OVERALL GOAL & OBJECTIVES

To encourage oncologists to appropriately utilize dose modifications and schedule changes for their patients with advanced renal cell carcinoma (RCC) with the aim of maximizing positive treatment outcome while minimizing adverse events. The goal of the educational initiative is to improve clinician knowledge and self-reported performance with the following aspects of clinical care for patients with metastatic RCC (mRCC):

- The targeted agents currently approved for the treatment of mRCC have unique adverse event profiles that can pose a particular challenge in patients with comorbid conditions or poor prognostic factors. To improve patient quality of life and enhance treatment outcomes, all members of the multidisciplinary cancer care team need to be knowledgeable about common adverse effects and how to monitor and manage these toxicities.
- Care for patients undergoing treatment with these medications should include education about the therapy, potential side effects, drug interactions, and the need for adherence to dosing schedules to affect the optimal outcome for patients. This information will have significant impact on the quality of life and treatment outcomes for these patients. Understanding the mechanism of action of each therapy, potential adverse effects, drug interactions, and the negative impact of reductions in recommended dosage will allow oncologists and other health care providers to provide comprehensive care for patients with advanced RCC.
- Oncologists, NPs, PAs, nurses and pharmacists must counsel patients to ensure that they are aware of potential treatment-related adverse effects and understand the need to contact their health care practitioner for early intervention so that therapy can be maintained. Although severe side effects may occur in spite of effective patient education and early intervention, their incidence can be minimized with implementation of recommended side-effect management strategies.

TECHNICAL APPROACH AND CURRENT ASSESSMENT OF NEED IN TARGET AREA

To describe the Roswell Park experience using a TKI, a sample of 30 mRCC patients from 2006-2012 was drawn to examine dose or scheduling changes due to toxicities (Table 1). For the sake of comparison, all patients were treated with the same drug and began with the 4 weeks on/2 weeks off schedule. Of those 30 patients, 27 initiated treatment at the standard dose of 50 mg. Seven patients at the 50 mg. dose experienced side effects in the range of 20-256 days into treatment. Two of those seven patients had treatment stopped a second time due to adverse effects. Two patients who initiated treatment at the 37.5 mg. dose also experienced side effects in the range of 105-139 days into treatment. Five patients required a dose reduction to better control the adverse treatment effects. Two of those five also had schedule changes that included continuous dosage at the reduced level.

What these limited data suggest is that tyrosine kinase inhibitors require vigilant monitoring to detect adverse effects . Almost 30% of the mRCC patients receiving a TKI regimen experienced side effects that required some modification to their treatment. By better controlling those issues, patient compliance with prescribed treatment regimens should help improve outcomes.

Consultations with a community oncologist at one of the largest private oncology practices in Western New York provided similar results. According to this source, approximately 50% of the patients who start treatment on a TKI drug experience side effects serious enough to require a hold on treatment. The most frequent adverse events observed in this population were diarrhea and nausea. This particular oncologist indicated that his

practice needs to emphasize better patient education to help control these problems early so that treatment doses and recommended schedules can be maintained.

The target learner audience for the initiative will be **medical oncologists, urologists, surgeons, nurse practitioners (NPs), Physician Assistants (PAs), oncology nurses, and oncology pharmacists.**

Table 1. Sample of Roswell Park Cancer Institute of mRCC patients from 2006-2012 (n= 30)

# Patients experiencing side effects significant enough to place a hold on treatment	50 mg. initial dose – 7 pts. 37.5 mg. initial dose – 2 pts.
# Days on Tx before 1st hold	Mean = 143 days @ 50 mg.; 122 days @ 37.5 mg Median = 161 days @ 50 mg.; 114 days @ 37.5 mg. Range = 20-256 days @ 50 mg.; 105-139 days @ 37.5 mg.
Experienced side effects forcing a 2nd hold	2 pts. @ 50 mg. dose
Outcomes	5 pts. had dose reduction from initial 50 mg. dose - 1 of the 5 resumed 50 mg. dose after 56 days - 3 of the 5 also had scheduling changes to Tx 1 pt. had dose reduction from initial 37.5 mg. dose - This patient also had scheduling changes to Tx

INTERVENTION DESIGN AND METHODS

Educational methodology will utilize case based discussions to focus on: 1) the impact of side effects on need for dose modifications and schedule changes in mRCC; 2) the importance of maintaining dose intensity in treatment of mRCC; 3) clinical data on the relationship between dose exposure and clinical benefit; 4) strategies for maximizing dose intensity, schedule changes, side effect management, and utilization of biomarkers to optimize patient benefit. Through real-world case presentation, clinician participants will learn about best practices in managing dose modifications and be better able to analyze clinical patient scenarios through peer-to-peer and expert feedback. **A teaching tool will be provided to all participants in both the live event and the subsequent enduring activity that details "at a glance" each biologic therapy, possible side effects, and recommendations for minimizing these side effects. A "decision tree" would also be provided so that clinicians would have a reminder on how best to proceed in the event that scheduling changes need to be made to a patient's treatment regimen.**

Learning Goals

Upon completion of this activity, participants will be able to:

- Compare and contrast targeted agents used for the treatment of mRCC with regard to their dosing schedule, side effect profiles, dosing flexibility, and dose intensity
- Describe the effect of dose reductions and interruptions on clinical outcomes of patients being treated with targeted therapies for mRCC
- Identify customized dosing strategies to maximize drug exposure for patients being treated with targeted therapies for mRCC
- Develop a comprehensive care plan to monitor and manage patients with mRCC

- Identify common side effects associated with agents used to treat mRCC and strategies for managing these toxicities
- Counsel patients with mRCC about adherence to oral therapy

EVALUATION DESIGN

The live education activity will be measured for participation (attendees participating in live event), satisfaction (CME/CE evaluations forms), and changes in medical knowledge/competence (CME/CE pre- and post-tests, 3-month follow-up). Prior to the start of the live Grand Rounds activity, RPCI will administer a Performance Improvement questionnaire to all participants (see Appendix C). This survey will assess current practice in treating patients with advanced renal cell carcinoma. Immediately following the event, another survey will assess changes in knowledge and level of commitment to change practice for these patients. Finally, three months post-activity, another survey will assess improvements in knowledge and application of the education with the clinician's individual practice. It is expected that participants will express greater confidence in 1) knowing when to institute schedule changes for the new biologic therapies; 2) more effectively monitoring patient progress as a result of the schedule change; 3) recognizing and managing side effects of the newer therapies. Outcomes data on reported change in practice will be segregated into two groups: Hospital-based oncologists and community-based oncologists. It is expected that at least 25% of the hospital-based oncologists will indicate a change in practice as a result of participating in this activity (ex., use of "at a glance" or "decision tree" handouts) when treating patients for mRCC. It is expected that approximately 75 % of community-based oncologists will indicate a change in practice.

During the live event, several questions will be posed to the audience using either an Audience Response System or ***Poll Everywhere*** to keep the participants engaged in the educational intervention. Engagement for the enduring activity will be encouraged through the placement of interactive questions throughout the activity, participations results of which will be assessed following activity completion.

The enduring education activity will be measured for participation (monthly participation statistics), satisfaction (CME evaluations forms), and medical knowledge/competence (CME post-tests). To further assess educational effectiveness of the enduring activity, RPCI and Medscape Oncology will compare individual learner responses to pre-assessment questions leading into the enduring activity with the learner's responses to the same post-assessment questions following the activity. Each question is mapped to an activity learning goal, and participant responses will be tracked and measured for change. This capture of baseline and post-participation responses—with learners serving as their own controls—provides for a determination of overall effect, and an assessment of knowledge and competency on a per-learner and overall participant basis.

For the enduring activity, statistical analyses will be performed on the Per-Protocol group (learners who complete all pre and post questions) to determine the significance of findings, with the effect size of the intervention calculated by comparing the pre- and post-assessment means. The Learning Concept group (learners who answer at least 1 matching pre and post-test question) will be evaluated using the difference between individual pre- and post-assessment question pairs. These analyses allow categorization of learners as follows:

- **Improved Learners:** Any incorrect response on a pre-assessment question with a correct response on the matched post-assessment question
- **Reinforced Learners:** Correct responses on any pre- and post-assessment matched question
- **Unaffected Learners:** Any incorrect responses on a post-assessment question, whether the response to the matched pre-assessment question was correct or not

Project outcomes may be considered for presentation at professional meetings, manuscript submission to peer-reviewed journals, and publication of free-access articles.

DETAILED WORKPLAN AND DELIVERABLES SCHEDULE

To address knowledge and clinical practice gaps at the community level, Roswell Park Cancer Institute will design and host a **live grand rounds activity** that will include a foundational and case-based discussion between a clinician expert, Dr. Roberto Pili, Professor of Oncology and Chief of the Genitourinary Section, Department of Medicine at RPCI, and a community-based oncologist. Dr. Pili will serve as chair for all initiative activities. All educational content will be reviewed by Dr. Pili, RPCI, and the Medscape Education Oncology Scientific Director, and will undergo compliance review by an external reviewer with no conflicts of interest to ensure fair balance. If there are any concerns regarding the content, a leading expert in the field will conduct additional peer review.

This live educational activity will be made available to oncologists and urologists practicing onsite at Roswell Park Cancer Institute (RPCI). Additionally, clinicians practicing locally at RPCI affiliate hospitals and independent practices in the regional area will be invited to participate in this event via Microsoft Lync.

RPCI will partner with Medscape Oncology to videotape the grand rounds activity and extend the reach of the lessons taught within the live program to a broader audience of clinicians practicing outside of the Western and Central New York region. An edited version of the live event will be developed into a 30-minute virtual grand rounds CME-certified activity, which will be hosted on Medscape with links from RPCI's education web site. The activity will highlight the segments from the live event, which provide context for the impact of dose modifications in mRCC and point-of-care strategies for maximizing dose intensity. A personalized educational reinforcement message will be emailed to each learner 30 days after completion of the online activity, which will synthesize key learning points to enhance and improve knowledge retention. The message also will provide links to related resources and activities of interest, thereby reengaging learners on the topic of dose intensity. See Appendix C for more the deliverables schedule.

DELIVERABLES SCHEDULE

Identify community oncologist for live event; reserve venue	August 2013
Develop outline, program materials, teaching tools for live event	August-October 2013
Conduct Live CME activity: Optimizing Dose Intensity for Patients with Metastatic Renal Cell Carcinoma	October 2013
Development of 30 minute enduring material: Optimizing Dose Intensity for Patients with Metastatic Renal Cell Carcinoma	November-December 2013
Enduring material posts to Medscape web site	January 2014
Three-month follow-up survey from live activity is conducted	January 2014
Analysis of outcomes data from live event is completed	April 2014
Enduring material expires	January 2015
Analysis of outcomes data from enduring material is completed	March 2015

APPENDIX C: PERFORMANCE IMPROVEMENT QUESTIONNAIRE

User generated ID: _____

Questions for pre and post-test:

1) What is the standard dosing schedule for patients just beginning a TKI? (Check only ONE response.)
   - ☐ Continuous dosing
   - ☐ Intermittent dosing
   - ☐ Depending on the drug

2) What is the standard dosing schedule for patients just beginning treatment with a TKI? (Check only ONE response.)
   - ☐ 2 weeks on/1 week off
   - ☐ 4 weeks on/2 week off
   - ☐ Continuous dosing
   - ☐ Depending on the patient

3) What is the next therapeutic step when patient is unable to tolerate the initial standard treatment with a TKI? (Check only ONE response.)
   - ☐ Dose reduction
   - ☐ Dose interruption
   - ☐ Depending on the patient's symptoms
   - ☐ Switch to a different drug

4) What is the next therapeutic step when patient is unable to tolerate the initial standard treatment with a tyrosine kinase inhibitor? (Check only ONE response.)
   - ☐ Maintain same dose but switch to a 2 weeks on/1 week off schedule
   - ☐ Reduce dose but maintain a 4 weeks on/2 week off schedule
   - ☐ Reduce dose and change to continuous dosing schedule
   - ☐ Switch to a different drug

5) Which **early** side effects are associated with TKI use in metastatic kidney cancer? (Check all that apply.)
   - ☐ Diarrhea
   - ☐ Fatigue
   - ☐ Hypertension
   - ☐ Mouth sores
   - ☐ Hand & foot syndrome

6) Which **late** side effects are associated with the use of TKI use in metastatic kidney cancer? (Check all that apply.)
   - ☐ Diarrhea
   - ☐ Fatigue
   - ☐ Hypertension
   - ☐ Mouth sores
   - ☐ Hand & foot syndrome

7) I am confident in my ability to address the prevention and treatment of adverse effects from the use of TKIs. (Check only ONE response.)
   - ☐ Strongly agree
   - ☐ Agree
   - ☐ Neutral
   - ☐ Disagree
   - ☐ Strongly disagree

8) What is the proper time frame for patient follow–up to check for toxicities after **initial** treatment with a TKI? (Check only ONE response.)
   - ☐ 1 week after first cycle of treatment is completed
   - ☐ 2 weeks after first cycle of treatment is completed
   - ☐ Just before the second cycle of treatment is started

9) If a patient develops a significant toxicity to a TKI treatment at the recommended dosing level (ex., hypertension), what should be your next course of action? (Check only ONE response.)
   - ☐ Treat the hypertension and continue at the recommended treatment levels
   - ☐ Reduce the dosing level
   - ☐ Change the dosing schedule
   - ☐ Discontinue use and try a different class of drug

10) Under which conditions should the use of TKIs be **discontinued,** as opposed to interrupted? (Check all that apply.)
   - ☐ Grade 3 or 4 drug-related hepatic adverse events that cannot be resolved
   - ☐ In the presence of clinical manifestations of congestive heart failure
   - ☐ Cases of severe hypertension
   - ☐ Patients undergoing major surgical procedures

11) What effect on clinical outcomes can result from dose reductions and schedule change of TKI treatment? (Check all that apply.)
   - ☐ Same clinical benefit as without dose reduction/schedule change
   - ☐ Decreased clinical benefit as without dose reduction/interruption
   - ☐ Same clinical benefit as without dose reduction/schedule change but reduced toxicities
   - ☐ Increased clinical benefit as without dose reduction/schedule change because patients are able to stay on treatment for a longer period of time