Contemporary treatment of metastatic renal cell carcinoma

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Abstract

The introduction of targeted therapy has revolutionized the treatment of patients with metastatic renal cell carcinoma (mRCC). The current standard of care focuses on the inhibition of angiogenesis through the targeting of the vascular endothelial growth factor receptor (VEGFR) and the mammalian target of rapamycin (mTOR). Over the past few years, research exploring novel targeted agents has blossomed, leading to the approval of various targeted therapies. Furthermore, results from the CheckMate025 and the METEOR trials have brought about two additional novel options: the programmed cell death 1 (PD-1) checkpoint inhibitor nivolumab and the MET/VEGFR/AXL inhibitor cabozantinib, respectively. With the variety of therapeutic agents available for treatment of mRCC, research examining appropriate sequencing and combinations of the drugs is ongoing.

This review discusses the role of prognostic criteria, such as those from the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria. It also covers the current standard of treatment for mRCC with targeted therapy in first-, second-, and third-line setting. Additionally, the novel mechanism of action of nivolumab and cabozantinib, therapeutic sequencing and ongoing clinical trials are discussed.

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Introduction

Kidney cancer is not an uncommon malignancy, with an estimated worldwide annual incidence of about 270,000 new cases.[1,2] Approximately 90% of kidney cancers are renal cell carcinoma (RCC).[2] For unknown reasons the overall incidence of metastatic RCC (mRCC) continues to rise by 2% per year.[3] 25-30% of patients initially present with metastatic disease, while approximately 30% of patients who are treated for local RCC will relapse.[4,5] Therapeutic intervention has moved away from cytokine immunotherapeutic agents, such as interferon-α (IFN-α) and interleukin-2, towards addressing molecular targets through targeted agents. Over the past decade, therapy for mRCC has been revolutionized through the introduction of mammalian target of rapamycin (mTOR) inhibitors and tyrosine kinase inhibitors (TKI), which target the vascular endothelial growth factor (VEGF) pathway.[6,7] Before this year, there were seven targeted agents approved for therapeutic use in mRCC patients: sunitinib, sorafenib, pazopanib, bevacizumab and axitinib, which target the VEGF pathway and the two mTOR inhibitors everolimus and temsirolimus.[3] Furthermore, recent clinical trials have identified cabozantinib, an inhibitor of VEGFR receptor (VEGFR), MET and AXL, and nivolumab, a programmed cell death-1 (PD-1) checkpoint inhibitor, as novel targeted agents against mRCC.[8,9]

Importance of prognostic factors

With the rapid developments in the mRCC field it remains critical to use prognostic factors, such as the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic criteria, to evaluate and identify the best possible treatment methods for different patient subgroups.[10,11]

A prognostic factor is a clinical or biologic characteristic, which allows for an objective determination of a possible outcome of the disease.[11] Currently, prognostic models addressing mRCC, such as the IMDC prognostic factors and the Memorial Sloan-Kettering Cancer Centre (MSKCC) prognostic criteria, are commonly used in the clinical and research setting.[10,12] The MSKCC model was validated during the cytokine therapy era, whereas the IMDC model has been validated and used in the setting of targeted therapy. Moreover, the same IMDC model has been validated in first- and second-line targeted therapy, while also displaying the ability to risk-stratify patients in third-line targeted therapy setting.[10,13,14]

The IMDC model includes the following factors: Karnofsky performance status (KPS) <80%, time from diagnosis to treatment <1 year, anemia, hypercalcemia, neutrophilia and thrombocytosis.[10] Patients with 0 risk factors, 1-2 factors, or >3 factors are considered favorable, intermediate, or poor risk, with a corresponding predicted overall survival (OS) of 43.2 months 22.5 months and 7.8 months, respectively.[10,15] The IMDC prognostic factors have been increasingly used to stratify

patients into different risk groups in a variety of clinical trials, such as the ADAPT trial (NCT01582672), which examined the effectiveness of autologous dendritic cell immunotherapy (AGS-003) in addition to sunitinib in mRCC.[16] The IMDC model was also used to stratify patients in the CheckMate214 trial (NCT 02231749) comparing sunitinib *versus* nivolumab in combination with ipilimumab in first-line setting.[17]

Prognostic factors carry importance in patient counseling and allow clinicians to have a survival reference point based on the risk profiles of these patients. It is important to note that prognosis is a dynamic process, meaning that prognostic prospects of patients can change over the course of the disease.[11] For example, with increasing information gathered on a patient who has survived a certain period of time, the prognosis of the patient may be different than what it originally was at baseline.

Prognostic factors can also aid in treatment selection. Patients with a poor risk factor profile would be eligible for the first-line mTOR inhibitor temsirolimus.[18] Temsirolimus was tested in 626 patients with previously untreated, poor-prognosis mRCC.[18] Patients were randomized to temsirolimus 25 mg IV weekly, IFN-α 18×10^6 IU times weekly, or temsirolimus + IFN-α 3 times weekly.[18] Results showed that patients receiving temsirolimus alone had a longer OS of 10.9 months relative to 7.3 months (P=0.008) in the IFN-α group.[18] As a result, the use of prognostic factors remains critical to identify the subgroup of poor risk mRCC patients.

Small subgroups of favorable risk mRCC patients may follow an indolent clinical course characterized by very slow tumor growth and no significant symptoms.[11] This small patient subgroup may benefit from active surveillance with regularly scheduled computed tomography scans to monitor their tumor growth.[19] Although a variety of clinical trials have displayed a significant survival benefit associated with the current targeted agents, they induce significant toxicities. A retrospective cohort study of patients treated at two centers for mRCC evaluated clinical outcomes in patients treated with deliberately deferred first-line targeted therapy.[19] In this study patients who were observed for an average of 18.7 months prior to treatment initiation had progression free survival (PFS) and OS comparable to those observed in the phase III clinical trial testing sunitinib *versus* IFN-α.[20] Moreover, data from a handful of retrospective and prospective studies confirmed these results by displaying that subgroups of favorable and intermediate risk patients may benefit from active surveillance.[21-23] Therefore, patients with slow tumor growth may be able to avoid being exposed to the toxicities associated with the targeted therapies, without lowering their survival benefit by going on active surveillance.

The IMDC model can also be used to help select patients that would benefit the most from a cytoreductive nephrectomy (CN); the resection of the primary tumor in mRCC patients.[24] Patients with four or more IMDC prognostic factors appear to be less likely to benefit from CN, because the incremental benefit of CN appears to decrease in patients with a shorter predicted survival.[24] Risk stratification for CN is aided with the use of the IMDC model however, it should not be used in isolation for clinical decision making since additional factors, such as brain metastasis, liver metastasis, the bulk of disease in the kidney *versus* systemically, and surgical resectability may influence whether or not patients would benefit from CN.[24]

First-line therapy

Sunitinib

After displaying superiority to cytokine immunotherapy, the multikinase inhibitor sunitinib that blocks VEGFRs 1, 2 and 3, platelet-derived growth factor (PDGF) receptor-β and related receptor tyrosine kinases (RTKs) has remained a standard of care for first-line therapy in

mRCC.[20,25] Results from a phase III randomized controlled trial displayed an objective response rate (ORR) of 31% *versus* 6% (P<0.001).[20] The PFS was 11 months in the sunitinib group *versus* 5 months in the IFN-α, corresponding to a hazard ratio (HR) of 0.42 [95% confidence interval (CI) 0.32-0.54; P<0.001], thus displaying a significant survival benefit associated with first-line suntinib.[20] The dose and schedule optimization of sunitinib continues to be under evaluation as seen in a prospective phase II study examining toxicity-driven dosages of sunitinib (NCT01499121), which aimed to expose patients to ≤ grade-2 toxicity.[26] Patients were started on 50 mg/day (d) on a 28/7 d schedule.[26] If the patient had > grade 2 toxicities, the schedule of sunitinib was altered first instead of altering the dose (*e.g.*, 2 weeks on 1 week off) in an effort to maximize dose intensity while maintaining a manageable and tolerable toxicity profile.[26] Patients who had no toxicities were dose escalated to 62.5 mg and then 75 mg on a 14/7 d schedule.[26] Patients treated in this manner had an impressive ORR of 50.6% and a disease control rate of 89.2%.[26] The benefit of the latter approach remains to be studied further.

Pazopanib

Pazopanib is a TKI of VEGFRs 1-3, PDGF receptors α and β, and the proto-oncogene c-Kit.[27] Pazopanib has previously been shown to significantly prolong PFS and ORR when compared with placebo in both, treatment-naïve and cytokine-pretreated patients with advanced RCC.[27] A PFS of 9.2 *versus* 4.2 months (P<0.0001) and an ORR of 30% *versus* 3% (P<0.001) was observed in the pazopanib and placebo groups, respectively.[27] Due to these promising results in first-line setting, the COMPARZ trial examined pazopanib *versus* the first-line standard of care TKI, sunitinib.[28] Of patients 1110 with clear-cell mRCC were randomized to receive pazopanib 800 mg once daily or sunitinib in 6-week cycles (50 mg once daily for 4 weeks, followed by 2 weeks off treatment).[28] Results confirmed pazopanib's noninferiority to sunitinib in terms of PFS.[28] Furthermore, pazopanib appears to have a favorable safety and quality-of-life profile in comparison to sunitinib.[28] ORR and OS did not differ significantly between the two treatment groups.[28] Adverse events, such as fatigue, hand-foot syndrome and mouth sores occurred more frequently in the sunitinib group.[28] In fact, patients who received pazopanib reported less fatigue, less soreness of extremities and of the mouth and throat but there was a higher incidence of liver toxicity.[28] Additionally, the PISCES trial evaluated patient preference for pazopanib or sunitinib. Patients were randomly assigned to receive pazopanib 800 mg/d for 100 weeks, a 2-week washout, then sunitinib 50 mg/d (4 weeks on/2 off/4 on), or the reverse sequence.[29] 70% of patients preferred pazopanib over sunitinib, 22% preferred sunitinib, while 8% had no preference (P<0.001), thereby further confirming patient preference for pazopanib.[29] Thus, pazopanib is another first-line treatment option.

Bevacizumab

Bevacizumab is a recombinant monoclonal antibody, which targets and binds circulating VEGF.[30] Bevacizumab + IFN-α had a significantly higher PFS than IFN-α alone of 10.2 months *versus* 5.4 months (P<0.0001) and an ORR of 31 *versus* 13% (P<0.0001), respectively.[30] There was no significant OS difference seen between the two groups. Currently there is no data available to determine whether bevacizumab alone or bevacizumab + IFN-α has a larger survival benefit.[30]

Second-line therapy

Axitinib

Axitinib is a selective second-generation inhibitor of VEGFR 1, 2 and 3, while also inhibiting PDGF-α, PDGF-β and the proto oncogene C-

Kit.[31-33] Patients were randomly assigned to receive either axitinib or sorafenib after previous treatment with sunitinib, bevacizumab, temsirolimus, or cytokines.[31] The primary endpoint was PFS, which was 6.7 months and 4.7 months (P<0.0001) for axitinib and sorafenib, respectively.[31] Common toxicities associated with axitinib were diarrhea, hypertension and fatigue.[31] ORR was 19% for axitinib and 9% for sorafenib (P=0.0001).[31] OS was not significantly different between the two drugs.[34] As a result axitinib is a second-line treatment option in mRCC patients (Table 1).

Cabozantinib

Cabozantinib inhibits the activity of VEGFR 1, 2, 3, hepatocyte growth factor receptor (MET), AXL, the angiopoetin receptor TIE-2, RET, c-Kit and FLT-3 *in vitro* and *in vivo*.[8,35-38] These receptors are mainly involved in tumor oncogenesis and angiogenesis.[36, 38] Chronic sunitinib treatment of RCC *in vitro* has displayed AXL and MET up-regulation, leading to increased prometastatic behavior and angiogenesis.[39] As a result, cabozantinib's novel mechanism of action could be used to override this resistance mechanism (Figure 1). In preclinical models with neuroendocrine, breast, pancreatic, lung, and glioma tumors, cabozantinib has also been shown to inhibit angiogenesis, tumor cell migration, tumor cell proliferation, while inducing cell death.[38,40]

Hypoxic tumor cells activate hypoxia inducible factor-1α, which leads to the upregulation of both VEGF and MET.[41,42] The upregulation of MET allows for more hepatocyte growth factor (HGF) to bind to the MET receptor, thereby increasing the invasiveness and motility of the tumor.[42,43] The increased expression of VEGF increases angiogenesis around the hypoxic tumor cells.[42,44] Continuous VEGF pathway inhibition through TKIs has been shown to initially slow tumor growth by decreasing the vasculature surrounding the tumor.[7,42] However, after a period of time the majority of patients develop resistance to VEGF-inhibition.[45,46] In fact, the HGF/MET pathway has been identified to act as antiangiogenic escape mechanism in sunitinib-resistant tumors.[47] Furthermore, MET activation has previously been shown to be correlated with worse disease-specific survival.[48] As a result, cabozantinib's novel mechanism of action targeting VEGFR, MET and AXL may be advantageous in patients who have developed resistance to previous TKIs.

Table 1. Selected clinical trials of second-line targeted therapies in renal cell carcinoma.

Agent	Mechanism	Trial arms	ORR (%)	PFS (Months)	OS (Months)
Axitinib	VEGFR inhibitor	Axitinib *versus* sorafenib	19 *versus* 9 P=0.0001	6.7 *versus* 4.7 P<0.0001	20.1 *versus* 19.2 P=0.3744 NS
Cabozantinib	VEGF, MET and AXL inhibitor	Cabozantinib *versus* everolimus	21 *versus* 5 P<0.001	7.5 *versus* 3.9 P<0.001	21.4 *versus* 16.5 P<0.001
Nivolumab	PD-1 inhibitor	Nivolumab *versus* everolimus	25 *versus* 5 P<0.001	4.6 *versus* 4.4 P=0.11 NS	25.0 *versus* 19.6 P=0.002

ORR, objective response rates; PFS, progression free survival; OS, overall survival; VEGFR, vascular endothelial growth factor receptor; NS, non-significant; PD-1, programmed cell death-1.
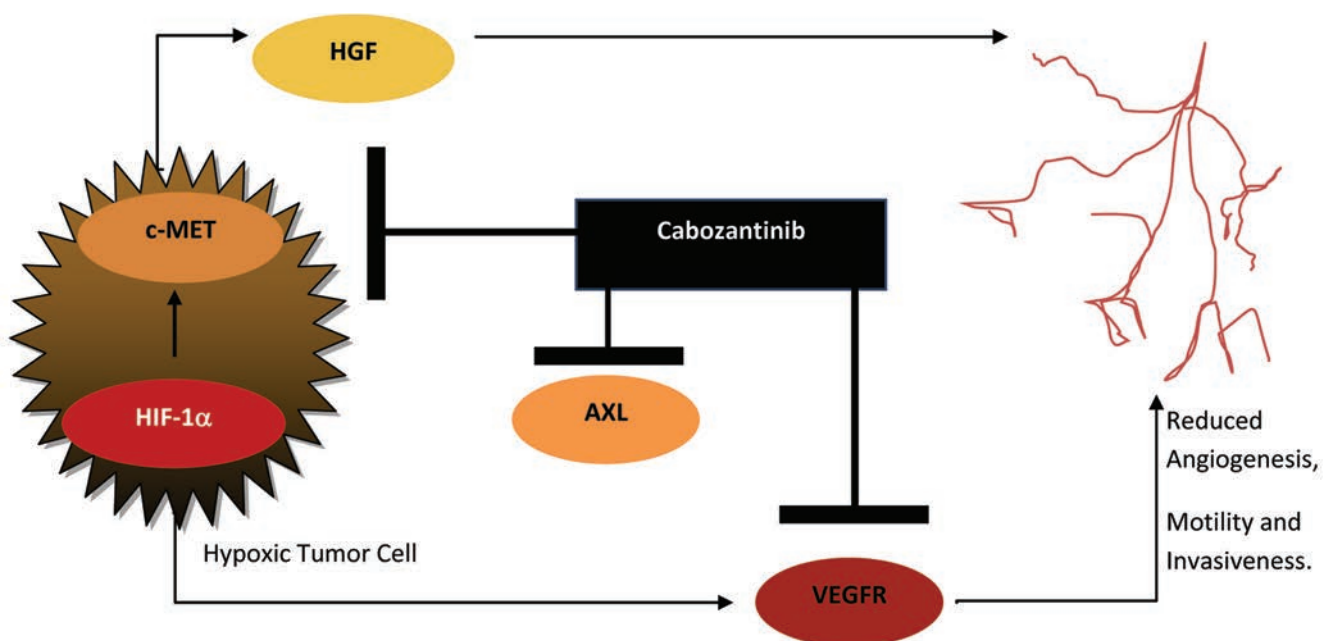

Figure 1. Mechanism of action of cabozantinib: cabozantinib inhibits the activity of c-MET, vascular endothelial growth factor receptor (VEGFR), AXL and other tyrosine kinases, thereby leading to reduced tumor angiogenesis, motility and invasiveness. HGF, hepatocyte growth factor; HIF-1α, hypoxia-inducible factor 1-α.

Cabozantinib has already gained the U.S. Food and Drug Administration (FDA) approval for treatment of medullary thyroid cancer.[49] In mRCC, the METEOR trial randomly assigned 658 patients who had previously received at least one VEGFR-TKI to receive either cabozantinib at 60 mg daily or everolimus at 10 mg daily.[8] Patients were required to have a KPS of at least 70% and previous mTOR inhibition therapy was not permitted.[8] Dose reductions for cabozantinib (40 mg, then 20 mg) and everolimus (5 mg then 2.5 mg) and interruptions of study treatment were allowed to manage adverse events.[8] The primary end-point was PFS, which was 7.4 months and 3.8 months with cabozantinib and everolimus, respectively.[8] The ORR was 21% with cabozantinib and 5% with everolimus (P<0.001).[8] OS was initially reported in an interim analysis, which displayed longer survival in the cabozantinib than in the everolimus group (HR: 0.67; P=0.005).[8] The median OS was 21.4 months for the cabozantinib group and 16.5 months for the everolimus group, with a 33% reduction in the rate of death (HR 0.67, 95% CI 0.53-0.83, P=0.0003).[50] Cabozantinib appears to be the only currently available targeted therapy that significantly increases ORR, PFS and OS in mRCC patients.[8,50] Frequent toxicities associated with cabozantinib were diarrhea, palmar-plantar erythrodysesthesia syndrome and dysgeusia.[8] Of patients 60% who received cabozantinib and 25% who received everolimus underwent dose reductions.[8] The incidence of grade 3 and 4 all-cause adverse events was higher in the cabozantinib group (68%) *versus* the everolimus group (58%).[8] Although a significant survival benefit was observed, cabozantinib dosing needs to be titrated carefully to reduce the number of adverse events seen in the METEOR trial.[8]

Nivolumab

Nivolumab is a fully human IgG4 PD-1 immune checkpoint inhibitor antibody that inhibits the interaction between PD-1 expressed on activated T-cells and PD-1 ligand (PD-L1) and PD-L2, which are expressed tumor cells.[51,52] Other PD-1 and PD-L1 inhibitors are also under development, including the PD-1 inhibitor pembrolizumab and the PD-L1 inhibitors atezolizumab and avelumab. T-cells normally recognize tumors through the tumor specific antigens docking to the T-cell receptors (Figure 2). T-cell activation requires both antigen recognition and antigen-independent co-regulatory signaling to occur.[53] Immune checkpoint pathways, such as PD-1 oversee the co-regulatory signaling step.[54] The cell surface receptor PD-1 belongs to the CD28 family of T-cell regulators, which are expressed on activated T-cells and other immune cells.[54,55] When PD-1 interacts with its ligands, PD-L1 and PD-L2, T-cells are switched off resulting in T-cell exhaustion, thereby significantly down-regulating immune response even in the presence of antigens that would normally trigger an immune response.[54,55] Healthy cells use the PD-1 pathway to prevent overstimulation of immune responses and to maintain immune tolerance of self-antigens.[56-58] Tumor cells on the other hand often overexpress PD-L1 and PD-L2 on their surface, thus allowing the tumor cells to deactivate tumor-infiltrating activated T-cells.[51,55] It has been postulated that the disruption of this interaction will lead to restored antitumor immunity.[59-61] Nivolumab inhibits the interaction between PD-1 expressed on the T-cells and PD-L1/PD-L2 expressed on the tumor, thereby leading to T-cell mediated killing of the malignant cells.[9]

The CheckMate025 trial compared the effectiveness of the PD-1 inhibitor nivolumab *versus* everolimus in 821 patients with advanced clear-cell RCC who have previously been treated with up to two regimens of VEGF therapy.[9] Patients were randomized to receive 3 mg of nivolumab per kilogram of body weight intravenously every 2 weeks for 60 min or 10 mg everolimus orally once a day.[9] The primary endpoint of OS was 25.0 months and 19.6 months for nivolumab *versus* everolimus,
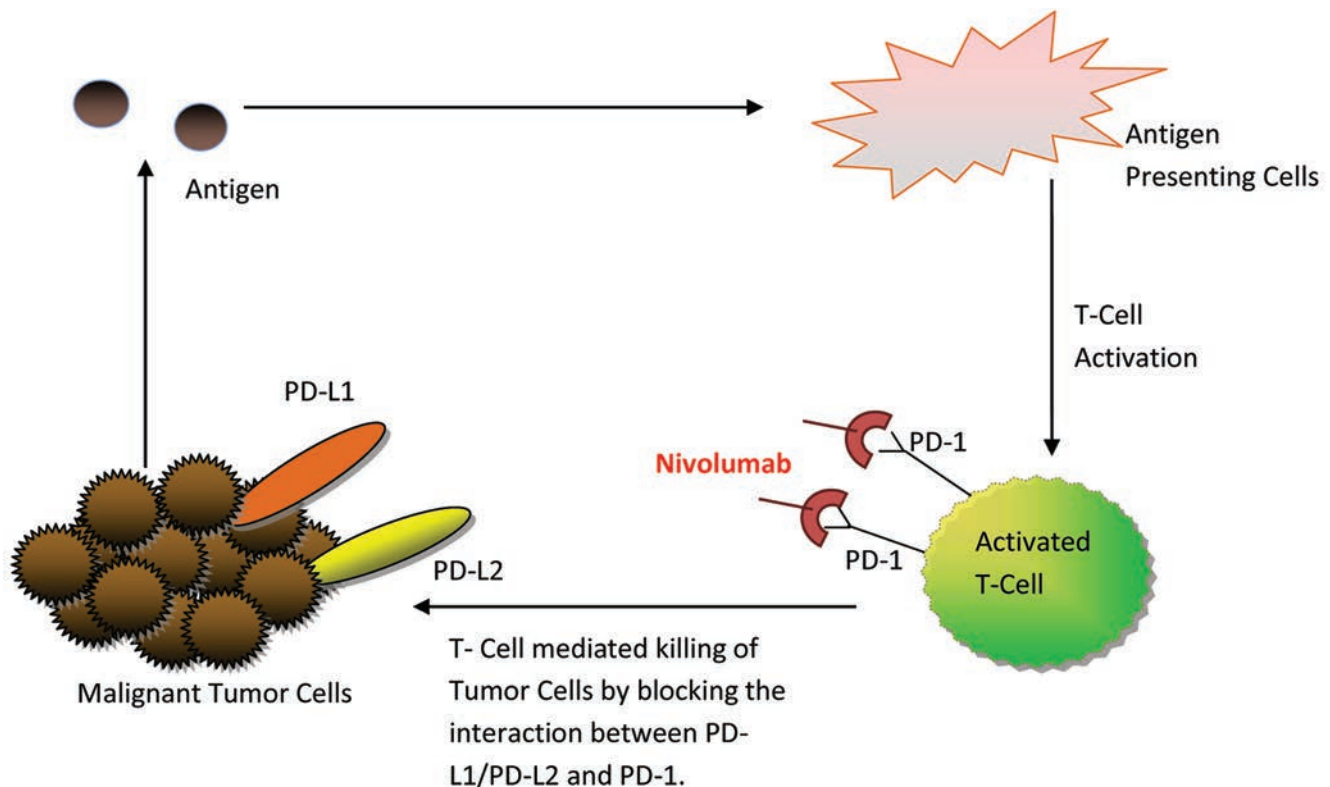

Figure 2. Mechanism of action of nivolumab: by blocking the interaction between programmed cell death-1 (PD-1) and PD-1 ligands (PD-L1/PD-L2), nivolumab assists with the induction of T-cell mediated killing of malignant cells.

respectively.[9] ORR was 25% for nivolumab and 5% for everolimus (P<0.001).[9] Adverse events were less common in patients receiving nivolumab (19%) than in patients on everolimus (37%).[9] The difference in PFS between the two agents was not statistically significant, possibly because patients treated with checkpoint inhibitors may exhibit pseudoprogression due to initial lymphocytic infiltration that may artificially make the tumors look slightly larger on imaging.[9] 26% of patients receiving everolimus had at least 1 dose reduction, whereas dose reductions in the nivolumab group were not permitted.[9] The most common adverse side-effects associated with nivolumab were nausea and pruritus.[9]

Furthermore, this trial examined the association between OS and tumor expression of PD-L1.[9] Previous studies have identified PD-L1 expression to be associated with poor prognosis RCC and as a result PD-L1 expression has been postulated to improve OS post-nivolumab treatment.[60-64] In the CheckMate025 trial 92% of patients had quantifiable PD-L1 expression.[9] 24% of patients with quantifiable PD-L1 expression had ≥1% PD-L1 expression, while 76% had <1%.[9] A subgroup analysis displayed a median OS of 21.8 months (N=94) and 27.4 months (N=276) in patients with ≥1% PD-L1 expression and <1% PD-L1 expression, respectively.[9] A median OS of 21.9 months (N=23) and 24.6 months (N=326) was observed in patients with ≥5% PD-L1 expression and <5% PD-L1 expression, respectively.[9] The results of this subgroup analysis suggest that PD-L1 expression is not a predictor of response to nivolumab treatment.[65-67]

Although results from the CheckMate025 trial are promising, the complete response rate or at least long term remission rate is still as low as with other targeted agents that are commonly used to treat mRCC. Additionally, the duration of treatment with nivolumab after pseudoprogression of mRCC tumors remains unclear and should be further examined. With the results of these recent trials, nivolumab, axitinib, and cabozantinib may become the standard second-line agents in the future, while moving everolimus beyond the third and fourth-line setting. Further studies will need to be conducted to directly compare the efficacy and safety of nivolumab *versus* cabozantinib as well as previously established agents such as axitinib. The possible relationship between PD-L1 expression as a predictive biomarker and survival outcome needs to be examined further, thereby optimizing treatment selection in the second-line setting for different subgroups of mRCC patients.

Everolimus

The mTOR inhibitor everolimus was the second-line standard of care until the introduction of cabozantinib and nivolumab, which demonstrated benefit over everolimus. In the pivotal RECORD-1 trial, RCC patients who previously progressed on sunitinib, sorafenib or both were randomized to daily oral everolimus at 10 mg or placebo.[68] The final results of the trial displayed a PFS of 4.9 months (everolimus) *versus* 1.9 months (placebo) (P<0.001) and an OS of 5.5 months (everolimus) *versus* 1.9 months (placebo) (P<0.001).[69] As a result, everolimus has been used in second-line setting following prior TKI failure.[69] The findings of both, the CheckMate025 and METEOR trials pushed Everolimus to the third-line setting and beyond.[8,9,68]

A phase II trial examining the oral multi target fibroblast growth factor receptor and VEGFR TKI lenvatinib after prior treatment with VEGF-targeted therapy was compared against lenvatinib and everolimus combination therapy and against everolimus alone.[70] The combination treatment of everolimus and lenvatinib recently received FDA approval in the United States for mRCC treatment.[71] Results displayed a statistically significant increase in PFS in the combination group (14.6 months) and the stand-alone lenvatinib group (7.4 months) *versus* patients that received everolimus (5.5 months).[70] There was no statistically significant difference in PFS between the lenvatinib and the combination group (P=0.12).[70] Furthermore, this

is the only combination that appears to significantly improve OS. The subsequent *post hoc* updated analysis displayed a significant difference in OS between patients in the combination group and those receiving everolimus only was seen [median OS 25.5 months (95% CI 16.4-NE) *versus* 15.4 months (95% CI 11.8-19.6)]; (HR 0.51, 95% CI 0.30-0.88, P=0.024). The OS was not significantly different between patients on lenvatinib and everolimus or the combination group. Grade 3 or 4 events occurred in 50% of patients receiving everolimus, 79% of patients receiving single agent lenvatinib and 71% of the combination group. A phase III trial is warranted to confirm a substantial survival benefit in order to justify the financial costs and side effects of combination therapy.[70] The combination therapy of lenvatinib and everolimus was granted accelerated approval due to FDA *breakthrough therapy designation*, which will require a post marketing confirmatory trial.[71]

Sorafenib

Sorafenib also remains a treatment option in later lines of therapy for advanced clear cell RCC.[72] A randomized phase II trial of first-line sorafenib *versus* IFN-α showed no significantly different PFS between the two treatment groups.[73] Sorafenib patients reported less toxicities and a better quality-of-life.[72] Additionally, the randomized phase III INTORSECT trial examined sorafenib *versus* temsirolimus in second-line setting in mRCC patients who have previously progressed on sunitinib.[74] Results displayed no significant PFS difference between the two treatment groups, however the sorafenib arm displayed a significantly larger OS of 16.6 months *versus* 12.3 months in the temsirolimus arm.[74]

Third line therapy

Currently, the GOLD and RECORD-1 trials are the only reported prospective randomized controlled trials evaluating third-line therapy in mRCC.[68,75] In the GOLD trial dovitinib, an oral multi-target TKI inhibiting both VEGF and FGF was tested *versus* sorafenib. Dovitinib was given at 500 mg orally 5 days on/2 days off, whereas sorafenib was given orally (400 mg twice daily).[75] Results displayed no significant difference between median PFS of the two drugs.[75] RECORD-1 tested the efficacy of everolimus 10 mg daily *versus* placebo in patients with mRCC with a clear cell component.[68] A subset analysis (N=108) of patients receiving third-line everolimus after previous treatment with VEGF-TKIs displayed a median PFS of 4.0 months in the everolimus group and 1.9 months in the placebo group.[68] ORR were close to 0% for both groups and there was no significant difference in OS.[68,69] This indicates that there is activity of everolimus in the third line although the response rates are negligible, which is historically consistent with mTOR inhibitors as disease stabilizing agents.

A retrospective study further examined the use of third-line targeted therapy in mRCC patients (N=1012).[14] 61.1% of patients displayed an ORR of stable disease or better.[14] There was no statistically significant difference between OS or PFS between the different third-line agents, however a significant survival difference was observed when stratifying patients into the IMDC prognostic groups.[14] An OS of 29.9, 15.5 and 5.5 months (P<0.0001) was observed in favorable, intermediate, and poor risk patients, respectively.[14] A similar trend in PFS was observed, with favorable risk patients having the highest PFS of 7.5 months.[14] Although there was no statistically significant difference associated between the different drug types, everolimus was most commonly used in 27.5% of the sample.[14] With cabozantinib and nivolumab set to take the spot as primary agents in second-line therapy, everolimus will likely be more frequently used in the third-line setting or beyond.

Targeted therapy in non-clear cell renal cell carcinoma

Although clear cell RCC is the most prevalent histology (75-80%), the papillary type (10-15%), chromophobe (5%) and rare forms, such as collecting ducts carcinoma (≤1%) also account for a significant portion of affected patients.[76] As a result, the treatment for those patients has been understudied and treatments are generally adopted based on the results of trials examining the drug efficacies in clear cell RCC populations.

Currently, a variety of promising trials are testing different therapeutic combinations in non clear cell RCC.[77] A phase II trial evaluating the efficacy of first-line AZD6094 (savolitinib, HMPL-504) in patients with papillary RCC is ongoing.[78] Results from the ASPEN trial assessing everolimus *versus* sunitinib in patients with non-clear cell mRCC displayed prolonged radiographic PFS and higher rates of severe toxicities in the sunitinib group.[79] Preliminary results from a prospective phase II trial display that pazopanib demonstrated a promising activity with a median PFS of 8.3 months in a non-clear cell cohort excluding collecting duct and sarcomatoid type RCC.[80] Various clinical trials examining MET inhibitors, such as crizontinib and cabozantinib are also currently being tested particularly in papillary RCC.[77] Other trials are examining the effects of cytotoxic chemotherapy, such as gemcitabine and doxorubicin in patients with RCC with sarcomatoid features.[77] Lastly, the PD-L1 pathway is currently also being examined through the use of antibody atezolizumab (NCT01375842) in papillary and sarcomatoid histologies, thus displaying the potential for treatment with immunomodulatory agents in non-clear cell mRCC.[81]

Optimization of targeted therapy sequencing in metastatic renal cell carcinoma

With the sheer amount of therapeutic agents available for RCC, the sequence of the most optimal therapies must be examined (Figure 3). Since cross trial comparison is not a reliable method to examine differences between drugs, physicians tend to use safety profiles of the drugs when facilitating therapeutic selection.[82] It remains critical to monitor and manage potential toxicities when treating mRCC patients with targeted agents.[83] With the addition of nivolumab and cabozantinib the ideal sequence of targeted agents in the highly heterogeneous mRCC population needs to be elucidated. Physicians are often left to decide which drug to use in the mRCC patients until further trials establish a more definitive answer.

The CheckMate214 phase II clinical trial is currently examining the use of nivolumab and ipilumumab, a monoclonal antibody targeting CTLA-4 *versus* sunitinib in first-line setting.[17] Depending on the results the nivolumab and ipilumumab combination may displace VEGF-inhibitors as the standard of care first-line agent in the future. The mTOR, VEGF, MET/VEGF and PD-1 mechanisms could also be targeted using a combination of the currently available targeted therapies. Results from the CheckMate016 (NCT01472081) phase I trial examining nivolumab together with VEGF inhibitors sunitinib or pazopanib showed encouraging anti-tumor activity as well as a manageable safety profile of combination therapy in mRCC patients.[84]

The use of biomarkers in mRCC will be critical in the future. Future treatment options may be directed by the presence of positive biomark-
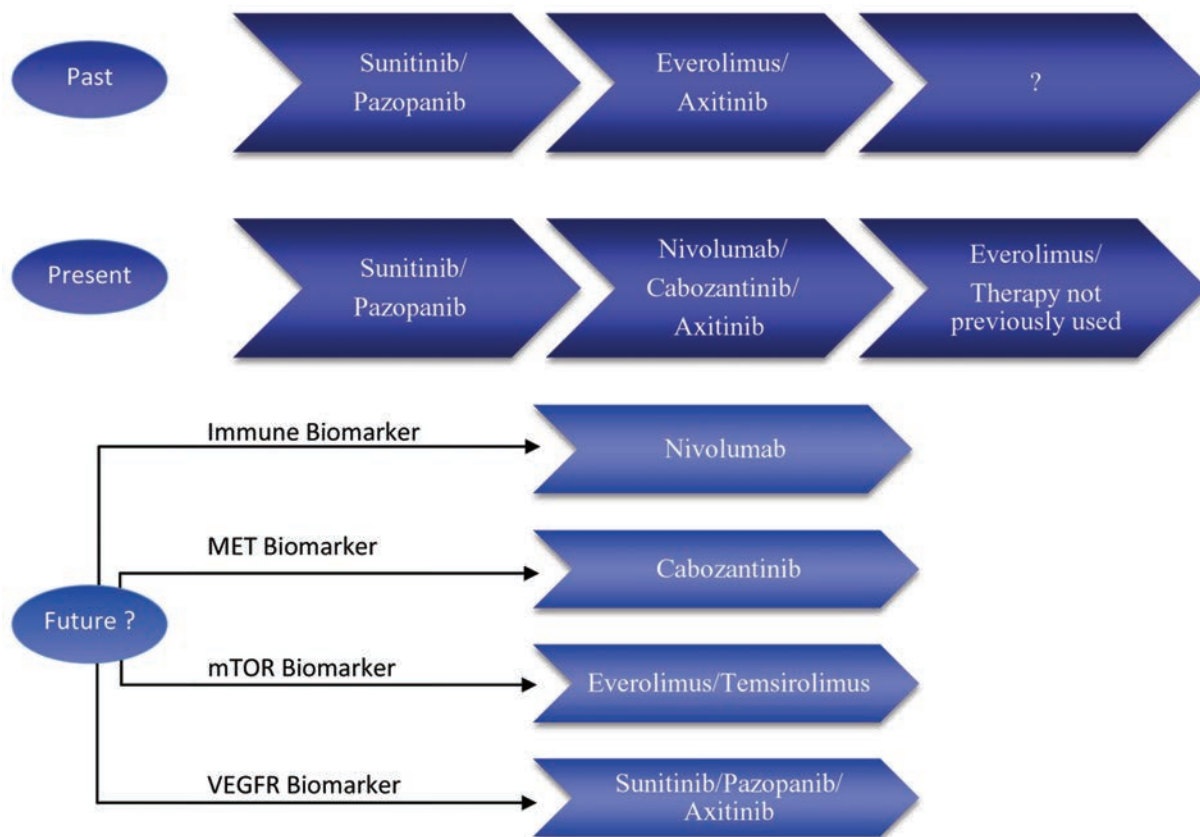

Figure 3. Past, current and future possibilities for renal cell carcinoma treatments. mTOR, mammalian target of rapamycin; VEGFR, vascular endothelial growth factor receptor.

ers, thereby optimizing treatment selection for patients. A hypothetical future treatment paradigm may have patients with up-regulated MET receive cabozantinib, a positive immune marker would prompt the use of nivolumab or other immunomodulatory agents, patients with upregulated mTOR would receive everolimus or temsirolimus, while patients with VEGFR upregulation may be more susceptible to sunitinib, pazopanib or axitinib treatment. These biomarkers may be discovered and used in the future and will require further validation. The identification of novel biomarkers and the usage of these biomarkers in the clinical setting will be critical to personalizing targeted therapies in mRCC. It is important to note that therapeutic choices are heavily influenced by funding availability and approved guidelines, thus depending on the institution patients may receive different interventions.

Conclusions

The treatment of mRCC continues to evolve faster than ever before. New targeted agents have been developed with treatment regimens continuing to be optimized. Novel agents, such as cabozantinib attempt to further prevent angiogenesis while other novel drugs such as nivolumab inhibit the immune checkpoint PD-1 pathway. A large number of clinical trials are ongoing to help elucidate the best therapy for patients with non-clear cell RCC.

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