Final results from a Phase II study of pemetrexed and cisplatin with concurrent thoracic radiation after Pem-Cis induction in patients with unresectable locally advanced non-squamous non-small cell lung cancer (NSCLC)

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ABSTRACT

Objectives: This single-arm multicenter Phase II study investigated the efficacy and safety of pemetrexed (Pem) and cisplatin (Cis) induction chemotherapy (CT) followed by full-dose Pem-Cis plus concurrent radiotherapy (RT) in patients with locally advanced non-squamous NSCLC.

Materials and methods: Patients with unresectable Stage III non-squamous NSCLC received two 21-day cycles of Pem 500 mg/m² (vitamin/folic acid supplementation and dexamethasone prophylaxis per Pem-label) + Cis 75 mg/m² on Day 1. Eligible patients who had not progressed continued with 2 further cycles of full-dose Pem-Cis plus concurrent RT (2 Gy/fraction, 5 days/week, 66 Gy total). Primary endpoint was the 1-year progression-free survival (PFS) rate.

Results: Of 90 patients enrolled (all treated; median age 61 years, male/female 57%/43%, ECOG performance status 0/1 66%/34%, adenocarcinoma 90%, Stage III 36%/62%), 75 (83%) completed induction CT and started concurrent CT+RT. 64 (71%) patients received all 4 CT cycles and an RT dose ≥60 Gy. The 1-year PFS rate was 51.3% (95%CI: 42.0, 60.5). Median PFS was 10.6 months (95%CI: 8.6, 17.3), median OS was 26.2 months (95%CI: 16.7, not estimable). One patient died from enteritis (treatment-related) during Cycle 4. Four patients discontinued due to treatment-related adverse events, 1 on induction CT (renal failure), 3 on concurrent CT+RT (1 hypoacusis, 2 acute esophagitis). During induction CT, 18.9% of patients reported Grade 3/4 CTCAEs, only neutropenia (2.2%) and syncope (2.2%) were reported by >1 patient. During concurrent CT+RT, 41.3% of patients reported G3/4 CTCAEs, mainly esophagitis (12.0%), neutropenia (10.7%), and leukopenia (9.3%).

Conclusion: In this study of Pem-Cis induction CT followed by full-dose Pem-Cis with concurrent RT, median PFS was 10.6 months and toxicity was manageable, in line with previous data on Pem-Cis plus RT.

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1. Introduction

Lung cancer remains the leading cause of cancer-related death worldwide. Non-small-cell lung cancer (NSCLC) accounts for approximately 85% of all cases, and about 25% of these have locally advanced disease [1]. Concurrent chemo- and radiotherapy (RT + CT) seems to be superior to sequential treatment, with a survival advantage of approximately 6.6% at 3 years [2,3]. Therefore, CT + RT has been recommended as current standard of care for patients with locally advanced, unresectable Stage III NSCLC [4]. However, the optimal strategy remains undefined, leading to a major clinical challenge of distant control as no third-generation agent can be given at full systemic dose when combined with thoracic radiation [5].

In 2 Phase-III-trials (Vokes study [5], Kim study [6]), patients with unresectable Stage III NSCLC received platinum-based CT with concurrent RT (planned dose 66 Gy), either with or without 2 preceding cycles of induction CT [5,6]. However, efficacy results in both studies failed to show an advantage of the induction CT arm versus the comparator arm, and in the Vokes study induction CT was associated with increased toxicity [5,6]. Despite these results we believe that induction CT followed by concurrent chemoradiotherapy in a regimen slightly different from those assessed in the aforementioned Phase-III-studies, i.e. with full-dose cisplatin (Cis), will provide benefit in patients with advanced NSCLC.

The combination of Cis and full-dose pemetrexed (Pem-Cis) has shown promising activity and tolerability in locally advanced unresectable Stage III disease when combined with RT [7–9].

So far, pemetrexed (Pem) may represent the only third-generation agent to be safely administered at full-dose in combination with Cis and RT, avoiding compromise on activity against distant disease while optimizing local control. In this study, we evaluated induction therapy with Pem-Cis, a standard combination used in Stage IV non-squamous NSCLC [10].

Based on previous data, the current Phase-II-study was designed to investigate efficacy and safety of 2 cycles of Pem-Cis induction CT followed by 2 cycles of full-dose Pem-Cis combined with concurrent RT in patients with locally advanced Stage III non-squamous NSCLC. Given the absence of any proven benefit in favor of one specific approach, we opted for an induction design considering it may offer some advantages: selection of suitable patients for local treatment, and tumor volume reduction prior to RT in CT-responders [5,11].

2. Materials and methods

2.1. Study design

H3E-EW-S128 was a single-arm, multicenter, open-label, Phase-II-study of 2 cycles of first-line Pem-Cis induction CT (induction CT), followed by 2 cycles of Pem-Cis with concurrent thoracic RT (concurrent CT + RT) in patients with locally advanced non-squamous NSCLC (Appendix Fig. A1). All patients were followed-up for ≥2 years after start of induction CT. The primary objective was to assess the 1-year progression-free survival (PFS) rate. Secondary outcomes included objective tumor response rate (ORR), overall survival (OS), safety, and tolerability. The study was approved by institutional review boards and conducted in accordance with the Declaration of Helsinki. All patients had to provide written informed consent before participating in the study. The study was registered at www.clinicaltrials.gov (NCT01000480).

2.2. Patients

Men and women (≥18 years old) with unresectable, measurable (≥1 unidimensionally measurable lesion) Stage IIIA or Stage IIIB non-squamous NSCLC, without malignant pleural/pericardial effusions (AJCC Version 6) [12] were recruited between October 2009 and July 2011 at 21 sites in France, Germany, Italy, and Spain. Patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, and no prior systemic therapy for lung cancer were eligible. Prior non-thoracic RT limited to ≤25% of bone marrow was allowed if completed 30 days before enrolment. Adequate bone-marrow reserve, adequate hepatic, renal, and pulmonary function (forced expiratory volume in 1 s [FEV1] >50% of predicted normal value, carbon monoxide lung-diffusing capacity [DLCO] >40% of predicted normal value), and a total lung volume receiving at least 20 Gy ($V_{20}$) ≤35% were mandatory.

2.3. Treatment

Chemotherapy: Patients received 2 cycles of induction CT with 500 mg/m² Pem infused over approximately 10 min, followed by 75 mg/m² Cis infused starting approximately 30 min after dosing of Pem, given every 21 days (q3w, Day 1 of each cycle). All patients received prophylactic oral dexamethasone, and folic acid and vitamin B₁₂ supplementation as per Pem-label. Cis was administered according to local practice. After 2 cycles of induction CT, patients with documented radiographic evidence of complete response (CR), partial response (PR), or stable disease (SD) (RECIST 1.0) [13] were eligible to start concurrent CT + RT if they had an ECOG PS of 0 or 1, total lung $V_{20}$ ≤35% and no residual neurological toxicity ≥grade (G) 2. Eligible patients received 2 additional cycles of full-dose Pem-Cis CT (as described above) with concurrent RT.

Radiotherapy: Thoracic RT started 22–36 days after the second infusion of Pem-Cis induction CT. Patients received 3-dimensional conformal RT at 2 Gy daily fractions (Monday through Friday), up to the total planned dose of 66 Gy. Gross tumor volume (GTV), clinical target volume (CTV), and planning target volume (PTV) were defined based on a mandatory computed tomography simulation scan performed after 2 cycles of induction CT, with patient in treatment position using specific devices. Treated volumes included the GTV or both primary tumor and nodal diseases, without elective nodal irradiation (CTV equal to GTV). Margins from CTV to PTV were depending on individual centers’ protocols, but generally in the range of 10–15 mm. According to each center’s protocol, respiratory gating could be used. Linear accelerators operating at a beam energy of ≥6 MV were to be used. If therapy interruption for ≤1 week was necessary, irradiation was then resumed and completed to the prescribed dose. If a consecutive interruption of RT >7 days was required, the patient was discontinued from study treatment and treated at the discretion of the investigator.

2.4. Outcomes and assessments

PFS was defined as the time from enrolment to the first date of objectively determined PD or death from any cause. OS was defined as time from enrolment to the date of death from any cause. A CT and an initial positron emission tomography (PET) scan were mandatory for tumor staging. Computed tomography scans (including spiral computed tomography) were used for response assessment. Tumor was assessed at baseline, at the end of Cycle 2, and 6–8 weeks after the last RT dose (in patients eligible for concurrent CT + RT). The follow-up was every 3 months through the first year and every 6 months the second year. ORR was defined as the proportion of patients with confirmed CR or PR according to RECIST criteria at the end of treatment; disease control rate (DCR) was defined as the proportion of patients with confirmed CR or PR.
or with SD. Adverse event (AE) data were collected at each visit up to 30 days after the last dose of study treatment (including the last RT dose); treatment-related serious AE data were collected until the end of the 2-year follow-up period. Laboratory data were collected up to the end of study treatment.

2.5. Statistical analysis

Sample size: A minimum of 53 events (PD or death) was required to achieve 90% power to demonstrate an improvement of the 1-year PFS rate from 45% (historical data) [14] to 60% at a 2-sided alpha-level of 5%. Assuming an accrual period of 18 months, a monthly follow-up of 1 year for all patients and a 10% drop-out rate, 88 patients were planned to be enrolled.

Analysis populations: Efficacy analyses were based on all enrolled patients. Safety analyses included all patients who received ≥1 dose of study treatment. Additional efficacy analyses were based on those patients starting concurrent CT + RT.

Primary analysis: The maximum-likelihood estimates for PFS and the appropriate 95% confidence intervals (CIs) were calculated based on exponential distribution, using the asymptotic normality of ln(\(\lambda\)), where \(\lambda\) is the exponential parameter [15]. If the lower confidence limit of the 1-year PFS rate was >0.45, the null-hypothesis could be rejected. As a supportive analysis, the 1-year PFS rate was estimated using Kaplan–Meier techniques [16]. PFS was censored at the date of the last objective progression-free assessment prior to any systemic post-discontinuation anti-cancer therapy.

Secondary analyses: median OS (mOS), median PFS (mPFS), and OS rates were estimated using Kaplan–Meier techniques. ORR and DCR were presented as exact binomial 95%CIs [17]. Incidence and maximum G of hematologic and non-hematologic toxicities were evaluated based on reported treatment-emergent AEs, using National Cancer Institute Common-Toxicity-Criteria AE terminology (Version 3.0) [18].

Post-hoc analyses: Tumor response was additionally summarized based on tumor assessments performed prior to post-discontinuation surgery. Duration of CR, defined as time from first date of objectively determined CR to first date of objectively determined PD or death from any cause, was analyzed descriptively.

Statistical Analysis Software version 9.2 was used (SAS®, SAS Institute Inc., Cary, USA).

3. Results

3.1. Disposition and patient characteristics

Of 113 patients screened, 90 patients started induction CT and 75 (83.3%) received concurrent CT + RT treatment (Fig. 1). Of these, 64 patients (71.1%) completed 4 cycles of full-dose CT with an RT dose of ≥60 Gy and therefore were considered to have completed the planned treatment.

Patients’ median age was 61.4 years; 56.7% were male; 90.0% had adenocarcinoma, and 62.2% had Stage IIIb disease (Table 1).

3.2. Dose and exposure

Eighty-five patients (94.4%) completed induction CT and 72 (80.0%) completed all 4 CT cycles (Table 2). Overall, patients received a median of 4 cycles of Pem and Cis with relative dose intensities >90% throughout induction CT and concurrent CT + RT phases (Appendix Table A1).

Most patients received the planned radiation dose of 66 Gy (65 of 90 patients, 72.2%) (Table 2), 4 patients received between 60 and 66 Gy, whereas 6 patients received <60 Gy.

Fig. 1. Patient disposition. CT = chemotherapy; RT = radiotherapy.

3.3. Progression-free and overall survival

With a 1-year PFS rate of 51.3% (95%CI: 42.0, 60.5), the study did not meet the primary endpoint. mPFS was 10.6 months (95%CI: 8.6, 17.3) (Fig. 2A). A total of 41 patients (54.7%) had documented PD. Of these, 19 patients (25.3%) experienced local disease progression (14 [18.7%] within the radiation field; 5 [6.7%] within the thorax but outside the radiation field) and 22 (29.3%) developed distant metastases.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patients enrolled (N = 90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), median (range)</td>
<td>61.4 (42.3, 80.5)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>51 (56.7)</td>
</tr>
<tr>
<td>Female</td>
<td>39 (43.3)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>90 (100)</td>
</tr>
<tr>
<td>Smoker, n (%)</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>28 (31.1)</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>55 (61.1)</td>
</tr>
<tr>
<td>Never smoked</td>
<td>7 (7.8)</td>
</tr>
<tr>
<td>ECOG performance status, n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>59 (65.6)</td>
</tr>
<tr>
<td>1</td>
<td>31 (34.4)</td>
</tr>
<tr>
<td>Initial pathological diagnosis, n (%)</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>81 (90.0)</td>
</tr>
<tr>
<td>Other histologies*</td>
<td>9 (10.0)</td>
</tr>
<tr>
<td>Stage of disease (AJCC Version 6), n (%)</td>
<td></td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>32 (35.6)</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>56 (62.2)</td>
</tr>
<tr>
<td>Stage IV*</td>
<td>2 (2.2)</td>
</tr>
<tr>
<td>Prior radiotherapy, n (%)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>FEV₁ [predicted], median (range)</td>
<td>77.5 (41.0, 141.0)</td>
</tr>
</tbody>
</table>

AJCC = American Joint Committee on Cancer Staging Manual; CT = chemotherapy; ECOG = Eastern Cooperative Oncology Group; FEV₁ = forced expiratory volume in 1 min; N = total number of patients; n = number of patients; NOS = not otherwise specified; NSCLC = non-small cell lung cancer; RT = radiotherapy.

* Other histologies included large cell lung carcinoma (7 patients), NSCLC, poorly differentiated (1 patient), and NSCLC, NOS (1 patient).

\* Two patients with Stage IV disease were enrolled (major protocol deviation). Both patients were discontinued from the study before starting the concurrent CT + RT period.

\* Was not assessed in 2 patients.
Table 2
Chemotherapy exposure and delivered radiotherapy (N = 90).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pemetrexed</th>
<th>Cisplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cycles received</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>4.0 (1, 4)</td>
<td>4.0 (1, 4)</td>
</tr>
<tr>
<td>Completed 2 cycles of induction CT, n (%)</td>
<td>85 (94.4)</td>
<td></td>
</tr>
<tr>
<td>Completed 4 cycles of CT, n (%)</td>
<td>72 (80.0)%</td>
<td></td>
</tr>
<tr>
<td>Relative dose intensity [%], median (range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Induction CT period</td>
<td>90.4 (64, 105)</td>
<td>91.6 (64, 105)</td>
</tr>
<tr>
<td>Concurrent CT + RT period</td>
<td>98.8 (0, 132)</td>
<td>97.6 (0, 132)</td>
</tr>
<tr>
<td>Overall treatment period</td>
<td>92.2 (53, 103)</td>
<td>92.3 (53, 105)</td>
</tr>
</tbody>
</table>

Radiotherapy

Received at least 1 dose of RT, n (%) 75 (83.3)

Total RT dose received [Gy]

<table>
<thead>
<tr>
<th>Median (range)</th>
<th>Full dose (66 Gy), n (%)</th>
<th>60 to &gt;66 Gy, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>66 (18.66)</td>
<td>65 (72.2)</td>
<td>4 (4.4)</td>
</tr>
<tr>
<td>&gt;60 Gy, n (%)</td>
<td>6 (6.7)%</td>
<td></td>
</tr>
</tbody>
</table>

Number of fractions delivered, median (range) 33 (9, 33)
Duration of RT [days], median (range) 46 (13, 63)
Total lung mean dose [Gy], median (range), (N = 68) 17.8 (1, 68)
Total lung V20 [\%], median (range), (N = 65) 28 (14, 41)
RT delivery method, n (%) 3-dimensional conformal 69 (92.0)
4-dimensional conformal 6 (8.0)

CT = chemotherapy; N = number of patients; RT = radiotherapy; V20 = volume to receive at least 20 Gy.

After a median follow-up of 25.4 months (range 0.1–35.4 months), the OS analysis was performed at 50% maturity. mOS was 26.2 months (95%CI: 16.7, not estimable); the 2-year OS rate was 54.2% (95%CI: 43.2, 64.0) (Fig. 2B).

For the 75 patients starting concurrent CT + RT, mPFS was 12.5 months (95% CI: 9, 16, 19.0), and mOS was 30.0 months (95% CI: 21.3, not estimable), with a 2-year OS rate of 60.4% (95% CI: 48.3, 70.6).

3.4. Post-discontinuation therapy

Although all patients had unresectable tumors at baseline 15 patients (16.7%) were able to undergo surgery after discontinuation of study treatment, and 6 patients had no measurable lesion after surgery. In addition, there were 3 patients with CR after concurrent CT + RT (Table 3).

Twenty-four patients (26.7%) received thoracic RT, and 33 (36.7%) received systemic therapy. Docetaxel (15 patients, 16.7%) and erlotinib (11 patients, 12.2%) were the agents used most frequently (Appendix Table A2).

3.5. Safety

Induction CT: The only hematologic G3/4 toxicity reported during induction CT was neutropenia in 2 patients (1 G3, 1 G4; 2.2%) (Fig. 3A). The only G4 non-hematologic toxicity was hyponatremia; the only G3 non-hematologic toxicity reported in >1 patient was syncope (Appendix Table A3). Most non-hematologic toxicities were of G1/2. Two patients discontinued treatment due to non-serious AEs associated with renal failure.
Concurrent CT + RT: Neutropenia and leukopenia were the most frequent hematologic toxicities (Fig. 3A). 10.7% of 75 patients had G3/4 neutropenia (12.0% G1/2); 1 patient experienced G3 febrile neutropenia. 9.3% of 75 patients had G3/4 leukopenia (13.3% G1/2). Esophagitis was the main non-hematologic toxicity during concurrent CT + RT (12.0% G3/4, 41.3% G1/2; Fig. 3B), but only 1 patient experienced G4 esophagitis (Fig. 3B). One patient died from study-drug related enteritis during cycle 4. No other G4 non-hematologic toxicities were reported. Dysphagia, nausea, and fatigue, mainly G1 and G2, were the only other non-hematologic toxicities reported by >20% of patients (Appendix Table A4). Four patients discontinued due to AEs: 2 because of esophagitis (serious, treatment-related), 1 because of hypoacusis (serious, treatment-related), and 1 because of acute pneumonia (serious, non-related).

Acute hematologic and non-hematologic toxicities reported throughout the complete 4 cycle treatment period are provided in Appendix Fig. A2 and Appendix Table A5. Two patients reported late stage AEs related to radiation (1 G3 pneumonitis starting 7 months after the last radiation; 1 G2 pneumonitis starting 1.5 months after the last radiation).

4. Discussion

This single-arm study in 90 patients with locally advanced non-squamous NSCLC evaluated 2 cycles of Pem-Cis induction CT followed by 2 cycles of full-dose Pem-Cis with full-dose (66 Gy) concurrent RT. The majority of patients (71.1%) received 4 cycles of full-dose Pem-Cis and the planned RT dose. Only 8% of patients starting concurrent CT + RT received a suboptimal radiation dose (<60 Gy). In another recent Phase-II-study by Garrido et al. [19] in Stage III NSCLC assessing non-platinum induction or consolidation CT added to concurrent CT + RT (60 Gy), a larger percentage of patients (20% [consolidation arm]; 12% [induction arm]) received suboptimal radiation doses. cis-based regimens have been studied most extensively, and are therefore recommended by current European Society for Medical Oncology (ESMO) guidelines for concurrent use with RT [4].

In the current study, Pem-Cis induction followed by full-dose Pem-Cis CT with concurrent RT was associated with a mPFS of 10.6 months (1-year PFS rate 51.3%), and a mOS of 26.2 months. These data are within the range seen in a previous Phase-II-study, in which patients received 2 cycles of Cis-based induction CT combined with docetaxel, followed by concurrent oral vinorelbine plus Cis (Vin-Cis) with RT (planned dose of 66 Gy) [11]. Similar results with Cis-based induction CT followed by Vin-Cis with concurrent RT (66 Gy) were reported by Fournel et al. [14], with mPFS of 11.5 months and mOS of 19.3 months.

Results are also available from 2 Phase-III-studies: in the Vokes study [5], the paclitaxel plus carboplatin (Pac-Carbo; 7 weekly cycles) induction CT arm (followed by Pac-Carbo with concurrent radiation at 66 Gy) achieved a mPFS of 8 months and a mOS of 14 months [5]; in the Kim study [6], the induction CT (two 21-day cycles of gemcitabine and cisplatin) arm (followed by 6 cycles of weekly paclitaxel 50 mg/m² and cisplatin 20 mg/m² with concurrent radiation at 66 Gy) achieved a mPFS of 7.5 months and a mOS of 12.6 months. However, both studies failed to demonstrate a survival advantage for induction chemoradiotherapy compared to chemoradiotherapy alone, with mPFS and mOS in comparator arms of 7 and 12 months in the Vokes study [5], and 11.6 and 18.2 months in the Kim study [6], respectively. In the Vokes study [5], this was possibly due to carboplatin being used in the induction and concurrent treatment regimens instead of cisplatin. In the Kim study [6], it may possibly be due to the low dose of cisplatin (20 mg/m²) used during concurrent chemoradiotherapy. Thus, there was no compelling evidence suggesting that the evaluated regimen with Pem and full-dose Cis cannot provide benefit in patients with locally advanced NSCLC.

The toxicity profile during Pem-Cis induction CT was similar to the known profile from Phase-III-studies evaluating Pem-Cis in advanced non-squamous NSCLC [10,20]. The only G3 hematologic...
toxicity reported during induction CT was neutropenia (2 patients), the only G3/4 non-hematologic toxicities reported were hypotension and syncope (1 patient each).

Toxicity was also manageable during the concurrent Pem-Cis with RT phase. G3/4 hematologic toxicity was in the range observed in other induction CT with concurrent CT + RT regimen in Phase-II trials. During the concurrent phase, G3/4 neutropenia occurred in 10.7% of patients (compared with 4–10.5% for Vin-Cis or docetaxel and carboplatin [Doc-Carbo]), and G3/4 leukopenia in 9.3% of patients (11% for Doc-Carbo) [11,19]. Less than 15% of patients reported G3/4 acute esophagitis (12%) and/or dysphagia (1.3%) (compared with 5.3% acute esophagitis/dysphagia for Vin-Cis, and 15% for Doc-Carbo) [11,19]. No G3/4 dyspnea was reported, and 2.7% of patients had G3/4 acute pneumonitis (0–2% for Vin-Cis or Doc-Carbo) [11,19]. Higher G3/4 toxicity rates were reported in the induction CT arm of the Vokes Phase-III study (neutropenia 31%, leukopenia 44%, acute esophagitis 36%, dyspnea 19%, acute pneumonitis 10%) [5].

Support for the manageable toxicity profile of Pem-Cis when used concurrently with radiation comes from interim safety data during the concurrent CT + RT period of the Phase-III study PROCLAIM [21]. Here, some toxicities (neutropenia, leukopenia, pneumonia) were seen significantly less frequently with Pem-Cis than with etoposide-Cis, and consistent with our study, the most frequent G3/4 toxicities in the Pem-Cis arm were neutropenia (18.4%), leukopenia (15.5%), and esophagitis (14.8%).

Additional safety data specifically for Pem-Cis during concurrent CT + RT are available from Phase-II studies [8,22]. Despite limited comparability with the current study due to different designs (e.g., induction CT followed by CT + RT versus CT + RT followed by consolidation CT), safety profiles are generally consistent across these studies. In the most recent 2-arm Phase-II study by Choy et al. [8], patients received 3 cycles of concurrent CT + RT with either Pem-Cis or Pem-Carbo plus a radiation dose of 64–68 Gy, followed by 3 cycles of Pem consolidation CT. In the Choy study, 13.5% of patients in the Pem-Cis arm reported treatment-related G3/4 neutropenia (Pem-Carbo arm 21.7%), compared with 8.9% of patients in the overall period (i.e., induction plus concurrent phase) of our study, and 7.7% reported treatment-related G3/4 leukopenia (Pem-Carbo 10.9%), compared with 7.8% in our study. Only 1 patient had G4 esophagitis (3.8% G3); no other G4 non-hematologic treatment-related toxicities were observed with Pem-Cis or Pem-Carbo. Dehydration was the most frequent G3 toxicity (Pem-Cis 9.6%, Pem-Carbo 6.5%) [8]. In the single-arm study by Brade et al. [22], patients with unresectable Stage III NSCLC received 2cycles of Pem-Cis plus a target RT dose of 61–66 Gy, followed by 2 cycles of Pem-Cis consolidation CT. G3/4 neutropenia was reported by 38.5% of patients, non-hematologic toxicities were manageable, and non-hematologic G3/4 toxicities included only single cases of esophagitis and pneumonitis, and 2 cases of late-stage esophageal stenosis.

5. Conclusions

The current study was limited by its non-comparative design, although the sample size (90 patients) was substantial for a single-arm Phase-II study [23]. The results provide clinically relevant insights on Pem-Cis induction CT followed by full-dose Pem-Cis CT with concurrent RT. Previously published data support our results, suggesting that the toxicity associated with this regimen is manageable in patients with unresectable Stage III NSCLC who are considered clinically fit for concurrent chemoradiotherapy.

Conflict of interest statement

Carla Visseren-Gril, Sophie Amerzychk, Victoria Soldatenkova, and Nadia Chouaki are Eli Lilly employees, Carla Visseren-Gril, Victoria Soldatenkova and Nadia Chouaki also own Eli Lilly Stock.

Pilar Garrido has participated on advisory boards and has worked as consultant for Eli Lilly, and has received speaker honoraria from Eli Lilly.

Walburga Engel-Riedel has participated on advisory boards for Eli Lilly, Amgen, and Boehringer Ingelheim.

Monika Serke has participated on advisory boards for Eli Lilly, Roche, and Boehringer Ingelheim, and has received honoraria from Roche, Eli Lilly, Astra Zeneca, Pfizer and Boehringer Ingelheim, and received congress invitations from Eli Lilly.

Philippe Giraud has participated on advisory boards for Merck Serono, and has received speaker honoraria from Astellas and Merck Serono.

Umberto Ricardo, Carmen Vallespo, and Silvia Novello have no conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.lungcan.2015.02.014.

References
