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Lenvatinib in Management of Solid Tumors

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

Abstract. Lenvatinib is a type I tyrosine kinase inhibitor exhibiting powerful antiangiogenic activity in cancer therapy. Displaying activity in multiple solid tumors, it has been approved in differentiated thyroid cancer, hepatocellular carcinoma, and renal cell carcinoma as single agent or in combination. In addition, lenvatinib has shown promise in several other tumor types including medullary, anaplastic thyroid, adenoid cystic, and endometrial cancer. Exploring synergy between angiogenic and immune checkpoint inhibitors, the lenvatinib/pembrolizumab combination is poised to become the next pair of active drugs in endometrial, lung, and gastrointestinal malignancies. Despite robust activity, the drug can be difficult to tolerate. Optimization of dose and biomarkers for prediction of efficacy and toxicities will be of great help. *The Oncologist* 2020;25:e302–e310

Implications for Practice: Readers will be presented with an update on U.S. Food and Drug Administration approval of lenvatinib and suggestions for off-label use in thyroid cancer and adenoid cystic carcinomas. They will become familiarized with the common side effects, frequency, and predicators of response. In addition, they will learn that different strengths of lenvatinib are prescribed and why. Finally, readers are pointed to the latest efforts to combine lenvatinib and pembrolizumab, as well as to unresolved issues such as long-term side effects/toxicities of this drug.

INTRODUCTION

Tyrosine kinases (TKs) are key regulators of cell function and constitute a large and functionally diverse group of family members sharing a conserved kinase domain. By adding a phosphate group from adenosine triphosphate (ATP) to the tyrosine residue on their substrate(s), TKs change the substrates activity, localization, and interaction with many other proteins [1, 2]. They are intimately involved in numerous cellular processes such as angiogenesis and cell cycle control [3, 4]. TKs are critical components of the cell signaling pathway, and their activities are strictly regulated. Aberrant activity of TKs has been linked to many disease states, including cancer; therefore, tyrosine kinase inhibitors (TKIs) are perhaps best studied in cancer. Starting from the success of imatinib for the treatment of chronic myeloid leukemia, TKIs are successively tested and introduced into the treatment of patients with cancer with remarkable improvement of cancer outcome [5, 6]. Here we review the discovery, development, clinical testing, and regulatory approval of the TKI lenvatinib (also known as E7080) with affinity to multiple receptor TKs (RTK). We also review the hurdles to compliance and highlight its future potential in the management of other solid tumors that are not currently approved.

Lenvatinib was initially reported in 2008 as a multi-targeted RTK inhibitor capable of inhibiting multiple kinases in nanomole concentration (half maximal inhibiting concentration (IC50) 4–100 nM) [7]. In animal experiments, lenvatinib potently inhibited angiogenesis, causing tumors to regress in mouse model. Further testing in a breast cancer model revealed it suppressed breast cancer metastasis to the lymph nodes and to the lungs by targeting vascular endothelial growth factor receptor (VEGFR) 3 during angiogenesis and lymphangiogenesis [8]. Activities were also shown in an orthotopic malignant mesothelioma mouse model, which is known to respond to angiogenesis inhibitor. Lenvatinib significantly prolonged the survival of mice injected with three mesothelioma cell lines [9] and mice carrying sarcoma xenograft [10]. Lenvatinib was further developed as an orally available TKI in solid tumor (see below).

Lenvatinib functions as an inhibitor to multiple RTKs. The IC50s to VEGF1–3 kinases assayed ranged from 2.3 to 4.7 nM, fibroblast growth factor receptor (FGFR) 1–4, 27–61 nM,

platelet-derived growth factor (PDGFR) α, β 29–39 Nm, and v-Kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog (KIT) 85 nM. In contrast, lenvatinib did not inhibit epidermal growth factor receptor (EGFR; IC50 6,500 nM) or other kinases such as Src or cyclin-dependent kinase 4 (all >10,000 nM) [7, 11]. In a mouse model of EGFR wild-type lung cancer, lenvatinib suppressed endothelial and lymph epithelial growth and decreased the numbers of lung nodules and metastatic foci [12]. Using a mouse model of human osteosarcoma, it was shown that lenvatinib did not have a big impact on tumor cell proliferation. However, it had profound effects on tumor cell migration and invasion, likely through suppressing FGFR and PDGFR because PDGFRβ-negative cell line was not affected by the drug. Knockdown of PDGFRβ had also inhibited tumor cell migration [13]. A kinetic interaction analysis of lenvatinib with VEGFR2 (KDR) and x-ray analysis of the crystal structure of VEGFR2-lenvatinib complexes showed a rapid association constant and relatively slow dissociation rate. Lenvatinib binds at its ATP mimetic moiety to the ATP binding site and neighboring region of VEGFR2 in a unique way different from several other known VEGFR2 TKIs such as sorafenib and sunitinib [14]. Lenvatinib is therefore a type I TKI [15].

Lenvatinib is rapidly absorbed and typically reaches its maximal concentration between 1 and 4 hours in healthy volunteers or patients with solid tumors after oral ingestion [16, 17]. The absorption followed a first- and zero-order kinetics not affected by elevated pH in the stomach. The absorption in patients with solid tumors followed a dose-dependent linear pharmacokinetic with no drug accumulation after once-daily doses (maximum concentration after multiple doses were the same as those after a single dose) [18]. The relative bioavailability in capsule form was 90%. Population pharmacokinetics analysis of 779 subjects with preserved liver function who received between 3.2 and 32 mg of oral lenvatinib once-daily dose confirmed a three-compartment model of linear elimination. The population mean value for lenvatinib apparent clearance as a function of bioavailability (CL/F) was 6.51 Liter/hour and was independent of dose or time. None of the factors including dose, sex, race, age, performance, renal function, or thyroid function (by thyroid-stimulating hormone) had any significant effects on CL/F. However, after the same dose, patients with lower body weight had higher steady-state concentration and 90% prediction intervals compared with those with a higher body weight, and those who were getting CYP3A4 inhibitors also had slightly higher steady-state concentration. Although lower albumin and high alkaline phosphatase increases drug exposure, none of them were clinically relevant to justify dose adjustment. To test how liver function affects pharmacokinetics of lenvatinib, patients with mild to moderate or severe liver impairment were compared with patients with normal hepatic function. Although mild to moderate liver function impairment had no clinically meaningful effects on lenvatinib pharmacokinetics, patients with severe liver dysfunction had area under the curve (AUC) increased to 170% and $T_{1/2}$ increase from 23 hours to 37 hours. It was recommended that patients with severe liver impairment start lenvatinib at 14 mg instead of 24 mg [19]. After a dose of 24 mg of C^{14} labeled lenvatinib, radioactivity peaked after 1.6 hours; lenvatinib remained mostly intact at the peak concentration and was 700 times higher than metabolites. After 10 days, recovery was 64% ± 11% in the feces and 25% ± 18% in the urine (89% recovery of administered dose). Lenvatinib is dosed differently in different cancer, according to body weight or whether it is in combination with another agent (see below for dosing considerations) [20].

Lenvatinib Use and Approval in Solid Tumors

Differentiated Thyroid Cancer

Initially, in a phase II trial enrolling 58 patients, lenvatinib showed robust activity in advanced, radiation-refractory differentiated thyroid cancer (RR-DTC; papillary, follicular, or Hurthle cell). The overall response rate (ORR) was 50%, lower in patients who had received one line of VEGFR inhibitor and higher in those who were naïve (41% vs. 54%). Median progression-free survival (PFS) was 12.6 months and median duration of response was 12.7 months. The toxicities were manageable [21].

Interestingly, molecular profiling revealed that patients who carried a RAS (rat sarcoma virus) mutation (KRAS or NRAS), which were present in 35% of all patients, had 100% response rate and significantly improved PFS (80% at 14 months vs. 20% in wild-type RAS group) [22].

Based on the above, the SELECT trial, a phase III study of lenvatinib [23], was conducted in the RR-DTC population with radiographic progression within the prior 12 months. Patients received 24 mg once daily of lenvatinib or placebo in a 28-day cycle at a 2:1 ratio in this trial enrolling a total of 392 (261:131) patients across 23 countries. Again, one line of prior anti-VEGFR therapy was allowed. Crossover from placebo was also allowed. Enrollment was completed after 3 years. At the end, the study met its primary endpoint: PFS. The median PFS was 18.3 months in the lenvatinib group compared with 3.6 months in the placebo group (hazard ratio [HR] 0.21; 99% confidence interval [CI] 0.14–0.31; $p < .001$). The benefit was across all prespecified subgroups. Complete response (CR) plus partial response (PR) was 64.8% versus 1.5% in the placebo ($p < .001$). The median overall survival was not reached in either group. Toxicities were manageable but significant. Discontinuation of drug occurred in 37 patients (14.2%) in the lenvatinib and 3 (2.3%) in the placebo group. Treatment-related adverse effects (AEs) occurred in more than 40% of the patients. They included hypertension (67.8%), diarrhea (59.4%) fatigue or asthenia (59%), decreased appetite (50.2%), decreased weight (46.4%), and nausea (41%). Of the 20 deaths that occurred during treatment, 6 were considered treatment related. Lenvatinib was subsequently approved by the U.S. Food and Drug Administration (FDA) for treatment of RR-DTC in August 2015 [24].

Medullary Thyroid Carcinoma

Lenvatinib inhibited rearranged during transfection (RET) kinase activity in early studies [7, 11]. Lenvatinib was active inhibiting RET fusion protein driven tumor in animal models [25]. Based on early indication of activity in thyroid cancer,

lenvatinib was tested in a phase II trial enrolling 59 patients with advanced medullary thyroid carcinoma who were unresectable or metastatic in the prior 12 months [26]. Prior use of anti-VEGF was allowed. ORR of lenvatinib was 36%, all of which were partial. Disease control rate (DCR) was 80%. ORR was comparable between patients who received (35%) or did not receive (36%) anti-VEGF therapy. Among the responders, median PFS was 9.0 months. Grade 3 and 4 (G3/4) AEs included diarrhea (14%), hypertension (7%), decreased appetite (7%), fatigue, and dysphagia. Although 67% of patients harbored a RET mutation (M918T or C634R), the presence of a RET mutation did not correlate with response. In contrast, lower levels of angiopoietin-2 were associated with greater tumor reduction and prolonged PFS. Lenvatinib is not approved by the FDA.

Anaplastic Thyroid Carcinoma

Anaplastic thyroid carcinomas (ATCs) are rare compared with other thyroid cancers but chart a very aggressive course. These cancers are treated aggressively with surgery and chemoradiation. However, 1-year survival is only 20%–40% [27–29]. In 2018, the FDA granted approval for dabrafenib and trametinib combination in ATC with V600E mutation, which are present in 20%–50% of all ATCs [30–32], based on an open-labeled trial in these patients. Of the 23 evaluable patients treated with the drug combo, PR and CR were 57% and 4%, respectively. Of the 14 patients who had response, 64% had no significant growth of tumor for 6 months or longer. Better treatment options are needed for this deadly cancer. Lenvatinib has been studied in ATCs and has been approved for use in patients with ATCs in Japan since 2015 [33].

In one retrospective study of lenvatinib [34], three of the five unresectable patients who were given lenvatinib had PR. Time to progression (TTP) was 88 days. Four patients had hypothyroidism. Other AEs included hypertension, diarrhea, fatigue, and decreased appetite.

In another retrospective study [33], a total of 23 patients were enrolled. They were evaluated for overall survival (OS). Ten patients were able to receive surgical debulking first; the remaining 13 were not. All were then started on lenvatinib as life-saving measures. ORR was 17.4% and DCR was 43.5%. Of the patients treated, 100% had AEs. Hypertension developed in 91.3%, and 39.1% had G3 or above toxicities. Ten patients had tumor fistula, and 9 of 23 discontinued drug because of G3 toxicities. OS was 166 days. Lenvatinib seemed active in ATC, and tumor fistula management was crucial for survival.

In a phase II, single-arm, open-labeled prospective study of lenvatinib in thyroid cancer, 17 patients with ATC were enrolled and received 24 mg once daily until disease progression or unacceptable toxicity. The median PFS was 7.4 months (95% CI 1.7–12.9). Median OS was 10.6 months (95% CI 3.8–19.8) with an ORR of 24% and DCR of 88%. Treatment-emergent adverse events (TEAEs) were present in all participants. The most frequent TEAEs were decreased appetite (82%), hypertension (82%), fatigue (59%), and proteinuria (59%). One patient required withdrawal that was not related to study drug [35]. In support of the lenvatinib efficacy in patients with ATCs, genetic analysis of 196 advanced ATCs by either Foundation One or Memorial Sloan Kettering-IMPACT gene panels revealed the following: (a) ATCs have accumulated more gene mutations per tumor compared with DTCs owing to DNA mismatch repair defects and apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like cytidine deaminase activity in a subset of ATCs; and (b) amplification of receptor kinase KDR (VEGFR2), KIT, and PDGFRα, which are all targets of lenvatinib [36]. In another report, 12 patients with ATCs treated with lenvatinib were analyzed for response and tumor expression of VEGFR2, a known target of lenvatinib. It was found that 4 of the 12 had PR, 3 had stable disease (SD), and 5 had progressive disease (PD). Interestingly, none of the responders or SD expressed VEGFR2 [37].

Hepatocellular Carcinoma

In a phase I study of 20 patients with hepatocellular carcinoma (HCC) with liver function as Child-Pugh A (CP-A, score 5–6) and Child-Pugh B (CP-B, score 7–8), 12 mg of lenvatinib once daily was given to CP-A and 8 mg to CP-B; this resulted in PR in 3 patients and 14 patients with any degree of tumor shrinkage [38].

The first phase II trial of lenvatinib in HCC was conducted in Japan and South Korea [39]. In this trial, lenvatinib 12 mg once daily in a 28-day cycle was given to patients with HCC who did not qualify for local therapies [39]. A total of 46 patients were enrolled. All but one was CP-A. PR was seen in 37% of the patients. With SD seen in 41% of patients, the DCR was 78%. Median OS was 18.7 months and TTP was 7.4 months. The most common AEs were hypertension (76%), palmar-plantar erythrodysesthesia syndrome (PPES; 65%), decreased appetite (61%), and proteinuria (61%). Seventy-four percent was dose reduced with 22% drug discontinuation.

The pivotal trial REFLECT sought to compare lenvatinib with the then–standard of care agent sorafenib for unresectable HCC in a noninferiority design [40]. Patients were deemed unresectable owing to either macroscopic portal vein invasion or extrahepatic spread or both. A total of 154 sites across 20 countries were involved, enrolling 954 eligible patients. Lenvatinib (n = 478) 12 mg (>60 kg of body weight) or 8 mg once daily (<60 kg) or sorafenib (n = 476) 400 mg twice a day were given to these patients in a 28-day cycle. The study met its noninferiority goal with set margin of 1.08. Hazard ratio was 0.92 (CI 0.79–1.06). Median OS was 13.6 months in the lenvatinib arm and 12.3 months in the sorafenib arm. The REFLECT trial also demonstrated a statistically significant improvement in PFS with lenvatinib as compared with sorafenib. Median PFS was 7.3 months in the lenvatinib arm and 3.6 months in the sorafenib arm (HR 0.64; 95% CI 0.55–0.75; p < .001). Common AEs for lenvatinib included hypertension (42%), diarrhea (39%), decreased appetite (34%), and decreased body weight (31%). Commonly seen in patients receiving sorafenib were PPES (52%), diarrhea (46%), hypertension (30%), and decreased appetite (27%). In addition, lenvatinib demonstrated a significantly higher ORR of 24% compared with 9% for sorafenib (odds ratio 3.13; 95% CI 2.15–4.56; p < .001). Based on these data, the FDA approved lenvatinib use in the first-line settings for unresectable HCC [41].

Renal Cell Carcinoma

In a phase I study [42], lenvatinib showed encouraging activity in kidney cancer. Median PFS was more than 500 days. Another phase I study also revealed response in kidney cancer [43]. Subsequently, a phase Ib study showed that lenvatinib at 12 mg or 18 mg (maximum tolerated dose [MTD]) in combination with 5 mg of everolimus given to unresectable or metastatic renal cell carcinoma (RCC) yielded a best of response of 83% (n = 18), PR 33% and SD 50% [44]. A randomized, phase II, open-label, multicenter trial [45] was performed at 37 centers in five countries, enrolling patients with advanced clear-cell RCC. Patients who had received treatment with a VEGF-targeted therapy and progressed on or within 9 months were included. Patients were randomized in a 1:1:1 ratio to receive lenvatinib (24 mg/day), everolimus (10 mg/day), or lenvatinib and everolimus (18 mg/day and 5 mg/day) in 28-day cycles until disease progression or unacceptable toxicity. The primary objective was PFS in the intention-to-treat population. In a little over 15 months, 153 patients were allocated to receive lenvatinib plus everolimus (n = 51), single-agent lenvatinib (n = 52), or single-agent everolimus (n = 50). Lenvatinib plus everolimus significantly prolonged PFS over everolimus alone (median 14.6 months vs. 5.5 months; HR 0.40; 95% CI 0.24–0.68; p = .0005). However, lenvatinib plus everolimus was not significantly different from lenvatinib alone (PFS 7.4 months; HR 0.66; 95% CI 0.30–1.10; p = .12). Single-agent lenvatinib significantly prolonged PFS compared with everolimus alone (HR 0.61; 95% CI 0.38–0.98; p = .048). G3 and 4 events were less common in patients allocated single-agent everolimus (50%) compared with those assigned to lenvatinib alone (79%) or lenvatinib plus everolimus (71%). The most common G3/4 treatment-emergent adverse event in patients allocated to lenvatinib plus everolimus was diarrhea (20%); in those assigned single-agent lenvatinib, it was proteinuria (19%); and in those assigned single-agent everolimus, it was anemia (12%). Two deaths occurred during treatment, one cerebral hemorrhage in the lenvatinib plus everolimus group and one myocardial infarction with single-agent lenvatinib, both deemed related to the study drug. Based on this trial, the FDA approved the combination of 18 mg of lenvatinib and 5 mg of everolimus once daily as a second-line treatment for patients with clear-cell RCC who have progressed after one previous VEGF-targeted therapy [46].

Adenoid Cystic Carcinoma

In a phase II study reported recently [47], 33 patients with recurrent and metastatic adenoid cystic carcinoma with radiographic progression or symptoms were treated with 24 mg of lenvatinib once daily. The primary endpoint for the study was ORR, and the secondary endpoints were PFS, toxicity, Myb expression, and genomic alteration. Of the 32 patients evaluable, 5 had PR (15.6%), 24 had SD (75%), 2 were discontinued (3.1%) and 1 had PD (1.5%). Median PFS was 17.5 months. In all, 23 patients needed dose modification and 18 patients were discontinued. The most common G3/4 toxicities were hypertension (n = 9, 28.1%) and oral pain (n = 3, 9.4%). There were three G4 toxicities: one myocardial infarction, one intracranial hemorrhage, and one posterior reversible encephalopathy syndrome. This study met its primary endpoint, and lenvatinib showed activity in these patients with side effects comparable to previous studies. Currently, lenvatinib is not approved for this indication.

DOSING CONSIDERATIONS

Lenvatinib tolerability and toxicity were tested alone or in combination in different tumor types in multiple phase I trials. In patients with toxicities, dose modification ensues.

The first phase I trial in 27 patients [48] was performed in solid tumors in a 2-weeks-on, 1-week-off schedule. Starting at 0.5 mg b.i.d., the dose went up to 13, 16, and 20 mg b.i.d. During cycle 1, no G3 or 4 toxicities were observed in patients receiving up to 13 mg b.i.d. Dose-limiting toxicities (DLTs) appeared when patients were given higher doses. They included G3 increase in aspartate aminotransferase/alanine aminotransferase in one patient at 16 mg b.i.d. and G3 platelet count decrease in two patients at 20 mg b.i.d. It was decided that lenvatinib up to 13 mg b.i.d. in a 2-weeks-on and 1-week-off schedule would likely have a manageable toxicity profile from this study.

Another phase I study was conducted in 87 patients. Lenvatinib dose was slowly escalated from 0.2 mg to 32 mg once daily in a 28-day cycle. Pharmacokinetics analyses were performed at day 1, 8, 15, 22, and 28. DLT was determined to be G3 proteinuria, and the MTD was 25 mg once daily [42]. Hence, the current recommended dose of lenvatinib is 24 mg daily when used alone in patients with solid tumors with preserved liver function.

A multicenter, open-label, phase I, dose-escalation study [38] was performed in patients with HCC refractory to standard therapy. They are stratified by hepatic function as CP-A (score, 5–6) and CP-B (score, 7–8). Lenvatinib was administered continually once daily for 4-week cycles. MTD was defined as the maximum dose associated with ≤1 DLT within the first cycle among six patients. Of the 20 patients enrolled (9 in CP-A and 11 in CP-B), the MTD was 12 and 8 mg once daily in CP-A and CP-B, respectively. DLTs included proteinuria, hepatic encephalopathy, and hyperbilirubinemia. The most common G3 toxicities included hypertension in CP-A and hyperbilirubinemia in CP-B. PRs were observed in 3 patients and tumor shrinkage occurred in 14 patients. Lenvatinib (12 mg once daily) was determined to be the dose that showed preliminary efficacy with manageable toxicity and was the recommended dose for patients with HCC with liver function as CP-A.

In a dose-finding study based on population pharmacodynamics and exposure–response analysis in patients with HCC with CP-A, it was found that there was an increase in AUC as body weight decreased in subjects with HCC. An exposure–response relationship was observed, with higher lenvatinib AUC and lower body weight resulting in earlier drug withdrawal or dose reduction. The best cutoff values for body weight and lenvatinib AUC were 57.8 kg and 2,430 ng·h/mL, respectively, to predict the group at high risk for early drug withdrawal or dose reduction. Therefore, 12 mg and 8 mg once-daily starting doses for patients ≥60 kg

Table 1. Adverse events from the SELECT trial in differentiated thyroid carcinoma[a]

Adverse event	Lenvatinib arm		Placebo arm	
	All grades, %	Grade ≥3, %	All grades, %	Grade ≥3, %
Hypertension	67.8	41.8	9.2	2.3
Diarrhea	59.4	8.0	8.4	0
Fatigue	59.0	9.2	27.5	2.3
Decreased appetite	50.2	5.4	11.5	0
Decreased weight	46.4	9.6	9.2	0
Nausea	41.0	2.3	13.7	0.8
Stomatitis	35.6	4.2	3.8	0
PPES	31.8	3.4	0.8	0
Proteinuria	31.0	10.0	1.5	0
Vomiting	28.4	1.9	6.1	0
Headache	27.6	2.7	6.1	0
Dysphonia	24.1	1.1	3.1	0
Arthralgia	18.0	0	0.8	0
Dysgeusia	16.9	0	1.5	0
Rash	16.1	0.4	1.5	0
Constipation	14.6	0.4	8.4	0
Myalgia	14.6	1.5	2.3	0
Dry mouth	13.8	0.4	3.8	0
Upper abdominal pain	13.0	0	3.8	0
Abdominal pain	11.5	0.4	0.8	0.8
Peripheral edema	11.1	0.4	0	0
Alopecia	11.1	0	3.8	0
Dyspepsia	10.0	0	0	0
Oropharyngeal pain	10.0	0.4	0.8	0
Hypercalcemia	6.9	2.7	0	0
Pulmonary embolism	2.7	2.7	1.5	1.5
Fatal TEAE (TR, %)	2.3		0	
Serious TEAE (TR, %)	30.3		6.1	

[a]Incomplete list of adverse events.
Abbreviations: PPES, palmar-plantar erythrodysesthesia syndrome (also known as hand and foot syndrome); TEAE, treatment-emergent adverse event; TR, treatment related.

Table 2. Adverse events from the REFLECT trial in hepatocellular carcinoma

Adverse event	Lenvatinib arm		Sorafenib arm	
	All grades, %	Grade ≥3, %	All grades, %	Grade ≥3, %
PPES	27	3	52	11
Diarrhea	39	4	46	4
Hypertension	42	23	30	14
Decreased appetite	34	5	27	1
Decreased weight	31	8	22	3
Fatigue	30	4	25	4
Alopecia	3	0	25	0
Proteinuria	25	6	11	2
Dysphonia	24	1	12	0
Nausea	20	1	14	1
Abdominal pain	17	2	18	3
Decreased platelet	18	5	12	3
Increased AST	14	5	17	8
Hypothyroidism	16	0	2	0
Vomiting	16	1	8	1
Constipation	16	1	11	0
Rash	10	0	16	1
Increased bilirubin	15	7	13	5
TEAE (TR, %)		57		49
Serious TEAE (TR, %)		18		10

Abbreviations: AST, aspartate aminotransferase; PPES, palmar-plantar erythrodysesthesia syndrome (also known as hand and foot syndrome); TEAE, treatment-emergent adverse event; TR, treatment related.

(Table 1). AEs characteristic of angiogenesis inhibitors included hypertension (68%), diarrhea (59%), PPES (32%), and proteinuria (31%). Stomatitis was reported in 36% of enrolled patients. Diarrhea, which typically appeared early in treatment and was managed by dose modification, was associated with improved OS according to analysis of the REFLECT trial [50]. Another study found hypertension as TEAE predicted better PFS (18.8 months vs. 12.9 months; HR 0.59; 95% CI 0.39–0.88; p = .0085) compared with those who did not have hypertension [51]. Better ORR (69% vs. 56%, not statistically significant) and better OS were also noted (not reached vs. 21.7 months; HR 0.43; 95% CI 0.27–0.69; p = .0003). Those patients who were older than 65 years had a higher percentage of G3 toxicity than those younger than 65 years (89% vs. 67%) [52].

Compared with sorafenib, lenvatinib caused more hypothyroidism (16% vs. 2%) and proteinuria (25% vs. 11%) but fewer PPES or hand-foot syndrome (27% vs. 52%) and alopecia (3% vs. 25%) in patients with HCC (Table 2) [40]. AEs that worsened when lenvatinib was combined with temsirolimus (combination vs. lenvatinib vs. temsirolimus) included diarrhea (85% vs. 72% vs. 34%), fatigue (59% vs. 50% vs. 36%), vomiting (45% vs. 39% vs. 10%), hypercholesterolemia (33% vs. 12% vs. 16%), and peripheral edema (27% vs. 15% vs. 18%) in the RCC trial (Table 3) [45].

and < 60 kg, respectively, were recommended for patients with HCC CP-A [49].

To find the safe dose for RCC, a phase Ib trial combining lenvatinib and everolimus was performed to treat the disease. Starting from lenvatinib 12 mg once daily (n = 7) in a three-plus-three fashion, lenvatinib went up to 18 mg (n = 11) and 24 mg (n = 2) in combination with 5 mg of everolimus, both given once a day. It was determined that the MTD was 18 mg of lenvatinib and 5 mg of everolimus a day [44].

SIDE EFFECTS AND PREDICTORS OF RESPONSE
In the phase III SELECT trial, serious TEAE related to treatment was 24% above the placebo arm with 2.3% fatal

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Table 3. Adverse events from the phase II study of lenvatinib plus everolimus for renal cell carcinoma

Adverse event	Lenvatinib/temsirolimus arm		Lenvatinib arm		Temsirolimus arm	
	All grades, %	Grade ≥3, %	All grades, %	Grade ≥3, %	All grades, %	Grade ≥3, %
Diarrhea	85	20	72	12	34	2
Decreased appetite	51	6	58	4	18	0
Fatigue/asthenia	59	14	50	8	36	2
Vomiting	45	8	39	4	10	0
Nausea	41	6	52	8	16	0
Cough	37	0	17	2	30	0
Hypercholesterolemia	33	2	12	2	16	0
Decreased weight	31	2	48	6	8	0
Stomatitis	29	0	25	2	42	2
Hypertriglyceridemia	35	8	14	4	24	8
Hypertension	41	14	48	17	10	2
Peripheral edema	27	0	15	0	18	0
Abdominal pain	30	4	31	4	10	0
Hypothyroidism	24	0	37	2	2	0
Arthralgia	24	0	25	0	4	0
Dyspnea	24	2	21	2	22	8
Dysphonia	20	0	37	0	4	0
Pyrexia	22	2	10	0	10	2
Epistaxis	18	0	8	0	22	0
Proteinuria	22	4	31	19	14	2
Rash	18	0	17	0	22	0
Hyperglycemia	16	0	6	0	22	10
Back pain	20	4	21	0	14	0
Headache	18	2	25	4	10	2
Insomnia	18	2	14	0	2	0
Any TEAE	99	71	94	79	96	50

Abbreviation: TEAE, treatment-emergent adverse event.

ANTIANGIOGENESIS AND CHECKPOINT BLOCKADE COMBINATION

Antiangiogenic therapy is known to reprogram the immunosuppressive tumor microenvironment and enhances immunotherapy [53, 54]. Angiogenic inhibitors do so through normalization of tumor vasculature and inhibition of immunosuppressive cells such as myeloid-derived suppressor cells [55]. This concept was explored in lung cancer and renal cell carcinoma with proof of concept.

In the IMpower150 trial enrolling patients with non-squamous non-small cell lung cancer appropriate for bevacizumab, the efficacies of carboplatin/paclitaxel/ bevacizumab (BCP) with or without atezolizumab were compared. Atezolizumab clearly improved the efficacy of the BCP combination with PFS and OS benefits. Interestingly, the addition of atezolizumab improved efficacy over those patients who were traditionally resistant to BCP. Such patients either harbored EGFR mutation or had baseline liver metastases. BCP and atezolizumab, carboplatin, paclitaxel regimen did not differ in PFS or OS. Bevacizumab and atezolizumab had clear synergy [56]. Atezolizumab was approved by the FDA on December 7, 2018, for this indication. Based on prior phase Ib data indicating synergy of angiogenesis inhibitor axitinib with pembrolizumab, the combination was compared with sunitinib in RCC in a phase III trial in the first-line setting [57]. After a median follow-up of 12.8 months, 12-month survival was better in the combination group than in the sunitinib group (89.9% vs. 78.3%; HR 0.53; 95% CI 0.38–0.74; p < .0001). There was also improved PFS (15.1 vs. 11.1 months; HR 0.69; 95% CI 0.57–0.84; p < .001) and ORR (59.3% vs. 35.7%; p < .001). G3 or above toxicities were similar in both groups. The FDA approved the indication on April 22, 2019. Avelumab added to axitinib outperformed sunitinib in the same patient population [58]. FDA approved the combination on May 14, 2019.

Axitinib was also given with pembrolizumab in another phase II clinical trial in patients with soft tissue sarcoma including alveolar soft part sarcoma (ASPS) [59]. A total of 33 patients, including 12 with ASPS, were enrolled. With a median follow-up of 14.7 months, 3-month PFS for all evaluable patients was 65.6%; this was slightly higher for ASPS at 72.7%. AEs included hypertension (15%), nausea (6%), and seizure (6%). Serious adverse events (SAEs) occurred in 21% patients, including hypertriglyceridemia.

Table 4. Concept under active exploration

Drug(s)	n	Cancer type	Phase	Primary objective	NCT no.
Lenvatinib/pembrolizumab	29	Advanced gastric	II	ORR	03609359
Lenvatinib/TACE	336	HCC	III	OS	03905967
Lenvatinib/pembrolizumab	24	Gastroesophageal	IIa	OS	03321630
Lenvatinib/cetuximab	16	Squamous cell carcinoma (head/neck, skin)	I/Ib	MTD	03524326
Lenvatinib/pembrolizumab	329	Selected solid tumor	I/II	MTD/DLT/ORR	02501096
Lenvatinib/pembrolizumab	60	DTC	II	CR, ORR	02973997
Lenvatinib/everolimus vs. lenvatinib/ pembrolizumab vs. sunitinib	1,050	RCC	III	PFS	02811861
Lenvatinib/pembrolizumab vs. chemotherapy	780	Endometrial	III	PFS, OS	03517449
Lenvatinib/eribulin	30	STS	Ib/II	ORR	03526679
Lenvatinib/pembrolizumab	694	Urothelial	III	PFS, OS	03898180
Lenvatinib/capecitabine/radiation	28	Rectal	I	MTD, DLT	02935309
Lenvatinib/pembrolizumab	660	Melanoma, first line	III	PFS, OS	03820986
Lenvatinib/pembrolizumab	100	Melanoma, second line	II	ORR	03776136
Lenvatinib/pembrolizumab or placebo	750	HCC	III	PFS, OS	03713593
Lenvatinib/pembrolizumab or chemotherapy	720	Advanced, recurrent endometrial	III	PFS, OS	03884101
Lenvatinib/everolimus	40	DTC	II	PFS	03139747
Lenvatinib/nivolumab	50	HCC	II	ORR, PR, CR	03841201
Lenvatinib ± carboplatin, pemetrexed/ pembrolizumab	726	Nonsquamous, non-small cell lung cancer	III	PFS, OS	03829319

Ongoing clinical trials of lenvatinib in solid tumors.

Abbreviations: CR, complete response; DLT, dose-limiting toxicity; DTC, differentiated thyroid cancer; HCC, hepatocellular carcinoma; MTD, maximum tolerated dose; NCT, National Clinical Trial; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; RCC, renal cell carcinoma; STS, soft tissue sarcoma; TACE, transarterial chemoembolization.

In a retrospective study of pembrolizumab added to 12 patients with ATC receiving lenvatinib, there were five PR (42%), four SD (33%), and three PD (25%). Median OS was 10.43 months with a 95% CI ranging from 6.02 to 14.83 months (5.4–40 months). Median OS from the time of adding pembrolizumab was 6.93, and median PFS was 2.96 months. AEs included hypertension, fatigue, and anemia [60].

Recently, a phase II study was also reported that evaluated the addition of lenvatinib to pembrolizumab in advanced and recurrent endometrial carcinoma [61]. The study enrolled 54 patients, of whom 53 were evaluable. With a median follow-up of 13.3 months, 21 of the 53 patients responded by week 24, ORR 39.6%. SAEs occurred in 16 of the 53 patients (30%), with one death. The most common AEs included hypertension (54%), fatigue (55%), diarrhea (51%), and hypothyroidism (47%). G3 hypertension was 34% and G3 diarrhea was 8%. Except for worsening hypothyroidism, no new AE was detected. This is clearly suggesting an active combination. A phase III trial is being planned.

Concept Under Exploration

Currently, lenvatinib is being investigated in a number of solid tumors including lung, gastrointestinal, hepatocellular,

endometrial, urothelial, renal cell, and melanoma, in combination with pembrolizumab; head and neck with cetuximab; and soft tissue sarcoma with eribulin (Table 4). Most tumor types are known to respond to both angiogenesis and immune checkpoint inhibitors.

Unresolved Issues

Through years of exploration, we clearly discovered a multi-targeted TKI that is active in multiple solid tumor malignancies. However, it is also clear that treatment-emergent adverse events are common and often cause dose interruption or treatment discontinuation [62]. Dose interruption more than 10% had worse outcome than dose interruption less than 10% [63]. Lower dose is being explored as to whether it will reduce toxicity but retain efficacy [64]. In addition, biomarkers that predict efficacy and/or drug toxicity need to be further explored so that patients are not exposed to unnecessary risk. Finally, lenvatinib seems to be active for tumors grown in the brain [65, 66]. Its role in controlling cancers metastasized to the brain should be explored further.

AUTHOR CONTRIBUTIONS

Conception/design: Zhonglin Hao
Provision of study material or patients: Zhonglin Hao
Collection and/or assembly of data: Zhonglin Hao, Peng Wang
Data analysis and interpretation: Zhonglin Hao, Peng Wang

Manuscript writing: Zhonglin Hao, Peng Wang
Final approval of manuscript: Zhonglin Hao, Peng Wang

DISCLOSURES

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