

## Rationale and Design of MILES-3 and MILES-4 Studies: Two Randomized Phase 3 Trials Comparing Single-Agent Chemotherapy Versus Cisplatin-Based Doublets in Elderly Patients With Advanced Non-Small-Cell Lung Cancer

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### Abstract

**Background:** Platinum-based chemotherapy is the cornerstone of treatment of advanced non-small-cell lung cancer (NSCLC) patients, but the efficacy of adding cisplatin to single-agent chemotherapy remains to be demonstrated in prospective phase III trials dedicated to elderly patients. Furthermore, the superiority of cisplatin/pemetrexed over cisplatin/gemcitabine in non-squamous NSCLC has not been confirmed prospectively. We present the rationale and design of two open-label, multicenter, randomized phase III trials for elderly patients with advanced NSCLC: Multi-center Italian Lung cancer in the Elderly Study (MILES)-3 and MILES-4. The aim is to evaluate the efficacy of adding cisplatin to single-agent chemotherapy (both trials) and the efficacy of pemetrexed versus gemcitabine in non-squamous tumors (MILES-4). **Patients and Methods:** Both trials are dedicated to first-line therapy of patients older than 70 years with advanced NSCLC, ECOG performance status 0-1. In the MILES-3 trial, patients are randomized in a 1:1 ratio to gemcitabine or cisplatin/gemcitabine. In the MILES-4 study patients with non-squamous histology are randomized, in a factorial design with 1:1:1:1 ratio, to four arms: gemcitabine (A), cisplatin/gemcitabine (B), pemetrexed (C), cisplatin/pemetrexed (D). Two comparisons are planned: A+C vs B+D to test the role of cisplatin; A+B vs C+D to test the role of pemetrexed. Primary endpoint of both trials is overall survival. Secondary and exploratory endpoints include progression-free survival, response rate, toxicity, and quality of life. **Conclusions:** MILES-3 and MILES-4 results will add important evidence about the role of cisplatin-based doublets and pemetrexed in the first-line therapy of elderly patients with advanced NSCLC.

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## Introduction

Lung cancer is the most common cancer and the leading cause of cancer-related deaths worldwide, with non-small cell lung cancer (NSCLC) accounting for about 85% of all new diagnosis.<sup>1</sup> According to an analysis by the Surveillance, Epidemiology, and End Results (SEER) database, of 373,489 lung cancer diagnoses, more than 50% were diagnosed in people aged  $\geq 70$  years, and about 15% of cases occurred in patients  $\geq 80$  years.<sup>2</sup> Thus, lung cancer represents a tumor frequently reported in the old age. Third-generation single-agent chemotherapy became the standard of care for elderly patients (age  $\geq 70$  years) affected by advanced NSCLC, following the results of 2 randomized phase 3 trials, ELVIS (Elderly Lung cancer Vinorelbine Italian Study) and MILES-1 (Multicenter Italian Lung cancer in the Elderly Study).<sup>3,4</sup> In the former trial, single-agent vinorelbine was associated with a prolongation of survival and a benefit in quality of life (QoL) compared to best supportive care.<sup>3</sup> In the latter trial, combination chemotherapy with gemcitabine plus vinorelbine did not show any significant benefit compared to single-agent treatment.<sup>4</sup>

Platinum-based chemotherapy is the cornerstone of treatment of advanced NSCLC patients,<sup>5,6</sup> but it is associated with significant toxicity, and the evaluation of the risk/benefit ratio might become particularly critical in elderly patients. Three prospective randomized phase 3 trials included platinum-based doublets in elderly patients. In these studies, the doses provided were similar to those used for adult patients; results regarding efficacy varied, but overall, a high incidence of adverse effects was reported.<sup>7-9</sup> A more reasonable approach requires developing platinum-based schemes within the population of elderly patients; thus, according to this strategy, our cooperative group performed the MILES-2P trial.<sup>10</sup> This study included 2 parallel phase 1 and 2 trials with the aims of determining the recommended dose of cisplatin in combination with gemcitabine or vinorelbine, and evaluating the feasibility of such 2-drug combinations. We found that 60 mg/m<sup>2</sup> is the maximum dose of cisplatin that can be safely combined with a standard dose of gemcitabine; however, the combination with vinorelbine was more toxic, and the maximum dose of cisplatin that could be safely combined with vinorelbine was 40 mg/m<sup>2</sup>. The combination cisplatin/gemcitabine was also effective enough to deserve phase 3 comparison vs. single-agent gemcitabine, while the combination of cisplatin/vinorelbine was less promising. Overall, the efficacy of adding cisplatin to single-agent chemotherapy must be demonstrated by prospective phase 3 trials dedicated to elderly patients.

NSCLC histology represents an important variable in decision making. Pemetrexed is currently approved in combination with platinum as a first-line treatment for NSCLC patients with other than predominantly squamous cell histology as a result of the findings reported in a subgroup analysis of a large phase 3 randomized trial. In fact, this pivotal noninferiority study was conducted in chemotherapy-naive patients with advanced NSCLC who received cisplatin 75 mg/m<sup>2</sup> on day 1 and gemcitabine 1250 mg/m<sup>2</sup> on days 1 and 8 (n = 863) or cisplatin 75 mg/m<sup>2</sup> and pemetrexed 500 mg/m<sup>2</sup> on day 1 (n = 862) every 3 weeks, for up to 6 cycles. Overall survival (OS) for cisplatin/pemetrexed was noninferior to cisplatin/gemcitabine (median OS, 10.3 vs. 10.3 months, respectively; hazard ratio [HR] 0.94; 95% confidence

interval [CI], 0.84-1.05).<sup>11</sup> OS was statistically superior for cisplatin/pemetrexed vs. cisplatin/gemcitabine in patients with adenocarcinoma (n = 847; 12.6 vs. 10.9 months, respectively) and large-cell carcinoma histology (n = 153; 10.4 vs. 6.7 months, respectively). In contrast, in patients with squamous cell histology, there was a significant improvement in OS with cisplatin/gemcitabine vs. cisplatin/pemetrexed (n = 473; 10.8 vs. 9.4 months, respectively).<sup>11</sup> A trend toward a higher efficacy of pemetrexed for patients with nonsquamous NSCLC has also been consistently shown in various retrospective analyses of other trials.<sup>12</sup>

The biochemical explanation of a greater efficacy of pemetrexed against nonsquamous tumors might rely on the fact that such tumors contain low levels of thymidylate synthase (TS). Pemetrexed inhibits multiple enzymes in the folate metabolic pathway, and TS is the main target.<sup>13</sup> In NSCLC cell lines, high baseline TS gene expression levels conferred resistance to pemetrexed,<sup>14</sup> and TS levels were correlated to pemetrexed efficacy in a variety of solid tumors.<sup>15,16</sup> In NSCLC, median TS gene expression is lower in adenocarcinoma than in squamous cell carcinoma.<sup>17</sup> A further retrospective analysis of the registering trial comparing cisplatin/pemetrexed to cisplatin/gemcitabine evaluated the outcomes in elderly patients. In this study, 32.7% of the 1252 nonsquamous patients were  $\geq 65$  and 12.8% were  $\geq 70$  years old. Patients treated with cisplatin/pemetrexed had significantly longer OS compared with those treated with cisplatin/gemcitabine, with HR values favoring pemetrexed of 0.89 (95% CI, 0.76-1.05), 0.75 (95% CI, 0.59-0.94), 0.83 (95% CI, 0.72-0.95), and 0.85 (95% CI, 0.59-1.22) for the < 65-,  $\geq 65$ -, < 70-, and  $\geq 70$ -year age groups, respectively. Dose intensity delivered and toxicities observed for patients treated with pemetrexed were manageable and similar between the older and younger age groups.<sup>18</sup> However, the suggested superiority of cisplatin/pemetrexed over cisplatin/gemcitabine has not been confirmed prospectively in adult nonsquamous NSCLC patients or in an elderly subgroup.

## Objectives

The primary objective of the MILES-3 study is to test whether the addition of cisplatin to gemcitabine prolongs OS compared to gemcitabine alone in elderly patients with chemotherapy-naive advanced NSCLC. Secondary objectives are to compare toxicity, progression-free survival (PFS), objective response rate (ORR), and QoL between the 2 arms. The MILES-3 trial is registered in [ClinicalTrials.gov](http://ClinicalTrials.gov) (NCT01405586).

The 2 primary objectives of the MILES-4 study are, first, to test whether the addition of cisplatin to single-agent chemotherapy (gemcitabine or pemetrexed) prolongs OS compared to single-agent chemotherapy in elderly patients with nonsquamous NSCLC; and second, to test whether pemetrexed prolongs OS compared to gemcitabine in elderly patients with nonsquamous NSCLC. Secondary end points included comparison of toxicity, PFS, ORR, and QoL within each planned comparison. Exploratory objective included analyses for the identification of prognostic and predictive factors of the efficacy of cisplatin and pemetrexed. The MILES-4 trial is registered in [ClinicalTrials.gov](http://ClinicalTrials.gov) (NCT01656551).

In both studies, OS is defined as the period of time elapsing from the date of randomization to the date of death or the date of last follow-up for patients alive at the end of the study. PFS is

## MILES-3 and MILES-4 Trials in Elderly NSCLC

considered to be the time from the date of randomization to the date of progression of disease or death without progression. Patients who are alive and whose disease has not progressed will be censored at the last follow-up date. Objective response rate (ORR), including complete and partial response, is assessed according to Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1).<sup>19</sup> Intensity of adverse events will be graded according to the current National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTC-AE, version 4.0) on a 5-point scale (grade 1 to 5).<sup>20</sup> QoL is measured through the European Organization for the Research and Treatment of Cancer (EORTC) questionnaires (QLQ-C30 and QLQ-LC13).

### Eligibility Criteria

In both trials, study entry is limited to patients aged > 70 years of age with histologically or cytologically confirmed metastatic or locally advanced NSCLC and with Eastern Cooperative Oncology Group performance status of 0 or 1. In MILES-4, only patients with nonsquamous histology and disease staged according to the 7th edition of the tumor, node, metastasis classification system are included. Adequate bone marrow, renal, and liver function are required. Patients with asymptomatic, treated brain metastases are eligible for trial participation.

Patients are excluded if previously treated for advanced disease (prior adjuvant chemotherapy is permitted if it did not contain gemcitabine and pemetrexed and if at least 6 months elapsed from the end of adjuvant chemotherapy); if they have a history of relevant cardiac disease or other relevant comorbidities; if other currently active malignancies are present (with the exception of nonmelanoma skin cancer); if they had carcinoma-in-situ of the cervix; or if they had surgically resected prostate cancer with normal prostate-specific antigen findings. Patients with epidermal growth factor receptor—mutation-positive disease according to local laboratory testing are also excluded, because for these patients, first-line treatment with a tyrosine-kinase inhibitor is recommended.

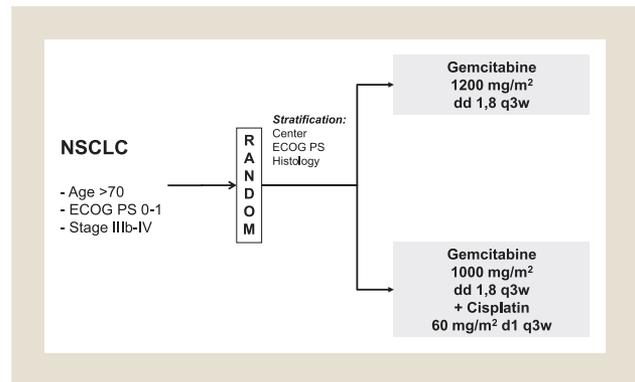
Informed consent will be obtained for every patient before initiation of any trial procedure or treatment.

The partial overlapping inclusion criteria (patients with nonsquamous tumors are potentially eligible for both trials) comes from the timing of approval: MILES-3 was approved by the coordinating ethical committee 21 months before MILES-4. However, there is no reason to formally exclude patients with nonsquamous histology from MILES-3, because there might be centers where only MILES-3 is approved and the trial remains ethically sound. With both trials open to accrual, it is anticipated that the accrual of patients with nonsquamous histology in MILES-3 will slow down. Thanks to the similar study design, however, a pooled analysis of the 2 trials for the question regarding the efficacy of cisplatin will be feasible.

### Study Design and Treatment Plan

MILES-3 is an open-label, multicenter, randomized phase 3 study (Fig. 1). Eligible patients will be randomly assigned in a 1:1 ratio to 1 of the 2 following study arms: gemcitabine 1200 mg/m<sup>2</sup> intravenously on days 1 and 8, every 3 weeks; or cisplatin 60 mg/m<sup>2</sup> intravenously on day 1 plus gemcitabine 1000 mg/m<sup>2</sup> intravenously on days 1 and 8, every 3 weeks.

**Figure 1** Treatment Schema of the Multicenter Italian Lung Cancer in the Elderly Study (MILES)-3



MILES-4 is an open label, multicenter, factorial randomized phase 3 study (Fig. 2). Eligible patients will be randomly assigned at a 1:1:1:1 ratio to one of the following treatment arms: gemcitabine 1200 mg/m<sup>2</sup>, days 1 and 8, every 3 weeks for 6 cycles (arm A); gemcitabine 1000 mg/m<sup>2</sup>, days 1 and 8, plus cisplatin 60 mg/m<sup>2</sup> day 1, every 3 weeks for 6 cycles (arm B); pemetrexed 500 mg/m<sup>2</sup>, day 1, every 3 weeks for 6 cycles (arm C); pemetrexed 500 mg/m<sup>2</sup>, day 1, plus cisplatin 60 mg/m<sup>2</sup> day 1, every 3 weeks for 6 cycles (arm D). Patients randomized in all arms receive oral folic acid (400 µg) daily plus vitamin B12 (1000 µg) injection every 9 weeks, beginning 1 to 2 weeks before the first dose and continuing until 3 weeks after the last dose, and dexamethasone 4 mg orally twice daily for 3 days, beginning on the day before chemotherapy until the day after chemotherapy.

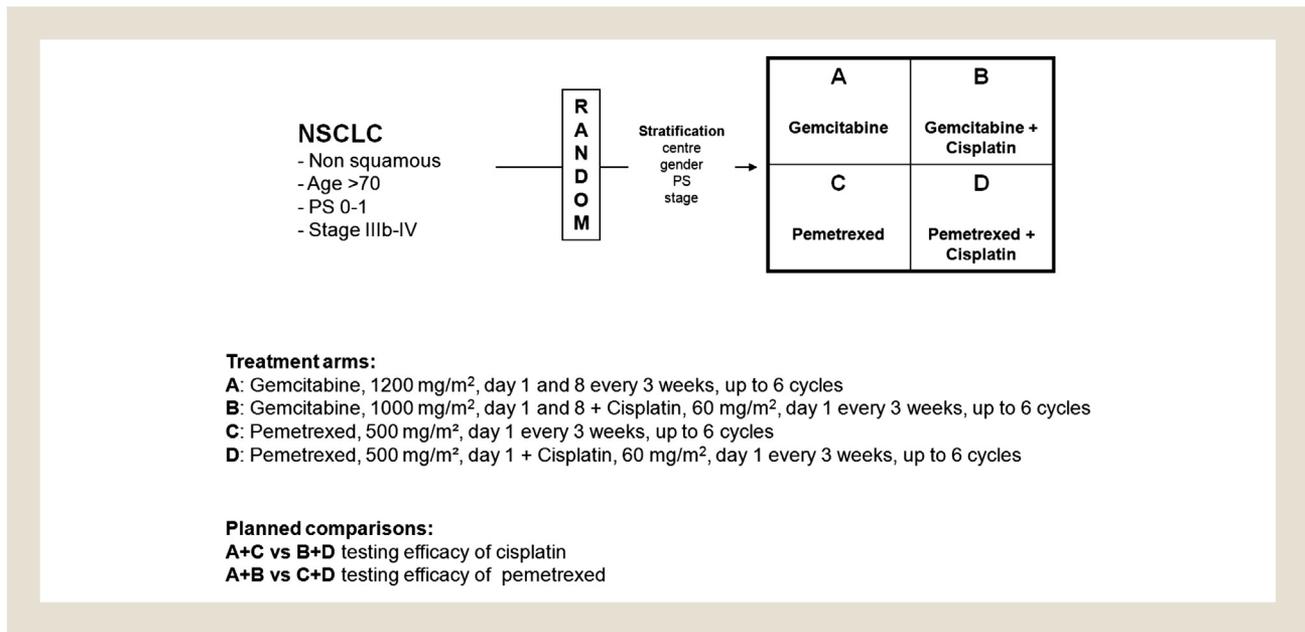
In both trials, before starting any study treatment, computed tomographic scans of the brain, chest, and abdomen; 12-lead electrocardiogram; and bone scan are required. Further assessments will be performed as clinically indicated. Tumor response will be evaluated at the end of cycles 3 and 6 (during weeks 9 and 18). QoL assessments will be completed by patients at baseline and at the end of each cycle during treatment; in MILES-3, QoL will be assessed at baseline, before day 8 of the first cycle and at the end of the first 3 cycles. A complete blood count and biochemistry analyses will be performed at baseline and before any treatment administration. Thereafter, all assessments will be performed every 12 weeks. All patients who prematurely discontinue treatment for any reason will be followed for survival.

### Expected Results

For the planned comparison, the MILES-3 study will have 80% power to detect a HR of death of 0.75, approximately corresponding to a prolongation of median OS from 7.5 to 10 months or an increase of the rate of patients alive at 1 year from 0.32 to 0.43. With 2-tailed alpha error 0.05, a total of 381 events (deaths) are required. With a planned enrollment of 20 patients per month, 480 patients could be enrolled in 24 months, and data for final analysis should be available within 8 months after the end of enrollment.

The study design of MILES-4 is based on 2 superiority survival comparisons (role of cisplatin and role of pemetrexed). For each of the 2 planned comparisons, with 2-tailed alpha error of 0.05, and 1

Figure 2 Treatment Schema of the Multicenter Italian Lung Cancer in the Elderly Study (MILES)-4



interim and 1 final analysis, the study will have 80% power to detect a HR of death of 0.75 (corresponding to a 3-month prolongation of median OS based on the expectation of 9-month median OS in the control arms) with 382 events (deaths). With a planned enrollment of 20 patients per month, 550 patients could be enrolled in 27.5 months, and data for final analysis might be available within 6 months after the end of enrollment. One interim analysis will be performed after approximately 191 events (half of the number required for final analysis) to refuse the null hypothesis and allow trial interruption in case of superiority of the experimental arm. An alpha spending function according to Lan–De Mets will be applied with boundaries defined according to O’Brien Fleming. In case the interim analysis will produce trial stoppage for only 1 of the 2 comparisons, the study will continue with 2 arms only, those including the winner drug.

Registration and randomization of patients in both studies is performed centrally at the Clinical Trials Unit of the National Cancer Institute of Naples, Italy, via a Web-based procedure that applies a minimization technique.

## Analytical Methods

The primary efficacy end point analyses will be performed on the intent-to-treat population, defined as all consenting patients randomized to trial treatment.

Analyses in the MILES-4 study will be conducted separately for the 2 factors (efficacy of the addition of cisplatin and relative efficacy of pemetrexed vs. gemcitabine).

Statistical significance of differences in OS and PFS between treatment arms will be tested by the log-rank test adjusted by the stratification factors used at randomization. Kaplan-Meier curves will be created, with median estimates and 95% CIs provided for each treatment arm. Cox modeling will be used for multivariable analysis with baseline variables involved in the minimization procedure as covariates.

In each comparison, ORR is defined as the rate of patients who will experience a complete or partial response according to RECIST (responders). Patients who do not experience a complete or partial response will be classified as non-responders.

For each patient and for each type of toxicity, the worst degree of toxicity experienced during treatment will be used for the analysis. Two sets of statistical analyses will be performed to compare toxicity. In the first set, the whole pattern of toxicity (each grade) will be considered for each item; analysis will be done by a linear rank test. In the second set, toxicity will be defined as severe (mostly including grade 3 or higher) and not severe (mostly including grades up to 2), and analysis will be performed by Chi square or Fisher’s exact test as appropriate.

The QoL changes from baseline evaluation and the proportion of patients with improvement, decline, or no change in their health-related QoL will be described.

## Conclusion

The MILES-3 and MILES-4 studies are designed to examine the role of cisplatin-based doublets and pemetrexed in the first-line therapy of elderly patients with advanced NSCLC. In the MILES-3 trial, patients with all NSCLC histologies will be randomized to receive either single-agent gemcitabine or cisplatin plus gemcitabine. In the MILES-4 trial, patients with nonsquamous NSCLC will be randomized to receive a single agent (gemcitabine or pemetrexed) or cisplatin doublets (cisplatin/gemcitabine or cisplatin/pemetrexed). The primary end point of both trials is OS, and a number of secondary and exploratory objectives will also be assessed.

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## Disclosure

Antonio Rossi acted as a consultant for Eli Lilly and received honoraria from Eli Lilly. Massimo Di Maio acted as a consultant for Eli Lilly and received honoraria from Eli Lilly. Saverio Cinieri received honoraria from Eli Lilly for participation in advisory boards. The other authors have stated that they have no conflicts of interest.

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