Received: 17 December 2019 | Revised: 30 June 2020 | Accepted: 7 July 2020

DOI: 10.1002/ijc.33238

CANCER THERAPY AND PREVENTION

IJC International Journal of Cancer

First-line pazopanib in intermediate- and poor-risk patients with metastatic renal cell carcinoma: Final results of the FLIPPER trial

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Funding information
Novartis Pharma GmbH, Grant/Award Number: PZP034ADE03T; Open access funding enabled and organized by Projekt DEAL.

Abstract

Temsirolimus has long been the only approved first-line standard of care (SOC) with overall survival (OS) benefit in poor-risk patients with advanced or metastatic renal cell cancer (mRCC). However, tyrosine kinase inhibitors are also commonly used in clinical practice. Pazopanib is an SOC for first-line mRCC treatment, but for poor-risk patients data are scarce. The FLIPPER (First-Line Pazopanib in Poor-Risk Patients with Metastatic Renal Cell Carcinoma) study aimed to assess efficacy and safety of first-line pazopanib in poor-risk mRCC patients. FLIPPER was a single-arm, multicenter, Phase IV trial. Key inclusion criteria were treatment-naive clear cell, inoperable advanced or mRCC, poor-risk according to MSKCC with slight modification, Karnofsky performance status (KPS) ≥60% and adequate organ function. Oral pazopanib 800 mg was given daily. Primary endpoint was the 6-month progression-free survival rate (PFS6). Secondary endpoints included

Abbreviations: AE, adverse event; CI, confidence interval; CR, complete response; DOR, duration of response; IFN, interferon; KPS, Karnofsky performance status; mITT, modified intention-to-treat; mRCC, locally advanced or metastatic renal cell carcinoma; MSKCC, Memorial Sloan Kettering Cancer Centre; mTOR, mammalian target of rapamycin; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PFS6, 6-month progression-free survival rate; PR, partial response; RCC, renal cell carcinoma; SAF, safety analysis set; SD, stable disease; SOC, standard of care; TEAE, treatment-emergent adverse event; TKI, tyrosine kinase inhibitor.

PFS, OS, overall response rate (ORR), duration of response (DOR) and safety. For analysis, descriptive statistics were used. Between 2012 and 2016, 60 patients had been included. Forty-three patients qualified for safety analyses, 34 for efficacy. Median age was 66 years, 64.7% of patients were poor-risk, 82.4% had a KPS ≤70%. PFS6 was 35.3% (95% CI, 19.7-53.5). Median PFS and OS were 4.5 months (95% CI, 3.6-7.8) and 9.3 months (95% CI, 6.6-22.2), respectively. ORR was 32.4% (95% CI, 17.4-50.5), median DOR 9.7 months (95% CI, 1.8-12.4). The most common treatment-related grade 3/4 adverse event reported in 4.7% of patients was hypertension. No treatment-related death occurred. Since pazopanib is active and well tolerated in poor-risk patients with clear cell mRCC, our results support its use as first-line treatment in this setting.

KEYWORDS

renal cell carcinoma, overall survival, pazopanib, poor-risk patients, progression-free survival

1 | INTRODUCTION

Renal cell carcinoma (RCC) is the most common type of kidney cancer with approximately 99 000 newly diagnosed cases and 39 000 deaths in Europe in 2018.[1] At diagnosis, almost one-third of the patients present with locally advanced and/or metastatic RCC (mRCC). 40% of patients with localized disease at primary diagnosis will develop metastases after nephrectomy.[2-4]

Prognosis of patients with mRCC is determined by criteria of the Memorial Sloan Kettering Cancer Center (MSKCC) based on five risk factors, that is, time from diagnosis to treatment <12 months, presence of anemia, elevated serum calcium concentrations, elevated lactate dehydrogenase concentrations and Karnofsky performance status <80%. These factors are predictive of survival and used to categorize patients into three distinct risk groups: favorable risk (no risk factor), intermediate risk (1-2 risk factors) and poor risk (≥3 risk factors).[5] Accordingly, 20% of patients diagnosed with mRCC are categorized as poor risk.[5] The 5-year survival in mRCC patients is less than 20%[6] and patients with poor prognostic features as defined by the MSKCC have a median overall survival (OS) ranging between 5 and 10.9 months.[5,7]

The MSKCC model was first published in 1999 and developed during the era of cytokines, but has been externally validated for targeted agents as well.[8] Tyrosine kinase inhibitors (TKI) including sunitinib, sorafenib and later also pazopanib were recommended first-line treatment options in poor-risk patients with mRCC according to guidelines valid during the conduction of FLIPPER (First-Line Pazopanib in Poor-Risk Patients with Metastatic Renal Cell Carcinoma).[9-12] The mTOR (mammalian target of rapamycin) inhibitor temsirolimus, however, was recommended as the standard of care (SOC) in this patient population,[9-12] since the pivotal temsirolimus Phase III study had demonstrated improvement in OS compared to interferon (IFN)-alpha.[7] Thus, temsirolimus has long been the only agent having Level 1 evidence for treatment-naive patients with mRCC at poor risk. At the time of the FLIPPER study initiation in 2011, prospective data on the use of pazopanib, a second-generation multi-targeted TKI, as first-line treatment for poor-risk patients with mRCC were missing. Only nine patients with poor prognosis had been included in the pivotal trial leading to market authorization of pazopanib in 2010 and no subgroup analysis of these patients has been reported.[13]

Thus, the objective of the FLIPPER trial was to evaluate the efficacy and safety of first-line pazopanib in poor-risk patients with mRCC.

What's new?

The tyrosine kinase inhibitor pazopanib was approved for treatment-naive or cytokine-pretreated patients with advanced or metastatic renal cell cancer (mRCC) independent of prognosis as determined by the MSKCC risk assessment model. The role of pazopanib in poor-risk patients remains understudied in trials. The FLIPPER Phase IV trial evaluated the efficacy and safety of pazopanib as first-line therapy in patients with mRCC with poor-risk features according to the MSKCC criteria. The results underline that pazopanib is active and well tolerated in poor-risk mRCC patients with clear-cell histology, supporting its use as first-line treatment. During this trial, no new safety signals emerged.

2 | PATIENTS AND METHODS

2.1 | Study design and patient eligibility

FLIPPER was a single-arm, open-label, prospective, multicenter, a trial in patients with mRCC and poor-risk features according to MSKCC criteria treated with first-line pazopanib. The trial was performed within the Interdisziplinäre Arbeitsgruppe Nierentumoren (IAG-N) of the German Cancer Society (DKG). Patients had been recruited at six sites across Germany.

Key eligibility criteria were age ≥18 years, mRCC with predominantly clear cell histology, at least one measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria version 1.1,[14] Karnofsky performance status (KPS) ≥60%, at least three of five study-specific predictors of short survival (according to MSKCC[5] with slight modification due to study protocol: that is, lactate dehydrogenase >1.5× upper limit of normal, hemoglobin limit of normal, corrected serum calcium level >10 mg/dL (2.5 mmol/L), time from diagnosis of RCC to occurrence of metastases of less than 1 year, KPS 60% or 70%), and adequate organ and bone marrow function. Key exclusion criteria were existence of other malignancies, prior systemic treatment for mRCC, central nervous system metastases or leptomeningeal carcinomatosis, clinically significant gastrointestinal abnormalities affecting the absorption of investigational product, infection with HIV or chronic hepatitis B or C, corrected QT interval > 480 ms, history of cardiovascular conditions within the past 6 months, poorly controlled hypertension, history of cerebrovascular accident, prior major surgery or trauma within 28 days prior to first dose of study drug, presence of any serious or unstable pre-existing medical condition that could comprise or interfere with the subject's safety, pregnancy or breast feeding.

2.2 | Treatment and study procedures

Patients received pazopanib 800 mg orally once daily until disease progression, inacceptable toxicity, development of a second

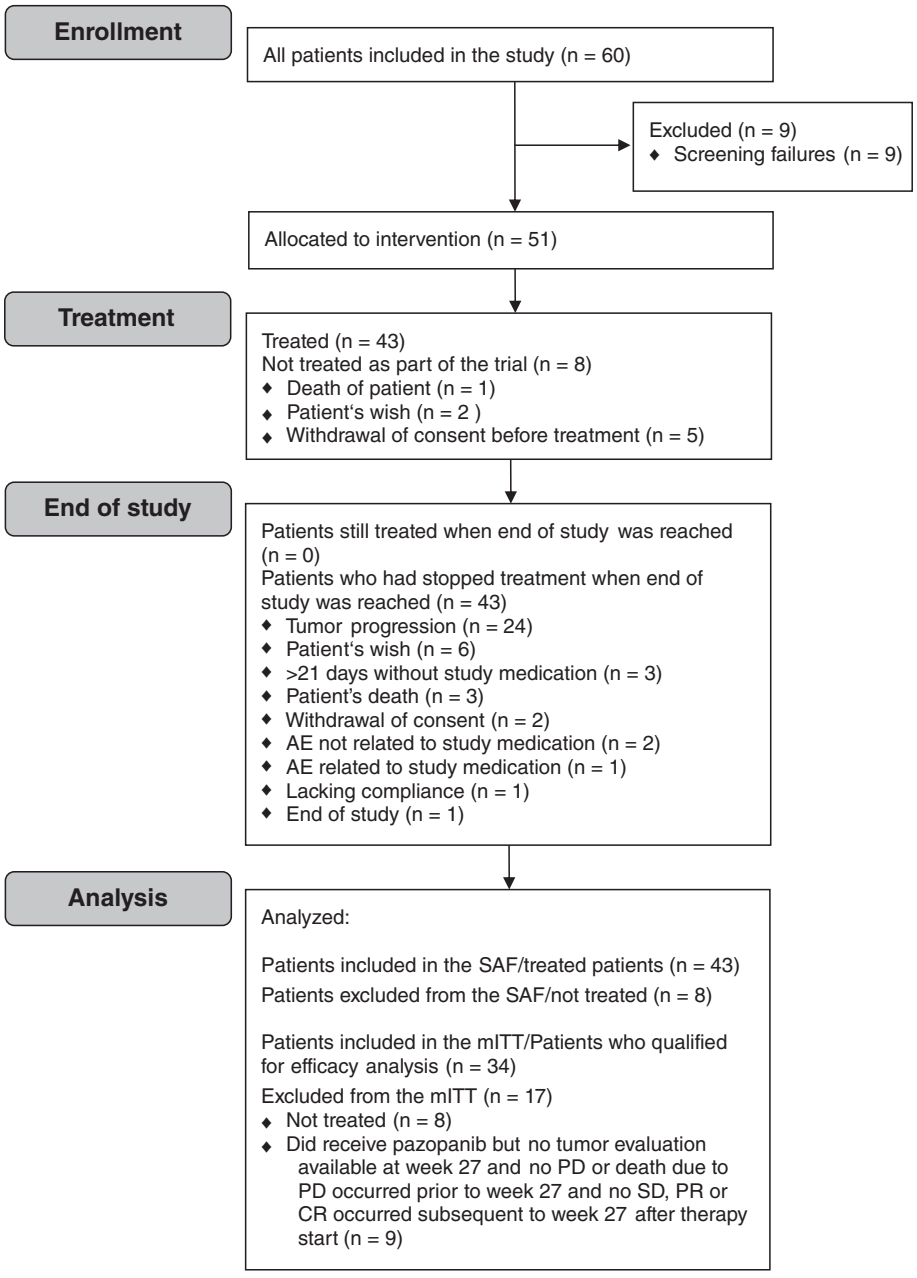

FIGURE 1 Disposition of patients—CONSORT flow diagram. AE, adverse event; CR, complete response; mITT, modified intention-to-treat population; PD, progressive disease; PR, partial response; SAF, safety analysis set; SD, stable disease

malignancy that required treatment or withdrawal of consent. Patients were instructed to take pazopanib either at least 1 hour before or 2 hours after a meal. Dose modifications were performed due to toxicity as predefined in the protocol. The maximum allowed time of treatment interruption was 21 consecutive days.

Tumor response evaluation (computed tomography or magnetic resonance imaging) according to RECIST version 1.1 was performed every 8 weeks (± 7 days) cycle-independently, except after 26 instead of 24 weeks (6 months).

Adverse events (AEs) were reported until 30 days after the last dose of pazopanib.

2.3 | Outcome variables

The primary endpoint was the 6-month PFS rate (PFS6). Secondary endpoints were PFS, OS, overall response rate (ORR), duration of response (DOR) and safety.

2.4 | Statistical analysis

At the time this non-randomized phase IV trial had been designed, there was limited information available regarding the efficacy of first-line therapy with pazopanib in poor-risk mRCC patients. Temsirolimus was the only agent having Level 1 evidence for treatment-naive patients with poor-risk mRCC. Therefore, the aim of the FLIPPER trial was to assess the efficacy and safety of pazopanib in patients with poor-risk mRCC. Due to the exploratory character of our study, no formal sample size calculation had been performed. Initially, enrollment of 80 patients had been planned.

Efficacy was assessed in the modified intention-to-treat (mITT) population, which comprised of patients who received at least one dose of pazopanib and which fulfilled one of the following criteria: progressive disease (PD) or death because of tumor progression prior to 26 weeks +7 days after therapy start, or assessable disease status at 26 weeks ±7 days after therapy start, or experience of stable disease (SD), partial response (PR) or complete response (CR) after 26 weeks +7 days after therapy start.

The PFS6 was defined as proportion of patients without progression or death at 6 months (26 weeks ±7 days) after start of pazopanib therapy. PFS was defined as the interval from first pazopanib administration to tumor progression or death of any cause before start of subsequent antineoplastic treatment. Patients without PD or death were censored at their last date of tumor evaluation. OS was defined as interval from first pazopanib administration to death of any cause. Patients alive at the end of the study were censored at the last documented contact. Time to events were analyzed using Kaplan-Meier estimates. ORR was defined as proportion of patients who achieved a complete or partial response as their best overall response based on RECIST v1.1. DOR was calculated as the time from first occurrence of a response to a documented PD or death of any cause. If a patient did not experience PD prior to onset of a subsequent therapy, the time

TABLE 1 Baseline patient and tumor characteristics

Characteristic	SAF (n = 43)	mITT (n = 34)
Age at start of treatment, years		
Median	66.0	66.0
Range	40.0-87.0	40.0-83.0
Gender, n (%)		
Female	9 (20.9%)	8 (23.5%)
Male	34 (79.1%)	26 (76.5%)
BMI at start of treatment, kg/m^2		
Median	24.3 (n = 42)	24.0 (n = 33)
Range	16.7-45.4	16.7-40.6
Karnofsky performance status, n (%)		
>70	7 (16.3%)	5 (14.7%)
<80 (ie, 60 or 70)	35 (81.4%)	28 (82.4%)
Missing	1 (2.3%)	1 (2.9%)
Hemoglobin, n (%)		
<LLN	37 (86.0%)	28 (82.4%)
≥LLN	6 (14.0%)	6 (17.6%)
Corrected serum calcium, n (%)		
>10 mg/dL	5 (11.6%)	5 (14.7%)
≤10 mg/dL	37 (86.0%)	28 (82.4%)
Missing	1 (2.3%)	1 (2.9%)
Lactate dehydrogenase, n (%)		
>1.5 times ULN	3 (7.0%)	2 (5.9%)
≤1.5 times ULN	39 (90.7%)	31 (91.2%)
Missing	1 (2.3%)	1 (2.9%)
Time from primary diagnosis to start of treatment, n (%)		
<1 year	36 (83.7%)	28 (82.4%)
≥1 year	5 (11.6%)	4 (11.8%)
Missing	2 (4.7%)	2 (5.9%)
MSKCC risk category,[a] n (%)		
Intermediate	11 (25.6%)	9 (26.5%)
Poor	29 (67.4%)	22 (64.7%)
Unknown	3 (7.0%)	3 (8.8%)
UICC tumor stage at initial diagnosis, n (%)		
II	1 (2.3%)	0 (0.0%)
III	7 (16.3%)	5 (14.7%)
IV	27 (62.8%)	21 (61.8%)
Missing	8 (18.6%)	8 (23.5%)
Prior nephrectomy, n (%)		
Radical	31 (72.1%)	26 (76.5%)
Partial	3 (7.0%)	1 (2.9%)
None	9 (20.9%)	7 (20.6%)

Note: Some percentages might not add up to 100% due to rounding.
Abbreviations: BMI, body mass index; LLN, lower limit of normal; mITT, modified intention-to-treat population; MSKCC, Memorial Sloan Kettering Cancer Center; SAF, safety analysis set; UICC, Union for International Cancer Control; ULN, upper limit of normal.
[a]According to Motzer et al[5]; for the patients listed as "unknown," an unambiguous assignment into one risk group was not possible.

was censored at last date of tumor evaluation or start of subsequent antineoplastic treatment, whatever came first.

Since no hypotheses were tested and due the relatively low number of patients included (mITT; n = 34), no subgroup or exploratory analyses were performed as part of our study.

Safety analysis was performed for all patients who received at least one dose of pazopanib (safety analysis set, SAF). AEs were coded according to MedDRA (Medical Dictionary for Regulatory Activities) version 20.0 and graded according to the NCI-CTCAE (National Cancer Institute-Common Terminology Criteria for Adverse Events) version 4.03.

The data analysis for our study was generated using the SAS software, Version 9.4 of the SAS System for Windows. Copyright© 2002-2012 SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.

The end of study was September 1, 2017.

3 | RESULTS

3.1 | Patient population

Between January 2012 and December 2016, 60 patients had been enrolled. Due to the low accrual, the recruitment had been stopped with the enrollment of the 60th patient.

Nine patients were later found to be ineligible due to violation of in- or exclusion criteria (n = 8) or lost to follow-up (n = 1). Of the remaining 51 patients, 43 patients received at least one dose of study medication and were analyzed for SAF. Eight patients did not receive treatment as part of the trial (1 patient died, 5 patients withdrew consent before treatment start, 2 patients did not want to have treatment). Three-four patients qualified for efficacy analysis according to mITT.

The disposition of patients is shown in Figure 1 (CONSORT flow diagram).

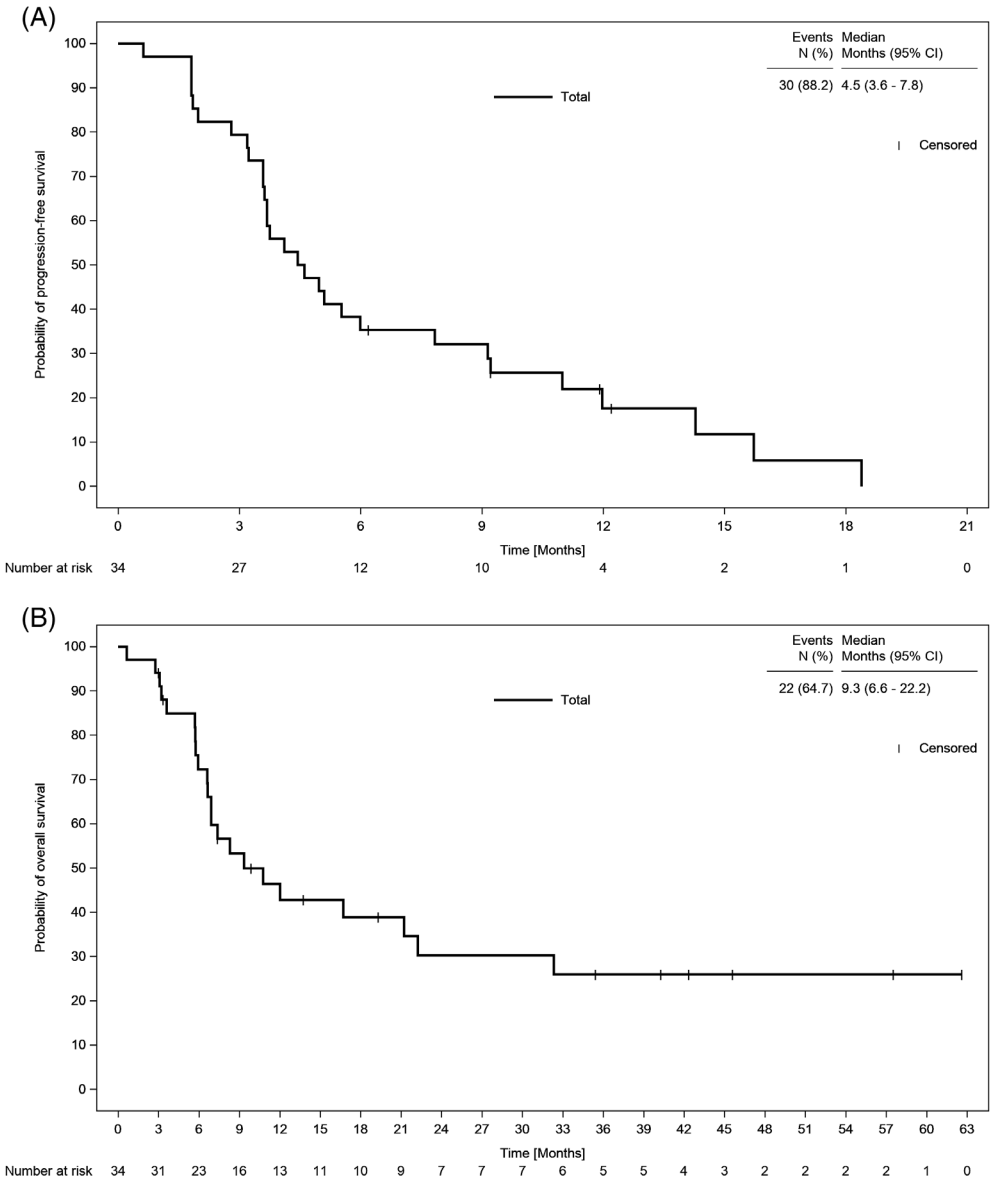

FIGURE 2 Kaplan-Meier survival curves of (A) progression-free survival (PFS) and of (B) overall survival (OS). CI, confidence interval

All patients had predominantly clear cell histology and almost 80% of patients had undergone prior nephrectomy (SAF: 79.1%, mITT: 79.4%). At inclusion, all patients had metastatic disease and the majority of patients were categorized as poor-risk (SAF: 67.4%, mITT: 64.7%; intermediate risk: SAF: 25.6%, mITT: 26.5%) according to MSKCC criteria.[5]

Baseline patient and tumor characteristics are summarized in Table 1 for both mITT and SAF.

3.2 | Efficacy

The primary endpoint PFS6 was 35.3% (95% CI 19.7-53.5). Median PFS was 4.5 months (95% CI, 3.6-7.8) (Figure 2A), and median OS was 9.3 months (95% CI, 6.6-22.2) (Figure 2B).

The ORR was 32.4% (95% CI, 17.4-50.5). No CR was observed. Eleven of 34 patients (32.4%) had a PR. Median DOR in patients with overall response was 9.7 months (95% CI, 1.8-12.4). Seventeen patients (50.0%) achieved disease stabilization, 5 patients (14.7%) had PD as best response and for 1 patient (2.9%) data were missing.

3.3 | Treatment exposure

Within the FLIPPER trial, 43 patients started oral pazopanib treatment with a median duration of pazopanib treatment of 17.0 weeks (range 1.6-92.0). The mean relative dose intensity of pazopanib was 98.2% (SD 6.44). The proportion of patients undergoing pazopanib dose reductions was 4.7% (n = 2). Permanent treatment discontinuation of pazopanib due to related AEs was documented in 2 patients (4.7%). Twenty-five patients (58.1%) received further anticancer therapy during study follow-up. Of the remaining 18 patients, 7 (16.3%) did not receive further antineoplastic treatment, 5 (11.6%) patients died within 2 months after the end of treatment, while for 6 patients (14.0%) data on subsequent antineoplastic treatment were missing.

TABLE 2 Summary of safety: adverse events (SAF, n = 43)

	Any grade (n,%)
Patients with any adverse event	40 (93.0%)
AEs occurring in ≥10% of patients	
Hypothyroidism	13 (30.2%)
Diarrhea	13 (30.2%)
Fatigue	8 (18.6%)
Nausea	7 (16.3%)
Decreased appetite	6 (14.0%)
Hypertension	5 (11.6%)
Vomiting	5 (11.6%)
	Grade 3/4 (n,%)
Patients with any adverse event	14 (32.6%)
AEs occurring in ≥5% of patients	
Fatigue	2 (4.7%)
Pleural effusion	2 (4.7%)
Hypertension	2 (4.7%)

Note: Adverse events (AEs) were evaluated in the safety analysis set (SAF) and were coded using MedDRA version 20.0. More than one reported Preferred Term (PT) per patient within a System Organ Class (SOC) was possible. "Hypothyroidism" includes the SOC "Endocrine disorders" with the PT "Hypothyroidism" and the MedDRA SOC "Investigations" with the PT "Blood thyroid stimulating hormone increased".

3.4 | Safety

Treatment-emergent AEs (TEAEs) of any grade were reported in 40 of 43 patients (93.0%), with hypothyroidism and diarrhea as the most common (reported in 30.2% of patients, respectively; Table 2). Grade 3/4 TEAEs were documented in 14 patients (32.6%; Table 2). The most frequent Grade 3/4 TEAEs occurring in 4.7% of patients each included fatigue, pleural effusion and hypertension (Table 2). Fatal

TABLE 3 Summary of safety: pazopanib-related adverse events (SAF, n = 43)

	Any grade (n, %)
Patients with any pazopanib-related AE	34 (79.1%)
Related AEs occurring in ≥5% of patients	
Hypothyroidism	13 (30.2%)
Diarrhea	11 (25.6%)
Fatigue	8 (18.6%)
Nausea	5 (11.6%)
Decreased appetite	5 (11.6%)
Abdominal pain upper	4 (9.3%)
Hypertension	4 (9.3%)
Vomiting	4 (9.3%)
Dysgeusia	3 (7.0%)
Weight decreased	3 (7.0%)
	Grade 3/4 (n,%)[a]
Patients with any pazopanib-related AE	8 (18.6%)
Hypertension	2 (4.7%)
Alanine aminotransferase increased	1 (2.3%)
Decreased appetite	1 (2.3%)
Diarrhea	1 (2.3%)
Fatigue	1 (2.3%)
Fistula	1 (2.3%)
Pleural effusion	1 (2.3%)

Note: Pazopanib-related adverse events (AEs) were evaluated in the safety analysis set (SAF) and were coded using MedDRA version 20.0. More than one reported Preferred Term (PT) per patient within a System Organ Class (SOC) was possible. "Hypothyroidism" includes the MedDRA SOC "Endocrine disorders" with the PT "Hypothyroidism" and the MedDRA SOC "Investigations" with the PT "Blood thyroid stimulating hormone increased".

[a]All related AEs classified as Grade 3/4 were of Grade 3 only (related AEs of Grade 4 did not occur).

TEAEs were reported in 7 patients (16.3%), although 6 of them were attributed to tumor progression. One patient died from bradycardia followed by cardiac arrest. TEAEs related to pazopanib treatment of any grade and of Grade 3/4 occurred in 34 patients (79.1%) and 8 patients (18.6%), respectively (Table 3). The most common Grade 3/4 treatment-related TEAE reported in 4.7% of patients was hypertension. Of note, all 8 related Grade 3/4 TEAEs were of Grade 3, since Grade 4 TEAEs had not been documented. For 2 patients (4.7%), a pazopanib-related TEAE leading to treatment discontinuation had been documented (pneumonia, fistula). No treatment-related death occurred.

4 | DISCUSSION

Prospective data on treatment of poor-risk patients with mRCC are rare. Temsirolimus has long been the only drug with Level 1 evidence for first-line treatment in these patients,[9-11,15] since the pivotal phase III study on temsirolimus had demonstrated improvement of OS compared to IFN-alpha monotherapy.[7] Pazopanib was approved for treatment-naive or cytokine-pretreated adult patients with mRCC independent of prognosis as determined by the MSKCC risk assessment model.[16] However, pivotal trials had only included low numbers of poor-risk patients, which left a gap with regard to the role of pazopanib in this patient population. FLIPPER was designed to investigate the efficacy and safety of pazopanib as first-line therapy in poor-risk mRCC patients.

Major strengths of our study are the prospective design and the clinical importance regarding the use of pazopanib as first-line treatment in poor-risk mRCC patients. However, there are several limitations. Due to the low accrual, the recruitment had been stopped with the enrollment of the 60th patient leading to a relatively small sample. Although most patients were of poor risk according to MSKCC (65%), a proportion of intermediate-risk patients was also included, since one MSKCC criterion used for FLIPPER differed slightly from that of the original model. In addition, the fairly stringent definition of the mITT set might have caused a positive selection bias. For the present study, no hypotheses were tested, and thus only descriptive statistics were performed. Moreover, no subgroup or exploratory analyses were performed. Interpretation of results may also be hampered by the single arm setting of our study.

The results of this analysis showing a PFS6 of 35.3%, a median PFS and OS of 4.5 months and 9.3 months, respectively, are comparable with those of the temsirolimus registration trial revealing a PFS6 of about 35%, a median PFS of 3.8 months and a median OS of 10.9 months, respectively, for patients with mRCC and a poor prognosis.[7] The pivotal trial leading to market authorization of pazopanib reported a median PFS of 11.1 months for the treatment-naive mRCC patient population.[13] However, of all patients included, only 3% of patients who underwent pazopanib were of poor risk while almost 40% were of favorable risk. Furthermore, no subgroup analysis for poor-risk patients has been shown. The ORR of 32.4% in the FLIPPER trial was considerably better than that of 8.6% observed in historical control with temsirolimus.[7] This result is in line with an ORR of approximately 30% seen in several prospective and retrospective trials investigating pazopanib in mRCC. Remarkably, the rate of poor-risk patients in these studies was significantly lower than in FLIPPER.[13,17,18] The median DOR was 9.7 months in our study, but not evaluated in the pivotal temsirolimus trial. Of note, the proportion of poor-risk patients defined according to MSKCC was similar between the temsirolimus registration trial and FLIPPER (69 vs 65%, respectively).[7] However, baseline demographic and clinical characteristics were different (data not shown here). Patients were younger in the temsirolimus trial (median age 58 vs 66 years) and more females were included (33 vs 24%).[7] The proportion of patients with clear cell carcinoma was lower in the temsirolimus registration trial (81%) compared to FLIPPER (100% predominantly clear cell carcinoma) and less patients in the temsirolimus trial had a prior debulking nephrectomy before initiating systemic therapy (66 vs 79% (radical and partial)/77% (radical) (FLIPPER trial)).[7] Data from the German clinical RCC Registry on more than 1400 patients with mRCC who had started first-line treatment were exploratory analyzed for potential prognostic factors for OS. In the multivariate Cox regression model, gender and prior partial/complete nephrectomy showed no tendency concerning OS advantage.[19] Higher age at start of first-line treatment (FLIPPER trial) and non-clear cell carcinoma (temsirolimus trial) tended to be associated with shorter OS.[19]

In the temsirolimus trial, common Grade 3/4 AEs reported in at least 10% of patients receiving temsirolimus were anemia, asthenia and hyperglycemia.[7] In the FLIPPER trial, fatigue, pleural effusion and hypertension were the only Grade 3/4 TEAEs experienced by approximately 5% of patients receiving pazopanib (4.7% each).

Our results indicate efficacy of pazopanib in first-line treatment of poor-risk patients and seem to be in line with recently published results of the head-to-head TemPa trial (Table 4).[20] In this two-arm, open-label phase II trial, patients with mRCC, major clear cell component and poor-risk features (according to Hudes et al[7]), were stratified by nephrectomy status and prior cytokine/vaccine therapy and randomized to receive pazopanib or temsirolimus as first-line treatment. According to the IMDC (International mRCC Database Consortium) risk assessment model,[26,27] 77% of patients (n = 26) had poor risk in the pazopanib group, while this proportion was 69% (n = 24) in the temsirolimus group.[20] Survival of IMDC poor-risk patients tended to be better if treated with pazopanib (median PFS: pazopanib 4.9 months, temsirolimus 1.9 months; median OS: pazopanib 9.6 months, temsirolimus 5.3 months). In addition, pazopanib yielded higher ORR than temsirolimus (24.0 vs 4.3%) in poor-risk patients and overall patient-reported outcome measures favored pazopanib. AEs observed in the TemPa trial were consistent with the known safety profiles of pazopanib and temsirolimus.[20] The most common Grade 3/4 AEs occurring in at least 10% of patients were hypertension, fatigue and ALT increased in the pazopanib group and fatigue and anemia in the temsirolimus group.[20] The TemPa trial shows that pazopanib seems to be at least as effective as temsirolimus, and if choosing between these two options pazopanib should be favored over temsirolimus as first-line treatment in patients with poor-risk

TABLE 4 Efficacy of FDA/EMA-approved agents in the first-line treatment of (predominantly) poor-risk patients with mRCC

		Proportion of poor-risk patients (%, (n))	Number of poor-risk patients in subgroups	Median PFS (months, [95% CI])	Median OS (months, [95% CI])	ORR (%, [95% CI])
FLIPPER Phase IV	Pazopanib	64.7 (22)[a]	n.a.	4.5 [3.6-7.8][b]	9.3 [6.6-22.2]	32.4 [17.4-50.5]
Temsirolimus registration trial[7] Phase III	Temsirolimus	69.4 (145)[a]	n.a.	3.8 [3.6-5.2][b] 5.5 [3.9-7.0][c]	10.9 [8.6-12.7]	8.6 [4.8-12.4]
TemPa[20] Phase II	Pazopanib	—	26[d]	4.9 [2.5-6.5][c]	9.6 [4.6-5.5]	24.0 (n = 25) [9.4-45.1]
	Temsirolimus	—	24[d]	1.9 [1.8-3.1][c]	5.3 [3.1-7.9]	4.3 (n = 23) [0.1-21.9]
COMPARZ[21] Phase III	Pazopanib	—	67[a]	n.a.	9.9 [7.3-12.3]	n.a.
	Sunitinib	—	52[a]	n.a.	7.7 [5.4-11.9]	n.a.
PRINCIPAL[22] Observational	Pazopanib	—	91[a]	4.2 [2.9-6.7][b]	9.6 [5.9-14.6]	19.2 (n = 73) [n.a.]
			153[d]	5.9 (n = 152) [4.1-8.0][b]	12.3 [8.7-16-4]	20.5 (n = 122) [n.a.]
CABOSUN[23,24] Phase II	Cabozantinib	—	15[d]	6.14 [n.a.][b] 6.8 [n.a.][c]	n.a.	n.a.
	Sunitinib	—	15[d]	2.77 [n.a.][b] 2.7 [n.a.][c]	n.a.	n.a.
CheckMate 214[25] Phase III	Nivolumab + Ipilimumab	—	102[d]	n.a.	HR for death 0.57 [95% CI, 0.39-0.82] in favor for Nivo+Ipi	Unweighted ORR[c] difference 27.8% [95% CI, 15.8-38.8] in favor for Nivo+Ipi
	Sunitinib	—	97[d]	n.a.		

Abbreviations: CI, confidence interval; EMA, European Medicines Agency; FDA, US Food and Drug Administration; HR, hazard ratio; Ipi, ipilimumab; mRCC, metastatic renal cell carcinoma; n.a., not applicable; Nivo, nivolumab; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

[a]According to MSKCC criteria[5].

[b]Estimate by site investigators.

[c]Estimate by independent radiologic assessment.

[d]According to IMDC criteria.

mRCC because of the favorable safety profile. However, the results of TemPa are limited by the small sample size of patients included, since the trial accrual was stopped before reaching the target number of patients after the results of the CheckMate 214[25] phase III and CABOSUN[23,24] phase II trials evaluating nivolumab plus ipilimumab or cabozantinib became available.[20]

According to guidelines, sunitinib is another reasonable option in patients with poor-risk mRCC.[9-12,28] A subgroup analysis of the sunitinib Phase III registration trial has shown efficacy of sunitinib in first-line treatment of poor-risk mRCC with a median OS of 5.3 months compared to 4.0 months for IFN-alpha.[29] After the start of FLIPPER, the results of two head-to-head studies (COMPARZ,[17] Table 4 and PISCES[30]) directly comparing pazopanib and sunitinib as first-line treatment of mRCC, were presented. The non-inferiority COMPARZ trial established both pazopanib and sunitinib as the SOC for patients with treatment-naive mRCC irrespective of prognostic risk group.[17] For patients with poor-risk disease according to MSKCC criteria, a subgroup analysis for OS was performed: median OS was 9.9 months among 67 patients in the pazopanib arm and 7.7 months among 52 patients in the sunitinib arm.[21] Results of median OS achieved by pazopanib in the COMPARZ trial[17] (9.9 months) and FLIPPER trial (9.3 months) compare well and support its use.

The PISCES study showed a significant patient preference for pazopanib (70%) over sunitinib (22%).[30] Less fatigue and better overall quality of life were the main reasons for preferring pazopanib. Physicians also preferred pazopanib (61%) over sunitinib (22%).[30] Even though no analyses for poor-risk patients are available for the PISCES trial, these two important prospective studies have clearly shown that both TKIs have similar efficacy, but safety and quality of life profiles favor pazopanib. The efficacy outcomes were recently confirmed in several retrospective analyses, claiming that pazopanib is at least as efficacious as sunitinib in poor-risk patients.[31,32]

Data collected in PRINCIPAL[22] (Table 4), the largest prospective real-world study, confirmed that pazopanib has a favorable overall risk benefit as first-line treatment for patients with mRCC. Median PFS and median OS for patients with poor-risk features were 4.2 and 9.6 months, respectively, and the safety profile was also consistent with clinical trials.[22]

Recently, results of the randomized Phase II trial CABOSUN[23,24] and the Phase III trial CheckMate 214[25,33] (Table 4), evaluating cabozantinib or nivolumab plus ipilimumab compared to sunitinib, respectively, demonstrated reasonable activity of these agents as first-line treatment in patients with mRCC and intermediate or poor risk. In both trials, analysis of patients in the IMDC poor-risk subgroup observed a survival benefit with cabozantinib or nivolumab plus ipilimumab, respectively, over sunitinib (CABOSUN,[23,24] median PFS: 6.14 (cabozantinib) vs 2.77 months (sunitinib); CheckMate 214,[25] hazard ratio for death 0.57 [95% CI, 0.39-0.82]) and were consistent with the overall results. Based on data from CABOSUN, cabozantinib was approved by the US Food and Drug Administration (FDA) for first-line treatment of patients with treatment-naive mRCC irrespective of the prognostic risk group in 2017. One year later, in 2018, cabozantinib was approved for first-line treatment of intermediate- or poor-risk mRCC by the European Medicines Agency (EMA). First-line nivolumab plus ipilimumab for patients with intermediate- or poor-risk mRCC was approved by the FDA in 2018 based on the results of the CheckMate 214 trial and by the EMA in 2019. In recent guidelines, the combination of ipilimumab and nivolumab has become the recommended SOC for first-line treatment of poor-risk patients with clear cell mRCC.[28] Despite the proven survival benefit of ipilimumab plus nivolumab and its important role in first-line treatment of poor- or intermediate-risk mRCC, one has to be aware of the observed increase in treatment-related side effects in the CheckMate 214 trial due to combination therapy.[25,33,34]

5 | CONCLUSIONS

In summary, the results of the FLIPPER trial suggest that pazopanib is an effective and reasonable first-line treatment option for patients with mRCC and poor-risk disease. In comparison with the results of the pivotal temsirolimus Phase III trial and in line with the recently presented results of the head-to-head TemPa trial, pazopanib seems to offer similar efficacy in this patient group. New agents, like the third-generation TKI cabozantinib and the combination of the checkpoint inhibitors nivolumab plus ipilimumab have changed the front-line treatment of mRCC. However, given its favorable tolerability profile, pazopanib remains a treatment alternative in patients with poor prognosis who are not candidates for immunotherapy.

ACKNOWLEDGMENTS

The authors would like to thank all investigators, site personnel and patients who participated in the FLIPPER trial. We thank Dr. Martin Indorf (iOMEDICO) for support during the project and Dr. Anja Kaiser-Osterhues (iOMEDICO) for review of the manuscript. The FLIPPER trial is managed and analyzed by iOMEDICO and has received continuous financial support from Novartis Pharma GmbH. Novartis Pharma had no role in study design, data collection and analysis, interpretation of results, decision to publish, or preparation of the manuscript. Open access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST

A. Panic, M. Merling, K. Potthoff, E. Herrmann, P. de Geeter, C. Vannier and C. Hogrefe 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. 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. 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 non-financial support from BMS and from Ipsen, personal fees and non-financial support from Roche, Novartis, and EISAI, personal fees from MSD, during the conduct of the study. Furthermore, VG has received grants, personal fees, non-financial support and other from MSD, AstraZeneca, and BMS, grants from Novartis, personal fees and non-financial support from Merck Serono and PharmaMar, personal fees from Roche, Pfizer, Lilly, Janssen and Nanobiotix outside the submitted work.

ETHICS STATEMENT

The FLIPPER trial had been approved by the responsible ethics committee and is registered at ClinicalTrials.gov (NCT01521715). Each patient had provided written informed consent before screening procedures were initiated.

DATA AVAILABILITY STATEMENT

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

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How to cite this article: Staehler M, Panic A, Goebell PJ, et al. First-line pazopanib in intermediate- and poor-risk patients with metastatic renal cell carcinoma: Final results of the FLIPPER trial. *Int. J. Cancer*. 2021;148:950–960. https://doi.org/10.1002/ijc.33238

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