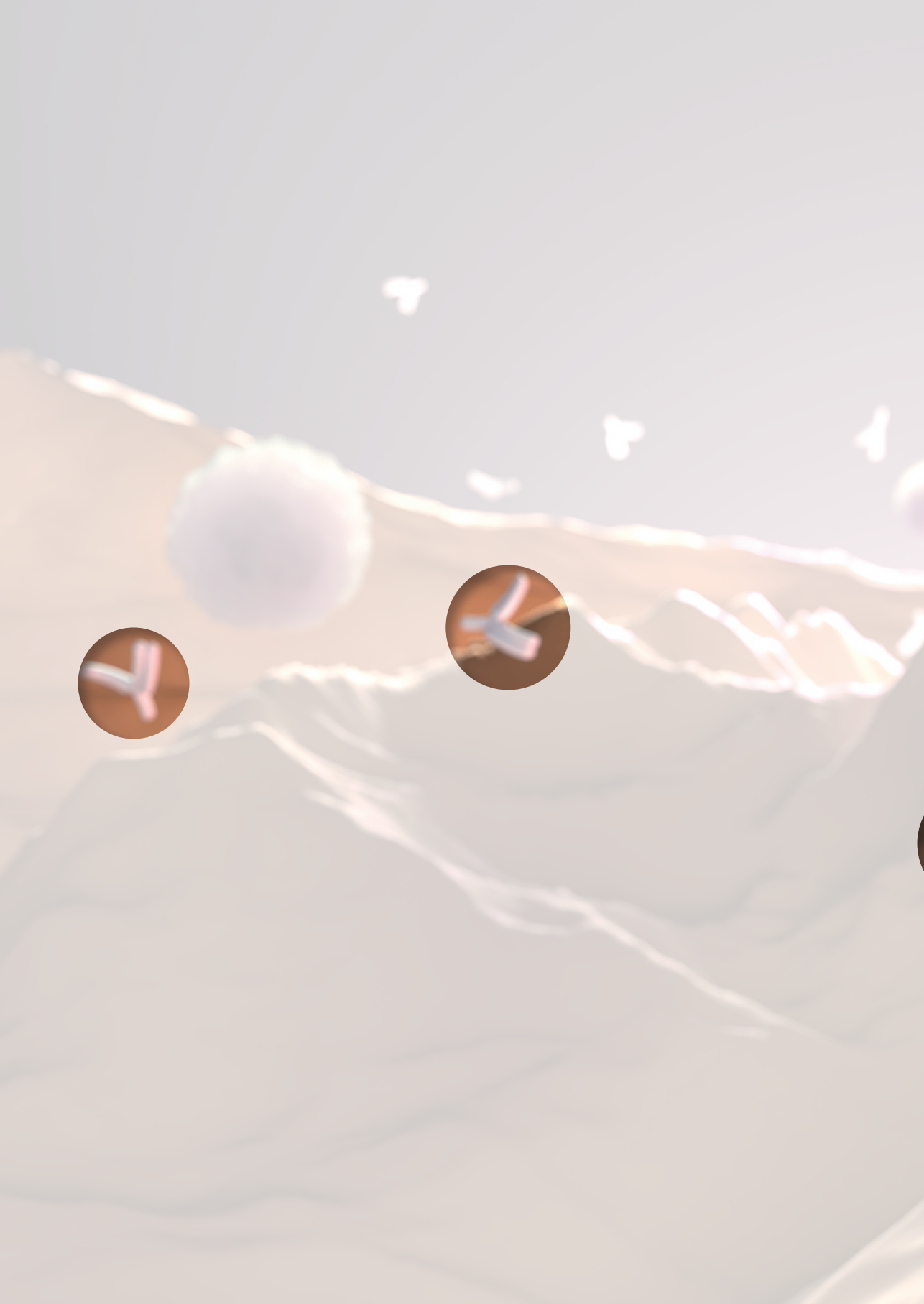
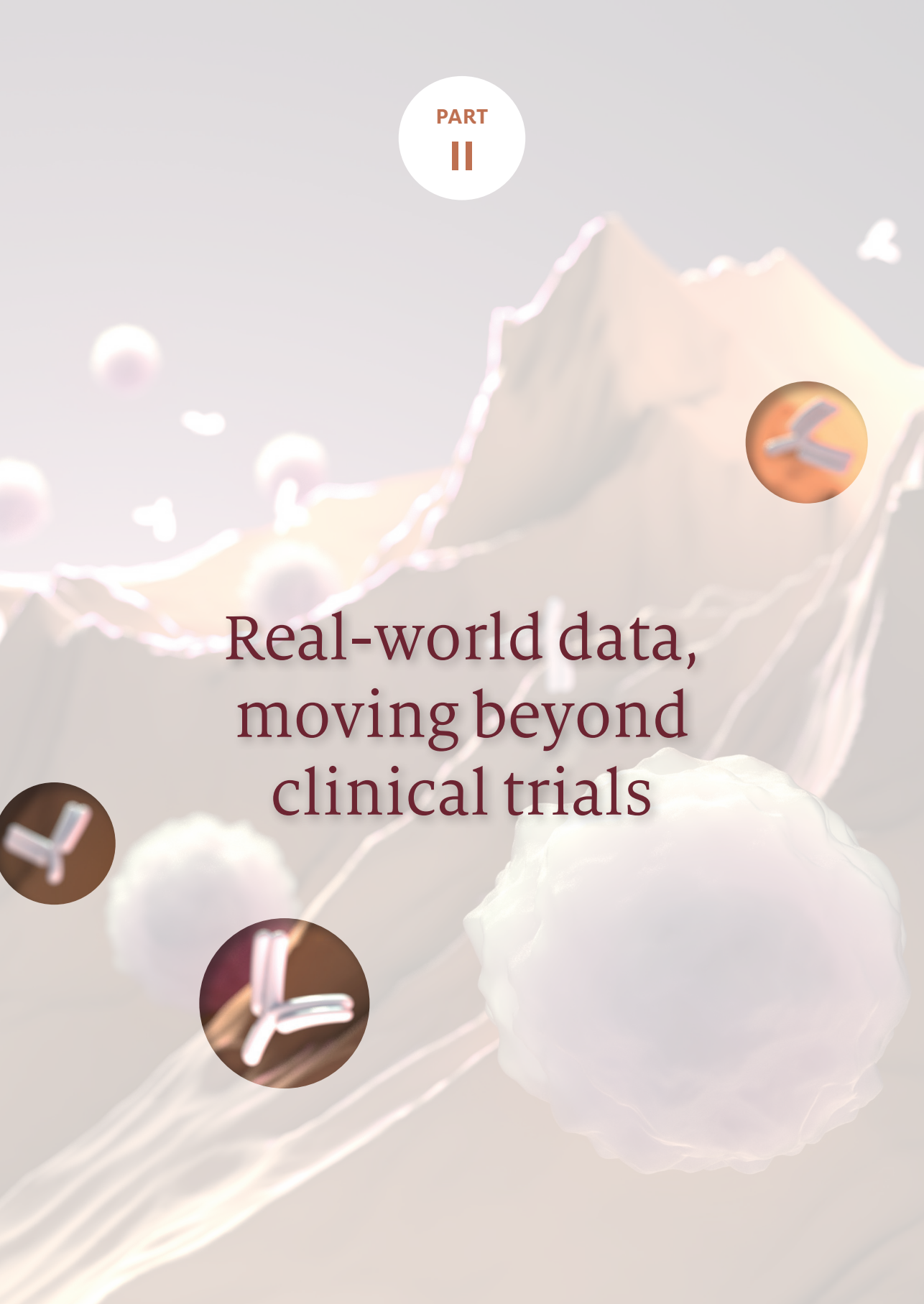
Immunotherapy in advanced melanoma: crossing borders

Kooij, M.K. van der



PART
II

Real-world data, moving beyond clinical trials



CHAPTER
5

Safety and efficacy of checkpoint inhibition in patients with melanoma and preexisting autoimmune disease: A Cohort Study

Annals of Internal Medicine 2021; 174:641-648

Winner of the LUMC Best Clinical Article Prize 2021

Monique K. van der Kooij, Karijn P.M. Suijkerbuijk, Maureen J.B. Aarts, Franchette W.P.J. van den Berkmortel, Christian U. Blank, Marye J. Boers-Sonderen, Jesper van Breeschoten, Alfonsus J.M. van den Eertwegh, Jan Willem B. de Groot, John B.A.G. Haanen, Geke A.P. Hospers, Djura Piersma, Rozemarijn S. van Rijn, Albert J. ten Tije, Astrid A.M. van der Veldt, Gerard Vreugdenhil, Michiel C.T. van Zeijl, Michel W.J.M Wouters, Olaf M. Dekkers, Ellen Kapiteijn

Abstract

Background: Because immune checkpoint inhibition (ICI) can cause immune-related adverse events (irAEs) mimicking immunologic diseases, patients with preexisting autoimmune disease (AID) have been excluded from clinical trials.

Objective: To evaluate the safety and efficacy of ICI in patients with advanced melanoma with and without AID.

Design: Nationwide cohort study.

Setting: The Netherlands.

Patients: 4367 patients with advanced melanoma enrolled in the Dutch Melanoma Treatment Registry (DMTR) between July 2013 and July 2018 and followed through February 2019.

Measurements: Patient, clinical, and treatment characteristics; irAEs of grade 3 or higher; treatment response; and survival.

Results: A total of 415 patients (9.5%) had AID, categorized as rheumatologic AID (*n* = 227), endocrine AID (*n* = 143), inflammatory bowel disease (IBD) (*n* = 55), or "other" (*n* = 8). Of these, 228 patients (55%) were treated with ICI (vs. 2546 [58%] without AID); 87 were treated with anti-cytotoxic T lymphocyte-associated protein 4 (CTLA-4), 187 with anti-programmed cell death 1 (PD-1), and 34 with the combination. The incidences of irAEs of grade 3 or higher in patients with AID were 30% (95% CI, 21% to 41%) with anti-CTLA-4, 17% (CI, 12% to 23%) with anti-PD-1, and 44% (CI, 27% to 62%) with combination therapy; for patients without AID, the incidences were 30% (CI, 27% to 33%) (n = 916), 13% (CI, 12% to 15%) (*n* = 1540), and 48% (CI, 43% to 53%) (*n* = 388), respectively. Patients with AID more often discontinued anti-PD-1 treatment because of toxicity than patients without AID (17% [CI, 12% to 23%] vs. 9% [CI, 8% to 11%]). Patients with IBD were more prone to anti-PD-1-induced colitis (6/31 = 19% [CI, 7% to 37%]) than patients with other AIDs (3% [CI, 0% to 6%]) and patients without AID (2% [CI, 2% to 3%]).

The objective response rate was similar in patients with versus without AID who were treated with anti-CTLA-4 (10% [CI, 5% to 19%] vs. 16% [CI, 14% to 19%]), anti-PD-1 (40% [CI, 33% to 47%] vs. 44% [CI, 41% to 46%]), or the combination (39% [CI, 20% to 59%] vs. 43% [CI, 38% to 49%]). Survival did not differ between patients with and those without AID (median, 13 months [CI, 10 to 16 months] vs. 14 months [CI, 13 to 15 months]).

Limitation: Information was limited on AID severity and immunosuppressive treatment.

Conclusion: Response to ICI with anti-CTLA-4, anti-PD-1, or their combination for advanced melanoma and overall incidence of any irAEs of grade 3 or higher were similar in patients with and without preexisting AID. However, severe colitis and toxicity requiring early discontinuation of treatment occurred more frequently among patients with preexisting IBD, warranting close follow-up.

Primary Funding Source: The Netherlands Organization for Health Research and Development.

Introduction

Immune checkpoint inhibition (ICI) has greatly improved survival of patients with advanced (that is, unresectable stage III or IV) melanoma[1-6]. Both anti-cytotoxic T lymphocyte-associated protein 4 (CTLA-4) and anti-programmed cell death 1 (PD-1) have been approved by the U.S. Food and Drug Administration and the European Medicines Agency for the treatment of melanoma. The number of indications is rapidly expanding to other solid and hematologic tumors, so more patients with cancer will potentially benefit from these therapies.

Immune checkpoint inhibition can lead to long-lasting responses. However, its use can be hampered by serious immune-related adverse events (irAEs) that mimic classic autoimmune diseases (AIDs)[7]. Trials studying ICI have excluded patients with preexisting AIDs because of concerns about unleashing their underlying autoimmunity. Case reports typically describe unique manifestations and are not generalizable to the population at large, which has limited recently published reviews[8-10]. Recent retrospective studies concluded that patients with melanoma or non-small cell lung cancer and a preexisting AID had relatively frequent irAEs, although mild and easily manageable[11,12]. A recent article described the safety of anti-CTLA-4 and anti-PD-1 monotherapy for patients with inflammatory bowel disease (IBD); the authors concluded that treatment was associated with a higher rate of gastrointestinal AEs[13]. The aforementioned studies used retrospectively collected data with associated risk of bias, such as selection bias. Our current study used prospectively collected data from a nationwide registry. Our objective was to test the hypothesis that irAEs of grade 3 or higher occur more frequently in patients with advanced melanoma and AID than in patients without AID. Furthermore, we compared baseline characteristics, treatment choices, response, and survival after ICI.

Methods

Patients

Since July 2013, all patients with advanced melanoma in the Netherlands have been referred to 1 of 14 expert hospitals, and their data are prospectively registered in the Dutch Melanoma Treatment Registry (DMTR)[14]. Data are collected from patient files by trained data managers and approved by the treating physician. All patients diagnosed with unresectable stage III or IV melanoma in the Netherlands between July 2013 and July 2018 were included in our study. The data cutoff was February 2019; patients who stopped ICI before February 2019 were also included. All patients who were registered by their treating physician as having concomitant AID based on their medical history were compared with all other patients. Registered AIDs were IBD, endocrine AID

(hypo- or hyperthyroidism or Graves disease), rheumatoid AID (rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), scleroderma, sarcoidosis, or vasculitis), or "other" (all AIDs not listed here). The DMTR does not collect specific information on whether patients have type 1 or 2 diabetes. Given the age distribution in our study, we assumed that most of our patients would have type 2 diabetes. Therefore, patients who were registered as having diabetes and an AID were classified as "other" because further information on their exact AID was missing.

At baseline, the following immunosuppressive therapies were registered: corticosteroids, azathioprine, interferon, or "other" (including biologics). Anticancer treatment included ICI with anti-CTLA-4 (ipilimumab), anti-PD-1 (nivolumab or pembrolizumab), or their combination (nivolumab and ipilimumab) and targeted therapy with BRAF inhibitors (vemurafenib, dabrafenib, or encorafenib) and/or MEK inhibitors (cobimetinib, trametinib, or binimetinib). The DMTR contains information on patient and tumor characteristics, treatment regimens, AEs and irAEs of grade 3 or higher, and clinical outcome.

In compliance with Dutch regulations, use of DMTR data for research was approved by the Medical Ethics Review Committee of Leiden University Medical Center and was not considered subject to the Medical Research Involving Human Subjects Act.

Outcomes

The primary outcome of our study was the safety of ICI in patients with and without AID. The DMTR reports only treatment-related AEs of grade 3 or higher (according to the Common Terminology Criteria for Adverse Events, version 4.0). Toxicity related to ICI is considered to result from the drugs' immunologic activity and hence is called an irAE. Additional information on the clinical consequences of any grade of toxicity of the different systemic treatments was obtained from the variable "reason to stop treatment." Response evaluation in this uncontrolled, real-world setting is based on clinical judgment of the treating physician, in line with the RECIST (Response Evaluation Criteria in Solid Tumors) 1.1 criteria[15]. Responses were defined as follows: complete response was disappearance of all lesions, partial response was at least 30% decrease from baseline, progressive disease was at least 20% increase, and stable disease was neither partial response nor progressive disease.

Best overall response was the best response evaluation that a patient received after initiation of treatment until start of a new melanoma therapy or last follow-up visit. Objective response rate was defined as having complete or partial response.

Overall survival (OS) was calculated from date of diagnosis of advanced melanoma to date of last follow-up visit (censored observation) or date of death. Melanoma-specific survival (MSS) was calculated from date of diagnosis to date of melanoma-related death, date of last follow-up visit (censored observation), or other cause of death (censored observation). In a competing-risk model, non-melanoma-related death was considered a competing event. Progression-free survival (PFS) was calculated from start of systemic treatment until date of first progression according to the response evaluation or death.

Statistical Analysis

All patients who were included in the DMTR were also included in the analysis of baseline characteristics. Descriptive statistics were used to summarize baseline characteristics at diagnosis of advanced melanoma and start of treatment.

We did a Pearson χ^2 analysis to test whether immunosuppressive treatment in the presence of AID influenced choice of systemic treatment. To compare the safety of ICI between patients with and those without AID, all patients were included who received at least 1 infusion of anti-CTLA-4 or anti-PD-1. Patients who received sequential treatment with anti-PD-1 and anti-CTLA-4 were included in these analyses. Data on toxicity were coupled to the appropriate ICI by the trained data manager and treating physician. The 95% CIs of the proportions of patients with irAEs and of patients who had to stop ICI because of toxicity were compared in patients with versus without AID and in patients with AID who used versus did not use immunosuppressive treatment. All patients who received at least 1 response evaluation were included in the response evaluation, which was mainly based on the RECIST 1.1 criteria. However, some patients did not receive radiologic assessment because quickly progressing disease was clinically evident; these patients are registered as having progressive disease. Patients who had not yet been evaluated for response were not included in the analysis. Pearson χ^2 analyses were used to compare the objective response rate after ICI in patients with versus without AID.

For all patients in the DMTR, at least 1 visit was registered before data cutoff. Therefore, all patients could be included in the survival analysis. Kaplan-Meier estimates of OS, MSS, and PFS were calculated; the incidence of death was plotted for OS and MSS. We report both unadjusted and adjusted associations between AID and survival (OS, MSS, and PFS) with a Cox proportional hazards model. In addition, to estimate the melanoma-related mortality risk, a cumulative incidence competing-risk method was used. To estimate subdistribution hazard ratios and corresponding 95% CIs, Fine and Gray competing-risk models were used with melanoma-related death as event and

non-melanoma-related death as competing risk[16, 17]. We adjusted for the following prognostic factors: lactate dehydrogenase levels, Eastern Cooperative Oncology Group performance status, distant metastasis in at least 3 organ sites, brain metastases, *BRAF* mutation, and age. The proportional hazards assumption was checked by visual inspection.

We used SPSS, version 25.0 (IBM), to generate descriptive statistics; to perform Pearson χ^2 analysis, survival analysis according to the Kaplan-Meier method, and Cox regression; and to calculate risk estimates.

We used Stata, version 14.1 (StataCorp), to calculate the cause-specific cumulative incidence function in the presence of competing risk (non-melanoma-related death) by using the user-written stcompet command. The stcrreg command was used to implement the Fine and Gray approach. To plot the cumulative incidence functions, the stcurve command was used.

Figures were created in GraphPad Prism, version 8.1.1 (GraphPad Software).

Role of the Funding Source

Representatives of the pharmaceutical companies that sponsor the DMTR and The Netherlands Organization for Health Research and Development had no role in writing the manuscript, collecting or analyzing the data, or interpreting the results.

Results

Baseline Characteristics

Our nationwide cohort included 4367 patients with advanced melanoma. Four hundred fifteen patients (9.5%) had preexisting AID (Table 1). Appendix Table 1 shows numbers of patients with and without AID per hospital.

At diagnosis, patients with AID were older than those without AID (67 vs. 63 years), were more frequently female (53% vs. 41%), had higher Eastern Cooperative Oncology Group performance status, and more often used immunosuppressive medication (36% vs. 18%). Although patients with AID had melanoma metastases in fewer organs and less often had brain metastases, lactate dehydrogenase levels did not differ (Table 1). Appendix Table 2 shows the number of patients included per condition that was classified as AID.

TABLE 1 Baseline Characteristics at Diagnosis and Initial Melanoma Therapy in Patients with and without Autoimmune Disease*

Characteristics	AID (*n*=415)	No AID (*n*=3952)
Age at diagnosis		
Mean (range), y	66.5 (24-92)	62.7 (2-97)
<65 y	162 (39)	1999 (51)
≥65 y	253 (61)	1953 (49)
Sex		
Male	193 (47)	2345 (59)
Female	222 (53)	1607 (41)
ECOG performance status		
0	163 (39)	1845 (47)
1	120 (29)	1107 (28)
2,3 or 4	64 (15)	500 (13)
Unknown	68 (16)	499 (12)
LDH		
Normal	232 (56)	2266 (57)
250-500 U/l	89 (21)	845 (21)
>500 U/l	65 (16)	507 (13)
Missing	29 (7)	334 (9)
Metastasis in ≥3 organ sites		
Yes	113 (27)	1262 (32)
No	302 (73)	2690 (68)
Brain metastases		
Yes	87 (21)	1048 (27)
Symptomatic	62 (15)	706 (18)
No	272 (66)	2550 (64)
Unknown	56 (13)	354 (9)
Mutational profile		
BRAF mutation	181 (44)	1945 (49)
V600E	140 (34)	1481 (38)
V600K	21 (5)	241 (6)
NRAS mutation	78 (19)	721 (18)
No BRAF/NRAS mutation	156 (38)	1295 (33)
Immunosuppressive treatment		
Yes	148 (36)	699 (18)
Corticosteroids	121 (35)	686 (17)
Azathioprine	6 (2)	2
Interferon	0	1
Other	31 (9)	19 (1)
No	267 (64)	3253 (82)

Initial treatment		
Systemic	186 (45)	1850 (47)
Local & Systemic	97 (23)	949 (24)
Local	71 (17)	686 (17)
Other treatment	0	21 (1)
No treatment	61 (15)	446 (11)

AID=autoimmune disease, ECOG=Eastern Cooperative Oncology Group, LDH=Lactate dehydrogenase, ULN=upper limit of normal.
*Values are numbers (percentages) unless otherwise indicated. Percentages may not sum to 100 due to rounding.

Treatment Patterns

First-line treatment was systemic therapy in 68% of patients with AID and 71% of patients without. Figure 1 shows the cumulative number of first-line treatments with targeted therapy or ICI over time for patients with versus without AID. Systemic treatment choices were similar over time. Patients with AID receiving immunosuppressive treatment received first-line targeted therapy more frequently and ICI less frequently than patients with AID without immunosuppression (Figure 1).

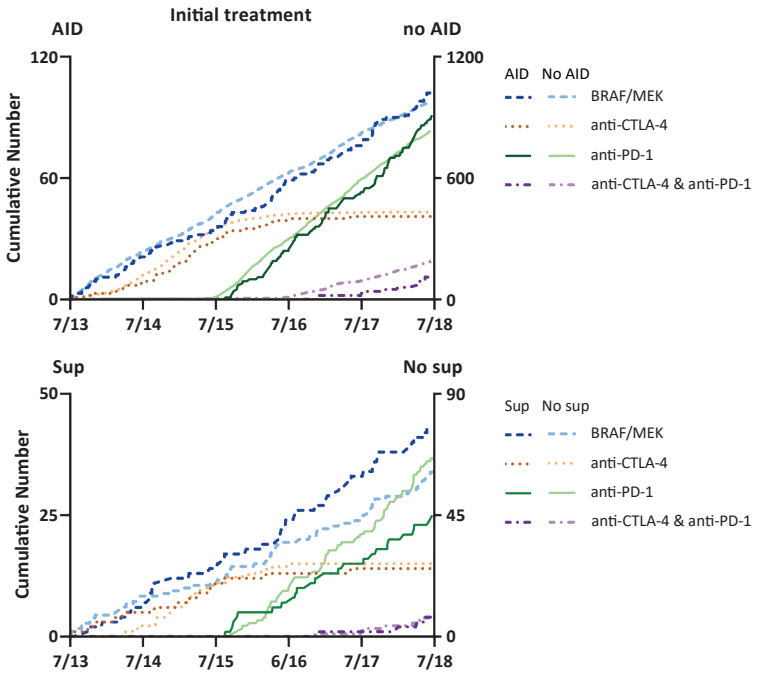


FIGURE 1 First-line systemic treatment initiated for advanced melanoma in patients with and without AID. AID = autoimmune disease; CTLA-4 = cytotoxic T lymphocyte–associated protein 4; PD-1 = programmed cell death 1; sup = immunosuppressive treatment. **Top**. Cumulative number of patients with and without AID treated with targeted therapy and immune checkpoint inhibition (ICI) over time since July 2013. **Bottom**. Cumulative number of patients with AID using sup and patients with AID not using sup receiving first-line targeted therapy and ICI since July 2013.

Timing of anti-CTLA-4 and anti-PD-1 treatment initiation was similar in patients with and without AID; almost half of the treated patients received these as first-line treatment (Appendix Table 3). Median follow-up time for patients with and without AID was 18 months for both with anti-CTLA-4; 14 and 15 months, respectively, after anti-PD-1 treatment initiation; and 3 and 5 months, respectively, after start of combination therapy with anti-CTLA-4 and anti-PD-1.

Choices for initial systemic treatment were similar among patients with IBD (*n* = 55), AID of endocrine origin (*n* = 143), and AID of rheumatologic origin (*n* = 227). Between 32% and 34% of patients in these groups did not receive systemic treatment; BRAF or MEK inhibition was prescribed to 24% to 26% of patients, anti-PD-1 to 20% to 24% of patients, and combination treatment with anti-CTLA-4 and anti-PD-1 to a minority of 2% to 3%. It seemed that patients with IBD received anti-CTLA-4 less often (6% [95% CI, 1% to 15%]) than those with rheumatologic (10% [CI, 7% to 15%]) or endocrine (12% [CI, 7% to 18%]) AID. However, the number of patients was limited.

Comparing second-line systemic treatment between patients with and those without AID, anti-CTLA-4 was less frequently prescribed to those with AID, whereas second-line treatment with anti-PD-1 tended to be prescribed more often, and targeted therapy prescription was similar.

Selection for ICI

Regardless of treatment line, 55% of patients with AID received ICI, versus 58% of patients without AID. When comparing patients with AID who received ICI (n = 143), targeted therapy (n = 104), another therapy (n = 107), and no initial treatment (n = 61), those receiving ICI more often had a normal level of lactate dehydrogenase before the start of treatment (71% [CI, 62% to 78%], 40% [CI, 31% to 50%], 10% [CI, 5% to 18%], and 21% [CI, 12% to 34%], respectively) (Appendix Table 4).

Anti-CTLA-4

Eighty-seven patients (21%) with AID were treated with anti-CTLA-4. Of these, 6 had IBD, 41 had a rheumatologic AID (2 vasculitis; 2 sarcoidosis; and 37 RA, SLE, or scleroderma), 43 had an endocrine AID (1 Graves disease and 42 hypo- or hyperthyroidism), and 2 had another AID.

Anti-PD-1

In 187 patients (42%) with AID, anti-PD-1 treatment was initiated; 31 had IBD, 89 had AID of rheumatologic origin (2 vasculitis; 3 sarcoidosis; and 84 RA, SLE, or scleroderma), 73 had AID of endocrine origin (all hypo- or hyperthyroidism), and 3 had AID of another origin.

Anti-CTLA-4 and Anti-PD-1

Thirty-four patients (8%) were treated with the combination of ipilimumab and nivolumab; 6 had IBD, 14 had AID of rheumatologic origin (3 sarcoidosis and 11 RA, SLE, or scleroderma), and 14 had AID of endocrine origin (all hypo- or hyperthyroidism).

TABLE 2 Number of Patients with Grade III/IV Immune-Related Adverse Events and Patients who Discontinued Therapy because of Toxicity.

	AID, n/N (% [95%CI])			no AID, n/N (% [95%CI])		
Immunosuppressive medication at baseline	**Yes**	**No**	**Total**	**Yes**	**No**	**Total**
Grade 3 or 4 irAEs						
Anti-CTLA-4	6/28 (21 [8-41])	20/59 (34 [22-47])	26/87 (30 [21-41])	24/104 (23 [15-32])	248/812 (31 [27-34])	272/916 (30 [27-33])
Anti-PD-1	10/68 (15 [7-25])	21/119 (18 [11-26])	31/187 (17 [12-23])	31/220 (14 [10-19])	175/1320 (13 [11-15])	206/1540 (13 [12-15])
Combination*	11/21 (52 [30-74])	4/13 (31 [9-61])	15/34 (44 [27-62])	38/83 (46 [35-57])	149/305 (49 [43-55])	187/388 (48 [43-53])
Treatment discontinued because of toxicity						
Anti-CTLA-4	2/28 (7 [1-24])	14/59 (24 [14-37])	16/87 (18 [11-28])	11/104 (11 [5-18])	127/812 (16 [13-18])	138/916 (15 [13-18])
Anti-PD-1	6/68 (9 [3-18])	25/119 (21 [14-29])	31/187 (17 [12-23])	20/220 (9 [6-14])	124/1320 (9 [8-11])	144/1540 (9 [8-11])
Combination*	2/13 (15 [2-45])	8/21 (38 [18-62])	10/34 (29 [15-47])	30/83 (36 [26-47])	115/305 (38 [32-43])	145/388 (37 [33-42])

AID = autoimmune disease; CTLA-4 = cytotoxic T lymphocyte–associated protein 4; irAE = immune-related adverse event; PD-1 = programmed cell death 1.
* Anti–CTLA-4 and anti–PD-1.

Safety of ICI

Anti-CTLA-4

The incidence of irAEs of grade 3 or higher associated with anti-CTLA-4 was 30% for both patients with and those without AID (Table 2; Appendix Table 5). No patients with AID died of toxicity, versus 3 patients without AID (0.3%).

Of the 28 patients who were receiving immunosuppressive treatment, 21% (CI, 8% to 41%) developed irAEs of grade 3 or higher, versus 34% (CI, 22% to 47%) of the 59 patients without. Because of the limited number of patients with AID treated with anti-CTLA-4, we could not draw any definite conclusions on the differences in reasons to terminate treatment or the influence of immunosuppressive treatment on toxicity.

Anti-PD-1

Incidence of irAEs of grade 3 or higher was similar in patients with and without AID (17% [CI, 12% to 23%] and 13% [CI, 12% to 15%], respectively) (Table 2; Appendix Table 6). No patients with AID died of toxicity, versus 5 patients without AID (0.3%).

Toxicity led to discontinuation of treatment more frequently in patients with AID (17% [CI, 12% to 23%]) than in those without (9% [CI, 8% to 11%]). Furthermore, patients with AID developed more colitis of grade 3 or higher (5% [CI, 3% to 10%] vs. 2% [CI, 2% to 3%]) (Appendix Table 6). The incidence of irAEs of grade 3 or higher did not differ in patients with AID who used versus did not use immunosuppressive treatment at baseline (15% [CI, 7% to 25%] of 68 patients vs. 18% [CI, 11% to 26%] of 119 patients, respectively) (Table 2).

Anti-CTLA-4 and Anti-PD-1

After combination therapy, 44% (CI, 27% to 62%) of 34 patients with versus 48% (CI, 43% to 53%) of 388 patients without AID had irAEs of grade 3 or higher (Table 2; Appendix Table 7). No patients with AID died of toxicity, versus 1 patient without AID (0.3%).

Specific AID Categories

Patients with IBD were more prone to anti-PD-1-induced colitis (6/31 = 19% [CI, 7% to 37%]) than those with other AIDs (3% [CI, 0% to 6%]) and those without AID (2% [CI, 2% to 3%]). In 5 of 6 patients with IBD who developed colitis, treatment with corticosteroids was initiated; 2 received additional treatment with tumor necrosis factor-a inhibitors, and 1 had an intestinal perforation. Because of the limited number of patients with IBD treated with anti-CTLA-4 with or without anti-PD-1, we could not draw any definite conclusions on the differences in safety between AID categories.

Response After ICI

Both best overall response and objective response rate after ICI were similar in patients with and without AID. The objective response rate after anti-CTLA-4 treatment was 10% (CI, 5% to 19%) of 78 patients with AID, versus 16% (CI, 14% to 19%) of 843 patients without AID. After anti-PD-1 treatment, 40% (CI, 33% to 47%) of 178 patients with AID had a response, versus 44% (CI, 41% to 46%) of 1491 patients without AID. Of 26 patients with AID treated with combination therapy, 39% (CI, 20% to 59%) had an objective response, versus 43% (CI, 38% to 49%) of 334 patients without AID (Appendix Table 8).

Survival

All Patients

Overall survival since diagnosis of advanced melanoma did not differ in patients with versus without AID (median, 13 months [CI, 10 to 16 months] vs. 14 months [CI, 13 to 15 months], respectively). Furthermore, there was no difference in crude or adjusted hazard ratios for MSS, OS, or PFS after ICI between patients with and those without AID (Figure 2; Appendix Table 9).

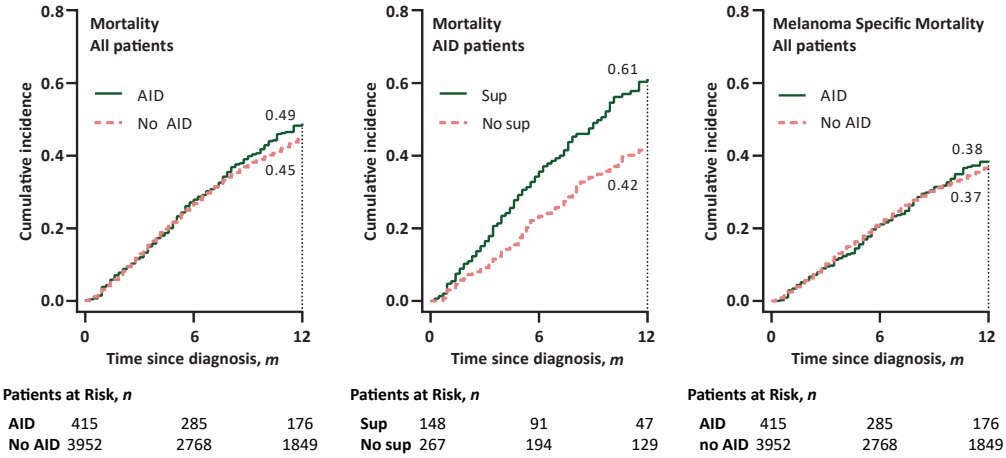


FIGURE 2 Cumulative incidence of mortality and melanoma-specific mortality.
AID = autoimmune disease; sup = immunosuppressive treatment. **Left**. Cumulative incidence of mortality of all patients with and without AID. **Center**. Cumulative incidence of mortality of patients with AID who use or do not use sup at baseline. **Right**. Cumulative incidence of melanoma-specific mortality of patients with and without AID.

Patients with AID who used immunosuppressive treatment at baseline seemed to have a higher cumulative incidence of death than patients with AID who did not use immunosuppressive treatment (Figure 2). However, this difference was no longer present after adjustment for known prognostic factors (adjusted hazard ratio, 1.18 [CI, 0.90 to 1.54]) (Appendix Table 10). The incidence of death was similar between AID categories (Appendix Figure).

Anti-CTLA-4

Overall survival was similar in patients with and without AID (median, 12 months [CI, 8 to 16 months] and 12 months [CI, 11 to 13 months], respectively). It did not differ between the 28 patients with AID who used immunosuppressive medication and the 59 patients with AID who did not (median, 10 months [CI, 8 to 12 months] and 16 months [CI, 7 to 25 months], respectively).

Anti-PD-1

Patients with and without AID had similar OS from start of anti-PD-1 therapy (median, 22 months [CI, 19 to 25 months] and 20 months [CI, 15 to 25 months], respectively). There was no statistically significant difference in OS between patients with AID with (n = 148) and without (n = 267) concomitant use of immunosuppressive treatment at baseline (median, 13 months [CI, 9 to 17 months] and 23 months [CI, 14 to 32 months], respectively).

Discussion

In the largest cohort reported to date, we observed that patients with AID and advanced melanoma in the Netherlands are treated with ICI as often as patients without AID. In patients with AID who used concomitant immunosuppressive medication, physicians seemed more hesitant to start ICI and more frequently prescribed targeted therapy. Incidence of irAEs of grade 3 or higher did not differ between patients with and those without AID. Toxicity and efficacy rates in patients with AID were largely in line with data from large phase 3 studies. Compared with anti-CTLA-4 monotherapy, anti-PD-1 with or without anti-CTLA-4 led to higher response rates and longer survival in both patients with and those without AID[3-6,18].

Half of the patients with advanced melanoma who are evaluated for ICI are not represented in phase 3 registration trials[19,20]. Patients with AID were excluded from these trials. To our knowledge, this is the first study to bridge this knowledge gap by presenting "real-world" data on the safety and efficacy of ICI on a national scale. In our population-based cohort, 9.5% of all patients with advanced melanoma had preexisting AID. This is higher than the estimated 7.6% to 9.4% described in nononcologic studies and national registry data[21].

Our findings on irAEs of grade 3 or higher after anti-CTLA-4 treatment in 87 patients with AID are in accordance with those of a previously published retrospective study by Johnson and colleagues[22], who described 30 patients with AID (incidence, 30% (CI, 21% to 41%) in our study vs. 33% (CI, 17% to 53%) in Johnson and colleagues').

The percentage of irAEs of grade 3 or higher after anti-PD-1 treatment in our patients with AID is similar to what Danlos and colleagues[23] reported. The difference in overall toxicity could be explained by the fact that Danlos and colleagues included grade 2 AEs in their analysis. The increased rate of treatment discontinuation due to toxicity in patients with AID in our study suggests that grade 2 irAEs might have been more frequent in our cohort as well[23]. A recent study using the DMTR database showed that patients who had toxicity management with tumor necrosis factor-α inhibitors had lower survival than those who were managed with steroids only[24]. In our study,

upfront use of immunosuppressive treatment was not clearly related to occurrence of irAEs of grade 3 or higher in patients with AID. The limited number of patients and events could explain why this difference was no longer statistically significant in multivariable analysis for patients with AID.

We compared treatment patterns in patients with different categories of AID. Patients with IBD were less often treated with anti-CTLA-4 than those with a rheumatologic or endocrine AID or those without AID. We speculate that this could be because of the known higher incidence of (gastrointestinal) AEs after this type of ICI or possibly fear of a flare of the preexisting IBD. The percentage of grade 3 or 4 colitis after anti-PD-1 treatment in our 31 patients with IBD was similar to that among the 85 patients in Abu-Sbeih and colleagues' retrospective study[13] (16% (CI, 7% to 37%) in our study vs. 19% (CI, 11% to 29%) in Abu-Sbeih and colleagues').

It was previously reported that the incidence of AEs after anti-PD-1 therapy differs among cancer types: Patients with melanoma have fewer AEs than those with, among others, ovarian cancer, sarcoma, or colorectal carcinoma[25]. A recent meta-analysis[26] compared the relative risk for AEs after anti-CTLA-4, anti-PD-1, and anti-programmed cell death ligand-1 treatment in multiple solid organ tumors compared with standard of care chemotherapy. Its subgroup analysis found similar odds ratios regardless of cancer type[26]. The similarities in relative risk strengthen our belief that our findings on safety of ICI in patients with advanced melanoma and AID might also be translatable to patients with other solid tumors.

A strength of our approach is that we used nation-wide, population-based data from the DMTR. All data are prospectively registered by trained data managers and approved by the treating physician. However, some limitations exist. Because only irAEs of grade 3 or higher are registered, mild to moderate flares of AID are not included in our analysis. Moreover, detailed information on exact type of AID, reason to prescribe immunosuppressive treatment, and prescribed dose is not available. The data presented reflect real-world treatment of patients with AID of rheumatologic or endocrine origin or IBD, but these data might not be generalizable to all AIDs. Rarer AIDs will be underrepresented in our cohort. Especially for myositis, myasthenia gravis, and Guillain-Barré syndrome, which are associated with high fatality rates when occurring as irAEs[27], caution is needed.

In 2017, combination therapy with anti-PD-1 and anti-CTLA-4 became readily available for patients with advanced melanoma in the Netherlands. Therefore, the number of patients treated with this combination is limited in our current database. It would be interesting to reevaluate the safety and efficacy of this combination therapy in patients with AID in the coming years.

In conclusion, we show that tumor response to ICI treatment with anti-CTLA-4, anti-PD-1, or their combination for advanced melanoma and incidence of irAEs of grade 3 or higher were similar in patients with and without preexisting AID of rheumatologic or endocrine origin in daily clinical practice. Therefore, we encourage physicians not to withhold ICI in most common AIDs. However, close monitoring in patients with IBD is advised because the incidence of severe colitis and early discontinuation of treatment due to toxicity was higher in this group.

Disclaimer

The views and opinions expressed here are those of the authors.

Financial Support

The DMTR was funded by grant 836002002 from The Netherlands Organization for Health Research and Development. From its foundation, the DMTR has been sponsored by Bristol-Myers Squibb, Novartis, Roche Nederland, Merck Sharp & Dohme, and Pierre Fabre via the Dutch Institute for Clinical Auditing.

Disclosures

Disclosures can be viewed at
www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M20-3419.

Author Contributions

Conception and design: M.K. van der Kooij, K.P.M. Suijkerbuijk, O.M. Dekkers, E. Kapiteijn. Analysis and interpretation of the data: M.K. van der Kooij, K.P.M. Suijkerbuijk, O.M. Dekkers, E. Kapiteijn. Drafting of the article: M.K. van der Kooij, K.P.M. Suijkerbuijk, O.M. Dekkers, E. Kapiteijn. Critical revision of the article for important intellectual content: M.K. van der Kooij, K.P.M. Suijkerbuijk, M.J.B. Aarts, F.W.P.J. van den Berkmortel, C.U. Blank, M.J. Boers-Sonderen, A.J.M. van den Eertwegh, J.W.B. de Groot, J.B.A.G. Haanen, G.A.P. Hospers, D. Piersma, R.S. van Rijn, A.J. ten Tije, A.A.M. van der Veldt, G. Vreugdenhil, M.C.T. van Zeijl, M.W.J.M Wouters, O.M. Dekkers, E. Kapiteijn. Final approval of the article: M.K. van der Kooij, K.P.M. Suijkerbuijk, M.J.B. Aarts, F.W.P.J. van den Berkmortel, C.U. Blank, M.J. Boers-Sonderen, J. van Breeschoten, A.J.M. van den Eertwegh, J.W.B. de Groot, J.B.A.G. Haanen, G.A.P. Hospers, D. Piersma, R.S. van Rijn, A.J. ten Tije, A.A.M. van der Veldt, G. Vreugdenhil, M.C.T. van Zeijl, M.W.J.M Wouters, O.M. Dekkers, E. Kapiteijn.

Provision of study materials or patients: K.P.M. Suijkerbuijk, M.J.B. Aarts, F.W.P.J. van den Berkmortel, C.U. Blank, M.J. Boers-Sonderen, A.J.M. van den Eertwegh, J.W.B. de Groot, J.B.A.G. Haanen, G.A.P. Hospers, D. Piersma, R.S. van Rijn, A.J. ten Tije, A.A.M. van der Veldt, G. Vreugdenhil, M.W.J.M Wouters, E. Kapiteijn. Statistical expertise: M.K. van der Kooij, O.M. Dekkers, E. Kapiteijn. Collection and assembly of data: M.K. van der Kooij, K.P.M. Suijkerbuijk, M.J.B. Aarts, F.W.P.J. van den Berkmortel, C.U. Blank, M.J. Boers-Sonderen, A.J.M. van den Eertwegh, J.W.B. de Groot, J.B.A.G. Haanen, G.A.P. Hospers, D. Piersma, R.S. van Rijn, A.J. ten Tije, A.A.M. van der Veldt, G. Vreugdenhil, M.W.J.M Wouters, E. Kapiteijn.

References

1 Wolchok JD, Rollin L, Larkin J. Nivolumab and ipilimumab in advanced melanoma [Letter]. N Engl J Med. 2017;377:2503-2504. [PMID: 29262279] doi:10.1056/NEJMc1714339

2 Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med. 2017;377:1345-1356. [PMID: 28889792] doi:10.1056/NEJMoa1709684

3 Carlino MS, Long GV, Schadendorf D, et al. Outcomes by line of therapy and programmed death ligand 1 expression in patients with advanced melanoma treated with pembrolizumab or ipilimumab in KEYNOTE-006: a randomised clinical trial. Eur J Cancer. 2018;101:236-243. [PMID: 30096704] doi:10.1016/j.ejca.2018.06.034

4 Hamid O, Puzanov I, Dummer R, et al. Final analysis of a randomised trial comparing pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory advanced melanoma. Eur J Cancer. 2017;86:37-45. [PMID: 28961465] doi:10.1016 j.ejca.2017.07.022

5 Hamid O, Robert C, Daud A, et al. Five-year survival outcomes for patients with advanced melanoma treated with pembrolizumab in KEYNOTE-001. Ann Oncol. 2019;30:582-588. [PMID: 30715153] doi:10.1093/annonc/mdz011

6 Larkin J, Minor D, D'Angelo S, et al. Overall survival in patients with advanced melanoma who received nivolumab versus investigator's choice chemotherapy in CheckMate 037: a randomized, controlled, open-label phase III trial. J Clin Oncol. 2018;36:383-390. [PMID: 28671856] doi:10.1200/JCO.2016.71.8023

7 Abdel-Wahab N, Shah M, Suarez-Almazor ME. Adverse events associated with immune checkpoint blockade in patients with cancer: a systematic review of case reports. PLoS One. 2016;11: e0160221. [PMID: 27472273] doi:10.1371/journal.pone.0160221

8 Abdel-Wahab N, Shah M, Lopez-Olivo MA, et al. Use of immune checkpoint inhibitors in the treatment of patients with cancer and preexisting autoimmune disease [Letter]. Ann Intern Med. 2018; 169:133-134. doi:10.7326/L18-0209

9 Donia M, Pedersen M, Svane IM. Cancer immunotherapy in patients with preexisting autoimmune disorders. Semin Immunopathol. 2017;39:333-337. [PMID: 27730287] doi:10.1007/s00281-016-0595-8

10 Calabrese LH. Sorting out the complexities of autoimmunity and checkpoint inhibitors: not so easy [Editorial]. Ann Intern Med. 2018;168:149-150. doi:10.7326/M17-3079

11 Leonardi GC, Gainor JF, Altan M, et al. Safety of programmed death-1 pathway inhibitors among patients with non-small-cell lung cancer and preexisting autoimmune disorders. J Clin Oncol. 2018;36:1905-1912. [PMID: 29746230] doi:10.1200/JCO.2017.77.0305

12 Menzies AM, Johnson DB, Ramanujam S, et al. Anti-PD-1 therapy in patients with advanced melanoma and preexisting autoimmune disorders or major toxicity with

ipilimumab. Ann Oncol. 2017;28:368-376. [PMID: 27687304] doi:10.1093/annonc/mdw443

13 Abu-Sbeih H, Faleck DM, Ricciuti B, et al. Immune checkpoint inhibitor therapy in patients with preexisting inflammatory bowel disease. J Clin Oncol. 2020;38:576-583. [PMID: 31800340] doi:10.1200/JCO.19.01674

14 Jochems A, Schouwenburg MG, Leeneman B, et al. Dutch Melanoma Treatment Registry: quality assurance in the care of patients with metastatic melanoma in the Netherlands. Eur J Cancer. 2017;72:156-165. [PMID: 28030784] doi:10.1016/j.ejca.2016.11.021

15 Schwartz LH, Litière S, de Vries E, et al. RECIST 1.1—update and clarification: from the RECIST committee. Eur J Cancer. 2016; 62:132-7. [PMID: 27189322] doi:10.1016/j.ejca.2016.03.081

16 de Glas NA, Kiderlen M, Vandenbroucke JP, et al. Performing survival analyses in the presence of competing risks: a clinical example in older breast cancer patients. J Natl Cancer Inst. 2016;108. [PMID: 26614095] doi:10.1093/jnci/djv366

17 Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. Stat Med. 2007;26:2389-430. [PMID: 17031868]

18 Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med. 2019;381:1535-1546. [PMID: 31562797] doi:10.1056/NEJMoa1910836

19 Donia M, Hansen SW, Svane IM. Real-world evidence to guide healthcare policies in oncology. Oncotarget. 2019;10:4513-4515. [PMID: 31360300] doi:10.18632/oncotarget.27077

20 Donia M, Kimper-Karl ML, Høyer KL, et al. The majority of patients with metastatic melanoma are not represented in pivotal phase III immunotherapy trials. Eur J Cancer. 2017;74:89-95. [PMID: 28335891] doi:10.1016/j.ejca.2016.12.017

21 Cooper GS, Bynum ML, Somers EC. Recent insights in the epidemiology of autoimmune diseases: improved prevalence estimates and understanding of clustering of diseases. J Autoimmun. 2009;33:197-207. [PMID: 19819109] doi:10.1016/j.jaut.2009.09.008

22 Johnson DB, Sullivan RJ, Ott PA, et al. Ipilimumab therapy in patients with advanced melanoma and preexisting autoimmune disorders. JAMA Oncol. 2016;2:234-40. [PMID: 26633184] doi:10.1001/jamaoncol.2015.4368

23 Danlos FX, Voisin AL, Dyevre V, et al. Safety and efficacy of anti-programmed death 1 antibodies in patients with cancer and pre-existing autoimmune or inflammatory disease. Eur J Cancer. 2018;91:21-29. [PMID: 29331748] doi:10.1016/j.ejca.2017.12.008

24 Verheijden RJ, May AM, Blank CU, et al. Association of anti-TNF with decreased survival in steroid refractory ipilimumab and anti-PD-1-treated patients in the Dutch Melanoma Treatment Registry. Clin Cancer Res. 2020;26:2268-2274. [PMID: 31988197] doi:10.1158/1078-0432.CCR-19-3322

25 Zhao B, Zhao H, Zhao J. Serious adverse events and fatal adverse events associated with nivolumab treatment in cancer patients: nivolumab-related serious/fatal adverse events. J Immunother Cancer. 2018;6:101. [PMID: 30285872] doi:10.1186/s40425-018-0421-z

26 Magee DE, Hird AE, Klaassen Z, et al. Adverse event profile for immunotherapy agents compared with chemotherapy in solid organ tumors: a systematic review and meta-analysis of randomized clinical trials. Ann Oncol. 2020;31:50-60. [PMID: 31912796] doi: 10.1016/j.annonc.2019.10.008

27 Wang DY, Salem JE, Cohen JV, et al. Fatal toxic effects associated with immune checkpoint inhibitors: a systematic review and meta-analysis. JAMA Oncol. 2018;4:1721-1728. [PMID: 30242316] doi:10.1001/jamaoncol.2018.3923

Appendix

APPENDIX TABLE 1 Number of Included Patients With and Without Autoimmune Disease per Melanoma Treatment Center

Treatment Center	AID (*n* = 415), *n* (%)	No AID (*n* = 3952), *n* (%)	Total (*n* = 4367), *n*
1	11 (8.3)	122 (91.7)	133
2	22 (13.1)	146 (86.9)	168
3	7 (5.5)	120 (94.5)	127
4	22 (9.4)	213 (90.6)	235
5	29 (7.3)	368 (92.7)	397
6	77 (7.3)	971 (92.7)	1048
7	28 (13.1)	184 (86.8)	212
8	64 (12.5)	450 (87.5)	514
9	23 (9.3)	225 (90.7)	248
10	10 (9.6)	94 (90.4)	104
11	47 (12.0)	345 (88.0)	392
12	22 (12.6)	153 (87.4)	175
13	33 (7.9)	387 (92.1)	420
14	20 (10.3)	174 (89.7)	194

AID = autoimmune disease.

APPENDIX TABLE 2 Number of Patients Included per Condition Classified as AID*

AID Category	Subtype	Patients, *n*
IBD	IBD	55
Endocrine	Hypo-/hyperthyroidism	141
Endocrine	Graves disease	3
Rheumatoid	RA/SLE/scleroderma	213
Rheumatoid	Sarcoidosis	10
Rheumatoid	Vasculitis	5
Other	Other	8

AID = autoimmune disease; IBD = inflammatory bowel disease; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus.

* Twenty patients with AID had multiple AIDs: 5 had rheumatoid and IBD, 12 had rheumatoid and endocrine, 1 had IBD and AID of endocrine origin, 1 had both Graves disease and hypo-/hyperthyroidism, and 1 had RA/SLE/scleroderma and sarcoidosis.

APPENDIX TABLE 3 Treatment Episodes Where Immune Checkpoint Inhibition Was Initially Given in Patients With and Without Autoimmune Disease*

Treatment Episode†	Anti–CTLA-4		Anti–PD-1		Anti–CTLA-4 and Anti–PD-1	
	AID (*n* = 87)	No AID (*n* = 916)	AID (*n* = 187)	No AID (*n* = 1540)	AID (*n* = 14)	No AID (*n* = 108)
1	41 (47)	432 (47)	91 (49)	834 (54)	1 (7)	38 (35)
2	30 (33)	372 (40)	59 (32)	456 (30)	8 (57)	50 (46)
3	10 (12)	80 (9)	27 (14)	159 (10)	3 (21)	12 (11)
4	4 (5)	25 (3)	7 (4)	70 (4)	1 (7)	4 (5)
5	1 (1)	6 (1)	2 (1)	10 (1)	0	2 (2)
≥6	1 (1)	1	1	11 (1)	1 (7)	1 (1)

AID = autoimmune disease; CTLA-4 = cytotoxic T lymphocyte–associated protein 4; PD-1 = programmed cell death 1.

* Values are numbers (percentages).

† Identified as the line of treatment after diagnosis of advanced melanoma. The first episode in which a patient received each individual drug is shown.

APPENDIX TABLE 4 Baseline Characteristics of Patients With Autoimmune Disease at Time of Initial Antitumor Treatment*

Characteristic	ICI (n = 143)†	Targeted Therapy (n = 104)‡	Other Treatment (n = 107)§	No Treatment (n = 61)‖
Age at treatment decision				
Mean (range), y	67 (24–89)	63 (32–87)	65 (33–89)	74 (33–92)
<65 y	53 (37)	53 (51)	48 (45)	8 (13)
≥65 y	90 (63)	51 (49)	59 (55)	53 (87)
Time since registration				
Median (IQR), wk	5 (1–9)	4 (0–8)	7 (0–14)	–
Sex				
Male	62 (43)	51 (49)	50 (47)	30 (49)
Female	81 (57)	53 (51)	57 (53)	31 (51)
ECOG performance status				
0	73 (51)	31 (30)	46 (43)	13 (21)
1	47 (33)	39 (37)	21 (20)	13 (21)
2, 3, or 4	11 (8)	24 (23)	13 (12)	16 (26)
Unknown	12 (8)	10 (10)	27 (25)	19 (31)
Lactate dehydrogenase level				
Normal	101 (71)	42 (40)	11 (10)	13 (21)
4.17–8.33 μkat/L (<2x ULN)	32 (22)	29 (28)	66 (62)	23 (38)
>8.33 μkat/L (>2x ULN)	8 (6)	30 (29)	21 (20)	7 (11)
Missing	2 (1)	3 (3)	9 (8)	18 (30)
Metastasis in ≥3 organ sites				
Yes	36 (25)	45 (43)	18 (17)	14 (23)
No	107 (75)	59 (57)	89 (83)	47 (77)
Brain metastases				
Yes	24 (17)	29 (28)	26 (24)	8 (13)
Symptomatic	13 (9)	22 (21)	21 (20)	6 (10)
No	107 (75)	65 (62)	60 (56)	40 (66)
Unknown	12 (8)	10 (10)	21 (20)	13 (21)
Immunosuppressive treatment				
Yes	43 (30)	43 (41)	35 (33)	27 (44)
No	100 (70)	61 (59)	72 (67)	34 (56)

ECOG = Eastern Cooperative Oncology Group; ICI = immune checkpoint inhibition; IQR = interquartile range; ULN = upper limit of normal.

* Values are numbers (percentages) unless otherwise indicated.

† Anti–programmed cell death 1, anti–cytotoxic T lymphocyte–associated protein 4, or the combination.

‡ BRAF inhibitors and MEK inhibitors.

§ Dacarbazine, talimogene laherparepvec, surgery, radiation, radiofrequency ablation, or hyperthermia.

‖ Best supportive care.

APPENDIX TABLE 5 Number of Patients with Grade III/IV Immune-related Adverse Events, Therapy Discontinuation, and Adverse Events Consequences following Anti-CTLA-4 Treatment*

Variable	IBD AID *n*=6	Endo AID *n*=43	Rheum AID *n*=41	All AID *n*=87†	no AID *n*=916
Reason to stop treatment					
Pre-planned	1 (17)	25 (58)	22 (54)	47 (54)	536 (59)
Progression	2 (33)	5 (12)	10 (24)	16 (18)	165 (18)
Toxicity	3 (50)	8 (19)	6 (15)	16 (18)	138 (15)
Patient choice	-	-	-	-	3
Patient Condition	-	3 (7)	2 (5)	5 (6)	46 (5)
Death	-	1 (2)	-	1 (1)	13 (1)
Other	-	-	1 (2)	1 (1)	4
Unknown	-	-	-	-	2
Not applicable	-	1 (2)	-	1 (1)	9 (1)
Grade III-IV irAE	2 (33)	13 (30)	12 (29)	26 (30)	272 (30)
Colitis	2 (33)	7 (16)	8 (20)	16 (18)	137 (15)
Intestinal perforation	-	-	1 (2)	-	4
Hepatitis	-	3 (7)	-	3 (3)	23 (3)
Adrenal insufficiency	-	-	2 (4)	2 (2)	25 (3)
Myelotoxicity	-	-	1 (2)	1 (1)	7 (1)
Neuropathy	-	-	-	-	2
Hypophyses insufficiency	-	-	2 (5)	2 (2)	50 (6)
Thyroid insufficiency	-	-	2 (5)	2 (2)	21 (2)
Skin toxicity	-	3 (7)	1 (2)	3 (3)	21 (2)
Uveitis	-	-	-	-	2
Other	-	3 (7)	4 (10)	7 (8)	56 (6)
Toxicity consequences					
Immunosuppressive medication	2 (33)	12 (28)	11 (27)	24 (28)	258 (28)
Corticosteroids	2 (33)	12 (28)	9 (22)	22 (25)	221 (24)
TNFa blocker	-	-	-	-	-
Other	2 (33)	6 (14)	6 (15)	14 (16)	85 (9)
Admitted outpatient clinic	-	-	1 (2)	1 (1)	14 (2)
Admitted hospital	-	7 (16)	10 (24)	17 (20)	192 (21)
Permanent damage	-	-	-	-	9 (3)
Death due to toxicity	-	-	-	-	3

AE = adverse event; AID = autoimmune disease; CTLA-4 = cytotoxic T lymphocyte–associated protein 4; IBD = inflammatory bowel disease; irAE = immune-related AE.

* Values are numbers (percentages).

† Five patients had both an AID of endocrine and one of rheumatologic origin. Two patients had an AID classified as "other."

APPENDIX TABLE 6 Number of Patients with Grade III/IV Immune-related Adverse Events, Therapy Discontinuation, and Adverse Events Consequences following Anti-PD-1 Treatment*

Variable	IBD AID *n*=31	Endo AID *n*=73	Rheum AID *n*=89	All AID *n*=187†	no AID *n*=1540
Reason to stop treatment					
Pre-planned	2 (7)	13 (18)	6 (7)	21 (11)	227 (15)
Progression	18 (58)	32 (44)	42 (47)	89 (48)	744 (48)
Toxicity	6 (19)	12 (16)	15 (17)	31 (17)	145 (9)
Patient choice	-		1 (1)	1	25 (2)
Patient condition	-	3 (4)	7 (8)	10 (5)	64 (4)
Death	-	1 (1)	1 (1)	2 (1)	30 (2)
Other	-	5 (7)	2 (2)	7 (4)	71 (5)
Unknown	1 (3)	-	-	1	10
Not applicable	4 (13)	7 (10)	15 (17)	25 (13)	224 (15)
Grade III-IV irAE	7 (23)	13 (18)	12 (14)	31 (17)	206 (13)
Colitis	6 (19)	-	4 (5)	10 (5)	34 (2)
Intestinal perforation	1 (3)	-	1 (1)	2 (1)	17 (1)
Hepatitis	-	3 (4)	3 (3)	5 (3)	25 (2)
Decline in renal function	-	-	1 (1)	1	11
Nephritis	-	-	1 (1)	-	9 (1)
Dyspnea	-	1 (1)	-	1	5
Pneumonia	-	2 (3)	2 (2)	4 (2)	17 (1)
Adrenal insufficiency	-	1 (1)	-	1	11 (1)
Myelotoxicity	-	-	-	-	6
Neuropathy	-	-	-	-	5
Hypophyses insufficiency	-	-	-	-	8 (1)
Thyroid insufficiency	-	1 (1)	-	1 (1)	13 (1)
Fatigue	-	2 (3)	1 (1)	3 (2)	12 (1)
Rash	-	-	2 (2)	2	10 (1)
Pruritis	-	-	-	-	2
Vitiligo	-	1 (1)	-	1	6
Other	1 (3)	5 (7)	3 (3)	9 (5)	82 (5)
Toxicity consequences					
Immunosuppressive medication	7 (23)	11 (15)	11 (12)	28 (15)	177 (12)
Corticosteroids	6 (19)	10 (14)	8 (9)	23 (12)	141 (9)
TNFa blocker	2 (7)	1 (1)	2 (2)	5 (3)	15 (1)
Other	-	-	-	-	12 (1)
Admitted outpatient clinic	3 (10)	1 (1)	-	4 (2)	8 (1)
Admitted hospital	4 (13)	9 (12)	6 (7)	19 (10)	104 (7)
Permanent damage	2 (7)	-	1 (1)	3 (2)	10 (1)
Death due to toxicity	-	-	-	-	5

AE = adverse event; AID = autoimmune disease; IBD = inflammatory bowel disease; irAE = immune-related AE; PD-1 = programmed cell death 1.
* Values are numbers (percentages).
† Five patients had both an AID of endocrine and one of rheumatologic origin, and 4 patients had both IBD and an AID of rheumatologic origin. Three patients had an AID classified as "other."

APPENDIX TABLE 7 Number of Patients With Grade 3 or 4 irAEs, Therapy Discontinuation, and AE Consequences After Anti-CTLA-4 Plus Anti-PD-1 Combination Treatment*

Variable	IBD AID (*n* = 6)	AID of Endocrine Origin (*n* = 14)	AID of Rheumatologic Origin (*n* = 14)	All AID (*n* = 34)	No AID (*n* = 388)
Reason to stop treatment					
Preplanned	–	–	–	–	26 (7)
Progression	2 (33)	4 (29)	4 (29)	10 (29)	100 (26)
Toxicity	1 (17)	7 (50)	2 (14)	10 (29)	145 (37)
Patient choice	–	–	–	–	5 (1)
Patient condition	1 (17)	1 (7)	1 (7)	3 (9)	29 (8)
Death	–	–	–	–	22 (6)
Other	–	–	–	–	6 (2)
Unknown	–	1 (7)	–	1 (3)	2 (1)
Not applicable	2 (33)	1 (7)	7 (50)	10 (29)	53 (14)
Grade 3 or 4 irAE	1 (17)	9 (64)	5 (36)	15 (44)	187 (48)
Diarrhea	–	–	1 (7)	1 (3)	26 (7)
Colitis	–	3 (21)	2 (14)	5 (15)	61 (16)
Hepatitis	1 (17)	3 (21)	1 (7)	5 (15)	73 (19)
Nephritis	–	–	–	–	7 (2)
Pneumonia	–	–	–	–	14 (4)
Adrenal insufficiency	–	–	–	–	6 (2)
Myelotoxicity	–	1 (7)	–	1 (3)	2 (1)
Neuropathy	–	–	–	–	5 (1)
Pituitary insufficiency	1 (17)	1 (7)	–	2 (6)	18 (5)
Thyroid insufficiency	–	1 (7)	1 (7)	2 (6)	12 (3)
Fatigue	–	–	–	–	3 (1)
Rash	1 (17)	–	–	1 (3)	15 (4)
Pruritus	–	–	–	–	5 (1)
Vitiligo	–	–	–	–	1
Other	–	3 (21)	3 (21)	6 (18)	39 (10)
Toxicity consequences					
Immunosuppressive medication	1 (17)	8 (57)	5 (36)	14 (41)	178 (46)
Corticosteroids	1 (17)	8 (57)	4 (29)	13 (38)	165 (43)
Tumor necrosis factor-a blocker	–	2 (14)	1 (7)	3 (9)	36 (9)
Other	1 (17)	2 (14)	–	3 (9)	22 (6)
Admitted to outpatient clinic	–	–	–	–	9 (2)
Admitted to hospital	1 (17)	6 (43)	2 (14)	9 (27)	112 (29)
Permanent damage	–	–	–	–	5 (1)
Death due to toxicity	–	–	–	–	1

AE = adverse event; AID = autoimmune disease; CTLA-4 = cytotoxic T lymphocyte–associated protein 4; IBD = inflammatory bowel disease; irAE = immune-related AE; PD-1 = programmed cell death 1.
* Values are numbers (percentages).

APPENDIX TABLE 8 Tumor Response After Immune Checkpoint Inhibition in Patients With and Without AID*

Treatment and Response	AID	No AID
Anti–CTLA-4	***n* = 78**	***n* = 843**
PD	40 (51 [40–63])	437 (52 [48–55])
SD	30 (38 [28–50])	270 (32 [29–35])
PR	6 (8 [3–16])	87 (10 [8–13])
CR	2 (3 [0–9])	49 (6 [4–8])
ORR†	8 (10 [5–19])	136 (16 [14–19])
Anti–PD-1	***n* = 178**	***n* = 1491**
PD	63 (35 [28–43])	502 (34 [32–36])
SD	44 (25 [19–32])	337 (23 [21–25])
PR	50 (28 [22–35])	455 (30 [28–33])
CR	21 (12 [7–17])	197 (13 [12–15])
ORR†	71 (40 [33–47])	652 (44 [41–46])
Anti–CTLA-4 and anti–PD-1	***n* = 26**	***n* = 334**
PD	12 (46 [27–67])	133 (40 [35–45])
SD	4 (15 [4–35])	57 (17 [13–22])
PR	9 (35 [17–56])	115 (34 [29–40])
CR	1 (4 [0–20])	29 (9 [5–12])
ORR†	10 (39 [20–59])	144 (43 [38–49])

AID = autoimmune disease; CR = complete response; CTLA-4 = cyto- toxic T lymphocyte–associated protein 4; ORR = objective response rate; PD = progressive disease; PD-1 = programmed cell death 1; PR = partial response; SD = stable disease.

* Values are numbers (percentages [95% CIs]).

† PR + CR.

APPENDIX TABLE 9 OS, MSS, and PFS for Patients With and Without AID

Patient Group and Survival	Events, n/N		HR (95% CI)	Adjusted HR (95% CI)
	AID	No AID		
All patients				
OS	258/415	2431/3952	1.04 (0.92–1.19)	0.98 (0.86–1.11)
MSS*				
Cox proportional hazards model	183/415	1859/3952	0.97 (0.83–1.13)	0.93 (0.80–1.08)
Competing-risk model	183/415	1859/3952	0.94 (0.81–1.09)	0.95 (0.81–1.11)
By initial treatment				
Anti–CTLA-4				
OS	59/87	662/916	0.95 (0.73–1.24)	0.90 (0.69–1.18)
MSS*				
Cox proportional hazards model	44/87	532/916	0.88 (0.65–1.20)	0.85 (0.62–1.16)
Competing-risk model	44/87	532/916	0.72 (0.45–1.14)	0.68 (0.42–1.11)
PFS	76/87	813/916	0.99 (0.78–1.25)	0.95 (0.75–1.20)
Anti–PD-1				
OS	91/187	725/1540	1.14 (0.92–1.42)	1.08 (0.87–1.34)
MSS*				
Cox proportional hazards model	68/187	573/1540	1.08 (0.84–1.39)	1.03 (0.80–1.32)
Competing-risk model	68/187	573/1540	1.14 (0.78–1.70)	1.12 (0.76–1.66)
PFS	126/187	1025/1540	1.15 (0.96–1.38)	1.11 (0.92–1.34)
Anti–CTLA-4 and anti–PD-1				
OS	14/34	178/388	1.13 (0.66–1.95)	-
MSS*				
Cox proportional hazards model	13/34	160/388	1.17 (0.67–2.06)	-
Competing-risk model	13/34	160/388	0.83 (0.31–2.23)	-
PFS	19/34	244/388	1.16 (0.73–1.86)	-

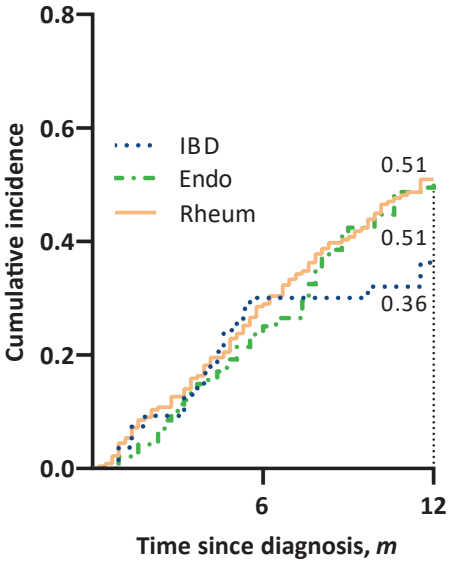
AID = autoimmune disease; CTLA-4 = cytotoxic T lymphocyte–associated protein 4; HR = hazard ratio; MSS = melanoma-specific survival; OS = overall survival; PD-1 = programmed cell death 1; PFS = progression-free survival.

* Calculated both using the Cox proportional hazards model and using the competing-risk model. In the competing-risk model, the subdistribution adjusted HR is shown.

APPENDIX TABLE 10 OS, MSS, and PFS for Patients with AID who use or do not use Immunosuppressive Medication.

Patient group and survival	Events, n/N		HR (95% CI)	Adjuste HR (95% CI)
	Immuno-suppressive medication	No Immuno-suppressive medication		
All patients				
OS	105/148	153/267	1.57 (1.23-2.02)	1.18 (0.90-1.54)
MSS*				
Cox proportional hazards model	73/148	110/267	1.15 (1.12-2.03)	1.02 (0.94-1.40)
Competing-risk model	73/148	110/267	1.33 (0.99-1.78)	0.87 (0.62-1.24)
Initial treatment				
Anti-CTLA-4				
OS	21/28	38/59	1.45 (0.85-2.47)	-
MSS*				
Cox proportional hazards model	17/28	27/59	1.65 (0.90-3.03)	-
Competing-risk model	17/28	27/59	1.29 (0.50-3.33)	-
PFS	24/28	52/59	1.22 (0.75-1.99)	-
Anti-PD-1				
OS	40/68	51/119	1.41 (0.93-2.14)	-
MSS*				
Cox proportional hazards model	33/68	35/119	1.69 (1.05-2.72)	-
Competing-risk model	33/68	35/119	2.34 (1.15-4.72)	-
PFS	50/68	76/119	1.22 (0.85-1.74)	-
Anti-CTLA-4 & anti-PD-1				
OS	7/13	7/21	1.27 (0.44-3.69)	-
MSS*				
Cox proportional hazards model	6/13	7/21	1.07 (0.35-3.24)	-
Competing-risk model	6/13	7/21	0.62 (0.06-5.92)	-
PFS	8/13	11/21	0.92 (0.36-2.31)	-

AID = autoimmune disease; CTLA-4 = cytotoxic T lymphocyte–associated protein 4; HR = hazard ratio; MSS = melanoma-specific survival; OS = overall survival; PD-1 = programmed cell death 1; PFS = progression-free survival.
* Calculated both using the Cox proportional hazards model and using the competing-risk model. In the competing-risk model, the subdistribution adjusted HR is shown.



Patients at Risk, *n

IBD	55	37	30
Endo	143	104	63
Rheum	227	150	86

APPENDIX FIGURE Cumulative incidence of mortality in patients with AID.

AID = autoimmune disease; IBD = inflammatory bowel disease.
* Some patients had multiple AIDs: 5 had rheumatoid AID and IBD, 12 had rheumatoid and endocrine AIDs, and 1 had IBD and endocrine AID.