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# Everolimus after failure of one prior VEGF-targeted therapy in metastatic renal cell carcinoma: Final results of the MARC-2 trial

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## Abstract

MARC-2, a prospective, multicenter phase IV trial, aimed to investigate clinical outcomes in patients with metastatic renal cell carcinoma (mRCC) treated with everolimus after failure of one initial vascular endothelial growth factor receptor tyrosine kinase inhibitor (VEGFR-TKI) therapy and to identify subgroups benefiting most, based on clinical characteristics and biomarkers. Patients with clear cell mRCC failing one initial VEGFR-TKI received everolimus until progression or unacceptable toxicity. Primary endpoint was 6-month progression-free survival rate (6moPFS). Secondary

**Abbreviations:** AE, adverse event; BMI, body mass index; CI, confidence interval; DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; HR, hazard ratio; mRCC, metastatic renal cell carcinoma; mTOR, mammalian target of rapamycin; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PP, per-protocol set; SAF, safety analysis set; SOC, standard of care; SmPC, summary of product characteristics; TEAE, treatment-emergent adverse event; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; 6moPFS, 6-month progression-free survival rate.

endpoints were overall response rate (ORR), PFS, overall survival (OS), and safety. Between 2011 and 2015, 63 patients were enrolled. Median age was 65.4 years (range 43.3-81.1). 6moPFS was 39.3% (95% confidence interval [CI], 27.0-51.3) overall, 54.4% (95% CI, 35.2-70.1) vs 23.7% (95% CI, 10.5-39.9) for patients aged ≥65 vs <65 years and 51.4% (95% CI, 34.7-65.7) vs 18.2% (95% CI, 5.7-36.3) for patients with body mass index (BMI) >25 vs ≤25 kg/m$^2$. A Cox proportional hazards model confirmed a longer PFS for patients aged ≥65 years (hazard ratio [HR] 0.46; 95% CI, 0.26-0.80) and a longer OS for patients with BMI >25 kg/m$^2$ (HR 0.36; 95% CI, 0.18-0.71). Median PFS and median OS were 3.8 months (95% CI, 3.2-6.2) and 16.8 months (95% CI, 14.3-24.3). ORR was 7.9% and disease control rate was 60.3%. No new safety signals emerged. Most common adverse events were stomatitis (31.7%), fatigue (31.7%), and anemia (30.2%). One patient died from treatment-related upper gastrointestinal hemorrhage. Everolimus remains a safe and effective treatment option for mRCC patients after one prior VEGFR-TKI therapy. Patients aged ≥65 years and patients with BMI >25 kg/m$^2$ benefited most.

**KEYWORDS**

6-month PFS rate, everolimus, phase IV, renal cell carcinoma, second-line

## 1 | INTRODUCTION

With the introduction of molecular targeted first-line and second-line therapies including vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR-TKIs) (sunitinib, sorafenib, pazopanib, axitinib, lenvatinib [in combination with everolimus], tivozanib, cabozantinib), VEGF-antibody (bevacizumab) and mammalian target of rapamycin (mTOR) inhibitors (everolimus, temsirolimus), treatment of metastatic renal cell carcinoma (mRCC) has markedly improved over the past decade.[1-5] Recently, novel, more specific immunotherapy agents such as immune checkpoint inhibitors (nivolumab ± ipilimumab) were introduced to systemic therapy of mRCC.[4] With the most recent approval of pembrolizumab plus axitinib for first-line mRCC treatment, a new era of combination therapies consisting of anti-PD-L1- or anti-PD1-antibodies and a VEGFR-TKI or VEGF-antibody has begun.[6,7] Owing to the broad range of approved targeted agents, especially for second-line and later line treatment, physicians are particularly faced with the challenge of choosing the optimal treatment for the individual patient. For a long time and when the present study was started, there have been no head-to-head trials available that provide information about the best second-line therapy after first-line VEGFR-TKI therapy. In addition, there remains a paucity of well-validated prognostic and predictive biomarkers to predict response to existing agents.[4,8,9] Everolimus (Afinitor) is a potent, orally administered mTOR inhibitor approved for the treatment of patients with mRCC, whose disease has progressed during or after treatment with a VEGF-targeted therapy. Approval was based on the results of the pivotal phase 3 RECORD-1 trial with a median progression-free survival (PFS) of 4.9 months compared to 1.9 months in the placebo arm (hazard ratio [HR], 0.33; $P < .001$) and a median overall survival (OS) of 14.8 months (everolimus) vs 14.4 months (placebo) (HR, 0.87; $P = .162$) in a heavily pretreated and refractory patient population after progression on sunitinib and/or sorafenib.[10] In a subgroup analysis of the RECORD-1 trial, patients who had been exposed to only one prior VEGFR-TKI, the PFS was 5.42 months in the everolimus-treated population.[11] Thus, at the time of the MARC-2 study initiation in 2011, everolimus has been considered a standard of care (SOC) for the treatment of clear cell mRCC in second- or third-line after failure of previous VEGF-targeted therapy.[12]

The goal of the MARC-2 clinical trial was to identify subgroups of mRCC patients who would benefit most from second-line everolimus after failure of exactly one first-line VEGFR-TKI therapy and to

### What's new

While different novel treatment options have been approved for the vascular endothelial growth factor receptor tyrosine kinase inhibitor (VEGFR-TKI) refractory setting in metastatic renal cell carcinoma (mRCC), choosing the optimal second-line therapy regimen remains a biologic and therapeutic challenge. The MARC-2 phase IV trial aimed to investigate clinical outcomes in mRCC patients treated with everolimus after failure of one VEGFR-TKI therapy and to identify subgroups benefiting most. According to the data, everolimus remains a safe and effective treatment option for mRCC patients after one prior VEGFR-TKI therapy, with the greatest benefit seen in patients ≥65 years or with BMI >25 kg/m$^2$.

identify predictive markers for personalized treatment selection. Here, we present the clinical results and patient outcomes.

## 2 | MATERIALS AND METHODS

### 2.1 | Study design and participants

The MARC-2 trial was a prospective, single-arm, open-label, multicenter phase IV trial performed within the Interdisziplinäre Arbeitsgruppe Nierentumoren (IAG-N) of the German Cancer Society (DKG) and conducted at 15 sites across Germany. Adult patients (aged ≥18 years) with predominant clear cell mRCC and measurable disease according to RECIST 1.1[13] who had progressed during or after exactly one prior VEGFR-TKI therapy, Eastern Cooperative Oncology Group (ECOG) score of 0-2 with adequate organ and bone marrow function were included. Key exclusion criteria were previous treatment with more than one VEGFR-TKI or with bevacizumab, VEGFR-TKI therapy within 14 days prior start of study drug, prior systemic mTOR inhibitor therapy, major surgery within 4 weeks or minor surgical procedures within 7 days prior study enrollment, non-healing wounds, ulcer, bone fracture, history of seizure(s), history or clinical evidence of central nervous system, chronic systemic immunosuppressive treatment, uncontrolled medical conditions (eg, uncontrolled diabetes, uncontrolled infection, impaired liver function Child-Pugh class C), active bleeding disorder and HIV seropositivity.

### 2.2 | Study procedures

Everolimus 10 mg was administered orally once daily according to summary of product characteristics (SmPC) until disease progression or symptomatic deterioration, inacceptable toxicity, death, withdrawal of consent or other reasons including patients' wishes or investigator's decision regarding patients' well-being. A cycle consisted of 28 days. Dose reductions and treatment interruptions were allowed according to SmPC with a maximum allowed treatment interruption of 21 days.

### 2.3 | Assessments

Radiologic assessments were carried out every 8 weeks (±7 days) until disease progression or start of subsequent antineoplastic therapy and tumor response was investigator-assessed according to RECIST 1.1.

Adverse events (AE) were monitored, coded to a preferred term using the Medical Dictionary for Regulatory Activities (MedDRA)

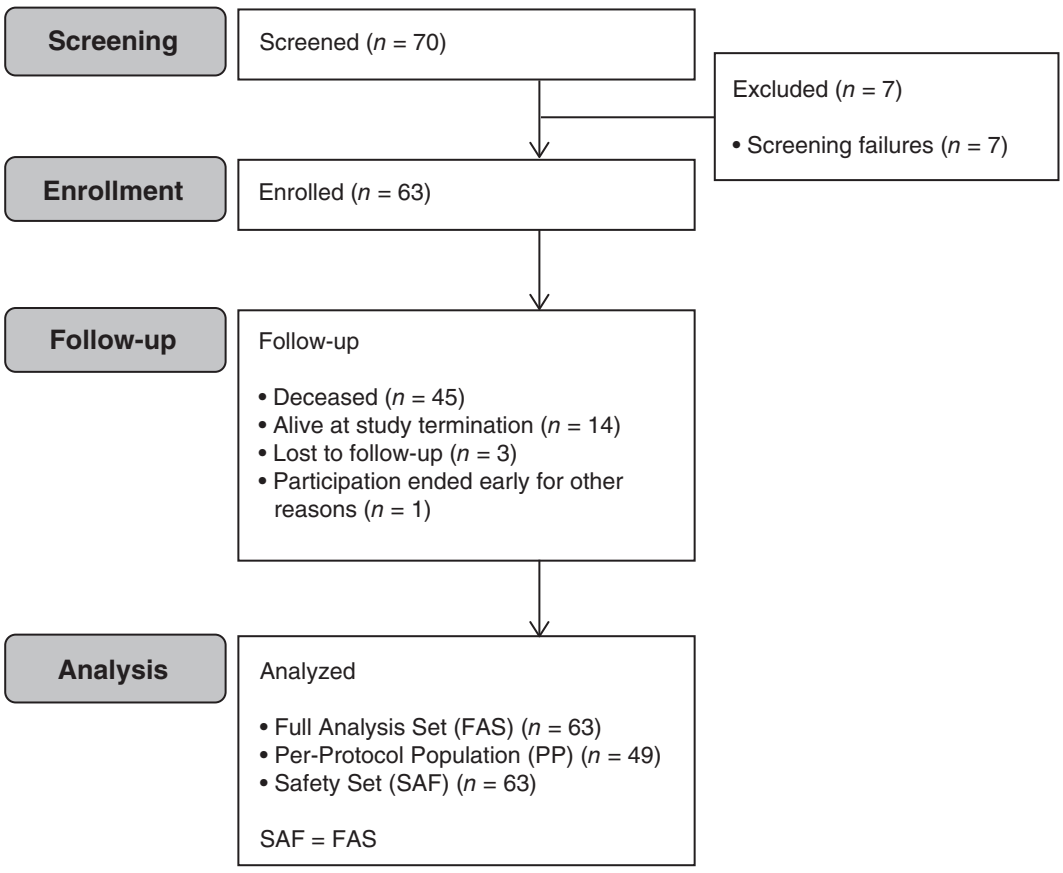


**FIGURE 1** Patient disposition - CONSORT diagram. FAS, full analysis set; PP, per-protocol population; SAF, safety analysis set

Version 20.0 and graded according to National Cancer Institute's Common Criteria for Adverse Events (CTCAE) version 4.02[14] until 30 days after discontinuation of everolimus treatment.

## 2.4 | Outcome assessment

The primary endpoint was 6-month PFS rate (6moPFS). Secondary endpoints were PFS, OS, overall response rate (ORR), disease control rate (DCR), duration of response (DOR) and safety. Biomarker analyses of circulating plasma markers, everolimus trough levels and dynamic contrast-enhanced magnetic resonance imaging were exploratory endpoints which will be published elsewhere.

## 2.5 | Statistical analyses

The primary objective of our study was to investigate clinical outcome (6moPFS) of mRCC patients treated with everolimus after failure of exactly one prior VEGFR TKI. With the assumption of a 6moPFS of 25%, enrollment of 80 patients was planned to reach a two-sided 95% confidence interval (CI) extending 10% from the observed proportion. A dropout rate of 10% was assumed. Due to low numbers, the recruitment was stopped after 70 patients had been screened. Of those patients screened, 63 patients were enrolled.

Efficacy analyses were based on the full analysis set (FAS) defined as all enrolled patients who received at least one dose of everolimus, and the per-protocol set (PP) defined as those patients of FAS who fulfilled all inclusion and no exclusion criteria, had a relative dose intensity of at least 50% in the first two treatment cycles and had a tumor response evaluation prior to day 182, or who progressed, discontinued treatment due to an AE or died before the minimum exposure requirements had been met. Since patient and disease characteristics can be independent prognostic factors in mRCC,[9] efficacy was not only assessed in the overall FAS/PP population but also in prespecified subgroups of the FAS population: sex, age at date of informed consent (≥65 vs <65 years), body mass index (BMI) at screening (>25 vs ≤25 kg/m$^2$), ECOG performance status at baseline (≥1 vs 0) as well as prior nephrectomy (cytoreductive and not cytoreductive, respectively, vs none). PFS and OS were estimated using the Kaplan-Meier method and described by median or rate at specific time points with their corresponding 95% CI. The median observation period was calculated using the reverse Kaplan-Meier estimate.[15] To adjust for potential confounders, a Cox proportional hazards model was performed including all variables used for the unadjusted subgroup analyses. As CIs give a good indication as to whether the observed differences are real, we included them for treatment data, response, survival data and for the regression model. CIs for the regression coefficients were based on the Wald statistics.

The safety analysis set (SAF) consisted of all patients of the FAS for whom at least one further post-baseline information was available. Since all patients in the FAS had one post-baseline information given, SAF and FAS were identical.

# 3 | RESULTS

## 3.1 | Baseline characteristics and disposition

Between March 2011 and August 2015, a total of 70 patients with mRCC were screened. Of those patients screened, 7 were screening

**TABLE 1** Baseline patient and tumor characteristics

| Characteristic | Total (n = 63) | Per-protocol (n = 49) |
|---|---|---|
| Age at date of informed consent, years | | |
| Median | 65.4 | 66.8 |
| Range | 43.3-81.1 | 43.3-81.1 |
| Gender, n (%) | | |
| Female | 15 (23.8%) | 9 (18.4%) |
| Male | 48 (76.2%) | 40 (81.6%) |
| BMI at screening, kg/m$^2$ | | |
| Median | 26.2 | 26.9 |
| Range | 20.3-38.1 | 20.8-37.8 |
| ECOG performance status, n (%) | | |
| Score 0 | 36 (57.1%) | 30 (61.2%) |
| Score 1 | 25 (39.7%) | 18 (36.7%) |
| Score 2 | 2 (3.2%) | 1 (2.0%) |
| Histology, n (%) | | |
| Predominantly clear cell | 62 (98.4%) | 49 (100.0%) |
| Other | 1 (1.6%) | |
| Previous anticancer therapy, n (%)[a] | | |
| Axitinib | 2 (3.2%) | 2 (4.1%) |
| Interferon + Interleukin 2 | 1 (1.6%) | 1 (2.0%) |
| Pazopanib | 21 (33.3%) | 17 (34.7%) |
| Peptid vaccination versus placebo | 1 (1.6%) | 1 (2.0%) |
| Radiotherapy | 13 (20.6%) | 11 (22.4%) |
| Sunitinib | 40 (63.5%) | 30 (61.2%) |
| Response to first-line VEGF-targeted therapy, n (%) | | |
| Primary refractory | 7 (11.1%) | 4 (8.2%) |
| Secondary refractory | 40 (63.5%) | 32 (65.3%) |
| No response data of first-line TKI treatment available | 16 (25.4%) | 13 (26.5%) |
| Nephrectomy, n (%)[b] | | |
| Cytoreductive | 19 (30.2%) | 15 (30.6%) |
| Non-cytoreductive | 41 (65.1%) | 31 (63.3%) |
| None | 3 (4.7%) | 3 (6.1%) |

Abbreviations: BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; VEGF, vascular endothelial growth factor.
[a]Multiple answers possible.
[b]Patients who underwent nephrectomy (total or partial) no more than 3 months prior to or during palliative therapy were summarized as "cytoreductive nephrectomy" group, all other patients as "non-cytoreductive."

failures, thus 63 patients were enrolled and followed up until September 2017. The disposition of patients is shown in Figure 1. A total of 40 patients had received sunitinib as previous treatment, 21 patients pazopanib and 2 patients axitinib. In addition, one patient had received interleukin-2 and interferon prior to sunitinib and one patient had been treated with peptide vaccination or placebo together with sunitinib within another clinical trial before enrollment. Seven patients presented with primary refractory disease. Baseline patient and tumor characteristics are summarized in Table 1.

## 3.2 | Treatment administration

The median duration of treatment was 3.7 months (0.7-34.7 months), the median relative dose intensity was 100% (range, 47.1-100). At least one dose reduction occurred in 14 patients, at least one treatment interruption in 26 patients. Interruptions were performed for safety/tolerability reasons in 20.6% of patients, investigator decision in 7.9% and patients' wishes in 6.3% of patients, respectively.

Main reason for treatment discontinuation was progressive disease (n = 46). For patients aged <65 years, 90.3% of patients (n = 28) discontinued study treatment due to progressive disease as compared to 56.3% of patients (n = 18) ≥65 years.

## 3.3 | Efficacy

All 63 patients were included in the FAS population, 49 patients in the PP population. Median observation period for all patients at end of study was 35.5 months. Data for PFS and OS including prespecified subgroups are depicted in Table 2 (FAS) and Figure 2 (PFS only).

The primary endpoint 6moPFS was 39.3% (95% CI, 27.0-51.3) overall and 44.6% (95% CI, 30.0-58.2) in the PP population. In prespecified subgroups of the FAS population, 6moPFS was 54.4% (95% CI, 35.2-70.1) for patients aged ≥65 years (n = 32) and 51.4% (95% CI, 34.7-65.7) for patients with baseline BMI >25 kg/m$^2$ (n = 41) (Table 2).

Median PFS was 3.8 months (95% CI, 3.2-6.2) overall (Table 2) and 5.3 months (95% CI, 3.2-8.1) in the PP population (Figure 2). Median PFS for patients aged ≥65 vs <65 years (FAS) was 6.9 months (95% CI, 3.7-9.4) vs 3.2 months (95% CI, 1.7-3.8) (HR, 0.46; 95% CI, 0.26-0.80; Figure 3).

Median OS was 16.8 months (95% CI, 14.3-24.3) overall (Table 2) and 22.9 months (95% CI, 15.8-36.1) in the PP population. Median OS for patients with BMI >25 vs ≤25 kg/m$^2$ (FAS) was 24.3 months (95% CI, 16.8-47.9) vs 12.0 months (95% CI, 4.0-15.8) (HR, 0.36; 95% CI, 0.18-0.71; Figure 3).

The ORR was 7.9% with partial response achieved in five out of 63 patients. No complete response was observed. The median DOR was 12.5 months (95% CI, 6.7-31.2). A total of 33 patients (52.4%) achieved a disease stabilization. The DCR was 60.3%.

## 3.4 | Safety

All 63 patients were included in the SAF. Sixty-one patients (96.8%) had at least one treatment-emergent AE (TEAE), 49 patients (77.8%) had a TEAE related to everolimus. Most common TEAEs of any grade were stomatitis, fatigue, anemia, rash, epistaxis, oedema peripheral and cough (Table 3).

**TABLE 2** Efficacy results

| | Subgroup | No. of patients | 6moPFS (%)[a] [95% CI] | Median PFS (months)[a] [95% CI] | No. of events [%] | Median OS (months)[b] [95% CI] | No. of events [%] |
|---|---|---|---|---|---|---|---|
| All patients | | 63 | 39.3 [27.0-51.3] | 3.8 [3.2-6.2] | 56 [88.9] | 16.8 [14.3-24.3] | 45 [71.4] |
| Age | <65 y | 31 | 23.7 [10.5-39.9] | 3.2 [1.7-3.8] | 30 [96.8] | 16.3 [8.9-21.8] | 23 [74.2] |
| | ≥65 y | 32 | 54.4 [35.2-70.1] | 6.9 [3.7-9.4] | 26 [81.3] | 24.3 [14.0-47.9] | 22 [68.8] |
| Gender | Female | 15 | 29.3 [9.2-53.3] | 3.6 [1.1-6.2] | 13 [86.7] | 16.3 [5.1-21.8] | 12 [80.0] |
| | Male | 48 | 42.2 [27.9-55.9] | 4.0 [3.2-8.1] | 43 [89.6] | 20.4 [14.3-36.1] | 33 [68.8] |
| BMI[c] | ≤25 kg/m$^2$ | 22 | 18.2 [5.7-36.3] | 2.2 [1.6-4.7] | 21 [95.5] | 12.0 [4.0-15.8] | 18 [81.8] |
| | >25 kg/m$^2$ | 41 | 51.4 [34.7-65.7] | 6.2 [3.6-8.4] | 35 [85.4] | 24.3 [16.8-47.9] | 27 [65.9] |
| ECOG-PS[c] | 0 | 36 | 41.6 [25.0-57.5] | 3.8 [2.0-9.3] | 30 [83.3] | 24.1 [15.8-59.7] | 23 [63.9] |
| | ≥1 | 27 | 37.0 [19.6-54.6] | 3.8 [2.1-6.4] | 26 [96.3] | 10.8 [6.8-22.9] | 22 [81.5] |
| Nephrectomy[d] | Cytoreductive | 19 | 36.1 [15.7-57.0] | 3.6 [1.7-9.4] | 17 [89.5] | 16.4 [8.3-59.7] | 14 [73.7] |
| | Non-cytoreductive | 41 | 43.7 [27.9-58.5] | 4.7 [3.2-8.1] | 36 [87.8] | 20.4 [14.3-24.5] | 28 [68.3] |
| | None | 3 | 33.3 [0.9-77.4] | 3.7 [1.1-3.8] | 3 [100.0] | 7.3 [1.8-36.1] | 3 [100.0] |

*Note:* Data of full analysis set (FAS) are depicted.

Abbreviations: 6moPFS, 6-month PFS rate; BMI, body mass index; CI, confidence interval; ECOG-PS, Eastern Cooperative Oncology Group performance status; FAS, full analysis set; OS, overall survival; PFS, progression-free survival.

[a]PFS is defined as time from first administration of everolimus to first occurrence of progressive disease or death. For three patients in FAS (1 in PP) symptomatic deterioration led to treatment discontinuation. These deteriorations were considered as event for PFS analysis.

[b]OS is defined as time from first administration of everolimus to death.

[c]At baseline.

[d]Patients who underwent nephrectomy (total or partial) no more than 3 months prior to or during palliative therapy were summarized as "cytoreductive nephrectomy" group, all other patients as "non-cytoreductive."

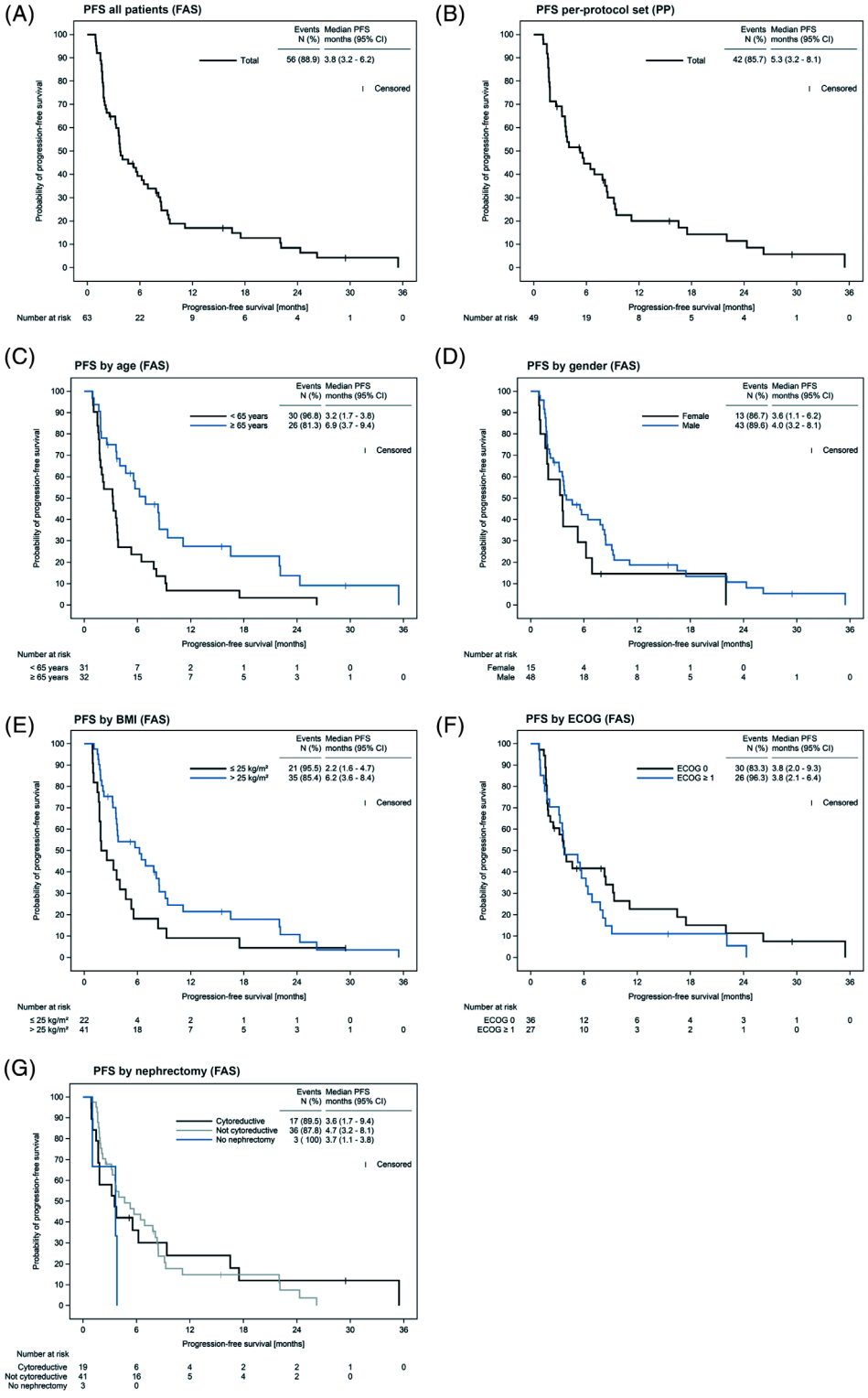


**FIGURE 2** Progression-free survival by Kaplan-Meier estimate of 63 patients in the full analysis set (A) and 49 patients in the per-protocol population (B); PFS of all patients (FAS) by age (C), by gender (D), by BMI at baseline (E), by ECOG performance status at baseline (F), and by nephrectomy (G). BMI, body mass index; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; PFS, progression-free survival; PP, per-protocol set [Color figure can be viewed at wileyonlinelibrary.com]

As assessed by the investigators, the most common TEAEs related to everolimus were stomatitis, fatigue, rash, anemia and pruritus (Table S1). Most common related TEAEs ≥ grade 3 were anemia (12.7%), hyperglycemia (6.3%), interstitial lung disease (3.2%), blood triglycerides increased (3.2%) and hypertriglyceridemia (3.2%). Only one everolimus-related pneumonitis grade 3 occurred.

Five fatal TEAEs were reported during everolimus treatment and 30-day follow-up period, thereof four with death reason being progression of the underlying mRCC (n = 3 with malignant neoplasm

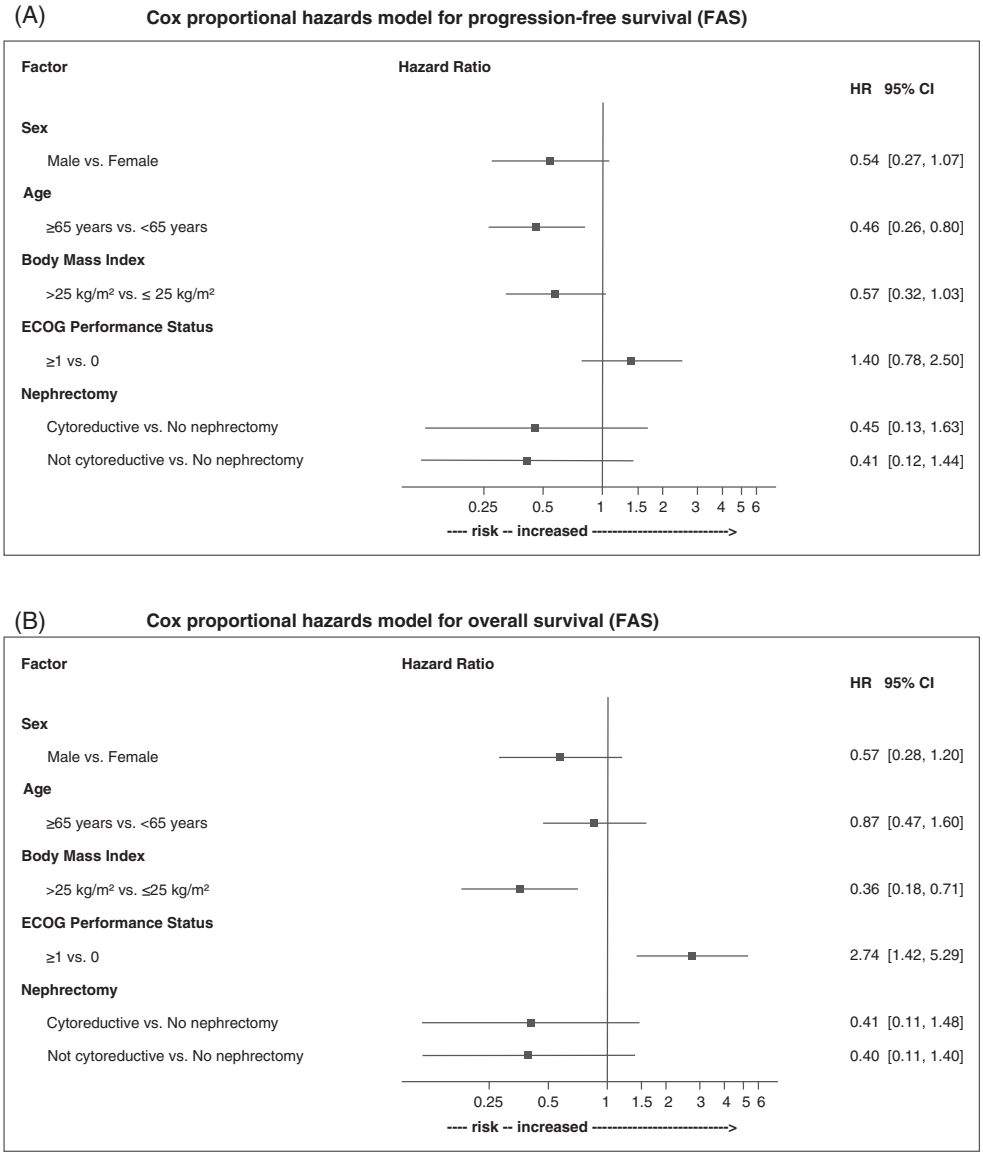


**FIGURE 3** Multivariate regression analysis - Cox proportional hazards model for progression-free survival (A) and overall survival (B) in the full analysis set (n = 63, thereof 11.1% censored cases). The parameters shown are an exhaustive list of co-variables used for the Cox proportional hazards model. CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; HR, hazard ratio

progression, n = 1 with metastases to central nervous system). The fifth patient, a male patient aged 73 years with ECOG 0 at baseline, died from upper gastrointestinal hemorrhage related to everolimus as assessed by the investigator. The patient died 3 days after the last intake of everolimus in cycle 5.

## 4 | DISCUSSION

While different novel treatment options have been approved for the VEGFR-TKI refractory setting, choosing the optimal second-line therapy regimen remains a biologic and therapeutic challenge. At the time of our study analysis, the only registered drugs in this setting were everolimus, axitinib and sorafenib. Now, approved second-line regimens also include cabozantinib, nivolumab and the combination of lenvatinib plus everolimus. Although various patient and disease characteristics as well as genetic parameters have been analyzed for their predictive impact so far,[16] there remains much work to be done in order to help to select the best second-line therapy for an individual patient, such as after one prior VEGFR-TKI treatment. Furthermore, the optimal treatment sequence in mRCC patients remains an area of research.[8] Despite the current era of precision medicine and tumor genomics and despite the significant changes in the therapeutic armamentarium for mRCC, present treatment recommendations for mRCC beyond first-line treatment are still mainly driven by patient status, comorbidities, safety profiles and prior therapy.

To our knowledge, the MARC-2 trial is the first phase IV study investigating the efficacy and safety of everolimus as second-line treatment after exactly one prior VEGFR-TKI in first-line with the aim of characterizing patients who would benefit most from everolimus treatment based on clinical characteristics and biomarker status.

**TABLE 3** Treatment-emergent adverse events occuring in >10% of patients

| MedDRA system organ class adverse event, preferred term | Any grade (n, %) | Grade 3/4 (n, %) |
|---|---|---|
| Patients with any event | 61 (96.8) | 36 (57.1) |
| Gastrointestinal disorders | 39 (61.9) | 6 (9.5) |
| Stomatitis | 20 (31.7) | 1 (1.6) |
| Diarrhea | 10 (15.9) | 1 (1.6) |
| Nausea | 9 (14.3) | 0 |
| General disorders and administration site conditions | 36 (57.1) | 19 (30.2) |
| Fatigue | 20 (31.7) | 3 (4.8) |
| Oedema peripheral | 15 (23.8) | 2 (3.2) |
| Pyrexia | 8 (12.7) | 1 (1.6) |
| Respiratory, thoracic and mediastinal disorders | 32 (50.8) | 4 (6.3) |
| Epistaxis | 17 (27.0) | 0 |
| Cough | 15 (23.8) | 0 |
| Dyspnoea | 14 (22.2) | 2 (3.2) |
| Pneumonitis | 9 (14.3) | 1 (1.6) |
| Metabolism and nutrition disorders | 30 (47.6) | 19 (30.2) |
| Decreased appetite | 13 (20.6) | 1 (1.6) |
| Hyperglycaemia | 9 (14.3) | 5 (7.9) |
| Skin and subcutaneous tissue disorders | 26 (41.3) | 1 (1.6) |
| Rash | 18 (28.6) | 1 (1.6) |
| Pruritus | 13 (20.6) | 0 |
| Blood and lymphatic system disorders | 19 (30.2) | 19 (30.2) |
| Anemia | 19 (30.2) | 11 (17.5) |
| Nervous system disorders | 19 (30.2) | 0 |
| Dysgeusia | 10 (15.9) | 0 |

*Note:* Adverse events were coded using MedDRA version 20.0. Time range: from first application of everolimus until 30 days after end of treatment. More than one reported preferred term per patient within a system organ class was possible.

Biomarker analysis will be addressed in another publication. Limitations of this trial are the rather small sample size and the single-arm design. Due to the lack of a control arm and given the exploratory nature of the subgroup analyses used for this work, the generalizability of results to populations not included in the trial is limited. Thus, results cannot serve as a general decision on effectiveness of everolimus. In the context of other studies in similar patient populations, the findings of our study, however, can contribute to the estimate of how effective and safe everolimus is.

With a 6moPFS of 39.3% (95% CI, 27.0-51.3), the MARC-2 trial revealed a 6moPFS tending to be higher compared to the 6moPFS of 26% (95% CI, 14-37) reported from the pivotal RECORD-1 trial.[10] This might be caused by slight differences in the patient disposition in both trials: in the RECORD-1 trial,[10,17] the majority of the patients (78.6%) had received more than one prior therapy and 26% of the patients were pretreated with both sunitinib and sorafenib, whereas in MARC-2, only one prior VEGFR-TKI therapy was permitted. Moreover, 13% of the patients in RECORD-1 had received prior chemotherapy as compared to none in our trial. Interestingly, in MARC-2, the median PFS was 3.8 months (95% CI, 3.2-6.2) in the overall population and 5.3 months (95% CI, 3.2-8.1) in the PP population, and thus in line with the results from the RECORD-1 trial with a median PFS of 4.9 months in the total population and of 5.4 months in a post hoc analysis of patients ≥65 years.[18] Since most patients in RECORD-1 received more than one previous treatment, the RECORD-4 study was designed to provide additional data on everolimus in a purely second-line setting.[19] Median PFS was 5.7 months in the cohort receiving sunitinib as first-line therapy and 7.8 months in the total population as well as in the patient cohort who had received a VEGFR-TKI therapy other than sunitinib. However, more patients included in RECORD-4 were of favorable prognostic risk according to MSKCC (Memorial Sloan Kettering Cancer Centre) than patients in the everolimus arm of RECORD-1.[19] In MARC-2, more than 60% of patients achieved a disease control, approximately 52% of them a stable disease. This is in line with results from RECORD-1 with 63% of patients on everolimus who achieved a stable disease,[10] and also with those from RECORD-4 with 64% of patients receiving first-line sunitinib and 73% of patients treated with another first-line VEGFR-TKI, respectively, who achieved a stable disease.[19] Based on the results of the unadjusted subgroup analyses and their conformation by confounder-adjusted Cox proportional hazards modeling, in MARC-2, everolimus was most effective in patients aged ≥65 years and in the patient subgroup with a BMI >25 kg/m$^2$. Multivariable analyses revealed longer PFS for patients aged ≥65 years (HR, 0.46; 95% CI, 0.26-0.80), while for OS, BMI was identified to be an independent prognostic factor, with higher BMI (>25 kg/m$^2$) leading to longer OS (HR, 0.36; 95% CI, 0.18-0.71). For both patients with a BMI >25 kg/m$^2$ and patients aged ≥65 years, median OS was 24.3 months. In comparison, median OS reported from other second-line trials, for example, INTORSECT, AXIS and RECORD-1, ranges from 12 to 20.1 months.[11,20,21] In a prospective German cohort of mRCC routine patients receiving systemic treatment, a high BMI has been shown to be associated with longer OS.[22] In RECORD-4, median duration of prior VEGFR-TKI therapy was reported to be a prognostic factor.[19] For the scope of the present work, the duration of patients' initial VEGFR-TKI therapy was not available and therefore the influence on OS under everolimus treatment was not analyzed.

Meanwhile, there has been considerable progress in the second-line treatment of mRCC in the last few years with the approval of the lenvatinib/everolimus combination, the checkpoint inhibitor nivolumab and the oral TKI cabozantinib which demonstrated superior efficacy compared to everolimus alone when used after VEGF-targeted therapy. Interestingly, the median OS of 21.4 months (95% CI, 18.7-not estimable) reported from the pivotal METEOR phase III trial in patients treated with cabozantinib[23] is comparable with the median OS of 22.9 months (95% CI, 15.8-36.1) in the PP population of MARC-2. In summary, efficacy results from the MARC-2 trial were in line with results from other published trials, where everolimus was administered after VEGF-targeted therapy.

The individual safety profile is an important aspect when making treatment decisions in mRCC patients, especially in elderly patients when comorbidities are present. In the MARC-2 trial, the safety profile of everolimus with most common TEAEs being stomatitis, fatigue, anemia, rash and epistaxis was consistent with the most common TEAEs seen in RECORD-1 and other studies.[17] Similarly, most common TEAEs reported for patients in the everolimus arm of CheckMate-025 and the lenvatinib pivotal trials were stomatitis, fatigue/asthenia, diarrhea, cough and fatigue, stomatitis, anemia, rash and cough, respectively.[2,24] Analyses of other targeted therapies have reported an increase in the frequency of AEs in elderly patients with mRCC.[25-27] In the MARC-2 trial, however, although the median age was >65 years, the safety profile was consistent with previously published data and an increase of AE frequency was not seen in the elderly patients. Thus, everolimus was well tolerated, no new safety signals emerged. No increase in everolimus-related pneumonitis was observed compared to published data from other studies.

Everolimus still represents a SOC for mRCC progressive to previous treatment with VEGFR-TKI. In the future, the growing evidence on the recently approved agents cabozantinib and nivolumab for second-line treatment of mRCC will determine the potential shift of everolimus to the third- and later line setting.

## 5 | CONCLUSIONS

The MARC-2 trial shows that everolimus can be regarded as an effective treatment option for mRCC patients after one previous VEGF-targeted therapy. Everolimus was most effective in patients aged ≥65 years or in patients with a BMI >25 kg/m$^2$. No new safety signals emerged. Thus, with its favorable safety and efficacy profile, second-line everolimus remains a SOC in mRCC.

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### CONFLICT OF INTEREST

M. Stöckle, D. C. Christoph, K. Potthoff, D. Klein, J. Harde, F Brüning, F. Roos and I. Benz-Rüd declare no conflict of interest concerning the topic of this publication. M. Staehler (MS) has received honoraria from Pfizer, GlaxoSmithKline, AVEO, Novartis, Bayer, EUSA Pharma, Astellas, Ipsen, Exelixis, Pelloton, EISAI, Bristol-Myers Squibb, and Merck Sharp & Dohme. MS has received research funding from Pfizer, GlaxoSmithKline, AVEO, Bristol-Myers Squibb, Novartis, Bayer, Roche/Genentech, Immatics, Wilex, Ipsen, Exelixis, and EISAI. Furthermore, MS has a role of a consultant at Pfizer, GlaxoSmithKline, Novartis, Bayer, Roche, Aveo, EUSA Pharma, Astellas, Ipsen, Exelixis, Pelloton, EISAI, Bristol-Myers Squibb, and Merck Sharp & Dohme. A. Stenzl (AS) has received personal fees from Ipsen Pharma, Janssen, Alere, Bristol-Myers-Squibb, Stebabiotech, Synergo, Ferring, CureVac, Astellas, Amgen, and Sanofi Aventis. AS has received grants from Johnson & Johnson, Roche, Cepheid, Amgen, Bayer AG, immatics biotechnologies GmbH, GemeDX Biosciences, Novartis AG, and from Karl Storz AG, outside the submitted work. M.-O. Grimm (MOG) has received grants and personal fees from Novartis and BMS; MOG has received personal fees from Pfizer, Bayer HealthCare, Astellas, Intuitive Surgical, Sanofi Aventis, Hexal, Apogepha, Amgen, AstraZeneca, MSD, Janssen Cilag, Ono Pharma, Ipsen Pharma, Medac, and Merck, outside the submitted work. P. J. Goebell (PJG) has received honoraria/support as a speaker from Astellas, AstraZeneca, Bayer, BMS, Eisai, Ipsen, Janssen, Novartis, Pfizer, Roche, Sanofi. PJG has received honoraria for participation in expert rounds from Astellas, AstraZeneca, Bayer, BMS, Eisai, Ipsen, Janssen, Novartis, Pfizer, Roche, Sanofi. M. Augustin (MA) has received grants from iOMEDICO during the conduct of the study. MA has received grants, personal fees and nonfinancial support from Novartis, BMS, Pfizer, and Roche, personal fees and nonfinancial support from IPSEN, grants from MSD, Morphosys, and AstraZeneca, nonfinancial support from Servier, grants and nonfinancial support from PharmaMar, outside the submitted work. N. Marschner (NM) has received support for clinical trials from Bayer, Ipsen, Pfizer, Novartis, Roche, and GlaxoSmithKline and honoraria for presentations from Novartis, Bayer, GlaxoSmithKline, and Ipsen. Furthermore, NM has received travel support from Pfizer, Novartis, Bayer, Roche, and Bristol-Myers Squibb and is advisory board member at Novartis, Bayer, GlaxoSmithKline, Ipsen, Pfizer, Bristol-Myers Squibb, Merck Sharp & Dohme. Furthermore, NM is Chief Executive Officer of iOMEDICO and holds shares of this company. V. Grünwald (VG) reports grants and personal fees from Pfizer and EUSA Pharma, grants, personal fees and nonfinancial support from BMS and from Ipsen, personal fees and nonfinancial support from Roche, Novartis, and EISAI, personal fees from MSD, during the conduct of the study. Furthermore, VG has received grants, personal fees, nonfinancial support and other from MSD, AstraZeneca, and BMS, grants from Novartis, personal fees and nonfinancial support from MerckSerono and PharmaMar, personal fees from Roche, Pfizer, Lilly, Janssen, and Nanobiotix, outside the submitted work.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

### ETHICS STATEMENT

The MARC-2 trial was conducted according to the ethical principles of the declaration of Helsinki. The study protocol was reviewed by the independent ethics committee or the institutional review board

for each center. Each patient had provided written informed consent before screening procedures were initiated. The trial is registered at ClinicalTrials.gov (NCT01266837).

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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