Renal cell carcinoma approval adds another notch to cabozantinib's belt

In April this year, the US Food and Drug Administration awarded regulatory approval to cabozantinib for the treatment of advanced renal cell carcinoma patients previously treated with anti-angiogenic therapy.[1] The small-molecule inhibitor, which targets multiple kinases, including the vascular endothelial growth factor receptors (VEGFRs) and the hepatocyte growth factor receptor (MET), had previously been approved for the treatment of medullary thyroid carcinoma in 2012.

The current approval followed positive results from the phase 3 METEOR trial, in which cabozantinib was compared with a standard of care for RCC, the mammalian target of rapamycin (mTOR) inhibitor everolimus.[2] A total of 658 patients aged 18 years or older, with advanced or metastatic RCC with a clear cell component, who had received prior therapy with at least one VEGFR-targeting drug, and had radiographic progression during treatment or within 6 months of the last dose of that drug, were randomized 1:1 to receive either a 60-mg oral dose of cabozantinib or a 10-mg oral dose of everolimus once daily until progression or development of unacceptable toxicity.

Patients were also required to have a Karnofsky performance-status score of at least 70% (on a scale of 0-100%, with a higher score indicating better performance status) and adequate organ and marrow function, and patients with brain metastases were eligible if they were adequately treated and stable. Patients who had been treated previously with an mTOR inhibitor or cabozantinib and those with a history of uncontrolled, clinically significant illness were not eligible for the study.

Randomization was stratified according to the number of previous VEGFR-targeting drugs received and prognostic risk category according to the Memorial Sloan Kettering Cancer Center (MSKCC) criteria. Treatment groups were balanced with respect to baseline demographics and disease characteristics. The median age of patients was 62 years and the majority had received one prior VEGFR inhibitor.

The primary endpoint was progression-free survival (PFS), defined as the interval between the date of randomization and the first documented disease progression, as assessed by an independent radiology review committee, or death from any cause. The median PFS was significantly improved in the cabozantinib arm, with a 42% reduction in the risk of disease progression or death (median PFS, 7.4 months vs 3.8 months; hazard ratio [HR], 0.58; $P < .001$). There was a consistent PFS benefit with cabozantinib across all prespecified subgroups, but it was particularly noteworthy among patients who received sunitinib as their only prior VEGFR inhibitor (median PFS, 9.1 months vs 3.7 months). Median overall survival (OS) was also significantly improved in patients treated with cabozantinib (median OS, 21.4 months vs 16.5 months; HR, 0.66; $P = .0003$), as was confirmed response rate (17% vs 3%).

The safety of cabozantinib was assessed in 331 patients over a median duration of treatment of 7.6 months and

What's new, what's important

The small-molecule inhibitor, cabozantinib, was approved for advanced RCC in patients who have received previous anti-angiogenic therapy. It is a multitargeted kinase inhibitor that inhibits angiogenic targets like the VEGFRs and blocks additional kinases such as MET and AXL, which are particularly relevant to kidney cancer. The approval was based on data from the phase 3 METEOR trial, in which patients received cabozantinib or everolimus. Median PFS was significantly improved with cabozantinib, with a 42% reduction in the risk of disease progression or death (median PFS, 7.4 vs 3.8 months for everolimus).

The recommended dose is 60 mg orally daily, with warnings that the drug should not be given to patients with or at risk for severe hemorrhage and that they are monitored for symptoms of GI perforations and fistulas. Patient blood pressure should be monitored before starting and during therapy, and those presenting with seizures, headaches, visual disturbances, confusion, or altered mental function should be evaluated for RPLS.

The most common AEs included diarrhea, fatigue, and nausea. Serious grade 3/4 AEs were reported for 68% of the cabozantinib patients (everolimus, 58%); grade 5 AEs occurred in 7% and 8% of patients, respectively, and were mostly related to disease progression. In the cabozantinib arm, the most common AEs included hypertension (15%), diarrhea (11%), and fatigue (9%). Dose reductions occurred in 60% of cabozantinib patients (everolimus, 25%). The AEs most commonly leading to dose reductions with cabozantinib were diarrhea (16%), PPES (11%) and fatigue (10%).

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Mechanism of action: cabozantinib

Blocking multiple targets to enhance efficacy and overcome resistance

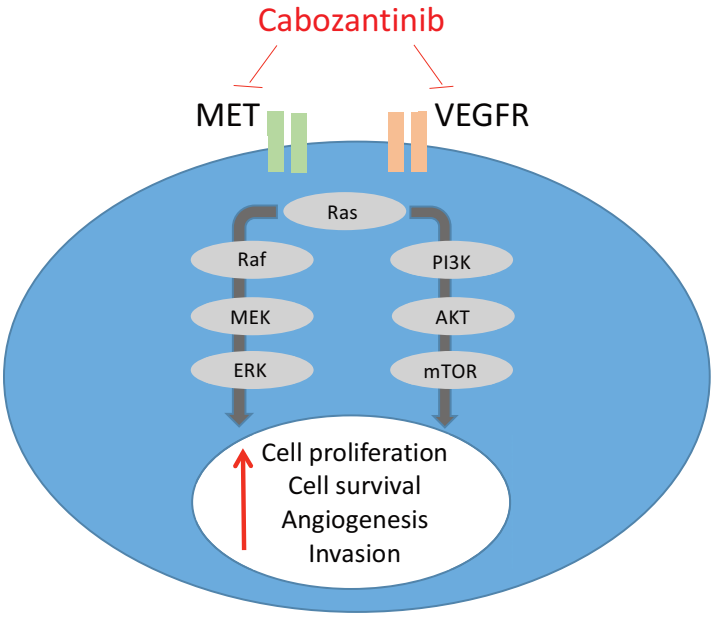
More than 90% of renal cell carcinoma (RCC) cases exhibit dysregulation of the von Hippel-Lindau (VHL) pathway. VHL is an enzyme that 'tags' target proteins in the cell with ubiquitin molecules that serve as a signal to the proteasomal machinery that those proteins should be destroyed and removed from the cell.

One of the proteins targeted by VHL is the hypoxia-inducible factor 1 alpha (HIF1-alpha), an oxygen-sensing transcription factor that mediates the expression of a number of genes in the nucleus, including the vascular endothelial growth factor (VEGF).

Since VEGF and its receptors (VEGFRs 1-3), play a key role in angiogenesis, which is the formation of new blood vessels from the existing vasculature and one of the hallmarks of cancer, and because kidney cancers are highly vascularized as a result of the corruption of these signals, it was suspected that RCC would be susceptible to anti-angiogenic therapy.

Drugs targeting both VEGF and the VEGFRs, as well as other kinases involved in angiogenesis, have been tested in RCC and paved the way for a decade of FDA approvals, including sunitinib and bevacizumab, but none of these drugs provide long-term durable remission and the search for new therapies continues. Further unraveling of the molecular mechanisms underpinning RCC yielded several inhibitors of the mammalian target of rapamycin (mTOR), including everolimus, which remains the only drug to improve overall survival.

Cabozantinib has a novel mechanism of action; it is a multi-targeted kinase inhibitor like sunitinib, but in addition to inhibiting angiogenic targets like the VEGFRs, it also blocks additional kinases, including MET and AXL, which are particularly relevant to kidney cancer.



Cabozantinib inhibits multiple tyrosine kinases, including the hepatocyte growth factor receptor (MET) and vascular endothelial growth factor receptors (VEGFRs). Both receptors are involved in angiogenesis, tumor cell proliferation and metastasis. MET is also thought to be involved in driving resistance to VEGFR-targeted therapies, thus targeting both kinases may provide added benefit.

The expression of MET and AXL are also upregulated in response to inactivation of VHL and the resulting dysregulation of HIFs. In addition to a role in angiogenesis, these kinases also play important roles in tumor cell proliferation, invasion and metastasis. Most notably, preclinical studies suggest that upregulation of MET and AXL offers a means of resistance to VEGFR-targeted therapies in RCC and other tumor types, thus targeting these multiple pathways has the potential for synergy and additional therapeutic benefit.

the most common adverse events (AEs) included diarrhea, fatigue, and nausea. Serious AEs (grade 3/4) were experienced by 68% of patients treated with cabozantinib and 58% of patients in the everolimus arm and grade 5 AEs occurred in 7% and 8% of patients, respectively, and were mostly related to disease progression. In the cabozantinib arm, these most commonly included hypertension (15%), diarrhea (11%), and fatigue (9%). Dose reductions occurred in 60% of patients treated with cabozantinib, compared with 25% of everolimus-treated patients. The AEs most commonly leading to dose reductions with cabozantinib were diarrhea (16%), palmar-plantar erythrodysesthesia syndrome (PPES; 11%) and fatigue (10%).

The prescribing information recommends a daily oral dose of 60 mg for cabozantinib and provides warnings and precautions and offers guidance on the management of key AEs.[3] Cabozantinib should not be administered to patients that have or are at risk for severe hemorrhage. Patients should be monitored for symptoms of gastrointestinal (GI) perforations and fistulas and cabozantinib should be discontinued in patients who develop an unmanageable fistula or GI perforation.

Patients should have their blood pressure monitored prior to initiation and regularly during treatment and those presenting with seizures, headaches, visual disturbances, confusion, or altered mental function should be evaluated for reversible posterior leukoencephalopathy syndrome (RPLS). Cabozantinib should be withheld for hyperten-

sion that is not adequately managed medically, in patients who develop intolerable grade 2 diarrhea or grade 3-4 diarrhea that cannot be managed with standard treatments, and among those who develop intolerable grade 2 or 3 PPES, and subsequently resumed at a reduced dose upon adequate resolution of the toxicity.

Cabozantinib, which is marketed by Exelixis Inc as Cabometyx, should be discontinued in patients who develop acute myocardial infarction or any other arterial thromboembolic complication, for severe hypertension that cannot be controlled with anti-hypertensive therapy, in patients who have evidence of hypertensive crisis or severe hypertension despite optimal medical management, and in patients who develop RPLS.

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