Final Results of a Non-Interventional Study Evaluating the Quality of Life in Second-line Treatment of Metastatic Renal Cell Carcinoma With Everolimus: The EVERPRO Study

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Keywords
Renal cell carcinoma · Everolimus · Targeted therapy · QoL

Introduction

The approval of targeted drugs has been a milestone in the therapy of metastatic renal cell carcinoma (mRCC). Vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR-TKIs) have shown clinical benefit for patients with treatment naïve or cytokine-pre-treated RCC by extending progression-free survival (PFS) or overall survival (OS) [1, 2]. Further increase in the prolongation of median OS is possible with sequential treatment of targeted drugs after the first-line therapy with VEGFR-TKIs [3]. Activation of the mammalian target of rapamycin (mTOR) pathway as a potential resistance principle of tyrosine kinases provides a rationale for...
of the patients with mRCC after the failure of VEGF-targeted therapy was a standard treatment option as recommended by international guidelines [8, 9]. The approval of new TKIs and immunotherapeutic agents for the second-line treatment of mRCC, since the start of the study, limits everolimus use in the second-line treatment; however, everolimus is still a valid treatment option in this setting [9–11].

The improvement in survival based on continuous treatment requires in-depth analysis of patient’s quality of life (QoL) in order to assess the risk-benefit ratio, especially in the second-line treatment [12]. Therefore, Cella and coworkers recommended measuring QoL in the second-line treatment of mRCC [13].

To gain more insight into QoL of the patients during the second-line treatment with everolimus under routine conditions, this study aimed to assess the following: (a) QoL using patient-reported outcome (PRO) questionnaires; (b) time burden due to medical visits/activities; (c) QoL based on time burden; (d) analysis of treatment sequences; (d) adverse events (AEs) during routine care with everolimus; and (e) time from baseline to progression.

Patients and Methods

Study Design

EVERPRO (evaluation of quality of life in second-line treatment with everolimus in patients with mRCC) was a prospective, single-arm, non-interventional study of second-line everolimus administered per routine clinical practice in patients with mRCC from registered sites in Germany. This non-interventional study was performed as a multicenter study in 75 oncological centers.

Patients and Treatment

Adult patients (aged ≥18 years) with mRCC, who had previously received no more than 1 drug for the treatment of RCC followed by the physician’s decision to treat with everolimus, were included in the study. Patients were ineligible if they were participating in an interventional clinical trial at the same time. The planned enrollment was 350 patients in up to 150 centers; due to slow patient accrual, the study was terminated after 209 patients (in 75 active centers).

Everolimus was used according to the approved product label in Europe. Patients received everolimus 10 mg once daily orally until disease progression or unacceptable toxicity occurred. The dose interruptions and/or reductions to 5 mg/day were allowed to manage side effects.

Analysis populations were defined as total population (all eligible patients documented at baseline) and analysis population (all patients of the total population with documented evidence of everolimus intake and at least 1 documented information under treatment). To get conclusive results, the observation period of this study was equivalent to the treatment duration with everolimus; hence, the study ended 12 months after the inclusion of the last patient in this study. Patient observation period started in July 2012 and ended in September 2016. Patient records, the patient registration form, and questionnaires for assessment of QoL were used as data sources. All data including AEs were documented in the electronic case report form (eCRF).

Assessment of HRQOL

The primary objective of the study was to assess the health-related QoL (HRQOL). HRQOL was assessed using National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy-Kidney Symptom Index 19 (NCCN-FACT FKSI-19) questionnaire and distance- and treatment time (DTT) questionnaire. NCCN-FACT FKSI-19 covered 4 subscales of the FKSI (DRS-P, disease-related symptoms subscale–physical; DRS-E, disease-related symptoms subscale–emotional; TSE, treatment side effects subscale; FWB, function and well-being subscale) [12]. The higher the subscores or the total score, the better is the QoL. The subscales were evaluable, if at least 50% of respective items were answered. The FKSI-19 questionnaire as a whole (= total score) was evaluable, if all subscales were evaluable and at least 80% of all items were answered. Valid observations were patients who filled out the questionnaires in such a way that questionnaires were evaluable with regard to the respective subscale or total score. Based on a report by Rao and colleagues [12] that takes into account minimally important differences (MIDs), a change plus or minus 6 points was considered

MID (minimally clinically relevant change) + (improvement) MID (deterioration) scored.

DTT questionnaire included the collection of data related to the time burden for visits at the treating physician or at the hospital (ambulatory or in-house), home visits, services of caretakers, phone contacts, and further measures. The time required includes the total time spent for visits at the physician’s place, visits at home, other contacts to physician, hospital visits, stays in rehabilitation clinics, and further therapeutic measures. The documentation of findings and patient questionnaires was collected at the study inclusion, and after 1, 2, 4, 6, 8, 10, and 12 months and so on, and at the treatment end. The distance- and time questionnaire was skipped at the inclusion into the study and at the documentation time point after 1 month. The FKSI-19 was skipped at 1 month after the inclusion.

The secondary objectives of the study included the analysis of treatment sequences (treatments before and after everolimus), du-
ration of treatment with everolimus, time to progression (TTP), PFS (time from baseline to progression or death), and safety profile of everolimus.

**Data Sources and Statistical Analysis**

Physicians collected patient information in the eCRF. iOMEDICO provided the required software, iostudy office edc, developed for recording of data and adapted to study needs. This software was password protected, validated, and certified according to ISO 9000:2001. An audit trail was available. All the findings recorded in the eCRF were transferred online into the study database at iOMEDICO AG. Transfer of data from the questionnaire into the database was tested and validated before study start. The parameters recorded in the eCRF were demographics, Karnofsky performance index (KPI), anamnesis of primary diagnosis (date, TNM classification, histological subtype, localization of tumor, Memorial Sloan Kettering Cancer Center [MSKCC] score at first-line), anamnesis of first appearance of metastasis (date, site of metastasis), number of resected and involved lymph nodes.

The coding of AEs was performed according to the Medical Dictionary for Regulatory Activities version 17.0 or higher and graded using the Common Terminology Criteria for Adverse Events version 4.03 [14]. For all serious AEs (SAEs), the potential causal relation to everolimus was assessed and documented by the treating physician. In the case that no information regarding potential relation was provided, a causal relationship to everolimus was assumed. All AEs were documented starting with the first administration of everolimus (independent of causality) until 30 days after the end of treatment.

The statistical analyses were performed using statistical version 10 (StatSoft Europe GmbH), SAS version 9.4, and statistics programme R, version 2.15.1 (www.r-project.org) and was based on the guidelines of the Committee for Proprietary Medicinal Products, "Biostatistical Methodology in Clinical Trials," and the ICH guidance E9 "Statistical Principles for Clinical Trials".

**Results**

**Patient Demographics**

A total of 209 patients from 75 sites were included in the study; for whom, the inclusion visit was documented. The safety population as well as the efficacy population

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**Table 1. Baseline characteristics of analysis population (n = 202)**

| Characteristics                                      | n = 202 |
|------------------------------------------------------|---------|
| Age, median years (range)                            | 71 (23–88) |
| Male, n (%)                                          | 153 (76) |
| KFI at study entry (n = 121), median index (range)    | 80 (50–100) |
| Localization of tumor, n (%)                         |                     |
| Left                                                 | 112 (55.4) |
| Right                                                | 89 (44.1) |
| Both sides                                           | 1 (0.5) |
| Clear cell histology, n (%)                          | 164 (81.2) |
| MSKCC risk state at first-line therapy, n (%)        |                     |
| High                                                 | 23 (11) |
| Medium                                               | 65 (32) |
| Low                                                  | 35 (17) |
| Unknown                                              | 79 (39) |
| Tumor stage (TNM at initial diagnosis), n (%)        |                     |
| I (T1, N0, M0)                                       | 20 (10) |
| II (T2, N0, M0)                                      | 16 (8) |
| III (T2, T3, N0, N1, M0)                             | 31 (15) |
| IV                                                   | 83 (41) |
| Not classified                                        | 52 (26) |
| Local recurrence                                     |                     |
| Yes                                                  | 36 (18) |
| No                                                   | 165 (82) |
| Unknown                                              | 1 (<1) |
| Synchroné metastases, n (%)                          | 71 (35) |
| Metachroné metastases, n (%)                         | 131 (65) |
| Patients with prior nephrectomy, n (%)               | 185 (92) |
| Patients without prior nephrectomy, n (%)            | 17 (8) |
| Comorbidities, n (%)                                 |                     |
| ≥1                                                   | 154 (76) |
| No                                                   | 48 (24) |
| Unknown                                              | 0 |

KFI = Karnofsky performance index, MSKCC = Memorial Sloan Kettering Cancer Center, TNM = classification of malignant tumors.

* Classification according to the European Association of Urology guidelines on renal cell carcinoma, update 2013 [21].
First-line | Number of patients | Number of patients (Observation) | Third-line (Planned) |
|-----------|-----------------|-------------------------------|---------------------|
| Sunitinib | 123             | Everolimus                    | Axitinib            |
| Pazopanib | 51              | Everolimus                    | Sorafenib           |
| Sorafenib | 10              | Everolimus                    | Sunitinib           |
| BEV + IFN | 15              | Everolimus                    | Pazopanib           |
| 3 patients used other therapy |

**Fig. 2.** Therapy sequences for analysis population (n = 202). BEV = bevacizumab, IFNα = interferon alpha.

![Graph showing PFS in analysis population (n = 202).](image)

**Fig. 3.** PFS in analysis population (n = 202).

![Graph showing FKSI-19 total score in analysis population (n = 179). Data for 23 patients are missing.](image)

**Fig. 4.** FKSI-19 total score in analysis population (n = 179). Data for 23 patients are missing.
involves 202 patients (analysis population); for whom, at least 1 prescription of everolimus was documented and at least 1 further information under therapy was available (fig. 1).

The median observation time (the first prescription of everolimus until the last contact or death) was 6.41 months (95% CI, 5.69–8.05). The number of patients declined to 164 at 2 months after the inclusion visit. At month 10 patient number decreased to 41 patients, at month 16 to 20 patients, at month 20 to 12 patients and after month 24, the number dropped to <10 patients. The baseline characteristics of the analysis population are shown in table 1.

Therapy Sequences

Of the 202 patients, 171 (84.7%) completed the therapy with everolimus by the end of their individual observation period of 12 months. Further therapy was planned for 103 patients, and the planned therapy sequences post everolimus treatment for these patients are shown in figure 2.

Exposure

The median duration of everolimus treatment for the analysis population was 4.4 months (95% CI, 3.8–5.3). The median absolute dose intensity for patients with a documented date therapy end (n = 189) was 62.6 mg/week (range, 5.5–70 weeks), and the median relative dose intensity was 89.4% (range, 7.9–100%).

Efficacy

The median TTP for the analysis population was 6.0 months (95% CI, 5.4–7.5). After stratifying the patients based on the duration of first-line therapy, the median TTP did not differ markedly between the groups. The median PFS was 5.7 months (95% CI, 4.8–7.1) (fig. 3); the PFS results of subgroup analyses based on MSKCC risk, histology, response to first-line treatment, and the duration of first-line treatment were not conclusive. The summary of events is shown in table 2.

Safety

Overall, 167 patients (82.7%) experienced 804 AEs in total including 314 SAEs. The most commonly reported AEs were malignant neoplasm progression (17%), dyspnea (16%), fatigue (14%), and anemia (14%) (table 3). 69 patients (34.2%) discontinued due to an AE, of these, 29 (14%) were considered to be related to everolimus. Of the total AEs, 347 were known to be treatment related including 287 grade 1 or 2 and 49 grade 3 or 4 AEs, respectively. A total of 118 patients (58.4%) experienced 314 SAEs, of

### Table 2. Summary of events in analysis population (n = 202)

|                          | Duration of therapy | TTP | PFS |
|--------------------------|---------------------|-----|-----|
| Censoring                | if no documentation of end of therapy or death in eCRF | if no documentation of progression | if no documentation of progression or death |
| Time of censoring        | last known intake of everolimus | date of last contact | date of last contact |
| Total patients           | 202                 | 202 | 202 |
| Censored, n (%)          | 30 (14.9)           | 80 (39.6) | 55 (27.2) |
| Not censored, n (%)      | 172 (85.1)          | 122 (60.4) | 147 (72.8) |
| Duration                 | 4.4 (3.8–5.3)       | 6 (5.4–7.5) | 5.7 (4.8–7.1) |
| Median (95% CI), months  | Upper quartile      | 3.6 (3–4.3) | 3.4 (2.5–3.9) |
|                         | 2.3 (1.9–2.7)       | 15.2 (10.7–23.2) | 12.2 (8.8–15.4) |
|                         | Lower quartile      | 8.7 (7.1–11.6) |  |

CI = confidence interval, eCRF = electronic case report form, PFS = progression-free survival, TTP = time to progression.

### Table 3. Adverse events occurring in ≥4% of patients in the analysis population (n = 202)

|             | All grades (n = 202) | Grade 3 or 4 (n = 202) |
|-------------|---------------------|-----------------------|
| Patients with adverse event (any event) | 167 (83) | 71 (35) |
| Malignant neoplasm progression | 34 (17) | 5 (3) |
| Dyspnea | 33 (16) | 6 (3) |
| Fatigue | 29 (14) | 3 (1) |
| Anemia | 28 (14) | 10 (5) |
| Diarrhea | 20 (10) | 2 (1) |
| Edema peripheral | 19 (9) | 1 (<1) |
| Nausea | 19 (9) | 2 (1) |
| Cough | 18 (9) | 0 |
| Stomatitis | 18 (9) | 2 (1) |
| Rash | 16 (8) | 0 |
| Decreased appetite | 15 (7) | 0 |
| General physical health deterioration | 14 (7) | 4 (2) |
| Back pain | 14 (7) | 6 (3) |
| Epistaxis | 13 (6) | 0 |
| Pleural effusion | 13 (6) | 4 (2) |
| Weight decreased | 12 (6) | 2 (1) |
| Pain | 11 (5) | 3 (1) |
| Pyrexia | 11 (5) | 0 |
| Pneumonitis | 11 (5) | 1 (<1) |
| Mucosal inflammation | 8 (4) | 1 (<1) |
| Vomiting | 8 (4) | 0 |
| Pruritus | 8 (4) | 0 |
| Hyperglycemia | 8 (4) | 6 (3) |

Table 2. Summary of events in analysis population (n = 202)

Table 3. Adverse events occurring in ≥4% of patients in the analysis population (n = 202)
which, 100 SAEs (12.4% of 804 AEs) in 58 patients were assessed as being related to treatment with everolimus. 42 patients (20.8%) died during the study including 7 deaths, which were assessed to be related to everolimus.

**Patient-Reported Outcomes**

**Evaluation of QoL**

A total of 692 of 1021 questionnaires provided to patients (67.8 ± 9.4%) were filled and returned to the physicians. The mean proportion of missing items in the whole questionnaire was 4.7% and was higher in the DTT questionnaire compared to the FKSI-19 (8.4% ± 12.6% vs. 1.7% ± 6.5%). The median FKSI-19 total score remained stable during the treatment (52.0 at therapy start, 55.0 at observation end) (fig. 4).

FKSI-19 subscales were DRS-P, DRS-E, TSE, FWB. The median score for DRS-P was 36.0 at baseline and 37.5 at the end of observation with a maximum score of 48. The maximum median improvement as compared to baseline was 3.4 points at month 16 and the maximum median change for the worse was -3 points at month 4, 6, 8 and 28. The median score for DRS-E was 2.0 at baseline and 1.0 at the end of observation with a maximum score of 4. There were only small changes in scores throughout the study, mainly after month 16. No change for the worse was reported during the course of the study, the maximum median improvement was 4.0 points at month 40.

Median scores for TSE were 10.0–12.0 throughout the observation period, with a median score of 9.0 at the end of observation with a maximum score of 12. There were no changes for the worse during the observation time and the maximum median improvement was 2.5 points at month 18. Median scores for FWB were between 5.0–10.5 throughout the observation period with a median score of 6.0 at the end of the observation period and a maximum score of 12. As compared to the median score at the inclusion visit, the maximum median improvement was 3.0 points at month 18, 22, 36 and thereafter. The maximum median decrease was −3.0 points recorded at month 34.

Altogether, the median change in total score increased slightly until month 24 with a maximum improvement of 8.4 points at month 16 as compared to the inclusion visit. The median change in total FKSI-19 score, overall/obs- tive response rate (ORR) and disease control rate (DCR) by month is shown in figure 5.

**Questionnaire of Time Burden Due to Medical Visits/Activities and Expenditure of Time Measured in Hours**

During the entire study duration, a median of 20.0 h was spent for therapy by each patient (0.0–2465.0 h; n = 191 observations, data of 11 patients missing) (fig. 6a). In total, 72.3% of the patients reported that they had visited a physician at least once; 3.0% of patients reported no physician visits, and no information was available for 24.8% of patients (fig. 6b). The median number of physician visits was 11.0 visits per patient throughout the observation time (range, 0.0–108.0 visits; n = 142); the total median time spent for visiting the physician was 18.0 h (0.0–136.0 h; n = 140).

**Limitations in Daily Activities**

Most of the patients stated to have “no limitations,” “a little,” or “moderate limitations” in their daily, social, and professional lives.

At the first observation point (month 2), data regarding limitations in daily routine were available for 122 of 164 patients. 20 patients (12.2% of 164 patients) stated
**Fig. 6.**
A. Total time effort needed for therapies in analysis population (n = 191). The data of 11 patients are missing.
B. Physician consultations in analysis population (n = 202).

**Fig. 7.**
A. Limitations in daily routine in analysis population (n = 164).
B. Total score limitations in analysis population (n = 202).
that they were not limited at all, 37 patients (22.6%) assessed their limitation as “a little,” 35 patients (21.3%) stated that they were “moderately limited,” and 22 patients (13.4%) stated that they were “considerably limited.” 8 patients (4.9%) assessed their limitations as “severe.” No information was available from 42 patients (25.6%) (fig. 7a).

Limitations in daily routine decreased slightly until month 10; at the bimonthly observation points, 15.3% at month 4 (n = 124), 16.7% at month 6 (n = 84), 16.9% at month 8 (n = 59), and 17.1% at month 10 (n = 41) stated that they had no limitations and 16.9, 22.6, 25.4, and 26.8% stated that they were only “a little” limited. In addition, there were only 4.8, 3.6, 3.4, and 0.0% of patients that were severely limited at these time points. However, the number of evaluable patients decreased from 124 patients at month 4 to 41 patients at month 10, and for those, there were 25% to 30% of data missing. For 191 patients, the observation end was documented; of which, 3.7% assessed their limitations as not limited, 5.8% “a little” limited, 2.1% as moderate, 3.7% considerably limited, and 1.6% considered their limitations “severe” (fig. 7a).

Total scores were calculated based on the 4 subscores related to limitations, including limitations in the daily routine, limitations in activity, limitations in professional life, and limitation caused by time burden. The total scores decreased during the observation period; however, the number of observations is very low (fig. 7b).

Discussion

Over the past decade, there has been a significant advancement in the treatment of mRCC, with the approval of targeting agents inhibiting VEGF and mTORC1. Various studies including the randomized phase 2 RECORD-3 study [6] and the real-world non-interventional CHANGE study [5] demonstrated the benefit of switching mode of action from VEGFR to mTOR. However, HRQOL outcomes have not been sufficiently documented in patients who receive second-line everolimus. This study provides a comprehensive overview of HRQOL that patients with mRCC experience during the second-line treatment with everolimus.

The patient population included in this study is at least representative of patients with mRCC in Germany, as patients were included based on the European Medicines Agency approval status and the study sites were distributed equally. With the broad inclusion criteria, patient characteristics of the study population are in accordance with the general mRCC patient population allowing the results to be generalizable and relevant to the larger population. Therapy sequences observed during this study mirror the treatment landscape of mRCC in Germany before the approval of nivolumab, cabozantinib, and lenvatinib. Sunitinib and pazopanib appeared to be the standard treatment options in the first-line setting while bevacizumab in combination with interferon-α and sorafenib played a subordinate role.

The duration of everolimus exposure may have the impact-associated symptoms as well as HRQOL in individual patients. Patients in this study had longer everolimus treatment duration with 4.4 months (95% CI, 3.8–5.3) compared to the RECORD-1 trial [15].

The results of the current study support the use of everolimus as post VEGFR-TKI treatment option for mRCC under “real-world conditions” with comparable efficacy as noted in the clinical trials in terms of median PFS (≈5.7 months) and TTP (≈6.0 months). Regardless of the drug administered, the second-line PFS was comparatively shorter in a German RCC registry (4.3 months) [16]. Similarly, PFS was longer in this study compared to RECORD-1 (4.9 months) [15] and a little shorter than the PFS of the CHANGE study (6.9 months) [5]. Due to the non-interventional nature of the study, no predefined tumor evaluation was performed, and the data are missing for a relatively high proportion of patients, which may lead to a bias in the efficacy results.

MSKCC risk, histology, response to first-line treatment, and duration of first-line treatment were used as stratification factors for subgroup analyses. However, the results of these analyses are not conclusive. Analysis of the median time to increase or decrease in Karnofsky performance status (KPS) data was not sufficient to draw any conclusions, since most of the patients were censored very early due to missing KPI assessments.

The safety profile of everolimus was consistent with the results of prior trials and German SmPC [7]. Overall, most AEs were manageable and the risk-benefit ratio was acceptable in the context of clinical benefit in patients with a fatal disease. Commonly reported AEs that were related to everolimus were stomatitis, dyspnea, fatigue, rash, nausea, and anemia. The majority of everolimus-related SAEs were respiratory, thoracic, and mediastinal disorders that occurred in ~10% of patients. Drug-related pneumonitis, a known class effect toxicity of rapalogs, was reported in 5.4% of patients. Thus, heightened awareness on this toxicity, appropriate diagnosis and management are crucial to optimize patient safety. The lack of prespecified toxicity management guidelines may have contributed to a high percentage (34.2%) of treatment discontinuation due to AEs in this non-interventional study than RECORD-1 study (10%) [15].

Similar to the previous reports [4, 15, 17], treatment with everolimus seems to improve the QoL although this effect appears marginal; however, everolimus certainly does not exert a negative effect on QoL. All the trends re-
mained stable or showed marginal increase without any significant change even after 10 months of observation. A review on the available HRQOL data from clinical trials noted that everolimus significantly delays and reduces the degree of KPS deterioration regardless of the tumor size [18].

Questionnaires and PRO instruments used in the study covered all relevant domains of RCC. The DTT questionnaire was developed and used for the first time in this study while NCCN-FACT FKSI-19 questionnaire is a validated and widespread tool to investigate QoL of patients with RCC. Overall, about 70% of the questionnaires were returned, and the median FKSI-19 scores and also the FKSI subscores were stable till month 8; then, the trend showed an improvement in scores. Since the number of questionnaires decreased rapidly, especially after month 8, only few observations were available, which made the interpretations difficult. Therefore, it might be the case that the questionnaires collected after 10 months were completed mostly by patients who were long-term responders with a well-tolerated safety profile.

Higher scores for PROs indicated an improved well-being, which was influenced by factors related to the AE profile and effectiveness of everolimus. An important association exists in the correlation of tumor response and measures of change in PROs [19]. It was demonstrated that PRO response duration was shorter than tumor response duration suggesting that the patients might detect worsening conditions before oncologists can detect cancer progression [19]. Overall, patients with higher QoL at baseline with a FKSI-19 total score of ≥52 did better throughout the study. Herrmann et al. [20] previously noted that the global HRQOL at baseline was significantly associated with tumor response, and patients with high baseline scores achieved significantly longer median PFS than those with baseline scores less than or equal to the median score.

Limitations questionnaire analyzed the data round key 4 limitations including “limitations in daily routine,” “social activities” and “professional life,” and “time burden due to therapy.” Majority of the patients assessed their limitations as “no limitations,” “very little,” or “moderate” throughout the observation period.

Non-interventional nature of this study was the primary limitation to detect the true association of PROs. Since no predefined schedule and broad inclusion criteria were preset, the internal validity of the data collected is limited. The study did not require standardized tumor response evaluation; hence, the tumor evaluations were not uniform and were performed at the discretion of the local investigator. In order to ensure an adequate documentation quality, a sample monitoring was performed during this non-interventional study, thus leading to the high documentation quality.

In conclusion, this non-interventional EVERPRO study reflects routine use of second-line everolimus in patients with mRCC. The present authors demonstrate that the QoL is maintained during everolimus therapy, and the treatment-associated limitations as well as the time efforts are acceptable for most patients. The study supports previous findings on switching mode of action after anti-VEGFR–targeted therapy to an mTOR inhibitor. Treatment duration, efficacy and safety results are consistent with the second-line data for everolimus after VEG-RF-TKIs from prior studies and German SmPC.

**Online Supplemental Material**

**Online Supplemental Fig. 1.** Map of represented study centers in Germany.

To access the online supplemental figure, please refer to www.karger.com/?DOI=494278.

**Acknowledgments**

The results are presented on behalf of all the participating sites of the EVERPRO study. We thank the patients for their participation in this study, as well as the staff at each study site and iOMED-ICO AG (Freiburg i. Br., Germany), all of whom significantly contributed to the success of the study.

We thank Anuradha Bandaru from Novartis Healthcare Pvt Ltd for providing medical editorial assistance for this manuscript.

This study was sponsored by Novartis Pharma GmbH, Nuremberg, Germany.

**Disclosure Statement**

PJG received honoraria for participation in expert rounds and honoraria/support as a speaker from Astellas, AstraZeneca, Bayer, BMS, Eisai, Ipsen, Janssen, Novartis, Pfizer, Sanofi. CD received personal fees from Novartis, during the conduct of the study. NM was supported by grants and personal fees from Novartis, during the conduct of the study; grants and personal fees from RCC, outside the submitted work. MOG received grants and personal fees from Novartis, grants and personal fees from Bristol Myers Squibb, personal fees from Pfizer, personal fees from Bayer HealthCare, personal fees from Astellas, personal fees from Intuitive Surgical, personal fees from SanofiAventis, personal fees from Hexal, personal fees from ApoGepha, personal fees from Amgen, personal fees from AstraZeneca, personal fees from MSD, personal fees from Janssen Cilag, personal fees from Ipsen, all of them outside the submitted work. AR is an employee of Novartis. CB was consulting advisory for Novartis, BMS, Pfizer, Ipsen, Roche and received a study grant by BMS Goethe University of Frankfurt. All other authors have nothing to disclose.
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