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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Impact of immune-related adverse events on survival in patients with advanced non-small cell lung cancer treated with nivolumab: long-term outcomes from a multi-institutional analysis

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Abstract

Purpose Immune-checkpoint inhibitors (ICIs) represent the standard of care for platinum-pretreated advanced non-small cell lung cancer patients. Patients treated with ICIs may experience immune-related adverse events (irAEs), that might reflect antitumor responses. Here we evaluated nivolumab efficacy according to the development of irAEs.

Methods We conducted a multicenter retrospective study of patients with advanced NSCLC treated with nivolumab between October 2013 and September 2017. IrAEs were defined as AEs having immunological basis that required intensive monitoring and interventions.

Results Among 195 patients [median (range) age, 63 (30–84) years; 128 men (65.6%), 67 women (34.4%)], irAEs were observed in 85 patients (43.6%), including 15 patients (7.6%) with grade 3 or 4 events. Median PFS was 5.7 months in irAEs group compared to 2.0 months of no-irAEs group [HR: 0.41 (95% CI 0.3–0.57), $P < 0.0001$]. Median OS was 17.8 months compared to 4.0 months of no-irAEs group [HR: 0.33 (95% CI 0.23–0.47), $P < 0.0001$]. IrAEs were significantly associated with improved clinical outcome in 12- and 6-week landmark analysis. Patients who developed ≥ 2 irAEs during treatment (*n*: 37) had a significantly longer median PFS and OS compared to those with one (*n*: 48) or none AEs (*n*: 110) (PFS: 8.5 months vs. 4.6 vs. 2.0, $P < 0.0001$; OS: 26.8 months vs. 11.9 vs. 4.0, $P < 0.0001$). Multivariable analysis revealed that irAEs were positively associated with PFS [HR: 0.48 (95% CI 0.34–0.67), $P < 0.0001$] and OS [HR: 0.38 (95% CI 0.26–0.56), $P < 0.0001$].

Conclusion In this study we confirmed that the development of irAEs was a strong predictor of survival outcomes in NSCLC patients treated with nivolumab monotherapy in landmark and multivariable models. Patients who experienced ≥ 2 irAEs had a more pronounced survival benefit compared to those with 1 irAE further suggesting a mechanistic association between irAEs and immunotherapy efficacy.

Keywords Immune-related AEs · Non-small cell lung cancer · Nivolumab

Introduction

Anti-PD-1 and anti-PD-L1 monoclonal antibodies (mAbs) currently represent the recommended second-line treatment for patients with advanced NSCLC who progress on or following a platinum-based first-line chemotherapy with no actionable driver mutations, having definitely shown to prolong overall survival (OS) compared to cytotoxic chemotherapy in phase III trials (Borghaei et al. 2015; Brahmer et al. 2015).

Differently from standard chemotherapy and targeted therapies, immune-checkpoint inhibitors (ICIs) are associated with the development of unique immune-related adverse events (irAEs). Of note, retrospective studies have

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suggested that the development of irAEs is associated with a survival benefit in patients with advanced melanoma, indicating that the occurrence of such events might reflect anti-tumor responses (Hua et al. 2016; Teulings et al. 2015; Freeman-Keller et al. 2016). The mechanisms underlying this association are still not completely understood, although it has been proposed that a molecular mimicry between melanoma-related antigens and normal melanocytes may contribute to this association (Hua et al. 2016; Teulings et al. 2015; Freeman-Keller et al. 2016; Sanlorenzo et al. 2015). Similarly, recent studies have suggested a similar association in patients with advanced NSCLC (Haratani et al. 2018; Sato et al. 2018; Teraoka et al. 2017). However, these analyses are flawed by several caveats including a short follow-up time and whether the occurrence of irAEs retains a predictive value in NSCLC patients treated with ICIs remains to be confirmed. Against this background, we conducted a multicenter retrospective analysis to investigate the association between the irAEs profile and nivolumab efficacy in patients with advanced NSCLC.

Methods

Study design

Patients with advanced or recurrent NSCLC who had progressed to a first-line platinum-based chemotherapy and had received at least one cycle of nivolumab were eligible for this study. Data were collected from prospectively maintained databases at three participating Institutions.

Patients characteristics included age, Eastern Cooperative Oncology Group (ECOG) performance status (PS), smoking status, histologic type, date of diagnosis of advanced disease, disease stage, central nervous system (CNS) involvement at baseline, genomic alteration (*EGFR, ALK*), treatments received, disease progression, and death or last contact if death had not occurred at the moment of the analysis.

Toxicity was assessed according with Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. IrAEs were defined as having an immunological basis that required intensive monitoring or treatment with immunosuppressive agents or endocrine therapy. Ethical approval for this study was obtained in each Institution and patients provided written informed consent for the collection of clinical information, analysis of their tumor specimens, and collection of clinical outcomes information.

Statistical analysis

Descriptive statistics were reported as frequencies and percentages for categorical variables and as median and range for continuous variables. Association between categorical and continuous variables was assessed by Wilcoxon-Mann-Whitney test or the Kruskal Wallis test, when appropriate. Tumor response was assessed every 6 cycles according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. The χ^2 test was used to determine differences in rates. Progression-free survival (PFS) and overall survival (OS) were calculated from the date of initiation of the first cycle of chemotherapy to the date of disease progression or death, respectively. PFS and OS functions were estimated using the Kaplan–Meier method, and the log-rank test was used to assess differences between groups. Patients who were alive and progression-free were censored at the date of the last follow-up update (March 2018). In light of the lead-time bias due to the time-dependent onset of irAEs we conducted a 12-week landmark analysis of including only patients who were progression free or alive at 90 days after starting nivolumab for PFS and OS, respectively. Seventy-two patients were excluded from the 12-week landmark analysis because of disease progression or death before day 90 of treatment with nivolumab for the analysis of PFS and 50 were excluded because of death before the landmark date for the estimation of OS. A 12-week cutoff was chosen for the primary landmark analysis to evaluate the impact of both early and late-onset irAEs and to minimize the lead-time bias. A complementary 6-week landmark analysis was also carried out to further corroborate the hypothesis. Multivariable analysis was performed using the Cox proportional hazards regression model. A two-sided P value ≤ 0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 24 (SPSS, Chicago, IL, USA).

Results

Characteristics of patients and irAEs profile

One hundred ninety-five patients were enrolled in this study. The median age was 63 years (range 30–84), most of them were male (65.6%), current or former smoker (85.6%), with PS 0/1 (82.1%) and non-squamous histology (78.9%). Patients' characteristics according to the development of irAEs are listed in Table 1. One hundred nineteen patients experienced nivolumab-related AEs. Of them, 85 were defined as having an immunological basis. The overall safety profile of nivolumab in the whole study population is reported in Table 2. Median time to onset of irAEs was consistent with that previously reported in clinical trials and real life-studies (Fig. 1). The distribution over time of individual irAEs is reported in Supplementary Fig. 1. Fifteen patients (7.6%) experienced one or more grade 3 irAEs. No treatment-related deaths were observed in this study. Twenty-two patients required systemic steroids for the treatment of irAEs

Table 1 Patients characteristics according to the development of immune-related adverse events (irAEs)

Characteristics	Number of patients (%)		
	Total (%)	With irAEs (%)	Without irAEs (%)
Number	195	85 (43.6)	110 (56.4)
Median age (range)	63 (30–84)	62 (30–84)	65 (37–81)
Gender			
Male	128 (65.6)	52 (61.2)	76 (69)
Female	67 (34.4)	33 (38.8)	34 (31)
ECOG performance status			
0–1	160 (82.1)	81 (95.3)	79 (71.8)
≥2	35 (17.9)	4 (4.7)	31 (28.2)
Smoking history[a]			
Current/former	167 (85.6)	74 (87.1)	93 (84.5)
Never	28 (14.4)	11 (12.9)	17 (15.5)
Histology			
Non-squamous NSCLC	154 (78.9)	74 (87.05)	80 (72.7)
Squamous NSCLC	41 (21.1)	11 (12.95)	30 (27.3)
Brain metastasis prior to nivolumab			
Yes	46 (23.6)	19 (22.4)	27 (24.5)
No	149 (76.4)	66 (77.6)	83 (75.5)
PD-L1 IHC[b]			
Positive	13 (6.7)	6 (7.1)	7 (6.3)
Negative	38 (19.5)	15 (17.6)	23 (21)
Not assessed	144 (73.8)	64 (75.3)	80 (72.7)
EGFR mutation status[c]			
Positive	16 (8.2)	8 (9.4)	8 (7.3)
Negative	101 (51.8)	44 (51.8)	57 (51.8)
Not assessed	78 (40)	33 (38.8)	45 (40.9)
ALK fusion status[c]			
Positive	1 (0.5)	1 (1.2)	–
Negative	105 (53.8)	49 (57.6)	56 (50.9)
Not assessed	89 (45.6)	35 (41.2)	54 (49.1)
Treatment lines before nivolumab			
1	105 (53.8)	41 (48.2)	64 (58.2)
2	54 (27.8)	29 (34.1)	25 (22.7)
3	18 (9.2)	11 (12.9)	7 (6.4)
≥4	18 (9.2)	4 (4.8)	14 (12.7)

ECOG Eastern Cooperative Oncology Group, *CNS* central nervous system, *EGFR* epidermal growth factor receptor gene, *ALK* anaplastic lymphoma kinase gene; IHC, immunohistochemistry, *PD-L1* programmed cell death ligand 1

[a]Current smokers were defined as individuals who had smoked ≥ 100 cigarettes including at least one within the year prior to the onset of nivolumab treatment; former smokers as those who had smoked ≥ 100 cigarettes but had quit > 1 year prior to the onset of nivolumab treatment; and never-smokers as those who had smoked < 100 cigarettes

[b]PD-L1 status was defined positive when expression levels scored ≥ 1% with IHC; PD-L1 status was defined as "not assessed" in case of not availability of tissue for the analysis

[c]EGFR/ALK status was defined as "unknown" in case of not availability of tissue for the analysis

and one patient received mycophenolate mofetil for the treatment of G3 nivolumab-induced hepatitis.

Association between irAEs and nivolumab efficacy

Patients with irAEs had a significantly higher objective response rate (ORR) and disease control rate (DCR) compared with no-irAEs group (43.5 vs 10.0%, $P < 0.0001$ and

Table 2 Nivolumab-related adverse events according to category and grade

Category	Number of patients (%)			
	Total (%)	Grade 1–2	Grade 3–4	Systemic steroid therapy
Any	119 (61)	118 (60.5)	15 (7.6)	22 (11.3)
Skin				
Rash	18 (9.2)	16 (8.2)	2 (1)	4 (2)
Psoriasis	3 (1.5)	3 (1.5)	NA	1 (0.5)
Pruritus	2 (1)	2 (1)	NA	NA
Dry skin	2 (1)	2 (1)	NA	NA
Skin desquamation	1 (0.5)	1 (0.5)	NA	NA
Paronychia	1 (0.5)	1 (0.5)	NA	NA
Pneumonitis	16 (8.2)	13 (6.6)	3 (1.5)	11 (5.6)
Endocrine				
Hyper/hypothyroidism	39 (20)	39 (20)	NA	NA
Hyperprolactinemia	16 (8.2)	16 (8.2)	NA	NA
ACTH elevation	4 (2)	4 (2)	NA	NA
Gastrointestinal				
Colitis	21 (10.7)	21 (10.7)	NA	3 (1.5)
Amylase increase	15 (7.6)	11 (5.6)	4 (2)	NA
Lipase increase	8 (4.1)	5 (2.5)	3 (1.5)	NA
Nausea/vomiting	8 (4.1)	8 (4.1)	NA	NA
Constipation	1 (0.5)	1 (0.5)	NA	NA
Abdominal pain	2 (1)	2 (1)	NA	NA
Xerostomia	1 (0.5)	1 (0.5)	NA	NA
Hepatobiliary system				
γ-GT	18 (9.2)	14 (7.1)	4 (2)	NA
ALT	16 (8.2)	14 (7.1)	2 (1)	3 (1.5)
AST	16 (8.2)	14 (7.1)	2 (1)	3 (1.5)
Alkaline phosphatase	16 (8.2)	13 (6.6)	3 (1.5)	NA
Other				
Conjunctivitis	2 (1)	2 (1)	NA	NA
Uveitis	1 (0.5)	1 (0.5)	NA	NA
Fatigue	38 (19.4)	37 (18.9)	1 (0.5)	NA
Arthritis	7 (3.5)	7	NA	NA
Polymyalgia rheumatica	1 (0.5)	1 (0.5)	NA	NA
Dermatomyositis	1 (0.5)	NA	1 (0.5)	NA
Anorexia	3 (1.5)	3 (1.5)	NA	NA
Anemia	1 (0.5)	1 (0.5)	NA	NA
Thrombocytopenia	3 (1.5)	3 (1.5)	NA	NA
Neutropenia	1 (0.5)	1 (0.5)	NA	NA

70.5 vs. 18.1%, $P < 0.0001$, respectively) (Supplementary Fig. 2). Median PFS was 5.7 months (95% CI 4.18–7.38) in patients with at least one irAE (*n*: 85) compared with 2.0 months (95% CI 1.69–2.31) of those without irAEs (*n*: 110) [HR: 0.41 (95% CI 0.3–0.57), $P < 0.0001$] (Fig. 2a). Median OS was 17.8 months (95% CI 11.6–24.1) compared to 4.0 months of no-irAEs patients (95% CI 3.32–4.76) [HR: 0.33 (95% CI 0.23–0.47), $P < 0.0001$] (Fig. 2b). When survival outcomes were analyzed according to the number of irAEs developed, patients who developed ≥ 2 irAEs (*n*: 37) had a significantly longer median PFS and OS compared to those with one (*n*: 48) or none AEs (*n*: 110) (PFS: 8.5 months vs. 4.6 vs. 2.0, $P < 0.0001$; OS: 26.8 months vs. 11.9 vs. 4.0, $P < 0.0001$) (Fig. 2c, d). Twelve-week landmark analysis confirmed that the development of irAEs was significantly associated with higher ORR (51.4 vs. 20%, $P = 0.0006$), DCR (84.3 vs. 34%, $P < 0.0001$) and longer median PFS [3.2 vs. 8.0 months, HR: 0.48 (95% CI 0.34–0.69), $P < 0.0001$] and OS [21.4 vs. 7.5 months, HR: 0.4 (95% CI 0.26–0.59), $P < 0.0001$] (Fig. 3a, b). A complementary analysis conducted with a 6-week landmark date showed a trend toward better PFS (5.0 vs. 2.8 months, $P = 0.08$) and a significantly prolonged OS for the irAEs group (17.8 vs. 9.1 months, $P = 0.021$) (Fig. 3c, d). Multivariable analysis confirmed that any irAEs, pneumonitis, colitis and endocrine irAEs were significantly associated with increased PFS and OS, along with a PS of 0–1, age > 70 years and absence of pre-treatment central nervous system (CNS) involvement (Table 3). Twelve patients discontinued treatment because of the development of irAEs. Among them, 11 are alive, have not yet progressed at the time of the analysis and are no receiving other treatments.

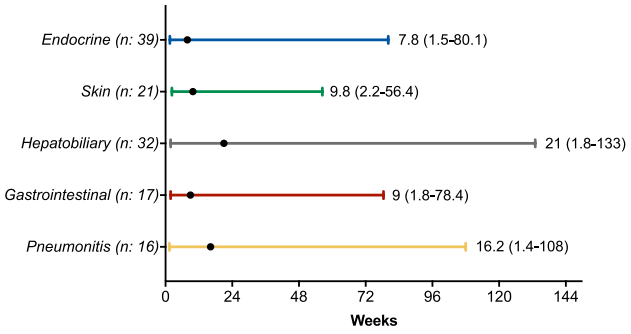

Fig. 1 Time to onset of immune-related adverse events (median with range)

Discussion

In this study the development of irAEs was found to be significantly associated with a better clinical outcome in patients with advanced NSCLC treated with nivolumab. Patients who experienced at least one irAE had significantly higher ORR and DCR and significantly longer PFS and OS as compared to no-irAEs group. In light of time-dependent nature of irAEs we also conducted a 12-week

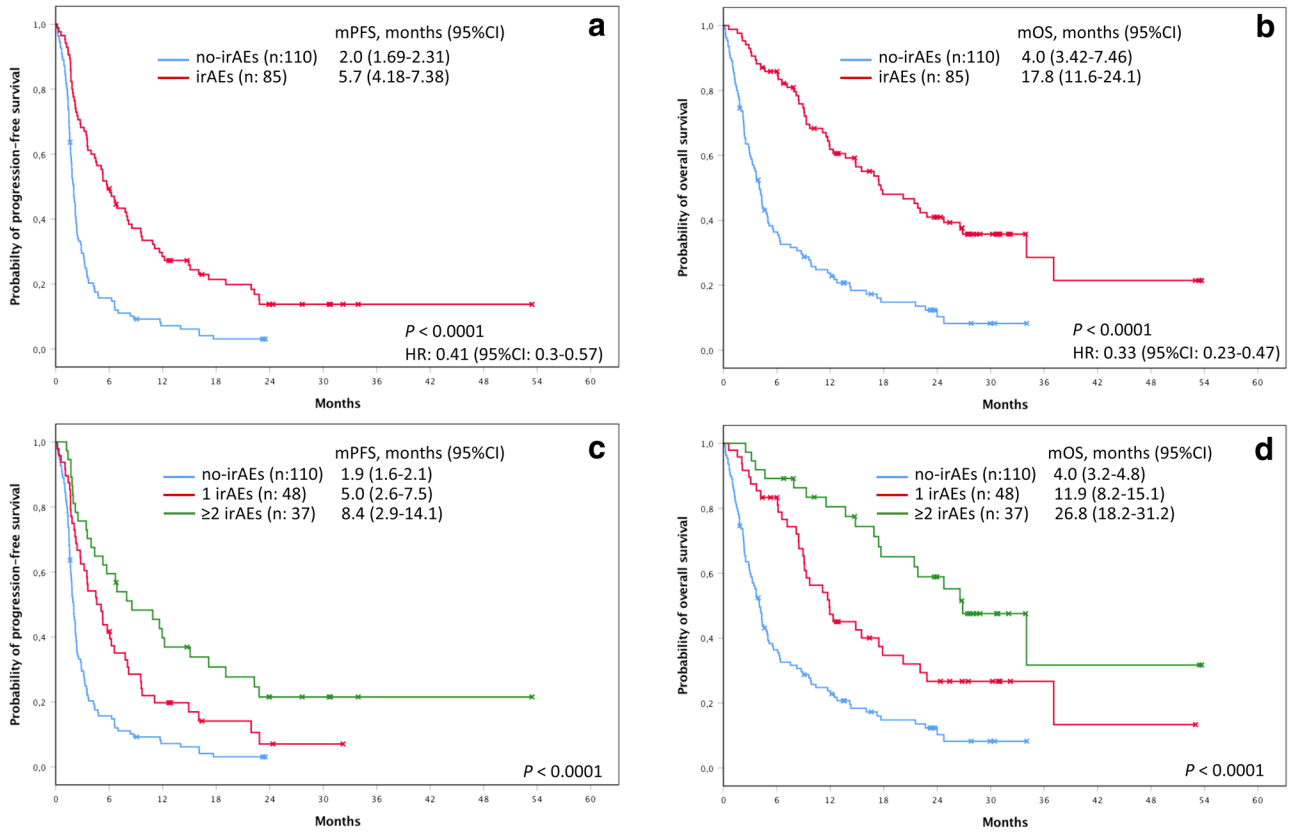

Fig. 2 Kaplan–Meier curves for (**a**) progression-free survival (**b**) and overall survival in patients with or without irAEs. Kaplan–Meier curves for (**c**) progression-free survival (**d**) and overall survival in patients with ≥ 2 irAEs compared to patients with one irAE and no irAEs

landmark analysis which confirmed that the occurrence of irAEs was significantly associated with better ORR, DCR and prolonged median PFS and OS. Consistently, the complementary 6-week landmark analysis that showed a trend toward better PFS (5 vs. 2.8 months, $P = 0.089$) and a significantly prolonged OS for the irAEs group (17.8 vs. 9.1 months, $P = 0.021$), thus further underscoring the relevance of our finding and suggesting that an early onset of irAEs might be predictive of durable clinical benefit in NSCLC patients treated with nivolumab. Detractors may argue that patients with treatment response have a longer exposure time and thus more treatment-related AEs. However, by including only patients with early irAEs in the 6- and 12-week landmark analyses we addressed this potential confounding factor.

Importantly, the development of irAEs was associated with PFS and OS in multivariable analysis, along with known prognostic factors (Table 3), indicating that treatment-related irAEs represent an independent predictor of nivolumab efficacy in NSCLC patients. Previously, several retrospective studies have shown an association between the occurrence of cutaneous irAEs and better outcome in patients with metastatic melanoma (Hua et al. 2016; Teulings et al. 2015; Freeman-Keller et al. 2016; Sanlorenzo et al. 2015). With regard to NSCLC, Haratani and colleagues have recently conducted a retrospective study based on a 6-week landmark analysis on 134 NSCLC patients treated with nivolumab and demonstrated a significant difference in both PFS and OS according to the development of irAEs (Haratani et al. 2018). However, the follow-up of this study was not long enough to address long-term survival outcome. Moreover, in light of the longer median time to onset of most irAEs reported in clinical trials and real-life studies, a 6-week landmark analysis could not correctly estimate the real predictive value of irAEs. In a recent prospective cohort study Takanada et al. demonstrated that NSCLC patients with nivolumab-related irAEs had higher ORR and longer PFS than no-irAE patients (ORR: 37 vs. 17% and PFS: 6.4 months vs. 1.5 months). However, in this study approximately 40% of irAEs consisted into pyrexia or rash, while endocrine AEs were not reported. Conversely, with a median follow-up of 26 months, our study is the first with a mature observation period to address long-term survival outcome. Another important strength of our study is that we expand upon the knowledge about the correlation between irAEs and ICI efficacy to the number of irAEs developed, with

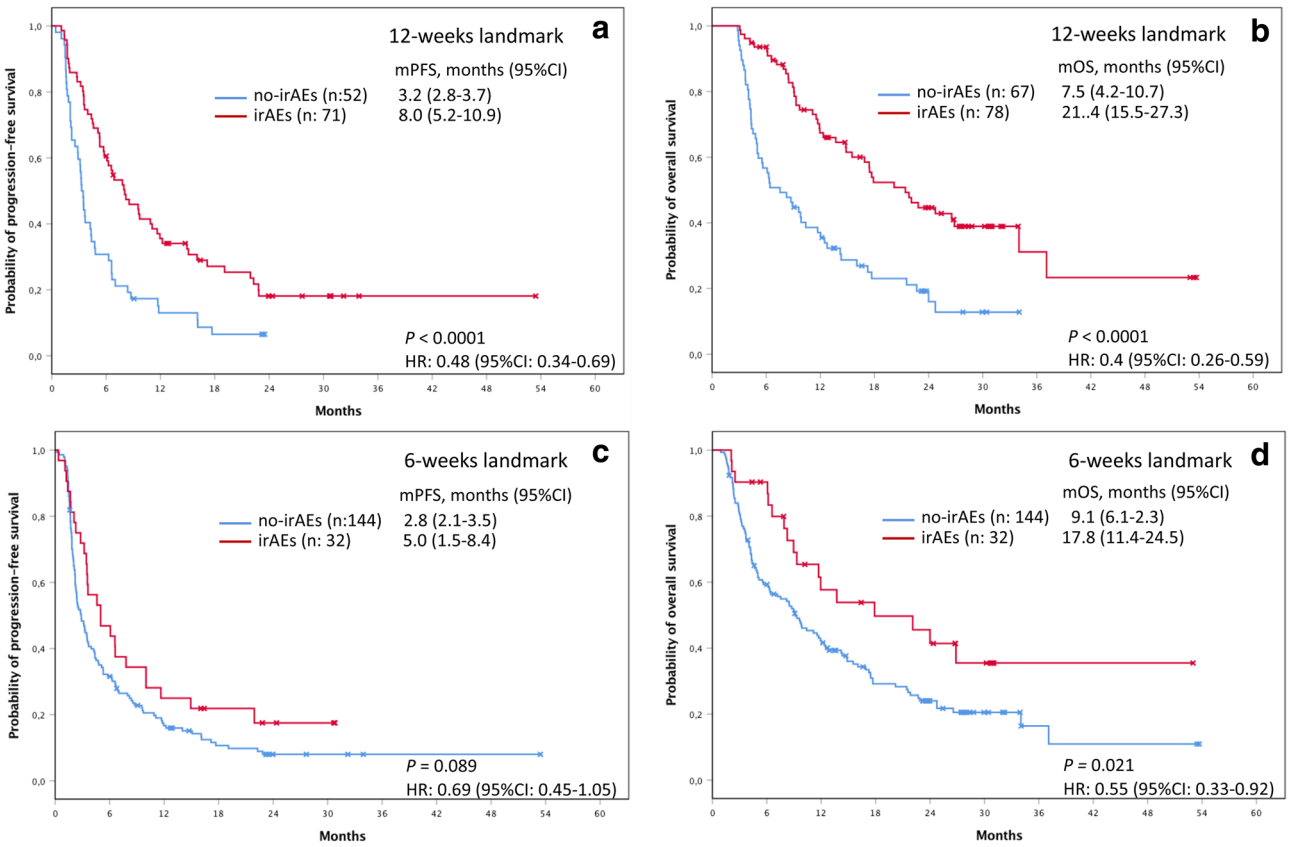

Fig. 3 Kaplan–Meier curves with 12-week landmark analysis for **a** progression-free survival and **b** overall survival in patients with or without irAEs. Kaplan–Meier curves with 6-week landmark analysis for **c** progression-free survival and **d** overall survival in patients with or without irAEs

Table 3 Cox proportional hazard regression analysis of the effect of irAE development on progression-free survival and overall survival

	Univariate hazard ratio (95% CI)	*P* value	Multivariate hazard ratio[a] (95% CI)	*P* value
PFS				
Any	0.41 (0.3–0.57)	$P<0.0001$	0.48 (0.34–0.67)	$P<0.0001$
Lung irAEs	0.54 (0.31–0.92)	$P=0.024$	0.56 (0.33–0.96)	$P=0.038$
Gastrointestinal irAEs	0.45 (0.26–0.77)	$P=0.004$	0.52 (0.3–0.9)	$P=0.021$
Endocrine irAEs	0.5 (0.34–0.72)	$P<0.0001$	0.59 (0.4–0.89)	$P=0.011$
Skin irAEs	0.51 (0.32–0.83)	$P=0.007$	0.57 (0.35–0.95)	$P=0.031$
Hepatobiliary irAEs	0.68 (0.4–1.16)	$P=0.16$	0.72 (0.41–1.24)	$P=0.23$
OS				
Any	0.33 (0.23–0.47)	$P<0.0001$	0.38 (0.26–0.56)	$P<0.0001$
Lung irAEs	0.41 (0.21–0.78)	$P=0.007$	0.46 (0.24–0.89)	$P=0.022$
Gastrointestinal irAEs	0.38 (0.2–0.73)	$P=0.004$	0.5 (0.26–0.98)	$P=0.045$
Endocrine irAEs	0.49 (0.34–0.72)	$P<0.0001$	0.45 (0.28–0.72)	$P=0.001$
Skin irAEs	0.6 (0.36–1.02)	$P=0.06$	0.8 (0.46–1.39)	$P=0.43$
Hepatobiliary irAEs	0.84 (0.48–1.47)	$P=0.55$	0.94 (0.53–1.66)	$P=0.83$

[a]Covariables included in multivariate analysis included those that showed a significant association in univariate analysis: age (< 70 vs. ≥ 70), PS ECOG (0–1 vs. ≥2) and brain metastasis (yes vs. no)

patients experiencing ≥ 2 irAEs showing an unprecedented OS with nivolumab (26.8 months) compared to the other two groups, which indicates that the development of multiple immune-mediated toxicities might reflect sustained anti-tumor responses. The mechanisms underlying this correlation remain to be determined. However, available data seems to suggest a potential molecular mimicry between lung cancer cells and tissues involved in irAEs. Accordingly, in patients with advanced melanoma the development of vitiligo has been reported to correlate with ICIs efficacy, while pneumonitis, colitis and endocrine irAEs were not (Freeman-Keller et al. 2016). Differently, in lung cancer clinical trials the incidence of vitiligo was extremely rare, suggesting that the occurrence of specific irAEs might depend on the type of cancer. On the other hand, another study showed that lymphocyte skin infiltration in patients with skin irAEs was different according to the histological type of NSCLC and correlated significantly with efficacy of nivolumab, further corroborating the hypothesis that antigens sharing may represent the molecular basis of this association (Hasan Ali et al. 2016). However, in our study skin and hepatobiliary irAEs did not correlate with overall survival in multivariate analysis, while lung, gastrointestinal and endocrine irAEs retained a statistically significant association with a longer PFS and OS also in the multivariate analysis. Certainly, some limitation affects our study including the retrospective design and the unknown mutational status of a proportion of patients for *ALK* and *EGFR* genes. However, these genetic alterations are widely recognized to be much more frequent in never smoker patients and in this study there was no imbalance between the two cohorts in term of smoke exposure.

In conclusion, this is the largest study with a mature follow-up to show that the development of irAEs is associated with nivolumab efficacy in patients with advanced NSCLC and to expand upon this correlation to the number of irAEs developed. This study provides relevant insight about the association of anti PD-1 mediated immune toxicities and anti-tumor efficacy. Further studies aimed to investigate the molecular mechanism underling this association will help to improve therapy with ICIs and eventually the management of their toxicities.

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Compliance with ethical standards

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

Conflict of interest The authors have no conflict of interest to disclose.

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