



Oncology Drug Crash Course

Lenvatinib (Lenvima) for Advanced Endometrial Cancer

FOR WHOM IS THIS DRUG APPROVED?

Lenvatinib is approved by the FDA for the following indications¹⁻⁵:

- » In combination with pembrolizumab (Keytruda) for the treatment of patients with advanced endometrial cancer who have disease progression after systemic therapy, are not candidates for curative surgery or radiation, and who are mismatch repair proficient (pMMR) or not microsatellite instability–high. This indication received accelerated approval from the FDA in September 2019, with regular approval granted in July 2021.
- » For patients with locally recurrent or metastatic, progressive, radioactive iodine–refractory differentiated thyroid cancer (2015)
- » In combination with everolimus (Afinitor) for patients with advanced renal cell carcinoma in the second-line setting (2016)
- » For patients with unresectable hepatocellular carcinoma in the first-line setting (2018)
- » In combination with pembrolizumab for patients with renal cell carcinoma in the first-line setting (2021)

WHAT EFFICACY DATA BACK IT UP?

The accelerated approval of lenvatinib was granted based on data from the phase 1/2 single-arm trial KEYNOTE-146 (NCT02501096).²

The full approval was supported by findings from the phase 3 KEYNOTE-775 trial (NCT03517449). This was a multicenter, open-label trial that compared lenvatinib plus pembrolizumab with physician's choice chemotherapy in women with advanced, recurrent, or metastatic endometrial cancer who had disease progression after platinum-based chemotherapy. Efficacy was based on results observed in the pMMR population, which included 346 patients in the combination arm and 351 patients in the chemotherapy-alone arm.

Objective responses were greater in the lenvatinib plus pembrolizumab group vs chemotherapy alone (30.3% vs 15.1%). Additionally, the median progression-free survival (PFS) was

6.6 months vs 3.8 months, respectively (HR, 0.60; 95% CI, 0.50-0.72; $P < .001$) and the median overall survival (OS) was 17.4 months vs 12.0 months, respectively (HR, 0.68; 95% CI, 0.56-0.84; $P < .001$).^{1,3}

The decision to approve lenvatinib for patients with thyroid cancer was supported by findings from the phase 3 SELECT trial (NCT01321554), which showed that lenvatinib was linked to a superior median PFS vs placebo in patients with iodine 131–refractory differentiated thyroid cancer.⁴

The 2016 approval in combination with everolimus for advanced renal cell carcinoma was supported by findings from a phase 2 trial (NCT01136733). The combination of lenvatinib and everolimus reduced the risk of progression or death by 63% in patients with advanced renal cell carcinoma who had been pretreated with antiangiogenetic therapy.⁵

The approved indication in unresectable hepatocellular carcinoma stems from findings from the REFLECT trial (NCT01761266) which demonstrated that lenvatinib was noninferior but not statistically superior to sorafenib (Nexavar) in boosting OS. However, in the REFLECT trial lenvatinib did significantly improve median PFS.⁶

Lastly, the agent was approved for advanced renal cell carcinoma in light of the CLEAR/KEYNOTE-581 trial (NCT02811861), which showed that the median PFS was significantly improved with the agent vs sunitinib.⁷

HOW IT WORKS

Lenvatinib is a tyrosine kinase inhibitor that inhibits the activity of multiple kinases involved with angiogenesis and tumor growth, including VEGF, FGFR, PDGFRA, KIT, and RET. Inhibition of these ultimately leads to decreased tumor growth and slowed cancer progression.¹

HOW IT'S ADMINISTERED

Lenvatinib is taken once daily by mouth, with or without food.¹ Lenvatinib at a dose of 12 mg/day or greater is considered moderate to high emetic risk; therefore, an oral 5HT₃ receptor antagonist such as ondansetron should be taken prior to each dose to prevent nausea and/or vomiting.



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Administer agents for breakthrough nausea as needed (for example, prochlorperazine).⁸

Concurrent pembrolizumab is given intravenously and may be given once every 21 days or once every 42 days depending on provider and patient preference.⁹

THE RECOMMENDED DOSE

The FDA-approved dose of lenvatinib for endometrial cancer is 20 mg once daily.¹ There also are data that show a lower starting dose (14 mg/day) may result in fewer adverse events (AEs) while maintaining efficacy.¹⁰ Some providers may choose to start at 14 mg/day to improve tolerability for their patients.

HOW TO MANAGE ASSOCIATED ADVERSE EVENTS

AEs seen in 20% or more of patients in patients with endometrial cancer who received lenvatinib plus pembrolizumab included hypothyroidism, hypertension, fatigue, diarrhea, musculoskeletal effects, nausea, decreased appetite, vomiting, stomatitis, reduction in weight, abdominal pain, urinary tract infection, proteinuria, constipation, headache, hemorrhagic events, palmar-plantar erythrodysesthesia syndrome (hand-foot-skin reaction), dysphonia, and rash.¹

There were no unforeseen AEs noted with the use of this combination regimen. The toxicities were manageable with dose interruptions and/or dose reductions of lenvatinib, as well as the use of supportive medications such as urea 10% cream for the prevention of hand-foot-skin reaction and dexamethasone oral rinse for the management of stomatitis.^{11,12}

WHAT TO INFORM PATIENTS ABOUT

Counsel patients on the most common AEs. Advise them to notify their provider if elevations in blood pressure are noted or an upcoming elective surgery is planned. Women of reproductive potential should use effective contraception during treatment, for at least 30 days after the last dose of lenvatinib, and for at least 4 months after the last dose of pembrolizumab.^{1,9}

ADVICE FOR NURSES WHO ADMINISTER THIS AGENT

Routine monitoring for patients on lenvatinib includes the following: liver function tests should be done at baseline, every 2 weeks for the first 2 months, then at least monthly; renal function,

electrolytes, serum calcium, and thyroid function should all be assessed at baseline and then at least monthly; and urine dipsticks should be checked for proteinuria at baseline and then periodically.¹

Lenvatinib has been shown to have several cardiac AEs, including hypertension and corrected QT interval (QTc) prolongation. Blood pressure should be trended from baseline, at week 1, then every 2 weeks for 2 months. Subsequent blood pressure monitoring should occur at least monthly thereafter. A baseline electrocardiogram should be considered in patients with cardiac comorbidities, including congenital long QT syndrome, and in those on concomitant QTc-prolonging drugs. Avoid use of multiple agents that can prolong the QT/QTc interval when able.¹ Some institutions may also recommend baseline echocardiograms as there are reports of cardiomyopathy and ventricular dysfunction.

Monitor patients for signs/symptoms of cardiac dysfunction, thromboembolic events, fistula formation, gastrointestinal perforation, bleeding/hemorrhage, diarrhea, dehydration, wound healing complications, and reversible posterior leukoencephalopathy syndrome. Lenvatinib should be held for at least 1 week prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing has occurred.¹ Additionally, osteonecrosis of the jaw has been reported with lenvatinib and therefore a dental exam at baseline and periodically throughout treatment is recommended.¹³

HOW TO SAFELY HANDLE THIS AGENT

Lenvatinib should be stored at room temperature in a dry area of the home to avoid exposure to moisture (ie, do not store in the bathroom). Keep the capsules in their original packaging. Do not open capsules unless directed by a provider. Wash hands for at least 20 seconds before and after touching the capsules. The use of disposable gloves is recommended when handling the capsules to avoid unnecessary exposures.¹⁴ If needing to dispose of unused lenvatinib, refer to local practice guidelines for disposal recommendations.

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