**Independent commentary by Associate Professor Arun Azad**

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**Publication overview**

This review summarises and discusses a retrospective study that analysed data from six prospective clinical trials of sunitinib for treatment of metastatic renal cell carcinoma (mRCC) to characterise the heterogeneity of patients with an intermediate prognosis and determine whether it affects response to sunitinib therapy. Patients had an intermediate prognosis using the Memorial Sloan Kettering Cancer Center (MSKCC) and International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk models. The MSKCC (n=548) and IMDC (n=517) groups were similar in terms of baseline patient characteristics and risk factors. Overall, 59% had one risk factor and 41% had two risk factors. The most common risk factor was a low haemoglobin level alone or with an interval of <1 year since diagnosis. In both the MSKCC and IMDC groups, patients with one risk factor had longer overall survival (OS) and progression-free survival (PFS) than those with two risk factors (p<0.001 for both outcomes). Patients in the IMDC group with one risk factor also had a higher objective response rate (p=0.023). In both groups, OS was longer for patients with Eastern Cooperative Oncology Group (ECOG) performance status 0 than for those with ECOG performance status 1 (p<0.001). An ECOG performance status of 0 was also associated with superior PFS and ORR in the MSKCC group (p=0.05). In summary, intermediate-prognosis patients with mRCC constitute a heterogeneous population, with the number of risk factors and ECOG performance status appearing to predict the survival outcome with sunitinib therapy.

**Introduction**

Sunitinib is a multiple receptor tyrosine kinase inhibitor (TKI) that is licensed and subsidised (Authority Required) in Australia for the first-line treatment of advanced renal cell carcinoma. **1** Prospective clinical trials have established the clinical efficacy of sunitinib for the treatment of metastatic renal cell carcinoma (mRCC) and its complex but manageable safety profile. **4** Current guidelines published by the European Association of Urology (EAU) and European Society for Medical Oncology (ESMO) recommend sunitinib as a standard first-line therapy for favourable-risk disease and as an optional first-line therapy for intermediate-risk disease in patients with mRCC. **5,6** Due to the heterogeneity of the mRCC population, the choice of treatment is driven mainly by prognostic factors. **4**

**Study background**

Patients with mRCC have varied characteristics and prognoses, which demands a patient-centric approach to treatment. **7** An individualised treatment approach is difficult to apply in the clinical phases of drug development and predictive models based on prognostic factors have been developed and used in clinical trials of targeted agents for treatment of mRCC. The Memorial Sloan Kettering Cancer Center (MSKCC) and International mRCC Database Consortium (IMDC) risk models have been validated, **8,9** and are among the most commonly used predictive models. **10** The MSKCC risk model was derived from patients who participated in cytokine clinical trials. **1** It stratifies patients with mRCC into three prognostic groups according to five laboratory and clinical risk factors. **1** The IMDC model was derived from patients treated with targeted therapies both in and outside of clinical trials. It uses four of the five variables included in the MSKCC risk model and two additional factors (Table 1).

**Table 1. Laboratory and clinical risk factors used in the Memorial Sloan Kettering Cancer Center (MSKCC) and International Metastatic Renal-Cell Carcinoma Database Consortium (IMDC) prognostic models.**

<table>
<thead>
<tr>
<th>MSKCC criteria</th>
<th>IMDC criteria</th>
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</thead>
<tbody>
<tr>
<td>1. Low serum haemoglobin (Hb).</td>
<td>1. Low serum haemoglobin (Hb).</td>
</tr>
<tr>
<td>2. Elevated serum calcium.</td>
<td>2. Elevated serum calcium.</td>
</tr>
<tr>
<td>3. Elevated serum lactate dehydrogenase.</td>
<td>3. Elevated neutrophil count.</td>
</tr>
<tr>
<td>5. An interval of &lt;1 year between diagnosis and treatment.</td>
<td>6. An interval of &lt;1 year between diagnosis and treatment.</td>
</tr>
</tbody>
</table>

Both of the MSKCC and IMDC models categorise mRCC patients as favourable-, intermediate-, or poor-risk. **1** The intermediate-prognosis risk group is characterised by the presence of one or two factors; hence, it encompasses 15 and 19 permutations of the MSKCC and IMDC risk factors, respectively. Consequently, mRCC patients categorised as intermediate-prognosis might differ depending on the types of laboratory and clinical risk factors that determined this categorisation.
The aim of this retrospective analysis was to characterise the heterogeneity of mRCC patients identified as having an intermediate prognosis according to the MSKCC and IMDC risk models and to determine the responses to sunitinib in patients with intermediate-prognosis mRCC, including sub-groups of this population.

**Expert comment**

The MSKCC and IMDC models have high clinical utility in mRCC and have been widely implemented into daily clinical practice. Nevertheless, heterogeneity exists within respective prognostic groups, and this particularly applies to the intermediate-risk group. Improved sub-classification within the intermediate-risk group may influence treatment selection.

**Study patients and methods**

Results were pooled from a database of 1059 patients with mRCC who were enrolled in six sunitinib clinical trials in the first-line (n=783; 74%) and second-line (n=276; 26%) treatment settings.\(^1\)\(^2\) Efficacy endpoints in the clinical trials included overall survival (OS) and progression-free survival (PFS) and objective response rate (ORR), both assessed by investigators using the Response Evaluation Criteria for Solid Tumours (RECIST, version 1.0).

Relevant patient inclusion criteria common to all six trials included: age ≥18 years; histologically-confirmed mRCC; presence of measurable disease; no known brain metastases; Eastern Cooperative Oncology Group (ECOG) performance status 0–1 (or Karnofsky performance status of ≥70% in one trial); and adequate organ function. The following sunitinib dosing schedules were used: 50mg once daily for four consecutive weeks followed by two weeks without treatment in repeated 6-week cycles (n=689; 65%) or 37.5mg on a continuous once-daily dosing schedule (n=370; 35%).

Pooled analyses were performed on the intermediate-prognosis groups as well as patient subgroups, defined by the presence of one versus two risk factors and ECOG performance status 0 versus 1 or 2, from the sunitinib arms of each trial. The Kaplan-Meier method was used to estimate the median PFS and OS for each subgroup, with 95% confidence intervals (CIs) calculated using the Brookmeyer and Crowley method. Between-group comparisons were performed using a log-rank test, with a Cox proportional hazards model used to calculate Hazard ratios (HRs) for these comparisons. Differences in the ORR between the patient sub-groups were determined using a Pearson chi-squared (χ²) test.

**Study results**

The MSKCC criteria identified 548 patients (52%) as having intermediate prognosis mRCC compared with 517 (49%) patients identified by the IMDC criteria. The baseline patient characteristics and risk factors are summarised in Table 2. The median age was 60 (range 24–87) years in both groups and most patients were male and had clear-cell histology and an ECOG performance status 0.

**Risk factor profiles**

Patients represented 14/15 possible intermediate-risk factor profiles (permutations of 1 or 2 risk factors) in the MSKCC group compared with 18/19 possible intermediate-risk factor profiles in the IMDC group. A total of 325 (59%) patients had only one risk factor and 223 (41%) patients had two risk factors in the MSKCC group compared with 303 (59%) patients with only one risk factor and 214 (41%) patients with two risk factors in the IMDC group. In the MSKCC versus IMDC groups, the most common risk factor profiles were an interval of <1 year since diagnosis only (n=210 [38%] vs n=186 [36%]) or a low haemoglobin (Hb) level only (n=90 [16%] vs n=69 [13%]), or both (n=161 [29%] vs n=127 [25%]). The small number of patients in each risk group illustrates the heterogeneous nature of the intermediate-prognosis population. For patients with an intermediate-risk factor profile, the ORR was 0–50.0% in the MSKCC group compared with 0–58.3% in the IMDC group.

**Clinical outcomes**

The median PFS was 8.4 (95%CI: 7.9–9.8) months in the MSKCC group and 9.2 (95%CI: 8.2–10.7) months in the IMDC group. The median OS was 22.9 (95%CI: 20.1–23.0) months in the MSKCC group and 26.3 (95%CI: 19.5–25.0) months in the IMDC group.

In the MSKCC and the IMDC groups, both PFS and OS were statistically significantly longer for patients with one risk factor than for those with two risk factors. The median PFS was 10.7 (95%CI: 8.7–12.0) months for patients with one risk factor versus 6.5 (95%CI: 5.1–7.8) months for patients with two risk factors in the MSKCC group (HR 0.684 [95% CI: 0.563–0.832; p<0.001, Figure 1A) and 10.7 (95%CI: 9.5–12.6) months for patients with one risk factor versus 7.4 (95%CI: 5.4–8.7) months for patients with two risk factors in the IMDC group (HR 0.702 [95% CI: 0.571–0.863; p<0.001, Figure 1B). The median OS was 26.3 (95%CI: 23.0–30.2) months for patients with one risk factor versus 14.1 (95%CI: 11.4–16.3) months for patients with two risk factors in the MSKCC group (HR 0.522 [95% CI: 0.420–0.648; p<0.001, Figure 1C) and 27.8 (95%CI: 24.0–31.0) months for patients with one risk factor versus 15.0 (95%CI: 12.9–16.7) months for patients with two risk factors in the IMDC group (HR 0.511 [95% CI: 0.406–0.641; p<0.001, Figure 1D).

**Table 2. Summary of patient characteristics and risk factors at baseline in sunitinib-treated metastatic renal cell carcinoma (mRCC) patients categorised as having intermediate-prognosis disease (data derived from six clinical trials).**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MSKCC Model</th>
<th>IMDC Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>548</td>
<td>517</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Median</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>24–87</td>
</tr>
<tr>
<td>Male gender</td>
<td>379 (69%)</td>
<td>361 (70%)</td>
</tr>
<tr>
<td>ECOG PS</td>
<td>0</td>
<td>332 (61%)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>208 (38%)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>8 (1)</td>
</tr>
<tr>
<td>Histologic type</td>
<td>Clear cell</td>
<td>509 (93%)</td>
</tr>
<tr>
<td></td>
<td>Non-clear cell</td>
<td>37 (7)</td>
</tr>
<tr>
<td>Risk factors (n)</td>
<td>1</td>
<td>325 (59%)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>223 (41%)</td>
</tr>
<tr>
<td>Sites of metastases</td>
<td>Lung</td>
<td>427 (78%)</td>
</tr>
<tr>
<td></td>
<td>Bones</td>
<td>171 (31)</td>
</tr>
<tr>
<td></td>
<td>Liver</td>
<td>129 (24)</td>
</tr>
<tr>
<td></td>
<td>Previous therapy</td>
<td>101 (18)</td>
</tr>
<tr>
<td></td>
<td>Cytokine</td>
<td>101 (18)</td>
</tr>
<tr>
<td></td>
<td>Radiation</td>
<td>85 (16)</td>
</tr>
<tr>
<td></td>
<td>Nephrectomy</td>
<td>426 (78)</td>
</tr>
</tbody>
</table>

Abbreviations: ECOG = Eastern Cooperative Oncology Group; IMDC = International mRCC Database Consortium; MSKCC = Memorial Sloan Kettering Cancer Center; PS = performance status.

*Histologic data missing for two patients (<1%).
The ORR was 38.9% (95% CI: 33.6–44.3) versus 30.1% (95% CI: 24.1–36.7; p=0.036). A similar analysis using the IMDC risk model demonstrated statistical superiority only for OS; the HR of OS for patients with ECOG performance status 0 versus 1 or 2 was 0.567 (95% CI: 0.452–0.711; p<0.001; median 25.7 months [95% CI: 23.0–30.9 months] vs 16.3 months [95% CI: 13.9–18.8 months]).

**Expert comment**

These are important results that demonstrate improved clinical outcomes for patients with one compared to two risk factors (by both IMDC and MSKCC criteria) treated with sunitinib.

**Study interpretation**

The MSKCC and IMDC risk models, the most widely used prognostic models at the time of this retrospective analysis, were consistent in their identification of mRCC patients with an intermediate prognosis: 52% and 49% of patients according to the MSKCC and IMDC group, respectively. These results agree with those determined in three trials of first-line TKIs in which intermediate-prognosis patients comprised 43–64% of participating patients.

The two groups had similar ORRs: 36.6% (95% CI: 32.4–40.9) of patients in the IMDC group versus 35.4% (95% CI: 31.4–39.6) of patients in the MSKCC group. The ORR was significantly higher for patients with one risk factor (40.6%; 95% CI: 35.0–46.4) than for those with two risk factors (30.8%; 95% CI: 24.7–37.5; p=0.023) in the IMDC group versus 35.4% (95% CI: 31.4–39.6) of patients in the MSKCC group.

In the analysis of the contribution of the ECOG performance status to the prognosis of patients with intermediate-risk prognosis, PFS and OS were both statistically superior for patients with ECOG performance status 0 versus 1 or 2 in the MSKCC group. The PFS for ECOG performance status 0 versus 1 or 2 was median 9.7 (95% CI: 8.0–10.7) months versus 7.8 (95% CI: 5.1–9.0) months (HR 0.797 [95% CI: 0.654–0.972; p=0.0242; Figure 2A] and the OS was median 24.7 (95% CI: 22.2–30.2) months versus 14.0 (95% CI: 11.7–16.3) months (HR 0.529 [95% CI: 0.426–0.657; p<0.001]; Figure 2B). The ORR was 38.9% (95% CI: 33.6–44.3) versus 30.1% (95% CI: 24.1–36.7; p=0.036). A similar analysis using the IMDC risk model demonstrated statistical superiority only for OS; the HR of OS for patients with ECOG performance status 0 versus 1 or 2 was 0.567 (95% CI: 0.452–0.711; p<0.001; median 25.7 months [95% CI: 23.0–30.9 months] vs 16.3 months [95% CI: 13.9–18.8 months]).
Both risk models showed significantly longer PFS and OS for patients with one versus two risk factors, supporting the hypothesis that patients with intermediate-prognosis mRCC are a heterogeneous group. If validated in additional analyses of first-line TKIs, this heterogeneity has potential implications for the outcomes of future clinical trials. The intermediate-prognosis group is the largest risk group in the mRCC population and patients in the intermediate-prognosis group might have different outcomes according to the number of risk factors. The results of this retrospective analysis suggest that stratification of intermediate-prognosis patients by the number of risk factors might reduce the heterogeneity of this group.

The PFS and OS outcomes were superior for mRCC patients with ECOG performance status 0 versus 1 or 2 in both the MSKCC and IMDC models in this retrospective analysis. Superior PFS was also demonstrated in mRCC patients with ECOG performance status 0 versus 1 using the MSKCC model who had been treated with first-line TKIs in two prospective clinical trials. Collectively, these results suggest that the clinical assessment of patients by physicians, using the ECOG performance status, may be the most important predictor of outcome with targeted therapy and should be evaluated in future clinical trials.

Limitations of this retrospective analysis were the same as those of the large database of six clinical trials of sunitinib upon which the analysis was based. These include differences in sunitinib treatment schedules, different phases of clinical development, different treatment schedules, under-representation of ethnic sub-populations, inclusion of non-clear cell histologic types, differences in previous nephrectomy rates in subgroup populations, and the use of previous cytokine therapy. The findings are also restricted to patients with measurable disease who participated in clinical trials.

**Take-home messages**

- The MSKCC and IMDC risk models use five and six factors, respectively, to segregate mRCC patients into favourable-, intermediate-, and poor-prognosis groups.
- mRCC patients with intermediate prognosis based on the MSKCC and IMDC risk models are a heterogeneous group.
- The intermediate-prognosis group is characterised by the presence of one or two risk factors.
- In patients with intermediate-prognosis mRCC treated with sunitinib:
  - PFS and OS were statistically significantly longer for patients with one versus two risk factors analysed using both risk models.
  - OS was statistically significantly longer for patients with ECOG performance status 0 versus 1 or 2 analysed using both risk models.
  - An ECOG performance status of 0 was also associated with superior PFS and ORR in the MSKCC group.
- These data confirm the importance of the ECOG performance status as a prognostic factor in patients with mRCC when using the MSKCC model.
- The number of risk factors and ECOG performance status appear to predict the survival outcome with sunitinib therapy.
- Number of risk factors and ECOG performance status should be considered when designing and interpreting the efficacy results of clinical trials of sunitinib or other TKIs.

**Expert’s concluding remarks**

This is an important study that highlights the heterogeneity of outcomes for patients classified as intermediate-risk mRCC. It may be postulated that patients with one risk factor only be classified as “favourable-intermediate” and those with two risk factors be classified as “unfavorable-intermediate”. In turn, those with unfavorable-intermediate disease may be more akin to patients with good-risk disease and therefore be suitable for treatment with a VEGF TKI alone. In comparison, those with unfavorable-intermediate disease would appear to be more suitable for treatment with nivolumab plus ipilimumab. It should be noted that this treatment approach pertains to first-line disease and to the current Australian landscape, where other treatment combinations are not yet approved or reimbursed.

**References**