Developments in the treatment of early NSCLC: when to use chemotherapy

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Approximately 30% of lung carcinomas are resected and these cases are candidates for adjuvant treatments. The PORT meta-analysis reported in 1999 that postoperative radiotherapy had a detrimental effect for pathological N0 and N1 patients, and a debatable effect for N2 patients. Following the results of the 1995 meta-analysis on the role of chemotherapy (CT) in non-small-cell lung cancer (NSCLC), many randomized, controlled trials were launched to evaluate the effect of adjuvant cisplatin-based CT after the complete resection of NSCLC. The Lung Adjuvant Ciplatin Evaluation pooled analysis included a total of 4584 patients recruited in five recent cisplatin-based adjuvant trials. It confirmed that adjuvant CT was associated with an absolute 5-year survival benefit of 5.3% (P = 0.0043). In addition, it showed that adjuvant cisplatin-based CT is detrimental in cases of stage IA resected NSCLC; it also suggested that the combination of vinorelbine and cisplatin was of more benefit than older two and three drug combinations. The individual data-based meta-analysis was also updated with a total of over 10,000 patients. It confirmed the substantial effect of postoperative CT, with or without postoperative radiotherapy, with a substantial overall benefit of 4% at 5 years. Recent results of biological programs suggest that evaluating the expression of various tumor markers, including excision repair cross-complementation group 1, may allow the identification of patients most likely to benefit from CT. If these results are confirmed, tailored therapy might be the next step forward for resected NSCLC.

Key words: adjuvant, chemotherapy, lung cancer, preoperative

In 2008, lung cancer was the most frequent cause of cancer death for men and the second most frequent for women: there were 1.4 million deaths and 1.6 million new cases worldwide [1]. In Europe, the number of men dying due to lung cancer in 2012 is predicted to be 183,592, with a 10% fall of the standardized rate in 5 years, from 41.3/100,000 to 37.2/100,000 men [2]. Because their smoking habits are more recent, the lung cancer burden for women will continue to increase in many countries and the projected rate of mortality in 2012 (13.4/100,000 women) is getting close to that of breast cancer (14.9/100,000) [2]. Around 85% of these tumors are non-small-cell lung cancer (NSCLC). Although surgery is regarded as the optimal treatment, only 25%–30% of NSCLC are likely to be suitable for potentially curative resection. Despite optimal surgical management, the 5-year survival rate of resected NSCLC is between 73%, for pathological stage IA, and 25%, for pathological stage IIIA [3]. Adjuvant CT uptake is very poor: only 31%–40% of the patients who underwent surgery since 2003 when adjuvant CT became a standard treatment receive this treatment [4, 5]. Identifying appropriate patients for adjuvant CT is an important issue.

major studies addressing adjuvant platinum-based CT

Large randomized adjuvant phase III trials were launched in the mid-90’s based on the meta-analysis of individual data by the Medical Research Council (MRC) and Institut Gustave Roussy (IGR) [6]. A 13% reduction in the risk of death was observed, suggesting that adjuvant CT provided an absolute benefit of 5% at 5 years (P = 0.08). We will review the major trials, highlighting patient selection and suboptimal therapeutic interventions. The molecular markers used in these studies are summarized in Table 1.

A North American Intergroup Trial (Int 0115) demonstrated that a combination of four cycles of CT (etoposide–cisplatin)–concomitant thoracic radiotherapy was not superior to radiotherapy alone given at the same dose in 463 patients with resected stage II and IIIA NSCLC. Age (cutoff 60 years) and stage, along with p53 and k-ras modifications, had no impact of the on the outcome [7, 8]. Currently, adjuvant radiotherapy is not recommended for completely resected stage I or II NSCLC, although questions have been raised about this position for pN2 patients (LungART trial ongoing, NCT00410683) [9].

In the Adjuvant Lung Project Italy (ALPI) trial, 1209 patients with completely resected stage I–IIIA NSCLC were randomly allocated to receive either MVP treatment (mitomycin C 8 mg/m2 on day 1; vindesine 3 mg/m2 on days 1 and 8; cisplatin 100 mg/m2 on day 1 every 3 weeks for three
cycles) or no adjuvant treatment [10]. A total of 1088 patients were analyzed with a median follow-up of 63 months. Hazard ratio (HR) was 0.94 for overall survival and 0.89 for disease-free survival (DFS), and not significant in either case. Triplets (three drug combinations) are now considered to be suboptimal due to higher toxic effect than cisplatin-based doublets in cases of metastases [11]. Indeed, 69% of 606 patients completed the CT but treatment was modified in half of these cases. Although only 25% of the total population were pN2 patients, radiotherapy was delivered to 43% of the patients.

In the post-operative subgroup of the Big Lung Trial, no benefit from two to three cycles of cisplatin-based adjuvant CT (with vindesine, mitomycin C–ifosfamide, mitomycin C–vinblastine or vinorelbine) was observed among 381 patients. However, the population studied was not homogeneous, in particular concerning the quality of the resection, and the compliance to CT was poor [12]. In addition, the median follow-up was only 2.9 years.

International Adjuvant Lung Trial (IALT) was a large randomized study aiming to determine the consequences for the overall survival of three or four cycles of a cisplatin-based CT regimen after complete surgical resection in patients with stage I–III NSCLC [13]. There were 932 patients allocated to CT and 67% received at least 300 mg/m² of cisplatin. The drug combined with cisplatin was etoposide (56%), vinorelbine (27%), vinblastine (11%) or vindesine (6%). There were 935 patients in the control arm. After a median follow-up of 56 months, the overall survival was substantially different between the two arms: 2- and 5-year survival rates were 70% and 45% in the CT arm versus 67% and 40% in the control arm, respectively [HR = 0.86 (0.76–0.98), P < 0.03]. No substantial interaction was observed with age, gender, performance status, type of surgery, pStage, histology, cisplatin dose, combined drug or radiotherapy. However, the effect was no longer significant at 90 months [HR = 0.91 (0.81–1.02), P = 0.10], due to a higher rate of non-cancer-related deaths in the CT arm. A number of biomarkers were studied in 783 exploitable tumor blocks (42%) retrieved, and in particular, excision repair cross-complementation group 1 (ERCC1) expression was investigated immunohistochemically (Table 1).

The NCI-Canada conducted a Phase III Trial (JBR-10) comparing surgery alone to surgery followed by adjuvant CT with cisplatin–vinorelbine in 459 eligible patients with stage IB and II resected NSCLC [14]. After a median follow-up of 5.1 years, the adjuvant CT was associated with a 15% benefit at 5 years (P = 0.012). The benefit was restricted to stage II patients. The same pattern was observed after a median follow-up of 9.3 years, with a slightly reduced benefit (9% at 5 years) [15].

In the Adjuvant Navelbine International Trialist Association (ANITA) I trial included 831 patients with completely resected NSCLC and compared CT consisting of four doses of cisplatin (100 mg/m² every 4 weeks) and 16 doses of vinorelbine (30 mg/m² weekly) to a control arm [16]. Survival rates were 68%, 51% and 45% at 2, 5 and 7 years in the CT arm versus 63%, 43% and 37%, respectively, in the control arm. Response rate (RR) was 0.80 (0.66–0.96) with a P-value of 0.017. The effect was independent of tumor histology [17].

In the Cancer and Leukemia Group B (CALGB) trial 9633, 344 completely resected stage IB (T2N0) patients were randomly assigned to four post-operative cycles of paclitaxel (200 mg/m²)–carboplatin (area under the curve = 6) CT or surgery alone [18]. The initial interim analysis was positive.

### Table 1. Recent randomized platin-based adjuvant trials and meta-analyses

<table>
<thead>
<tr>
<th>Trial</th>
<th>Number of patients</th>
<th>Stage</th>
<th>Chemotherapy</th>
<th>Median follow-up (months)</th>
<th>5-year benefit</th>
<th>Death rate</th>
<th>Hazard ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALPI [10]</td>
<td>1209</td>
<td>I–IIIA</td>
<td>MVdP&lt;sup&gt;a&lt;/sup&gt;</td>
<td>64.5</td>
<td>3</td>
<td>0.5%</td>
<td>0.96 (0.81 to 1.13)</td>
<td>0.589</td>
</tr>
<tr>
<td>IALT [57]</td>
<td>1867</td>
<td>I–IIIA</td>
<td>VincaP or EP&lt;sup&gt;a&lt;/sup&gt;</td>
<td>90</td>
<td>4</td>
<td>0.8%</td>
<td>0.91 (0.81 to 1.02)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.1&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>BLT [12]</td>
<td>381</td>
<td>I–IIIA</td>
<td>Platin-based&lt;sup&gt;a&lt;/sup&gt;</td>
<td>34.6</td>
<td>–2 (2 yrs)</td>
<td>—</td>
<td>1.02 (0.77 to 1.35)</td>
<td>0.90</td>
</tr>
<tr>
<td>BR10 [34]</td>
<td>482</td>
<td>IB–II</td>
<td>VnP</td>
<td>111.6</td>
<td>11</td>
<td>0.8%</td>
<td>0.78 (0.61 to 0.99)</td>
<td>0.04&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>CALGB [18]</td>
<td>344</td>
<td>IB</td>
<td>PC</td>
<td>61.2</td>
<td>15</td>
<td>—</td>
<td>0.69 (0.52 to 0.91)</td>
<td>0.04</td>
</tr>
<tr>
<td>ANITA [16]</td>
<td>840</td>
<td>IB–IIIA</td>
<td>VnP&lt;sup&gt;a&lt;/sup&gt;</td>
<td>76</td>
<td>9</td>
<td>2%</td>
<td>0.8 (0.66 to 0.96)</td>
<td>0.017</td>
</tr>
<tr>
<td>NATCH [32]</td>
<td>424</td>
<td>IA (T &gt; 2 cm), IB, II and T3N1</td>
<td>PC</td>
<td>51</td>
<td>1.5</td>
<td>0.6%</td>
<td>1.01 (0.62 to 1.65)</td>
<td>0.97</td>
</tr>
<tr>
<td>LACE–MRC [36]</td>
<td>4584</td>
<td>I–IIIA</td>
<td>Cisplatin-based&lt;sup&gt;a&lt;/sup&gt;</td>
<td>62.4</td>
<td>5</td>
<td>—</td>
<td>0.89 (0.82 to 0.96)</td>
<td>0.005</td>
</tr>
<tr>
<td>IALT</td>
<td>8447</td>
<td>I–IIIA</td>
<td>Cisplatin-based in 22 of 30 trials</td>
<td>66</td>
<td>4</td>
<td>—</td>
<td>HR = 0.86 (0.81 to 0.92)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

<sup>a</sup>Optional adjuvant radiotherapy.
<sup>b</sup>Updated data. Sat 4 years.

after a median follow-up of 34 months [HR = 0.62; 90% confidence interval (CI) = 0.44–0.89; P = 0.014], which prompted the early termination of the study. Survival was not significantly different between the two arms (HR = 0.83; 90% CI: 0.64–1.08; P = 0.12) after a median follow-up of 74 months.

lessons from data
- Adjuvant CT has been validated in patients aged <75 with a PS of 0 or 1 and without surgical complications.
- Adjuvant CT should begin within 2 months of surgery. Its value after this period is unclear.
- Three to four cycles of cisplatin-based CT are recommended (the cumulative dose of cisplatin from 240 to 400 mg/m²); vinorelbine–cisplatin is the most validated regimen in randomized trials, whereas carboplatin should only be favored in the case of contraindications to cisplatin.

major studies of platinum-based induction CT
The first randomized phase II trial comparing induction CT with surgery alone was closed after only 26 patients were enrolled due to disease progression in four patients. However, two randomized phase III studies published in the 1990s increased the popularity of induction CT [19–21]. Each of these two trials was interrupted after 60 stage IIIA patients were randomized because of positive interim results. Roth et al. [20] compared surgery alone to three cycles of cyclophosphamide/etoposide/cisplatin followed by surgery, without adjuvant radiotherapy. The first publication reported that after 37 months of follow-up, the median survival was 64 months for the group receiving induction CT and 11 months for controls (P = 0.008) [22]. After a longer follow-up of 82 months, the median survival was 21 and 14 months in the two groups, respectively (P = 0.056) [20]. In the second study, Rosell et al. [21] reported the outcome of cN2 patients treated either with surgery or with three cycles of MIP (mitomycin C/ifosfamide/cisplatin) followed by surgery and radiotherapy. Updated median survival was 22 months for the induction therapy group and a poor 10 months for controls (P = 0.005).

Few published randomized phase III studies have attained the numbers of patients initially planned and other studies stopped their recruitment, mostly because adjuvant CT became standard such that a surgery only control arm could not be constituted. A French study randomized IB to IIIA (cN2, pN2 was optional) NSCLC patients to surgery alone or to two induction cycles with MIP, and in responders only (64% of the cohort), an additional two adjuvant cycles with MIP [23]. Adjuvant radiotherapy was planned for pT3 and pN2 patients and for patients with incomplete resection. Although there was a trend favoring the survival of the experimental arm, the statistical hypothesis of a 15% benefit for 2-year survival was not confirmed (HR = 0.78; 95% CI = 0.60–1.02). After a median follow-up of 13.8 years, the 10-year survival rate was 20.8% for the surgery only arm and 29.4% for the experimental arm (P = 0.12) [24]. An unplanned post hoc analysis showed that the 10-year survival rates for patients with stage I and II disease were 23.1% and 37.6%, respectively (P = 0.04).

In the MRC LU22/Dutch Society of Pulmonologists (NVALT) 2/European Organisation for Research and Treatment of Cancer (EORTC) 08012 trial, 519 patients were randomly selected for either treatment with surgery alone or with three cycles of CT [25]. Most of the patients had stage I disease (61%), and only 7% had stage III. The CT regimens included vinorelbine–cisplatin (45%), gemcitabine–cisplatin (GC; 25%), mitomycin C–vinblastine–cisplatin (12%) or docetaxel–carboplatin (12%). The RR was 49% (95% CI = 43%–55%), but no overall survival benefit was seen (HR = 1.02; 95% CI = 0.80–1.31, P = 0.86).

The CT for Early Stages Trial compared surgery alone with three cycles of GC followed by surgery in 270 of 700 planned patients with stage IB–IIIA disease (without N2) NSCLC [26]. The median follow-up was 3.3 years for CT plus surgery (range 0–8.5 years) and 2.6 years for surgery alone (range 0–8.5 years). Stage IB/IIIA disease was observed in 49% and 55% of the patients, respectively. The primary end point, progression-free survival, was higher in the CT arm (HR = 0.70, 95% CI: 0.50–0.97; P = 0.003). The median survival was 7.8 years (95% CI: 5.7 years to N/E; censorship, 64%) for the CT plus surgery arm and 4.8 years (95% CI: 3.1 years to N/E; censorship, 55%) for the surgery alone arm. The adjusted HR of 0.63 (95% CI: 0.43–0.92; P = 0.02) for the overall survival favored CT plus the surgery arm. There was no treatment-by-histology interaction.

The benefit of a cisplatin-free regimen was evaluated in 354 patients (600 planned) with stage IB–IIIA disease (without N2). About 67% of the patients had stage IB–IIA disease, and 33% were stage IIIB or IIIA. After 31 months of follow-up, the HR for death was 0.84 (95% CI: 0.63–1.18; P = 0.32), indicating better outcomes for three cycles of paclitaxel–carboplatin (PC) than following surgery alone [27]. After 53 months of follow-up, the HR was 0.81 (95% CI: 0.60–1.10; P = 0.19) [28].

Cisplatin and carboplatin-based regimens were directly compared in the Intergroupe Francophone de Cancérologie Thoracique (IFCT) 0002 study. Patients with stage IA–II NSCLC were randomized to four cycles of preoperative CT or two cycles of preoperative CT and two postoperative cycles, using either GC or PC [29]. In the 528 patients included, the RRs were similar after two cycles of the two regimens (52% for GC and 49% for PC) and the 3-year survival did not differ among the groups (69.5% for GC and 67.9% for PC). This trial also demonstrated that, surprisingly, two cycles of induction CT resulted in the same rate of complete pathologically documented response (pathological response) as four cycles, raising questions about the view that the optimal number of cycles given in the peri-operative trials is 3 or 4.

lessons from data
- Cisplatin-based regimen should be favored in the neoadjuvant setting, 3–4 cycles are recommended.

the uracil/tegafur case
Although its efficacy in advanced cases of NSCLC has not been demonstrated, uracil/tegafur (UFT) was evaluated as an adjuvant treatment in Japanese populations. The data for 2003 patients from six studies were pooled in a meta-analysis based on individual data [30]. Most of the patients had an
Adjuvant UFT benefit is demonstrated in stage I Asian patients. Its use cannot currently be recommended in Caucasian populations.

which is the best setting and appropriate stage for treatment?

Only one randomized phase III trial has compared two different strategies that combined PC plus surgery (an induction arm and an adjuvant arm) to a surgery alone arm [32]. The 624 patients included had stage IAA (tumor size >2 cm) to non-N2 III NSCLC. The 3-year DFS rates (primary end point) were 41.9% in the surgery, 48.4% in the preoperative arm and 44.9% in the adjuvant group. Compared with the surgery group, the HR for progression or death in the preoperative arm and adjuvant arm were 0.92 (95% CI: 0.81–1.04; P = 0.176) and 0.96 (95% CI: 0.75–1.22; P = 0.74), respectively. No subgroup of patients was identified as benefiting better from the CT.

To evaluate the benefit of cisplatin-based adjuvant CT, the Lung Adjuvant Cisplatin Evaluation (LACE) meta-analysis pooled individual data for 4584 patients included in the ALPI, IALT, ANITA, BLT and JBR-10 trials [33]. All five trials were conducted after the IGR-MRC 1995 meta-analysis and recruited more than 300 patients. Disease stages in this population were as follows: IA, 8%; IB, 30%; II, 35%; III, 27%. With a median follow-up of 5.1 years (3.1–5.9), the 5-year survival rate was substantially higher in the CT group (HR for death = 0.89, 95% CI: 0.82–0.96, P = 0.004), with an absolute benefit of 5.3% for CT. The benefit differed according to the stage of disease (test for trend, P = 0.046). This pooled analysis supports the use of cisplatin-based CT in stage II and III patients [HR = 0.83 (0.73–0.95) and 0.83 (0.73–0.95), respectively]. The use of such regimens is detrimental for stage IA, with an HR of 1.41 (95% CI: 0.96–2.09), and the benefit not established for stage II [HR = 0.93 (0.78–1.10)]. To identify a potential subgroup of stage IB patients that may clearly benefit from adjuvant CT, stage IB was dichotomized according to the tumor size. In the JBR-10 study, patients with tumors of 4 cm or larger derived clinically meaningful benefit from CT [HR = 0.66 (0.39–1.14), P = 0.13] compared with those with tumors smaller than 4 cm [HR = 1.73 (0.98–3.04), P = 0.06] [34]. This predictive cutoff for tumor size regarding overall survival was also relevant in ANITA and an adjuvant carboplatin-based study of stage IB patients [16, 18]. As a consequence, the population eligible for the ongoing adjuvant CT trial ECOG 1505 includes stage I cases with tumors >4 cm. Additional factors may help classify the prognosis of stage I disease. A functional imaging study of stage I cases suggests that the maximum standardized uptake value (cutoff 4.7) of TEP-FDG could be a relevant factor to select an eligible patient for adjuvant treatment [35].

The IGR-MRC individual patient meta-analysis (1995) was updated and republished 15 years later [6, 36]. The authors compared CT combined with surgery to treatment with surgery alone. The median follow-up for all trials was 5.5 years. Based on 34 trial comparisons, the analysis of 8447 patient outcomes (as opposed to 2312 patients in the 1995 analysis) favored the use of adjuvant CT over that of surgery alone (HR = 0.86, 95% CI: 0.81–0.92, P < 0.0001). Platinum-based therapy was used in 26 trial comparisons (without tegafur and uracil or tegafur alone in 18 trial comparisons and with tegafur and uracil or tegafur alone in 8). In the subgroup of patients that received platinum without tegafur or uracil, the overall HRs for survival relative to those for the control group suggested absolute improvements in the 5-year survival of 3% (95% CI: 2–5) for stage IA (from 70% to 73%, poorly significant due to the large CI), 5% (2–7) for stage IB (from 55% to 60%), 5% (3–8) for stage II (from 40% to 45%) and 5% (3–8) for stage III disease (from 30% to 35%). The stage IB in the seventh TNM classification (2009) includes tumors with a maximum diameter of up to 5 cm. Noted that all the adjuvant trials included in the meta-analysis were based on the sixth or earlier classification in which stage IB was defined as tumors larger than 3 cm with no upper size limit. Consequently, the improvement of a 5-year survival by 5% in this subgroup of patients may not be applicable to stage IB as defined in 2011.

In the neoadjuvant setting, only meta-analyses of studies based on abstracted or pooled data are available. In 2006, Burdett et al. [37] included 7 of the 12 eligible randomized trials (five trials were excluded, as the data that could be extracted from the published studies were insufficient). A total of 988 patients were included and authors found that preoperative CT improved survival, with a HR of 0.82 (95% CI: 0.69–0.97, P = 0.02). This meta-analysis was subsequently updated, incorporating the MRC LU22/NVALT 2/EORTC 08012 trial. With a total of 1507 patients, a HR of 0.88 (95% CI: 0.76–1.01, P = 0.07) was obtained, equivalent to an absolute improvement in survival of 5% at 5 years [25]. A more recent study based on 13 randomized trials (3224 patients) found a benefit of platinum-based induction CT (HR = 0.84; 95% CI: 0.77–0.92, P = 0.0001) [38]. There was no difference when the effect of induction CT was analyzed in the subgroup of patients with clinical stage III disease, but these data should be interpreted with caution because four of these trials were published in China and involved very heterogeneous CT regimens. Some concerns have been raised regarding the safety of pneumonectomy after induction therapy. In a meta-analysis of 27 studies, 30-day and 90-day perioperative mortalities were 7% and 12%, respectively [39]. Among 15 studies providing side-specific 30-day mortality, cumulative mortalities were 11% and 5% for right and left pneumonectomies, respectively. It should be stressed that some studies evaluated induction chemoradiotherapy strategies, leading to very high mortality [40]. In a multicentric retrospective study of 228 patients,
induction CT, the 90-day mortality rates were 10.3% (12 of 117) for right pneumonectomy and 8.2% (9 of 111) for left pneumonectomy ("p = 0.65") [31]. This highlights that pneumonectomy is not contraindicated after induction CT, even concerning the right lung, after the rigorous selection of the patients.

**lessons from data**
- Data supporting the use of adjuvant CT are more conclusive and robust than those for induction CT, although efficacy may be comparable (Table 3).
- Platinum-based CT is standard in radically resected stage II and IIIA patients.
- Platinum-based CT is optional for stage IB patients (in particular those superior to 4 cm) and is not recommended for stage IA patients.

**selecting by age, histology or type of surgery**

Although the median age of patients with lung cancer is 70 years, the median age in the MRC-IGR meta-analyses was 61 years (range 18–84) and only 14% of patients were older than 70 years [36]. There was no difference regarding the benefit of CT among patients older and younger than 70 years, but the regimens used in the older subgroup are not specified, and in particular, the proportion of patients treated with cisplatin-based CT is not reported. In the LACE analysis, the effect of CT did not vary according to age but the scarcity of the data is such that caution is required concerning the findings about the use of adjuvant CT in this population [41]. The effect of adjuvant therapy did not depend on histology, according to the LACE analysis; this analysis evaluated mainly the combination of cisplatin and etoposide or vinca-alkaloids, which are known to be active against all NSCLC subtypes [41]. Drugs approved for metastatic non-squamous NSCLC, such as pemetrexed, are not approved in the adjuvant setting because of the absence of appropriate randomized trials. The type of surgery (pneumonectomy versus lobectomy) is not predictive of the benefit of adjuvant CT in the LACE analysis [41]. Careful evaluation of the impact of lung sparing surgery is now essential because early studies suggest that tolerance of CT improves with decreasing post-operative complications of video-assisted thoracic surgery [42].

**acute and long-term toxic effect**

The acute toxic effect of platin-based CT is roughly similar in the perioperative and the metastatic settings, but the death rate ranges from 0% to 2% in the adjuvant trials (Tables 1 and 2). In a phase II trial, the toxic effect of adjuvant CT was lower for pemetrexed–cisplatin than vinorelbine–cisplatin: the prevalence of grade 3/4 toxic effects was 10% versus 74%, respectively ("p < 0.001") [43]. This resulted in better compliance with pemetrexed–cisplatin. IALT, CALGB and JBR-10 trials with longer follow-ups have been reported [15, 18, 44]. The benefit of the adjuvant CT decreased with time, such that two of the three trials were not positive at the longest time points (Table 3). One possible explanation of this effect is the long-term toxic effect of the cytotoxic agents in a population. However, the substantial excess mortality of 20% to 40% in the lung cancer population is not clearly understood [45]. A higher rate of non-cancer-related deaths was reported in the IALT

**Table 2.** Recent randomized platin-based induction trials and meta-analyses

<table>
<thead>
<tr>
<th>Trial</th>
<th>Number of patients</th>
<th>Stage</th>
<th>Chemotherapy</th>
<th>ORR (%)</th>
<th>Median follow-up (months)</th>
<th>5-year benefit (%)</th>
<th>Hazard ratio (95% CI)</th>
<th>Death rate (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosell [21]</td>
<td>60</td>
<td>IIA</td>
<td>MIP</td>
<td>60</td>
<td>60</td>
<td>17</td>
<td>—</td>
<td>0.84</td>
<td>0.005</td>
</tr>
<tr>
<td>Roth [20]</td>
<td>60</td>
<td>IIA</td>
<td>CEP</td>
<td>35</td>
<td>82</td>
<td>21</td>
<td>—</td>
<td>0.84</td>
<td>0.056</td>
</tr>
<tr>
<td>Depierre [23]</td>
<td>373</td>
<td>IB–IIIA</td>
<td>MIP</td>
<td>64</td>
<td>165</td>
<td>9.5</td>
<td>0.82 (0.65–1.04)</td>
<td>0.8</td>
<td>0.12</td>
</tr>
<tr>
<td>LU22 [25]</td>
<td>519</td>
<td>I–IIIA</td>
<td>VnrP, GemP, MVdP, Doc/carbo</td>
<td>49</td>
<td>41</td>
<td>–1</td>
<td>1.02 (0.80 to 1.31)</td>
<td>0.8</td>
<td>0.86</td>
</tr>
<tr>
<td>Ch.E.S.T. [26]</td>
<td>270</td>
<td>IB–IIIA</td>
<td>GemP</td>
<td>35</td>
<td>21</td>
<td>7.8</td>
<td>0.63 (0.43 to 0.92)</td>
<td>0.8</td>
<td>0.02</td>
</tr>
<tr>
<td>NATCH [22]</td>
<td>413</td>
<td>IA (T &gt; 2 cm), IB, II and T3N1</td>
<td>PacCb</td>
<td>53</td>
<td>51</td>
<td>2.6</td>
<td>0.88 (0.69 to 1.12)</td>
<td>0.6</td>
<td>0.56</td>
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<tr>
<td>Burdett [37]</td>
<td>988</td>
<td>I–IIIA</td>
<td>Cisplatin-based</td>
<td>—</td>
<td>NR</td>
<td>6</td>
<td>0.82 (0.69 to 0.97)</td>
<td>—</td>
<td>0.02</td>
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<tr>
<td>Meta-analysis</td>
<td>1507</td>
<td>I–IIIA</td>
<td>Cisplatin-based</td>
<td>—</td>
<td>NR</td>
<td>NR</td>
<td>0.88 (0.76 to 1.01)</td>
<td>—</td>
<td>0.07</td>
</tr>
<tr>
<td>2007 [25]</td>
<td>3224</td>
<td>I–IIIA</td>
<td>Most cisplatin-based</td>
<td>—</td>
<td>NR</td>
<td>NR</td>
<td>0.84 (0.77–0.92)</td>
<td>—</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

*Updated data.

trial after 5 years of follow-up, but this has not been reported in all the trials [16, 24, 44].

**Lessons from data**
- Acute toxic effect lead to toxicity death in up to 2% of the patients, highlighting the importance of a rigorous selection.
- The benefit of platinum-based CT persists even when the follow-up is superior to 5 years.

**Selecting for targeted therapies?**

The understanding of lung cancer biology may be exploited to help develop novel therapies. Drugs approved in the metastatic setting (EGFR inhibitors such as erlotinib or gefitinib and the antiangiogenic monoclonal antibody bevacizumab) are currently being developed for the adjuvant setting. The effects of a 2-year treatment with adjuvant gefitinib (250 mg/day) versus placebo were investigated in the BR.19 trial run by the National Cancer Institute of Canada with 503 unselected stage IB–IIIA NSCLC patients [46]. The study was closed prematurely after the publication of inconclusive results for the efficacy of gefitinib in advanced NSCLC patients. Among the patients included, 49% had stage IB disease, 38% stage II and 13% stage III. Adenocarcinoma was the most frequent pathology (59%) and 17% of the patients received an adjuvant CT. After a median follow-up of 4.7 years, the median DFS was 4.2 years for gefitinib versus not yet reached for placebo, HR = 1.22 (95% CI: 0.93–1.61, P = 0.15). EGFR mutations were not predictive of better DFS with gefitinib. The ongoing RADIANT (Randomized Double-blind Trial in Adjuvant NSCLC with Tarceva) study is exploring the activity of erlotinib (150 mg/day) in patients with immunohistochemically EGFR-positive tumors.

The use of the anti-vascular endothelial growth factor antibody bevacizumab (15 mg/kg every 3 weeks for 1 year) in association with three different CT regimens involving cisplatin is currently being tested in the adjuvant setting (ECOG 1505 trial). The interim results for toxic effect in 557 treated patients showed a substantial increase in overall grade 3/4 toxic effect with bevacizumab (from 68.5% in controls to 83.4%, P < 0.001), mostly involving hypertension, proteinuria and abdomen pain [47]. Grade 5 toxic effect rates in the control and treatment groups do not differ substantially and recruitment is planned to end in 2013. The oral antiangiogenic agent pazopanib has been evaluated in the preoperative setting, and no increase in postoperative complications was detected [48]. Tumor size was reduced in 86% of patients after a median treatment duration of 16 days. A randomized phase II/III trial of adjuvant pazopanib versus placebo in stage I NSCLC patients is underway (study IFCT 0703, NCT00775307).

Other non-CT approaches are being investigated in a large randomized trial. The treatments include MAGE-A3 antigen-specific cancer immunotherapeutic agents and the low-molecular-weight tinzaparin to prevent cancer relapse (NCT00480025, NCT00475098).

**Lessons from data**
- None of the targeted therapies approved in the advanced setting should be offered in the perioperative setting outside a clinical trial, even in molecularly selected patients.

**Biomarkers**

A number of biomarkers have been explored for their value in identifying subgroups of patients for whom adjuvant treatment would be particularly beneficial. DNA repair pathways have been extensively analyzed as a mechanism of resistance to CT. A rate-limiting enzyme in the process, the ERCC1 enzyme, recognizes and eliminates cisplatin-induced DNA adducts. Immunohistochemistry has been used to study ERCC1 in 761 tumors from patients included in the IALT to determine whether chemoresistance is associated with the abundance of the protein [49]. The OS of patients with ERCC1-negative tumors (56% of the cases) was substantially prolonged by cisplatin-based CT (HR = 0.65, 95% CI: 0.50–0.86, P = 0.002), whereas for patients with ERCC1-positive tumors, this therapy had no effect (HR = 1.14, 95% CI: 0.84–1.55, P = 0.40). In a prospective trial, CT for advanced NSCLC patients was adapted to ERCC1 expression, leading to an improved overall RR [50]. To determine whether these findings can be applied to cisplatin use as adjuvant therapy, feasibility and predictive value is being tested randomized trials [51]. In the era of high throughput technology and system biology, a single marker may be of limited value. Indeed, recent data suggest that ERCC1 could be evaluated as part of the DNA repair network of each histological subgroup [52]. Other biomarkers have been evaluated in the IALT study, and in particular, cell cycle regulators, multidrug resistance proteins and apoptotic proteins [53–55]. Other biomarkers may predict the benefit of particular drugs, for example RRM1 expression and beta-tubulin expression for gemcitabine and taxanes [56].

Table 3. Summary of guidelines for adjuvant chemotherapy

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Year</th>
<th>Adjuvant chemotherapy</th>
<th>Chemotherapy</th>
<th>Neoadjuvant chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCP</td>
<td>2007</td>
<td>Stage I and IB : not recommended stage II and III : standard treatment</td>
<td>Platin-based chemotherapy</td>
<td>Stage I and II : N/A stage IIIA : not recommended</td>
</tr>
<tr>
<td>ASCO clinical care Ontario</td>
<td>2007</td>
<td>IA and IB : not recommended II and III : standard treatment</td>
<td>Cisplatin-based chemotherapy</td>
<td>N/A</td>
</tr>
<tr>
<td>ESMO</td>
<td>2010</td>
<td>II and III : standard treatment</td>
<td>Cisplatin-based chemotherapy</td>
<td>Stage IIIA–N2 : cisplatin-based combination chemotherapy</td>
</tr>
</tbody>
</table>

ACCP, American college of chest physicians; ASCO, American society of clinical oncology; ESMO, European society for medical oncology.
lessons from data
• None of the NSCLC biomarkers (including EGFR or KRAS mutations, ERCC1 expression) are ready for prime time, their use should be restricted to clinical trials.

In conclusion, the results of the recently reported large randomized studies of adjuvant CT suggest a 4 to 5% improvement of survival at 5 years. The LACE pooled analysis of the new generation of trials and, more recently, the update of the MRC-IGR meta-analysis confirmed the contribution of adjuvant CT in cases of resected NSCLC, except for stage IA patients. In stage IB patients, tumors greater than 4 cm are eligible for perioperative treatment in most ongoing trials. Based on three randomized trials, vinorelbine is the most robust compound as an adjuvant in association with cisplatin. The treatment should ideally begin within 2 months of surgery in PS 0–1 patients, because a longer interval has been associated with decreased efficacy. Other third generation cytotoxic agents, such as taxanes, gemcitabine and pemetrexed, have been shown to have favorable safety profiles when combined with cisplatin in adjuvant phase II studies. Unfortunately, the efficacy of these adjuvant regimens has not been compared in randomized trials to the vinorelbine plus cisplatin combination. Induction CT data are not as strongly validated as data for the adjuvant setting. HRs for death in meta-analysis for both peri-operative strategies are mostly in the range 0.8–0.9 arguing for an equivalence of the strategies. There are still no validated biomarkers for routine use allowing any customization of treatment.

disclosures
The authors have declared no conflicts of interest.

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