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Gynecologic Oncology

Characterization and Management of Adverse Reactions in Patients with Advanced Endometrial Carcinoma Treated with Lenvatinib Plus Pembrolizumab

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Endometrial carcinoma • Lenvatinib • Pembrolizumab • Adverse reactions • Management

Abstract

Background. The combination of lenvatinib plus pembrolizumab has shown efficacy in treatment of advanced endometrial carcinoma (that is not microsatellite instability–high or mismatch repair deficient) following prior systemic therapy in any setting in the open-label, single-arm, phase Ib/II Study 111/KEYNOTE-146. With the exception of hypothyroidism, the safety profile of the combination was comparable to that of each monotherapy. Given the medical complexity and fragility of patients with endometrial carcinoma, further characterization of adverse reactions (ARs) associated with treatment will help health care professionals to optimize treatment with lenvatinib plus pembrolizumab combination therapy.

Patients and Methods. In Study 111/KEYNOTE-146, patients received lenvatinib at a starting dose of 20 mg orally once daily and pembrolizumab 200 mg intravenously every 3 weeks. Selected ARs (hypertension, fatigue, nausea/vomiting, diarrhea, decreased appetite/weight loss, hypothyroidism, palmar-plantar erythrodysesthesia syndrome, musculoskeletal pain, stomatitis, and proteinuria) were chosen for detailed post hoc analyses.

Results. Median times to first onset of the selected ARs in this analysis all occurred within the first 10 weeks of treatment. Of the selected ARs, grade ≥3 severity of fatigue, hypertension, and nausea occurred in ≥5% of patients. Overall incidence of hypothyroidism was 51%, primarily of grade 2 severity (46%). Most of the ARs assessed were managed with a combination of study drug dose modifications and concomitant medications.

Conclusion. No new safety signals were identified and the toxicity profile in this study was manageable with supportive medications, dose interruptions, and/or lenvatinib dose reductions. This analysis provides AR management guidance for patients with endometrial cancer receiving lenvatinib plus pembrolizumab combination therapy. ***The Oncologist*** 2021;26:e1599–e1608

Implications for Practice: Lenvatinib plus pembrolizumab has shown efficacy in the treatment of patients with advanced endometrial carcinoma (that is, not microsatellite instability–high or mismatch repair deficient) following at least one prior systemic therapy in any setting. Patients may experience toxicity associated with this combination, including adverse reactions of hypertension, fatigue, nausea/vomiting, diarrhea, decreased appetite/weight loss, hypothyroidism, palmar-plantar erythrodysesthesia syndrome, musculoskeletal pain, stomatitis, and proteinuria. These adverse reactions may be managed with a combination of concomitant supportive care medications and judicious lenvatinib dose modifications. This article provides context and guidance for the recognition and management of adverse reactions in patients receiving lenvatinib plus pembrolizumab.

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Introduction

Endometrial cancer is the most common gynecologic cancer [1], with rising incidence and associated disease mortality; it is predicted to account for an estimated 66,570 new cases and 12,940 deaths in the U.S. in 2021 [2]. Recently, pembrolizumab, an immune checkpoint inhibitor, demonstrated efficacy in patients with solid tumors (including endometrial cancer) that are microsatellite instability–high (MSI-H), mismatch repair deficient (dMMR), or have high tumor mutational burden [3, 4]. In preclinical studies, combination of an antiprogrammed cell death 1 (PD-1) antibody with the multikinase inhibitor lenvatinib demonstrated greater antitumor activity than either treatment alone [5]. Study 111/KEYNOTE-146, a phase Ib/II trial, investigated lenvatinib plus pembrolizumab (a PD-1 inhibitor) in selected advanced solid tumors and determined the recommended phase II dose to be lenvatinib 20 mg orally daily with pembrolizumab 200 mg intravenously (IV) every 3 weeks [6].

Results from the endometrial carcinoma (EC) cohort of Study 111/KEYNOTE-146 led to accelerated approval in several countries of lenvatinib plus pembrolizumab for the treatment of advanced EC that is not MSI-H or dMMR, with disease progression following prior systemic therapy, pending results of the confirmatory phase III trial [7, 8]. Specifically, in previously treated EC that was not MSI-H or dMMR ($n = 94$), the objective response rate (ORR) was 38.3% (95% confidence interval [CI], 29–49) by independent radiologic review via RECIST version 1.1 [7–9]. Among responders, 69% of patients experienced a duration of response ≥6 months [7, 8]. Median progression-free survival for this cohort was 5.4 months (95% CI, 4.4–7.6) [10] and median overall survival was 16.4 months (95% CI, 13.5–25.9).

The safety profile of lenvatinib plus pembrolizumab in Study 111/KEYNOTE-146 was consistent with previous monotherapy experience of each drug [7, 8], with the exception of an increased incidence of low-grade hypothyroidism in Study 111/KEYNOTE-146. The most common adverse reactions (ARs) in the EC study cohort among patients who were not MSI-H or dMMR were fatigue, hypertension, musculoskeletal pain, diarrhea, decreased appetite, hypothyroidism, nausea, stomatitis, vomiting, decreased weight, abdominal pain, headache, constipation, urinary tract infection, dysphonia, hemorrhagic events, hypomagnesemia, palmar-plantar erythrodysesthesia syndrome (PPES), dyspnea, cough, and rash [7, 8]. Overall, in the EC cohort, lenvatinib and/or pembrolizumab was interrupted because of a treatment-related adverse event (AE) in 70.2% of patients, and lenvatinib was dose reduced because of a treatment-related AE in 62.9% of patients [9].

This post hoc analysis focuses on the characterization and management of toxicities experienced by patients with EC that was not MSI-H or dMMR from Study 111/KEYNOTE-146.

Materials and Methods

Patients and Study Design

Eligibility criteria for Study 111/KEYNOTE-146 have previously been published [6]. Selected eligibility criteria and a summary of the study endpoints are detailed in the supplemental online Methods. Lenvatinib was administered at a starting dose of 20 mg orally once daily and pembrolizumab was administered at 200 mg IV every 3 weeks.

Post Hoc Subgroup Analyses

This analysis focuses on the characterization and management of ARs in patients with EC that was not MSI-H or dMMR who received prior systemic treatment ($n = 94$), consistent with the U.S. Food and Drug Administration (FDA)-approved indication. The lenvatinib and pembrolizumab FDA prescribing information (PI) pools AE preferred terms into ARs, and therefore these pooled terms will be focused on herein. The most common ARs (≥20%), as pooled in the lenvatinib and pembrolizumab PIs, are shown in Table 1.

Selected ARs were chosen for further analysis based on incidence, association with study treatment, and available interventions, regardless of causality. The PIs of lenvatinib and pembrolizumab should be referred to for monitoring and management details on other important, if less common, ARs that may occur during treatment with lenvatinib plus pembrolizumab. AR criteria are discussed further in the supplemental online Methods.

Results

Results herein focus on selected ARs relevant to the lenvatinib plus pembrolizumab combination, from the start

Table 1. Adverse reactions that occurred in ≥20% of patients

Most common adverse reactions (≥ 20%)	Incidence ($n = 94$), %
Fatigue	65
Hypertension	65
Musculoskeletal pain	65
Diarrhea	64
Decreased appetite	52
Hypothyroidism	51
Nausea	48
Stomatitis	43
Vomiting	39
Weight loss	36
Abdominal pain	33
Headache	33
Constipation	32
Urinary tract infection	31
Dysphonia	29
Hemorrhagic events	28
Hypomagnesemia	27
PPES	26
Dyspnea	24
Cough	21
Rash	21

Abbreviations: PPES, palmar-plantar erythrodysesthesia syndrome.

of enrollment on September 10, 2015, until the data cutoff date of January 10, 2019. General management recommendations and guidance for addressing ARs associated with the lenvatinib plus pembrolizumab combination, plus detailed advice specific to management of hypertension, hypothyroidism, and proteinuria, are reported in the supplemental online Results. Additional data, including dose modifications, exposure, median tumor shrinkage, last dose of lenvatinib prior to response, and tumor responses are also included in the supplemental online Results.

Selected Adverse Reactions

Selected ARs analyzed include hypertension, fatigue, nausea/vomiting, diarrhea, decreased appetite/weight loss, hypothyroidism, PPES, musculoskeletal pain, stomatitis, and proteinuria. These ARs include preferred terms that were pooled in accordance with the PIs for lenvatinib and pembrolizumab, as shown in Table 2.

Median times to first onset of the selected ARs in this analysis all occurred within the first 10 weeks of treatment (Fig. 1). AR episodes experienced per patient varied across the selected ARs, although most patients who experienced a particular AR experienced one or two episodes (Table 3). Importantly, most patients who experienced hypertension had only a single episode. Of the selected ARs, incidence of grade ≥3 fatigue, hypertension, and nausea occurred at rates ≥5%, and among each of these ARs, the duration of episodes was variable (range, 1–273 days).

Table 2. Adverse events included in each adverse reaction by preferred term

Adverse reaction	Preferred terms included
Hypertension	Essential hypertension, hypertension, and hypertensive encephalopathy
Fatigue	Asthenia, fatigue, and malaise
Nausea	Nausea
Vomiting	Vomiting
Diarrhea	Diarrhea, gastroenteritis, gastrointestinal viral infection, and viral diarrhea
Decreased appetite	Decreased appetite and early satiety
Weight loss	Weight decreased
Hypothyroidism	Increased blood thyroid stimulating hormone and hypothyroidism
PPES	Palmar-plantar erythrodysesthesia syndrome
Musculoskeletal pain	Arthralgia, arthritis, back pain, breast pain, musculoskeletal chest pain, musculoskeletal pain, musculoskeletal stiffness, myalgia, neck pain, noncardiac chest pain, and pain in extremity
Stomatitis	Glossitis, mouth ulceration, oral discomfort, oral mucosal blistering, oropharyngeal pain, and stomatitis
Proteinuria	Proteinuria

Abbreviations: PPES, palmar-plantar erythrodysesthesia syndrome.

Hypertension

Hypertension is commonly graded according to criteria outlined in supplemental online Table 1 [11]. In Study 111/KEYNOTE-146, hypertension was graded strictly on blood pressure (BP) without reference to the number of antihypertensive therapies. In this analysis of patients with EC that was not MSI-H or dMMR, the median time to first onset of hypertension was 2.1 weeks (Fig. 1), and the incidence of hypertension (highest grade per patient) was as follows: overall, 65%; grade 1, 4%; grade 2, 22%; grade 3, 36%; grade 4, 2%). There were 43 episodes of grade ≥3 hypertension, with an average episode duration of 21.5 days.

Management strategies for hypertension included concomitant administration of antihypertensives and lenvatinib dose modifications; notably, the protocol for Study 111/KEYNOTE-146 recommended medical management of hypertension (where appropriate and there was no imminent risk) before dose reduction. As such, 53.2% of patients were administered at least one medication to treat hypertension while receiving study drugs (Table 4). Among patients in this analysis who experienced at least one AR leading to a study drug dose modification, 15% received a lenvatinib dose interruption and 1% received a pembrolizumab dose interruption because of hypertension; 12% of patients received a lenvatinib dose reduction because of hypertension. Although two patients experienced grade 4 hypertension, no patients discontinued lenvatinib or pembrolizumab because of hypertension (Fig. 1).

Fatigue

Fatigue is graded according to criteria outlined in supplemental online Table 1 [11]. In this analysis, the median time to first onset of fatigue was 3.3 weeks (Fig. 1). Incidence of the highest grade of fatigue per patient was the following: overall, 65%; grade 1, 20%; grade 2, 28%; grade 3, 17%. Of the 18 episodes of grade 3 fatigue, the average duration was 32.9 days.

Overall, 5.3% of patients received at least one medication to treat fatigue while receiving study drug (Table 4). Among patients who experienced at least one AR leading to a study drug dose modification, 16% experienced a lenvatinib dose interruption, 14% experienced a pembrolizumab dose interruption, and 24% experienced a lenvatinib dose reduction because of fatigue. No patients required pembrolizumab discontinuation, and 1% of patients required lenvatinib discontinuation because of fatigue (Fig. 1).

Nausea and Vomiting

Nausea is graded according to criteria outlined in supplemental online Table 1 [11]. The median time to first onset among patients with EC that was not MSI-H or dMMR was 4.7 weeks for patients with nausea and 5.9 weeks for patients with vomiting (Fig. 1). Most incidences of the highest grade of nausea/vomiting per patient were grade 1 or 2 (overall, 48%/39%; grade 1, 26%/28%; grade 2, 17%/12%; grade 3, 5%/0%, respectively). Of the five episodes of grade 3 nausea, the average duration was 12.0 days.

In addition to the general toxicity management strategies from the PIs and study protocol included in the supplemental

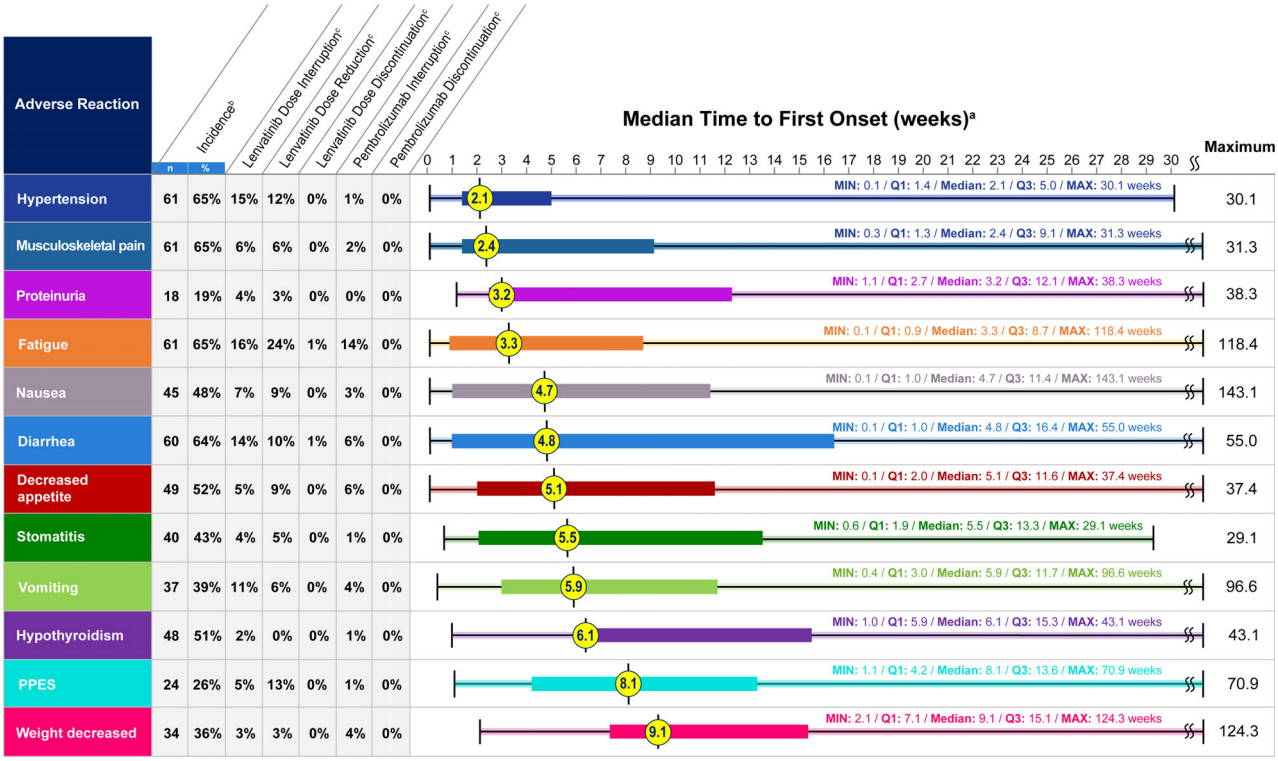

Figure 1. Post hoc analysis of time to first onset of selected adverse reactions.
[a]Median time to first onset in patients who experienced the adverse reaction.
[b]All grades.
[c]Percentages are based on the number of patients with an adverse reaction leading to a dose modification.
Abbreviations: PPES, palmar-plantar erythrodysesthesia syndrome; Q1, first quartile; Q3, third quartile.

online Results (management of selected adverse reactions) for lenvatinib and pembrolizumab, nausea and vomiting were also managed with concomitant medications; the study protocol required medical management of nausea and vomiting before lenvatinib dose reduction. As a result, 29.8% of patients in the study were administered at least one medication for nausea while receiving study drugs, and 13.8% of patients were given at least one medication for vomiting while receiving study drugs (Table 4).

Given these recommendations, among patients in this analysis who experienced at least one AR that led to a study drug dose modification, 7%/11% (nausea/vomiting) required a lenvatinib dose interruption, and 3%/4% required a pembrolizumab dose interruption; 9%/6% required a lenvatinib dose reduction because of nausea or vomiting. No patients required discontinuation of either lenvatinib or pembrolizumab because of nausea or vomiting (Fig. 1).

Diarrhea

Diarrhea is graded according to criteria outlined in supplemental online Table 1 [11]. Among patients who experienced diarrhea, the median time to first onset of diarrhea was 4.8 weeks (Fig. 1), and the majority of patients who experienced diarrhea had low-grade events (overall, 64%; grade 1, 36%; grade 2, 23%; grade 3, 4%).

Management strategies to treat diarrhea used in this analysis included treatment with concomitant antidiarrheals in addition to the general management strategies described in the supplemental online Results (management of selected adverse reactions). In general, the lenvatinib PI suggests promptly initiating management for severe diarrhea and withholding or discontinuing of lenvatinib based on severity; the study protocol recommended optimal medical management before any study drug interruption or reduction. Within this analysis, 28.7% of patients were administered at least one medication for diarrhea while receiving study drugs (Table 4). Moreover, among patients in this analysis who experienced an AR leading to a study drug dose modification, 14% of patients required a lenvatinib dose interruption, and 6% required a pembrolizumab dose interruption; 10% of patients required a lenvatinib dose reduction because of diarrhea. No patients discontinued pembrolizumab because of diarrhea; and 1% of patients discontinued lenvatinib because of diarrhea (Fig. 1).

Decreased Appetite and Weight Loss

Weight loss is characterized by a decrease in overall body weight in adults and is graded according to criteria outlined in supplemental online Table 1 [11]. The median times to first onset of decreased appetite and weight loss were 5.1 weeks and 9.1 weeks, respectively (Fig. 1). Incidences (decreased appetite/weight loss) according to the highest grade per patient were the following: overall, 52%/36%; grade 1, 26%/9%; grade 2, 27%/24%; grade 3, 0%/3%, respectively.

In addition to dose modifications described in the supplemental online Results (management of selected adverse reactions), decreased appetite/weight loss was managed

Table 3. Number of episodes per patient of selected adverse reactions of any grade

Number of episodes	Patients ($n = 94$), n (%)
Hypertension	
1	42 (44.68)
2	11 (11.70)
≥3	8 (8.51)
Fatigue	
1	39 (41.49)
2	18 (19.15)
≥3	4 (4.26)
Nausea	
1	29 (30.85)
2	10 (10.64)
≥3	6 (6.38)
Vomiting	
1	20 (21.28)
2	5 (5.32)
≥3	12 (12.77)
Diarrhea	
1	36 (38.30)
2	12 (12.77)
≥3	12 (12.77)
Decreased appetite	
1	39 (41.49)
2	8 (8.51)
3	2 (2.13)
Weight loss	
1	31 (32.98)
2	3 (3.19)
Hypothyroidism	
1	45 (47.87)
2	3 (3.19)
PPES	
1	17 (18.09)
2	7 (7.45)
Musculoskeletal pain	
1	31 (32.98)
2	9 (9.57)
≥3	21 (22.34)
Stomatitis	
1	27 (28.72)
2	9 (9.57)
≥3	4 (4.26)
Proteinuria	
1	10 (10.64)
2	5 (5.32)
≥3	3 (3.19)

Abbreviation: PPES, palmar-plantar erythrodysesthesia syndrome.

with concomitant appetite stimulants and other treatments. Among patients in this analysis, 4.3% were given at least one medication reported to treat decreased appetite and 3.2% were given medications reported to treat weight loss while receiving study drugs (Table 4). Furthermore, among patients who experienced an AR leading to study drug dose modification, 5%/3% (decreased appetite/weight loss) of patients experienced a lenvatinib dose interruption, 6%/4% of patients experienced a pembrolizumab dose interruption, and 9%/3% of patients experienced a lenvatinib dose reduction because of decreased appetite/weight loss; no patients required dose discontinuation for lenvatinib or pembrolizumab because of either AR.

Hypothyroidism

Hypothyroidism is graded according to criteria outlined in supplemental online Table 1 [11]. The median time to first onset of hypothyroidism was 6.1 weeks (Fig. 1). Among patients in this analysis, most incidences of hypothyroidism were grade 2 (overall, 51%; grade 1, 4%; grade 2, 46%; grade 3, 1%). Of note, no grade 4 events of hypothyroidism were reported in this study.

Management strategies for hypothyroidism mostly included concomitant thyroid hormone replacement therapy, but some dose modifications were used when necessary. Specifically, for grade 3–4 events, thyroid hormone replacement therapy with levothyroxine or liothyronine was indicated per standard of care, and therapy with pembrolizumab was allowed to continue while thyroid replacement therapy was instituted. In this analysis, 47.9% of patients received the thyroid preparation levothyroxine during treatment (Table 4). Dose modifications for patients with hypothyroidism were minimal; 2% of patients within this analysis who experienced at least one AR that led to study drug dose modification required a lenvatinib dose interruption and 1% of patients required a pembrolizumab dose interruption because of hypothyroidism. No patients required a lenvatinib dose reduction or dose discontinuation for either study drug because of hypothyroidism (Fig. 1).

Palmar-Plantar Erythrodysesthesia Syndrome

PPES is also known as hand-foot syndrome and is graded according to criteria outlined in supplemental online Table 1 [11]. The median time to first onset of PPES was 8.1 weeks (Fig. 1). Incidence in this study was recorded by highest grade per patient: overall, 26%; grade 1, 12%; grade 2, 11%; grade 3, 3%.

Management of PPES was done through dose modifications, as described in the supplemental online Results (Management of selected adverse reactions), and administration of concomitant medication. Overall, 11.7% of patients were administered at least one medication for PPES while receiving study drugs (Table 4). Among patients who experienced an AR that led to a study drug dose modification, 5% of patients had a lenvatinib interruption, 1% had a pembrolizumab interruption, and 13% of patients had a lenvatinib dose reduction. No patients required dose discontinuation for either study drug because of PPES (Fig. 1).

Table 4. Concomitant medications received to treat adverse reactions of interest

Adverse reaction, medications received[a] (class)	Patients ($n = 94$), n^b (%)
Hypertension	50 (53.2)
Losartan (angiotensin II antagonist)	25 (26.6)
Amlodipine (calcium channel blocker)	23 (24.5)
Lisinopril (ACE inhibitor)	8 (8.5)
Metoprolol (beta blocker)	8 (8.5)
Hydralazine (active on arteriolar smooth muscle)	6 (6.4)
Labetalol (beta blocker)	5 (5.3)
Clonidine (antiadrenergic)	5 (5.3)
Hydrochlorothiazide (diuretic/thiazide)	4 (4.3)
Irbesartan (angiotensin II antagonist)	3 (3.2)
Enalapril (ACE inhibitor)	3 (3.2)
Fatigue	5 (5.3)
Sodium chloride (IV solution)	3 (3.2)
Nausea	28 (29.8)
Ondansetron (antiemetic/antinauseant)	16 (17.0)
Prochlorperazine (antiemetic/antinauseant)	8 (8.5)
Lorazepam (anxiolytic)	8 (8.5)
Olanzapine (antipsychotic)	6 (6.4)
Promethazine (antiemetic/antinauseant)	3 (3.2)
Sodium chloride (IV solution)	3 (3.2)
Vomiting	13 (13.8)
Ondansetron (antiemetic/antinauseant)	6 (6.4)
Prochlorperazine (antiemetic/antinauseant)	4 (4.3)
Olanzapine (antipsychotic)	4 (4.3)
Lorazepam (anxiolytic)	3 (3.2)
Sodium chloride (IV solution)	3 (3.2)
Diarrhea	27 (28.7)
Loperamide (antipropulsive)	23 (24.5)
Diphenoxylate and atropine (antipropulsive)	4 (4.3)
Metronidazole (antibacterial)	3 (3.2)
Sodium chloride (IV solution)	3 (3.2)
Decreased appetite	4 (4.3)
Weight loss	3 (3.2)
Hypothyroidism	45 (47.9)
Levothyroxine (thyroid preparation)	45 (47.9)
Palmar-plantar erythrodysesthesia syndrome	11 (11.7)
Paraffin (emollient/protective)	3 (3.2)
Urea (emollient/protective)	3 (3.2)
Hydroxyquinoline (antiseptic/disinfectant)	3 (3.2)
Musculoskeletal pain	27 (28.7)
Paracetamol (acetaminophen) (analgesic/antipyretic)	10 (10.6)
Oxycodone (opioid)	9 (9.6)
Fentanyl (opioid)	5 (5.3)
Morphine (opioid)	4 (4.3)
Ibuprofen (nonsteroidal anti-inflammatory)	4 (4.3)
Diclofenac (topical product for joint and muscle pain)	3 (3.2)
Stomatitis	24 (25.5)
Dexamethasone (stomatological preparation)	14 (14.9)
Lidocaine (stomatological preparation)	7 (7.4)
Triamcinolone (stomatological preparation)	4 (4.3)
Nystatin (stomatological preparation)	3 (3.2)
Mouth preparations (stomatological preparation)	3 (3.2)
Proteinuria	0

[a]Medications listed are those received by more than two patients.
[b]Patients may have received more than one medication to treat a specific adverse reaction.
Abbreviations: ACE, angiotensin-converting enzyme; IV, intravenous.

Musculoskeletal Pain

Musculoskeletal pain is graded according to criteria outlined in supplemental online Table 1 [11]. The median time to first onset of musculoskeletal pain was 2.4 weeks (Fig. 1), and the overall incidence in this analysis was 65%. The majority of patients had events that were a highest grade of grade 1 or 2 (grade 1, 31%; grade 2, 31%; grade 3, 3%).

Management strategies for musculoskeletal pain included concomitant medications and the general dose modification strategy described in the supplemental online Results (management of selected adverse reactions). Within this analysis, 28.7% of patients were given at least one medication for musculoskeletal pain while receiving study drugs (Table 4). Among patients who experienced an AR leading to a study drug dose modification, 6% of patients experienced a lenvatinib dose interruption, and 6% received a dose reduction because of musculoskeletal pain. No patients discontinued lenvatinib as a result of musculoskeletal pain. No patients discontinued pembrolizumab, and 2% of patients received a pembrolizumab interruption, because of musculoskeletal pain (Fig. 1).

Stomatitis

Stomatitis is graded according to criteria outlined in supplemental online Table 1 [11]. In this assessment of patients with EC that was not MSI-H or dMMR, the median time to first onset of stomatitis was 5.5 weeks (Fig. 1). The overall incidence in this analysis was 43% (grade 1, 31%; grade 2, 12%).

Management strategies for stomatitis included concomitant medications and dose modifications, as outlined in the supplemental online Results (management of selected adverse reactions). Among patients in this analysis, 25.5% were given at least one medication for stomatitis while receiving study drugs (Table 4). Overall, among patients in this analysis who had an AR that led to study drug dose modification, 4% of patients experienced a lenvatinib dose interruption and 5% received a dose reduction

because of stomatitis. No patients required lenvatinib or pembrolizumab discontinuation as a result of stomatitis, and 1% of patients required a pembrolizumab interruption because of stomatitis (Fig. 1).

Proteinuria

Proteinuria is graded according to criteria outlined in supplemental online Table 1 [11]. The median time to first onset of proteinuria in this analysis was 3.2 weeks (Fig. 1), and the overall incidence in this analysis was 19%. Most patients had events that were a highest grade of grade 1 or 2 (grade 1, 9%; grade 2, 10%; grade 3, 1%).

Management strategies for proteinuria included regular monitoring and dose modifications. Further details on proteinuria management can be found in the supplemental online Results (management of selected adverse reactions). Within this analysis, no patients were given medication reported to treat proteinuria (Table 4). Among patients in this analysis who had an AR leading to a study drug dose modification, 4% of patients experienced a lenvatinib dose interruption, and 3% received a dose reduction because of proteinuria. No patients discontinued lenvatinib as a result of proteinuria. No patients required a pembrolizumab interruption or discontinuation because of proteinuria (Fig. 1).

Discussion

The safety profile of lenvatinib plus pembrolizumab in EC that was not MSI-H or dMMR in Study 111/KEYNOTE-146 is generally consistent with the established profiles of each agent as monotherapy [8, 12, 13].

In this analysis of ARs, one important difference noted with the lenvatinib plus pembrolizumab combination therapy was that hypothyroidism occurred at a higher frequency (51%) than with either monotherapy (8% with pembrolizumab monotherapy across multiple indications; 21% of grade ≤2 in patients with unresectable hepatocellular carcinoma who received lenvatinib monotherapy [Keytruda PI, Lenvima PI]). However, the severity of hypothyroidism remained low (1% incidence of grade 3, no grade 4 or 5) and no dose reductions (lenvatinib) or discontinuations (either study drug) were needed because of hypothyroidism.

Hypertension is one of the most frequently occurring ARs with lenvatinib plus pembrolizumab treatment (Table 1). Cardiovascular events, including hypertension, are widely associated with the use of tyrosine kinase inhibitors (TKIs), likely as a result of vascular endothelial growth factor (VEGF) signaling inhibition [14–16]. Although guidance from Study 111/KEYNOTE-146 and the lenvatinib PI is informative, clinicians should ideally ensure that optimal BP control has been achieved before initiating lenvatinib therapy, as is the case for any anti-VEGF targeting therapy. A panel composed of members of the Angiogenesis Task Force of the National Cancer Institute and experts in management of hypertension and cardiovascular toxicities in patients with cancer provided five specific recommendations for the recognition and management of hypertension associated with VEGF-targeted therapies: (a) a risk assessment of patients to determine those potentially likely to develop hypertension, (b) addressing potential hypertension before onset of VEGF-targeted therapy, (c) active monitoring throughout treatment but particularly within the first cycle, (d) setting goals for hypertension control, and (e) aggressive management through carefully chosen antihypertensive therapies [17]. It has also been suggested that patients with a high risk for hypertension, such as those on lenvatinib treatment, perform at-home BP monitoring [17, 18] with clear education regarding BP levels that warrant clinician notification. Such active BP home-monitoring is encouraged for patients on lenvatinib therapy. Regarding the initial antihypertensive choice, prior studies have reported that VEGF inhibitor-induced hypertension can be effectively managed with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers and/or calcium channel blockers [17, 18].

Immune-related AEs that were observed in this study including colitis, rash, hepatitis, and pneumonitis are known to occur with anti-PD-1 therapy, likely as a result of general immunologic enhancement [15, 19].

Overall, no new safety signals were identified, and the toxicity profile in this study was manageable with supportive medications, dose interruptions, and/or lenvatinib dose reductions. Among assessed patients, 16.0% experienced an AR leading to discontinuation of both study drugs, 22.3% experienced an AR leading to lenvatinib discontinuation, and 20.2% experienced an AR leading to pembrolizumab discontinuation. Of note, the onset of most of the selected ARs occurred within the first 2 months. Therefore, proactive management and close monitoring early after treatment onset may be critical to help maintain patients on the combination therapy and maximize outcomes. General management strategies for AEs associated with TKIs include concomitant supportive medications for symptom management, patient education, and dose modifications [14, 20] and are similar to those used in Study 111/KEYNOTE-146.

A prompt and proactive approach in contending with emergent ARs is crucial, and several steps can be taken to optimize AR management in patients treated with lenvatinib plus pembrolizumab. Clinicians should thoroughly self-educate regarding the common ARs of lenvatinib and pembrolizumab. Additionally, as physician assistants, nurse practitioners, and registered nurses are often the first and most frequent points of contact with patients, training the entire clinical team in recognition and management of selected ARs is important so ARs can be addressed preemptively or immediately after onset. When appropriate, teams should consider early consultant/subspecialist involvement in cases that are recalcitrant to appropriate supportive care measures and in instances of high-grade toxicities, because a multidisciplinary management approach to optimize patient care is often necessary. ARs such as hypertension, nausea, and weight loss should be controlled before initiating therapy and preemptively addressed to the maximal extent.

Certain ARs, including diarrhea and liver enzyme elevation, may be initially considered attributable to either study drug. As management strategies differ, it is important to determine the causative agent, versus an alternative etiology, that is most likely inciting the toxicity. Timing of AR onset and AR resolution with treatment interruption can be

evaluated in the context of the shorter half-life of lenvatinib. In instances in which both agents could incite an AR, if dose interruption of lenvatinib does not lead to clinical improvement, an immune-mediated AR should be considered. In the case of diarrhea, patients should be monitored for signs and symptoms of enterocolitis (i.e., diarrhea, abdominal pain, and blood or mucus in stool with or without fever). Patients with grade ≥2 diarrhea who are suspected of colitis should undergo further evaluation and consider consultation with a gastrointestinal specialist. In the case of liver enzyme elevation, patients should be monitored for signs and symptoms of hepatitis (i.e., jaundice and malaise with or without fever), and elevated liver enzymes should be monitored frequently.

Patients should be educated before treatment onset regarding the common ARs and should be well versed in the management plan of these reactions. Prophylactic prescriptions for supportive care therapies (e.g., antihypertensives, antiemetics) with clear instructions regarding initiation parameters could be considered. Teams should monitor potential ARs closely and consider weekly visits for the first two to three cycles of treatment; however, continued vigilance is important. Attention to emergent ARs should not wane over time, as late-onset ARs (particularly immune-mediated events) can arise.

This exploratory post hoc analysis of ARs in the EC cohort of Study 111/KEYNOTE-146 had several limitations. The study population was small. Moreover, as very few analyses were prespecified, results were descriptive in nature. Despite these limitations, this study indicated that ARs in patients treated with lenvatinib and pembrolizumab combination therapy are consistent with the known profiles of each monotherapy.

Importantly, continued reductions in tumor size over time were observed among patients, despite lenvatinib dose reductions in 69.1% of patients (supplemental online Table 2). It is notable that most of the responses (23/36; 64%) were seen at the 20-mg dose. This suggests that clinicians should start treatment at the recommend dose of lenvatinib 20 mg orally once daily plus pembrolizumab 200 mg IV every 3 weeks and reduce lenvatinib dosage as necessary and per label to prioritize safety and tolerability along with maximization of supportive care efforts. The data suggest that antitumor activity can continue to occur with reduced dosages of lenvatinib; however, lower starting doses could lead to inferior efficacy and not necessarily less toxicity [21]. This is supported by a recent study of lenvatinib in patients with differentiated thyroid cancer, which found that ORR was not noninferior in patients who started treatment at a lower starting dose compared with a higher dose [22]. Similar outcomes were also seen in a recent prospective study of lenvatinib plus everolimus in patients with renal cell carcinoma, in which a reduced starting dose of lenvatinib (14 mg/day) was not found to be noninferior to the approved lenvatinib starting dose of 18 mg/day [23], suggesting that optimal lenvatinib therapy may be achieved by starting at a higher dose and reducing as medically necessary following maximization of supportive care.

A small-scale, single-institution, retrospective study of patients who had recurrent endometrial cancer and who were treated with lenvatinib plus pembrolizumab showed a shorter median time to treatment toxicity (defined as the time from the start of treatment until lenvatinib dose reduction or discontinuation related to toxicity, whichever occurred sooner) in patients who received the recommended 20 mg lenvatinib starting dose ($n = 16$) versus those who received reduced starting doses ($n = 54$), with no significant differences in efficacy [24]. Although the results of How et al. are hypothesis-generating as to whether a lower starting dose of lenvatinib could be considered in some patients, the retrospective nature of the analysis, which included 16 patients who received lenvatinib 20 mg/day as the starting dose, should be considered. Results from prospective cohort studies published to date (across various indications) do not support alternative lenvatinib starting doses [22, 23]. Additionally, patient-reported health-related quality-of-life data among patients with endometrial cancer from Study 309/KEYNOTE-775 were recently presented [25] and showed that, over 12 weeks of follow-up, similar changes in Global Health Score/quality-of-life outcomes were observed for patients receiving lenvatinib and pembrolizumab and those receiving treatment of physician's choice (doxorubicin or paclitaxel; −5.97; 95% CI, −8.36 to −3.58 vs. −6.98; 95% CI, −9.63 to −4.33). Therefore, despite dose holds, interruptions, and/or dose reductions that occurred in the lenvatinib and pembrolizumab arm, patient quality of life did not differ significantly from treatment of physician's choice based on the lenvatinib dose. These results further support the overall favorable benefit/risk profile of lenvatinib and pembrolizumab.

Several studies in different indications have also highlighted the importance of optimally managing patient toxicities rather than discontinuing treatment. A pooled analysis of AEs in patients with radioiodine-refractory thyroid cancer treated with lenvatinib or sorafenib concluded that early intervention and management of AEs could minimize unnecessary treatment discontinuations and improve patients' quality of life [26]. These results are consistent with an assessment of AEs in patients with hepatocellular carcinoma treated with lenvatinib that found prolonged median overall survival in patients who did not discontinue lenvatinib because of severe AEs [27].

Conclusion

Because patients may receive clinical benefit even after pembrolizumab treatment interruptions and lenvatinib dose interruptions and/or reductions, thorough clinical team and patient education, comprehensive patient assessments, maximization of supportive care measures, and subspecialist involvement can significantly improve patient tolerance and quality of life. Lenvatinib plus pembrolizumab combination therapy has robust, durable, and clinically meaningful activity in advanced EC that is not MSI-H or dMMR, and as clinicians gain more experience, it is our hope that this work will provide context and guidance regarding AR management for patients receiving lenvatinib plus pembrolizumab combination therapy.

Acknowledgments

Medical writing support was provided by Heather A. Mitchell, Ph.D., of Oxford PharmaGenesis Inc., Newtown, PA, and was funded by Eisai Inc., Woodcliff Lake, NJ, and also by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ. This study was funded by Eisai Inc., Woodcliff Lake, NJ, and also by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ. Dr. Makker is supported in part by the National Institutes of Health/National Cancer Institute Cancer Center Support Grant P30 CA008748.

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Disclosures

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(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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