Considerations for the Design of Future Clinical Trials in Metastatic Renal Cell Carcinoma

Bernard Escudier,[1] Daniel Y.C. Heng,[2] Arthur Smyth-Medina,[3] Camillo Porta[4]

Abstract

Metastatic renal cell carcinoma (mRCC) remains incurable in most cases, and there is a need to improve outcomes through clinical research, which will include development of novel molecularly targeted or immunotherapeutic agents. There are also many remaining questions regarding the optimization of currently available regimens, including the utility of dose escalation, the benefit of combination therapy, and the optimal sequences of therapies. Addressing these clinical questions will require careful planning and the inclusion of novel elements in trial designs. Future trials should include molecular phenotyping and selection of patients most likely to benefit from targeted therapies. In this article, we consider lessons learned from previous trials in mRCC and discuss how these lessons might be implemented in the design of future trials that focus on clinically useful questions and provide results that can be readily interpreted. The ultimate aim of the next generation of mRCC trials will be rapid cost-effective identification, testing, and approval of agents that can improve prognosis in this challenging disease.

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Introduction

In 2006, the publication of the first phase III trial of a targeted agent, sorafenib,[1] opened a new era for the treatment of metastatic renal cell carcinoma (mRCC). At the time of this writing, there are 7 targeted agents available for its treatment; sorafenib has been joined by other tyrosine kinase inhibitors (TKIs) (sunitinib,[2] pazopanib,[3] and axitinib[4]), the vascular endothelial growth factor (VEGF)-directed monoclonal antibody bevacizumab[5,6] in combination with interferon (IFN), and the mammalian target of rapamycin (mTOR) inhibitors everolimus[7] and temsirolimus.[8] There is strong evidence that survival has improved in the era of targeted agents: in a registry, median adjusted overall survival (OS) was 10.9 months in the period 2000 to 2005 and was 16.1 months during 2006 to 2008.[9] In a specialized center, median OS in patients treated with sequential TKI therapy was 25.8 months.[10] However, mRCC remains incurable in most cases, and there is a need to improve outcomes through targeted clinical research.

[1]Institut Gustave Roussy, Villejuif, France
[2]Department of Medical Oncology, Tom Baker Cancer Center, University of Calgary, Calgary, Alberta, Canada
[3]Darwin Healthcare Communications, Sterling House, Oxford Road, Kingston Bagpuize, United Kingdom
[4]IRCCS San Matteo University Hospital Foundation, Pavia, Italy

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Address for correspondence: Bernard Escudier, MD, Institut Gustave Roussy, 114 rue Edouard Vaillant, 94805 Villejuif, France
Fax: -011-33142115211; e-mail contact: Bernard.Escudier@igr.fr

Enrollment in RCC clinical trials has never been as good as it is now: at the time of this writing there are 406 open studies of RCC (any stage) listed on clinicaltrials.gov. Recent examples such as the TIVO-1 trial (A Study to Compare Tivozanib (AV-951) To Sorafenib in Subjects With Advanced Renal Cell Carcinoma [tivozanib vs. sorafenib in first-line therapy]) have shown it is feasible to do large trials quickly. However, there are some significant hurdles, which will be discussed in this article.

Future trials will investigate new agents acting on novel immune targets (CTLA-4, PD-1, vaccines) and alternative molecular targets (eg, PI3-K/Akt pathway, c-MET, fibroblast growth factor [FGF], interleukin [IL]-8, mTOR complex [mTORC]1/2), as well as clinical questions relating to the use of current agents, including the utility of dose escalation, the benefit of combination therapy, and the optimal sequences of therapies. Addressing these clinical questions will require careful planning and novel elements of trial design. In this article, we discuss considerations for future clinical trials of novel agents and trials investigating unanswered questions regarding current agents (eg, dose escalation).

Hurdles in Conducting Clinical Trials

For academic research groups, there are many hurdles to conducting a clinical trial, not least of which are the administrative costs and the demands of regulatory authorities. Recruitment is frequently a major hurdle, and there are usually greater incentives for both investigators and patients to participate in industry-sponsored trials rather than investigator-sponsored studies. In

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industry-sponsored studies, investigators receive money for their research, and patients receive travel expenses and tend to be more willing to accept a novel agent than an existing one. This is unfortunate, because there is often a conflict between questions of interest to industry and academically interesting questions. For example, for phase III registration trials, it might be seen by the sponsoring company as advantageous to select the comparator perceived as "weaker" and to have mixed populations, whereas academically interesting questions are better answered using the standard of care as the comparator and homogeneous populations, as discussed further on. Several recent industry-sponsored trials in mRCC have recruited extensively from centers in eastern Europe, but the reduced number of available treatment options after progression in these regions means survival in mRCC may be lower than that observed in western Europe and North America, and results from trials conducted in one region may not be generalizable in another.

Phases of Clinical Development

The traditional phases of clinical development (phases I, II, III, and IV [postmarketing]) are well established, but targeted agents for treatment of mRCC have had journeys to approval that have differed in terms of the types of trials used, number of patients in each phase, and time to registration.

The current drug development system is associated with high cost and a low success rate: the estimated development cost of a drug reaching US Food and Drug Administration (FDA) approval is as high as US $1 billion,[11] yet only 34% of oncology phase III trials conducted in 2003 to 2010 achieved statistical significance in their primary end point.[12] In addition, the current system focuses on a small number of promising compounds and regimens, and many potential therapies are left uninvestigated or discarded early. Many agents arrived at phase III with few earlier trials to determine the optimal schedule (Table 1). This means that uncertainty remains regarding current agents' starting dose, dose escalation, and treatment breaks, and it is likely that the registered schedules are not optimal. There may be a better way of identifying clinically useful compounds, selecting the correct dose, and investigating clinical efficacy and safety, as discussed further on.

Role of Phase II Trials

Randomized multiarm parallel-group phase II trials have become very common in mRCC; such a study was a step in the development of 5 of 8 agents included in Table 1. Stadler et al have argued that small randomized phase II trials with appropriate end points are useful to explore hypotheses and prioritize agents for phase III, because although there is a risk of false-negative results, we should be able to detect dramatically positive results, with the understanding that more subtle (but clinically interesting) effects may be missed.[13]

In our opinion, although the control arm provides context, randomized parallel-group phase II trials are associated with some limitations and redundancy. Low patient numbers mean that randomized phase II trials are underpowered to detect differences that may be clinically significant. The phase II randomized trial of 3 doses of temsirolimus (25, 75, and 250 mg),[14] for example, included only 36 to 38 patients per arm. Temsirolimus 25 mg/wk was selected as the dose to progress to phase III because it appeared to have some efficacy and the lowest toxicity, but the trial was not powered to detect differences in efficacy between arms. BEST (A Randomized Phase II Study of VEGF, RAF Kinase, and mTOR Combination Targeted Therapy (CTT) With Bevacizumab, Sorafenib and Temsirolimus in Advanced Renal Cell Carcinoma) was a randomized phase II trial with 4 arms of 90 patients each investigating bevacizumab vs. bevacizumab + temsirolimus vs. bevacizumab + sorafenib vs. temsirolimus + sorafenib.[15] With small treatment arms, the best that investigators could have done was identify the least active arm ("drop the loser"). In the event, however, no combination was associated with improved progression-free survival (PFS) compared with bevacizumab monotherapy. This may have been because of lack of power, and the results are of limited clinical value. In our opinion, this emphasizes the lack of utility of small multiarm randomized phase II trials in mRCC and the need to find more cost-effective alternatives.

A second problem with randomized phase II trials is that the control arm often serves little purpose: the conclusions would often have been the same regardless of whether it was randomized or single-arm. An example is provided by TORAVA (Combination of Temsirolimus and Bevacizumab in Patients With Metastatic Renal Cell Carcinoma), a phase II trial of bevacizumab + temsirolimus vs. bevacizumab + IFN vs. sunitinib.[16] The conclusion was that bevacizumab + temsirolimus was associated with limited clinical benefit and unacceptable toxicity, but this could be concluded without reference to the control arms, particularly the sunitinib arm. Moreover, the bevacizumab + IFN arm was associated with a spuriously high median PFS (16.8 months), again illustrating how treatment arms included for "context" provide little or misleading information. The phase III trial of bevacizumab + temsirolimus (INTORACT [Study Comparing Bevacizumab + Temsirolimus vs. Bevacizumab + Interferon-Alfa In Advanced Renal Cell Carcinoma Subjects]) was already initiated before the results of TORAVA were available. INTORACT found no difference between bevacizumab + temsirolimus and bevacizumab + IFN in terms of median PFS (9.1 vs. 9.3 months, respectively) or median OS (25.8 vs. 25.5 months, respectively).[17] This is a cautionary example; ideally, investigators and sponsoring companies should wait for phase II results before phase III is started. If this is not possible for commercial reasons, there should be processes in place to halt a phase III trial in good time to minimize exposure of patients to inefficacious or harmful agents.

During the development of the TKIs, it became clear that they more frequently led to stable disease (SD) than to inducing tumor regression, and randomized discontinuation trials (RDTs) were proposed to differentiate drug effects from intrinsic growth patterns in patients with SD. Phase II RDTs have been used in the development of 3 of the mRCC agents (Table 1). Using the first RDT in this setting as an example, a large group of patients (n = 202) was treated with sorafenib during a 12-week run-in phase, and at the end of the run-in, patients with SD were randomized to receive either sorafenib or placebo.[18] Afterward, patients with tumor shrinkage $\geq$ 25% continued on sorafenib in an open-label extension. In the early days of targeted therapy, RDTs identified activity early and demonstrated that SD achieved with TKIs was clinically significant.[19] Now that the significance of SD is known, it is