Comparative Assessment of Sunitinib-associated Adverse Events as Potential Biomarkers of Efficacy in Metastatic Renal Cell Carcinoma (mRCC)

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Disclosure

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Introduction

Prior retrospective analyses of pooled data from five clinical mRCC trials have separately identified the following treatment-associated AEs as potential biomarkers of sunitinib efficacy:

- hypertension\(^1\)*
- neutropenia\(^3\)
- asthenia/fatigue\(^4\)
- hand–foot syndrome\(^2\)
- thrombocytopenia\(^3\)

AEs were chosen for study if they were common, manageable, readily and systematically measurable, and potentially reflective of intended target inhibition with sunitinib.

We assessed the relative strength and independence of each biomarker in a combined analysis using the same database.

*This efficacy biomarker analysis included three trials, excluding two trials that used continuous daily dosing (CDD), rather than the approved Schedule 4/2.

Sunitinib-associated Hypertension (HTN) Has Been Associated with Improved Clinical Outcomes

- HTN-associated complications were investigated by expanding the safety analysis with 4,373 patients from an expanded access trial
  - AE rates were similar for patients with and without SBP-defined HTN; however, patients with HTN had somewhat more renal AEs (5% vs. 3%; P=0.013)

Sunitinib-associated Hand–foot Syndrome (HFS) Has Been Associated with Improved Clinical Outcomes

With HFS (n=179)
Median OS, 38.2 months

Without HFS (n=591)
Median OS, 18.9 months

P<0.0001

Sunitinib-associated Myelosuppression Has Been Associated with Improved Clinical Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Neutropenia</th>
<th>Median OS, months</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade ≥2</td>
<td>366</td>
<td>35.6</td>
<td>31.4–39.5</td>
</tr>
<tr>
<td>Grade &lt;2</td>
<td>404</td>
<td>15.8</td>
<td>13.3–17.7</td>
</tr>
<tr>
<td><em>P</em>&lt;0.001</td>
<td></td>
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</tr>
</tbody>
</table>

- Neutropenia- and thrombocytopenia-related AEs were investigated by expanding the safety analysis with 4,388 patients from an expanded access trial
  - Related AEs were more frequent with neutropenia grade ≥2 and thrombocytopenia grade >1 (*P*<0.001)

Sunitinib-associated Asthenia/Fatigue (A/F) Has Been Associated with Improved Clinical Outcomes


With A/F (n=583)
Median OS, 26.2 months

Without A/F (n=187)
Median OS, 15.0 months
P<0.001
Study Designs and Treatments

- A retrospective analysis with pooled data from 770 mRCC patients who received sunitinib in five clinical trials\(^1\)–\(^5\)
  - 1st-line (n=494; 64%)
  - 2nd-line (n=276; 36%)

- Oral sunitinib was administered at:
  - 50 mg once daily on Schedule 4/2 (n=544; 71%)
  - 37.5 mg CDD (n=226; 29%)

Patient Eligibility

- Eligibility criteria common to all patients were:
  - age 18 years or older
  - histologically confirmed mRCC
  - adequate organ function
  - presence of measurable disease
  - no known presence of brain metastases
  - Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1
Statistical Methods

- A multivariate Cox proportional-hazard regression model was used to analyze potential independent AE biomarkers
  - repeated using a 12-week landmark to address potential bias from longer treatment (i.e., AEs evaluated up to the first 12 weeks)
  - performed separately for patients on Schedule 4/2 and both schedules combined

- The following were used as covariates for prediction of PFS and OS:
  - hypertension (SBP $\geq$ 140 mmHg)*
  - neutropenia and thrombocytopenia (both CTCAE grade $>1$)
  - any CTCAE grade hand–foot syndrome and asthenia/fatigue
  - dose reduction (adjusted for time on treatment)
  - relative dose intensity for the overall treatment period
  - previously identified prognostic factors$^{1-3}$

*Results of prior biomarker analyses were similar using DBP-defined hypertension$^4$

## Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>2nd-line, Schedule 4/2 Phase II trial(^1) (n=63)</th>
<th>2nd-line, Schedule 4/2 Phase II trial(^2) (n=106)</th>
<th>1st-line, Schedule 4/2 Phase III trial(^3) (n=375)*</th>
<th>1st-line, Schedule CDD Phase II trial(^4) (n=119)</th>
<th>2nd-line, Schedule CDD Phase II trial(^5) (n=107)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (range) age, years</td>
<td>60 (24–87)</td>
<td>56 (32–79)</td>
<td>62 (27–87)</td>
<td>58(^*) (24–78)</td>
<td>59 (29–80)</td>
</tr>
<tr>
<td>ECOG PS, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>34 (54)</td>
<td>58 (55)</td>
<td>231 (62)</td>
<td>63 (53)</td>
<td>61 (57)</td>
</tr>
<tr>
<td>1</td>
<td>29 (46)</td>
<td>48 (45)</td>
<td>144 (38)</td>
<td>56 (47)</td>
<td>45 (42)</td>
</tr>
<tr>
<td>≥2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Prior nephrectomy, n (%)</td>
<td>58 (92)</td>
<td>106 (100)</td>
<td>340 (91)</td>
<td>112 (94)</td>
<td>100 (93)</td>
</tr>
<tr>
<td>Prior cytokine therapy, n (%)</td>
<td>63 (100)</td>
<td>106 (100)</td>
<td>0</td>
<td>0</td>
<td>107 (100)</td>
</tr>
<tr>
<td>No. of disease sites, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>8 (13)</td>
<td>13 (12)</td>
<td>55 (15)</td>
<td>30 (25)</td>
<td>12 (11)</td>
</tr>
<tr>
<td>≥2</td>
<td>55 (87)</td>
<td>93 (88)</td>
<td>320 (85)</td>
<td>87 (73)(^†)</td>
<td>95 (89)</td>
</tr>
</tbody>
</table>

*The 375 patients cited in the table are those who received sunitinib in this trial
\(^*\)Mean value presented
\(^†\)Data missing for two patients

Final Multivariate Models of Associations Between AEs and Survival for mRCC Patients on Schedule 4/2

<table>
<thead>
<tr>
<th>AE</th>
<th>Endpoint</th>
<th>AE at any time point</th>
<th>AE by the 12-week landmark</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Hypertension</td>
<td>PFS</td>
<td>0.29</td>
<td>0.22–0.40</td>
</tr>
<tr>
<td></td>
<td>OS</td>
<td>0.30</td>
<td>0.24–0.43</td>
</tr>
<tr>
<td>Hand–foot syndrome</td>
<td>PFS</td>
<td>0.75</td>
<td>0.60–0.94</td>
</tr>
<tr>
<td></td>
<td>OS</td>
<td>0.58</td>
<td>0.44–0.77</td>
</tr>
<tr>
<td>Asthenia/fatigue</td>
<td>PFS</td>
<td>0.49</td>
<td>0.38–0.64</td>
</tr>
<tr>
<td></td>
<td>OS</td>
<td>0.72</td>
<td>0.54–0.96</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>PFS</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>OS</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>PFS</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>OS</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

NS, not significant
*Wald chi-square test
Results, cont’d

- Neutropenia and thrombocytopenia were not significant in any of the multivariate analyses, possibly due to a statistically significant correlation of both with hypertension and asthenia/fatigue ($r \geq 0.08$; $P < 0.05$, Fisher’s exact test), but not with hand–foot syndrome.

- Dose reduction, adjusted for time on treatment, was not associated with clinical outcome.

- Results were similar with both schedules (Schedule 4/2 and CDD) combined.
Conclusions

- Combined multivariate analyses indicate that hypertension and hand–foot syndrome, and to a lesser degree asthenia/fatigue, may serve as independent on-treatment biomarkers of sunitinib efficacy in mRCC.

- The inconsistent landmark results warrant further study, but suggest that hypertension and hand–foot syndrome may be more reliable early predictors of OS than of PFS with sunitinib.

- Neutropenia and thrombocytopenia were not significant in the multivariate analyses; however, a statistically significant correlation of both with hypertension and asthenia/fatigue was seen.

- Further study into underlying biological mechanisms is warranted.

- Providers who observe these AEs are encouraged to continue sunitinib therapy, managing AEs with standard medical treatment with or without dose reduction as clinically indicated.
Acknowledgments

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