A Review in the Treatment Options for Renal Cell Cancer

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RENAL CELL CANCER (RCC) INCIDENCE

Worldwide, RCC is the ninth most common cancer, with about 337,860 new cases diagnosed in 2012.

In 2013, cancers of the kidney and renal pelvis were estimated to occur in 65,150 patients in the United States, resulting in 13,680 deaths.

In the World Health Organization Europe region, an estimated 121,629 new cases of RCC occurred in 2012, of which 75,676 affected men.

The incidence of RCC varies geographically with the highest incidence in developed countries.

In a recent review of 3001 patients without symptoms being imaged for computed tomography colonography, 14% of patients harbored a renal mass greater than 1 cm in size.
RISK FACTORS

• Social factors
  • Cigarette smoking
  • Obesity
  • Hypertension
  • End Stage Renal Disease (ESRD)

• Environmental/Occupational factors
  • Know to increase risk factors
    • Trichloroethylene
    • Phenacetin-containing analgesia
  • Associated with increase in development
    • Asbestos
    • Polycyclic aromatic Hydrocarbons

• Acquired Cystic Kidney Disease

GENETIC RISK FACTORS

• Von-Hippel Lindau (VHL) syndrome
  • 23-45% lifetime risk of RCC with VHL disease
  • Abnormality on chromosome 3p in the VHL gene

• Hereditary papillary renal carcinoma (HPRC)

• Hereditary leiomyomatosis renal cell carcinoma (HLRCC)

• Birt-Hogg-Dube (BHD)
CLINICAL PRESENTATION

- Many are asymptomatic until disease is advanced
- Classic Triad
  - Hematuria
  - Flank pain
  - Palpable mass
- Non-specific symptoms
- Paraneoplastic syndromes
- Systemic symptoms

MEMORIAL SLOAN KETTERING RISK CRITERIA

Motzer RJ et al. JCO 2002:20:289-296. Taken with permission
STAGING AND PROGNOSIS

AMERICAN JOINT COMMITTEE ON CANCER

- Many are asymptomatic until disease is advanced
- Classic Triad
  - Hematuria
  - Flank pain
  - Palpable mass
- Non-specific symptoms
- Paraneoplastic syndromes
- Systemic symptoms

SURVIVAL BY STAGE

<table>
<thead>
<tr>
<th>Stage</th>
<th>5-year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>96%</td>
</tr>
<tr>
<td>II</td>
<td>82%</td>
</tr>
<tr>
<td>III</td>
<td>64%</td>
</tr>
<tr>
<td>IV</td>
<td>23%</td>
</tr>
</tbody>
</table>

MANAGEMENT OF RCC

- Stage I – III (Localized disease)
  - Nephrectomy
  - No established role for adjuvant therapy
- Stage IV (Metastatic disease)
  - Surgery – nephrectomy / Immunotherapy
    - HD Interleukin-2
    - Interferon-alfa
    - Nivolumumab
  - Targeted therapies
CYTOREDUCTIVE NEPHRECTOMY

- Patients with stage IV disease are also candidates for surgery
  - Minimal regional adenopathy
  - Primary RCC and a solitary site of metastasis
  - Develop a solitary recurrence after nephrectomy
  - Symptoms related to primary tumor

- Cytoreductive nephrectomy before systemic therapy is recommended
- Radiation therapy may be administered for bone metastasis

THERAPIES IN RCC

FIRST-LINE THERAPY
- Pazopanib
- Sunitinib
- Bevacizumab + IFN
- Temsirolimus
- Axitinib
- High-dose IL-2

SECOND-LINE THERAPIES
- Cabozatinib
- Nivolumab
- Axitinib
- Lenvatinib + everolimus
- Everolimus
- Pazopanib
- Sorafenib
- Sunitinib
- Bevacizumab
- High-dose IL-2
- Temsirolimus

NCCN Guidelines Version 2.2017
INTERLEUKIN-2

FDA approved for the treatment of RCC
• MOA: induces T-lymphocyte and natural killer cell activity
• Dosing
  • 600,000 IU/kg Q8 hours IV over 15 minutes x 5 days, then repeat 6-10 days off therapy
  • Also Given CIVI and subcutaneously
• Complete response of 5-9% with many patients not relapsing for up to 17 years
• Used in combination with other agents but clinical benefit unknown

INTERLEUKIN-2

Adverse Effects:
• Capillary leak syndrome
• Hypotension
• Oliguria or anuria
• Arrhythmias
• Mental status changes
• Electrolyte abnormalities
• Increased LFT
• Rash
• Flushing
SORAFENIB

• Mechanism of action
  • Inhibits tumor cell proliferation by targeting the Raf/MEK/ERK pathway at the level of Raf kinase
  • Exhibits anti-angiogenic effects by targeting receptor tyrosine kinases VEGFR-2 and PDGFR and associated signaling cascades
SORAFENIB

- FDA approved for the treatment of RCC and hepatocellular cancer
- Dosing:
  - 400mg BID on an empty stomach
  - 1 hour before or 2 hours after a meal
- Dosage adjustment for skin toxicity
- Continue treatment until:
  - Clinical benefit is no longer evident
  - Unacceptable toxicity

SORAFENIB

- Phase II discontinuation trial
- 202 patients with advanced RCC received 12 weeks of sorafenib 400mg BID, if response then randomized to sorafenib or placebo
- 65 patients included in randomization
- Results:
  - 24 wks: 50% sorafenib group vs. 18% placebo group were progression free
  - PFS longer in sorafenib group 163 days vs. 41 days for placebo (p=0.0001)
SORAFENIB

• Phase III placebo-controlled trial - TARGET
• Randomized trial in patients with advanced RCC who had received one prior systemic therapy
• Primary endpoint: overall survival
• Sorafenib 400mg po BID or placebo
• Results:
  • Median overall survival 19.3 vs. 14.3 months
  • Median progression free survival (PFS) 167 vs. 84 days for sorafenib vs. placebo (p<0.01)
  • Reduced risk of death with sorafenib
  • Crossover patients had 30% improvement in survival

SORAFENIB

- Hand-foot skin reaction
- Emergent hypertension
  - Monitor BP weekly during the first 6 wks
- Hemorrhage
- Cardiac ischemia
- Warfarin co-administration
- Increase in INR

### OVERALL SURVIVAL

#### Table 1: Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Any Grade</th>
<th>Grade 2</th>
<th>Grade 3 or 4</th>
<th>Any grade number (percentage)</th>
<th>Grade 2 number (percentage)</th>
<th>Grade 3 or 4 number (percentage)</th>
<th>P Value (Grade 3 vs 4)</th>
<th>P Value (Grade 2 vs 4)</th>
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<tbody>
<tr>
<td>Carcinoid syndrome</td>
<td>16 (15)</td>
<td>6 (6)</td>
<td>10 (10)</td>
<td>39 (37)</td>
<td>13 (13)</td>
<td>26 (25)</td>
<td>0.0000</td>
<td>&lt;0.0001</td>
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<tr>
<td>Metastatic or differentiated hemangioendothelioma</td>
<td>34 (8)</td>
<td>14 (3)</td>
<td>20 (40)</td>
<td>54 (13)</td>
<td>8 (2)</td>
<td>46 (10)</td>
<td>0.25</td>
<td>&lt;0.0001</td>
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<tr>
<td>Constitutional</td>
<td>Fatigue</td>
<td>105 (33)</td>
<td>54 (27)</td>
<td>22 (11)</td>
<td>127 (88)</td>
<td>99 (22)</td>
<td>28 (5)</td>
<td>0.84</td>
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<tr>
<td>Other symptoms</td>
<td>46 (10)</td>
<td>9 (2)</td>
<td>6 (14)</td>
<td>46 (9)</td>
<td>8 (2)</td>
<td>9 (1)</td>
<td>1.00</td>
<td>1.00</td>
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<tr>
<td>Weight loss</td>
<td>46 (10)</td>
<td>21 (5)</td>
<td>9 (2)</td>
<td>46 (9)</td>
<td>8 (2)</td>
<td>9 (1)</td>
<td>1.00</td>
<td>1.00</td>
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<tr>
<td>Gastrointestinal</td>
<td>Diarrhea</td>
<td>195 (43)</td>
<td>54 (12)</td>
<td>32 (9)</td>
<td>195 (43)</td>
<td>54 (12)</td>
<td>32 (9)</td>
<td>0.06</td>
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<tr>
<td>Veins</td>
<td>192 (42)</td>
<td>27 (6)</td>
<td>3 (1)</td>
<td>192 (42)</td>
<td>27 (6)</td>
<td>3 (1)</td>
<td>1.00</td>
<td>0.94</td>
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<tr>
<td>Anemia</td>
<td>173 (40)</td>
<td>24 (5)</td>
<td>3 (1)</td>
<td>173 (40)</td>
<td>24 (5)</td>
<td>3 (1)</td>
<td>0.75</td>
<td>0.82</td>
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<td>Nausea</td>
<td>173 (40)</td>
<td>24 (5)</td>
<td>3 (1)</td>
<td>173 (40)</td>
<td>24 (5)</td>
<td>3 (1)</td>
<td>0.75</td>
<td>0.82</td>
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<tr>
<td>Constipation</td>
<td>48 (11)</td>
<td>21 (5)</td>
<td>4 (1)</td>
<td>48 (11)</td>
<td>21 (5)</td>
<td>4 (1)</td>
<td>1.00</td>
<td>0.97</td>
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<tr>
<td>Nausea</td>
<td>39 (9)</td>
<td>4 (1)</td>
<td>1 (0)</td>
<td>39 (9)</td>
<td>4 (1)</td>
<td>1 (0)</td>
<td>1.00</td>
<td>0.86</td>
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<td>Pain</td>
<td>Abdominal</td>
<td>43 (9)</td>
<td>7 (2)</td>
<td>6 (15)</td>
<td>43 (9)</td>
<td>7 (2)</td>
<td>6 (15)</td>
<td>0.89</td>
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<td>Headache</td>
<td>47 (10)</td>
<td>7 (2)</td>
<td>3 (0)</td>
<td>47 (10)</td>
<td>7 (2)</td>
<td>3 (0)</td>
<td>1.00</td>
<td>0.94</td>
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<tr>
<td>Joint pain</td>
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<td>7 (2)</td>
<td>3 (0)</td>
<td>45 (9)</td>
<td>7 (2)</td>
<td>3 (0)</td>
<td>1.00</td>
<td>1.00</td>
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<tr>
<td>Bone pain</td>
<td>31 (7)</td>
<td>5 (1)</td>
<td>1 (0)</td>
<td>31 (7)</td>
<td>5 (1)</td>
<td>1 (0)</td>
<td>0.07</td>
<td>0.07</td>
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<tr>
<td>Tumor pain</td>
<td>31 (7)</td>
<td>5 (1)</td>
<td>1 (0)</td>
<td>31 (7)</td>
<td>5 (1)</td>
<td>1 (0)</td>
<td>0.07</td>
<td>0.07</td>
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<tr>
<td>Pulmonary</td>
<td>Cough</td>
<td>42 (9)</td>
<td>7 (2)</td>
<td>6 (15)</td>
<td>42 (9)</td>
<td>7 (2)</td>
<td>6 (15)</td>
<td>1.00</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>45 (9)</td>
<td>21 (5)</td>
<td>4 (1)</td>
<td>45 (9)</td>
<td>21 (5)</td>
<td>4 (1)</td>
<td>1.00</td>
<td>0.93</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>Rash or desquamation</td>
<td>180 (40)</td>
<td>59 (12)</td>
<td>4 (1)</td>
<td>180 (40)</td>
<td>59 (12)</td>
<td>4 (1)</td>
<td>0.57</td>
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<tr>
<td>Hand-foot skin reaction</td>
<td>124 (29)</td>
<td>51 (12)</td>
<td>20 (4)</td>
<td>124 (29)</td>
<td>51 (12)</td>
<td>20 (4)</td>
<td>0.00</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Alopecia</td>
<td>153 (35)</td>
<td>71 (16)</td>
<td>11 (2)</td>
<td>153 (35)</td>
<td>71 (16)</td>
<td>11 (2)</td>
<td>0.00</td>
<td>&lt;0.0001</td>
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<tr>
<td>Prophylaxis</td>
<td>85 (19)</td>
<td>21 (5)</td>
<td>3 (0)</td>
<td>85 (19)</td>
<td>21 (5)</td>
<td>3 (0)</td>
<td>0.00</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Adverse events of any grade occurring in at least 2% of patients (with a breakdown of grade 2 events) and adverse events of grade 1 or 4 occurring in at least 2% of patients.

**P values are for the comparison between the sorafenib group and the placebo group, with respect to grade 3 or 4 adverse events.

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SUNITINIB

- **Mechanism of action**
  - Selective inhibitor of multiple tyrosine kinases
    - PDGFR, VEGFR, KIT, FLT3, CSF-1R, and RET
  - Anti-tumor activity
    - Inhibition of angiogenesis
    - Direct anti-proliferative effects

SUNITINIB

- FDA approved for advanced RCC and Gastrointestinal stromal tumors (GIST) after disease progression on or intolerance to imatinib mesylate (Gleevec®)
- **Dosing:**
  - 50 mg PO daily x 4 weeks, then 2 weeks off
  - May be taken with or without food
- Dosing adjustments should be made in increments of 12.5mg
SUNITINIB

• Phase II trials of sunitinib as second line therapy in cytokine refractory RCC
  • Study I (n=63) 37% Overall response rate (ORR)
    • Duration of response (DR) 54 weeks (12.5 months)
    • 27% patients – stable disease (SD) lasting ≥3 months
    • Median time to progression (TTP) - 8.7 months
  • Study II (n=106) 34% ORR
    • DR 27.1 weeks
      • Premature due to only 15% of responders had experienced disease progression

SUNITINIB

• Phase III trial in previously untreated metastatic RCC patients
  • Randomized 750 patients to receive sunitinib vs. INFα
  • Primary endpoint: progression free survival
  • Results:
    • Median PFS 11 months for sunitinib vs. 5 months for INFα
    • Objective response rate (ORR) 31% for sunitinib vs. 6% for INFα
    • Similar rates of stable disease in both groups (48% sunitinib vs. 49% INFα)
    • Overall survival was longer with sunitinib (26.4 months vs. 21.8 months)
# Sunitinib – Adverse Effects

<table>
<thead>
<tr>
<th>Category</th>
<th>Effect</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>HTN</td>
<td>15%</td>
</tr>
<tr>
<td>GI</td>
<td>Diarrhea</td>
<td>40%</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>31%</td>
</tr>
<tr>
<td></td>
<td>Mucositis/stomatitis</td>
<td>29%</td>
</tr>
<tr>
<td>Dermatological</td>
<td>Rash</td>
<td>14%</td>
</tr>
<tr>
<td></td>
<td>Skin discoloration</td>
<td>30%</td>
</tr>
<tr>
<td></td>
<td>Hand-Foot Syndrome</td>
<td>14%</td>
</tr>
<tr>
<td>Neurology</td>
<td>Altered taste</td>
<td>21%</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>13%</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Dyspnea</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>Cough</td>
<td>8%</td>
</tr>
<tr>
<td></td>
<td>Bleeding</td>
<td>18%</td>
</tr>
<tr>
<td></td>
<td>Hypophosphatemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Musculoskeletal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Arthralgia</td>
<td>12%</td>
</tr>
<tr>
<td></td>
<td>Back pain</td>
<td>11%</td>
</tr>
</tbody>
</table>

# Sunitinib – Precautions

- Heart failure
  - Consider baseline and periodic evaluations of LVEF
- Emergent hypertension
  - Monitored carefully and started on appropriate antihypertensive medications
- Adrenal Function
  - Monitor for adrenal insufficiency in patients who experience stress
- Hemorrhagic Events

# Drug Interactions

- Increase sunitinib concentrations
  - Strong CYP3A4 inhibitors
    - Reduce dose to 37.5mg daily
  - Grapefruit
- Decrease sunitinib concentrations
  - CYP3A4 inducers
    - Select an alternative medication
    - Increase dose to 87.5mg daily
PAZOPANIB

- Pazopanib, an oral angiogenesis inhibitor, has high affinity for PDGFR and VEGFR 1, 2 and 3 and also targets C-kit
- Clinical efficacy of pazopanib demonstrated in a Phase II trial in patients with advanced renal cell carcinoma (RCC) ORR, 34.7%
  - PFS, 11.9 mos vs 6.2 mos (placebo)

PAZOPANIB

- The study was a randomized, open-label, phase 3 trial of pazopanib versus sunitinib.
- Randomization was stratified according to Karnofsky performance status score (70 or 80 vs. 90 or 100), level of lactate dehydrogenase (>1.5 vs. ≤1.5 times the upper limit of the normal range), and nephrectomy (yes vs. no).
- Patients were randomly assigned to one of the two study drugs in a 1:1 ratio in permuted blocks of four.
- Pazopanib was administered orally at a once-daily dose of 800 mg, with continuous dosing.
- Sunitinib was administered orally in 6-week cycles at a once-daily dose of 50 mg for 4 weeks, followed by 2 weeks without treatment.
- Dose reductions for pazopanib (to 600 mg and then to 400 mg) and sunitinib (to 37.5 mg and then to 25 mg) were determined according to the severity of adverse events.
- Patients were treated until progression of disease, the occurrence of unacceptable toxic effects, or withdrawal of consent.
### PAZOPANIB ADVERSE EVENTS

<table>
<thead>
<tr>
<th>Event</th>
<th>All Grades</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>All Grades</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>165 (11)</td>
<td>3 (2)</td>
<td>0 (0)</td>
<td>165 (11)</td>
<td>3 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Clostridium difficile</td>
<td>141 (10)</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>141 (10)</td>
<td>1 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Rash</td>
<td>91 (6)</td>
<td>2 (1)</td>
<td>0 (0)</td>
<td>91 (6)</td>
<td>2 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>85 (6)</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>85 (6)</td>
<td>1 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>71 (5)</td>
<td>3 (2)</td>
<td>0 (0)</td>
<td>71 (5)</td>
<td>3 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>41 (3)</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>41 (3)</td>
<td>1 (1)</td>
<td>0 (0)</td>
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<tr>
<td>Fatigue</td>
<td>81 (6)</td>
<td>2 (1)</td>
<td>0 (0)</td>
<td>81 (6)</td>
<td>2 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>81 (6)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>81 (6)</td>
<td>0 (0)</td>
<td>0 (0)</td>
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<tr>
<td>Nausea</td>
<td>71 (5)</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>71 (5)</td>
<td>1 (1)</td>
<td>0 (0)</td>
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<td>Pruritus</td>
<td>67 (5)</td>
<td>2 (1)</td>
<td>0 (0)</td>
<td>67 (5)</td>
<td>2 (1)</td>
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<td>Dyspepsia</td>
<td>51 (4)</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>51 (4)</td>
<td>1 (1)</td>
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<tr>
<td>Gastrointestinal bleeding</td>
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<td>0 (0)</td>
<td>51 (4)</td>
<td>0 (0)</td>
<td>0 (0)</td>
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<tr>
<td>Glomerular filtration</td>
<td>51 (4)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>51 (4)</td>
<td>0 (0)</td>
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<tr>
<td>Increased WBC</td>
<td>31 (2)</td>
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<td>0 (0)</td>
<td>31 (2)</td>
<td>0 (0)</td>
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### PAZOPANIB THERAPEUTIC EFFECTS

**Table 1.** Therapeutic Effects and Laboratory Evaluations During Treatment for VHL or Renal Cell Carcinoma: Difference (95% CI) between Groups.*

<table>
<thead>
<tr>
<th>Effect</th>
<th>All Grades</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>All Grades</th>
<th>Grade 3</th>
<th>Grade 4</th>
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</thead>
<tbody>
<tr>
<td>Change in Hb</td>
<td>0.14 (0.1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0.14 (0.1)</td>
<td>0 (0)</td>
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<tr>
<td>Change in WBC</td>
<td>6.7 (6.7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>6.7 (6.7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
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</tbody>
</table>

*Table shows the mean change from baseline to end of treatment for various hematologic and laboratory parameters. Differences are reported as the mean change from baseline to end of treatment. The differences between groups were analyzed using the Student’s t-test for continuous variables. Differences with 95% confidence intervals that do not include zero were considered to be significant. The mean change from baseline to end of treatment for Hb, WBC, and platelets was significantly higher with pazopanib than with sunitinib. The mean change in creatinine was significantly higher with sunitinib than with pazopanib. The mean change in creatinine was significantly higher with pazopanib than with sunitinib.
SECOND-LINE TREATMENT OPTIONS

- Axitinib
- Cabozatinib
- Nivolumuab

AXITINIB

Most Selective for VEGFR -1, -2, and -3

<table>
<thead>
<tr>
<th>Target Selectivity</th>
<th>Axitinib(1)</th>
<th>Sorafenib(2)</th>
<th>Sunitinib(3)</th>
<th>Pazopanib(4)</th>
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<tbody>
<tr>
<td>VEGFR-2</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>PDGFR b</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>c-kit</td>
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<tr>
<td>FLT-3</td>
<td></td>
<td>+</td>
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<td>+</td>
</tr>
<tr>
<td>CSF-1R</td>
<td>ND</td>
<td></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Raf-1</td>
<td>ND</td>
<td></td>
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</tbody>
</table>

* Inhibition of receptor kinase comparable (≤ 5 times) to potency for VEGFR-2
ND: not determined

### PHASE III AXIS STUDY: AXITINIB VS SORAFENIB AS SECOND-LINE THERAPY FOR MRCC

**Stratified by previous regimen, ECOG PS (0 vs 1)**

Patients with clear-cell mRCC, refractory to 1 previous first-line therapy (N = 723)

- **Axitinib**
  - 5 mg BID (n = 361)

- **Sorafenib**
  - 400 mg BID (n = 362)

*Starting dose 5 mg BID with option for dose titration to 10 mg BID.

- Primary endpoint: PFS (independent review committee [IRC])
- Secondary endpoints: OS, ORR (RECIST), duration of response, safety, QoL

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### AXIS TRIAL

<table>
<thead>
<tr>
<th>Patients at Risk, n</th>
<th>Axitinib</th>
<th>Sorafenib</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>361</td>
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<tr>
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</table>

**mPFS, Mos 95% CI**

- Axitinib: 6.7 [6.3-8.6]
- Sorafenib: 4.7 [4.6-5.6]

Stratified HR: 0.665 (95% CI: 0.544-0.812; log-rank P < .0001)
AXIS TRIAL: EFFICACY RESULTS

<table>
<thead>
<tr>
<th>Previous Treatment Regimen</th>
<th>Axitinib (n = 361)</th>
<th>Sorafenib (n = 362)</th>
<th>HR</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokines (n = 251)</td>
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<tr>
<td>IRC</td>
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<td>6.5</td>
<td>0.464</td>
<td>&lt; .0001</td>
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<tr>
<td>Investigator</td>
<td>12.0</td>
<td>8.3</td>
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<td>.0049</td>
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<td>Sunitinib (n = 389)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>IRC</td>
<td>4.8</td>
<td>3.4</td>
<td>0.741</td>
<td>.0107</td>
</tr>
<tr>
<td>Investigator</td>
<td>6.5</td>
<td>4.5</td>
<td>0.636</td>
<td>.0002</td>
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<tr>
<td>Temsirolimus (n = 24)</td>
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<td>Bevacizumab (n = 59)</td>
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<td>IRC</td>
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<tr>
<td>Investigator</td>
<td>6.5</td>
<td>4.5</td>
<td>0.753</td>
<td>.2126</td>
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</tbody>
</table>

*1-sided log-rank test stratified by ECOG PS


CABOZATINIB

- Inhibitor of MET and VEGF receptor
- Striking response seen in bone of patients with prostate cancer
- Agent is being explored in multiple other cancers, including RCC
- Currently FDA approved for use in patients with progressive, metastatic medullary thyroid cancer

OncoTarets and Therapy 2016;9:5825—5837
CABOZATINIB STUDY DESIGN

- Patients were randomly assigned in a 1:1 ratio to receive either cabozantinib or everolimus.
- Randomization was stratified according to the number of previous VEGFR-targeting tyrosine kinase inhibitors (1 or ≥2) and prognostic risk category (favorable, intermediate, or poor).
- Cabozantinib was administered orally at a dose of 60 mg once daily, and everolimus was administered orally at a dose of 10 mg once daily.
- Treatment was continued as long as clinical benefit was observed by the investigator or until the development of unacceptable toxic effects. Crossover between treatment groups was not allowed.
CABOZATINIB SIDE EFFECTS

PARTIAL BONE SCAN RESOLUTION/PAIN RELIEF IN SYMPTOMATIC PATIENT WITH BONE METS

Previous therapies include sorafenib, everolimus, and sunitinib

- Patient substantially reduced narcotic use by 7 wks; continued on reduced narcotics until Wk 25
- Another patient with bone metastases and pain at baseline reported complete resolution of pain by 4 wks
  - Pain free 90+ wks on study

Enrolled patients
- Previously treated advanced or metastatic clear-cell RCC
- 1 or 2 prior anti-angiogenic treatments

Randomize 1:1

Nivolumab (N = 410)
3 mg/kg every 2 weeks intravenous

Everolimus (N = 411)
10 mg/day oral

Disease assessments
- Every 8 weeks from randomization through 12 months
- Then every 12 weeks until progression or treatment discontinuation

Primary endpoint
- Overall survival (OS)

Treat until progression or intolerable toxicity
- Treatment beyond progression was permitted if drug was tolerated and clinical benefit was noted

Median OS, months (95% CI)
- Nivolumab (N = 410) 25.0 (21.8–NE)
- Everolimus (N = 411) 19.6 (17.6–23.1)

HR (98.5% CI), 0.73 (0.57–0.93)
P = 0.0018

The risk of death was reduced by 27% in patients in the nivolumab treatment group compared with those in the everolimus group
- Study stopped after planned interim analysis (398 deaths) because assessment by an independent data monitoring committee concluded that the study met its primary endpoint, demonstrating superior OS for nivolumab

HR, hazard ratio; NE, not estimable.
NIVOLUMUMAB ADVERSE EVENTS

- Grade 3 or 4 treatment-related AEs were less frequent with nivolumab than with everolimus and treatment-related adverse events leading to discontinuation were experienced by fewer patients treated with nivolumab.
- The most common treatment-related AEs of any grade reported in the nivolumab arm were fatigue (33%), nausea (14%), and pruritus (14%), and in the everolimus arm, fatigue (34%), stomatitis (29%), and anemia (24%).
- There were no treatment-related deaths in the nivolumab treatment arm.

AE, adverse event; mRCC, metastatic renal cell carcinoma.

SELECTED CLINICAL TRIALS
SECOND-LINE THERAPY

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism</th>
<th>Trial arms</th>
<th>ORR (%)</th>
<th>PFS (Months)</th>
<th>OS (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axitinib</td>
<td>VEGFR inhibitor</td>
<td>Axitinib versus sorafenib</td>
<td>19 versus 9</td>
<td>6.7 versus 4.7</td>
<td>20.1 versus 19.2</td>
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<tr>
<td></td>
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<td>P=0.0001</td>
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<td>P=0.3744</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Cabozantinib</td>
<td>VEGF, MET and AXL inhibitor</td>
<td>Cabozantinib versus everolimus</td>
<td>21 versus 5</td>
<td>7.5 versus 3.9</td>
<td>21.4 versus 16.5</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>P&lt;0.001</td>
<td>P&lt;0.001</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>PD-1 inhibitor</td>
<td>Nivolumab versus everolimus</td>
<td>25 versus 5</td>
<td>4.6 versus 4.4</td>
<td>25.0 versus 19.6</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>P&lt;0.001</td>
<td>P=0.11</td>
<td>P=0.002</td>
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</tbody>
</table>
SUMMARY

• Current therapies continue to emerge in Renal Cell Cancer
• Second line strategies are emerging, especially with the advent of Checkpoint Inhibitors
• Patient specific treatments need to be mitigated based on a therapies adverse outcome profile