


# A phase II study of cisplatin plus vinorelbine combined with atezolizumab as adjuvant therapy for completely resected non-small-cell lung cancer with *EGFR* mutation (West Japan Oncology Group 11719L/ADJUST study)

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## Abstract

**Background:** Epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) is a standard treatment in *EGFR*-mutated advanced non-small-cell lung cancer (NSCLC); however, previous data have suggested that EGFR-TKI has limited potential as adjuvant therapy. On the contrary, based on subset analysis with the immune checkpoint inhibitor (ICI) plus platinum-doublet chemotherapy in advanced NSCLC with *EGFR* mutation, we hypothesized that this combination was worth testing as adjuvant therapy in patients with *EGFR*-mutated NSCLC.

**Methods:** Herein, we introduce our phase II study of cisplatin plus vinorelbine combined with atezolizumab as adjuvant therapy for completely resected NSCLC with *EGFR* mutation. Accrued patients will be pathological stage II–IIIA with completely resected NSCLC and whose tumors have *EGFR* mutation. Treatment comprises four cycles of cisplatin plus vinorelbine combined with atezolizumab followed by maintenance with atezolizumab. The primary endpoint is the disease-free survival (DFS) rate at 2 years. Secondary endpoints are DFS, overall survival, and safety. In total, 18 patients will be enrolled in this study.

**Discussion:** Ongoing phase III trials of adjuvant ICI allow the inclusion of patients with *EGFR* mutation, but our current trial will provide the earliest clinical data on the efficacy of platinum-doublet chemotherapy with atezolizumab.

**Keywords:** adjuvant chemotherapy, atezolizumab, cisplatin, *EGFR* mutation, vinorelbine

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## Introduction

Epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) is the standard treatment in patients with *EGFR*-mutated advanced non-small-cell lung cancer (NSCLC).<sup>1</sup> Recently, there has been increasing interest over the benefit of EGFR-TKI in patients with early stage NSCLC. Phase III trials compared EGFR-TKI as adjuvant therapy with platinum-doublet

chemotherapy in patients with completely resected NSCLC with *EGFR* mutation.<sup>2</sup> Although disease-free survival (DFS) in the EGFR-TKI group was significantly longer than that in the chemotherapy group, the overall survival (OS) showed no significant difference. Moreover, whether adjuvant EGFR-TKI therapy is effective in this population is controversial. Therefore, the current standard treatment in this

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population is still platinum-doublet chemotherapy, regardless of *EGFR* mutation status.

Immune-checkpoint inhibitors (ICIs), such as anti-programmed cell death 1 (PD-1) or programmed death ligand 1 (PD-L1) antibody, showed favorable antitumor activities for the treatment of advanced NSCLC.<sup>3</sup> However, a meta-analysis, which compared anti-PD-1/PD-L1 antibody with docetaxel, reported that *EGFR*-mutated NSCLC was less likely to be sensitive to ICI than *EGFR* wild-type NSCLC.<sup>4</sup> IMpower150 is a phase III trial that compared the combination of atezolizumab plus platinum-doublet chemotherapy plus bevacizumab with platinum-doublet chemotherapy plus bevacizumab in advanced nonsquamous NSCLC.<sup>5</sup> In addition, subgroup analysis in patients with *EGFR*-mutated NSCLC demonstrated that platinum-doublet chemotherapy plus atezolizumab in *EGFR*-mutated NSCLC had longer progression-free survival (PFS) than chemotherapy [median PFS, 10.2 months *versus* 6.9 months; hazard ratio (HR), 0.61; 95% confidence interval, 0.36–1.03].<sup>6</sup> Based on these backgrounds, we hypothesized that the combination of platinum-doublet chemotherapy and atezolizumab could potentially improve the cure rate in patients with completely resected NSCLC with *EGFR* mutation.

### Study protocol

This study aims to investigate the efficacy of cisplatin plus vinorelbine combined with atezolizumab as adjuvant therapy for patients with completely resected NSCLC with *EGFR* mutation. It is a multicenter, single-arm prospective, phase II study. Figure 1 summarizes the study design.

The primary endpoint is the DFS rate at 2 years. Secondary endpoints are DFS, OS, and safety.

Patients who fulfill all the inclusion criteria will be included, whereas those who meet the exclusion criteria will be excluded. The key inclusion criteria are: (a) patients who have complete resection within 21–56 days of registration; (b) patients with a pathologically confirmed tumor of stage II-IIIa NSCLC with *EGFR* mutation (exon 19 deletion or exon 21 Leu858Arg); (c) patients aged  $\geq 20$  years; (d) patients with Eastern Cooperative Oncology Group performance status of 0 to 1; (e) patients with adequate organ function. The key exclusion criteria are: (a) any

history of malignancy in the past 5 years; (b) any history of autoimmune disease (patients who have controlled thyroid dysfunction or skin disease that does not require systemic therapy are eligible); (c) interstitial lung disease based on chest computed tomography (CT); (d) positive for human immunodeficiency virus, hepatitis B virus antigen, or hepatitis C virus RNA; (e) history of active infection within 14 days of registration; (f) history of taking corticosteroid or other immunosuppressive drugs within 14 days of registration.

### Treatment

Patients will be administered cisplatin (80 mg/m<sup>2</sup> intravenously on day 1), vinorelbine (25 mg/m<sup>2</sup> intravenously on days 1 and 8), and atezolizumab (1200 mg/body intravenously on day 1) every 3 weeks for four cycles. Thereafter, patients will be administered atezolizumab monotherapy (1200 mg/body intravenously every 3 weeks for 1 year), until relapse, or unacceptable toxicity.

### Follow up and assessment

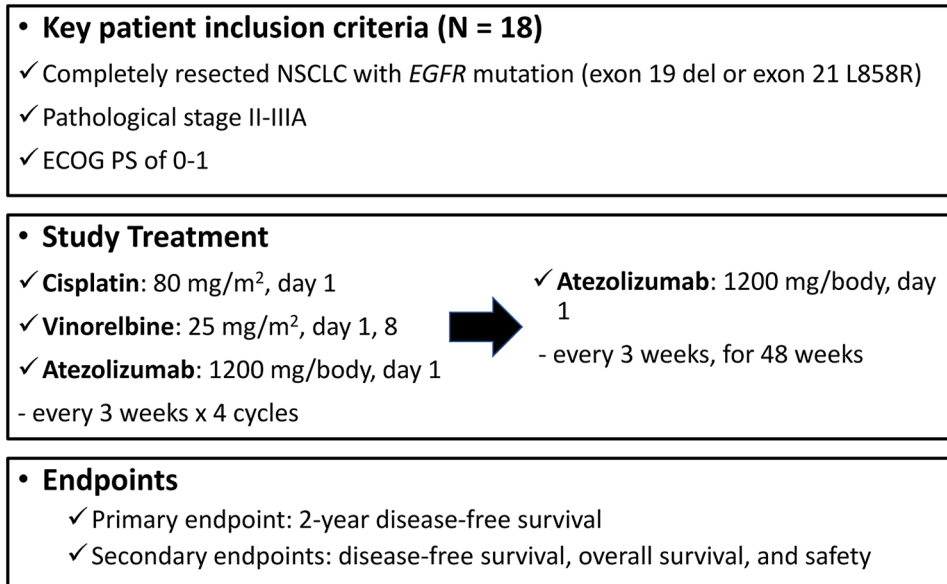
To assess efficacy, chest and abdominal CT will be performed every 6 months. Magnetic resonance imaging or CT of the brain will be performed at 2 years from registration. Adverse events will be graded using the Common Terminology Criteria for Adverse Events, Version 5.0.

### Statistical analysis

In advanced NSCLC, platinum-doublet chemotherapy with atezolizumab that marked an HR of 0.37–0.94 in the PFS was compared with platinum-doublet chemotherapy. Thus, the sample size for this study was calculated based on the hypothesis that the HR of cisplatin plus vinorelbine combined with atezolizumab will achieve 55% improvement in DFS over cisplatin plus vinorelbine. A total of 16 eligible patients are required to ensure a statistical power of 0.80 at a one-sided  $\alpha$ -error of 0.10. Assuming a drop-out rate of 12%, 18 patients need to be enrolled in this study.

### Ethical considerations

The study will be conducted in compliance with the principles of the Declaration of Helsinki, and the Wakayama Medical University Institutional Review Board approved this protocol on 2 July 2019 (approval number: 1-01008A). This clinical trial was registered in the Japic Clinical Trials



**Figure 1.** Study design.

ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor.

Information, Japan (protocol identification no. JapicCTI-194849). Written informed consent will be obtained from all patients before any screening or inclusion procedures.

## Discussion

To develop novel adjuvant treatment among patients with *EGFR*-mutated NSCLC who underwent complete resection, *EGFR*-TKI was tested in clinical trials. Previously, first-generation *EGFR*-TKI as adjuvant therapy did not show prolongation of OS compared with platinum-doublet chemotherapy despite prolongation of DFS.<sup>2,7</sup> The recent phase III trial compared osimertinib with placebo in patients with completely resected NSCLC with *EGFR* mutation and showed a significant prolongation of DFS compared with placebo (HR, 0.17).<sup>8</sup> However, as their median follow up was just 22.1 months, it cannot be known if *EGFR*-TKI can induce cure in this population. Therefore, various strategies besides *EGFR*-TKI need to be considered in this population.

Among patients with metastatic NSCLC with *EGFR* mutation, subgroup analysis of the IMpower150 trial suggested the efficacy of adding ICIs to chemotherapy, whereas subgroup analysis of another phase III trial (IMpower130) did not show prolongation of PFS in the atezolizumab arm.<sup>6,9</sup> As both were small sample-sized subgroup analyses, it is not possible to draw any definite

conclusions. Furthermore, preclinical study justified the use of ICI in early stage NSCLC because completely resected tumors have a lower tumor burden and different microenvironment compared with the metastatic setting.<sup>10</sup>

The necessity for the addition of anti-angiogenic antibody is another debatable issue. Although the quadrat regimen (platinum-doublet chemotherapy + bevacizumab + atezolizumab) showed the most promising efficacy in metastatic NSCLC (IMpower 150 trial), the pivotal adjuvant phase III trial (E1505) failed to demonstrate the benefit of adding bevacizumab to platinum-doublet chemotherapy and it increased toxicity.<sup>11</sup> Therefore, we are determined to avoid the addition of bevacizumab in our trial.

## Conclusion

Ongoing phase III trials of adjuvant ICI allow the inclusion of patients with *EGFR* mutation, but our current trial will provide the earliest clinical data on the efficacy of platinum-doublet chemotherapy with atezolizumab. Thus, the current trial for completely resected NSCLC with *EGFR* mutation will provide a solution for an important clinical question.

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### Author contributions

RS, HA, and NY were involved in the study conception and design. RS, HA, KY, and NY will be involved in the analysis and interpretation of the data. All authors have read and approved the final manuscript.

### Availability of data and material

All data generated or analyzed during this study are included in this published article.

### Conflict of interest statement

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