


# Update on Adjuvant Treatment in Resectable Non-Small Cell Lung Cancer and Potential Biomarkers Predicting Postoperative Relapse

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## Abstract

A significant proportion of patients with non-small cell lung cancer (NSCLC) is diagnosed in the early and resectable stage. Despite the use of platinum-based adjuvant chemotherapy, there was only a marginal increase in overall survival and a 15% decrease in relapse. With the advents of immunotherapy and epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), the landscape of adjuvant treatment in completely resectable NSCLC is changing. Postoperative radiotherapy can be beneficial to patients who underwent surgical resection in certain clinical settings. In addition, new biomarkers that predict efficacy of EGFR TKI and immunotherapy as adjuvant treatment are also necessary. In this review, recent updates in adjuvant treatment in resectable NSCLC were briefly explained.

**Keywords:** Carcinoma, Non-Small-Cell Lung; Protein Kinase Inhibitors; Chemotherapy, Adjuvant; Recurrence; Biomarkers

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## Introduction

A significant proportion of patients with non-small cell lung cancer (NSCLC) are diagnosed in the early and resectable stage. About 20% of patients are diagnosed with stages I–II, and 30% with stage III in NSCLC<sup>1</sup>. In stage I–IIIA, the treatment of choice is complete resection, if resectable. However, the 5-year recurrence rate is as high as 45% in stage 1b, 62% in stage II, and 76% in stage III<sup>2</sup>. Lung adjuvant cisplatin evaluation (LACE) meta-analysis showed that cisplatin-based adjuvant chemotherapy results in a 5.4% increase in 5-year overall survival (OS) in resectable NSCLC patients<sup>2</sup>. About 48 to 57% of patients with resectable NSCLC with stages IB–IIIA undergo adjuvant chemotherapy. In contrast, higher proportions of patients with stage II–IIIA disease receive the treatment when compared to stage

IB. Many risk factors are associated with increased postoperative recurrence in patients who underwent complete resections: high carcinoembryonic antigen, lymphatic invasion, pleural invasion, poor histological differentiation, vessel invasion, nodal involvement, and large tumor size<sup>3</sup>. Recently, high programmed death-ligand 1 (PD-L1) expression was shown to have an association with increased postoperative recurrence<sup>4</sup>.

Despite use of platinum-based adjuvant chemotherapy, there was only marginal benefit in OS, and 15% decrease in relapse<sup>5</sup>. With the advents of immunotherapy and epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), landscape of adjuvant treatment in completely resectable NSCLC is changing. With the favorable outcomes using EGFR TKI and immunotherapy in advanced NSCLC, attempts to incorporate these relatively new treatment modalities in adjuvant setting

is undergoing.

In this narrative review, recent updates in adjuvant treatment in resectable NSCLC were briefly explained.

## EGFR TKI and Anaplastic Lymphoma Kinase Inhibitor as Adjuvant Therapy

Attempts to utilize EGFR TKI in adjuvant treatments had been made since early 2010s. Goss et al.<sup>6</sup> conducted a phase 3 double-blind-placebo randomized controlled study, comparing the efficacy of gefitinib and placebo in resectable IB–IIIA NSCLC. No significant difference in disease-free survival (DFS) and OS between the two arms was present. However, there were only 15 patients with EGFR mutation among 503 study patients<sup>6</sup>.

In the phase 3 randomized RADIANT study, the efficacy of erlotinib as an adjuvant treatment was evaluated in stage IB–IIIA NSCLC. DFS of the erlotinib arm was tended to superior to the placebo group, but no statistically significant difference was present. It should be noted that there were 161 patients with positive EGFR mutation among 973 study patients, and EGFR positivity was defined by immunohistochemistry (IHC) and/or fluorescence *in situ* hybridization (FISH)<sup>7</sup>.

The SELECT study, an open-label phase 2 single-arm study showed a possibility of erlotinib as an adjuvant treatment. In all patients with sensitizing EGFR mutation, 2-year DFS was 88% which was better than the historical genotype-matched control<sup>8</sup>.

In the context of previous results, the CTONG trial has shown that the use of gefitinib as adjuvant treatment was associated with significantly superior DFS when compared with a placebo in the resectable NSCLC. In an open-label phase 3 study, the efficacy of gefitinib versus vinorelbine plus cisplatin as adjuvant treatment was compared in completely resected stage II–IIIA patients with exon 19 deletion or exon 21 Leu858Arg mutation. Gefitinib showed significantly better DFS when compared with the vinorelbine+cisplatin arm (hazard ratio [HR], 0.60; 95% confidence interval [CI], 0.42 to 0.87;  $p=0.0054$ ) in the intention-to-treat population (ITT). The superiority in DFS was repeatedly shown in the modified ITT population (HR, 0.70; 95% CI, 0.49 to 0.99;  $p=0.044$ ). However, better DFS did not translate to evident benefits in OS, and recurrence in the central nervous system was not uncommon in the gefitinib arm. The results of the CTONG study did not change the clinical practice<sup>9,10</sup>.

ADAURA trial has shown potential for a possible major breakthrough in the management of early NSCLC. ADAURA study is a phase 3 randomized double-blind placebo study, including 682 EGFR mutant patients

with NSCLC. In comparison to the placebo group, osimertinib showed an 80% reduction in the risk of disease recurrence in patients who underwent complete resection. In stage II–IIIA disease of 470 patients, the osimertinib group showed significantly better DFS than the placebo group (HR, 0.17; 95% CI, 0.11 to 0.26;  $p=0.001$ ). In stage IB–IIIA NSCLC, the superiority in DFS for osimertinib was maintained (HR, 0.20; 95% CI, 0.14 to 0.30;  $p<0.001$ )<sup>11</sup>. Furthermore, osimertinib showed significantly better DFS regardless of prior adjuvant platinum-based chemotherapy, type of EGFR mutation (Ex19del or L858R), or stages. With the evident advantage of DFS in resectable NSCLC with sensitizing EGFR mutations, U.S. Food and Drug Administration (FDA) approved osimertinib as the first adjuvant treatment for patients with NSCLC with Ex19del or L858R.

It is undeniable that ADAURA study results would change the landscape of adjuvant treatment after complete resection of NSCLC<sup>12</sup>. Nevertheless, some questions need to be answered. First, whether the clinical benefit of postoperative osimertinib is maintained after discontinuation of the medication. ADAURA study suggests 3 years of use. Second, despite the low incidence of grade III–IV adverse events (AEs), the use of osimertinib for a long duration would entail AEs for patients who would not have experienced it if osimertinib was not used<sup>13</sup>. Lastly, in many countries including Korea, the use of osimertinib as an adjuvant treatment is not reimbursed by the national health insurance, and the patients will experience a heavy financial burden.

Attempts to utilize anaplastic lymphoma kinase (ALK) inhibitor as an adjuvant treatment is ongoing as well. ALINA study (NCT03456076) is a phase III study on the efficacy and safety of alectinib as adjuvant therapy in patients with stage IB–IIIA ALK-positive NSCLC. The randomized control trial is to compare alectinib and platinum-based regimens. Participants in the experiment are given alectinib at 600 mg orally twice daily for 24 months. This trial will show whether ALK inhibitors can be another option in adjuvant settings (Table 1)<sup>14</sup>.

## Immunotherapy as Adjuvant Therapy

Immune checkpoint inhibitors changed the landscape of metastatic NSCLC treatment. As a single agent and in combination with a platinum regimen, immunotherapy was associated with improved OS and progression-free survival (PFS) in locally advanced and metastatic NSCLC. Based on the clinical benefits of advanced NSCLC, attempts to incorporate immunotherapy in an adjuvant setting are ongoing.

Among recent relevant studies, Impower010 is the

**Table 1.** Targeted therapy and immunotherapy as adjuvant treatment in NSCLC patients who underwent complete resection

Study	Description	Outcome	Reference
<b>Targeted therapy as adjuvant treatment</b>			
RADIANT study	A phase 3 randomized double-blind, placebo-controlled study on the efficacy of erlotinib as adjuvant treatment in stage IB–IIIA NSCLC. There were 161 patients with EGFR mutation among 973 study patients.	DFS of the erlotinib arm tended to be superior to the placebo arm, but no statistically significant difference was present.	7
Goss et al.	A phase 3 randomized double-blind placebo-controlled study, comparing the efficacy of gefitinib and placebo in resectable IB–IIIA NSCLC.	There was no difference in DFS and OS between the two arms.	6
SELECT study	Open-label phase 2 single-arm study evaluating the efficacy of erlotinib as an adjuvant treatment.	In all patients with EGFR mutation, 2-year DFS was 88% which was better than the historical genotype-matched control.	8
CTONG trial	Open-label phase 3 study comparing the efficacy of gefitinib versus vinorelbine plus cisplatin in completely resected stage II–IIIA patients with exon 19 deletion or exon 21 Leu858Arg mutation.	Gefitinib showed significantly better DFS when compared with the vinorelbine+cisplatin arm (HR, 0.60; 95% CI, 0.42–0.87; p=0.0054) in the intention-to-treat population. However, better DFS did not translate to evident benefits in OS.	10
ADAURA trial	A phase 3 randomized double-blind placebo study, including 682 EGFR mutant patients with NSCLC.	In stage II–IIIA disease of 470 patients, the osimertinib group showed significantly better DFS than the placebo group (HR, 0.17; 95% CI, 0.11–0.26; p=0.001). In stage IB–IIIA NSCLC, the superiority in DFS for osimertinib was maintained (HR, 0.20; 95% CI, 0.14–0.30; p<0.001).	11
ALINA study (NCT03456076)	A phase III study on efficacy and safety of alectinib as adjuvant therapy in patients with stage IB–IIIA ALK-positive NSCLC. The efficacy of alectinib and platinum-based regimen is to be compared.	No results reported yet.	14
<b>Immunotherapy as adjuvant treatment</b>			
Impower010	A randomized, multicenter, open-label, phase 3 study including patients with completely resected stage 1B (tumors ≥4 cm) to IIIA NSCLC according to AJCC 7th edition.	In patients with PD-L1 TC ≥1% (SP263) stage II–IIIA, atezolizumab showed significantly better DFS than in best supportive care (HR, 0.66; 95% CI, 0.50–0.88; p=0.004). In patients with stage II–IIIA and stage IB–IIIA NSCLC, atezolizumab showed significantly better DFS when compared to the best supportive care group.	15
PEARLS study (NCT02504372)	Assesses the effectiveness of pembrolizumab as adjuvant treatment in participants with stage IB/II–IIIA who have undergone complete resection, regardless of adjuvant chemotherapy.	Adjuvant pembrolizumab showed a statistically significant DFS improvement in patients who had undergone complete resection.	18

Table 1. Continued

Study	Description	Outcome	Reference
MK-3475-671/ KEYNOTE-671	A phase III, randomized trial evaluating the efficacy of pembrolizumab in combination with platinum doublet neoadjuvant chemotherapy before surgery, and also in the adjuvant phase in patients with resectable T3-4N2 NSCLC.	No results reported yet.	19
ANVIL study	Evaluates the potential efficacy of nivolumab in improving OS and DFS in patients with stage IB-IIIa NSCLC.	No results reported yet.	47

NSCLC: non-small cell lung cancer; EGFR: epidermal growth factor receptor; DFS: disease-free survival; OS: overall survival; HR: hazard ratio; CI: confidence interval; ALK: anaplastic lymphoma kinase; AJCC: American Joint Committee on Cancer; PD-L1: programmed death-ligand 1; TC: tumor cell; PEARLS: Study of Pembrolizumab (MK-3475) vs. Placebo for Participants With Non-small Cell Lung Cancer After Resection With or Without Standard Adjuvant Therapy (MK-3475-091/KEYNOTE-091); ANVIL: Adjuvant Nivolumab in Resected Lung Cancers.

most notable one. Impower010 is a randomized, multi-center, open-label, phase 3 study, and included patients with completely resected stage 1B (tumors  $\geq 4$  cm) to IIIA NSCLC according to American Joint Committee on Cancer (AJCC) 7th edition. In the ITT population, 1,005 patients were randomly assigned (507 were assigned to the atezolizumab group and 498 were assigned to the best supportive care group). Analysis of the data was done in a hierarchical statistical manner. In patients with PD-L1 tumor cell (TC)  $\geq 1\%$  (SP263) stage II-IIIa, atezolizumab showed significantly better DFS than in best supportive care (HR, 0.66; 95% CI, 0.50 to 0.88;  $p=0.004$ ). In patients with stage II-IIIa and stage IB-IIIa NSCLC, atezolizumab showed significantly better DFS when compared to the best supportive care group as well. In comparison to the best supportive care group, the atezolizumab group showed a higher proportion of any grade and grades 3-4 AEs<sup>15</sup>.

American Society of Clinical Oncology (ASCO) recently published a rapid recommendation update for adjuvant systemic therapy in stage I-IIIa completely resected NSCLC. Adjuvant atezolizumab is recommended for all patients with PD-L1  $\geq 1\%$  and without sensitizing EGFR mutations after cisplatin-based chemotherapy<sup>16</sup>. In addition, FDA approved atezolizumab as an adjuvant treatment for NSCLC.

Clinical trials including other immune checkpoint inhibitors such as pembrolizumab or nivolumab are also in progress. Study of Pembrolizumab (MK-3475) vs. Placebo for Participants With Non-small Cell Lung Cancer After Resection With or Without Standard Adjuvant Therapy (MK-3475-091/KEYNOTE-091) (PEARLS) study assesses the effectiveness of pembrolizumab as an

adjuvant treatment in participants with stage IB/II-IIIa who have undergone complete resection, regardless of adjuvant chemotherapy<sup>17</sup>. DFS was significantly improved in the pembrolizumab arm when compared to the placebo group (in the all-comers population) (median 53.6 months vs. 42.0 months; HR, 0.76; 95% CI, 0.63 to 0.91;  $p=0.0014$ )<sup>18</sup>. MK-3475-671/KEYNOTE-671 is a phase III, randomized trial evaluating the efficacy of pembrolizumab in combination with platinum doublet neoadjuvant chemotherapy before surgery, and also in adjuvant phase in patients with resectable T3-4N2 NSCLC<sup>19</sup>. Adjuvant Nivolumab in Resected Lung Cancers (ANVIL) study evaluates the potential efficacy of nivolumab in improving OS and DFS in patients with stage IB-IIIa NSCLC<sup>20</sup>. If other immune checkpoint inhibitors show improved primary outcomes in resectable NSCLC, more clinical options can be provided to patients with resectable NSCLC.

## Postoperative Radiotherapy

Several studies on the efficacy of postoperative radiotherapy (PORT) had been performed. According to current standards, radiotherapy techniques decades ago had been underdeveloped and collateral damage to normal lung tissues had been fatal. SEER study, a retrospective analysis of 7,465 patients showed that PORT was associated with improved survival in patients with N2 disease; however, no clinical benefit was shown in patients with N0-1<sup>21,22</sup>. A retrospective study by Dai et al.<sup>23</sup>, including 221 patients with pIIIA-N2, showed that PORT had clinical benefits in significantly improving OS and DFS. In addition, locoregional recurrence-free

survival (LRFS) and distant metastasis-free survival were prolonged. NCDB study also retrospectively analyzed 4,483 pN2 patients and showed an association between PORT and improved 5-year-OS<sup>24</sup>. Another retrospective study enrolling 1,401 pIIIA N2 patients showed that PORT significantly reduced the risk of locoregional relapse risk, and in some patients with risk factors such as heavy smoking history and a high number of positive lymph nodes, showed improvement in OS<sup>25</sup>. Based on the results of a series of studies, two notable randomized controlled trials were performed.

LUNG-ART trial is an open-label, randomized phase 3 trial that enrolled 501 pN2 NSCLC patients who underwent complete resection. The study patients were randomized to either the PORT arm (n=252) or the no-PORT arm (n=249). The PORT group tended to show superior DFS than the no-port group, but no statistical significance was present (p=0.18). In terms of safety profiles, the PORT group showed a higher prevalence of deaths when compared with the control group (15% vs. 5%). In the PORT group, 11 patients died due to cardiopulmonary causes, while none did in the control group. AEs of grade 3 or 4 occurred in 24% of the PORT group and 15% of the control group. Despite a significant reduction in a mediastinal relapse in the PORT group, no significant differences between the two groups in DFS and OS were present. Furthermore, a significant risk in the safety issue deterred PORT from being a routine postoperative process in pN2 NSCLC<sup>26</sup>.

Another randomized clinical trial, PORT-C is a single-center trial, but it should be taken into account that the majority of the patients had undergone intensity-modulated radiation therapy (IMRT), which is an advanced radiotherapy technique minimizing collateral damage to normal tissue adjacent to tumors. A total of 394 patients were randomized to either the observation arm or the PORT arm. No significant difference in DFS or OS was observed in modified intention to treat (mITT) analysis, but a statistically significant difference in DFS was observed in both per-protocol and treatment analyses (p=0.05 and p=0.02, respectively). In all types of analyses, the PORT arm showed better LRFS<sup>27</sup>.

PORT may not be a routine practice in patients with completely resected stage III–N2, as not enough evidence supporting improvement in OS and DFS was shown. However, in certain clinical settings such as persistent N2 disease after chemotherapy or extensive mediastinal involvement, PORT can be considered to reduce the risk of postoperative relapse<sup>28</sup>. Moreover, upon request of thoracic surgeons who performed complete resection, PORT can also be performed to reduce locoregional relapse risk. Most importantly,

the decision to perform PORT should be preceded by careful discussions among the multidisciplinary team to avoid unnecessary treatment-related toxicity and maximize clinical benefits.

## Safety Issues

Despite the potential benefits of the new treatment modalities in adjuvant settings, predicting possible treatment-related AEs should come beforehand. Considering that adjuvant treatment is performed to decrease the risk of postoperative relapse, avoiding unnecessary hazards to patients should be the priority. The ADAURA study has shown that osimertinib after complete resection is relatively safe. Among 337 patients who underwent osimertinib treatment, AEs of grade 3 or higher were reported in 20% of the osimertinib group in comparison to 13% in the placebo group, and no fatal AEs were reported in the osimertinib group. Frequently reported AEs included diarrhea, paronychia, dry skin, pruritus, and cough. Interstitial lung disease was reported in 3% of the osimertinib group<sup>11</sup>.

The IMpower010 study showed that treatment-related AEs occurred in 335 (68%) among the 495 patients of the atezolizumab group, while grade 3 or 4 severity AEs occurred in 53 (11%) patients in the same group. The most common AEs related to atezolizumab were hypothyroidism, pruritus, and rash. Treatment-related AEs of serious degree occurred in 7% of the atezolizumab group<sup>15</sup>. Immunotherapy-related AEs can affect various organs including the lung, skin, endocrine organs, gastrointestinal tract, kidney, and others<sup>29-31</sup>. Evaluation of risk factors associated with immunotherapy-related AEs, such as autoimmune diseases, or pre-existing interstitial lung disease is important<sup>32,33</sup>, and checking patients' general conditions before the initiation of the immunotherapy-combined adjuvant treatment is necessary to reduce the possibility of immunotherapy-related AEs.

Since PORT did not show a definite clinical benefit in the majority of patients who underwent complete resection, radiotherapy-induced toxicity should be an important concern. In the LUNG-ART trial, cardiopulmonary-associated deaths occurred in the PORT arm<sup>26</sup>. In an analysis of the SEER database, PORT was associated with a significant increase in heart disease-related deaths in the 1980s<sup>34</sup>. However, the technical improvements in radiotherapy have led to benefits in reducing toxicity. Moreover, if patients are to undergo additional adjuvant treatment, the risk for radiotherapy-related pneumonitis can increase. More recent radiotherapy techniques such as 3D conformal radiation therapy,

IMRT, or volumetric modulated arc therapy showed potential benefits while reducing the risks of radiotherapy-related toxicities<sup>35-38</sup>.

To minimize possible PORT-related toxicity, it is recommended that a multidisciplinary tumor board including thoracic surgeons, radiation-oncologists, and pulmonologists discuss the possible risks and benefits of PORT before treatment is started.

## Potential Biomarkers Predicting Postoperative Outcome

Relapse after complete resection is usually assessed radiologically using computed tomography or other modalities. However, it is difficult to distinguish the postoperative change of normal lung tissue from local recurrence, and it is not easy to detect minimal residual disease (MRD) which could not be seen radiologically, possibly delaying the chance of early treatment. Furthermore, with the advents of new adjuvant treatment modalities such as immune checkpoint inhibitors and EGFR TKI, it is necessary to find new biomarkers that account for genetic and molecular backgrounds.

Among various studied biomarkers detecting postoperative relapse, a series of studies on circulating tumor DNA (ctDNA) had been published recently. ctDNA is a short sequenced DNA fragment shed by TCs and can be distinguished by detecting novel mutations which were not found in normal tissues<sup>39</sup>. The mutations include EGFR, KRAS, BRAF, TP53, ERBB2, and many other tumor drivers. Multiple platforms such as CAPP Seq, Signatera, and whole exome sequencing were studied for the detection of MRD after the complete resection of tumors. Allele frequency is important as it is suggested as a potential cutoff for detecting ctDNA. Allele frequency as high as 0.2% is a widely used cutoff in relevant studies. Detection of ctDNA was associated with the development of early-stage lung cancer or postoperative relapse of lung cancer after complete resection. ctDNA has strengths in that it is non-invasive, can be measured serially, can detect disease relapse ahead of radiologic diagnosis, and can simultaneously detect concurrent types of mutation. On the other hand, ctDNA is expensive and allele frequency which has a role of cutoff dividing positive versus negative is not standardized yet. Moreover, false positives can also happen. Some cancer-related mutations can also be detected in benign conditions. In addition, the value of ctDNA as a biomarker may be low and detection can be difficult in the operable stage because the tumor burden is relatively small when compared to more advanced cancer<sup>40</sup>.

Studies on detecting MRD using ctDNA in NSCLC patients suggested the possibility to utilize ctDNA positivity as an indication for adjuvant treatment. In a study that enrolled 100 patients who underwent complete resection, 13 out of 14 patients who showed ctDNA positivity after surgery showed recurrence, while only one of 10 patients who were ctDNA negative showed recurrence during observation time<sup>41</sup>. In one study, using targeted next-generation sequencing, ctDNA was assessed for predicting dynamic recurrence risk and clinical benefit of adjuvant chemotherapy. Positive ctDNA detected after both surgical resection and adjuvant chemotherapy were significantly associated with an increased risk of recurrence. Patients with postsurgical ctDNA positivity benefited from adjuvant chemotherapy. On the other hand, ctDNA negative patients showed a low risk of postsurgical relapse regardless of adjuvant chemotherapy<sup>42</sup>.

Other immune and various protein signatures from tumor tissues were shown to have an association with predictive value in NSCLC. PD-L1 expression is traditionally known for being predictive of immunotherapy response, and it was shown in Impower010, atezolizumab adjuvant treatment showed a more evident treatment response in patients with PD-L1 expression TC  $\geq 50\%$ <sup>15</sup>. AXL overexpression of the tissue along with circulating TCs has shown an association with OS in resectable adenocarcinoma<sup>43</sup>. One retrospective cohort study including 725 patients with surgically removed NSCLC showed c-MET overexpression was a positive factor associated with OS, and further suggested that it could also be a possible biomarker for predicting platinum-based adjuvant chemotherapy response<sup>44</sup>. Immunohistochemical assays of CD47 and CD68 from resected tumor tissues also predicted outcomes of patients with NSCLC<sup>45</sup>. An analytical study of 292 patients with early-stage cancer suggested that an increased proportion of non-Treg CD4+ T cells and plasma cells were correlated with a decreased chance of recurrence. The study also suggested that stratification based on levels of four immune cell types helped identify patients who are at higher risk of recurrence after surgery<sup>46</sup>. As such intratumoral immune cell composition is becoming more important due to the incorporation of immunotherapy as a new adjuvant treatment modality.

## Conclusion

Due to unmet needs in adjuvant treatment in resectable NSCLC, several treatment modalities such as EGFR TKI and immunotherapy were utilized to improve

recurrence-free survival. With evident success in showing superior PFS by osimertinib and immunotherapy in resectable NSCLC, the prognosis of patients with resectable PFS is expected to improve in the near future. Furthermore, it is necessary to find new biomarkers with genetic and immunologic backgrounds that are predictive of clinical outcomes of resectable NSCLC.

## Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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