## Treatment Regimens for Oral Therapies Indicated for Renal Cell Carcinoma

<table>
<thead>
<tr>
<th>DRUG</th>
<th>CLASS</th>
<th>INITIAL DOSE</th>
<th>DOSING INSTRUCTIONS</th>
<th>TIMING OF DOSING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunitinib</td>
<td>Tyrosine kinase inhibitor</td>
<td>50 mg</td>
<td>Once daily for 4 weeks (28 days), then 2 weeks (14 days) off therapy</td>
<td>With or without food</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>Multitargeted kinase inhibitor</td>
<td>400 mg</td>
<td>Twice daily</td>
<td>Without food</td>
</tr>
<tr>
<td>Everolimus</td>
<td>mTOR inhibitor</td>
<td>10 mg</td>
<td>Once daily</td>
<td>With or without food</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>Multitargeted kinase inhibitor</td>
<td>800 mg</td>
<td>Once daily</td>
<td>1 hour before or 2 hours after meals</td>
</tr>
<tr>
<td>Axitinib</td>
<td>Multitargeted kinase inhibitor</td>
<td>5 mg</td>
<td>Twice daily</td>
<td>With or without food</td>
</tr>
</tbody>
</table>

### 2013 Algorithm for MRCC Therapy

<table>
<thead>
<tr>
<th>Setting</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-line therapy</td>
<td>Good- or intermediate-risk (clear cell) Sunitinib or Pazopanib or Bev + IFN-α (HD IL-2 and sorafenib for select patients)</td>
</tr>
<tr>
<td>Poor-risk (any histological subtype)</td>
<td>Temsirolimus</td>
</tr>
<tr>
<td>Second-line therapy</td>
<td>Prior cytokine Axitinib*, sorafenib*, sunitinib* pazopanib*, temsirolimus*, bev*</td>
</tr>
<tr>
<td>Prior VEGFR inhibitor</td>
<td>Axitinib*, everolimus*, sorafenib*, sunitinib*, temsirolimus, bev, pazopanib</td>
</tr>
<tr>
<td>Prior TKI and mTOR inhibitor</td>
<td>Clinical trial</td>
</tr>
</tbody>
</table>

* Category 1; ‡ Category 2

**VEGFR** = Vascular Endothelial Growth Factor Receptor  |  **TKI** = Tyrosine Kinase Inhibitor  
**mTOR** = mammalian Target Of Rapamycin
<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Bevacizumab</th>
<th>Sunitinib</th>
<th>Sorafenib</th>
<th>Pazopanib</th>
<th>Temsirolimus/Everolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>-</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Rash</td>
<td>-</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>-</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Hypertension</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>-</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Nausea</td>
<td>-</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>-</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Myelosuppression</td>
<td>-</td>
<td>++</td>
<td>-</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>Bleeding</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+++</td>
</tr>
</tbody>
</table>
## Side Effects of multitargeted kinase inhibitors for Metastatic Renal Cell Carcinoma (Sorafenib, Sunitinib, Pazopanib, Axitinib)

### Early Side Effects

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>LIKELIHOOD OF OCCURRENCE</th>
<th>RX</th>
<th>FOLLOW-UP WITH PATIENT</th>
<th>PATIENT EDUCATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>Frequently</td>
<td>Imodium, then Lomotil</td>
<td>Check at 6 weeks; if still symptomatic, call MD/clinic sooner</td>
<td>If symptoms persist – call MD/clinic</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>Frequently</td>
<td>Compazine</td>
<td>Check at 6 weeks; if symptomatic, call MD/clinic right away</td>
<td>If symptoms persist – call MD/clinic</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Occasionally</td>
<td>Beta blockers or calcium channel blockers (check for drug interactions)</td>
<td>Check after 6 weeks. In cases of severe hypertension, temporary suspension of the agent is recommended until controlled. Monitor every 2 days until stabilized. Continued every 2 day monitoring to stabilization after dosing restarted.</td>
<td>Patient self-monitor blood pressure, if systolic &gt;150 or diastolic &gt;85, call MD</td>
</tr>
</tbody>
</table>

### Late Side Effects

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>LIKELIHOOD OF OCCURRENCE</th>
<th>RX</th>
<th>FOLLOW-UP WITH PATIENT</th>
<th>PATIENT EDUCATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucositis</td>
<td>Frequently</td>
<td>Physician’s choice of agent</td>
<td>Check after 2 weeks; or as per MD clinical judgement</td>
<td>See patient handout materials</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Frequently</td>
<td>Imodium, then Lomotil</td>
<td>Check after 1 week or as per MD clinical judgement</td>
<td>See patient handout materials</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Frequently</td>
<td>Physician’s choice of agent</td>
<td>Check other contributing factors, such as: Anemia, Nutrition (anorexia, gastrointestinal problems), Pain, Depression/emotional distress, Sleep disturbance, Hypothyroidism, Patient activity level, Other medications (including over-the-counter and herbal products)</td>
<td>Report to Physician</td>
</tr>
<tr>
<td>Hand &amp; Foot Syndrome</td>
<td>Occasionally</td>
<td>Urea 40% cream, fluocinonide ointment</td>
<td>Escalating or sever pain requires immediate hold or decrease of medication dose</td>
<td>See patient handout materials</td>
</tr>
</tbody>
</table>
Dose Modifications and Schedule Changes for Sunitinib Therapy in Metastatic Renal Cell Carcinoma

**EARLY - HYPERTENSION**

Start Tx with 1st line TKI
Sunitinib - 50 mg
4 wks on/2 wks off
Taken with or without food

Patient self-monitor blood pressure, if systolic >150 or diastolic >85, call MD
MD check within 6 weeks

Hypertension develops?
YES
Initiate/increase hypertension medication
Re-check within 2 weeks

Hypertension persists?
YES
Initiate dose modification of TKI
(2 wks on/1 wk off)

Hypertension persists?
NO
Maintain dose of TKI

Hypertension develops?
NO
Maintain dose of TKI
Re-check within 6 weeks

Hypertension develops?
YES
Initiate/increase hypertension medication
Re-check within 2 weeks

Hypertension persists?
NO
Maintain or increase dose of TKI

Hypertension persists?
NO
Maintain dose of TKI
Re-check within 6 weeks

**HYPERTENSION**

**GRADE 1**
Asymptomatic OR transient (<24 hours)
increase of >20 mm Hg (diastolic) OR >150/100 mm Hg if previously WNL
CONTINUE Sunitinib therapy at same dose level

**GRADE 2**
Recurrent or persistent (≥24 hours) OR symptomatic increase of >20 mm Hg (diastolic)
OR >150/100 mm Hg if previously WNL
CONTINUE Sunitinib therapy at same dose level except in the event of an asymptomatic decrease in LVEF by an absolute value of 20% and below LLN OR nonurgent ventricular paroxysmal dysrhythmia requiring intervention INTERRUPT Sunitinib therapy until grade ≤1 or return to baseline, then RESUME at reduced dose level

**GRADE 3**
Requiring more than 1 drug OR more intensive therapy than previously
INTERRUPT Sunitinib therapy until grade ≤1 or return to baseline, then RESUME at same or reduced dose level

**GRADE 4**
Life-threatening (eg, hypertensive crisis)
DISCONTINUE Sunitinib therapy
Dose Modifications and Schedule Changes for Sunitinib Therapy in Metastatic Renal Cell Carcinoma

**LATE - DIARRHEA/FATIGUE/HAND & FOOT SYNDROME/MUCOSITIS**

### HAND & FOOT SYNDROME

- **GRADE 1:** Minimal skin changes or dermatitis (e.g., erythema) without pain
  - CONTINUE Sunitinib therapy at same dose level

- **GRADE 2:** Skin changes (e.g., peeling, blisters, bleeding, edema) or pain, not interfering with function
  - CONTINUE Sunitinib therapy at same dose level

- **GRADE 3:** Ulcerative dermatitis or skin changes with pain interfering with function
  - INTERRUPT Sunitinib therapy until grade ≤1 or return to baseline, then RESUME at same or reduced dose level. Recurring grade 3 toxicity requires Sunitinib dose reduction

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### FATIGUE

- **GRADE 1:** Mild fatigue over baseline
  - CONTINUE Sunitinib therapy at same dose level

- **GRADE 2:** Moderate or causing difficulty performing some ADL
  - CONTINUE Sunitinib therapy at same dose level

- **GRADE 3:** Severe fatigue interfering with ADL
  - INTERRUPT Sunitinib therapy until grade ≤1 or return to baseline, then RESUME at same or reduced dose level. Recurring grade 3 toxicity requires Sunitinib dose reduction

- **GRADE 4:** Disabling
  - INTERRUPT Sunitinib therapy until grade ≤1 or return to baseline, then RESUME at reduced dose level or DISCONTINUE

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**Check for the following by week 6:**
- Diarrhea
- Fatigue
- Hand & Foot syndrome
- Mucositis

**Toxicities develop?**
- **NO**
  - Maintain dose of TKI
- **YES**
  - Initiate supportive care treatment

**Side effects alleviated?**
- **NO**
  - Initiate dose modification of TKI (2 wks on/1 wk off)
- **YES**
  - Maintain dose
## Other Considerations for Follow-Up Care

### MYALGIAS/BODY ACHEs
- May be more common in more active people
- Trial of acetaminophen, ibuprofen
- Be careful to monitor doses of ibuprofen given potential for renal insufficiency

### HAIR DEPIGMENTATION/ SKIN DISCOLORATION: MANAGEMENT
- Educate patients on potential for hair and skin color changes
- Hair changes can occur with sunitinib, pazopanib or sorafenib (lightening or curling or thinning)

### HYPOTHYROIDISM
**All patients should be observed closely for signs and symptoms of hypothyroidism during therapy**
- Baseline laboratory measurement of thyroid function is recommended
- Routine monitoring every 2 or 3 months, and at increasing frequency of monitoring if serum thyroid-stimulating hormone is abnormal
- Thyroid function abnormalities can be seen with all of the tyrosine kinase inhibitors

### HEADACHE
- Ask about coexisting symptoms—nausea, hypertension, scalp sensitivity
- Benzodiazepams, acetaminophen, ibuprofen premedication are all useful strategies
- For coexisting hypertension, need to address BP
- Consider evening dosing of once daily agents
- Confusion or decreased level of consciousness constitutes an emergency!