# Efficacy of Pemetrexed as Second-Line Therapy in Advanced NSCLC after Either Treatment-Free Interval or Maintenance Therapy with Gemcitabine or Erlotinib in IFCT-GFPC 05-02 Phase III Study

*Olivier Bylicki, MD,*† Céline Ferlay, MD,‡ Christos Chouaid, MD, PhD,‖ Armelle Lavolé, MD,¶ Fabrice Barlési, MD, PhD,** Cathérine Dubos, MD,†† Virginie Westeel, MD, PhD,‡‡ Jacky Créquit, MD,§§ Roman Corre, MD,‖‖ Alain Vergnenègre, MD, PhD,¶¶ Isabelle Monnet, MD,*** Hervé Le Caer, MD,††† Pierre Fournel, MD,‡‡‡ Fabien Vaylet, MD,§§§ Lionel Falchero, MD,‖‖‖ Michel Poudenx, MD,¶¶¶ Pauline Linard, MSc,‡ David Pérol, MD,‡ Gérald Zalcman, MD, PhD,**** and Maurice Pérol, MD§*

**Introduction:** Maintenance therapy in advanced non–small-cell lung cancer (NSCLC) might lead to resistance to subsequent treatments. IFCT–GFPC 0502 study showed a progression-free survival (PFS) benefit with gemcitabine or erlotinib maintenance compared with observation after cisplatin-gemcitabine chemotherapy. The trial included a pre-defined pemetrexed second-line therapy, allowing post-hoc assessment of its efficacy according to previous maintenance treatment or treatment-free interval.

**Methods:** Stage IIIB/IV NSCLC patients were randomized after four cycles of cisplatin-gemcitabine chemotherapy to either observation or to receive maintenance therapy with gemcitabine or erlotinib. Pemetrexed was given as second-line treatment on disease progression in all arms. PFS and overall survival (OS) were assessed from the beginning of pemetrexed therapy according to randomization arm.

**Results:** Of the 464 randomized patients, 360 (78 %) received second-line pemetrexed (130 [84%], 114 [74%], and 116 [75%] in observation, gemcitabine, and erlotinib arm, respectively). Median number of pemetrexed cycles was 3 (1–40) in all arms. Median PFS did not differ between gemcitabine and observation arms (4.2 versus 3.9 months, hazard ratio [HR] [95% confidence interval [CI] 0.81 [0.62–1.06]) or between erlotinib and observation arms (4.2 versus 3.9 months, HR 0.83 [0.64–1.09]). OS data showed a non-significant improvement with gemcitabine arm versus observation arm (8.3 versus 7.5 months, HR 0.81 [0.61−1.07]) or erlotinib arm versus observation arm (9.1 versus 7.5 months, HR 0.80 [0.61−1.05]). Results were similar for non-squamous patients. Grade 3 to 4 treatment-related adverse events (AEs) were comparable in all arms.

**Conclusions:** Maintenance therapy with gemcitabine continuation or erlotinib does not seem to impair efficacy of second-line pemetrexed comparatively to administration after a treatment-free interval.

**Key Words:** Maintenance, Pemetrexed, Non–Small-Cell Lung Cancer, Second line.

(*J Thorac Oncol.* 2013;8: 906-914)

*Hospices Civils de Lyon; †Department of Respiratory Diseases, Hôpital d'Instruction des Armées Desgenettes; ‡Biostatistics & Clinical Research Unit, Centre Léon Bérard; §Medical Oncology Department, Centre Léon Bérard, Lyon, France; ‖Department of Respiratory Diseases, Hôpital Saint-Antoine; ¶Department of Respiratory Diseases, Tenon University Hospital, Paris, France; **Service d'Oncologie Multidisciplinaire & Innovations Thérapeutiques, Aix-Marseille University – Assistance Publique Hôpitaux de Marseille, Marseille, France; ††Medical Oncology Department, Centre François Baclesse, Caen, France; ‡‡Department of Respiratory Disease and Thoracic Oncology, University Hospital, Besançon, France; §§Department of Respiratory Diseases, Centre Hospitalier de Creil, Creil, France; ‖‖Department of Respiratory Disease and Thoracic Oncology, Centre Hospitalier Universitaire de Rennes, Rennes, France; ¶¶Department of Respiratory Disease and Thoracic Oncology, University Hospitals, Limoges, France; ***Department of Respiratory Diseases, Centre Hospitalier Intercommunal de Créteil, Créteil,France; †††Department of Respiratory Disease, Centre Hospitalier de Draguignan, Draguignan, France; ‡‡‡Department of Medical Oncology, Institut de Cancérologie de la Loire, Saint Etienne, France; §§§Department of Respiratory Diseases, Hôpital d'Instruction des Armées Percy, Clamart, France; ‖‖‖Department of Respiratory Diseases, Centre Hospitalier de Villefranche, Villefranche, France; ¶¶¶Department of Medical Oncology, Centre Antoine Lacassagne, Nice, France; and ****Pulmonology and thoracic oncology Department, Caen University Hospital, France.

Address correspondence to: Maurice Pérol, MD, Département de Cancérologie Médicale, Centre Léon Bérard, 28 rue Laënnec, 69373 LYON Cedex 08, France. E-mail: maurice.perol@lyon.unicancer.fr



ISSN: 1556-0864/13/0807-0906

Non–small-cell lung cancer (NSCLC) is the leading cause of cancer-related deaths in the world.[1] Approximately 40% of new lung cancers are diagnosed at the stage of metastatic disease. First line treatment of advanced NSCLC is based on platinum-doublet chemotherapy for most of patients, with a median overall survival (OS) of 10 to 13 months.[2–6] A key challenge is to improve the outcome of patients who have received adequate first-line therapy and have achieved at least stable disease. For these patients, maintenance therapy constitutes a strategic advance, defined as the continuation of an adapted treatment after the maximal response to "induction" chemotherapy has been obtained, to delay disease progression with the ultimate goal to prolong OS.[7,8] There

are several ways to administer maintenance therapy: the first one is to continue with a targeted therapy initially used in combination with platinum-based induction chemotherapy, for example bevacizumab. The second one is to continue with the drug that has been combined to cis- or carboplatin during induction chemotherapy, called "continuation" maintenance. Another way is to immediately introduce a new treatment at the end of induction treatment, particularly one drug validated for second-line therapy such as docetaxel, pemetrexed or erlotinib. This strategy is usually called "switch" maintenance. Two drugs have been approved for maintenance therapy in advanced NSCLC: pemetrexed as either "switch" or "continuation" maintenance for patients with non-squamous carcinoma histology[9–12] and erlotinib as "switch" maintenance in unselected patients, except for European countries in which approval has been restricted to patients with stable disease after induction chemotherapy.[11,13–15]

However, there are still unanswered questions about maintenance strategy, especially concerning the selection of patients who will benefit most from either "continuation " maintenance or " switch " maintenance therapy. Another issue is the impact of maintenance therapy, in particular for "continuation" maintenance, on the effectiveness of subsequent lines of treatment. Continuous exposure of tumor cells to maintenance therapy in advanced NSCLC might lead to select tumor cell clones resistant to subsequent treatments.[7,16–18]

The Intergroupe Francophone de Cancérologie Thoracique–Groupe Francais de Pneumo-Cancérologie (IFCT–GFPC) 0502 study showed a progression-free survival (PFS) benefit with gemcitabine continuation maintenance or erlotinib switch maintenance compared with observation after cisplatin-gemcitabine induction chemotherapy.[11] This trial included a predefined second-line therapy with pemetrexed, allowing post-hoc assessment of its efficacy and safety, according to previous maintenance treatment or treatment-free interval. Since the study was designed before the interaction of pemetrexed with histology was known, we enrolled patients irrespective of histological subtype. The primary end point was PFS measured from the beginning of second-line pemetrexed therapy. Secondary end points included response rate, OS and tolerance to pemetrexed second-line therapy.

## PATIENTS AND METHODS

Eligibility criteria included patients of IFCT–GFPC 0502 study in whom disease progression (Response Evaluation Criteria In Solid Tumors version 1.0 [RECIST 1.0])[19] had occurred under maintenance by gemcitabine or erlotinib, or in the observation arm. Enrolled patients were greater than 18 years of age, with histologically or cytologically proven stage IIIB with pleural effusion or stage IV NSCLC and an Eastern Cooperative Oncology Group performance status of 0 or 1. Other inclusion criteria included: adequate renal (creatinine clearance >60 ml/mn), hepatic (bilirubin <20 micromol/l, alanine transaminase or aspartate transaminase less than 2.5 × upper normal limit or less than 5 × upper normal limit in case of liver metastasis) and hematologic (absolute neutrophils count greater than $1.5 \times 10^9$/l and platelet count greater than $100 \times 10^9$/l) functions, measurable disease per RECIST 1.0.[19]

Exclusion criteria included small cell or neuroendocrine lung cancer, prior chemotherapy for NSCLC, symptomatic brain metastases; prior treatment with EGFR-tyrosine kinase inhibitor; any concurrent radiotherapy, unless palliative localized bone radiotherapy; concomitant treatment with rifampicin, carbamazepine, phenobarbital, phenytoin, other serious comorbid conditions, such as congestive heart failure, unstable angina, significant arrhythmia or history of myocardial infarction in the 12 months preceding the trial entry, interstitial lung disease, uncontrolled infection status, use of non-steroid anti-inflammatory agents and second-line treatment other than pemetrexed.

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and approved by the institutional ethics committee from the Hospices civils de Lyon, sponsor of the trial. All patients signed written informed consent before treatment.

### Study Design and Treatment

During the first part of the IFCT–GFPC 0502 study, induction chemotherapy consisted of gemcitabine 1,250 mg/m$^2$ (administered intravenously on days 1 and 8) plus cisplatin 80 mg/m$^2$ (administered intravenously on day 1, every 21 days) for a maximum of four cycles. Patients who demonstrated complete response, partial response, or stable disease were randomized to either observation, continuation maintenance with gemcitabine 1,250 mg/m$^2$ (administered intravenously on days 1 and 8, every 21 days) or maintenance with oral erlotinib (150 mg/day). Randomization was stratified according to center, gender, histology (adenocarcinoma/other), smoking status (current/former versus never), and response to cisplatin–gemcitabine induction chemotherapy (objective response/stable disease) using a minimization adaptive randomization method. At the occurrence of disease progression, all patients were being proposed second-line chemotherapy with pemetrexed. Patients began taking oral folic acid supplement (350–1,000 μg/day) at least 7 days before the first dose of pemetrexed. Vitamin $B_{12}$ (1,000 μg) was given intramuscularly once within 7 days before the first dose and then every 9 weeks thereafter. Premedication with corticosteroids (equivalent to 4 mg of dexamethasone twice daily) was administered for three days starting the day before pemetrexed perfusion. Pemetrexed was administered by a 10 minutes intravenous perfusion the first day of each 21-day cycle. Subsequent treatments after second-line pemetrexed were selected at the discretion of each investigator.

### Dose Modifications

During pemetrexed second-line therapy, patients experiencing a nadir platelets count lower than $50.10^9$/l or a neutropenia less than $0.5 \times 10^9$/l required a 25% dose reduction of pemetrexed. If the neutrophil count was below $1.5 \times 10^9$/l or the platelet count was below $100.10^9$/l on day 1 of any cycle, chemotherapy was postponed until recovery. Dose modifications for other grade 3 and 4 toxicities also consisted in a 25% dose reduction. Any reduction at a lower level dose was definitive (no subsequent re-increase in dose). The recurrence of grade 3 to 4 toxicity after two dose reductions led to definitive pemetrexed discontinuation.

 

**TABLE 1.** Patients Characteristics

| Characteristic | Arm A (Observation) (*n* = 130) Number of Patients (%) | | Arm B (Gemcitabine) (*n* = 114) Number of Patients (%) | | Arm C (Erlotinib) (*n* = 116) Number of Patients (%) | | *p* Value |
|---|---|---|---|---|---|---|---|
| Age, yrs | | | | | | | |
| Median | 58.95 | | 57.50 | | 56.25 | | 0.229 |
| Range | 36.50–72.10 | | 29.20–70 | | 35.50–71.20 | | |
| Sex | | | | | | | |
| Male | 94 | 72.3 | 80 | 70.2 | 85 | 73.3 | 0.863 |
| Female | 36 | 27.7 | 34 | 29.8 | 31 | 26.7 | |
| Smoking status | | | | | | | |
| Never-smoker | 8 | 6.2 | 14 | 12.3 | 15 | 12.9 | 0.143 |
| Former/current smoker | 121 | 93.8 | 100 | 87.7 | 101 | 87.1 | |
| Stage of disease | | | | | | | |
| IIIB | 12 | 9.4 | 10 | 9.0 | 9 | 8.2 | 0.972 |
| IV | 116 | 90.6 | 101 | 91.0 | 101 | 91.8 | |
| ECOG performance status | | | | | | | |
| 0 | 57 | 44.2 | 47 | 41.6 | 41 | 36.0 | 0.480 |
| 1 | 70 | 54.3 | 62 | 54.9 | 68 | 59.6 | |
| 2 | 1 | 0.8 | 4 | 3.5 | 4 | 3.5 | |
| Histologic types | | | | | | | |
| Squamous cell carcinoma | 28 | 21.5 | 23 | 20.2 | 18 | 15.5 | 0.546 |
| Adenocarcinoma | 82 | 63.1 | 77 | 67.5 | 76 | 65.5 | |
| Other: NSCLC, NOS | 20 | 15.3 | 14 | 12.2 | 22 | 19.0 | |
| Response after CT induction | | | | | | | |
| Stable disease | 56 | 43.1 | 51 | 44.7 | 50 | 43.1 | 0.963 |
| CR/PR | 74 | 56.9 | 63 | 55.3 | 66 | 56.9 | |

CR, complete response; CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; NOS, not otherwise specified; NSCLC, non–small-cell lung cancer; PR, partial response.

## Assessments

Evaluations of the antitumor effect of second-line chemotherapy were conducted in accordance with the habits of each center. Disease status was assessed according to RECIST 1.0 by each investigator, without independent or panel review.[19]

Toxicity grading was performed according to the National Cancer Institute Common Toxicity Criteria for adverse events (AEs) (NCI-CTCAE), version 3.0.[20]

## Statistical Methods

This is a post-hoc analysis of the effectiveness of pemetrexed in second-line after either treatment-free interval or maintenance therapy with gemcitabine or erlotinib in IFCT–GFPC 0502 phase III study. The primary end point is PFS, defined as the time from the beginning of pemetrexed to the time of documented disease progression or death, or censored at last follow-up for living patients. Secondary end points included tumor response assessed by investigators (RECIST 1.0), OS, calculated from the date of beginning of pemetrexed to the date of death from any cause or to last follow-up for living patients (censured observation) and safety. Analysis restricted to the subgroup of patients with non-squamous cell carcinomas was also performed because of the lack of recognized effectiveness to pemetrexed in squamous cell carcinoma.

Differences in survival estimates between arms were assessed using a two-sided log-rank test. PFS and OS were analyzed using Cox proportional hazards regression models and presented as Kaplan–Meier estimates with hazard ratio (HR) and 95% confidence intervals (CI). Similarly to the first part of the study, only separate comparisons of each maintenance arm with the observation control arm were performed All patients receiving pemetrexed were included in the efficacy analysis for primary objective (PFS) and were considered assessable for toxicity from the time of their treatment by pemetrexed.

# RESULTS

## Patient Characteristics

From July 2006 through June 2009, 464 patients were enrolled at 51 institutions in France and randomized after four cycles of cisplatin-gemcitabine induction chemotherapy to observation (*n* = 155), gemcitabine (*n* = 154), or erlotinib (*n* = 155) maintenance treatment (Table 1). Figure 1 provides a flow diagram for patient throughout the post-hoc analysis. Only a few patients received a second line different from that imposed by the protocol. Seventy-eight percent (360 out of 464) of patients included in IFCT–GFPC 0502 study received

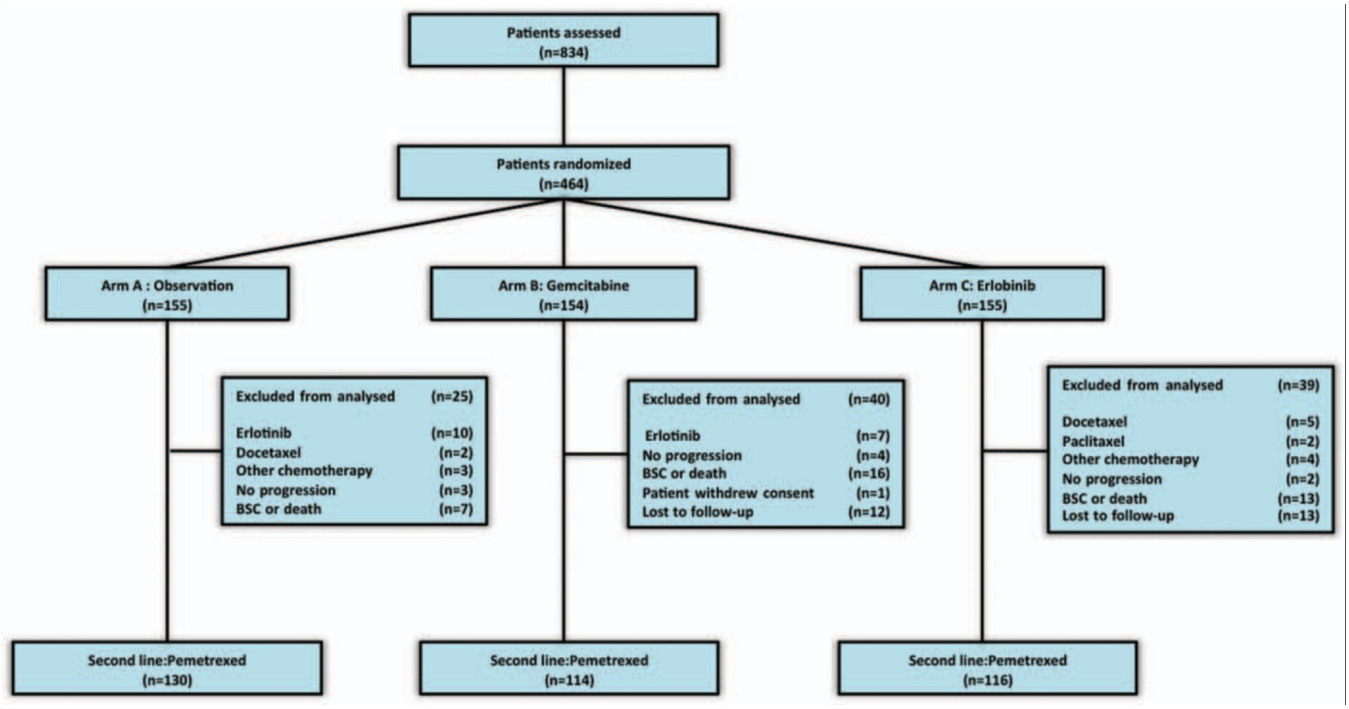


**FIGURE 1.** Patient disposition diagram. BSC, best supportive care; CT, chemotherapy.

pemetrexed as second-line treatment, with 83%, 74%, and 75% in observation arm, gemcitabine arm, and erlotinib arm, respectively ($\chi^2$ test, $p = 0.0070$). The baseline characteristics of this second-line pemetrexed population (Table 1) were representative of the entire population of the study (Table 2). The median age for the population treated with pemetrexed was 57.7 years (ranges 29–72 years). The study groups were well balanced in terms of prognostic factors and other baseline characteristics (Table 1). Most patients were male and three-fifths had an Eastern Cooperative Oncology Group performance status of 1. Most patients had a history of smoking and nearly 66% of patients had non-squamous cell histology; the proportion of patients with squamous-cell carcinoma was similar in the three arms.

## Response to pemetrexed and PFS

The median number of delivered pemetrexed cycles was three, with no difference between the three arms (Kruskal–Wallis test, $p = 0.659$) (Table 3). Dose reductions of pemetrexed were mainly caused by neutropenia and thrombocytopenia, without difference between the three arms. Two hundred twenty-nine patients (63.4% of patients receiving pemetrexed) were evaluable for response. There was no significant difference in terms of objective responses and disease control rate across the three arms (Fisher's exact test $p = 0.446$) (Table 3). For non-squamous carcinoma, response assessment was available for 199 patients (65% of non-squamous patients treated with pemetrexed), with a non significant trend toward a better response rate for observation and erlotinib arms, but without difference for the disease control rate between the three arms (Fisher's exact test $p = 0.207$) (Table 3).

PFS from the start of second-line pemetrexed treatment for patients randomly assigned to gemcitabine did not differ significantly from that of patients in the observation arm (median PFS 4.2 versus 3.9 months; HR [95% CI] 0.81 [0.62–1.06], $p = 0.124$) (Fig. 2). Similarly, the PFS for erlotinib arm was not different from that of observation arm (median PFS 4.2 versus 3.9 months; HR 0.83 [0.64–1.09], $p = 0.174$) (Fig. 2*A*). When analysis was restricted to non-squamous patients, PFS remained similar for gemcitabine and observation arms (4.1 versus 4.2 months) and for erlotinib and observation arms (4.2 versus 4.2 months**)** **(**Fig. 2*B*).

## Subsequent Treatments

Data on further treatments (third-line chemotherapy) was available for 293 of 360 patients, with 108, 93, and 92 in control, gemcitabine, and erlotinib arms, respectively (Table 4). Erlotinib was the most frequently used third-line drug in the observation and gemcitabine arms. Docetaxel was the most prescribed systemic chemotherapy when progression occurred after pemetrexed (10.2%, 21.2%, and 48.9% for control, gemcitabine, and erlotinib arms, respectively). Approximately 20% of patients in each arm were not treated with a third-line drug and only received best supportive care.

## OS From the Beginning of Second-Line Pemetrexed

OS did not statistically differ between gemcitabine arm and control arm (median OS 8.3 versus 7.5 months; HR = 0.81 [0.61–1.07], $p = 0.12$), and between erlotinib arm and control arm (median OS 9.1 versus 7.5 months; HR = 0.80 [0.61–1.05], $p = 0.108$) (Fig. 3). Analysis of OS restricted to

 

**TABLE 2.** Comparison between Baseline Characteristics of Patients Treated with Pemetrexed as Second-Line Therapy and Those of the Entire Population of the Study

| | Arm A (Oservation) | | | | Arm B (Gemcitabine) | | | | Arm C (Erlotinib) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Entire Population of the 0502 Study | | Second-line Pemetrexed Population | | Entire Population of the 0502 Study | | Second-line Pemetrexed Population | | Entire Population of the 0502 Study | | Second-line Pemetrexed Population | |
| | (*n* = 155) | | (*n* = 130) | | (*n* = 154) | | (*n* = 114) | | (*n* = 155) | | (*n* = 116) | |
| **Characteristic** | **Number of Patients** | **%** | **Number of Patients** | **%** | **Number of Patients** | **%** | **Number of Patients** | **%** | **Number of Patients** | **%** | **Number of Patients** | **%** |
| Age, yrs | | | | | | | | | | | | |
| Median | 59.8 | | 58.95 | | 57.9 | | 57.50 | | 56.4 | | 56.25 | |
| Range | 37.0–72.0 | | 36.50–72.10 | | 29.0–71.0 | | 29.20–70 | | 36.0–71.0 | | 35.50–71.20 | |
| Sex | | | | | | | | | | | | |
| Male | 113 | 72.9 | 94 | 72.3 | 113 | 73.4 | 80 | 70.2 | 113 | 72.9 | 85 | 73.3 |
| Female | 42 | 27.1 | 36 | 27.7 | 41 | 26.6 | 34 | 29.8 | 42 | 27.1 | 31 | 26.7 |
| Smoking status | | | | | | | | | | | | |
| Never-smoker | 12 | 7.7 | 8 | 6.2 | 17 | 11.0 | 14 | 12.3 | 17 | 11.0 | 15 | 12.9 |
| Former/current smoker | 143 | 92.3 | 121 | 93.8 | 137 | 89.0 | 100 | 87.7 | 138 | 89.0 | 101 | 87.1 |
| Stage of disease | | | | | | | | | | | | |
| IIIB | 14 | 9.2 | 12 | 9.4 | 14 | 9.3 | 10 | 8.7 | 11 | 7.4 | 9 | 7.8 |
| IV | 139 | 90.8 | 116 | 89.2 | 137 | 90.7 | 101 | 88.5 | 137 | 92.6 | 101 | 87.0 |
| Unknown | 2 | 1.3 | 2 | 1.4 | 3 | 1.9 | 3 | 2.6 | 7 | 4.5 | 6 | 5.2 |
| ECOG performance status | | | | | | | | | | | | |
| 0 | 68 | 44.2 | 57 | 44.2 | 61 | 40.1 | 47 | 41.6 | 58 | 37.9 | 41 | 36.0 |
| 1 | 81 | 52.6 | 70 | 54.3 | 82 | 53.9 | 62 | 54.9 | 85 | 55.6 | 68 | 59.6 |
| 2 | 4 | 2.6 | 1 | 0.8 | 7 | 4.6 | 4 | 3.5 | 8 | 5.2 | 4 | 3.5 |
| Histologic types | | | | | | | | | | | | |
| Squamous cell carcinoma | 30 | 19.3 | 28 | 21.5 | 34 | 22.1 | 23 | 20.2 | 27 | 17.4 | 18 | 15.5 |
| Adenocarcinoma | 103 | 66.5 | 82 | 63.1 | 101 | 65.6 | 77 | 67.5 | 97 | 62.6 | 76 | 65.5 |
| Other: NSCLC, NOS | 22 | 14.2 | 20 | 15.3 | 19 | 12.3 | 14 | 12.2 | 31 | 20.0 | 22 | 19.0 |
| Response after CT induction | | | | | | | | | | | | |
| Stable disease | 73 | 47.1 | 56 | 43.1 | 73 | 47.1 | 51 | 44.7 | 73 | 52.9 | 50 | 43.1 |
| CR/PR | 82 | 52.9 | 74 | 56.9 | 81 | 52.6 | 63 | 55.3 | 82 | 47.1 | 66 | 56.9 |

CR, complete response; CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; NOS, not otherwise specified; NSCLC, non–small-cell lung cancer; PR, partial response.

patients with non-squamous carcinoma showed similar results (Fig. 3*A,B*)

## Safety of Second-Line Pemetrexed

Two hundred sixty-nine patients (74.7%) reported an AE of any grade, with a similar distribution across the three arms (76.2%, 74.6%, and 73.3% in observation, gemcitabine, and erlotinib arms, respectively, $\chi^2$ test, $p = 0.873$) (Table 5). Grade 3 to 4 AEs were reported in 108 (30%) patients who received pemetrexed. Overall rates of grade 3 and 4 hematologic and non-hematologic AEs in each arm are shown in Table 5. Neutropenia was the most common AE in the three arms (13.1%, 19.3%, and 9.5% in observation, gemcitabine, and erlotinib arms, respectively) followed by thrombocytopenia and anemia. Non-hematologic AEs were grade 3 to 4 fatigue (4.7%), pain (3.6%), and constitutional symptoms (3.1%). There was no grade 5 AE. Overall, the level of toxicity did not differ between the observation control arm and both maintenance arms.

## DISCUSSION

IFCT–GFPC 0502 study showed that continuation maintenance with gemcitabine provides a large PFS benefit (HR = 0.56) but with a limited impact on OS. Similarly, meta-analysis of continuation maintenance studies demonstrated a consistent PFS benefit without significant impact on OS.[21,22] However, these meta-analyses did not include the Paramount study which is the only study showing that PFS benefit from continuation maintenance with pemetrexed did result in an OS benefit. One hypothesis to explain these results is that there could be a negative interaction between continuous exposure of tumor cells to chemotherapy during maintenance treatment, leading to cross-resistance and ineffectiveness of subsequent treatments, especially second-line chemotherapy; moreover,

**TABLE 3.** Duration and Effectiveness of Pemetrexed Second-Line Therapy

| | Arm A (*N* = 130) (%) | | Arm B (*N* = 114) (%) | | Arm C (*N* = 116) (%) | |
|---|---|---|---|---|---|---|
| | **All Patients (*N* = 130)** | **Non-Squamous Patients (*N* = 102)** | **All Patients (*N* = 114)** | **Non-Squamous Patients (*N* = 91)** | **All Patients (*N* = 116)** | **Non-Squamous Patients (*N* = 98)** |
| Median number Of cycles (range) | 3 (1–18) | | 3 (1–40) | | 3 (1–15) | |
| Response to second-line pemetrexed | | | | | | |
| Number evaluable patients (%) | 89 (68.5) | 70 (68.6) | 67 (58.7) | 57 (62.6) | 73 (62.9) | 62 (63.3) |
| CR (%) [95% CI] | 0 (0.0) [0.0–4.1] | 0 (0.0) [0.0–5.1] | 0 (0.0) [0.0–5.4] | 0 (0.0) [0.0–6.3] | 1 (1.4) [0.0–7.4] | 1 (1.6) [0.0–8.7] |
| PR (%) [95% CI] | 13 (14.6) [8.0–23.7] | 13 (18.6) [10.3–29.7] | 4 (6.0) [1.7–14.6] | 4 (7.0) [2.0–17.0] | 9 (12.3) [5.8–22.1] | 9 (14.5) [6.9–25.8] |
| SD (%) [95% CI] | 39 (43.8) [33.3–54.8] | 33 (47.1) [35.1–59.5] | 33 (49.3) [36.9–61.8] | 30 (50.9) [28.5–51.9] | 29 (39.7) [28.5–51.9] | 23 (37.1) [25.2–50.3] |
| PD (%) [95% CI] | 37 (41.6) [31.2–52.5] | 24 (34.3) [23.4–46.6] | 30 (44.8) [32.6–57.4] | 24 (42.1) [34.8–58.6] | 34 (46.6) [34.8–58.6] | 29 (46.8) [34.0–59.9] |

CI, confidence intervals; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.
Median number of cycles: Kruskal–Wallis $p = 0.659$. Response for all patients: Fisher's exact $p = 0.446$; response for non-squamous patients: Fisher's exact $p = 0.207$.

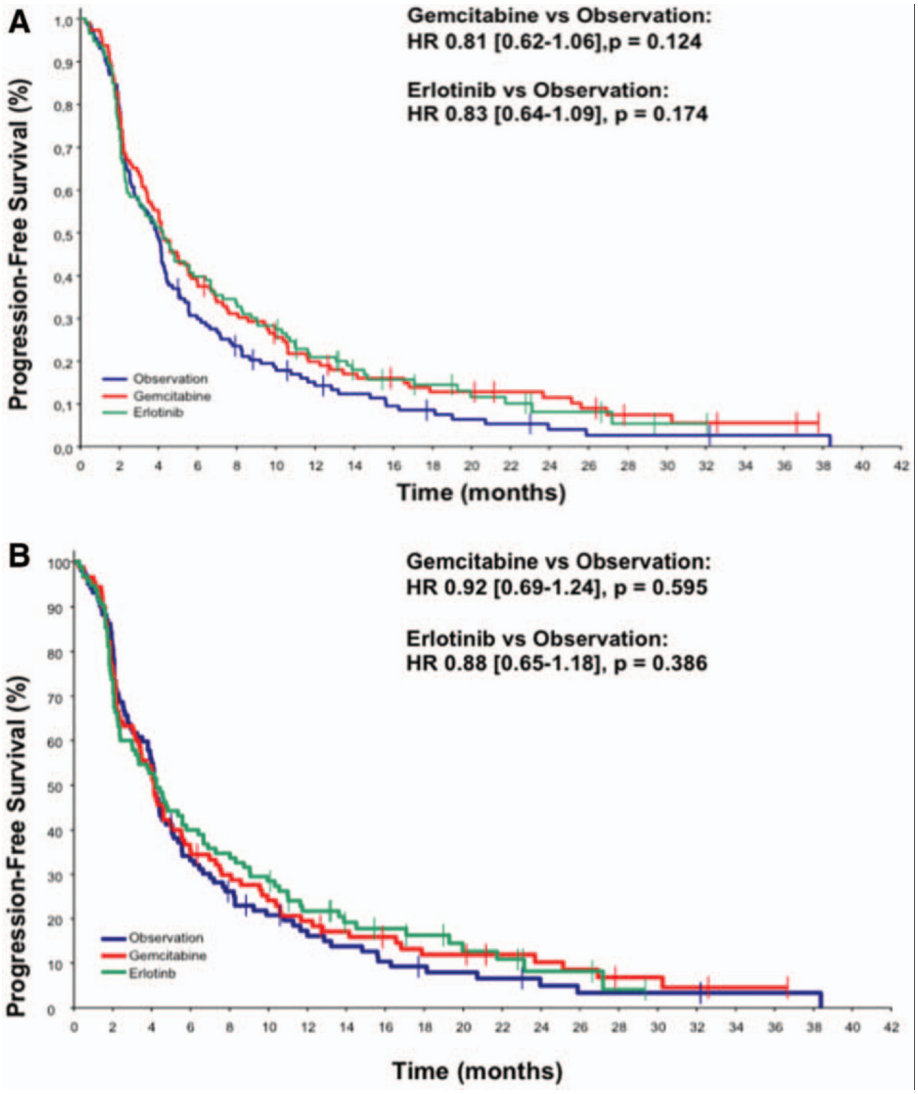


**FIGURE 2.** *A,* Progression-free survival from the beginning of pemetrexed second-line therapy for patients treated with gemcitabine maintenance versus observation and for patients treated with erlotinib maintenance versus observation. *B,* Progression-free survival from the beginning of pemetrexed second-line therapy for patients with non-squamous-cell carcinoma.

**TABLE 4.** Summary of Further Treatment Received by Patients

| | Arm A (Observation) ($n$ = 108) | | Arm B (Gemcitabine) ($n$ = 93) | | Arm C (Erlotinib) ($n$ = 92) | |
|---|---|---|---|---|---|---|
| | Number of Patients | % | Number of Patients | % | Number of Patients | % |
| All classes | 88 | 81.5 | 74 | 79.6 | 67 | 72.8 |
| BSC | 20 | 18.5 | 19 | 20.4 | 25 | 27.2 |
| Docetaxel | 11 | 10.2 | 20 | 21.5 | 45 | 48.9 |
| Paclitaxel | 3 | 2.8 | 4 | 4.3 | 7 | 7.6 |
| Erlotinib | 68 | 63.0 | 49 | 52.7 | 3 | 3.3 |
| Gemcitabine | 4 | 3.7 | 0 | 0.0 | 7 | 7.6 |
| Vinorelbine | 2 | 1.9 | 1 | 1.0 | 2 | 2.2 |
| Others clinical trials | 0 | 0.0 | 0 | 0.0 | 3 | 3.3 |

BSC, best supportive care.

maintenance with cytotoxic chemotherapy could increase the toxicity of subsequent second-line treatment precluding complete administration of treatment. The IFCT–GFPC 0502 study including a pre-defined and similar second-line therapy in observation arm and both maintenance arms provided a unique opportunity to study the effectiveness and tolerance of second-line chemotherapy according to either a treatment-free interval after induction chemotherapy or a maintenance treatment and to the kind of maintenance treatment, i.e., continuation maintenance with chemotherapy or maintenance with erlotinib. There was no strong preclinical or clinical data to support the hypothesis of cross-resistance between gemcitabine and pemetrexed. Phase II data exploring the combination of gemcitabine and pemetrexed suggest that the schedule with pemetrexed followed by gemcitabine was more effective and less toxic than the opposite schedule.[23–26]

There was a very high proportion of patients receiving a second-line treatment (226 of 293 patients, 77%), both in the control arm and in maintenance arms. This is much higher than in other maintenance trials[10–15,27] and in clinical practice,[28,29] with only a range of 51 to 63% of patients able to receive approved second-line treatment after maintenance therapy and of 58 to 67% after a treatment-free interval.[13,14,30]

The reasons were twofold: the good tolerance profile of pemetrexed as second-line agent; the compliance of investigators to the protocol with a large majority of patients receiving predefined pemetrexed as second-line treatment. The proportion of patients undergoing a second line was 83% for the observation arm and approximately 74.5% for both maintenance arms. If we include other drugs used in second-line, this proportion reach 94.5% in observation arm and 83% in both maintenance arms. Even if maintenance therapy after induction chemotherapy can reduce access to second-line treatment and therefore the translation of the PFS benefit into an OS gain, it does without any negative impact on OS as shown in the OS analysis of our study[11] and in Paramount trial in which maintenance with pemetrexed provides a significant survival benefit despite of a lower proportion of patients receiving a second-line treatment.[15] Maintenance therapy in advanced NSCLC is a strategy that capitalizes on the benefits of the first line, precisely because the effectiveness of the second line remains very modest in advanced NSCLC.

Median PFS from the beginning of pemetrexed second-line therapy was 3.9 months in the observation arm and 4.2 months for both erlotinib and gemcitabine maintenance arms, without any statistical difference for each maintenance arm compared with control observation arm. The PFS was higher than that found in other second-line studies in NSCLC.[31–34] For example, PFS obtained with pemetrexed was 2.9 months in the pivotal study comparing pemetrexed with docetaxel[35] and PFS of second-line treatment was 11.7 weeks in the meta-analysis of Di Maio et al.[31–34] Patients randomized in the maintenance phase of this study were selected patients, with either stable or responsive disease after induction chemotherapy. These patients represent a subgroup of patients with better prognosis, more likely to be controlled in the second line compared with trials that include all patients, notably patients with disease progression during the first line treatment.[36]

Efficacy of second-line pemetrexed appears comparable with or without previous maintenance therapy, and whatever kind of maintenance, gemcitabine continuation maintenance or switch maintenance with erlotinib. The median number of delivered cycles of treatment was the same in all three arms, disease control rate were similar and PFS from the beginning of second-line pemetrexed did not differ between the three arms. Regarding the response rate, a lower rate of objective response was observed in gemcitabine arm than in both other but without impact on PFS. The analysis did not change when restricted to non-squamous patients. These results are valid for both the gemcitabine-pemetrexed and erlotinib-pemetrexed sequences but not necessarily applicable to sequences with other drugs. Nevertheless, the positive Paramount results for OS suggest that indeed continuation maintenance with pemetrexed does not impair effectiveness of subsequent treatments.

Nearly three-quarters of patients reported AEs, including 30% of grade 3 to 4 toxicity (NCI-CTCAE). Patients previously exposed to cytotoxic drugs were more likely to have hematological AEs with second-line chemotherapy than patients experiencing a treatment-free interval after induction chemotherapy or treated with a non-cytotoxic maintenance drug like erlotinib. Neutropenia was the most frequently reported AE with a non-statistically significant increased rate in the gemcitabine arm compared with observation or erlotinib arms (19% versus 9.5% versus 13.5%, respectively). This rate of neutropenia was higher than that found in studies of second-line pemetrexed, 13.5% (for the three arms) versus 4% to 5%.[32,33] Other AEs were comparable to data from the literature. However, occurrence of neutropenia in the gemcitabine arm did not result in a higher rate of febrile neutropenia or infection, with 2.8% in all three arms and no treatment-related death. Moreover, the fact that the median number of delivered cycles was the same with or without previous maintenance also suggests that there is no cumulative toxicity due to maintenance treatment preventing administration of second-line chemotherapy.

Nevertheless, the limitations of this study imply that its results must be taken with caution. It is an exploratory

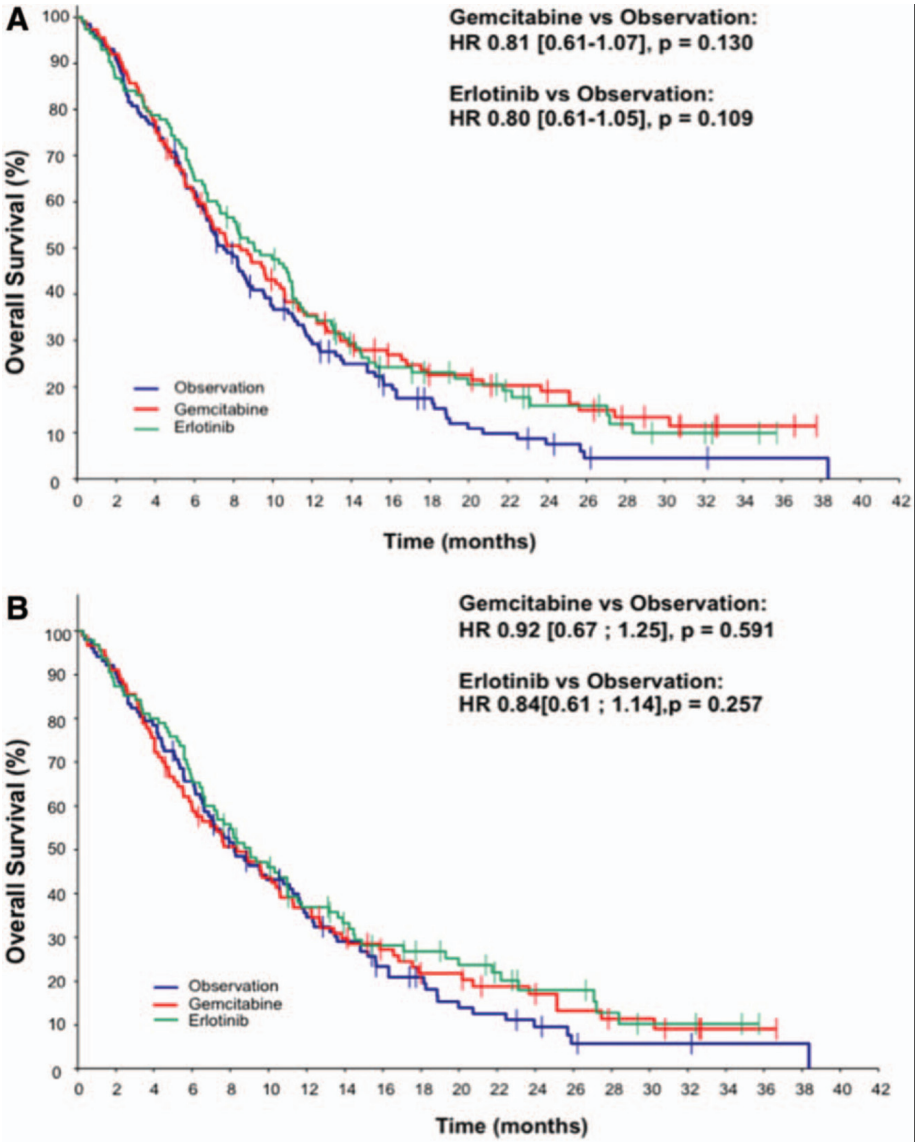


**FIGURE 3.** *A,* Overall survival from the beginning of pemetrexed second-line therapy for patients treated with gemcitabine maintenance versus observation and for patients treated with erlotinib maintenance versus observation. *B,* Overall survival from the beginning of pemetrexed second-line therapy for patients with non-squamous-cell carcinoma.

**TABLE 5.** Treated Patients with Common Toxicity Criteria Grade 3 or 4 Drug-Related Toxicities

| | Arm A (Observation) ($n$ = 130) | | Arm B (Gemcitabine) ($n$ = 114) | | Arm C (Erlotinib) ($n$ = 116) | | |
|---|---|---|---|---|---|---|---|
| | Number of Patients | % | Number of Patients | % | Number of Patients | % | $p$ Value |
| Hemotologic | | | | | | | |
| Anemia | 7 | 5.4 | 8 | 7.0 | 5 | 4.3 | 0.623 |
| Neutropenia | 17 | 13.1 | 22 | 19.3 | 11 | 9.5 | 0.099 |
| Thrombocytopenia | 8 | 6.2 | 10 | 8.8 | 4 | 3.4 | 0.236 |
| Non-hematologic | | | | | | | |
| Fatigue | 14 | 10.8 | 3 | 2.6 | 11 | 9.5 | 0.032 |
| Infection | 3 | 2.3 | 3 | 2.6 | 4 | 3.4 | 0.922 |
| Pain | 4 | 3.1 | 5 | 4.4 | 4 | 3.4 | 0.882 |

Only toxicities reported in at least 2% of patients on at least one arm are listed.

post-hoc analysis, response evaluation was not available for all patients and PFS was assessed by investigators, without independent review. However, the lack of difference for PFS between the 3 arms strongly suggests that efficacy of second-line pemetrexed was not decreased by previous maintenance treatment.

In conclusion, maintenance therapy with gemcitabine continuation or erlotinib does not seem to impair efficacy, nor to increase the toxicity of second-line pemetrexed comparatively to administration after a treatment-free interval.

## REFERENCES

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2008. *CA Cancer J Clin* 2008;58:71–96.
2. 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;355:2542–2550.
3. Pirker R, Pereira JR, Szczesna A, et al.; FLEX Study Team. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung

 

cancer (FLEX): an open-label randomised phase III trial. *Lancet* 2009;373:1525–1531.
4. Reck M, von Pawel J, Zatloukal P, et al.; BO17704 Study Group. Overall survival with cisplatin-gemcitabine and bevacizumab or placebo as first-line therapy for nonsquamous non-small-cell lung cancer: results from a randomised phase III trial (AVAiL). *Ann Oncol* 2010;21:1804–1809.
5. 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;26:3543–3551.
6. Ramalingam S, Belani C. Systemic chemotherapy for advanced non-small cell lung cancer: recent advances and future directions. *Oncologist* 2008;13 Suppl 1:5–13.
7. Stinchcombe TE, Socinski MA. Maintenance therapy in advanced non-small cell lung cancer: current status and future implications. *J Thorac Oncol* 2011;6:174–182.
8. Azzoli CG, Baker S Jr, Temin S, et al.; American Society of Clinical Oncology. American Society of Clinical Oncology Clinical Practice Guideline update on chemotherapy for stage IV non-small-cell lung cancer. *J Clin Oncol* 2009;27:6251–6266.
9. Azzoli CG, Temin S, Aliff T, et al.; American Society of Clinical Oncology. 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;29:3825–3831.
10. Ciuleanu T, Brodowicz T, Zielinski C, et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. *Lancet* 2009;374:1432–1440.
11. Pérol M, Chouaid C, Pérol D, et al. Randomized, phase III study of gemcitabine or erlotinib maintenance therapy versus observation, with predefined second-line treatment, after cisplatin-gemcitabine induction chemotherapy in advanced non-small-cell lung cancer. *J Clin Oncol* 2012;30:3516–3524.
12. Paz-Ares L, de Marinis F, Dediu M, et al. Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): a double-blind, phase 3, randomised controlled trial. *Lancet Oncol* 2012;13:247–255.
13. Fidias PM, Dakhil SR, Lyss AP, et al. Phase III study of immediate compared with delayed docetaxel after front-line therapy with gemcitabine plus carboplatin in advanced non-small-cell lung cancer. *J Clin Oncol* 2009;27:591–598.
14. Cappuzzo F, Ciuleanu T, Stelmakh L, et al.; SATURN investigators. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. *Lancet Oncol* 2010;11:521–529.
15. Paz-Arez L, De Marinis F, Dediu M, Thomas M, Pujol JL, Bidoli P et Al. PARAMOUNT: Final overall survival results of the phase III study of maintenance pemetrexed plus best supportive care versus placebo plus BSC immediately following induction treatment with pemetrexed plus cisplatin for advanced non-squamous non-small cell lung cancer. *J Clin Oncol* (Meeting Abstracts) May2012 vol. 30 no. 15_suppl LBA7507.
16. Stinchcombe TE, Socinski MA. Treatment paradigms for advanced stage non-small cell lung cancer in the era of multiple lines of therapy. *J Thorac Oncol* 2009;4:243–250.
17. Sun JM, Park JO, Won YW, et al. Who are less likely to receive subsequent chemotherapy beyond first-line therapy for advanced non-small cell lung cancer? Implications for selection of patients for maintenance therapy. *J Thorac Oncol* 2010;5:540–545.
18. Fidias P, Novello S. Strategies for prolonged therapy in patients with advanced non-small-cell lung cancer. *J Clin Oncol* 2010;28:5116–5123.
19. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;92:205–216.
20. Arbuck SG, Ivy SP, Setser A, et al: The Revised Common Toxicity Criteria: Version 3.0. http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf. Accessed March 2013.
21. Behera M, Owonikoko TK, Chen Z, Kono SA, Khuri FR, Belani CP, Ramalingam SS. Single agent maintenance therapy for advanced stage non-small cell lung cancer: A meta-analysis. *Lung Cancer* doi:10.1016/j.lungcan.2012.03.019.
22. Zhang X, Zang J, Xu J, et al. Maintenance therapy with continuous or switch strategy in advanced non-small cell lung cancer: a systematic review and meta-analysis. *Chest* 2011;140:117–126.
23. West HL, Wakelee HA, Perry MC, Belt RJ, Chen R, Obasaju C. Gemcitabine and pemetrexed administered in rapid sequence as front-line chemotherapy for advanced non-small-cell lung cancer: a phase II clinical trial. *Ann Oncol* 2009;20:850–856.
24. Monnerat C, Le Chevalier T. Review of the pemetrexed and gemcitabine combination in patients with advanced-stage non-small cell lung cancer. *Ann Oncol*. 2006;17 Suppl 5:86–90.
25. Treat J, Bonomi P, McCleod M, et al. Administration of pemetrexed immediately following gemcitabine as front-line therapy in advanced non-small cell lung cancer: a phase II trial. *Lung Cancer* 2006;53:77–83.
26. Ma CX, Nair S, Thomas S, et al.; North Central Cancer Treatment Group; Mayo Clinic; Eli Lilly & Company. Randomized phase II trial of three schedules of pemetrexed and gemcitabine as front-line therapy for advanced non-small-cell lung cancer. *J Clin Oncol* 2005;23:5929–5937.
27. Brodowicz T, Krzakowski M, Zwitter M, et al.; Central European Cooperative Oncology Group CECOG. Cisplatin and gemcitabine first-line chemotherapy followed by maintenance gemcitabine or best supportive care in advanced non-small cell lung cancer: a phase III trial. *Lung Cancer* 2006;52:155–163.
28. Gerber DE, Rasco DW, Le P, Yan J, Dowell JE, Xie Y. Predictors and impact of second-line chemotherapy for advanced non-small cell lung cancer in the United States: real-world considerations for maintenance therapy. *J Thorac Oncol* 2011;6:365–371.
29. Sun JM, Park JO, Won YW, et al. Who are less likely to receive subsequent chemotherapy beyond first-line therapy for advanced non-small cell lung cancer? Implications for selection of patients for maintenance therapy. *J Thorac Oncol* 2010;5:540–545.
30. Coudert B, Ciuleanu T, Park K, et al.; SATURN Investigators. Survival benefit with erlotinib maintenance therapy in patients with advanced non-small-cell lung cancer (NSCLC) according to response to first-line chemotherapy. *Ann Oncol* 2012;23:388–394.
31. Di Maio M, Chiodini P, Georgoulias V, et al. Meta-analysis of single-agent chemotherapy compared with combination chemotherapy as second-line treatment of advanced non-small-cell lung cancer. *J Clin Oncol* 2009;27:1836–1843.
32. Hanna N, Shepherd FA, Fossella FV, 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;22:1589–1597.
33. Felip E, Gridelli C, Baas P, Rosell R, Stahel R; Panel Members Metastatic non-small-cell lung cancer: consensus on pathology and molecular tests, first-line, second-line, and third-line therapy 1st ESMO Consensus Conference in Lung Cancer; Lugano 2010. *Ann Oncol* 22: 1507–1519, 2011.
34. Ciuleanu T, Stelmakh L, Cicenas S, 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;13:300–308.
35. Hanna N, Shepherd FA, Fossella FV, 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;22:1589–1597.
36. Weiss GJ, Rosell R, Fossella F, et al. The impact of induction chemotherapy on the outcome of second-line therapy with pemetrexed or docetaxel in patients with advanced non-small-cell lung cancer. *Ann Oncol* 2007;18:453–460.

 