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Sunitinib in Patients With Metastatic Renal Cell Carcinoma: Clinical Outcome According to International Metastatic Renal Cell Carcinoma Database Consortium Risk Group

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Abstract

Background: Sunitinib malate, a targeted tyrosine kinase inhibitor, is standard of care for metastatic renal cell carcinoma (mRCC) and serves as the active comparator in several ongoing mRCC clinical trials. This analysis reports benchmarks for clinical outcomes based on International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk groups for patients treated with sunitinib for mRCC in a front-line setting.¹

Materials and Methods: A retrospective analysis was performed on data from sunitinib treated patients (n=375) in the pivotal phase III trial of sunitinib versus IFN- α as first-line treatment for mRCC. Objective response rates (ORR) were determined from independently reviewed radiologic assessments. The Kaplan–Meier method was used to estimate median progression-free survival (PFS) and median overall survival (OS) by patient risk group.

Results: Median PFS (95% confidence interval [CI]) was 14.1 (13.4–17.1), 10.7 (10.5–12.5), 2.4 (1.1–4.7), and 10.6 (8.1–10.9) months in sunitinib-treated patients in the IMDC favorable-(n=134), intermediate- (n=205), poor- (n=34), and intermediate + poor-risk (n=239) groups, respectively. Median OS (95% CI) was 23.0 (19.8–27.8), 5.1 (4.3–9.9), and 20.3 (16.8–23.0) months in

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Trial Registration number: [ClinicalTrials.gov](https://clinicaltrials.gov),

sunitinib-treated patients by IMDC intermediate-, poor-, and intermediate + poor-risk groups, respectively, and was not reached in the favorable-risk group (>50% of patients were alive at data cut-off¹). ORR (95% CI) was 53.0% (44.2–61.7%), 33.7% (27.2–40.6%), 11.8% (3.3–27.5%), and 30.5% (24.8–36.8%) in sunitinib-treated patients in IMDC favorable-, intermediate-, poor-, and intermediate + poor-risk groups, respectively.

Conclusions: Results of this retrospective analysis demonstrates differences in patient outcomes for PFS, OS, and ORR based on IMDC prognostic risk group assignment for patients with mRCC.

Micro Abstract

A retrospective analysis of patient outcome according to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic model from a phase III trial of sunitinib versus interferon- α as treatment for metastatic renal cell carcinoma was performed; IMDC benchmarks from this analysis for objective response rate, progression-free survival and overall survival for sunitinib-treated patients are reported.

Keywords

Targeted therapy; Prognosis; MSKCC; IMDC; Risk stratification

Introduction

Over the last decade, the prognosis for patients with metastatic renal cell carcinoma (mRCC) has been improved by the development of molecularly targeted drugs, including those that target vascular endothelial growth factor.^{1–3} In the course of clinical trials aimed at advancing treatment of mRCC, knowledge of patient profiles and outcomes has been compiled, allowing investigators to develop models for stratification of patients by risk based on readily available biological factors.^{4,5} Risk stratification is widely used for patient counseling and in the design of clinical trials.

The International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic model, first proposed and validated by Heng et al in 2009, was specifically developed using patient data of molecularly targeted cancer therapies.⁶ The model uses 6 readily available factors (diagnosis to treatment-time interval, Karnofsky Performance Status [KPS], hemoglobin level, platelet count, neutrophil count, and serum calcium concentration) in order to classify patients into favorable- (0 risk factors), intermediate- (1 or 2 risk factors), and poor-risk (3 risk factors) prognostic groups.⁶

The Memorial Sloan Kettering Cancer Center (MSKCC) prognostic model has also been used to stratify patients by risk. The MSKCC model, proposed in 2002, was developed from clinical data and patient profiles from multiple trials of interferon- α (INF- α) as a first-line treatment for mRCC. This model includes 5 factors, 4 of which are shared with the IMDC model: time from diagnosis to treatment, KPS, hemoglobin, and serum calcium. The MSKCC model also includes serum lactate dehydrogenase concentration as a factor. Similar to the IMDC model, the MSKCC model has also been used to stratify patients into favorable-, intermediate-, and poor-risk groups.⁷

Sunitinib malate, a globally approved, multi-targeted, tyrosine kinase inhibitor, has become a reference standard of care for mRCC, and serves as the active comparator in multiple mRCC clinical trials in which enrollment may be restricted to prespecified, prognostic risk groups.^{8–12} Notably, 2 recently reported randomized trials using sunitinib as the standard arm focused on IMDC intermediate- and poor-risk populations and reported clinical outcomes specifically in this population.^{12,13} The interpretation and analysis of current and future clinical trials involving sunitinib treatment in patients with mRCC would be aided by the availability of benchmarks for patient responses to sunitinib treatment based on IMDC risk group, as use of this model has increasingly become the default choice for patient risk stratification in investigations of targeted therapies.

To produce these benchmarks, a retrospective analysis of outcome from a pivotal phase III clinical trial comparing sunitinib with IFN- α in patients with mRCC¹⁴ was performed according to IMDC risk group. Patients from this trial had been previously stratified for risk by the MSKCC model¹ as earlier analyses of data were performed before the introduction and routine use of the IMDC prognostic model.

Materials and Methods

Study Design

A retrospective analysis was performed on data from an international, multicenter, randomized, phase III trial of sunitinib versus IFN- α as first-line treatment for mRCC.¹ Benchmark values for these outcomes by IMDC risk groups were derived from independently reviewed radiologic tumor progression measurements from the intent-to-treat (ITT) population. A supportive analysis of data from investigator measurements of tumor progression was also performed according to IMDC risk group. For the purpose of additional comparison, the independently reviewed radiologic data for patient outcomes and OS were also analyzed by MSKCC risk groups.

In the clinical trial, treatment-naïve patients with mRCC (with a clear-cell component) in all prognostic risk groups were randomized into 2 separate arms and treated with sunitinib or IFN- α .¹ Tumor assessments, response, and progression were defined by Response Evaluation Criteria in Solid Tumors (RECIST) v1.0 criteria and evaluated by an independent, third-party radiology laboratory; clinical trial investigators performed supplemental tumor assessment.

Tumor assessment was performed on day 28 (28-day cycle) of cycles 1–4, and every 2 cycles thereafter until the end of treatment for patients receiving sunitinib. The primary efficacy endpoint was progression-free survival (PFS); secondary study endpoints included objective response rate (ORR) and median overall survival (OS), all in the ITT population. Benchmark values are reported for these data. Complete details of the clinical study design, including patient population data and inclusion/exclusion criteria, were reported previously.^{1,14}

Statistical Methods

All efficacy endpoints were assessed in the ITT population. The primary endpoint of the study (PFS assessed by independent radiology review committee) and secondary study endpoints have been reported previously.¹ In the current post-hoc analyses, patients were grouped according to the IMDC and MSKCC prognostic models. For each prognostic model, patients were grouped into favorable-, intermediate-, or poor-risk groups. Patients in the intermediate-risk group were also grouped according to the presence of 1 or 2 risk factors. Time-to-event endpoints of PFS and OS were estimated using Kaplan–Meier methods. The median event times and corresponding 95% confidence intervals (95% CI) were provided. For ORR, 95% CIs were obtained using the exact method based on a binomial distribution. All analyses were performed with SAS software (version 9.4). Data cut-off for PFS, ORR, and OS analyses was November 2005.¹

Results

Patients

A total of 750 patients were enrolled for the clinical trial at 101 centers in multiple countries including the United States. Of these, 375 patients were randomized to the sunitinib treatment arm. All 375 patients in the sunitinib group received at least 1 dose of the study drug.¹ Median duration of treatment for sunitinib-treated patients during the period analyzed was 6 months (range 1–15), and patients were followed for at least 28 days after their last dose.¹ Baseline demographic and disease characteristics for sunitinib-treated patient are shown in Table 1.

Efficacy by IDMC and MSKCC Risk Group

Of the 375 sunitinib-treated patients (ITT population), 134 (37.5%) were classified as favorable risk, 205 (54.7%) as intermediate risk ($n = 134$ [35.7%] with 1 risk factor, $n = 71$ [18.9%] with 2 risk factors), and 34 (11%) as poor risk, according to IMDC; 2 patients were not classified due to missing data. A total of 360 patients in the trial were treated with IFN- α and were not included in the current analysis.

The number of patients classified at the start of treatment as favorable, intermediate, and poor risk by IMDC or MSKCC are shown by risk group in Figure 1. Compared with the MSKCC model, a similar proportion of patients were assigned by the IMDC model to the poor-risk group ($n = 34$ [9.1%] vs. 23 [6.1%], IMDC and MSKCC, respectively) and the intermediate-risk group with 2 risk factors ($n = 71$ [18.9%] vs. 60 [16.0%], IMDC vs. MSKCC, respectively). Patient numbers in the more-favorable risk groups were slightly lower for IMDC versus MSKCC. The median sunitinib treatment duration and median number of cycles for patients classified by IMDC as favorable, intermediate, and poor risk were: 16.7 months and 12 cycles, 11.0 months and 8 cycles, and 2.6 months and 2.0 cycles, respectively.

Median PFS and ORR benchmark values for patients with IMDC classifications of favorable risk, intermediate risk, poor risk, intermediate plus poor risk, intermediate risk with 1 risk factor (intermediate-1 risk), and intermediate risk with 2 risk factors (intermediate-2 risk)

are shown in Table 2 (based on independent radiology laboratory data) and Table 3 (based on investigator measurements). In both data sets, median PFS was different (ie, no overlap of the 95% CI for the values) between the 3 main risk groups. Median PFS was longest for the favorable-risk group and progressively shorter for the intermediate- and poor-risk groups, as expected. This order in degrees of treatment response was also seen in ORR, although there is overlap of 95% CI for the response values of the intermediate- and poor-risk groups with both independent radiology laboratory data and investigator assessment data; there is also an overlap between the favorable- and intermediate-risk groups in the investigator assessment data. Based on independent radiology laboratory data the PFS (95% CI) was 10.6 months (4.2–11.8%) for patients with bone metastases, which was not different from PFS for patients without bone metastases at 10.7 months (8.1–11.1%).

Median PFS and ORR values based on independent radiology laboratory data for patients with MSKCC classifications of favorable risk, intermediate risk, poor risk, intermediate plus poor risk, intermediate-1 risk, and intermediate-2 risk are shown in Table 4. As with the patients stratified by IMDC, the median PFS was different between the 3 main risk groups; median PFS was longest for the favorable-risk group and shortest for the poor-risk group with no overlap of 95% CI for the PFS values for the 3 groups. Objective response rate was highest in the favorable-risk group and was progressively lower in the intermediate- and poor-risk groups with overlap of 95% CI between these latter 2 groups. These results are similar to the findings (based on the same independent radiology laboratory data) with patients stratified by IMDC.

The Kaplan–Meier plots for PFS estimation for patients with IMDC classifications of favorable risk, intermediate-1 risk, intermediate-2 risk, and poor risk based on independent radiology laboratory data (Figure 2) and investigator measurements (Figure 3) are shown.

Median OS benchmark values for sunitinib-treated patients by IMDC and MSKCC risk group are shown in Table 5. Because the majority of favorable-risk patients were still alive at the time of data cut-off, median OS was not determined for this group. For groups stratified by IMDC there was a marked difference in median OS between the intermediate-risk and poor-risk groups, with no overlap of 95% CI. There was also a difference in median OS between the patients classified as intermediate-1 risk versus intermediate-2 risk, with no overlap of 95% CI.

Discussion

The MSKCC and IMDC models are both currently used to determine patient risk group for the purpose of patient counseling, clinical trial design, and data interpretation.¹⁵ The IMDC model is the more recently derived of the 2 models, having been developed after the emergence of molecularly targeted therapies as the standard of care for mRCC.¹⁶ The IMDC model has been extensively validated for risk stratification of patients treated with targeted therapy in both first-line and second-line settings.^{17,18}

The benchmark values for PFS, ORR, and OS based on independent radiology laboratory data are broadly similar for IMDC and MSKCC stratified risk groups across all risk

classifications for this population of 375 patients receiving first-line sunitinib treatment for mRCC. The similar number of patients in this study classified as intermediate and poor risk by IMDC compared with the MSKCC model is consistent with previous studies.^{16,19} The analysis suggests that IMDC and MSKCC models may have comparable prognostic value when applied to cohorts similar to the one examined in this study.

The data reported here provide context for interpretation of recently reported prospective trials, namely the CABOSUN randomized phase II and CheckMate-214 phase III trials. CABOSUN enrolled exclusively IMDC intermediate and poor risk patients, with a reported ORR of 12% and median PFS of 5.6 months¹² for sunitinib-treated patients. These numbers are significantly lower than those reported in this retrospective analysis. Several explanations are possible, including differences in performance status of patients (ECOG PS 1 was 52.8%¹² for sunitinib-treated patients in CABOSUN and 38.4% for patients in this study [Table 1]) and the percentage of patients with bone metastases (sunitinib-treated patients in CABOSUN with bone metastases at baseline was 35.9%¹² vs. 31.8% for corresponding risk group patients in this study [Table 1]). The CheckMate-214 data are more consistent with the present analysis, albeit with a slightly lower ORR and lower PFS.¹³ Overall survival data in the present analysis are numerically lower than data reported in more recent trials¹² and are likely not reflective of current expectations given the greatly expanded number of post-progression treatment options now available.¹³

The values for PFS and ORR for patients classified as intermediate risk, intermediate-1 risk, and intermediate-2 risk were not different for the IMDC or MSKCC stratified risk groups (independent radiology laboratory assessment). For median PFS, the 95% CI for the intermediate-risk and intermediate-1 risk groups overlapped with the intermediate-2 risk group, suggesting they are not statistically different. However, in analyses using investigator assessment, there was a marked difference in median PFS between the intermediate-1 risk and intermediate-2 risk groups (IMDC risk stratification). It is likely that there could be meaningful differences between the 2 intermediate IMDC subgroups depending on treatment received, method of assessment, and other undefined factors.

Overall survival was different for intermediate-1 risk (28.2 months; 95% CI 23.0-not evaluable) versus intermediate-2 risk (16.3 months; 95% CI 13.2–19.4), suggesting that closer review of the patient profiles in the intermediate-risk group may have additional prognostic value. This finding is consistent with previously published analyses that the intermediate-risk group of mRCC patients, as classified by either IMDC and MSKCC, is more heterogeneous than the favorable- and poor-risk groups.²⁰ Because intermediate-risk patients are the largest group presenting for treatment of mRCC,¹³ further examination of the heterogeneity of this group and the implications for prognostication are especially warranted.

This study has certain limitations; firstly, it is limited by nature of being a retrospective post hoc analysis. In addition, the original clinical trial design and patient recruiting were conducted before the introduction of the IMDC model, which should be considered when comparisons are made with trials designed and run after use of the IMDC model became routine. The OS data from this study are no longer contemporary in light of developments in

the post-disease progression setting, particularly those changes due to the emergence of immune-oncology therapies.

Conclusions

This retrospective analysis provides benchmarks for median PFS, median OS, and ORR for treatment responses in mRCC by IMDC. These benchmark values can aid current and future design and interpretation of clinical trials in mRCC. Results of this analysis demonstrate clear differences in patient outcomes based on IMDC prognostic risk group. For all risk groups, PFS, ORR, and OS were broadly similar in the IMDC and MSKCC stratified groups within this study. The difference in OS between intermediate-1 risk compared with intermediate-2 risk in the IMDC stratified groups supports the possibility that prognostic difference can be determined by substratifying the intermediate-risk group.

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Abbreviations:

CI	confidence interval
INF-α	interferon- α
ITT	intent-to-treat
KPS	Karnofsky Performance Status
mRCC	metastatic renal cell carcinoma
ORR	objective response rate
OS	overall survival
PFS	progression-free survival

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Clinical Practice Points

- Results of this study suggest there may be significant prognostic differences between the intermediate-1 and intermediate-2 IMDC risk groups and that this should be considered when counseling patients identified to be in one of these groups.
- Some differences in ORR were seen depending on whether independently reviewed radiologic assessments or investigator assessments were used to derive outcomes. These differences are possibly due to investigator bias and/or the non-uniformity of treatment centers that participated in this study.
- The clinical outcomes based on independent radiology laboratory data are broadly similar for IMDC and MSKCC stratified risk groups across all risk classifications in this study. This supports the continued usage of either model in stratifying patient risk for counseling purposes.

Figure 1. Stratification of Sunitinib-treated Patients by IMDC and MSKCC Prognostic Models

Abbreviations: IMDC = International Metastatic Renal Cell Carcinoma Database

Consortium; MSKCC = Memorial Sloan Kettering Cancer Center.

Figure 2. Kaplan–Meier Estimate of PFS for Sunitinib: Independent Radiology Laboratory Assessment by IMDC* *ITT population

Abbreviations: IMDC = International Metastatic Renal Cell Carcinoma Database

Consortium; Int = intermediate; ITT = intent to treat; mPFS = median progression-free survival.

**Figure 3. Kaplan–Meier Estimate of PFS for Sunitinib: Investigator Measurement by IMDC*
*ITT population**

Abbreviations: IMDC = International Metastatic Renal Cell Carcinoma Database

Consortium; Int = intermediate; ITT = intent to treat; mPFS = median progression-free survival.

Table 1**Sunitinib-treated Patients' Demographic and Clinical Characteristics at Baseline**

Characteristic	Sunitinib-treated patients (N = 375)
Median age, years (range)	62 (27–87)
Sex, n (%)	
Male	267 (71.2)
Female	108 (28.8)
ECOG performance status, n (%)	
0	231 (61.6)
1	144 (38.4)
Patients with metastases at baseline by site, n (%)	
Bone	113 (30.1) *
Liver	99 (26.4)
Lung	292 (77.9)
Previous nephrectomy	340 (90.6)

* Patients in IMDC intermediate and poor risk groups with bone metastases at baseline = 31.8%

Abbreviations: IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; ECOG = Eastern Cooperative Oncology Group.

Table 2

Median PFS and ORR Benchmark Values for Sunitinib-treated Patients by IMDC Risk Group: Independent Radiology Laboratory Assessment*

IMDC Risk Group	Median PFS (95% CI), Months	ORR (95% CI), %
Favorable (n= 134)	14.1 (13.4–17.1)	53.0 (44.2–61.7)
Intermediate (n = 205)	10.7 (10.5–12.5)	33.7 (27.2–40.6)
Poor (n = 34)	2.4 (1.1–4.7)	11.8 (3.3–27.5)
Intermediate + poor (n = 239)	10.6 (8.1–10.9)	30.5 (24.8–36.8)
Intermediate with 1 risk factor (n = 134)	10.9 (10.6–13.1)	32.8 (25.0–41.5)
Intermediate with 2 risk factors (n = 71)	10.6 (7.1–13.7)	35.2 (24.2–47.5)

* ITT population.

Abbreviations: CI = confidence interval; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; ITT = intent to treat; ORR = objective response rate; PFS = progression-free survival.

Table 3

Median PFS and ORR for Sunitinib-treated Patients by IMDC Risk Group: Investigator Measurement *

IMDC Risk Group	Median PFS (95% CI), Months	ORR (95% CI), %
Favorable (n = 134)	16.0 (13.6–17.3)	58.2 (49.4–66.7)
Intermediate (n = 205)	10.7 (8.6–12.5)	42.4 (35.8–49.7)
Poor (n = 34)	2.5 (2.3–6.5)	17.6 (6.8–34.5)
Intermediate + poor (n = 239)	9.7 (8.1–10.7)	38.9 (32.8–45.6)
Intermediate with 1 risk factor (n = 134)	11.2 (9.7–13.6)	43.3 (35.0–52.5)
Intermediate with 2 risk factors (n = 71)	8.5 (5.6–10.7)	40.8 (29.3–53.2)

*
ITT population.

Abbreviations: CI = confidence interval; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; ITT = intent to treat; ORR = objective response rate; PFS = progression-free survival.

Table 4

Median PFS and ORR for Sunitinib-treated Patients by MSKCC Risk Group: Independent Radiology Laboratory Assessment*

MSKCC Risk Group	Median PFS (95% CI), Months	ORR (95% CI), %
Favorable (n = 142)	14.8 (13.4–17.1)	50.7 (42.2–59.2)
Intermediate (n = 210)	10.7 (9.0–11.5)	32.9 (26.5–39.7)
Poor (n = 23)	2.8 (1.1–4.7)	17.4 (5.0–38.8)
Intermediate + poor (n = 233)	10.6 (8.1–10.9)	31.3 (25.4–37.7)
Intermediate with 1 risk factor (n = 150)	10.7 (9.0–11.5)	33.3 (25.9–41.5)
Intermediate with 2 risk factors (n = 60)	10.7 (4.2–14.8)	31.7 (20.3–45.0)

* ITT population.

Abbreviations: CI = confidence interval; ITT = intent to treat; MSKCC = Memorial Sloan Kettering Cancer Center; ORR = objective response rate; PFS = progression-free survival.

Table 5

Median OS for Sunitinib-treated Patients by IMDC Risk Group *

Median OS (95% CI), by Risk Group, months						
	Favorable	Intermediate	Poor	Intermediate + Poor	Intermediate With 1 Risk Factor	Intermediate With 2 Risk Factors
IMDC	n = 134	n = 205	n = 34	n = 239	n = 134	n = 71
Prognostic model	NE (NE-NE)	23.0 (19.8–27.8)	5.1 (4.3–9.9)	20.3 (16.8–23.0)	28.2 (23.0–NE)	16.3 (13.2–19.4)
MSKCC	n = 142	n = 210	n = 23	n = 233	n = 150	n = 60
Prognostic model	NE (NE-NE)	20.9 (18.2–25.6)	5.3 (4.2–10.0)	20.1 (16.8–23.0)	23.1 (20.2–30.2)	16.7 (11.4–20.3)

* ITT population.

Abbreviations: CI = confidence interval; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; ITT = intent to treat; MSKCC = Memorial Sloan Kettering Cancer Center; NE = not evaluable; OS = overall survival.