

Lenvatinib expands its reach into renal cell carcinoma

The US Food and Drug Administration (FDA) expanded the approval of the multitargeted tyrosine kinase inhibitor lenvatinib to a second indication in 2016. In addition to thyroid cancer, the drug is now approved in combination with the mammalian target of rapamycin (mTOR) inhibitor everolimus for the treatment of advanced renal cell carcinoma (RCC) after one prior anti-angiogenic therapy.

The current approval was based on the demonstration of synergistic efficacy and a manageable toxicity profile for the combination in a randomized, open-label, phase 2 clinical trial performed at 37 centers in 5 countries. Patients were eligible for the study if they were aged 18 years or older and had histologically verified clear cell RCC, measurable disease as assessed by RECIST (Response Evaluation Criteria in Solid Tumors) version 1.1, radiographic evidence of progression or metastasis within 9 months of ending previous treatment, 1 previous disease progression with anti-angiogenic therapy, ECOG (Eastern Cooperative Oncology Group) performance status of 0 or 1, and adequately controlled blood pressure and renal, bone marrow, blood coagulation, liver and cardiac function. Exclusion criteria included brain metastases, previous exposure to lenvatinib or mTOR inhibitors, and receipt of any anticancer therapy or major surgery within 3 weeks of the start of the study.

From March 16, 2012 to June 19, 2013, 153 patients were randomly assigned in a 1:1:1 ratio to 3 treatment arms; lenvatinib 18 mg plus everolimus 5 mg, lenvatinib 24 mg monotherapy, or everolimus 10 mg monotherapy, all administered once daily. Randomization was stratified according to hemoglobin (men ≤ 130 g/L and >130 g/L; women ≤ 115 g/L and >115 g/L) and corrected serum calcium (≥ 2.5 mmol/L and <2.5 mmol/L).

Radiographic tumor response assessments were performed every 8 weeks from randomization until disease progression or the start of another anticancer treatment. To enable pharmacokinetic analyses, 6 blood samples were obtained on day 1 of the first 3 treatment cycles for all patients. In addition, 9 samples were obtained over a 24-hour period for 9-12 patients in each treatment group to provide intensive samples.

The primary endpoint of the study was progression-free survival (PFS), which was significantly improved with a combination of lenvatinib and everolimus, compared with single-agent everolimus. Median PFS was 14.6 months,

What's new, what's important

The multitargeted TKI, lenvatinib, has received approval advanced RCC, in addition to its original approval for thyroid cancer. The latest approval is in combination with everolimus, following anti-angiogenic therapy. It was based on the demonstration of synergistic efficacy and a manageable toxicity profile for the combination in a randomized, open-label, phase 2, multicenter clinical trial. Patients were randomized in a 1:1:1 ratio to 3 treatment arms; lenvatinib 18 mg plus everolimus 5 mg, lenvatinib 24 mg monotherapy, or everolimus 10 mg monotherapy, all once daily. Radiographic tumor response assessments were performed every 8 weeks from randomization until disease progression or the start of another anticancer treatment.

The recommended dose for the lenvatinib-everolimus combination is lenvatinib, 18 mg (1 x 10 mg capsule and 2 x 4 mg capsules) with 5 mg everolimus orally daily, with or without food, until disease progression or unacceptable toxicity. Patients should be warned the risk of fetal harm and monitored for blood pressure changes, signs of cardiac decompensation and proteinuria, and liver function changes. Treatment should be discontinued in the event of life-threatening hypertension, grade 4 cardiac dysfunction, arterial thromboembolic events, hepatic failure, grade 3 diarrhea that persists despite medical management, severe or persistent renal impairment, GI perforation or life-threatening fistula formation, severe and persistent neurologic symptoms, and grade 4 hemorrhage.

— Jame Abraham, MD, FACP (abrahamj5@ccf.org)

compared with 5.5 months, respectively (hazard ratio [HR], 0.40; $P = .0005$), translating into a 63% reduction in the risk of disease progression or death. In the lenvatinib monotherapy group, median PFS was 7.4 months.

Over a median follow-up of 24.2 months there was also a significant difference in overall survival (OS) between the combination arm and single-agent everolimus (24.2 months vs 15.4 months, respectively). Objective responses were seen in 43% of patients in the combination arm and 6% and 27% of patients in the everolimus and lenvatinib monotherapy arms, respectively. The median duration of response was 13 months, 8.5 months, and 7.5 months in the 3 treatment arms, respectively.

All patients had at least 1 treatment-related adverse event (AE), almost all considered to be related to the study drug.

Mechanism of action: lenvatinib and everolimus

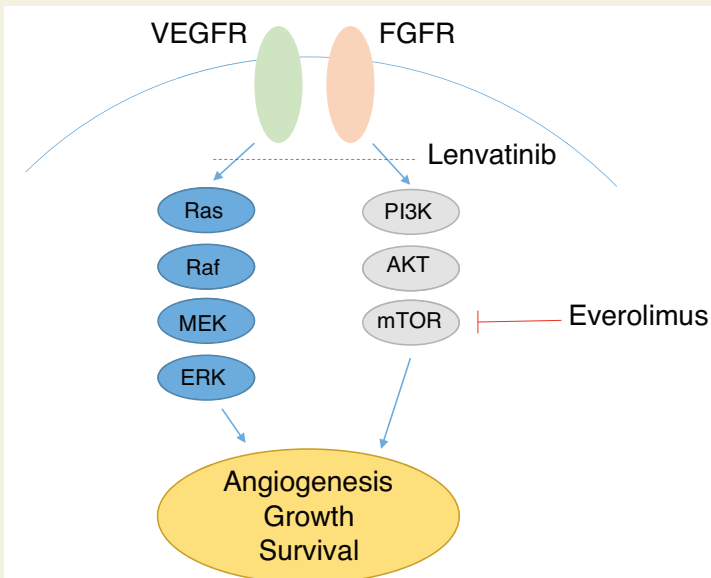
Simultaneous inhibition of critical pathways in RCC

The overwhelming majority of clear cell renal cell carcinomas (RCCs) display dysregulation of a particular signaling network, involving the Von Hippel Lindau (VHL) tumor suppressor protein. VHL plays a key role in the removal of damaged or surplus proteins from the cell, by “tagging” them for destruction by the proteasomal machinery.

One outcome of a dysfunctional VHL pathway is concomitant dysregulation of the proteins it targets for destruction, which include the transcription factor hypoxia inducible factor 1 alpha (HIF1-alpha). In the presence of a defective VHL protein, HIF-alpha is no longer disposed of as it should be, leading to its accumulation in the cell and overactivation of the genes it transcriptionally regulates in the nucleus, including the vascular endothelial growth factor (VEGF), which plays a key role in regulating the formation of new blood vessels from the pre-existing vasculature (otherwise known as angiogenesis). Dysregulated angiogenesis and, as a consequence, the formation of dilated, tortuous, and hyperpermeable blood vessels, is a hallmark of cancer.

VEGF and its receptor, VEGFR, have thus emerged as important targets for therapy in RCC, as has the mammalian target of rapamycin (mTOR), a central signaling protein in numerous pathways related to cell growth and survival, which is particularly important to the development of RCC because of its role in the regulation of HIF1-alpha and VEGF.

Current treatment paradigms for metastatic RCC incorporate both VEGF/R and mTOR pathway inhibitors; 4 multitargeted kinase inhibitors and a monoclonal antibody targeting the former and small molecule inhibitors of the latter are all approved by the FDA as monotherapy, but have resulted in only modest improvements in patient survival. It has long been suspected that simultaneous targeting of multiple signaling pathways through combination therapy might enhance the efficacy of these drugs.



The combination of lenvatinib, a multitargeted tyrosine kinase inhibitor, and everolimus, an mTOR inhibitor, permits simultaneous inhibition of several pathways critical to the progression of renal cell carcinoma.

Lenvatinib is a novel receptor tyrosine kinase (RTK) inhibitor that blocks the kinase activities of the VEGFRs, in addition to a number of other RTKs that are implicated in angiogenesis, as well as other cellular processes central to tumor growth and progression, including the fibroblast growth factor receptors (FGFRs), platelet derived growth factor receptor alpha (PDGFR-alpha), KIT and RET.

Combining lenvatinib treatment with an mTOR inhibitor would therefore permit multiple signaling pathways in which the target proteins of these drugs are involved to be inhibited simultaneously, to provide more complete blockade of the cellular processes they conduct and to circumvent various potential mechanisms of resistance. Combination of these drugs in preclinical models demonstrated synergistic antitumor activity and has served as the rationale for their clinical development.

Among patients treated with lenvatinib and everolimus, 24% discontinued therapy because of AEs, whereas the rate of discontinuation was 12% and 25% among patients treated with everolimus or lenvatinib monotherapy, respectively. There was 1 instance of a trans-arterial embolization leading to death that was judged to be probably treatment related in the combination arm, compared with 2 in the everolimus arm, neither judged treatment-related, and 3 in the lenvatinib arm, 1 of which was considered to be possibly treatment related.

The rates of grade 3/4 AEs were 71% for combination therapy, compared with 50% and 79%, respectively, among

patients treated with everolimus or lenvatinib alone. Most commonly, in the combination arm, these included renal failure (11%), dehydration (10%), anemia (6%), thrombocytopenia (5%), diarrhea (5%), vomiting (5%), and dyspnea (5%).

The prescribing information carries warnings and precautions about hypertension, cardiac dysfunction, arterial thromboembolic events, hepatotoxicity, proteinuria, diarrhea, renal failure and impairment, gastrointestinal perforation, and fistula formation, QT interval prolongation, hypocalcemia, reversible posterior leukoencephalopathy syndrome, hemorrhagic events, and impairment of thyroid

stimulating hormone suppression or thyroid dysfunction, all of which have been reported in clinical trials of lenvatinib and everolimus. Patients should also be warned about the risk of fetal harm.

Blood pressure should be closely monitored prior to treatment, after 1 week and then every 2 weeks for the first 2 months, then at least monthly thereafter during treatment. Patients should be monitored for signs of cardiac decompensation and proteinuria. Liver function should be monitored before initiating therapy, every 2 weeks for the first 2 months and then at least monthly while treatment continues. Electrolyte abnormalities should be monitored and corrected, blood calcium levels should be monitored at least monthly, and thyroid function should be evaluated before and at least monthly during treatment.

The prescribing information details dose reductions and modifications for AEs. Treatment should be withheld for grade 3 hypertension, grade 3 cardiac dysfunction, grade 3

or greater hepatotoxicity, proteinuria >2 g/24 hours, grade 3 diarrhea, grade 3/4 renal failure or impairment, corrected QT interval prolongation >500 ms, hypocalcemia as necessary, reversible posterior leukoencephalopathy syndrome confirmed by magnetic resonance imaging, and grade 3 hemorrhagic events.

Treatment discontinuation should occur in the event of life-threatening hypertension, grade 4 cardiac dysfunction, arterial thromboembolic events, hepatic failure, grade 3 diarrhea that persists despite medical management, severe or persistent renal impairment, gastrointestinal perforation or life-threatening fistula formation, severe and persistent neurologic symptoms, and grade 4 hemorrhage. The recommended dose for lenvatinib, which is marketed as Lenvima by Eisai Inc, is 18 mg (1 x 10 mg capsule and 2 x 4 mg capsules) in combination with 5 mg everolimus orally taken daily, with or without food, until disease progression or unacceptable toxicity.

References

1. Lenvima (lenvatinib) capsules, for oral use. Prescribing information. Woodcliff Lake, NJ: Eisai Inc; 2016. <http://www.lenvima.com/pdfs/prescribing-information.pdf>. Accessed November 17, 2016.
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3. US Food and Drug Administration. Lenvatinib in combination with everolimus. <http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm501070.htm>. Last updated May 16, 2016. Accessed November 17, 2016.