Association of Anti-TNF with Decreased Survival in Steroid Refractory Ipilimumab and Anti-PD1–Treated Patients in the Dutch Melanoma Treatment Registry

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ABSTRACT

Purpose: Unleashing the immune system by PD-1 and/or CTLA-4 blockade can cause severe immune-related toxicity necessitating immunosuppressive treatment. Whether immunosuppression for toxicity impacts survival is largely unknown.

Experimental Design: Using data from the prospective nationwide Dutch Melanoma Treatment Registry (DMTR), we analyzed the association between severe toxicity and overall survival (OS) in 1,250 patients with advanced melanoma who were treated with immune checkpoint inhibitors (ICI) in first line between 2012 and 2017. Furthermore, we analyzed whether toxicity management affected survival in these patients.

Results: A total of 1,250 patients were included, of whom 589 received anti-PD1 monotherapy, 576 ipilimumab, and 85 combination therapy. A total of 312 patients (25%) developed severe (grade ≥3) toxicity. Patients experiencing severe ICI toxicity had a significantly prolonged survival with a median OS of 23 months compared with 15 months for patients without severe toxicity [hazard ratio (HR_{adj}) = 0.77; 95% confidence interval (CI), 0.63–0.93]. Among patients experiencing severe toxicity, survival was significantly decreased in patients who received anti-TNF ± steroids for steroid-refractory toxicity compared with patients who were managed with steroids only ($HR_{adj} = 1.61$; 95% CI, 1.03–2.51), with a median OS of 17 and 27 months, respectively.

Conclusions: Patients experiencing severe ICI toxicity have a prolonged OS. However, this survival advantage is abrogated when anti-TNF is administered for steroid-refractory toxicity. Further prospective studies are needed to assess the effect of different immunosuppressive regimens on checkpoint inhibitor efficacy.

See related commentary by Weber and Postow, p. 2085

Introduction

The immune checkpoint inhibitors (ICI) ipilimumab, pembrolizumab, and nivolumab have improved the prognosis of a wide range of advanced stage malignancies (1–3). Blocking CTL-associated protein (CTLA-4) with ipilimumab and/or programmed cell-death 1 (PD-1) with nivolumab or pembrolizumab reinvigorates tumor-specific T cells, potentially resulting in long-lasting antitumor immune response (4, 5).

Blocking these immunologic checkpoints may come with immune-related adverse events (irAE) ranging from mild (grade 1–2) to severe (grade 3–4) and even fatal (6). Toxicity of any grade occurs in approximately 60% to 85% of patients treated with ipilimumab, 57% to 85% of patients treated with anti-PD1 therapy, and 95% of patients who received combined anti-PD1 and anti-CTLA4 therapies (3). Furthermore, 10% to 27%, 2% to 20%, and 55% of patients treated with anti-CTLA4, anti-PD1, or combined ICI develop grade 3 or higher toxicity, respectively (3, 7).

If considering ICI toxicity the reflection of immune-activation resulting from effective checkpoint blockade, one would anticipate a correlation between toxicity and efficacy in checkpoint inhibitor patients. Nevertheless, data on the correlation between ICI toxicity and efficacy have been conflicting (8–11).

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Translational Relevance

Our results suggest that ICI efficacy is compromised when anti-TNF is given for steroid-refractory toxicity. More data on the effect of immunosuppressive therapy on survival of ICI-treated patients are needed to provide guidance on optimal ICI toxicity management.

Despite their widespread use, ICI toxicity guidelines are largely expert opinion-based and data on the effect of immunosuppressive treatment on tumor control are lacking. Horvat and colleagues showed no difference in overall survival (OS) between ipilimumab-treated patients with melanoma who received steroids to treat toxicity compared with those who did not (8). Although steroids are mostly used as first-line immunosuppression, early administration of the monoclonal anti-TNF antibody infliximab has increasingly been propagated, especially for colitis, due to its fast and frequent efficacy (12).

Here, we assessed whether severe ICI toxicity is associated with prolonged OS in patients with advanced melanoma in what to our knowledge is the largest cohort described thus far. Furthermore, we analyzed how immunosuppressive treatment of toxicity affects survival in this population.

Materials and Methods

Patients

All patients who started first-line ipilimumab, nivolumab, or pembrolizumab registered in the Dutch Melanoma Treatment Registry (DMTR) from July 1, 2012, to December 31, 2017, were included. As registration in the DMTR is mandatory for reimbursement, this registry encompasses clinical data from all patients with unresectable stage III and stage IV melanoma in the Netherlands since 2012. Data from July 2012 to July 2013 were retrospectively retrieved from medical records. From July 2013 onwards, data were prospectively registered by trained data managers and checked by the treating physician (13). 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. Patients of whom toxicity data were missing were excluded ($n = 35$). Additional information on type of second-line immunosuppressive medication was retrieved from patient records. Toxicities were graded according to the Common Terminology Criteria of Adverse Events (CTCAE) 4.03. In the DMTR, only severe irAEs (defined as CTC grade ≥3 toxicity) were reported. OS was defined as the absence of reported death of any cause until and including the last registered doctors contact. Reintroduction was defined as start of a new treatment episode with the same or another checkpoint inhibitor after ICI therapy, with exception of immediate nivolumab continuation after combination therapy.

Statistical analyses

Correlation of severe toxicity with OS was tested using Cox proportional hazard regression and Kaplan–Meier curves for the three types of ICI together and separately. Multivariable Cox proportional hazard regression was performed to adjust for age, sex, WHO performance status, number of comorbidities, stage of disease (according to AJCC v8), total number of metastases, and lactate dehydrogenases (LDH). Because on average 3.9% of data per covariate were missing which would lead to a drop-out of 289 of 1,250 patients (23%) in this multivariable analyses, missing covariate data were imputed together with data on lymph node metastases, radiotherapy, and date of diagnosis. The mice package in R was used, creating 23 multiple imputations through five iterations, corresponding to the percentage of patients of whom covariate data were missing (14). We repeated our analysis after excluding patients who died in the first 9 weeks of treatment to minimalize bias resulting from the time-dependency of irAEs. This cutoff was chosen based on the median time to treatment discontinuation for adverse events reported previously (15).

Next, we evaluated the effect of immunosuppressive treatment on survival, comparing OS for patients who received steroids only, anti-TNF (either in addition to steroids or as monotherapy) or no immunosuppressive medication for severe toxicity using Kaplan–Meier estimates and multivariable Cox regression. All analyses were done using two-sided tests. P values <0.05 were considered significant. SPSS version 26 and R version 3.5.1 were used including mice, survival, and survminer packages.

Results

A total of 1,250 patients were included, of whom 576 patients were treated with ipilimumab, 589 with anti-PD1 therapy (pembrolizumab or nivolumab), and 85 with combined ipilimumab plus nivolumab therapy, all as their first-line of treatment. Patient characteristics are shown in **Table 1**. Although baseline characteristics were roughly similar for ipilimumab and anti-PD1 therapy, patients treated with combination therapy had on average a lower age and less comorbidities, but worse prognostic parameters (e.g., WHO-performance score

Table 1. Baseline characteristics of patients with melanoma treated with first-line checkpoint inhibitors.

	All therapies	Ipilimumab	Anti-PD1	Ipilimumab+ nivolumab
Number of patients	1,250	576	589	85
Male gender, *n* (%)	757 (60.0)	361 (62.7)	346 (58.8)	50 (58.8)
Age, median (SD)	63 (13)	62 (12)	65 (13)	56 (13)
WHO-performance, *n* (%)				
0	773 (66.1)	383 (71.1)	350 (63.8)	40 (48.8)
1	358 (30.6)	143 (26.5)	175 (31.9)	40 (48.8)
2	35 (3.0)	11 (2.0)	22 (4.0)	2 (2.4)
3	4 (0.3)	2 (0.4)	2 (0.4)	0 (0.0)
Number of comorbidities, *n* (%)				
0	443 (35.8)	210 (36.9)	191 (32.6)	42 (51.9)
1–2	611 (49.4)	286 (50.3)	288 (49.1)	37 (45.7)
≥3	182 (14.7)	73 (12.8)	107 (18.3)	2 (2.5)
Stage, *n* (%)				
Unresectable stage III	65 (5.4)	17 (3.1)	42 (7.3)	6 (7.2)
IV, M1a	128 (10.6)	66 (11.9)	59 (10.3)	3 (3.6)
IV, M1b	197 (16.3)	91 (16.4)	97 (16.9)	9 (10.8)
IV, M1c	597 (49.3)	289 (52.2)	261 (45.4)	47 (56.6)
IV, M1d	225 (18.6)	91 (16.4)	116 (20.2)	18 (21.7)
Number of metastases, *n* (%)				
<5	194 (18.3)	89 (17.7)	96 (19.7)	9 (13.2)
≥5	866 (81.7)	415 (82.3)	392 (80.3)	59 (86.8)
LDH > ULN, *n* (%)	370 (30.0)	135 (23.9)	193 (33.1)	42 (50.0)

Note: Age in years; Stage, according to AJCC v8.
Abbreviation: ULN, upper limit of normal.

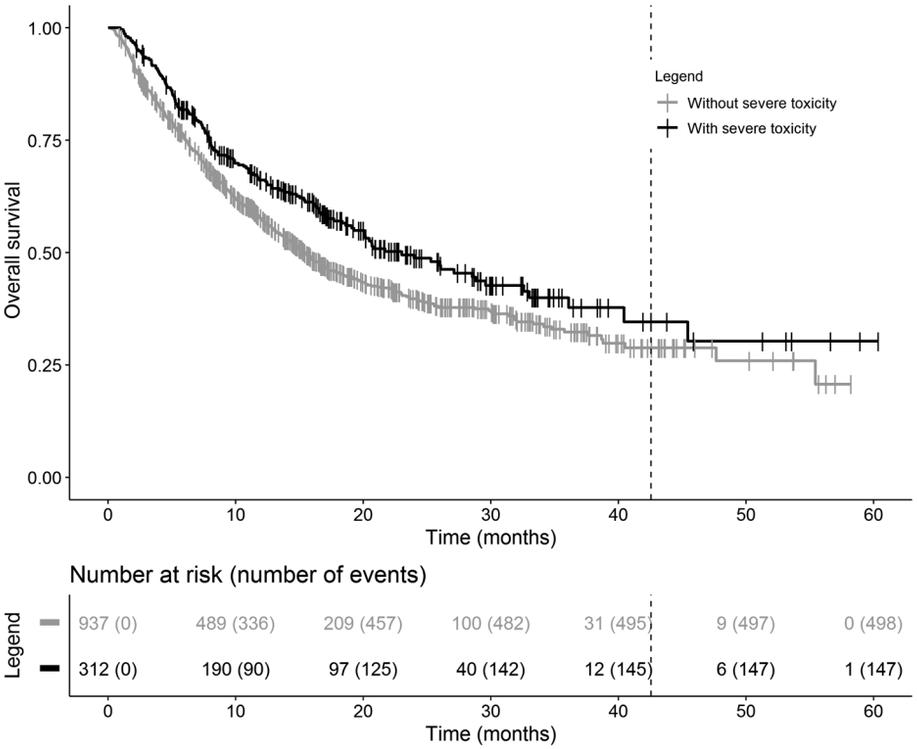

Figure 1.
Kaplan–Meier estimates for OS in patients with melanoma treated with any checkpoint inhibitor in first-line with severe irAEs vs. those without. Dotted lines indicating <10 patients at risk in toxicity arm (43 months).

≥1, higher stage of disease, number of metastases, and LDH). Median follow-up time from start of ICI until death or censoring was 11 months for all patients and 13, 11, and 9 months for patients treated with ipilimumab, anti-PD1 therapy, and combination therapy, respectively. Among 1,250 patients, 6 patients died because of ICI toxicity, which was related to ipilimumab in 3 patients and to anti-PD1 in 3 other patients.

Toxicity and survival

In total, 312 of 1,250 patients (25%) developed severe toxicity during follow-up. Severe toxicity occurred in 175 patients treated with ipilimumab (30%), 79 patients treated with anti-PD1 therapy (13%), and 58 patients during combination therapy (68%). In the three ICI groups together, survival was significantly longer in patients who experienced severe toxicity (median OS = 23 months; 95% CI, 19–33) compared with those who did not (median OS = 15 months; 95% CI, 14–17; **Fig. 1**). The hazard ratio (HR) for death for patients experiencing severe irAEs versus patients without was 0.76 (95% CI, 0.63–0.91). Multivariable analysis demonstrated that this correlation was independent of gender, age, performance status, number of comorbidities, number of metastases, and LDH (HR_{adj} = 0.77; 95% CI, 0.63–0.93; Supplementary Table S1). Furthermore, when excluding deaths before 9 weeks, the correlation persisted (HR = 0.82; 95% CI, 0.67–0.99). When evaluating the three therapies separately in univariate analyses, survival was significantly higher in patients with severe toxicity in both ipilimumab (median OS = 19 vs. 12 months; HR = 0.79; 95% CI 0.63–0.98) and anti-PD1 treatment groups [median OS = not reached (NR) vs. 19 months; HR = 0.57; 95% CI, 0.37–0.88] and nonsignificantly higher in the combination therapy group (medians = NR; HR = 0.48; 95% CI, 0.23–1.03; **Fig. 2**). In multivariable analyses, OS for patients with severe toxicity was nonsignificantly improved in ipilimumab-treated patients (HR_{adj} = 0.90; 95% CI, 0.72–1.13) and was significantly higher in patients treated with anti-PD1 (HR_{adj} = 0.54; 95% CI, 0.35–0.84) or combined therapy (HR_{adj} = 0.31; 95% CI, 0.13–0.74) when compared with patients without severe toxicity.

Management of toxicity

Management strategy of toxicity was registered for 264 patients (85%). Sixteen patients (6%) did not receive any systemic immunosuppressive treatment for toxicity, whereas 157 patients (59%) received steroids only. Ninety-one patients (34%) received immunosuppression other than steroids, consisting of a TNF-inhibitor in 65 patients and other or unknown second-line immunosuppression in the remaining 26 patients; whereas 61 patients received anti-TNF in addition to steroids, four patients received anti-TNF only. Of anti-TNF–treated patients, 45 received, ipilimumab, 8 received anti-PD1, and 12 received combined ipilimumab + nivolumab. Among steroid-treated patients, 77 received ipilimumab, 46 anti-PD1, and 34 combined therapy. Sixty-one of 65 anti-TNF–treated patients experienced ICI-induced colitis, 38 experienced endocrine toxicity, 5 hepatitis, 4 dermatitis, 3 pneumonitis, and 7 experienced other toxicities. For which type of toxicity anti-TNF was indicated was not registered. Baseline characteristics of the anti-TNF ± steroid and steroid only treated patients were similar for known prognostic factors of advanced stage melanoma, including serum LDH, age, gender, WHO performance status, and tumor stage.

Immunosuppression and survival

The 26 patients who received second-line immunosuppression other than anti-TNF or of unknown therapeutic were excluded from survival analyses. Among patients with toxicity, survival was significantly decreased in 65 patients treated with anti-TNF ± steroids (median OS = 17 months) compared with 157 patients whose toxicity was managed with steroids only (median OS = 27 months;

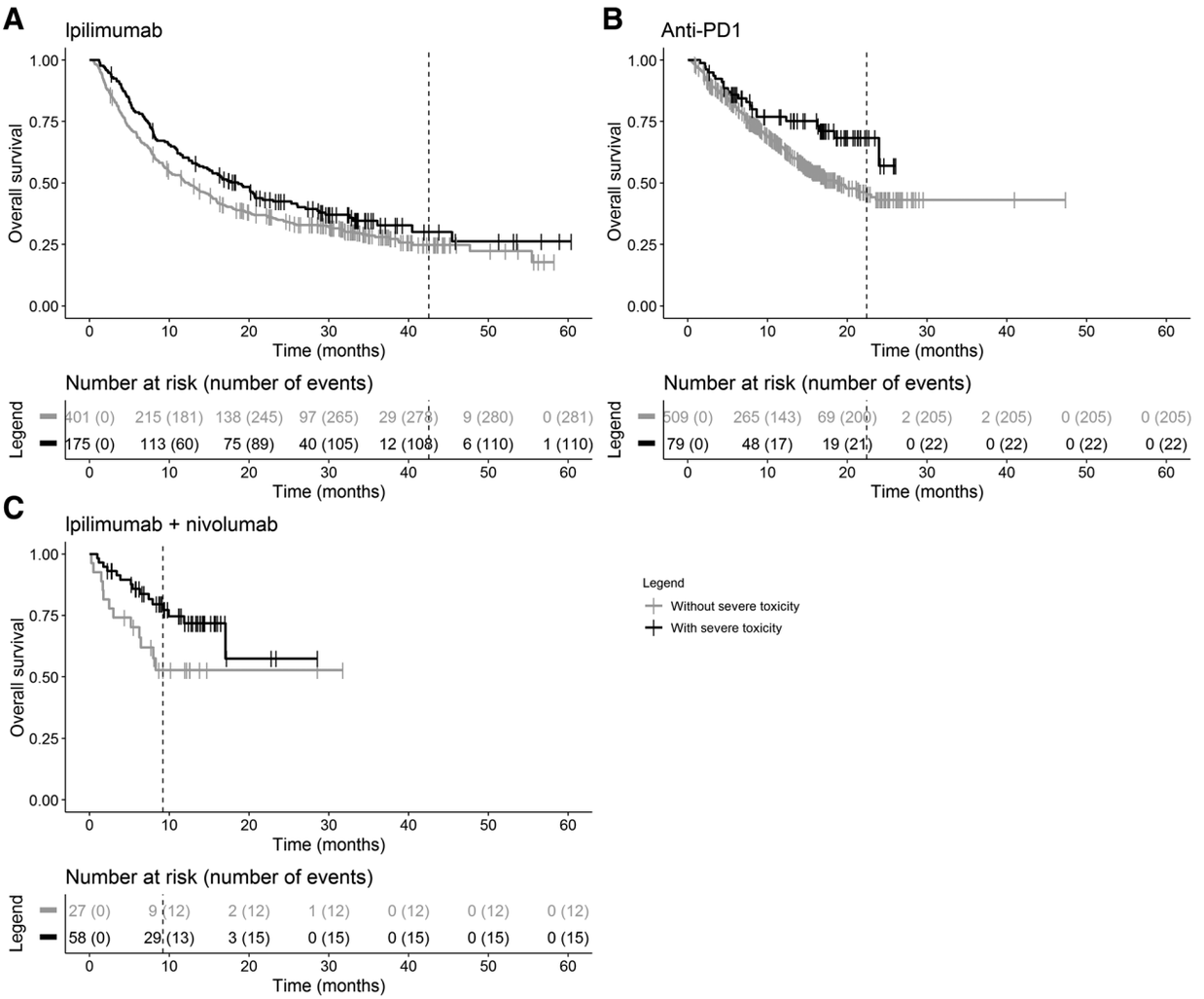

Figure 2.

Kaplan–Meier estimates for OS in patients with melanoma with severe irAEs versus those without for ipilimumab (**A**), anti-PD1 (**B**), or combined ipilimumab + nivolumab (**C**). Dotted lines indicating <10 patients at risk in toxicity arm.

HR = 1.50; 95% CI, 1.00–2.24; **Fig. 3**). This correlation remained significant in multivariable analysis corrected for age, gender, WHO performance status, number of comorbidities, stage of disease, number of metastases, serum (LDH) level, and checkpoint inhibitor regimen (HR_{adj} = 1.61; 95% CI, 1.03–2.51; Supplementary Table S2). When analyzing melanoma specific mortality, this was also significantly increased in anti-TNF ± steroids versus steroid only treated patients (HR_{adj} = 1.77; 95% CI, 1.08–2.88). When compared with patients without severe toxicity, patients treated with corticosteroids for toxicity management had a significantly decreased risk of dying (HR_{adj} = 0.65; 95% CI, 0.50–0.85), whereas in patients treated with anti-TNF ± steroids, the risk of dying was not significantly different from patients without severe toxicity (HR_{adj} = 0.93; 95% CI, 0.66–1.31). Risk of dying was decreased in patients with nonimmunosuppression treated toxicity compared with patients without toxicity (HR_{adj} = 0.36; 95% CI, 0.13–0.96), whereas OS was not significantly different between patients who did not receive immunosuppression for toxicity management compared with those who did (HR_{adj} = 0.48; 95% CI, 0.17–1.36).

OS did not differ significantly between patients with colitis compared with patients with other toxicities in both unadjusted analyses (HR = 1.30; 95% CI, 0.97–1.79) and when adjusted for type of ICI (HR_{adj} = 1.15; 95% CI, 0.82–1.60). Ninety-five steroid-only treated patients (61%) did not receive any subsequent systemic anticancer therapy compared with 38 anti-TNF ± steroid treated patients (59%). ICI was reintroduced as often in anti-TNF–treated patients as in patients whose toxicity was managed without immunosuppression or with steroids only [univariable risk ratio (RR) 1.24; 95% CI, 0.79–1.94]. Two out of 65 anti-TNF–treated patients died due to toxicity compared with 3 of 173 steroid- or nonimmunosuppressant-treated patients.

Discussion

Here we show, in the largest nationwide cohort to date, that patients with advanced melanoma who experience severe toxicity during checkpoint blockade have a significantly prolonged survival compared with patients who do not. These results are consistent when corrected

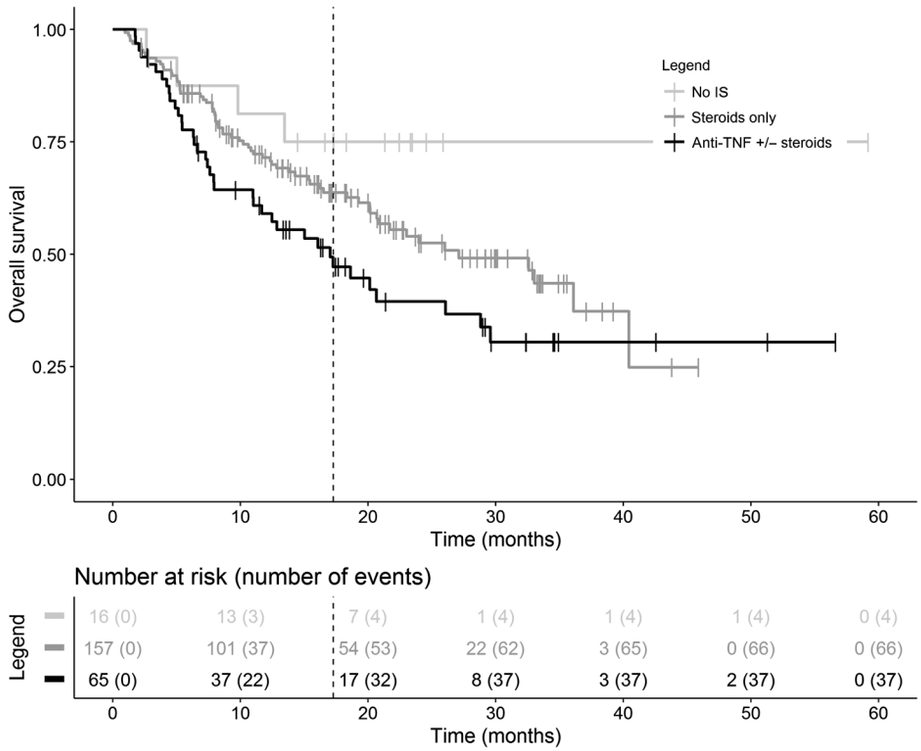

Figure 3.
Kaplan–Meier estimates for OS in first-line immune checkpoint inhibitor treated patients with melanoma with severe irAEs receiving anti-TNF ± steroids compared with patients receiving steroids only or no immunosuppression for irAE management. Dotted line indicating <10 patients at risk in no immunosuppression arm. IS, immunosuppression.

for potential confounders, when stratified for distinct therapies and when assumedly corrected for bias resulting of time-dependency of toxicity. In addition, within the group of patients experiencing severe toxicity, anti-TNF treatment for steroid-refractory toxicity was associated with decreased survival.

Studies reporting on the association between toxicity and survival have shown conflicting results. In patients with non–small cell lung cancer (NSCLC), several studies have shown an increased PFS and OS for patients experiencing nivolumab-associated toxicity (10, 11, 17). Contrarily, in patients with melanoma treated with nivolumab, ipilimumab, or combined checkpoint inhibition, no significant survival benefit has been found for patients with any or severe toxicity (8, 9, 16, 18). Interpretation is complicated as most studies lack adjustment for probable confounders or do not correct for bias resulting of toxicity's time-dependency. Furthermore, many studies report on all toxicities, including low-grade toxicities that are less reliably reproduced (3).

Analyzing survival according to immunosuppressive regimen, we showed that patients who were treated with anti-TNF for severe toxicity either as monotherapy or in addition to steroids had a significantly shorter survival than patients whose toxicity was managed with steroids only. Although the number of patients in our cohort is too small to present survival for each therapy separately, the association between anti-TNF use and survival remained unchanged when adjusted for ICI regimen in multivariable analyses. Therefore, it is unlikely that decreased survival in the anti-TNF group is explained by an overrepresentation of ipilimumab-treated patients. Although in our cohort anti-TNF was mostly prescribed in the context of colitis, the increased mortality in anti-TNF–treated patients was not linked to colitis, as survival did not significantly differ between patients experiencing colitis and patients experiencing other severe toxicities. ICI was reintroduced as often in patients who received anti-TNF as in patients who did not, so hesitation of physicians to reintroduce ICI in patients who received second-line immunosuppressants does not explain the difference in survival. Toxicity-related mortality was also an improbable cause of the decreased survival, because only 2 of 6 patients who died from toxicity were anti-TNF treated and melanoma-specific mortality was significantly different between anti-TNF- and steroid-treated patients.

Two recent smaller studies have reported outcomes in patients receiving anti-TNF for ICI toxicity, comparing survival to historical controls. Lesage and colleagues found a median OS of 12 months in 27 ICI-treated patients with melanoma who received anti-TNF for toxicity (19), which is lower than the median OS for anti-TNF–treated patients in our cohort and compares unfavorable to recent studies (15). Burdett and colleagues found an even lower median OS of 9 months in 16 patients with advanced melanoma and 3 patients with NSCLC receiving second-line immunosuppressive treatment, of whom the majority received infliximab (20).

Recently Perez-Ruiz and colleagues showed that mice that received anti-TNF added to combined CTLA-4- and PD-1-blockade had a higher rate of tumor control and survival than mice that were treated with CTLA-4- and PD-1-blockade only (21). These findings were in line with other mouse data from Bertrand and colleagues who demonstrated that combining anti-TNF and anti-PD1 led to more tumor regression and improved survival as compared with anti-PD1 alone (22). Our data seem to be in contrast to these mouse studies. However, timing of anti-TNF is different in our cohort and most of our anti-TNF–treated patients also received high-dose steroids, which was not the case in the mouse studies. A phase Ib clinical trial is currently ongoing, examining the safety and efficacy of anti-TNF given concurrently with nivolumab and ipilimumab in patients with advanced melanoma (NCT03293784, clinicaltrials.gov).

Obviously, this study has some limitations. First, no data on time to first toxicity are available in the DMTR, prohibiting a proper landmark analysis. Nevertheless, our results did not change when we excluded all deaths before nine weeks to compensate for bias due to toxicity's time-dependency. Second, the type of second-line immunosuppressive regimen is missing for 26 of the 91 patients who received more than steroids for toxicity management. Although we think that the majority of these patients has been treated with other immunosuppressants such as mycophenolic acid, we cannot completely rule out that some of these patients did receive anti-TNF. Although limited by small numbers, the survival for the 26 patients treated with other/unknown second-line immunosuppressants was not significantly different from survival of patients treated with no immunosuppression or steroids ($HR_{adj} = 0.93$; 95% CI, 0.50–1.75). Although this could suggest that the effect observed is related to TNF-inhibition, we cannot rule out a general effect of escalated immunosuppression due to limited data. Notably, when comparing patients with severe toxicity who were not treated with immunosuppressants to patients who were steroid and/or anti-TNF treated, there was a trend for improved survival. Although the number of patients in this group is low and the difference not statistically significant, this could indicate that the difference is explained by the detrimental effect of cumulative immunosuppression on survival instead of an anti-TNF–specific effect. Unfortunately, timing and dose of immunosuppressants were not registered in the DMTR. Therefore, it is possible that extended duration of high-dose steroids prior to anti-TNF could have negatively impacted survival in these patients.

In conclusion, we showed that patients with advanced melanoma who experience severe ICI toxicity have a prolonged overall survival. Strikingly, within the group of patients experiencing severe ICI toxicity, survival was significantly reduced for patients with steroid-refractory toxicities treated with anti-TNF. Further studies are needed to prospectively assess the potential detrimental effect of immunosuppressants on ICI efficacy.

Disclosure of Potential Conflicts of Interest

C.U. Blank 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. A.J.M. van den Eertwegh 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. J.W. de Groot is a paid consultant for Bristol-Myers Squibb and MSD. G.A. Hospers is an unpaid consultant/advisory board member for Bristol-Myers Squibb, MSD, Roche, and Novartis. A.A.M. van der Veldt is a paid consultant for Bristol-Myers Squibb, MSD, Novartis, Roche, Pfizer, Eisai, Ipsen, Pierre Fabre, Sanofi, and Bayer. J.B.A.G. Haanen 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. E. Kapiteijn 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. K.P.M. Suijkerbuijk 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. No potential conflicts of interest were disclosed by the other authors.

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