INTRODUCTION

Renal cell carcinoma (RCC) accounts for approximately 4.1% of all new cancer diagnoses, with around 431,000 patients diagnosed and 179,000 deaths worldwide in 2020 [1,2]. Notably, 37.8% of these patients were under 60 years old at the time of diagnosis. The majority (85%) of kidney tumors are identified as RCC, of which about 70% exhibit clear cell histology. A recent analysis of the SEER (Surveillance, Epidemiology, and End Results) database reported an annual average increase in RCC incidence of 0.6% [3].

Localized RCC represents 70% of new RCC diagnoses, and the proportions of cases with regional and distant metastasis are approximately 15%, respectively [2]. Patients diagnosed with resectable locoregional RCC often undergo surgical resection with curative intent; however, up to 50% subsequently progress to metastatic disease [4,5]. While complete tumor removal through nephrectomy is the primary standard treatment, the advantages of additional adjuvant therapy following surgery remain a subject of debate. Tumor stage, grade, and regional nodal metastasis are pivotal prognostic factors, with patients who present these factors considered at high risk for relapse and metastasis [6].

Significant efforts have been made to translate clinical benefits from the metastatic to the adjuvant setting. Patients with relapsed or metastatic RCC have a markedly reduced survival rate. Adjuvant therapies, such as interferon-alpha and interleukin-2, which were principally utilized in the conventional systemic treatment of RCC until 2000, have been investigated to determine whether they can reduce recurrence [7]. However, clinical trials evaluating adjuvant
therapy have not demonstrated notable improvements in either overall survival (OS) or disease-free survival (DFS). Although these trials sought to improve the long-term prospects of patients confronting the challenges of relapsed or metastatic RCC, the results have not confirmed significant benefits in terms of prolonged survival or disease management. Therefore, the pursuit of more effective adjuvant therapies persists, necessitating ongoing research and investigation to discover innovative strategies for improving outcomes and quality of life for individuals dealing with this daunting disease. In the early 2000s, a noteworthy breakthrough in comprehending the underlying causes of RCC led to the development of a promising treatment strategy: tyrosine kinase inhibitors (TKIs), specifically those targeting the vascular endothelial growth factor (VEGF) family [8]. While these TKIs transformed the management of metastatic RCC, signifying a crucial moment in the battle against RCC and presenting new opportunities for improved patient care, numerous clinical trials did not corroborate the hoped-for improvements in either DFS or OS. In addition to TKIs, researchers have explored various treatment approaches over the years, but their efficacy has remained indeterminate. Despite these challenges, the search for effective adjuvant therapies for RCC continues, propelled by the necessity to improve the outcomes of patients confronting this challenging disease. As immune checkpoint inhibitors (ICIs), including programmed cell death-1 (PD-1) inhibitors and cytotoxic T lymphocyte antigen-4 inhibitors, have also proven to be effective against RCC, various treatment options have emerged [9,10]. Consequently, recent clinical trials have been conducted to assess the efficacy and safety of new drugs in adjuvant settings.

This comprehensive review seeks to examine the current landscape of adjuvant therapy for RCC, highlighting recent trials that investigate the effectiveness of treatment modalities such as TKIs and ICIs.

**TKIs AS ADJUVANT THERAPY**

Over the last 2 decades, targeted therapies such as VEGFR-TKIs (e.g., sunitinib, sorafenib, axitinib, and pazopanib) have revolutionized the treatment of metastatic RCC, propelling the initiation of clinical trials aimed at identifying effective adjuvant treatments. Globally, 5 phase 3 trials have been conducted; however, they have yielded inconsistent results for DFS. A summary of these studies is presented in Table 1.

### 1. S-TRAC Trial

The S-TRAC trial, a pivotal phase 3 study, evaluated sunitinib as an adjuvant treatment in RCC patients with clear cell histology, involving 615 high-risk locoregional clear-cell RCC (ccRCC) patients and assigning them randomly to receive either sunitinib or a placebo [11]. Patients on sunitinib showed a noticeable increase in median DFS, recording 6.8 years compared to 5.6 years with placebo (p=-0.03), though the trial did not demonstrate a definitive between-group difference in the median OS. Sunitinib’s approval by the U.S. Food and Drug Administration (FDA) as an adjuvant therapy for high-risk RCC patients, following the success of the S-TRAC trial, marked a significant advancement in RCC management. However, despite its demonstrated benefits for DFS, questions persist regarding its impact on OS, and its application remains a matter of medical debate due to potential toxicities and side effects, including diarrhea, fatigue, hypertension, and rashes, that can impinge upon patients’ quality of life [12,13].

### 2. Other VEGFR-TKI Trials

The ASSURE study examined sunitinib and sorafenib as additional treatments in 1943 RCC patients at high risk of recurrence [14]. Both sunitinib (adjusted from 50 to 37.5 mg) and sorafenib (adjusted from 400 to 200 mg twice daily) required dose changes due to side effects. However, the study did not find any differences in DFS or OS. In the later SORCE study, sorafenib failed to show any benefits in terms of DFS or OS compared to a placebo [15]. The trial included patients with intermediate-risk or high-risk ccRCC as well as non-clear cell RCC (nccRCC), as defined by the Leibovich risk model. They were given sorafenib or a placebo for 3 years, and after 10 years, the survival rates were similar among these groups. The PROTECT study tested adjuvant pazopanib in patients with locally advanced RCC who were at a high risk of recurrence after surgery [16]. Unfortunately, the study did not meet its main goal of showing improved improvement in overall survival (OS) or disease-free survival (DFS).
Table 1. Overview of adjuvant clinical trials utilizing tyrosine kinase inhibitors in renal cell carcinoma treatment

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>Starting dose</th>
<th>Adjusted dose</th>
<th>Treatment duration</th>
<th>AEs (grade 3 or worse)</th>
<th>Most common AEs</th>
<th>No.</th>
<th>Treatment regimen</th>
<th>Time</th>
<th>Primary end point</th>
<th>Outcome</th>
<th>Notes</th>
<th>Histologic subtype</th>
<th>Recurrence Risk scoring system</th>
<th>Designation of high risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASSURE 3</td>
<td>50-mg sunitinib, 800-mg sorafenib</td>
<td>37.5-mg sunitinib, 800-mg sorafenib</td>
<td>54 Weeks</td>
<td>63% sunitinib, 800-mg sorafenib</td>
<td>Sunitinib: hypertension, fatigue (17%), hand-foot syndrome (15%), diarrhea (10%)</td>
<td>Sunitinib vs. placebo</td>
<td>1,943</td>
<td>Sorafenib or sunitinib vs. placebo</td>
<td>1 Year</td>
<td>DFS</td>
<td>No significant differences, Sunitinib; 5.8 years HR, 1.02; 97.5% CI, 0.85 to 1.23; p=0.8038</td>
<td>ccRCC or nccRCC</td>
<td>UISS</td>
<td>pT3/4 grade 3/4 or and T, N+</td>
<td></td>
</tr>
<tr>
<td>S-TRAC 3</td>
<td>50-mg sunitinib</td>
<td>-</td>
<td>1 Year</td>
<td>63%</td>
<td>Diarrhea (67%), Hand-foot syndrome (50%), Hypertension (37%)</td>
<td>Sunitinib vs. placebo</td>
<td>615</td>
<td>Sorafenib vs. placebo</td>
<td>1 Year</td>
<td>DFS</td>
<td>Significant differences, Sunitinib; 6.8 years HR, 0.76; 95% CI, 0.59 to 0.98; p=0.03</td>
<td>ccRCC</td>
<td>UISS</td>
<td>T3 high and T4 and any T, N+</td>
<td></td>
</tr>
<tr>
<td>PROTECT 3</td>
<td>800-mg pazopanib</td>
<td>600-mg pazopanib</td>
<td>1 Year</td>
<td>60%</td>
<td>Hypertension (25%), LFT elevation (16%), diarrhea (7%)</td>
<td>Pazopanib vs. placebo</td>
<td>1538</td>
<td>Pazopanib vs. placebo</td>
<td>1 Year</td>
<td>DFS</td>
<td>No significant differences, HR, 0.86; 95% CI, 0.70 to 1.06; p=0.165</td>
<td>ccRCC</td>
<td>SSIGN</td>
<td>pT2G3-4N0, pT3-T4 ant G, and/or N+</td>
<td></td>
</tr>
<tr>
<td>ATLAS 3</td>
<td>10-mg axitinib</td>
<td>-</td>
<td>1–3 Years</td>
<td>61%</td>
<td>Hypertension (60%), diarrhea (47%), dysphonia (38%)</td>
<td>Axitinib vs. placebo</td>
<td>724</td>
<td>Axitinib vs. placebo</td>
<td>3 Year</td>
<td>DFS</td>
<td>No significant differences, HR, 0.870; 95% CI, 0.666 to 1.147; p=0.3211</td>
<td>&gt;50% component of ccRCC</td>
<td>Fuhrman grade</td>
<td>pT3 with Fuhrman grade 3 or pT 4 and/or N+, and T, any Fuhrman grade, M0</td>
<td></td>
</tr>
<tr>
<td>SORCE 3</td>
<td>800-mg sorafenib</td>
<td>400-mg sorafenib</td>
<td>1 or 3 Years</td>
<td>58% sorafenib 1 year 64% sorafenib 3 years</td>
<td>Sorafenib 1 year: hypertension (26%), hand-foot syndrome (24%), rash (7%), Sorafenib 3 years: hypertension (24%), hand-foot syndrome (24%), rash (15%)</td>
<td>Sorafenib vs. placebo</td>
<td>1711</td>
<td>Sorafenib vs. placebo</td>
<td>3 Year</td>
<td>DFS</td>
<td>No significant differences, HR, 1.01; 93% CI, 0.83 to 1.23, p=0.95</td>
<td>ccRCC or nccRCC</td>
<td>Leibovich risk model</td>
<td>Leibovich high risk</td>
<td></td>
</tr>
</tbody>
</table>

AEs, adverse events; DFS, disease-free survival; HR, hazard ratio; CI, confidence interval; ccRCC, clear cell renal cell carcinoma; nccRCC, non-clear cell renal cell carcinoma; UISS, UCLA Integrated Staging System; FDA, Food and Drug Administration; SSIGN, stage, size, grade and necrosis; pT, pathological tumor; N, node; M, metastasis; G, grade.
DFS. No significant differences in OS were found between the pazopanib and placebo groups. In the ATLAS trial, which involved 724 patients who had more than 50% ccRCC and had undergone nephrectomy, patients received axitinib or a placebo for over 3 years. However, axitinib did not reach the main goal of improving DFS compared to the placebo [17]. OS also showed no significant difference between the treatment arms. The results of these trials indicate that VEGFR-TKIs did not enhance survival outcomes in the adjuvant setting [18].

3. EVEREST Trial

The EVEREST study initially investigated an mTOR inhibitor, everolimus, as a postsurgery adjuvant treatment for RCC and provided key insights into disease management, even though it did not significantly improve recurrence-free survival (RFS) across all patient groups [19]. Administered for up to a year, everolimus demonstrated a nuanced pattern of efficacy, with subgroup analyses revealing a tangible RFS benefit among very high-risk patients, while showing no such benefit in intermediate-high-risk patients. Notably, the 5-year RFS was 67% with everolimus versus 63% with placebo, although this difference did not reach the pre-specified p-value for statistical significance. The study, which included 1,545 patients, highlighted the complexity and urgency of preventing metastatic progression in early-stage RCC, especially given the diverse responses among different risk stratifications. The findings from the EVEREST study underline the importance of focused investigations into mTOR inhibition, particularly for very high-risk RCC patients, and suggest the possibility of an approach where everolimus is considered concomitantly with a precise patient selection strategy that centers around identifying those at the highest risk for recurrence [20]. Despite 46% of patients experiencing grade 3 or higher adverse events (AEs) with everolimus compared to 11% with placebo, the EVEREST study offers vital insights into its application as an adjuvant treatment for RCC. Nonetheless, there is a need for more refined studies, aimed at enhancing risk assessment tools and selecting optimal patients for treatment, by going beyond conventional TNM staging and investigating the complex molecular diversity within RCC.

Regarding the use of adjuvant TKIs in RCC, sunitinib has been approved both in the United States and in Korea for adjuvant therapy, specifically in patients with a high risk of recurrence, a decision grounded on the demonstrable DFS advantage observed in the S-TRAC trial. Specifically, in Korea, it is authorized for use in high-risk RCC patients who have undergone nephrectomy. However, a prevailing issue remains that it is not covered by national insurance, requiring patients to bear the financial burden. Conversely, other trials of anti-VEGF agents have not successfully met their primary efficacy endpoints, and not one, sunitinib included, has shown a clear benefit for OS. Furthermore, a meta-analysis revealed no noticeable benefit in terms of DFS or OS and reported a significant increase in AEs [18,21].

ADJUVANT IMMUNOTHERAPY IN RCC: SHIFTING THE PARADIGM

Immunotherapy (IO), whether utilized alone or in combination with other treatments, has significantly advanced the therapy for metastatic RCC. This progress has mirrored its postoperative successes in melanoma, through stimulating immune responses against residual disease and distant micro-metastases. Consequently, ICIs—particularly agents that inhibit PD-1 and its ligand (PD-L1)—have emerged as a promising adjuvant treatment, prompting extensive research in the setting of adjuvant treatment for kidney cancer. Recent randomized studies have explored the influence of IO-based treatments in the adjuvant setting for RCC, reporting a spectrum of results. Key trials on IO drugs in the adjuvant setting are organized and presented in Table 2.

1. KEYNOTE-564 Trial

Several clinical trials have explored the role of IO in the adjuvant setting, and some of them are still ongoing. One of the most noteworthy among them is the adjuvant pembrolizumab trial (KEYNOTE-564) [22]. Pembrolizumab demonstrated promising potential in reducing recurrence risk in RCC patients, as evidenced by the KEYNOTE-564 trial. While it is used as a monotherapy and is not FDA-approved for the metastatic setting, it has demonstrated benefits for DFS and potentially even OS when used in the
adjuvant setting. The results of the KEYNOTE-564 trial led to the FDA’s approval of pembrolizumab as an adjuvant treatment for high-risk RCC patients by demonstrating a 32% decrease in disease recurrence risk, with a DFS hazard ratio (HR) of 0.68 (95% CI, 0.53–0.87; p=0.001). However, while data on DFS have been optimistic, OS data are still under examination, necessitating long-term follow-up to confirm potential long-term survival benefits. Subgroup analyses highlighted a noteworthy DFS benefit in M1 patients with no evidence of disease [23].

Despite the advancements presented by the trial, ongoing and further explorations are critical for understanding pembrolizumab’s potential and limitations from a holistic standpoint. Its immune-related AEs and the implications for subsequent treatment following metastatic disease relapse warrant consideration, emphasizing the necessity for continued scrutiny in future clinical practices and patient discussions [24]. While the role of pembrolizumab has solidified, particularly for high-risk RCC patients, ongoing investigations and long-term follow-up studies are crucial to ensure that its therapeutic applications are both thoroughly understood and judiciously applied in clinics.

2. Other IO Trials in an Adjuvant Setting

While the results from the KEYNOTE-564 trials showed noteworthy findings, the results from other clinical trials, especially the Phase 3 IMmotion010 trial, have introduced a complex narrative in the adjuvant IO landscape. The IMmotion010 trial scrutinized the impact of adjuvant atezolizumab (an anti-PD-L1 antibody) on resected RCC patients, identified with either a clear cell or sarcomatoid component, who were at an increased risk of recurrence [25]. Enrolled patients, reflecting demographics similar to prior studies, were randomized to receive atezolizumab or a placebo for 1 year, after nephrectomy with or without metastasectomy. With a median follow-up of 44.7 months, no significant difference was observed in DFS between the treatment and control arms, with a median investigator-assessed DFS of 57.2 versus 49.5 months (HR, 0.93; 95% CI, 0.75–1.15; p=0.50). Furthermore, no distinct patient subgroups, including M1 patients with no evidence of disease (HR, 0.93; 95% CI, 0.58–1.49), demonstrated discernible benefits from the therapy. Additionally, although OS data have yet to fully mature, current signals do not point toward a significant benefit, with an HR of 0.97 for a reduced mortality risk and a 3-year OS rate of 90.3% versus 89.8% when compared to the placebo.

The CheckMate 914 trial was conducted to examine the effectiveness of the adjuvant nivolumab/ipilimumab combination versus placebo (part A) and nivolumab monotherapy versus placebo (part B) [26]. Enrolled patients, particularly those with clear cell histology and a higher risk of recurrence, were the focus of CheckMate 914. Part A randomized patients with completely resected RCC (predominantly of clear cell histology) and an increased risk

<table>
<thead>
<tr>
<th>Clinical trial</th>
<th>No.</th>
<th>Tumor features</th>
<th>Treatment arms</th>
<th>Duration of treatment</th>
<th>DFS</th>
<th>RFS</th>
<th>OS</th>
<th>Grade 3 or worse AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>KEYNOTE-564</td>
<td>994</td>
<td>Intermediate-high-risk M0 M1 Clear-cell RCC/sarcomatoid</td>
<td>Pembrolizumab Placebo</td>
<td>1 Year</td>
<td>HR, 0.63; 95% CI: 0.50–0.80; p=0.004</td>
<td>75.2% (95% CI, 70.8–78.1)</td>
<td>65.5% (60.9–69.7)</td>
<td>HR, 0.52; 95% CI: 0.31–0.86; p=0.0048</td>
</tr>
<tr>
<td>IMmotion010</td>
<td>778</td>
<td>Intermediate-high-risk M0 M1 NED Clear-cell RCC sarcomatoid</td>
<td>Atezolizumab Placebo</td>
<td>1 Year</td>
<td>HR, 0.93; 95% CI: 0.75–1.15; p=0.50</td>
<td>N/A</td>
<td>N/A</td>
<td>HR, 0.97 (95% CI: 0.67–1.42)</td>
</tr>
<tr>
<td>Checkmate-914</td>
<td>816</td>
<td>Intermediate-high-risk M0 Clear-cell RCC sarcomatoid</td>
<td>Nivolumab+Ipilimumab Placebo</td>
<td>At least 24 weeks</td>
<td>HR, 0.92; 95% CI: 0.71–1.20</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>PROSPER</td>
<td>819</td>
<td>Intermediate-high-risk M0 or M1 NED RCC of any histology</td>
<td>Nivolumab neoadjuvant Adjuvant placebo</td>
<td>40 Weeks (one dose prior to surgery followed by 9 doses)</td>
<td>N/A</td>
<td>HR, 0.97 (95% CI, 0.74–1.28; P1-sided=0.43)</td>
<td>HR, 1.48; (95% CI: 0.89–2.48; P1-sided=0.93)</td>
<td>20%</td>
</tr>
</tbody>
</table>

DFS, disease-free survival; RFS, relapse-free survival; OS, overall survival; AEs, adverse events; NED, no evidence of disease; RCC, renal cell carcinoma; HR, hazard ratio; CIs, confidence intervals; N/A, not applicable.
of recurrence based on TNM stage and histologic grade. They were assigned to receive a 6-month treatment of either combined ipilimumab/nivolumab therapy or a placebo. Following a median follow-up of 37 months in part A, no significant difference in median DFS was observed (not reached vs. 50.7 months; HR, 0.92; 95% CI, 0.71–1.19). The 24-month DFS rates stood at 76.4% and 74% in the experimental and control arms, respectively. Although patients with sarcomatoid features, a small subgroup, seemed to significantly benefit from the ipilimumab/nivolumab combination, the advantage was offset by a notable 29% discontinuation of treatment due to AEs and a 23% necessity for corticosteroid use to manage immune-related AEs in the combination treatment arm. Part B of the ongoing trial, investigating the role of nivolumab monotherapy as an adjuvant treatment, is anticipated to expand the current understanding of single PD-1 inhibition in the adjuvant setting.

The PROSPER trial adopted a unique phase 3 trial design, randomizing 819 patients to receive either perioperative nivolumab or surgery alone [27]. The regimen involved administering one dose of nivolumab before surgery, followed by 9 adjuvant doses (480 mg intravenously every 4 weeks). Of the patients enrolled, 53% were diagnosed with cT2 disease, 47% with cT3/4, 17% with N+, and 4% with cM1, and 83% exhibited clear cell histology. The Data Safety and Monitoring Board prematurely halted the trial due to its futility for RFS (HR, 0.97; p=0.43). Although the OS data remain immature, initial indicators do not suggest a beneficial outcome (HR, 1.48; 95% CI, 0.89–2.48; p=0.93).

The results from IMmotion010, CheckMate 914, and PROSPER have not shown progress in DFS, thus raising questions regarding the exact role of IO in an adjuvant setting. The exact reasons behind these trial shortcomings remain elusive and might relate to differences in patient populations, the mechanisms of ICIs, and the duration of follow-up [28]. Given the disappointing outcomes from these trials, ongoing inquiry and evaluation are essential for expanding our understanding of how to prevent recurrence and improve outcomes for patients with RCC [29,30].

**COMPARING IO AND TKIs IN THE ADJUVANT SETTING**

In the adjuvant treatment landscape for RCC, a comparative analysis between TKIs and ICIs has emerged as a critical consideration. These 2 major classes of therapeutics offer distinct mechanisms of action and have undergone rigorous evaluations. As mentioned above, sunitinib gained FDA approval as the first adjuvant therapy based on data from the S-TRAC trial. This phase 3 trial demonstrated an improvement in DFS with sunitinib. However, updated data did not reveal a significant difference in OS. The introduction of IO into adjuvant RCC treatment marked a significant paradigm shift. The KEYNOTE-564 trial evaluated adjuvant pembrolizumab and reported statistically significant and clinically meaningful DFS benefits. This trial resulted in FDA approval for high-risk RCC patients. Conversely, ICIs’ DFS benefits have the potential to translate into long-term survival advantages, although more extended follow-up is required for definitive confirmation. Analyzing the data between TKIs and IO uncovers subtleties. TKIs, while showing benefits for DFS, have not consistently translated to OS advantages. In contrast, IO’s DFS benefits have the potential to lead to OS benefits, although more extended follow-up is needed to confirm this. Additionally, the consideration of toxicity is also very important, as ICIs may induce immune-related AEs, necessitating a meticulous risk-benefit evaluation. Moreover, the utilization of ICIs as adjuvant therapy can significantly impact subsequent treatment decisions in cases of disease relapse with metastasis [31]. The selection between TKIs and ICIs in adjuvant RCC therapy is complex. The choice depends on individual patient factors, risk profiles, and the significance placed on DFS versus OS. Ongoing research continues to shape our understanding of the comparative efficacy and safety of these approaches.

**ONGOING AND FUTURE TRIALS**

The dynamic landscape of adjuvant therapy for RCC continues to evolve with ongoing and future trials. International phase 3 adjuvant RCC studies, including RAMPART and LITESPARK-022, are actively enrolling patients, offering the promise of further improving outcomes for RCC patients.
following resection. The LITESPARK 002 study is examining belzutifan, a hypoxia-inducible factor 2 alpha (HIF-2α) inhibitor, in combination with pembrolizumab, as compared to a placebo plus pembrolizumab. Belzutifan targets a key mechanism in kidney cancer development linked to VHL mutations, effectively blocking HIF-related transcription. The trial targets ccRCC patients at intermediate-high or high risk, including those identified as M1 with no evidence of disease. The primary endpoint is DFS, and the study aims to enroll 1,600 patients [32]. The study is anticipated to be ongoing until approximately July 2024. Another phase 3 trial, RAMPART, is exploring the impact of durvalumab and tremelimumab on intermediate- to high-risk RCC patients postsurgery [33]. The trial will evaluate DFS and OS, with 1,750 patients planned for enrollment. Expected to achieve its primary completion by approximately July 2024, a distinct aspect of this trial is that it includes patients with Leibovich risk scores between 3 and 5, constituting 25% of the trial populations, as well as various RCC cell types.

In total, the RAMPART and LITESPARK 002 phase 3 trials together plan to recruit over 3,000 patients. The eligibility percentages vary due to different criteria. The collective efforts of patients participating in these trials, coupled with collaborative analysis, will guide the selection of the most appropriate adjuvant therapy for each individual with RCC in clinical practice. These trials aim to further refine treatment strategies, expand therapeutic options, and address unanswered questions.

**CHALLENGES IN ADJUVANT THERAPY SELECTION IN KOREA**

In Korea, applying adjuvant IO in a real-world setting demands careful consideration of several interconnected factors. Decisions about adjuvant therapy are significantly influenced by the country’s healthcare system and its strict reimbursement policies [34]. In Korea, as of 2023, the administration of adjuvant chemotherapy for RCC is entirely non-reimbursable, meaning that patients are required to pay the full cost of the medication themselves. These policies impose certain limitations on physicians regarding the selection of available adjuvant treatments for RCC patients.

Beyond financial aspects, addressing concerns about the potential for persistent and long-term AEs in some patients undergoing IO is vital. Identifying the most appropriate patients for treatment, taking into account variables such as distinct histological features and disease stage, is crucial. Alongside this, maintaining awareness of the limitations of IO—most notably, its relatively low objective response rate and the absence of predictive biomarkers—is essential for clarifying its applicability and efficacy across varied RCC patient demographics. Moreover, as we investigate further into therapeutic strategies, deciding on the next steps when adjuvant IO fails becomes necessary. Choosing between an ICI + ICI combination and an ICI + TKI regimen after recurrence requires a comprehensive approach that takes into account both patient-centered factors and the broader clinical perspective. This situation illustrates the complex challenges involved in integrating adjuvant IO into South Korea’s healthcare landscape. Furthermore, if RCC recurs, utilizing IO as a primary palliative treatment is neither approved nor logistically feasible following adjuvant IO treatment. These factors jointly highlight the complex interaction between healthcare policies and patient care in South Korea, emphasizing the necessity for continual evaluation and potential policy modifications to enhance patient access to optimal treatments.

**CONCLUSION**

No firmly established consensus exists regarding adjuvant chemotherapy for RCC, despite recent successful trials. Although VEGF inhibitors have shown a survival benefit, previously conducted trials of TKIs in the adjuvant setting have failed. Two recent meta-analyses also reported no benefits in DFS and OS [21,22]. The differences between successful and failed trials remain somewhat unclear. One contributor to the results may be the high toxicity rates. Patients treated with VEGF inhibitors commonly experienced toxicity. This can lead to poor compliance or low completion rates for TKIs, causing failure to extend DFS or OS. While VEGF inhibitors remain an effective treatment option for metastatic or unresectable RCC, they have failed to demonstrate a survival benefit in patients undergoing curative surgical resection. Further research will be needed to explain the mechanism underlying these discrepancies.
Pembrolizumab is currently the recommended adjuvant therapy for high-risk RCC. However, its application in nccRCC lacks substantial supporting evidence. ccRCC is the predominant subtype among diagnosed patients, and the majority of research has concentrated on this specific type. Conversely, our understanding of nccRCC remains limited, coupled with relatively weak treatment-related evidence. As a result, a pressing need exists for additional research studies focusing on individuals with nccRCC, aiming to improve our understanding and establish more effective treatment strategies within this patient subgroup. Moreover, we need to identify patients who notably benefit from adjuvant chemotherapy. A need persists to investigate more effective and established adjuvant treatments for these patients.

NOTES

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• ORCID
  Hyerim Ha: https://orcid.org/0000-0001-8889-144X
  Joo Han Lim: https://orcid.org/0000-0002-5330-1996

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