**Additional file 1.** Baseline characteristics of patients with OS ≥24 versus <24 months in the placebo titration arm

<table>
<thead>
<tr>
<th>Baseline Characteristics, n (%)</th>
<th>OS ≥24 months</th>
<th>OS &lt;24 months</th>
<th>p-value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td>n = 30</td>
<td>n = 20&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>19 (63)</td>
<td>15 (75)</td>
<td>0.5382</td>
</tr>
<tr>
<td>≥65</td>
<td>11 (37)</td>
<td>5 (25)</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>25 (83)</td>
<td>14 (70)</td>
<td>0.3109</td>
</tr>
<tr>
<td>Female</td>
<td>5 (17)</td>
<td>6 (30)</td>
<td></td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>26 (87)</td>
<td>18 (90)</td>
<td>1.0000</td>
</tr>
<tr>
<td>Asian</td>
<td>3 (10)</td>
<td>2 (10)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 (3)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Weight, kg</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤65</td>
<td>4 (13)</td>
<td>6 (30)</td>
<td>0.2321</td>
</tr>
<tr>
<td>&gt;65, ≤76</td>
<td>6 (20)</td>
<td>5 (25)</td>
<td></td>
</tr>
<tr>
<td>&gt;76, ≤89</td>
<td>12 (40)</td>
<td>4 (20)</td>
<td></td>
</tr>
<tr>
<td>&gt;89</td>
<td>8 (27)</td>
<td>5 (25)</td>
<td></td>
</tr>
<tr>
<td><strong>ECOG PS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>19 (63)</td>
<td>10 (50)</td>
<td>0.3927</td>
</tr>
<tr>
<td>≥1</td>
<td>11 (37)</td>
<td>10 (50)</td>
<td></td>
</tr>
<tr>
<td><strong>Histological classification</strong></td>
<td></td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td>Clear cell</td>
<td>30 (100)</td>
<td>20 (100)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Prior nephrectomy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>22 (73)</td>
<td>17 (85)</td>
<td>0.4895</td>
</tr>
<tr>
<td>No</td>
<td>8 (27)</td>
<td>3 (15)</td>
<td></td>
</tr>
<tr>
<td><strong>No. of metastatic sites</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2</td>
<td>17 (57)</td>
<td>7 (35)</td>
<td>0.1588</td>
</tr>
<tr>
<td>≥3</td>
<td>13 (43)</td>
<td>13 (65)</td>
<td></td>
</tr>
<tr>
<td><strong>Site of metastasis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung only</td>
<td>4 (13)</td>
<td>0</td>
<td>0.1400</td>
</tr>
<tr>
<td>Lung + others</td>
<td>26 (87)</td>
<td>20 (100)</td>
<td></td>
</tr>
<tr>
<td><strong>Site of metastasis, individual</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>20 (67)</td>
<td>14 (70)</td>
<td>1.0000</td>
</tr>
<tr>
<td>Lymph node</td>
<td>14 (47)</td>
<td>12 (60)</td>
<td>0.3991</td>
</tr>
<tr>
<td>Kidney</td>
<td>10 (33)</td>
<td>5 (25)</td>
<td>0.7536</td>
</tr>
<tr>
<td>Liver</td>
<td>5 (17)</td>
<td>8 (40)</td>
<td>0.1004</td>
</tr>
<tr>
<td>Adrenal</td>
<td>7 (23)</td>
<td>7 (35)</td>
<td>0.5216</td>
</tr>
<tr>
<td>Bone</td>
<td>4 (13)</td>
<td>7 (35)</td>
<td>0.0902</td>
</tr>
<tr>
<td></td>
<td>Pancreas</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>----------</td>
<td>-----------</td>
<td>-----------</td>
</tr>
<tr>
<td><strong>Time from histopathological diagnosis to treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1 year</td>
<td>12 (40)</td>
<td>5 (25)</td>
<td>0.3654</td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>18 (60)</td>
<td>15 (75)</td>
<td></td>
</tr>
<tr>
<td><strong>Time from metastatic diagnosis to treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1 year</td>
<td>2 (7)</td>
<td>2 (10)</td>
<td>1.0000</td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>28 (93)</td>
<td>18 (90)</td>
<td></td>
</tr>
<tr>
<td><strong>Sum of longest diameter for target lesion</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤Median</td>
<td>14 (48)</td>
<td>7 (35)</td>
<td>0.3942</td>
</tr>
<tr>
<td>&gt;Median</td>
<td>15 (52)</td>
<td>13 (65)</td>
<td></td>
</tr>
<tr>
<td><strong>Presence of metastases (de novo) at initial diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>16 (53)</td>
<td>6 (30)</td>
<td>0.1480</td>
</tr>
<tr>
<td>Yes</td>
<td>14 (47)</td>
<td>14 (70)</td>
<td></td>
</tr>
<tr>
<td><strong>Baseline LDH</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1.5 × ULN</td>
<td>28 (93)</td>
<td>19 (95)</td>
<td>1.0000</td>
</tr>
<tr>
<td>&gt;1.5 × ULN</td>
<td>2 (7)</td>
<td>1 (5)</td>
<td></td>
</tr>
<tr>
<td><strong>Baseline Hb</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥LLN</td>
<td>19 (63)</td>
<td>12 (60)</td>
<td>1.0000</td>
</tr>
<tr>
<td>&lt;LLN</td>
<td>11 (37)</td>
<td>8 (40)</td>
<td></td>
</tr>
<tr>
<td><strong>Baseline Neu</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ULN</td>
<td>28 (93)</td>
<td>15 (75)</td>
<td>0.1003</td>
</tr>
<tr>
<td>&gt;ULN</td>
<td>2 (7)</td>
<td>5 (25)</td>
<td></td>
</tr>
<tr>
<td><strong>Baseline Plt</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ULN</td>
<td>29 (97)</td>
<td>17 (85)</td>
<td>0.2885</td>
</tr>
<tr>
<td>&gt;ULN</td>
<td>1 (3)</td>
<td>3 (15)</td>
<td></td>
</tr>
</tbody>
</table>

*Abbreviations: ECOG PS Eastern Cooperative Oncology Group performance status, Hb haemoglobin, LDH lactate dehydrogenase, LLN lower limit of normal, NA not applicable Neu neutrophil, OS overall survival, Plt platelet, ULN upper limit of normal

a Excluded 6 patients who were censored <24 months in OS.

b Fisher’s exact test was used for all, except weight, for which Cochran-Armitage trend test was used.

c 1 patient in the OS≥24 months group did not have any measurable target lesion; hence, was not included in the analysis.