Validation and Implementation of Biomarkers for Precision Oncology, from the Instituto de Salud Carlos III, Ministerio de Economía y Competitividad (PIE15/00068), awarded to RC, and the projects JR 17/00007 and PI17/008, awarded to NR-L

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2018.10.014.

References

[1] 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;373:1627–39.
[2] 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;373:123–35.
[3] Gettinger SN, Horn L, Gandhi L, et al. Overall survival and long-term safety of nivolumab (Anti-Programmed Death 1 Antibody, BMS-936558, ONO-4538) in patients with previously treated advanced non-small-cell lung cancer. J Clin Oncol 2015 Jun 20; 33(18):2004–12.
[4] Weber JS, D'Angelo SP, Minor D, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomized, controlled, open-label, phase 3 trial. Lancet Oncol 2015 Apr;16(4):375–84.
[5] Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med 2015 Jan 22;372(4):320–30.
[6] Postow MA, Chesney J, Pavlick AC, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. N Engl J Med 2015 May 21;372(21):2006–17.

[7] Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med 2017 Oct 5;377(14):1345–56.
[8] Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med 2015 Nov 5;373(19):1803–13.
[9] McDermott DF, Drake CG, Sznol M, et al. Survival, durable response, and long-term safety in patients with previously treated advanced renal cell carcinoma receiving nivolumab. J Clin Oncol 2015 Jun 20;33(18):2013–20.
[10] Ferris RL, Blumenschein Jr G, Fayette J, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. N Engl J Med 2016 Nov 10;375(19):1856–67.
[11] Sharma P, Callahan MK, Bono P, et al. Nivolumab monotherapy in recurrent metastatic urothelial carcinoma (CheckMate 032): a multicenter, open-label, two-stage, multi-arm, phase 1/2 trial. Lancet Oncol 2016 Nov;17(11):1590–8.
[12] Sharma P, Retz M, Siefker-Radtke A, et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicenter, single-arm, phase 2 trial. Lancet Oncol 2017 Mar;18(3):312–22.
[13] Ansell SM, Lesokhin AM, Borrello I, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. N Engl J Med 2015 Jan 22;372(4):311–9.
[14] Haverkos BM, Abbott D, Hamadani M, et al. PD-1 blockade for relapsed lymphoma post-allogeneic hematopoietic cell transplant: high response rate but frequent GVHD. Blood 2017 Jul 13;130(2):221–8.
[15] El-Khoueiry AB, Sangro B, Yau T, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet 2017;389:2492–502.
[16] Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1–positive non–smallcell lung cancer. N Engl J Med 2016;375:1823–33.
[17] Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, et al. Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med 2015 Jun 25;372(26):2521–32.
[18] Bauml J, Seiwert TY, Pfister DG, et al. Preliminary results from KEYNOTE-055: pembrolizumab after platinum and cetuximab failure in head and neck squamous cell carcinoma (HNSCC). J Clin Oncol 2016;35:1542–9.
[19] Nghiem PT, Bhatia S, Lipson EJ, et al. PD-1 blockade with pembrolizumab in advanced merkel-cell carcinoma. N Engl J Med 2016;374:2542–52.
[20] Bellmunt J, de Wit R, Vaughn DJ, Fradet Y, Lee JL, Fong L. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. N Engl J Med 2017;376(11):1015–26.
[21] Abdel-Wahab N, Shah M, Suarez-Almazor ME. Adverse events associated with immune checkpoint blockade in patients with cancer: a systematic review of case reports. PLoS One 2016 Jul;11(7), e0160221.
[22] De Velasco G, Je Y, Bossé D, et al. Comprehensive meta-analysis of key immune-related adverse events front CTLA-4 and PD-1/PD-L1 inhibitors in cancer patients. Cancer Immunol Res 2017 Apr;5(4):312–8.
[23] Weber JS, Yang JC, Atkins MB, et al. Toxicities of immunotherapy for the practitioner. J Clin Oncol 2015 Jun 20;33(18):2092–9.
[24] Postow MA, Sidlow R, Hellman MD. Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med 2018;378:158–68.
[25] Chen TW, Razak AR, Bedard PL, Siu LL, et al. A systematic review of immune-related adverse event reporting in clinical trials of immune checkpoint inhibitors. Ann Oncol 2015 Sep;26(9):1824–9.
[26] Wang PF, Chen Y, Song SY, et al. Immune-related adverse events associated with anti-PD-1/PD-L1 treatment for malignancies: a meta-analysis. Front Pharmacol 2017 Oct 18;8:730.
[27] Freeman-Keller M, Kim Y, Cronin H, et al. Nivolumab in resected and unresectable metastatic melanoma: characteristics of immune-related adverse events and association with outcomes. Clin Cancer Res 2016;22:886–94.
[28] Haratani K, Hayashi H, Chiba Y, et al. Association of immune-related adverse events with nivolumab efficacy in non-small-cell lung cancer. JAMA Oncol 2018;4:374–8.
[29] Sato K, Akamatsu H, Murakami E, et al. Correlation between immune-related adverse events and efficacy in non-small cell lung cancer treated with nivolumab. Lung Canc 2018;115:71–4.
[30] Hua C, Boussemart L, Mateus C, et al. Association of Vitiligo With Tumor Response in Patients With Metastatic Melanoma Treated With Pembrolizumab. JAMA Dermatol 2016;152:45–51.
[31] Teraoka S, Fujimoto D, Morimoto T, et al. Early immune-related adverse events and association with outcome in advanced non-small cell lung cancer patients treated with nivolumab: a prospective cohort study. J Thorac Oncol 2017 Dec;12(12):1798–805.
[32] Teulings HE, Limpens J, Jansen SN, et al. Vitiligo-like depigmentation in patients with stage III-IV melanoma receiving immunotherapy and its association with survival: a systematic review and meta-analysis. J Clin Oncol 2015;33:773–81.
[33] Seymour L, Bogaerts J, Perrone A, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol 2017 Mar;18(3):e143–52.
[34] Fujii T, Colen RR, Bilen MA, et al. Incidence of immune-related adverse events and its association with treatment outcomes: the MD Anderson Cancer Center experience. Invest N Drugs 2018 Aug;36(4):638–46.
[35] Vansteenkiste J. Nivolumab for NSCLC in Japanese patients: similar benefits, but beware of pneumonitis. ESMO Open 2016;1, e000119.