Patterns of Care

Renal Cell Cancer Edition

Patterns of Systemic Management of Renal Cell Cancer

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Research To Practice®

CME INFORMATION

OVERVIEW OF ACTIVITY

Advances in the biologic understanding of renal cell carcinoma (RCC) and the emergence of clinical trial data with targeted therapeutic agents have resulted in the availability of novel treatment strategies for this challenging disease. However, which treatment strategy is optimal may be highly debatable in certain clinical scenarios and includes issues such as the tolerability of therapeutic agents and regimens, the sequencing of therapeutic agents and the management of the primary tumor in patients with de novo metastatic RCC. To address the existing management uncertainties of clinician learners, this CME activity focuses on the self-described treatment approaches and perspectives of 150 randomly selected community medical oncologists and 12 clinical investigators in a variety of key clinical scenarios in RCC. This program will provide information on national patterns of care and current clinical research strategies to assist medical oncologists and other cancer clinicians in the formulation of optimal clinical management strategies for patients with RCC.

LEARNING OBJECTIVES

- Evaluate management issues in cases of RCC for which relative agreement or heterogeneity exist in patterns of care, and make treatment decisions considering this information.
- Counsel appropriately selected patients with RCC about participation in ongoing clinical trials.

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This program is supported by an educational grant from GlaxoSmithKline.

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HARDWARE/SOFTWARE REQUIREMENTS

An Internet connection that is at least 28.8 Kbps
A monitor set to 1280 x 1024 pixels or more
Internet Explorer 6.x or newer, Firefox 2.x or newer, or Safari 2.x or newer
Macromedia Flash plug-in 6.0 or greater
Adobe Acrobat Reader
(Optional) Sound card and speakers for audio

Last review date: June 2010
Expiration date: June 2011

Patterns of Care

Renal Cell Cancer Edition

To go directly to the slides and comments, **click here**.

Over the past year, our oncology CME group has implemented a multifaceted educational curriculum designed to address many of the complex issues defining the current management of renal cell carcinoma (RCC), a somewhat uncommon but critically important disease with a rapidly evolving clinical research database.

For this, the final chapter in our integrated effort, we once again take a look at what's happening in practice, and to that end we present the results from a Patterns of Care survey conducted with 150 US-based community oncologists and the 12 clinical investigators who participated in the **three integrated audio programs** that were key components of this curriculum. The survey focused on a number of related and salient management issues, and in our **slide program** we present select poll results accompanied by perspectives on the findings from MD Anderson's Dr Eric Jonasch, who was one of the 12 faculty respondents. The key survey questions listed below are ordered based on our impressions of the current level of interest among oncologists:

1. **Should patients presenting with an asymptomatic primary RCC and metastases have the primary tumor removed?**

This is clearly controversial. For the analogous situation in colorectal cancer, practicing oncologists are routinely holding off on sending patients to surgery and are initiating systemic therapy. However, in RCC, perhaps because many primary tumors end up causing symptoms, investigators like Dr Jonasch have been mixed in their acceptance of this strategy, particularly with two older randomized interferon-era trials demonstrating a benefit with "cytoreductive nephrectomy."

2. **What's the usual first-line therapy for advanced disease?**

For patients without major adverse clinical presenting factors, there is consensus that sunitinib is up first, but Dr Jonasch notes that pazopanib and bevacizumab/interferon are also reasonable choices, depending on the patient. Temsirolimus is suggested when adverse clinical and biochemical parameters are present. Second-line therapy is even more up for grabs, but the only agent studied and reported on specifically in this situation is everolimus.

3. **How should significant side effects from TKIs be managed? Is it important to maintain the dose "under the curve"?**

While there is disagreement over the "Level 3" scientific answers to these questions, many investigators, including Dr Jonasch, express concern that in community practice the duration of these therapies may be suboptimal, possibly undermining patient benefit. There is general agreement on the methods to modify doses based on toxicity — although Dr Jonasch is one of the few researchers who do not hesitate to go to a two weeks on, one week off schedule of sunitinib.

4. **Should adjuvant systemic therapy be administered outside a protocol setting?**

Investigators — including a very vehement Dr Jonasch — agree that this should not be done as the outcome could potentially be either beneficial or harmful. Eligible patients have the opportunity to participate in one of the available trials. However, 21 percent of oncologists offer sunitinib in some adjuvant scenarios.

Coming up next week... the 5-Minute Journal Club returns with our initial take on ASCO.

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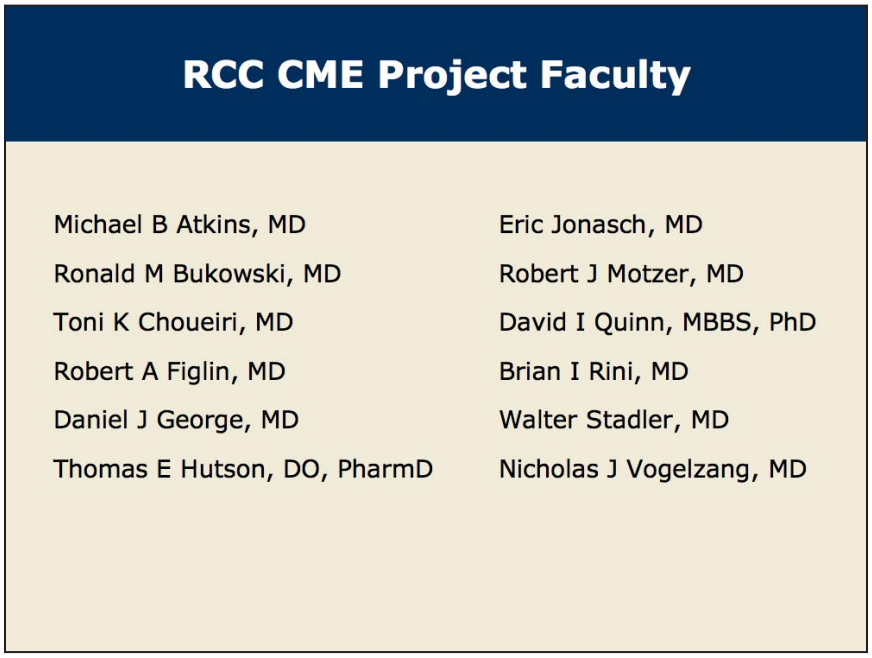
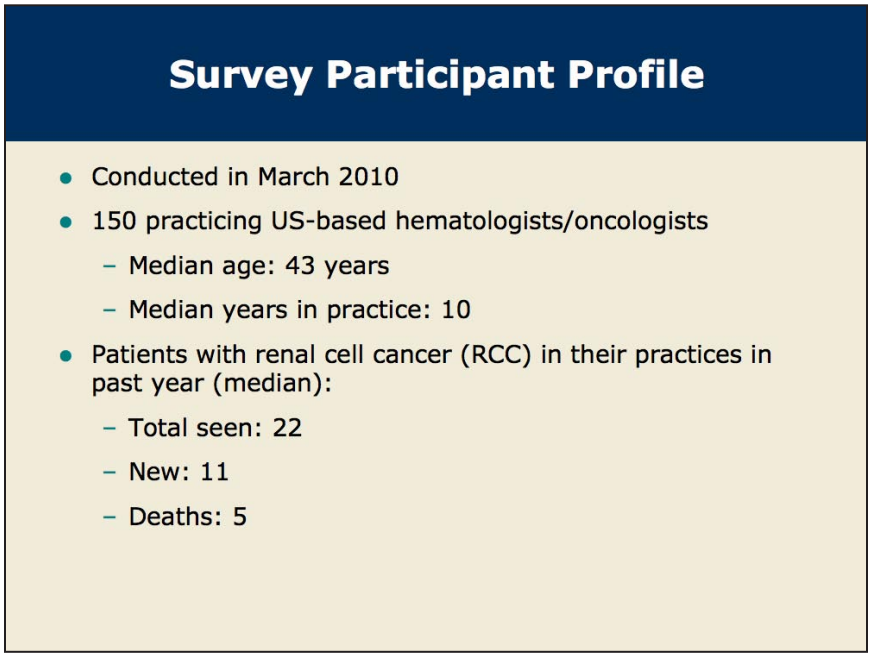
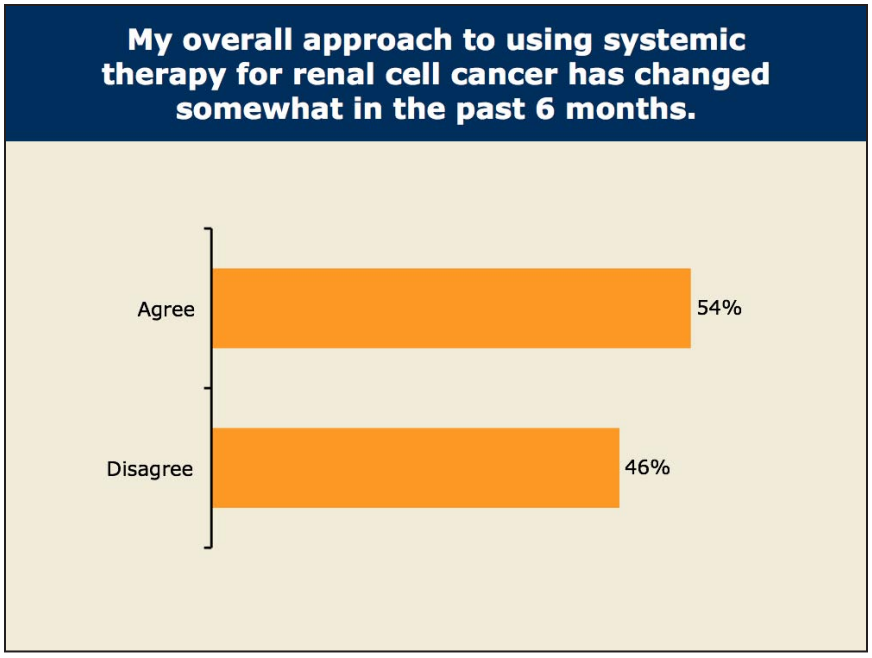
Editor's Comment (Neil Love, MD)



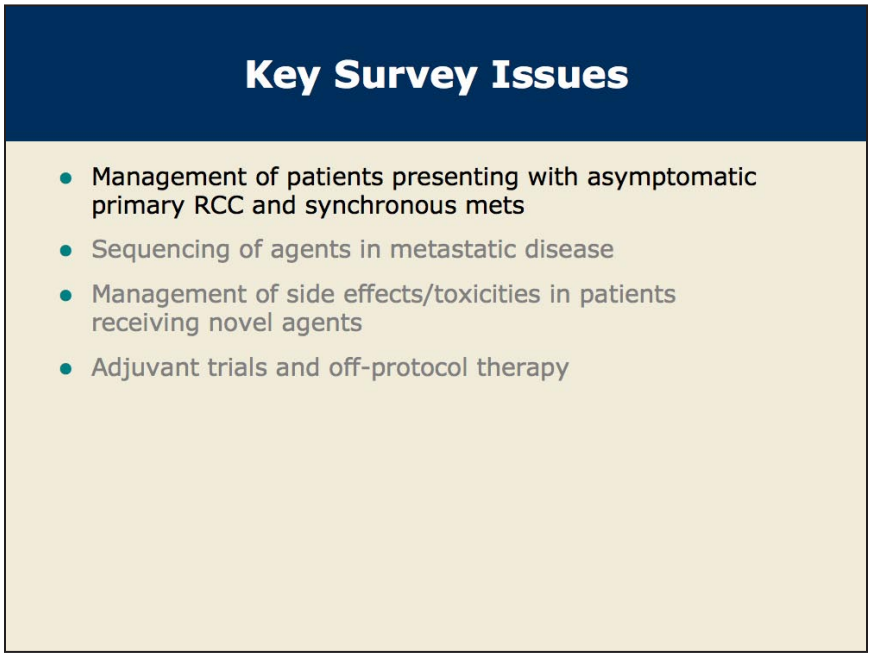
Slide 1
This March 2010 national survey of 150 US-based medical oncologists is the final part of a yearlong effort to address important CME needs in the management of renal cell cancer. The interventions in the project included three nationally distributed audio programs and three virtual video web presentations. A faculty of 12 RCC clinical investigators participated in the needs assessment, education programs and Patterns of Care studies. My editor's comments for this slide set include select results from a survey of our faculty. A printable, downloadable version of this program is available.



Slide 2
The physicians surveyed were perhaps slightly younger than average. While RCC is less common in practice than breast, colon and lung cancer, it is still the focus of about one new patient visit per month and a number of deaths per year.



Slide 3
Clinical research on systemic therapy for RCC continues to evolve rapidly, and reflecting this, about half of the oncologists stated that they have changed their approach to this disease in the past six months.



Slide 4
The survey focused on several issues that were identified both in the three CME activities by the faculty and in prior polls of oncologists in practice. I met with one of the faculty, Dr Eric Jonasch, on June 18, 2010 for an interview. We reviewed the major findings, and edited comments from Dr Jonasch are included on four slides of our 47-slide set.

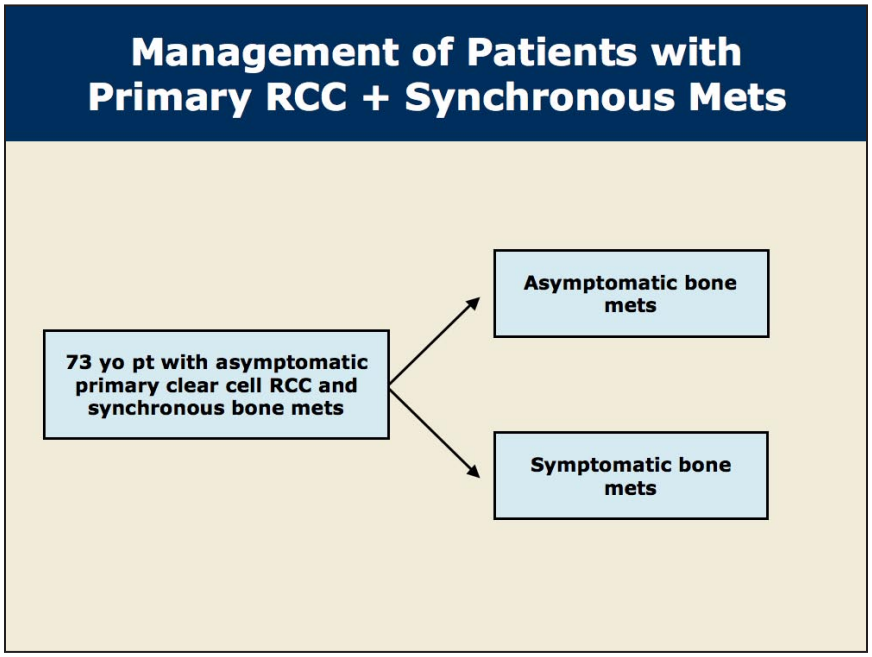
Management of Patients Presenting with Asymptomatic Primary RCC and Synchronous Mets

If you look at the eligibility criteria for the cytoreductive nephrectomy trials published in 2001, you see that those patients had good performance statuses, not too many sites of metastatic disease and resectable primary tumors. I still believe that outside of a clinical trial, those people should have a nephrectomy first and then undergo systemic therapy. That may change when we complete the studies that are being done in Europe, which are asking the question whether nephrectomy should be used at all. But right now in 2010, that's what should be done.

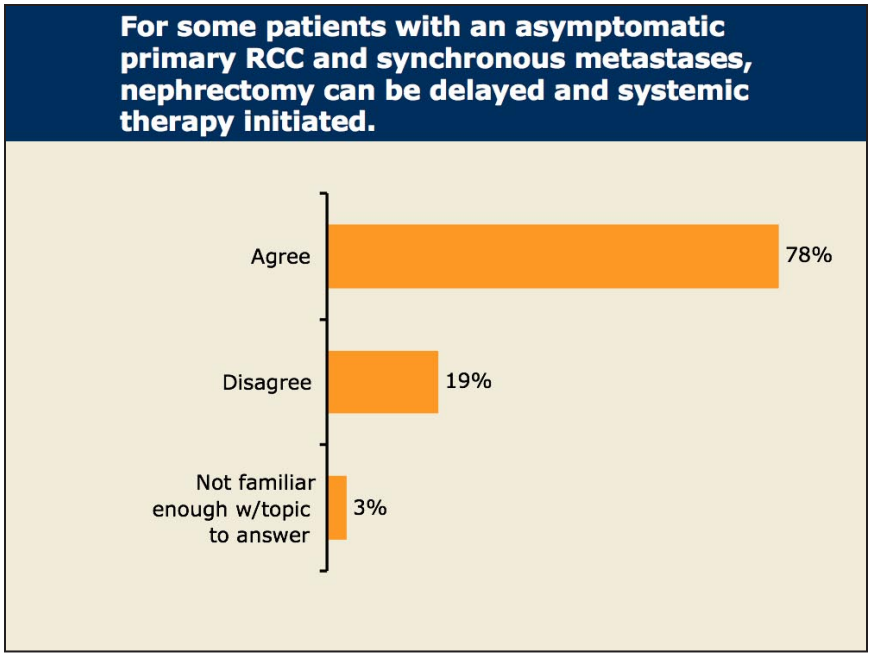
That does not mean that the individual who has a large and difficult-to-manage primary tumor or who has extensive metastases and a poor performance status should undergo nephrectomy — that's not been tested. Clearly some individuals receive systemic therapy and then their disease recedes, their primary tumors get smaller and become resectable and maybe then they can undergo resection of their primary tumor, if it appears appropriate. That's the algorithm we use outside of clinical trials.

Interview with Eric Jonasch, MD, June 18, 2010

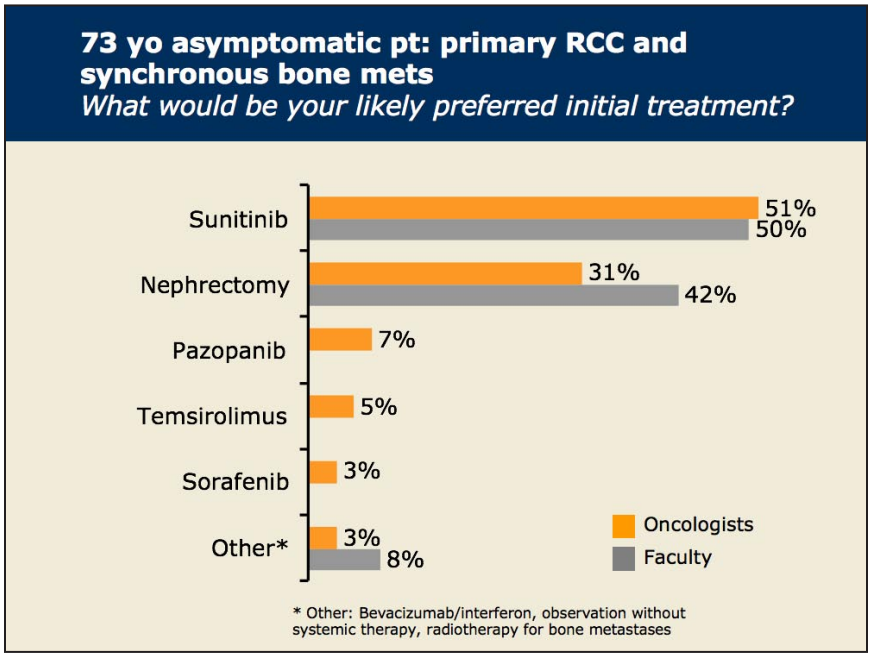
Slide 5
Dr Jonasch's approach to these patients reflects that of most of the faculty, who often recommend nephrectomy if it can be done without great risk.



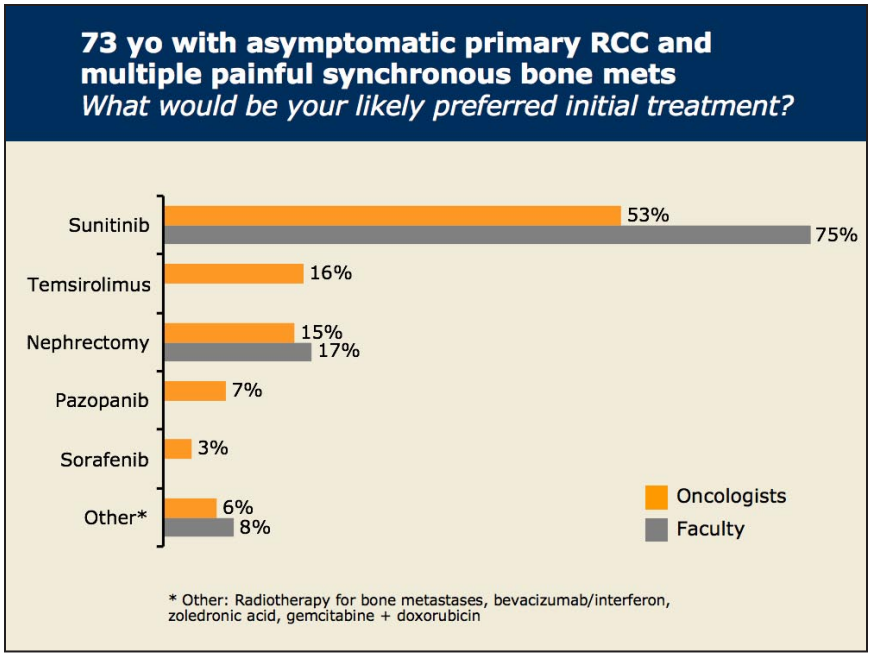
Slide 6
Somewhat surprisingly, the RCC issue of greatest interest to oncologists was the management approach for patients presenting with asymptomatic primary tumors and synchronous mets. We asked about two scenarios, one in which the mets were asymptomatic and the other with more extensive mets that were symptomatic.



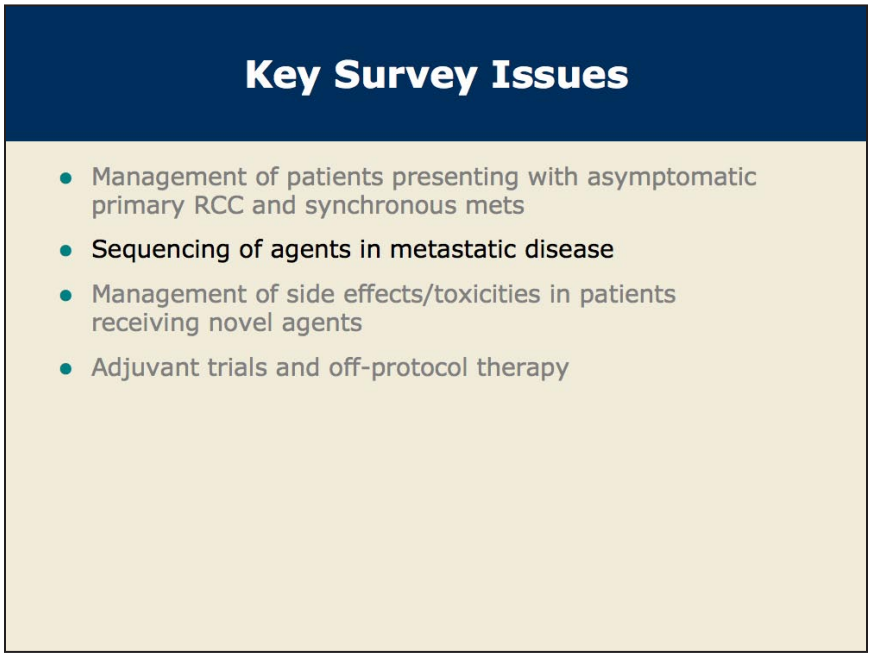
Slide 7
The management approach for patients presenting with an asymptomatic primary RCC and synchronous mets is controversial and may reflect an uncommon scenario, but 78 percent of oncologists — perhaps following a model recently integrated into the management of the analogous situation in colorectal cancer — strongly consider initial systemic therapy rather than cytoreductive nephrectomy. As will be clear, the faculty is less enthused about this practice.



Slide 8
For an otherwise healthy 73-year-old asymptomatic patient with primary RCC and synchronous bone mets, there is clear-cut controversy. About a third of the oncologists would send the patient to surgery, and the faculty was split evenly between nephrectomy and systemic therapy.



Slide 9
When the scenario is altered by having the patient in pain from the mets, a significant shift occurs toward systemic therapy, and now nine of 12 investigators agree.



Slide 10
The second major CME topic relates to the selection of systemic therapy in advanced disease. There is considerable variation currently, reflecting the recent evolution of three new classes of agents that have proven helpful with the disease: TKIs, mTOR inhibitors and anti-VEGF agents such as bevacizumab.

Sequencing of Agents in Metastatic Disease

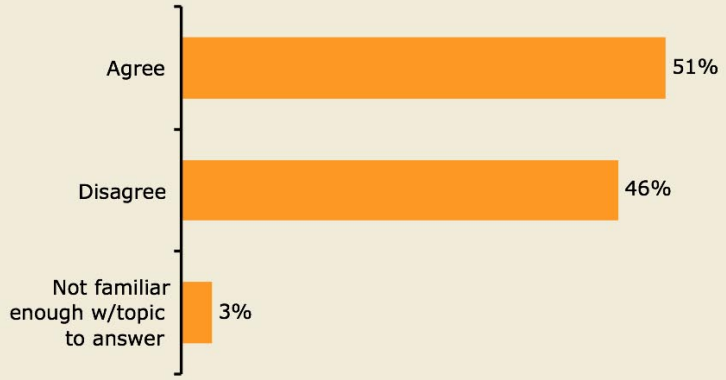
Sunitinib, pazopanib or bevacizumab with interferon are the de facto front-line choices for individuals with good- or intermediate-risk clinical and biochemical parameters. Those with poor-risk criteria should receive temsirolimus. Because of the relative paucity of data in the second-line setting, it's hard to say what's standard. We do have Level 1 evidence that everolimus prolongs PFS for individuals who experience disease progression on TKIs. Beyond that, it's dealer's choice. Sometimes you have to get to the third line to find the winner for a particular patient, and if you haven't harmed that patient with the first or second drug, he or she might enjoy prolonged PFS.

Sunitinib seems to be the dominant agent still, but it will be interesting to see over the next year if major changes occur in the use of pazopanib or bevacizumab/interferon. One suggestion, based on noncomparative data, is that pazopanib may have a better toxicity profile than sunitinib, but we don't yet have a head-to-head comparison. So although we have been using pazopanib in the front-line setting, we anxiously await the Phase III study results.

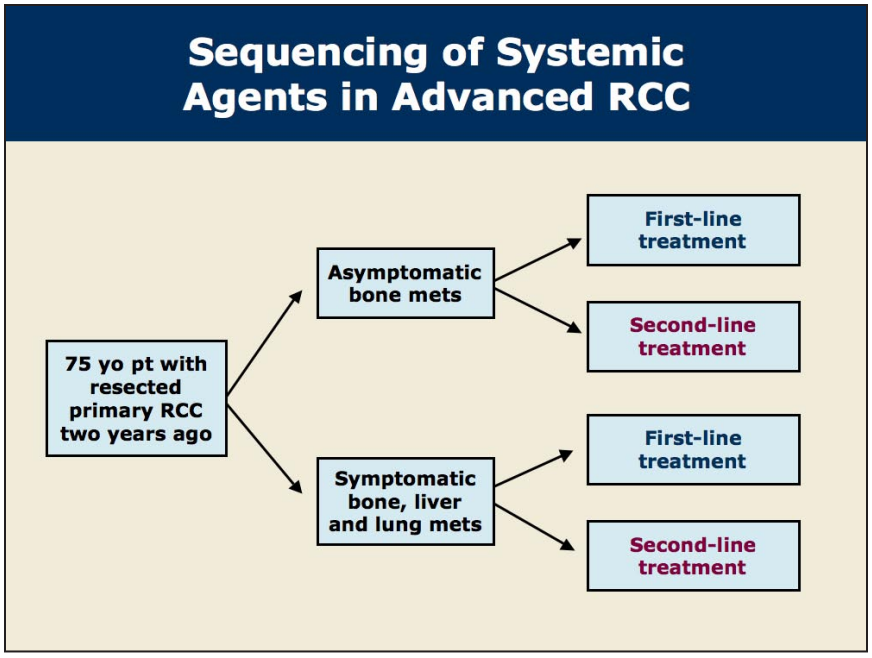
Interview with Eric Jonasch, MD, June 18, 2010

Slide 11
Dr Jonasch notes that in the most common scenario, in which patients do not have emergent clinical and biochemical findings, the evidence-based first-line options in his mind are sunitinib, pazopanib and bevacizumab/interferon. For first-line treatment of patients with poor-risk disease, temsirolimus has been studied the most extensively and is standard, and while there is no standard second-line treatment after TKIs, everolimus has clinical trial data supporting its use for these patients.

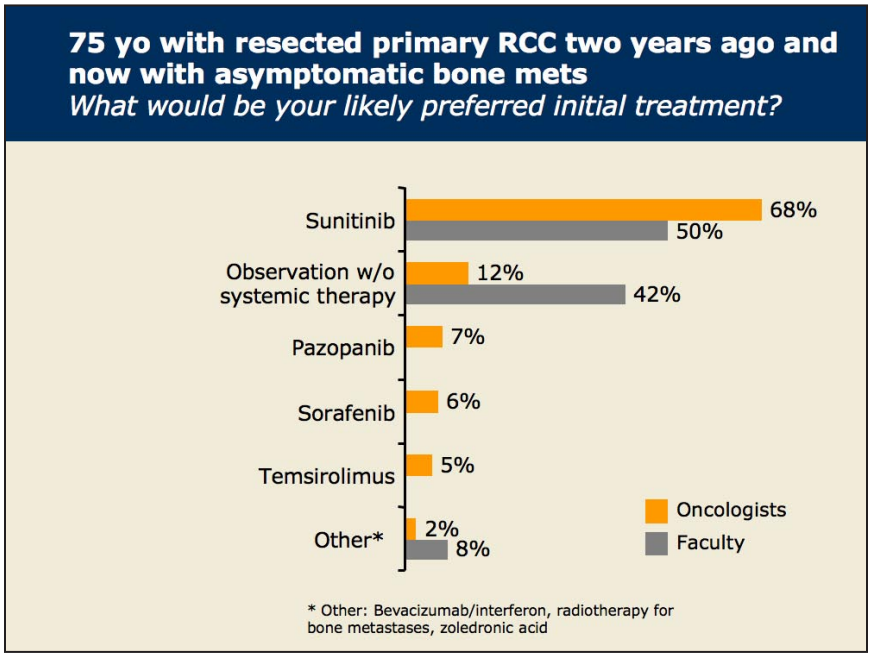
For some asymptomatic patients presenting with metastatic renal cell cancer, a "watch and wait" observation plan is reasonable, even for younger patients.



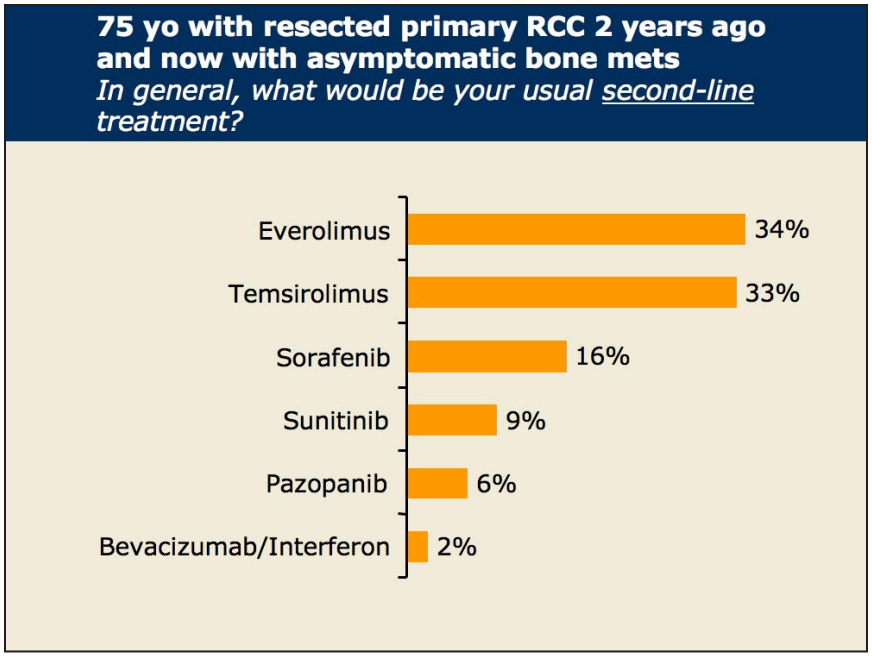
Slide 12
The initial education event in this initiative was a "Think Tank" co-chaired by Dr Robert Figlin. We gathered six investigators and spent the day in our recording studio in Miami planning an initial survey evaluation of our target education audience (medical oncologists) and establishing a series of major content objectives that are capsulized in our list of four. One of the faculty, Dr Michael Atkins, was particularly convinced that the strategy of expectant observation without specific treatment perhaps could be used more, but half of our oncologists don't seem to support this strategy in this situation.



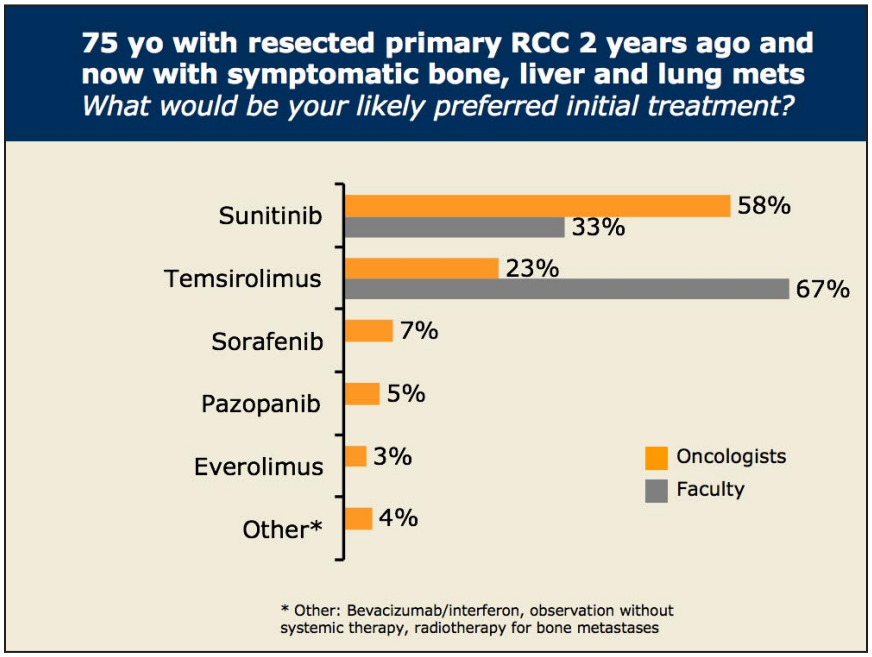
Slide 13
With the faculty's advice we created a series of four questions that relate to the choice and sequence of agents in advanced disease. The first scenario relates to the choice of treatment in both the first- and second-line settings for patients with asymptomatic bone mets, and the second scenario focuses on the patient with widespread symptomatic mets.



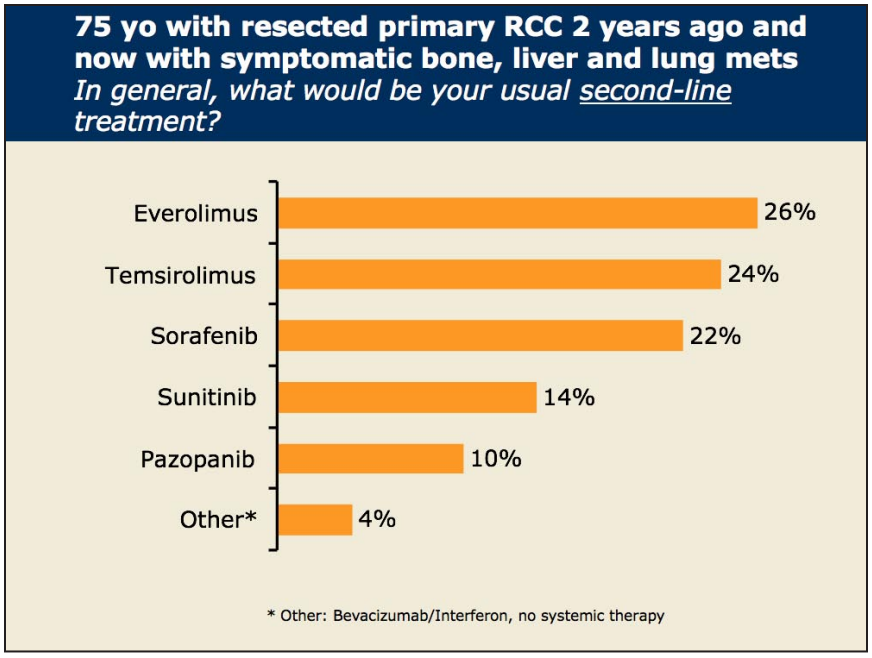
Slide 14
Almost 90 percent of oncologists would treat rather than observe an asymptomatic patient with mets, and the most common treatment is sunitinib. The faculty were evenly split on using sunitinib or observing off therapy.



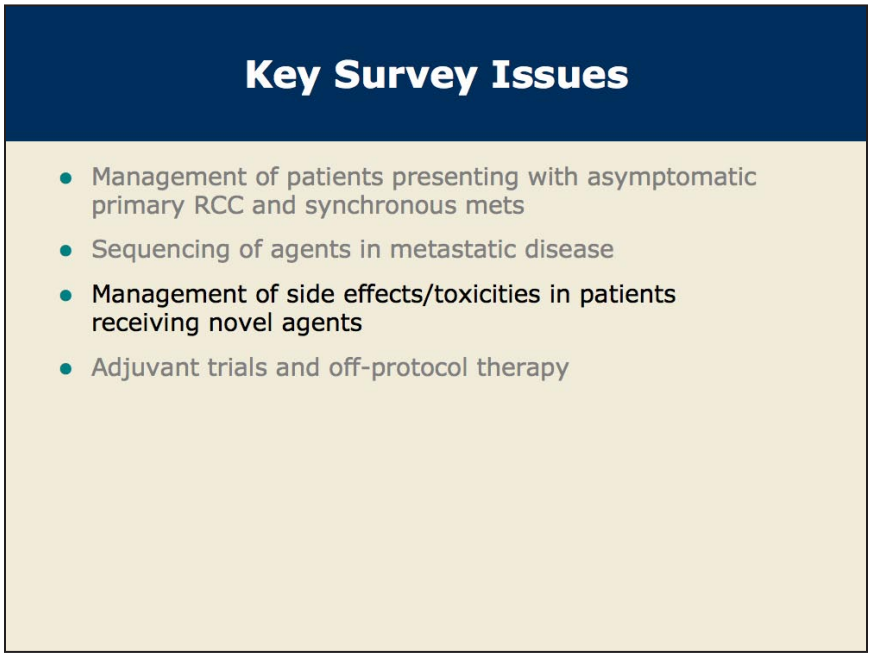
Slide 15
For second-line therapy for such a patient, the two mTOR inhibitors are common choices, with some interest in TKIs — presumably if these were not used first line.



Slide 16
When the case is changed to state that the patient has widespread symptomatic liver, lung and bone mets, there is a noticeable increase in the use of temsirolimus among the oncologists, but sunitinib is still the most frequently chosen agent. Eight of our 12 faculty preferred to use temsirolimus as their first-line treatment.



Slide 17
Second-line therapy preferences for the patient with widespread symptomatic mets look very similar to those for the prior patient with asymptomatic bone mets only.



Slide 18
The third major education objective of this program involves the care of patients receiving novel agents to treat RCC.

Management of Side Effects/Toxicities in Patients Receiving Novel Agents

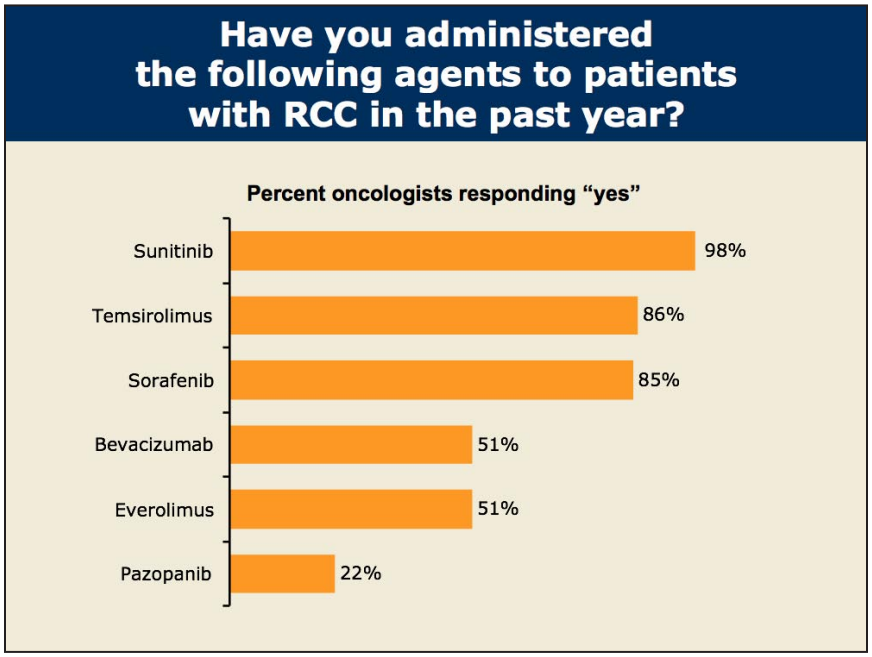
The sunitinib package insert says that if you want to reduce the dose, you reduce it to 37.5 mg and then down to 25 mg in the four weeks on, two weeks off schedule, but we presented a paper at the GU Symposium this year on a schedule of two weeks on, one off, which resulted in a trend toward improved outcome. Data with sunitinib suggest that the greater the area under the curve — the greater the dose density — the greater the benefit. So although you want to find the balance, in general it seems that more is probably better — but you have to find a way to treat the disease without hurting your patient.

Some data suggest that the duration of treatment in the community is dramatically less than in tertiary centers, and it is mainly because these new agents are sometimes difficult to deal with. If you have a relative paucity of patients with renal cell cancer and you're treating many diseases, then learning the ins and outs of a particular therapy — especially one that will require a lot of extra time — can be a huge problem.

Interview with Eric Jonasch, MD, June 18, 2010

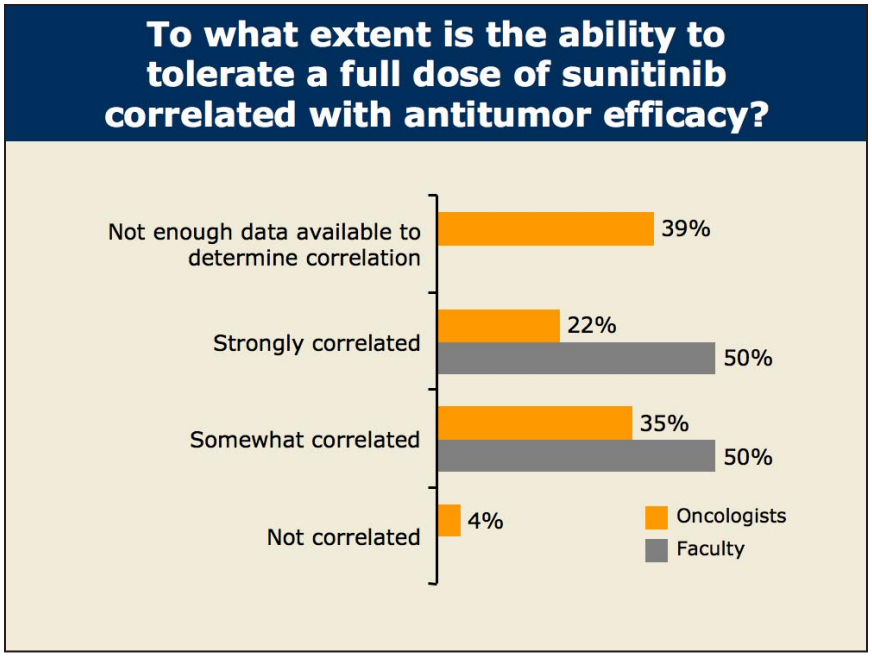
Slide 19

Dr Jonasch helped create these questions and believes that a new sunitinib schedule of two weeks on, one week off that his group has piloted may result in greater efficacy and fewer side effects by altering the time for recovery and still allowing full antitumor effects.

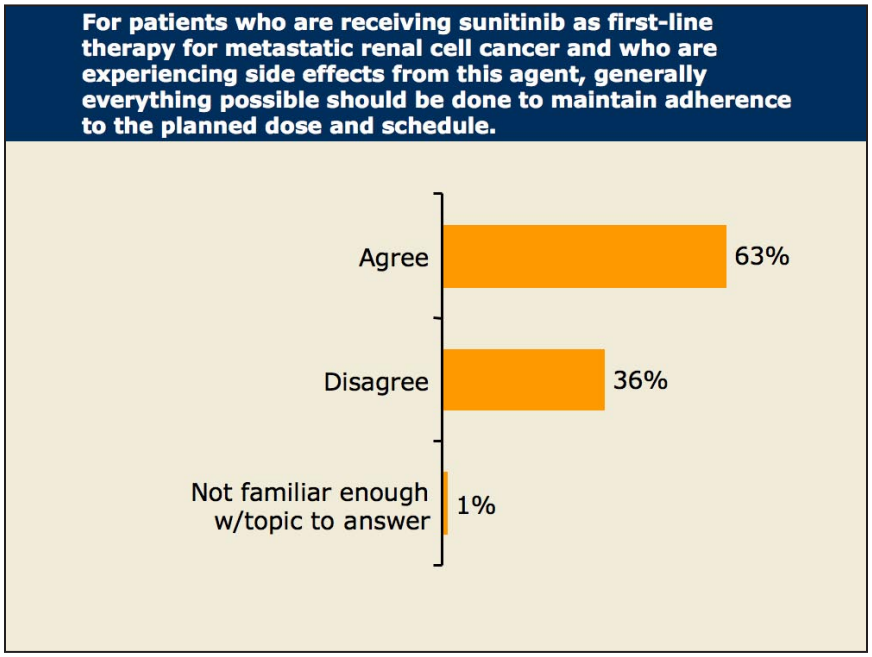


Slide 20

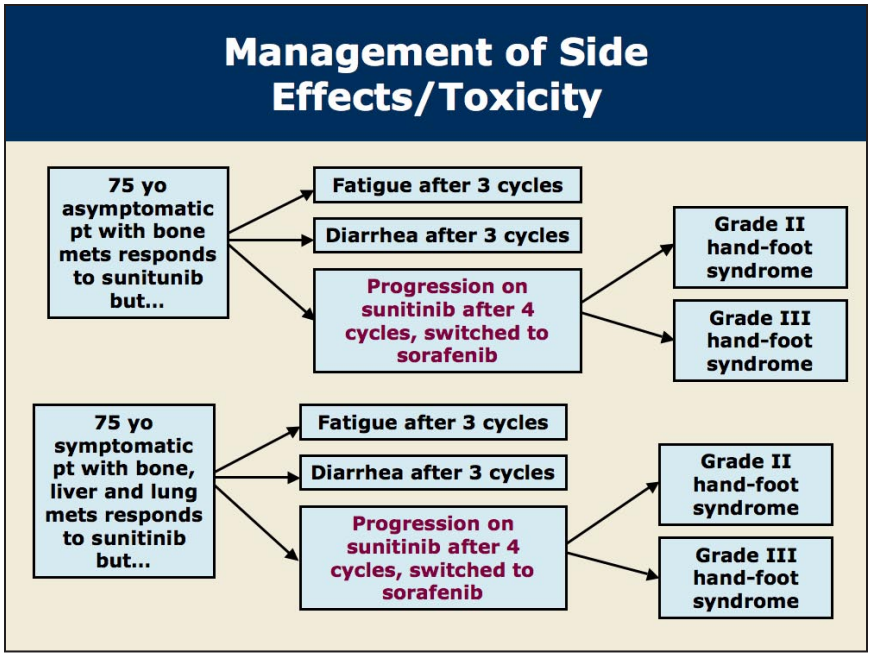
Although most of these agents have become available only in the last few years, our survey demonstrated that while most physicians have used TKIs and the intravenous mTOR inhibitor temsirolimus, a little less than 50 percent of these docs have not used bev/interferon or everolimus.



Slide 21
A key controversial issue in the use of these challenging agents is whether there is a significant correlation between drug dose and the duration of exposure the patient receives and treatment benefit. Only a little more than half of the practicing oncologists support a correlation of benefit with the ability to maintain a full sunitinib dose, while all of the faculty believe there is at least some correlation between dose and exposure duration and treatment benefit.

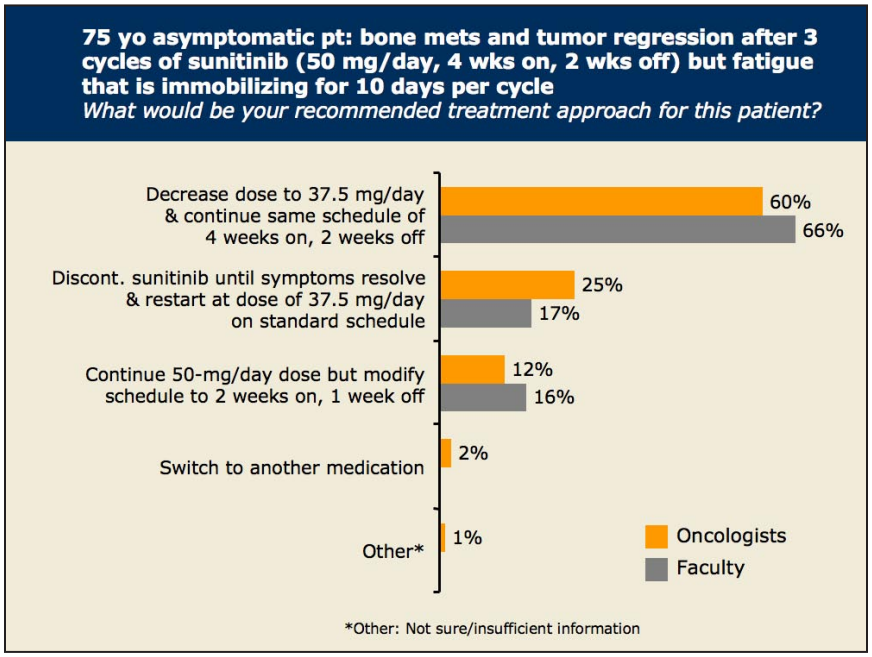


Slide 22
We used another poll question to address this critical issue and found that globally, two thirds of physicians believe that an "area under the curve" phenomenon occurs.



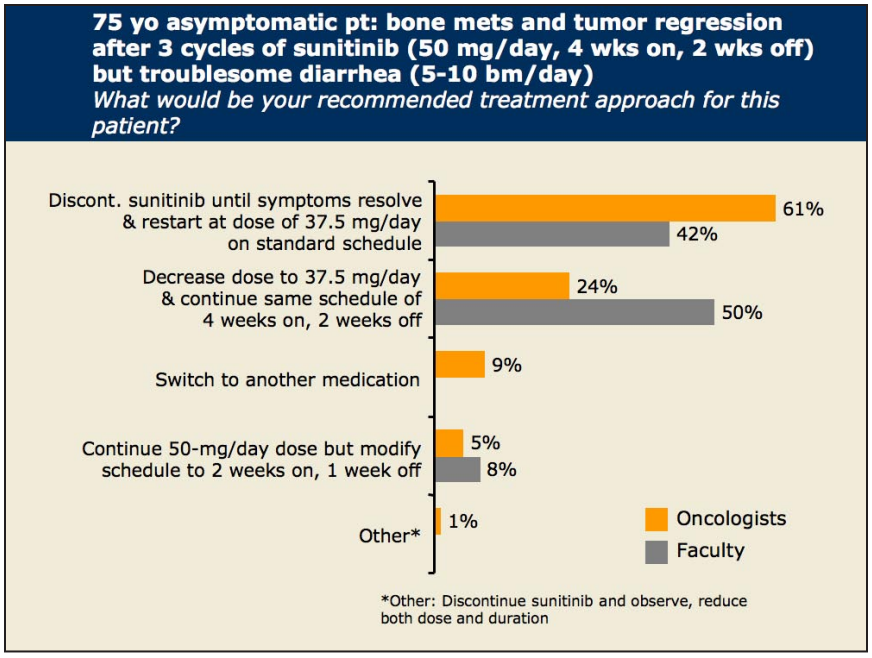
Slide 23

To test the clinical algorithm for 2010 in this disease, we presented two similar variants of a challenging case in which the patient has an antitumor response to sunitinib but experiences toxicity. In variant one the asymptomatic patient has bone mets but develops debilitating fatigue in one case and debilitating diarrhea in another. In the second variant the mets are more widespread and symptomatic. For both scenarios we asked about second-line therapy also.

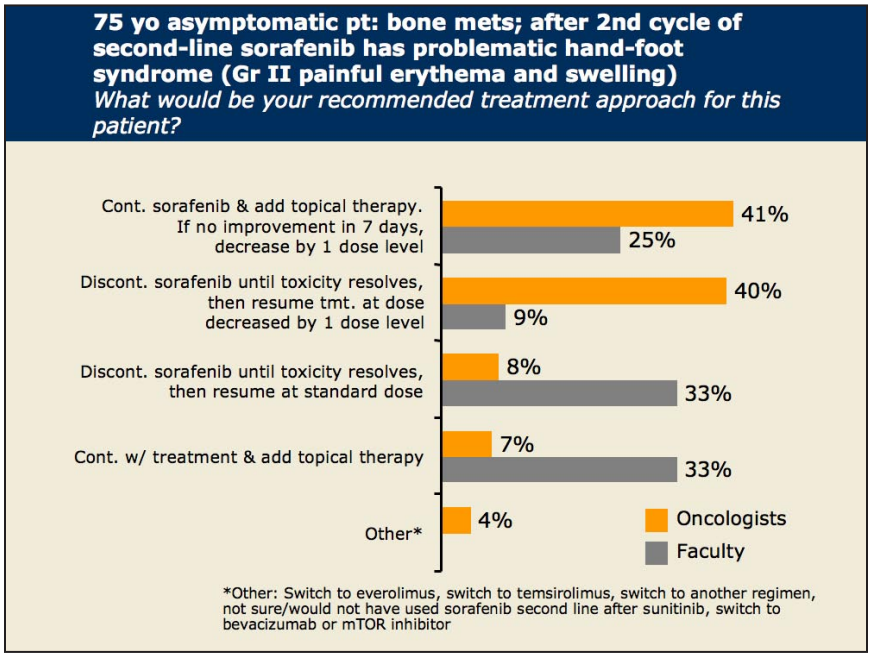


Slide 24

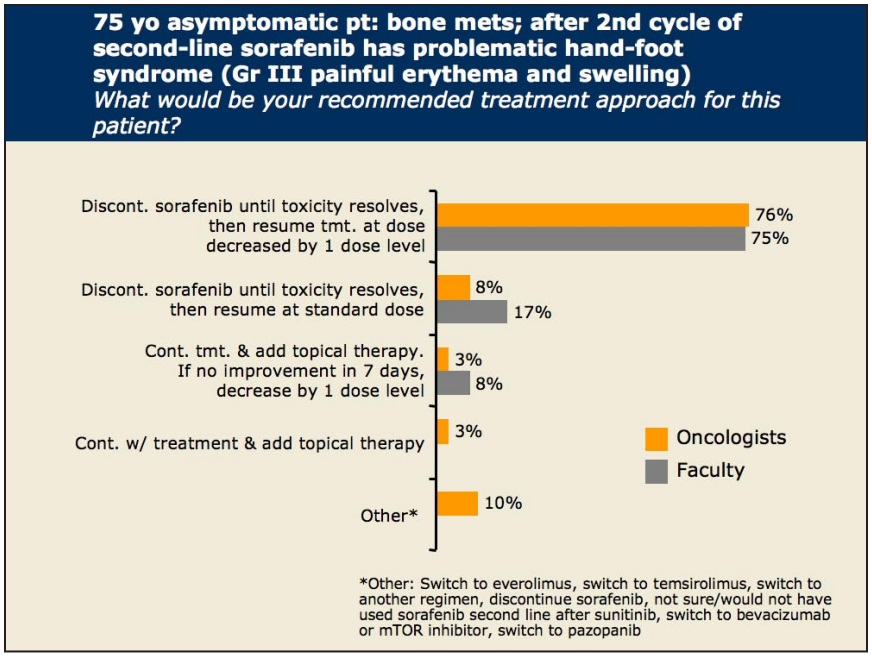
For the patient with asymptomatic bone mets and immobilizing treatment-related fatigue, there is agreement about decreasing the next dose level, in some cases after a treatment break. The exact method used to alter the medication differs among the physicians.



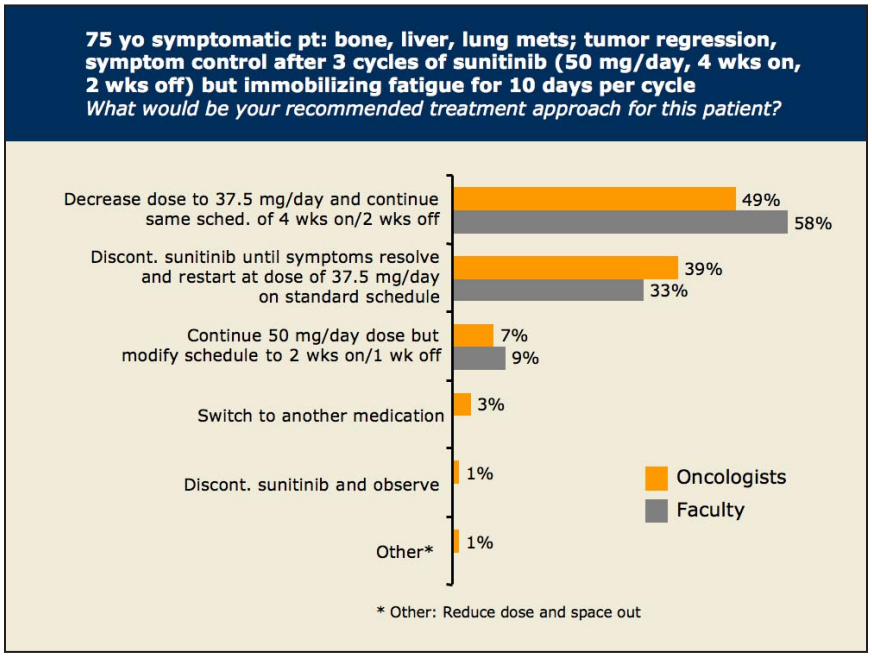
Slide 25
For the patient with asymptomatic bone mets and troublesome treatment-related diarrhea, the management strategy is the same for both the practicing oncologists and the faculty, and the majority recommend decreasing the next dose level after a treatment break and resolution of symptoms.



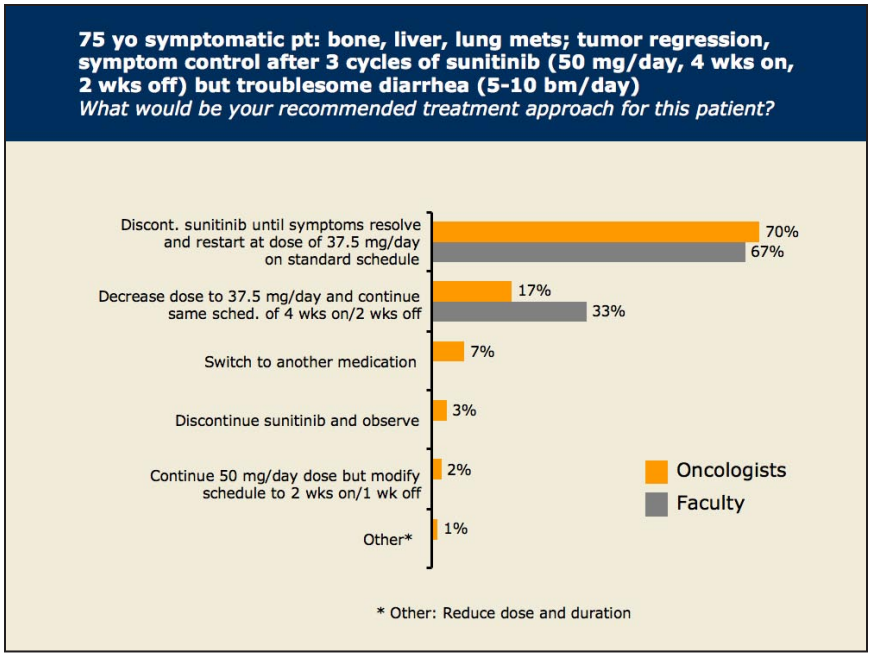
Slide 26
For the patient with asymptomatic bone mets and Grade II hand-foot syndrome on second-line sorafenib, there is a major division about whether to hold off on therapy in both oncologists and faculty.



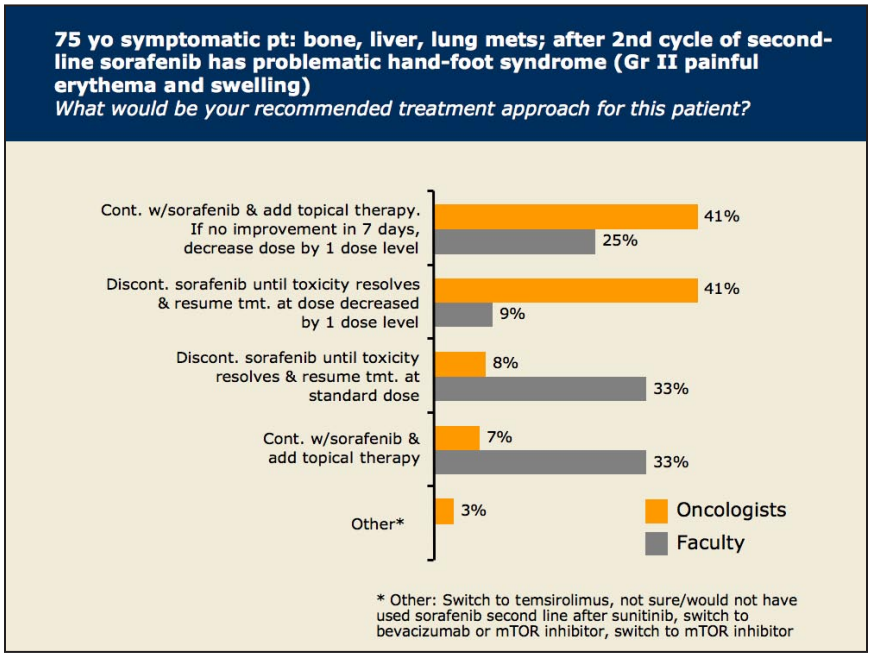
Slide 27
For the patient with asymptomatic bone mets and Grade III hand-foot syndrome on second-line sorafenib, the consensus in both groups is to discontinue treatment until healing occurs and then restart at a lower dose.



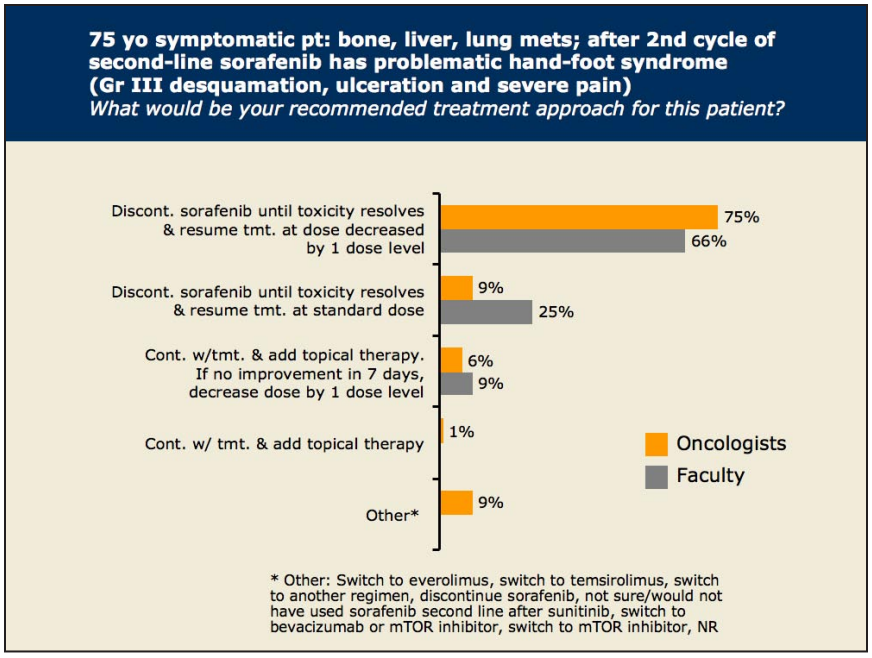
Slide 28
For the patient with widespread symptomatic mets and immobilizing treatment-related fatigue, similar to what was seen for the previous patient with asymptomatic bone mets, there is agreement in both groups about decreasing the next dose level, in some cases after a treatment break. The exact method used to alter the medication differs among the physicians.



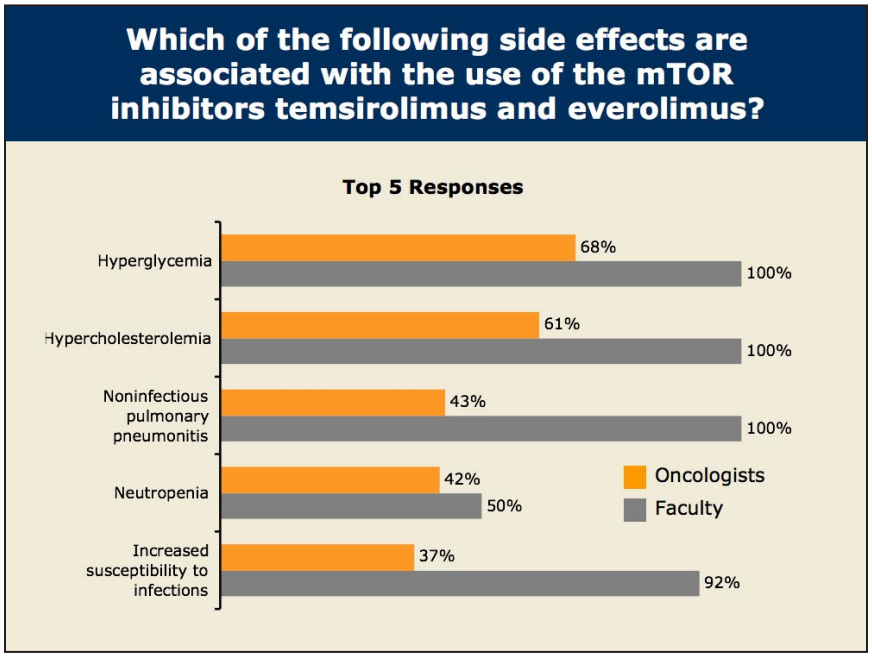
Slide 29
For the patient with widespread symptomatic mets and troublesome treatment-related diarrhea, the majority of both oncologists and faculty recommend decreasing the next dose level after a treatment break and resolution of symptoms, which is similar to what was seen for the previous patient with asymptomatic bone mets.



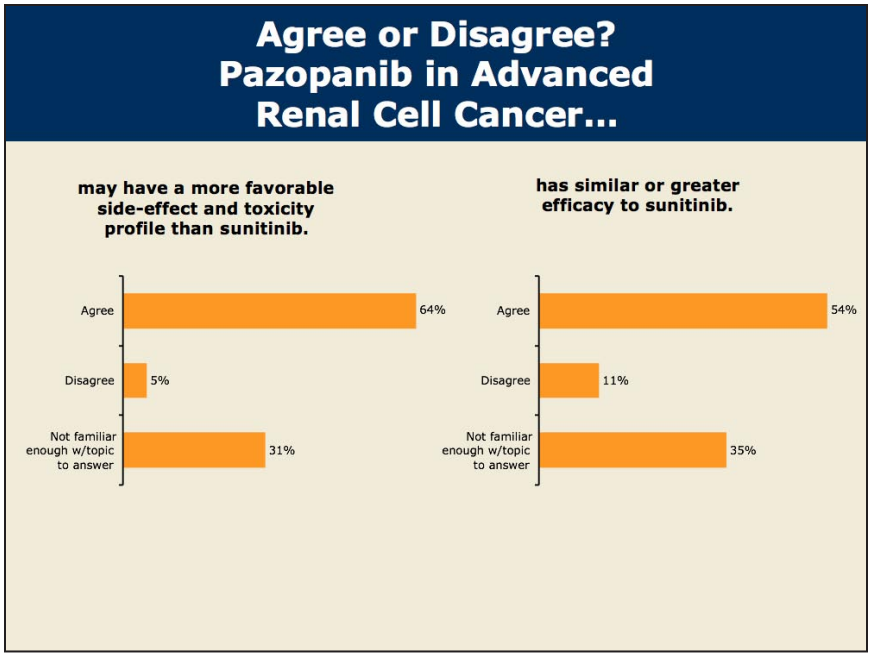
Slide 30
For the patient with widespread symptomatic mets and Grade II hand-foot syndrome on second-line sorafenib, similar to what was seen for the previous patient with asymptomatic bone mets, there is a major division about whether to hold off on therapy or not in both oncologists and faculty.



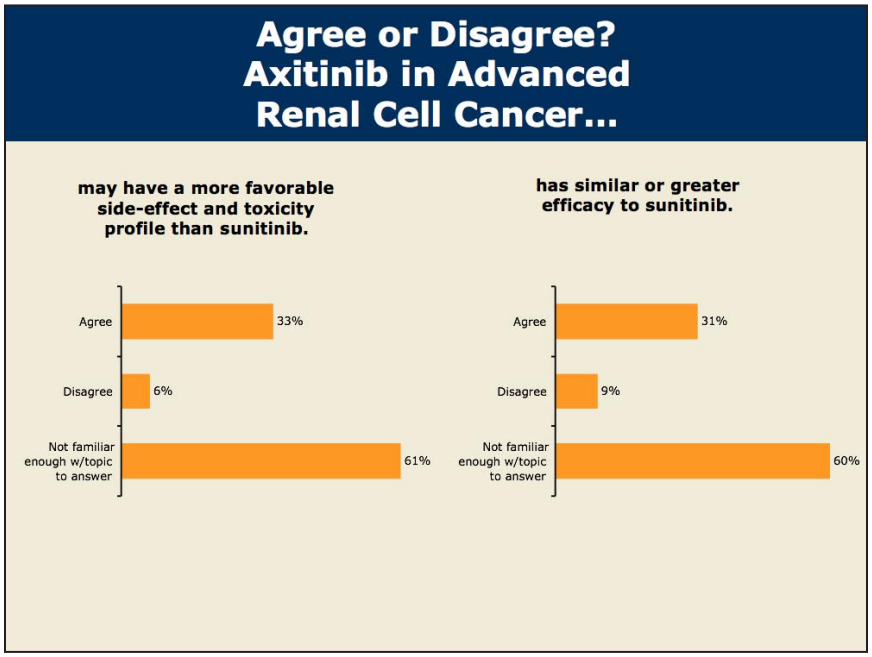
Slide 31
For the patient with widespread symptomatic mets and Grade III hand-foot syndrome on second-line sorafenib, the consensus is to discontinue treatment until healing occurs and then restart at a lower dose, similar to what was seen for the previous patient with asymptomatic bone mets.



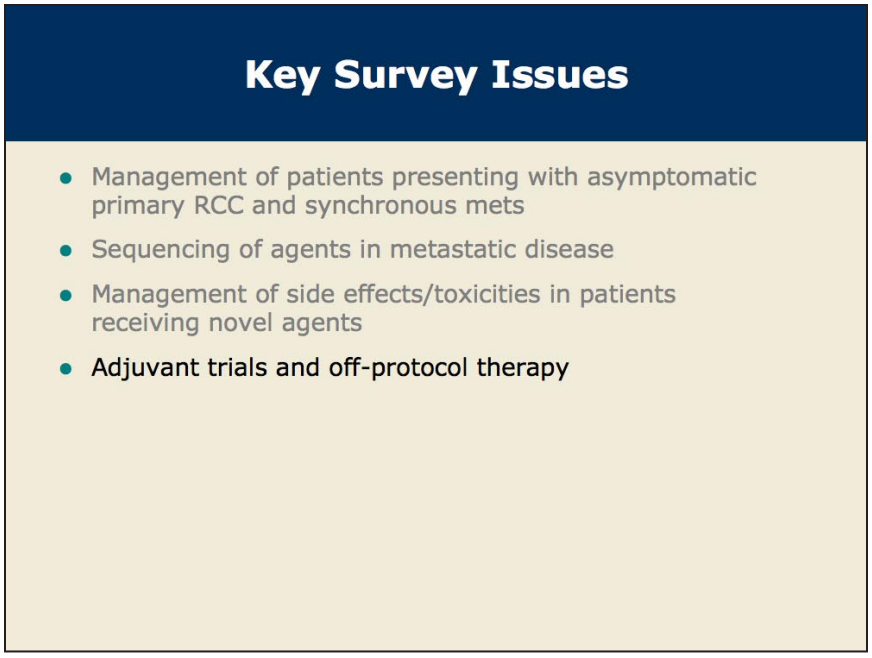
Slide 32
When we asked about the side effects associated with mTOR inhibitors, we found that four specific complications that are well known to virtually our entire faculty are not quite so well known to practicing oncologists, more than one third of whom were not aware of the association of these important complications with these agents.



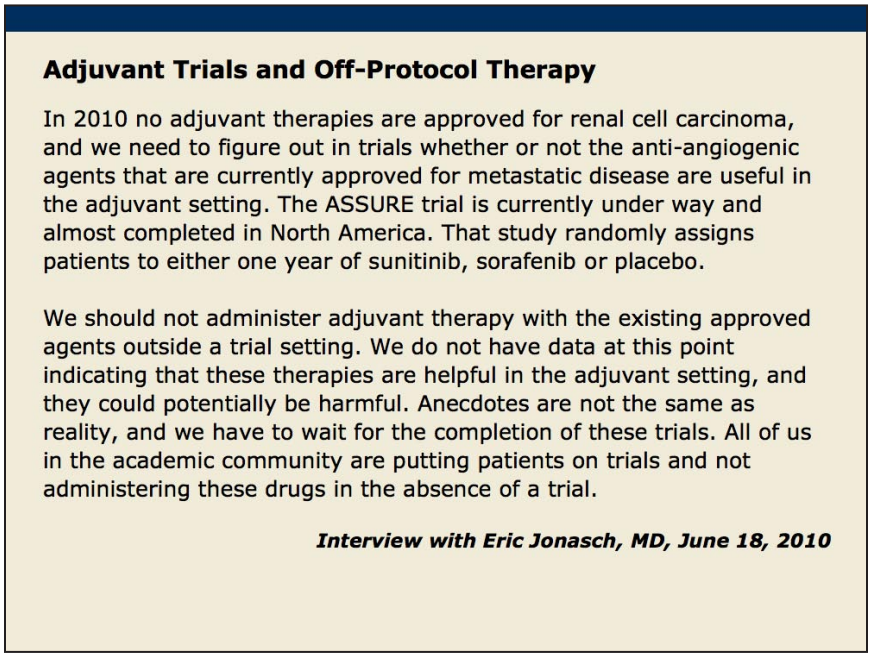
Slide 33
An important clinical issue is whether administering new and similar agents may result in greater efficacy and tolerability. Our poll respondents believe that the new TKI pazopanib may have a better safety profile with similar or greater efficacy to sunitinib.



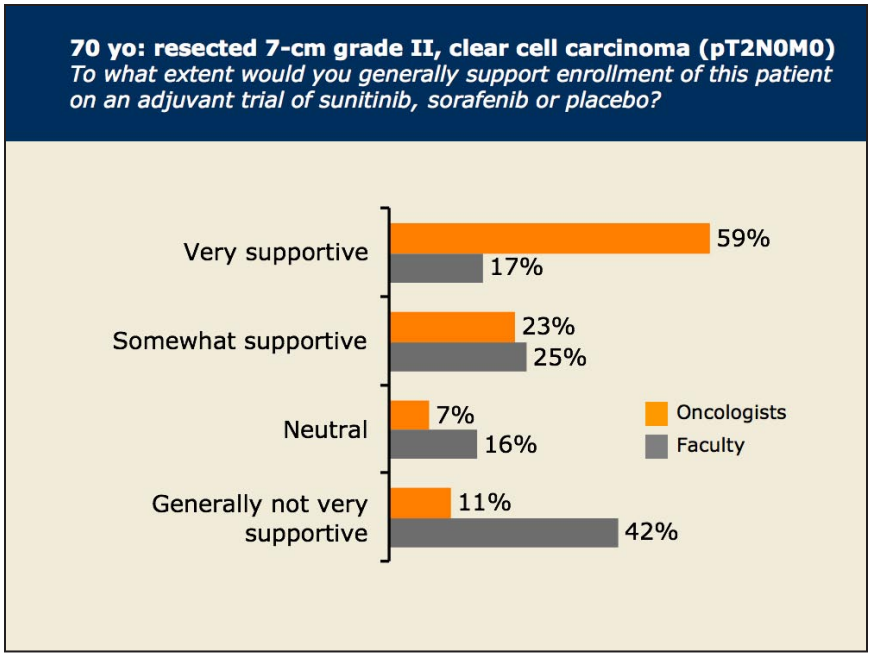
Slide 34
Physicians were less familiar with the data and effects of axitinib.



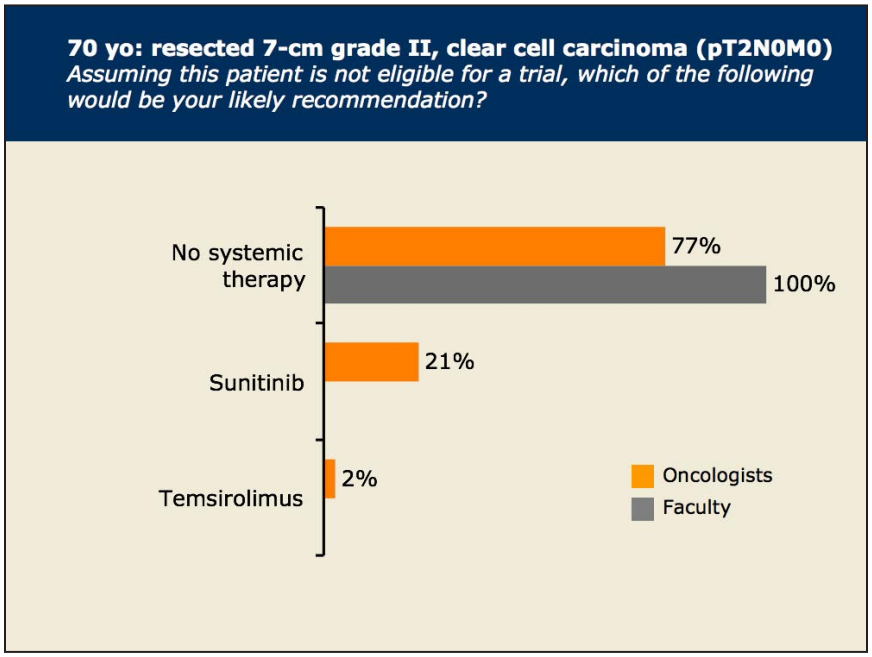
Slide 35
New clinical research is the final key RCC topic and one with great importance.



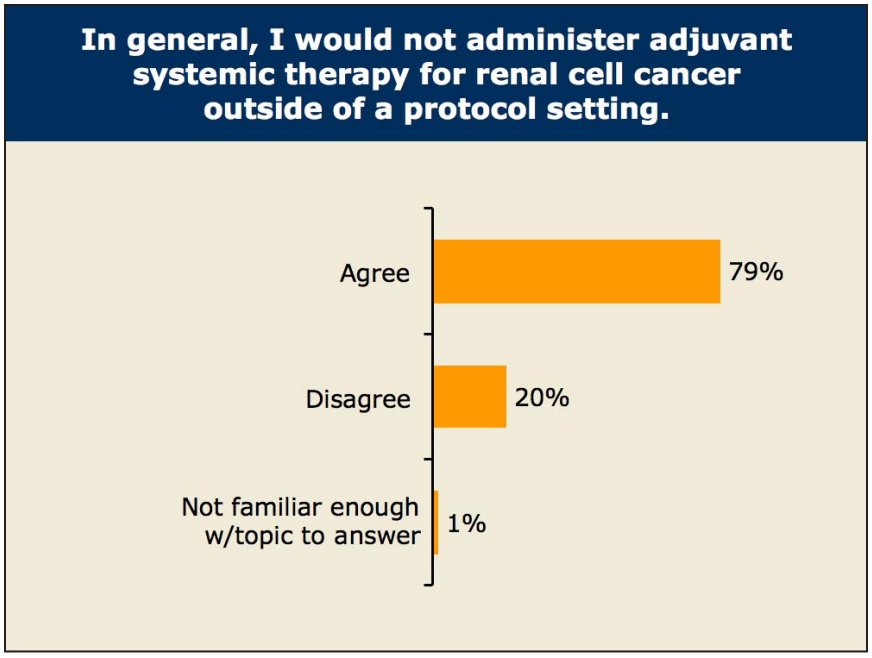
Slide 36
Perhaps the most important question in RCC clinical research involves the use of novel systemic agents as adjuvant therapy. Dr Jonasch has strong feelings against the use of this strategy outside of a protocol setting.



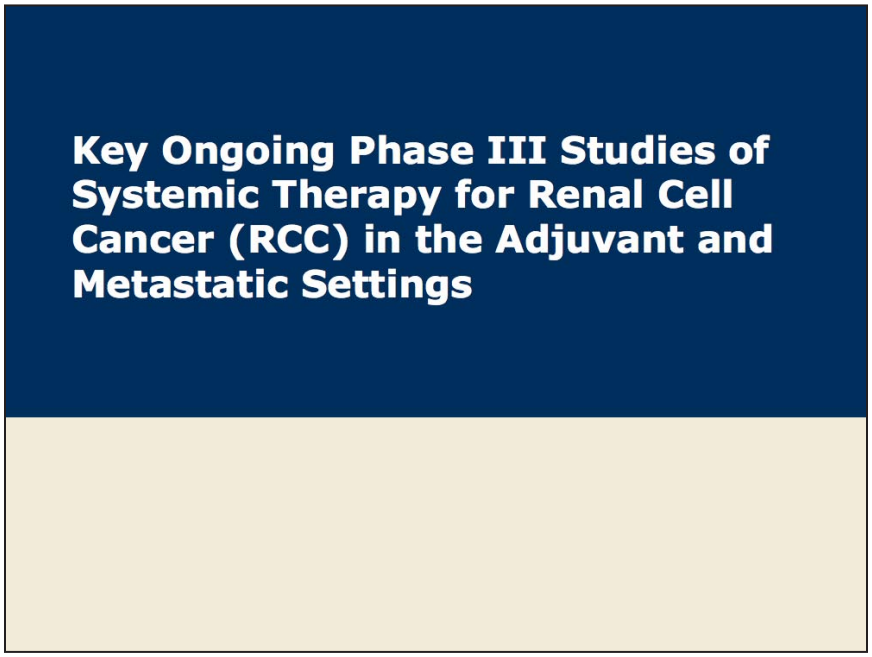
Slide 37
Oncologists state that they are generally supportive of patients entering the large randomized adjuvant trials.



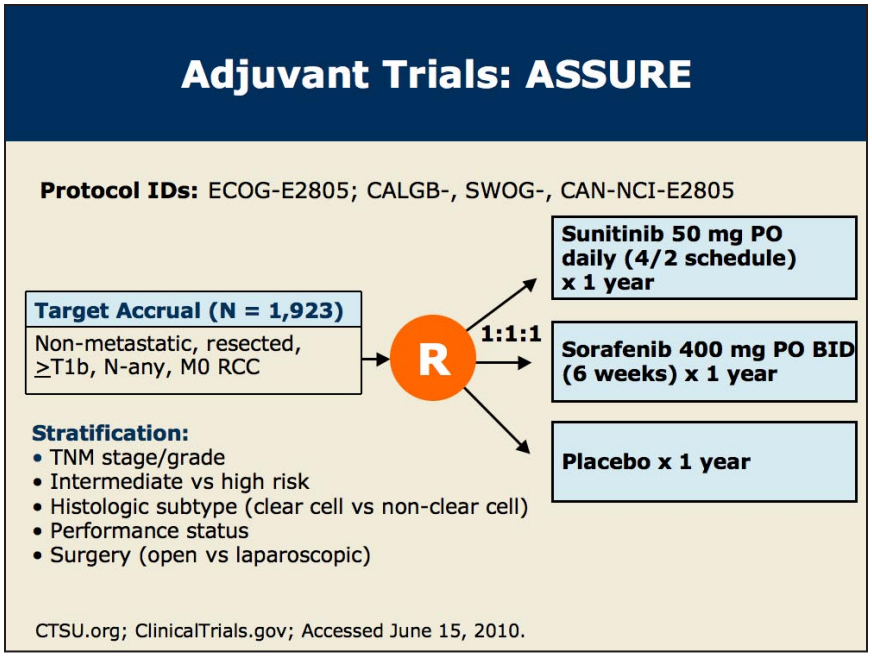
Slide 38
For patients not eligible for studies, most oncologists do not use off-protocol adjuvant treatment although a sizeable minority will offer sunitinib, a practice that is not used by any of our faculty.



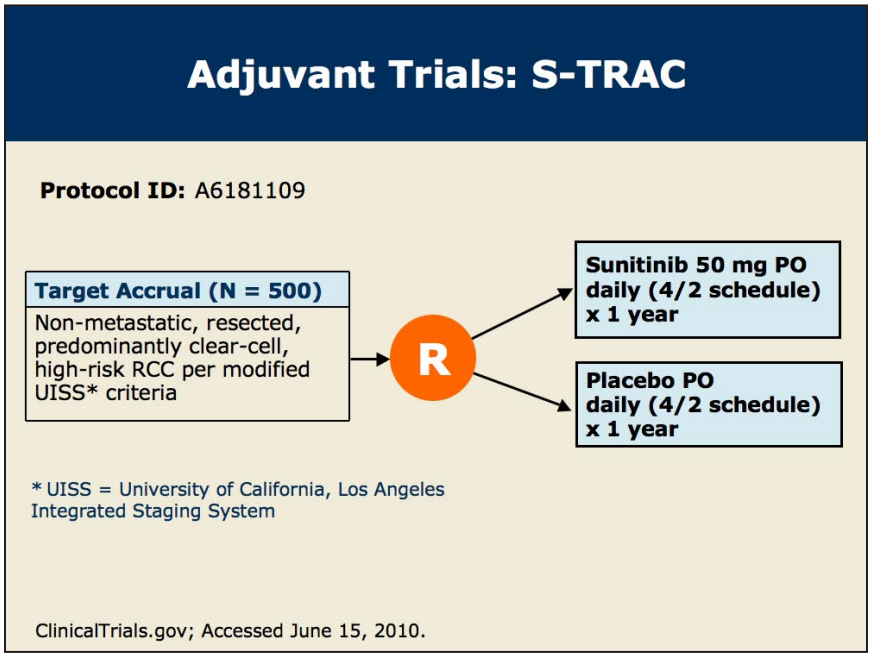
Slide 39
As further testimony to the attitude of these physicians, more than 78 percent say they don't offer adjuvant therapy off study, which is also the practice of all of our faculty.



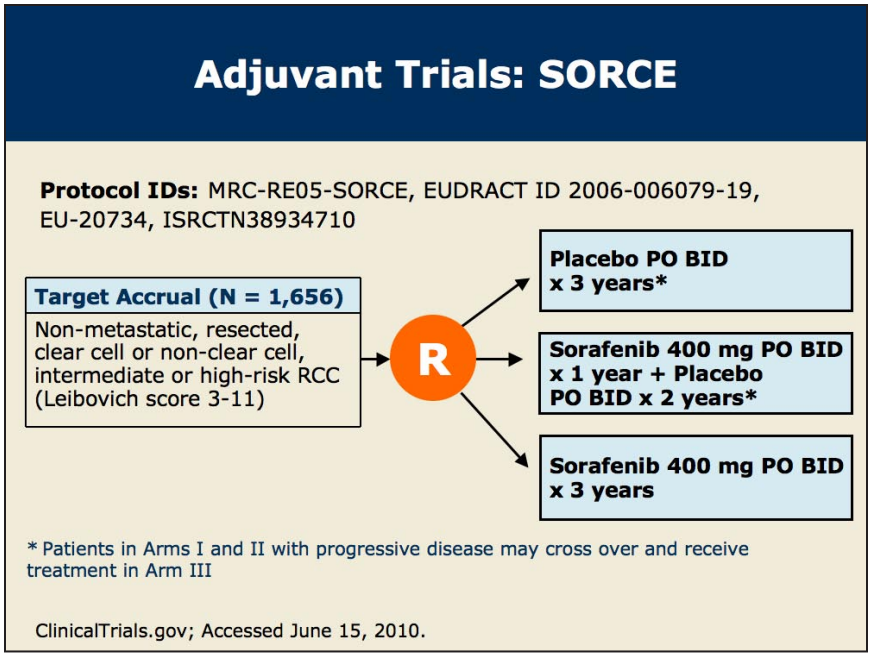
Slide 40
The most exciting studies in RCC are the adjuvant trials and the studies in metastatic disease evaluating new agents.



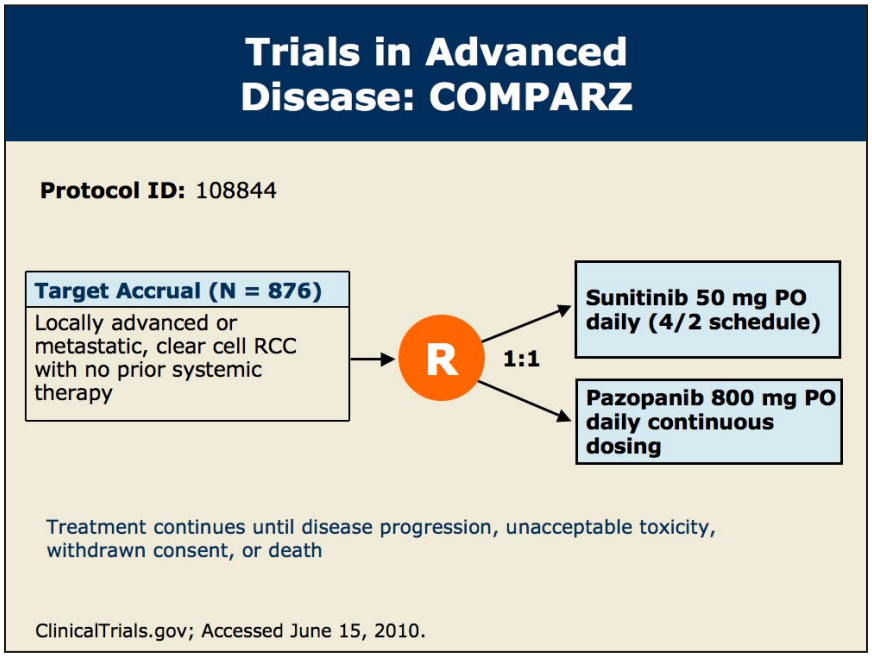
Slides 41-43
Three major placebo-controlled trials are evaluating VEGF TKIs in the adjuvant setting.



Slide 42



Slide 43



Slides 44-47
At least four major trials in advanced disease are attempting to do head-to-head comparisons of novel agents.

Trials in Advanced Disease: PISCES

Protocol ID: 113046

Target Accrual (N = 132)

Locally advanced or metastatic RCC of any histology with no prior systemic therapy

R

Sunitinib 50 mg PO daily x 10 wks (4/2 schedule) → 2 wks washout → Pazopanib 800 mg PO x 10 wks

Pazopanib 800 mg PO daily x 10 wks → 2 wks washout → Sunitinib 50 mg PO x 10 wks (4/2 schedule)

Primary Objective: Assess how tolerability and safety differences between pazopanib and sunitinib translate into the patient's stated drug preference for continuation of treatment at the end of the study

ClinicalTrials.gov; Accessed June 15, 2010.

Slide 45

Trials in Advanced Disease: AXIS

Protocol ID: A4061032

Target Accrual (N = 650)

Metastatic RCC with a component of clear cell after failure on one prior 1st-line regimen

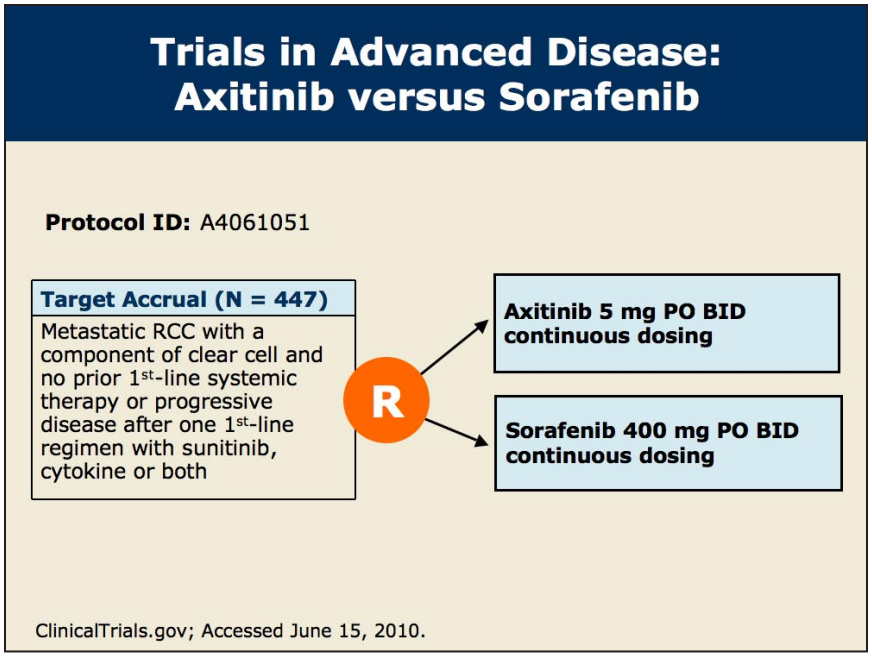
R

Axitinib 5 mg PO BID continuous dosing

Sorafenib 400 mg PO BID continuous dosing

ClinicalTrials.gov; Accessed June 15, 2010.

Slide 46



Slide 47