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EXPERT OPINION

Pharmacoeconomic and clinical implications of sequential therapy for metastatic renal cell carcinoma patients in Central and Eastern Europe

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Introduction: The incidence and mortality rates of kidney cancer in the Central and Eastern European (CEE) region are among the highest in the world. Access to second and subsequent lines of metastatic renal cell carcinoma (mRCC) therapies is highly varied in the region. Despite the increasing body of evidence supporting the clinical benefit of multiple lines of treatment, access to treatment beyond first line is restricted in many of these countries.

Areas covered: The adoption of targeted therapies for the first-line treatment of mRCC in the region was slow and faced many obstacles. In order to evaluate the current status of treatment beyond the first-line setting in the CEE region, this review examines the availability and reimbursement of mRCC drugs and clinical practice in institutions that treat patients with mRCC.

Expert opinion: This review highlights the need to raise awareness among physicians, payers and regulators on clinical trial and cost-effectiveness data regarding the treatment of mRCC beyond the first line. The obstacles to mRCC drug access highlighted in this review need to be overcome to ensure that patients are receiving the best treatment available.

Keywords: axitinib, cytokines, everolimus, metastatic renal cell carcinoma, molecular-targeted agents, pazopanib, receptor tyrosine kinase inhibitors, sorafenib, sunitinib, temsirolimus

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1. Introduction

Cancer incidence and mortality rates in the Central and Eastern European (CEE) region are among the highest in Europe and are increasing. Immediate action – such as the implementation of best practice strategies encompassing primary prevention, early detection, and the use of the best available treatments – is required to tackle these problems.[1–5] However, the limited availability of healthcare resources in countries with transitioning economies is a main obstacle to the effective management of patients with cancer.[6]

Economies in the CEE region are transitioning: gross domestic product per capita in CEE countries ranges from 1.2- to 9.1-fold lower than the EU's Big 5 (France, Germany, Italy, Spain and the UK).[7, 8] To further compound the high rates of cancer mortality, healthcare expenditure per capita in CEE countries is considerably lower – ranging from 607.6 USD in Kazakhstan to 2046 USD in the Czech Republic – than in the EU's Big 5, where it ranges from 3040.1 to 4617 USD.[9]

Renal cell carcinoma (RCC) accounts for ~90% of kidney malignancies and 2 – 3% of all adult malignancies.[10, 11] The global incidence of RCC continues to gradually rise, with 209,000 new cases and 102,000 deaths reported per year.[10]

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Article highlights.

- The incidence and mortality rates of renal cell carcinoma (RCC) in the Central and Eastern European (CEE) region are among the highest in the world.
- The use of sequential targeted therapies has been shown to be highly clinically beneficial for patients with metastatic RCC (mRCC).
- There are many obstacles to the use of second-line and beyond therapies in the CEE region, owing to the limited availability of drugs, reimbursement restrictions, lack of cost-effectiveness data for mRCC drugs and the complexity of some reimbursement systems.
- Increasing awareness of clinical trial and cost-effectiveness data as well as tackling obstacles regarding reimbursement restrictions will increase the number of treatment options available to patients with mRCC in the CEE region.
- Increased access to optimal treatment strategies will be highly effective in tackling the high mortality rates associated with mRCC in this region.
- The situation regarding access to second-line therapies in Russia is considered separately in Box 1.

This box summarizes key points contained in the article.

Rates in the CEE region are among the highest in Europe and the world according to estimates made by the International Agency for Research on Cancer in 2012.[12] Among the CEE countries considered in this review, the Czech Republic reports the highest rates of kidney cancer incidence and mortality, followed by Slovakia and Belarus.[12] The reasons for the high RCC incidence in the region are not fully understood but may be related in part to external risk factors.[7]

At present, the main aim of treatment in advanced RCC/metastatic RCC (mRCC) is to extend both progression-free survival (PFS) and overall survival (OS) with the fewest adverse events (AEs) while maintaining the best possible quality of life (QoL).[13, 14] In the past decade, the introduction of targeted agents has dramatically improved the PFS and OS of patients with mRCC compared with that observed during the cytokine era; such improvements suggest that it may be possible to convert mRCC into a chronic disease in some cases.[13,15,16] To obtain maximum benefit from targeted agents in the treatment of mRCC, it is essential that healthcare professionals have the knowledge to select the appropriate choice of treatment/treatment sequence and to effectively manage patients receiving targeted therapies.[10,17]

Targeted agents are the standard of care in all lines of therapy.[10,11] The significant benefits of first-line therapy with targeted agents are well documented and increasing attention is now focused on optimal therapeutic options following disease progression.[15] Disease progression can result from developing resistance to first-line therapy;[15] however, the use of agents from the same class can be effective in subsequent lines of therapy.[18] To gain maximum benefit from targeted therapies, the patient should be closely monitored throughout treatment to ensure decisions appropriate to the individual's needs are made.[19] An important component of this is the selection of second-line therapy.

2. Overview of current treatment options second line and beyond for mRCC

Current European Society for Medical Oncology (ESMO) guidelines recommend the use of several lines of targeted treatment for the management of patients with advanced RCC/mRCC.[10] Two options are recommended as standard second-line therapy after VEGF-targeted therapy: the VEGF-tyrosine kinase inhibitor (TKI), axitinib or the mammalian target of rapamycin (mTOR) inhibitor, everolimus.[10] In addition, ESMO guidelines recommend everolimus as third-line treatment in patients previously treated with two TKIs or a TKI and bevacizumab plus IFN-α. Although first-line IFN-α usage is limited, axitinib is also recommended for use post cytokines.

Appropriate treatment sequencing can optimize outcomes in patients with mRCC.[13,20–23] Clinical trials investigating the use of sequential treatment strategies in mRCC have shown that single targeted agents can cause tumor shrinkage, slow disease progression and demonstrate significant PFS and QoL benefits.[18,24,25] The benefit of targeted therapy second line and beyond in patients with mRCC has been demonstrated through the analysis of data from 2705 patients, obtained from the International mRCC Database Consortium, which indicated that patients who are able to receive more lines of targeted therapy live longer than those who receive fewer.[26] Despite the overlapping targets of TKIs, numerous studies have demonstrated the efficacy of sequential TKI therapies.[18,27,28] Similarly, mTOR-inhibitor usage following TKI therapy extends PFS compared with placebo in the second line.[24]

2.1 Post-VEGF inhibition: TKI and mTOR inhibitors

Axitinib, which is a more specific and potent VEGF-TKI than sunitinib, sorafenib or pazopanib, is approved as a second-line treatment in many countries.[29–31] The efficacy and safety of axitinib as a second-line treatment for patients with clear cell mRCC was compared with sorafenib in the Phase III randomized trial, AXIS.[18,25] It is worth noting that pazopanib was not available when this trial was designed, so the trial does not provide evidence for the efficacy of second-line axitinib after first-line pazopanib.

In the AXIS trial, most patients (389/723) received first-line sunitinib as recommended in the ESMO guidelines,

reinforcing the relevance of the data to the effective management of patients with mRCC.[10,18,25] The primary end point, PFS, was significantly improved in the axitinib arm compared with the sorafenib arm [6.7 vs 4.7 months; hazard ratio (HR) = 0.665; p < 0.001].[25] Although there was no significant difference in OS between arms, this may have been confounded by subsequent active treatments after progression. The investigator-assessed objective response rate reported with the use of axitinib in the AXIS trial was 23%.[18] The data obtained also evidenced the distinct safety profiles of axitinib and sorafenib.[18] The most common Grade III or higher treatment-related AEs associated with axitinib were hypertension, fatigue and diarrhea compared with hand–foot syndrome, hypertension and diarrhea in the sorafenib arm. Importantly, the proportion of patients who experienced Grade III or higher hand–foot syndrome in the sorafenib treatment arm was nearly three times that of those treated with axitinib (17 vs 6%).

In a Phase III trial, (RECORD-1), the superiority of everolimus over placebo in second line and beyond was demonstrated in 416 patients. PFS was prolonged in the everolimus arm compared with the placebo arm (4.9 vs 1.9 months; HR = 0.33; p < 0.001).[24] It is also worth noting that everolimus prolonged PFS compared with placebo (4.0 vs 1.8 months; HR = 0.32) in patients who had received two prior lines of TKI treatment (sunitinib and sorafenib).[24] In addition, most patients (79%) received everolimus in third line or beyond; thus, the results of this trial provide evidence that everolimus is effective following two or more lines of VEGF-targeted treatment.[24] Again, pazopanib was not available when this trial was designed so it does not provide any evidence of the efficacy of second- and subsequent-line everolimus after first-line pazopanib. This increases the number of treatment options for patients because everolimus would be expected to be effective following treatment with axitinib in the second line; it is recommended in this setting in the ESMO guidelines.[10] The median OS did not significantly differ between the two treatment arms; however, as in many trials, this is probably because of patients from the placebo group crossing over to receive everolimus.[24] Infections, dyspnea, stomatitis and fatigue were the most common Grade III or higher treatment-related AEs with everolimus.

In a randomized Phase III trial (INTORSECT) involving 512 patients, there was no significant difference in median PFS after first-line sunitinib: 4.3 months with temsirolimus compared with 3.9 months with sorafenib (p = 0.19).[27] Despite this, median OS was significantly longer (p = 0.01) in patients treated in the second line with the TKI sorafenib (16.6 months) than with the mTOR inhibitor temsirolimus (12.3 months) following disease progression with first-line sunitinib treatment (HR = 1.31; 95% CI 1.05 – 1.63).[27]

2.2 Post-cytokine therapy

Cytokines are no longer considered the standard of care as first-line mRCC therapy; however, the efficacy of TKI therapies axitinib, sorafenib, pazopanib and sunitinib in patients with cytokine-refractory mRCC has been demonstrated in various studies.[32–36]

2.3 Treatment strategies beyond first line: 'real-world' retrospective analyses

In the absence of comparative trials, real-world experience can provide valuable insights into treatment strategies. For example, the Czech Clinical Registry of Renal Cell Cancer Patients (RENIS) is a highly valuable resource, providing information on the treatment of patients with mRCC that is particularly relevant to the CEE region.[20–23, 32] Data of 218 patients with mRCC treated with sunitinib and sorafenib obtained from RENIS showed a strong correlation between responses to first- versus second-line VEGF inhibitor (p < 0.001); however, duration of response on the first-line VEGF-targeted therapy was not a valuable indicator of response to second-line VEGF-targeted therapy.[22] Whereas retrospective analysis of data from the International mRCC Database Consortium on 464 patients with mRCC who had been treated with VEGF inhibitors in the first and second line demonstrated that patients can benefit from second-line VEGF-targeted therapy regardless of the response in first line.[37] In this study, there was neither an association between partial response, stable disease, or progressive disease rates in the first- and second-line setting (p = 0.17) nor any correlation between median PFS in the first and second line (p = 0.59). The RENIS registry data were also used to compare the efficacy of the sequences sorafenib followed by sunitinib (n = 122), or sunitinib followed by sorafenib (n = 138). There was no significant difference in PFS between patients treated with sorafenib–sunitinib (18.8 months) compared with sunitinib–sorafenib (17.7 months; p < 0.47).[20]

At present, there is limited and conflicting evidence regarding the optimal second-line treatment. A large, multicenter analysis involving 2106 patients from 12 cancer centers compared the use of VEGF inhibitor–VEGF inhibitor with VEGF inhibitor–mTOR inhibitor sequence; however, these results were not definitive because there was no significant difference in patient outcomes.[38] Conversely, in a systematic review and meta-analysis, a significantly longer OS was reported following second-line treatment with mTOR inhibitor compared with VEGF-TKI (HR = 0.82; p = 0.028).[39] It is important to note, firstly, that >60% of patients were treated with sorafenib and none with axitinib in the second-line VEGF-TKI group; and secondly, significant heterogeneity (p = 0.001) in estimated second-line treatment effects was reported.

A retrospective study analyzed data obtained from 23 centers in Italy involving 2065 patients treated with up to

three consecutive lines of therapy in one of the following sequences: VEGF inhibitor–VEGF inhibitor–mTOR inhibitor or VEGF inhibitor–mTOR inhibitor–VEGF inhibitor [40]; this study was also included in the aforementioned systematic review.[39] VEGF inhibitors included sunitinib, sorafenib, pazopanib, axitinib and bevacizumab plus IFN-α; mTOR inhibitors included temsirolimus and everolimus. Of the 2065 patients, 281 received three lines of targeted therapy. Both median combined PFS and median OS were longer, the latter being significantly longer ($p = 0.004$), in patients treated with VEGF inhibitor–VEGF inhibitor–mTOR inhibitor (mTOR inhibitor: OS 36.5 months; PFS 50.7 months) than in patients treated with VEGF inhibitor–mTOR inhibitor–VEGF inhibitor (OS 29.3 months; PFS 37.8 months). In a smaller study comparing the treatment sequences TKI–everolimus–TKI ($n = 14$) and TKI–TKI–everolimus ($n = 19$), both PFS with the second agent (6.5 vs 11 months) and combined PFS (23 vs 31 months) showed a trend in favor of the latter sequence.[41] Furthermore, median OS was prolonged in 131 patients (treated with VEGF inhibitors in the first line) who received TKI rather than mTOR inhibitor therapy in the second line at the Institut Gustave Roussy (20.8 vs 16.6 months; $p = 0.12$).[42] Another retrospective analysis of 216 patients treated in the first line with VEGF-targeted therapy (TKIs or bevacizumab) showed a significantly longer ($p = 0.014$) time to treatment failure in the second line when VEGF-targeted therapy (4.9 months) was compared with mTOR inhibitors (2.5 months).[43]

At present, there are no clinical trial data evaluating the efficacy of second-line axitinib or everolimus after first-line pazopanib, but real-world experience provides some insight into the use of VEGF inhibitors compared with mTOR inhibitors following first-line pazopanib. For example, in a retrospective analysis of data from 35 patients treated in the second line with everolimus or temsirolimus following first-line pazopanib, a PFS of 5.7 months and an OS of 16.0 months were reported.[44] In a retrospective analysis, median PFS was significantly prolonged ($p = 0.009$) in patients treated with anti-VEGF therapy ($n = 22$, 5.6 months) compared with mTOR inhibitor ($n = 13$, 2.4 months) following pazopanib therapy in the first ($n = 28$) or second line (post cytokines; $n = 7$).[45] Although axitinib was not one of the anti-VEGF therapies used, 20 of the 22 patients were treated with a VEGF-TKI, supporting the use of a second TKI after treatment with pazopanib. These results contrast with those reported in a retrospective analysis of data from patients treated with everolimus ($n = 233$), temsirolimus ($n = 178$), or sorafenib ($n = 123$) following first-line VEGF-TKI therapy, in which everolimus significantly prolonged OS compared with sorafenib.[46] However, as with other studies investigating the use of the VEGF-TKI–mTOR inhibitor sequence, very few patients were treated in the first line with pazopanib; therefore, it is difficult to determine the clinical impact of these results with regard to treatment sequencing.[46,47]

In this review, the current status of treatment second line and beyond in CEE countries is considered, with a focus on the challenges surrounding access to and reimbursement for multiple lines of treatment. Its aim is to highlight both the current status and the importance of patient access to effective therapies beyond first line.

3. Current status of sequential therapy in CEE countries

To obtain up-to-date information on the situation in the CEE region, an online questionnaire consisting of 31 questions about current practice in the management of RCC was developed by a group of regional experts. The questionnaire was distributed to oncologists and payers in this region over the period July – September 2014. In total, 40 responses were received from the following 15 countries: Belarus, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Estonia, Hungary, Kazakhstan, Latvia, Poland, Romania, Serbia, Slovakia, Slovenia and Turkey; these countries will be the focus of the review. Kazakhstan and Turkey have been included because of similarities in terms of the economic climate and healthcare systems between these countries and the CEE countries. Of the 40 respondents, 32 were clinicians and 8 were payers. With the exception of two of four physicians from Slovakia and one of five from Turkey, all physicians were from the public sector or academic hospitals. Although RCC is an uncommon disease, all respondents had a relatively high level of experience with treating the disease: 26 of the 40 respondents indicated that their institutions see > 20 new RCC patients per year and 8 respondents indicated that their institutions see > 50 new RCC patients per year. Following receipt of the completed questionnaires, the results were collated for each country and shared with country-specific health economics and outcomes research experts to ensure the data regarding access and reimbursement were correct and to resolve any inconsistencies.

3.1 Market access and reimbursement

In most of the 15 CEE countries, with the exception of Serbia and Latvia, most RCC drugs are available (licensed) and reimbursed. All RCC drugs are reimbursed in the Czech Republic; all mRCC drugs except bevacizumab are reimbursed in Turkey and all except bevacizumab and IL-2 are reimbursed in Hungary. There are, however, some restrictions in the region on availability; for example, only sunitinib is reimbursed in Serbia. In addition, access to both axitinib and IL-2 is limited to a minor extent as neither is approved in Bosnia and Herzegovina or Bulgaria and axitinib is not approved in Belarus. There are also restrictions on the reimbursement of RCC drugs, which is most commonly provided by national funding (13 of 15 countries). A restriction

Table 1. Reimbursement of drugs for the treatment of mRCC in any line of therapy.

Country (n)	Reimbursed mRCC treatments								
	Axitinib	Bevacizumab	Everolimus	IFN-α	IL-2	Pazopanib	Sorafenib	Sunitinib	Temsirolimus
Belarus (n = 2)	–	✓	✓	✓	✓	✓	✓	✓	✓
Bosnia and Herzegovina (n = 1)	–	–	✓	–	–	–	–	✓	–
Bulgaria* (n = 3)	✓	✓	✓	✓	–	✓	✓	✓	✓
Croatia (n = 2)	✓	–	✓		–	✓	✓	✓	✓
Czech Republic (n = 5)*	✓	✓	✓	✓	✓	✓	✓	✓	✓
Estonia (n = 3)	✓	✓	–	✓	–	✓	✓	✓	✓
Hungary* (n = 3)	✓	–	✓	✓	–	✓	✓	✓	✓
Kazakhstan* (n = 2)	–	✓	✓	✓	✓	✓	✓	✓	–
Latvia (n = 1)	–	–	–	✓	–	✓	–	–	–
Poland (n = 4)	✓	–	✓	✓	–	✓	✓	✓	–
Romania* (n = 2)	–	✓	–	✓	–	–	✓	✓	✓
Serbia (n = 1)*	–	–	–	–	–	–	–	✓*	–
Slovakia (n = 4)*,‡	–§	–	✓	✓	–	✓	✓	✓	✓
Slovenia (n = 2)	–	✓	✓	✓	–	✓	✓	✓	✓
Turkey (n = 5)	✓	–	✓	✓	✓	✓	✓	✓	✓

*Specific restrictions apply, including duration of previous lines of therapy (see Section 3.2 and Table 2).

‡The use of all drugs for the treatment of mRCC must be discussed with the HIC representative and approval for the reimbursement of treatment obtained every 3 months.

§Treatment costs are covered for a limited number of patients based on individual agreements with HICs.

HIC: Health insurance company; mRCC: Metastatic renal cell carcinoma.

common to eight of the countries is that poor performance status patients are not eligible to receive targeted therapy. Similarly, in seven countries, Memorial Sloan Kettering Cancer Center poor-risk patients are not eligible. A summary of reimbursed RCC drugs is provided in Table 1. Another potential barrier to RCC drug access in this region is the requirement for special permission to be granted by either the Ministry of Health/health authority, another government organization, or an insurance company. Special permission is required in seven countries (Belarus, Bosnia and Herzegovina, Croatia, Poland, Romania, Serbia, Slovakia and Turkey) before starting targeted treatment for mRCC with most available drugs. Although special permission usually takes < 4 weeks, delays in treatment initiation of > 2 months were reported in Bosnia and Herzegovina. With regard to the funding process, differences exist between the CEE countries. In Belarus and Kazakhstan, there is centralized procurement on a tender basis: the government buys a quantity of each drug per year, which can be used in any line but is only available while the supply lasts (personal communication).

3.2 Second-line therapy

To evaluate the usage of second-line targeted therapies in the CEE region, respondents were asked to estimate the proportion of patients receiving second-line therapy both in their country and within their center. Interestingly, there was a trend for respondents to indicate that more patients received second-line therapy at their own center compared with the whole country, which may reflect the respondents' high level of experience in terms of the management of mRCC. In both instances, the most usual estimate of the proportion of patients receiving second-line therapy was 50 – 65%. This proportion tended to be lower in countries with many restrictions to access, such as Bosnia and Herzegovina, where sunitinib and everolimus are the only two mRCC drugs reimbursed. In the CEE countries, there is very limited access to third-line therapy. Throughout the CEE countries, more respondents stated that they favored the sequential use of TKIs (22 respondents) rather than TKI followed by mTOR inhibitor in the first and second line (15 respondents). One respondent stated that they favored the sequential use of mTOR inhibitors.

In most countries considered, at least two lines of therapy are reimbursed although with many restrictions. Second-line therapy is completely unavailable in both Latvia and Serbia and only one line of therapy is allowed. The system in Slovakia is complex: all drugs for the treatment of mRCC have to be discussed with the health insurance company (HIC) representative and approval for the reimbursement of treatment obtained every three months.

Specific restrictions on reimbursement for everolimus, axitinib and sorafenib in the second line are summarized in Table 2. Everolimus is reimbursed following first-line targeted therapy in 10 of the countries, including Turkey, Poland and Hungary. In Kazakhstan, everolimus is

Table 2. Restrictions on the reimbursement of everolimus, axitinib and sorafenib in second line (beyond regulatory approval).

		Belarus		Bosnia and Herzegovina	Bulgaria*		Croatia‡		Czech Republic			Estonia		Hungary			Kazakhstan		Poland			Romania	Slovakia			Slovenia		Turkey		
Drugs reimbursed in second line		E	S	E	E	S	E	S	A	E	S	A	S	A	E	S	E	S	A	E	S	S	A	E	S	E	S	A	E	S
Restrictions	Specific subpopulations only	✓	✓	✓	–	✓	–	–	✓	–	✓**	✓	✓	–	–	–	–	–	✓	✓	✓	–	✓##	–	✓***	–	–	–	–	–
	Prior cytokine treatment required	–	–	–	–	–	–	–	–	–	✓	–	✓	–	–	✓	✓	–	–	–	✓¶¶	✓	–	–	✓	–	–	✓	–	✓
	Good-/ intermediate-prognosis patients only	✓	✓	–	✓	✓	✓	✓	✓§	–	✓§	✓	✓	✓	✓	✓	✓	–	–	✓	–	–	–	–	–	–	–	–	–	–
	Based on first-line agent used	–	–	–	✓	✓	✓	–	✓	✓#	✓‡‡	–	✓	✓	✓	✓	✓	–	✓§§	✓§§	✓	–	–	✓	–	–	–	✓	✓	–
	Based on response to first-line therapy	–	–	–	–	–	–	–	✓	✓	✓	✓	–	✓	–	–	–	–	–	–	–	–	–	–	✓	✓	✓	✓	–	–
	Other restrictions	✓	–	–	–	–	✓	✓	✓¶	✓	✓	–	✓	–	–	–	–	–	✓	✓	–	–	–	✓	✓	–	–	–	✓	–

*Expected reimbursement Q1 2015 for second line after progression with TKI therapy.

‡Everolimus, restrictions: no brain metastases; AST and ALT < 5 times upper limit of normal, creatinine clearance ≥30 mL/min; sorafenib, restrictions: no brain metastases.

§Axitinib and sorafenib only reimbursed in patients with ECOG performance status of 0 or 1 and no CNS metastases.

¶Axitinib reimbursed only following treatment with sunitinib.

#Everolimus reimbursed only following TKI therapy.

**Sorafenib reimbursed only following cytokine treatment if the patient is intolerant to sunitinib.

‡‡Sorafenib reimbursed only following treatment with cytokines.

§§Axitinib and everolimus reimbursed only following targeted treatment.

¶¶Sorafenib reimbursed only after IFN.

##Treatment costs are covered for a limited number of patients based on individual agreements with HICs.

***Officially only reimbursed after cytokines, but often approved by HIC representatives following targeted therapy because of decreasing use of cytokines.

A: Axitinib; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; E, Everolimus; ECOG: Eastern Cooperative Oncology Group; HIC: Health insurance company; S: Sorafenib; TKI: Tyrosine kinase inhibitor.

Box 1. The status of second and subsequent lines of treatment for renal cell carcinoma in Russia.

In addition to the 15 countries that are the focus of this review, 11 responses were received from Russia. Owing to the major differences between Russia and the rest of the Central and Eastern European (CEE) region in the availability and reimbursement of targeted agents, the situation in Russia is considered separately. In Russia, major differences also exist between regions; therefore, the situation in seven regions (North West, Moscow, East Siberia, West Siberia, Volga and South) was analyzed.

The reimbursement system in Russia is complex; therefore, reimbursement experts in the region were contacted to clarify the responses received. The federal essential drug list details the drugs that should be provided free of charge or at a discounted price by the state; the price of each drug must be listed. With regard to targeted agents for metastatic renal cell carcinoma (mRCC), only sunitinib, everolimus, sorafenib and bevacizumab appear on the essential drug list. Reimbursement for drugs is possible through other routes, although they are based on the essential drug list. All targeted therapies, with the exception of axitinib, are listed for reimbursement through some route in at least one region. There are two outpatient programs: the additional medical supplies program (DLO), in which regional reimbursement is provided to specific disease groups, particularly severe or chronic diseases (such as cancer); and the essential drug coverage program (ONLS), which is a reimbursement program that operates on a regional level. For both inpatients and outpatients, reimbursement may be provided through the outpatient–inpatient (OMI) program. Reimbursement may also be granted by special request to the regional Ministry of Health. Reimbursement routes for targeted agents are summarized in Table 3. Access to axitinib is highly restricted because reimbursement is only possible through special request to the regional Ministry of Health. Respondents indicated that reimbursement authorization for most RCC drugs takes an average of 2 — 4 weeks and that excessive cost/lack of cost-effectiveness data were the most common reasons that drugs for mRCC are not recommended for reimbursement.

The complexity of the reimbursement system in Russia was reflected in the answers given by the respondents. Many answers from respondents within the same region were inconsistent, suggesting a lack of understanding of the reimbursement processes. Most respondents (n = 7) stated that three or more lines of targeted therapy are reimbursed. However, there was inconsistency between and within regions about whether second-line reimbursement is (n = 7) or is not (n = 3) affected by the choice of first-line therapy. Similar to other countries, disease progression – determined by the oncologist – is the most frequent determinant of the switch from first- to second-line targeted therapy. Most respondents (n = 9) indicated that second-line treatment is not affected by the duration of first-line targeted therapy.

In Russia, the complex reimbursement system and the limited financial resources allocated to cancer treatment are the main obstacles restricting patient access to second-line treatments. Action must be taken to ensure physicians have a clear understanding of the process and also to raise awareness of the benefits of targeted therapies with few reimbursement options, with a focus on axitinib.

reimbursed following cytokine but not TKI therapy. Choice of first-line agent, response to first-line agent, and patient prognosis were the most common restrictions to the reimbursement of everolimus. However, in two (Belarus and Slovenia) out of the 10 countries in which everolimus is reimbursed and there is more than one approved first-line agent, choice of first-line treatment is not a restriction. The use of axitinib following TKI therapy is currently reimbursed in only six countries (Croatia, Czech Republic, Estonia, Hungary, Poland and Turkey), as shown in Table 1; there are many restrictions to reimbursement. Although axitinib is not officially reimbursed in Slovakia, HICs cover the cost of axitinib treatment for a limited number of patients. Within these seven countries there are many restrictions to reimbursement. For instance, although everolimus is reimbursed following any VEGF-targeted therapy in the Czech Republic and Hungary, axitinib is only reimbursed following first-line treatment with sunitinib. In Turkey, cytokines must be used in the first line, following which axitinib can be used in the second line, or the third line following a different VEGF-targeted therapy, whereas everolimus is reimbursed only in the third line following VEGF-targeted therapy. Sorafenib (which is recommended as an option rather than standard treatment in the ESMO guidelines) is officially reimbursed following TKI treatment in only four countries, but is reimbursed in a further eight countries following prior cytokine treatment.

Respondents indicated that the most common reason for switching from first-line to second-line therapy was disease progression. Furthermore, nearly half (n = 20) of the respondents – including those from Hungary and Poland – indicated that authorities require first-line treatment to be terminated following RECIST-defined progression. However, 13 respondents indicated that in some instances the patient is allowed to remain on therapy despite evidence of progressive disease; for example, if it can be managed with local therapy or if QoL is maintained and patient is still benefiting. In most countries, the oncologist is responsible for determining whether progression has occurred; however, in Belarus, Croatia and some centers in the Czech Republic, Estonia, Slovakia and Turkey, the radiologist is responsible. In most countries, second-line treatment is not affected by the duration of first-line therapy, but in Bulgaria, Kazakhstan and Romania the patient must have received $\geq$ 3 months of first-line targeted therapy; this increases in Slovakia to $\geq$ 6 months before initiating second-line treatment. In Hungary, axitinib cannot be used if the patient progressed within the first 3 months of first-line treatment with sunitinib, whereas everolimus can be used regardless of the duration of first-line therapy; thus, it can be used in cases of primary resistance to the first-line TKI. In Turkey, the

Table 3. Reimbursement for targeted agents for patients with mRCC in Russia.

	Essential drug program (ONLS)/ additional medical supplies program (DLO)	OMI program	Regional reimbursement on patient request to the regional Ministry of Health
Axitinib	–	–	✓
Bevacizumab	✓	In some regions	✓
Everolimus	–	In some regions	✓
Pazopanib	–	In some regions	✓
Sorafenib	–	In some regions	–
Sunitinib	–	In some regions	✓
Temsirolimus	–	In some regions	–

OMI: Outpatient–inpatient; ONLS: Essential drug coverage program; mRCC: Metastatic renal cell carcinoma.

prescription for first-line treatment is written for 6 months, but treatment can be changed earlier if progression occurs.

3.3 Requirements for health economic data

In most of the CEE countries (Bosnia and Herzegovina, Croatia, Czech Republic, Estonia, Hungary, Latvia, Poland, Romania, Serbia, Slovakia, Slovenia and Turkey), health outcomes/pharmacoeconomic data are required as part of the negotiations for reimbursement. Respondents indicated that lack of cost-effectiveness data and budget-impact estimates data were the main reasons why drugs for the treatment of mRCC are not accepted for reimbursement; lack of OS data was mentioned by respondents from the Czech Republic and Poland. In Serbia, criteria for reimbursement are currently under discussion and oncologists have suggested that, given the lack of resources, priority should be given to OS data. Following questionnaire data collation, it was necessary to verify the answers about health economic data requirements with health economics and outcomes research experts. This process highlighted the possible lack of awareness among respondents on these specific requirements for reimbursement.

4. Discussion

4.1 Market access and reimbursement

The data presented in this review indicate that the situation regarding access to targeted treatment varies throughout the CEE region. The initiation of targeted treatment can be delayed when special permission is required for reimbursement approval. Access to axitinib in particular is limited in this region. The clinical benefits of axitinib, everolimus and sorafenib post sunitinib have been demonstrated in clinical trials, and axitinib and everolimus are recommended in the ESMO guidelines.[10,18,24] The data from this survey also highlighted the reimbursement restrictions preventing poor performance status and Memorial Sloan Kettering Cancer Center poor-prognosis patients from accessing second-line targeted treatment.

4.2 Second-line therapy

The clear benefit of targeted therapy in the second line and beyond is supported by clinical trials and real-world data.[18,20–26,32,48] Estimates from respondents indicated that 50 – 65% of patients are receiving second-line treatment, which is quite high compared with that previously reported; for example, in the RECORD-3 trial, only 43% of 471 patients received second-line treatment.[49] Similarly, analysis of data from 2705 patients from the International mRCC Database Consortium showed that only 43% of patients received treatment in the second line and beyond.[26] However, the respondents' estimates are likely to be more reflective of current practices than the figures reported in studies done several years ago. It is important, however, to emphasize that respondents in the current study were based at centers that had high levels of experience; therefore, it is likely that their answers represent best practice and not necessarily the country as a whole. Respondents were asked to indicate the proportion of patients receiving second-line treatment in the country as a whole; however, the data provided were estimates and possibly influenced by experiences at their own center. In addition, it is possible that these data are masked by poor access to first-line treatment.

It is interesting to consider differences in the reimbursement restrictions applied to everolimus and axitinib in several countries in relation to the available on treatment sequencing. As discussed in Section 2.1, the efficacy of axitinib following first-line treatment with sunitinib was evidenced in the AXIS trial and axitinib is reimbursed only following sunitinib therapy in the Czech Republic and Hungary. By contrast, despite the lack of clinical data about the efficacy of everolimus following first-line treatment with pazopanib, it is reimbursed following any VEGF-targeted therapy in the Czech Republic and Hungary. Conversely, in Turkey, axitinib is reimbursed following both first-line cytokine therapy and VEGF-targeted therapy following first-line cytokine therapy, whereas everolimus is only reimbursed following first-line cytokine therapy and second-line VEGF-targeted therapy. This illustrates the fact that sometimes indications outlined in drug-marketing authorizations are not reflective of the investigated drug sequences within the registration trial. For example, in its summary of product characteristics, axitinib is indicated for use following sunitinib treatment only, whereas according to the FDA label it can be used after any type of first-line

systemic therapy. By contrast, in Europe, everolimus is indicated for use after first-line TKI therapy, whereas the FDA label covers its use only after sunitinib or sorafenib treatment. These discrepancies highlight the need to determine optimal treatment sequences and to ensure they are available to patients.

Disease progression is the most common reason for the switch from first- to second-line therapy. Use of RECIST may result in patients with a mixed response being considered to have disease progression.[50] This could result in the termination of therapy in patients who may otherwise continue to receive clinical benefit.[39,51] In five CEE countries, duration of first-line treatment was indicated as a restriction to second-line treatment. However, as some data suggest that there is no relationship between responses to first- and second-line agents [37,52] or duration of response to first-line therapy,[22] it is not appropriate to the latter to determine the choice of second-line therapy when establishing the optimal treatment strategy. Despite the fact that no mTOR inhibitor is recommended in the first line for good- or intermediate-prognosis patients, one respondent indicated that their favored treatment sequence was sequential mTOR inhibitors.

4.3 Requirements for health economic data

The limited economic resources in CEE countries are likely to restrict access to second-line treatments. As discussed earlier, cost-effectiveness data are important in determining whether RCC drugs are reimbursed. Although data are limited, several studies have demonstrated the cost-effectiveness of second-line treatments. An extensive literature review of US-based studies performed between January 2001 and February 2013 indicated that the use of second-line targeted agents was cost-effective in patients following failure of the first-line agent.[53] Results from this study also indicated that drugs administered orally, rather than intravenously, were more cost-effective. One method to determine whether a treatment is economically feasible is to assess the number of total life-years and quality-adjusted life-years gained.[7] Using this method, second-line sorafenib was shown to be more cost-effective than best supportive care.[54] By contrast, the use of second-line everolimus was deemed not to be cost-effective compared with best supportive care.[55] However, in a study where the two were directly compared, the results indicated that everolimus was more cost-effective.[56]

5. Conclusions

In this review, access to second-line RCC treatments in the CEE region was considered. The data obtained through questionnaires showed that, although most RCC drugs are licensed and reimbursed in the 15 countries considered, there are numerous restrictions to reimbursement and access is varied. In most countries considered at least two lines of therapy are reimbursed, although with many restrictions that are not necessarily reflective of clinical benefit; access to axitinib in particular is limited in this region.

Increased access to optimal treatment strategies will be highly effective in tackling the high mortality rates associated with mRCC in this region; therefore, it is important that action is taken to increase awareness of the benefits of sequential targeted treatment and to ensure reimbursement systems are reflective of this.

6. Expert opinion

Access to second-line therapy has many obstacles in CEE countries, including the limited availability of drugs, reimbursement restrictions, lack of cost-effectiveness data for mRCC drugs and the complexity of some reimbursement systems. As a result, patients with mRCC are unlikely to be receiving optimal treatment. Considering the clinical benefits of therapy second line and beyond, action needs to be taken so that patients with mRCC have access to multiple lines of therapy. It is of great importance to ensure that there is wide access in all CEE countries to the standard drugs recommended after progression on VEGF-targeted therapy, namely axitinib and everolimus. Although everolimus and axitinib are reimbursed in the second line in several countries, including Poland, Hungary and Turkey, there are various restrictions, including those based on duration and choice of first-line treatment. Therefore, to ensure that patients are receiving optimal treatment, steps must be taken to ensure that reimbursement restrictions are relevant to clinical benefit. In addition, in countries where the options for several lines of treatment are limited, such as Bosnia and Herzegovina, Latvia and Serbia, the benefits of such treatment must be highlighted and changes to reimbursement restrictions encouraged so that they reflect optimal treatment strategies. In addition, much work is required in Serbia to ensure that patients have access to more than one option (sunitinib) of targeted therapy. Access to targeted treatments for poor-prognosis patients also needs to be improved as they are at present limited by reimbursement restrictions in many CEE countries. Furthermore, action must be taken throughout the CEE region to ensure increased access to agents in the third line.

To overcome problems associated with reimbursement restrictions, the benefits of treating mRCC using multiple lines of treatment must be highlighted to payers and physicians. As discussed earlier in many CEE countries – including Hungary, Poland and Turkey – health/pharmaco-economic data are required for reimbursement approval. Increased knowledge of the reimbursement system by physicians will benefit patients and help to ensure that they have access to all available optimal treatments. In countries such as Slovakia, in which reimbursement approval is required from HICs, it is

particularly important that actions are taken to ensure individuals working for HICs are aware of the clinical benefits of the use of targeted treatments as well as the individual needs of the patient. The substantial cost of AEs has a large impact on the cost-effectiveness of targeted treatments; therefore, it is essential to ensure that healthcare professionals are aware of how to effectively manage AEs.[17]

The data presented in this article indicate that the reasons used by clinicians to decide whether to switch to second-line treatment may not be based on clinical benefit. For example, many clinicians in CEE countries – including in Hungary and Poland – are required to use RECIST to define progression and then terminate treatment. It is, therefore, of great importance to ensure that the physician responsible is able to accurately interpret tumor images and define progression. Physicians should also be made aware of the evidence from clinical trials that highlight the benefits of sequential TKIs in addition to the lack of evidence to support the use of sequential mTOR inhibitors.

Increasing awareness of clinical trial and cost-effectiveness data as well as tackling obstacles associated with reimbursement restrictions will increase the number of treatment options available to patients with mRCC in the CEE region. Increased access to optimal treatment strategies will be highly effective in tackling the high mortality rates associated with mRCC in this region.

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Supplementary material available online

Questionnaire_for SUBMISSION.pdf