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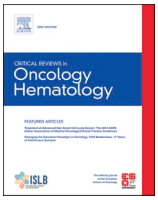

Adjuvant immunotherapy in high-risk renal cell carcinoma: Indications, limitations, and perspectives. A consensus statement from the GIOTTO uro-oncology group

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ABSTRACT

Renal cell carcinoma (RCC) is often diagnosed at a localized stage and treated with surgery. However, up to 40 % of patients may experience recurrence despite complete resection. The introduction of immune checkpoint inhibitors, particularly pembrolizumab, has changed the adjuvant treatment landscape. The Tuscan Interdisciplinary Uro-Oncological Group (GIOTTO) provides practical guidance on patient selection and clinical use of adjuvant pembrolizumab in RCC.

1. Introduction

Renal cell carcinoma (RCC) accounts for about 2–3 % of all adult cancers and is the most common kidney tumor (Rini et al., 2009). Its incidence is rising worldwide, likely due to greater use of abdominal imaging and increased exposure to environmental and metabolic risk factors, such as obesity, high blood pressure, and smoking (Rini et al., 2009).

Currently, about 70 % of RCC patients are diagnosed at a localized stage and are treated with either radical or partial nephrectomy. This is considered the standard curative approach. However, even after complete surgery, a significant number of patients—estimated between 20 % and 40 %—will experience recurrence, either locally or at distant sites, often within months or a few years (Mahvi et al., 2018).

Managing patients at high risk of recurrence after surgery remains a clinical challenge. In this context, adjuvant therapy is used to lower the chance of disease relapse, with the goal of improving disease-free survival (DFS) and, ideally, overall survival (OS).

In recent years, the treatment landscape has changed thanks to the introduction of immunotherapy, especially immune checkpoint inhibitors (ICIs). After disappointing results from targeted therapies (TKIs), the phase III trial KEYNOTE-564 showed promising results for adjuvant pembrolizumab in patients with high-risk clear cell RCC (Choueiri et al., 2021). Based on these results, the drug was approved by the Food and Drug Administration (FDA) and European Medicine Agency (EMA) and included in major guidelines ("GAZZETTA UFFICIALE DELLA REPUBBLICA ITALIANA PARTE PRIMA SI PUBBLICA TUTTI I GIORNI NON FESTIVI DIREZIONE E REDAZIONE PRESSO IL MINISTERO DELLA GIUSTIZIA-UFFICIO PUBBLICAZIONE LEGGI E DECRETI-VIA ARENULA 70–00186 ROMA AMMINISTRAZIONE PRESSO L'ISTITUTO POLIGRAFICO E ZECCA DELLO STATO-LIBRERIA DELLO STATO-PIAZZA G," n.d.; Motzer et al., 2025; Powles et al., 2024).

This consensus paper based on statement from the Tuscan Interdisciplinary Uro-Oncological Group (GIOTTO) aims to offer practical, shared recommendations for the use of adjuvant therapy in surgically treated RCC patients. The goal is to improve patient selection, support informed decisions, and guide clinical practice based on current evidence.

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1.1. Available evidence

Adjuvant therapy in RCC has been studied for over twenty years, starting with vaccines, cytokines, TKIs and more recently with immunotherapy. The main available evidence in this setting is summarized below.

1.2. Studies with TKIs

Initial studies on adjuvant systemic treatment used TKIs, drugs already proven in advanced RCC, to try to prevent recurrence after surgery. Several phase III trials tested the effectiveness of sunitinib, pazopanib, and axitinib (Table 1).

The ASSURE trial compared sunitinib or sorafenib to placebo in high-risk patients but demonstrated no significant improvement in DFS or OS, while reporting considerable side effects (Haas et al., 2016). Similarly, PROTECT trial, which tested pazopanib, showed only a slight improvement in DFS at higher doses, with no benefit in OS (Motzer et al., 2021). The ATLAS trial, testing axitinib, was stopped early due to lack of benefit (Gross-Goupil et al., 2018). Among these, the only study with a statistically significant improvement in DFS was S-TRAC, which showed that sunitinib extended DFS (median 6.8 vs 5.6 years) in patients with high-risk clear cell RCC (Ravaud et al., 2016a). However, it did not improve OS and was criticized for selective patient enrolment and poor management of side effects.

Overall, adjuvant TKIs were associated with relevant toxicity (fatigue, hypertension, hand-foot syndrome, liver issues) and reduced quality of life, often requiring dose adjustments or treatment interruption. For these reasons, international guidelines (ESMO, NCCN, AIOM) do not recommend routine use of adjuvant TKIs, except in clinical trials. Notably, sunitinib was approved for adjuvant use by the FDA, but not by the EMA (Ravaud et al., 2016b).

1.3. Studies with immunotherapy

Checkpoint inhibitors (anti-PD-1/PD-L1) have changed the treatment of metastatic RCC, and their role in the adjuvant setting has been evaluated in several phase III clinical trials (Table 2).

The CheckMate 914 trial investigated the efficacy of adjuvant nivolumab combined with ipilimumab versus a placebo in patients with localized RCC. The combination therapy did not meet the primary endpoint of DFS (Motzer et al., 2023). Importantly, this study exclusively included patients without metastatic disease. These findings are consistent with results from other recent trials in the adjuvant RCC setting, such as IMmotion010 and PROSPER (Allaf et al., 2024; Pal et al., 2022). In IMmotion010, adjuvant treatment with atezolizumab did not demonstrate a DFS advantage over placebo (Pal et al., 2022). Similarly, the PROSPER study, which assessed perioperative nivolumab (a single preoperative dose followed by nine postoperative doses) compared to surgery alone with observation, showed no DFS improvement in its interim analysis (Allaf et al., 2024).

These results contrast with those of the KEYNOTE-564 trial, published in 2021 (Choueiri et al., 2021). This was a phase III, randomized, double-blind trial comparing pembrolizumab to placebo in patients with clear cell RCC who had undergone complete resection and were at high risk of recurrence. Inclusion criteria were: pT2 tumors with high grade (G4), pT3 or pT4 stages, positive lymph nodes (N +), or completely resected metastatic disease (M1 NED) within 1 year from renal surgery. Patients received pembrolizumab 200 mg every 3 weeks for up to one year.

After a median follow-up of around 24 months, pembrolizumab significantly improved DFS, reducing the risk of recurrence or death by 37 % (HR 0.63; 95 % CI 0.50–0.80). The benefit was seen in almost all subgroups, including M1 NED, although this group was small and not analyzed separately. After 3 years, DFS was 77 % with pembrolizumab compared to 68 % with placebo.

During the 2024 American Society of Clinical Oncology Genitourinary Cancers Symposium T.K. Choueiri presented the third pre specified interim analysis of overall survival from the trial. With a median follow up of 57.2 months, pembrolizumab demonstrated a significant improvement in overall survival compared to placebo (medians not reached, HR 0.62, 95 % CI 0.44 −0.87; p = 0.0024). This benefit was consistent across key subgroups. Additionally, the observed disease-free survival benefit with pembrolizumab vs placebo remained in line with prior interim analyses (HR 0.72; 95 % CI 0.59 −0.87). (Toni K. Choueiri et al. Overall survival results from the phase 3 KEYNOTE-564 study of adjuvant pembrolizumab versus placebo for the treatment of clear cell renal cell carcinoma (ccRCC) (Choueiri et al., 2024).

The safety profile of pembrolizumab was consistent with expectations. Grade ≥ 3 adverse events occurred in 32.4 % of patients compared to 17.7 % in the placebo group, while immune-mediated events were reported in 34.6 % of patients (grade 3 in 8.6 %). These included manageable immune-related adverse events such as thyroiditis, colitis, and hepatitis. Approximately 20.7 % of patients discontinued treatment due to toxicity, although overall quality of life remained acceptable. Based on these results, pembrolizumab has been approved for adjuvant use in high-risk RCC patients by both FDA and EMA ("EMA recommends pembrolizumab for the adjuvant treatment of RCC - Kidney Cancer UK," n.d., "FDA approves pembrolizumab for adjuvant treatment of renal cell carcinoma | FDA," n.d.). It is currently the only adjuvant systemic therapy with a proven DFS and OS benefit and has been included in major guidelines as a standard option for selected patients, including some M1 NED cases.

Nevertheless, significant questions remain concerning the optimal management of relapse after adjuvant immunotherapy and the best criteria for selecting eligible patients, particularly those who presented with metastatic disease at diagnosis

1.4. Patients eligible for adjuvant therapy

Selecting patients for adjuvant treatment with pembrolizumab after nephrectomy is a key step to ensure the best balance between benefit and risk. Patient eligibility is mainly based on the inclusion criteria from the KEYNOTE-564 trial, which are also reflected in international guidelines.

Adjuvant therapy is generally recommended for patients who have

Table 1
Major Studies on the Use of TKIs in Adjuvant Therapy for Renal cell carcinoma.

Study [ref]	Drug	Design	Main results	Toxicity	Conclusions
ASSURE (Haas et al., 2016)	Sunitinib / Sorafenib	Phase III, placebo-controlled	No benefit in DFS or OS	High (fatigue, hypertension, dose reductions)	Negative
PROTECT (Motzer et al., 2021)	Pazopanib	Phase III, placebo-controlled	Marginal DFS benefit only at high doses; no OS effect	Significant, especially at high doses	Negative
ATLAS (Gross-Goupil et al., 2018)	Axitinib	Phase III, placebo-controlled	Study stopped for futility	Significant toxicity	Negative
S-TRAC (Ravaud et al., 2016a)	Sunitinib	Phase III, placebo-controlled	Improved DFS (6.8 vs 5.6 years), no OS benefit	High; frequent discontinuations	Only study with DFS benefit; criticized for methodological flaws

TKIs, tyrosine kinase inhibiotrs; DFS, disease free survival; OS, overall survival.

Table 2
Major Studies on the Use of ICIs in Adjuvant Therapy for Renal cell carcinoma.

Clinical trial [ref]	Tumor features	Treatment arms	Duration of treatment	Main results	Conclusion
KEYNOTE−564 (Choueiri et al., 2021)	Intermediate-high risk M0-M1 NED Clear cell RCC/sarcomatoid	Pembrolizumab Placebo	1 year	Benefits in DFS and OS	Positive
IMmotion010 (Pal et al., 2022)	Intermediate-high risk M0-M1 NED Clear cell RCC/sarcomatoid	Atezolizumab Placebo	1 year	No benefit in DFS or OS	Negative
Checkmate−914 (Motzer et al., 2023)	Intermediate-high risk M0 Clear cell RCC/sarcomatoid	Nivolumab+Ipilimumab Placebo	At least 24 weeks	No benefit in DFS or OS	Negative
PROSPER (Allaf et al., 2024)	Intermediate-high risk, M0 or M1 NED RCC of any histology	Nivolumab neoadjuvant-adjuvant Placebo	40 weeks (one dose prior surgery followed by 9 doses)	No benefit in RFS or OS	Negative

ICIs, immune checkpoint inhibitors; RCC, renal cell carcinoma; DFS, disease free survival; RFS, relapse free survival; OS, overall survival; NED, non-evidence of disease.

undergone complete surgical resection but still have a high risk of recurrence, based on established clinical and pathological factors. The main high-risk features include:

- Tumors classified as pT3 or pT4, regardless of lymph node status, and node-positive tumors (N +), as long as there is no evidence of distant metastasis (M0).
- Patients with previously metastatic disease that has been completely resected, known as M1 NED ("no evidence of disease"), in whom all metastases were surgically removed either at the time of nephrectomy or shortly after. Although data in this group are limited, these patients were included in the pivotal trial.

It is also essential that patients have a good general condition (ECOG performance status 0–1), so they can tolerate a treatment duration of up to one year and manage potential immune-related side effects effectively.

Overall, patient selection should be strict and shared within a multidisciplinary team, ideally including oncologists, urologists, pathologists, and, when needed, immunologists or other specialists. A summary of eligibility criteria for adjuvant therapy with pembrolizumab in RCC is reported in Table 3.

2. Exclusions and contraindications to adjuvant therapy

Although pembrolizumab is a promising option to reduce the risk of recurrence in high-risk RCC, not all surgically treated patients are suitable for this treatment. A careful and comprehensive evaluation is required, taking into account various clinical, biological, and individual factors that may exclude or discourage the use of immunotherapy.

First, patients with absolute contraindications to ICIs must be excluded. These include active autoimmune diseases, previous severe immune-related conditions (such as myocarditis, pneumonitis, or severe colitis), chronic immunosuppressive therapy (*e.g.*, after organ transplant), and uncontrolled chronic infections (like HBV, HCV, or HIV).

Furthermore, adjuvant pembrolizumab is not indicated for patients with non-clear cell histologies or rare subtypes, where clinical evidence is lacking.

Table 3
Eligibility criteria for adjuvant therapy with pembrolizumab in Renal cell carcinoma.

Category	Specific Criteria
Disease Stage	Locally advanced tumor: pT3 or pT4, any N, M0 Node-positive disease: N + M0 Resected metastatic disease: M1 NED
Histology	Clear cell or predominantly clear cell renal carcinoma
Performance Status*	ECOG 0 or 1

ECOG. Eastern Cooperative Oncology Group; NED, non-evidence of disease.
* Functional status should be assessed comprehensively, especially in older or frail patients, using validated geriatric screening tools (e.g., G8, VES-13).

Finally, this therapy is not justified in patients at low risk of recurrence, such as those with pT1 or low-grade pT2 tumors with negative surgical margins. For these patients, active surveillance remains the most appropriate approach to avoid overtreatment.

In conclusion, the decision to forgo adjuvant pembrolizumab should be made after a thorough multidisciplinary evaluation, considering tumor characteristics, the patient's overall health, medical history, and personal preferences.

2.1. Special considerations

Particular attention should be given to elderly or frail patients, who may have reduced tolerance to immunotherapy side effects. While chronological age alone is not a contraindication, it is essential to assess functional status, geriatric performance (preferably using screening tools such as G8 or VES-13)(Bouzan and Horstmann, 2023; Kroc et al., 2016), comorbidities, especially competitive ones, the ability to adhere to treatment, and social support. In such cases, a geriatric oncology assessment can help guide the decision. The potential benefit in DFS must always be weighed against the risk of immune toxicity, which could impact quality of life or lead to serious complications.

A summary of exclusions and contraindications to adjuvant therapy with pembrolizumab for RCC is reported in Table 4.

2.2. Consensus recommendations

Based on current evidence and clinical experience, our multidisciplinary group has developed the following recommendations for the use of adjuvant therapy in patients with RCC who have undergone complete

Table 4
Exclusions and contraindications to adjuvant therapy with pembrolizumab.

Category	Details
Absolute Contraindications	- Active or flaring autoimmune diseases - History of severe immune-related events (e.g., myocarditis, pneumonitis, severe colitis) - Need for chronic immunosuppression (e.g., post-organ transplant) - Uncontrolled or reactivatable chronic infections (HBV, HCV, HIV)
Advanced Age / Frailty	-Clinical and functional frailty regardless of chronological age (functional status and geriatric performance should be prioritized over chronological age) - Competitive comorbidities - Limited adherence or social support - Geriatric oncology assessment recommended
Non-eligible Tumor Histology	- Non-clear cell tumors - Rare or pure sarcomatoid histologies - Lack of supporting evidence
Low Recurrence Risk	- pT1 or pT2 tumors with low grade - Negative surgical margins - High expected disease free survival with observation alone

surgical resection.

2.3. Adjuvant immunotherapy

- Pembrolizumab is the only approved adjuvant option with a high level of evidence (phase III trial). It is recommended for high-risk patients, specifically:

o pT2 grade 4 or sarcomatoid.
o pT3 or pT4 tumors without distant metastases (M0), regardless of nodal status.
o Node-positive disease (N +) after complete resection.
o Patients with completely resected metastatic disease (M1 NED).

- Eligible patients should have:

o Clear-cell histology or predominantly clear-cell RCC.
o ECOG performance status of 0–1.
o No contraindications to immunotherapy (e.g., active autoimmune disease, prior severe immune-related events, or organ transplants).

- The recommended treatment duration is 1 year (17 cycles of pembrolizumab), as long as the patient does not experience unacceptable toxicity or disease recurrence.
- A multidisciplinary assessment is essential before initiating therapy, involving an oncologist, urologist, and, if needed, an immunologist or internist for immune-related risk management.

2.4. Targeted therapies (TKIs)

- Although the S-TRAC study showed a DFS benefit with sunitinib, the lack of OS benefit, high toxicity, and negative results from other trials (ASSURE, PROTECT, ATLAS) raise concerns about the routine use of TKIs in the adjuvant setting (Gross-Goupil et al., 2018; Haas et al., 2016; Motzer et al., 2021; Ravaud et al., 2016a).
- Therefore, TKIs are not recommended in routine practice and should be restricted to experimental protocols.

2.5. Shared decision-making

- A patient-centered approach is essential:

o Detailed discussions about expected benefits, risks (including management of immune-related toxicities), treatment duration, and impact on quality of life.
o Use of shared decision tools (*e.g.*, informative brochures, consent forms), especially for elderly patients or those with comorbidities.

- In cases of uncertainty regarding indication (*e.g.*, T2 tumors with biological risk factors), referral to a center with active clinical trials or a strategy of close follow-up is recommended.

2.5.1. Critical points and open questions in the use of adjuvant immunotherapy for M1 NED patients

One of the main uncertainties about adjuvant immunotherapy in RCC concerns patients with M1 NED—those with initially metastatic disease who achieved complete resection and had "no evidence of disease" at the start of adjuvant therapy.

In the KEYNOTE-564 study, M1-NED patients comprised only about 6 % of the study population, and no specific subgroup analysis was performed. No significant OS benefit has been demonstrated in this group, and the generalizability of the DFS benefit remains unclear (Choueiri et al., 2021). Therefore, pembrolizumab should be considered with caution in M1 NED patients and preferably offered within data collection programs or clinical trials.

Another unresolved issue concerns the initial treatment approach for these patients. The strategy of cytoreductive surgery followed by adjuvant immunotherapy presumes that the disease can be biologically controlled through a sequential surgical-systemic approach. However, it is not known whether treating these patients upfront as metastatic—using systemic combination therapy (ICI + TKI)—would result in better outcomes.

An often-overlooked aspect is the site of initial metastases, which can significantly influence prognosis and treatment decisions. Metastases in critical sites such as the liver, bone, central nervous system (CNS), or multiple visceral organs are often linked to more aggressive disease and a high risk of early recurrence, even after surgery.

In these cases, radical surgery followed by immunotherapy may not offer real benefit, especially without clear OS data. Instead, upfront systemic therapy may be more appropriate, using combinations proven effective in metastatic settings (*e.g.*, ICI + TKI) to target micrometastatic disease from the start.

Thus, surgical resection of metastases in M1 NED patients should be carefully considered, especially for high-risk or rapidly progressive sites. Surgery is more appropriate when clinical conditions are favorable, the disease is oligometastatic and controlled, and realistic benefit is expected. Multidisciplinary evaluation, including high-quality imaging and team discussion, is essential to avoid inappropriate treatment and ensure a personalized approach.

In patients who relapse after adjuvant pembrolizumab, several clinical questions remain unanswered:

- Is it appropriate to reintroduce another ICI despite previous exposure and potential resistance?
- Or is it better to switch to a TKI monotherapy or use an ICI + TKI combination not previously used in the adjuvant setting?

Currently, no specific guidelines or comparative data support one strategy over another. Decisions should be individualized based on time to recurrence, patient characteristics, disease burden, and previous treatment-related toxicity.

Overall, M1 NED management remains a grey area in RCC. Including these patients in adjuvant trials creates new opportunities but also raises unresolved clinical questions. Future prospective studies and focused analyses will be crucial to better define:

- Who should undergo surgery with curative intent;
- Who should be treated as metastatic from the start with systemic therapy;
- And which is the best treatment algorithm in case of recurrence after adjuvant immunotherapy.

2.6. Management of recurrence after nephrectomy and adjuvant pembrolizumab

When disease recurrence occurs after adjuvant pembrolizumab, treatment should be personalized according to the type and timing of recurrence as well as tumor biology. Based on the SITC immunotherapy resistance taskforce suggestions (Kluger et al., 2020), a clinical interpretation is proposed below and synthetized in Fig. 1.

In the setting of oligorecurrence treatment should be individualized. In selected patients, local therapies such as surgery or stereotactic radiotherapy may contribute to disease control. In cases of indolent recurrence or in asymptomatic patients, active surveillance may represent a reasonable option, allowing the deferral of systemic treatment initiation.

In the presence of systemic recurrence, therapeutic decision-making should consider the interval since the last administration of pembrolizumab in the adjuvant setting:

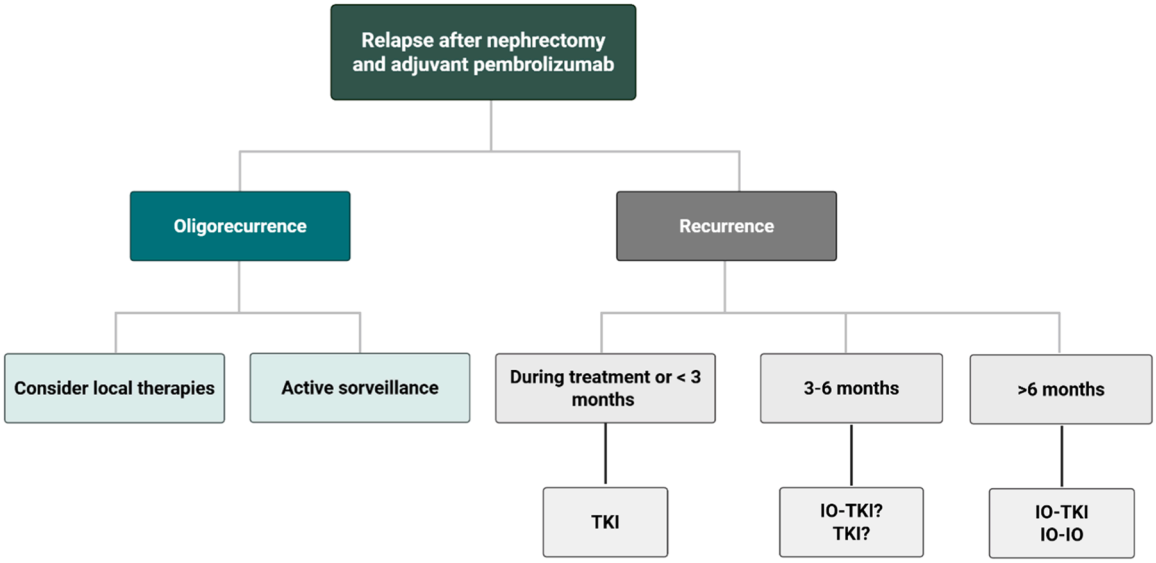

Fig. 1. Therapeutic algorithm in patients treated with pembrolizumab in adjuvant setting.

- Recurrence during treatment or within 3 months after completion: In this scenario, monotherapy with a tyrosine kinase inhibitor (TKI), such as cabozantinib or sunitinib, is generally the preferred option.
- Recurrence between 3 and 6 months: Therapeutic strategies may include either the combination of an immune checkpoint inhibitor (ICI) with a TKI or TKI monotherapy. The choice should be guided by the patient's prior clinical response and treatment tolerability.
- Recurrence beyond 6 months: In this case, both ICI + TKI combinations (e.g., pembrolizumab + axitinib/lenvatinib or nivolumab + cabozantinib) and dual ICI combinations (e.g., nivolumab + ipilimumab) may be considered, particularly in patients with a favorable clinical profile.

3. Conclusions

Managing recurrence risk after nephrectomy in high-risk RCC patients remains a clinical challenge. Adjuvant immunotherapy represents a significant advancement in post-surgical care, offering an active strategy to reduce disease recurrence.

Results from the KEYNOTE-564 study showed a clinically meaningful DFS and OS benefit with pembrolizumab, without unexpected toxicity.

Our consensus group agrees that:

- Adjuvant pembrolizumab should be considered the standard of care for patients with radically resected clear-cell RCC with high recurrence risk
- Identification of ideal candidates requires multidisciplinary evaluation of pathological, clinical, and functional factors
- TKI use in the adjuvant setting is not recommended outside clinical trials
- A shared, informed decision-making process is essential, transparently addressing benefits, risks, and uncertainties

In summary, adjuvant therapy is a promising opportunity for high-risk RCC patients after surgery. Its implementation in clinical practice must be guided by careful selection, clinical responsibility, and personalized care.

Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

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