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ORIGINAL ARTICLE

Outcomes of immune-checkpoint inhibitor rechallenge in metastatic clear-cell renal cell carcinoma: results from a global real-world evidence study

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Background: Immune-checkpoint inhibitors (ICIs), with or without tyrosine kinase inhibitors (TKIs), represent the backbone first-line treatment of patients (pts) with metastatic clear-cell renal cell carcinoma (mccRCC). Although multiple ICI-based regimens are approved in the metastatic setting, limited data exist on the efficacy of ICI rechallenge, particularly in relation to the timing and efficacy of rechallenge initiation.

Patients and methods: Using the TriNetX research database, we conducted a large-scale, retrospective analysis of pts with mccRCC treated with ≥2 lines of ICI-based therapy across major international centers (2016-2024). Kaplan—Meier analysis was used to estimate progression-free survival (PFS) and overall survival (OS) following ICI rechallenge. Propensity score matching (PSM) was applied to adjust for age, sex, disease stage, metastatic sites, prior ICI type, and treatment sequencing strategy.

Results: Among 6737 pts with mccRCC, 288 (4.3%) received ≥2 lines of ICI. Median age was 63.8 years. The most common first-line regimens were nivolumab (N) + cabozantinib (44.1%), N + ipilimumab (26.5%), pembrolizumab (P) + axitinib (20%), and P + lenvatinib (8.4%).

ICI rechallenge sequences were: N>N (47.6%), P>P (22.2%), N>P (17%), and P>N (13.2%). Median duration of prior ICI therapy was 19.5 months, and the median interval between ICI therapies was 8.91 months.

After a median follow-up of 19.3 months, median OS following ICI rechallenge was 33.2 months, and median PFS was 8.5 months.

Rechallenge ≥6 months after prior ICI was associated with improved PFS (8.8 versus 5.2 months) and OS (34.9 versus 19.4 months; $P = 0.014$). PSM confirmed that the OS benefit was independent of covariates ($P = 0.03$).

Conclusions: Our results outline opportunities for optimal ICI rechallenge, regardless of the prior immunotherapy administered. Improved outcomes with longer intervals (≥6 months) between treatments suggest timing is a key driver of efficacy and should be investigated in prospective trials as a surrogate marker of likely treatment response.

Key words: clear-cell renal cell carcinoma, immune-checkpoint inhibitors, real-world data, immunotherapy rechallenge

INTRODUCTION

Over the past decade, immune-checkpoint inhibitors (ICIs), alone or in combination with tyrosine kinase inhibitors (TKIs), have become the backbone of first-line treatment of patients with metastatic clear-cell renal cell carcinoma (mccRCC).[1-4]

However, their introduction as first-line regimens has brought uncertainty for therapeutic sequences: whether ICI rechallenge after failure can improve clinical outcomes—either immediately following prior ICI therapy, after a treatment interruption, or through reuse of the same agent in subsequent lines of therapy—remains largely unknown.[5,6]

To date, data from several phase II trials evaluating ICI rechallenge as monotherapy have yielded disappointing results.[7-9]

Two recent pivotal phase III trials—CONTACT-03[10] and TiNivo-2[11]—have evaluated ICI rechallenge in combination with TKIs in mccRCC. CONTACT-03 compared atezolizumab

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[a programmed death-ligand 1 (PD-L1) inhibitor] plus cabozantinib versus cabozantinib monotherapy in patients who had progressed on prior ICI-based therapy in the first or second line. TiNivo-2 assessed the addition of nivolumab (a PD-1 inhibitor) to tivozanib in the second- or third-line setting in patients who had progressed after ICI-based treatment or received a TKI 'wash-out' line. In both studies, ICI rechallenge failed to demonstrate a clinical benefit and was associated with increased toxicity compared with control arms.

Although these phase III trials were negative, they did not stratify outcomes by the interval between ICI treatments.

Few studies conducted in other tumor types have directly addressed the potential impact of the timing between ICI treatments.[12,13] The interval between ICI regimens, especially in cases with a bridging TKI-based therapy, may play a critical role in modulating the immune system, potentially reprogramming it toward a more inflamed, immunoresponsive tumor microenvironment.[14-18] Also, as the tumor and its antigenic repertoire evolve, so does the T cell clonal selection, laying foundation for effective ICI-triggered antitumor responses despite prior failure.[19-21]

This concept underscores the need for a deeper understanding of how temporal dynamics influence response to subsequent ICI therapy. We hypothesized that rechallenge after longer inter-treatment intervals might yield improved clinical outcomes.

To address this knowledge gap, we conducted a large-scale, retrospective analysis of patients with mccRCC who received at least two lines of ICI-based therapy across multiple international health care systems. Our aim was to characterize treatment patterns and assess survival outcomes following ICI rechallenge, with a specific focus on the role of inter-treatment timing.

PATIENTS AND METHODS

Patient selection and data collection

A global population-based retrospective study was carried out using the TriNetX research database for a large-scale search of patients with mccRCC who underwent two lines of ICIs in their therapeutic course at health care organizations (HCOs) collaborating through a TriNetX-mediated network.[22] TriNetX is a global federated health research platform that provides access to anonymized electronic medical records, including diagnoses, procedures, medications, laboratory, and genomic information from >135 million patients affected by different diseases, including cancer, internationally (USA, Europe, Asia-Pacific, Latin America regions).[22] The platform provides access to structured data including diagnoses, procedures, medications, laboratory values, and genomic information.

The study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[23]

Patients were initially identified using ICD-10-CM (International Classification of Diseases, Tenth Revision, Clinical Modification) codes for renal cell carcinoma. To specifically select patients with clear-cell histology, we used the histology filter available in TriNetX, which allows identification of patients based on structured pathology data and ICD for Oncology (ICD-O) coding where available. Additional inclusion criteria were age ≥18 years and evidence of at least two distinct courses of ICI-based therapy (monotherapy or combination) between January 2016 and April 2024.

ICI rechallenge was operationally defined as the initiation of a second ICI-containing regimen following a previous ICI-based treatment course, regardless of any intervening therapies.

A total of 143 global HCOs contributed to the dataset.

The main ICIs used for mccRCC, nivolumab, pembrolizumab, and ipilimumab, were considered in the study. Other ICIs were not included due to their more limited adoption in real-world practice at the time of data collection.

Statistical analyses

Descriptive statistics were used to summarize baseline clinical and demographic characteristics, reported as frequencies and percentages for categorical variables, and as medians with interquartile ranges (IQR), means, and standard deviations for continuous variables. Comparisons between groups were carried out using Fisher's exact test for categorical variables and Student's *t*-test for continuous variables, as appropriate. Non-parametric tests were not applied due to the limitations of the TriNetX platform.

Progression-free survival (PFS) and overall survival (OS) following ICI rechallenge were estimated using the Kaplan—Meier method, with time-to-event measured from the initiation of the second ICI regimen. Survival distributions were compared using the log-rank test.

To adjust for potential baseline imbalances and reduce confounding, propensity score matching (PSM) was carried out using a 1 : 1 nearest-neighbor algorithm without replacement, based on age, sex, stage at initial diagnosis, metastatic sites, and type of prior ICI. Matched analyses were conducted to evaluate the impact of ICI rechallenge timing, using prespecified intervals of <6 versus ≥6 months and <12 versus ≥12 months from discontinuation of the first ICI to initiation of the second.

These thresholds were traditionally used in evaluating treatment rechallenges in solid tumors[24] and are increasingly recognized as relevant in the context of immunotherapy.[25]

All statistical tests were two-sided, and a *P*-value <0.05 was considered statistically significant.

All analyses were conducted within the TriNetX platform environment (TriNetX, Cambridge, MA, USA) on 16 April 2025.

RESULTS

From a total of 6737 patients with mccRCC, 2773 were treated with ICIs and a cohort of 288 patients (10.4%) treated with ≥2 sequential ICIs between 2016 and 2024 was identified (Figure 1).

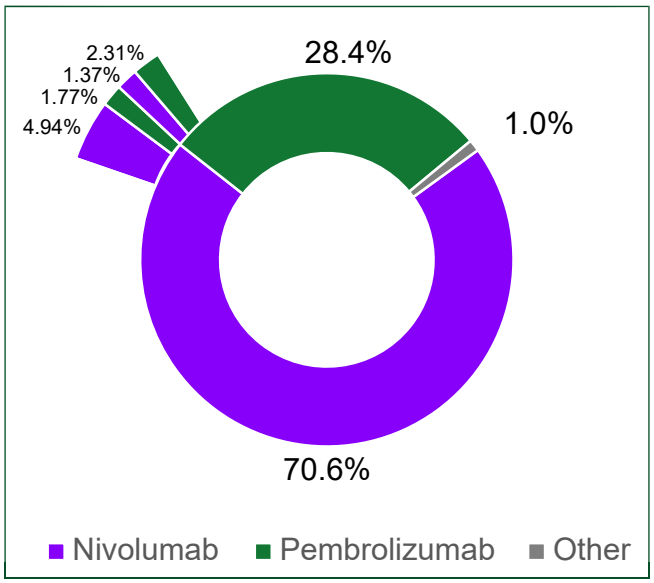

Figure 1. ICI sequencing in the analyzed population. In the sunburst diagram of the overall cohort of the analyzed patients treated with an ICI (2337 patients), the use of a second ICI occurred in 10.38% (288) of them. The most frequent rechallenge sequences were nivolumab followed by nivolumab (4.94%), pembrolizumab followed by pembrolizumab (2.31%), nivolumab followed by pembrolizumab (1.77%), and pembrolizumab followed by nivolumab (1.37%).
ICI, immune-checkpoint inhibitor.

Among them, 87 (30.0%) were female, and the median age at diagnosis was 63.8 years (range 30-90 years). At diagnosis, 63% had stage I-III disease, and 37% had stage IV. The most frequent metastatic sites were lymph nodes (64%) and lung (46%), followed by liver (38%), bone (24%) and brain (11%) (Table 1). Radical nephrectomy had been carried out in 38.7% of patients and 4.86% of patients presented a sarcomatoid component.

Of the 288 patients, 107 (37%) received the second ICI as direct sequence and 181 (63%) received intervening treatments between ICIs (Table 1).

The most common first-line therapies were nivolumab plus cabozantinib (44.1%), followed by nivolumab plus ipilimumab (26.5%), pembrolizumab plus axitinib (20%), and pembrolizumab plus lenvatinib (8.4%). The median duration on prior ICI treatment was 19.5 months (range 16-27.5 months) in the overall population.

The median interval from the end of prior ICI therapy to the start of ICI rechallenge was 8.91 months (range 3.0-44 months). Specifically, the median interval was 8.2 months (range 3.1-44 months) for patients initially treated with nivolumab ($n = 186$), and 9.9 months (range 3.2-24.6 months) for those treated with pembrolizumab ($n = 102$).

Regarding timing, 48 patients (16.7%) were rechallenged within $<$6 months of the prior ICI; 240 (83.3%) after $\geq$6 months; 140 (48.6%) within $<$12 months; and 148 (51.4%) after $\geq$12 months.

Regarding sequencing strategy, 37% of patients ($n = 107$) received ICI rechallenge immediately, whereas 63% ($n = 181$) had at least one intervening systemic therapy before rechallenge.

Table 1. Characteristics of the selected patients before starting rechallenge ICI.

Characteristic	*N* 288 (%)
Female sex	87 (30.03)
Median age at diagnosis, years [range]	63.8 [30-90]
Race	
White	199 (69.16)
Black	29 (9.9)
Asian	8 (2.68)
Unknown/Other	49 (16.89)
Stage at diagnosis	
I-III	181 (63)
IV	107 (37)
Site(s) of metastases	
Nodes	184 (64)
Bone	69 (24)
Lung	132 (46)
Liver	109 (38)
Brain	32 (11)
Previous radical nephrectomy	
Yes	111 (38.7)
No or not reported	177 (61.3)
Lines of ICIs	
Nivolumab → pembrolizumab	49 (17)
Pembrolizumab → pembrolizumab	64 (22.2)
Pembrolizumab → nivolumab	38 (13.2)
Nivolumab → nivolumab	137 (47.6)
Timing ICI rechallenge	
$<$6 months	48 (16.7)
$\geq$6 months	240 (83.3)
$<$12 months	140 (48.6)
$\geq$12 months	148 (51.4)
ICI sequencing strategy	
ICI after ICI directly	107 (37)
ICI rechallenging after other intervening systemic treatments	181 (63)

ICI, immune-checkpoint inhibitor.

The most frequent rechallenge sequences were nivolumab followed by nivolumab (47.6%), pembrolizumab followed by pembrolizumab (22.2%), nivolumab followed by pembrolizumab (17%), and pembrolizumab followed by nivolumab (13.2%).

After a median follow-up of 19.3 months, the median PFS following ICI rechallenge was 8.54 months (range 0-69.9 months), and the median OS was 33.2 months (range 6.4-72.3 months). Among patients with sarcomatoid features ($n = 14$), median OS was 35.1 months, with a median PFS of 6.56 months (range 2.00-23.78 months).

Patients treated with nivolumab followed by nivolumab ($n = 137$) had a median PFS of 8.0 months (range 0.03-69.9 months), whereas those receiving pembrolizumab after prior nivolumab ($n = 49$) had a median PFS of 7.0 months (range 0-11.8 months). For patients treated with pembrolizumab followed by pembrolizumab ($n = 64$), the median PFS was 7.4 months (range 1.08-13.8 months), whereas nivolumab rechallenge after pembrolizumab ($n = 38$) was associated with a median PFS of 9.2 months (range 0.66-38.8 months).

Median PFS following nivolumab plus ipilimumab ($n = 71$) was 7.9 months (range 0.1-55 months), compared with 8.5 months (range 0.3-69.9 months) observed with ICI–TKI combinations ($n = 217$) (Table 2)

Table 2. Rechallenge sequences and efficacy outcomes in the selected cohort.

Characteristic	*N* (%)
Most common first-line ICI regimens	
Nivolumab + cabozantinib	1223 (44.1)
Nivolumab + ipilimumab	735 (26.5)
Pembrolizumab + axitinib	555 (20.0)
Pembrolizumab + lenvatinib	233 (8.4)
Other(s)	27 (1.0)
Most frequent rechallenge sequences	
Nivolumab → nivolumab	137 (47.6)
Pembrolizumab → pembrolizumab	64 (22.2)
Nivolumab → pembrolizumab	49 (17.0)
Pembrolizumab → nivolumab	38 (13.2)
	Months
Median duration of prior ICI therapy (overall)	19.5
Median interval between ICI therapies (overall)	8.91
First-line nivolumab ($n = 186$)	8.2
First-line pembrolizumab ($n = 102$)	9.9
Median PFS across treatment subgroups	
Overall ($n = 288$)	8.54
Nivolumab → nivolumab ($n = 137$)	8.05
Nivolumab → pembrolizumab ($n = 49$)	7.0
Pembrolizumab → pembrolizumab ($n = 64$)	7.44
Pembrolizumab → nivolumab ($n = 38$)	9.21
PFS by first-line combination type	
Nivolumab + ipilimumab (n =71)	7.9
ICI + TKI combinations ($n = 217$)	8.55

ICI, immune-checkpoint inhibitor; TKI, tyrosine kinase inhibitor.

Patients rechallenged ≥6 months after prior ICI therapy had a median PFS of 8.8 months (range 0.3-69.9 months), compared with 5.2 months (range 0.2-31.4 months) in those rechallenged within <6 months. Similarly, patients rechallenged ≥12 months had a median PFS of 9.1 months (range 0.5-69.9 months), versus 7.2 months (range 0.4-42.3 months) in those rechallenged within <12 months.

Of note, median OS was significantly longer in patients rechallenged ≥6 months after prior ICI therapy compared with those rechallenged within <6 months (34.9 versus 19.4 months; $P = 0.014$) (Figure 2A). Although median OS was numerically higher for patients rechallenged ≥12 months after prior ICI, this difference did not reach statistical significance (34.9 versus 25.9 months; $P = 0.312$, log-rank test) (Figure 2B).

After PSM adjustment, the differences in OS in patients treated with a second ICI before and after 6 months from the previous ICI appeared independent of sex, age at the diagnosis, sites, stages, type of previous ICI, and the sequencing strategy of ICI rechallenge (direct versus post-intervening treatment) ($P = 0.03$) (Figure 3A-C).

DISCUSSION

In this large, real-world, retrospective cohort study of patients with mccRCC, we evaluated clinical outcomes associated with ICI rechallenge following prior ICI-based therapy. Compared with the broader cohort of mccRCC patients treated with ICIs in our database, we found that ICI rechallenge—although infrequent—was more commonly employed than initially expected, with 10.39% of patients receiving a second course of ICI-based treatment.

This relatively high percentage of rechallenge use likely reflects the limited availability of effective therapeutic options following progression on first-line ICI-containing regimens.[26] Notably, the majority of patients received rechallenge after a treatment-free interval, possibly because ICI rechallenge immediately following ICI failure remains less well-established than TKI-based strategies, both after IO—IO and most IO—TKI combinations.

Our findings suggest that PFS appeared to be broadly comparable across different ICI rechallenge sequences. As expected, switching agents within the same class and mechanism of action did not result in improved efficacy.

A further point of interest is the subgroup of patients with sarcomatoid features (4.9%, $n = 14$). Despite the known higher immunogenicity typically associated with this feature, their median OS (35.1 months) and PFS (6.6 months) after ICI rechallenge did not show a clear advantage over the overall cohort (median OS 33.2 months; PFS 8.5 months). Although these data are descriptive and limited by small numbers, they suggest that the benefit of ICI rechallenge in this subgroup may not be substantially enhanced.

Recognizing the negative results from two recent prospective randomized trials evaluating ICI rechallenge in clear-cell RCC,[10,11] our study instead focused on a less explored but potentially impactful variable: the interval between ICI exposures. This aspect was not explicitly addressed in these trials. In CONTACT-03, a key inclusion criterion was the use of an ICI in the immediately preceding line of therapy,[10] whereas in TiNivo-02, most patients (71%) had received an ICI as their most recent treatment.[11]

Building on these observations, a key finding of our analysis is the apparent influence of this interval on both PFS and OS. Patients who were rechallenged ≥6 months after the discontinuation of their prior ICI experienced significantly longer OS compared with those rechallenged within 6 months (34.9 versus 19.4 months; $P = 0.014$). Although the OS benefit was numerically greater in patients rechallenged after ≥12 months, this difference did not reach statistical significance (34.9 versus 25.9 months; $P = 0.312$), potentially due to limited statistical power or unmeasured confounding factors.

Notably, temporal association remained statistically significant after PSM adjustment ($P = 0.03$), further supporting the robustness of this association.

These findings support the hypothesis that the timing of ICI rechallenge—rather than the specific agent selected—may be a critical determinant of its efficacy.

This temporal effect may be biologically explained by the restoration of immune homeostasis, reduction of immune exhaustion, or resolution of immunotherapy-induced immune suppression. Following sustained

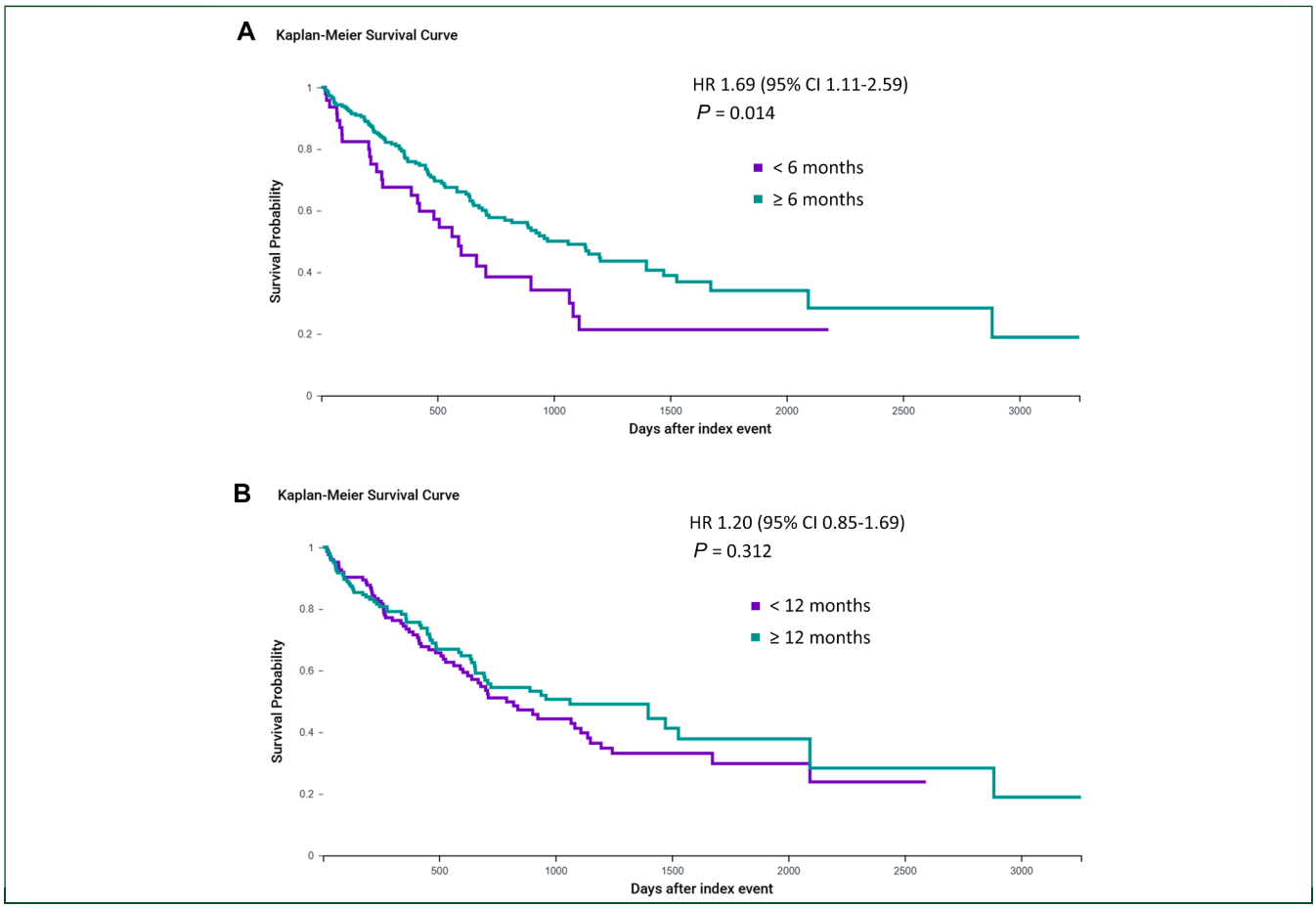

Figure 2. Kaplan—Meier curves showing overall survival (OS) according to the interval between ICI exposures. (A) Patients rechallenged ≥6 months after discontinuation of prior ICI had significantly longer OS compared with those rechallenged within 6 months (34.9 versus 19.4 months; $P = 0.014$). (B) Although OS was numerically longer in patients rechallenged ≥12 months after prior ICI compared with those rechallenged earlier, the difference was not statistically significant (34.9 versus 25.9 months; $P = 0.312$), potentially due to limited statistical power or unmeasured confounding factors.

PD-1/PD-L1 blockade, T-cell populations may experience functional exhaustion, decreased proliferative capacity, and upregulation of inhibitory receptors. Over time, discontinuation of ICI therapy allows partial recovery of T-cell function, restoration of antigen presentation, and recruitment of new immune clones, collectively enhancing sensitivity to subsequent checkpoint blockade.[19-21] Our results are supported by several studies that have shown that reactivation of T-cell function and changes in the tumor immune microenvironment may occur over time, which could enhance response to subsequent ICI exposure.[14-18]

These observations suggest that, despite negative results from recent clinical trials,[10,11,27] select patients may still derive meaningful benefit from ICI rechallenge, particularly when there are no other viable treatment options or suitable eligible trials and the rechallenge occurs after a substantial treatment-free interval.

Therefore, our findings indicate that the concept of ICI rechallenge should not be categorically dismissed. Instead, it may warrant further exploration in prospective clinical trials, with an emphasis on timing between immunotherapy exposures, rather than the specific ICI agents themselves.

Our study has several limitations inherent to its retrospective design. Firstly, the lack of randomization introduces potential for selection bias and confounding, although we attempted to mitigate this through PSM. Additionally, differences in clinical practice patterns, surveillance intensity, and data reporting across participating institutions may introduce heterogeneity. Diagnostic coding was based solely on ICD-10 classifications, and centralized pathological or radiological review was not feasible. Furthermore, important clinical data such as response depth, symptomatic benefit, and toxicity profiles were often unavailable. Finally, information regarding patient participation in clinical trials could not be assessed.

Despite these limitations, our study provides important real-world insights into ICI rechallenge in mccRCC. Our findings suggest that this strategy, although not universally effective, may provide clinical benefit in selected patients, especially when rechallenged after a treatment-free interval.

These results underscore the need for prospective clinical trials to clarify the role of timing in ICI rechallenge, identify predictive biomarkers, and optimize immunotherapy sequence strategies to maximize efficacy.

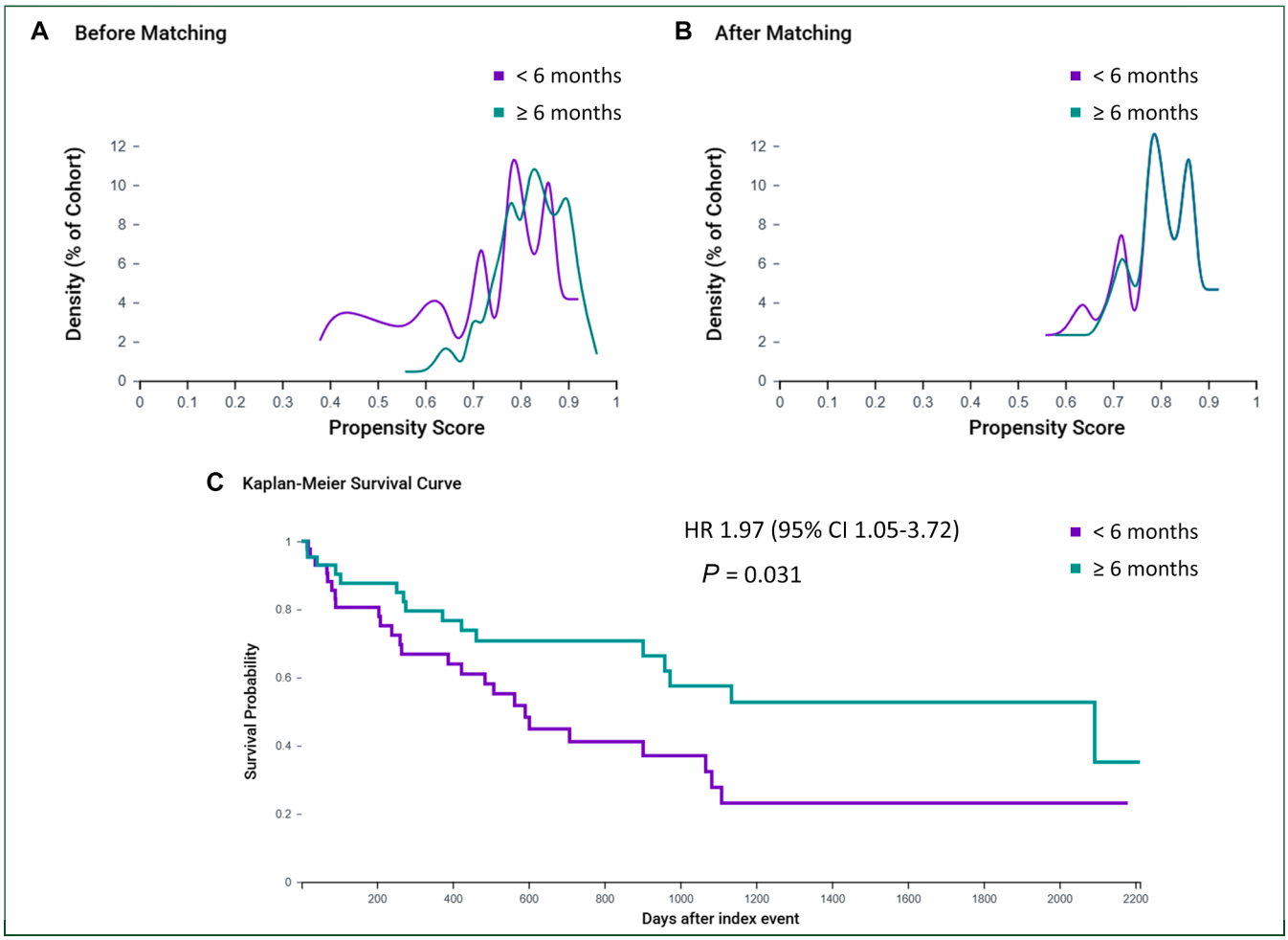

Figure 3. Propensity score matching and overall survival analysis. (A, B) Propensity score density functions before (A) and after matching (B) for patients rechallenged within <6 months (purple) versus ≥6 months (green) after ICI discontinuation. (C) Kaplan–Meier curve of overall survival (OS) comparing the two groups after propensity score matching (PSM).

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DISCLOSURE

The authors have declared no conflicts of interest.

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