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Original research

Safety of pembrolizumab as adjuvant therapy in a pooled analysis of phase 3 clinical trials of melanoma, non–small cell lung cancer, and renal cell carcinoma

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ABSTRACT

Background: The safety profile of adjuvant pembrolizumab was evaluated in a pooled analysis of 4 phase 3 clinical trials.

Methods: Patients had completely resected stage IIIA, IIIB, or IIIC melanoma per American Joint Committee on Cancer, 7th edition, criteria (AJCC-7; KEYNOTE-054); stage IIB or IIC melanoma per AJCC-8 (KEYNOTE-716); stage IB, II, or IIIA non–small cell lung cancer per AJCC-7 (PEARLS/KEYNOTE-091); or postnephrectomy/metastasectomy clear cell renal cell carcinoma at increased risk of recurrence (KEYNOTE-564). Patients received adjuvant pembrolizumab 200 mg (2 mg/kg up to 200 mg for pediatric patients) or placebo every 3 weeks for approximately 1 year. Adverse events (AEs) were summarized for patients who received ≥ 1 dose of treatment.

Results: Data were pooled from 4125 patients treated with pembrolizumab (n = 2060) or placebo (n = 2065). Median (range) duration of treatment was 11.1 months (0.0–18.9) with pembrolizumab and 11.2 months (0.0–18.1) with placebo. Treatment-related AEs occurred in 78.6 % (1620/2060) of patients in the pembrolizumab group (grade 3–5, 16.3 % [336/2060]) and 58.7 % (1212/2065) in the placebo group (grade 3–5, 3.5 % [72/2065]). Immune-mediated AEs (e.g. adrenal insufficiency, hypophysitis, and thyroiditis) occurred in 36.2 % (746/2060) of patients in the pembrolizumab group (grade 3–5, 8.6 % [177/2060]) and 8.4 % (174/2065) in the placebo group (grade 3–5, 1.1 % [23/2065]). Of patients with ≥ 1 immune-mediated AE or infusion reaction, systemic corticosteroids were required for 35.2 % (268/761) and 20.2 % (39/193) of patients in the pembrolizumab and placebo groups, respectively.

Conclusions: Adjuvant pembrolizumab demonstrated a manageable safety profile that was comparable to prior reports in advanced disease.

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Study Name	Clinicaltrial.gov identifier
KEYNOTE-054	NCT02362594
KEYNOTE-716	NCT03553836
PEARLS/KEYNOTE-091	NCT02504372
KEYNOTE-564	NCT03142334

1. Introduction

The programmed cell death protein 1 (PD-1) inhibitor pembrolizumab, alone or in combination with other agents, is a standard-of-care therapy for many advanced solid tumors [1,2]. Pembrolizumab also is approved in the adjuvant setting for patients with stage IIB, IIC, or III melanoma following complete resection, for patients with stage IB, II, or IIIA non–small cell lung cancer (NSCLC) following resection and platinum-based chemotherapy, and for patients with renal cell carcinoma (RCC) at increased risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions [1,2].

Clinical trial and surveillance data have demonstrated that pembrolizumab has a manageable and consistent safety profile in patients with advanced or metastatic disease. The most common adverse events (AEs; ≥20 % of patients) reported with pembrolizumab monotherapy include fatigue, musculoskeletal pain, rash, diarrhea, pyrexia, cough, decreased appetite, pruritus, dyspnea, constipation, pain, abdominal pain, nausea, and hypothyroidism [1]. Based on its mechanism of action, a significant proportion of AEs with pembrolizumab are associated with immune-mediated adverse reactions, including immune-mediated pneumonitis, colitis, hepatitis, endocrinopathies, nephritis with renal dysfunction, dermatologic adverse reactions, and solid organ transplant rejection [1]. These immune-mediated adverse reactions can be severe or fatal in some cases [1]. Management strategies for adverse reactions with pembrolizumab include withholding or permanently discontinuing treatment and/or supportive care such as the administration of systemic corticosteroids or other immunosuppressant medications, end-organ hormone replacement for certain endocrinopathies, and other supportive therapies [1–3].

Although the safety profile of pembrolizumab is well established in the advanced or metastatic setting, it has not been characterized across indications in the adjuvant setting, where the benefit/risk balance differs because the treatment is given to decrease risk of relapse and not to treat active disease. This study aimed to evaluate the safety profile of pembrolizumab as adjuvant therapy in melanoma, NSCLC, and RCC using data pooled from more than 4000 patients enrolled in 4 phase 3 clinical trials.

2. Materials and methods

2.1. Study population

Data for the current analysis were pooled from KEYNOTE-054 (NCT02362594; data cutoff, April 3, 2020) [4], KEYNOTE-716 (NCT03553836; data cutoff, January 4, 2022) [5], PEARLS/KEYNOTE-091 (NCT02504372; data cutoff, September 20, 2021) [6], and KEYNOTE-564 (NCT03142334; data cutoff, June 14, 2021) [7]. Patients in KEYNOTE-054 had completely resected stage IIIA, IIIB, or IIIC melanoma per American Joint Committee on Cancer (AJCC), 7th edition, criteria [4]. Patients in KEYNOTE-716 had completely resected stage IIB or IIC melanoma per AJCC, 8th edition, criteria [5]. Patients in PEARLS/KEYNOTE-091 had completely resected stage IB, II, or IIIA NSCLC per AJCC, 7th edition, criteria [6]. Patients in KEYNOTE-564 had postnephrectomy/metastasectomy RCC with a clear cell component at increased risk of recurrence [7]. Patients in these studies received adjuvant pembrolizumab 200 mg (2 mg/kg up to 200 mg for pediatric patients) or placebo every 3 weeks for approximately 1 year (up to 17 cycles in KEYNOTE-716 and KEYNOTE-564; up to 18 cycles in KEYNOTE-054 and PEARLS/KEYNOTE-091) [4–8].

2.2. Safety assessments and analyses

In all 4 trials, AEs were monitored throughout treatment and for up to 30 days thereafter (90 days for serious AEs or AEs of clinical interest) [4–7,9]. AEs were graded per the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. 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.

Safety analyses were based on the as-treated population, which included all patients who received at least 1 dose of study treatment. Safety data, including the incidence of all-cause AEs, treatment-related AEs, immune-mediated AEs and infusion reactions, time to onset of AEs, and treatments used for AE management, were summarized descriptively.

3. Results

3.1. Patients

This analysis included 4125 patients treated with pembrolizumab (n = 2060) or placebo (n = 2065). The pembrolizumab group included 509 patients from KEYNOTE-054, 483 patients from KEYNOTE-716, 580 patients from PEARLS/KEYNOTE-091, and 488 patients from KEYNOTE-564. The placebo group included 502 patients from KEYNOTE-054, 486 patients from KEYNOTE-716, 581 patients from PEARLS/KEYNOTE-091, and 496 patients from KEYNOTE-564. Baseline characteristics and patient demographics are presented in Table 1 (region of enrollment in Supplementary Table A.1). Of 2060 patients in the pembrolizumab group, 59.0 % completed treatment, and of 2065 patients in the placebo group, 68.5 % completed treatment (Figure 1). The remaining patients discontinued treatment before receiving the maximum number of administrations, most commonly because of AEs in the pembrolizumab group (19.1 %) and progressive disease in the placebo group (22.9 %). The median time from randomization to data cutoff was 59.1 months (range, 40.6–55.3) in KEYNOTE-054, 27.4 months (range, 14.0–39.4) in KEYNOTE-716, 35.6 months (range 16.5–68.0) in PEARLS/KEYNOTE-091, and 30.1 months (range, 20.8–47.5) in KEYNOTE-564.

Table 1
Baseline characteristics and demographics.

	Pembrolizumab n = 2060	Placebo n = 2065
Age, median (range), years	61.0 (16–88)	61.0 (17–87)
≥ 65 years	759 (36.8)	793 (38.4)
Sex		
Male	1351 (65.6)	1343 (65.0)
Female	709 (34.4)	722 (35.0)
Region		
United States	226 (11.0)	220 (10.7)
Non–United States	1834 (89.0)	1845 (89.3)
Cancer stage		
I	85 (4.1)	84 (4.1)
II	823 (40.0)	840 (40.7)
III	1111 (53.9)	1100 (53.3)
IV	39 (1.9)	41 (2.0)
Missing	2 (0.1)	0 (0)
Parent study		
KEYNOTE-054 (melanoma)	509 (24.7)	502 (24.3)
KEYNOTE-716 (melanoma)	483 (23.4)	486 (23.5)
PEARLS/KEYNOTE-091 (NSCLC)	580 (28.2)	581 (28.1)
KEYNOTE-564 (RCC)	488 (23.7)	496 (24.0)

Data are n (%) unless otherwise specified.

The median duration of pembrolizumab treatment was 11.1 months (range, 0.0–18.9) in the pooled population and was 11.8 months (range, 0.0–15.7) in KEYNOTE-054, 11.1 months (range, 0.0–16.4) in KEYNOTE-716, 11.7 months (range, 0.0–18.9) in PEARLS/KEYNOTE-091, and 11.1 months (range, 0.0–14.3) in KEYNOTE-564. The median number of pembrolizumab administrations was 17 (range, 1–18) in the pooled population, and 18 (range, 1–18), 17 (range, 1–17), 17 (range, 1–18), and 17 (range, 1–17), in KEYNOTE-054, KEYNOTE-716, PEARLS/KEYNOTE-091, and KEYNOTE-564, respectively. The median duration of placebo was 11.2 months (range, 0.0–18.1) in the pooled population and the median number of administrations was 17.0 (range, 1.0–19.0).

3.2. All-cause AEs

Overall, 95.5 % of the 2060 patients treated with pembrolizumab experienced at least 1 AE of any grade; grade ≥ 3 AEs occurred in 31.7 % of patients, and serious AEs (SAEs) occurred in 23.0 %. All-cause AEs led to treatment discontinuation in 18.1 % of patients in the pembrolizumab group and death in 0.7 %. At least 1 all-cause AE of any grade occurred in 91.1 % of the 2065 patients treated with placebo; grade ≥ 3 AEs occurred in 20.9 % of patients and SAEs occurred in 15.7 %. AEs led to treatment discontinuation in 4.1 % of patients in the placebo group and death in 0.6 %. All-cause AE data were similar across the trials (Supplementary Table A.2).

3.3. Treatment-related AEs

In the pembrolizumab group, 78.6 % of patients experienced at least 1 treatment-related AE. The most common (≥10 %) were fatigue (19.8 %), pruritus (19.5 %), hypothyroidism (17.0 %), diarrhea (16.2 %), rash (11.5 %), and arthralgia (11.1 %) (Table 2; treatment-related AE data for each trial are provided in Supplementary Table A.3). Grade ≥ 3 treatment-related AEs occurred in 16.3 % of patients and SAEs occurred in 11.6 %. Treatment-related AEs led to discontinuation of pembrolizumab in 15.8 % of patients. Four patients (0.2 %) receiving pembrolizumab died from treatment-related AEs; all were in the PEARLS/KEYNOTE-091 study (1 from cardiogenic shock and myocarditis; 1 from septic shock and myocarditis; 1 from pneumonia; 1 from sudden death). The median time to onset of the first treatment-related AE in the pembrolizumab group was 36 days (range, 1–426).

In the placebo group, 58.7 % of patients experienced at least 1 treatment-related AE. The most common (≥10 %) were fatigue (17.1 %), diarrhea (11.5 %), and pruritus (10.7 %) (Table 2; Supplementary Table A.3). Grade ≥ 3 treatment-related AEs occurred in 3.5 % of patients and SAEs occurred in 1.5 %. Treatment-related AEs led to discontinuation of placebo in 2.1 % of patients. No patients died because of treatment-related AEs in the placebo group. The median time to onset of the first treatment-related AE in the placebo group was 42 days (range, 1–421).

3.4. Immune-mediated AEs and infusion reactions

In the pembrolizumab group, 36.2 % of patients had at least 1 immune-mediated AE; the most common (≥10 %) were hypothyroidism (18.5 %) and hyperthyroidism (11.0 %) (Table 3; immune-mediated AE data for each trial are provided in Supplementary Table A.4). Grade ≥ 3 immune-mediated AEs occurred in 8.6 % of patients, with only severe skin reactions (1.8 %), hepatitis (1.4 %), and colitis (1.4 %) occurring in ≥ 1 % of patients. Serious immune-mediated AEs occurred in 7.8 % of patients in the pembrolizumab group, and immune-mediated AEs led to treatment discontinuation in 8.5 %. Immune-mediated AEs led to death in 2 patients (0.1 %) in the pembrolizumab group; both were the aforementioned cases of myocarditis observed in the PEARLS/KEYNOTE-091 study. Infusion reactions occurred in 1.3 % of patients treated with pembrolizumab. Grade 3 or 4 infusion reactions occurred in 0.2 % of patients in the pembrolizumab group, and there were no grade 5 infusion reactions. The median time to onset of the first occurrence of

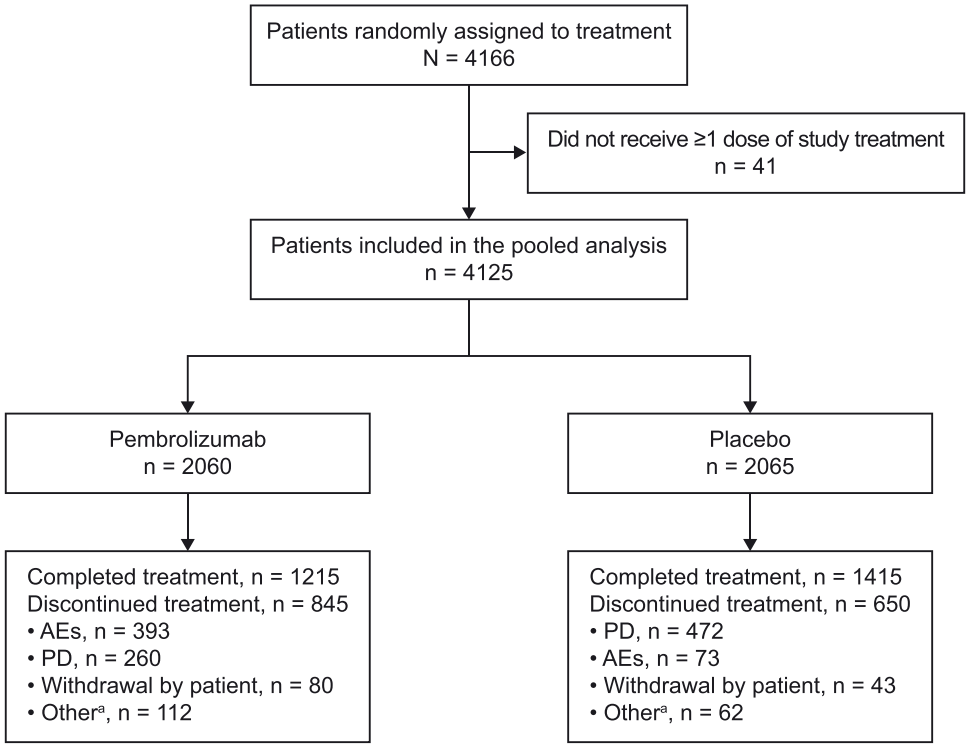

Fig. 1. Disposition in the pooled analysis. [a]Other includes administrative reasons, ineligibility, investigator's decision, lost to follow-up, noncompliance with protocol, noncompliance with study drug, other malignancy, patient's decision not related to toxicity, physician decision, protocol violation, and "other" (defined as any other reason not previously listed). AE, adverse event; PD, progressive disease.

Table 2
Summary of treatment-related adverse events.

	Pembrolizumab $n = 2060$		Placebo $n = 2065$	
Any treatment-related AEs	1620 (78.6)		1212 (58.7)	
Grade 3–5	336 (16.3)[a]		72 (3.5)[b]	
Serious	238 (11.6)		31 (1.5)	
Led to discontinuation	326 (15.8)		44 (2.1)	
Time to onset of first treatment-related AE, median (range), days	36 (1–426)		42 (1–421)	
Any-grade treatment-related AEs in ≥ 2 % of patients and corresponding grade 3–5 treatment-related AEs	**Any grade**	**Grade 3–5**	**Any grade**	**Grade 3–5**
Fatigue	407 (19.8)	10 (0.5)	354 (17.1)	6 (0.3)
Pruritus	401 (19.5)	5 (0.2)	220 (10.7)	2 (0.1)
Hypothyroidism	350 (17.0)	2 (0.1)	58 (2.8)	0 (0)
Diarrhea	334 (16.2)	23 (1.1)	237 (11.5)	5 (0.2)
Rash	236 (11.5)	13 (0.6)	120 (5.8)	1 (<0.1)
Arthralgia	228 (11.1)	9 (0.4)	159 (7.7)	1 (<0.1)
Hyperthyroidism	204 (9.9)	3 (0.1)	21 (1.0)	0 (0)
Nausea	165 (8.0)	1 (<0.01)	114 (5.5)	0 (0)
Asthenia	147 (7.1)	4 (0.2)	115 (5.6)	0 (0)
ALT increased	120 (5.8)	20 (1.0)	72 (3.5)	5 (0.2)
Rash maculo-papular	117 (5.7)	8 (0.4)	48 (2.3)	0 (0)
Myalgia	109 (5.3)	5 (0.2)	58 (2.8)	0 (0)
AST increased	97 (4.7)	10 (0.5)	48 (2.3)	3 (0.1)
Headache	89 (4.3)	0 (0)	70 (3.4)	1 (<0.1)
Decreased appetite	78 (3.8)	3 (0.1)	24 (1.2)	0 (0)
Dry mouth	78 (3.8)	1 (<0.1)	21 (1.0)	0 (0)
Pneumonitis	67 (3.3)	13 (0.6)	22 (1.1)	3 (0.1)
Dyspnea	63 (3.1)	3 (0.1)	34 (1.6)	0 (0)
Dry skin	60 (2.9)	0 (0)	50 (2.4)	0 (0)
Cough	59 (2.9)	1 (<0.1)	45 (2.2)	0 (0)
Vomiting	50 (2.4)	1 (<0.1)	23 (1.1)	0 (0)
Blood creatinine increased	49 (2.4)	1 (<0.1)	24 (1.2)	0 (0)
Colitis	48 (2.3)	20 (1.0)	8 (0.4)	1 (<0.1)
Dizziness	43 (2.1)	0 (0)	28 (1.4)	0 (0)

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase.
Data are *n* (%) unless otherwise specified.
[a] All grade 5 treatment-related AEs occurred in the PEARLS/KEYNOTE-091 study: 1 because of cardiogenic shock and myocarditis, 1 because of septic shock and myocarditis, 1 because of pneumonia, and 1 because of sudden death.
[b] No grade 5 treatment-related AEs occurred in the placebo group.

an immune-mediated AE or infusion reaction in the pembrolizumab group was 80 days (range, 1–465) (Figure 2). The median time to onset of any occurrence of an immune-mediated AE in the pembrolizumab group was 106 days (range, 1–492), and the median time to resolution was 45 days (range, 1–1185) (Supplementary Table A.5).

In the placebo group, 8.4 % of patients had at least 1 immune-mediated AE, of which the most common (≥2 %) was hypothyroidism (3.7 %) (Table 3; Supplementary Table A.4). Grade 3 or 4 immune-mediated AEs occurred in 1.1 % of patients, with no specific immune-mediated AE occurring in ≥ 1 %. No patients in the placebo group died because of immune-mediated AEs. Serious immune-mediated AEs occurred in 0.8 % of patients, and immune-mediated AEs led to treatment discontinuation in 0.9 %. Infusion reactions occurred in 0.9 % of patients in the placebo group (all grade 1 or 2). The median time to onset of any occurrence of an immune-mediated AE in the placebo group was 145 days (range, 1–448), and the median time to resolution was 43 days (range, 2–1191) (Supplementary Table A.5).

Table 3
Summary of immune-mediated adverse events.

	Pembrolizumab $n = 2060$		Placebo $n = 2065$	
Any immune-mediated AEs	746 (36.2)		174 (8.4)	
Grade 3–5	177 (8.6)		23 (1.1)	
Serious	161 (7.8)		16 (0.8)	
Led to discontinuation	176 (8.5)		18 (0.9)	
Led to death	2 (0.1)[c]		0 (0)	
All immune-mediated AEs	**Any grade**	**Grade 3–5**	**Any grade**	**Grade 3–5**
Hypothyroidism	382 (18.5)	2 (0.1)	76 (3.7)	0 (0)
Hyperthyroidism	227 (11.0)	3 (0.1)	27 (1.3)	0 (0)
Pneumonitis	82 (4.0)	17 (0.8)	29 (1.4)	4 (0.2)
Colitis	62 (3.0)	29 (1.4)	14 (0.7)	2 (0.1)
Severe skin reactions	44 (2.1)	38 (1.8)	9 (0.4)	7 (0.3)
Adrenal insufficiency	38 (1.8)	16 (0.8)	5 (0.2)	1 (<0.1)
Thyroiditis	34 (1.7)	2 (0.1)	6 (0.3)	0
Hepatitis	35 (1.7)	29 (1.4)	8 (0.4)	5 (0.2)
Hypophysitis	32 (1.6)	11 (0.5)	1 (<0.1)	0 (0)
Type 1 diabetes mellitus	17 (0.8)	17 (0.8)	0 (0)	0 (0)
Sarcoidosis	17 (0.8)	1 (<0.1)	0 (0)	0 (0)
Nephritis	16 (0.8)	6 (0.3)	1 (<0.1)	0 (0)
Myositis	10 (0.5)	4 (0.2)	3 (0.1)	0 (0)
Pancreatitis	6 (0.3)	3 (0.1)	3 (0.1)	2 (0.1)
Myocarditis	7 (0.3)	6 (0.3)	2 (0.1)	2 (0.1)
Myasthenic syndrome	6 (0.3)	2 (0.1)	0 (0)	0 (0)
Vasculitis	3 (0.1)	2 (0.1)	0 (0)	0 (0)
Uveitis	3 (0.1)	0 (0)	1 (<0.1)	0 (0)
Encephalitis	1 (<0.1)	1 (<0.1)	0 (0)	0 (0)
Myelitis	1 (<0.1)	1 (<0.1)	0 (0)	0 (0)

AE, adverse event.
Data are *n* (%).
[c] Both deaths occurred in PEARLS/KEYNOTE-091 and were due to myocarditis.

3.5. Treatment of immune-mediated AEs and infusion reactions

3.5.1. Corticosteroids

Of 761 patients with at least 1 immune-mediated AE or infusion reaction in the pembrolizumab group, 35.2 % required treatment with systemic corticosteroids (Table 4). The immune-mediated AEs most frequently (≥80 %) treated with systemic corticosteroids were vasculitis (3 of 3 patients, 100 %), myelitis (1 of 1, 100 %), adrenal insufficiency (33 of 38, 86.8 %), colitis (53 of 62, 85.5 %), hepatitis (29 of 35, 82.9 %), and pneumonitis (66 of 82, 80.5 %). Among the 761 patients in the pembrolizumab group, 1384 immune-mediated AE or infusion reaction episodes occurred. Of those episodes, 276 (19.9 %) required initial treatment with high-dose corticosteroids (≥40 mg/day prednisone or equivalent) (Supplementary Table A.6). The median starting dose of corticosteroids for these episodes was 70 mg/day (range 40–1250), and the median duration of treatment with high-dose corticosteroids was 7 days (range 1–987). Of the 1384 episodes that occurred in patients in the pembrolizumab group, 140 (10.1 %) required initial treatment with low-dose corticosteroids (<40 mg/day prednisone or

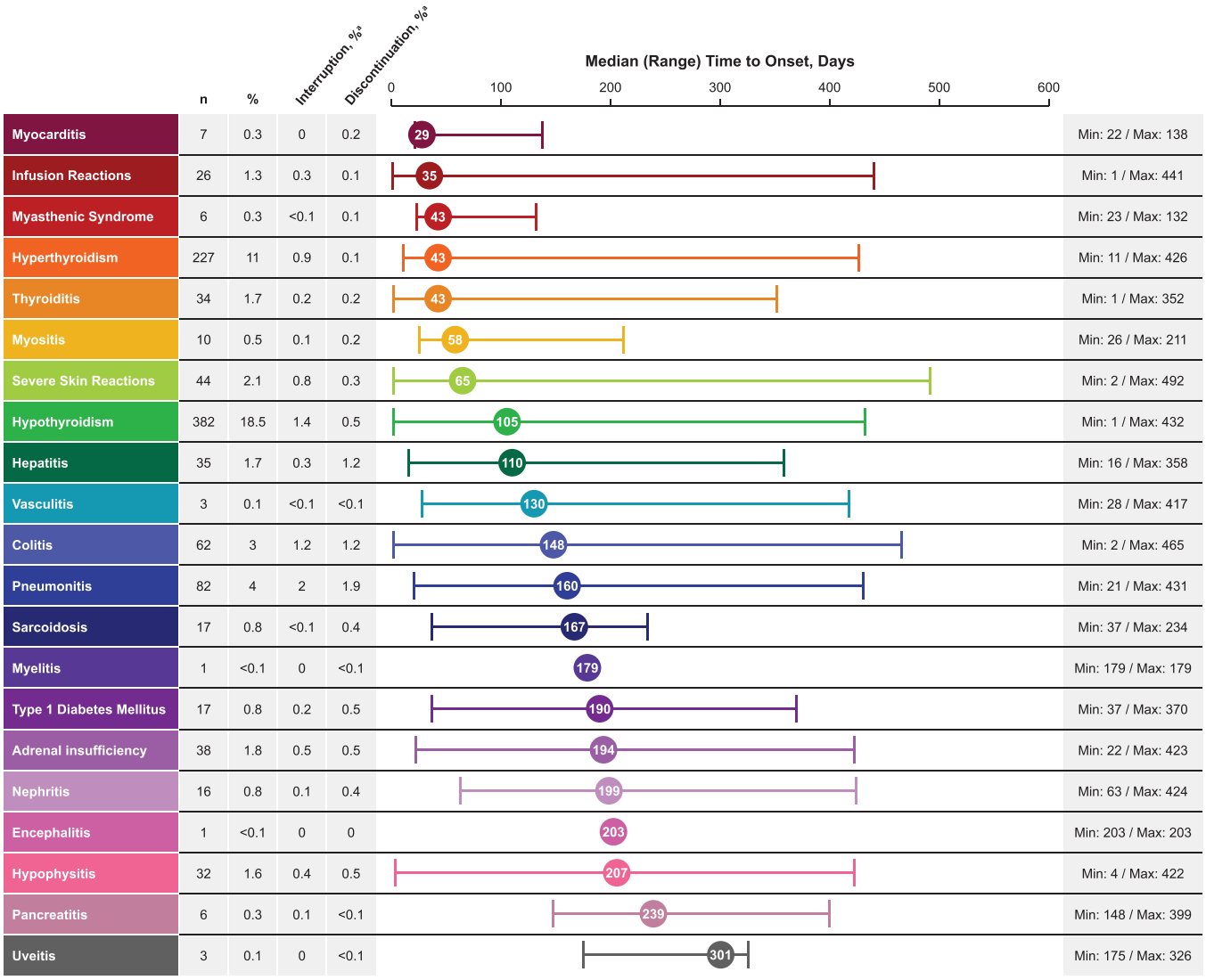

Fig. 2. Time to onset of first occurrence of immune-mediated adverse events or infusion reactions with pembrolizumab as adjuvant therapy. [a]Percentages are based on the number of patients with an adverse event that led to treatment interruption or discontinuation.

equivalent) (Supplementary Table A.6). The median starting dose of corticosteroids for these episodes was 20 mg/day (range 0–38), and the median duration of treatment was 9 days (range 1–803). No corticosteroids were used to treat the remaining 967 (69.9 %) immune-mediated AE or infusion reaction episodes.

Of 193 patients treated with placebo who had at least 1 immune-mediated AE, 20.2 % required treatment with systemic corticosteroids (Table 4). The immune-mediated AEs most frequently (≥80 %) treated with systemic corticosteroids in the placebo group were nephritis (1 of 1 patient, 100 %) and uveitis (1 of 1 patient, 100 %). Among the 193 patients in the placebo group, 253 immune-mediated AE or infusion reaction episodes occurred. Of those episodes, 31 (12.3 %) required initial treatment with high-dose corticosteroids (Supplementary Table A.7). The median starting dose of corticosteroids for these episodes was 75 mg/day (range 40–1500), and the median duration of treatment with high-dose corticosteroids was 4 days (range, 1–17). Of the 253 episodes that occurred in patients in the placebo group, 25 (9.9 %) required initial treatment with low-dose corticosteroids (Supplementary Table A.7). The median starting dose of corticosteroids for these episodes was 20 mg/day (range 1–30), and the median duration of treatment with low-dose corticosteroids was 8 days (range 1–1273). No corticosteroids were used to treat the remaining 197 (77.9 %) immune-mediated AE or infusion reaction episodes.

3.5.2. *Hormone replacement therapies*

Corticosteroid replacement therapy was required for 36 of 38 patients (94.7 %) in the pembrolizumab group and for 3 of 5 patients (60.0 %) in the placebo group with adrenal insufficiency (Table 4). Hormone replacement therapy (HRT) was required for 31 of 32 patients (96.9 %) and 1 of 1 patient (100 %) with hypophysitis in the pembrolizumab and placebo groups, respectively. All 17 patients (100 %) who developed type 1 diabetes mellitus in the pembrolizumab group received insulin (Table 4). Thyroid therapy was required for 326 of 382 patients with hypothyroidism (85.3 %) in the pembrolizumab group and for 35 of 76 patients with hypothyroidism (46.1 %) in the placebo group, and for 16 of 34 (47.1 %) and 5 of 6 patients (83.3 %) with thyroiditis, respectively (Table 4).

4. Discussion

In the phase 3 KEYNOTE-054, KEYNOTE-716, PEARLS/KEYNOTE-091, and KEYNOTE-564 clinical trials, adjuvant pembrolizumab was associated with significant prolongation of disease-free survival compared with placebo in patients with resected melanoma, NSCLC, and RCC [4–8]. In this pooled analysis of more than 4000 patients from these trials, adjuvant pembrolizumab was shown to have a manageable safety profile that was consistent with the established profile of

Table 4
Proportion of patients with immune-mediated adverse events and infusion reactions requiring select therapies.

	Pembrolizumab $n = 2060$	Placebo $n = 2065$
Systemic corticosteroids		
Any immune-mediated AE or infusion reaction	35.2 (268/761)	20.2 (39/193)
Myelitis	100 (1/1)	NA
Vasculitis	100 (3/3)	NA
Adrenal insufficiency	86.8 (33/38)	40.0 (2/5)
Colitis	85.5 (53/62)	42.9 (6/14)
Hepatitis	82.9 (29/35)	75.0 (6/8)
Pneumonitis	80.5 (66/82)	34.5 (10/29)
Hypophysitis	78.1 (25/32)	0 (0/1)
Nephritis	75.0 (12/16)	100 (1/1)
Myasthenic syndrome	66.7 (4/6)	NA
Pancreatitis	66.7 (4/6)	33.3 (1/3)
Myositis	60.0 (6/10)	0 (0/3)
Severe skin reactions	59.1 (26/44)	66.7 (6/9)
Myocarditis	42.9 (3/7)	0 (0/2)
Thyroiditis	23.5 (8/34)	0 (0/6)
Infusion reactions	23.1 (6/26)	26.3 (5/19)
Sarcoidosis	11.8 (2/17)	NA
Hyperthyroidism	3.5 (8/227)	7.4 (2/27)
Hypothyroidism	2.1 (8/382)	0 (0/76)
Type 1 diabetes mellitus	0 (0/17)	NA
Uveitis	0 (0/3)	100 (1/1)
Hormone replacement therapy		
Type 1 diabetes mellitus	100 (17/17)	NA
Hypophysitis	96.9 (31/32)	100 (1/1)
Adrenal insufficiency	94.7 (36/38)	60.0 (3/5)
Thyroid therapy		
Hypothyroidism	85.3 (326/382)	46.1 (35/76)
Thyroiditis	47.1 (16/34)	83.3 (5/6)

AE, adverse event; NA, not applicable (no patient had an event).
Data are % (number of patients treated with therapy/number of patients with ≥1 event).

pembrolizumab in advanced unresectable disease [1,2,10–14]. Most treatment-related AEs in patients who received pembrolizumab were mild or moderate in severity, and only a small proportion led to treatment discontinuation. Similar results were observed for immune-mediated AEs, which were effectively managed with corticosteroids and end-organ HRT. No new safety signals were reported, either by type of AE or incidence. These results suggest that the safety profile of pembrolizumab is consistent across disease stages.

In the current analysis, 78.6 % of patients in the pembrolizumab group experienced at least 1 treatment-related AE and 16.3 % experienced at least 1 grade ≥ 3 treatment-related AE. These rates are comparable with those reported in advanced cancers, including melanoma, NSCLC, and RCC. In a pooled analysis of the safety of pembrolizumab in patients with advanced melanoma ($N = 1567$), treatment-related AEs occurred in 80.7 % of patients, and grade 3/4 events occurred in 17.7 % [10]. Similarly, in a pooled analysis of the safety and efficacy of pembrolizumab monotherapy in patients with advanced NSCLC by age group ($n = 1472$), the incidence of treatment-related AEs was 65.2 % (862/1323) in patients < 75 years and 68.5 % (102/149) in patients ≥ 75 years, with grade ≥ 3 events reported in 16.9 % (224/1323) and 24.2 % (36/149) of patients, respectively [12]. Although the safety of pembrolizumab has more often been evaluated in combination with other agents in advanced RCC, pembrolizumab as monotherapy was evaluated in patients with advanced clear-cell RCC in the phase 2 KEYNOTE-427 study ($N = 110$) [13]. Treatment-related AEs in KEYNOTE-427 occurred in 82.7 % of patients, and grade 3–5 events in 30.0 %. In the current analysis, the most common treatment-related AEs were fatigue, pruritus, hypothyroidism, diarrhea, rash, and arthralgia, which is consistent with the studies above. As in advanced cancers [10,12,13], only a small proportion of patients (15.8 %) discontinued pembrolizumab and very few patients died because of treatment-related AEs (0.2 %). Although the incidence and severity of AEs seem similar in the advanced setting for the considered cancer types, the context differs between treatment settings. As adjuvant therapy treats risk of recurrence rather than active disease, it is important to carefully consider the severity and incidence of long-term AEs.

There was a wide range of time to onset for immune-mediated AEs. The risk of experiencing myocarditis, AEs involving the thyroid (i.e. hypothyroidism, hyperthyroidism, and thyroiditis), and infusion reactions was higher earlier in treatment. The most common immune-mediated AEs were hypothyroidism (18.5 %), hyperthyroidism (11.0 %), and pneumonitis (4.0 %), which is consistent with studies conducted in patients with advanced melanoma, NSCLC, and RCC [10,12,13]. In the pooled analysis of patients with advanced melanoma who received pembrolizumab, immune-mediated AEs occurred in 23.0 % of patients, of which the most common were hypothyroidism (9.1 %), pneumonitis (3.3 %), and hyperthyroidism (3.0 %) [10]. In the pooled analysis of pembrolizumab in patients with advanced NSCLC by age group, immune-mediated AEs and infusion reactions were reported in 25.0 % (331/1323) of patients < 75 years of age and 24.8 % (37/149) of patients ≥ 75 years [12]. The most commonly reported in both age groups were hypothyroidism (<75 years, 10.4 %; ≥75 years, 8.7 %), pneumonitis (6.8 %; 7.4 %), and hyperthyroidism (5.7 %; 5.4 %). Immune-mediated AEs occurred in 32.7 % of patients with RCC in KEYNOTE-427, with the most common being hypothyroidism (13.6 %), colitis (6.4 %), hyperthyroidism (5.5 %), and pneumonitis (4.5 %) [13]. In both this analysis and other studies of advanced cancers, immune-mediated AEs and infusion reactions are generally managed with the use of supportive medications, including systemic corticosteroids and end-organ HRT. Notably, the incidence of immune-mediated type 1 diabetes mellitus was low in the current analysis, occurring in 0.8 % of patients treated with pembrolizumab, all of whom received insulin.

The consistent safety profile of pembrolizumab provides a rationale for exploring combinations to further improve efficacy. Pembrolizumab plus V940, an individualized neoantigen therapy, and a coformulation of vibostolimab, an anti-TIGIT monoclonal antibody, with pembrolizumab are also being investigated as adjuvant therapy. Pembrolizumab has also demonstrated efficacy and safety in combination with chemotherapy in the neoadjuvant setting [15,16].

Patient-reported outcomes were not included as part of this pooled analysis. However, previously published data from KEYNOTE-054 [17], KEYNOTE-716 [18], and KEYNOTE-564 [19], have demonstrated that treatment with adjuvant pembrolizumab does not result in a deterioration in health-related quality of life in patients with melanoma or RCC. Health-related quality of life data for patients with NSCLC treated with adjuvant pembrolizumab in the PEARLS/KEYNOTE-091 study are not yet available.

The primary limitation of this analysis is that the clinical study protocols do not include a requirement for long-term collection of safety data. AEs in the trials were only monitored for up to 30 days after treatment discontinuation, or 90 days for serious AEs or AEs of clinical interest. Consequently, data on delayed immune-related AEs were not collected. Although these are rare (~5 %) and mostly develop during treatment, they can occur more than 3 months after the last dose of treatment is received [20]. It has also been theorized that treatment with immune checkpoint inhibitors may impact fertility, pregnancy, and sexuality [21], but data were not directly collected on these aspects of safety as pregnancy was an exclusion criterion, and contraceptive measures were required for all patients of reproductive potential. Chronic fatigue may also be associated with immune checkpoint inhibitor treatment and requires further study to fully characterize [22]. AE data in these trials were also collected through patient or caregiver report and investigator review. The lack of central confirmation may have impacted the accuracy of the results. This analysis also was limited to patients with melanoma, NSCLC, and RCC, reflecting the indications for which phase 3 trial data are available.

To our knowledge, this is the largest pooled safety dataset of

adjuvant immunotherapy to date. The results showed that pembrolizumab given as adjuvant therapy has a safety profile that is manageable and similar to that previously observed in patients with unresectable advanced disease while providing clinical benefit over placebo. These results support the use of pembrolizumab as adjuvant therapy.

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Data Sharing Statement

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 legitimate scientific research. MSD is also obligated to protect the rights and privacy of trial participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. The MSD data sharing website (available at: http://engagezone.msd.com/ds_documentation.php) outlines the process and requirements for submitting a data request. Applications will be promptly assessed for completeness and policy compliance. Feasible requests will be reviewed by a committee of MSD subject matter experts to assess the scientific validity of the request and the qualifications of the requestors. In line with data privacy legislation, submitters of approved requests must enter into a standard data-sharing agreement with MSD before data access is granted. Data will be made available for request after product approval in the US and EU or after product development is discontinued. There are circumstances that may prevent MSD from sharing requested data, including country or region-specific regulations. If the request is declined, it will be communicated to the investigator. Access to genetic or exploratory biomarker data requires a detailed, hypothesis-driven statistical analysis plan that is collaboratively developed by the requestor and MSD subject matter experts; after approval of the statistical analysis plan and execution of a data-sharing agreement, MSD will either perform the proposed analyses and share the results with the requestor or will construct biomarker covariates and add them to a file with clinical data that is uploaded to an analysis portal so that the requestor can perform the proposed analyses.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.114146.

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