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Lenvatinib dose, efficacy, and safety in the treatment of multiple malignancies

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Abstract

Introduction: Lenvatinib is an oral multitargeted tyrosine kinase inhibitor that has shown efficacy and manageable safety across multiple cancer types. The recommended starting doses for lenvatinib differ across cancer types and indications based on whether it is used as monotherapy or as combination therapy.

Areas covered: This review covers clinical trials that established the dosing paradigm and efficacy of lenvatinib and defined its adverse-event profile as a monotherapy; or in combination with the mTOR inhibitor, everolimus; or the anti-PD-1 antibody, pembrolizumab; and/or chemotherapy.

Expert opinion: Lenvatinib has been established as standard-of-care either as a monotherapy or in combination with other anticancer agents for the treatment of radioiodine-refractory differentiated thyroid carcinoma, hepatocellular carcinoma, renal cell carcinoma, and endometrial carcinoma, and is being investigated further across several other tumor types. The dosing and adverse-event management strategies for lenvatinib have been developed through extensive clinical trial experience. Collectively, the data provide the rationale to start lenvatinib at the recommended doses and then interrupt or dose reduce as necessary to achieve required dose intensity for maximized patient benefit. The adverse-event profile of lenvatinib is consistent with that of other tyrosine kinase inhibitors, and clinicians are encouraged to review and adopt relevant symptom-management strategies.

Keywords

Dosing; endometrial carcinoma; hepatocellular carcinoma; lenvatinib; pembrolizumab; renal cell carcinoma; safety; thyroid carcinoma; TKI

1. Introduction

Lenvatinib is an oral multitargeted tyrosine kinase inhibitor (TKI) that has shown antitumor, antiangiogenic, and immunomodulatory activity across multiple cancer types [1,2]. Lenvatinib is approved in more than 70 countries for at least 1 of the following indications: as monotherapy in radioiodine-refractory differentiated thyroid carcinoma [3], unresectable hepatocellular carcinoma [4], and unresectable thymic carcinoma (Japan) [5];

in combination with pembrolizumab (an anti-programmed death-1 [anti-PD-1] antibody) for the first-line treatment of advanced renal cell carcinoma [6] and for advanced or recurrent endometrial carcinoma in patients who have disease progression on or following prior systemic therapy in any setting and are not candidates for curative surgery or radiation [1,7,8]; and in combination with everolimus (a mammalian target of rapamycin inhibitor) for advanced renal cell carcinoma following 1 prior vascular endothelial growth factor (VEGF)-targeted therapy [9]. The combination of lenvatinib and pembrolizumab is being investigated in more than 30 phase II and III trials globally.

The recommended starting doses for lenvatinib differ across cancer types and indications based on whether it is used as monotherapy or in combination with other anticancer therapies: 24 mg daily (as monotherapy in radioiodine-refractory differentiated thyroid carcinoma [1,10] and in unresectable thymic carcinoma [Japan] [5]); 12 mg daily and 8 mg daily (as monotherapy for hepatocellular carcinoma; for patients with body weight ≥60 kg and body weight <60 kg, respectively [1,10]); 20 mg daily (as combination therapy with pembrolizumab 200 mg intravenously (IV) every 3 weeks for tumors including renal cell carcinoma and endometrial carcinoma [1,10,11]); and 18 mg daily (as combination therapy with everolimus 5 mg by mouth daily in renal cell carcinoma [1,11]). In the United States and the European Union, 2 postapproval assessments were conducted to evaluate whether a lower starting dose of lenvatinib would maintain similar efficacy with a better safety profile in patients with radioiodine-refractory differentiated thyroid carcinoma (as a monotherapy) or with renal cell carcinoma (in combination with everolimus) [12–15]. Here, we present key data that established the dosing paradigm and efficacy of lenvatinib and defined its adverse-event profile both as a monotherapy and in combination with everolimus or pembrolizumab and/or chemotherapy. Strategies to manage lenvatinib-associated adverse events are also discussed.

2. Mechanisms of action

2.1. Lenvatinib monotherapy

The efficacy of lenvatinib as a monotherapy and in combination with other therapies across a broad spectrum of indications is likely related to its unique biological mechanism of action. Lenvatinib is a multitargeted TKI that targets VEGF receptors (VEGFR) and fibroblast growth factor (FGF) receptors (FGFR), platelet-derived growth factor receptor alpha (PDGFRα), KIT, and RET [16]. VEGF and FGF signaling are key mediators of angiogenesis, which is essential for tumor growth and metastasis [17–20]. In addition to its antiangiogenic effects, inhibition of VEGF and FGF signaling by lenvatinib converts the intrinsically immunosuppressive tumor microenvironment to an immune-stimulatory state [21–25]. Dual inhibition of VEGFR1–3 and FGFR1–4 signaling activity by lenvatinib results in potent antitumor and antiangiogenic effects, including reversion of FGF-mediated acquired resistance to VEGF blockade [26–28].

The multifactorial mechanism of action of lenvatinib drives antiangiogenic, direct antitumor, and immunomodulatory effects and contributes to its efficacy either as a monotherapy or in combination with other anticancer agents.

2.2. Rationale for combining lenvatinib with other systemic anticancer therapies

Anti-PD-1 antibodies, such as pembrolizumab, prevent PD-1 from binding to its ligands, thereby restoring T-cell activation and increasing antitumor effects [29]. The transformation of the tumor microenvironment to an immune-stimulatory state by lenvatinib can potentiate the antitumor effects of anti-PD-1 antibodies [21,22,30]. Inhibition of dual VEGF and FGF signaling by lenvatinib and immune checkpoint blockade by pembrolizumab may result in enhanced antitumor effects compared to each agent alone (Figure 1A) [30,31]. This mechanistic model is supported by studies in mouse tumor models where lenvatinib was shown to modulate cancer immunity in the tumor microenvironment and, when combined with PD-1 blockade, showed enhanced antitumor activity (ie, lenvatinib improved immune checkpoint blockade), providing a scientific rationale for the combination therapy of lenvatinib with pembrolizumab [23,24].

Inhibition of angiogenesis by lenvatinib has been shown to result in normalization of tumor vasculature, which may increase delivery and uptake of chemotherapy into cancer cells [32,33]; and in preclinical studies, lenvatinib monotherapy showed activity in chemotherapy-resistant human tumor xenografts [34]. Chemotherapy has a direct antitumor effect but also has the capacity to promote antitumor immunogenicity via the release of tumor-associated antigens and the maturation of antigen-presenting cells, resulting in activation of cytotoxic T cells (Figure 1B) [35,36]. Certain chemotherapies display immunomodulatory capacity and can increase immune activation when combined with PD-1 blockade. PD-1 blockade can increase the efficacy of chemotherapy and can contribute to reversal of chemotherapeutic resistance [36].

The combination of lenvatinib plus everolimus showed superior antitumor activity and enhanced inhibition of mammalian target of rapamycin/S6K/S6 signaling compared with that of either treatment alone in four different mouse models bearing human xenografts [37,38]. The combined activity of lenvatinib and everolimus appears to be based on enhanced inhibition of VEGF- and FGF-driven angiogenesis and the combination of the antiangiogenic activity of lenvatinib and antiproliferative activity of everolimus (Figure 1C) [30,37–39].

3. Lenvatinib clinical trials experience

3.1. Phase I monotherapy trials

Four phase I studies (Studies 101, 102, 103, 105) were conducted to determine the maximum tolerated dose (MTD)/recommended phase II dose (RP2D) and schedule of lenvatinib monotherapy [40–43]. These 4 trials enrolled 195 patients across different regions (United States, Europe, and Japan) at escalating doses of lenvatinib administered once or twice daily using continuous or interrupted dosing schedules.

Study 101 was an open-label, nonrandomized, dose-escalation assessment of the safety and efficacy of lenvatinib, with a starting dose of 0.2 mg daily and dose escalation up to 32 mg daily, in 82 patients with advanced, refractory solid tumors [40]. Responses were observed more frequently in patients from the higher dose cohorts. With dose-limiting toxicities (DLTs) observed at 32 mg daily, the MTD/RP2D was determined to be 25 mg

daily (Table 1). Across all doses tested, grade ≥3 hypertension occurred in 11% of patients (9 of 82) and grade ≥3 proteinuria occurred in 7% of patients (6 of 82); a trend was observed for increases in the occurrence of hypertension and proteinuria with increasing doses of lenvatinib. The adverse events observed with lenvatinib were consistent with those of many other multitargeted TKI agents and are likely related to the mechanism of action of angiogenesis inhibitors [44–47]. Inhibition of VEGF signaling can cause hypertension by inhibiting vasomotor effects and promoting microvascular rarefaction [48–50]. By inhibiting VEGF signaling, TKIs also reduce production of nephrin, a protein expressed on glomerular podocytes and involved in the formation and maintenance of the glomerular filtration barrier. Reduced nephrin production is associated with proteinuria [49].

In a pharmacokinetic/pharmacodynamic modeling study based on the data from Study 101, an exposure-response relationship was captured for both hypertension, which fit an indirect-effect model, and the probability of experiencing proteinuria, best described by a Markov transition model [51]. Based on these findings, the proposed starting dose of lenvatinib was 25 mg/day and it was recommended that patients who develop hypertension (diastolic blood pressure ≥ 100 mm Hg) should receive antihypertensive therapy while maintaining lenvatinib dose intensity for maximum benefit [40]. Further supporting these findings, a small dose-escalation study (Study 105) in which 9 Japanese patients with solid tumors that were refractory to standard therapies received lenvatinib at either 20 mg or 24 mg daily in 28-day cycles, reported no DLTs in either group (Table 1) [41].

Additional dose-escalation studies (Study 102 and Study 103) evaluated lenvatinib treatment with a twice-daily schedule and continuous or intermittent dosing (2-week-on/1-week-off schedule or 1-week-on/1-week-off) [42,43]. Study 102 (n = 77) evaluated 2 dosing schedules in patients with solid tumors or lymphoma: schedule 1 examined escalating doses of lenvatinib ranging from 0.1 to 3.2 mg twice daily (1-week-on/1-week-off); schedule 2 examined doses ranging from 3.2 to 12 mg twice daily (continuous dosing). No DLTs were observed in the first 6 patients who received 10 mg twice daily, and this dose was considered well-tolerated. Thus, the MTD/RP2D for lenvatinib was determined to be 10 mg twice daily in patients with solid tumors or resistant/refractory lymphomas. In Study 103, which enrolled 27 Japanese patients with advanced solid tumors, the starting dose of lenvatinib was 0.5 mg with dose escalation up to 20 mg twice daily [43]. The MTD/RP2D was determined to be 13 mg twice daily in a 2-week-on/1-week-off schedule based on the observed DLTs (Table 1).

To determine the benefits of daily versus twice-daily dosing, a population pharmacokinetic/pharmacodynamic analysis of data pooled from Studies 101 and 102 was performed [52]. Higher lenvatinib exposure was correlated with progression-free survival (PFS), tumor response (partial response/stable disease), and the probability of developing hypertension and proteinuria. Lenvatinib at MTD/RP2D of 25 mg daily allowed for the targeting of higher exposures compared with MTD of 10 mg twice daily [52].

3.2. Phase I/II trials

3.2.1. Lenvatinib monotherapy

3.2.1.1. Hepatocellular carcinoma.: Altered hepatic function from underlying liver disease may affect lenvatinib exposure because the drug is metabolized via the liver through a cytochrome-P450-3A-based mechanism [53]. Thus, lenvatinib doses appropriate for patients with hepatocellular carcinoma would be expected to differ from those appropriate for patients with other tumor types. A specific dose-finding study was undertaken to determine the optimum starting dose of lenvatinib in patients with hepatocellular carcinoma [54–56]. Study 202 was a dose-escalation (phase I, n = 9) and expansion (phase II, n = 46) study in patients with advanced hepatocellular carcinoma and Child-Pugh A liver function, and a dose-determination study (n = 11) for patients with advanced hepatocellular carcinoma with Child-Pugh B liver function [54,55]. Per results of the dose-escalation portion of the study, recommended doses of lenvatinib were 12 mg daily for patients with Child-Pugh A liver function and 8 mg daily for patients with Child-Pugh B liver function (Table 1). In the dose-expansion part of the study, which enrolled 46 patients with Child-Pugh A liver function, clinical efficacy outcomes were encouraging (objective response rate [ORR], 37% [17 of 46 patients]; median overall survival [OS], 18.7 months) with the recommended lenvatinib starting dose of 12 mg daily (Table 2) [55]. Sequential reductions of lenvatinib doses to 8 mg and 4 mg daily were permitted. Dose reductions owing to adverse events occurred in 74% of the patients. Patients who experienced early dose reductions or discontinuations had a lower median body weight (54.1 kg) compared with those who did not experience reductions or discontinuations (median body weight 67.6 kg). Baseline body weight and minimum concentration of lenvatinib (C_{trough}) 15 days after treatment initiation were identified as potential differentiators for patients who required early dose discontinuation or reduction of lenvatinib versus those who did not (descriptive statistics) [55]. Results from pharmacokinetic and exposure-response analyses conducted on data from patients with hepatocellular carcinoma in Study 202 suggested a dosing regimen based on body weight in this patient population [56]. Per a post hoc exploratory analysis, recommended doses included lenvatinib 8 mg daily for patients weighing below 60 kg and lenvatinib 12 mg daily for patients weighing 60 kg or above [56]. The dose-reduction algorithm implemented in Study 202 followed the strategy of maximizing the starting dose of lenvatinib and modifying or interrupting dosing as clinically appropriate. This dosing regimen and strategy were implemented in the pivotal phase III trial, REFLECT (Study 304) [4].

3.2.1.2. Radioiodine-refractory differentiated thyroid carcinoma.: Simulations based on data from patients with radioiodine-refractory differentiated thyroid carcinoma and a pharmacokinetic model [57] predicted tumor response over 24 weeks for 7 lenvatinib dosing regimens (24 mg, 20 mg, 18 mg, and 14 mg, [the latter 3 doses with or without uptitration to 24 mg]) [58]. Compared with the approved lenvatinib 24 mg dose, the 14-mg dose without uptitration was found likely to lower the ORR, and the 20-mg dosing regimen would not provide sufficiently different exposure. Based on these results, a lenvatinib starting dose of 18 mg/day was chosen for comparison of efficacy and safety versus the recommended dose of 24 mg/day in a post-approval study (Study 211) [58].

In the randomized Study 211 [59], the lenvatinib 18 mg/day starting dose (n = 77) failed to demonstrate noninferiority versus the recommended lenvatinib 24 mg/day starting dose (n = 75) in patients with radioiodine-refractory differentiated thyroid carcinoma, based on ORR at week 24 (Table 2). ORR and PFS results were supportive of the 24 mg/day starting dose. Notably, the primary safety-profile endpoint was comparable across treatment arms and overall safety results in both arms were similar to the known safety profile of lenvatinib in patients with radioiodine-refractory differentiated thyroid carcinoma (Table 2) [59].

3.2.1.3. Unresectable thymic carcinoma.: In a single-arm, multicenter, phase II trial (REMORA study), the activity and safety of lenvatinib at a 24 mg/day starting dose was studied in 42 Japanese patients with unresectable advanced or metastatic thymic carcinoma previously treated with platinum-based chemotherapy [60]. ORR was 38% (16 of 42 patients; 90% CI, 25.6–52.0). The median PFS was 9.3 months, and the median OS was not reached at the data cutoff date (Table 2). The most common grade 3 treatment-related adverse events were hypertension (64%) and palmar-plantar erythrodysesthesia syndrome (7%) [60]. Based on results from the REMORA study, lenvatinib was approved in Japan for the treatment of patients with unresectable thymic carcinoma [5].

3.2.2. Lenvatinib in combination with pembrolizumab—The MTD/RP2D and safety of lenvatinib in combination with pembrolizumab were studied in the phase Ib/II, open-label Study 111/KEYNOTE-146, which enrolled patients with a variety of tumor types [61]. The malignancy type and patient cohort numbers in the initial part of the study were as follows: renal cell carcinoma (n = 30), endometrial cancer (n = 23), squamous cell carcinoma of the head and neck (n = 22), melanoma (n = 21), non-small cell lung cancer (n = 21), or urothelial cancer (n = 20). Given the dosing strategy supporting efficacy with the higher starting dose of lenvatinib, the initial dose studied for the combination was lenvatinib 24 mg/day (with dose de-escalation as appropriate) plus pembrolizumab 200 mg once every 3 weeks. In the lenvatinib 24 mg/day dose cohort (n = 3), DLTs of grade 3 arthralgia (n = 1) and grade 3 fatigue (n = 1) were reported; no DLTs were reported in the lenvatinib 20 mg/day cohort (n = 10) (Table 1). The most common treatment-related adverse events across tumor types were fatigue (58%), diarrhea (52%), and hypertension (47%) (Table 3). ORR at week 24 of treatment was as follows: renal cell carcinoma, 63% (19 of 30 patients); endometrial cancer, 52% (12 of 23 patients); melanoma, 48% (10 of 21 patients); squamous cell carcinoma of the head and neck, 36% (8 of 22 patients); non-small cell lung cancer, 33% (7 of 21 patients); and urothelial cancer, 25% (5 of 20 patients). Based on this study, lenvatinib 20 mg/day with pembrolizumab 200 mg IV once every 3 weeks was determined to be the MTD/RP2D [61]. Following this report, cohort sizes for patients with several malignancy types, including endometrial cancer and renal cell carcinoma, were expanded. Based on the phase Ib/II Study 111/KEYNOTE-146 results, lenvatinib plus pembrolizumab received accelerated approvals in some regions for previously treated endometrial carcinoma (that was not microsatellite instability-high or mismatch repair deficient) [62,63].

3.2.2.1. Endometrial carcinoma.: Among patients with previously treated endometrial carcinoma (n = 108), the efficacy of lenvatinib (20 mg daily by mouth plus pembrolizumab 200 mg once every 3 weeks IV) was evaluated in the expansion phase of Study 111/

KEYNOTE-146 [63]. The median follow-up duration was 18.7 months. The overall ORR at week 24 of treatment was 38.0% (41 of 108 patients; 95% CI, 28.8% to 47.8%). Importantly, among subgroups, the ORR at week 24 of treatment was 63.6% (7 of 11 patients; 95% CI, 30.8% to 89.1%) in patients with microsatellite instability-high tumors and 36.2% (34 of 94 patients; 95% CI, 26.5% to 46.7%) in patients with microsatellite-stable tumors [63]. Median PFS was 7.4 months (95% CI, 5.3–8.7), and median OS was 16.7 months (95% CI, 15.0–not estimable) (Table 2). The most frequent treatment-related adverse events in the lenvatinib-plus-pembrolizumab group were hypertension (61.1%), diarrhea (52.8%), and fatigue (51.9% each) (Table 3). With extended follow-up in 108 patients (median follow-up duration, 34.7 months), tumor responses (ORR, 39.8% [43 of 108 patients]; 95% CI, 30.5–49.7) and maintenance of benefits in PFS (median, 7.4 months; 95% CI 5.2–8.7) and OS (median, 17.7 months; 95% CI, 15.5–25.8) were observed. The most common grade ≥ 3 treatment-related adverse events were hypertension (33.3%), lipase increased (9.3%), fatigue (8.3%), and diarrhea (7.4%) [64].

3.2.2.2. Renal cell carcinoma.: Patients with renal cell carcinoma who were either treatment-naïve or previously treated with or without immune checkpoint inhibitors were included (n = 143 for efficacy analyses; n = 145 for safety analyses) in the expansion phase of Study 111/KEYNOTE-146, evaluating lenvatinib-plus-pembrolizumab at the previously determined starting dose [65]. The median follow-up was 19.8 months (interquartile range, 14.3–28.4 months). The objective response at week 24 was 72.7% for treatment-naïve patients (16 of 22 patients; 95% CI, 49.8–89.3), 41.2% (7 of 17 patients; 95% CI, 18.4–67.1) for previously treated immune-checkpoint-inhibitor–naive patients, and 55.8% for immune-checkpoint-inhibitor–pretreated patients (58 of 104 patients; 95% CI, 45.7–65.5) (Table 2). Overall, the most common treatment-related adverse events were fatigue (58.6%), diarrhea (55.2%), and hypertension (40%) (Table 3) [65].

3.2.3. Lenvatinib in combination with everolimus

3.2.3.1. Renal cell carcinoma.: The phase Ib part of Study 205 investigated the safety of escalating lenvatinib starting doses of 12 mg (n = 7), 18 mg (n = 11), and 24 mg (n = 2) daily by mouth in combination with everolimus 5 mg daily by mouth in patients with advanced or metastatic renal cell carcinoma [66]. In the lenvatinib 24 mg daily cohort, there were 2 patients with DLTs (grade 3 nausea and vomiting, n = 1; and failure to administer >75% of the planned dose due to grade 2 mucosal inflammation, n = 1), compared with 1 patient in the 18 mg daily cohort (failure to administer >75% of the planned dose due to grade 3 elevated creatinine phosphokinase, grade 2 fatigue, and grade 1 reflux); thus, the starting dose of 18 mg daily for lenvatinib in combination with everolimus 5 mg daily was determined to be the MTD/RP2D (Table 1). The ORR was 28.6% (2 of 7 patients) for the lenvatinib 12 mg daily cohort and 36.4% (4 of 11 patients) for the 18 mg daily cohort [66].

In the phase II part of Study 205 [9], PFS was significantly prolonged with lenvatinib plus everolimus (n = 51; median, 14.6 months) compared with everolimus alone (n = 50; median, 5.5 months; hazard ratio [HR], 0.40; 95% CI, 0.24–0.68; P = 0.0005). Lenvatinib monotherapy also prolonged PFS compared with everolimus alone (HR, 0.61; 95% CI 0.38–0.98; P = 0.048), but with a lesser margin. The ORRs were 43% (22 of 51 patients;

95% CI, 29–58) with lenvatinib plus everolimus, 27% (14 of 52 patients; 95% CI, 16–41) with lenvatinib alone, and 6% (3 of 50 patients; 95% CI, 1–17) with everolimus alone (Table 2); 1 patient (of 51; 2%) in the combination-therapy cohort had a complete response with none noted in the other cohorts. Lenvatinib dose reductions were needed by 71% (36 of 51) of patients assigned to receive lenvatinib plus everolimus and 62% (32 of 52) of patients assigned to receive lenvatinib alone. The most common any-grade treatment-emergent adverse events in the lenvatinib-plus-everolimus group were diarrhea (84.3%), decreased appetite (51.0%), and fatigue or asthenia (58.8%); and in the lenvatinib-alone group, diarrhea (71.2%), nausea (61.5%), and decreased appetite (57.7%) were the most common (Table 3) [9]. The compelling PFS, OS, and ORR results from this study led to the regulatory approval of lenvatinib plus everolimus for the treatment of patients with advanced renal cell carcinoma following 1 prior antiangiogenic therapy in the United States and Europe [1,9,11].

A postapproval, phase II study (Study 218) compared a lower daily starting dose of lenvatinib (ie, 14 mg with uptitration to 18 mg if no intolerable grade 2 or any grade ≥3 adverse events required dose reduction within cycle 1) to the approved 18 mg dose algorithm (both in combination with everolimus 5 mg) [67]. These doses were selected based on exposure-response simulations corroborated by the United States Food and Drug Administration that suggested a lenvatinib 14 mg starting dose may show better or comparable tumor inhibition to the 18 mg starting dose [68,69]. Noninferiority could not be claimed for the starting dose of lenvatinib 14 mg plus everolimus 5 mg versus lenvatinib 18 mg plus everolimus 5 mg based on ORRs at week 24 of treatment. A numerical benefit observed for PFS and OS was supportive of the lenvatinib 18 mg starting dose (Table 2). The overall safety profiles and the primary safety endpoint were comparable between treatment arms (Table 2). Thus, these data further supported the currently approved starting dose regimen of lenvatinib 18 mg/day plus everolimus 5 mg/day in patients with renal cell carcinoma [67].

3.3. Phase III trials

Lenvatinib has shown clinically meaningful efficacy and a consistent and manageable safety profile in phase III trials across a variety of malignancies, both as a monotherapy and in combination with other therapeutics.

3.3.1. Radioiodine-refractory differentiated thyroid carcinoma—Lenvatinib demonstrated clinical benefit for patients with radioiodine-refractory differentiated thyroid carcinoma in the phase III randomized, double-blind SELECT study (Study 303), in which the lenvatinib starting dose of 24 mg daily by mouth (n = 261) was compared to placebo (n = 131) in patients with progressive radioiodine-refractory differentiated thyroid carcinoma [3]. The primary endpoint, PFS, was significantly improved in lenvatinib-treated patients compared with placebo (median, 18.3 months versus 3.6 months; HR, 0.21; 99% CI, 0.14–0.31; $P < 0.001$) (Table 4). This study was designed prospectively to start all patients at lenvatinib 24 mg daily and modify dosing based on the observed adverse events [14]. Exploratory post hoc analyses assessed the relationship between duration of dose interruption and response. Compared with placebo, lenvatinib improved efficacy regardless

of duration of dose interruption. Patients with shorter dose interruptions had greater benefit compared with those who had longer interruptions [70].

The reduction in tumor size with lenvatinib was most pronounced at the first tumor assessment conducted at 8 weeks after randomization. Thereafter, the rate of change was slower but remained continuous. Tumor size reduction was correlated with treatment exposure in the first 8 weeks and overall treatment duration [71]. The median time to first objective response was 2 months, which was sooner than the median time to first dose reduction (3 months) [3]. The most common treatment-related adverse events were hypertension (67.8%), diarrhea (59.4%), and fatigue or asthenia (59.0%) (Table 3). Overall, the safety profile was considered manageable with dose modifications as necessary following maximization of supportive care.

The activity of lenvatinib increases with higher doses and this correlates with the incidence of hypertension, which is a consequence of anti-VEGF activity [50]. As such, treatment-emergent hypertension (defined to include blood pressure increases of ≥140/90 mm Hg as assessed by investigators) correlated with efficacy in an exploratory analysis of the SELECT study [72]. Patients with treatment-emergent hypertension (n = 190), when compared with patients without treatment-emergent hypertension (n = 71), had higher ORR (69% versus 56%; odds ratio, 1.72; 95% CI, 0.98–3.01), longer PFS (median 18.8 months versus 12.9 months; HR, 0.59; 95% CI, 0.39–0.88; unstratified log-rank $P = 0.0085$), and longer OS (median not reached versus 21.7 months; HR, 0.43; 95% CI, 0.27–0.69; nominal $P = 0.0003$) [72]. Caution should be exercised to ensure that hypertension is controlled by antihypertensive treatments, as well as with dose interruptions or reductions as indicated for patient safety. In this study, treatment-emergent hypertension was most often managed with concomitant medication (68%; 177 of 261 patients), with only 1 patient (3%) requiring drug discontinuation [72].

These post hoc analyses provide the rationale for the treatment strategy of achieving dose-intensity with the recommended dose of lenvatinib at the start of treatment to establish efficacy, followed by necessary use of dose modification as required to address adverse events over the course of sustained treatment.

3.3.2. Unresectable hepatocellular carcinoma—Treatment with lenvatinib was associated with clinical benefit for the first-line treatment of patients with unresectable hepatocellular carcinoma based on the phase III REFLECT study (Study 304) [4]. In this study, lenvatinib 8 mg (if patient body weight was <60 kg) or lenvatinib 12 mg (if patient body weight was ≥60 kg) daily, or sorafenib 400 mg twice daily were evaluated in patients with unresectable hepatocellular carcinoma and Child-Pugh class A liver function [4]. Lenvatinib was found to be noninferior to sorafenib in OS (median OS duration 13.6 months versus 12.3 months; HR, 0.92; 95% CI, 0.79–1.06). Per investigator tumor assessments, median PFS was longer with lenvatinib when compared with sorafenib (7.4 months versus 3.7 months). ORR was also improved with lenvatinib compared with sorafenib (24.1% versus 9.2%) (Table 4). The most common treatment-emergent adverse events of any grade in patients treated with lenvatinib were hypertension (42%; grade ≥3, 23%), diarrhea (39%; grade ≥3, 4%), and decreased appetite (34%; grade ≥3, 5%) (Table

3); incidence of any-grade rash was 16% with sorafenib (grade ≥3, <1%) and 10% with lenvatinib (grade ≥3, 0%). Quality-of-life scores demonstrated a clinically meaningful delay in deterioration observed with lenvatinib compared with sorafenib for multiple domains. Overall, the safety profile of lenvatinib in REFLECT was manageable and generally consistent with previous studies (Table 3) [4]. Among patients of either body weight group who experienced a lenvatinib dose reduction, the median time to first dose reduction was 10.0 weeks (interquartile range, 3.4–22.3) [73]. Importantly, in a post hoc analysis including patient data from REFLECT, the efficacy and safety outcomes were similar between both lenvatinib body weight-based cohorts (<60 kg and ≥60 kg) [73]. Another post hoc analysis exploring the correlation between the incidence of adverse events and efficacy outcomes in patients from REFLECT revealed that the occurrence of hypertension, diarrhea, proteinuria, or hypothyroidism was generally associated with longer OS in patients with unresectable hepatocellular carcinoma, highlighting the importance of optimal adverse-event management to derive maximal clinical benefit [74].

3.3.3. Renal cell carcinoma—Lenvatinib plus pembrolizumab demonstrated clinical benefit for the first-line treatment of adult patients with advanced renal cell carcinoma in the CLEAR study (Study 307/KEYNOTE-581) [6]. This trial evaluated lenvatinib 20 mg by mouth once daily plus pembrolizumab 200 mg IV once every 3 weeks (n = 355), or lenvatinib 18 mg by mouth once daily with everolimus 5 mg by mouth once daily (n = 357), or sunitinib 50 mg by mouth once daily 4 weeks on/2 weeks off (n = 357) in patients with advanced renal cell carcinoma. PFS was longer with lenvatinib plus pembrolizumab versus sunitinib (median, 23.9 versus 9.2 months; HR, 0.39; 95% CI, 0.32–0.49; $P < 0.001$); OS was also longer with lenvatinib plus pembrolizumab than with sunitinib (median not reached; HR, 0.66; 95% CI, 0.49–0.88; $P = 0.005$). Lenvatinib plus everolimus showed improvements versus sunitinib in PFS (median, 14.7 versus 9.2 months; HR, 0.65; 95% CI, 0.53–0.80; $P < 0.001$) but not with OS (HR, 1.15; 95% CI, 0.88–1.50; $P = 0.30$). The ORRs were 71.0% (252 of 355; 95% CI, 66.3–75.7) with lenvatinib plus pembrolizumab versus 36.1% (191 of 357; 95% CI, 31.2–41.1) with sunitinib (Table 4); and complete response rates were 16.1% (57 of 355 patients) with lenvatinib plus pembrolizumab and 4.2% (15 of 357 patients) with sunitinib. The most common any-grade treatment-emergent adverse events in the lenvatinib plus pembrolizumab group were diarrhea (61.4%), hypertension (55.4%), and hypothyroidism (47.2%) (Table 3). Overall, the combination therapy of lenvatinib plus pembrolizumab significantly improved efficacy as measured by PFS, OS, and ORR, and showed a manageable safety profile [6].

3.3.4. Endometrial carcinoma—The phase III Study 309/KEYNOTE-775 served as a confirmational study and further evaluated lenvatinib 20 mg by mouth daily plus pembrolizumab 200 mg IV every 3 weeks versus chemotherapy (doxorubicin 60 mg/m^2 IV every 3 weeks or paclitaxel 80 mg/m^2 IV once weekly [3 weeks on/1 week off]) in patients with advanced endometrial cancer and prior treatment with platinum-based chemotherapy regimen(s) [8]. Median PFS was longer in patients treated with lenvatinib plus pembrolizumab versus chemotherapy (mismatch repair-proficient [pMMR] group: 6.6 versus 3.8 months; HR, 0.60; 95% CI, 0.50–0.72; $P < 0.001$; all patients [irrespective of MMR status]: 7.2 versus 3.8 months; HR, 0.56; 95% CI, 0.47–0.66; $P < 0.001$). Median OS

was also longer with lenvatinib plus pembrolizumab versus chemotherapy (pMMR group: 17.4 versus 12.0 months; HR, 0.68; 95% CI, 0.56–0.84; $P < 0.001$; all patients [irrespective of MMR status]: 18.3 versus 11.4 months; HR, 0.62; 95% CI, 0.51–0.75; $P < 0.001$) (Table 4). The median time to first dose reduction of lenvatinib was 1.9 months (range, 0.1–22.8 months). The median time to response for the pMMR group was 2.1 months (range, 1.5–9.4) and for all patients (irrespective of MMR status) was 2.1 months (range, 1.5–16.3) in the lenvatinib plus pembrolizumab arm; correspondingly, for patients in the chemotherapy arm, the median time to response for the pMMR group was 3.5 months (range, 1.0–7.4) and for all patients (irrespective of MMR status) was 2.1 months (range, 1.0–7.4). The most frequent any-grade treatment-emergent adverse events in all patients (safety population) of the lenvatinib plus pembrolizumab arm were hypertension (64.0%), hypothyroidism (57.4%), and diarrhea (54.2%) (Table 3). Overall, the safety of this combination was manageable, and efficacy was significantly improved compared with chemotherapy [8].

3.3.5. Non-small cell lung cancer—In the randomized, double-blind, placebo-controlled, 2-part, phase III study, LEAP-006, the following combination was evaluated in patients with treatment-naïve nonsquamous non-small cell lung cancer: lenvatinib (8 mg daily) with pembrolizumab (200 mg every 3 weeks) and pemetrexed 500 mg/m^2 with carboplatin area-under-the-curve-5 or cisplatin 75 mg/m^2 (every 3 weeks for 4 cycles) followed by lenvatinib 8 mg daily plus pembrolizumab 200 mg every 3 weeks (up to 35 cycles) with pemetrexed 500 mg/m^2. The open-label, safety run-in part 1 of the study (n = 13) showed manageable safety and tolerability with 2 DLTs reported —both grade 3 hyponatremia in patients receiving cisplatin. Preliminary evidence of antitumor efficacy (overall ORR 69.2%, 95% CI 38.6–90.9) was observed (Table 1). The randomized, double-blind, placebo-controlled part 2 of this trial is ongoing [75]. Moreover, the lenvatinib 8 mg starting dose is also being investigated, in combination with pembrolizumab plus other chemotherapies, in phase II/III studies in other tumor indications including gastroesophageal adenocarcinoma (clinicaltrials.gov identifier: NCT04662710), small cell lung cancer (clinicaltrials.gov identifier: NCT04924101), and esophageal cancer (clinicaltrials.gov identifier: NCT04949256).

4. Adverse-event management and dosing strategy

Across lenvatinib trials, judicious use of lenvatinib dose modifications (interruptions/dose reductions) have been used concomitant with supportive care measures to manage adverse events (Table 3). The most common adverse events across trials leading to dose reductions of lenvatinib included hypertension, proteinuria, diarrhea, and fatigue [1]. Given that a number of these adverse events are consistent with known adverse-event profiles of VEGF TKIs, the treatment team should be prepared to manage emerging adverse events promptly and effectively [76,77].

The key to managing adverse events successfully is to communicate and coordinate with both the multidisciplinary clinical team and the patient to maximize supportive care measures. Physicians and their teams review efficacy indications and educate patients regarding potential adverse events that may arise during treatment. Nurses and pharmacists address the practical aspects of adverse-event management, and a consistent management

strategy for common adverse events is developed by clinical teams and practices. Early detection and management of adverse events (eg, hypertension) may decrease the need for lenvatinib dose modifications. Patients can be proactively involved in recognizing any potential adverse events by utilizing strategies such as monitoring blood pressure at home [78] and, hence, patient education regarding common adverse events and active patient engagement is of critical importance. Among patients with unresectable hepatocellular carcinoma, endometrial cancer, and renal cell carcinoma, the median time to first onset of most key adverse reactions (pooled preferred terms grouped per the Food and Drug Administration) [1] for patients treated with lenvatinib plus pembrolizumab (based on data publicly available to date) is within the first 1–3 months of treatment [77–79]. This highlights the importance of close monitoring of patients during the initial phase of treatment, while understanding that attention to patient care should not wane over time so that patients are appropriately managed throughout their treatment.

5. Lenvatinib: looking forward

The efficacy, safety, and dosing of lenvatinib, either as a monotherapy or in combination therapy, is being evaluated across additional tumor types with a wide variety of etiologies. Specifically, in adults, lenvatinib plus pembrolizumab is being evaluated in patients with gastric cancer, colorectal cancer, glioblastoma, biliary tract cancer, melanoma, hepatocellular carcinoma, non-small cell lung cancer, head and neck cancer, and urothelial carcinoma [80]. Importantly, lenvatinib is also being assessed for the treatment of pediatric solid tumors as a monotherapy, in combination with everolimus, or in combination with chemotherapy [81–83]. The dosing paradigm employed in these studies mirrors the strategy used in adults of starting at the recommended lenvatinib dose and modifying as necessary based on adverse events; the recommended doses for lenvatinib monotherapy, lenvatinib with everolimus, and lenvatinib with chemotherapy are equivalent to those in adults [81–83]. As the amount of data supporting the therapeutic profile of lenvatinib continues to grow, it is important for clinicians to review dosing paradigms associated with each indication to benefit and manage patients most effectively.

6. Conclusions

Lenvatinib is a multitargeted TKI with potent antiangiogenic, antitumor, and immunomodulatory activity with efficacy across a variety of solid tumor types. Lenvatinib is approved as both a monotherapy (ie, for unresectable hepatocellular carcinoma, radioiodine-refractory differentiated thyroid carcinoma, and unresectable thymic carcinoma [Japan]) and in combination with pembrolizumab (renal cell carcinoma and endometrial cancer) or everolimus (renal cell carcinoma). Starting doses vary by indication based on whether it is used as monotherapy or as combination therapy to maximize patient benefit, while reducing adverse events that are generally associated with VEGF TKIs as a class. The data in conglomerate provide the rationale to reduce dose as necessary to achieve required dose-intensity.

Lenvatinib continues to be established as an effective, multitargeted TKI and is being further studied in a variety of indications. In combination with pembrolizumab, lenvatinib is being

developed in a large program of drug development in oncology with over 30 trials across approximately 14 tumor types.

7. Expert opinion

Lenvatinib, either as a monotherapy or in combination with other therapies, has been established as a standard treatment across a range of indications based on data from the described clinical trials and consequent approvals by regulatory agencies worldwide.

Lenvatinib is a preferred TKI for use in the first-line treatment of radioiodine-refractory differentiated thyroid carcinoma, per the National Comprehensive Cancer Network guidelines. Results from the REFLECT trial of patients with hepatocellular carcinoma (excluding patients with a high burden of intrahepatic lesions) emphasized the efficacy and manageable safety of lenvatinib as a first-line therapy for patients with Child-Pugh class A liver function. Moreover, lenvatinib appears to be effective in hepatocellular carcinoma irrespective of disease etiology or line of treatment. In Japanese patients with hepatocellular carcinoma, lenvatinib has shown potential as a second-line or later therapy. Further research should confirm the effectiveness of lenvatinib in these patient populations and establish management strategies for patients with poor liver function.

Management of renal cell carcinoma in patients with metastatic disease requires a multidisciplinary approach, as angiogenesis, immune escape, and proliferation are included in its pathophysiology, and the combination of lenvatinib plus pembrolizumab is noteworthy as a first-line therapy with impressive efficacy and manageable safety, as observed in the CLEAR study. In the second-line setting, lenvatinib plus everolimus is an established and recommended therapy. Ongoing studies are analyzing the combination of lenvatinib plus pembrolizumab with other immunotherapies or with belzutifan, a novel HIF-2α inhibitor. Further biomarker-driven research should be pursued to aid in personalizing treatments for patients.

The approval of the combination of lenvatinib and pembrolizumab for patients with previously treated, advanced endometrial carcinoma was a landmark development, and not only marked the first approval of an endometrial cancer therapy since 1971 but was also the first combination to show this degree of efficacy in advanced endometrial cancer. Additionally, the fact that efficacy was not limited by histotype, PD-L1 status, mismatch repair status, and number of prior therapies, is also historic and highly compelling. This combination therapy has forever changed the management of advanced endometrial cancer and is being used in day-to-day clinical practice. This regimen has been established as the standard of care following platinum therapy for advanced endometrial cancer. We believe that the lenvatinib-plus-pembrolizumab combination should be evaluated in the first-line setting. This combination regimen should also be potentially evaluated in combination with chemotherapy. Additional research needs to address treatment of patients after immunotherapy exposure.

Treatment of resistance is a major challenge in the use of TKIs or immune checkpoint inhibitors as monotherapies; therefore, combination therapies are being explored and

established as a strategy to overcome mechanisms of resistance. The LEAP program was designed to further evaluate the efficacy and safety of lenvatinib plus pembrolizumab with or without chemotherapy in a broad range of solid cancers. Work to bolster physician confidence regarding efficacy of this combination and the management of adverse events is important and efforts in this arena must continue to ensure global adoption into clinical practice. The adverse-event profile observed with this treatment combination is consistent with what would be expected from any immunotherapy or VEGF TKI; it is imperative that clinicians review and adopt management strategies to tackle these adverse events.

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Article highlights

- Lenvatinib, an oral multitargeted tyrosine kinase inhibitor (TKI), has shown antitumor, antiangiogenic, and immunomodulatory activity across multiple cancer types either as a monotherapy or in combination with other anticancer agents.
- The recommended starting doses for lenvatinib differ across cancer types and indications based on whether it is used as monotherapy, or in combination with other anticancer therapies: 24 mg daily (as monotherapy in radioiodine-refractory differentiated thyroid carcinoma and unresectable thymic carcinoma), 12 mg daily and 8 mg daily (as monotherapy for hepatocellular carcinoma; for patients with body weight ≥60 kg and body weight <60 kg, respectively), 20 mg daily (as combination therapy with pembrolizumab 200 mg intravenously once every 3 weeks across tumors including endometrial carcinoma and renal cell carcinoma), and 18 mg daily (as combination therapy with everolimus 5 mg by mouth daily in renal cell carcinoma).
- Taken together, data from clinical trials provide the rationale to start lenvatinib at the recommended dose and reduce or interrupt as necessary to achieve required dose-intensity for maximum patient benefit.
- The adverse-event profile of lenvatinib is generally consistent with that of other multitargeted TKIs; management strategies for these adverse events are well-established in the prescribing information and should be reviewed by clinicians and the multidisciplinary team.

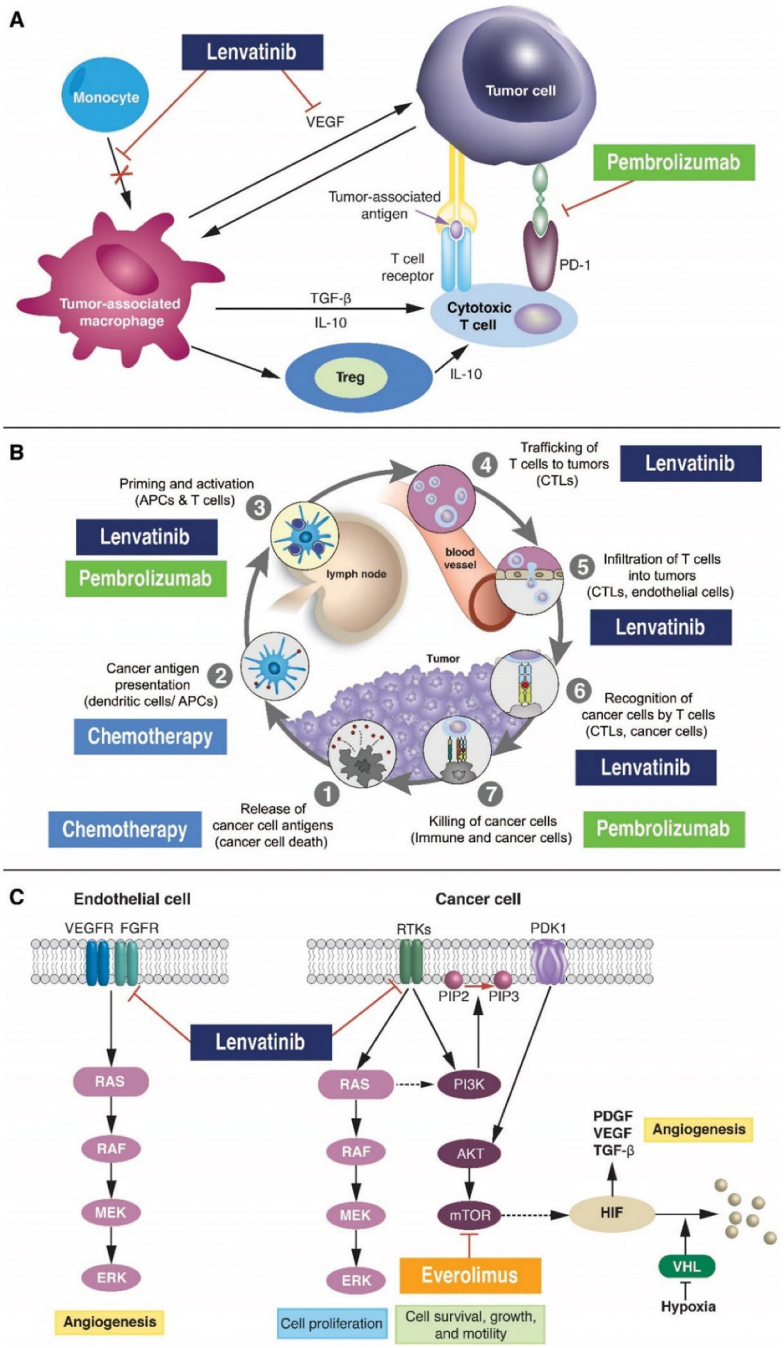

Figure 1.

The mechanisms of action of lenvatinib and its combination therapies[a]: (A) lenvatinib and pembrolizumab; (B) lenvatinib, pembrolizumab, and chemotherapy; (C) lenvatinib and everolimus [21,23,25,30,31,35,36,38]. [a]Figure 1A reprinted from Oncology, Vol number 93, Kudo M, Immuno-Oncology in Hepatocellular Carcinoma: 2017 Update, pages 147–159, 2017, with permission from S. Karger AG, Basel. Figure 1B reprinted from Cell Press, Vol number 39, Chen DS and Mellman I, Oncology Meets Immunology: The Cancer-Immunity Cycle, pages 1–10, 2013, with permission from Elsevier. Figure 1C: Therapeutics & Clinical

Risk Management 2017:13,799–806. Adapted and originally published by and used with permission from Dove Medical Press Ltd.

Table 1.

Studies with lenvatinib dose escalations.

Study (number of patients, tumor type)	Lenvatinib dosing and schedule	Dose; Dose-limiting toxicities (number of patients)	Lenvatinib maximum tolerated dose/ recommended phase II dose	Efficacy outcomes(number of patients)	References
Study 101 (n = 82; solid tumors)	Daily, 28-day cycles 0.2, 0.4, 0.8, 1.6, 3.2, 6.4, 12.5, 16, 20, 25, 32 mg	6.4 mg daily: grade 3 febrile neutropenia (n = 1 of 21) 12.5 mg daily: grade 4 thrombocytopenia (n = 1 of 30) 16 mg daily: grade 3 hypertension and grade 3 fatigue (n = 1 of 30) 32 mg daily: grade 3 proteinuria (n = 2 of 7)	25 mg daily	SD[a]: 46% (n = 38 of 82)	[40]
Study 102 (n = 77; solid tumors, lymphoma, and melanoma)	Schedule 1 (n = 18): twice daily, 7 days on/7 days off 0.1, 0.2, 0.4, 0.8, 1.6, 3.2 mg Schedule 2 (n = 33): twice daily, continuous 3.2, 5.0, 8.0, 12.0 mg Melanoma cohort (n = 26): twice daily, continuous 10 mg	Schedule 1: none Schedule 2, 12 mg twice daily: grade 3 hypertension (n = 3 of 7); grade 3 fatigue (n = 1 of 7); grade 2 proteinuria (n = 1 of 7) Melanoma cohort: none (of 6)	10 mg twice daily	ORR[b]: 11.7% (n = 9 of 77) SD[b]: 51.9% (n = 40 of 77)	[42]
Study 103 (n = 27; solid tumors)	Twice daily, 2-week-on/1-week-off cycle 0.5, 1, 2, 4, 6, 9, 13, 16, 20 mg	16 mg twice daily: grade 3 AST/ALT increase (n = 1 of 3) 20 mg twice daily: grade 3 platelet count decrease (n = 2 of 2)	13 mg twice daily	ORR[a]: 4% (n = 1 of 25) SD[a]: 84% (n = 21 of 25)	[43]
Study 105 (n = 9; solid tumors)	Daily, continuous schedule 20 mg (n = 3) 24 mg (n = 6)	None	–	ORR[c]: 11% (n = 1 of 11) SD[c]: 45.5% (n = 5 of 11)	[41]
Study 202 phase 1 (n = 20; HCC)	CP A (n = 9): 12 mg daily, with escalation to 16 mg daily, then to 20 mg daily CP B (n = 11): lowest tolerable dose from CP A A lower dose level of 8 mg daily was planned for both CP A and CP B if 12 mg daily was not tolerable	12 mg daily (CP A): grade ≤2 fever/vomiting (n = 1 of 6) 16 mg daily (CP A): grade 3 proteinuria (n = 1 of 3); grade 3 hepatic encephalopathy (n = 1 of 3) 12 mg (CP B): grade 3 hepatic encephalopathy (n = 1 of 5); grade 3 increased AST, grade 3 hyperbilirubinemia, grade 2 increased creatinine (n = 1 of 5) 8 mg (CP B): none (of 6)	CP A: 12 mg daily CP B: 8 mg daily	ORR[c] (CP A): 22.2% (n = 2 of 9) SD[c] (CP A): 44.4% (n = 4 of 9) ORR[c] (CP B): 9.1% (n = 1 of 11) SD[c] (CP B): 54.5% (n = 6 of 11)	[54]
Study 205 phase Ib (n = 20; RCC)	12 mg daily (n = 7), 18 mg daily (n = 11), 24 mg daily (n = 2), all + everolimus 5 mg daily	12 mg daily: grade 3 abdominal pain (n = 1 of 7) 18 mg daily: failure to administer >75% of planned dose due to grade 3 elevated creatinine phosphokinase, grade 2 fatigue, and grade 1 reflux (n = 1 of 11) 24 mg daily: grade 3 nausea and vomiting (n = 1 of 2); failure to administer >75% of planned dose due to grade 2 mucosal inflammation (n = 1 of 2)	18 mg daily (with everolimus 5 mg daily)	ORR[c] (12 mg daily): 28.6% (n = 2 of 7) SD[c] (12 mg daily): 57.1% (n = 4 of 7) ORR[c] (18 mg daily): 36.4% (n = 4 of 11) SD[c] (18 mg daily): 45.5% (n = 5 of 11) ORR[c] (24 mg daily): 0% (n = 0 of 2) SD[c] (24 mg daily): 50.0% (n = 1 of 2)	[66]

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Study (number of patients, tumor type)	Lenvatinib dosing and schedule	Dose; Dose-limiting toxicities (number of patients)	Lenvatinib maximum tolerated dose/ recommended phase II dose	Efficacy outcomes(number of patients)	References
Study 111/ KEYNOTE-146 phase Ib/phase II initial expansion (n = 137; solid tumors)	24 mg daily (n = 3), 20 mg daily (n = 134), both + pembrolizumab 200 mg every 3 weeks	24 mg daily: grade 3 arthralgia (n = 1 of 3) and grade 3 fatigue (n = 1 of 3) 20 mg daily: none (of 10)	20 mg daily (with pembrolizumab 200 mg every 3 weeks)	ORR at week 24[d] RCC: 63% (n = 19 of 30) EC: 52% (n = 12 of 23) Melanoma: 48% (n = 10 of 21) SCCHN: 36% (n = 8 of 22) NSCLC: 33% (n = 7 of 21) UC: 25% (n = 5 of 20) SD (overall)[d] RCC: 27% (n = 8 of 30) EC: 44% (n = 10 of 23) Melanoma: 33% (n = 7 of 21) SCCHN: 46% (n = 10 of 22) NSCLC: 48% (n = 10 of 21) UC: 45% (n = 9 of 20)	[61]
LEAP-006 safety run-in (n = 13; NSCLC)	8 mg daily (n = 13), + pembrolizumab 200 mg every 3 weeks + carboplatin or cisplatin and pemetrexed 500 mg/m^2 every 3 weeks × 4 cycles) followed by lenvatinib 8 mg daily (with pembrolizumab 200 mg every 3 weeks [up to 35 cycles] + pemetrexed 500 mg/m^2 every 3 weeks × 4 cycles)	With cisplatin: grade 3 hyponatremia (n = 2 of 6)	8 mg daily (with pembrolizumab 200 mg every 3 weeks + carboplatin or cisplatin and pemetrexed 500 mg/m^2 every 3 weeks × 4 cycles) followed by lenvatinib 8 mg daily (with pembrolizumab 200 mg every 3 weeks [up to 35 cycles] + pemetrexed 500 mg/m^2 every 3 weeks × 4 cycles)	ORR[c]: 69.2% (n = 9 of 13) SD: 23.1% (n = 3 of 13)	[75]

[a] per RECIST

[b] per RECIST (version 1.0)

[c] per RECIST (version 1.1)

[d] per immune-related RECIST.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CP = Child-Pugh; EC = endometrial carcinoma; HCC = hepatocellular carcinoma; NSCLC = non-small cell lung cancer; ORR = objective response rate; RCC = renal cell carcinoma; RECIST = Response Evaluation Criteria In Solid Tumors; SCCHN = squamous cell carcinoma of head and neck; SD = stable disease; UC, urothelial cancer.

Table 2.

Studies with phase II evaluations of lenvatinib.

Study (number of patients, tumor type)	Lenvatinib dosing and schedule	Primary efficacy outcomes	Other outcomes	References
Study 202 (n = 46; HCC)	CP A: 12 mg daily	TTP (median [95% CI]) 7.4 months (5.5–9.4)	ORR (n of n) per mRECIST 37% (17 of 46) OS (median [95% CI]) 18.7 months (12.7–25.1)	[55]
Study 205 (n = 153; RCC)	18 mg daily (n = 51) + everolimus 5 mg daily, 24 mg daily (n = 52) (monotherapy), (everolimus 10 mg daily [n = 50] [monotherapy])	PFS (median [95% CI]) per RECIST version 1.1 Lenvatinib + everolimus: 14.6 months (5.9–20.1) Lenvatinib monotherapy: 7.4 months (5.6–10.2) Everolimus monotherapy: 5.5 months (3.5–7.1) HR 0.40; 95% CI 0.24–0.68; $P = 0.0005$ (lenvatinib + everolimus vs everolimus monotherapy) HR 0.66; 95% CI 0.39–1.10; $P = 0.12$ (lenvatinib + everolimus vs lenvatinib monotherapy)	ORR (n of n) per RECIST version 1.1 Lenvatinib + everolimus: 43% (22 of 51) Lenvatinib monotherapy: 27% (14 of 52) Everolimus monotherapy: 6% (3 of 50) OS (median [95% CI]) Lenvatinib + everolimus: 25.5 (16.4–NE) Lenvatinib monotherapy: 19.1 (13.6–26.2) Everolimus monotherapy: 15.4 (11.8–19.6)	[9]
Study 111/KEYNOTE-146 (phase II expansion) (n = 108; previously treated EC)	20 mg daily + pembrolizumab 200 mg every 3 weeks	ORR at week 24 (n of n; 95% CI) per irRECIST MSS/pMMR: 36.2% (34 of 94; 26.5–46.7) MSI-H/dMMR: 63.6% (7 of 11; 30.8–89.1) Overall: 38.0% (41 of 108; 28.8–47.8)	Overall PFS (median [95% CI]) per irRECIST 7.4 months (53–8.7) Overall OS (median [95% CI]) 16.7 months (15.0–NE)	[63]
Study 111/KEYNOTE-146 (phase II expansion) (n = 143; RCC)	20 mg daily + pembrolizumab 200 mg every 3 weeks	ORR at week 24 (n of n; 95% CI) per irRECIST Treatment naïve: 72.7% (16 of 22; 49.8–89.3) Previously treated, ICI-naïve: 41.2% (7 of 17; 18.4–67.1) ICI pretreated: 55.8% (58 of 104; 45.7–65.5)	PFS (median [95% CI]) per irRECIST ICI pretreated: 12.2 months (9.5–17.7) OS (median [95% CI]) ICI pretreated: NR (NR-NR)	[65]
REMORA (Japan) (n = 42; unresectable thymic carcinoma)	24 mg daily in 4-week cycles	ORR (n of n; 90% CI) per RECIST version 1.1 38% (16 of 42; 25.6–52.0)	Overall PFS (median [95% CI]) per RECIST version 1.1 9.3 months (7.7–13.9) Overall OS (median [95% CI]) NR (16.1-NR)	[60]
Dose-comparison studies **Study 211** (n = 152; RR-DTC) (Data on file, Eisai Inc.)	24 mg daily (n = 75), 18 mg daily (n = 77)	ORR at week 24 (n of n; 95% CI) per RECIST version1.1[a] 18 mg: 40.3% (31 of 77; 29.3–51.2) 24 mg: 57.3% (43 of 75; 46.1–68.5) Odds ratio 0.50 (95% CI 0.26–0.96)	Overall ORR (n of n) per RECIST version 1.1 18 mg: 46.8% (36 of 77) 24 mg: 64% (48 of 75) PFS[b] (median [95% CI]) per RECIST version 1.1 18 mg: 24.4 months (14.7–NE) 24 mg: NR (22.1-NE) HR (18 mg vs 24 mg) 1.44 (95% CI 0.76–2.74) Stratified[c] log-rank $P = 0.2648$ OS (median [95% CI]) NR (NE) for both arms HR (18 mg vs 24 mg) 1.26 (95% CI 0.55–2.89) Stratified[c] log-rank $P = 0.5867$	[59]
Study 218 (n = 311; RCC) (Data on file, Eisai Inc.)	14 mg (n = 156), 18 mg (n = 155), Both + everolimus 5 mg daily	ORR at week 24 (n of n; 95% CI) per RECIST version 1.1[d] 14 mg: 32.1% (50 of 156; 24.7–39.4) 18 mg: 34.8% (54 of 155; 27.3–42.3)	Overall ORR (n of n) per RECIST version 1.1 14 mg: 34.6% (54 of 156) 18 mg: 40.6% (63 of 155) PFS[e]	[67]

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Study (number of patients, tumor type)	Lenvatinib dosing and schedule	Primary efficacy outcomes	Other outcomes	References
		Odds ratio 0.88 (95% CI 0.59–1.32); *P* (1-sided) = 0.2676	(median, 95% CI) per RECIST version 1.1 14 mg: 11.1 months (9.0–12.9) 18 mg: 14.7 months (11.1–20.3) HR[f] (14 mg vs 18 mg) 1.42 (95% CI 1.08–1.86) OS (median [95% CI]) 14 mg: 27.0 months (18.3–NE) 18 mg: NE (23.8-NE) HR[f] (14 ma vs 18 ma) 1.20 (95% CI 0.87–1.65)	

[a] Noninferiority margin is 0.4 based on odds ratio. Noninferiority could be claimed if the lower bound of the 95% CI of odds ratio for ORR at week 24 of treatment (18 mg/24 mg daily doses) > 0.4.

[b] The primary safety endpoint was TEAEs of grade ≥3 in the first 24 weeks after randomization (24 mg arm: 61.3%; 18 mg arm: 57.1%). Most common TEAEs: 24 mg arm: hypertension (57.3%), diarrhea (56.0%), weight decreased (36.0%); 18 mg arm: hypertension (51.9%), diarrhea (51.9%), weight decreased (42.9%). Discontinuation of lenvatinib due to TEAEs: 24 mg dose: 14.7%; 18 mg dose: 16.9%. Reduction of lenvatinib due to TEAEs: 24 mg dose: 69.3%; 18 mg dose: 59.7%.

[c] Stratified by the randomization stratification factors (ECOG PS: 0 vs 1 or 2; age group: ≤65 vs >65 years).

[d] Noninferiority margin is 0.76 based on odds ratio of objective response rate at week 24. Noninferiority could be claimed if the *P* (1-sided) < 0.045 for noninferiority testing of odds ratio for ORR at week 24 (14 mg/18 mg daily doses) after adjusting for 2 interim analyses. Analysis included patients in the per-protocol analysis set 1.

[e] The primary safety endpoint was intolerable grade 2 or any grade ≥3 TEAEs within 24 weeks of randomization (18 mg arm: 79.6%; 14 mg arm: 82.8%). Most common TEAEs: 18 mg arm: diarrhea (72.0%), hypertension (35.7%), proteinuria (35.7%); 14 mg arm: diarrhea (68.2%), decreased appetite (35.3%), stomatitis (34.1%).

[f] Stratified by MSKCC prognostic group and prior PD-1/PD-L1 treatment from IxRS data. For MSKCC prognostic group from IxRS, the poor risk group is pooled with the intermediate risk group in the model. Hazard ratio of lenvatinib 14 mg over lenvatinib 18 mg was based on a Cox Proportional Hazard Model including treatment group as a factor, Efron method is used for ties.

CI = confidence interval; CP = Child-Pugh; dMMR = mismatch repair-deficient; EC = endometrial carcinoma; ECOG PS = Eastern Cooperative Oncology Group performance status; HCC = hepatocellular carcinoma; HR = hazard ratio; ICI = immune checkpoint inhibitor; irRECIST = immune-related RECIST; IV = intravenously; IxRS = Interactive Voice/Web Response System; mRECIST = modified RECIST; MSI-H = high levels of microsatellite instability; MSKCC = Memorial Sloan Kettering Cancer Center; MSS = microsatellite stable; MTD = maximum tolerated dose; NE = not estimable; NR = not reached; ORR = objective response rate; OS = overall survival; PD-1, programmed cell death-1; PD-L1, programmed cell death ligand-1; PFS = progression-free survival; pMMR = mismatch repair-proficient; RCC = renal cell carcinoma; RECIST = Response Evaluation Criteria In Solid Tumors; RR-DTC = radioiodine-refractory differentiated thyroid carcinoma; TEAE = treatment-emergent adverse event; TTP = time to progression.

Table 3.

Most common adverse events and dose modifications of lenvatinib in selected studies.

Study	Tumor type and population	Lenvatinib dosing and schedule	Most common TEAEs or TRAEs	Lenvatinib discontinuations due to TEAEs/TRAEs (%)	Lenvatinib dose reductions/ interruptions (%)	Median time to dose reductions	References
Study 111/ KEYNOTE-146	RCC (n = 30); EC (n = 23); SCCHN (n = 22); Melanoma (n = 21); NSCLC (n = 21); UC (n = 20)	24 mg daily (n = 3) 20 mg daily (n = 134) *In combination with pembrolizumab 200 mg every 3 weeks*	TRAEs Fatigue (58%) Diarrhea (52%) Elypertension (47%)	13% (due to TRAEs)	85% (reduction or interruption due to TRAEs)	~2 months	[61,63,65]
	EC expansion (n = 108)	*20 mg daily In combination with pembrolizumab 200 mg every 3 weeks*	TRAEs Hypertension (61.1%) Diarrhea (52.8%) Fatigue (51.9%)	–	–	–	
	RCC expansion (n = 145)	*20 mg daily In combination with pembrolizumab 200 mg every 3 weeks*	TRAEs Fatigue (58.6%) Diarrhea (55.2%) Hypertension (40.0%)	13% (due to TRAEs)	65.0% (reduction due to TRAEs)	2.2 months (interquartile range 1.4–5.2)	
Study 205	RCC (n = 51, lenvatinib + everolimus; n = 52, lenvatinib monotherapy)	18 mg daily *In combination with everolimus 5 mg daily*	TEAEs Diarrhea (84.3%) Decreased appetite (51.0%) Fatigue/asthenia (58.8%)	24% (due to TEAEs)	71% (reduction)	First reduction within the first 3 cycles: 49%	[9]
		24 mg daily (monotherapy)	TEAEs Diarrhea (71.2%) Decreased appetite (61.5%) Fatigue/asthenia (57.7%)	24% (due to TEAEs)	71% (reduction)	First reduction within the first 3 cycles: 38%	
Study 303	RR-DTC (n = 261)	24 mg daily	TRAEs Elypertension (67.8%) Diarrhea (59.4%) Fatigue/asthenia (59.0%)	14.2% (due to TEAEs)	67.8% (reduction) 82.4% (interruption)	3.0 months (95% CI 27–3.7)	[3]
Study 304	uHCC (n = 476)	12 mg daily (patients ≥ 60 kg) 8 mg daily (patients < 60 kg)	TEAEs Elypertension (42%) Diarrhea (39%) Decreased appetite (34%)	9% (due to TRAEs)	37% (reduction due to TRAEs) 40% (interruption due to TRAEs)	–	[4]
Study 309/ KEYNOTE-775	EC (n = 406, lenvatinib + pembrolizumab population only)	20 mg daily *In combination with pembrolizumab 200 mg IV every 3 weeks*	TEAEs Elypertension (64.0%) Elypothyroidism (57.4%) Diarrhea (54.2%)	30.8% (due to TEAEs)	66.5% (reduction due to TEAEs) 58.6% (interruption due to TEAEs)	1.9 months (range 0.1–22.8)	[8]
Study 307/ KEYNOTE-581	RCC (n = 352, lenvatinib + pembrolizumab population only)	20 mg daily *In combination with pembrolizumab 200 mg IV every 3 weeks*	TEAEs Diarrhea (61.4%) Elypertension (55.4%) Elypothyroidism (47.2%)	25.6% (due to TEAEs)	68.8% (reduction due to TEAEs)	–	[6]

AE = adverse event; CI = confidence interval; EC = endometrial carcinoma; IV = intravenously; NSCLC = non-small cell lung cancer; RCC = renal cell carcinoma; RR-DTC = radioiodine-refractory differentiated thyroid carcinoma; SCCHN = squamous cell carcinoma of the head and neck; TEAE = treatment-emergent adverse event; TRAE = treatment-related adverse event; UC = urothelial cancer; uHCC = unresectable hepatocellular carcinoma.

Table 4.

Phase III trials of lenvatinib as monotherapy or combination therapy.

Study (N)	Tumor type	Regimens	Progression-free survival Median, months (95% CI)	Overall survival Median, months (95% CI)	Objective response rate % (n of n)	References
SELECT (Study 303, N = 392)	RR-DTC	Lenvatinib 24 mg daily or placebo	Lenvatinib[a]: 18.3 (15.1-NE) Placebo[a]: 3.6 (2.2–3.7) HR (lenvatinib vs placebo) 0.21 (99% CI 0.14–0.31); $P < 0.001$	Lenvatinib: NR Placebo: NR HR (lenvatinib vs placebo) 0.73 (95% CI 0.50–1.07); $P = 0.10$[b]	Lenvatinib[a]: 64.8% (169 of 261) Placebo[a]: 1.5% (2 of 131) Odds ratio (lenvatinib vs placebo) 28.87 (95% CI 12.46–66.86); $P < 0.001$	[3]
REFLECT (Study 304, N = 954)	uHCC	Lenvatinib 12 mg daily (≥ 60 kg) 8 mg daily (< 60 kg) or sorafenib 400 mg twice daily	Lenvatinib[c]: 7.4 (6.9–8.8) Sorafenib[c]: 3.7 (3.6–4.6) HR (lenvatinib vs sorafenib) 0.66 (95% CI 0.57–0.77); Log-rank $P < 0.0001$	Lenvatinib: 13.6 (12.1–14.9) Sorafenib: 12.3 (10.4–13.9) HR (lenvatinib vs sorafenib) 0.92 (95% CI 0.79–1.06)	Lenvatinib[c]: 24.1% (115 of 478) Sorafenib[c]: 9.2% (44 of 476) Odds ratio (lenvatinib vs sorafenib) 3.13 (95% CI 2.15–4.56); $P < 0.0001$	[4]
CLEAR (Study 307/ KEYNOTE-581, N = 1069)	aRCC	Lenvatinib 20 mg daily + pembrolizumab 200 mg every 3 weeks or Lenvatinib 18 mg daily + everolimus 5 mg daily or sunitinib 50 mg daily (4 weeks on/2 weeks off)	Lenvatinib + pembrolizumab[a]: 23.9 (20.8– 27.7) Lenvatinib + everolimus[a]: 14.7 (11.1–16.7) Sunitinib[a]: 9.2 (6.0–11.0) HR (lenvatinib + pembrolizumab vs sunitinib): 0.39 (95% CI 0.32–0.49); $P < 0.001$	Lenvatinib + pembrolizumab: NR (33.6–NE) Lenvatinib + everolimus: NR (NE-NE) Sunitinib: NR (NE-NE) HR (lenvatinib + pembrolizumab vs sunitinib): 0.66 (95% CI 0.49–0.88); $P = 0.005$	Lenvatinib + pembrolizumab[a]: 71.0% Lenvatinib + everolimus[a]: 53.5% Sunitinib: 36.1% Relative risk (lenvatinib + pembrolizumab vs sunitinib): 1.97 (95% CI 1.69–2.29)	[6]
Study 309/ KEYNOTE-775 (N = 827)	aEC	Lenvatinib 20 mg daily + pembrolizumab 200 mg every 3 weeks or chemotherapy (doxorubicin 60 mg/m^2 every 3 weeks or paclitaxel 80 mg/m^2 every week (3 weeks on/1 week off)	<u>All patients (irrespective of MMR status)</u> Lenvatinib + pembrolizumab[d]: 7.2 (57–7.6) Chemotherapy[a]: 3.8 (3.6–4.2) HR (lenvatinib + pembrolizumab vs chemotherapy) 0.56 (95% CI 0.47–0.66); $P < 0.001$ <u>pMMR group</u> Lenvatinib + pembrolizumab[a]: 6.6 (5.6–7.4) Chemotherapy[a]: 3.8 (3.6–5.0) HR (lenvatinib + pembrolizumab vs chemotherapy) 0.60 (95% CI 0.50–0.72); $P < 0.001$	<u>All patients (irrespective of MMR status)</u> Lenvatinib + pembrolizumab: 18.3 (15.2–20.5) Chemotherapy: 11.4 (10.5–12.9) HR (lenvatinib + pembrolizumab vs chemotherapy) 0.62 (95% CI 0.51–0.75); $P < 0.001$ <u>pMMR group</u> Lenvatinib + pembrolizumab: 17.4 (14.2–19.9) Chemotherapy: 12.0 (10.8–13.3) HR (lenvatinib + pembrolizumab vs chemotherapy) 0.68 (95% CI 0.56–0.84); $P < 0.001$	<u>All patients (irrespective of MMR status)</u> Lenvatinib + pembrolizumab[a]: 31.9% Chemotherapy[a]: 14.7% <u>pMMR group</u> Lenvatinib + pembrolizumab[a]: 30.3% Chemotherapy[a]: 15.1%	[8]
LEAP-006 (N = 13) *d*	NSCLC	Lenvatinib 8 mg daily or matching placebo, all + pembrolizumab 200 mg every 3 weeks + carboplatin or cisplatin and pemetrexed 500	Not available	Not available	Not available	[75]

Study (N)	Tumor type	Regimens	Progression-free survival Median, months (95% CI)	Overall survival Median, months (95% CI)	Objective response rate % (n of n)	References
		mg/m^2 every 3 weeks × 4 cycles followed by lenvatinib 8 mg daily + pembrolizumab 200 mg every 3 weeks (up to 35 cycles) + pemetrexed 500 mg/m^2 every 3 weeks × 4 cycles				

[a] Per RECIST version 1.1.

[b] When a potential crossover bias was considered, the median OS was not reached for both arms and adjusted HR was 0.62 (95% CI 0.40–1.00); $P = 0.05$.

[c] investigator review per mRECIST.

[d] Enrollment is ongoing for Part 2. Data from the safety run-in (Part 1) is included in Table 1.

aEC = advanced endometrial carcinoma; aRCC = advanced renal cell carcinoma; CI = confidence interval; HR = hazard ratio; MMR = mismatch repair; mRECIST; modified RECIST; NE = not estimable; NR = not reached; NSCLC = non-small cell lung cancer; pMMR = mismatch repair-proficient; RECIST = Response Evaluation Criteria In Solid Tumors; RR-DTC = radioiodine-refractory differentiated thyroid carcinoma; SD = standard deviation; uHCC = unresectable hepatocellular carcinoma.