Original Study

Real-world Experience With Sunitinib Treatment in Patients With Metastatic Renal Cell Carcinoma: Clinical Outcome According to Risk Score

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Abstract

ADONIS is an ongoing observational study designed to evaluate treatment patterns/outcomes in patients with metastatic renal cell carcinoma treated with first-line sunitinib and/or second-line axitinib post sunitinib. We report an evaluation of sunitinib efficacy by risk group, in the real-world setting examined by ADONIS. Sunitinib efficacy was also assessed in intermediate-risk subgroups with 1 and 2 risk factors.

Background: ADONIS is an ongoing observational study in 9 European countries, designed to evaluate treatment patterns/outcomes in patients with metastatic renal cell carcinoma (mRCC) treated with first-line sunitinib and/or second-line axitinib post sunitinib. We present an evaluation of sunitinib efficacy by risk group, in the real-world setting examined in ADONIS. **Patients and Methods:** Patients were enrolled at the start of first-line sunitinib treatment or second-line axitinib post sunitinib treatment. Evaluation of sunitinib efficacy was assessed by International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) and Memorial Sloan Kettering Cancer Center risk criteria. **Results:** For all patients in this analysis (N = 467), the median progression-free survival was 23.8 months (95% confidence interval [CI], 16.5-28.5 months), 11.8 months (95% CI, 8.1-17.4 months), and 4.6 months (95% CI, 2.5-7.7 months) for IMDC favorable-, intermediate-, and poor-risk groups, respectively. The median overall survival was 97.1 months (95% CI, 46.3 months-not evaluable [NE]), 33.5 months (95% CI, 20.5-46.6 months), and 10.0 months (95% CI, 4.5-19.8 months) for the respective risk groups. Data on individual risk factors were available for a subgroup of patients, allowing analysis by intermediate risk by 1 versus 2 risk factors. When including this subgroup (n = 120), the median overall survival for IMDC favorable-, intermediate-1, and intermediate-2 risk factors was 21.6 months (95% CI, 16.3 months-NE), 20.5 months (15.5 months-NE), and 15.1 months (4.1 months-NE), respectively. **Conclusions:** For patients overall and by risk-group stratification, survival estimates were aligned with previously published data. In patients with intermediate-1 risk, overall survival was very similar to patients with favorable risk. However, further exploration of outcome data from different sources is needed to confirm these observations.

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Introduction

More than 400,000 cases of kidney cancer are diagnosed worldwide each year, and approximately 175,000 deaths are attributed to the disease. The rate of kidney cancer is higher in developed counties versus less-developed countries, with approximately 115,000 new cases in Europe annually.[1,2] The majority of

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these cases, upwards of 90%, are renal cell carcinoma (RCC).[1,2] The ADONIS trial is an ongoing, prospective/retrospective, observational study initiated at 158 sites distributed among 9 European countries, and has been designed to evaluate treatment patterns and outcomes in patients with metastatic RCC (mRCC) treated with first-line sunitinib and/or second-line axitinib post sunitinib.

Sunitinib is an orally available, small molecule, tyrosine kinase inhibitor (TKI) of vascular endothelial growth factor receptor (VEGF) receptors 1-3, platelet-derived growth factor (PDGF) receptor-α, PDGF receptor-β, and other receptor tyrosine kinases that promote angiogenesis. It has been approved globally for the treatment of advanced RCC and has been a standard of treatment for over 12 years.[3,4] It is currently considered an option for use in first-line treatment strategies for patients with mRCC and favorable-risk in both the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO) guidelines.[4-7] Axitinib is also an orally available, small molecule TKI of VEGF receptors 1-3 with anti-angiogenesis activity, approved for second-line treatment of mRCC in the United States (US) and Europe since 2012.[8] In April 2019, the combination of pembrolizumab and axitinib was approved by the US Food and Drug Administration (FDA) for the treatment of mRCC in the first-line setting; this was closely followed in May 2019 by FDA approval of the combination of avelumab and axitinib, in the same patient setting.[9-12] In September and October of 2019, the combinations of pembrolizumab and axitinib, and avelumab and axitinib, were approved respectively for the treatment of mRCC in the first-line by the European Medicines Agency.[13,14]

Previously, the combination of checkpoint inhibitors nivolumab plus ipilimumab was approved in the United States and Europe for patients with mRCC who have not received previous systemic treatment and who have intermediate/poor-risk classification. This approval was based on improved outcomes in patients with intermediate/poor risk with nivolumab/ipilimumab versus sunitinib in the Checkmate 214 trial.[6] As a secondary endpoint, outcomes (progression-free survival [PFS], overall response rate [ORR], and overall survival [OS]) were evaluated for favorable-risk patients. In this population, sunitinib and nivolumab/ipilimumab efficacy were not statistically different.[6,15]

The analysis presented here includes the evaluation of sunitinib efficacy by International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) and Memorial Sloan Kettering Cancer Center (MSKCC) risk criteria. The IMDC prognostic model, first proposed and validated in 2009, uses 6 factors (diagnosis to treatment-time interval, Karnofsky performance status scale, 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 ($\geq$ 3 risk factors) prognostic groups.[16]

The MSKCC model, first proposed in 2002, uses 5 factors, 4 of which are shared with the IMDC model: time from diagnosis to treatment, Karnofsky performance status, hemoglobin, and serum calcium. The MSKCC model also includes serum lactate dehydrogenase concentration. The MSKCC model has also been used to stratify patients into favorable- (0 risk factors), intermediate- (1 or 2 risk factors), and poor-risk ($\geq$ 3 risk factors) groups.[17]

In the current study, an additional analysis of sunitinib efficacy was performed in a subset of patients identified as the risk factor set (RFS), for whom individual risk factor data were available. This analysis was performed by IMDC intermediate-risk with 1 risk factor (intermediate-1) versus 2 risk factors (intermediate-2). The safety profile for sunitinib in real-world settings as observed in the ADONIS trial is also reported.

This study presents a real-world assessment of sunitinib efficacy and safety that confirms outcomes reported from the clinical trial setting. As sunitinib remains a first-line option for patients with favorable risk, along with the newly approved axitinib and checkpoint inhibitor combinations, a deeper understanding of their efficacy and safety, as demonstrated in the real-world setting, can help inform considerations of their use as an option in the treatment of mRCC going forward.[6,12]

Future analyses of the ADONIS study will include treatment sequencing data for sunitinib followed by axitinib as well as other treatments (cabozantinib, nivolumab, and others), sunitinib and axitinib therapy management strategies, and patient-reported quality of life measures.

Patients and Methods

Patients and Study Design

Patients were enrolled at the start of first-line treatment with sunitinib or second-line axitinib post sunitinib treatment. The full analysis set (FAS) includes all eligible patients enrolled in the study. The safety analysis set (SAS) includes all patients with at least 1 treatment intake documented (ie, date of first intake available), regardless of treatment (sunitinib or axitinib). For patients in the RFS, data on the 6 individual IMDC risk factors were available, allowing additional analysis by intermediate-1 and intermediate-2 risk factors.

The first patient was enrolled in this study on October 23, 2014. The data cutoff for this analysis was May 31, 2018. Analysis focused on first-line sunitinib in the metastatic setting. Data collection for the complete ADONIS trial is continuing, and as of May 1, 2019, 555 patients were enrolled.

Key Eligibility Criteria

Patients were $\geq$ 18 years of age and had histologically confirmed diagnosis of mRCC (clear-cell or non−clear-cell renal tumor) with measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Enrolled patients were treated with first-line sunitinib or second-line axitinib according to the approved therapeutic indication (except post cytokines) in Europe.

Statistical Analysis

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. The RFS population had intermediate risk by IMDC and were additionally 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. Patients who discontinued the study for any reason or who were free of event at the cutoff date were censored at the time of their last disease assessment. Many patients in ADONIS are still under treatment, meaning that they did not have the events of interest. Two-sided log-rank tests were used to compare survival curves for sub-groups of interest. These

comparisons were exploratory in nature. The type I error was set at 5%. ORR was reported based on confirmed patient responses as assessed by treating clinicians.

Table 1 Patient Characteristics at Sunitinib Initiation in First-line Treatment

	Prospective Group (SU in First-line at Inclusion) n = 318, n (%)	Retrospective/ Prospective Group (AXI in Second-line at Inclusion) n = 149, n (%)	Total N = 467, n (%)
Treatment at inclusion			
n	318	149	467
SU first-line	318 (100.0)	0 (0.0)	318 (68.1)
AXI second-line	0 (0.0)	149 (100.0)	149 (31.9)
Age at SU initiation, y			
n	314	147	461
Missing	4	2	6
Mean (SD)	63.8 (10.0)	60.9 (11.0)	62.9 (10.4)
Median	65	62	64
Min-max	33-90	31-88	31-90
Q1-Q3	57-71	53-68	56-70
Age at SU initiation category, y			
n	314	147	461
Missing	4	2	6
<65	153 (48.7)	88 (59.9)	241 (52.3)
≥65	161 (51.3)	59 (40.1)	220 (47.7)
Gender			
n	318	149	467
Male	237 (74.5)	126 (84.6)	363 (77.7)
Female	81 (25.5)	23 (15.4)	104 (22.3)
ECOG PS at SU initiation			
n	260	108	368
Missing	58	41	99
0	123 (47.3)	57 (52.8)	180 (48.9)
1	114 (43.8)	38 (35.2)	152 (41.3)
2	21 (8.1)	11 (10.2)	32 (8.7)
3	2 (0.8)	2 (1.9)	4 (1.1)

Abbreviations: AXI = axitinib; ECOG PS = Eastern Cooperative Oncology Group performance status; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; SU = sunitinib.

Results

Patient Population

At the time of data cutoff, there was a total of 467 patients in the FAS, with 462 patients in the SAS. Of the FAS group, there were 120 patients for whom complete individual risk data were available (ie, the RFS subgroup). Overall, patients in the study were a median age of 63 years (range, 31-90 years). The population was predominantly (77.7%) male. At sunitinib initiation, 90.2% of patients had Eastern Cooperative Oncology Group performance score < 2 and 9.8% had Eastern Cooperative Oncology Group performance score ≥ 2. The median follow-up time for patients treated with sunitinib in the first-line at inclusion was 9.2 months (range, 0.0-40.0 months) (Table 1). The majority (81%) of patients were started on sunitinib 50 mg/day on schedule 4/2 with some patients started at either a lower dose (primarily 37.5 or 25 mg/day) and/or an alternate schedule (primarily schedule 2/1).

Outcomes

Overall, patients in FAS treated with first-line sunitinib had a median PFS of 10.4 months (95% confidence interval [CI], 9.3-12.5 months) and a median OS of 34.0 months (95% CI, 28.3-46.6 months). PFS and OS by IMDC risk group are shown in Table 2, and the Kaplan-Meier plots for these results are shown in Figure 1. Kaplan-Meier PFS and OS plots by MSKCC risk group for FAS are shown in Figure 2, with results summarized in Table 3.

PFS and OS estimates by IMDC intermediate-1 risk factor versus intermediate-2 risk factors calculated for the RFS subgroup of patients (n = 120) are shown in Table 4, with corresponding Kaplan-Meier plots illustrated in Figure 3. PFS and OS estimates were also calculated for the RFS subgroup, with patients with favorable- and intermediate-1 risk factor grouped together versus patients with poor- and intermediate-2 risk factors. These data are shown in Table 5, with corresponding Kaplan-Meier plots illustrated in Figure 4. Additionally, the analysis of the frequency of individual risk factors for the RFS subgroup confirmed the findings published by Sella et al[18] with time from diagnosis to treatment < 1 year (65.8%) and low hemoglobin level (43.3%) to be the 2 most frequent risk factors presented by patients with mRCC at diagnosis, as shown in Table 6.

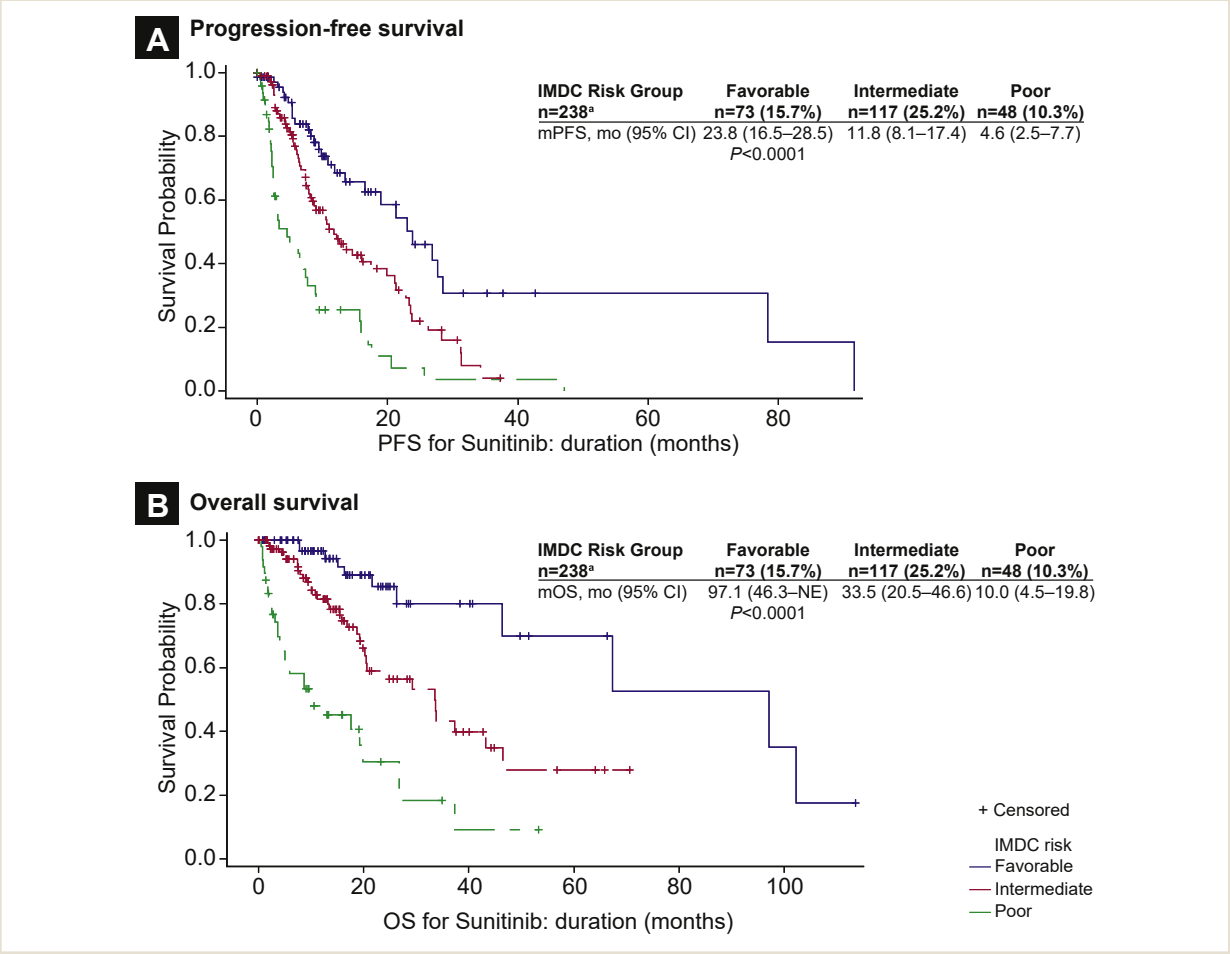
ORR by MSKCC risk group are presented in Table 7. Risk classification was not provided by investigators for 217 (46.8%) patients. The response rate for sunitinib-treated patients without risk classification (42.1%) was comparable with favorable-risk patients (41.8%).

Table 2 PFS and OS for First-line Sunitinib-treated Patients, by IMDC Risk Group

IMDC Risk Group n = 238[a]	Favorable n = 73 (15.7%)	Intermediate n = 117 (25.2%)	Poor n = 48 (10.3%)
Median PFS, mos (95% CI)	23.8 (16.5-28.5)	11.8 (8.1-17.4)	4.6 (2.5-7.7)
Median OS, mos (95% CI)	97.1 (46.3-NE)[b]	33.5 (20.5-46.6)	10.0 (4.5-19.8)

Abbreviations: CI = confidence interval; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; NE = not evaluable; OS = overall survival; PFS = progression-free survival.
[a]Risk classification was not provided by investigators for 226 (48.7%) patients.
[b]Median OS assessed on a very small set of patients at risk (n = 3). Susceptible to change with a longer follow-up.

Figure 1 Kaplan-Meier Estimate of PFS (A) and OS (B) for First-Line Sunitinib, by IMDC Risk Group. [a]Risk Classification for 226 (48.7%) Patients was Not provided by Investigators



Abbreviations: CI = confidence interval; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; mOS = median overall survival; mPFS = median progression-free survival; NE = not evaluable.

Safety of Sunitinib

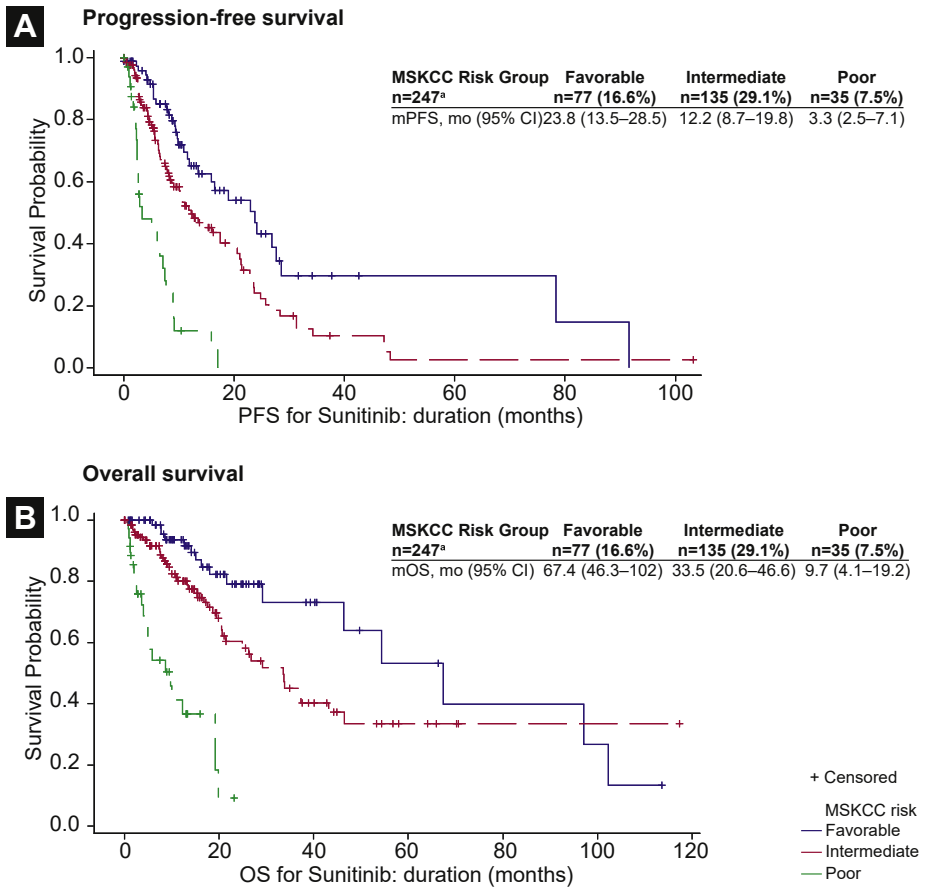
Safety endpoints were evaluated in all 462 patients enrolled in this study that were treated at least once with either sunitinib or axitinib (SAS). Results were aligned with previous experience, and no new or unexpected safety events were observed so far.

Discussion

In the current NCCN and ESMO treatment guidelines, sunitinib, along with 2 other VEGF-targeted treatments, pazopanib and bevacizumab plus interferon, are listed as first-line treatment options for patients with mRCC and favorable risk.[5,7,19] ESMO treatment guidelines also include the selective VEGF inhibitor tivozanib as an option in the first-line treatment of patients with favorable risk.[5] Nivolumab/ipilimumab is currently the preferred first-line treatments for patients with intermediate-/poor-risk factors and also an option for patients with favorable risk, with cabozantinib as an option in both scenarios.[5,7,19] Additionally, the combinations of pembrolizumab/axitinib and avelumab/axitinib were approved by the FDA in April 2019 and May 2019, respectively, for the treatment of patients with mRCC and any prognostic risk.[9,11,20,21] The European Medicine Agency approved the pembrolizumab/axitinib and avelumab/axitinib combinations for the treatment of mRCC in the first-line in September and October of 2019 respectively.[13,14] Although sunitinib is not the newest treatment option for patients with intermediate-/poor-risk prognostic factors, it may still be considered for these patients if newer treatments are unavailable owing to local approval status, or in consideration of the greater clinical experience with the safety profile and efficacy of VEGF-targeted agents (ie, patients with features and comorbidities like compromised immune-system conditions will not be good candidates for immuno-oncology therapy).[5,9,11]

As the mRCC treatment landscape continues to evolve, established VEGF-targeted agents, such as sunitinib, pazopanib, and tivozanib, are likely to continue to also have utility in second-line treatment after progression post nivolumab/ipilimumab, post axitinib/pembrolizumab, post axitinib/avelumab, or post cabozantinib treatment, as well as in potential combination therapy with immuno-oncology agents. There have been reports of efficacy for

Figure 2 Kaplan-Meier Estimate of PFS (A) and OS (B) for First-Line Sunitinib, by MSKCC Risk Group. [a]Risk Classification for 217 (46.8%) Patients was Not provided by Investigators



Abbreviations: CI = confidence interval; mOS = median overall survival; mPFS = median progression-free survival; MSKCC = Memorial Sloan Kettering Cancer Center.

VEGF-targeted treatments in patients with mRCC who experience relapse post checkpoint inhibitor therapy.[22-30]

Aspects of the real-word efficacy data for sunitinib in first-line treatment of mRCC reported here reflect the gains in clinical experience in the treatment of mRCC with targeted therapies, specifically sunitinib, over the past decade (ie, managing adverse events and maintaining patients on treatment at optimal dose). For example, in the pivotal sunitinib phase III trial, PFS for patients with IMDC favorable risk was 16.0 months (95% CI, 13.6-17.3 months),[31] whereas the PFS for all patients with favorable risk in the current ADONIS study was 23.8 months (95% CI, 16.5-28.5 months).

The survival data presented here add to the context for interpretation of the reported efficacy of sunitinib from other prospective clinical trials.[3,31,32] CABOSUN, a randomized phase II trial that enrolled only patients with intermediate/poor risk according to IMDC criteria, reported an ORR of 12% and a median PFS of 5.6 months (95% CI, 3.4-8.1 months) for patients with mRCC treated with sunitinib in the first line. These results are lower than the efficacy for patients in the FAS with IMDC intermediate/poor risk reported in ADONIS, with an ORR of 36% and a median PFS of 8.9 months (95% CI, 7.4-12.2 months).[33] Differences in patient population and study design may have contributed to the relatively shorter PFS in the sunitinib cohort in CABOSUN as compared

Table 3 PFS and OS for First-line Sunitinib-treated Patients, by MSKCC Risk Group

MSKCC Risk Group n = 247[a]	Favorable n = 77 (16.6%)	Intermediate n = 135 (29.1%)	Poor n = 35 (7.5%)
Median PFS, mos (95% CI)	23.8 (13.5-28.5)	12.2 (8.7-19.8)	3.3 (2.5-7.1)
Median OS, mos (95% CI)	67.4 (46.3-102)	33.5 (20.6-46.6)	9.7 (4.1-19.2)

Abbreviations: CI = confidence interval; MSKCC = Memorial Sloan Kettering Cancer Center; NE = not evaluable; OS = overall survival; PFS = progression-free survival.
[a]Risk classification was not provided by investigators for 217 (46.7%) patients.

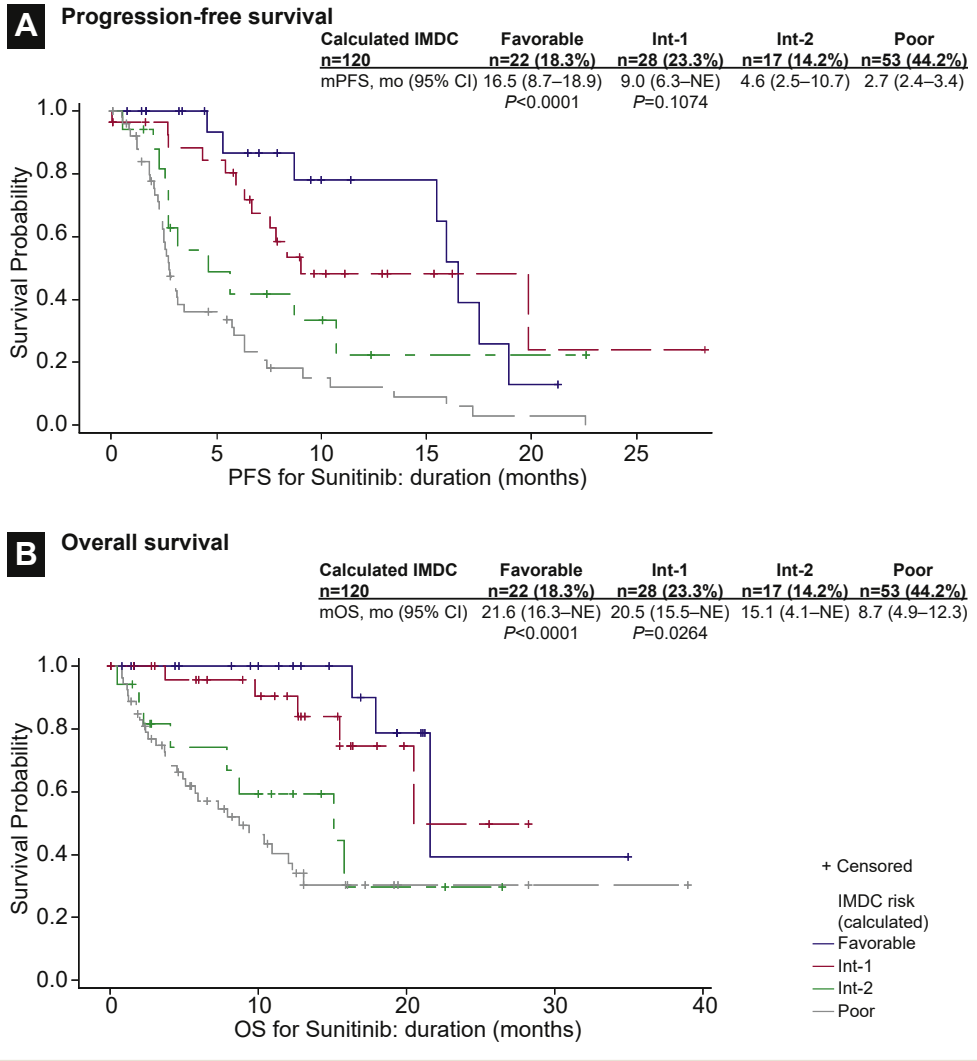
Table 4 PFS and OS for First-line Sunitinib-treated Patients, by IMDC Risk Group, Including Intermediate-1 Versus -2 Risk Factors at Start

Calculated IMDC n = 120	Favorable n = 22 (18.3%)	INT-1 n = 28 (23.3%)	INT-2 n = 17 (14.2%)	Poor n = 53 (44.2%)
Median PFS, mos (95% CI)	16.5 (8.7-18.9)[a]	9.0 (6.3-NE)[b]	4.6 (2.5-10.7)	2.7 (2.4-3.4)
Median OS, mos (95% CI)	21.6 (16.3-NE)[c]	20.5 (15.5-NE)[d]	15.1 (4.1-NE)	8.7 (4.9-12.3)

Abbreviations: CI = confidence interval; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; INT-1/-2 = intermediate risk with 1/2 risk factors; NE = not evaluable; OS = overall survival; PFS = progression-free survival.
[a]Log-rank test *P*-value < .001 for the comparison of favorable patients versus all other groups.
[b]Log-rank test *P*-value = .1074 for the comparison of INT-1 versus INT-2.
[c]Log-rank test *P*-value < .001 for the comparison of favorable patients versus all other groups.
[d]Log-rank test *P*-value = .0264 for the comparison of INT-1 versus INT-2 patients.

with the real-world data presented here. However, the efficacy reported for the FAS population in ADONIS is similar to that reported for patients with IMDC intermediate/poor risk (ORR, 31%) in a retrospective study of data from the pivotal sunitinib phase III trial.[31] Also, the median PFS in the phase III trial was 10.6 months (95% CI, 8.1-10.9 months) for patients with IMDC

Figure 3 Kaplan-Meier Estimate of PFS (A) and OS (B) for First-Line Sunitinib, by IMDC Risk Group Individual Risk Factor



Abbreviations: CI = confidence interval; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; Int-1 = 1 intermediate risk factor; Int-2 = 2 intermediate risk factors; mOS = median overall survival; mPFS = median progression-free survival; NE = not evaluable.

Table 5 PFS and OS for First-line Sunitinib-treated Patients in the Risk Factor Set, by IMDC Risk Group, Favorable/Intermediate-1 Versus Intermediate-2/Poor Risk Factors at Start

Calculated IMDC n = 120	Favorable/INT-1 n = 50 (41.7%)	INT-2/Poor n = 70 (58.3%)
Median PFS, mos (95% CI)	15.9 (8.3-18.9)[a]	2.8 (2.5-5.1)
Median OS, mos (95% CI)	21.6 (20.5-NE)[a]	9.4 (5.7-15.1)

Abbreviations: CI = confidence interval; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; INT-1/-2, intermediate risk with 1/2 risk factors; NE = not evaluable; OS = overall survival; PFS = progression-free survival.
[a]Log-rank test *P*-value < .001 for the comparison of favorable/INT-1 versus INT-2/poor.

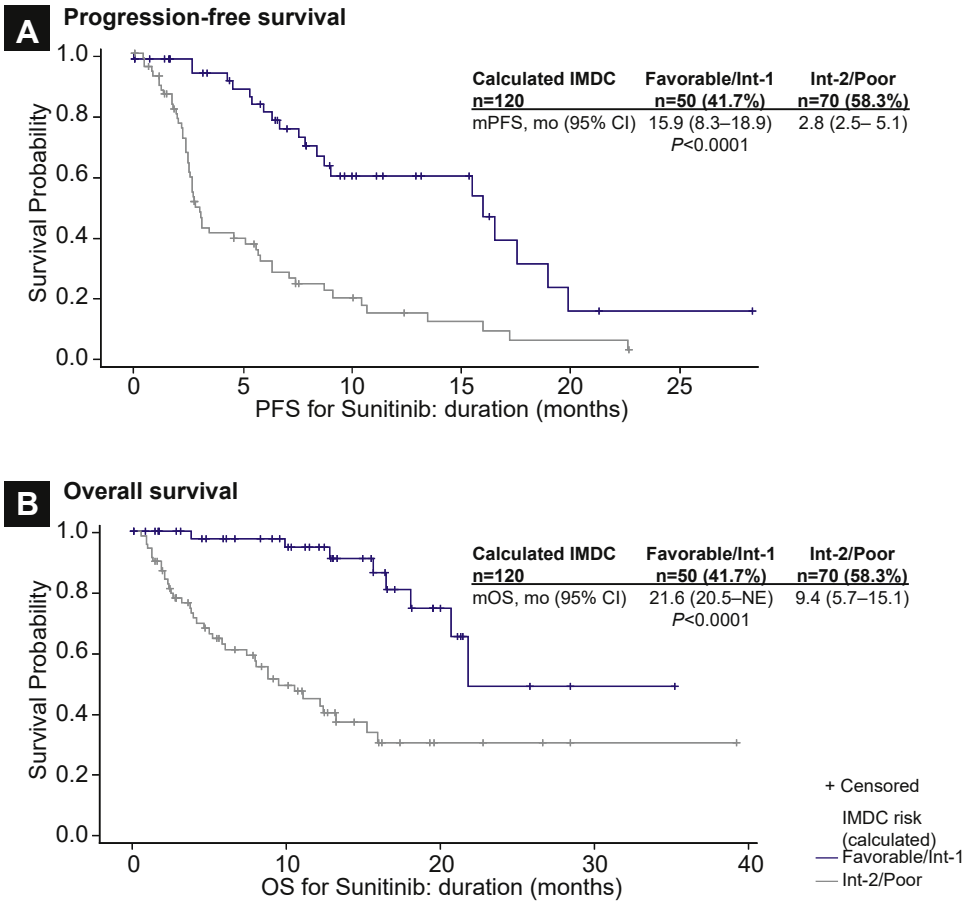
intermediate/poor risk; in other words, survival results in the phase III study were also longer than the PFS reported in CABOSUN.[31]

In the retrospective study of the aforementioned pivotal sunitinib phase III trial, the median PFS results in patients with intermediate-risk with 1-risk factor versus 2-risk factors were similar (10.9 months [95% CI, 10.6-13.1 months] vs. 10.6 months [95% CI, 7.1-13.7 months]).[31] In contrast, the median PFS for patients with intermediate-1 and intermediate-2 risk in the RFS subgroup population were not similar (9.0 vs. 4.6 months, respectively). This difference is possibly owing to the subgroup of patients in the RFS subgroup not being fully representative of the FAS of the current study.[31]

The median OS in the pivotal sunitinib phase III trial was 28.2 months (95% CI, 23.0 months-NE) and 16.3 months (95% CI, 13.2-19.4 months) in patients with intermediate-1 risk factor and intermediate-2 risk factors, respectively. The current study also observed a difference between patients with 1 risk versus 2 risk factors in patients in the RFS subgroup. Moreover, patients in the RFS subgroup with favorable risk had a very similar median OS as patients with 1 risk factor.[31]

The finding reported here — that patients with intermediate-risk and 1 risk versus 2 risk factors may have different outcomes — supports published analyses that suggest the intermediate-risk group, as defined by IMDC or MSKCC criteria, may be more

Figure 4 Kaplan-Meier Estimate of PFS (A) and OS (B) for First-Line Sunitinib, by IMDC Risk Group Individual Risk Factors: Favorable/Intermediate-1 Versus Intermediate-2/Poor



Abbreviations: CI = confidence interval; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; Int-1 = 1 intermediate risk factor; Int-2 = 2 intermediate risk factors; mOS = median overall survival; mPFS = median progression-free survival; NE = not evaluable.

Table 6 Frequency of Individual IMDC Risk Factors for Patients in the Risk Factor Set[a] at Start

IMDC Risk Factor	Factor Present, n (%)	Factor Absent, n (%)	Data Missing
< 1 year from diagnosis	79 (65.8)	41 (34.2)	–
Hemoglobin < LLN	52 (43.3)	68 (56.7)	–
Platelets > ULN	36 (30.0)	84 (70.0)	–
Neutrophils > ULN	32 (27.1)	86 (72.9)	2
Corrected calcium > ULN	31 (26.5)	86 (73.5)	3
KPS < 80%	14 (15.6)	76 (84.4)	30

Abbreviations: IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; KPS = Karnofsky performance status; LLN = lower limit of normal ~12 g/dL; ULN = upper limit of normal for platelets ~150,000-400,000 cells/μL; ULN = upper limit of normal for neutrophils ~2.0-7.0 × 10^9 cells/L; ULN = upper limit of normal for corrected calcium ~8.5-10.2 mg/dL.
[a]n = 120.

heterogeneous than patients with mRCC in the favorable- or poor-risk groups.[18] Patients identified as intermediate risk have been the largest risk group entering treatment for mRCC in daily practice, with 20% diagnosed as having favorable risk, 45% with intermediate risk, and 35% with poor risk.[34] Further exploration of the heterogeneity of this intermediate-risk group and the implications for use of prognostic tools are needed.[35]

This study has some limitations. One, it is limited by the nature of the retrospective post hoc component of the analysis. In addition, the RFS subgroup of patients was considerably smaller than the FAS population in this study, as the 6 individual risk factor data needed to calculate the IMDC risk score were only available for the smaller subset. As such, the RFS may not be fully representative of the larger FAS. Also, the OS data from this study may not represent the current and projected post disease-progression setting, owing to the emergence of immune-oncology therapies that have modified the treatment landscape. For example, the combination of pembrolizumab and axitinib demonstrated OS benefit over sunitinib in all IMDC patient risk groups in the phase III pivotal trial.[12]

Conclusions

For patients overall and by risk-group stratification, survival estimates for patients with mRCC treated with sunitinib in the ADONIS real-world study were aligned with results reported from the pivotal sunitinib phase III trial and with improvements seen in clinical practice over the past decade. The real-world characteristics of the study population support the soundness of these results. In patients with intermediate-risk with 1-risk factor, OS was very similar to patients with favorable-risk factors. However, further exploration is needed to confirm these observations.

Clinical Practice Points

- Real-word efficacy data from the ADONIS trial for sunitinib in first-line treatment of mRCC confirm the efficacy of sunitinib as reported in the pivotal phase III trial and reflect the gains in clinical experience over the last decade.
- Established VEGF-targeted agents, such as sunitinib, pazopanib, and tivozanib (only in Europe), are currently often used options for first-line treatment of mRCC for patients with favorable risk. For patients with intermediate- or poor-risk factors, newer treatments have been demonstrated to have survival benefits over targeted agents.
- The established targeted agents are likely to continue to have some utility in the first-line for patients with favorable risk.
- Targeted agents will also likely continue to have utility in second-line treatment after progression post nivolumab/ipilimumab, post axitinib/pembrolizumab, or post axitinib/avelumab, as well as in potential combination therapy with immuno-oncology agents.

Data Sharing Statement

Upon request, and subject to certain criteria, conditions, and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines and medical devices (1) for indications that have been approved in the United States and/or European Union or (2) in programs that have been terminated (ie, development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data

Table 7 Objective Response Rate for First-line Sunitinib-treated Patients, by MSKCC Risk Group

MSKCC Risk Group n = 247[a]	Favorable n = 77 (16.6%)	Intermediate n = 135 (29.1%)	Poor n = 35 (7.5%)	NA[a] n = 217 (46.8%)	Total N = 464
ORR with sunitinib					
n	67	107	23	183	380
Not reported	10	28	12	34	84
No response, n (%)	39 (58.2)	68 (63.6)	15 (65.2)	106 (57.9)	228 (60.0)
Response, n (%)	28 (41.8)	39 (36.4)	8 (34.8)	77 (42.1)	152 (40.0)

Abbreviations: CI = confidence interval; MSKCC = Memorial Sloan Kettering Cancer Center; NA = not available; ORR = overall response rate.
[a]Risk classification was not provided by investigators for 217 (46.8%) patients.

may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

CRediT authorship contribution statement

Manuela Schmidinger: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Writing - review & editing, Supervision, Project administration, Visualization. **Camillo Porta:** Conceptualization, Methodology, Formal analysis, Investigation, Resources, Writing - review & editing, Supervision. **Stephane Oudard:** Conceptualization, Methodology, Formal analysis, Investigation, Resources, Writing - review & editing, Supervision. **Gwenael Denechere:** Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data curation, Writing - review & editing, Supervision, Project administration, Visualization. **Yves Brault:** Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data curation, Writing - review & editing, Supervision. **Lucile Serfass:** Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data curation, Writing - review & editing, Supervision, Project administration. **Nuno Costa:** Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data curation, Writing - review & editing, Supervision, Project administration. **James Larkin:** Conceptualization, Methodology, Formal analysis, Investigation, Resources, Writing - review & editing, Supervision, Project administration.

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