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Treatment-free survival outcomes from the phase II study of nivolumab and salvage nivolumab/ipilimumab in advanced clear cell renal cell carcinoma (HCRN GU16-260-Cohort A)

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ABSTRACT

Background As part of a partitioned survival analysis, treatment-free survival (TFS) can characterize the overall survival time patients spend between the cessation of immunotherapy and the start of subsequent therapy; both with and without toxicity. Significant TFS was reported for the nivolumab/ipilimumab arms of the CheckMate 067 and 214 trials for patients with advanced melanoma or renal cell carcinoma (aRCC), respectively, where immunotherapy was often halted for toxicity rather than a predefined treatment endpoint. We therefore sought to assess TFS in the HCRN GU16-260 trial, which was designed to reduce toxicity and cap immunotherapy duration.

Methods Data were analyzed from 128 patients with clear-cell aRCC treated with first-line nivolumab monotherapy for up to 2 years. Salvage nivolumab/ipilimumab for up to 1 year was provided to eligible patients with disease progression at any point or stable disease at 48 weeks (29% of patients). TFS was defined as the area between Kaplan-Meier curves for a time from registration to protocol therapy cessation and for a time from registration to subsequent systemic therapy initiation or death, estimated from 36-month mean times. The time on or off protocol treatment with grade 3+treatment-related adverse events (TRAEs) was also captured.

Results At 36 months from enrollment, 68.3% of patients were alive: 96.8% of International Metastatic RCC Database Consortium (IMDC) favorable-risk patients and 56.6% of those with intermediate/poor-risk, respectively. The 36-month mean time on protocol therapy was 11.5 months including 0.6 months with grade 3+TRAEs (16.0 months for favorable-risk patients and 9.6 months for intermediated/poor-risk patients). The 36-month mean TFS for the whole population was 9.4 months (12.9 months including 1.5 months with grade 3+TRAEs for favorable-risk and 8.0 months including 1.0 months with grade 3+TRAEs for intermediate/poor-risk). At 36 months, 65.6% of favorable-risk patients and 27.1% of intermediate/poor-risk patients were alive and subsequent systemic treatment-free.

Conclusions Nivolumab monotherapy with salvage nivolumab/ipilimumab in non-responders is an active treatment approach in treatment-naïve patients with aRCC and, similar to nivolumab/ipilimumab in CheckMate 214, results in substantial TFS and toxicity-free TFS. TFS was

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Significant treatment-free survival (TFS) has been reported for the nivolumab/ipilimumab arms of the CheckMate 067 and CheckMate 214 trials for patients with advanced melanoma or renal cell carcinoma (aRCC), respectively, where immunotherapy was halted mostly for toxicity or disease progression. TFS and toxicity-free TFS have not been previously examined in a study where treatment was also halted at a predefined time point.

WHAT THIS STUDY ADDS

⇒ Nivolumab monotherapy with salvage nivolumab/ipilimumab in non-responders is an active treatment approach in treatment-naïve patients with aRCC and, similar to nivolumab/ipilimumab in CheckMate 214, results in substantial TFS and toxicity-free TFS. TFS was greatest in patients with International Metastatic RCC Database Consortium (IMDC) favorable-risk disease.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study suggests that in patients with clear cell aRCC treated with a pure immunotherapy regimen, either nivolumab monotherapy only or with salvage combination nivolumab/ipilimumab, that prolonged TFS and toxicity-free TFS is possible, and is likely enhanced with a regimen that halts treatment in patients without disease progression at 2 years. The extensive TFS benefit in patients with IMDC favorable-risk disease supports the use of an immunotherapy-only regimen as initial systemic therapy in this population.

greatest in patients with favorable-risk disease, supporting the use of an immunotherapy-only regimen in this population.

INTRODUCTION

Treatment of cancer with immunotherapy can be associated with prolonged disease control after treatment discontinuation without the need for further anticancer therapy. Toxicity from therapy can also persist after treatment cessation. Treatment-free survival (TFS) with and without toxicity can characterize a portion of the overall survival time in which patients are free of treatment with or without residual toxicity. Significant TFS occurred in all arms of CheckMate 067 trial in patients with metastatic melanoma, with a combination of nivolumab/ipilimumab exhibiting the most TFS.[1] In particular, the 5-year restricted mean percentage of time spent in TFS was 33% for the patients treated with nivolumab/ipilimumab, which was nearly double that seen with nivolumab monotherapy. TFS was also examined in the CheckMate 214 trial, in which patients with metastatic clear cell renal cell cancer (RCC) were randomly assigned to receive either sunitinib or combination nivolumab/ipilimumab; the largest TFS again occurred in patients treated with nivolumab/ipilimumab.[2] In this study, TFS was prolonged with nivolumab/ipilimumab relative to sunitinib in patients with International Metastatic RCC Database Consortium (IMDC) favorable-risk disease even though this regimen is not Food and Drug Administration (FDA)-approved for this population. Although nivolumab/ipilimumab is associated with a higher rate of grade 3–4 treatment-related adverse events (TRAEs), the mean time spent either on treatment or in TFS with grade 3–4 toxicity on the nivolumab/ipilimumab arm of CheckMate 214 represented an average of less than 3% (<2 months) of the total 42-month survival period.[2] In both of these studies, treatment was halted for toxicity, disease progression or patient preference, and there was no predefined treatment endpoint, confounding the analysis of TFS as, conceivably, some patients with the controlled disease may have stayed on maintenance immunotherapy that was no longer contributing to their observed freedom from disease progression. Therefore, we assessed partitioned overall survival and TFS including time with TRAEs, either on therapy or while in TFS, in the HCRN GU16–260 trial, which was designed to reduce the toxicity of combination immunotherapy by starting with nivolumab monotherapy and to cap immunotherapy duration at a maximum of 2 years.[3]

METHODS

Patients

All patients in this analysis were enrolled in the HCRN GU 16–260 trial. This study tested nivolumab monotherapy in patients with treatment-naïve advanced RCC at 12 US institutions. The results of the clinical trial have been previously reported.[3 4] As the study remained open to accrual for another year following the published report to obtain additional tissue specimens for biomarker studies. Five more patients were included in this analysis. The study was approved by the Institutional Review Boards at all institutions. All patients signed an informed consent form for participation which included mention of this correlative endpoint analysis.

Protocol treatment regimen

The treatment schema is shown in figure 1. All patients initiated treatment with nivolumab monotherapy (Part A). Those with an objective response (partial or complete) received a maximum of 96 weeks of nivolumab treatment. Those with progressive disease or stable disease at 48 weeks could receive a combination nivolumab/ipilimumab boost every 3 weeks for up to four doses (12 weeks), followed by nivolumab monotherapy for a maximum of 48 additional weeks (Part B). Protocol therapy was stopped for toxicity, progressive disease, or treatment regimen completion. For purposes of this TFS analysis, treatment with Part A followed by Part B therapy was considered one regimen. That is, for patients that went on to Part B, the date of the last Part B treatment was chosen as the

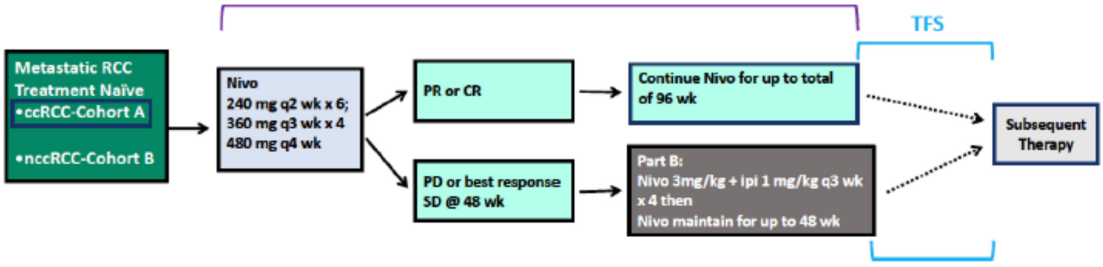

Figure 1 Schema for TFS analysis. This figure displays the study design for the treatment-free survival (TFS) component of the HCRN GU16-260 trial. This analysis was restricted to the 128 patients enrolled in Cohort A-clear cell RCC. For purposes of this analysis, starting with Part A (nivolumab monotherapy) and going on to Part B (nivolumab+ipilimumab boost) at either the time of progressive disease or if biopsy confirmed radiographic stable disease at 48 weeks was considered one regimen. In this analysis, TFS (blue brackets) begins when treatment stops for either a treatment-related adverse event (TRAE), progressive disease or treatment completion (Part A: up to 96 weeks, Part A to Part B: usually up to 108 weeks) and ends with the start of subsequent systemic therapy or death. ccRCC, clear cell renal cell carcinoma; CR, complete response; nccRCC, non-clear cell renal cell carcinoma; PD, progressive disease; PR partial response; RCC, renal cell carcinoma; stable disease.

date of the last study treatment. Accordingly, the best treatment response in Part A and B is reported as the overall best treatment response; however, the first disease progression, which typically occurred in Part A, is used for reporting progression-free survival (PFS).

This analysis was limited to Cohort A of the study which consisted of 128 patients with treatment-naïve metastatic clear cell renal cancer. Patients were followed with tumor imaging every 12 weeks until disease progression in each Part of the study. Survival follow-up included a collection of data about subsequent therapies and resolution or the occurrence of new TRAEs following protocol therapy cessation.

Statistical analysis, endpoints, and survival states definitions

Time to protocol therapy cessation was defined as the time from the start of treatment to discontinuation of treatment; patients still on therapy were censored at the date of the last treatment. Time to subsequent therapy initiation or death was defined as the time from the start of treatment to the earlier of subsequent anticancer therapy initiation or death; patients who were alive and yet to initiate subsequent anticancer therapy were censored at the date last known alive. Overall survival was defined as the time from the start of treatment to death; patients who were alive were censored at the date last known alive. The distribution of these three time-to-event endpoints was estimated using Kaplan-Meier methodology, and 36-month milestone survival probabilities and restricted mean survival times (ie, area under the Kaplan-Meier curve) were obtained. 36 months was chosen to reflect the quality of follow-up data at the current data cut-off.

TFS is defined as the area between the Kaplan-Meier curves for time to protocol therapy cessation and time to subsequent systemic treatment initiation or death, and estimated as the difference in respective restricted mean times. Time on protocol therapy and TFS were further characterized as time with and without grade 3+TRAEs. based on the sum of the number of unique days with one or more TRAEs.

Overall survival was partitioned to estimate 36-month mean times in health states of time on protocol therapy (with or without grade 3+TRAEs), TFS (with or without grade 3+TRAEs), and survival after subsequent therapy. The bootstrap resampling method (with 1,000 resamples) was used to obtain 95% CI of restricted mean time estimates.

RESULTS

128 patients were enrolled and initiated nivolumab monotherapy in this study (table 1) with a median (Q1, Q3) follow-up of 37.7 months (32.5, 46.1). 37 (29%) of these 128 patients went on to receive the nivolumab/ipilimumab boost in Part B.

Updated efficacy results by IMDC category are shown in table 2. The overall (Part A and B) objective response rate was 35.9% (95% CI 27.7% to 44.9%) with 57.9% (95% CI 40.8% to 73.7%) of favorable-risk and 26.7% (95% CI 17.9% to 37.0%) of intermediate/poor-risk patients exhibiting at partial or complete response. Three-year Kaplan-Meier estimates of endpoints for treatment duration, initiation of subsequent therapy, and overall survival are also shown in table 2. For the intent-to-treat (ITT) population, 68.3% are alive at 3 years and 38.5% of all patients are alive and free of subsequent treatment. For the favorable-risk patients, 96.8% (all except one) remained alive at 3 years and 65.6% were alive and free of subsequent treatment, while for the intermediate/poor-risk patients, 56.6% were alive at 3 years and 27.1% were alive and free of subsequent treatment. Four, more recently enrolled, patients remained on protocol therapy (ranging from 7.6 to 22.2 months) at the time of data lock.

Table 1 Characteristics of patients with treatment-naïve metastatic clear cell renal cancer enrolled in Cohort A of the HCRN GU 16–260 trial

Characteristic	N=128
Age, median (range), years	65 (32–86)
ECOG PS (0, 1, 2)	81 (63%), 46 (36%), 1 (1%)
Male, n (%)	92 (72%)
IMDC risk category, n (%)	
Favorable	38 (30)
Intermediate	78 (61)
Poor	12 (9)
Sarcomatoid features	22 (17)
Prior nephrectomy	105 (82)

ECOG, Eastern Cooperative Oncology Group; IMDC, International Metastatic RCC Database Consortium; PS, performance status; RCC, renal cell carcinoma.

Figure 2A displays the entire 3-year distributions of these endpoints with the 3-year landmark Kaplan-Meier estimates as listed in table 2 (at the right of the figure). The maximum treatment duration of 96 weeks (approximately 22 months) for patients on Part A is denoted. As evident from figure 2A, only two patients received treatment longer than 108 weeks (the maximum for patients transitioning at 48 weeks to Part B). This was due to a slight delay in assessing the eligibility for Part B related to the protocol-defined necessity to obtain a biopsy to confirm tumor persistence for Part B eligibility.

In figure 2B, the 36-month period is partitioned by these Kaplan-Meier curves into time on protocol therapy (in purple), TFS (in blue), survival after subsequent systemic therapy initiation (in dark gray), and time following death (in light gray). The numbers displayed in Table 3 represent the mean months under (for overall survival and protocol therapy) or between the various Kaplan-Meier curves and the per cent proportion those months represent of the 36-month total period. The mean time either on or off therapy with grade 3+toxicity is shown graphically in light purple or light blue, respectively. Similar graphs for both

Table 2 Efficacy results by IMDC category, after a median follow-up of 37.7 months

	IMDC risk category			
Best response during Part A	Favorable (n=38)	Intermediate (n=78)	Poor (n=12)	Overall (n=128)
ORR, N (%)*	22 (57.9)	20 (25.6)	4 (33.3)	46 (35.9)
(95% CI)	(40.8 to 73.7)	24 (26.7)	(17.9 to 37.0)	(27.7 to 44.9)
SD	15 (39.5)	27 (34.6)	4 (33.3)	46 (35.9)
PD	1 (2.6)	31 (39.7)	4 (33.3)	36 (28.1)
Kaplan-Meier estimates of 3-year endpoints				
PFS†	31.2%	7.2%		14.6%
OS	96.8%	56.6%		68.3%
Alive and subsequent systemic Rx free (following Part A and Part B, if proceeded thereto)	65.6%	27.1%		38.5%
On protocol therapy	0%	0%		0%

*Parts A and B, N=37 proceeded to Part B.
†Patients entering Part B for disease progression are not considered progression-free.
IMDC, International Metastatic RCC Database Consortium; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; Rx, treatment; SD, stable disease.

the favorable-risk patients and the intermediate/poor-risk patients are shown in figure 2C,D, respectively with the restricted mean months and percentages also dislayed in Table 3. The Kaplan-Meier curve for time on protocol treatment for the IMDC favorable risk patients shows a steep drop at 96 weeks, indicating that approximately one-third of patients completed all of Part A therapy and stopped treatment as per protocol.

The survival states for the ITT population and separate IMDC subgroups are displayed in table 3. For the ITT population, the 36-month mean overall survival was 29.9 months (95% CI 27.9 to 31.8 months), which consisted of: protocol treatment-11.5 months (95% CI 10.2 to 12.9 months); TFS-9.4 months (95% CI 7.6 to 11.3 months); and survival after the start of subsequent therapy-8.9 months (95% CI 6.8 to 11.0 months). For the favorable-risk patients, the mean TFS was 12.9 months (95% CI 9.7 to 16.1 months) or 36% of the 36-month period, and mean overall survival was 35.7 months (95% CI 35.3 to 36.2) or 99% of the 36-month period as the one patient death occurred at 28 months after study registration. For the intermediate/poor-risk patients, the mean TFS was 8 months (95% CI 5.8 to 10.2 months) or 22% of the 36-month period and the overall survival mean was 27.4 months (95% CI 24.9 to 29.9 months) or 76% of the 36-month period. The mean time on protocol treatment with grade 3+toxicity was about 0.6 months (95% CI 0.2 to 0.9 months) or 2% of the total period, while the TFS time with grade 3+toxicity represented only 1.2 months (95% CI 0.5 to 1.9 months) or 3% of the total period. The time spent with grade 3+TRAEs either on therapy or during TFS was similar for both the favorable-risk and intermediate/poor-risk patients.

The enhanced event history (swimmer's plot; figure 3A) displays each patient's partitioned overall survival for the major survival states (time on protocol therapy, TFS, the time after subsequent therapy initiation). The timing of response and disease progression (in Part A and/or B) for each patient are also indicated. In this plot, the 0 time point on the x-axis represents the time of protocol therapy cessation.

Reasons for patients stopping therapy are shown in online supplemental table S1. Partitioned survival for each individual patient separated by reason for stopping Part A therapy is displayed in figure 3B. It shows that the majority of patients who completed protocol therapy or stopped because of an adverse event (AE) remain treatment-free for prolonged periods (beyond 12 months). Specifically, nine patients who came off treatment due to an AE remain treatment free. Of note, eight patients remain subsequent treatment-free despite having exhibited progressive disease while on protocol therapy and only one of these patients has had subsequent progressive disease while treatment-free. In most instances, these patients had isolated progressive disease that was controlled with local therapy (each surgery or radiation therapy).

DISCUSSION

A partitioned survival analysis assesses how survival time is spent on average for patients on a particular treatment regimen. TFS is a component of a partitioned survival analysis and can be used as a novel clinical trial endpoint that complements commonly used efficacy measures such as median PFS, median overall survival, objective response rate, and duration of response. TFS is particularly evident with immunotherapy, as the majority of the tumor responses are durable and can be maintained after treatment stops. For example, 80% of patients with metastatic melanoma who exhibited tumor response to nivolumab/ipilimumab remain in response and over 94% of these are treatment-free at 6.5 years from treatment initiation.[5] Similarly, for patients with advanced RCC treated on

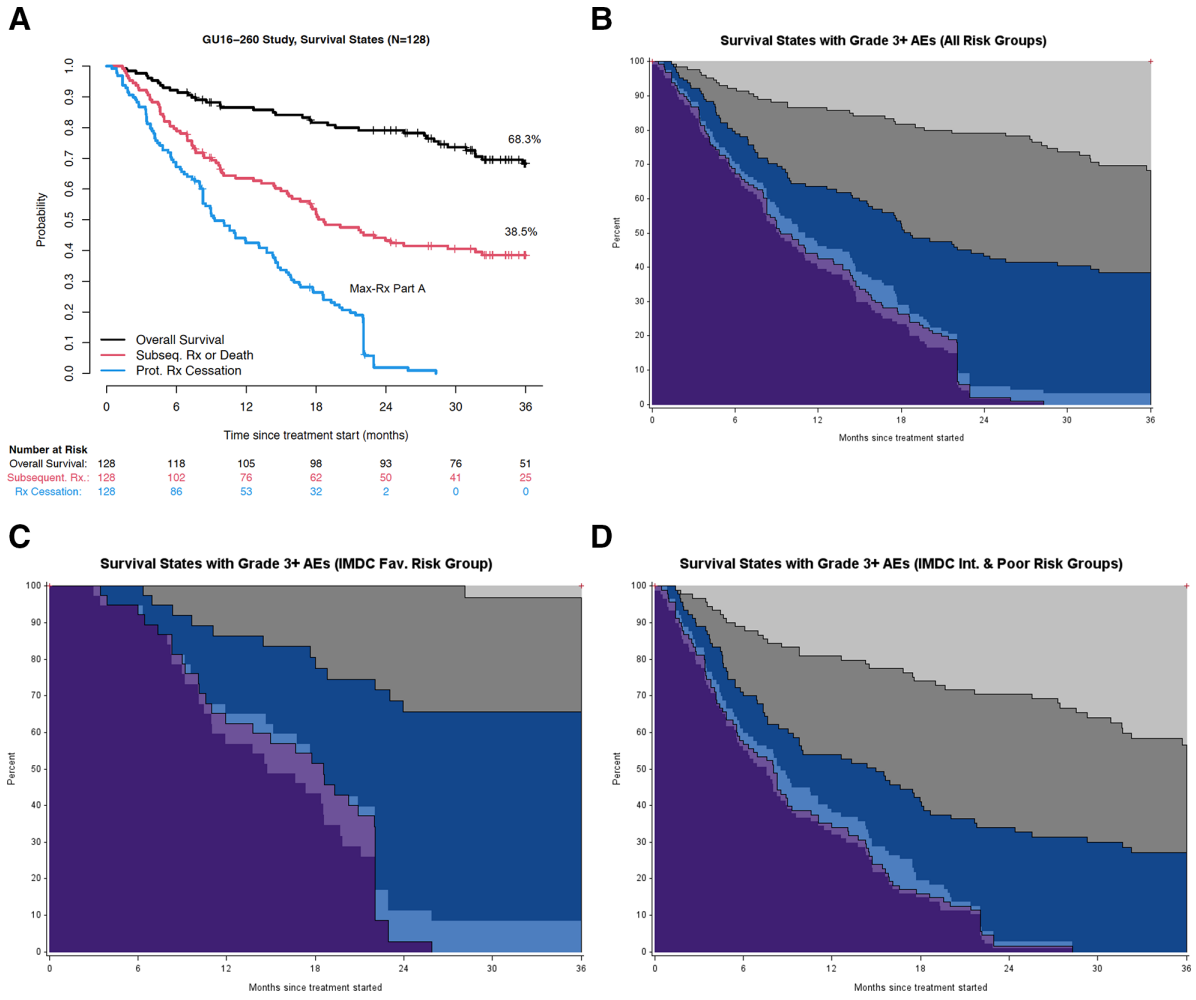

Figure 2 Kaplan-Meier plots of survival states. (A) Displays the Kaplan-Meier curves for time to protocol therapy cessation, time to subsequent therapy initiation or death, and overall survival for all study patients over a restricted 36 months period. The right end of the curves denotes the 36-month landmarks for each of these curves. The 96-week maximum treatment for those on Part A is denoted. (B) Displays the same Kaplan-Meier curves with the areas between the curves colored to denote specific survival states. Time on protocol treatment is in purple, time of treatment-free survival (TFS) is in blue, time after subsequent systemic therapy is in dark gray and time not alive is in light gray. Further, the light purple and light blue areas represent the time on treatment and time treatment-free, respectively, with grade 3–4 toxicity. The mean area (months and percentage of 36 months) for the areas beneath the OS and time on protocol therapy curves and between the various Kaplan-Meier curves are provided in Table 3. (C,D) Represent the same plot restricted to patients with International Metastatic RCC Database Consortium-favorable-risk or intermediate/poor-risk, respectively. OS, overall survival; Rx, treatment; TRAE, treatment-related adverse event.

the nivolumab/ipilimumab arm of CheckMate 214 trial, 86% of patients with a complete response remained in response, with 55% of these responders being alive, off-treatment and free of subsequent therapy at 30 months from treatment initiation.[6] Further, 61% of patients (95 of 156) with partial response remained in response with the majority being off treatment. At 60 months from treatment initiation, 56% of all responders still remained in response.[7]

These durable responses that were maintained off immunotherapy led to considerable TFS in both of the above studies. In the CheckMate 067 study, TFS represented a mean of 19.7 months or 33% of the initial 60-month follow-up period for those treated with nivolumab/ipilimumab and 9.9 months or 17% for those treated with nivolumab monotherapy. In the CheckMate 214 study, TFS for the ITT population was a mean of 11.1 months or 18.5% of the initial 60-month follow-up period, including 14.4 months (24%) and 10.1 months (16.7%) for IMDC favorable-risk and intermediate/poor-risk subpopulations, respectively.[8]

In contrast, TFS is not seen with Vascular Endothelial Growth Factor Receptor (VEGFR) tyrosine kinase inhibitor (TKI)-based therapies such as sunitinib for metastatic RCC, as treatment typically continues until disease progression and then patients are switched to an alternative therapy. For example, on the sunitinib arm of CheckMate 214, the mean TFS was only 4.4 months (or 7.3%) of the initial 60-month follow-up period and was similar for patients with IMDC favorable-risk (5.5 months) and

Table 3 Partitioned overall survival endpoints and survival states over 36 months since the start of protocol treatment

Survival state	36-month mean (95% CI) time, mos (% of 36-month period)					
	Overall N=128		FAV N=38		I/P N=90	
Time alive (OS)	29.9 (27.9 to 31.8)	(83%)	35.7 (35.3 to 36.2)	(99%)	27.4 (24.9 to 29.9)	(76%)
Time on protocol therapy	11.5 (10.2 to 12.9)	(32%)	16.0 (13.9 to 18.1)	(44%)	9.6 (8.1 to 11.2)	(27%)
With grade 3+TRAEs	0.6 (0.2 to 0.9)	(2%)	1.0 (0.1 to 1.9)	(3%)	0.4 (0.0 to 0.8)	(1%)
TFS	9.4 (7.6 to 11.3)	(26%)	12.9 (9.7 to 16.1)	(36%)	8.0 (5.8 to 10.2)	(22%)
With grade 3+TRAEs	1.2 (0.5 to 1.9)	(3%)	1.5 (0.1 to 2.8)	(4%)	1.0 (0.2 to 1.7)	(3%)
Time surviving after subsequent therapy	8.9 (6.8 to 11.0)	(25%)	6.9 (3.4 to 10.3)	(19%)	9.8 (7.3 to 12.4)	(27%)

FAV, favorable; I/P, intermediate/poor; OS, overall survival; TFS, treatment-free survival; TRAE, treatment-related adverse event .

intermediate/poor-risk (4.1 months). Of note, regimens combining programmed cell death protein-1 (PD-1) pathway blockade and VEGFR TKIs (axitinib+pembrolizumab, axitinib+avelumab and cabozantinib+nivolumab) appear to have mean TFS similar to sunitinib (<3 months of the initial 30-month follow-up),[9] suggesting either a lack of response persistence once therapy is stopped or, as with sunitinib, a reluctance to stop VEGFR TKIs until disease progression is observed.

Substantial TFS was seen in the HCRN GU 16–260 study, which capped treatment administration at 96 weeks for those remaining on Part A and approximately 108 weeks for those transitioning from Part A to Part B. The mean TFS was 9.6 months or 26.6% of the restricted 36-month follow-up time) for the ITT population, with mean TFS of 12.9 months (36% of the restricted 36-month follow-up time) and 8.0 months (22%) for patients with IMDC favorable-risk and intermediate/poor-risk RCC, respectively. These TFS numbers were numerically superior to the corresponding 36-month TFS for nivolumab/ipilimumab reported in the CheckMate 214 trial[10]—ITT 6.8 months (19%), favorable-risk 9.8 months (27%), intermediate/poor-risk 5.8 months (16%) despite that fact that nivolumab/ipilimumab had a higher overall response rate (39% vs 36%) and longer median PFS (12.3 vs 8.3 months)[7] indicating the impact of a defined treatment completion time on TFS. This further suggests that many of the approximately 25% of patients on CheckMate 214 who were treated beyond 2 years[2] might not have needed the additional treatment, and if the protocol would have had a defined treatment cessation time point, the mean TFS period might have been greater. It should be cautioned that HCRN GU 16–260 is a single-arm study and like many such trials, its findings cannot directly be applied to an individual patient or the population as a whole, nor directly to the CheckMate 214 trial.[11 12]

As noted above, IMDC favorable-risk patients had particularly promising TFS that was nearly 5 months greater than the TFS observed in intermediate/poor-risk population. In particular, 65.6% of favorable-risk patients were estimated to be off of treatment and free of subsequent therapy initiation at the 3-year landmark, compared with only 27.1% of patients with intermediate/poor-risk disease. This ability to stop treatment and remain free of subsequent treatment initiation for extended periods of time is of particular benefit to favorable-risk patients, many of whom are asymptomatic from their disease at the time of treatment initiation and, thus, could have their quality of life negatively impacted by the side effects of prolonged treatment. In addition, this individual patient 3-year landmark treatment-free data may be tantamount to a "functional cure", an endpoint that patient survey data suggests is the most highly desired treatment outcome for patients with metastatic RCC.[13] Current FDA-approved immunotherapy containing regimens for patients with IMDC favorable-risk disease are restricted to anti-PD-1/VEGFR TKI combinations (axitinib+pembrolizumab, cabozantinib+nivolumab, and lenvatinib+pembrolizumab) despite there being no evidence for extended TFS or improved overall survival beyond that observed with sunitinib (HRs for overall survival were around 1.0 for each of these studies) for this population.[14] The TFS results in the favorable-risk population on the HCRN GU 16–260 study, when added to the promising efficacy results in this trial, further support the need for an approved immunotherapy-only regimen for this population.

The partitioned overall survival analysis also provides an opportunity to look at the longitudinal extent of toxicity during survival time. Such an analysis is distinct from the traditional AE reporting in clinical trials which focuses on the worst grade toxicities experienced by individual patients during the course of treatment or the 30–100 days time period following treatment cessation without regard to the duration of the side effects. In this trial, using the partitioned survival method, the number of days experiencing TRAE(s) of grades 3–4 represented a relatively small portion of the overall survival. Specifically, the mean time on protocol treatment with grade 3+toxicity was about 0.6 months (2% of the total 36-month period) while the TFS time with grade 3+toxicity represented only 1.2 months or 3% of the total period. Such an analysis, similar to the classic Q-TWiST analysis,[15 16] provides a better measure of the burden of side effects that the average patient experiences once beginning

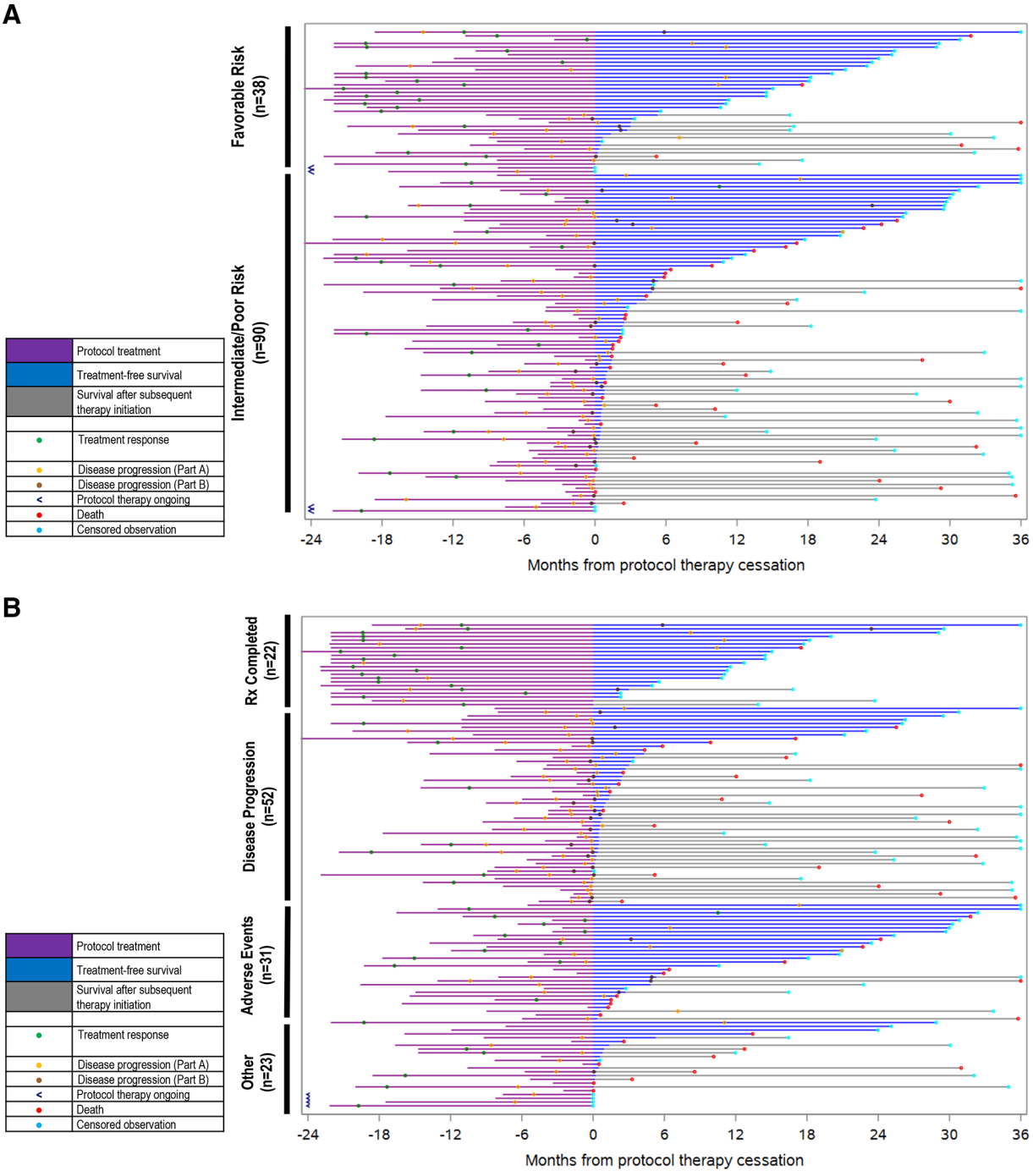

Figure 3 Modified swimmer's plots. (A) Displays the treatment course for each of the 128 patients by International Metastatic RCC Database Consortium risk category with time 0 on the x-axis denoting the time at which protocol therapy was stopped. Therefore, the lines to the left of time 0 (shown in purple) represent time on protocol therapy and to the right of time 0 represent time in TFS (blue) and after subsequent protocol therapy initiation (gray). Various trial milestones for each patient are represented by the circles (green=time of disease response, yellow=time of disease progression on Part A, brown=time of disease progression on Part B, red=time of death and blue=time of follow-up censoring for being alive either still subsequent treatment free (in TFS) or after initiating subsequent therapy. The<at the left of the figure denotes the four patients still on protocol therapy at the time of the data lock. (B) Represents the same data now separated by reasons for stopping protocol therapy: either completed protocol therapy (completed), progressive disease, toxicity (adverse event) or other. Rx, treatment; TFS, treatment-free survival.

therapy, including the possibility that some side effects may present or persist after treatment cessation. Providing such information together with TFS results adds value to traditionally reported trial results such as median PFS, median overall survival, objective response rates, and toxicity percentages. This information could prove valuable in helping patients balance risks and benefits when making treatment decisions. It would be useful to have

similar analyses performed in the context of other trials so that physicians could make more informed recommendations and patients make more educated decisions.

Of note, patients who stopped treatment due to toxicity had a pattern of treatment-free intervals like those of patients who completed therapy, and markedly longer than those who stopped treatment for either progressive disease or other reasons suggesting that immune-related (ir) AEs are often linked with treatment efficacy[17] and/or that shorter treatment durations may be possible in at least some patients. Also, some patients with disease progression appear to exhibit long and ongoing freedom from subsequent systemic therapy, suggesting that local treatment measures may be sufficient to control isolated sites of disease progression in some patients. The value of such an approach may be worth exploring further in patients with RCC treated with various immunotherapy regimens.

Future studies may look at both partitioned survival and quality of life, not just during the treatment period, but for a defined period of at least 3 years and conceivably until death, and could employ not just objective criteria for treatment cessation but also for initiating subsequent systemic therapy, thereby providing an even more complete and robust measure of how various regimens perform and are experienced by patients. Such data may not only add further depth of knowledge about how treatments perform, but also identify properties that distinguish one treatment regimen from another that might be useful in assessing the overall value of a treatment approach for a particular population.

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Contributors MBA, OAJ, DFM and MMR conceived of and designed the study with the assistance of DE and PJC. MBA, NBH, DFM, MAB, MS, JS, RA, ERP, MCO, MH, DJP and HH collected the data. OAJ, MMR and MBA analyzed the data. MBA wrote the manuscript. All authors reviewed and revised the manuscript and approved the submission. MBA is responsible for overall content as the guarantor.

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Competing interests MBA has/had an advisory role for Bristol-Myers Squibb, Merck, Novartis, Eisai, Exelixis, Aveo, Pfizer, Werewolf, Fathom, Pyxis Oncology, PACT, Elpis, X4Pharma, ValoHealth, ScholarRock, Surface, Takeda, Simcha, Roche, SAB Bio, Pliant Therapeutics, Atreca, OncoRena, Sanofi and GSK and has served as a consultant: Bristol-Myers Squibb, Merck, Novartis, Pfizer, Roche, Agenus, Asher Bio, and AstraZeneca. He reports research support to his institution from Bristol-Myers Squibb and Merck. He holds stock/stock options in Pyxis Oncology, Werewolf and Elpis. OAJ—none. NBH is a paid consultant to BMS, Eisai, Exelixis, Merck and Roche Genentech. DFM has acted as a paid consultant for and/or as a member of the advisory boards of BMS, Pfizer, Merck, Alkermes, Inc, EMD Serono, Eli Lilly and Company, Iovance, Eisai Inc., Werewolf Technologies, Calithera Biosciences, Synthekine, Inc., Johnson served on speakers bureaus for Bristol Myers Squibb and Merck; received institutional research funding from Bristol Myers Squibb, Pfizer, Merck, AstraZeneca, Astellas, Aravive, and Surface Oncology; has received reimbursement for travel and accommodations expenses from Bristol Myers Squibb, Pfizer, Eisai, and Exelixis. MH has served on Advisory Boards for Bristol Myers Squibb, CRISPR Therapeutics, Exelixis, Nektar Therapeutics, Janssen and has received research support to his institution from Alpine, Achilles Therapeutics, Apexigen, Arrowhead, Astellas, AstraZeneca, Bayer, Bristol Myer Squibb, CRISPR Therapeutics, Corvus, Eli Lilly, Endocyte, Fate Therapeutics, Genentech, Genmab, GSK, Innocrin, Iovance, KSQ, Merck, Nektar Therapeutics, Novartis, Pfizer, Progenics, Sanofi Aventis, SeaGen, Tmunity, Torque, Unum. He also reports Spouse salary from Gamida Cell, Arvinas. DJP holds stock in Bristol-Myers Squibb and Merck. DE reports research funding to institution from Bristol-Myers Squibb, Cardiff Oncology, Mink Therapeutics, Novartis, Puma Biotechnology, and Sanofi, as well as discounted research sequencing from Foundation Medicine and honorarium from OncLive. PJC—none. HH has acted as a paid consultant for and/or as a member of the advisory boards of Exelixis, BMS, Pfizer, Merck, Corvus, Armo Biosciences, Eisai, Eli Lilly, Surface Oncology, Aveo and Novartis and has received grants to his institution from Merck, Bristol-Myers Squibb, Surface Oncology and Aravive for work performed as outside of the current study. MMR reports research funding to institution from AstraZeneca, Bayer, Biotheranostics, Bristol-Myers Squibb, DebioPharm, Ipsen, Novartis, Pfizer, Roche, TerSera Therapeutics, all outside of the current study, and a consulting or advisory role for AstraZeneca, Bristol-Myers Squibb, DebioPharm, Ipsen, TerSera Therapeutics, Tolmar Pharmaceuticals.

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Data availability statement Data are available upon reasonable request. The authors are committed to the concept that data sharing is essential for expedited translation of research results. Members of our groups will adhere to the policy that the timely release and sharing of data obtained from the research will be made available at the time of publication. Members of our group will also share results from our studies at national meetings and with other investigators based on their availability. Data will be kept free of identifiers that would permit linkages to individual patients and variables that could lead to disclosure of their identity.

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