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ORIGINAL RESEARCH

Second-line therapy with gefitinib in combination with docetaxel for advanced non-small cell lung cancer: a phase II randomized study

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Abstract This randomized, open-label, parallel-group, phase II study evaluated the efficacy and safety of gefitinib and docetaxel in combination, as second-line therapy for advanced or metastatic non-small cell lung cancer (NSCLC). Eighty-nine patients who had failed first-line, platinum-based chemotherapy were randomly assigned to gefitinib (250 mg/day orally) in combination with docetaxel (75 mg/m^2 every 3 weeks) or single-agent docetaxel (75 mg/m^2 every 3 weeks). Objective response rates were 6.8% with gefitinib plus docetaxel and 9.1% with docetaxel alone. Disease control was experienced by a higher proportion of patients receiving gefitinib plus docetaxel (59.1%) versus docetaxel alone (34.1%). Median progression-free and overall survival appeared to be longer with gefitinib plus docetaxel (3.9 months [95% CI:2.3–5.4] and 7.6 months [95% CI:5.4–10.4], respectively) than with docetaxel alone (2.1 months [95% CI:2.1–3.7] and 6.2 months [95% CI:5.2–7.2], respectively). The most common non-hematological adverse events were diarrhea, alopecia, rash and dry skin in the combination arm, and vomiting and asthenia with docetaxel alone. Gefitinib and docetaxel combination therapy has antitumor activity and may be a feasible treatment option in patients with advanced NSCLC who have failed platinum-based chemotherapy.

Keywords Epidermal growth factor receptor · Epidermal growth factor receptor-tyrosine kinase inhibitor · Gefitinib · IRESSA · Non-small cell lung cancer

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Introduction

Platinum-based regimens are established as first-line chemotherapy for advanced non-small cell lung cancer (NSCLC). However, few agents have demonstrated efficacy in advanced NSCLC after failure of standard first-line chemotherapy.

When this study was designed, the cytotoxic agent docetaxel was the only approved second-line treatment option for advanced NSCLC [1], having demonstrated second-line activity in two phase III studies [2, 3]. In these studies, docetaxel significantly improved median survival compared with best supportive care (7.5 versus 4.6 months) [3], and demonstrated similar median survival (5.7 months) to vinorelbine/ifosfamide (5.6 months) [2]. However, there is still an unmet need for more effective agents with improved toxicity profiles for the treatment of advanced NSCLC. In addition to docetaxel, in some markets current second-line treatment options include the epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) gefitinib (IRESSA) and erlotinib (TARCEVA) [4] and the cytotoxic agent pemetrexed (ALIMTA) [5].

Gefitinib had demonstrated promising efficacy in pretreated patients with advanced NSCLC in phase II studies at the time of this study [6, 7], with objective response rates (ORRs) of 12.0–18.4%, disease-related symptom improvement rates of 40.3–43.1%, and one-year survival rates of 25–35%. Novel agents such as gefitinib have different modes of action from cytotoxic agents such as docetaxel; therefore, their combination could result in improved efficacy without overlapping toxicity. This strong rationale for investigating gefitinib and docetaxel in combination was supported by preclinical data. Gefitinib enhanced the efficacy of chemotherapy agents including docetaxel in a variety of preclinical tumor models, including lung [8]. However, in two first-line phase III trials (IRESSA NSCLC Trial Assessing Combination Treatment [INTACT] 1 and 2), no survival advantage was observed with the addition of gefitinib (250 mg/day and 500 mg/day) to platinum-based chemotherapy doublets (gemcitabine/cisplatin or paclitaxel/carboplatin) in advanced NSCLC [9, 10]. The reasons for this lack of additional benefit with gefitinib when combined with first-line platinum chemotherapy are not clear, but may be due to competition for signaling pathways when multiple combination regimens are used.

As gefitinib had demonstrated promising efficacy in the second-line setting, and given the synergy between docetaxel and gefitinib in the preclinical setting, the aim of this study was to evaluate the efficacy and safety of gefitinib and docetaxel combination therapy for advanced or metastatic NSCLC who had failed first-line platinum chemotherapy.

Patients and methods

Study design

This was a multicenter, randomized, open-label, parallel-group phase II study (code 1839IL/0137) of gefitinib in combination with docetaxel versus docetaxel alone in patients with unresectable advanced or metastatic NSCLC who had failed standard first-line platinum-based chemotherapy due to toxicity or disease progression. The primary objective was to evaluate the ORR (complete response [CR] + partial response [PR]) using the Response Evaluation Criteria in Solid Tumors (RECIST) [11]. Secondary objectives were to assess disease control rates (CR + PR + stable disease [SD]) using RECIST, progression-free survival (PFS) and overall survival (OS). The safety objective was to evaluate the safety and tolerability of the combination of gefitinib and docetaxel, and docetaxel alone, and to further characterize the safety profile of gefitinib 250 mg/day (in the gefitinib plus docetaxel arm after docetaxel treatment was discontinued). The quality-of-life objective was to evaluate patient quality-of-life for each treatment arm.

This study protocol was approved by the independent ethics committee of Brest, and the study was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki [12].

Patients

Patients with unresectable advanced or metastatic NSCLC who had failed to respond during, or after, standard first-line platinum-based chemotherapy, with a World Health Organization (WHO) performance status of ≤2, life expectancy of >3 months, age ≥18 years and at least one measurable lesion (according to RECIST) were eligible for inclusion in the study. The details of the main exclusion criteria are given in Table 1. (See Appendix 1 for patient exclusion criteria.)

Treatment plan

Patients were randomized to receive gefitinib (250 mg/day orally) in combination with docetaxel (75 mg/m^2 intravenously [i.v.] every 3 weeks) or docetaxel alone (75 mg/m^2 i.v. every 3 weeks). Before administration of docetaxel at the start of each cycle, patients were reassessed to ensure that their absolute neutrophil count (ANC) was $\geq 1.5 \times 10^9$/l and platelet count was $\geq 100 \times 10^9$/l. Patients received corticosteroid premedication (dexamethasone 8 mg twice daily) for 3 days starting 1 day before the docetaxel infusion. At least six cycles of docetaxel were planned for both treatment arms, or until the patient stopped receiving

Table 1 Baseline patient demographics (intent-to-treat population)

	Gefitinib plus docetaxel arm (n=44)	Docetaxel alone arm (n=44)	Total (n=88)
Median age, years (range)	59 (33–80)	59 (52–68)	59 (33–81)
Gender, *n* (%)			
Male	33 (75.0)	38 (86.4)	71 (80.7)
Female	11 (25.0)	6 (13.6)	17 (19.3)
WHO PS			
0	22 (50.0)	22 (50.0)	44 (50.0)
1	19 (43.2)	19 (43.2)	38 (43.2)
2	3 (6.8)	3 (6.8)	6 (6.8)
No. prior chemotherapy regimens			
1	37 (84.1)	31 (70.5)	68 (72.3)
2	8 (18.2)	12 (27.3)	20 (22.7)
3	0 (0.0)	1 (2.3)	1 (1.1)
Prior radiotherapy, *n* (%)	12 (27.3)	20 (45.5)	32 (36.4)
Prior surgery, *n* (%)	19 (43.2)	17 (38.6)	36 (40.9)
Histology, *n* (%)			
Squamous-cell carcinoma	11 (25.0)	20 (45.5)	31 (35.2)
Adenocarcinoma	25 (56.8)	16 (36.4)	41 (46.6)
Large-cell carcinoma	2 (4.5)	2 (4.5)	4 (4.5)
Mixed squamous and adenocarcinoma	1 (2.3)	1 (2.3)	2 (2.3)
Undifferentiated	5 (11.4)	5 (11.4)	10 (11.4)
Disease stage			
IIIb	5 (11.4)	4 (9.1)	9 (10.2)
IV	39 (88.6)	40 (90.9)	79 (89.8)
Sites of metastases, *n* (%)			
Adrenal	9 (20.5)	8 (18.2)	17 (19.3)
Liver	5 (11.4)	10 (22.7)	15 (17.0)
Bone	11 (25.0)	11 (25.0)	22 (25.0)
Lymph nodes	14 (31.8)	10 (22.7)	24 (27.3)
Skin/soft tissue	2 (4.5)	3 (6.8)	5 (5.7)
Other	3 (6.8)	4 (9.1)	7 (8.0)
No. of metastatic sites, *n* (%)			
1	15 (34.1)	14 (31.8)	29 (33.0)
2	18 (40.9)	17 (38.6)	35 (39.8)
≥3	11 (25.0)	13 (29.5)	24 (27.3)
Current or previous smoker	38 (86.4)	41 (93.2)	79 (89.8)
Non-smoker	6 (13.6)	3 (6.8)	9 (10.2)

WHOPS World Health Organization performance status

clinical benefit. Patients continued to receive study medication until unacceptable toxicity or disease progression, withdrawal of consent, patient lost to follow-up or protocol non-compliance. In the combination arm, patients showing evidence of clinical benefit at the end of the combination phase could continue to receive gefitinib monotherapy.

Dose reductions for patients receiving gefitinib 250 mg/day were not permitted, but treatment could be interrupted for a maximum of 14 days to manage toxicity. Repeat dose interruptions were allowed as required.

Dose interruptions of docetaxel were also allowed, with infusion delayed for up to 2 weeks if the patient had not fully recovered from the toxicity of the previous chemotherapy administration. If docetaxel treatment was delayed twice, or severe toxicity occurred, the dose was reduced to 60 mg/m^2. No dose re-escalation was allowed.

Assessments

Efficacy

Objective tumor assessments were performed according to RECIST at the end of every three treatment cycles. All objective responses were confirmed four weeks later. Disease control was defined as an objective response for ≥4 weeks, or SD for ≥6 weeks during the study or at study closure. PFS was assessed from the date of first treatment to the earlier date of disease progression or death of any cause, or the last on-trial tumor assessment. OS was assessed from the date of first treatment to the date of patient death, or to the last date the subject was known to be alive. All responses were reviewed and confirmed by a panel of experts from the Groupe Français de Pneumocancérologie (GFPC).

Safety and tolerability

Patients were monitored for adverse events (graded by National Cancer Institute Common Toxicity Criteria, version 2.0 [13]), laboratory and vital sign abnormalities, and electrocardiogram changes throughout the study and for 30 days following the last treatment dose.

Quality of life

Quality of life was assessed by the Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire and symptom improvement by the Lung Cancer Subscale (LCS) of FACT-L, at baseline and study endpoint (last questionnaire completed after cycle 1). The LCS monitors the severity of lung cancer symptoms, including shortness of breath, cough, chest tightness, difficulty breathing, loss of appetite, weight loss, and lack of clear thinking, and consists of statements that are rated by the patient on a 0–4 Likert scale (range: 0–28; a higher score represents improved symptoms). As well as symptom improvement, the FACT-L questionnaire encompasses social, functional, and physical and emotional well-being, and the score ranges from 0–136, with a higher score representing improved quality of life [14, 15]. "Improved" symptoms and quality of life were defined as a clinically meaningful score change of ≥2 points on the LCS or ≥6 points on the FACT-L questionnaire [14, 16]. LCS and FACT-L improvement rates were defined as the percentage of all analyzed patients with a best overall score response of "improved," which consisted of two visit responses of "improved" a minimum of 28 days apart with no interim or prior visit response of worsened.

Statistical analyses

The sample size of 44 patients with a critical value of six responses was considered sufficient to test the null hypothesis that the ORR would be 6% or less (at a one-sided significance level of 5%) and achieve a power of approximately 90% against the alternative hypothesis that the ORR is 20% or more. This analysis was based on an expected ORR of 20% in the combination arm, and 6% in the docetaxel alone arm. There were no formal comparisons of response between treatment groups. The intent-to-treat (ITT) population was used to analyze efficacy parameters. ORR and the disease control rate were summarized together with 95% confidence intervals (CI). PFS and OS were assessed using Kaplan-Meier analysis at study closure. Tolerability and quality-of-life endpoints were described using standard summary statistics.

Retrospective analyses

The effect of smoking on OS was analyzed by Cox regression analysis using time-to-death as the response variable, while smoking history (current or previous smokers versus non-smokers) and treatment group were explanatory variables. The effect of third-line treatment on OS was analyzed using by Cox regression analysis time-to-death as the response variable while prior third-line treatment and treatment group were explanatory variables.

Results

Patients

Eighty-nine patients from 21 centers enrolled in the study from July 2003 to November 2004, with 44 in the gefitinib plus docetaxel arm and 45 in the docetaxel alone arm. One patient recruited to the docetaxel alone arm had disease progression before receiving study treatment and therefore was not included in the ITT population. Baseline demographic characteristics were broadly similar between treatment groups for the majority of the parameters. However, there was a higher proportion of females, patients who failed first-line chemotherapy treatment and adenocarcinoma histology, and a lower proportion of patients who had received prior radiotherapy, in the gefitinib plus docetaxel arm compared with the docetaxel alone arm (Table 1).

There were 177 cycles of docetaxel in the gefitinib plus docetaxel arm and 164 cycles in the docetaxel alone arm. Median duration of gefitinib treatment was 83 days (including the gefitinib monotherapy phase). A median of four cycles (range 1–6) of docetaxel was administered per patient in the gefitinib plus docetaxel arm and three cycles (range 1–9) per patient in the docetaxel alone arm. Sixteen (36.4%) and 12 (27.3%) patients completed six planned cycles of docetaxel treatment in the gefitinib plus docetaxel alone arm and the docetaxel alone arm, respectively. Sixteen patients completed the combination phase, and four patients continued gefitinib monotherapy until the end of the study.

Efficacy

Seventy-nine patients were evaluable for response; 38 in the gefitinib plus docetaxel arm and 41 in the docetaxel alone arm. Nine patients were non-evaluable; six in the gefitinib plus docetaxel arm and three in the docetaxel alone arm (two patients had non-evaluable target lesions, one patient had disease progression, one had pleural

effusion and six withdrew early from the study or died before evaluation). The ORRs (calculated according to ITT analysis) were 6.8% (3 patients) (95% CI:1.4–18.7) with gefitinib plus docetaxel, and 9.1% (4 patients) (95% CI:2.5–21.7) with docetaxel alone (all responses were partial responses). In addition, 23 patients in the gefitinib plus docetaxel arm and 11 patients in the docetaxel alone arm had stable disease, leading to disease control rates of 59.1% (95% CI:43.2–73.7) and 34.1% (95% CI:20.5–49.9), respectively.

Median PFS was 3.9 months (95% CI:2.3–5.4) with gefitinib plus docetaxel and 2.1 months (95% CI:2.0–3.7) with docetaxel alone (Fig. 1a). PFS at 6 months was 27.3% (95% CI:14.1–40.4) and 25.0% (95% CI:12.2–37.8) of patients in the gefitinib plus docetaxel arm and docetaxel alone arm, respectively. Median OS was 7.6 months (95% CI:5.4–10.4) with gefitinib plus docetaxel and 6.2 months (95% CI:5.2–7.2) with docetaxel alone, respectively (Fig. 1b).

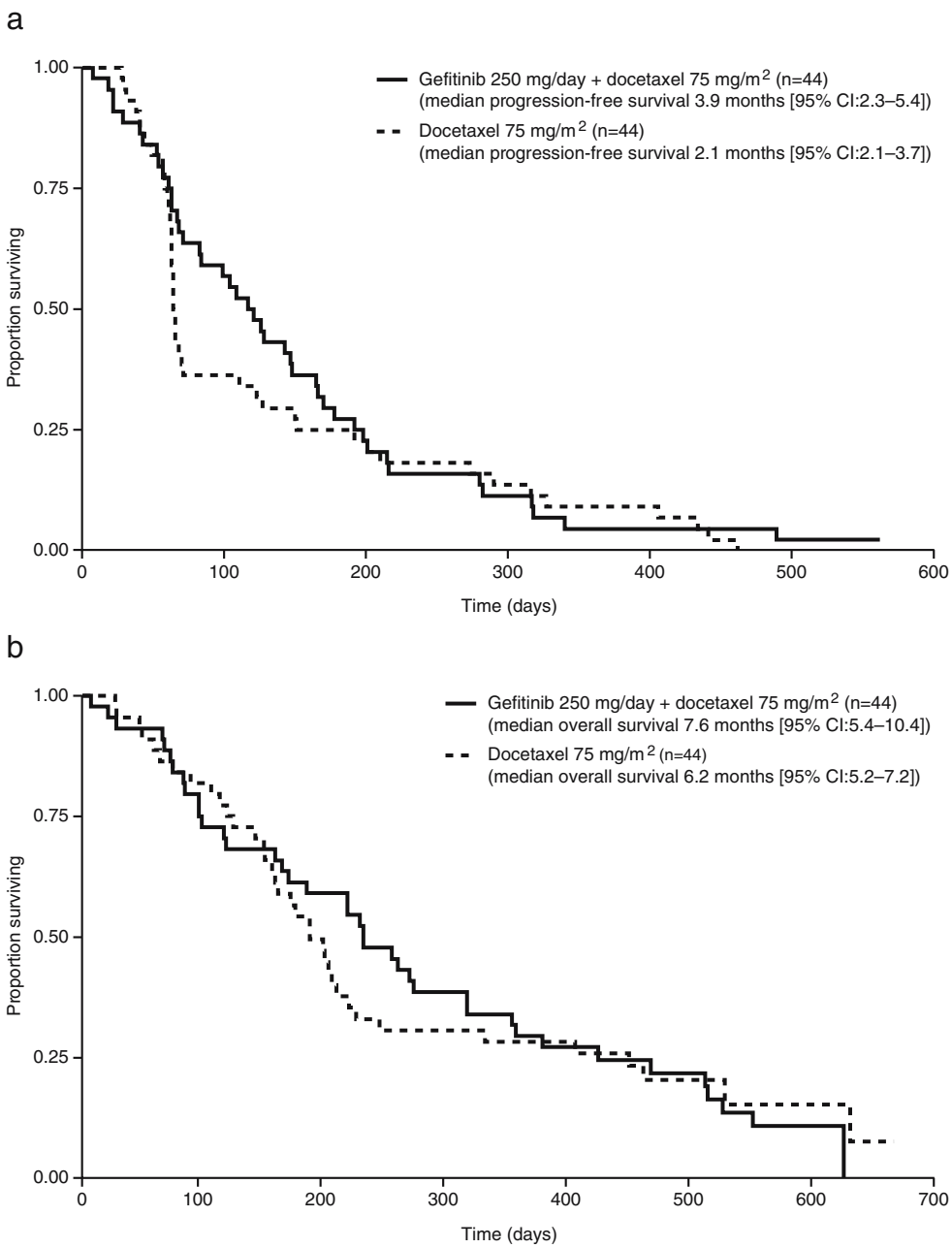

Fig. 1 Kaplan-Meier plot of **a** progression-free survival and **b** overall survival

Safety

In the ITT population (n=88), nine (20.5%) patients in the gefitinib plus docetaxel arm had at least one gefitinib dose interruption (14 dose interruptions in total; 11 due to toxicity, 3 due to dose forgotten or tablets lost) with a median duration of interruption of 9 days. In the gefitinib plus docetaxel arm, 13 (29.5%) patients had at least one docetaxel dose interruption (five due to toxicity and eight for other reasons) and four (9.1%) patients had dose reductions (75 mg/m^2 to 60 mg/m^2), three due to toxicity and one due to weight loss. In the docetaxel alone arm, seven (15.9%) patients had at least one docetaxel dose interruption (one due to toxicity and six for other reasons) and two (4.5%) patients had dose reductions, one due to toxicity and one to neutropenia. Adverse events occurring during both treatment arms are summarized in Tables 2 and 3. There was no incidence of interstitial lung disease reported in this study.

In the gefitinib plus docetaxel arm, nine patients withdrew from the combination phase due to adverse events of any causality (cardiac failure, asthenia, pulmonary embolism, lung disorder, rash, diarrhea, abdominal pain, vomiting, anorexia, peripheral neuropathy, pneumonia, erythema multiforme, and sudden death), 14 due to disease progression, and two due to poor tolerability. Three patients had adverse events with fatal outcomes (cardiac failure [in a patient with a history of cardiac disease], pulmonary embolism, acute death [probably due to pulmonary embolism]) that were considered by the investigator to not be related to either gefitinib or docetaxel. In the docetaxel alone arm, four patients withdrew from the combination phase due to adverse events of any causality (diarrhea, skin disorder, septic shock, bone marrow depression, pulmonary embolism, dyspnoea, and confusion), and 26 due to disease progression. Two patients had adverse events with fatal outcomes (bone marrow depression and septic shock in one patient, and pulmonary embolism and acute dyspnoea in another patient) that were considered by the investigator to be related to docetaxel.

Table 2 Most common non-hematological adverse events occurring in >10% of patients, n (%)

	Gefitinib plus docetaxel (n=44)		Docetaxel alone (n=44)	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Non-hematological				
Diarrhea	20 (45.5)	1 (2.3)	2 (4.5)	1 (2.3)
Alopecia	12 (27.3)	0 (0)	5 (11.4)	0 (0)
Rash*	10 (22.7)	1 (2.3)	2 (4.5)	0 (0)
Nausea	6 (13.6)	1 (2.3)	6 (13.5)	0 (0)
Dry skin	7 (15.9)	0 (0)	0 (0)	0 (0)
Asthenia	5 (11.4)	2 (4.5)	7 (15.9)	0 (0)
Vomiting**	5 (11.4)	0 (0)	7 (15.9)	0 (0)
Acne	5 (11.4)	0 (0)	0 (0)	0 (0)

*Includes rash not otherwise specified (NOS); ** includes vomiting NOS

Table 3 Most common hematological laboratory parameters occurring in >10% of patients, n (%)

	Gefitinib plus docetaxel (n=44)		Docetaxel alone (n=44)	
	Grade 3/4	All grades	Grade 3/4	All grades
Anemia	3 (6.8)	43 (97.7)	2 (4.5)	42 (95.5)
Leucopenia	21 (47.7)	33 (75.0)	11 (25.0)	30 (68.2)
Neutropenia	28 (63.6)	34 (77.3)	18 (40.9)	33 (75.0)
Thrombocytopenia	0 (0.0)	5 (11.4)	0 (0.0)	7 (15.9)

Quality of life

The median LCS and FACT-L scores at baseline were 18.6 and 91.0, respectively (gefitinib plus docetaxel arm) and 20.0 and 91.4, respectively (docetaxel alone arm) indicating that the patients had impaired quality of life. At end point (last questionnaire completed after cycle 1), median scores were 17 (LCS) and 84 (FACT-L) with gefitinib plus docetaxel, and 18 (LCS) and 82 (FACT-L) with docetaxel alone. Quality-of-life and symptom improvement rates were both 7.7% in the gefitinib plus docetaxel arm, and were 23.1 and 0%, respectively, in the docetaxel alone arm.

Retrospective analyses

The risk of death over the follow-up period was 220% higher in current or previous smokers compared with non-smokers (hazard ratio [HR] 3.22; 95% CI:1.29–8.07; p= 0.0126) and 64% lower in patients who received third-line treatment (versus no third-line treatment) (HR 0.36; 95% CI:0.22–0.59; p<0.0001).

Discussion

Our results show that the combination of gefitinib and docetaxel has antitumor activity for the treatment of advanced NSCLC in the second-line setting. A number of clinical trials have demonstrated clinical benefit of gefitinib or docetaxel monotherapy consistent with our study. The large phase III ISEL (IRESSA Survival Evaluation in Lung cancer) trial showed some improvement in survival compared with placebo that failed to reach statistical significance in the overall population and in patients with adenocarcinoma. However, there was a statistically significant improvement

in ORR and time to treatment failure for gefitinib, compared with placebo in the overall population. For example, the ORR was 8.0% with gefitinib 250 mg/day monotherapy treatment compared with 1.3% with placebo (odds ratio 7.28; 95% CI:3.1–16.9; $p<0.0001$) [17]. Phase III monotherapy studies of docetaxel have reported ORRs of 6.7–7.1% [2, 3, 5]. A phase II study (SIGN, Second-line Indication of Gefitinib in NSCLC) investigated gefitinib versus docetaxel as second-line monotherapy in patients with advanced NSCLC and reported ORRs of 13.2 and 13.7% [18].

Gefitinib and docetaxel in combination has also been investigated [19–21]. A pilot study assessed the safety, pharmacokinetics and efficacy of two doses of gefitinib (250 and 500 mg/day) in combination with docetaxel (75 mg/m^2) in patients with locally advanced or metastatic NSCLC as first- and second-line treatment. Six patients received gefitinib 250 mg/day, of whom two patients had a PR (one of which was in non-measurable disease). However, compared with the current randomized study, this was a small study where patient selection was not randomized and therefore subject to possible selection bias. Preliminary data from a phase II study of gefitinib 250 mg/day plus docetaxel 75 mg/m^2 in patients with advanced NSCLC, reported an ORR of 25.0% and disease control rate of 58.3% in patients who had failed platinum-based chemotherapy [20]. Also, preliminary results from a phase II study of gefitinib 250 mg/day plus docetaxel 75 mg/m^2 as first-line treatment in elderly patients with advanced NSCLC reported an ORR of 38% and disease control rate of 62% [21]. Our results, together with other studies that have investigated gefitinib and docetaxel combination therapy [20], show that the combination of gefitinib and docetaxel is feasible and is generally well tolerated. The adverse events reported in our study were as expected from the safety profiles of gefitinib and docetaxel, with the most common adverse events being diarrhea, nausea, asthenia, and rash. The incidence of grade 3/4 neutropenia and leucopenia in the combination arm was slightly higher than would be expected since gefitinib is not typically associated with hematological toxicity [22], and therefore the observed toxicity would be expected to be comparable to the incidence reported for the docetaxel alone group. However in this study, the incidence of grade 3/4 neutropenia with docetaxel is lower than previously reported [23]. The incidence of grade 3/4 neutropenia (28/44 [63.6%]) for gefitinib plus docetaxel in our study is consistent with previous reports of 46.7 and 67% [19, 20]. These results are also consistent with other phase II and III studies of single-agent docetaxel reporting neutropenia incidence rates of 67.3% (grade 3/4) [3], 40.2% (grade 3/4) [5], 54% (grade 4) [2] and 46.0% (grade 3/4) [18].

Epidermal growth factor receptor tyrosine kinase inhibitos (EGFR-TKIs) in combination with first-line platinum-based chemotherapy doublets have also been investigated [9]. These studies showed no survival benefit for the addition of gefitinib or erlotinib to first-line platinum chemotherapy [10, 24, 25].

Certain clinical characteristics may be associated with response to gefitinib including adenocarcinoma histology, never having smoked, female gender, and Asian origin [6, 7, 17, 26]. In the phase III ISEL study, marked heterogeneity in survival was observed between patient groups with those who had never smoked and patients of Asian origin achieving a significant survival improvement with gefitinib versus placebo [17]. Consistent with these studies, we observed a significant survival benefit with gefitinib and docetaxel combination therapy for those who had never smoked.

The current study investigated gefitinib and docetaxel in the second-line setting. Although the majority of patients had failed first-line treatment, there was some heterogeneity in the number of previous lines of chemotherapy treatment received. Some patients had also failed second-line chemotherapy (18.2 and 27.3%, in the gefitinib plus docetaxel arm, and the docetaxel alone arm, respectively), and one patient (2.3%) in the docetaxel alone arm had failed third-line treatment. These differences in the number of previous lines of chemotherapy received, as well as differences in other baseline demographics between treatment groups (higher proportion of females and adenocarcinoma histology, and less prior radiotherapy), may have contributed to the better survival outcomes observed in the gefitinib plus docetaxel combination arm.

Quality-of-life improvement rates were lower for gefitinib plus docetaxel compared to docetaxel alone (7.7 and 23.1%, respectively) in the current study. This was surprising as quality-of-life improvement rates of 25.5–33.8% for single-agent gefitinib and 26.0% for single-agent docetaxel have been reported previously [17, 18].

Our results indicate that gefitinib and docetaxel combination therapy has antitumor activity and may be a feasible treatment option in patients with advanced NSCLC who have failed platinum-based chemotherapy. Further investigation of combination treatment with gefitinib and docetaxel is warranted in this disease setting.

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Potential conflict of interest Dr. Robinet et al. report receiving research grants from AstraZeneca (AZ). Ms. Tisseron-Carrasco reports

being a full-time employee of AZ. No other potential conflict of interest relevant to this article was reported.

Appendix 1. Patient exclusion criteria

Patients were excluded from the study if they had: no prior treatment with a platinum-based regimen; prior treatment with a docetaxel-containing regimen; prior treatment with an anti-EGFR monoclonal antibody or EGFR-TKI; radiotherapy treatment within three weeks of enrollment; concurrent or prior treatment with any other systemic cancer therapy or investigational product within 30 days of enrolment; incomplete wound healing from surgery; cerebral metastasis; co-existing malignancies diagnosed within the last 5 years (with the exception of basal cell carcinoma or cervical cancer in situ); any unresolved chronic toxicity greater than National Cancer Institute-Common Toxicity Criteria (NCI-CTC) grade 2 from previous anticancer therapy (except alopecia); any pre-existing neurosensory disorder greater than CTC grade 1; an absolute neutrophil count (ANC) $<2.0\times10^9$/l or platelets $<100\times10^9$/l; serum bilirubin greater than the upper limit of normal; any evidence of severe or uncontrolled systemic disease (e.g., unstable or uncompensated respiratory, cardiac, hepatic or renal disease) in the opinion of the investigator; or liver enzymes (alanine aminotransaminase or aspartate aminotransaminase) >2.5 times the upper limit of normal (or >1.5 times the upper normal limit and alkaline phosphatase >2.5 times the upper normal limit if no demonstrable liver metastases, or >3.5 times in the presence of liver metastases).

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