

Original Article

Efficacy and safety of subsequent molecular targeted therapy after immuno-checkpoint therapy, retrospective study of Japanese patients with metastatic renal cell carcinoma (AFTER I-O study)

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Abstract

Objectives: Guidelines for treatment of mRCC recommend nivolumab monotherapy (NIVO) for treated patients, and nivolumab plus ipilimumab combination therapy (NIVO+IPI) for untreated IMDC intermediate and poor-risk mRCC patients. Although molecular-targeted therapies (TTs) such as VEGFR-TKIs and mTORi are recommended as subsequent therapy after NIVO or NIVO+IPI, their efficacy and safety remain unclear.

Methods: Outcome of Japanese patients with mRCC who received TT after NIVO (CheckMate 025) or NIVO+IPI (CheckMate 214) were retrospectively analyzed. Primary endpoints were investigator-assessed ORR of the first TT after either NIVO or NIVO+IPI. Secondary endpoints included TFS, PFS, OS and safety of TTs.

Results: Twenty six patients in CheckMate 025 and 19 patients in CheckMate 214 from 20 centers in Japan were analyzed. As the first subsequent TT after NIVO or NIVO+IPI, axitinib was the most frequently treated regimen for both CheckMate 025 (54%) and CheckMate 214 (47%) patients. The ORRs of TT after NIVO and NIVO+IPI were 27 and 32% (all risks), and median PFSs were 8.9 and 16.3 months, respectively. During the treatment of first TT after either NIVO or NIVO+IPI, 98% of patients experienced treatment-related adverse events, including grade 3–4 events in 51% of patients, and no treatment-related deaths occurred.

Conclusions: TTs have favorable antitumor activity in patients with mRCC after ICI, possibly via changing the mechanism of action. Safety signals of TTs after ICI were similar to previous reports. These results indicate that sequential TTs after ICI may contribute for long survival benefit.

Key words: renal cell carcinoma, molecular targeted therapy, nivolumab, ipilimumab

Introduction

Molecular-targeted therapies (TTs) have been the standard therapy for metastatic renal cell carcinoma (mRCC) after cytokine era (1). Four vascular endothelial growth factors tyrosine kinase receptor inhibitors (VEGFR-TKIs), sorafenib, sunitinib, axitinib and pazopanib, and two mammalian targets of rapamycin inhibitors (mTORis), temsirolimus and everolimus, are approved as TTs for mRCC in Japan. Because all of the TTs have antiangiogenic effects, via inhibition of HIF-1 α generation driven by hypoxia, mechanism of action (MOA) for their antitumor activity lacks diversity. Benefit of sequential therapy of TTs was limited, especially among first-line VEGFR-TKI-resistant mRCC patients (2–6).

Immuno-checkpoint molecule inhibitors including anti-programmed death 1 (PD-1) antibody and anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibody, novel MOA for treatment of mRCC, emerged as promising treatment from the results of phase I studies (7–9). Immuno-checkpoint inhibitor (ICI) regimens, such as nivolumab monotherapy (NIVO) and nivolumab and ipilimumab combination therapy (NIVO+IPI), significantly improved overall survival of patients with mRCC in the randomized phase III studies, CheckMate 025 (10–12) and CheckMate 214 (13–15).

Results of these phase III studies prompted a drastic paradigm shift in mRCC treatment, namely the identification of new target molecules independent of anti-angiogenesis, such as PD-1 and CTLA-4, for mRCC treatment. Although ICI regimens became standard therapies for mRCC among recent guidelines (16–18), antiangiogenic TTs such as VEGFR-TKIs and mTORis, still play important role in mRCC treatment. Since 35% of CheckMate 025 patients and 20% of IMDC intermediate/poor risk CheckMate 214 patients were evaluated as PD for their BOR, and majority of patients discontinued ICI because of disease progression, efficacy and safety data of sequential therapy after ICI regimens are essential for determining the treatment strategies of mRCC.

TTs are recommended as subsequent therapy after discontinuation of NIVO and NIVO+IPI (16, 17). Reported efficacy and safety data of TTs after ICIs are generally favorable without new safety signals (19–29), but most of the reports were analyzed among several ICI regimens except for few reports (22, 28, 29), the impact of TTs after NIVO and NIVO+IPI remains unclear. Aim of this study is to clarify the benefit of TTs after discontinuation of NIVO or NIVO+IPI independently, by evaluating the efficacy and safety of first TT, after discontinuation of NIVO or NIVO+IPI, in patients with mRCC.

Patients and methods

“AFTER I-O Study” is a multicenter, retrospective, observational study conducted in Japan. Patients participated in CheckMate 025 or CheckMate 214, treated with TT as subsequent therapy before 31 March 2019, after discontinuation of NIVO or NIVO+IPI were analyzed. Primary endpoints were overall response rates (ORRs) of the first TT after discontinuation of NIVO or NIVO+IPI. Secondary endpoints included treatment-free survival (TFS), efficacy of TT after ICI discontinuation, such as progression-free survival (PFS), time to treatment failure (TTF), overall survival (OS) and safety. TFS was defined as time from last dose of NIVO or NIVO+IPI to first dose of TT after ICI discontinuation, and PFS was defined as time from first TT dose after ICI discontinuation to PD or death.

AFTER I-O study was approved by the independent ethics committees of each institution, and conducted according to Declaration of Helsinki and Ethical Guidelines for Medical and Health Research Involving Human Subjects. This study is registered with the University hospital Medical Information Network (UMIN), number UMIN000036063. This retrospective study used medical records for analysis; therefore, informed consent from patients was not required.

Statistical analyses

Unless otherwise specified, continuous variables were analyzed using Student's *t*-test or Mann–Whitney *U*-test for parametric and non-parametric data, respectively, and categorical variables were analyzed using chi-squared test. OS, PFS, TTF and TFS were estimated by the Kaplan–Meier method. Hazard ratios and corresponding 95% confidence intervals (CIs) for each treatment arm were determined using hierarchical Bayesian survival analysis and Cox's proportional-hazards model. Stepwise multivariate analysis was used to assess the significance of each BOR variable. SAS (SAS Institute Japan Ltd., version 9.4) was used for all analyses.

Results

Patients

The present study retrospectively analyzed 45 patients from 20 Japanese centers: 28 of 37 (76%) Japanese patients were treated with TT after NIVO in CheckMate 025 (11–12), and 19 of 38 (50%) Japanese patients (all risks) treated were treated with TT after NIVO+IPI in CheckMate 214 (15), before 31 March 2019. Since two patients from CheckMate 025 refused to participate in this study, data from 26 patients of CheckMate 025 and 19 patients of CheckMate 214, a total 45 patients, were analyzed in the present study. Patient characteristics at the first dose of TT treatment after ICI discontinuation are summarized in Table 1 (Patient characteristics for patients with intermediate/poor risks in CheckMate 214 are summarized in Supplementary Table S1). Patients received TTs as third- to fifth-line therapy in CheckMate 025, and second-line therapy in CheckMate 214 after ICI discontinuation. Although patients in CheckMate 025 had received prior therapy before NIVO, compared with patients in CheckMate 214, higher proportion of patients had ECOG PS 0 at the first dose of TT after ICI discontinuation. Overall, 23% of patients in CheckMate 025 and 32% of patients in CheckMate 214 patients discontinued ICI due to adverse events, and most patients discontinued ICI because of disease progression. Major metastatic sites were lung and lymph node. Median follow-up periods from treatment of first TT after ICI discontinuation to date of analysis or death were 22.1 and 20.3 months, for patients of CheckMate 025 and CheckMate 214, respectively. At the date of analysis, 11 patients of CheckMate 025 (42%) and 13 patients of CheckMate 214 (68%) were alive. As shown in Table 2, axitinib was the most commonly treated TT after both NIVO (54%) and NIVO+IPI (47%) discontinuation (TT regimens after ICI discontinuation among patients in CheckMate 214 with intermediate/poor risks are in Supplementary Table S2).

Efficacy

Primary endpoints, ORRs of the first TT were 27% after NIVO, and 32% after NIVO+IPI (all risks). Disease control rates (DCRs) were 89 and 84% (all risks), for TT after NIVO and NIVO+IPI, respectively (Table 3, ORR, BOR and DCR of TT

Table 1. Patient characteristics at first TT treatment after ICI discontinuation

		CheckMate 025		CheckMate 214	
				All risks	
		N = 26		N = 19	
Sex, n (%)	Male	17	(65)	17	(90)
	Female	9	(35)	2	(11)
Age, years	Median (range)	69.0	(40–83)	70.0	(45–82)
Regimens before ICI, n (%)	1	14	(54)		
	2	8	(31)		
	3	4	(15)		
TTF of ICI, months	Median (range)	9.4	(0.5–59.4)	6.2	(0.0–27.6)
Reason for ICI discontinuation, n (%)	Progression	20	(77)	13	(68)
	Adverse events	6	(23)	6	(32)
Surgery after ICI discontinuation, n (%)	Yes	1	(4)	3	(16)
	No	25	(96)	16	(84)
ECOG PS, n (%)	0	20	(77)	10	(53)
	1	4	(15)	5	(26)
	≥2	1	(4)	3	(16)
	Unknown	1	(4)	1	(5)
MSKCC risk classification at first subsequent TT after ICI, n (%)	Favorable	6	(23)		
	Intermediate	14	(54)		
	Poor	4	(15)		
	Unknown	2	(8)		
IMDC risk classification at first subsequent TT after ICI, n (%)	Favorable			1	(5)
	Intermediate			14	(74)
	Poor			3	(16)
	Unknown			1	(5)
Primary tumor	Yes	5	(19)	3	(16)
Metastatic site	Lung	19	(73)	12	(63)
	Bone	6	(23)	7	(37)
	Brain	2	(8)	1	(5)
	Liver	7	(27)	3	(16)
	Lymph node	9	(35)	8	(42)

TT, molecular targeted therapy; ICI, immune checkpoint inhibitor; TTF, time to treatment failure; ECOG PS, Eastern Cooperative Oncology Group performance status; MSKCC, Memorial Sloan Kettering Cancer Center; IMDC, International Metastatic RCC Database Consortium

Table 2. First TT after ICI discontinuation

		CheckMate 025		CheckMate 214	
				All risks	
		N = 26		N = 19	
TT, n (%)	Sunitinib	8	(31)	6	(32)
	Axitinib	14	(54)	9	(47)
	Pazopanib	1	(4)	3	(16)
	Everolimus	3	(12)	1	(5)

TT, molecular targeted therapy; ICI, immune checkpoint inhibitor

among patients in CheckMate 214 with intermediate/poor risks are in [Supplementary Table S3](#)). Furthermore, 84% (21/25) of patients who received TT after NIVO and 67% (12/18) of patients who received TT after NVO + IPI experienced tumor shrinkage

([Fig. 1](#)). Median PFS of TT after NIVO was 8.9 (95% CI: 6.9–21.0) months ([Fig. 2A](#)), and after NIVO+IPI was 16.3 [95% CI: 11.0-not reached (NR), all risks] months ([Fig. 2B](#), PFS among patients in CheckMate 214 with intermediate/poor risks is in [Supplementary Fig. S1](#)). Median OS of TT after NIVO was 29.5 (95% CI: 14.5-NR) months ([Fig. 3A](#)). Median OS of TT after NIVO+IPI was NR (95% CI: 18.1-NR), and estimated survival rates at 12, 24 and 36 months were 90, 68 and 54%, respectively ([Fig. 3B](#), OS among patients in CheckMate 214 with intermediate/poor risks is in [Supplementary Fig. S2](#)). At the time of analysis, two patients (8%) were still on first TT after NIVO, whereas most patients (73%) were treated with subsequent therapy after NIVO-TT failure ([Fig. 4A](#)) and three patients (16%, all risks) were still on first TT after NIVO+IPI, whereas most patients (75%, all risks) were treated with subsequent therapy after NIVO+IPI-TT failure ([Fig. 4B](#), TTF of ICI, TFS, TTF of TT therapy after ICI discontinuation among patients in CheckMate 214 with intermediate/poor risks are in [Supplementary Fig. S3](#)). Major regimens for second subsequent therapy after ICI discontinuation were VEGFR-TKIs ([Table 4](#), second

Table 3. Response rates of TT after ICI discontinuation

	CheckMate 025		CheckMate 214		Total		
	All risks						
	N = 26		N = 19		N = 45		
ORR, n (%)	7	(27)	6	(32)	13	(29)	
DCR, n (%)	23	(88)	16	(84)	39	(87)	
BOR, n (%)	CR	0	0	0	0		
	PR	7	(27)	6	(32)	13	(29)
	SD	16	(62)	10	(53)	26	(58)
	PD	2	(8)	2	(11)	4	(9)
	NE	1	(4)	1	(5)	2	(4)

TT, molecular targeted therapy; ICI, immune checkpoint inhibitor; ORR, overall response rate; DCR, disease control rate; BOR, best overall response; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable

Table 4. Second treatment after ICI discontinuation

		CheckMate 025		CheckMate 214	
		All risks			
		N = 19		N = 12	
Second treatment after ICI discontinuation, n (%)	Sunitinib	1	(5.3)	0	(0.0)
	Axitinib	3	(15.8)	5	(41.7)
	Pazopanib	6	(31.6)	5	(41.7)
	Everolimus	3	(15.8)	1	(8.3)
	Temsirolimus	4	(21.1)	0	(0.0)
	Nivolumab	2	(10.5)	1	(8.3)

ICI, immune checkpoint inhibitor

treatment after ICI discontinuation among patients in CheckMate 214 with intermediate/poor risks is in [Supplementary Table S4](#)). Median TFS was 0.95 month between NIVO and TT, and 2.46 months (all risks) between NIVO+IPI and TT ([Fig. 4A](#) and [Fig. 4AB](#)).

Safety

Almost all patients experienced treatment-related adverse events (TRAEs) while receiving TT after ICI, and 51% of patients experienced grade 3–4 events ([Table 5](#)). Major all-grade TRAEs were hypertension (n = 17, 38%), fatigue (n = 16, 36%), hoarseness (n = 15, 33%), and anorexia (n = 14, 31%). Major grade 3–4 TRAEs included hypertension, decreased neutrophil counts, elevated AST and elevated ALT (four patients each, 9%). Grade 4 TRAEs were decreased platelet count, vomiting and pneumonitis (one patient each, 2%). Among the grade 3–4 TRAEs, most were grade 3 and no treatment-related deaths.

Discussion

In the present study, we firstly demonstrate efficacy and safety of TT after NIVO+IPI in Japanese cohorts.

Auvray et al. reported the efficacy of VEGFR-TKIs after NIVO+IPI failure in 33 patients. ORR and DCR were 36 and 76%, respectively; median PFS was 8 months, and 12-months

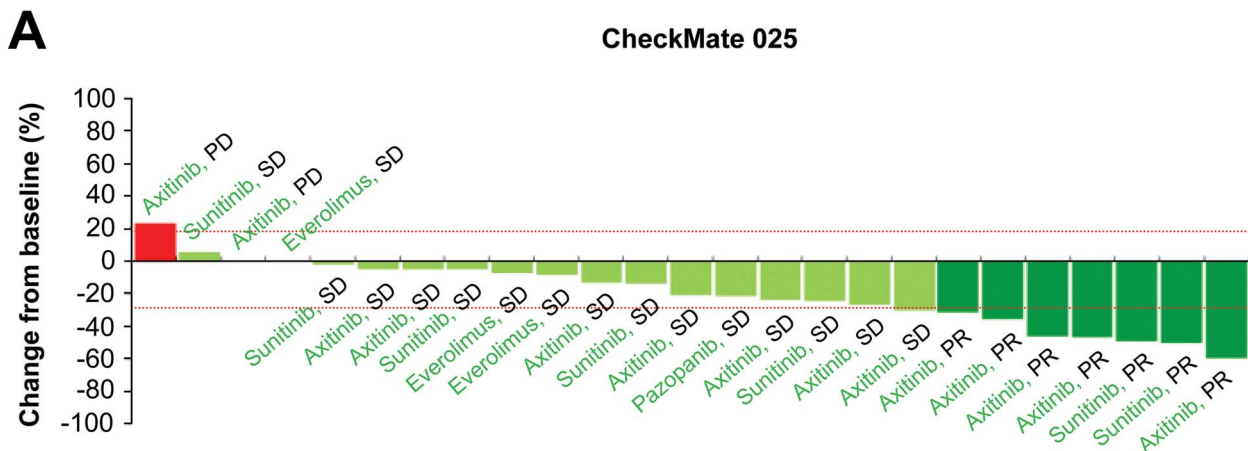
Table 5. Treatment-related adverse events of TT after ICI discontinuation occurring in >15% of patients

Event	n (%)			
	Any grade		Grade 3–4	
Hypertension	44	(98)	23	(51)
Fatigue	17	(38)	4	(9)
Hoarseness	16	(36)	1	(2)
Anorexia	15	(33)	0	(0)
Platelet count reduction	14	(31)	3	(7)
Proteinuria	13	(29)	4	(9)
Hypothyroidism	13	(29)	2	(4)
Palmar–plantar erythrodysesthesia syndrome	13	(29)	1	(2)
Diarrhea	12	(27)	1	(2)
Anemia	12	(27)	0	(0)
Creatinine elevation	11	(24)	1	(2)
Aspartate aminotransferase elevation	8	(18)	0	(0)
White blood cell count reduction	7	(16)	4	(9)
Lymphocyte count reduction	7	(16)	2	(4)

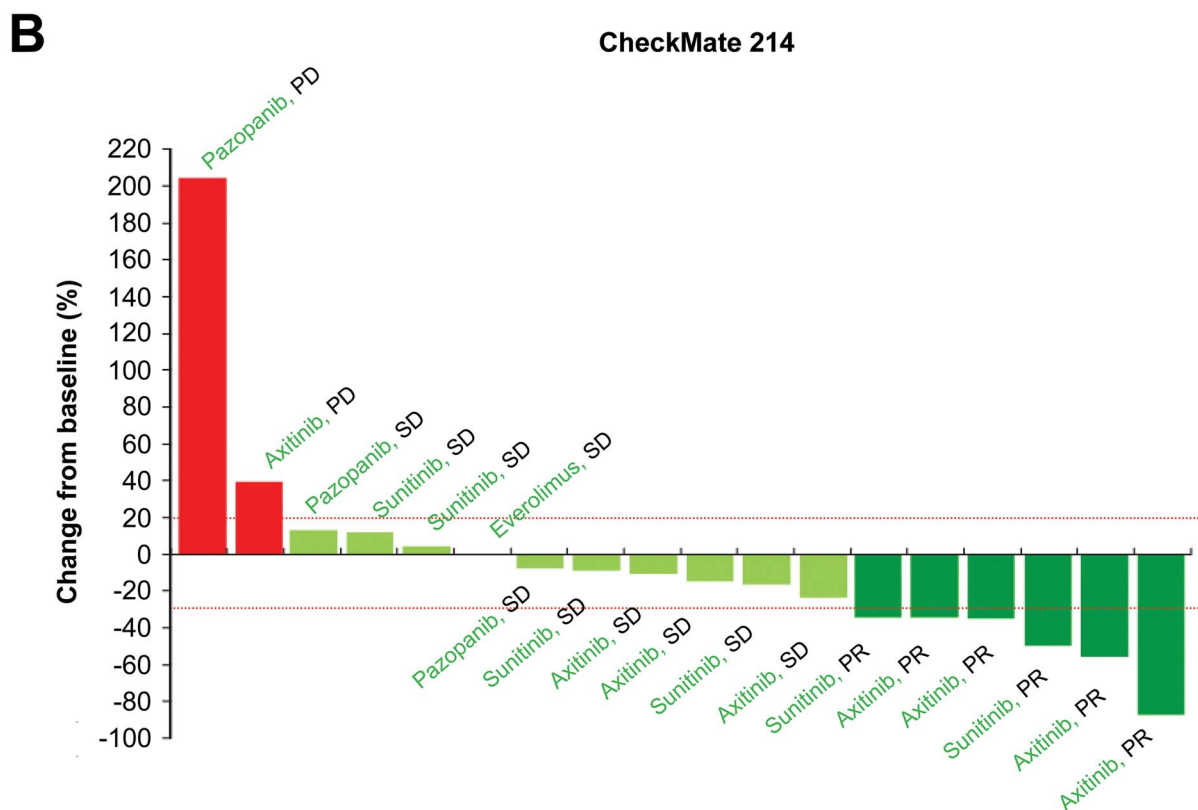
TT, molecular targeted therapy; ICI, immune checkpoint inhibitor

OS rate was 54%. 42% of patients developed grade 3–4 adverse events ([22](#)). Our results of 19 patients of CheckMate 214 ORR of TT after NIVO+IPI was 32% (all risks), and median PFS was 16.3 months (all risks). Although the number of the patients is small, the present data revealed comparable ORR and longer PFS, indicating similar efficacy for Japanese patients to those reported above. In dose titration study, similar PFS, 14.6 months, was achieved with axitinib in first-line setting ([30](#)), so that it is not of surprise for longer, 16.3 months median PFS, because these 19 patients were VEGFR-TKI-naïve.

Another promising data obtained in the present study is favorable results in TT after discontinuation of NIVO in CheckMate 025. TT was applied as third to fifth line of the treatments including at least one prior TT. In the similar setting, Numakura et al. reported PR for 3 patients, and SD for 6 patients out of 13 patients who failed NIVO ([28](#)). And Ishihara et al. reported efficacy of third-line axitinib after first-line VEGFR-TKI and second-line NIVO. ORR and DCR were 29 and 94%, respectively; median PFS was 12.8 months, and 1-year OS rate was 72% ([29](#)). No safety data are available for TT after NIVO discontinuation. It is difficult to compare these series of patients, but the result of the present study was comparable with the former study in terms of response. Median PFS of TT after discontinuation of NIVO, 8.9 months, was similar to that of second-line axitinib, 6.7 months, in AXIS trial ([31](#)), and longer than third-line dovitinib, 3.7 month, in GOLD trial ([32](#)), third-line everolimus, 4.0 month, in RECORD-1 trial ([33](#)). These data indicated that the prior treatment with ICI may not deteriorate the sensitivity to sequential TTs in patients with mRCC, resulting in moderate-to-favorable ORRs and excellent DCRs. As for safety of TTs after NIVO or NIVO+IPI, ratio of patients with all grade and grade 3–4 TRAEs



*One patient evaluated as NE for its BOR of TT after NIVO was excluded.



*One patient evaluated as NE for their BOR of TT after NIVO+IPI was excluded.

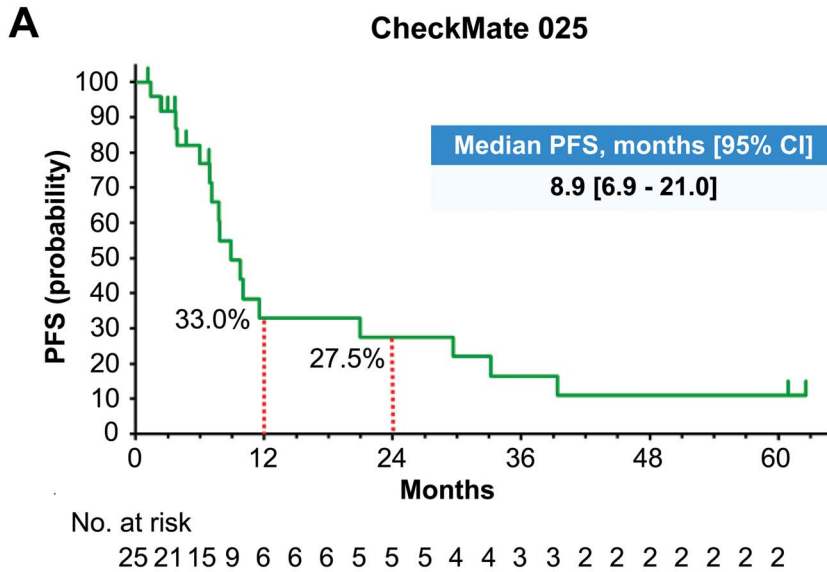
Figure 1. Best tumor burden shrinkage of TT after ICI discontinuation. 1A. CheckMate 025; 1B. CheckMate 214 (all risks) TT, molecular targeted therapy; ICI, immune checkpoint inhibitor; PD, progressive disease; SD, stable disease; PR, partial response; NE, not evaluable; BOR, best overall response; NIVO, nivolumab; IPI, ipilimumab.

was comparable to the recent reports (34–37), without any new safety signal.

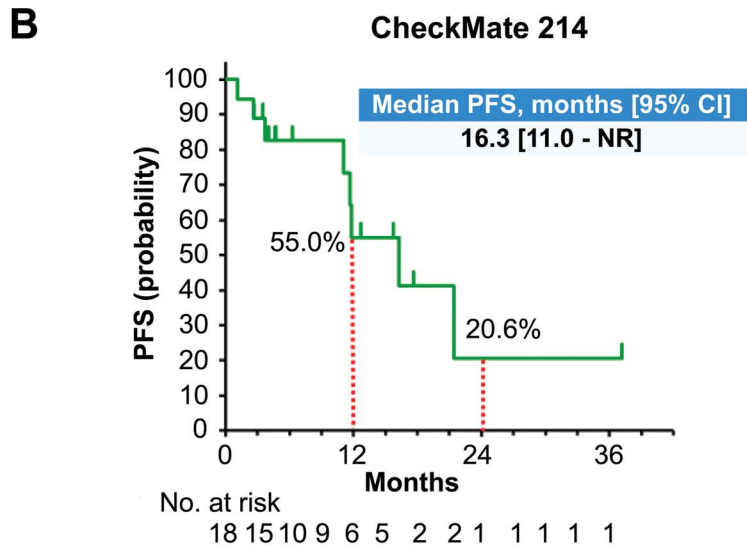
Costantini et al. (38), Harada et al. (39) and Kato et al. (40) have described the benefit of subsequent chemotherapy after ICI discontinuation for patients with non-small cell lung cancer (NSCLC). However, MOA to explain the benefit of chemotherapy after ICI discontinuation is not clear. Osa et al. detected NIVO binding to

T cells in blood at >20 weeks after treatment discontinuation in patients with NSCLC (41) so that residual NIVO binding to T cells after treatment discontinuation might improve the efficacy of the sequential chemotherapy. Presumably, such MOA might anticipate anti-angiogenic TTs in patients with mRCC.

Another possibility is that cessation period of exposure to VEGFR-TKI might restore their sensitivity. Indeed, numerically lower



*One patient evaluated as NE for its BOR of TT after NIVO was excluded.



*One patient evaluated as NE for their BOR of TT after NIVO+IPI was excluded.

Figure 2. PFS of TT after ICI discontinuation. 2A. CheckMate 025; 2B. CheckMate 214 PFS, progression-free survival; TT, molecular targeted therapy; ICI, immune checkpoint inhibitor; CI, confidence interval; NR, not reached; NE, not evaluable; NIVO, nivolumab; IPI, ipilimumab.

efficacy for consecutive VEGFR-TKIs after first-line ICI + VEGFR-TKI (ORR: 10%; median PFS: 5.6 months) (20) or VEGFR-TKI (ORR: 16.6–32%; median PFS: 7.14–9.3 months) (42–44) were reported. Previous reports suggested that sensitivity of EGFR-TKI might improve after EGFR-TKI-free interval for EGFR-TKI-resistant NSCLC patients (45). Treatment of NIVO may restore sensitivity of sequential TT by delivering VEGFR-TKI-free interval for RCC patients.

Both CheckMate 025 (10) and CheckMate 214 (13), pivotal phase III studies of NIVO and NIVO+IPI, reported a significant OS benefit with moderate improvement in PFS. The favorable efficacy of sequential TTs might possibly have contributed to the long survival

benefit in these phase III trials. Besides, quality of life in survival is also important, and to minimize deterioration of ordinary life including adverse events is crucial. It is more favorable to achieve stable of disease without any treatment following induction therapy. There appeared stable of disease or even shrinkage of metastases after discontinuation of ICI. Such TFS after ICI was reported by McDermott et al. (46), median TFS for ITT patients who discontinued NIVO+IPI in CheckMate 214 was 3.0 months. Median TFS after NIVO+IPI in this study, in which patients were the subgroup of CheckMate 214, was similar (2.46 months, Fig. 4B) to overall population (46), though between the two analysis, patient population slightly differs. In addition to obtain better QOL, treatment-free

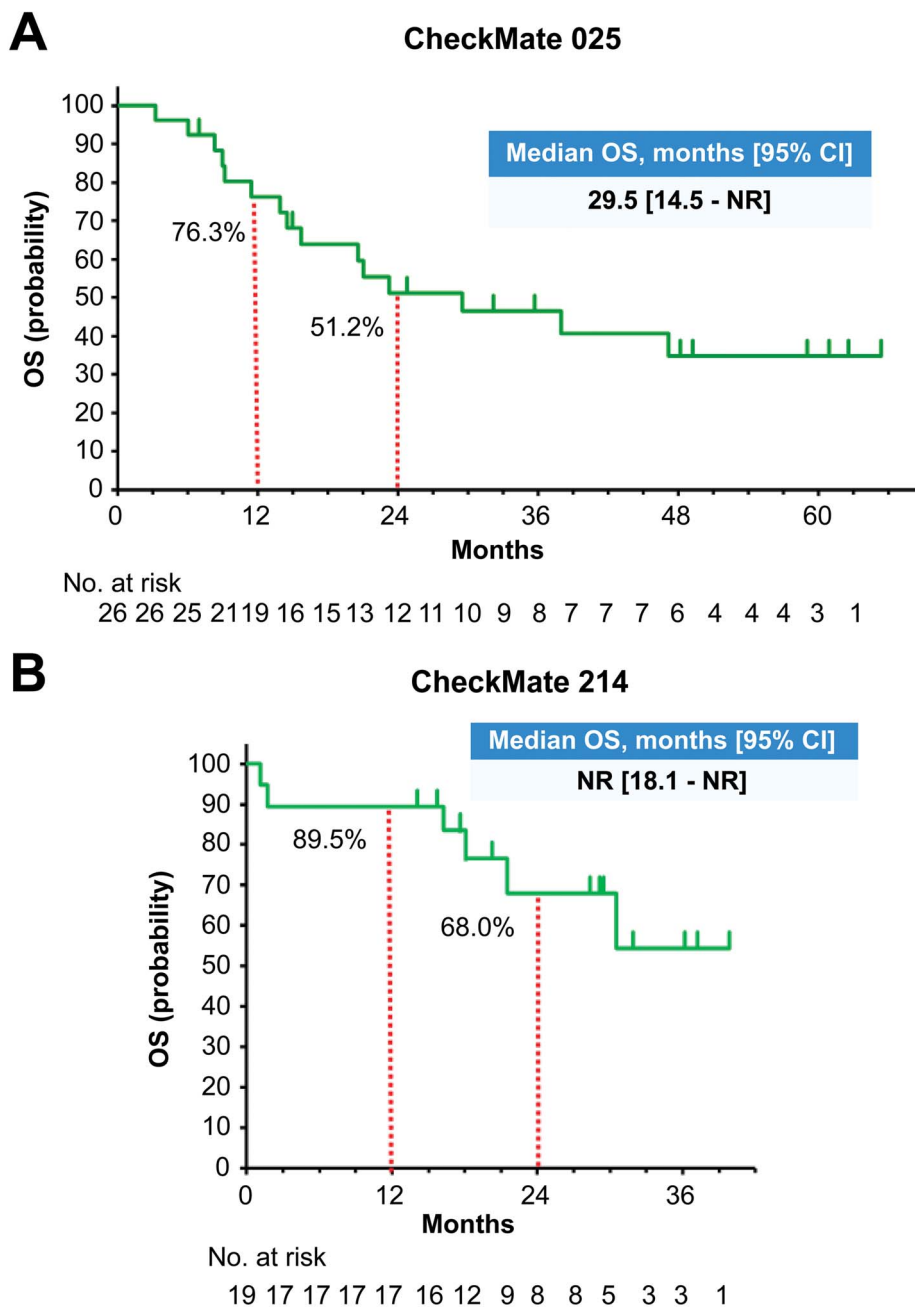


Figure 3. OS of TT after ICI discontinuation. 3A. CheckMate 025; 3B. CheckMate 214 OS, overall survival; TT, molecular targeted therapy; ICI, immune checkpoint inhibitor; CI, confidence interval; NR, not reached.

period may also contribute to restoration of sensitivity to VEGFR-TKI as mentioned above.

The AFTER I-O study had some limitations, which must be addressed. First, this was a retrospective study with a small sample size. In addition, the patients analyzed in this study were those who met the inclusion criteria of phase III trials; therefore, the results may not directly reflect the treatment in real-world settings. Lastly, the patients in CheckMate 025 or CheckMate 214 who continued to receive ICI or discontinued ICI without subsequent TT could not be analyzed in this study; this may have resulted in selection bias.

In conclusion, TTs as subsequent therapy after NIVO or NIVO+IPI discontinuation exhibits favorable antitumor activity for mRCC, possibly due to changes in the MOA between treatment lines. Safety signals of first subsequent TT after ICI regimens were similar to the previous reports, and no treatment-related deaths occurred. These results indicate that sequential TTs after ICI may contribute for long survival benefit in patients with mRCC, the nature of retrospective study, and the sample size was small. Prospective study is warranted to fully elucidate the favorable results, since the present study is retrospective study with small sample size.

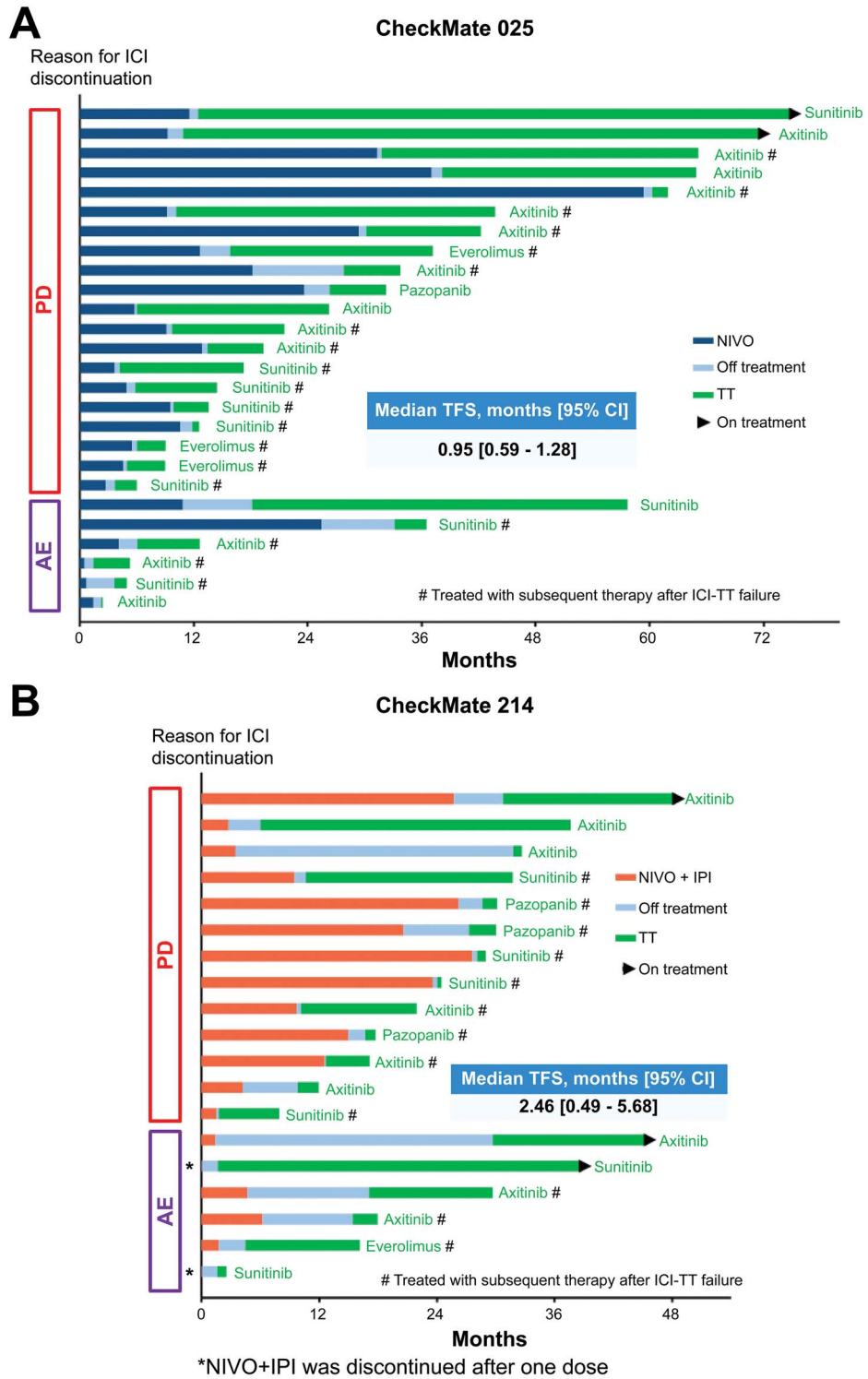


Figure 4. TTF of ICI, TFS, and TTF of TT therapy after ICI discontinuation. 4A: CheckMate 025; 4B: CheckMate 214 TTF, time to treatment failure; TFS, treatment-free survival; TT, molecular targeted therapy; ICI, immune checkpoint inhibitor; NIVO, nivolumab; IPI, ipilimumab; CI, confidence interval.

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Author contributions

Tomita, Kabu and Tajima have full access to all the data in the study and take responsibility for the integrity of the data and the

accuracy of the data analysis. Study concept and design: Tomita, Kabu, and Tajima. Provision of study materials or patients: Tomita, Kimura, Fukasawa, Numakura, Sugiyama, Yamana, Naito and Oya. Collection and assembly of data: Tomita, Kabu and Tajima.

Data analysis and interpretation: All authors.

Drafting of the manuscript: Tomita, Kabu and Tajima.

Critical revision of the manuscript for important intellectual content: All authors.

Final approval of manuscript: All authors.

Supplementary material

Supplementary Material can be found at *Japanese Journal of Clinical Oncology* online.

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Yohei Tajima is an employee of Ono Pharmaceutical Co., Ltd.

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Conflict of interest

Yoshihiko Tomita has received consultancy/advisory fees from Novartis, Ono Pharmaceutical Co., Ltd. and Taiho; and honoraria from Astellas, Bristol-Myers Squibb, Novartis and Ono Pharmaceutical Co., Ltd. Satoshi Fukasawa, Kazuyuki Numakura, Yutaka Sugiyama, Kazutoshi Yamana, Sei Naito do not have any conflict of interest to disclose.

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