5 Minute JournalClub

Everolimus in Patients with Cytokine-Pretreated mRCC

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CME INFORMATION

OVERVIEW OF ACTIVITY

Advances in the biologic understanding of renal cell cancer and the emergence of clinical trial data with targeted therapeutic agents have resulted in the availability of novel treatment strategies for this challenging disease. In order to offer optimal patient care — including the option of clinical trial participation — the practicing medical oncologist must be well informed of these rapidly evolving data sets. To bridge the gap between research and patient care, this CME activity will deliver a serial review of recent key presentations and publications and expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists and other cancer clinicians in the formulation of optimal clinical management strategies for patients with renal cell cancer.

LEARNING OBJECTIVE

- Identify the clinical efficacy and hematologic/nonhematologic adverse events associated with delivery of 10 milligrams daily of everolimus for metastatic renal cell carcinoma.

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5 MinuteJournalClub

As you may already know from our Post-ASCO 5-Minute Journal Club emails, one of the highlights of our steamy Miami summer was a series of daylong clinical investigator think tanks. Perhaps the most memorable of these fascinating events was a gathering of six clinical investigators whose brains we picked about one of the most rapidly evolving corners of medical oncology — renal cell carcinoma (RCC). The just-released **audio highlights program** of this adventure serves as the launch for a six-month integrated curriculum of activities designed to provide an array of interesting and relevant perspectives related to RCC management. A key focus of this comprehensive initiative is to better understand how investigators and practicing clinicians manage RCC, and to that end we recently conducted a national Patterns of Care study with 100 US community-based medical oncologists and the 12 curriculum faculty members, attempting to figure out how these physicians manage a disease that affects more individuals than CML, AML, CLL and ALL combined. Some of the RCC issues most asked about by oncologists in practice and discussed throughout the think tank include:

1. The role of nephrectomy for patients presenting with a primary tumor and metastatic disease, and the role of neoadjuvant systemic therapy for patients with unresectable or difficult-to-resect primary tumors

Two prior randomized trials demonstrated a benefit with nephrectomy for patients with metastases (Flanigan 2001, Mickisch 2001), but the studies are of questionable relevance in the new era of novel biologics. Ultimately, RCC could end up following the colorectal cancer paradigm, in which up-front systemic therapy is becoming standard for patients presenting with an asymptomatic primary tumor and metastatic disease. In RCC, this is far from a settled issue, as demonstrated by our Patterns of Care survey, in which 49 percent of the physicians surveyed would initiate systemic therapy for a patient with an asymptomatic primary tumor and mets, while 51 percent would send that same patient to nephrectomy as the first intervention. An ongoing Phase III trial hopes to address this critical and highly controversial question, but results will not be available for a while.

Neoadjuvant therapy seems to be even more problematic, and although **the new paper** by Jonasch and colleagues featured here demonstrates that 52 percent of patients experienced some regression of the primary lesion with single-agent bevacizumab, clinical investigators agree that preop systemic treatment, including attempts to convert primary tumors to resectability, should at this point be done only as part of a clinical trial.

2. Optimal sequence of systemic agents in metastatic disease

The FDA approval of bevacizumab/interferon makes this algorithm even more complicated, and the ODAC's recent vote unanimously supporting the approval of pazopanib likely paves the way for another player to join an already crowded field, which should be a good thing for patients. One tricky and unanswered issue is the contribution of interferon to the efficacy of bev, but there is no doubt about its adverse impact on quality of life in a palliative situation.

These days, virtually all investigators use a VEGF TKI — specifically sunitinib — as first-line therapy for metastases, but many use the mTOR inhibitor temsirolimus for patients with poor-risk disease. An important research question on the table is whether VEGF TKIs or mTOR inhibitors can be rationally administered as first-line treatment for metastatic disease regardless of risk status. In the future, the RCC model may mimic what's seen in endocrine therapy for breast cancer, where physicians choose from a menu of agents with similar efficacy but differences in tolerability.

3. Management of toxicities of biologic therapy

VEGF TKIs have only recently come into the oncologist's armamentarium, but RCC is also the first common tumor for which mTOR inhibitors are being regularly used. As evident from the **recent publication by Amato** evaluating the oral mTOR inhibitor everolimus, the spectrum of toxicities with these interesting agents is quite unlike any other treatment being used in contemporary medical oncology. Of particular importance is noninfectious pneumonitis, which in the Amato study occurred as Grade III or IV in 18 percent of patients. Our POC survey demonstrated that 40 percent of oncologists are not familiar with this complication and other toxicities associated with these agents, including hyperglycemia and hyperlipidemia.

4. The correlation, if any, between "dose intensity" of VEGF TKIs and treatment benefit, and how new agents like pazopanib and axitinib will stack up in terms of safety and benefit

Investigators have expressed concern that oncologists in practice may be prematurely bailing out on sunitinib or reducing the dose too quickly, and that this may be resulting in less benefit to patients than was demonstrated in clinical trials. While axitinib seems by indirect comparison to have similarly challenging tolerability issues as sunitinib, pazopanib holds the hope of a different and perhaps improved safety profile that may result in not only better quality of life but also perhaps greater efficacy by allowing full doses to be administered for longer.

Other critical issues being studied in current trials include the role of adjuvant systemic therapy and the use of combinations of biologics. Hopefully, the rapid pace of progress in RCC will continue and eventually result in substantial improvements in survival and cure rates for patients with this disease.

Be on the lookout for other activities in our integrated RCC curriculum as we attempt to efficiently provide information and perspectives about what is arguably the current forefront of solid tumor oncology.

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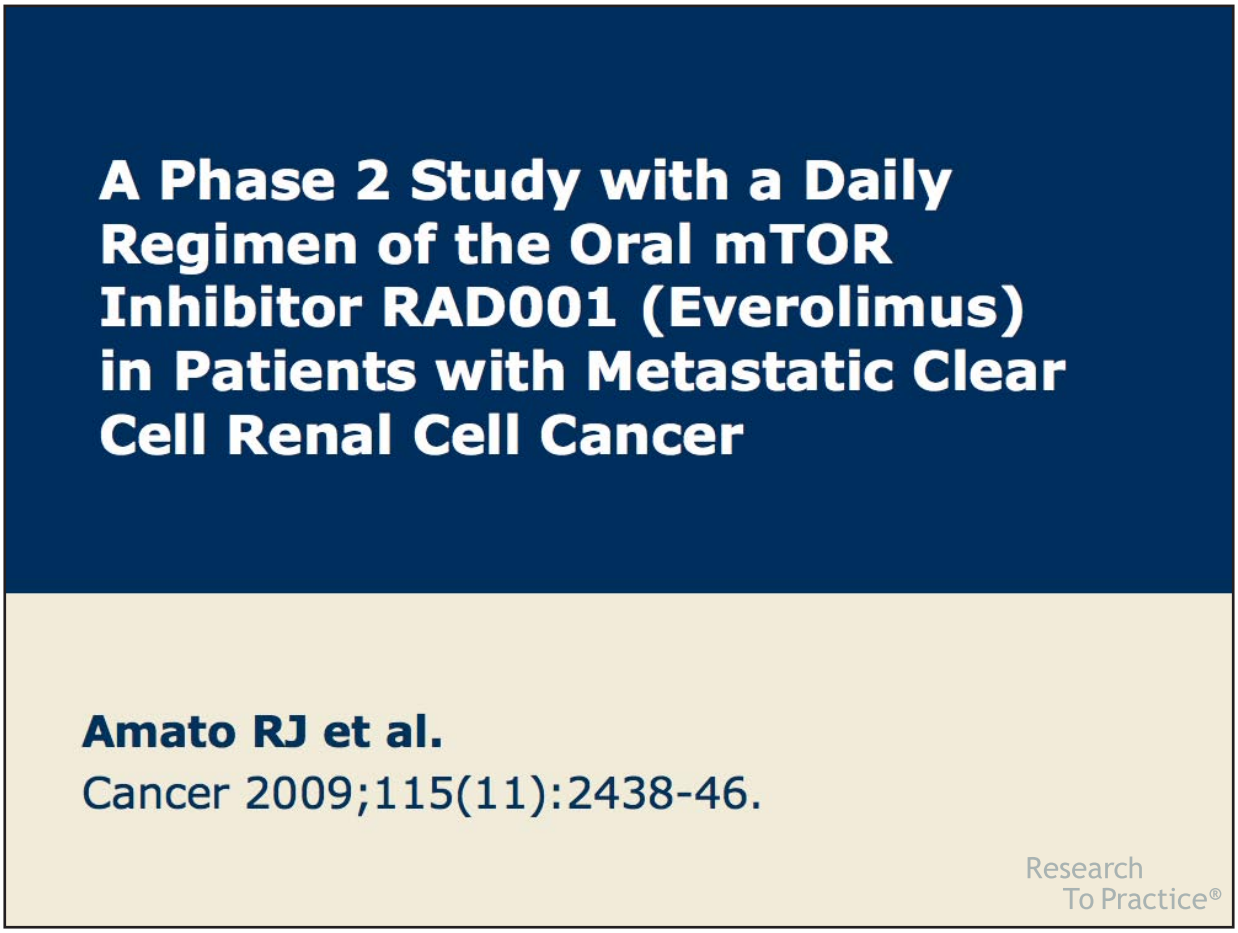
Everolimus in Patients with Cytokine-Pretreated mRCC

Presentation discussed in this issue:

Amato RJ et al. **A phase 2 study with a daily regimen of the oral mTOR inhibitor RAD001 (everolimus) in patients with metastatic clear cell renal cell cancer.** *Cancer* 2009;115(11):2438-46. **Abstract**

Slides from the presentation and excerpts from a related interview with Robert A Figlin, MD (October 7, 2009)



Introduction

- Everolimus, an oral mammalian target of rapamycin (mTOR) inhibitor, has antitumor activity in patients with metastatic renal cell cancer (mRCC), including those with prior exposure to VEGFR inhibitors (NEJM 2007;356:2271; JCO 2008;26:1588; JCO 2008:26s)
- In preclinical studies, a more consistent inhibition of mTOR signaling was achieved with daily 10-mg everolimus dosing when compared to the 70-mg weekly regimen (JCO 2008;26:1596; JCO 2008;26:1603)
- This single-arm, two-stage study aimed to assess the efficacy and safety of 10-mg daily everolimus for patients with advanced clear cell RCC treated with ≤ one prior therapy (chemotherapy, immunotherapy or a molecular-targeted agent other than an mTOR inhibitor)
  - Primary objective: Progression free survival (PFS)
  - Secondary objectives: Response rate (RR), duration of response (DOR), safety, toxicity, overall survival (OS)

Source: Amato RJ et al. *Cancer* 2009;115(11):2438-46.

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Study Design

Primary Eligibility Criteria (n=41)

- Histologically confirmed mRCC
- ≥ 75% clear cell characteristics
- ≤ 1 prior therapy (including chemotherapy, immunotherapy, targeted therapy except mTOR inhibitors)
- No prior DVT, PE or TIA with activity-limiting claudication in the past 6 months

↓

Treatment

Stage 1 (n=21): Everolimus 10mg/day

↓

At 6 months, if ≥ 3 patients are free of disease progression, continue accrual

↓

Stage 2 (n=20): Everolimus 10mg/day

Evaluations performed at baseline; q4wk (safety); q8wk (efficacy), decreased from 12wk to 8wk intervals after accrual of first 29 patients

Source: Amato RJ et al. *Cancer* 2009;115(11):2438-46.

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Treatment-Related Nonhematologic Adverse Events (n=39*)

Adverse Event	Grade 1	Grade 2	Grade 3/4
Anorexia	38.5%	0	0
Nausea	35.9%	2.6%	0
Diarrhea	23.1%	7.7%	0
Rash	17.9%	7.7%	0
Stomatitis	10.3%	20.5%	0
Vomiting	7.7%	15.4%	0
Pneumonitis	5.1%	25.6%	17.9%

* Study sample with confirmed eligibility and receiving at least one dose of study drug

Source: Amato RJ et al. *Cancer* 2009;115(11):2438-46.

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Hematologic and Biochemical Treatment-Related Adverse Events (n=39)

Adverse Event	Grade 1	Grade 2	Grade 3
Alkaline phosphatase	61.5%	30.8%	7.7%
ALT	35.9%	20.5%	10.3%
Hyperglycemia	41.0%	10.3%	7.7%
Hypercholesterolemia	30.8%	7.7%	5.1%
Hypophosphatemia	28.2%	2.6%	0%
Hypertriglyceridemia	25.6%	25.6%	5.1%
Thrombocytopenia	61.5%	30.8%	7.7%
Anemia	30.8%	0%	0%

Source: Amato RJ et al. *Cancer* 2009;115(11):2438-46.

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Efficacy

Median Progression Free Survival	11.2 months	
Median Overall Survival	22.1 months	
Response	**Investigator Assessment (n = 37)**	**Independent Assessment (n = 31*)**
Complete response (CR)	0%	0%
Partial response (PR)	13.5%	6.5%
Stable disease ≥3 mo	73.0%	74.2%
Stable disease ≥6 mo	56.8%	58.1%
Progressive/stable disease <3 mo	13.5%	19.4%

* CT scans from six patients not available for independent assessment

Source: Amato RJ et al. *Cancer* 2009;115(11):2438-46.

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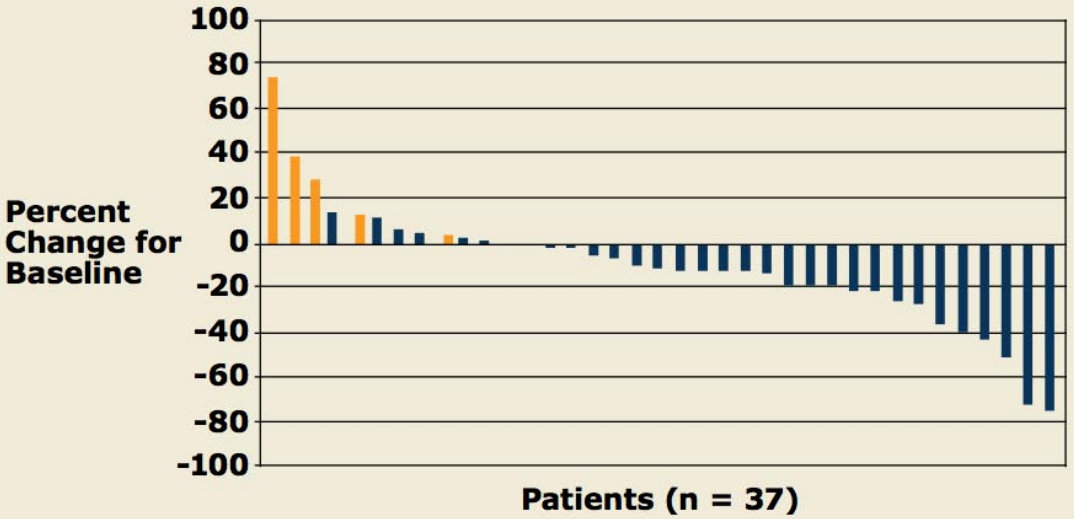
Waterfall Plot of Tumor Reduction for Target Lesion by RECIST



24 patients (65%) had some decrease in size of target lesion

Source: With permission from Amato RJ et al. *Cancer* 2009; 115(11):2438-46.

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Conclusions

- Daily everolimus of 10 mg produced responses and durable disease control in a small population of patients with mRCC (n = 37), many with disease progression on prior cytokine therapy
  - PFS = 11.2 months
  - Stable disease ≥ 6 mo = 58%
- Frequency and severity of biochemical abnormalities, nausea, stomatitis, rash, diarrhea, anorexia and vomiting were consistent with the results of other studies of everolimus monotherapy and other mTOR inhibitors
- Frequency of pneumonitis (overall and Grade III) was greater than previously reported
- Additional studies of everolimus as monotherapy or combined with anti-VEGF agents are underway (NCT00597506; NCT00849550)

Sources: Amato RJ et al. *Cancer* 2009; 115(11):2438-46. NCI Physician Data Query October, 2009

ROBERT A FIGLIN, MD: Dr Amato and colleagues reported in *Cancer* the results of a Phase II study with the daily regimen of an oral mTOR inhibitor everolimus — now commercially available for the treatment of renal cell carcinoma — with patients experiencing disease progression after up-front TKI therapy with either sorafenib or sunitinib.

Dr Amato studied these patients prior to everolimus becoming commercially available. They enrolled 41 patients and evaluated the efficacy of everolimus in this setting. Most of the patients had MSKCC intermediate performance status, and approximately one third of the patients had a good performance status.

One notable aspect of this study that is helpful is that the majority of patients had received prior cytokine therapy and had not received prior VEGF-targeted therapy. Why is that important? Currently, everolimus is indicated by the NCCN guidelines as treatment for such patients after disease progression or intolerance to targeted agents, such as sorafenib and sunitinib. So this provides a window into how everolimus might have activity in patients who have not received prior targeted therapy but had received prior cytokine-based therapy or in patients who had not received any prior therapy at all.

The authors demonstrate, as we would have expected, no complete responses, a 6.5 percent partial response rate and, by independent assessment, approximately 75 percent of patients experienced stable disease. That's consistent with our observations about mTOR inhibition, with which the overall response rates are quite low but the absence of progression is quite high. This study thus demonstrates that everolimus may have a benefit in patients who have not received prior cytokine therapy, and this will certainly be evaluated in up-front clinical trials.

Dr Amato discusses the progression-free and overall survival. I believe that in the era of targeted therapy, it's not prudent to consider these results in a predictive way because this was a single-institution clinical trial with a small number of patients. We now have large Phase III trials with which to understand the benefits of agents such as everolimus in patients with metastatic renal cell carcinoma.

The toxicity profile was comparable to what we experience with everolimus, although Dr Amato did point out that approximately 18 percent of patients had Grade III pneumonitis. This underscores our understanding that mTOR inhibitors have a spectrum of toxicity that is different from the TKIs and one must watch for hypercholesterolemia, hyperlipidemia, hyperglycemia and pneumonitis associated with these agents that are not found with the VEGF TKIs.

In this study Dr Amato demonstrates that everolimus has clinical activity in a small number of patients with previously untreated or cytokine-refractory metastatic clear cell carcinoma, and in this setting, everolimus might be an appropriate choice.

Some of the current clinical trials that are underway with these mTOR inhibitors in the clinic are comparisons of combination therapy — temsirolimus or everolimus with bevacizumab compared to bevacizumab and interferon in the previously untreated population. These studies may help us to understand how to use these targeted agents in the up-front setting for these patients.

Dr Figlin is Acting Cancer Center Director, Arthur and Rosalie Kaplan Professor of Medical Oncology as well as Chair of the Division of Medical Oncology and Experimental Therapeutics at the City of Hope National Medical Center/Beckman Research Institute in addition to Associate Director for Clinical Research at the City of Hope Comprehensive Cancer Center in Duarte, California.