Lenvima (Lenvatinib), a Multireceptor Tyrosine Kinase Inhibitor, Approved by the FDA for the Treatment of Patients with Differentiated Thyroid Cancer

By Loretta Fala, Medical Writer

Thyroid cancer, cancer that starts in the thyroid gland, accounts for 3.8% of all cancer cases in the United States. There were an estimated 62,980 new cases of thyroid cancer and 1890 deaths resulting from thyroid cancer in 2014. Thyroid cancer is most common in people aged 45 to 54 years (median age, 50 years), and it occurs 2 to 3 times more often in women than in men. The incidence of thyroid cancer has risen steadily in recent years. Although this increasing rate can be attributed largely to disease detection at an earlier stage, the incidence of larger tumors has also increased.

Thyroid cancer is classified into 3 types—differentiated (includes papillary, follicular, and Hurthle tumors); medullary tumors; and anaplastic (aggressive undifferentiated tumors). Differentiated thyroid cancer accounts for more than 90% of all cases of thyroid carcinoma.

An estimated 566,708 patients were living with thyroid cancer in the United States in 2011. Approximately 68.2% of patients are diagnosed at the local stage of thyroid cancer; for patients with localized thyroid cancer, the 5-year survival rate is currently 99.9%. However, 10% to 30% of patients who are thought to be disease-free after the initial treatment will have disease recurrence and/or metastases. For patients with differentiated thyroid cancer that is refractory to radioactive iodine [131-isotope, also known as 131I] therapy, the 10-year survival rate is only 10% from the time that metastatic disease is detected.

According to a recent study, the estimated annual US healthcare costs (undiscounted) for thyroid cancer were $1.4 billion in 2010; these costs are projected to reach $2.1 billion in 2015 and to exceed $3.1 billion by 2019. The authors noted that thyroid cancer is a major public health issue, particularly for women, given the increasing incidence (especially of papillary carcinoma) of the disease among women. According to another study, differentiated thyroid cancer accounted for total societal costs of approximately $1.6 billion annually in the United States in 2013. Furthermore, the annual costs attributable to differentiated thyroid cancer were projected to approach $3.5 billion by 2030 in that study.

The treatment of differentiated thyroid cancer generally includes surgery, when possible, followed by radioactive iodine treatment in appropriate patients, and thyroxine therapy. Systemic therapy, including the recently approved tyrosine kinase inhibitors, may be used for patients with significant disease progression, nonresectable tumors, or tumors that are nonresponsive to radioactive iodine therapy.

The multitargeted tyrosine kinase inhibitors have demonstrated a clinical benefit in locally recurrent, unresectable and metastatic medullary thyroid cancer and in radioactive iodine–refractory differentiated thyroid cancer. Optimal management of the side effects associated with tyrosine kinase inhibitor therapy and/or dose modification are key considerations when managing thyroid cancer with this class of drugs. The tyrosine kinase inhibitors represent an important advancement in the treatment of thyroid cancer, because they target multiple molecular pathways that are involved in the pathogenesis of thyroid tumors.

Lenvatinib: A New Oral Option for Differentiated Thyroid Cancer

On February 13, 2015, lenvatinib (Lenvima; Eisai), an oral, multireceptor tyrosine kinase inhibitor, was approved by the US Food and Drug Administration (FDA) to treat patients with locally recurrent or metastatic, progressive, radioactive iodine–refractory differentiated thyroid cancer. Lenvatinib was granted an expedited review by the FDA, using its priority review process, based on the drug’s potential to provide a significant improvement in safety or effectiveness in treating a serious condition over available medications. In addition, lenvatinib received an orphan drug designation, because it is designated to treat a rare condition.

Richard Pazdur, MD, Director of the Office of Hematology and Oncology Products in the FDA’s Center for Drug Evaluation and Research, said, “The development of new therapies to assist patients with refractory disease is of high importance to the FDA. Today’s approval
gives patients and healthcare professionals a new therapy to help slow the progression of DTC [differentiated thyroid cancer].”9

Steven I. Sherman, MD, Associate Vice Provost, Clinical Research, M.D. Anderson Cancer Center, and principal investigator of a pivotal phase 3 study on lenvatinib led by researchers at the University of Texas M.D. Anderson Cancer Center, noted that advances in thyroid cancer treatment have been made in recent years, particularly for patients with metastatic disease who do not respond to radioactive iodine therapy.10 Dr Sherman stated, “For decades, in this patient population, the treatment was often to repeat ineffective doses of radioactive iodine, and possibly salvage therapy with chemotherapy.” He added, “About 10 years ago, with the growing availability of novel targeted agents and multi-targeted kinase inhibitors, we began to recognize potential for treating this subgroup of patients with anti-angiogenic therapy and sought to enroll those with refractory disease in clinical trials.”10

Mechanism of Action

Lenvatinib is a multireceptor tyrosine kinase inhibitor that inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4). Lenvatinib also inhibits other receptor tyrosine kinases that have been implicated in pathogenic angiogenesis, tumor growth, and cancer progression in addition to their normal cellular functions, including the fibroblast growth factor receptors FGFR1, 2, 3, and 4; and the platelet-derived growth factor receptor alpha, KIT, and RET.11

Dosing and Administration

The recommended dose of lenvatinib is 24 mg orally, once daily. In patients with severe renal or hepatic impairment, the dose is reduced to 14 mg once daily.11 Lenvatinib is available in a 4-mg and a 10-mg capsule.11

Clinical Studies

The SELECT Trial

The safety and efficacy of lenvatinib were evaluated in the SELECT trial, a multicenter, randomized (in a 2:1 ratio), double-blind, placebo-controlled study.5 The study included 392 patients with locally recurrent or metastatic radioactive iodine–refractory differentiated thyroid cancer and radiographic evidence of disease progression within 12 months before study randomization, as confirmed by an Independent Radiologic Review (IRR).5,11

Radioactive iodine–refractory was defined as (1) ≥1 measurable lesions with no iodine uptake on radioactive iodine scan, (2) iodine uptake with progression within 12 months of radioactive iodine therapy, or (3) having received cumulative radioactive iodine activity of >600 mCi (22 GBq) with the last dose administered at least 6 months before study entry.11

In this study, patients were randomized to receive lenvatinib 24 mg once daily (N = 261) or placebo (N = 131) until disease progression. Randomization was stratified by geographic region, previous VEGF/VEGFR-targeted therapy, and age. The median age of the patients was 63 years. Overall, 99% of the patients had metastatic disease.11

The primary efficacy outcome measure was progression-free survival, as determined by a blinded IRR using

<table>
<thead>
<tr>
<th>Efficacy variable</th>
<th>Lenvatinib cohort (N = 261)</th>
<th>Placebo cohort (N = 131)</th>
<th>Hazard ratio b</th>
<th>P &lt; .001 c</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression-free survivala</td>
<td>107 (41)</td>
<td>113 (86)</td>
<td>0.21 (95% CI, 0.16-0.28)</td>
<td>.001</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>93 (36)</td>
<td>109 (83)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>14 (5)</td>
<td>4 (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median progression-free survival, mo</td>
<td>18.3 (95% CI, 15.1-NE)</td>
<td>3.6 (95% CI, 2.2-3.7)</td>
<td></td>
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</tr>
<tr>
<td>Objective response rate</td>
<td>65 (95% CI, 59%-71%)</td>
<td>2 (95% CI, 0%-4%)</td>
<td></td>
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</tr>
<tr>
<td>Complete response, %</td>
<td>2</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial response, %</td>
<td>63</td>
<td>2</td>
<td></td>
<td>.001</td>
</tr>
<tr>
<td>Overall survivalb</td>
<td>71 (27)</td>
<td>47 (36)</td>
<td></td>
<td>.10</td>
</tr>
<tr>
<td>Median overall survivalb</td>
<td>NE</td>
<td>NE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazard ratiob</td>
<td>0.73 (95% CI, 0.50-1.07)</td>
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</table>

aIndependent radiologic review.
bEstimated with Cox proportional hazard model stratified by region (Europe vs North America vs other), age-group (≤65 vs >65 years), and previous VEGF/VEGFR-targeted therapy (0 vs 1).
cLog-rank test stratified by region (Europe vs North America vs other), age-group (≤65 vs >65 years), and previous VEGF/VEGFR-targeted therapy (0 vs 1).

Clinical studies

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The primary efficacy outcome measure was progression-free survival, as determined by a blinded IRR using
Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1). Secondary efficacy outcome measures included objective response rate and overall survival. Patients in the placebo group could receive lenvatinib after an independent review confirmation of disease progression.

As shown in Table 1, a significant prolongation in progression-free survival was demonstrated in patients receiving lenvatinib compared with patients who received placebo. Patients in the lenvatinib group had a 14.7-month longer median progression-free survival than patients in the placebo group. Moreover, 65% of patients in the lenvatinib group had an objective response compared with 2% of patients in the placebo group. Overall survival was not estimable in either group.

**Safety**

The most common adverse reactions (with an incidence of ≥30%) associated with lenvatinib are shown in Table 2. The most common serious adverse reactions (at least 2%) were pneumonia (4%), hypertension (3%), and dehydration (3%).

The most common adverse reactions (at least 1%) resulting in discontinuation of lenvatinib were hypertension (1%) and asthenia (1%). Lenvatinib has no known contraindications.

**Drug Interactions**

*Effect of other drugs on lenvatinib.* CYP3A is one of the main metabolic enzymes of lenvatinib. No dose adjustment of lenvatinib is recommended when coadministered with CYP3A, P-glycoprotein (P-gp), and breast cancer resistance protein inhibitors and CYP3A and P-gp inducers.

**Warnings and Precautions**

*Hypertension.* Blood pressure should be controlled prior to treatment with lenvatinib. Lenvatinib should be withheld for grade 3 hypertension despite optimal hypertensive therapy. For patients with life-threatening hypertension, lenvatinib should be discontinued.

*Cardiac failure.* Patients should be monitored for clinical symptoms or signs of cardiac decompensation. Lenvatinib should be withheld for grade 3 cardiac dysfunction. For patients with grade 4 cardiac dysfunction, lenvatinib should be discontinued.

*Arterial thromboembolic events.* Lenvatinib should be discontinued following an arterial thromboembolic event.

*Hepatotoxicity.* Before initiation of lenvatinib and periodically throughout treatment, liver function tests should be monitored. For patients with grade 3 or greater liver impairment, lenvatinib should be withheld. Lenvatinib should be discontinued for patients with hepatic failure.

*Proteinuria.* Before initiating lenvatinib therapy and periodically through treatment with lenvatinib, patients should be monitored for proteinuria. Lenvatinib should be withheld in patients with ≥2 g of proteinuria for 24 hours. Lenvatinib should be discontinued in patients with nephritic syndrome.

*Renal failure and impairment.* Lenvatinib should be withheld for grade 3 or 4 renal failure or impairment.

*Gastrointestinal perforation and fistula formation.* Lenvatinib should be discontinued in patients who develop gastrointestinal perforation or life-threatening fistula.

*QT interval prolongation.* Electrolyte abnormalities should be monitored and corrected in all patients.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Lenvatinib versus Placebo: Adverse Events (All Grades Incidence ≥30%)</th>
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</thead>
<tbody>
<tr>
<td>Adverse reaction</td>
<td>All grades, %</td>
</tr>
<tr>
<td>Lenvatinib 24 mg (N = 261)</td>
<td>Placebo (N = 131)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>73</td>
</tr>
<tr>
<td>Fatigue</td>
<td>67</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>67</td>
</tr>
<tr>
<td>Arthralgia/myalgia</td>
<td>62</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>54</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>51</td>
</tr>
<tr>
<td>Nausea</td>
<td>47</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>41</td>
</tr>
<tr>
<td>Headache</td>
<td>38</td>
</tr>
<tr>
<td>Vomiting</td>
<td>36</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>34</td>
</tr>
<tr>
<td>Palmar-plantar erythrodysesthesia (hand-foot) syndrome</td>
<td>32</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>31</td>
</tr>
<tr>
<td>Dysphonia</td>
<td>31</td>
</tr>
</tbody>
</table>

*aIncludes hypertension, hypertensive crisis, increased blood pressure diastolic, and increased blood pressure.

*bIncludes asthenia, fatigue, and malaise.

*cIncludes musculoskeletal pain, back pain, pain in extremity, arthralgia, and myalgia.

*dIncludes aphthous stomatitis, stomatitis, glossitis, mouth ulceration, and mucosal inflammation.

*eIncludes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness, epigastric discomfort, and gastrointestinal pain.

Source: Lenvima (lenvatinib) capsules prescribing information; February 2015.
patients who develop grade ≥3 QT interval prolongation, lenvatinib should be withheld.\textsuperscript{11}

\textbf{Hypocalcemia.} Blood calcium levels should be monitored at least monthly and calcium should be replaced as necessary during treatment with lenvatinib.\textsuperscript{11}

\textbf{Reversible posterior leukoencephalopathy syndrome (RPLS).} Lenvatinib should be withheld for patients with RPLS until the RPLS is fully resolved.\textsuperscript{11}

\textbf{Hemorrhagic events.} Lenvatinib should be discontinued for patients with grade 3 hemorrhage. Lenvatinib should be discontinued for patients with grade 4 hemorrhage.\textsuperscript{11}

\textbf{Impairment of thyroid-stimulating hormone (TSH) suppression.} TSH levels should be monitored monthly and thyroid replacement medication should be adjusted as needed in patients with differentiated thyroid cancer.\textsuperscript{11}

\textbf{Embryofetal toxicity.} Lenvatinib can cause fetal harm. Women of reproductive potential should be advised about the potential risk to the fetus and the use of effective contraception.\textsuperscript{11}

\section*{Use in Specific Populations}

\textbf{Lactation.} It is not known whether lenvatinib is present in human milk. Because of the potential for serious adverse reactions in nursing infants from lenvatinib, women should be advised to discontinue breastfeeding during treatment with lenvatinib.\textsuperscript{11}

\textbf{Pregnancy.} Lenvatinib can cause fetal harm when administered to a pregnant woman. Pregnant women should be advised of the potential risk to the fetus.\textsuperscript{11}

\textbf{Females and males of reproductive potential.} Lenvatinib may result in reduced fertility in women of reproductive potential. Lenvatinib may result in damage to male reproductive tissues leading to reduced fertility of unknown duration.\textsuperscript{11}

\textbf{Pediatric use.} The safety and effectiveness of lenvatinib in pediatric patients have not been established.\textsuperscript{11}

\textbf{Geriatric use.} In clinical studies, no overall differences in safety or effectiveness were observed between patients aged ≥65 years and those aged <65 years.\textsuperscript{11}

\textbf{Renal impairment.} No dose adjustment is recommended in patients with mild or moderate renal impairment. In patients with severe renal impairment, the recommended dose of lenvatinib is 14 mg taken once daily. Patients with end-stage renal disease were not studied.\textsuperscript{11}

\textbf{Hepatic impairment.} No dose adjustment is recommended in patients with mild or moderate hepatic impairment. In patients with severe hepatic impairment, the recommended dose of lenvatinib is 14 mg taken once daily.\textsuperscript{11}

\section*{Conclusion}

With the FDA approval of lenvatinib, a new, once-daily oral treatment option became available to help slow the progression of differentiated thyroid cancer, the most common type of thyroid cancer, in patients with locally recurrent or metastatic, radioactive iodine-refractory disease.\textsuperscript{9}

With the FDA approval of lenvatinib, a new, once-daily oral treatment option became available to help slow the progression of differentiated thyroid cancer, the most common type of thyroid cancer.

Treatment with lenvatinib, a multitargeted tyrosine kinase inhibitor, demonstrated a statistically significant prolongation in progression-free survival in patients with progressive, radioactive iodine-refractory differentiated thyroid cancer. In the SELECT clinical study, the median progression-free survival in the lenvatinib group was 18.3 months versus 3.6 months in the placebo group (P < .001).\textsuperscript{5,11}

\section*{References}