Role of adjuvant therapy in T1-2N0 resected non-small cell lung cancer

Gavitt A. Woodard, MD, Andrew Li, MD, and Daniel J. Boffa, MD

Feature Editor's Introduction—The pace of treatment modifications for non-small cell lung cancer (NSCLC) in the advanced setting has exponentially increased over the past decade with refinements and new innovations in targeted therapy and the adoption of checkpoint inhibitors as monotherapy and in combination with chemotherapy. Innovations in improving survival in patients undergoing complete resection for early-stage or locally advanced NSCLC have been slower in comparison. Adjuvant chemotherapy for resected stage IA/B NSCLC has been evaluated in clinical trials dating back to the 1980s and 1990s with little proven survival benefit for stage IA/B disease, with the exception for tumors 4 cm or greater based on the 7th edition American Joint Committee on Cancer staging. The use of adjuvant targeted therapy in patients harboring actionable mutations (particularly epidermal growth factor receptor [EGFR]-mutated stage IB-IIIa NSCLC) has been explored with mixed results when comparing adjuvant erlotinib with placebo.^{1,2} Recently, adjuvant osimertinib was found to improve disease-free survival in completely resected stage IB-IIIa EGFR-mutated NSCLC with hazard ratios (0.17-0.20) that are rarely observed in clinical trials. The stage IB patients in this study appeared to derive some benefit (hazard ratio, 0.37) but only in the absence of standard adjuvant chemotherapy.³ In the end, this treatment will only benefit a small subset of patients with resected stage IB NSCLC because the prevalence of EGFR mutations in patients with early-stage lung cancer is approximately 10% to 15%. In contrast, KRAS, the most frequent mutation (~30%) observed in resected NSCLC, has been targeted with sotorasib (directed at KRAS G12C-mutation) with early indications of a survival benefit in advanced NSCLC.⁴ This should prompt interest in studying such an inhibitor in the adjuvant setting after R0 resection of KRAS mutated NSCLC.

In this featured Expert Opinion, Woodard and colleagues have succinctly summarized the published data for adjuvant

NCCN adjuvant chemotherapy guidelines and suggested guidelines.

CENTRAL MESSAGE

Use of platinum-based adjuvant therapy is recommended for select patients with stage IB and greater based on pathologic features. In EGFR mutant tumors, adjuvant osimertinib should also be considered.

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See Commentary on page 1693.

chemotherapy and targeted therapy for resected T1-2N0 NSCLC and introduced the concepts of prognostic and predictive biomarkers. The authors also acknowledge the plethora of ongoing investigations of adjuvant checkpoint inhibition for resected stage IB-IIIa NSCLC. Given the complex evolving landscape of treatment options for resectable NSCLC in both the adjuvant and neoadjuvant settings, it is important for thoracic surgeons to understand categories of treatment options (and their side effects) for their patients and the vocabulary associated with the integration of multi-modality treatments supported by these practice-changing clinical trials.

Michael Lanuti, MD

Over the past 2 decades, the role of adjuvant therapy after surgery in stage I non-small cell lung cancer (NSCLC)

From the Section of Thoracic Surgery, Department of Surgery, Yale School of Medicine, New Haven, Conn.

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Address for reprints: Gavitt A. Woodard, MD, Section of Thoracic Surgery, Yale School of Medicine, 330 Cedar St, BB 205, New Haven, CT 06520 (E-mail: gavitt.woodard@yale.edu).

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has evolved. The following overview is meant to outline the data and rationale behind current treatment recommendations in hopes of enhancing the shared decision-making process for oncology teams and their patients. This overview focuses on the role of adjuvant therapy after tumors have been completely resected, as opposed to patients with residual disease, for whom adjuvant therapy is more broadly recommended.

THE ASSUMPTIONS OF ADJUVANT THERAPY IN EARLY-STAGE LUNG CANCER

The rationale for administering systemic therapy to patients recovering from a complete R0 resection of an early-stage lung cancer is based on 2 key assumptions: (1) micrometastatic disease remains, and (2) additional therapy improves survival.

- Micrometastatic disease remains. Treating patients after surgery only makes sense if cancer remains after surgery. Among stage I adenocarcinomas, multi-institution studies have observed a 26% recurrence rate after complete surgical resection.⁵ Therefore, it is clear that some patients retain micrometastatic disease after complete resection of early-stage lung cancer.
- Systemic therapy improves survival in patients with micrometastatic disease. Chemotherapy would only make sense after surgery if chemotherapy effectively kills the cells that are left behind. A growing body of randomized evidence has identified a survival advantage to giving

adjuvant chemotherapy to certain subsets of completely resected lung cancer (Table 1).

ADJUVANT CHEMOTHERAPY TRIALS IN EARLY-STAGE NON–SMALL CELL LUNG CANCER: THE DATA BEHIND THE GUIDELINES

Clinical trials to study the impact of adjuvant chemotherapy in resected NSCLC began in the 1960s and showed conflicting results through the 1990s when the first meta-analysis was performed by the Non–Small Cell Lung Cancer Collaborative Group. This meta-analysis of 52 randomized clinical trials demonstrated a 5% 5-year overall survival benefit to patients who underwent adjuvant chemotherapy after surgical resection.¹³ Although the survival advantage was not statistically significant ($P = .08$), multiple subsequent studies with a renewed interest in adjuvant therapy followed (Table 1).

The Adjuvant Lung Project Italy randomized 1200 patients with stage I, II, and IIIA NSCLC to adjuvant mitomycin, vindesine, or cisplatin, or observation after surgical resection. This was a negative study showing no significant survival benefit to adjuvant chemotherapy among patients of any stage.⁶ Another early negative trial was the Big Lung Trial from Great Britain, which randomized 381 patients with stage I, II, and IIIA to different chemotherapy regimens versus observation and found no improvements in disease-free survival (DFS) or overall survival.¹⁰

TABLE 1. Summary of trials of adjuvant chemotherapy in early-stage non–small cell lung cancer

Clinical trial	Years patients enrolled	No. of patients	Chemotherapy regimen	Stage IA	Stage IB	Stage II
Adjuvant Lung Project Italy (ALPI) ⁶	1994-1999	482	Mitomycin, vindesine, or cisplatin vs observation	No benefit	No benefit	No benefit
Adjuvant Navelbine International Trialist Association (ANITA) ⁷	1994-2000	840	Cisplatin/vinorelbine	-	No benefit	Benefit (HR, 0.71)
JBR-10 ⁸	1994-2001	482	Cisplatin/vinorelbine	-	No benefit	Benefit (HR, 0.59)
International Adjuvant Lung Trial (IALT) ⁹	1995-2001	1867	Cisplatin/mitomycin	No benefit	No benefit	No benefit
Big Lung Trial (BLT) ¹⁰	1995-2001	381	Cisplatin, vindesine, or vinorelbine	No benefit	No benefit	No benefit
Cancer and Leukemia Group B (CALGB) 9633 ¹¹	1996-2003	344	Carboplatin/paclitaxel	-	No benefit overall; benefit in tumors ≥ 4 cm (HR, 0.69)	-
Eastern Cooperative Oncology Group (E1505) ¹²	2007-2013	1501	Cisplatin-based chemo vs cisplatin-based chemotherapy plus bevacizumab	-	No benefit to adding bevacizumab to chemotherapy	No benefit to adding bevacizumab to chemotherapy

HR, Hazard ratio.

The first large clinical trial to provide convincing evidence of the benefit of adjuvant chemotherapy in NSCLC after complete surgical resection was the International Adjuvant Lung Cancer Trial in 2003, although this benefit was not observed in the patient population with early-stage disease. After surgical resection, 1867 patients with stage I to III disease were randomized to cisplatin-based adjuvant chemotherapy or observation. Among all stages, patients treated with cisplatin-based adjuvant chemotherapy had improved 5-year overall survival (44.5% vs 40.4%, $P < .03$). However, with an analysis by stage, 681 randomized patients with stage I disease had a 34.5% mortality rate when treated with adjuvant chemotherapy and 35% when observed (hazard ratio [HR] for mortality not significant), and 452 patients with stage II had a 53.5% mortality rate when treated with adjuvant chemotherapy and 56.8% when observed (HR not significant), demonstrating no significant survival benefit to cisplatin-based adjuvant chemotherapy in the patient population with early-stage disease.⁹

JBR.10 was the North American Intergroup phase III clinical trial to study adjuvant vinorelbine/cisplatin versus observation in patients with stage IB and II NSCLC after complete surgical resection. Today, JBR.10 remains the clinical trial that demonstrates the greatest survival advantage to adjuvant chemotherapy. Overall recurrence rates were lower in the patients treated with adjuvant chemotherapy 36.0% than in patients in the observation group 49.6% ($P = .003$), and an absolute survival advantage was observed at 5 years in patients treated with adjuvant vinorelbine/cisplatin 69% versus those who were observed 54% ($P = .03$). However, for the patient population with early-stage disease, no statistical benefit was observed among those with stage IB specifically, although at 5 years, there did appear to be a survival advantage to adjuvant chemotherapy, and the authors cautioned that the negative findings among stage IB patients be interpreted with caution. JBR.10 also stratified patients on the basis of the presence of a *RAS* mutation. The presence of a *RAS* mutation alone was not an independent predictor of survival; however, an interesting benefit to adjuvant chemotherapy was observed in patients with *RAS* wild-type (HR, 0.69; 95% confidence interval [CI], 0.49-0.98; $P = .03$), and in patients with *RAS* mutant, no survival advantage to adjuvant chemotherapy was observed (HR, 0.95; 95% CI, 0.53-1.71; $P = .87$).⁸

The Adjuvant Navelbine International Trialist Association trial was a phase III trial of patients with stage IB, II, and IIIA NSCLC randomized to adjuvant vinorelbine/cisplatin or observation with or without adjuvant radiation. Patients in the Adjuvant Navelbine International Trialist Association trial treated with adjuvant vinorelbine/cisplatin had an 8.6% improvement in overall survival at 5 years (HR, 0.80; 95% CI, 0.66-0.96; $P = .017$). In concordance with other trials, the benefit of adjuvant chemotherapy was not seen in patients with stage IB disease (pT2N0 based

on staging at the time), in whom 5-year survival was 62% with adjuvant chemotherapy and 64% with observation. Although a test of the interaction of tumor stage and chemotherapy on survival was not significant ($P = .07$), the interaction between nodal status and chemotherapy did significantly affect survival ($P = .004$); patients with N0 showed no survival benefit after adjuvant chemotherapy.⁷

The use of size as a criterion for adjuvant chemotherapy is derived from data from the Cancer and Leukemia Group B (CALGB) 9633 trial. Preliminary results of the CALGB 9633 trial indicated improved survival in patients with stage IB NSCLC treated with adjuvant paclitaxel/carboplatin; patient accrual was stopped early because of this interim analysis.¹⁴ However, when mature analysis of the CALGB 9633 cohort was published in 2008, the median survival times were 95 months in the chemotherapy group and 78 months in the observation group (HR, 0.83; $P = .125$). Ironically, the study was underpowered to show statistical significance to this survival difference and ultimately showed no survival advantage in patients with stage IB overall.¹¹ An unplanned subgroup analysis to look for patient populations who benefitted from adjuvant chemotherapy did show that there was a benefit to adjuvant paclitaxel/carboplatin therapy among the subset of patients with tumors greater than 4 cm,¹¹ and this is the basis for size greater than 4 cm to be included as a high-risk criteria for adjuvant chemotherapy in the current National Cancer Center Network (NCCN) treatment guidelines.

The Lung Adjuvant Cisplatin Evaluation (LACE) collaborative group pooled data from 5 major studies to evaluate the benefit of adjuvant cisplatin on more than 4500 patients, including more than 1700 stage I patients. LACE found an 11% reduction in risk of death in patients treated with adjuvant chemotherapy overall and beneficial reduction in mortality among patients with stage II and III disease. However, the trend, although not significant, was seen in patients with stage IB disease, and no benefit was seen in stage IA patients.¹⁵

The only randomized clinical trial to show an adjuvant chemotherapy survival benefit in patients with stage I NSCLC was the Japan Lung Cancer Research Group study of approximately 1000 patients with stage I adenocarcinoma. Patients were randomized to oral uracil-tegafur for 2 years or observation after a complete surgical resection. In a subset of patients with T2 disease, this trial demonstrated a survival advantage of 85% in the uracil-tegafur treatment group versus 74% in the observation group. In patients with T1 disease and tumors greater than 2 cm, there was also a significant survival advantage.¹⁶

The Eastern Cooperative Oncology Group E1505 trial examined the benefit of adding bevacizumab to platinum-based adjuvant chemotherapy regimens in completely resected stage IB to IIIA NSCLC. This phase 3, randomized, open-label trial of 1501 patients was ultimately negative

and did not show an overall survival benefit with the addition of bevacizumab.¹²

CURRENT ADJUVANT CHEMOTHERAPY GUIDELINES

It is important to note that not all treatment guidelines from respected sources are in complete agreement across all oncologic scenarios. Because many recommendations are classified as Category 2A, they include consensus opinion and are expected to vary from organization to organization. The NCCN recommends adjuvant chemotherapy for completely resected stage I high-risk patients. High-risk tumors may include tumors larger than 4 cm, poorly differentiated tumors, vascular invasion, visceral pleural involvement, wedge resection, and unknown lymph node status (Nx) (Figure 1). Observation remains the NCCN-recommended approach for tumors less than 3 cm, which under the eighth edition staging system is classified as stage IA.¹⁷ Although the NCCN currently recommends adjuvant chemotherapy for the stage I scenarios outlined, the American College of Chest Physician guidelines state that only stage II and greater tumors should receive adjuvant platinum-based chemotherapy.¹⁸

We recently examined more than 50,000 patients in the National Cancer Database to assess the survival benefit of adjuvant chemotherapy when NCCN high-risk pathologic features and size were considered simultaneously and found the following:¹⁹

- For tumors less than 3 cm, adjuvant chemotherapy did not seem to improve outcomes (HR, 1.10; $P = .17$).
- For tumors 3 to 4 cm, adjuvant chemotherapy only added benefit if the tumor had been removed by wedge resection (HR, 0.72; $P = .004$).
- For tumors 4 to 5 cm, adjuvant chemotherapy only benefited patients in the presence of at least 1 of the NCCN high-risk features (ie, if no high-risk features were present, chemotherapy did not help in this size category) (HR, 0.67; $P = .02$).
- For tumors greater than 5 cm, adjuvant chemotherapy seemed to have a benefit, even in the absence of any high-risk features (HR, 0.75; $P = .004$).

PERSONALIZED MEDICINE, TARGETED THERAPIES CURRENTLY AVAILABLE OR ON THE HORIZON

Adjuvant Targeted Therapy

The past decade has solidified the observation that the natural history of cancer can be altered through the systemic administration of novel therapies designed to target specific genetic changes within the cancer cells or therapies that disrupt an immune-escape mechanism. More recently, these trials have moved into the adjuvant setting for earlier-stage tumors (Table 2).

Based on the success of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors in advanced lung cancer, the RADIANT trial was designed to study the benefit of the tyrosine kinase inhibitor erlotinib in the adjuvant setting. A total of 973 patients with stage IB to IIIA were randomized in this international, double-blind, placebo-controlled study 2:1 to daily erlotinib or placebo for 2 years. Among patients with EGFR mutant tumors, DFS favored erlotinib (HR, 0.61, $P = .039$); however, this was not considered to be statistically significant because of between-arm imbalances and the hierarchical testing procedure.¹

Recently, interim results from the ADAURA trial were published, showing dramatic improvements in DFS among patients with stage II and IIIA EGFR mutant tumors who were treated with 3 years of adjuvant osimertinib (HR, 0.17; 99% CI, 0.11-0.26, $P < .001$).³ Differences in patients with stage IB EGFR mutant tumors were not significant, and there were no differences in overall survival in this interim analysis; however, the dramatic DFS results led to the approval of osimertinib for use in the adjuvant setting. It is worth noting that 60% of patients in the ADAURA trial were treated with adjuvant chemotherapy in addition to adjuvant osimertinib, and thus decisions about whom to treat with adjuvant platinum-based chemotherapy remain even when targeted therapies are used.

Adjuvant Immunotherapy

Immune checkpoint inhibitors remain investigational only among patients with early-stage disease, with many active ongoing clinical trials (Table 2). Given the benefit of adjuvant immunotherapy after chemotherapy and radiation in locally advanced disease, there is enthusiasm for their potential benefit in the adjuvant setting after surgical resection. However, it is unclear if immune checkpoint inhibitors will retain their benefit once the majority of a tumor burden has been removed. In this setting, we are reliant on the presence of residual micrometastatic disease to trigger an immune response. One large international phase III trial with mature results, the MAGRIT trial, was ultimately negative and failed to show a benefit to adding MAGE-A3 cancer immunotherapeutic to adjuvant chemotherapy regimens. The MAGRIT trial was a randomized, double-blind, placebo-controlled trial of MAGE-A3 cancer immunotherapeutic in patients with completely resected stage IB, II, and IIIA MAGE-A3-positive NSCLC who did or did not receive adjuvant chemotherapy. There was no benefit in DFS compared with placebo (HR, 1.02; $P = .74$).²⁰

The Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial (ALCHEMIST) is an initiative to address the role of genomic testing and personalized therapies in the adjuvant treatment of NSCLC. The ANVIL arm is currently investigating adjuvant nivolumab among patients with stage IB to IIIA NSCLC after complete surgical

FIGURE 1. NCCN adjuvant chemotherapy guidelines and suggested guidelines. *EGFR*, Epidermal growth factor receptor; *NCCN*, National Cancer Center Network.

resection who cannot enroll in EGFR or ALK targeted trials. Many of the current clinical trials use adjuvant immunotherapy in addition to standard adjuvant chemotherapy (Table 2); therefore, similarly to targeted therapies, decisions about adjuvant cytotoxic chemotherapy still need to be made.

Prognostic and Predictive Gene Signatures

In the cancer biomarker world, there is an understanding that “prognostic” (likelihood to die) does not necessarily equate to “predictive” (likelihood systemic therapy kills cancer). However, there is some overlap in their clinical relevance. With this in mind, a number of studies have examined the role of biomarkers in the selection of patients

for adjuvant therapy after complete resection of early-stage lung cancer.

Tumor Protein Expression Markers

Single gene/protein markers to predict a benefit from cisplatin-based adjuvant chemotherapy have been described. For example, tumors with excision repair cross-complementation group 1 protein expression on immunohistochemistry have been shown to have a worse response to cisplatin-based adjuvant chemotherapy and shorter DFS times than tumors without excision repair cross-complementation group 1 expression.²¹ Breast cancer 1 protein expression on immunohistochemistry also has been shown to predict worse DFS after adjuvant

TABLE 2. Ongoing trials of targeted adjuvant therapy and immunotherapy

Trial name		Phase	Population	Target	Adjuvant treatment	Enrollment dates/status	Results
ADAURA Trial (NCT02511106)		III	IB-III A	EGFR	Osimertinib $\times$ 3 y $\pm$ chemotherapy	Active, not recruiting	Improvement in DFS in stage II and IIIA leading to FDA approval; OS results pending
ALCHEMIST Trials	EGFR (NCT02193282)	III	IB-III A	EGFR	Erlotinib $\times$ 2 y after complete resection and standard postoperative therapy	Suspended	Suspended
	ALK (NCT02201992)	III	IB-III A	ALK	Crizotinib $\times$ 2 y after complete resection $\pm$ adjuvant chemotherapy/radiation	Enrolling	Pending
	ANVIL (NCT02595944)	III	IB-III A	PD-L1	Nivolumab $\times$ 1 y after complete resection	Active, not recruiting	Pending
IMpower-010 (NCT02486718)		III	IB-III A	PD-L1	Atezolizumab $\times$ 16 cycles after complete resection and adjuvant chemotherapy	Active, not Recruiting	Pending
BR31 (NCT02273375)		III	IB-III A	PD-L1	Durvalumab $\times$ 1 y after complete resection $\pm$ adjuvant chemotherapy	Active, not recruiting	Pending
MERMAID-1 (NCT04385368)		III	II-III	PD-L1	Durvalumab after complete resection and chemotherapy	Enrolling	Pending
PEARLS (NCT02504372)		III	IB-III A	PD-L1	Pembrolizumab $\times$ 1 y after complete resection $\pm$ adjuvant chemotherapy	Active, not recruiting	Pending
NCT03053856		II	N2+ IIIA	PD-L1	Pembrolizumab $\times$ 2 y after complete resection and neoadjuvant chemoradiotherapy	Not yet Recruiting	Pending

DFS, Disease-free survival; FDA, Food and Drug Administration; OS, overall survival.

chemotherapy.²¹ However, these studies of single biomarkers have not randomized patients to adjuvant chemotherapy versus observation; therefore, it has not been demonstrated that these tumor protein expression markers are predictive of poor response to adjuvant chemotherapy or are just prognostic markers of worse survival outcomes overall.

Tumor Genetic Signatures

Early-stage NSCLC remains an area ripe for the application of personalized medicine because these patients are either fully cured with a surgical resection alone or harbor micro-metastatic disease and at risk of recurrence. Identifying those patients at the greatest risk of harboring occult disease, and therefore most likely to benefit from adjuvant

chemotherapy in this patient population, remains an area of active research interest.

In addition to single gene predictive markers, there have been a number of studies published on prognostic gene signatures,²² and most of them lack external validation. The only rigorously validated prognostic assay is a 14-gene expression profile (DetermaRx, OncoCyte Corp, Alameda, Calif). This assay has been internationally validated in more than 2000 patients²³ and among node-negative lesions smaller than 2 cm,²⁴ and validated prospectively.²⁵ It provides a prognostic risk assessment of mortality after surgical resection of a nonsquamous NSCLC. Its predictive accuracy in identifying patients with early-stage disease, even stage IA, who benefit from platinum-based adjuvant chemotherapy has been demonstrated prospectively.²⁶ An international, prospective, randomized clinical trial is currently enrolling patients to further support these findings.

IMPORTANT NOTES RELATED TO ADJUVANT THERAPY

Changes in the Staging System

Changes in staging nomenclature should not be used to justify changes in the adjuvant therapy approach. Because the stage classification system is continually updated, changing from the eighth to ninth to tenth editions of the AJCC staging manual, patients may appear to change their staging designation overnight. For example, a patient with a 4.1-cm T2aN0M0 (stage IB) tumor under the seventh edition is upstaged to a 4.1-cm T2bN0M0 (stage IIA) tumor using the eighth edition. If a patient's stage designation changes from one for which you would not administer chemotherapy to one for which you would, this change in stage designation should not be used to justify a change in management.²⁷

Try to Understand the “Driver of the Patient’s Demise”

For many patients with lung cancer, there are multiple competing risks to their survival relating to their recently resected cancer, including risk recurrence, other cancers, and health concerns unrelated to cancer. We have recently shown that the benefit of a lobectomy over a wedge resection diminishes considerably among patients with shorter life expectancy due to age and comorbidities.²⁸ The decision for adjuvant chemotherapy may be heavily influenced by their potential to survive long enough to derive a benefit from additional therapy. In addition, it is critical to understand the goals of care for each individual patient and not assume that all patients who might obtain a small theoretical survival benefit are willing to undergo adjuvant treatments. In our experience, many older patients and those

with poor functional status favor observation if the anticipated benefit from adjuvant chemotherapy is small.

CONCLUSIONS

The appropriate selection of patients with early-stage NSCLC for adjuvant chemotherapy after complete surgical resection remains a challenge with conflicting trial data. Currently, there are no data to support the use of adjuvant chemotherapy among unselected patients with stage IA. Patients with stage IB and IIA with high-risk pathologic features are likely to obtain a benefit from adjuvant chemotherapy, but the decision should follow a thoughtful discussion with consideration for the individual patient's preferences. More sophisticated guidelines for what constitutes high-risk pathology, perhaps based on tumor genetics or molecular markers, are needed. The role of targeted therapies and immunotherapy in the adjuvant setting remains investigational and would be to supplement and not to replace adjuvant platinum-based chemotherapy.

Conflict of Interest Statement

The authors reported no conflicts of interest.

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