International Urology and Nephrology (2019) 51:2107–2117
https://doi.org/10.1007/s11255-019-02264-5

UROLOGY - REVIEW

Game of thrones: immunotherapy versus molecular targeted therapy in renal cell cancer scenarios

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Received: 2 July 2019 / Accepted: 19 August 2019 / Published online: 29 August 2019

Abstract

Objectives Treatment for advanced renal cell carcinoma (RCC) has become increasingly more complex over the last several years. Objective 1 is to which treatment option is immunotherapy, targeted therapy, or the combination of immunotherapy with targeted therapy the best for patients? Objective 2 is to study which regimens with the highest chance of cure/durable response and what is the optimal sequence in advanced RCC.

Materials and methods Between 2016 and 2018, 6 adult patients admitted to our institute with RCC were reviewed. Clinical information, treatment and outcomes were retrieved for further analysis. This applies to all risk groups as determined by the International Metastatic RCC Database Consortium criteria. We have intended to provide the reader with a comprehensive and authoritative review of the broad subject of RCC.

Results Immunotherapy-based regimens and the functioning of various growth-and survival-promoting kinases, specifically, receptor-associated tyrosine kinases have dramatically changed the treatment landscape of advanced RCC. Recent phase III trials have demonstrated a survival benefit for front-line ipilimumab plus nivolumab therapy, and immune checkpoint inhibition plus anti-vascular endothelial growth factor combination therapy in metastatic clear-cell RCC.

Conclusion In renal cell carcinoma, rapid and successful drug development has resulted in multiple treatment options, requiring careful decision making for individual patients and have emphasized how newly developed therapies work.

Keywords Metastatic renal cell carcinoma · Tyrosine kinase inhibitors · Immunotherapy

Introduction

Why do we use molecular targeted therapy or immunotherapy in RCC?

Renal cell carcinoma (RCC) is not a single disease and encompasses several histologically, biologically, and clinically distinct entities [1, 2]. The most common RCC histology is the conventional clear cell subtype accounting for 75–80% of all RCCs. The remaining subtypes including papillary (10–15%), chromophobe (5–10%), medullary (< 1%), and collecting duct carcinoma (< 1%). The Cancer Genome Atlas has performed a molecular characterization of RCC that serve each of the subtypes as a specific molecular feature. There were also able to separate the different subtypes using copy number alteration and RNA sequencing. Clear cell carcinoma is a chromosome 3 disease. 3p loss and the von Hippel Lindau (VHL) (3p25) mutation are common molecular alterations in clear cell RCC [3]. Under normal conditions, VHL binds to HIFα and polyubiquinates it to mark it for destruction in the cellular proteasome. Clear cell RCC is characterized by loss of VHL, which leads to the accumulation of HIF and subsequent expression of proangiogenic factors such as vascular endothelial growth factor (VEGF). Therefore, targeting VEGF has been the rationale for multiple therapies to treat RCC (Fig. 1). VEGF pathway inhibitors include several small molecule VEGF tyrosine kinase inhibitors (VEGF TKIs), including first-generation TKI (sorafenib, sunitinib, pazopanib), second-generation TKI (axitinib, tivozanib) and third-generation TKI (lenvatinib, cabozantinib). The other important class of agents that have gained a place in metastatic RCC therapeutics are

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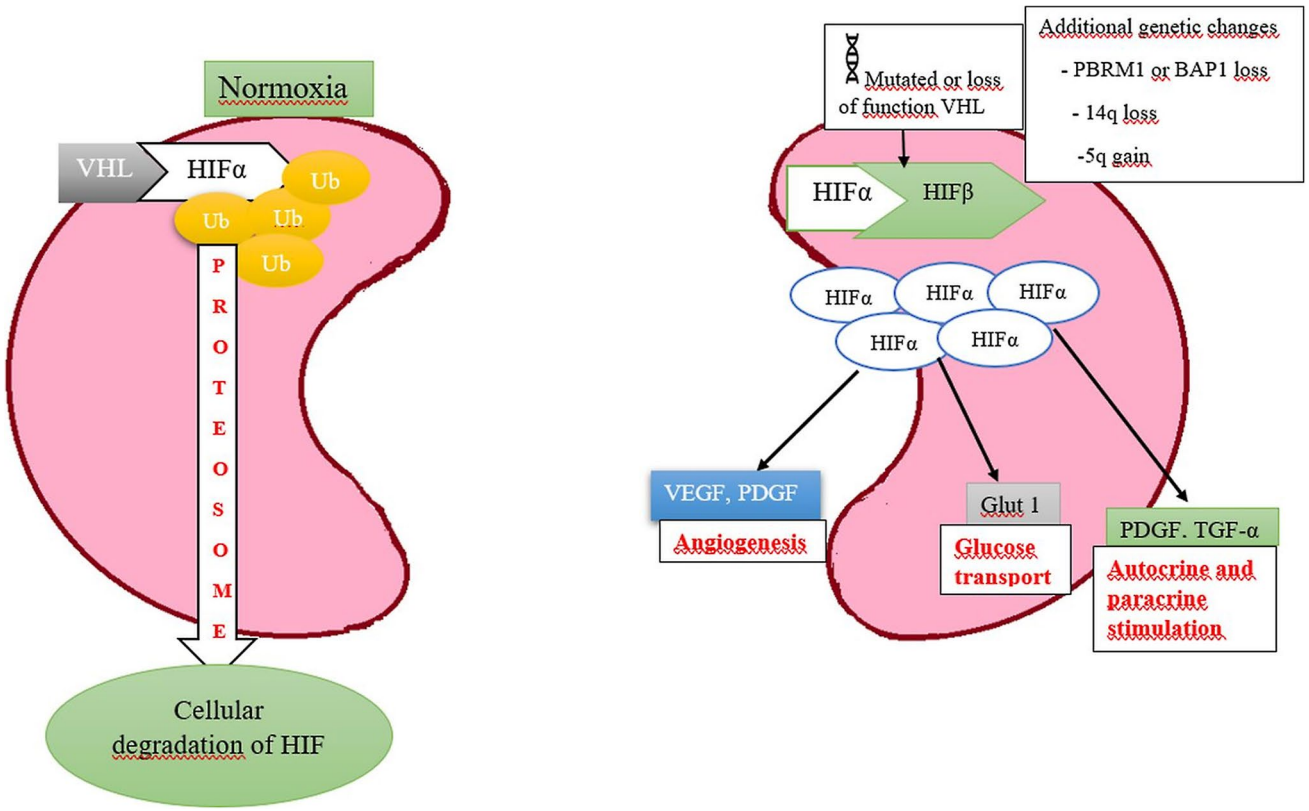

Fig. 1 Normal function of VHL in the normoxic state compared to the aberrant VHL state/hypoxia

the mTOR inhibitors (temsirolimus, everolimus). RCC is a prototype of the immunogenic tumor that has stimulated intensive efforts to harness the immune system to offer the best chance of achieving patient goals (Fig. 2) [4]. In recent years immune checkpoint inhibition (ICI) with blocking antibodies that target cytotoxic T-lymphocyte antigen-4 and the programmed cell death protein 1 pathway/programmed death-ligand 1 have emerged as promising agents in treatment of RCC.

Discussion

When do we use molecular targeted therapy or immunotherapy in RCC?

Clinical scenario 1

A 60-year-old woman underwent a right radical nephrectomy for a 12 cm renal mass identified during the evaluation of flank pain and unexplained weight loss. Histopathologic evaluation reveals a grade 3 clear-cell RCC, with evidence of invasion into the perinephric fat. Her urologist confined that no evidence of metastatic disease. What is the most effective therapy for patients with stage III RCC?

Retrospective case series suggest that the use of currently available targeted agents before nephrectomy does not result in frequent downsizing of primary tumors [5, 6] and exposes patients to the risk of progression [7] and increased complexity of ensuing surgical management. Neoadjuvant TKI therapy is currently not standard of care in RCC. Tumor shrinkage usually less than 10–20%. No proven benefit on overall survival (OS). Recurrence develops in a significant proportion of patients after surgical resection so TKI therapy use is appealing in an adjuvant setting, although there are many uncertainties regarding optimal choice of agent and dose and duration of therapy (Table 1) [8–11]. In addition, the toxicities of these agents may limit their usefulness in the adjuvant setting. None of those trials improved OS. Adjuvant TKI therapy is currently not standard of care in RCC and their use is not recommended. Ongoing adjuvant clinical trials investigating immunotherapy including nivolumab, atezolizumab, pembrolizumab and nivolumab plus ipilimumab should be supported in an effort to identify an efficacious adjuvant strategy. All of these trials have recruited and final analysis can be expected in the coming years.

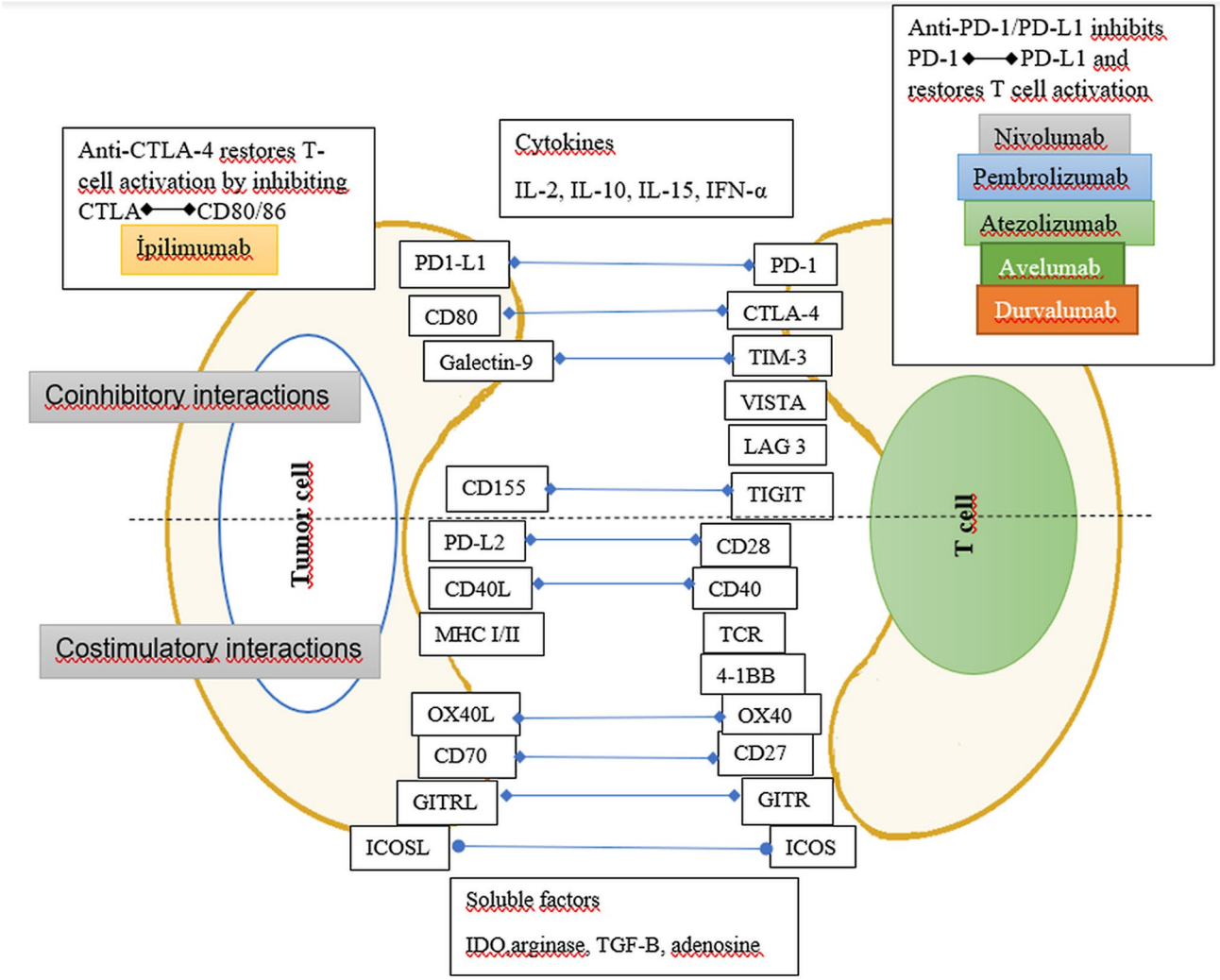

Fig. 2 Selected immune checkpoints, cytokines, and soluble factors in the tumor microenvironment. Green represents stimulatory, and red represents inhibitor factor. *PD-L1* programmed cell death protein ligand 1, *IL* interleukin, *IFN-α* interferon α, *PD-1* programmed cell death protein 1, *PD-L2* programmed cell death protein ligand 2, *CTLA-4* cytotoxic Tlymphocyte antigen 4, *TIM-3* T-cell immunoglobulin and mucin domain 3, *VISTA* V-domain immunoglobulin suppressor of T-cell activation, *MHC* major histocompatibility complex, *TCR* Tcell receptor, *LAG-3* lymphocyte-activation gene 3, *TIGIT* T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains, *GITRL* glucocorticoid-induced tumor necrosis factor receptor–related protein ligand, *GITR* glucocorticoid-induced tumor necrosis factor receptor–related protein, *ICOSL* inducible T-cell costimulator ligand, *IDO* indoleamine 2,3-dioxygenase, *TGF-β* transforming growth factor β, *ICOS* inducible T-cell costimulator

Clinical scenario 2

64-year-old woman with an ECOG performance status of 0, presented with 1-year history of chronic cough; scans revealed bilateral pulmonary nodules. Abdominal CT showed a 7 cm left renal mass and bulky retroperitoneal lymph nodes. Fine-needle aspirate of left lower lobe of the lung was positive for malignant cells identified as renal cell carcinoma. Which is the best treatment option for this patient?

Cytoreductive nephrectomy had been standard of care metastatic RCC based on trial data showing greater benefit of nephrectomy plus cytokine therapy versus cytokine therapy [12–14]. The Carmena study carry out that head-to-head comparison of cytoreductive nephrectomy plus targeted therapy versus targeted therapy alone in metastatic RCC [15]. The randomized trial, conducted among 450 patients with poor-and intermediate-risk disease, found that median overall survival was noninferior in the patients who received sunitinib alone compared with those who first had surgery and then received sunitinib (18.4 vs 13.9 months). Patients with good risk factors and low metastatic load were not included in this study. The SURTIME study which is a randomized study examined the optimal sequence of sunitinib

Table 1 Phase 3 clinical trials of VEGF inhibitors in adjuvant treatment of renal cell carcinoma

Trial	Treatment arms	*n*	Disease histology	Disease stage	DFS HR (95% CI)	*p*	OS HR (95% CI)
[8]Assure	Sunitinib (37.5–50 mg) vs placebo	647	Any	pT1b (G3-4) N0M0 or pT2-4 (Gx) N1-3M0	1.02	0.8	1.17
[8]Assure	Sorafenib (400–800 mg) vs placebo	540	Any	Intermediate or high risk	0.72	0.72	0.98
[9]S-trac	Sunitinib (50 mg) vs Placebo	309	Predominantly clear cell	High risk pT3-4, N+	0.76	0.003	1.01
[10]Atlas	Axitinib vs placebo	724	> 50% clear cell	pT2-4N0M0 or pTxN1M0	0.870	0.3211	Immature
[11]Protect	Pazopanib vs placebo	571	Clear cell or predominantly clear cell	pT2(G3-4) N0 or pT3-4 (Gx) N0 or pTx (Gx) N1M0	0.86	0.16	0.79

therapy and surgery in 99 patients with metastatic RCC [16]. The patients were randomized to immediate cytoreductive nephrectomy followed by sunitinib therapy ($n = 50$) or three cycles of sunitinib followed by surgery in the absence of progression followed by sunitinib ($n = 49$). Progression-free survival (PFS) at 28 weeks was not improved when patients began sunitinib therapy ($n = 50$) before planned cytoreductive nephrectomy versus after, although OS was higher. PFS at 28 weeks was not improved when patients began sunitinib therapy ($n = 50$) before planned cytoreductive nephrectomy versus after, however, there was an improvement in OS in the intention-to-treat population, where the median OS of deferred and immediate CN was 32.4 months and 15.0 months, respectively. Results of CARMENA and SURTIME, however, give us further insight into this treatment option and encourage a multidisciplinary approach to the initial treatment of this disease.

In summary, immediate cytoreductive nephrectomy is not recommended intermediate- and high-risk patients requiring sunitinib, or an equivalent VEGFR-TKI. Cytoreductive nephrectomy is most likely to benefit patients who are good surgical candidates such as those with good performance status, a relatively slow rate of disease progression, and those with relatively low metastatic burden.

Patient does not undergo nephrectomy; renal biopsy reveals clear-cell RCC. Sunitinib was planned and it was decided to reevaluate the patient after 3 months.

How do we use molecular targeted therapy or immunotherapy?

First-line metastatic clear cell RCC

Clinical scenario 3

A 51-year-old male is diagnosed with clear-cell RCC with limited metastases (lung nodules). He undergoes nephrectomy. 15 months after nephrectomy, he presented with retroperitoneal lymph node metastases and progression of lung lesions. Patient has good performance status (PS) and no International Metastatic RCC Database Consortium (IMDC) risk factors. What is the most effective first-line therapy for patients with stage IV clear cell RCC?

What does the patient want at the initial presentation? First, patients want to be cured of their disease. Second, they would like to have limited toxicity you know during or after therapy and potentially the ability to stop therapy and want to live longer if they cannot be cured of their disease. Third, obviously they want to maintain quality of life.

Validated prognostic models are used in clinical practice to aid patient counseling as well as this risk assessment is really important because not only gives you an idea of the prognosis of your patient but this risk assessment is going to provide choose your right treatment (Fig. 3) [17]. Patient-specific profiles that can delineate an individualized management strategy looking at the molecular characteristics of tumors will help further in our understanding of the clinical, biologic, and genomic heterogeneity of renal cancers. Still a role for TKI in first-line treatment in the checkpoint inhibitors era? Some patients cannot receive immunotherapy (autoimmune disease, viral disease).

The primary targeted approaches in this first-line setting include pazopanib, sunitinib, tivozanib (anti-VEGFR 1-2-3) and cabozantinib (anti-MET,anti-AXL,anti-VEGFR1-2-3). First-line metastatic RCC in the COMPARZ phase 3 trial compared with pazopanib, sunitinib resulted in no difference in PFS (median, 8.4 versus 9.5 months, HR 1.05, 95% CI 0.90–1.22) and OS (median, 28.3 versus 29.1 months, HR 0.92, 95% CI 0.79–1.06) [18]. The most common adverse events (AEs) were fatigue (63% on sunitinib versus 55% on pazopanib), thrombocytopenia (78% versus 41%), and hand-foot syndrome (50% versus 29%) and increased levels of alanine aminotransferase (43% versus 60%). Motzer and colleagues compared the activity of tivozanib versus sorafenib as initial targeted therapy in advanced RCC in

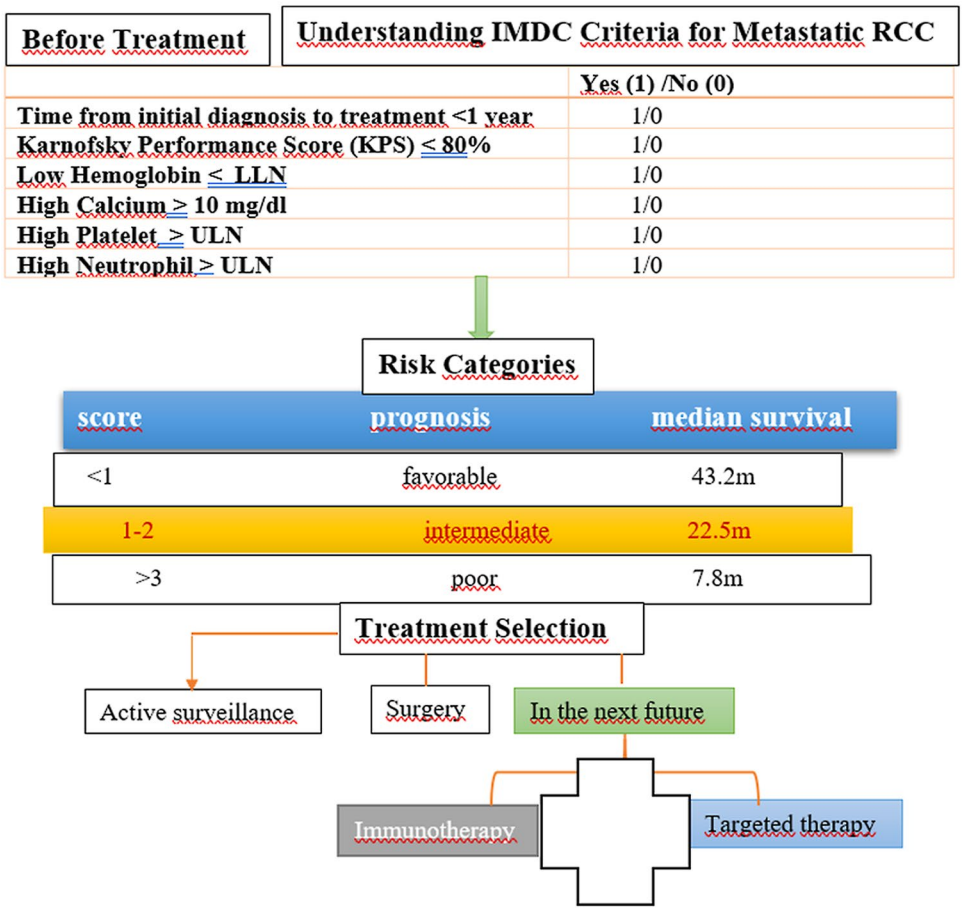

Fig. 3 Adverse prognostic factors and risk stratification based on adverse prognostic factors in patients treated with first-line vascular endothelial growth factor (VEGF) targeted therapy [17]

a phase III randomized, open-label, multicenter trial [19]. Tivozanib was associated with a statistically meaningful improvement in PFS (median 11.9 months for tivozanib vs. 9.1 months for sorafenib, HR 0.797, 95% CI 0.639–0.993, $p=0.042$). Certain (AEs were more common with tivozanib including hypertension (44% vs. 34%) and dysphonia (21% vs. 5%), whereas sorafenib produced greater hand-foot skin reaction (54% vs. 14%) and diarrhea (33% vs. 23%).

Overall, tivozanib was shown to be well tolerated with minimal off-targeted toxicities. Patients with metastatic RCC with previously untreated intermediate or poor prognosis compared cabozantinib (60 mg/day) or sunitinib (50 mg/day for 4 weeks on each 6-week cycle) [20]. PFS, the primary endpoint of the trial, was significantly prolonged with cabozantinib (median, 8.6 versus 5.3 months, HR 0.48, 95% CI 0.31–0.74). All-causality grade 3 or 4 adverse events were 67% for cabozantinib included fatigue, hypertension, diarrhea, abnormal liver function tests, anorexi and palmar-plantar erythrodysesthesia syndrome being among the most common toxicities. Compared to sunitinib, it had a lower hematological toxicity profile such as neutropenia and thrombocytopenia.

The phase III Checkmate 214 trial of patients with previously untreated advanced clear cell RCC was compared to nivolumab plus ipilimumab or to sunitinib [21]. This study showed that higher response rate and higher complete response rate and also better duration of response with nivolumab plus ipilimumab compared to sunitinib and also better survival (Table 2). The combination of nivolumab and ipilimumab is approved as frontline therapy for patients with intermediate and poor risk advanced RCC. The quality of life was better for nivolumab plus ipilimumab compared to sunitinib. We can still see this response for patients who stop treatment while in response or having stable disease with nivolumab plus ipilimumab. Engrossingly, about 40 percent of those patients were still free from progression and for subsequent therapy 2 years later while the median time to needing subsequent therapy on this sunitinib arm was about a month. Grade 3 or 4 events occurred in patients 46% treated with nivolumab plus ipilimumab and patients (63%) treated with sunitinib patients. Treatment-related AEs leading to discontinuation occurred in 22% in the nivolumab-plus-ipilimumab group and patients 12%) in the sunitinib group. TKI have still a role in favorable risk patients (Table 2).

What about first-line anti–PD-1 monotherapy? Single-agent ICI with pembrolizumab is being studied in the Keynote 427 trial which 110 patients with advanced or metastatic clear-cell RCC [22]. We see that the response rate was

Table 2 CheckMate 214 study

Outcome	Indermediate/poor risk		Favorable risk	
	Nivo + Ipi ($n = 425$)	Sun ($n = 422$)	Nivo + Ipi ($n = 125$)	Sun ($n = 124$)
ORR, % (95% CI)	41.9 (37.1–46.7)	29.4 (25.1–34.0)	39.2 (30.6–48.3)	50 (40.9–59.1)
Best response, %				
CR	11.3	1.2	8.0	4.0
PR	30.6	28.2	31.2	46.0
Stable disease	25.9	41.2	44.0	38.7
Progressive disease	24.9	19.0	12.0	4.8
PFS, median	11.6 (8.7–15.5)	8.4 (7.0–10.8)	15.3 (9.7–20.3)	25.1 (20.9–NE)
(95% CI), months	HR 0.82, 95% CI 0.64–1.05			
OS, median	NR (28.2–NE)	26.0 (22.1–NE)		
(95% CI), months	HR for death: 0.63 (99.8% CI 0.44–0.89; $p < 0.001$)			

about 38% with pembrolizumab the first-line setting. The overall objective response rate was very similar to with the nivolumab plus ipilimumab. There were about 3% complete responses. The response rate in the intermediate and poor was slightly higher than the favorable risk (42 versus 32%). If you look at PDL one's expression the response rates were 50% in the patients that had PDL 1 the expression greater than 1 percent but still 27% in patients that had a low PDL 1 expression. So what about nivolumab in the frontline setting. Well there are still no data for nivolumab in treatment naïve patients. The HCRN GU16-260 trial (NCT03117309) is investigating nivolumab in patient with treatment-naïve RCC but if patients whom receiving nivolumab progress or fail to respond by a year then they get ipilimumab added as salvage therapy. Anti–PD-1-based therapy is active in treatment-naive patients including favorable-risk patients. Anti–PD-1 monotherapy with nivolumab/ipilimumab salvage might be a reasonable strategy when one is concerned about the toxicity of nivolumab/ipilimumab. A trial of nivolumab/ipilimumab vs nivolumab in frontline RCC is indicated. Given the results of CABOSUN and CheckMate-214 demonstrating the superiority of cabozantinib and nivolumab/ipilimumab over sunitinib in intermediate- and poor-risk patients, it is unlikely sunitinib would be the preferred option.

Combination treatments with ICI therapy plus targeted therapy (angiogenesis inhibitors, tyrosine kinase inhibitors) also hold promise for improved efficacy [A + B > A followed by B (or B followed by A)]. Combining immunotherapy agents with TKIs may have a synergistic effect because immunotherapy has the notorious ability to induce a low percentage but more durable responses whereas, targeted agents blocking driver oncogenes in RCC induces rapid tumor responses, but typically shorter in duration (Fig. 4) [23–32]. If we tackled two of the potential tumor progression mechanism involved in RCC may be we can increase the efficacy of for treatment (Table 3).

IMmotion 151 is an ongoing phase 3, randomized, multicenter trial that is comparing sunitinib with a combination of the PD-L1 inhibitor atezolizumab with bevacizumab, an antiangiogenic monoclonal antibody that targets VEGF, in patients with untreated metastatic RCC (clear cell in 92%) [33]. In the PD-L1 positive patients, PFS, a coprimary endpoint of the trial, was longer with atezolizumab plus bevacizumab compared with sunitinib (median 11.2 versus 7.7 months, HR 0.74). Although OS data were immature at minimum follow-up of 12 months, they suggested atezolizumab/bevacizumab had greater efficacy in patients with PD-L1-positive RCC than sunitinib (not reached vs 23.3, respectively; HR 0.68; 95% CI 0.46, 1.00). The most common grade 3–4 AEs in the immunotherapy arm were hypertension, diarrhea, asthenia, and proteinuria. JAVELIN Renal 101 indicates that avelumab plus axitinib therapy is associated with a high rate of objective responses and improved PFS or death over sunitinib both in the overall and PD-L1 + group [34]. OS date was immature at data. Grade ≥ 3 toxicities were similar between the two groups. Immune-related AEs were seen in 38% of combination treatment patients, with 9% having grade ≥ 3 events. It is noteworthy that Keynote 426 trial the combination of pembrolizumab and axitinib had positive outcomes and showed superiority over sunitinib in terms of PFS (HR for progression or death 0.69, 95% CI 0.57–0.84) and the objective response rate (59% vs 36%) [35]. The pembrolizumab trial also showed a benefit with respect to OS (HR for death, 0.53, 95% CI 0.38–0.74). Grade 3 or higher AEs occurred in 76 percent of those receiving pembrolizumab-axitinib and 71% receiving sunitinib.

The next stage in terms of research will be to determine the best therapy for the right patient with advanced RCC. The optimal biomarker must have correlated molecular gene expression signatures with clinical outcomes, prognostic risk groups, tumour histology and host immune status. In patients receiving sunitinib, high angiogenesis gene expression (GE) signatures were associated with improved PFS, HR 0.59, 95% CI, 0.47–0.75) [36]. Angiogenesis GE was found to be

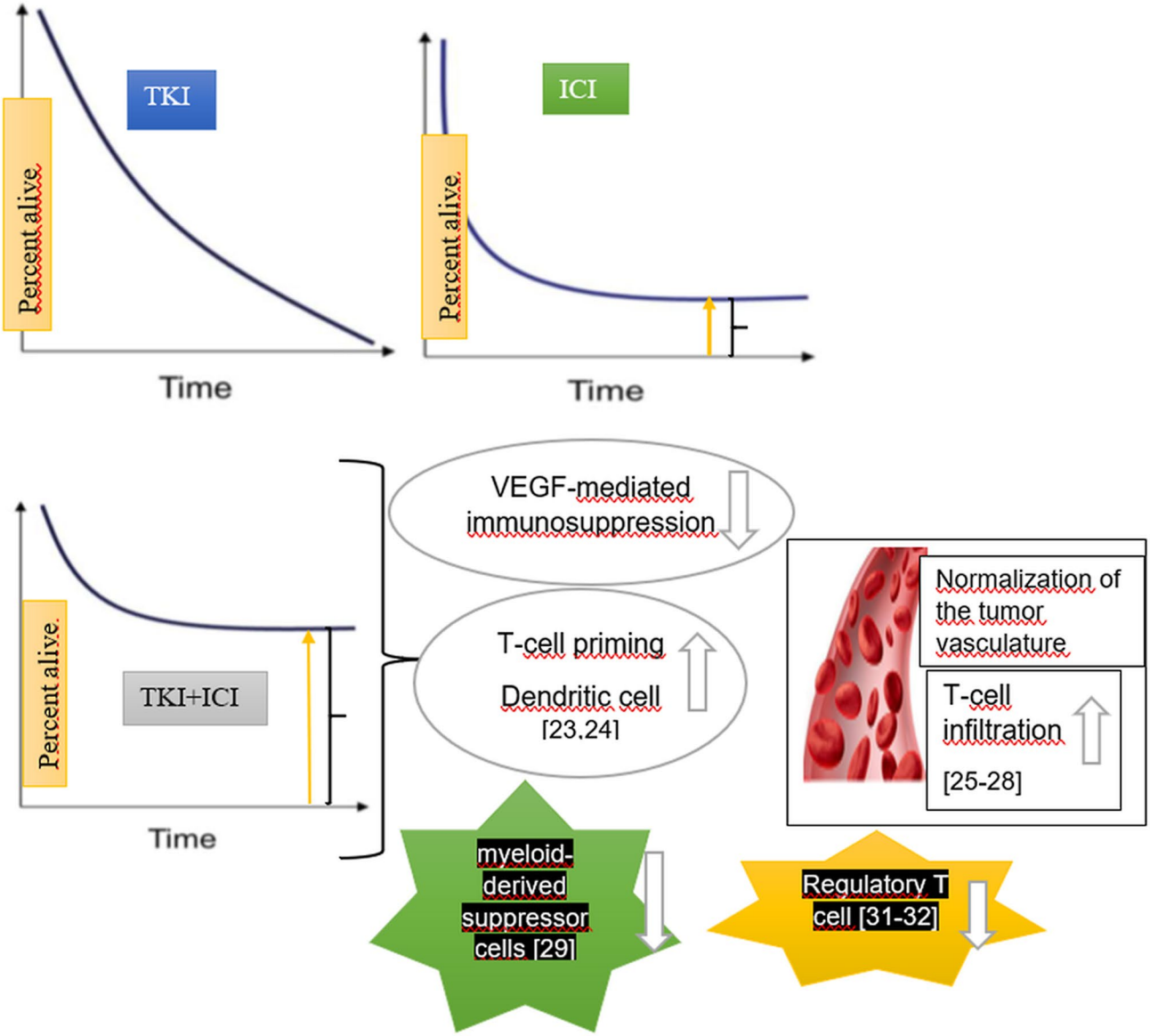

Fig. 4 Rationale for combination TKI/ICI

higher in favourable versus intermediate to poor MSKCC risk groups ($p = 4.28^{e-06}$).

The ability to produce durable treatment-free responses with VEGF plus checkpoint inhibitor combination was yet to be established. Subsequent therapy was uncertain. Unclear how immunotherapy + TKI combination will compare with nivolumab/ipilimumab, especially for OS. Additional information should come from other ongoing phase III trials: Lenvatinib plus everolimus versus lenvatinib plus pembrolizumab versus sunitinib (NCT02811861) and nivolumab plus cabozantinib versus sunitinib (NCT03141177).

We suggest pembrolizumab plus axitinib to treatment-naïve patients with any IMDC risk metastatic clear-cell RCC. For patients with intermediate- or poor-risk disease, we suggest ipilimumab plus nivolumab to treatment-naïve patients with metastatic clear-cell RCC.

Pembrolizumab plus axitinib initiation is planned this patient but the patient just wanted to receive immunotherapy.

How do we use molecular targeted therapy or immunotherapy?

Clinical scenario 4

A 68-year-old man comes to his physician complaining of 2 months of increasing right flank pain with 1 month of worsening hematuria. Imaging shows a 10-cm solid mass in the right kidney. His with intermediate-risk disease

Table 3 Phase III IO-based combinations in RCC

Regimen	Study	Study design	ORR (%)	CR rate (%)	PFS (HR)	OS (HR)
Nivolumab + ipilimumab	CheckMate 214 [21]	Previously untreated advanced ccRCC, ECOG PS 0 or 1 ($N=847$)	39	9	No (0.98)	Yes (0.68)
Atezolizumab + bevacizumab	IMmotion151 [33]	Treatment-naive advanced or metastatic RCC with clear-cell and/or sarcomatoid histology; KPS ≥ 70; tumor tissue available for PD-L1 staining ($N=915$)	43	5&	Yes (0.83)	No (0.81)
Avelumab + axitinib	JAVELIN Renal 101 [34]	Treatment-naive advanced RCC with a clear-cell component; ECOG PS 0 or 1; tumor tissue for PD-L1 staining ($N=886$)	55.2	3	Yes (0.69)	No (0.78)
Axitinib + pembrolizumab	KEYNOTE-426 [35]	Patients with treatment-naive advanced clear-cell RCC; KPS ≥ 70%; tumor tissue for PD-L1 staining ($N=861$)	59	7.7	Yes (0.69)	Yes (0.53)

underwent nephrectomy for T3 clear cell RCC. Six months later, he developed enlarging lung nodules consistent with progressive metastases. He began treatment with sunitinib and achieved a partial response (PR) at 2 months, but 1 month later developed extensive metastatic disease in the lungs, bones, and liver. He had an ECOG PS 2. What is the most appropriate therapy in this case?

Second line (and beyond) metastatic setting

In the phase III METEOR trial, cabozantinib (60 mg/day) was compared with everolimus (10 mg/day) in patients with advanced RCC. [37]. Patients were stratified by their MSKCC risk group (favorable vs intermediate vs poor) as well as TKI history (1 vs ≥ 2). The median OS was significantly higher for patients randomized to cabozantinib vs patients randomized to everolimus (21.4 vs 16.5 months, respectively), with an overall HR of 0.66 (95% CI 0.53–0.83; $p=0.00026$). In addition, median PFS was also significantly improved with cabozantinib vs everolimus (7.4 vs 3.8 months, respectively; HR 0.51; 95% CI 0.41–0.62; $p<0.0001$). Cabozantinib may have particular value in patients with bone metastases, a subset that has a relatively poor prognosis in patients with advanced RCC [38].

There are also encouraging phase II data showing an OS benefit with the combination of lenvatinib and everolimus. A phase II open-label trial randomized 153 patients with advanced ccRCC to either lenvatinib (24 mg/day), everolimus (10 mg/day), or lenvatinib and everolimus (18 mg/day and 5 mg/day, respectively) [39]. Lenvatinib and everolimus significantly PFS vs everolimus (median 14.6 months [95% CI 5.9–20.1] vs 5.5 months [3.5–7.1]; HR 0.4, 95% CI 0.24–0.68; $p=0.0005$), but not vs lenvatinib (7.4 months [95 CI 5.6–10.2]; HR 0.66, 95% CI 0.30–1.10; $p=0.12$). Lenvatinib alone significantly prolonged PFS vs everolimus (HR 0.61, 95% CI 0.38–0.98; $p=0.048$). When considering second-line therapy after nivolumab and cabozantinib, lenvatinib plus everolimus becomes a very intriguing option. If next-generation sequencing showed a mutation in the mTOR pathway, early lenvatinib and everolimus combination therapy may be warranted.

Axitinib would also be a suitable choice given the research demonstrating its superiority over sorafenib in the second-line setting [40, 41]. Treatment with axitinib resulted in a significant improvement in PFS compared with sorafenib (median, 8 versus 6 months, HR 0.66, 95% CI 0.55–0.78). There was no significant difference in OS (median, 20 versus 19 months, HR 0.96, 95% CI 0.80–1.17).

A phase III study compared nivolumab monotherapy with everolimus in 821 patients who metastatic RCC with ≤ 2 prior antiangiogenic therapies and ≤ 3 total prior systemic regimens [42]. The median OS was significantly increased with nivolumab compared with everolimus (median, 25.0 versus 19.6 months, hazard ratio [HR] 0.73, 95% CI 0.57–0.93). The overall ORR was 25% with nivolumab versus 5% with everolimus (25% versus 5%; OR 5.98; 95% CI 3.68–9.72; $p<.001$) but the median PFS asked for nivolumab in the second-line setting was in the four to five-month range. Decision made to start ipilimumab plus nivolumab this patient.

Managing patients with renal cell carcinoma which brain metastases

Clinical scenario 5

A 67-year-old female with an ECOG performance status of 0, a 7 cm left renal mass, retroperitoneal adenopathy and hepatic metastases that have doubled in size over 4 weeks. You evaluate the patient and order a cranial MRI

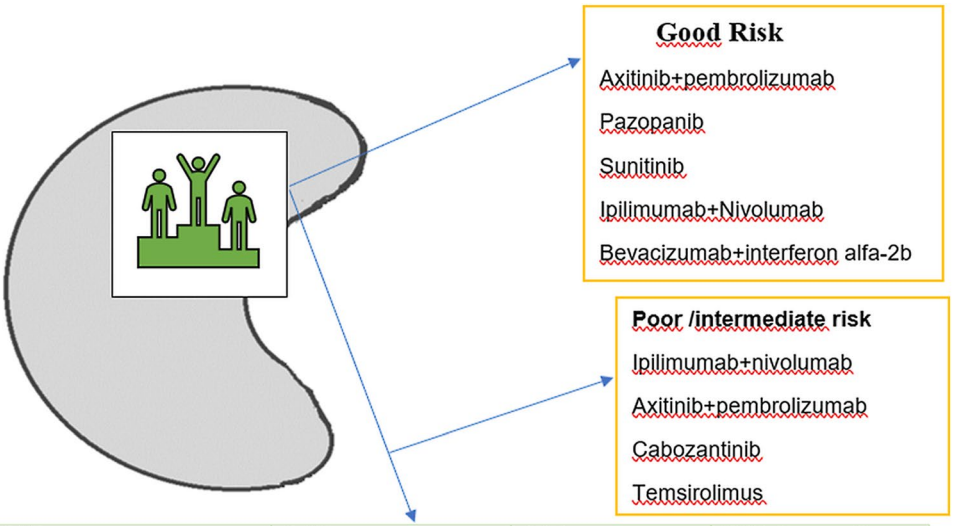

Fig. 5 Personalized therapy in advanced-stage clear cell RCC: current therapeutic landscape

1st line	2nd line	3rd line	With these other options
VEGF/VEGFRs targeting agent	Nivolumab	Cabozantinib	Axitinib, Everolimus
VEGF/VEGFRs targeting agent	Cabozantinib	Nivolumab	Everolimus, Axitinib
VEGF/VEGFRs targeting agent	Any VEGFR-TKI	Nivolumab or Cabozantinib	Everolimus
Nivolumab + Ipilimumab	AnyVEGFR-TKI	?	AnyVEGFR-TKI, Everolimus

examination, which reveals a 3-cm solitary lesion with surrounding vasogenic edema, present in the posterior fossa. What is the next step in management?

Surgical resection and stereotactic radiotherapy (SRS) are effective treatments for central nervous system (CNS) metastases from RCC. A total of 166 patients were identified from the Cleveland Clinic's as having received SRS for metastatic RCC [43]. In 38% of patients, there were additional distant CNS metastases at a median of 12.8 months after SRS. The median time to progression (either local or distant) was estimated to be 9.9 months. Data from studies that directly compare nivolumab plus ipilimumab with combinations of molecular targeted therapy in patients with clear cell RCC and brain metastases are lacking. Tawbi et al. evaluated the efficacy of nivolumab plus ipilimumab in patients with melanoma who had untreated asymptomatic small brain metastases [44]. Ipilimumab plus nivolumab appears to produce an approximately 50–60% durable progression-free survival rate at 1 year. The correct integration of radiotherapy and systemic therapy for patients with RCC and CNS metastases requires further study. Patient undergoes gamma knife radiation to CNS lesion. We planned to begin treatment with immunotherapy ± TKI.

How do we use molecular targeted therapy in non-clear cell RCC?

Clinical scenario 6

A 55-year-old woman is referred to you for further management of metastatic type 2 papillary renal cell cancer. One year ago, she underwent a left radical nephrectomy for an 8 cm renal mass. Complete staging evaluation at the time also revealed extensive mediastinal and hilar adenopathy and multiple bone lesions consistent with metastatic disease. What do you recommend patients with non-clear cell renal cancer?

Metastatic non-clear cell RCC prognosis is inferior to metastatic clear cell RCC. The introduction of new therapeutic agents resulted in cancer-specific mortality improvement over time [45]. However, this effect exclusively applies to patients with metastatic clear cell RCC, but not to those with metastatic non-clear cell RCC. VEGFR inhibitors show modest activity in papillary RCC but are active only in clear cell RCC. Prospective phase II trials with sunitinib have demonstrated that this agent is associated with low response rates (5–10%) in papillary RCC and the median PFS was approximately six months [46]. Binding of ligand hepatocyte growth factor (HGF) to MET triggers constitutive activation of the receptor tyrosine kinase activity by

autophosphorylation, leading to downstream effectors that regulate cellular programs supporting cell growth, differentiation, and invasive growth [47–50]. Both the MET receptor tyrosine kinase and the HGF ligand are potential therapeutic targets in some forms of papillary RCC. A phase III clinical trial comparing savolitinib with sunitinib is planned in patients with MET-driven papillary RCC (NCT03091192).

Enrolment on a well-designed clinical study is a reasonable consideration in this patient.

Conclusion

Summary and recommendations

Looking at this review, various RCC scenario that we have discussed in this section, as well as some recently published studies provide a different window into the optimization of treatment selection. There are multiple treatment options available for patients with advanced clear cell RCC. Inhibiting these T cell checkpoints has been revolutionary in the treatment of clear cell RCC. TKI are still used in all lines of metastatic clear cell RCC in monotherapy or in combination (Fig. 5). A subgroup of clear cell RCC is particularly sensitive to VEGFR-TKIs. Although it is hoped that current trials will soon yield positive results, and negative results contribute to our knowledge. Immunotherapy plus TKI combination therapies are likely to dominate the next several years of clinical drug development in RCC. With increasing therapeutic options, we continue to be in search about how to optimization of treatment selection and better understanding about sequencing strategies of current agents.

Compliance with ethical standards

Conflict of interest All authors declare no conflict of interest

Research involving human participants and/or animals This article does not contain any studies with human participants performed by any of the authors.

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