

***Making Optimal Therapeutic Decisions in Patients with Advanced Renal Cell Carcinoma***  
Educational Grant

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## **PURPOSE**

The key objective of this educational program is to improve the competence and performance of oncologists, nurses, and pharmacists who manage patients with advanced renal cell carcinoma. Through this educational offering, learners will be exposed to patient scenarios and cases, as well as didactic lecture. These educational formats will enhance learner competence and performance.

## **SCOPE**

Until a decade ago, systemic treatment options for advanced renal cell carcinoma (RCC) were limited to cytokine therapy and clinical trials of novel agents. With an increased understanding of renal cell biology coupled with more recent pivotal phase III trial data, there are now other classes of agents available for treatment of advanced renal cell cancer: tyrosine kinase inhibitors (TKIs) targeting the vascular endothelial growth factor (VEGF) pathway such as sunitinib, sorafenib, pazopanib, axitinib, and bevacizumab; and mammalian target of rapamycin (mTOR) inhibitors, namely everolimus and temsirolimus. Axitinib and everolimus are FDA-approved for second-line treatment.

### *Multiple First-line Options*

Clinicians and patients now have multiple therapeutic options available to them which are capable of doubling time to disease progression and which also extend overall survival.

In untreated patients with advanced RCC, phase III trials have demonstrated improved progression free survival with single-agent sunitinib,<sup>1</sup> with bevacizumab plus interferon,<sup>2-5</sup> and more recently with single agent pazopanib.<sup>6,7</sup> In addition, improved overall survival has been demonstrated with sunitinib in the first line setting.<sup>8</sup> Improved overall survival is seen with temsirolimus in poor-risk patients.<sup>9</sup> Tivozanib, a highly selective VEGF inhibitor, is now under regulatory review as a therapy in the first line setting.

Since these advances occurred in quick succession, studies were conducted in parallel and the agents were not compared in head-to-head clinical trials. Therefore, determining an optimal agent as first-line therapy is challenging. Complicating the decision process further is the broad regulatory approval of these agents for all patients with metastatic RCC. Therefore the best approach would be to apply high-level clinical evidence to make the optimal treatment decision.

### *Making treatment decision based on tumor biology and clinical characteristics*

The pivotal trials of all the targeted agents were conducted mainly in patients with clear-cell histology with the exception of temsirolimus. Taking this into account, in order to select appropriate therapy using available clinical evidence, patients are categorized according to histologic subtype (clear cell versus non-clear cell). In addition to histology, based on the inclusion criteria in the pivotal clinical trials, using either the Memorial Sloan Kettering Cancer Center criteria (MSKCC) or the Heng's prognostic models, the patients are classified into prognostic risk groups (good, intermediate, and poor) for therapy selection.<sup>10-12</sup>

There is high-level evidence to support the use of TKIs or high-dose IL-2 as first-line therapy in good-risk patients.<sup>6-8</sup> In poor-risk patients, high level evidence supports the first-line use of temsirolimus.<sup>9</sup> When using these therapies outside of the established setting, treating individual patients with unique needs remain challenging.

### *Safety and Toxicity Considerations*

Another challenge in selecting first-line treatment for a given patient lies in evaluating its safety, and tolerability, and effectively managing toxicities and side-effects.<sup>13</sup> The molecular targeted therapies are associated with toxicity profiles distinctly different from those seen with conventional cytotoxic therapies. In addition, safety profile and effectiveness of the targeted agents often change when these drugs are used in a wider, less carefully selected population than patients included in clinical trials. If not recognized and managed appropriately, these side effects may interfere with a patient's ability to continue on a treatment regimen and may lead to poor outcomes or premature termination of an effective treatment choice. For example, fatigue, loss of taste, diarrhea, hand-foot syndrome, and hypertension are the most common side effects of TKIs which can be managed with exercise, antimotility agents, emollient creams, and antihypertension drugs respectively.

It is important to adhere to the FDA approved dosing schedule in the package insert for each agent, which is the schedule proven to be effective in the pivotal trials that supported the approval of the drug. In some instances, when toxicities cannot be managed with appropriate supportive care, dose modifications may need to be considered for potential drug interactions and or for management of toxicities. In some patients a break from treatment might help improve the patients' quality of life without significantly compromising efficacy of treatment.

### *Second-line Treatment Options and Optimal Sequence*

Despite significant improvements in response and survival with the use of TKIs and mTOR inhibitors as first-line therapy, progression is universal in patients with RCC. Nearly every patient with metastatic renal cancer requires second, third, fourth, or further lines of therapy. The challenge lies in determining what best sequence of treatment to use that will provide maximum benefit.

While all the FDA approved targeted agents have a broad regulatory approval, axitinib and everolimus are approved only as second-line treatment options. In patients with disease progression after first-line cytokine-based therapy, high level evidence supports the use of sorafenib,<sup>14,15</sup> pazopanib,<sup>16</sup> axitinib,<sup>17</sup> or sunitinib<sup>18,19</sup> In patients failing to respond to first-line VEGF receptor-targeted therapies, phase III data support use of everolimus<sup>20</sup> or axitinib.<sup>17</sup> The role of immunotherapy (IL-2), is an option as well, however, it remains controversial and of limited efficacy in patients with extensive disease burden. Often times, clinicians and patients are tasked with choosing either sequential VEGF pathway inhibitor therapy (VEGF targeting therapy after progressing on a VEGF targeting agent) or a change in the mechanism of action to an mTOR complex inhibitor (VEGF targeting therapy after progressing on an mTOR inhibitor) and there is very little comparative data to guide this clinical decision. There is a phase II trial underway, called the START trial (Trial ID: NCT01217931), which is looking at sequencing, with randomization to pazopanib, bevacizumab, or everolimus in first-line therapies, and then re-randomization to one of two remaining agents in second-line. This study will provide insight into how sequence may matter with regard to subclasses of agents.

All patients with advanced RCC require optimal supportive care.<sup>21</sup> Advances have been made in supportive care treatment as well. For example, new bone modifying agents drugs with novel mechanism of action (e.g., denosumab) are available for treatment of metastatic bone disease.<sup>22</sup>

Despite these advances, none of the newer therapies have yielded a long-term solution for patients. Even today, the majority of patients are diagnosed with locally advanced or metastatic disease. The American Cancer Society estimates over 65,150 Americans will be diagnosed with kidney cancer in 2013 and over 13,680 will die of the disease.<sup>1</sup> The rate of RCC has increased by 2% per year for the past 65 years. The reason for this increase is unknown. With the introduction of targeted therapy, the survival rate has increased slowly over time, however, for those with advanced disease, the 5-year survival rate is still dismal, in the order of 10%.<sup>2, 3</sup> The rapid expansion of knowledge has presented numerous clinical challenges for clinicians, such as determining choice of treatments according to prognostic category and tumor histology, the optimal sequence, and balancing the benefit of treatment against the toxicities. An understanding of these issues along with knowledge of the available clinical data from pivotal trials will help practitioners take an evidence-based approach to treatment and optimize patient outcomes.

### **Gap Analysis:**

NCCN utilizes the knowledge and expertise of its in-house scientific staff to identify gaps, needs, and areas of development. This information is then incorporated into an overall activity planning meeting, along with previous activity evaluation data and recommendations from the NCCN Educational Program Advisory Committee (EPAC). The Guidelines staff conduct literature searches as well as identify which guidelines have recent and/or major updates, what research is in the pipeline, and other new or upcoming scientific developments. Literature that outlines the use of guidelines in practice, published research identifying cancer or tumor sites that are underserved or have developed new treatment advances, and feedback from activity participants when they are asked the oncologic topics for which they would like education ensures that NCCN aligns its educational programs with learners' knowledge gaps. In all instances, NCCN compares current practice patterns to best practices to determine where the educational gaps lie.

### **Learning Objectives**

Following this educational intervention, learners will be able to:

- Apply the existing and emerging clinical research data to make evidence-based selection of first-line therapy for treatment of advanced renal cell cancer.
- Select optimal subsequent lines of treatment to improve outcomes of patients with advanced RCC
- Describe the toxicities of targeted therapies used in treatment of renal cell cancer and outline the strategies used to effectively manage them

### **Target Audience**

This educational program is designed to meet the educational needs of medical oncologists, urologists, nurses, pharmacists, and other healthcare professionals who manage patients with advanced kidney cancer.

This activity will meet the following clinician competencies:

- IOM: Employ evidence-based practice
- ACGME/ABMS: Demonstrate medical knowledge
- ACPE: Practice evidence-based medicine; deliver patient-centered care
- ANCC: Demonstration of a learned skill and implementation of that skill in practice/healthcare setting

## **METHODS**

NCCN plans to offer a live streaming webinar, featuring both didactic lecture and patient vignette videos. Once the webinar has ended, it will be archived as a webcast on NCCN's learning management system, <http://education.nccn.org> for one year. Two non-educational strategies will be offered: a link to the NCCN Guidelines® for Kidney Cancer and a reminder email to learners featuring key clinical pearls.

### **Description of Program**

NCCN plans to launch a live webinar stream, consisting of slides, audio, and video. The live webinar will include didactic lecture and videos of patient vignettes. The short vignettes will consist of physicians speaking with patients with RCC regarding sequencing and disease management. The live webinar will be accredited for one hour for physicians, nurses, and pharmacists.

The multiplatform format for this activity series will be a unique educational event in which clinical data will be presented along with simulated experiences of physicians and their patients. This compelling format will provide both patient and physician perspectives. The program will not simply present the NCCN Guidelines concerning RCC, but will discuss the application of these guidelines in an office setting with a focus on a specific patient situation.

In order to extend the reach of this program, NCCN will archive the session from this activity in NCCN's new Learning Management System, <http://education.nccn.org>. NCCN anticipates a minimum of 200 viewers for this archived webcast. Approximately 0.75 continuing education units will be offered for the enduring materials. The archived recordings will consist of slides, audio, and patient videos.

NCCN believes that it is important to continually support its learners through their ongoing decision process with patients. Therefore, NCCN intends to utilize two non-educational strategies to enhance the acquisition of knowledge education gained through the live and archived educational activities. The first non-educational strategy is to provide a link to the NCCN Clinical Practice Guidelines in Oncology: Kidney Cancer® to all webinar and archived webcast learners via NCCN's Learning Management System. Secondly, NCCN plans to send a reminder email to learners post-activity. The reminder email will contain key clinical pearls from the live and archived presentations and will serve as a learning enhancement to supplement clinician performance.

### **Rationale for Selection of Educational Formats**

To determine the best possible format for educational programming, NCCN uses the following approach:

- An analysis of components of existing programs

- An assessment of an educational need or knowledge gap
- Identification of the target learners, including their healthcare role and past and current experiences in the identified program area
- Development of learning objectives to address the educational gaps
- Identification of the most efficacious learning formats for the learner and the learning objectives
- Assessment of means of measuring the outcomes of the program.

This educational program implements a number of adult learning principles, including the following:

- The need to know the reason for learning
- Experience as the basis for learning activities
- Relevance of content
- Problem-centered nature of learning
- Self-direction, independent learning, and empowerment

The proposed educational activity will result in Level 5 outcomes, according to Moore's 2009 expanded outcome framework. Level 5 is defined by Moore as the degree to which participants do what the CME activity intended them to be able to do. To measure the effectiveness of this activity, NCCN's outcome measurement will collect self-reported data on clinician application of content from the educational activity to practice and change in practice. Thus NCCN will measure the activity for Level 5 subjective outcomes through self-report of performance.

Past activity evaluations demonstrate community oncologists' self-reported intent to change their practice. The evaluations show that community oncologists who participate in NCCN educational programs intend to change their practice as a result of the education and plan to implement Guideline updates learned at the educational activity into their practice.

## **RESULTS**

NCCN will collect data through various instruments: the pre-test, the activity evaluation, an immediate post-test, a 30-day post-test, and a post-activity follow-up survey. The pre-test will measure baseline practice. The evaluation and follow-up surveys will ask learners about their practice patterns during these specified time intervals. Analysis of this information will determine whether a practice change/performance improvement has occurred.

The activity evaluations assess:

- The extent to which the educational objectives are being met;
- The quality of the instructional method, faculty and content;
- Change in participant's knowledge and attitudes;
- Change in practice as a result of participation;
- Use of clinical algorithms and impact of activity; and
- How participants will apply what they learned to their practice.

The average score of pre-test takers for both the live webinar and the enduring webinar are shown below.

	<b>Pre-Test</b>	<b>Immediate Post Test</b>	<b>30 day Post Test</b>
<b>Live Webinar</b>	65.4%	75.1%	90.5%
<b>Enduring Webinar (Average)</b>	68.3%	75.4%	76.4%

The increase in average test score from pre-test to immediate post test to 30 day follow up post test coupled with a 100% self-reported knowledge retention indicate effective programming where educational content and the multiple formats align with learning objectives.

More specifically, key takeaways from this activity include:

- 95.7% of respondents agreed or strongly agreed that this activity helped to achieve the learning objectives.
- 93.5% of respondents agreed or strongly agreed that participation in this activity increased their knowledge of the presented topic.
- 100% respondents stated that they applied changes in their practice/healthcare role as a result of participation in this activity.