Treatment Selection in Metastatic Renal Cell Carcinoma: More Confusion or a Path Forward?

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Abstract: Meaningful progress has been realized in the treatment of metastatic renal cell carcinoma with the recent approval of a number of new agents; more new agents are on the horizon. Despite the recent completion of many clinical trials that have changed or will change practice, many questions remain. In this manuscript, we highlight the most noteworthy developments in the first- and second-line treatment of metastatic renal cell carcinoma, as these are the areas of greatest change. We also emphasize ongoing trials and those areas that are most in need of study in order to move the field forward. Although more data are needed, exciting progress is being made.

Introduction

Clinical research has brought unprecedented excitement over the last decade for clinicians and their patients with metastatic renal cell carcinoma (mRCC). Seven new treatments have been introduced since 2005,[1] and more are on the horizon. The complexity of the National Comprehensive Cancer Network guidelines increases with each new therapy, as there are now 8 first-line options listed and numerous alternatives in subsequent lines of therapy.[2] Despite the existence of resources such as the National Comprehensive Cancer Network, the American Society of Clinical Oncology (ASCO), and continuing medical education programs, it can be difficult to keep up with the latest research. Furthermore, the recommendations are not clear-cut because of a lack of comparative effectiveness research, limited understanding of the underlying biology, and limited insights into real-world experiences. Clinicians are often left scratching their heads about the best way to treat a given patient.

Although few definitive answers exist when comparing agents such as immunotherapies (eg, interleukin 2 [IL-2]), the anti-vascular endothelial growth factor (anti-VEGF) monoclonal antibody bevacizumab (Avastin, Genentech), tyrosine kinase inhibitors (TKIs), and mammalian target of rapamycin (mTOR) inhibitors, we will highlight the most recent findings and discuss new therapies that are showing promise.

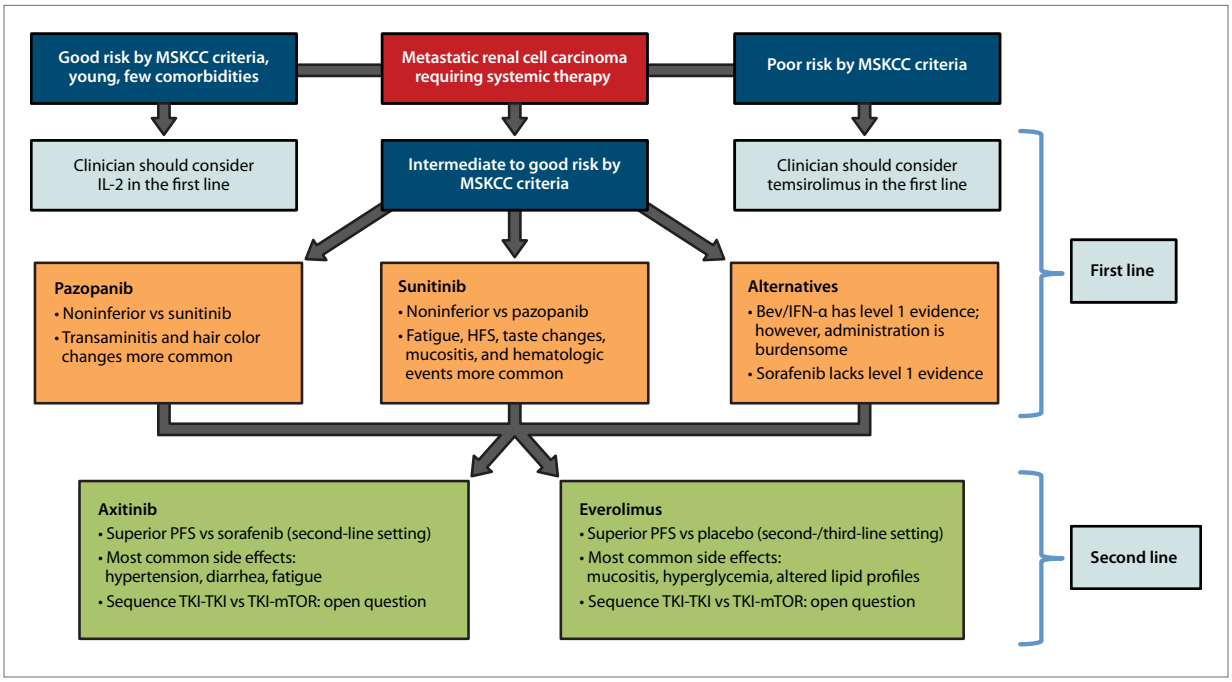

Figure. Proposed treatment algorithm for patients with metastatic renal cell carcinoma.

Bev, bevacizumab; HFS, hand-foot syndrome; IFN-α, interferon alfa; IL-2, interleukin 2; MSKCC, Memorial Sloan-Kettering Cancer Center; mTOR, mammalian target of rapamycin; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

Standard of Care in First-Line Therapy

Evidence in the first-line setting is evolving quickly, which is helping to inform the standard of care. While there continues to be a role for high-dose IL-2 in younger patients who have an excellent performance status and few comorbidities, as well as for temsirolimus (Torisel, Wyeth) in patients who are considered poor risk by Memorial Sloan-Kettering Cancer Center (MSKCC) criteria, we will focus on the role of TKIs in good- to intermediate-risk patients. This is the area of greatest change, and prior discussions already outline approaches to poor-risk patients and the balance of risks and benefits for treatment with IL-2. Our approach is outlined in the figure.

Sunitinib vs Pazopanib

For good- to intermediate-risk mRCC patients with clear cell histology, the decision at present primarily comes down to a choice between sunitinib (Sutent, Pfizer) and pazopanib (Votrient, GlaxoSmithKline). Sunitinib was approved by the US Food and Drug Administration (FDA) in 2006 for the treatment of mRCC. As shown in the table, which outlines the landmark clinical trials, patients treated with sunitinib were found to have a significantly prolonged median progression-free survival (PFS) interval of 11 months vs 5 months for those treated with interferon alfa (IFN-α) (hazard ratio [HR], 0.42 [95% CI, 0.32-0.54]).[3] All-grade adverse events (AEs) occurring in more than 20% of patients included diarrhea, fatigue, nausea/vomiting, stomatitis/mucosal inflammation, hypertension, and hand-foot syndrome (HFS). An update in 2009 demonstrated a median overall survival (OS) that numerically favored sunitinib at 26.4 vs 21.8 months with IFN-α (HR, 0.821 [95% CI, 0.673-1.001]) but did not meet statistical significance by prespecified criteria.[4] This established sunitinib as the standard of care at the time for good- to intermediate-risk patients.

Pazopanib was subsequently approved in 2009, based on a phase 3 trial of mRCC patients who were relatively evenly divided between those who were treatment naive and those who had received 1 prior cytokine-based therapy. PFS among the treatment-naive patients was 11.1 months with pazopanib vs 2.8 months with placebo (HR, 0.40 [95% CI, 0.27-0.60]).[5] In cytokine-refractory patients, PFS was 7.4 vs 4.2 months (HR, 0.54 [95% CI, 0.35-0.84]). All-grade AEs occurring in more than 20% of patients included diarrhea, hypertension, hair color changes, nausea/vomiting, and anorexia. OS results were published in April of 2013 and showed a nonsignificant improvement of 22.9 vs 20.5 months (HR, 0.91 [95% CI, 0.71-1.16]).[6] Per the authors, "extensive crossover from placebo to pazopanib confounded final OS analysis."

As there are limitations to cross-trial comparisons, head to head randomized controlled trials comparing sunitinib with pazopanib in the first-line setting were needed

Table. Summary of Landmark Trials for Agents in First-Line Treatment of mRCC for Favorable/Intermediate-Risk Patients With Clear Cell Disease

Agents	No. of Patients	Median PFS, mo	Median OS, mo
Sunitinib vs IFN-α[3,4]	750	11 vs 5[a]	26.4 vs 21.8
Pazopanib vs placebo[5,6]	233	11.1 vs 2.8[a]	22.9 vs 20.5
Bev + IFN-α vs IFN-α [10,11]	649	10.2 vs 5.4[a]	23.3 vs 21.3
Bev + IFN-α vs IFN-α [12,13]	732	8.5 vs 5.2[a]	18.3 vs 17.4
Sorafenib vs IFN-α[16, b, c]	189	5.7 vs 5.6	Not reported
Axitinib vs sorafenib[17]	288	10.1 vs 6.5	Pending
Tivozanib vs sorafenib[23]	362	11.9 vs 9.1[a]	28.8 vs 29.3

Bev, bevacizumab; IFN- α, interferon alfa; mRCC, metastatic renal cell carcinoma; No., number; OS, overall survival; PFS, progression-free survival.

[a] Achieved statistical significance.

[b] Randomized phase 2 study.

[c] All trials phase 3 trials except sorafenib vs IFN-α.

to build upon the landmark trial data and inform clinicians regarding the selection of patients for one treatment vs the other. In 2012, two GlaxoSmithKline-sponsored randomized controlled trials comparing pazopanib with sunitinib were presented to help address this need,[7,8] one of which has now been published.[9] Both studies have limitations. In PISCES (Patient Preference Study of Pazopanib Versus Sunitinib in Advanced or Metastatic Kidney Cancer), which was presented at the ASCO annual meeting in 2012, a novel crossover design was used to evaluate patient preference for pazopanib vs sunitinib.[7] One hundred sixty-eight patients were randomly assigned to a 10-week course of 1 of the 2 agents, followed by a 2-week washout, and crossover to the other agent for an additional 10 weeks. Patients were surveyed prior to unblinding at 22 weeks regarding their preferred regimen and, among 114 patients who received at least 1 treatment with each agent, 70% preferred pazopanib, 22% preferred sunitinib, and 8% reported no preference. The most common reasons cited for preference of pazopanib were superior quality of life (QOL) and less fatigue. The study has been criticized for its small sample size, the censoring of early progressors, and the timing of the QOL assessment, which occurred immediately prior to the rest period for those receiving sunitinib, often when treatment-related side effects are at their worst. Regarding this final point, ignoring the effect that intermittent dosing has on QOL (and only assessing during peak toxicity periods) was a decision that leaves us with an incomplete picture of the true tolerance and longitudinal preferences of patients. If compared following the 2 weeks off therapy with sunitinib, the results would likely have been different.

COMPARZ (Comparing the Efficacy, Safety, and Tolerability of Pazopanib vs Sunitinib) was a noninferiority trial that compared pazopanib with sunitinib as first-line therapy in 1100 patients. The results of this trial were presented at the European Society for Medical Oncology (ESMO) annual meeting in 2012 and were recently published in the *New England Journal of Medicine*.[8,9] While the PFS trend favored sunitinib at 9.5 vs 8.4 months (HR, 1.047 [95% CI, 0.90-1.22]), it did not exceed the prespecified noninferiority boundary of 1.25 for the upper limit of the 95% CI and thus met the primary endpoint definition of noninferiority. Safety was similar for the 2 agents in terms of dose interruptions (44% for pazopanib vs 49% for sunitinib), dose reductions (44% vs 51%), and dose discontinuations for AEs (24% vs 20%). The QOL findings favored pazopanib, although many of the differences were small in absolute terms. Fatigue, HFS, taste alternations, and thrombocytopenia occurred more commonly in the sunitinib arm, while transaminitis and hair color changes were more common with pazopanib. Similarly to the PISCES trial, this trial had incomplete assessment of QOL throughout the intermittent treatment cycle of sunitinib that created a biased representation of tolerance for this agent. While the hope was that these trials would lay to rest discussions about the relative efficacy and toxicity of these agents, they did not. The trials demonstrated the noninferiority of pazopanib, at least by this trial's prespecified criteria, and nuanced differences in the patient experience of each drug.

The final word when comparing these agents for good- to intermediate-risk patients is still unclear, as shown in the figure. Publication of the PISCES data is eagerly awaited, as it will provide greater insight into the relative patient experience and nuances of the trial design and conduct. At present, some providers continue to use sunitinib owing to their experience with it (eg, dose modifications, AE management), evidence of noninferior efficacy vs pazopanib, and easy approval of its use owing to its long-standing inclusion on formularies. Other clinicians have taken the COMPARZ data and the preliminary PISCES

data on patient preference and QOL metrics to heart and, reassured by the noninferiority data, have transitioned to pazopanib as first-line therapy. In the end, either of these approaches is valid as long as one takes into account the relative toxicity profiles when making the decision, such as significantly increased risk of grade 3/4 liver toxicity for pazopanib-treated patients (alanine aminotransferase/aspartate aminotransferase increases in 15%/11% with pazopanib vs 4%/3% with sunitinib) and the significantly increased risk of grade 3/4 fatigue for sunitinib-treated patients (10% with pazopanib vs 17% with sunitinib).[9]

Alternative Agents

Other agents can be considered in the first line for good- to intermediate-risk patients beyond IL-2, sunitinib, and pazopanib; however, none have compelling evidence supporting their preferential use in routine practice. The combination of IFN-α and bevacizumab[10-13] is an acceptable alternative, with level 1 evidence supporting its use; however, no data exist as to its superiority over other agents and the intensity of administration complicates the picture. In the AVOREN (Phase III Trial of Bevacizumab Plus Interferon Alfa-2a in Patients With Metastatic Renal Cell Carcinoma) trial,[10,11] there was a significant increase in PFS of 10.2 months with bevacizumab plus IFN-α vs 5.4 months with IFN-α alone (HR, 0.63 [95% CI, 0.45-0.72]), along with a significantly higher overall response rate (31% vs 13%). A similar comparison between the 2 regimens in the CALGB 90206 (Cancer and Leukemia Group B 90206) trial led to the same conclusion.[12,13] Neither trial found an OS benefit with this combination, and the burden on patients was substantial, with bevacizumab requiring intravenous administration every 2 weeks and IFN-α requiring subcutaneous administration 3 times per week.

Sorafenib (Nexavar, Bayer/Onyx) does not have level 1 evidence, as its initial approval was based on the phase 3 TARGET (Treatment Approaches in Renal Cancer Global Evaluation Trial) study in cytokine-refractory patients.[14,15] In this trial, OS was not significantly longer for sorafenib than for placebo (17.8 vs 15.2 months; HR, 0.88 [95% CI, 0.74-1.04]). A separate randomized phase 2 trial among treatment-naive patients did not show a PFS benefit with sorafenib compared with IFN-α.[16] Axitinib (Inlyta, Pfizer) is another TKI of interest. In a phase 3 trial of 288 treatment-naive patients, PFS was longer for axitinib than for sorafenib (10.1 vs 6.5 months; HR, 0.767 [95% CI, 0.585-1.053]) and there was an objective response rate of 32% vs 14%; however, the study did not meet its statistical endpoint for PFS and the OS data are not yet mature.[17] As such, among the agents available today, sunitinib and pazopanib have the most compelling evidence outside of clinical trials for good- to intermediate-risk patients who are not IL-2 candidates. There are ongoing trials in the first line such as the SWITCH (Sequential Study to Treat Renal Cell Carcinoma) trial, which compares sequential therapy with sorafenib followed by sunitinib vs sunitinib followed by sorafenib, which will further elucidate therapy choices.[18] This trial may help answer the question of whether it is best to lead with a more- or less-potent VEGF receptor (VEGFR) TKI.

Additional Treatment Considerations in the First Line

A number of additional questions come up regularly. Does it make sense to use an mTOR inhibitor up front in this patient population, or to wait and use it in the second line or beyond? Are combinations potentially superior to single-agent regimens? Are there truly class differences, or are all TKIs alike? New evidence is helping to advance our understanding of many of these issues.

The recently presented RECORD-3 (Efficacy and Safety Comparison of RAD001 Versus Sunitinib in the First-line and Second-line Treatment of Patients With Metastatic Renal Cell Carcinoma) trial was designed to help answer the question of agent sequence. In this randomized, open-label, phase 2 trial of 471 treatment-naive mRCC patients, 233 patients received sunitinib until disease progression followed by everolimus (Afinitor, Novartis), while the remaining 238 patients started with everolimus and switched to sunitinib at progression.[19] Interesting results were presented at the ASCO annual meeting in 2013. First, leading with sunitinib resulted in superior PFS of 10.7 months vs 7.9 months with everolimus (HR, 1.43 [95% CI, 1.15-1.77]), with an OS trend in favor of sunitinib at 32.0 months for the sunitinib arm vs 22.4 months for the everolimus arm (HR 1.24 [95% CI, 0.94-1.64]); however, the data are limited owing to a high percentage of censored patients who withdrew from the study following progression after first-line therapy. Specifically, only 53.7% of patients who started with everolimus made it to second-line therapy with sunitinib and only 51.6% of sunitinib patients made it to everolimus on the trial. It is unclear how many of these patients received second-line therapy outside of this trial, but it highlights the challenges of sequential therapy trials and why the initial agent choice may be critical, as patients may not make it to subsequent treatments.

There has been a great deal of interest in robust combinations. In light of the varying mechanisms and relative impact of the classes of agents, it is logical that combination therapies would be promising. Unfortunately, the data have not been favorable to date. For example, in the BEST (Bevacizumab, Sorafenib Tosylate, and Temsirolimus in Treating Patients With Metastatic Kidney Cancer) trial, presented at the ASCO Genitourinary Cancers

Symposium in 2013, bevacizumab alone was compared with bevacizumab plus temsirolimus, bevacizumab plus sorafenib, and sorafenib plus temsirolimus.[20] Despite the limited efficacy of single-agent therapy with bevacizumab, none of the agents showed significant superiority, with a PFS of 8.7 months for bevacizumab as compared with 7.3, 11.3, and 7.7 months, respectively, for the combinations. As would be expected, toxicities were higher in the combination arms. This once again demonstrates the limited role of combination therapies in mRCC, exhibiting results similar to those seen elsewhere such as in the TORAVA (Temsirolimus and Bevacizumab, or Sunitinib, or Interferon Alfa and Bevacizumab for Patients With Advanced Renal Cell Carcinoma) and INTORACT (Randomized Phase IIIb Trial of Temsirolimus and Bevacizumab versus Interferon and Bevacizumab in Metastatic Renal Cell Carcinoma) studies.[21,22]

While not fully understood, there are variations in efficacy and toxicity for agents within the same classes. The recent tivozanib story helps to highlight these differences. Briefly, Aveo Pharmaceuticals was denied approval for tivozanib by the FDA despite meeting the primary endpoint of its phase 3 trial, TIVO-1 (Tivozanib Versus Sorafenib in First Line Advanced RCC). Although the trial demonstrated a PFS advantage for tivozanib vs sorafenib of 11.9 vs 9.1 months (HR, 0.797 [95% CI, 0.639-0.993]),[23] a trend toward a negative survival effect was seen, with a median OS benefit of 28.8 months for tivozanib vs 29.3 months for sorafenib (HR, 1.245 [95% CI, 0.954-1.624]).[24] Second-line treatment was imbalanced in this study, which provided crossover to the tivozanib arm for the sorafenib-treated patients but not vice versa. Because the HR point estimate suggested worse survival with tivozanib, differential crossover issues notwithstanding, the Oncologic Drugs Advisory Committee for the FDA recommended against approval owing to the perceived unfavorable risk-benefit profile.

Still, some elements of this trial are instructive. As with other direct comparisons of TKIs, the toxicity profiles were quite different, with wide variations in rates of all-grade AEs such as hypertension (46% with tivozanib vs 36% with sorafenib), HFS (13% vs 54%), and diarrhea (22% vs 32%), among others.[23] The rate of dose reductions and discontinuations also varied across agents. In TIVO-1, dose reductions and discontinuations due to AEs were 12% and 4% with tivozanib, respectively, compared with 43% and 5% with sorafenib. In COMPARZ, dose reductions and discontinuations due to AEs occurred in 44% and 24% of patients treated with pazopanib, compared with 51% and 20% with sunitinib.[9] While caveats regarding cross-trial comparisons apply, the relative differences seen in phase 3 trials demonstrate real in-class differential efficacy and toxicity profiles among VEGFR TKIs.

Second-Line Therapies

The role of various agents in the second line can be equally complex. After failure with a TKI, one could logically assume that use of an alternative class of agent, such as an mTOR inhibitor, should be the next choice. However, this is not necessarily consistent with the available evidence.

The INTORSECT (Investigating Torisel As Second-Line Therapy) trial raised questions regarding the role of mTOR inhibition in the treatment of mRCC. In this randomized, open-label, phase 3 trial, 512 patients previously treated with sunitinib received second-line treatment with either temsirolimus (TKI-mTOR sequence) or sorafenib (TKI-TKI sequence).[25] Unlike many of the other trials, it allowed patients with non–clear cell histologies to enroll. PFS was 4.3 months in the TKI-mTOR group and 3.9 months among TKI-TKI recipients (HR, 0.87 [95% CI, 0.71-1.07]). However, OS significantly favored TKI-TKI with a median OS for TKI-mTOR of 12.3 months vs 16.6 months for TKI-TKI (HR, 1.31 [95% CI, 1.05-1.63]). The OS findings are concerning, but raise more questions than they answer. One aspect that has drawn attention is that the OS benefit for TKI-TKI recipients was more distinct in those who had a prolonged response—greater than 6 months—to first-line sunitinib. This needs to be studied prospectively, but it is likely that a nuanced approach, hopefully based on biomarkers, is needed. The breakdown between PFS and OS is also noteworthy and calls into question whether PFS, which has been the regulatory endpoint used for approval of all the targeted agents except one, remains a valid endpoint on which to base drug approval.

The PFS findings in INTORSECT may be juxtaposed against those seen in the RECORD-1 trial, comparing everolimus with placebo among those whose disease progressed after treatment with either 1 or 2 TKIs (sorafenib and/or sunitinib).[26-28] PFS with everolimus was 4.9 months vs 1.9 months with placebo (HR, 0.22 [95% CI, 0.09-0.55]) in this setting. No OS benefit was seen with its use, but the rate of crossover from placebo to everolimus was high, and most of those who responded had stable disease. This trial demonstrates that there does appear to be a benefit of mTOR inhibition in TKI-refractory patients, but the question remains as to whether there is an impact on OS and whether use of mTOR inhibitors should be reserved for later lines of therapy (ie, third line and beyond).

The AXIS (Comparative Effectiveness of Axitinib Versus Sorafenib in Advanced Renal Cell Carcinoma) trial, a phase 3 comparison of axitinib to sorafenib in the second line, has suggested that axitinib is the preferred TKI to be used in the second line.[29,30] In this trial, 723 patients who had previously received 1 agent (54% sunitinib, 35% a cytokine, 8% bevacizumab, and 3% temsirolimus) were randomly assigned to receive either

axitinib or sorafenib in the second line. Although there was no difference in OS, axitinib recipients had a significantly higher PFS (8.3 vs 5.7 months; HR, 0.66 [95% CI, 0.55-0.78]), with the most dramatic findings when it was used after a cytokine (12.2 vs 8.2 months; HR, 0.51 [95% CI, 0.37-0.68]) or sunitinib (6.5 vs 4.4 months; HR, 0.72 [95% CI, 0.57-0.90]). The rates and types of AEs differed; the most common AEs in people taking axitinib were hypertension (17%), diarrhea (11%), and fatigue (10%), and people taking sorafenib were most likely to experience HFS (17%), hypertension (12%), and diarrhea (8%).

It is tempting to extrapolate the results of INTORSECT, RECORD-1, and AXIS to seemingly similar treatment settings; however, there are a number of limitations to performing such an analysis. Taking into account the fact that all mTOR inhibitors are unlikely to be equivalent, comparisons between the temsirolimus results in INTORSECT and the everolimus results in RECORD-1 are misleading. And while sorafenib is the comparator in INTORSECT and AXIS, it also true that the study designs were quite different and no OS advantage was documented, making sorafenib a viable option. All of that being said, further study of TKIs vs everolimus in the second-line setting is needed with prospective clinical trials.

Third-Line Therapies

The RECORD-1 trial provides evidence for the effectiveness of mTOR inhibition with everolimus in the third-line setting.[26] While all patients' disease had progressed with at least 1 prior VEGFR TKI, most had received a systemic therapy in addition to a VEGFR TKI and 26% of patients had received both sunitinib and sorafenib. Among those who had received 2 prior VEGFR TKIs, the median PFS was 4.0 months with everolimus vs 1.8 months with placebo (HR, 0.32 [95% CI, 0.19-0.54]).

The GOLD (Global Oncologic Leanings for Dovitinib) trial, recently reported by Motzer and colleagues at ESMO 2013, demonstrated the continued benefit of VEGF inhibition after both anti-VEGF therapy and mTOR inhibition.[31] Following both of these therapies, 570 patients were randomly assigned to receive either sorafenib at 400 mg twice a day or dovitinib at 500 mg daily, on a 5 days on, 2 days off schedule. Dovitinib is a TKI against fibroblast growth factor receptors 1, 2, and 3 in addition to VEGFRs, platelet-derived growth factor receptors, and c-Kit. Median PFS with dovitinib was similar to median PFS with sorafenib, at 3.7 vs 3.6 months (HR, 0.86 [95% CI, 0.72-1.04]), as was median OS, at 11.1 vs 11.0 months (HR, 0.96 [95% CI, 0.75-1.22]). Although this was a negative study that did not demonstrate the benefit of fibroblast growth factor receptor inhibition in addition to VEGF-targeted therapy, it establishes benchmarks for PFS and OS by which to design future trials in this setting.

Future Directions

The field of mRCC will evolve in the coming years. First, classes of agents such as VEGFR TKIs, and possibly mTOR inhibitors, will continue to grow, further muddying the waters about the role of individual treatments. Second, new classes of agents will be introduced, such as novel immunotherapies, that will expand the treatment armamentarium. Third, biomarkers and other insights into disease biology will allow more-nuanced patient selection for various treatments. Finally, real-world data will be used to generate more-robust comparative effectiveness evidence. It is the job of the research community to ensure that these changes lead to an improvement in the care paradigm instead of driving still greater uncertainty.

Ongoing Trials

As new agents continue to be introduced, especially within the same class, we need to figure out how to better target therapies to patients most likely to respond. Otherwise, additional TKIs and mTOR inhibitors are likely to result in diminishing returns. Regardless, many continue to progress through development. Exelixis has initiated a phase 3 trial of cabozantinib (Cometriq, Exelixis), a dual Met and VEGFR2 TKI, comparing it with everolimus in mRCC patients who have failed to respond to 1 or 2 TKIs (METEOR; A Study of Cabozantinib [XL184] vs Everolimus in Subjects With Metastatic Renal Cell Carcinoma).[32,33] The Alliance for Clinical Trials in Oncology cooperative group has also opened a randomized phase 2 trial with the same agent, comparing it with sunitinib in treatment-naive patients.[34] The agent already has orphan drug approval for the treatment of progressive metastatic medullary thyroid cancer. As discussed previously, there are variations in efficacy and toxicity within the TKIs, which we might expect with these multitargeted agents as well. Unfortunately, the current empirical study designs are unlikely to add to our understanding of patient selection and are instead likely to demonstrate a relatively small incremental clinical benefit in an unselected patient population.

Entirely new classes of agents are also being developed for the treatment of mRCC. As an example, while novel immunotherapies have gained traction in areas such as prostate cancer and melanoma, their introduction into mRCC treatment has been limited to date. Argos Therapeutics is sponsoring the ADAPT (Phase 3 Trial of Autologous Dendritic Cell Immunotherapy Plus Standard Treatment of Advanced Renal Cell Carcinoma) trial in which an autologous dendritic cell immunotherapy (AGS-003) is being tested among 450 patients with newly

diagnosed mRCC in combination with the standard of care.[35] If approved in this setting, it would likely be the first combination therapy for mRCC to gain wide acceptance. The hope is that the increased cost and complexity would be outweighed by the benefit to patients.

Agents targeting programmed cell death 1 (PD-1) and programmed cell death 1 ligand 1 (PD-L1) also show promise. PD-1 is a T-cell coinhibitory receptor that regulates effector T-cell activity. Upregulation is associated with poor outcomes and is promising as a prognostic factor.[36] PD-L1, also known as B7-H1, binds to its receptor (PD-1) on immune cells such as activated T cells. Bristol-Meyers Squibb is developing nivolumab (BMS-936558), an anti–PD-1 antibody, and other companies including GlaxoSmithKline, Merck, and Genentech/Roche have agents in development. Early-phase studies with multiple solid tumor types have shown promise. For example, a phase 1 dose-escalation study of nivolumab included 33 patients with mRCC.[37] Of these, 9 experienced major tumor response and 9 had stable disease for at least 24 weeks. The agent is presently in phase 3 testing across a number of cancer types, including a trial in mRCC comparing it with everolimus in TKI-refractory patients[38] and an early-phase trial in combination with sunitinib, pazopanib, or ipilumumab (Yervoy, Bristol-Myers Squibb).[39] Pending the results of these ongoing trials, testing nivolumab in the first-line setting also seems reasonable.

Finally, there is evidence that with mTOR complex 1 (mTORC1) inhibition by everolimus or temsirolimus, a compensatory increase in phosphatidylinositol 3-kinase and Akt leads to upregulation of mTORC1 and further Akt and hypoxia-inducible factor (HIF) activation. Therefore, a strategy of inhibiting mTORC1 and HIF-2α with compounds such as BEZ-235 has been proposed as a way to overcome resistance to mTOR inhibition.[40] A phase 1b/2 study of BEZ-235 in mRCC[41] and a BEZ-235 plus everolimus dose-finding study in solid tumors[42] are under way. The armamentarium will only grow from here.

Biomarkers

As the number of agents continues to increase, both within a given class and across classes, it becomes imperative that we understand how best to utilize the therapies. The trials referenced in this review break down mRCC patient cohorts by MSKCC risk criteria and long-standing pathologic subtypes (clear cell vs non–clear cell). Some incremental changes have been seen, such as the introduction of the Heng criteria as an update to the MSKCC criteria for patients treated with a VEGFR TKI. In the Heng criteria,[43] the prognostic consideration of whether a patient had a prior nephrectomy was changed to evaluate whether the time from diagnosis to therapy was less than 1 year. Thrombophilia and neutrophilia were also added to the assessment, while serum lactate dehydrogenase (LDH) was dropped (owing to inconsistent measurement of LDH in the data set). These types of changes, while critical, have been limited in scope and the reality is that the tumor biology is far more complex than is presently understood. An analysis by Gerlinger and coauthors published in the *New England Journal of Medicine* in 2012 demonstrated that our approach to the analysis of biopsy specimens likely vastly underestimates the heterogeneity present in a single tumor as well as the associated metastases.[44]

As a first step, the development of more robust molecular biomarkers is needed in order to better reflect this heterogeneity. Nixon and colleagues reported on the predictive abilities of IL-6 and hepatocyte growth factor at the 2013 annual ASCO meeting.[45] In their study population, high-risk vs low-risk scores based on values of IL-6 and hepatocyte growth factor predicted median OS of 10 vs 32 months in a validation set. As another example of this type of work, Armstrong and colleagues published evidence in 2012 that serum LDH predicts an OS benefit in patients treated with mTOR inhibitors.[46] They found that an LDH level above the upper limit of normal predicted benefit from temsirolimus compared with IFN-α (6.9 vs 4.2 months; $P<.002$) while a normal LDH level did not predict benefit (11.7 vs 10.4 months; $P=.514$).

Numerous molecular markers have been studied and show promise, such as the expression of carbonic anhydrase IX,[47] the proliferation marker Ki67,[47] HIF-1,[48] and the U3 small nucleolar ribonucleoprotein IMP3 (insulin-like growth factor II mRNA binding protein 3)[49]; however, none has an established use to date beyond what can be inferred from traditional staging. Molecular genetic classification has demonstrated *PBMR1* and *BAP1* mutations to be important, and largely mutually exclusive, alterations.[50-52] Rathmell and colleagues used gene expression microarray data to show that RCC can be divided into 2 subtypes, designated clear cell type A (ccA) and type B (ccB), with different survival rates.[53] The Cancer Genome Atlas has also provided potential markers.[54] These findings, while promising, just scratch the surface of both what is possible and what is needed as the field continues to evolve. In addition to these exploratory studies, the results need to be validated in prospective trials through the cooperative groups and elsewhere in order to generate reliable and timely data.

Real-World Data

Finally, the reliance on randomized clinical trials to inform treatment decisions may be untenable owing to long acquisition times for clinical trial data. As the options and complexity in the field increase exponentially, we will not always have randomized trials to answer the critical questions owing to the associated time, cost, complexity, and

limitations to enrollment. The field is changing rapidly enough that once trials are reported, they may have limited relevance. In addition, the treatment permutations are becoming increasingly complex as the treatment options grow. Choosing pazopanib or sunitinib as first-line therapy and axitinib or everolimus as second-line therapy as outlined in this manuscript results in 4 potential sequences. If one includes temsirolimus, everolimus, and bevacizumab/IFN-α as first-line options, it becomes still more complex. RECORD-3 tried to address a limited aspect of the sequencing concern, but it took quite a while to complete, and similar trials are not feasible as a long-term solution for all the available questions, including: How many lines of therapy are appropriate? Does axitinib work as well in the fourth line as it does in the second line? Outside of tightly controlled trial settings, what AEs do patients truly experience and how are they best managed? Well-designed registries can help fill the knowledge gaps. As an example, we are beginning to publish results from retrospective real-world data in partnership with Acorn Research to shed light on treatment patterns and outcomes in the community.[55,56] It is critical to develop a more robust infrastructure that allows prospective data collection so that rapid-learning health care systems can be operationalized.

Conclusion

While the field of mRCC has seen great advances in the last decade, there is still work to be done. Among patients with good- or intermediate-risk mRCC with clear cell histology, the roles of sunitinib and pazopanib are becoming increasingly defined. COMPARZ and PISCES helped to elucidate differences between the 2 agents and their respective roles; however, both are commonly used as first-line therapies at this time and a focus on their differing toxicity profiles is helpful. The evidence for the use of sorafenib and axitinib in the first line is not as clear, based on the lack of convincing phase 3 study data. Although there is evidence for axitinib in the second line, the optimal use of everolimus and other mTOR inhibitors in treatment-refractory patients is not well understood. Recent abstracts on studies such as RECORD-3 provide evidence for the sequential use of TKIs, and abstracts on studies such as BEST continue to call into question the role of combinations. TIVO-1, as with many other TKI comparisons, highlights the differences among agents even within the same class.

Two themes are important moving forward. As new agents continue to be introduced, we must move beyond high-level, primarily clinical classifications such as MSKCC and Heng criteria, to truly understand the underlying biology. Molecular classifications and biomarkers are urgently needed. Until these are validated for clinical use, we cannot hope to maximize the value of these agents to our patients. We must also use real-world data to understand the patient experience in routine clinical practice, instead of using data only from tightly controlled clinical trial settings. The data being generated in practice (a "real-world" setting), if of adequate quality, can help to answer many of the questions that cannot, and will not, be addressed in clinical trials owing to cost, complexity, and accrual issues.

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