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Eligibility Criteria and Endpoints in Metastatic Renal Cell Carcinoma Trials

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Abstract

Objectives: Treatments for metastatic renal cell carcinoma (mRCC) are often compared across trials, but trial eligibility criteria and endpoints differ. In an effort to better align trials, the Definition for the Assessment of Time to event Endpoints in CANcer trials (DATECAN) project published recommendations in 2015 to be used in mRCC clinical trial design. We analyzed mRCC trial criteria to determine if DATECAN's recommendations were followed.

Materials and Methods: We compared eligibility criteria across 29 phase 3 mRCC trials conducted between 2003 and 2019. We then evaluated endpoints used in 10 phase 3 trials activated between 2015 and 2019 to determine their compliance with DATECAN's recommendations.

Results: Among the 29 trials, performance status, renal function, and disease characteristics differed in terms of requirements and measures used. In terms of endpoints, the 10 trials did not entirely follow DATECAN's recommendations. In total, 7/10 trials' primary endpoint was progression-free survival (PFS) as recommended; 4/9 trials used PFS as an endpoint but did not publish their definition of PFS, and the 5 that did, included "death from any cause" instead of DATECAN's recommendation of "death from kidney cancer."

Conclusions: Key eligibility criteria were somewhat inconsistent across the phase 3 mRCC trials studied. Endpoints in the newer trials did not align with DATECAN's recommendations. Not only is greater standardization needed to facilitate meta-analyses and cross-trial comparisons, but as evident from lack of adherence to DATECAN's recommendations, greater promotion and adoption of recommendations are needed to better harmonize trial design.

Keywords

cancer; kidney; eligibility; endpoints; harmonization

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Randomized-controlled clinical trials are considered the “gold standard,” but performing multiple comparative trials is not always practical in a rapidly changing treatment landscape. Therefore, many clinicians rely on meta-analyses and cross-trial comparisons to understand how best to use a new drug or drug combination. Despite their convenience, cross-trial comparisons are not ideal because even trials in the same disease and patient population have different eligibility criteria and endpoints.¹

Until more recently, there have been limited efforts to harmonize trial eligibility criteria in metastatic renal cell carcinoma (mRCC), leading to significant heterogeneity across trials in terms of both eligibility and endpoints. Many have also argued for eligibility criteria to be adjusted to better represent the real-world patient population. During trial recruitment, ~25% of patients will screen fail, largely due to not meeting eligibility criteria.² These high screen failure rates not only cost time, money, and resources but may also ultimately affect the generalizability of trial results. A recent study by Heng et al³ compared mRCC patients who were and were not trial eligible and treated with a vascular endothelial growth factor receptor tyrosine kinase inhibitor. The response rate, median progression-free survival (mPFS), and median overall survival were all significantly lower in the trial-ineligible group, suggesting that trial results may not be directly generalizable to trial-ineligible patients. Few studies have analyzed the differences in eligibility criteria between trials and the suitability of specific criteria for the real-world mRCC patient population.

Efforts to improve trial design have been largely concentrated on harmonizing endpoints. In December 2015, Definition for the Assessment of Time-to-event Endpoints in CANcer trials (DATECAN)⁴ published recommendations for time to event endpoints (TEE) in mRCC trials. Expert consensus pinpointed and defined 2 TEEs for mRCC: kidney cancer-specific survival (death from RCC or protocol treatment) and PFS (death from RCC or local, regional, or metastatic progression). Before DATECAN’s TEE guidelines, TEEs varied significantly across trials, and many trials did not clearly define the “starting point” and the “event of interest” for their endpoints.⁵ DATECAN hoped that its recommendations would become standard practice for future clinical trials, but the preliminary effectiveness and uptake of its guidelines has not previously been assessed.

The primary aim of this study was to examine eligibility criteria across phase 3 mRCC trials. The secondary aim was to assess the effectiveness of DATECAN’s efforts towards trial harmonization by comparing trial endpoints to DATECAN’s endpoint recommendations.

MATERIALS AND METHODS

We reviewed randomized trials assessing chemotherapy, immunotherapy, and targeted therapies for mRCC that included at least 100 participants. We searched [ClinicalTrials.gov](https://clinicaltrials.gov) using the term “metastatic kidney cancer” and the filters: “phase 3 trials,” and “interventional studies.” To assess eligibility criteria across trials, we used trials that started between 2003 and 2019. To assess endpoints, we used trials that started between September 2015 and 2019.

We collected eligibility criteria and endpoints from [ClinicalTrials.gov](https://clinicaltrials.gov), trial protocols, and published articles from PubMed.

We also reviewed the DATECAN publications to establish endpoints suggested for mRCC trials.

RESULTS

In total, 48 phase 3 trials were reviewed for eligibility criteria, 29 of which were deemed eligible. Of 15 phase 3 trials evaluating endpoints, 10 were eligible (Fig. 1).

Eligibility Criteria

Five eligibility criteria were assessed with our methodology. The results are summarized in Table 1.

Performance Status (PS)

There is variation between trials using either Karnofsky Performance Status (KPS) (16/29, 57%) or Eastern Cooperative Oncology Group (ECOG) Performance Status (12/29, 43%) (Fig. 2A). Despite the difference in the mode of measurement, PS requirements were relatively consistent, within each line of treatment and across all treatments, with most trials (27/28, 96%) requiring roughly equivalent ECOG PS 0–1 and/or KPS ≥ 70%.

Renal Function

Discrepancies in how renal function was measured and cutoffs were observed across all lines of treatment. In total, 38% (11/29) of trials did not publish their renal function requirements. Of those that published, 50% (9/18) used only serum creatinine, 22% (4/18) used only calculated creatinine clearance, and 28% (5/18) used both (Fig. 2B). Both the required serum creatinine and creatinine clearance values varied across trials.

Presence of Central Nervous System (CNS) Metastases

In total, 38% (11/29) of trials excluded patients with CNS metastases, whereas 62% (18/29) permitted CNS metastases as long as they were treated and stable, inactive, and/or asymptomatic (Fig. 2C).

Measurable Disease According to Response Evaluation Criteria in Solid Tumors (RECIST) Guidelines

All but 1 trial (CALGB 90206) indicated that eligible patients must have measurable disease according to RECIST criteria (Fig. 2D), with variations again seen in the imaging modalities being used to assess disease.

Disease Progression

In total, 75% (9/12) of trials investigating second-line treatments indicated that eligible patients must have experienced disease progression, with variation in the definition of “progression” (Fig. 2F).

Endpoints

In total, 70% (7/10) of newer trials (after 2015) used the recommended PFS as their primary endpoint; of the 3 trials that did not, 2 included PFS as a secondary endpoint, and 1 did not include PFS as an endpoint at all. Only 6/9 trials using PFS as an endpoint published definitions for PFS, and their definitions did not align with DATECAN's recommended definition. All trials included "local, regional, or metastatic progression" as a progression event, following DATECAN, but they differed by including "death due to any cause" as a progression event, whereas DATECAN's definition limits it to "death due to RCC."

In total, 23/29 trials used Memorial Sloan-Kettering Cancer Center (MSKCC) criteria to stratify patients into favorable, intermediate, and poor risk subgroups for data analysis. Five trials used the International Metastatic RCC Database Consortium (IMDC) risk score for stratification, and 1 trial did not publish its stratification methods.

DISCUSSION

Key eligibility criteria and endpoint definitions were somewhat inconsistent across the phase 3 mRCC trials we evaluated, suggesting a need for more consistency in trial design. Developing a uniform set of eligibility criteria for trials studying similar disease states and treatments and ensuring these criteria are applicable to the target population will be important as new treatments continue to be evaluated developed in mRCC.

The ECOG PS and Karnofsky PS are two of the most widely used methods to assess functional status. We found variability in which scales were being used. ECOG has fewer categories, while the KPS (which is used in both MSKCC and IMDC criteria) has more, but generally the correlation between the two is quite good. One approach to consider in the context of clinical trials is to provide both scales so physicians can use the scale with which they are the most comfortable.

Another key criterion that differed across trials was renal function. Unlike PS, it is difficult to convert between serum creatinine and creatinine clearance without patient specifics, such as age and weight. Currently, national renal organizations recommend using estimated glomerular filtration rate from the Cockcroft-Gault equation or the Modification of Diet in Renal Disease Study equation. An estimated glomerular filtration rate more accurately reflects physiological status of patients compared with a static creatinine measurement. It is a universal measurement independent of US or SI units, and would be preferable for consistency across clinical trials. As well as differing in mode of measurement, trials differed in renal function cutoffs. Differences in renal function may affect trial results; for example, patients with chronic renal dysfunction may have shorter survival.³⁵ Thus, trials requiring better renal function may generate better results. In total, 3/4 trials requiring a higher creatinine clearance were newer immunotherapy trials, possibly because of concern that immunotherapies may cause immune-mediated renal injury.³⁶ However, we now know that renal side effects are not that common,³⁶ so there may be an argument for decreasing the renal function cutoffs for immunotherapy trials. Some also suggest loosening or omitting renal function criteria altogether from RCC trials if study agents are not renally metabolized, thus expanding access to clinical trials for RCC patients.³⁵

The 29 mRCC trials also differed in whether or not they considered patients with CNS metastases as trial eligible. Over one third of the trials disallowed CNS metastases (Fig. 2C). When comparing older and newer trials, 70% (7/10) of trials started before 2009 excluded patients with CNS metastases, whereas only 20% (4/20) of trials started in 2009 or later excluded, CNS metastases. Interestingly it has been shown that patients with stable CNS metastases perform similarly to those without; and it is rare for most treatments to cause CNS side effects.³⁷ Furthermore, CNS metastases is one of the most common reasons for cancer trial ineligibility.³ Because, ~3.5% to 17% of RCC patients develop CNS metastases, and if treated locally, do well with systemic therapy, they should ideally not be excluded from trials.³⁸

We also observed that all but 1 trial required patients to have measurable disease according to different versions of the RECIST criteria and with different measurement techniques (Figs. 2D, E). Measurable disease is required for trials to evaluate PFS, but the difference in criteria between RECIST 1.0 and 1.1 is that 1.1 accepts patients with smaller lesions and possibly lower cancer burden. This makes it harder to compare older and newer trials because the latter accepts patients with smaller lesions and likely lower cancer burden.^{39,40} However, these criteria are updated over time, so there will always be such variability when comparing older and newer trials.

The different measurement techniques between trials also presents an obstacle to trial harmonization and cross-trial comparisons, as a physical examination, computed tomography (CT) and magnetic resonance imaging (MRI) all present different levels of specificity, sensitivity, and accuracy.⁴¹ Both RECIST 1.0 and 1.1 recommend CT as the preferred measurement technique.^{39,40} However, over half of the trials did not specify a measurement technique, and the rest required a mix of measurement by clinical caliper, CT and MRI, possibly leading to trials defining “measurable disease” slightly differently and therefore possibly recruiting slightly different patient populations.

Trials’ criteria for disease progression shared similar inconsistencies as criteria for measurable disease, with some using RECIST criteria, while others accepting clinical progression, and many not specifying type of progression (Fig. 2F). Mandating patients to have progressed radiologically on previous treatment presents an obstacle for mRCC patients, as sometimes, there is a gap between radiologic progression and clinical progression. Radiologic imaging can show minor increases in lesion size such that the patient is not considered to have “progressive disease” by RECIST criteria, but conversely, the patient can experience a significant increase in cancer symptoms, thus denoting clinical progression. Off-trial, those experiencing symptoms without clear radiologic progression would most likely switch to a new treatment.⁴² However, their trial options would be limited, as many trials require radiologic progression. Loosening trial criteria to accept patients who progress clinically on their previous treatment, such as what the INTORSECT trial has done,²⁹ will likely provide more trial options for mRCC patients and increase trial accrual. This is the case in other cancers. For example, patients entering trials of advanced prostate cancer may have progressed radiologically, clinically, or by serum prostate specific antigen criteria (PSA). Patients who progress by PSA criteria alone can be often stratified for primary endpoint analyses.

Beyond the 5-key eligibility criteria that were analyzed in this study, other eligibility criteria, such as bone marrow function, liver function, and absence of other clinically serious medical conditions, were largely consistent across trials. Bloodwork parameters, such as hemoglobin 9.0 g/dL, neutrophils 1500/mm³, platelets 100,000/μL were similar, as was exclusion of patients with active autoimmune disease, with immunodeficiencies, or on systemic steroids, for immunotherapy trials due to the risk of immune-mediated adverse events.

As well as harmonizing eligibility criteria, endpoints must also be harmonized. None of the new trials started after September 2015 completely followed DATECAN's recommendations for defining PFS. DATECAN's definition of PFS included 2 events as follows: (1) "death due to RCC"; (2) "local, regional, or metastatic progression."⁴ All trials followed event 2, but for event 1, all used the event "death due to any cause" instead of "death due to RCC" (Table 2). This failure to apply DATECAN's recommendations may be due partly to the difficulty in ascertaining the exact cause of death, especially in older patients who are increasingly likely to die from conditions other than cancer or with nonspecific deterioration in health.⁴³ As the average age of patients diagnosed with kidney cancer is 64,³⁸ the reasons for their deaths may be challenging and both time and resource consuming to determine. For example, pulmonary embolism (PE) is a common manifestation of RCC, so if a patient dies of a PE, would a physician record it as "death due to PE" or "death due to RCC?"

Nevertheless, consistent endpoint and eligibility criteria are critical to interpreting study results. We found that 28/29 trials published the criteria they used to stratify patients into prognostic subgroups for analysis, with 23 trials using MSKCC criteria and 5 newer trials (CheckMate 9ER, COSMIC-313, KEYNOTE-679, PDIGREE, and TIVO-3) using the IMDC risk score. When analyzing trial results using MSKCC subgroups, the older trials of angiogenesis inhibitors showed less differences CNS metastases between MSKCC subgroups, whereas the newer immunotherapy trials revealed that the immunotherapy treatments may be more efficacious in the intermediate/poor risk subgroups.¹³ Because of this difference in efficacy between MSKCC subgroups in immunotherapy trials, studies with higher proportions of intermediate/poor risk patients may generate better results; however, because studies stratify and report their population composition consistently, readers can take that into account when comparing results across trials. In the more recent trials of immunotherapy plus angiogenesis inhibitors, the impact of MSKCC subgroups may be slightly less given that both the KEYNOTE 426 trial and the JAVELIN Renal 101 trial no difference in outcomes according to the MSKCC subgroups.^{18,19} Regardless, adhering to consistent patient stratification and reporting will continue to be integral to facilitating interpretation of study results.

As we look ahead, ensuring harmonization across trials in both trial eligibility criteria and key endpoints may help to significantly expedite drug development and our fundamental understanding of this disease.

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FIGURE 1.
Consort diagram of eligible trials.

FIGURE 2.

Comparison of Key Eligibility Criteria Used in mRCC Trials. A. Performance status. B. Renal function. C. Brain metastases. D. Measurable disease. E. Method of disease assessment. F. Progression required for trial entry. CrCl indicates creatinine clearance; CT, computed tomography; ECOG, European Cooperative Oncology Group; KPS, Karnofsky Performance Score; MRI, magnetic resonance imaging; RECIST, response evaluation criteria in solid tumors.

TABLE 1.

Eligibility Criteria in mRCC Trials (n = 29)

Trial Identifier Investigated	Treatments	PS	Renal Function	Presence of CNS Metastases	Measurable Disease	Progressed on Last Treatment	Investigators
1st line							
ARCC		KPS 60%	Serum 1.5×ULN	Not permitted unless treated and stable, no corticosteroids	Required (RECIST 1.0)	NA	Hudes et al ⁶
NCT00065468							
	Temsirolimus vs. Temsirolimus + IFN-α vs. IFN-α						
CALGB 90206		KPS 70%	Serum 1.5×ULN	Not permitted	Not required	NA	Rini et al ⁷
NCT00072046							
	Bevacizumab + IFN-α vs. IFN-α						
Sunitinib vs. IFN-α		ECOG 0-1	NI	Not permitted	Required (RECIST 1.0)	NA	Motzer et al ⁸
NCT00083889							
	Sunitinib vs. IFN-α-2a						
COMPARZ		KPS 70%	CrCl 30mL/min	Not permitted unless treated and stable	Required (RECIST 1.0, CT/MRI)	NA	Motzer et al ⁹
NCT00720941							
	Pazopanib vs. Sunitinib						
INTORACT		KPS 70%	Serum 1.5×ULN	Not permitted	Required (RECIST 1.0, CT/MRI)	NA	Rini et al ¹⁰
NCT00631371							
	Bevacizumab + Temsirolimus vs. IFN-α						
SWITCH		ECOG 0-1	Serum 2.0×ULN	Not permitted unless asymptomatic or stable	Required (RECIST 1.0, CT/MRI)	NA	Eichelberg et al ¹¹
NCT00732914							
	Sunitinib-sorafenib vs. Sorafenib-sunitinib						
Cross-J-RCC		ECOG 0-1	Serum 1.5×ULN	Not permitted unless asymptomatic, no corticosteroids	Required (RECIST 1.1)	NA	Tomita et al ¹²
NCT01481870							
	Sorafenib-sunitinib vs. Sunitinib-sorafenib						
CheckMate 214		KPS 70%	Serum 1.5×ULN CrCl 40 mL/min	Not permitted	Required (RECIST 1.1)	NA	Motzer et al ¹³
NCT02231749							
	Nivolumab + Ipilimumab vs. Sunitinib						

Trial Identifier Investigated	Treatments	PS		Renal Function		Presence of CNS Metastases		Measurable Disease	Progressed on Last Treatment	Investigators
		KPS	70%	Serum	2.0×ULN	Not permitted unless asymptomatic or stable	Required (RECIST 1.1, CT/MRI)			
SWITCH-II NCT01613846	Sorafenib-pazopanib vs. Pazopanib-sorafenib								NA	Retz et al ¹⁴
CheckMate 9ER NCT03141177		NI		NI		Not permitted unless treated and stable	NI		NA	Choueiri et al ¹⁵
Nivolumab + Cabozantinib vs. Sunitinib										
KEYNOTE-679 NCT03260894		KPS	70%	Serum	1.5×ULN CrCl 30 mL/min	Not permitted unless inactive	Required (RECIST 1.1)		NA	Jones et al ¹⁶
Pembrolizumab + Epacadostat vs. Sunitinib or Pazopanib										
CLEAR NCT02811861		KPS	70%		NI	Not permitted unless treated and stable, no corticosteroids	Required (RECIST 1.1)		NA	Grunwald et al ¹⁷
Lenvatinib + Everolimus vs. Lenvatinib + Pembrolizumab vs. Sunitinib										
KEYNOTE-426 NCT02853331		KPS	70%		NI	Not permitted unless inactive	Required (RECIST 1.1)		NA	Rini et al ¹⁸
Pembrolizumab + Axitinib vs. Sunitinib										
JAVELIN Renal 101 NCT02684006		ECOG	0–1	CrCl	50 mL/min	Not permitted unless inactive	Required (RECIST 1.1)		NA	Motzer et al ¹⁹
Avelumab + Axitinib vs. Sunitinib										
Benpegaldesleukin + Nivolumab NCT03729245		KPS	70%		NI	Not permitted unless treated and stable	Required (RECIST 1.1)		NA	Tannir et al ²⁰
Benpegaldesleukin + Nivolumab vs. Sunitinib or Cabozantinib										
COSMIC-313 NCT03937219		KPS	70%		NI	Not permitted unless inactive	Required (RECIST 1.1)		NA	Bjarnason et al ²¹
Cabozantinib + Nivolumab + Ipilimumab vs. Nivolumab + Ipilimumab										
PDIGREE		KPS	70%	CrCl	30 mL/min	Not permitted unless asymptomatic and stable	Required (RECIST 1.1)		NA	Zhang et al ²²

Trial Identifier	Treatments Investigated	PS	Renal Function	Presence of CNS Metastases	Measurable Disease	Progressed on Last Treatment	Investigators
	NCT03793166 Nivolumab + Ipilimumab followed by Nivolumab alone vs. Cabozantinib						
	1st or 2nd lines						
	VEG105192	ECOG 0-1	CrCl 30 mL/min	Not permitted	Required (RECIST 1.0)	NI	Sternberg et al ²³
	NCT00334282 Pazopanib vs. Placebo						
	TIVO-1	ECOG 0-1	Serum 2.0xULN	Not permitted unless treated and stable	Required (RECIST 1.0)	NI	Motzer et al ²⁴
	NCT01030783 Tivozanib vs. Sorafenib						
	Axitinib	ECOG 0-1	NI	Not permitted	Required (RECIST 1.0)	Radiologic PD (RECIST 1.0)	Hutson et al ²⁵
	NCT00920816 Axitinib vs. Sorafenib						
	RENAVIV	ECOG 0-1	NI	Not permitted unless treated and stable	Required (RECIST 1.1)	Radiologic PD (RECIST 1.0)	Aggarwal et al ²⁶
	NCT03592472 Pazopanib ± Abexinostat						
	2nd line						
	TARGET	ECOG 0-1	NI	Not permitted	Required (RECIST 1.0, CT/MRI)	NI	Escudier et al ²⁷
	NCT00073307 Sorafenib vs. Placebo						
	AXIS	ECOG 0-1	NI	Not permitted	Required (RECIST 1.0)	Radiologic PD (RECIST 1.0)	Rini et al ²⁸
	NCT00678392 Axitinib vs. Sorafenib						
	INTORSECT	ECOG 0-1	Serum 2.0xULN	Not permitted	Required (RECIST 1.0)	Radiologic PD (RECIST 1.0) or clinical PD	Hutson et al ²⁹
	NCT00474786 Sorafenib vs. Temsirolimus						
	2nd line						
	RECORD-1	KPS 70%	NI	Not permitted unless treated and stable, no corticosteroids	Required (RECIST 1.0, physical examination/CT/MRI)	Progressed on Sunitinib or Sorafenib w/in 6 mo	Motzer et al ³⁰
	NCT00410124 Everolimus vs. Placebo						

Trial Identifier	Treatments Investigated	PS	Renal Function	Presence of CNS Metastases	Measurable Disease	Progressed on Last Treatment	Investigators
	GOLD RCC NCT01223027	KPS 70%	Serum 1.5×ULN	Not permitted	Required (RECIST 1.1, CT/MRI)	Radiologic PD w/in 6 mo of last therapy	Motzer et al ³¹
	Dovitinib vs. Sorafenib						
	METEOR NCT01865747	KPS 70%	Serum 2.0×ULN CrCl 30 mL/min	Not permitted unless treated and stable	Required (RECIST 1.1)	Progressed on/after VEGFR tyrosine kinase inhibitor w/in 6 mo	Choueiri et al ³²
	Cabozantinib vs. Everolimus						
	CheckMate 025 NCT01668784	KPS 70%	Serum 1.5×ULN CrCl 40mL/min	Not permitted	Required (RECIST 1.1)	Progressed on/after last treatment w/in 6 mo	Motzer et al ³³
	Nivolumab vs. Everolimus						
	TIVO- NCT02627963	ECOG 0–1	Serum 1.5×ULN CrCl 40mL/min	Not permitted unless treated and stable	Required (RECIST 1.1)	Progressed on/after 2 or 3 systemic regimens, one of which includes a VEGFR TKI	Rini et al ³⁴
	3Tivozanib vs. Sorafenib						

CNS indicates central nervous system; CrCl, creatinine clearance; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; GFR, glomerular filtration rate; IFN- α , interferons α ; KPS, Karnofsky Performance Score; mRCC, metastatic renal cell carcinoma; MRI, magnetic resonance imaging; NA, not applicable; NI, not indicated; PD, progressive disease; PS, performance status; RECIST, response evaluation criteria in solid tumors; ULN, upper limit of normal; VEGFR TKI, vascular endothelial growth factor receptor tyrosine kinase inhibitor.

TABLE 2.

Endpoints in New mRCC Trials (n = 10)

DATECAN Definition: PFS = Death From RCC or Local, Regional, or Metastatic Progression		
	Trial Definition of PFS	Alignment With DATECAN
JAVELIN Renal 101 NCT02684006	PD (RECIST 1.1) or death due to any cause	No—definition includes “any cause” instead of DATECAN’s RCC or PD only
CLEAR NCT02811861	No published definition	NE
KEYNOTE-426 NCT02853331	PD (RECIST 1.1) or death due to any cause	No—definition includes “any cause” instead of DATECAN’s RCC or PD only
TIVO-3 NCT02627963	PD (RECIST 1.1) or death due to any cause	No—definition includes “any cause” instead of DATECAN’s RCC or PD only
Bempegaldesleukin + Nivolumab vs. TKI NCT03729245	PFS as secondary endpoint No published definition	No—PFS as secondary endpoint instead of primary endpoint
RENAVIV NCT03592472	PD (RECIST 1.1) or death due to any cause	No—definition includes “any cause” instead of DATECAN’s RCC or PD only
CheckMate 9ER NCT03141177	No published definition	NE
COSMIC-313 NCT03937219	PD (RECIST 1.1) or death due to any cause	No—definition includes “any cause” instead of DATECAN’s RCC or PD only
KEYNOTE-679 NCT03260894	PFS not included as an endpoint	NE
PDIGREE NCT03793166	PFS as secondary endpoint PD (RECIST 1.1) or death due to any cause	No—PFS as secondary endpoint instead of primary endpoint Definition includes “any cause” instead of DATECAN’s RCC or PD only

DATECAN indicates Definition for the Assessment of Time-to-event Endpoints in CANcer trials; mRCC, metastatic renal cell carcinoma; NE, not evaluable; PD, progressive disease; PFS, progression-free survival; RCC, renal cell carcinoma; RECIST, response evaluation criteria in solid tumors.