original report

# Assessment of Treatment Patterns for Metastatic Renal Cell Carcinoma in Brazil

abstract

**Background** Although multiple therapies have emerged for the treatment of metastatic renal cell carcinoma (mRCC), it is unclear whether application of these agents is consistent in developed and developing countries. We sought to determine patterns of care for mRCC in Brazil as a representative developing country.

**Material and Methods** A commercial database was used to acquire information pertaining to patients with mRCC receiving treatment at private or public hospitals in Brazil between March 2013 and October 2016. Basic clinical and demographic criteria were available, as well as information to ascertain the International Metastatic Renal Cell Carcinoma Database Consortium risk. Treatment-related data across multiple lines of therapy were collected.

**Results** Of 4,379 patients assessed, 3,990 (91%) had metastatic disease, and 26%, 48%, and 26% of patients had good, intermediate, and poor International Metastatic Renal Cell Carcinoma Database Consortium risk disease, respectively. Although 3,149 patients (79%) received first-line therapy, only 641 (20%) and 152 (5%) received second- and third-line therapy, respectively. In the first-line setting, vascular endothelial growth factor–directed agents represented the most commonly used therapy, whereas in the second-line setting, vascular endothelial growth factor– and mammalian target of rapamycin–directed agents were used with similar frequency. Marked differences were seen in receipt of systemic therapy on the basis of treatment in private or public hospitals.

**Conclusion** Relative to developed countries, marked attrition is noted between each subsequent line of therapy in Brazil. Patterns of care also vary greatly in private and public settings, pointing to financial constraints as a potential cause for discordances in treatment.

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Paulo G. Bergerot
Cristiane D. Bergerot
Nazli Dizman
Stenio Zequi
Andre Fay
Yash Dara
Manuel Caitano Maia
Brendan N. Cotta
Edna Prado Gonçalves
Maria Nirvana Formiga
Milena Shizue Tariki
Diego Abreu Clavijo
Toni K. Choueiri
Gilberto Lopes
Sumanta K. Pal

Author affiliations and support information (if applicable) appear at the end of this article.

**Corresponding author:** Paulo G. Bergerot, MD, Universidade Federal de Sao Paulo, Rua Napoleao de Barros, 754, Sao Paulo-SP Brazil 04024-002; e-mail: paulobergerot@gmail.com.

## INTRODUCTION

Cancers of the kidney (including primarily renal cell carcinoma [RCC] and upper tract urothelial cancers) represent the fourth most common malignancy worldwide, with approximately 337,800 patients diagnosed in 2012.[1] The incidence varies across individual countries. In developed countries such as the United States, an estimated 63,990 patients will be diagnosed with cancers of the kidney in 2017, and 14,400 patients will die of the disease.[2] In developing countries, formal estimates are often challenging to obtain. However, using Brazil as an example, GLOBOCAN estimates suggest that 6,255 patients were diagnosed in 2012, and 3,291 patients died of the disease.RCC represents the most common cancer derived from the kidney, constituting approximately 90% of patients. Patients with metastatic RCC (mRCC) are generally considered incurable, although the prognosis in this disease state has improved markedly in recent years. In the cytokine era, when treatment typically constituted agents such as interleukin-2 and interferon alpha, median overall survival (OS) was estimated at slightly longer than 1 year.[3] However, with the advent of targeted therapies abrogating signaling via vascular endothelial growth factor (VEGF) and the mammalian target of rapamycin (mTOR), median OS estimates now are typically in the range of 25 to 30 months.[4] The recent advent of novel targeted therapies such as cabozantinib and selective immunotherapeutic agents such as nivolumab have pushed estimates for OS even further.[5,6]A foreseeable challenge is that developing and developed countries may have differential access to novel therapies for mRCC. Furthermore, developing countries often have a heterogeneous array of practice settings, with a large dichotomy between public and private practices. In Brazil, the health care system includes public and private settings. Public settings are open to all Brazilian citizens

**Table 1.** Patient Characteristics

| Characteristic | Overall Cohort | Private | Public |
|---|---|---|---|
| No. | 4,379 | 2,473 | 1,906 |
| Median age, years (range) | 59.5 (13-98) | 60.5 (14-98) | 58 (13-89) |
| Female, No. (%) | 1,418 (32) | 7,79 | 639 |
| Male, No. (%) | 2,961 (68) | 1,694 | 1,267 |
| Histology, No. (%) | | | |
| Clear cell | 3,496 (80) | 1,942 | 1,490 |
| Nonclear cell | 248 (5.5) | 128 | 120 |
| Unknown | 635 (14.5) | 372 | 263 |
| Heng risk, No. (%) | | | |
| Good | 928 (26) | 514 | 414 |
| Intermediate | 1,670 (48) | 959 | 711 |
| Poor | 908 (26) | 485 | 423 |
| Metastatic disease, No. (%) | 3,990 (91) | 2,289 | 1,701 |
| Lines of therapy, No. (%) | | | |
| First | 3,149 (79) | 1,723 | 1,426 |
| Second | 641 (20) | 424 | 217 |
| Third | 152 (5) | 103 | 49 |
| Fourth | 47 (1) | 40 | 7 |

and foreigners, and private settings are open to those who possess supplemental health insurance or, rarely, those who can afford it. Using data acquired across a diverse array of practices in Brazil, we sought to determine patterns in use of systemic therapy for mRCC. Within this database, information from both private and public institutions was housed. The trends we observed were juxtaposed against published data reflecting mRCC practice patterns in developed countries.

## MATERIAL AND METHODS

### Participants and Setting

We used the Close-Up International database, a commercial data set housing clinical information from both private and public institutions in 55 cities across 18 states in Brazil. The database is more heavily representative of southeast Brazil, with 50% of institutions coming from this territory. Practitioners at participating institutions were queried twice per year regarding patients they had treated for RCC. In a retrospective fashion, data were submitted pertaining to basic demographic characteristics (such as age and gender) and disease stage. When available, histologic data were submitted (eg, clear cell versus nonclear cell). Furthermore, sufficient clinical characteristics were provided for computation of the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk category. Practitioners submitted treatment-related information, including the type and sequence of systemic agents rendered. For the current study, consecutive patients assessed from March 2013 to October 2016 were assessed.

### Statistical Analysis

Descriptive statistics were used to assess the frequency of administration of first-, second-, and third-line therapy in the overall cohort and to characterize trends in specific systemic therapies rendered (eg, sunitinib, pazopanib, etc). The $X^2$ test was used to compare the frequency of use of systemic therapy across first-, second- and third-line settings in private versus public hospitals.

## RESULTS

### Patient Characteristics

Characteristics of the overall study population (N = 4,379) are listed in Table 1. The majority of patients were male (68%), and the median age of the cohort was 59.5 years. The most common histology encountered was clear cell RCC, constituting 80% of the cohort. Most patients were intermediate risk by IMDC criteria. Demographics and clinicopathologic characteristics of patients in private versus public institutions are listed in Table 1. A significantly higher incidence in the proportion of poor-risk patients was identified in patients treated at public versus private hospitals ($P = .01$), as shown in Figure A1.

### Treatment-Related Data

In total, 3,990 patients were identified with metastatic disease. Of them, 3,149 patients (79%) were noted to receive first-line therapy, as highlighted in Figure 1. The most common first-line treatment was sunitinib (57%), followed by pazopanib (28%). mTOR inhibitors were infrequently used in this setting (6%). Among patients receiving first-line therapy, only 641 patients (20%) received second-line treatment. In this setting, VEGF and mTOR inhibitors were used with a relatively similar frequency. The most common mTOR inhibitor used for second-line therapy was everolimus, whereas a relatively even proportion of patients received sorafenib, pazopanib, and

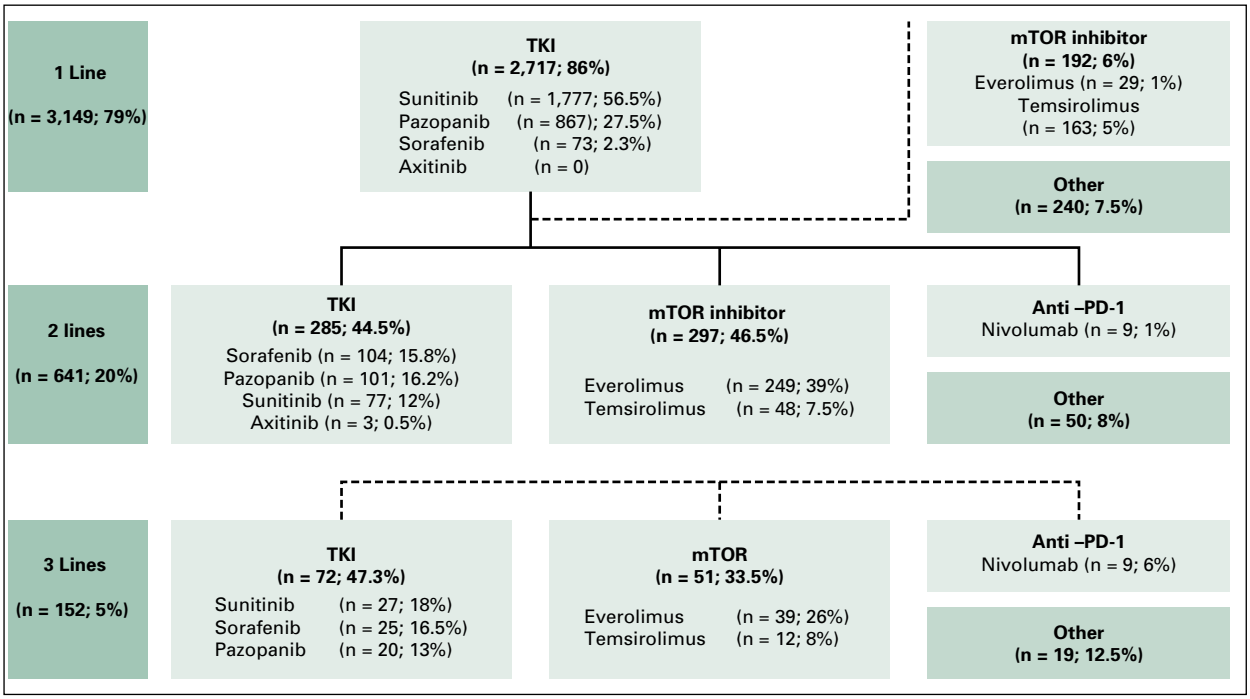


**Fig 1.** CONSORT diagram outlining the nature of systemic therapies rendered for patients with metastatic renal cell carcinoma (N = 3,990). IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; mTOR, mammalian target of rapamycin; PD-1, programmed death-1; TKI, tyrosine kinase inhibitor.

sunitinib in the second-line setting. More limited data were available for third-line therapy. Among patients who received first-line treatment, only 5% received third-line treatment. In this setting, a slight preponderance of patients received VEGF tyrosine kinase inhibitors.

### Use of Treatments by Time Period (March 2013 to October 2016)

Figure 2 highlights the use of individual systemic therapies over the study period. As noted in Fig 2A, sunitinib and pazopanib were the most frequently used first-line therapies throughout the study period, and a significant trend toward increasing use of pazopanib and decreasing use of sunitinib was observed. In the second-line setting (Fig 2B), everolimus represented the most frequently used agent throughout the study period, and no significant variations in the use of other VEGF tyrosine kinase inhibitors were observed. Figure 3C highlights a lack of consistent treatment patterns across third-line therapy.

### Use of Treatments by Setting

Patients with mRCC treated in a private setting more frequently received systemic therapy compared with those treated within a public setting. In the first-line setting (Fig 3), a significantly higher proportion of patients received systemic therapy in a private versus public setting (55% *v* 45%; $P = .001$). A similar trend was observed in the second-line setting (14% *v* 7%; $P = .001$). Although there was a higher proportion of patients in private hospitals versus public hospitals receiving third-line therapy, this difference did not reach statistical significance (3% *v* 2%; $P = .16$).

## DISCUSSION

The current data set reflects the largest experience related to treatment patterns for patients with mRCC in Brazil. This study identified that, in general, treatment patterns for patients with mRCC in Brazil have some overlap with treatment patterns in developed countries. Consistent with reports from US-based commercial databases assessing the same period, the vast majority of patients with mRCC received VEGF-directed treatments in the front-line setting, and a relatively even distribution received mTOR- and VEGF-directed agents as second-line therapy.[7] One concerning element of our data set, however, pertains to the attrition observed from first- to second-line therapy and from second- to third-line therapy. Our data also highlight marked disparities in treatment between private and public hospitals.Previous reports from the IMDC suggest that approximately 48% of patients who receive first-line therapy proceed to second-line

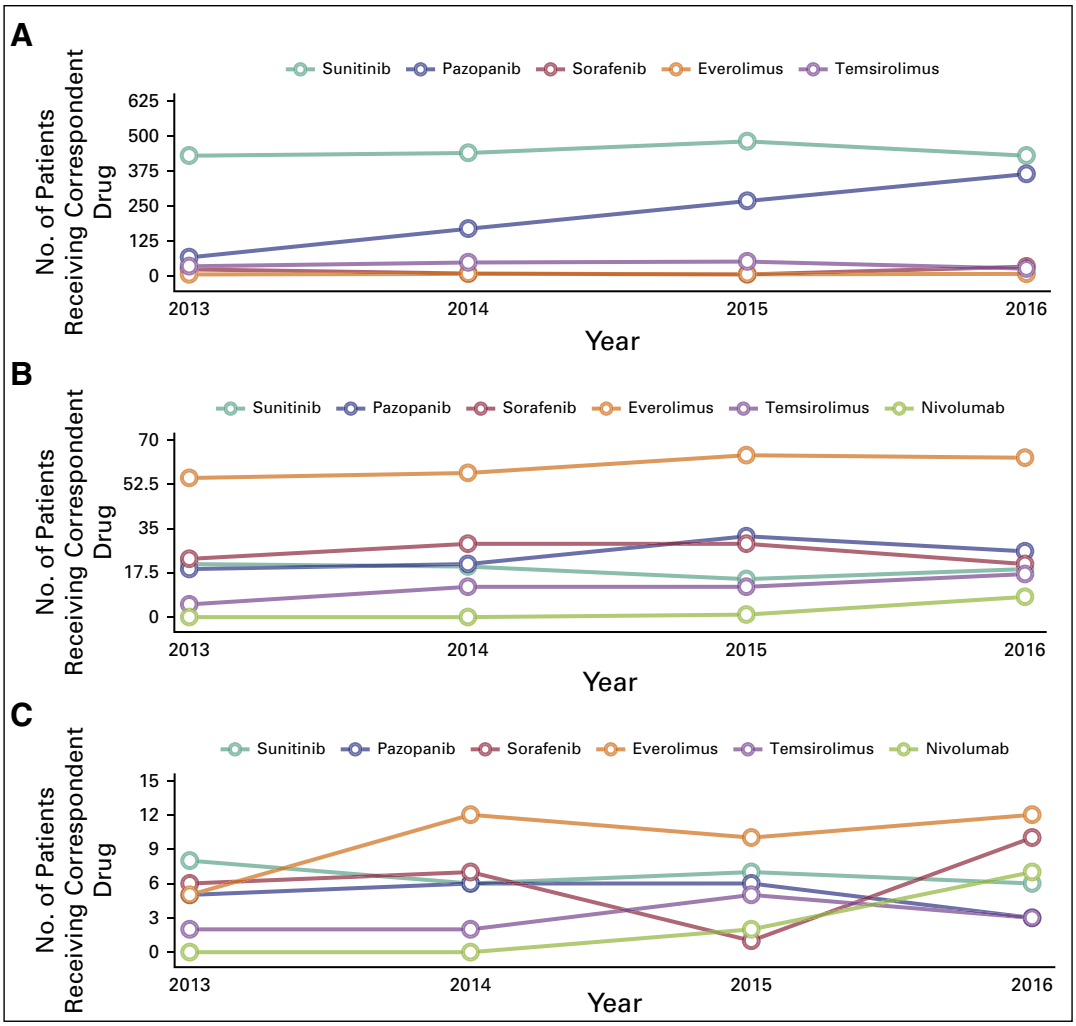


**Fig 2.** Trends in use of the five most common systemic therapies across the (A) first-line, (B) second-line, and (C) third-line settings.

therapy.[8] In addition, among patients who received first-line therapy in this experience, approximately 21% received third-line therapy. Figure A2 highlights the disparities between the IMDC experience and the Brazilian experience reported herein. The lower frequency of receipt of second- and third-line therapy could hinge on a number of different factors. In particular, we suspect limited availability and cost of second-line treatments to be a barrier, although our data set did not have the capability of confirming this. Another barrier to receipt of second-line therapy might be educational gaps among practitioners. Emerging data from phase III studies supporting the use of agents in the refractory setting may not be widely broadcast.The discordance in receipt of therapies in private and public settings is perhaps the greatest indication that financial and social barriers likely affect treatment paradigms in Brazil. Across each setting (first-line, second-line, and so on), there was a trend toward decreased use in public practice settings. Again, it is impossible to ascertain whether educational gaps could also contribute to this discordance. Evidence of this is shown in Figure A3, which shows the diversity of nontraditional therapies that are applied toward mRCC in Brazil. Although some rationale could be construed

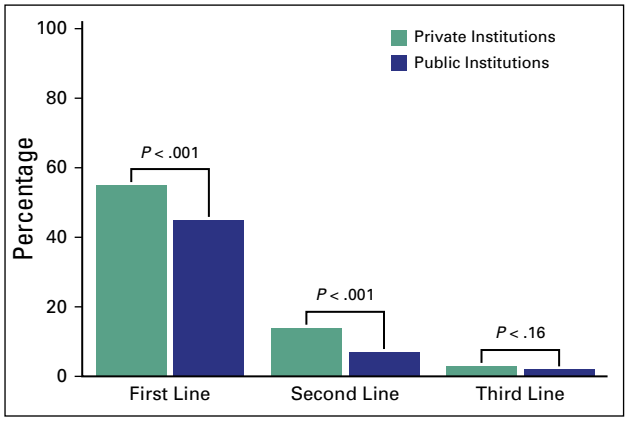


**Fig 3.** Comparison of use of first-, second- and third-line therapy in public and private hospitals in Brazil.

for regimens such as doxorubicin/gemcitabine (which has potential applications in sarcomatoid RCC), the vast majority of cytotoxic regimens listed have little evidence base in mRCC.[9] Furthermore, it seems that expensive novel therapies such as nivolumab are occasionally used in the first-line setting. This expensive application of immunotherapy outside of standard indications is particularly disconcerting in a cost-constrained setting. Limitations of our study include the inability to ascertain treatment-related outcome. It is possible that patients receiving care in resource-limited practices receive first-line therapy for longer periods by more effectively employing dose modification and adverse effect management strategies. These methods may substantially delay the need for second-line therapy. A second limitation is that our data were collected in a retrospective fashion, making it particularly prone to missing data. Finally, although we intend to represent the cumulative experience in Brazil, the majority of centers included in the study were from the southwest region of the country. These areas tend to be less economically deprived, which could artificially inflate our estimates of receipt of therapy. In summary, the current study highlights overarching similarities in the nature of treatments rendered for mRCC between Brazil and other developed countries, and could be representative of other developing countries. Specifically, VEGF-directed therapies represent the mainstay of treatment in the first-line setting, whereas second-line therapy is evenly divided between VEGF- and mTOR inhibitors. With the caveat that our data were collected before the widespread availability of nivolumab and newer targeted therapies, we would anticipate that these trends will persist. However, our data highlight a concerning attrition of systemic therapy use in the second- and third-line setting, extending far beyond what is observed in developed countries. Resources must be allocated to balance these discordances. Furthermore, and perhaps more readily achievable, efforts must be made to educate practitioners regarding the availability and efficacy of novel agents.

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## AUTHOR CONTRIBUTIONS

**Conception and design:** Paulo G. Bergerot, Cristiane D. Bergerot, Brendan N. Cotta, Milena Shizue Tariki, Toni K. Choueiri, Gilberto Lopes, Sumanta K. Pal
**Financial support:** Toni K. Choueiri, Sumanta K. Pal
**Administrative support:** Maria Nirvana Formiga, Diego Abreu Clavijo, Toni K. Choueiri, Gilberto Lopes, Sumanta K. Pal
**Provision of study materials or patients:** Edna Prado Gonçalves, Toni K. Choueiri, Gilberto Lopes, Sumanta K. Pal
**Collection and assembly of data:** Paulo G. Bergerot, Edna Prado Gonçalves, Toni K. Choueiri, Gilberto Lopes, Sumanta K. Pal
**Data analysis and interpretation:** Paulo G. Bergerot, Cristiane D. Bergerot, Nazli Dizman, Stenio Zequi, Andre Fay, Yash Dara, Manuel Caitano Maia, Maria Nirvana Formiga, Diego Abreu Clavijo, Toni K. Choueiri, Gilberto Lopes, Sumanta K. Pal
**Manuscript writing:** All authors
**Final approval of manuscript:** All authors
**Accountable for all aspects of the work:** All authors

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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**Paulo G. Bergerot**
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**Cristiane D. Bergerot**
No relationship to disclose

**Nazli Dizman**
No relationship to disclose

**Stenio Zequi**
**Consulting or Advisory Role:** Pfizer, Astelas Brazil
**Speakers' Bureau:** Pfizer, Astelas, Bayer, Jansen

**Andre Fay**
**Honoraria:** Pfizer, Novartis, Bristol-Myers Squibb, AstraZeneca, Roche
**Consulting or Advisory Role:** Novartis, Roche, Pfizer

**Yash Dara**
No relationship to disclose

**Manuel Caitano Maia**
No relationship to disclose

**Brendan N. Cotta**
**Employment:** University of Miami

**Edna Prado Gonçalves**
No relationship to disclose

**Maria Nirvana Formiga**
No relationship to disclose

**Milena Shizue Tariki**
No relationship to disclose

**Diego Abreu Clavijo**
No relationship to disclose

**Toni K. Choueiri**
**Honoraria:** National Comprehensive Cancer Network, UpToDate
**Consulting or Advisory Role:** Pfizer, Bayer, Novartis, GlaxoSmithKline, Merck, Bristol-Myers Squibb, Roche/Genentech, Eisai, Foundation Medicine, Cerulean Pharma, AstraZeneca, Peloton Therapeutics, Exelixis, Prometheus, Alligent, Ipsen
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**Travel, Accommodations, Expenses:** Advisory boards/consultancy

**Gilberto Lopes**
**Honoraria:** AstraZeneca, Roche/Genentech, Merck Serono, Merck Sharp & Dohme, Fresenius Kabi, Novartis, Bristol-Myers Squibb, Janssen-Cilag, Boehringer Ingelheim, Pfizer, CIPLA, Sanofi, Eisai, Eli Lilly
**Consulting or Advisory Role:** Pfizer, Bristol-Myers Squibb, Eli Lilly/ImClone
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**Expert Testimony:** Sanofi

**Sumanta K. Pal**
**Honoraria:** Novartis, Medivation, Astellas Pharma
**Consulting or Advisory Role:** Pfizer, Novartis, Aveo, Myriad Pharmaceuticals, Genentech, Exelixis, Bristol-Myers Squibb, Astellas Pharma, Ipsen, Eisai
**Research Funding:** Medivation

## Affiliations

**Paulo G. Bergerot** and **Cristiane D. Bergerot**, Universidade Federal de Sao Paulo; **Stenio Zequi**, **Maria Nirvana Formiga**, and **Milena Shizue Tariki**, A.C. Camargo Comprehensive Cancer Center; **Edna Prado Gonçalves**, Close-Up International, Sao Paulo; **Andre Fay**, PUCRS School of Medicine, Porto Alegre, Brazil; **Paulo G. Bergerot**, **Cristiane D. Bergerot**, **Nazli Dizman**, **Yash Dara**, **Manuel Caitano Maia**, **Brendan N. Cotta**, and **Sumanta K. Pal**, City of Hope Comprehensive Cancer Center, Duarte, CA; **Diego Abreu Clavijo**, Pasteur Hospital, Montevideo, Uruguay; **Toni K. Choueiri**, Dana-Farber Cancer Institute, Boston, MA; and **Gilberto Lopes**, University of Miami Sylvester Cancer Center, Miami, FL.

## REFERENCES

1. Ferlay J, Soerjomataram I, Ervik M, et al: GLOBOCAN 2012 v1.0, cancer incidence and mortality worldwide. IARC CancerBase No 11. http://globocaniarcfr
2. Siegel RL, Miller KD, Jemal A: Cancer statistics, 2017. CA Cancer J Clin 67:7-30, 2017
3. Motzer RJ, Bacik J, Murphy BA, et al: Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. J Clin Oncol 20:289-296, 2002
4. Motzer RJ, Hutson TE, Cella D, et al: Pazopanib versus sunitinib in metastatic renal-cell carcinoma. N Engl J Med 369:722-731, 2013
5. Choueiri TK, Escudier B, Powles T, et al: Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): Final results from a randomised, open-label, phase 3 trial. Lancet Oncol 17:917-927, 2016
6. Motzer RJ, Escudier B, McDermott DF, et al: Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med 373:1803-1813, 2015
7. Pal SK, Signorovitch JE, Li N, et al: Patterns of care among patients receiving sequential targeted therapies for advanced renal cell carcinoma: A retrospective chart review in the USA. Int J Urol 24:272-278, 2017
8. Heng DYC, Stukalin I, Wells C, et al. Third-line therapy in metastatic renal cell carcinoma (mRCC): Results from the International mRCC Database Consortium (IMDC). J Clin Oncol 33, 2015 (abstr e15578)
9. Haas NB, Lin X, Manola J, et al: A phase II trial of doxorubicin and gemcitabine in renal cell carcinoma with sarcomatoid features: ECOG 8802. Med Oncol 29:761-767, 2012

## Appendix

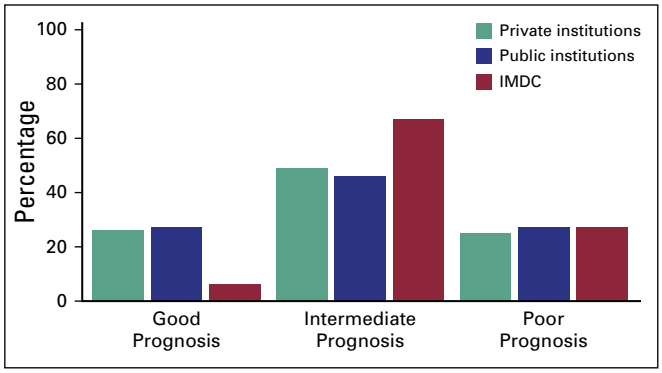
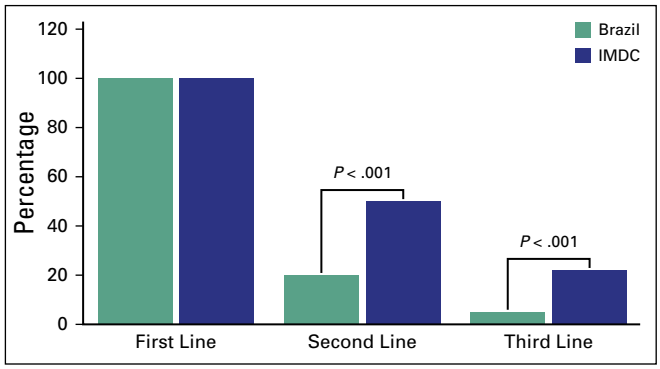



**Fig A1.** Comparison of International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk status of patients treated at private versus public institutions.

**Fig A2.** Comparison first-, second- and third-line therapy use in Brazil versus the International mRCC International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) data set.[8]



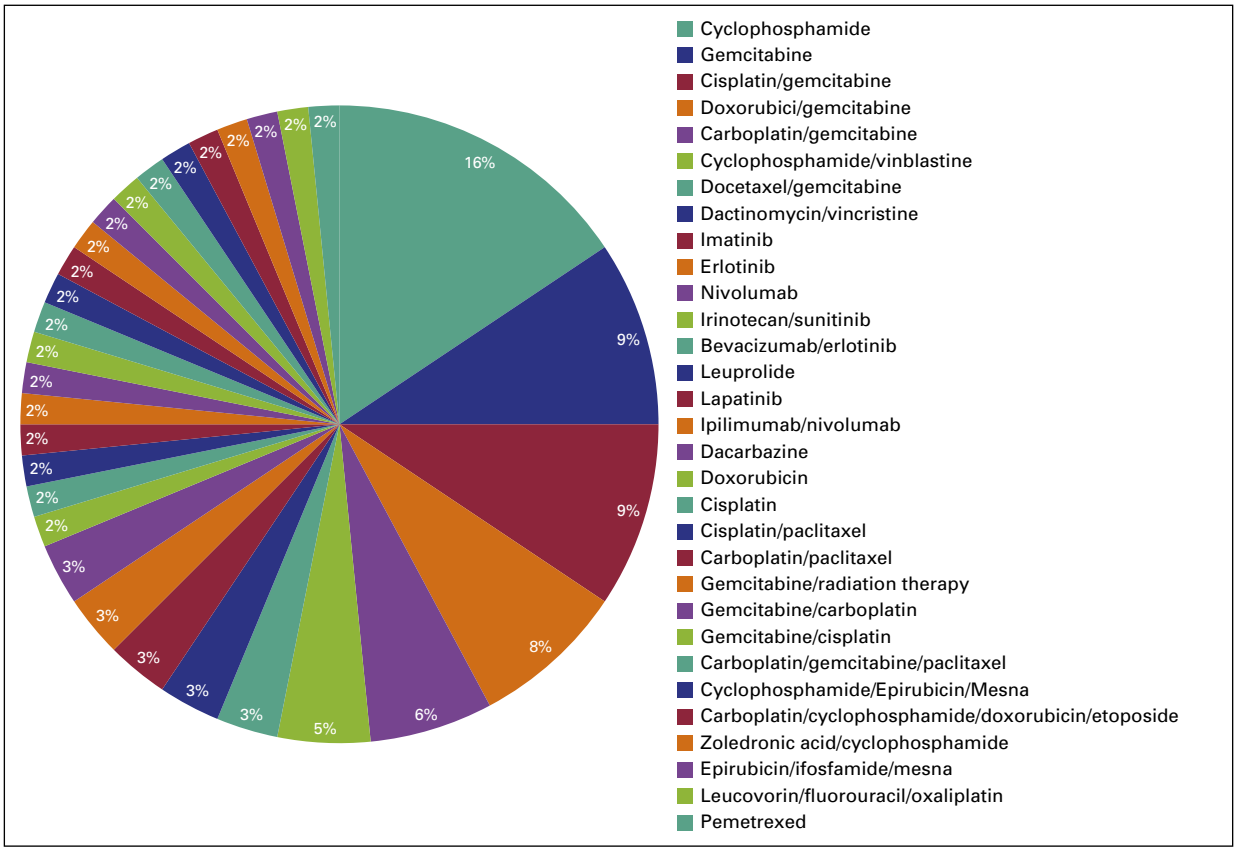



**Fig A3.** Use of nontraditional therapies (eg, therapies lacking regulatory approval for metastatic renal cell cancer) in the first-line setting (n = 240).