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Safety of pemetrexed plus platinum in combination with pembrolizumab for metastatic nonsquamous non-small cell lung cancer: A post hoc analysis of KEYNOTE-189

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ABSTRACT

Objectives: This post hoc analysis assessed the safety of pemetrexed and platinum in combination with pembrolizumab, including time-to-onset and time-to-resolution of all-cause any-grade and grade ≥3 adverse events (AEs) and renal AEs.

Materials and Methods: Patient-level data from KEYNOTE-189 were analyzed in the all-subjects-as-treated population (pembrolizumab arm, n = 405; placebo arm, n = 202), and among patients who received ≥5 cycles of pemetrexed (pemetrexed/pembrolizumab/platinum arm, n = 310; pemetrexed/placebo/platinum arm, n = 135). All-cause AEs were selected based on ≥2 % incidence from previously reported KEYNOTE-189 data and included neutropenia, febrile neutropenia, anemia, thrombocytopenia, asthenia, fatigue, dyspnea, diarrhea, nausea, vomiting, pneumonitis, and renal events. Descriptive statistics summarized all-cause AEs. Medians and interquartile ranges were used to examine time-to-onset and time-to-resolution. The data cutoff was November 8, 2017.

Results: In both treatment arms, most non-hematologic (nausea, vomiting, diarrhea, and asthenia), and hematologic (febrile neutropenia, thrombocytopenia, and neutropenia) grade ≥3 AEs with ≥2 % incidence had a median time-to-onset within the first 4 cycles, and a median time-to-resolution of within 2 weeks from onset. A small number of AEs had longer median time-to-onset (pneumonitis and fatigue) and median time-to-resolution (pneumonitis, fatigue, acute kidney injury, and anemia). Among patients who received ≥5 cycles of pemetrexed, the incidence of any-grade renal toxicity in the pemetrexed/pembrolizumab/platinum arm was 2.3 % in Cycles 1–4, 4.8 % in Cycles 5–8, 2.6 % in Cycles 9–12, and 2.5 % in Cycles ≥13; and, in the pemetrexed/placebo/platinum arm, 0.7 % in Cycles 1–4, 1.5 % in Cycles 5–8, 1.3 % in Cycles 9–12, and 2.0 % in Cycles ≥13.

Conclusion: Pemetrexed/pembrolizumab/platinum has manageable toxicity with longer duration of treatment. While the incidence of renal toxicity was slightly higher in the pembrolizumab combination as compared to pemetrexed, the incidence did not increase in later treatment cycles. These results support the safe use of the KEYNOTE-189 regimen in clinical practice.

Clinical Trial Registration Number: NCT02578680 (clinicaltrials.gov).

Abbreviations: PD-1, programmed cell death protein-1; PD-L1, programmed cell death ligand-1.

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1. Introduction

The approvals of several immune checkpoint inhibitors have advanced the standard-of-care for patients with metastatic non-small cell lung cancer (NSCLC) in first-line settings and after platinum-based chemotherapy treatment failure [1–3]. The ability of immune checkpoint inhibitors to restore tumor-specific T cell responses has resulted in substantial improvement of survival outcomes [4,5].

Preclinical and clinical studies suggest that combining immune checkpoint inhibitors with chemotherapy improves immunotherapy anti-tumor effects via various mechanisms, including reduced tumor load, release of tumor antigens in vivo, and enhanced anti-tumor immune response [6]. Pemetrexed, an established, multi-targeted antifolate, has demonstrated positive immune modulation [7]. In several clinical trials of patients with advanced NSCLC, pemetrexed/platinum demonstrated improvements in efficacy over standard-of-care, with a tolerable safety profile in first-line and maintenance settings [8–10].

In 2017, the combination of pemetrexed/pembrolizumab/carboplatin was approved by the United States Food and Drug Administration as a first-line treatment for metastatic nonsquamous (NSQ) NSCLC after demonstrating a significantly improved overall response rate compared with pemetrexed/carboplatin in the phase 2 KEYNOTE-021 study [11, 12]. The superior efficacy of pemetrexed/pembrolizumab/carboplatin was subsequently confirmed in the phase 3 KEYNOTE-189 study [13, 14]. After a median follow-up of 10.5 months, pemetrexed/pembrolizumab/platinum improved overall survival (OS; hazard ratio, 0.49, $p < 0.001$) and progression-free survival (PFS; hazard ratio, 0.52, $p < 0.001$) irrespective of PD-L1 expression, compared with pemetrexed/placebo/platinum [14]. Efficacy benefits were consistently demonstrated after a median follow-up of 23.1 months [13] and 31.0 months [15].

The combination of pemetrexed/pembrolizumab/platinum has also demonstrated a tolerable safety profile [13–15]. The proportion of patients who experienced grade ≥3 adverse events (AEs) was similar among those receiving pemetrexed/pembrolizumab/ platinum compared with pemetrexed/placebo/platinum (71.9 % vs 66.8 %) [13]. The most common immune-mediated any-grade and grade ≥3 AEs among patients receiving pemetrexed/pembrolizumab/platinum were hypothyroidism (7.9 %) and pneumonitis (3.0 %), respectively [13]. A greater percentage of those treated with pemetrexed/pembrolizumab/platinum experienced acute kidney injury compared with patients receiving pemetrexed/placebo/platinum (6.2 % vs 0.5 %) [13].

Real-world data from Flatiron Health's database (May 2017 – October 2019) show that, among patients continuing treatment after 4 cycles with pemetrexed/pembrolizumab/platinum, 37 % received combination pembrolizumab and pemetrexed maintenance, while 41 % received pembrolizumab monotherapy maintenance, and 21 % switched between pemetrexed or pembrolizumab monotherapy and pembrolizumab/pemetrexed combination maintenance therapy [16]. We hypothesize this may be due to perceived toxicity concerns for the maintenance combination of pembrolizumab/pemetrexed, particularly renal toxicity [17]. However, to our knowledge, no study has examined the safety profile of pembrolizumab/pemetrexed specifically in the maintenance phase (Cycle 5 and beyond).

This study provides an in-depth assessment of the safety profile, including renal toxicity, of pembrolizumab/pemetrexed over time in all treated patients, and among patients who received pembrolizumab/pemetrexed for ≥5 treatment cycles. The incidence of all-cause any-grade AEs and grade ≥3 AEs, as well as time-to-onset and time-to-resolution of AEs, by study arm were also examined.

2. Materials and methods

2.1. Study design and treatment

The KEYNOTE-189 study design has been previously reported (including CONSORT flow diagram) [14]. Briefly, patients in this double-blind, phase 3 study had pathological confirmed metastatic NSQ NSCLC, without sensitizing *EGFR* or *ALK* mutations, and received no prior systemic therapy for metastatic disease. Patients were randomly assigned (2:1) to receive either 200 mg pembrolizumab or placebo. All patients received pembrolizumab or placebo plus pemetrexed (500 mg per square meter), administered intravenously every 3 weeks, in combination with 4 cycles of cisplatin (75 mg per square meter of body surface area) or carboplatin (area under the concentration time curve, 5 mg per milliliter per minute). Treatment continued until radiographic progression, unacceptable toxicity, investigator decision, patient withdrawal, or up to 35 cycles for pembrolizumab. If toxicity was clearly attributed to 1 agent, that agent alone could be discontinued. Data reported here are from the interim analysis cutoff of November 8, 2017 (median follow-up time of 10.5 months).

The trial protocol and all amendments were approved by the appropriate ethics panel at each center. The trial was conducted in accordance with the Declaration of Helsinki and was overseen by an external monitoring committee. All patients provided informed written consent prior to enrollment.

2.2. Patients

A total of 616 patients were allocated to either the pemetrexed/pembrolizumab/platinum (n = 410) or pemetrexed/placebo/platinum arm (n = 206) [13]. This analysis included 405 (98.9 %) patients from the pemetrexed/pembrolizumab/platinum arm and 202 (98.1 %) from the pemetrexed/placebo/platinum arm who received treatment (all-subjects-as-treated population).

A subcohort of 310 (76.5 %) patients from the pemetrexed/pembrolizumab/ platinum arm and 135 (66.8 %) patients from the pemetrexed/placebo/platinum arm who received ≥5 cycles of pemetrexed were included in analyses investigating maintenance pemetrexed therapy.

2.3. Outcomes

Adverse events of any cause were identified by system organ class and preferred term (Medical Dictionary for Regulatory Activities [MedDRA] 20.1). All-cause AEs of any-grade, as well as grade ≥3 AEs, were investigated. The grade ≥3 AEs were identified based on previously reported KEYNOTE-189 safety profiles and included grade ≥3 AEs of any cause that occurred in ≥2 % of either treatment arm (specifically: neutropenia, febrile neutropenia, anemia, thrombocytopenia, asthenia, fatigue, dyspnea, diarrhea, nausea, vomiting, and pneumonitis) [13,14]. Renal adverse events were selected as a composite AE of special interest and additionally investigated, as noted in previous KEYNOTE-189 results [13,14]. Renal AEs were identified by system organ class and preferred term (MedDRA 20.1). The composite term for renal events included: acute kidney injury, chronic kidney disease, renal failure, proteinuria, renal tubular necrosis, creatinine renal clearance decreased, creatinine renal clearance increased, renal impairment, prerenal failure, renal disorder, acute prerenal failure, renal infarct, and nephropathy. Renal events and changes in serum creatinine were summarized every 4 cycles.

2.4. Statistical analyses

Descriptive statistics were used to summarize baseline demographic and patient characteristics, as well as any-grade all-cause AEs, grade ≥3 all-cause AEs, renal AEs, and discontinuation due to AEs. Patient-level median and interquartile ranges (IQR) for time-to-onset and time-to-resolution of AEs were described. Patient-level data were analyzed for the all-subjects-as-treated population, and separately for patients who received pemetrexed for ≥5 cycles (maintenance population).

3. Results

3.1. Baseline characteristics

Demographic and clinical characteristics of the all-subjects-as-treated and the maintenance patient populations were similar in both populations and were generally balanced between the pemetrexed/pembrolizumab/platinum and pemetrexed/placebo/platinum arms (Supplemental Table 1).

3.2. All-subjects-as-treated

3.2.1. Exposure to study treatment

Patients in the pemetrexed/pembrolizumab/platinum arm had a mean treatment duration of 7.4 months (standard deviation [SD], 4.7); 334 (82.5 %) patients received 4 cycles of platinum, 320 (79.0 %) received ≥5 cycles of pembrolizumab or pemetrexed, and only 9 (2.2 %) entered the maintenance therapy phase without pemetrexed. In the pemetrexed/placebo/platinum arm, the mean treatment duration was 5.4 months (SD, 4.3); 150 (74.3 %) patients received 4 cycles of platinum, 138 (68.3 %) patients received ≥5 cycles of pemetrexed or placebo, and only 3 (1.5 %) patients entered the maintenance therapy phase without pemetrexed. There were 113 (27.9 %) patients in the pemetrexed/pembrolizumab/platinum arm who received ≥15 cycles of any study drug; 86 (76.1 %) of these patients received ≥15 cycles of pemetrexed. There were 30 (14.9 %) patients in the pemetrexed/placebo/platinum arm who received ≥15 cycles of any study drug; 25 (83.3 %) of these patients received ≥15 cycles of pemetrexed.

3.2.2. All-cause adverse events

All-cause any-grade AEs were reported in 404 (99.8 %) patients in the pemetrexed/pembrolizumab/platinum arm, and 200 (99.0 %) patients in the pemetrexed/placebo/platinum arm; all-cause grade ≥3 AEs were reported in 272 (67.2 %) and 133 (65.8 %) patients in the pemetrexed/pembrolizumab/platinum arm and the pemetrexed/placebo/platinum arm, respectively (Supplemental Table 2). The incidence of grade ≥3 AEs was similar between the pemetrexed/pembrolizumab/platinum and pemetrexed/placebo/platinum arms for both hematologic and non-hematologic events for the all-subjects-as-treated population. A breakdown of these AEs is included in Supplemental Table 2, and has been previously described [14].

Of the grade ≥3 non-hematologic AEs, acute kidney injury, nausea, vomiting, diarrhea, and asthenia all had a median time-to-onset within the first 4 cycles of treatment for both study arms (Fig. 1, Panel A). In the pemetrexed/pembrolizumab/platinum arm, pneumonitis was the only grade ≥3 non-hematologic AE with a median time-to-onset that occurred after the first 4 cycles and had a median time-to-onset of 125 days (6 cycles). In the pemetrexed/placebo/platinum arm, fatigue was the only grade ≥3 non-hematologic AE with a median time-to-onset occurring after the first 4 cycles (91 days; 4.3 cycles). The median time-to-onset was the earliest (6 days) for grade ≥3 nausea, and the latest for grade ≥3 pneumonitis, both in the pemetrexed/ pembrolizumab/platinum arm (Fig. 1, Panel A). Grade ≥3 AEs of nausea, vomiting, diarrhea, and asthenia all had a median time-to-resolution of ≤2 weeks from onset in both study arms (Fig. 1, Panel B). In the pemetrexed/pembrolizumab/platinum arm, grade ≥3 pneumonitis and grade ≥3 acute kidney injury had a median time-to-resolution of 25 days

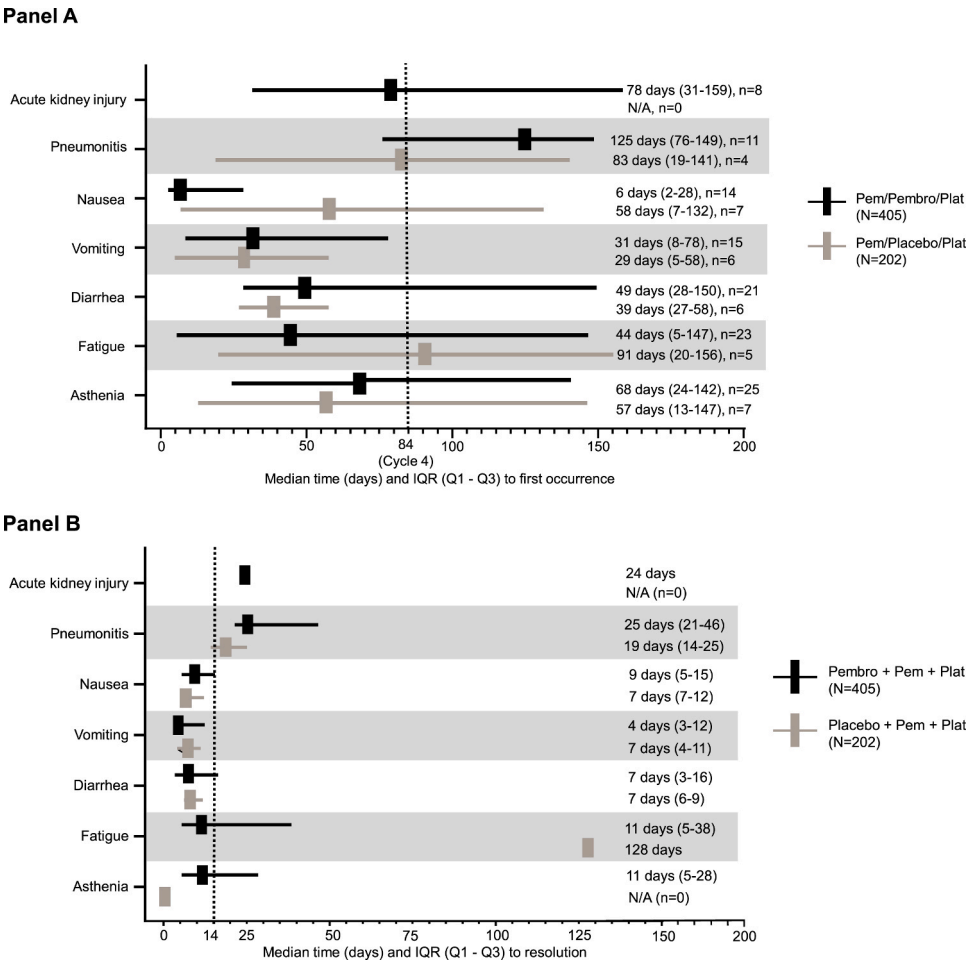

Fig. 1. Time-to-onset (Panel A) and time-to-resolution (Panel B) of non-hematologic grade ≥3 adverse events that occurred in ≥2 % of the all-subjects-as treated population. Abbreviations: IQR, interquartile range; N/A, not applicable; Pem, pemetrexed; Pembro, pembrolizumab; Plat, platinum, Q1, quartile 1; Q3, quartile 3.

(3.6 weeks) and 24 days (3.4 weeks), respectively (Fig. 1, Panel B). In the pemetrexed/pembrolizumab/platinum arm, grade ≥3 fatigue had a median time-to-resolution within 2 weeks (11 days). In the pemetrexed/placebo/platinum arm, grade ≥3 pneumonitis and grade ≥3 fatigue had a median time-to-resolution of 19 days (2.7 weeks) and 128 days (18.3 weeks), respectively (Fig. 1, Panel B).

All hematologic grade ≥3 AEs (febrile neutropenia, thrombocytopenia, neutropenia, and anemia) had a median time-to-onset within the first 4 cycles (Fig. 2, Panel A). Most grade ≥3 hematologic AEs (febrile neutropenia, thrombocytopenia, and neutropenia) had a median time-to-resolution within 2 weeks from onset (Fig. 2, Panel B). Grade ≥3 anemia had a median time-to-resolution of 21 days (3 weeks), and 11 days (1.6 weeks) in the pemetrexed/placebo/platinum arm and the pemetrexed/pembrolizumab/platinum arm, respectively (Fig. 2, Panel B).

Across all study cycles cumulatively, in the pemetrexed/pembrolizumab/platinum arm, pemetrexed or pembrolizumab were discontinued for 112 (27.7 %) patients due to AEs and, of these, 37 (33.0 %) discontinued during the first 4 cycles. The discontinuation rate for pemetrexed and pembrolizumab was similar across all treatment cycles, never exceeding 3 % in any study cycle (Fig. 3).

3.3. Patients receiving ≥5 cycles of pemetrexed (maintenance population)

3.3.1. Exposure to study treatment

In the pemetrexed/pembrolizumab/platinum arm, patients received a median of 11 cycles (range, 5–30) of pemetrexed compared with a median of 9.0 cycles (range, 5–24) of pemetrexed in the pemetrexed/placebo/platinum arm.

3.3.2. All-cause adverse events

The proportion of grade ≥3 AEs is shown in both Fig. 4 (for individual AEs, by treatment arm), and Supplemental Fig. 1 (AEs with ≥2 % incidence, by cycle). The incidence of grade ≥3 AEs increased moderately (by approximately 6–8 %) among patients in the pemetrexed/pembrolizumab/platinum arm compared with the pemetrexed/placebo/platinum arm in Cycles 9–12 and ≥13 (Supplemental Fig. 1). Grade ≥3 hematologic toxicities of neutropenia, thrombocytopenia, and anemia occurred more frequently in the first 4 cycles compared with Cycle 5 and later in both treatment arms (Fig. 4). Compared to patients in the pemetrexed/placebo/platinum arm, patients in the pemetrexed/pembrolizumab/platinum arm had a higher proportion of renal AEs across all cycles (Fig. 4).

3.3.3. Immune-mediated adverse events

The two most common immune-mediated AEs were any-grade hypothyroidism, occurring in 25 (8.1 %) patients, and any-grade pneumonitis, occurring in 15 (4.8 %) patients in the pemetrexed/pembrolizumab/platinum arm. In the pemetrexed/placebo/platinum arm, any-grade hypothyroidism occurred in 4 (3.0 %) patients, and any-grade pneumonitis in 3 (2.2 %) patients. Grade ≥3 hypothyroidism occurred in 2 (0.6 %) patients in the pemetrexed/pembrolizumab/platinum arm, and no patients in the pemetrexed/placebo/platinum arm. Grade ≥3 pneumonitis occurred in 8 (2.6 %) patients in the

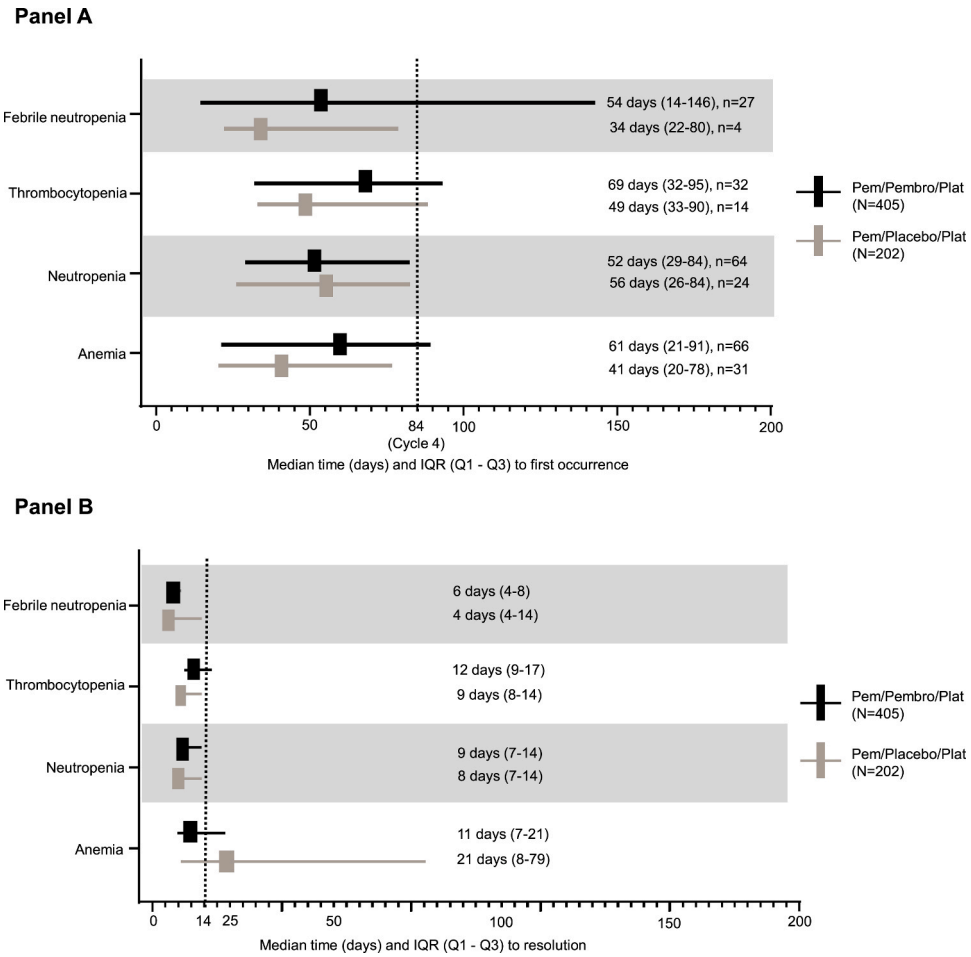

Fig. 2. Time-to-onset (Panel A) and time-to-resolution (Panel B) of hematologic grade ≥3 adverse events that occurred in ≥2 % of the all-subjects-as treated population.
Abbreviations: IQR, interquartile range; Pem, pemetrexed; Pembro, pembrolizumab; Plat, platinum; Q1, quartile 1; Q3, quartile 3.

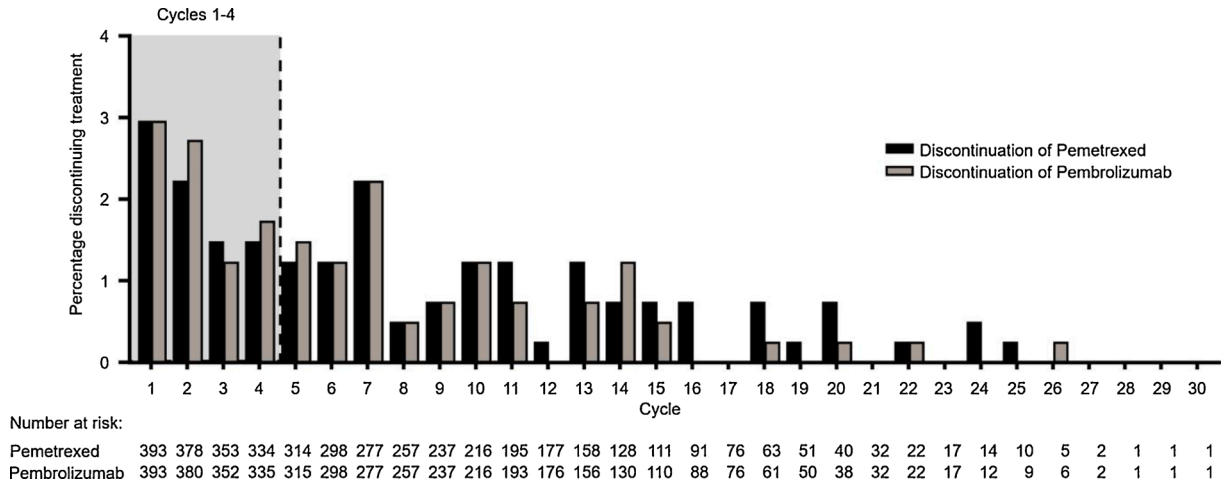

Fig. 3. The percentage of patients who discontinued either pemetrexed or pembrolizumab due to an adverse event in each cycle of treatment in pemetrexed/pembrolizumab/platinum arm of the all-subjects-as-treated population.

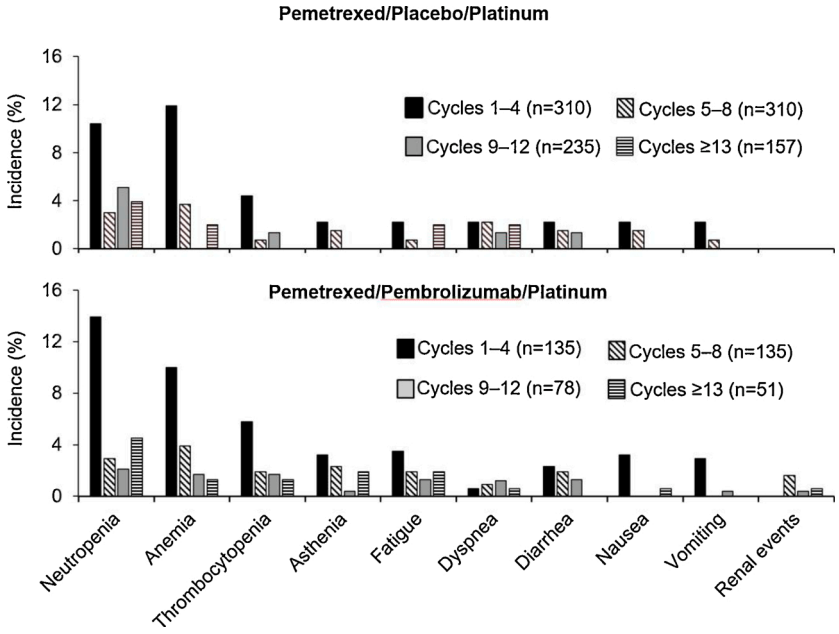

Fig. 4. Incidence of grade ≥3 adverse events over cycles of pemetrexed in patients who received ≥5 cycles of pemetrexed, by study arm.
Data are a percentage of patients who experienced ≥1 grade ≥3 adverse event. The composite term for renal events included the following Medical Dictionary for Regulatory Activities 20.1 preferred terms: acute kidney injury, chronic kidney disease, renal failure, proteinuria, renal tubular necrosis, creatinine renal clearance decreased, creatinine renal clearance increased, renal impairment, prerenal failure, renal disorder, acute prerenal failure, renal infarct, and nephropathy.

Table 1
Incidence of any-grade[a] renal adverse event over cycles of pemetrexed in patients who received ≥5 cycles of pemetrexed.

n[b] (%)	Pem/pembro/plat n = 310				Pem/placebo/plat n = 135			
	Cycles 1–4 (n = 310)	Cycles 5–8 (n = 310)	Cycles 9–12 (n = 235)	Cycles ≥13 (n = 157)	Cycles 1–4 (n = 135)	Cycles 5–8 (n = 135)	Cycles 9–12 (n = 78)	Cycles ≥13 (n = 51)
Renal events	7 (2.3)	15 (4.8)	6 (2.6)	4 (2.5)	1 (0.7)	2 (1.5)	1 (1.3)	1 (2.0)
Acute kidney injury	4 (1.3)	4 (1.3)	3 (1.3)	1 (0.6)	0	0	0	0
Chronic kidney disease	0	2 (0.6)	0	0	0	0	0	1 (2.0)
Creatinine renal clearance decreased	0	1 (0.3)	0	1 (0.6)	1 (0.7)	0	0	0
Renal failure	1 (0.3)	6 (1.9)	1 (0.4)	1 (0.6)	0	2 (1.5)	1 (1.3)	0
Other renal events[c]	2 (0.6)	2 (0.6)	1 (0.4)	1 (0.6)	0	0	0	0

[a] For the pemetrexed/pembrolizumab/platinum arm: in Cycles 1–4, no grade ≥3 adverse events occurred; in Cycles 5–8, n = 5 (1.6 %) grade ≥3 adverse events occurred including 2 acute kidney injury (0.6 %), 1 acute prerenal failure (0.3 %), and 2 renal failure (0.6 %); in Cycles 9–12, n = 1 (0.4 %) grade ≥3 adverse event occurred (proteinuria); and in Cycles ≥13, n = 1 (0.4 %) grade ≥3 adverse event (acute kidney injury) occurred. In the pemetrexed/placebo/platinum arm, no grade ≥3 adverse events occurred in any of the study cycles. [b] The n reported in each column represents the patients who experienced ≥1 any-grade renal adverse event. Percentages for each column were calculated based on column-specific sample sizes. [c] Other renal events include: acute prerenal failure, nephropathy, proteinuria, renal disorder, and renal impairment. Abbreviations: pem, pemetrexed; pembro, pembrolizumab; plat, platinum.

pemetrexed/pembrolizumab/platinum arm and 2 (1.5 %) patients in the pemetrexed/placebo/platinum arm.

3.3.4. Renal adverse events

The incidence of any-grade renal toxicity ranged from a minimum of 2.3 % in Cycles 1−4 among patients in the pemetrexed/pembrolizumab/platinum arm, to a maximum of 4.8 % in Cycles 5−8 (Table 1). In the pemetrexed/placebo/platinum arm, no grade ≥3 renal adverse events were reported; the incidence of any-grade renal events ranged from a minimum of 0.7 % in Cycles 1−4 to a maximum of 2.0 % in Cycles ≥13 (Table 1). The most common any-grade renal events among patients in the pemetrexed/pembrolizumab/platinum arm were acute kidney injury and renal failure; the most common renal events among patients in the pemetrexed/placebo/platinum arm were chronic kidney disease and renal failure (Table 1). In the pemetrexed/pembrolizumab/platinum arm, there were no grade ≥3 AEs in Cycles 1−4, n = 5 (1.6 %) in Cycles 5−8, n = 1 (0.4 %) in Cycles 9−12, and n = 1 (0.4 %) in Cycles ≥13 (Table 1). No grade ≥3 renal AEs occurred in the pemetrexed/placebo/platinum arm in any study cycle.

4. Discussion

These results provide an in-depth characterization of patterns of AE onset and resolution, and renal toxicity incidence, in patients from the KEYNOTE-189 trial. This detailed safety profile is critical to optimize toxicity management, given treatment-induced toxicities can have detrimental consequences, such as high pemetrexed discontinuation rates (which may negatively affect efficacy outcomes) and a decrease in health-related quality of life. Data presented here may help set expectations for physicians regarding common toxicities and the average duration of these toxicities.

Across both treatment arms in this study, most non-hematologic grade ≥3 AEs with incidence ≥2 % occurred in the first 4 cycles and resolved within 2 weeks from onset. The outliers of these onset and resolution ranges were pneumonitis and acute kidney injury, which were the most common AEs leading to pembrolizumab discontinuation (3 % and 2 %, respectively). Although it is well known that those immune-related AEs have late onset, pneumonitis in this study occurred slightly later (approximately 18 weeks) compared to the previously reported median time-to-onset (8–10 weeks) of immune-related pneumonitis after immunotherapy was initiated [18,19]. All hematologic AEs with incidence ≥2 % in both treatment arms occurred in the first 4 cycles and resolved within 2 weeks from onset. The percentage of patients who discontinued pemetrexed or pembrolizumab due to an AE ranged from 1.5 % to 3 % during the first 4 cycles, and never surpassed 3 % in subsequent cycles. Over the course of the study, the incidence of grade ≥3 hematologic or non-hematologic AEs did not increase in either treatment arm.

Real-world data previously demonstrated that the majority of patients with NSQ NSCLC who received the KEYNOTE-189 treatment regimen did not receive combination pembrolizumab/pemetrexed maintenance after the first 4 cycles [16], possibly due to perceived safety concerns, including renal toxicity [17,20–22]. Renal toxicity, which can occur during therapy with single-agent pembrolizumab [21] or pemetrexed [22], appears to be more frequent in the combination setting of pembrolizumab/pemetrexed compared with either agent alone [17], and has been documented for immune checkpoint inhibitors [20] and pemetrexed [22]. Renal function may become impaired through several distinct mechanisms – either via the programmed cell death protein-1 (PD-1)/PD-L1 pathway, or by tubular toxicity from chemotherapeutic agents [17]. In one retrospective, hospital-based, cohort study of 359 patients consecutively enrolled who had NSCLC and were treated with pemetrexed, 21 % experienced clinically relevant decline in renal function after pemetrexed treatment, and 8.1 % discontinued pemetrexed due to nephrotoxicity; cumulative pemetrexed dose was identified as a risk factor for nephrotoxicity [22]. In our study, a slightly higher percentage of patients in the pemetrexed/pembrolizumab/platinum arm compared to the control arm experienced renal events, including acute kidney injury; however, grade ≥3 renal AE incidence was consistently low, remaining below 2 %, in both treatment arms across the study treatment period, by cycle. The incidence of any-grade renal AEs was slightly higher in Cycles 5−8 compared to Cycles 1−4, but it later stabilized and did not show a constantly increasing pattern across all treatment cycles in either study arm. Of note, this analysis examined the proportion of renal AEs at each treatment cycle and was not adjusted for differences in overall exposure. Previous evidence suggests both immune checkpoint inhibitors and chemotherapy may contribute to renal toxicity [20–22]. Thus, it is recommended that patients who continue prolonged pembrolizumab/pemetrexed therapy are monitored for renal function [17]. Understanding and diagnosing the underlying mechanisms causing renal toxicity may be useful in treating acute kidney injury among patients treated with pembrolizumab/pemetrexed [20]. Although regimens that do not involve maintenance chemotherapy in chemoimmunotherapy regimens have been evaluated [23], there are no data to date showing a direct comparison.

Pemetrexed and pembrolizumab each have a well-characterized monotherapy safety profile for NSQ NSCLC treatment [9,24]. Hematologic toxicities such as anemia and neutropenia were the most common grade 3–4 AEs among patients receiving pemetrexed/platinum in the phase III PARAMOUNT study [9]. Non-hematologic toxicities such as diarrhea, severe skin reaction, and pneumonitis were the most common grade ≥3 AEs among patients receiving pembrolizumab monotherapy in KEYNOTE-024 [24]. Any-grade immune-mediated AEs also occurred at a higher rate among patients receiving pembrolizumab (29.2 %) compared with patients receiving chemotherapy (4.7 %) [24]. For the duration of this study, there were no differences observed in hematologic and non-hematologic AEs between treatment arms. Immune-mediated AEs were slightly more common among patients receiving pembrolizumab.

When interpreting the results presented in this post hoc exploratory KEYNOTE-189 study, the following limitations should be considered. The subgroup analyses of patients receiving ≥5 cycles of pemetrexed excluded patients who discontinued due to progression or AEs occurring within the first 4 cycles. Additionally, this study was analyzed with data from the first interim analysis. Since then, additional safety analyses were reported from the final data analysis [15]; however, there were no substantial differences observed in grade ≥3 AEs from each data cutoff (interim analysis: pemetrexed/pembrolizumab/platinum arm, 67.2 %; pemetrexed/placebo/platinum arm, 65.8 % [14] vs final analysis: pemetrexed/pembrolizumab/platinum arm, 72.1 %; pemetrexed/placebo/platinum arm, 66.8 % [15]). We additionally analyzed median time-to-onset of the first grade ≥3 AE, regardless of incidence, in the all-subjects-as-treated population from each data cutoff and found no substantial differences (Supplemental Table 3).

4.1. Conclusions

In KEYNOTE-189, most grade ≥3 AEs first occurred within 3 months from administering the first study treatment and resolved within 2 weeks from onset. In addition, most discontinuations due to AEs occurred during the first 4 cycles. These results suggest toxicity was not accumulated in later treatment cycles, thus discontinuation of pemetrexed should be carefully considered due to the benefit of combination with pembrolizumab. Overall renal AE incidence was low across both treatment arms but slightly higher in the pembrolizumab combination. Importantly, the incidence did not continue to increase across all treatment cycles. In addition to the previous KEYNOTE-189 reports, these results provide useful safety information and details on the timing and management of the most commonly occurring AEs.

Role of the funding source

This study was supported by Eli Lilly and Company and Merck Sharpe & Dohme Corp. Eli Lilly and Company and Merck Sharpe & Dohme Corp. were involved in the study design, data collection, and data analysis.

Data availability statement

Eli Lilly and Company provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the US and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, and blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.

Transparency document

The Transparency document associated with this article can be found in the online version.

CRediT authorship contribution statement

Edward B. Garon: Investigation, Resources, Writing - review & editing. **Joachim Aerts:** Investigation, Resources, Writing - review & editing. **Jong Seok Kim:** Conceptualization, Funding acquisition, Investigation, Project administration, Supervision, Visualization, Writing - original draft, Writing - review & editing. **Catherine E. Muehlenbein:** Conceptualization, Funding acquisition, Investigation, Visualization, Writing - original draft, Writing - review & editing. **Patrick Peterson:** Data curation, Formal analysis, Methodology, Software, Validation, Writing - review & editing. **Maria Teresa Rizzo:** Funding acquisition, Investigation, Project administration, Supervision, Visualization, Writing - original draft, Writing - review & editing. **Shirish M. Gadgeel:** Investigation, Resources, Writing - review & editing.

Declaration of Competing Interest

Edward B. Garon reports grants (clinical trial funding) from Eli Lilly and Company and Merck, as part of this submitted work; grants (clinical trial funding) from AstraZeneca, Bristol Myers Squibb, Eli Lilly and Company, Dynavax, Genentech, Mirati, Iovance, and Neon, outside of this submitted work; grants (clinical trial funding) and serving on an advisory board for EMD Serano, Novartis, and Merck, outside of this submitted work; and serving on an advisory board for GlaxoSmithKline, Dracen, Shiogi, and Boehringer Ingelheim, outside of this submitted work. Joachim Aerts reports personal fees from Bristol Myers Squibb, Eli Lilly and Company, Merck, Sharp & Dohme, BIOCAD, Boehringer Ingelheim, and Roche, outside of this submitted work; and grants and personal fees from Amphera, outside of this submitted work. Joachim Aerts also reports having two licensed patents: one allogenic tumor cell lysate patent, and one biomarker for immunotherapy patent. Jong Seok Kim, Catherine E. Muehlenbein, and Maria Teresa Rizzo are current employees and shareholders of Eli Lilly and Company. Patrick Peterson is a current employee of Eli Lilly and Company. Shirish M. Gadgeel reports personal fees from Merck for presentations and travel; serving on an advisory board for AstraZeneca, Novartis, Bristol Myers Squibb, Xcovery, Boehringer Ingelheim, Takeda, and Daichii-Sankyo; and serving on an advisory board and receiving a travel grant from Genentech/Roche.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2021.02.021.

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