

Transcript Details

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RAI-R DTC: Explore This Pivotal Study Data

This video is for educational purposes only and includes Dr. Lupo's subjective views about a treatment option for radioactive iodine-refractory differentiated thyroid cancer (RAI-R DTC). The video and the doctor's views are not intended to be, nor should they be interpreted as, medical advice, medical instructions, or replacing your doctor's advice. You are advised to consult your own doctor or other health care provider for all matters involving your health care.

Dr. Lupo:

My name is Mark Lupo. I am a medical director of the Thyroid & Endocrine Center of Sarasota, Florida. It's an endocrinology practice focused on thyroid disease. I'm an endocrinologist, and my subspecialty is thyroid disease. And my special interest would be thyroid nodules and thyroid cancer management.

LENVIMA® (lenvatinib) is specifically indicated for patients with advanced thyroid cancer – that is, patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer. And the recommended dose of LENVIMA in this population is 24 milligrams.

SELECT study data are based on a phase III multicenter, randomized, double-blind, placebo-controlled trial in patients with locally recurrent or metastatic radioactive iodine-refractory differentiated thyroid cancer who have had radiographic evidence of disease progression within 12 months prior to randomization, as confirmed by independent radiologic review. Patients may have received zero or one prior VEGF targeted therapy. Meaning a 20% or more growth in their structural disease within a 12-month period of time, that was confirmed by central radiology. So that's the important part about this randomized clinical trial is, it was confirmed progression. So, we knew exactly where these patients were coming from when they were enrolled.

A randomized clinical trial is important. It's considered the best level of evidence. It's a very structured way of conducting a trial. And in this case, it's comparing LENVIMA, or lenvatinib, to placebo in a group of patients that are not very common, but for whom we did not have very good options up until almost 10 years ago. Patients were randomized geographically. They were also randomized by whether or not they had previously had a VEGF inhibitor – VEGF is vascular endothelial growth factor, which drives blood flow. So, most of these medications will block angiogenesis, or blood flow. So about 24% of the patients in the trial had been exposed to a VEGF inhibitor.

These are patients who have radioactive iodine-refractory, progressive, differentiated thyroid cancer. So, a very difficult group to treat. They don't respond to radioactive iodine. Typically, more surgery doesn't help; more radiation therapy, external beam doesn't help. So having, you know, something to see, if we could achieve a benefit, was very important. So, the SELECT trial was an international trial – enrolled 392 patients with documented progression of their differentiated thyroid cancer. And it's a two-to-one enrollment, which means for every one patient on placebo, two patients were offered LENVIMA at a dose of 24 milligrams. The SELECT trial enrolled in that way, and then allowed the patients on placebo that progressed – remember, these patients were progressing within 12 months prior to enrollment – so once they continued progression, then they could be offered open-label LENVIMA. It was an open-label extension for the placebo patients who progressed.

The primary endpoint was progression-free survival, recognizing that these patients had documented progression within 12 months of enrollment. And so, the idea would be to extend that time as long as possible in deferring progression, or preventing progression, for these patients. The primary endpoint was confirmed by RECIST (Response Evaluation Criteria in Solid Tumors) criteria [v1.1]. Patients on LENVIMA had a median progression-free survival of 18.3 months, compared to patients who received placebo, who had a median progression-free survival of 3.6 months.

So in the study, 107 events, or 41% of the subjects, [occurred] in the LENVIMA arm, and 113, or 86% of subjects, in the placebo arm had an event. 93 [subjects], or 36%, who received LENVIMA progressed versus 109, or 83%, who received placebo. Death occurred in 14 patients, or 5%, who received LENVIMA, and 4, or 3%, in the placebo group.

So, we can see that when you look at the Kaplan-Meier estimates of the statistics, it was a 79% reduction in the risk of an event. So, the

event would be death or progression due to disease. So, LENVIMA had a very strong impact on progression-free survival. Now with these studies, we also look at secondary endpoints.

One would be overall response rate, which would be – a response means there's a 30% reduction in tumor volume – or a complete response, so no evidence of disease. And in this case, there was a 65% overall response rate in the LENVIMA arm. If patients responded, which 65% did, it was about a 30-month durable response.

Another endpoint that's looked at in these trials is overall survival. But the median overall survival could not be calculated. If you have a placebo [recipient] that's then offered LENVIMA, it's hard to statistically prove overall survival in that regard. So that was not achieved.

Voiceover:

Adverse reactions, some of which can be serious or fatal, may occur with LENVIMA, including hypertension, cardiac dysfunction, arterial thromboembolic events, hepatotoxicity, renal failure or impairment, proteinuria, diarrhea, fistula formation and gastrointestinal perforation, QT interval prolongation, hypocalcemia, reversible posterior leukoencephalopathy syndrome, hemorrhagic events, impairment of thyroid-stimulating hormone suppression/thyroid dysfunction, impaired wound healing, osteonecrosis of the jaw, and embryo-fetal toxicity. Based on its mechanism of action and data from animal reproduction studies, LENVIMA can cause fetal harm when administered to a pregnant woman. Females of reproductive potential should be advised to use effective contraception. Based on the severity of the adverse reaction, LENVIMA should be interrupted, reduced, and/or discontinued.

Dr. Lupo:

I'd like to review the safety information from the SELECT trial. The most common ARs (adverse reactions) observed in LENVIMA-treated patients – occurred at more than 30% – were: hypertension (44%), fatigue (11%), diarrhea (9%), arthralgia/myalgia (5%), decreased appetite (7%), decreased weight (13%), nausea (2%), stomatitis (5%), headache (3%), vomiting (2%), proteinuria (11%), palmar-plantar erythrodysesthesia, or PPE syndrome (3%), abdominal pain (2%), and dysphonia (1%).

The most common serious side effects or adverse reactions (at least 2%) were pneumonia (4%), hypertension (3%), and dehydration (3%).

Adverse reactions led to dose reductions in 68% and discontinuation in 18% of patients receiving LENVIMA. The most common adverse reactions (at least 10%) resulting in dose reductions were hypertension (13%), proteinuria (11%), decreased appetite (10%), and diarrhea (10%).

The most common adverse reactions (at least 1%) resulting in discontinuation of LENVIMA were hypertension (1%) and asthenia (1%).

As we look at the SELECT study, we look at the efficacy – which is very compelling, but we have to balance that out with safety and that's very well documented in SELECT studies.

Voiceover:

INDICATION

LENVIMA® (lenvatinib) 10 mg and 4 mg capsules is indicated for the treatment of adult patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer (RAI-refractory DTC).

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

Hypertension. In DTC (differentiated thyroid cancer), hypertension occurred in 73% of patients on LENVIMA (44% grade 3-4). In RCC (renal cell carcinoma), hypertension occurred in 42% of patients on LENVIMA + everolimus (13% grade 3). Systolic blood pressure ≥ 160 mmHg occurred in 29% of patients, and 21% had diastolic blood pressure ≥ 100 mmHg. In HCC (hepatocellular carcinoma), hypertension occurred in 45% of LENVIMA-treated patients (24% grade 3). Grade 4 hypertension was not reported in HCC.

Serious complications of poorly controlled hypertension have been reported. Control blood pressure prior to initiation. Monitor blood pressure after 1 week, then every 2 weeks for the first 2 months, and then at least monthly thereafter during treatment. Withhold and resume at reduced dose when hypertension is controlled or permanently discontinue based on severity.

Cardiac Dysfunction. Serious and fatal cardiac dysfunction can occur with LENVIMA. Across clinical trials in 799 patients with DTC, RCC, and HCC, grade 3 or higher cardiac dysfunction occurred in 3% of LENVIMA-treated patients. Monitor for clinical symptoms or signs of cardiac dysfunction. Withhold and resume at reduced dose upon recovery or permanently discontinue based on severity.

Arterial Thromboembolic Events. Among patients receiving LENVIMA or LENVIMA + everolimus, arterial thromboembolic events of any severity occurred in 2% of patients in RCC and HCC and 5% in DTC. Grade 3-5 arterial thromboembolic events ranged from 2% to 3%.

across all clinical trials.

Among patients receiving LENVIMA with pembrolizumab, arterial thrombotic events of any severity occurred in 5% of patients in CLEAR, including myocardial infarction (3.4%) and cerebrovascular accident (2.3%).

Permanently discontinue following an arterial thrombotic event. The safety of resuming after an arterial thromboembolic event has not been established, and LENVIMA has not been studied in patients who have had an arterial thromboembolic event within the previous 6 months.

Hepatotoxicity. Across clinical studies enrolling 1327 LENVIMA-treated patients with malignancies other than HCC, serious hepatic adverse reactions occurred in 1.4% of patients. Fatal events, including hepatic failure, acute hepatitis and hepatorenal syndrome, occurred in 0.5% of patients. In HCC, hepatic encephalopathy occurred in 8% of LENVIMA treated patients (5% grade 3-5). Grade 3-5 hepatic failure occurred in 3% of LENVIMA-treated patients; 2% of patients discontinued LENVIMA due to hepatic encephalopathy, and 1% discontinued due to hepatic failure.

Monitor liver function prior to initiation, then every 2 weeks for the first 2 months, and at least monthly thereafter during treatment. Monitor patients with HCC closely for signs of hepatic failure, including hepatic encephalopathy. Withhold and resume at reduced dose upon recovery or permanently discontinue based on severity.

Renal Failure or Impairment. Serious including fatal renal failure or impairment can occur with LENVIMA. Renal impairment was reported in 14% and 7% of LENVIMA-treated patients in DTC and HCC, respectively. Grade 3-5 renal failure or impairment occurred in 3% of patients with DTC and 2% of patients with HCC, including 1 fatal event in each study. In RCC, renal impairment or renal failure was reported in 18% of LENVIMA + everolimus-treated patients (10% grade 3).

Initiate prompt management of diarrhea or dehydration/hypovolemia. Withhold and resume at reduced dose upon recovery or permanently discontinue for renal failure or impairment based on severity.

Proteinuria. In DTC and HCC, proteinuria was reported in 34% and 26% of LENVIMA-treated patients, respectively. Grade 3 proteinuria occurred in 11% and 6% in DTC and HCC, respectively. In RCC, proteinuria occurred in 31% of patients receiving LENVIMA + everolimus (8% grade 3). Monitor for proteinuria prior to initiation and periodically during treatment. If urine dipstick proteinuria $\geq 2+$ is detected, obtain a 24-hour urine protein. Withhold and resume at reduced dose upon recovery or permanently discontinue based on severity.

Diarrhea. Of the 737 LENVIMA-treated patients in DTC and HCC, diarrhea occurred in 49% (6% grade 3). In RCC, diarrhea occurred in 81% of LENVIMA + everolimus-treated patients (19% grade 3). Diarrhea was the most frequent cause of dose interruption/reduction, and diarrhea recurred despite dose reduction. Promptly initiate management of diarrhea. Withhold and resume at reduced dose upon recovery or permanently discontinue based on severity.

Fistula Formation and Gastrointestinal Perforation. Of the 799 patients treated with LENVIMA or LENVIMA + everolimus in DTC, RCC, and HCC, fistula or gastrointestinal perforation occurred in 2%. Permanently discontinue in patients who develop gastrointestinal perforation of any severity or grade 3-4 fistula.

QT Interval Prolongation. In DTC, QT/QTc interval prolongation occurred in 9% of LENVIMA-treated patients and QT interval prolongation of >500 ms occurred in 2%. In RCC, QTc interval increases of >60 ms occurred in 11% of patients receiving LENVIMA + everolimus and QTc interval >500 ms occurred in 6%. In HCC, QTc interval increases of >60 ms occurred in 8% of LENVIMA-treated patients and QTc interval >500 ms occurred in 2%.

Monitor and correct electrolyte abnormalities at baseline and periodically during treatment. Monitor electrocardiograms in patients with congenital long QT syndrome, congestive heart failure, bradyarrhythmias, or those who are taking drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics. Withhold and resume at reduced dose upon recovery based on severity.

Hypocalcemia. In DTC, grade 3-4 hypocalcemia occurred in 9% of LENVIMA treated patients. In 65% of cases, hypocalcemia improved or resolved following calcium supplementation with or without dose interruption or dose reduction. In RCC, grade 3-4 hypocalcemia occurred in 6% of LENVIMA + everolimus-treated patients. In HCC, grade 3 hypocalcemia occurred in 0.8% of LENVIMA-treated patients. Monitor blood calcium levels at least monthly and replace calcium as necessary during treatment. Withhold and resume at reduced dose upon recovery or permanently discontinue depending on severity.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS). Across clinical studies of 1823 patients who received LENVIMA as a single agent, RPLS occurred in 0.3%. Confirm diagnosis of RPLS with MRI. Withhold and resume at reduced dose upon recovery or permanently discontinue depending on severity and persistence of neurologic symptoms.

Hemorrhagic Events. Serious including fatal hemorrhagic events can occur with LENVIMA. In DTC, RCC, and HCC clinical trials, hemorrhagic events, of any grade, occurred in 29% of the 799 patients treated with LENVIMA as a single agent or in combination with everolimus. The most frequently reported hemorrhagic events (all grades and occurring in at least 5% of patients) were epistaxis and hematuria. In DTC, grade 3-5 hemorrhage occurred in 2% of LENVIMA-treated patients, including 1 fatal intracranial hemorrhage among 16 patients who received LENVIMA and had CNS metastases at baseline. In RCC, grade 3-5 hemorrhage occurred in 8% of LENVIMA + everolimus-treated patients, including 1 fatal cerebral hemorrhage. In HCC, grade 3-5 hemorrhage occurred in 5% of LENVIMA-treated patients, including 7 fatal hemorrhagic events. Serious tumor-related bleeds, including fatal hemorrhagic events, occurred in LENVIMA-treated patients in clinical trials and in the post-marketing setting. In post-marketing surveillance, serious and fatal carotid artery hemorrhages were seen more frequently in patients with anaplastic thyroid carcinoma (ATC) than other tumors. Safety and effectiveness of LENVIMA in patients with ATC have not been demonstrated in clinical trials.

Consider the risk of severe or fatal hemorrhage associated with tumor invasion or infiltration of major blood vessels (eg, carotid artery). Withhold and resume at reduced dose upon recovery or permanently discontinue based on severity.

Impairment of Thyroid Stimulating Hormone Suppression/Thyroid Dysfunction. LENVIMA impairs exogenous thyroid suppression. In DTC, 88% of patients had baseline thyroid stimulating hormone (TSH) level ≤ 0.5 mU/L. In patients with normal TSH at baseline, elevation of TSH level >0.5 mU/L was observed post baseline in 57% of LENVIMA-treated patients.

In RCC and HCC, grade 1 or 2 hypothyroidism occurred in 24% of LENVIMA + everolimus-treated patients and 21% of LENVIMA-treated patients, respectively. In patients with normal or low TSH at baseline, elevation of TSH was observed post baseline in 70% of LENVIMA-treated patients in HCC and 60% of LENVIMA + everolimus-treated patients in RCC.

Monitor thyroid function prior to initiation and at least monthly during treatment. Treat hypothyroidism according to standard medical practice.

Impaired Wound Healing. Impaired wound healing has been reported in patients who received LENVIMA. Withhold LENVIMA 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. The safety of resumption of LENVIMA after resolution of wound healing complications has not been established.

Osteonecrosis of the Jaw (ONJ). ONJ has been reported in patients receiving LENVIMA. Concomitant exposure to other risk factors, such as bisphosphonates, denosumab, dental disease, or invasive dental procedures, may increase the risk of ONJ.

Perform an oral examination prior to treatment with LENVIMA and periodically during LENVIMA treatment. Advise patients regarding good oral hygiene practices and to consider having preventive dentistry performed prior to treatment with LENVIMA and throughout treatment with LENVIMA.

Avoid invasive dental procedures, if possible, while on LENVIMA treatment, particularly in patients at higher risk. Withhold LENVIMA for at least 1 week prior to scheduled dental surgery or invasive dental procedures, if possible. For patients requiring invasive dental procedures, discontinuation of bisphosphonate treatment may reduce the risk of ONJ.

Withhold LENVIMA if ONJ develops and restart based on clinical judgement of adequate resolution.

Embryo-Fetal Toxicity. Based on its mechanism of action and data from animal reproduction studies, LENVIMA can cause fetal harm when administered to pregnant women. In animal reproduction studies, oral administration of lenvatinib during organogenesis at doses below the recommended clinical doses resulted in embryotoxicity, fetotoxicity, and teratogenicity in rats and rabbits. Advise pregnant women of the potential risk to a fetus and advise females of reproductive potential to use effective contraception during treatment with LENVIMA and for 30 days after the last dose.

Adverse Reactions

In DTC, the most common adverse reactions ($\geq 30\%$) observed in LENVIMA-treated patients were hypertension (73%), fatigue (67%), diarrhea (67%), arthralgia/myalgia (62%), decreased appetite (54%), decreased weight (51%), nausea (47%), stomatitis (41%), headache (38%), vomiting (36%), proteinuria (34%), palmar-plantar erythrodysesthesia syndrome (32%), abdominal pain (31%), and dysphonia (31%). The most common serious adverse reactions ($\geq 2\%$) were pneumonia (4%), hypertension (3%), and dehydration (3%). Adverse reactions led to dose reductions in 68% of LENVIMA-treated patients; 18% discontinued LENVIMA. The most common adverse reactions ($\geq 10\%$) resulting in dose reductions were hypertension (13%), proteinuria (11%), decreased appetite (10%), and diarrhea (10%); the most common adverse reactions ($\geq 1\%$) resulting in discontinuation of LENVIMA were hypertension (1%) and asthenia (1%).

Use in Specific Populations

Because of the potential for serious adverse reactions in breastfed children, advise women to discontinue breastfeeding during treatment and for 1 week after the last dose. LENVIMA may impair fertility in males and females of reproductive potential.

No dose adjustment is recommended for patients with mild (CLcr 60-89 mL/min) or moderate (CLcr 30-59 mL/min) renal impairment. LENVIMA concentrations may increase in patients with DTC, RCC, or EC (endometrial carcinoma) and severe (CLcr 15-29 mL/min) renal impairment. Reduce the dose for patients with DTC, RCC, or EC and severe renal impairment. There is no recommended dose for patients with HCC and severe renal impairment. LENVIMA has not been studied in patients with end-stage renal disease.

No dose adjustment is recommended for patients with HCC and mild hepatic impairment (Child-Pugh A). There is no recommended dose for patients with HCC with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment. No dose adjustment is recommended for patients with DTC, RCC, or EC and mild or moderate hepatic impairment. LENVIMA concentrations may increase in patients with DTC, RCC, or EC and severe hepatic impairment. Reduce the dose for patients with DTC, RCC, or EC and severe hepatic impairment.

For more information about LENVIMA, please see available full Prescribing Information: <http://bit.ly/LenvimaPI>

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