INTRODUCTION

Locally advanced non-small-cell lung cancer (NSCLC) can potentially be cured with platinum-based chemoradiotherapy (CRT). However, most patients show recurrence, with 5-year progression-free survival (PFS) and overall survival (OS) rates of 15% and 20%, respectively. Thus, further development of novel treatment modalities is required to improve treatment outcomes.

The discovery of epidermal growth factor receptor (EGFR) mutations has generated novel targeted therapeutic approaches for advanced disease. Gefitinib, an EGFR-tyrosine kinase inhibitor (EGFR-TKI), yielded a greater PFS advantage over platinum-based chemotherapy. Osimertinib, a third-generation EGFR-TKI, has also shown a significant survival advantage over gefitinib or erlotinib [OS hazard ratio: 0.799 (0.641-0.997)]. Currently, EGFR-TKI is a key agent in EGFR-mutated advanced disease settings. However, the role of EGFR-TKI remains unclear in unresectable, stage III, EGFR-mutant NSCLC. Further confirmatory studies are needed.

Key words: non-small-cell lung cancer, locally advanced setting, chemoradiation, epidermal growth factor receptor inhibitor (EGFR-TKI), radiation pneumonitis grade 3 or treatment-related death did not occur.

Conclusions: This is the first prospective study to demonstrate the favorable efficacy and safety of EGFR-TKI induction followed by standard CRT in EGFR-mutant, stage III NSCLC. Further confirmatory studies are needed.
EGFR mutations can be detected in 17%-30% of patients, particularly those with non-squamous tumors.9,12

Additionally, it is theoretically suggested that as the tumor volume increases, the doubling time may be prolonged and then the percentage of tumor cells in the proliferative phase may decrease.13 In addition, the rate of tumor shrinkage following treatment may depend on the tumor growth rate.13 Therefore, EGFR-mutant tumors might be made more sensitive to subsequent CRT by reducing the tumor volume by initial exposure to EGFR-TKI, a highly sensitive molecularly targeted therapy.

We carried out a phase II trial (clinical trial registration number: UMIN 000005086, https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&recept no=R000006047&type=summary&language=E) to evaluate the efficacy and safety of gefitinib induction followed by standard CRT in patients with unresectable, stage III, EGFR-mutant NSCLC.

PATIENTS AND METHODS

Patient eligibility

The eligibility criteria were previously documented in detail,14,15 including: age ≤74 years; Eastern Cooperative Oncology Group performance status of 0-1; pathologically proven, unresectable, stage IIIA/IIIB diseases with mutated EGFR in exon 19 or 21 but not in exon 20 T790M; and presence of any measurable lesion. The seventh lung cancer TNM (tumor—node—metastasis) classification and staging system was applied for staging. Pathological confirmation of nodal involvement was recommended. Each participant provided written informed consent before the study. This study was conducted in compliance with the principles of the Declaration of Helsinki, with approval from the institutional review boards of all participating institutes [Okayama University Hospital Ethics Committee (approval no. rin1045)].

Treatment

Interventional treatment consisted of induction and CRT phases (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2021.100191). In the induction phase, gefitinib was administered at a dose of 250 mg/day for 8 weeks. Assuming the potential risk of developing EGFR-TKI-related pneumonitis,16,17 sequential administration of gefitinib was designed before CRT to prevent overlapping radiation pneumonitis. We used 8-week administration of gefitinib because this time period is nearly equal to that of neoadjuvant chemotherapy, which is typically composed of two cycles.18

For the CRT phase, CRT treatment was started 2 weeks after completion of the induction phase, under the condition that the disease had not progressed. The regimen consisted of docetaxel 40 mg/m² and cisplatin 40 mg/m² on days 1, 8, 29, and 36, and no additional cycles were planned as consolidative therapy.

Three-dimensional conformal thoracic irradiation was initiated concurrently from day 1 of chemotherapy using a linear accelerator (6-10 MV) in 2-Gy single daily fractions, with a total dose of 60 Gy. The gross tumor volume represented the primary tumor and clinically positive lymph nodes detected in radiological findings at the time of diagnosis. The internal target volume was defined as the area of gross tumor volume and ventilatory motion. The clinical target volume and planning target volume margins were set to 0.5 cm beyond the internal target volume and at least 0.5 cm beyond the clinical target volume, respectively. Regarding the response to gefitinib monotherapy, we allowed the gross tumor volume to decrease if needed. The volume of both lungs exposed to >20 Gy of the total volume of 35% or less was allowed.

We set the early feasibility step (step 1) with the first six registered patients, to assess the feasibility of the interventional treatment throughout the induction and CRT phases. We proceeded to step 2 when any of the following events were observed in ≤2 of the 6 subjects: (i) grade 4 thrombocytopenia or anemia related to the interventional treatment, (ii) grades 3-4 non-hematological toxicity related to the interventional treatment, or (iii) pneumonitis. In step 2, no predefined interim analysis was set, and the same intervention was used to assess efficacy.

Endpoints and statistical analysis

The primary endpoint was set as the 2-year OS rate. Secondary endpoints included the objective response rate (ORR), adverse events, treatment compliance, and PFS. The treatment response was evaluated according to the standard RECIST version 1.1. Toxicity was assessed based on the Common Terminology Criteria for Adverse Events version 4.0. Radiation pneumonitis was assessed during the delayed period until 6 months after completing thoracic radiation as well as during the acute period.

OS and PFS were calculated from the date of registration until the date of death or the patient’s last visit and until the first documented date of disease progression or death, respectively. The survival curve was drawn by the Kaplan—Meier method. Statistical analyses were carried out with SAS version 9.4 (SAS Institute, Cary, NC) and STATA version 11 (StataCorp, College Station, TX).

When assuming a 2-year OS rate as the primary endpoint, historical data should be derived from the effect caused by standard CRT in EGFR-mutant tumors; however, available data were limited to EGFR-mutant tumors. Therefore, we considered the lower limit of interest to be 60% yielded by standard CRT in the EGFR-mutant-unselected population. The additional effect of single-agent gefitinib in the locally advanced setting was expected to be 85% after the original amendment,19 which was based on recent data for a 2-year OS >80% with the addition of gefitinib to platinum, even in the metastatic setting.19 Using a one-sided α = 0.05 and β = 0.8, 21 patients were needed for this study by the normal approximation to binomial distribution.
Detailed methods and procedures followed have been described in detail previously.14,15

RESULTS

Patients and treatment delivery

Patient registration was initiated in April 2011; however, the trial was terminated early with 20 of the planned 21 patients in January 2017 because of slow accrual. However, as this planned number of patients was initially set to include potential dropouts, the predefined statistical power was successfully guaranteed with the registered 20 patients, all of whom were assessed for the endpoints. The patient demographics are listed in Table 1. Nine patients (45%) were male, and 11 patients (55%) were diagnosed with stage IIIB diseases. The N status was evaluated using positron emission tomography—computed tomography scan in 17 patients (85%), and 3 patients (15%) were staged using invasive methods including endobronchial ultrasound-guided transbronchial needle aspiration. Ten patients (50%) had tumors with exon 19 deletions.

In the early feasibility step with the first six patients [male/female: 3/3; median age: 64 years (range: 54-66 years)], two developed the predefined events (grade 3 aminotransferase elevation in both patients, and grade 3 febrile neutropenia in one patient). Thus, the step 1 feasibility criteria were met (≤2 of 6), allowing the study to proceed to step 2 and enrollment of the additional patient cohort.

Overall, 17 (85%) patients completed gefitinib monotherapy. The administered days of therapy ranged from 30 to 56, with a median of 56 days. Three (15%) patients discontinued treatment because of disease progression, hepatic injury, and the patient’s wish to undergo proton therapy (n = 1 each). Gefitinib treatment was interrupted in 5 of 20 patients because of hepatic toxicity (n = 3), intestinal infection (n = 1), gingival infection (n = 1), and arthritis (n = 1). Seventeen (85%) patients proceeded with the CRT phase, 16 (94%) of whom completed CRT. However, one (6%) patient, while awaiting recovery from myelosuppression that occurred after chemotherapy on day 29, interrupted in 13 (76.5%) and 6 (35.3%) patients, respectively. One patient developed grade 3 transient gingival infection that did not require invasive intervention. Myelosuppression was less common, and no patients developed pneumonitis. In contrast, hematological toxicity was prominent during the CRT phase, with grade 3 events for the study treatment are listed in Table 3. Hepatic dysfunction was most common during the induction phase, with grade ≥3 aspartate aminotransferase and alanine aminotransferase elevations of 25% and 45%, respectively. One patient developed grade 3 transient gingival infection that did not require invasive intervention. Myelosuppression was less common, and no patients developed pneumonitis. In contrast, hematological toxicity was prominent during the CRT phase, with grade ≥3 leucopenia and neutropenia at 77% and 65%, respectively. Febrile neutropenia occurred in 12% of patients, without fatal events. Aspartate aminotransferase and alanine aminotransferase elevations were less frequently observed. For radiation-related toxicity, 4 (24%) and 12 (71%) patients developed grade ≤2 dermatitis and esophagitis, respectively, without any grade ≥3 cases.

Radiation pneumonitis, the most clinically important toxicity, occurred in 12 (71%; grade 1) and 2 (12%; grade 2) patients; these events improved within 6 months after the completion of thoracic irradiation. No clinical factor influenced substantially pneumonitis-free survival rates, calculated from the day of CRT initiation [Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2021.100191].

Survival and response

All patients were followed up to assess the primary endpoint. The median follow-up time in the survival analysis was 47.5 months (range: 9.5-96.8). The 2-year OS rate was 90.0% [90% and 95% confidence intervals (CIs): 71.4% to 96.8% and 65.6% to 97.4%, respectively], which met the predefined criteria (Figure 1A). For PFS, the 1- and 2-year rates were 58.1% [95% CI: 33.4% to 76.4%] and 36.9% (95% CI: 16.6% to 57.6%), respectively (Figure 1B).

The ORR was 75.0% (15 of 20 patients; 95% CI: 56.0% to 94.0%) in the induction phase (Table 2). Throughout the treatment phase, 1 (5.0%) and 16 (80.0%) patients achieved complete and partial responses, respectively, with an ORR of 85.0% (95% CI: 69.4% to 100%).

No large differences in the overall response or survival were evident according to the types of EGFR mutations and other clinical factors (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2021.100191).

Toxicity

The toxicity profiles for the study treatment are listed in Table 3. Hepatic dysfunction was most common during the induction phase, with grade ≥3 aspartate aminotransferase and alanine aminotransferase elevations of 25% and 45%, respectively. One patient developed grade 3 transient gingival infection that did not require invasive intervention. Myelosuppression was less common, and no patients developed pneumonitis. In contrast, hematological toxicity was prominent during the CRT phase, with grade ≥3 leucopenia and neutropenia at 77% and 65%, respectively. Febrile neutropenia occurred in 12% of patients, without fatal events. Aspartate aminotransferase and alanine aminotransferase elevations were less frequently observed. For radiation-related toxicity, 4 (24%) and 12 (71%) patients developed grade ≤2 dermatitis and esophagitis, respectively, without any grade ≥3 cases.

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Table 1. Patient characteristics (n = 20)

| Clinical factors                  | n     |
|----------------------------------|-------|
| Age, years                       | 66 (53-74) |
| Sex, n (%)                       | 9 (45) |
| Male                             | 11 (55) |
| Performance status, n (%)        | 12 (60) |
| 0                                | 8 (40) |
| Smoking history, n (%)           | 10 (50) |
| Never                            | 7 (35) |
| Former                           | 3 (15) |
| Type of EGFR mutations, n (%)    | 10 (50) |
| Exon 19                          | 10 (50) |
| Exon 21                          | 9 (45) |
| Disease stage, n (%)             | 11 (55) |
| IIA                              | 20 (100) |
| IIIB                             |       |
| Tumor histology, n (%)           |       |
| Adenocarcinoma                   |       |

EGFR, epidermal growth factor receptor.
Throughout the study treatment, no treatment-related deaths were observed.

Relapse sites and post-progression treatment
As shown in Table 4, as of the date of data cut-off, 15 (75%) of the 20 patients experienced recurrences; 2 (10%) were locoregional and 13 (65%) at distant sites. Thirteen were administered post-progression EGFR-TKI monotherapy (gefitinib in seven, afatinib in three, and erlotinib in three patients).

DISCUSSION
This is the first study to demonstrate the clinical utility of EGFR-TKI in an EGFR-mutant, locally advanced setting. Single-agent gefitinib therapy followed by CRT showed favorable efficacy with a 2-year OS rate of 90.0% (90% CI: 71.4% to 96.8%). The ORR throughout the treatment protocol was 85.0% (17 of 20). The safety findings were consistent with the known safety profiles of all agents administered.

The 2-year OS, the primary endpoint, was favorable as compared to existing survival data from a pivotal phase III trial of an EGFR-mutation-unselected, stage III population administered standard platinum-based CRT (2-year OS rate of 45%-60%)\textsuperscript{1-3} and the recent, less robust retrospective study results of ~80% in EGFR-mutant, stage III disease with standard CRT (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2021.100191).\textsuperscript{9-12} We also found a 2-year PFS rate of 36.9%, which appears promising compared to EGFR-mutation-unselected population data (20%-30%)\textsuperscript{1-3} and EGFR-mutant population
data (10%-25%) with standard CRT alone. Taken together, these results support that our treatment protocol should be further evaluated. However, most patients showed progression or recurrence (Figure 1B). The high 2-year OS may have arisen mainly from retreatment with EGFR-TKI at recurrence rather than as a preventive measure. Thus, it is unlikely that gefitinib induction yielded an actual effect on the cure rates beyond prolongation from post-progression use of EGFR-TKI. To achieve a higher cure rate, as a strategy for future treatment development for EGFR-mutant, stage III disease, it is essential to clarify how to incorporate EGFR-TKIs into standard CRT. This includes evaluating the best time at which to introduce EGFR-TKI while delivering standard CRT and which generation of EGFR-TKIs should be used. The LAURA study is ongoing, comparing consolidation EGFR-TKI monotherapy with placebo in the post-CRT setting in EGFR-mutant, stage III diseases (NCT03521154). In addition, we are planning an exploratory phase II study to evaluate the efficacy and safety of osimertinib induction and sequential CRT followed by consolidative durvalumab therapy. This design was derived based on the substantial survival advantage of osimertinib over gefitinib8 and of durvalumab consolidation over the placebo20 as described below. These studies will provide insight into the tolerability and effectiveness of adding the latest generation EGFR-TKI before or after CRT.

Recently, the PACIFIC study revealed 2-year OS rates of 66.3% and 55.6% with and without durvalumab consolidation therapy, respectively, in patients who achieved non-progressive disease with standard platinum-based CRT.20 Patients in the placebo arm (n = 236) were administered standard CRT alone; their efficacy data should be considered as reliable historical control data based on our study. However, these data have not been reported publicly, although the 2-year PFS rate can be estimated from the Kaplan–Meier curve as ~20%. Further, the PACIFIC data were not produced in untreated, stage III population, but limited to those who were successfully administered standard CRT without progression at the time of completion. Because of this difference in the targeted populations of the PACIFIC study, we were unable to accurately compare the efficacy data in this study. In addition, we should note that the survival advantage of durvalumab consolidation in EGFR-mutated NSCLC has not been fully understood because of the limited registered number of this subpopulation,21,22 and that its use has been recently questioned in several retrospective studies.21,23

As for adverse events, gefitinib induction induced hepatic insufficiency with a grade ≥3 alanine aminotransferase

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**Table 2. Objective response**

|                | Induction phase (n = 20) | Entire phase (n = 20) |
|----------------|--------------------------|-----------------------|
| Complete response, n (%) | 0                        | 1 (5.0)               |
| Partial response, n (%)  | 15 (75.0)                | 16 (80.0)             |
| Stable disease, n (%)    | 4 (20.0)                 | 2 (10.0)              |
| Progressive disease, n (%) | 1 (5.0)                 | 1 (5.0)               |
| Objective response rate  | 15 (75.0%)               | 17 (85.0%) (69.4% to 94.0%) |

* 95% confidence interval.

**Table 3. Toxicity**

|                        | Any grade n (%) | Grade ≥3 n (%) |
|------------------------|-----------------|----------------|
| **Induction phase (n = 20)** |                 |                |
| Leukopenia             | 1 (5)           | 0              |
| Neutropenia            | 4 (20)          | 0              |
| Anemia                 | 8 (40)          | 0              |
| Thrombocytopenia       | 5 (25)          | 0              |
| Aspartate aminotransferase elevation | 20 (100) | 5 (25) |
| Alanine aminotransferase elevation | 19 (95) | 9 (45) |
| Creatinine elevation   | 1 (5)           | 0              |
| Hyperbilirubinemia     | 1 (5)           | 0              |
| Hyponatremia           | 3 (15)          | 0              |
| Hypokalemia            | 3 (15)          | 0              |
| Fatigue                | 4 (20)          | 0              |
| Appetite loss          | 2 (10)          | 0              |
| Diarrhea               | 4 (20)          | 0              |
| Acneiform eruption     | 16 (80)         | 0              |
| Oral mucositis         | 6 (30)          | 0              |
| Pneumonitis            | 0               | 0              |
| Gingival infection     | 1 (5)           | 1 (5)          |
| Paronychia             | 2 (10)          | 0              |
| **CRT phase (n = 17)** |                 |                |
| Leukopenia             | 17 (100)        | 13 (77)        |
| Neutropenia            | 17 (100)        | 11 (65)        |
| Anemia                 | 14 (82)         | 0              |
| Thrombocytopenia       | 14 (82)         | 0              |
| Aspartate aminotransferase elevation | 11 (65) | 1 (6) |
| Alanine aminotransferase elevation | 13 (77) | 1 (6) |
| Creatinine elevation   | 2 (12)          | 0              |
| Hyponatremia           | 16 (94)         | 1 (6)          |
| Hypokalemia            | 5 (29)          | 1 (6)          |
| Fatigue                | 9 (53)          | 1 (6)          |
| Appetite loss          | 8 (47)          | 1 (6)          |
| Diarrhea               | 6 (35)          | 0              |
| Febrile neutropenia    | 2 (12)          | 2 (12)         |
| Acneiform eruption     | 3 (18)          | 0              |
| Oral mucositis         | 4 (24)          | 0              |
| Depression             | 1 (6)           | 1 (6)          |
| Syncope                | 1 (6)           | 1 (6)          |
| Radiation dermatitis   | 4 (24)          | 0              |
| Radiation esophagitis  | 12 (71)         | 0              |
| Radiation pneumonitis  | 14 (82)         | 0              |

CRT, chemoradiotherapy.
elevation of 45%, although there were no treatment-related deaths. A prior phase II trial of concurrent gefitinib therapy with standard CRT also showed grade 3-4 alanine aminotransferase elevations of 37.1% in 38 patients with EGFR-mutation-unselected stage III diseases. However, few adverse events in the induction phase occurred during the subsequent CRT phase. Other adverse event profiles throughout the induction and CRT phases were nearly consistent with existing known safety profiles, including pneumonitis.

There are several limitations to this study. Mainly, this study was carried out to generate a hypothesis, and the strength of our conclusions is limited by the small-scale, exploratory nature of the study. Thus, careful interpretation is required. The target patients are quite rare; however, considering their distinct clinical courses and outcomes of those with EGFR wild-type tumors (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2021.100191), the development of treatment strategies specific to this subpopulation is needed.

In conclusion, we provide the first evidence of the clinical efficacy and safety of gefitinib induction in an EGFR-mutant, unresectable, stage III population. Our results might raise a critical point that needs to be evaluated in further studies to improve the cure rate.

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REFERENCES

1. Segawa Y, Kiura K, Takigawa N, et al. Phase III trial comparing docetaxel and cisplatin combination chemotherapy with mitomycin, vindesine, and cisplatin combination chemotherapy with concurrent thoracic radiotherapy in locally advanced non-small-cell lung cancer: OLCSG 0007. J Clin Oncol. 2010;28:3299-3306.

2. Senan S, Brade A, Wang LH, et al. PROCLAIM: randomized phase III trial of pemetrexed-cisplatin or etoposide-cisplatin plus thoracic radiation therapy followed by consolidation chemotherapy in locally advanced nonsquamous non-small-cell lung cancer. J Clin Oncol. 2016;34:953-962.

3. Yamamoto N, Nakagawa K, Nishimura Y, et al. Phase III study comparing second- and third-generation regimens with concurrent thoracic radiotherapy in patients with unresectable stage III non-small-cell lung cancer: West Japan Thoracic Oncology Group WJTOG0105. J Clin Oncol. 2010;28:3739-3745.

https://doi.org/10.1016/j.esmoop.2021.100191
4. Kuyama S, Hotta K, Tabata M, et al. Impact of HER2 gene and protein status on the treatment outcome of cisplatin-based chemoradiotherapy for locally advanced non-small cell lung cancer. J Thorac Oncol. 2008;3:477-482.

5. Nogami N, Takigawa N, Hotta K, et al. A phase II study of cisplatin plus S-1 with concurrent thoracic radiotherapy for locally advanced non-small-cell lung cancer: the Okayama Lung Cancer Study Group Trial 0501. Lung Cancer. 2015;87:141-147.

6. Maemondo M, Inoue A, Kobayashi K, et al. The impact of clinical outcomes of thoracic radiotherapy for inoperable stage III non-small-cell lung cancer. Lung Cancer. 2005;10:370-381.

7. Akamatsu H, Kaira K, Murakami H, et al. Epidermal growth factor receptor mutation is associated with longer local control after thoracic irradiation in patients with stage III nonsquamous non-small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2015;91:140-148.

8. Nakamura M, Kageyama S, Niho S, et al. Impact of EGFR mutation and ALK translocation on recurrence pattern after definitive chemoradiotherapy for inoperable stage III non-squamous non-small-cell lung cancer. Clin Lung Cancer. 2019;20:e256-e264.

9. Norton L. Conceptual and practical implications of breast tissue geometry: toward a more effective, less toxic therapy. Oncologist. 2005;10:370-381.

10. Hisamoto A, Sasaki J, Takigawa N, et al. A phase II trial of induction gefitinib monotherapy followed by cisplatin-docetaxel and concurrent thoracic irradiation in patients with EGFR-mutant locally advanced non-small-cell lung cancer (LA-NSCLC). LOGIK0902/OLCG0905 intergroup trial. J Clin Oncol. 2012;30(suppl). abstr 7045.

11. Hotta K, Kiura K, Takigawa N, et al. Comparison of the incidence and pattern of interstitial lung disease during erlotinib and gefitinib treatment in Japanese patients with non-small cell lung cancer: the Okayama Lung Cancer Study Group experience. J Thorac Oncol. 2010;5:179-184.

12. Hotta K, Sasaki J, Takigawa N, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med. 2010;362:2380-2388.

13. Yagishita S, Horinouchi H, Katsui Taniyama T, et al. Epidermal growth factor receptor mutation is associated with longer local control after definitive chemoradiotherapy in patients with stage III nonsquamous non-small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2015;91:140-148.

14. Hotta K, Sasaki J, Saeki S, et al. Gefitinib combined with standard chemoradiotherapy in EGFR-mutant locally advanced non-small-cell lung cancer: the LOGIK0902/OLCG0905 intergroup study protocol. Clin Lung Cancer. 2016;17:75-79.

15. Hisamoto A, Sasaki J, Takigawa N, et al. A phase II trial of induction gefitinib monotherapy followed by cisplatin-docetaxel and concurrent thoracic irradiation in patients with EGFR-mutant locally advanced non-small-cell lung cancer (LA-NSCLC): LOGIK0902/OLCG0905 intergroup trial. J Clin Oncol. 2012;30(suppl). abstr 7045.

16. Hotta K, Kiura K, Takigawa N, et al. Comparison of the incidence and pattern of interstitial lung disease during erlotinib and gefitinib treatment in Japanese patients with non-small cell lung cancer: the Okayama Lung Cancer Study Group experience. J Thorac Oncol. 2010;5:179-184.

17. Hotta K, Kiura K, Tabata M, et al. Interstitial lung disease in Japanese patients with non-small cell lung cancer receiving gefitinib: an analysis of risk factors and treatment outcomes in Okayama Lung Cancer Study Group. Cancer J. 2005;11(5):417-424.

18. Rusch VW, Giroix DJ, Kraut MJ, et al. Induction chemoradiation and surgical resection for superior sulcus non-small-cell lung carcinomas: long-term results of Southwest Oncology Group Trial 9416 (Intergroup Trial 0160). J Clin Oncol. 2007;25:313-318.

19. Sugawara S, Oizumi S, Minato K, et al. Randomized phase II study of concurrent versus sequential alternating gefitinib and chemotherapy in patients with EGFR-mutated advanced NSCLC. Ann Oncol. 2015;26:888-894.

20. Antonia SJ, Villegas A, Daniel D, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. N Engl J Med. 2018;379:2342-2350.

21. Aredo JV, Mambetsariev I, Hellyer JA, et al. Durvalumab for stage III EGFR-mutated NSCLC after definitive chemoradiotherapy. J Thorac Oncol. 2021;16:1030-1041.

22. Hellyer JA, Aredo JV, Das M, et al. Role of consolidation durvalumab in patients with EGFR- and HER2-mutant unresectable stage III NSCLC. J Thorac Oncol. 2021;16:868-872.

23. Faire-Finn C, Vicente D, Kurata T, et al. Four-year survival with durvalumab after chemoradiotherapy in stage III NSCLC—an update from the PACIFIC Trial. J Thorac Oncol. 2021;16:860-867.

24. Niho S, Ohe Y, Ishikura S, et al. Induction chemotherapy followed by gefitinib and concurrent thoracic radiotherapy for unresectable locally advanced adenocarcinoma of the lung: a multicenter feasibility study (JCOG 0402). Ann Oncol. 2012;23:2253-2258.

25. Hotta K, Takigawa N, Matsuo K, et al. Cure- or care-oriented regimen for stage III non-small-cell lung cancer? J Clin Oncol. 2011;29:e320.