Continuous vs. Fixed 2-year Duration Immune Checkpoint Inhibitor Treatment of Patients With Non–Small Cell Lung Cancer: A Single Institution Database Analysis

日本大学大学院医学研究科博士課程

内科系呼吸器内科学専攻

小林　　玄機

修了年　　2024 年

指導教員　　權　寧博

Original Study

Continuous vs. Fixed 2-year Duration Immune Checkpoint Inhibitor Treatment of Patients With Non–Small Cell Lung Cancer: A Single Institution Database Analysis

Haruki Kobayashi,[1,2] Kazushige Wakuda,[1,2] Tateaki Naito,[1] Nobuaki Mamesaya,[1,2] Ryo Ko,[1] Akira Ono,[1] Hirotsugu Kenmotsu,[1] Haruyasu Murakami,[1] Tetsuo Shimizu,[2] Yasuhiro Gon,[2] Toshiaki Takahashi[1]

Abstract

The proper duration of immune checkpoint inhibitor (ICI) treatment for advanced non–small cell lung cancer (NSCLC) patients remains unclear. The medical records of 425 NSCLC patients receiving ICI were retrospectively reviewed. ICI treatment for > 2 years did not significantly prolong the time to treatment failure compared with that for 2 years but increased the incidence of treatment-related adverse events.

Introduction/Background: The proper duration of immune checkpoint inhibitor (ICI) treatment for patients with advanced non–small cell lung cancer (NSCLC) remains unclear. Previously, sponsor-initiated clinical trials have more often used either a maximum 2-year fixed duration of ICI treatment or continuous treatment until documented disease progression. The study aimed to evaluate the association between ICI treatment duration (2-year fixed or continuous) and prognosis in patients with advanced NSCLC. **Patients and Methods:** The medical records of 425 patients with NSCLC who received ICI before August 31, 2019 were retrospectively reviewed. **Results:** No differences in time to treatment failure > 24 months (TTF-24) were detected between patients who underwent ICI treatment for > 2 years and patients who stopped ICI treatment at 2 years. Treatment-related adverse events tended to be higher in the patients with ICI treatment > 2 years. **Conclusion:** ICI treatment > 2 years did not significantly prolong the TTF compared with ICI treatment = 2 years, but it did increase the incidence of treatment-related adverse events.

Clinical Lung Cancer, Vol. 24, No. 6, 498–506 © 2023 The Author(s). Published by Elsevier Inc.

Keywords: Patient survival, Treatment duration time to treatment failure, Optimal ICI treatment duration, Treatment-related adverse events, Immune-related adverse events

Introduction

Immune checkpoint inhibitor (ICI) ± chemotherapy prolongs survival in patients with advanced non–small cell lung cancer (NSCLC). Some sponsor-initiated clinical trials, such as KEYNOTE024[1] (ICI monotherapy as first-line treatment), KEYNOTE010[2] (ICI monotherapy as second-line treatment), ChecMate003[3] (ICI monotherapy as any line), CHECKMATE227[4] (dual immunotherapy), and IMPOWER150[5] (ICI + chemotherapy), have been conducted with a fixed 24-month maximum ICI treatment duration. Other sponsor-initiated clinical trials, such as ChecMate017[6]/057[7] and the OAK study[8] (ICI monotherapy as second/third line) were conducted with ICI treatment continued until documented disease progression, discontinuation due to toxicity, withdrawal of consent, or study end, even when the treatment was >24 months. However, the optimal ICI treatment duration has not been established.

Moreover, exploratory analysis of CheckMate153,[9] which used a continuous versus 1-year fixed-duration ICI treatment protocol in previously treated patients with advanced NSCLC, demonstrated

Abbreviations: ICI, immune checkpoint inhibitor; NSCLC, non–small cell lung cancer; PD, progressive disease; RECIST, Response Evaluation Criteria in Solid Tumors; TNM, tumor, node, metastasis; PD-L1, programmed cell death 1 ligand 1; BMI, body mass index; TTF, time to treatment failure; PFS, progression-free survival; OS, overall survival; TPS, tumor proportion score; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; irAE, immune-related adverse events; HR, hazard ratio; CI, confidence interval.

[1]Division of Thoracic Oncology, Shizuoka Cancer Center, Shizuoka, Japan
[2]Division of Respiratory Medicine, Nihon University School of Medicine, Tokyo, Japan

Submitted: Feb 8, 2023; Revised: Apr 28, 2023; Accepted: Jun 12, 2023; Epub: 15 June 2023

Address for correspondence: Haruki Kobayashi, MD, Division of Thoracic Oncology, Shizuoka Cancer Center, 1007 Shimonagakubo, Nagaizumi-cho Sunto-gun, Shizuoka 411-8777, Japan
E-mail contact: h.kobayashi@scchr.jp

1525-7304/$ - see front matter
https://doi.org/10.1016/j.cllc.2023.06.005

that the continuous use of ICI beyond 1-year improved prognosis in these patients. This study aimed to compare the effects of 2-year fixed or continuous ICI treatment on prognosis in patients with advanced NSCLC.

Patients and Methods

Patients

Patients with advanced NSCLC who underwent ICI ± chemotherapy until August 31, 2019 at the Shizuoka Cancer Center were enrolled in this study. Among them, the patients who had undergone 2 years of ICI ± chemotherapy were analyzed in detail. Because patients with early discontinuation of therapy due to immune-related adverse events were excluded from this analysis, the inclusion criteria were set as follows: administration of >26 cycles of nivolumab therapy or >17 cycles of pembrolizumab or atezolizumab therapy within 2 years from treatment initiation, administration of >1 cycle of ICI treatment >21 months from treatment initiation, and no progressive disease (PD) according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria[10] excluding oligoprogression (Supplemental Figure 1). The definition of oligoprogression in this study was progression at only one metastatic disease site after achieving stable disease following local radiation therapy or surgery. Patients with simultaneously progressing metastatic diseases were excluded from the study. The radiotherapy dose was selected regardless of curative or palliative intent, and the operative method depended on the physician in cases of complete treatment of the oligoprogressive disease (R0 resection).

Tumor, Node, and Metastasis (TNM) Stages, Adverse Events, and Cancer Cachexia

The disease stages were evaluated according to the TNM classification of lung cancer (7th edition).[11] Adverse events in our study were evaluated using the National Cancer Institute Common Terminology Criteria version 5.0.[12] Programmed cell death 1 ligand 1 (PD-L1) stain was evaluated by histology, excluding cell block, and by Dako PD-L1 IHC 22C3, 28-8 pharmaDx Assays, and VENTANA PD-L1 IHC SP263 Assay.

Cancer cachexia was defined as unintentional weight loss ≥ 5% for a body mass index (BMI) ≥ 20 or unintentional weight loss ≥2% for a BMI < 20 during the 6-month period prior to the end of 2-year ICI treatment.[13] The patient's weight was usually checked at chemotherapy administration. Skeletal muscle mass was not measured in clinical practice; therefore, it was not considered to be a criterion for cancer cachexia in this study.

Statistical Analysis

All categorical variables were analyzed using Fisher's exact test. Progression-free survival (PFS) was calculated from the start of ICI treatment to the date of PD or death from any cause. Overall survival (OS) was defined as the time from the start of the ICI treatment to death. Time to treatment failure (TTF) was calculated from ICI treatment initiation to the date of clinical PD or death from any cause. TTF-24 was defined as TTF > 24 months. The Kaplan–Meier method was used to estimate the event time. The Cox proportional hazards model was used to perform univariate and multivariate analyses of the TTF-24. The log-rank test was used to compare the cumulative survival in each group. All *P* values were reported as two-sided, with values < 0.05 accepted as indicative of statistical significance. The end date for the survival analyses was defined as August 31, 2022. All statistical analyses were performed in JMP 15.1.0 software (SAS Institute, Cary, NC).

The study protocol was approved by the institutional review board of the Shizuoka Cancer Center (IRB no. 29-J112-29-1-3).

Results

Patient Characteristics

Overall, 425 patients with advanced NSCLC were treated with ICIs during the study interval (Table 1). The Dako PD-L1 IHC 22C3 (n = 301), 28-8 (n = 2) pharmaDx Assays, and VENTANA PD-L1 IHC SP263 (n = 1) Assay were used to obtain a tumor proportion score (TPS) to measure PD-L1 expression. In combination with chemotherapy was defined as ICI + platinum-based chemotherapy. The most-used regimen was pembrolizumab plus pemetrexed and cisplatin. Among the 425 patients, 41 patients with NSCLC received ICI ± chemo for ≥2 years (Table 2, Supplemental Table 1). We observed that higher PD-L1 TPS in tumor cells was associated with a higher proportion of patients treated with ICI ± chemo > 2 years: the proportions were 3%, 9%, and 15% for PD-L1 TPS 0%, 1% to 49%, and ≥50%, respectively. However, there was no additional effect of adding platinum-based chemotherapy for 2-year treatment. The proportions of patients treated with ICI + chemotherapy and ICI monotherapy were 9.3% and 9.7%, respectively.

The proportion of patients with nonsquamous-NSCLC harboring epidermal growth factor receptor (EGFR) mutation was 16% included in this study. These kinds of mutation were four patients with del 19, 1 patient with L858R, and 1 patient with a minor mutation. One of 6 patients had been a heavy smoker of >40 packs per year. The PFS for first-time treatment with EGFR-tyrosine kinase inhibitors (TKIs), including 2 patients treated with gefitinib, 2 treated with erlotinib, and one treated with osimertinib, ranged from 9.63 to 22.9 months. The numbers of EGFR-mutant patients were 2, 1, and 2 for PD-L1 TPS of 0%, 1% to 49%, and ≥50%, respectively.

Among 41 patients, 29 and 12 patients had continued ICI ± chemotherapy and had stopped ICI ± chemotherapy, respectively. There were no significant differences in the characteristics of these patients (Supplemental Table 2).

Greater Than 2 Years of ICI Treatment

The median follow-up period for the censored cases was 43.1 months (range, 27.9-70.2) months. The median PFS at the ICI ± chemotherapy for the 41 patients was 50.8 months (Figure 1A). Three patients had local PD < 24 months from ICI ± chemotherapy initiation. The respective metastatic sites were the brain, ovary, and lymph node. Surgery or radiation therapy had been administered as local therapy, and ICI ± chemotherapy was continued ≥2 years from ICI ± chemotherapy initiation. The median OS after ICI therapy for the 41 patients treated with ICI ± chemotherapy was not reached (Figure 1B).

Figure 2A shows the Kaplan–Meier curve for the TTF-24 for 41 patients, and the median TTF-24 was 48.3 months.

Figure 1 (A) PFS and (B) OS curves of 41 patients with NSCLC who underwent ICI treatment for ≥2 years. PFS, progression-free survival; OS, overall survival; NSCLC, non–small cell lung cancer; ICI, immune checkpoint inhibitor

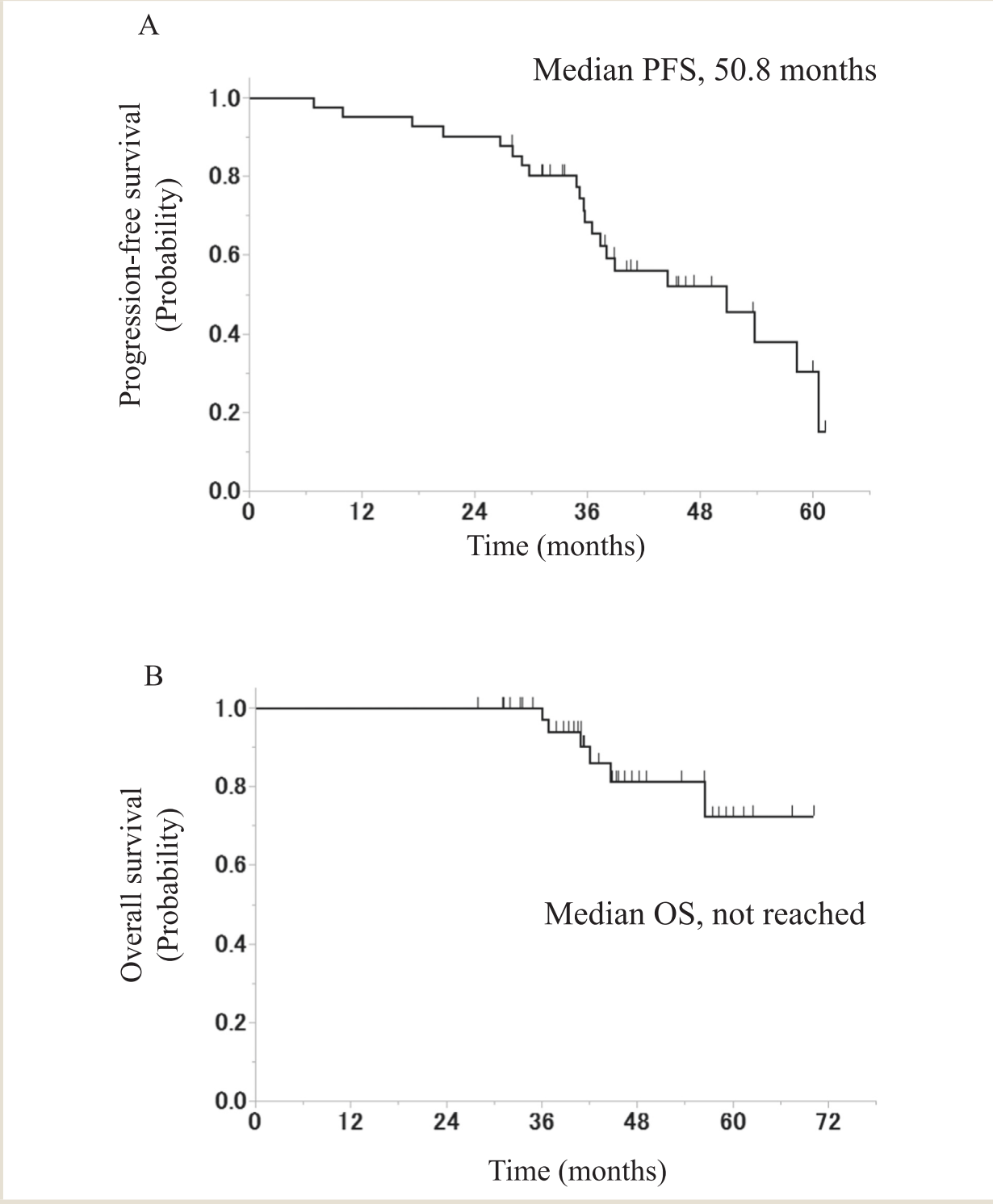


Table 1 Characteristics of 425 Patients With NSCLC Treated With ICIs

Variable	Result
Age at ICI treatment, median (range), years	68 (33-94)
Sex, male/female	286/139
ECOG-PS at ICI treatment, 0/1/2	77/302/46
Clinical stage*, III/IV/recurrence	11/252/162
Smoking status, packs per year, <40/≥40	241/184
Pathology, squamous/nonsquamous	73/352
Biomarker (EGFR or ALK), yes/ no/unknown	72/301/52
PD-L1 TPS, unknown/0/1-49/≥50	121/66/119/119
Line, first/second/third and later	130/146/149
Regimen, nivolumab/pembrolizumab/atezolizumab	179/200/46
Combination with chemotherapy, yes/no	54/371

Abbreviations: ALK = anaplastic lymphoma kinase; ECOG-PS = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor; NSCLC = non-small cell lung cancer; ICI = immune checkpoint inhibitor; PD-L1 = Programmed cell Death 1- Ligand 1.
* Clinical staging according to the 7th edition of the TNM classification of lung cancer.

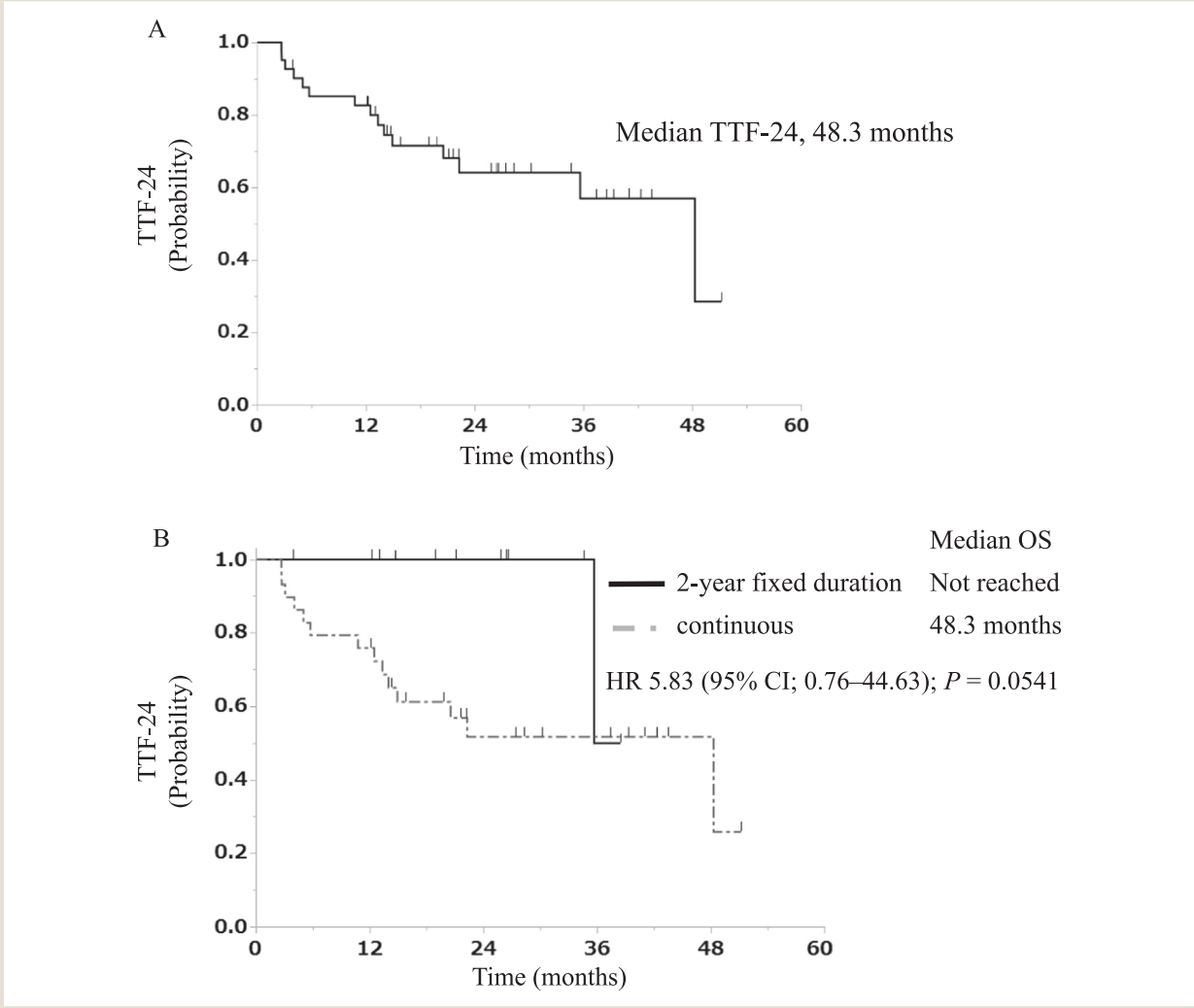
Table 2 Baseline Characteristics of 41 Patients With NSCLC Treated With an ICI for ≥2-Years

Variable	Result
Age at 2-years treatment, median (range), years	67 (35-86)
<65/≥65 years	14/27
Sex, male/female	29/12
ECOG-PS at 2-year treatment, 0/1/2	12/26/3
*Clinical stage, III/IV/recurrence	1/25/15
Smoking status, packs per year, <40/≥40	25/16
Pathology, squamous/nonsquamous	3/38
Biomarker (EGFR or ALK), yes/no/unknown	7/31/3
PD-L1 TPS, unknown/0/1-49/≥50	10/2/11/18
Line, first/ second/third and later	15/17/9
Duration of ICI treatment, fixed 2-year duration/continuous	12/29
Combination with chemotherapy, yes/no	5/36
Cachexia existence at 2-year treatment, yes/no	9/32

Abbreviations: ALK = anaplastic lymphoma kinase; ECOG-PS = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor; NSCLC = non-small cell lung cancer; ICI = immune checkpoint inhibitor; PD-L1 = Programmed cell Death 1- Ligand 1.
* Clinical staging according to the 7th edition of the TNM classification of lung cancer.

Supplemental Table 3 summarizes the univariate and multivariate analysis results of TTF-24 for the 41 patients. In the univariate analysis, TTF-24 tended to be shorter for the patients treated with ICI ± chemotherapy > 2 years than for those treated with ICI ± chemotherapy for only 2 years (median TTF-24, 48.3 months vs. not reached, $P = .0541$; Figure 2B). Other categorical variables, including PD-L1 TPS, Eastern Cooperative Oncology Group performance status, biomarkers, or treatment line, also did not show significant differences in TTF-24. The multivariate analysis showed that there were no significant differences in TTF-

Figure 2 (A) TTF-24 curve of 41 patients with NSCLC administered ICI treatment for ≥2 years. (B) TTF-24 curve according to the duration of ICI treatment. TTF, time to treatment failure; NSCLC, non–small cell lung cancer; ICI, immune checkpoint inhibitor



24 between the categorical variables, including the ICI treatment duration ($P = .0811$).

Clinical Course of 41 Patients After ICI ± Chemotherapy Initiation

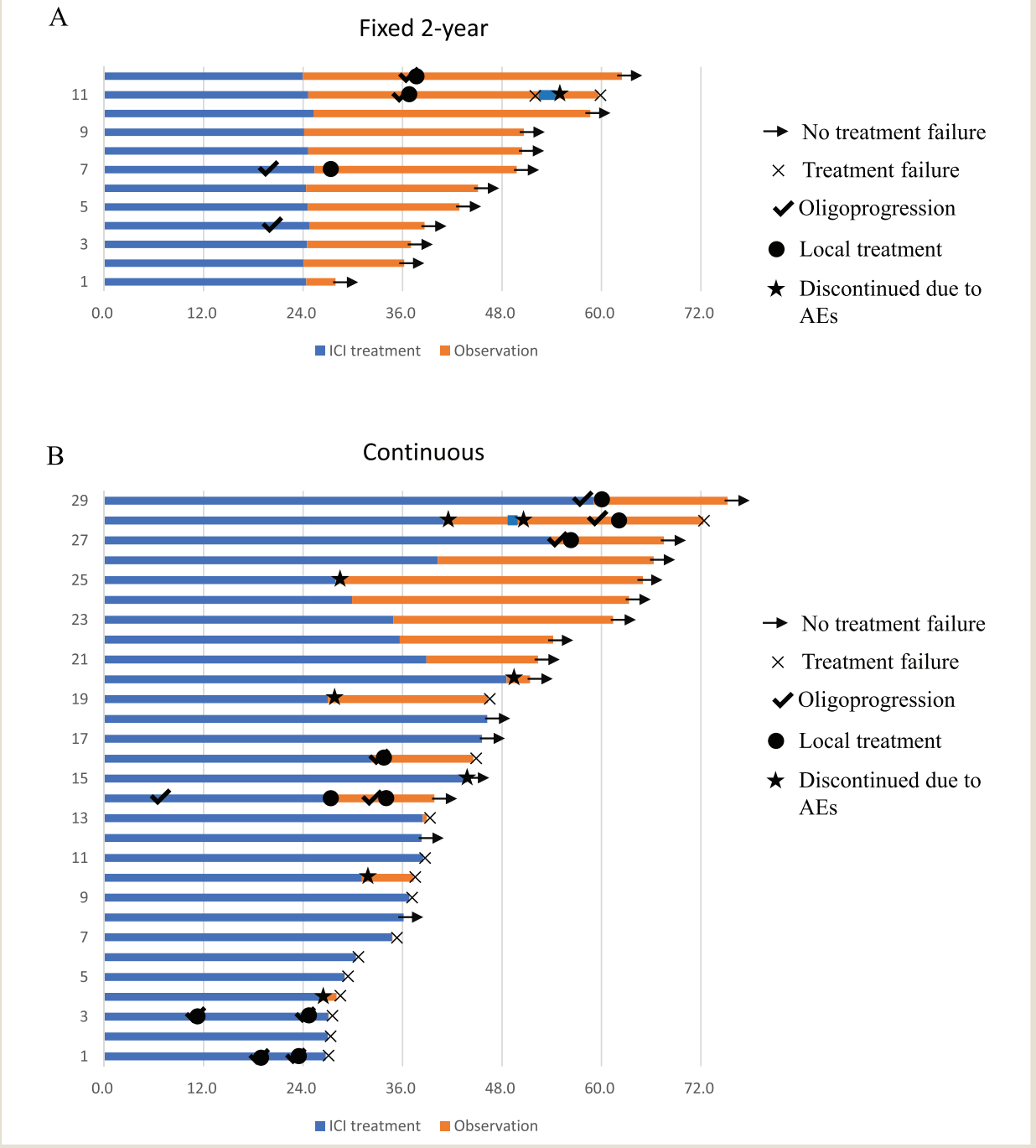
Swimmer plots are shown in Figures 3A and B for 12 patients treated with ICI ± chemotherapy for 2 years and 29 patients treated for > 2 years. Figure 3A shows that no patient was administered steroids because of immune-related adverse events (irAEs) during follow-up. One (8%) patient had stomatitis Gr3 as an irAE after ICI readministration and discontinued ICI treatment. Two (17%) of 12 patients had oligoprogression recurrence < 24 months after ICI ± chemotherapy initiation.

In contrast, in Figure 3B shows that seven (24%) patients discontinued ICI treatment ± chemo because of AE, including 5 patients with irAE. The irAEs included 2 patients with pneumonitis Gr2, one with adrenal insufficiency Gr4, 1 with diarrhea Gr3, 1 with plural effusion Gr2 due to pleuritis, and 3 patients who required steroid treatment. Three (10%) of 29 patients had oligoprogression recurrence < 24 months from ICI ± chemotherapy initiation.

There were no significant differences in the proportions of recurrence < 24 months from ICI ± chemotherapy initiation between the 2 groups ($P = .6197$), but the patients who underwent a fixed 2-year duration of ICI ± chemotherapy tended to have more oligoprogression recurrence. Also, no patients had difficulty in continuing ICI treatment because of AE occurrence < 24 months from ICI ± chemotherapy initiation between the groups.

There were no significant differences in the proportions of ICI treatment discontinuation because of AEs during the TTF-24 interval between the two groups ($P = .3984$), but patients with ICI ± chemotherapy > 2 years tended to have more AEs caused by ICI ± chemotherapy. Six patients without AEs or PD discontin-

Figure 3 (A) Swimmer's plots of 12 patients with NSCLC who were administered ICI treatment for a fixed 2-year duration. (B) Swimmer's plots of 29 patients with NSCLC who were administered ICI treatment for a >2-year duration. NSCLC, non–small cell lung cancer; ICI, immune checkpoint inhibitor; AE, adverse event



ued ICI ± chemotherapy after 2 years on the advice of their physicians.

Discussion

The optimum duration of ICI ± chemotherapy for advanced NSCLC remains unclear. Recent sponsor-initiated clinical trials have often used a fixed 2-year treatment duration for investigational ICIs.[14-16] The present study showed that the continuous use of ICIs > 2 years in patients with stable disease did not improve their prognosis. Although there were no significant differences in TTF-24, it tended to be shorter for the patients who underwent ICI ± chemotherapy > 2 years than for those treated for a fixed

2-year duration. The causes could be increasing irAEs, which led to discontinuation of ICI ± chemotherapy. Exploratory analysis of the Checkmate 153 trial[9] demonstrated that the continuous use of ICI > 1-year in patients with stable disease led to a higher incidence of irAEs, including discontinuation of nivolumab treatment. The IFCT-1701 trial,[17] which evaluated nivolumab plus ipilimumab 6-month treatment versus continuation of treatment in patients with advanced NSCLC, reported that patients treated over 6-month period tended to have a shorter PFS period and more severe irAEs; notably, the trial was stopped because nivolumab plus ipilimumab therapy was not administered by European Medicines Agency. Therefore, this study and the above-mentioned trial reported that a longer duration of ICI treatment increased the incidence of irAEs. Moreover, updated analysis[18] of the Keynote-024 trial showed that 46% of patients who completed 35 cycles of pembrolizumab were alive without PD or subsequent therapy for NSCLC at the data cutoff. After an assessment of PD, 83% of the patients showed disease control after readministration of pembrolizumab. The results of the present study suggest that the potential optimal duration of ICI ± chemotherapy for patients with NSCLC could be 2 years, the same as used in many sponsor-initiated clinical trials. Whether or not a shorter initial duration of ICI treatment is enough for patients with advanced NSCLC will be reported after completion of the JCOG 1701 study[19] in the future.

In the present study, 41 (9.6%) patients were able to undergo ICI ± chemotherapy for ≥2 years, which was a lower percentage than in previous trials, such as the Keynote042[20] (16.0%), Keynote189[21] (13.7%), Keynote 407[22] (19.7%), and CheckMate227[23] (12.1%) trials. The reason for the lower percentage could be that the patients included in this study had poor performance status,[24] received ICI treatment as a late line, or had NSCLC harboring driver mutations.[25] Of 425 patients with NSCLC treated with ICIs at least once, five (9.3%) received ICI + chemotherapy and 36 (9.7%) received ICI monotherapy for > 2 years. This result is similar to that obtained from the Keynote042[20] (16.0%) versus Keynote189[21] (13.7%) or Keynote 407[22] (19.7%) trials. In contrast, a higher PD-L1 TPS in tumor cells was associated with a higher proportion of patients treated with ICI ± chemotherapy for > 2 years, as shown by the Keynote024[18] (25.3%) result versus the Keynote042[20] result. However, in the analysis of 41 patients treated with ICI ± chemo for > 2 years, the PD-L1 TPS in tumor cells was not correlated with the TTF-24. Therefore, the PD-L1 TPS in tumor cells cannot be used as a biomarker of very long responders.

Of 72 patients with NSCLC harboring an EGFR mutation or anaplastic lymphoma kinase (ALK) rearrangement, seven patients (9.7%) could tolerate ICI ± chemotherapy > 2 years. Most sponsor-initiated clinical trials concerning ICI have exclusion criteria of biomarkers, such as EGFR mutation or ALK rearrangement, because patients with NSCLC harboring an EGFR mutation or ALK rearrangement are less likely to respond to ICI treatment.[16] Some reports have shown that higher PD-L1 TPS in tumor cells, shorter TKI duration, and EGFR mutation subtypes, such as L858R or minor mutations, are associated with better ICI response in EGFR-mutant patients.[26,27] However, in the patients with NSCLC harboring an EGFR mutation in this study, TTF-24 was not associated with the above-mentioned factors. Therefore, a biomarker predictive of very long response to ICI treatment against advanced NSCLC harboring an EGFR mutation has not yet been identified. It is also important to remember that ICI treatment should be tried for patients with NSCLC harboring an EGFR mutation even if they have a poorer response.

A limitation of this study was the potential bias caused by the physicians' choices of the ICI treatment duration for their patients. However, we enrolled consecutive patients for analysis during the study, and there were no significant differences in these patients' characteristics.

In conclusion, the study results showed that ICI treatment > 2 years did not significantly improve prognosis (longer TTF and/or survival) and increased the incidence of irAEs. In the future, the time taken to discontinue individual ICI treatment should be assessed and ICI treatment could be decided to discontinue in 1 or 2 years after studying a biomarker using liquid biopsies.

Ethics Approval and Consent to Participate

The study protocol was approved by the institutional review board of the Shizuoka Cancer Center (IRB no. 29-J112-29-1-3).

Data availability

The datasets used and/or analyzed in the current study are available through the corresponding author on reasonable request.

Clinical Practice Points

- Immune checkpoint inhibitor (ICI) ± chemotherapy prolongs survival in patients with advanced nonsmall cell lung cancer (NSCLC). Some sponsor-initiated clinical trials have been conducted with a fixed 24-month maximum ICI treatment duration. However, the proper duration of ICI treatment for patients with advanced NSCLC remains unclear.
- The exploratory analysis of CheckMate153, which used a continuous versus 1-year fixed-duration ICI treatment protocol in previously treated patients with advanced NSCLC, demonstrated that the continuous use of ICI beyond 1-year improved prognosis in these patients.
- This study aimed to compare the effects of 2-year fixed or continuous ICI treatment on treatment failure in patients with advanced NSCLC who could undergo ICI treatment for 2 years without clinical progressive disease or severe adverse event.
- The medical records of 425 patients with NSCLC who received ICI were retrospectively reviewed. In the univariate analysis, Time to failure (TTF) tended to be shorter for the patients treated with ICI ± chemotherapy > 2 years than for those treated with ICI ± chemotherapy for only 2 years (median TTF, 48.3 months vs. not reached, $P = 0.0541$; Figure 2B). The multivariate analysis showed that there were no significant differences in TTF between the categorical variables, including the ICI treatment duration ($P = 0.0811$). Moreover, patients with ICI ± chemotherapy > 2 years tended to have more AEs caused by ICI ± chemotherapy.
- In conclusion, the study results showed that ICI treatment > 2 years did not significantly improve prognosis and increased the incidence of AEs.

Competing Interest

Haruki Kobayashi reports personal fees from Eli Lilly, Novartis, Taiho Pharmaceutical, Chugai pharma, AstraZeneca, Ono Pharmaceutical, Bristol-Myers Squibb Japan, outside the submitted work. Kazushige Wakuda reports grants from AstraZeneca, Chugai pharma, Novartis, Abbvie, AMGEN, Daiichi Sankyo, Dizal Pharma; personal fees from Chugai pharma, AstraZeneca, Taiho Pharmaceutical, Boehringer Ingelheim, Eli Lilly, MSD, Ono Pharmaceutical, Daiichi Sankyo, Jassen Pharmaceutial, Takeda, Nippon Kayaku, outside the submitted work. Tateaki Naito reports grants from Otsuka Pharmaceutical; personal fees from Ono Pharmaceutical, HELSINN SA, outside the submitted work. Nobuaki Mamesaya reports grants from Boehringer Ingelheim; personal fees from Chugai pharma, AstraZeneca, Boehringer Ingelheim, Taiho Pharmaceutical, MSD, Ono Pharmaceutical, outside the submitted work. Ryo Ko reports grants from MSD, AstraZeneca; personal fees from Taiho Pharmaceutical, Chugai Pharmaceutical, Eli Lilly, Boehringer Ingelheim, Pfizer, AstraZeneca, Ono Pharmaceutical, Daiichi Sankyo, Takeda, MSD, outside the submitted work. Akira Ono reports personal fees from Chugai pharma, AstraZeneca, Ono Pharmaceutical, outside the submitted work. Hirotsugu Kenmotsu reports grants from Ono Pharmaceutical, Novartis, Eli Lilly, AstraZeneca, Loxo Oncology; personal fees from AMGEN, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Chugai pharma, Daiichi Sankyo, Eli Lilly, Kyowa Hakko Kirin, Merck, MSD, Novartis, Ono Pharmaceutical, Pfizer, Taiho Pharmaceutical, Takeda, outside the submitted work. Haruyasu Murakami reports grants from AstraZeneca, Chugai pharma, Takeda, Abbvie, Daiichi Sankyo, IQvia; personal fees from AstraZeneca, Chugai pharma, Takeda, Abbvie, Daiichi Sankyo, MSD, Ono Pharmaceutical, Bristol-Myers Squibb Japan, Pfizer, Novartis, Eli Lilly Japan, Taiho Pharmaceutical, Boehringer Ingelheim, Eisai, Nippon Kayaku, outside the submitted work. Tetsuo Shimizu reports personal fees from Eli Lilly, Taiho Pharmaceutical, Chugai Pharma, AstraZeneca, Ono Pharmaceutical, Bristol-Myers Squibb Japan, Takeda, outside the submitted work. Yasuhiro Gon reports personal fees from Chugai pharma, outside the submitted work. Toshiaki Takahashi reports grants from AstraZeneca, Chugai Pharma, Eli Lilly Japan, Ono Pharmaceutical, MSD, Pfizer, AMGEN, Boehringer Ingelheim, Merck Biopharma; personal fees from AstraZeneca, Chugai Pharma, Eli Lilly Japan, Ono Pharmaceutical, MSD, Pfizer, Boehringer Ingelheim, Roche Diagnostics, Takeda, Yakult, outside the submitted work.

Acknowledgments

Not applicable. This research did not receive any specific grants from any funding agencies in the public, commercial, or not-for-profit sectors.

References

1. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med*. 2016;375(19):1823–1833. doi:10.1056/NEJMoa1606774.
2. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet*. 2016;387(10027):1540–1550. doi:10.1016/S0140-6736(15)01281-7.
3. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med*. 2012;366(26):2443–2454. doi:10.1056/NEJMoa1200690.
4. Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus ipilimumab in advanced non-small-cell lung cancer. *N Engl J Med*. 2019;381(21):2020–2031. doi:10.1056/NEJMoa1910231.
5. Socinski MA, Jotte RM, Cappuzzo F, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. *N Engl J Med*. 2018;378(24):2288–2301. doi:10.1056/NEJMoa1716948.
6. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med*. 2015;373(2):123–135. doi:10.1056/NEJMoa1504627.
7. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med*. 2015;373(17):1627–1639. doi:10.1056/NEJMoa1507643.
8. Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet*. 2017;389(10066):255–265. doi:10.1016/S0140-6736(16)32517-X.
9. Waterhouse DM, Garon EB, Chandler J, et al. Continuous versus 1-year fixed-duration nivolumab in previously treated advanced non-small-cell lung cancer: CheckMate 153. *J Clin Oncol*. 2020;38(33):3863–3873. doi:10.1200/JCO.20.00131.
10. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228–247 version 1.1. doi:10.1016/j.ejca.2008.10.026.
11. Goldstraw P, Crowley J, Chansky K, et al. The IASLC lung cancer staging project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. *J Thorac Oncol*. 2007;2(8):706–714. doi:10.1097/JTO.0b013e31812f3c1a.
12. Common Terminology Criteria for Adverse Events (CTCAE) Version 5. Published: November 27. US Department of Health and Human Services, National Institutes of Health, National Cancer Institute. Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm.
13. Fearon K, Strasser F, Anker SD, et al. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol*. 2011;12(5):489–495. doi:10.1016/S1470-2045(10)70218-7.
14. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non–small-cell lung cancer. *N Engl J Med*. 2018;378(22):2078–2092. doi:10.1056/NEJMoa1801005.
15. Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus chemotherapy for squamous non–small-cell lung cancer. *N Engl J Med*. 2018;379(21):2040–2051. doi:10.1056/NEJMoa1810865.
16. Paz-Ares L, Ciuleanu T-E, Cobo M, et al. First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): an international, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2021;22(2):198–211. doi:10.1016/S1470-2045(20)30641-0.
17. Zalcman G, Molinier AMFO, Dayen C, et al. Nivolumab plus ipilimumab 6-months treatment versus continuation in patients with advanced non-small cell lung cancer: results of the randomized IFCT-1701 phase III trial. *Ann Oncol*. 2022;33:S448–S554. doi:10.1016/j.annonc.2022.07.1100.
18. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Five-year outcomes with pembrolizumab versus chemotherapy for metastatic non-small-cell lung cancer with PD-L1 tumor proportion score ≥ 50 >/= 50. *J Clin Oncol*. 2021;39(21):2339–2349. doi:10.1200/JCO.21.00174.
19. Nomura S, Goto Y, Mizutani T, et al. A randomized phase III study comparing continuation and discontinuation of PD-1 pathway inhibitors for patients with advanced non-small-cell lung cancer (JCOG1701, SAVE study). *Jpn J Clin Oncol*. 2020;50(7):821–825. doi:10.1093/jjco/hyaa054.
20. Mok TSK, Wu Y-L, Kudaba I, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. *Lancet*. 2019;393(10183):1819–1830. doi:10.1016/S0140-6736(18)32409-7.
21. Rodríguez-Abreu D, Powell SF, Hochmair MJ, et al. Pemetrexed plus platinum with or without pembrolizumab in patients with previously untreated metastatic nonsquamous NSCLC: protocol-specified final analysis from KEYNOTE-189. *Ann Oncol*. 2021;32(7):881–895. doi:10.1016/j.annonc.2021.04.008.
22. Paz-Ares L, Vicente D, Tafreshi A, et al. A randomized, placebo-controlled trial of pembrolizumab plus chemotherapy in patients with metastatic squamous NSCLC: protocol- specified final analysis of KEYNOTE-407. *J Thorac Oncol*. 2020;15(10):1657–1669. doi:10.1016/j.jtho.2020.06.015.
23. Brahmer JR, Lee JS, Ciuleanu T-E, Reyes Bernabe Caro, et al. Five-Year Survival Outcomes with Nivolumab Plus Ipilimumab versus Chemotherapy as First-Line Treatment for Metastatic Non–small-Cell Lung Cancer in CheckMate 227. *J Clin Oncol*. 2023;41(6):1200–1212.
24. Petrillo LA, El-Jawahri A, Nipp RD, et al. Performance status and end-of-life care among adults with non–small cell lung cancer receiving immune checkpoint inhibitors. *Cancer*. 2020;126(10):2288–2295. doi:10.1002/cncr.32782.
25. Lee CK, Man J, Lord S, et al. Clinical and molecular characteristics associated with survival among patients treated with checkpoint inhibitors for advanced non-small cell lung carcinoma: a systematic review and meta-analysis. *JAMA Oncol*. 2018;4(2):210–216. doi:10.1001/jamaoncol.2017.4427.

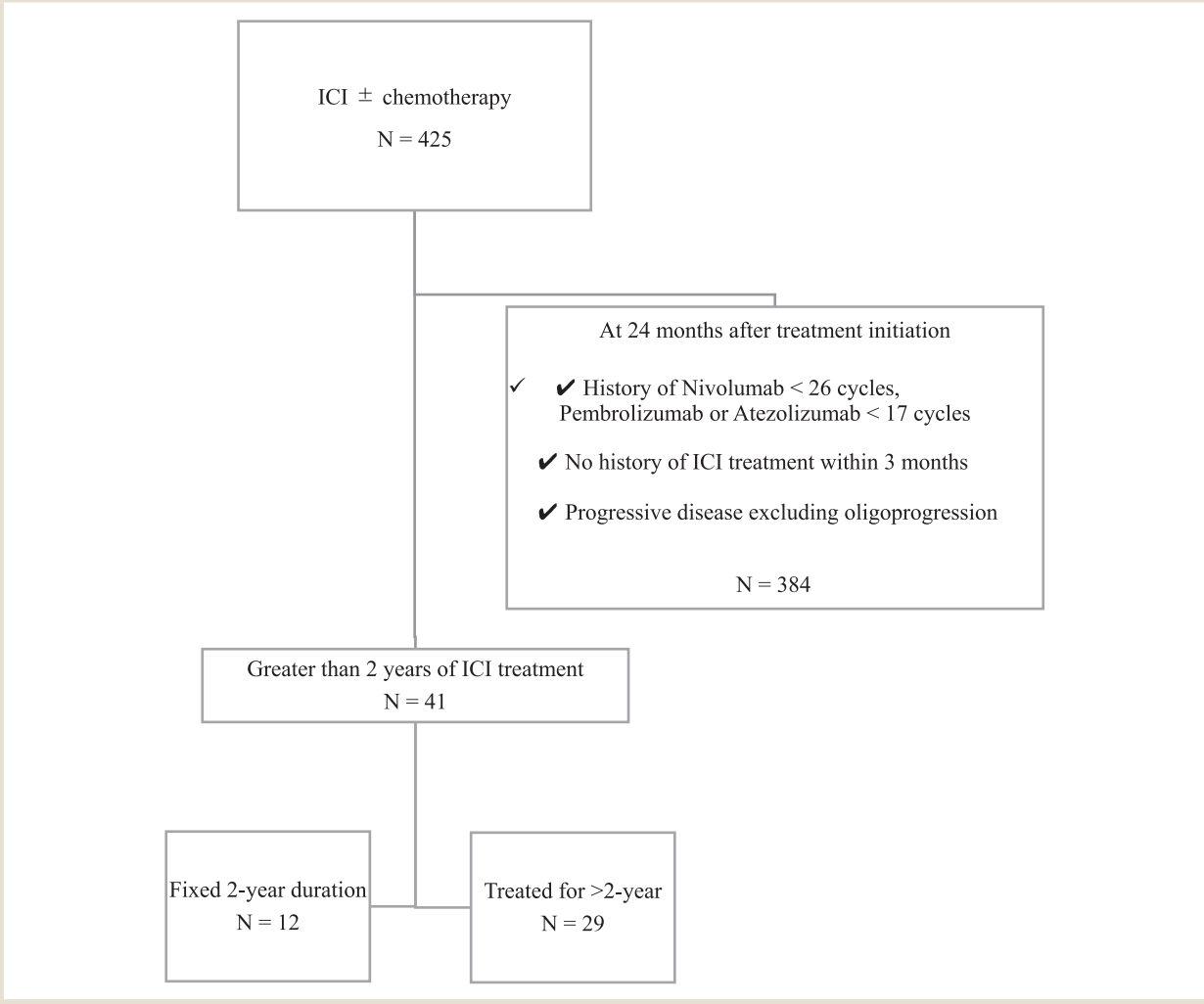
26. Ichihara E, Harada D, Inoue K, et al. Characteristics of patients with EGFR-mutant non-small-cell lung cancer who benefited from immune checkpoint inhibitors. *Cancer Immunol Immunother*. 2021;70(1):101–106. doi:10.1007/s00262-020-02662-0.

27. Hastings K, Yu HA, Wei W, et al. EGFR mutation subtypes and response to immune checkpoint blockade treatment in non-small-cell lung cancer. *Ann Oncol*. 2019;30(8):1311–1320. doi:10.1007/s00262-020-02662-0.

Supplementary materials

Supplemental Figure 1, Supplemental Table 1, 2, 3.

Consort diagram of all the patients with NSCLC who underwent ICI treatmentNSCLC, non–small cell lung cancer; ICI, immune checkpoint inhibitor



Supplemental Table 1 Frequency of chemotherapy regimens ($n = 41$)

Fixed 2-year group ($n = 12$)	
	n
Pembrolizumab monotherapy	8
Pembrolizumab + Cisplatin + Pemetrexed	2
Pembrolizumab + Carboplatin + Pemetrexed	1
Nivolumab monotherapy	1

Continuous group ($n = 29$)	
	n
Pembrolizumab monotherapy	12
Pembrolizumab + Cisplatin + Pemetrexed	1
Pembrolizumab + Carboplatin + Pemetrexed	1
Nivolumab monotherapy	12
Atezolizumab	3

Supplemental Table 2 Subanalysis of 41 patients with NSCLC treated with ICI >2 years

Variable	ICI, stop N = 12	ICI, ongoing N = 29	*P*-value
Age at 2-years treatment, median (range), years <65/≥65 years	69 (38–86) 5/7	67 (35–79) 9/20	0.7186
Sex, male/female	10/2	19/10	0.4521
ECOG-PS at 2-years, 0–1/2	10/2	28/1	0.2002
Cachexia existence at 2-years treatment, yes/no	4/8	5/24	0.4077
*Clinical stage, III or recurrence/IV	4/8	12/17	0.7342
Smoking status, packs per year, <40/≥40	5/7	20/9	0.1606
Pathology, squamous/nonsquamous	1/11	2/27	1.0000
Biomarker (EGFR or ALK), yes/no	0/12	7/22	0.0842
PD-L1 TPS, 0/1–49/≥50 <50 or ≥50	0/4/8 4/8	2/7/10 9/10	0.4840
Line, 1st–2nd/3rd and later	10/2	22/7	0.7017
Combination with chemotherapy, yes/no	3/9	2/27	0.1394

NSCLC, non-small cell lung cancer; ICI, immune checkpoint inhibitor; ECOG-PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; PD-L1, Programmed cell death 1- Ligand 1; TPS, tumor proportion score
* Clinical staging according to the 7th edition of the TNM classification of lung cancer

Supplemental Table 3 Univariate and multivariate analyses of TTF-24 in 41 patients with NSCLC treated with ICI >2 years

Variable	Univariate analysis			Multivariate analysis		
	Relative risk	95% CI	*P*-value	Relative risk	95% CI	*P*-value
Sex, male	0.76	0.26–2.24	0.6161			
Age at 2 years treatment ≥65 years	1.44	0.45–4.64	0.5345			
ECOG-PS at 2 years treatment = 0	1.19	0.40–3.52	0.7503	0.89	0.28–2.83	0.8458
Clinical stage IV	1.33	0.44–3.97	0.6122			
Smoking status, ≥40 packs per year	0.58	0.18–1.86	0.3544			
Pathology, squamous	1.76^{e-9}		0.2501			
Biomarker (EGFR or ALK), yes	2.13	0.59–7.66	0.2360			
PD-L1 TPS, ≥50	0.42	0.13–1.34	0.1311	0.41	0.11–1.53	0.1840
Line, 1st	0.50	0.14–1.80	0.2779	0.49	0.10–2.41	0.3763
ICI, ongoing	5.83	0.76–44.63	0.0541	7.39	0.78–69.92	0.0811
Combination with chemotherapy, yes	0.81	0.10–6.31	0.8406			
Cachexia existence at 2 years treatment, yes	1.68	0.53–5.37	0.3766			

TTF, time to treatment failure; NSCLC, non-small cell lung cancer; ICI, immune checkpoint inhibitor; ECOG-PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; PD-L1, Programmed cell death 1- Ligand 1; TPS, tumor proportion score

Continuous vs. Fixed 2-year Duration Immune Checkpoint Inhibitor Treatment of Patients With Non–Small Cell Lung Cancer: A Single Institution Database Analysis

内科系呼吸器内科学専攻　小林玄機

＜背景＞
進行非小細胞肺癌において、免疫チェックポイント阻害薬の登場で飛躍的に予後が延長した。しかしながら、長期奏効例においては、いつまで治療を継続すべきかは明らかとなっていない。
過去ならびに現在の企業治験では、免疫チェックポイント阻害薬の治療期間を最大 2 年間と定めて、それまで定期投与した後、一旦休薬するプロトコルが多いが、一方で許容できない有害事象もしくは病勢増悪を認めるまで治療継続を実施するプロトコルもある。さらに探索的な検討となるが、CheckMate153 試験においては、1 年で休薬するよりも治療を継続した方が予後は良好であったという報告もある。
今回、進行非小細胞肺癌を対象に、免疫チェックポイント阻害薬を長期使用した症例で、適切な治療期間の検討を後ろ向きに行った。

＜方法＞
静岡がんセンターで 2019 年 8 月 31 日までに、進行肺癌に対して免疫チェックポイント阻害薬を含んだレジメンで治療を受けた症例をすべて抽出し、その中で 2 年間以上免疫チェックポイント阻害薬での治療を継続出来た症例を詳細に検討行った。

＜結果＞
＜全体の症例について＞
検討期間中に 425 例（患者背景は table1）が進行肺癌に対して免疫チェックポイント阻害薬を含んだレジメンで治療を行っていた。その中で、systemic な腫瘍増悪なく、2 年間治療を継続出来た症例は 41 例存在し、患者背景を table2 に示す。腫瘍の PD-L1 値が高いほど、2 年間治療出来た割合が多く、一方で、殺細胞性抗癌剤の併用は 2 年間治療出来た割合に寄与しなかった。41 例中 29 例は 2 年経過しても治療を継続した群で、12 例は 2 年で治療中止した群であった。
また免疫チェックボイント阻害薬が 2 年継続できなかった 384 例と継続できた 41 例を比較した Table ならびに生存曲線 FigA.B を下記に示す。患者背景のみでは免疫チェックボイント阻害薬が 2 年継続可能かどうかは判断不可能であった。検討期間中の 425 例の無増悪生存期間中央値は 3.5 ヶ月で、全生存期間は 16.3 ヶ月であった。

＜2 年間治療が継続出来た症例について＞

Figure 1 に示すように、免疫チェックポイント阻害薬治療開始からの無増悪生存期間中央値は 50.8 ヶ月で、全生存期間は未到達であった。また、Figure 2 A では免疫チェックポイント阻害薬治療開始から 2 年経過した時点を起点に治療成功期間の生存曲線であり、中央値は 48.3 ヶ月であった。サブ解析で 2 年を超えて治療を継続した群と 2 年で治療を中止した群の患者背景を Supplemental　table 2 、2 ‘ (下記に示す)、生存曲線を Figure 2 B に示す。2 年間治療を継続した群の免疫チェックポイント阻害薬での治療成功期間中央値は 48.3 ヶ月で、2 年で治療を中止した群は未到達であった。Figure 2 B や Supplemental　table 3 、3 ‘（下記に示す）が示すように、両群の治療成功期間において独立した予後規定因子はみとめなかった。また 2 群間での治療効果(CR/PR/SD)の比率は、2 年を超えて治療継続した群（N=29）：CR/PR/SD/PD＝0/72.4/17.2/10.3(%)、2 年で治療を中止した群（N=12）：CR/PR/SD/PD＝8.3/75.0/0/16.7(%)であった。

＜41 例の臨床経過＞

Figure3A に 2 年で治療を中止した症例、3B に 2 年を超えて治療を継続した症例のスイマープロットを示す。Figure3A では毒性中止は 1 例(8%)（口内炎）のみで、一方 Figure3B では、7 例(24%)（肺臓炎（N=2)、副腎不全（N=1)、下痢（N=1)、胸膜炎（N=1)、脳膿瘍（N=1)、好酸球増多症（N=1)）が毒性中止を経験した。両群統計学的な差は認めなかったが、治療を継続することで、毒性中止にいたるような有害事象は増える傾向になった。

＜結論＞

進行期非小細胞肺癌において、2 年間の免疫チェックポイント阻害薬を継続出来た症例は、治療を中止しても継続した症例と比較して効果は変わりなく、また有害事象も発症頻度が少ない傾向にあった。

< **Table** >

Table. 425 patients with NSCLC treated with ICI

Variable	**ICI <2-year**	**ICI ≥2-year**	***P-value***
Age at ICI treatment, median (range), years	68 (33–94)	67 (35–86)	0.0518
Sex, male/female	257/127	29/12	0.7272
ECOG-PS at ICI treatment, 0/1/2	65/276/43	12/26/3	0.1380
Clinical stage, III/IV/recurrence	10/227/147	1/25/15	0.8993
Smoking status, packs per year, <40/≥40	216/168	25/16	0.4608
Pathology, squamous/nonsquamous	70/314	3/38	0.1207
Biomarker (EGFR or ALK), yes/ no/unknown	65/270/49	7/31/3	0.5179
PD-L1 TPS, unknown/0/1–49/≥50	111/64/108/111	10/2/11/18	0.0804
Line, $1^{st}/2^{nd}/3^{rd}$ and later	115/129/140	15/17/9	0.8834
Combination with chemotherapy, yes/no	49/335	5/36	0.9004

Supplemental Table 2‘. Subanalysis of 41 patients with NSCLC treated with ICI >2 years

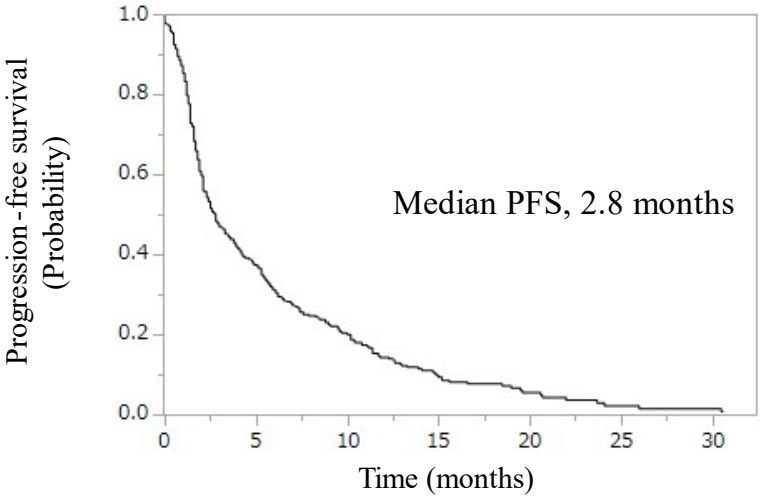
Variable	ICI, stop N = 12	ICI, ongoing N = 29	*P*-value
Age at 2-years treatment, median (range), years	69 (38–86)	67 (35–79)	0.7186
<65/≥65 years	5/7	9/20	
Sex, male/female	10/2	19/10	0.4521
ECOG-PS at 2-years, 0–1/2	10/2	28/1	0.2002
Cachexia existence at 2-years treatment, yes/no	4/8	5/24	0.4077
Clinical stage, III or recurrence/IV	4/8	12/17	0.7342
Smoking status, packs per year, <40/≥40	5/7	20/9	0.1606
Pathology, squamous/nonsquamous	1/11	2/27	1.0000
Biomarker (EGFR or ALK), yes/no	0/12	7/22	0.0842
PD-L1 TPS, 0/1–49/≥50	0/4/8	2/7/10	0.4840
<50 or ≥50	4/8	9/10	
Line, 1^{st}–2^{nd}/3^{rd} and later	10/2	22/7	0.7017
Combination with chemotherapy, yes/no	3/9	2/27	0.1394
CR, PR, SD/PD at 2-years treatment	10/2	26/3	0.6197
CR, PR/SD, PD at 2-years treatment	10/2	21/8	0.6937

Supplemental Table 3'. Univariate and multivariate analyses of TTF-24 in 41 patients with NSCLC treated with ICI >2 years

Variable	Univariate analysis			Multivariate analysis		
	Relative risk	95% CI	*P*-value	Relative risk	95% CI	*P*-value
Sex, male	0.76	0.26–2.24	0.6161			
Age at 2 years treatment ≥65 years	1.44	0.45–4.64	0.5345			
ECOG-PS at 2 years treatment = 0	1.19	0.40–3.52	0.7503			
Clinical stage IV	1.33	0.44–3.97	0.6122			
Smoking status, ≥40 packs per year	0.58	0.18–1.86	0.3544			
Pathology, squamous	1.76^{e-9}		0.2501			
Biomarker (EGFR or ALK), yes	2.13	0.59–7.66	0.2360			
PD-L1 TPS, ≥50	0.42	0.13–1.34	0.1311	0.55	0.13–2.33	0.4209
Line, 1^{st}–2^{nd}	0.50	0.14–1.80	0.2779	0.49	0.10–2.41	0.7909
ICI, ongoing	5.83	0.76–44.63	0.0541	4.43	0.54–36.1	0.1645
Combination with chemo, yes	0.81	0.10–6.31	0.8406			
Cachexia existence at 2 years treatment, yes	1.68	0.53–5.37	0.3766			
CR, PR, SD/PD at 2-years treatment	0.54	0.12–2.43	0.4103			
CR, PR/SD, PD at 2-years treatment	0.27	0.09–0.83	0.0142	0.30	0.08–1.13	0.0751

<**Figure**>

Fig. A（384例のprogression-free survival curve, Overall survival curve）



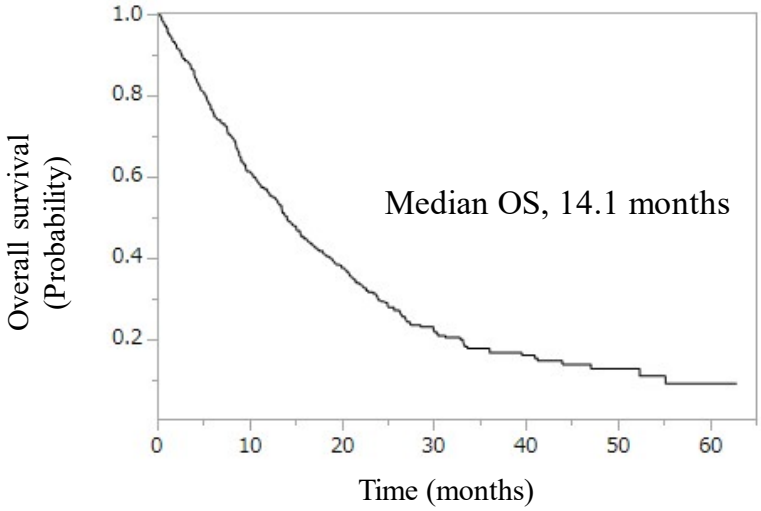


Fig. B（425例のprogression-free survival curve, Overall survival curve）