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Review

Adjuvant Therapy in Renal Cell Cancer

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Abstract. A number of adjuvant trials have attempted to improve outcomes for patients following nephrectomy for renal cell carcinoma (RCC). This was initially with cytokines and then Vascular Endothelial Growth Factor (VEGF) targeted therapies. More recently, a series of adjuvant immune checkpoint inhibitor (ICI) studies have been published. To date, only the KEYNOTE—564 study using adjuvant pembrolizumab has positive Disease-Free Survival (DFS) data with an acceptable toxicity profile. There are many negative ICI and anti-VEGF adjuvant trials, which raises uncertainty. Further randomised trials may be required but importantly biomarker studies are needed to identify those individuals who may benefit from adjuvant therapy.

Keywords: Adjuvant, immune checkpoint inhibitors, anti-VEGF TKIs, post nephrectomy, renal cell carcinoma

INTRODUCTION

Over the last 20 years, a number of adjuvant trials have attempted to improve outcomes for patients following nephrectomy for renal cell carcinoma (RCC) [1]. This was initially with cytokines and then VEGF targeted therapies. More recently, a series of adjuvant immune checkpoint inhibitor (ICI) studies have been published. To date, only adjuvant pembrolizumab has positive Disease-Free Survival (DFS) data with an acceptable toxicity profile. There are many negative ICI and anti-Vascular Endothelial Growth Factor (VEGF) adjuvant trials, which raises uncertainty. Further randomised trials may be required but importantly biomarker studies are needed to identify those individuals who may benefit from adjuvant therapy.

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ADJUVANT IMMUNE CHECKPOINT INHIBITION IN RENAL CELL CARCINOMA

There have been four recent trials investigating ICIs in the perioperative setting, of which only one trial was positive.

The only positive adjuvant ICI trial to date is the Keynote-564 study (KN564). Keynote-564 investigated adjuvant pembrolizumab (PD-1 inhibitor) after nephrectomy for patients with intermediate-high risk of RCC recurrence (pT2 grade 4, pT3/4 or node positive, or metastatic [M1] with no evidence of disease [NED]) post-surgery. A total of 496 patients were randomly allocated to receive 12 months of either adjuvant pembrolizumab or placebo. The most recent follow up shows an ongoing DFS benefit (Hazard Ratio [HR] of 0.63 [95% CI: 0.50–0.80]) but

Overall Survival (OS) data remains immature with a HR of 0·52 (95% CI: 0.31–0.86) [2, 3]. The results of the subset analysis were also consistent, showing further benefit across subgroups. The HR for DFS for intermediate and high-risk groups is 0.68 (95% CI: 0.52–0.89) and 0.60 (95% CI: 0.33–1.10), respectively. Patients with sarcomatoid features also derive further benefit from adjuvant pembrolizumab with a DFS HR of 0.54 (95% CI: 0.29–1.00) [3]. The toxicity profile is in line with previous studies of pembrolizumab and 24-month analysis of the KN564 study. Serious adverse events attributed to study treatment occurred in 12% ($n = 59$) participants in the pembrolizumab group. This study provides a strong rationale towards why adjuvant ICI may show efficacy. As a result, adjuvant pembrolizumab has become the standard of care following nephrectomy for high-risk RCC [4].

The positive results of KN564 led the community to expect positive results for adjuvant ipilimumab (anti-CTLA-4) and nivolumab (anti-PD1), however this was not the case. The phase III CheckMate-914 study (CM914) had a similar study design to KN564, comparing adjuvant ipilimumab and nivolumab vs placebo in high risk RCC patients following nephrectomy (Table 1). The trial had a robust study design and median follow up of 37 months (31.3–43.7), however the trial failed to reach it's DFS primary endpoint with a HR of 0.92 (95% CI:0.71–1.19, $p = 0.53$). Overall survival was not reached [6]. The grade 3-4 adverse event rate was 154 (38%) and 42 (10%) in the pembrolizumab and placebo group, respectively. The lack of efficacy may be explained due to differences in drug administration regime (6-weekly ipilimumab vs 3-weekly in the advanced disease setting) or because the duration of therapy was only six months post nephrectomy (compared to 12 months adjuvant therapy in KN564). Additionally, there was higher toxicity rate of the combination compared to the observed rates in the advanced setting. All-case grade 3 or 4 adverse events occurred in 38% ($n = 154$) and 10% ($n = 42$) of patients receiving the ipilimumab/nivolumab combination and placebo, respectively, leading to a higher rate of treatment discontinuation in the combination arm compared to placebo (32% vs 2%). This may have reduced drug delivery. Nevertheless, trend towards a positive result would still be expected, particularly as the ipilimumab and nivolumab combination has efficacy in the front-line setting in CM214 [7]. The results of this study question the contribution of ipilimumab. However, in the advanced setting the ipilimumab/nivolumab combination shows a significant and impressive survival benefit [8], but single agent nivolumab has not previously been investigated the frontline disease. A randomised trial comparing the combination of ipilimumab and nivolumab with nivolumab alone in advanced disease is ongoing (CA209-8Y8, NCT03873402). There is a third study group of the CheckMate-914 trial whereby patients are assigned to single agent nivolumab plus placebo which has not yet been reported and results may address some of the questions raised (NCT03138512).

Nivolumab monotherapy shows a survival advantage in patients who have previously received treatment for RCC [9]. It has also been studied as a monotherapy in the peri-operative setting. The randomised phase III study PROSPER investigated neoadjuvant nivolumab prior to nephrectomy followed by adjuvant nivolumab in patients with high-risk RCC, compared to surgery followed by surveillance. Patients on the experimental arm received one dose of nivolumab, prior to surgery followed by nine adjuvant doses every four weeks. The study was conducted on 819 patients and the primary endpoint was recurrence free survival (RFS). The trial was stopped early by due to futility. The median RFS was not reached but was similar between the two arms with a HR of 0.97 (95% CI:0.74–1.28, $p = 0.43$). Although OS data was immature, no significant differences were observed between study arms (HR 1.48, 95% CI:0.89–2.48, $p = 0.93$). There were imbalances in the two arms, in that patients in the intervention arm required a biopsy [10]. Although one might expect a similar result to adjuvant PD-1 in the KN564 study, and the reasons for the differences are not clear, cross-trial comparisons have limitations and should be avoided. The requirement for pre-operative biopsies in the experimental arm may have introduced delays in curative-intent surgery.

The phase III study IMmotion010 (IM010) investigated atezolizumab (anti-PD-L1) vs placebo in patients with high-risk RCC following nephrectomy [11]. 778 patients were included into the study receiving adjuvant atezolizumab 3-weekly for up to 16 cycles, one year or disease recurrence versus placebo. Median follow up was 45 months. The trial failed to show a DFS advantage with a HR 0.93 (95% CI:0.75–1.15, $p = 0.50$) [11]. Overall survival data was immature (HR 0.97 [95% CI: 0.67–1.42]). There are multiple hypotheses that might offer an explanation for the negative result of this trial. It is important to note the different receptor target (PD-L1 rather

Table 1
Summary of adjuvant studies in RCC using immune checkpoint inhibitors

Trial	Patients included	Therapy	Duration of treatment	Median follow up	PFS HR (95% Confidence Interval)	OS HR (95% Confidence Interval)
KEYNOTE-564 NCT03142334	Intermediate-high-risk RCC following-nephrectomy $n = 496$	Pembrolizumab 200 mg or placebo intravenously every 3 weeks	12 months	30.1 months follow up (IQR 25.7–36.7)	0.63 (95% CI: 0.50–0.80).	HR 0.52 (95% CI: 0.31–0.86)
CheckMate-914 NCT03138512	High-risk RCC following nephrectomy. $n = 816$	Nivolumab (240 mg) intravenously every 2 weeks for 12 doses plus ipilimumab (1 mg/kg) intravenously every 6 weeks for four doses vs placebo	6 months	37 months (31.3–43.7)	0.92 (95% CI:0.71–1.19, $p = 0.53$	Not Reached
PROSPER NCT03055013	High-risk RCC before and after nephrectomy. $n = 819$	Neoadjuvant nivolumab (1 cycle) prior to nephrectomy followed by adjuvant nivolumab (9 cycles, 4 weekly) vs surgery followed by surveillance.	9 months	16 months	0.97 (95% CI:0.74–1.28, $P = 0.43$).	1.48 (95% CI:0.89–2.48, $P = 0.93$).
IMmotion010 NCT03024996	High-risk RCC following nephrectomy. $n = 778$	Atezolizumab 3 weekly	12 months	45 months	HR 0.93 (95% CI:0.75–1.15, $p = 0.50$)	HR 0.97 (95% CI: 0.67–1.42)

than PD-1), and it may be that anti-PD-1 immune checkpoint inhibitors are more active in RCC. There are also differences in patient inclusion when compared to KN-564. For example, more patients in the IMmotion010 study had node positive or M1 NED, representing a higher proportion of patients with aggressive disease, compared to the KN564 patient population. It is noteworthy that there was more early censoring of patients in IM010.

Combinations of immune checkpoint inhibitors in the adjuvant RCC population is currently being investigated (RAMPART, NCT03288532) [12] and in combination with HIF-2α inhibitor, Belzutifan (LITESPARK-022, NCT05239728) [13].

ADJUVANT VEGF TKI STUDIES

Anti-VEGF TKIs, such as sunitinib, are an effective treatment for metastatic RCC and remain a useful treatment option for patients with advanced IMDC (International Metastatic RCC Database Consortium) good risk disease [14]. Overall, VEGF-targeted adjuvant therapy has been explored in a number of prospective randomised trials including S-TRAC, ASSURE, SORCE, PROTECT and ATLAS. Of these trials, none has shown any trend toward OS benefit (Table 2).

The S-TRAC randomised phase III study investigated sunitinib in the adjuvant setting for high risk RCC, following nephrectomy. 615 patients with high risk RCC were enrolled in the trial and randomised to receive either sunitinib 50 mg on a 4:2 regime, or placebo for one year following nephrectomy. The patients in the sunitinib arm had a longer duration of DFS than those receiving placebo (HR 0.76 [95% CI:0.59–0.98, $p = 0.03$]). Overall Survival data was negative [15]. The higher DFS rate observed with sunitinib also came with a higher rate of toxicity and adverse events and lower qual-

Table 2
Summary of adjuvant studies in RCC using anti-VEGF Tyrosine Kinase Inhibitors and other targeted therapies

Trial	Patients included	Therapy	Duration of treatment	Median follow up	PFS HR (95% confidence interval)	OS HR (95% confidence interval)
S-TRAC NCT00375674	High-risk RCC following nephrectomy. $n = 615$	Sunitinib 50 mg once daily oral (4:2 regime) vs placebo	12 months	5.4 years	0.76 (95% CI:0.59–0.98, $p = 0.03$).	Not Reached
ASSURE NCT00326898	High-risk RCC following nephrectomy. $n = 1069$ in high risk group ($n = 1943$ in whole trial)	Sunitinib 50 mg once daily oral (4:2 regime) vs Sorafenib 400 mg twice per day oral (6 week cycle) vs placebo	54 weeks	10 years.	Sunitinib vs placebo HR 0.94 (97.5% CI:0.74–1.19, $p = 0.54$) Sorafenib vs placebo HR 0.90 (97.5% CI:0.71–1.14, $p = 0.30$).	Sunitinib vs placebo HR 1.06 (97.5% CI: 0.78–1.45, $p = 0.66$]. Sorafenib vs placebo HR 0.80 (97.5% CI: 0.58–1.11, $p = 0.12$).
EVEREST NCT01120249	Intermediate-high or high- risk RCC following nephrectomy. $n = 1545$	10 mg oral everolimus once daily oral vs placebo	54 weeks	76 months (IQR 61–92)	0.85 (95% CI: 0.72 – 1.00, $p = 0.051$)	Not reached 0·90, (95% CI:0·71–1·13, $p = 0{\cdot}36$)
SORCE NCT00492258.	Intermediate or high-risk RCC following nephrectomy. $n = 1711$	2:3:3 Arm A: 3 years placebo Arm B: 1 year of sorafenib 400 mg twice daily oral (amended to once daily) followed by 2 years of placebo Arm C: 3 years of sorafenib 400 mg twice daily oral (amended to once daily)	3 years	6.5 years (IQR 4.9–8.0 years)	Not Reached HR 1.01 (95% CI: 0.83–1.23; $p = 0.95$).	Not Reached
PROTECT NCT01235962	High-risk RCC following nephrectomy. $n = 1538$	Pazopanib 600 mg once daily oral vs placebo.	12 months	Pazopanib 76 months (IQR 66–84) placebo 77 months (IQR 69–85)	0.94 (95% CI: 0.77–1.14, $p = 0.5$)	1.0 (95% CI: 0.80–1.26, $p > 0.9$)
ATLAS NCT01599754	High-risk RCC following nephrectomy. $n = 724$	Axitinib 5 mg twice daily oral vs placebo	Up to 3 years	–	HR 0.87,95% CI: 0.66–1.15, $p = 0.3211$)	Not Reached

ity of life scores. Sunitinib was approved by the Food and Drug Administration (FDA), but not the European Medicines Agency (EMA) for use in the adjuvant setting for high-risk patients with RCC. However, adjuvant sunitinib and sorafenib had been previously explored in the randomised phase III trial ASSURE but failed to show an improvement in DFS or OS [16]. A total of 1069 patients with high risk RCC were randomised to receive either sunitinib, sorafenib or placebo for 1 year following nephrectomy. There was also a higher rate of grade 3 adverse events in the treatment arms (66% for suni-

tinib, 72% for sorafenib) compared to placebo (28%) [16].

Further adjuvant studies investigating sorafenib, pazopanib and axitinib were also negative, failing to show a PFS or OS benefit [17–19]. Similarly, other drugs such as adjuvant everolimus (an mTOR inhibitor), also failed to show benefit for patients with intermediate or high risk RCC following nephrectomy [20].

CONCLUSION

An important question in RCC is whether biomarkers can predict who will benefit from adjuvant ICI therapy. There are currently none in use. In advanced disease the IMDC classification has been used to select intermediate and poor risk disease benefit with ICI combinations [21], but it is likely that this is an oversimplification. It appears IMDC risk does not accurately correlate with the biology of the disease [22]. Most patients who relapse post-nephrectomy have low disease burden due to early detection as a result of regular surveillance imaging. Many of these patients will have few IMDC risk parameters and be categorised as lower risk disease. However, good risk IMDC favours use of VEGF rather than ICIs. Together these challenge the role IMDC classification in selecting patients for ICIs. It would be preferential to use the biology of the cancer and tissue based or circulating biomarkers instead.

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FJS and TP were responsible for review conception. FJS conducted literature review and led the manuscript preparation. MY, AJ and BS all reviewed the manuscript and contributed edits. TP had project oversight and approved final version of the manuscript.

CONFLICT OF INTEREST

FJS has received travel expenses from EUSA. MY and AS have no conflicts of interests to declare. BS has received travel expenses and research funding from Roche, Genentech, Merck Sharp & Dohme, Pfizer and Bristol Myers Squibb, and has received honoraria from Merck, Roche, Pfizer, Ellipses and Ipsen. TP is an Editorial Board Member of this journal, but was not involved in the peer-review process of this paper, nor had access to any information regarding its peer-review. TP has received travel expenses and research funding from Roche, Pfizer, MSD, AstraZeneca, Ipsen, BMS, Merck, Exelixis, Novartis, Seattle Genetics, Merck Serono, Astellas, Johnson & Johnson and Eisai, and has received honoraria from Roche, Pfizer, MSD, AstraZeneca, Ipsen, BMS, Merck, Exelixis, Incyte, Novartis, Seattle Genetics, Merck Serono, Astellas, Johnson & Johnson and Eisai. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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