Original Research

Associations between patient and disease characteristics and severe adverse events during immune checkpoint inhibitor treatment: An observational study

Edwin A. Basak a,*,1, Niels S. Vermeerb,1, Karlijn de Joode a, Daan P. Hurkmansa, Dorian E.M. Velthuis a, Esther Oomen-de Hoopa, Marco W.J. Schreurs c, Sander Bins a, Stijn L.W. Koolena,b, Reno Debets a, Astrid A.M. van der Veldta,d, Joachim G.J.V. Aertsc, Arjen Joossea, Ron H.J. Mathijssena

a Dept. of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, the Netherlands
b Dept. of Hospital Pharmacy, Erasmus University Medical Center, Rotterdam, the Netherlands
c Dept. of Immunology, Erasmus University Medical Center, Rotterdam, the Netherlands
d Dept. of Radiology and Nuclear Medicine, Erasmus University Medical Center, Rotterdam, the Netherlands
e Dept. of Pulmonology, Erasmus University Medical Center, Rotterdam, the Netherlands

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Abstract  Aim: With increasing use of immune checkpoint inhibitors (ICIs) more patients will develop severe and potentially life-threatening immune-related adverse events (irAEs). So far, predictive models for the occurrence of grade ≥3 irAEs are lacking. Therefore, we analysed associations between patient and disease characteristics, and the occurrence of grade ≥3 irAEs.

Methods: Patients with cancer who were treated with anti-PD-1 (+/- anti-CTLA-4) between July 2015 and February 2020, and who were prospectively included in the MULTOMAB-trial, were eligible for this cohort study. Time to and occurrence of grade ≥3 irAEs according to CTCAE v5.0 were retrospectively registered. The associations between patient and disease characteristics and irAE occurrence were analysed using the competing risk cox-regression model of Fine and Gray. Analyses were performed separately in patients treated with monotherapy (anti-PD-1) and combination therapy (anti-PD-1 + anti-CTLA-4). Subgroup analyses were performed in tumour types with the highest number of patients; melanoma and NSCLC.

* Corresponding author: Dept. of Medical Oncology, Erasmus MC Cancer Institute, PO Box 5201, 3008 AE Rotterdam, the Netherlands. Fax: +31 10 704 10 03.
E-mail address: e.basak@erasmusmc.nl (E.A. Basak).
1 Both authors contributed equally.

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1. Introduction

Immune checkpoint inhibitors (ICIs) blocking programmed cell death 1 (PD-1) or cytotoxic T lymphocyte-associated antigen (CTLA-4) such as nivolumab, pembrolizumab, and ipilimumab can cause immune-related adverse events (irAEs). Examples of irAEs are dermatitis, hepatitis, colitis, pneumonitis, hypophysitis, and thyroiditis [1,2], although virtually every organ system may be affected. Despite anti-PD-1 monotherapy being tolerated by the majority of patients, around 7–20% of the patients experience grade 3 or higher adverse events (SAEs) graded according to Common Terminology Criteria for Adverse Events (CTCAE) [3–8]. When anti-PD-1 therapy is combined with anti-CTLA-4, up to 55% of the patients experience grade $\geq$ 3 irAEs [6].

SAEs may have various serious consequences. First, in a small fraction of patients, SAEs may lead to mortality. Second, SAEs may require life-long treatment, e.g. hydrocortisone replacement therapy in adrenal failure or hypophysitis. Third, anti-cancer treatment may be delayed or permanently discontinued due to SAEs, precluding further treatment with a potentially effective drug. Fourth, patients may also experience a significant impact on quality of life due to irAE consequences. This might become more relevant, now that ICIs are used in lower disease stages (e.g. in an adjuvant setting), where patients already received treatment with curative intent. Also, immunosuppressants such as prednisone or infliximab may be necessary to resolve irAEs [1], which may be accompanied by (potentially long-term) side effects of their own. Moreover, for infliximab, a negative impact on treatment outcomes has been described for patients with melanoma [9]. Finally, fatal irAEs may occur in a small number of patients: from 0.36% in patients receiving anti-PD-1 monotherapy up to 1.23% when receiving combination therapy [10]. Therefore, predictive models to identify patients who do not tolerate ICIs are urgently needed.

Some biomarkers are associated with a higher risk of irAEs during anti-PD-1 therapy, such as high tumour mutational burden, possibly due to differences in neo-antigenic load between cancer types [11]. Moreover, for example, the neutrophil-to-lymphocyte ratio was associated with irAEs in solid tumours [12]. Recently, activated CD4 memory T cells and TCR diversity has been linked to severe irAE occurrence [13]. Also, the occurrence of specific irAEs differs between cancer types. Possibly due to different neoantigen profiles between those tumour types [14]. However, since most biomarkers have yet failed to sufficiently predict the onset of severe irAEs [15], we aimed to investigate the association of readily available clinical parameters with the occurrence of severe irAEs. Therefore, we studied associations between SAEs and patient and disease characteristics in a large real-life cohort of patients receiving anti-PD-1 therapy with or without anti-CTLA-4 therapy.

2. Materials and methods

2.1. Patient selection

Patients with cancer starting anti-PD-1 treatment with or without anti-CTLA-4 between July 2015 and February 2020, who were prospectively included in the MULTOMAB-trial (Dutch Trial Register Number NTR7015; trialsearch.who.int), and treated at the Erasmus Medical Center (Rotterdam, the Netherlands) were eligible for this cohort study. The local ethics committee of the Erasmus Medical Center approved the study (METC 16-011). The only exclusion criteria for the MULTOMAB-trial is the inability to draw blood for study purposes. All patients were followed for the occurrence of grade $\geq$ 3 irAEs until loss of follow-up, death, or data lock point (August 2020).

2.2. Data classification and outcome definition

All data were retrospectively collected from the hospitals’ electronic patient record system. The following baseline characteristics were collected: tumour type, sex, age at treatment start, type of administered ICI, World Health Organisation (WHO) performance status, lactate dehydrogenase (LDH) level, number of organ sites with metastases, the presence of brain metastases, number of...
prior treatment lines, treatment setting (e.g. adjuvant therapy), and non-small cell lung cancer (NSCLC) histology. Missing data were not imputed.

The presence of an SAE, defined as a grade ≥3 irAEs, was based on the grading by the clinician and was recorded from the electronic patient record system from the start of treatment until the end of follow-up. Grades of irAEs were scored using CTCAE v5.0. Furthermore, time from treatment start until onset of the first SAE was noted. To characterise each SAE, the type of clinical management was noted (e.g. prednisone), as well as its consequence regarding ICI therapy (e.g. temporary discontinuation) and outcome (recovered, ongoing, or fatal). Only SAEs related to ICI therapy and that were not pre-existent were included.

2.3. Data analysis

The relationship between baseline clinical parameters and the risk of SAEs was retrospectively studied by means of the proportional hazards model for the subdistribution as described by Fine & Gray [16] where the occurrence of death before SAE onset was regarded as a competing risk. As the risk of SAEs varies substantially between mono- and combination ICI therapy, analyses were conducted separately for these groups. As SAE occurrence might also differ between tumour types, further subgroup analyses were performed for tumour types with the highest number of patients in our cohort: NSCLC and melanoma in the monotherapy cohort and melanoma in the combination therapy cohort.

The following variables were included in the analysis for all cohorts: age, sex, number of prior treatment lines, WHO performance status, type of anti-PD-1, number of organ sites with metastases, and presence of brain metastases. Additionally, tumour type was included as a variable for the monotherapy and combination therapy cohorts, histological type of NSCLC for the monotherapy cohort, whereas treatment setting (i.e. adjuvant treatment versus treatment for metastatic disease) was included for the melanoma monotherapy cohort, and LDH level for the melanoma monotherapy and combination therapy cohorts.

All variables were univariately tested for their association with the occurrence of first SAEs. Variables with a p-value <0.1 in univariable analyses were selected for multivariable analyses where backward selection was applied with a threshold of p <0.05. Categories with <10 patients were excluded.

A sensitivity analysis was performed to investigate any interference of follow-up time in patients with SAEs versus those without SAEs, therefore all analyses were duplicated excluding patients with <3 months of follow-up. Furthermore, treatment duration between patients with and without SAEs was compared using the Mann–Whitney U test.

All clinical data were captured using OpenClinica. Statistical analyses were performed using IBM SPSS Statistics, v25 (Chicago, IL) and STATA (v 16.1 StataCorp.; College Station, TX). A p-value <0.05 was considered statistically significant.

3. Results

A total of 641 patients who started ICI therapy between July 2015 and February 2020 were prospectively included (see Table 1). The indication for ICI therapy was melanoma in 293 (46%) patients, NSCLC in 181 (28%), mesothelioma in 71 (11%), renal cell carcinoma in 65 (10%), and urothelial cell carcinoma (UCC) in 31 (5%) patients. Overall, 226 (35%) patients were female, and the median age at treatment initiation was 66 (IQR: 58–72) years. A total of 550 patients (86%) were treated with nivolumab (n = 393) or pembrolizumab (n = 157) monotherapy, and 91 (14%) patients were treated with nivolumab–ipilimumab combination therapy, of whom 62 patients (68%) were treated with ipilimumab 3 mg/kg and 29 (32%) with ipilimumab 1 mg/kg. Out of all patients treated in the palliative setting, for 319 (59%) patients ICI therapy was the first line of treatment. A total of 58 melanoma patients received ICI monotherapy in an adjuvant setting. Patients with NSCLC were frequently treated with one or more prior lines of systemic therapy (146 out of 181; 81%), and had a WHO performance status of 2 or higher in 10% of cases (n = 18). Median follow-up time was 10.3 months (IQR: 5.6–18.9).

Overall, 106 patients developed a total of 129 CTCAE grade 3 or higher irAEs during follow-up, most frequently gastro-intestinal toxicity (n = 37), hepatitis (n = 21), skin toxicity (n = 15), pneumonitis (n = 13), and renal toxicity (n = 11) (see Table 2). One event of myocarditis had a fatal outcome and five events concerned grade 4 irAEs (including colitis n = 2, hepatitis, hyperglycemia and myositis). Details of grade ≥4 irAEs are shown in Supplementary Table 1. The remaining 123 (95%) events were grade 3 irAEs. The median time to onset was 2.1 months, and ranged by type of reaction from a median of 0.9 months (neurological autoimmune disease) to a median of 7.5 months (rheumatic disease; see Fig. 1).

The overall incidence of SAEs was higher among patients receiving combination therapy with ipilimumab (40 out of 91 patients; 44%) as compared to patients receiving monotherapy (66 out of 550 patients; 12%). Of the 62 patients receiving ipilimumab 3 mg/kg, 31 patients experienced SAEs (50%), whereas 9 out 29 patients receiving ipilimumab 1 mg/kg had an SAE (31%). Of all patients treated with anti-PD-1 monotherapy or anti-PD-1 and anti-CTLA-4 combination therapy, no variables were significantly associated with the occurrence of SAEs (Table 3). In the subgroup analysis, no
variables were associated with the occurrence of SAEs in patients with melanoma or NSCLC receiving monotherapy (Supplementary Table 2) or melanoma patients receiving combination therapy (Supplementary Table 3). However, out of 34 patients with NSCLC with a WHO performance score of 0 none developed SAEs. Whereas of 118 patients with NSCLC with a WHO performance score above 0, 20 developed SAEs (17%). Therefore, this variable could not be analysed in NSCLC patients. One category contained <10 patients and was therefore excluded from analysis (being giant-cell NSCLC histology).

In the sensitivity analysis, no variables were significantly associated with SAEs. Median treatment duration between patients with and without SAEs were comparable in both the monotherapy (5.1 versus 5.0 months, p = 0.883) and combination therapy cohorts (2.5 versus 2.8 months, p = 0.474).

Most SAEs were treated with prednisone (dose range 0.1–2.0 mg/kg; 106 out of 129; 82%), and led to temporary discontinuation of ICI treatment (in 45% of the cases). Furthermore, most irAEs fully recovered (75%; Supplementary Table 4).

4. Discussion

Our analysis shows that patient and disease characteristics are not able to predict the occurrence of SAEs in patients treated with ICIs. Of the patients with melanoma treated with anti-PD-1 monotherapy, 31 patients (13%) developed SAEs, which is consistent

| Table 1
| Baseline characteristics of study population (n = 641). |
|-----------------|-----------------|-----------------|-----------------|
|                 | Total cohort (n = 641) | Monotherapy (n = 550) | Combination therapy (n = 91) |
|                 | NSCLC (n = 181) | Melanoma (n = 231) | NSCLC (n = 62) |
| **Sex, n (%)** | Male 415 (65%) | 356 (65%) | 103 (57%) | 140 (61%) | 59 (65%) | 37 (60%) |
|                 | Female 226 (35%) | 194 (35%) | 78 (43%) | 91 (39%) | 32 (35%) | 25 (40%) |
| **Age at start of treatment** | ≤65 years 316 (49%) | 252 (46%) | 92 (51%) | 110 (48%) | 64 (70%) | 48 (77%) |
|                 | >65 years 325 (51%) | 298 (54%) | 89 (49%) | 121 (52%) | 27 (30%) | 14 (23%) |
| **Drug treatment, n (%)** | Nivolumab 393 (61%) | 393 (72%) | 128 (71%) | 170 (74%) | 0 (0%) | 0 (0%) |
|                 | Pembrolizumab 157 (24%) | 157 (29%) | 53 (29%) | 61 (26%) | 0 (0%) | 0 (0%) |
|                 | Nivolumab + ipilimumab 91 (14%) | 0 (0%) | 0 (0%) | 0 (0%) | 91 (100%) | 62 (100%) |
| **WHO performance status** | 0 258 (40%) | 214 (39%) | 34 (19%) | 145 (63%) | 44 (48%) | 33 (53%) |
|                 | 1 287 (45%) | 247 (45%) | 100 (55%) | 64 (28%) | 40 (44%) | 25 (40%) |
|                 | 2 34 (5%) | 29 (5%) | 17 (9%) | 4 (2%) | 5 (6%) | 2 (3%) |
|                 | 3+ 1 (0.2%) | 1 (0%) | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) |
|                 | Unknown 61 (10%) | 59 (11%) | 29 (16%) | 18 (8%) | 2 (2%) | 2 (3%) |
| **LDH ≤1× ULN** | 345 (54%) | 300 (55%) | 42 (23%) | 166 (72%) | 45 (49%) | 25 (40%) |
| **LDH >1× ULN** | 166 (26%) | 120 (22%) | 40 (22%) | 60 (26%) | 46 (51%) | 37 (60%) |
| **LDH Unknown** | 130 (20%) | 130 (24%) | 99 (55%) | 5 (2%) | 0 (0%) | 0 (0%) |
| **No. of organ sites with metastasis** | 0 118 (18%) | 114 (21%) | 13 (7%) | 62 (27%) | 4 (4%) | 2 (3%) |
|                 | 1 169 (26%) | 146 (27%) | 53 (29%) | 51 (22%) | 23 (25%) | 11 (18%) |
|                 | 2 166 (26%) | 147 (27%) | 64 (35%) | 56 (24%) | 19 (21%) | 12 (19%) |
|                 | 3 120 (19%) | 100 (18%) | 39 (22%) | 42 (18%) | 20 (22%) | 15 (24%) |
|                 | 4 45 (7%) | 32 (6%) | 8 (4%) | 15 (7%) | 13 (14%) | 11 (17%) |
|                 | ≥5 22 (3%) | 10 (2%) | 4 (2%) | 5 (2%) | 12 (13%) | 11 (17%) |
| **Brain metastasis** | Yes 52 (8%) | 35 (6%) | 19 (11%) | 15 (7%) | 17 (19%) | 17 (27%) |
|                 | No 588 (92%) | 514 (94%) | 161 (89%) | 216 (94%) | 74 (81%) | 45 (73%) |
| **No. of prior treatment lines** | Unknown 1 (0%) | 1 (0%) | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) |
| **No. of prior treatment lines** | 0 319 (50%) | 245 (45%) | 34 (19%) | 204 (88%) | 74 (81%) | 45 (73%) |
|                 | 1 252 (39%) | 235 (43%) | 120 (66%) | 25 (11%) | 17 (19%) | 17 (27%) |
|                 | 2 61 (10%) | 61 (11%) | 23 (13%) | 2 (1%) | 0 (0%) | 0 (0%) |
|                 | 3 8 (1%) | 8 (2%) | 3 (2%) | 0 (0%) | 0 (0%) | 0 (0%) |
| **Brain metastasis** | Unknown 1 (0%) | 1 (0%) | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) |
| **Treatment setting** | Adjuvant 58 (9%) | 58 (11%) | 0 (0%) | 58 (25%) | 0 (0%) | 0 (0%) |
with earlier findings (5–19%) [17,18]. Regarding NSCLC, SAE occurrence in our cohort (n = 25; 13%) was comparable to earlier studies (7–27%) [3,7,19,20]. The number of SAEs in the melanoma combination therapy groups was close to those reported in the CheckMate-067 phase 3 clinical trial (50% versus 55%) [6]. In all our cohorts, gastro-intestinal irAEs were the most occurring severe irAEs. While skin toxicities have been reported as the most occurring irAEs in literature, gastro-intestinal irAEs were shown to be the most occurring severe irAEs [1]. The median time until onset of most types of irAEs was within three months, as is described earlier [1]. However, small discrepancies exist regarding median time to onset in our cohort compared to literature for some irAEs, e.g. neurological AEs and nephritis [21,22]. This is possibly due to a different distribution across monotherapy and combination therapy in our cohort and low numbers of cases experiencing those irAEs.

Studies using real-world data generated conflicting results regarding the association between age and irAEs. A previous analysis regarding patients with melanoma treated with anti-PD-1 monotherapy showed no association between age and SAEs [17]. Other studies also did not demonstrate a significant relationship between age and irAEs [23–26]. However, two studies found significantly more AEs in either older or younger patients, depending on which type of AEs was investigated [27,28]. Looking at the association between sex and AEs, two studies found an increased risk for either men or women for specific types of AEs [29,30]. However, again, many other studies have found no association between sex and AEs at all [17,25,26,31–33]. Those conflicting outcomes per investigated type of AEs underline the caution that should be taken when interpreting relationships between AEs and patient characteristics. Our study showed no association with age or sex and SAE occurrence, confirming that they are

| Type of reaction | Total number of events | Median time to onset, months (range) | Number of events, n (%) | Monotherapy | Combination therapy |
|------------------|------------------------|-------------------------------------|-------------------------|-------------|---------------------|
|                  |                        |                                     |                         | Total (n = 550) | Melanoma (n = 231) | NSCLC (n = 181) | Total (n = 91) |
| Colitis, diarrhoea | 37                     | 1.8 (0.2–21)                       | 22 (4.0%)               | 13 (5.6%)   | 8 (4.4%)            | 15 (16%)       |
| Hepatitis, ALAT and/or ASAT increase | 21 | 2.2 (0.6–14.8) | 10 (1.8%) | 2 (0.9%) | 7 (3.9%) | 11 (12%) |
| Dermatitis, rash | 15                     | 1.3 (0.2–13.8)                    | 9 (1.6%)                | 4 (1.7%)    | 3 (1.7%)            | 6 (7%)         |
| Pneumonitis      | 13                     | 2.8 (0.2–20.6)                    | 9 (1.6%)                | 2 (0.9%)    | 5 (2.8%)            | 4 (4%)         |
| Nephritis, acute kidney injury | 11 | 2.7 (0.7–5.8) | 5 (0.9%) | 2 (0.9%) | 1 (0.6%) | 6 (7%) |
| Neurological autoimmune disease | 9 | 0.9 (0.2–11.5) | 5 (0.9%) | 4 (1.7%) | – | 4 (4%) |
| Pancreatitis b | 5                      | 5.8 (3.4–22.0)                    | 3 (0.5%)                | 1 (0.4%)    | 1 (0.6%)            | 2 (2%)         |
| Hyperglycemia b | 5                      | 1.6 (0.6–22.6)                    | 4 (0.7%)                | 2 (0.9%)    | –                  | 1 (1%)         |
| Rheumatic disease | 4                  | 7.5 (2.6–23.7)                    | 4 (0.7%)                | 4 (1.7%)    | –                  | –              |
| Thyroiditis      | 2                      | 1.7 (0.7–2.8)                     | 2 (0.4%)                | 1 (0.4%)    | 1 (0.6%)            | –              |
| Other c         | 7                      | 0.6 (0.3–1.3)                     | 4 (0.7%)                | 2 (0.9%)    | –                  | 3 (3%)         |
| **Total number of SAEs** | **129** | **1.9 (0–23.7)** | **75** | **35** | **26** | **51** |
| **Number of patients with SAEs** | **106** | **66 (12%)** | **31 (13%)** | **25 (13%)** | **40 (44%)** |

* a Median time to onset taking into account the concerning events.
* b Pancreatitis/hyperglycemia: 2 patients experienced both pancreatitis and hyperglycemia.
* c Other events included (all reported once): hemophagocytic lymphohistiocytosis, graft versus host disease, infusion reaction, febrile neutropenia, metabolic acidosis, fever, and myocarditis.

Fig. 1. Time to onset of SAEs since treatment initiation. Box represents 25 to 75th percentile, whiskers represent 5th to 95th percentile. The dots show the outliers.
not to be used for clinical decision-making in daily practice.

Contradicting results regarding the relationship between tumour burden or disease stage and the risk of irAEs have been described for different tumour types [18,34,35]. For patients with melanoma, a lower disease stage was associated with more severe irAEs [17]. While a pooled analysis showed no association between NSCLC disease stage and AEs due to ICIs [36]. Furthermore, more AEs were seen in the adjuvant setting compared to anti-PD-1 treatment in advanced disease [18,35]. On the contrary, for NSCLC, a high tumour burden was associated with severe irAEs [34].

Table 3
Investigated variables and their correlation with the occurrence of a first ≥grade 3 irAEs in the total monotherapy cohort and total combination therapy cohort.

| Variables                          | Total monotherapy cohort (n = 550) | Total combination therapy cohort (n = 91) |
|-----------------------------------|-----------------------------------|----------------------------------------|
|                                   | Events/total (%) | Univariable | Events/total (%) | Univariable |
|                                   | sHR (95% CI)     | P-value     | sHR (95% CI)     | P-value     |
| **Tumour type**                   |                    |             |                    |             |
| Melanoma                          | 30/231 (13%)       | Ref         | 31/62 (50%)       | Ref         |
| NSCLC                             | 25/181 (14%)       | 1.07 (0.63–1.82) | 0.792           |             |
| Mesothelioma                      | 5/71 (7%)          | 0.55 (0.22–1.43) | 0.222           |             |
| RCC                               | 2/36 (6%)          | 0.42 (0.10–1.74) | 0.231           |             |
| UCC                               | 4/31 (13%)         | 0.99 (0.34–2.89) | 0.980           |             |
| **Age**                           |                    |             |                    |             |
| ≤65 years                         | 25/252 (10%)       | Ref         | 29/64 (45%)       | Ref         |
| >65 years                         | 41/298 (14%)       | 1.43 (0.87–2.34) | 0.159           |             |
| **Sex**                           |                    |             |                    |             |
| Male                              | 37/356 (10%)       | Ref         | 25/59 (42%)       | Ref         |
| Female                            | 29/194 (15%)       | 1.49 (0.92–2.43) | 0.105           |             |
| **No. of prior treatment lines**  |                    |             |                    |             |
| In steps of one                   | 0.74 (0.46–1.19)  | 0.215      | 0.87 (0.39–1.92)  | 0.732       |
| **WHO status**                    |                    |             |                    |             |
| 0                                 | 21/214 (10%)       | Ref         | 17/44 (39%)       | Ref         |
| ≥1                                | 37/277 (13%)       | 1.40 (0.82–2.38) | 0.220           |             |
| **Type of anti-PD1**              |                    |             |                    |             |
| Nivolumab                         | 40/393 (10%)       | Ref         | 22/45 (49%)       | 1.32 (0.65–2.68) | 0.436   |
| Pembrolizumab                     | 26/157 (17%)       | 1.57 (0.96–2.58) | 0.073           |             |
| **No. of organ sites with metastasis** |                    |             |                    |             |
| 0–1                              | 27/260 (10%)       | Ref         | 13/27 (48%)       | Ref         |
| 2–3                              | 37/247 (15%)       | 1.40 (0.85–2.30) | 0.182           |             |
| 4–5                              | 2/41 (5%)          | 0.41 (0.10–1.69) | 0.218           |             |
| **Brain metastasis**             |                    |             |                    |             |
| No                                | 60/514 (12%)       | Ref         | 31/74 (42%)       | Ref         |
| Yes                               | 5/35 (14%)         | 1.11 (0.46–2.68) | 0.809           |             |
| **LDH range**                    |                    |             |                    |             |
| Normal                            | 38/300 (13%)       | Ref         | 20/45 (44%)       | Ref         |
| >1×ULN                            | 16/120 (13%)       | 1.02 (0.57–1.82) | 0.950           |             |

Table 3 Investigated variables and their correlation with the occurrence of a first ≥grade 3 irAEs in the total monotherapy cohort and total combination therapy cohort.

E.A. Basak et al. / European Journal of Cancer 174 (2022) 113–120
the association between SAEs and efficacy. However, our cohort consists of different tumour types, treatment regimens, and disease stages, reducing the reliability of such analysis. IrAEs may occur after a long time, e.g. one patient experienced colitis after 21 months, while some patients are followed for a short period, e.g. due to death caused by disease progression. To account for any time bias, we conducted a competing risk cox-regression analysis, in which death was considered a competing risk. Moreover, we compared the treatment duration between patients with and without SAEs. Also, when excluding patients with <3 months of follow-up, no differences were found compared to the main analyses. Moreover, data lock point was >6 months after inclusion of the last patient, allowing for sufficient follow-up time. These findings suggest that study outcomes are not due to varying follow-up times.

In conclusion, no associations were found between patient and disease characteristics and SAEs in the total monotherapy and total combination therapy cohorts, nor in the separate NSCLC and melanoma cohorts. Of interest, despite results from earlier publications, we found no association between disease severity measured as treatment setting, LDH level and number of organ sites with metastases and the occurrence of SAEs. Therefore, future analyses should focus on other possible predictors of adverse events.

Author contributions

All authors contributed to the final approval of the manuscript and are accountable for all aspects of the work. EAB, NSV, KdJ, DPH, AJ, RHJM contributed to the concept and design of the manuscript. EAB, NSV, DEMV, AAMvdV, JGJVA, AJ, RHJM contributed to data acquisition. EAB, NSV, KdJ, EOHN, MWJS, SB, SLWK, RD, AAMvdV, JGJVA, AJ, RHJM contributed to data analysis and interpretation. EAB, NSV, AJ contributed to drafting the manuscript. KdJ, DPH, DEMV, EOHN, MWJS, SB, SLWK, RD, AAMvdV, JGJVA, AJ, RHJM contributed to critical revision of the manuscript. EAB, NSV, EOHN, AJ contributed to the statistical analysis. DEMV provided administrative support.

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Conflict of interest statement

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2022.07.015.

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