FINAL RESULTS OF PHASE IV STUDY MARC-2

EVEROLIMUS AS SECOND-LINE THERAPY FOR METASTATIC RENAL CELL CARCINOMA

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INTRODUCTION

Approximately 16,500 patients are diagnosed with kidney cancer each year in Germany. Renal cell carcinoma (RCC) accounts for 85% of all malignant tumors of the kidney with almost one third of patients presenting with advanced disease[1]. Treatment options in metastatic RCC (mRCC) have increased with the introduction of molecular targeted therapies including vascular endothelial growth factor receptor (VEGFR)-targeted treatment [sunitinib, sorafenib, pazopanib, axitinib], vascular endothelial growth factor (VEGF)-antibody [bevacizumab] and mammalian target of rapamycin (mTOR)-inhibitors [everolimus, temsirolimus], and outcome of mRCC has markedly improved over the past decade.

Everolimus (Afinitor®), an oral mTOR inhibitor, is a registered drug indicated for the treatment of patients with advanced RCC, whose disease has progressed on or after treatment with VEGF-targeted therapy. The aim of the MARC-2 study was to characterize patients most likely to benefit from everolimus treatment.

SUMMARY

This phase IV trial investigated the efficacy and safety of everolimus as second-line treatment of mRCC patients after failure of one VEGFR-TKI. The primary endpoint 6-months PFS rate was 39.3% (95%-CI 27.0-51.3). Median Kaplan-Meier estimate for PFS was 3.8 months (95%-CI 3.2-6.2) and for overall survival 16.8 months (95%-CI 14.3-24.3). These efficacy data are in line with results of other studies including the pivotal phase III trial of everolimus[2,3] and more recent trials that used everolimus after VEGF-targeted therapy[4,5]. However, differences were noted for 6-month PFS rate in pre-specified subgroups. 6-month PFS rate of > 50% under everolimus treatment was observed for patients aged ≥ 65 years (n=32; 54.4%, 95%-CI: 35.2% - 70.1%) and BMI > 25 kg/m² (n=41; 51.4%, 95%-CI: 34.7% - 65.7%). However, small sample sizes have to be considered. The observed safety profile of everolimus with most common TEAEs being stomatitis, fatigue, anemia, rash, and epistaxis was consistent with that seen in other studies.

METHODS

MARC-2 was a single-arm, open-label, multicenter phase IV trial conducted at 15 sites across Germany. Key inclusion criteria were mRCC of predominant clear cell histology, failure of exactly one prior VEGFR tyrosine kinase inhibitor (TKI) therapy, ECOG performance status 0-2, and at least one measurable lesion. Patients were not allowed more than one prior VEGFR-TKI nor prior bevacizumab or systemic mTOR inhibitor treatment. Further key exclusion criteria included evidence of central nervous system metastases, major surgery within 4 weeks of study entry, non-healing wounds, ulcer, bone fracture, and active bleeding disorders. Written informed consent was obtained for each patient.

Patients received 10 mg everolimus per os once daily until disease progression, unacceptable toxicity, or withdrawal of consent. Dose reductions and treatment interruptions were permitted in those patients that were unable to tolerate the protocol-specified dosing. The maximum allowed time of interruption was 21 days. Radiologic assessments were carried out every 8 weeks (± 7 days) until disease progression or start of subsequent anti-neoplastic therapy. Tumor response was evaluated by the investigators according to RECIST criteria.

Primary objective was the rate of patients free of disease progression after 6 months (6-month PFS rate). Secondary endpoints were progression-free survival (PFS), overall survival, response, duration of response, and safety. In addition, correlation between biomarkers and clinical benefit was assessed.

Analyses were conducted on the Full Analysis Set (FAS) comprising patients having received at least one everolimus dose. For sensitivity, primary and secondary endpoints were additionally analyzed on the Per Protocol (PP) population, a subset comprising patients meeting all inclusion/exclusion criteria, having had a tumor assessment until day 182 and a relative dose intensity ≥50% over the first 2 cycles (or progressed, discontinued for adverse event or died before this minimum exposure requirement could be met).

All analyses were descriptive in nature. Time-to-event analyses (duration of treatment, duration of response, PFS (including primary endpoint), OS) were calculated using Kaplan-Meier method.

RESULTS

A total of 70 patients were screened, thereof 63 were enrolled between March 2011 and August 2015, and followed up until September 2017. Median duration of follow up for patients alive at end of study was 27.6 months. Baseline patient and tumor characteristics are depicted in **Table 1**.

The median duration of treatment was 3.7 months (range 0.7 – 34.7 months), median relative dose intensity was 100% (range 47.1-100%; 25% quartile: 88.3%, 75% quartile: 100%). Main reason for treatment discontinuation was progressive disease (73.0%, n=46). For patients aged <65 years, 90.3% (n=28) of patients discontinued study treatment due to progressive disease as compared to 56.3% (n=18) of patients aged ≥65 years.

The primary endpoint 6-months PFS rate was 39.3% (95%-CI 27.0-51.3) overall and 44.6% (95%-CI 30.0-58.2) in the per-protocol population. Median PFS was 3.8 months (95%-CI 3.2-6.2) overall and 5.3 months (95%-CI 3.2-8.1) in the per-protocol population (**Figure 1**). Median overall survival was 16.8 months (95%-CI 14.3-24.3) and 22.9 months (95%-CI 15.8-36.1), respectively. 6-months PFS rate, PFS and overall survival for the full analysis set and as assessed in pre-specified subgroups is depicted in **Table 2**.

No complete response was observed during treatment with everolimus. 5 patients achieved a partial tumor remission resulting in an overall response rate of 7.9%. For those patients, median duration of response was 12.5 months (95%-CI 6.7-31.2); further 33 patients (52.4%) achieved disease stabilization.

Sixty-one patients (96.8%) had at least one treatment-emergent adverse event (TEAE), 49 (77.8%) had a TEAE related to everolimus treatment. Most common TEAEs of any grade were stomatitis, fatigue, anemia, rash, epistaxis, edema peripheral, and cough (**Table 3**). Five patients were reported with fatal TEAEs during the study: four patients with tumor progression. None of these four fatal TEAEs was reported as being related to everolimus. The fifth patient with a fatal TEAE died from upper gastrointestinal hemorrhage documented by the investigator as being related to everolimus. The patient died three days after last application of everolimus in cycle 5.

Table 1

Characteristic	Total (N=63)	Per-protocol (N=49)
Age at date of informed consent, years		
Median (Range)	65.4 (43.3 – 81.1)	66.8 (43.3 – 81.1)
Gender, n (%)		
Female	15 (23.8%)	9 (18.4%)
Male	48 (76.2%)	40 (81.6%)
BMI at screening, kg/m²		
Median (Range)	26.2 (20.3 – 38.1)	26.9 (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%)
Previous cancer therapy, n (%)		
Axitinib	2 (3.2%)	2 (4.1%)
Interferon*	1 (1.6%)	1 (2.0%)
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%)
Responsiveness to first-line VEGF-targeted therapy, n (%)		
No response data of first-line TKI treatment available	16 (25.4%)	13 (26.5%)
Primary refractory#	7 (11.1%)	4 (8.2%)
Secondary refractory	40 (63.5%)	32 (65.3%)

*One patient had received interleukin-2 and interferon prior sunitinib treatment.
**One patient had received peptide vaccination or placebo in combination with sunitinib.
#Primary refractory defined as progressive disease as best response to first-line treatment

Table 1. Baseline patient and tumor characteristics

Table 2

Outcome	Subgroup	N of Patients	6-Month PFS Rate (95% CI)	Median PFS [months] (95% CI)	Median OS [months] (95% CI)
All patients		63	39.3% (27.0% - 51.3%)	3.8 (3.2 - 6.2)	16.8 (14.3 - 24.3)
Age	<65 years	31	23.7% (10.5% - 39.9%)	3.2 (1.7 - 3.8)	16.3 (8.9 - 21.8)
	≥65 years	32	54.4% (35.2% - 70.1%)	6.9 (3.7 - 9.4)	24.3 (14.0 - 47.9)
Gender	Female	15	29.3% (9.2% - 53.3%)	3.6 (1.1 - 6.2)	16.3 (5.1 - 21.8)
	Male	48	42.2% (27.9% - 55.9%)	4.0 (3.2 - 8.1)	20.4 (14.3 - 36.1)
BMI at baseline	≤25kg/m²	22	18.2% (5.7% - 36.3%)	2.2 (1.6 - 4.7)	12.0 (4.0 - 15.8)
	>25kg/m²	41	51.4% (34.7% - 65.7%)	6.2 (3.6 - 8.4)	24.3 (16.8 - 47.9)
ECOG performance status at baseline	0	36	41.6% (25.0% - 57.5%)	3.8 (2.0 - 9.3)	24.1 (15.8 - 59.7)
	≥1	27	37.0% (19.6% - 54.6%)	3.8 (2.1 - 6.4)	10.8 (6.8 - 22.9)

Data of full analysis set are depicted.

Table 2. Efficacy results

Table 3

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%)
Diarrhoea	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%)**
Anaemia	19 (30.2%)	11 (17.5%)
Nervous system disorders	**19 (30.2%)**	**0**
Dysgeusia	10 (15.9%)	0

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.

Table 3. Treatment-emergent adverse events occurring in >10% of patients

Figure 1

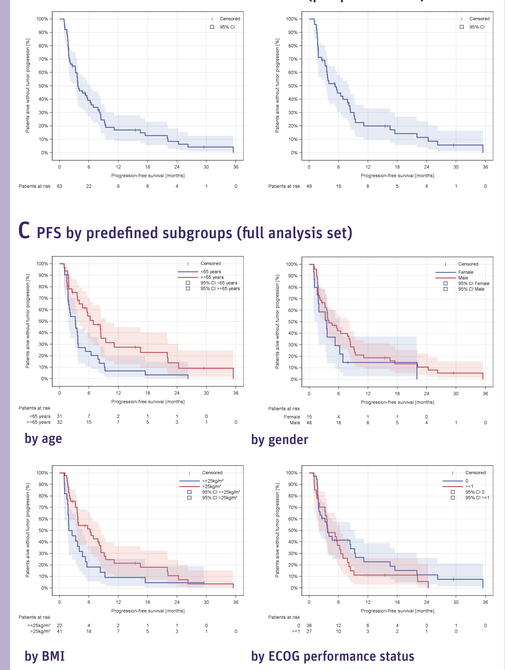

Figure 1. Progression-free survival
Progression-free survival (PFS) by Kaplan-Meier estimate of 63 patients in the full analysis set (A) and 49 patients in the per-protocol population (B), and PFS by predefined subgroups of the full analysis set (C).

Abbreviations:
CI: Confidence Interval | (m)RCC: (metastatic) renal cell carcinoma | VEGF(R) vascular endothelial growth factor (receptor) | TKI: tyrosine kinase inhibitor | 6-month PFS rate: rate of patients free of disease progression at 6 months after start of treatment | PFS: progression-free survival | BMI: body mass index

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Conflicts of Interest:
Staehler: Consultant: Pfizer, GlaxoSmithKline, Novartis, Bayer, Roche, Aveo, EUSAPharm, Astellas, Ipsen, Exelixis, Pelloton, EISAI; Honoraria: Pfizer, GlaxoSmithKline, AVEO, Novartis, Bayer, EUSAPharm, Astellas, Ipsen, Exelixis, Pelloton, EISAI; Research Funding: Pfizer, GlaxoSmithKline, AVEO, Novartis, Bayer, Roche/Genentech, Immatics, Wilex, Ipsen, Exelixis, EISAI

Christoph: Consultant: Novartis; Honoraria: Novartis

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