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ORIGINAL ARTICLE

Pazopanib or placebo in completely resected stage I NSCLC patients: results of the phase II IFCT-0703 trial

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Background: Adjuvant treatment in resected stage I non-small-cell lung cancer (NSCLC) is generally not recommended. Pazopanib is an oral tyrosine kinase inhibitor of VEGFR-1/2/3 and PDGFR-α/β. We explored the feasibility and efficacy of adjuvant pazopanib in this population.

Patients and methods: In this double-blind phase II/III trial, patients with resected stage I NSCLC were randomized to placebo or pazopanib 800 mg/day (P800) for 6 months with a two-step Fleming design. The primary endpoint was compliance (percentage of patients receiving ≥3 months pazopanib). From the interim analysis after 64 patients were included, the IDMC recommended reducing to pazopanib 400 mg/day (P400) due to insufficient compliance, with a one-step Fleming. Although unplanned, survival data were analyzed.

Results: A total of 71 patients were enrolled in each arm; 61% were male, 91% were smokers, median age was 60 years, 80% had pathological stage IA, and 16% had squamous cell carcinoma. Pazopanib compliance was 38% [95% confidence interval (CI) 23–55] with P800, increasing to 69% (95% CI 50–84; $P = 0.027$) with P400. Two patients had grade 4 toxicities with P800. The most common grade 3 toxicities were increased transaminases (16%), hypertension (13%), and diarrhea (9%) with P800, and gastrointestinal disorders (16%; 6% diarrhea) and hypertension (6%) with P400. Median follow-up was 47 months. Three-year recurrence-free survival was 76% (95% CI 65%–86%) with pazopanib and 83% (95% CI 74%–92%) with placebo [hazard ratio = 1.3 (95% CI 0.6–2.7), $P = 0.53$]. Five-year overall survival was 83% (95% CI 72–94) with pazopanib and 94% [95% CI 88–100] with placebo [hazard ratio = 1.8 (95% CI 0.6–5.5), $P = 0.26$].

Conclusions: In resected stage I NSCLC patients adjuvant 400 mg/day pazopanib but not 800 mg/day was feasible, although possibly infra-therapeutic and failed to improve relapse-free survival.

Key words: non-small-cell lung cancer, pazopanib, randomized phase 2 trial, adjuvant, compliance, survival

Introduction

Lung cancer is the leading cause of cancer death in males and the second cause in females worldwide, with approximately 1.4 million deaths and 1.6 million new cases annually [1]. Surgery remains the principal curative treatment option for patients with early stage non-small-cell lung cancer (NSCLC), but only 25%–30% of patients are eligible for curative resection. Furthermore,

relapse rates remain significant after surgery with a 5-year survival rate between 73% for pathological stage IA and only 25% for pathological stage IIIA (7th TNM edition) [2]. Treatment strategies using adjuvant chemotherapy have been proposed to treat micro-metastatic disease. Cisplatin-based chemotherapy is considered as the standard treatment of stage II/III resected NSCLC and deleterious in stage IA [3]. Its use in stage IB is still a matter of debate [4]. Uracil–tegafur (UFT), an oral adjuvant treatment, increased overall survival (OS) in Japanese studies, mainly after complete resection of stage I adenocarcinoma [4]. This strategy has not been evaluated in Caucasian patients.

Pazopanib is an oral angiogenic inhibitor targeting vascular endothelial growth factor receptor VEGFR)-1/2/3, platelet-derived growth factor receptor type-α/β, and c-Kit [5]. It is approved for metastatic renal carcinoma and soft tissue sarcoma. Pazopanib demonstrated single-agent activity in patients with early stage NSCLC in a neoadjuvant window-of-opportunity trial [6]. Thirty-five patients were treated with pazopanib 800 mg/day for a median of 16 days, 30 of whom (85.7%) achieved a reduction in tumor volume. Almost all patients (94.3%) experienced adverse events. Grade 3 and 4 toxicities were acceptable (five patients), including elevations of hepatic transaminases ($n = 2$) and lymphopenia ($n = 1$). Given the paucity of options and a clear unmet medical need for early stage NSCLC, the current study was designed in 2006 to investigate the feasibility of pazopanib administration in early stage NSCLC in the adjuvant setting.

Patients and methods

Patients

Patients ($\geq$18 to $\leq$70 years) with completely resected stage I NSCLC (7th TNM edition), an Eastern Cooperative Oncology Group performance status of 0 or 1, and adequate hematologic, hepatic, renal, and blood coagulation function were eligible. All patients had to perform a preoperative PET scan, and either complete mediastinal lymph node resection or adequate medastinal lymph node sampling according to the protocol specification at the time of resection. Major exclusion criteria included history of other malignancies within 5 years, *in situ* lepidic carcinoma of lobar or multilobar involvement (discrete solitary radiological mass or nodule was eligible). The study was approved by local institutional review board and ethic committee (CPP Ile de France X). All patients provided written informed consent.

Study design and end points

This double-blind, multicenter, phase II/III study assigned by central randomization (1:1, block method) patients to pazopanib (GlaxoSmithKline) or placebo, with stratification on stage (IA versus IB) and histology (squamous versus non-squamous cell carcinoma). The authorized delay between surgery and randomization or treatment start ranged from 4 to 8 weeks. Pazopanib was administered at 800 mg once a day for 6 months. Chest CT scans were carried out post-operatively then each 6 months for 5 years. A brain CT scan or MRI was mandatory within 2 months before randomization. Patients were followed-up once a month until 6 months or treatment discontinuation, and then every 3 months for 2.5 years and every 6 months for 2 years and until death, withdrawal of consent, or 5 years following the last patient enrolled.

The primary end point for the phase II component of the study was compliance. Patients were classified as compliant if they received treatment of at least 12 weeks, irrespective of the dose, during the 24 weeks after randomization. Patients who stopped treatment prematurely in the first 12 weeks due to lung cancer recurrence or death not related to pazopanib were not evaluable for compliance. Compliance was based on both self-reporting and pill counts. Secondary end points included OS (defined as the interval between the date of randomization and death of any cause), recurrence-free survival (RFS; defined as the interval between the date of randomization and the earliest disease recurrence or death of any cause), toxicity using National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0), and the change in quality of life (QoL) from baseline scores to 12 and 24 weeks using the EORTC-QLQ-C30 with LC-13 and EQ-5D. A second primary cancer was not considered an event, except in cases of death.

Statistical methods and analysis

A two-step phase II Fleming's design was used to monitor compliance in the pazopanib arm [7]. A compliance rate $\leq$60% was considered unacceptable. In order to conclude 80% as a good compliance rate, sample size computation was based on the following assumption: P0 = 60%; Pa = 80%; statistical power of 0.90; type I error rate (one-sided) of 0.05. After 64 patients were included (interim analysis), the independent data monitoring committee (IDMC) recommended reducing the pazopanib dose to 400 mg/day given insufficient compliance (supplementary Figure S1, available at *Annals of Oncology* online). As study recruitment was not on-hold, 16 additional patients were included at 800 mg/day and these 80 patients are reported as a single cohort. A one-step Fleming design was used with the new dose and 62 more patients were included, 31 per arm. The threshold for concluding good compliance was to observe at least 23 patients with good compliance in the pazopanib 400 mg/day arm (supplementary Figure S1, available at *Annals of Oncology* online). Analyses were conducted using the intention-to-treat population, including all randomized patients except one randomized without written consent. Sensitivity analyses were conducted for compliance excluding patients taking less than 8 days of treatment or having recurrence within 12 weeks. Methods used for QoL analysis is described in supplementary material, available at *Annals of Oncology* online.

Following the decision to not continue the phase III part of the study because of the laboratory policy, exploratory analyses on OS and RFS were planned. OS and RFS curves were estimated with the Kaplan–Meier method and compared with the log-rank test. All tests were two-sided and *P*-values <0.05 were considered significant. Data were analyzed with SAS statistical software (version 9.3). This study is registered at ClinicalTrials.gov, number NCT00775307.

Results

Patient characteristics

Between March 2009 and August 2012, 143 patients were randomly assigned, 72 to pazopanib and 71 to placebo, in 29 centers. One patient (pazopanib arm) was ineligible being randomized without consent (and did not receive any treatment) and was excluded from all analyses. An additional five patients were lost to follow-up (three placebo, two pazopanib) secondary to consent withdraw (supplementary Figure S2, available at *Annals of Oncology* online). The median follow-up was 47 months (range 0.3–66 months). Baseline characteristics were well balanced between arms (Table 1). Only 8% of the patients were never-smokers, 75% had an adenocarcinoma and 80% were stage IA.

Compliance

Of 142 included patients, 69 received at least one dose of pazopanib, and 69 received one dose of placebo (supplementary Figure S2, available at *Annals of Oncology* online). In the intent-to-treat

Table 1. Patient characteristics

		Pazopanib		Placebo	
		n = 71		*n* = 71	
		N	%	*N*	%
Gender	Female	30	42	26	37
	Male	41	58	45	63
Median age (range), years		57 (33–70)		61 (44–71)	
ECOG performance status	0	47	66	58	82
	1	24	34	13	18
Ethnicity	Caucasian	69	97	69	97
	Other	2	3	2	3
Smoker	Never	6	8	6	8
	Current/former	65	92	64[a]	92
Stage	IA	54	76	59	83
	IB	16[b]	24	12	17
Pathology	Adenocarcinoma	51	72	56	79
	Squamous cell carcinoma	12	17	11	15
	Other	8	11	4	6

[a]Data missing for one patient.
[b]One patient pT1pN0M1.
ECOG, Eastern Cooperative Oncology Group.

population, the compliance rates at 800 mg/day were 38% [95% CI: 23–55] in the pazopanib arm (39 patients) and 88% [73–96] in placebo arm (41 patients; Table 2). Compliance rates at 400 mg/day were 69% [50–84] in pazopanib arm (32 patients) and 93% [77–99] in placebo arm (30 patients), giving a significant improvement in compliance between 800 and 400 mg/day in the pazopanib arm ($P = 0.027$, χ^2 test, exploratory analysis). There was no significant difference in the placebo arm between the two administration periods. Median duration of treatment was 7.2 weeks in the pazopanib 800 mg/day arm and 22.6 weeks in the 400 mg/day arm, compared with 24.1 and 24.3 for the placebo arms (Table 3).

At 800 mg/day, 16 patients (41%) had a dose modification versus two (5%) with placebo. At 400 mg/day, dose modification occurred in 12 patients (38%) versus two (7%) with placebo. Drug was interrupted for 51% and 47% of the patients on pazopanib 800 and 400 mg/day, respectively, versus 32% and 30% in the placebo arm. Excluding the patients who did not start treatment or took it for less than 8 days (9 in the pazopanib arm and 5 in the placebo arm; supplementary Tables S1 and S2, available at *Annals of Oncology* online) gave the following compliance rates: 45% [28–64] in pazopanib arm and 95% [82–99] with placebo for the 800 mg dose and 76% [56–90] in pazopanib arm and 100% [88–100] in placebo arm for the 400 mg dose.

Toxicity

At 800 mg/day, toxicities were more frequent and generally more severe in the pazopanib arm than in the placebo arm, notably diarrhea (62% versus 27%), fatigue (59% versus 46%), hypertension (54% versus 27%), and ALAT increase (44% versus 29%) (Figure 1, supplementary Table S3, available at *Annals of Oncology* online). At 400 mg/day, diarrhea was more frequent with pazopanib than in the placebo arm (66% versus 25%), as were fatigue (81% versus 50%), hypertension (50% versus 7%) or ALAT (44% versus 14%). The proportions of patients with at least one grade 3/4 toxicity were 49% (19/39) in the pazopanib 800 mg/day arm and 38% (12/32) with 400 mg/day versus 17% (7/41) and 27% (8/30) in the respective control arms. Elevated ALAT was the most frequent grade 3/4 event in the pazopanib 800 mg/day arm (13% with grade 3), but was not reported at 400 mg/day (supplementary Table S4, available at *Annals of Oncology* online). No toxic deaths were observed. Two patients at 800 mg/day had grade 4 toxicities (fatigue in pazopanib arm, GGT in the placebo arm). Of note, there were no increased toxicities of specific concern in the post-operative setting, such has bleeding, wound-healing or infection.

Excluding biological toxicities, at least one grade 3/4 toxicity was reported in 33% [19–49] (13/40) of patients in the pazopanib 800 mg/day arm and 38% [21–56] (12/32) with 400 mg/day, versus 12% [4–26] (5/41) and 20% [8–39] (6/30) in the respective control arms. The presence of such toxicity events may explain that clinicians and patients often correctly guessed which treatment was given in spite of the double blinding (92% pazopanib and 70% placebo; supplementary Tables S7–S9, available at *Annals of Oncology* online).

Overall and disease-free survival

Among the 14 deaths on-study, nine occurred in the pazopanib arm and five in the placebo arm. All deaths were secondary to tumor recurrence, and two of which were related to cardiac toxicity (one placebo, one pazopanib). Five-year OS was 83% [95% CI 72–94] in the pazopanib arm and 94% [95% CI 88–100] with

Table 2. Compliance rate by planned dose and treatment arm

		Total number of patients	Compliant patients		
Cohort	**Arm**	***n***	***n***	**%**	**95% CI (%)**
800 mg/day	Pazopanib	39	15	38	[23–55]
	Placebo	41	36	88	[73–96]
400 mg/day	Pazopanib	32	22	69	[50–84]
	Placebo	30	28	93	[77–99]

CI, confidence interval.

Table 3. Treatment duration by planned dose and treatment arm

		Total number of patients	Treatment duration(weeks)		
Cohort	**Arm**	***N***	**Median**	**Min**	**Max**
800 mg/day	Pazopanib	38[a]	7.2	0.3	26.0
	Placebo	39[b]	24.1	0.3	26.4
400 mg/day	Pazopanib	31[a]	22.6	0.7	26.6
	Placebo	30	24.3	0.3	26.3

[a]Excludes one patient not starting treatment.
[b]Excludes two patients not starting treatment.

placebo (hazard ratio [HR]=1.8 [0.6–5.5], $P = 0.26$) (supplementary Figure S4A, available at *Annals of Oncology* online). Thirty patients experienced a total of 32 RFS events, 17 in the pazopanib arm and 13 in the placebo arm. Types of events are described in supplementary Figure S3, available at *Annals of Oncology* online. Three-year RFS was 76% [95% CI 65%–86%] in the pazopanib arm and 83% [95% CI 74%–92%] in the placebo arm (HR = 1.3, 95% CI 0.6–2.7, $P = 0.53$) (supplementary Figure S4b, available at *Annals of Oncology* online). Second primary cancers occurred in 11 patients in the 800 mg/day cohort (supplementary Tables S5 and S6, available at *Annals of Oncology* online), eight in the placebo arm and three with pazopanib. No second cancers occurred in the 400 mg/day cohort.

Quality of life

Among the 142 included patients, 101 had at least two QoL evaluations: one at baseline and one at the follow-up time (12 and/or 24 weeks), however the proportion of patients available for QoL analysis was significantly different between the two arms: 56% (40/72) in the pazopanib arm and 86% (61/71) in the placebo arm ($P < 0.0001$). Among these patients, there was a significant difference ($P = 0.0004$) in baseline age, with median [range] of 56 [39–68] and 61 [44–71] respectively in the pazopanib and placebo arms. There were no significant differences, at baseline or over time (adjusted on age), between the two arms (supplementary Table S5, available at *Annals of Oncology* online), among the six pre-specified dimensions or symptoms from the EORTC QLQ-C30 and -LC13 scales. Similar results were observed with EQ5D (data not shown).

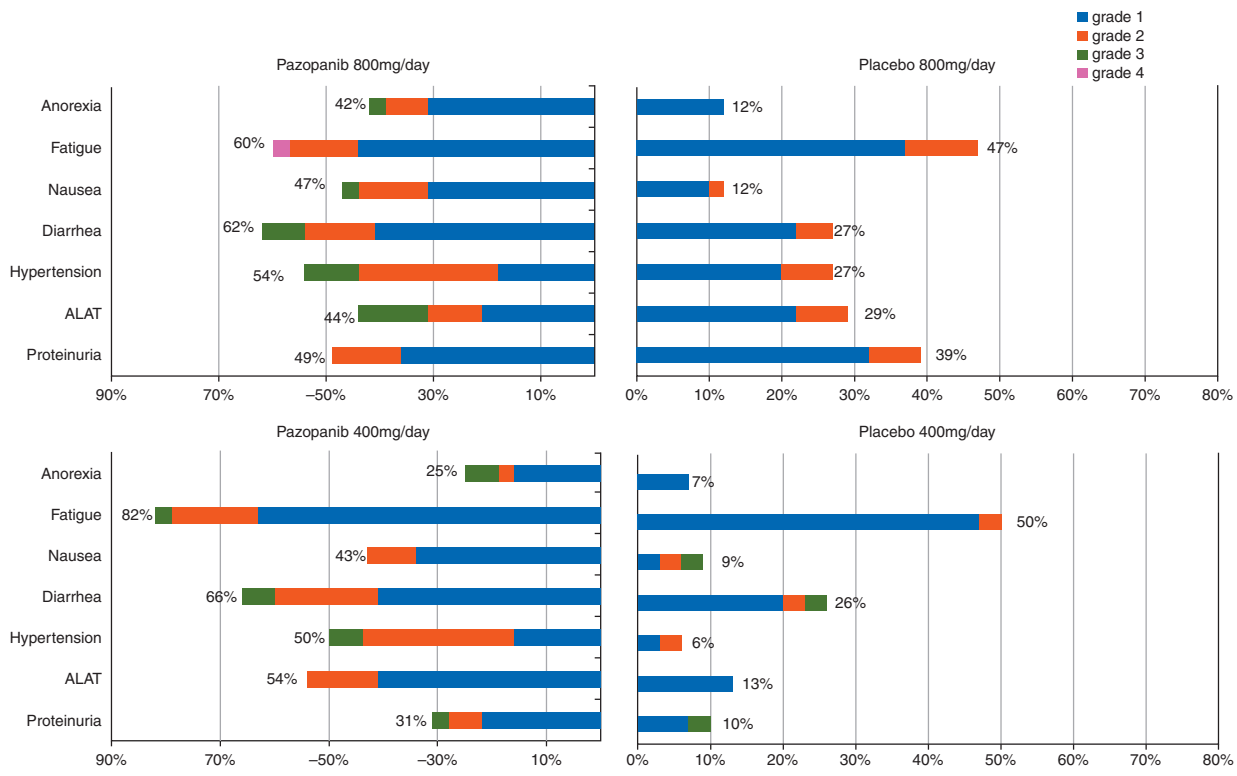

Figure 1. Adverse events of special interest by cohort (800 versus 400 mg/day) and by treatment arm.

Discussion

To our knowledge the IFCT-0703 study is the first adjuvant trial using an oral tyrosine kinase inhibitor targeting angiogenesis in resected lung cancer patients. Compliance with pazopanib 800 mg/day was poor, with 38% [95% CI, 23–55] of the patients receiving 12 weeks of treatment. This led to the IDMC recommending a decrease of the pazopanib dose. Pazopanib 400 mg/day was thus evaluated and appeared feasible with compliance improving to 69% [95% CI 50–84] and acceptable toxicity. Importantly, there were no toxic deaths, in particular significant bleeding. The phase III component, that aimed to evaluate survival, was not initiated due to outcome of exploratory efficacy data and lack of optimal pazopanib dosing.

Similar poor tolerance has been reported in adjuvant trials with sorafenib and sunitinib, two TKIs targeting VEGFR for other cancers. TKIs were discontinued in 44%–45% of the patients, an unexpected outcome given the good compliance in the metastatic setting [8, 9]. Dose was reduced for toxicity in 13% of patients for sorafenib and 20% for sunitinib. As in our study, their protocol was amended to reduce the starting dose. Patients' expectations in term of safety differ in the curative and palliative settings, with patients generally more willing to take an active drug despite side-effects in the latter case. As an illustration, compliance of adjuvant bevacizumab, an antibody that targets VEGF with less side-effect than TKIs, was comparable to adjuvant pazopanib in resected NSCLC, with 61% of patients that remained on treatment at 3 months [10]. Regarding QoL, as some missing evaluations during follow-up may be related to patient's poor compliance, it is not possible to draw definitive conclusion about the observed absence of difference in QoL between the two arms.

Despite the fact that the phase II part of the trial was not designed for comparison, we considered *ad hoc* survival analyses important in order to glean a maximum of data from the phase 2 part of our study. The 5-year OS of 94% [95% CI 88–100] in the placebo arms is much higher than expected. In a meta-analysis of NSCLC patients included in adjuvant trials of, 5-year survival for patients without chemotherapy ranged from 70% to 80% for stage IA, and from 55% ($n = 448$) to 75% for stage IB [4]. However, a different TNM definition was used, with stage IB including larger tumors with worse prognosis. Our better outcome is probably due to patient selection, as our inclusion criteria were restrictive, notably for age (less than 70 years), performance status (PS 0 or 1), limitation of comorbidities and probably most importantly absence of post-operative morbidity such as cardiac arrhythmia requiring long-term anticoagulation.

Although this analysis was obviously underpowered, no survival trend favoring pazopanib over placebo was observed in this setting. The HR for OS of 1.8 [95% CI 0.6–5.5] ($P = 0.23$) reflects fewer events in the placebo arm than in the pazopanib arm. Antiangiogenic TKIs have not been successful to date in the adjuvant setting. No benefit was reported with sorafenib or sunitinib in the adjuvant setting after resection of a renal cell carcinoma or local treatment of hepatocellular carcinoma [11–13]. Wakelee et al. reported recently the negative outcome of the E1505 trial assessing adjuvant chemotherapy with or without bevacizumab, a VEGF-targeted monoclonal antibody, in resected NSCLC (HR = 0.99, 95% CI 0.81–1.21, $P = 0.93$). Moreover, bevacizumab did not prolong disease-free survival when added to adjuvant chemotherapy in resected stage II and III colon cancer or triple-negative breast cancer [14, 15]. Lastly, one study even suggested a potential detrimental effect on OS effect with bevacizumab plus oxaliplatin-based adjuvant therapy in colon cancer [14].

Several reasons may account for the failure of the pazopanib in this setting. The benefit of inhibiting a known target could potentially be negated by the lack of TKI specificity for a single target and their inhibition of other targets, known as off-target effects. Indeed, Pazopanib objective response rate in NSCLC is modest [6, 16]. Second, in the absence of predictive factors for the efficacy of antiangiogenic treatment in any cancer type, it was not possible to select a population more likely to benefit from pazopanib. Third, evidence that systemic treatment may improve survival in stage I NSCLC was based on TNM classification previous that the 7th. In 2009, the IASCL modified the TNM classification, defining new stage I tumors as $\leq$5 cm. As we used the latter more stringent classification, we selected a population requiring highly potent treatments to derive a benefit in the adjuvant setting. Fourth, the dose of 400 mg/day might be suboptimal. A pharmacokinetically guided individualized dosing algorithm led to advanced cancer patients being treated at dosages ranging from 400 to 1800 mg daily [17]. Fifth, the duration of treatment might have been insufficient. Our 6-month choice was driven by the experience from the Japanese UFT trial in stage I patients showing that compliance falls dramatically from 6 to 12 months treatment (80.4% versus 50.9%) [18]. Finally, a deleterious effect of VEGFR TKIs in the adjuvant setting cannot be ruled out as showed experimentally in genetically modified mice [19].

In conclusion, this study does not support further evaluation of antiangiogenic TKIs after resection of stage I NSCLC patients. Alternative strategies currently incorporate treatment stratification based on prognostic markers and immunotherapy, and IFCT has launched with NCIC-CTG a new adjuvant phase 3 trial (IFCT 1401-BR31, NCT02273375) actually using a PD-L1 monoclonal antibody.

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