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VEGF and PD-1 pathway inhibitors in renal cell carcinoma

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Abstract

Advanced renal cell carcinoma has historically carried a poor prognosis with very limited treatment options. However, in recent years, the treatment landscape has changed drastically with many new therapeutic options and improved survival for patients. Novel treatments consist of molecularly targeted agents against the vascular endothelial growth factor (VEGF) pathway as well as the immune checkpoint inhibitors (ICIs), which stimulate an anti-tumor immune response. Recent strategy has focused on the development of combination therapy with the use of VEGF inhibitors and ICIs in the first-line setting. As more treatments are approved and the options for therapy expand further, there is a growing need for predictive biomarkers to personalize treatment choices for individual patients. Prospective clinical trials comparing the sequencing of treatments are needed to help determine the best therapeutic approach.

Precis:

The treatment paradigm of renal cell carcinoma has changed drastically in the past decade and more changes are likely in the coming years. New treatments and novel combinations are yielding improved response rates, complete responses, longer progression-free survival, and improved overall survival for patients.

Keywords

Renal Cell Carcinoma; Vascular Endothelial Growth Factors; Programmed Cell Death 1 Receptor; Immunotherapy; Combination Drug Therapy

Introduction

In 2018, it is estimated that over 65,000 new cases of kidney cancer were diagnosed in the United States and almost 15,000 people died from the disease.[1] Kidney cancer is one of the 10 most common types of cancer in men and women. The main type of kidney cancer is renal cell carcinoma (RCC), which arises from the cortex of the kidney.[1] The most common

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subtypes of RCC include clear cell (65–70%), papillary (15–20%) and chromophobe (5–7%).[2] Sarcomatoid differentiation can be seen in any of these subtypes and is associated with a more aggressive disease course.[3] Despite a slight decline in the mortality rate in recent years, the prognosis for metastatic RCC (mRCC) remains poor with estimated five-year survival at 11.6% as of 2014.[1]

Historically, mRCC has not responded well to systemic treatment with chemotherapy. In the 1990s and early 2000s, treatment of metastatic disease focused on stimulating the immune system with cytokines such as high-dose interleukin-2 (HD IL-2) and interferon alpha (IFN). HD IL-2 can result in durable disease control for some patients but administration is limited to centers with expertise given associated significant, systemic toxicity. Cytokine therapy benefits only a small subset of patients. Therefore, recent treatment strategy has focused on the development of molecularly targeted agents as well as immunotherapy. Over the past fifteen years, more than ten new therapies have been approved by the United States Food and Drug Administration (FDA).[4] The focus of current research is centered on the development of novel drug combinations, drastically changing the treatment landscape of RCC and holding promise for improvement in patient outcomes

VEGF inhibitors

Development of new blood vessels is essential for tumor growth and RCC is known to be a highly vascular tumor. Therefore, in the treatment of mRCC, many strategies aim to inhibit angiogenesis. In RCC, the von Hippel-Lindau (VHL) tumor suppressor gene is frequently mutated. VHL is involved in the pathway that leads to degradation of hypoxia-inducible factor (HIF). When VHL is mutated, HIF is not degraded and leads to the transcription of many genes including VEGF, which induces angiogenesis.[5,6] Over the past decade, treatment of mRCC has focused on inhibiting the VEGF pathway with targeted agents including tyrosine kinase inhibitors (TKIs), which block VEGF receptors and other receptors involved in angiogenesis, as well as an anti-VEGF monoclonal antibody.[7] The TKIs sorafenib, sunitinib, pazopanib, axitinib, cabozantinib, and lenvatinib as well as the anti-VEGF monoclonal antibody, bevacizumab, have been shown to improve disease control in clinical trials.

Since the era of cytokine therapy, there have been multiple VEGF inhibitors approved for the first-line treatment of mRCC. Sorafenib was the first new agent to be FDA approved in 2005 after it was shown to improve progression-free survival (PFS) in patients with mRCC who were resistant to standard therapy compared to placebo.[8] Sorafenib has since been replaced by newer generations of VEGF inhibitors. Sunitinib was FDA approved for treatment of mRCC in 2006 and currently remains a first-line treatment option for patients with favorable risk disease. In a randomized, phase III trial sunitinib had an objective response rate (ORR) of 31%, median PFS of 11 months (HR 0.42, 95% CI 0.32–0.54, P<0.001), and overall survival (OS) of 26.4 months (HR 0.818; 95% CI 0.669–0.999, P=0.049) in the first-line setting compared to IFN.[9,10] Bevacizumab was approved in combination with IFN in 2009 based on a higher ORR of 25.5% and improved PFS of 8.5 months (HR 0.71, 95% CI 0.61–0.83, P<0.0001) compared to IFN alone.[11] Median OS was 18.3 months and not significantly different than with IFN alone (HR 0.86, 95% CI 0.73–1.01, P=0.69).[12]

Bevacizumab is no longer a preferred treatment agent but has recently been studied in combination therapy. Pazopanib is another TKI which was approved for the treatment of mRCC in 2009 based on a phase III trial showing improved ORR, PFS, and OS compared to placebo in the first- or second-line treatment setting.[13] Pazopanib was later compared to sunitinib in treatment-naïve patients with a median PFS of 8.4 months (HR 1.05, 95% CI 0.90–1.22) and median OS of 28.4 months (HR 0.91, 95% CI 0.76–1.08), which did not differ significantly from sunitinib. Health-related quality of life scores significantly favored pazopanib over sunitinib in 11 of 14 comparisons including fatigue and treatment side effects and the remaining 3 comparisons were not significantly different between treatment arms. 24% of patients discontinued treatment with pazopanib compared to 20% in the sunitinib arm with more liver-related adverse events in the pazopanib arm.[14] The most recent TKI to gain approval for treatment of mRCC in the first-line setting was cabozantinib. Cabozantinib was initially approved as a treatment option after failure of prior anti-angiogenic therapy in 2016 based on a phase III trial which showed improved PFS of 7.4 months compared to 3.8 months with everolimus in the second-line setting (HR 0.58, 95% CI 0.45–0.75, P<0.001).[15] Overall survival was also improved at 21.4 months with cabozantinib versus 16.5 months with everolimus as a second-line treatment (HR 0.66, 95% CI 0.53–0.83, P=0.00026)[16]. Cabozantinib was later approved for first-line treatment in 2017 based on a phase II trial comparing cabozantinib to sunitinib in treatment-naïve patients with intermediate and poor risk disease. Cabozantinib improved median PFS to 8.2 months compared to 5.6 months with sunitinib in the first-line setting (HR 0.66, 95% CI 0.46–0.95, one-sided P=0.12).[17] OS was 26.6 months with cabozantinib and 21.2 months with sunitinib (HR 0.80, 95% CI 0.53–1.21).[18]

Several TKIs are approved for treatment of mRCC in the second-line setting. Axitinib is a selective inhibitor of VEGF receptors which was FDA approved for mRCC with progressive disease after first-line therapy in 2012. Axitinib was initially compared to sorafenib in the second-line setting with improved PFS of 6.7 months compared to 4.7 months (HR 0.665, 95% CI 0.544–0.812, P<0.0001) but similar OS of 20.1 and 19.2 months, respectively (HR 0.969, 95% CI 0.800–1.174, P=0.374).[19,20] Axitinib was later compared to sorafenib in the first-line setting with a median PFS of 10.1 months (HR 0.77, 95% CI 0.56–1.05; P=0.038) and OS of 21.7 months (HR 0.995, 95% CI 0.731–1.356, P=0.488) which were not statistically different than with sorafenib.[21,22] Lenvatinib is the newest FDA approved TKI for treatment of mRCC in combination with everolimus in the second-line setting. In a phase II trial of lenvatinib vs. everolimus vs. the combination in 153 patients with mRCC who progressed on prior VEGF targeted therapy, the combination improved PFS and OS compared to everolimus alone. PFS was 14.6 months and OS was 25.5 months with lenvatinib plus everolimus compared to 5.5 months and 15.4 months with everolimus alone (OS HR 0.51, 95%CI 0.30–0.88, P=0.024).[23]

Advances in the development of VEGF inhibitors has transformed the treatment paradigm of mRCC. VEGF inhibitors can be used in sequence with clinical responses seen even after failure of a prior VEGF inhibitor. However, the majority of patients need to continue with ongoing therapy and durable responses are very rare. Eventually, most patients develop resistance to anti-angiogenic agents after a median of 6 to 15 months of treatment.[5] Clinical evidence suggests that resistance to VEGF blockade develops due to changes in the

microenvironment which allow resumption of angiogenesis.[5] Extensive research is currently focused on overcoming this resistance through various mechanisms including combining VEGF inhibition with ICIs.

ICIs

RCC is considered to be a highly immunogenic tumor and many current treatment strategies are aimed at harnessing the immune system to target malignant cells. RCC tumors have been shown to contain an immune cell infiltrate of T-cells, dendritic cells, macrophages, and natural killer cells.[24] In rare cases, RCC metastases spontaneously regress after nephrectomy which has been hypothesized to be the result of an innate immune response against the malignant cells.[25] However, in most cases, the immune system fails to target the malignant cells and the tumor continues to grow and spread. These observations and the lack of antitumor activity of chemotherapy lead to the development of agents aimed at activating the immune system such as IL-2, a cytokine signaling molecule which leads to the differentiation and activation of T-cells. The application of HD IL-2 served as proof of principle that immunotherapy could lead to durable complete response (CR) in a subset of patients with clear-cell RCC but is associated with significant toxicity.[26, 27, 28] Over the last decade, substantial progress has since been made in the field of tumor immunology that led to the development of ICIs, which have been shown to promote antitumor immunity in many different cancer types, including RCC.

Programmed cell death-1 (PD-1) is a protein on the surface of T-cells that inhibits an immune response when bound to programmed death ligand-1 (PD-L1). PD-L1 is normally expressed on antigen presenting cells such as dendritic cells and macrophages but can also be expressed on malignant cells.[24] The development of antibodies to PD-1 and PD-L1 has revolutionized the treatment of many types of malignancy.

Nivolumab is an anti-PD-1 antibody and the first ICI approved for second-line treatment of RCC in 2015.[29] Nivolumab was studied in the phase III clinical trial CheckMate 025 vs. everolimus in patients with mRCC who had progressed after prior anti-angiogenic therapy. Nivolumab showed a higher ORR of 25% compared to 5% with everolimus and a longer median OS of 25 months compared to 19.6 months with everolimus (HR 0.73, 98.5% CI 0.57–0.93, P=0.002). Median PFS was similar in the two treatment groups. However, there was a late separation of curves and a sensitivity analysis of patients who had not progressed or died at 6 months showed a longer PFS of 15.6 months with nivolumab compared to 11.7 months with everolimus (HR 0.64, 95% CI 0.47–0.88). The rate of grade 3–4 AEs was lower in nivolumab at 19% compared to everolimus at 37%.[30] Data on the activity of nivolumab monotherapy in the first-line treatment setting is limited. In a phase I clinical trial of nivolumab monotherapy in mRCC, there were 24 treatment-naïve patients who received nivolumab. In the first-line setting, ORR was 13% with 2 (8%) CR and 4% partial response (PR). Median overall survival was not reached in the first-line setting.[31]

Pembrolizumab is a PD-1 inhibitor which was recently studied in the first-line treatment setting in a single arm phase II study KEYNOTE-427. In the cohort of patients with clear cell mRCC at a database cutoff of March 2018, ORR was 38.2% with 2.7% CR and 35.5%

PR. Median PFS was 8.7 months and median OS had not been reached. For patients with PD-L1 positive disease with a combined positive score greater than or equal to 1, ORR was 50% with 6.5% CR and 43.5% PR. Grade 3–5 treatment-related AEs occurred in 21.8% of patients.[32]

Avelumab, an anti-PD-L1 antibody, was studied in a phase I, open-label, dose-escalation trial as a first- or second-line therapy for patients with advanced solid tumors. In the cohort of 82 patients with mRCC, 62 patients received avelumab as first-line treatment and 20 patients as second-line treatment. The ORR was 16.1% in first-line and 10% in second-line. The median PFS was 8.3 and 5.6 months, respectively. In the first-line setting, median follow-up was 14.2 months with median OS not estimable. In the second-line setting, median follow-up was 22.1 months with a median OS of 16.9 months.[33]

The cytotoxic T-lymphocyte-associated-antigen 4 inhibitor, ipilimumab, has been shown to improve ORR, PFS, and OS in combination with nivolumab in another immunogenic malignancy, advanced melanoma.[33,34] Ipilimumab was studied in combination with nivolumab compared to sunitinib in CheckMate 214, a phase III trial of patients with untreated, mRCC. In patients with intermediate/poor risk disease, the ORR of nivolumab plus ipilimumab (nivo/ipi) was 42% with 9% CR vs. 27% with 1% CR in the sunitinib arm. The PFS of nivo/ipi was 11.6 months compared to 8.4 months with sunitinib which was not statistically significant according to the predefined threshold (HR 0.82, P=0.03). Median OS was not reached with nivo/ipi compared to 26 months with sunitinib (HR 0.63, P<0.001). An exploratory analysis of favorable risk patients showed a higher ORR with sunitinib compared to nivo/ipi (52% vs. 29%; P<0.001) as well as a longer median PFS (25.1 vs. 15.3 months, HR 2.18, 99.1% CI 1.29–3.68, P<0.001). Grade 3–4 AEs occurred in 46% of patients on nivo/ipi and 63% of patients on sunitinib. 35% of patients on nivo/ipi experienced immune-related AEs requiring high-dose glucocorticoids, and there were 8 treatment related deaths compared to 4 in the sunitinib arm .[35] Immune-related AEs are unique side effects that can occur in any organ due to activation of the immune system targeting normal tissue. In some cases, immune-related AEs can become serious, and early diagnosis and treatment is critical. Nivo/ipi was approved for the treatment of intermediate or poor risk RCC patients in 2018. Nivo/ipi has not been compared to single agent ICI. In Europe, a phase III, double-blind, randomized clinical trial of nivolumab combined with ipilimumab versus nivolumab monotherapy for untreated patients with intermediate and poor risk mRCC is ongoing (EudraCT Number: 2018–004695-35; Sponsor Protocol Number: CA209–8Y8).

Combining VEGF inhibitors and ICIs

A major focus of current research is in combining VEGF inhibitors and ICIs. In addition to stimulating angiogenesis, preliminary data suggest that VEGF may contribute to cancer immune evasion. In the setting of high expression of VEGF, fewer and less differentiated antigen-presenting dendritic cells are found in tumor tissue and more immunosuppressive myeloid cells are seen in the peripheral blood.[36,37] Preclinical studies have shown an increase in T-cells within a tumor after treatment with VEGF blockade. In a phase I clinical study, after treatment with bevacizumab, there was an expected decrease in vascular markers

and in addition, there were increases in chemokines associated with T-cell migration, in tumor major histocompatibility complex class 1 protein expression, and in the presence of tumor specific T-cells.[38] After treatment with the combination of bevacizumab and atezolizumab, further increases in T-cells were seen. These findings suggest that the anti-VEGF treatment, bevacizumab, can trigger an antitumor immune response which may be further augmented with use of an ICI .[38]

The first reported phase III trial of treatment with a combination of VEGF inhibition and ICIs was the IMmotion151 study. This was a randomized clinical trial of atezolizumab, an anti-PD-L1 antibody, plus bevacizumab vs. sunitinib in patients with untreated, mRCC. Median PFS was significantly longer at 11.2 months for patients with PD-L1 positive tumors who received atezolizumab plus bevacizumab compared to 7.7 months for sunitinib (HR 0.74, 95% CI 0.57–0.96, P=0.0217). Results were similar for the overall population with a median PFS of 11.2 months for atezolizumab plus bevacizumab vs. 8.4 months for sunitinib (HR 0.83, 95% CI 0.70–0.97, descriptive P=0.0219). ORR for atezolizumab plus bevacizumab was 43% in the PD-L1 positive patients and 37% in the overall population compared to ORR with sunitinib of 35% and 33%, respectively. At a second interim analysis with median follow up of 24 months, 43% of patients in the atezolizumab plus bevacizumab group and 42% of patients in the sunitinib group had died (HR 0.93, 95% CI 0.76–1.14, P=0.475). Grade 3 or higher AEs were seen in 40% of patients treated with atezolizumab plus bevacizumab and 54% of patients treated with sunitinib. 12% of patients on atezolizumab plus bevacizumab and 8% of patients on sunitinib had to discontinue treatment due to AEs.[39]

The recently published KEYNOTE-426 study was a randomized phase III clinical trial of pembrolizumab plus axitinib vs. sunitinib in patients with untreated, advanced clear-cell RCC. Treatment with pembrolizumab plus axitinib resulted in a significantly longer median PFS of 15.1 months compared to 11.1 months with sunitinib (HR 0.69, 95% CI 0.57–0.84; P<0.001). OS was also significantly longer with 89.9% of patients who received pembrolizumab plus axitinib alive at 12 months compared to 78.3% of patients who received sunitinib (HR 0.53, 95% CI 0.38–0.74, P<0.0001). The ORR was higher at 59.3% with pembrolizumab plus axitinib vs. 35.7% with sunitinib (P<0.001). The CR rate was 5.8% with pembrolizumab plus axitinib compared to 1.9% with sunitinib. The median duration of response has not yet been reached in the pembrolizumab plus axitinib group and was 15.2 months in the sunitinib group. AEs were similar between treatment arms and grade 3 or higher attributed to treatment were 62.9% with pembrolizumab plus axitinib and 58.1% with sunitinib. 30.5% of patients discontinued treatment of either pembrolizumab or axitinib and 10.7% discontinued use of both medications due to AEs. 13.9% of patients taking sunitinib discontinued treatment due to AEs.[40] Pembrolizumab plus axitinib was FDA approved for the first-line treatment of mRCC on April 19, 2019.

The Javelin Renal 101 study was a randomized phase III clinical trial of avelumab plus axitinib vs. sunitinib in patients with untreated, advanced renal-cell carcinoma. Median PFS was significantly longer for patients with PD-L1 positive tumors who received avelumab plus axitinib at 13.8 months compared to sunitinib at 7.2 months (HR 0.61, 95% CI 0.47–0.79, P<0.001). In PD-L1 positive patients, death from any cause occurred in 13.7% with

avelumab plus axitinib and 15.2% with sunitinib (HR 0.81, 95% CI 0.53–1.28, P=0.38) in an interim analysis with follow up of 11.6 and 10.7 months, respectively. Further overall survival results are awaited. Longer median PFS was also seen in the overall treatment population at 13.8 months for avelumab plus axitinib vs. 8.4 months for sunitinib (HR 0.69, P<0.001). In the overall population, ORR was higher for avelumab plus axitinib at 51.4% compared to sunitinib at 25.7%. CR were seen in 3.4% of patients who received avelumab plus axitinib compared to 1.8% of patients treated with sunitinib. Grade 3 or higher AEs were similar and seen in 71.2% of patients in the avelumab plus axitinib group and 71.5% in the sunitinib group. Patients discontinued treatment due to AEs in 7.6% of the avelumab and axitinib group compared to 13.4% of the sunitinib group.[41] Avelumab in combination with axitinib was recently FDA approved for first-line treatment of patients with mRCC on May 14, 2019.

The recently reported trials of combination therapy with VEGF inhibition and ICIs show improved PFS when compared to prior standard-of-care first-line treatment, sunitinib. The improved OS with a HR of 0.53 in KEYNOTE-426 is promising. There are no single agent ICI treatment arms in these studies. Therefore, it is unclear how much additional clinical benefit the combination provides compared to immune checkpoint blockade alone and whether any additional benefit is additive or synergistic. Giving a combination of VEGF inhibition and ICI therapy first-line should improve outcomes as patients who would have responded to one treatment and not the other will now have a treatment response upfront. Whether the improved outcomes are due to capturing this treatment response in more patients or from the combination augmenting a response that would not have been seen with either agent alone in sequence is unknown. Other trials such as KEYNOTE-427 showed a 38% ORR, 2.7% CR, and 8.7-month PFS with PD-1 inhibition alone.[32] A phase II clinical trial, IMmotion150, compared treatment with atezolizumab alone or in combination with bevacizumab vs. sunitinib in treatment-naïve mRCC. The median PFS was 11.7 months with atezolizumab plus bevacizumab, 8.4 months with sunitinib, and 6.1 months with atezolizumab. ORR was 32% with 7% CR for atezolizumab plus bevacizumab, 29% with 5% CR for sunitinib, and 25% with 11% CR for atezolizumab.[42] These studies show a significant response from ICI alone and if or to what degree there is an augmentation of immune response from VEGF blockade is not yet understood. Currently, there are multiple other VEGF and ICI combination treatments being studied (, , , ,).

Sequencing VEGF inhibitors, ICIs, and combination therapies

There is limited data on outcomes after sequencing VEGF inhibitors, ICIs, and combination therapy. A retrospective review of 33 patients treated with nivo/ipi on Checkmate 214 who subsequently received second-line VEGF inhibitor treatment showed 36% PR, 39% stable disease, and 15% progressive disease.[43] After the start of second-line therapy, median PFS was 8 months.[43] This suggests that response rates to VEGF inhibition in the second-line setting after immunotherapy failure are similar to response rates seen in the first-line setting but larger, prospective trials are needed. A recently published abstract reported response rates to second-line VEGF TKI after first-line treatment with VEGF and PD-1 combination or nivo/ipi combination therapy. There was a trend toward higher ORR with second-line VEGF TKI after nivo/ipi at 45% vs. 13% after VEGF and PD-1 combination though this

was not statistically significant (P=0.07). No difference in time to treatment failure was found.[44] In a retrospective review of 30 patients who received nivo/ipi after failure of first-line immunotherapy there was 23% PR, 13% stable disease, and 53% progressive disease.[45] This suggests clinical activity of nivo/ipi after failure of other immunotherapy. These trials are limited due to the small patient populations and retrospective nature. Larger, prospective clinical trials are needed to determine optimal treatment sequencing such as the ongoing phase III clinical trial () of molecularly targeted agents followed by immunotherapy combination vs. immunotherapy combination followed by molecularly targeted agents in advanced melanoma. Historically, prospective sequencing trials have been challenging due to slow accrual and high drop-out rates.

Combining vs. sequencing VEGF inhibitors and ICIs

With the addition of many new treatment options in recent years and new combinations likely on the way, a method for identifying the best treatment approach for an individual patient is needed. Currently, preferred first-line treatment options for patients with clear-cell mRCC include a VEGF inhibitor, combination immunotherapy with nivo/ipi, or the recently approved VEGF inhibitor and ICI combinations. Second-line therapy includes the above treatment options as well as nivolumab monotherapy. Combination treatment with VEGF inhibitors and ICIs became a new therapeutic option with the recent FDA approvals of pembrolizumab plus axitinib as well as avelumab plus axitinib, making the choice of first-line treatment more complex. Further studies are needed to help guide the appropriate treatment choice for an individual patient.

As treatment regimens move toward combination therapy, it remains unclear which patients truly benefit from a combination of treatments vs. monotherapy. Clinical trials cannot be directly compared given differences in patient populations and trial methods. Table 1 shows the ORR, CR, PFS, and OS for the key trials in first- and second-line VEGF inhibitor and ICI monotherapy. There is limited data on the activity of single agent PD-1 inhibitors in the first-line setting and phase III trials of combination therapy did not use single agent ICI as a comparison arm, therefore, it is not known which patients benefit from the combination of nivo/ipi vs. anti-PD-1 monotherapy at this time. Table 2 shows the ORR, CR, PFS, and OS in first-line combination therapy trials in mRCC. A significant benefit to treatment with combination therapy is a 9% CR rate with nivo/ipi and a 9% and 5% CR rate with atezolizumab plus bevacizumab in PD-L1 positive patients and intention-to-treat population, respectively.[35,39] While VEGF inhibitor and ICI combinations showed improved ORR and PFS compared to sunitinib monotherapy, it remains to be determined if these benefits are additive or synergistic. If benefits are additive then treatments could be used in sequence as opposed to combination. If benefits are synergistic then in the absence of biomarkers or clinical data to guide treatment choice, the combination would be beneficial. While combination therapy risks exposing some patients who would have responded to monotherapy to unnecessary additional treatment with more side effects, sequencing therapy risks some patients not surviving long enough to have the opportunity to receive each therapy. Further studies are needed to help determine whether VEGF inhibitors and ICIs should be used as monotherapy in sequence, added as a combination therapy in the setting of progression on one agent, or used as combination therapy upfront. Large trials with multiple

arms that can accommodate new treatments as they are developed such as the STAMPEDE trial in prostate cancer would be helpful to guide decision making. Currently, there are several trials evaluating the sequence of single agent or combination therapy such as OMNIVORE () and PEDIGREE (). As new treatments are approved and become standard-of-care, the control arm of future clinical trials needs to be changed to reflect the current best treatment option. Outcomes of prospective clinical trials comparing these first-line treatment options with a focus on obtaining deep, durable clinical responses are needed.

The ideal treatment strategy would involve using biomarkers of an individual patient to predict the clinical response to specific treatment regimens in order to provide a personalized therapeutic approach. While there is significant research ongoing in this area, there are no predictive biomarkers currently validated for use in RCC.

Potential biomarkers being explored include tumor genetic mutations, expression levels of specific proteins, and characteristics of the tumor microenvironment. While higher expression of PD-L1 has been shown to correlate with clinical response in other malignancies,[46] results in RCC are less clear. Prior to the use of ICIs, PD-L1 could be used as a prognostic marker with higher levels correlated with worse OS in RCC.[47] As a biomarker predictive of treatment response, results are conflicting. In the CheckMate 214 study, patients with PD-L1 expression >1% had a higher ORR to nivo/ipi but even in the subset of patients with <1% expression, ORR and OS were still higher with nivo/ipi compared to sunitinib.[35] Despite having low PD-L1 expression, some patients have a durable response to immunotherapy.[47] In the IMmotion150 study, there was a trend toward improved PFS with atezolizumab plus bevacizumab vs. sunitinib in patients with PD-L1 positive tumors (HR, 0.64; 95% CI 0.38 to 1.08; P=0.095).[42] IMmotion150 explored other potential biomarkers in mRCC. Levels of gene expression associated with angiogenesis, immune response, and myeloid inflammation were associated with clinical outcome in a small number of patients. In patients treated with sunitinib, high levels of gene expression for angiogenesis were associated with improved ORR and PFS compared to low levels. In the setting of low levels of gene expression for angiogenesis, atezolizumab plus bevacizumab produced longer PFS than sunitinib. In patients treated with atezolizumab plus bevacizumab, high levels of gene expression for immune response were associated with improved ORR and PFS compared to low levels. With high levels of immune response gene expression, atezolizumab plus bevacizumab had improved PFS compared to sunitinib. Myeloid inflammation has been associated with immune suppression. In the setting of high levels of genes associated with myeloid inflammation, decreased PFS with atezolizumab and atezolizumab plus bevacizumab but not sunitinib was seen. In the setting of both high levels of genes associated with immune response and myeloid inflammation, atezolizumab plus bevacizumab had longer PFS than atezolizumab alone.[42] Although genomic instability has previously been associated with clinical response in other malignancies,[48,49] there was no association between tumor mutation burden, tumor neoantigen burden, small insertions and deletions, or frameshift mutation burden and gene expression associated with immune response or clinical benefit in any treatment group in IMmotion150.[42] The frequently mutated genes VHL and PBRM1 in RCC were also evaluated for association with treatment outcome. There was no association seen between VHL and PFS in any treatment group. In patients treated with sunitinib, improved PFS was seen in the setting of PBRM1 mutation

compared to wildtype. In the patients with PBRM1 mutations, both sunitinib and atezolizumab plus bevacizumab were associated with improved PFS compared to atezolizumab alone.[42] This is consistent with prior studies showing a correlation between PBRM1 mutation and improved PFS with VEGF inhibitors and ICIs.[50,51] Larger clinical trials investigating the use of potential biomarkers are needed.

Conclusion

The treatment paradigm of RCC has changed rapidly in the past decade and more changes are likely in the coming years. Newer treatments are yielding improved ORR, CR, PFS, and OS for patients. With treatments aimed at targeting the immune system, the goal of achieving a CR with durable treatment-free survival is currently possible in a subset of patients and further research is needed to identify and expand this patient population. Prospectively validated biomarkers are needed to help determine the best treatment strategy between VEGF inhibitors, ICI monotherapy, ICI combination therapy, or VEGF inhibitor and ICI combination therapy. Goals of treatment should focus on improving overall survival by selecting patients for therapy to avoid primary resistance. Ultimately, obtaining deep, durable responses is desirable. As the results of ongoing research become available, a consensus on preferred treatment sequencing is needed.

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Table 1:

Summary of key clinical trial results for monotherapy in RCC. Data are not intended for cross-trial comparisons. All trials include favorable, intermediate, and poor risk patients with the exception of CABOSUN trial which was intermediate/poor risk patients only. mo=months; NR= not reached

Study	Line of treatment	Treatment	ORR (%)	CR (%)	Median PFS (mo)	Median OS (mo)
[9,10]	First	Sunitinib	31	0	11	26.4
		IFN	6	0	5	21.8
COMPARZ[14]	First	Pazopanib	31	1	8.4	28.4
		Sunitinib	25	3	9.5	29.3
NCT00920816[21,22]	First	Axitinib	32	0	10.1	21.7
		Sorafenib	15	0	6.5	23.3
METEOR[15,16]	Second	Cabozantinib	21	0	7.4	21.4
		Everolimus	5	0	3.8	16.5
CABOSUN[17,18]	First	Cabozantinib	33	1	8.2	26.6
		Sunitinib	12	0	5.6	21.2
[23]	Second	Lenvatinib plus everolimus	43	1	14.6	25.5
		Lenvatinib	27	0	7.4	19.4
		Everolimus	6	0	5.5	15.4
Checkmate 025[30]	Second	Nivolumab	25	1	4.6	25.0
		Everolimus	5	<1	4.4	19.6
KEYNOTE-427[32]	First	Pembrolizumab	38.2	2.7	8.7	NR

Table 2:

Summary of clinical trial results for first-line combination therapy in RCC. Data are not intended for cross-trial comparisons. n= number of patients assigned to treatment arm; mo=months; f/u=follow up

Study	Treatment	n	ORR (%)	CR (%)	Median PFS (mo)	Median f/u at PFS (mo)	Patients Alive (%)	Median f/u for survival (mo)
Checkmate 214[35]	Nivolumab plus ipilimumab	550	39	9	12.4	25.2	83	12
	Sunitinib	546	32	1	12.3	25.2	77	12
IMmotion 151[39]	Atezolizumab plus bevacizumab	454	37	5	11.2	15	72.9	15
	Sunitinib	461	33	2	8.4	15	69.4	15
KEYNOTE-426[40]	Pembrolizumab plus axitinib	432	59.3	5.8	15.1	12.8	89.9	12.8
	Sunitinib	429	35.7	1.9	11.1	12.8	78.3	12.8
Javelin Renal 101[41]	Avelumab plus axitinib	442	51.4	3.4	13.8	10.8	85.7	12
	Sunitinib	444	25.7	1.8	8.4	8.6	83.1	11.5