Original Article

Checkpoint Inhibitors in Patients With Metastatic Renal Cell Carcinoma: Results From the International Metastatic Renal Cell Carcinoma Database Consortium

Steven M. Yip, MD, MSc [1]; Connor Wells, [1]; Raphael Moreira MD[2]; Alex Wong, MD[3]; Sandy Srinivas, MD[4]; Benoit Beuselinck, MD[5]; Camillo Porta, MD[6]; Hao-Wen Sim, MBBS [7]; D. Scott Ernst, MD[8]; Brian I. Rini, MD[9]; Takeshi Yuasa, MD[10]; Naveen S. Basappa, MD[3]; Ravindran Kanesvaran, MD[11]; Lori A. Wood, MD[12]; Christina Canil, MD[13]; Anil Kapoor, MD[14]; Simon Y.F. Fu, MD[15]; Toni K. Choueiri, MD [16]; and Daniel Y.C. Heng, MD, MPH[1*]

BACKGROUND: To the authors' knowledge, outcomes and prognostic tools have yet to be clearly defined in patients with metastatic renal cell carcinoma (mRCC) who are treated with immuno-oncology (IO) checkpoint inhibitors (programmed death-ligand 1 [PD-L1] inhibitors). In the current study, the authors aimed to establish IO efficacy benchmarks in patients with mRCC and update patient outcomes in each International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic class. **METHODS:** A retrospective analysis was performed using the IMDC database with data from 38 centers. It included patients with mRCC who were treated with ≥1 line of IO. Overall response rates (ORRs), duration of treatment (DOT), and overall survival (OS) were calculated. Patients were stratified using IMDC prognostic factors. **RESULTS:** A total of 687 patients (90% with clear cell and 10% with non-clear cell) were included. The ORR was 27% in evaluable patients (461 patients). In patients treated with first-line nivolumab and ipilimumab (49 patients), the combination of PD-L1 inhibitor and vascular endothelial growth factor inhibitor (72 patients), and PD-L1 inhibitor (51 patients), the ORR was 31%, 39%, and 40%, respectively, and the median DOT was 8.3 months, 14.7 months, and 8.3 months, respectively. The ORR for second-line, third-line, and fourth-line nivolumab was 22%, 24%, and 26%, respectively. The median DOT was 5.7 months, 6.2 months, and 8.3 months, respectively, in the second-line, third-line, and fourth-line settings. When segregated into IMDC favorable-risk, intermediate-risk, and poor-risk groups, the median OS rates for the first-line, second-line, third-line, and fourth-line treatment settings were not reached (NR), NR, and NR, respectively ($P = .163$); NR, 26.7 months, and 7.4 months, respectively ($P < 0.0001$); 36.1 months, 28.2 months, and 11.1 months, respectively ($P = .016$); and NR, NR, and 6.7 months, respectively ($P = .047$). **CONCLUSIONS:** The ORR was not found to deteriorate from the first-line to the fourth-line of IO therapy. In the second line through fourth line, the IMDC criteria appropriately stratified patients into favorable-risk, intermediate-risk, and poor-risk groups for OS. ***Cancer* 2018;124:3677-3683.** © *2018 American Cancer Society*.

KEYWORDS: checkpoint inhibitor, immunotherapy, International Metastatic Renal Cell Carcinoma Database Consortium (IMDC), metastatic, programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), renal.

INTRODUCTION

Each year, renal cell carcinoma (RCC) is diagnosed in 338,000 patients in the United States and leads to the death of 114,000 patients.[1] On average, approximately one-third of patients will present with a de novo diagnosis of metastatic RCC (mRCC).[2] Many patients treated with first-line vascular endothelial growth factor (VEGF) inhibitor targeted therapies (eg, sunitinib, pazopanib) will develop disease progression and require second-line therapy.

Given the immunogenic nature of RCC, programmed death-ligand 1 (PD-L1), programmed cell death protein 1 (PD-1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors have significantly impacted the mRCC therapeutic landscape.[3] In the CheckMate 025 trial, nivolumab, a PD-1 inhibitor, was compared with everolimus in patients with clear cell mRCC who previously received anti-VEGF therapy.[4] Nivolumab was identified as improving overall survival (OS), in contrast to everolimus (hazard ratio [HR], 0.73; $P = .002$).[4] Combination immuno-oncology (IO) therapy with nivolumab plus ipilimumab, a CTLA-4 inhibitor, was compared with sunitinib in the first-line

Corresponding author: Daniel Y.C. Heng, MD, MPH, Tom Baker Cancer Center, 1331 29 St NW, Calgary, AB Canada T2N 4N2; daniel.heng@ahs.ca

[1]Department of Medical Oncology, Tom Baker Cancer Center, Calgary, Alberta Canada; [2]Department of Oncology, Américas Medical Service/Brazil, United Health Group, Sao Paulo, Brazil; [3]Department of Medical Oncology, Cross Cancer Institute, University of Alberta, Edmonton, Alberta Canada; [4]Department of Medical Oncology, Stanford University, Stanford, California; [5]Department of General Medical Oncology, University Hospitals Leuven, Leuven, Belgium; [6]Department of Medical Oncology, IRCCS San Matteo University Hospital Foundation, Pavia, Italy; [7]Department of Medical Oncology, Princess Margaret Hospital, Toronto, Ontario Canada; [8]Department of Medical Oncology, London Health Sciences Centre, London, Ontario Canada; [9]Department of Oncology, Cleveland Clinic Taussig Cancer Institute, Cleveland, Ohio; [10]Department of Urology, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan; [11]Department of Medical Oncology, National Cancer Centre Singapore, Singapore, Singapore; [12]Division of Medical Oncology, QEII Health Sciences Centre, Halifax, Nova Scotia Canada; [13]Division of Medical Oncology, University of Ottawa, Ottawa, Ontario Canada; [14]Division of Urology, Juravinski Cancer Centre, McMaster University, Hamilton, Ontario Canada; [15]Department of Medicine, Auckland City Hospital, Auckland, New Zealand; [16]Department of Medical Oncology, Dana-Farber Cancer Center, Boston, Massachusetts

The last 2 authors are senior authors and contributed equally to this article.

DOI: 10.1002/cncr.31595, **Received:** January 19, 2018; **Revised:** May 2, 2018; **Accepted:** May 7, 2018; **Published online:** October 11, 2018 in Wiley Online Library (wileyonlinelibrary.com)

clear cell mRCC treatment setting in the CheckMate 214 trial.[5] In patients with intermediate-risk or poor-risk disease according to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC), the median OS in the combination IO arm was not reached (NR) versus 26.0 months in the sunitinib arm (HR, 0.63; $P<.001$).[5] In this same risk group, the overall response rate (ORR) was reported to be 41.6% in the combination IO arm, in contrast to 26.5% in the sunitinib arm ($P<.0001$).[5,6]

In patients with PD-L1-positive mRCC who are treated in the first-line setting, the IMmotion 150 phase 2 trial reported an HR of 0.64 ($P=.095$) for a progression-free survival benefit in favor of atezolizumab (a PD-L1 inhibitor) plus bevacizumab (a VEGF inhibitor) compared with sunitinib.[7] In the phase 3 IMmotion 151 trial, a progression-free survival benefit also was reported in favor of patients with PD-L1-positive mRCC who were treated with atezolizumab and bevacizumab, in contrast with patients receiving sunitinib (HR, 0.74; $P=.02$).[8] Patients with PD-L1-positive disease were reported to achieve an ORR of 43% with the combination of atezolizumab and bevacizumab versus 35% with sunitinib.[8] However, there was a discordance in the results between independent and central review.[8]

To the best of our knowledge, outcomes and prognostic tools have yet to be clearly defined in patients with mRCC who are treated with IO checkpoint inhibitors. In this patient population, benchmarks for duration of treatment (DOT) and OS are required for clinical trial design and patient counseling. The objective of the current retrospective analysis was to establish IO efficacy benchmarks and update patient outcomes (OS) in each IMDC prognostic class for patients with mRCC who received IO treatment.[6]

MATERIALS AND METHODS

Design, Setting, and Participants

A retrospective data analysis was performed using the IMDC database, using data gathered regarding 9136 patients. A total of 38 international cancer centers in Canada, the United States, Denmark, Greece, South Korea, Australia, New Zealand, Japan, Singapore, Belgium, and Italy provided consecutive patient data collected from hospital and pharmacy records using uniform database software and templates. Data were collected between 2005 and April 1, 2018. Institutional review board approval was obtained from each participating center.

All patients with clear cell and non-clear cell mRCC who were treated with IO checkpoint inhibitors were included. Patients may have received IO therapy as first-line, second-line, third-line, or fourth-line treatment. Patients treated with single-agent nivolumab in the second-line, third-line, and fourth-line setting were included to reduce the heterogeneity of patients (see Table 1). Patients treated with nivolumab plus ipilimumab, single-agent PD-1, or PD-L1 inhibitors and combination VEGF inhibitor plus PD-L1 inhibitor therapy were included. To respect the confidentiality of clinical trials not yet reported, patient outcomes of nonapproved combinations were reported in aggregate by class of therapy.

Tumor histology was recorded using pathology reports generated by pathologists as part of routine patient diagnosis, before and independent of the current study.

Outcome Measurements

The IMDC collects demographic data, baseline patient characteristics, and outcome data. ORRs (investigator assessed), DOT, and OS were calculated. The ORR was examined in evaluable patients. DOT was defined as the time from the initiation of targeted therapy to treatment discontinuation for any reason. OS was calculated from the time of the initiation of IO therapy to the time of death from any cause or censored at the time of last follow-up.

An additional endpoint of the current study was the evaluation of the IMDC prognostic model's categorization of patients with mRCC who were treated in the second-line, third-line, and fourth-line settings with IO agents into IMDC risk groups using the following prognostic factors: hemoglobin < the lower limit of normal, corrected calcium >the upper limit of normal (ULN), neutrophil count > the ULN, platelet count >the ULN, Karnofsky performance status <80%, and time from diagnosis to treatment of <1 year.[6] The IMDC criteria are collected at the beginning of each line of therapy, except for time from diagnosis to treatment, which always is captured at the time of initiation of first-line therapy. Patients were stratified into IMDC prognostic risk groups as determined by the presence of 0 (favorable risk), 1 or 2 (intermediate risk), or ≥ 3 (poor risk) of these prognostic factors.

Statistical Analysis

The estimated median DOT and OS were calculated using the method of Kaplan and Meier. Patients stratified by IMDC criteria into the second-line, third-line, and fourth-line settings were compared for OS because

TABLE 1. IO Checkpoint Inhibitors, Line of Therapy, and Baseline Characteristics at Time of Diagnosis of mRCC

	First-Line IO[a]			Second-Line IO	Third-Line IO	Fourth-Line IO
Characteristics	Ipilimumab+Nivolumab N=49	PD-L1+VEGF N=72	PD-L1 N=51	Nivolumab N=294	Nivolumab N=150	Nivolumab N=71
Male sex	38/49 (78%)	46/72 (64%)	34/51 (67%)	226/294 (77%)	107/150 (71%)	55/71 (77%)
Median age, y	60	61	63	64	64	64
Age > 70 y	8/49 (16%)	8/72 (11%)	10/51 (20%)	88/294 (30%)	35/150 (23%)	19/71 (27%)
Prior nephrectomy	43/48 (90%)	62/70 (89%)	48/51 (94%)	253/289 (88%)	134/147 (91%)	66/71 (93%)
Non-clear cell	5/47 (11%)	7/71 (10%)	10/33 (30%)	23/274 (8%)	15/141 (11%)	5/67 (7%)
Brain metastases	1/43 (2%)	3/56 (5%)	2/32 (6%)	13/213 (6%)	9/117 (8%)	1/62 (2%)
>1 site of metastasis	36/43 (84%)	47/60 (78%)	36/41 (88%)	207/265 (78%)	107/138 (78%)	46/65 (71%)
KPS < 80%	2/46 (4%)	2/57 (4%)	1/45 (2%)	25/252 (10%)	24/121 (20%)	3/54 (6%)
Time from diagnosis to treatment <1 y	22/49 (45%)	41/72 (57%)	20/51 (39%)	144/294 (49%)	77/149 (52%)	28/71 (39%)
Hypercalcemia	8/35 (23%)	5/41 (12%)	6/42 (14%)	19/234 (8%)	8/110 (7%)	5/54 (9%)
Anemia	19/44 (43%)	20/64 (31%)	15/46 (33%)	122/266 (46%)	44/121 (36%)	18/59 (31%)
Neutrophilia	6/44 (14%)	7/64 (11%)	1/46 (2%)	23/263 (9%)	9/119 (8%)	7/55 (13%)
Thrombocytosis	8/44 (18%)	9/61 (15%)	5/46 (11%)	29/265 (11%)	13/121 (11%)	5/59 (8%)
IMDC criteria at IO initiation						
Favorable	8/35 (23%)	13/35 (37%)	17/40 (43%)	30/216 (14%)	13/104 (12%)	6/53 (11%)
Intermediate	20/35 (57%)	15/35 (43%)	18/40 (45%)	141/216(65%)	64/104 (62%)	33/53 (62%)
Poor	7/35 (20%)	7/35 (20%)	5/40 (12%)	45/216 (21%)	27/104 (26%)	14/53 (27%)

Abbreviations: IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IO, immuno-oncology; KPS, Karnofsky performance status; mRCC, metastatic renal cell carcinoma; PD-L1, programmed death-ligand 1; VEGF, vascular endothelial growth factor.

[a]First-line IO therapies other than ipilimumab and nivolumab in combination currently are not approved and thus were combined into the categories of PD-L1 inhibitors and PD-L1 inhibitors plus VEGF inhibitors.

there was sufficient power with which to perform such an analysis. Strata were compared by log-rank testing. Although sample sizes were limited in the first-line and fourth-line settings, the DOT, OS, and ORR were examined in the first line through fourth line because to the best of our knowledge benchmarks in outcomes have yet to be established in these IO treatment settings. A univariable analysis was performed in the first line to fourth line of therapy, examining clear cell versus non-clear cell histological subtypes in relation to OS. In the first-line treatment setting, a multivariable analysis was performed to examine the impact of combination therapy (PD-L1 inhibitor plus VEGF inhibitor and nivolumab plus ipilimumab) versus single-agent PD-L1 inhibition alone, adjusted for IMDC risk group.

The best overall response was documented as complete response (CR), partial response, stable disease, or progressive disease based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 guidelines when available.[9] The ORR included the percentage of patients with CR and partial response as their best response.

The case deletion method was used when missing data were encountered. SAS statistical software (version 9.4; SAS Institute Inc, Cary, North Carolina) was used to perform statistical analyses.

RESULTS

A total of 687 patients with mRCC who were treated with IO were included. Of the 633 patients who had histological subtyping available, 90% of patients (568 patients) had clear cell and 10% (65 patients) had non-clear cell mRCC. Baseline characteristics and risk factors are outlined and were similar to those of the general mRCC patient population encountered in clinical practice (Table 1). The line of therapy and respective checkpoint inhibitors and combination therapies are detailed in Table 1. First-line therapies and histological subtypes were heterogenous. In the first-line treatment setting, 28% (49 of 172 patients), 42% (72 of 172 patients), and 30% (51 of 172 patients) of patients, respectively, were treated with nivolumab plus ipilimumab, PD-L1 inhibitor plus VEGF inhibitor, and a single-agent PD-L1 inhibitor.

TABLE 2. IO Treatment Outcomes

	First-Line IO			Second-Line IO	Third-Line IO	Fourth-Line IO
	Ipilimumab+Nivolumab N=49	PD-L1+VEGF N=72	PD-L1 N=51	Nivolumab N=294	Nivolumab N=150	Nivolumab N=71
Best response						
Overall	14/45 (31%)	20/51 (39%)	12/30 (40%)	41/187 (22%)	22/90 (24%)	15/58 (26%)
CR	1/45 (2%)	2/51 (4%)	2/30 (7%)	4/187 (2%)	1/90 (1%)	2/58 (3%)
PR	13/45 (29%)	18/51 (35%)	10/30 (33%)	37/187 (20%)	21/90 (23%)	13/58 (22%)
SD	23/45 (51%)	30/51 (59%)	13/30 (43%)	60/187 (32%)	34/90 (38%)	25/58 (43%)
PD	13/45 (29%)	1/51 (2%)	5/30 (17%)	86/187 (46%)	34/90 (38%)	18/58 (31%)
Duration of treatment (95% CI), mo	8.3 (3.7-15.1)	14.7 (8.4-16.1)	8.3 (5.5-11.8)	5.7 (4.6-8.0)	6.2 (3.9-8.5)	8.3 (5.5-NR)
Median follow-up, mo	22.1	11.2	8.3	9.9	11.8	9.5
HR of OS for non-clear cell vs any clear cell (95% CI)	7.64 (3.15-18.50) P<.0001			0.87 (0.38-2.01) P=.74	1.85 (0.77-4.41) P=.17	1.15 (0.15-8.69) P=.89

Abbreviations: 95% CI, 95% confidence interval; CR, complete response; HR, hazard ratio; IO, immuno-oncology; OS, overall survival; PD, progressive disease; PD-L1, programmed death-ligand 1; PR, partial response; SD, stable disease; VEGF, vascular endothelial growth factor; NR, not reached.

In patients who were evaluable (461 patients), the ORR to IO therapy was 27% (124 patients) (Table 2). Patients responded across each line of therapy. In the first-line setting, the ORR in patients treated with nivolumab and ipilimumab, PD-L1 inhibitor plus VEGF inhibitor, and a single-agent PD-L1 inhibitor was 31% (14 of 45 patients), 39% (20 of 51 patients), and 40% (12 of 30 patients), respectively. The measured ORR was 22% (41 of 187 patients) in the second-line, 24% (22 of 90 patients) in the third-line, and 26% (15 of 58 patients) in the fourth-line treatment settings. CR was demonstrated in 3% (12 of 461 patients) of the sample. The CR rate in the first-line treatment setting was 4%, in which CR was identified in 1 of 45 patients, 2 of 51 patients, and 2 of 30 patients, respectively, who were treated with nivolumab and ipilimumab, PD-L1 inhibitor plus VEGF inhibitor, and a single-agent PD-L1 inhibitor. The measured CR rates were 2% (4 of 187 patients) in the second-line, 1% (1 of 90 patients) in the third-line, and 3% (2 of 58 patients) in the fourth-line nivolumab treatment settings.

The DOT in the first-line treatment setting with nivolumab plus ipilimumab, PD-L1 inhibitor plus VEGF inhibitor, and a single-agent PD-L1 inhibitor was 8.3 months (95% confidence interval [95% CI], 3.7-5.1 months), 14.7 months (95% CI, 8.4-16.1 months), and 8.3 months (95% CI, 5.5-11.8 months), respectively (Table 2). The DOT was 5.7 months (95% CI, 4.6-8.0 months) in the second-line, 6.2 months (95% CI, 3.9-8.5 months) in the third-line, and 8.3 months (95% CI, 5.5 to NR) in the fourth-line treatment settings.

With regard to OS, patients treated with second-line, third-line, and fourth-line IO therapy were appropriately categorized into favorable-risk, intermediate-risk, and poor-risk prognosis groups using the IMDC model (Table 2). In the second-line setting, the median OS was not reached (95% CI, NR-NR) in the favorable-risk group, 26.7 months (95% CI, 20.6-48.5 months) in the intermediate-risk group, and 7.4 months (95% CI, 4.8-16.7 months) in the poor-risk group ($P < .0001$) (Fig. 1). The IMDC model appropriately divided patients according to their respective risk groups in the third-line setting, with median OS times of 36.1 months (95% CI, 23.6 months-NR) in the favorable-risk group, 28.2 months (95% CI, 12.0 months-NR) in the intermediate-risk group, and 11.1 months (95% CI, 4.5-39.1 months) in the poor-risk group ($P = .016$) (Fig. 2). In the fourth-line setting, patients were appropriately stratified into favorable-risk, intermediate-risk, and poor-risk groups using the IMDC model; the corresponding median OS times were not reached (95% CI, NR-NR), not reached (95% CI, 11.7 months-NR), and 6.7 months (95% CI, 1.1 months-NR), respectively ($P = .047$) (Fig. 3). When combining all patients in the first-line treatment setting, the median OS was NR in all favorable-risk, intermediate-risk, and poor-risk groups using the IMDC model ($P = .163$) (Fig. 4). The data currently are immature in the first-line setting and will be updated in the future.

In recognition of the heterogeneity of patients with clear cell and non-clear cell histological subtypes,

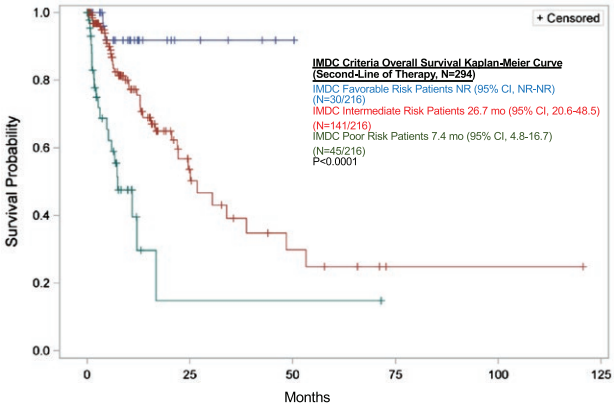

Figure 1. International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria for overall survival (OS): Kaplan-Meier curve for second line of therapy. 95% CI indicates 95% confidence interval; NR, not reached.

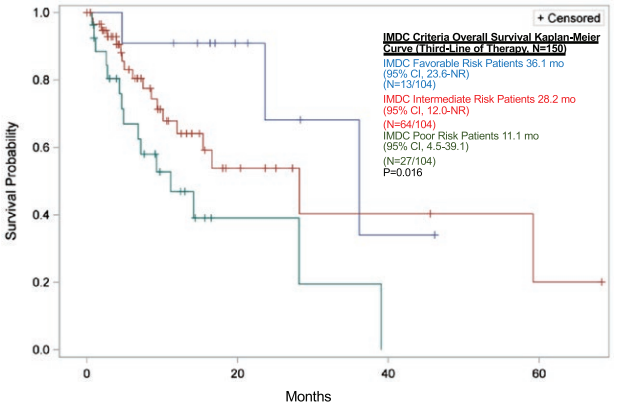

Figure 2. International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria for overall survival (OS): Kaplan-Meier curve for third line of therapy. 95% CI indicates 95% confidence interval; NR, not reached.

a univariable analysis was performed in the first-line through fourth-line treatment settings, examining clear cell versus non-clear cell histological subtypes in relation to OS (Table 2). The first-line results indicated a statistically significant HR of 7.64 (95% CI, 3.15-18.50; $P < .0001$) for death, favoring clear cell over non-clear cell histological subtypes. Although the second-line HR of 0.87 (95% CI, 0.38-2.01; $P = .74$), third-line HR of 1.85 (95% CI, 0.77-4.41; $P = .17$), and fourth-line HR of 1.15 (95% CI, 0.15-8.69; $P = .89$) for death were not statistically significant, it appears that there is an overall general trend favoring clear cell RCC compared with non-clear cell histological subtypes.

A multivariable analysis was performed to examine the impact of combination therapy (PD-L1 inhibitor plus VEGF inhibitor and nivolumab plus ipilimumab) versus single-agent PD-L1 inhibition alone, adjusted for IMDC risk group. The HR for death for nivolumab plus ipilimumab versus a single-agent PD-L1 inhibitor was 1.11 (95% CI, 0.32-3.93; $P = .87$). The HR for death for the PD-L1 inhibitor and VEGF inhibitor combination was 0.98 (95% CI, 0.24-3.93; $P = .97$) compared with a single-agent PD-L1 inhibitor. These results demonstrated no statistically significant difference between combination IO therapies and a single-agent PD-L1 with regard to risk of death.

DISCUSSION

The current large retrospective series of patients with mRCC who were treated with checkpoint inhibitors enhances our

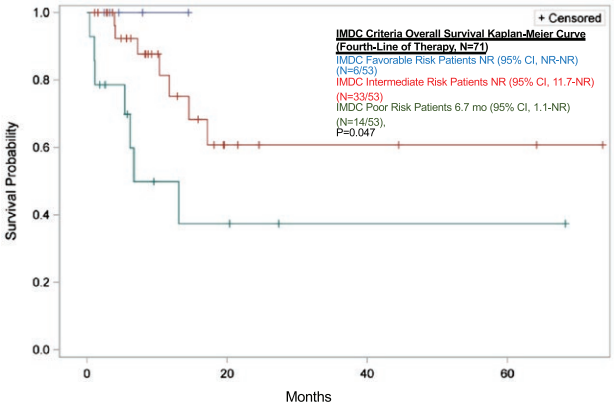

Figure 3. International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria for overall survival (OS): Kaplan-Meier curve for fourth line of therapy. 95% CI indicates 95% confidence interval; NR, not reached.

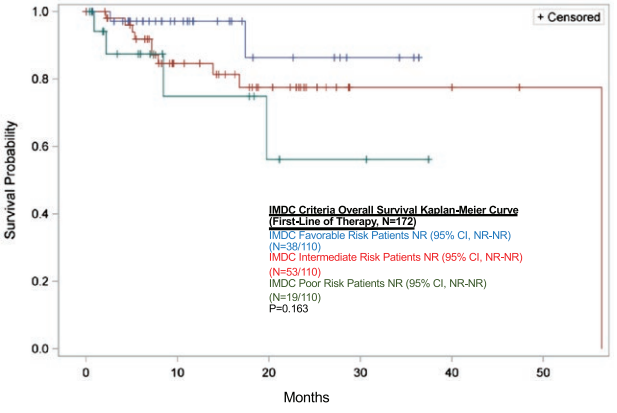

Figure 4. International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria for overall survival (OS): Kaplan-Meier curve for first line of therapy. 95% CI indicates 95% confidence interval; NR, not reached.

understanding of IO outcomes and prognosis in patients with mRCC. The IMDC prognostic criteria appropriately stratified patients into poor-risk, intermediate-risk, and favorable-risk groups in the second-line, third-line, and fourth-line settings, according to OS.

The results of the current study demonstrate that the ORR to IO does not deteriorate when checkpoint inhibitors are used from the first-line to fourth-line treatment settings. The measured second-line and third-line ORRs were similar to the reported CheckMate 025 ORR of 25% for single-agent nivolumab.[4] Although this series' ORR result of 31% for first-line nivolumab and ipilimumab was less than that of the CheckMate 214 trial (ORR of 42%), this latter ORR was reported specifically for IMDC intermediate-risk and poor-risk patients.[5] Given that the CheckMate 214 exploratory analysis identified an ORR of 29% for IMDC favorable-risk patients, it appears that the current study result is likely representative of an expected ORR for first-line nivolumab and ipilimumab combination therapy across IMDC risk groups.[5]

The DOT of the patient sample in the current study was similar to the reported DOT of 5.5 months with nivolumab in the CheckMate 025 trial.[4] However, the DOTs for the third-line and fourth-line settings appear to be somewhat longer at 6.2 months and 8.3 months, respectively. This observed longer DOT may be influenced by clinicians' consideration of treatment beyond disease progression; however, pseudoprogression is reported to occur in only 6% to 12% of cases.[10–13] Alternatively, it could be due to the lack of availability of further lines of therapy in some jurisdictions, less radiological imaging, or fewer rigorous treatment algorithm stopping rules in the general population compared with a clinical trial.

It appears that there generally is a trend favoring clear cell over non-clear cell histological subtypes for death in patients treated with IO. Although the first-line treatment results indicated a statistically significant HR for death, the HRs for death in the second-line to fourth-line treatment settings were not found to be statistically significant. Although patients with clear cell mRCC may potentially derive a greater survival benefit, in our opinion these results do not provide substantial support for the use of histological subtype (clear cell vs non-clear cell) as a predictive factor for IO outcomes in patients with mRCC.

A limitation of these data could be selection bias; however, consecutive patient series were used to reduce this. Although it was possible to include only those patients treated with single-agent nivolumab in the second-line, third-line, and fourth-line settings to reduce the heterogeneity of the patient sample, this was not possible in the first-line treatment setting. To capture a large enough sample, patients treated in the first-line setting may have received combination therapy, which contributed to the heterogeneity of this patient sample. However, there was no statistically significant difference noted in the current study results between combination IO therapies and a single-agent PD-L1 for death for the first-line setting. Furthermore, the follow-up time was relatively short for some lines of therapy. IMDC risk factors and outcomes data were limited as a result of some unavailable results and some patients' lack of evaluable disease. These unevaluable patients did not have radiographically measurable metastatic lesions. Although the majority of clinical trials require measurable disease to objectively measure responses, we included these unevaluable patients to ensure that our treatment outcome benchmarks described were applicable to patients regardless of measurable disease.

At the time of last follow-up, no data were available regarding patients treated beyond disease progression, but this currently is being investigated. Future efforts will be required to examine PD-L1 status and its association with outcomes in patients treated with IO. This is particularly relevant given the recent CheckMate 214 trial results, which demonstrated mixed evidence regarding the predictive use of PD-L1 expression ≥ 1% for treatment response.[5]

CONCLUSIONS

Checkpoint inhibitors have shown evidence of high activity in patients with mRCC. We believe the results of the current study have established efficacy benchmarks regarding ORR and DOT that can be used for clinical trial design and patient counseling. ORRs continue to be substantial, even when IO agents are used later in the third-line and fourth-line settings. The IMDC prognostic criteria can be applied in the IO treatment setting of mRCC because they appropriately stratify patients into favorable-risk, intermediate-risk, and poor-risk groups in the second-line, third-line, and fourth-line settings for OS.

FUNDING SUPPORT

No specific funding was disclosed.

CONFLICT OF INTEREST DISCLOSURES

Sandy Srinivas has acted in a consulting or advisory role for Genentech/Roche, Pfizer, Medivation, and Novartis; as a member of the Speakers' Bureau for Genentech; and received research funding from Bristol-Myers Squibb and Pfizer for work performed outside of the current study. Camillo Porta has acted in a consulting or

advisory role for Pfizer, Bristol-Myers Squibb, Ipsen, Eisai, Peloton Therapeutics, and Novartis Pharma KK; as a member of the Speakers' Bureau for Pfizer, Bristol-Myers Squibb, and Novartis Pharma KK; and received grants from Pfizer for work performed outside of the current study. Brian I. Rini has acted in a consulting or advisory role for Pfizer; received travel and accommodations expenses from Pfizer; and received research funding from Pfizer, Roche/Genentech, and Bristol-Myers Squibb for work performed as part of the current study. Naveen S. Basappa has acted in a consulting or advisory role for Pfizer, Novartis, Bristol-Myers Squibb, Janssen, Astellas Pharma, AstraZeneca, and Boehringer Ingelheim; received travel and accommodations expenses from Novartis, Janssen, and Astellas Pharma; and received honoraria from Pfizer, Novartis, Janssen, and Astellas Pharma for work performed outside of the current study. Ravindran Kanesvaran has acted in a consulting or advisory role for Pfizer, Astellas Pharma, Novartis, and Mundipharma; received travel and accommodations expenses from Astellas Pharma; received honoraria from Astellas Pharma, Novartis, and Janssen; and received research funding from Sanofi and Janssen for work performed outside of the current study. Lori A. Wood has received research funding from GlaxoSmithKline, Bristol-Myers Squibb, Pfizer, Roche Canada, Exelixis, Merck, and AstraZeneca for work performed outside of the current study. Christina M. Canil has received honoraria from Bayer, Astellas Medivation, and Janssen; acted in a consulting or advisory role for Sanofi, BMS Brazil, Pfizer, Bayer, AstraZeneca, and Roche-Peru; acted as a member of the Speakers' Bureau for Sanofi, Hoffman La Roche, Astellas, AstraZeneca, and Janssen; and received patents, royalties, or other intellectual property from Pfizer for work performed outside of the current study. Toni K. Choueiri has acted in a consulting or advisory role for Pfizer, Bayer, Novartis, GlaxoSmithKline, Merck, Bristol-Myers Squibb, Roche/Genentech, Eisai, Foundation Medicine, Cerulean Pharma, AstraZeneca, Peloton Therapeutics, Exelixis, Prometheus Laboratories, and Alligent; received travel and accommodations expenses, acted on advisory boards/consultancy, or received honoraria from the National Comprehensive Cancer Network and UpToDate; and received research funding from Pfizer, Novartis, Merck, Exelixis, TRACON Pharma, GlaxoSmithKline, Bristol-Myers Squibb, AstraZeneca, Peloton Therapeutics, Roche/Genentech, Celldex, and Agensys for work performed outside of the current study. Daniel Yick Chin Heng has acted in a consulting or advisory role for Pfizer, Novartis, Bristol-Myers Squibb, Janssen, and Astellas Pharma for work performed outside of the current study.

AUTHOR CONTRIBUTIONS

Steven M. Yip: Conceptualization, methodology, formal analysis, writing-original draft, and writing-review and editing. **Connor Wells**: Conceptualization, methodology, formal analysis, and writing-review and editing. **Raphael Moreira**: Methodology, formal analysis, and writing-review and editing. **Alex Wong**: Methodology, formal analysis, and writing-review and editing. **Sandy Srinivas**: Methodology, formal analysis, and writing-review and editing. **Benoit Beuselinck**: Methodology, formal analysis, and writing-review and editing. **Camillo Porta**: Methodology, formal analysis, and writing-review and editing. **Hao-Wen Sim**: Methodology, formal analysis, and writing-review and editing. **D. Scott Ernst**: Methodology, formal analysis, and writing-review and editing. **Brian I. Rini**: Methodology, formal analysis, and writing-review and editing. **Takeshi Yuasa**: Methodology, formal analysis, and writing-review and editing. **Naveen S. Basappa**: Methodology, formal analysis, and writing-review and editing. **Ravindran Kanesvaran**: Methodology, formal analysis, and writing-review and editing. **Lori A. Wood**: Methodology, formal analysis, and writing-review and editing. **Christina Canil**: Methodology, formal analysis, and writing-review and editing. **Anil Kapoor**: Methodology, formal analysis, and writing-review and editing. **Simon Y.F. Fu**: Methodology, formal analysis, and writing-review and editing. **Toni K. Choueiri**: Conceptualization, methodology, formal analysis, writing-original draft, and writing-review and editing. **Daniel Y.C. Heng**: Conceptualization, methodology, formal analysis, writing-original draft, and writing-review and editing.

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2015;136:E359-E386.
2. Kroeger N, Choueiri TK, Lee JL, et al. Survival outcome and treatment response of patients with late relapse from renal cell carcinoma in the era of targeted therapy. *Eur Urol*. 2014;65:1086-1092.
3. Thompson RH, Kuntz SM, Leibovich BC, et al. Tumor B7-H1 is associated with poor prognosis in renal cell carcinoma patients with long-term follow-up. *Cancer Res*. 2006;66:3381-3385.
4. Motzer RJ, Escudier B, McDermott DF, et al; CheckMate 025 Investigators. Nivolumab versus everolimus in advanced renal-cell carcinoma. *N Engl J Med*. 2015;373:1803-1813.
5. Motzer RJ, Tannir NM, McDermott DF, et al; CheckMate 214 Investigators. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *N Engl J Med*. 2018;378:1277-1290.
6. Heng DY, Xie W, Regan MM, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. *JClin Oncol*. 2009;27:5794-5799.
7. McDermott DF, Atkins MB, Motzer RJ, et al. A phase II study of atezolizumab (atezo) with or without bevacizumab (bev) versus sunitinib (sun) in untreated metastatic renal cell carcinoma (mRCC) patients (pts). *JClin Oncol*. 2017;35(6 suppl):431.
8. Motzer RJ, Powles T, Atkins MB, et al. IMmotion151: a randomized phase III study of atezolizumab plus bevacizumab vs sunitinib in untreated metastatic renal cell carcinoma (mRCC). *JClin Oncol.* 2018;36(6 suppl):578.
9. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45:228-247.
10. Chiou VL, Burotto M. Pseudoprogression and immune-related response in solid tumors. *JClin Oncol*. 2015;33:3541-3543.
11. Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. *Clin Cancer Res*. 2009;15:7412-7420.
12. Hodi FS, Sznol M, Kluger HM, et al. Long term survival of ipilimumab-naive patients (pts) with advanced melanoma (MEL) treated with nivolumab (anti-PD-1, BMS-936558, ONO-4538) in a phase I trial. *JClin Oncol*. 2014;32(15 suppl):9002.
13. Hodi FS, Ribas A, Daud A, et al. Evaluation of immune-related response criteria (irRC) in patients (pts) with advanced melanoma (MEL) treated with the anti-PD-1 monoclonal antibody MK-3475. *JClin Oncol.* 2014;32(15 suppl):3006.