Emerging Efficacy Endpoints for Targeted Therapies in Advanced Renal Cell Carcinoma

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Several novel targeted agents are being tested for the treatment of advanced renal cell carcinoma (RCC), and results of phase I and II trials have been encouraging. A recently completed phase III, placebo-controlled study showed that median progression-free survival doubled from 12 weeks to 24 weeks in patients treated with the multi-kinase inhibitor sorafenib (Nexavar) (hazard ratio [HR], 0.44; \( P < .00001 \)), and approximately three-quarters of patients had some degree of tumor regression. Furthermore, interim analysis showed an estimated 39% improvement in overall survival in sorafenib-treated patients (HR, 0.72; \( P = .018 \)) and an investigator-assessed response rate of 10%, indicating that many more patients had clinical benefit than had tumor regression qualifying as response by traditional criteria. These data and others have added to the evidence of lack of correlation between response rate and clinical benefit in RCC patients (as well as in other tumor types) treated with targeted therapies. Issues surrounding study endpoints and biologic efficacy markers for molecular targeted agents in RCC are discussed in this article, with a focus on results of the Treatment Approaches in Renal Cancer Global Evaluation Trial (TARGETs).

Advanced renal cell carcinoma (RCC) is relatively resistant to systemic therapy. Response rates (RRs) to the chemotherapy agents studied most extensively, primarily fluorouracil (5-FU), have ranged from 0% to 14% in the majority of trials.[1] Current standard treatment with cytokines including interferon (IFN) and interleukin-2 (IL-2, Proleukin) benefit only selected patients, with few surviving long term, and is associated with significant toxicities.[1] Based on better understanding of the genetics of RCC, several targeted therapies have been investigated in this disease,[2] and results from recent randomized phase II and III trials of multitargeted agents have been encouraging.[3-6]

In the largest phase III trial in advanced RCC completed to date, the Treatment Approaches in Renal Cancer Global Evaluation Trial (TARGETs), progression-free survival (PFS) doubled from 12 weeks to 24 weeks (\( P < .00001 \)) vs placebo among patients who received sorafenib (Nexavar; formerly known as BAY 43-9006), an inhibitor of serine-threonine kinases c-raf and b-raf, as well as multiple tyrosine kinases, mainly vascular endothelial growth factor receptor 2 (VEGFR2).[3,5] However, RR among sorafenib-treated patients, based on investigator assessment, was 10%, supporting the increasing evidence that RRs are rarely the best surrogates for anticancer treatment-induced clinical benefit,[7] particularly for targeted therapies. Patients treated with targeted agents may achieve stabilization of disease, decreased tumor growth rate, or tumor regression, rather than shrinkage in tumor size qualifying as objective response based on traditional criteria, such as Response Evaluation Criteria in Solid Tumors (RECIST) or World Health Organization (WHO) criteria. Furthermore, the high variability of tumor growth rates as well as rare spontaneous regressions known to exist in RCC present additional caveats in evaluating efficacy of targeted cytostatic, or even cytotoxic agents in this tumor.[1,8-11] For example, it may be difficult to differentiate treatment effect from the natural history of the disease in patients with slow-growing tumors. Furthermore, if tumor growth rates vary substantially in a study population, the statistical power of the findings is diluted, requiring a larger sample size for valid results.[12]

These issues and recent findings of discordance between RR and clinical benefit in TARGETs and other trials of molecular targeted therapies have raised new questions regarding optimal methodologies to evaluate and monitor activity of these agents.[13,14] This article will review some of those questions, focusing on recent studies in RCC.

An Endpoint Hierarchy

The quantity of novel targeted agents becoming available (as well as the high proportion of "negative" phase III trials despite promising phase II findings) underscores the importance of defining endpoints that reliably predict efficacy of these agents.[15] A hierarchy of endpoints for outcome measures was proposed by Fleming,[16] who described a true clinical efficacy measure as being at
the top of the hierarchy. While improving survival is the clear primary goal, this endpoint requires large sample sizes and a long duration, and therefore conducting such a trial with this primary endpoint would be costly. Surrogate endpoints follow on this hierarchy, and those that can be validated are of most value. Notably, one important example of a validated surrogate endpoint accepted by the US Food and Drug Administration (FDA) for regulatory drug approval is the use of 3-year disease-free survival (DFS) as a surrogate for the previously accepted 5-year overall survival (OS) for adjuvant therapy in colorectal cancer (CRC). (Specific details are described in detail elsewhere in this supplement by Sargent.) Validation of this surrogate was based on meta-analysis of data from 20,898 patients who participated in 18 trials worldwide.[17,18] PFS is increasingly accepted as a surrogate endpoint for survival in oncology, including RCC. However, improved PFS (and implied clinical benefit) in the absence of a placebo control may be difficult to validate and to interpret, especially in particular tumor types (e.g., advanced RCC). Advantages of using PFS as the primary outcome measure in clinical trial design are that data can be obtained earlier than survival results and outcome is less affected by subsequent-line therapies. Although large-volume data sets validating PFS as a reliable surrogate are lacking, especially from phase III studies, results of several prospective randomized comparisons of cytokine regimens in patients with advanced RCC suggest that increases in PFS may correlate with OS benefit in this disease.[19-21]

Biologic Surrogate Markers
Additionally, pharmacodynamic markers or measures of mechanism-based effects are also needed to confirm whether the treatment modulates the intended target protein, and whether patient outcome improves as a result. The majority of genetic alterations in clear-cell RCC, the most common histologic subtype, derive primarily from changes in the von Hippel-Lindau (VHL) tumor suppressor gene.[22,23] Changes in VHL contribute to RCC tumorigenesis through pathways including VEGF, platelet-derived growth factor-beta (PDGF-B), and transforming growth factor-alpha (TGF-α), as well as other downstream target proteins (Figure 1).[2,22,24] Thus, multiple molecular pathways (and perhaps redundant pathways) play active roles in this tumor, and most of the novel agents that have demonstrated some efficacy in RCC are targeted to multiple proteins, which complicates identification of useful pharmacodynamic markers of efficacy. In patients with RCC, there currently is no biomarker that can be obtained from blood; tumor biopsies are also difficult to obtain routinely for biomarker analysis.

The TARGETs Trial and Potential New Endpoints in RCC
Results of several clinical trials of therapies directed against growth factors active in RCC initiation and carcinogenesis support the use of these agents in patients with advanced RCC.[2-6,13,25] A promising targeted therapy, sorafenib, is an oral, small-molecule multi-kinase inhibitor that induces antiproliferative and antiangiogenic effects primarily through Raf kinase and VEGFR pathways. On December 20, 2005, the FDA approved sorafenib to treat adults with advanced RCC, the most
common type of kidney cancer. Awada and coworkers demonstrated preliminary evidence of activity for sorafenib in RCC in a small phase I study.[26] This agent also demonstrated efficacy in a phase II trial double-blind randomized discontinuation design trial (RDT).[12] The RDT design selects a more homogenous patient population in which to study drug activity, to help address the heterogeneity of tumor growth rates in RCC, as mentioned previously. All patients initially receive the experimental therapy, and only patients who achieve stable disease (SD) at a certain time point are subsequently randomized to continue or discontinue therapy.

In the phase II sorafenib RDT study, conducted by Ratain et al.[12] 202 RCC patients received 400 mg bid oral sorafenib for 12 weeks. At that point, 65 patients with SD were randomly assigned to continue sorafenib or to receive placebo. Median PFS was 23 vs 6 weeks (P = .0001; hazard ratio [HR] 0.29), and 50% vs 18% of patients were progression-free at 24 weeks, respectively.[12] While a low RR was noted, tumor regressions were observed across the majority of the study population, a result that has been duplicated in the phase III setting.

Escudier et al reported the only phase III, prospective, randomized controlled trial of targeted therapy in RCC completed to date—TARGETs trial. In this double-blind trial, the multi-kinase inhibitor sorafenib was compared with placebo in 903 patients with advanced clear-cell RCC who had received one previous systemic treatment.[3,5] A total of 451 patients received oral sorafenib 400 mg bid and 452 received placebo.[5] At 3 months post-randomization, 82% of patients on sorafenib were progression free vs 43% of those on placebo.[5] Median PFS durations were 24 and 12 weeks, respectively (HR, 0.44; P < .00001), and 74% vs 20% of sorafenib vs placebo patients had some degree of tumor shrinkage. While partial response rate (PR), based on independent assessment, was 2% in the first 769 patients, 82% of patients achieved SD while undergoing sorafenib therapy. Clearly, many more patients had clinical benefit than showed response, as assessed by RECIST criteria. Tolerability was favorable, with rash, diarrhea, hand-foot skin reaction, fatigue, and hypertension as the most common drug-related effects. Grade 3/4 effects were reported in 30% and 22% of sorafenib- and placebo-treated patients, respectively.

A recently reported interim analysis of OS (the primary study endpoint) in the TARGETs trial supports the findings of significant clinical benefits of sorafenib in patients with RCC despite a relatively low RR.[3] This planned analysis was based on 220 survival events (patient deaths) that had occurred by May 31, 2005. Results showed an estimated 39% improvement in survival for patients receiving sorafenib vs those receiving placebo (HR, 0.72; P = .018). Also, the corresponding investigator-assessed RR was 10%. While the findings of the interim analysis did not reach statistical significance, the data clearly suggest a favorable survival trend for patients receiving sorafenib. The final survival analysis (after 540 events) of this ongoing study is eagerly awaited. Therefore, overall results to date from TARGETs indicate that while sorafenib achieved a relatively low RR in the overall study population (based on either independent or investigator assessment), objective response and/or clear clinical benefit for individual study patients was notable, similar to that shown in previous phase trials.[3,5]

Other targeted therapies have also been studied in patients with RCC.[2,4,6,13,14,25] Currently, the data from the completed/ongoing trials cannot be rigidly compared statistically owing to potential differences in patient populations, response criteria, or other trial-design issues. Direct, randomized comparisons of targeted agents are warranted.

Tumor Blood Flow as a Surrogate Endpoint

Data derived from the TARGETs trial are also useful in illustrating potential new outcome measures in RCC. For example, the VEGF pathway is a key regulator of angiogenesis in RCC and other tumors. Several researchers have measured and quantified post-treatment changes in tumor blood flow as a surrogate marker of VEGFR inhibition.[27,28] Figure 2 illustrates a comparison of blood flow in the abdominal aorta vs in RCC liver metastases before and after VEGFR inhibitor treatment. As shown, blood flow in the metastases is reduced to zero during treatment but remains stable in the aorta.
A correlation between decreased tumor blood flow and clinical benefit response (CBR) has been shown in RCC as well as colorectal cancer after treatment with VEGFR inhibitors, using dynamic contrast-enhanced magnetic resonance imaging (MRI).[27,28] Furthermore, in an ancillary study of the sorafenib TARGETs trial, tumor blood flow was prospectively evaluated using color Doppler ultrasonography with perfusion software and contrast.[29] Examinations were conducted at baseline and at 3 and 6 weeks in a subset of patients whose tumors were accessible for ultrasound. Among the 27 patients who were fully assessable, 9 were treated with sorafenib and 18 received placebo; the difference in PFS between these two groups of patients was statistically significant \( (P = .03) \). Among the nine patients who received sorafenib, five were poor responders (according to decrease in blood perfusion), and four were good responders. Furthermore, changes in tumor blood flow were highly predictive of an improvement in PFS (Figure 3).
A novel tool to detect early clinical signals of efficacy of cytostatic agents in RCC utilizes the calculation of actual tumor area at the time of best response. Data for each patient are plotted, and the areas under the curves (which include data for all patients under study) determine the maximum percent reductions in tumor sizes for a specified treatment group. To illustrate this tool, data from the TARGETs trial are plotted in Figure 4. As shown, 74% of sorafenib-treated patients vs 20% in the placebo group achieved some degree of tumor shrinkage. This tool could be used in the phase II setting for either single-arm or comparative studies, and subsequently might be correlated with PFS. Indeed, the use of this novel tool offers significant promise to validate clinical endpoints in large data sets from RCC trials (or other tumor types) that investigate targeted agents. Furthermore, improved imaging techniques can provide more precise measurements of even minor responses or of volumes of necrotic tissue for use in this or other endpoint determinations.
Conclusion

Positive results with molecular targeted therapy in advanced RCC are providing novel treatment options for this relatively chemoresistant tumor. In particular, the phase III TARGETs trial has demonstrated a high level of clinical benefit in the majority of RCC patients treated with the multikinase inhibitor sorafenib, with an estimated 39% survival improvement based on interim analysis despite an investigator-assessed response rate of 10%.[3] These data as well as those from studies in other neoplasms support that clinical trial design and outcome measures for evaluation of targeted therapies may be different from those traditionally used to evaluate cytotoxic agents. Moreover, the increasing use of PFS (but not RR) as a surrogate endpoint for OS is indicative of this trend. The validity of PFS from placebo-controlled vs uncontrolled studies is also highlighted, especially in specific tumor types (eg, RCC). Research into alternative endpoints and mechanistic-based efficacy biomarkers is ongoing. As shown by the ancillary study of RCC patients who participated in the phase III sorafenib trial, Doppler ultrasonography methods are simple noninvasive strategies to evaluate antiangiogenic effects, and may be useful in providing early clinical signals regarding efficacy of antiangiogenic agents.[29] Another proposed tool to assess the extent of therapeutic response at an earlier time point involves the calculation of tumor area at the time of best response for each patient; the respective data are plotted and area under the concentration-time curves (AUCs) are compared. Additional studies are warranted to validate statistically (and from both clinical and regulatory perspectives) the use of PFS (or other surrogate endpoints) for survival benefit in RCC patients who receive targeted therapy, and to identify useful pharmacodynamic efficacy markers.
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References:
9. Vogelzang NJ, Priest ER, Borden L: Spontaneous regression of histologically proved pulmonary


18. Sargent D: Disease-free survival versus overall survival as an endpoint for adjuvant colon cancer studies: Data from randomized trials [transcript]. Presented at: FDA Oncology Drugs Advisory Committee; May 5, 2004; Washington DC.


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