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REVIEW

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Precision adjuvant therapy after nephrectomy for high-risk clear-cell renal cell carcinoma: a narrative review

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This article belongs to the Special Issue: Renal Cell Carcinoma: From Pathophysiology to Novel Therapeutic Approaches

Abstract

Adjuvant therapy for renal cell carcinoma has moved from repeated negative trials to an evolving postoperative treatment landscape. Pembrolizumab is the first systemic therapy after nephrectomy to demonstrate both disease-free survival (DFS) and overall survival (OS) benefit in patients with clear-cell renal cell carcinoma (ccRCC) at increased risk of recurrence. However, clinicopathological eligibility exposes some patients already cured by surgery to immune-related toxicity and cannot identify microscopic residual disease. This narrative review integrates mature KEYNOTE-564 outcomes, the active-control LITESPARK-022 trial of pembrolizumab plus belzutifan, RAMPART findings, prior negative immune checkpoint inhibitor and tyrosinekinase inhibitor trials, and emerging biomarkers. We explicitly distinguish established standard care, promising but not yet mature strategies, and interventions that remain investigational. One year of pembrolizumab is the established evidence-based option for medically suitable KEYNOTE-564-eligible patients. Pembrolizumab plus belzutifan improves DFS versus pembrolizumab alone and is approved in the United States, but OS is immature, toxicity is greater, and its place in other regions remains unsettled. Dual-checkpoint blockade, postoperative treatment allocation based on kidney injury molecule-1 (KIM-1) or circulating tumor DNA (ctDNA), molecular subtypes, programmed death-ligand 1 expression, and radiomics remain investigational. No biomarker is validated to select routine adjuvant therapy, and efficacy in non-clear-cell histologies has not been established. We propose a conceptual three-axis framework integrating clinicopathological recurrence risk, candidate residual-disease signals, and treatment fitness or patient preference. It is a decision aid, not a validated algorithm. At present, precision resides mainly in risk stratification, fitness assessment, and shared decision-making; molecular treatment selection awaits prospective validation.

Keywords: Renal cell carcinoma, precision oncology, targeted therapy, immunotherapy, biomarkers

Introduction

Surgery is curative for many patients with localized renal cell carcinoma (RCC), yet recurrence remains common after resection of high-risk clear-cell RCC (ccRCC). Postoperative imaging may show no evidence of disease even when occult systemic deposits persist; at the same time, many trial-eligible patients have already been cured by nephrectomy alone. Adjuvant therapy therefore requires a favorable balance between a delayed or prevented recurrence and toxicity delivered to an asymptomatic population.

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Earlier cytokine and vascular endothelial growth factor receptor (VEGFR) tyrosine-kinase inhibitor (TKI) trials largely failed to improve overall survival (OS), and discrepant disease-free survival (DFS) findings did not establish a broadly accepted European standard [1-6]. The phase 3 KEYNOTE-564 trial changed this landscape: adjuvant pembrolizumab improved DFS and subsequently showed a statistically significant OS benefit [7-10]. More recent trials have expanded the decision beyond pembrolizumab alone. LITESPARK-022 demonstrated superior DFS with pembrolizumab plus belzutifan compared with pembrolizumab alone, while RAMPART reported a DFS benefit with durvalumab plus tremelimumab but not with durvalumab monotherapy [11-13]. Clinicians must now consider whom to treat, whether to intensify, for how long, and how to integrate biological markers of residual disease.

This narrative review provides a clinically oriented update focused on the decisions created by 2024–2026 evidence. Its purpose is to interpret and categorize the available evidence rather than to issue de novo guideline recommendations. Unlike a previous systematic review from our group, which compared first-generation adjuvant trials [14], the present article addresses an active-control intensification trial, the first positive OS evidence for adjuvant immunotherapy, emerging postoperative biomarkers, treatment after adjuvant relapse, and a conceptual three-axis decision aid.

Evidence acquisition

The literature was last updated on 10 September 2026 using PubMed/MEDLINE, ClinicalTrials.gov, current guideline documents and primary congress reports. Search concepts combined renal cell carcinoma with adjuvant, perioperative, pembrolizumab, belzutifan, immune checkpoint inhibitor, biomarker, kidney injury molecule-1 (KIM-1), circulating tumor DNA (ctDNA), minimal residual disease and post-adjuvant relapse. Sources were eligible when they reported adult human data on perioperative or adjuvant systemic therapy, postoperative recurrence biomarkers, or treatment after adjuvant relapse in localized or completely resected RCC; priority was given to randomized phase 3 trials, mature updates, prespecified translational analyses and current guidelines. Preclinical-only studies, metastatic-only reports without relevance to post-adjuvant sequencing, non-RCC studies, duplicate reports and non-primary commentary were excluded. For multiple reports from the same trial, the most mature peer-reviewed source was prioritized; earlier reports were retained only when they added a distinct prespecified analysis. Congress abstracts were retained only when they provided the most current results of a pivotal trial. Because source selection was purposive and practice-oriented, no protocol registration, duplicate screening, formal risk-of-bias assessment or meta-analysis was undertaken.

To align the strength of the language with this narrative method, we use three evidence categories: established standard (randomized evidence of sufficient maturity and current guideline support for routine use), promising but not yet mature (positive phase 3 or regulatory evidence with immature OS, incomplete publication, or limited guideline uptake), and investigational only (biomarker-directed allocation or regimens without adequate evidence for routine care). These categories are interpretive and do not constitute formal certainty grading.

Defining risk after nephrectomy

Pathological stage, World Health Organization/International Society of Urological Pathology grade, nodal status, sarcomatoid differentiation and tumor necrosis remain the foundation of recurrence prediction. The Leibovich score and University of California, Los Angeles Integrated Staging System improve prognostic discrimination compared with stage alone, but they were not developed as predictive biomarkers for a specific drug [15, 16]. Trial eligibility should therefore not be equated with certainty of benefit for an individual patient.

KEYNOTE-564 enrolled patients with a clear-cell component and intermediate-high risk (pT2 grade 4 or sarcomatoid, N0 M0; or pT3 any grade, N0 M0), high risk (pT4 any grade, N0 M0; or any pT, any grade, N-positive M0), or M1 no evidence of disease after complete resection of metastases. These categories provide the current evidence boundary. Patients with non-clear-cell histology, lower-risk disease, major autoimmune disease, organ transplantation or a need for chronic immunosuppression were not adequately represented. In these groups, extrapolation should be cautious.

Risk of recurrence is only one side of the decision. Competing mortality, baseline renal function, cardiovascular disease, frailty, fertility and pregnancy considerations, autoimmune history, access to rapid toxicity management and willingness to accept a potentially permanent endocrine adverse event are equally relevant. Shared decision-making should communicate absolute benefit rather than hazard ratios (HR) alone.

The established standard: pembrolizumab

KEYNOTE-564 randomly assigned 994 patients to pembrolizumab 200 mg every three weeks for up to 17 cycles or placebo after nephrectomy, with or without metastasectomy [7]. At the prespecified OS analysis, median follow-up was 57.2 months. Estimated OS at 48 months was 91.2% with pembrolizumab and 86.0% with placebo (HR 0.62, 95% confidence interval [CI] 0.44–0.87), while the DFS advantage remained clinically meaningful [9]. Five-year follow-up continued to support durable DFS and OS benefit [10]. On this basis, contemporary European guidelines strongly recommend offering adjuvant pembrolizumab to trial-defined patients, preferably within 12–16 weeks after surgery [17].

The OS result is decisive because several earlier agents improved, or appeared to improve, DFS without demonstrating longer survival. However, relative benefit must be

interpreted alongside overtreatment. Most control-group patients were alive at four years and many remained recurrence-free. Treatment-related grade 3–5 adverse events, discontinuation, immune-mediated endocrinopathy, hepatitis, pneumonitis, colitis and nephritis are especially consequential in patients who may already have reduced nephron mass. Toxicity can persist beyond the planned one-year treatment period.

Within KEYNOTE-564 eligibility, the absolute-risk rationale may be strongest for pT4, node-positive, sarcomatoid and completely resected M1 no-evidence-of-disease states; however, these subgroup estimates are imprecise and should not be interpreted as proof of differential treatment effect. For pT3 low-grade disease, the expected absolute benefit may be smaller and patient preference carries greater weight. Baseline evaluation in routine care generally includes performance status, renal and hepatic function, thyroid function, medication review, autoimmune history and postoperative imaging excluding residual disease.

Why other adjuvant strategies failed

The negative or discordant TKI experience illustrates the limitations of transporting activity from metastatic disease into the minimal-residual-disease setting. ASSURE found no DFS or OS benefit with sunitinib or sorafenib; S-TRAC showed a centrally reviewed DFS advantage for sunitinib but no OS benefit and substantial toxicity; PROTECT, ATLAS and SORCE did not establish a favorable overall benefit-risk profile for pazopanib, axitinib or sorafenib [1-6]. Everolimus did not significantly improve recurrence-free survival in the overall EVEREST population [18].

The immune checkpoint inhibitor (ICI) class is not uniformly effective. IMmotion010 (atezolizumab), CheckMate 914 (nivolumab plus ipilimumab) and PROSPER RCC (perioperative nivolumab) missed their primary efficacy endpoints [19-21]. Differences in drug target, treatment schedule, perioperative design, risk composition, histology and statistical power probably contributed. These trials also show that efficacy in metastatic RCC does not validate an adjuvant regimen and that programmed death 1, programmed death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte-associated protein 4 strategies cannot be treated as interchangeable. The principal phase 3 perioperative trials and their current clinical interpretation are summarized in Table 1.

Intensification beyond pembrolizumab

Belzutifan plus pembrolizumab

Belzutifan inhibits hypoxia-inducible factor 2 alpha, a central downstream effector of von Hippel-Lindau loss in ccRCC. This mechanism makes it a biologically rational partner for programmed death 1 blockade. In LITESPARK-022, 1,841 participants were randomly assigned to pembrolizumab plus belzutifan or pembrolizumab plus placebo. The combination significantly improved DFS (HR 0.72, 95% CI 0.59–0.87; $P = 0.0003$), with estimated 24-month DFS of 80.7% *vs*. 73.7% after 28.4 months' median follow-up [11]. Grade 3 or higher treatment-emergent adverse events occurred in 52.1% *vs*. 30.2% of participants, with anemia and hypoxia among the characteristic added toxicities [11]. OS was immature. This active-control trial is a major advance, but the combination is best classified as promising but not yet mature rather than as a universal standard. Belzutifan adds anemia, hypoxia, fatigue and monitoring burden, and a DFS

Table 1. Practice-changing and contextual phase 3 perioperative trials.

Trial	Population	Comparison	Key finding	Evidence category and interpretation
KEYNOTE-564	994; ccRCC	Pembrolizumab *vs*. placebo	DFS and OS benefit; 48-month OS 91.2% *vs*. 86.0%, HR 0.62	Established standard: randomized DFS and OS benefit
LITESPARK-022	1,841; high-risk ccRCC	Pembrolizumab + belzutifan *vs*. pembrolizumab	DFS HR 0.72; OS immature; grade ≥ 3 treatment-emergent adverse events 52.1% *vs*. 30.2%	Promising but not yet mature: approved in the United States; OS immature and toxicity greater
RAMPART	Resected RCC; multi-arm	Durvalumab ± tremelimumab *vs*. active monitoring	Combination DFS signal; durvalumab alone not significant	Investigational only: congress-level DFS result; mature OS and full publication needed
IMmotion010	778; RCC	Atezolizumab *vs*. placebo	No DFS benefit	Negative phase 3 evidence; no routine adjuvant role
CheckMate 914	816; predominant ccRCC	Nivolumab + ipilimumab *vs*. placebo	No DFS benefit; toxicity	Negative phase 3 evidence; no routine adjuvant role
PROSPER RCC	819; RCC	Perioperative nivolumab *vs*. surgery alone	No recurrence-free survival benefit	Negative phase 3 evidence; no routine perioperative role
S-TRAC/ASSURE	High-risk RCC	Adjuvant VEGFR-TKIs	Discordant or negative DFS; no OS benefit	Negative or discordant evidence; no routine adjuvant role

Notes: ccRCC: clear-cell renal cell carcinoma; DFS: disease-free survival; HR: hazard ratio; OS: overall survival; RCC: renal cell carcinoma; TKI: tyrosine-kinase inhibitor; VEGFR: vascular endothelial growth factor receptor.

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improvement does not establish an OS benefit. The combination received US Food and Drug Administration approval in June 2026 [22]. By contrast, the currently cited European guideline recommendation remains one year of pembrolizumab for KEYNOTE-564-defined risk [17]. Treatment should therefore follow current regional authorization and guidance; counseling should explicitly address immature OS, added toxicity and uncertainty about long-term quality of life.

Dual immune checkpoint blockade

RAMPART used a multi-arm, multi-stage design and included broader RCC histologies. Durvalumab plus tremelimumab improved DFS compared with active monitoring, with the largest effect in a prespecified higher-risk group, whereas durvalumab monotherapy did not reach statistical significance [12, 13]. The combination also increased grade 3 toxicity. These congress-level findings are promising, but dual-checkpoint blockade remains investigational only pending mature OS, full peer-reviewed reporting and adequately powered histology-specific analyses.

Limits of extrapolation to non-clear-cell RCC

Histology is an evidence boundary rather than a minor subgroup variable. KEYNOTE-564 and LITESPARK-022 required a clear-cell component, whereas PROSPER RCC and RAMPART allowed non-clear-cell histologies [7, 11, 21, 23]. PROSPER was negative overall and included only 17% non-clear-cell disease; available RAMPART reports have not provided adequately powered, prospective efficacy estimates for individual non-clear-cell subtypes [12, 13, 21, 23]. These tumors are biologically heterogeneous: papillary RCC includes MET-driven and other molecular classes, while chromophobe RCC is characterized by distinctive chromosome losses and mitochondrial or metabolic alterations, with natural history and immunobiology that differ from ccRCC [24]. No adjuvant systemic regimen has established efficacy for non-ccRCC. Accordingly, ccRCC-derived treatment claims should not be extrapolated; surveillance and histology-specific clinical trials should be discussed according to individual risk and availability.

Biomarkers for precision adjuvant treatment

A useful adjuvant biomarker must do more than predict recurrence. It should ideally identify residual disease, predict differential benefit from a specific treatment, be reproducible across laboratories and add information beyond pathology. No available biomarker currently satisfies all of these requirements.

KIM-1

Post-nephrectomy plasma KIM-1 is a promising marker of occult disease. Higher levels were associated with worse DFS and OS in prospective trial cohorts [25, 26]. In an exploratory IMmotion010 analysis, patients with high KIM-1 appeared to derive greater relative benefit from atezolizumab than those with low KIM-1 [26]. This observation is hypothesis-generating, cannot be generalized to pembrolizumab and does not validate treatment allocation outside a trial. Serial change may be more informative than a single value. Nevertheless, assay thresholds, timing, renal-function effects and prospective treatment-assignment utility remain unresolved. KIM-1 should not yet be used to deny pembrolizumab to an otherwise eligible patient.

ctDNA and minimal residual disease

ctDNA is conceptually attractive because postoperative positivity can represent molecular residual disease before radiological recurrence. RCC is relatively low-shedding, particularly when tumor volume is microscopic, so a negative plasma assay may reflect limited sensitivity rather than cure. Tumor-informed assays, methylation signatures, fragmentomics and combined plasma-urine approaches may improve detection [27, 28]. Prospective trials should test whether ctDNA-guided escalation improves outcomes and whether persistently negative patients can safely avoid or shorten treatment. At present, ctDNA remains investigational in localized RCC.

Tumor and imaging biomarkers

PD-L1 expression is prognostic in some RCC cohorts but has not reliably selected benefit from adjuvant therapy. von Hippel-Lindau loss or inactivation is central to ccRCC biology but is not, by itself, a clinically useful selector. Gene-expression programs describing angiogenic, proliferative and immune-infiltrated phenotypes, spatial immune architecture, tumor mutational features, radiomics and computational pathology may refine risk [29, 30]. Their principal limitation is external validation: a high-performing retrospective classifier may fail when pathology processing, imaging protocols or patient mix changes. The potential value, principal limitations and current role of postoperative biomarkers are summarized in Table 2.

A practical decision framework

As a conceptual approach, the postoperative consultation can proceed in four steps. First, confirm pathological review, clear-cell component, stage, grade, nodal status, margin status, sarcomatoid features and absence of residual disease on imaging. Second, quantify recurrence risk using a validated model and map the patient to trial-defined eligibility. Third, assess treatment fitness and competing risks, with specific attention to autoimmune disease, transplant status, renal function, tolerance for uncertainty and toxicity, and patient values. Fourth, discuss observation, established adjuvant pembrolizumab and relevant clinical trials in a multidisciplinary setting. Experimental biomarker results may support trial enrollment but should not override routine eligibility or determine treatment outside a study.

Within the terminology used in this review, one year of pembrolizumab is the established standard to discuss with medically suitable KEYNOTE-564-eligible patients after balanced counseling. Observation remains a valid option

Table 2. Biomarkers for postoperative risk and treatment selection.

Marker	Potential value	Principal limitation	Current role
Clinicopathological models	Validated recurrence prognosis; immediately available	Not drug-predictive; intratumoral biology incompletely captured	Established for prognostic risk estimation; not drug-predictive
Plasma KIM-1	Postoperative level associated with recurrence; dynamic signal	Thresholds and treatment-predictive validation incomplete	Investigational only; research or trial stratification
ctDNA/molecular residual disease	May identify residual disease when positive; serial monitoring is possible	Low shedding, small cohorts and false-negative results in localized RCC	Investigational only; no routine treatment assignment
Integrated tissue and imaging markers	PD-L1, gene-expression, spatial immune, radiomic and computational-pathology signals may capture heterogeneity	No single assay is externally validated to select adjuvant therapy; protocol dependence and bias remain	Investigational only; do not use PD-L1 alone

Notes: ctDNA: circulating tumor DNA; KIM-1: kidney injury molecule-1; PD-L1: programmed death-ligand 1.

Table 3. Proposed three-axis framework for postoperative precision treatment.

Axis	Q	Current measure	Decision contribution
1. Recurrence risk	How likely is clinically relevant relapse?	Pathology, stage, grade, nodal and sarcomatoid status; validated model	Defines evidence boundary and expected absolute benefit
2. Residual-disease assessment	Is residual disease detectable radiologically or through investig-ational biomarkers?	Postoperative imaging; KIM-1 and ctDNA only in research	May eventually support trial enrollment or allocation; not ready for routine treatment selection
3. Treatment fitness and preference	Can the patient accept treatment burden and uncertainty?	Renal function, autoimmune or transplant history, frailty, compe-ting risk, values and access	Determines whether expected benefit outweighs toxicity and burden
Integrated decision	Do all three axes support interven-tion?	Multidisciplinary review and shared decision-making	Observation, established pembrolizumab, or a clinical trial; regionally approved intensification requires explicit discussion of immature OS and added toxicity

Notes: This framework is a clinical synthesis proposed by the authors. It has not been prospectively validated, does not assign therapy according to biomarkers and should not replace regulatory labeling, guidelines or individualized multidisciplinary judgment. Abbreviations: ctDNA: circulating tumor DNA; KIM-1: kidney injury molecule-1; OS: overall survival.

when expected absolute benefit is limited, contraindications are substantial or the informed patient declines therapy. In the United States, pembrolizumab plus belzutifan is approved in the United States and represents a promising but not yet mature option, because OS is immature and toxicity is greater; its use elsewhere depends on current local authorization and guidance. Dual-checkpoint blockade and biomarker-directed escalation or de-escalation remain investigational only. Table 3 summarizes the proposed framework. Figure 1 illustrates how the three axes inform observation, standard pembrolizumab or clinical-trial consideration.

Treatment after relapse following adjuvant pembrolizumab

Prospective phase 3 data specific to recurrence after adjuvant pembrolizumab are unavailable, so sequencing guidance is extrapolated from ICI-pretreated metastatic disease and expert consensus. Relapse during pembrolizumab or within 6 months of completion is generally treated as ICI-refractory or early progression and may reflect primary or rapidly acquired resistance. Potential mechanisms include pre-existing immune exclusion, an angiogenic or myeloid-dominant microenvironment and acquired immune escape; these remain hypotheses extrapolated from metastatic biology rather than validated post-adjuvant treatment selectors [29]. Current European Association of Urology guidance weakly favors VEGFR-TKI monotherapy and advises against immediate ICI rechallenge in this setting [31]. A European Delphi consensus likewise distinguishes recurrence by the interval after adjuvant therapy [32]. The early-relapse approach is supported indirectly by CONTACT-03 and TiNivo-2, in which adding an ICI to a VEGFR-TKI after prior ICI exposure did not improve outcomes [33, 34]. For relapse more than 12 months after completion, that consensus supports reconsidering standard first-line options, including an ICI-based combination; possible renewed ICI sensitivity remains a hypothesis rather than a prospectively proven post-adjuvant phenomenon [32]. The 6–12-month interval remains a gray zone without consensus and warrants multidisciplinary review and, when feasible, clinical-trial enrollment [32].

Toxicity, survivorship and value

Adjuvant toxicity occurs in patients without measurable disease and must be evaluated differently from toxicity in metastatic RCC. Immune-related endocrinopathies may require lifelong replacement; nephritis has particular relevance after nephrectomy; and treatment visits affect employment, travel and caregiver burden. Real-world evidence confirms that serious adverse events can lead to

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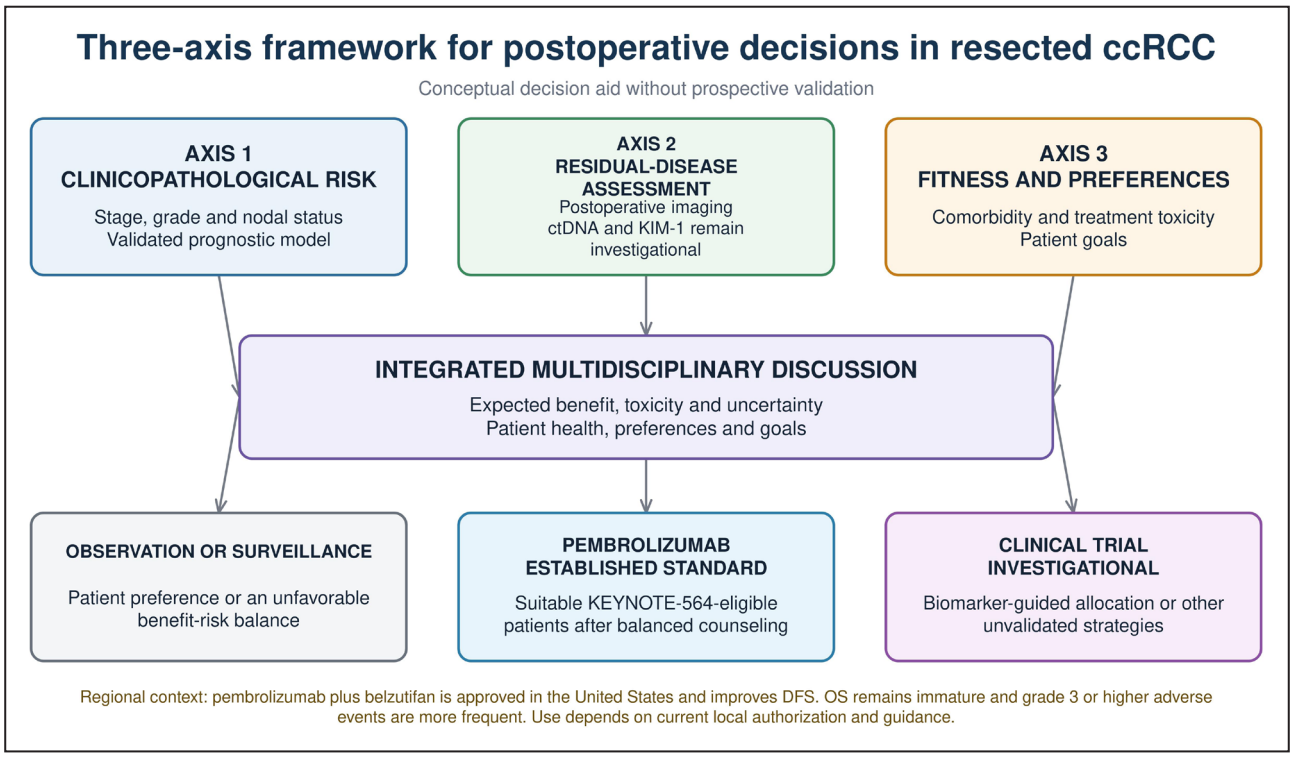


Figure 1. **Conceptual three-axis decision framework after nephrectomy for clear-cell renal cell carcinoma**. Clinicopathological risk defines the evidence boundary and expected absolute benefit; treatment fitness and patient preferences determine whether the balance is acceptable; candidate residual-disease markers currently direct clinical-trial consideration only. The figure is not a validated treatment algorithm and does not replace current labeling, guidelines or multidisciplinary judgment. ccRCC, clear-cell renal cell carcinoma; ctDNA, circulating tumor DNA; DFS, disease-free survival; KIM-1, kidney injury molecule-1; OS, overall survival.

pembrolizumab discontinuation in a clinically relevant proportion of patients [35]. Belzutifan introduces chronic anemia and hypoxia risk. Patient-reported outcomes, decisional regret and financial toxicity should therefore be incorporated as important prospective outcomes in future trials rather than treated as secondary descriptive endpoints.

Value depends on absolute recurrence risk, durable OS improvement, treatment cost and the proportion of patients exposed without benefit. Biomarker-enriched designs could improve both clinical value and statistical efficiency. De-escalation is equally important: optimal duration may be shorter than one year for some patients, while persistent molecular residual disease may justify longer or combination treatment in others.

Research priorities

Four priorities should guide the next generation of studies. First, mature OS and long-term safety are required for every intensified regimen. Second, biospecimens should be collected longitudinally to validate KIM-1, ctDNA and integrated tissue-imaging signatures as predictive—not merely prognostic—tools. Third, trials should incorporate treatment duration and de-escalation questions. Fourth, subsequent-therapy outcomes must be captured so that adjuvant benefit is not assessed in isolation from the metastatic treatment sequence.

Adaptive platform designs may be useful in RCC because biological subgroups can be refined as biomarkers mature. Future trials should test whether eligibility can safely move from broad anatomical risk toward composites of clinicopathological risk, residual-disease detection and tumor-immune state. Until those strategies are prospectively validated, they should not be used to intensify or omit routine treatment.

Strengths and limitations

This review integrates the first adjuvant regimen with proven OS benefit, the first active-control intensification trial, contemporary biomarker evidence and post-adjuvant sequencing in one clinically focused synthesis. It was not conducted as a systematic or scoping review: source selection was purposive, and duplicate screening, formal risk-of-bias assessment and certainty grading were not performed. Its evidence categories are therefore interpretive rather than formal recommendations. Several 2025–2026 findings remain available only as congress reports, OS is immature for intensified therapy, and prospective sequencing evidence after adjuvant pembrolizumab is absent. The proposed three-axis framework is hypothesis-generating and requires prospective validation; regional regulatory and guideline positions may also change.

Conclusions

One year of adjuvant pembrolizumab is the established evidence-based option to discuss with medically suitable

patients with resected ccRCC at KEYNOTE-564-defined increased risk because randomized evidence demonstrates both DFS and OS benefit. Pembrolizumab plus belzutifan is a promising, regionally approved intensification option, but immature OS, greater toxicity and unsettled guideline uptake preclude describing it as a universal standard. RAMPART dual-checkpoint blockade and all biomarker-directed treatment allocation remain investigational. No biomarker is validated to select or omit routine adjuvant therapy, and these ccRCC-derived conclusions should not be extrapolated to non-clear-cell histologies. At present, precision resides mainly in clinicopathological risk stratification, assessment of treatment fitness and shared decision-making; molecular selection awaits prospective validation.

Declarations

Author contributions: Made substantial contributions to conception and design of the study: Rodríguez Parras P, Arrabal Polo MA; performed data acquisition (literature review and evidence synthesis): Rodríguez Parras P; performed data analysis and interpretation (literature verification and clinical interpretation): Zambudio Munuera A, Millán Ramos I, Morales Martínez A, Gutiérrez Tejero F, Arrabal Polo MA; drafted the work: Rodríguez Parras P. All authors read and approved the final manuscript.

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References

1. Haas N, Manola J, Dutcher J, Flaherty K, Uzzo R, Atkins M, *et al*. Adjuvant treatment for high-risk clear cell renal cancer: updated results of a high-risk subset of the ASSURE randomized trial. *JAMA Oncol*, 2017, 3(9): 1249-1252. [Crossref]
2. Ravaud A, Motzer R, Pandha H, George D, Pantuck A, Patel A, *et al*. Adjuvant sunitinib in high-risk renal-cell carcinoma after nephrectomy. *N Engl J Med*, 2016, 375(23): 2246-2254. [Crossref]
3. Motzer R, Ravaud A, Patard J, Pandha H, George D, Patel A, *et al*. Adjuvant sunitinib for high-risk renal cell carcinoma after nephrectomy: subgroup analyses and updated overall survival results. *Eur Urol*, 2018, 73(1): 62-68. [Crossref]
4. Motzer R, Haas N, Donskov F, Gross-Goupil M, Varlamov S, Kopyltsov E, *et al*. Randomized phase III trial of adjuvant pazopanib versus placebo after nephrectomy in patients with localized or locally advanced renal cell carcinoma. *J Clin Oncol*, 2017, 35(35): 3916-3923. [Crossref]
5. Gross-Goupil M, Kwon T, Eto M, Ye D, Miyake H, Seo S, *et al*. Axitinib versus placebo as an adjuvant treatment of renal cell carcinoma: results from the phase III, randomized ATLAS trial. *Ann Oncol*, 2018, 29(12): 2371-2378. [Crossref]
6. Eisen T, Frangou E, Oza B, Ritchie A, Smith B, Kaplan R, *et al*. Adjuvant sorafenib for renal cell carcinoma at intermediate or high risk of relapse: results from the SORCE randomized phase III intergroup trial. *J Clin Oncol*, 2020, 38(34): 4064-4075. [Crossref]
7. Choueiri T, Tomczak P, Park S, Venugopal B, Ferguson T, Chang Y, *et al*. Adjuvant pembrolizumab after nephrectomy in renal-cell carcinoma. *N Engl J Med*, 2021, 385(8): 683-694. [Crossref]
8. Powles T, Tomczak P, Park S, Venugopal B, Ferguson T, Symeonides S, *et al*. Pembrolizumab versus placebo as post-nephrectomy adjuvant therapy for clear cell renal cell carcinoma (KEYNOTE-564): 30-month follow-up analysis of a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*, 2022, 23(9): 1133-1144. [Crossref]
9. Choueiri T, Tomczak P, Park S, Venugopal B, Ferguson T, Symeonides S, *et al*. Overall survival with adjuvant pembrolizumab in renal-cell carcinoma. *N Engl J Med*, 2024, 390(15): 1359-1371. [Crossref]
10. Haas N, Powles T, Tomczak P, Park S, Venugopal B, Symeonides S, *et al*. Five-year follow-up results from the phase 3 KEYNOTE-564 study of adjuvant pembrolizumab (pembro) for the treatment of clear cell renal cell carcinoma (ccRCC). *J Clin Oncol*, 2025, 43(16_suppl): 4514-4514. [Crossref]
11. Choueiri T, Motzer R, Karam J, Yip W, Suárez C, Ye D, *et al*. Adjuvant pembrolizumab plus belzutifan for renal-cell carcinoma. *N Engl J Med*, 2026, 395(1): 32-43. [Crossref]
12. Larkin J, Powles T, Frangou E, Stewart G, Albiges L, Davis I, *et al*. LBA93 first results from RAMPART: an international phase III randomised-controlled trial of adjuvant durvalumab monotherapy or combined with tremelimumab for resected primary renal cell carcinoma (RCC) led by MRC CTU at UCL. *Ann Oncol*, 2025, 36: S1635. [Crossref]
13. Larkin J, Powles T, Frangou E, Stewart G, Albiges L, Davis I, *et al*. Durvalumab monotherapy versus active monitoring for resected primary renal cell carcinoma in RAMPART: an international, phase 3, randomized controlled trial. *J Clin Oncol*, 2026, 44(17_suppl): LBA4511-LBA4511. [Crossref]
14. Arrabal-Polo M, Gómez-Morón L, Gutiérrez-Tejero F, Zambudio-Munuera A, Millán-Ramos I, & Arrabal-Martín M. Adjuvant treatment in intermediate/high-risk clear cell renal cell carcinoma. Systematic review. *Actas Urol Esp*, 2025, 49(2): 501685. [Crossref]
15. Leibovich B, Blute M, Cheville J, Lohse C, Frank I, Kwon E, *et al*. Prediction of progression after radical nephrectomy for patients with clear cell renal cell carcinoma: a stratification tool for prospective clinical trials. *Cancer*, 2003, 97(7): 1663-1671. [Crossref]
16. Zisman A, Pantuck A, Dorey F, Said J, Shvarts O, Quintana D, *et al*. Improved prognostication of renal cell carcinoma using an integrated staging system. *J Clin Oncol*, 2001, 19(6): 1649-1657. [Crossref]
17. Bex A, Ghanem Y, Albiges L, Bonn S, Campi R, Capitanio

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U, *et al*. European Association of Urology Guidelines on renal cell carcinoma: the 2025 update. *Eur Urol*, 2025, 87(6): 683-696. [Crossref]
18. Ryan C, Tangen C, Heath E, Stein M, Meng M, Alva A, *et al*. Adjuvant everolimus after surgery for renal cell carcinoma (EVEREST): a double-blind, placebo-controlled, randomised, phase 3 trial. *Lancet*, 2023, 402(10407): 1043-1051. [Crossref]
19. Pal S, Uzzo R, Karam J, Master V, Donskov F, Suarez C, *et al*. Adjuvant atezolizumab versus placebo for patients with renal cell carcinoma at increased risk of recurrence following resection (IMmotion010): a multicentre, randomised, double-blind, phase 3 trial. *Lancet*, 2022, 400(10358): 1103-1116. [Crossref]
20. Motzer R, Russo P, Grünwald V, Tomita Y, Zurawski B, Parikh O, *et al*. Adjuvant nivolumab plus ipilimumab versus placebo for localised renal cell carcinoma after nephrectomy (CheckMate 914): a double-blind, randomised, phase 3 trial. *Lancet*, 2023, 401(10379): 821-832. [Crossref]
21. Allaf M, Kim S, Master V, McDermott D, Harshman L, Cole S, *et al*. Perioperative nivolumab versus observation in patients with renal cell carcinoma undergoing nephrectomy (PROSPER ECOG-ACRIN EA8143): an open-label, randomised, phase 3 study. *Lancet Oncol*, 2024, 25(8): 1038-1052. [Crossref]
22. US Food and Drug Administration, 2026. FDA approves belzutifan with pembrolizumab for adjuvant treatment of renal cell carcinoma. [Crossref] (accessed 10.09.26).
23. Oza B, Frangou E, Smith B, Bryant H, Kaplan R, Choodari-Oskooei B, *et al*. RAMPART: a phase III multi-arm multi-stage trial of adjuvant checkpoint inhibitors in patients with resected primary renal cell carcinoma (RCC) at high or intermediate risk of relapse. *Contemp Clin Trials*, 2021, 108: 106482. [Crossref]
24. Ricketts C, De Cubas A, Fan H, Smith C, Lang M, Reznik E, *et al*. The Cancer Genome Atlas comprehensive molecular characterization of renal cell carcinoma. *Cell Rep*, 2018, 23(1): 313-326.e315. [Crossref]
25. Xu W, Puligandla M, Halbert B, Haas N, Flaherty K, Uzzo R, *et al*. Plasma KIM-1 is associated with recurrence risk after nephrectomy for localized renal cell carcinoma: a trial of the ECOG-ACRIN research group (E2805). *Clin Cancer Res*, 2021, 27(12): 3397-3403. [Crossref]
26. Rini B, Albiges L, Tang X, Koeppen H, Bex A, Suárez C, *et al*. Circulating kidney injury molecule-1 (KIM-1) and association with outcome to adjuvant immunotherapy in renal cell carcinoma. *Ann Oncol*, 2025, 36(12): 1525-1534. [Crossref]
27. Smith C, Moser T, Mouliere F, Field-Rayner J, Eldridge M, Riediger A, *et al*. Comprehensive characterization of cell-free tumor DNA in plasma and urine of patients with renal tumors. *Genome Med*, 2020, 12(1): 23. [Crossref]
28. Correa A, Kalashnikova E, Wu H, Winters R, Balcioglu M, Sudhaman S, *et al*. Association of circulating tumor DNA with patient prognosis in surgically resected renal cell carcinoma. *Oncologist*, 2024, 29(10): 887-893. [Crossref]
29. Motzer R, Banchereau R, Hamidi H, Powles T, McDermott D, Atkins M, *et al*. Molecular subsets in renal cancer determine outcome to checkpoint and angiogenesis blockade. *Cancer Cell*, 2020, 38(6): 803-817.e804. [Crossref]
30. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of clear cell renal cell carcinoma. *Nature*, 2013, 499(7456): 43-49. [Crossref]
31. Bedke J, Ghanem Y, Albiges L, Bonn S, Campi R, Capitanio U, *et al*. Updated European Association of Urology Guidelines on the use of adjuvant immune checkpoint inhibitors and subsequent therapy for renal cell carcinoma. *Eur Urol*, 2025, 87(4): 491-496. [Crossref]
32. Grünwald V, Bex A, Rottey S, Suárez C, Procopio G, Velasco G, *et al*. Current status of adjuvant immunotherapy and relapse management in renal cell carcinoma: insights from a European Delphi study. *Eur J Cancer*, 2025, 225: 115569. [Crossref]
33. Pal S, Albiges L, Tomczak P, Suárez C, Voss M, de Velasco G, *et al*. Atezolizumab plus cabozantinib versus cabozantinib monotherapy for patients with renal cell carcinoma after progression with previous immune checkpoint inhibitor treatment (CONTACT-03): a multicentre, randomised, open-label, phase 3 trial. *Lancet*, 2023, 402(10397): 185-195. [Crossref]
34. Choueiri T, Albiges L, Barthélémy P, Iacovelli R, Emambux S, Molina-Cerrillo J, *et al*. Tivozanib plus nivolumab versus tivozanib monotherapy in patients with renal cell carcinoma following an immune checkpoint inhibitor: results of the phase 3 TiNivo-2 study. *Lancet*, 2024, 404(10460): 1309-1320. [Crossref]
35. Kopp R, Massari F, Grande E, Schieber T, Ürün Y, Kopecký J, *et al*. Real-world evidences on adjuvant pembrolizumab for renal cell carcinoma: results from the multicenter real-world ARON-1 study. *Cancer Immunol Immunother*, 2025, 74(12): 374. [Crossref]

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