THE ADJUVANT TREATMENT OF KIDNEY CANCER: A MULTIDISCIPLINARY OUTLOOK

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ABSTRACT | About 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 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.

INTRODUCTION

Estimates suggest that kidney cancer is the twelfth most common cancer worldwide, with 338,000 new cases diagnosed in 2012[1]. In 2017, around 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 US[2]. About 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 are resected 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 tumor and can ultimately lead to death. Data from the US National Cancer Database indicate that although the observed 5-year cancer-specific survival of TNM (tumour, node, metastases) 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 in order to develop rational adjuvant strategies. A number of predictive models have been developed to accomplish this goal. These models all incorporate widely available, easily obtainable, clinicopathologic 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 UCLA Integrated Scoring System (UISS)[8] and the Leibovich score[9].

The UISS includes two tumor-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 these features stratifies patients into low, intermediate and high-risk prognostic categories. In patients with non-metastatic disease, the application of the UISS system correctly predicted 2 year and 5-year survival rates irrespective of tumor histology in 76.5-86.3% of patients[8]. The UISS is also prognostic in the metastatic setting.

In 2003, Leibovich and colleagues identified 5 features in patients with clear cell renal cell carcinoma (ccRCC) — tumor stage, regional lymph node status, tumor size, nuclear grade, and histologic tumor 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%. The UISS and Leibovich models were both 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 SSIGN[11], Karakiewicz[12] and Kattan[13] models (Table 1) serve as adjunctive tools for patient counseling 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 the Kattan nomogram[13]. Conversely, a patient with 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 clinicopathologic variables are not able to capture the biology of the tumor, resulting in a substantial bias that the application of gene expression technologies to tumor characterization is trying to overcome. ClearCode34 is a 34-gene expression panel that can be used to classify ccRCC into two subtypes, clear cell A (ccA) and clear cell B (ccB), that are significantly associated with relapse-free survival (RFS), cancer-specific survival (CSS) 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 score) 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 BAP1-mutant group and a lower risk PBRM1-mutant group[18]. Notably, 80% of patients in the development and validation cohorts had localized (or loco-regional) disease; therefore the population in this study was fairly similar to that of the recurrence score study described above.

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 widespread 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 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 disease-free survival (DFS) and/or overall survival, with the exception of a trial of an autologous renal tumour cell vaccine that was published in 2004[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, a RCT tested the hypothesis that 6-months of adjuvant therapy with interferon-α (IFN) could improve overall and event-free survival (EFS) in patients with radically resected Robson stage II kidney cancer (i.e. a tumor invading perinephric fat but not extended beyond Gerota's fascia) or Robson stage III kidney cancer (i.e. a tumor invading the renal vein or inferior vena cava and/or spreading to regional lymph nodes)[20]. Notably, the study protocol recommended unilateral para-aortic lymph node dissection and the researchers relied on the pathologic report to verify that lymphadenectomy was performed. The overall survival 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; Hazard Ratio [HR], IFN vs control 1.040, 95% confidence interval (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 IFN versus control = 1.412, 95% CI 0.927–2.149) [18].

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 IFN 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 IFN-based immunotherapy might benefit patients at high risk of relapse due 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-up, the 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). 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 huge 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 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 an in extenso publication reporting on overall survival 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 relapse-free survival 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[33]. This study compared girentuximab, an anti-anhydrase carbonic IX (CAIX) monoclonal antibody, to observation in 864 patients with radically resected kidney cancer. CAIX is a tumor-associated transmembrane protein that is overexpressed in *VHL*-mutated clear cell kidney cancers and other hypoxic solid tumors 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 overall survival (HR 0.99, 95% CI 0.74-1.32) compared with placebo[33]. A subgroup analysis showed a nonsignificant trend 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 (e.g. chemotherapy, hormonal agents or 'old-fashioned' radiotherapy), limited patient numbers in many studies, the enrollment 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, particularly between vaccines, cytokines and other types of treatment. These findings suggest that the lack of equivalence between different treatments in terms of efficacy could be related to the nature of the therapeutic intervention itself[36]. These observations suggest that novel adjuvant immunotherapeutic strategies with specific mechanisms of action (for example, immune checkpoint inhibitors) might have a role in the future treatment of patients with kidney cancer, and 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 the Von Hippel Lindau tumor suppressor gene (*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 physiologic cellular response to hypoxia. In conditions of normoxia, pVHL binds the hypoxia-inducible factors (HIF)-1a and HIF-2a, leading to their ubiquitination 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 the hyperproduction of a number of pro-angiogenic cytokines, including the vascular endothelial growth factor (VEGF)[40,41]. For this reason, agents that target VEGF and VEGF receptor (VEGFR) pathways have been developed as agents for the treatment of metastatic RCC (Figure 1).

To date, 5 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 disease-free survival after nephrectomy in patients with predominantly ccRCC have now been published (Table 3).[42-44]

The multi-center, 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 1:1 to receive either 50 mg sunitinib once daily on a four 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). Based on these data, the US FDA approved sunitinib for the adjuvant treatment of adult patients at high-risk of recurrent RCC following nephrectomy in November 2017[47].

The Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma (ASSURE) study, which included 1,943 patients with RCC at intermediate or high-risk of relapse (according to the UISS model), did not find an improvement in DFS or overall survival with 1 year of adjuvant sunitinib or sorafenib therapy compared with placebo[42]. During this study, the starting doses were reduced due to toxicity issues from 50 mg to 37.5 mg daily for sunitinib and from 800 mg to 400 mg for the first one or two cycles of sorafenib. 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-not estimable [NE]) in the sorafenib group (HR 0.97, 97.5% CI 0.80-1.17, p=0.7184) and 6.6 years (IQR 1.5-NE) in the placebo group[42]. Furthermore, a secondary analysis of the trial results found that neither the prognostic category of the tumor nor the dose intensity of therapy altered the lack of difference in DFS or overall survival 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 based on TNM risk stratification, failed to report a DFS or overall survival benefit[44]. PROTECT was originally designed with pazopanib 800 mg once daily as the starting dose. However, similar to the ASSURE trial, the primary objective of PROTECT had to be amended to study DFS in a cohort that received a reduced starting dose of pazopanib (600 mg) owing to a high rate of adverse events. Unfortunately, no DFS benefit was observed for pazopanib 600 mg once daily compared to placebo. The DFS results of the primary analysis of the intention-to-treat (ITT) cohort favoured pazopanib 600mg but did not show a significant improvement over placebo (HR 0.86; 95% CI 0.70–1.06; P = 0.165)[44]. By contrast, the secondary analysis of DFS in the 800mg pazopanib subgroup of the ITT cohort (n = 403) yielded an HR of 0.69 (95% CI 0.51–0.94)[44], suggesting superiority compared with placebo. However, a higher rate of treatment discontinuations owing to adverse events (particularly hypertension, fatigue and hand-foot syndrome) were 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 overall survival with adjuvant VEGFR-targeted therapies. As expected, high-grade adverse events (e.g 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 and in contrast to the US FDA, decided in 2018 not to consider adjuvant sunitinib for approval based on 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 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

pre-planned interim analysis at 203 DFS events[45]. The available data show 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 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 overall survival 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 everolimus 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[52]. However, given the disappointing findings discussed above, positive results seem unlikely.

As the mechanism of action of VEGF-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 if this prolongation would translate into a clinically meaningful benefit in the absence of proven overall survival 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 be 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 (i.e. reduction in the risk of relapse) and toxicity (that is, they are less likely to accept a low efficacy, highly toxic therapy), compared to 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 loco-regional 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 (Figure 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 in patients with ≥T2 or T any N+ RCC includes a short neoadjuvant period as well as adjuvant therapy[59]. The investigators plan to enroll 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 prior to 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 per 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 than as a result of their kidney malignancy[65,66]. Thus, the nephrological management of patients with resected localized RCC should focus on preserving kidney function, reducing cardiovascular risk and preventing complications (Figure 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-operatory evaluation should 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 reduces the risk of postoperative deterioration of GFR[65].

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 nephro-angiosclerosis 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% do 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 post-nephrectomy. In the US, some patients who undergo radical resection of kidney tumours will receive adjuvant sunitinib therapy. Around 30% of these patients will ultimately relapse so will require active oncological treatment with either VEGFR-TKI or immune checkpoint inhibitors. As concomitant CKD increases the risk of use of suboptimal dose-intensities and treatment-related toxicities, especially when VEGFR-TKI 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 huge 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), smarter clinical trial design, the use of active, biology driven treatments and improved management of therapy (to maintain ideal dose intensities) is 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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All Authors researched the data, contributed to discussions of the content, wrote the article and reviewed or edited the manuscript before submission.

Competing interests

CP and AB contributed to the 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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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 US; however this drug has not been approved as an adjuvant therapy in Europe.
- Positive results with immune checkpoint inhibitors in metastatic renal cell carcinoma suggest that these agents might also be effective adjuvant therapies; trials of these agents are underway.
- Preservation of kidney function in patients with renal cell carcinoma is important to reduce morbidity; therefore multidisciplinary management should be mandatory for almost all patients with radically resected kidney cancer.

Box 1 | TNM staging of kidney tumours

Tumour (T)
Tx: The primary tumor cannot be assessed
T0: No evidence of a primary tumor
T1: Kidney-confined tumor <7 cm in diameter
- 1a: <4 cm
- 1b: >4 cm and <7 cm

T2: Kidney-confined tumor >7 cm in diameter
- 2a: >7 cm and <10 cm
- 2b: >10 cm

T3: The tumor is growing into a major vein or into tissue around the kidney, but it is not growing into the adrenal or beyond Gerota's fascia
- 3a: the tumor is growing into the renal vein or into fatty tissue around the kidney
- 3b: the tumor is growing into intra-abdominal vena cava
- 3c: the tumor is growing into the vena cava above the diaphragm

T4: The tumor has spread beyond Gerota's fascia or into the adrenal gland

Nodes (N)
Nx: Regional lymph nodes cannot be assessed
N0: No spread to nearby lymph nodes
N1: Tumor has spread to nearby lymph nodes

Metastases (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

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

Biolological

- Inability to eradicate occult disease as antiangiogenic agents act on tumor 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, tumor angiogenesis starts regrowing within a few days of withdrawal of the antiangiogenic agent

Pharmacological

- 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 AUC of VEGFR-TKIs and their activity

Patient related

- 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

VEGFR-TKI, Vascular Endothelial Growth Factor Receptors Tyrosine Kinase Inhibitors; AUC, area under the plasma drug concentration-time curve.

Figure 1 | Mechanisms of action of VEGFR-TKI in RCC. In normoxic conditions, VHL binds hypoxia-inducible factor 1α (HIF1α) and HIF1β and targets them for proteasomal degradation. Genetic loss or inactivation of the VHL gene 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 tumor 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 VEGFR using tyrosine kinase inhibitors such as pazopanib, sunitinib, sorafenib or axitinib.

Figure 2 | Mechanisms of action of immune checkpoint inhibitors in RCC. 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 (i.e. in the periphery) where they block the interaction between CTLA4 expressed on naive T cells and B7 expressed on dendritic cells so enable the activation and proliferation of tumour antigen-specific T cells. Anti-PD1 and anti-PD-L1 usually act within the tumour microenvironment (i.e. centrally) where they block interactions between PD-1 expressed on tumour-reactive T cells and PD-L1 and/or PD-L2 on tumour cells so enhance anti-tumour immune responses.

Figure 3 | The role of nephrologists in the management of resected RCC. The optimal management of patients with resected localized 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.

Table 1 | Commonly used clinico-pathologic predictive models for risk of relapse of RCC following surgical resection

Model	Predictor variables	Histology	Outcome predicted	Positive predictive value	Refs
UISS	• Pathologic stage • Nuclear grading • ECOG performance status	Histoype independant	Overall survival in patients with non-metastatic and metastatic RCC	• Non-metastatic RCC: 76.5-86.3% • Metastatic RCC: 64-77%	8
SSIGN	• Pathologic 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	• Pathologic 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	• Pathologic stage (excluding metastasis stage) • Nuclear grading • Major dimension of the tumour • Mode of presentation	Histoype independant	Cause-specific survival	86-88%	12
Kattan	• Patient's 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

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

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

Study	*Intervention*	*Patients*		*Results*	*Observations and/or limitations*	*Refs*
		N	*Criteria*			
Cytokine-based immunotherapy						
Pizzocaro (2001)	IFN-α2b (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 = ns for both)	• IFN-α2b had a statistically significant harmful effect in patients with pN0 RCC (n = 97; HR 2.228) • IFN-α2b 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 ap-plications 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	• HR 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-up, HRs for tumour progression were 1.58 (95% CI = 1.05-2.37) and 1.59 (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 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 IV 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 • pTany, 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 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 summerized in this table. For a full list of early adjuvant trials see Supplementary table 1. i.m. , intramuscular; MU, mega units; TNM, Tumor, Nodes, Metastasis staging system; RFS, relapse-free (or recurrence-free) survival; IV, intravenous; HR, hazard ratio; CI, confidence interval; OS, overall survival; IFN, interferon.

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

Trial	Inclusion criteria	Treatment (dose*)	Patients (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 PS 0–1 • Normal liver and haematological function • Creatinine clearance >30ml/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 PS 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	• Fewer than 50% of patients completed treatment • Dose reductions in 51% and 60% of patients in the 600 mg and 800 mg groups, respectively • Treatment discontinuation due 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 PS 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 placebl group	45

ECOG PS, Eastern Cooperative Oncology Group Performance Status; HR, Hazard Ratio; CI, confidence interval; KPS, Karnofsky performance status; UISS, UCLA Integrated Staging System; AEs, adverse events. *In ASSURE, high rates of toxicity-related discontinuation occurred after 1,323 patients had enrolled. Therefore, the starting dose for each drug was reduced than 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 starting dose. An amendment to the protocol was introduced to reduce the starting dose to 600 mg once daily due 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.

Supplementary table 1 | Early randomized trials of adjuvant therapy for radically resected kidney cancer

Miscellaneous						
Author, year	***No.***	***Interventions***	***Stage/risk class of treated patients***	***Main results***	***Observations/criticisms***	***Refs****
Kjaer M, et al., 1987	72	*Arm A* – Radiotherapy (50 Gy in 20 fractions of 2.5 Gy each, four fractions per week) to the kidney bed, ipsi- and contralateral lymph nodes *Arm B* – observation	• 33 and 32 pts, out of the 65 analyzed were in stage II and III, according to the Holland classification, respectively	• No differences in RFS • Pts with stage II tumours survived significantly better than those with stage III tumours ($p<0.05$), but no significant differences in survival has been demonstrated between pts randomized to postoperative radiotherapy or observation	• 7 pts were excluded from analysis due to major protocol violations; • 44% of treated pts had significant complications from stomach, duodenum or liver; in 19% of them, postirradiatory complications lead (or contributed) to death	19
Pizzocaro G, et al., 1987	136	*Arm A* – Medroxyprogeste-rone acetate 500 mg per os, 3 t.i.w., for 1 year *Arm B* – observation	• M0 pts	• No differences in RFS (32.7% vs 33.9%) of relapsing pts in the treatment and control arm, respectively	• 56.9% of pts experienced treatment-related complications	30
Naito S, et al., 1997	71	*Arm A* – UFT (Tegafur and Uracil in a 1:4 molar concen-tration) 300 to 600 mg (as Tegafur) o.d., for 2 years *Arm B* – observation	• Stage I or II according to Robson (54 out of 71 were pT2)	• No differences in 5-year non recurrence rates (80.5% for UFT-treated pts vs 77.1), as well as 5-year renal cell carcinoma specific survival (90.6% vs 82.1%)	• 5 pts were not evaluable; • 2 pts received immunotherapy together with UFT; • 2 pts asked to discontinue the drug due to adverse gastro-intestinal effects; • 1 patient was lost to the follow-up at 8 weeks after starting therapy	31
Margulis V, et al. 2009	46	*Arm A* – Thalidomide 100 mg o.d. per os, for 2 weeks, then 200 mg o.d. for 2 weeks, followed by the maximum dose of 300 mg o.d. for a maximum of 2 years, or until untolerable toxicity	• T2 (high grade, any N), T3/T4 (any grade, any N), or node-positive (any grade, any T) tumors • any histologic subtype	• Pts on Thalidomide had inferior 2- and 3-year probabilities of RFS, compared with controls (47.8% vs 69.3% and 28.7% vs 69.3%, res-pectively) • 2- and 3-year CSS was similar for both groups	• Treatment stopped at first interim analysis, after a median follow up of 43.9 months (range: 9.7-74.2 months), given the minimal likelihood that adjuvant Thalidomide would demonstrate the clinically significant benefit projected	32

		Arm B – observation				
Chamie K, et al., 2017	864	*Arm A* – single loading i.v. dose of Girentuximab, 50 mg (week 1), followed by Girentuximab 20 mg/week (weeks 2-24) *Arm B* – placebo	High risk pts defined as: • pT3/pT4, Nx/N0, M0 • pTany, N+, M0 • pT1b/pT2, Nx/N0, M0 with nuclear grade 3 or greater	• No differences 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 for Girentuximab and never reached for placebo • Median OS was never reached regardless of treatment	• No differences in safety between treatment and placebo arm	33
Vaccines						
Author, year	***No.***	***Interventions***	***Stage/risk class of treated patients***	***Main results***	***Observations/criticisms***	***Refs***
Adler A, et al., 1987	43	*Arm A* – immuno-hormono-therapy arm (immunotherapy consisted of autologous irra-diated tumor cells, admixed with bacillus Calmette-Guérin, administered by the intra-dermal and endolymphatic route) *Arm B* – hormonotherapy alone (HT)	• Stage I to IV (i.e. included also metastatic pts)	• Not statistically significant trend in favor of the experimental arm, over the control one, in terms of DFI in stages I-III (i.e. localized) disease	• Mixed radically resected, with metastatic pts • A correlation was established between induction of cutaneous delayed hypersensitivity to auto-logous irradiated tumor cells and prolonged PFI and OS	26
Galligioni E, et al. 1996	120	*Arm A* – active specific immunotherapy consisting of 3 intradermal injections of 10^7 autologous irradiated tumor cells mixed with 10^7 Bacillus Calmette-Guerin (in the first 2 vaccinations) *Arm B* – observation	• Stage I (just 3 pts) to III, according to the TNM staging system • At least hylar lymphade-nectomy was performed in all pts	• The probability of 5-year DFS was 63% for treated patients, and 72% for controls (p = n.s.), respectively • The corresponding probability of 5-year overall survival (OS) was 69% and 78%, respectively (p = n.s.)	• One month after completing active specific immunotherapy, 38 of 54 immunized patients showed a significant (p < 0.01) DTCH response to autologous tumor, but not to autologous normal renal cells • No significant differences in DFS and OS were observed in the treated pts, according to the intensity of the DTCH response	27
Jocham D, et al. 2004	379	*Arm A* – six intradermal ap-plications of an	• Stage pT2/3b pN0-3 M0	• HR for tumor progression were 1.58 (95% CI =	• Vaccination was extremely well tolerated • QoL was similar in the two	28

		autologous renal tumour cell vaccine at 4-week intervals postoperatively *Arm B* – observation	• pT1 as well as pT4 were excluded • Surgery other than radical nephrectomy was an exclusion criterion	1.05-2.37) and 1.59 (95% CI = 1.07-2.36), respectively, in favour of the vaccine group (p=0·0204 • 5-year and 70-month PFS rates were 77.4% and 72%, respectively, in the vaccine group and 67.8% and 59.3%, respectively, in the control group	study arms • Study had significant methodological flaws (see text)	
Wood C, et al. 2018	818	*Arm A* – Vitespen™ vaccine (i.e. an heat-shock protein [glycoprotein 96]–peptide complex derived from autologous tumors) give intradermally at the dose of 25 µg once a week for 4 weeks, then every 2 weeks until vaccine supply depletion or disease progression *Arm B* – observation	• cT1b/T4, N0, M0 • cTany, N1-2, M0	• Recurrences were reported in 136 (37.7%) patients in the vaccine group and 146 (39.8%) in the observation group (HE = 0.923, 95% CI = 0.729-1.169, p=0.506)	• Possible improvement in RFS in pts with early stage (stage I or II) disease, though the observed difference was not statistically significant (HR = 0.576, 95% CI = 0.324-1.023, p=0.056)	29
Cytokine-based immunotherapy						
Author, year	***No.***	***Interventions***	***Stage/risk class of treated patients***	***Main results***	***Observations/criticisms***	***Refs***
Pizzocaro G, et al. 2001	247	*Arm A* - IFN-α2b (6 MU i.m. tiw for 6 months starting within 1 month from surgery) *Arm B* – observation	Stage II or III according to the 1987 TNM classification: • pT3a, N0, M0 • pT3b, N0, M0 • pT2/3, N1-3, M0	• 5-year overall and event-free survival probabilities were 0.665 and 0.671, respectively, for controls, and 0.660 and 0.567, respectively, for the treated group (p = n.s. for both)	• A statistically significant harmful effect of IFN-α2b in the 97 treated pN0 patients (HR = 2.228), and a protective effect in the 13 treated pN2/3 patients (0.191) was observed	20
Messing E, et al., 2003	283	*Arm A* – Up to 12 cycles of IFN-αNL, daily for 5 days a week, every 3 weeks (3 MU/m^2, day 1, 5 MU/m^2,	• pT3 • pT4a • Any N+ (according to the 1987 TNM classification)	• Median OS: 7.4 years in the observation arm vs 5.1 years in the treatment arm (log-rank p = 0.09)	• A proportional hazards model examining the effects of treatment arm and time to recurrence on survival after recurrence among pts who recurred	21

		day 2, 20 MU/m^2, days 3, 4 and 5) *Arm B* – observation		• Median RFS: 3.0 years in the observation arm vs 2.2 years in the treatment arm (p = 0.33)	found that random assignment to IFN-αNL (p = 0.009) and shorter time to recurrence (p < 0.0001) were independent predictors of shorter survival • Grade 4 AEs occurred in 11.4% of IFN-αNL-treated pts	
Clark JI, et al. 2003	69	*Arm A* – IL-2 600.000 UI/Kg i.v. bolus over 15', every 8 hours on days 1 to 5, and again on days 15 to 19, for a maximum of 28 doses *Arm B* – observation	• pT3b-c • pT4 • pN1-3 • completely resected M1 (pT3b and pN1 patients allowed after an amend-ment done in order to increase accrual)	• 2- and 3-year DFS was 48% and 32% for IL-2 treated pts, and 55% and 45% for observed pts, respectively • 2- and 3-year OS was 86% and 80% for IL-2 treated pts, and 86% and 86% for observed pts, respectively	• Early study closure occurred when an interim analysis determined that the 30% improvement in 2-year DFS could not be achieved despite full accrual • 88% of the 33 pts treated with IL-2 experienced at least one grade 3 or 4 AE, hypotension being the commonest	22
Passalacqua R, et al. 2007	310	*Arm A* – s.c. IL-2 for 5 days a week during a 4-week period at the dose of 1 MU/m^2 b.i.d. on days 1 and 2, and o.d. on days 3, 4 and 5 + IFN-α 1.8 MU/m^2 on days 3 and 5 of each week; cycles as described were repeated every 4 months for the first 2 years, and then every 6 months for the subsequent 3 years *Arm B* – observation	• pT2-3b, N0-3, M0 (according to the 1993 UICC classification)	• RFS at 5 years was 0.73 in both the treatment group, as well as in the control one HR = 0.84) • 5-year OS was 0.80 and 0.85 in the treatment and control groups, respectively (HR = 1.07)	• RFS survival curves were superimposible during the first 5 years of observation and then tended to separate (without any statistical significance) • Unplanned subgroup analysis showed a positive effect of the treatment for pts with age 60 years or younger, pN0, tumor grade 1 or 2, and pT3a stage; among pts with at least 2 of these factors, immunotherapy had a positive effect on RFS (HR = 0.44), as compared with pts with less than 2 factors (HR = 2.27)	24
Chemo-immunotherapy						
Author, year	***No.***	***Interventions***	***Stage/risk class of treated patients***	***Main results***	***Observations/criticisms***	***Refs***
Atzpodien J, et al., 2005	203	*Arm A* – one 8-week treatment cycle of s.c. IFN-α2a (5 MU/m^2, day 1, weeks 1 + 4; days 1, 3, 5, weeks 2 + 3; 10 MU/m^2, days 1, 3, 5, weeks 5–8), s.c.	High risk patients defined as: • pT3b/c, pN0; • pT4, pN0 • pN+ • M+ (solitary lesion), but R0	• 2-, 5-, and 8-year survival probabi-lities were 81, 58, and 58% on the experimental arm, and 91, 76, and 66% on the observation arm	• Included also patients with solitary metastased, though radically resected • 18 patients did receive previous systemic treatments (no further explanations) • No safety data available	23

		IL-2 (10 MUm^2, b.i.d., days 3–5, weeks 1 + 4; 5 MU/m^2, days 1, 3, 5, weeks 2 + 3) and i.v. 5-FU (1000 mg/m^2, day 1, weeks 5–8); a 20% dose reduction of s.c. IL-2 was given to patients ≥ 60 years of age *Arm B* – observation		• 2-, 5-, and 8-year RFS probabilities were 54, 42, and 39% on the experimental arm, with a median RFS of 2.75 years (range: 0–8.2 years), and 62, 49, and 49% on the observation arm, with a median RFS of 4.25 years (range, 0–9.7 years) • OS was significantly decreased (log rank P = 0.0278) after treatment with immunochemotherapy (range: 0.2–8.4 years), when compared with the control (range: 0.3–9.7 years)		
Aitchinson M, et al., 2014	309	*Arm A* – IL-2 (20 MU/m^2, s.c., days 1, 3 and 5, week 1; 5 MU/m^2, days 1, 3 and 5, weeks 2-3; 20 MU/m^2, days 1, 3 and 5, week 4), IFN-α (6 MU/m^2, s.c., day 1, week 1; 6 MU/m^2, days 1, 3 and 5, weeks 2-3; 6 MU/m^2, day 1, week 4; 9 MU/m^2, days 1, 3 and 5, weeks 5-8) and 5-FU 750 mg/m^2, i.v. bolus, day 1, weeks 5-8 *Arm B* – observation	High risk patients defined as: • T3b/c or T4 • any pT, pN1 or pN2 or • any pT with positive microscopic margins or microscopic vascular invasion	• DFS at 3 years was 50% with observation and 61% with treatment (HR = 0.84, 95% CI = 0.63-1.12, p=0.233) • OS at 5 years was 63% with observation and 70% with treatment (HR = 0.87, 95% CI = 0.61-1.23, p=0.428)	• 35% of pts did not complete the treatment, primarily due to toxicity (92% of patients experienced ≥ grade 2 AEs, 41% ≥ grade 3 AEs)	25

*Reference numbers refer to the reference list in the main text of the Review. Pts, patients; RFS, relapse-free (or recurrence-free) survival; t.i.w., three times in a week; o.d., once a day; b.i.d., twice a day; CSS, cancer-specific survival; PFI, progression-free interval; n.s., not significant; DTCH, delayed type cutaneous hypersensitivity; QoL, quality of life; i.v., intravenous; HR, hazard ratio; CI, confidence interval; OS, overall survival; IFN, Interferon; s.c., subcutaneous; IL-2, Interleukin-2; AEs, adverse events.

Supplementary table 2 | Unpublished phase III trials of targeted agents for the adjuvant treatment of resected RCC

Trial	Inclusion criteria	Treatment	Patients (n)	Primary end point	Status	Refs*
ATLAS (NCT01599754)	• Preponderant clear cell histology (defined as >50%) • pT2, N0 or Nx, M0 and ECOG PS 0-1 • pT3, N0 or Nx, M0 and ECOG PS 0-1 • pT4, N0 or Nx, M0 and ECOG PS 0-1 Any pT, N1, M0 and ECOG PS 0-1	Axitinib 5 mg twice a day for 3 years versus placebo (same schedule)	722	RFS	Completed Did not meet primary end point	45
EVEREST (NCT01120249)	• Clear cell or non-clear cell RCC • Considered pathologically either intermediate high-risk or very high-risk • Radical or partial nephrectomy • Removal of all clinically positive nodes • Patients with microvascular invasion of the renal vein of any grade or stage (as long as M0) allowed	Everolimus 10 mg once a day on days 1-42 repeated every 6 weeks for 9 courses versus placebo (same schedule)	1,545	RFS	Active but not recruiting Results pending	52
SORCE (NCT00492258)	• Clear cell or non-clear cell histology • Intermediate or high-risk disease (Leibovich score 3–11)	Sorafenib 400 mg twice a day for 1 year followed by oral placebo twice a day for 2 years versus oral sorafenib twice a day for 3 years versus oral placebo twice a day for 3 years	1,656	DFS	Completed Results pending	46

*Reference numbers refer to the reference list in the main text of the Review. ECOG, Eastern Cooperative Oncology Group; RFS, relapse-free survival; DFS, disease-free survival.

Supplementary table 3 | Ongoing trials with immune checkpoint inhibitors in the setting of the adjuvant treatment of resected RCC

Trial	Drug (target)	Patients (n)	Histology allowed	Duration of adjuvant Tx	Risk inclusion criteria	Treatment arms	Primary end point	Refs*
PROSPER (NCT03055013)	Nivolumab (anti-PD-1)	766	All (but cap for nccRCC at 15%)	10 months (1 month of neo-adjuvant Tx, then 9 months of adjuvant Tx)	• > cT2a, N0, M0 • cTany, N1, M0 (metastasectomy excluded)	Neoadjuvant nivolumab 240 mg Q2W x 2 [resect] + adjuvant nivolumab 240 mg Q2W x 6 and 480 mg Q4W x 6 versus observation	≥13% improvement in RFS	59
Immotion 010 (NCT03024996)	Atezolizumab (anti-PD-L1)	664	Clear cell component or any subtype with sarcomatoid component required	12 months (16 cycles)	• pT2, Gr4 or • pT3a, Gr3-4 or • pT3b-T4, Grany or • N1, pTany, Grany or • M1 NED	atezolizumab 1200mg Q3W x 16 versus placebo Q3W x 16	DFS	60
Keynote-564 (NCT03142334)	Pembrolizumab (anti-PD-1)	1000	Clear cell or clear cell component with or without sarcomatoid features	12 months (17 cycles)	• pT2, Gr 4 (sarcomatoid), N0 or • pT3, Gr 3-4, N0 or • pT4, Grany, N0 or • N1, pT_{any}, Grany or • M1 NED	Pembrolizumab 200 mg Q3W x 17 versus placebo Q3W x17 (12 months)	DFS	61
RAMPART (NCT03288532)	Durvalumab (anti-PD-L1) and Tremelimumab (anti-CTLA4)	1750	All except pure oncocytoma, collecting duct, medullary and transitional cell cancer	12 months (max 13 cycles)	At the start of recruitment patients with Leibovich score 3-11 will be eligible for randomisation. Recruitment of intermediate risk patients (Leibovich score 3-5) after 3 years or when intermediate risk patients contribute 25% of the total accrual target, whichever is earlier. Recruitment of patients with Leibovich Score 6-11 will continue until the accrual target is reached	Active monitoring for 1 year versus durvalumab 1500 mg 4 weekly for 1 year (13 cycles maximum) versus durvalumab (as above) + tremelimumab (75 mg) on day 1 and week 4 visits (i.e. 2 cycles)	DFS and OS	62
CheckMate 914, NCT03138512	Ipilimumab (anti-CTLA4) and Nivolumab (anti-PD1)	800	Predominant histology, including sarcomatoid	24 weeks	• pT2a, G3 or G4, N0 or • pT2b, Gany, N0	Nivolumab plus ipilimumab	DFS	63

			features		• or pT3, Gany, N0 or pT4, Gany, N0 or • pTany, Gany, N1			

*Reference numbers refer to the reference list in the main text of the Review. PD-1 – Programmed death-1; ECOG – Eastern Cooperative Oncology Group; nccRCC – non clear cell Renal Cell Carcinoma; Tx – treatment; Q2W – every two weeks; Q4W – every four weeks; RFS – relapse-free survival; PD-L1 – Programmed death ligand-1; SUO CTC – Society of Urological Oncology Clinical Trials Consortium; Gr – grade; NED – without evidence of residual disease; Q3W – every three weeks; DFS – disease-free survival; CTLA-4 – Cytotoxic T-Lymphocyte Antigen 4; UCL – University College London; OS – overall survival.