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Role of chemotherapy and targeted therapy in early-stage non-small cell lung cancer

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Abstract

Introduction: Adjuvant platinum based chemotherapy is accepted as standard of care in stage II and III non-small cell lung cancer (NSCLC) patients and is often considered in patients with stage IB disease who have tumors ≤ 4 cm. The survival advantage is modest with approximately 5% at 5 years.

Areas covered: This review article presents relevant data regarding chemotherapy use in the perioperative setting for early stage NSCLC. A literature search was performed utilizing PubMed as well as [clinical trial.gov](https://clinicaltrials.gov). Randomized phase III studies in this setting including adjuvant and neoadjuvant use of chemotherapy as well as ongoing trials on targeted therapy and immunotherapy are also discussed.

Expert commentary: With increasing utilization of screening computed tomography scans, it is possible that the percentage of early stage NSCLC patients will increase in the coming years. Benefits of adjuvant chemotherapy in early stage NSCLC patients remain modest. There is a need to better define patients most likely to derive survival benefit from adjuvant therapy and spare patients who do not need adjuvant chemotherapy due to the toxicity of such therapy. Trials for adjuvant targeted therapy, including adjuvant EGFR-TKI trials and trials of immunotherapy drugs are ongoing and will define the role of these agents as adjuvant therapy.

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Declaration of interest

SM Gadgeel has sat on the advisory board for Genentech, Roche, Ariad, AstraZeneca and Pfizer. The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. A reviewer on this manuscript has disclosed that they have acted as a speaker for AstraZeneca, Roche, and Pfizer. They have also acted in an advisory role of AstraZeneca, Boehringer Ingelheim, Bristol Meyers Squibb, Celgene, G1 Therapeutics, Merck, Pfizer, Pierre Fabre, and Roche. Lastly, they have received financial support due to travels undertaken while working for Roche. Peer reviewers on this manuscript have no other relevant financial or other relationships to disclose.

Keywords

Non-small-cell lung cancer; early-stage; adjuvant chemotherapy; neoadjuvant chemotherapy; adjuvant targeted therapy; adjuvant immunotherapy

1. Introduction

Lung cancer is the most common cancer worldwide, with about 1.8 million new cases and 1.6 million deaths in 2012 [1]. In the United States, it occurs in about 225,000 patients and causes over 160,000 deaths annually [2]. Non-small cell lung cancer (NSCLC) constitutes about 85% of all lung cancer and its main subtypes include adenocarcinoma and squamous cell carcinoma. Treatment of NSCLC depends heavily upon its stage. Approximately 20–25% of the patients are candidates for surgical resection [3].

Whenever feasible, patients with early-stage NSCLC are treated surgically with curative intent. However, many patients are at risk of lung cancer recurrence even after complete resection. The 5-year survival rate in resected NSCLC patients has been reported to be over 70% in stage I patients to only 25% in stage IIIA patients [4–6]. A high proportion of patients with resected NSCLC die of recurrent NSCLC, suggesting that a good proportion of these patients have micrometastatic disease at the time of surgical resection. In an attempt to improve survival of early-stage NSCLC, many trials have been conducted and some have demonstrated the benefits of adjuvant chemotherapy.

2. Current standard of care for chemotherapy in early stage NSCLC

2.1. Adjuvant trials

Adjuvant trials have been conducted since the late 1960s. However, none of the initial adjuvant chemotherapy trials demonstrated survival advantage. The first evidence of potential benefit with adjuvant chemotherapy was observed in a meta-analysis, reported in 1995. In this meta-analysis, cisplatin-based adjuvant chemotherapy demonstrated improved survival with an overall hazard ratio (HR) of 0.87 ($p = 0.08$), resulting in an absolute survival benefit of 3% at 2 years and 5% at 5 years [7]. Several adjuvant trials evaluating platinum-based chemotherapy were initiated to confirm the benefit observed in this meta-analysis. Some of these trials did show a survival advantage similar to the benefit observed in the meta-analysis.

To gain a comprehensive understanding of the benefits of adjuvant chemotherapy, the Lung Adjuvant Cisplatin Evaluation (LACE) meta-analysis was conducted. This meta-analysis included five of the largest trials evaluating adjuvant cisplatin-based chemotherapy conducted since the previous meta-analysis. The LACE meta-analysis included 4584 patients and had a median follow-up of 5.2 years. The results demonstrated a 5.4% absolute survival benefit at 5 years with a HR of death at 0.89 (95% CI 0.82–0.96, $p = 0.005$). Findings based on stage showed a trend toward worse survival among patients with stage IA disease with a HR of 1.40 (95% CI 0.95–2.06) and a trend toward improved survival in stage IB disease with a HR of 0.93 (95% CI 0.78–1.1). Survival benefits were seen in stage II and

IIIA with a HR of 0.83 (95% CI 0.73–0.95) and HR 0.83 (95% CI 0.72–0.94), respectively (Table 1) [8].

Many of these trials utilized chemotherapy that is not comparable to currently used regimens. Only two adjuvant trials evaluated ‘modern’ platinum-based chemotherapy regimen, namely cisplatin and vinorelbine (Table 2). The JBR.10 trial conducted in North America was a phase III study of vinorelbine plus cisplatin compared with observation in completely resected stage IB and II NSCLC patients. The updated survival analysis of JBR.10 showed an absolute improvement in 5-year survival of 11% at a median follow-up of 9.3 years. Patients with stage II had a significant benefit in survival from chemotherapy with the HR of 0.68 (95% CI 0.5–0.92, $p = 0.01$). The HR for stage IB was 1.03 (95% CI 0.7–1.52, $p = 0.87$), suggesting that the benefit of adjuvant treatment was confined to patients with N1 disease [9]. Though the study had planned for four cycles of chemotherapy, the median number of cycles delivered was three. Major adverse events included fatigue, anorexia, nausea, and febrile neutropenia.

Adjuvant Navelbine International Trialists Association was a trial conducted in Europe evaluating adjuvant use of cisplatin plus vinorelbine versus observation in completely resected stage IB–IIIA NSCLC patients ($N = 840$). With a median follow-up of 6.3 years, the adjusted risk for death was significantly reduced in patients assigned to chemotherapy with a HR of 0.8 (95% CI 0.66–0.96) and the 5-year survival was improved by 8.6%. The authors further analyzed their data based on the lymph node status. In patients with N0 status, the 5-year survival was 58% (95% CI 51–66) in the chemotherapy arm and 61% (95% CI 53–68) in the observation arm, while corresponding values for 5-year survival were 52% (95% CI 42–62) versus 36% (95% CI 28–45) for patients with N1 status and 40% (95% CI 30–49) versus 19% (95% CI 11–27) for N2 status [10].

Similar to LACE, the Cochrane meta-analysis by Burdett et al. also demonstrated the benefit of adjuvant chemotherapy in early-stage NSCLC. Among 8447 patients from 26 trials who were treated surgically without radiation, there was clear evidence of a benefit of adding chemotherapy after surgery with a HR of 0.86 (95% CI 0.81–0.92, $p < 0.0001$), with an absolute increase in survival of 4% at 5 years [13].

3. Factors influencing adjuvant chemotherapy

Several factors including, stage, age, chemotherapy regimens, and timing after surgery are considered in making decisions regarding adjuvant therapy. In addition, patients should have adequate performance status and organ function to be candidates for adjuvant chemotherapy. There are patients who do not recover adequately following a thoracotomy and therefore are unable to receive adjuvant therapy.

3.1. Data on stage IB

Several trials and meta-analysis have shown that benefit of adjuvant chemotherapy is restricted to patients with stage II and stage III disease. Cancer and Leukemia Group B (CALGB) 9633 is the only randomized adjuvant trial that was restricted to stage IB patients. It is also unique in that it is the only trial to assess adjuvant carboplatin-based chemotherapy.

In this study, 344 patients with stage IB NSCLC were randomly assigned to adjuvant carboplatin plus paclitaxel or observation. With a median follow-up of 74 months, survival was not significantly different, HR 0.83 (95% CI 0.64–1.08, $p = 0.12$). However, exploratory analysis demonstrated a significant survival improvement with adjuvant chemotherapy for patients who had tumors ≥ 4 cm in diameter (HR 0.69, 95% CI 0.48–0.99, $p = 0.043$) [14]. Since most adjuvant trials were conducted utilizing cisplatin-based regimens, the use of cisplatin has been preferred in this setting. However, data from CALGB9633 suggest that carboplatin could serve as a feasible alternative in patients who are not candidates for cisplatin-based therapy.

The JBR.10 also evaluated the potential benefit from adjuvant chemotherapy based on tumor size. In patients with tumor size ≥ 4 cm, chemotherapy provided a HR 0.66 (95% CI 0.39–1.14, $p = 0.13$), while those with tumors < 4 cm had a HR 1.73 (95% CI 0.98–3.04, $p = 0.06$). The 5-year survival for patients with tumors ≥ 4 cm was 59% on observation versus 79% with chemotherapy [9].

The exploratory analysis from CALGB9633 and JBR-10 has become the basis for considering adjuvant chemotherapy in patients with stage IB NSCLC, whose tumors ≥ 4 cm. Careful risk–benefit assessment should be performed before considering adjuvant chemotherapy in this population.

3.2. Chemotherapy regimens

Several different cisplatin-based chemotherapy regimens can be utilized as adjuvant therapy. In the randomized phase II TREAT study, patients with stage IB–IIIA were randomized to cisplatin with pemetrexed or vinorelbine. The primary objective of this study was to assess the feasibility of delivering either of these adjuvant regimens. In this study, more patients were able to complete the pemetrexed combination without significant toxicity (95.5% vs. 75.4%, respectively, $p < 0.0001$) [15].

The E1505 adjuvant trial was designed to evaluate the benefits of adding bevacizumab to adjuvant chemotherapy. The trial permitted cisplatin in combination with one of the following drugs, vinorelbine, docetaxel, gemcitabine, or pemetrexed (non-squamous patients only). The study failed to show any benefits with the addition of bevacizumab. In a retrospective analysis, no differences in overall survival (OS) or disease-free survival were observed between the different adjuvant cisplatin-based chemotherapy regimens. However, patients with non-squamous tumors who received cisplatin plus pemetrexed had significantly less total grade 3–5 toxicities ($p < 0.001$) than the patients who received other regimens [16].

These data suggest that any of the platinum-based regimens utilized in patients with advanced NSCLC patients can be utilized as adjuvant therapy. Given better feasibility and tolerability, pemetrexed is considered the favored partner drug with cisplatin in patients with non-squamous histology.

3.3. Pathologic features

The presence of certain pathologic features such as visceral pleural invasion and angio-lymphatic invasion is known to be associated with worse prognosis [17–19]. The NCCN

guidelines do recommend the consideration of adjuvant therapy for high-risk characteristics such as poorly differentiated tumor, vascular invasion, visceral pleural invasion, and neuroendocrine tumors [20]. There is no conclusive evidence that patients with these features alone derive benefit with adjuvant chemotherapy and careful assessment of risk–benefit should be conducted before determining the need for adjuvant chemotherapy.

3.4. Timing of adjuvant chemotherapy

Although the optimal timing of initiation of adjuvant chemotherapy is unknown, treatment is typically offered within 8–10 weeks of surgery, as this was the time frame used in the studies for adjuvant therapy. It is well recognized that not all patients recover from thoracic surgery within this time period. In a retrospective analysis of the Ontario Cancer Registry, the median time to start adjuvant chemotherapy was 8 weeks. However, a third of the patients started adjuvant chemotherapy after 10 weeks and their survival was not inferior compared to those who received chemotherapy within 10 weeks of surgery [21]. Recently, a retrospective study utilizing the National Cancer Database showed that while patients who had chemotherapy started within 39–56 days postoperatively had the lowest mortality risk, initiation of chemotherapy after this interval (57–127 days; the later cohort) did not increase mortality (HR 1.037, 95% CI 0.972–1.105, $p = 0.27$). Furthermore, the patients who received chemotherapy during the later interval had a lower mortality risk than those treated with surgery only (HR 0.664, 95% CI 0.623–0.707, $p < 0.001$) [22]. Therefore, adjuvant chemotherapy could still be considered and may still have benefit even after 10 weeks of surgery, as long as the patient has recovered and is able to tolerate therapy.

3.5. Age

The actual median age of lung cancer patients in the United States is 71 years, whereas many of the adjuvant trials enrolled patients with a median age of early 60s. Therefore, the applicability of the data from these adjuvant trials may be limited in the general NSCLC patient population. Although the LACE meta-analysis reported a trend toward survival advantage with adjuvant chemotherapy even in patients ≥ 70 years with HR 0.9 (95% CI 0.7–1.16, $p = 0.29$) [8] and the JBR.10 trial also reported a survival benefit with adjuvant chemotherapy even in patients ≥ 65 years with HR 0.61 (95% CI 0.38–0.98, $p = 0.04$) [9], very little prospective data exist regarding the utility of adjuvant chemotherapy in patients ≥ 75 years. Adequate risk–benefit evaluation must be undertaken before initiating adjuvant chemotherapy in the elderly population. Elderly patients are more likely to have baseline renal insufficiency and/or hearing impairment and may be also sensitive to volume overload based on their cardiac function. Therefore, carboplatin should be considered in the elderly population.

4. Neo-adjuvant chemotherapy

Compared to the robust data for adjuvant chemotherapy, data on neo-adjuvant chemotherapy are limited. However, there are potential advantages to neo-adjuvant chemotherapy including improved tolerability, possible down-staging, and earlier treatment of micrometastases.

Two small randomized studies from the early 1990s found improved survival for patients receiving neo-adjuvant therapy [23,24], although there are concerns regarding their small sample size, imbalances between the arms, and the poor survival rates of patients in the control arms.

The S9900 was one of the largest studies evaluating neo-adjuvant chemotherapy [25]. Stage IB–IIIA patients were randomized to three cycles of neo-adjuvant chemotherapy with carboplatin and paclitaxel followed by surgery or surgery alone. This study closed early to enrollment because data on the benefits of adjuvant chemotherapy became available, making it challenging to randomize patients to the surgery alone arm. Among the 354 patients enrolled, S9900 reported that neo-adjuvant chemotherapy provided improvement in survival with a median of 62 versus 41 months (HR 0.79, $p = 0.11$) and progression-free survival (PFS) with a median of 33 versus 20 months (HR 0.8, $p = 0.1$), although not statistically significant, likely due to lower than planned enrollment. The surgical resection rates were similar; 87% in the surgery alone arm and 84% in the neo-adjuvant arm. The post-operative adverse events were similar, with the exception of higher postoperative mortality in patients who underwent pneumonectomy following neo-adjuvant chemotherapy (4/24 died vs. 0 out of 26).

Several meta-analyses of trials evaluating neo-adjuvant chemotherapy were conducted. These meta-analyses showed that neo-adjuvant chemotherapy improved survival with an absolute benefit of 5–6% at 5 years, which was very similar to the benefit seen with adjuvant chemotherapy [26,27].

The NATCH trial was one of the few trials that compared neo-adjuvant and adjuvant chemotherapy. It randomized stage I, II, and IIIA (only with T3N1) patients to surgery alone, neo-adjuvant chemotherapy with carboplatin and paclitaxel followed by surgery and surgery followed by same adjuvant chemotherapy [28]. The study failed to demonstrate improvement in survival with either neo-adjuvant or adjuvant chemotherapy. It was speculated that the lack of benefit was due to a large proportion of patients on the trial having stage I disease, a group not known to benefit from adjuvant chemotherapy. However, the survival outcomes with neo-adjuvant or adjuvant chemotherapy were similar. In addition, 97% of the neo-adjuvant arm started chemotherapy whereas only 66% in the adjuvant group ($p < 0.0001$), suggesting that the neo-adjuvant approach may be better tolerated. The neo-adjuvant studies mentioned in this section and ongoing studies are summarized in Table 3.

5. Data on targeted therapy in early-stage NSCLC

Patients with advanced or metastatic NSCLC are offered systemic therapy based on their mutational status. Epidermal growth factor receptor (EGFR) mutation is the most common targetable mutation in NSCLC which accounts for 10–35% of NSCLC patients. Erlotinib, gefitinib, and afatinib, tyrosine kinase inhibitors of EGFR, have proven their efficacy in the treatment of patients with advanced stage NSCLC with tumors harboring the EGFR sensitizing mutations (such as the exon 19 deletion and the L858R point mutation in exon 21) [29,30].

The RADIANT trial was a randomized, double-blind phase III trial designed to evaluate the efficacy of adjuvant erlotinib. In this study, a total of 973 patients with stage IB–IIIA NSCLC tumors which expressed EGFR protein by immunohistochemistry or EGFR amplification by fluorescence *in situ* hybridization were randomized 2:1 to erlotinib or placebo for 2 years. Adjuvant erlotinib did not improve disease-free survival, with a HR of 0.9 (95% CI 0.74–1.1, $p = 0.324$). In patients with EGFR mutation-positive NSCLC, disease-free survival favored erlotinib, with a HR of 0.61 (95% CI 0.38–0.91, $p = 0.039$) although this was not statistically significant because of the hierarchical testing procedure [31]. Furthermore, an updated analysis presented showed no disease-free survival benefit with erlotinib with a HR 0.75 (95% CI 0.48–1.16) in the patient with tumors harboring the exon 19 deletion or L858R substitutions [32].

The SELECT trial is a single arm, multi-institutional, prospective phase II study of adjuvant erlotinib for 2 years in resected stage IA–IIIA patients with the EGFR-mutated tumors. A number of 100 patients enrolled, with 45% stage I, 27% stage II, and 28% being stage IIIA. With a median follow-up of 3 years (and with 89 patients having reached their 2 years), the 2-year disease-free survival was 90% (95% in stage I, 73% in stage II, and 92% in stage IIIA). This 2-year disease-free survival rate was higher than the expected rate of 72% [33]. The authors commented that the median time to recurrence after stopping erlotinib was 8.5 months and patients who recurred had a significantly shorter duration of treatment than those who were recurrence free, suggesting that a longer duration of adjuvant treatment may be beneficial [34]. Although the results appear encouraging, caution needs to be exercised about the results since it is a single-arm study.

More recently, Wu et al. reported a phase III trial (CTONG1104) randomizing patients with resected stage II–IIIA NSCLC with EGFR-activating mutations either to gefitinib for 2 years versus vinorelbine plus cisplatin for four cycles. With a median follow-up period of 36.5 months (range 0.1–62.8), gefitinib had a significantly longer median disease-free survival (28.7 months, 95% CI 24.9–32.5) than vinorelbine plus cisplatin (18 months, 95% CI 13.6–22.3; HR 0.6; 95% CI 0.42–0.87, $p = 0.005$). Three-year disease-free survival was significantly better with gefitinib (34% vs. 27%, $p = 0.013$). OS results were not reported since the data are immature [35].

The available data suggest that adjuvant use of currently available EGFR-TKIs could improve PFS but this may not translate into improved OS. It is possible that the improved PFS but no improvement in OS could be a result of EGFR-TKIs not completely eliminating micrometastatic disease.

6. Important ongoing trials

6.1. The ALCHEMIST and trials on targeted therapy

The Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial, or the ALCHEMIST, is perhaps one of the most important ongoing adjuvant trials (Figure 1). Sponsored by the National Cancer Institute (NCI), the ALCHEMIST is a clinical trial platform that consists of several integrated protocols including ALCHEMIST-Screening (A151216;), ALCHEMIST-EGFR (A081105;), ALCHEMIST-ALK (E4512;), and

ALCHEMIST-nivo (EA5142;). In ALCHEMIST-Screening, up to 8000 patients with stage IB–IIIA NSCLC will be enrolled. The tumors of patients enrolled on the trial will undergo genomic testing. Patients with EGFR or ALK tumors will be offered 2 years of adjuvant treatment with erlotinib versus observation or crizotinib versus observation, respectively. Those that are negative for EGFR or ALK sensitizing mutations will be randomized to adjuvant nivolumab versus observation for 1 year.

There are other ongoing trials comparing adjuvant EGFR-TKIs to adjuvant platinum-based chemotherapy (, WJOG6401L) as well as a trial evaluating 3 months versus 2 years of adjuvant afatinib, a second-generation EGFR-TKI (). The phase III ADAURA study is evaluating the adjuvant use of AZD9291 (osimertinib), a third-generation EGFR-TKI which also inhibits T790M, in patients with stage IB–IIIA following complete tumor resection with or without adjuvant chemotherapy ().

6.2. Adjuvant and neo-adjuvant immunotherapy trials

Pembrolizumab, nivolumab, and atezolizumab, which are checkpoint inhibitors targeting the PD1–PDL1 axis, have completely changed the landscape of the treatment of advanced/metastatic stage NSCLC [36–40]. Given promising results from the advanced/metastatic setting, these agents are now being assessed for the treatment of early stage NSCLC.

As mentioned earlier, the ALCHEMIST trial includes the ALCHEMIST-nivo (EA5142;) arm, in which patients will be given adjuvant nivolumab versus observation for up to 1 year. Other adjuvant immunotherapy trials include a global phase III, randomized, open-label trial, IMpower010 (), which is being conducted to evaluate the efficacy and safety of atezolizumab versus best supportive care following adjuvant cisplatin-based chemotherapy in patients with resected stage IB (tumors ≤ 4 cm)–IIIA NSCLC [41]. Selected phase III studies utilizing immunotherapy in the adjuvant setting are summarized in Table 4.

The PACIFIC trial is a phase III study comparing a PDL1 inhibitor durvalumab versus placebo in unresectable stage III NSCLC patients following chemoradiation therapy. Their interim analysis reported a median PFS of 16.8 (durvalumab) versus 5.6 months (placebo) with a HR 0.52 (95% CI 0.42–0.65, $p < 0.001$) [42]. Although this study evaluated the use of immunotherapy post-chemoradiation, the results of this study raise the possibility that adjuvant or neo-adjuvant use of checkpoint inhibitors will improve survival in patients with resected NSCLC.

Atezolizumab is also being evaluated in the neo-adjuvant setting. The is a phase II, open-label, single-arm study designed to evaluate the efficacy and safety of atezolizumab as a neo-adjuvant and adjuvant therapy in patients with Stage IB, II, or IIIA NSCLC prior to curative-intent resection.

The is a phase II neo-adjuvant trial which enrolled patients with Stage IB–IIIA NSCLC. Patients received two doses of nivolumab 3 mg/kg over 4 weeks before surgery. Early results presented at ASCO 2017 showed that among the 21 attempted resections, 1 tumor was unresectable and 9/21 (43%, 95% CI 24–63%) had a major pathologic response ($<10\%$

viable tumor cells in resection specimen). Authors reported that 18 patients (86%) remain alive and recurrence free with a median postop follow-up of 9 months [43].

The checkmate 816 () is a phase III, randomized, open-label trial of nivolumab plus ipilimumab versus platinum-doublet chemotherapy as neo-adjuvant treatment for early-stage NSCLC. In this study, patients with resectable stage IB/II/IIIA NSCLC will be enrolled and be randomized to receive nivolumab + ipilimumab or platinum-doublet chemotherapy [44].

Results of these trials will define the role of these drugs as adjuvant or neo-adjuvant therapy in resectable NSCLC patients.

7. Summary

Adjuvant platinum-based chemotherapy is recommended in stage II and III NSCLC patients and considered in patients with stage IB disease but with tumors ≤ 4 cm. Careful risk–benefit should be conducted when considering adjuvant chemotherapy in stage IB patients with other high-risk features such as the presence of visceral pleural invasion, vascular invasion, or neuroendocrine tumors, as high-quality evidence is lacking in this setting. Data on neo-adjuvant chemotherapy are some-what limited but seem to offer similar survival benefits to adjuvant chemotherapy. Trials for adjuvant targeted therapy and immunotherapy are ongoing but there are no definitive data as of yet and these results are eagerly awaited.

8. Expert commentary and 5-year view

The percentage of patients being diagnosed with early stage NSCLC patients may increase in the coming years with the increasing utilization of screening CT scans. A multidisciplinary team approach to the evaluation, staging, and management of early stage NSCLC patients is essential to maximize therapeutic outcomes. Decisions regarding neoadjuvant or adjuvant chemotherapy with or without radiation should be done at the time of diagnosis and initial evaluation of these patients.

Patients with early-stage NSCLC are treated surgically with curative intent. However, many patients are at risk of lung cancer recurrence even after complete resection. Based on available data, four cycles of adjuvant platinum-based chemotherapy are the current standard of care for patients with stage II and III NSCLC and are strongly considered in patients with tumors ≤ 4 cm [9,14]. Ability to deliver planned adjuvant chemotherapy is restricted by patient's performance status, comorbidities, and the ability to tolerate four cycles of platinum-based chemotherapy following thoracotomy. Therefore, appropriate assessment of patient and a detailed discussion with the patient are necessary before adjuvant chemotherapy is initiated.

Targeted therapy and immunotherapy have changed the treatment landscape of advanced metastatic stage NSCLC. Trials for adjuvant and neo-adjuvant targeted therapy and immunotherapy are ongoing and thus far have shown promising results. However, whether utilizing these agents in the early stage NSCLC patients will improve survival of these patients remains uncertain.

Identifying those patients who would benefit from perioperative systemic therapy is as important as accurately identifying those patients who would not need such therapy, as not all patients who receive perioperative therapy derive survival advantage and there are toxicities with these therapies. Currently decision to use systemic therapy is based on stage of the tumor, even though some of these patients may not relapse and in some patients, despite adjuvant therapy disease recurrence occurs. It is therefore imperative that biomarkers that have prognostic and predictive utility are identified so that only appropriate patients receive the most effective systemic therapy. Ongoing clinical trials should not only assess the perioperative benefits of specific therapeutic agents but also assess biomarkers that can identify patients most likely to benefit.

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Key issues

- Adjuvant chemotherapy is recommended for stage II and III NSCLC.
- Adjuvant therapy should also be considered in stage IB patients, with tumors 12344 cm.
- Adjuvant chemotherapy should be started within 8–10 weeks of surgery.
- Four cycles of platinum-based doublet chemotherapy regimens should be utilized.
- Neoadjuvant chemotherapy could be considered especially when the feasibility of surgery is a concern.
- Trials for adjuvant targeted therapy and immunotherapy are ongoing but there are no definitive data as of yet.

Figure 1.
Diagram for the ALCHEMIST.
*EGFR Exon 19 deletion or Exon L858R.

Table 1.

Results from the LACE Meta-Analysis based on stage.

<i>N</i>	Stage	Hazard ratio (95% CI)
347	IA	1.40 (0.95–2.06)
1371	IB	0.93 (0.78–1.1)
1616	II	0.83 (0.73–0.95)
1247	IIIA	0.83 (0.72–0.94)

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Table 2.

Adjuvant trials using newer platinum-based combinations.

Trial	N	Stage	Chemotherapy	Planned number of doses/cycles	Median actual dose/number of doses given	% of patients completing all planned cycles	Median F/U (years)	5-year survival benefit (%)	Hazard ratio, <i>p</i> value
JBR-10 [9]	482	IB–II	Cisplatin/vinorelbine	Total of cisplatin 400 mg/m ² Total of vinorelbine 400 mg/m ²	Median dose of cisplatin 336 mg/m ² Median dose of vinorelbine 208 mg/m ²	50	9.3	11	0.78, <i>p</i> = 0.04
ANITA [10]	840	I–IIIA	Cisplatin/vinorelbine	Vinorelbine 30 mg/m ² on days 1, 8, 15, and 22 (cycles q4 weeks; total 16 doses) and cisplatin 100 mg/m ² every 4 weeks; total 4 doses	Cisplatin 4 Vinorelbine 10	50	6.3	8.6	0.80, <i>p</i> = 0.017
LACE [8] ^a	4584	I–IIIA	Several	3–4 Cycles of several different combination	59% of patients received at least 240 mg/m ² of cisplatin	NA	5.2	5.4	0.89 (95% CI 0.82–0.96) <i>p</i> = 0.005

^aThe five trials that LACE included were Adjuvant Lung Project Italy (ALPD) [11], International Adjuvant Lung Cancer Trial (IALT) [12], Big Lung Trial (BLT), JBR.10, and Adjuvant Navelbine International Trialists Association (ANITA).

Table 3.

Phase III neo-adjuvant studies.

First author or NCT trial number	Agent(s)	Phase	Setting	No. of patients	Primary end points
Rosell et al. [23]	Three courses of preoperative chemo with mitomycin, ifosfamide, and cisplatin	III	Stage IIIA: sx Alone vs. neo-adjuvant chemo followed by sx	60	Median survival 26 (neo-adjuvant) vs. 8 months (sx alone); $p < 0.001$ Median DFS 20 (neo-adjuvant) vs. 5 months (sx alone); $p < 0.001$
Roth et al. [24]	Three cycles of cyclophosphamide, etoposide, cisplatin preop and three cycles postop	III	Stage IIIA: sx Alone vs perioperative chemo + sx	60	Median survival 64 (perioperative chemo) vs. 11 months (sx alone); $p < 0.008$. Estimated 2 and 3 year OS: 60 and 56% for perioperative chemo, 25 and 15% for sx alone
Pisters et al. S9900 [25]	Three cycles of preoperative chemo with paclitaxel + carboplatin	III	Stage IB-III A: sx Alone vs. neo-adjuvant chemo followed by sx	^a 354	Median OS 62 (neo-adjuvant) vs. 41 months (sx alone) HR 0.79; 95% CI 0.6–1.06, $p = 0.11$ Median PFS 3 (neo-adjuvant) vs. 20 months (sx alone) HR 0.8; 95% CI 0.61–1.04, $p = 0.10$
Felip et al. NATCH [28]	Preoperative or adjuvant paclitaxel + carboplatin	III	Stage I-III A (only T3N1)	624	5-year DFS 38.3% (neo-adjuvant) vs. 34.1% (sx alone); HR 0.92, $p = 0.176$ 5-year DFS 36.6% (adjuvant) vs. 34.1% (sx alone); HR 0.96, $p = 0.74$

^aStudy closed prematurely.

Table 4.

Select ongoing phase III studies utilizing immunotherapy in the adjuvant and neo-adjuvant setting.

NCT trial number	Agent(s)	Phase	Setting	No. of patients	Primary end points being assessed
PEARLS KN091	Pembro vs. placebo	III	Stage IB-III/A post-surgery ± chemo	1380	Disease-free survival
ANVIL	Nivo vs. observation	III	Stage IB-III/A NSCLC post-sx + chemo	714	DFS OS
ImpowerO10	Atezo vs. best supportive care	III	Stage IB-III/A post-surgery + chemo	1127	DFS OS
PACIFIC	Durvalumab vs. placebo	III	Unresectable stage III post-CRT	713 Enrolled	Interim analysis: median PFS 16.8 (durvalumab) vs. 5.6 months (placebo); HR 0.52, 95% CI 0.42–0.65, $p < 0.001$ OS to be reported at full analysis
	Nivo vs. placebo	III	Unresectable stage III/A or IIIB post-CRT	660	OS PFS
	Atezo	II	Adjuvant/Neo-adjuvant stage IB-III/A NSCLC eligible for sx	180	Percentage of participants with major pathologic response based on surgical resection
CM816	Nivo + ipi	III	Neo-adjuvant, stage IB-III/A, operable NSCLC	326	MPR rate

CRT: Chemotherapy and Radiation Therapy; MPR: major pathological response.