in vivo *37*: 2229-2236 (2023)
doi:10.21873/invivo.13324

Serious Immune-related Adverse Events Are Associated With Greater Efficacy of Nivolumab Therapy Against Non-small Cell Lung Cancer

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Abstract. *Background/Aim: The aim of this study was to investigate possible association between adverse events of nivolumab therapy and the effectiveness of treatment in patients with non-small cell lung cancer (NSCLC). Focusing on serious adverse events (i.e., those of grade ≥3), we evaluated overall survival (OS), progression-free survival (PFS), as well as objective response rate (ORR) to treatment. Patients and Methods: We retrospectively analyzed a set of patients from the TULUNG database of NSCLC treated with nivolumab in eight oncology centers. We evaluated OS data based upon this set. To reduce possible bias, we further evaluated a subgroup of patients treated at the University Hospital in Pilsen, where the occurrence of adverse events, PFS, and ORR were independently examined by two experienced physicians. Survival statistics were evaluated using the Kaplan-Meier method and Cox analysis. Results: We observed significantly greater OS, PFS, and ORR in the group of patients experiencing adverse events upon nivolumab treatment versus in those patients without such events. Although the univariable model analyzing the data set of all patients demonstrated higher OS in patients with serious adverse events, only a nonsignificant trend was observed in the Cox multivariable model. In a subgroup of patients with PFS and ORR evaluation, we did observe significant, favorable effects for patients having had serious adverse effects. Conclusion: Patients experiencing severe adverse events show a tendency toward better OS, PFS, and ORR compared to patients without or having only mild adverse events with nivolumab treatment.*

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Key Words: Lung cancer, nivolumab, adverse events, overall survival.

Treatment of advanced non-small cell lung cancer (NSCLC) has advanced greatly in recent years with the introduction of new drugs in the field of targeted therapy and immunotherapy. While relatively reliable predictive markers in the form of specific mutations in driver oncogenes are known for targeted treatment, no reliable predictive marker except PD-L1 exists for immunotherapy in NSCLC (1). However, PD-L1 expression has a number of shortcomings, which make this marker far from optimal (2). This is why ongoing efforts search for additional markers for predicting response to immunotherapy.

Adverse events have been suggested as predictors of treatment effectiveness as shown with erlotinib, for which the occurrence of rash was associated with a better response to treatment (3). It was therefore important to find out how immune-related adverse events (irAEs) after immunotherapy reflect treatment efficacy. One of the first reports of this possible influence is the publication by Assi *et al*. in 2013, which describes two cases of patients treated with ipilimumab with a long response to treatment despite adverse events (4). Subsequently, due to extensive application of immunotherapy across many indications in oncology, several authors have dealt with this issue in various types of tumors. The greater association of the effectiveness of immunotherapy with the occurrence of irAEs has been described in melanoma, upper gastrointestinal tract cancer, as well as renal carcinoma treated with nivolumab (5-9). Also, an extensive meta-analysis investigating the influence of irAEs on the effectiveness of treatment with checkpoint inhibitors generally demonstrates this phenomenon (10).

Regarding NSCLC, this phenomenon has also been investigated by several authors, including, among others, those referenced in a meta-analysis by Zhao *et al*. (11). In a group of 8,452 NSCLC patients treated with various anti-PD1 inhibitors, they demonstrated significant improvement in overall survival (OS), progression-free survival (PFS), and objective response rate (ORR) in patients who had irAEs. Similar results were obtained in studies where nivolumab was used for the treatment of NSCLC (12-15).

Most of these studies, however, did not address the possible difference between mild and severe side effects of immunotherapy. The meta-analysis by Hussaini *et al*. already mentioned points to poorer OS in patients with solid tumors and grade 3 or 4 side effects upon immunotherapy (10). In contrast, Guezour *et al*., in their group of patients with NSCLC, described longer OS even in patients with high-grade side effects of immunotherapy (16). Therefore, we consider this topic to be insufficiently investigated. Our aim was to determine any association of severe immune-related side effects (defined as grade ≥3) with the effectiveness of nivolumab treatment in patients with advanced NSCLC.

Patients and Methods

Study design and treatment. Clinical data of patients with cytologically or histologically confirmed advanced NSCLC treated with nivolumab were analyzed retrospectively. The patients were treated in the first or higher line of treatment at eight Oncology and Pneumooncology Departments in the Czech Republic between the years 2015 and 2021 (cutoff 16 September 2021). Nivolumab was administered intravenously at the approved doses of 3 mg/kg or a flat dose of 240 mg every 2 weeks. The treatment was administered until progression or unacceptable toxicity for a maximum of 2 years. In case of treatment-related toxicity, administration of corticosteroids and/or interruption of nivolumab was recommended. Clinical follow-ups including physical examination, chest X-ray, and routine laboratory tests were performed at least every 4 weeks. Computed tomography (CT) or positron emission tomography (PET)/CT were performed at regular intervals according to the local standards or in case progression was suspected based on clinical or chest X-ray examination. The data were retrieved from the national register TULUNG, a noninterventional post-registration database of epidemiological and clinical data of patients with advanced-stage NSCLC treated with targeted or biological therapies in the Czech Republic. All patients had signed informed consent to be included into this database and to have their data used for scientific purposes. The foundation of the TULUNG Registry had been approved by the Institutional Ethics Committees of all participating centers [University Hospital Olomouc, University Hospital Pilsen, University Hospital Brno, University Hospital Hradec Kralove, University Hospital Motol (Prague), University Hospital Bulovka (Prague), Thomayer Hospital (Prague), Jihlava Hospital, Masaryk Memorial Cancer Institute, Masaryk Hospital (Usti nad Labem), Na Homolce Hospital (Prague), and VFN (Prague)]. This study was approved by the Ethics Committee of the University Hospital Hradec Kralove on the11th of May 2018 (approval number: 201805 I134R).

Data from all centers were used to calculate OS. A patient data set from the University Hospital in Pilsen (hereinafter referred to as the "subgroup of patients") that was used to calculate ORR and PFS was reviewed independently on the basis of patient documentation (in relation to ORR, PFS, OS, and adverse events associated with nivolumab) by two experienced physicians. In case of discrepancies between the results obtained by these two physicians, the findings were discussed to reach mutual agreement.

Statistical methods. Standard frequency tables and descriptive statistics were used to characterize the sample data set. The overall response rate (ORR) was defined as the best response defined according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1) (17). PFS was determined from the date of nivolumab treatment initiation until the date of first documented progression (as per RECIST 1.1) or death. OS was determined from the date of nivolumab treatment initiation until the date of death due to any cause. Patients who had not progressed or died were censored at the date of the last follow-up.

Differences in survival between two groups were assessed using the Gehan-Wilcoxon test, multivariable analysis of survival was carried out with the Cox proportional hazards model. Simple associations of adverse events with ORR were examined using Fisher's exact test, and multivariable analysis of ORR was performed with multivariable logistic regression.

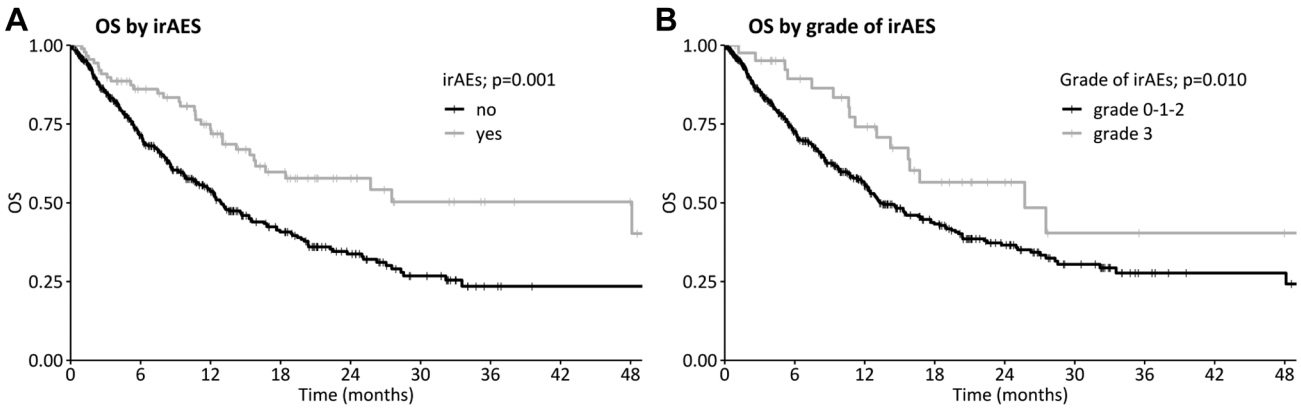

Figure 1. *Kaplan-Meier curves for the group of all patients for overall survival (OS). A) patients with vs. without adverse events, B) patients without adverse events/with adverse events grades 1-2 vs. patients with adverse events grade ≥3.*

All reported *p*-values are two-tailed and α=0.05 was used in deciding statistical significance. The analysis was performed using Statistica (ver. 12 Cz, TIBCO Software Inc., Palo Alto, CA, USA), MATLAB (The MathWorks Inc., Natick, MA, USA), IBM SPSS, Statistics (version 25.0, IBM, Armonk, NY, USA), and R software (version 3.5.1, R Foundation, Vienna, Austria).

Results

Patient characteristics. For evaluating OS, 662 patients from all centers were analyzed. Data for 84 patients from the subgroup of patients were available for ORR and PFS evaluation. Patient characteristics for both groups are summarized in Table I.

irAEs related to nivolumab. In the whole group of patients, irAEs associated with nivolumab were reported in 93 (14%) patients. Of these, 15 (16.1%) were classified as skin reactions and/or thyropathy. In the remaining patients (83.9%), reactions other than skin and/or thyropathy were described. irAEs reached grades 1-2 in 50 (53.8%) patients and grade ≥3 in the remaining 43 (46.2%) patients. The median time to occurrence of the first irAEs was 2.5 months.

In the subgroup of patients, irAEs occurred in 25 (29.8%) patients. Of these, one adverse event occurred in 19 patients, two in four patients, and three in two patients in association with nivolumab treatment. Grade 1 irAEs were observed in four patients (4.8%), grade 2 in nine patients (10.7%), and grade 3 in 12 patients (14.3%). The most common irAEs included exanthema (eight patients – 3× grade 1, 3× grade 2, 2× grade 3), arthralgia (seven patients – 2× grade 2, 5× grade 3), and diarrhea (six patients – 1× grade 2, 2× grade 2, 3× grade 3). Other irAEs were: pneumonitis (5×), pruritus (2×), renal insufficiency (1×), hepatitis (1×), thyropathy (1×), diplopy (1×), and bulbar paralysis (1×). Corticosteroids were used in the treatment of 18 patients with adverse events.

Table I. *Patient characteristics*.

Patients characteristics	All patients n (%)	Pilsen subgroup n (%)
Number of patients	662 (100)	84 (100)
Sex		
Male	436 (65.9)	58 (69.0)
Female	226 (34.1)	26 (31.0)
Smoking		
Nonsmoker	89 (13.4)	11 (13.1)
Ex-smoker	257 (38.8)	59 (70.2)
Smoker	316 (47.7)	14 (16.7)
ECOG PS		
0	125 (18.9)	1 (1.2)
1	532 (80.4)	73 (86.9)
2	5 (0.8)	10 (11.9)
Histology		
Non-squamous	382 (57.7)	42 (50.0)
Squamous	280 (42.3)	42 (50.0)
Line of treatment		
1	13 (2.0)	0 (0.0)
2	436 (65.8)	43 (51.2)
3	128 (19.3)	25 (29.8)
4	62 (9.4)	12 (14.3)
≥5	23 (3.5)	4 (4.8)
irAEs reported		
No	569 (86.0)	59 (70.2)
Yes	93 (14.0)	25 (29.8)

ECOG: Eastern Cooperative Oncology Group; irAEs: immune-related adverse events; PS: performance status.

Nivolumab treatment had to be discontinued in 20 patients with irAEs. The median time to occurrence of the first irAEs was 3.9 months.

Overall survival analysis. In the group of all patients, OS was significantly longer in patients with irAEs (median 48.1

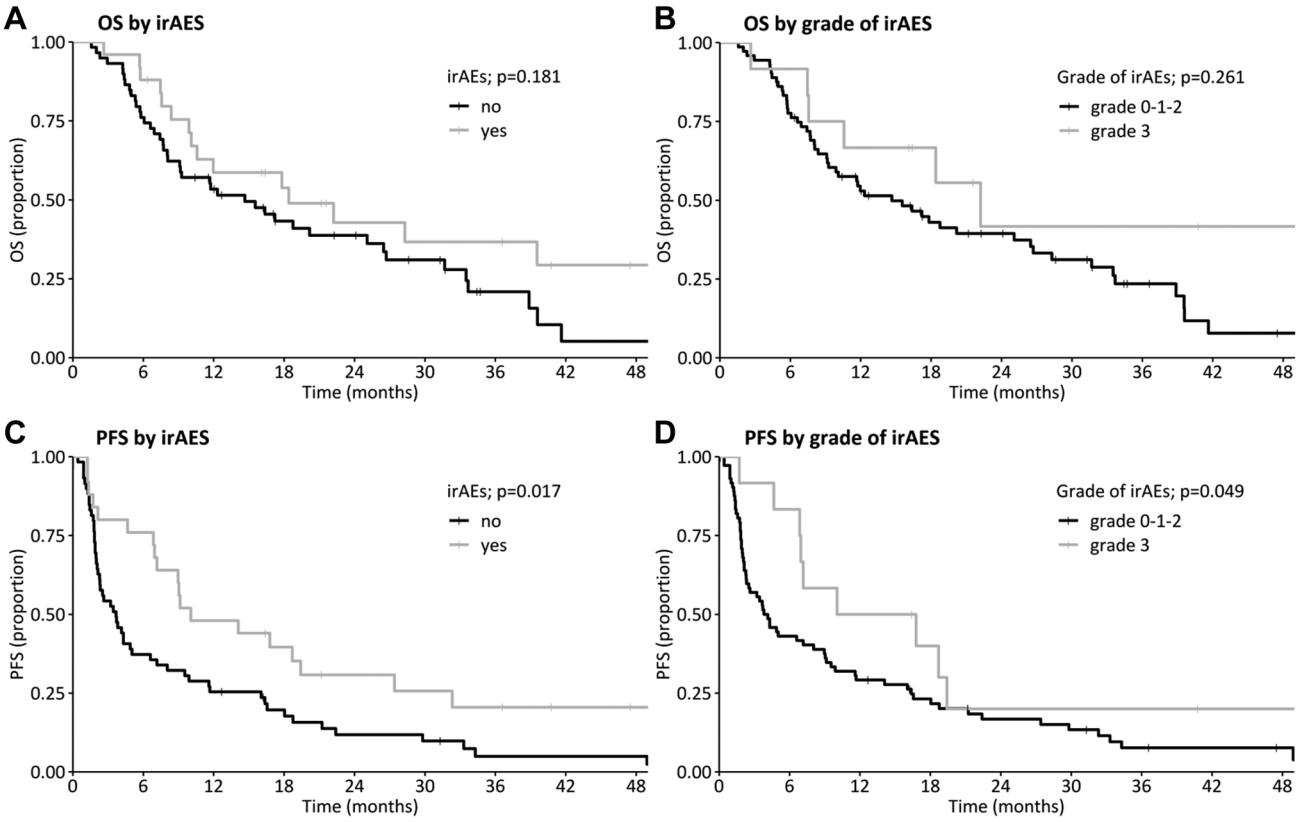

Figure 2. *Kaplan-Meier curves for the subgroup of patients from the University Hospital in Pilsen for A) overall survival (OS) of patients with vs. without adverse events, B) OS of patients without adverse events/with adverse events grades 1-2 vs. patients with adverse events grade ≥3, C) progression-free survival (PFS) of patients with vs. without adverse events, D) PFS of patients without adverse events/with adverse events grades 1-2 vs. patients with adverse events grade ≥3.*

months, 95%CI=16.7–NA) *vs*. in patients without adverse events (median 12.9 months, 95%CI=11.7-16.6; *p*=0.001) (Figure 1A). We also observed significantly longer OS for patients with irAEs grade ≥3 (median 25.7 months, 95%CI=15.7–NA) *vs*. patients without irAEs or irAEs grade 1-2 (median 13.3 months, 95%CI=12.3-17.7; *p*=0.010) (Figure 1B). Patients with skin irAEs and/or thyropathies had significantly longer OS (median not reached) than did patients with other types of irAEs (median 14.2 months, 95%CI=12.4-17.7; *p*=0.028).

In the subgroup of patients, we observed only a nonsignificant difference in OS between patients with irAEs (median 18.3 months, 95%CI=10.0-40.6) and those without irAEs (median 14.1 months, 95%CI=8.1-23.9; *p*=0.181). The Kaplan-Meier curve is shown in Figure 2A. Furthermore, we observed no significant difference in OS between patients with events grade ≥3 (median 19.9 months, 95%CI=7.7–NA) and patients without irAEs or irAEs grades 1-2 (median 14.4 months, 95%CI=9.2-23.5; *p*=0.261). The Kaplan-Meier curve is shown in Figure 2B. We also observed no significant differences either between patients with 1 *vs*. ≥2 irAEs (*p*=0.18) or for patients treated and those not treated with corticosteroids (*p*=0.09). There was a nonsignificant tendency, however, toward a better OS in patients on corticosteroid treatment.

Progression-free survival analysis. In the subgroup patients, we observed a significantly better PFS in patients with irAEs (median 10.1 months, 95%CI=7.1-21.0) *vs*. those without irAEs (median 3.6 months, 95%CI=2.2-5.0; *p*=0.017). The Kaplan-Meier curve is shown in Figure 2C. We also observed significantly longer PFS for patients with irAEs grade ≥3 (median 10.1 months, 95%CI=6.9-19.1) *vs*. patients without irAEs or with irAEs grade 1-2 (median 4.0 months, 95%CI=2.3-8.5; *p*=0.049). The Kaplan-Meier curve is shown in Figure 2D. We observed no significant difference in PFS between patients with 1 *vs*. ≥2 irAEs (*p*=0.30), and this was the case also for patients treated *vs*. not treated with corticosteroids (*p*=0.14). There was nevertheless a nonsignificant trend toward a better PFS in corticosteroid-treated patients.

Objective response rate analysis. In the subgroup patients, we observed significantly better ORR in patients with irAEs

Table II. *Multivariable Cox models for overall survival for the group of all patients: assessment in patients with/without adverse events.*

Category		HR (95%CI)	*p*-Value
irAEs	No	Ref. category	–
	Yes	0.55 (0.38-0.79)	**0.001**
Age	(in years)	0.98 (0.96-0.99)	**<0.001**
Sex	Male	Ref. category	-
	Female	0.91 (0.69-1.21)	0.529
Smoking	Non-smoker	Ref. category	–
	Ex-smoker	0.89 (0.60-1.32)	0.561
	Smoker	0.91 (0.62-1.33)	0.615
Histology	Squamous	Ref. category	–
	Non-squamous	0.96 (0.73-1.27)	0.792
Stage	III	Ref. category	–
	IV	1.50 (0.99-2.25)	0.053
ECOG PS	0	Ref. Category	–
	1+2	1.62 (1.17-2.24)	**0.004**

Bold values indicate statistical significance. HR: Hazard ratio; irAEs: immune-related adverse events; ECOG PS: Eastern Cooperative Oncology Group performance status.

Table III. *Multivariable Cox models for OS for the group of all patients: assessment in patients without adverse events or with adverse events grade 1 or 2 vs. patients with adverse events grade ≥3.*

Category		HR (95%CI)	*p*-Value
irAEs	No or grade 1-2	Ref. category	–
	Grade ≥3	0.61 (0.37-1.03)	0.063
Age	(in years)	0.98 (0.96-0.99)	**<0.001**
Sex	Male	Ref. Category	–
	Female	0.92 (0.70-1.22)	0.560
Smoking	Nonsmoker	Ref. category	–
	Ex-smoker	0.88 (0.60-1.31)	0.540
	Smoker	0.88 (0.60-1.29)	0.521
Histology	Squamous	Ref. category	–
	Non-squamous	0.96 (0.73-1.26)	0.758
Stage	III	Ref. category	–
	IV	1.48 (0.98-2.22)	0.061
ECOG PS	0	Ref. Category	–
	1+2	1.66 (1.20-2.30)	**0.002**

Bold values indicate statistical significance. CI: Confidence interval; ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio; irAEs: immune-related adverse events; PS: performance status.

[complete response (CR) or partial response (PR) achieved in 60% of patients] *vs*. without (13.6% of patients; $p<0.0001$). We also observed significantly higher ORR for patients with irAEs grade ≥3 (with 58.3% exhibiting CR or PR) *vs*. patients without irAEs or irAEs grade 1-2 (22.2%; $p=0.015$). We observed no significant difference between patients with 1 *vs*. ≥2 irAEs ($p=0.34$), and this was the case also for patients treated *vs*. not treated with corticosteroids ($p=0.55$).

Multivariable analysis. In the whole patient cohort, the Cox proportional hazards model showed that even in the context of other clinical parameters, occurrence of irAEs was associated with significantly better OS [hazard ratio (HR)=0.55, 95%CI=0.38-0.79, $p=0.001$) as an independent prognostic factor (Table II). In the Cox model, when assessing the effect of irAEs grade ≥3 in comparison to none or grade ≤2, we observed only a nonsignificant improvement of OS in patients with more serious irAEs (HR=0.61, 95% CI=0.37-1.03, $p=0.063$) (Table III). Higher age and lower Eastern Cooperative Oncology Group performance score (ECOG PS) were associated with statistically better OS in both models.

In the subgroup patients, we observed significantly longer OS (HR=0.47, 95%CI=0.24-0.90, $p=0.02$) and PFS (HR=0.42, 95%CI=0.24-0.74), as well as higher probability of achieving ORR levels of CR or PR (probability ratio 14.66, 95%CI=4.08-52.73, $p<0.0001$) for patients with irAEs *vs*. patients without irAEs (Table IV). ECOG PS value of 2 was also associated with significantly worst prognosis for OS and PFS.

Discussion

In our overall group and in a more specific subset of patients, we confirmed the generally accepted concept of better effectiveness of nivolumab treatment in advanced NSCLC in patients with irAEs, which had been described earlier in a large meta-analysis (11). Moreover, we showed that this applies also to patients with serious irAEs, as this group of patients trended toward longer OS and better PFS and ORR.

In the meta-analysis by Hussaini *et al*. investigating the relationship between irAEs and efficacy of immune checkpoint inhibitors in solid cancers, better ORR but poorer OS were described in patients with grade 3 or 4 irAEs (10). This contrasts with our results for patients with NSCLC having grade 3 or 4 irAEs, where we noted better PFS, ORR, and OS (OS only for the whole group; for the subgroup of patients there probably was not sufficient statistical power for evaluating OS). A possible explanation may be the inclusion of different types of treatment [both PD-(L)1 and CTLA-4 inhibitors], as well as different types of tumors in the aforementioned meta-analysis (10). A possible more substantial influence of the type of immunotherapy than of the type of tumor has been indicated in patients with melanoma and renal carcinoma treated with PD-1 antibodies as in our study (8, 18). In their study of 147 patients with advanced melanoma treated with pembrolizumab, Bisschop *et al*. showed longer ORR, PFS, and OS in patients with high-grade toxicity (18). Ishihara *et al*. did not find a significant difference between patients with grade <3 and grade ≥3 irAEs in their study of 47 patients with metastatic renal cell carcinoma treated with nivolumab (8).

Table IV. *Multivariable analysis of the subgroup of patients from the University Hospital in Pilsen: Multivariable Cox model for overall survival (OS), progression-free survival (PFS), and multivariable logistic regression for objective response rate (ORR).*

Category		OS		PFS		ORR	
		HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value	Relative probability of achieving ORR levels of CR or PR (95%CI)	*p*-Value
Age	<65 years	1	0.881	1	0.706	1	0.543
	≥65 years	1.04 (0.60-1.81)		1.10 (0.67-1.80)		0.67 (0.20-2.37)	
Sex	Male	1	0.542	1	0.169	1	0.682
	Female	0.83 (0.45-1.52)		0.69 (0.41-1.17)		1.31 (0.36-4.74)	
Smoking	No/ex-smoker	1	0.182	1	0.349	1	0.2386
	Yes	1.59 (0.80-3.15)		1.37 (0.71-2.63)		0.35 (0.06-2.02)	
Histology	Non-squamous	1	0.995	1	0.471	1	0.890
	Squamous	1.00 (0.56-1.76)		0.83 (0.50-1.38)		0.91 (0.25-3.34)	
ECOG PS	0+1	1	**0.006**	1	**0.018**	1	0.194
	2	2.93 (1.36-6.31)		2.34 (1.16-4.73)		0.28 (0.04-1.91)	
irAEs	No	1	**0.025**	1	**0.003**	1	**<0.001**
	Yes	0.47 (0.24-0.91)		0.42 (0.24-0.74)		14.66 (4.08-52.73)	

Bold values indicate statistical significance. CI: Confidence interval; CR: complete response; ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio; irAEs: immune-related adverse events; PR: partial response; PS: performance status.

We found in the PubMed database three studies dealing with the importance of irAEs severity in a group of patients with NSCLC (16, 19, 20). Shankar *et al*. demonstrated a significant improvement in PFS for patients with both grade ≥3 irAEs in a multivariable analysis (HR=0.34, *p*=0.001) (19). For OS, however, they demonstrated only a nonsignificant trend for patients with grade ≥3 (HR=0.75, *p*=0.434), similar to our study. In their study with 222 patients, Wang *et al*. showed a nonsignificant difference in PFS between patients with mild and severe irAEs (20). In contrast to our results, OS was significantly poorer in patients with severe irAEs compared to in those with mild irAEs. Guezour *et al*. compared OS in patients with *vs*. without grade 3-4 irAEs (16). OS was significantly better in patients who experienced severe irAEs, both in univariable as well as multivariable analysis (in contrast to the mere nonsignificant tendency that we observed). The differences between these results could be explained by the fact that, in addition to the severity of irAEs, the type of adverse effects may also play a role (20, 21). In our study, for example, we demonstrated higher OS in patients with skin irAEs or thyropathies compared to other types of irAEs. Similarly, Wang *et al*. observed different OS according to type of irAEs (20). This phenomenon was demonstrated also by Xing *et al*. in their meta-analysis of patients with NSCLC, where the ORR upon nivolumab therapy in NSCLC patients was positively correlated with the incidence rate of skin, gastrointestinal, and endocrine irAEs but not with the incidence of hepatic, pulmonary, or renal irAEs (21). The different representation of each type of irAEs in the studies cited above could explain the different results for the efficacy of nivolumab treatment in patients with severe irAEs.

Retrospective studies based on databases are more prone to underreporting irAEs after treatment. In the group of all patients, we recorded grade ≥3 adverse events in 6.5% of cases. This is slightly less than in the registration studies with nivolumab, where irAEs were recorded in 7% and 10% of cases (22, 23). This may relate to the fact that all side effects were reported in the registration studies, but not all (*e.g*., fatigue) were necessarily related to the given treatment. On the contrary, only apparently immune-related side effects were reported in our database, and that would explain the small difference in their occurrence compared to registration studies. Conversely, in the more specific subset of patients, where all adverse effects were taken into account, we observed irAEs grade 3 in 14.3% of cases. This is similar to other real-life studies dealing with this topic, where serious irAEs were reported in 7-18% of cases (12, 13, 16, 24).

A limitation of our study is its retrospective design, which may have led to underreporting of milder side effects, especially in the overall cohort of patients. For these reasons, we compared patients with severe irAEs with all other patients in order to eliminate this bias as much as possible. Also, ORR and PFS data may not be completely accurate in registry data. That is why we evaluated only OS-related data in this data set. In a subset of patients, we then chose to have two experienced physicians independently examining the data in order to eliminate this bias to the greatest possible extent. Furthermore, subsequent lines of therapy after progression on nivolumab were not considered, and thus survival data may

be influenced by patients who rapidly progressed on nivolumab or developed serious adverse events resulting in a switch to alternative therapies. In this study, we did not analyze the correlation between the length of treatment and the risk of irAEs inasmuch as it was not a pre-specified endpoint. In our study, however, most irAEs occurred within the first 6 months of immunotherapy treatment, and very few thereafter. That corresponds to the experiences reported in the literature (25). Moreover, in patients with Grade 3-4 irAEs, immunotherapy was interrupted, and patients re-challenged very rarely, thus leading to a short duration of treatment in such patients. That could have interfered with a potential future analysis of the length of immunotherapy treatment.

In conclusion, NSCLC patients with severe irAEs during nivolumab treatment showed significantly better OS, PFS, and ORR in univariable analysis. In multivariable analysis however, we observed a similar trend (but not a statistically significant) toward better OS for patients with severe irAEs. Overall, serious irAEs under nivolumab treatment in NSCLC probably constitute a positive predictive factor. However, this observation does not necessarily apply to all types of irAEs.

Conflicts of Interest

The Authors declare, regarding the publication of the article, that they provided consulting services to the company BMS and had scientific/educational events co-financed by this company. Marek Stastny is an employee of BMS in the position of Medical Advisor.

Authors' Contributions

JB and MSv contributed to data collection, analysis, interpretation, and writing of the manuscript. PH and KH contributed to the interpretation and statistical evaluation of data. MB, JK, MH, MC, PZ, JK, LK, and MSt contributed to sample processing and evaluation, laboratory analysis, and interpretation of the data.

Acknowledgements

This study was supported by the Cooperation Program, research area SURG, by UNCE/MED/006 Charles University — Center of Clinical and Experimental Liver Surgery), by the grant of the Ministry of Health of the Czech Republic - Conceptual Development of Research Organization (Faculty Hospital in Pilsen - FNPl, 00669806), and by the project National Institute for Cancer Research – NICR (Programme EXCELES, ID Project No. LX22NPO5102) - Funded by the European Union - Next Generation EU.

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Received May 21, 2023
Revised June 7, 2023
Accepted June 8, 2023