NCCN Clinical Practice Guidelines in Oncology
(NCCN Guidelines®)

Kidney Cancer

Overall management of Kidney Cancer from diagnosis through recurrence is described in the full NCCN Guidelines® for Kidney Cancer. Visit NCCN.org to view the complete library of NCCN Guidelines.

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### RELAPSE OR STAGE IV: FIRST-LINE THERAPY FOR CLEAR CELL HISTOLOGY

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Preferred Regimens</th>
<th>Other Recommended Regimens</th>
<th>Useful under certain circumstances</th>
</tr>
</thead>
</table>
| Favorable risk | • Pazopanib (category 1)  
• Sunitinib (category 1) | • Ipilimumab + nivolumab  
• Cabozantinib (category 2B) | • Active surveillance  
• Axitinib (category 2B)  
• Bevacizumab + interferon alfa-2b (category 1)  
• High-dose IL-2 |
| Poor/intermediate risk | • Ipilimumab + nivolumab  
• Cabozantinib | • Pazopanib (category 1)  
• Sunitinib (category 1) | • Axitinib (category 2B)  
• Bevacizumab + interferon alfa-2b (category 1)  
• High-dose IL-2  
• Temsirolimus (category 1) |

### RELAPSE OR STAGE IV: SUBSEQUENT THERAPY FOR CLEAR CELL HISTOLOGY

<table>
<thead>
<tr>
<th>Regimens</th>
<th>Preferred Regimens</th>
<th>Other Recommended Regimens</th>
<th>Useful under certain circumstances</th>
</tr>
</thead>
</table>
| • Cabozantinib (category 1)  
• Nivolumab (category 1)  
• Ipilimumab + nivolumab | • Axitinib (category 1)  
• Lenvatinib + everolimus (category 1)  
• Everolimus  
• Pazopanib  
• Sunitinib | • Bevacizumab (category 2B)  
• Sorafenib (category 2B)  
• High-dose IL-2 for selected patients (category 2B)  
• Temsirolimus (category 2B) |
### RELAPSE OR STAGE IV: SYSTEMIC THERAPY NON-CLEAR CELL HISTOLOGY

<table>
<thead>
<tr>
<th>Preferred regimens</th>
<th>Other recommended regimens</th>
<th>Useful under certain circumstances</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Clinical trial</td>
<td>• Cabozantinib</td>
<td>• Axitinib</td>
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<tr>
<td>• Sunitinib</td>
<td>• Everolimus</td>
<td>• Bevacizumab</td>
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<tr>
<td></td>
<td></td>
<td>• Erlotinib</td>
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<tr>
<td></td>
<td></td>
<td>• Lenvatinib + everolimus</td>
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<tr>
<td></td>
<td></td>
<td>• Nivolumab</td>
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<tr>
<td></td>
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<td>• Pazopanib</td>
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<td>• Bevacizumab + erlotinib for</td>
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<td></td>
<td></td>
<td>selected patients with advanced</td>
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<tr>
<td></td>
<td></td>
<td>papillary RCC including HLRCC</td>
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<tr>
<td></td>
<td></td>
<td>• Bevacizumab + everolimus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Temsirolimus (category 1 for poor-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>prognosis risk group;(m) category</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2A for other risk groups)</td>
</tr>
</tbody>
</table>

**HLRCC:** Hereditary leiomyomatosis and renal cell cancer

\(m\) See Risk Models to Direct Treatment (Predictors of Short Survival Used to Select Patients for Temsirolimus) (KID-C).

\(n\) In clear cell and non-clear cell RCC with predominant sarcomatoid features, gemcitabine + doxorubicin (category 2B) and gemcitabine + sunitinib (category 2B) have shown benefit.

\(o\) For collecting duct or medullary subtypes, partial responses have been observed with cytotoxic chemotherapy (carboplatin + gemcitabine, carboplatin + paclitaxel, or cisplatin + gemcitabine) and other platinum-based chemotherapies currently used for urothelial carcinomas.

**Note:** All recommendations are category 2A unless otherwise indicated.

**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
Indication and Important Safety Information Provided by Exelixis

**INDICATION**

CABOMETYX (cabozantinib) is indicated for the treatment of patients with advanced renal cell carcinoma (RCC).

**WARNINGS AND PRECAUTIONS**

**Hemorrhage:** Severe and fatal hemorrhages have occurred with CABOMETYX. In RCC trials, the incidence of Grade ≥ 3 hemorrhagic events was 3% in CABOMETYX patients. Do not administer CABOMETYX to patients that have or are at risk for severe hemorrhage.

**Gastrointestinal (GI) Perforations and Fistulas:** In RCC trials, GI perforations were reported in 1% of CABOMETYX patients. Fatal perforations occurred in patients treated with CABOMETYX. In RCC studies, fistulas were reported in 1% of CABOMETYX patients. Monitor patients for symptoms of perforations and fistulas, including abscess and sepsis. Discontinue CABOMETYX in patients who experience a GI perforation or a fistula that cannot be appropriately managed.

**Thrombotic Events:** Thrombotic events increased with CABOMETYX. In RCC trials, venous thromboembolism occurred in 9% (including 5% pulmonary embolism) and arterial thromboembolism occurred in 1% of CABOMETYX patients. Fatal thrombotic events occurred in the cabozantinib clinical program. Discontinue CABOMETYX in patients who develop an acute myocardial infarction or any other arterial thromboembolic complication.

**Hypertension and Hypertensive Crisis:** Treatment-emergent hypertension, including hypertensive crisis, was reported in 44% (18% Grade ≥3) of CABOMETYX patients. Monitor blood pressure prior to initiation and regularly during CABOMETYX treatment. Withhold CABOMETYX for hypertension that is not adequately controlled with medical management; when controlled, resume CABOMETYX at a reduced dose. Discontinue CABOMETYX if there is evidence of hypertensive crisis or for severe hypertension that cannot be controlled with antihypertensive therapy or medical management.

**Diarrhea:** In RCC trials, diarrhea occurred in 74% of CABOMETYX patients. Grade 3 diarrhea occurred in 11% of CABOMETYX patients. Withhold CABOMETYX in patients who develop intolerable Grade 2 diarrhea or Grade 3-4 diarrhea that cannot be managed with standard antidiarrheal treatments until improvement to Grade 1; resume CABOMETYX at a reduced dose.

**Palmar-Plantar Erythrodysesthesia (PPE):** In RCC trials, PPE occurred in 42% of CABOMETYX patients. Grade 3 PPE occurred in 8% of CABOMETYX patients. Withhold CABOMETYX in patients who develop intolerable Grade 2 PPE or Grade 3 PPE until improvement to Grade 1; resume CABOMETYX at a reduced dose.

**Reversible Posterior Leukoencephalopathy Syndrome (RPLS):** RPLS, a syndrome of subcortical vasogenic edema diagnosed by characteristic finding on MRI, occurred in the cabozantinib clinical program. Evaluate for RPLS in patients presenting with seizures, headache, visual disturbances, confusion, or altered mental function. Discontinue CABOMETYX in patients who develop RPLS.

**Embryo-fetal Toxicity:** CABOMETYX can cause fetal harm. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during CABOMETYX treatment and for 4 months after the last dose.

**ADVERSE REACTIONS**

The most commonly reported (≥25%) adverse reactions were: diarrhea, fatigue, nausea, decreased appetite, hypertension, PPE, weight decreased, vomiting, dysgeusia, and stomatitis.

**DRUG INTERACTIONS**

**Strong CYP3A4 Inhibitors:** If concomitant use with strong CYP3A4 inhibitors cannot be avoided, reduce the CABOMETYX dosage.

**Strong CYP3A4 Inducers:** If concomitant use with strong CYP3A4 inducers cannot be avoided, increase the CABOMETYX dosage.

**USE IN SPECIFIC POPULATIONS**

**Lactation:** Advise women not to breastfeed while taking CABOMETYX and for 4 months after the final dose.

**Hepatic Impairment:** In patients with mild to moderate hepatic impairment, reduce the CABOMETYX dosage. CABOMETYX is not recommended for use in patients with severe hepatic impairment.

Please see accompanying full Prescribing Information.
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