Online Only: Suggested Display Items

APPENDIX

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

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This appendix has been developed to provide readers with relevant supplemental information.

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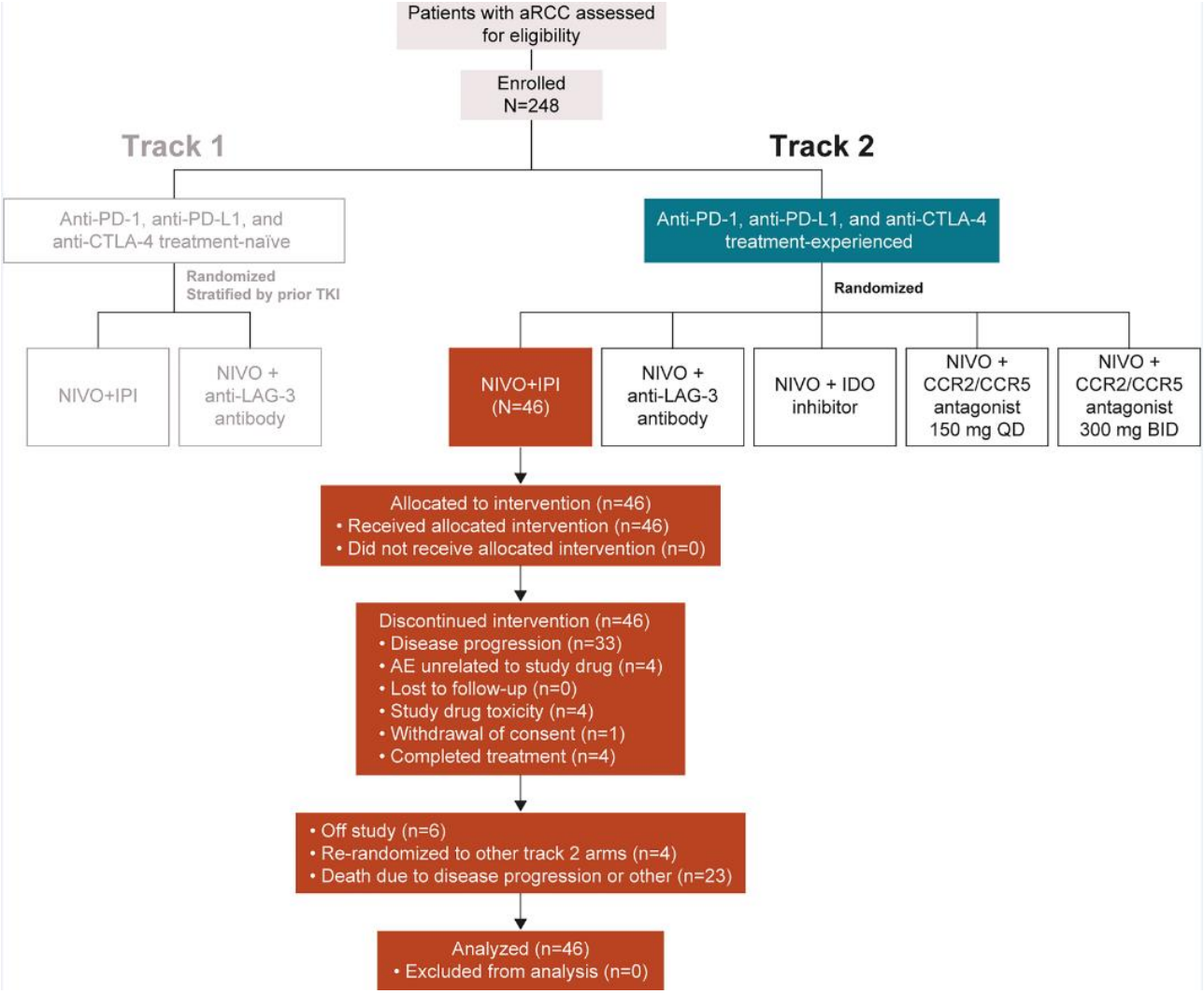
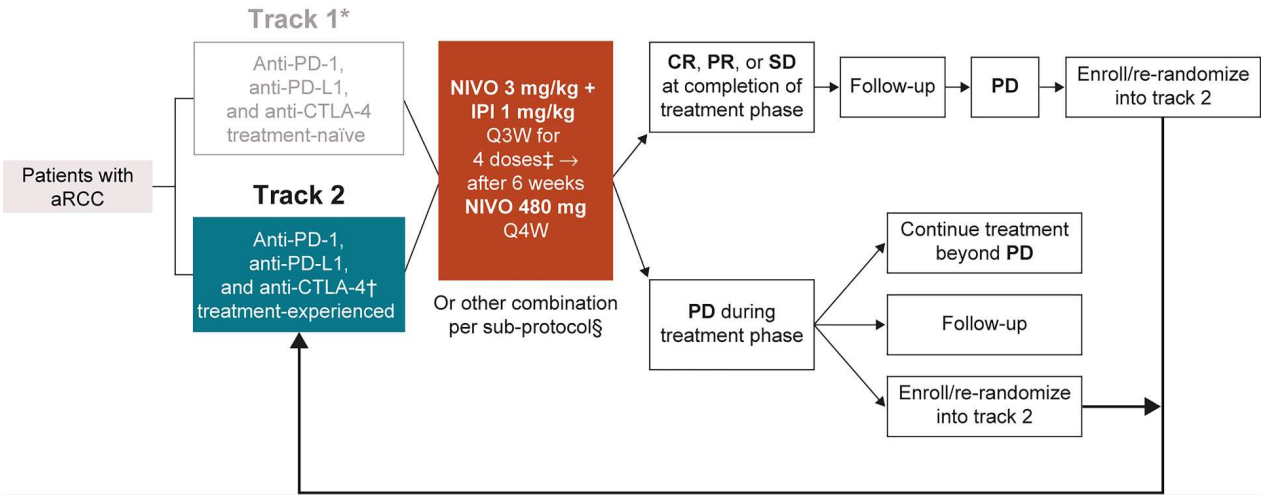
Supplemental Figure 1 CONSORT diagram and study flow



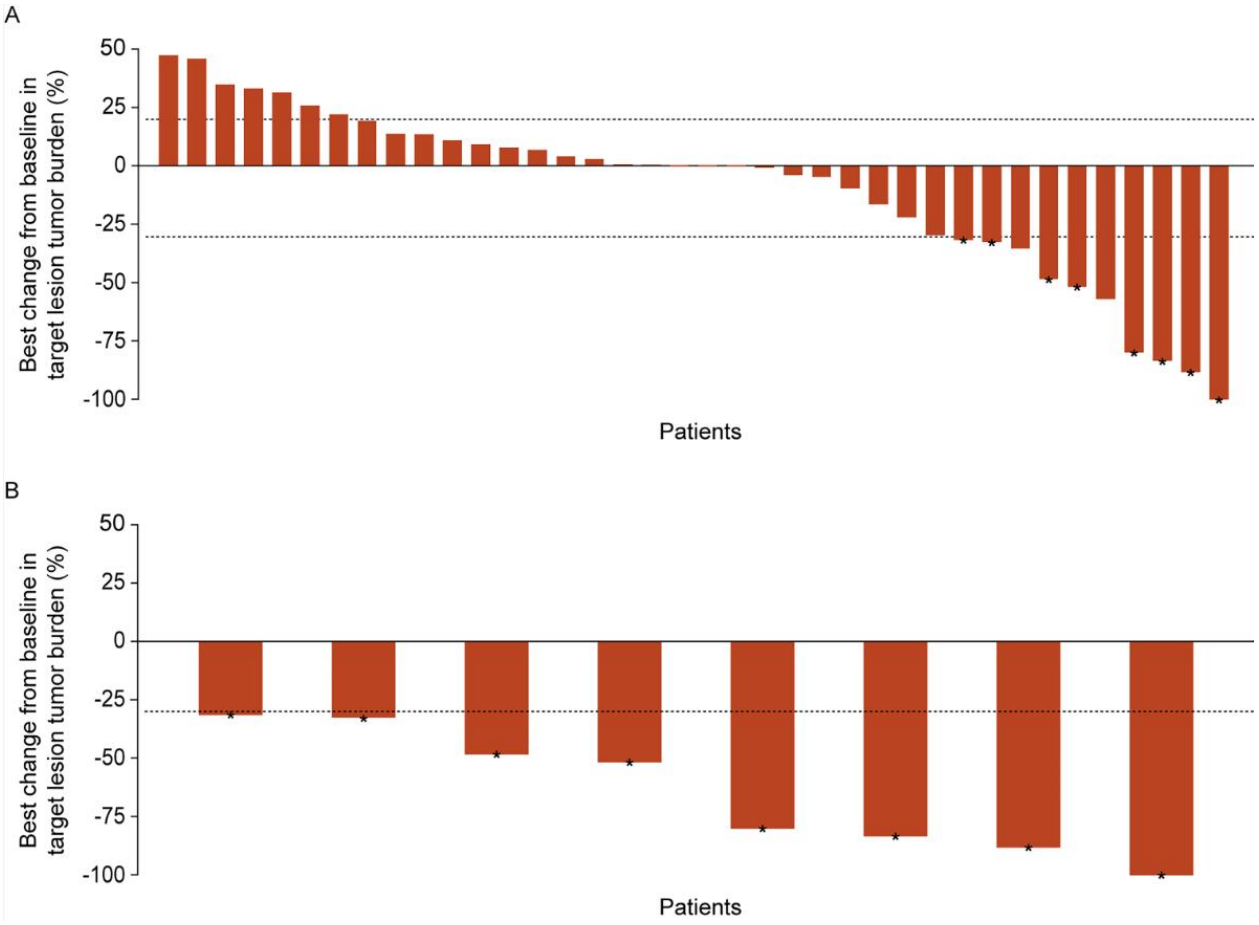
Patients were enrolled in one of two tracks. Patients who were anti-PD-1, anti-PD-L1, and anti-CTLA-4 treatment naïve were eligible for track 1 and were stratified according to whether they had prior TKI treatment. Patients who did have prior anti-PD-1, anti-PD-L1, or anti-CTLA-4 treatment (but not prior combination IO therapy) were assigned to track 2. Track 2 included five possible treatment arms, all of which included nivolumab in combination with another IO therapy. A total of 46 patients were enrolled in the nivolumab plus ipilimumab arm of track 2.
aRCC, advanced renal cell carcinoma; BID, twice daily; CCR2, C-C chemokine receptor type 2, CCR5, C-C chemokine receptor type 2; CTLA-4, cytotoxic T lymphocyte antigen-4; IDO, indolamine 2,3-dioxygenase; -3, lymphocyte-activation gene 3; IO, immuno-oncology; PD-1, programmed death 1; PD-L1, programmed death ligand 1; QD, once daily; TKI, tyrosine kinase inhibitor.

Supplemental Figure 2 FRACTION study design



Patients who received prior anti-PD-1, anti-PD-L1, or anti-CTLA-4 treatment (but not prior combination IO therapy) were enrolled in track 2 and randomized to nivolumab in combination with ipilimumab or to one of the FRACTION-RCC study treatment combinations. Patients who achieved CR, PR, or SD at the completion of the treatment phase entered safety follow-up. If those patients subsequently progressed during follow-up, they were eligible to be randomized to a different combination within track 2. Alternately, if patients experienced PD during the initial treatment phase, they could either be treated beyond progression, enter study follow-up, or be randomized into a different combination arm within track 2.
*Track 1 data not shown.
†If patients were previously treated with anti-CTLA-4 therapy in combination with anti-PD-1/PD-L therapy, they were not eligible for enrollment in the nivolumab plus ipilimumab arm of track 2 per the subprotocol.
‡Patients were permitted to discontinue treatment with ipilimumab for a number of pre-specified reasons. Please refer to the published protocol for a complete list of potential reasons. Patients who discontinued treatment with ipilimumab were permitted to remain on-study in track 2.
§Investigational combinations for which there is scientific rationale from prior phase 1 study data in this setting (multiple arms).
aRCC, advanced renal cell carcinoma; CR, complete response; CTLA-4, cytotoxic T lymphocyte antigen-4; IO, immuno-oncology; PD-1, programmed death 1; PD-L1, programmed death ligand 1; PR, partial response; Q×W, every × weeks; SD, stable disease.

Supplemental Figure 3 Best percent change from baseline in target lesion tumor burden (per investigator), all patients with ≥1 target lesion at baseline and ≥1 post-baseline tumor assessment (n=38) (panel A); best percent change from baseline in target lesion tumor burden (per investigator), all responders (n=8) (panel B)



Patients with a target lesion at baseline and at least one postbaseline tumor assessment. Best reduction is maximum reduction in sum of diameters of target lesions (negative value means true reduction, positive value means increase only observed over time).
Horizontal reference line indicates the 30% reduction consistent with a Response Evaluation Criteria in Solid Tumors v1.1 response.
Asterisks represent responders.

Supplemental Table 1 Baseline demographic and clinical characteristics

	Nivolumab plus ipilimumab (N = 46)
Age, median (range), years	60.5 (36.0-82.0)
Sex, male	37 (80.4)
Race, Caucasian	43 (93.5)
IMDC risk group*	
Favorable	11 (23.9)
Intermediate	28 (60.9)
Poor	6 (13.0)
Not reported	1 (2.2)
Stage of disease at study entry	
III	1 (2.2)
IV	44 (95.7)
Not reported	1 (2.2)
No. of organs with at least one lesion†	
1	3 (6.5)
2	11 (23.9)
3	7 (15.2)
4	8 (17.4)
≥5	17 (37.0)
Prior systemic therapy‡,§	45 (97.8)
Chemotherapy	4 (8.7)
Targeted therapy	41 (89.1)
TKI	37 (80.4)
Immunotherapy	46 (100.0)
Anti–PD-1 or anti–PD-L1	46 (100.0)
Other immunotherapy‖	19 (41.3)
Other prior therapies	4 (8.7)
No. of prior therapies‡,§	
0	1 (2.2)
1	10 (21.7)
2	12 (26.1)
3	10 (21.7)
≥4	13 (28.3)
Prior nephrectomy	
Yes	40 (87.0)
No	6 (13.0)

Data are n (%) unless indicated otherwise.

*At study entry/baseline.
†Includes both target and non-target lesions.
‡One patient in track 2 was rerandomized from track 1 and was immuno-oncology treatment-naïve at the time of enrollment; however, the patient did receive anti–PD(L)-1 therapy before track 2.
§Forty-five patients received treatment in the metastatic setting, and one patient received treatment in the adjuvant setting.
‖Other than anti-PD-1/anti-PD-L1 or anti-CTLA-4 therapies.
IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; PD-1, programmed cell death 1; PD-L1, programmed death ligand 1; TKI, tyrosine kinase inhibitor.

Supplemental Table 2 Best overall response on most recent prior immuno-oncology therapy

No. (%)	BOR on most recent prior IO therapy			
BOR on nivolumab plus ipilimumab	**Partial response**	**Stable disease**	**Progressive disease**	**Not reported**
Partial response	2 (4.3)	3 (6.5)	3 (6.5)	0
Stable disease	1 (2.2)	10 (21.7)	5 (10.9)	3 (6.5)
Partial response	2 (4.3)	7 (15.2)	5 (10.9)	0
Unable to determine	1 (2.2)	0	3 (6.5)	1 (2.2)

BOR, best overall response; IO, immuno-oncology.

Supplemental Table 3 Treatment-related adverse events

No. (%)	Nivolumab plus ipilimumab (N=46)	
	Any grade	**Grade 3–4**
All patients with a treatment-related AE*	36 (78.3)	13 (28.3)
Rash	10 (21.7)	1 (2.2)
Fatigue	9 (19.6)	1 (2.2)
Diarrhea	8 (17.4)	4 (8.7)
Nausea	7 (15.2)	0
Vomiting	4 (8.7)	1 (2.2)
Pruritus	7 (15.2)	0
Decreased appetite	5 (10.9)	0
Increased amylase	3 (6.5)	3 (6.5)
Increased lipase	3 (6.5)	3 (6.5)
All patients with a treatment-related serious AE†	5 (10.9)	3 (6.5)
All patients with a treatment-related AE leading to discontinuation	4 (8.7)	3 (6.5)

*Preferred terms included any-grade events in ≥10% of patients or grade 3–4 events in ≥5% of patients.
†Preferred terms were all n=1 and included Addison's disease, enterocolitis, fatigue, sialadenitis, sinusitis, increased amylase, increased lipase, and dyspnea.
Serious AEs were defined per protocol as any untoward medical occurrence that, at any dose, resulted in death, was life-threatening, required inpatient hospitalization or causes prolongation of existing hospitalization (some exceptions apply), resulted in persistent or significant disability/incapacity, may have jeopardized the patient, or may require intervention (eg, medical or surgical) to prevent another serious outcome.
AE, adverse event.

Supplemental Table 4 Treatment-related immune-mediated adverse events

	Nivolumab plus ipilimumab (N=46)	
	Any grade, n (%)	**Grade 3–4, n (%)**
Rash	13 (28.3)	1 (2.2)
Diarrhea/colitis	8 (17.4)	5 (10.9)
Hepatitis	4 (8.7)	1 (2.2)
Hypothyroidism	2 (4.3)	0
Nephritis and renal dysfunction	2 (4.3)	0
Diabetes mellitus	1 (2.2)	0
Hypophysitis	1 (2.2)	0
Adrenal insufficiency	1 (2.2)	0

Immune-mediated adverse events are those that may differ from or be more severe than adverse events caused by non-immunotherapies, and whose early recognition and management may mitigate severe toxicity; these can include subcategories of endocrine events (eg, adrenal disorders, diabetes, pituitary disorders, and thyroid disorders).