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An Open-Label, Multicenter, Randomized, Phase II Study of Pazopanib in Combination with Pemetrexed in First-Line Treatment of Patients with Advanced-Stage Non–Small-Cell Lung Cancer

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Introduction:

This randomized open-label phase II study evaluated the efficacy, safety, and tolerability of pazopanib in combination with pemetrexed compared with the standard cisplatin/pemetrexed doublet in patients with previously untreated, advanced, nonsquamous non–small-cell lung cancer.

Methods:

Patients were randomized (2:1 ratio) to receive pemetrexed 500 mg/m^2 intravenously once every 3 weeks plus either oral pazopanib 800 mg daily or cisplatin 75 mg/m^2 intravenously once every 3 weeks up to six cycles. All patients received folic acid, vitamin B12, and steroid prophylaxis. The primary endpoint was progression-free survival (PFS).

Results:

The study was terminated after 106 of 150 patients were randomized due to a higher incidence of adverse events leading to withdrawal from the study and severe and fatal adverse events in the pazopanib/pemetrexed arm than in the cisplatin/pemetrexed arm. At the time enrolment was discontinued, there were three fatal adverse events in the pazopanib/pemetrexed arm, including ileus, tumor embolism, and bronchopneumonia/sepsis. Treatment with pazopanib/pemetrexed was discontinued resulting in more PFS data censored for patients in the pazopanib/pemetrexed arm than those in the cisplatin/pemetrexed arm. There was no statistically significant difference between the pazopanib/pemetrexed and cisplatin/pemetrexed arms for PFS (median PFS, 25.0 versus 22.9 weeks, respectively; hazard ratio = 0.75; 95% confidence interval, 0.43%–1.28%; p = 0.26) or objective response rate (23% versus 34%, respectively; 95% confidence interval, –30.6% to 7.2%; p = 0.21).

Conclusion:

The combination of pazopanib/pemetrexed in first-line treatment of non–small-cell lung cancer showed some antitumor activity but had unacceptable levels of toxicity.

Key words

- Non–small-cell lung cancer;
- Pazopanib;
- Pemetrexed;
- Cisplatin

The role of chemotherapy in the treatment of advanced non–small-cell lung cancer (NSCLC) remains mainly palliative, although platinum-based doublet chemotherapy has been proven to significantly improve survival, disease-related symptoms, and quality of life.[1],[2] In this context, the addition of cisplatin to a single cytotoxic agent confers an undeniable but moderate benefit for chemotherapy-naive patients with inoperable NSCLC in randomized studies.[3],[4] Thus, the trade-off between activity and chemotherapy-related side effects must always be adequately considered in the individual patient.

Few randomized trials have directly compared platinum-based regimens with nonplatinum combinations, but they have generally demonstrated comparable response rates and median survival times.[5, 6, 7, 8 and 9] Although platinum-free doublets including third-generation agents have been proven to be equally active,[10] clinicians do not commonly use these regimens in daily clinical practice unless platinum agents are contraindicated. The addition of an antiangiogenic monoclonal antibody to a standard cytotoxic doublet provides an additional benefit in terms of disease control[11,12] and overall survival (OS)[12] in selected patients with metastatic NSCLC.

Efforts to identify drugs that inhibit key pathways involved in the pathogenesis of cancer, such as angiogenesis, have also led to the development of multitargeted tyrosine kinase inhibitors (TKI) in the last decade. Pazopanib is a TKI of the vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor, and stem cell growth factor receptor (c-KIT), and it is approved for the treatment of patients with advanced renal cell carcinoma[13] and advanced soft-tissue sarcoma who have received prior chemotherapy.[14] Pazopanib has demonstrated activity in NSCLC, with 86% of patients with early-stage NSCLC who participated in a preoperative study experiencing volumetric reduction of their tumor after a median duration of 16 days treatment with single-agent pazopanib and with a modest toxicity profile.[15]

Pemetrexed is one of the most active cytotoxic agents used for nonsquamous NSCLC and is a potent inhibitor of thymidylate synthase[16,17] and other folate-dependent enzymes, including dihydrofolate reductase and glycinamide ribonucleotide formyl transferase.[18] Pemetrexed currently has regulatory approval in combination with cisplatin for first-line treatment of malignant pleural mesothelioma[19] and nonsquamous NSCLC[20] and as a single agent for second-line[21] and maintenance treatment.[22, 23 and 24]

Theoretically in NSCLC, the combination of pazopanib and pemetrexed had the premise for clinically meaningful therapeutic activity coupled with a safe nonoverlapping toxicity profile, potentially better than platinum-based chemotherapy, based on the toxicity profile of each individual agent. A phase Ib study of the combination in patients with solid tumors identified a maximum tolerated dose of pazopanib 800 mg plus pemetrexed 500 mg/m^2.[25] To further explore the activity and the toxicity of this doublet, a randomized, multicenter phase II study was conducted in first-line patients with advanced nonsquamous NSCLC to compare the combination of pazopanib and pemetrexed versus cisplatin and pemetrexed.

PATIENTS AND METHODS

Patient Selection

Chemotherapy-naive patients with histologically or cytologically proven predominantly nonsquamous cell stage IIIB wet (with confirmed malignant pleural effusion) or stage IV NSCLC according to the 6th edition of Tumor, Node, Metastasis classification,[26] at least 18 years of age, with an Eastern Cooperative Oncology Group performance status of 0 or 1, measurable disease as defined by the Response Evaluation Criteria in Solid Tumors 1.0,[27] and a predicted life expectancy of at least 12 weeks were eligible. Prior surgery and/or localized irradiation for NSCLC were permitted at a minimum of 4 weeks before study entry. Patients with previously treated, clinically stable, central nervous system metastases were eligible.

Patients were required to have adequate bone marrow, hepatic, and renal function. Exclusion criteria included poorly controlled hypertension; history of cerebrovascular accident, including transient ischemic attack, pulmonary embolism, or untreated deep venous thrombosis within the past 6 months; recent hemoptysis; and known endobronchial lesions.

This study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines and was approved by each participating institution's independent ethics committee. All patients provided written informed consent before any study procedures were performed.

Study Design and Treatment

Eligible patients were randomly assigned (2:1 ratio) to receive either (1) pemetrexed 500 mg/m^2 intravenously (IV) once every 3 weeks for a maximum of six cycles plus oral pazopanib (Votrient; GlaxoSmithKline, Research Triangle Park, NC) 800 mg once daily until completion of the combination treatment and then as pazopanib monotherapy at 800 mg once daily (until disease progression, unacceptable toxicities, or death) or (2) pemetrexed 500 mg/m^2 IV plus cisplatin 75 mg/m^2 IV once every 3 weeks for a maximum of six cycles. Patients were randomized in a 2:1 ratio to obtain sufficient data on the tolerability profile of the pazopanib/pemetrexed combination. Patients on both arms received standard premedication for pemetrexed including dexamethasone (or equivalent corticosteroid), folic acid, and vitamin B12. Patients on the pemetrexed/cisplatin combination were allowed to receive single-agent pazopanib at the time of progression.

Dose modification guidelines for adverse events were prespecified. Cycle delays for pemetrexed or pemetrexed/cisplatin or interruption of pazopanib treatment for up to 14 days were permitted for recovery from adverse events. Concomitant supportive therapies, such as erythropoiesis-stimulating agents or granulocyte colony-stimulating factors, were allowed according to the American Society of Clinical Oncology guidelines.[28]

A Safety Review Committee (SRC), independent of the study team, was established to monitor aggregated safety and efficacy data for each treatment arm on a monthly basis during the conduct of the study. Data reviews began after the first 10 patients in the study had completed the first cycle of treatment. The data reviewed by the SRC included all deaths (disease-related and fatal serious adverse events), serious adverse events, adverse events, study treatment discontinuations, and laboratory investigations (including a targeted review of hematologic toxicity). The SRC was guided by the following criteria in recommending consideration of a study modification or study cessation: "Sufficient evidence to suggest that the true risk of adverse outcomes (e.g., pulmonary hemorrhage, hepatotoxicity, or other adverse events) among patients in the test arm is in excess of that among control patients at a rate that significantly alters the risk-benefit ratio for the patients being treated."

Initially, the SRC reported an increased frequency of severe (grade 3 and grade 4) neutropenia in the pazopanib/pemetrexed arm compared with the cisplatin/pemetrexed arm and an imbalance in discontinuation rates of study treatment suggestive of broader toxicity in the pazopanib/pemetrexed arm. At this time, a total of four deaths were reported in the pazopanib/pemetrexed arm; three deaths were attributed to disease. As a result of the SRC findings, the protocol was amended (amendment 01) to reduce the starting dose of pazopanib from 800 to 600 mg daily in the pazopanib/pemetrexed arm for all new patients enrolled in the study, and new and more stringent pazopanib dose modification guidelines for hematologic toxicity were implemented. After another month, the SRC reported an imbalance in deaths across the two treatment arms. As a result of this finding, the protocol was urgently amended (amendment 02) to stop new enrolment in the study and patients being treated with pazopanib plus pemetrexed were taken off treatment. In amendment 03, a decision was made not to reactivate enrolment in the study and to remove the requirement for posttreatment disease assessments and survival follow-up. The study remained open to enable patients receiving treatment with pazopanib monotherapy or with cisplatin/pemetrexed to complete their scheduled treatments.

Study Endpoints and Assessments

The primary efficacy endpoint was progression-free survival (PFS), defined as the interval between the date of randomization and the first occurrence of progressive disease or death. Secondary endpoints included OS, defined as the interval from the date of randomization to the date of death; objective response, defined as the percentage of patients (i.e., responders) who achieved either a complete response or partial response as per Response Evaluation Criteria in Solid Tumors 1.0 criteria[27] for at least 4 weeks at any time during randomized treatment; and safety and tolerability.

Disease assessments were repeated approximately every 6 weeks for the first 18 weeks and every 8 weeks thereafter until disease progression. Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria, version 3.0.

Statistical Analysis

The study was designed as a descriptive study using the selection method.[29] Using this design, with a sample size of 150 patients, the probability of correctly selecting the pazopanib/pemetrexed regimen over the cisplatin/pemetrexed regimen based on an observed hazard ratio (HR) favoring the pazopanib/pemetrexed regimen was 86%.

Efficacy analyses were conducted on the intent-to-treat population, which comprised all patients who were randomized to receive treatment and were analyzed based on the assigned randomized treatment and not based on the actual treatment received (or not received). The safety population comprised all patients who had received at least one dose of each study drug in at least one cycle of treatment.

PFS and OS were summarized using Kaplan–Meier survival curves and compared between the treatment arms (pazopanib/pemetrexed versus cisplatin/pemetrexed) using an unstratified log-rank test. The Pike estimator[30] of the treatment HR based on the log-rank test was provided along with the corresponding 95% confidence interval (CI). Early discontinuation of enrolment compromises the power to detect differences in OS between the treatment arms. As a consequence, the OS estimate should be interpreted with caution. Approximate 95% CIs for objective response rates (ORR) were calculated for each regimen. The treatment difference in the ORR and the approximate 95% CI was also calculated.

RESULTS

Patient Characteristics

Between July 09, 2009, and March 30, 2010, 106 of a planned 150 patients were randomly assigned in a 2:1 ratio to receive pazopanib/pemetrexed (n = 71) or cisplatin/pemetrexed (n = 35) (Figure 1); 103 of these patients received treatment.

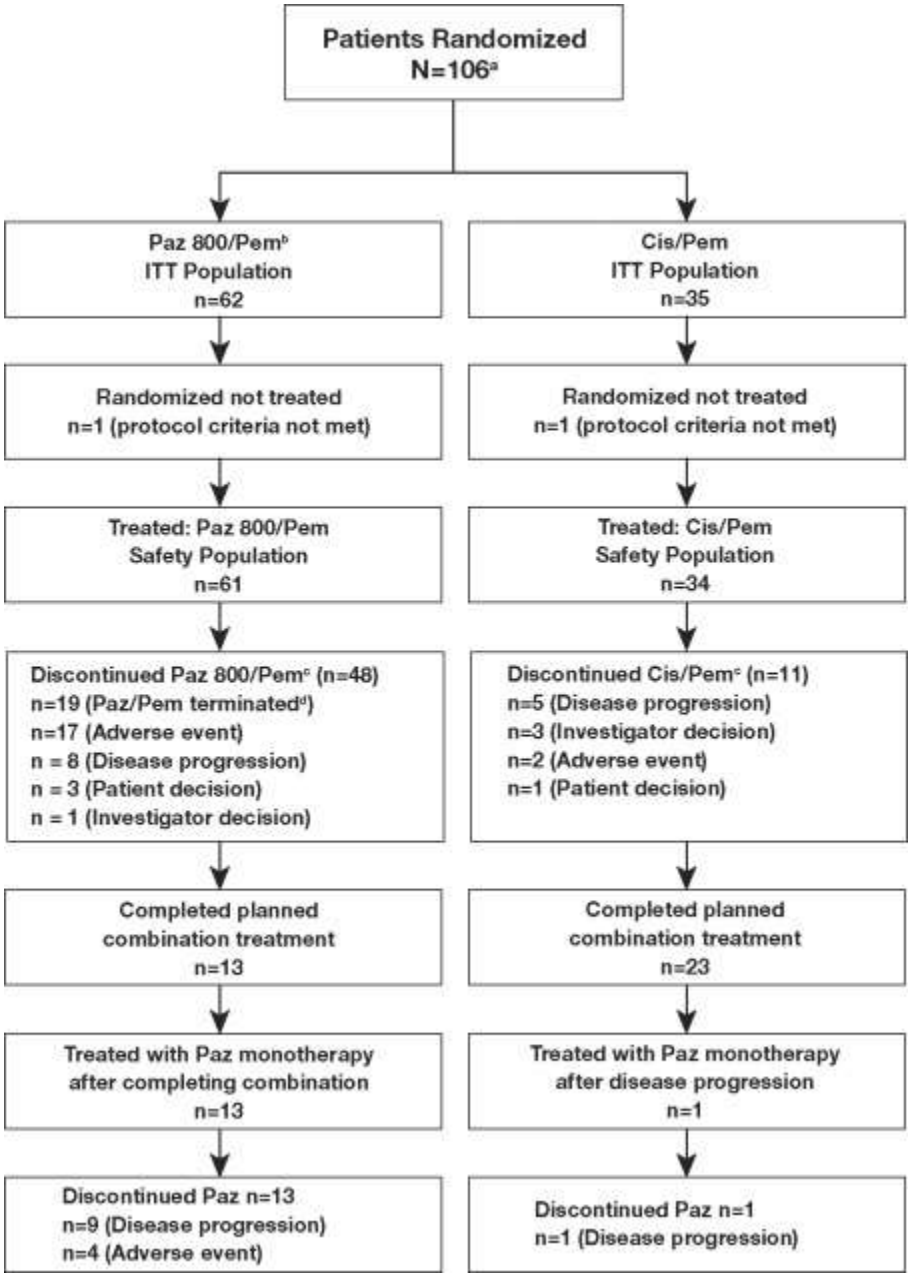

FIGURE 1.

Consort diagram of the study. [a]No data were available for two additional patients who were randomized but not treated. [b]Nine additional patients were randomized and eight of these patients were treated with pazopanib (600 mg) after the implementation of amendment 01, which lowered the dose of pazopanib. All patients in this group had treatment discontinued as a result of amendment 02. [c]A patient was counted as discontinued if they did not complete the planned combination treatment with both study treatments. [d]Investigational combination treatment discontinued due to an imbalance in toxicity. Paz, pazopanib; Pem, pemetrexed; Cis, cisplatin; Paz 600/Pem, pazopanib 600 mg plus pemetrexed; Paz 800/Pem, pazopanib 800 mg plus pemetrexed; Cis/Pem, cisplatin plus pemetrexed; ITT, intent-to-treat.

After 62 patients were randomized to the pazopanib/pemetrexed arm, the SRC recommended a reduction of the starting daily dose of pazopanib from 800 to 600 mg in the pazopanib/pemetrexed arm for all new patients randomized into the study due to an increased frequency of severe neutropenia (grade 3 and grade 4) in the pazopanib combination arm compared with the control arm, as well as an imbalance in drug discontinuations (Figure 1). Only nine patients were randomized to this reduced-dose pazopanib/pemetrexed treatment, eight of whom received treatment, before this combination treatment was permanently discontinued and enrolment into the study was halted by the SRC recommendation due to a detected imbalance in mortality between the

treatment arms. These eight patients were not included in the efficacy analysis because of the small sample size and limited efficacy data.

Demographic and baseline characteristics were generally balanced for age, sex, race, and some disease-related characteristics between the pazopanib/pemetrexed and cisplatin/pemetrexed arms; however, some imbalances were observed in baseline Eastern Cooperative Oncology Group performance status, history of tobacco use, and unintentional weight loss (Table 1).

TABLE 1.

Baseline Patient and Disease Characteristics for the Intent-to-Treat Population

	Pazopanib 600/	**Pazopanib 800/**	**Cisplatin/**
	Pemetrexed	**Pemetrexed**	**Pemetrexed**
Characteristic	**(*n* = 9)**	**(*n* = 62)**	**(*n* = 35)**
Age, median (range), yr	66.0 (25–71)	62.0 (40–75)	64.0 (36–74)
Age <65 yr, *n* (%)	4 (44)	38 (61)	21 (60)
Age, ≥65 yr, *n* (%)	5 (56)	24 (39)	14 (40)
Sex, *n* (%)			
Female	2 (22)	23 (37)	12 (34)
Male	7 (78)	39 (63)	23 (66)
Race, *n* (%)			
African descent	0	1 (2)	0
Central/South Asian	1 (11)	0	0
White	8 (89)	61 (98)	35 (100)
History of tobacco use: no. Median	of pack years 39.0	39.5	22.0
Range	1–40	1–90	1–182
Unintentional weight loss within 6 mo of starting study, *n* (%)			
Yes, ≥5%	1 (11)	7 (11)	9 (26)
Yes, <5%	1 (11)	12 (19)	5 (14)
No	7 (78)	42 (68)	21 (60)
Missing	0	1 (2)	0

	Pazopanib 600/ Pemetrexed	Pazopanib 800/ Pemetrexed	Cisplatin/ Pemetrexed
Characteristic	**(*n* = 9)**	**(*n* = 62)**	**(*n* = 35)**
Stage of disease, *n* (%)			
IIIb	0	2 (3)	3 (9)
IV	9 (100)	59 (95)	32 (91)
Missing	0	1 (2)	0
ECOG performance status			
0	4	39	16
1	4	22	17
2	0	0	1
Missing	1	1	1
Histologic type			
Adenocarcinoma	7	56	27
Large-cell carcinoma	2	5	4
Bronchioloalveolar	0	0	4
Missing	0	1	0

ECOG, Eastern Cooperative Oncology Group.

Treatment

More patients in the cisplatin/pemetrexed arm completed the planned number of cycles of chemotherapy treatment than those in the pazopanib/pemetrexed arm (Figure 1). Patients received a median total of four cycles (range, 1–6 cycles) in the cisplatin/pemetrexed arm and three cycles (range, 1–6 cycles) in the pazopanib/pemetrexed arm. The median dose of pemetrexed was 500 mg/m^2 in each treatment arm. In the pazopanib/pemetrexed arm, 61 patients received 91% of the planned pazopanib dose of 800 mg daily. Fourteen patients received pazopanib monotherapy; 13 of these patients after completion of pazopanib/pemetrexed treatment and one patient after disease progression on cisplatin/pemetrexed (Figure 1). Because of the early discontinuation of the study, data on poststudy therapies were not systematically collected.

Efficacy

Table 2 summarizes the investigator-assessed Kaplan–Meier estimates for PFS. There was no statistically significant difference between the pazopanib/pemetrexed arm and the cisplatin/pemetrexed arm for PFS (median PFS, 25.0 versus 22.9 weeks, respectively; HR = 0.75;

95% CI, 0.43%–1.28%; $p = 0.26$). More patients in the pazopanib/pemetrexed arm (35 [56%]) had their PFS data censored than those in the cisplatin/pemetrexed arm (8 [23%]) because of early discontinuation of pazopanib/pemetrexed and subsequent initiation of new anticancer therapy due to the SRC recommendation to halt new enrolment and terminate treatment with the investigational combination (Supplementary Table 1, Supplementary Digital Content 1, http://links.lww.com/JTO/A478).

Table 2.

Kaplan–Meier Estimates of Progression-Free Survival for the Intent-to-Treat Population

Variable	**Pazopanib 800/ Pemetrexed**	**Cisplatin/ Pemetrexed**
No. of patients	62	35
Progressed or died, *n* (%)	27 (44)	27 (77)
Censored, follow-up[a] ended, *n* (%)	35 (56)	8 (23)
Hazard ratio[b]		
Estimate	0.75	
95% CI	0.43, 1.28	
Log-rank *p* value	0.2647	
Estimates (wk)		
Median	25.0	22.9
95% CI	17.3, 34.1	18.4, 27.7

CI, confidence interval.

a

Follow-up was classified as ongoing if the patient was still on-study and progression-free as of their last disease assessment.

b

Hazard ratios were estimated using a Pike estimator. A hazard ratio <1 indicated a lower risk with this treatment compared with the control group.

Table 3 summarizes objective responses for both treatment arms. The ORR (complete response + partial response) was 23% in the pazopanib/pemetrexed arm and 34% in the cisplatin/pemetrexed arm (a difference of –12% with 95% CI, –30.6% to 7.2%; $p = 0.21$).

TABLE 3.

Confirmed Objective Responses

Response	Pazopanib 800/ Pemetrexed (*n* = 62)	Cisplatin/Pemetrexed (*n* = 35)
CR, *n* (%)	0	0
PR, *n* (%)	14 (23)	12 (34)
Stable disease[a], *n* (%)	13 (21)	14 (40)
Progressive disease, *n* (%)	6 (10)	5 (14)
Unknown, *n* (%)	29 (47)	4 (11)
Response rate (CR + PR), *n* (%)	14 (23)	12 (34)
95% CI for % response rate	12.2–33.0	18.6–50.0

CR, complete response; PR, partial response; CI, confidence interval.

a

In order to qualify as an objective response of stable disease, a response of stable disease had to be observed at a minimum of 11 weeks.

More patients in the pazopanib/pemetrexed arm had unknown responses than those in the cisplatin/pemetrexed arm (47% versus 11%, respectively) because of early discontinuation of pazopanib/pemetrexed. At the time enrolment was discontinued, eight deaths were reported of 103 patients treated: seven in the pazopanib/pemetrexed arm (three considered disease related) and one in the cisplatin/pemetrexed arm (considered disease related). At the time of study closure, 25 deaths (41%) occurred in the pazopanib/pemetrexed arm and 12 deaths (35%) occurred in the cisplatin/pemetrexed arm. Eighteen deaths (30%) were attributed to disease progression in patients in the pazopanib/pemetrexed versus 10 (29%) in the cisplatin/pemetrexed arm, and no further data were collected in the study. Available OS data are presented in Table 4 (see also Supplementary Figure 1, Supplementary Digital Content 2, http://links.lww.com/JTO/A479). A median OS could not be estimated based on the collected data before the study was closed and survival follow-up ceased; however, the Kaplan–Meier estimate of OS based on available data was 1.22 with 95% CI (0.64–2.33) ($p = 0.55$).

Table 4.

Kaplan–Meier Estimates of Overall Survival for the Intent-to-Treat Population

Variable	Pazopanib 800/ Pemetrexed	Cisplatin/ Pemetrexed
No. of patients	62	35
Died, *n* (%)	26 (42)	13 (37)
Censored, follow-up[a] ended, *n* (%) Hazard ratio[b]	36 (58)	22 (63)

Variable	Pazopanib 800/ Pemetrexed	Cisplatin/ Pemetrexed
Estimate	1.22	
95% CI	0.64, 2.33	
Log-rank *p* value Estimates (wk)	0.5519	
Median	—	—
95% CI	39.3, —	44.1, —

CI, confidence interval.

a

Survival data were not collected after the implementation of amendment 03.

b

Hazard ratios were estimated using a Pike estimator. A hazard ratio <1 indicated a lower risk with this treatment compared with the control group.

Safety

Neutropenia, diarrhea, increased alanine aminotransferase, hypertension, leukopenia, abdominal pain, increased aspartate aminotransferase, and decreased weight occurred at a higher frequency in patients in the pazopanib/pemetrexed arm than those in the cisplatin/pemetrexed arm (Table 5). Although the incidence of neutropenia was higher in the pazopanib/pemetrexed arm than in the cisplatin/pemetrexed arm (66% versus 26%, respectively), the incidence of febrile neutropenia was similar in both treatment arms (7% versus 6%, respectively). Nausea, anemia, constipation, noncardiac chest pain, vomiting, and lymphopenia occurred at a higher frequency (>10% difference) in patients in the cisplatin/pemetrexed arm than those in the pazopanib/pemetrexed arm. Hypertension occurred in 19 patients (31%) in the pazopanib/pemetrexed arm and four patients (12%) in the cisplatin/pemetrexed arm. Grade 3 hypertension occurred in five patients (8%) in the pazopanib/pemetrexed arm and none in the cisplatin/pemetrexed arm. There was no severe (grade 3 or above) hemorrhagic events reported in the study.

TABLE 5.

Adverse Events Reported by Grade[a]

	All Grades[b]	Grade 3	Grade 4

Event[c]	Pazopanib 800/Pemetrexed (*n* = 61) *n* (%)	Cisplatin/Pemetrexed (*n* = 34) *n* (%)	Pazopanib 800/Pemetrexed (*n* = 61) *n* (%)	Cisplatin/Pemetrexed (*n* = 34) *n* (%)	Pazopanib 800/Pemetrexed (*n* = 61) *n* (%)	Cisplatin/Pemetrexed (*n* = 34) *n* (%)
Nonhematologic						
Fatigue/asthenia[d]	32 (52)	20 (59)	4 (7)	1 (3)	0	0
Diarrhea	25 (41)	6 (18)	3 (5)	1 (3)	0	0
Nausea	25 (41)	21 (62)	3 (5)	2 (6)	0	0
Hypertension	19 (31)	4 (12)	5 (8)	0	0	0
Increased alanine aminotransferase	16 (26)	1 (3)	4 (7)	1 (3)	2 (3)	0
Vomiting	15 (25)	13 (38)	2 (3)	0	0	0
Epistaxis	14 (23)	8 (24)	0	0	0	0
Abdominal pain	13 (21)	3 (9)	5 (8)	0	1 (2)	0
Decreased appetite	13 (21)	7 (21)	2 (3)	0	0	0
Mucosal inflammation/stomatitis[d]	13 (21)	7 (21)	3 (5)	0	0	0
Rash	11 (18)	5 (15)	1 (2)	0	0	0
Dyspnea	10 (16)	9 (26)	1 (2)	1 (3)	1 (2)	0
Abdominal pain upper	9 (15)	4 (12)	0	0	0	0
Increased aspartate aminotransferase	9 (15)	1 (3)	3 (5)	1 (3)	1 (2)	0
Constipation	9 (15)	11 (32)	2 (3)	0	0	1 (3)
Dizziness	9 (15)	4 (12)	0	0	0	0
Decreased weight	9 (15)	2 (6)	0	0	0	0

	All Grades[b]		Grade 3		Grade 4	
Event[c]	**Pazopanib 800/ Pemetrexed (*n* = 61) *n* (%)**	**Cisplatin/Pemetrexed (*n* = 34) *n* (%)**	**Pazopanib 800/ Pemetrexed (*n* = 61) *n* (%)**	**Cisplatin/Pemetrexed (*n* = 34) *n* (%)**	**Pazopanib 800/ Pemetrexed (*n* = 61) *n* (%)**	**Cisplatin/Pemetrexed (*n* = 34) *n* (%)**
Pyrexia	8 (13)	7 (21)	0	0	0	0
Increased blood bilirubin	6 (10)	0	2 (3)	0	0	0
Cough	6 (10)	5 (15)	0	0	0	0
Increased lacrimation	6 (10)	4 (12)	0	0	0	0
Noncardiac chest pain	3 (5)	6 (18)	1 (2)	0	0	0
Decreased creatinine renal clearance	1 (2)	4 (12)	0	0	0	0
Tinnitus	1 (2)	4 (12)	0	0	0	0
Hematologic						
Neutropenia	40 (66)	9 (26)	21 (34)	3 (9)	15 (25)	0
Leukopenia	14 (23)	3 (9)	6 (10)	0	3 (5)	0
Thrombocytopenia	9 (15)	7 (21)	5 (8)	1 (3)	3 (5)	0
Anemia	8 (13)	11 (32)	1 (2)	1 (3)	1 (2)	0
Lymphopenia	8 (13)	8 (24)	4 (7)	0	1 (2)	1 (3)

a

Only adverse events reported in at least 10% of patients in either the pazopanib/pemetrexed or cisplatin/pemetrexed arm were listed.

b

Total no. of adverse events of any grade reported during all treatment phases.

c

Adverse events were listed in descending order based on the incidence in the pazopanib/pemetrexed arm.

d

No patient reported both adverse events.

Grade 3 and grade 4 adverse events occurred at a higher frequency in patients in the pazopanib/pemetrexed arm than those in the cisplatin/pemetrexed arm, primarily because of a higher incidence of hematologic toxicities in the pazopanib/pemetrexed arm, particularly neutropenia (59% versus 9% in the cisplatin/pemetrexed arm) (Table 5).

More patients withdrew from the study because of adverse events in the pazopanib/pemetrexed arm than those in the cisplatin/pemetrexed arm (34% versus 9%, respectively), primarily because of a higher incidence of liver toxicity events (elevated alanine aminotransferase and aspartate aminotransferase), gastrointestinal adverse events (abdominal pain and nausea), and fatigue.

At the time enrolment was discontinued, seven deaths were reported in the pazopanib/pemetrexed arm of which four were not considered related to disease: one was a suicide that occurred more than 28 days after pazopanib treatment was discontinued and three deaths were fatal serious adverse events (ileus, tumor embolism, and bronchopneumonia/sepsis; see Supplementary Table 2, Supplementary Digital Content 3, http://links.lww.com/JTO/A480). The death reported in the cisplatin/pemetrexed arm at this time was considered disease related. At the time of study closure, the incidence of deaths not attributed to the disease under study was higher in the pazopanib/pemetrexed arm than in the cisplatin/pemetrexed arm (7 [12%] versus 2 [6%], respectively). Nevertheless, no specific fatal toxicity was observed that could explain the imbalance (Supplementary Table 2, Supplementary Digital Content 3, http://links.lww.com/JTO/A480).

DISCUSSION

Although this study was discontinued early due to unexpected toxicity, it demonstrated that the combination of an anti-VEGFR-TKI and a cytotoxic drug had some antitumor activity.

The initial goal of this study was to determine whether a platinum agent like cisplatin could be replaced by pazopanib. With the limitation of the available data from this study, it cannot be excluded that the pazopanib/pemetrexed combination has activity with a HR for PFS of 0.75 (despite the proportion of censored data); however, the observed trade-off between activity and toxicity does not allow further clinical exploration for this combination.

The combination of pazopanib and pemetrexed in this study was not tolerated; there was a higher incidence of severe and fatal toxicities and toxicity leading to treatment discontinuation with the pazopanib/pemetrexed combination. In a previously conducted phase Ib study of this combination,[25] in patients with previously treated advanced solid tumors, the incidence of nonhematologic toxicity was consistent with that observed with each individual agent; however, a higher rate of hematologic toxicity (primarily brief reversible neutropenia) was observed with the combination. The incidence of neutropenia was considered to have been influenced by the extent of prior treatment (72% of patients received the combination as at least third-line therapy). The first clear signal of toxicity identified in this study with the pazopanib/pemetrexed combination in a population that had not received any prior treatment was again an increased incidence of severe, short-lasting neutropenia despite all patients having received the required premedication for pemetrexed to counteract hematologic toxicity. This toxicity signal was accompanied by an increased incidence of treatment discontinuations due to adverse events other than neutropenia that was suggestive of a broader toxicity.

Although TKIs are generally better tolerated than cytotoxic chemotherapy, side effects develop in many patients from on-target and off-target effects, which require aggressive management to

maintain patient compliance, optimize therapy, and avoid potentially life-threatening consequences. In this study, monthly safety reviews by an independent SRC facilitated prompt action to be taken with the emerging safety profile of the pazopanib/pemetrexed combination; initially, a dose reduction of pazopanib was implemented and shortly afterward enrolment was halted and treatment terminated.

Patients with advanced renal cell carcinoma and advanced soft-tissue sarcoma who have received prior chemotherapy form the basis for the safety profile of pazopanib monotherapy.[14] Experience with pazopanib monotherapy in NSCLC is limited; however, preliminary data suggested that the safety profile of pazopanib monotherapy in NSCLC was similar to the safety profile in patients with advanced renal cell carcinoma and advanced soft-tissue sarcoma.[15] The safety profile of pemetrexed has been well established with folic acid/vitamin supplementation.[31]

At the time this study was initiated, experience with VEGFR-TKIs in combination with chemotherapy in the first-line setting was limited. Randomized studies with sorafenib,[32] cediranib,[33] and motesanib[34] in combination with platinum-based doublets were ongoing, and preliminary reports of imbalances in toxicity and an increased risk of mortality with these triplet regimens were emerging. At that time, a clear relationship to specific toxicities or a specific mechanistic explanation for these observations remained to be defined, although several risk factors had been suggested, including squamous cell histology, prior hemoptysis, and the presence of central nervous system metastases. Nevertheless, in the second-line setting of NSCLC, it had been previously shown that the doublet combination of single cytotoxic agents and a VEGFR-TKI, such as vandetanib, was safe and had demonstrated antitumor activity.[35,36]

For the pazopanib/pemetrexed combination, pharmacokinetic analysis carried out in a phase Ib study[25] did not indicate that a pharmacokinetic interaction could be responsible for the increased toxicity seen with the combination. The exposure (area under the concentration–time curve) and clearance of pemetrexed were unchanged by the administration of pazopanib, even though a small increase of 22% in the maximum concentration of pemetrexed was reported. In another study, single-agent pemetrexed was well tolerated when administered at high doses (600–1400 mg/m^2) with vitamin supplementation in patients with locally advanced or metastatic cancer, despite an increase in pemetrexed exposure.[37] Therefore, the increased toxicity observed with the combination of pazopanib and pemetrexed in this study is likely independent of pemetrexed exposure.

In addition, an exploratory evaluation of three biomarkers of folic acid and vitamin B12 metabolism (cystathionine, homocysteine, and methylmalonic acid) was initiated using samples collected during the phase Ib study to explore the possibility that increased neutropenia resulted from pazopanib interfering with vitamin metabolism; however, there was no relationship between pazopanib, pemetrexed, the vitamin biomarkers, and grade 3/4 neutropenia, suggesting that folic acid and vitamin B12 insufficiencies do not seem to explain the relatively high rate of hematologic toxicity with the pazopanib/pemetrexed combination.[25]

Of interest, recent data have emerged suggesting that even the doublet combination of sunitinib and pemetrexed[38] and erlotinib and pemetrexed[39] in second-line treatment of NSCLC is similarly associated with a high level of both hematologic and nonhematologic toxicity, indicating that combinations of a TKI and pemetrexed should be undertaken only with great caution.

In conclusion, this study, despite evidence of activity, demonstrated that the combination of pazopanib and pemetrexed in NSCLC had unacceptable levels of toxicity. The combination of pazopanib and pemetrexed will not be evaluated further; however, this does not rule out the possibility for further investigation of pazopanib alone or in combination with other agents in the treatment of advanced NSCLC.

Because two thirds of patients randomized to the investigational arm lost the chance to receive the standard treatment, in further studies, pazopanib should be evaluated as a combination with a

platinum doublet in the first-line setting, as a combination with docetaxel in the second-line setting, or as a monotherapy in the third-line setting.

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