

Patients with advanced and metastatic renal cell carcinoma treated with targeted therapy in the Czech Republic: twenty cancer centres, six agents, one database

Alexandr Poprach, Zbyněk Bortlíček, Tomáš Büchler, Bohuslav Melichar, Radek Lakomý, Rostislav Vyzula, Petr Brabec, Marek Svoboda, et al.

Medical Oncology

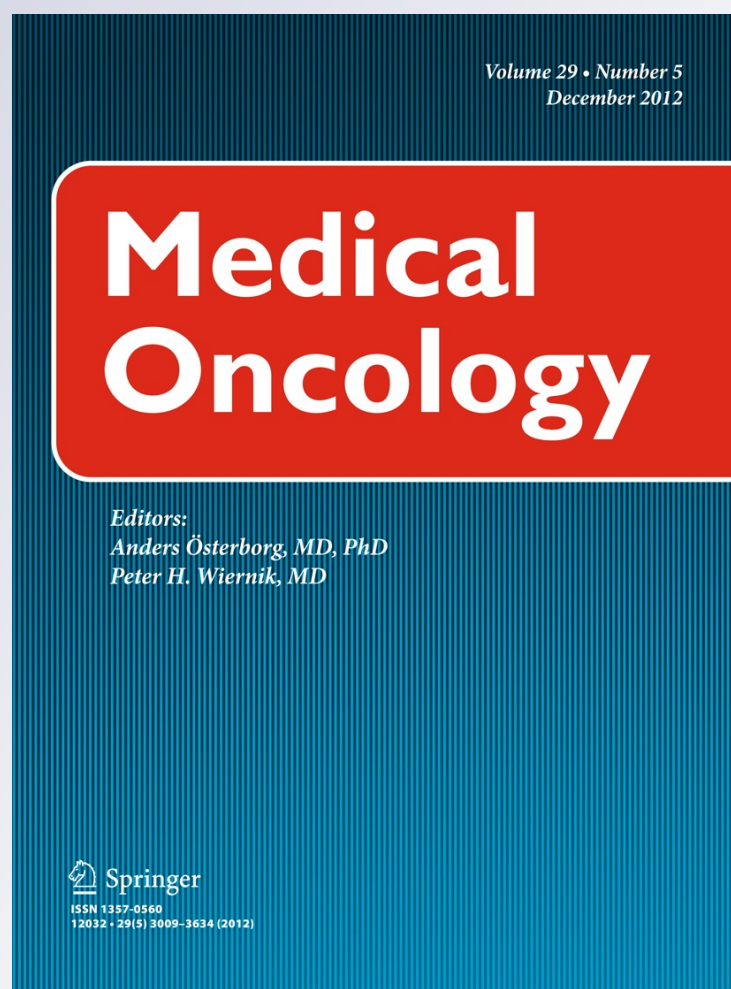
ISSN 1357-0560

Volume 29

Number 5

Med Oncol (2012) 29:3314-3320

DOI 10.1007/s12032-012-0286-9



Your article is protected by copyright and all rights are held exclusively by Springer Science+Business Media, LLC. This e-offprint is for personal use only and shall not be self-archived in electronic repositories. If you wish to self-archive your work, please use the accepted author's version for posting to your own website or your institution's repository. You may further deposit the accepted author's version on a funder's repository at a funder's request, provided it is not made publicly available until 12 months after publication.

Patients with advanced and metastatic renal cell carcinoma treated with targeted therapy in the Czech Republic: twenty cancer centres, six agents, one database

Alexandr Poprach · Zbyněk Bortlíček · Tomáš Büchler · Bohuslav Melichar · Radek Lakomý · Rostislav Vyzula · Petr Brabec · Marek Svoboda · Ladislav Dušek · Jakub Gregor

Received: 20 March 2012 / Accepted: 14 June 2012 / Published online: 30 June 2012
© Springer Science+Business Media, LLC 2012

Abstract The incidence and mortality of renal cell carcinoma (RCC) in the Czech Republic are among the highest in the world. Several targeted agents have been recently approved for the treatment of advanced/metastatic RCC. Objective: Presentation of a national clinical database for monitoring and assessment of patients with advanced/metastatic RCC treated with targeted therapy. The RenIS (RENal Information System, <http://renis.registry.cz>) registry is a non-interventional post-registration database of epidemiological and clinical data of patients with RCC treated with targeted therapies in the Czech Republic. Twenty cancer centres eligible for targeted therapy administration participate in the project. As of November 2011, six agents were approved and reimbursed from public health insurance, including bevacizumab, everolimus, pazopanib, sorafenib, sunitinib, and temsirolimus. As of 10 October 2011, 1,541 patients with valid records were entered into the database. Comparison with population-based data from the Czech National Cancer

Registry revealed that RCC patients treated with targeted therapy are significantly younger (median age at diagnosis 59 vs. 66 years). Most RenIS registry patients were treated with sorafenib and sunitinib, many patients sequentially with both agents. Over 10 % of patients were also treated with everolimus in the second or third line. Progression-free survival times achieved were comparable to phase III clinical trials. The RenIS registry has become an important tool and source of information for the management of cancer care and clinical practice, providing comprehensive data on monitoring and assessment of RCC targeted therapy on a national level.

Keywords Renal cell carcinoma · Targeted therapy · Clinical registry · Cancer care · Database · Population-based data

Introduction

The incidence and mortality of renal cell carcinoma (RCC) in the Czech Republic are among the highest in the world [1], with 27.14 new cases and 11.13 deaths per 100,000 persons per year [2, 3]. The disease is more frequent in men, who contribute 63 % to the total incidence. Almost 40 % of RCCs are diagnosed at advanced or metastatic stage.

Systemic treatment of advanced and metastatic RCC using immunotherapy (interleukin-2 and/or interferon alpha) was effective only in a minority of patients and was accompanied by substantial toxicity. Development and introduction into the clinical practice of targeted therapies, that is new agents with significantly higher specificity for particular cancer-related pathways, have improved survival of patients with advanced RCC, generally with a lower rate of adverse effects. Several targeted agents have been

A. Poprach · R. Lakomý · R. Vyzula · M. Svoboda
Department of Complex Oncology Care,
Masaryk Memorial Cancer Institute, Žlutý kopec 7,
656 53 Brno, Czech Republic

Z. Bortlíček · P. Brabec · L. Dušek · J. Gregor (✉)
Institute of Biostatistics and Analyses, Masaryk University,
Kamenice 126/3, 625 00 Brno, Czech Republic
e-mail: gregor@iba.muni.cz

T. Büchler
Department of Oncology, First Faculty of Medicine,
Thomayer Hospital and Charles University, Vídeňská 800,
140 59 Prague, Czech Republic

B. Melichar
Department of Oncology, Palacký University Medical School
and Teaching Hospital Olomouc, I. P. Pavlova 185/6,
779 00 Olomouc, Czech Republic

recently approved for treatment by US and European authorities, including drugs targeting vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) pathways; clinical trials with these agents have been recently reviewed elsewhere [4].

Targeted therapy has been available for Czech patients with advanced RCC since 2006 when sunitinib and sorafenib were approved. As of November 2011, six agents were approved and reimbursed from public health insurance, including bevacizumab, everolimus, pazopanib, sorafenib, sunitinib, and temsirolimus. Treatment with these drugs is restricted to twenty specialised cancer centres that agreed to enter all patients into the RenIS registry. Patient characteristics and treatment course and outcomes are monitored by means of an observational clinical database established by the national expert panel of the Czech Oncological Society (COS).

Since treatment with most of the targeted agents was introduced only recently, currently there are only limited published data on the use of these drugs in the routine clinical practice, particularly in sequence. The PREDICT study was a non-interventional study monitoring safety and outcomes of sorafenib [5]. Other authors have reported results of various therapy sequences after failure of the first-line setting of a particular targeted therapy [6–11], including data from the Czech database described here [12].

In the present paper, we aim to describe the Czech patient cohort from the epidemiological perspective based on the data from the clinical registry that allows the monitoring and assessment of the advanced RCC treatment by different targeted agents in clinical practice.

Patients and methods

The clinical registry RenIS (RENal Information System, <http://renis.registry.cz>) is a non-interventional post-registration database of epidemiological and clinical data of patients with renal cell carcinoma treated with targeted therapies in the Czech Republic. All six targeted anticancer agents currently registered for the treatment of metastatic RCC have been included (bevacizumab, everolimus, pazopanib, sorafenib, sunitinib, and temsirolimus). The project was initiated in June 2007. Collected data allow for monitoring of patients' epidemiological characteristics, treatment regimens, therapeutic responses, modelling of risk factors for survival, and detailed analysis of adverse effects. Data collection system is primarily oriented on the treatment of advanced/metastatic disease, but it also contains the necessary information related to the primary tumour.

Data on individual patients and their treatment are entered into the database by the twenty cancer centres providing specialised cancer care including targeted therapy. This means that, with the exception of few patients enrolled into the clinical trials, all RCC patients receiving targeted therapy in the Czech Republic are registered in the database. The limited number of involved healthcare facilities allows for accurate and reliable data collection and assessment of treatment results and safety. All patient data are fully anonymised and remain an intellectual property of the appropriate centre. Publication of data must be approved by the project board.

The technological base of the project is provided by the Institute for Biostatistics and Analyses, Masaryk University, Brno. The database system was originally based on a modified version of TrialDB system [13], which has been subsequently customised for the collection of specific clinical data of the RenIS project. The database is implemented online and uses internet and database technologies featuring multilevel architecture (client–web server–database server). All submitted data are collected in a central server, where they are safely stored in a database administered in the ORACLE 11g system. The registry is accessible via internet from any PC equipped with one of the recent versions of MS Internet Explorer or Mozilla Firefox, which support encrypted communication with a 128-bit SSL protocol. Access to the database is protected by a hierarchical system of access rights.

The Kaplan–Meier method was used for survival analysis. Overall survival was calculated as the time from the first targeted therapy initiation until death from any cause. Progression-free survival was calculated as the time from the particular targeted therapy initiation until progression or death from any cause. Statistical differences in age distribution were assessed using the two-sample *t* test.

Results

Data export for this study was carried out on 10 October 2011. As of this date, the registry contained records on 1,567 patients with advanced or metastatic RCC treated with targeted therapy. Information on the date of diagnosis or the start of targeted therapy was not available in 26 patients; these were excluded from subsequent analysis. Therefore, the analysis was performed on data of 1,541 patients.

The largest proportion of patients was diagnosed with RCC between 55 and 59 years of age (21.2 %) and started targeted therapy at the age between 60 and 64 years (21.8 %). Mean age of patients at time of diagnosis and targeted therapy initiation was 59 and 62 years, respectively. There were significantly more men than women (70 % and 30 %, respectively), corresponding to overall

distribution of RCC in Czech population. Clear-cell RCC was the most frequent morphological type (94.7 %), followed by papillary carcinoma (4.1 %). Other types occurred rarely. A detailed description of the patient cohort is shown in Table 1.

Whole population-based data on cancer epidemiology were obtained from the Czech National Cancer Registry (CNCR) accessible online via the web portal SVOD [2]. To compare the population-based data with those from the RenIS registry, a cohort of patients, who were diagnosed in clinical stage IV or experienced disease recurrence in the period of 2006–2008, was analysed. This group is clinically similar to the group of RCC patients who are indicated for

targeted therapy and thus recorded in the registry. The analysis revealed that the most frequent age category at diagnosis was 60–64 years (17.6 %), but in contrast to the RenIS cohort, there was a much higher proportion of patients diagnosed in age over 65 years ($p < 0.05$) (Fig. 1). This difference documents that the targeted therapy tends to be administered to younger RCC patients. Most patients in the RenIS registry have received prior cytokine therapy.

The registry design allows for comprehensive monitoring of various types of targeted therapy and their sequences in individual patients, including dose modifications, adherence to guidelines, and assessment of therapy results. Therapy sequences recorded in the registry are shown in Fig. 2. Because sunitinib and sorafenib were the first two targeted therapies for RCC in the Czech Republic, it is not surprising that most of the RenIS registry patients were treated by these two drugs, either alone or in sequence. Over 10 % of patients were also treated by everolimus in the second or third line. Bevacizumab and temsirolimus were administered rarely. Pazopanib was approved for reimbursement under the Czech healthcare system in 2011, not allowing sufficient follow-up at the time in the present registry analysis.

The median overall survival of all patients in the registry from the first targeted therapy initiation was 26.9 months (Fig. 3). Progression-free survival measured from the particular targeted therapy initiation is shown in Table 2. Toxicity and safety were also recorded during the treatment. Most of the adverse effects recorded were skin, gastrointestinal, haematological, and cardiovascular toxicities (Table 3). Overall toxicity profiles corresponded to those in registration studies and the respective summary of product characteristics of the targeted agents.

Discussion

The RenIS registry is providing a large amount of data that may be used in the management of cancer care and clinical practice. It has become an important tool for physicians, researchers, managers, and healthcare payers. Information on patient characteristics and treatment can be obtained, including ECOG performance status, weight loss, laboratory tests, histology, staging, sequence of treatments, treatment outcomes, and disease course. Each recurrence or progression is linked with relevant clinical data. This allows a number of analyses, for example assessment of therapy sequences [12], comparison of accepted MSKCC prognostic criteria with new prognostic and predictive factors (thrombocytosis, neutrophilia, and others), impact of any treatments given before targeted therapy such as nephrectomy or immunotherapy, and many more.

Since the RenIS cohort includes patients with different characteristics, baseline status, and therapy sequences and

Table 1 Basic characteristics of the patient cohort

Number of records (patients)	1,567	
Number of valid records (patients)	1,541	
Age of patients	RenIS	Overall population*
Age at diagnosis (mean/median)	59/59 years	67/67 years
Age at targeted therapy initiation (mean/median)	62/62 years	–
Proportion of patients diagnosed in age over 65 years (%)	26.7	58.3
Gender (number, %)		
Males	1,087 (70.5)	
Females	454 (29.5)	
Disease status at diagnosis (number, %)		
Localised/locally advanced	678 (44.0)	
Metastatic	685 (44.4)	
Unknown/not stated	178 (11.6)	
Morphology (number, %)		
Clear cell	1,460 (94.7)	
Papillary	63 (4.1)	
Chromophobe	9 (0.6)	
Collecting duct	3 (0.2)	
Unknown/not stated	6 (0.4)	
Preceding surgery** (number, %)		
Nephrectomy	1,279 (83.0)	
Partial nephrectomy	38 (2.5)	
Other type of surgery	359 (23.3)	
No surgery	144 (9.3)	
Preceding palliative radiotherapy (number, %)		
Yes	323 (21.0)	
No	1,218 (79.0)	
Preceding immunotherapy		
Yes	947 (61.5)	
No	594 (38.5)	

* Stage IV and recurrences in the period of 2006–2008

** One patient may undergo more surgical procedures

Fig. 1 Age distribution of patients in the RenIS registry and overall population (stage IV and recurrences in the period of 2006–2008; data source: Czech National Cancer Registry)

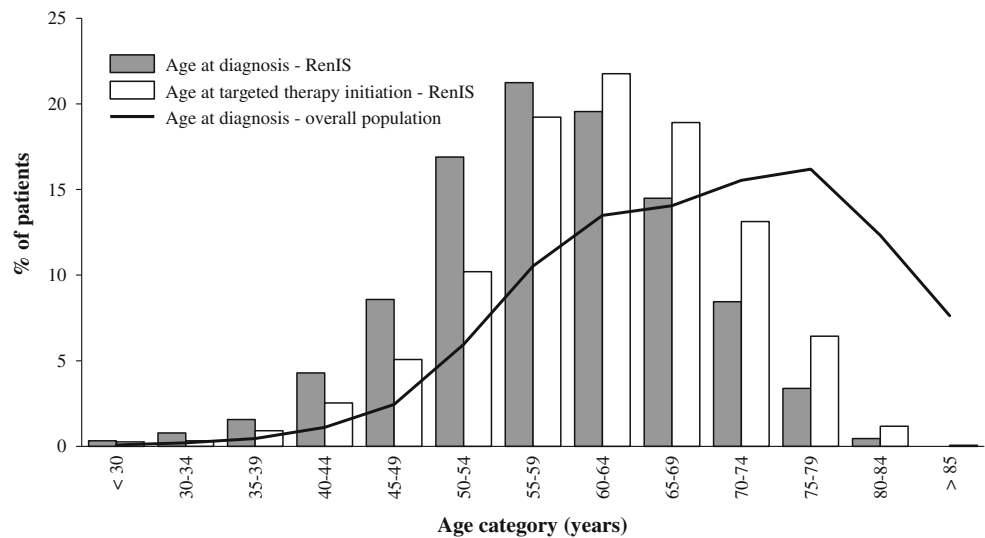


Fig. 2 Sequences of targeted therapies recorded in the RenIS registry

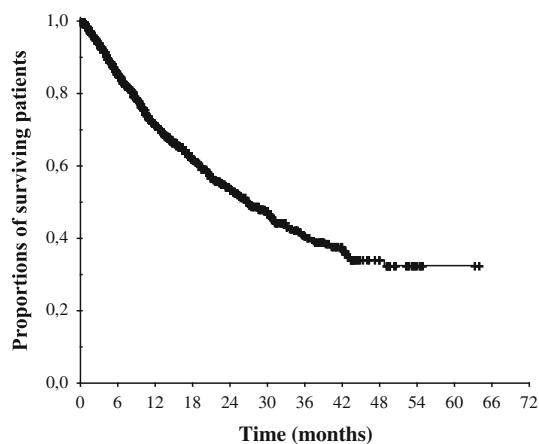
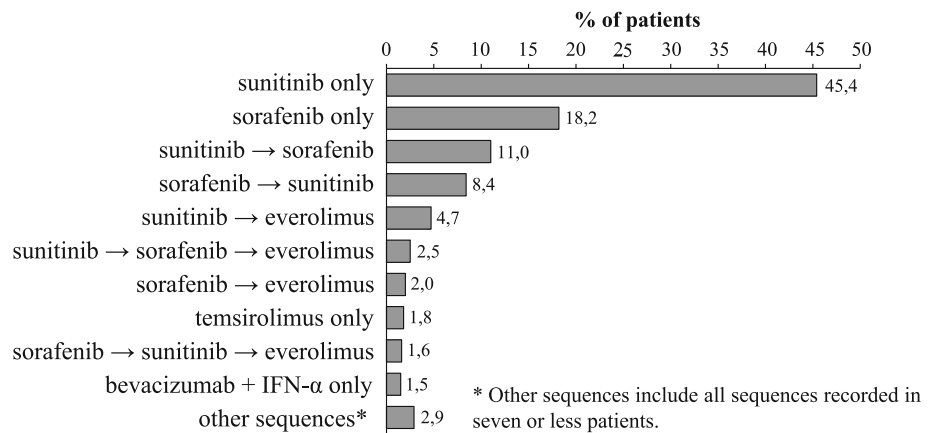


Fig. 3 Overall survival of patients with advanced RCC treated with targeted therapy

the drugs are administered in different treatment lines, it may be difficult to compare the results with published clinical trials, which are usually focused on one medication and are based on strict inclusion/exclusion criteria. It

should also be noted that the number of patients treated with bevacizumab and temsirolimus included in the present analysis is relatively low. However, it is evident that the progression-free survival reached in the RenIS registry patients was comparable with that in phase III clinical trials [14–18].

Clear-cell RCC comprises approximately 70–75 % of all renal cell carcinomas, followed by papillary (10 %), chromophobe (5 %), and further histological subtypes [19]. Proportion of the histological subtypes was different in the RenIS registry, as almost 95 % of tumours fall into the clear-cell subtype. This difference again illustrates the fact that the registry is treatment-oriented and includes information only on patients receiving targeted agents. On the other hand, it reflects the real-life clinical practice and allows for detailed monitoring and assessment of the targeted therapy administration and results.

Data are entered into the registry on a continuous basis, and detailed analyses are performed twice per year. Recent information on therapy and response, best achieved response and its duration are therefore available and up to

Table 2 Progression-free survival of patients since initiation of the particular targeted therapy and its comparison with clinical trials

Therapy	PFS—RenIS Median (95 % CI) Number of patients	PFS—clinical trials (months)	Reference
Bevacizumab (combined with interferon alpha)	15.2 months* (7.6; 22.9) <i>N</i> = 37 patients	10.2	Escudier et al. 2007 [14]
Everolimus	4.8 months (3.6; 6.1) <i>N</i> = 175 patients	4.9	Motzer et al. 2010 [15]
Sorafenib	6.9 months (6.1; 7.7) <i>N</i> = 698 patients	5.5	Escudier et al. 2007 [16]
Sunitinib	10.0 months (9.0; 11.1) <i>N</i> = 1,162 patients	11.0	Motzer et al. 2007 [17]
Temsirolimus	4.1 months (3.2; 5.1) <i>N</i> = 46 patients	5.5	Hudes et al. 2007 [18]

* A pilot analysis performed with a low number of patients with short follow-up. Please note a broad 95 % confidence interval

Table 3 Overview of adverse events (AE) recorded in the registry

Therapy	Most frequent AE (% of patients)	% of patients without AE
Bevacizumab (<i>N</i> = 38 patients)	Cardiovascular (7.9 %) Skin (5.3 %)	76.3
Everolimus (<i>N</i> = 179 patients)	Skin (5.6 %) Haematological (4.5 %) Metabolic 5 (2.8 %)	77.7
Sorafenib (<i>N</i> = 704 patients)	Skin (30.0 %) Gastrointestinal (14.8 %) Cardiovascular (5.5 %)	51.1
Sunitinib (<i>N</i> = 1,174 patients)	Haematological (12.1 %) Gastrointestinal (11.6 %) Skin (11.2 %)	61.3
Temsirolimus (<i>N</i> = 46 patients)	Skin (10.9 %) Gastrointestinal (6.5 %)	69.6

date. The median overall survival from the first targeted therapy initiation was 26.9 months. This value reflects treatment with various targeted agents and their sequences and is not informative about survival of all patients with stage IV or inoperable recurrence in the Czech Republic,

because many of these patients did not receive any targeted therapy due to different reasons.

When comparing epidemiological data from the RenIS registry with other studies or databases, some differences were found. In contrast to the population-based data from the Czech National Cancer Registry, age distribution of patients with advanced RCC was shifted to lower age groups (median age at diagnosis 59 vs. 66 years, most frequent age category 55–59 vs. 75–79 years). This demonstrates that the targeted therapy is more commonly administered to younger patients. Several factors may be suggested to explain the difference in age structure between the overall population of RCC patients and those treated with targeted therapy. While the age itself is not a contraindication for targeted therapies, elderly patients are more likely present with significant comorbidities and/or poor performance status that makes them ineligible for targeted agents. Additional socio-economic factors cannot be excluded, but currently available data are not sufficient to draw any definite conclusions on their impact.

Introduction of a number of targeted agents and their use in different sequences have led to more frequent use of progression-free survival instead of overall survival when evaluating the benefits of a particular therapy. Moreover, patients in clinical trials often cross over from one treatment group to another. Progression-free survival observed in patients included in the RenIS database is comparable not only to the results of large phase III clinical trials [14–18], but also to retrospective studies on patients pretreated with different targeted therapies [6, 8, 9, 20–22].

The patients included in the RenIS database have been treated with targeted agents outside of clinical trials. Therefore, the physicians are not limited by additional requirements given by clinical trial criteria, and the overall treatment schedule corresponds to common clinical practice better than clinical trials. This results in a significantly higher heterogeneity of collected clinical data. Nevertheless, the RenIS registry design enables retrospective monitoring and assessment of all sequentially administered therapies. Continuous data collection from a network of twenty cancer centres requires careful project management to ensure comparability and completeness of patient records. Therefore, the data undergo thorough validation prior to processing and analysis. When these necessary procedures are in place, clinical registries represent an indispensable source of information extending those obtained in clinical trials and are a valuable tool for epidemiologists, clinicians, managers, and healthcare payers involved not only in cancer care, but in the whole health-care system. Due to standardised parametric data collection system, they may also provide easily accessible information for international comparisons or serve as integral part of international clinical studies and research.

In conclusion, the RenIS registry provides an important tool for monitoring the administration of targeted therapy on a national level. The comparable outcomes of patients in the RenIS registry and prospective clinical trials indicate that in the Czech Republic, a careful patient selection is taking place for targeted therapy of metastatic RCC.

Acknowledgments Authors would like to thank all cancer centres involved in data collection for the RenIS registry: University Hospital Brno—Otakar Bednařík, MD; St. Ann's University Hospital, Brno—Jana Katolická, MD, PhD; Masaryk Memorial Cancer Institute, Brno—prof. Rostislav Vyzula, MD, PhD; Hospital České Budějovice—Václav Janovský, MD, Alena Šináková, MD; University Hospital Hradec Králové—prof. Jiří Petera, MD, PhD, assoc. prof. Josef Dvořák, MD, PhD; Hospital Chomutov—Martina Chodacká, MD; Hospital Jihlava—Lubomír Slavíček, MD, Věra Benešová, MD; Regional Hospital Liberec—Jiří Bartoš, MD, MBA, Věra Hejzlarová, MD; Hospital and Health Centre in Nový Jičín—assoc. prof. Renata Soumarová, MD, PhD, MBA, Josef Gruna, MD; University Hospital Olomouc—prof. Bohuslav Melichar, MD, PhD, Petr Beneš, MD, PhD; University Hospital Ostrava—David Feltl, MD, PhD, Martina Vybíralová, MD; Regional Hospital Pardubice—assoc. prof. Jaroslav Vaňásek, MD, PhD, Iveta Kolářová, MD; University Hospital Plzeň—assoc. prof. Jindřich Fínek, MD, PhD, Vladimíra Arnetová, MD; Hospital Na Bulovce, Prague—Vladimíra Stáhalová, MD; Hospital Na Homolce, Prague—Martin Šafanda, MD, PhD; General University Hospital in Prague—prof. Luboš Petruželka, MD, PhD; University Hospital Motol, Prague—Jana Prausová, MD, PhD, Stanislav Batko, MD; Thomayer Hospital, Prague—prof. Jitka Abrahámová, MD, PhD; Masaryk Hospital in Usti nad Labem—Milan Lysý, MD, David Šulc, MD; T. Baťa Regional Hospital, Zlín—Milan Kohoutek, MD, Alena Jakšičová, MD. This work was supported by the Project MZ0MOU2005 of the Czech Ministry of Health. The RenIS registry is supported by research grants from Novartis, Pfizer, Bayer, Roche, and GlaxoSmithKline.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. GLOBOCAN 2008 v1.2, cancer incidence and mortality worldwide: IARC CancerBase no. 10 (online). International Agency for Research on Cancer, Lyon, France, 2010. Available from: <http://globocan.iarc.fr>.
2. Dušek L, Mužík J, Kubásek M, Koptíková J, Žaloudík J, Vyzula R. Epidemiology of malignant tumours in the Czech Republic (online). Masaryk University, Czech Republic. 2005. Available from: <http://www.svod.cz>. Version 7.0 [2007], ISSN 1802-8861.
3. Dušek L, Mužík J, Gelnarová E, Fínek J, Vyzula R, Abrahámová J. Cancer incidence and mortality in the Czech Republic (in Czech). Klin Onkol. 2010;23(5):311–24.
4. Coppin C, Kollmannsberger C, Le L, Porzsolt F, Wilt TJ. Targeted therapy for advanced renal cell cancer (RCC): a Cochrane systematic review of published randomised trials. BJU Int. 2011;108(10):1556–63.
5. Jäger D, Ma J, Korbenfeld E, Zemanová M, Leonhartsberger N, Stauch K, et al. PREDICT (Patient Characteristics in RENal Cell Carcinoma and Daily PractiCe Treatment With Sorafenib) non-interventional study—final report. Eur J Cancer. 2011;47(1):S520.
6. Rini BI, Michaelson MD, Rosenberg JE, Bukowski RM, Sosman JA, Stadler WM, et al. Antitumor activity and biomarker analysis of sunitinib in patients with bevacizumab refractory metastatic renal cell carcinoma. J Clin Oncol. 2008;26(22):3743–8.
7. Di Lorenzo G, Buonerba C, Federico P, Rescigno P, Milella M, Ortega C, et al. Third-line sorafenib after sequential therapy with sunitinib and mTOR inhibitors in metastatic renal cell carcinoma. Eur Urol. 2010;58(6):906–11.
8. Garcia JA, Hutson TE, Elson P, Cowey CL, Gilligan T, Nemec C, et al. Sorafenib in patients with metastatic renal cell carcinoma refractory to either sunitinib or bevacizumab. Cancer. 2010;116(23):5383–90.
9. Grünwald V, Seidel C, Fenner M, Ganser A, Busch J, Weikert S. Treatment of everolimus-resistant metastatic renal cell carcinoma with VEGF-targeted therapies. Br J Cancer. 2011;105(11):1635–9.
10. Grünwald V, Weikert S, Seidel C, Busch J, Johannsen A, Fenner M, et al. Efficacy of sunitinib re-exposure after failure of an mTOR inhibitor in patients with metastatic RCC. Onkologie. 2011;34(6):310–4.
11. Bergmann L, Kube U, Kindler M, Koepke T, Steiner G, Janssen J, et al. A noninterventional study of everolimus in metastatic renal cell cancer after use of one VEGFR-TKI: results of a pre-planned interim analysis of a prospective study. American Society of Clinical Oncology (ASCO) annual meeting; 3–7 June 2011; Chicago, Illinois, USA.
12. Büchler T, Klapka R, Melichar B, Brabec P, Dušek L, Vyzula R, et al. Sunitinib followed by sorafenib or vice versa for metastatic renal cell carcinoma—data from the Czech registry. Ann Oncol. 2012;23(2):395–401.
13. Nadkarni PM, Brandt C, Frawley S, Sayward FG, Einbinder R, Zelterman D, et al. Managing attribute—value clinical trials data using the ACT/DB client–server database system. J Am Med Inf Assoc. 1998;5(2):139–51.
14. Escudier B, Pluzanska A, Koralewski P, Ravaud A, Bracarda S, Szczylik C, et al. AVOREN trial investigators. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. Lancet. 2007;370(9605):2103–11.
15. Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, et al. Phase 3 trial of everolimus for metastatic renal cell carcinoma final results and analysis of prognostic factors. Cancer. 2010;116(18):4256–65.
16. Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Siebels M, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med. 2007;356(2):125–34.
17. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med. 2007;356(2):115–24.
18. Hudes G, Carducci M, Tomczak P, Dutcher J, Figlin R, Kapoor A, et al. Global ARCC Trial. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med. 2007;356(22):2271–81.
19. Eble JN, Sauter G, Epstein JI, Sesterhenn IA. Pathology and genetics of tumours of the urinary system and male genital organs. Lyon: IARC Press; 2004.
20. Vickers MM, Choueiri TK, Rogers M, Percy A, Finch D, Zama I, et al. Clinical outcome in metastatic renal cell carcinoma patients after failure of initial vascular endothelial growth factor-targeted therapy. Urology. 2010;76(2):430–4.
21. Heng DY, Mackenzie MJ, Vaishampayan UN, Bjarnason GA, Knox JJ, Tan MH, et al. Primary anti-vascular endothelial growth factor (VEGF)-refractory metastatic renal cell carcinoma: clinical

- characteristics, risk factors, and subsequent therapy. *Ann Oncol*. Nov 5 2011 [Epub ahead of print].
22. Busch J, Seidel C, Kempkensteffen C, Johannsen M, Wolff I, Hinz S, et al. Sequence therapy in patients with metastatic renal cell carcinoma: comparison of common targeted treatment options following failure of receptor tyrosine kinase inhibitors. *Eur Urol*. 2011;60(6):1163–70.