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Updated Results of a Prospective Noninterventional Study of Everolimus After Failure of the First VEGF-Targeted Therapy

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BACKGROUND

- In recent years, multiple targeted agents have been approved for the treatment of patients with metastatic renal cell carcinoma (mRCC), including the vascular endothelial growth factor (VEGF) receptor–tyrosine kinase inhibitors (VEGFr-TKIs) sunitinib, sorafenib, and pazopanib, the combination of the anti-VEGF monoclonal antibody bevacizumab with interferon-α, and the mammalian target of rapamycin (mTOR) inhibitors everolimus and temsirolimus
- Most patients with mRCC receive a VEGF-targeted therapy in the first-line setting; however, durable responses are rare,[1-3] and subsequent therapy is needed
- The international, randomized, double-blind, placebo-controlled RECORD-1 phase 3 trial established the safety and efficacy of the mTOR inhibitor everolimus in patients with mRCC who have progressed on previous VEGFr-TKI therapy[4,5]
  - Everolimus significantly improved median progression-free survival (PFS) compared with placebo (4.9 months vs 1.9 months; hazard ratio, 0.33; 95% CI, 0.25-0.43; *P* <.001) and doubled the rate of disease stabilization according to RECIST (67% vs 32%)[5]
  - A subgroup analysis of RECORD-1 patients who had recieved only 1 previous VEGFr-TKI showed a longer median PFS (5.4 months)[6]
  - Adverse events (AEs) associated with everolimus therapy were predictable, mostly low grade, medically manageable, and reversible with no decrease in dose required in most patients
- Current clinical practice guidelines uniformly recommend use of everolimus in patients who progress after initial VEGFr-TKI therapy[7-10]
  - However, prospective data on the efficacy and safety of everolimus following the first VEGFr-TKI treatment have yet to be reported
  - Data on the use of everolimus in routine clinical practice also are limited
- To assess the effectiveness and safety of everolimus after the first anti-VEGF therapy in routine clinical practice, we conducted a noninterventional study
- Herein, we present results of the second preplanned interim analysis of patients treated with everolimus after failure of a single VEGFr-TKI or other targeted anti-VEGF therapy

PATIENTS AND METHODS

Study Design and Patient Population

- This is a prospective, multicenter, noninterventional, observational study of everolimus administered per routine clinical practice in Germany
  - Patient accrual occurred between August 2009 and January 2012. A total of 382 patients was documented in 132 centers
- Patients with mRCC of any histology were documented when the physician intended to treat with everolimus following failure of 1 targeted anti-VEGF therapy (ie, either a VEGFr-TKI or bevacizumab)
  - Patients could be documented if everolimus was initiated <90 days previously or the patient had received ≤1 imaging analysis since everolimus initiation
- Everolimus was used according to the approved product label in Europe[11]
  - Patients were administered everolimus 10 mg once daily until disease progression or unacceptable toxicity
  - Dose interruptions and/or dose reduction to 5 mg/day could be used to manage side effects
- This noninterventional study was initiated to determine the effectiveness of everolimus in routine clinical practice, defined as the time between first everolimus intake to progression (TTP) due to any cause
- Other points of investigation included duration of everolimus treatment, best overall response according to the treating physician, adherence, treatment after everolimus, and safety and tolerability
- AEs of any grade and serious AEs were collected and coded to a preferred term using the Medical Dictionary for Regulatory Activities (MedDRA)
- The planned study enrollment was 360 patients, and enrollment was terminated according to the observational plan on January 20, 2012
  - Per the observational plan, the first interim analysis was performed after the enrollment of 100 patients who were followed for ≥3 months
  - The second interim analysis (reported here) was performed after the patients analyzed in the first interim analysis were followed for another 10 months
- Patient populations analyzed in this second interim analysis were:
  - Total population: All patients documented at baseline for at least 3 months prior to analysis
  - Safety population: All patients from the total population who had documented intake/prescription of everolimus and ≥1 postbaseline assessment
  - Efficacy population: All patients from the safety population who were documented before or <90 days after initiation of everolimus treatment and had received a single VEGFr-TKI or a second VEGFr-TKI for ≤1 month before everolimus
  - 1 prior VEGFr-TKI population: All patients from the efficacy population who were treated with 1 prior VEGFr-TKI

RESULTS

Demographics and Disease Characteristics

- Between August 2009 and September 30, 2011, 196 patients with mRCC had been followed for at least 3 months at 79 German sites and comprised the total population; other populations included in the analysis were the:
  - Safety population, n = 195
  - Efficacy population, n = 165
  - 1 prior VEGFr-TKI population, n = 121
- Patients had been followed for a median time of 142 days (range, 9-665 days) at the time of the second interim analysis (data cutoff: September 30, 2011)
  - 186 patients were enrolled before everolimus initiation
  - 1 patient did not receive everolimus treatment
  - 10 patients met the criteria for enrollment after everolimus initiation
  - 20 patients had received ≥2 VEGFr-TKIs before everolimus initiation
- Baseline patient demographics and disease characteristics are shown in **Table 1**
  - The majority of patients enrolled (72%) had received only 1 previous antineoplastic therapy
- The most common previous targeted anti-VEGF therapy was sunitinib (80%), with a median treatment duration of 9 months (**Table 2**)

Table 1. Baseline Demographics and Disease Characteristics of the Total Population

	Total Population N = 196
Age, median (range), y	66 (22-89)
Sex, n (%)	
Male	147 (75)
Female	49 (25)
Clear-cell histology, n (%)[a]	170 (87)
Karnofsky performance status, median (range)	80 (50-100)
Time since mRCC diagnosis, median (range), y	1.8 (0-16)
MSKCC risk status at start of first-line therapy, n (%)	
Favorable	45 (32)
Intermediate	85 (61)
Poor	10 (7)
Number of previous antineoplastic therapies, n (%)	
1	141 (72)
2	44 (22)
≥3	11 (6)

mRCC, metastatic renal cell carcinoma; MSKCC, Memorial Sloan-Kettering Cancer Center.
[a]Based on 185 patients for whom information on tumor histology was available.

Table 2. Previous Therapy in the Total Population (N = 196)

Previous Therapy[a]	Patients, n (%)	Duration of Treatment, Median (Range), months
Sunitinib	156 (80)	9 (0-49)
Sorafenib	45 (23)	6 (0-41)
Bevacizumab[b]	22 (11)	4 (1-21)
Cytokines[c]	37 (19)	7 (0-104)

[a]Patients could have received multiple previous therapies and could have received a second VEGFr-TKI for a maximum duration of 1 month before initiating everolimus treatment.
[b]Given as monotherapy in 6 patients and as part of combination therapy in 16 patients.
[c]Excludes patients who received cytokines in combination with bevacizumab.

Patient Disposition

- At the time of the second interim analysis, 60 patients in the safety population remained on treatment; the remaining 135 patients (69%) had discontinued treatment at the time of the analysis
  - The most common reasons for discontinuation were disease progression (35%), AEs (18%), and death (11%) (**Table 3**)
  - Of the 131 patients for whom information was available, 59 patients (45%) went on to receive additional targeted therapy after everolimus, which was most frequently a VEGFr-TKI (sunitinib or sorafenib) (**Table 4**)
- Median duration of everolimus treatment in the total population was 6.7 months (95% CI, 4.9-9.8 months) (**Figure 1**)
  - Median duration of everolimus treatment was 6.7 months (95% CI, 4.9-9.8 months) in the safety population, 7.3 months (95% CI, 4.7-10.9 months) in the efficacy population, and 7.5 months (95% CI, 4.9-11.1 months) in patients who previously received 1 VEGFr-TKI

Table 3. Reasons for Discontinuation of Everolimus in the Safety Population (n = 195)

Reason[a]	Patients[b], n (%)
Disease progression	69 (35)
Adverse event(s)	35 (18)
Death	21 (11)
Patient request	18 (9)
Lost to follow-up	9 (5)
Lack of efficacy	7 (4)
Withdrawal of consent	5 (3)

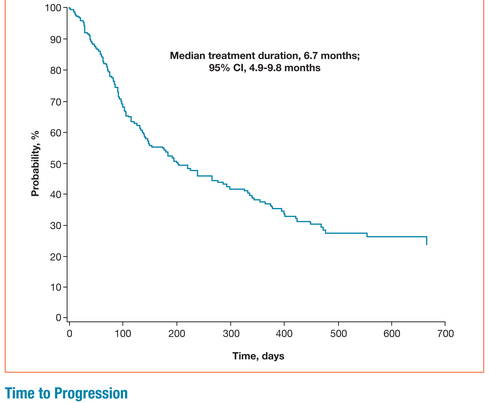
[a]Patients could have stopped therapy for multiple reasons.
[b]At the time of the analysis, 135 patients had discontinued treatment.

Table 4. Therapy After Discontinuation of Everolimus (n = 59)

Therapy[a, b]	Patients, n (%)
Sorafenib	24 (41)
Sunitinib	17 (29)
Pazopanib	8 (14)
Temsirolimus	4 (7)
Bevacizumab	2 (3)
Other	5 (8)

[a]Patients could have received multiple therapies.
[b]Based on data from 131 patients for whom information about subsequent treatment was available.

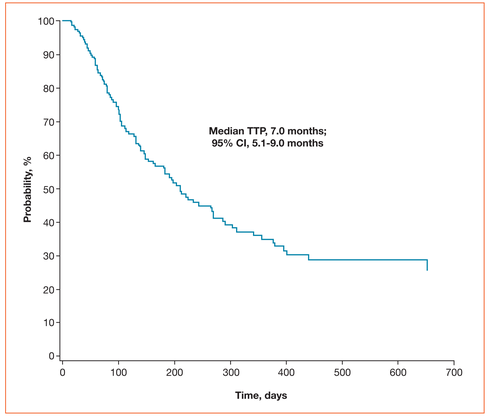
Figure 1. Median duration of everolimus treatment in the total study population (N = 196).



Time to Progression

- Median TTP in the safety population (n = 195) was 6.6 months (95% CI, 5.0-8.8 months)
- Median TTP in the efficacy population (n = 165) was 7.0 months (95% CI, 5.1-9.0 months) (**Figure 2**)
- Median TTP in patients who previously received only 1 VEGFr-TKI (n = 121) was 7.1 months (95% CI, 5.5-9.0 months)

Figure 2. Median time to progression (TTP) in the efficacy population (n = 165).



Safety

- In the safety population (n = 195), 136 patients (70%) experienced a total of 600 AEs
  - 67 patients (34%) experienced a total of 148 serious AEs, 114 patients (58%) experienced 417 adverse drug reactions, and 36 patients (18%) experienced 80 serious adverse drug reactions. In comparison, serious AEs were reported in 40.1% of patients in the everolimus arm of the RECORD-1 trial[12]
  - 27 patients died on treatment: 23 due to tumor progression and 4 due to other causes (stroke [n = 1], surgical complications [n = 2], renal failure determined not to be related to everolimus [n = 1])
  - Most commonly reported AEs of any grade and severe AEs are shown in **Table 5**
- Dose adjustment was required in 26% of patients, and treatment interruption in 13% (n = 26), with a median duration of treatment interruption of 16 days (range, 5-53 days). Compared with the everolimus arm of the RECORD-1 trial, 7% of patients had at least 1 dose reduction and 38% of patients had at least 1 treatment interruption[5]
- Overall, >75% of physicians reported a high assessment of tolerance to everolimus and high adherance to therapy
- The majority of physicians (57%) reported a positive assessment of tolerance after everolimus discontinuation

Table 5. Adverse Events That Occurred in >5% of Patients in the Safety Population (n = 195)

Adverse Event	Any Grade, n (%)	Severe, n (%)
Dyspnea	27 (14)	8 (4)
Anemia	25 (13)	7 (4)
Nausea	18 (9)	5 (3)
Pain	17 (9)	8 (4)
Stomatitis	16 (8)	3 (2)
Cough	14 (7)	3 (2)
Fatigue	14 (7)	4 (2)
Pruritis	12 (6)	1 (1)
Peripheral edema	11 (6)	0

CONCLUSIONS

- **Relative to the first interim analysis,[13,14] this second preplanned interim analysis of the first prospective, multicenter, noninterventional study of everolimus in patients with mRCC had longer duration of patient follow-up and an increased number of patients enrolled. This enabled the determination of median TTP in patients who previously received 1 VEGFr-TKI, which had not been reached at the time of the first interim analysis.**
- **In patients treated with 1 previous VEGFr-TKI, everolimus was associated with a median TTP of 7.1 months (95% CI, 5.1-9.0 months).**
- **These interim results suggest that median TTP with everolimus in routine clinical practice is longer than median PFS (4.9 months)[5] of all patients in the everolimus arm of the phase 3 RECORD-1 trial as well as median PFS of the subgroup of everolimus-treated RECORD-1 patients who received only 1 previous VEGFr-TKI (5.4 months).[6]**
- **The prolonged TTP observed in this study may be because the majority of patients (72%) received everolimus as second-line therapy, whereas in RECORD-1, 21% of patients received everolimus as second-line therapy.[5]**
- **The safety profile of everolimus observed in this study is consistent with that observed in the RECORD-1 trial,[4,5] and everolimus was well tolerated in the majority of patients.**
- **These interim findings support the use of everolimus for patients with mRCC who have failed a single VEGF-targeted therapy (ie, VEGFr-TKI or bevacizumab + interferon-α).**

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