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Adverse Reaction Profiles and Management Strategies for Lenvatinib plus Pembrolizumab in Advanced Endometrial Cancer

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ABSTRACT

The pairing of lenvatinib and pembrolizumab showed substantially superior effectiveness relative to chemotherapy in subjects with late-stage endometrial carcinoma (aEC), independent of MSI status or histological type, in cases where progression occurred post prior platinum-containing regimens, according to findings from Study-309/KEYNOTE-775. The tolerability profile for this dual therapy largely matched established patterns for the individual agents and for their use together in endometrial carcinoma plus various other malignancies. Given the frequent clinical challenges in aEC cases, the present work aims to profile major adverse events (ARs) linked to this regimen and summarize handling tactics, thereby delivering actionable advice on AR control to enhance oncologic gains and lower risks of therapy cessation. Within Study-309/KEYNOTE-775, subjects received lenvatinib (20 mg by mouth daily) combined with pembrolizumab (200 mg IV every 3 weeks) or chemotherapy (doxorubicin or paclitaxel). Rates of occurrence, average time to initial AR appearance, dosage changes, and supportive drugs are reported. Major ARs assessed comprise hypothyroidism, hypertension, fatigue, diarrhea, musculoskeletal disorders, nausea, decreased appetite, vomiting, stomatitis, weight decreased, proteinuria, and palmar-plantar erythrodysesthesia syndrome. Predictably, prevalent all-grade major ARs encompassed hypothyroidism, hypertension, fatigue, diarrhea, and musculoskeletal disorders. Severe (grade 3-4) major ARs affecting ≥10% of cases involved hypertension, fatigue, and weight decreased. Major ARs generally emerged in the initial approximate 3 months of therapy. Handling tactics for ARs aligned with product labeling and trial protocol are outlined. Optimal control of ARs during lenvatinib plus pembrolizumab therapy entails informing patients and the full care team, applying prophylactic steps alongside rigorous surveillance, and prudent employment of dosage changes plus supportive agents.

Keywords: Endometrial cancer, Lenvatinib, Pembrolizumab, Chemotherapy

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Introduction

Uterine cancer occurrence and associated death rates continue to climb. Forecasts suggest uterine cancer will overtake colorectal cancer as the 3rd leading cancer by occurrence (per average annual percent change) and the 4th primary cancer mortality cause in U.S. women [1, 2]. On a global scale, uterine corpus malignancy is the 6th leading diagnosed cancer among women, recording over 417 000 novel diagnoses and 97 000 fatalities in 2020 [3]. Within the U.S., for the 69% presenting with localized stage, 5-year overall survival (OS) stood at 95%, dropping to 18% in distant-stage cases [4]. Most major cancers have seen survival gains since the mid-1970s, yet endometrial cancer (EC) stands out as an exception owing to scarce therapeutic advancements [4]. Carboplatin-paclitaxel remains the frontline standard, validated via the GOG0209 study [5, 6]. Follow-up chemotherapy yields modest gains, featuring median progression-free survival (PFS) near 4 months [6], underscoring predominant chemotherapy resistance in pretreated advanced EC (aEC). Thus, a major therapeutic gap endures for aEC subjects needing superior options.

Lenvatinib (a tyrosine kinase inhibitor) paired with pembrolizumab (an immune checkpoint inhibitor) produced notably superior results versus chemotherapy in aEC subjects enrolled in Study-309/KEYNOTE-775 (Clinicaltrials.gov identifier: NCT03517449) [7]. Meaningful statistical and clinical gains in PFS, OS, and objective response rate (ORR) emerged for the pairing over chemotherapy across the full cohort and mismatch-repair proficient (pMMR) group—the primary analysis sets. The mismatch-repair deficient (dMMR) cohort likewise displayed extended PFS/OS and elevated ORR favoring the pairing [7]. While post hoc findings require careful reading, PFS/OS advantages for the pairing versus chemotherapy appeared consistent over all histological categories (even hard-to-treat ones) and irrespective of earlier (neo)adjuvant exposure or interval without platinum since the last such regimen [8]. Subjects with solely 1 prior platinum line displayed better hazard ratios on OS/PFS versus those exceeding 1 line, favoring prompt pairing deployment [8]. Among those on lenvatinib plus pembrolizumab, chemotherapy ranked as the top follow-on anticancer option; such subjects retained notable PFS gains in later lines relative to controls [9].

Following data from Study-309/KEYNOTE-775, regulatory authorities in the United States authorized the use of lenvatinib combined with pembrolizumab for managing cases of late-stage endometrial carcinoma classified as mismatch repair proficient (pMMR) (verified using an FDA-endorsed assay) or lacking high microsatellite instability, where progression has occurred after any prior systemic regimen, in individuals ineligible for surgical cure or radiotherapy [10]. Within Europe, this dual therapy has been sanctioned for cases of late-stage or relapsed endometrial carcinoma showing advancement during or after platinum-inclusive treatment across any context, among those unsuitable for surgical cure or radiotherapy [11].

During Study-309/KEYNOTE-775, the tolerability of lenvatinib together with pembrolizumab proved controllable and largely mirrored recognized patterns for the separate agents, along with their joint application in endometrial carcinoma and diverse other solid malignancies [7, 10, 12-14]. Treatment responses and endurance in individuals with advanced endometrial carcinoma can furthermore be shaped by aspects like physical vulnerability, accompanying illnesses, and chronological age [15]. This evaluation seeks to examine prominent unwanted events in individuals with advanced endometrial carcinoma administered lenvatinib combined with pembrolizumab within Study-309/KEYNOTE-775, thus furnishing healthcare groups with an extensive resource for forward-planning event oversight, appropriate for practitioners at diverse expertise stages. We further delineate oversight tactics for such events aligned with product labeling and trial guidelines, intended to bolster individual well-being, promote therapy persistence, and enhance prospects for deriving advantage from the anti-malignancy potential of this key regimen. In conclusion, a stepwise illustration of deploying these tactics appears via an illustrative patient scenario.

Materials and Methods

Patients and study design

Prior publications have outlined the trial framework and inclusion requirements [7]. Cases involving advanced endometrial carcinoma with advancement post a single earlier platinum-based chemotherapeutic course underwent randomization (1:1) to obtain lenvatinib (commencing at 20 mg by mouth daily) alongside pembrolizumab (200 mg by vein every 3 weeks) or physician-selected chemotherapy.

Adverse reactions

Employing records through the cutoff of October 26, 2020, this review emphasized delineating and overseeing unwanted events, matching product labeling [10, 12], in pretreated advanced endometrial carcinoma cases from Study-309/KEYNOTE-775 who underwent randomization and took a minimum of 1 dose of lenvatinib together with pembrolizumab. The designated descriptors clustered for every prominent unwanted event appear in **Figure 1**. Such events might have arisen amid dosing of lenvatinib and/or pembrolizumab, or inside the guideline-stipulated surveillance interval of roughly 30 days post ultimate study dosing or ahead of commencing fresh anti-malignancy intervention, depending on which preceded. Event intensity underwent evaluation per Common Terminology Criteria for Adverse Events v4.03.

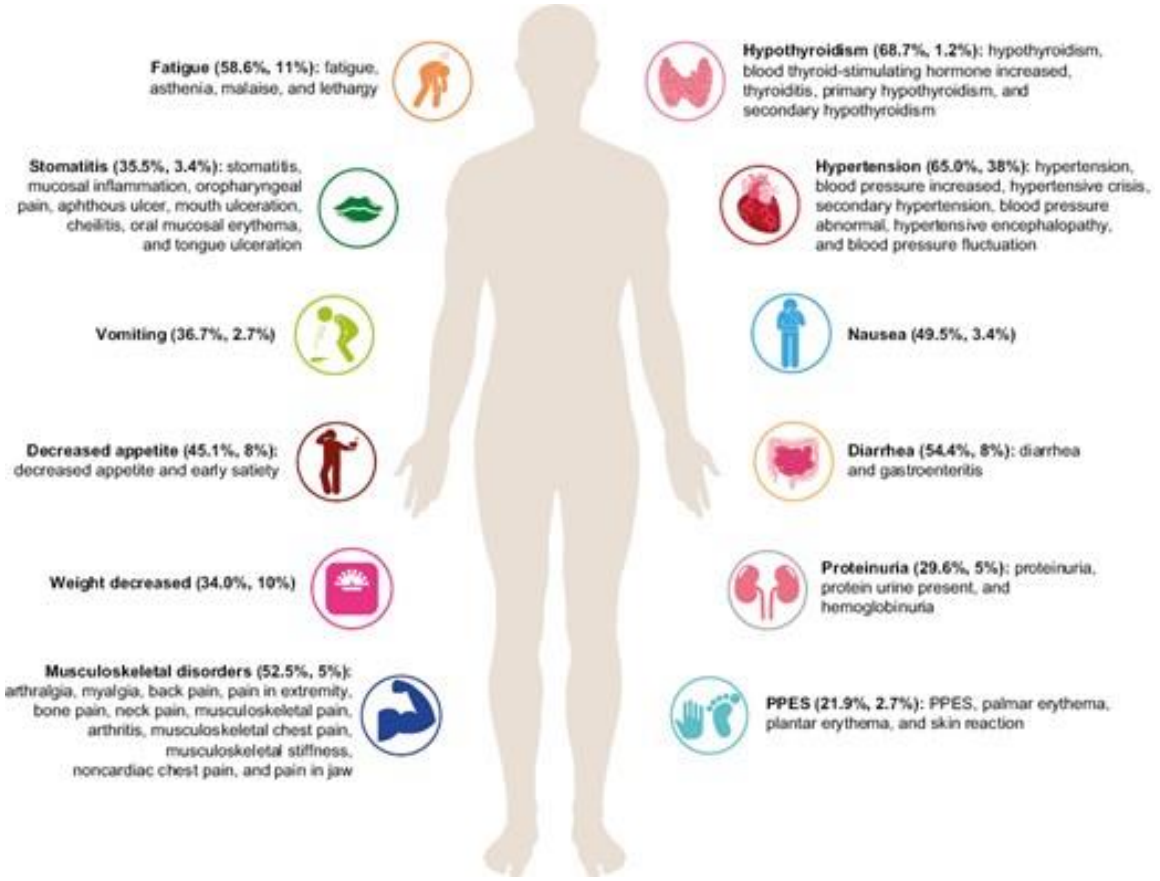

Figure 1. Designated descriptorsa clustered by prominent unwanted event in Study-309/KEYNOTE-775 (safety cohort). aDesignated descriptors (% any grade, % grades 3-4) derived from National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0. PPES, palmar-plantar erythrodysesthesia syndrome. Template adapted from Powered Template https://poweredtemplate.com/

Results and Discussion

Patients

From the total enrollment, 411 individuals were allocated via randomization to the lenvatinib plus pembrolizumab group (of whom 406 underwent treatment) [7]. Within the pMMR cohort, 346 individuals were allocated to this group (with 342 undergoing treatment) [7]. Prior reports have covered patient flow and starting features [7]. Across all participants, the median length of exposure to lenvatinib plus pembrolizumab reached 231 days (ranging from 1 to 817) [7].

Common and key adverse reactions

Events impacting over 50% of participants involved hypothyroidism (overall cohort, 68.7%; pMMR, 67.0%), hypertension (overall, 65.0%; pMMR, 66.7%), fatigue (overall, 58.6%; pMMR, 57.9%), diarrhea (overall, 54.4%; pMMR, 55.0%), and musculoskeletal issues (overall, 52.5%; pMMR, 52.9%); **(Figure 2).** Owing to the near-identical rates across the full cohort and pMMR subset, subsequent details emphasize the entire treated population (those with ≥1 dose).

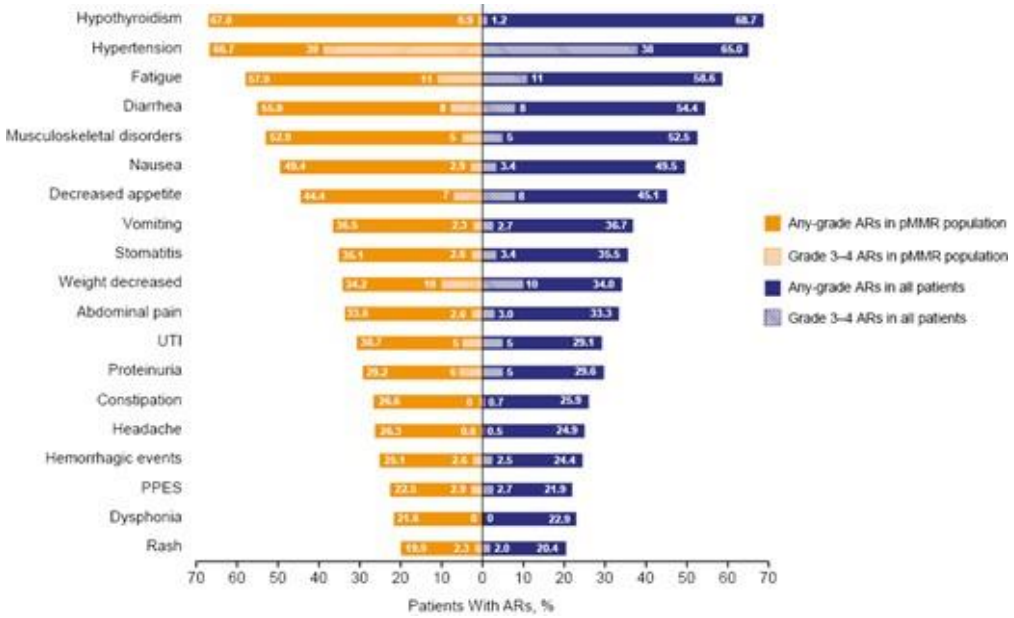

Figure 2. Events with rates exceeding 20% across the full cohort and pMMR subset in the lenvatinib plus pembrolizumab group from Study-309/KEYNOTE-775 (safety cohort).a Values are all percentages. Among major events, no grade 5 occurrences were noted except one instance (0.2%) of grade 5 appetite loss (judged unrelated to investigational agents by the investigator). aGrade 3-4 events (shaded) form part of any-grade events (solid). AR, adverse reaction; pMMR, mismatch repair proficient; PPES, palmar-plantar erythrodysesthesia syndrome; UTI, urinary tract infection.

Major events examined here **(Figure 1)** cover hypothyroidism, hypertension, fatigue, diarrhea, musculoskeletal issues, nausea, appetite loss, vomiting, stomatitis, weight loss, proteinuria, and palmar-plantar erythrodysesthesia syndrome (PPES). Following exposure adjustment, top-ranking major events by rate were diarrhea, hypertension, and musculoskeletal issues. Grade 3-5 event frequencies appear in **Figure 2**. Median delays to first appearance of major events, plus linked dosage actions, are illustrated in **Figure 3**.

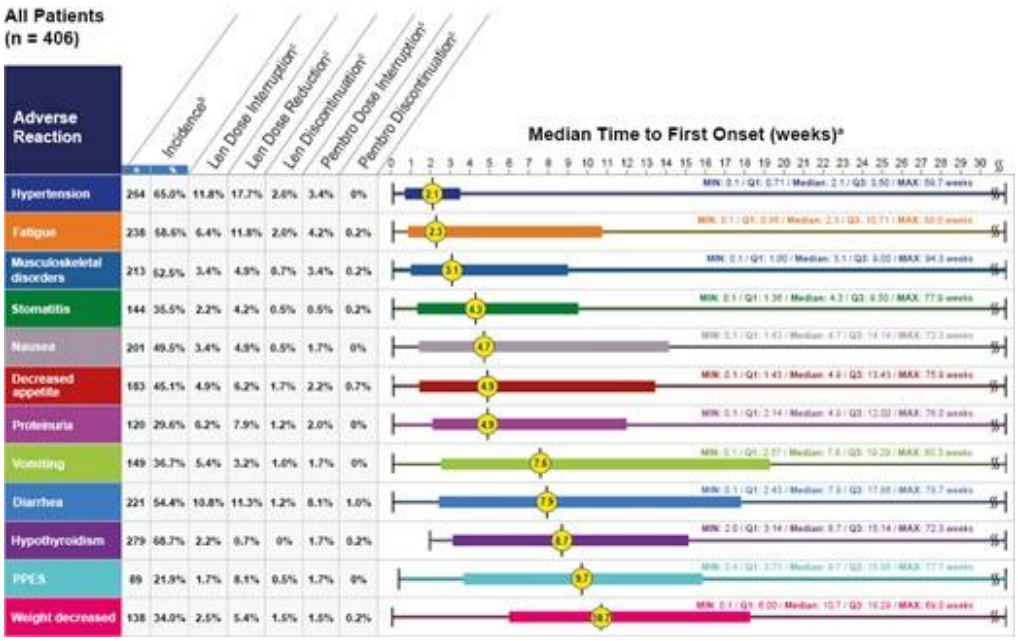

Figure 3. Median delay to initial appearancea of major events and patient dosage handling in the lenvatinib plus pembrolizumab group of Study-309/KEYNOTE-775 (safety cohort). aMedian delay among those developing the event. bAll grades. cDose change and stoppage rates derived from the safety set. Len,

lenvatinib; max, maximum; min, minimum; Pembro, pembrolizumab; PPES, palmar-plantar erythrodysesthesia syndrome; Q, quartile.

General management strategies

Ahead of therapy start, proactively prepare the whole care team by highlighting typical events and standardizing response plans, as widespread familiarity drives successful oversight. Equally crucial is guiding patients toward ideal control of blood pressure (BP), nausea, stool patterns, discomfort, food consumption, and skin conditions prior to launching lenvatinib plus pembrolizumab.

Initial response involves pinpointing the likely culprit—lenvatinib or pembrolizumab—perhaps via onset patterns or improvement after dosing. For nearly all major events **(Figure 4)**, lenvatinib labeling advises pausing for lasting or poorly tolerated grade 2 or any grade 3 events, and stopping permanently for most grade 4 events [10]. After improvement to grade ≤1 or pretreatment levels, stepwise lenvatinib reductions (to 14 mg, then 10 mg, then 8 mg daily) become possible [10] **(Figure 4)**. Within Study-309/KEYNOTE-775, sponsor-approved drops to 4 mg were also feasible. Trial rules permitted restarting lenvatinib at lowered levels once most events eased to acceptable grade 2 or grade ≤1, barring specific exceptions [7].

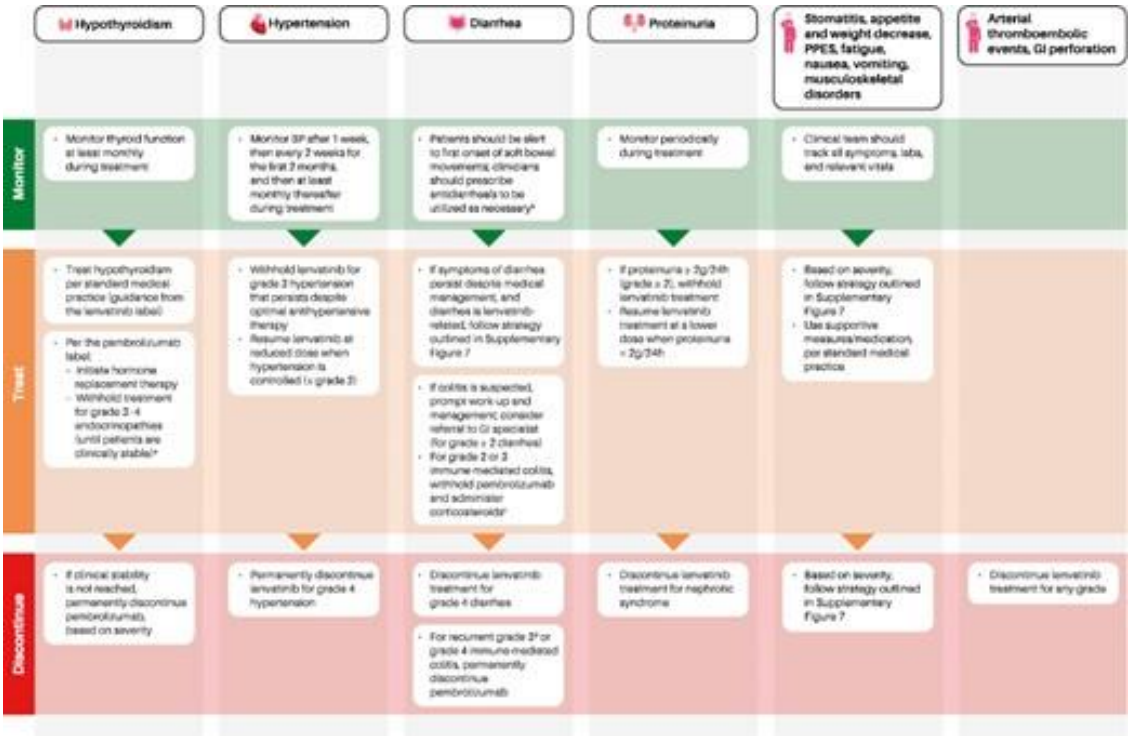

Figure 4. Handling of selected ARs throughout the treatment period. For cases involving nausea, vomiting, hypertension, hypothyroidism, and/or diarrhea, thorough supportive care is advised before considering any pause or lowering of lenvatinib dosage. Pembrolizumab dosage adjustments downward are not advised. aAccording to trial guidelines, pembrolizumab could continue during grades 2-4 hypothyroidism alongside starting thyroid hormone replacement (such as levothyroxine or liothyronine) following standard practice. bSelection of antidiarrheal medication should be tailored to the individual's situation and align with routine clinical care. cRestart pembrolizumab once full or partial improvement (grades 0 to 1) occurs after completing corticosteroid reduction. Stop permanently if improvement is absent within 12 weeks of starting steroids or if prednisone cannot be tapered to 10 mg per day or less (or equivalent) within 12 weeks. dPer trial guidelines, pembrolizumab requires permanent cessation for repeated grade 3 or any grade 4 immune-related colitis. AR, adverse reaction; BP, blood pressure; GI, gastrointestinal; PPES, palmar-plantar erythrodysesthesia syndrome; QD, every day.

Information on handling ARs linked to pembrolizumab can be found in its product labeling [12]. Lowering pembrolizumab dosage is not advised [12] **(Figure 4).** For the majority of immune-related adverse reactions (imARs) from pembrolizumab reaching grade 2 or 3, dosing should be paused and restarted only after

improvement to grade 0 or 1 following steroid taper. Permanent cessation of pembrolizumab is required for grade 4 (life-threatening) imARs, repeated severe grade 3 imARs needing systemic immunosuppression, failure to improve within 12 weeks of steroid initiation, or inability to taper corticosteroids to ≤10 mg prednisone daily (or equivalent) within 12 weeks. Steroid tapering should begin once the imAR reaches grade 0 or 1 and last at least 4 weeks. In severe or life-threatening imARs, start with intravenous corticosteroids before switching to oral forms. Additional immunosuppressive agents should be considered if corticosteroids fail to control the imAR [7, 12].

For nausea, vomiting, hypertension, hypothyroidism, and/or diarrhea, comprehensive supportive treatment is suggested before pausing or reducing lenvatinib [7]. Detailed handling approaches, including dosage adjustments for certain key ARs along with pre- and on-treatment monitoring, are covered in the following sections. Supportive drugs form an integral component of AR control per routine practice; usage patterns for frequent supportive medications in patients from Study-309/KEYNOTE-775 are summarized **(Table 1).**

Table 1. Overview of supportive medications used for managing key adverse reactions across all patients in Study-309/KEYNOTE-775 (safety analysis population)

Adverse reaction	Description	n (%)
Hypothyroidism	Patients experiencing this AR	279 (100.0)
	Patients receiving ≥1 concomitant drug	216 (77.4)
	Levothyroxine sodium	213 (76.3)
Hypertension	Patients experiencing this AR	264 (100.0)
	Patients receiving ≥1 concomitant drug	216 (81.8)
	Amlodipine	80 (30.3)
	Amlodipine besilate	49 (18.6)
	Losartan	28 (10.6)
	Captopril	21 (8.0)
	Ramipril	20 (7.6)
	Furosemide	18 (6.8)
	Nifedipine	17 (6.4)
	Hydrochlorothiazide	16 (6.1)
	Lisinoprol	14 (5.3)
Fatigue	Patients experiencing this AR	238 (100.0)
	Patients receiving ≥1 concomitant drug	12 (5.0)
	Dexamethasone	4 (1.7)
Diarrhea[c]	Patients experiencing this AR	221 (100.0)
	Patients receiving ≥1 concomitant drug	141 (63.8)
	Loperamide hydrochloride	61 (27.6)
	Loperamide	58 (26.2)
Musculoskeletal disorders	Patients experiencing this AR	213 (100.0)
	Patients receiving ≥1 concomitant drug	125 (58.7)
	Paracetamol	59 (27.7)
	Ibuprofen	23 (10.8)
	Loxoprofen sodium	14 (6.6)
	Prednisone	11 (5.2)
Nausea	Patients experiencing this AR	201 (100.0)
	Patients receiving ≥1 concomitant drug	131 (65.2)
	Ondansetron	41 (20.4)
	Metoclopramide hydrochloride	36 (17.9)
	Metoclopramide	31 (15.4)

	Prochlorperazine	16 (8.0)
Decreased appetite	Patients experiencing this AR	183 (100.0)
	Patients receiving ≥1 concomitant drug	42 (23.0)
	Megestrol acetate	10 (5.5)
Vomiting	Patients experiencing this AR	149 (100.0)
	Patients receiving ≥1 concomitant drug	52 (34.9)
	Metoclopramide	17 (11.4)
	Ondansetron	16 (10.7)
	Metoclopramide hydrochloride	13 (8.7)
Stomatitis	Patients experiencing this AR	144 (100.0)
	Patients receiving ≥1 concomitant drug	91 (63.2)
	Nystatin	19 (13.2)
	Dexamethasone	12 (8.3)
	Sodium gualenate	10 (6.9)
	Chlorhexidine gluconate	8 (5.6)
	Lidocaine	8 (5.6)
Weight loss	Patients experiencing this AR	138 (100.0)
	Patients receiving ≥1 concomitant drug	17 (12.3)
	Nutrients, NOS	4 (2.9)
Proteinuria	Patients experiencing this AR	120 (100.0)
	Patients receiving ≥1 concomitant drug	5 (4.2)
	Akritoin	1 (0.8)
Palmar–plantar erythrodysesthesia syndrome	Patients experiencing this AR	89 (100.0)
	Patients receiving ≥1 concomitant drug	62 (69.7)
	Clobetasol propionate	15 (16.9)
	Mucopolysaccharide polysulfuric acid ester	9 (10.1)
	Urea	9 (10.1)
	Heparinoid	6 (6.7)
	Difluprednate	5 (5.6)

aMedications listed are those used by ≥5% of patients or the primary supportive agent for the indicated AR. Percentages are derived from the number of patients experiencing the AR.
bAn individual patient may have taken multiple medications for one AR.
cDiarrhea includes only diarrhea and gastroenteritis, excluding colitis, which is immune-mediated and managed with steroids and other agents.
AR, adverse reaction; nos, not otherwise specified.

Hypothyroidism

Hypothyroidism has been documented previously with lenvatinib or pembrolizumab used alone [10, 12]. Within Study-309/KEYNOTE-775, hypothyroidism of any grade affected 68.7% (n = 279) of patients, with median onset at 8.7 weeks **(Figures 2 and 3).** The majority of cases were mild and controllable through hormone replacement without requiring dosage changes. According to lenvatinib labeling, thyroid function must be assessed before starting therapy and monthly thereafter; hypothyroidism should be managed according to routine clinical standards **(Figure 4)** [10].

Per pembrolizumab labeling, hormone replacement should be started for hypothyroidism, with pembrolizumab paused for grades 3-4 endocrinopathies (until clinical stability) or stopped permanently based on severity [12]. Trial guidelines allowed continuation of pembrolizumab during grades 2–4 hypothyroidism while beginning thyroid hormone replacement per standard care [7].

Hypertension

Hypertension of any grade developed in 65.0% (n = 264) of patients, with median onset at 2.1 weeks **(Figures 2 and 3).**

Blood pressure should be stabilized and well-controlled before treatment initiation and checked frequently during therapy [10]; patients should ideally approach normal values. Those with existing hypertension need to be on a steady antihypertensive regimen for at least 1 week prior to starting the combination. Per trial rules, hypertension grading relies solely on blood pressure readings, not on the quantity of antihypertensive drugs [7]. Lenvatinib should be paused for grade 3 hypertension despite maximal antihypertensive treatment, or whenever hypertensive crisis appears imminent, or when substantial risks for complications from uncontrolled hypertension exist; resumption at a lower dose is possible once controlled to grade 2 or below [10]. Permanent cessation of lenvatinib is required for grade 4 hypertension [10] **(Figure 4).**

Diarrhea

Diarrhea of any grade affected 54.4% (n = 221) of patients, with a median onset at 7.9 weeks **(Figures 2 and 3).** Early intervention for diarrhea is advised [10]. Patients should be instructed to report the earliest signs of loose stools and to stay well-hydrated with clear liquids. Healthcare providers should supply antidiarrheal medications at the start of therapy for use as required. Selection of the antidiarrheal should be tailored to the individual's condition and conform to routine clinical guidelines [7]. Lenvatinib dosing should be paused and later restarted at a reduced level or stopped permanently, depending on diarrhea severity [10].

Pembrolizumab may trigger immune-mediated colitis; therefore, patients require surveillance for signs of enterocolitis (diarrhea, abdominal discomfort, blood or mucus in stool, with or without fever) [7, 12]. When colitis is suspected, timely diagnostic evaluation—including imaging and endoscopy—should be performed, supportive care started immediately, and a gastroenterology consultation obtained (for grade ≥2 diarrhea) where appropriate. For grade 2-3 immune-mediated diarrhea/colitis, pembrolizumab should be paused and systemic corticosteroids initiated (starting at 1-2 mg/kg prednisone or equivalent, followed by gradual taper); recurrent grade 3 or any grade 4 immune-mediated diarrhea/colitis warrants permanent discontinuation of pembrolizumab **(Figure 4)** [7, 12].

Nausea and vomiting

Nausea of any grade developed in 49.5% (n = 201) of patients, with median onset at 4.7 weeks **(Figures 2 and 3)**. Vomiting of any grade occurred in 36.7% (n = 149) of patients, with median onset at 7.6 weeks **(Figures 2 and 3).** Providers should prescribe antiemetic agents at therapy initiation for as-needed use and address nausea and vomiting fully before considering any lenvatinib dose reduction.

Proteinuria

Proteinuria of any grade was observed in 29.6% (n = 120) of patients, with median onset at 4.9 weeks **(Figures 2 and 3).**

Assessment of proteinuria before starting treatment and regular checks during therapy are recommended [10] **(Figure 4).** Lenvatinib should be paused for proteinuria ≥2 g/24 h and restarted at a lower dose once levels fall below 2 g/24 h [11]. Therapy should be stopped permanently in the event of nephrotic syndrome [10] **(Figure 4).**

Overlapping toxicities

In Study-309/KEYNOTE-775, the tolerability profile of lenvatinib combined with pembrolizumab aligned closely with the established profiles of each drug alone and of the combination in endometrial cancer as well as other solid malignancies, without emergence of novel safety concerns [7, 10, 12-14].

When an adverse reaction could stem from either agent (for example, diarrhea or elevated liver enzymes), onset timing and response to temporary lenvatinib pause can be assessed, taking into account lenvatinib's shorter half-life. If withholding lenvatinib fails to yield improvement, an immune-mediated event should be suspected. Certain severe reactions may necessitate pausing both agents and rapid therapeutic intervention.

For persistent diarrhea despite supportive care, lenvatinib should be interrupted and later resumed at a reduced dose or discontinued according to severity. If colitis is suspected, thorough investigation is needed to establish the cause or rule out alternatives such as infectious agents. If confirmed as immune-mediated, corresponding management protocols should be applied. For raised liver enzymes, potential contributors (e.g., acetaminophen),

infections (such as viral hepatitis), or progressive metastases should be excluded, while adhering to recommendations in the product labeling.

Case study vignette

Building on the description of major adverse reactions linked to lenvatinib plus pembrolizumab outlined earlier, we present a step-by-step clinical scenario drawn from actual practice **(Figure 5)** to illustrate how patient care can be optimised to preserve treatment efficacy while limiting the risk of permanent cessation. The treating team conducted pretreatment screening and optimisation, confirming stable blood pressure, acceptable urine protein, and normal cardiac status. Consultations with specialists (cardiology, nutrition, gastroenterology) were sought at key intervals as required, promoting thorough oversight and facilitating rapid resolution or amelioration of adverse reactions. Causality attribution to one or both drugs was established where feasible, and the multidisciplinary group followed label and protocol directives, thereby allowing sustained therapy **(Figure 5).**

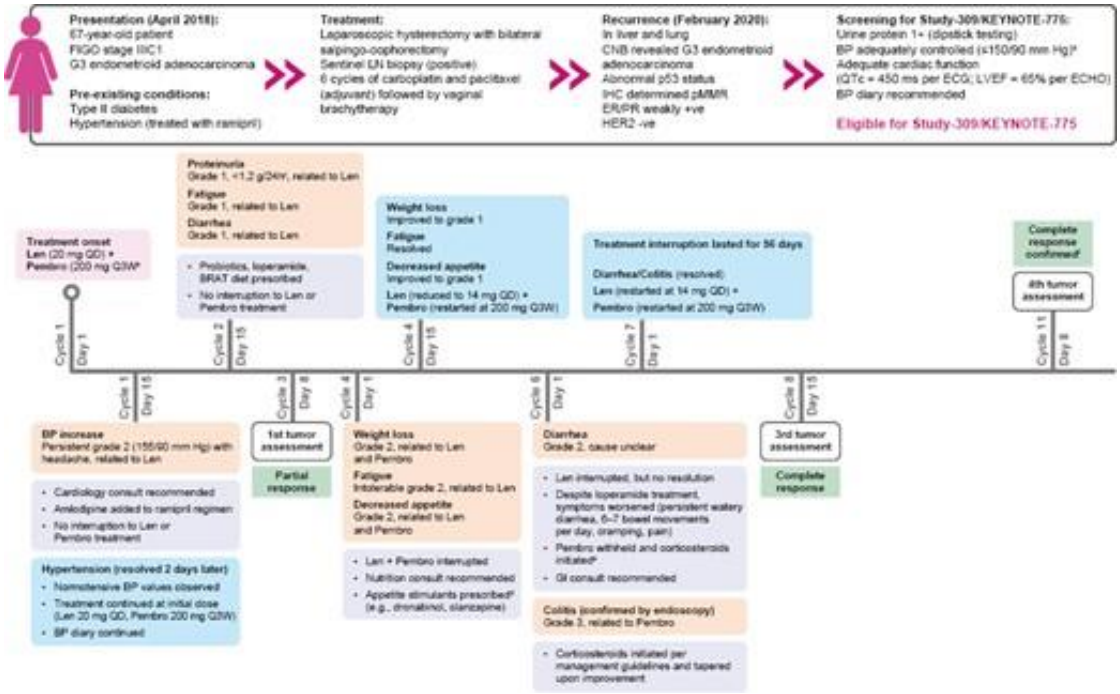

Figure 5. Clinical vignette illustration. aBlood pressure was satisfactorily managed (using ramipril for at least 1 week before starting therapy) in line with protocol criteria (≤150/90 mmHg). bTherapy commenced in March 2020. cDipstick urinalysis indicated 2+ proteinuria, subsequently classified as grade 1 after 24-hour collection (<1.2 g/24 h). dRecommendations included small, frequent, calorie-dense meals (such as full-fat milk, yogurt, cheese, peanut butter, avocado) plus nutritional supplements. ePrednisone started at 1 mg/kg, with tapering upon symptom improvement. fThe patient received 35 cycles of pembrolizumab and remained on lenvatinib. BP, blood pressure; BRAT, bananas, rice, applesauce, and toast; CNB, core needle biopsy; ECG, electrocardiogram; ECHO, echocardiogram; IHC, immunohistochemistry; Len, lenvatinib; LVEF, left ventricular ejection fraction; Pembro, pembrolizumab; pMMR, mismatch-repair proficient; QD, once daily; Q3W, every 3 weeks.

Tyrosine kinase inhibitors commonly produce adverse reactions including hypertension, fatigue, nausea, and diarrhea across multiple indications [10, 16-18], while immune checkpoint inhibitors frequently lead to immune-mediated reactions such as pneumonitis, colitis, and hepatitis [12, 19-21]. To optimise outcomes with a dual regimen like lenvatinib plus pembrolizumab, clinicians must become proficient in handling adverse reactions associated with each individual agent and with their combined use. Effective approaches encompass educating patients and the care team, implementing preventive surveillance, recognising treatment-emergent events, and applying dose adjustments and/or supportive drugs when appropriate.

The contribution of a multidisciplinary group—comprising nurses, nurse practitioners, physician assistants, physicians, and pharmacists—to timely and suitable adverse reaction handling is essential. Equally vital is

engaging patients and caregivers through clear communication and collaborative decision-making. Before therapy begins, targeted education for nurses, nurse practitioners, and physician assistants is particularly valuable, as they typically serve as primary or most regular contacts for patients and families.

In Study-309/KEYNOTE-775, the therapeutic advantage of lenvatinib plus pembrolizumab persisted throughout the trial even with protocol-allowed dose adjustments [22]; evidence from various oncology trials reinforces initiating lenvatinib at the approved dose and subsequently interrupting or reducing as required [13, 23-25]. Comprehensive supportive care should be prioritised, with pauses in lenvatinib and/or pembrolizumab or reductions in lenvatinib guided by the relevant product labeling.

Regular review of concurrent medications during visits and assessment for potential overlapping toxicities attributable to either agent are advised.

Within Study-309/KEYNOTE-775, adverse reactions from lenvatinib plus pembrolizumab typically emerged within roughly 3 months of starting treatment in both the overall and pMMR cohorts. Those with the earliest median onset (<4 weeks) were hypertension, fatigue, and musculoskeletal disorders. Reactions with later median onset (>8 weeks) included hypothyroidism, PPES, and weight decreased. Since most events manifest early, conducting weekly evaluations during the first 2-3 treatment cycles enables rapid intervention. Addressing preexisting conditions requiring optimisation before initiation, combined with rigorous ongoing monitoring per labeling and recommendations, remains key, given that reactions may develop anytime.

Fostering patient empowerment through encouragement to report emerging issues promptly proves invaluable, facilitating management at milder severity, preventing progression, and allowing timely supportive measures or specialist input to enhance prospects for sustained clinical gain.

Conclusion

In Study-309/KEYNOTE-775, effective adverse reaction handling involved patient preparation and education, prophylactic strategies, vigilant oversight, dosage alterations, and supportive medications. The tolerability profile of lenvatinib combined with pembrolizumab aligned broadly with profiles observed for the individual agents and for the combination across endometrial carcinoma and other solid malignancies. The healthcare team holds a pivotal position in early detection and control of adverse reactions and must adhere to guidance in the respective product labels to promote better tolerance of the regimen, thereby aiming to optimise antitumor activity while safeguarding patient safety and well-being.

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Conflict of Interest: None

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Ethics Statement: None

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