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Safety Profile of Nivolumab Monotherapy: A Pooled Analysis of Patients With Advanced Melanoma

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ABSTRACT

Purpose
We conducted a retrospective analysis to assess the safety profile of nivolumab monotherapy in patients with advanced melanoma and describe the management of adverse events (AEs) using established safety guidelines.

Patients and Methods
Safety data were pooled from four studies, including two phase III trials, with patients who received nivolumab 3 mg/kg once every 2 weeks. We evaluated rate of treatment-related AEs, time to onset and resolution of select AEs (those with potential immunologic etiology), and impact of select AEs and suppressive immune-modulating agents (IMs) on antitumor efficacy.

Results
Among 576 patients, 71% (95% CI, 67% to 75%) experienced any-grade treatment-related AEs (most commonly fatigue [25%], pruritus [17%], diarrhea [13%], and rash [13%]), and 10% (95% CI, 8% to 13%) experienced grade 3 to 4 treatment-related AEs. No drug-related deaths were reported. Select AEs (occurring in 49% of patients) were most frequently skin related, GI, endocrine, and hepatic; grade 3 to 4 select AEs occurred in 4% of patients. Median time to onset of select AEs ranged from 5 weeks for skin to 15 weeks for renal AEs. Approximately 24% of patients received systemic IMs to manage select AEs, which in most cases resolved. Adjusting for number of doses, objective response rate (ORR) was significantly higher in patients who experienced treatment-related select AEs of any grade compared with those who did not. ORRs were similar in patients who did and patients who did not receive systemic IMs.

Conclusion
Treatment-related AEs with nivolumab monotherapy were primarily low grade, and most resolved with established safety guidelines. Use of IMs did not affect ORR, although treatment-related select AEs of any grade were associated with higher ORR, but no progression-free survival benefit.

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INTRODUCTION

Nivolumab is a fully human immunoglobulin G4 programmed death-1 (PD-1) checkpoint inhibitor antibody that selectively blocks the interaction of the PD-1 receptor with its known ligands, programmed death ligand-1 (PD-L1) and programmed death ligand-2 (PD-L2), disrupting signals that downmodulate T-cell activation and proliferation.[1] Nivolumab has significant clinical activity either as monotherapy or in combination with ipilimumab in several tumor types, including non–small-cell lung cancer, melanoma, and renal cell carcinoma.[2-8] A majority of responses have been durable and persisted after treatment discontinuation in patients who stopped therapy for reasons other than disease progression.[4,9]

CheckMate 066, a recently completed phase III trial of nivolumab monotherapy, showed significant improvement in progression-free survival (PFS) and overall survival (OS) and a manageable safety profile compared with chemotherapy in patients with previously untreated, advanced melanoma.[10] In another phase III study, CheckMate 037, nivolumab induced a higher objective response rate (ORR) compared with investigator's choice of chemotherapy in patients with advanced melanoma who experienced progression after prior ipilimumab therapy or ipilimumab plus a BRAF inhibitor in cases of *BRAF* mutation–positive disease.[7]

In nivolumab studies to date, treatment-related adverse events (AEs) have included dermatologic, GI, endocrine, hepatic, renal, and pulmonary toxicities. Most AEs have been low grade and managed successfully with supportive care. Most grade 3 to 4 AEs have resolved with nivolumab dose delay or permanent discontinuation, with or without administration of systemic corticosteroids or other suppressive immune-modulating agents (IMs).

To better characterize the safety profile of immune checkpoint inhibitors including nivolumab, a classification of the most common and clinically significant immune-related (ie, select) AEs associated with these drugs was developed. Select AEs were classified into organ categories, for which specific guidelines were developed.[7,10] These guidelines or algorithms include the use of IMs, particularly systemic corticosteroids, to manage AEs with a potential immune-related etiology.[11] To further describe the safety profile of nivolumab in advanced melanoma and examine outcomes of select AE management on the basis of the use of the proposed safety management guidelines, we conducted a pooled data analysis for patients receiving nivolumab at 3 mg/kg every 2 weeks, across multiple recent clinical trials.

PATIENTS AND METHODS

Patients

All patients in this analysis received at least one dose of nivolumab at 3 mg/kg once every 2 weeks in one of the following clinical trials:

- Phase I dose-ranging study in previously treated, advanced solid tumors (CA209-003; clinical trial information: NCT00730639; n = 17 [patients with melanoma in the 3-mg/kg cohort])[6,9]
- Phase I exploratory biomarker study in advanced melanoma (CA209-038; clinical trial information: NCT01621490; n = 85)
- Phase III study of nivolumab versus chemotherapy in advanced melanoma after progression with ipilimumab or ipilimumab plus a BRAF inhibitor in cases of *BRAF* V600 mutation–positive disease (CheckMate 037; clinical trial information: NCT01721746; n = 268)[7]
- Phase III study of nivolumab versus dacarbazine in patients with previously untreated melanoma without a *BRAF* mutation (CheckMate 066; clinical trial information: NCT01721772; n= 206)[10]

Patients were treated until disease progression or unacceptable toxicity in the phase III trials or for up to 2 years in the phase I trials. Only patients in studies CA209-038 and CheckMate 037 had received prior ipilimumab therapy (n = 44) and (n 268), respectively, with a minimum time between the last dose of ipilimumab and the first dose of nivolumab of 6 weeks.

Efficacy and Safety Assessments

Safety evaluations included assessment of treatment-related AEs, treatment-related select AEs, time to onset and resolution of select AEs, and use of IMs to manage select AEs. Select AEs were defined as having a potential immunologic basis that required more frequent monitoring and potential intervention with immune suppression and/or endocrine replacement therapy. AEs were coded using the Medical Dictionary for Regulatory Activities version 16.1 for CheckMate 037 and CA209-038 and version 17.0 for CA209-003 and CheckMate 066.

AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 for CA209-003 and version 4.0 for all other studies. Data on time to onset and resolution of treatment-related select AEs and on IM use were available from the two phase III trials: CheckMate 037 and CheckMate 066 (n = 474). Time to resolution of a select AE was defined as the longest time from onset to complete resolution or improvement to the baseline grade, among all clustered select AEs belonging to a select AE category experienced by the patient.

An exploratory analysis evaluated the relationship between the development of select AEs and ORR or PFS, with AEs occurring before the date of event for PFS included in these analyses. To evaluate the potential impact of AE management on the efficacy of nivolumab, ORRs were

Table 1. All AEs, Treatment-Related AEs, and Treatment-Related Select AEs* by Organ Category

AE Term†	Patients With AE (%)‡ (N = 576)	
	Any Grade	Grade 3 to 4
Any AE, regardless of attribution	95.3	34.9§
Any treatment-related AE in ≥ 5% of patients	71.0	9.9‖
Fatigue	24.8	0.3
Pruritus	17.2	0.2
Diarrhea	12.7	0.5
Rash	12.7	0.3
Nausea	12.0	0
Vitiligo	7.8	0
Arthralgia	6.8	0
Asthenia	6.8	0
Constipation	5.6	0
Hypothyroidism	5.2	0
Decreased appetite	5.2	0
Any treatment-related AE leading to discontinuation of study drug	3.0	2.1
Treatment-related select AEs	49.0	3.6
Skin	34.0	0.7
Pruritus	17.2	0.2
Rash	12.7	0.3
Vitiligo	7.8	NA
Rash maculopapular	4.5	0.2
GI	13.4	1.2
Diarrhea	12.7	0.5
Colitis	1.0	0.7
Endocrine	7.8	0.3
Hypothyroidism	4.2	0
Hyperthyroidism	2.1	0.2
Hypophysitis	0.2	0.2
Hepatic	4.2	1.0
AST increased	2.8	0.3
ALT increased	1.9	0.7
γ-glutamyltransferase increased	0.2	0.2
Hepatitis	0.2	0.2
Liver function test abnormal	0.2	0.2
Pulmonary	1.9	0
Pneumonitis	1.7	0
Renal	1.4	0.3
Blood creatinine increased	0.5	0
Renal failure acute	0.2	0.2
Tubulointerstitial nephritis	0.2	0.2

Abbreviations: AE, adverse event; NA, not applicable.

*Select AEs are defined as AEs with a potential immunologic cause that need frequent monitoring and potential intervention with immune suppression and/or endocrine treatment. All grade 3 to 4 select AEs are shown.

†Terms are per Medical Dictionary for Regulatory Activities version 16.1 for CA209-038 and CheckMate 037 and version 17.0 for CA209-003 and CheckMate 066.

‡Individual patients may have had more than one event.

§In addition, rate of any grade 5 event (none were attributed to treatment) was 5.2%.

‖Grade 3 to 4 events that were not select AEs included general disorders (eg, fatigue, peripheral edema), vomiting, abdominal pain, musculoskeletal and connective tissue disorders, certain laboratory investigations, metabolism and nutrition disorders (eg, hyperglycemia), nervous system disorders, blood and lymphatic system disorders, infections, infusion-related reactions, vascular disorders, cardiac disorders, and eye disorders.

compared in patients who received systemic IMs and in those who did not. Systemic IM use was defined as the use of systemic corticosteroids on the basis of detailed information reported only in the two phase III trials. Tumor assessments were performed using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 (CA209-003) or version 1.1 (CA209-038, CheckMate 037, and CheckMate 066). Patients evaluable for response had a baseline tumor assessment, first treatment evaluation scan 9 to 12 weeks after random assignment, and confirmatory scan at least 4 weeks after the first documented response. There was no apparent heterogeneity between studies in rate of AEs, and we did not control for other end points or study-specific effects.

Statistical Analysis

ORRs with 95% CIs were estimated using the Clopper-Pearson method. Medians for PFS were calculated using the Kaplan-Meier method. Multivariate analyses were conducted when evaluating relationships between select AEs and ORRs, to adjust for imbalances across patients in number of nivolumab doses (which relates to time receiving therapy), baseline lactate dehydrogenase (LDH), and tumor PD-L1 expression. Additionally, a landmark analysis at 12 weeks was performed for PFS, including only patients alive at follow-up starting at 12 weeks after the first treatment (n = 309). The PFS analysis was performed on the basis of this landmark assessment of immune-related AEs that developed within the first 12 weeks, comparing survival curves for patients with no select AEs versus those with one to two AEs and three or more AES as well as all patients versus those with all-grade AEs and grade 3 to 4 AEs, using data starting at 12 weeks post-treatment. The Cochran-Mantel-Haenszel method of weighting was used to determine odds ratios and *P* values for ORRs. All analyses were conducted using SAS software (version 9; SAS Institute, Cary, NC).

RESULTS

A total of 576 nivolumab-treated patients were included in this analysis. Baseline characteristics are shown in Appendix Table A1 (online only). Median age was 61 years; 43% of patients had elevated serum LDH levels, and 12% had treated brain metastases. A total of 312 patients (54%) had received prior ipilimumab therapy. Median treatment duration was 3.7 months, and patients received a median of nine doses of nivolumab. Median follow-up was 7.2 months (range, 0.3 to 62.5 months). Patients who experienced treatment-related select AEs of any grade received a greater median number of doses of nivolumab (13 *v* seven) and had longer median treatment duration (6.0 *v* 2.8 months; Appendix Table A2, online only).

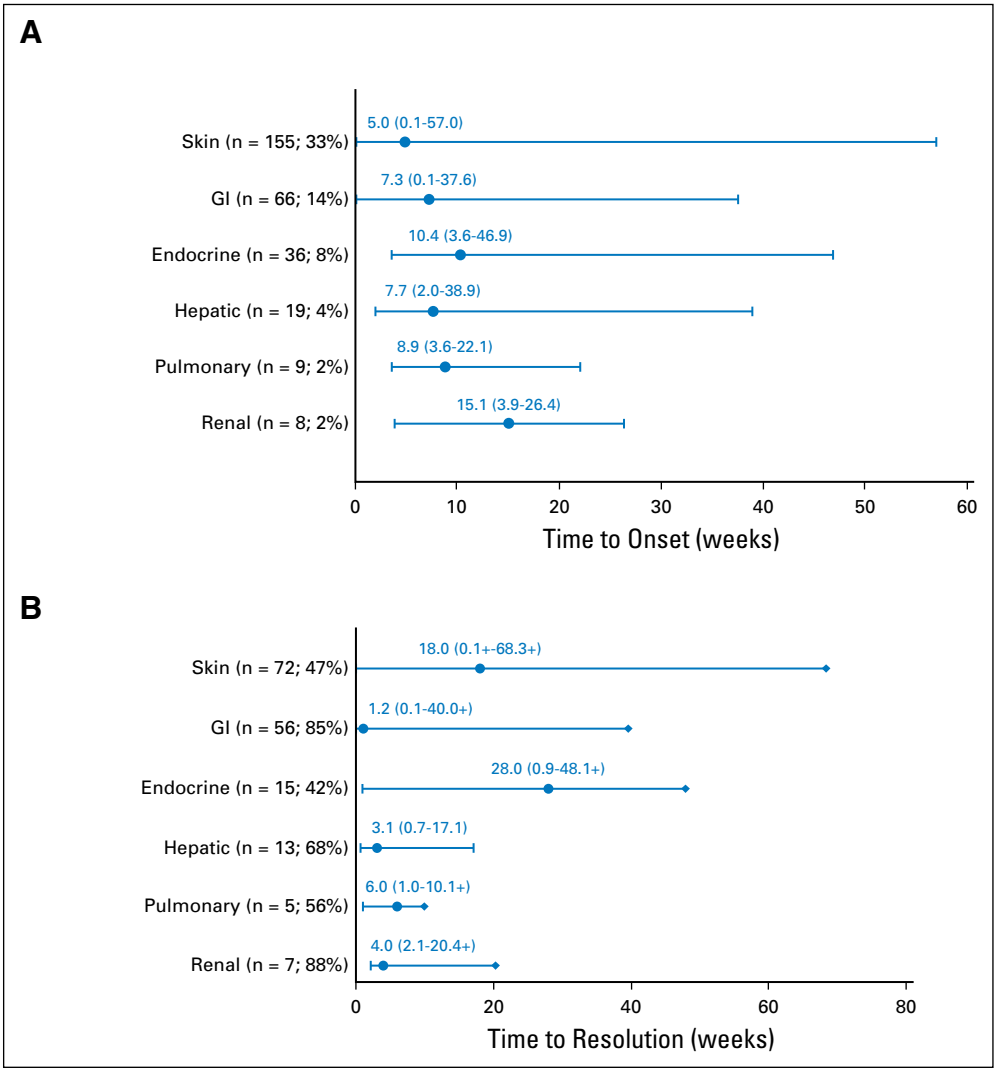


Fig 1. Time to onset and resolution of treatment-related select adverse events (AEs) of any grade, with or without use of immune-modulating agents. Circles represent medians, and bars indicate ranges (values shown above bars). The treatment population included those in phase III trials (N = 474). (A) For time to onset, number and percent indicate AE incidence. (B) For time to resolution, number and percent indicate patients' whose AE resolved. The symbols "+" in ranges and "♦" on bars indicate censored values.

Pooled Safety Analysis

At the time of analysis, 149 patients (26%) had died. The most commonly reported cause of death was disease progression (140 of 149; 94%). Other reported causes of death were acute myocardial infarction, cardiopulmonary arrest, heart failure, hypoxia, sepsis with multiorgan failure, subarachnoid bleeding (suspected cause), and probable pulmonary embolism; in two patient cases, the cause of death was unknown. No deaths were attributed to nivolumab toxicity.

Treatment-related AEs of any grade occurred in 71% of patients (95% CI, 67% to 75%). The most frequently reported events were fatigue (25%), pruritus (17%), diarrhea (13%), and rash (13%), as listed in Table 1 and Appendix Table A3 (online only). AEs regardless of attribution are listed in Appendix Table A4, (online only). Grade 3 to 4 treatment-related AEs were reported in 57 patients (10%; 95% CI, 8% to 13%). Of note, grade 3 to 4 neurologic AEs (all grade 3) were reported in five patients (1%): dizziness (resolved); autoimmune neuropathy (resolved in 16 weeks); central demyelination (ongoing for $>$ 3 weeks before death resulting from disease progression); Guillain-Barré syndrome (unresolved for $>$ 16 weeks at time of database lock); and involuntary muscle contractions (resolved).

Treatment-related AEs leading to discontinuation were reported in 17 patients (3%), with the most common being colitis, increased alanine aminotransferase, increased lipase, and pneumonitis (two patients [0.3%] each). There were no instances of GI perforation.

The rates of any-grade and grade 3 to 4 treatment-related AEs in patients who had received prior ipilimumab were 69% and 8%, respectively, similar to the rates in the overall study population. Likewise, AE rates in the overall population were consistent with those in patients $\geq$ 65 years of age (any grade, 73%; grade 3 to 4, 15%); $\geq$ 75 years of age (any grade, 72%; grade 3 to 4, 18%); with brain metastases (any grade, 61%; grade 3 to 4, 8%); with M1c stage disease (any grade, 71%; grade 3 to 4, 9%); with PD-L1 expression greater than 5% (any grade, 80%; grade 3 to 4, 14%); and with elevated LDH (any grade, 67%; grade 3 to 4, 8%).

Treatment-related select AEs occurred in 49% of patients and were most commonly observed in the skin (34%) and GI tract (13%); grade 3 to 4 treatment-related select AEs were reported in 4% of patients (Table 1). Median time to onset for treatment-related select AEs of any grade ranged from 5.0 weeks for skin AEs to 15.1 weeks for renal AEs (Fig 1A). Select AEs generally resolved within several weeks, with the shortest time to resolution for GI events (Fig 1B). Endocrine select AEs had the longest median time to resolution, because some events, although clinically resolved and medically controlled, were not considered resolved while there was a continuing need for hormone replacement therapy. The kinetics of onset and resolution of the most common treatment-related select AEs are shown in Figure 2, which demonstrates the median times to onset and resolution of select AEs of all grades by organ category. Among 282 patients who experienced new treatment-related select AEs, 85% did so within the first 16 weeks of treatment (Fig 3).

Impact of AEs on Response Rates and PFS

In all patients receiving nivolumab monotherapy (N = 576), the ORR was 31.4%, and median PFS was 4.7 months (95% CI, 3.4 to 5.6). In a multivariable analysis adjusting for differences in number of nivolumab doses received, baseline LDH, and tumor PD-L1 expression, ORR was significantly better in patients who experienced treatment-related select AEs of any grade compared with those who did not, with greater benefit in patients who reported three or more or one to two treatment-related select AEs, compared with those with none (Table 2). In contrast, there was no significant difference in ORR on the basis of the occurrence of grade 3 to 4 treatment-related select AEs (Table 2). Exclusion of patients who experienced progression before 12 weeks in a landmark PFS analysis revealed no difference in PFS between patients without AEs and those with one to two AEs or between those with any-grade AE and all patients (Appendix Fig A1, online only).

Use of IMs to Manage Select AEs

A total of 114 of 474 (24%) of patients in the two phase III trials received systemic corticosteroids to manage treatment-related AEs of any kind. In addition, 76 (16%) were administered topical corticosteroids to manage skin-related AEs, and five (1%) received inhaled corticosteroids (Appendix Table A5, online

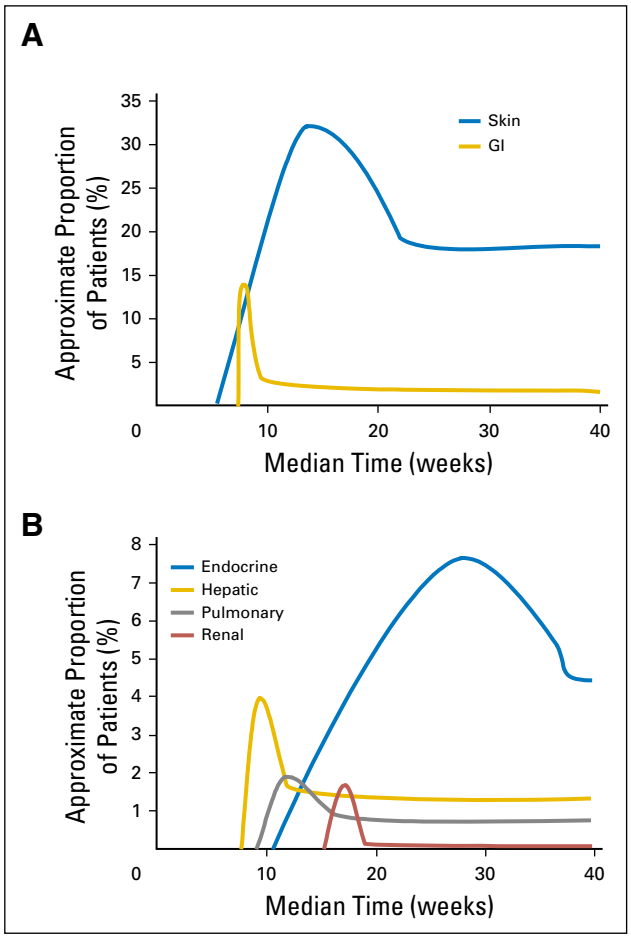
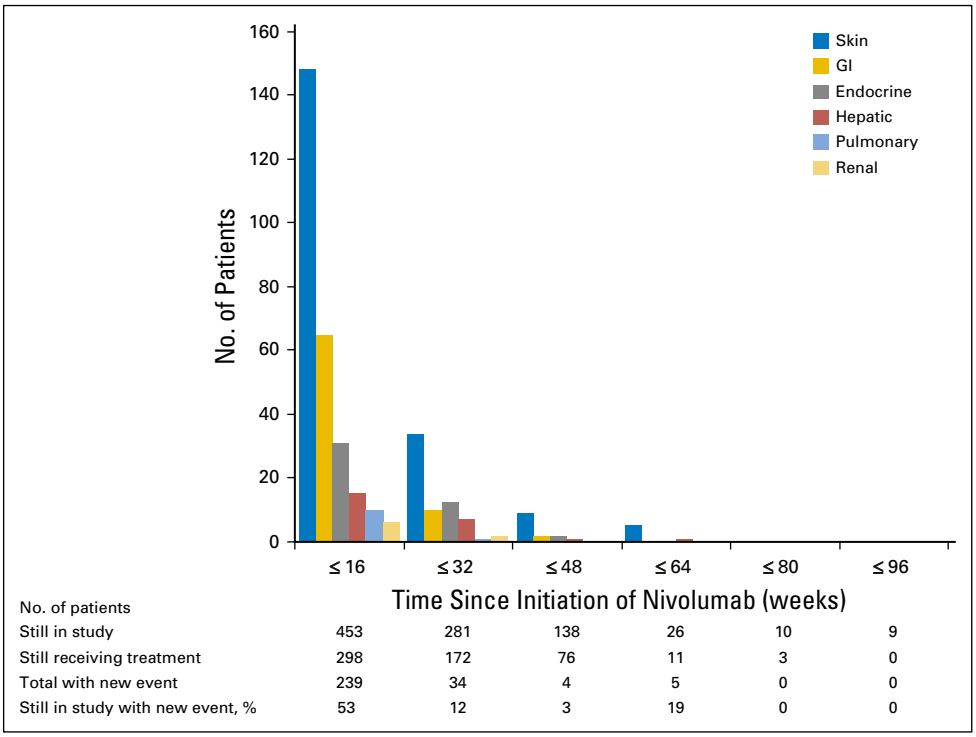


Fig 2. Kinetics of onset and resolution of (A) most common ($\geq$ 10%) and (B) less common ($<$ 10%) treatment-related select adverse events (AEs) of any grade. The beginning and end of each curve represent the median time to onset and median time to resolution, respectively. The peak of each curve shows the proportion of patients who developed that AE, and the tail represents the proportion of patients whose AE did not resolve.



No. of patients						
Still in study	453	281	138	26	10	9
Still receiving treatment	298	172	76	11	3	0
Total with new event	239	34	4	5	0	0
Still in study with new event, %	53	12	3	19	0	0

Fig 3. Occurrence of new treatment-related select adverse events of any grade over time (n = 282 of 576).

only). Only three patients (0.6%) received a secondary immunosuppressive agent: infliximab for grade 3 arthritis and grade 4 lipase increase in CheckMate 037, (n = 2); and mycophenolic acid for grade 3 hepatitis in CheckMate 066 after subsequently receiving ipilimumab off study, (n = 1).

When examining treatment-related select AEs for which IMs were initiated, a majority of events (58%) resolved. Median time to resolution of treatment-related select AEs of any grade with IMs ranged from 3.3 weeks for hepatic AEs to 28.6 weeks for skin AEs (Fig 4). Among 13 patients with grade 3 to 4 treatment-related select AEs who received IMs, all patients experienced resolution except one with skin AE (rash), who was treated with systemic corticosteroids and experienced improvement to a grade 1 event.

Impact of Systemic IMs on Response Rates

A total of 114 patients who received systemic IMs to manage treatment-related AEs and 462 who did not receive IMs were evaluable for tumor response. There was no significant difference in ORRs between patients who did versus those who did not receive systemic IMs (Table 2). Median duration of response was not reached (95% CI, 9.3 to not reached) in patients receiving IMs and was 22.0 months (95% CI, 22.0 to not reached) in those not receiving IMs.

DISCUSSION

To our knowledge, this report pooling data from four melanoma trials is the largest and most comprehensive analysis to date of the safety profile of anti–PD-1 monotherapy. We found that approximately 50% of patients experienced AEs with a potential immunologic etiology (select AEs). Select AEs were typically mild to moderate in intensity, being severe (grade 3 to 4) in less than 4% of patients. They most commonly occurred in the skin, GI tract, and endocrine organs. The types of select AEs observed with nivolumab therapy were similar to those previously observed with another immune checkpoint inhibitor, ipilimumab (anti–cytotoxic T-cell lymphocyte-4), in advanced melanoma.[12] However, their

Table 2. Impact of Treatment-Related Select AEs and IM Use on Response to Nivolumab Therapy

		Any-Grade Treatment-Related Select AEs*				Grade 3 to 4 Treatment-Related Select AEs		Patients Receiving Systemic IM	
	All Patients (N = 576)	Any (n = 255)	None (n = 321)	1-2 (n = 242)	≥ 3 (n = 13)	Yes (n = 18)	No (n = 558)	Yes (n = 114)	No (n = 462)
ORR, No. of patients (%)	181 (31.4)	124 (48.6)	57 (17.8)	113 (46.7)	11 (84.6)	5 (27.8)	176 (31.5)	34 (29.8)	147 (31.8)
95% CI	27.6 to 35.4	42.3 to 54.9	13.7 to 22.4	40.3 to 53.2	54.6 to 98.1	9.7 to 53.5	27.7 to 35.6	21.6 to 39.1	27.6 to 36.3
P		< .001		< .0001†	< .001†	1.00		.736	

Abbreviations: AE, adverse event; IM, immune-modulating agent; ORR, objective response rate.
*Data in these columns are for patients with the indicated numbers of any-grade treatment-related select AEs: any AE, no AEs, 1-2 AEs, and ≥ 3 AEs.
†Versus no treatment-related select AEs.

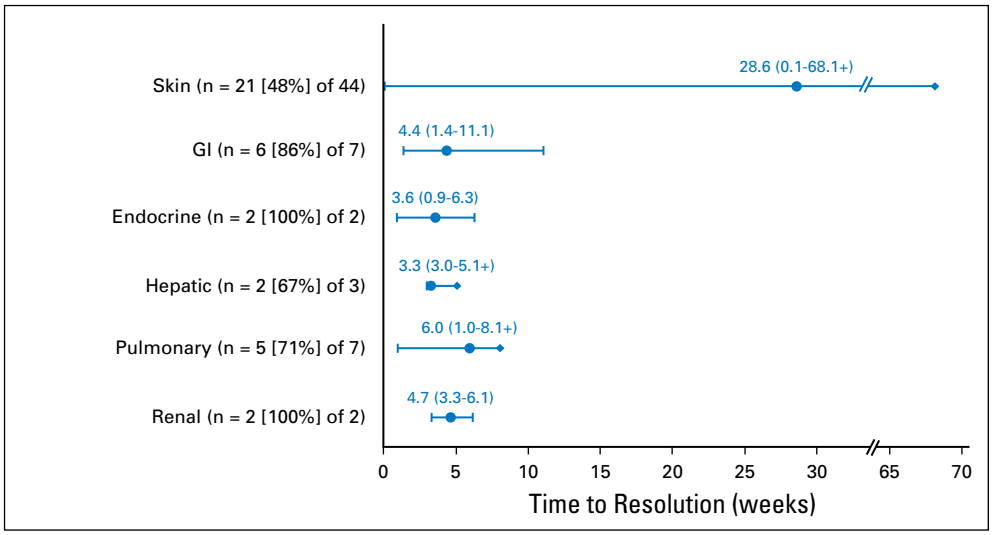


Fig 4. Time to resolution of treatment-related select adverse events (AEs) of any grade with immune-modulating agents. Circles represent medians, and bars indicate ranges (values shown above bars). Number and percent indicate patients whose AEs resolved. The symbols "+" in ranges and "♦" on bars indicate censored values. Grade 3 to 4 events were as follows: in two patients with skin AEs, median time to resolution was not reached (range, 2.6 to 48.6+ weeks); in five patients with GI AEs, median time to resolution was 1.4 weeks (range, 0.6 to 3 weeks); in two patients with endocrine AEs, median time to resolution was 3.6 weeks (range, 0.9 to 6.3 weeks); in two patients with hepatic AEs, median time to resolution was 2.7 weeks (range, 2.0 to 3.3 weeks); and in two patients with renal AEs, median time to resolution was 4.7 weeks (range, 3.3 to 6.1 weeks).

prevalence differed, with GI events being less common with nivolumab than ipilimumab.[3]

Although treatment-related deaths resulting from pneumonitis were reported in patients with lung cancer (n = 2) and colorectal cancer (n = 1) in an early trial of nivolumab monotherapy,[6] no deaths from nivolumab-related pneumonitis have been reported to date in melanoma trials or in registrational lung trials. Pneumonitis was infrequent in our analysis, occurring in less than 2% of patients (grade 1 to 2 only). However, rare and unusual AEs are possible. For example, grade 3 neurologic toxicities were seen in five patients in our analysis. Although a neurologic AE management algorithm by the manufacturer of nivolumab is available, further information is required on the optimal approach to these AEs.

Critical to the successful management of select AEs is early recognition. In general, most select AEs appeared within 1 to 2 months after the start of treatment, with skin AEs being the earliest (median, 5 weeks), whereas renal select AEs were delayed (median, 15 weeks). These patterns of onset were similar to those reported previously with ipilimumab therapy in melanoma.[13] In some cases, patients treated with nivolumab experienced select AEs many months or more than 1 year after starting treatment, or even after completing treatment, reinforcing the importance of vigilance for safety events by the health care team.

Among the 576 patients analyzed here, 312 (54%) had received ipilimumab in other clinical trials or as standard of care before nivolumab therapy. Consistent with previous studies,[14,15] the incidences of any-grade and grade 3 to 4 treatment-related AEs in the overall population were similar to those among patients who had received prior ipilimumab, suggesting that prior immunotherapy with ipilimumab does not affect the safety profile of nivolumab in advanced melanoma when administered at least 6 weeks before the first dose of nivolumab. Importantly, the overall incidence of select AEs with nivolumab monotherapy seemed to be lower than that previously observed with ipilimumab monotherapy. In a phase III study that evaluated each of these monotherapies as well as nivolumab combined with ipilimumab as first-line therapy for advanced melanoma, select AEs of any grade and grade 3 to 4, respectively, occurred in 62% and 8% of patients receiving nivolumab monotherapy and 74% and 19% of patients receiving ipilimumab monotherapy.[3] In our analysis of nivolumab monotherapy, any-grade and grade 3 to 4 select AEs were experienced by 49% and 4% of patients, respectively.

Treatment guidelines for managing AEs with a potential immunologic etiology were established during the ipilimumab clinical development program.[11,16] Appropriate management of select AEs is essential to reduce the risk for severe toxicity and enable nivolumab therapy to be continued where possible, maximizing its potential benefits. Using the nivolumab safety management guidelines, involving the use of IMs (primarily systemic corticosteroids), all but one grade 3 to 4 select AE resolved.

Although there is a theoretic concern that using immune-suppressant drugs to mitigate select AEs might interfere with an anticancer immune response, the results of our analysis suggest that IMs do not negatively affect the rate or quality of antitumor responses after nivolumab therapy. Similarly, published findings with ipilimumab suggest that corticosteroids do not affect the development of antitumor responses (if administered before documentation of the tumor response) or response duration (if administered after the patient has achieved a response).[17-20]

It has been proposed that development of immune-related AEs may be associated with response to immune checkpoint–blocking drugs. This phenomenon was first described in patients with melanoma receiving ipilimumab therapy,[18,21-24] although not all evidence supports this hypothesis.[25] One recent retrospective analysis found that neither immune-related AE development nor systemic corticosteroid use affected OS or time to treatment failure in patients treated with ipilimumab.[26] In an analysis of nivolumab studies that used a landmark approach, OS was greater in patients who experienced a select AE compared with those who did not, particularly for individuals with three or more select AEs.[27] In our analysis, we found a significantly higher ORR, but no impact on median PFS, when a landmark analysis was used that excluded patients who experienced progression early, in patients who experienced any-grade select AEs compared with those who did not. Prospective validation of these findings in future studies is required.

In conclusion, we found that treatment-related AEs with nivolumab monotherapy in advanced melanoma were primarily low grade and were not influenced by prior ipilimumab treatment. An awareness of the typical timing of onset of immune-related select

AEs may aid in their early recognition and management in clinical practice. However, because these data were from clinical trials excluding patients with autoimmune disease, organ dysfunction, and active brain metastases, safety in these contexts requires further study. Importantly, almost all grade 3 to 4 select AEs resolved using nivolumab safety management guidelines, and use of systemic IMs to manage high-grade AEs did not seem to have an impact on antitumor benefit.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

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Provision of study materials or patients: Jeffrey S. Weber, F. Stephen Hodi, Dirk Schadendorf, Georgina V. Long
Collection and assembly of data: Jeffrey S. Weber, F. Stephen Hodi, Dirk Schadendorf, Mario Sznol, Georgina V. Long, Hewei Li, Ian M. Waxman, Caroline Robert
Data analysis and interpretation: Jeffrey S. Weber, F. Stephen Hodi, Jedd D. Wolchok, Suzanne L. Topalian, Dirk Schadendorf, James Larkin, Mario Sznol, Georgina V. Long, Ian M. Waxman, Joel Jiang, Caroline Robert
Manuscript writing: All authors
Final approval of manuscript: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Safety Profile of Nivolumab Monotherapy: A Pooled Analysis of Patients With Advanced Melanoma

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Appendix

Table A1. Baseline Characteristics of Patients Receiving Nivolumab Monotherapy (N = 576)

Characteristic	Percentage of Patients
Age, years	
Median	61
Range	18-89
≥ 65	37.8
≥ 75	13.2
Sex	
Male	60.6
Female	39.4
ECOG performance status	
0	63.5
1	35.6
2	0
Not reported	0.9
LDH > ULN	43.4
M stage at study entry	
M0	5.6
M1A	9.4
M1B	17.0
M1C	64.1
Not reported	4.0
Brain metastasis	11.6
BRAF status	
Mutant	14.2
Wild type	81.1
Not reported	4.7
PD-L1 expression ≥ 5%	
Yes	25.7
No or indeterminate	39.6
Not evaluable or unknown	19.4
Not reported	15.3
Previous therapy	
Chemotherapy	33.2
Immunotherapy	64.4
Ipilimumab	54.2
Radiotherapy	38.4
Surgery	99.3
No. of nivolumab doses	
Median	9
Range	1-61
Treatment duration, months	
Median	3.7
Range	0.0-21.7

Abbreviations: ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; M, metastasis; PD-L1, programmed death ligand-1; ULN, upper limit of normal.

Table A2. Demographic Characteristics of Patients Receiving Nivolumab Monotherapy on the Basis of Development of Treatment-Related Select AEs (N = 576)

Characteristic	Percentage of Patients	
	Any Treatment-Related Select AEs (n = 255)	No Treatment-Related Select AEs (n = 321)
Age, years		
Median	62	59
Range	21-86	18-89
Sex		
Male	59.2	61.7
Female	40.8	38.3
ECOG performance status		
0	63.9	63.2
1	35.7	35.5
LDH > ULN	38.0	47.7
M stage at study entry		
M0	7.5	4.0
M1A	10.6	8.4
M1B	16.1	17.8
M1C	61.6	66.0
Brain metastasis	7.8	14.6
BRAF status		
Mutant	9.8	17.8
Wild type	85.5	77.6
PD-L1 expression ≥ 5%		
Yes	28.2	23.7
No or indeterminate	42.0	37.7
Not evaluable or unknown	19.6	19.3
Not reported	10.2	19.3
Previous therapy		
Chemotherapy	29.0	36.4
Immunotherapy	60.4	67.6
Radiotherapy	32.2	43.3
Surgery	98.8	99.7
No. of nivolumab doses		
Median	13	7
Range	1-61	1-35
Treatment duration, months		
Median	6.0	2.8
Range	0-22	0-16

Abbreviations: AE, adverse event; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; M, metastasis; PD-L1, programmed death ligand-1; ULN, upper limit of normal.

Table A3. Treatment-Related AEs Occurring in ≥ 1% of Patients* Receiving Nivolumab Monotherapy (N = 576)

AE Term	No. of Patients Reporting AEs (%)	
	Any Grade	Grade 3 to 4
Any AE	409 (71.0)	57 (9.9)
General disorders and administration site conditions	218 (37.8)	3 (0.5)
Fatigue	143 (24.8)	2 (0.3)
Asthenia	39 (6.8)	0
Pyrexia	28 (4.9)	0
Chills	12 (2.1)	0
Edema peripheral	10 (1.7)	1 (0.2)
Influenza-like illness	8 (1.4)	0
Skin and subcutaneous tissue disorders	215 (37.3)	4 (0.7)
Pruritus	99 (17.2)	1 (0.2)
Rash	73 (12.7)	2 (0.3)
Vitiligo	45 (7.8)	0
Rash maculopapular	26 (4.5)	1 (0.2)
Dry skin	24 (4.2)	0
Erythema	14 (2.4)	0
Alopecia	8 (1.4)	0
Photosensitivity reaction	8 (1.4)	0
Eczema	7 (1.2)	0
Rash papular	7 (1.2)	0
GI disorders	175 (30.4)	11 (1.9)
Diarrhea	73 (12.7)	3 (0.5)
Nausea	69 (12.0)	0
Constipation	32 (5.6)	0
Vomiting	26 (4.5)	2 (0.3)
Abdominal pain	20 (3.5)	1 (0.2)
Dry mouth	15 (2.6)	0
Colitis	6 (1.0)	4 (0.7)
Musculoskeletal and connective tissue disorders	77 (13.4)	3 (0.5)
Arthralgia	39 (6.8)	0
Myalgia	23 (4.0)	0
Pain in extremity	11 (1.9)	0
Investigations	69 (12.0)	14 (2.4)
AST increased	16 (2.8)	2 (0.3)
Weight decreased	14 (2.4)	0
ALT increased	11 (1.9)	4 (0.7)
Lipase increased	10 (1.7)	6 (1.0)
Lymphocyte count decreased	7 (1.2)	1 (0.2)
Nervous system disorders	61 (10.6)	5 (0.9)
Headache	22 (3.8)	0
Dysgeusia	12 (2.1)	0
Dizziness	7 (1.2)	1 (0.2)
Metabolism and nutrition disorders	45 (7.8)	5 (0.9)
Decreased appetite	30 (5.2)	0
Hyperglycemia	6 (1.0)	4 (0.7)
Endocrine disorders	42 (7.3)	2 (0.3)
Hypothyroidism	30 (5.2)	0
Hyperthyroidism	15 (2.6)	1 (0.2)
Blood and lymphatic system disorders	39 (6.8)	7 (1.2)
Anemia	25 (4.3)	3 (0.5)
Lymphopenia	12 (2.1)	3 (0.5)
Respiratory, thoracic and mediastinal disorders	38 (6.6)	0
Cough	15 (2.6)	0
Dyspnea	13 (2.3)	0
Pneumonitis	10 (1.7)	0
Eye disorders	26 (4.5)	1 (0.2)
Vision blurred	6 (1.0)	0
Injury, poisoning, and procedural complications	22 (3.8)	1 (0.2)
Infusion-related reaction	18 (3.1)	1 (0.2)
Infections and infestations	21 (3.6)	2 (0.3)
Nasopharyngitis	6 (1.0)	0
Vascular disorders	19 (3.3)	2 (0.3)
Hot flush	6 (1.0)	0
Ear and labyrinth disorders	11 (1.9)	0
Cardiac disorders	10 (1.7)	1 (0.2)
Renal and urinary disorders	10 (1.7)	2 (0.3)

(continued on following page)

Table A3. Treatment-Related AEs Occurring in ≥ 1% of Patients* Receiving Nivolumab Monotherapy (N = 576) (continued)

AE Term	No. of Patients Reporting AEs (%)	
	Any Grade	Grade 3 to 4
Immune system disorders	9 (1.6)	0
Hypersensitivity	9 (1.6)	0
Psychiatric disorders	9 (1.6)	0
Reproductive system and breast disorders	7 (1.2)	0

Abbreviation: AE, adverse event.
*Among events occurring in < 1% of patients, notable events included one instance each of grade 3 to 4 pancreatitis, autoimmune neuropathy, demyelination, Guillain-Barré syndrome, involuntary muscle contractions, and uveitis.

Table A4. All-Cause AEs Occurring in ≥ 5% of Patients Receiving Nivolumab Monotherapy (N = 576)

AE Term	No. of Patients Reporting AEs (%)		
	Any Grade	Grade 3 to 4	Grade 5
Total patients with an event	549 (95.3)	201 (34.9)	30 (5.2)
Fatigue	229 (39.8)	8 (1.4)	0
Diarrhea	141 (24.5)	7 (1.2)	0
Nausea	138 (24.0)	3 (0.5)	0
Pruritus	125 (21.7)	1 (0.2)	0
Constipation	109 (18.9)	2 (0.3)	0
Rash	103 (17.9)	2 (0.3)	0
Decreased appetite	97 (16.8)	1 (0.2)	0
Cough	93 (16.1)	0	0
Pyrexia	82 (14.2)	2 (0.3)	0
Headache	81 (14.1)	3 (0.5)	0
Arthralgia	78 (13.5)	0	0
Anemia	76 (13.2)	19 (3.3)	0
Vomiting	73 (12.7)	7 (1.2)	0
Dyspnea	69 (12.0)	6 (1.0)	0
Back pain	68 (11.8)	8 (1.4)	0
Asthenia	66 (11.5)	4 (0.7)	0
Abdominal pain	60 (10.4)	11 (1.9)	0
Edema peripheral	58 (10.1)	5 (0.9)	0
Pain in extremity	55 (9.5)	4 (0.7)	0
Pain	50 (8.7)	7 (1.2)	0
Vitiligo	47 (8.2)	0	0
Insomnia	46 (8.0)	1 (0.2)	0
Musculoskeletal pain	45 (7.8)	1 (0.2)	0
Dizziness	45 (7.8)	1 (0.2)	0
Nasopharyngitis	44 (7.6)	0	0
Malignant neoplasm progression	44 (7.6)	19 (3.3)	22 (3.8)
Dry skin	40 (6.9)	0	0
Hypothyroidism	40 (6.9)	0	0
AST increased	39 (6.8)	10 (1.7)	0
Myalgia	38 (6.6)	0	0
Weight decreased	37 (6.4)	0	0
ALT increased	30 (5.2)	11 (1.9)	0
Anxiety	29 (5.0)	1 (0.2)	0
Hypertension	29 (5.0)	6 (1.0)	0

Abbreviation: AE, adverse event.

Table A5. Immunomodulatory Agents Used for Management of AEs in Patients Receiving Nivolumab in Phase III Trials (n = 474)

Medication	No. of Patients (%)
Any immune-modulating agent	166 (35.0)
Corticosteroid, systemic	114 (24.1)
Prednisone	43 (9.1)
Dexamethasone	39 (8.2)
Methylprednisolone	33 (7.0)
Hydrocortisone	16 (3.4)
Prednisolone	16 (3.4)
Meprednisone	5 (1.1)
Betamethasone	4 (0.8)
Corticosteroid	2 (0.4)
Fludrocortisone	1 (0.2)
Triamcinolone	1 (0.2)
Corticosteroid, dermatologic preparation	76 (16.0)
Betamethasone, topical	22 (4.6)
Hydrocortisone, topical	21 (4.4)
Triamcinolone, topical	13 (2.7)
Mometasone	8 (1.7)
Clobetasol	6 (1.3)
Methylprednisolone, topical	4 (0.8)
Prednicarbate	4 (0.8)
Desonide	3 (0.6)
Dexamethasone, topical	3 (0.6)
Diflucortolone	3 (0.6)
Betamethasone/calcipotriene	2 (0.4)
Betamethasone/fusidic acid	2 (0.4)
Betamethasone/salicylic acid	2 (0.4)
Budesonide, topical	2 (0.4)
Prednisolone, topical	2 (0.4)
Ciptop/hctop	1 (0.2)
Clioquinol/flumethasone	1 (0.2)
Flumethasone/triamcinolone	1 (0.2)
Fluocortolone, topical	1 (0.2)
Fluticasone, topical	1 (0.2)
Prednisone, topical	1 (0.2)
Corticosteroid, inhaled	5 (1.1)
Budesonide/formoterol	3 (0.6)
Beclomethasone	1 (0.2)
Beclomethasone inhaler	1 (0.2)
Nonsteroidal systemic immunosuppressive agents	3 (0.6)
Infliximab	2 (0.4)
Mycophenolic acid	1 (0.2)
Immunoglobulin	1 (0.2)
Gamma globulin	1 (0.2)

Abbreviation: AE, adverse event.

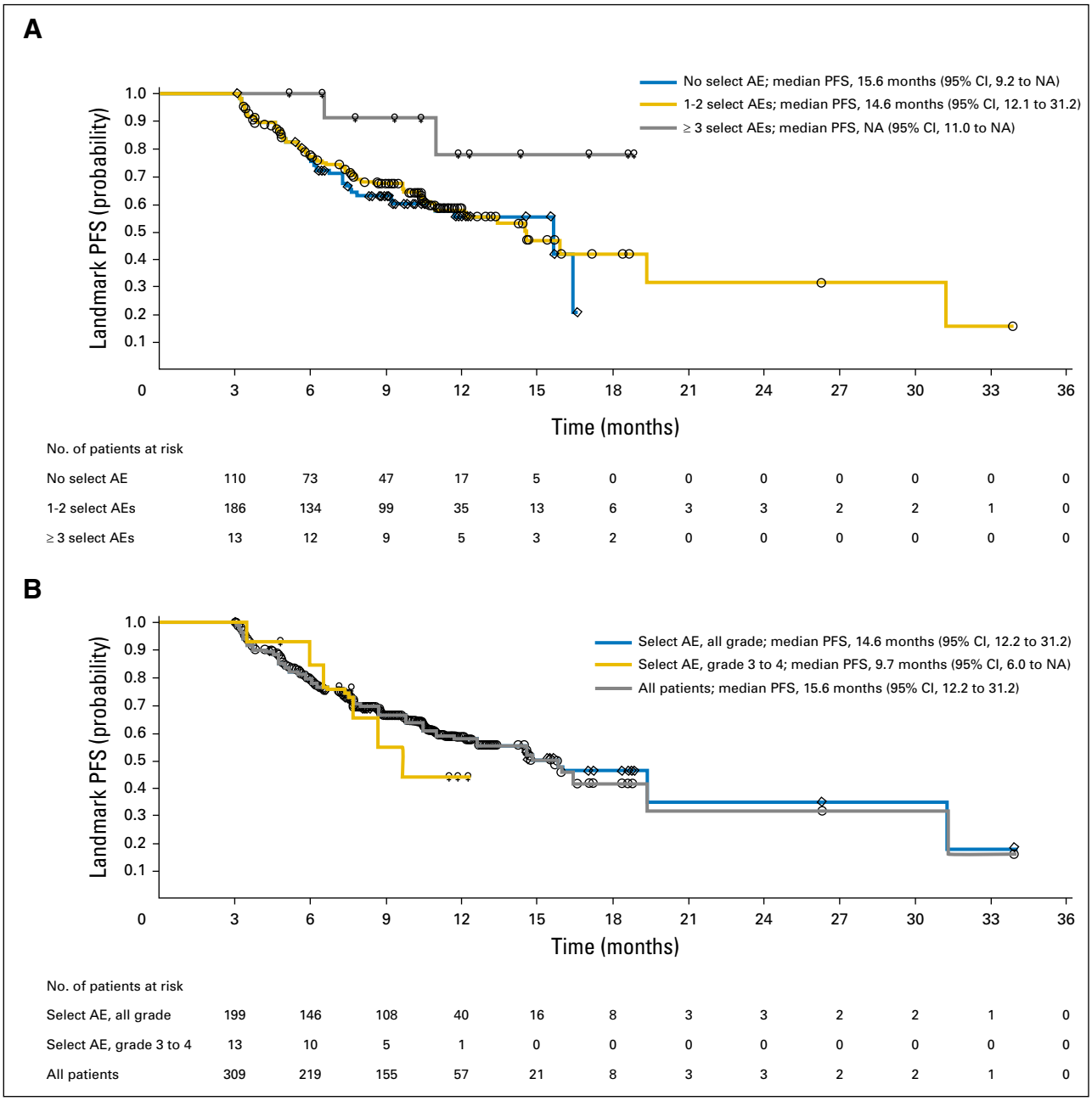

Fig A1. Kaplan-Meier plot of PFS in (A) patients with 0, 1-2, or 3+ treatment-related select AEs and (B) patients with all grade treatment-related select AEs, grade 3-4 treatment-related select AEs, and all patients. The symbols "+," "○," and "◊" indicate censored points. AE, adverse event; NA, not assessable; PFS, progression-free survival.