Published in final edited form as:
Clin Genitourin Cancer. 2014 October ; 12(5): 335–340. doi:10.1016/j.clgc.2014.03.003.

First-Line Mammalian Target of Rapamycin Inhibition in Metastatic Renal Cell Carcinoma: An Analysis of Practice Patterns From the International Metastatic Renal Cell Carcinoma Database Consortium

Lauren C. Harshman[1,2], **Nils Kroeger**[3], **Sun Young Rha**[4], **Frede Donskov**[5], **Lori Wood**[6], **Srinivas K. Tantravahi**[7], **Ulka Vaishampayan**[8], **Brian I. Rini**[9], **Jennifer Knox**[10], **Scott North**[11], **Scott Ernst**[12], **Takeshi Yuasa**[13], **Sandy Srinivas**[2], **Sumanta Pal**[14], **Daniel Y. Heng**[3], and **Toni K. Choueiri**[1]

[1]Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

[2]Stanford Cancer Institute, Stanford, CA

[3]Tom Baker Cancer Centre, Calgary, Alberta, Canada

[4]Yonsei Cancer Center/Yonsei University College of Medicine, Seoul, South Korea

[5]Aarhus University Hospital, Aarhus, Denmark

[6]Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia, Canada

[7]University of Utah, Huntsman Cancer Institute, Salt Lake City, UT

[8]Karmanos Cancer Institute, Wayne State University, Detroit, MI

[9]Cleveland Clinic Taussig Cancer Institute, Cleveland, OH

[10]Princess Margaret Cancer Centre, Toronto, Ontario, Canada

[11]Cross Cancer Institute, Edmonton, Alberta, Canada

[12]London Regional Cancer Program, London, Ontario, Canada

[13]The Cancer Institute Hospital of JFCR, Tokyo, Japan

Address for correspondence: Lauren C. Harshman, MD, Kidney Cancer Center, Dana-Farber Cancer Institute/Brigham and Women's Hospital and Harvard Medical School, 450 Brookline Ave (DANA 1230), Boston, MA 02215, Fax: 617-632-2165; LaurenC_Harshman@dfci.harvard.edu.

Disclosure

Lauren C. Harshman: advisory boards for Aveo, Pfizer, and Bristol-Myers Squibb, past research funding from BMS and Novartis; Frede Donskov: research funding from Novartis; Lori Wood: consultant (uncompensated) for Pfizer and Glaxo-Smith Kline, research funding from Pfizer, Glaxo-Smith Kline, and Novartis; Ulka Vaishampayan: consultant for Novartis, honoraria from Novartis and Pfizer, research support from Pfizer; Brian I. Rini: consultant and research funding from Pfizer; Jennifer Knox: consultant for Aveo, research funding from Pfizer; Scott Ernst: consultant/advisory boards for Bristol-Myers Squib, Roche, Novartis, and Glaxo-Smith Kline; Sandy Srinivas: consultant for Pfizer, Glaxo-Smith Kline, and Genentech, research funding from Bristol-Myers Squibb, Pfizer, Glaxo-Smith Kline, and Novartis; Sumanta Pal: honoraria from Novartis; Daniel Y. Heng: consultant for Pfizer, Novartis, and Bayer; Toni K. Choueiri: advisory boards for Glaxo-Smith Kline, Pfizer, Novartis, Genentech, Bayer, and AVEO, research funding from Pfizer. The remaining authors have stated that they have no conflicts of interest.

[14]City of Hope, Duarte, CA

Abstract

Using an established international renal cell carcinoma (RCC) database, we retrospectively characterized the use and efficacy of mammalian target of rapamycin (mTOR) inhibitors in treatment-naive metastatic RCC (mRCC) patients. Front-line mTOR inhibitors are used in clinical practice mostly in select patients, who have non-clear cell histology, poor prognostic features, or as part of clinical trials.

Introduction/Background—Approval of the mTOR inhibitors for the treatment of mRCC was based on efficacy in poor-risk patients in the first-line setting for temsirolimus and in vascular endothelial growth factor inhibitor-refractory patients for everolimus. We strove to characterize temsirolimus and everolimus use and effectiveness in the first-line setting.

Patients and Methods—We performed a retrospective database analysis of mRCC patients who received mTOR inhibitors as first-line targeted therapy. The Kaplan-Meier product-limit method was used to estimate the distribution of progression-free survival (PFS) and overall survival (OS).

Results—We identified 127 mRCC patients who had received a first-line mTOR inhibitor. Temsirolimus was administered in 93 patients (73%) and everolimus in 34 patients (27%). The main reasons for choice of temsirolimus were poor-risk disease (38%), non-clear cell histology (27%), and clinical trial availability (15%), whereas clinical trial (82%) and non-clear cell histology (6%) drove everolimus selection. Of the temsirolimus and everolimus patients, 58% and 32% were poor-risk according to the International mRCC Database Consortium criteria, respectively. The median PFS and OS were 3.4 and 12.5 months and 4.8 and 15.9 months with temsirolimus and everolimus, respectively. Although limited by small numbers, this study characterizes a real-world, international experience with the use of mTOR inhibition in treatment-naive mRCC patients.

Conclusion—Poor-risk RCC, non-clear cell histology, and clinical trials were the predominant reasons for mTOR inhibitor selection in the front-line setting. Because of the different patient populations in which they were administered, direct comparisons of the front-line efficacy of temsirolimus and everolimus cannot be made.

Keywords

Everolimus; mTOR inhibitor; Targeted therapy; Temsirolimus; Treatment-naive

Introduction

Two major classes of targeted therapies, the vascular endothelial growth factor (VEGF) inhibitors and the mammalian target of rapamycin (mTOR) inhibitors, have been developed for the treatment of metastatic renal cell carcinoma (mRCC). By inhibiting angiogenesis and growth factor pathways critical to the growth of mRCC, these agents elicit significant improvements in progression-free survival (PFS), in objective responses, and in some cases, overall survival.[1–12]

Mammalian target of rapamycin is integral to the regulation of cell growth, proliferation, metabolism, and autophagy.[13] Two mTOR inhibitors are approved to treat advanced renal cell carcinoma (RCC): temsirolimus and everolimus. Through an allosteric interaction, these rapalogs complex with an intracellular protein, FK 506 binding protein-12, bind to mTOR, and competitively inhibit its signaling.[14] Because of its role in the regulation of hypoxiainducible factor (HIF), mTOR blockade also inhibits angiogenesis and other key HIF genes critical to tumorigenesis and survival.[15]

With their similar mechanisms of action, temsirolimus and everolimus are often assumed to have equivalent efficacy. However, they were prospectively studied in very different patient populations.[3,4] Temsirolimus is approved for use in treatment-naive patients based on level 1 evidence that it increases overall survival in poor-risk disease. However, it is important to remember that it has not been directly compared with a VEGF-targeted therapy in that setting. Everolimus is a standard therapy in the second-line setting based on its ability to stabilize disease and prolong PFS in VEGF inhibitor-refractory patients. To enhance our knowledge of their efficacy and to understand the reasons they are chosen over VEGF inhibitors, we interrogated the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) databank and the longitudinal medical records of our institutions for the outcomes of patients who received mTOR inhibitors as first-line targeted therapy in a real-world, unselected setting.

Patients and Methods

Patient Population

The IMDC is a group of academic institutions from Canada, the United States, Singapore, Denmark, and South Korea. Patient inclusion into the database requires advanced or metastatic RCC of any histology and treatment with a targeted therapy. For the current study, 14 centers had data on RCC patients who had received firstline mTOR inhibitors. Patients were excluded if they received a concurrent VEGF-targeted therapy.

We queried the database for baseline demographic, clinical, laboratory, and outcomes information. Investigators retrospectively reviewed clinic notes to assess the reason behind the choice of an mTOR inhibitor. Reasons included IMDC[16] or Memorial Sloan-Kettering Cancer Center (MSKCC)[17] poor-risk status, non-clear cell histology or sarcomatoid features, clinical trial, comorbidity or toxicity concerns with administration of a VEGF inhibitor, physician choice, insurance issues, history of renal transplant (with the rationale that rapamycin would be effective at preventing rejection too), and unknown. Survival data were retrieved from the patient's medical record or publically available records. Institutional review board approval was secured from each center.

Statistical Analysis

Summary descriptive statistics were created for baseline characteristics. The Kaplan-Meier product limit method was used to estimate the distributions of PFS and overall survival for all patients, and stratified by prognostic groups defined at therapy initiation or by other covariates of interest. Comparisons between groups were conducted using the log rank test.

PFS was defined as time from drug initiation to progression, cessation of therapy, death, or censored at last follow-up. Overall survival was defined as time from drug initiation to death or censored at last follow-up. Statistical analyses were performed using SAS 9.2 (SAS Institute, Cary, NC). The cutoff date for data analysis was February 4, 2013.

Results

From July 2004 to January 2013, 127 patients received a first-line mTOR inhibitor for metastatic RCC. Median follow-up was 22.1 months. Temsirolimus was administered in most cases and 34 patients received everolimus. Baseline demographic characteristics are shown in Table 1. Median age in both cohorts was 61 to 62 years. Median Karnofsky performance status was slightly lower in the temsirolimus group at 80% compared with 90% in the everolimus group. Approximately half of the patients in each group had clear cell disease with 40% to 41% of the patients having non-clear cell disease. Sarcomatoid features were present in 14% of the temsirolimus patients and in 26% of the everolimus patients. Temsirolimus patients had a lower incidence of previous nephrectomy (62% vs. 82%) and a greater number of metastatic sites (> 1 site: 84% vs. 76%) compared with the everolimus cohort. Of the temsirolimus and everolimus patients, 58% and 32% were poor risk according to IMDC criteria, 27% and 29% were intermediate risk, and 6% and 15% were favorable risk, respectively.

Retrospective review of clinic notes revealed the reasons behind the choice of an mTOR inhibitor. Reasons identified included IMDC or MSKCC poor-risk status, non-clear cell histology or sarcomatoid features, clinical trial, comorbidity or toxicity concerns prohibiting administration of a VEGF inhibitor, physician choice, insurance issues, history of renal transplant (with the justification that rapamycin would also be effective at preventing rejection too), and unknown. Poor risk status (38%), non-clear cell histology (27%), and clinical trial (15%) motivated physicians to select temsirolimus and clinical trial (82%) and non-clear cell histology (6%) drove choice of everolimus (Table 2).

The median PFS in all patients was 3.4 months (n = 90) for temsirolimus and 4.8 (n = 32) months for everolimus (Table 3). There were no significant differences in efficacy between the clear cell and non-clear cell subsets (Kaplan-Meier curves not shown). In clear cell disease, temsirolimus induced a median PFS of 3.3 months (n = 47) and 4.8 months (n = 36) in non-clear cell disease ($P = .61$). Median PFS was 5.5 months (n = 17) for clear cell disease and 3.3 months (n = 14) for non-clear cell disease when treated with everolimus ($P = .6$). Temsirolimus elicited a median PFS of 8.3 (n = 6), 5.3 (n = 25), and 3.1 (n = 40) months in good-, intermediate-, and poor-risk patients, respectively. Everolimus administration resulted in a median PFS of 11.3 (n = 5), 2.3 (n = 10), and 5.3 (n = 7) months in good-, intermediate-, and poor-risk patients.

Median overall survival was 12.5 and 15.9 months for temsirolimus and everolimus, respectively (Table 3). Non-clear cell disease patients lived a median of 14.3 months if they received temsirolimus (n = 36) compared with 12.5 months (n = 49) if they had clear cell disease ($P = .81$). Everolimus induced a median overall survival of 20.6 months (n = 14) in non-clear cell disease and clear cell patients attained a median overall survival of 17.2

months (n = 19). Median overall survival for good-, intermediate-, and poor-risk patients who received temsirolimus was 16.2 (n = 6), 14.5 (n = 25), and 5.3 (n = 42) months, respectively. For the everolimus cohort, median overall survival was 16.2 (n = 5), 15.9 (n = 10), and 19.4 (n = 7) months for the good-, intermediate-, and poor-risk patients.

In the 97 patients with response data, partial responses were achieved in 5% and 8% of temsirolimus and everolimus patients, respectively. Most patients experienced disease stabilization as best response (53% for temsirolimus; 58% for everolimus) for an overall clinical benefit of 58% with temsirolimus and 66% for everolimus. Primary refractory disease with progressive disease as best response occurred in 41% of temsirolimus patients and 33% of everolimus patients.

At the time of the analysis, 52 patients (41%) had received a second-line therapy; 44% of everolimus and 40% of temsirolimus patients. VEGF inhibitors were chosen in most cases (92%).

Discussion

The mTOR inhibitors are a distinct class of targeted therapies approved for the treatment of advanced RCC. Although they can provide clinical benefit in the form of stabilizing disease and prolonging time to disease progression, outstanding questions persist with respect to the optimal timing, sequencing, and patient population in which to use these agents. We undertook the current study to assess the practice patterns and efficacy of first-line mTOR inhibition in an unselected, real-world population of patients with metastatic RCC of any histology.

In our study, reasons for choosing an mTOR inhibitor over a VEGF targeted therapy were consistent with their approved indications and current thinking on their most appropriate use at the time of the selection. The lower utilization of everolimus reflects that it was not approved in the first-line setting and thus. it was not surprising that clinical trial was the most common reason for its upfront use (82%). In the case of temsirolimus, the most common reasons for administration were poor-risk disease (38%) followed by non-clear cell histology (27%) and clinical trial availability (15%). Comorbidities and preferable toxicity profile were additional justifications for choosing an mTOR inhibitor over a VEGF targeted agent. These latter results likely highlight physician knowledge of the well characterized VEGF inhibitor cardiovascular toxicities and concerns for the potential to exacerbate preexisting refractory hypertension or clinically significant congestive heart failure as motivating factors for the choice of mTOR inhibition over VEGF blockade in some cases.[18,19]

To provide a historical perspective in which to frame our results, in the global phase III registration study, temsirolimus achieved a median PFS of 3.7 months and overall survival of 10.9 months in previously untreated patients with extensive disease and multiple poor prognostic risk features such as absence of nephrectomy, anemia, increased calcium levels, increased lactate dehydrogenase, poor performance status, and multiple sites of metastases.[3] In our unselected patient population, median PFS was 3.4 months in the entire cohort and

3.1 months in the poor-risk patients with median overall survivals of 12.5 months and 5.3 months, respectively. In a recently published prospective observation trial of temsirolimus use in Germany, 42% of patients received the drug in the first-line setting.[20] In the treatment-naive patients, median PFS and overall survival were 5.3 and 10.5 months. MSKCC risk stratification data were missing in > 100 patients, but in those for whom it was available, median PFS and overall survival were significantly better in the intermediate risk patients compared with the poor risk patients at 5.3 versus 2.4 months ($P = .001$) and 11.6 versus 5.6 months ($P < .001$), which was consistent with our data. Clear cell or non-clear cell histology did not affect outcomes in terms of PFS, overall survival, or clinical benefit in the German study.

In our everolimus cohort, the median PFS was 4.8 months, which is more in line with a historical second-line VEGF or mTOR inhibitor response.[21] This inferior outcome might reflect the higher percentage of poor risk patients in our cohort (21%) and a lower percentage of good risk patients (15%). In addition, risk status was unknown in 35% of our patients making an even higher degree of less favorable disease patients possible. Because of the retrospective nature of our study, no direct comparisons should be made to the temsirolimus cohort. However, the slightly better PFS in our everolimus cohort likely reflects that most of these patients were healthy enough to be deemed eligible for a clinical trial. Past work by our group using the same IMDC database has shown that mRCC patients eligible for a clinical trial have significantly better clinical outcomes in terms of objective responses, PFS, and overall survival compared with patients who would likely be considered ineligible.[22]

The most informative trial regarding the effectiveness of everolimus in the front-line setting is the recently reported randomized phase II study, RECORD-3, which assessed whether everolimus was noninferior to sunitinib in treatment-naive patients (n = 471).[23] RECORD-3 is the first prospective study to provide data on everolimus' efficacy in treatment-naive and more favorable risk patients (MSKCC: 29% good, 56% intermediate). Everolimus elicited a median PFS of 7.9 months but did not achieve 'noninferiority' against sunitinib (10.7 months). Focusing on patients with good-risk disease, the median PFS of 11.3 months elicited by everolimus in our study was in line with that seen in the RECORD-3 good-risk everolimus cohort (11.1 months). In our study and RECORD-3, everolimus' effect in treatment-naive patients with poor-risk disease was dismal. Further, the RECORD-3 trial emphasized that these poor risk patients have bleak outcomes regardless of the type of therapy administered (median PFS: 2.6 vs. 3.0 months with everolimus and sunitinib, respectively), underscoring the critical need for novel agents or therapeutic strategies in this patient population.

Because of reports of upregulation of the mTOR pathway in non-clear cell disease, the question has loomed as to whether mTOR inhibitors should be the preferred first-line selection for the non-clear cell histologies in the absence of a definitive clinical trial.[3] In the phase 3 registration trial for temsirolimus, approximately 20% of patients had non-clear cell disease, most of which were the papillary subtype. PFS ranged from 5.9 months for papillary disease to 7 months for all non-clear cell histologies to 5.5 months for the clear cell subset.[24] In a single-arm phase II study of 49 patients with non-clear cell RCC, everolimus elicited

objective responses in 10%, disease stabilization in 51%, and a median PFS of 5.2 months.[25] Previous VEGF blockade did not decrease the efficacy of everolimus compared with patients who were treatment-naive. In our study, each cohort was comprised of approximately 40% of patients with non-clear cell disease. Temsirolimus induced a median PFS of 4.8 months and everolimus a median of 5.5 months. Comparatively, in prospective single arm studies and the Expanded Access Program, sunitinib achieved objective response rates of 5% to 36%, median PFS ranging from 2.7 to 7.8 months, and median overall survival of 13.4 to 25.6 months in non-clear cell disease.[26–28] In the RECORD-3 trial, subset analysis of very small cohorts showed that everolimus did not outperform sunitinib in non-clear cell disease (median PFS, 5.1 months; n = 24/31 vs. 7.2 months; n = 23/35). Ultimately, 2 prospective trials powered to compare the efficacy of everolimus with sunitinib in mRCC patients with non-clear cell histology will shed additional light on this issue (NCT01108445, NCT01185366).

Finally, the question remains as to whether these agents, which are assumed to have very similar mechanisms of action, are indeed equivalently therapeutic. In our study, because of the different populations in which they were administered, we cannot make direct comparisons of the front-line efficacy of temsirolimus compared with everolimus. Most temsirolimus patients were poorrisk, which their dismal PFS and survival reflect, and the better outcomes in the everolimus patients highlight that most were not poor-risk and were healthy enough to be eligible for clinical trials. In addition to efficacy considerations, ease and route of administration, availability, and cost, all factor into drug selection. Temsirolimus' intravenous formulation ensures compliance and absorption but conversely requires the significant time commitment of weekly trips to the clinic. Everolimus provides easy oral administration and less frequent visits but does not always assure compliance, and its absorption might be compromised by food or gastrointestinal disorders. With respect to cost and resources, an observational, retrospective study of a large nationwide community oncology network found everolimus to be more cost-effective and resourcesaving than temsirolimus.[29]

The limitations of our study are its retrospective nature and the small numbers of patients who received mTOR inhibition as their first-line treatment. Because this was not a prospective study, clinical outcomes data were investigator-assessed and thus, subject to clinician bias. Nonstandardized scan intervals might have resulted in lead or length time bias in calculating PFS. Finally, pathology was not centrally reviewed and as such there might be a degree of variability in histologic classification. However, this work characterizes a real-world experience of first-line mTOR inhibition in an unselected patient population, which makes these results potentially more generalizable than results of highly selected clinical trial populations.

Conclusion

Because of the results of the prospective RECORD-3 trial, upfront VEGF inhibition or clinical trial is preferred over mTOR blockade in advanced, treatment-naive patients with clear cell RCC. Temsirolimus can be considered an option for poor prognosis, treatment-naive patients in the first-line setting, but the disappointing outcomes observed in our

analysis and in the RECORD-3 trial by either class of agents in poor-risk disease targets this population as prime for investigation of novel agents.

References

1. Escudier B, Bellmunt J, Negrier S, et al. Phase III trial of bevacizumab plus interferon alfa-2a in patients with metastatic renal cell carcinoma (AVOREN): final analysis of overall survival. J Clin Oncol. 2010; 28:2144–2150. [PubMed: 20368553]
2. Escudier B, Eisen T, Stadler WM, et al. Sorafenib for treatment of renal cell carcinoma: final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial. J Clin Oncol. 2009; 27:3312–3318. [PubMed: 19451442]
3. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med. 2007; 356:2271–2281. [PubMed: 17538086]
4. Motzer RJ, Escudier B, Oudard S, et al. Phase 3 trial of everolimus for metastatic renal cell carcinoma: final results and analysis of prognostic factors. Cancer. 2010; 116:4256–4265. [PubMed: 20549832]
5. Motzer RJ, Escudier B, Tomczak P, et al. Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomised phase 3 trial. Lancet Oncol. 2013; 14:552–562. [PubMed: 23598172]
6. Motzer RJ, Hutson TE, Cella D, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. N Engl J Med. 2013; 369:722–731. [PubMed: 23964934]
7. Motzer RJ, Hutson TE, Tomczak P, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol. 2009; 27:3584–3590. [PubMed: 19487381]
8. Motzer RJ, Nosov D, Eisen T, et al. Tivozanib versus sorafenib as initial targeted therapy for patients with metastatic renal cell carcinoma: results from a phase III trial. J Clin Oncol. 2013; 31:3791–3799. [PubMed: 24019545]
9. Rini BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase III trial. Lancet. 2011; 378:1931–1939. [PubMed: 22056247]
10. Rini BI, Halabi S, Rosenberg JE, et al. Phase III trial of bevacizumab plus interferon alfa versus interferon alfa monotherapy in patients with metastatic renal cell carcinoma: final results of CALGB 90206. J Clin Oncol. 2010; 28:2137–2143. [PubMed: 20368558]
11. Soerensen AV, Donskov F, Hermann GG, et al. Improved overall survival after implementation of targeted therapy for patients with metastatic renal cell carcinoma: results from the Danish Renal Cancer Group (DARENCA) study-2. Eur J Cancer. 2014; 50:553–562. [PubMed: 24215846]
12. Sternberg CN, Davis ID, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol. 2010; 28:1061–1068. [PubMed: 20100962]
13. Meric-Bernstam F, Gonzalez-Angulo AM. Targeting the mTOR signaling network for cancer therapy. J Clin Oncol. 2009; 27:2278–2287. [PubMed: 19332717]
14. Abraham RT, Gibbons JJ. The mammalian target of rapamycin signaling pathway: twists and turns in the road to cancer therapy. Clin Cancer Res. 2007; 13:3109–3114. [PubMed: 17545512]
15. Land SC, Tee AR. Hypoxia-inducible factor 1alpha is regulated by the mammalian target of rapamycin (mTOR) via an mTOR signaling motif. J Biol Chem. 2007; 282:20534–20543. [PubMed: 17502379]
16. Heng DY, Xie W, Regan MM, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. J Clin Oncol. 2009; 27:5794–5799. [PubMed: 19826129]
17. Motzer RJ, Mazumdar M, Bacik J, et al. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. J Clin Oncol. 1999; 17:2530–2540. [PubMed: 10561319]

18. Hall PS, Harshman L, Srinivas S, Witteles RM. The frequency and severity of cardiovascular toxicity from targeted therapy in advanced renal cell carcinoma patients. JACC Heart Fail. 2013; 1:72–78. [PubMed: 24621801]

19. Richards CJ, Je Y, Schutz FA, et al. Incidence and risk of congestive heart failure in patients with renal and nonrenal cell carcinoma treated with sunitinib. J Clin Oncol. 2011; 29:3450–3456. [PubMed: 21810682]

20. Schrader AJ, Seseke S, Keil C, et al. Temsirolimus in daily use: results of a prospective multicentre noninterventional study of patients with metastatic kidney cancer. Eur Urol. Published online August 31, 2013; http://dx.doi.org/10.1016/j.eururo.2013.08.055.

21. Motzer RJ, Escudier B, Oudard S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet. 2008; 372:449–456. [PubMed: 18653228]

22. Heng DY, Choueiri TK, Rini BI, et al. Outcomes of patients with metastatic renal cell carcinoma that do not meet eligibility criteria for clinical trials. Ann Oncol. 2014; 25:149–154. [PubMed: 24356626]

23. Motzer RJ, Barrios CH, Kim TM, et al. RECORD-3: phase II randomized trial comparing sequential first-line everolimus and second-line sunitinib versus firstline sunitinib and second-line everolimus in patients with metastatic renal cell carcinoma. J Clin Oncol. 2013; 31 (abstract 4504).

24. Dutcher JP, de Souza P, McDermott D, et al. Effect of temsirolimus versus interferon-alpha on outcome of patients with advanced renal cell carcinoma of different tumor histologies. Med Oncol. 2009; 26:202–209. [PubMed: 19229667]

25. Koh Y, Lim HY, Ahn JH, et al. Phase II trial of everolimus for the treatment of nonclear-cell renal cell carcinoma. Ann Oncol. 2013; 24:1026–1031. [PubMed: 23180114]

26. Gore ME, Szczylik C, Porta C, et al. Safety and efficacy of sunitinib for metastatic renal-cell carcinoma: an expanded-access trial. Lancet Oncol. 2009; 10:757–763. [PubMed: 19615940]

27. Lee JL, Ahn JH, Lim HY, et al. Multicenter phase II study of sunitinib in patients with non-clear cell renal cell carcinoma. Ann Oncol. 2012; 23:2108–2114. [PubMed: 22228449]

28. Tannir NM, Plimack E, Ng C, et al. A phase 2 trial of sunitinib in patients with advanced non-clear cell renal cell carcinoma. Eur Urol. 2012; 62:1013–1019. [PubMed: 22771265]

29. Vogelzang NJ, Bhor M, Liu Z, et al. Everolimus vs. temsirolimus for advanced renal cell carcinoma: use and use of resources in the US Oncology Network. Clin Genitourin Cancer. 2013; 11:115–120. [PubMed: 23063578]

Clinical Practice Points

- Temsirolimus and everolimus are mTOR inhibitors approved for the treatment of advanced RCC. Temsirolimus was approved for use in the first-line setting in patients with poor-risk features while everolimus was initially evaluated in patients whose disease had progressed after treatment with a VEGF inhibitor.
- We examined the reasons for choice and the resultant efficacy of front-line mTOR inhibitor administration in our international database consortium.
- In clinical practice, we observed that use of mTOR inhibitors in the first-line setting tended to be in select patients, who had non-clear cell histology, poor prognostic features, or as part of clinical trials.
- Temsirolimus can be considered an option for poor prognosis, treatment-naive patients, but has never been directly compared with a VEGF targeted therapy in this setting. Because of the results of the prospective RECORD-3 trial, which did not prove everolimus to be noninferior to sunitinib, VEGF inhibition or clinical trial is generally preferred over mTOR blockade in advanced treatment-naive RCC patients.
- The disappointing outcomes observed in our retrospective population-based analysis and the prospective RECORD-3 trial by either class of agents in poor-risk disease highlight the need for novel treatment strategies and targets in this population.

Table 1

Patient and Tumor Characteristics (n = 127)

Characteristic	Temsirolimus (n = 93)	Everolimus (n = 34)
Median Age at Initiation of Therapy, Years	61	62
Median Performance Score (KPS)	80%	90%
Sex		
Male	66 (71)	26 (76)
Female	27 (29)	8 (24)
Pathology		
Clear Cell	48 (52)	17 (50)
Non-Clear Cell	37 (40)	14 (41)
Unknown	8 (9)	3 (9)
Sarcomatoid Features		
Yes	13 (14)	9 (26)
No	67 (72)	21 (62)
Unknown	13 (14)	4 (12)
Previous Nephrectomy		
Yes	58 (62)	28 (82)
No	35 (38)	6 (18)
Number of Metastases >1	78 (84)	26 (76)
Metastatic Site		
Lung	61 (66)	18 (53)
Lymph node	59 (63)	19 (56)
Bone	38 (41)	10 (29)
Liver	26 (28)	8 (24)
Brain	8 (9)	2 (6)
IMDC Risk Group[a]		
Favorable	6 (6)	5 (15)
Intermediate	25 (27)	10 (29)
Poor	42 (45)	7 (21)
Unknown	20 (22)	12 (35)

Data are presented as n (%) except where otherwise noted.

Abbreviations: IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; KPS = Karnofsky performance status.

[a] IMDC poor prognosis risk factors include absence of nephrectomy, KPS < 70%, hemoglobin level below normal, high serum corrected calcium, high absolute neutrophil count, and thrombocytosis.

Table 2

Reason for mTOR Inhibitor Selection Over VEGF-Targeted Therapy

Reason	Temsirolimus (n = 93)	Everolimus (n = 34)
Poor Risk	38% (35)	3% (1)
Non-Clear Cell Histology	27% (25)	6% (2)
Clinical Trial	15% (14)	82% (28)
Comorbidity or Toxicity Concerns	10% (9)	6% (2)
Physician's Choice	4% (4)	0% (0)
Insurance Issues	3% (3)	0% (0)
Other[a]	3% (3)	3% (1)

Data are presented as percentage (n).

[a] Other included: status post renal transplant (n = 2), sarcomatoid histology (n = 1), unknown (n = 1).

Table 3

Progression-Free Survival and OS According to Drug, Risk Status, and Histology

Survival	All Patients	Good Risk	Intermediate Risk	Poor Risk	Clear Cell	Non-Clear Cell
Median PFS, Months						
Temsirolimus	3.4 (n = 90)	8.3 (n = 6)	5.3 (n = 25)	3.1 (n = 40)	3.3 (n = 47)	4.8 (n = 36)
Everolimus	4.8 (n = 32)	11.3 (n = 5)	2.3 (n = 10)	5.3 (n = 7)	5.5 (n = 17)	3.3 (n = 14)
Median OS, Months						
Temsirolimus	12.5 (n = 92)	16.2 (n = 6)	14.5 (n = 25)	5.3 (n = 42)	12.5 (n = 49)	14.3 (n = 36)
Everolimus	15.9 (n = 34)	16.2 (n = 5)	15.9 (n = 10)	19.4 (n = 7)	17.2 (n = 19)	20.6 (n = 14)

Abbreviations: OS = overall survival; PFS = progression-free survival.