ORIGINAL RESEARCH

High body mass index and pre-existing autoimmune disease are associated with an increased risk of immune-related adverse events in cancer patients treated with PD-(L)1 inhibitors across different solid tumors

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Background: Treatment with anti-PD-(L)1 antibodies, approved for several oncology indications, can lead to immune-related adverse events (irAEs). We aimed to investigate risk factors associated with an increased reporting of irAEs in patients treated with PD-(L)1 inhibitors approved for solid tumor indications.
Patients and methods: A retrospective review was performed of individual data from patients in phase II/III registrational studies for PD-(L)1 inhibitors in solid tumors. Data on baseline characteristics and adverse events were extracted. Univariate and multivariable logistic regression models were used to identify risk factors.
Results: In total, 5123 patients were included from 15 studies reporting on the use of four PD-(L)1 inhibitors for five solid tumor indications. Univariate analysis suggested that type of study drug ($P < 0.001$), indication ($P = 0.003$), body mass index (BMI) ($P = 0.001$), and baseline autoimmune disease ($P < 0.001$) were associated with an increased occurrence of any irAE. Using logistic regression analyses, three factors were identified as increasing the risk of irAE: BMI $\geq$ 30 kg/m^2 [odds ratio (OR) 1.5, 95% confidence interval (CI) 1.2-1.8] in comparison to normal BMI, having an autoimmune disease at baseline (OR 1.8, 95% CI 1.1-2.7), and use of a PD-L1 inhibitor (OR 1.6, 95% CI 1.2-2.0). The latter finding is probably biased due to the selection of the studies in the dataset with complete information on baseline characteristics.
Conclusion: This study was conducted using a large dataset of individual patient data from clinical trials comprising multiple solid tumor indications. We demonstrated that patients with obesity and concurrent autoimmune disease were at increased risk of developing irAEs.
Key words: immune related, adverse event, anti-PD, solid tumor, retrospective, obesity, autoimmune disease

INTRODUCTION

Treatment with anti PD-(L)1 antibodies blocks the ligand—receptor interaction in the tumor environment and thereby facilitates enhanced antitumor immunity by diminishing T-cell inhibitory activity.[1-4] Immune checkpoint inhibitors (ICIs) are a major development in anticancer therapy and PD-(L)1 antibodies have shown anticancer effects in a wide range of cancers and are approved by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) for various oncology indications.

ICIs have a different toxicity profile than conventional cytotoxic chemotherapy, with adverse events (AEs) usually being less severe than those associated with chemotherapies. These AEs in response to immunotherapy and associated with an increased reactivity of the immune system are defined as immune-related adverse events (irAEs). The overall incidence rate of irAEs in patients treated with anti-PD-(L)1 is ~26%, whereas the rate of severe-grade irAE in these patients is 6%.[5] It is important for clinicians to identify the risk of irAEs early on, so that they may be treated when needed or even be prevented.[6-8] Therefore an overview of risk factors that may increase or decrease the incidence and severity of irAEs is helpful.

The aim of this study was to identify risk factors associated with the occurrence or severity of irAEs in patients with solid tumors treated with anti-PD-(L)1 therapy. To our knowledge this is the first study that uses a very large dataset consisting of individual data including multiple PD-(L)1 inhibitors, several indications, and a substantial number

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METHODS

Search strategy

All indications approved by the EMA for inhibitors of PD-1 and PD-L1 monotherapy for the treatment of solid tumors were identified to be included in this study. For approval, clinical study reports had to be submitted by the marketing authorization holder (MAH) within the document management system of the Medicines Evaluation Board (MEB). Availability of individual study patient data of the submitted phase II/III studies was assessed.

Variables of interest

Baseline factors potentially associated with the risk of experiencing an immune event were identified in the available scientific literature.[7,9-13] These included a history of autoimmune disease, cardiovascular medication (antiarrhythmic and antihypertensive medication), antibiotics, central nervous system (CNS)-related medication (anticonvulsants and antipsychotics), thyroid hormones, and body mass index (BMI). The variables of interest were manually extracted from individual data listings in the clinical study report of the individual studies as presented by the MAH, for example, treatment specifics (PD-1 or PD-L1 inhibitor, indication, study identifier), patient characteristics (age [years], gender, PD-L1 expression [%], smoking [yes/no], weight, height, Eastern Cooperative Oncology Group [ECOG] performance status), and data on irAEs (any irAE, type and number of irAE(s), irAE grade $\geq$3).

For easy clinical reference, BMI, age, and comedication were divided into categories; age was divided into categories 18-64, 65-74, and $\geq$75 years and BMI into underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), and obese ($\geq$30 kg/m^2). Groups of comedication belonging to the same functional class were grouped into antiarrhythmics, antihypertensives, anticonvulsants, and antipsychotics (see Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2021.100107).

With respect to PD-L1 expression, there is no uniform cut-off used for PD-L1 positivity between the selected clinical trials. To enable cross-study comparison, a consensus definition was laid upon the individual PD-L1 expression data. The following consensus definition was used: no expression/negative ($<1\%$) or positive ($\geq1\%$) based on PD-L1 expression on tumor cells as provided by the MAH.

Collection of immune-related adverse events

IrAEs were collected according to the definitions given by the MAHs. The criteria used for scoring of any irAE slightly differed among MAHs. Overlapping in the definition was the need for AEs (of special interest) to be categorized by the MAH as 'immune-related AEs', when medical review was considered consistent with an immune-mediated mechanism of action, when the use of systemic steroids or other immunosuppressant or endocrine therapy was required, and when there was no clear alternate etiology. Differences in the definition of irAE between MAHs were related to time dependency of the irAE, varying in that irAE should have started after several days of treatment (thus excluding infusion reactions) or should occur within 30 or 100 days of treatment. Most definitions required immunological, serological, and histological evidence as support. A difference in grade dependency was also observed between MAHs. For example, some MAHs include a specific grade in the definition of irAE or the need of dose modifications or use of systemic steroids, whereas other MAHs did not include this specification. In all dossiers only drug-related irAEs were collected. IrAEs were divided into gastrointestinal (colitis, diarrhea), endocrine (hypothyroidism, hyperthyroidism, adrenal insufficiency), pulmonary (pneumonitis, interstitial lung disease), renal (nephritis, increased blood creatinine), hepatic (alanine and aminotransferase increase, autoimmune hepatitis), skin (different types of rash), hypersensitivity (infusion related reactions), others (any other organ that could be affected but was uncommonly [$\leq2\%$] reported like neurological, ocular, pancreatic, and cardiac), and irAE Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or higher. Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2021.100107, provides an overview of which irAEs belong to which system organ class.

Statistical analysis

Statistical analyses were conducted using IBM SPSS statistical software (version 20.0, Armonk, New York, USA) for Windows. Descriptive characteristics were first explored using frequencies and percentages. Next, potential risk factors for any irAE were assessed by univariate analyses (histograms, crosstabs, and chi-square test). The statistical significance level of univariate analysis was determined by Pearson's chi-square test. A value of $P < 0.05$ was regarded as significant. The selected variables with a significant difference in the univariate analysis were included in the multivariable analysis. Multivariable analyses with logistic regression were used to assess the association between multiple potential risk factors and the occurrence of irAE. Model building was performed in three steps. The first step was to build a 'full' model with irAE as dependent variable and all potential risk factors as covariates. Risk factors with a $P < 0.05$ in the full model were identified and a reduced model including only these factors was compared with the full model. This testing was performed by comparing the difference of -2 log likelihood of the full model and that of the reduced model. Results are shown as odds ratio (OR) and 95% confidence interval (CI) for the significant risk factors.

RESULTS

Selection of clinical trials

Between 2015 and 2018, four PD-(L)1 inhibitors were approved in the European Union as monotherapy for seven
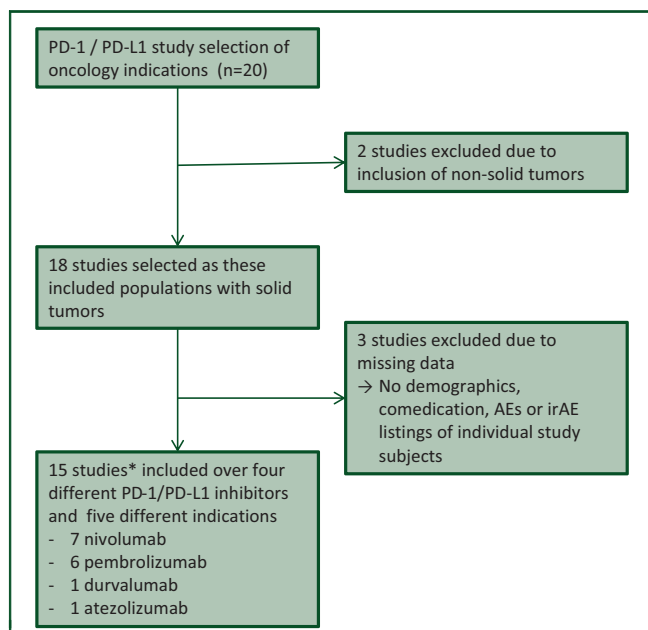
Figure 1. Flowchart for the selection of clinical trials to identify risk factors correlating with immune-related adverse events (irAEs) risk.
*Study name and clinical trial registry numbers (NCT) are available in Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2021.100107.

oncology indications. The dossiers underlying these marketing approvals were based on 20 phase II and phase III studies. In total, five studies were excluded due to the following reasons: indication in non-solid tumors (Hodgkin's lymphoma; n = 2), limited data (n =1), or missing key individual demographic data (n = 2; Figure 1 and Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2021.100107).

Characteristics of trials and study patients

In total, 15 clinical phase II/III monotherapy studies with 5123 study patients (defined as the total study population) across five histologies were included. Four PD-(L)1 antibodies, namely, nivolumab, pembrolizumab, durvalumab, and atezolizumab, were evaluated (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2021.100107). Of the included study patients, 2204 (43.0%) were treated for non-small-cell lung carcinoma (NSCLC), 1038 (20.3%) for melanoma, 988 (19.3%) for urothelial carcinoma, 483 (9.4%) for head and neck squamous cell carcinoma, and 410 (8.0%) for renal cell carcinoma (Table 1). Several clinical trials were performed per PD-(L)1 antibody with variable median treatment duration. The nivolumab studies were performed at a dosage of 3 mg/kg every 2 weeks, with the median treatment duration ranging from 2.6 (CHECKMATE 057) to 6.5 months (CHECKMATE 066). The pembrolizumab studies were performed at a dosage of 2 or 10 mg/kg every 2 or 3 weeks or at a fixed dose of 200 mg every 3 weeks, with the median treatment duration ranging between 85 (KEYNOTE-040) and 183 days (KEYNOTE-006). Both atezolizumab (1200 mg every 3 weeks) and durvalumab (10 mg/kg every 2 weeks) had one single study entry (Supplementary

Table 1. Baseline characteristics of total study population (N = 5123)

Demographic data (N = 5123)	
Category	n (%)
Age (years)	
18-64	2757 (53.8)
65-74	1657 (32.3)
≥75	709 (13.8)
Gender	
Female	1659 (32.4)
Male	3464 (67.6)
Body mass index	
Underweight	197 (3.8)
Normal weight	1865 (36.4)
Overweight	1416 (27.6)
Obese	787 (15.4)
Missing[a]	858 (16.7)
Autoimmune disease	
Yes	112 (2.2)
No	4411 (86.1)
Missing[b]	600 (11.7)
Indication	
Non-small-cell lung carcinoma	2204 (43.0)
Melanoma	1038 (20.3)
Urothelial cell carcinoma	988 (19.3)
Head and neck squamous cell carcinoma	483 (9.4)
Renal cell carcinoma	410 (8.0)
Active drug	
Pembrolizumab	2279 (44.5)
Nivolumab	1768 (34.5)
Atezolizumab	600 (11.7)
Durvalumab	476 (9.3)
PD-1/PD-L1	
PD-1	4047 (79.0)
PD-L1	1076 (21.0)
PD-L1 expression	
<1%	879 (17.2)
≥1%	1788 (34.9)
Missing[a]	2456 (47.9)

Medication overview (N = 5123)			
Usage			
Medication	Yes, n (%)	No, n (%)	Missing, n (%)
Cardiovascular[c]	1988 (38.8)	2535 (49.5)	600 (11.7)
Antibiotics	479 (9.3)	4044 (78.9)	600 (11.7)
Central nervous system[d]	988 (19.3)	3535 (69.0)	600 (11.7)
Steroids	639 (12.5)	3884 (75.8)	600 (11.7)
Allopurinol	145 (2.8)	4378 (85.5)	600 (11.7)
Salicylates	626 (12.2)	3897 (76.1)	600 (11.7)
Thyroid hormones	513 (10.0)	4010 (78.3)	600 (11.7)
Metformin	333 (6.5)	4190 (81.8)	600 (11.7)

[a] Missing due to empty fields in database and no submitted data.
[b] Missing, no data submitted in one study in patients with non-small-cell lung carcinoma.
[c] Includes antiarrhythmic and antihypertensive medications; complete data missing due to incomplete records of one study.
[d] Includes antipsychotics and anticonvulsants; complete data missing due to incomplete records of one study.

Table S2, available at https://doi.org/10.1016/j.esmoop.2021.100107).

As shown in Table 1, more men (67.6%) than women (32.4%) had participated in the clinical trials. In the study population, 2757 (53.8%) were between 18 and 64 years, 1657 (32.3%) between 65 and 74 years, and 709 (13.8%) ≥75 years. Moreover, 1865 (36.4%) patients had a normal weight (BMI 18.5-24.9 kg/m^2), 1416 (27.6%) were overweight (BMI 25.0-29.9 kg/m^2), 787 (15.4%) were obese

Table 2. Baseline characteristics of the compete cases set (*N* = 4265)

Demographic data	
Category	n (%)
Age (years)	
18-64	2286 (53.6)
65-74	1374 (32.2)
≥75	605 (14.2)
Gender	
Female	1351 (31.7)
Male	2914 (68.3)
Body mass index[a]	
Underweight	197 (4.6)
Normal weight	1865 (43.7)
Overweight	1416 (33.2)
Obese	787 (18.5)
Autoimmune disease	
Yes	106 (2.5)
No	4159 (97.5)
Indication	
Non-small-cell lung carcinoma	1441 (33.8)
Melanoma	1003 (23.5)
Urothelial cell carcinoma	964 (22.6)
Head and neck squamous cell carcinoma	467 (10.9)
Renal cell carcinoma	390 (9.1)
PD-1/PD-L1	
PD-1	3913 (91.7)
PD-L1	352 (8.3)

[a] Underweight, normal weight, overweight, and obese are defined as body mass index <18.5 kg/m^2, 18.5-24.9 kg/m^2, 25.0-29.9 kg/m^2, and ≥30 kg/m^2, respectively.

(BMI ≥30 kg/m^2), and 197 (3.8%) were underweight (BMI <18.5 kg/m^2). In this pooled analysis the main come-dication used in the clinical trials was cardiovascular medication, such as antihypertensive and antiarrhythmic drugs (38.8%). Unfortunately the data records were not complete for all study patients, as listings of medication use at baseline and whether a patient had an autoimmune disease were not available for 11.7% of the cases and BMI was not available for 16.7% of the study population. A small group of patients [112 (2.2%)] had an autoimmune disease at baseline (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2021.100107). Cases with missing demographic data were used for the univariate analysis but excluded for the multivariable analysis that used complete cases. Table 2 shows the baseline characteristics of the complete cases set.

PD-L1 expression was available in 2667 patients; 879 (17.2%) patients were scored as having negative expression (<1%) and 1788 (34.9%) as having positive expression (≥1%). In 2456 patients (47.9%) data on PD-L1 expression was missing (Table 1). Because of a large amount of missing data, the PD-L1 expression is not included in further analyses.

Immune-related adverse events

Overall, 19.2% (*n* = 983) of the study population experienced one or more irAE(s) (any grade), of whom 25% (*n* = 246) experienced a grade ≥3 irAE (Figure 2A; see Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2021.100107, for an overview of scored irAEs). irAEs were endocrine related (48%, *n* = 471),

pulmonary related (21%, *n* = 209), skin related (17%, *n* = 164), gastrointestinal related (10%, *n* = 102), hepatic related (5%, *n* = 45), hypersensitivity related (5%, *n* = 54), renal related (2%, *n* = 24), and other (*n* = 38).

To assess which baseline patient-specific risk factors are associated with an increased reporting of irAE during PD-1/PD-L1 therapy, chi-square analyses were performed. Factors significantly associated with developing an irAE (any grade) were BMI (*P* = 0.001), autoimmune disease (*P* < 0.001), targeted indication (*P* = 0.003), and specific study drug (*P* < 0.001; Figure 2B). For all the other factors no association with irAEs could be determined. Risk factors for the development of a grade 3 or higher irAE were autoimmune disease (*P* < 0.001), cardiovascular medication (*P* = 0.004), salicylates (*P* = 0.006), and thyroid hormones (*P* = 0.010; Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2021.100107). For all the other factors (e.g. gender, PD-L1 expression, smoking, ECOG) no association with grade ≥3 irAE was shown.

To further assess the possible association of multiple baseline risk factors and whether there is an increased risk for the development of an irAE, multivariable logistic regression was performed. The multivariable logistic regression was performed in the complete case set that included only study patients for whom all variables of interest were present and thus the dataset was complete. It comprised 83.3% (*n* = 4265) of the total study population (see also Table 2). As a post-hoc sensitivity analysis, univariate analyses were repeated using the complete cases set, which confirmed the statistically significant associations of an irAE with BMI, autoimmune disease, targeted indication, and specific study drug. Within the complete case set, three factors were identified for which the odds of experiencing any grade irAE was significantly increased: patients with BMI ≥30 kg/m^2 (obese) at baseline (OR 1.5, 95% CI 1.2-1.8) compared with normal BMI (18.5-24.9 kg/m^2), use of a PD-L1 inhibitor (OR 1.6, 95% CI 1.2-2.0), and study patients listed as having an autoimmune disease at baseline (OR 1.8, 95% CI 1.2-2.7; Table 3). Patients with an autoimmune disease at baseline (OR 2.9, 95% CI 1.6-5.2) or patients using salicylates at study entry (OR 1.6, 95% CI 1.1-2.3) were more at risk of experiencing a grade ≥3 irAEs (Table 4).

As an exploratory analysis, we investigated whether there was an association between certain risk factors and the occurrence of irAEs within a specific organ system. Univariate associations (*P* < 0.05) are not shown. For outcomes of multivariable regression analyses per organ system, refer to Table 4.

DISCUSSION

In this retrospective study, we used a large dataset of pooled individual patient data from clinical trials of anti PD-(L)1-treated patients to identify risk factors associated with irAE occurrence during treatment. To the best of our knowledge, this is the first study with a very large study population that includes multiple drugs, indications, and possible baseline risk factors for analysis of individual
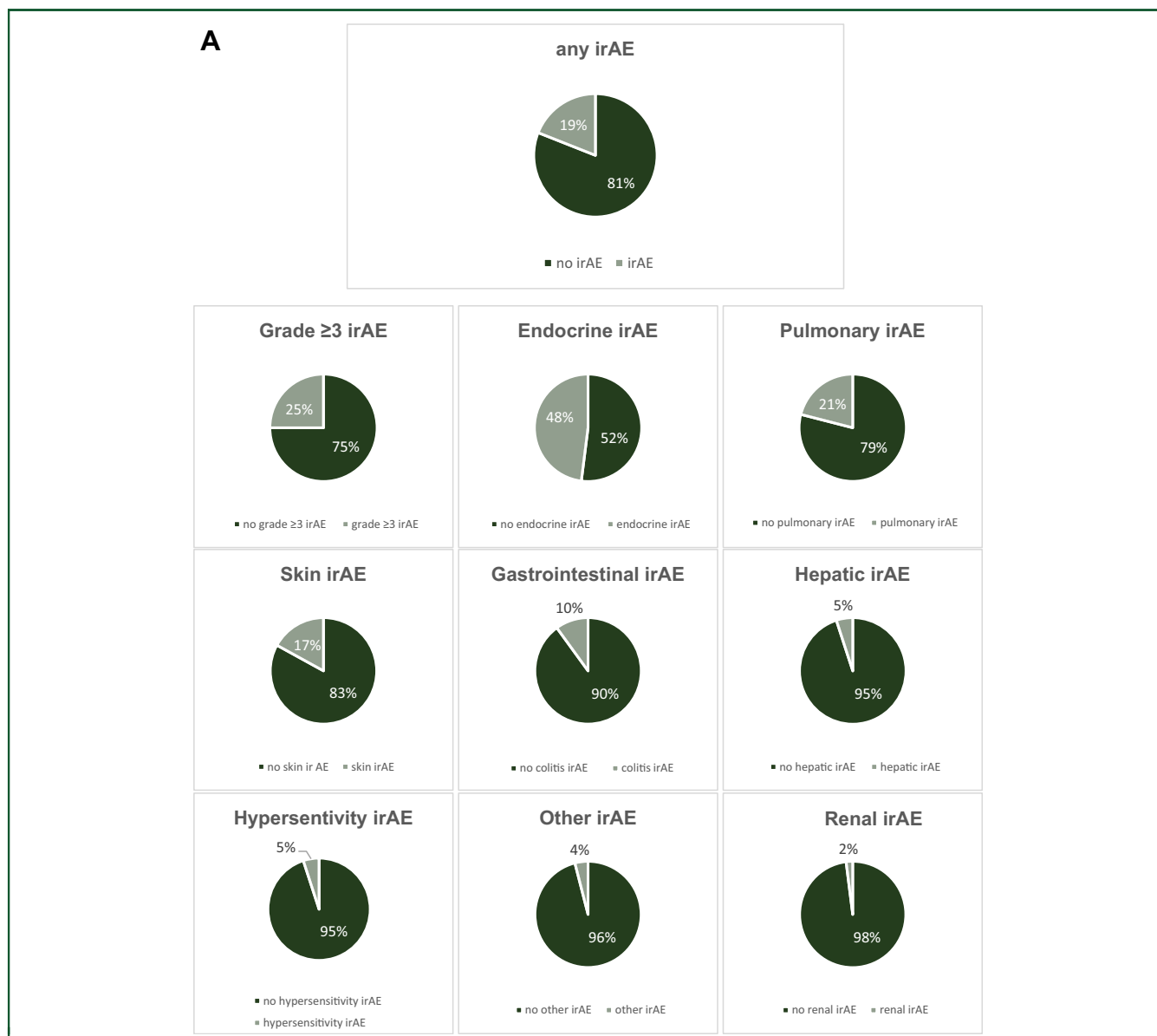
Figure 2. Occurrence of immune-related adverse events (IrAEs) and factors associated with developing any grade irAE in the total study population.
(A) Immune-related adverse events (irAEs) in the total study population. Percentages of subcategories are shown for the population that experienced at least one irAE, which is 19% of the total study population. Others correspond to neurological, ocular, musculoskeletal, and pancreatic categories. Note: One patient could have multiple irAEs in multiple categories, and therefore the sum of the experienced irAEs over the subcategories is not 100%. Refer to Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2021.100107, for the total number of patients per subcategory. (B) Factors significantly associated with developing any grade irAE in the total study population based on chi-square analyses. HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small-cell lung carcinoma; RCC, renal cell carcinoma; UCC, urothelial carcinoma.

patient data from a prospective database systematically documented during the treatment period.

In the study population of 5123 patients, 19% experienced at least one irAE; among these patients, 25% experienced at least one severe irAE (grade ≥3). Our findings are in line with the general incidence rate, which is reported to be ~26%, with 23% being grade ≥3.[14] Based on the final prediction model in the complete case set for risk factors associated with the occurrence of irAEs, three baseline risk factors were identified to be associated with increased odds of experiencing an irAE: being obese, the use of a PD-L1 inhibitor (compared with PD-1 inhibitor), and having an autoimmune disease at baseline. Additional analysis

identified that autoimmune disease and salicylate use were associated with greater odds of developing a grade ≥3 irAE.

Higher BMI has previously been reported to be associated with an increased risk of irAEs for patients treated with PD-1/PD-L1 inhibitors.[15-18] The mechanism behind this association is not entirely clear. Cortellini et al.[16,17] reported an association between high BMI and increased irAEs and additionally reported that responses and survival outcomes were significantly better for overweight/obese patients compared with normal weight patients. The association between BMI and survival has indeed been previously described[19-21] in both patients treated with ICIs and other therapies. However, whether the association between BMI
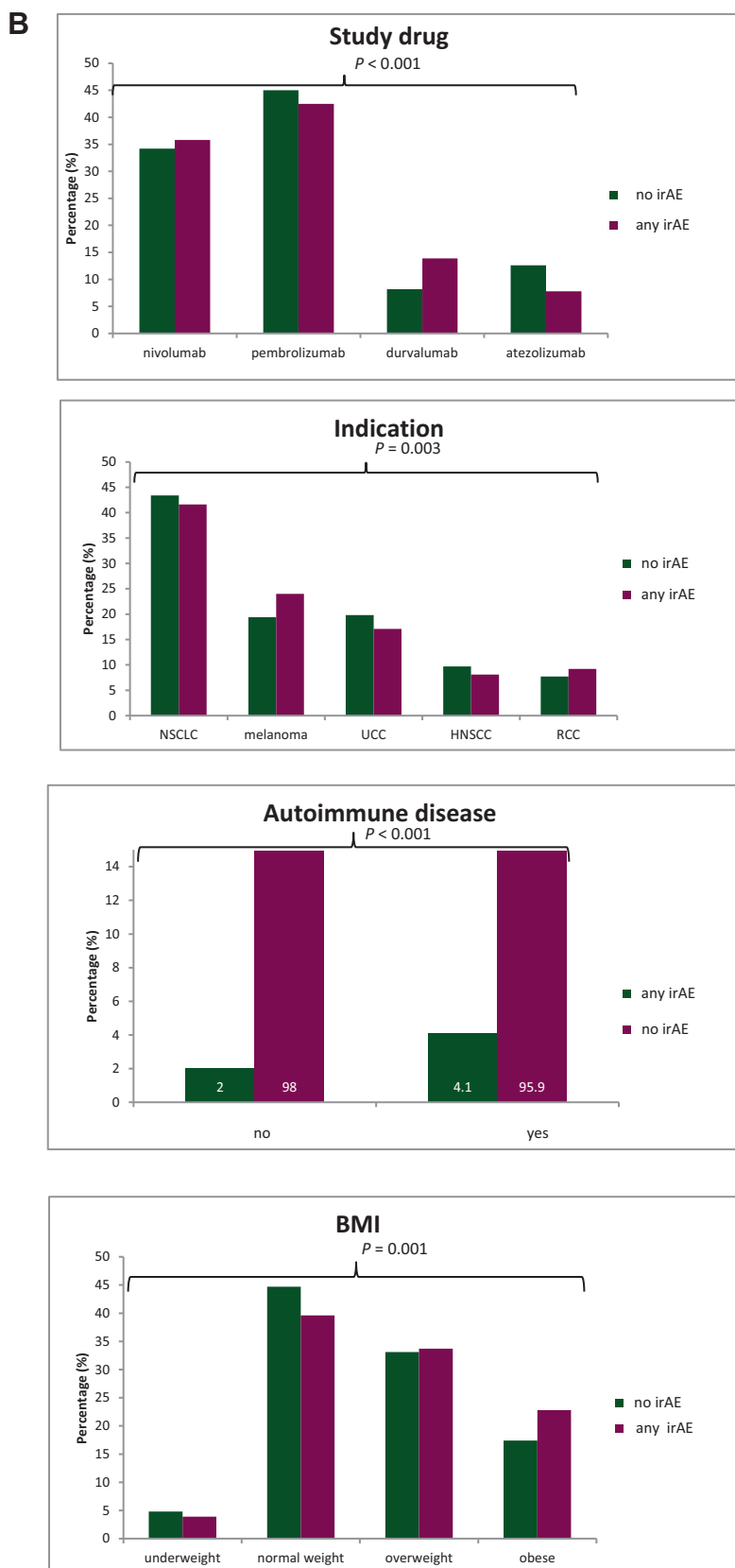
B

Study drug

P < 0.001

- no irAE
- any irAE

Indication

P = 0.003

- no irAE
- any irAE

Autoimmune disease

P < 0.001

- any irAE
- no irAE

BMI

P = 0.001

- no irAE
- any irAE

Figure 2. (Continued)

Table 3. Multivariable logistic regression of baseline factors associated with increased risk for development of any grade irAE

Baseline characteristic	OR	95% CI Lower	95% CI Upper	P value[b]
BMI[a] reference (normal weight)				0.001
BMI underweight	0.92	0.62	1.36	0.667
BMI overweight	1.17	0.98	1.39	0.083
BMI obese	1.49	1.22	1.82	<0.001
PD-1 versus PD-L1	1.59	1.24	2.04	<0.001
Autoimmune disease no versus yes	1.75	1.15	2.67	0.009

Hosmer and Lemeshow results showed chi-square = 0.131; df = 3; P = 0.988. Test population is 83.3% (n = 4265) of the total study population; some data missing due to empty records and non-submitted data. List of scored autoimmune diseases are presented in Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2021.100107.
BMI, body mass index; CI, confidence interval; OR, odds ratio; PD-1, anti PD-1 treatment; PD-L1, anti-PD-L1 treatment.
[a] Underweight, normal weight, overweight, and obese are defined as BMI <18.5 kg/m^2, 18.5-24.9 kg/m^2, 25.0-29.9 kg/m^2, and ≥30 kg/m^2, respectively.
[b] Statistically significant when $P < 0.05$.

and irAEs is an effect of increased survival or exposure to PD-(L)1 inhibitors (e.g. by longer time on treatment or increased exposure due to weight-based dosing) of patients with high BMI remains unknown. Alternatively, because a high BMI leads to a chronic, low-grade obesity-associated inflammation, it could be hypothesized that this may exacerbate immune-related toxicity. Besides, hypotheses regarding obesity-associated increased expression of PD-1/PD-L1 on immune cells, which facilitates targeting by anti-PD-1/PD-(L)1, have been postulated.[9,21,22] Further prospective research on this subject is thus required.

In addition, having an autoimmune disease was associated with an increased risk of developing any grade and severe irAE in patients using a ICI. While the clinical studies used in our analysis had as exclusion criterion 'active autoimmune disease or which requires usage of systemic steroids/immunosuppressants', still 2.2% of the total study population reported having at least one type of autoimmune disease, such as psoriasis or diabetes mellitus type 1. In this group, 33% of the patients experienced any type of irAE and had an increased risk of developing severe irAEs. Other studies also reported an increased risk of developing irAEs in patients with pre-existing autoimmune disease who were treated with ICIs.'[23–26] A retrospective study by Kehl and colleagues[27] showed that hospitalization due to irAE was associated with pre-existing autoimmune disease. Two other studies showed that nonactive/preexisting autoimmune disease did not increase irAE occurrence, but could exacerbate previous autoimmune disease.[28,29] Although it cannot be excluded that in our study exacerbation of an autoimmune disease may have played a role, it should be noted that the aforesaid studies included a different patient population. The previously published studies assessed a smaller population ($N < 125$) and appeared to focus more on patients with autoimmune disease, whereas our study included a more general population of patients undergoing PD-L1/PD-1 therapy, thus enabling a more solid comparison between those with and without pre-existing autoimmune disease and possibly explaining the found differences.

Table 4. Results of logistic regression models of subcategories of irAEs

Subcategory irAE	OR	95% CI Lower	95% CI Upper	P value[b]
Grade ≥3				
Autoimmune disease	2.9	1.6	5.2	0.001
Usage of salicylates	1.6	1.1	2.3	0.012
Endocrine				
BMI[a] category				0.053
Underweight	1.1	0.7	1.8	0.779
Overweight	1.3	1.0	1.6	0.026
Obese	1.4	1.1	1.8	0.017
Study drug category				0.006
Gender male	0.8	0.7	1.0	0.047
Thyroid hormone usage	0.5	0.3	0.7	0.001
CNS medication usage	0.7	0.6	1.0	0.025
Constant	0.1			<0.001
Pulmonary				
Study drug category				<0.001
CNS medication usage	1.5	1.0	2.1	0.029
Constant				<0.001
Gastrointestinal				
BMI category				0.069
Underweight	0.3	0.0	2.1	0.214
Overweight	1.0	0.6	1.6	0.936
Obese	1.7	1.0	2.8	0.440
Study drug category				0.001
Autoimmune disease	2.9	1.2	6.8	0.016
Constant				<0.001
Skin				
Study drug category				<0.001
Indication category				0.009
Melanoma	1.7	1.0	2.8	0.041
Urothelial	0.9	0.5	1.5	0.585
HNSCC	0.8	0.4	1.5	0.446
Renal cell carcinoma	0.2	0.4	1.6	0.547
Constant	0.1			<0.001

The complete case set is 83.3% (n = 4265) of the total study population due to missing data. This set included 199 patients with grade ≥3 irAEs, 439 patients with endocrine irAEs, 161 patients with pulmonary irAEs, 91 patients with gastrointestinal irAE, and 137 with skin irAEs. List of scored autoimmune diseases are presented in Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2021.100107.
BMI, body mass index; CI, confidence interval; CNS, central nervous system; HNSCC, head and neck squamous cell carcinoma; irAE, immune-related adverse event; OR, odds ratio; PD-1, anti PD-1 treatment; PD-L1, anti-PD-L1 treatment.
[a] Underweight, normal weight, overweight, and obese are defined as BMI <18.5 kg/m^2, 18.5-24.9 kg/m^2, 25.0-29.9 kg/m^2, and ≥30 kg/m^2, respectively.
[b] Statistically significant when $P < 0.05$.

Furthermore, for severe irAEs, no studies have been published describing the association of irAE development with multiple risk factors. Evaluating risk factors that are associated with more severe irAEs could be of importance for clinical practice as increased monitoring or precautions could be investigated to mitigate these risks. There was only one small study that investigated factors associated with severe irAEs in patients with NSCLC using univariate analyses, and it concluded that high tumor burden could increase the risk of irAE.[30] Therefore, the results presented here could serve as a good starting point for further in-depth research of the identified combinations of risk factors.

With respect to the finding that study patients being treated with a PD-L1 inhibitor have an increased risk of any irAE occurrence compared with those treated with a PD-1 inhibitor, it should be noted that this finding might be biased due to the selection of studies in the complete cases

set and that the different studies used slightly different criteria to score irAEs. The increased risk of irAEs with the use of a PD-L1 inhibitor was concluded based on multivariable logistic regression performed using the complete cases set. Compared with the total population, mainly patients using a PD-L1 inhibitor were excluded in the complete cases set (see also Table 1) and no association was observed in the total study population. In addition, conflicting findings are reported in the literature. One systematic literature analysis of patients with NSCLC showed that the toxicity profile of PD-1 and PD-L1 inhibitors were similar,[31] whereas another meta-analysis in different cancer types reported a lower incidence of any grade irAE when using PD-L1 compared with PD-1 inhibitors.[15,32,33] The association found in the complete cases set between the use of a PD-L1 inhibitor and the occurrence of irAEs is therefore likely to be biased and definitive conclusions cannot be drawn based on the dataset used in this study.

Previous studies suggest comedication as a possible factor in the development of autoimmunity.[7,11] In our study, comedication was not associated with the development of irAEs in general, although in the exploratory analyses for some specific organ sites, there were medications associated with an increased risk of an irAE. For example, salicylate use was identified as a risk increasing factor for severe irAEs. On the contrary, it is hypothesized that salicylate use could confer a protecting role through immune-suppression mechanisms; however, no clinical studies have yet confirmed this role.[7] A possible explanation could be that salicylate use is confounded with cardiovascular disease or comorbidities, which we could not incorporate into our multivariable model. Furthermore, for endocrine-related irAEs, two types of comedication use at baseline showed a risk decreasing effect: thyroid hormones and CNS-related medication. In the literature, CNS medication has been suggested as a risk increasing factor for the development of autoimmune events.[7] Concerning the effect of thyroid hormones, no studies have been published; however, because a majority of endocrine AEs include hypothyroidism, it can be imagined that the use of thyroid hormones is associated with a decreased risk of these AEs. Of note, for the analyses of comedication the complete case set was used, and therefore may be subject to selection bias while data on comedication use during treatment were not available.

Although our study has the advantage of using a large dataset across a number of different anti PD-(L)1 treatment options, there are several limitations. First, the dataset was generated using available data from clinical studies that were submitted as part of the marketing application dossiers. Even though the database was extensive, not all of the data collected as part of the clinical trials were submitted and the data records were not complete for all study patients. As there was no uniform data collection method between studies, the inclusion of several factors into our database was hindered, such as PD-L1 expression. Besides,

there were small differences in irAE scoring definitions over the studies as described in 'Methods' section. More specifically, some studies scored an irAE when it was above a specific grade or when corticosteroids were needed, while others scored every grade of the same type of irAE. Unfortunately this study did not include an assessment of treatment outcomes such as overall survival and progression-free survival due to incomplete data on an individual level. Finally, since we focused on the outcome of an irAE, it should be recognized that the ability to observe an irAE is dependent on a patient being able to survive long enough to experience an irAE without experiencing another event that led to treatment discontinuation. Unfortunately we were not able to take such competing risks into account in our analysis. While this may have an impact on the understanding of the exact causal relation between the risk factor and irAEs, for clinical practice and management, the interest is focused on the identification of potential risk factors associated with experiencing an irAE. In the example of BMI, if patients with a lower BMI are more at risk of dying earlier, then they are also at lower risk of experiencing an irAE. Thus, it is considered that the methods used to identify risk factors in this study are valid for this research question in the presence of competing risks.

Of note, there are also reports that time dependency of toxicity did not influence survival in advanced melanoma patients experiencing severe toxicity during checkpoint blockade.[17,34] Despite its limitations, the strength of the study is the very large dataset which enabled us to identify clinically relevant associations that may have otherwise been hampered by a lack of power.

We believe that the addition of biological/histological (PD-L1 expression, tumor burden) parameters or efficacy (overall survival) and pharmacokinetic data (exposure) could provide further insight into the development or irAEs. The ultimate goal would be to use this on an individual patient level and translate into the clinic, improving irAE management and allowing to prevent and/or reduce irAE occurrence in cancer patients treated with PD-(L)1 inhibitors.

In conclusion, in this study we showed that patients with BMI ≥ 30 kg/m^2 (obese) in comparison to patients with a normal BMI and patients with an autoimmune disorder at baseline are at an increased risk of developing an irAE across cancer types and study drugs. For severe types of irAEs, our model showed that having an autoimmune disease and salicylate use increase the risk of having an irAE. Although our study indicates that several factors increase the risks for development of irAEs, predicting which patients will or will not develop (severe) irAEs remains a challenge as this is a multifactorial process. Nonetheless, our results are considered relevant due to the large size of the database, the use of studies which have systematically and prospectively collected all AEs, and the assessment of individual patient data taking into account multiple baseline variables.

DISCLOSURE

The authors have declared no conflicts of interest.

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