A Randomized Phase 2 Study Comparing Nivolumab with Carboplatin-Pemetrexed for
EGFR-Mutated NSCLC with Resistance to EGFR Tyrosine Kinase Inhibitors
(WJOG8515L)

Hidetoshi Hayashi,¹ Shunichi Sugawara,² Yasushi Fukuda,³ Daichi Fujimoto,⁴ Satoru Miura,⁵
Keiichi Ota,⁶ Yuichi Ozawa,⁷ Satoshi Hara,⁸ Junko Tanizaki,⁹ Koichi Azuma,¹⁰ Shota Omori,¹¹
Motoko Tachihara,¹² Kazumi Nishino,¹³ Akihiro Bessho,¹⁴ Yasutaka Chiba,¹⁵ Koji Haratani,¹
Kazuko Sakai,¹⁶ Kazuto Nishio,¹⁶ Nobuyuki Yamamoto,⁷ Kazuhiko Nakagawa¹

¹Department of Medical Oncology, Kindai University Faculty of Medicine, 377-2 Ohno-
higashi, Osaka-Sayama, Osaka 589-8511, Japan
²Department of Pulmonary Medicine, Sendai Kousei Hospital, 4-15 Hirose-machi, Aoba-ku,
Sendai, Miyagi 980-0873, Japan
³Department of Respiratory Medicine, Kurashiki Central Hospital, 1-1-1 Miwa, Kurashiki,
Okayama 710-8602, Japan
⁴Department of Respiratory Medicine, Kobe City Medical Center General Hospital,
2-1-1 Minatojima-Minamimachi, Chuo-ku, Kobe, Hyogo 650-0047, Japan
⁵Department of Internal Medicine, Niigata Cancer Center Hospital, 2-15-3 Kawagishi-cho,
Chuo-ku, Niigata, Niigata 951-8566, Japan
⁶Research Institute for Diseases of the Chest, Graduate School of Medical Sciences, Kyushu
University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan
⁷Third Department of Internal Medicine, Wakayama Medical University, 811-1 Kimiidera,
Wakayama 641-8509, Japan
⁸Department of Respiratory Medicine, Itami City Hospital, 1-100 Koyalke, Itami, Hyogo 664-
8540, Japan
⁹Department of Medical Oncology, Kishiwada City Hospital, 1001 Gakuhara, Kishiwada,
Osaka 596-8501, Japan
¹⁰Division of Respirology, Neurology, and Rheumatology, Department of Internal Medicine,
Kurume University School of Medicine, 67 Asahi-machi, Kurume, Fukuoka 830-0011, Japan
¹¹Division of Thoracic Oncology, Shizuoka Cancer Center, 1007 Shimonagakubo,
Nagaizumi-cho, Sunto-gun, Shizuoka 411-8777, Japan
¹²Division of Respiratory Medicine, Department of Internal Medicine, Kobe University
Graduate School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe, Hyogo 650-0017, Japan
¹³Department of Thoracic Oncology, Osaka International Cancer Institute, 3-1-69 Otemae,
Chuo-ku, Osaka 541-8567, Japan
Department of Respiratory Medicine, Japanese Red Cross Okayama Hospital, 2-1-1 Aoe, Kita-ku, Okayama 700-8607, Japan

Clinical Research Center, Kindai University Hospital, 377-2 Ohno-higashi, Osaka-Sayama, Osaka 589-8511, Japan

Department of Genome Biology, Kindai University Faculty of Medicine, 377-2 Ohno-higashi, Osaka-Sayama, Osaka 589-8511, Japan

Running title: Nivolumab for EGFR-Mutated NSCLC with TKI Resistance

Key words: NSCLC, EGFR, Resistance, PD-1, nivolumab

Corresponding author: Dr. Hidetoshi Hayashi, Department of Medical Oncology, Kindai University Faculty of Medicine, 377-2 Ohno-higashi, Osaka-Sayama, Osaka 589-8511, Japan. Tel.: +81-72-366-0221. Fax: +81-72-360-5000. Email: hidet31@med.kindai.ac.jp

Word count for main text: 3804
No. of tables/figures: 2/4

Authors’ Disclosures
LTD., Chugai Pharmaceutical Co. Ltd., Daiichi Sankyo Co. Ltd., Eli Lilly Japan K.K., MSD K.K.,
Novartis Pharmaceuticals K.K., Ono Pharmaceutical Co. Ltd., Taiho Pharmaceutical Co. Ltd. and
Pfizer; YO reports honoraria from Ono Pharmaceutical Co. Ltd.; JT reports honoraria from
AstraZeneca K.K., Boehringer Ingelheim Japan Inc., Bristol-Myers Squibb Co. Ltd., Chugai
Pharmaceutical Co. Eli Lilly Japan K.K., MSD K.K., and Taiho Pharmaceutical Co. Ltd; KA reports
honoraria from AstraZeneca K.K., Bristol-Myers Squibb Co. Ltd., Chugai Pharmaceutical Co. Ltd.,
MSD K.K., and Ono Pharmaceutical Co. Ltd.; SO reports research support from Daiichi Sankyo Co.
Ltd. outside the submitted work as well as honoraria from AstraZeneca K.K., Amgen K.K., Chugai
Pharmaceutical Co. Ltd., Daiichi Sankyo Co. Ltd., Novartis Pharmaceuticals K.K., and Ono
Pharmaceutical Co. Ltd.; MT reports honoraria from Ono Pharmaceutical Co. Ltd.; K Nishino reports
research support from Boehringer Ingelheim Japan Inc., Bristol-Myers Squibb Co. Ltd., and Ono
Pharmaceutical Co. Ltd. outside the submitted work as well as honoraria from AstraZeneca K.K.,
Boehringer Ingelheim Japan Inc., Chugai Pharmaceutical Co. Ltd., Eli Lilly Japan K.K., Merck,
Novartis Pharmaceuticals K.K., Roche Diagnostic, and Pfizer; YC reports honoraria from Chugai
Pharmaceutical Co. Ltd.; AB reports research support from Ono Pharmaceutical Co. Ltd. Outside the
submitted work as well as honoraria from Ono Pharmaceutical Co. Ltd. and Bristol-Myers Squibb Co.
Ltd.; KH reports research support from AstraZeneca K.K., and MSD K.K. outside the submitted work
as well as honoraria from AS ONE Corporation, AstraZeneca K.K., Bristol-Myers Squibb Co. Ltd.,
Chugai Pharmaceutical Co. Ltd., MSD K.K., and Ono Pharmaceutical Co. Ltd.; KS reports from
honoraria from AstraZeneca K.K., Bio-Rad Laboratories, Chugai Pharmaceutical Co. Ltd., Roche
Diagnostics, and Hitachi, Ltd.; K Nishio reports research support from Ono Pharmaceutical Co. Ltd.
and Bristol Myers Squibb Co. Ltd. outside the work, grants from I ignyta Inc., Eli Lilly Japan K.K.,
Boehringer Ingelheim Japan Inc., Korea Otsuka Pharmaceutical Co. Ltd., Thoracic Oncology
Research Group, North East Japan Study Group, Nichirei Biosciences Inc., Osaka-minami hospital as
well as honoraria from Solasia Pharma, Otsuka Pharmaceutical Co. Ltd., Eli Lilly Japan K.K., SymBio
Pharmaceuticals Co. Ltd., Boehringer Ingelheim Japan Inc., Chugai Pharmaceutical Co. Ltd., Eisai
Co. Ltd., Pfizer, Novartis Pharmaceuticals K.K., MSD K.K. Ono Pharmaceutical Co. Ltd., Bristol-Myers
Squibb Co. Ltd., Life Technologies Japan, Yakult Honsha Co. Ltd., Roche Diagnostics, AstraZeneca
K.K., Sanofi K.K., Guardant Health. Inc, Amgen K.K., and Merck Biopharma; NY reports research
support from Ono Pharmaceutical Co. Ltd. and Bristol Myers Squibb Co. Ltd. outside the work,
honoraria from MSD K.K., AstraZeneca K.K., Ono Pharmaceutical Co. Ltd., Thermo Fisher Scientific,
DAIICHI SANKYO CO., LTD., TAIHO PHARMACEUTICAL CO., LTD., Takeda Pharmaceutical CO.,
LTD., Chugai Pharmaceutical CO., LTD., Eli Lilly Japan K.K., Boehringer Ingelheim Japan Inc.,
Novartis Pharmaceuticals K.K., Pfizer Inc., Bristol-Myers Squibb, NIPPON KAYAKU, GlaxoSmithKline
K.K., Sanofi K.K., Hisamitsu Pharmaceutical Co.,Inc., and Merk biopharma, Participation on a Data
Safety Monitoring Board or Advisory Board of Life Technologies Japan Ltd., NIPPON KAYAKU,
Amgen Inc., Guardant Health Japan, and Janssen Pharmaceutical K.K. as well as Leadership or
Translational Relevance

This first randomized phase 2 study for nivolumab versus standard cytotoxic chemotherapy in patients with metastatic *EGFR*-mutated non–small cell lung cancer previously treated with *EGFR* tyrosine kinase inhibitors found no survival benefit of nivolumab therapy. Gene expression profiling identified some patients with a favorable tumor immune microenvironment that was associated with nivolumab efficacy.
ABSTRACT

Purpose: Although the efficacy of programmed cell death–1 (PD-1) blockade is generally poor for non–small cell lung cancer (NSCLC) with activating mutations of the epidermal growth factor receptor (EGFR) gene, EGFR tyrosine kinase inhibitors (TKIs) may improve the tumor immune microenvironment. We performed a randomized study to assess whether nivolumab improves outcome compared with chemotherapy in such patients previously treated with EGFR-TKIs.

Patients and Methods: Patients with EGFR-mutated NSCLC who acquired EGFR-TKI resistance not due to a secondary T790M mutation of EGFR were randomized 1:1 to nivolumab (n=52) or carboplatin-pemetrexed (n=50). The primary endpoint was progression-free survival (PFS).

Results: Median PFS and 1-year PFS probability were 1.7 months and 9.6% for nivolumab versus 5.6 months and 14.0% for carboplatin-pemetrexed [log-rank \(P < 0.01\); hazard ratio (HR) of 1.92, with a 60% confidence interval (CI) of 1.61–2.29]. Overall survival was 20.7 and 19.9 months [HR = 0.88 (95% CI, 0.53-1.47)], and response rate was 9.6% and 36.0% for nivolumab and carboplatin-pemetrexed, respectively. No subgroup including patients with a high tumor mutation burden showed a substantially longer PFS with nivolumab than with carboplatin-pemetrexed. The T cell–inflamed gene expression profile score (0.11 versus –0.17, \(P = 0.036\)) and expression of genes related to cytotoxic T lymphocytes or their recruitment were higher in tumors that showed a benefit from nivolumab.

Conclusions: Nivolumab did not confer a longer PFS compared with carboplatin-pemetrexed in the study patients. Gene expression profiling identified some cases with a favorable tumor immune microenvironment that was associated with nivolumab efficacy.

Clinical trial registration: UMIN000001919/jRCTs051180133
Introduction

Non–small cell lung cancer (NSCLC) is the most common cause of death from cancer worldwide (1). Treatment for advanced NSCLC depends on the molecular characteristics of the tumor. Mutations of the epidermal growth factor receptor (EGFR) gene are present in ~32% of Asians and ~7% of individuals of other ethnic groups with NSCLC, with deletions in exon 19 and an L858R point mutation in exon 21 accounting for ~90% of such genetic alterations detected at diagnosis (2).

In patients with advanced or recurrent EGFR mutated NSCLC, EGFR tyrosine kinase inhibitors (TKIs) are considered the standard initial treatment based on their demonstrated definite benefit (3,4). Eventually, all treated patients develop resistance to EGFR-TKIs, due to several types of resistance pattern including a T790M secondary mutation of EGFR (5). Third-generation EGFR-TKIs such as osimertinib have been found to confer a survival benefit compared with cytotoxic chemotherapy in T790M-positive (6). Additionally, osimertinib provided significantly longer PFS and OS compared with standard EGFR-TKIs in the overall population (7,8).

Cancer immunotherapy including the administration of immune checkpoint inhibitors (ICIs) has markedly changed the treatment paradigm for NSCLC. Programmed cell death–1 (PD-1) and its ligands, PD-L1, a receptor expressed on the surface of activated T and B cells (9), play an important suppressive role in the immune system by preventing the activation of T cells (10-12). Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody to PD-1 that inhibits its binding to PD-L1. Based on the clinical trial results (13-15), ICIs have emerged as a standard of care for advanced NSCLC without oncogenic driver mutations.

Subgroup analysis of such clinical trials has suggested that inhibition of the PD-1–PD-L1 axis is less effective in patients positive for EGFR mutations than in those wild type for EGFR (16). However, cases of EGFR mutation–positive lung cancer are diverse, with some likely to benefit from ICI treatment. Our previous findings have suggested that subgroups of EGFR-mutated NSCLC patients—such as those with tumors that are positive for PD-L1, that have a high tumor mutation burden (TMB), or that have acquired resistance to EGFR-TKIs by a mechanism other than development of the T790M mutation—indeed achieve a benefit from treatment with ICIs (17). We also recently showed that EGFR-TKI treatment was associated with an increase in both PD-L1 expression on tumor cells and TMB, suggesting that such treatment induces changes in the tumor immune microenvironment of EGFR-mutated NSCLC that might increase the efficacy of subsequent ICI therapy (18). We have therefore now performed a randomized phase 2 trial to evaluate the efficacy and safety of nivolumab compared with the combination of carboplatin and pemetrexed as a standard cytotoxic chemotherapy for patients with EGFR-mutated NSCLC who develop T790M-independent resistance to EGFR-TKIs.
Patients and Methods

Study design

This prospective, randomized phase 2 trial (jRCTs051180133, WJOG8515L) was performed at 37 sites of West Japan Oncology Group (WJOG). The full study protocol is available in appendix materials. As previously described (19), patients were randomly assigned on a 1:1 basis to receive nivolumab in an experimental arm or to receive the combination of carboplatin and pemetrexed in a control arm. Random assignment was stratified according to (1) institution, (2) smoking history (current or former versus never), (3) history of treatment with a third-generation EGFR-TKI (yes versus no), (4) progression-free survival (PFS) for previous EGFR-TKI therapy as an initial treatment (≥270 versus <270 days), and (5) age (≥75 versus <75 years old).

Patients

Eligibility criteria included a histologically confirmed diagnosis of locally advanced, metastatic, or recurrent nonsquamous NSCLC positive for an activating mutation of EGFR—including L858R, an exon-19 deletion, G719X, L861Q, or S768I—as well as no previous systemic therapy other than EGFR-TKI treatment for advanced disease. At the time the study was launched, patients who developed resistance after treatment with a first- or second-generation EGFR-TKI but who were negative for T790M were included. The protocol was subsequently amended, however, to include patients with T790M-positive tumors after such treatment who developed resistance after subsequent therapy with a third-generation EGFR-TKI or those who developed resistance after initial treatment with a third-generation EGFR-TKI, according to a shift in the standard of care for EGFR-TKI treatment of EGFR-mutated NSCLC. All patients had measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Additional eligibility criteria included an Eastern Cooperative Oncology Group performance status of 0 or 1, no symptomatic brain metastasis, and adequate organ function. Patients were excluded if they had contraindications for nivolumab. The study protocol was approved by the institutional review board at central certified review board of Wakayama Medical University, and the study was conducted in accordance with the provisions of the Declaration of Helsinki. All patients provided written informed consent before study entry.

Study treatment

Patients in the experimental arm received nivolumab (3 mg/kg) on day 1 every 2 weeks until disease progression or the development of unacceptable toxicity. Those in the control group
received pemetrexed at 500 mg/m² and carboplatin at an area under the curve of 6 mg/mL per minute on day 1 every 3 weeks for four cycles followed by optional indefinite pemetrexed maintenance therapy, with the exception that older patients (≥75 years of age) received carboplatin at an area under the curve of 5 mg/mL per minute, as previously described (20,21).

**Evaluation of response and safety**

A computed tomography or magnetic resonance imaging scan of the brain, computed tomography scans of the chest and abdomen, a bone scan or positron emission tomography scan, and an electrocardiogram were required before initiation of study treatment. Patients underwent tumor assessment at baseline, every 6 weeks during the first 12 months, and every 12 weeks thereafter. Tumor response was evaluated in accordance with RECIST (version 1.1). PFS was defined as the time from enrollment to the date of confirmation of progressive disease or the date of death from any cause (whichever occurs earlier). Overall survival (OS) was defined as the time from enrollment until death from any cause. Duration of response was defined as the time from the date a confirmed response is detected to the date of confirmation of progressive disease or the date of death from any cause (whichever occurs earlier). Adverse events (AEs) were recorded on the basis of the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0).

**Statistical analysis**

Analysis of efficacy was performed with the intent-to-treat population. The purpose of the primary analysis was to test the hypothesis that nivolumab is superior to carboplatin-pemetrexed with regard to PFS. The expected 1-year PFS probability for patients with EGFR-mutated NSCLC who receive standard platinum-pemetrexed chemotherapy is 10% on the basis of a Japanese phase 2 clinical trial of the combination of carboplatin and pemetrexed (22). A sample size of 94 patients, 47 per arm, was determined to provide 80% power (at an overall one-sided 20% significance level) for detection of an increase in 1-year PFS probability from 10% in the control arm to 20% in the experimental arm. Allowing for protocol deviation in 5% of patients, we planned the total number of patients as 50 per arm.

Secondary end points included OS, objective response rate (ORR), duration of response, safety, as well as OS and PFS according to PD-L1 expression. Both OS and PFS were estimated with the Kaplan-Meier method and were compared between arms with the stratified log-rank test and with (1) institution, (2) smoking history, (3) history of treatment with a third-generation EGFR-TKI, (4) PFS for initial EGFR-TKI treatment (≥270 versus <270 days), and (5) age (≥75 versus <75 years old) as stratification factors. Hazard ratios (HRs) were derived with stratified Cox proportional hazard (PH) models. Subgroup analysis of OS
and PFS was performed with unstratified Cox regression models. ORR and the disease control rate were compared between arms. For the primary analysis of PFS, a one-sided \( P \) value was calculated, with a significance level of 0.20, and both 60% and 95% confidence intervals (CIs) were estimated for HR. For subgroup analysis and other end points, only 95% CIs were estimated and calculated \( P \) values were two-sided, with the significance level being undefined. Statistical analysis was performed with SAS (version 9.4), SPSS version 25 (IBM), and GraphPad Prism version 9 (GraphPad) software.

**Assessment of tumor immune characteristics**

Protocols for immunohistochemistry of PD-L1 and assessment of TMB and immune-related gene expression profile (GEP) are described in Supplementary Patients and Methods.

**Results**

**Patient characteristics**

Between April 2016 and June 2019, 102 patients were enrolled and randomized. Patient flow is summarized in Figure 1, and the trial scheme is summarized in Supplementary Figure S1. Although age was significantly higher in the nivolumab arm (\( P = 0.023 \), Mann-Whitney test), demographic characteristics were otherwise well balanced between the two arms of the study (Table 1). PD-L1 expression on tumor cells was evaluated for 37 patients in the nivolumab arm and 40 patients in the carboplatin-pemetrexed arm.

**Efficacy**

The data cutoff date for the efficacy analysis was 30 June 2020. Median follow-up time was 25.5 months (range, 0.1–46.1 months) for the nivolumab arm and 23.4 months (range, 1.6–48.0 months) for the carboplatin-pemetrexed arm. At the cutoff date, there were 49 (94.2%) patients in the nivolumab arm with an event (progressive disease or death), compared with 48 (96.0%) patients in the carboplatin-pemetrexed arm. Median PFS was 1.7 months (95% CI, 1.3–2.3 months) and 5.6 months (95% CI, 3.2–6.8 months) in the nivolumab and carboplatin-pemetrexed arms, respectively (stratified log-rank test \( P = 0.001 \); stratified Cox PH model HR of 1.92, with a 60% CI of 1.61–2.29 and 95% CI of 1.27–2.90), and the study thus did not meet its primary end point (Fig. 2A). The 1-year PFS probability was 9.6% and 14.0% in the nivolumab and carboplatin-pemetrexed arms, respectively. No definite benefit of nivolumab with regard to PFS was apparent in any patient subset, including those based on PD-L1 tumor proportion score (TPS) or TKI resistance pattern (Fig. 2B, Supplementary Fig. S2–S5).

Median OS was 20.7 months (95% CI, 15.2–28.0 months) and 19.9 months (95% CI,
12.2–22.6 months) in the nivolumab and carboplatin-pemetrexed arms, respectively (stratified log-rank test \( P = 0.517 \); stratified Cox PH model HR of 0.884, with a 95% CI of 0.53–1.47) (Fig. 2C). No subgroup showed an obvious difference in OS between nivolumab and carboplatin-pemetrexed (Supplementary Fig. S6). Details of treatment after disease progression during trial therapy are shown in Supplementary Table S1. Among the 52 patients in the nivolumab arm, 5 patients (9.6%) had a partial response, 15 patients (28.8%) stable disease, and 30 patients (57.7%) progressive disease as their best overall response and 2 patients were not evaluable, whereas one patient (2.0%) had a complete response, 17 patients (34.0%) a partial response, 20 patients (40.0%) stable disease, and 12 patients (24.0%) progressive disease in the carboplatin-pemetrexed arm (\( n = 50 \)). The ORR was thus 9.6% and 36.0% in the nivolumab and carboplatin-pemetrexed arms, respectively, and the median duration of response was similar for nivolumab and carboplatin-pemetrexed [5.3 months (95% CI, 4.6 months to not reached) versus 5.5 months (95% CI, 2.9–8.0 months), respectively; HR of 0.42 (95% CI, 0.12–1.48)] (Supplementary Fig. S7 and S8).

Safety

AEs related to study treatment occurred in 60.8% (grade 3–5, 9.8%) and 82.0% (grade 3–5, 12.0%) of patients in the nivolumab and carboplatin-pemetrexed arms, respectively (Table 2). The most common AEs of grade 3 or 4 were fatigue and skin toxicity (3.8% each) in the nivolumab arm and neutropenia (32.0%), anemia (28.0%), leukopenia (22.0%), and thrombocytopenia (16.0%) in the carboplatin-pemetrexed arm. Serious AEs were observed in 25.5% and 16.0% of patients in the nivolumab and carboplatin-pemetrexed arms, respectively. Treatment discontinuation due to AEs occurred in 3 patients in the nivolumab arm (2 with arthritis and 1 with bilirubin increased) and 7 patients in the carboplatin-pemetrexed arm (2 each with renal failure and hepatic dysfunction as well as 1 each with anaphylactic shock, severe fatigue, and thromboembolism). There was 1 case of treatment-related interstitial lung disease (ILD) of grade 1 in the nivolumab arm. Treatment-related death was not apparent in either arm.

TMB

To investigate the relation of TMB or specific oncogenic mutations to nivolumab efficacy, we performed targeted sequencing for 50 patients (28 in the nivolumab arm and 22 in the carboplatin-pemetrexed arm). The overall results are shown in Figure 3. The most common genetic alterations were in TP53 [12 patients (24.0%)], MET [5 patients (10.0%)], and RB1, PIK3CA, ERBB4, and SMAD4 [2 patients each (4.0%)], and the median TMB was 6.2 mutations/Mb. Consistent with previous findings (23), TMB tended to be higher in patients without (\( n = 36 \)) than in those with (\( n = 14 \)) the T790M mutation (7.0 versus 5.6...
mutations/Mb). There was no significant difference in PFS between nivolumab and carboplatin-pemetrexed for patients with a high or low TMB (with the median as cutoff) (Supplementary Fig. S9).

Immune-related GEP
To investigate the role of the immunologic phenotype of the tumor microenvironment in the response to nivolumab in EGFR-mutated NSCLC, we performed immune-related gene expression analysis for tumor samples from 27 and 28 patients in the nivolumab and carboplatin-pemetrexed arms, respectively. Among the 27 patients treated with nivolumab, those \( (n = 6) \) with a durable clinical benefit (DCB), defined as a PFS of >6 months, showed a higher T cell–inflamed GEP score than did those \( (n = 21) \) with no clinical benefit (NCB), with mean (95% CI) values of 0.11 (0.06–0.15) and –0.17 (–0.16 to –0.18), respectively (Mann-Whitney test, \( P = 0.036 \)) (Fig. 4A), implicating immune phenotype as a determinant of nivolumab efficacy in the study population. To identify immune cell types associated with nivolumab response, we performed an unsupervised clustering analysis for 183 selected genes. Hierarchical clustering for the 27 nivolumab-treated and 28 carboplatin-pemetrexed–treated patients is shown in Figure 4B and Supplementary Figure S10, respectively.

Whereas no clear association was apparent between clusters of cases and response to therapy in the carboplatin-pemetrexed arm, nivolumab-treated patients with a longer PFS tended to be present in neighboring clusters. On the basis of this hierarchical clustering for the 27 nivolumab-treated patients, we selected two gene subclusters that were expressed at a higher level in the NCB group (subcluster 1) or in the DCB group (subcluster 2) (Fig. 4B). Genes for receptor tyrosine kinases (such as \( \text{ERBB2} \) and \( \text{EGFR} \)) and their downstream signaling molecules (such as \( \text{STAT3} \) and \( \text{AKT1} \)) as well as genes for angiogenesis-related factors (such as \( \text{HIF1A} \) and \( \text{VEGFA} \)) were included in subcluster 1. In contrast, subcluster 2 contained \( \text{CD8} \), genes for cytolytic molecules expressed in cytotoxic T cells and natural killer cells (such as \( \text{GZMA} \) and \( \text{PRF1} \)), as well those for costimulatory molecules including \( \text{PDCD1} \) (encoding PD-1), \( \text{PDCD1LG2} \) (encoding PD-L2), and \( \text{LAG3} \). In addition, genes corresponding to a lymphoid compartment pathway tended to be expressed at a higher level in the DCB group than in the NCB group (Supplementary Fig. S11).

We also performed single-gene analysis with the 27 specimens from nivolumab-treated patients (Fig. 4C, Supplementary Fig. S12). The expression of genes for chemokines related to recruitment of \( \text{CD8}^+ \) T cells (\( \text{CXCL9} \) and \( \text{CXCL10} \)) (24) as well as that of \( \text{GZMA} \) was up-regulated in the DCB group, whereas that of genes related to epithelial-mesenchymal transition, especially of cancer-associated fibroblasts (such as \( \text{ITGB3} \), \( \text{ITGA2} \), \( \text{MMP7} \), and \( \text{CD36} \)) (25), was up-regulated in the NCB group.

Finally, to explore the mechanism underlying the general lack of response to
nivolumab in EGFR mutation–positive NSCLC, we examined the relation between the
expression of genes that constitute the T cell–inflamed GEP and that of those related to the
EGFR signaling pathway and EGFR-TKI resistance with the use of all 55 specimens from
the study patients (Fig. 4D). Whereas genes related to cytotoxic T lymphocytes,
chemokines, and cell-mediated cytotoxicity were strongly correlated with each other, those
for receptor tyrosine kinases and downstream signaling proteins were negatively correlated
with the immune modulatory genes.

Discussion
In the present randomized study, we have evaluated the efficacy of nivolumab relative to that
of platinum-doublet chemotherapy in EGFR-mutated NSCLC patients who developed EGFR-
TKI resistance mediated by various mechanisms. Our results show that PFS for nivolumab
was inferior to that for the standard cytotoxic chemotherapy in these patients.

At the time the present study was designed, the efficacy of ICIs for EGFR mutation–
positive NSCLC was uncertain. Meta-analysis for subgroups of prior phase 3 trials had
revealed a lower efficacy of PD-1/PD-L1 inhibitor treatment for EGFR-mutated NSCLC
compared with EGFR–wild type NSCLC, but the OS inferiority for such treatment compared
with cytotoxic chemotherapy was still not clear, with little detailed efficacy information,
including results for long-term efficacy outcome, having been reported (26). Our present
data, obtained with a randomized study design, provide more reliable evidence to support
the notion that, in general, ICI monotherapy does not confer a clinical benefit for patients
with EGFR mutation–positive NSCLC. A small phase 2 trial that investigated the efficacy of
the PD-1–targeted antibody pembrolizumab in EGFR-TKI–naïve patients with EGFR-
mutated NSCLC did not detect a response or achieve sustained duration of treatment for >1
year, even though it was restricted to patients with a high PD-L1 TPS (≥50%) (27). In the
present study, which was performed with EGFR-TKI–treated patients, 5 out of 52 patients
(9.6%) treated with nivolumab achieved a PFS of >1 year. Randomized controlled trials of
cytotoxic chemotherapy combined with an antibody to PD-1 for EGFR mutation–positive
NSCLC are currently ongoing (NCT02864251 and NCT03515837). Given that combination
treatment with an antibody to PD-L1 and cytotoxic chemotherapy confers prolonged survival
and has become the standard of care for patients with extensive-stage small cell lung cancer
(28), for which PD-1/PD-L1 inhibitors alone show a 1-year PFS probability of only ~10% (29),
the potential for combination treatment with cytotoxic chemotherapy and a PD-1 inhibitor in
patients with EGFR mutation–positive NSCLC remains.

Although the number of cases compared was small, disease control by nivolumab
tended to be more durable for patients who developed T790M-negative resistance to first- or
second-generation EGFR-TKIs or for those who progressed during initial treatment with a
third-generation EGFR-TKI than for those who became resistant to third-generation EGFR-TKI treatment after the initial development of T790M-positive resistance, all of whom showed tumor progression within 3 months (Supplementary Fig. S4). We previously found that T790M mutation–positive NSCLC patients have a poor tumor immune microenvironment and show a poor response to antibodies to PD-1 (17,18), and our present results suggest that this is also the case for T790M-positive patients after subsequent treatment with a third-generation TKI. These observations may be explained in part by the lower TMB of T790M-positive NSCLC compared with T790M-negative tumors (18,23). However, our present results did not detect an association between TMB and nivolumab efficacy, suggesting that other factors might also play a role.

The toxicity of nivolumab in the present study was consistent with previous findings, with the drug being well tolerated. The frequency of ILD was previously found to be 38% in EGFR-mutated NSCLC patients treated concurrently with the PD-L1–targeted antibody durvalumab and osimertinib (30). In addition, EGFR-TKI therapy immediately after PD-1/PD-L1 inhibitor treatment has been associated with a high incidence of ILD (31). Lung toxicity of nivolumab administered after EGFR-TKI treatment was thus a potential concern in the present study. However, only one case of immune-related pneumonitis (of grade 1) was apparent in the nivolumab arm, indicating that the safety of PD-1 inhibition after EGFR-TKI treatment is acceptable.

Studies of various types of cancer including NSCLC have implicated TMB and immune-related gene expression as potential biomarkers for prediction of ICI efficacy (32). Furthermore, characterization of gene expression patterns may identify factors that act to suppress or promote antitumor immunity in EGFR-mutated NSCLC. We have now found that the T cell–inflamed GEP score was significantly higher in patients who benefited from nivolumab therapy, whereas, unexpectedly, no clear association between TMB and nivolumab efficacy was apparent. Of note, analysis of the expression of individual genes and pathway analysis for the lymphoid compartment suggested that cytotoxic T cells and the chemokines that recruit them contribute to an active tumor immune microenvironment in EGFR-mutant NSCLC that may confer nivolumab efficacy in some cases. With regard to the underlying causes of the poor tumor immune microenvironment in most such patients, activation of the EGFR signaling pathway in EGFR mutation–positive NSCLC has been found to result in tumor immune evasion through various mechanisms (33,34). EGFR signaling thus induces down-regulation of the transcription factor IRF1 concurrently with that of its target gene for CXCL10 through the PI3K-AKT signaling pathway (33). We also found that the expression of EGFR and AKT1 showed a weak negative correlation with that of IRF1 in tumor specimens of the study patients. Of interest, genes for angiogenesis-related proteins such as VEGFA and that (NT5E) for CD73, which produces the immunosuppressive
mediator adenosine (35,36), were found in close proximity to EGFR in subcluster 1 of the
hierarchical clustering analysis (Fig. 4B). The combination of agents that target these
molecules with an ICI might thus be a promising treatment approach. However,
individualized treatment strategies will be required given the diverse factors that determine
the immunosuppressive tumor microenvironment in EGFR-mutated NSCLC.

Our trial has several limitations. First, it included patients who became resistant to
EGFR-TKIs at various stages of their treatment and as a result of different mechanisms.
Although randomization yielded a clear negative result overall for the efficacy of nivolumab in
these patients, the small number of subjects may limit the conclusions that can be drawn
from the subgroup and biomarker analyses. Further validation analysis for immune-related
gene expression in an independent data set for EGFR-mutated NSCLC is needed. Second,
PD-L1 expression on tumor cells, which has been established as an important predictive
factor for the efficacy of PD-1–targeted antibodies in NSCLC, was not evaluated in all
patients and could not be used for stratification. And third, tissue specimens subjected to
genetic and pathological analyses were obtained at various times including before and after
EGFR-TKI treatment, which might limit interpretation of the biomarker analysis results.
Nevertheless, our prospective study has important implications for the future development of
immunotherapy in oncogenic driver mutation–positive NSCLC, given that it has shown that,
even among such patients, some individuals possess a favorable tumor immune
microenvironment for a durable response to ICIs.

In conclusion, nivolumab was clearly inferior to standard platinum-combination
chemotherapy with regard to PFS in EGFR-mutated NSCLC patients with acquired EGFR-
TKI resistance. Nevertheless, a small proportion of such patients experienced a longer-term
response to nivolumab, and biomarker analysis identified potential target molecules for
future immunotherapy in this patient population.

Acknowledgments
This study was conducted by WJOG under a funding contract with Ono Pharmaceutical Co.
Ltd. (Osaka, Japan) and Bristol Myers Squibb Co. Ltd. (Tokyo, Japan). We thank the
patients, their families, WJOG data center staff (especially Koji Takeda, Shinichiro
Nakamura, and Seiko Tanaka), and all of the investigators who participated in the study.
References


Table 1. Characteristics of the study patients (n = 102).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nivolumab (n = 52)</th>
<th>Carboplatin-pemetrexed (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>70.5</td>
<td>51–84</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>24</td>
<td>46.2</td>
</tr>
<tr>
<td>Female</td>
<td>28</td>
<td>53.8</td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>29</td>
<td>55.8</td>
</tr>
<tr>
<td>Past or current</td>
<td>23</td>
<td>44.2</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>17</td>
<td>32.7</td>
</tr>
<tr>
<td>1</td>
<td>35</td>
<td>67.3</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIB</td>
<td>2</td>
<td>3.8</td>
</tr>
<tr>
<td>IV</td>
<td>41</td>
<td>78.8</td>
</tr>
<tr>
<td>Postoperative recurrence</td>
<td>9</td>
<td>17.3</td>
</tr>
<tr>
<td>Metastatic sites</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td>18</td>
<td>34.6</td>
</tr>
<tr>
<td>Treated with radiotherapy</td>
<td>7</td>
<td>13.5</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>52</td>
<td>100</td>
</tr>
<tr>
<td>EGFR mutation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exon-21 L858R</td>
<td>28</td>
<td>53.8</td>
</tr>
<tr>
<td>Exon-19 deletion</td>
<td>24&lt;sup&gt;a&lt;/sup&gt;</td>
<td>46.2</td>
</tr>
<tr>
<td>Other</td>
<td>1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.9</td>
</tr>
<tr>
<td>T790M on enrollment in study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>18</td>
<td>34.6</td>
</tr>
<tr>
<td>Negative</td>
<td>34</td>
<td>65.4</td>
</tr>
<tr>
<td>EGFR-TKI as first-line therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gefitinib</td>
<td>16</td>
<td>30.8</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>18</td>
<td>34.6</td>
</tr>
<tr>
<td>Afatinib</td>
<td>11</td>
<td>21.2</td>
</tr>
<tr>
<td>Osimertinib</td>
<td>4</td>
<td>7.7</td>
</tr>
<tr>
<td>Other</td>
<td>2&lt;sup&gt;d&lt;/sup&gt;</td>
<td>3.8</td>
</tr>
<tr>
<td>PFS for first-line EGFR-TKI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥270 days</td>
<td>36</td>
<td>69.2</td>
</tr>
<tr>
<td>&lt;270 days</td>
<td>16</td>
<td>30.8</td>
</tr>
<tr>
<td>PD-L1 TPS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1%</td>
<td>19</td>
<td>36.5</td>
</tr>
<tr>
<td>1–49%</td>
<td>10</td>
<td>19.2</td>
</tr>
<tr>
<td>≥50%</td>
<td>8</td>
<td>15.4</td>
</tr>
<tr>
<td>Unknown</td>
<td>15</td>
<td>28.8</td>
</tr>
</tbody>
</table>
ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; PFS, progression-free survival; PD-L1, programmed cell death–ligand 1; TPS, tumor proportion score.

a One case with two mutations: an exon-19 deletion and L858R.

b Exon-18 G719X plus exon-20 S768I.

c Exon-18 G719X (n = 1) and exon-18 G719S plus exon-21 L861Q (n = 1).

d Investigational EGFR-TKI.
Table 2. Treatment-related adverse events of any grade in ≥10% of patients.

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Nivolumab (n = 52)</th>
<th>Carboplatin-pemetrexed (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Nonhematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>15</td>
<td>28.8</td>
</tr>
<tr>
<td>Skin toxicity</td>
<td>8</td>
<td>15.4</td>
</tr>
<tr>
<td>Anorexia</td>
<td>7</td>
<td>13.5</td>
</tr>
<tr>
<td>ALT increased</td>
<td>6</td>
<td>11.5</td>
</tr>
<tr>
<td>Nausea</td>
<td>6</td>
<td>11.5</td>
</tr>
<tr>
<td>AST increased</td>
<td>4</td>
<td>7.7</td>
</tr>
<tr>
<td>ALP increased</td>
<td>4</td>
<td>7.7</td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC decreased</td>
<td>2</td>
<td>3.8</td>
</tr>
<tr>
<td>Neutrophil decreased</td>
<td>2</td>
<td>3.8</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2</td>
<td>3.8</td>
</tr>
<tr>
<td>Anemia</td>
<td>4</td>
<td>7.7</td>
</tr>
</tbody>
</table>

Adverse events are defined according to MedDRA preferred terms. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; WBC, white blood cell.
**Figure Legends**

**Figure 1.** CONSORT diagram.

**Figure 2.** Efficacy of nivolumab relative to that of carboplatin-pemetrexed. 

A, Kaplan-Meier plots for progression-free survival (PFS) of patients treated with nivolumab or carboplatin-pemetrexed (CbP). CI, confidence interval; HR, hazard ratio. 

B, Forest plots of the hazard ratio for nivolumab versus carboplatin-pemetrexed with regard to PFS in patient subsets. Resistance patterns A, B, and C refer to patients who developed resistance to treatment with a first- or second-generation epidermal growth factor receptor–tyrosine kinase inhibitor (EGFR-TKI) but who were negative for T790M, those with T790M-positive tumors after such treatment and who developed resistance after subsequent therapy with a third-generation EGFR-TKI (3G TKI), and those who developed resistance after initial treatment with a third-generation EGFR-TKI, respectively. PD-L1, programmed cell death–ligand 1; TPS, tumor proportion score; NA, not applicable. 

C, Kaplan-Meier plots for overall survival (OS) of patients treated with nivolumab or carboplatin-pemetrexed.

**Figure 3.** Individual treatment outcome and response for 50 patients with specimens available for analysis of tumor mutation burden (TMB) according to tumor characteristics. Progression-free survival (PFS) and best objective response (CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable) for nivolumab or carboplatin-pemetrexed (CbP) are shown in the top panel. Black arrows indicate ongoing response at data cutoff date. TMB (mutations/Mb) is shown in the middle panel. The distribution of selected gene alterations, smoking status, epidermal growth factor receptor gene (EGFR) mutation type, programmed cell death–ligand 1 (PD-L1) tumor proportion score, PFS for initial EGFR tyrosine kinase inhibitor (TKI) treatment, timing for collection of tumor tissue for analysis (before or after initial EGFR-TKI treatment), and pattern of EGFR-TKI resistance (see legend to Figure 2 for explanation of A, B, and C) are shown in the bottom panel. 3G, third-generation.

**Figure 4.** Immune-related gene expression analysis of tumor specimens. 

A, Dot plots for the T cell–inflamed gene expression profile (GEP) score according to nivolumab efficacy for 27 patients. The mean and standard error of the mean values are also shown, and the P value was determined with the Mann-Whitney test. DCB, durable clinical benefit, defined as a partial response or stable disease lasting >6 months; NCB, no clinical benefit. 

B, Heat map of immune-related gene expression for 27 patients treated with nivolumab (middle panel). Hierarchical clustering of the 27 tumors was performed according to the expression of 183 selected immune-related genes. A dendrogram was generated by clustering, resulting in the identification of several clusters, with two main clusters being designated A and B. The details of two representative subclusters (subclusters 1 and 2) of these two clusters are shown expanded in the bottom panels because of their potential...
importance for a biological explanation of nivolumab efficacy based on their constituent genes. The color scale represents the Z score for the expression of each individual gene, with the highest expression shown in yellow, medium in black, and lowest in blue. Progression-free survival (PFS) and best objective response for nivolumab as well as other patient characteristics are presented in the top panel as in Figure 3. C, Lists of the top 10 and bottom 10 genes whose expression was associated with PFS for nivolumab as revealed by comparison of single-gene expression between DCB and NCB groups (Supplementary Fig. S12). D, Correlation between expression of the 18 genes constituting the T cell–inflamed GEP and that of genes related to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) resistance in 55 patients of the current trial. The color scale indicates Pearson’s correlation coefficient.
Fig. 1

102 Patients randomly assigned

52 Patients assigned to nivolumab
51 Patients received nivolumab
1 Died before initiation of study treatment
1 Ongoing
50 Discontinued
46 Had disease progression
3 Discontinuation due to toxicity
2 Arthritis
1 Bilirubin increased
1 Refusal not due to toxicity

50 Patients assigned to chemotherapy
50 Patients received chemotherapy
1 Ongoing
49 Discontinued
38 Had disease progression
7 Discontinuation due to toxicity
2 Renal failure
2 Hepatic dysfunction
1 Anaphylactic shock
1 Severe fatigue
1 Thromboembolism
4 Refusal
3 Due to toxicity
1 Not due to toxicity
**Fig. 2**

**A**

<table>
<thead>
<tr>
<th>Treatment arm</th>
<th>N</th>
<th>Events</th>
<th>Median (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>52</td>
<td>49</td>
<td>1.7 (1.3 to 2.3)</td>
</tr>
<tr>
<td>CbP</td>
<td>50</td>
<td>48</td>
<td>5.6 (3.2 to 6.8)</td>
</tr>
</tbody>
</table>

HR, 1.92 (60% CI, 1.61 to 2.29; 95% CI, 1.27 to 2.90): Stratified log-rank $P = 0.001$

**B**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nivolumab</th>
<th>CbP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>No. of events</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>No. of patients</td>
<td>28</td>
</tr>
<tr>
<td>Male</td>
<td>No. of events</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>No. of patients</td>
<td>24</td>
</tr>
<tr>
<td>Never smoker</td>
<td>No. of events</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>No. of patients</td>
<td>29</td>
</tr>
<tr>
<td>Current or former smoker</td>
<td>No. of events</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>No. of patients</td>
<td>23</td>
</tr>
<tr>
<td>Age &lt;75 years</td>
<td>No. of events</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>No. of patients</td>
<td>44</td>
</tr>
<tr>
<td>≥75 years</td>
<td>No. of events</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>No. of patients</td>
<td>8</td>
</tr>
<tr>
<td>EGFR-TKI PFS ≥270 days</td>
<td>No. of events</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>No. of patients</td>
<td>36</td>
</tr>
<tr>
<td>&lt;270 days</td>
<td>No. of events</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>No. of patients</td>
<td>16</td>
</tr>
<tr>
<td>EGFR exon-21 L858R</td>
<td>No. of events</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>No. of patients</td>
<td>28</td>
</tr>
<tr>
<td>exon-19 deletion</td>
<td>No. of events</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>No. of patients</td>
<td>24</td>
</tr>
<tr>
<td>other mutations</td>
<td>No. of events</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>No. of patients</td>
<td>NA</td>
</tr>
<tr>
<td>Resistance pattern</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A_T790M negative</td>
<td>No. of events</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>No. of patients</td>
<td>29</td>
</tr>
<tr>
<td>B_3G TKI for T790M</td>
<td>No. of events</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>No. of patients</td>
<td>19</td>
</tr>
<tr>
<td>C_after initial 3G TKI</td>
<td>No. of events</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>No. of patients</td>
<td>4</td>
</tr>
<tr>
<td>Previous radiotherapy</td>
<td>No. of events</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>No. of patients</td>
<td>40</td>
</tr>
<tr>
<td>Brain metastasis</td>
<td>No. of events</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>No. of patients</td>
<td>12</td>
</tr>
<tr>
<td>B</td>
<td>No. of events</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>No. of patients</td>
<td>34</td>
</tr>
<tr>
<td>PD-L1 TPS &lt;1%</td>
<td>No. of events</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>No. of patients</td>
<td>18</td>
</tr>
<tr>
<td>1-49%</td>
<td>No. of events</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>No. of patients</td>
<td>10</td>
</tr>
<tr>
<td>≥50%</td>
<td>No. of events</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>No. of patients</td>
<td>8</td>
</tr>
<tr>
<td>Unknown</td>
<td>No. of events</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>No. of patients</td>
<td>15</td>
</tr>
</tbody>
</table>

HR (95% CI)

Favors nivolumab Favors CbP
Clinical Cancer Research

A Randomized Phase 2 Study Comparing Nivolumab with Carboplatin-Pemetrexed for EGFR-Mutated NSCLC with Resistance to EGFR Tyrosine Kinase Inhibitors (WJOG8515L)

Hidetoshi Hayashi, Shunichi Sugawara, Yasushi Fukuda, et al.

Clin Cancer Res  Published OnlineFirst December 17, 2021.

Updated version
Access the most recent version of this article at:
doi:10.1158/1078-0432.CCR-21-3194

Supplementary Material
Access the most recent supplemental material at:
http://clincancerres.aacrjournals.org/content/suppl/2021/12/17/1078-0432.CCR-21-3194.DC1

Author Manuscript
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, use this link http://clincancerres.aacrjournals.org/content/early/2021/12/16/1078-0432.CCR-21-3194.
Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.