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FRACTION-RCC: nivolumab plus ipilimumab for advanced renal cell carcinoma after progression on immuno-oncology therapy

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ABSTRACT

Background The role and sequencing of combination immuno-oncology (IO) therapy following progression on or after first-line IO therapy has not been well-established. The Fast Real-time Assessment of Combination Therapies in Immuno-ONcology (FRACTION) program is an open-label, phase 2 platform trial designed to evaluate multiple IO combinations in patients with advanced renal cell carcinoma (aRCC) who progressed during or after prior IO therapy. Here, we describe the results for patients treated with nivolumab plus ipilimumab. For enrollment in track 2 (reported here), patients with histologically confirmed clear cell aRCC, Karnofsky performance status ≥70%, and life expectancy ≥3 months who had previously progressed after IO (anti-programmed death 1 (PD-1), anti-programmed death-ligand 1 (PD-L1), or anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4)) therapy were eligible. Previous treatment with anti-CTLA-4 therapy plus anti-PD-1/PD-L1 therapy precluded eligibility for enrollment in the nivolumab plus ipilimumab arm. Patients were treated with nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks for four doses, followed by nivolumab 480 mg every 4 weeks for up to 2 years or until progression, toxicity, or protocol-specified discontinuation. The primary outcome measures were objective response rate (ORR), duration of response (DOR), and progression-free survival (PFS) rate at 24 weeks. Secondary outcomes were safety and tolerability up to 2 years. Overall survival (OS) was a tertiary/exploratory endpoint. Overall, 46 patients were included with a median follow-up of 33.8 months. The ORR was 17.4% (95% CI, 7.8 to 31.4) with eight (17.4%) patients achieving partial response. Stable disease was achieved in 19 (41.3%) patients, while 14 (30.4%) had progressive disease. Median DOR (range) was 16.4 (2.1+ to 27.0+) months. The PFS rate at 24 weeks was 43.2%, and median OS was 23.8 (95% CI, 13.2 to not reached) months. Grade 3–4 immune-mediated adverse events were reported in seven (15.2%) patients. No treatment-related deaths were reported. Patients with aRCC treated with nivolumab plus ipilimumab may derive durable clinical benefit after progression on previous IO therapies, including heavily pretreated patients, with a manageable safety profile that was consistent with previously published safety outcomes. These outcomes contribute to the knowledge of optimal sequencing of IO therapies for patients with aRCC with high unmet needs.

Trial registration number NCT02996110.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Immuno-oncology (IO) options, including immune checkpoint inhibitor (ICI) monotherapy and combination therapies, currently constitute the backbone of both first-line and second-line treatments for patients with advanced renal cell carcinoma (aRCC).

⇒ Despite the promising efficacy of IO combination treatments, disease progression is inevitable for many patients, and no standard of care exists for those whose ICI combination treatment failed.

⇒ The optimal selection and sequencing of IO treatment after progression on IO therapy is not well known.

WHAT THIS STUDY ADDS

⇒ The Fast Real-time Assessment of Combination Therapies in Immuno-ONcology Study in Patients With aRCC (FRACTION-RCC) is a signal-seeking randomized phase 2 trial with an adaptive-platform design that enables evaluation of IO combinations in patients with aRCC who had previously progressed on IO therapy.

⇒ The observed outcomes in this IO pretreated patient population contribute to the knowledge on optimal sequencing of IO therapies for patients with aRCC.

⇒ The findings show ongoing clinical benefits among some patients receiving nivolumab plus ipilimumab after progression on previous IO therapies, with a manageable safety profile that was consistent with previously published safety outcomes.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ There is a persistent unmet need for patients in the IO pretreated setting, and this study contributes to the limited evidence on which to base future treatment decision-making, and hopefully will stimulate the conduct of additional prospective studies in this patient population.

⇒ Clinical benefits were realized among some patients receiving nivolumab plus ipilimumab after progression on previous IO therapies; therefore, this combination may be a viable option for select patients after progression on IO therapy

BACKGROUND

Since the introduction of tyrosine kinase inhibitors (TKIs) and mammalian target of rapamycin (mTOR) inhibitors in the early 2000s, the management of advanced renal cell carcinoma (aRCC) has progressed into an era where combination immuno-oncology (IO) treatment has become the standard of care.[1–8] Immune checkpoint inhibitors (ICIs) in particular have revolutionized the treatment paradigm for aRCC, reflecting a fundamental shift in the approach to treating aRCC by leveraging the immune system to attack cancer cells, rather than targeting pathways underlying tumor pathogenesis, as with TKIs or mTOR inhibitors.[1 2 9 10]

Nivolumab was the first-in-class ICI, targeting the programmed death 1 (PD-1) checkpoint in aRCC.[11] US Food and Drug Administration (FDA) approval was granted on the basis of results from the CheckMate 025 phase 3 clinical trial in 2015, which compared nivolumab and everolimus in the second-line and third-line settings, in which nivolumab demonstrated superiority.[1 11 12]

After the successes of IO therapy in patients with disease progression on conventional targeted therapies, the randomized phase 3 pivotal CheckMate 214 trial evaluated combination immune checkpoint blockade in treatment-naïve patients with advanced clear cell RCC, resulting in FDA approval of nivolumab plus ipilimumab in patients with International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) intermediate or poor risk.[9 13 14] Thereafter, approaches incorporating dual immune checkpoint blockade with a PD-1 or programmed death ligand 1 (PD-L1) inhibitor along with cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibition, or immune checkpoint blockade plus a vascular endothelial growth factor (VEGF)-targeted therapy, has become an accepted standard of care for treatment-naïve aRCC on the basis of unprecedented response rates and improved survival.[1–10] Nivolumab is now widely used in monotherapy or in combination for the treatment of aRCC, and the clinical benefit of IOs and their combination with antiangiogenic agents is evident in both untreated and treated patients with aRCC.[3 11 15] IO options currently constitute the backbone of both first-line and second-line treatments.[1 3 13]

Despite the promising efficacy of these combination treatments, disease progression is inevitable for many patients, and no standard of care exists for those who did not respond to an ICI combination in the first-line setting.[1 9 15 16] In clinical practice, the potential benefits of ICIs or ICI combinations when given beyond the first-line and second-line setting have not been fully elucidated.[9 13] When patients develop resistance or toxicity to immune checkpoint blockade in the first-line treatment of aRCC, a new challenge has emerged regarding how to optimally treat patients in the second-line and beyond in patients who have received prior IO therapy.[1 2 13] Several studies investigated the addition of ipilimumab to nivolumab in a sequential manner and showed that this approach was not always feasible and of limited benefit, with efficacy appearing to be less than that of concomitant nivolumab plus ipilimumab in untreated patients with intermediate/poor-risk disease (CheckMate 214 trial).[14 17–21] Data from OMNIVORE, TITAN-RCC, and HCRN GU16-260-cohort A did not support a response-adaptive strategy for PD-1/CTLA-4 inhibitors in metastatic RCC.[17–21]

Ongoing efforts are focused on the sequencing of subsequent-line options after progression on IO monotherapy or combination therapies.[1 2 9 16 22] A small number of recent retrospective analyses have suggested that patients whose disease progressed after IO therapy may derive substantial benefit from single-agent ICI and ICI combinations in later treatment lines as well.[1 2 9 16 22]

Thus far, although the optimal sequencing of ICI treatment across different lines of treatment is neither supported by high-level prospective evidence nor by treatment guidelines, real-world evidence suggests that heavily pretreated patients may benefit from treatment with ICI or ICI combinations.[1 2 9 16 22] This underscores the unmet need for patients in the IO therapy pretreated setting, and ongoing clinical trials will provide insights on which to base future best practice and guideline recommendations.

The Fast Real-time Assessment of Combination Therapies in Immuno-ONcology Study in Patients With aRCC (FRACTION-RCC) is a signal-seeking randomized phase 2 trial with an adaptive-platform design that enables evaluation of IO combinations.[23] FRACTION-RCC assesses efficacy and safety outcomes with nivolumab plus ipilimumab in patients with aRCC who are either IO-treatment naïve (track 1) or whose disease previously progressed during or after IO (track 2); we focus here on track 2. To our knowledge, FRACTION-RCC is the first and only adaptive platform study to prospectively evaluate IO combination regimens in patients with aRCC progressing after previous IO therapy.

METHODS

The master FRACTION study design was described previously.[23] At present, the study is no longer recruiting and no patients remain on study. FRACTION-RCC aims to determine the most promising IO therapy combinations available for patients with aRCC, thus reducing the time and number of patients needed to identify potentially

beneficial regimens for evaluation in phase 2 or 3 trials.[23] Patients were enrolled in one of the two tracks (online supplemental figure 1). Track 1 enrolled patients with aRCC who were naïve to IO treatment (anti-PD-1/anti-PD-L1, and anti-CTLA-4) and were stratified according to whether the patient had prior TKI treatment, and track 2 enrolled patients with previous IO treatment experience. Patients in both tracks were randomized to receive nivolumab plus ipilimumab or other treatment combinations, all of which included nivolumab (online supplemental figures 1 and 2). Patients whose disease progressed were eligible for enrollment in another track 2 FRACTION regimen that differed from what the patient previously received. This report focuses on outcomes in patients randomized to nivolumab and ipilimumab in track 2 and includes mature follow-up data.[23]

Patients with histologically confirmed clear cell aRCC, life expectancy ≥3 months, and Karnofsky performance status ≥70% whose disease progressed on any previous line of anti-PD-1/anti-PD-L1 or anti-CTLA-4 treatment were assigned to receive nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks for four doses, followed by nivolumab 480 mg monotherapy every 4 weeks for up to 2 years or until disease progression, toxicity, or protocol-specified discontinuation.[23] Patients who were previously treated with anti-CTLA-4 therapy in combination with anti-PD-1/PD-L1 therapy were not eligible for enrollment in the nivolumab plus ipilimumab arm of track 2 per the subprotocol. Patients who were intolerant to or progressed on nivolumab plus ipilimumab were eligible to be randomized to other FRACTION-RCC regimens within track 2. All patients provided an institutional review board-approved written consent before entering the screening phase.

Sample sizes were guided by Simon two-stage (optimal) designs. Recommendations for stopping or progressing to the next stage were based on the number of objective responses observed. In track 2, 21 patients per study treatment combination arm were treated in stage 1, and preliminary efficacy was assessed when those patients were evaluable. On the observation of ≥2 responses, stage 2 was initiated with the goal of enrolling an additional 20 patients, for a total of at least 41 patients per study treatment combination arm.

The primary outcome measures were objective response rate (ORR) per investigator using Response Evaluation Criteria in Solid Tumors V.1.1, duration of response (DOR), and progression-free survival (PFS) rate at 24 weeks.[23] Secondary outcomes were safety and tolerability up to 2 years.[23] Immune-mediated adverse events (IMAEs) include subcategories of endocrine events (eg, adrenal disorders, diabetes, pituitary disorders, and thyroid disorders). Overall survival (OS) was a tertiary/exploratory endpoint.

Table 1 Objective response rate

	Nivolumab plus ipilimumab (N=46)
All treated patients	
Objective response rate (95% CI), %	17.4 (7.8 to 31.4)
Disease control rate (95% CI), %*	58.7 (43.2 to 73.0)
Best overall response, n (%)	
Complete response	0
Partial response	8 (17.4)
Stable disease	19 (41.3)
Progressive disease	14 (30.4)
Not evaluable/available†	5 (10.9)
Patients with measurable tumor PD-L1 expression	
Objective response rate (95% CI), %	
PD-L1 ≥1%	12.5 (0.3 to 52.7)
PD-L1 <1%	14.3 (3.0 to 36.3)

*Proportion of patients with a best overall response of complete response, partial response, or stable disease.
†Patients were considered not evaluable or available if either no imaging/measurement was done at a specific time point or if only a subset of lesion measurements were done at an assessment.
PD-L1, programmed death ligand 1.

RESULTS

Baseline characteristics

Forty-six patients with aRCC previously treated with IO therapies were included. The median (range) age was 60.5 (36–82) years; most had intermediate IMDC risk (60.9%); most were Caucasian (93.5%), and men (80.4%; online supplemental table 1).

All patients received previous anti-PD-1 or anti-PD-L1 therapy. No patients had been treated with anti-CTLA-4 therapy or with anti-CTLA-4 therapy in combination with anti-PD-1/PD-L1 therapy (per inclusion criteria). Approximately 50% of the patients received three or more systemic therapies before enrollment.

Treatment exposure, duration, and patient disposition

The median cumulative duration of therapy, including the combination and monotherapy phases, was 6.4 months; no patients remained on treatment as of the database lock. The median number (range) of nivolumab doses received overall was four (1–26), and four (1–4) for ipilimumab. Of the 46 patients who discontinued study therapy, disease progression (71.7%) was the most common reason for discontinuation. Eleven of the 46 patients in track 2 were previously enrolled in other FRACTION-RCC tracks (either 1 or 2); after progressing on treatment with nivolumab plus ipilimumab, four were enrolled in another track 2 arm.

Objective response rate and duration of response

ORR was assessed in all 46 patients included in this arm of track 2. After a median follow-up (range) of 33.8 (24.1–45.2) months, the ORR (95% CI) in the entire

Table 2 Characteristics of patients with a response to nivolumab plus ipilimumab* † ‡

Patient	Age, years	Sex	KPS score	No. of prior therapies§	Most recent prior IO therapy¶	Most recent prior therapy¶	BOR on most recent prior IO	Time on NIVO+IPI, months	Time to subsequent therapy, months** ††
1	Mid-70s	M	80	3	NIVO monotherapy	NIVO monotherapy	PD	23.1	25.5
2	Early 50s	M	90	2	NIVO monotherapy	NIVO monotherapy	SD	2.1	–
3	Early 80s	M	80	2	NIVO monotherapy	NIVO monotherapy	SD	5.3	–
4	Late 60s	M	80	8	NIVO+anti-LAG-3 antibody	NIVO+anti-LAG-3 antibody	SD	19.4	–
5	Late 70s	M	80	8	NIVO+anti-LAG-3 antibody	NIVO+anti-LAG-3 antibody	PD	6.2	4.6
6	Late 40s	F	70	1	NIVO+anti-LAG-3 antibody	NIVO+anti-LAG-3 antibody	PD	14.5	9.9
7	Early 70s	M	80	3	Avelumab/axitinib	TAK-228	PR	5.4	–
8	Early 50s	M	100	2	Atezolizumab/ bevacizumab	Cabozantinib	PR	23.8	–

*All patients had clear cell histology and all had metastatic disease at study entry.
†All patients had a nephrectomy.
‡All patients were Caucasian.
§The number of prior therapies includes patients who received prior IO therapy in a different FRACTION cohort.
¶The regimen setting for all prior regimens in all patients was metastatic disease.
**Dash indicates that at the time of the database lock, subsequent therapy was not initiated, documented, or was unable to be determined.
††Refers to subsequent therapy after progression or lack of response to nivolumab plus ipilimumab.
BOR, best overall response; IO, immuno-oncology; IPI, ipilimumab; KPS, Karnofsky performance status; LAG-3, lymphocyte-activation gene 3; NIVO, nivolumab; PD, progressive disease; PR, partial response; SD, stable disease.

population (N=46) was 17.4% (7.8 to 31.4), with eight (17.4%) partial responders; table 1.

Most patients achieved a best overall response (BOR) of stable disease (19; 41.3%) or progressive disease (14; 30.4%); five patients (10.9%) were not evaluable or available. Among patients with baseline tumor PD-L1 expression ≥1% versus <1%, the ORR was 12.5% vs 14.3%, respectively.

The best change from baseline in target lesion tumor burden was evaluated in all patients with a baseline and at least one postbaseline assessment (n=38). Of these, 17 patients (44.7%) had a decrease in target lesion tumor burden; 10 had a decrease of ≥30% in target lesion tumor burden and 4 had a decrease of ≥75%, whereas 7 had an increase of ≥20%. The median time to response (range) was 2.9 (1.5–12.7) months and the median DOR (range) was 16.4 (2.1+ to 27.0+) months. Among the eight patients who responded, five (62.5%) had an ongoing response.

Characterization of partial responders

The eight responders received a range of one to eight prior therapies before enrollment; most (6/8; 75%) received either nivolumab monotherapy or nivolumab-based combination therapy as the most recent prior IO (table 2).

The best response on prior IO in responders was progressive disease in three, stable disease in three, and partial response in two patients. BOR to nivolumab plus ipilimumab is also presented by BOR on most recent prior IO therapy in online supplemental table 2.

Of all responders, five patients achieved ≥50%, four of whom achieved >75% decrease in tumor burden (online supplemental figure 3).

Progression-free survival and overall survival

All 46 patients were included in the analyses for PFS and OS, including the five patients who were not evaluable for ORR. These five patients were either censored or died. Thirty-one of the 46 (67.4%) patients experienced disease progression on treatment. Median PFS (95% CI) was 3.7 (2.0 to 7.3) months (figure 1A) with 43.2% PFS rate at 6 months. Among the 19 patients with a BOR of stable disease, the median PFS (95% CI) was 7.2 (3.4 to 11.0) months; 12 of the 19 (63.2%) experienced a progression event overall. In these patients, the PFS rate (95% CI) at 6 months was 54.5% (27.4 to 75.3).

Twenty-three of 46 (50.0%) patients died of any cause. Median OS (95% CI) was 23.8 (13.2 to not estimable) months (figure 1B) with 66.6% OS probability at 12 months.

Safety

Of the 46 patients, any-grade treatment-related adverse events (AEs) were reported in 36 (78.3%) patients and grade 3–4 treatment-related AEs were reported in 13 (28.3%) patients (online supplemental table 3). Treatment-related AEs leading to discontinuation

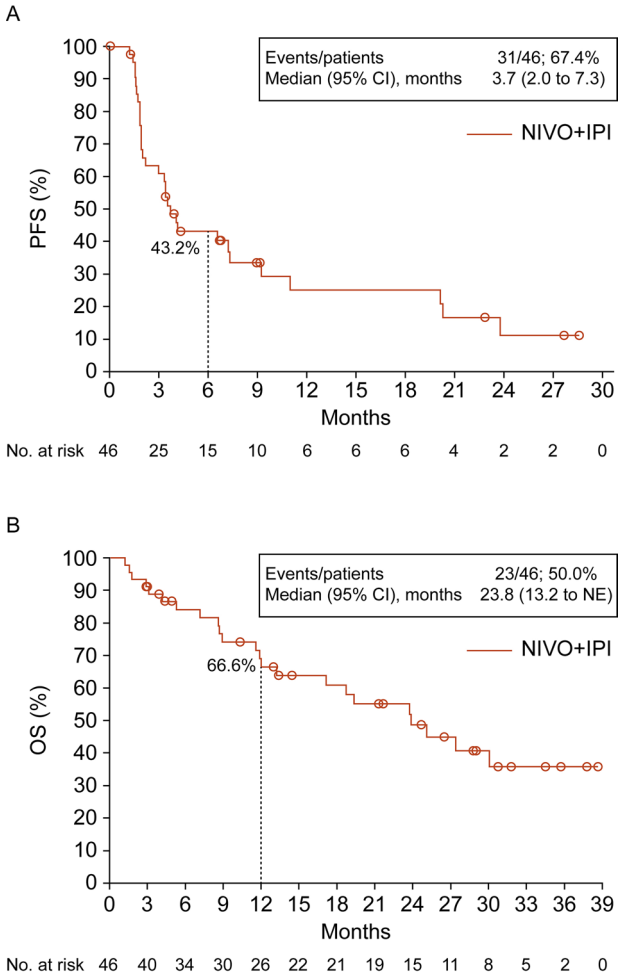

Figure 1 Kaplan-Meier plots of progression-free survival (PFS; A) and overall survival (OS; B). NE, not estimable; NIVO+IPI, nivolumab plus ipilimumab.

occurred in four (8.7%) patients, three (6.5%) of which were categorized as grade 3–4. Five patients (10.9%) had any-grade treatment-related serious AEs and three (6.5%) experienced a grade 3–4 serious treatment-related AE. No grade 5 treatment-related AEs were reported. A total of 32 any-grade IMAEs for nivolumab plus ipilimumab were reported in 23 (50.0%) of the 46 treated patients, with 7 (15.2%) patients reporting grade 3–4 IMAEs (online supplemental table 4). No grade 5 IMAEs were reported. Seven (15.2%) of the 46 treated patients required ≥40 mg prednisone daily or equivalent to manage any-grade IMAEs, as did 5 patients for grade 3–4 IMAEs.

DISCUSSION

The results from FRACTION-RCC track 2 contribute to the knowledge on optimal sequencing of IO therapies for patients with aRCC. Given the evolution of the use of front-line combinations of oral multikinase inhibitors with a single-agent IO, the appreciation that a subset of patients who progress on front-line therapy including a single anti-PD-1 agent may still achieve durable remissions with combination IO is important.

Several studies have evaluated a sequential approach in which nivolumab monotherapy is administered first, and then a response-adaptive strategy is used to determine which patients are eligible for combination treatment with nivolumab plus ipilimumab.[17–21] In OMNIVORE (included all IMDC risk patients), HCRN GU16-260 (included all IMDC risk patients), and TITAN-RCC (included only intermediate/poor-risk patients), all patients initiated nivolumab monotherapy; those who progressed on monotherapy were then eligible for treatment with nivolumab plus ipilimumab.[17–21] In aggregate, the studies generally suggest that the sequential approach was not always feasible, and though the ORR was improved with combination therapy, efficacy overall may be limited compared with initial combination therapy with PD-1/CTLA-4 therapy.[17–21]

Despite the lower response rate (17.4%) observed in the IO-pretreated patients in FRACTION-RCC versus the response rate (39%) reported in the treatment-naïve patients in CheckMate 214, the outcomes are encouraging.[14] In FRACTION-RCC, the results showed that patients who had already progressed on IO therapy still derived clinical benefit, some with durable responses (median DOR 16.4 months), suggesting that this combination is an option in patients whose tumors progress on prior PD-1/PD-L1 inhibitors. Of note, it is not possible to discern the individual contribution of each drug, and it is possible that most of the efficacy could come from the CTLA-4 inhibitor ipilimumab as the patients were not exposed to it previously.

In the full cohort of 46 patients, of those who achieved a partial response (n=8), three received treatment with nivolumab plus an anti-LAG-3 agent before enrollment in track 2. Of the 46 patients who did not achieve a response (n=38), 7 were treated with nivolumab plus an anti-LAG-3 drug in a prior line of therapy. Of these seven patients, two maintained stable disease and one was not evaluable (due to early discontinuation) after switching to nivolumab plus ipilimumab, and four had progressive disease.

The FRACTION-RCC adaptive approach allowed for an efficient method for optimizing treatment sequencing in previously treated patients with a high unmet need.

The findings show ongoing clinical benefits among some patients receiving nivolumab plus ipilimumab after progression on previous IO therapies, with a manageable safety profile that was consistent with previously published safety outcomes.

The FRACTION study platform is expected to support future translational research by contributing to the understanding of key pathways and biomarkers associated with treatment resistance and mechanisms of action of therapies. Biomarkers such as PD-L1, LAG-3, and CTLA-4 will inform future studies and clinical practice about the expression of checkpoints in the immune pathway and their implications on response to treatment and treatment sequencing. Additionally, immune markers such as Ki-67, CD8+, MPO, and FOXP3 may provide insights into mechanisms of action of and resistance to therapies.

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Ethics approval This study was conducted in accordance with Good Clinical Practice, as defined by the International Council for Harmonisation in accordance with the ethical principles underlying European Union Directive 2001/20/EC United States Code of Federal Regulations, Title 21, Part 50 (21CFR50), and applicable local requirements. Participants gave informed consent to participate in the study before taking part.

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