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Safety profile of pembrolizumab monotherapy based on an aggregate safety evaluation of 8937 patients

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.113530.

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Abstract

Background: Pembrolizumab has a manageable safety profile as described in its label, which was primarily based on 2799 patients who participated in clinical trials for melanoma or non-small cell lung cancer. Here, we evaluated the safety of pembrolizumab in a broader population of patients from 31 advanced cancer clinical trials across 19 cancer types.

Methods: Safety was analyzed in patients who received at least one dose of pembrolizumab (200 mg every 3 weeks [Q3W], 10 mg/kg Q2W or Q3W, or 2 mg/kg Q3W). Adverse events (AEs) and immune-mediated AEs and infusion reactions were evaluated.

Results: Safety data from 8937 patients in 31 trials of pembrolizumab monotherapy were pooled (median, seven administrations; range, 1–59). Median duration on treatment was 4.1 months (range, 0.03–40.1). AEs occurred in 96.6% of patients. Grade 3–5 AEs occurred in 50.6% of patients. AEs led to pembrolizumab discontinuation in 12.7% of patients and death in 5.9%. Immune-mediated AEs and infusion reactions occurred in 23.7% of patients (4.6% experienced multiple immune-mediated AEs/infusion reactions) and led to pembrolizumab discontinuation in 3.6% and death in 0.2%. Grade 3–5 immune-mediated AEs occurred in 6.3% of patients. Serious immune-mediated AEs and infusion reactions occurred in 6.0% of patients. Median time to immune-mediated AE onset was 85 days (range, 13–163). Of 2657 immune-mediated AEs,

22.3% were initially treated with prednisone ≥ 40 mg/day or equivalent, and 8.3% were initially treated with lower steroid doses.

Conclusions: This pooled analysis of 31 clinical trials showed that pembrolizumab has a consistent safety profile across indications.

Keywords

Safety; Pembrolizumab; Programmed cell death 1 receptor; Neoplasms

Trial registry information.

KEYNOTE-001	NCT01295827
KEYNOTE-002	NCT01704287
KEYNOTE-006	NCT01866319
KEYNOTE-010	NCT01905657
KEYNOTE-012	NCT01848834
KEYNOTE-013	NCT01953692
CITN-09/KEYNOTE-017	NCT02267603
KEYNOTE-024	NCT02142738
KEYNOTE-028	NCT02054806
KEYNOTE-040	NCT02252042
KEYNOTE-042	NCT02220894
KEYNOTE-045	NCT02256436
KEYNOTE-048	NCT02358031
KEYNOTE-052	NCT02335424
KEYNOTE-055	NCT02255097
KEYNOTE-057	NCT02625961
KEYNOTE-059	NCT02335411
KEYNOTE-061	NCT02370498
KEYNOTE-062	NCT02494583
KEYNOTE-087	NCT02453594
KEYNOTE-158	NCT02628067
KEYNOTE-164	NCT02460198
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KEYNOTE-177	NCT02563002
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KEYNOTE-361	NCT02853305
KEYNOTE-427	NCT02853344
KEYNOTE-629	NCT03284424

1. Introduction

Since the approval of programmed cell death protein 1/ligand 1 (PD-1/L1) inhibitors in 2014, the survival of patients with many tumor types has substantially improved. The PD-1 inhibitor pembrolizumab is approved for use as monotherapy and in combination with other agents for the treatment of solid tumors and hematologic malignancies in more than 95 countries. Pembrolizumab has a manageable and consistent safety profile across indications that has been established using continuous signal detection and evaluation of safety data [1,2]. Due to its mechanism of action, pembrolizumab can be associated with the development of immune-mediated adverse events (AEs), which can occur in any organ system or tissue at any time after initiating treatment or after discontinuation. The most common immune-mediated AEs occurring with pembrolizumab are endocrinopathies, pneumonitis, colitis, dermatologic adverse reactions, hepatitis and nephritis [1,2]. Although these are generally low grade and manageable and resolve with treatment, they can rarely become severe or fatal [1,2]. Immune-mediated AEs may also last longer than 6 months (e.g. endocrinopathies) and have a late onset. [3] Management of immune-mediated AEs depends on severity and can include withholding or permanently discontinuing pembrolizumab and/or administering systemic corticosteroids, other immunosuppressants or other supportive therapies [1,2]. As with any intravenous antibody-based therapies, the administration of pembrolizumab can also result in infusion reactions, although these are less common. Since the initial filings for pembrolizumab monotherapy, a pooled safety dataset containing information on the incidence, nature, severity and clinical management of immune-mediated AEs and infusion reactions has been maintained to provide a consistent data source for submissions. This consists of a locked dataset of 2799 patients with advanced melanoma or non-small cell lung cancer (NSCLC) from three randomized, open-label, active--controlled clinical trials (KEYNOTE-002, KEYNOTE-006 and KEYNOTE-010) and one single-arm trial (KEYNOTE-001), referred to here as the label safety dataset [1,2]. We sought to assess the safety profile in a broader population of patients. This pooled analysis of data from 31 clinical trials further evaluates the safety profile of pembrolizumab monotherapy across additional tumor types, with particular emphasis on the incidence, characterization and management of immune-mediated AEs and infusion reactions.

2. Materials and methods

Patients included in the current analysis had advanced cancer and received at least one dose of pembrolizumab monotherapy in one of 31 phase 1–3 clinical trials (Appendix Table A.1). Of the 8937 patients, 65.4% received pembrolizumab 200 mg every 3 weeks, 25.8% received pembrolizumab 10 mg/kg every 2 or 3 weeks and 8.9% received pembrolizumab 2 mg/kg every 3 weeks. In most trials, patients received pembrolizumab for ≤ 2 years (35 cycles) or until disease progression, unacceptable toxicity or patient or investigator decision to withdraw. The studies were conducted in accordance with the principles of Good Clinical Practice and were approved by the appropriate institutional review boards and regulatory agencies. All patients provided written informed consent. AEs reflected in this evaluation were coded using the Medical Dictionary for Regulatory Activities, version 25.1, and graded according to the National Cancer Institute Common Terminology Criteria for

Adverse Events, version 4.0. Safety evaluations included any-cause AEs, immune-mediated AEs and infusion reactions and other events of clinical interest. Any-cause AEs were defined as any untoward medical occurrence that was temporally associated with pembrolizumab, whether or not it was considered related to pembrolizumab treatment. Immune-mediated AEs and infusion reactions were based on a list of preferred terms intended to capture known risks of pembrolizumab and were considered regardless of attribution to study treatment by the investigator. These events are pneumonitis, colitis, hepatitis, nephritis, adrenal insufficiency, hypophysitis, hyperthyroidism, hypothyroidism, thyroiditis, type 1 diabetes mellitus, severe skin reactions, uveitis, pancreatitis, myositis, Guillain-Barré syndrome, myocarditis, encephalitis, sarcoidosis, infusion reactions, myasthenic syndrome, myelitis, vasculitis, cholangitis sclerosing, hypoparathyroidism, arthritis, hemophagocytic lymphohistiocytosis, optic neuritis and infusion reaction. Other events of particular interest to PD-1 inhibitor treatment that are not in the list of terms for an immune-mediated AEs were graft-versus-host disease and pericarditis. Patients treated with pembrolizumab who have received allogenic hematopoietic stem cell transplant are at risk of graft-versus-host disease. Pericarditis remains under routine monitoring as there is not sufficient evidence for causality. Safety data were pooled from the 31 trials listed in Appendix Table A.1. The incidence, nature and severity of immune-mediated AEs and infusion reactions were also summarized for the four trials that are the basis for the label safety dataset (KEYNOTE-001, KEYNOTE-002, KEYNOTE-006 and KEYNOTE-010). The conditional incidence rates for immune-mediated AEs and infusion reactions in the 31-trial pooled safety dataset were calculated based on the number of patients experiencing the first occurrence of the event in each time period (6 weeks) divided by the effective number of patients still on study at risk for the event (and naive to the specific event) in each respective period, expressed as a percentage.

3. Results

3.1. Patients

A total of 8937 patients were included in the 31-trial pooled safety dataset. The median age was 63 years (range, 15–95), 66.1% of patients were male, 77.6% were White, 16% were Asian, 7.5% were of Hispanic or Latino ethnicity, 53.4% had an Eastern Cooperative Oncology Group performance status of 1, and 70.0% were enrolled outside the United States (Table 1). Patients in the 31-trial pooled safety dataset received a median of seven administrations (range, 1–59) of pembrolizumab, and the median duration on treatment was 4.1 months (range, 1 day to 40.1 months). Baseline characteristics were generally comparable between the 31-trial pooled safety dataset and the label safety dataset (Table 1). Similarly, in the label safety dataset, patients received a median of seven pembrolizumab administrations (range, 1–59), and the median duration of treatment was 4.2 months (range, 1 day to 30.4 months).

3.2. AEs

In the 31-trial pooled safety dataset, almost all patients (96.6%) who received pembrolizumab experienced at least one AE of any cause (Table 2). The most frequently reported any-cause AEs (≥20%) were fatigue (29.7%), nausea (20.4%) and decreased

appetite (20.3%). Any-cause grade 3–5 AEs occurred in 50.6% of patients and were most commonly (≥ 2%) anemia (5.4%), pneumonia (4.0%), hyponatremia (2.7%), fatigue (2.6%) and dyspnea (2.1%) (Appendix Table A.2). Any-cause serious AEs were reported by 39.3% of patients, with pneumonia being the only serious AE occurring in ≥ 2% of patients (Appendix Table A.3). AEs that led to discontinuation of pembrolizumab occurred in 12.7% of patients, and the most common (≥ 1%) was pneumonitis (1.4%) (Appendix Table A.4). A total of 5.9% of patients died because of an any-cause AE (Appendix Table A.5). The AE profile summary in the 31-trial pooled safety dataset was comparable to that observed in the label safety dataset (Table 2).

3.3. Immune-mediated AEs and infusion reactions

In the 31-trial pooled safety dataset, any-grade immune-mediated AEs and infusion reactions were reported by 23.7% of patients, and the most common (≥ 3%) were hypothyroidism (10.5%), pneumonitis (4.2%) and hyperthyroidism (4.0%) (Table 3; Fig 1). Grade 3–5 immune-mediated AEs and infusion reactions occurred in 6.3% of patients, and the majority were grade 3 (5.3%) (Appendix Table A.6). The most common grade 3–5 events were pneumonitis (1.4%), severe skin reactions (1.2%) and colitis (1.1%). Serious immune-mediated AEs and infusion reactions occurred in 6.0% of patients, and 3.6% of patients discontinued pembrolizumab because of an immune-mediated AE or infusion reaction (Table 3). Of the 8937 patients, 22 (0.2%) died of an immune-mediated AE (pneumonitis, n = 15 [0.2%]; colitis, n = 2 [<0.01%]; myocarditis, n = 2 [< 0.01%]; Guillain-Barré syndrome, n = 1 [< 0.01%]; myositis, n = 1 [< 0.01%] and severe skin reaction, n = 1 [< 0.01%]) (Appendix Table A.6). The immune-mediated AE and infusion reaction profile was comparable to that reported for the label safety dataset (Table 3). The time to onset of any immune-mediated AE or infusion reaction after initiating pembrolizumab ranged from 13 to 163 days (median, 85) (Fig 1). The risk of some immune-mediated events, such as hypothyroidism, hyperthyroidism, thyroiditis and infusion reactions, was higher earlier during the treatment period. This is reflected by a higher conditional incidence rate for these events, which peaked in the first 3–4 months of treatment and leveled off throughout subsequent treatment periods (see hypothyroidism example in Appendix Figure A.1). For the remaining immune-mediated events, the conditional incidence was generally consistent over the treatment course (see pneumonitis example in Appendix Figure A.2). Overall, 2657 immune-mediated AE episodes (excluding infusion reactions) occurred in 1984 of the 8937 patients (22.2%) in the 31-trial pooled safety dataset. Of those 2657 episodes, 592 (22.3%) required initial treatment with prednisone ≥ 40 mg/day or equivalent; the median starting dose for these episodes was 75 mg/day (range, 40–1250), and the median duration of initial treatment at doses of ≥ 40 mg/day was 7 days, after which the dose was tapered to < 40 mg/day (Table 4). Of all immune-mediated AE episodes (excluding infusion reactions), 1842 (69.3%) were not treated with corticosteroids. Many immune-mediated AEs were endocrinopathies, which may require long-term end-organ hormone replacement therapy rather than anti-inflammatory corticosteroid medication. Hormone replacement therapy was required for 81.4% of patients with an immune-mediated endocrinopathy, most commonly hypothyroidism (757 of 939 patients [80.6%]), adrenal insufficiency (65 of 69 patients [94.2%]), thyroiditis (45 of 65 patients [69.2%]), hypophysitis (40 of 41 patients [97.6%]) and type 1 diabetes mellitus (23 of 29 patients [79.3%]). At the time of AE reporting, most

of the immune-mediated AEs were reported as resolved or resolving. The more common events that were usually unresolved at the time of AE reporting were pneumonitis and, due to the need for long-term hormone replacement, endocrinopathies. Some immune-mediated AEs were more likely to be observed in certain indications. Hypothyroidism occurred more frequently in patients with head and neck carcinoma (16.2% vs 9.8% with other types of cancer), pneumonitis occurred more frequently in patients with lung cancer (4.9% vs 3.4% with other types of cancer), and vitiligo occurred more frequently in patients with melanoma (10.8% vs 0.2% with other types of cancer). Among the 8937 patients, 407 (4.6%) experienced more than one type of immune-mediated AE involving different organ systems: 350 (3.9%) had two immune-mediated AEs, 50 (0.6%) had three immune-mediated AEs and seven (< 0.1%) had four immune-mediated AEs. No specific pattern of multiple immune-mediated AEs was observed. Immune-mediated AEs affecting more than one body system can occur simultaneously, but this was not a pattern for all patients. Other events of clinical interest with pembrolizumab included graft-versus-host disease and pericarditis. In this analysis, graft-versus-host disease occurred in six patients; all six had hematopoietic malignancies and received a bone marrow transplant within 20 days to 2 months after discontinuing pembrolizumab. The median time to onset for graft-versus-host disease was 213 days (range, 142–407), and four episodes required treatment with corticosteroids. Two episodes were grade 2 in severity, two were grade 3, one was grade 4, and one was grade 5. Four episodes were reported as resolved. Pericarditis occurred in 13 patients (0.1%), with a median time to onset of 46 days (range, 3–566). Ten of 16 episodes required treatment with corticosteroids, with eight requiring prednisone ≥ 40 mg/day or equivalent (median dose, 68 mg/day prednisone equivalent). Eleven patients were reported as having pericarditis resolved or resolving; pericarditis was resolved for two patients. There were no deaths due to pericarditis.

4. Discussion

This pooled analysis of 8937 patients from 31 clinical trials represents the largest analysis to date of the safety of pembrolizumab monotherapy in patients with advanced cancer. The safety profile was consistent with that of the labeled profile of pembrolizumab, despite a larger dataset and more diverse cancer population [1]. No new safety signals were observed, and the immune-mediated AE and infusion reaction profile for pembrolizumab remained unchanged from that observed in the label safety dataset [1,4,5]. The most frequent any-cause AEs in the 31-trial pooled safety dataset and the label safety dataset were similar, although only fatigue, nausea and decreased appetite were reported in ≥ 20% of patients in the 31-trial pooled safety dataset. The incidence of immune-mediated AEs and infusion reactions in the 31-trial pooled safety dataset was 23.7%, and were also generally consistent with the label safety dataset [1]. The most commonly reported immune-mediated AEs (> 1%) in both datasets were hypothyroidism, pneumonitis, hyperthyroidism, colitis and severe skin reactions, consistent with the label safety dataset [1]. Type 1 diabetes mellitus and arthritis were relatively rare in both datasets (≤ 0.3% of patients). A higher rate of hypothyroidism was observed in patients with head and neck carcinoma than other types of cancer, which may be because of prior radiation exposure. Infusion reactions occurred in 2.0% of patients in the 31-trial pooled safety dataset (grade 3–5,

0.2%) compared with 2.5% (grade 3–5, 0.2%) in the label safety dataset. Twenty-two patients (0.2%) died of immune-mediated AEs in the 31-trial pooled safety dataset; the majority of these deaths were due to pneumonitis (n = 15). Few patients (4.6%) experienced multiple immune-mediated AEs. For each type of immune-mediated AE in the 31-trial pooled safety dataset, there was a wide range of time to onset. The risks of experiencing immune-mediated AEs affecting the thyroid (i.e. hypothyroidism, hyperthyroidism and thyroiditis) and infusion reactions were higher earlier in treatment. This was reflected by conditional incidence rates for these events that peaked earlier in treatment before leveling off throughout subsequent time periods. In contrast, other events, such as pneumonitis, had consistent conditional incidence rates across time periods. The strategies recommended to manage AEs and immune-mediated AEs that occur with pembrolizumab include: treatment interruption or permanent discontinuation; use of immunosuppressants, most commonly systemic glucocorticoids; hormone replacement therapy; and other supportive strategies [1]. Only a small proportion of patients discontinued treatment due to toxicity in this analysis (12.7% because of all-cause AEs and 3.6% because of immune-mediated AEs or infusion reactions). Corticosteroid doses of ≥ 40 mg/day prednisone or equivalent were used for 22.3% of immune-mediated AE episodes, with a median duration of 7 days. Initial treatment with < 40 mg/day of prednisone or equivalent was required for 8.3% of episodes, and 69.3% of immune-mediated AE episodes were not treated with corticosteroids. Notably, investigators chose to administer the highest starting doses of corticosteroids for neurologic events, including myasthenic syndrome (median, 675 mg/day), encephalitis (median, 267 mg/day) and myelitis (median, 142 mg/day). The most frequent immune-mediated AEs and infusion reactions were thyroid endocrinopathies, which are managed with hormone replacement rather than anti-inflammatory steroid use. National cancer organizations and other published treatment guidelines provide recommendations for the use of additional immunomodulators beyond steroids [6,7]. Although the larger clinical trial dataset allows for more precision in defining the AE profile relative to the label safety dataset and demonstrates the consistency of the AE profile with the label safety dataset, there are some limitations to this study. Very rare immune-mediated events may have not been observed in the nearly 9000 patients included in the 31-trial pooled safety dataset. There was also a lack of data regarding time to immune-mediated AE resolution as AEs were only captured up to 30 days after discontinuing pembrolizumab treatment. The safety profile of pembrolizumab continues to be monitored using postmarketing and ongoing trial data, and safety information is updated as necessary.

5. Conclusions

The results of this large, pooled analysis of data from 31 clinical trials show that pembrolizumab had a consistent safety profile across tumor types.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships that may be considered as potential competing interests:

1. **Julie R. Brahmer** reports grants or contracts from AstraZeneca and Bristol Myers Squibb; consulting fees from AstraZeneca, BMS, Incyte, Genentech/Roche, Regeneron, MSD, Johnson & Johnson, Janssen, and Sanofi; participation on a Data Safety Monitoring Board or Advisory Board for Johnson & Johnson/Janssen and GlaxoSmithKline; a leadership or fiduciary role at the Society for Immunotherapy of Cancer; and receipt of drugs from Bristol Myers Squibb and Syndax.

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Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD) is committed to providing qualified scientific researchers access to anonymized data and clinical study reports from the company's clinical trials for the purpose of conducting

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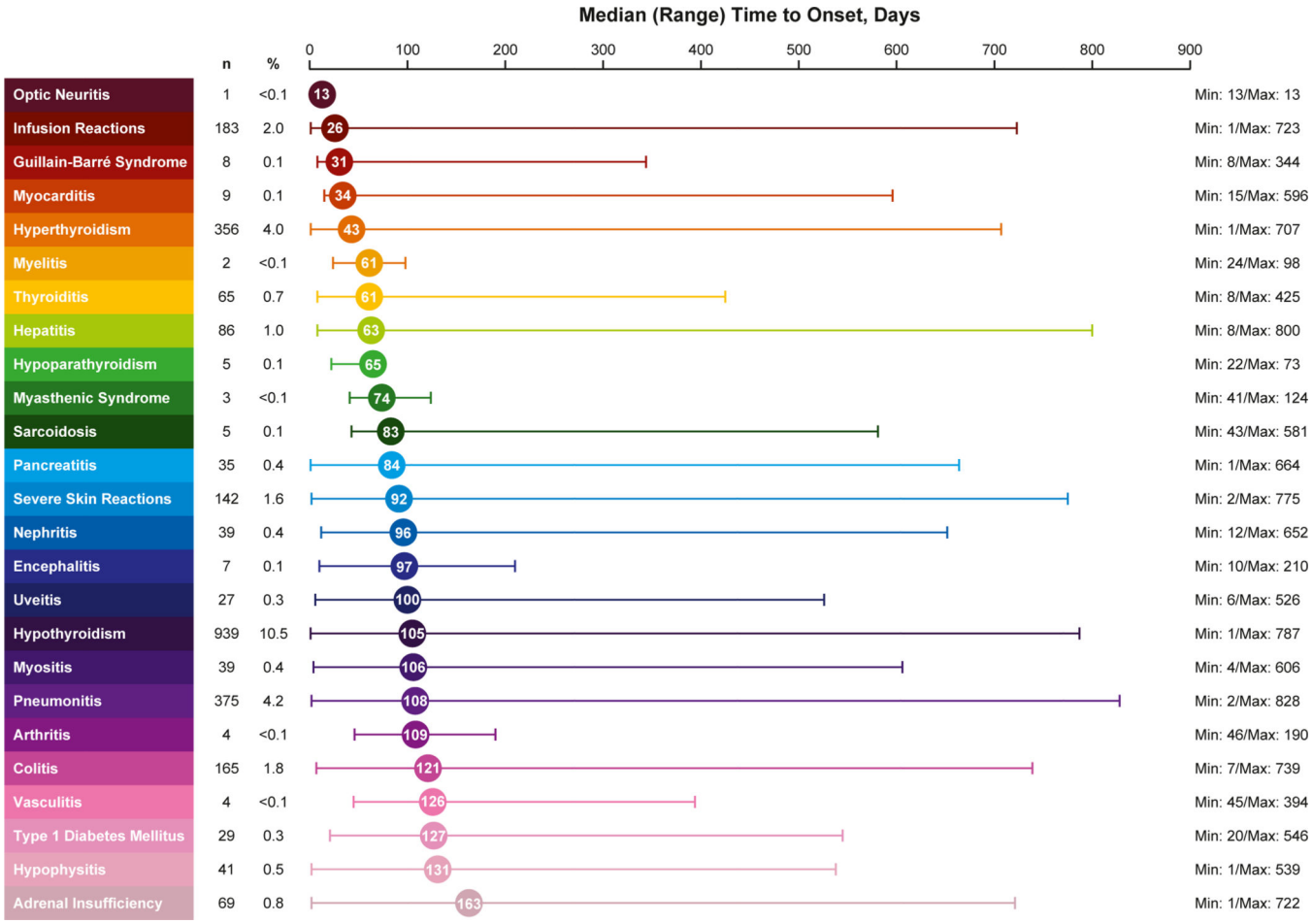

Fig. 1.

Time to onset of first occurrence of immune-mediated adverse events or infusion reactions.

Table 1

Baseline characteristics.

	31-trial pooled safety dataset N = 8937	Label safety dataset N = 2799
Age, median (range), years	63 (15–95)	62 (15–94)
Age category		
< 65 years	4935 (55.2)	1587 (56.7)
≥ 65 years	4002 (44.8)	1212 (43.3)
Sex		
Male	5908 (66.1)	1659 (59.3)
Female	3029 (33.9)	1140 (40.7)
Race		
American Indian or Alaska Native	69 (0.8)	7 (0.3)
Asian	1432 (16.0)	233 (8.3)
Black or African American	171 (1.9)	48 (1.7)
Multiracial	97 (1.1)	11 (0.4)
Native Hawaiian or Other Pacific Islander	10 (0.1)	4 (0.1)
White	6931 (77.6)	2474 (88.4)
Unknown/missing	227 (2.5)	22 (0.8)
Ethnicity		
Hispanic or Latino	669 (7.5)	128 (4.6)
Not Hispanic or Latino	7660 (85.7)	2582 (92.2)
Not reported	406 (4.5)	47 (1.7)
Unknown/missing	202 (2.3)	42 (1.5)
ECOG performance status		
0	3848 (43.1)	1446 (51.7)
1	4773 (53.4)	1347 (48.1)
Other/missing	316 (3.5)	6 (0.2)
Geographic region		
United States	2678 (30.0)	1250 (44.7)
Rest of world	6259 (70.0)	1549 (55.3)
Primary cancer type		
Bladder cancer	1198 (13.4)	0
Cervical cancer	106 (1.2)	0
Cervical cancer, TMB-H	16 (0.2)	0
Classical Hodgkin lymphoma	389 (4.4)	0
Colorectal cancer	277 (3.1)	0
Cutaneous squamous cell carcinoma	159 (1.8)	0
Esophageal cancer	458 (5.1)	0
Gastric cancer	877 (9.9)	0
Head and neck squamous cell carcinoma	909 (10.2)	0
Hepatocellular carcinoma	104 (1.2)	0

	31-trial pooled safety dataset **N = 8937**	**Label safety dataset** **N = 2799**
Melanoma	1567 (17.6)	1567 (56.0)
Merkel cell carcinoma	50 (0.6)	0
Microsatellite instability–high cancer	351 (4.0)	0
Non-small cell lung cancer	2106 (23.6)	1232 (44.0)
Primary mediastinal large B-cell lymphoma	74 (0.8)	0
Renal cell carcinoma	110 (1.2)	0
Small cell lung cancer	97 (1.1)	0
Small cell lung cancer, TMB-H	34 (0.4)	0
TMB-H cancer	55 (0.6)	0

Data are n (%) unless otherwise specified.

ECOG, Eastern Cooperative Oncology Group; TMB-H, tumor mutational burden–high.

Table 2

Summary of all-cause AEs.

	31-trial pooled safety dataset N = 8937	Label safety dataset N = 2799
AEs of any cause	**8630 (96.6)**	**2727 (97.4)**
Grade 3–5 AEs	4525 (50.6)	1273 (45.5)
Serious AEs	3513 (39.3)	1042 (37.2)
Led to discontinuation	1135 (12.7)	334 (11.9)
Led to death	527 (5.9)	110 (3.9)
Any AE in ≥ 10% of patients in either dataset		
Fatigue	2654 (29.7)	1044 (37.3)
Nausea	1827 (20.4)	685 (24.5)
Decreased appetite	1812 (20.3)	630 (22.5)
Diarrhea	1773 (19.8)	625 (22.3)
Constipation	1585 (17.7)	498 (17.8)
Cough	1570 (17.6)	615 (22.0)
Pruritus	1522 (17.0)	580 (20.7)
Arthralgia	1480 (16.6)	636 (22.7)
Anemia	1458 (16.3)	347 (12.4)
Dyspnea	1332 (14.9)	534 (19.1)
Rash	1212 (13.6)	508 (18.1)
Vomiting	1198 (13.4)	387 (13.8)
Pyrexia	1182 (13.2)	357 (12.8)
Asthenia	1059 (11.8)	362 (12.9)
Back pain	1019 (11.4)	344 (12.3)
Hypothyroidism	935 (10.5)	236 (8.4)
Abdominal pain	923 (10.3)	274 (9.8)
Headache	885 (9.9)	400 (14.3)

Data are n (%).

AE, adverse event.

Table 3

Summary of immune-mediated AEs and infusion reactions.

	31-trial pooled safety dataset N = 8937		Label safety dataset [1] N = 2799	
Immune-mediated AEs or infusion reactions	**2121 (23.7)**		**601 (21.5)**	
Grade 3–5 AEs	563 (6.3)		155 (5.5)	
Serious AEs	538 (6.0)		162 (5.8)	
Led to discontinuation	326 (3.6)		86 (3.1)	
Led to death	22 (0.2)[a]		4 (0.1)[b]	
Any immune-mediated AE or infusion reaction	**Any grade**	**Grade 3–5**	**Any grade**	**Grade 3–5**
Hypothyroidism	939 (10.5)	11 (0.1)	237 (8.5)	3 (0.1)
Pneumonitis	375 (4.2)	125 (1.4)	94 (3.4)	36 (1.3)
Hyperthyroidism	356 (4.0)	8 (0.1)	96 (3.4)	4 (0.1)
Infusion reactions	183 (2.0)	16 (0.2)	70 (2.5)	6 (0.2)
Colitis	165 (1.8)	95 (1.1)	48 (1.7)	32 (1.1)
Severe skin reactions	142 (1.6)	109 (1.2)	39 (1.4)	30 (1.1)
Hepatitis	86 (1.0)	68 (0.8)	18 (0.6)	13 (0.5)
Adrenal insufficiency	69 (0.8)	36 (0.4)	22 (0.8)	10 (0.4)
Thyroiditis	65 (0.7)	4 (< 0.1)	16 (0.6)	0
Hypophysitis	41 (0.5)	23 (0.3)	17 (0.6)	9 (0.3)
Myositis	39 (0.4)	11 (0.1)	11 (0.4)	1 (< 0.1)
Nephritis	39 (0.4)	20 (0.2)	9 (0.3)	5 (0.2)
Pancreatitis	35 (0.4)	22 (0.2)	9 (0.3)	6 (0.2)
Type 1 diabetes mellitus	29 (0.3)	26 (0.3)	6 (0.2)	5 (0.2)
Uveitis	27 (0.3)	3 (< 0.1)	14 (0.5)	1 (< 0.1)
Myocarditis	9 (0.1)	8 (0.1)	0	0
Guillain-Barré syndrome	8 (0.1)	6 (0.1)	2 (0.1)	1 (< 0.1)
Encephalitis	7 (0.1)	6 (0.1)	1 (< 0.1)	1 (< 0.1)
Hypoparathyroidism	5 (0.1)	0	1 (< 0.1)	0
Sarcoidosis	5 (0.1)	0	2 (0.1)	0
Arthritis	4 (< 0.1)	4 (< 0.1)	0	0
Vasculitis	4 (< 0.1)	3 (< 0.1)	2 (0.1)	1 (< 0.1)
Myasthenic syndrome	3 (< 0.1)	2 (< 0.1)	2 (0.1)	1 (< 0.1)
Myelitis	2 (< 0.1)	2 (< 0.1)	1 (< 0.1)	1 (< 0.1)
Optic neuritis	1 (< 0.1)	0	1 (< 0.1)	0

AE, adverse event.

Data are n (%).

[a] A total of 22 patients (0.2%) in the 31-trial pooled safety dataset died due to an immune-mediated AE (pneumonitis, n = 15; colitis, n = 2; myocarditis, n = 2; Guillain-Barré syndrome, n = 1; myositis, n = 1; severe skin reaction, n = 1).

[b] Four patients (0.1%) in the label safety dataset died due to an immune-mediated AE (pneumonitis, n = 4).

Table 4

Summary of concomitant corticosteroid use for immune-mediated AEs.

	No corticosteroid	Low-dose corticosteroid (40 mg/day prednisone equivalent)			High-dose corticosteroid (≥ 40 mg/day prednisone equivalent)		
	Episodes, n/N (%)	Episodes, n/N (%)	Starting dose, median (range), mg/day	Duration, median (range), days	Episodes, n/N (%)	Starting dose, median (range), mg/day	Duration, median (range), days
Any immune-mediated AE	1842/2657 (69.3)	220/2657 (8.3)	20 (1–38)	8 (1–1239)	592/2657 (22.3)	75 (40–1250)	7 (1–1607)
Adrenal insufficiency[a]	12/72 (16.7)	44/72 (61.1)	8 (1–38)	16 (1–504)	15/72 (20.8)	67 (40–126)	2 (1–164)
Arthritis	1/5 (20.0)	1/5 (20.0)	5 (5–5)	120 (120–120)	3/5 (60.0)	53 (40–60)	3 (2–5)
Colitis[a]	59/184 (32.1)	14/184 (7.6)	28 (1–33)	7 (2–31)	110/184 (59.8)	64 (40–625)	7 (1–369)
Encephalitis	2/7 (28.6)	2/7 (28.6)	2 (1–3)	5 (4–5)	3/7 (42.9)	267 (80–1250)	2 (1–3)
Guillain-Barré syndrome	5/8 (62.5)	0/8 (0)	–	–	3/8 (37.5)	90 (63–107)	7 (1–421)
Hepatitis	27/89 (30.3)	6/89 (6.7)	23 (10–27)	8 (1–715)	56/89 (62.9)	80 (40–625)	5 (1–66)
Hyperthyroidism	354/370 (95.7)	4/370 (1.1)	18 (10–30)	31 (13–44)	12/370 (3.2)	73 (40–100)	6 (1–50)
Hypoparathyroidism	5/5 (100)	0/5 (0)	–	–	0/5 (0)	–	–
Hypophysitis	4/42 (9.5)	25/42 (59.5)	10 (3–25)	60 (1–1239)	13/42 (31.0)	63 (40 –160)	4 (1–29)
Hypothyroidism	1001/1018 (98.3)	9/1018 (0.9)	10 (3–25)	57 (1–296)	8/1018 (0.8)	60 (40–625)	6 (2–22)
Myasthenic syndrome	1/3 (33.3)	0/3 (0)	–	–	2/3 (66.7)	675 (100–1250)	5 (3–7)
Myelitis	0/2 (0)	1/2 (50.0)	1 (1–1)	3 (3–3)	1/2 (50.0)	142 (142–142)	1 (1–1)
Myocarditis	1/9 (11.1)	2/9 (22.2)	19 (4–33)	4 (3–5)	6/9 (66.7)	103 (65–725)	5 (1–9)
Myositis	24/44 (54.5)	7/44 (15.9)	20 (5–27)	15 (4–22)	13/44 (29.5)	80 (40–1000)	9 (1–71)
Nephritis	5/39 (12.8)	2/39 (5.1)	25 (20–30)	29 (12–46)	32/39 (82.1)	73 (40–625)	9 (1–121)
Optic neuritis	0/1 (0)	0/1 (0)	–	–	1/1 (100)	80 (80–80)	10 (10–10)
Pancreatitis	21/38 (55.3)	3/38 (7.9)	13 (10–20)	7 (2–318)	14/38 (36.8)	78 (40–213)	6 (1–1110)
Pneumonitis[a]	120/423 (28.4)	58/423 (13.7)	25 (1–38)	8 (1–168)	244/423 (57.7)	75 (40–1250)	7 (1–1607)
Sarcoidosis	4/5 (80.0)	0/5 (0)	–	–	1/5 (20.0)	60 (60–60)	36 (36–36)
Severe skin reactions	74/155 (47.7)	37/155 (23.9)	20 (1–38)	8 (1–198)	44/155 (28.4)	75 (40–267)	7 (1–153)
Thyroiditis	61/68 (89.7)	3/68 (4.4)	8 (5–8)	5 (3–22)	4/68 (5.9)	74 (60–725)	4 (1–22)
Type 1 diabetes mellitus	36/38 (94.7)	0/38 (0)	–	–	2/38 (5.3)	64 (60–69)	4 (3–4)
Uveitis	24/28 (85.7)	2/28 (7.1)	30 (30–30)	6 (1–11)	2/28 (7.1)	50 (40–60)	12 (7–17)
Vasculitis	1/4 (25.0)	0/4 (0)	–	–	3/4 (75.0)	60 (60–75)	7 (6–29)

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AE, adverse event.

[a] Starting dose missing for one episode.