

Everolimus in Metastatic Renal Cell Carcinoma after Failure of Initial Vascular Endothelial Growth Factor Receptor-Tyrosine Kinase Inhibitor (VEGFr-TKI) Therapy: Results of an Interim Analysis of a Non-Interventional Study

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Keywords

Everolimus · Advanced cancer · Metastatic disease · Renal cell carcinoma · Sequential therapy · Sunitinib · Sorafenib

Summary

Background: Everolimus is approved for treatment of anti-vascular endothelial growth factor (VEGF)-refractory patients with metastatic renal cell carcinoma (mRCC). Clinical trials rarely mirror treatment reality. Thus, a broader evaluation of everolimus is valuable for routine use. **Patients and Methods:** A German multicenter non-interventional study documented mRCC patients starting everolimus after failure of initial VEGF-targeted therapy. Primary endpoint was effectiveness, defined as time to progression (TTP) according to investigator assessment (time from first dose to progression). **Results:** Of 382 documented patients, 196 were included in this interim analysis. In the efficacy population ($n = 165$), median TTP was 7.0 months (95% confidence interval (CI) 5.1–9.0). Among patients with $< \text{or} \geq 6$ months of previous VEGF-targeted therapy, median TTP was 6.6 months (95% CI 3.8–not estimable) and 7.4 months (95% CI 4.6–9.6), respectively. Most common adverse events were anemia (13%) and dyspnea (14%). Physicians assessed high tolerance and documented high adherence to everolimus therapy (approximately 97%). **Conclusion:** In routine clinical practice, everolimus is effective, as measured by median TTP (longer than median progression-free survival in RECORD-1 trial), and well tolerated. Our results support everolimus use in anti-VEGF-refractory patients with mRCC.

Schlüsselwörter

Everolimus · Fortgeschrittene Krebserkrankung · Metastasierte Krebserkrankung · Nierenzellkarzinom · Sequentielle Therapie · Sunitinib · Sorafenib

Zusammenfassung

Hintergrund: Everolimus ist für die Behandlung des metastasierten Nierenzellkarzinoms (mRCC) nach Versagen einer gegen VEGF (vascular endothelial growth factor) gerichteten Therapie zugelassen. Daten aus Zulassungsstudien reflektieren nicht alle Aspekte einer späteren Anwendung in der Routine. Daher stellt eine systematische Untersuchung von Everolimus in der Praxis eine wichtige Quelle klinisch relevanter Daten dar. **Patienten und Methoden:** Patienten wurden in einer deutschen, multizentrischen, nicht-interventionellen Studie unter Everolimus-Therapie eines mRCC nach Versagen der ersten gegen VEGF gerichteten Therapie dokumentiert. Primärer Zielparameter war die Effizienz von Everolimus, definiert als Zeit bis zum Progress (TTP; Zeit von erster Dosis bis Progress). **Ergebnisse:** Von 382 dokumentierten Patienten gingen 196 Patienten in die Zwischenanalyse ein. In der Effizienzpopulation ($n = 165$) war die mediane TTP (mTTP) 7,0 Monate (95%-Konfidenzintervall (KI) 5,1–9,0). Patienten nach vorangegangener gegen VEGF gerichteter Therapie < 6 Monate oder ≥ 6 Monate wiesen eine mTTP von 6,6 Monaten (95%-KI 3,8–nicht erreicht) bzw. 7,4 Monaten (95%-KI 4,6–9,6) auf. Die häufigsten unerwünschten Ereignisse waren Anämie (13%) und Dyspnoe (14%). **Schlussfolgerung:** In der Praxisroutine war die mTTP von Everolimus länger als das mediane progressionsfreie Überleben der RECORD-1-Studie. Unsere Ergebnisse unterstützen den Einsatz von Everolimus bei Patienten mit mRCC nach Versagen initialer gegen VEGF-gerichteter Therapie.

Introduction

Everolimus is an orally administered selective inhibitor of the mammalian target of rapamycin (mTOR), a serine-threonine kinase which is up-regulated in several types of human cancer cells. Inhibition of tumor cell proliferation and growth as well as a reduction of metabolism in solid tumors are class effects of everolimus. In addition, mTOR inhibition is associated with anti-angiogenic actions through reduction of endothelial cell proliferation, vascular endothelial growth factor (VEGF) levels, and the response of endothelial vascular cells to stimulation by VEGF [1, 2]. These mechanisms of action may be beneficial, especially in patients who fail initial VEGF-targeted therapy.

In a multicenter, randomized, double-blind, phase III study, everolimus 10 mg/day demonstrated clinical benefit over placebo in patients with metastatic renal cell carcinoma (mRCC), who had failed previous therapy with sunitinib and/or sorafenib. Prior treatment with interferon-alpha and bevacizumab was allowed. Everolimus significantly prolonged median progression-free survival (PFS) per RECIST criteria by 3 months; from 1.9 months (95% confidence interval (CI) 1.8–1.9 months) with placebo to 4.9 months (95% CI 4.0–5.5 months) with everolimus ($p < 0.001$) [3]. Median overall survival (OS) was 14.8 months in the everolimus group and 14.4 months in the placebo group ($p = 0.162$); the majority of patients in the placebo group crossed over to receive everolimus upon progression. A rank-preserving structural failure time model accounted for the crossover effect and calculated a median survival for patients in the placebo arm of 10.0 months instead of 14.4 months.

This non-interventional study (NIS) was initiated shortly after everolimus (Afinitor®, Novartis Pharma GmbH, Nuremberg, Germany) was approved in August 2009 for the treatment of patients with advanced RCC, who had progressed during or after treatment with 1 VEGF-targeted therapy [4–6]. Since clinical phase III trials rarely mirror treatment reality, the objective of the study was to systematically evaluate the efficacy and safety of everolimus in patients with mRCC, who failed 1 previous VEGF-targeted therapy (VEGF receptor-tyrosine kinase inhibitor (VEGFr-TKI) or anti-VEGF antibody) in routine clinical practice.

Patients and Methods

Study Design and Patient Population

This prospective multicenter, non-interventional, observational study was initiated following commercial availability of everolimus for the treatment of mRCC in Germany. The study was performed in accordance with the German drug law and the relevant guidelines of German health authorities and the pharmaceutical industry for conducting a NIS. The observational plan was approved by the local ethics committee of the scientific head of the study, and the respective responsible ethics committees at each participating site were informed. Patients provided written informed consent prior to start of documentation.

Patients were entered at centers across Germany between August 2009 and January 2012. Patients ≥ 18 years old with mRCC could be documented if the treating physician had decided to prescribe everolimus in accordance with the summary of product characteristics (SmPC) [7], i.e. following failure with 1 VEGF-targeted therapy (e.g. sunitinib, sorafenib, pazopanib, or bevacizumab). Previous exposure to cytokine-based regimens such as interleukin-2, interferon-alpha, or bevacizumab plus interferon-alpha was allowed. Pretreatment with a second VEGFr-TKI for a period of ≤ 1 month because of intolerability was also permitted. Patients could be included if their treatment with everolimus had been ongoing for < 90 days, or ≤ 1 imaging follow-up investigation had been performed since the start of everolimus. Patients received oral everolimus 10 mg once daily according to usual routine practice as outlined in the SmPC.

Documentation of each patient was performed in accordance with routine assessments for the duration of everolimus treatment. Because of the non-interventional nature of the study, time point and method of determination of disease progression were not defined but instead followed routine medical care as decided by the physician. Tumor response and progression were assessed by the treating physician and the radiologist according to the hospital's established practice. In accordance with the observational plan, enrolment was terminated at 382 patients, on January 20, 2012. Also in accordance with the observational plan, the first interim analysis was performed after enrollment of 100 patients who were documented for ≥ 3 months or had documented therapy discontinuation and reported elsewhere [8]. A second interim analysis (reported here) was performed after the patients analyzed in the first interim analysis were followed up for an additional 10 months. Patient populations were defined as 'total population' which included patients documented within 3 months of starting treatment with everolimus; 'safety population' which included patients from the total population who had documented intake/prescription of everolimus and ≥ 1 post-baseline assessment; 'efficacy population' which included patients from the safety population who were documented before or < 90 days after initiation of everolimus and had received a single VEGFr-TKI or a second VEGFr-TKI for ≤ 1 month before everolimus; '1 previous VEGFr-TKI population' which included patients from the efficacy population who were treated with 1 previous VEGFr-TKI; ' < 6 months duration of previous VEGF-targeted therapy population' which included patients who received 0 to < 6 months of previous treatment with VEGFr-TKI therapy and/or bevacizumab; and ' ≥ 6 months duration of previous VEGF-targeted therapy population' which included patients who received ≥ 6 months of previous treatment with VEGFr-TKI therapy and/or bevacizumab.

Objectives

Study objectives were everolimus effectiveness and duration of therapy. Effectiveness was measured by time to progression (TTP), which was defined as time from first dose of everolimus to disease progression according to the investigator assessment. Information on treatment regimens before and after everolimus was also collected. Additional objectives included Karnofsky performance status (KPS) in patients treated with everolimus, and assessment of adherence and tolerability at each visit during routine administration of everolimus.

Statistics

Due to the nature of the non-interventional design, there was no formal sample size calculation. Thus, sample size was based on disease incidence, sample size in comparison to the overall population, and the expected recruitment within the enrollment period. The sample size comprised $> 10\%$ of the total population, considering approximately 2,500–3,000 patients in need of targeted therapy after initial VEGF-targeted therapy (VEGFr-TKI or anti-VEGF antibody) per year. A detailed statistical analysis plan (SAP) was developed prior to the start of the study and finalized before the first interim analysis. The study was analyzed using descriptive statistical methods.

Results

Demographics and Disease Characteristics

This analysis was based on 196 patients (total population) enrolled at 79 German sites between August 2009 and September 30, 2011 who had been followed for at least 3 months or discontinued treatment at the time of database lock for this interim analysis. Subpopulations analyzed comprised: safety population (n = 195), efficacy population (n = 165), 1 previous VEGFr-TKI population (n = 121), < 6 months duration of previous VEGF-targeted therapy population (n = 69), and ≥ 6 months duration of previous VEGF-targeted therapy population (n = 121). At the data cut-off of this analysis (September 30, 2011), the median observational time was 142 days (range 9–665 days) for the total population. Among documented patients, 186 individuals were observed starting

with everolimus initiation, 1 patient did not receive treatment, 10 patients met the criteria for enrolment after everolimus initiation, and 20 patients had received ≥ 2 VEGFr-TKIs prior to everolimus initiation. Baseline patient and disease characteristics are summarized in table 1. The majority of patients were male (75%) and had clear cell histology (92%). At baseline, a median of 2 organ systems (range 1–7) were involved in metastatic spread, most frequently involving the lungs and skeletal system. The main reason for initiating everolimus was progression during previous therapy (84%), and the majority of patients enrolled had received only 1 previous antineoplastic therapy (72%, table 2). The most common previous VEGF-targeted therapy was sunitinib (80%), with a median (range) treatment duration of 9.0 (0.0–49.4) months among the total population (table 2). Median (range) treatment duration of previous therapy with sorafenib, bevacizumab (given as monotherapy or in combination with interferon-alpha), and cytokines was 5.9 (0.1–41.4) months, 4.0 (0.3–20.7) months, and 7.1 (4.0–13.0) months, respectively.

Table 1. Baseline characteristics in the total population (n = 196)

Age, years	67 (22–89)
Male sex, n (%)	147 (75)
KPS, median (range), %	80 (50–100)
Period since diagnosis, median (range), years	
RCC	3.3 (0.4–22.9)
mRCC	1.8 (0.0–15.8)
Histology ^a , n (%)	
Clear cell	170 (92)
Non-clear cell	15 (8)
MSKCC risk status 1st-line ^b , n (%)	
Favorable	45 (32)
Intermediate	85 (61)
Poor	10 (7)
Reasons for initiation of everolimus ^c , n (%)	
Progression	164 (84)
Not triggered by progression	22 (11)
Patient's request	17 (9)
Route of administration of everolimus	1 (< 1)
Metastatic spread ^d	
Number of organs affected, median (range)	2 (1–7)
Type of organs affected, n (%)	
Lung	126 (64)
Lymph nodes	91 (46)
Skeletal	77 (39)
Liver	53 (27)
Adrenal	35 (18)
Renal (contralateral)	24 (12)
Central nervous system	10 (5)
Other	52 (27)

^aMissing data for 11 patients.

^bNot done in 45 patients and missing data for 11 patients.

^cMore than 1 answer per patient possible.

KPS = Karnofsky performance status; mRCC = metastatic renal cell carcinoma; MSKCC = Memorial Sloan-Kettering Cancer Center.

Effectiveness

According to Kaplan Meier estimates, median duration of everolimus therapy for the efficacy population was 7.3 months (95% confidence interval (CI) 4.7–10.9 months). Among the subpopulations of patients who had received < 6 months or ≥ 6 months duration of previous VEGF-targeted therapy, median treatment durations with everolimus were 7.5 months (95% CI 4.9–11.1 months) and 7.4 months (95% CI 4.8–10.9 months), respectively (table 3). At the time of data cut-off, 60 patients remained on everolimus (31%), and treatment had

Table 2. Previous medical treatment and surgical intervention in the total population (n = 196)

Previous intervention	n (%)
Previous systemic therapies, n	
1	141 (72)
2	44 (22)
≥ 3	11 (6)
Agents	
Sunitinib	156 (80)
Sorafenib	45 (23)
Bevacizumab ^a	22 (11)
Cytokines (aldesleukin, interleukin, interferon)	37 (19)
Other drugs	24 (12)

^aGiven as monotherapy to 6 patients and as part of combination therapy to 16 patients.

	Duration, median (range)	
	< 6 months (n = 69)	≥ 6 months (n = 121)
Duration of observed treatment with everolimus, months	7.5 (4.9–11.1)	7.4 (4.8–10.9)
Time since initial diagnosis of RCC, years	2.1 (0.4–20.7)	3.5 (0.7–22.9)
Time since initial diagnosis of mRCC, years	0.9 (0.1–13.9)	2.2 (0.3–15.8)
Duration of last therapy before everolimus, months	4.0 (0.0–156.4)	19.0 (6.0–186.1)

mRCC = Metastatic renal cell carcinoma.

Table 3. Previous duration of VEGF-targeted therapy subanalysis – patient demographics

Table 4. Termination of participation in the study (total population, n = 196)

Parameter	n (%)
Patients with termination	136 (69)
Reasons for termination ^a	
Progress	69 (35)
Death	21 (11)
Adverse event	35 (18)
Patient's wish	18 (9)
Patient did not reappear	9 (5)
Lack of efficacy	7 (4)
Consent withdrawn	5 (3)
Everolimus dose at time of termination ^b	
10 mg	104 (85)
5 mg	18 (15)
Subsequent treatment	
Sunitinib	17 (29)
Sorafenib	24 (41)
Pazopanib	8 (14)
Temsirolimus	4 (7)
Interferon	1 (2)
Vinblastine	2 (3)
Other	3 (5)

^aMore than 1 answer per patient possible.

^bMissing data for 14 patients.

Table 5. Adverse events reported in at least 5% of 195 patients (safety population, n = 195)

Event	Patients, n (%)		
	adverse event ^a	serious adverse event	severe adverse event (grade 3/4)
Dyspnea	27 (14)	5 (3)	8 (4)
Anemia	25 (13)	8 (4)	6 (3)
Nausea	18 (9)	3 (2)	6 (3)
Pain	17 (9)	5 (3)	8 (4)
Stomatitis	16 (8)	1 (<1)	3 (2)
Cough	14 (7)	1 (<1)	3 (2)
Pruritis	12 (6)	1 (<1)	1 (1)
Peripheral edema	11 (6)	1 (<1)	0 (0)

^aSerious and non-serious events.

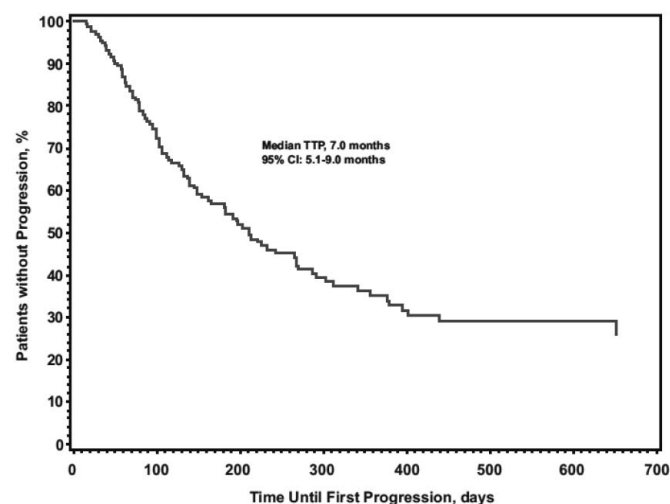


Fig. 1. Median time to progression (TTP) in the efficacy population.

been discontinued in the remaining patients due to disease progression (35%), adverse events (AEs, 18%), death (11%), or other reasons (table 4). Among 136 patients who had discontinued everolimus treatment at the time of analysis, 59 patients (45%) received additional anticancer treatment after everolimus, most commonly a VEGFr-TKI such as sorafenib, sunitinib, or pazopanib. In the efficacy population (n = 165), median TTP after initiation of everolimus was 7.0 months (95% CI 5.1–9.0 months) (fig. 1). Results were similar in patients who received exactly 1 previous VEGFr-TKI (n = 121) (median TTP 7.1 months; 95% CI 5.5–9.0 months). In a sub-analysis of the efficacy population by duration of prior therapy (fig. 2), median TTP was 6.6 months (95% CI 3.8 months–not reached) among patients who had received < 6 months previous VEGF-targeted therapy (n = 68) and 7.4 months (95% CI 4.6–9.6 months) in patients who had received prior VEGF-targeted therapy for ≥ 6 months (n = 93). At the time of this analysis, median OS had not been reached for any population.

Safety

Among the safety population, 136 patients (70%) developed at least one AE, with 67 patients (34%) experiencing a total of 148 serious AEs (SAEs), 114 patients (58%) experiencing at least 1 adverse drug reaction (ADR), and 36 patients (18%) experiencing 80 serious ADRs (SADR). Grade 3 or grade 4 AEs were reported for 67 patients (34%). 27 patients in the safety population died during treatment, with 23 deaths due to tumor progression and 4 deaths due to other causes (stroke (n = 1), surgical complications (n = 2), and renal failure (n = 1) determined not to be related to everolimus). The most commonly reported AEs of any grade were dyspnea (14%), anemia (13%), and pain (9%), and the most frequently occurring SAEs were anemia (4%), dyspnea (3%), and pain (3%) (table 5). Pneumonitis was reported as an AE for 3% of

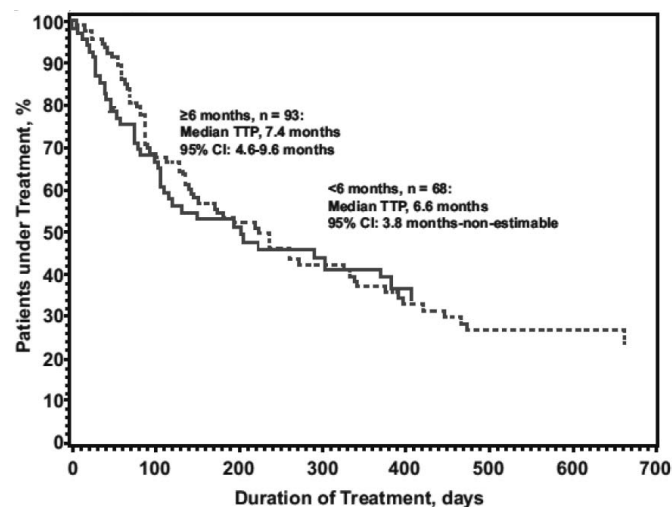


Fig. 2. Median time to progression (TTP) in the efficacy population according to duration of last VEGF-targeted therapy (< 6 months, solid line; ≥ 6 months, broken line) before everolimus.

patients and as a SAE for 2% of patients. Everolimus dose adjustments were required for 26% of the total population, and treatment interruptions were necessary for 13% (n = 26) of the patients, with a median duration of 16 days (range 5–53 days). Time to $\geq 10\%$ reduction in KPS according to Kaplan-Meier estimates was 7.3 months (95% CI 5.6–10.1 months) for the safety population. Overall, $> 75\%$ of physicians reported a high assessment of tolerance to everolimus and high degree of adherence to therapy (approximately 97%).

Discussion

Multiple targeted agents are available for the treatment of patients with mRCC, posing the question of how to best use these agents in sequence [5, 9]. Research has suggested that mechanisms of resistance to anti-VEGF therapy might partly be overcome by a consecutive VEGF-targeted agent [9]. VEGF-targeted agents available for treatment of patients with mRCC include the VEGFr-TKIs axitinib, pazopanib, sorafenib, and sunitinib and the VEGF inhibitor bevacizumab. Based on results of the phase III AXIS trial [10], axitinib was recently approved by the European Medicines Agency for treatment of patients with mRCC, who failed first-line therapy with cytokines or sunitinib [11]. Pazopanib is approved for treatment of patients with mRCC either as first-line or after cytokine therapy, and is currently being evaluated in a phase II trial of VEGFr-TKI-refractory patients with mRCC (*clinicaltrials.gov* identifier NCT01157091). These results may offer increased insight into sequential VEGFr-TKI treatment. Availability of compounds with different modes of action provides the opportunity to change mechanistic classes with different lines of treatment. The mTOR inhibitor everolimus is approved for treatment of patients with mRCC, who failed initial VEGFr-TKI therapy, based on results of the phase III RECORD-1 trial which demonstrated the efficacy of everolimus in this patient population [3]. Temsirolimus is available for first-line treatment of patients with mRCC, who are of poor prognosis. Clinical trials evaluating sequential treatment with VEGFr-TKIs agents versus mTOR inhibitors in a direct head-to-head fashion will further inform physicians and patients about treatment choices after first-line treatment with a VEGFr-TKI. The INTORSECT trial recently revealed that temsirolimus offers no significant benefit over sorafenib in patients who failed first-line therapy with sunitinib (*clinicaltrials.gov* identifier NCT00474786) [12]. The RECORD-3 trial is currently assessing the sequences of everolimus and sunitinib versus sunitinib and everolimus in treatment-naïve patients with mRCC (*clinicaltrials.gov* identifier NCT00903175). In addition, clinical experience has shown that changing the mode of action, such as sequential treatment with a VEGFr-TKI, an mTOR inhibitor, and a VEGFr-TKI, is clinically beneficial [13, 14].

This NIS represents the first systematic evaluation of everolimus in routine use among patients with advanced RCC after failure of 1 VEGF-targeted therapy. Treatment with everolimus was associated with a median TTP of 7.0 months in this NIS. Although the end points cannot be directly compared, a median PFS (RECIST) of 4.9 months (central review) or 5.5 months (investigator assessment) was reported in the placebo-controlled, phase III RECORD-1 study [3]. The longer TTP associated with everolimus in this NIS could have resulted from the subjective definition of progression.

A pre-planned subgroup analysis of RECORD-1 demonstrated that treatment with 2 previous VEGFr-TKIs was associated with a shorter median PFS for everolimus than treatment with 1 previous VEGFr-TKI (4.0 months compared with 5.4 months, respectively) [15]. Patients treated only with sunitinib before everolimus exhibited a median PFS of 4.6 months in post hoc analysis of RECORD-1 [15]. In this NIS, 73% of patients received exactly 1 previous VEGFr-TKI, which correlated with a median TTP of 7.1 months.

The duration for which a patient had received VEGF-targeted therapy (< 6 months or ≥ 6 months) did not appear to affect the duration a patient would receive everolimus. Median TTP with everolimus was longer for patients who had a longer duration of previous VEGF-targeted therapy, suggesting that patients who benefit from a long duration of previous VEGF-targeted therapy may also experience slightly prolonged benefit from everolimus. This observation is in line with a previous report showing that prolonged PFS with first-line VEGFr-TKI therapy may predict improved survival with everolimus [16]. In contrast, short treatment durations with VEGF-targeted therapy and everolimus may be attributable to aggressive tumor biology of the underlying disease.

The safety profile of everolimus in this NIS was consistent with previous reports [3, 17, 18], and everolimus was well tolerated in the majority of patients. In RECORD-1, 7% of patients required ≥ 1 everolimus dose reduction and 38% required treatment interruption [3]. In this study, dose adjustment was more common (26%), but fewer patients required treatment interruption (13%), suggesting that dose adjustment is effective in a routine clinical setting to manage everolimus-related toxicity.

The incidence of all AEs was considerably lower in this NIS compared with clinical studies of everolimus. Possible reasons for the lower incidences of AEs reported in routine clinical practice are under-reporting by participating physicians compared with clinical trials, frequency of follow-up visits, growing experiences with the use of everolimus in patients with mRCC, and less severe disease status. Other limitations of this NIS include the limited median follow-up time compared with the calculated treatment duration and TTP, verification of source data for 25% of patients, and that interventions in terms of pre-specified procedures such as visit scheduling or imaging could not be defined due to the observational nature of the study. Although the non-interventional

character of a NIS results in limited data quality compared with a clinical trial, crucial insights into the value of everolimus in the treatment of mRCC can be gained by this tool for structured evaluation of routine medical care.

Conclusion

This NIS interim analysis adds evidence from daily medical practice to support the favorable benefit/risk profile of everolimus as reported from the randomized RECORD-1 phase III study. Physicians should be aware that prolonged duration of previous VEGF-targeted therapy may lead to longer median TTP for their patients with mRCC, who failed initial VEGF-targeted therapy and subsequently received everolimus; the safety profile of everolimus is consistent regardless of previous treatment duration. Results of this NIS provide evidence of the safety and effectiveness of everolimus use in routine clinical practice for treatment of patients with mRCC, who failed initial VEGF-targeted therapy.

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