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REVIEW

Optimal Choice of Adjuvant Treatment for Renal Cell Carcinoma Following Nephrectomy

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Abstract: Renal cell carcinoma (RCC) is the fourteenth most common cancer worldwide. In about 55% of cases, it is diagnosed at a localised and/or locally advanced stage and therefore amenable to a curative approach. Although nephrectomy still represents the cornerstone of non-metastatic RCC (nmRCC) treatment, a relapse is observed in about 25–30% of patients undergoing curative surgery. Prognosis is drastically influenced by lymph nodal involvement. After the first disappointing results with a cytokine-based strategy, tyrosine kinase inhibitors (TKIs) were tested as adjuvant agents. Despite their efficacy in the metastatic setting, results in terms of disease-free survival (DFS) are not unequivocal and the overall survival (OS) benefit has not been demonstrated. Moreover, their toxicity profile induced a remarkable percentage of patients to discontinue the treatment. On the contrary, the KEYNOTE-564 trial showed the benefit of adjuvant pembrolizumab compared with placebo in terms of DFS with promising results in term of OS. Patients included were at intermediate or high risk of relapse, or patients with no evidence of disease after metastasectomy (M1 NED). The updated analysis presented at the American Society of Clinical Oncology Genito-Urinary (ASCO GU) 2022 confirmed the benefit of pembrolizumab versus placebo over time, although OS data are still immature. A longer follow-up and the several ongoing trials with immune checkpoint inhibitors (ICIs) will provide further data about adjuvant immuno-oncology (IO). Furthermore, the patients' selection based on clinical or biological features will be crucial in order to identify who benefits most from treatments.

Keywords: RCC, post-operative, TKIs, immunotherapy, clear cell, pembrolizumab

Introduction

Renal cell carcinoma (RCC) is the fourteenth most common cancer worldwide, with the diagnosis of 431,288 new cases every year.[1] About 55% of RCC are detected at an early stage (localized or locally advanced), still amenable to a curative approach.[2]

Nowadays, radical or partial nephrectomy represents the standard of care for non-metastatic RCC (nmRCC) whereas the role of cytoreductive nephrectomy is still debated.[3–5] Lymph nodal involvement drastically influences the prognosis, reducing to 71% the 5-year relative survival rate, compared with 93% in case of tumor localized to kidney.[6] Unfortunately, RCC recurrence is observed in about 25–30% of patients undergoing curative surgery,[2] emphasizing the unmet need of adjuvant therapy.

This review aims to summarize the foremost clinical trials exploring the role of adjuvant therapies in RCC patients at intermediate and high risk of relapse, including the subgroup with no evidence of disease after metastasectomy (M1 NED).

The Long Road to the Post-Operative Treatment

Adjuvant Pre-TKIs Era

Before the anti-vascular-endothelial growth factor (VEGF) tyrosine-kinase inhibitors (TKIs) era, the available options for metastatic RCC (mRCC) were chemotherapeutic agents and cytokine-based treatments. Interleukin-2 (IL-2) and/or

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interferon alpha (IFNα) represented the most common therapeutic options for mRCC, despite disappointing results in terms of efficacy and toxicity.[7,8]

To reduce the risk of relapse in patients undergoing curative nephrectomy, cytokines and bacillus Calmette-Guerin (BCG) were tested in several clinical trials as an *ante-litteram* immuno-oncology (IO) adjuvant therapy but the results were disappointing with severe adverse events (AEs).[9]

Nowadays, cytokine-based therapies can be considered outdated and only deserve a historical mention in the treatment of RCC.

Attempts and Disappointments of Anti-VEGF TKIs as Adjuvant Therapy

ASSURE Trial

The phase III double-blinded ASSURE trial evaluated the efficacy of sunitinib or sorafenib as adjuvant therapy versus placebo. The trial enrolled 1943 patients after nephrectomy for high-risk RCC (Table 1). [10]

The study did not meet its primary endpoint, as there was no benefit in terms of median disease-free survival (DFS) in both treatment arms: 6.1 vs 6.6 years, for sorafenib versus placebo respectively, hazard ratio (HR) 0.97 (97.5% confidence interval [CI] 0.80–1.17, $p = 0.7184$); for sunitinib versus placebo respectively, 5.8 vs 6.6 years, HR 1.02 (97.5% CI 0.85–1.23, $p = 0.8038$). Furthermore, no significant difference was described in terms of overall survival (OS) between groups: for sorafenib versus placebo, HR 0.98 (97.5% CI 0.75–1.28, $p = 0.8577$); for sunitinib versus placebo, HR 1.17 (97.5% CI 0.90–1.52, $p = 0.1762$). Later, the follow up at 5 years confirmed the negative results in term of DFS.[11]

Regarding the toxicity profile, grade 3–4 AEs were reported in 72% of patients in the sorafenib arm and 63% of patients in the sunitinib arm, compared with 25% in the placebo arm. As a result, about 45% of patients with sorafenib and 44% of those with sunitinib permanently discontinued the treatment because of AEs.[11]

S-TRAC Trial

Similarly, sunitinib was assessed as adjuvant therapy versus placebo in the phase III double-blinded S-TRAC trial, that enrolled 615 patients diagnosed with high-risk resected RCC.

The S-TRAC trial met its primary endpoint: in fact, at 5.4 years of follow-up, an improvement in terms of DFS by the blinded independent central review (BICR) was reported in the sunitinib arm, compared with the placebo arm (6.8 vs 5.6 years, HR 0.761 [95% CI 0.594–0.975, $p = 0.030$]). DFS assessed by the investigator did not confirm the results (HR 0.81 [95% CI 0.64–1.02, $p = 0.077$]).

Magnitude of benefit was higher for patients at higher risk of relapse (defined as T3, no/undetermined nodal involvement, Fuhrman Grade [FG] ≥ 2, and Eastern Cooperative Oncology Group Performance Status [ECOG PS] ≥ 1 or T4, local nodal involvement, or both), DFS by BICR was 6.2 compared with 4 years in the placebo arm (HR 0.74 [95% CI 0.55–0.99, $p = 0.04$]).[12]

Nevertheless, in an updated analysis of 2017, no benefit in terms of OS was described in the experimental arm compared with placebo (HR 0.92 [95% CI 0.66–1.28, $p = 0.6$]).[13]

Grade 3–4 AEs were reported in about 65% of patients treated with sunitinib, in contrast to 23.3% in the placebo group; 28.1% of patients in the experimental arm discontinued treatment due to AEs (Table 1).

Since the results of the S-TRAC trial, sunitinib was approved in 2017 by the Food and Drug Administration (FDA) as an adjuvant treatment for loco-regional RCC after nephrectomy.[14] Nevertheless, due to the lack of benefit in terms of OS and the conflicting results of sunitinib in the ASSURE trial, the European Association of Urology (EAU) did not recommend sunitinib as post-operative treatment after nephrectomy for RCC patients.[15]

PROTECT Trial

The phase III double-blinded PROTECT trial enrolled 1538 patients diagnosed with pT2-4N0M0 or pN1M0 RCC. The trial was aimed at assessing the efficacy of pazopanib 800 mg daily versus placebo, administered for up to one year, in high-risk patients after nephrectomy.[16]

Due to a severe drug-related hepatotoxicity, the dose of pazopanib was reduced to 600 mg daily, and the entire trial amended: DFS in an intention-to-treat (ITT) 600 mg (ITT_{600mg}) group versus placebo was considered as primary

Table 1 Trials Testing TKIs as Adjuvant Therapy

	ASSURE **Sorafenib vs Sunitinib vs Placebo**[10,11]	**S-TRAC** **Sunitinib vs Placebo**[12,13]	**PROTECT** **Pazopanib vs Placebo**[16,17]	**ATLAS** **Axitinib vs Placebo**[18]	**SORCE** **Sorafenib vs Placebo**[19]	**EVEREST** **Everolimus vs Placebo**[20]
N	1943	615	1538	724	1711	1545
Population	pT1b G3-4 N0 M0 or pT2-4 N0 M0 or pT any N+ M0	pT3 G2-4 N0 M0 or pT2-4 N0 M0 or pT any N+ M0	pT2 G3-4 N0 M0 or pT3-4 N0 M0 or pT any N1 M0	pT2-4 N0 M0 any or pT any N1 M0 any	pT1b-4 N0 M0 or pT any N1 M0	pT1 G3-4 N0 or pT3a G1-2 pT3a G3-G4 pT4 G any N+
Duration of treatment	54 w	1 yrs	1 yrs	1–3 yrs	3 vs 1 yrs	54 w
Primary Endpoint	DFS	DFS	DFS	DFS	DFS	RFS
DFS	**HR 0.97 (0.8–1.17)** **HR 1.02 (0.85–1.23)**	**HR 0.761 (0.594–0.975)**	**HR 0.94 (0.77–1.14)**	**HR 0.87 (0.66–1.147)**	**HR 1.01 (0.82–1.23)** **HR 0.94 (0.77–1.14)**	**HR 0.85 (0.72–1)**
OS	**HR 0.98 (0.75–1.28)** **HR 1.17 (0.9–1.52)**	**HR 0.92 (0.66–1.28)**	**HR 1.0 (0.8–1.26)**	-	**HR 1.06 (0.82–1.38)** **HR 0.92 (0.71–1.20)**	**HR 0.90 (0.71–1.13)**

Abbreviations: N, number of patients; w, weeks; yrs, years; DFS, disease-free survival; RFS, relapse-free survival; OS, overall survival; HR, hazard ratio.

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endpoint whereas DFS in an ITT 800 mg (ITT_{800mg}) group and in all enrolled patients (ITT_{All}) was chosen as secondary endpoint.

No benefit in terms of DFS was reported in the ITT_{600mg} group compared with placebo (HR 0.862 [95% CI 0.699–1.063, $p = 0.1649$]), as confirmed by the updated follow-up analysis (HR 0.94 [95% CI 0.77–1.14, $p = 0.51$]).[17] Conversely, a DFS advantage was observed in the ITT_{All} cohort (HR 0.84 [95% CI 0.71–0.99, $p = 0.04$]) and in the ITT_{800mg} cohort (HR 0.66 [95% CI 0.49–0.90, $p = 0.008$]) in comparison with patients treated with placebo (Table 1).

In the recently updated final OS analysis, no benefit was described in terms of OS in the ITT_{All} group (HR 1.0 [95% CI 0.80–1.26, $p > 0.9$]).[17] Therapy with pazopanib was complicated by a higher rate of grade 3 or worse AEs and about 60% of patients in ITT_{800mg} group and 51% of those in ITT_{600mg} group needed a dose reduction.[16]

ATLAS Trial

The role of axitinib as an adjuvant agent was assessed by the ATLAS trial, a phase III, randomized and double-blinded study, randomizing 724 patients to receive axitinib or placebo after nephrectomy. The starting dose of axitinib was 5 mg twice a day for up to 3 years, with a 1-year minimum. ATLAS trial did not meet its primary endpoint at the pre-planned interim analysis, as axitinib did not confer a benefit in terms of DFS in ITT population (HR 0.87 [95% CI 0.66–1.147, $p = 0.3211$]); as a result, the study was stopped due to futility. Furthermore, the axitinib arm was burdened by a higher rate of treatment-related AEs than the control arm (91% versus 56%), as well as treatment-related grade 3–4 AEs (Table 1).[18]

SORCE Trial

Efficacy and safety of sorafenib as adjuvant therapy was assessed by SORCE trial, an international, randomized, double-blinded, three-arm study: 1.711 patients at intermediate or high risk of recurrence after nephrectomy were randomized to 3 years of placebo (ARM A), 1 year of sorafenib followed by 2 years of placebo (ARM B), or 3 years of sorafenib (ARM C). The initial sorafenib dose of 400 mg twice a day orally was reduced to 400 mg once a day due to the high rate of treatment-related AEs.

SORCE did not meet its primary endpoint, as 3 years of sorafenib failed to provide an advantage over placebo in terms of DFS (HR 1.01 [95% CI 0.82–1.23, $p = 0.95$]); moreover, no benefit was observed comparing 1 year of sorafenib versus placebo, as well (HR 0.94 [95% CI 0.77–1.14, $p = 0.51$]). In terms of OS, sorafenib did not result to be superior to placebo, both in the 3-year treatment arm (HR 1.06 [95% CI 0.82–1.38, $p = 0.64$]), and in the 1-year treatment arm (HR 0.92 [95% CI 0.71–1.20, $p = 0.54$]) (Table 1). Interestingly, one year after the start of the trial, sorafenib was permanently discontinued by about half of patients due to AEs.[19]

EVEREST Trial

EVEREST trial was a phase III double-blinded study aiming to evaluate the impact of the mTOR inhibitor everolimus as adjuvant therapy.

Overall, 1545 patients as having intermediate-high (defined as pT1 G3-G4 N0 to pT3a G1-2 N0) or very high risk (defined as pT3a G3-4 to pT4 G-any or N+) of relapse of RCC after curative nephrectomy were randomized to everolimus 10 mg daily versus placebo, up to 54 weeks.

Non-clear cell renal cell carcinoma (nccRCC) was included in the trial.

Relapse-free survival (RFS) was the primary endpoint and secondary endpoints encompassed OS and toxicity profile.

As reported at ASCO 2022, the study did not meet its primary endpoint, although RFS was improved with everolimus versus placebo (HR 0.85 [95% CI 0.72–1.00, $p = 0.025$]), just missing the pre-specified, one-sided significance level of 0.022.

Median RFS was not accomplished: the 6-year RFS estimate was 61% for placebo, compared with 64% for everolimus. Nevertheless, everolimus showed RFS benefit in the very high-risk group (HR 0.79 [95% CI 0.65–0.97, $p = 0.011$]) compared with intermediate–high-risk group patients (HR 0.99 [95% CI 0.73–1.35, $p = 0.48$]).

No difference in terms of OS was reported in both arms (HR 0.90 [95% CI 0.71–1.13, $p = 0.178$]).

The toxicity profile of everolimus significantly impacted the adherence to the therapy as 45% of patients completed the 54 weeks of study treatment versus 69% in the placebo arm.[20]

Immunotherapy: How the Game is Changing

IO, both alone and in combination, has modified the landscape of mRCC therapy,[21–24] so its role in the adjuvant setting has been investigated.

IO already has proven to be effective as a post-operative treatment in melanoma,[25] for instance, by inducing an immune response against any residual disease and micro-metastases at distance: consequently, kidney cancer was considered the next step.

KEYNOTE-564 Trial

KEYNOTE-564 was a phase III, randomized double-blinded study, randomizing 994 patients at high risk of RCC after nephrectomy to receive adjuvant pembrolizumab or placebo for a year. Although most patients, both in the pembrolizumab arm (86.1%) and in the placebo arm (86.9%), were affected by RCC with M0 intermediate-high risk of recurrence (defined as stage II with nuclear grade (G) 4 or sarcomatoid differentiation; stage III or higher and N+), 5.8% of the patients in each group had undergone nephrectomy and metastasectomy (M1 NED).

The primary endpoint was DFS according to the investigator's assessment, whereas OS and safety were secondary endpoints.

KEYNOTE-564 met its primary endpoint, as pembrolizumab conferred a statistically significant benefit in terms of DFS compared with placebo: at 24 months, 77.3% versus 68.1% (HR for recurrence or death 0.68 [95% CI 0.53–0.87; $p = 0.002$]). An OS benefit was reported, as well: even if median OS was not reached in either group (HR for death 0.54 [95% CI 0.30–0.96]), at 24 months the percentage of patients alive was 96.6% (95% CI 94.3–98.0) in pembrolizumab arm and 93.5% (95% CI 90.5–95.6) in the placebo arm. The advantage of IO compared with placebo resulted more consistently in the long term, as at 12 months the percentage of patients alive was 98.6% (95% CI 97–99.3) and 98.0% (95% CI 96.3–98.9) in pembrolizumab and placebo group, respectively.

96.3% of patients in pembrolizumab group and 91.1% in placebo group reported at least one AE of any grade: the most common included fatigue, diarrhoea, pruritus and arthralgia. Nevertheless, grade 3 or worse AEs were mostly reported in the pembrolizumab arm (32.4%) rather than the placebo arm (17.7%). Finally, 7.6% of patients treated with IO permanently discontinued pembrolizumab, due to AEs.[26]

Afterwards, in 2022 the advantage of pembrolizumab in terms of DFS was confirmed by the 30-month updated analysis (HR 0.68 [95% CI 0.50–0.80] $p < 0.0001$), and reported in all subgroups: in fact, patients with M0 intermediate–high risk of recurrence (HR 0.68 [95% CI 0.52–0.89]), M0 high risk of recurrence (HR 0.60 [95% CI 0.33–1.10]) or M1 NED (HR 0.28 [95% CI 0.12–0.66]) reported a benefit by adjuvant IO. The estimated DFS rate at 24 months was 78.3% and 67.3% with pembrolizumab and placebo, respectively.[27]

A post hoc exploratory analysis revealed that pembrolizumab provides an advantage even in terms of progression-free survival 2 (PFS2), as well (HR 0.52 [95% CI 0.34–0.81] $p = 0.0018$); furthermore, this benefit seems to improve over time: at 12 months, at 18 months, at 24 months and at 30 months, PFS2 rates for pembrolizumab group were respectively 98.4%, 95.2%, 93.6% and 93.1%, compared with 95.3%, 92.2%, 88.3% and 85.7% in the placebo group, respectively.[23] PFS2 was defined as the time from randomization to disease progression on next-line anticancer drug therapy, or death from any cause, whichever occurred first and supports the efficacy of pembrolizumab even in progressing patients. Nevertheless, data are still not mature, as only 63 patients in the pembrolizumab arm and 86 patients in the placebo arm received subsequent anticancer drug therapy.[28]

In the updated analysis, the additional follow-up did not report any increase in AEs, and no greater use of steroids for immune-related AEs was observed.[27]

KEYNOTE-564 trial can be considered the cornerstone of adjuvant trial in RCC as it is a truly changing practice trial.

Adjuvant Immunotherapy Ongoing Trials

The role of IO in the adjuvant setting is still under evaluation in several trials, such as Immotion010[29] (ClinicalTrials.gov Identifier: NCT03024996), CheckMate-914[30] (ClinicalTrials.gov Identifier: NCT03138512), RAMPART[31] (ClinicalTrials.gov Identifier: NCT03288532) and LITESPARK-022[32] (ClinicalTrials.gov Identifier: NCT03142334) (Table 2).

Table 2 Ongoing Trials Testing IO in the Adjuvant Setting

	IMmotion010 NCT03024996[29]	CHECKMATE 914 NCT03138512[30]	RAMPART NCT03288532[31]	LITESPARK-022 NCT03142334[32]	PROSPER NCT03055013[44]
Phase	III	III	III	III	III
Treatment arms	Atezolizumab vs placebo	Nivolumab +/- ipilimumab vs placebo	Durvalumab +/- tremelimumab vs observation	Pembrolizumab + placebo vs pembrolizumab + belzutifan	Nivolumab vs observation
Duration of treatment	1 year	6 months	1 year	1 year	1 month neoadjuvant; 9 months adjuvant
Histology	ccRCC	ccRCC	ccRCC nccRCC	ccRCC	ccRCC nccRCC
Primary endpoint	DFS	DFS	DFS	DFS	DFS

Abbreviations: ccRCC, clear cell renal cell carcinoma; nccRCC, non-clear cell renal cell carcinoma; DFS, disease-free survival.

Non-Clear Cell Renal Carcinoma: Children of a Lesser God?

Clear cell renal cell carcinoma (ccRCC) accounts for about 75% of RCC, the remaining 25% encompasses a heterogeneous group of tumours with peculiar pathological and molecular features, categorized as nccRCC. The most frequent variant of nccRCC is the papillary RCC (10–15%), followed by chromophobe RCC (5%), collecting (Bellini) duct carcinoma (1%), medullary carcinoma (1%), and microphthalmia transcription factor (MiT) family translocation RCC (1%).[33]

Albeit their rarity, a tailored treatment for nccRCC patients is an unmet need. Indeed, they are treated as if they were ccRCC, despite some of them suffering from a lower response to therapy with either mTOR-target agents and VEGF-TKIs, and a poorer OS as well.

Although several trials in metastatic setting attempted to evaluate efficacy of VERGFR inhibitors or IO therapies in nccRCC scenario,[34–43] they are often small studies or retrospective reports as these patients are commonly excluded from pivotal trials.

Nevertheless, nccRCC were included in some adjuvant trials, such as ASSURE,[10] SORCE,[19] Immotion010,[29] RAMPART,[31] CASE12815 (ClinicalTrials.gov Identifier: NCT02762006), MK-3475-031 (ClinicalTrials.gov Identifier: NCT02212730), EVEREST[20] and PROSPER:[44] in particular, a pre-planned subgroup analysis about DFS in nccRCC patients was included as a secondary endpoint by PROSPER trial (Table 2).

Future Perspective: Beyond IO, How to Change Our Point of View?

The hypoxia-inducible factor-2 alpha (HIF-2α) is one of the most important drivers for development and progression of ccRCC, highlighting the therapeutic potential of HIF-2 antagonists in this disease.[45]

Belzutifan,[46–48] a second-generation HIF-2α inhibitor, demonstrated efficacy in heavily pre-treated patients with advanced ccRCC. Based on a preclinical study which suggested potential enhanced efficacy of HIF-2a inhibitor with IO,[47,48] the MK-6482-022 trial, an ongoing phase III study (ClinicalTrials.gov Identifier: NCT05239728), will evaluate the efficacy of belzutifan in combination with pembrolizumab in the adjuvant setting.

The Unsolved Question of M1 NED Patients

Data from non-randomized studies investigating the role of local treatment in oligometastatic disease suggest that a complete resection of metastases, also in the case of multiple lesions, is associated with an improvement of the survival benefit.[49–51] However, prospective randomized trials comparing metastasectomy with systemic treatment alone in mRCC have not yet been provided.

Recently, radiotherapy has been figured out as a feasible strategy for oligometastatic patients to defer systemic therapy initiation and to allow sustained systemic therapy breaks for selected patients.[52] Few data are available regarding the possible role of adjuvant therapy for this group of patients.

The RESORT trial was the first prospective study that evaluated the role of a targeted therapy after radical metastasectomy in mRCC. It showed that systemic treatment with sorafenib did not improve relapse-free survival (RFS) as compared with observation (OBS) alone. However, this prospective study confirmed that, in well-selected patients, surgery of metastases is associated with better survival.[43,53]

Similarly, the E2810 trial, a randomized, double-blind, placebo-controlled multicenter study, demonstrated that pazopanib did not improve DFS compared with placebo.[54]

As previously reported, the updated analysis of KEYNOTE-564 confirmed M1 NED patients as a subgroup with the highest benefit of pembrolizumab.[27] It is noteworthy that the number of M1 NED patients was lower compared with the population included in the study (5.8% of patients in both groups of study) and the biology of this subpopulation might be more like the metastatic setting than to T2/3 patients.

It would be desirable, though, to encourage clinical trials that only include M1 NED patients in order to study a more homogeneous population.

Biological Basis of Adjuvant IO: Why Targeting Angiogenesis Does Not Work

The biological basis underlying the different outcomes reported for IO treated patients is mostly unknown. One reason could be that cancer angiogenesis might not have a critical role in the micro-metastases survival and spread, due to the lack of a rich vascular scaffold compared with more evident solid metastasis: as a result, targeting the VEGF pathway could be ineffective in preventing a relapse after nephrectomy.[55,56]

Furthermore, the low rate of complete response achieved by patients with mRCC and treated with TKIs seems to suggest a cytostatic action by these agents, rather than a cytotoxic effect.[55,57]

Nevertheless, it is important to underline that the high frequency of treatment-related AEs led to an excessive rate of TKIs discontinuation and, consequently, a reduced drug exposure in patients who were otherwise asymptomatic and less inclined to toxic therapy.

On the other hand, the efficacy of IO in the post-operative setting lies with its interaction with the immune system response. In their preclinical study on mice, O'Donnell et al observed how tumour-specific CD8+ T-cells can be reinforced by the administration of IO: by their reintroduction into the bloodstream, these cells can kill the micro-metastases and keep immune surveillance high. Moreover, after the resection of the primary tumour, the circulating CD8+ T-cells and those located in the sites of metastases demonstrated to have an increased T-cell:tumor ratio: this proportion might provide an advantage in the destruction of remaining tumour tissue.[56]

Discussion

Surgery still represents the gold standard for localized RCC but disease recurrence is observed in almost 30% of patients and correlates with dismal prognosis.[6]

TKIs used in the metastatic setting have been regularly tested as adjuvant therapy, with contradictory results. Sorafenib, sunitinib, pazopanib and axitinib did not demonstrate to be efficacious in delaying DFS in non-metastatic patients probably because the VEGF pathway is not implied in the RCC micrometastases biology.[56]

Nowadays IO promises to change practice in adjuvant RCC as KEYNOTE-465 showed a DFS advantage for pembrolizumab compared with placebo in completely resected RCC.[26]

However, despite the results of KEYNOTE-564 leading to pembrolizumab approval in the adjuvant setting by the FDA[58] and European Medicines Agency (EMA),[28] some doubts still remain.

Despite the recent update, follow-up data still have not demonstrated a benefit in terms of OS for adjuvant pembrolizumab. In a methodological perspective, the role of DFS instead of OS as a surrogate of efficacy is still debated. Although the former was the primary endpoint of most of the aforementioned trials, a recent meta-analysis observed that there seems not to be a robust correlation between these two parameters.[59] The sometimes indolent course of RCC could explain this discrepancy as recurrence can spread out even after many years. Nevertheless, OS is

invariably influenced by the succeeding treatments, whereas DFS still may offer more detailed information about the efficacy of adjuvant treatment.

In this perspective, the outcomes in terms of PFS2 are encouraging; although it represents a surrogate endpoint attempting to push the bar a little further, the benefit of pembrolizumab is maintained over time[28] as a result of an immune system response that carries on over time. Due to the small number of patients who experienced progressive disease, the influence of subsequent anticancer treatment on PFS2 and OS is mostly unknown.

It is worth noting that 18.9% of patients experience grade 3 or worse IO-related AEs, requiring high dose of corticosteroids, and long-term consequences, such as permanent hypothyroidism.[27]

Indeed, further issues arise from the financial toxicities for IO itself and long-term and short-term AEs.

Considering the hypothesis that a variable percentage of patients is cured by surgery alone, the possibility of an overtreatment exists. In this scenario, it is crucial to select cases worthy of treatment based on reliable risk scores.

Finally, the role of ICIs in the post-surgery setting will be confirmed by the several ongoing trials but the definition of the risk of recurrence is crucial.[60]

The UCLA Integrated Staging System (UISS), the Leibovich system and Stage, Size, Grade and Necrosis (SSIGN) system are some of the classifications aiming to prognosticate the risk of relapse and OS in patients undergoing radical nephrectomy with curative intent.[61–64]

Molecular features as the expression of 34 genes, ClearCode34, have been proposed to categorize patients with clear cell nmRCC in two subgroups with different prognosis, but data are still immature.[65]

Likewise, the Recurrence Score (RS) tool, based on 16 genes, aims to detect those patients who will really benefit from an adjuvant treatment.[66,67]

Until then, EMA and EAU recommend pembrolizumab as adjuvant therapy in selected cases, after careful patient counselling regarding immature OS and potential long-term adverse events.[15,28]

Conclusions

IO is changing the paradigm of adjuvant therapy in RCC due to the encouraging results of the KEYNOTE-564 trial. Some patients could be cured by surgery alone, so clinical and molecular biomarkers are an unmet need to select patients. Furthermore, subgroups of patients, such as nccRCC and M1 NED, need to be studied in more homogeneous trials.

Abbreviations

RCC, renal cell carcinoma; nmRCC, non-metastatic renal cell carcinoma; VEGF, vascular-endothelial growth factor; TKIs, tyrosine kinase inhibitors; DFS, disease-free survival; OS, overall survival; M1 NED, no evidence of disease after metastasectomy; ASCO GU, American Society of Clinical Oncology Genito-Urinary; ICIs, immune checkpoint inhibitors; IO, immune-oncology; IL-2, interleukine-2; IFNα, interferon alpha; BCG, bacillus Calmette-Guerin; HR, hazard ratio; CI, confidence interval; AEs, adverse events; BICR, blinded independent central review; FG, Fuhrman Grade; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FDA, Food and Drug Administration; EAU, European Association of Urology; PFS2, progression-free survival 2; nccRCC, non-clear cell renal cell carcinoma; RFS, relapse-free survival; ccRCC, clear cell renal cell carcinoma; MiT, microphthalmia transcription factor; WHO, World Health Organization; HIF-2α, hypoxia-inducible factor-2 alpha; OBS, observation; EMA, European Medicines Agency; UISS, UCLA Integrated Staging System; SSIGN, Stage, Size, Grade and Necrosis.

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References

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA a Cancer J Clin*. 2021;71(3):209–249. doi:10.3322/caac.21660
2. AIOM, AIRTUM. NUMBERS OF CANCER IN ITALY. EDITION; 2021. Available from: https://www.aiom.it/wp-content/uploads/2021/11/2021_NDC.pdf. Accessed October 13, 2022.
3. Méjean A, Ravaud A, Thezenas S, et al. Sunitinib alone or after nephrectomy in metastatic renal-cell carcinoma. *N Engl J Med*. 2018;379(5):417–427. doi:10.1056/NEJMoa1803675
4. Stellato M, Santini D, Verzoni E, et al. Impact of previous nephrectomy on clinical outcome of metastatic renal carcinoma treated with immune-oncology: a real-world study on behalf of Meet-URO Group (MeetUro-7b). *Front Oncol*. 2021;11:682449. doi:10.3389/fonc.2021.682449
5. Bex A, Mulders P, Jewett M, et al. Comparison of immediate vs deferred cytoreductive nephrectomy in patients with synchronous metastatic renal cell carcinoma receiving sunitinib: the SURTIME randomized clinical trial. *JAMA Oncol*. 2019;5(2):164. doi:10.1001/jamaoncol.2018.5543
6. The American Cancer Society medical and editorial content team. Kidney cancer early detection, diagnosis, and staging; 2020. Available from: https://www.cancer.org/content/dam/CRC/PDF/Public/8661.00.pdf. Accessed July 3, 2022.
7. Gebrosky NP, Koukol S, Nseyo UO, Carpenter C, Lamm DL, Novick AC. Treatment of renal cell carcinoma with 5-fluorouracil and alfa-interferon. *Urology*. 1997;50(6):863–868. doi:10.1016/S0090-4295(97)00542-6
8. Fosså SD, Droz JP, Pavone-Macaluso MM, Debruyne FJJ, Vermeylen K, Sylvester R. Vinblastine in metastatic renal cell carcinoma: EORTC Phase II Trial 30882. *Eur J Cancer*. 1992;28(4–5):878–880. doi:10.1016/0959-8049(92)90139-S
9. Galligioni E, Quaia M, Merlo A, et al. Adjuvant immunotherapy treatment of renal carcinoma patients with autologous tumor cells and bacillus Calmette-Guèrin: five-year results of a prospective randomized study. *Cancer*. 1996;77(12):2560–2566. doi:10.1002/(SICI)1097-0142(19960615)77:12<2560::AID-CNCR20>3.0.CO;2-P
10. Haas NB, Manola J, Uzzo RG, et al. Adjuvant sunitinib or sorafenib for high-risk, non-metastatic renal-cell carcinoma (ECOG-ACRIN E2805): a double-blind, placebo-controlled, randomised, Phase 3 trial. *Lancet*. 2016;387(10032):2008–2016. doi:10.1016/S0140-6736(16)00559-6
11. Haas NB, Manola J, Dutcher JP, 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. doi:10.1001/jamaoncol.2017.0076
12. Ravaud A, Motzer RJ, Pandha HS, et al. Adjuvant sunitinib in high-risk renal-cell carcinoma after nephrectomy. *N Engl J Med*. 2016;375(23):2246–2254. doi:10.1056/NEJMoa1611406
13. Motzer RJ, Ravaud A, Patard JJ, 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. doi:10.1016/j.eururo.2017.09.008
14. Food and Drug Administration. FDA approves sunitinib malate for adjuvant treatment of renal cell carcinoma; 2018. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-sunitinib-malate-adjuvant-treatment-renal-cell-carcinoma. Accessed July 3, 2022.
15. Ljungberg B, Albiges L, Bedke J, et al. EAU guidelines. Edn. Presented at the EAU annual congress Amsterdam; 2022. Available from: https://d56bochluxqnz.cloudfront.net/documents/full-guideline/EAU-Guidelines-on-Renal-Cell-Carinoma-2022.pdf. Accessed October 13, 2022.
16. Motzer RJ, Haas NB, Donskov F, et al. Randomized Phase III trial of adjuvant pazopanib versus placebo after nephrectomy in patients with localized or locally advanced renal cell carcinoma. *JCO*. 2017;35(35):3916–3923. doi:10.1200/JCO.2017.73.5324
17. Motzer RJ, Russo P, Haas N, et al. Adjuvant pazopanib versus placebo after nephrectomy in patients with localized or locally advanced renal cell carcinoma: final overall survival analysis of the Phase 3 PROTECT trial. *Eur Urol*. 2021;79(3):334–338. doi:10.1016/j.eururo.2020.12.029
18. Gross-Goupil M, Kwon TG, Eto M, 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. doi:10.1093/annonc/mdy454
19. Eisen T, Frangou E, Oza B, et al. Adjuvant sorafenib for renal cell carcinoma at intermediate or high risk of relapse: results from the SORCE randomized Phase III intergroup trial. *JCO*. 2020;38(34):4064–4075. doi:10.1200/JCO.20.01800
20. Ryan CW, Tangen C, Heath EI, et al. EVEREST: everolimus for renal cancer ensuing surgical therapy—A phase III study (SWOG S0931, NCT01120249). *JCO*. 2022;40(17_suppl):LBA4500. doi:10.1200/JCO.2022.40.17_suppl.LBA4500
21. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. *N Engl J Med*. 2015;373(19):1803–1813. doi:10.1056/NEJMoa1510665
22. Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *N Engl J Med*. 2018;378(14):1277–1290. doi:10.1056/NEJMoa1712126
23. Rini BI, Plimack ER, Stus V, et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med*. 2019;380(12):1116–1127. doi:10.1056/NEJMoa1816714
24. Motzer R, Alekseev B, Rha SY, et al. Lenvatinib plus pembrolizumab or everolimus for advanced renal cell carcinoma. *N Engl J Med*. 2021;384(14):1289–1300. doi:10.1056/NEJMoa2035716
25. Thomas D, Bello DM. Adjuvant immunotherapy for melanoma. *J Surg Oncol*. 2021;123(3):789–797. doi:10.1002/jso.26329
26. Choueiri TK, Tomczak P, Park SH, et al. Adjuvant pembrolizumab after nephrectomy in renal-cell carcinoma. *N Engl J Med*. 2021;385(8):683–694. doi:10.1056/NEJMoa2106391
27. Choueiri TK, Tomczak P, Park SH, et al. Pembrolizumab as post nephrectomy adjuvant therapy for patients with renal cell carcinoma: results from 30-month follow-up of KEYNOTE-564. *JCO*. 2022;40(6_suppl):290. doi:10.1200/JCO.2022.40.6_suppl.290
28. European Medicines Agency. Assessment report – keytruda; 2021. Available from: https://www.ema.europa.eu/en/documents/variation-report/keytruda-h-c-003820-ii-0108-epar-assessment-report-variation_en.pdf. Accessed July 3, 2022.
29. Uzzo R, Bex A, Rini BI, et al. A phase III study of atezolizumab (atezo) vs placebo as adjuvant therapy in renal cell carcinoma (RCC) patients (pts) at high risk of recurrence following resection (IMmotion010). *JCO*. 2017;35(15_suppl):TPS4598. doi:10.1200/JCO.2017.35.15_suppl.TPS4598
30. Bex A, Russo P, Tomita Y, et al. A phase III, randomized, placebo-controlled trial of nivolumab or nivolumab plus ipilimumab in patients with localized renal cell carcinoma at high-risk of relapse after radical or partial nephrectomy (CheckMate 914). *JCO*. 2020;38(15_suppl):TPS5099. doi:10.1200/JCO.2020.38.15_suppl.TPS5099
31. Oza B, Frangou E, Smith 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. doi:10.1016/j.cct.2021.106482

32. Choueiri TK, Bedke J, Karam JA, et al. LITESPARK-022: a phase 3 study of pembrolizumab + belzutifan as adjuvant treatment of clear cell renal cell carcinoma (ccRCC). *JCO*. 2022;40(16_suppl):TPS4602. doi:10.1200/JCO.2022.40.16_suppl.TPS4602
33. Ahrens M, Scheich S, Hartmann A, Bergmann L; IAG-N Interdisciplinary Working Group Kidney Cancer of the German Cancer Society. Non-clear cell renal cell carcinoma - pathology and treatment options. *Oncol Res Treat*. 2019;42(3):128–135. doi:10.1159/000495366
34. Dutcher JP, de Souza P, McDermott D, et al. Effect of temsirolimus versus interferon-α on outcome of patients with advanced renal cell carcinoma of different tumor histologies. *Med Oncol*. 2009;26(2):202–209. doi:10.1007/s12032-009-9177-0
35. Motzer RJ, Barrios CH, Kim TM, et al. Phase II randomized trial comparing sequential first-line everolimus and second-line sunitinib versus first-line sunitinib and second-line everolimus in patients with metastatic renal cell carcinoma. *JCO*. 2014;32(25):2765–2772. doi:10.1200/JCO.2013.54.6911
36. Armstrong AJ, Halabi S, Eisen T, et al. Everolimus versus sunitinib for patients with metastatic non-clear cell renal cell carcinoma (ASPEN): a multicentre, open-label, randomised Phase 2 trial. *Lancet Oncol*. 2016;17(3):378–388. doi:10.1016/S1470-2045(15)00515-X
37. Escudier B, Molinie V, Bracarda S, et al. Open-label phase 2 trial of first-line everolimus monotherapy in patients with papillary metastatic renal cell carcinoma: RAPTOR final analysis. *Eur J Cancer*. 2016;69:226–235. doi:10.1016/j.ejca.2016.08.004
38. Koh Y, Lim HY, Ahn JH, et al. Phase II trial of everolimus for the treatment of nonclear-cell renal cell carcinoma. *Ann Oncol*. 2013;24(4):1026–1031. doi:10.1093/annonc/mds582
39. Buti S, Bersanelli M, Maines F, et al. First-line PAzopanib in NOn–clear-cell renal cArcinoMA: the Italian Retrospective Multicenter PANORAMA Study. *Clin Genitourin Cancer*. 2017;15(4):e609–e614. doi:10.1016/j.clgc.2016.12.024
40. Matrana MR, Duran C, Shetty A, et al. Outcomes of patients with metastatic clear-cell renal cell carcinoma treated with pazopanib after disease progression with other targeted therapies. *Eur J Cancer*. 2013;49(15):3169–3175. doi:10.1016/j.ejca.2013.06.003
41. Jay R, McKay R, Werner L, et al. Phase 2 trial of sunitinib and gemcitabine in patients with sarcomatoid and/or poor-risk metastatic renal cell carcinoma. Michaelson MD, McKay RR, Werner L, Atkins MB, Van Allen EM, Olivier KM, Song J, Signoretti S, McDermott DF, Choueiri TK. Cancer. 2015 Oct 1;121(19):3435–3443. [Epub 2015 Jun 8]. *Urol Oncol*. 2017;35(3):117–118. doi:10.1016/j.urolonc.2016.12.023
42. Twardowski PW, Tangen CM, Wu X, et al. Parallel (randomized) Phase II evaluation of tivantinib (ARQ197) and tivantinib in combination with erlotinib in papillary renal cell carcinoma: SWOG S1107. *KCA*. 2017;1(2):123–132. doi:10.3233/KCA-170018
43. Procopio G, Apollonio G, Cognetti F, et al. Sorafenib versus observation following radical metastasectomy for clear-cell renal cell carcinoma: results from the Phase 2 randomized open-label RESORT Study. *Eur Urol Oncol*. 2019;2(6):699–707. doi:10.1016/j.euo.2019.08.011
44. Harshman LC, Puligandla M, Haas NB, et al. PROSPER: a phase III randomized study comparing perioperative nivolumab (nivo) versus observation in patients with localized renal cell carcinoma (RCC) undergoing nephrectomy (ECOG-ACRIN 8143). *JCO*. 2019;37(7_suppl):TPS684. doi:10.1200/JCO.2019.37.7_suppl.TPS684
45. Shen C, Kaelin WG. The VHL/HIF axis in clear cell renal carcinoma. *Semin Cancer Biol*. 2013;23(1):18–25. doi:10.1016/j.semcancer.2012.06.001
46. Courtney KD, Infante JR, Lam ET, et al. Phase I dose-escalation trial of pt2385, a first-in-class hypoxia-inducible factor-2α antagonist in patients with previously treated advanced clear cell renal cell carcinoma. *JCO*. 2018;36(9):867–874. doi:10.1200/JCO.2017.74.2627
47. Choueiri TK, Bauer TM, Papadopoulos KP, et al. Inhibition of hypoxia-inducible factor-2α in renal cell carcinoma with belzutifan: a Phase 1 trial and biomarker analysis. *Nat Med*. 2021;27(5):802–805. doi:10.1038/s41591-021-01324-7
48. Han G, Stevens C, Cao Z, et al. Abstract 4022: PT2385, a novel HIF-2α antagonist, combines with checkpoint inhibitor antibodies to inhibit tumor growth in preclinical models by modulating myeloid cells and enhancing T cell infiltration. *Cancer Res*. 2016;76(14_Supplement):4022. doi:10.1158/1538-7445.AM2016-4022
49. Alt AL, Boorjian SA, Lohse CM, Costello BA, Leibovich BC, Blute ML. Survival after complete surgical resection of multiple metastases from renal cell carcinoma. *Cancer*. 2011;117(13):2873–2882. doi:10.1002/cncr.25836
50. Kavolius JP, Mastorakos DP, Pavlovich C, Russo P, Burt ME, Brady MS. Resection of metastatic renal cell carcinoma. *JCO*. 1998;16(6):2261–2266. doi:10.1200/JCO.1998.16.6.2261
51. Vogl UM, Zehetgruber H, Dominkus M, et al. Prognostic factors in metastatic renal cell carcinoma: metastasectomy as independent prognostic variable. *Br J Cancer*. 2006;95(6):691–698. doi:10.1038/sj.bjc.6603327
52. Tang C, Msaouel P, Hara K, et al. Definitive radiotherapy in lieu of systemic therapy for oligometastatic renal cell carcinoma: a single-arm, single-centre, feasibility, phase 2 trial. *Lancet Oncol*. 2021;22(12):1732–1739. doi:10.1016/S1470-2045(21)00528-3
53. Mennitto A, Verzoni E, Cognetti F, et al. Radical metastasectomy followed by sorafenib versus observation in patients with clear cell renal cell carcinoma: extended follow -up of efficacy results from the randomized phase II RESORT trial. *Expert Rev Clin Pharmacol*. 2021;14(2):261–268. doi:10.1080/17512433.2021.1879639
54. Appleman LJ, Puligandla M, Pal SK, et al. Randomized, double-blind phase III study of pazopanib versus placebo in patients with metastatic renal cell carcinoma who have no evidence of disease following metastasectomy: a trial of the ECOG-ACRIN cancer research group (E2810). *JCO*. 2019;37(15_suppl):4502. doi:10.1200/JCO.2019.37.15_suppl.4502
55. Naumov GN, Akslen LA, Folkman J. Role of angiogenesis in human tumor dormancy: animal models of the angiogenic switch. *Cell Cycle*. 2006;5(16):1779–1787. doi:10.4161/cc.5.16.3018
56. O'Donnell JS, Hoefsmit EP, Smyth MJ, Blank CU, Teng MWL. The Promise of Neoadjuvant Immunotherapy and Surgery for Cancer Treatment. *Clin Cancer Res*. 2019;25(19):5743–5751. doi:10.1158/1078-0432.CCR-18-2641
57. Choueiri TK, Kaelin WG. Targeting the HIF2–VEGF axis in renal cell carcinoma. *Nat Med*. 2020;26(10):1519–1530. doi:10.1038/s41591-020-1093-z
58. Food and Drug Administration. FDA approves pembrolizumab for adjuvant treatment of renal cell carcinoma; 2021. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-adjuvant-treatment-renal-cell-carcinoma. Accessed July 3, 2022.
59. Harshman LC, Xie W, Moreira RB, et al. Evaluation of disease-free survival as an intermediate metric of overall survival in patients with localized renal cell carcinoma: a trial-level meta-analysis: DFS as a metric of overall survival in RCC. *Cancer*. 2018;124(5):925–933. doi:10.1002/cncr.31154
60. Swami U, Nussenzveig RH, Haaland B, Agarwal N. Revisiting AJCC TNM staging for renal cell carcinoma: quest for improvement. *Ann Transl Med*. 2019;7(S1):S18–S18. doi:10.21037/atm.2019.01.50
61. Zisman A, Pantuck AJ, Dorey F, et al. Improved prognostication of renal cell carcinoma using an integrated staging system. *JCO*. 2001;19(6):1649–1657. doi:10.1200/JCO.2001.19.6.1649
62. Patard JJ, Kim HL, Lam JS, et al. Use of the university of California los angeles integrated staging system to predict survival in renal cell carcinoma: an international multicenter study. *JCO*. 2004;22(16):3316–3322. doi:10.1200/JCO.2004.09.104

63. Leibovich BC, Blute ML, Cheville JC, 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. doi:10.1002/cncr.11234
64. Frank I, Blute ML, Cheville JC, Lohse CM, Weaver AL, Zincke H. An outcome prediction model for patients with clear cell renal cell carcinoma treated with radical nephrectomy based on tumor stage, size, grade and necrosis: the SSIGN score. *J Urol*. 2002;168(6):2395–2400. doi:10.1097/01.ju.0000035885.91935.d5
65. Brooks SA, Brannon AR, Parker JS, et al. ClearCode34: a prognostic risk predictor for localized clear cell renal cell carcinoma. *Eur Urol*. 2014;66(1):77–84. doi:10.1016/j.eururo.2014.02.035
66. Rini B, Goddard A, Knezevic D, et al. A 16-gene assay to predict recurrence after surgery in localised renal cell carcinoma: development and validation studies. *Lancet Oncol*. 2015;16(6):676–685. doi:10.1016/S1470-2045(15)70167-1
67. Rini BI, Escudier B, Martini JF, et al. Validation of the 16-gene recurrence score in patients with locoregional, high-risk renal cell carcinoma from a Phase III trial of adjuvant sunitinib. *Clin Cancer Res*. 2018;24(18):4407–4415. doi:10.1158/1078-0432.CCR-18-0323