

Targeted therapies for renal cell carcinoma: understanding their impact on survival

Sumanta Kumar Pal · Robert A. Figlin

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Abstract Within the past 5 years, the United States Food and Drug Administration have approved six targeted agents for the treatment of metastatic renal cell carcinoma (mRCC). While this offers great potential to patients afflicted with this disease, oncologists are faced with the challenge of applying each agent in the appropriate clinical setting. Doing so requires an intricate understanding of the pivotal trials evaluating these agents. Herein, we have provided a detailed analysis of the study design employed in these trials. Use of appropriate comparator arms for targeted therapies (i.e., interferon- α or placebo) is addressed. Furthermore, we discuss the relative merits of using progression-free survival (PFS) or overall survival (OS) as a primary endpoint—importantly, the two endpoints may not be precisely correlated. Strategies to appropriately interpret OS in the context of post-study therapies and crossover designs are described. Ultimately, head-to-head trials comparing targeted therapies are necessary to resolve clinical equipoise. Several ongoing efforts juxtaposing the approved agents for mRCC are discussed.

Keywords Targeted therapy · Survival · Metastatic renal cell carcinoma · Sunitinib · Bevacizumab · Sorafenib · Temsirolimus · Everolimus · Axitinib

Introduction

To the patient with newly diagnosed metastatic renal cell carcinoma (mRCC), the wealth of novel targeted therapies at the clinician's disposal represents a greater opportunity for clinical benefit. To the clinician, however, the numerous options may lead to clinical equipoise. The reasons for this are multifold—firstly, the targeted therapies applicable to mRCC share a number of mechanistic features. Of the six approved agents, four (sunitinib, sorafenib, pazopanib, and bevacizumab) directly inhibit vascular endothelial growth factor (VEGF)-mediated signaling, and two (everolimus and temsirolimus) inhibit the mammalian target of rapamycin (mTOR) downstream [1]. Secondly, outside of mechanistic similarities, it is challenging to discern the relative efficacy of these agents on the basis of available clinical trial data. These trials are varied in their use of study endpoints (i.e., overall survival [OS], or progression-free survival [PFS]), and in the patient population assessed (i.e., treatment-naïve or treatment-refractory, clear cell carcinoma or renal cell carcinoma of any histology, varying degrees of good, intermediate, or poor prognosis patients, and varying status of the primary tumor). Algorithms such as that proposed in Table 1 provide a useful tool to the clinician. However, even from such schema, it is evident that common clinical scenarios (i.e., first-line therapy of good- or intermediate-risk patients with clear cell mRCC) can be managed with one of several appropriate strategies. Unquestionably, the goal of using each of these therapies is to prolong meaningful survival for patients. Herein, we explore the impact of targeted therapies as they pertain to this goal. Furthermore, we attempt to provide the clinician with appropriate background with which to interpret the relative benefit of each agent in a now crowded therapeutic landscape.

S. K. Pal (✉) · R. A. Figlin
Department of Medical Oncology & Experimental Therapeutics,
City of Hope Comprehensive Cancer Center,
Duarte, CA 91010, USA
e-mail: spal@coh.org

R. A. Figlin
e-mail: rfiglin@coh.org

Table 1 A proposed algorithm for management of metastatic renal cell carcinoma (mRCC). Adapted from National Comprehensive Cancer Network Clinical Practice Guidelines: Renal Cell Carcinoma (Available at <http://www.nccn.org>; last accessed April 1, 2010)

Disease and Line of Therapy	Setting	Therapy	
		Phase III Data	Phase II Data
Clear cell mRCC, First-line	Good/intermediate risk	Sunitinib, Bevacizumab + IFN- α , Pazopanib	High dose IL-2
	Poor risk	Temsirolimus ^a	
Clear cell mRCC, Second-line	Prior cytokines	Sorafenib	Sunitinib, bevacizumab
	Prior VEGF TKI	Everolimus	
	Prior bevacizumab		Sunitinib

^a Although recommendations are cited for clear cell mRCC, the pivotal trial of temsirolimus included non-cell histologies. This agent may therefore be applied in patients with poor risk disease, irrespective of histology.

IFN- α : a worthy comparator?

In 2002, Motzer et al. reported the clinical outcome of 463 patients with mRCC treated with interferon- α (IFN- α) as first-line therapy in six prospective trials [2]. This analysis identified a median PFS of 4.7 months, and a median OS of 13 months. On the basis of these data, the authors of this study concluded, “PFS and OS for IFN- α treatment can be used as a baseline for assessment of new therapies in phase II and phase III investigations.” In keeping with this strategy, several subsequent trials for treatment-naïve patients utilized IFN- α as a comparator arm. For example, a phase III trial comparing the VEGF-tyrosine kinase inhibitor (TKI) sunitinib to IFN- α enrolled a total of 750 patients with mRCC [3]. In this study, median OS was prolonged in those patients receiving sunitinib (26.4 versus 21.8 months, $p=0.051$ per unstratified log-rank test, $p=0.013$ per unstratified Wilcoxon test), as was median PFS (11 versus 5 months, $p<0.001$). Two subsequent phase III studies assessed bevacizumab, a monoclonal antibody with affinity for VEGF. First, in the AVOREN study, 649 patients were randomized to either bevacizumab with placebo or bevacizumab with IFN- α [4]. No OS benefit was observed in this study (22.9 versus 20.6 months, $p=0.13$), although there was a substantial benefit in PFS (10.4 versus 5.5 months, $p=0.0001$). Second, the Cancer and Leukemia Group B (CALGB) 90206 study randomized 732 patients to either bevacizumab and IFN- α or IFN- α alone [5]. Again, no improvement in OS was observed with the addition of bevacizumab (18.3 versus 17.4 months, $p=0.097$), although there was an appreciable increase in median PFS (8.4 versus 3.9 months, $p<0.0001$).

While the phase III experiences with bevacizumab exclusively assessed the combination of targeted agent and IFN- α , the pivotal trial of temsirolimus assessed both combination therapy and the targeted agent alone [6]. Patients with poor risk were enrolled on the study, as defined by six factors: (1) serum LDH more than 1.5 \times the upper limit of normal, (2) hemoglobin below the lower limit of normal, (3) corrected serum calcium of more than 10 mg/dL, (4) time from initial

diagnosis to randomization of less than 1 year, (5) Karnofsky performance status of 60 or 70, and (6) metastases in multiple organs. In contrast to other first-line studies, the pivotal trial of temsirolimus included non-clear cell histologies. A total of 626 patients were randomized to receive either temsirolimus, temsirolimus with IFN- α , or IFN- α alone. Median OS in these treatment arms was 10.9, 8.4 and 7.3 months, respectively, with a statistically significant difference in OS between patients receiving temsirolimus alone and IFN- α alone ($p=0.008$).

Is IFN- α a reasonable comparator in these pivotal studies? Outside of the aforementioned meta-analysis, data in support of IFN- α as a comparator emerges from a phase III study in which the agent was compared to medroxyprogesterone. The primary endpoint of this study was OS, and with 111 patients randomized; there was an observed improvement in median OS (8.5 versus 6 months, $p=0.017$) [7]. Furthermore, IFN- α improved PFS from 3 to 4 months. Knowing the benefit elicited by IFN- α therapy, it is somewhat challenging to interpret subsequent forays that have not used this agent as a control arm. The phase III trial of pazopanib, for instance, was first conceived as a trial for patients with prior cytokine failure and utilized a placebo as a comparator [8]. The trial was initiated when data for VEGF-TKIs was emerging and was therefore amended to include treatment-naïve patients as well. Ultimately, more treatment-naïve patients were enrolled in this study than cytokine-refractory (233 versus 202 patients). The primary endpoint of this study was PFS, and there was a significant improvement in PFS associated with pazopanib therapy (9.2 versus 4.2 months, $p<0.0001$) [9]. As might be anticipated, this difference was far more pronounced in the treatment-naïve subset (11.1 versus 2.8 months, $p<0.0001$). Notably, survival data has yet to mature from this study. The preliminary report of this study has led to a Category 1 recommendation from the National Comprehensive Cancer Network (NCCN) for use of pazopanib in both the first-line setting and after cytokine failure [10]. Despite this recommendation, one may question whether pazopanib has faced appropriate rigor in its

evaluation as first-line therapy, given the use of a placebo control.

PFS versus OS: an evaluation of primary endpoints

While OS remains a gold standard for interpreting efficacy, other metrics have been deemed acceptable for purposes of drug approval by both the United States Food and Drug Administration (US FDA) and the European Medicines Agency (EMA) [11–14]. A report from the US FDA suggested that among 57 oncology drugs receiving standard approval between 1990 and 2002, only 18 had demonstrated a benefit in OS [13]. The remainder had gained approval on the basis of other measures of clinical benefit (i.e., response rate, PFS, etc.). Similarly, among 28 drugs approved by the EMA between 2000 and 2004, only six were approved on the basis of OS [14]. An additional 11 drugs were approved on the basis of PFS, and the remaining 11 were approved on the basis of response rate.

What are the relative benefits of assessing PFS and OS? OS appears to be more universally accepted as a clinically meaningful endpoint, and is based on a precise statistic (date of death) [15]. In the current climate, however, OS analyses are complicated by a number of factors. Increasing survival among patients with cancer lengthens trials in which OS is set as the primary endpoint. In meta-analyses of data from clinical trials for metastatic breast and colorectal cancer, it appears that OS has increased greatly over the past two decades [16, 17]. The same phenomenon may be occurring in mRCC (see Table 2). As an example of this, in the previously noted meta-analysis of IFN- α therapy

trials published by Motzer et al. in 2002, OS with IFN- α was estimated at 13 months [2]. In the recent AVOREN trial, however, OS in the arm treated with IFN- α alone was 20.6 months [4]. As discussed in the next section, use of secondary therapies could drive this observation, as could advances in supportive care. Irrespective of the cause, the lengthened duration of clinical trials powered to explore OS could delay clinical implementation of active therapies.

Use of PFS as opposed to OS as a primary endpoint therefore has the benefit of shortening trial duration. Furthermore, given increasing availability of second- and third-line options in mRCC, PFS provides a more direct assessment of tumor growth [15]. However, several issues plague assessment of PFS. Firstly, whether radiographic, laboratory or clinical criteria are used, designation of progression may be subject to investigator bias. A mechanism to combat this is use of blinded, independent central review. Rates of discrepancy between independent and central review are projected to be in the range of 24–40% [18, 19]. However, even with the added burden of central review, bias may still exist—in one report, inter-reader discrepancies among central reviewers occurred in nearly 40% of cases [19]. Another pitfall in interpreting PFS data is the presence of evaluation time-bias. Frequently, studies mandate disease evaluation on intervals of 2–3 months; most surely, progression occurs during, and not at, these intervals. A lack of uniformity in disease assessment schedules in trials of mRCC therefore makes it challenging to juxtapose PFS data from distinct studies.

In the setting of several malignancies, a correlation between PFS and OS has been observed. Such a correlation makes it possible to employ PFS as a surrogate for OS in

Table 2 Endpoints (EP) and differences in progression-free survival (PFS)/overall survival (OS) in pivotal trials of targeted therapy in metastatic renal cell carcinoma

Study	Design	1° EP	2° EP	N	Δ PFS (<i>P</i> -value)	Δ OS (<i>P</i> -value)
<i>VEGF-Directed Therapy</i>						
Motzer et al. [3]	First-line: Sunitinib v IFN- α	PFS	OS	750	6.0 mos (<i>p</i> <0.001)	4.6 mos (<i>p</i> =0.013) ^a
Escudier et al. [27]	Cytokine Failure: ^b Sorafenib v placebo	OS	PFS	903	2.7 mos (<i>p</i> <0.01)	3.4 mos (<i>p</i> =0.02) ^c
Sternberg et al. [8]	First-line + Cytokine Failure: Pazopanib v placebo	PFS	OS	435	5.0 mos (<i>p</i> <1 \times 10 ⁻⁷)	N.A. ^d
Escudier et al. [4]	First-line: Bevacizumab/IFN- α v placebo/IFN- α	OS	PFS	649	4.8 mos (<i>p</i> =0.0001)	2.0 mos (<i>p</i> =0.13)
Rini et al. [5]	First-line: Bevacizumab/IFN- α v IFN- α	OS	PFS	732	3.5 mos (<i>p</i> <1 \times 10 ⁻⁴)	0.9 mos (<i>p</i> =0.097)
<i>mTOR Inhibitors</i>						
Kay et al. [44]	VEGF-TKI failure: Everolimus v placebo	PFS	OS	410	3.0 mos (<i>p</i> <0.001)	0.39 mos (<i>p</i> =0.177)
Hudes et al. [6]	First-line: ^e Temsirolimus v IFN- α	OS	PFS	626	1.9 mos (<i>p</i> =NR) ^f	3.6 mos (<i>p</i> =0.008)

^a The *p*-value was 0.051 per unstratified log-rank test, and 0.013 by the unstratified Wilcoxon test.

^b The majority of patients in this study (>80%) had received prior cytokine-based therapy with either IL-2 or IFN- α .

^c The *p*-value in this study failed to meet pre-specified O'Brien-Fleming boundaries for statistical significance.

^d OS did not meet pre-specified O'Brien-Fleming boundaries for reporting.

^e A third arm in this study was randomized to temsirolimus with IFN- α . Data reported pertain only to the stated comparison.

^f To the author's knowledge, the *p*-value associated with PFS for temsirolimus has not been reported to date.

study design and interpretation. For instance, in ovarian cancer, a meta-analysis of seven pivotal US-based trials of first-line therapy for advance disease showed an association between PFS and OS [20]. Similar observations were made in the setting of colorectal cancer. Analysis of the ACCENT database, which includes 20,898 patients with non-metastatic colorectal cancer, showed a strong association between 3-year disease-free survival (DFS) and 5-year OS [21]. This experience led to a decision by the Oncologic Drugs Advisory Committee (ODAC) to accept 3-year DFS as a primary end point for full drug approval in non-metastatic colorectal cancer. Correlations between PFS and OS have also been demonstrated in a meta-analysis of 39 randomized controlled trials enrolling patients with advanced colorectal cancer [22].

In mRCC, recent efforts have also outlined a potential association between PFS and OS. Delea et al. reported a systematic review of 21 controlled trials in which patients were treated with either cytokines (IL-2 or IFN- α) or one of six targeted therapies (sunitinib, sorafenib, pazopanib, bevacizumab, temsirolimus or everolimus) [23]. A total of 6,182 patients were included in the analysis, with 35 treatment comparisons among the studies assessed. Whereas the median difference in time to disease progression was 1.3 months, the median difference in OS was 2.8 months.

Using weighted ordinary least-squares regression, it was determined that a 1-month improvement in disease progression was associated with a 1.4-month improvement in OS ($p < 0.0001$). In individual studies, this association may not be as clear. The association between PFS and OS was examined in the context of CALGB 90206 [24]. Specifically, the log rank test and proportional hazards model were used to examine the effect of PFS at 3 and 6 months in predicting OS. In patients who had not progressed at 3 months, median OS was 6.0 months (95%CI 5.3–6.9) versus 25.2 months (95%CI 22.2–28.5) in patients at this interval (HR 2.6, $p < 0.001$). Despite these compelling results, tau rank correlation assessment suggested only modest association between PFS and OS.

The effect of crossover and subsequent therapies

A major challenge in interpreting OS data in the setting of mRCC is the influence of subsequent treatments and crossover. Table 3 summarizes use of such treatments in the pivotal trials leading to the approval of sunitinib and bevacizumab as first-line therapies. Detailed analyses have accompanied these data. In the pivotal trial of sunitinib, of 375 patients randomized to IFN- α therapy, 117 patients

Table 3 Distribution of patients who underwent crossover or received subsequent therapies in three pivotal mRCC studies

Study	Design	Experimental	Comparator
Motzer et al. [3]	First-line: Sunitinib v IFN- α	Total patients: 323 ≥1 Treatment: 182 (56%) Sunitinib: 36 (11%) Other VEGF Inhibitors: 106 (33%) Cytokines: 63 (20%) mTOR: 28 (9%) Chemotherapy: 21 (6%)	Total patients: 359 ≥1 Treatment: 213 (59%) Sunitinib: 117 (33%) Other VEGF Inhibitors: 115 (32%) Cytokines: 47 (13%) mTOR: 16 (4%) Chemotherapy: 20 (6%)
Escudier et al. [4]	First-line: Bevacizumab/IFN- α v Placebo/IFN- α	Total patients: 327 ≥1 Treatment: 180 (55%) Sunitinib: 83 (25%) Sorafenib: 60 (18%) Bevacizumab: 10 (3%) mTOR: 14 (4%) Cytokines: 32 (10%) Chemotherapy: 28 (9%)	Total patients: 322 ≥1 Treatment: 202 (63%) Sunitinib: 92 (29%) Sorafenib: 50 (16%) Bevacizumab: 12 (4%) mTOR: 6 (2%) Cytokines: 52 (16%) Chemotherapy: 47 (15%)
Rini et al. [5]	First-line: Bevacizumab/IFN- α v IFN- α	Total patients: 340 ≥1 Treatment: 166 (49%) VEGF-Directed: 199 (35%) Bevacizumab: 21 (6%) Cytokines: 27 (8%) Chemotherapy: 46 (14%) Investigational: 27 (8%)	Total patients: 332 ≥1 Treatment: 188 (57%) VEGF-Directed: 160 (48%) Bevacizumab: 50 (15%) Cytokines: 30 (10%) Chemotherapy: 47 (14%) Investigational: 29 (9%)

ultimately received post-study therapy with sunitinib. Censoring 25 patients who had crossed over to sunitinib while on study, a larger absolute difference in OS was noted, favoring patients who had received sunitinib treatment up-front (26.4 versus 20.0 months; HR 0.808, $p=0.036$). When all patients who had received second-line therapy were censored, a profound difference in OS was noted that favored the sunitinib group (28.1 versus 14.1 months; HR=0.647, $p=0.003$).

A similar effect of secondary therapies was observed in CALGB 90206 [5]. While an absolute difference in overall survival of 0.9 months was noted between the primary treatment arms, the difference was more profound when stratified by subsequent therapies. Among 408 patients who had received second-line therapy, survival was 31.4 months in the bevacizumab and IFN- α arm, and 26.8 months in the IFN- α arm (HR 0.80; $p=0.055$). A similar absolute difference (~4 months) was seen in those patients who did not receive second-line therapy, again favoring the bevacizumab and IFN- α arm (13.1 versus 9.1 months; HR 0.82, $p=0.108$). Given that 57% of patients treated in the IFN- α arm received second-line therapy as compared to only 49% of patients in the bevacizumab and IFN- α arm, it is likely that second-line therapies stifled differences in OS seen between the two treatment arms in the study population at large.

The AVOREN study was unblinded after PFS data was reported [4]. At this time, roughly 12 patients crossed over to bevacizumab therapy. Censoring these patients in the analysis yielded a slightly higher absolute difference in OS, although this difference was not statistically significant (23.3 versus 20.8 months, $p=0.0766$). Similarly, directly comparing patients in this study who had received subsequent sunitinib or sorafenib yielded greater absolute differences in OS, favoring therapy with bevacizumab and IFN- α . For patients who received bevacizumab and IFN- α followed by a VEGF-TKI, median OS was 38.6 months as compared to 33.6 months for patients who originally received IFN- α with placebo (HR 0.80; 0.56–1.13).

Rank-preserving structural failure time (RPSFT), proposed by Robins and Tsiatis, represents a novel statistical method that may account for the effect of crossover [25]. In this non-parametric model, survival differences are identified that would have been observed if all patients remained on protocol therapy. RPSFT analysis has been applied to a phase III trial comparing sunitinib and placebo in patients with advanced gastrointestinal stromal tumor (GIST) [26]. Using conventional analyses, it appeared that there was convergence in OS (74.7 weeks with sunitinib versus 64.9 weeks with placebo; $p=0.128$). Using the RPSFT method, a revised estimate for survival on the placebo arm negating the effect of crossover was generated (30 weeks). With this revised estimate, a significant difference in OS was recorded ($p<0.0001$). There is preliminary data

available using the RPSFT method in the pivotal trial comparing everolimus to best supportive care in patients with mRCC who have progressed on sunitinib and/or sorafenib [12]. In this analysis, it was estimated that survival was nearly twice as long with everolimus therapy (relative risk 1.93, 95% CI 0.5–8.50).

Ongoing comparative trials

Arguably, head-to-head clinical trials comparing targeted therapies represent the most ideal way to identify the optimal therapeutic strategy. Several of these studies are currently ongoing. In the first-line setting, the phase III COMPARZ trial aims to randomize 876 patients with treatment-naïve, clear cell mRCC to either sunitinib or pazopanib [27]. The primary endpoint of this study is PFS, and the study is estimated to complete accrual by November of 2010. While COMPARZ assesses the efficacy of two VEGF-TKIs, the RECORD-3 trial represents the only ongoing phase III effort to juxtapose the clinical activity of an mTOR inhibitor against a VEGF-TKI [28]. In this study, previously untreated patients with mRCC will receive either sunitinib or everolimus. At the time of progression, patients will be crossed over to the opposing arm. The primary endpoint of this trial is PFS, and the study is powered to detect non-inferiority of everolimus. A total of 390 patients are anticipated to enroll in this effort by April 2013.

Data comparing the effectiveness of bevacizumab to VEGF-TKIs in the first-line setting are notably lacking. The only comparison of bevacizumab to a VEGF-TKI may be derived from the ongoing BeST study [29]. In this trial, patients are randomized to one of four regimens (bevacizumab monotherapy, bevacizumab with sorafenib, bevacizumab with temsirolimus and sorafenib with temsirolimus). The latter two arms juxtapose therapy with bevacizumab and sorafenib, albeit in combination with temsirolimus. The study is expected to accrue a total of 360 patients and will conclude by May 2012. Two other first-line studies explore the combination of bevacizumab and mTOR inhibitors. In the phase II RECORD-2 study, bevacizumab and IFN- α is compared to bevacizumab with everolimus [30]. This study is expected to include 360 patients and will conclude by February 2012. Using a similar design, the phase IIIb INTORACT study will randomize patients to either bevacizumab and IFN- α or bevacizumab and temsirolimus [31]. The study is also expected to complete enrollment by February 2012 and is projected to accrue a total of 800 patients.

Second-line therapy is also a competitive landscape in mRCC. Retrospective data point to the efficacy of re-challenge with distinct VEGF-TKIs. For instance, in a series of 23 patients treated with sorafenib followed by sunitinib, 4 patients (17%) obtained a partial response with

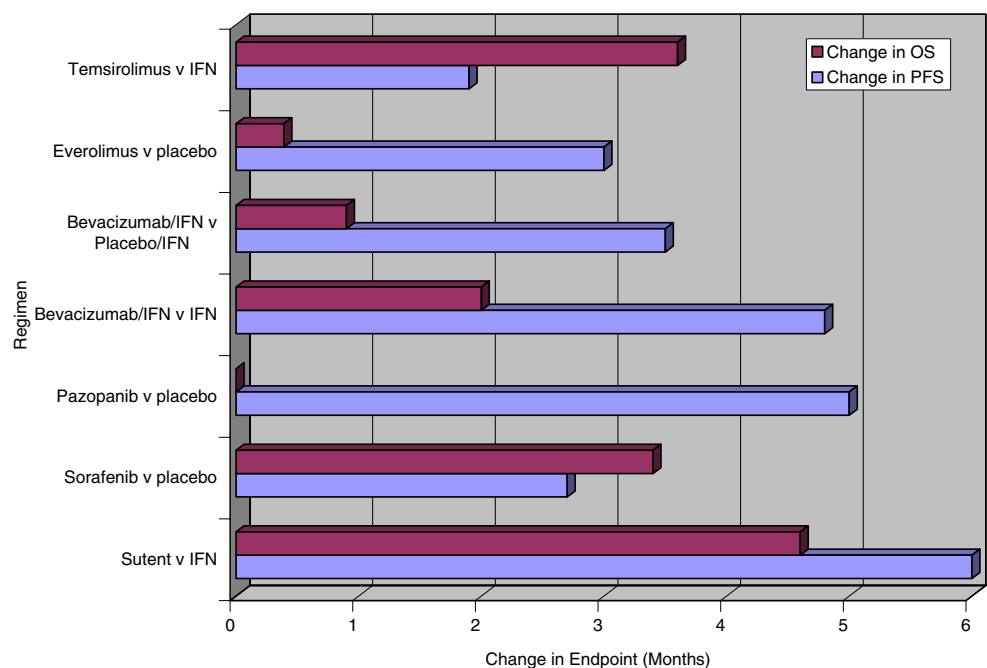
the agent, and the median duration of stable disease after starting sunitinib was 32 weeks [32]. Registry data indicate that this practice may be widespread and further suggest that the efficacy of VEGF-TKIs as second-line therapy may be superior to that of mTOR antagonists [33]. To test this premise prospectively, an ongoing randomized trial is comparing sorafenib versus temsirolimus as second-line therapy in patients who have failed first-line sunitinib, with a primary endpoint of PFS [34]. The trial is anticipated to complete accrual by May 2011. Another randomized study is based on encouraging phase II data for the novel VEGF-TKI axitinib in the second-line setting [35]. In this study, axitinib and sorafenib are being directly compared in 650 patients who have failed one prior systemic therapy [36]. The study is expected to complete accrual by July 2010.

Conclusions

As the studies presented herein attest, novel therapies for mRCC bring both new hope and new challenges. In the absence of substantial comparative data to juxtapose approved agents against one another, oncologists must scrutinize the available data to make an informed decision. In counseling the patient with mRCC, a balanced discussion of both efficacy and safety associated with each agent is imperative. Schema such as that presented in Fig. 1 may also be used to determine the level of evidence available for targeted agents and cytokine therapy in varied clinical settings. In the absence of relevant comparative trials or biomarker data to guide therapy, the oncologist may rely more heavily on factors such as patient co-morbidity or cost.

Moving ahead, two principal efforts may aid in resolving clinical equipoise. First, the comparative studies described herein will allow the oncologist to appropriately distinguish the efficacy of different targeted agents. Second, development of biomarkers to characterize response may allow application of targeted agents in a more nuanced fashion, tailoring treatment to the patient. Biomarkers may be both laboratory-based and clinical. As an example of the former, lower baseline levels of hepatocyte growth factor (HGF), IL-6 and IL-8 appear to predict greater tumor shrinkage with pazopanib therapy in a randomized discontinuation trial evaluating the drug [37]. Prospective validation of these findings may yield a molecular profile that can be used to define appropriate candidates for pazopanib therapy. Another promising biomarker lends itself to the biology of mRCC—Gordan et al. have identified role of differential hypoxia inducible factor (HIF) expression [38]. Concomitant HIF-1 α and HIF-2 α expression appears to be correlated with enhanced Akt/mTOR and ERK/MAPK signaling. In contrast, expression of only HIF-2 α results in increased c-myc activity. Thus, based on HIF status, clinical strategies could be tailored to target these differential expression patterns. Finally, Rini et al. have recently reported a detailed genomic analysis on tumor specimens derived from 931 patients who underwent nephrectomy at the Cleveland Clinic between 1985 and 2003 [39]. A total of 448 genes were noted to be significantly associated with recurrence-free interval (RFI; $p < 0.05$). Ultimately 16 genes remained predictive in a multivariate model after adjustment for false discovery and clinicopathologic covariates. This gene signature will be assessed in validation cohorts using similarly sized tissue repositories. This is a novel

Fig. 1 A graphic representation of absolute differences in PFS and OS in pivotal trials of targeted agents for mRCC



approach that may ultimately yield a “recurrence score” that can be applied to non-metastatic disease, and can potentially identify a subset of patients with high-risk localized disease that could be targeted with systemic therapy.

With respect to clinical biomarkers, hypertension is slowly emerging as a predictor of clinical response. Data from the pivotal trial of sunitinib suggest that OS is markedly improved in those patients who achieve a maximum systolic blood pressure greater than 140 mmHg (30.5 versus 7.8 months, $p < 0.0001$) or a maximum diastolic blood pressure greater than 90 mmHg (32.1 versus 15.0 months, $p < 0.0001$) [40]. Similar findings have been noted with bevacizumab therapy in mRCC, as well as other solid tumors [41, 42]. Based on this association, a prospective trial of axitinib aims to titrate the medication dose to a target blood pressure in order to optimize response [43]. Forward-thinking trials such as these are necessary to optimize therapeutic gains from currently available agents.

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