Resolved: Combination immunotherapy + VEGF targeted therapy is the optimal systemic strategy for metastatic RCC

Elizabeth R. Plimack MD MS
Director, Genitourinary Clinical Research
Associate Professor, Department of Hematology/Oncology
Goals of Care in mRCC

- Prevent / Palliate symptoms
- Preserve Quality of Life
- Extend Length of Life

Future Goals
- Achieve durable disease control
- ? Cure
Evolution of Targeted Therapy in mRCC

2006

2007

2008

2009

2010

2011

2012

2013

2014

= FDA approves drug

Slide courtesy Daniel Geynisman MD
The Frontline Toolbox of the Future

**VEGF TKIs**
(sunitinib, pazopanib, axitinib)

**PD-1 / PD-L1 inhibitors**
(nivolumab, pembrolizumab, MPDL3280A)

---

**Pazopanib Overall Survival**

**Frontline**

<table>
<thead>
<tr>
<th>Months</th>
<th>Patients at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pazopanib</td>
</tr>
<tr>
<td>0</td>
<td>290</td>
</tr>
<tr>
<td>1</td>
<td>213</td>
</tr>
<tr>
<td>2</td>
<td>147</td>
</tr>
<tr>
<td>3</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>25</td>
</tr>
</tbody>
</table>

Hazard ratio = 0.91
95% CI, 0.71 to 1.16
\(P = .224\)

Median OS
Pazopanib: 22.9 mo
Placebo: 20.5 mo

---

**Nivolumab Overall Survival**

(Second line data)

- 0.3 mg/kg (events: 36/60)
- 2 mg/kg (events: 29/54)
- 10 mg/kg (events: 32/54)

Median OS, months (80% CI)
- 0.3 mg/kg: 18.2 (16.2–24.0)
- 2 mg/kg: 25.5 (19.8–28.8)
- 10 mg/kg: 24.7 (15.3–26.0)

---


Proposed mechanisms of synergy

VEGF + PD-1 inhibition

**Immunologic**

- Elevated VEGF may inhibit dendritic cell maturation causing immunosuppression

- VEGF inhibition may reduce numbers of Tregs and tumor invading myeloid-derived suppressor cells

- VEGF therapy primes for better effect with anti PD-/PD-L1.

**Empiric**

- PD-1 works in mRCC

- VEGF works in mRCC

- VEGF + PD-1 will work better!

Gunturi A, McDermott DF: *Current treatment options in oncology* 2014
Nivolumab + Sunitinib or Pazopanib
Clinical Trial Design

Arm P Expansion
Pazopanib + Nivolumab
5 mg/kg IV Q3W

Arm S Expansion
Sunitinib + Nivolumab
5 mg/kg IV Q3W

Arm S Escalation
Sunitinib 50 mg + Nivolumab 2 mg/kg IV Q3W
(planned escalation to 5 mg/kg Q3W)

Arm P Escalation
Pazopanib 800 mg/d + Nivolumab
2 mg/kg IV Q3W (planned escalation to 5 mg/kg Q3W)

Primary objective
• Safety/tolerability, maximum tolerated dose (MTD), recommended phase II dose

Secondary objective
• Preliminary antitumor activity


- Age ≥18 years
- mRCC
- KPS ≥80%
- Favorable/intermediate-risk MSKCC score
- Measurable disease (RECIST v1.1)

Including patients who received prior pazopanib

Including patients who received prior sunitinib

Treatment-naive patients
# Nivolumab + Sunitinib or Pazopanib

## Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>S + N (n=33)</th>
<th>P + N (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years, mean (SD)</strong></td>
<td>58.0 (9.1)</td>
<td>56.3 (8.5)</td>
</tr>
<tr>
<td><strong>Male, n (%)</strong></td>
<td>26 (78.8)</td>
<td>18 (90.0)</td>
</tr>
<tr>
<td><strong>Female, n (%)</strong></td>
<td>7 (21.2)</td>
<td>2 (10.0)</td>
</tr>
<tr>
<td><strong>MSKCC risk category, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Favorable</td>
<td>8 (24.2)</td>
<td>4 (20.0)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>24 (72.7)</td>
<td>14 (70.0)</td>
</tr>
<tr>
<td>Poor</td>
<td>1 (3.0)</td>
<td>2 (10.0)</td>
</tr>
<tr>
<td><strong>Systemic therapy, n (%)</strong></td>
<td>14 (42.4)</td>
<td>20 (100)</td>
</tr>
<tr>
<td>VEGF-TKI</td>
<td>5 (15.2)</td>
<td>17 (85.0)</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>2 (6.1)</td>
<td>0</td>
</tr>
<tr>
<td>Cytokine</td>
<td>9 (27.3)</td>
<td>10 (50.0)</td>
</tr>
<tr>
<td>mTOR inhibitor</td>
<td>0</td>
<td>3 (15.0)</td>
</tr>
<tr>
<td><strong>Prior lines of therapy, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>14 (42.4)</td>
<td>14 (70.0)</td>
</tr>
<tr>
<td>≥2</td>
<td>0</td>
<td>6 (30.0)</td>
</tr>
</tbody>
</table>

# Nivolumab + Sunitinib or Pazopanib

## Toxicity

<table>
<thead>
<tr>
<th>Grade 3/4 treatment-related adverse events (AEs) occurring in ≥10% of patients</th>
<th>Sunitinib + Nivolumab (n = 33)</th>
<th>Pazopanib + Nivolumab (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any grade</td>
<td>Grade 3-4</td>
<td>Any grade</td>
</tr>
<tr>
<td><strong>Total patients with an event, n (%)</strong></td>
<td>33 (100)</td>
<td>27 (81.8)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>16 (48.5)</td>
<td>6 (18.2)</td>
</tr>
<tr>
<td>Elevated alanine aminotransferase</td>
<td>13 (39.4)</td>
<td>6 (18.2)</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>6 (18.2)</td>
<td>5 (15.2)</td>
</tr>
<tr>
<td>Decreased lymphocyte count</td>
<td>6 (18.2)</td>
<td>5 (15.2)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>20 (60.6)</td>
<td>3 (9.1)</td>
</tr>
<tr>
<td>Elevated aspartate aminotransferase</td>
<td>12 (36.4)</td>
<td>3 (9.1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>27 (81.8)</td>
<td>3 (9.1)</td>
</tr>
</tbody>
</table>

- No treatment related deaths
Nivolumab + Sunitinib or Pazopanib Toxicity

Treatment-related AEs leading to discontinuation of TKI or both study drugs (≥5% of patients)

<table>
<thead>
<tr>
<th>Event, %</th>
<th>S + N (n=33)</th>
<th>P + N (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients discontinuing due to treatment-related AEs, %</td>
<td>36.4</td>
<td>25.0</td>
</tr>
<tr>
<td>ALT increased</td>
<td>12.1</td>
<td>15.0</td>
</tr>
<tr>
<td>AST increased</td>
<td>6.1</td>
<td>15.0</td>
</tr>
<tr>
<td>Renal failure acute</td>
<td>9.1</td>
<td>0</td>
</tr>
</tbody>
</table>
Nivolumab + Sunitinib or Pazopanib

Efficacy

Change in baseline target lesions (%)

S + N (n = 30)
P + N (n = 19)

Sunitinib + Nivolumab

Pazopanib + Nivolumab
Clinical Trial Results:
Response Characteristics

Responders at first assessment (6 weeks):
S + N = 7/17 (41.2%)
P + N = 5/9 (55.6%)

Ongoing responders:
S + N = 10/17 (58.8%)
P + N = 3/9 (33.3%)

Patients discontinuing treatment (not due to progression) who continued to respond:
S + N = 4/17 (23.5%)
P + N = 1/9 (11%)
Perhaps the synergy lies in the response kinetics?

- TKIs can yield quick but non-durable responses.
- PD-1 inhibitors can yield deep and durable responses but can be slow to act.

Hypothesis: Combination VEGF and PD-1 targeted therapy leads to early responses due to VEGF inhibition that are sustained due to PD-1 inhibition
Sunitinib:

Early responses $\rightarrow$

Eventual Progression

Nivolumab:

Early Progression $\rightarrow$

(Durable) Response


Motzer et al Randomized, dose-ranging phase II trial of nivolumab for metastatic renal cell carcinoma (mRCC) ESMO 2014.
Clinical Trial Results:
Nivolumab + Sunitinib or Pazopanib

S + N, prior treated
(n=13)

S + N5, treatment-naïve
(n=15)

P + N
(n=19)

Change in baseline (%)

Time since first dose (weeks)

+1st occurrence of new lesion

Amin A, et al. ASCO 2014
In Summary

• VEGF inhibitors can induce early responses, but eventual progression is inevitable.
• PD-1 targeted therapies can produce durable but often delayed responses.
• Combination inhibition of VEGF and PD-1 inhibition shows an encouraging response pattern at the expense of higher toxicity.
• Further investigation of VEGF + PD-1/PD-L1 combinations should be of high priority in mRCC.
VEGF + PD-1/PD-L1 targeted combination trials currently underway

• Bevacizumab +/- MPDL3280A (NCT01984242)
• Pazopanib + Pembrolizumab (NCT02014636)
• Axitinib + Pembrolizumab (NCT02133742)
Thank You