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ESMO Open Cancer Horizons

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► Additional material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/esmoopen-2020-000945).

To cite: Verheijden RJ, May AM, Blank CU, *et al*. Lower risk of severe checkpoint inhibitor toxicity in more advanced disease. *ESMO Open* 2020;**5**:e000945. doi:10.1136/esmoopen-2020-000945

Received 24 July 2020
Revised 1 October 2020
Accepted 19 October 2020

Published online 16 November 2020

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ABSTRACT

Background Immune checkpoint inhibitor (ICI) can cause severe and sometimes fatal immune-related adverse events (irAEs). Since these irAEs mimick immunological disease, a female predominance has been speculated on. Nevertheless, no demographic or tumour-related factors associated with an increased risk of irAEs have been identified until now.

Methods Risk ratios of severe (grade ≥3) irAEs for age, sex, WHO performance status, number of comorbidities, stage of disease, number of metastases and serum lactate dehydrogenases (LDH) were estimated using data from anti-PD1-treated patients with advanced melanoma in the prospective nationwide Dutch Melanoma Treatment Registry.

Results 111 (11%) out of 819 anti-programmed cell death 1 treated patients experienced severe irAEs. Patients with non-lung visceral metastases (stage IV M1c or higher) less often experienced severe irAEs (11%) compared with patients with only lung and/or lymph node/soft tissue involvement (stage IV M1b or lower; 19%; adjusted risk ratio (RR_{adj}) 0.63; 95% CI 0.41 to 0.94). Patients with LDH of more than two times upper limit of normal had a non-significantly lower risk of developing severe irAEs than those with normal LDH (RR_{adj} 0.65; 95% CI 0.20 to 2.13). None of the other variables were associated with severe irAEs.

Conclusion In patients with melanoma, more advanced disease is associated with a lower rate of severe irAEs. No association with sex was found.

Key questions

What is already known about this subject?

► Immune checkpoint inhibitor can cause severe and sometimes fatal immune-related adverse events (irAEs). No demographic or tumour-related factors associated with an increased risk of irAEs have been identified until now.

What does this study add?

► This study demonstrates that more advanced disease is associated with a significant decreased risk of severe irAEs in patients with melanoma.

How might this impact on clinical practice?

► By improving irAE risk prediction in individual patients, these data contribute to better informed shared decision-making.

INTRODUCTION

Through the blockage of programmed cell-death 1 (PD-1), the immune checkpoint inhibitors (ICIs) nivolumab and pembrolizumab reinvigorate tumour-specific T cells, potentially resulting in long-lasting antitumour response and increased overall survival in several types of malignancies, such as advanced melanoma, non-small cell lung cancer and renal cell carcinoma.[1 2] On the other hand, checkpoint inhibition can cause immune-related adverse events (irAEs), ranging from mild to severe, which can be irreversible and in some cases fatal.[3]

As ICIs are now used as adjuvant treatment, trying to improve cure rates for stage III and resected stage IV melanoma and non-squamous cell lung cancer, it is becoming more and more important to identify patients who are at increased risk for severe ICI toxicity.

IrAEs mimic autoimmune disease that are known to have a female predominance.[4] In line with that, women might be more prone to develop irAEs during checkpoint inhibition.[5 6] In addition, the high toxicity rates in early (neo)adjuvant studies have led to the hypothesis that irAEs occur more frequently in patients with lower tumour load.[7]

Studies so far investigating determinants of anti-PD(L)1 toxicity were of limited sample size with a median of 78 patients at risk (IQR 50–128).[8–21] Here we analysed whether demographic and disease-specific patient characteristics present at start of treatment were associated with an increased risk of severe irAEs using a large dataset from our nationwide melanoma treatment registry.

METHODS

Patients

The Dutch Melanoma Treatment Registry (DMTR) prospectively registers demographic and clinical data from all unresectable patients with stage III and IV melanoma in the Netherlands since 2012.[22] In this report, we included all patients who received either nivolumab or pembrolizumab monotherapy from 1 July 2012 until 31 December 2017 as first ICI. Patients who were previously treated with ipilimumab or combined ipilimumab plus nivolumab were not included in this report to exclude the possibility of overlapping toxicity. Patients who were censored due to data cut-off within 3 months after treatment initiation were excluded, as they had a substantial risk of getting an irAE after censoring.[23] Toxicities were graded according to the Common Terminology Criteria of Adverse Events V.4.03. In the DMTR, only severe irAEs are registered (ie, ≥grade 3). In compliance with Dutch regulations, the DMTR was approved by the medical ethical committee and was not subject to the Medical Research Involving Human Subjects Act.

Statistical analyses

Variables age, sex, WHO performance status (0 vs 1 vs ≥2), number of comorbidities, stage of disease (American Joint Committee on Cancer V.8; unresectable stage III/stage IV M1a/M1b vs stage IV M1c/M1d), number of metastatic sites (<5 vs ≥5) and serum lactate dehydrogenase (LDH; ≤upper limit of normal (ULN; 250 U/L) vs 1–2× ULN vs >2× ULN) at start of treatment were tested for correlation with severe irAEs. Furthermore, in a subgroup of patients who were solely in stage M1c/M1d, the correlation of symptomatic brain metastases with severe irAEs was tested. At first, since irAE is a frequently occurring outcome,[24 25] unadjusted risk ratio (RR) of severe irAEs including 95% CI was calculated using Poisson regression. Then, multivariable Poisson regression analysis was used to calculate adjusted RR for each variable, with all other variables and follow-up time (time from start of treatment until death/censoring) as covariate. Both univariable and multivariable analyses were performed in treatment-naive patients and in patients receiving first ICI treatment irrespective of line of systemic treatment (including first line) with additional adjustment for line of therapy in the multivariable analyses. Significant results were then verified in only patients who were alive 3 months after treatment initiation to account for time dependency of severe irAEs. For multivariable analyses, missing variable data were imputed using the mice package in R.[26] For each analysis, a number of imputed datasets were created, corresponding to the percentage of patients in which at least one variable was missing (eg, 16 for first-line anti-PD1 and 18 for all line anti-PD1 therapy).[27] Mann-Whitney U test was used to test for differences in treatment duration, as this was not normally distributed. All analyses were done using two-sided tests. P values <0.05 were considered significant. R V.3.5.1 was used including dplyr, mice, stats and survival packages.

RESULTS

In total, 927 patients receiving nivolumab (n=283) or pembrolizumab (n=644) in any line between 2012 and 2017 were registered. Sixty-two patients were excluded because of missing toxicity status. Additionally, 46 patients who were censored due to data cut-off within 3 months after start of therapy were excluded; the remaining 819 patients were included in this study. Median follow-up after start of treatment was 11 months (IQR 5–17). Patients received a median of seven cycles of anti-PD1 therapy (IQR 3–15). A total of 557 patients were treated in first line, 208 were treated in second line, 39 in third line and 15 in later lines (table 1).

Among patients treated with anti-PD1 in any line, 111 (14%) suffered severe (ie, grade ≥3) irAEs. These included colitis (n=23; 2.8%), hepatitis (n=14; 1.7%), dermatitis (n=13; 1.6%), pneumonitis (n=10; 1.2%), endocrine toxicities (n=9; 1.1%), including thyroiditis (n=5; 0.6%) and other toxicities (n=56; 6.8%). Four patients died because of treatment related grade 5 toxicity. Median duration on treatment was 139 days (IQR=58–313) for patients with severe irAEs and 105 days (42–252) for patients without, which was not significantly different (p=0.14). Data on treatment duration were incomplete in 8% and 16% of patients with and without severe irAEs.

Patients with stage IV M1c or higher significantly less often experienced severe irAEs: 63 (11%)/565, compared with 45 (19%)/232 with stage IV M1b or lower disease (RR 0.57; 95% CI 0.39 to 0.85; RR_{adj} 0.63; 95% CI 0.41 to 0.94). Of note, when including solely those 706 patients who were alive 3 months after treatment initiation, the association remained significant (RR_{adj} 0.65; 95% CI 0.42 to 0.99). Patients with an LDH ≥2× ULN had a non-significant decreased risk of severe irAEs compared with patients with normal LDH (RR_{adj} 0.65; 95% CI 0.20 to 2.13). Neither in univariable nor multivariable Poisson regression analysis, any of the other tested variables age, sex, WHO performance status, number of comorbidities, stage of disease, number of metastases and line of therapy were significantly associated with severe irAEs (table 2).

When analysing first-line anti-PD1-treated patients only, 78 (14%) of the first-line anti-PD1-treated patients experienced severe irAEs. A total of 44 (12%)/359 patients with stage IV M1c or higher had severe irAEs compared with 33 (18%)/186 patients with stage M1b or lower, resulting in a unadjusted RR for severe irAEs of 0.69 (95% CI 0.44 to 1.09) and an adjusted risk ratio (RR_{adj}) of 0.73 (95% CI 0.45 to 1.18), which was not significantly different. Again, patients with LDH >2× ULN had a non-significantly lower risk of developing severe irAEs compared with those with normal LDH (RR_{adj} 0.73; 95% CI 0.17 to 3.00). None of the other variables were significantly associated with severe irAEs in either univariable or multivariable analysis (online supplemental table 1).

In the subgroup of 565 patients with stage IV M1c/M1d treated in any line of systemic therapy, 12 (12%)/103 patients with symptomatic brain metastases experienced

Table 1 Baseline characteristics

	Anti-PD1, any line	Anti-PD1, first line
Number of patients	819	557
Age median (IQR)	65 (55–73)	67 (56–74)
Sex		
Male	472 (58%)	327 (59%)
Female	346 (42%)	229 (41%)
WHO performance status		
0	454 (61%)	332 (64%)
1	256 (34%)	166 (32%)
2	36 (5%)	21 (4%)
3	2 (0%)	2 (0%)
Number of comorbidities		
0	279 (34%)	179 (32%)
1–2	398 (49%)	276 (50%)
≥3	137 (17%)	100 (18%)
Stage of disease		
Unresectable stage III	53 (7%)	41 (8%)
IV, M1a	77 (10%)	55 (10%)
IV, M1b	102 (13%)	90 (17%)
IV, M1c	360 (45%)	250 (46%)
IV, M1d	205 (26%)	109 (20%)
Symptomatic brain metastases	103 (13%)	56 (10%)
Number of metastatic sites		
0	87 (11%)	63 (12%)
1	251 (33%)	180 (35%)
2	222 (29%)	146 (28%)
3	143 (19%)	84 (16%)
4	50 (7%)	33 (6%)
5	12 (2%)	9 (2%)
6	1 (0%)	1 (0%)
LDH		
≤ULN	548 (68%)	369 (67%)
1–2 × ULN	210 (26%)	155 (28%)
>2 × ULN	50 (6%)	27 (5%)
ICI treatment		
Nivolumab	261 (32%)	178 (32%)
Pembrolizumab	558 (68%)	379 (68%)
Line of systemic therapy		
1	557 (68%)	
2	208 (25%)	
3	39 (5%)	
≥4	15 (2%)	

ICI, immune checkpoint inhibitor; LDH, lactate dehydrogenase; PD1, programmed cell death 1; ULN, upper limit of normal (defined as 250 U/L).

severe irAEs compared with 38 (11%)/360 of patients without any brain metastases (RR 1.10; 95% CI 0.55 to 2.05; RR_{adj} 1.47; 95% CI 0.77 to 2.83). In the 359 first-line treated patients with stage IV M1c/M1d, 11 (20%)/56 of patients with symptomatic brain metastases experienced severe irAEs, compared with 25 (10%)/250 patients without any brain metastases (RR 1.96; 95% CI 0.93 to 3.89; RR_{adj} 2.35; 95% CI 1.11 to 4.97).

Approximately 60% of patients with symptomatic brain metastases received steroids at baseline, compared with 22% in all patients. Unfortunately, data on baseline steroid use were missing in 35% of patients. We did not observe a significant difference in frequency of severe irAEs in patients with (15.7%) and without (12.9%) baseline steroids for patients treated in any line (RR 1.21; 95% CI 0.69 to 2.03). Nevertheless, when we repeated the multivariable analyses with additional adjustment for baseline steroid use, the correlation between disease severity and severe irAEs did not change relevantly in patients treated in any line of therapy (RR_{adj} for stage 0.49; 95% CI 0.28 to 0.84) and first-line treated patients only (RR_{adj} 0.46; 95% CI 0.24 to 0.90). Notably, there was no imbalance of baseline autoimmune disorders between patients with high stage (3.7%) compared with low-stage disease (1.8%; χ^2 p value 0.231).

DISCUSSION

In the largest prospective cohort thus far, using data from the nationwide DMTR, we aimed to identify patient-related and tumour-related factors associated with the occurrence of severe irAEs in patients with advanced melanoma treated with anti-PD1. We observed that patients with more advanced disease (stage IV M1c or higher) had a significantly decreased risk of severe irAEs compared with patients with lower-stage disease (stage IV M1b or lower). None of the other factors were associated with the occurrence of severe irAEs. When looking at first-line treated patients only, we observed comparable results, although the association for more advanced disease was not significant, probably due to lower number of patients.

Recently, the high toxicity rates in early (neo)adjuvant studies have led to the hypothesis that irAEs occur more frequently in patients with smaller tumour load.[7 28] Although no data on tumour volumes are available in the DMTR, tumour load was previously reported to be larger in stage M1c or higher than in patients with a lower stage of disease,[29] pointing in the same direction. Moreover, the non-significant lower risk we observed in the small group of LDH ≥2× ULN patients supports this. Interestingly, also response rates to anti-PD1 are lower in patients with stage IV M1c melanoma compared with lower stages,[30] in patients with higher tumour load[29] and LDH ≥2× ULN.[31] As we and others have recently shown a correlation between ICI response and toxicity,[32 33] one may hypothesise that immunological responses in these patients are less strong, which might be due to the increased immunosuppressive tumour microenvironment in large volume disease.[34]

It is unlikely that the observed association between stage and severe irAEs is explained by immortal time bias, as we

Table 2 Determinants of severe immune-related adverse events in any line anti-PD1-treated patients using both univariable and multivariable Poisson regression

		Univariable analysis		Multivariable analysis		
	RR	95% CI	P value	RR_{adj}	95% CI_{adj}	P value
Age	1.01	0.99–1.02	0.491	1.00	0.99–1.02	0.676
Sex						
Male	ref			ref		
Female	1.18	0.81-1.71	0.389	1.18	0.81–1.73	0.397
WHO performance status						
0	ref			ref		
1	0.52	0.53-1.24	0.363	0.96	0.62–1.49	0.845
≥2	0.89	0.31-2.00	0.805	1.04	0.41–2.64	0.942
Number of comorbidities						
0	ref			ref		
1–2	1.27	0.83-1.98	0.277	1.16	0.73–1.86	0.529
≥3	1.27	0.72-2.07	0.397	1.21	0.65–2.28	0.539
Stage of disease						
Unresectable stage III/M1a/M1b	ref			ref		
M1c/M1d	0.57	0.39-0.85	0.046	0.63	0.41–0.94	0.026
Number of metastatic sites						
<3	ref			ref		
≥3	0.77	0.47-1.21	0.271	1.03	0.65–1.62	0.906
LDH						
≤ULN	ref			ref		
1–2 × ULN	0.95	0.61-1.44	0.812	1.12	0.72–1.74	0.623
>2 × ULN	0.43	0.10-1.14	0.148	0.65	0.20–2.13	0.475
Line of therapy	1.01	0.76-1.26	0.950	1.12	0.86–1.46	0.417

CI_{adj}, adjusted CI; LDH, lactate dehydrogenase; ; PD1, programmed cell death 1; RR, risk ratio; RR_{adj}, adjusted risk ratio; ULN, upper limit of normal (defined as 250 U/L); the multivariable analysis was additionally adjusted for follow-up time.

adjusted for follow-up time. Furthermore, the association persisted when we excluded patients who died within the first 3 months after treatment initiation, in which most toxicities occur.[23] Moreover, patients with symptomatic brain metastases—who have a very poor prognosis—had a similar or even increased irAE risk when compared with patients with stage IV M1c without brain metastases. Furthermore, treatment duration did not differ significantly between patients with and those without severe irAEs. However, this should be interpreted with caution as treatment duration is unknown in a considerable proportion of patients, presumably because these patients are still on treatment. This may have resulted in an underestimation of treatment duration, which is probably more pronounced in patients without irAEs. Together, this suggests that the lower risk in patients with high-stage disease was not due to decreased time at risk.

Several others have tried to identify determinants of ICI induced toxicity. For example, baseline body mass index, platelet to lymphocyte ratio, absolute lymphocyte count and absolute eosinophil count were reported to be correlated with irAEs resulting from anti-PD1 therapy.[11 17 18] However, sample sizes in these studies were small (n<200 at risk), resulting in wide confidence intervals. Most studies also report numerous other tested variables without significant predictive value.

As most autoimmune diseases display a female predominance,[4] sex differences in irAEs have been hypothesised, but reports on the association of sex with irAEs are contradictory. Two cohort studies of <250 patients demonstrated an increased frequency of irAEs in females compared with males, although for frequency of grade ≥3 irAEs one of the studies showed no difference between both sexes.[8 9] Contrastingly, in a retrospective analysis using insurance data of 4438 ICI-treated patients, Kehl *et al* reported no significant difference in risk of irAEs (RR_{adj} 1.11; 95% CI 0.91 to 1.34) between females and males.[35] Similarly, the frequency of severe irAEs was not higher in females in our cohort compared with males. With a median age of 65 years, and with just 65 females younger than 50 years, our real-world cohort encompasses mainly postmenopausal women. As differences between male and female immune responses alter with age, with a supposedly important role of sex hormones, the discrepancy between sex-differences

in autoimmune diseases compared with irAEs may be age-related. Besides, most severe irAEs (such as colitis) resemble autoimmune diseases with a sex distribution close to 50% (such as ulcerative colitis),[36] while rheumatological and thyroidal irAEs are often lower grade and therefore in general not included in our registry. Of note, reports on the association of sex with ICI efficacy are contradictory.[6 30 37]

In conclusion, we demonstrated that anti-PD1-treated patients with more advanced disease have a lower risk of developing severe irAEs. No associations of sex or other patient-related and tumour-related factors with severe irAEs were found. As toxicity profiles are similar between tumour types, the results of this study are possibly applicable to other patients treated with anti-PD1 therapy.

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Funding The Netherlands Organisation for Health Research and Development funded the start-up of the Dutch Melanoma Treatment Registry (DMTR). Grant number: 836 002 002. This grant was awarded under the effectiveness research for high-cost medicine programme. From its foundation, the DMTR has been sponsored by BMS, Novartis, Roche Nederland BV, MSD and Pierre Fabre via the Dutch Institute for Clinical Auditing (DICA).

Competing interests CUB reports receiving commercial research grants from Novartis, Bristol-Myers Squibb, and NanoString; is a paid advisory board member for Bristol-Myers Squibb, MSD, Roche, Novartis, GlaxoSmithKline, AstraZeneca, Pfizer, Lilly, GenMab and Pierre Fabre; and holds ownership interest in Uniti Cars, Neon Therapeutics and Forty Seven. AJMvdE reports receiving commercial research grants from Bristol-Myers Squibb; reports receiving speakers bureau honoraria from Bristol-Myers Squibb and Novartis; and is an unpaid consultant/advisory board member for Bristol-Myers Squibb, Novartis, MSD, Pierre Fabre and AMGEN. JWdG is a paid consultant for Bristol-Myers Squibb and MSD. GAH is an unpaid consultant/advisory board member for Bristol-Myers Squibb, MSD, Roche and Novartis. AAMvdV is a paid consultant for Bristol-Myers Squibb, MSD, Novartis, Roche, Pfizer, Eisai, Ipsen, Pierre Fabre, Sanofi and Bayer. JBAGH is a paid consultant for AIMM, Neon Therapeutics, Immunocore, Vaximm and Neogene Therapeutics, and reports receiving commercial research grants from Bristol-Myers Squibb, MSD, Novartis and Neon Therapeutics. EK is a paid advisory board member for Bristol-Myers Squibb, Novartis, Merck/MSD and Pierre Fabre, and reports receiving commercial research grants from Bristol-Myers Squibb. KPMS reports receiving speakers bureau honoraria from Novartis and Roche, and is an unpaid consultant/advisory board member for Novartis, Roche, MSD, Pierre Fabre and Bristol-Myers Squibb.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

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