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The adjuvant treatment of kidney cancer: a multidisciplinary outlook

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Abstract | Approximately 70% of cases of kidney cancer are localized or locally advanced at diagnosis. Among patients who undergo surgery for these cancers, 30–35% will eventually develop potentially fatal metachronous distant metastases. Effective adjuvant treatments are urgently needed to reduce the risk of recurrence of kidney cancer and of dying of metastatic disease. To date, almost all of the tested adjuvant agents have failed to demonstrate any benefit. Only two trials of an autologous renal tumour cell vaccine and of the vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitor sunitinib have shown positive results, but these have been criticized for methodological reasons and conflicting data, respectively. The results of two additional trials of targeted agents as adjuvant therapies have not yet been published. Novel immune checkpoint inhibitors are promising approaches to adjuvant therapy in kidney cancer, and a number of trials are now underway. An important component of the management of patients with kidney cancer, particularly those who undergo radical resection for localized renal cell carcinoma, is the preservation of kidney function to reduce morbidity and mortality. The optimal management of these patients therefore requires a multidisciplinary approach involving nephrologists, oncologists, urologists and pathologists.

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Estimates suggest that kidney cancer is the twelfth most common cancer worldwide, with 338,000 new cases diagnosed in 2012 (REF.[1]). In 2017, approximately 63,990 new cases of kidney cancer (40,610 in men and 23,380 in women) and 14,400 deaths owing to kidney cancer (9,470 in men and 4,930 in women) were estimated to occur in the USA[2]. Approximately 70% of cases of kidney cancer are localized or locally advanced at diagnosis and thus are potentially curable by means of surgical resection alone[3]. However, 30–35% of patients who undergo resection for a localized or locally advanced kidney tumour will eventually develop metachronous distant metastases[4], which may occur even decades after resection of the primary tumour and can ultimately lead to death. Data from the US National Cancer Database indicate that although the observed 5-year cancer-specific survival rates of patients with tumour–node–metastasis (TNM) stage I and II kidney cancers (BOX 1) are 81% and 74%, respectively, the observed 5-year survival of patients with stage III kidney cancers falls dramatically to 53%[5], mainly owing to the development of distant metastases. Effective adjuvant treatments are essential to reduce the risk of recurrence and associated mortality, especially in high-risk patients.

For decades, the adjuvant treatment of radically resected kidney cancer has remained a 'black hole' of medical oncology, as almost all of the tested agents have failed to demonstrate a benefit[6]. Despite the significant improvement in survival achieved with the use of vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKIs) in the metastatic setting[7], randomized controlled trials (RCTs) of these agents as adjuvant therapies have yielded conflicting results.

In this Review, we discuss the issue of defining the risk of relapse of kidney cancer and comment on the results of trials of early adjuvant therapies and VEGFR TKIs. We also discuss the potential of immune checkpoint inhibitors as adjuvant therapies and highlight the need for true multidisciplinary management of patients with radically resected kidney cancer.

Evaluating the risk of relapse

The identification of patients who are at increased risk of relapse is key for the development of rational adjuvant strategies. A number of predictive models have been developed to accomplish this goal. These models all incorporate widely available, easily obtainable, clinicopathological variables that are associated with prognosis following surgery. The two most commonly used models, which are utilized in the present generation of adjuvant trials, are the University of California at Los Angeles (UCLA) Integrated Scoring System (UISS)[8] and the Leibovich score[9].

Key points

- Effective adjuvant treatments for kidney cancer are needed to reduce the risk of recurrence and of dying of metastatic disease.
- To date, almost all of the tested adjuvant agents have failed to demonstrate any benefit in clinical trials; the two positive trials were criticized for methodological reasons and conflicting results.
- Only one drug — sunitinib — has been approved for the adjuvant treatment of kidney cancer in the USA; however, this drug has not been approved as an adjuvant therapy in Europe.
- Positive results with immune checkpoint inhibitors in metastatic renal cell carcinoma (RCC) suggest that these agents might also be effective adjuvant therapies; trials of these agents are underway.
- Preservation of kidney function in patients with RCC is important to reduce morbidity; therefore, multidisciplinary management should be mandatory for almost all patients with radically resected kidney cancer.

The UISS includes two tumour-specific features — the TNM stage and Fuhrman grade (a pathology classification based on nuclear characteristics) — together with a patient-specific feature such as the Eastern Cooperative Oncology Group (ECOG) performance status[8]. This combination of features stratifies patients into low-risk, intermediate-risk and high-risk prognostic categories. In patients with non-metastatic disease, the application of the UISS correctly predicted 2-year and 5-year survival values irrespective of tumour histology in 76.5–86.3% of patients[8]. The UISS is also prognostic in the metastatic setting.

In 2003, Leibovich and colleagues identified five features in patients with clear cell renal cell carcinoma (ccRCC) — tumour stage, regional lymph node status, tumour size, nuclear grade and histological tumour necrosis — that were significantly associated with progression to metastatic RCC[9]. When used in combination, these features were able to differentiate between patients at higher and lower risk of dying of metastatic disease, with a predictive accuracy of >80%. Both the UISS and Leibovich models were externally validated, but the Leibovich model has been shown to be superior in terms of predictive accuracy[10]. These models and others such as the Stage, Size, Grade and Necrosis staging system (SSIGN)[11] and the Karakiewicz[12] and Kattan[13] models (TABLE 1) serve as adjunctive tools for patient counselling but do not provide clear guidance on when to use adjuvant therapy. Furthermore, different prognostic systems may yield very different risk estimates[14]. For example, the 5-year disease-free survival (DFS) estimate for a patient with primary TNM stage T2, N0 disease (Fuhrman grade 2) would be 85.4% according to the Leibovich model but only 66% according to the Kattan nomogram[13]. Conversely, a patient with pathological stage T3 (pT3), N0 disease (Fuhrman grade 3) would have a 5-year DFS estimate of only 50% using the Leibovich model versus 74% using the Kattan nomogram[13].

Unfortunately, prognostic systems based on clinicopathological variables are not able to capture the biology of the tumour, resulting in a substantial bias that researchers are trying to overcome by characterizing tumours using gene expression technologies. ClearCode34 is a 34-gene expression panel that can be used to classify ccRCC into two subtypes, good-risk clear cell A (ccA) and poor risk clear cell B (ccB), that are significantly associated with relapse-free survival (RFS), cancer-specific survival and overall survival (OS)[15,16]. In a cohort of 265 patients with ccRCC, the predictive accuracy of ClearCode34 was found to be superior to that of other prognostic scores (including the UISS) in predicting death and recurrence[15].

A separate 16-gene expression panel was used to build a scoring system that can predict recurrence after surgery in stage I–III ccRCC[17]. This score, which was validated in an independent French cohort of 626 patients, was significantly associated with recurrence following surgery for localized disease[17]. In multivariable analyses, the recurrence score was significantly associated with the risk of tumour recurrence after stratification by stage and adjustment for tumour size, grade or Leibovich score. This score was able to identify a clinically significant number of high-risk patients with stage I disease as well as low-risk patients with more advanced disease (stage II and III)[17].

Another study identified mutation-defined subtypes of ccRCC with distinct clinical outcomes: a high-risk group characterized by mutations in *BAP1* (which encodes ubiquitin carboxyl-terminal hydrolase BAP1) and a lower-risk group characterized by mutations in *PBRM1* (which encodes protein polybromo 1)[18]. Although the population in this study was fairly similar to that of the recurrence score study described above, the gene alterations that were identified as being prognostic differed between these studies.

Although a molecular gene expression model would be ideal for the stratification of radically resected patients in clinical trials, none of the available scores are ready for everyday clinical use owing to the expertise needed, the associated costs and the unresolved discrepancies between the different sets of genes found to be prognostic in the different scores. In our opinion, the Leibovich score is currently the best model for predicting risk of relapse in everyday clinical practice.

Early adjuvant trials

Before the era of VEGFR TKIs, trials of adjuvant treatments for renal cell carcinoma (RCC) including radiotherapy[19], cytokines (with or without chemotherapy)[20–25], vaccines[26–29], single-agent chemotherapy and other agents such as medroxyprogesterone acetate, thalidomide and girentuximab[30–33] yielded no benefits in terms of DFS and/or OS, with the exception of a trial of an autologous renal tumour cell vaccine that was published in 2004 (REF.[28]) (Supplementary Table 1). In our opinion, four of these early adjuvant trials[20,28,29,33], including the tumour cell vaccine trial[28], warrant further discussion (TABLE 2).

In 2001, an RCT tested the hypothesis that 6 months of adjuvant therapy with IFNα could improve OS and event-free survival (EFS) in patients with radically resected Robson stage II kidney cancer (that is, a tumour invading perinephric fat but not extended beyond the Gerota fascia) or Robson stage III kidney cancer (that is, a tumour invading the renal vein or inferior vena cava and/or spreading to regional lymph nodes)[20]. Notably,

Box 1 | **TNM staging of kidney tumours**[81]

Tumour (T)

- Tx: the primary tumour cannot be assessed
- T0: no evidence of a primary tumour
- T1: kidney-confined tumour <7 cm in diameter
  - 1a: <4 cm
  - 1b: >4 cm and <7 cm
- T2: kidney-confined tumour >7 cm in diameter
  - 2a: >7 cm and <10 cm
  - 2b: >10 cm
- T3: the tumour is growing into a major vein or into tissue around the kidney, but it is not growing into the adrenal gland or beyond the Gerota fascia
  - 3a: the tumour is growing into the renal vein or into fatty tissue around the kidney
  - 3b: the tumour is growing into the intra-abdominal vena cava
  - 3c: the tumour is growing into the vena cava above the diaphragm
- T4: the tumour has spread beyond the Gerota fascia or into the adrenal gland

Node (N)

- Nx: regional lymph nodes cannot be assessed
- N0: no spread to nearby lymph nodes
- N1: tumour has spread to nearby lymph nodes

Metastasis (M)

- M0: no distant metastases
- M1: distant metastases

TNM stage

- Stage I
  - T1, N0, M0
- Stage II
  - T2, N0, M0
- Stage III
  - T1 or T2, N0, M0
  - T3, N0 or N1, M0
- Stage IV
  - T4, any N, M0
  - Any T, any N, M1

the study protocol recommended unilateral para-aortic lymph node dissection, and the researchers relied on the pathological report to verify that lymphadenectomy was performed. The OS probability at 5 years after surgery was 0.665 for the control group and 0.660 for the treated group; this difference was not statistically significant ($P = 0.861$; HR of IFNα versus control 1.040, 95% CI 0.671–1.613). The corresponding EFS probabilities (0.671 and 0.567, respectively) also did not differ significantly between the study groups ($P = 0.107$; HR IFNα versus control 1.412, 95% CI 0.927–2.149).

A subgroup analysis of this RCT reported no significant difference in the cumulative probability of death among patients in the treated versus control groups with pN0 (0.16 versus 0.10) and pN1 tumours (0.25 versus 0.25)[20]. Among patients with pN2 or pN3 tumours, the observed difference in probability of death between the treatment and control groups clearly and significantly favoured the treated patients (0.39 for IFNα versus 0.92 for control). This observation has no practical relevance because of the extremely low number of patients with pN2 or pN3 tumours included in the study ($n = 13$ in each study group). However, one could speculate that interferon-based immunotherapy might benefit patients at high risk of relapse owing to massive lymph node involvement.

The renal tumour cell vaccine trial investigated the effect of this therapy on the risk of progression in 558 patients with stage pT2-3b, pN0-3 M0 RCC who were scheduled to undergo radical nephrectomy at 55 institutions in Germany[28]. The patients were randomly assigned to receive either six intradermal applications of the vaccine at 4-week intervals after surgery or no adjuvant treatment. All patients were assessed using standardized diagnostic investigations at 6-month intervals for a minimum of 4.5 years[28]. At 5-year and 70-month follow-ups, the hazard ratios for tumour progression were 1.58 (95% CI 1.05–2.37) and 1.59 (95% CI 1.07–2.36), respectively, in favour of the vaccine group ($P = 0.0204$). Progression-free survival in the vaccine group was 77.4% at 5 years and 72% at 70 months. In the control group, progression-free survival at these time points was 67.8% and 59.3%, respectively[28].

Although the results were positive, this study was criticized for substantial methodological biases, including unblinded treatment assignment, a substantial imbalance in patient characteristics (76% of those in the vaccine group had clear cell histology versus only 68% in the control group) and a high number of protocol violations (87 of 276 patients allocated to the vaccine and 55 of 277 patients allocated to observation did not receive the allocated treatment). The high number of patients who withdrew consent and the lack of a comprehensive publication reporting on OS results also affected the overall quality of the study. Moreover, manufacture of the vaccine was complex and expensive.

In 2008, the efficacy of an autologous, tumour-derived, heat shock protein peptide complex (HSPPC-96) as an adjuvant treatment was studied in 819 patients at high risk of recurrence after resection of locally advanced RCC[29]. No difference was found in RFS between patients who received HSPPC-96 and those who did not receive treatment after nephrectomy. However, a subgroup analysis of the study reported a trend towards an improvement in RFS in patients with early-stage disease who received HSPPC-96 (HR 0.576, 95% CI 0.324–1.023; $P = 0.056$)[29].

Finally, the results of the first adjuvant trial using a targeted agent were published in 2017 (REF.[33]). This study compared girentuximab, an anti-anhydrase carbonic IX (CAIX) monoclonal antibody, with observation in 864 patients with radically resected kidney cancer. CAIX is a tumour-associated transmembrane protein that is overexpressed in Von Hippel Lindau tumour suppressor gene (*VHL*)-mutated clear cell kidney cancers and other hypoxic solid tumours but is expressed at low levels in most normal tissues including normal kidney[34]. Despite the strong rationale for use of this agent in kidney cancer, girentuximab therapy yielded no statistically significant improvement in DFS (HR 0.97, 95% CI 0.79–1.18) or OS (HR 0.99, 95% CI 0.74–1.32) compared with placebo[33]. A subgroup analysis showed a nonsignificant trend

Table 1 | **Predictive models for risk of relapse of RCC following surgical resection**

Model	Predictor variables	Histology	Outcome predicted	Positive predictive value (%)	Refs
UISS	• Pathological stage • Nuclear grading • ECOG performance status	Histotype-independent	Overall survival in patients with non-metastatic and metastatic RCC	• Non-metastatic RCC: 76.5–86.3 • Metastatic RCC: 64–77	8
SSIGN	• Pathological stage (including metastasis stage) • Nuclear grading • Major dimension of the tumour • Presence of coagulative necrosis	Valid only for clear cell RCC	Cause-specific survival	82–88	11
Leibovich	• Pathological stage (excluding metastasis stage) • Nuclear grading • Major dimension of the tumour • Presence of coagulative necrosis	Valid only for clear cell RCC	Metastases-free survival	>80	9
Karakiewicz	• Pathological stage (excluding metastasis stage) • Nuclear grading • Major dimension of the tumour • Mode of presentation	Histotype-independent	Cause-specific survival	86–88	12
Kattan	• Patient symptoms (incidental, local or systemic) • Histology (clear cell, papillary or chromophobe) • Tumour size • Pathological stage	Valid for clear cell, papillary or chromophobe RCC	RCC recurrence-free survival	74	13

ECOG, Eastern Cooperative Oncology Group; RCC, renal cell carcinoma; SSIGN, Stage, Size, Grade and Necrosis staging system; UISS, University of California at Los Angeles (UCLA) Integrated Staging System.

towards benefit of girentuximab therapy with increasing CAIX score[33]. These inconclusive findings highlight the potential risk of trial failure as a result of testing novel targeted agents without selecting or enriching the study population for the relevant target, a mistake that has hampered the development of several anticancer agents.

As all the published trials have yielded negative or at best highly biased and inconclusive results, no adjuvant therapy has emerged as a standard treatment for patients with kidney cancer. Credible reasons for these dismaying results include the use of extremely low active (at least in kidney cancer) treatment strategies (for example, chemotherapy, hormonal agents or old-fashioned radiotherapy), limited patient numbers in many studies, the enrolment of patients with very different prognoses (sometimes including those with metastatic disease) in the same trials, the use of different disease classifications and staging systems in different studies, a lack of understanding of the mechanisms of action of immunotherapeutics (cytokines and vaccines) and the use of end points other than DFS and OS, which are the only recommended end points for this setting[35].

We performed a meta-analysis of aggregated data from phase III RCTs and found no clinical benefit of any type of adjuvant therapy for kidney cancer in relation to the primary end point of 5-year RFS or the secondary end points of 2-year RFS and 2-year and 5-year OS[36]. Our additional subgroup analysis showed no significant qualitative or quantitative interaction between different adjuvant strategies. However, we did observe nonsignificant positive effects in terms of 5-year RFS in the qualitative interaction between different adjuvant treatment strategies; vaccines were less ineffective than cytokines, which in turn were less ineffective than other treatment strategies. These observations suggest that novel immunotherapeutic strategies with specific mechanisms of action (for example, immune checkpoint inhibitors) might have a role in the future adjuvant treatment of patients with kidney cancer and will hopefully yield a positive outcome.

Tyrosine kinase inhibitors

A number of different genetic alterations with pathogenic consequences have been identified in RCC and particularly in ccRCC, which is by far the most common histotype. These alterations include allele deletion in *VHL*, mutations in the remaining *VHL* allele and *VHL* gene inactivation through gene silencing by methylation[37–39]. Biallelic *VHL* gene inactivation is observed in the vast majority of ccRCCs[37–39]. The product of the *VHL* gene, pVHL, is a 213-amino-acid protein component of an ubiquitin ligase complex that mediates the physiological cellular response to hypoxia. In conditions of normoxia, pVHL binds the hypoxia-inducible factors (HIF1α) and HIF2α (also known as EPAS1), leading to their ubiquitylation and subsequent proteasomal degradation. In the setting of hypoxia or in the presence of a defective *VHL* gene, HIFs are not degraded, and their accumulation leads to the transcription of hypoxia-inducible genes, which ultimately results in

Table 2 | **Selected early randomized trials of adjuvant therapy for radically resected kidney cancer**

Study (year)	Intervention	Patients		Results	Observations and/or limitations	Refs
		n	Criteria			
Cytokine-based immunotherapy						
Pizzocaro (2001)	IFNα2b (6 MU i.m. 3 times a week for 6 months starting within 1 month after surgery) versus observation	247	TNM stage II or III: • pT3a, N0, M0 • pT3b, N0, M0 • pT2/3, N1–3, M0	No significant difference in 5-year OS and event-free survival (control group 0.665 and 0.671, respectively, intervention group 0.660 and 0.567, respectively; *P* = not significant for both)	• IFNα2b had a statistically significant harmful effect in patients with pN0 RCC (*n* = 97; HR 2.228) • IFNα2b had a protective effect in patients with pN2/3 RCC (*n* = 13; HR 0.191)	20
Vaccines						
Jocham (2004)	Autologous renal tumour cell vaccine (6 intradermal applications at 4-week intervals postoperatively) versus observation	558	• Stage pT2/3b pN0-3 M0 • Patients with pT1 or pT4 RCC were excluded • Patients who had undergone surgery other than radical nephrectomy were excluded	• HRs for tumour progression were 1.58 (95% CI 1.05–2.37) and 1.59 (95% CI 1.07–2.36), respectively, in favour of the vaccine group (*P* = 0.0204) • At 5-year and 70-month follow-ups, HRs for tumour progression were 1.58 (95% CI 1.05–2.37) and 1.59 (95% CI 1.07–2.36), respectively, in favour of the vaccine group (*P* = 0.0204)	• Vaccination was extremely well tolerated • Similar quality of life in the two groups • Study had important methodological flaws including imbalance in patient characteristics and protocol violations	28
Wood (2008)	HSPPC-96 (25 μg intradermally once a week for 4 weeks and then every 2 weeks until vaccine supply depletion or disease progression) versus observation	818	• cT1b/T4, N0, M0 • cT any, N1–2, M0	No significant difference in disease recurrence, which occurred in 136 (37.7%) patients in the vaccine group and 146 (39.8%) patients in the observation group (HR 0.923, 95% CI 0.729–1.169; *P* = 0.506)	Possible improvement in RFS in patients with stage I or II disease, but the observed difference was not statistically significant (HR 0.576, 95% CI 0.324–1.023; *P* = 0.056)	29
Monoclonal antibody						
Chamie (2017)	Girentuximab (single i.v. dose of 50 mg in week 1 followed by 20 mg per week from weeks 2–24) versus placebo	864	High-risk patients defined as: • pT3/pT4, Nx/N0, M0 • pT any, N^+, M0 • pT1b/pT2, Nx/N0, M0 with nuclear grade 3 or greater	• No significant difference in DFS (HR 0.97, 95% CI 0.79–1.18) or OS (HR 0.99, 95% CI 0.74–1.32) • Median DFS was 71.4 months in the girentuximab group and was not reached in the placebo group • Median OS was not reached in either group	No difference in safety between treatment and placebo groups	33

Adjuvant trials that are extensively discussed within the text of this Review are summarized in this table. For a full list of early adjuvant trials, see Supplementary Table 1. DFS, disease-free survival; i.m., intramuscular; i.v., intravenous; MU, mega units; OS, overall survival; RCC, renal cell carcinoma; RFS, relapse-free survival; TNM, tumour–node–metastasis.

the hyperproduction of a number of pro-angiogenic cytokines, including vascular endothelial growth factor (VEGF)[40,41]. For this reason, agents that target VEGF and VEGFR pathways have been developed as agents for the treatment of metastatic RCC (FIG. 1).

To date, five phase III RCTs have been designed to evaluate the efficacy of VEGFR-targeted therapies versus placebo in patients with early (that is, non-metastatic) RCCs at high risk of relapse following nephrectomy[42–46]. The results of four of these trials, which investigated the effects of 1 year of treatment with sunitinib, sorafenib, pazopanib and axitinib on DFS after nephrectomy in patients with predominantly ccRCC, have now been published[42–44] (TABLE 3).

The multi-centre, international double-blind placebo-controlled S-TRAC trial investigated the efficacy of sunitinib in 615 patients at high risk of recurrence of RCC (according to the UISS model) following surgical removal of the primary tumour[43]. Patients were randomly assigned in a 1:1 ratio to receive either 50 mg sunitinib once daily on a 4 weeks on and 2 weeks off treatment schedule or placebo for 1 year. The median DFS was significantly higher in the sunitinib group (6.8 years) than in the placebo group (5.6 years; HR 0.76, 95% CI 0.59–0.98; *P* = 0.03). On the basis of these data, the US Food and Drug Administration (FDA) approved sunitinib for the adjuvant treatment of adult patients at high risk of recurrent RCC following nephrectomy in November 2017 (REF.[47]).

The Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma (ASSURE) study, which included 1,943 patients with RCC at intermediate risk or high risk of relapse (according to the UISS model), did not find an improvement in DFS or OS with 1 year of

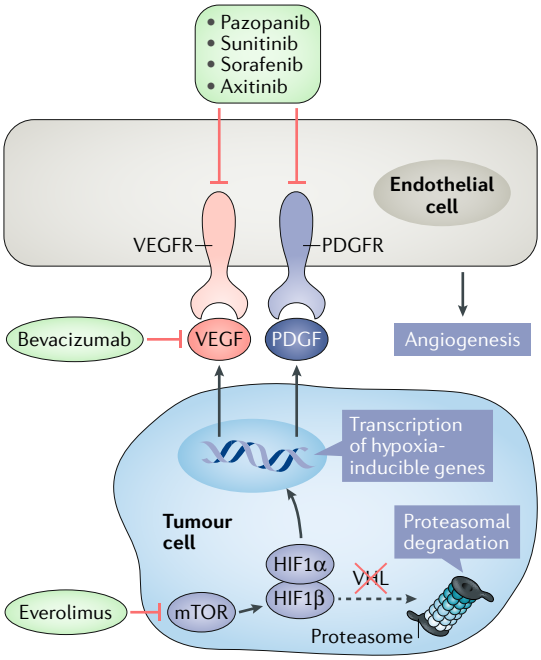

Fig. 1 | **Mechanisms of action of targeted therapies in renal cell carcinoma.** In normoxic conditions, pVHL binds hypoxia-inducible factor 1α (HIF1α) and HIF1β and targets them for proteasomal degradation. Hypoxia or genetic loss or inactivation of the Von Hippel Lindau tumour suppressor gene (*VHL*) owing to mutation, deletion or hypermethylation leads to the accumulation of HIF1α and HIF1β, which dimerize and translocate to the nucleus. The HIF complex induces the transcription of hypoxia-inducible genes and the overproduction of proangiogenic factors including vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF). Binding of these proangiogenic factors to their receptors on endothelial cells leads to the stimulation of angiogenesis, which enables the tumour to grow beyond 2–3 mm and to access the general circulation — the first step in the process of metastasis. Angiogenesis can be inhibited by blocking circulating VEGF using monoclonal antibodies such as bevacizumab or by inhibiting the tyrosine kinase activity of the VEGF receptor (VEGFR) using tyrosine kinase inhibitors such as pazopanib, sunitinib, sorafenib or axitinib. As activation of mTOR leads to increased synthesis of multiple proteins, including HIFs, mTOR inhibition using everolimus also indirectly leads to inhibition of VEGF-driven angiogenesis. PDGFR, PDGF receptor.

adjuvant sunitinib or sorafenib therapy compared with placebo[42]. During this study, the protocol starting doses were reduced from 50.0 mg to 37.5 mg daily for sunitinib and from 800 mg to 400 mg for the first 1 or 2 cycles of sorafenib owing to toxicity issues. The primary analysis reported a median DFS of 5.8 years (interquartile range (IQR) 1.6–8.2) in the sunitinib group (HR 1.02, 97.5% CI 0.85–1.23, $P = 0.8038$), 6.1 years (IQR 1.7 to not estimable) in the sorafenib group (HR 0.97, 97.5% CI 0.80–1.17; $P = 0.7184$) and 6.6 years (IQR 1.5 to not estimable) in the placebo group[42]. Furthermore, a secondary analysis of the trial results found that neither the prognostic category of the tumour nor the dose intensity of therapy altered the lack of difference in DFS or OS with the adjuvant therapies versus placebo[48].

Similarly, the Pazopanib As Adjuvant Therapy in Localized/Locally Advanced RCC After Nephrectomy (PROTECT) study, which evaluated the efficacy of 1 year of pazopanib as an adjuvant therapy for patients with locally advanced RCC at high risk of relapse after surgery on the basis of TNM risk stratification, failed to report a DFS or OS benefit[44]. PROTECT was originally designed with pazopanib 800 mg once daily as the starting dose. However, similar to the ASSURE trial, the starting dose of pazopanib was reduced (from 800 mg to 600 mg) owing to a high rate of adverse events. Unfortunately, no DFS benefit was observed for pazopanib 600 mg once daily compared with placebo (HR 0.86, 95% CI 0.70–1.06; $P = 0.165$)[44]. By contrast, the secondary analysis of DFS in the 800 mg pazopanib subgroup of the ITT cohort ($n = 403$) yielded a hazard ratio of 0.69 (95% CI 0.51–0.94; $P = 0.02$)[44], suggesting superiority compared with placebo. However, a higher rate of treatment discontinuations owing to adverse events (particularly hypertension, fatigue and hand–foot syndrome) was observed in this group of patients. Interestingly, a post hoc analysis of the PROTECT trial data concluded that higher pazopanib exposure was associated with improved DFS and did not increase the rate of treatment discontinuations or grade 3 (severe) and 4 (life-threatening) adverse events, with the exception of hypertension[49].

The European Association of Urology (EAU) Renal Cell Carcinoma Guideline Panel performed a pooled analysis of the ASSURE and S-TRAC data to assess the potential impact of 1 year of adjuvant sunitinib therapy on DFS and adverse events[50]. This analysis failed to detect a statistically significant improvement in DFS or OS with adjuvant VEGFR-targeted therapies. As expected, high-grade adverse events (for example, hypertension, fatigue and hand–foot syndrome) were more frequent in patients treated with adjuvant sunitinib than in those who received placebo. The EAU panel, which included representatives from a patient advocate group (The International Kidney Cancer Coalition), also rated the quality of the evidence, the harm-to-benefit ratio, patient preferences and costs. Following a vote, they reached a consensus not to recommend adjuvant therapy with sunitinib for patients with high-risk RCC after nephrectomy[50]. Interestingly, the European Medical Agency (EMA) reached the same conclusion on the basis of the S-TRAC data[51].

The S-TRAC results and the pazopanib exposure data from PROTECT suggest a possible association between drug exposure and improved DFS[43,49]. Trial investigators have suggested that patients who are able to tolerate a full-dose regimen may experience prolonged DFS[49]. However, given the high rate of toxicity attrition in these trials, it is unlikely that full doses of adjuvant VEGFR-targeted therapy would be tolerable for the majority of patients in the real-world setting. As mentioned above, reductions of the initially planned starting doses were required to reduce the rate of adverse events in the ASSURE and PROTECT studies[42,44], and all three studies were burdened by drug discontinuations related to VEGFR TKI toxicity[42–44]. Although the reduction in starting dose ameliorated the toxicities observed in the

Table 3 | **Phase III trials of VEGFR TKIs as adjuvant therapies for radically resected RCC**

Trial	Inclusion criteria	Treatment (dose[a])	*n* (drug; placebo)	Disease-free survival	Treatment adherence	Refs
ASSURE (NCT00326898)	• pT1b high-grade, N0, M0 or N^+, M0 • Clear cell or non-clear cell RCC • ECOG performance status 0–1 • Normal liver and haematological function • Creatinine clearance >30 ml/min/1.73 m^2	Sunitinib (50 mg per day for the first 28 days of each 6-week cycle)	647; 647	HR 1.02 (97.5% CI 0.85–1.23); $P = 0.8038$	• 42% of patients received the intended dose at cycle 3 • Among patients starting sunitinib at full or reduced dose, the rates of treatment discontinuation were 44% and 34%, respectively	42
		Sorafenib (400 mg twice per day)	649; 647	HR 0.97 (97.5% CI 0.80–1.17); $P = 0.7184$	• 31% of patients received the intended dose at cycle 3 • Among patients starting sorafenib at full or reduced dose, the rates of treatment discontinuation were 45% and 30%, respectively	42
S-TRAC (NCT00375674)	• Stage III–IV, M0 (UISS modified criteria) • Clear cell RCC • ECOG performance status 0–2	Sunitinib (50 mg per day on a 4 weeks on, 2 weeks off schedule for 1 year)	309; 306	HR 0.761 (95% CI 0.594–0.975); $P = 0.030$	• Dose reductions or interruptions because of adverse events in 34.3% and 46.4% of patients, respectively • Treatment discontinuations owing to adverse events in 86 patients (28.1%)	43
PROTECT (NCT01235962)	• pT2 high-grade, pT3–4, N0, M0 or N^+, M0 • Clear cell RCC • KPS ≥80%	Pazopanib (600 mg per day with optional dose escalation to 800 mg per day after 8–12 weeks; treatment for 1 year)	571; 564	HR 0.862 (95% CI 0.699–1.063); $P = 0.1649$	• 49% of patients completed pazopanib treatment • Dose reductions in 51% and 60% of patients in the 600 mg and 800 mg groups, respectively • Treatment discontinuation owing to adverse events in 35% and 39% of patients in the 600 mg and 800 mg groups, respectively	44
ATLAS (NCT01599754)	• ≥ pT2 and/or N^+ • Any Fuhrman grade • ECOG performance status 0–1 • Clear cell RCC	Axitinib (5 mg twice per day for ≤3 years with a 1-year minimum)	363; 361	HR 0.870 (95% CI 0.660–1.147); $P = 0.3211$	The percentage of patients with adverse events leading to dose reductions (56% versus 8%), dose interruptions (51% versus 22%) and permanent discontinuations (23% versus 11%) was greater in the axitinib group than the placebo group	45

ASSURE, Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma; ATLAS, Axitinib Versus Placebo in Patients at High Risk of Recurrent Renal Cell Carcinoma; ECOG, Eastern Cooperative Oncology Group; KPS, Karnofsky Performance Status; PROTECT, Pazopanib As Adjuvant Therapy in Localized/Locally Advanced RCC After Nephrectomy; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor; UISS, University of California at Los Angeles (UCLA) Integrated Staging System; VEGFR, vascular endothelial growth factor receptor. [a]In ASSURE, high rates of toxicity-related discontinuation occurred after 1,323 patients had enrolled. Therefore, the starting dose for each drug was reduced and then individually titrated up to the original full doses. The starting doses were amended to 37.5 mg for sunitinib or 400 mg for sorafenib for the first 1–2 cycles of therapy. In PROTECT, the trial was originally designed with pazopanib 800 mg once daily as the starting dose. An amendment to the protocol was introduced to reduce the starting dose to 600 mg once daily owing to a higher than expected treatment discontinuation; 198 patients received a starting dose of 800 mg, of whom 53% experienced adverse events and had their dosage reduced and 51% discontinued treatment. Following protocol amendment, 568 patients were recruited; these patients served as the group for primary analysis.

ASSURE trial, it is remarkable that 55% of patients who received reduced dosages of sunitinib or sorafenib still experienced high-grade adverse effects[42]. Moreover, the post hoc subset analyses that evaluated dose intensity in the ASSURE trial found no relationship with outcome[48].

In 2018, another adjuvant trial, the Axitinib Versus Placebo in Patients at High Risk of Recurrent Renal Cell Carcinoma (ATLAS) study, was stopped owing to futility at a preplanned interim analysis at 203 DFS events[45]. The available data showed no significant difference in DFS according to the independent review committee (IRC) assessment (HR 0.870, 95% CI 0.660–1.147; $P = 0.3211$). In the highest-risk subpopulation, a 36% and 27% reduction in risk of a DFS event with axitinib

Box 2 | **Possible reasons for failure of VEGFR TKIs in the adjuvant setting**

Biological reasons

- Inability to eradicate occult disease because antiangiogenic agents act on tumour blood vessels rather than tumour cells
- Inadequacy of 1–2 years of antiangiogenic treatment for a malignancy that is often characterized by late relapses even decades after resection of the primary tumour; in preclinical models, tumour angiogenesis starts regrowing within a few days of withdrawal of the antiangiogenic agent

Pharmacological reasons

- Poor tolerability — a major issue in potentially cured patients — could result in an excess of dose reductions and treatment pauses and ultimately lead to a suboptimal dose intensity of the adjuvant treatment; a direct relationship exists between the area under the plasma drug concentration–time curve (AUC) of VEGFR TKIs and their activity

Patient-related reasons

- Risk of non-adherence to treatment or treatment withdrawal in patients who often consider themselves to be cured by surgery so are not willing to accept treatment-related adverse events

TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.

was observed in the investigator assessment (HR 0.641, 95% CI 0.468–0.879; $P = 0.0051$) and IRC assessment (HR 0.735, 95% CI 0.525–1.028; $P = 0.0704$), respectively. The OS data were not mature.

Two ongoing post-nephrectomy RCTs are evaluating the efficacy of adjuvant sorafenib therapy for 1 year or 3 years (SORCE study)[46] and of everolimus (a serine threonine kinase inhibitor) for 54 weeks (EVEREST study)[52] (Supplementary Table 2). The SORCE results are expected in the first few months of 2019, whereas the estimated study completion date for EVEREST is October 2021 (REF.[52]). However, given the disappointing findings discussed above, positive results seem unlikely.

As the mechanism of action of VEGFR TKIs is inhibition of angiogenesis, one might speculate that use of these drugs as adjuvant therapy would not eradicate occult disease (BOX 2). Indeed, these agents failed to eradicate occult disease in other types of cancer[53], including colorectal cancer[54]. Neoangiogenesis may not be present in very early subclinical metastases; therefore, these lesions may not be susceptible to inhibition of neovascularization. In the adjuvant setting, inhibition of neoangiogenesis using VEGFR TKIs in patients with subclinical metastases might only delay, rather than prevent, the radiographic progression of their mostly asymptomatic lesions. Although such a delay might result in prolonged DFS, it is questionable whether this prolongation would translate into a clinically meaningful benefit in the absence of proved OS benefits. In view of this uncertainty, patients face the dilemma of whether to accept the toxicity of full-dose treatment in order to take advantage of the potential full-dose effect or to continue treatment at a lower dose that is more tolerable but has not been shown to improve DFS. Importantly, it is clinically evident that patients who are potentially cured of cancer are willing to accept a completely different trade-off between efficacy (that is, reduction in the risk of relapse) and toxicity (that is, they are less likely to accept a low-efficacy, highly toxic therapy) than those with metastatic disease.

Immune checkpoint inhibitors

The immune checkpoint inhibitors anti-PD-1, anti-PD-L1 and anti-CTLA4 have been reported to show efficacy in metastatic RCC either as monotherapies or in combination with other agents including VEGF-targeted therapies[55–58]. This success has generated enthusiasm to test these therapies in the adjuvant setting. Five phase III RCTs are currently exploring the effect of immune checkpoint inhibitor therapy in the adjuvant setting for locoregional high-risk RCC[59–63] (Supplementary Table 3). The rationale for use of these therapies is that immune checkpoint inhibition might be more effective than VEGFR-targeted therapy in eliminating circulating tumour cells and micrometastases (FIG. 2).

Preclinical and early clinical studies suggest that neoadjuvant immunotherapy (that is, treatment before nephrectomy) might have increased efficacy compared with adjuvant immunotherapy (following primary tumour resection) for eradicating metastatic disease[64]. The rationale for a neoadjuvant strategy is that it enables the primary tumour antigens to prime the immune response against early occult disease. The ongoing PROSPER phase III trial of nivolumab (anti-PD-1) in patients with ≥T2 or T any, N^+ RCC includes a short neoadjuvant period as well as adjuvant therapy[59]. The investigators plan to enrol 766 patients. As nephrectomy will potentially be deferred in the control group for 4 weeks, the study is designed as an unblinded trial with observation rather than placebo in the control group.

Currently, no combinations of immune checkpoint inhibitors and VEGF-targeted therapies are being tested in the adjuvant setting. Given the problems of tolerability, it seems unlikely that multi-modal treatments using these agents would be a rational strategy for adjuvant therapy.

Preservation of kidney function

In patients who undergo radical resection for localized RCC, morbidity related to chronic kidney disease (CKD) as a result of loss of nephron mass and/or complications related to comorbid disease is an important issue. The prevalence of CKD in patients with RCC is twice that of the general population, varying from 10% among those presenting with a small renal mass to 26% among those with a tumour, irrespective of size and even before surgical resection[65]. Moreover, retrospective studies in patients with kidney cancer have reported that the prevalence of CKD increased from 10–26% before tumour resection to 16–52% after surgery[66,67]. Partial nephrectomy results in a mean decrease in glomerular filtration rate (GFR) of 13 ml/min/1.73 m^2 (30%), and reduction in renal volume seems to be a prognostic factor for GFR decline[68]. Nephrectomy is also associated with a 33.7% risk of acute kidney injury (AKI)[61], and postoperative AKI[69–71] is a key determinant of GFR decline. Importantly, patients with CKD undergoing nephrectomy, even those with T1 tumours, are more likely to die as a result of CKD-related complications, such as cardiovascular disease, or dialysis-related complications, such as infections, vascular access complications or arrhythmias, than as a result of their kidney malignancy[65,66]. Thus, the nephrological management of patients with

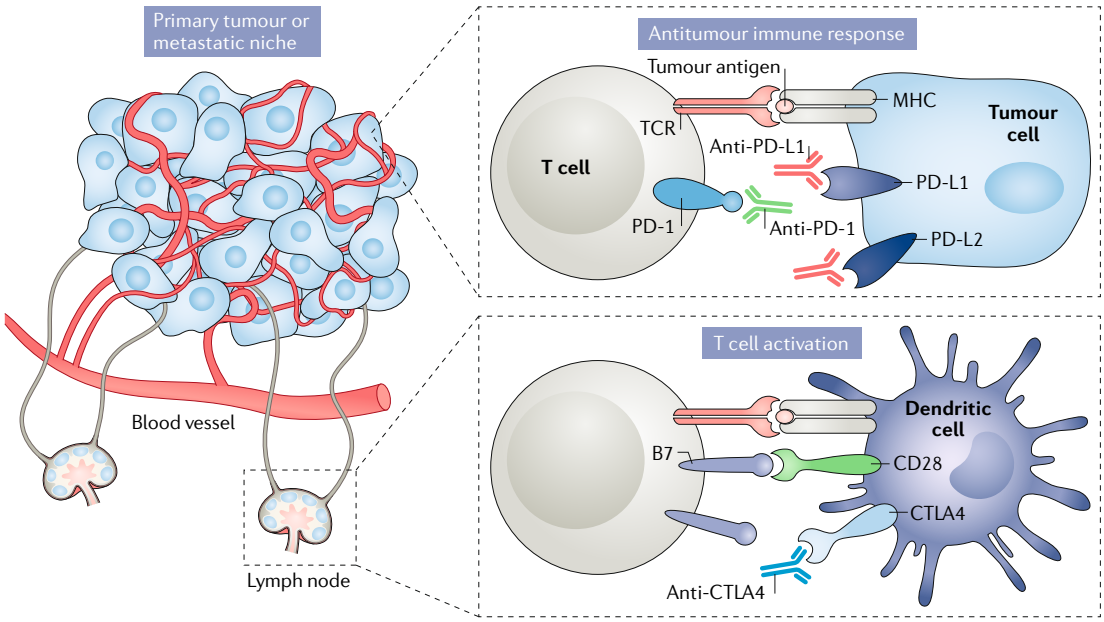

Fig. 2 | **Mechanisms of action of immune checkpoint inhibitors in renal cell carcinoma.** Immune checkpoint blockade using anti-CTLA4, anti-PD-1 and/or anti-PD-L1 monoclonal antibodies removes inhibitory signals that limit T cell responses. CTLA4 inhibitors usually act within lymph nodes (that is, in the periphery), where they block the interaction between CTLA4 expressed on naive T cells and B7 expressed on dendritic cells and thus enable the activation and proliferation of tumour antigen-specific T cells. Anti-PD-1 and anti-PD-L1 usually act within the tumour microenvironment (that is, centrally), where they block interactions between PD-1 expressed on tumour-reactive T cells and PD-L1 and/or PD-L2 on tumour cells to enhance antitumour immune responses. MHC, major histocompatibility complex; TCR, T cell receptor.

resected localized RCC should focus on preserving kidney function, reducing cardiovascular risk and preventing complications (FIG. 3).

In most patients, particularly those with comorbidities including hypertension or diabetes[65], nephrologists should carefully evaluate kidney function before nephrectomy, taking into account the type of planned surgery (either radical or nephron sparing), to evaluate the risk of de novo kidney injury or worsening of pre-existing CKD. Ideally, such pre-operative evaluation should be performed for all patients, but if this is not practical, it can be avoided in those who have normal renal function and no relevant comorbidities[72]. Renal nuclear scintigraphy can be used to determine the proportional GFR of each kidney in order to better assess the potential impact of renal resection (either partial or radical nephrectomy)[73]. Optimization of glycaemic and blood pressure control and prevention of AKI through avoidance of nephrotoxins and renal hypoperfusion also reduce the risk of postoperative deterioration of GFR[65].

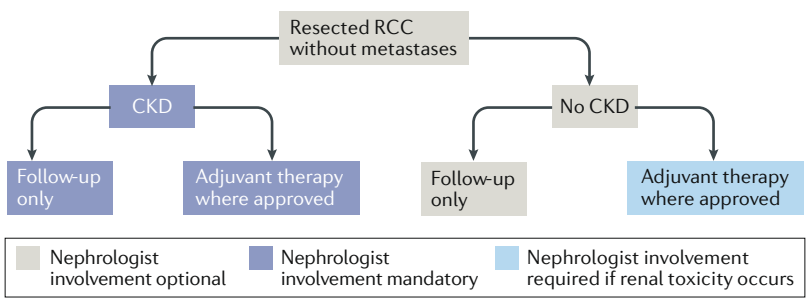

Fig. 3 | **The role of nephrologists in the management of resected renal cell carcinoma.** The optimal management of patients with resected localized renal cell carcinoma (RCC) should involve a multidisciplinary approach with input from oncologists, pathologists and nephrologists. We propose that involvement of a nephrologist should be mandatory for all patients with chronic kidney disease (CKD), including those receiving adjuvant therapies, with a focus on preserving kidney function, reducing cardiovascular risk and preventing complications. Nephrology involvement is also required for patients without CKD receiving adjuvant therapy if renal toxicity occurs.

The evaluation of tumour nephrectomy specimens has always centred around the neoplastic renal mass, but careful assessment of the non-neoplastic kidney parenchyma may reveal the presence of undiagnosed common non-neoplastic renal diseases such as nephroangiosclerosis or glomerulonephritis and provide a wealth of information regarding future risk of CKD and its progression. Since 2010, the College of American Pathologists has required that the non-neoplastic parenchyma is evaluated and reported for every renal malignancy[74]. However, a 2012 survey of European genitourinary pathologists found that >25% did not examine the non-neoplastic part of the kidney in nephrectomy specimens[75].

After major kidney surgery, patients should undergo nephrology evaluation in order to minimize future deterioration in kidney function[65,72]. In these patients, the timing of follow-up is dictated by the residual renal function after nephrectomy. In the USA, some patients who undergo radical resection of kidney tumours will receive adjuvant sunitinib therapy. Approximately 30% of these patients will ultimately relapse and thus will require active oncological treatment with either VEGFR TKIs or immune checkpoint inhibitors. As concomitant CKD increases the risk of use of suboptimal dose

intensities and treatment-related toxicities, especially when VEGFR TKIs are used[76,77], this issue highlights the key importance of preventing deterioration in kidney function in patients with kidney cancer[68,69,78,79].

Conclusions

Over the past two decades, the survival of patients with metastatic RCC has improved substantially[80]. Among patients with radically resected tumours, however, the lack of active adjuvant treatments means that the risk of dying because of metastatic relapse has not decreased. The main reasons for this failure are difficulties in clearly identifying patients who are at high risk of relapse, historic use of poorly active treatments, tolerability issues with novel targeted agents leading to the use of suboptimal doses and limited knowledge of the genetic and molecular mechanisms that lead to the occurrence of metachronous metastases. Furthermore, the results of the only two positive adjuvant trials reported to date are inconclusive and thus surrounded by a substantial amount of uncertainty.

Novel immune checkpoint inhibitors hold promise for the adjuvant therapy of RCC. However, improved patient selection and stratification (on the basis of risk of relapse), the use of active, biology-driven treatments and improved management of therapy (to maintain ideal dose intensities) are required to prevent the future failure of these and other novel agents. Finally, multidisciplinary management of all patients with RCC, including those potentially cured by surgery, is mandatory. In particular, input from nephrologists is important to minimize loss of renal function following nephrectomy, reduce associated morbidity and mortality and manage renal toxicities from oncological treatments.

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Author contributions

All authors researched the data, contributed to discussions of the content, wrote the article and reviewed or edited the manuscript before submission.

Competing interests

C.P. and A.B. contributed to the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) discussion regarding approval of sunitinib as an adjuvant treatment for resected renal cell carcinoma. The other authors declare no competing interests.

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Supplementary information

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