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RESEARCH ARTICLE

A multicentre observational study of the effectiveness, safety and economic impact of nivolumab on non-small-cell lung cancer in real clinical practice

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Abstract

Background Immunotherapy has become a standard treatment for lung cancer; however, the high cost makes it necessary to assess health outcomes. *Objective* The aim of this study was to evaluate the effectiveness, safety and economic cost of nivolumab in real-world clinical practice. *Setting* Fifteen regional and academic hospitals from Spain participated in this study. *Methods* This study was a retrospective, multicentre and observational study involving patients who experienced progression after first-line therapy for non-small-cell lung cancer and were treated with nivolumab between January 2016 and July 2017. Effectiveness and safety were evaluated by the oncologist, and the data from the electronic clinical records of the patients were collected by the research team. Economic cost was calculated using the cost of acquiring nivolumab for the public health system. *Main outcome measures* Effectiveness variables were overall survival (OS) and progression-free survival (PFS). The safety variable was the incidence of adverse events (AEs), and the cost per life-year gained (LYG) was the economic variable. *Results* A total of 221 patients were enrolled (83.7% men). The mean age was 64.5 years, and 84.6% of the patients had an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0–1. Squamous tumours accounted for 59.7% of the total, and 78.7% of the patients presented a time since platinum therapy (TPT) > 6 months. The mean nivolumab dose was 216 mg (SD 211), and the treatment duration was 7.0 months (95% CI 5.8–8.1). The median PFS was 5.3 months (95% CI 3.2–7.3), and OS was 9.7 months (95% CI 7.6–11.8). The median PFS and OS values were statistically significantly superior for patients with an ECOG score of 0–1 and for patients with a TPT > 6 months. The median OS was also statistically significantly superior for patients with non-squamous histology. Regarding safety, 71% of the patients presented AEs of any grade, and in 18.6%, the nivolumab treatment had to be delayed or discontinued. The cost of nivolumab per patient was €19,910.00 (SD 19,369), and the cost per LYG was €110,026.00 (€77,557.00–€231,171.00). *Conclusions* This study confirms that the efficacy and safety of nivolumab treatment in a real population are comparable to the results obtained in clinical trials. A greater clinical benefit of nivolumab therapy was observed in patients with an ECOG score of 0–1, a TPT > 6 months or non-squamous histology. Despite the benefit observed, the cost per LYG is above the threshold of efficiency established by public health institutes.

Keywords Immunotherapy · Nivolumab · Non-small-cell lung cancer · Real-world data · Spain

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Impacts on Practice

- Real-world data allow the determination of whether the effectiveness and efficiency of nivolumab treatment are comparable to the outcomes observed in clinical trials.
- The identification of patient subgroups with a greater clinical benefit provides selection criteria for the sustainable use of nivolumab.

Introduction

Lung cancer ranks as the leading cause of tumour-related deaths worldwide [1]. The mean age at the time of diagnosis ranges between 55 and 75 years, with a higher incidence rate in men than in women. The most common histology type is non-small-cell lung cancer (NSCLC), accounting for 80–85% of lung cancer cases [2].

Cytotoxic chemotherapy with a platinum-based doublet is currently the first-line standard of care for locally advanced or metastatic NSCLC in patients without targetable mutations. Few alternatives are available for subsequent lines of treatment, and these consist of chemotherapy protocols with docetaxel or pemetrexed, if the latter agent had not been used previously as a first-line or maintenance treatment [3]. Recently, immunotherapy has been incorporated into the treatment of NSCLC [4]. Drugs within this category, which includes nivolumab, are monoclonal antibodies that prevent the binding between the PD-1 receptor on T cells and its ligand, PD-L1, on tumour cells. The inactivation of the T cells that is the result of this binding is reverted, and antitumour immunity is reactivated [5].

Nivolumab is indicated for the treatment of patients with metastatic squamous and non-squamous NSCLC after the failure of prior or current platinum-based chemotherapy [6]. The authorization for nivolumab use is supported by two independent phase III randomized clinical trials [7, 8], which demonstrated a significantly better median overall survival for patients treated with nivolumab than for patients receiving the standard, second-line docetaxel regimen for both squamous and non-squamous histologies. In addition, regarding its safety, treatment-related adverse events of grade 3–4 were less frequent in patients treated with nivolumab than in those treated with docetaxel in both clinical trials.

The efficacy and safety results obtained have led to the inclusion of nivolumab as a second-line treatment option in the updated NCCN [4] and ESMO [9] clinical guidelines for NSCLC.

Due to the high cost nivolumab, it is necessary to know whether the results of the controlled clinical trials are comparable to those in clinical practice and to determine the conditions for the use of this drug to ensure a real benefit for patients and the health system.

Aim of the study

The aim of this study was to assess the health-related outcomes of nivolumab, in terms of its effectiveness, safety and cost-effectiveness, for the treatment of locally advanced NSCLC in real-world patients who had received at least one prior line of chemotherapy.

Ethics approval

The study was conducted in accordance with the Declaration of Helsinki and good clinical practice guidelines. The protocol was approved by the Ethics Committee of each hospital and by the National Regulatory Agency (MAR-NIV-2017-01). Because this study was intended to reflect usual clinical practice and real-world data, no compensation was provided to the participating patients or physicians.

Methods

This was a multicentre, retrospective, observational study carried out at 15 hospitals in southern Spain. All NSCLC patients receiving nivolumab-containing therapy between January 2016 and July 2017 at the participating hospitals were included. Only those patients receiving nivolumab as part of another clinical trial were excluded. All treatment decisions were at the physicians' discretion, including the dose, schedule and duration of nivolumab and chemotherapy, the scheduling of patient visits, and the method and frequency of clinical assessments.

All study variables were collected from the available hospital records, including an electronic prescribing oncology pharmacy application and patient medical history, as well as other complementary sources (pathology, laboratory and radiology records). All the data were introduced into a database created ad hoc.

Effectiveness measures included progression-free survival (PFS) (time from the start of the initial nivolumab-containing therapy to the first recorded occurrence of physician-assessed disease progression or death), overall survival (OS) (time from the start of the nivolumab-containing therapy to death or censoring), and response rate as described in the patient medical history records. Patients without an event who remained in follow-up were censored on July 2017.

Information included the patient age, gender, relevant medical history events, cancer history (histological tumour type, sites of metastasis, date of and stage at initial diagnosis, date of advanced disease diagnosis, dates of disease progression and death), prior chemotherapy lines and the time since platinum therapy (TPT), nivolumab-based treatment (dose, schedule, line and duration of treatment and best response to the nivolumab-based treatment), adverse events (AEs) and the number and duration of hospitalizations, either directly or indirectly related to treatment with nivolumab.

All AEs were graded using the National Cancer Institutes-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0 and were coded according to the Medical Dictionary for Regulatory Activities (MedDRA).

The costs of nivolumab were obtained from the acquisition prices invoiced to the public health system hospitals (€9.17 per mg), and the costs associated with a hospital stay for lung cancer were obtained from the Spanish National Health System statistical site (€5293.03) [10]. The cost per life-year gained (LYG) was obtained by calculating the benefit in OS (months) and the incremental cost of nivolumab therapy for all patients as follows:

1. [OS benefit for each patient] = [OS with nivolumab] − [OS with docetaxel]
    1.1. [OS with nivolumab] = OS of this study
    1.2. -[OS with docetaxel] = according to the results of the following formulas depending on the tumour histology of the patient:
    [OS with docetaxel] = [OS with nivolumab] x [HR 0.59; 95% CI 0.44–0.79] for squamous [7] or
    [OS with docetaxel] = [OS with nivolumab] x [HR 0.73; 95% CI 0.59–0.89] for *non-squamous* [8]
2. [OS benefit for all patients] (years) = ∑ [OS benefit for each patient]/12
3. Cost LYG = [OS benefit for all patients]/[Incremental cost of nivolumab therapy for all patients].

The mean, standard deviation (SD), median, range, and counts and percentages (for categorical data) were calculated for the demographic and cancer characteristics. The overall incidence of AEs was summarized in terms of patient counts.

PFS and OS were expressed as the median survival times, with the 95% confidence interval (95% CI), using the Kaplan–Meier method to estimate the survival curves; the log-rank test was used to compare the curves. The Cox proportional-hazards model was used to calculate hazard ratios (HRs) and 95% CIs. Statistical analyses were performed using G-Stat 2.0 software; Dep. Biometría GSK, Madrid, Spain.

Results

Patient characteristics

A total of 221 NSCLC patients (83.7% male) were included with a median age of 64.5 years (SD 9.2). The patient demographics and tumour characteristics are summarized in Table 1. One hundred and fifty-two patients (68.8%) were smokers, and 60 (27.1%) had never smoked or had stopped smoking more than 6 months before the time of the diagnosis. One hundred and thirty-two patients (59.7%) had squamous tumour histology, and 84 (38%) had non-squamous histology. One hundred and eighty-seven patients (84.6%) had ECOG score of 0–1 at the beginning of the nivolumab treatment, and the rest had PS 2. At the time of the first diagnosis, 53.8% of the patients had Stage IV disease, while 37.6% had Stage III disease, and the rest had Stage I or Stage II disease. At the start of the treatment with nivolumab, all the patients had progressed to metastatic or locally advanced stages after being treated with platinum-based therapy. The median number of metastatic locations per patient was 2 (range 1–5), the most frequent being lung metastases (n = 115, 52.0%), lymph node metastases (n = 72, 32.6%), bone metastases (n = 69, 31.2%), liver metastases (n = 41, 18.6%) and brain metastases (n = 22, 10.0%).

The treatment with nivolumab started at a mean of 15.6 months (SD 15.9) after the beginning of first-line platinum-based therapy; for 21.3% of patients, this period of time was less than 6 months. At the time this study ended, 74 patients were still under treatment, 103 patients had stopped treatment because of progression, 23 patients had stopped due to adverse events, and 21 patients had died.

All the patients received the standard dose of 3 mg/kg every 2 weeks with a mean dose per patient and dose-intake of 216 mg (SD 211). The mean number of cycles administered was 9.7 (SD 9.1, range [1–48]). The median duration of treatment was 4.1 months (95% CI 3.2–5). All the patients had been previously treated with a platinum-based doublet, and one patient had also received bevacizumab. Twenty-one (9.5%) patients had received prior radiotherapy. One hundred and forty-four patients had received one prior therapy line, while 61 patients had received two therapy lines, and the rest had received 3 or more therapy lines before the nivolumab therapy.

Table 1 Patient characteristics

	No. patients (%) (n = 221)
Sex (n = 221)	
Male	185 (83.7%)
Female	36 (16.3%)
Age (n = 221)	
< 70 years	162 (73.3%)
> 70 years	59 (26.7%)
Smoking status (n = 212)	
Never/former-smoker	60 (27.1%)
Current-smoker	152 (68.8%)
Histology (n = 216)	
Squamous	132 (59.7%)
Non-squamous	84 (38%)
ECOG score (n = 217)	
0	62 (28.1%)
1	125 (56.6%)
2	30 (13.6%)
Stage (n = 221)	
IV	119 (53.8%)
III	83 (37.6%)
II	14 (6.3%)
I	5 (2.3%)
Number of metastatic locations (n = 209)	
1	100 (45.2%)
2	64 (29.0%)
3	32 (14.5%)
> 3	13 (5.9%)
Type of metastatic locations (n = 209)	
Lung	115 (52.0%)
Lymph nodes	72 (32.6%)
Bone	69 (31.2%)
Liver	41 (18.6%)
Brain	22 (10.0%)
Others	45 (20.4%)
Time since platinum therapy (months)	
Mean (SD)	15.6 (15.9)
< 6 months	47 (21.3%)
> 6 months	174 (78.7%)

Effectiveness

The median PFS and OS times were 5.3 months (95% CI 3.2–7.3) and 9.7 months (95% CI 7.6–11.8), respectively. The effectiveness results obtained for all the variables are shown in Table 2. In the univariate analysis, no statistically significant differences in the median PFS time were found in relation to sex, an age > 70 years, histology, smoking status or the number of metastatic sites. The median PFS time was significantly longer in patients with an ECOG score of 0–1 versus an ECOG score of 2 (7.6 months vs. 1.9 months, respectively, $p < 0.0001$) and in patients with a TPT > 6 months versus a TPT < 6 months (6 months vs. 3.1 months, respectively, $p = 0.003$).

There was no statistically significant difference in the median OS time according to sex, an age > 70 years, smoking status or the number of metastatic sites. The median OS time was significantly longer in those patients with a non-squamous histology vs a squamous histology (12.8 months vs. 6.9 months, respectively, $p = 0.015$), in patients with an ECOG score of 0–1 versus an ECOG score of 2 (12.8 months vs. 2.9 months, respectively, $p > 0.0001$) and in patients with a TPT > 6 months vs a TPT < 6 months (11.8 months vs. 3.7 months, respectively, $p < 0.0001$).

These results were subsequently confirmed by a multivariate analysis of OS in a model including the variables tumour histology, ECOG score and TPT. A significant difference was observed for OS in the hazard ratio risk functions based on the tumour histology, HR 0.586 (95% CI 0.374–0.917), $p = 0.019$, the ECOG score, HR 0.290 (95% CI 0.18–0.467), $p < 0.0001$, and the TPT, HR 0.971 (95% CI 0.953–0.989), $p = 0.002$.

The objective response rate (ORR), defined as the combination of the complete response rate and the partial response rate, was 16.7% with 0.9% with a complete response. Disease stability was reached in 32.6% of the patients. Sixty-one patients (27.6%) had no response to nivolumab. No data were available in 22.6% of the cases.

Safety

Treatment-related AEs of any grade occurred in 71% of the patients (n = 157), and 18.6% of the patients (n = 41) had their nivolumab treatment delayed or discontinued because of AEs. Table 3 shows the AE incidence by type and severity.

Seventy-three patients (33%) had at least one episode of hospital admission during the course of the nivolumab treatment, with a total number of 98 hospital admissions (mean = 1.3) and a total of 900 days of hospital stay (mean = 12.3). Costs related to hospital admissions amounted to €518,716.94.

Costs

The total cost for treatment with nivolumab in our study population was €4420,142.00, with a mean cost per patient of €19,910.00 (SD 19,369.00), assuming complete use, with no discards, of all the vials for the preparation of the mixtures. This value means an incremental cost in relation to the reference therapy of €4,384,561.00, based

Table 2 PFS and OS (univariate analysis)

	PFS			OS		
	Median (m) [95% CI]	p (log rank)	HR [95% CI]	Median (m) [95% CI]	p (log rank)	HR [95% CI]
Population	5.3 [3.2–7.3]	–	–	9.7 [7.6–11.8]	–	–
Sex						
Male	4.7 [3.2–6.2]	0.191	0.72 [0.44–1.18]	9.5 [4.9–14.2]	0.326	0.76 [0.44–1.32]
Female	9.6 [5.2–14.1]			11.8 [6.5–17.0]		
Age						
< 70 years	5.2 [3.2–7.2]	0.662	0.92 [0.62–1.36]	9.7 [6.9–12.5]	0.821	0.95 [0.61–1.49]
> 70 years	5.1 [0.4–9.7]			12.8 [3.4–22.3]		
Smoking status						
Never/former-smoker	8.0 [3.6–12.3]	0.377	1.20 [0.80–1.81]	9.7 [5.7–13.7]	0.676	1.10 [0.70–1.74]
Smoker	5.2 [3.1–7.3]			9.8 [6.0–13.7]		
Histology						
Squamous	4.7 [2.7–6.8]	0.212	0.79 [0.55–1.14]	6.9 [3.6–10.2]	0.015	0.59 [0.38–0.91]
Non-squamous	6.1 [2.9–9.3]			12.8 [7.8–17–9]		
Nº of metastatic locations						
1	6.3 [3.1–9.6]	0.399	1.17 [0.81–1.69]	6.9 [3.7–10.1]	0.263	0.79 [0.52–1.19]
> 1	4.2 [2.9–5.6]			9.5 [7.7–11.7]		
ECOG score						
0–1	7.6 [5.2–9.9]	< 0.0001	3.94 [2.53–6.11]	12.8 [9.5–16.1]	< 0.0001	3.85 [2.40–6.18]
2	1.9 [0.5–3.3]			2.9 [0.2–5.6]		
TPT						
< 6 months	3.0 [0.7–5.3]	0.003	0.53 [0.34–0.80]	3.7 [1.5–5.9]	< 0.0001	0.39 [0.26–0.60]
> 6 months	6.1 [3.9–8.3]			11.8 [8.2–15.3]		

on the docetaxel cost/treatment of €161.00 [11]. Only pharmacological treatment costs were considered in this analysis.

The benefit in OS reached for the entire study population was an estimated 478.2 months with a minimum benefit of 227.6 months and a maximum of 678.4 months, which indicates a mean cost per LYG of €110,026.00, with a minimum cost of €77,557.00 and a maximum cost of €231,171.00, according to the central HR value and the upper and lower 95% CI values in Checkmate studies, respectively.

Discussion

The effectiveness of nivolumab on PFS, 5.3 months (95% CI 3.2–7.3), and on OS, 9.7 months (95% CI 7.6–11.8), reached in our real-world population is comparable to the efficacy results achieved in the authorized clinical trials for both the squamous [7] and non-squamous histologies [8]. Our results were not uniform in all patient subgroups. We identified significant differences in PFS and OS according to the ECOG score and the TPT and in OS according to the

Table 3 Treatment-related adverse events

	Any grade		Delayed or discontinued treatment	
	n	%	n	%
	157	71.0	41	18.6
Side effect				
Asthenia	85	38.5	7	3.2
Other	45	20.4	11	5.0
Dyspnoea	33	14.9	6	2.7
Diarrhoea	26	11.8	4	1.8
Cough	21	9.5	4	1.8
Pneumonitis	17	7.7	12	5.4
Rash	16	7.2	3	1.4
Pain	15	6.8	1	0.5
Pruritus	15	6.8	1	0.5
Arthralgia	15	6.8		
Nausea	14	6.3		
Hypothyroidism	12	5.4	2	0.9
Fatigue	11	5.0	2	0.9
Peripheral oedema	10	4.5		
Anaemia	10	4.5	1	0.5
Pneumonia	10	4.5	5	2.3
Heartburn	8	3.6		
Constipation	6	2.7		
Skin dryness	6	2.7	1	0.5
Liver enzymes elevation	6	2.7	2	0.9
Watery eyes	4	1.8	1	0.5
Lack of appetite	4	1.8		
Dysgeusia	3	1.4		
Peripheral neuropathy	2	0.9		
Stomatitis	1	0.5	1	0.5
Mucosal inflammation	1	0.5		
Hyperglycaemia	1	0.5		

histological type. The differences in effectiveness among these patient subsets are consistent with what has been published in similar studies [12–14]; however, the median PFS and OS values obtained in some of these studies differ from our results [12].

Our report shows the use of nivolumab in patients with an ECOG score of 2, in contrast with all the phase III clinical trials of nivolumab, where this patient subgroup was excluded. According to our results, the effectiveness of nivolumab is significantly lower in patients with an ECOG score of 2 than in patients with an ECOG score of 0–1; hence, treatment with nivolumab in this patient type would not be supported by the ability of this therapy to accomplish the expected benefits. Further efficacy data are required to establish recommendations in this subgroup of patients.

The effectiveness results also show a significant difference between a TPT > 6 months and a TPT < 6 months. Patients with a rapidly progressing disease benefit less in terms of PFS and OS; therefore, several guidelines have been published wherein the use of nivolumab is not recommended if the patient experiences rapid progression or fails first-line therapy [15]. All of these results were confirmed in the multivariate analysis.

To the best of our knowledge, our study is the first in a real-world setting to demonstrate that patients with a non-squamous histology achieve a longer OS than patients with a squamous histology. This significant difference was also observed in the authorized clinical trials [7, 8], although in our study, this difference is greater.

Regarding the safety of the treatment, our results show a profile of AEs that is similar to the profile described in the phase III clinical trials [7, 8]. Nevertheless, the data collection system could be one of the limitations of our study, as the methodology was not standardized, and there is a high variability in the clinical history records that we used as the source of information. Because of this limitation, the incidence of treatment-related AEs in our report might be biased.

The overall treatment-related AEs were lung toxicity, skin toxicity and gastrointestinal toxicity, as was described in the authorized clinical trials of nivolumab. Almost 20% of patients discontinued or delayed treatment with nivolumab because of AEs, which gives us information about the rate of toxicities, grade 2 or above [6].

Hospital admissions for any cause occurred in 33% of patients, with a mean hospital stay length of 12 days. We consider that these admissions are not excessive, since nivolumab is used in an advanced disease situation.

Following the WHO recommendations from the WHO-CHOICE project, the profitability threshold of health interventions should be lower than three times the gross domestic product of the country per year of life adjusted to disability. In Spain, the value of the gross domestic product is €25,000.00, and the efficiency threshold would be fixed at €75,000.00. In our study, the cost per LYG is €110,026.00, exceeding this efficiency threshold. This value is also above the £50,000.00 "end-of-life" criteria of NICE.

Conclusions

The results regarding the effectiveness of nivolumab in our study population are comparable to those obtained in the authorized clinical trials. Nevertheless, these results are not consistent in all the patient subgroups. The clinical benefit of nivolumab therapy is superior in patients with an ECOG score of 0–1 and a TPT > 6 months. We cannot explain the great difference in overall survival between patients with a

non-squamous histology and patients with a squamous histology. In terms of safety, the incidence of adverse events was similar to that obtained in the authorized clinical trials. The cost per LYG exceeds any efficiency line defined in our field; thus we consider that treatment with nivolumab should be prioritized to subsets of patients with a higher benefit.

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Conflicts of interest The authors declare that they have no conflicts of interest.

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