Adjuvant treatment with the oral antiangiogenic drugs sorafenib and sunitinib doesn’t improve survival after complete resection of non-metastatic renal cell carcinoma (RCC), reports a placebo-controlled trial in The Lancet. The study included 1943 patients with completely resected, non-metastatic clear-cell or non-clear-cell RCC considered at high risk of recurrence. After stratification for recurrence risk and other characteristics, patients were randomly assigned to 54 weeks of treatment with sunitinib, sorafenib, or placebo. Disease-free survival was assessed by intention to treat. The two active treatments had high rates of discontinuation related to toxic effects: 44 percent with sunitinib and 45 percent with sorafenib. This prompted reduction in the starting doses, which were then titrated up to the original full doses. However, toxicity remained high even at the reduced dosing regimen. The trial was halted early owing to low conditional power for the primary end-point. Disease-free survival was not significantly different between groups median 5.8 years with sunitinib, 6.1 years with sorafenib, and 6.6 years with placebo. Frequent grade 3 adverse events included hypertension, hand-foot syndrome, rash, and fatigue. There were five deaths either related to treatment or occurring within 30 days after the end of treatment.

Findings

No Benefit of Adjuvant Antiangiogenic Drugs in Renal Cell Carcinoma

During the clinical studies, the most commonly reported adverse reactions leading to discontinuation of VELTASSA were gastrointestinal adverse reactions (7.7%), including vomiting (0.8%), diarrhea (0.6%), constipation (0.5%) and flatulence (0.5%). Mild to moderate hypersensitivity reactions were reported in 0.3% of patients treated with VELTASSA in clinical trials. Reactions have included edema of the lips. Laboratory Abnormalities Approximately 4.7% of patients in clinical trials developed hypokalemia with a serum potassium value < 3.5 mEq/L. Approximately 9% of patients in clinical trials developed hypomagnesemia with a serum magnesium value < 1.4 mg/dL.

DRUG INTERACTIONS

No formal drug interaction studies have been conducted in humans. In in vitro binding studies, VELTASSA was shown to bind about half of the oral medications that were tested. Binding of VELTASSA to other oral medications could cause decreased gastrointestinal absorption and loss of efficacy when taken together to close the time when VELTASSA is administered. Direct oral medications at least 6 hours before or 6 hours after VELTASSA. Monitor for clinical response and/or blood levels where possible.

USE IN SPECIFIC POPULATIONS

The most common adverse reactions (≥3% and at least 1% greater than placebo) in controlled trials of VELTASSA were gastrointestinal adverse reactions that resulted in discontinuation of VELTASSA (7.7%), including vomiting (0.8%), diarrhea (0.6%), constipation (0.5%), and flatulence (0.5%). Mild to moderate hypersensitivity reactions were reported in 0.3% of patients treated with VELTASSA in clinical trials. Reactions have included edema of the lips. Laboratory Abnormalities Approximately 4.7% of patients in clinical trials developed hypokalemia with a serum potassium value < 3.5 mEq/L. Approximately 9% of patients in clinical trials developed hypomagnesemia with a serum magnesium value < 1.4 mg/dL.

INDICATION AND LIMITATION OF USE

VELTASSA is indicated for the treatment of hyperkalemia. Limitation of Use: VELTASSA should not be used as an emergency treatment for life-threatening hyperkalemia because of its delayed onset of action.

CONTRAINdications

VELTASSA is contraindicated in patients with a history of a hypersensitivity reaction to VELTASSA or any of its components (see Adverse Reactions). WARNINGS AND PRECAUTIONS

Binding to Other Orally Administered Medications VELTASSA binds many orally administered medications, which could decrease their gastrointestinal absorption and lead to reduced efficacy. Administer other oral medications at least 6 hours before or 6 hours after VELTASSA. Choose VELTASSA or the other oral medication if adequate dosing separation is not possible (see Warnings and Precautions and Drug Interactions).

Worsening of Gastrointestinal Motility Avoid use of VELTASSA in patients with severe constipation, bowel obstruction or impaction, including abnormal post-operative bowel motility disorders, because VELTASSA may be ineffective and may worsen gastrointestinal constipation. Patients with a history of bowel obstruction or major gastrointestinal surgery, severe gastrointestinal disorders, or swallowing disorders were not included in the clinical studies.

Hypomagnesemia VELTASSA binds to magnesium in the colon, which can lead to hypomagnesemia. In clinical studies, hypomagnesemia was reported as an adverse reaction in 5.3% of patients treated with VELTASSA (see Adverse Reactions). Monitor serum magnesium. Consider magnesium supplementation in patients who develop low serum magnesium levels on VELTASSA.

ADVERSE REACTIONS

The following adverse reaction is discussed in greater detail elsewhere in the label:

• Hypomagnesemia (see Warnings and Precautions)

Clinical Trials Experience Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of VELTASSA cannot be directly compared to rates in the clinical trials of other drugs and may not reflect the rates observed in practice. In the safety and efficacy clinical trials, 666 adult patients received at least one dose of VELTASSA, including 219 exposed for at least 6 months and 149 exposed for at least one year. Table 1 provides a summary of the most common adverse reactions (occurring in ≥ 2% of patients) in patients treated with VELTASSA in these clinical trials. Most adverse reactions were mild to moderate. Constipation generally resolved during the course of treatment.

Table 1: Adverse Reactions Reported in ≥ 2% of Patients

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Patients treated with VELTASSA (N=666)</th>
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<tbody>
<tr>
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Incompatible Live-Donor Kidney Transplant Improves Survival, Compared to Waiting

Patients who receive a kidney from an HLA-incompatible live donor have better survival than those who receive a deceased-donor transplant or who remain on the waiting list, concludes a study in The New England Journal of Medicine. The study included 1025 adults who received kidney transplants from HLA-incompatible live donors at 22 US centers between 1997 and 2011. They were matched to control groups of patients who either remained on the waiting list or received a kidney from a deceased donor, and patients who remained on the waiting list without receiving a transplant.

One-year survival was 95.0 percent for patients who received kidneys from HLA-incompatible live donors versus 94.0 percent for patients who received kidneys from deceased donors and 89.6 percent for the waiting-list-only controls. The differences remained significant through 8 years, when survival was 76.5, 62.9, and 43.9 percent, respectively. The 8-year survival advantage of live-donor kidney transplant remained significant at all donor-specific antibody levels. For patients with a positive Luminex assay but a negative flow-cytometric cross-match, transplant from an incompatible live donor increased survival by 24.2 percentage points compared to waiting-list-or-transplant controls and by 42.1 percentage points for waiting-list-alone controls. The differences were 13.0 and 33.3 percentage points for patients with a positive flow-cytometric cross-match but a negative cytotoxic cross-match, and 5.9 and 27.4 percentage points for those with a positive cytotoxic cross-match, respectively. The findings were similar on sensitivity analysis excluding patients from the highest-volume center (Orandi B), et al. Survival benefit with kidney transplants from HLA-incompatible live donors. N Engl J Med [2016; 374: 940-950].

WARNING: BINDING TO OTHER ORAL MEDICATIONS

VELTASSA binds to many orally administered medications, which could decrease their absorption and reduce their effectiveness. Administer other oral medications at least 6 hours before or 6 hours after VELTASSA. Choose VELTASSA or the other oral medication if adequate dosing separation is not possible (see Warnings and Precautions and Drug Interactions).

Dosing Recommendations Inform patients to take VELTASSA as directed (N=666). Choose VELTASSA or the other oral medication if adequate dosing separation is not possible (see Warnings and Precautions and Drug Interactions).

During the clinical studies, the most commonly reported adverse reactions leading to discontinuation of VELTASSA were gastrointestinal adverse reactions (7.7%), including vomiting (0.8%), diarrhea (0.6%), constipation (0.5%) and flatulence (0.5%). Mild to moderate hypersensitivity reactions were reported in 0.3% of patients treated with VELTASSA in clinical trials. Reactions have included edema of the lips. Laboratory Abnormalities Approximately 4.7% of patients in clinical trials developed hypokalemia with a serum potassium value < 3.5 mEq/L. Approximately 9% of patients in clinical trials developed hypomagnesemia with a serum magnesium value < 1.4 mg/dL.

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USE IN SPECIFIC POPULATIONS

Pregnancy Risk Summary VELTASSA is not absorbed systemically following oral administration and maternal use is not expected to result in fetal risk. Lactation Risk Summary VELTASSA is not absorbed systemically by the mother, so breastfeeding is not expected to result in risk to the infant. Pediatric Use Safety and efficacy in pediatric patients have not been established.

Geriatric Use Of the 666 patients treated with VELTASSA in clinical studies, 59.8% were age 65 and over, and 19.8% were age 75 and over. No overall differences in effectiveness were observed between these patients and younger patients. Patients age 65 and older reported more gastrointestinal adverse reactions than younger patients. Renal Impairment Of the 666 patients treated with VELTASSA in clinical studies, 83.8% had chronic kidney disease (CKD). No special dosing adjustments are needed for patients with renal impairment.

OVERDOSAGE

Doses of VELTASSA in excess of 50.4 grams per day have not been tested. Excessive doses of VELTASSA may result in hypokalemia. Restore serum potassium if hypokalemia occurs.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Drug Interactions Advise patients who are taking other oral medication to separate the dosing of VELTASSA by at least 6 hours before or after (see Drug Interactions).

Dosing Recommendations Inform patients to take VELTASSA as directed with food and adhere to their prescribed diets. Instruct patients to prepare each dose separately using the preparation instructions provided in the FDA-approved patient labeling (Medication Guide). Inform patients that VELTASSA should not be heated (e.g., microwave) or added to heated foods or liquids and should not be taken in its dry form.

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Manufactured for:
Relypsa, Inc.
Redwood City, CA 94063
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