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ORIGINAL ARTICLE

Assessment of the Role of Everolimus Therapy in Patients with Renal Cell Carcinoma Based on Daily Routine and Recent Research Results

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Abstract Everolimus is indicated for adults with metastatic renal cell carcinoma (mRCC) after failure of vascular endothelial growth factor receptor-tyrosine kinase inhibitors (TKI). Currently, the therapeutic applicability of EVE has been changing. Multicenter evaluation of efficacy and safety of everolimus in daily routine and definition of patient characteristics with favorable outcome. Data of 165 patients from 9 oncology institutes in Hungary were analyzed retrospectively. Everolimus therapy was used after one TKI in 10 mg starting dose. Physical and laboratory examinations and imaging tests were performed monthly and every 3 months, respectively. Median progression-free survival (PFS) was 5.4 months. Median overall survival (OS) was 16.2 months. PFS and OS results were more favorable in patients with ECOG 0–1 (p_{PFS} = 0.033, p_{OS} = 0.008) and after >9 months of TKI therapy (p_{PFS} = 0.019, p_{OS} = 0.045). Survival was longer in nonanemic patients with ECOG 0–1 than in anemic patients with ECOG 2–3, 30.9 and 7.7 months, respectively (p = 0.029). Dose reduction and treatment delay was required in 6.2% and 8.9% of patients, respectively. Common adverse events were exanthema, edema, stomatitis, anemia, and abnormal kidney functions and glucose levels. Results of this study show that everolimus is safe and efficacious in a real-world setting. Everyday practice showed that nonanemic patients with good performance status receiving TKI therapy for >9 months are favorable candidates for this treatment. Despite the efficiency of novel, registered drugs, everolimus still plays an important role during and after second-line therapy for mRCC when availability of modern remedies is limited.

Keywords Metastatic kidney cancer · mTOR inhibitor · Everolimus · Anemia · ECOG · RCC

Introduction

Everolimus (Afinitor®, Novartis) (EVE), an oral mammalian target of rapamycin (mTOR) inhibitor, has been evaluated in

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preclinical studies and in numerous clinical trials in the past decade [1]. PI3K/AKT/mTOR is an intracellular signaling pathway in which mTOR is a protein kinase involved in the regulation of several cellular functions such as proliferation, growth and survival [2]. This mentioned pathway plays a central role in tumorigenesis of renal cell cancers (RCC) [3]. The anti-tumor effect of EVE had been confirmed in the therapy of advanced or metastatic RCC (mRCC), and then neuroendocrine tumors of pancreatic origin, of other gastrointestinal or lung origin, and hormone receptor-positive advanced breast cancers [4–7].

The first registration study of EVE was a phase 3 placebo-controlled study for the treatment of advanced RCC (RECORD-1), in which the patients' disease has previously progressed on or after sunitinib and/or sorafenib therapy. Progression-free survival (PFS) was significantly longer in patients who received EVE than those who received placebo (4.9 months vs 1.9 months) [4]. The difference between the overall survival (OS) of the two arms was equalized due to crossover after progression (14.8 months with EVE vs 14.4 months with placebo) [8]. The results of the subgroup after failure on one line vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitor (TKI) therapy demonstrated more favorable PFS (5.4 months) [9]. According to the international guidelines (e.g., NCCN, ESMO, EAU), EVE can be used to treat patients with mRCC whose condition progressed during or after anti-VEGFR TKI [10–12].

Currently, the therapeutic administration of EVE has been changing. The results of one new phase 2 and two phase 3 studies have been published in the past two years with respect to mRCC, in which EVE was the comparator of the investigated drugs. The survival rates were more favorable in the immune checkpoint inhibitor nivolumab, TKI cabozantinib, and also in the tri-specific targeted VEGFR-, RET- and fibroblast growth factor receptor (FGFR) inhibitor lenvatinib combined with the EVE arms compared to EVE administered alone [13–16] [Table 1]. According to the recent guidelines, the role of EVE should be amended in the clinical practice [17].

Besides the therapeutic efficiency of novel remedies, the availability of new therapeutic options also influences the survival of oncologic patients. In some economic regions, the financing of new therapies with high cost is limited, so in the everyday practice, the oncologist has to maximize the efficiency of new therapeutic options with the available resources.

Aim of our study was to retrospectively analyze the maximal efficiency and the side-effects of EVE in the everyday practice of different oncology centers. We wished to define patient characteristics which made the therapy more effective.

Patients and Methods

Patients Everolimus was administered to 165 patients with mRCC between January 2010 and December 2013 in nine Hungarian oncological institutes. The study was performed in accordance with the Hungarian drug law and relevant guidelines of the Hungarian health authorities. The study design was approved by the ethics committee (registration number WHO 3483).

Patients were administered everolimus after they had progressed mostly on sunitinib, and in some cases on sorafenib or pazopanib therapy. Histological and staging examinations, such as abdominal and chest CT (if clinically indicated, bone scintigraphy and skull CT) were performed before initiating the therapy. 71% of the patients had a comorbidity that required treatment.

Everolimus Therapy Everolimus 10 mg daily was administered orally in continuous 28-day cycles. A minimum washout period of 4 weeks followed the previously administered anti-VEGFR therapy. Treatment was started when patients' general condition was good; they did not suffer from side-effects of the previous therapies, and after stabilization of symptoms caused by new metastases (e.g., cerebral metastasectomy, brain or bone irradiation, anemia control, etc.). Dose reduction

Table 1 Second and third line clinical trials with everolimus in clear cell renal cell cancer

Trial, Author	Phase	N	Arms	mPFS (months)	ORR (%)	mOS (months)
RECORD-1	III	416	EVE	4.9	2	14.8
Motzer et al. [4, 8]			PBO	1.9	0	14.4 (crossover)
CheckMate 025	III	821	NIVO	4.6	25	25.0
Motzer et al. [13]			EVE	4.4	5	19.6
METEOR	III	658	CABO	7.4	17	21.4
Choueiri et al. [14, 15]			EVE	3.9	3	16.5
Motzer et al. [16]	II	151	LEN + EVE	14.6	43	25.5
			LEN	7.4	27	18.4
			EVE	5.5	6	17.5

CABO cabozantinib, *EVE* everolimus, *LEN* lenvatinib, *mOS* median overall survival, *mPFS* median progression free survival, *NIVO* nivolumab, *ORR* overall response rate, *PBO* placebo

or delay was performed according to the Summary of Product Characteristics [1]. Physical examination and laboratory tests were performed every 4 to 8 weeks. Imaging examinations were performed 8 weeks after the initiation of everolimus therapy, and once every twelve weeks thereafter, as indicated by the National Health Insurance. Tumor response was evaluated every 12 weeks according to RECIST 1.0 [18]. Severity of AEs was evaluated based on the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3.0 (88% in case of 145 patients) [19]. The patients' general condition was assessed according to ECOG scale [20]. After progression on everolimus, treatment in clinical studies, therapy with interferon, progesterone derivatives, and best supportive care were available as therapeutic options. Our data were collected retrospectively.

Statistical Analysis Statistical analyses were performed by using SPSS 20.0 for Windows (SPSS Inc., Chicago, IL, USA). The association between PFS, OS and age was analyzed using COX regression. The influence of other therapy-related factors (duration of TKI therapy and the time that elapsed between the cessation of TKI therapy and the initiation of everolimus), and patient-related factors (gender, type of previous therapy, ECOG status, and anemia) on PFS and OS was analyzed with Kaplan-Meier analysis.

Results

Patient Characteristics Out of the 165 patients who participated in the study, 76.4% were men and 23.6% were women [Table 2]. The mean age was 63.2 (range, 28–79) years, and 93.9% of patients had undergone nephrectomy. The general condition of the patients was good with 27.9% and 63.6% of patients having ECOG scores of 0 and 1, respectively; 6.1% and 2.1% of patients had ECOG scores of 2 and 3, respectively. Common comorbidities were hypertension, other cardiovascular disorders, and diabetes.

Table 2 Patient characteristics

		Patients N = 165	
Mean age, years ± SE		63.2 ± 0.9	
Age range, years		28–79	
		n	%
Gender	Male	126	76.4
	Female	39	22.6
ECOG	0	46	27.9
	1	105	63.6
	2	10	6.1
	3	4	2.1
Comorbidities		n	%
Hypertension		66	40.0
Other cardiovascular disorders		16	9.7
Diabetes		18	10.9
Secondary tumors		13	7.9.
Hematological disease		4	2.4
Asthma		4	2.4
Psoriasis		3	1.8
Metastases			
Mean number of metastatic sites (range)		2.4 (1–6)	
Location of metastases		n	%
Lung		142	86.0
Bone		67	40.6
Distant lymph node		60	36.4
Liver		31	18.8
Brain		21	12.7
Suprarenal gland		15	9.1
Other (peritoneum, pleura, pancreas, local relapse, contralateral kidney, thyroid gland)		–	‹8
Histopathological types		n	%
Purely clear cell renal cell type (ccRCC)		146	88.5
ccRCC with sarcomatoid morphology		9	5.45
ccRCC with papillary- / chromophobe- / both morphology		2 / 2 / 2	1.2 / 1.2 / 1.2
ccRCC with sarcomatoid + papillary- / chromophobe- / or both morphology		1 / 1 / 1	0.6 / 0.6 / 0.6
ccRCC with collecting duct component		1	0.6

ECOG Eastern Cooperative Oncology Group, *n* number of involved patients, *N* number of analyzed patients, *ccRCC* clear cell renal cell cancer, *SE* standard error

The mean number of metastatic sites was 2.4 (range, 1–6), and the most common sites of metastasis were the lungs, bones, distant lymph nodes and the liver. The histological type of the tumors was mainly clear cell renal cell cancer (ccRCC) in case of all patients, in most cases pure ccRCC. No rare variants could be detected, only sarcomatoid, papillary, chromophobe or collecting duct morphologies and transformations in the ccRCC were present [Table 2].

No genetic analyses were performed to prove the familial origin of the renal cancer. Renal cancer has developed in 11 (7.27%) and in 3 (1.8%) patients under 50 and 40 years of age, respectively. In these cases, there was no information about any benign tumor, paraganglioma, pheochromocytoma or bilateral tumor. Familial origin and multifocality could be observed in 1 and 2 cases, respectively. Bilateral renal cancer and secondary malignancy (3 rectal cancers, 2 CLLs, 1 breast cancer) could be detected in 5 and 6 cases, respectively.

Previous Therapies After undergoing nephrectomy, 9.1% of the patients received adjuvant INF treatment, and 4.8% of patients received IFN before the administration of VEGFR-targeted therapy. Before receiving everolimus, 93.9%, 4.8%, and 1.2% of patients were given sunitinib, sorafenib, and pazopanib, respectively. The mean (±SE) duration of TKI therapy was 11.7 (±0.9) months. The duration of TKI was <3 months in 15.7% of patients, who were defined as being resistant to primary TKI therapy [21]. The mean (±SE) duration between the end of TKI therapy and the beginning of everolimus was 97. 7 (±10.1) days (period between TKI–EVE) [Table 3].

Dose Parameters Overall, 6.2% of the patients required a dose reduction to manage pneumonitis (4.1%), grade 2 skin problems (1.4%), and face and neck edema (0.7%). Furthermore, 8.9% of the patients required a dose delay with a mean duration of 24 (range, 5–75) days. The reasons for delaying the dose for >7 days were cardiovascular symptoms, elevation of renal functions that required dialysis (10 days each), grade 3 diarrhea (9–14 days), cerebral metastasectomy (20 days), and pneumonitis in 2 cases (28 and 30 days).

Efficacy At the time of the analysis, 26.2% of the patients were being treated, and 53.8% of the patients were alive. Partial regression, stable disease, and progression occurred in 12.9%, 60.7% and 26.4% of the patients, respectively. No patients experienced complete regression (CR). The objective tumor response was 12.9%, and the clinical benefit rate was 73.6% (partial regression + stable disease). The median PFS at a median follow-up time of 21.2 months (*95%CI 7.05–31.45*) was 5.4 months (*95%CI 3.83–6.97*). The median overall survival time (OS) (based on data from 145 patients) was 16.2 months (*95%CI 12.95–19.45*).

AEs The most common AEs were exanthema (25%), peripheral edema (19%), stomatitis (19%), pneumonitis (13%), nausea, weight loss, fatigue (11% each), diarrhea (10%), dyspnea (10%), and mucositis (9%). The most common abnormalities identified in laboratory findings were anemia (72%), and elevation in renal function (45%), liver function (25%), blood glucose (51%), cholesterol (44%) and lipids (35%). AEs compared with data from the phase III study are presented in Table 4. No severe or life threatening AEs occurred.

Table 3 Previous therapies before everolimus treatment

	Patients N = 165	
Previous therapies	n	%
Nephrectomy	155	93.9
Adjuvant IFN	22	13.3
First line IFN before VEGFR-TKI	21	12.7
Sunitinib	155	93.9
Sorafenib	8	4.8
Pazopanib	2	1.2
First line VEGFR-TKI	157	95.1
Second line VEGFR-TKI after IFN	8	4.8
Duration of previous therapy		
Mean duration of VEGFR-TKI, months (±SE)	11.7 (±0.9)	
Duration of VEGFR-TKI <3 months, n (%)	26	15.7
Mean duration between VEGFR-TKI and EVE, days (±SE)	97.7 (±10.1)	

EVE everolimus, *IFN* interferon-α, *n* number of involved patients, *N* number of analyzed patients, *SE* standard error, *TKI* tyrosine kinase inhibitor, *VEGFR* vascular endothelial growth factor receptor

Table 4 Adverse events of patients who received everolimus

Most common adverse events	Hungarian analysis			RECORD-1 Registration study [4]	
	n = 145			*n* = 269	
	All grade %	Grade 2%	Grade 3%	All grade %	Grade 3/4%
Exanthema (rash)	25	5	1	29	1/0
Peripheral edema	20	–	1	25	<1 / 0
Stomatitis	24	2	–	44	4 / <1
Weight loss (asthenia)	17	1	–	33	3 / <1
Fatigue/ Weakness	21	–	–	31	5 / 0
Diarrhea	13	2	–	31	1 / 0
Nausea	15	–	–	26	1 / 0
Mucositis	13	2	–	19	1 / 0
Dyspnea	12	–	–	24	6 / 1
Pneumonitis	11	2	1	14	4 / 0
Decreased hemoglobin	73	21	6	91	9 / <1
Elevated creatinine	43	5	1	46	<1 / 0
Elevated liver transaminases	21	4	1	25–21	0–1
Elevated glucose level	53	6	–	50	12 / 0
Elevated cholesterol	45	3	–	76	3 / 0
Elevated lipid	37	4	–	71	<1 / 0
Hypothyroidism/ hyperthyroidism	<1 / <1	–	–	–	–

n number of analyzed patients

Factors Influencing Efficacy PFS and OS with everolimus were not influenced by the patients' gender, age, the number and type of metastatic organ systems, the presence of the metastasis only in the lungs, the length and type of the previous TKI therapy, or the time between the cessation of TKI treatment and initiating everolimus.

Patients without lung metastasis showed favorable outcome (PFS 5.3 vs 9.1 months $p = 0.042$, OS 10.3 vs 15.9 months $p = 0.006$) [Table 5].

Median PFS and OS of patients treated with TKI therapy ≤3 months, vs > 3 months were 3.0 vs 5.2 months and 16.0 vs 19.9 months, respectively; however, the differences were not

Table 5 Factors influencing the outcome of everolimus therapy

Specifications		PFS ± SE (months)	*p* -value	OS ± SE (months)	*p* -value
Gender	Man/Woman	5.3 ± 0.7/ 6.4 ± 1.7	0.929	19.9 ± 3.5 /18.2 ± 2.7	0.544
Number of metastatic organs	1 / More	5.3 ± 1.5/ 5.5 ± 1.0	0.660	18.0 ± 1.9/16.6 ± 3.2	0.186
Only lung met. / Other met.		4.2 ± 0.5/ 6.4 ± 0.9	0.116	15.5 ± 3.1/21.9 ± 6.6	0.916
Presence / Lack of lung met.		5.3 ± 0.6 / 9.1 ± 2.8	**0.042**	10.3 ± 1.1 / 15.9 ± 4.7	**0.006**
ECOG status	0–1 / 2–3	6.4 ± 1.1/ 3.5 ± 0.2	**0.033**	19.9 ± 6.7/7.5 ± 0.6	**0.008**
Duration of TKI therapy (months)	≤3 / >3	3.4 ± 0.6/ 5.9 ± 0.8	0.250	16.0 ± 4.5/ 19.9 ± 5.9	0.244
	≤6 / >6	4.7 ± 0.8/ 6.4 ± 1.3	0.090	21.9 ± 7.2/ 16.6 ± 2.4	0.840
	≤9 / >9	4.5 ± 0.8/ 7.2 ± 1.5	**0.019**	16.0 ± 2.8/ 41.2 ± 18.6	**0.045**
Type of TKI	SU / SO / PA	5.5 / 6.9 / 2.8	0.140	18 / 19.9 / 30.9	0.690
Period between TKI–EVE (days)	≤30 / >30	6.5 ± 0.9/ 5.3 ± 0.9	0.774	11.5 ± 5.4/ 30.9 ± 6.8	0.106
	≤60 / >60	5.6 ± 0.6/ 4.5 ± 1.3	0.601	19.9 ± 4.9/ 16.5 ± 6.8	0.624
Anemia	G0 / G1–2-3	4.8 ± 1.2/ 6.4 ± 1.0	0.612	30.9 ± 6.1/16.2 ± 1.4	**0.020**
PFS (months)	<12 / ≥12	–	–	15.5 ± 1.8/41.2 ± 9.5	**0.001**

ECOG Eastern Cooperative Oncology Group, *EVE* everolimus, *G* grade, met –metastasis, *OS* median overall survival, *PA* pazopanib, *PFS* median progression-free survival, *SE* standard error, *SO* sorafenib, *SU* sunitinib, *TKI* tyrosine kinase inhibitor

Significant level is: $p < 0.05$

statistically significant ($p = 0.250$ and $p = 0.244$, respectively). PFS and OS were more favorable for patients who received everolimus after receiving TKI therapy for >9 months (PFS $p = 0.019$, OS $p = 0.045$) and for patients with an ECOG performance status of 0 or 1 (PFS $p = 0.033$, OS $p = 0.008$).

The presence of anemia predicted a poorer survival rate ($p = 0.020$), while a PFS >12 months was a favorable prognostic factor ($p = 0.762$) [Table 5]. Only 25.5% of the patients received third-line therapy: progesterone derivatives (17.9%), a TKI in a clinical study (4.1%), and INF therapy (3.5%). OS was not significantly different between patients who received these specific third-line therapies and patients who did not receive oncological therapy after everolimus (post EVE therapy) ($p = 0.001$). Examining the effect of ECOG performance status and anemia on survival, the most favorable median OS was observed for patients without anemia and with an ECOG performance status of 0 or 1 (30.9 ± 2.5 months), whereas it was the most unfavorable median OS observed in patients with anemia and with an ECOG performance status of 2 or 3 (7.7 ± 4.5 months) ($p = 0.029$). None of other patient or therapy related parameters influenced PFS or OS [Fig. 1].

Discussion

Modifying the mTOR signal transduction pathway by blocking the proliferation, migration, growing and survival and by indirectly inhibiting VEGF is an important therapeutic strategy of hypervascular RCCs [3]**.** EVE as an orally administered mTOR serine/threonine kinase inhibitor shows efficiency in second- and third-line therapies of patients with mRCC after failure of at least one VEGFR-TKI. The safety profile of the drug is favorable. No clear predictive biomarkers are known related to efficacy of EVE. The real world data could confirm results of registration studies and help understand the integration of novel drugs into the daily routine practice.

Values of our retrospective post-registration study with EVE are the multicenter data processing, the high case number in comparison to the population, and the homogeneity of the patients regarding previous therapies.

In our analysis, EVE monotherapy was associated with favorable PFS and OS in patients with mRCC refractory to previous VEGFR-TKI therapy. Our reported median PFS of 5.3 months is slightly longer than the median PFS of 4.9 months reported in the RECORD-1 registration study [4], and similar to the median PFS of 5.4 months reported in the subgroup of RECORD-1 patients, who had previously received only one line of TKI therapy [9]. The median OS of patients in our study was 16.2 months. In RECORD-1, the median OS was 14.8 in the everolimus arm [8]. Based on the previous details, results of survival data in our study are comparable to the results of the registration study and even the EVE standard arm in recent clinical studies (Checkmate 025 PFS_{EVE}: 4.4 months, OS_{EVE}: 19.6 months), METEOR (PFS_{EVE}: 3.9 months, OS_{EVE} 16.5 months), LEN-EVE (PFS_{EVE}: 5.5 months, OS_{EVE}: 17.5 months) [13–16] [Table 1].

Regarding PFS, as an indicator of the efficiency of an active agent, results from the everyday practice can be compared with and do not differ significantly from the newly published results. Overall survival data that refer to efficiency of therapeutic sequences based on new results suggest that introducing new therapeutic options positively affect the OS [4, 13, 14].

In the registration studies and retrospective analyses of EVE, and new active agents (carbozantinib and nivolumab), the safety profiles were homogenous [4, 13, 14, 22].

In our study, the mean duration between ceasing VEGFR-TKI treatment and initiating everolimus therapy was 97.7 days. There were several reasons for delaying the start of the administration of everolimus, including resolving AEs associated with VEGFR-TKI therapy to at least to grade 1, stabilizing symptoms caused by new metastases (if necessary cerebral metastasectomy, brain or bone irradiation), patient flow between the institutes, organizing radiological examinations, and drug

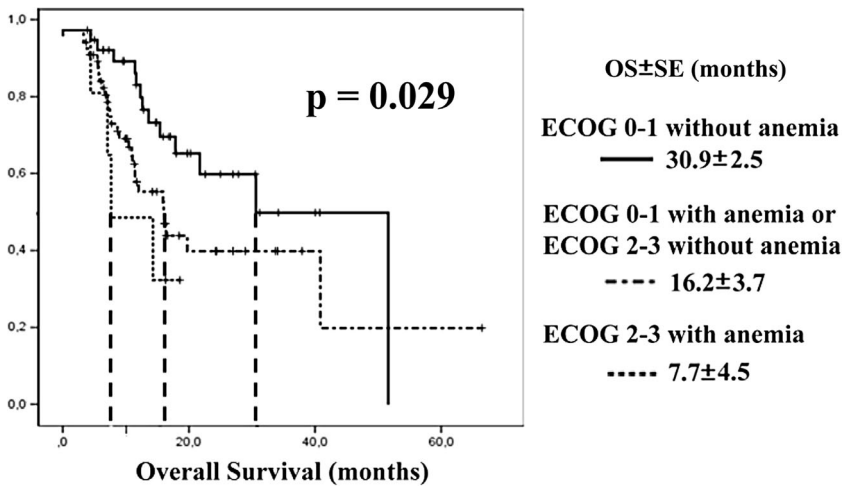

Fig. 1 Effect of ECOG status and anemia on overall survival. Kaplan-Meier analysis of OS was compared in patients with anemia and ECOG 2–3 status *(7.7 ± 4.5 months)* vs the absence of anemia and ECOG 0–1 status *(30.9 ± 2.5 months)* vs only one unfavorable prognostic factor is present *(16.2 ± 3.7 months) (p = 0.029)*. (ECOG – Eastern Cooperative Oncology Group, OS – overall survival, SE – standard error)

availability. The length of time between TKI and mTOR inhibitor therapies was similar to the time between ending TKI therapy and beginning everolimus following progression on placebo in the RECORD-1 study. Surprisingly, despite the length of time between TKI-EVE, we could not have proven any unambiguous, negative effect of it in our population.

We also investigated parameters that could influence the efficacy of everolimus.

Patients' favorable general condition (ECOG 0–1) was associated with a longer PFS and OS. The lack of anemia was associated with longer survival. After the introduction of new, registered therapeutic options, analysis of these prognostic factors might be useful during the evaluation of early experience.

We did not find a correlation between patients' other general characteristics, the type of previous TKI therapy or and its therapeutic outcome. We also evaluated the effect of primary resistance to VEGFR-TKI therapy on subsequent everolimus efficacy. Although differences were not statistically significant, PFS and OS tended to be less favorable in patients who experienced primary TKI resistance. Similar results have been reported in international studies [23]. Similarly to our results, Bergmann et al. found no correlation between the type or duration (< or >3 or 6 months) of previous TKI therapy and the efficacy of everolimus in VEGF-refractory patients with mRCC [24]. In our study, we found that patients whose VEGFR-TKI therapy was >9 months had significantly more favorable PFS and OS [24].

The prognostic score system published by Motzer for second-line therapy demonstrated unfavorable prognosis in the presence of 3 factors: anemia, poor general health (Karnofsky performance status <80), and a high level of corrected calcium (>10 mg/dL or >2.4 mmol/L), instead of the 5 factors used to determine prognosis for first-line therapy [25]. In our population, we demonstrated that poor general health negatively influenced survival. If the patients' general condition was good, and they did not have anemia, the OS was 30.9 months, but if they had poor health and anemia, OS time decreased to 7.7 months. In our analysis, we found that ECOG performance status was one of the most important factors that affect PFS. OS was remarkably better in patients with a duration of everolimus therapy >12 months. This underlines the importance of appropriate patient selection. After longer duration of everolimus therapy, the number of third-line therapies decreased without influencing survival, so the properly selected, effective second-line therapy determined the patients' life expectancy.

Conclusions mTOR inhibition is an effective way to treat patients with VEGFR-TKI refractory mRCC. According to experience in the Hungarian everyday practice, VEGFR-TKI refractory patients in good general health, having adequate hematological values, and >9 months of previous VEGFR-TKI therapy may experience delayed disease progression and improved survival while maintaining good quality of life during the second-line everolimus therapy. Despite the more favorable efficiency of new, registered drugs, EVE therapy still plays role during and after second-line therapy for mRCC in regions where modern remedies are only limitedly available, they have not been introduced yet, or their administration is contraindicated due to medical reasons.

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Compliance with Ethical Standards

Conflict of Interest Anikó Maráz has received honoraria from Bayer, Bristol-Myers Squibb, and has served on advisory boards for Novartis.

András Csejtei has served on advisory boards for Novartis and Pfizer.

Judit Kocsis has received honoraria from Bayer and served as a member of advisory board: Novartis, Bristol-Myers Squibb and Pfizer.

Miklós Szűcs has received honoraria from Bayer, Novartis, Bristol-Myers Squibb and has served on advisory boards for Novartis and Pfizer.

Zsuzsanna Kahán has no actual or potential conflicts of interest to report.

György Bodoky has received honoraria from Bayer, Bristol-Myers Squibb and Pfizer and has served on advisory boards for Novartis and Pfizer.

Magdolna Dank has received honoraria from Bayer, Novartis and Pfizer and has served on advisory boards for Novartis and Pfizer.

László Mangel has received honoraria from Pfizer and has served on advisory boards for Novartis and Pfizer.

János Révész has served on advisory boards for Novartis and Pfizer.

Zoltán Varga has no actual or potential conflicts of interest to report.

Lajos Géczi has received honoraria from Bayer, Novartis, Bristol-Myers Squibb and Pfizer and has served on advisory boards for Bristol-Myers Squibb, Novartis and Pfizer.

Ethical Approval All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study no formal consent is required.

Support This was a non-sponsored study.

References

1. Afinitor EMEA Summary of Product Characteristics: http://www.ema.europa.eu/docs/hu_HU/document_library/EPAR_-_Product_Information/human/001038/WC500022814.pdf
2. Hay N, Sonenberg N (2004) Upstream and downstream of mTOR. Genes Dev 18:1926–1945
3. Eisen HJ, Tuzcu M, Dorent R et al (2003) Everolimus for the prevention of allograft rejection and vasculopathy in cardiac-transplant patients. N Engl J Med 349:847–858
4. Motzer RJ, Escudier B, Oudard S et al (2008) Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet 372:449–456

5. Yao JC, Shah MH, Ito T et al (2011) Everolimus for Advanced Pancreatic Neuroendocrine Tumors. N Engl J Med 364:514–523
6. Yao JC, Fazio N, Singh S et al (2016) Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. Lancet 387:968–977
7. Baselga J, Campone M, Piccart M et al (2012) Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. N Engl J Med 366:520–529
8. Motzer RJ, Escudier B, Oudard S et al (2010) Phase 3 trial of everolimus for metastatic renal cell carcinoma: final results and analysis of prognostic factors. Cancer 116:4256–4265
9. Calvo E, Escudier B, Motzer RJ et al (2011) Everolimus in metastatic renal cell carcinoma: subgroup analysis of patients with 1 or 2 previous vascular endothelial growth factor receptor-tyrosine kinase inhibitor therapies enrolled in the phase III RECORD-1 study. Eur J Cancer 48:333–339
10. NCCN Guideline. https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf
11. Escudier B, Porta C, Schmidinger M et al (2014) Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 25:49–56
12. Ljungberg B, Bensalah K, Canfield S et al (2015) EAU Guidelines on Renal Cell Carcinoma: 2014 Update. Eur Urol 67:913–924
13. Motzer RJ, Escudier B, McDermott DF, el al (2015) Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med 373:1803–1813
14. Choueiri TK, Escudier B, Powles T et al (2015) Cabozantinib versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med 373:1814–1823
15. Choueiri TK, Escudier B, Powles T et al (2016) Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial. Lancet Oncol 17:917–927
16. Motzer RJ, Hutson TE, Glen H et al (2015) Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomized, phase 2, open-label, multicenter trial. Lancet Oncol 16:1473–1482
17. Escudier B, Porta C, Schmidinger M et al (2016) Renal Cell Carcinoma: ESMO Clinical Practice Guidelines. Ann Oncol 27: 58–68
18. Therasse P, Arbuck SG, Eisenhauer EA et al (2000) New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 92:205–214
19. Common Terminology Criteria for Adverse Events, version 3.0 issued by National Cancer Institute EORTC, 09. 08 (2006) http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf
20. ECOG performance status. http://ecog.dfci.harvard.edu/general/perf_stat.html
21. Rini BI, Flaherty K (2008) Clinical effect and future considerations for molecularly-targeted therapy in renal cancer. Uro Oncol Semin Orig Investig 26:543–549
22. Grünwald V, Karakiewicz PI, Bavbek SE et al (2012) An international expanded-access programme of everolimus: addressing safety and efficacy in patients with metastatic renal cell carcinoma who progress after initial vascular endothelial growth factor receptor-tyrosine kinase inhibitor therapy. Eur J Cancer 48:324–332
23. Calvo E, Ravaud A, Bellmunt J (2013) What is the optimal therapy for patients with metastatic renal cell carcinoma who progress on an initial VEGFr-TKI? Cancer Treat. Rev. 39:366–374
24. Bergmann L, Kube U, Doehn C et al (2015) Everolimus in metastatic renal cell carcinoma after failure of initial anti–VEGF therapy: final results of a noninterventional study. BMC Cancer 15:303
25. Motzer RJ, Bacik J, Schwartz LH et al (2004) Prognostic factors for survival in previously treated patients with metastatic renal cell carcinoma. J Clin Oncol 22:454–463