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Randomized open-label non-comparative multicenter phase II trial of sequential erlotinib and docetaxel versus docetaxel alone in patients with non-small-cell lung cancer after failure of first-line chemotherapy: GFPC 10.02 study

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ABSTRACT

Background: Concomitant administration of erlotinib with standard chemotherapy does not appear to improve survival among patients with non-small-cell lung cancer (NSCLC), but preliminary studies suggest that sequential administration might be effective.
Objective: To assess the efficacy and tolerability of second-line sequential administration of erlotinib and docetaxel in advanced NSCLC.
Methods: In an open-label phase II trial, patients with advanced NSCLC, EGFR wild-type or unknown, PS 0-2, in whom initial cisplatin-based chemotherapy had failed were randomized to sequential erlotinib 150 mg/d (day 2–16) + docetaxel (75 mg/m^2 d1) (arm ED) or docetaxel (75 mg/m^2 d1) alone (arm D) (21-day cycle). The primary endpoint was the progression-free survival rate at 15 weeks (PFS 15). Secondary endpoints included PFS, overall survival (OS), the overall response rate (ORR) and tolerability. Based on a Simon optimal two-stage design, the ED strategy was rejected if the primary endpoint was below 33/66 patients at the end of the two Simon stages.
Results: 147 patients were randomized (median age: 60 ± 8 years, PS 0/1/2: 44/83/20 patients; males: 78%). The ED strategy was rejected, with only 18 of 73 patients achieving PFS15 in arm ED at the end of stage 2 and 17 of 74 patients in arm D. In arms ED and D, respectively, median PFS was 2.2 and 2.5 months and median OS was 6.5 and 8.3 months.
Conclusion: Sequential erlotinib and docetaxel was not more effective than docetaxel alone as second-line treatment for advanced NSCLC with wild-type or unknown EGFR status.
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1. Introduction

Non-small-cell lung cancer (NSCLC) accounts for 80% of lung cancers, and most patients already have advanced or metastatic

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disease at diagnosis. Combination platinum chemotherapy is recommended as first-line chemotherapy [1] but most patients progress; second-line chemotherapy is recommended for those whose performance status remains acceptable [1,2]. Several agents have been shown to improve survival in this setting, including docetaxel, pemetrexed and erlotinib. These treatments give response rates of 5 to 10% and a progression-free survival (PFS) of two to three months [3–8]. A large phase III trial [9] showed that a combination of cisplatin and pemetrexed was superior to cisplatin plus gemcitabine in most patients with non-squamous NSCLC than second-line options were usually restricted to docetaxel and erlotinib fort these patients.

NSCLC management has been transformed by the identification of drug targets in a subset of molecularly defined tumors. However, initial experience with targeted treatments for unselected NSCLC patients has shown only modest and inconsistent improvements in outcomes. The addition of bevacizumab to first-line two-agent chemotherapy improved median survival by two months in one randomized study but failed to improve survival in another [10,11]. Four randomized trials showed no benefit of concomitant epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) therapy and first-line chemotherapy over chemotherapy alone in unselected patients with NSCLC [12–15]. However, preclinical studies suggest that there may be antagonism between TKIs and chemotherapy: EGFR TKIs cause cell cycle arrest in G1 phase, protecting cells against the cytotoxic effects of chemotherapy agents, which act essentially in the M and G2/S phases of the cell cycle [16–19]. Sequential administration of TKIs after chemotherapy appears to be more effective [20–22]. Early clinical evidence suggests that sequential administration of docetaxel or pemetrexed followed by erlotinib has promising activity in previously treated patients [19–22].

The main objective of this study was to assess the efficacy and tolerability of second-line sequential erlotinib plus docetaxel in advanced NSCLC with wild-type or unknown EGFR status.

1.1. Patients and methods

1.1.1. Study design

The objective of this multicenter, open-label, phase II randomized study (GFPC 10.02) was to assess the efficacy and tolerability of second-line sequential erlotinib plus docetaxel in advanced NSCLC. Patients were randomized into two groups (1:1) using blocks of size 2 and 4 with stratification by center and recurrent versus refractory (no response to induction chemotherapy). The primary endpoint was the rate of progression-free survival (PFS) at 15 weeks (PFS15). Secondary endpoints were PFS at 12 months, overall survival (OS) at 12 months, the overall response rate (ORR) at 15 weeks, and tolerability. The protocol was approved by an independent ethics committee in Limoges on behalf of all participating centers, and the study complied with good clinical practices and the Helsinki Declaration. This trial is registered with ClinicalTrials.gov, under number NCT01350817.

1.1.2. Eligibility criteria

The inclusion criteria were: age 18 years or more, performance status (PS) 0, 1 or 2, cytologically or histologically proven stage IV or IIIB NSCLC with T4 staging by neoplastic pleural effusion, already treated with first-line cisplatin-based chemotherapy, with wild-type or unknown EGFR status, a measurable tumor, life expectancy of more than three months, and biological status compatible with chemotherapy (bilirubin concentration <1.25 times the upper limit of normal (ULN), transaminase activity <3 ULN, alkaline phosphatase <2.5 ULN, polynuclear neutrophils $>1.5 \times 10^9$/l, and platelets $>100 \times 10^9$/l). The non-inclusion criteria were more than one previous line of chemotherapy, previous treatment with erlotinib or docetaxel, symptomatic brain metastases, unstable heart disease, uncontrolled infection, neuropathy of grade 2 or higher, and a concurrent metastatic malignancy. The experimental arm (arm ED) received 150 mg of erlotinib per day on days 2 to 16 plus 75 mg/m^2 docetaxel on day 1 (21–day cycle). The control arm (arm D) received 75 mg/m^2 docetaxel alone, on day 1 (21–day cycle). Treatments were administered until progression or unacceptable toxicity. The dose could be reduced in case of grade 3/4 toxicity (docetaxel from 75 to 60 mg/m^2; erlotinib from 150 mg to 100 mg/d), but the protocol treatment was stopped if the doses of both drugs needed to be reduced.

Patients were monitored for adverse events, biological abnormalities, vital signs and electrocardiographic changes, using the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 4.0.

Objective tumor responses were assessed every two chemotherapy cycles (and at 15 weeks), by CT scans of the chest, abdomen and brain, until progression or withdrawal from the trial, regardless of the reason. OS was calculated from the date of randomization to the date of death from any cause, or the last date on which the patient was known to be alive. All responses were reviewed centrally and confirmed by a panel of experts convened by GFPC (Groupe Français de Pneumo-Cancérologie).

1.1.3. Statistical analysis

We calculated the sample size based on the results of key phase III studies of second-line NSCLC treatment, which reported median PFS values of less than 3 months. The hypothetical optimal efficacy (P1) in the experimental group (arm ED) was a PFS15 of 60%, and the minimum threshold for efficacy (P0) was set at 40%. In a Simon's optimal two-stage design [23] with an α risk of 5% and a β risk of 10%, 25 patients were required for stage 1, at the end of which at least 12 patients had to have achieved PFS15 for the study to continue to stage 2; this required the recruitment of an additional 41 patients per arm, giving a total of 66 patients. The hypothesis was rejected if, at the end of the study, fewer than 33 of the patients had achieved PFS15. It was decided to include the same number of subjects in arm D and to take into account possible losses to follow-up and ineligibility in both arms. Hence, 78 subjects per group (156 in total) were required.

The analysis was performed on an intention-to-treat basis, using SAS software v9.3 (INC Institute, Carry, USA).

Quantitative data are expressed as the mean, standard deviation and range; qualitative data are expressed as the frequency and percentage. All tests were two-tailed, and p values <0.05 were considered significant. Quantitative variables were compared using Student's t test or the Mann–Whitney U test if the groups were too small or the data were not normally distributed. Qualitative parameters were compared using the Chi^2 test or Fisher's test. PFS15, PFS and OS were assessed by Kaplan–Meier analysis. An exploratory analysis was used to compare OS between patients with refractory and recurrent disease.

Role of the sponsors: the sponsors had no role in the design or performance of the study, data analysis or manuscript preparation. The results belong to GFPC. The data were analyzed by the GFPC statistician and interpreted by the authors.

2. Results

One hundred fifty six patients were recruited by 33 centers between June 2011 and February 2013, of whom 151 were randomized. Two patients in each arm withdrew their consent. In total, 147 patients were included in the analysis, 73 in arm ED and 74 in arm D (Fig. 1). The patients in the two groups had similar baseline characteristics (Table 1). Most of the patients were men (80.8% and

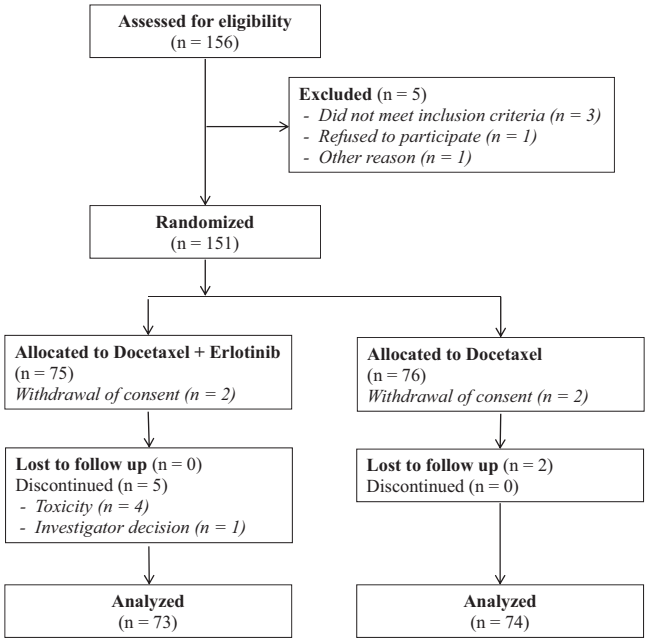


Fig. 1. Study design.

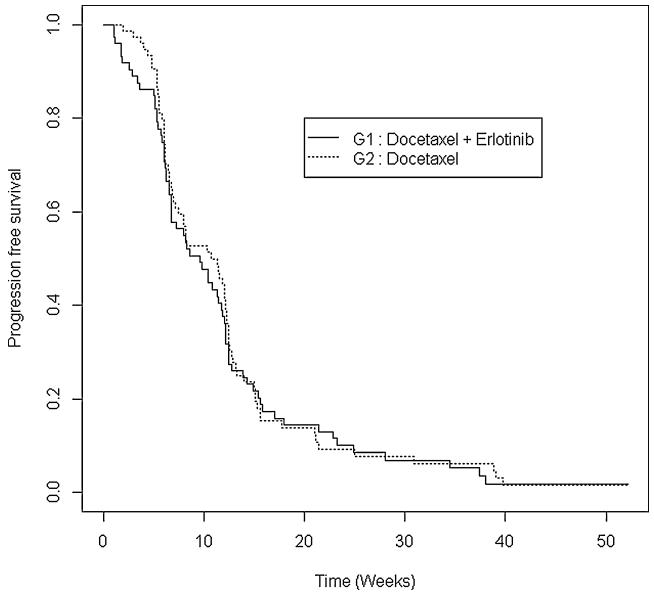


Fig. 2. Kaplan–Meier curve: progression free survival arm ED (sequential erlotinib +docetaxel) and arm D (docetaxel).

75.7% in arms ED and D, respectively). Mean age was 59.1 ± 8.5 and 59.6 ± 7.6 years, and adenocarcinomas represented 76% and 79% of malignancies, respectively. Most of the patients had wild-type EGFR (66% and 68%, respectively) and recurrent disease (65.7% and 64.8%, respectively). Most of the patients were current or former smokers (87.4% in arm ED and 98.2% in arm D), but the frequency of non-smokers was significantly higher in arm ED than in arm D (12.5% versus 2.7%; $p = 0.014$).

2.1. Efficacy

At the end of stage 1, 8 of 25 patients in arm ED achieved PFS15. The independent monitoring committee nonetheless authorized stage 2 to be launched. Indeed, analysis of the first 25 assessable patients showed a high rate of refractory disease (10/25 patients), as well as encouraging results in patients with recurrence (8 of 15 patients at PFS15), acceptable and expected toxicity, and a high inclusion rate at the time of analysis (133/156 patients included). The mean number of treatment cycles received was 3 ± 1.8 in arm ED and 3.8 ± 2.5 in arm D.

The ED strategy was finally rejected, with only 18 of 73 patients achieving PFS15 in arm ED at the end of stage 2, compared to 17 of 74 patients in arm D.

In arms ED and D, respectively, PFS was 2.2 [95% CI: 1.5–2.7] and 2.5 [95% CI: 1.6–2.8] months (Fig. 2); OS was 6.5 [95% CI: 4.43–10.1] and 8.3 [95% CI: 4.5–11.1] months, and the one-year survival rate was 35.6% [95% CI: 24.9–46.5] and 37.8% [95% CI: 26.9–48.7]. An objective response was seen at 15 weeks in 4.4% and 1.4% of patients in arms ED and D, respectively. The frequency of objective responses according to RECIST criteria was 12.3% in arm ED and 6.6% in arm D. The disease control rates at 15 weeks were 13.4% and 11.4% in arms ED and D, respectively. In an exploratory post hoc analysis, refractory patients had significantly worse PFS than recurrent patients: 1.6 (95% CI: 1.4–2.4) versus 2.8 months (95% CI: 1.9–2.9), $p = 0.023$. In arm ED, we found no difference in PFS between recurrent patients and refractory patients (median PFS of 2.6 [95% CI:1.53–2.8] versus 1.9 months [95% CI:1.4–2.5]

Table 1
characteristics of the intention-to-treat population (ED: sequential erlotinib-docetaxel, D: docetaxel alone).

	All patients $n = 147$(%)	ED $n = 73$ (%)	D $n = 74$ (%)	p Value
Age (years)	59.4 ± 8	59.1 ± 8.5	59.7 ± 7.6	0.6
Male	115 (78.2%)	59 (80.8%)	56 (75.7%)	0.4
Smoking status				
Non-smokers	11 (7.5%)	9 (12.5%)	2 (2.7%)	0.01
Former smokers	84 (57.6%)	34 (47.2%)	50 (67.6%)	
Current smokers	51 (34.9%)	29 (40.3%)	22 (29.7%)	
Unknown	1	1	0	
PS				
0	44 (29.9%)	21 (28.8%)	23 (31.1%)	0.3
1	83 (56.5%)	45 (61.6%)	38 (51.3%)	
2	20 (13.6%)	7 (9.6%)	13 (17.6%)	
Histologic types				
Squamous	20 (13.6%)	12 (16.4%)	8 (10.8%)	0.5
Adenocarcinoma	115 (78.2%)	56 (76.0%)	59 (79.0%)	
Others	12 (8.2%)	5 (6.8%)	7 (9.5%)	
Maintenance	72 (49.0%)	33 (45.2%)	39 (52.7%)	0.4
EGFR status				
Wild-type	98 (66.0%)	48 (66.0%)	50 (68.0%)	0.8
Unknown	49 (34.0%)	25 (34.0%)	24 (32.0%)	
Recurrent disease	96 (65.3%)	48 (65.7%)	48 (64.9%)	0.9
Refractory disease	51 (35.7%)	25 (34.3%)	26 (35.1%)	

Table 2a
Safety analysis.

	All patients $n=147$	ED $n=73$	D $n=74$
Patients with 31 AE of NCI-CTCAE grade 3/4			
Hematologic			
Anemia	8 (5.4%)	5(6.8%)	3(4.0%)
Neutropenia	41 (27.9%)	22 (30.1%)	19(25.7%)
Leukopenia	11(7.5%)	8 (11.0%)	3(4.0%)
Febrile neutropenia	16 (10.9%)	12 (16.4%)	4(5.4%)
Non-hematologic			
Fatigue	19 (12.9%)	11 (15.0%)	8 (10.8%)
Dyspnea	18 (12.2%)	8 (11.0%)	10 (13.5%)
Pain	5 (3.4%)	1 (1.4%)	4 (5.4%)
Anorexia	5 (3.4%)	4 (5.5%)	1 (1.3%)
Patients with AEs of NCI-CTCAE grade 5			
	10 (6.8%)	4 (5%)	6 (8%)

$p=0.4371$), whereas there was a significant difference in arm D, with a higher PFS in patients with recurrent disease (2.9 [95% CI:1.9–3]) than in those with refractory disease (1.5 months [95% CI:1.2–2.7]) ($p=0.01$).

2.2. Toxicity

In the intention-to-treat analysis, 140 (95.2%) of 147 patients had at least one adverse event of any grade: 94.5% in arm ED and 96% in arm D ($p=0.71$). Hematologic grade 3 to 4 AEs occurred in 25 patients in arm ED and 16 patients in arm D (Table 2a). Neutropenia was the most common AE in both arms. The principal non hematologic AEs of at least grade 3 were fatigue (12.9%), dyspnea (12.2%), pain (3.4%) and anorexia (3.4%), with no significant difference between the arms ($p=0.4$, $p=0.6$, $p=0.3$ and 0.2, respectively) (Table 2a). The most frequent grade 1 to 2 non hematologic AEs are shown in Table 2b. A significant difference between the arms was found regarding patients who had at least one adverse event of grade 2 or less, with a higher frequency of diarrhea (31.5% versus 12.2%, $p=0.0045$), oral mucositis (20.5% versus 4.0%, $p=0.0023$) and rash (23.3% versus 0%, $p<0.0001$) in arm ED than in arm D. Ten patients died, 4 in arm ED and 6 in arm D. None of these deaths were considered treatment-related.

3. Discussion

This randomized open-label non comparative phase II trial in patients with advanced NSCLC and wild-type or unknown EGFR status showed that, despite acceptable toxicity, a sequential combination of erlotinib plus docetaxel was not as efficacious as expected in the second-line setting. The PFS of about 2.5 months in both arms is consistent with published findings [3–8]. In a similar population, a multicenter study gave a median PFS of 2.8 months with pemetrexed and 2.5 months with docetaxel [24]. Similarly, a recent phase III study of second-line treatment for wild-type EFGR NSCLC gave a median PFS of 2.9 months with docetaxel and 2.4 months with erlotinib [7]. In view of these previous results, our primary end point (a PFS of 3.5 months in 60% of the patients) was probably too ambitious.

Trials of concomitant TKI treatment and chemotherapy have shown no superiority over chemotherapy alone [12–15]. By contrast, several studies with cell lines and tumor models have shown higher levels of anti-proliferative and cytotoxic activity following sequential administration of erlotinib and chemotherapy [20–22]. The results of our study, like those of recent studies in unselected populations, do not support the superiority of sequential treatment. A randomized phase II trial compared erlotinib monotherapy with a combination of erlotinib and single-agent chemotherapy adapted to tumor histology in an unselected European NSCLC population [25]. There was no difference in terms of PFS (primary endpoint) (4.9 versus 6.1 months; hazard ratio 0.76, $p=0.06$), but a significant benefit was seen in terms of OS (5.5 months for erlotinib and 7.8 months for the combination, $p=0.01$). In this latter study, EFGR status was assessed in only 33% of patients and only three patients were found to have an activating mutation.

Erlotinib has also been tested in sequential administration with first-line cisplatin–gemcitabine chemotherapy [26]. In the subgroup of patients with wild-type EFGR, sequential administration had no benefit in terms of PFS (6.7 versus 5.9 months; HR = 0·97; $p=0{\cdot}85$). By contrast, in patients with unknown EGFR status it was associated with significantly longer PFS (7.1 versus 6 months; HR = 0.61; $p=0.0009$). However, as pointed out by the authors, the study population was Asian and had a high prevalence EGFR mutation (around compared to 10% in French residents [27]). A recent study of a clinically selected population (Asian non-smokers, non-squamous histology) confirmed these results [28]. Second-line treatment in this latter study was randomized to erlotinib monotherapy, pemetrexed monotherapy or a sequential combination of pemetrexed and erlotinib (on d2–d16). The combination yielded a significant improvement in PFS (HR: 0.57; $p=0.003$), with values of 7.4, 3.8 and 4.4 months for the combined treatment, erlotinib alone and pemetrexed alone, respectively. However, 55.8% of the patients in this study ($n=43$) had an activating mutation of EGFR, making it difficult to compare the results with those of

Table 2b
Non hematologic toxicity of grade 1–2 (>10%).

	All patients (110 AEs)	ED arm (58 AEs)	D arm (52 AEs)
AEs of NCI-CTCAE grade 1–2			
Fatigue	46 (41.82%)	24 (41.38%)	22 (42.31%)
Diarrhea	32 (29.09%)	23 (39.65%)	9 (17.31%)
Oral mucositis	18 (16.36%)	15 (25.86%)	3 (5.77%)
Anorexia	18 (16.36%)	12 (20.69%)	6 (11.54%)
Nausea	17 (15.45%)	9 (15.52%)	8 (15.38%)
Vomiting	14 (12.73%)	10 (17.24%)	4 (7.69%)
Alopecia	13 (11.82%)	6 (5.17%)	7 (13.46%)
Acneiform rash	17 (15.45%)	17 (29.31%)	0 (0.00%)

our study and potentially accounting for the greater sensitivity to erlotinib adjunction.

One noteworthy characteristic of our study population was the high frequency of disease refractory to first-line treatment (35%). Patients with refractory disease had a worse response to second-line treatment. In the TITAN study [29], refractory first-line patients had a PFS of 1.5 months in the erlotinib group and 2 months in the chemotherapy group. This poor prognosis was also found in both arms of our study, with a median PFS of 1.9 and 1.5 months with ED and D, respectively.

No particular or unexpected toxicity was observed in our study, and there was no significant difference between the arms with respect to adverse events of grade 3 or more. However, there were fewer grade 1/2 adverse events with docetaxel monotherapy.

In conclusion, sequential administration of erlotinib with standard second-line chemotherapy for NSCLC in Caucasian patients with wild-type or unknown EGFR status did not support the expectation of better results than monotherapy. Although the combination was more toxic, adverse effects remained acceptable. These results do not support the reported superiority of erlotinib and standard chemotherapy when given sequentially.

Conflict of interest statement

JB Auliac received fees for attending scientific meetings, speaking, organizing research or consulting from Boehringer Ingelheim, Hoffman la Roche, Lilly and Pzifer. C Chouaid received fees for attending scientific meetings, speaking, organizing research or consulting from Astra Zeneca, Boehringer Ingelheim, Glaxo Smith Kline, Hoffman la Roche, Astra Zeneca, Sanofi Aventis, Lilly, Novartis and Amgen. L Greillier received fees for attending scientific meetings, speaking, organizing research or consulting from Astra Zeneca, Lilly and Hoffman la Roche. I Monnet received fees for attending scientific meetings from Lilly. H Le Caer received fees for attending scientific meetings from Lilly and Hoffman la Roche. R Corre received fees for attending scientific meetings, speaking, organizing research or consulting from Lilly, Hoffman la Roche. R Descourt received fees for attending scientific meetings, speaking, organizing research or consulting from Lilly. S Bota received fees for attending scientific meetings, speaking, organizing research or consulting from Astra Zeneca, Boehringer ingelheim, Lilly. P Fournel received fees for attending scientific meetings, speaking, organizing research or consulting from Boehringer Ingelheim, Hoffman la Roche, Lilly. A Vergnenegre received fees for attending scientific meetings, speaking, organizing research or consulting from Boehringer Ingelheim, Hoffman la Roche, Lilly. Others authors declare no conflict of interest.

References

[1] Peters S, Adjei AA, Gridelli C, et al. Metastatic non-small-cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012;23:vii56–64.

[2] Azzoli CG, Temin S, Giaccone G, et al. 2011 Focused update of 2009 American society of clinical oncology clinical practice guideline update on chemotherapy for stage IV non-small-cell lung cancer. J Clin Oncol 2011;29:3825–31.

[3] Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non–small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 2000;18:2095–103.

[4] Fossella FV, DeVore R, Kerr RN, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non small-cell lung cancer previously treated with platinum-containing chemotherapy regimens, The TAX 320 non-small cell lung cancer study group. J Clin Oncol 2000;18:2354–62.

[5] Hanna N, Shepherd F, Fossella F, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non–small-cell lung cancer previously treated with chemotherapy. J Clin Oncol 2004;22:1589–97.

[6] Kim ES, Hirsh V, Mok T, et al. Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): a randomised phase III trial. Lancet 2008;372:1809–18.

[7] Garassino M, Martelli O, Broggini M, et al. Erlotinib versus docetaxel as second-line treatment of patients with advanced non-small-cell lung cancer and wild-type EGFR tumours (TAILOR): a randomised controlled trial. Lancet Oncol 2013;14:981–8.

[8] Shepherd FA, Peirera JR, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 2005;353:123–32.

[9] Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol 2008;26:3543–51.

[10] Sandler A, Gray R, Perry MC, et al. Paclitaxel–carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 2006;14:2542–50.

[11] Reck M, von Pawel J, Zatloukal P, et al. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAil. J Clin Oncol 2009;27:1227–34.

[12] Giaccone g Herbs Rt Manegold C, et al. Gefitinib in combination with gemcitabine and cisplatin in advanced non-small-cell lung cancer: a phase III trial—INTACT 1. J Clin Oncol 2004;22:777–84.

[13] Herbst R, Giaccone G, Schiller J, et al. Gefitinib in combination with paclitaxel and carboplatin in advanced non-small-cell lung cancer: a phase III trial—INTACT 2. J Clin Oncol 2004;22:785–94.

[14] Gatzemeier U, Pluzanska A, Szczesna A, et al. Phase III study of erlotinib in combination with cisplatin and gemcitabine in advanced non–small-cell lung cancer: the Tarceva lung cancer investigation trial. J Clin Oncol 2007;25:1545–52.

[15] Herbst R, Prager D, Hermann R, et al. TRIBUTE: a phase III trial of erlotinib hydrochloride (OSI-774) combined with carboplatin and paclitaxel chemotherapy in advanced non-small-cell lung cancer. J Clin Oncol 2005;23:5892–9.

[16] Milano G, Spano P, Leyland-Jones B. EGFR-targeting drugs in combination with cytotoxic agents: from bench to bedside, a contrasted reality. Br J Cancer 2008;99:1–5.

[17] Davies AM, Ho C, Lara Jr PN, et al. Pharmacodynamic separation of epidermal growth factor receptor tyrosine kinase inhibitors and chemotherapy in non-small-cell lung cancer. Clin Lung Cancer 2006;7:385–93.

[18] Mahaffey CM, Davies AM, Lara Jr PN, et al. Schedule-dependent apoptosis in K-ras mutant non-small-cell lung cancer cell lines treated with docetaxel and erlotinib: Rationale for pharmacodynamic separation. Clin Lung Cancer 2007;8:548–53.

[19] Davies AM, Hesketh PJ, Beckett L, et al. Pharmacodynamic separation of erlotinib and docetaxel (DOC) in advanced non-small-cell lung cancer (NSCLC): overcoming hypothesized antagonism. J Clin Oncol 2007;25:S7618, 413s.

[20] Davies AM, Ho C, Beckett L, et al. Intermittent erlotinib (ERL) in combination with pemetrexed (PEM): phase I schedules designed to achieve pharmacodynamic separation. J Clin Oncol 2008;26(1431):(S8032).

[21] Mok t Yi-Long W, Chong-Jen Y, et al. Randomized, placebo-controlled, phase II study of sequential erlotinib and chemotherapy as first-line treatment for advanced non-small-cell lung cancer. J Clin Oncol 2009;27:5080–7.

[22] Sangha R, Davies AM, Lara PN, et al. Intercalated erlotinib-docetaxel dosing schedules designed to achieve pharmacodynamics separation: results of a phase I/II trial. J Thorac Oncol 2011;6:2112–21.

[23] Simon R. Optimal two-stage designs for phase II clinical trials. Control Clin Trials 1989;10:1–10.

[24] Vergnenegre A, Corre R, Berard H, et al. Cost-effectiveness of second-line chemotherapy for non-small cell lung cancer: an economic, randomized, prospective, multicenter phase III trial comparing docetaxel and pemetrexed: the GFPC 05-06 study. J Thorac Oncol 2011;6:161–8.

[25] Aerts JG, Codrington H, Lankheet NA, et al. A randomized phase II study comparing erlotinib versus erlotinib with alternating chemotherapy in relapsed non-small-cell lung cancer patients: the NVALT-10 study. Ann Oncol 2013;24:2860–5.

[26] Wu YL, Lee JS, Thongprasert S, et al. Intercalated combination of chemotherapy and erlotinib for patients with advanced stage non-small-cell lung cancer (FASTACT-2): a randomised, double-blind trial. Lancet Oncol 2013;14:777–86.

[27] Barlesi F, Blons H, Beau-Faller M, et al. Biomarkers (BM) France: results of routine EGFR, HER2, KRAS, BRAF, PI3KCA mutations detection and EML4-ALK gene fusion assessment. J Clin Oncol 2013;31:S8000.

[28] Lee DH, Lee JS, Kim SW, et al. Three-arm randomized controlled phase 2 study comparing pemetrexed and erlotinib to either pemetrexed or erlotinib alone as second-line treatment for never-smokers with non-squamous non-small-cell lung cancer. Eur J Cancer 2013;49:3111–21.

[29] Tudor Ciuleanu, Lilia Stelmakh, Saulius Cicenas, et al. Efficacy and safety of erlotinib versus chemotherapy in second-line treatment of patients with advanced, non-small-cell lung cancer with poor prognosis (TITAN): a randomised multicentre, open-label, phase 3 study. Lancet Oncol 2012;13:300–8.