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## Systematic Review

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# Post-Metastasectomy Adjuvant Therapy in Patients with Renal Cell Carcinoma: A Systematic Review

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### Abstract.

**BACKGROUND:** Pembrolizumab is established as adjuvant therapy for patients with high-risk clear cell renal cell carcinoma (ccRCC) after resection. Patients with completely resected metastatic disease (M1 NED) seem to have greater benefit from adjuvant pembrolizumab in both disease-free survival (DFS) and overall survival (OS); yet, with other agents, adjuvant therapy has not been shown to improve survival. As newer therapies evolve, it is important to understand the efficacy of systemic agents in this patient population.

**OBJECTIVE:** We aimed to systematically review available trials investigating adjuvant therapy after metastasectomy in RCC.

**METHODS:** Following PRISMA guidelines, we performed a systematic literature search using PubMed and Embase through January 2024. For inclusion, studies were required to include completely resected patients with known metastatic RCC. Patients with only locally advanced and/or regional nodal involvement (N1) alone were excluded. Titles and abstracts were screened to identify articles for full-text, and then a descriptive review was performed.

**RESULTS:** A total of 149 articles were initially identified. Ultimately 9 articles published before the end of January 2024 met our inclusion criteria and were included in the analysis. Data were extracted and organized to reflect the role of adjuvant treatment - both targeted therapies as well as immunotherapy in patients who had undergone metastasectomy and rendered M1 NED. With the exception of pembrolizumab, adjuvant therapy in M1 NED was not found to be associated with improved survival.

**CONCLUSIONS:** Pembrolizumab appears to benefit M1 NED ccRCC patients after resection even more than other high-risk ccRCC patients. Yet, this same benefit has not been seen with other agents. Future research should focus on trying to establish which M1 NED patients benefit from adjuvant treatment.

Keywords: Kidney cancer, metastasectomy, adjuvant, systemic therapy

## INTRODUCTION

Metastasectomy is a key treatment option for patients with oligometastatic renal cell carcinoma (RCC), with the most common sites of non-kidney resection being the lungs, bone, lymph nodes, adrenal glands, pancreas, and liver, respectively [1, 2].

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The optimal therapy for patients with metastatic renal cell carcinoma rendered free of disease after resection, often called “M1 NED patients”, is unclear. NCCN guidelines recommend adjuvant pembrolizumab within 1 year of nephrectomy for those patients with metastatic clear cell RCC (ccRCC) following complete resection of disease [3].

In the last four decades, despite sustained effort in the adjuvant setting, only two positive trials have been reported to improve disease-free survival (DFS). Among targeted therapies, the tyrosine kinase inhibitor (TKI) sunitinib was shown to modestly improve DFS, and among immune checkpoint inhibitors (ICIs), pembrolizumab was shown to significantly improve DFS and overall survival (OS) as part of the Keynote 564 trial [4–7]. Other systemic therapy trials have had less favorable results, including those with tyrosine kinase inhibitors (sorafenib, pazopanib, axitinib), and mTOR inhibitor (everolimus) [8–12], as well as those with immune checkpoint inhibitors (atezolizumab, ipilimumab+nivolumab, and nivolumab) [13–15]. Differences in efficacy between these trials have led to speculation regarding the activity of these drugs, specifically in the context of immunotherapy. Even though both pembrolizumab and nivolumab are programmed death-1 (PD-1) inhibitors, the former has been shown to bind to the PD-1 receptor with higher affinity [16]. Further, drugs such as atezolizumab inhibit the programmed death-ligand 1 (PD-L1) receptor instead, and this drug is not used in the context of kidney cancer due to a lack of overall survival benefit in phase-III clinical trials [17]. Other factors include, differences in inclusion criteria (inclusion of non-clear histologies in the IMmotion010 (atezolizumab) trial, duration of adjuvant therapy (six months in the CheckMate-914 trial (ipilimumab+nivolumab) vs. one year in KEYNOTE-564 trial (pembrolizumab)).

Among adjuvant-treated patients, those with completely resected metastatic disease – i.e., M1 NED patients - are at a uniquely higher risk for progression. Within Keynote 564, the M1 NED subgroup had the lowest DFS HR for pembrolizumab compared to placebo in a sub-group analysis, suggesting that this sub-group may benefit most from adjuvant therapy [4]. The NCCN recommendation in favor of adjuvant pembrolizumab is based on these results.

While several adjuvant studies, including S-TRAC, EVEREST, and Checkmate 914, did not include the M1NED high-risk subgroup [7, 12, 13]. Several others did. In this review, we sought to

systematically provide a review of the existing trials of systemic therapy after complete resection of metastatic RCC.

## METHODS

### *Search strategy*

A systematic literature search was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [18]. A search was performed in electronic databases, including PubMed/MEDLINE and Scopus. The search terms included (Renal cell carcinoma OR kidney cancer) AND (adjuvant AND tyrosine kinase inhibitor OR sunitinib OR sorafenib OR pazopanib OR axitinib OR everolimus OR immune checkpoint OR nivolumab OR ipilimumab OR pembrolizumab OR avelumab OR atezolizumab OR IL2) AND (metastectomy or M1NED). An additional manual search was performed to identify published abstracts from the European Society of Medical Oncology and the American Society of Clinical Oncology (ASCO) annual meetings. We excluded non-English articles, articles without original data (e.g. review articles or editorials), and repeated publications on the same cohort. In multiple publications on the same trial, we reported the most recent publication with the longest follow-up. Ultimately, 9 papers were included in the final review, as shown in Fig. 1.

## RESULTS

### *Description of results*

A PRISMA flow-diagram for the selection process of included studies is provided in Fig. 1. The initial online search yielded 149 articles of which 9 were included in final analysis. Table 1 summarizes the basic findings of these articles. Three articles were randomized trials of adjuvant immunotherapy in high-risk patients including an M1 NED subgroup, two articles were randomized trials of adjuvant TKI specifically in M1 NED patients, two articles were retrospective series (one of multiple TKI therapies and one of interferon alpha era treatments), one article was a randomized trial of high-dose IL-2, and one article was a non-randomized trial of a novel RCC vaccine.

Among the trials identified, only Keynote 564 established a survival advantage with pembrolizumab

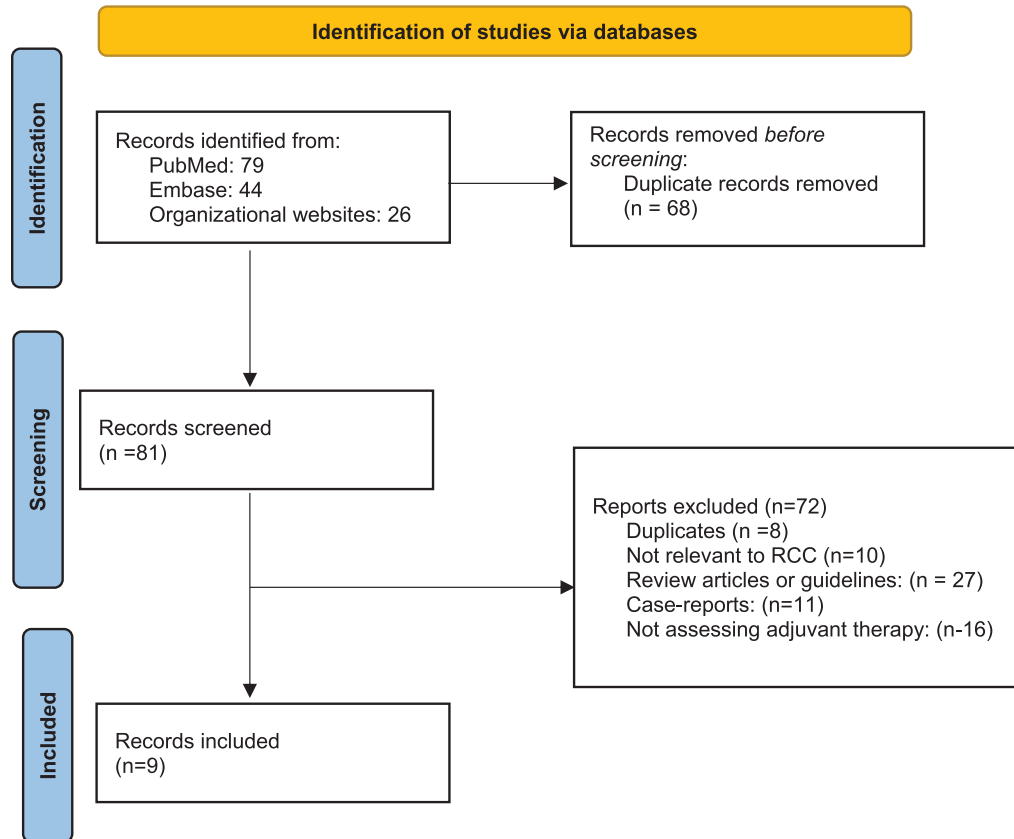


Fig. 1. PRISMA flowchart.

in the overall cohort, an advantage that appeared more pronounced within the M1 NED subgroup. DFS hazard ratio (HR) was reported as 0.40 (95% CI: 0.20–0.82) in M1 NED patients in comparison to 0.72 (95% CI: 0.59–0.87) for the overall cohort [6]. A more pronounced HR for OS was also observed for the M1 NED subgroup for pembrolizumab but with the 95% CI crossing unity: HR 0.51 (95% CI: 0.15–1.75) in M1 NED subgroup compared to 0.62 (95% CI: 0.44–0.87) for the overall subgroup [5].

Despite the impressive results of pembrolizumab, within the other large adjuvant immunotherapy trial that also included an M1 NED sub-group, IMmotion 010, the same trend was not observed with adjuvant atezolizumab [15]. The M1 NED subgroup within IMmotion 010 had a DFS HR of 0.93 (95% CI: 0.58–1.49), similar to the DFS HR of the overall study, 0.93 (95% CI: 0.75–1.15). Similarly, in the other large adjuvant immunotherapy trial, PROSPER, which included neoadjuvant priming with one dose of nivolumab followed by adjuvant nivolumab after nephrectomy, the M1 NED group did not seem to

uniquely benefit from adjuvant therapy. In fact, the M1 NED subgroup DFS HR within PROSPER was 0.89 (95% CI: 0.31–2.57), compared to the overall DFS HR of 0.97 (95% CI: 0.74–1.28). However, it is worth noting that within PROSPER, the number of patients in the M1 NED subgroup was small, with only 28 total patients (4% of the overall sample). Previously conducted trials and retrospective series using cytokines such as interleukin-2 (IL2) or interferon- $\alpha$  also did not show significant improvement in DFS when administered adjuvantly in the post-metastasectomy setting [19, 20]. (Table 1)

The two trials that evaluated adjuvant TKIs after metastasectomy include RESORT (comparing sorafenib to observation in 76 patients pretreated with nephrectomy and undergoing radical metastasectomy) [21] and the ECOG-ACRIN trial E2810 (comparing pazopanib to placebo in 129 patients with NED following metastasectomy) [22]. Both were negative trials, with a trend towards worse overall survival with pazopanib and worse relapse-free survival with sorafenib, suggesting a very limited role

Table 1  
Studies describing the role of adjuvant systemic therapy in M1 NED patients

Study	Study Drug	Control Arm	Immunotherapy Trials				Outcome in M1 NED patients (And for overall study when others included)
			Histological Inclusion	Pathologic Inclusion	Median Follow-up	No. of patients (Overall and M1 NED)	
Keynote-564 [4–6]	Pembrolizumab 200 mg every 3 weeks for up to 1 year	Placebo	ccRCC+/- sarcomatoid component	pT2 (grade 4 or sarcomatoid) or $\geq$ pT3 (any grade) pTxN1 or M1 NED (within 1 year of nephrectomy)	57.2 months	989 total 57 M1 NED	Disease Free Survival M1 NED Subgroup HR (0.40 0.20–0.81) [Overall HR (0.72 0.59–0.87)]  Overall Survival M1 NED Subgroup HR 0.51 (0.15–1.75) [Overall HR 0.62 (0.44–0.87)]
Immotion-010 [15]	Atezolizumab 1,200 mg every 3 weeks for 1 year	Placebo	ccRCC or RCC with sarcomatoid component	pT2 (gr4) or pT3a (gr 3 or gr 4) or $\geq$ pT3b (any grade) or pTxN1 or M1 NED (within 1 year of nephrectomy)	44.7 months	773 total 108 M1 NED - 84 metachronous resection - 24 synchronous resection	Disease Free Survival M1 NED Subgroup HR 0.93 (0.58–1.49) [Overall HR 0.93 (0.75–1.15)]
PROSPER [14]	Nivolumab 480 mg IV q4 weeks 1 doses preoperatively, and up to 9 monthly doses post-operatively	Observation	Any histology (80% ccRCC)	pT2-4 or M1 NED (capable of being rendered NED within 12 weeks of surgery)	16 months	779 total 28 M1 NED	Disease Free Survival M1 NED Subgroup HR 0.89 (0.31–2.57) [Overall 0.97 (0.74–1.28)]

Targeted Therapy/Tki							
Study	Study Drug	Control Arm	Histological Inclusion	Pathologic Inclusion	Median Follow-up	No. of patients (Overall and M1 NED)	Outcome in M1 NED patients (And for overall study when others included)
E2810 [22]	Pazopanib 800 mg daily for 1 year	Placebo	ccRCC	M1 NED only	30 months	129 M1 NED	Disease Free Survival HR 0.85 (0.55–1.31)
RESORT [21]	Sorafenib 400 mg twice daily for 1 year	Observation	ccRCC	M1 NED only	38 months	69 M1 NED	Disease Free Survival HR 1.35 (0.72–2.54)
Park et al Retrospective series [23]	Immediate Adjuvant TKI Therapy (Sunitinib, Sorafenib, or Pazopanib)	Retrospective control with deferred treatment	Any histology (90% ccRCC)	M1 NED only	12 months	53 patients - 19 received immediate post-op TKI - 34 received delayed TKI	Disease Free Survival (immediate vs. delayed TKI) HR 0.418 (0.118–0.859) Cancer-specific Survival (immediate vs. delayed TKI) HR 0.640 95% CI (0.258–2.093)
CYTOKINES							
Study	Study Drug	Control Arm	Histological Inclusion	Pathologic Inclusion	Median Follow-up	No. of patients (Overall and M1 NED)	Outcome in M1 NED patients (And for overall study when others included)
Cytokine Working Group Randomized Trial [19]	High-dose bolus IL2 – q8 hours days 1–5 and 15–19 for maximum 28 doses.	Observation	RCC (majority were ccRCC)	pT3b-4 or N1-N3 or M1 NED	22 months	69 total 25 M1 NED	Disease Free Survival No formal HR, though not significant for M1 NED or overall cohort, 0.43 and 0.49. Overall Survival No formal HR, though not significant for M1 NED or overall cohort, 0.91 and 0.29.
Kwak et al. Retrospective series [20]	Multiple historical interventions: IFN-alpha, IL-2, 5-FU	Untreated control	RCC ( 80% ccRCC)	M1 NED only	22 months	93 patients, 70 systemically treated patients, 23 observed patients	<b>Overall survival</b> HR 1.54 (0.765–3.115)
MISCELLANEOUS							
Study	Study Drug	Control Arm	Histological Inclusion	Pathologic Inclusion	Median Follow-up	No. of patients (Overall and M1 NED)	Outcome in M1 NED patients (And for overall study when others included)
Rausch UroRCC Peptide Vaccine [24]	Synthetic multi-peptide vaccine	Retrospective contemporary control	RCC (not specified)	M1 NED only	56 months	83 patients 19 treated patients M1 NED (vs 44 controls)	<b>Overall survival</b> HR 0.19 (0.05–0.69)

for adjuvant TKIs in patients with resected metastatic disease. A retrospective series conducted by Park et al., compared outcomes of 53 metastatic RCC patients who underwent metastasectomy after pre-operative targeted therapy [23]. Of these, 34 patients (64.1%) stopped targeted therapy after metastasectomy, and 19 patients (35.9%) continued targeted therapy. They found DFS to be better in patients who received immediate postoperative targeted therapy, although the cancer-specific mortality was not significantly different between the two groups.

A recent phase 1/2 clinical trial identified 19 patients with no residual disease after metastasectomy for mRCC, who were treated with a patient-specific multi-peptide vaccine [24]. Median OS for patients receiving adjuvant UroRCC was not reached (mean: 112.6 months, 95% CI: 92.1–133.1 vs. 57.96 months; 95% CI: 92.1–133.1 in the control group) and remained significant after adjustment for Memorial Sloan Kettering Cancer Center risk groups, age, and metastatic sites, thus making this a promising strategy warranting further study.

## DISCUSSION

Among resected RCC patients, those with completely resected metastatic RCC have demonstrated systemic disease and have a high risk of recurrence. Many adjuvant therapy trials have not included these M1 NED patients. The more pronounced DFS HR of the small M1 NED subgroup within Keynote 564 suggested this patient population had a more pronounced benefit from adjuvant immunotherapy. Despite the impressive results of pembrolizumab, other adjuvant immunotherapy trials, IMmotion 010 and PROSPER did not show similar results. While an argument can be made for these trials having smaller subgroups, the IMmotion 010 had a higher proportion of M1 NED patients (14% versus 6% in Keynote 564), and one would have expected to see similar results between the two studies. The discrepant results may reflect differences in the agents used, pembrolizumab acting on PD-1 vs atezolizumab acting on PDL-1, especially as atezolizumab in combination with bevacizumab has not demonstrated OS benefit in metastatic ccRCC [17]. This has previously been demonstrated in a pan-tumor meta-analysis where, anti-PD-1 drugs were shown to be clinically superior to anti-PD-L1 drugs and has been proven using molecular analyses [25]. PROSPER, another clinical trial that involved neoadjuvant priming with nivolumab followed by adjuvant

nivolumab after nephrectomy, was negative, though it included only 28 total patients with M1NED, thus making it difficult to draw meaningful conclusions. Prior to the advent of immune-checkpoint inhibitors, other cytokine based therapies such as interleukin-2 (IL2), interferon (IFN)- $\alpha$  had been the standard of care based on improved survival in metastatic RCC [26]. However, subsequent evaluation in the adjuvant setting did not show clinical benefit and these drugs were not adopted for use after nephrectomy or complete metastasectomy [20].

The two trials that evaluated targeted therapies, specifically tyrosine kinase inhibitors [RESORT (sorafenib) and the ECOG-ACRIN trial E2810 (pazopanib)] were specifically designed for patients who had undergone metastasectomy. They were both negative trials, suggesting a limited role for TKIs in resected metastatic disease. Mechanistically, it maybe because immunotherapy, which has been shown to yield prolonged complete responses in a subset of patients with gross metastatic disease, may also be more likely to eradicate micrometastases as compared to TKIs.

In addition to the studies presented in this systematic review, there are ongoing trials that include M1NED patients. The pending LITESPARK-022 trial, comparing pembrolizumab plus belzutifan or pembrolizumab plus placebo, will provide unique insights into whether the addition of belzutifan to pembrolizumab will yield extra benefit in this patient population [27].

The major unanswered question of adjuvant therapy in RCC is identifying which patients are cured with surgery alone and which patients are at high risk for recurrence. Clinical models exist, but predictive biomarkers are not yet established. Tissue-based genomic and transcriptomic biomarkers that may be associated with the risk of recurrence are being investigated [28]. Additionally, circulating tumor DNA, which has shown promise in other cancers, is being investigated to detect minimal residual disease in RCC. Currently, however, RCC is considered a low-shedding tumor, and circulating tumor DNA is often only detected in those patients with larger burden of disease [29, 30]. Ongoing efforts to develop more sensitive assays should aim to circumvent this shortcoming.

Another important aspect of adjuvant treatment in resectable RCC is that it should maximize the proportion of patients cured without adding undue burden. It is important to consider that in the Keynote 564 trial, the rate of discontinuation of drug due to any adverse

event was higher in the pembrolizumab arm (21.1% vs. 2.2%). Patients in the pembrolizumab arm experienced a higher incidence of serious adverse events of any cause (20.7% vs. 11.5%), as well as drug-related high-grade adverse events (18.6% vs. 1.2%) [5]. Thus inclusion of medical side effects of treatment as well as the financial toxicity is important to consider, as adjuvant pembrolizumab has only been found to be cost-effective in the highest-risk patients [31].

This systematic review has several limitations. As has been shown in previous studies, prognosis of patients with kidney cancer is dependent on additional clinical factors such as metastatic sites involved, and time since nephrectomy [32, 33]. However, granular details regarding sites of metastases resected, number of lesions subjected to metastasectomy, and interval since nephrectomy were not available in the papers cited from clinical trials in this review and should be a topic of a future analysis if such details could be made available. While searching literature for evidence, we found that some studies that did not report numerical data on survival and in the context of M1NED patients. Therefore, due to lack of data, a merged analysis of outcomes was not possible. Moreover, this being a systematic review, data was collected in a retrospective manner, and was thus prone to errors. There are also prior studies to suggest that there can be a publication bias associated with systematic reviews, in that prior studies with only significant results may get over-selected when gathering evidence [34].

Further studies to evaluate the role of adjuvant systemic therapy in M1NED patients should focus on the incorporation of biomarkers to identify patients at the highest risk of relapse, whether in the form of minimal residual disease assessment from circulating tumor DNA analysis or refined molecular techniques, such as transcriptomic signatures. Further, the inherent risk of subjecting these patients to adverse events from these systemic drugs should be considered when designing future trials for this patient population that may have been cured with metastasectomy alone.

## CONCLUSION

No adjuvant TKI trial has shown improvement in DFS for M1 NED patients with ccRCC. The markedly lower DFS HR for the M1 NED subgroup for pembrolizumab within Keynote 564 has not been replicated in other immunotherapy trials using nivolumab and atezolizumab. The Checkmate-914

trial, that tested the combination of nivolumab plus ipilimumab and did not include M1NED patients, was speculated to be negative due to the lack of oligometastatic disease patients when compared to the pembrolizumab trial; the present review however points out that trials that had included a similar population were also negative. The conflicting results within adjuvant immunotherapy trials suggest more research is needed to determine which patients are at highest risk of relapse and would thus benefit most from adjuvant immunotherapy, specifically pembrolizumab.

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## AUTHOR CONTRIBUTIONS

SM, PNL and SG contributed to the conception, performance and interpretation of data review for this paper.

## CONFLICTS OF INTEREST

PNL is co-Editor-in-Chief of this journal and SG is an Editorial Board Member of this journal, but they have not been involved in the peer-review process of this paper, nor had access to any information regarding its peer-review. SM has no conflicts of interest to report.

## DATA AVAILABILITY

The data supporting the findings of this study are available on request from the corresponding author.

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