RESULTS FROM THE FLIPPER-STUDY

FIRST-LINE PAZOPANIB IN POOR-RISK PATIENTS WITH METASTATIC RENAL CELL CARCINOMA

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INTRODUCTION

The average annual number of newly diagnosed cases of malignant neoplasms of the kidney, of which renal cell carcinoma (RCC) accounts for 90% of all cases, is estimated to be 15,100 for the year 2018 in Germany[1]. Almost one third of the patients present with advanced disease at diagnosis and a further 20-40% of patients with local disease at diagnosis will develop metastases after nephrectomy.

Pazopanib is approved for the first-line treatment of advanced RCC (aRCC) and for patients who have received prior cytokine therapy for advanced disease. Currently, temsirolimus is the only agent especially licensed for the treatment of patients with poor-risk metastatic RCC (mRCC) according to the Memorial Sloan Kettering Cancer Center (MSKCC) criteria adapted by Hudes et al.[2] Despite the availability of temsirolimus, treatment options remain limited for the poor-risk patient group and further trials are needed to assess the potential benefits of other targeted agents in this setting.

The aim of the FLIPPER study was to assess the efficacy and safety of first-line pazopanib in poor-risk patients with aRCC (i.e., locally advanced and/or mRCC).

METHODS

FLIPPER was a single arm, multicenter, national, phase IV trial, designed to prospectively collect data on patients with poor-risk aRCC treated with first-line pazopanib. Key inclusion criteria were locally advanced and/or mRCC with predominantly clear-cell histology, at least one measurable lesion, at least three of five study-specific predictors of short survival (i.e., lactate dehydrogenase >1.5 x ULN, hemoglobin <LLN, 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, Karnofsky Performance Status (KPS) of 60 or 70), KPS ≥60, and adequate organ as well as bone marrow function. Key exclusion criteria were existence of other malignancies and prior systemic treatment for RCC.

Patients received 800 mg pazopanib orally once daily until disease progression, inacceptable toxicity, development of a second malignancy that required treatment, or withdrawal of consent. It was recommended to perform dose modifications in 200 mg decrements or increments in a stepwise fashion based on individual tolerability and in accordance with protocol-defined management for selected adverse events (AEs). The maximum allowed time of interruption was 21 consecutive days.

Radiologic assessments were carried out after week 8, 16, 26 and 32 (± 7 days) and subsequently at 8-week intervals after start of treatment until disease progression or permanent treatment discontinuation. Tumor response was evaluated by the investigators according to RECIST 1.1 criteria.

Primary objective was to evaluate efficacy of pazopanib assessed by the rate of patients free of disease progression after 6 months after start of treatment (6-month PFS rate). Secondary endpoints included overall survival (OS), PFS, objective response rate (ORR), duration of response (DOR), and safety. Descriptive statistics were used to analyze the data.

RESULTS

From January 2012 to December 2016, 60 patients with aRCC and predominantely clear-cell histology were recruited at 6 sites across Germany and followed up until July 2017. 43 patients of those received at least one dose of pazopanib and qualified for safety analysis (SAF). For efficacy analysis, 34 patients were evaluable (modified intention-to treat analysis, mITT). Baseline patient and tumor characteristics are depicted in **Table 1**.

The median duration of treatment with pazopanib was 17.0 weeks (range 1.6-92.0) with a mean relative dose intensity of 98.2% (StD 6.44). 89.5% of documented cycles (264 of 295 cycles) were administered without dose modifications. Main reason for treatment discontinuation was progressive disease, experienced by 24 of 43 patients (55.8%).

The 6-month PFS rate (primary endpoint) was 35.3% (95% CI, 19.7-53.5), median PFS was 4.5 months (95% CI, 3.6-7.8) and median OS was 9.3 months (95% CI, 6.6-22.2) (**Figure 1** and **2**). The ORR was 32.4% (95% CI, 17.4-50.5). No complete response was observed during treatment with pazopanib. Eleven of 34 patients had a partial response (**Table 2**). Median DOR in patients with objective response was 9.7 months (95% CI, 1.8-12.4).

Treatment-emergent AEs (TEAEs) of any grade were experienced by 40 of 43 patients (93.0%). 14 patients (32.6%) developed grade 3/4 events (**Table 3**). Grade 3/4 events experienced by most patients (n=2, 4.7% each) were fatigue, pleural effusion, and hypertension. Treatment-related TEAEs of any grade and of grade 3/4 occurred in 34 patients (79.1%) and 8 patients (18.6%), respectively. Seven patients (16.3%) were reported with fatal TEAEs during the study ((malignant) neoplasm progression (n=3), haemothorax due to malignant neoplasm of pleura (n=1), osteolysis (due to tumor progression) (n=1), bradycardia followed by cardiac arrest (n=1), acute kidney injury (n=1)). None of these was reported to be related to pazopanib.

CONCLUSION

The FLIPPER trial showed that pazopanib is active and well tolerated in mRCC patients with clear-cell histology and intermediate-/poor-risk features according to MSKCC criteria. In comparison to the results of the pivotal temsirolimus phase III trial[2] and in line with the recently presented results of the head-to-head TemPa trial[3,4] and real-world data (PRINCIPAL trial[5]), pazopanib seems to be at least equally effective in this patient group. Thus, given its favorable tolerability profile, especially in comparison to other approved tyrosine kinase inhibitors, pazopanib represents an alternative treatment option for patients with poor-risk mRCC.

Figure 1

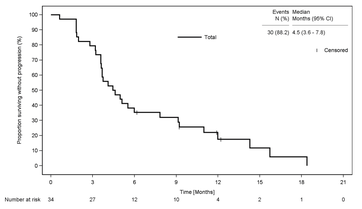

Figure 1 - Kaplan-Meier estimate of PFS

Figure 2

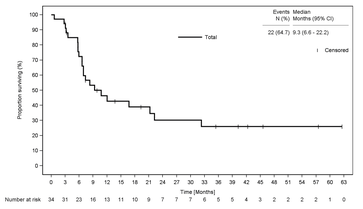

Figure 2 - Kaplan-Meier estimate of OS

Table 1

Characteristic	mITT (N=34)
Age at start of treatment, years	
Median	66.0
Range	40.0 – 83.0
Gender, n (%)	
Female	8 (23.5)
Male	26 (76.5)
BMI at screening, kg/m²	
Median	24.0 (N=33)
Range	16.7 – 40.6
Karnofsky Performance Status, n (%)	
>70	5 (14.7)
≤70	28 (82.4)
Missing	1 (2.9)
Previous nephrectomy, n (%)	
Radical	26 (76.5)
Partial	1 (2.9)
None	7 (20.6)
Metastatic status, n (%)	
M1	34 (100)
MSKCC, n (%)	
Intermediate	9 (26.5)
Poor	22 (64.7)
Missing	3 (8.8)

BMI, body mass index; MSKCC, Memorial Sloan Kettering Cancer Center

Table 1 – Baseline patient and tumor characteristics

Table 2

	mITT (N=34)	Exact binomial 95% CI (Clopper-Pearson)
Best Response (n [%])		
CR	0 (0.0)	N.A.
PR	11 (32.4)	17.4 - 50.5
SD	17 (50.0)	32.4 - 67.6
PD	5 (14.7)	5.0 - 31.1
Missing	1 (2.9)	0.1 - 15.3
Objective response (n [%])		
Yes	11 (32.4)	17.4 - 50.5
No	22 (64.7)	46.5 - 80.3
Missing	1 (2.9)	0.1 - 15.3

CR, complete response; N.A., not applicable; PD, progressive disease; PR, partial response; SD, stable disease

Table 2 – Response

Table 3

MedDRA System Organ Class Adverse Event, Preferred Term	Any grade (n,%)	Grade 3/4 (n,%)
Patients with any event	40 (93.0)	14 (32.6)
Gastrointestinal disorders	23 (53.5)	1 (2.3)
Diarrhoea	13 (30.2)	1 (2.3)
Nausea	7 (16.3)	0
Vomiting	5 (11.6)	0
General disorders and administration site conditions	14 (32.6)	3 (7.0)
Fatigue	8 (18.6)	2 (4.7)
Investigations	12 (27.9)	1 (2.3)
Blood thyroid stimulating hormone increased	6 (14.0)	0
Endocrine disorders	7 (16.3)	0
Hypothyroidism	7 (16.3)	0
Metabolism and nutrition disorders	7 (16.3)	2 (4.7)
Decreased appetite	6 (14.0)	1 (2.3)
Vascular disorders	5 (11.6)	2 (4.7)
Hypertension	5 (11.6)	2 (4.7)

Adverse events were coded using MedDRA version 20.0. Time range: from first administration of pazopanib 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 occuring in 10% or more of treated patients

Abkürzungen:
AE: Adverse Events | aRCC: advanced Renal Cell Carcinoma | BMI: Body Mass Index | CI: Confidence Interval | DOR: Duration of Response | KPS: Karnofsky Performance Status | LLN: Lower Limit of Normal | mITT: modified Intention-to-Treat | mRCC: metastatic Renal Cell Carcinoma | MSKCC: Memorial Sloan Kettering Cancer Center | N.A.: Not Applicable | ORR: Objective Response Rate | OS: Overall Survival | PFS: Progressive-Free Survival | RCC: Renal Cell Carcinoma | RECIST: Response Evaluation Criteria in Solid Tumors | SAF: Safety Analysis Set | StD: Standard Deviation | TEAE: Treatment-Emergent Adverse Event | ULN: Upper Limit of Normal

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Conflicts of Interest:
Staehler: Consultant: Pfizer, GlaxoSmithKline, Novartis, Bayer, Roche, AVEO, EUSA Pharma, Astellas, Ipsen, Exelixis, Peloton, Eisai; Honoraria: Pfizer, GlaxoSmithKline, AVEO, Novartis, Bayer, EUSA Pharma, Astellas, Ipsen, Exelixis, Peloton, Eisai; Research Funding: Pfizer, GlaxoSmithKline, AVEO, Novartis, Bayer, Roche/Genentech, Immatics, Wilex, Ipsen, Exelixis, Eisai

Hermann: Consultant: BMS, Ipsen, Novartis; Honoraria: BMS, Ipsen, Novartis

Grünwald: Honoraria: BMS, Ipsen, Eisai, Novartis, Pfizer, Roche, Astra Zeneca, Bayer, Cerulean; Ownership of business stakes, stocks or funds: Astra Zeneca, BMS, MSD; Research Funding: Astra Zeneca, BMS, MSD, Pfizer, Novartis; Other financial relationships: Novartis

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