KIDNEY CANCER UPDATE

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Lenvatinib/Everolimus Improves Survival Better Than Everolimus Alone in Metastatic Renal Cell Cancer

Based on a presentation by Robert Motzer, MD, at the American Society of Clinical Oncology Annual Meeting

Progression-free survival (PFS) was longer with a combination of lenvatinib (Lenvima, Eisai) and everolimus (Afinitor, Novartis) than with everolimus alone as second-line treatment for metastatic renal cell cancer (RCC), according to the results of a phase 2 trial. Dr Robert Motzer, a professor of medicine at Weill Cornell Medical College in New York, New York, presented results from the study at the recent meeting of the American Society of Clinical Oncology.[1]

The addition of lenvatinib to everolimus increased median PFS from 5.5 months to 14.6 months. In addition, there was a trend toward increased overall survival (OS) in the combination group vs everolimus.

An International, Randomized Phase 2 Study

This international, randomized phase 2 open-label study (NCT0113673) enrolled 153 patients with RCC that had progressed after 1 prior vascular endothelial growth factor (VEGF)-targeted therapy. A total of 51 patients received the combination therapy, 52 patients received lenvatinib alone, and 50 patients received everolimus alone.

The primary objective was to compare PFS with the combination vs everolimus, and lenvatinib alone vs everolimus. Secondary objectives included comparing PFS with the combination vs lenvatinib alone and assessment of objective response rate (ORR), OS, safety, and tolerability.

The key eligibility criteria included advanced or metastatic RCC, measurable disease, progression on or after 1 prior VEGF-targeted therapy, progression within 9 months of discontinuing prior therapy, and an Eastern Cooperative Oncology Group performance status of 0 or 1. Patients were randomly assigned to treatment according to the stratification factors of hemoglobin (normal vs low) and corrected serum calcium (≥10 mg/dL vs <10 mg/dL).

"The demographics were quite typical" of a pretreated RCC population, said Dr Motzer. The most common previous VEGF-targeted treatment was sunitinib (Sutent, Pfizer), followed by pazopanib (Votrient, GlaxoSmithKline). Prior therapies other than VEGF-targeted inhibitors were allowed, but only 13% of the patients had prior cytokine or checkpoint inhibitor therapy in a previous clinical trial.

For the combination treatment, lenvatinib was given orally at 18 mg daily with everolimus orally at 5 mg daily. Lenvatinib monotherapy was given orally at 24 mg daily, and everolimus monotherapy was given orally at 10 mg daily (the standard dosing schedule). Patients were treated until disease progression or unacceptable toxicity, and there was no crossover within the context of the study. Efficacy and safety metrics were assessed at prespecified intervals according to standard criteria. PFS and ORR were measured using the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Safety was assessed using physical examination, clinical investigation, and adverse event monitoring.

This study was designed with 70% power to detect a 50% improvement in an assumed 5-month PFS for everolimus alone. PFS and OS were assessed by stratified log-rank tests. The data cutoff for the primary analysis was June 13, 2014; however, the steering committee suggested updating the OS analysis to a later date (December 10, 2014) following a review of the primary data.

Primary Endpoint Analysis

At the time of the primary endpoint analysis, 23 patients remained on treatment. The median duration of treatment for the combination, lenvatinib alone, and everolimus alone was 7.6, 7.4, and 4.1 months, respectively. Dose reduction of lenvatinib in combination and as monotherapy was common (71% and 62%, respectively). Dose modification of everolimus was required in 26% of patients. Most toxicities were managed by dose modification; however, 9 patients, 11 patients, and 5 patients discontinued the combination, lenvatinib, and everolimus, respectively, owing to adverse events. The most common reason for drug discontinuation was progression.

The median PFS was the longest for patients receiving the combination treatment (14.6 months), followed

by lenvatinib alone (7.4 months) and everolimus alone (5.5 months). The combination significantly improved PFS compared with everolimus (hazard ratio [HR], 0.40; 95% CI, 0.24-0.68; *P*<.001). Lenvatinib monotherapy also significantly improved PFS compared with everolimus (HR, 0.61; 95% CI, 0.38-0.98; *P*=.048). The highest ORR was seen in patients treated with the combination (43%) compared with lenvatinib (27%) and everolimus (6%). Most patients had partial responses, although 1 complete remission was observed in a patient treated with the combination. The duration of ORR also was longer with the combination treatment (13 months) compared with lenvatinib (7.5 months) and everolimus (8.5 months).

At the primary planned OS analysis, the investigators observed a trend of increased OS for the combination vs everolimus (HR, 0.55; 95% CI, 0.30-1.10; *P*=.062). The median OS was 25.5 months for the combination, 18.4 months for lenvatinib alone, and 17.5 months for everolimus alone. In an updated analysis, the OS difference between patients who received the combination vs everolimus reached significance (HR, 0.51; 95% CI, 0.30-0.88; *P*=.024) with a median OS of 25.5 months vs 15.4 months, respectively. The updated OS for lenvatinib alone was 19.1 months.

A secondary objective was to compare the efficacy of the lenvatinib/everolimus combination vs lenvatinib alone. The median PFS and OS for the combination were numerically higher than lenvatinib (PFS, 14.6 months and 7.4 months, respectively; OS, 25.5 months and 19.1 months, respectively), but this was not a significant change (PFS, *P*=.121; OS, *P*=.316). There was also a trend toward a higher ORR with the combination vs lenvatinib (43% vs 27%, respectively; *P*=.101).

Treatment-Emergent Adverse Events

All patients experienced at least 1 treatment-emergent adverse event. Patients treated in each of the 2 lenvatinib-containing arms had more grade 3 and a similar proportion of grade 4 adverse events compared with patients in the everolimus-alone arm. Prominent grade 3 adverse events associated with lenvatinib included diarrhea, fatigue, nausea, vomiting, and hypertension.

Notably, the combination arm had a 23% incidence of grade 3 diarrhea, which "highlights the need for the recognition and management of this toxicity," especially in this combination. However, there were relatively few grade 4 events in any of the 3 arms. Two grade 5 adverse events were attributed to the study drug, 1 in each lenvatinib-containing arm.

An Unmet Need in Relapsed or Refractory RCC

"There is an unmet need for improved treatment outcome" for patients with RCC that has relapsed or is refractory to standard VEGF and mammalian target of rapamycin (mTOR) inhibitors, said Dr Motzer. Some research suggests that these tumors have activation of the fibroblast growth factor (FGF) pathway as a mechanism of resistance to VEGF-targeted therapies.[2] Lenvatinib is a highly potent tyrosine kinase inhibitor of VEGF receptors 1 to 3 and FGF receptors 1 to 4, meaning it could be beneficial for these patients.[3-5] In mouse RCCs xenograft models, lenvatinib and the combination of lenvatinib with the mTOR inhibitor everolimus demonstrated antitumor activity. The highest activity was achieved with the combination vs either drug alone.

Dr Motzer said that his group previously conducted a phase 1 study in RCC patients that established a maximum tolerated dose for lenvatinib (18 mg daily) and everolimus (5 mg daily), and found that using these doses resulted in an ORR of 30%.[6]

Further Study of Lenvatinib

Dr Motzer concluded that this randomized phase 2 trial met its primary endpoint, showing an improved PFS efficacy for the combination of lenvatinib/everolimus and lenvatinib monotherapy compared with everolimus monotherapy in patients who had progressed on 1 prior VEGF-targeted drug. Although the improved PFS benefit was observed in both the lenvatinib-containing arms, the magnitude of the PFS, the high ORR, and the longer OS results speak to the high level of efficacy observed in this study for the combination. The adverse events were generally higher for the lenvatinib-containing arms compared with the everolimus arm; however, these adverse events were predictable and generally managed with dose modification. Based on these results, said Dr Motzer, "further study of lenvatinib is warranted in RCC."

References

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